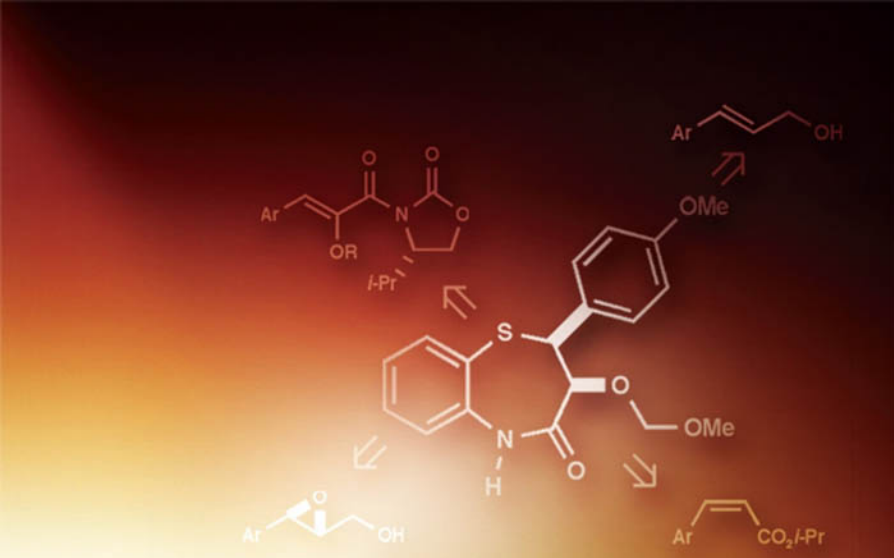

Paul Wyatt · Stuart Warren

ORGANIC SYNTHESIS

Strategy and Control

WILEY

Organic Synthesis

Organic Synthesis: Strategy and Control

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Contents

Preface

We would like to thank those who have had the greatest influence on this book, namely the undergraduates at the Universities of Bristol and Cambridge. But, particularly we would like to thank the organic chemists at Organon (Oss), AstraZeneca (Alderley Park, Avlon Works, Mölndal and Macclesfield), Lilly (Windlesham), Solvay (Weesp) and Novartis (Basel) who contributed to the way the book was written more than they might realise. These chemists will recognise material from our courses on The Disconnection Approach, Advanced Heterocyclic Chemistry, New Synthetic Methods and Asymmetric Synthesis. Additionally we would like to thank the participants at the SCI courses organised by the Young Chemists Panel. All these industrial chemists participated in our courses and allowed us to find the best way to explain concepts that are difficult to grasp. This book has changed greatly over the ten years it was being written as we became more informed over what was really needed. The book is intended for that very audience – final year undergraduates, graduate students and professional chemists in industry.

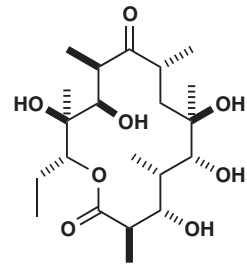
PJW
SGW
July 2006

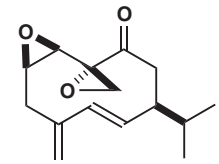
Section A: Introduction: Selectivity

1 Planning Organic Syntheses: Tactics, Strategy and Control

The roll of honour inscribed with successful modern organic syntheses is remarkable for the number, size, and complexity of the molecules made in the last few decades. Woodward and Eschenmoser's vitamin B_{12} synthesis,[1] completed in the 1970s, is rightly regarded as a pinnacle of achievement, but since then Kishi[2] has completed the even more complex palytoxin. The smaller erythromycin and its precursors the erythronolides[3] **1**, and the remarkably economical syntheses of the possible stereoisomers of the cockroach pheromones **2** by Still[4] deal with a greater concentration of problems.

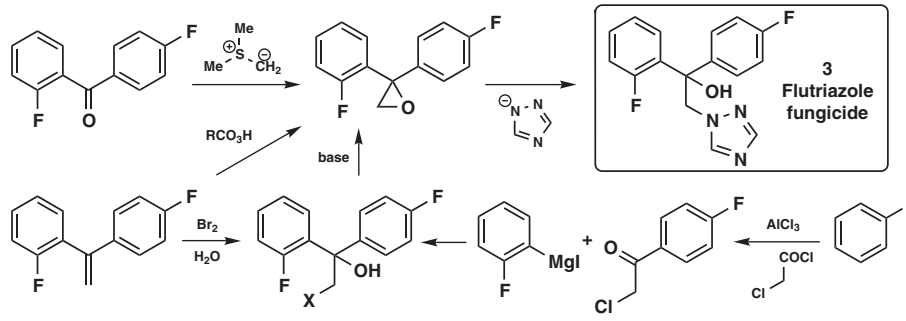
1
erythronolide A



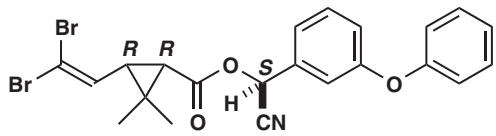


2
periplanone-B

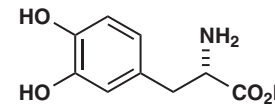
Less applauded, but equally significant, is the general advance in synthetic methods and their industrial applications. AstraZeneca confess that it took them nearly a century to bring Victor Grignard's methods into use, but are proud that Corey's sulfur ylid chemistry made it in a decade. Both are used in the manufacture of the fungicide flutriafol[5] **3**.



Optically active and biodegradable deltamethrin[6] **4** has taken a large share of the insecticide market, and asymmetric hydrogenation is used in the commercial synthesis of DOPA **5** used to treat Parkinson's disease.[7] These achievements depend both on the development of new methods and on strategic planning:[8] the twin themes of this book.

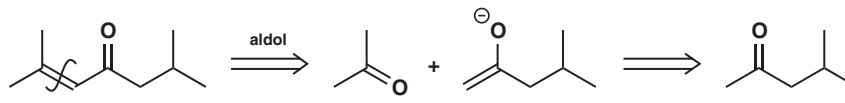


4
deltamethrin



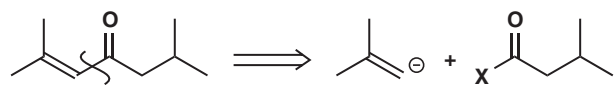
5
(*S*)-L-(–)-DOPA

To make any progress in this advanced area, we have to assume that you have mastered the basics of planning organic synthesis by the disconnection approach, roughly the material covered in our previous books.[9] There, inspecting the target molecule, identifying the functional groups, and counting up the relationships between them usually gave reliable guidelines for a logical synthesis. All enones were tackled by some version of the aldol reaction; thus **6** would require the attack of enolate **7** on acetone. We hope you already have the critical judgement to recognise that this would need *chemoselectivity* in enolising **7** rather than acetone or **6**, and *regioselectivity* in enolising **7** on the correct side.



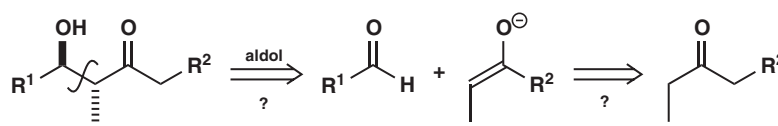
6 **7**

In this book we shall explore two new approaches to such a problem. We shall see how to make specific enol equivalents for just about any enolate you might need, and we shall see that alternative disconnections such as **6a**, the acylation of a vinyl anion **8**, can be put into practice. Another way to express the twin themes of this book is *strategy and control*: we solve problems either by finding an alternative strategy or by controlling any given strategy to make it work. This will require the introduction of many new methods - a whole chapter will be devoted to reagents for vinyl anions such as **8**, and this will mean exploring modern organometallic chemistry.



6a **8** **9**

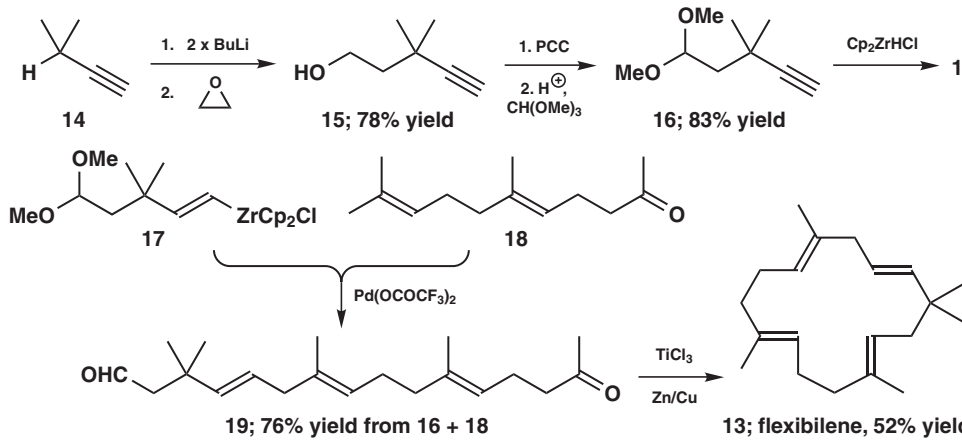
We shall also extend the scope of established reactions. We hope you would recognise the aldol disconnection in TM **10**, but the necessary stereochemical control might defeat you. An early section of this book describes how to control every aspect of the aldol reaction: how to select which partner, i.e. **11** or **12**, becomes an enolate (*chemoselectivity*), how to control which enolate of the ketone **12** is formed (*regioselectivity*), and how to control the stereochemistry of the product **10** (*stereoselectivity*). As we develop strategy, we shall repeatedly examine these three aspects of control.



10 **11** **12**

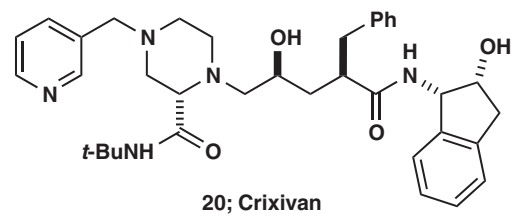
The target molecules we shall tackle in this book are undoubtedly more difficult in several ways than this simple example **10**. They are more complex quantitatively in that they combine functional

groups, rings, double bonds, and chiral centres in the same target, and qualitatively in that they may have features like large rings, double bonds of fixed configuration, or relationships between functional groups or chiral centres which no standard chemistry seems to produce. Molecules **1** to **5** are examples: a quite different one is flexibilene **13**, a compound from Indonesian soft coral. It has a fifteen-membered ring, one di- and three tri-substituted double bonds, all *E* but none conjugated, and a quaternary centre. Mercifully there are no functional groups or chiral centres. How on earth would you tackle its synthesis? One published synthesis is by McMurry.[10]



This short synthesis uses seven metals (Li, Cr, Zr, Pd, Ti, Zn, and Cu), only one protecting group, achieves total control over double bond geometry, remarkable regioselectivity in the Zr-Pd coupling reaction, and a very satisfactory large ring synthesis. The yield in the final step (52%) may not look very good, but this is a price worth paying for such a short synthesis. Only the first two steps use chemistry from the previous books: all the other methods were unknown only ten years before this synthesis was carried out but we shall meet them all in this book.

An important reason for studying alternative strategies (other than just making the compound!) is the need to find short cheap large scale routes in the development of research lab methods into production. All possible routes must be explored, at least on paper, to find the best production method and for patent coverage. Many molecules suffer this exhaustive process each year, and some sophisticated molecules, such as Merck's HIV protease inhibitor **20**, a vital drug in the fight against AIDS, are in current production on a large scale because a good synthesis was found by this process.[11]



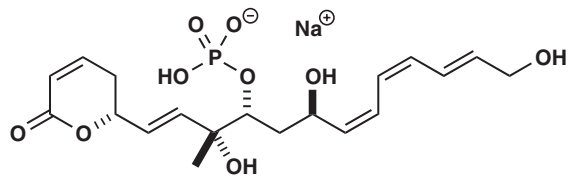
You might think that, say organometallic chemistry using Zr or Pd would never be used in manufacture. This is far from true as many of these methods are catalytic and the development of polymer-supported reagents for flow systems means that organo-metallic reagents or enzymes may be better than conventional organic reagents in solution with all the problems of by-product disposal and solvent recovery. We shall explore the chemistry of B, Si, P, S, and Se, and of metals

such as Fe, Co, Ni, Pd, Cu, Ti, Sn, Ru and Zr because of the unique contribution each makes to synthetic methods.

In the twenty years since McMurry's flexibilene synthesis major developments have changed the face of organic synthesis. Chiral drugs must now be used as optically pure compounds and catalytic asymmetric reactions (chapters 25 and 26) have come to dominate this area, an achievement crowned by the award of the 2001 Nobel prize for Chemistry to Sharpless, Noyori and Knowles. Olefin metathesis (chapter 15) is superseding the Wittig reaction. Palladium-catalysed coupling of aromatic rings to other aromatic rings, to alkenes, and to heteroatoms (chapter 18) makes previously impossible disconnections highly favourable. These and many more important new methods make a profound impact on the strategic planning of a modern synthesis and find their place in this book.

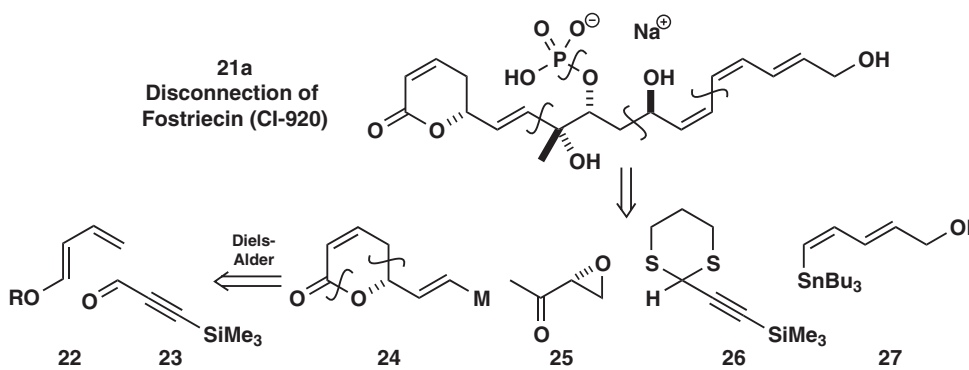
A Modern Synthesis: Fostriecin (CI-920)

The anti-cancer compound Fostriecin **21** was discovered in 1983 and its stereochemistry elucidated in 1997. Not until 2001 was it synthesised and then by two separate groups.[12] Fostriecin is very different from flexibilene. It still has alkene geometry but it has the more challenging three-dimensional chirality as well. It has plenty of functionality including a delicate monophosphate salt. A successful synthesis must get the structure right, the geometry of the alkenes right, the relative stereochemistry right, and it must be made as a single enantiomer.



21; Fostriecin (CI-920)

The brief report of Jacobsen's total synthesis starts with a detailed retrosynthetic analysis. The compound was broken into four pieces **21a** after removal of the phosphate. The unsaturated lactone **24** (M is a metal) could be made by an asymmetric oxo-Diels-Alder reaction from diene **22** and ynal **23**. The epoxide **25** provides a second source of asymmetry. One *cis* alkene comes from an alkyne **26** and the rest from a dienyl tin derivative **27**.



The synthesis is a catalogue of modern asymmetric catalytic methods. The epoxide **25** was resolved by a hydrolytic kinetic resolution (chapter 28) using a synthetic asymmetric cobalt complex. The asymmetric Diels-Alder reaction (chapter 26) was catalysed by a synthetic chromium

complex. The vinyl metal derivative **24** was made by hydrozirconation of an alkyne (this at least is similar to the flexibilene synthesis) and the secondary alcohol chiral centre was derived from the dithian **26** by hydrolysis to a ketone and asymmetric reduction with a synthetic ruthenium complex (chapter 24). The dienyl tin unit **27** was coupled to the rest of the molecule using catalytic palladium chemistry (chapter 18). Almost none of these catalytic methods was available in 1983 when flexibilene was made and such methods are a prominent feature of this book. Organic synthesis nowadays can tackle almost any problem.[13]

Please do not imagine that we are abandoning the systematic approach or the simpler reagents of the previous books. They are more essential than ever as new strategy can be seen for what it is only in the context of what it replaces. Anyway, no-one in his or her right mind would use an expensive, toxic, or unstable reagent unless a friendlier one fails. Who would use pyrophoric tertiary butyl-lithium in strictly dry conditions when aqueous sodium hydroxide works just as well? In most cases we shall consider the simple strategy first to see how it must be modified. The McMurry flexibilene synthesis is unusual in deploying exotic reagents in almost every step. A more common situation is a synthesis with one exotic reagent and six familiar ones. The logic of the previous books is always our point of departure.

The organisation of the book

The book has five sections:

A: Introduction, selectivity, and strategy
B: Making Carbon-Carbon bonds
C: Carbon-Carbon double bonds
D: Stereochemistry
E: Functional Group Strategy

The introductory section uses aldol chemistry to present the main themes in more detail and gives an account of the three types of selectivity: *chemo-*, *regio-*, and *stereo-selectivity.* We shall explore alternative strategies using enones as our targets, and discuss how to choose a good route using cyclopentenones as a special case among enones. Each chapter develops strategy, new reagents, and control side-by-side. To keep the book as short as possible (like a good synthesis), each chapter in the book has a corresponding chapter in the workbook with further examples, problems, and answers. You may find that you learn more efficiently if you solve some problems as you go along.

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General references are given on page 893

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2 Chemoselectivity

Definitions

Introduction: three types of control

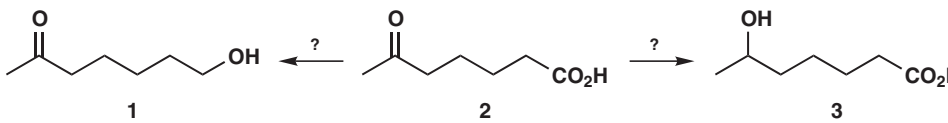
Behind all grand strategic designs in organic synthesis must lie the confidence that molecules can be compelled to combine in the ways that we require. We shall call this *control* and divide it into three sections by mechanistic arguments. These sections are so important that we shall devote the next three chapters to the more detailed explanation of just what the divisions mean. If you can recognise what might go wrong you are in a better position to anticipate the problem and perhaps avoid it altogether. Our three types of control are over chemoselectivity (selectivity between different functional groups), regioselectivity (control between different aspects of the same functional group), and stereoselectivity (control over stereochemistry). Examples of selectivity of all three kinds are given in *The Disconnection Approach*: Chemoselectivity in chapter 5, Regioselectivity in chapter 14, and Stereoselectivity in chapters 12 and 38. These aspects will not be addressed again in the present book.

Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

Chemoselectivity: simple examples and rules

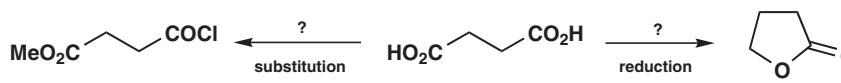
Chemoselectivity is the most straightforward of the three types and might seem too elementary to appear in an advanced textbook. Counting the number of protecting groups in the average synthesis reveals this as a naive view. Selectivity between functional groups might involve:

(a) Selective reaction of one among several functional groups of different reactivity, as in the reduction of the keto-acid **2** to give either product **1** or **3** at will.



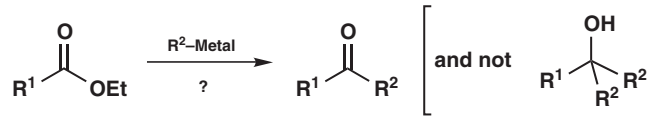
1 **2** **3**

(b) Selective reaction of one of several identical functional groups, as in the conversion of the symmetrical diacid **5** to the half ester, half acid chloride **4**, or the lactone **6** in which one of the two acids has been reduced. There is a more subtle example of this at the end of the chapter.



4 **5** **6**

(c) Selective reaction of a functional group to give a product which could itself react with the same reagent, as in the classical problem of making a ketone **8** from an acid derivative **7** without getting the alcohol **9** instead.

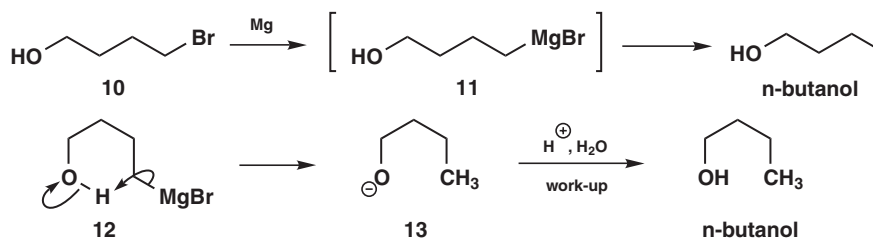


7 **8** **9**

Organic chemists are developing ever more specific reagents to do these jobs. These reagents must carry out the reaction they are designed for and must *not*:

(i) react with themselves.
(ii) react with functional groups other than the one they are aimed at.
(iii) react with the product.

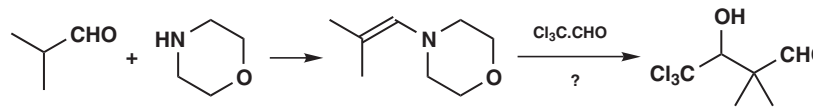
Proviso (ii) is obvious, but (i) and (iii) perhaps need some explanation. It seems hardly worth stating that a reagent should not react with itself, but it is only too easy to suggest using a reagent such as **11** without realising that the organo-metallic reagent will act as a base for its own hydroxyl group **12** and destroy itself. The traditional solution to this problem is protection of the OH group in **10** but ideally we should like to avoid protection altogether though this is not yet possible.



10 **11** n-butanol

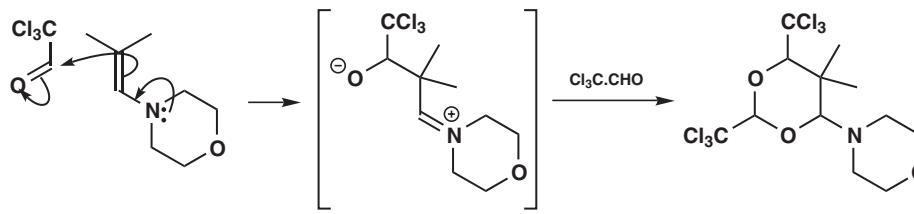
12 **13** n-butanol

Proviso (iii) is more obvious and yet perhaps more often catches people out. It is not always clear in exactly what form the product is produced in the reaction mixture, though a good mechanistic understanding and careful thought should reveal this. The reaction between the simple aldehyde **14** and chloral ($Cl_3C.CHO$) looks like a straightforward route to the aldol **17**, and might reasonably be carried out via the enamine **16**.



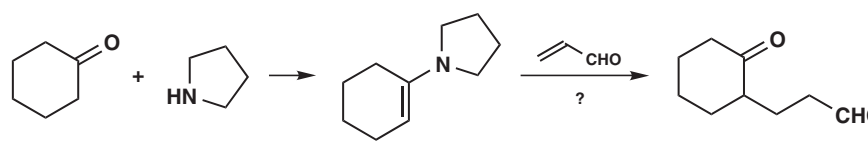
14 **15** **16** **17**

However, mixtures of **16** and chloral, in any proportion, give only the 2:1 adduct **20** which can be isolated in 83% yield.[1] Obviously the immediate product **19** reacts with chloral at least as fast as does **16**. Fortunately the synthesis can be rescued by acid-catalysed cleavage of **20** with HCl which gives a good yield of the target **17**.



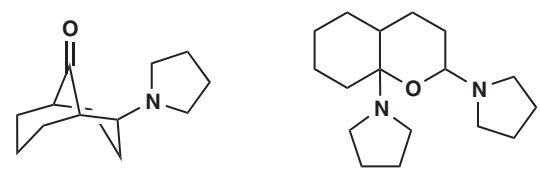
18 **19** **20**

Enamines are excellent at Michael additions and another plausible synthesis which "goes wrong" is the addition of acrolein to cyclohexanone mediated by the enamine **21** formed this time with pyrollidine.



21 **22**

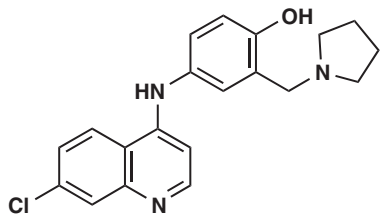
If the product is isolated by distillation, a good yield (75%) of the bicyclic ketone **23** is obtained.[2] A more detailed investigation disclosed that **24** is the immediate product, that **23** is formed from it on distillation, and that the expected Michael adduct **22** can be isolated in good yield simply by the hydrolysis of **24**. In other words, don't distil! If things "go wrong" in a synthesis, this may be a blessing, as here. There are lots of ways to control Michael additions, but few ways to make bicyclic ketones like **23**, and this is now a standard method.[3] The moral is to make sure you know what is happening, and to be prepared to welcome the useful and unexpected result.



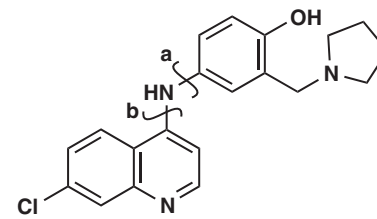
23 **24**

Chemoselectivity by Reactivity and Protection: An anti-Malaria Drug

We need to see some of these principles in action and a proper synthesis is overdue. The anti-malarial drug amopyroquine **25** might have been derived from quinine as it has a quinoline nucleus. It also has five functional groups – three amines (all different - one aromatic, one tertiary, and one secondary), a phenol and an aryl chloride. There are four rings, three aromatic and one saturated heterocyclic.

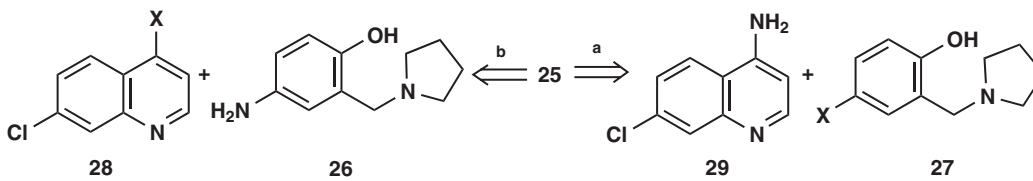


25
Amopyroquine



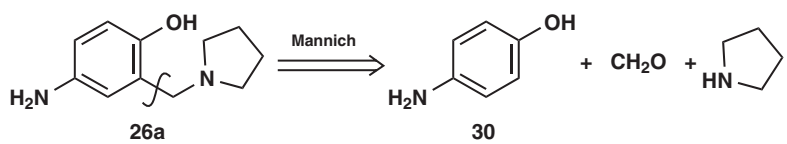
25a, b
Amopyroquine disconnections

There are many possible disconnections, but we should prefer to start in the middle of the molecule to achieve the greatest simplification. Disconnection **25a** would require a nucleophilic displacement (X = a leaving group) on an unactivated benzene ring **27** and looks unpromising. Disconnection **25b** requires nucleophilic displacement at position 4 in a pyridine ring, an acceptable reaction because of the electron-withdrawing effect of the nitrogen atom in the ring, so this is the better route, though we may be apprehensive about controlling the chemoselectivity as there are three potential nucleophiles in **26** and two potential electrophiles in **28**.

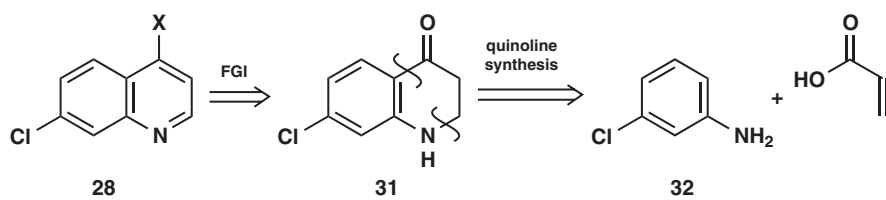


28 **26** **29** **27**

Further disconnections of **26** by the Mannich reaction[4] and of **28** by standard heterocyclic methods give simple starting materials.[5]



26a **30**

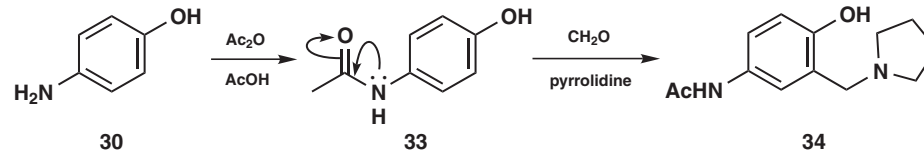


28 **31** **32**

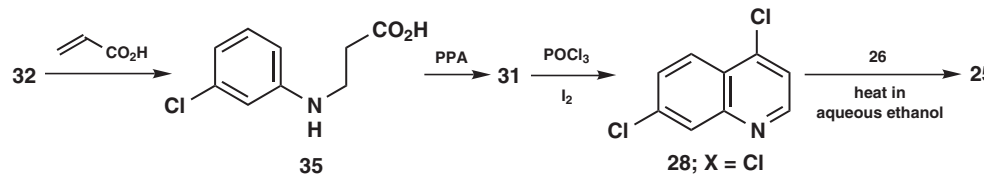
Protection to allow a less reactive group to react

Now the fun begins! Attempted Mannich reaction on the aminophenol **30** would be dominated by the more nucleophilic NH_2 group and is no good. Acylation moderates the NH_2 group by delocalisation

and **33** is a good choice for starting material as it is paracetamol, the common analgesic. Mannich reaction now chemoselectively gives **34** and alkaline hydrolysis of the amide gives **26**.



Michael addition of acrylic acid to the chloroamine **32** is straightforward and Friedel-Crafts cyclisation of **35** gives only **31**, presumably because the position next to the chlorine atom is slightly disfavoured both sterically and electronically. Chlorination and oxidation are conveniently carried out in the same step and the two halves (**26** and **28**) of this convergent synthesis are combined to give amopyroquine **25**.

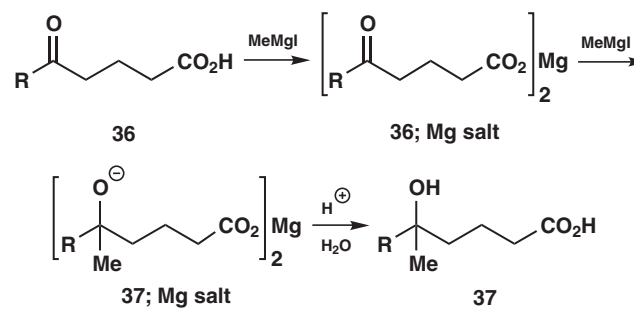


In the last step we return to the original question of chemoselectivity: Only the primary amine in **26** reacts because it is more nucleophilic than OH and because the more nucleophilic tertiary amine adds reversibly – it cannot lose a hydrogen atom as it does not have one. Only the 4-chlorine atom in the pyridine **28** reacts, presumably because addition to the other position would require the disruption of both aromatic rings. Though this compound has been succeeded by better anti-malarials, its synthesis illustrates the all-important principle that predictions of chemoselectivity must be based on sound mechanistic understanding. If doubt remains it is worth trying a model reaction on simpler compounds or, of course, an alternative strategy.

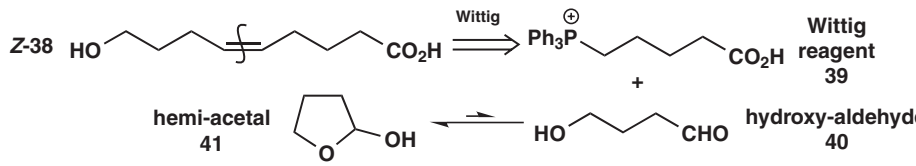
When Protection is not Needed

Dianions: wasting reagent to achieve selectivity

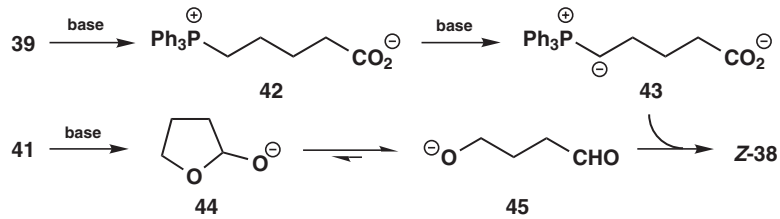
In that synthesis we moderated an over-reactive amino group by protection. Sometimes, protection is not necessary if we are prepared to squander some of our reagents. A trivial example is the addition of methyl Grignard to the ketoacid **36**. We have already seen how acidic protons destroy Grignard reagents, but if we are prepared to waste one molecule of the Grignard, we get automatic protection of the carboxylic acid by deprotonation. Nucleophilic MeMgI will not add to the anion of a carboxylic acid but adds cleanly to the ketone to give, after workup, the alcohol **37**.



At first sight, the synthesis of *Z*-**38** by the Wittig reaction seems too risky. The phosphonium salt **39** has a more acidic proton (CO_2H) than the one we want to remove to make the ylid, and the aldehyde **40** not only also has an acidic proton (OH), but it prefers to remain as the cyclic hemiacetal **41** so that there is no carbonyl group at all.

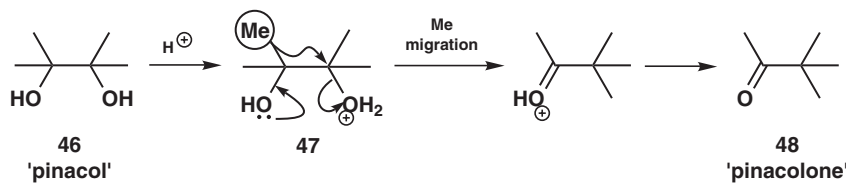


However, simply using a large excess of base makes the reaction work without any protection. The phosphonium salt **39** does indeed lose its first proton from the CO_2H group **42**, but the second molecule of base forms the ylid **43** as the two anions are far enough apart not to influence each other.[6] Base also catalyses the equilibrium between the anions **44** and **45** so that **43** and **45** can react to give the target molecule. The transition state for this reaction has three partial negative charges, but they are well apart from each other and there is obviously not too much electrostatic repulsion as the reaction goes well. This case is opposite to the previous ones: careful mechanistic analysis shows that expected chemoselectivity problems do not materialise.



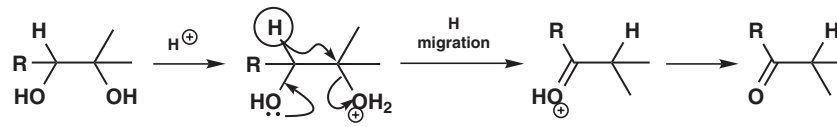
Chemoselectivity by Reagent: The Pinacol Rearrangement

So far we have discussed chemoselectivity between different functional groups. The situation gets more complicated if the functional groups are similar, or even the same. The pinacol rearrangement is a useful route to carbonyl compounds from diols, the classical example being the rearrangement of **46** in acid solution to give the *t*-alkyl ketone **48**. There are no chemoselectivity problems here: the two hydroxyl groups in **46** are the same so it does not matter which gets protonated and, in the rearrangement step **47**, all four potential migrating groups are methyl.

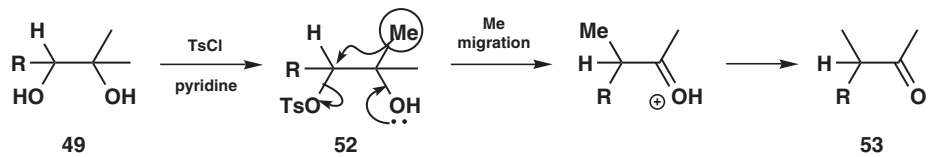


Selectivity between secondary and tertiary alcohols by reagent

Unsymmetrical diols provide a serious problem of chemoselectivity with an ingenious solution.[7] Treatment of the diol **49** with acid leads to loss of OH from what would be the more stable *t*-alkyl cation and hence, by hydrogen shift, to the ketone **51**.

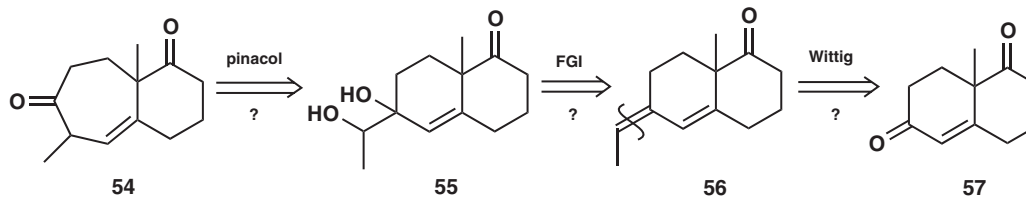


The alternative, more interesting rearrangement to give **53** can be initiated by tosylation of the diol **49** in weak base. It is impossible to tosylate tertiary alcohols under these conditions, as both the *t*-alcohol and TsCl are large, so only the secondary alcohol becomes sulfonylated and so leaves, and the rearranged ketone **53** is the only product.

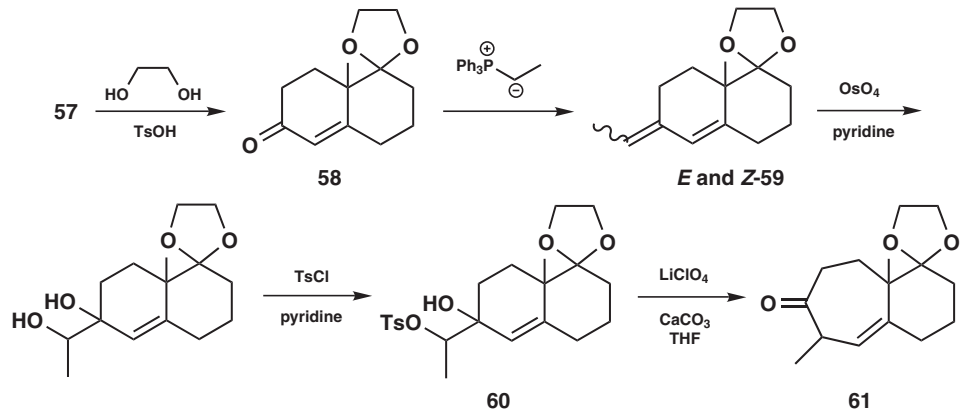


Corey's longifolene synthesis

The question of which group migrates in a pinacol rearrangement is also a question of chemoselectivity, and usually groups that can participate because they have lone pair or π-electrons migrate best. In Corey's longifolene synthesis,[8] the 6/7 fused enone **54** was an important intermediate. Synthesis from the readily available Robinson annelation product **57** is very attractive, but this demands a ring expansion step such as the pinacol rearrangement of **55** of unknown selectivity. 1,2-Diols such as **55** normally come from the hydroxylation of an alkene, in this case the diene **56** which might be made by a Wittig reaction on the dione **57**. Every step in this sequence raises a question of chemoselectivity. Which of the two ketones in **57** is more reactive? Which of the two double bonds in **56** is more easily hydroxylated? Which side of the ring migrates in the pinacol rearrangement on **55**?



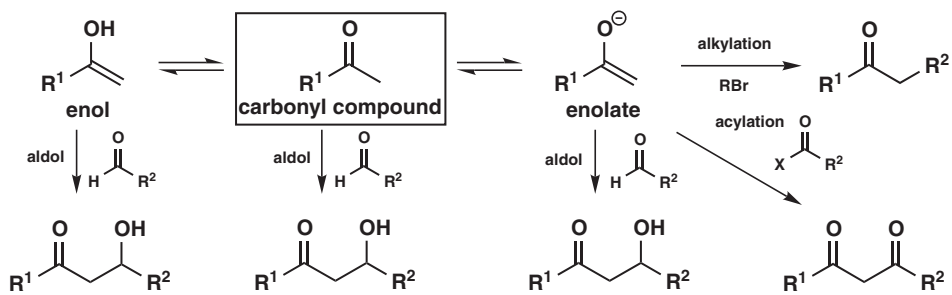
One of the ketones in **57** is conjugated, and one is not. The unconjugated one is less stable and we can therefore use *thermodynamic control* if we protect as an acetal, a reversible process. The unconjugated ketone would also be more *kinetically* reactive towards the Wittig reagent. Of the two double bonds in **59**, the one outside the ring is more reactive towards electrophilic reagents, again for both kinetic and thermodynamic reasons. The tosylation route ensures that the right OH group leaves in the pinacol rearrangement and because the remaining π-bond migrates better than the simple alkyl group when **60** rearranges with a weak Lewis acid, all is well. The synthesis therefore follows the route below, with all questions of chemoselectivity neatly solved. The acetal protecting group was also useful later in the synthesis.



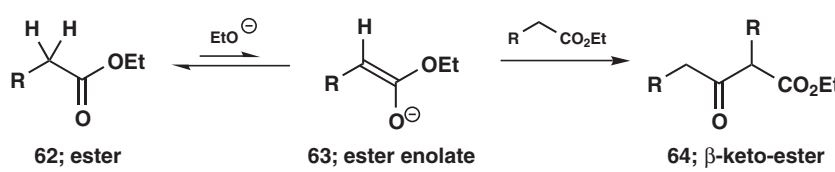
Chemoselectivity in Enol and Enolate Formation

General discussion of enols and enolates

We have concentrated so far on two functional groups within the same molecule. The chemoselectivity problem is just as important when we want two molecules to react together in a certain way, but, because both molecules have similar functional groups, the reaction can occur the other way round, or one of the molecules may react with itself and ignore the other. This problem is particularly acute in reactions involving enolisation. The alkylation or acylation of enols or enolates and the reaction of one carbonyl compound with another, the aldol reaction, are classical and important examples summarised in the general scheme below. We shall concentrate in this chapter on the chemoselectivity of these processes, that is we shall look at the enolisation of esters, aldehydes, and the like.

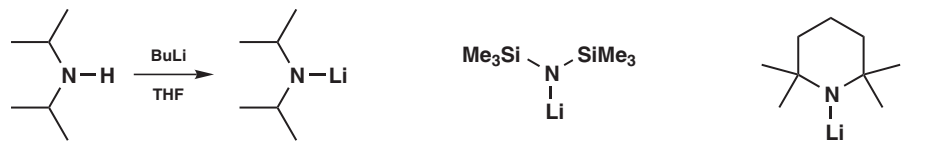


Reaction of an ester **62** with its own alkoxide ion produces a small amount of enolate **63** that reacts with unenolised ester to give the ketoester **64**. This reaction, though useful in its own right, precludes the direct alkylation of esters under these conditions.



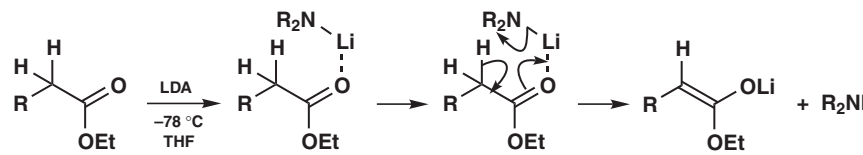
Formation of specific enol equivalents

What is needed for the alkylation is rapid conversion of the ester into a reasonably stable enolate, so rapid in fact that there is no unenolised ester left. In other words *the rate of proton removal must be faster than the rate of combination of enolate and ester.* These conditions are met when lithium enolates are made from esters with lithium amide bases at low temperature, often −78 °C. Hindered bases must be used as otherwise nucleophilic displacement will occur at the ester carbonyl group to give an amide. Popular bases are LDA (Lithium Di-isopropyl Amide, **66**), lithium hexamethyldisilazide **67**, and lithium tetramethylpiperidide **68**, the most hindered of all. These bases are conveniently prepared from the amine, e.g. **65** for LDA, and BuLi in dry THF solution.



65 Di-isopropylamine | **66; LDA** Li Di-isopropyl Amide | **67; LHMDS** Li HexaMethylDiSilyazide | **68; LTMP** Li TetraMethylPiperidide

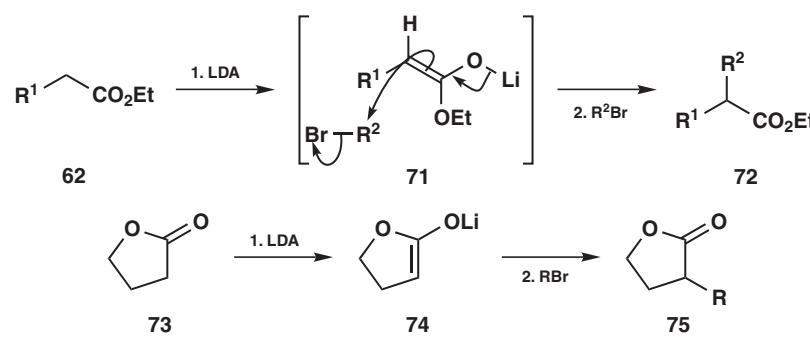
Treatment of a simple ester **62** with one of these bases at −78 °C leads to a stable lithium enolate **70** by initial coordination of lithium to the carbonyl group **69** and proton removal via a six-membered cyclic transition state **69a**.



62; ester | **69** | **69a** | **70**

Lithium enolates, enamines and silyl enol ethers

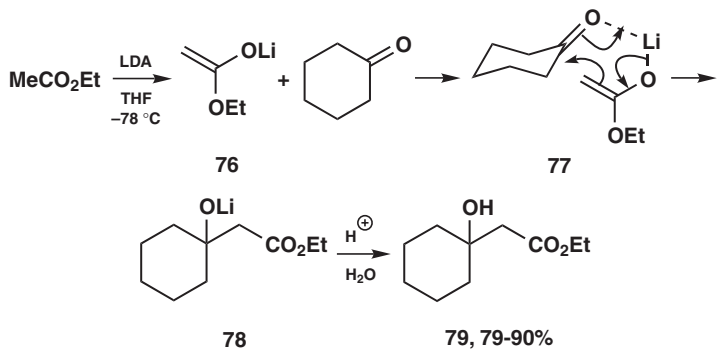
Direct alkylation of lithium enolates of esters[9] **62** and lactones **73**, *via* the lithium enolates **71** and **74**, with alkyl halides is usually successful.



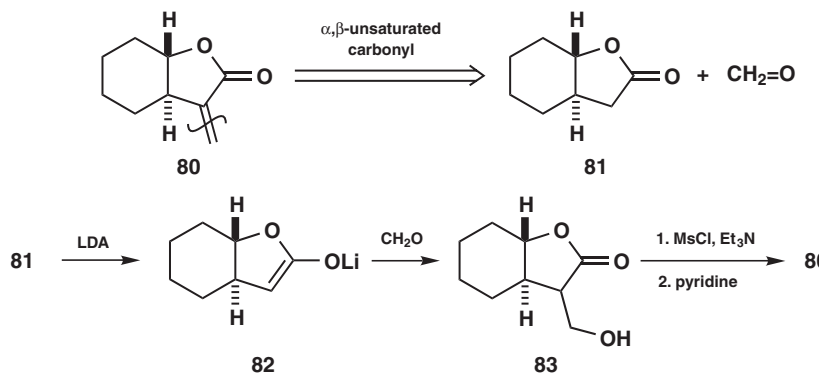
62 | **71** | **72**

73 | **74** | **75**

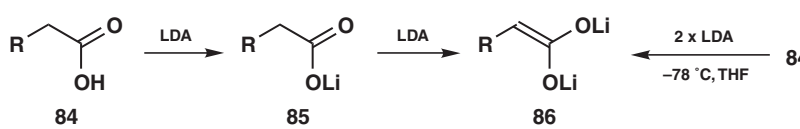
More impressive and more important is the performance of these lithium enolates in aldol reactions. Ester enolates are awkward things to use in reactions with enolisable aldehydes and ketones because of the very efficient self-condensation of the aldehydes and ketones. The traditional solutions involve such devices as Knoevenagel-style reactions with malonates.[11] Lithium enolates of esters, e.g. **76**, react cleanly with enolisable aldehydes and ketones to give high yields of aldols,[12] e.g. **79** in a single step also involving a six-membered cyclic transition state **77**.



They even react cleanly with formaldehyde, thus solving the problem that the Mannich reaction is not applicable to esters. The synthesis of the *exo*-methylene lactone **80** can be accomplished this way. Enone disconnection[13] reveals formaldehyde as the electrophilic component in a crossed aldol reaction, realised with a lithium enolate **82**.[14] The mono-adduct **83** of formaldehyde and the lactone **81** can be isolated and the cautious dehydration step is to avoid migration of the double bond into the ring.

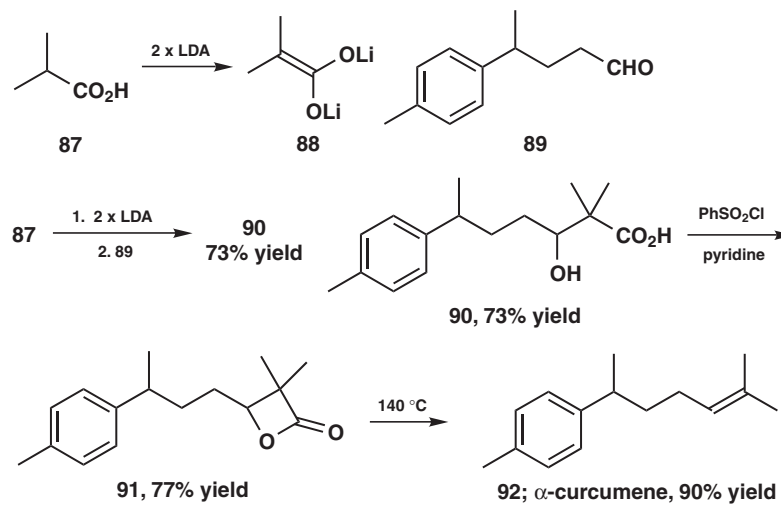


The same technique can even be applied to carboxylic acids themselves **84** providing two molecules of base are used. The first removes the acid proton to give the lithium salt **85** and the second forms the lithium enolate **86**.

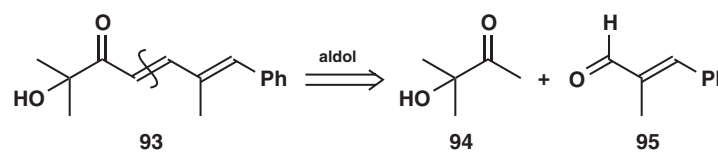


These lithium derivatives are also well behaved in alkylations and aldol reactions. Krapcho's synthesis[15] of the sesquiterpene α-curcumene **92** starts with the chemoselective condensation of

the dilithium derivative of the acid **87** with the enolisable aldehyde **89**. The aldol product **90** is converted into the β-lactone **91** and hence by heating and loss of CO_2 into α-curcumene **92**.

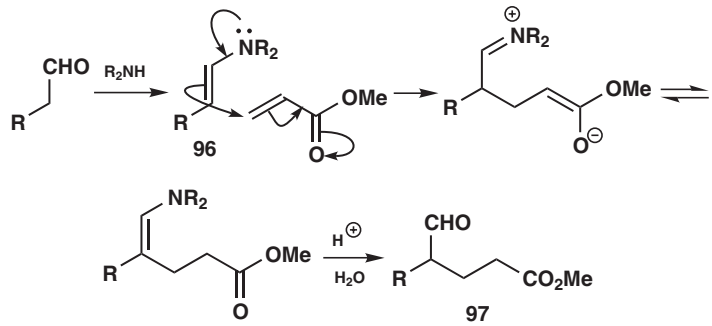


You might be forgiven for thinking that lithium enolates solve all problems of enolate chemoselectivity at a stroke and wonder why they are not always used. They are very widely used, but they require strictly anhydrous conditions at low temperatures (usually −78 °C, the temperature of a dry ice/acetone bath) and no-one in their right mind would use these conditions if mixing the reagents in ethanol at room temperature with a catalytic amount of NaOH did nearly as well. These are the conditions of many simple aldol reactions and are preferred where practical, particularly in industrial practice. The intermediate **93** was needed in a synthesis of geiparvirin. The best aldol disconnection in the middle of the molecule gives a ketone **94**, that must be enolised in the only possible position, and then react with an unenolisable and more electrophilic aldehyde **95**. No selectivity problems arise and an equilibrating aldol reaction between **94** and **95** catalysed by NaOEt in EtOH gives **93** in 89% yield.[16]

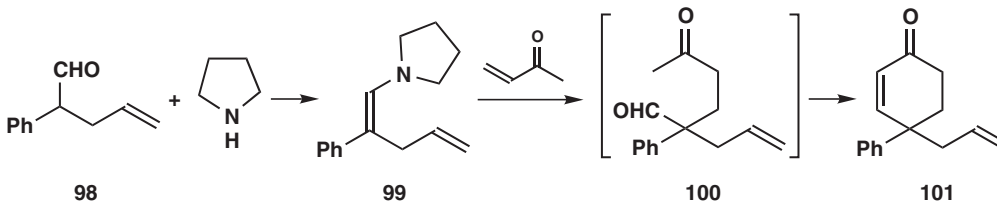


Enamines

Lithium enolates do not even solve all problems of chemoselectivity: most notoriously, they fail when the specific enolates of aldehydes are needed. The problem is that aldehydes self-condense so readily that the rate of the aldol reaction can be comparable with the rate of enolate formation by proton removal. Fortunately there are good alternatives. Earlier in this chapter we showed examples of what can go wrong with enamines. Now we can set the record straight by extolling the virtues of the enamines **96** of aldehydes.[17] They are easily made without excessive aldol reaction as they are much less reactive than lithium enolates, they take part well in reactions such as Michael additions, a standard route to 1,5-dicarbonyl compounds, e.g. **97**.[18]

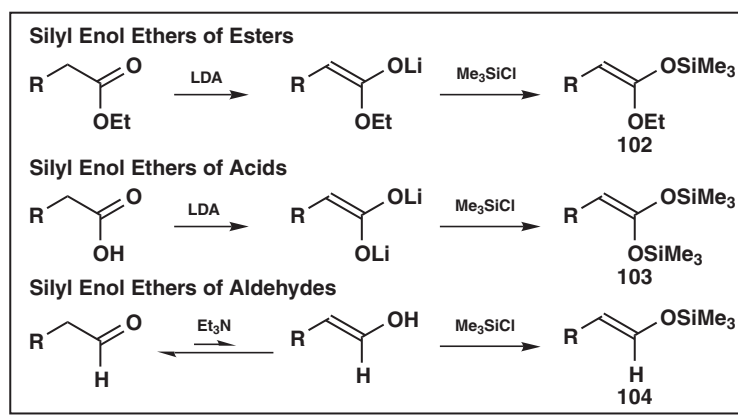


An impressive example[19] is the Robinson annelation of the unsaturated aldehyde **98** where neither aldol reaction nor double bond migration in the enamine **99** interferes. The 1,5-dicarbonyl compound **100** cyclises spontaneously to the enone **101**.



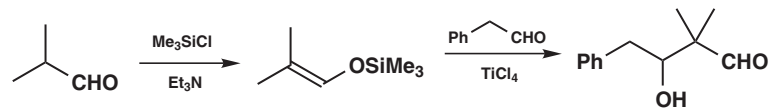
Silyl enol ethers

For all their usefulness, enamines have now largely been superseded by silyl enol ethers. These (**102**-**104**) can be made directly with Me_3SiCl from the lithium enolates of esters or acids or from aldehydes under milder conditions with a tertiary amine. The silicon atom is an excellent electrophile with a strong preference for more electronegative partners and it combines with the oxygen atom of an enolate so rapidly that no self condensation occurs even with aldehydes.

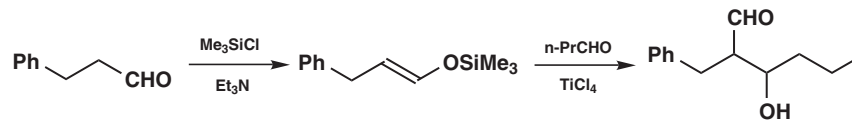


The silyl enol ethers **102** and **104** are shown as single geometrical isomers for convenience: in fact they are normally formed as mixtures, though this does not usually affect their reactions. They are thermodynamically stable compounds but are easily hydrolysed with water or methanol and are usually prepared when they are needed. They are much less reactive than lithium enolates, or even enamines, and their reactions with electrophiles are best catalysed by Lewis acids, often

$TiCl_4$. The aldehydes **105** and **108**, the one branched and the other not, are simply converted into their silyl enol ethers **106** and **109** and combined with two different enolisable aldehydes to give high yields of aldol products **107** and **110** without any self condensation of any of the four aldehydes or any cross-condensation the wrong way round.[20]

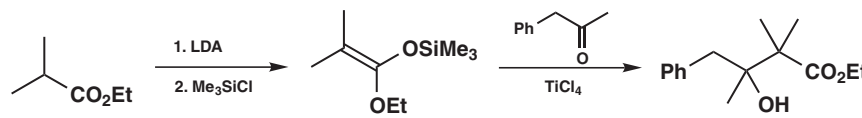


105 **106** **107; 86% yield**

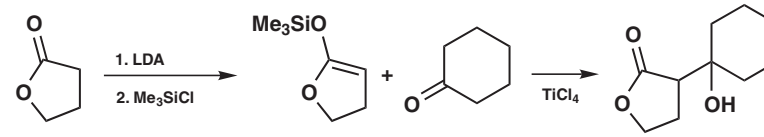


108 **109** **110; 78% yield**

The silyl enol ethers of esters, e.g. **111** and lactones, e.g. **114** similarly take part in efficient aldol reactions with enolisable aldehydes and ketones with Lewis acid catalysis, again with complete regioselectivity. Example **113** is particularly impressive as the very enolisable ketone gives a high yield of an aldol product with two adjacent quaternary centres.[21]



111 **112** **113, 94% yield**

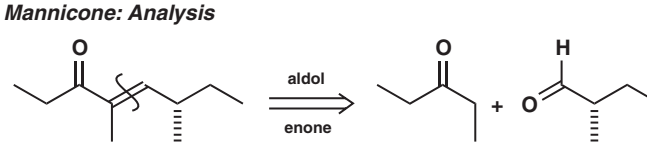


114 **115** **116**

Synthesis of the ant alarm pheromone mannicone

The synthesis of the ant alarm pheromone mannicone **117** is a good example. Enone disconnection reveals that we need a crossed aldol condensation between the symmetrical ketone **118**, acting as the enol component, and the enolisable aldehyde **119**.

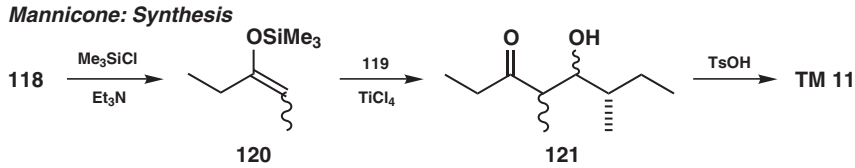
Mannicone: Analysis



117 **118** **119**

The ketone gives a mixture of geometrical isomers of the silyl enol ether **120** which condense with the aldehyde **119** to give the aldol **121** as a mixture of diastereoisomers which dehydrates to mannicone **117** in acid.[22] It is particularly impressive that the optically active aldehyde **119** has its

stereogenic centre at the enol position and yet optically active mannicone is formed by this route without racemisation.

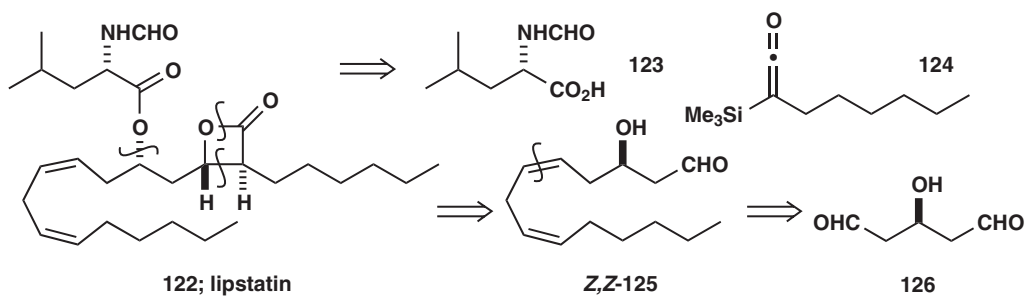


We shall discuss further aspects of the aldol reaction in the next two chapters where we shall see how to control the enolisation of unsymmetrical ketones, and how to control the stereochemistry of aldol products such as **121**. We shall return to a more comprehensive survey of specific enol equivalents in chapter 10. In this chapter we are concerned to establish that chemoselective enolisation of esters, acids, aldehydes, and symmetrical ketones can be accomplished with lithium enolates, enamines, or silyl enol ethers, and we shall be using all these intermediates extensively in the rest of the book.

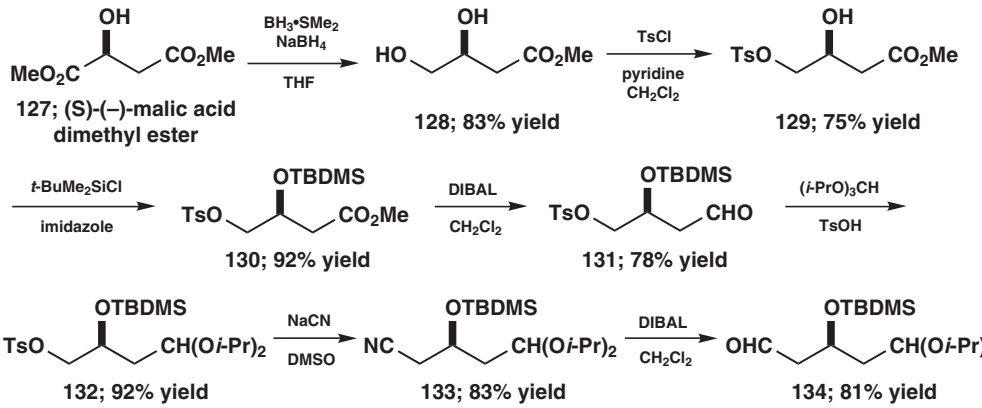
Examples of Chemoselective Reactions in Synthesis

Synthesis of lipstatin

The synthesis of lipstatin **122** is too complex to discuss here in detail but an early stage in one synthesis uses a clever piece of chemoselectivity.[23] Kocienski planned to make the β-lactone by a cycloaddition with the ketene **124** and to add the amino acid side chain **123** by a Mitsunobu reaction involving inversion. They therefore needed *Z*,*Z*-**125** to join these pieces together. This was to be made in turn by a Wittig reaction from **126**. The problem now is that **126** is symmetrical and cannot carry stereochemistry and that aldehydes are needed at both ends.

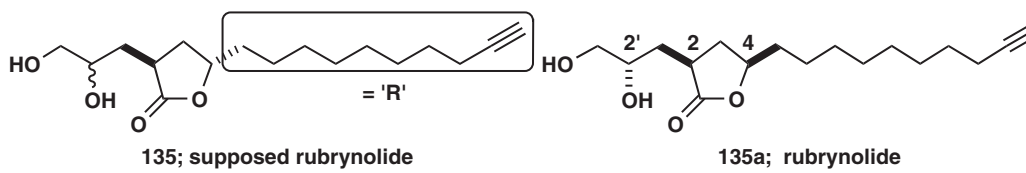


The way they solved the problem was this. (*S*)-(−)-Malic acid is available cheaply. Its dimethyl ester **127** could be chemoselectively reduced by borane to give **128**. Normally borane does not reduce esters and clearly the borane first reacts with the OH group and then delivers hydride to the nearer carbonyl group. The primary alcohol was chemoselectively tosylated **129** and the remaining (secondary) OH protected with a silyl group **130** (TBDMS stands for *t*-butyldimethylsilyl and is sometimes abbreviated to TBS). Now the remaining ester can be reduced to an aldehyde **131** and protected **132**. Displacement of tosylate by cyanide puts in the extra carbon atom **133** and reduction gives **134**, that is the dialdehyde **126** in which one of the two aldehydes is protected. This compound was used in the successful synthesis of lipstatin.

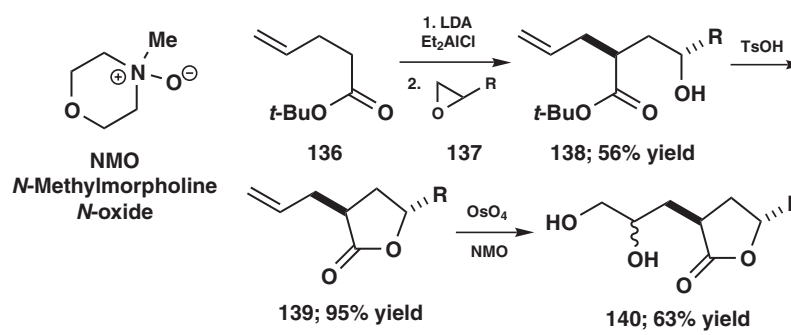


The synthesis of rubrynolide

The synthesis of the natural product rubrynolide from the Brazilian tree *Nectandra rubra* presents rather different problems. When the synthesis was planned it was supposed that rubrynolide was a *trans* lactone **135** but the third centre was not defined. The synthesis revealed that this structure is wrong: the lactone is actually *cis* and the stereochemistry[24] is 2*S*,4*R*,2'*S* **135a**.

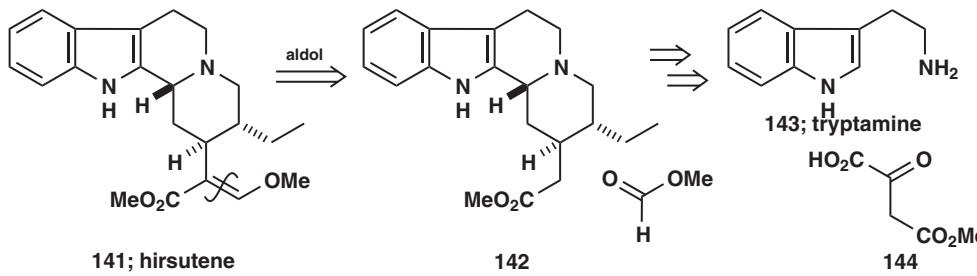


The synthesis was planned around the reaction of a specific enolate of ester **136** with the epoxide **137**. This reaction was expected to give mainly *trans* **138** and is chemoselective both because of the usual enolate problem and because **137** contains a terminal alkyne. The lithium enolate was too basic and the aluminium enolate was used instead. The reaction gave an 85:15 mixture of *trans* and *cis* **138** and also an 85:15 mixture of *trans* and *cis* **139** after cyclisation. Dihydroxylation by osmylation gave a mixture of diols **140**: this was deliberate so that they could determine the stereochemistry at C-2'. To the surprise of the chemists, natural rubrynolide was identical to one of the *minor* (i.e. *cis*) diols in the 15% part of the mixture. Careful NMR analysis showed that it was **135a**.

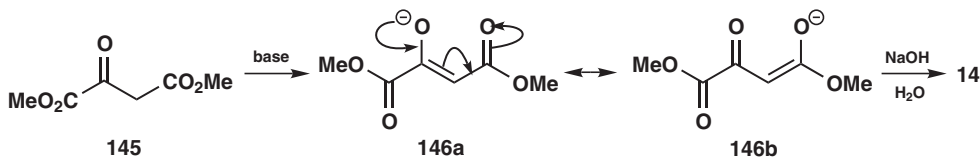


The synthesis of hirsutene

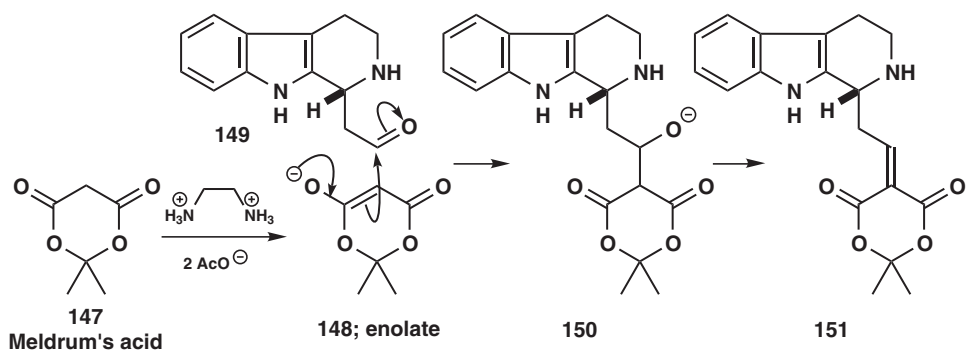
Tietze's synthesis of hirsutene **141**, an alkaloid from *Uncaria rhynchophylla* used in Chinese traditional medicine and with promising activity against influenza viruses, uses many chemoselective reactions of which we shall discuss just three - one at the start, one in the middle, and one at the end of the synthesis.[25]



The first reaction was the combination of the simple keto-diacid derivative **144** with tryptamine **143**. How to make **144** was the problem. The diacid or its diester (the biologist's 'oxaloacetate') is readily available and they decided to hydrolyse the enolate of the diester **145** with aqueous NaOH. It seems a strange decision to attack an anion with another anion but the enolate **146** is delocalised so that one ester group **146b**, but not the other, shares the negative charge. The ester that does *not* share the negative charge is preferentially attacked by hydroxide ion.

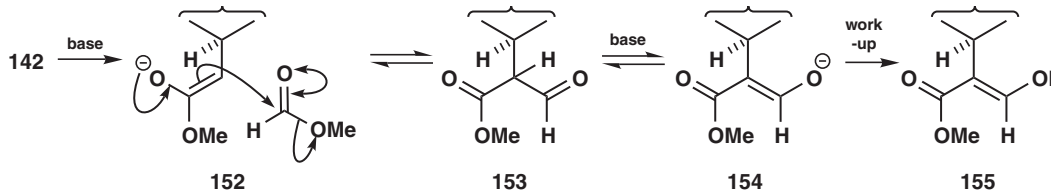


The second is an aldol reaction between the enolate **148** of 'Meldrum's acid' **147** and the enolisable aldehyde **149**. Because the enolate **148** is exceptionally stable, it can be made from **147** with a weak base and chemoselectivity (enolisation of **149**) is not a problem. The unsaturated ester **151** is used immediately in a Diels-Alder reaction.



At the end of the synthesis, the curious alkene, better described as an enol ether, must be introduced. The anion of the ester in **142** was prepared in base and condensed **152** with ethyl

formate. The chemoselectivity required is that ester **142** should react only with ethyl formate and not with itself. There is a further complication: the first product **153** has a more acidic proton than that in **142** and will form the enolate **154** under the reaction conditions. The whole system is in equilibrium and must be driven over by irreversible deprotonation by a strong base. Either LDA or Na^+ Ph_3C^- will do. After work-up the stable conjugated enol **155** is formed. Finally the enol is converted into the enol ether with acidic methanol to give hirsutene itself.



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3 Regioselectivity: Controlled Aldol Reactions

Definition

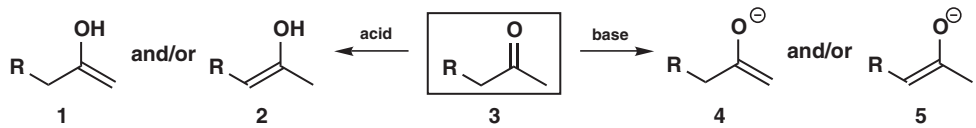
Introduction and definition

Regioselectivity means controlling different aspects of the same functional group. Classic examples are controlling direct (1,2) or conjugate (Michael or 1,4) addition to unsaturated carbonyl compounds, a subject we shall tackle in chapter 9, or controlling electrophilic substitution on unsymmetrical alkenes, which we shall meet in chapter 17. In this chapter we shall continue our study of enolisation by looking at regioselectivity in aldol and related reactions.

Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

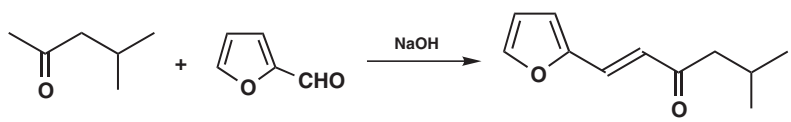
Regioselectivity in enol and enolate formation

Reactions in which the enol or enolate (or equivalent) of one carbonyl compound reacts with an electrophilic carbonyl compound (usually both are aldehydes or ketones) are often loosely called aldol reactions. In the last chapter we saw how the use of lithium enolates and other specific enolate equivalents conquers the problem of chemoselectivity in enolisation of aldehydes and acid derivatives. In this chapter, we are going to use the same intermediates to solve the problem of regioselectivity in crossed aldol reactions in which the enolising component is an unsymmetrical ketone.

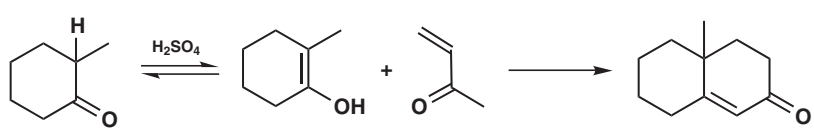


Regioselectivity by conditions: acid or base

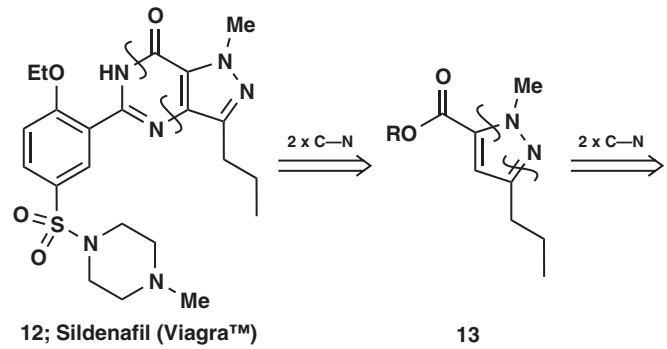
The fundamental mechanistic distinction on which all methods ultimately depend is a precarious difference between kinetic and thermodynamic enolisation. A ketone **3**, in which R is a simple alkyl group, has protons which are *slightly* more acidic on the less substituted side, the methyl group. This is because each alkyl group reduces the number and, by a weak electron donation, the acidity of the remaining hydrogens. An analogy is that *t*-BuLi is a stronger base than *s*-BuLi which is in turn stronger than *n*-BuLi. Condensation of **3** with a non-enolisable aldehyde (to avoid problems of chemoselectivity!) tends to give more aldol from **4** than from **5** when catalysed by NaOH, but the distinction is often too small to be useful. The ketone **3**; R = *i*-Pr does condense regioselectively at the methyl group with furfuraldehyde **6** and NaOH to give the enone **7** in a useful 80% yield.[1] Kinetic control favours the less substituted enolate.



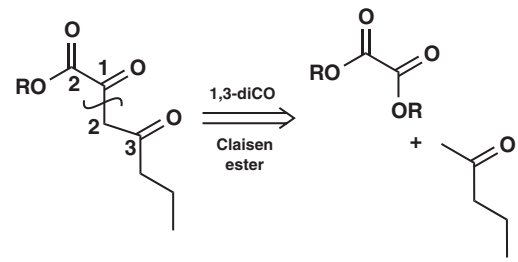
By contrast, the enol, and also the enolate when in combination with a metal atom, is more stable when the double bond is more substituted. Our ketone **3** will tend to produce more of enol **2** than enol **1** in acid solution, particularly if the enols are in equilibrium. Once again the distinction is usually too small to be useful. One example where it does succeed is the acid-catalysed Robinson annelation of ketone **8** with butenone **10** where reaction occurs predominantly on the more substituted enol **9**: the yield of **11** is only 50%, but it is at least a one-step operation. Thermodynamic control favours the more substituted enol.[2]



An important application of thermodynamic control occurs in the manufacture of Viagra **12**, Pfizer's treatment for impotence.[3] The NE corner of the molecule comes from the pyrazole acid **13**: removal of the hydrazine portion reveals the one piece of continuous carbon skeleton **14**. 1,3-Dicarbonyl disconnection gives an unenolisable diester (an oxalate) and an unsymmetrical ketone, pentan-2-one **15**.

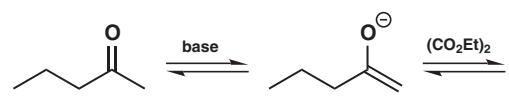


12; Sildenafil (Viagra™) **13**

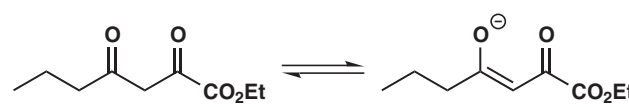


14 **15**

Condensation of **15** with diethyl oxalate in base without any control gives **14** because the true product of the reaction is the stable enolate of **14**. The enolate **16** at the methyl group is preferred and the stable enolate of **14** is also preferred to the alternative because it is less substituted. This product was condensed with hydrazine to give first the pyrazole **13** and then Viagra.



15 **16**



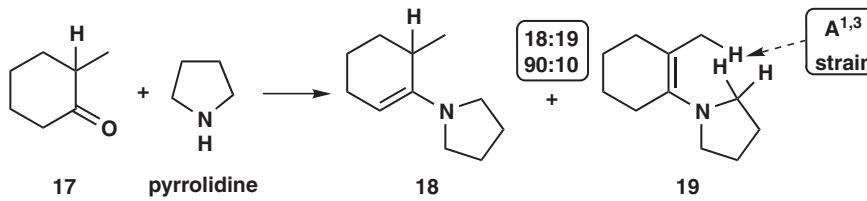
14; R = Et **enolate of 14; R = Et**

Specific Enol Equivalents

A survey of the thousands of examples of traditional aldol reactions in the back of *Organic Reactions* volume 16 shows how feeble this effect often is. Hardly any compounds are formed in good yield by chemoselective reactions using catalytic acid or base alone. The situation is different with modern methods.

Regioselectivity of formation of enamines

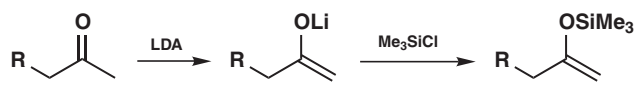
Enamines show an amplified preference for the less substituted double bond: at first this seems to contradict what we have just said, but the effect is greatest in cyclic ketones, e.g. **17**, with cyclic amines.[4†] It is steric in origin and arises from the eclipsing of hydrogen atoms ($A^{1,3}$ strain) shown in the more substituted enamine **19**. Enamines of acyclic ketones can be persuaded to give only the less substituted regio-isomer by equilibration of the immonium salt in weak base.[5]



17 pyrrolidine **18** **19**

Lithium enolates

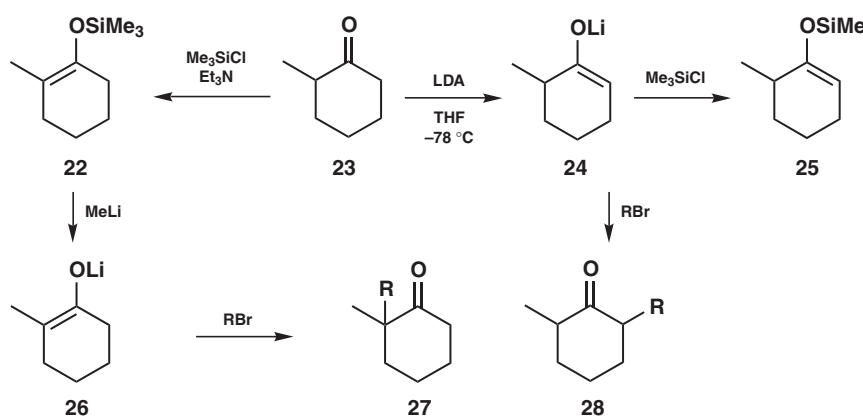
The most important method[6] for the regioselective synthesis of less substituted enolates is kinetic enolate formation with strong irreversible bases (LDA etc). Since the lithium enolate[7] **20** can be converted into the silyl enol ether[8] **21** directly without isolation, we have access to the two most valuable specific enol equivalents for the less substituted isomer. Alkylation of the lithium enolate of **23** goes more than 99% on the less substituted side.[9]



3 **20** **21**

Silyl enol ethers

There is no such perfect method for getting enolisation to go on the more substituted side. The best is thermodynamic control in the formation of the silyl enol ether,[10,11] which gives an approximate 90:10 ratio of **22**:**25** from **23**. Silyl enol ethers can be converted into lithium enolates with MeLi (the by-product is Me_4Si: useful for NMRs) and hence we can achieve alkylation on the more substituted side, e.g. **26** is benzylated with $PhCH_2Br$ to give **27**; R = CH_2Ph in up to 84% yield.[12]



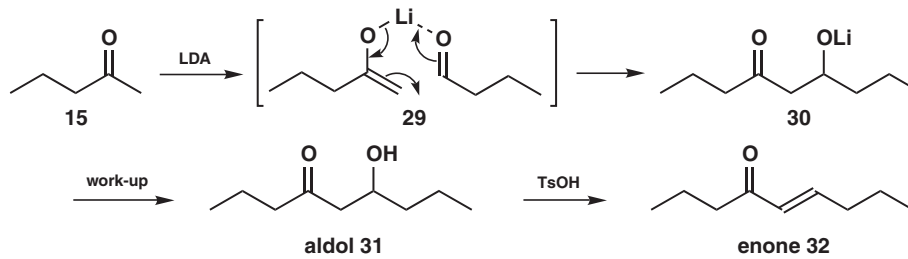
22 **23** **24** **25** **26** **27** **28**

† enamine review: Whitesell, *Synthesis*, 1983, 517

Regioselective Aldol Reactions

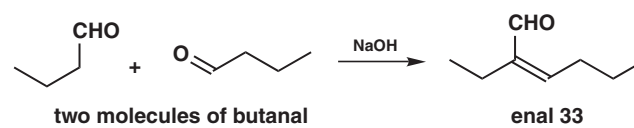
Aldol reactions with specific enol equivalents

Lithium enolates can be used directly in aldol reactions, even with enolisable aldehydes, a simple example[6] being the synthesis of the enone **32**. The ketone **15** forms mostly the less substituted lithium enolate which condenses **29** with butanal to give aldol **31** in reasonable yield. Elimination is usually carried out in acid solution.



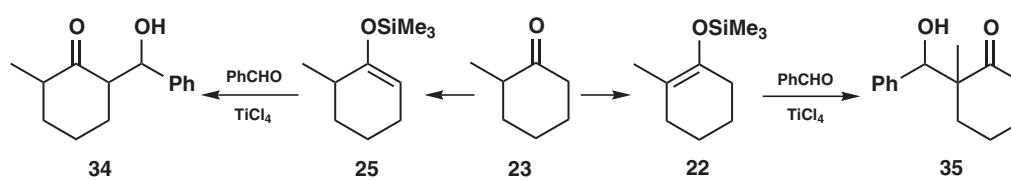
Contrast with equilibrium methods

Traditional equilibration methods [mix **15**, PrCHO and NaOH] would give the enal **33** from self-condensation of butanal. The aldehyde would ignore the less enolisable and less electrophilic ketone.



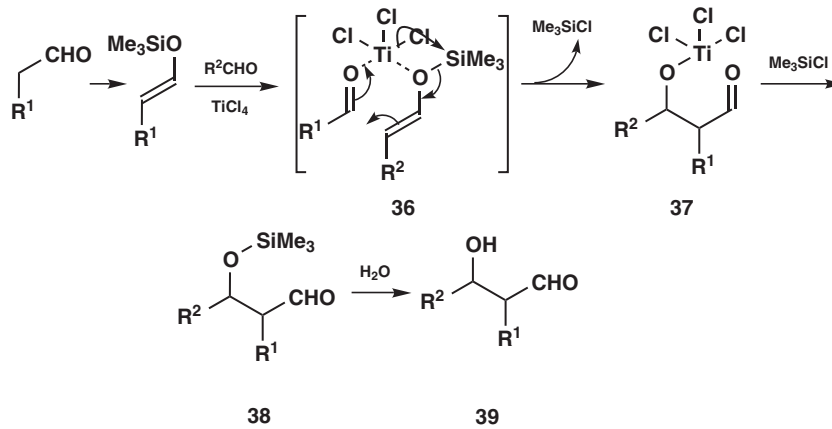
Aldols with Lewis acid catalysis: silyl enol ethers

Silyl enol ethers also combine with aldehydes and ketones in efficient aldol reactions catalysed by Lewis acids such as $SnCl_4$, $ZnCl_2$, $AlCl_3$, and $TiCl_4$, the last being the most popular.[13] Thus each of the silyl enol ethers **25** and **22** derived from the unsymmetrical ketone **23** gives a different aldol product **34** and **35** with benzaldehyde.[11,14]



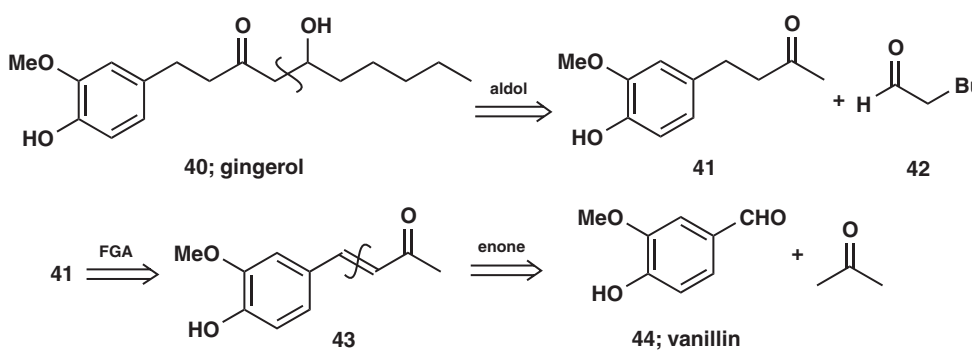
The mechanism is a slightly more complicated example of the six-membered cyclic transition state we met in the last chapter.[13] The titanium atom bonds to both oxygen atoms (of the enolate and the aldehyde) **36**. As the new carbon-carbon bond is formed, one chlorine atom is transferred

from titanium to silicon so that the immediate product is the titanium alkoxide **37**. This quickly combines with Me_3SiCl to give the silylated aldol as the true product **38**, and hence the aldol **39** on work-up in a hydroxylic solvent.

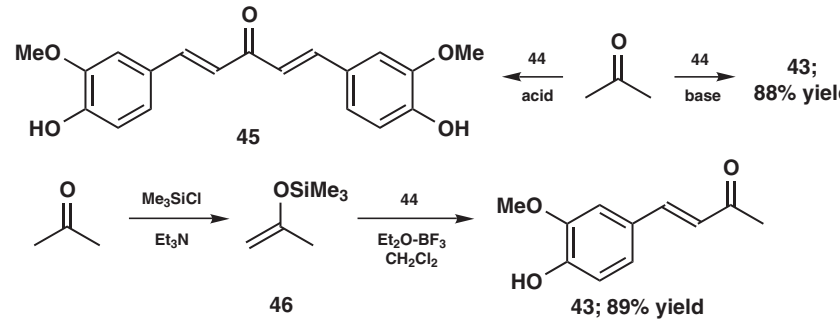


Application to the synthesis of gingerol

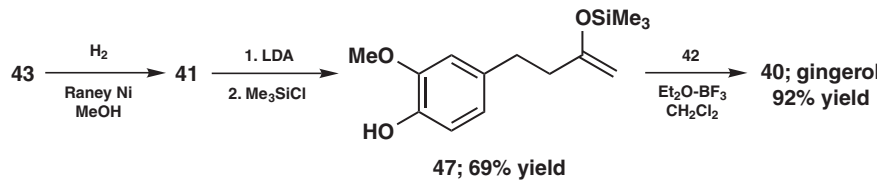
Mukaiyama's synthesis[14] of gingerol **40**, the pungent flavouring principle of ginger, illustrates these methods.[15] The obvious aldol disconnection shows that we require a specific enol of an unsymmetrical ketone **41** on the less substituted side to combine with an enolisable aldehyde **42**. The ketone can be made by the FGA[16] (Functional Group Addition) strategy using another aldol reaction, this time between acetone and the non-enolisable and readily available aldehyde vanillin **44**, the flavouring principle of vanilla.



The first aldol can actually be carried out by traditional methods: in acid solution condensation occurs on both sides of acetone to give **45**, but in alkaline solution **43** is formed in 88% yield. Mukaiyama[15] preferred to use the silyl enol ether of acetone **46** with BF_3 as the Lewis acid, and this worked as well (89% yield).

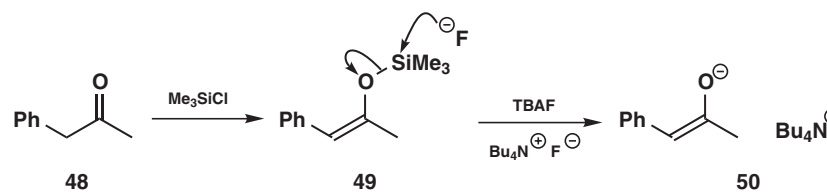


Catalytic reduction with Raney nickel removed the double bond, and the regioselective aldol - now the silyl enol ether is essential - was carried out by isolating the silyl enol ether **47** and using $TiCl_4$ as the Lewis acid. The yield of gingerol **40** was an impressive 92%.



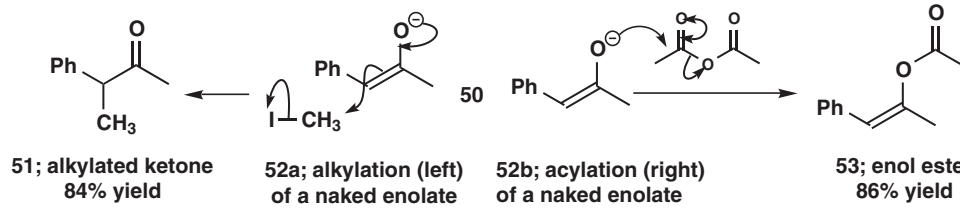
Reaction at Oxygen or Carbon? Silylation, Acylation and Alkylation

Now that you are acquainted with the three main types of regiocontrolled specific enol equivalents (lithium enolates, silyl enol ethers, and enamines) we should consider how well they perform in the other tasks commonly required of enols. Here we shall face another problem of regioselectivity: enols, enolates, and their equivalents have two nucleophilic sites, the required carbon atom and a heteroatom (oxygen in lithium enolates and silyl enol ethers and nitrogen in enamines). We have seen this regioselectivity in action when lithium enolates reacted with aldehydes and ketones at carbon, but with Me_3SiCl at oxygen. We normally want reaction at carbon, the site favoured by frontier orbital[17] and thermodynamic control rather than at the heteroatom, the site favoured by charge (or Coulombic) and kinetic control.



Naked enolates

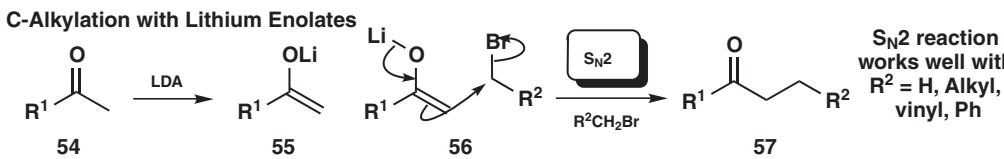
"Naked enolates'' without any complexation can be made from silyl enol ethers using fluoride ion, a very selective nucleophile for silicon **49**, and a non-metallic cation, usually a tetra-alkylammonium ion. The commonest reagent is "TBAF'' (TetraButylAmmonium Fluoride $Bu_4N^+ F^-$). In this way the "naked enolate'' **50** was made. It proved to be acylated with acetic anhydride exclusively at oxygen to give the enol acetate **53** and alkylated with MeI at carbon to give the ketone **51** in 84% isolated yield.[18]



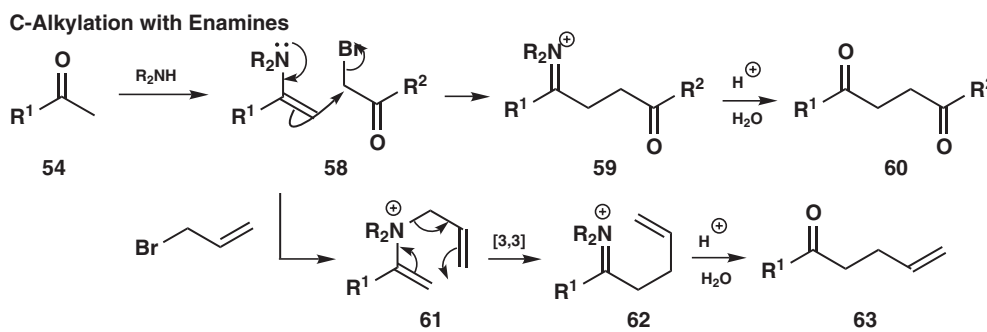
Alkylation at carbon, problems with enamines

Of our three specific enolate equivalents, the lithium enolates are most similar to naked enolates: most reactive and most basic. The enamines are less reactive, only weakly basic but still nucleophilic in their own right, while the silyl enol ethers are the least reactive, not basic at all, and are rather like alkenes with slightly increased nucleophilicity because of an electron-donating substituent. We have already seen that they usually need a Lewis acid for efficient reaction, just like an alkene in, say, the Friedel-Crafts reaction.

Simple alkylation works well with lithium enolates **55**, but is a tight S_N2 reaction **56** and works best with methyl, primary alkyl, allyl, and benzylic halides.[9] Halides with acidic hydrogen atoms, such as α-halocarbonyl compounds may destroy the basic enolate by acting as an acid instead of an electrophile.

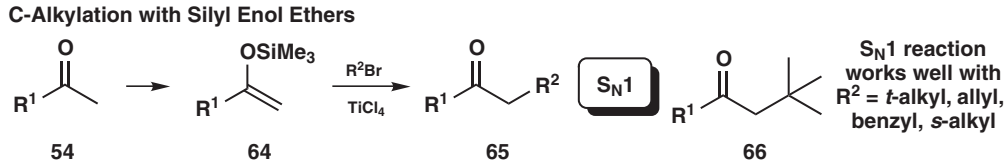


Enamines are inclined to react at nitrogen with alkyl halides, but react particularly well with α-halo carbonyl compounds **58** to give 1,4-dicarbonyl products **60**, and with allylic halides by reaction at nitrogen followed by a [3,3] sigmatropic rearrangement **61** to give γ,δ-unsaturated ketones **63**.



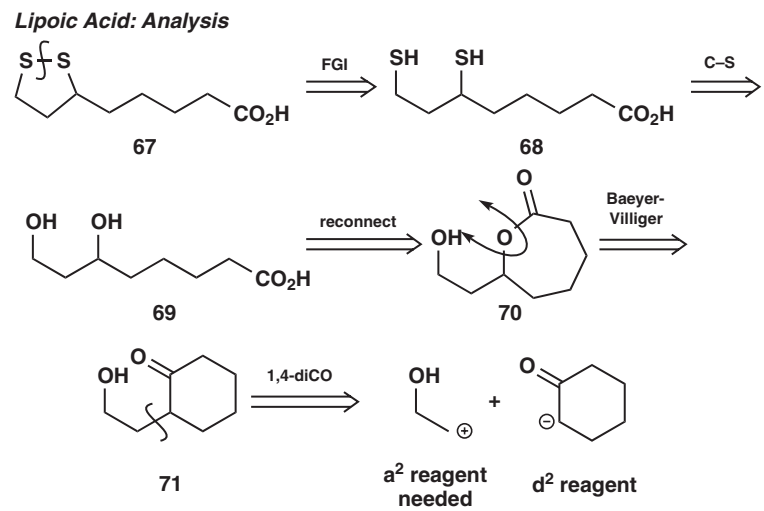
Silyl enol ethers **64** need Lewis acid catalysis which generates at least a partial positive charge on the alkyl group so they react best with tertiary, allylic, and benzylic halides, and reasonably

well with secondary halides. In this way all types of alkyl halide can be added regioselectively to carbonyl compounds. We have already seen examples of alkylation of the two isomeric lithium enolates of the ketone **23**, giving products **27** or **28** at will with benzyl, methyl, primary alkyl, or allyl halides.



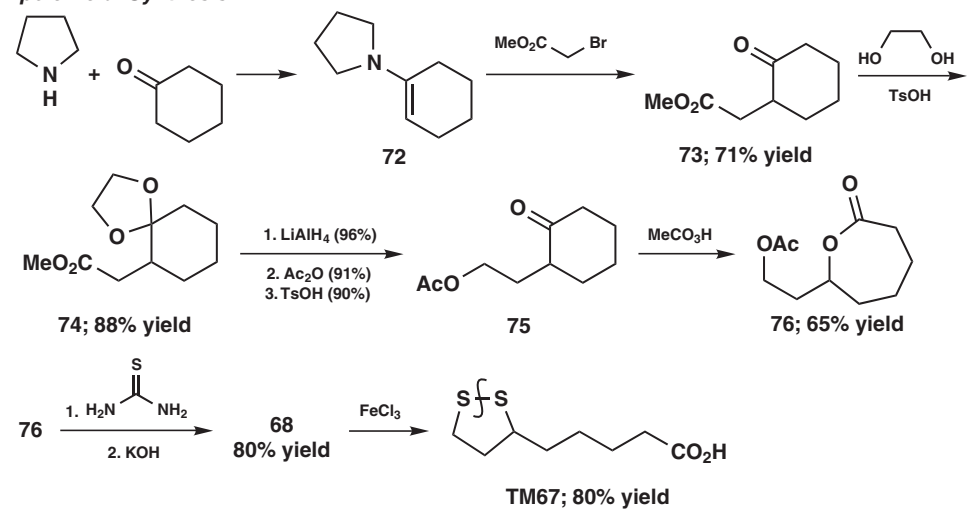
Application to the synthesis of lipoic acid

An example of the use of enamines comes in a synthesis[19] of lipoic acid **67**, the primary metabolite of redox pathways. This is an early synthesis (1957) but it has a simple and direct strategy and revises aspects of chemoselectivity as well as regioselectivity. The disulfide linkage comes from the oxidation of the two thiols in **68**, and these will be made by some sort of displacement on the diol **69**. There are 1,3 and 1,6 relationships in this diol acid: the 1,6 offers an opportunity to use the reconnection strategy[20] via the lactone **70**. Seven-membered lactones are usually made by the Baeyer-Villiger reaction[21] on cyclohexanones, here **71**, so we come finally to the need to alkylate cyclohexanone itself with some reagent for an a^2 synthon.



An epoxide would give the right oxidation level, but the efficient alkylation of enamines with α-halo carbonyl compounds evidently appealed and methyl bromoacetate was combined with the pyrrolidine enamine **72** in good yield. Chemoselective reduction of the ester inevitably required protection of the more reactive ketone The leaving group selected for eventual displacement by a sulfur nucleophile was an ester because the Baeyer-Villiger route will provide just such a leaving group at the other position.

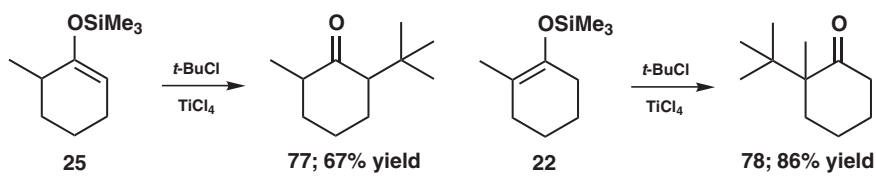
Lipoic Acid: Synthesis



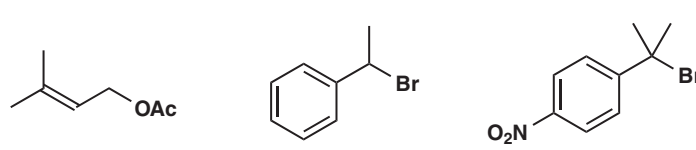
The Baeyer-Villiger rearrangement illustrates an important aspect of regioselectivity: which group migrates? This is not the same as the chemoselective aspect of the pinacol rearrangement discussed in the last chapter as there is only one leaving group here. The usual rule is followed: the more highly substituted group migrates. Displacement with a sulfur nucleophile is a classic problem of chemoselectivity, the problem being to prevent two alkylations at the same sulfur atom. Thiourea is used here,[22] and the final oxidation is carried out with Fe(III).

Alkylation with tertiary alkyl groups

Alkylation with tertiary halides is the special preserve of silyl enol ethers. Both the familiar isomers **22** and **25** give regiospecific alkylation in good yield with Lewis acid catalysis.[23] The formation of **78** is remarkable as it puts two quaternary centres next to one another.

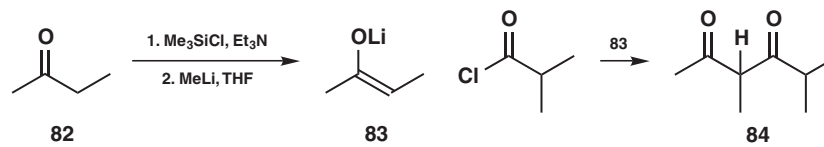


Silyl enol ethers also react well with allylic halides, or with the hemiterpene fragment prenyl acetate[24] **79** or with secondary[25] **80** and tertiary[26] **81** benzylic halides (Zn salts are used as catalysts in these examples). In each case, regioselectivity has been demonstrated with the same two isomers **22** and **25**.



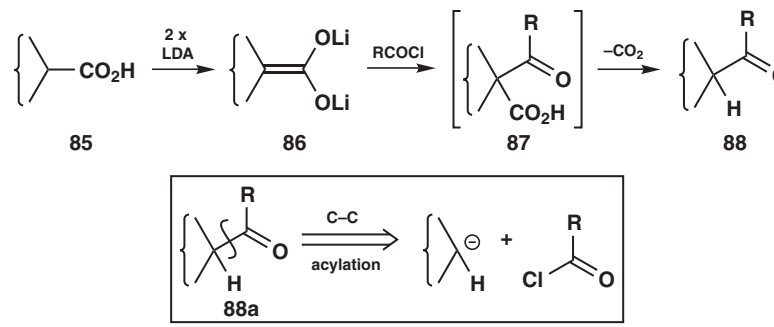
Acylation at Carbon

Acylation at carbon is the usual route to 1,3-dicarbonyl compounds[27] and here the regioselectivity problem is more serious as enolates tend to react with acylating agents on oxygen to give enol esters. Fortunately all three specific enolate equivalents perform well with acid chlorides. The lithium enolate **83** is on the more substituted side of the ketone **82** and so must be prepared via the silyl enol ether. Acylation goes in reasonable yield[28] (55%) for the acylation of a basic enolate The problem is that the acylation products are carbon acids which often "quench unreacted enolate at a rate that exceeds acylation.'' The proton marked H in **84** is between two carbonyl groups and so is easily lost to form a stable enolate. Alternatively, oxidise the corresponding aldol.[29]



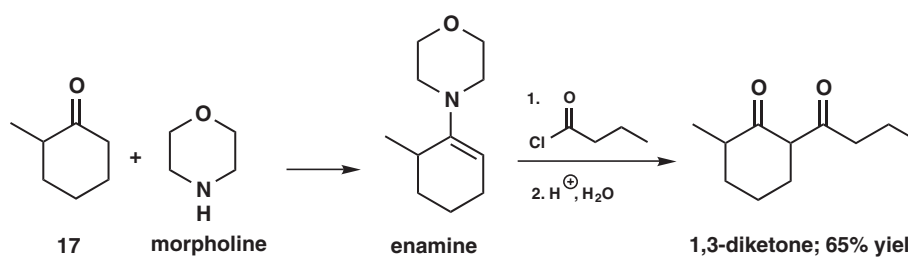
Lithium enolates of carboxylic acids

Even the dilithium derivatives **86** of carboxylic acids **85** are acylated at carbon by acid chlorides.[30] When the product **87** is worked up, it loses CO_2 in the usual way, making this a synthesis of ketones **88**. Branched carboxylic acids work well in this sequence so it is the equivalent of the acylation of a secondary carbanion, i.e. the disconnection **88a** is now acceptable.

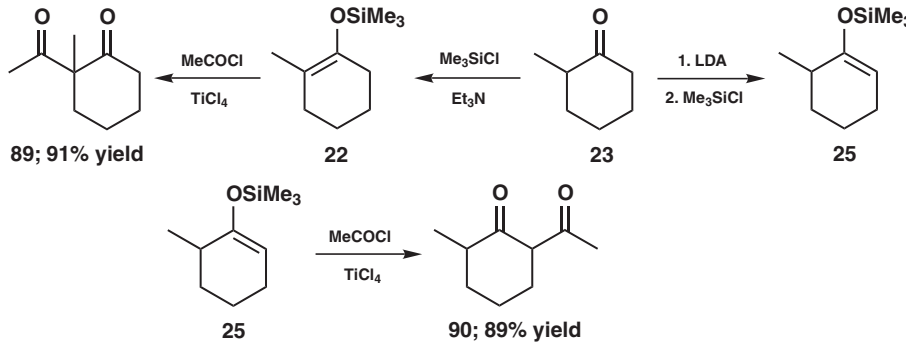


Enamines and silyl enol ethers

The best enamines for acylation seem to be those of morpholine. The cyclohexanone **17** forms the enamine on the less substituted side and this is acylated with a simple enolisable acid chloride in reasonable yield.[31]



Silyl enol ethers react with acid chlorides and Lewis acids in what is effectively a Friedel-Crafts reaction.[32] Both silyl enol ethers **22** and **25** derived from the ketone **23** give regiospecific acylation with MeCOCl and $TiCl_4$. The yields of the two 1,3-diketones **89** and **90**, formed as a mixture of diastereoisomers, are excellent.

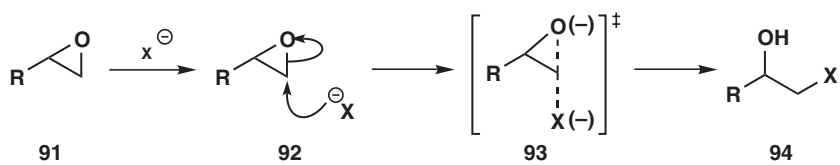


Acylation at a methyl group in an unsymmetrical ketone, e.g. **15** usually occurs regioselectively even with traditional methods (ester as acylating agent, corresponding alkoxide as base). We shall return to this subject in chapter 10 with other specific enol equivalents, but you can see already that virtually any 1,3-diketone can be made by one of these methods.

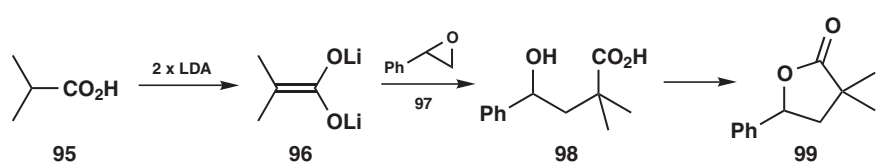
Reactions with Other Electrophiles

α-Halo carbonyl compounds and epoxides

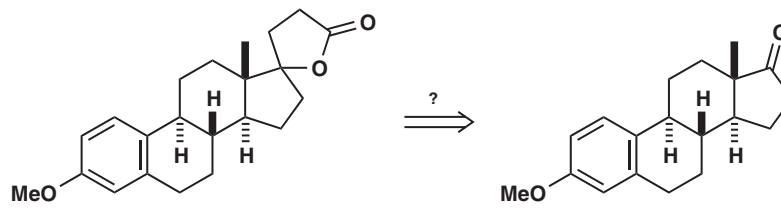
1,4-Dicarbonyl compounds can be made from enolates by alkylation of enamines with α-halo-carbonyl compounds[33] or any specific enol equivalent with allylic halides as just discussed, followed in the latter case by oxidative cleavage of the double bond.[34] The reactions of enolates with epoxides provides 1,4-difunctionalised compounds[35] at a different oxidation level and so we should discuss another interesting question of regioselectivity. Unsymmetrical epoxides **91** are usually opened at the less substituted end **92** by strongly nucleophilic reagents to give **94** via a tight S_N2 mechanism **93**.



There has been remarkably little work in this area, but the dilithium derivatives of acids, e.g. **96** do react with unsymmetrical epoxides at the less hindered end. A simple example is styrene oxide **97** which is attacked at its less substituted end to give the lactone **99** in 84% yield after cyclisation.[36]

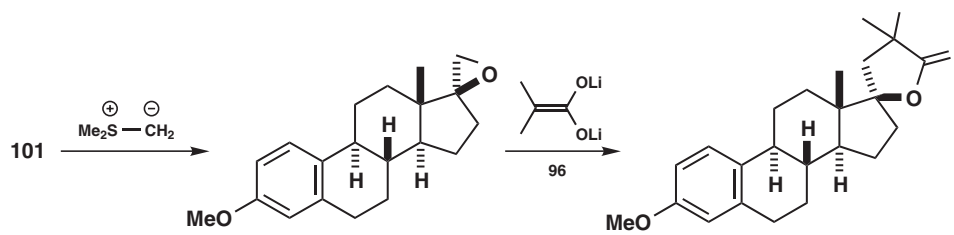


Spirocyclic lactones of structures such as **100** are interesting because of potential biological activity, and might be made from available steroids such as oestrone **101**.



100 **101**

The sulfur ylid[37] $Me_2S{=}CH_2$ reacts stereoselectively from the bottom face of the ketone **101** to give the epoxide **80** which in turn gives the lactone[36] **100a** with the lithium dienolate **96**.

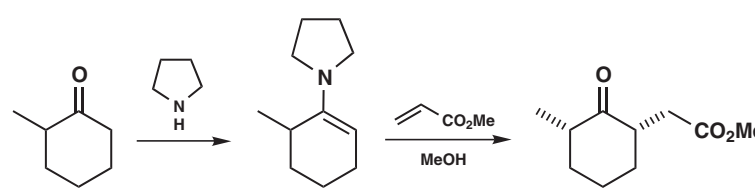


102 **100a**

Michael reactions

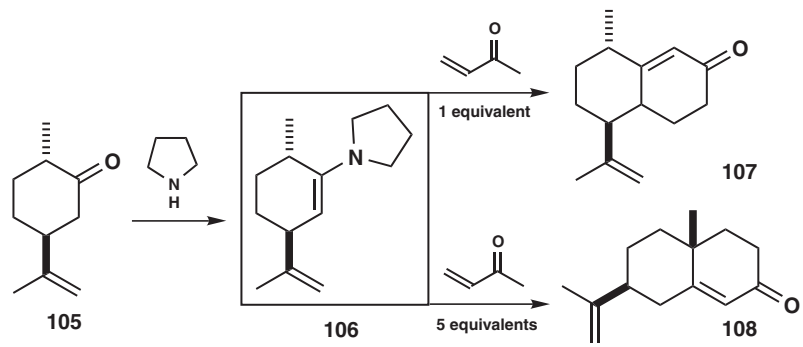
1,5-Dicarbonyl compounds are usually made by Michael (conjugate) addition of enols to α,β-unsaturated carbonyl compounds. Here too is another regioselectivity problem, the one raised at the start of the chapter concerning direct (1,2) versus conjugate (1,4 or Michael) addition to such electrophiles. This question will be more fully developed in chapter 9 but it is appropriate to examine here the performance of our three specific enol equivalents in tackling this question of regioselectivity. In general, direct addition is the kinetically controlled reaction favoured by more reactive irreversible nucleophiles and more reactive electrophiles (Michael acceptors) such as α,β-unsaturated aldehydes, while conjugate addition is the thermodynamic process favoured by less reactive or reversible nucleophiles and less reactive Michael acceptors such as esters of α,β-unsaturated acids. From this analysis we should expect the less reactive enamines and silyl enol ethers to be good at Michael additions, and we would be right.

The enamine **103** of our familiar unsymmetrical ketone **23** gives a clean Michael addition with methyl acrylate on the less substituted side to give the ketoester *syn*-**104** as the only product providing that the reaction is carried out in MeOH.[38]

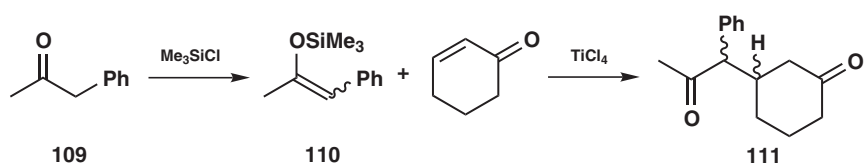


23 **103** ***syn*-104**

Just to make the point that chemistry has surprises even for the best informed, the rather similar Robinson annelation of dihydrocarvone **105** again using the pyrrolidine enamine **106** goes on the less substituted side **107** when one molecule of enone is used, but on the more substituted side **108** if a large excess (fivefold) of the enone is used.[38] Both reactions are of course very useful but an affront to our orderly instincts: we shall meet other examples where only experiment can lay down the ground rules of selectivity.



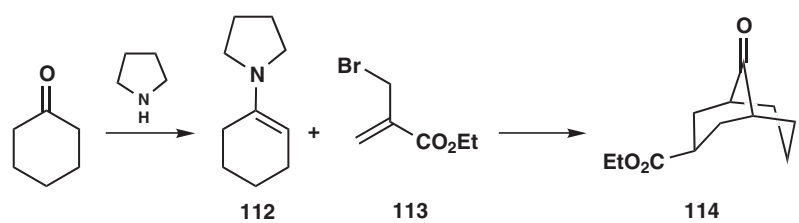
Silyl enol ethers need Lewis acid catalysis for efficient Michael reactions, such as the more substituted (and conjugated) isomer **110** forming a 1,5-diketone **111** from cyclohexenone in good yield.[39] This product **111** is a mixture of diastereoisomers as have been many of the products in this chapter. We have also seen some reactions giving single diastereoisomers but without explanation. It is high time that we addressed the question of stereoselectivity and this is the subject of the next chapter.



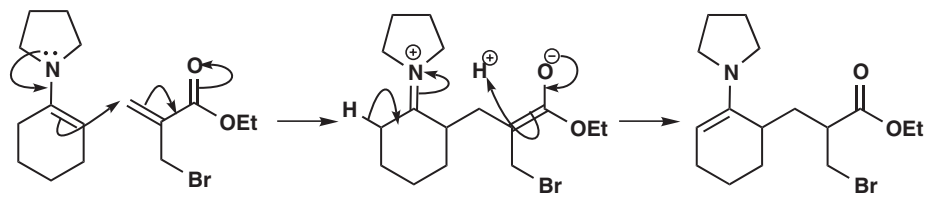
A Final Example

Double Michael reactions with enamines

But before we go, a special example[40] of double regioselectivity with a doubly nucleophilic enol equivalent attacking a double electrophile. When the pyrrolidine enamine **112** of cyclohexanone attacks the unsaturated ester **113**, the bicyclic ketone **114** is formed in good yield.

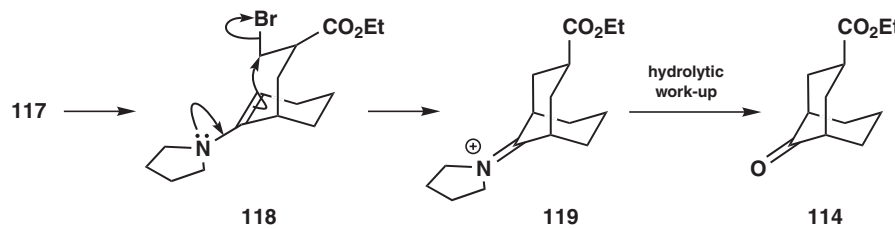


The first step is probably the Michael addition **115** of the enamine **112** to the unsaturated ester **113**. The resulting iminium salt **116** loses a proton to regenerate an enamine. But it does so on the side away from the first reaction to avoid forcing the side chain into the same plane as the pyrrolidine ring. The new enamine is **117**.



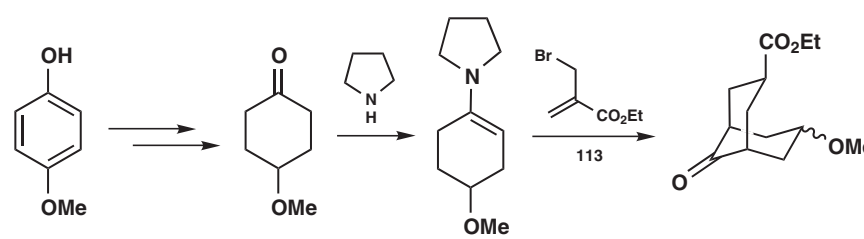
115 **116** **117**

Now the newly formed enamine **117** can be alkylated by the allylic bromide in the side chain. To do this reaction, the molecule must put the side chain in an axial position **118**. The resulting iminium salt **119** is hydrolysed on work-up to the bridged bicyclic product **114**.



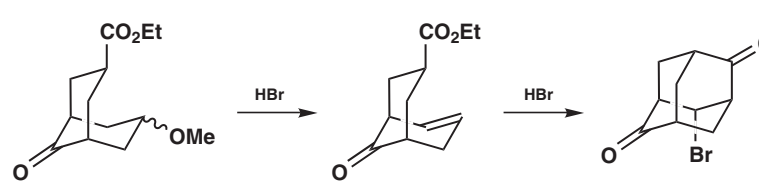
118 **119** **114**

The same treatment on 4-methoxycyclohexanone **121** derived from 4-methoxyphenol **120** by reduction and then oxidation gives compound **123**.



120 **121** **122** **123**

This can be cyclised in refluxing 62% HBr to an adamantane derivative, the dione **125**. The mechanism of this cyclisation is by no means obvious, but with the hint that the alkene **124** is an intermediate and that the stereochemistry of the ester can change by acid-catalysed enolisation, you might see what is going on.



123 **124** **125**

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4 Stereoselectivity: Stereoselective Aldol Reactions

Stereoselectivity is at first sight the easiest of the three selectivities to understand and the most difficult to exercise. It simply means control over stereochemistry. More precisely it means the control over new stereochemistry. In many reactions, whether new carbon-carbon bonds are being formed or whether some functional group is merely being altered, stereochemistry appears. It may be that a double bond is formed which can have *E* or *Z* geometry, or that a new stereogenic centre is formed, perhaps by reduction of a ketone, and therefore a relationship develops with other stereogenic centres in the molecule. If these aspects are controlled then we have stereoselectivity.

One special distinction you should master from now on is that stereo*specificity* has a different meaning. It refers to the *specific* transfer of stereochemistry during a reaction because the mechanism of the reaction demands this stereochemical outcome. An S_N2 reaction goes with inversion, whether the molecule likes it or not, because an S_N2 reaction is stereospecific. In the reduction of a ketone the molecule may *select* the stereochemistry of the new OH group: this reaction is not stereospecific though it may be stereoselective.

From this chapter onwards stereochemistry will be our constant companion as it is a major concern of modern organic chemistry. To start with we shall discuss diastereoselectivity alone. Soon, in chapter 15, we shall discover how to control the geometry of double bonds. Later on, in chapters 20–21 we shall discuss how to exercise stereoselectivity in general and in chapters

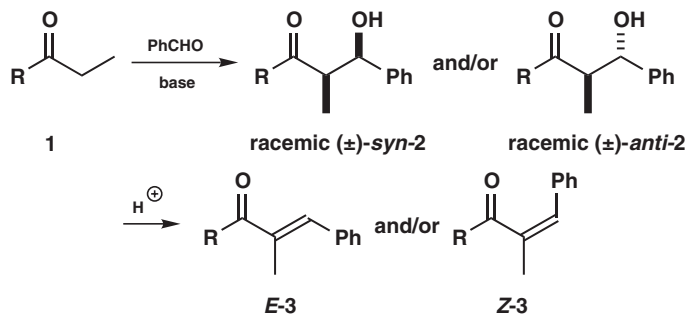
Organic synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

22–29, there will be a section on asymmetric synthesis, that is the synthesis of optically active compounds. In this chapter we shall continue the discussion of enolate reactions by exploring stereoselective aldol reactions.

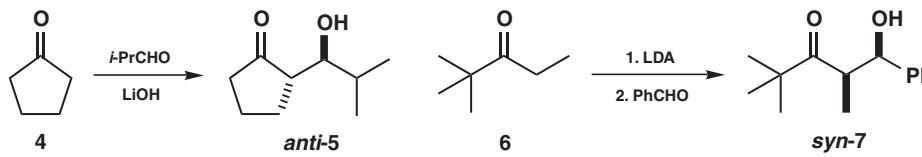
The Stereochemistry of the Aldol Reaction

Introduction and stereochemical control: syn,anti and E,Z

Aldol reactions typically produce new stereogenic centres at either end of the new carbon-carbon bond.[1] The enolisable ketone **1** might condense with benzaldehyde to give a mixture of diastereoisomers of the aldol **2** in which the methyl and hydroxyl groups can be either on the same side (*syn*-**2**) or opposite sides (*anti*-**2**) of the carbon skeleton.[2] If the aldol is dehydrated to the enone **3** there is again a question of stereoselectivity as the new double bond can be *E* or *Z*.

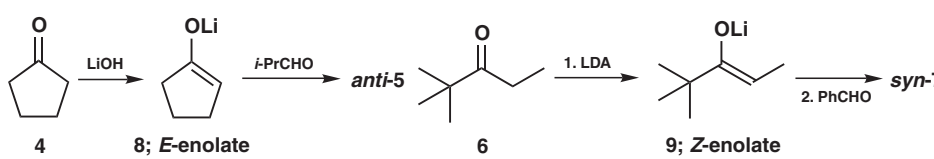


Only in modern times has aldol stereochemistry seemed a subject worth studying, or indeed even accessible to chemists. Formerly it was left to look after itself. Then Dubois carried out some simple experiments on the condensations between cyclic ketones and aldehydes in base.[3] Though largely neglected at the time, these results showed that if LiOH (not NaOH) was used as the base, the *anti* aldol predominated. Indeed, with cyclopentanone and *i*-PrCHO, >95% *anti*-**5** was formed, and *syn*-**5** could not be detected. Later Heathcock[4] showed that the lithium enolate of the open chain ketone **6** condensed with PhCHO to give >98:2 *syn:anti* aldol **7**.



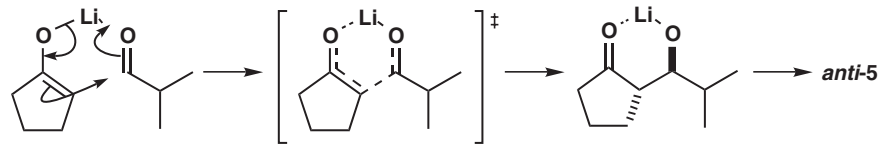
Relationship between enolate geometry and aldol stereochemistry

These apparently conflicting results can be rationalised if there is a relationship between the geometry of the enolate and the stereochemistry of the aldol product. Cyclic ketones are forced to give *E* enolates, thus cyclopentanone must give **8**. Ketone **6** might well prefer to form the *Z* enolate **9** with the large *t*-Bu group *anti* to the methyl group.



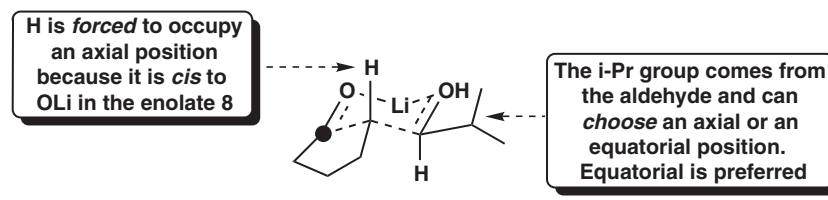
The Zimmermann-Traxler transition state

The relationship between enolate geometry and aldol stereochemistry has now been well established for many aldol reactions. The geometry of lithium enolates expresses itself through the so-called Zimmerman-Traxler[5] transition state which is nothing more than the six-membered cyclic transition state that we met in the last chapter. When a lithium enolate reacts with an aldehyde, both the enolate and aldehyde oxygen atoms coordinate to the lithium atom **10** so that the transition state **11** is a partly unsaturated six-membered ring.



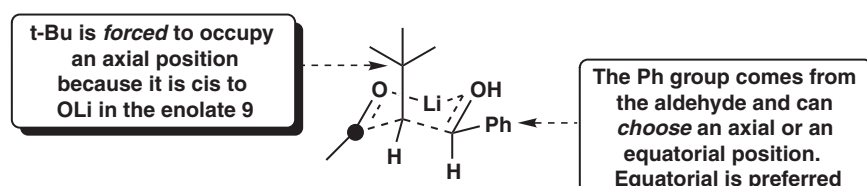
10 **11** **Zimmerman-Traxler transition state** **12**

If we assume that the cyclic transition state **11** adopts an approximate chair conformation **13**, we can explain the results. One carbon atom, marked with a spot, remains trigonal throughout the reaction and its substituent remains in a plane. All the other carbon atoms have axial and equatorial substituents. The enolate substituent is forced to occupy one of these positions because of the configuration of the enolate. The five-membered ring in **13** is equatorial because it is *anti* to the enolate oxygen and it no doubt enjoys this position. So far we have been dealing with stereo*specificity*. The substituent on the aldehyde can occupy either axial or equatorial positions, so it generally prefers the equatorial. You will see that the *i*-propyl group in **13** is indeed equatorial. This is stereo*selectivity*. The consequences are most easily appreciated by inspecting the marked hydrogen atoms: in **13**: they are clearly *anti* and this is the relationship found in the aldol product *anti*-**5**.



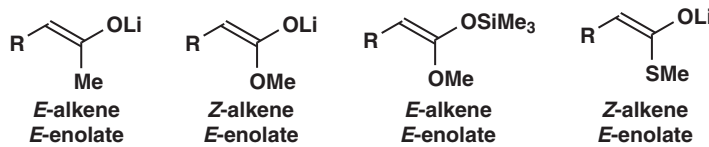
13

When the *Z*-enolate **9** reacts with benzaldehyde, one aspect of the Zimmermann-Traxler transition state **14** is quite different. The *t*-butyl group in **14** is *forced* to be axial because it is *syn* to the enolate oxygen even though it will not enjoy this position at all. The only alternative is to abandon the chair transition state and that would evidently lead to a worse energy penalty. The phenyl group still has a choice and it will again *choose* to be equatorial in **14**. If we inspect the marked hydrogen atoms in **14** we can see that they are *syn* and so they will remain *syn* in the aldol product *syn*-**7**.

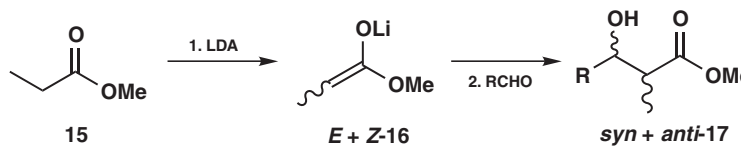


14

This is the basis behind many stereoselective aldol reactions, but in general it is not easy to choose carbonyl compounds that will reliably give *E* or *Z* enolates. We shall restrict our discussion to one or two of the more reliable. There is a problem in defining enolates as *E* or *Z*. If we follow the rules strictly, a series of enolates with the same geometry, such as the four below, would change from *E* to *Z* as we changed the metal on the enolate or as we changed from ketone to ester to thiolester. When we are discussing enolates, we shall name them *E* or *Z* according to the relationship between the substituent R and the OMetal substituent. This is the generally agreed method and takes no notice whether the enolates are strictly *E* or *Z* alkenes.



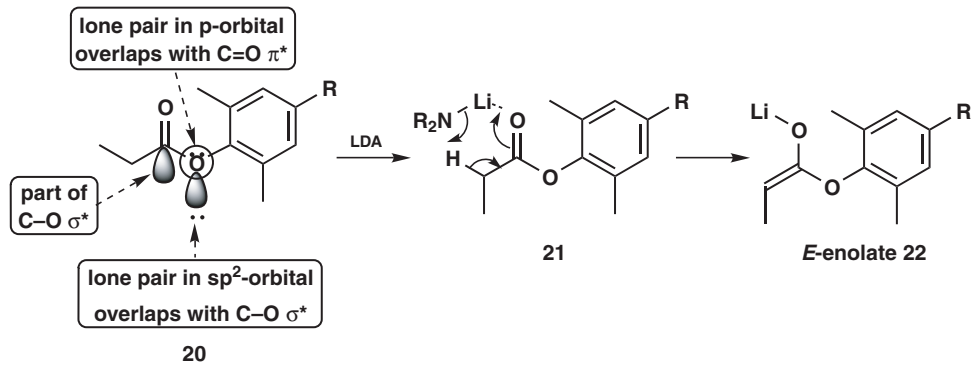
The first two examples are based on esters, one giving the *anti* aldol and the other the *syn*. Lithium enolates of simple esters like $EtCO_2Me$ give clean aldol reactions with aldehydes but the products **17** are more or less 50:50 mixtures of *syn*- and *anti*- diastereoisomers.[1] Evidently the lithium enolate **16** is also formed as a 50:50 *E:Z* mixture and this is hardly surprising as OMe and OLi must be about the same size.



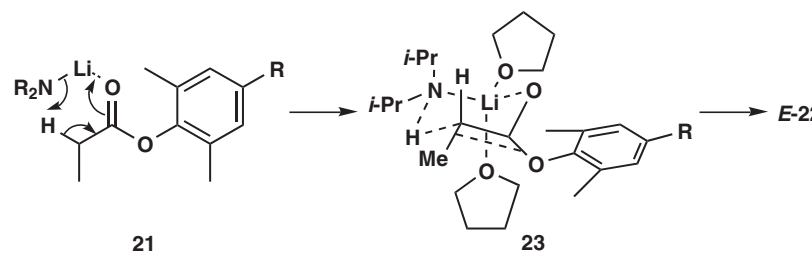
Anti-selective aldols of lithium enolates of hindered aryl esters

Hindered aryl esters[6] such as **18** perform very much better. Only the *E* enolate is formed and very high ratios of *anti:syn* aldols **19** are produced, especially with branched aldehydes such as *i*-PrCHO.[7]

The ester prefers the conformation **20** because of the anomeric effect, the bonding interaction between one of the lone pairs on the ester oxygen atom and the antibonding orbital of the *sigma* bond of the carbonyl group, and normal conjugation with the other lone pair of electrons on the ester oxygen atom keeps the aryl group in the plane of the carbonyl group. Perhaps this means that the deprotonation by LDA **21** can take place only when the methyl group is *anti* to the C=O bond.

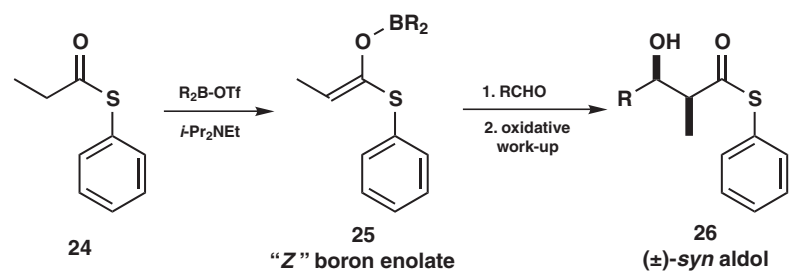


Alternatively one could argue that a six-membered chair transition state **23** is again involved with large axial groups (*i*–Pr and the THF ligand on Li) and the large aryl group enhancing the methyl group's natural preference for an equatorial position.



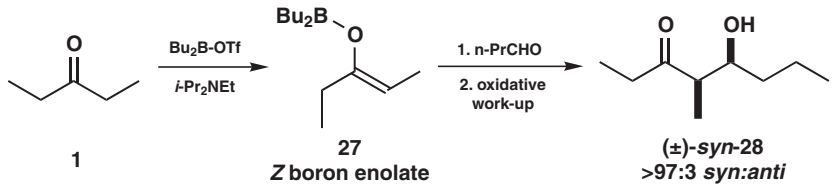
Syn-selective aldols of boron enolates of PhS-esters

Most esters prefer to form *E* enolates, and one must turn to a different substituent and a different "metal" to get good *syn* selectivity. Evans and Masamune have developed the boron enolates of phenythio (PhS) esters **24** in this role.[8,9] The boron enolate **25** is prepared with a dialkyl boron triflate and Hünig's base *i*-Pr_2NEt. The alkyl groups on boron can be butyl or cyclopentyl or else 9-BBN (9-borabicyclononane, see chapters 17 and 24) can be used.[10] Triflate is trifluoromethanesulfonate, one of the best leaving groups known. Only the "*Z*" enolate **25** is formed, maybe because of equilibration with this relatively weak base and the lack of an anomeric effect in PhS esters. Aldol reactions now give high yields of *syn* aldols **26** helped by the short B–O bonds[9] in the Zimmerman-Traxler transition state, cf. **23**.

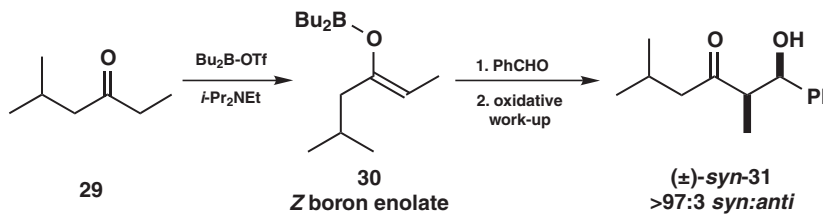


Stereochemistry of aldols from enols and enolates of ketones

Other than for the cyclic or *t*-alkyl ketones we met at the beginning of the chapter, controlling aldol reactions of ketones has been more difficult. Evans' boron enolates work well in some cases and it is fortunate that the *Z* enolates are preferentially formed as these react stereoselectively with aldehydes to give *syn* aldols whereas the *E* enolates show poor stereoselectivity. Thus the symmetrical ketone **1** gives almost exclusively (>97:3) the *Z* boron enolate **27** and hence *syn* aldol **28** with the enolisable aldehyde n-PrCHO.[8]

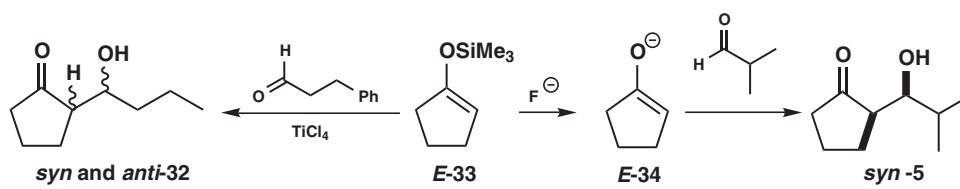


Some unsymmetrical ketones show regioselectivity in favour of the less hindered side: **29** is an impressive example as both sides of the ketone are primary with branching occurring on one side only at the β carbon atom.[8] You are advised to consult the literature before planning a stereoselective synthesis with ketone enolates.



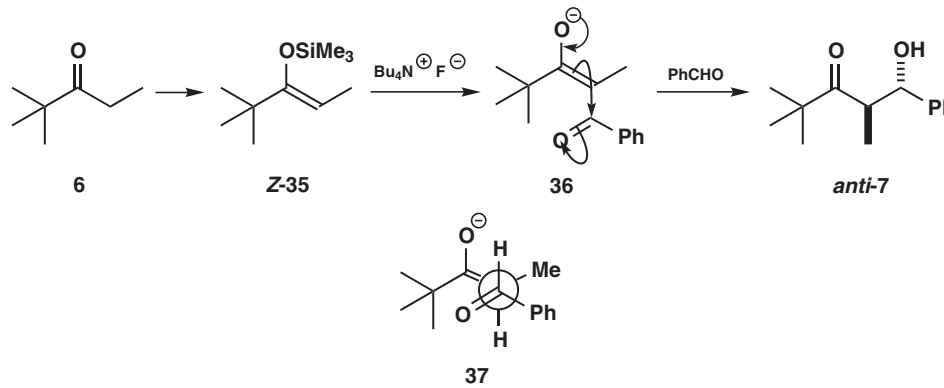
Silyl enol ethers and the open transition state

A second kind of stereoselectivity is observed with silyl enol ethers. When made from cyclic ketones they must have *E* geometry but often react in a stereorandom fashion, as in the $TiCl_4$ catalysed reaction of the silyl enol ether *E*-**33** of cyclopentanone with $PhCH_2CH_2CHO$. This is totally chemoselective, but gives a 50:50 mixture of stereoisomers[11] of **32**. The corresponding lithium enolate is very stereoselective in the *anti* sense. The situation is quite different if the reactions are catalysed by fluoride ion instead of by a Lewis acid. Now the same silyl enol ether *E*-**33** reacts stereoselectively, but in the *syn* sense[12] to give *syn*-**5**.



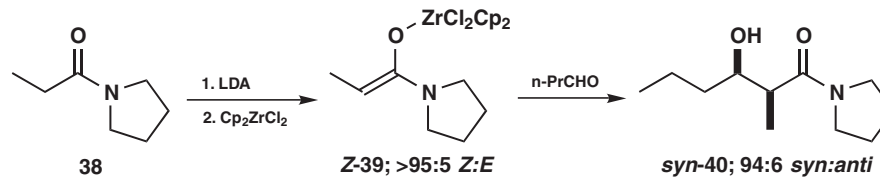
The *Z* silyl enol ether **35** from the ketone **6** also shows reversed stereoselectivity from the lithium enolate, giving the *anti* aldol **7** in high yield.[12] Further study[1] revealed that these reactions, which take place via an "open" (rather than a chelated) transition state **37**, are thermodynamically

controlled because they are reversible. Both geometrical isomers of many silyl enol ethers favour the same diastereoisomer of an aldol.

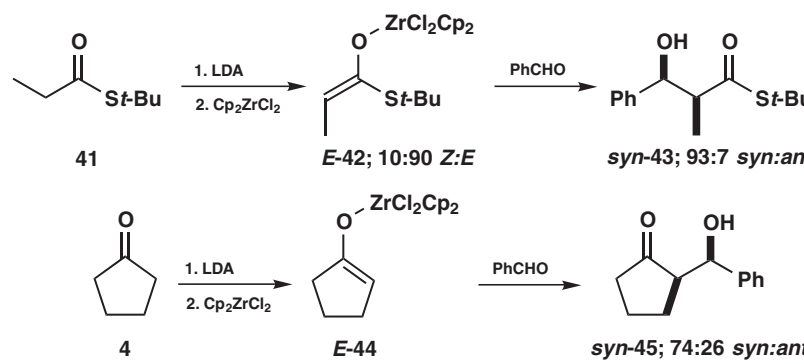


Syn selective aldols with zirconium enolates

Some kinds of metal enolate also give highly stereoselective reactions in the same sense whatever the geometry of the enolate. At first sight the reactions of zirconium enolates seem like lithium enolates. Using the pyrrolidine amide **38** as an example, we get the *Z*-enolate **39** only and this gives *syn* aldol products **40** with aldehydes.[13]



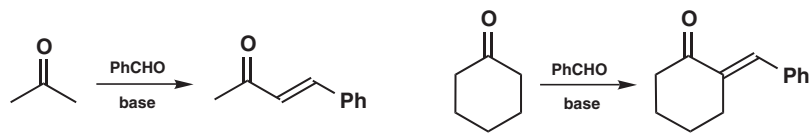
However, the *t*-butylthiol ester **41** gives mostly the *E*-enolate **42** and yet still favours the *syn* aldol **43**. Cyclopentanone, which can of course give only the *E* enolate **44** also favours the *syn* aldol[14] **45**. In short, *all* zirconium enolates give *syn* aldols regardless of geometry. This selectivity is explained in the workbook.



There are many more methods now developed for stereochemical control in the aldol reaction, as this is an active area of research, but we hope that we have studied enough examples in this chapter to add to the examples of chemo- and regioselectivity in the last two chapters to convince you that good control is possible over most of the types of aldol reaction that you might want to use in a synthesis. We shall leave further diastereoselectivity to chapters 20–22 and the question of making optically active aldols until chapters 23–30.

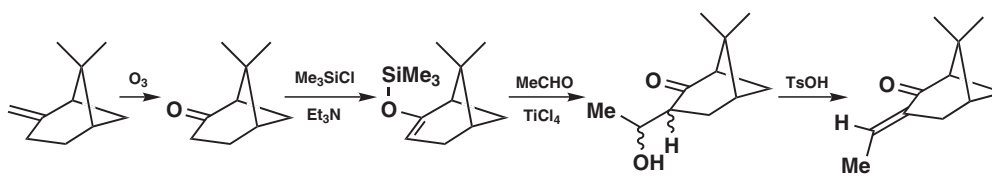
The synthesis of enones

The aldol reaction is often used to make enones by dehydration of the aldol itself, a reaction which often occurs under equilibrating aldol conditions, but has to be induced in a separate step when lithium enolates or silyl enol ethers are used. In general one has to accept whatever enone geometry results from the dehydration, and this is usually controlled by thermodynamics, particularly if enone formation is reversible. Simple enones such as **46** normally form as the *E* isomer but the *Z* isomer is difficult to prepare. When the double bond is *exo* to a ring, e.g. **47**, the *E* isomer is again favoured, but other trisubstituted double bonds have less certain configurations.



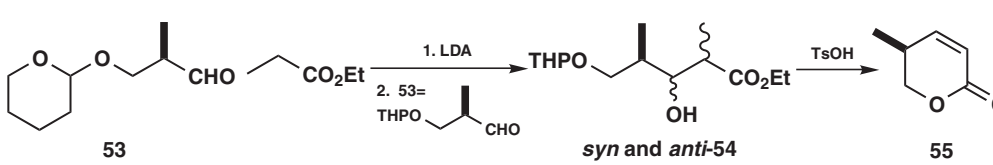
***E*-46** ***E*-47**

Yoshikoshi's synthesis[15] of nootkatone (then supposed to be the flavouring principle of grapefruit) uses an optically active enone **52** prepared from β-pinene **48** by ozonolysis to (+)-nopinone **49** and a chemo- and regioselective aldol condensation using the silyl enol ether **50**. Though the aldol reaction produces a mixture of diastereoisomers of **51**, all dehydrate to the same enone *E*-**52**.



(–)-48 **(+)-49** **50** ***syn* and *anti*-51** ***E*-52**

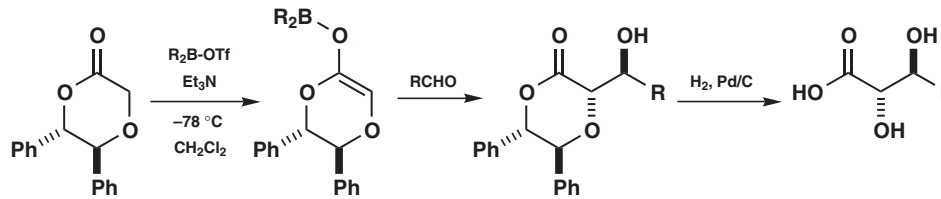
Still's monensin synthesis[16] uses the lactone **55** which inevitably has a *Z* double bond. This can again be made by an aldol reaction, this time using the lithium enolate of $EtCO_2Et$ and the optically active aldehyde **53**. A mixture of diastereomeric aldols **54** is again produced, but all dehydrate to the *Z* unsaturated lactone without racemising the original stereogenic centre. Cyclisation may precede dehydration, or the *E* compound may equilibrate.



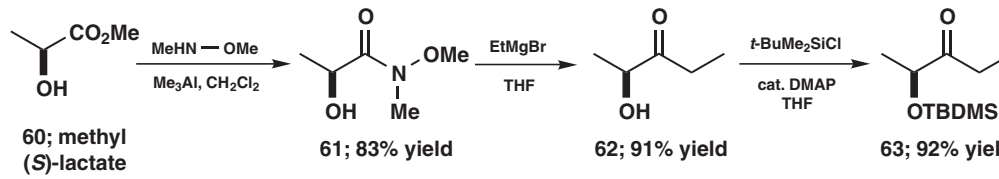
53 ***syn* and *anti*-54** **55**

Recent Developments in Stereoselective Aldol Reactions

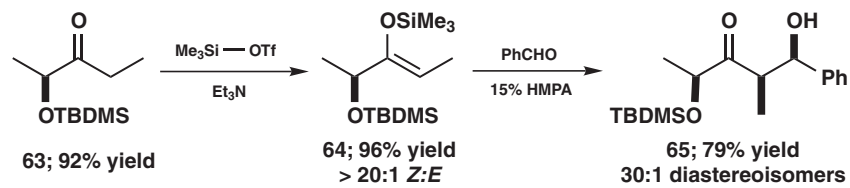
Recent developments tend to focus on the asymmetric aspects of stereoselective aldols but the diastereoselectivity is just as important. The cyclic ester **56** must of course form an *'E'* enolate and when the boron enolate *E*-**57** reacts with aldehydes the *anti*-aldol products **58** are formed with good stereoselectivity ranging from 4:1 to >20:1. The predominate isomer is that expected from the Zimmerman-Traxler transition state. The two benzylic-O bonds can be cleaved by hydrogenation and the 2,3-dihydroxy acids *anti*-**59** released in good yield.[17]



A particularly interesting case reported by Denmark[18] reveals several types of selectivity. The methyl ester **60** of natural (*S*)-lactic acid forms a Weinreb amide **61** with Me_3Al as catalyst. These amides are designed to react only once with Grignard reagents and organolithiums thus solving a classical chemoselectivity problem (chapter 2). Here the starting material **63** for the aldol reaction is prepared by reaction of ethyl Grignard with **61** and protection of the OH group by silylation.



The silyl enol ether **64** is formed from **63** with the *Z* configuration because of the enormous OTBDMS protecting group and reacts with benzaldehyde to give essentially one diastereoisomer of the *syn*-aldol **65**. The 1,3-stereochemical control across the carbonyl group is discussed in chapter 21.



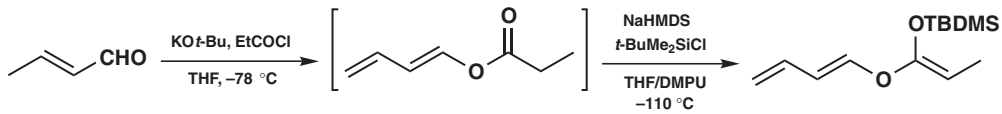
Stereoselectivity outside the Aldol Relationship

A Synthesis of Juvabione

There are of course many kinds of stereoselectivity not involving the aldol reaction and many will appear in the rest of the book. Just for example, we give a recent synthesis of juvabione,

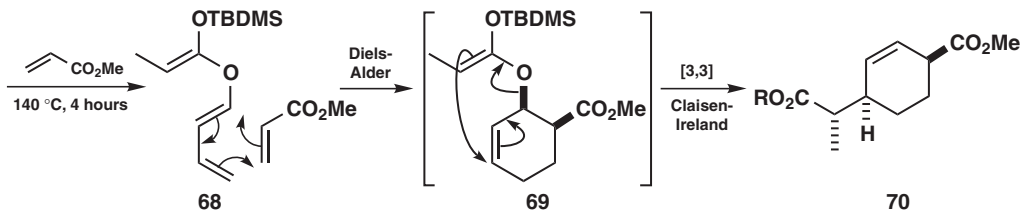
a pheromone that controls insect biology. It illustrates two types of pericyclic reaction and an electrophilic addition to an alkene. We are anticipating many later chapters in giving you this taste of things to come.[19]

Enol ester formation from crotonaldehyde gives the expected *E*-selectivity **66**. Now the silyl enol ether is formed from this ester, also with the expected double bond geometry. The product **67** has three alkenes: each is conjugated with at least one oxygen atom.



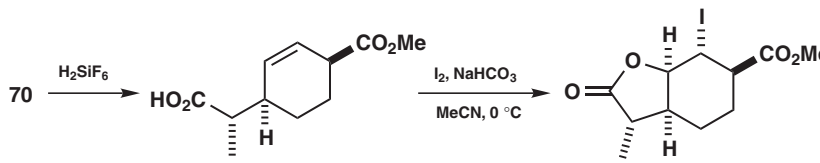
66; 66% yield **67; 84% yield**

The next stage occurs on heating the triene **67** with ethyl acrylate. First a Diels-Alder reaction **68** with the orientation and *endo*-stereoselectivity expected of this famous process gives an adduct with only two alkenes positioned so that it undergoes a [3,3]-sigmatropic (Claisen-Ireland) rearrangement **69** to give the product **70** with only one alkene.



68 **69** **70**

Both these reactions are more or less diastereoselective and give more or less one diastereoisomer of **70**. To discover the stereochemistry of the major adduct, the silyl ester (R = SiMe*t*-Bu) was hydrolysed to the free acid **71** (note the designer chemoselectivity) and this was treated with buffered iodine in MeCN to give a crystalline iodo-lactone **72**. An X-ray of this compound revealed that the structure of **71** was as shown and that the [3,3]-sigmatropic rearrangement must have had a boat transition state.

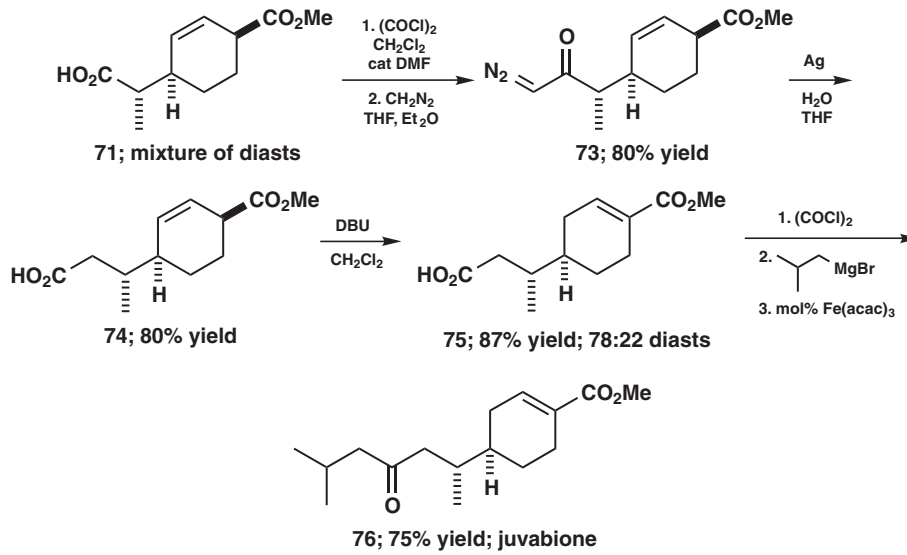


71; 60% yield
47:29:24 diasts

72; 71% yield
major diast crystallises

Now the synthesis could resume with the elaboration of intermediate **71** into juvabione **76**. Acylation of diazomethane with the acid chloride of **71** gave the diazoketone and hence by rearrangement the chain extended acid **74**. This new acid **74** is still a mixture of three diastereoisomers but isomerisation to the conjugated ester **75** reduces this to two in an acceptable 78:22 ratio.

Acylation of the acid chloride of **75** with a Grignard reagent catalysed by Fe(III) completes a synthesis of juvabione **76** with good stereochemical control.



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A Note on Stereochemical Nomenclature

We shall use the terms *syn* and *anti* because they have easily understood meanings and because they *must* refer to a diagram. Terms like *erythro* and *threo* or R*R* and R*S* or worst of all *ul* and *lk* are very difficult to understand and we shall not use them. They are of course the terms used by official bodies such as IUPAC and the Royal Society of Chemistry, probably for that very reason. Please note that the wiggly line will be used to mean that both isomers are present. It is sometimes used to mean that the stereochemistry is *unknown*.

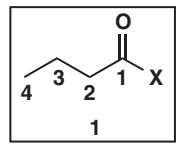
If you think you are interested in stereochemical nomenclature, you should consult the papers below and then read C. H. Heathcock in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, Orlando, Volume 3, 1984, page 112–115 to cheer you up again.

D. Seebach and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 654.

F. A. Carey and M. E. Kuehne, *J. Org. Chem.*, 1982, **47**, 3811.

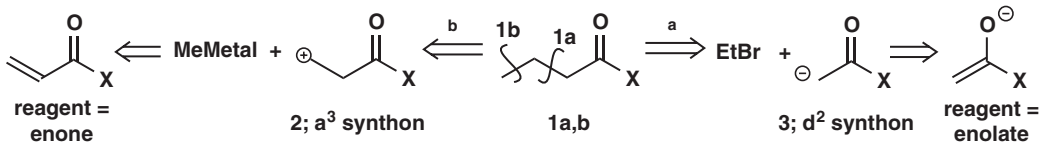
5 Alternative Strategies for Enone Synthesis

We have already seen how the aldol reaction may be used to prepare enones and other unsaturated carbonyl compounds. The past three chapters have introduced a lot of new methods without much analysis of strategy. This chapter and the next will redress the balance by looking at the various approaches to the synthesis of α, β-unsaturated carbonyl compounds (which we shall often loosely call *enones*, a term strictly reserved for α, β-unsaturated *ketones*) in this chapter, and then choosing which are most suitable for a particular class of enones, the cyclopentenones, in the next. One aim of this chapter in particular is to get you to think in terms of strategy. We shall be using words and phrases descriptive of strategy including a series of terms introduced by Seebach[1] to describe the electronic nature of synthons.

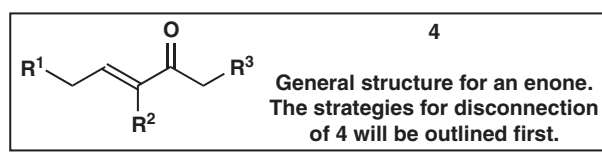


The Seebach nomenclature for synthons: d^2, a^3 etc.

Any functionalised carbon atom in the target molecule, but most commonly a carbonyl group, is numbered 1 and the atoms then numbered in turn along the chain so that the position of each relative to the C=O group is clear **1**. A disconnection, say **1a** will then require a synthon of a particular type and polarity. Thus **1a** requires an alkyl halide and the synthon **3** with a nucleophilic (or **d**onor) carbon in position 2, so we call this a $\mathbf{d^2}$ synthon. Similarly the disconnection **1b** could be realised by adding an organometallic derivative (MeMetal) to the synthon **2** with an electrophilic (or **a**cceptor) carbon at position 3. This becomes an $\mathbf{a^3}$ synthon. You will of course see that we could use an enolate for the $\mathbf{d^2}$ synthon, and an enone for the $\mathbf{a^3}$ synthon. All the enolates, and the other specific enol equivalents we have been discussing so far, are reagents for $\mathbf{d^2}$ synthons. Not everyone is happy about this labelling, but it is sometimes useful and we shall use it from time to time.



You will perhaps realise from these particular examples that the $\mathbf{d^2}$ synthon will be represented in real life by an enolate or its equivalent and the $\mathbf{a^3}$ synthon by an α, β-unsaturated carbonyl compound, both displaying the natural polarity of these fragments. It is generally true that *even* numbered *donor* synthons ($\mathbf{d^2}$, $\mathbf{d^4}$, etc.) and *odd* numbered *acceptor* synthons ($\mathbf{a^1}$, $\mathbf{a^3}$, etc.) have natural polarity while the odd numbered donor synthons ($\mathbf{d^1}$, $\mathbf{d^3}$, etc.) and the even numbered acceptor synthons ($\mathbf{a^2}$, $\mathbf{a^4}$, etc.) have unnatural polarity or *umpolung*. This makes the numbering of such synthons a useful quick check on the type of reagent likely to be needed.

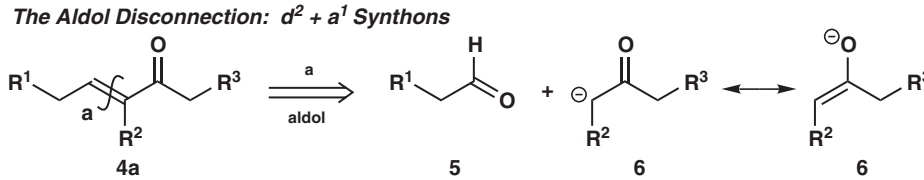


The Synthesis of Enones by Many Strategies

Introduction to the various strategies

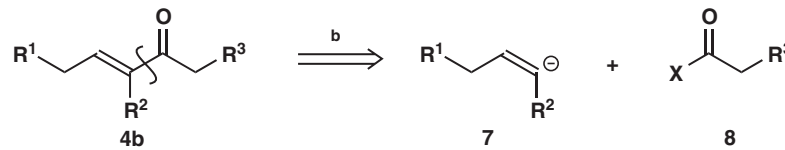
Now we start a systematic analysis of most of the possible disconnections which might be used in planning the synthesis of enones using the generalised structure **4** as our example. The first disconnection both in importance and in order of discussion is the aldol, that is disconnection of the enone double bond **4a**. You know from previous chapters that we can find a reagent for the enolate **6** when either R^2 or R^3 is hydrogen, providing there is branching on one side, or if $R^2 = R^3$.

The Aldol Disconnection: $d^2 + a^1$ Synthons



Next we shall tackle the important disconnection **4b** between the carbonyl group and the double bond. In many ways this is theoretically the best strategy as it is right in the centre of the molecule. This means we shall be examining the reactions between vinyl metals **7** and acylating agents **8** (where X is a leaving group such as Cl or OR). The nature of the metal and the stereochemistry of the vinyl group may be important here.

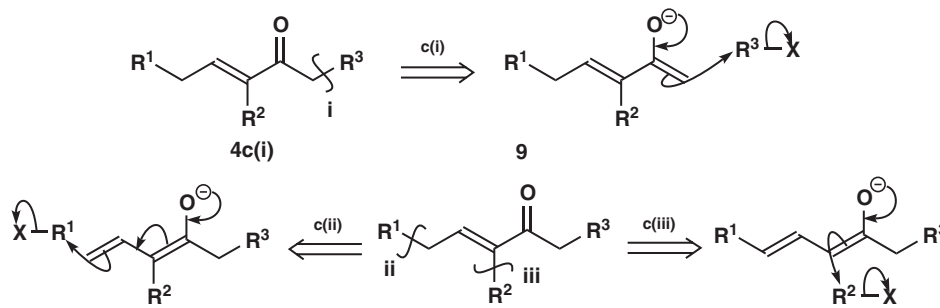
Acylation of a Vinyl Anion: another a[1] Synthon



4b **7** **8**

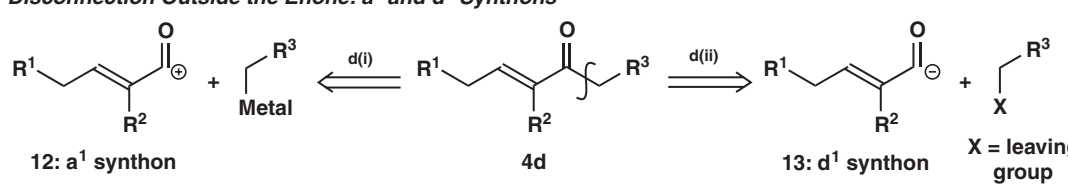
An important family of disconnections follows. The alkylations represented by **4c(i)**, **4c(ii)** and **4c(iii)** belong to extended enolate chemistry and you will learn to call the synthons **9**, **10** and **11** the α', γ and α extended enolates. Synthons **9** and **11** react in the normal d^2 position but **10** has d^4 reactivity. There are obvious questions of regioselectivity in this family. This chemistry will not be discussed further in this chapter as it is the subject of chapter 11.

The Extended Enolate Family of Disconnections: d[2] and d[4] Synthons

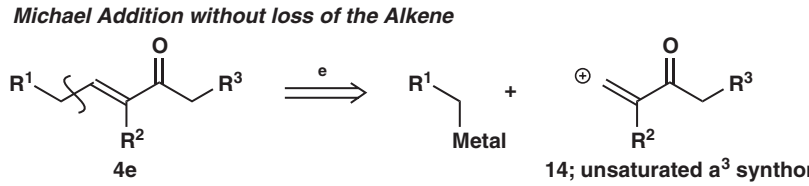


The syntheses represented by disconnection **4d** belong to a group where the alkene part of the enone is almost irrelevant: they involve either acylation of an organometallic compound **4d(i)** or alkylation of an acyl anion equivalent (a d^1 reagent) **4d(ii)**.

Disconnection Outside the Enone: a[1] and d[1] Synthons



Another disconnection outside the enone system is **4e** which looks at first sight like a conventional conjugate addition to an a^3 Michael acceptor. However we need to get the alkene back again after the Michael addition has occurred. The a^3 synthon **14** is unsaturated.



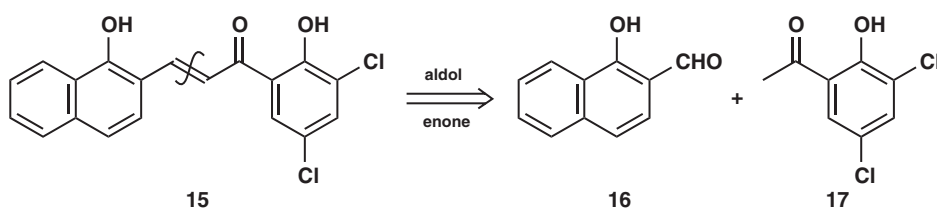
We shall also explore combinations of two disconnections, that is three-component syntheses, and strategies based on the addition of functional groups (here the double bond and the carbonyl group). This strategic tour is valuable in its own right as it should give you some useful methods, but its value also lies in your grasping the possibility of many different approaches to even such a simple compound as **4**. Throughout this chapter and even more so in the next chapter we shall consider the reasons for choosing one strategy or another from this perhaps rather bewildering array when faced with the synthesis of a particular compound.

Strategy 4a: The Aldol Route to Enones

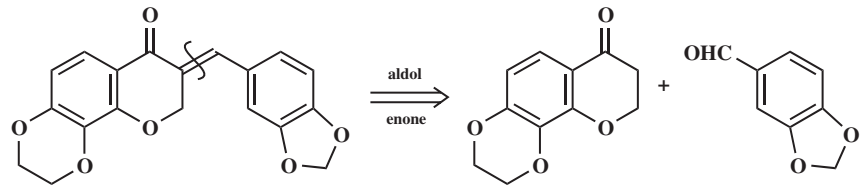
We have already seen several examples of this reaction in the synthesis of enones.[2] It is the first disconnection you should try in planning the synthesis of any enone and you should assess the likelihood of success by the aldol reaction before going on to any other disconnection, if only to get inside the skin of the problem. Almost any enone can be made nowadays by the aldol reaction, but it is worth considering in turn the features which make it specially suitable, and those which suggest that an alternative strategy should be attempted.

When the aldol strategy is ideal

The most obvious pointer to its success is if the double bond is roughly in the middle of the molecule, or if it separates two rings. This means that the disconnection will quickly lead to much simpler starting materials. We obviously want to make the enone **15** from two different aromatic starting materials and the aldol disconnection gives us an unenolisable aldehyde **16** and a very enolisable methyl ketone **17** with no problems of selectivity. Simply mixing **16** and **17** with KOH gives[3] an 87% yield of the enone **15**.



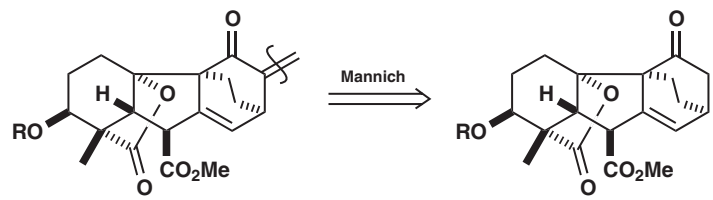
The double bond in enone **18** sprouts from a ring and aldol disconnection does indeed simplify the problem considerably since the starting materials are an unenolisable aldehyde **20** and a cyclic enolisable ketone **19**. There is only one place for enolisation in either molecule. The condensation between **19** and **20** with HCl in $MeCO_2H$ gives the enone **18** in 75% yield.[4] The stereochemistry of the enone double bond is under thermodynamic control (chapter 4).



18 **19** **20**

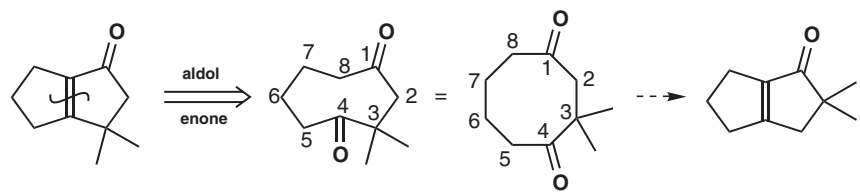
When the aldol strategy is not ideal

Conversely if the target is a vinyl ketone, then the aldol disconnection removes only one carbon atom - not much of a simplification! Even so, the aldol and its modifications such as the Mannich reaction are often used for such syntheses. An extreme example comes in Corey's synthesis of antheridic acid[5] where an aldol disconnection of an advanced intermediate **21** removes just one carbon atom but makes the remainder **22** of this complex molecule much easier to synthesise.



21 **22**

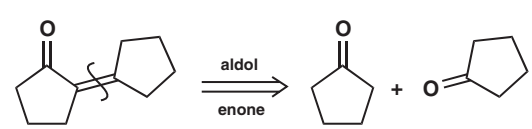
If the double bond is embedded in the middle of the molecule there may be no simplification at all, indeed the proposed starting material might be much harder to make than the target itself! The simple bicyclic ketone **23** disconnects to the dione **24** which is an unsymmetrical octa-1,4-dione difficult to make and which might cyclise to give **25** if C-5 enolises and attacks C-1 instead of C-8 enolising and attacking C-4 as we require. We shall see in the next chapter how to make such enones.



23 **24** **24a** **25**

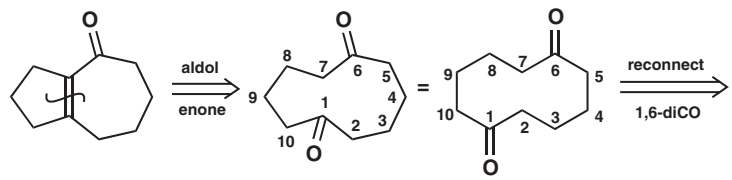
Symmetry as a guide

Symmetry may guide us. The simple enone **26** disconnects to two molecules of the same symmetrical ketone **27** and is therefore easily made without selectivity problems.[2] Acid or base-catalysed self-condensation of cyclopentanone gives the enone **26** in good yield.

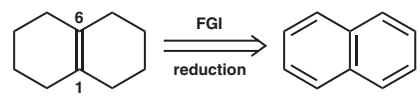


26 **27** **27**

The bicyclic compound **28** looks a poor subject for the aldol until we realise that the starting material **29** is symmetrical and as its two carbonyl groups have a 1,6-relationship, it can be made by the reconnection strategy.[6] The cyclisation to give **28** goes in 96% yield.[2] There is an obvious contrast with the failed synthesis of **23**. There the two ketones in **24** were different so there were three possible sites for enolisation. In **29** the two ketones are the same and all four sites for enolisation are the same. There are no selectivity problems.

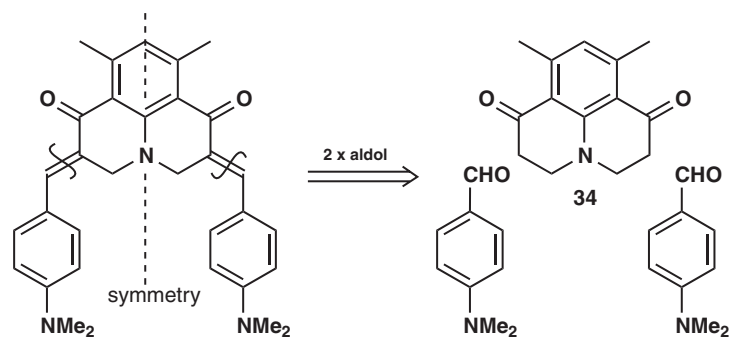


28 **29** **29a**



30 **31**

The complicated heterocyclic compound **32** is symmetrical about a vertical plane and two aldol disconnections give the symmetrical ketone **34** and two molecules of the unenolisable aldehyde **33**. Condensation with KOH gives[7] 93% of **32**.



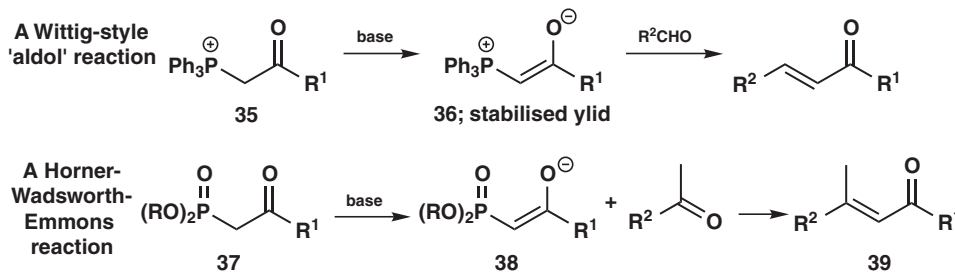
32 **34** **33** **33**

Mechanism may help us. If the required enolate is particularly easy to make, or the electrophile particularly reactive and/or unable to enolise, these are good points. If there are problems of chemo- or regioselectivity we cannot solve, then these are bad points. Stereochemistry may be a problem too. There is not much you can do about the stereochemistry of an enone made by the aldol reaction as you tend to get the thermodynamically more stable isomer (*E* or *Z*) and if you want the other you should try a different strategy.

Wittig-style aldol methods

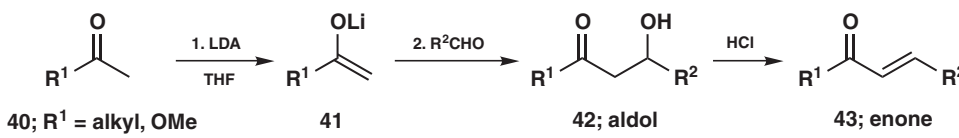
One version of the aldol is particularly suitable for enones as it uses Wittig-style chemistry and makes alkenes in one step. As you will see in chapter 15, reactions of stabilised ylids **36** or

phosphonate anions **38** (that is those of the aldol type) with aldehydes give *E*-alkenes selectively. Phosphonate anions also react with ketones.

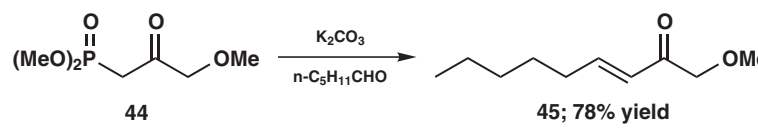


In general, the aldol strategy should be your first choice. If you feel that the chemo- and regioselectivity of the aldol reaction can be controlled and that the stereochemistry is likely to be correct, you should try the aldol approach. Of course, as in all aspects of synthetic chemistry, a literature search for precedents might save a lot of time. Even the aldol fails sometimes.

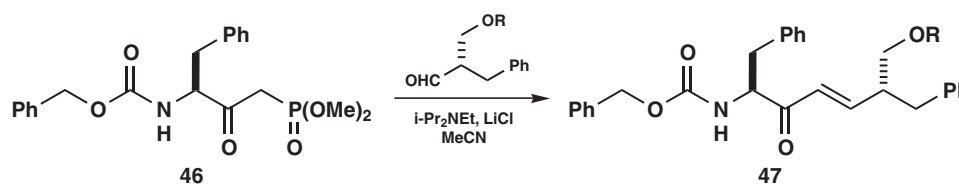
In a recent study of asymmetric conjugate addition, Simon Woodward and co-workers[8] required a series of enones **43**. Some they made with lithium enolates **41** of ketones or esters **40** added to aldehydes to give the aldols **42** that were dehydrated to the enones **43** with concentrated HCl.



Others they made by Wittig or Horner-Wadsworth-Emmons reactions such as the methoxyketone **45** from the phosphonate ester **44**. The 78% yield is of pure *E*-enone **45**.

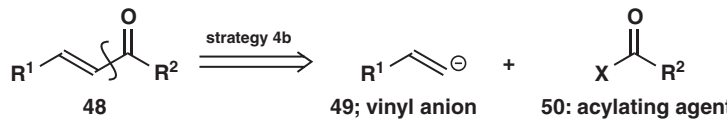


The search for anti-HIV drugs led workers in New Zealand[9] to potential peptide mimics with the central amide bond replaced by a *trans* alkene **47**. These compounds would have roughly the same shape as natural peptides and might inhibit HIV protease. To get the right diastereoisomer two single enantiomers were coupled by the Horner-Wadsworth-Emmons reaction of phosphonate **46** and the right aldehyde. The slightly odd conditions avoided racemisation of the aldehyde.



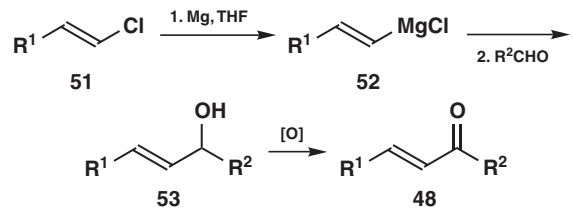
Strategy 4b: Acylation of a Vinyl Anion

Strategy 4b involves the disconnection **48** of the bond between the double bond and the carbonyl group of the enone and requires the acylation of a vinyl anion **49** or its synthetic equivalent with some a[1] reagent **50**, an acylating agent, usually an acid derivative.

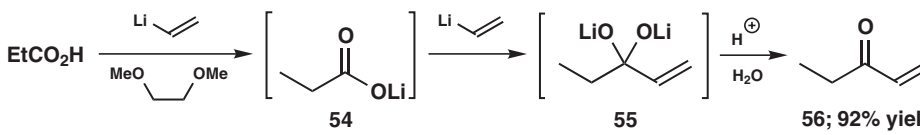


Vinyl metal reagents

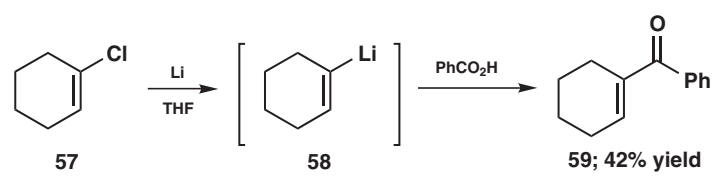
Its most elementary realisation is the reaction of a vinyl Grignard reagent **52** or vinyl lithium, usually prepared from a vinyl chloride **51** in THF, with an aldehyde followed by oxidation to the enone **48**. The Swern oxidation is particularly useful for the oxidation of allylic alcohols such as **53** to enones.



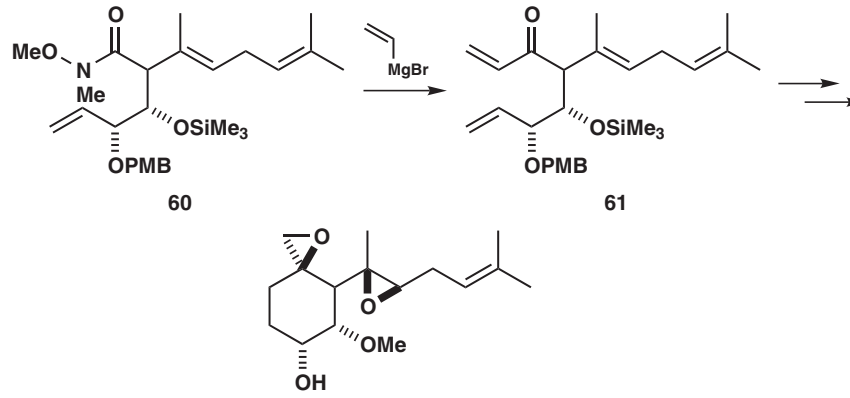
A more direct version is the treatment of vinyl-lithiums with carboxylic acids.[10] Vinyl-lithium itself reacts with $EtCO_2H$ in DME (DiMethoxyEthane) to give the enone **56** in high yield.[11] The first molecule of vinyl-lithium forms the lithium salt **54** and the second molecule adds to give the di-lithium derivative **55**, an intermediate which might remind you of the lithium enolates of carboxylic acids discussed in the previous three chapters. Hydrolysis during normal work-up gives the enone **56**.



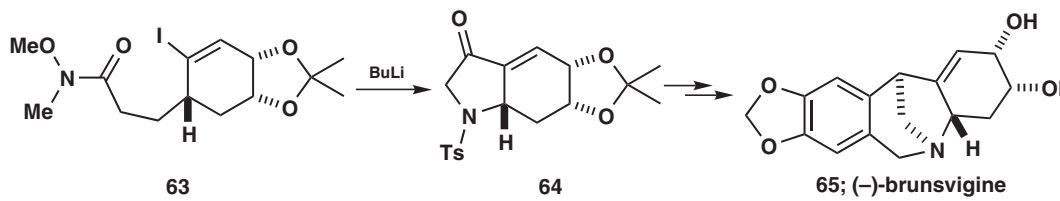
This reaction often gives much poorer yields in other cases, though the cyclic vinyl-lithium **58** prepared from the vinyl chloride **57**, gives a moderate yield[12] of **59**.



The most popular method these days for the acylation of Grignard or organolithium reagents is the Weinreb amide (also discussed in chapter 8). Acylation of vinyl Grignard with the complex intermediate **60** was part of a synthesis of (−)-fumagillol[13] **62**.

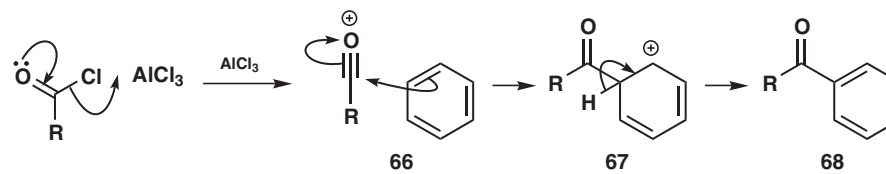


The intramolecular acylation of the vinyl lithium derivative of **63**, prepared by exchange of iodine with lithium (chapter 8) with the Weinreb amide on the side chain gives the five-membered heterocyclic ring in **64**, an intermediate on the way to (−)-brunsvigine **65**, an alkaloid of the montanine group.[14]

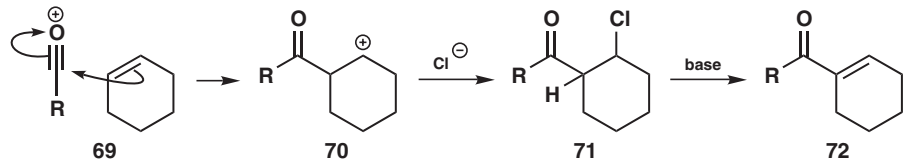


The aliphatic Friedel-Crafts reaction

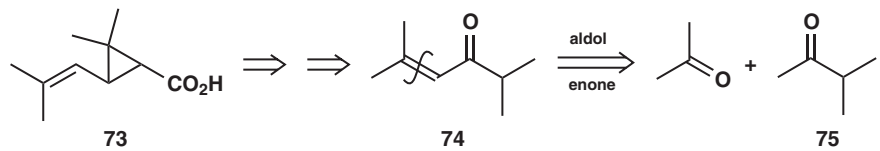
In chapter 16 we shall discover that vinyl-copper reagents can be prepared with stereochemical control over double bond geometry and acylated directly with acid chlorides. We shall also meet vinyl silanes and see how they too can be acylated with acid chlorides. In this chapter we shall consider only the acylation of alkenes themselves with acid chlorides, that is the aliphatic Friedel-Crafts reaction.[15] The normal Friedel-Crafts reaction **66** combines an aromatic compound with an acid chloride and a Lewis acid to give a cation **67** which loses a proton to give an aryl ketone **68**.



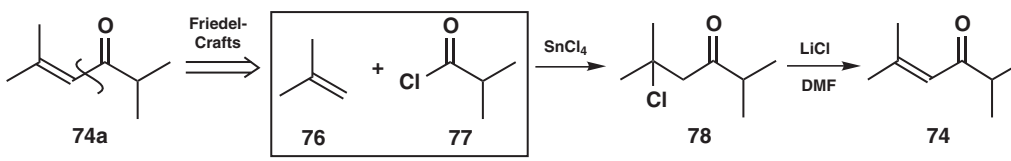
An alkene, if it is reactive enough, can give the same sort of intermediate **70** but there is no longer the same urgency to lose a proton, as there is no aromaticity to regenerate, and a chloride ion usually adds to give the β-chloroketone **71**. Base is needed to give the enone **72**. By this method the enone **72** was made in 40% yield but only after extensive fractionation.[12]



The simple enone **74** was needed for a synthesis of *trans* chrysanthemic acid **73**, a component of the natural insecticide pyrethrin.[16] An aldol approach would require a cross-condensation between two enolisable ketones, one of them **75** unsymmetrical, and although this could easily be done an alternative was sought.



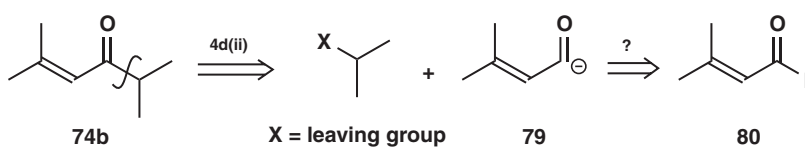
Disconnection between C=O and C=C with the aliphatic Friedel-Crafts reaction in mind would require acylation of the unsymmetrical alkene **76** with the acid chloride **77**. The alkene **76** is ideal for acylation as it is tri-substituted and therefore relatively electron-rich and will react at the required (less substituted) end. The β-chloroketone **78**, formed when $SnCl_4$ was used as the Lewis acid, was treated with base without isolation to give the enone **74** in 60% overall yield. Lithium chloride may not look very basic, but in dipolar aprotic solvents like DMF (DiMethylFormamide, Me_2NCHO), that do not solvate anions, chloride is a good base.



Strategy 4c: Unsaturated Acyl Cations and Anions

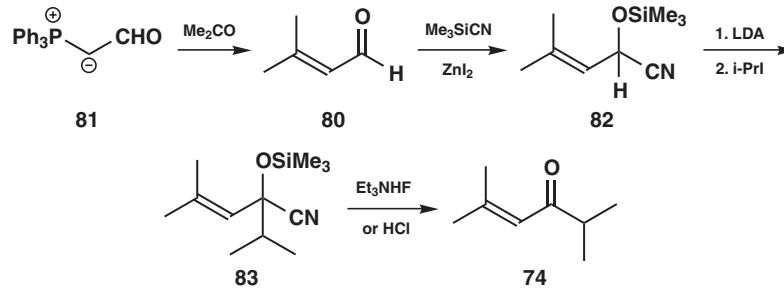
Acyl anion equivalents (d^1 reagents)

Strategy **d(ii)** (see **4d**) follows logically as similar methods are involved. The same enone **74** can be made by this strategy **74b** if an acyl anion equivalent (a d^1 reagent) for the synthon **79** can be alkylated at the carbon atom of the carbonyl group.



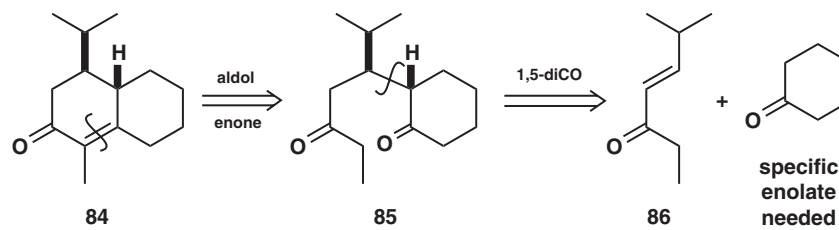
The point of this is that the proposed starting material **80** can then be made by a simple Wittig reaction with the stable ylid **81**, the equivalent of an enolate of MeCHO, as the extra ylid stabilisation avoids any regioselectivity problems in enolisation. The cyanohydrin derivative **82** can lose the marked proton with strong base and alkylation occurs as planned. The product **83** can be hydrolysed

with anions chemoselective for silicon (fluoride or chloride) to regenerate the carbonyl group with the formation of the enone[17] **74**. We shall meet further examples of acyl anions (d^1 reagents) in chapter 14.

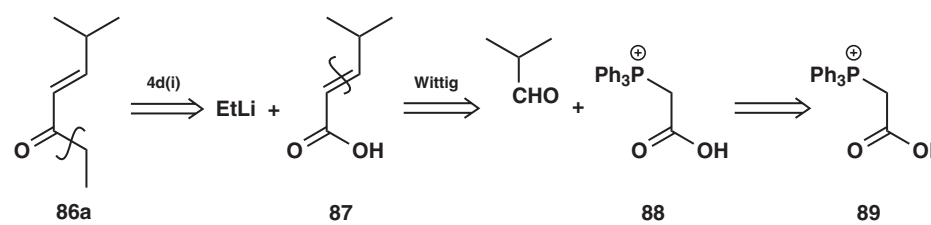


An example with two enones made by different strategies

The same strategy, but with the opposite polarity, along with other enone approaches is illustrated by the bicyclic enone **84** needed for the synthesis of the terpene cadinene. Aldol disconnection gives the 1,5-diketone **85** which we expect to make by a Michael addition.[18] Hence we require a specific enol equivalent of cyclohexanone to add to the enone **86**, and we have rediscovered the Robinson annelation.[19]

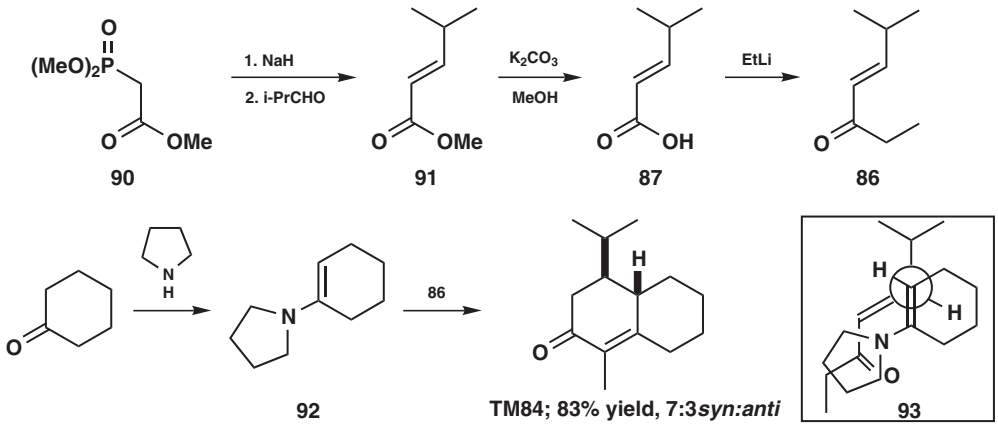


Disconnection of the enone **86** by the strategy we have just used for **74**, with the reverse polarity, gives the unsaturated acid **87** again accessible by a Wittig reaction with the protected reagent **89**. We have in mind using an alkyl-lithium instead of a vinyl-lithium as a nucleophile to make **86**.



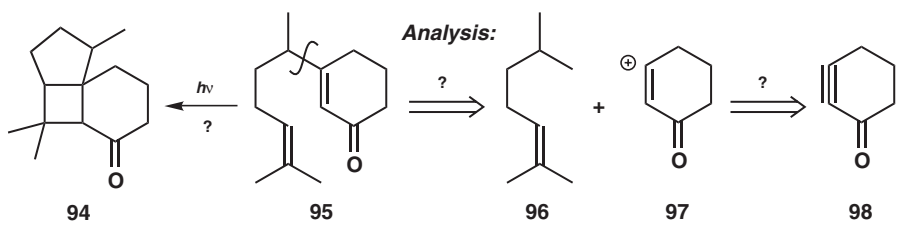
The phosphonate **90** version of the Wittig reaction, often used when there is an anion stabilising group (here CO_2Me) present, gives 65% of pure *E*-**91**, easily hydrolysed to the free acid **87**. Now we need to add EtLi, made from EtBr and Li metal, which gives *E*-**86** in 92% with some recovered starting material. Finally, the Robinson annelation goes in excellent yield (83%) to give the required bicyclic enone **84**. There is also reasonable selectivity in the Robinson annelation (7:3 in favour of the required *syn* isomer), presumably through a transition state such as **93**. This is a Newman projection, often the best way to visualise the simultaneous creation of two

new stereogenic centres. Note that this is not aldol stereo-selectivity: it is akin to the examples discussed at the end of chapter 4 and to be discussed in chapters 20–22.

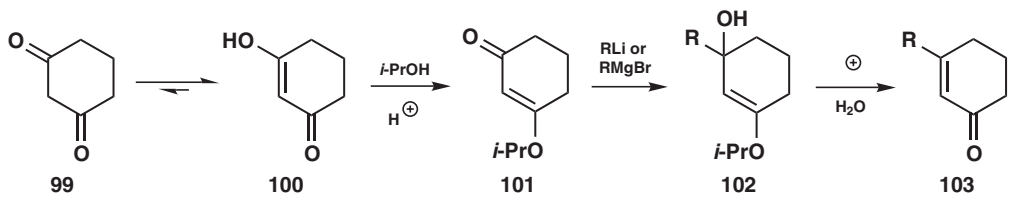


Strategic bonds in enone synthesis

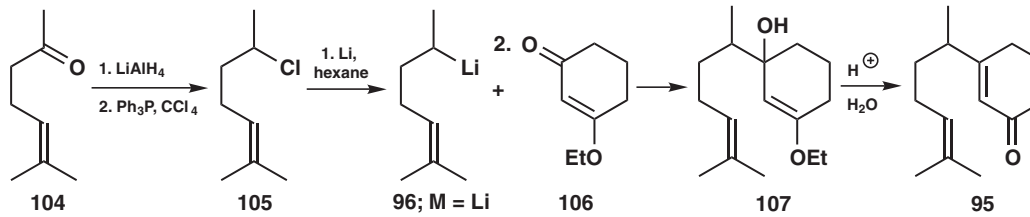
When Fétizon[20] wanted to synthesise members of the cedrene and acorene classes of terpene, he chose to try the photochemical cyclisation[21] of the dienone **95**, hoping to get **94**. The best disconnection strategically is of the bond between the two branchpoints **95**. This bond is also roughly in the middle of the molecule and separates a ring from a chain and so cries out to be disconnected. We shall call such bonds *strategic bonds* in future. We might try an organometallic reagent **96** (M = metal) and some reagent for the synthon **97**. As the enone is cyclic we cannot use the "obvious" ynone **98**.



A more practical strategy uses the chemistry of 1,3-diones **99** which exist as an equilibrium mixture with the predominant enol form **100**. Reaction with an alcohol (MeOH or *i*-PrOH are most popular) gives enol ethers such as **101** which react cleanly with organo-metallic reagents (such as **96**; M = Li or MgBr). However, attack occurs at the carbonyl group to give **102**; and not at the double bond, so the molecule is turned back to front by this reaction to give the enone **103**.

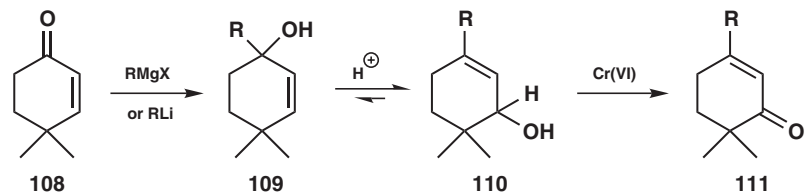


When you have realised, as we hope you did from the way we drew the product **101**, that enol ether formation occurs randomly at either end of the 1,3-dione system, you should also see that only symmetrical diones are suitable for this reaction. Returning to the original problem, the synthesis of **95**, the ketone **104** is readily made,[22] so this route is suitable using the lithium derivative made from the chloride **105** and the ethyl vinyl ether **106**.

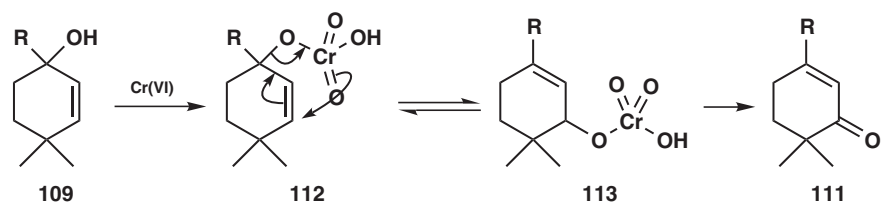


Rearrangements of allylic alcohols with Cr(VI)

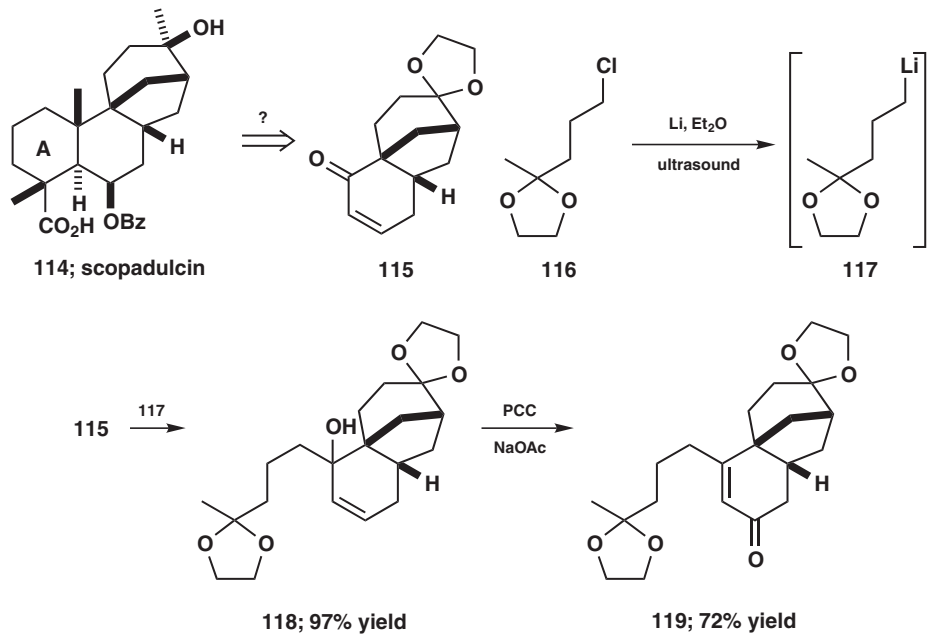
A regiospecific version[23] of the same strategy starts with an unsymmetrical enone, such as the Robinson annelation product **108**. An organometallic compound is again added direct to the carbonyl group, but now the rearrangement is accomplished by oxidation with Cr(VI). The starting material **109** cannot be oxidised as it is a tertiary alcohol, but the product of allylic rearrangement, being a secondary alcohol **110**, can, and the enone **111** must result.



This is probably a [3,3] sigmatropic rearrangement **112** of the chromate ester of the tertiary alcohol so that **109** is oxidised directly to **111** via the chromate ester **113** without any secondary alcohol **110** actually being formed. An important way to carry out this strategy appears in chapter 18 under the Heck reaction.

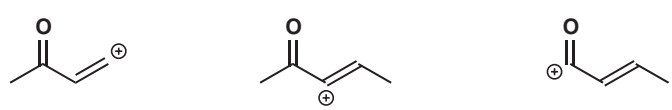


This strategy was recently applied to the synthesis of scopadulcin[24] **114**. They had already made the enone **115** and wished to use it as starting material so means had to be found to bolt ring A onto the bottom left hand side of the enone. Addition of the lithium derivative **117**, made from the chloride **116** with the aid of ultrasound (often a help in heterogeneous reactions) to the enone **115** gave the allylic alcohol **118** and this duly rearranged on Cr(VI) oxidation.



Looking forward to the chemistry of S and Se

Modern organic chemistry, particularly using the special reactivity of sulfur and selenium compounds, has developed regiospecific reagents for all three synthons **120**, **121**, and **122**, and the three negative synthons of the same structure, needed for this family of strategies. We shall postpone a detailed discussion of this chemistry until chapters 16 and 18. The nucleophilic synthon corresponding to **121** will also appear as extended enolate chemistry, disconnections (7c), in chapter 11. Finally, there are some further strategies we have not even mentioned which depend on the late addition of either the carbonyl group or the double bond. These also involve sulphur and selenium chemistry and will appear in chapter 33 under the heading "FGA strategy". You will appreciate that there are many approaches to the synthesis of enones. How you are to decide which one to adopt in a particular case is the subject of the next chapter.



120 **121** **122**

References

General references are given on page 893

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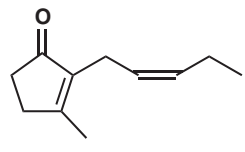
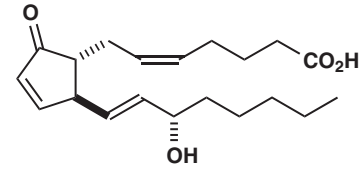
6 Choosing a Strategy: The Synthesis of Cyclopentenones

Strategies Based on an Aldol Reaction

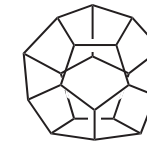
Five-membered rings occur throughout Nature and in many exciting molecules made by man. The perfumery constituent *cis*-jasmone **1** might claim to be the molecule synthesised in most different ways. The prostaglandins, molecules which control human physiology, contain five-membered rings and some, like PGA_2 **2** are cyclopentenones. Dodecahedrane **3**, the highly symmetrical $(CH)_{20}$ hydrocarbon, consists of nothing but five-membered rings, twelve of them in all, and has been approached from various cyclopentenones.



1; *cis*-jasmone



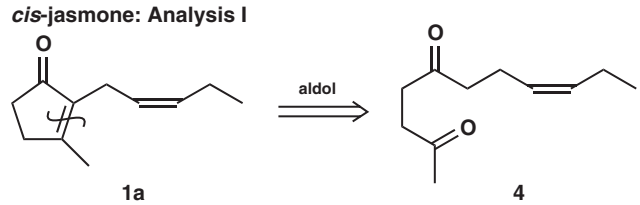
2; PGA_2



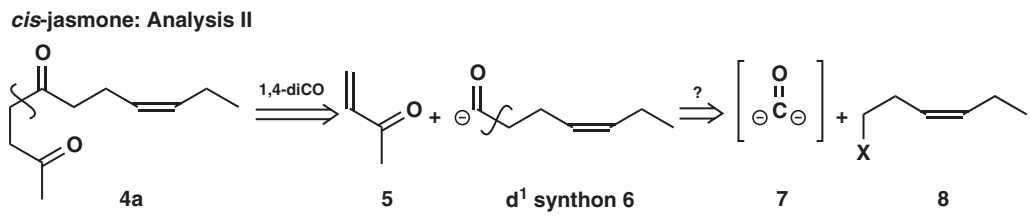
3; $C_{20}H_{20}$ dodecahedrane

We shall look at the many different strategies used to make cyclopentenones: some will be similar to the methods explored in the last chapter, some will be totally different. Some will introduce more advanced chemistry that we shall meet later in the book, but the point of this chapter is the strategy: in each case we hope you will ask yourself why that particular route was followed.

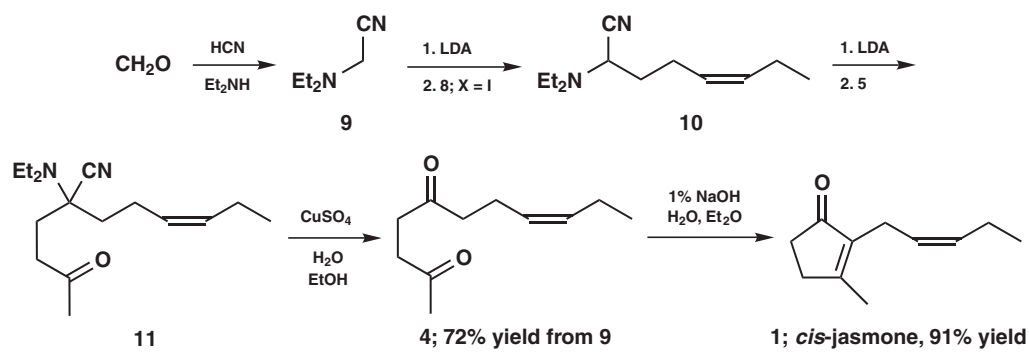
When Stork[1] wished to synthesise *cis*-jasmone **1**, he considered how helpful it would be if there were an equivalent to the famous Robinson annelation[2] which would make five-membered instead of six-membered rings. Analysis would start in the same way (cf. chapter 5) **1a** but the starting material **4** for cyclisation would be a 1,4-diketone instead of a 1,5-diketone.



Disconnection **4a** to an enone **5** is still possible, but we should have to add a d^1 reagent, or acyl anion equivalent **6** instead of an enolate. At the time of Stork's work, there were no d^1 reagents which reliably added Michael fashion, so he invented one. It would obviously be convenient if the d^1 reagent would also act as an alkylating agent in the synthesis of **6**, that is if it would act as the doubly nucleophilic synthon **7**.

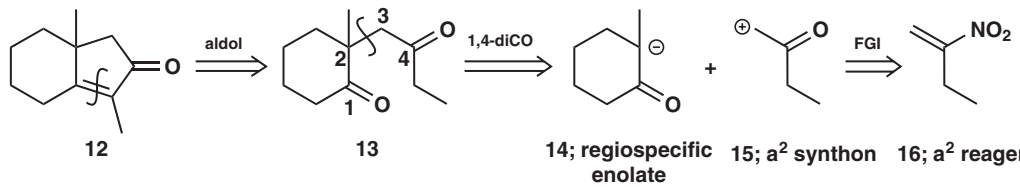


The amino nitrile **9** fulfils all these hopes. It is easily made, it can be alkylated to give **10**, and the anion from removal of its second proton gives a clean Michael reaction to form **11**. Finally, the amino-nitrile functionality is easily hydrolysed at room temperature and neutral pH (unlike so many such compounds: see chapter 14) with Cu(II) catalysis to give the ene-dione **4** and hence *cis*-jasmone **1** by thermodynamically controlled cyclisation in weak base.[1] This process of adding a new five-membered ring, not necessarily to give a cyclopentenone, is often called cyclopentannelation and there are now many such methods.[3]

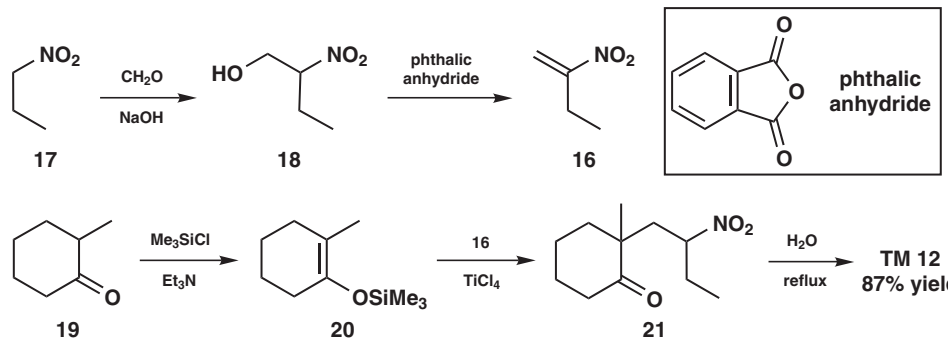


This first approach kept the Michael acceptor half **5** of the Robinson annelation. The alternative would be to keep the enolate half and replace the Michael acceptor by an a^2 synthon. An example is the synthesis of the cyclopentenone **12** by Yoshikoshi.[4] As before, aldol disconnection gives a 1,4-diketone **13**, but this time there is a strategic bond for disconnection leading logically to a regiospecific enolate **14** and a regiospecific a^2 synthon **15**. From chapter 3 we know that a silyl enol ether is the best choice for a more substituted enol. It is less obvious to choose an unsaturated nitro compound **16** as the a^2 reagent, but you should be aware that aliphatic nitro compounds can be converted into ketones, and that the great anion stabilising ability of the nitro group makes the synthesis of unsaturated nitro compounds a simple matter.[5] Putting these two ideas together makes

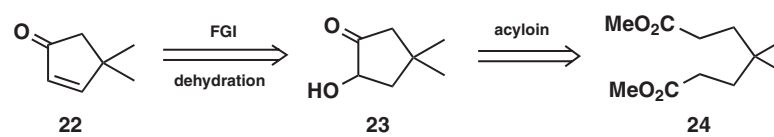
this a good strategy, particularly as the same anion-stabilisation will make the Michael addition a good reaction too.



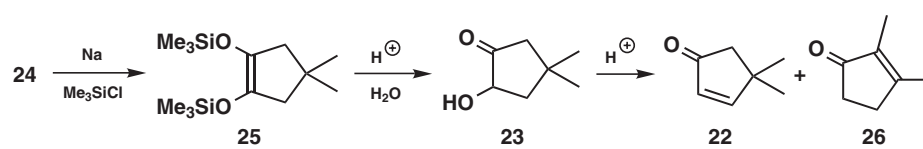
Nitropropane **17** can be condensed directly with CH_2O to give the alcohol **18** which is dehydrated with phthalic anhydride to give nitroalkene **16**. The silyl enol ether **20** can be made directly from the unsymmetrical ketone **19** under equilibrating conditions and reacts with the nitroalkene under Lewis acid ($TiCl_4$ as usual) catalysis to give the adduct **21**. Normally one needs quite vigorous conditions to convert nitroalkanes to ketones, and the very mild hydrolysis used in this example suggests that **21** hydrolyses unusually easily. The result is another efficient cyclopentannelation by a different strategy.[4]



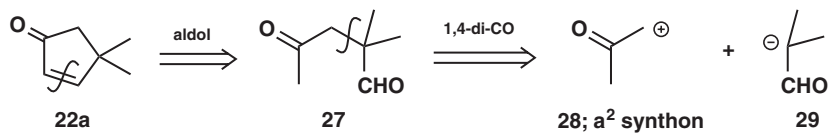
The first strategy one normally considers is the one which is already in the literature. In the case of the cyclopentenone **22**, widely used in natural product synthesis,[6] the near symmetry led to an unusual strategy via the acyloin product **23** and hence to the symmetrical diester **24** as starting material.[7]



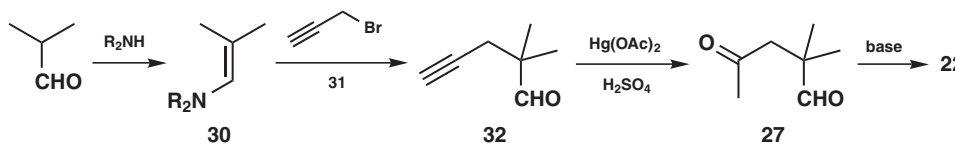
This synthesis works well, using the silicon modification **25** of the acyloin reaction, but the final dehydration leads to a mixture of enone **22** with the rearranged enone **26**. This problem was not realised until chemists[8] began to use this published procedure,[9] and is a warning to all chemists involved in synthesis to check the structure of their intermediates carefully by NMR.



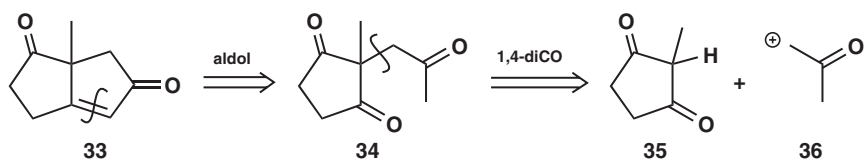
A more conventional analysis, using the aldol disconnection **22a**, leads to a strategy similar to that used for **12** and we must decide which half of the 1,4-keto-aldehyde **27** should have the natural, and which the unnatural polarity. The two methyl groups help as they do not hinder chemoselective enol formation from $Me_2CH.CHO$, but would make the a^2 reagent sterically less reactive towards an S_N2 reaction.



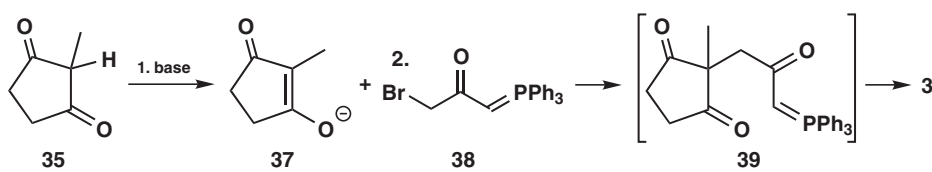
The choice for a specific enol equivalent is easily made: we used aldehyde enamines for just these sorts of reactions in chapter 3. You may wonder why a simple α-haloketone was not chosen for the a^2 reagent. This was a matter for personal preference dictated by the need to make large quantities of **22**. Stevens[10] and his group preferred the propargyl halide **31** even though this meant using an Hg(II) salt to catalyse the hydration of the triple bond[11] to give **27**. Aldol cyclisation completed the synthesis.



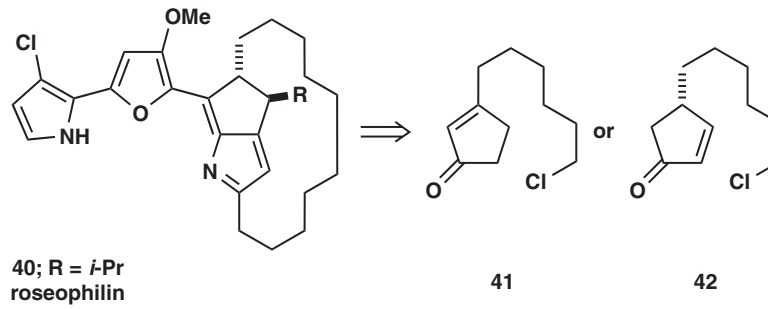
Sometimes even the aldol reaction fails to perform with its usual reliability and we must give it some help. The bicyclic enone **33** continues the contrast with Robinson annelation as it resembles the Wieland-Miescher ketone, used as a starting material for steroid syntheses,[12] but with two five-membered instead of two six-membered rings. Aldol disconnection reveals the 1,4-diketone **34** but it turns out that closing the second five-membered ring this way works rather badly.



The solution is to make the intramolecular aldol into a Wittig reaction. There are many ways to do this using reagents such as **38** on the stable enolate **37**. Note that this reagent **38** is an ylid not a phosphonium salt, so there are no acidic protons to destroy the enolate of the dione **37**. This is one example of a family of reagents[3] that act first as electrophiles and then as enolate equivalents. This bicyclic enone **33** has been used in the synthesis of coriolin.[13]

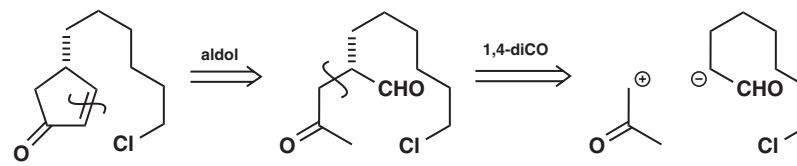


Modern versions of these strategies were needed for Robertson's synthesis[14] of the heterocyclic core of roseophilin **40**. He decided to use the cyclopentenones **41** or **42** as starting materials.



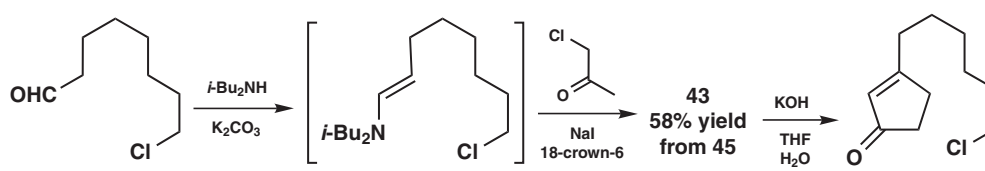
40; R = *i*-Pr roseophilin **41** **42**

The standard aldol disconnection on enone **42a** reveals the ketoaldehyde **43** best disconnected at the branchpoint to the simple aldehyde **44** and some a^2 reagent derived from acetone.



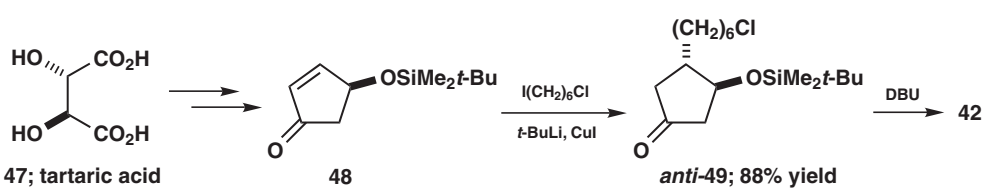
42a **43** **44**

The synthesis involved the formation of an enamine **46** from the aldehyde **45** and alkylation with chloroacetone to give the ketoaldehyde **43**. Then events took a twist. Aldol reaction under equilibrating conditions (KOH, THF, H_2O) gave **41** rather than **42**.



45 **46; enamine** **41; 100% yield**

Though milder conditions (NaOH, Et_2O) gave **42** in 86% yield, this was of course racemic. The single enantiomer was made from tartaric acid **47** by conversion into the enone **48**, conjugate addition of a lithium cuprate with excellent *anti*-selectivity **49** and elimination with DBU.[14]

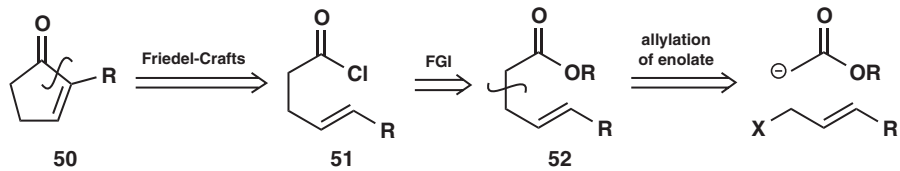


47; tartaric acid **48** ***anti*-49; 88% yield**

Using the Aliphatic Friedel-Crafts Reaction

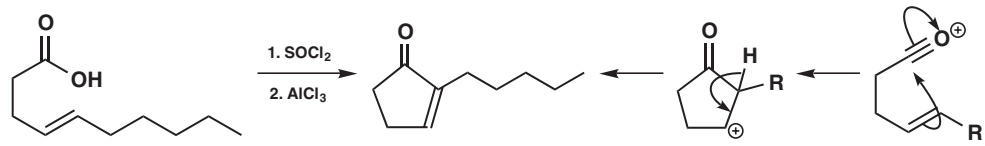
Strategy B of chapter 5, disconnection between the double bond and the carbonyl group **50**, looks at first sight to be of little use as it would require an intramolecular aliphatic Friedel-Crafts reaction

on a compound of equal size. It is of value because the starting material **51** comes from some acid derivative **52** that can be made by allylation of an enolate. The Friedel-Crafts should be regioselective as cyclisation of the other end of the alkene would give a four-membered ring.



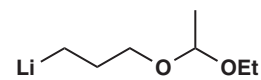
50 **51** **52**

This strategy has been used to make the simple cyclopentenone **54** from the unsaturated carboxylic acid **53** presumably by intramolecular aliphatic Friedel-Crafts reaction **56** and loss of a proton from the resulting cation **55**. This strategy was used because **53** was available by the telomerisation of butadiene, but it would be simple to make such unsaturated acids in other ways.

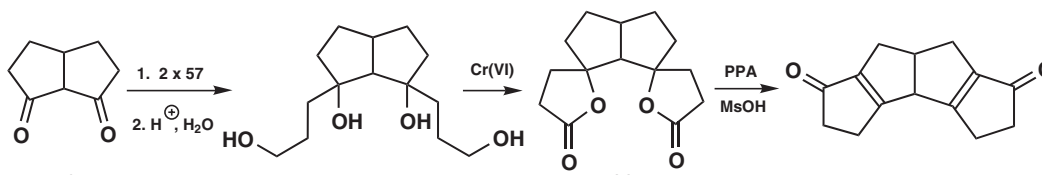


53 **54** **55** **56**

A more exciting version[15] adds a three carbon unit (the d^3 reagent **57**) twice to the symmetrical diketone **58**, oxidises the resulting tetraol **59** to a diacid which spontaneously cyclises to the dilactone **60**, and generates the acylating agent and the double bond needed for the Friedel-Crafts reaction by acid-catalysed dehydration. The resulting curved row of cyclopentane rings **61** is clearly one possible starting point for the synthesis of dodecahedrane **3**.

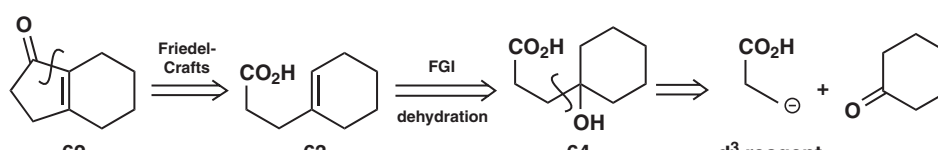


57; d^3 reagent



58 **59** **60** **61**

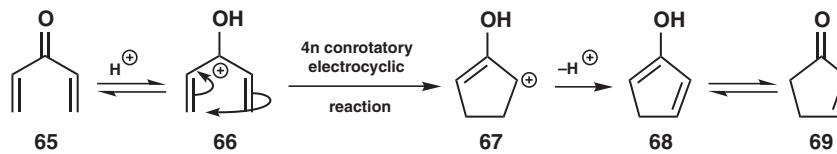
The first disconnection **50** or **62** is the same for both these approaches, giving in each case an unsaturated acid as the intermediate. In the open chain case **52**, we could proceed by a Wittig disconnection of the double bond or a simple alkylation with an allylic halide **53**. For the cyclic case (using a six-membered ring as the second ring) **63** these are much less attractive. The bond joining the ring to the chain is a strategic bond and we can disconnect it after FGI to the alcohol **64** reveals the need for a d^3 reagent or homoenolate. Further examples of these reagents appear in chapter 13.



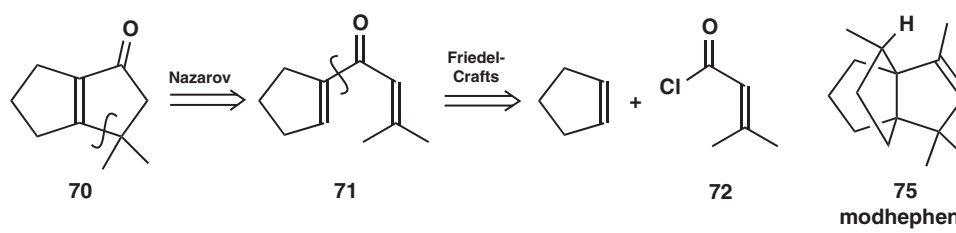
62 **63** **64** **d^3 reagent**

The Nazarov Reaction

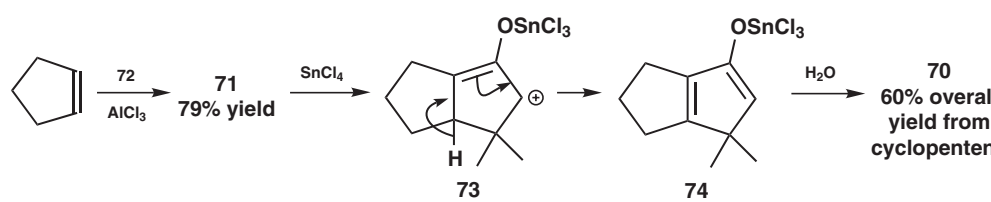
In addition to the application of known and established strategies, each structural type of target molecule may have special methods developed for, in this case, cyclopentenones alone. The Nazarov reaction is historically important as one of the few unexplained reactions which led Woodward towards the Woodward-Hofmann rules for pericyclic reactions.[16] Treatment of a cross-conjugated dienone, **65** being a minimalist example, with acid or Lewis acid leads to a cyclisation in which two electrophilic atoms react with each other to give a cyclopentenone **69**. Seen as an ionic reaction, it makes no sense, but as a conrotatory 4n electrocyclic reaction[17] it is entirely reasonable. Protonation gives a pentadienyl cation **66** which cyclises to a cyclopentenyl cation **67**, the driving force being formation of a new σ-bond that more than compensates for the loss of conjugation. Loss of a proton and enol-keto tautomerism complete the reaction.



Inspection of the starting material and the product reveal that the disconnection is of the bond in the ring opposite the carbonyl group. Applying this to the molecule **70** we discussed in chapter 5, and for which we rejected the aldol strategy, we discover that we need the dienone **71**. An attractive disconnection corresponds to the Friedel-Crafts reaction we have just been discussing and requires in this instance cyclopentene and the unsaturated acid chloride **72**.

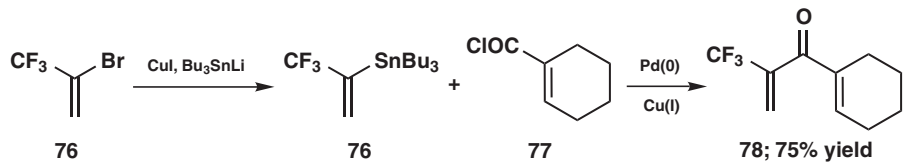


Oppolzer,[18] who wanted this cyclopentenone for the synthesis of modhephene **75** followed this strategy and found that the Friedel-Crafts went well with $AlCl_3$ as catalyst and the Nazarov cyclisation with another Lewis acid, $SnCl_4$. You will notice the position of the double bond in the final product: there are no protons on one side of the cation **73** so one must be lost from the other side. In cases where there is a choice, the more substituted alkene results, as here. The product is ideally functionalised for development into modhephene **75**.

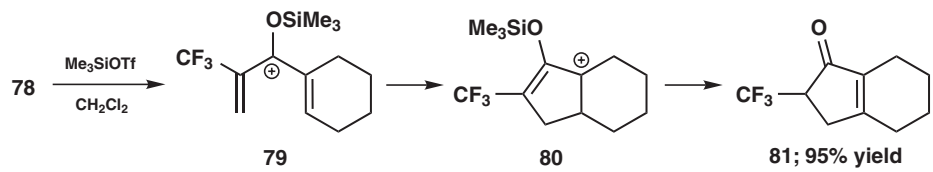


In chapter 16 we shall see how the use of vinyl silanes has solved some of the regioselectivity problems inherent in the Nazarov reaction.[19] Meanwhile we look at some recent developments on

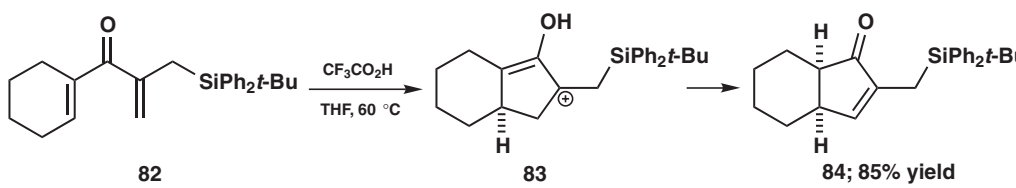
the effects of substituents on the reaction. The introduction of fluorine into organic molecules is of the greatest importance for the synthesis of new drugs. The synthesis of the trifluromethyldienone **78** gives you a preview of methods we shall see later involving Sn and Pd. For the moment accept that this is a way to produce a potential substrate for a Nazarov cyclisation.[20]



The Nazarov reaction is carried out with Me_3SiOTf as Lewis acid through intermediates **79** and **80**. Elimination occurs exclusively away from the CF_3 group to give **81** in excellent yield.

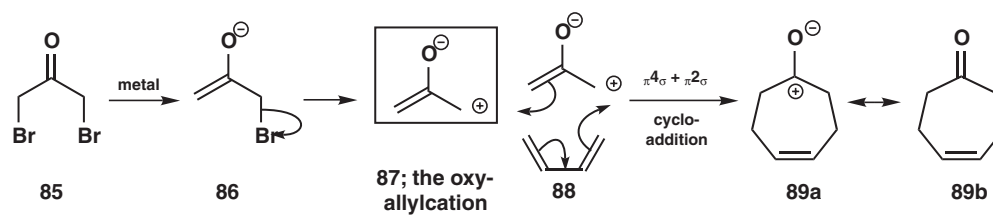


A silyl group, on the other hand, attracts the alkene in the product. The dienone **82** cyclises easily in acid to give only the less substituted cyclopentenone **84** in excellent yield.[21] We shall discuss the stabilisation of cations such as **83** and allyl silanes such as **84** in chapter 12.

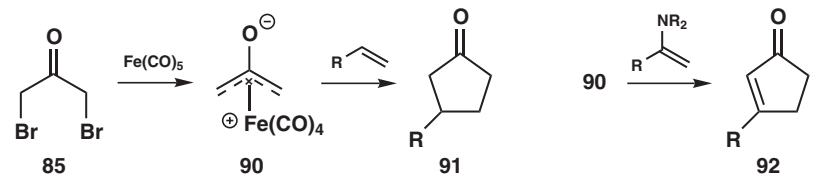


Cycloadditions of $Fe(CO)_4$ Complexes of Oxyallyl cations

These Nazarov approaches add three extra carbon atoms (usually CH_2CH_2CO) onto a ketone to form the five-membered ring. It is also possible to add the three atoms $CH_2CO.CH_2$ onto an alkene to form a cyclopentenone of different structure. The oxyallyl cation **87**, which can be made by the action of a metal, often zinc, to α,α′-dibromoketones **85**, might provide the three carbon atoms. Unfortunately it is a *two* electron system and so adds to dienes **88** rather than mono-enes giving cycloheptenones **89** in good yield.[22]

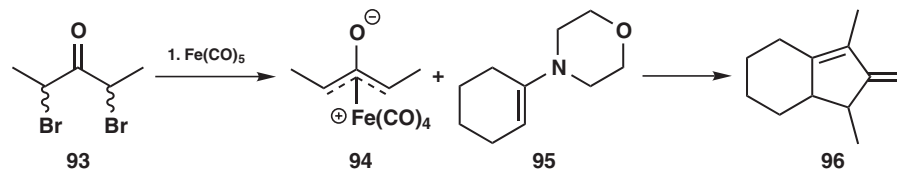


If iron carbonyl is used to generate the oxyallyl cation, the iron supplies two extra electrons in the complex **90** which now adds[23] to mono-enes to give cyclopentanones **91**. We shall see more examples of transition metal complexes altering selectivity later in the book. To get a cyclopent*en*one **92** we need an extra degree of unsaturation, best provided by using the enamine of a ketone instead of a simple alkene.



85 90 91 92

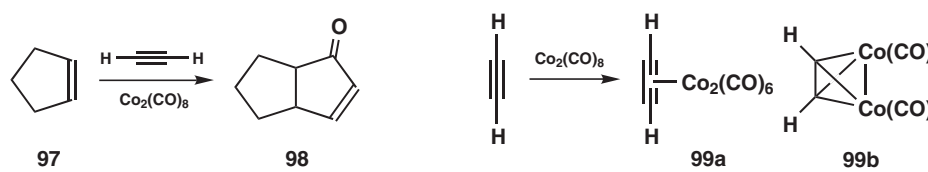
This cycloaddition works best with substituted oxyallyl cations, like the one from the dibromoketone **93** which reacts with the morpholine enamine of cyclohexanone **95** to give the cyclopentenone **96** in excellent yield.[24] You should mark the difference in structure between the Nazarov products, e.g. **70**, formed in an electrocyclic reaction, and these cycloadducts, e.g. **96**. Each strategy has its part to play and must be chosen according to the structure of the target molecule.



93 94 95 96

The Pauson-Khand Reaction

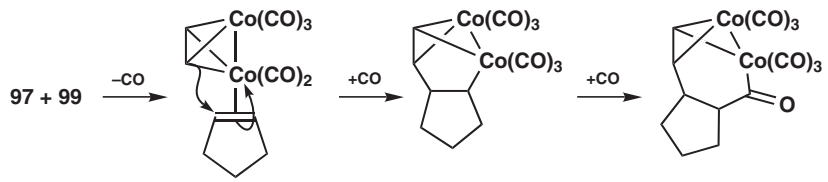
The typical Nazarov strategy **51** followed by **53** disconnects the rest of the ring from the double bond, but you cannot be quite sure where the double bond will end up in the ring. Another special method, the Pauson-Khand reaction,[24, 25] differs in both respects. It adds the enone portion of the ring to the rest of the molecule and you can be quite certain where the new double bond will be. The reaction is between an alkene, say cyclopentene **97**, an alkyne, and $Co_2(CO)_8$ to form a cyclopentenone[26] **98** in one step. A complex **99** is first formed between the alkyne and the cobalt atoms with the two π-bonds replacing two CO molecules (both are two-electron donors). You may see this complex drawn as **99a** but it really has a tricyclic 'tetrahedrane' structure **99b** composed of three-membered rings and with a Co–Co bond.



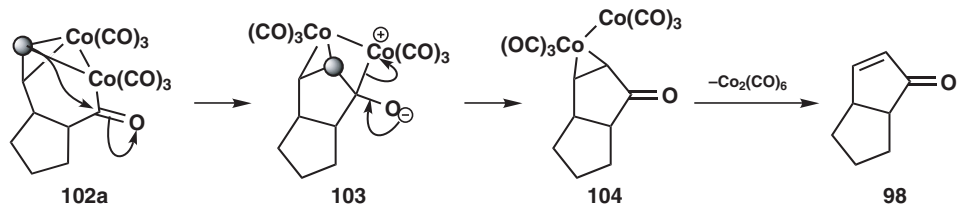
97 98 99a 99b

The π-bond of the alkene then replaces another CO on one Co atom (we hope you are alert to the difference between Co and CO!) to give the π-complex **100**. A returning molecule of CO displaces the alkene from the π-complex and forces it to make the first new σ-bond, between one end

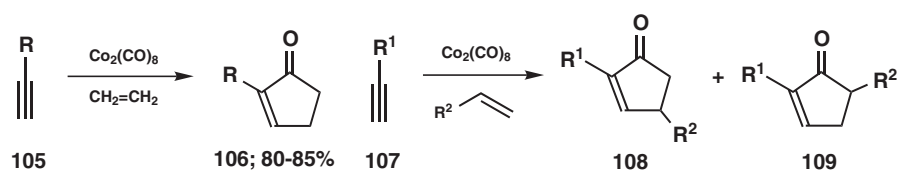
on the alkene and one end of the alkyne, sacrificing one C-Co σ-bond to give the σ-complex **101**. Another molecule of CO returning to the Co atom forces one of the other CO molecules to insert into the Co-C bond to give the acyl σ-complex **102**. This is a standard reaction of organometallic compounds which we shall meet again later.



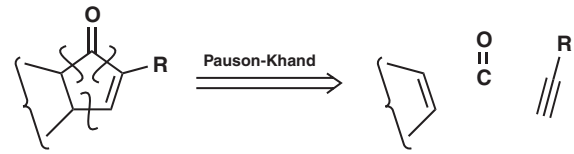
The cobalt-acyl σ-complex **102** is unstable and forms the third and last C–C σ-bond by addition of the carbon end (marked with a blob) of a C–Co bond to the carbonyl group **102a** and decomposition of the adduct **103** with loss of another Co–C bond. The product **104** is an unstable cobalt complex of an alkene so the cobalt atoms drop out of the molecule altogether, leaving a π-bond **98** where the old alkyne used to be. Cobalt carbonyl complexes of alkynes are stable: those of alkenes are unstable. The mechanism **102a** to **103** to **104** is very much an organic chemist's view of things: inorganic chemists may well be sceptical.



There is good regioselectivity with unsymmetrical alkynes, e.g. 1-heptyne **105**; R = n-pentyl forms the 2-substituted cyclopentenone **106** in excellent yield[26] but unsymmetrical alkenes give much poorer selectivity, e.g. 1-octene gives 21% each of the cyclopentenones **108** and **109**; R^1 = n-pentyl R^2 = n-hexyl.[27] It must be admitted that this combined yield of 40–50% yield is more typical than the 80–85% of **106**, but this can be forgiven in a three-component reaction that accomplishes so much. In the formation of the first σ-bond a substituent on the alkyne evidently prefers the blobby position in **102** while substituents on the alkene are indifferent about remaining on the atom joined to cobalt.

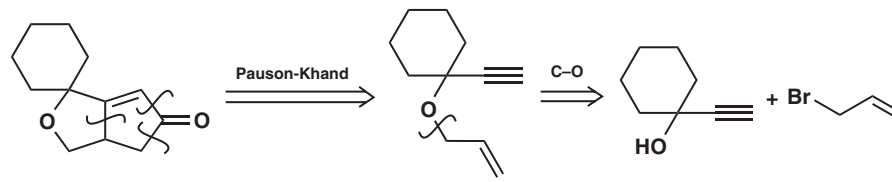


The disconnections are simple **110** but one must look for a symmetrical alkene and make sure that the substituent on the alkyne is next to the ketone.



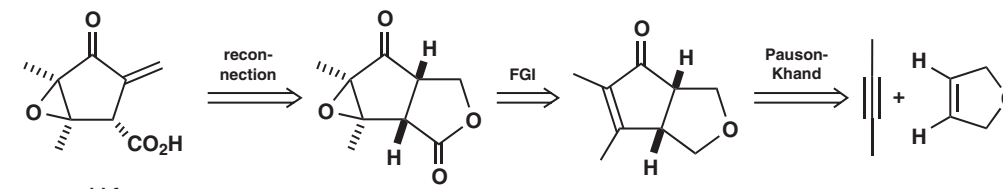
110

Intramolecular Pauson-Khand reactions are often regioselective because it is physically impossible for the molecule to cyclise any other way. Pauson-Khand disconnection of bicyclic **111** reveals an allyl ether **112** of the alcohol **113**, easy to make from acetylene and cyclohexanone. In the cobalt-catalysed cyclisation, only one regioisomer is possible and this, the TM**111**, is formed in an excellent 80% yield.[28]



111 **112** **113**

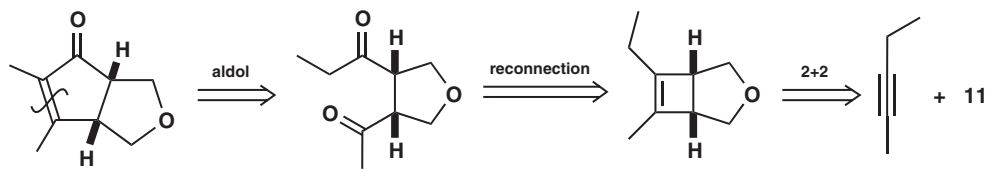
The synthesis of the antibiotic methylenomycin A **114** is instructive on the choice between modern and traditional methods. The key intermediate **116** has been converted into methylenomycin by several groups whose strategy differs only in the synthesis of **116**. The Pauson-Khand disconnection is simplicity itself, requiring the symmetrical unsaturated ether **117** and symmetrical butyne.



114
methylenomycin A

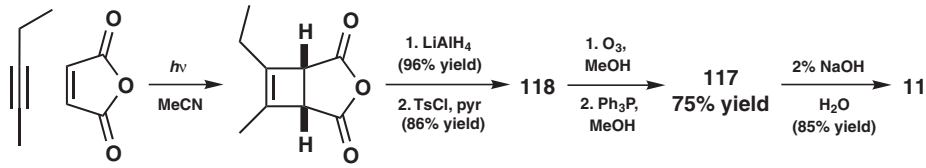
115 **116** **117**

The traditional aldol analysis requires a 1,4-diketone **117** whose stereochemistry suggests a 2 + 2 photochemical cycloaddition[29] also on **117** and oxidative cleavage of the product **118**.



116 **117** **118**

This approach was used by Amos Smith[30] starting with maleic anhydride to get an efficient photochemical reaction. Every step goes in good yield and can be carried out on a large scale, but there are five separate steps and only a 42% overall yield.

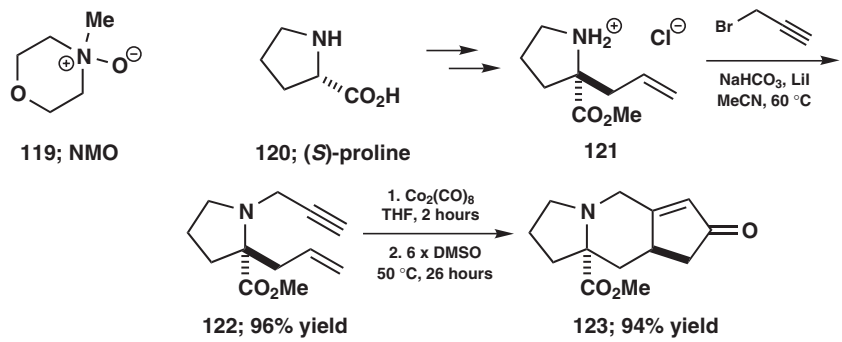


In contrast the Pauson-Khand approach used by Billington[31] is only one step, but gave less than 20% yield when first attempted. Gradually this was pushed up until it was claimed as a 70% yield, but there is a lot of recovered starting material and the conversion is lower. You must make your own choice!

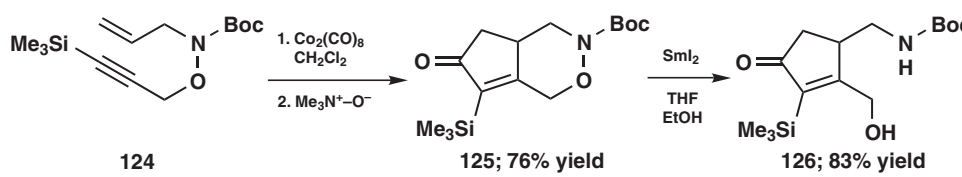
Improvements in the Pauson-Khand procedure using silica support,[28] ultrasound,[26,32] and, best of all, reaction in the presence of promoters such as *N*-methylmorpholine *N*-oxide[33] (NMO) **119** have led to increased yields. Probably most of the yields quoted so far could be improved if this last method were used.

Recent Developments in the Pauson-Khand Reaction

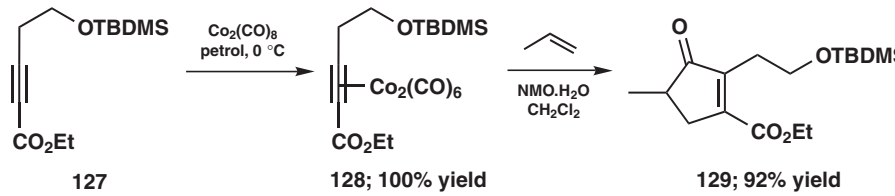
Asymmetry as well as improved procedures has been a high priority recently. The heterocyclic enyne **122** prepared from natural proline **120** gave initially only a 6% yield of the tricyclic amine **123**. Addition of NMO **119** increased this to 72% but DMSO ($Me_2S{=}O$) was the best promoter raising the yield of a single diastereoisomer of **123** to near quantitative.[34]



Since the intramolecular reactions are so much the best, others have linked the alkene and the alkyne by a weak bond that can later be sacrificed. This is the 'tether' strategy you will meet in chapter 36. An N–O bond is ideal and with the alkyne additionally blocked with a silyl group **124**, good yields of Pauson-Khand product **125** and of the amino alcohol **126** could be achieved even with an amine *N*-oxide as promoter. Samarium(II) iodide was used as the reducing agent.[35]

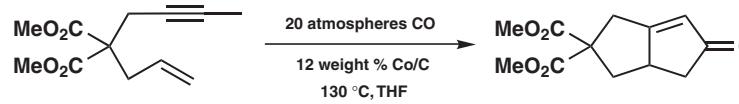


Other recent developments include a high yielding and totally regioselective intermolecular reaction between an unsymmetrical alkyne **127** and propene. The cobalt complex **128** was isolated and treated with propene using NMO hydrate as promoter to give a high yield of the cyclopentenone **129**. The methyl group from propene ends up next to the ketone as expected but the regioselectivity of the alkyne, evidently due to the conjugating ester group, is remarkable.[36]



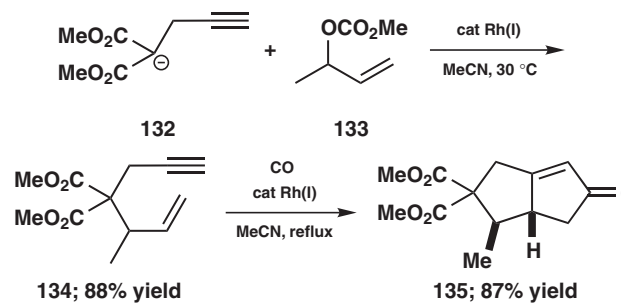
127 **128; 100% yield** **129; 92% yield**

Other catalysts have been developed. Cobalt deposited on charcoal is effective in a range of regioselective intramolecular reactions, though a 20 atmosphere pressure of CO must be used.[37]



130 **131; 98% yield**

In chapter 19 you will meet palladium allyl cations as useful reagents and Evans and Robinson[38] have combined the Pauson-Khand reaction with allyl cation complexes using rhodium as a compromise between Pd and Co. The enolate **132** combines with the Rh(I) cation complex from the allylic carbonate **133** to give the enyne **134** that gives the Pauson-Khand product **135** in 87% yield with the same catalyst but at higher temperatures.

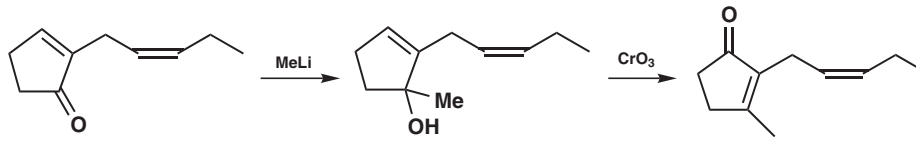


132 **133**

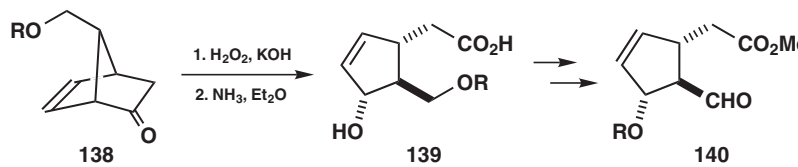
134; 88% yield **135; 87% yield**

Oxidative Rearrangement of Tertiary Allylic Alcohols

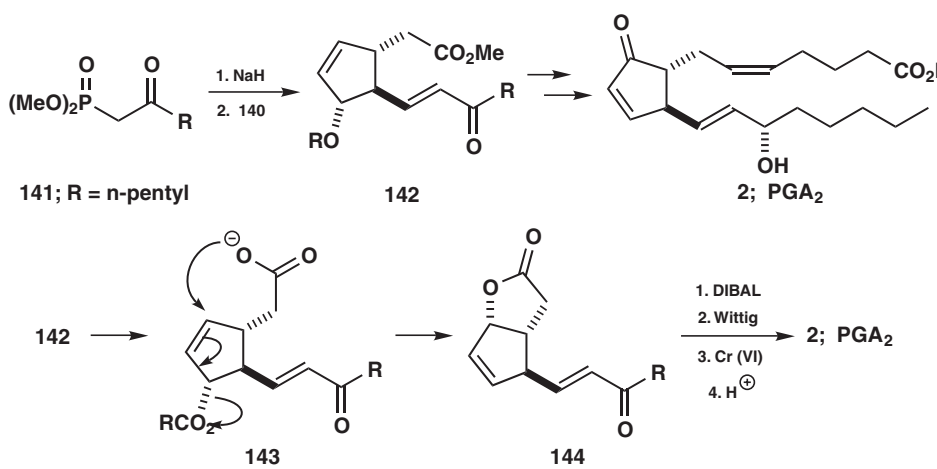
The oxidative rearrangement route (chapter 5) has been used in many syntheses of cyclopentenones. Büchi's route[39] to *cis* jasmone **1** simply involves treating the cyclopentenone **136** with MeLi and oxidatively rearranging the product **137** directly to *cis* jasmone **1**.



The natural prostaglandins, like PGA_2 **2** are usually made by the oxidation of an allylic alcohol.[40] This apparently trivial strategy is used because the stereochemistry around the five-membered ring is easily derived from the bicyclic enone **138** by Baeyer-Villiger rearrangement.[41] Interesting principles of chemoselective oxidation are involved both in the formation of **139** and in the synthesis of the starting material **138**.



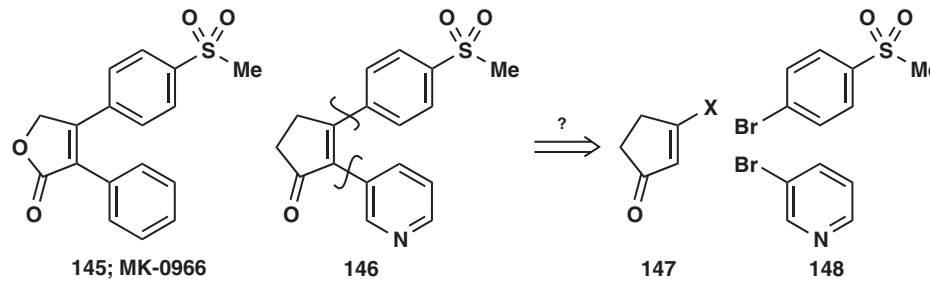
In the PGA synthesis, a Wittig-style reaction puts in one side chain to give **142** which has the wrong arrangement of double bond and OH group. This time oxidation cannot be used to force the rearrangement as the alcohol is secondary, so a displacement is used **143**. This is stereospecific because the incoming CO_2H group is physically constrained to approach from underneath to give the *cis* fused lactone **144**. A reduction and another Wittig reaction complete the synthesis. PGAs are so easily made that they are now used as large scale intermediates in the synthesis of other PGs.[42]



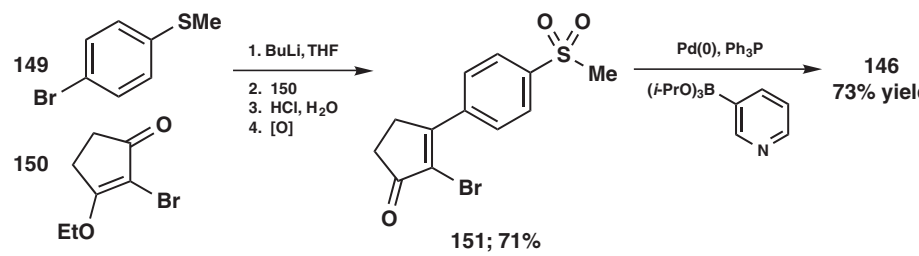
Other Methods

The recent discovery that unsaturated five-membered carbonyl compounds bearing two aromatic rings such as Merck's MK-0966 **145** are new generation anti-inflammatory compounds led

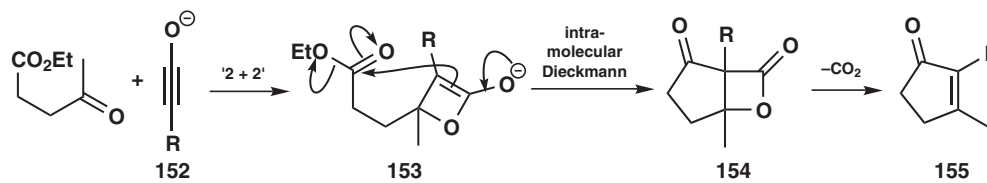
medicinal chemists[43] to make analogues such as **146**. Ideal disconnections would be the removal of the two aromatic rings with the idea that they could be added as organometallic compounds to the two electrophilic sites in **147**. A similar idea was used for a cyclohexenone, compound **95** in chapter 5.



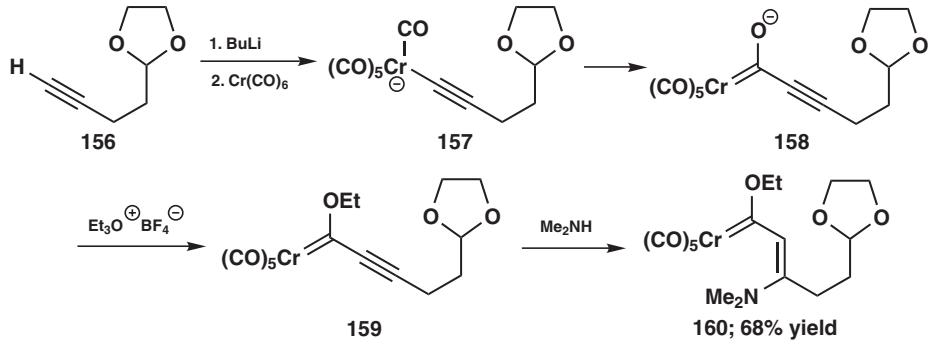
The enol ether **150** was reacted with the lithium derivative of the thioether **149** to give the intermediate **151** after oxidation. A Suzuki coupling, as you will learn to call it, linked the boronic acid derivative of the pyridine to the bromoenone to give the cyclopentenone **146** in just two steps.



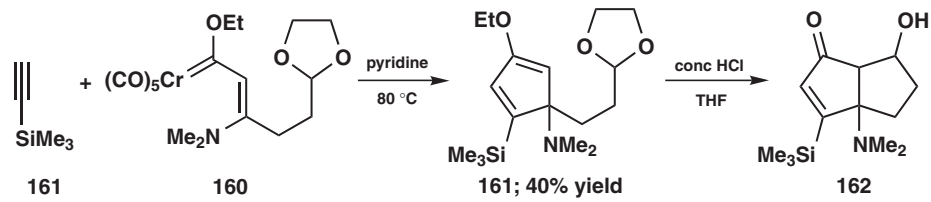
Among the many new methods, one deserves special attention because it is so simple to carry out and yet includes such remarkable reactions.[44] The ynoate **152** reacts with ketones to give four membered cyclic ester enolates that can cyclise **153** onto neighbouring ester groups to give bicyclic keto-lactones **154** that readily lose CO_2 to give cyclopentenones **155**. The origin of **152** and the mechanistic implications of each step are explored in the workbook.



Finally another extraordinary route to nitrogen-containing cyclopentenones using interesting chemistry. de Meijere[45] used chromium carbonyl complexes **160** formed from terminal alkynes **156** via addition to $Cr(CO)_6$, insertion of the alkyne into one of the CO ligands to give the carbene complex **158**, alkylation on oxygen to give **159** and conjugate addition of a secondary amine.



These complexes reacted with a second alkyne **161** without carbonyl insertion to give the cyclopentadiene **161**. This intermediate is also the enol ether of a cyclopentenone and hydrolyses in strong aqueous acid to give a bicyclic compound **162**.



Old and new chemistry provides many ways to make cyclopentenones. This chapter only hints at the richness of modern organic chemistry. As we progress through the book most of these methods will be explained in more detail.

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Section B:
Making Carbon–Carbon Bonds

7 The *Ortho* Strategy for Aromatic Compounds

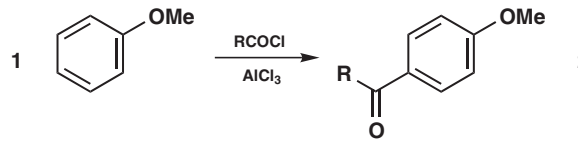
Most of this chapter is dedicated to ortho-*lithiation—a powerful synthetic technique. Part I looks at more traditional methods that do not include lithiation.*

Introduction

Building aromatic compounds by electrophilic substitution using *ortho* and *para* or *meta* directing effects is part of the early training of all organic chemists. Reactions such as the Friedel-Crafts acylation, that efficiently build carbon-carbon bonds between aromatic rings and aliphatic side chains are well known and have been assumed so far in this book. It is usually assumed that the *ortho* and *para* mixtures, that arise when such reactions are applied to activated aromatic rings, are acceptable because they can be carried out on a large scale and separation is usually simple. This may be true for very simple compounds as uses can often be found for the unwanted isomer,

Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

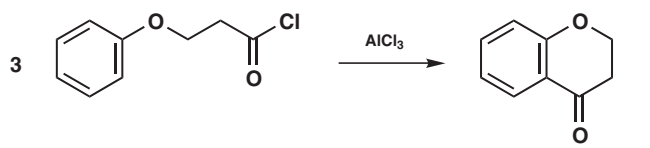
but the modern organic chemist needs ways to control or divert such mixtures into high yields of single compounds. Making the *para* substituted compound is not usually difficult as large substituents direct *para*. Making high yields of *ortho* compounds regardless of the size or electronic nature of the substituents is no such easy matter and is the subject of this chapter.



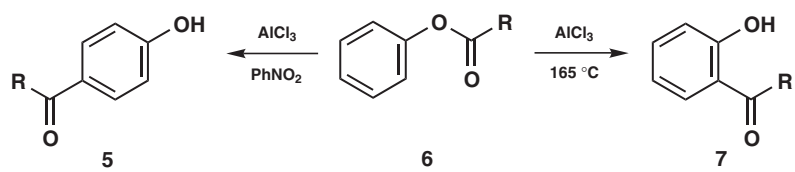
Part I

Friedel-Crafts Reaction and Fries Rearrangement

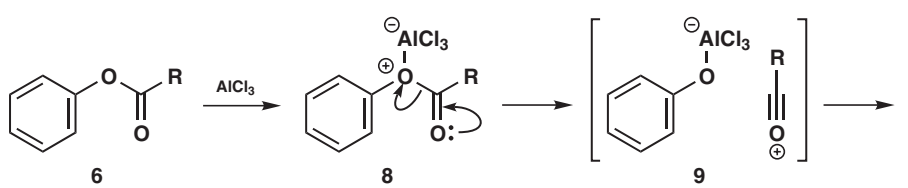
The Friedel-Crafts acylation[1] on simple aryl ethers such as anisole PhOMe **1** usually gives almost quantitative yields of the *para* ketone **2**. If the acid chloride is attached to the oxygen atom by a short chain of carbon atoms (a 'tether') **3** the resulting intramolecular reaction is forced to give the *ortho* product **4**, and these reactions also go in good yield.[2]



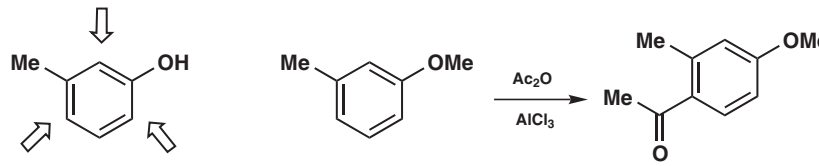
If the acid group is joined directly to the oxygen atom as an ester **6** we have the Fries rearrangement[3] which can be controlled to give either the *para* or *ortho* products. In polar solutions such as nitrobenzene,[4] the *para* product **5** is formed in high yield, e.g. R = Me, 75%, while in non-polar solvents or in the absence of solvent, the *ortho* product **7** is formed in similar yield, e.g. R = Me, 70%.



This is not a concerted rearrangement mechanism of the usual cationic sort, like the pinacol (Chapter 2), but a normal ionic reaction. The Lewis acid catalyses the breakdown of the ester **8** into an acylium ion and a metal complex of the phenol which remain associated as an ion pair **9** in non-polar solvents. This naturally tends to give the *ortho* product as the acylium ion is held close to the *ortho* position by electrostatic interactions. In polar solvents, the ion pair is separated into two independent ions which show the normal Friedel-Crafts selectivity, that is high preference for the *para* product.

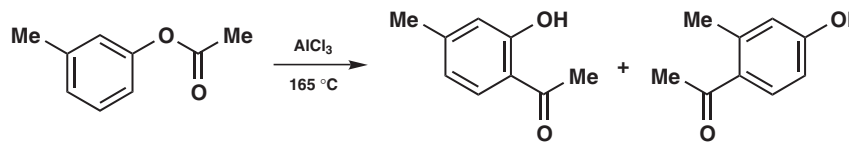


Derivatives of *meta* cresol **10** are even more complicated. Three different sites are activated (arrows on **10**), but Friedel-Crafts acylation of simple ethers **11** favours the position *para* to the ether group almost exclusively, anhydrides being the best acylating agents.[3]



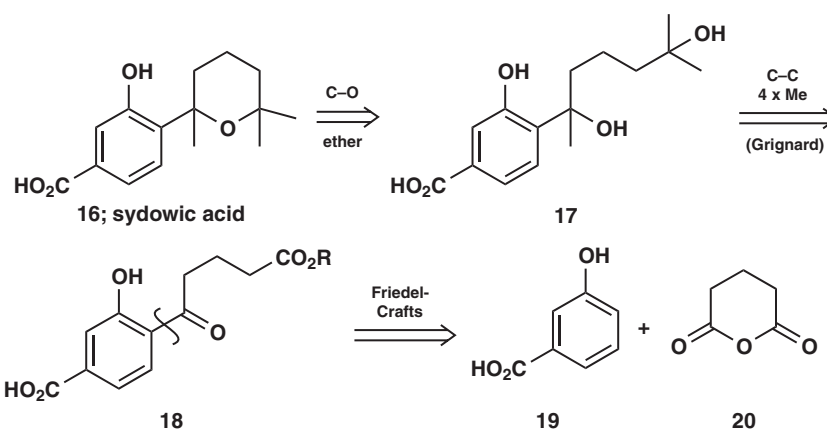
10 **11** **12; 87% yield**

The Fries rearrangement on simple esters **13** by contrast favours one of the *ortho* positions equally exclusively, a very high yield of the ketone **14** being obtained in the absence of solvent.[3,4] In nitrobenzene, 28% of **14** and 64% of **15** are formed.[5]



13 **14; 95% yield** **15**

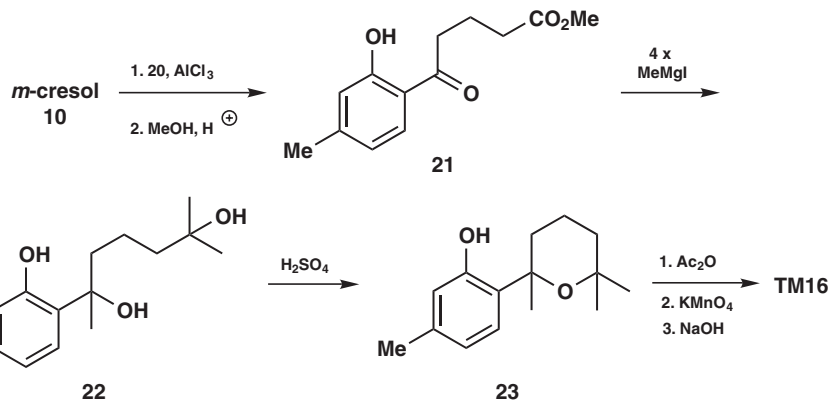
When Rao[6] wanted to make sydowic acid **16**, a sesquiterpene from *Aspergillus sydowi*, he chose to disconnect the ether first and to make the triol **17** by addition of three methyl groups to the keto-ester **18**. This is clearly a Friedel-Crafts product but how are we to get the correct position on the aromatic ring?



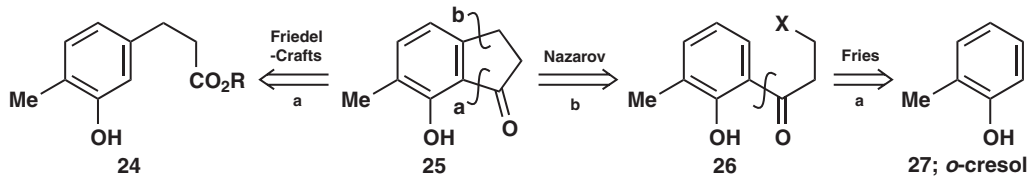
16; sydowic acid **17**

18 **19** **20**

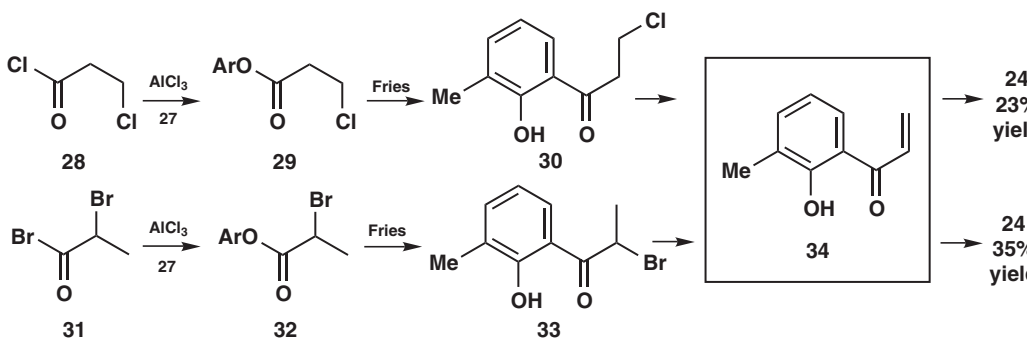
Knowing more about the behaviour of *meta* cresol **10** than of the hydroxy-acid **19** with the same substitution pattern, Rao chose to work at the 'wrong' oxidation level through the Fries, using the cyclic anhydride **20** as the acylating agent. This gave the right isomer **21**, and, by addition of *four* molecules of methyl Grignard (one is used up by the free OH group), and acid-catalysed cyclisation, the intermediate **23**. Sadly, direct oxidation destroys the phenol, so it must be protected as an ester. This short synthesis involves regioselectivity twice: the obvious *ortho* Fries selectivity and regioselectivity again in the formation of a six- instead of a four- or eight-membered ring in the cyclisation of **22**.



The remaining site in *meta* cresol **10**, between the OH and Me groups, is very difficult to get into, as is commonly the case when one tries to insert a largish substituent between two others which are already there. A better strategy is usually to put two next to each other and add an outside substituent last. When Wiesner[7] was planning the synthesis of some delphinine alkaloids, he required the indanone **25** as a starting material in large amounts (150 g scale). The Friedel-Crafts disconnection of **25** would require an acylation of **24** between two substituents and will not give **25**.



Indanones are an aromatic variety of the cyclopentenones we were considering in Chapter 6, and the Nazarov strategy looks appealing as it becomes a Friedel-Crafts reaction on *ortho* cresol **27** with the acid chloride of acrylic acid. The problem is to make the reaction give just that isomer, that is the one having *four* adjacent substituents. The Fries rearrangement is the answer as it transfers the acyl group to the next carbon atom round the ring and the alkylation step has to occur at the next *ortho* atom in turn. The unsaturated acid chloride is too reactive, but either of the halides **28** or **31** will do the trick.[7,8]

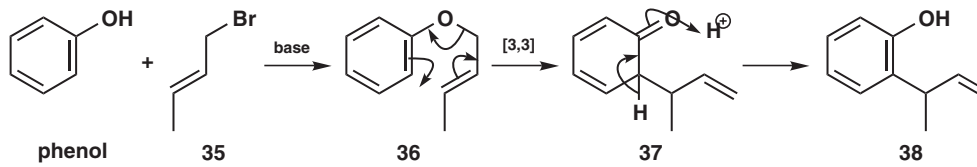


The yields are not wonderful, but this is the first step and it accomplishes a lot in one reaction. Presumably either haloester or the haloketones **30** or **33** derived from them can form the double

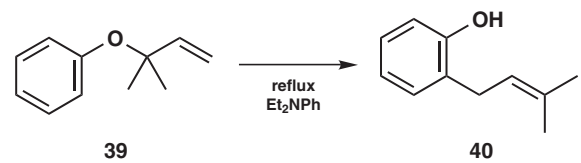
bond under the reaction conditions so that the Nazarov intermediate **34** is formed and cyclised by the same Lewis acid.

The Claisen Rearrangement

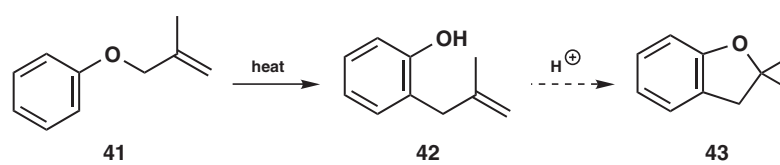
One reaction much used to produce the *ortho* relationship is the Claisen rearrangement.[9] An allyl ether **36** from a phenol and an allylic halide **35** undergoes [3,3] sigmatropic rearrangement to give an intermediate **37** that is the "keto form" of a new phenol **38** with the allyl group now in the *ortho* position.



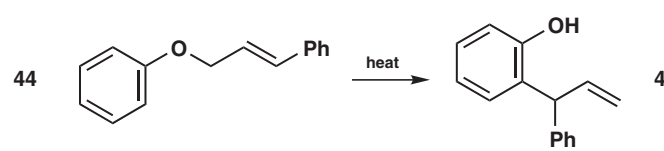
The rearrangement is regiospecific with regard to the allyl portion, substituents starting next to the oxygen atom **39** finishing at the far end of the double bond **40**. This example is particularly favourable as the double bond becomes more highly substituted as the reaction proceeds.



Substituents in the middle of the allyl system **41** produce no regioselectivity problem, but the products **42** are rather inclined to cyclise to ethers **43** by protonation of the double bond.[10]

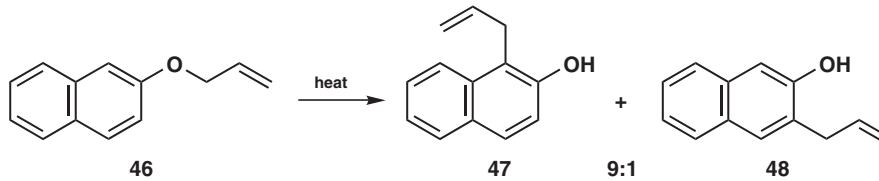


Substituents which start at the end of the double bond should finish next to the ring: the formation of **45** is a particularly impressive example as the double bond moves out of conjugation. These are the most tricky type of Claisen rearrangement and other products can be formed if conditions are not carefully controlled.[9]



There can be some regioselectivity if there are two different *ortho* positions. This is usually attributed to 'double bond fixation' as in the naphthalene **46** where the structure drawn represents

more than just a Kekulé form. The bonds marked double are shorter than those marked single and the products are 9:1 in favour of migration to the 'better' ring double bond in **47**.

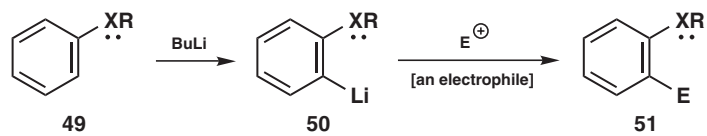


The side chain produced by the Claisen rearrangement contains a useful alkene that can be elaborated by epoxidation, for example, and the reaction is slightly more versatile than it appears at first sight.

Part II

Using Lithium

So far, the only metal in sight to help us form aromatic compounds has been aluminium. Now we look at a metal that activates aromatics in an entirely different way—lithium. Lithium is introduced *ortho* to a ring substituent that already exists **50** and the process itself called *ortho*- or directed lithiation.

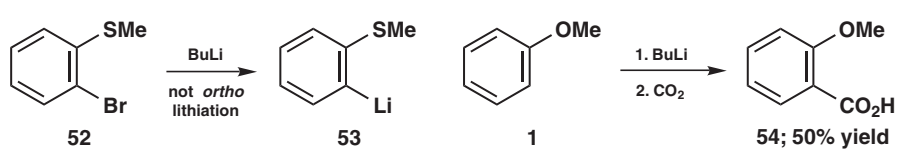


Ortho-lithiation

Before we go any further we should be clear that *ortho*-lithiation is a proton-lithium exchange reaction and is not to be confused with halogen-lithium exchange. For instance, the exchange of bromine for lithium in **52** occurs, it just so happens, next to another substituent. But to call that reaction an *ortho*-lithiation would be misleading because we would not want to imply that the methylsulfanyl group had anything to do with it – the bromine will exchange whether the sulfide is there or not.

Anisole

We have already seen how anisole **1** may be functionalised by using a Friedel-Crafts reaction. Anisole is a simple, perhaps the most simple, functionalised benzene ring that can be lithiated by *ortho*-lithiation. We use it here to introduce the reaction.

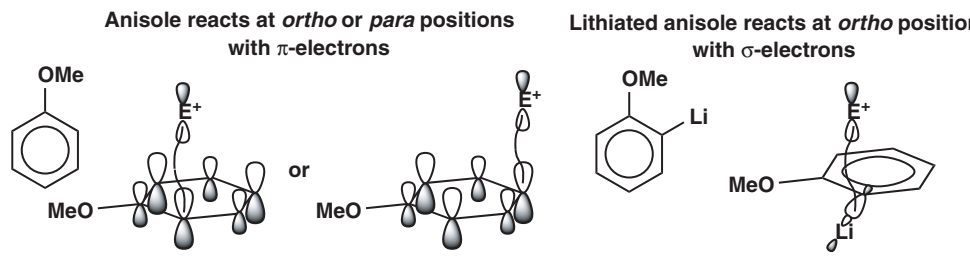


Firstly, let us consider the substituent *ortho* to the newly introduced lithium. The *ortho* directing group here is a methoxy group and within it is the oxygen atom that is doing the work. Without concerning ourselves with the mechanism of the reaction too much at this stage, the lone pair on the oxygen atom coordinates to the organolithium reagent. Notice that the oxygen is attached directly to the ring – anisole is a phenyl ether. We shall see examples later where the heteroatom is more remote. The group which directs the lithiation we shall refer to as the '*ortho*-director' although it is called other things by different authors (DMG for Directed Metallation Group for instance).[11]

Regioselectivity I—The ortho versus para question

Even without lithium, the reactivity of aromatic rings is nucleophilic. But the source of that nucleophilicity is very different when a lithium atom is in place. The lithium atom does more than dramatically increase the reactivity of the benzene ring, it alters its character entirely.

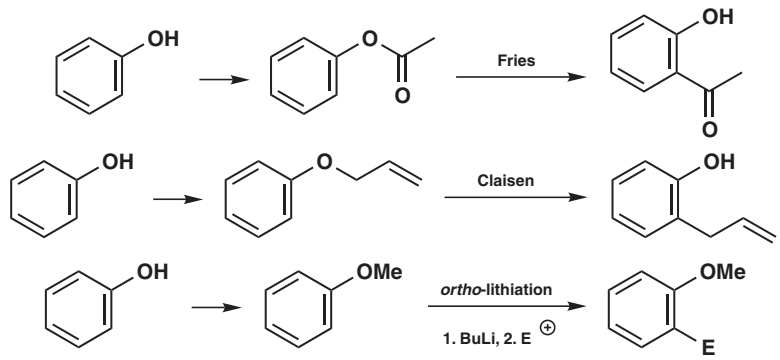
When benzene reacts with an electrophile like NO_2^+, it is the π electrons of the ring that attack the electrophile and the aromaticity of the benzene ring is necessarily disrupted. Any one of six carbon atoms may be the focus for the attack on NO_2^+, it makes no difference. With a substituted benzene ring, we know that some sites are more reactive than others due to the influence of the substituent – usually the *ortho* and *para* positions. But with a lithiated benzene ring the situation is different. Now the attacking electrons are not π but σ. They are localised and have no choice as to which carbon atom they attack from. And it doesn't matter if the substituent increases the π-electron density a little at this or that carbon because it will not compete with the full negative charge from the C-Li bond. A 'full negative charge' would imply that we have an anion. This is not the case but organolithium reagents are carbanion σ-complexes (chapter 8). Once the lithium atom is in place the reaction with electrophile is regiospecific.



But what about where the lithium atom goes in the first place? If, as is usually the case, the directing substituent coordinates to the organolithium reagent, then the reaction is directed to the *ortho* position and the introduction of lithium is regiospecific. The organolithium reagent cannot reach any further round the ring. We shall deal with two competing *ortho* positions and more exceptional cases later but for now *ortho*-lithiation means what it says.

Directing groups

The Fries and Claisen rearrangements need an oxygen atom next to the site where the new bond is to be formed. From a strategy point of view, it's good to start with your oxygen in place because it can be difficult to introduce.[12] *Ortho*-lithiation strategy can make use of an oxygen substituent too, but it also works extremely well with other directing groups. The nature and diversity of these other directing groups gives *ortho*-lithiation very broad scope and makes it a powerful reaction. After all, not all aromatic target molecules have C–O bonds of any kind, let alone Ar–O bonds next to another substituted position.



As we now discuss these other directing groups, it would be a good time to consider the mechanism of the reaction more closely. We should then understand why some groups work better than others and be able to predict which ones will make a successful synthesis.

There are two basic aspects to the function of any directing group. It may—

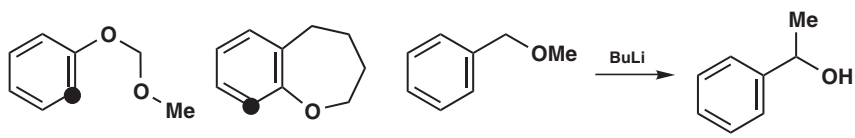
i) coordinate to the lithium reagent
ii) increase the acidity of its neighbouring hydrogen atoms.

Both aspects may be operative, as they are in the case of anisole for instance, but they need not *both* be present in the director. A director which does not coordinate to lithium must acidify the positions next to it considerably if it is to be effective. We shall see that fluorine is such a substituent. Conversely, if the hydrogen atoms are not activated in any way by the director then it must compensate by being a very effective donor to lithium.

The consequences of having two different directing groups, one which relies upon mostly coordination and the other which relies upon mostly increased acidity, are discussed in *Regioselectivity II* later.

Directing groups containing oxygen

We have already seen that oxygen directs lithiation in anisole **1** very effectively. Here are two more examples of aromatic compounds **55** and **56** with an oxygen substituent that can be lithiated at the marked atoms. But oxygen (unaccompanied by any other heteroatom) is a very *poor* director of lithiation when it is any further away from the ring. Attempts, for instance, to direct a lithiation within methoxybenzyl ether **57**, fail. Deprotonation at the benzylic position occurs instead and the molecule undergoes a Wittig rearrangement. Utilising a benzyl oxygen atom *alone* is bad strategy – if it is used it must be done in conjunction with another directing group.

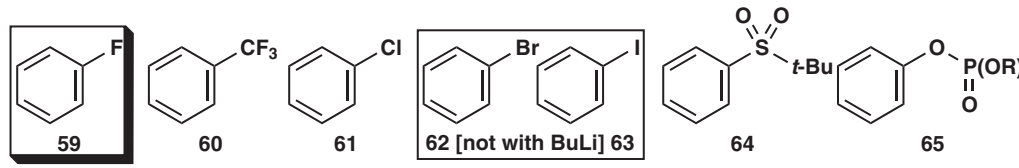


55 **56** **57** **58; 26% yield**

There are plenty of other groups which are known to be *ortho*-directors. The halogens can behave as *ortho*-directors and fluorine is perhaps the best (which is why it is in a box in the figure). However, if you were attempting to use either bromine or iodine as an *ortho*-director then you'd better watch out. It would be essential not to use butyl lithium as the lithiating reagent—they

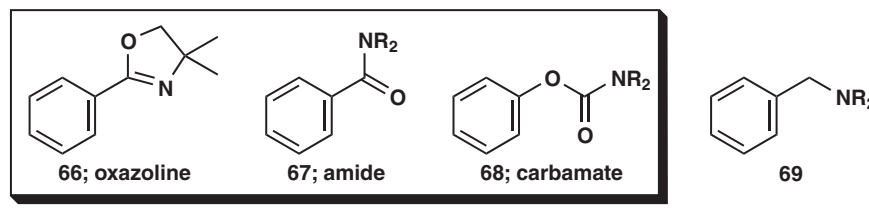
would simply undergo a lithium – halogen exchange instead. Sulfones **64** and phosphates **65** are also known as *ortho*-directors but then anything which either acidifies protons at the *ortho* position or would bind to an alkyl lithium reagent placing it next to an *ortho* proton has . . . well, at least the *potential* to behave as an *ortho*-director.

Halogens, sulfones and phosphates

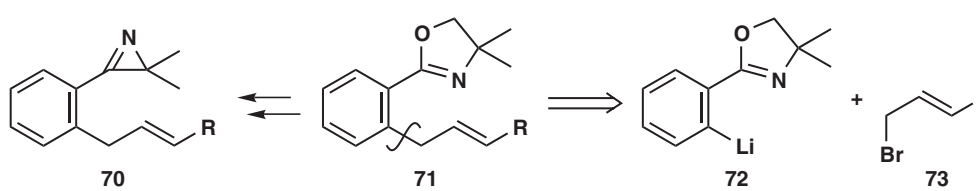


Directing groups containing nitrogen

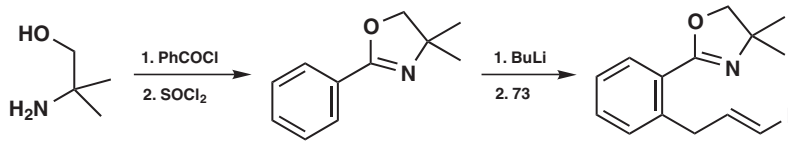
Oxazolines **66**, amides **67** and carbamates **68** are the three kings of the *ortho*-director world. These are the most widely used *ortho* directing groups and among the best. Best means that they not only give high yields but that their action is reliable. We shall also see that they are usually easy to introduce and versatile in subsequent reactions. Be careful to note the difference between an amide and a carbamate – they look very similar when their structures are not drawn out in full ($CONR_2$ vs. $OCONR_2$). Although benzylic ethers often fail in *ortho*-lithiation reactions due to the Wittig rearrangement, benzylic amines **69** are fine. They do not, however, approach the generality of the 'three kings'.



Oxazoline **71** is an intermediate in the synthesis of the azirine **70** which was used in investigations into cycloaddition reactions.[13] Let's consider how we would make the oxazoline. Clearly we can disconnect the bond between the aromatic ring and the side chain to reveal **72**, the lithium derivative of oxazoline **75**, which can be coupled with an electrophilic side-chain.[14]



The synthesis is straightforward. The oxazoline **66** directs the *ortho*-lithiation and then the lithium derivative is reacted with an allyl bromide. One thing we did not consider in the analysis was the synthesis of the oxazoline itself and perhaps we should. One way to make oxazolines (and there are many) is to react an acid chloride with an amino alcohol **74** followed by thionyl chloride.

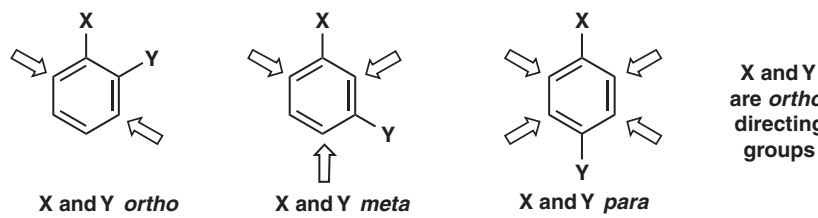


74 66 71

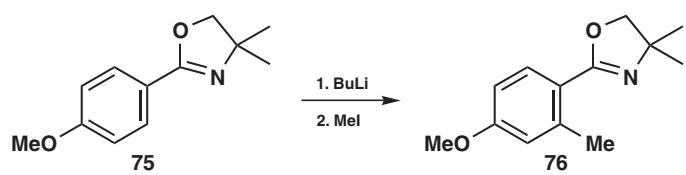
Oxazolines are versatile functional groups. It is entirely possible for one *ortho*-director to direct the introduction of a new group that is then an *ortho*-director in its own right. This leads to all sorts of interesting possibilities and is discussed in **Several Lithiations**.

Regioselectivity II—ortho versus ortho

What happens when there is more than one directing group on the same ring? There are of course two fundamental possibilities – either they compete or they work together. There are three basic substitution patterns because the second directing group can either be *ortho*, *meta* or *para* to the first.

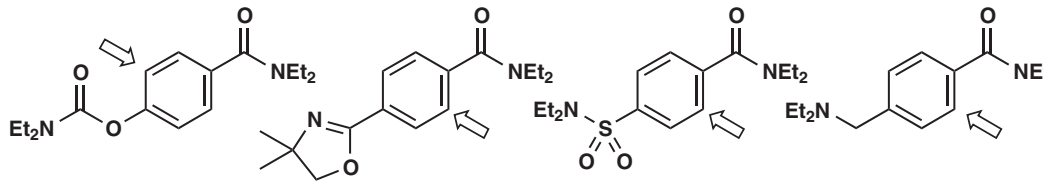


There are two '*ortho*' positions in the first case, three in the second, and four in the third. We notice, of course, that although all four sites in the *para* case can react, there are only two different sorts of proton due to the plane of symmetry. The *para* substitution pattern is the example we look at first. Oxazoline **75** has two *para* related *ortho*-directors and two possible sites for lithiation on the ring. We can clearly see from the result that the oxazoline ring was the more potent director because the product **76** has the new methyl group *ortho* to it rather than *ortho* to the methoxy group.



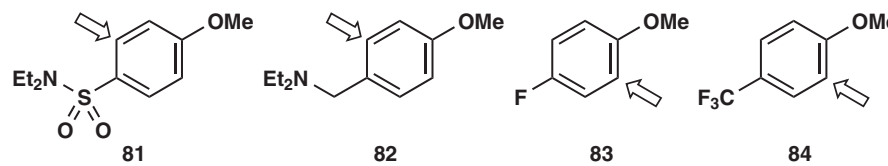
75 76

In general, if one of the directing groups is much more potent than the other, we would expect that directing group to direct lithiation *ortho* to itself. And that is indeed what we see although the situation is, in fact, more complicated than this because in some cases we can *choose* which group we would like to lithiate next to. This issue is discussed later. Direct comparison between an amide and other *ortho*-directing groups in compounds such as **77** to **80** reveal that only a carbamate is a more powerful director than an amide while oxazoline, sulfonamide and benzylamine etc. are less powerful.[11,15]



77 78 79 80

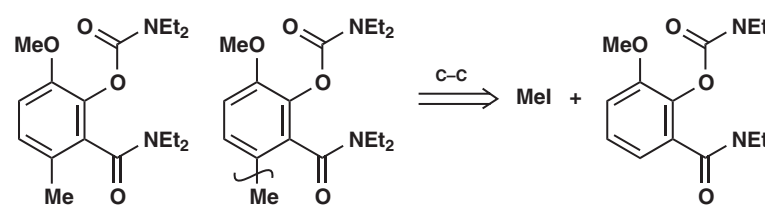
In the same way, direct comparison with other groups[15] shows that the simple methoxy director is less powerful than a sulfonamide **81** or a benzylic amine **82**, but more powerful than F, CF_3, NR_2, or $(CH_2)_2NR_2$.



81 82 83 84

Multiple Directed Lithiations

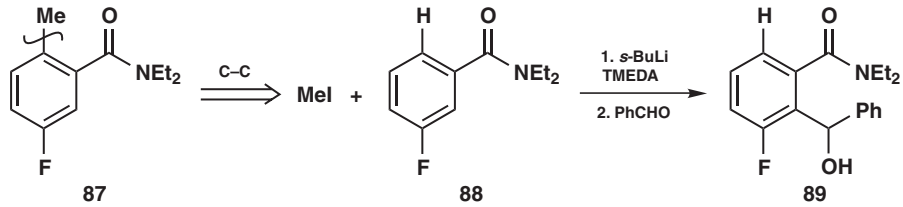
Let's consider how we might make compound **85**. For a start three of the four groups on the aromatic core are good *ortho*-directors. We have just seen that an amide is a more powerful directing group than a methoxy group so we can safely disconnect the methyl group **85a** in the knowledge that the lithiation of **86** will go where we want it to. The synthesis is really very easy. The reaction of **86** with *sec*-BuLi and TMEDA followed by methyl iodide yields the compound we want.



85 85a 86

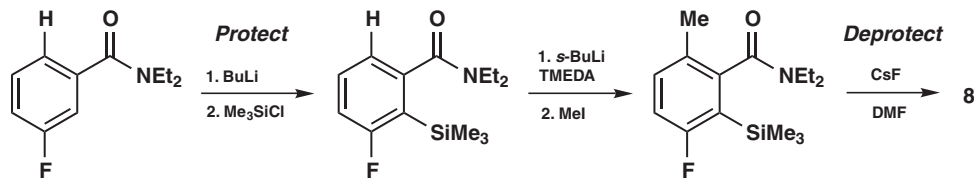
Further, a carbamate – the most potent *ortho*-director of the three – sits in between the other two. This can be used. We will come back and look at this compound again in the next section and disconnect it further but apply another concept to its analysis – that of multiple *ortho*-lithiation. For now we restrict ourselves to the one disconnection.

The amide **87** contains two *ortho*-directing groups—the amide and the fluoride. The methyl group could be introduced by reacting a lithium derivative with methyl iodide. However, this is where we run into trouble because the lithium atom will not be introduced where we want it to be. Since both fluoride and the amide are *ortho*-directors and since they are *meta* substituted then they can cooperate with one another. This was illustrated with a reaction done with benzaldehyde.



87 88 89

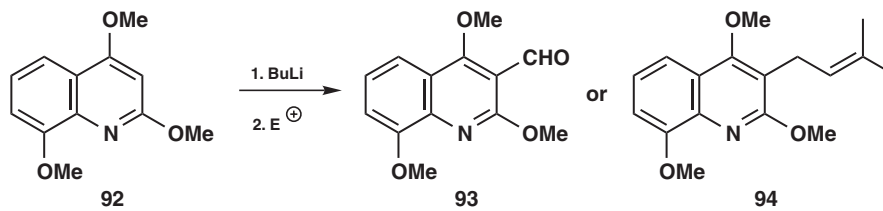
We could, of course, use a protecting group to block the position between the two *ortho*-directors. There is now just one thing to consider – which of the two remaining *ortho* positions with be lithiated. The amide is a better director than the fluoride so there is no problem – the lithiation goes the way we want it to.[16] The protecting group that we use is trimethylsilyl. The lithiation is then achieved using *sec*-BuLi and TMEDA and the lithium derivative reacted with MeI. Deprotection of the silyl group is done using a source of fluoride which is CsF in this case.



88 90 91

The fact that the two groups cooperate with one another needs to be emphasised. From our experience of chemistry we might expect a proton between two other groups to be more difficult to get at. This is not true with *ortho*-lithiation and with a *meta* substitution pattern you can expect cooperation.

Quinolines such as **92** have been widely used in the synthesis of alkaloids. We might imagine that almost any position in **92** could be lithiated, but the position between the two MeO groups is preferred. When the electrophile is $Me_2C{=}CH.CH_2Br$ the product is **94**, and when it is $R_2N.CHO$ the aldehyde **93** is produced. Each of these compounds was developed into γ-fagarine, from **94** starting with ozonolysis,[17] and from **93** by a Wittig reaction.[18]



92 93 94

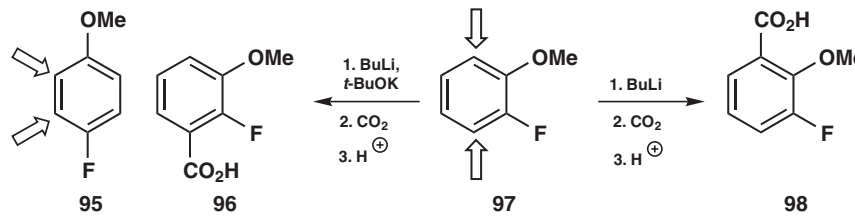
Choice in ortho-*lithiation*

In some cases we can *choose* which group we would like to lithiate next to. This choice arises from the two mechanisms that directing groups use and is one of the more subtle aspects of directed lithiation. Perhaps the best evidence for these different mechanisms is the change in regioselectivity with competing directing groups when the reaction conditions are changed.

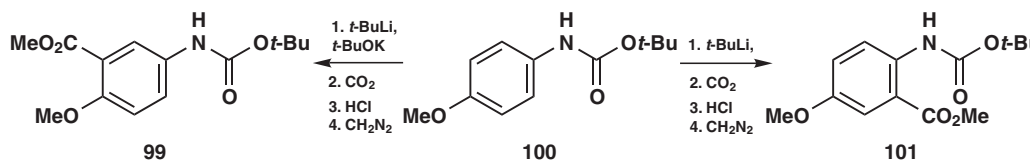
Reactions of Fluoroanisoles

Fluoroanisoles **95** and **97** each have two different sites that could be lithiated.[19] In each case, the site next to oxygen can be lithiated if a coordination mechanism is operative and the site next to fluorine can be lithiated if an acid-base mechanism is operative. If *ortho*-fluoroanisole **97** is

reacted with BuLi followed by solid CO_2, the product is exclusively the carboxylic acid **98**. However, if it is reacted with a mixture of BuLi and potassium *tert*-butoxide followed by solid CO_2 then the product is – again exclusively – the regioisomer **96**.

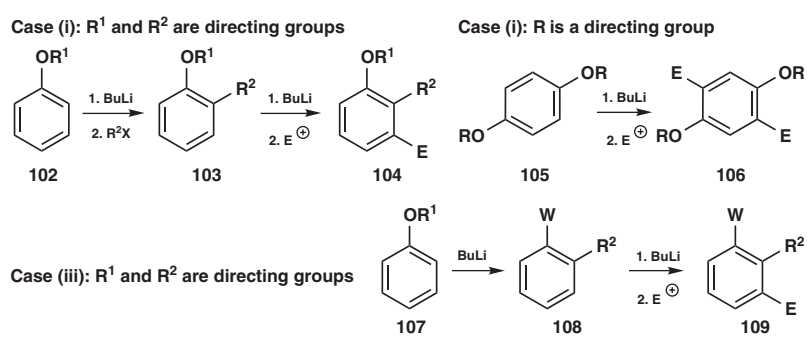


The situation is, however, even more subtle than this. Not only is it possible to exploit the difference between an acid-base mechanism and a coordination mechanism, it is also possible to choose between one coordinating director and *another* coordinating director.[20] This is the case with **100**. Both the nitrogen and oxygen atoms have the potential to coordinate to lithium. In a 'superbasic' mixture BuLi and KOBu^t, the lithiation proceeds next to the most electronegative atom – oxygen **99**. The reagent is not bothered about coordination but just plucks off the most acidic proton – the one next to the most electronegative atom. When BuLi is used on its own, the lithiation proceeds next to the nitrogen atom **101**. Nitrogen coordinates lithium better than oxygen and so in this case the reaction goes via a coordination mechanism.[20]



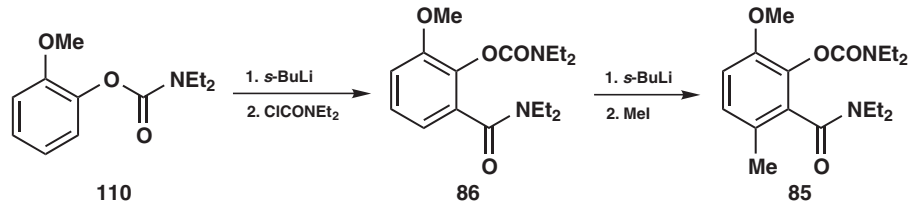
Several lithiations

One powerful aspect of *ortho*-lithiation strategy is the ability to do more than one lithiation on the same ring. Exactly how this is done varies. One might imagine a situation where – i) The new group introduced by *ortho*-lithiation to give **103** can itself direct a further *ortho*-lithiation. ii) There could be two directing groups on the ring in the first place **105** and they may be able to direct two lithiations to make a dilithiated ring. And iii) the lithium derivative reacts intramolecularly with its *own* directing group to yield a product **108** with a *different* directing group and new functionality at the position of the original directing group (W). If the last example sounds a bit complicated, all will become clear with examples of the three types.[15]



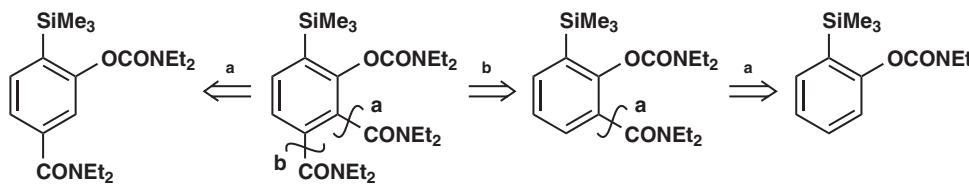
Case (i) One ortho-director leads to another

The carbamate **110** reacts with *sec*-butyl lithium followed by Et_2NCOCl to yield the new amide **86**. This reacts with *sec*-butyl lithium and methyl iodide to give the tetra-substituted aromatic compound[21] **85**.



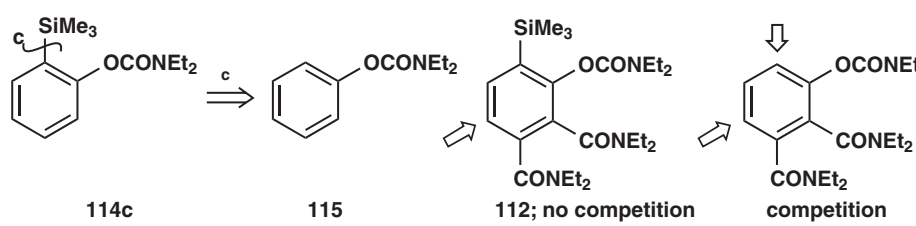
110 **86** **85**

The tetrasubstituted benzene **112** was synthesised by multiple *ortho*-lithiations. Three of the four groups are *ortho*-directors themselves. The question of which group to disconnect first is not simplified in this case by the knowledge that the group must be introduced by an adjacent *ortho*-director because *all* the groups are adjacent to at least one other. Let's consider disconnection **a**. The forwards reaction from **111** would not lead to a problem of regioselectivity because the two *ortho*-directors direct lithiation to this site. The problem is which *ortho*-directing do we disconnect next? We do not have two adjacent directing groups so we cannot use one to introduce the other. This forces us to adopt an alternative strategy sometimes referred to as a 'walk around the ring'.



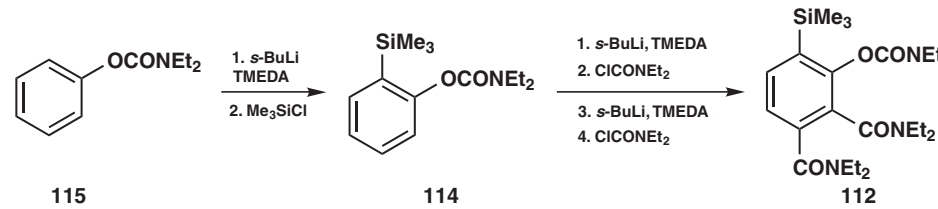
111 **112** **113** **114**

We start **b** at one end of the three *ortho*-directors and disconnect them successively. After two disconnections we are left with the carbamate **114**. The silyl group will be introduced by *ortho*-lithiation too. The introduction of the silyl group stops the sequence of *ortho*-lithiations proceeding in an anti-clockwise manner and hence prevents any competition that might otherwise arise after the between the carbamate and the amide in subsequent *ortho*-lithiations.



114c **115** **112; no competition** competition

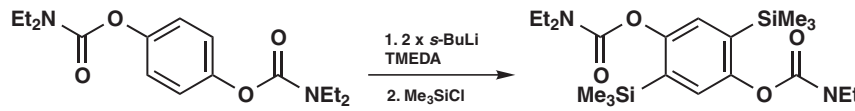
The three lithiation reactions use *sec*-BuLi and TMEDA. Trimethylsilyl chloride is the first electrophile and diethyl carbamoyl chloride is used twice to give our target material **112**.



115 114 112

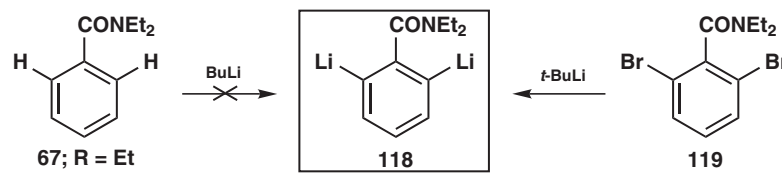
ii) Dilithiations

True dilithiated species generated by *ortho*-lithiation in which there are two lithium atoms on the *same* ring are very rare (with dilithiated species formed by halogen/lithium exchange being more common). It is not a surprise that in those examples where dilithiated species *do* exist[22] the lithium atoms are usually *para* to one another **117**.



116 117; 67% yield

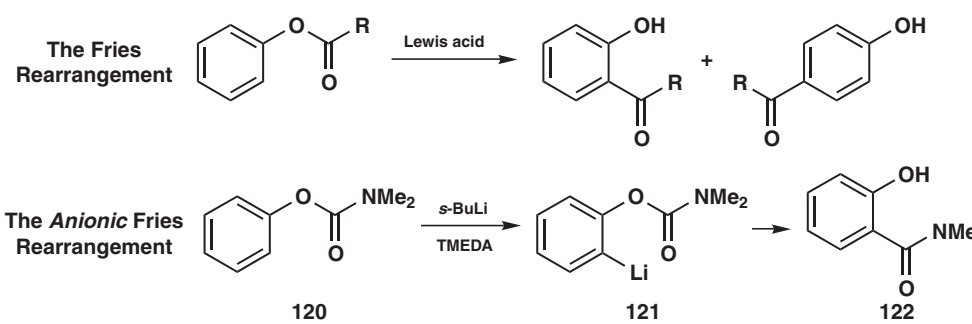
Putting two lithium atoms closer together is more difficult and while the 2,6-dilithium derivative **118** can be made, it cannot be made by double *ortho*-lithiation of **67**; R = Et. Instead it must be made from dibromide **119** and *tert*-BuLi.



67; R = Et 118 119

iii) One ortho*-director rearranges into another – the anionic Fries reaction*

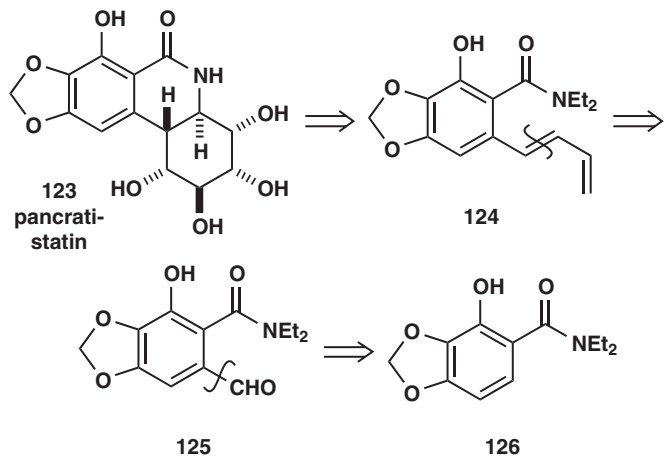
We have come across the Fries rearrangement previously in this chapter before lithium had even made its entrance. A similar rearrangement can occur in the realm of *ortho*-lithiated species and is sometimes call the anionic Fries rearrangement. Compare the two.



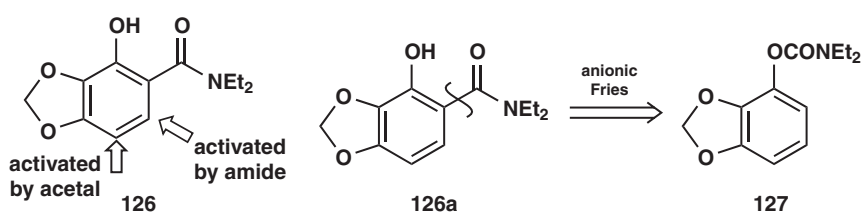
120 121 122

The carbamate **120** is lithiated with *sec*–butyl lithium to form the intermediate **121** that reacts further to form the amide **122**. From the *ortho*-lithiation point of view we now have a different *ortho*-director in the molecule and, if we protect the phenol group, we can continue lithiation around the ring. This chemistry was used in the synthesis of the diene **124** needed for the anti-tumour compound pancratistatin[23] **123**.

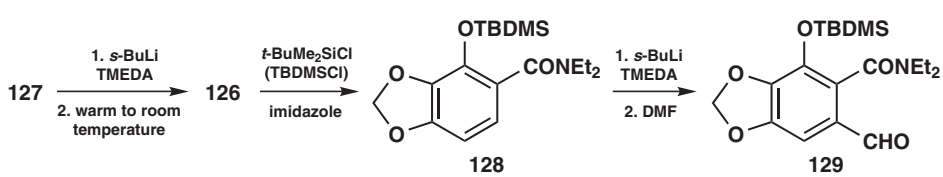
Disconnection of **124** across the double bond closest to the ring reveals the aldehyde **125**. This aldehyde can be introduced by the action of an *ortho*–lithium species (as the dialkylamide in **126** is a good *ortho*-director) on a formylating reagent.



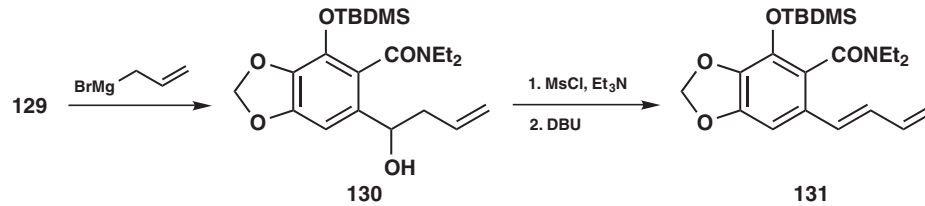
The amide is a good *ortho*–director but so is the acetal function. The regioselectivity (actually there is the issue of chemoselectivity here too) of the lithiation reaction will depend upon which of the two is the more potent. Amides were one of our 'three kings' of the *ortho*-directors and are more powerful than acetals. Now it is time for an anionic Fries rearrangement (in the retrosynthetic direction) to give the starting material **127**.



We *ortho*-lithiate **127** using *sec*-BuLi and TMEDA. The lithiation goes where we want it – *ortho* to the carbamate rather than *ortho* to the acetal. The lithiated intermediate is then allowed to warm up – we will come back to this in a moment – to yield phenol **126**. This is reacted with TBDMSCl and imidazole to give the protected phenol **128**. Once again, the acetal loses out and the amide does the directing during the second lithiation. Formylation is achieved using DMF.



The aldehyde **129** is attacked using allyl Grignard. The alcohol **130** is converted to the mesylate and then an elimination reaction using DBU as the base gives diene **131**. The protecting silyl group can easily be removed to give **124** but in fact it was retained for protection during the rest of the synthesis.



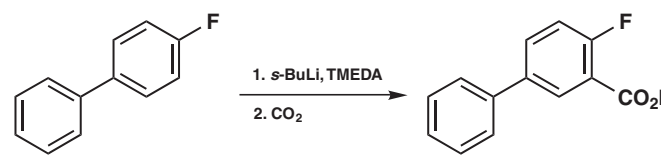
130 131

It is important to recognise the element of *choice* that exists in the anionic Fries rearrangement. After the initial lithiation of **127** we can *either* let it warm up and do the rearrangement *or*, if we are careful, we can keep it cold so that the rearrangement does not take place and we can introduce another electrophile to react with the intermediate lithiated compound instead.[11]

Halogens

Fluorine as an ortho*-director*

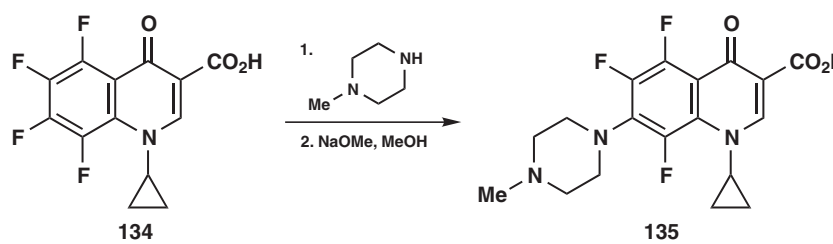
Fluorine is a good *ortho*-director.[24] It directs the lithiation of fluorobiphenyl without the assistance of another directing group and does so very efficiently.



132 133; 79% yield

Fluorine as a leaving group

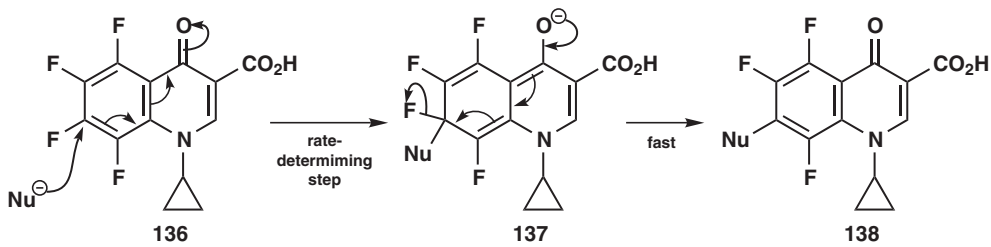
Fluorine can also function as a leaving group from aromatic rings.[25] The C—F bond is very strong and it would be misleading to describe fluorine as a *good* leaving group (even though many of the reactions in which it leaves *are* good). Nucleophiles attack because the *ipso* carbon is made electrophilic by the strongly electronegative fluorine. In compound **134** there are four fluorine atoms on the benzene ring: one is displaced by nucleophiles to yield the quinolone antibiotic[25] **135**.



134 135

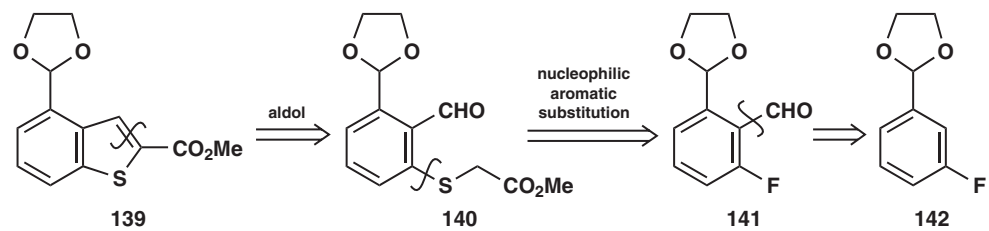
The electron-withdrawing group on the aromatic ring is essential. Since direct S_N2 displacement reactions on sp^2 centres do not occur, the electron-withdrawing group gives the electrons somewhere

to go in the intermediate before expulsion of fluoride. The same process occurs when a nucleophile reacts with an acid chloride.

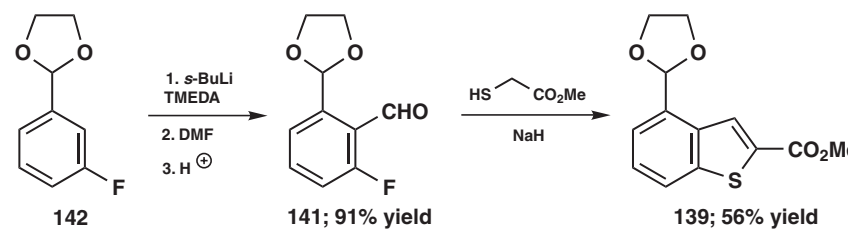


Fluoride as ortho*-director and leaving group*

A method developed by Bridges[24] enables the synthesis of the benzothiophene **139** and other similar derivatives using a combination of fluorine as both an *ortho*-director and a leaving group. Disconnection of the acetal will not get us very far but the double bonds of the thiophene ring also forms part of an α,β-unsaturated ester. A simple aldol disconnection here gives us aldehyde **140**. The next disconnection relies on our knowledge that fluorine can behave as a leaving group from aromatic rings. The aldehyde is the necessary electron withdrawing group. We now **141** have three substituents round the ring. The acetal, although a poor *ortho*-director in its own right, will assist the fluorine in a lithiation. We can remove the formyl group with an *ortho*-lithiation in mind.



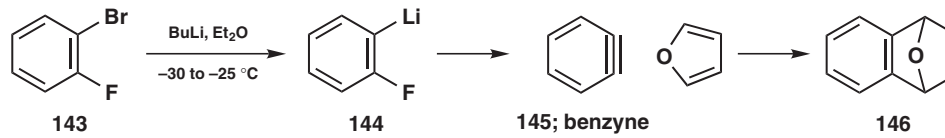
The acetal **142** is lithiated with *sec*-BuLi and TMEDA and formylated with DMF to give, after workup, the aldehyde **141**. The next couple of reactions happen in one pot under the same set of reaction conditions. The thiol is reacted with NaH and the anion added to a solution of the aldehyde **141**. After workup the product is the target material.[24]



The next three sections – Benzyne Formation, α-Lithiations and Lateral Lithiations – are just a brief look at some of the other lithiation reactions that are available to the synthetic organic chemist. They are also words of warning. They show what other reactions can take place in the frame of lithiation of aromatic substrates and are intended to prime you for potential traps.

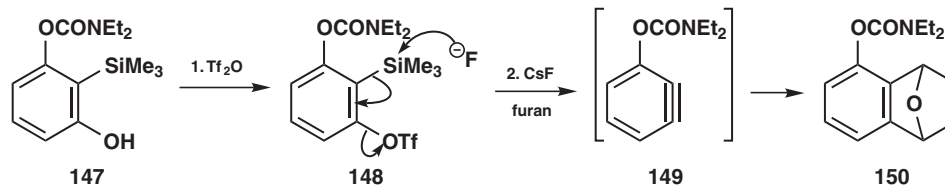
Benzyne Formation—A different aromatic strategy

Benzynes are readily formed when we have a leaving group *ortho* to a lithium atom. Thus when *ortho*-bromofluorobenzene **143** is reacted with butyl lithium, the intermediate formed is *ortho*-lithiofluorobenzene **144**. Lithium fluoride can eliminate from this to yield benzyne **145**. Benzynes are reactive species and do not hang about. Here, *ortho*-bromofluorobenzene is treated with butyl lithium in the presence of furan. When the benzyne forms it rapidly reacts with furan in a cycloaddition reaction to form the adduct **146** in a 68% yield.



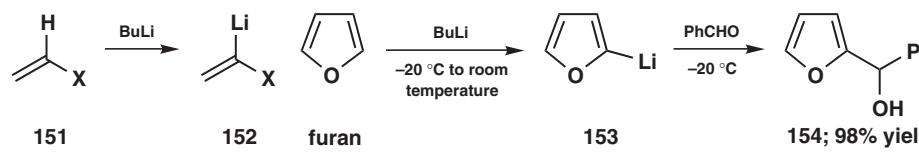
Note the *ortho* relationship between the lithium and fluorine atoms on the benzene ring. We have previously seen lithium next to the fluorine *without* benzyne formation and yet here the very same species forms benzyne! The crucial difference between the two cases is temperature. The *ortho*-fluoro-aryllithium is stable at −78 °C and the benzyne does not form until the temperature reaches −40 °C to −50 °C. Aromatic rings with lithium adjacent to other halogens (such as bromine) are less stable and form benzynes at lower temperatures.

An *ortho* relationship between a triflate and a silyl group is another way to generate benzynes.[26] The benzyne **149** is formed when the silyl group is removed[11,27] using the fluoride ion **148**.

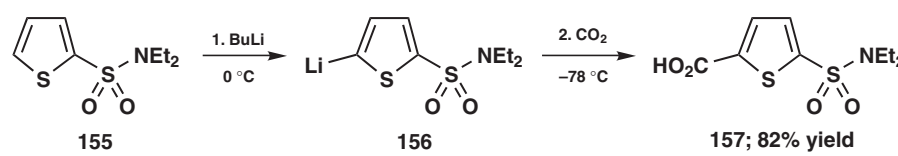


α-Lithiation

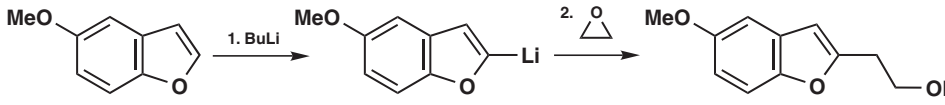
An α-lithiation reaction is characterised by a lithiation occurring at an sp^2 centre and α to a heteroatom[28] **152**. Lithiation of furan with BuLi and reaction with benzaldehyde gives alcohol **154** in 98% yield.



We might expect that the sulfonamide group in **155** would direct lithiation of the thiophene ring to its adjacent site in an '*ortho*'-lithiation. It doesn't. An α-lithiation to give **156** occurs instead.



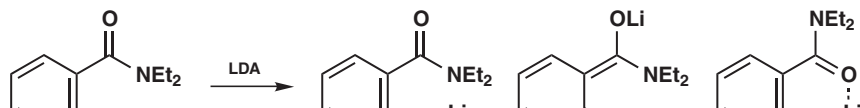
One last word of warning with regard to α-lithiations. The benzofuran **158** has a methoxy group on the benzene ring and we might expect this to direct an *ortho*-lithiation. It would be easy to overlook the α-lithiation of the furan ring: this, in fact, happens instead.



155 **156** **157; 62% yield**

Lateral Lithiation

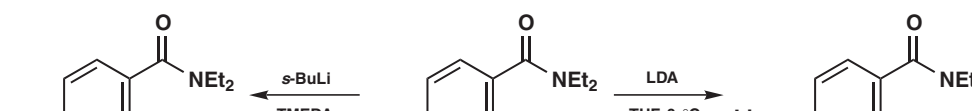
A lateral lithiation occurs at a benzylic position[29] (**161** reacting to **162**) rather than on the benzene ring itself. These reactions are quite common so we must discuss them briefly here as the same functional groups that behave as *ortho*-directors are also lateral lithiation directors as in the case of the amide **161** below. The lithiated species can be represented as a lithium enolate **163** or even with chelation **164**. This is not possible with an *ortho*-lithiation where the 'charge' is localised in a C-Li σ-bond.



161 **162** **163** **164**

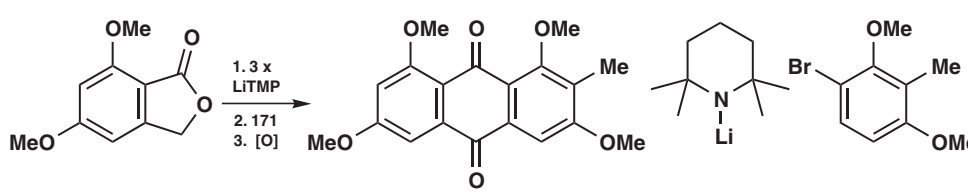
Chemoselectivity

Lateral lithiations do not necessarily need an adjacent (*ortho*) director. So LDA will happily deprotonate the *para* methyl group of the amide **166** in THF at 0 °C. Once again the 'charge' can delocalise into the electron withdrawing group. But reaction with a much stronger base at low temperature, *sec*-BuLi at −78 °C, gives the *ortho*-lithiation **165** we have come to expect. The lateral lithiation gives the thermodynamically more stable lithiated product whereas the *ortho*-product **165** is the kinetic product as complexation of the alkyl lithium reagent with the amide accelerates the lithiation.[30]



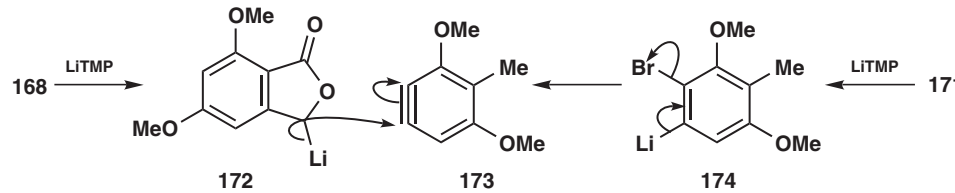
165 **166** **167**

Here is an example **168** of a reaction in which both benzyne formation and lateral lithiation are involved. What's going on here? Try to work out the mechanism before reading the explanation. You have the clues you need – the reaction involves the formation of a benzyne and a lateral lithiation.[31]

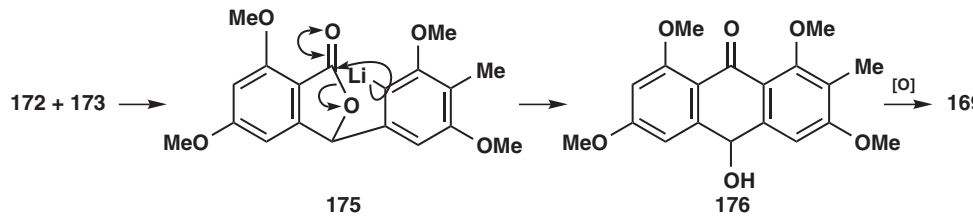


168 **169; 66% yield** **170** **LiTMP** **171**

The lactone **168** is lithiated at the benzylic site by lithium tetramethyl piperidide (LiTMP) **167** to give **172**. Notice that this 'charge' can delocalise into the carbonyl group and that *ortho*-lithiation between the two methoxy groups does not occur. One of the reactive species then is **172**. The aromatic bromide **171** is lithiated *ortho* to the bromide **174**, eliminates lithium bromide, and generates a benzyne **173**. These two species then combine.



The benzyne **173** is attacked regioselectively. By attacking *meta* to the methoxy group, the lithium atom ends up *ortho* to the methoxy group (**175**). The C-Li bond can then attack the lactone and spring it open to give **176**. We are now very close, and a little oxidation will take **176** to the anthraquinone[31] **169**.



Summary

In this chapter we have introduced many powerful reactions. We have seen that—

- *Ortho*-lithiation turns aromatic compounds into much more powerful nucleophiles.
- The range of groups that direct lithiation is extensive though some are better than others.
- More than one *ortho*-director can lead to competition or cooperation. In some cases there is a *choice* over the *ortho*-lithiation site.
- We have also seen that *ortho*-lithiation can be used in conjunction with other reactions – such as fluoride displacement or an anionic Fries rearrangement – that make *ortho*-lithiation a particularly versatile strategy.

Summary of Reagents

BuLi	BuLi is often sufficiently reactive to bring about an *ortho*-lithiation on its own. It coordinates to electronegative groups before it deprotonates in the *ortho* position. With tert-BuOK it forms a 'super' base. However, halogens will often undergo halogen/lithium exchange with BuLi. A nitrogen base (like LDA) is more appropriate in such cases.
sec-BuLi	*sec*-BuLi is a stronger base than BuLi. It is often used in conjunction with TMEDA to *ortho*-lithiate.
LDA	LDA prefers to deprotonate rather than react with a halogen. When an aromatic bromide reacts with BuLi a by-product is BuBr (a carbon – bromine bond). If LDA

were to lithiate an aromatic bromide the by-product would contain a week nitrogen – bromine bond and so the reaction does not occur.

LTMP Lithium tetramethylpiperidide is a stronger, more hindered, and more expensive version of LDA.

- Notice that *ortho*-lithiations frequently use BuLi or *sec*-BuLi but that the lateral lithiations frequently use lithium amide bases like LDA and LiTMP instead. This is not insignificant.

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General references are given on page 893

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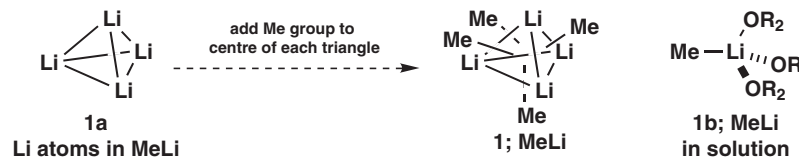
8 σ-Complexes of Metals

Introduction *The structure of organo-lithium compounds*

Every reader of this book is familiar with Grignard reagents, the first useful organometallic compounds, and with lithium derivatives of organic compounds as we have already discussed these at some length in the first seven chapters. We must now widen our discussion to include all compounds with a direct metal–carbon bond and we shall call these σ-complexes in contrast to the more common η and π complexes that we shall meet in later chapters. A saturated carbon atom has no lone pair electrons or accessible empty orbitals and we can treat the metal–carbon σ-bond like the boron-carbon or silicon-carbon bond without discussing back-bonding or invoking d-orbitals. We should still recognise that the apparently simple compound MeLi actually exists as trimers and tetramers[1] such as **1**. In this chapter we shall be concerned with the synthesis of σ-complexes of metals such as Li, Mg, Cu, and Zr. We shall see how far simple-minded organic mechanistic ideas can be extended to these undoubtedly more complex structures, and that we need not in general worry about their polymeric nature as they often react in solution as monomers[2] **1b**.



1a
Li atoms in MeLi

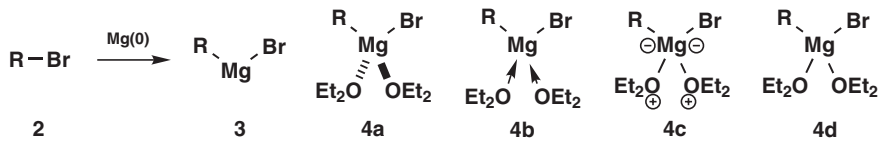
1; MeLi

1b; MeLi
in solution

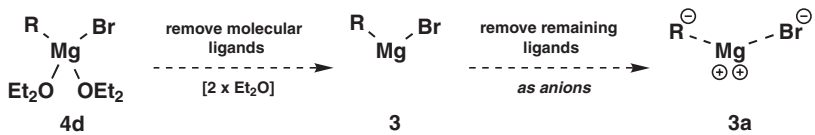
We have just been considering the formation of aryl-lithiums by deprotonation with the more basic alkyl-lithiums, normally BuLi, and you are also aware that protons may be removed from many molecules to give lithium derivatives. We shall not discuss this further in this chapter, but concentrate instead on three other approaches, oxidative addition (insertion), transmetallation, and hydrometallation.

Making organo-metallic σ-complexes by oxidative insertion

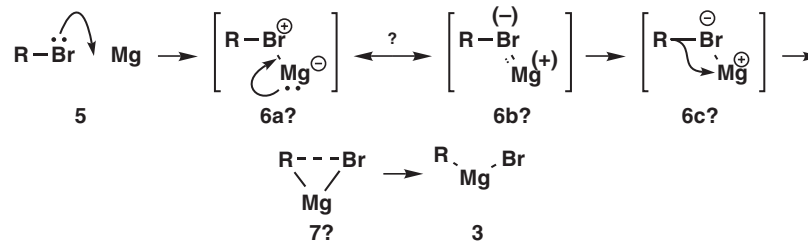
You are familiar with the normal method of making a Grignard reagent: an alkyl halide **2** reacts with magnesium metal in ether solution to give something we normally write as RMgBr, but which certainly contains a tetrahedral Mg atom, the remaining sites being occupied by ether molecules **4a**. This is at least one of the species present in such solutions. In making these new bonds, magnesium has accepted electrons from the ether ligands. In a simple organic structure formed like this we should put charges on the atoms **4c**, or draw the bonds as arrows **4b**. Structure **4c** is most unattractive for a metal complex as the metal ends up with a double negative charge. The best compromise is just to draw all bonds as lines **4d** and leave out the charges.



We shall call this reaction *oxidative insertion* (or oxidative addition) because the metal atom inserts itself between the carbon and halogen atoms and simultaneously undergoes oxidation from Mg(0) to Mg(II). If you are unhappy at assigning an oxidation state to a metal in a complex, then the quickest way is to remove the ligands from the metal. First remove all the real molecules (two of Et_2O in this case) as you can obviously do this without changing the oxidation state of the metal. Then remove the remaining ligands as anions **3a** (two in this case), leaving the same number of positive charges on the electropositive metal. The number of charges gives the oxidation state of the metal. We therefore describe **4** as a sigma complex of a carbanion with Mg(II).



In detail, the oxidative insertion probably begins with an interaction between the electron-rich halogen atom and the electron-poor metal **5**. Back-bonding from the metal also builds up in the intermediate **6**, weakening the carbon-halogen bond. The electrons of the C-Br bond then abandon the halogen atom and form a bond to the metal **6c**. The carbon atom has undergone *electrophilic* substitution, while the metal has made two new bonds, using an empty orbital for one and a lone pair for the other. You may object that if the metal has been oxidised, then something must have been reduced, and this is the carbon atom which is like R^+ in RBr and is now like R^- in the complex. Words like *might*, *probably*, and *could* are used a lot in this area and question marks litter both the structures of the intermediates and the reaction pathways. We should still take pride in attempting to understand these reactions even if the details of the mechanisms are uncertain.



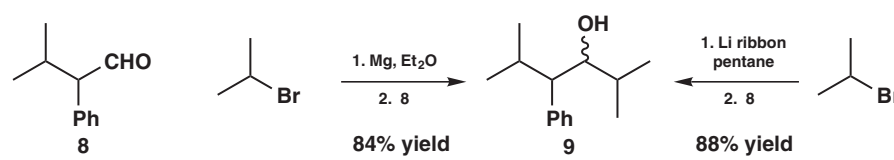
Magnesium probably undergoes oxidative insertion more easily than the other metals we use, but lithium, used as wire, hammered-out sheets, or even slices[3] inserts quite easily into alkyl or aryl halides, particularly in THF solution.[4] A one-electron donor like lithium probably follows a similar pathway to Mg but with single electron arrows. Palladium forms aryl Pd(II) derivatives in the same way,[5] but the Pd must be added as a soluble complex like $Pd(Ph_3P)_4$. Other transition metals are much less successful.

Structures of organo-lithium and magnesium reagents

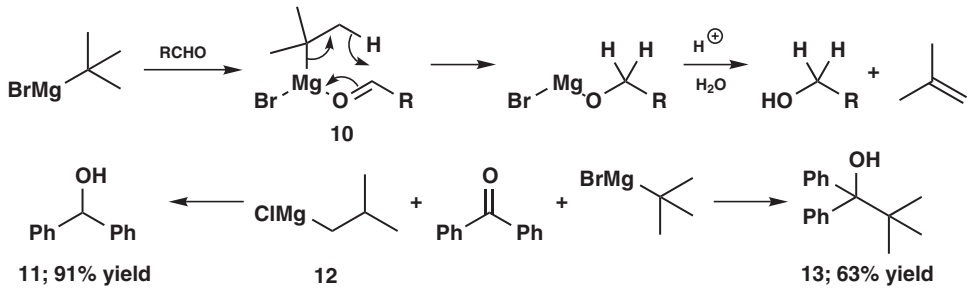
We may describe these species as σ-complexes of carbanions with metals but they are not carbanions. As normally prepared from alkyl halides and Mg(0) or Li(0) in ether solvents (Et_2O or THF), they are soluble in organic solvents as tetrahedral complexes and are not salts. Chemists are happy to draw the monomeric species RLi or RMgX and it is likely these are the reactive entities in many reactions.

Reactions of organo-lithium and organo-magnesium reagents

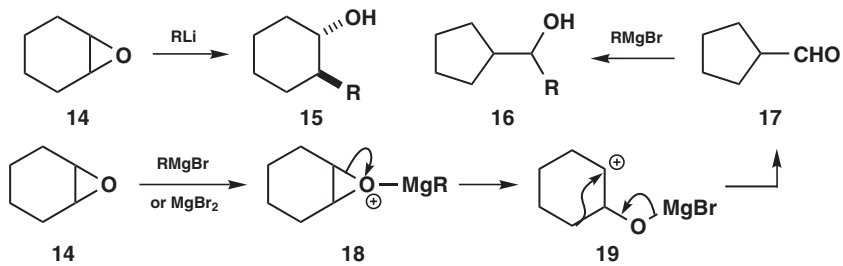
Grignard reagents and alkyl-lithiums, organometallic reagents of very electropositive metals with a strong affinity for oxygen, are useful reagents, as you are aware. They are very reactive, basic nucleophiles, combining well with hard electrophiles such as carbonyl compounds, but less successfully with softer electrophiles such as alkyl halides. A brief exploration of these reactions will make it clear why other organometallic σ-complexes are needed. When Cram[6] was studying the stereochemistry of addition to chiral aldehydes, he compared the behaviour of *i*-propyl Grignard (*i*-PrMgBr) with *i*-PrLi in nucleophilic attack on the aldehyde **8**. He was interested in the diastereomer ratio in the product **9**, but we can note the almost identical yields from the two reagents.



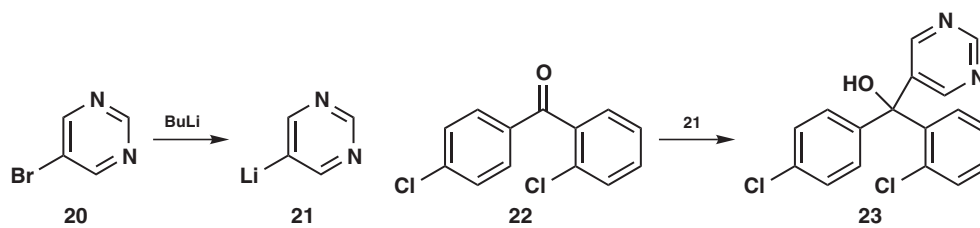
Additions of either RLi and RMgBr to most aldehydes and ketones give good yields, and there are many examples known.[7,8] The only problems likely to arise are enolisation by RLi or reduction by RMgX. The latter is more serious, especially with branched Grignard reagents **10**. It appears erratically[8] - the very unreactive ketone Ph_2CO gives[9] mostly addition **13** with *t*-BuMgCl, but only reduction **11** with *iso*-butyl Grignard **12**, quite the reverse of what we might expect.



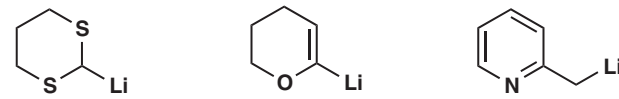
Reaction with epoxides are generally excellent with RLi, but deprotonation leading to rearrangement can be a problem.[10] Grignard reagents react well with ethylene oxide itself, but with other epoxides rearrangement can occur because of the Lewis acid effects of Mg(II). Cyclohexene oxide **14** reacts as expected with RLi to give **15**, but can give the surprising product **16** with Grignard reagents, by rearrangement to the aldehyde **17** before addition. A famous example is Robinson's reported synthesis of **15**; R = $PhCH_2CH_2$- in 92% yield, later corrected to **16**; R = $PhCH_2CH_2$-, and hence useless for the synthesis of steroids.[11]



Reaction with alkyl halides is generally thwarted by the rapid exchange of Mg or Li between the two species. This can be used to advantage if the new organo-lithium reagent is more stable than the old, as in the synthesis of aryl-lithiums from aryl halides and BuLi. Direct lithiation by replacement of hydrogen generally occurs in positions *ortho* to heteroatoms (chapter 7) but a halogen, as in the bromo-pyrimidine **20** directs the lithium atom to that same site giving **21**. Addition to the unreactive dichloro-diarylketone **22** gives the fungicide fenarimol[12] **23**.



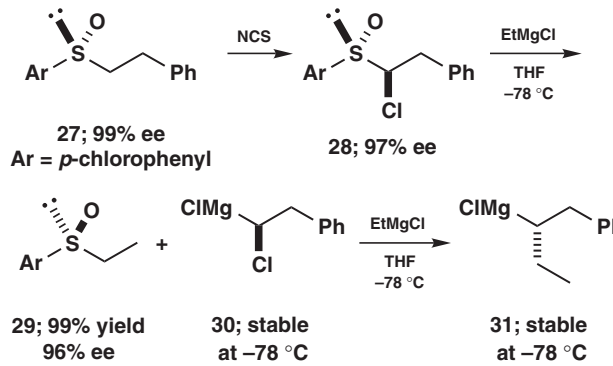
Many alkynyl, alkenyl, aryl, and functionalised alkyl-lithiums behave well in alkylation reactions because they are more stable anions than those derived from the simple unfunctionalised alkyl halides with which they are to react. Examples are **24**, **25**, and **26** and these will be treated in later chapters with the reactions of Grignard reagents with allyl halides.



24 **25** **26**

Chiral Grignard reagents

It has long been supposed that enantiomerically pure Grignard reagents cannot be made. Certainly[13] 'enantiomerically pure Grignard reagents…are not accessible from enantiomerically pure secondary alkyl halides by reaction with magnesium metal since electron transfer processes and the intervention of radicals annihilates the stereochemical information.' Hoffmann's recent success in this difficult area[13,14] also illustrates the reactions of a simple Grignard reagent, EtMgBr.



27; 99% ee
Ar = *p*-chlorophenyl

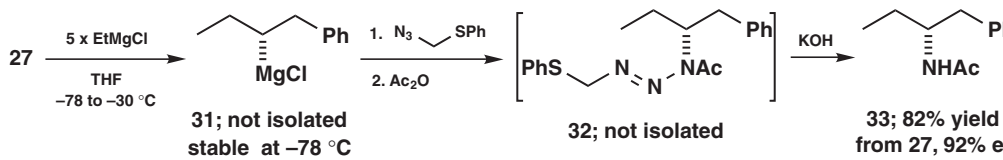
28; 97% ee

29; 99% yield
96% ee

30; stable
at –78 °C

31; stable
at –78 °C

The enantiomerically pure sulfoxide **27** is chlorinated with NCS (*N*-chlorosuccinimide) to give the enantiomerically pure **28** easily separated from its diastereoisomer. Reaction with EtMgCl occurs in two stages. Nucleophilic attack at the sulfoxide with inversion to give **29** expels a single enantiomer of the chloro-Grignard **30**. Still at low temperature an excess of EtMgCl displaces chloride with inversion from **30** to give the simple secondary Grignard reagent **31**. This compound maintains its stereochemical integrity at −78 °C. If the Grignard reagent **31** is prepared and immediately reacted with an electrophile compatible with the conditions a product **33** can be isolated in good yield and high ee showing that **31** reacts with retention.



31; not isolated
stable at –78 °C

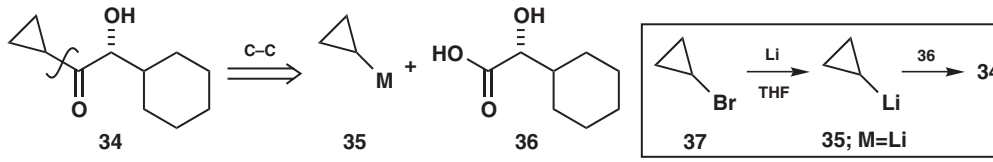
32; not isolated

33; 82% yield
from 27, 92% ee

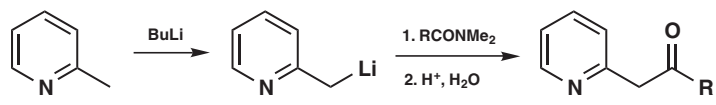
Acylation at carbon with Grignard and organo-lithium reagents

Acylation at carbon is always a difficult problem because the product (usually an aldehyde or ketone) may be more reactive than the acylating agents in two ways: more electrophilic at the carbonyl group and more acidic because of enolisation. Nitriles often perform well in the acylation of RLi or RMgBr, and the reaction of lithium salts of carboxylic acids with RLi is a strategy already discussed in chapter 2. Both these methods rely on the product being released during the work-up after all RLi is quenched. One example is the cyclopropyl ketone **34** needed by

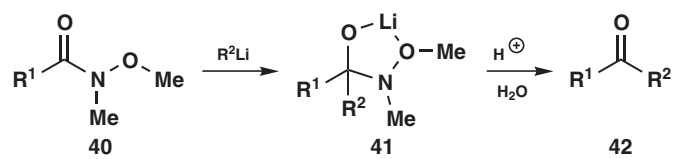
Masamune as an intermediate in his amphotericin synthesis.[15] Disconnection to the hydroxyacid **36** was particularly attractive as optically active **36** was available. Cyclopropyl-lithium **35**; M=Li is actually easier to make than other *s*-alkyl-lithiums as the three-membered ring stabilises the anion in the σ-complex.[16] Acylation with **36** needed *three* molecules of **35**; R = Li as two are consumed by the acidic OHs, but the reaction is an efficient acylation at carbon.



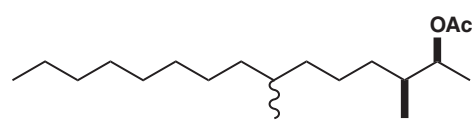
More commonly, acylating agents are based on tertiary amides because they are much less reactive than ketones, or on lactones because they are about as reactive than ketones. This paradox arises because tertiary amides $RCONMe_2$ add alkyl-lithiums but the tetrahedral intermediate does not decompose while RLi is present. Hence **26** gives good yields of the ketones[17] **39**.



The "Weinreb amides" **40** are particularly efficient in acylating reactive carbon nucleophiles.[18] An alkyl-lithium adds to form the chelated lithium derivative **41** which decomposes on work-up to give the ketone **42**. Compounds **60** and **63** in chapter 5 are examples of Weinreb amides.

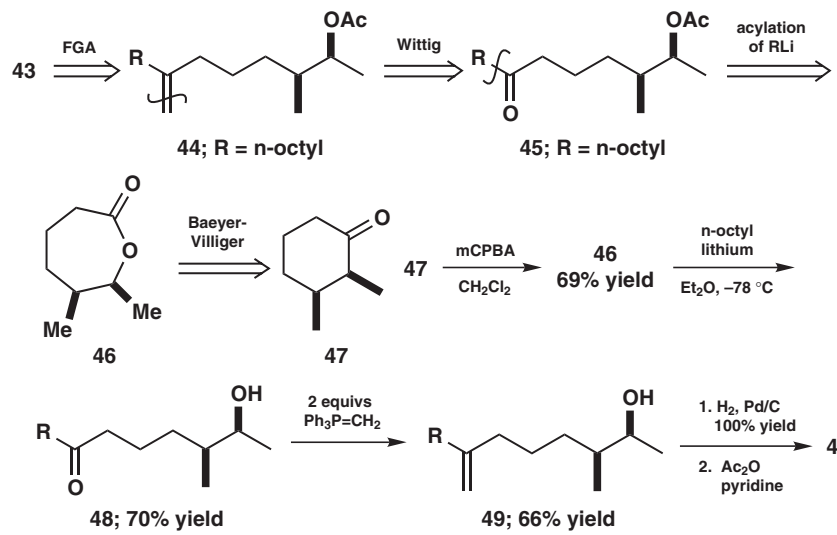


Lactones have similar reactivity to ketones and at low temperature one molecule of an alkyl-lithium may give the ketone in good yield. In his synthesis of the pine saw fly sex attractant **43**, Magnusson[19] chose to replace the more-or-less central methyl group by a double bond **44** so that disconnection to a ketone **45** was possible.



43

Reconnection to the lactone **46** then provides a means of controlling the stereochemistry using the Baeyer-Villiger rearrangement of the cyclohexanone **47**. Acylation of the lactone **46** with n-octyl-lithium at low temperatures gives a 70% yield of the hydroxyketone **48**, which in turn gives the pheromone **43**.

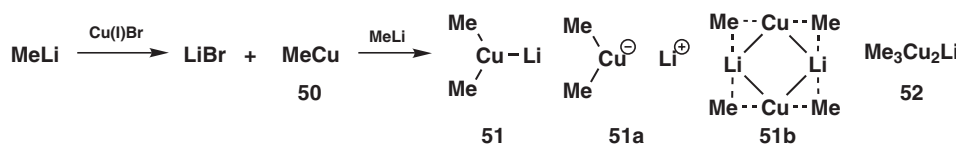


Transition Metal Complexes

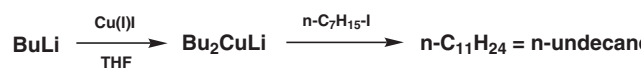
Acylation with acid chlorides

These methods of acylation are devices to solve the problem that acid chlorides and organo-lithium or magnesium derivatives are not good partners. To get good acylation with acid chlorides, as well as good alkylation with alkyl halides, we need to turn to other metals which provide softer carbanion complexes, less basic compounds with metals showing a lower affinity for oxygen. The most important is copper.

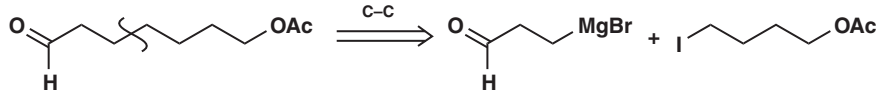
The difficulties of direct oxidative insertion with metals other than Mg or Li mean that σ-complexes are often made from organo-lithium or Grignard reagents by metal exchange. This reaction amounts to a nucleophilic substitution at the metal without a change of oxidation state so the metal is used in whatever oxidation state is finally needed. Attack of methyl lithium on a Cu(I) halide gives methyl copper **50**, a σ-complex of Me^- and Cu(I). If an excess of MeLi is present an "ate" complex is formed, lithium dimethylcuprate **51**. This is formally a compound of a copper anion **51a**, just as BF_4^- is a borate. The term "ate complex" refers to such formally anionic complex in which the metal has one extra anionic ligand. Its true structure is dimeric **51b** and it exists as an equilibrium with **52** in solution.[20]



Cuprates couple efficiently with alkyl halides, as in the simple synthesis of n-undecane[21] via the cuprate prepared from BuLi. When a Grignard reagent is involved, a Cu(I) compound is usually added in catalytic amounts for coupling with an alkyl halide.

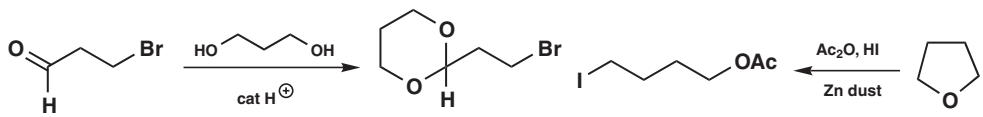


The acetoxy-aldehyde **53** has a 1,7-relationship between the functional groups and there is no well established approach for this relationship. Disconnection to the alkyl halide **55** is appealing as it can be made from THF in one step. It might be coupled to the Grignard reagent **54** provided we protect the CHO group and exchange Mg for Cu.

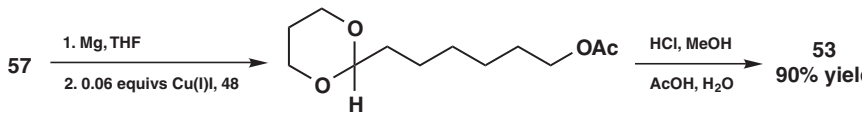


53 **54** **55**

The coupling actually needs only 0.06 moles of Cu(I) per mole of Grignard reagent from **57** and gives the product in two simple steps.[22] Cuprates are often further complexed with Me_2S, cyanide, or BR_3 and couple well with tosylates as well as halides.[23]

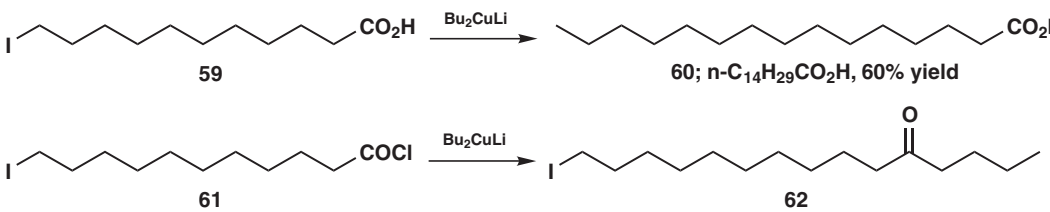


56 **57** **55; 80% yield**



58; 77% yield

Acylation of copper derivatives with acid chlorides works well, but they do not react with free carboxylic acids, unlike the more basic alkyl-lithiums. A dramatic illustration of chemoselectivity comes in the interaction of Bu_2CuLi with the free acid **59** and its acid chloride **61**. Reaction occurs[24] at the alkyl iodide with the one to give **60** and at the acid chloride with the other to give the ketone **62**. Acylation can also be achieved by many other metal complexes, from Al to Zr, but to make those we need hydrometallation, the subject of the next section.



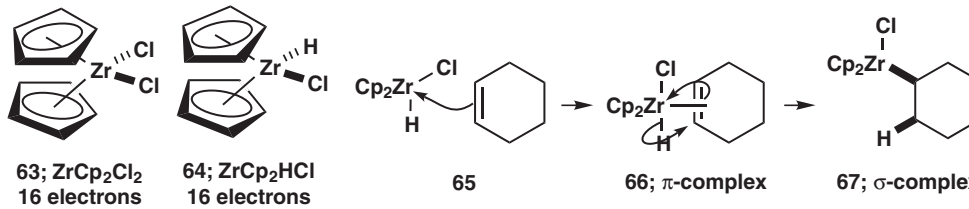
59 **60; n-$C_{14}H_{29}CO_2H$, 60% yield**

61 **62**

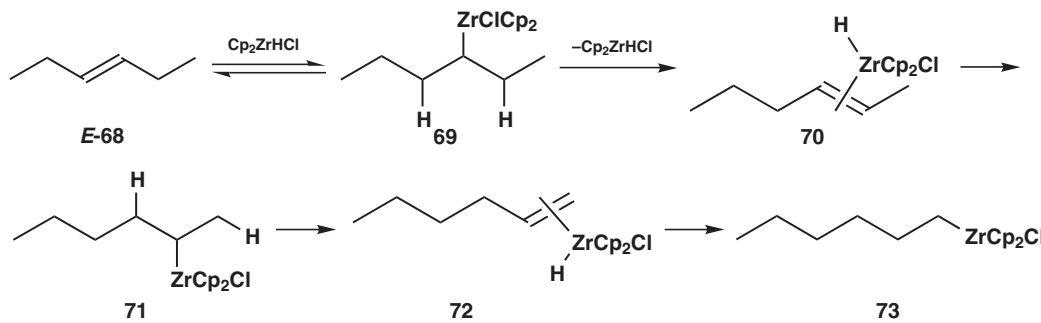
Hydrometallation

Hydrometallation is the addition of a metal hydride across a double or triple bond. It might be familiar to you through hydroboration (see chapter 17) while that other not-very-metallic metal, silicon, can be added through hydrosilylation. We shall concentrate here on hydrozirconation. Zirconium is a fairly abundant transition metal in the same group as that very useful metal titanium (see chapters 2–5) with stable oxidation states of +2 and +4. It is normally used in organic synthesis as *bis* cyclopentadienyl complexes such as Cp_2ZrCl_2 **63** or Cp_2ZrHCl **64**. We met complexes like these in chapter 4 where zirconium enolates gave *syn*-selective aldol reactions. Hydrometallation with **64** and an alkene involves the formation **65** of an unstable 18-electron

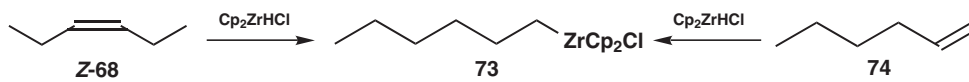
complex with the two π-electrons of the double bond and the reorganisation of this back to a 16-electron σ-complex by a hydride transfer from Zr to carbon **66**. The result is a carbanion-Zr(II) complex **67**.



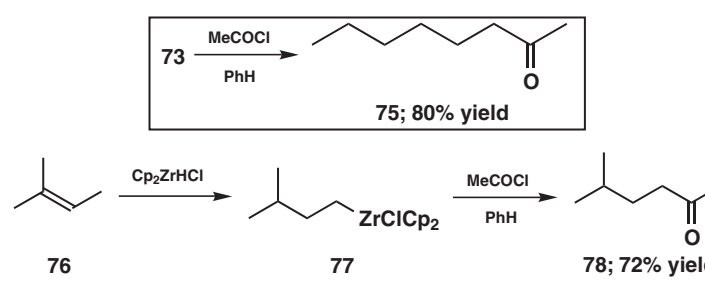
This is a good point to address an irritating problem with σ-complexes: their tendency to decompose by β-elimination of metal hydrides. We have already met the tendency of crowded Grignard reagents to donate β-hydrogen atoms **10** and act as reducing agents. Alkyl zirconium complexes prefer to lose the same hydrogen atom by transferring it to the metal in a β-elimination. Complex **69**, formed by hydrozirconation of *E*-hex-3-ene **68** could go back to starting material, or on, via complex **70** to a π-complex of hex-2-ene **71** and hence via **72**, to the terminal σ-complex **73**.



This means that any positional **74** or geometrical *Z*-**68** isomer, or a mixture such as might be formed in a dehydration or Wittig reaction, gives the same terminal Zr σ-complex **73**.

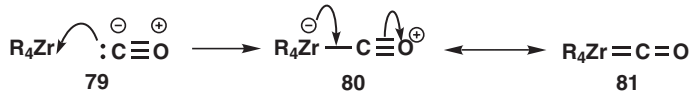


These organo-zirconium derivatives give good acylations with simple acid chlorides[25] (and even better yields if treated with $AlCl_3$). Thus any linear hexene gives 2-octanone **75** by zirconation and acetylation, and even branched chain alkenes such as **76** are acylated at the terminus **78** by this method.

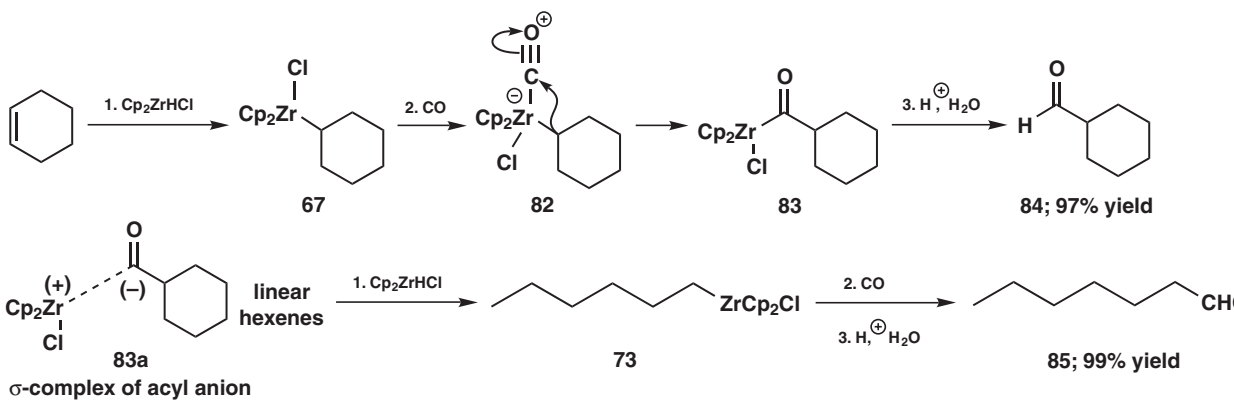


Carbonylation of organometallic complexes

Formylation (addition of an electrophilic CHO group) has always been a difficult operation. It cannot be accomplished with HCOCl as this decomposes to HCl and CO. Some metal complexes will react with CO and this gives us another approach to acylation at carbon. The tendency of transition metal σ-complexes to lose an H atom by β-elimination is just one symptom of the poor performance of alkyl groups as ligands. A simple σ-bond gives nowhere near the stability conferred by ligands that can simultaneously donate and accept electrons. The outstanding examples that we shall meet again and again are the phosphines, such as Ph_3P, and CO. Phosphines donate their lone pair electrons and accept electrons from the metal into empty d-orbitals. On balance they are electron donors. Carbon monoxide donates its lone pair (from carbon) **79** and accepts electrons into the π* orbital **80**. On balance CO is an electron acceptor: though the resulting complex can be represented with a metal-carbon double bond **81**, two of these electrons come from the metal and CO is a two electron donor and two electron acceptor.



Alkyl zirconium complexes such as **67** react with CO to give an unstable 18e complex **82** that transfers the alkyl group from the metal to the CO π* orbital to give the metal acyl complex **83**. This is a Zr(IV) complex of an acyl anion **83a** and can be protonated to give the aldehyde **84** in excellent yield. These zirconium complexes are usually made from alkenes so that any hexene or mixture of hexenes gives **85** again in excellent yield.[26]

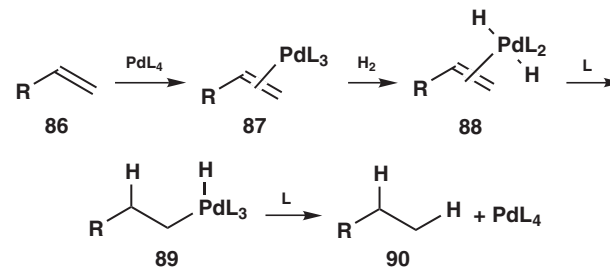


Palladium σ-complexes

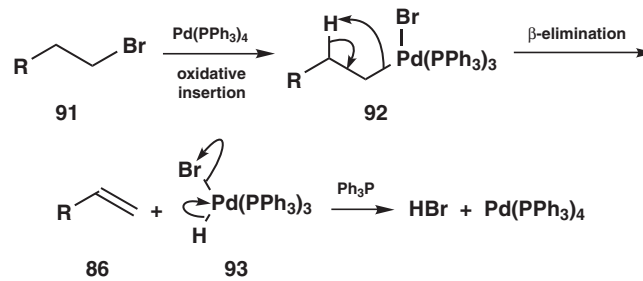
The metal for carbonylation reactions, and for many other extraordinary transformations is palladium. You will be familiar with this metal's excellent performance in hydrogenation reactions, usually as a finely divided powder on charcoal, and so you are aware that Pd(0) is stable. It also has a stable Pd(II) state, and there is little to choose between them in stability or in importance to organic chemists. Soluble reagents such as $Pd(PPh_3)_4$, $PdCl_2$, or $Pd(OAc)_2$ are often used in reactions. Palladium is expensive and catalytic reactions are preferred. Mg(II), as in RMgBr, is

more stable than Mg(0), as in the metal, by 2.4 eV but Pd(II) is more stable than Pd(0) by only 0.2 eV. Once Mg has been oxidised to Mg(II) it will not return to the metal without serious reduction. On the other hand, Pd(II) can easily return to Pd(0) during a chemical reaction. Pd can be used catalytically: Mg cannot.

Hydrogenation works in solution because Pd forms stable π-complexes **87** with alkenes **86**, easily inserts into a hydrogen molecule to give **88** and transfers H atoms one at a time to the alkene to give a σ-complex **89** and eventually the alkane **90**.

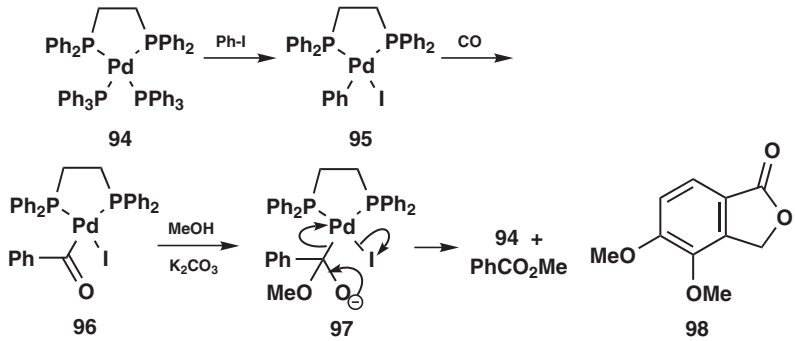


This well known reaction can deceive us into thinking that σ-complexes of Pd are stable. They are not. All the steps between **86** and **89** are reversible and in the absence of hydrogen, the reaction runs backwards. Palladium readily does the oxidative insertion into an alkyl halide to give the σ-complex **92**, a carbanion complex of Pd(II), but this immediately loses hydrogen by β-elimination and the alkene **86** is formed with the loss of a PdHBr complex. Notice that this Pd(II) complex immediately reverts **93** to Pd(0).

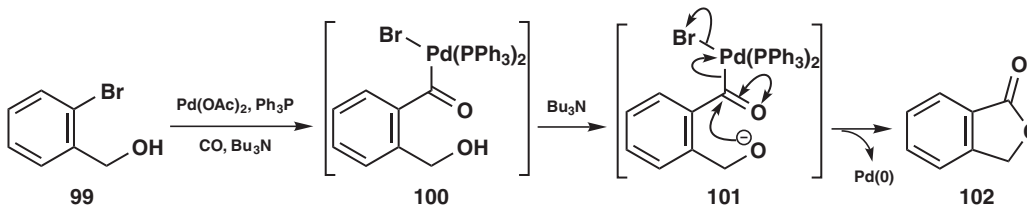


Pd is very widely used in organic synthesis[27] and we shall meet η^2 alkene and η^3 allyl complexes later. This chapter will end with a brief description of Pd σ-complexes. Stable Pd σ-complexes can be formed from ArX, MeX, and a few blocked alkyl compounds with no β-hydrogens. They react well with alkyl and acyl halides, but a major application is in carbonylation reactions.[28]

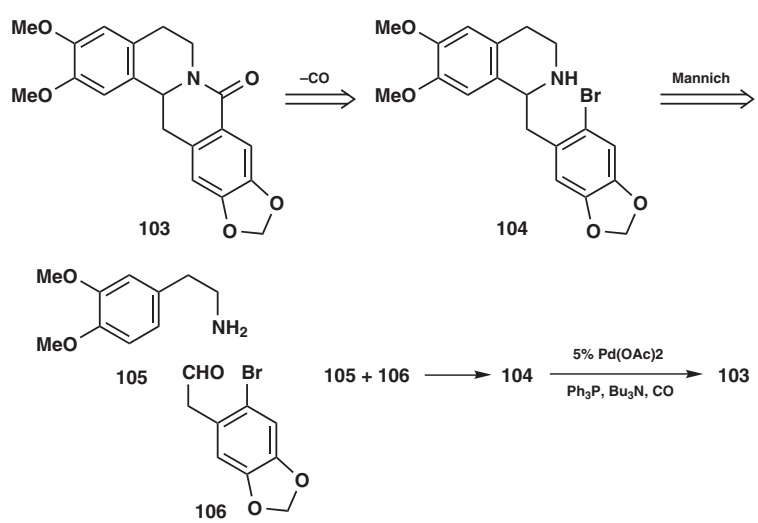
A simple example is the oxidative insertion of Pd(0) into PhI and its reaction with CO to give the complex **96**. This illustrates several important points though the reaction is no great news as a synthesis. First, soluble Pd often comes quite exotically wrapped, here as the "diphos" complex **94**, chiral versions of which we shall meet in chapters 25 and 26. Then the decomposition of the acyl-Pd complex **96** by a nucleophile rather than acid leads to the loss of the metal as leaving group since it reverts to Pd(0) as it goes **97**. In the corresponding reaction with zirconium, the Zr left as Zr(IV) as it has no tendency to drop down to Zr(II), let alone Zr(0). Finally, the reaction is modestly catalytic in Pd, only 0.2 equivalents being required (20 mol%).



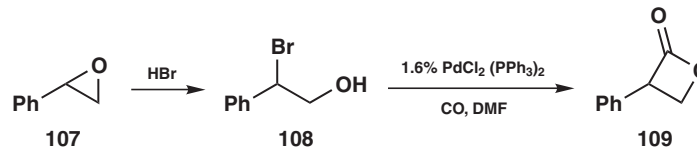
Much more impressive examples come in intramolecular reactions where the nucleophile (usually an OH group, but it can be NH) is built into the starting material before carbonylation. In these examples, Pd is often added as $PdCl_2$ or $Pd(OAc)_2$ for convenience and reduced to Pd(0) (by Ph_3P?) *in situ*. The alcohol **99** gives an excellent yield (82%) of the lactone[29] **102** *via* the complexes **100** and **101**. The yield falls off when the lactone size is increased to six (70%) or seven (42%). The natural product pseudomeconin **98** has been made by this method.[30]



Adaption to the synthesis of alkaloids such as **103** requires as the disconnection simply the removal of the CO group! This is good strategy as disconnecting one bond in the middle ring allows a second disconnection (Mannich or Pictet-Spengler[31]) to two simple starting materials **105** and **106**. The Pd-catalysed carbonylation needs 5% Pd and uses a nitrogen nucleophile to decompose the intermediate Pd-acyl complex.



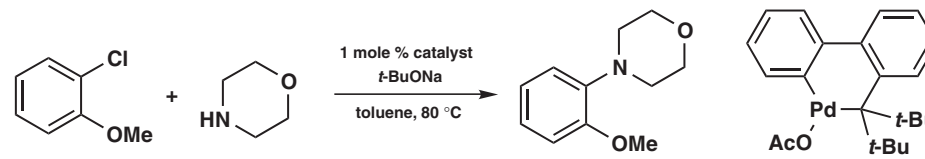
Just occasionally a Pd reaction with an alkyl σ-complex is successful. One instance is the remarkable synthesis of four-membered ring lactones **109** from styrene oxide **107** with 1.6% Pd in 63% yield.[30] Probably the OH group on the same carbon as the β-Hs in **108** inhibits β-elimination.



107 **108** **109**

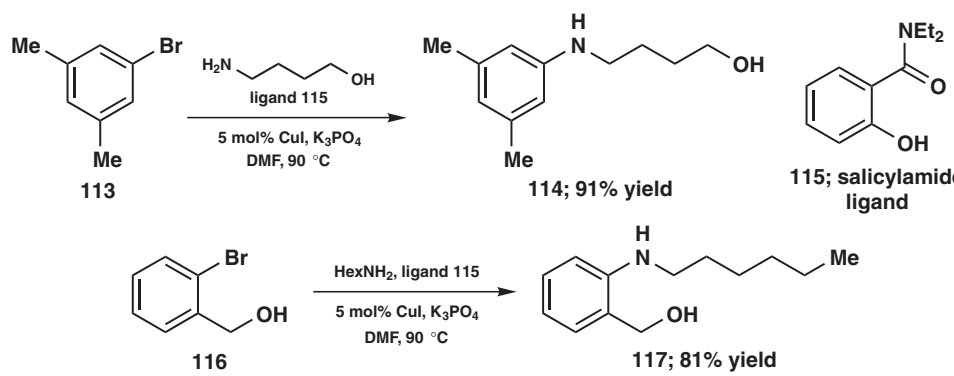
Recent results with Cu(I) and Pd σ-complexes

The displacement of halides from benzene rings by nucleophiles is traditionally a reaction that requires strongly electron-withdrawing groups, such as nitro, in the *ortho*- or *para*-positions. A highly significant recent discovery is that Pd(0) and Cu(I) can catalyse such reactions in simple unactivated aryl halides with, for example, amine nucleophiles. Even aryl chlorides with electron-donating substituents such as **110** combine with simple amines providing a trace of the palladium catalyst **112** is present giving excellent yields[32] of amines **111**.



110 morpholine **111; 95% yield** **112; catalyst**

The copper-catalysed reactions are not so well developed but aryl bromides combine with primary amines catalysed by Cu(I) using the salicylamide ligand **115**. Free OH groups are tolerated in either partner: the amine or the aryl halide.[33]



113 **114; 91% yield** **115; salicylamide ligand**

116 **117; 81% yield**

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General references are given on page 893

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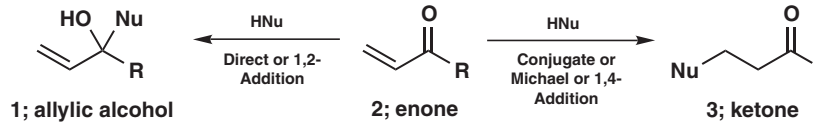
9 Controlling the Michael Reaction

Introduction: *Conjugate, 1,4- or Michael addition vs direct or 1,2-addition*
Sulfur and phosphorus ylids
Where direct (1,2-) addition is necessary
Using Copper (I) to Achieve Michael Addition
Stereoselectivity in Michael additions of organo-copper(I) compounds
Trapping the enolate intermediate by silylation
Michael Addition followed by Reaction with Electrophiles
Tandem Michael/aldol reactions
A Double Nucleophile: An Interlude without Copper
A Michael Reaction Coupled to a Photochemical Cyclisation: Copper Again
Michael Additions of Heteroatom Nucleophiles
Michael Additions with and without Copper: Functionalised Michael Donors

Introduction: *Conjugate, 1,4- or Michael addition vs direct or 1,2-addition*



1; allylic alcohol **2; enone** **3; ketone**

The Michael reaction (also known as conjugate or 1,4-addition) is at its simplest the addition of a nucleophile to an electrophilic alkene, usually an unsaturated carbonyl compound **2**, to give the product of 1,4-addition **3** rather than direct addition at the carbonyl group **1**. It is a useful reaction in synthesis since the nucleophile can be a heteroatom (O, N, S etc) or a variety of carbon compounds (organometallic compounds, enolates, aromatic rings etc). It has been extensively reviewed[1] and the ground rules[2] are:

Direct (1,2) attack at the C=O group is dominated by charge interactions and the allylic alcohol **1** is the kinetic product.

Conjugate, Michael, or 1,4-addition is dominated by frontier orbital interactions and the saturated C=O compound **3** is the thermodynamic product.

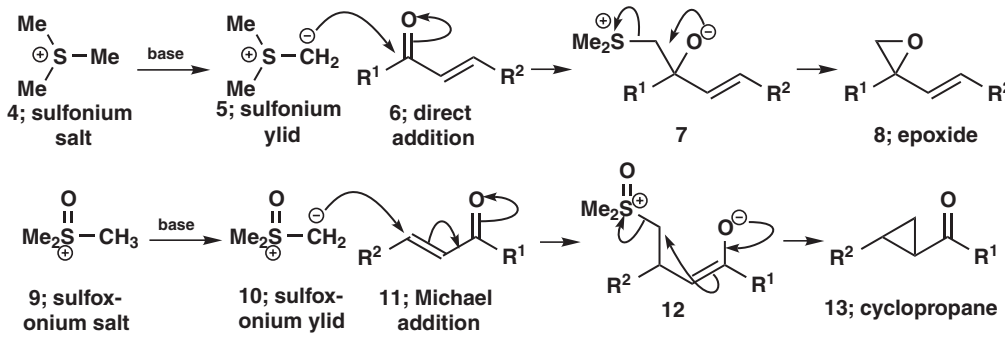
The most reactive Michael acceptors tend to give 1,2-addition (roughly CHO>AlkCO>ArCO>CO_2R>CN) while the least reactive tend to give 1,4-addition (reverse order).

The most reactive, most basic or *hard*, nucleophiles tend to give 1,2-addition: the least reactive, least basic or *soft* nucleophiles tend to give 1,4-addition.

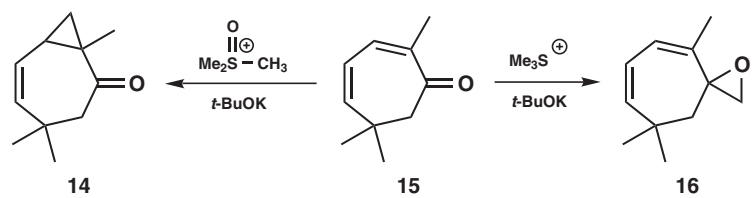
Steric effects matter: large groups next to the C=O end (a^1) or at the a^3 position can deflect addition to the other end.

Sulfur and phosphorus ylids

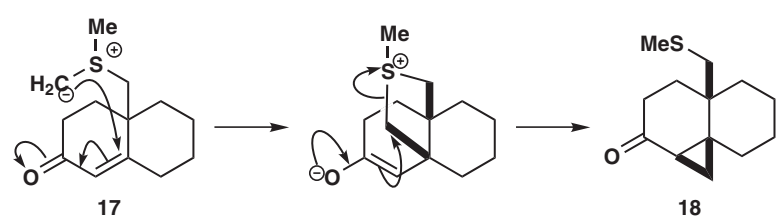
Sulfur and phosphorus ylids provide good illustrations. Simple sulfur ylids **5** react with aldehydes and ketones to give epoxides.[3] But what if the electrophile is a conjugated aldehyde or ketone? Two reactions are possible: direct addition **6** to give the epoxide **8** and 1,4-addition **11** to give the cyclopropyl ketone[4] **13**. The structure of the acceptor cannot generally be altered so that of the ylid must. The least stabilised, least reversible, and hardest ylids are those **5** derived from Me_3S^+ **4** and these give epoxides, while the extra anion-stabilising ability of an S=O bond in the sulfoxonium ylids **10** makes them softer and more reversible, and they give the cyclopropyl ketones.



A good example is the natural product eucarvone **16** mentioned in the original Corey papers.[5] The simple sulfonium ylid **5** gives the epoxide **16** in 93% yield by direct addition while the sulfoxonium ylid **10** gives the cyclopropane **14** in 88% yield by conjugate addition to the nearer alkene. In an extended conjugated system the alkene nearest to the carbonyl group is normally the most electrophilic.

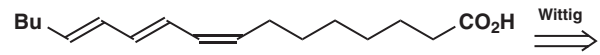


That sulfonium ylids can add in a Michael fashion is neatly shown by an intramolecular reaction of the ylid **17**. Direct attack would form an awkward 7-membered ring but conjugate attack **17** gives a five-membered ring intermediate with both new C−C bonds necessarily formed *cis* to the ylid.[6] Here is regio- and stereoselectivity.

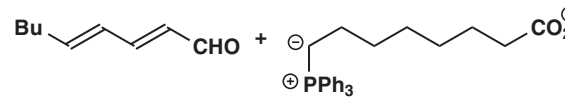


Where direct (1,2-) addition is necessary

For some reactions, 1,2-addition is essential. The synthesis of allylic alcohols by reduction of enones, enals, or enoate esters requires a hard reducing agent and $LiAlH_4$ is usually suitable (chapter 19). The Wittig reaction[7] also requires 1,2-addition otherwise the usual four-centred elimination of a phosphine oxide is impossible. In fact 1,2 addition is generally preferred with hard unstabilised ylids, and if the ylid is stabilised, Michael addition may be reversible. In the synthesis of α-eleostearic acid[8] **19** any of the double bonds could have been disconnected. The *cis* double bond was preferred both because unstabilised ylids usually give *Z*-alkenes, and because both starting materials, the dienal **20** and the ylid **21** are easily made.

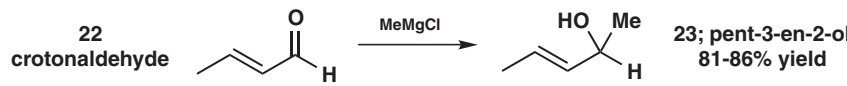


19; α-eleostearic acid



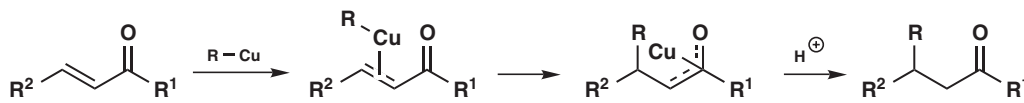
20 **21**

You may guess that Grignard reagents and alkyl-lithiums are also very likely to give 1,2-addition, especially with aldehydes. A classic example is the addition of methyl Grignard to crotonaldehyde **22** to give the allylic alcohol **23** in high yield.[9]



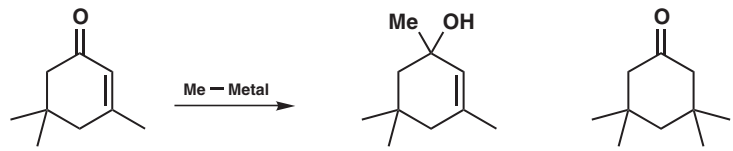
Using Copper (I) to Achieve Michael Addition

That was a useful synthesis of allylic alcohols, but the greater need is to accomplish 1,4-addition reliably with hard or soft nucleophiles and reactive or unreactive Michael acceptors. The organo-copper σ-complexes we met in the previous chapter are the answer. There is some discussion[10] over the exact mechanism of addition of organo-copper compounds to enones, but we shall present the simplest possibility. Organo-copper reagents may add to enones by first making an η^2-complex **24** with the alkene. Transfer of the ligand R from copper to the enone forms the η^3 allyl (enolate) complex **25** which gives the Michael adduct **26** on protonation.



24; η^2 alkene complex **25; η^3 enolate complex** **26**

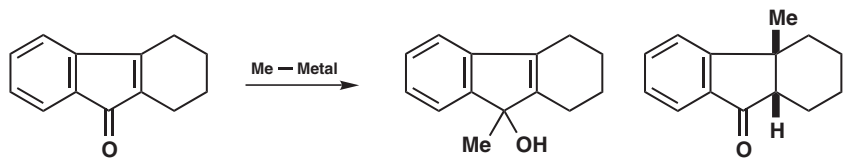
The addition[11] may be carried out using a Cu(I) catalysed Grignard reaction, a discrete RCu species with or without other ligands such as Me_2S, or with the R_2CuLi complexes described in chapter 8. A typical (and very early!) result[12] is the addition of MeMgBr to the enone **27** giving mostly the allylic alcohol **28** by 1,2-addition. The same reagent with catalytic Cu_2Cl_2 reverses the regioselectivity to a reasonable degree.



27	28; allylic alcohol	29; saturated ketone
Me — Metal = MeMgBr	98.5:	:1.5
Me — Metal = MeMgBr + cat. Cu_2Cl_2	17.5:	:82.5

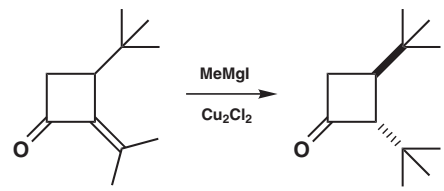
Stereoselectivity in Michael additions of organo-copper(I) compounds

Better results are achieved with stoichiometric copper reagents, either RCu [alone or as a complex with sulfides Me_2S, phosphines Bu_3P, or phosphites $(MeO)_3P$] or cuprates R_2CuLi. Thus Me_2CuLi adds exclusively[13] 1,4 to the difficult enone **30**, while the Cu-catalysed Grignard reaction gives mostly allylic alcohol **31**. The *syn* stereochemistry of the 1,4-product **32** is thermodynamically controlled and appears on protonation during the acidic work-up to give the more stable *cis* ring junction.



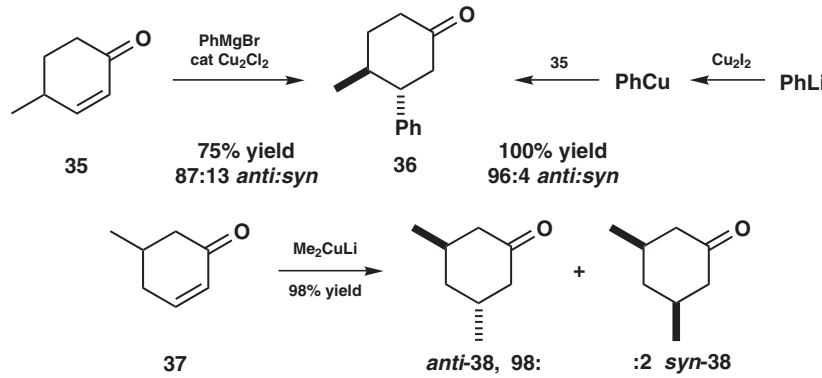
30	31; allylic alcohol	32; saturated ketone
Me — Metal = MeMgI, $Cu_2(OAc)_2$	56%	34%
Me — Metal = Me_2CuLi	0%	100%

In other cases *anti* stereochemistry is preferred. An ingenious synthesis of the *trans* di-*t*-butyl cyclobutanone **34** uses Michael addition to the enone **33**. Here a Cu-catalysed Grignard reaction gives total regio- and stereoselectivity as well as a quantitative yield.[14] The stereochemistry again comes from protonation of an enolate during work-up, but this time it is better to have the two large groups *anti* on the rigid four-membered ring.

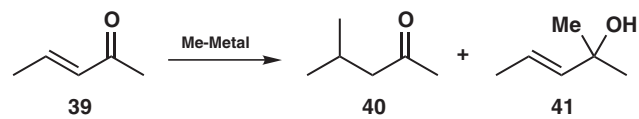


33 **34**

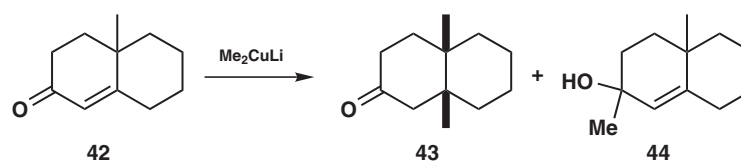
Similar stereoselectivities are found when the new chiral centre is formed during the addition rather than in the work-up, but the stoichiometric reagents generally perform better. Thus PhCu adds to the enone **35** to give *anti*-**36** in both a better yield and a better stereoselectivity than a copper-catalysed Grignard reagent.[15] The 1,3-stereoselection in Me_2CuLi addition to **37** is also excellent,[16] and results largely from axial addition rather than a preference for *anti* addition. These conformational aspects of stereoselectivity are discussed in chapters 20–21.



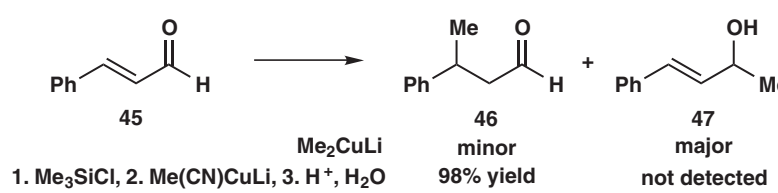
Open chain compounds often give good regioselectivity too.[11] The simple enone **39** adds a variety of organo-copper compounds[17] in up to 95% yield of the 1,4-adduct **40**. Unsaturated esters generally give good results too.



Unsaturated aldehydes and enones with heavy β-substitution in particular often give poor results either by competing 1,2-addition or by aldol condensation of the enolate products. Thus the enone[18] **42** and most aldehydes give predominantly 1,2-adducts **44** even with Me_2CuLi. These problems can be avoided if the reaction is carried out in the presence of Me_3SiCl.



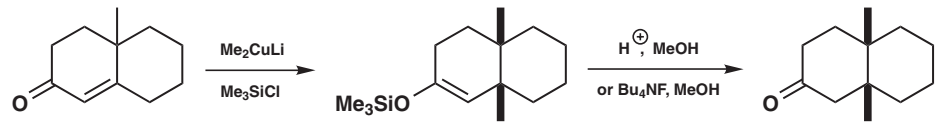
Cinnamaldehyde **45** gives mostly the alcohol **47** with Me_2CuLi but if Me_3SiCl is added before the organo cuprate, the less reactive cyanocuprate Me(CN)CuLi can be used and the 1,4-adduct **46** isolated in 98% yield.



Trapping the enolate intermediate by silylation

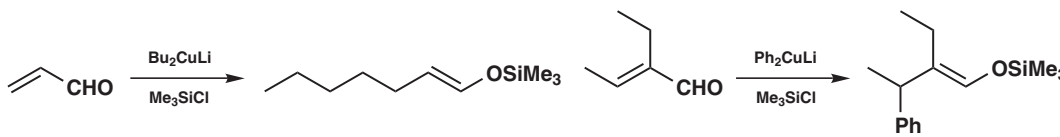
Cuprates react only very slowly with Me_3SiCl so it can be present during the Michael addition reaction, enhancing the rate of the reaction and the proportion of 1,4-addition, and trapping the enolate product as the silyl enol ether.[18–22] Thus the troublesome enone **42** gives good yields of

48 under a variety of conditions, and the 1,4-product **43** released by acid- or fluoride-catalysed hydrolysis.



42 **48** **43**

Cuprates generally perform better than RCu in additions to aldehydes. Acrolein itself **49** gives the 1,4-product **50** in 88% yield with Bu_2CuLi, and even β-substitution in the crowded enal **51** does not prevent Ph_2CuLi adding 1,4 to give **52** in 99% yield.[20]

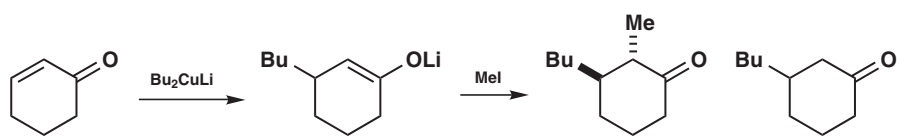


49 **50; 88% yield** **51** **52; 99% yield**

Michael Addition followed by Reaction with Electrophiles

Both these silyl enol ethers **50** and **52** could of course be hydrolysed to the saturated aldehydes, but that would be to sacrifice the useful reactivity of these intermediates in aldol and other reactions explored in chapters 2-6. A more productive development is to react the silyl enol ether with an electrophile and hence develop a synthesis from three components in two consecutive reactions.[23] This approach has formed the basis of many modern syntheses as it develops the target molecule so quickly and is discussed in chapter 37 under 'tandem reactions'. It is not necessary to trap the enolate with Me_3SiCl when lithium cuprates are used with ketones as the lithium enolate is the product of 1,4-addition. You may choose the lithium enolate or the silyl enol ether, whichever is more appropriate for the next step.

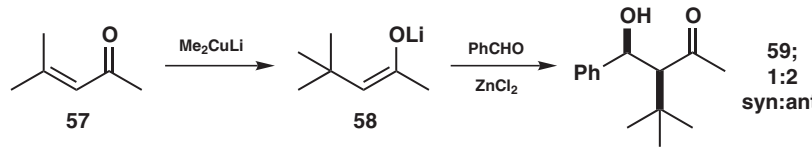
Cyclohexenone adds Bu_2CuLi to give the lithium enolate **54** which is quenched with methyl iodide to give the *anti* disubstituted[24] ketone **55**. This could in principle be made from the ketone **56**, but whatever regioselectivity **56** might show with LDA cannot be expected to favour **54**.



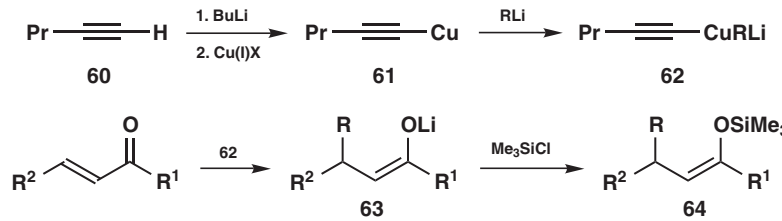
53 **54** **55** **56**

Tandem Michael/aldol reactions

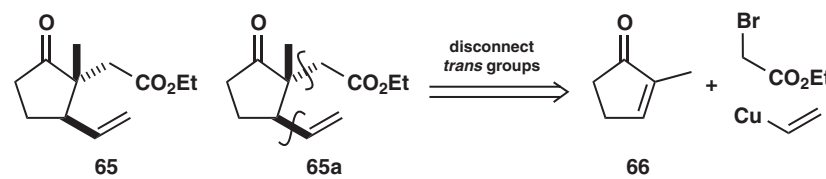
Aldol reactions with lithium enolates are improved if zinc(II) salts are present, or, if silyl enol ethers are used, $TiCl_4$ is also helpful. We have chosen the example of Me_2CuLi addition to the enone **57** as the examples in the literature[23] are overwhelmingly of cyclic enones, and we wanted an acyclic example. The aldols (mixed diastereoisomers) **59** are formed in 96% yield.[25]



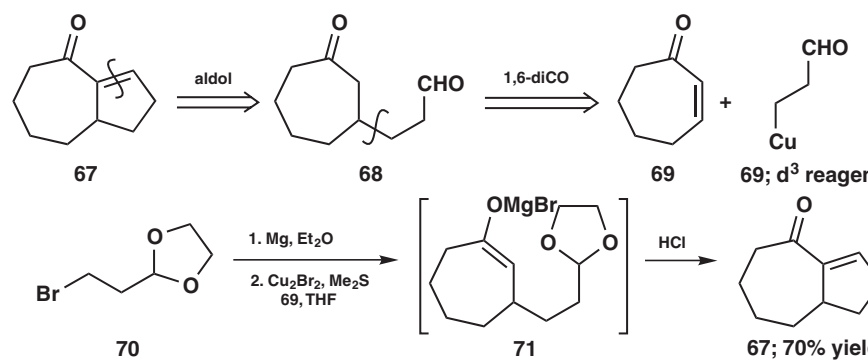
Before looking further at syntheses developed with this strategy, we must deal with an annoying feature of cuprates of the type R_2CuLi. Only one of the two R groups is transferred to the enone from the copper: the other is lost during the work-up. If this is simply Me, Bu, or Ph there is no problem, and that is why all our examples have been selected from these cuprates. Where the group attached to copper has itself been synthesised, perhaps including some stereochemical features, it is not acceptable to waste half of one's labours. Copper prefers to retain the better complexing group, that is the one with more π-bonds, or the one which forms the more stable anion.[26] There is particularly good selectivity between alkynes (retained) and alkanes (donated) so complexes such as **62** donate the alkyl group to enones and then alkynyl copper **61** can be recycled. Pent-1-yne **60** is commonly used for this sequence as it is the smallest liquid terminal alkyne (only just liquid - b.p. 40 °C).



The disconnection for these three-component syntheses is to remove the *trans* substituents from the α and β positions. Thus the ketone **65** disconnects to the enone **66**, a vinyl-Cu derivative and an electrophilic bromoester. In the event, a Cu_2I_2 catalysed Grignard addition followed by alkylation of the magnesium enolate gives pure *trans*-**65** in 91% yield.[27]

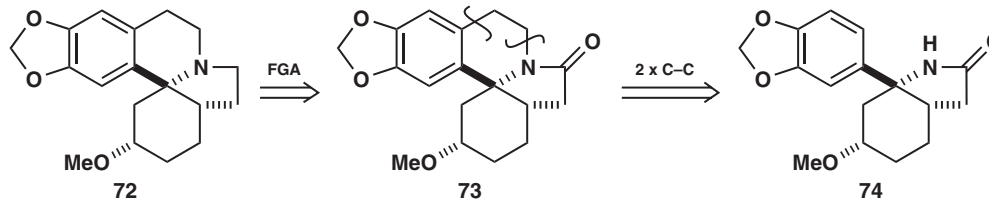


Functionalised nucleophiles normally need to be protected, as in the synthesis of the bicyclic enone **67** which requires the addition of a d^3 reagent to cycloheptenone **69**. The Me_2S complex of the Cu(I) derivative of **70** fills this role; deprotection and cyclisation being accomplished in acid solution.[28] This synthesis also illustrates that tandem Michael-aldol sequences of this kind with an intramolecular aldol are perfectly satisfactory.



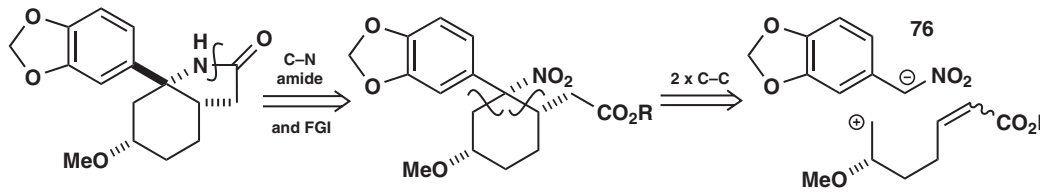
A Double Nucleophile: An Interlude without Copper

The *Erythrina* alkaloids such as dihydroerythramine **72** have an awkward junction of three rings at one carbon atom. The amide **73** offers the opportunity of disconnection of one ring but this still leaves the quaternary carbon atom intact **74**.



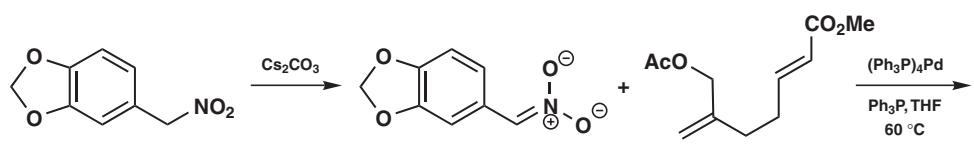
72 **73** **74**

One successful approach imagines two C−C disconnections around that carbon atom **75** using a nitro group to stabilise the anion **76** and a double electrophile **77** with a Michael acceptor on one side and some suitable a[2] reagent, perhaps an epoxide, on the other.[29]

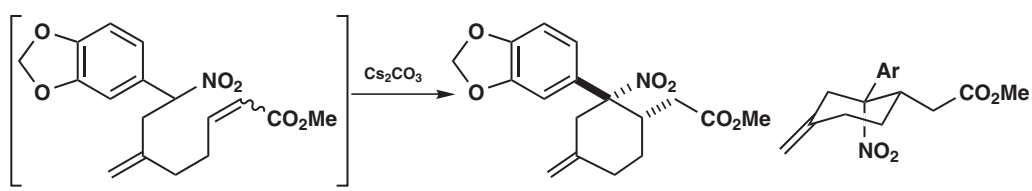


74a **75** **77**

A palladium-catalysed reaction of an allylic acetate (chapter 19) was used for the first C−C bond formation and the planned Michael addition for the second though the intermediate **79** was not isolated. The conformational diagram of **80** should help you to see why that diastereoisomer was favoured.



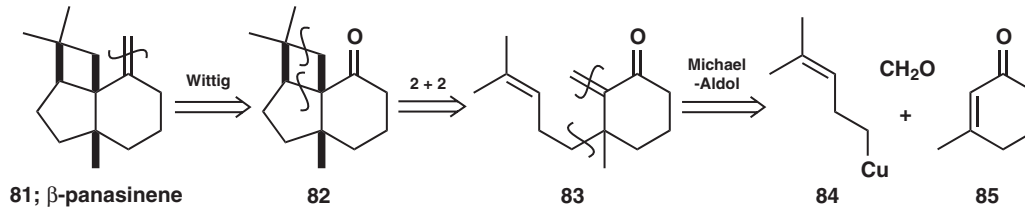
78 **76** **78**



79 **80; 79% yield, 4:1 diastereoisomers major diastereoisomer of 80**

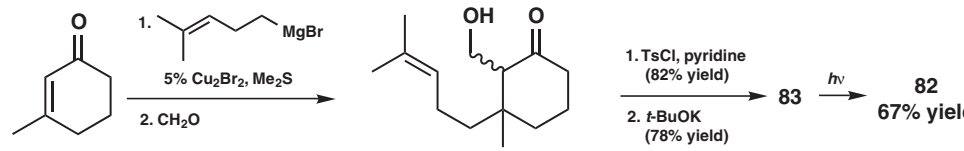
A Michael Reaction Coupled to a Photochemical Cyclisation: Copper Again

An intermolecular three-component step may be followed by other intramolecular reactions. In the synthesis[30] of β-panasinene **81**, a principal component of ginseng oil, the obvious Wittig disconnection leads to an equally obvious 2+2 photochemical cycloaddition[31] from dienone **83**. Either group may be disconnected from the β-position of **83** so it makes sense to remove the larger **84**.



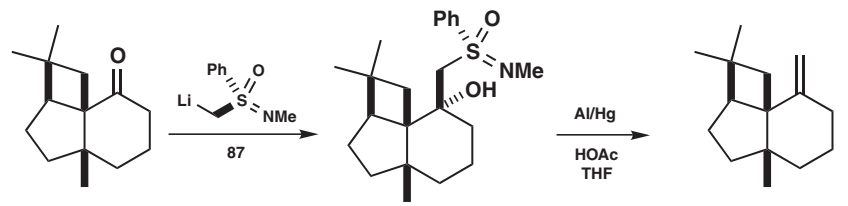
81; β-panasinene **82** **83** **84** **85**

Copper-catalysed Michael addition followed by an aldol reaction with formaldehyde, gives a 1:1 mixture of diastereoisomers of the aldol **86** that can be eliminated to the enone **83**. The resulting efficient photochemical cycloaddition gives ketone **82** with total regioselectivity probably because it is intramolecular.



85 **86; 90% yield, 1:1 *syn:anti***

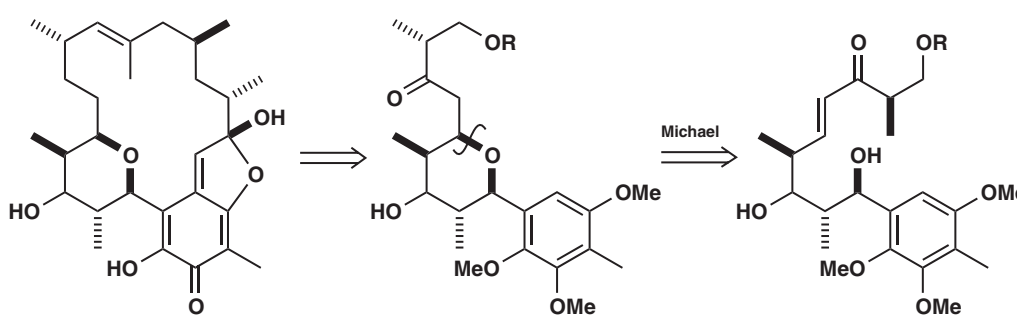
Then came a nasty surprise. The ketone **82** is rather crowded and would not undergo a Wittig reaction with $Ph_3P{=}CH_2$, but Johnson turned this to advantage by using his asymmetric reagent **87** to resolve the compound and do the methylenation in one step. Optically active **88** can be isolated in 42% yield (out of a maximum of 50%) and gives natural (−)-panasinene **81**.



82 **(+)-88; 42% yield** **(–)-81; β-panasinene**
92% yield

Michael Additions of Heteroatom Nucleophiles

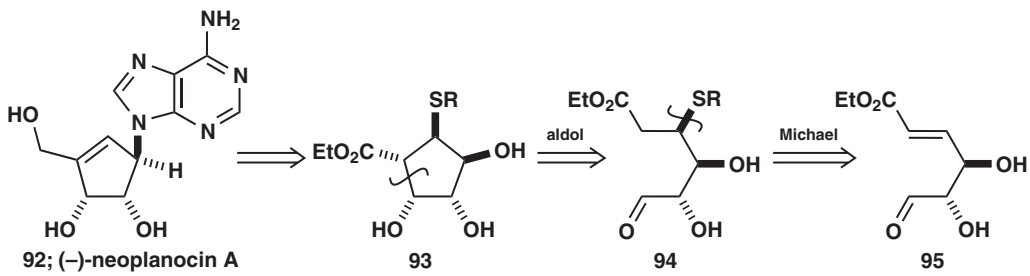
Michael additions of heteroatoms (O, N, S etc.) have been developed in modern chemistry to a high degree of regio- and stereoselectivity. Intramolecular Michael addition is particularly favoured and contributes a key reaction in Mulzer's synthesis of the antibiotic kedomycin[32] **89**. The intermediate **90** contains all the stereochemistry of the left hand side of kendomycin, the awkward quinone methide ring is replaced by a benzene ring, and, most significantly, a ketone has been introduced to allow Michael disconnection of a strategic C−O bond.



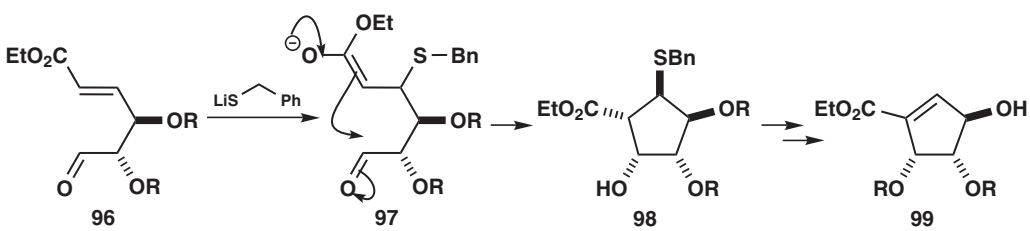
89; kendomycin **90** **91**

The enone **91** was made by a Horner-Wadsworth-Emmons reaction (chapter 15) and so has the *E*-configuration. The cyclisation to **90** in dilute methanolic acid in 92% yield occurs with remarkable selectivity. Only one of the two free OH groups reacts, only conjugate addition occurs, and the stereoselectivity is 97:3 in favour of the isomer shown.

Michael additions of heteroatoms can be coupled to reactions of the specific enolate produced. The synthesis of the modified carbonucleoside (−)-neoplanocin A **92** required some cyclopentane to which the heterocyclic purine could be joined. The decision was taken to close the cyclopentane by an aldol reaction. This required an aldehyde and an ester in a compound such as **94** to combine regio- and stereo-selectively without epimerisation of any chiral centres. The aldehyde is enolisable so there are serious problems.[33]



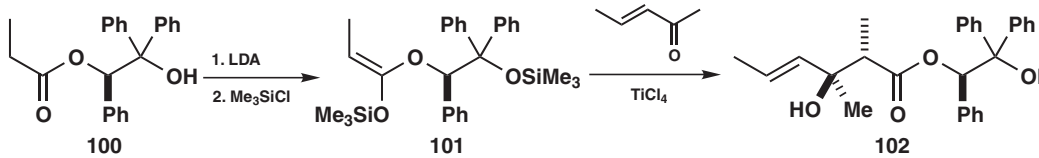
A sulfur atom was introduced to supply the control. Michael addition of a thiol ($PhCH_2SH$ was actually used) to the unsaturated ester **95** would give a specific enolate that might cyclise onto the aldol fast enough to prevent enol exchange. In practice the hydroxyl groups had to be protected and the lithium thiolate was added to **96** to give the specific enolate **97** that cyclised with good stereoselectivity to give mainly **98**. Elimination of the SBn group by oxidation (chapter 15) gave **99**, used to complete the synthesis.



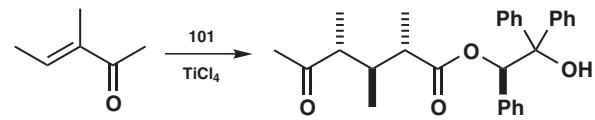
Michael Additions with and without Copper: Functionalised Michael Donors

Perhaps the major disadvantage of the copper-catalysed Michael reaction is the need to protect functional groups. Michael reactions with heteroatom nucleophiles or functionalised carbon nucleophiles are usually carried out without copper. Many such nucleophiles, particularly enol equivalents, are excellent at Michael reactions, and are often to be preferred for ease of working. Silyl enol ethers, enamines, and stabilised enolates all carry out Michael reactions. In the next chapter we shall look at specific enol equivalents in more detail and note which ones are good at Michael additions.

Do not suppose that the regioselectivity problem is now trivial. In a study mainly aimed at achieving asymmetric reactions, Braun[34] showed just how narrow is the gap between 1,2 and 1,4 addition. The silyl enol ether **101**, easily made from the enantiomerically pure ester **100**, gave mainly (>95:5) direct (1,2) addition to a simple enone under the usual conditions ($TiCl_4$ catalysis) for Michael addition.



A minor change in the structure of the enone: the addition of an α-methyl group to give **103**, led to an almost complete reversal of the regioselectivity: the Michael (1,4) adduct **104** was formed in a 95:5 ratio to the 1,2 adducts. The only difference is a slight increase in steric hindrance for direct addition but the switch from one reaction to the other is remarkable and a warning not to be complacent about our understanding of selectivity.



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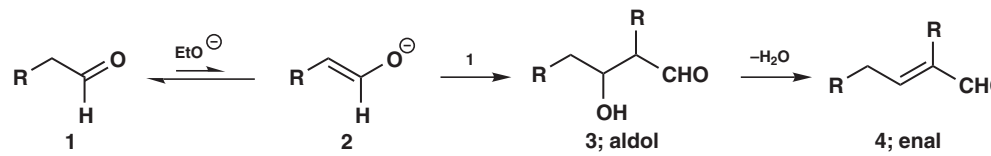
10 Specific Enol Equivalents

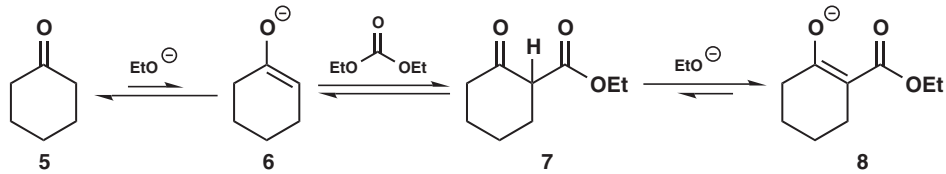
Introduction: *Equilibrium and Specific Enolates*

Almost every chapter so far has mentioned enolates in one form or another and their chemistry is central to organic synthesis. Now it is time to take stock of the various d^2 reagents developed to play the role of enolates, to see what reactions they are particularly suited for, what chemo- regio- and stereo-selectivity they show, and some examples of their use in total synthesis.

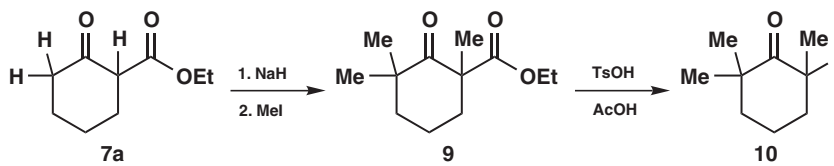
This is only a very brief summary of simple enolates. They are discussed more fully in *The Disconnection Approach*, chapters 18-28, pages 140-239. Originally enolates were generated by treating carbonyl compounds with weak bases, that is bases too weak to convert the carbonyl compound entirely into its enolate. Under these conditions, self-condensation with unenolised carbonyl compound is always a risk. With aldehydes it is unavoidable. Treating an aldehyde **1** with an alkoxide produces a small amount of enolate **2** that reacts rapidly with unenolised **1** to give aldols **3**, enals **4**, and further condensation products.



The less reactive ketones can be persuaded to react with other, usually non-enolisable, carbonyl compounds as in the reaction of cyclohexanone **5** with diethyl carbonate to give the β-keto-ester **7**. This reaction is really under thermodynamic control as the favourable equilibrium between the product **7** and its stable enolate **8** more than compensates for the unfavourable equilibrium between **5** and its unstable enolate **6**. This stable enolate **8** is a specific enolate.

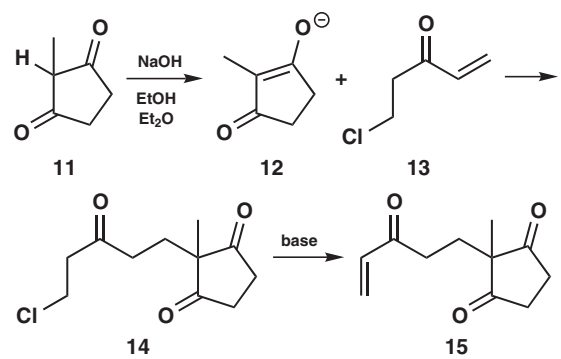


This product can be used to make 2,2,6-trimethylcyclohexanone **10** by methylation under forcing conditions to replace all the enolisable hydrogen atoms in **7a** and give **9**. In this reaction both the stable enolate **8** and the unstable enolates on the other side of the ketone must be methylated. The reaction[1] is completed by hydrolysis and decarboxylation of the CO_2Et group and the overall yield is a reasonable 41%.

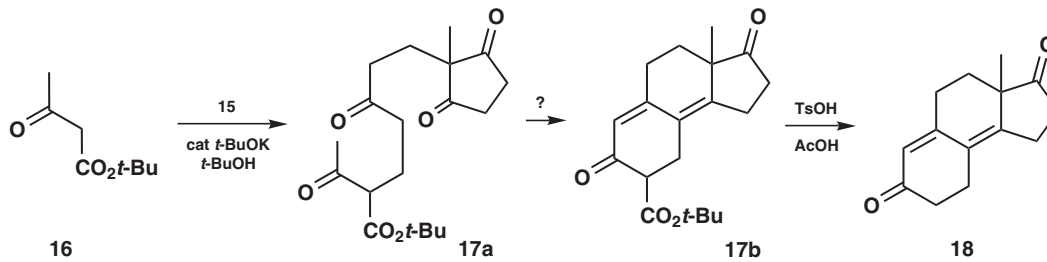


Enolates from 1,3-di-Carbonyl Compounds

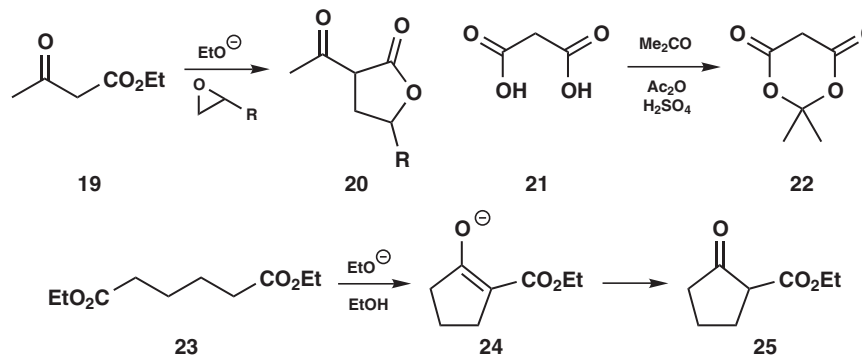
A simple example[2] should remind you of these useful reagents. Condensation of the stable enolate **12** of the 1,3-diketone **11** with the enone **13** gives the Michael adduct **14**. Elimination generates a new enone **15**.



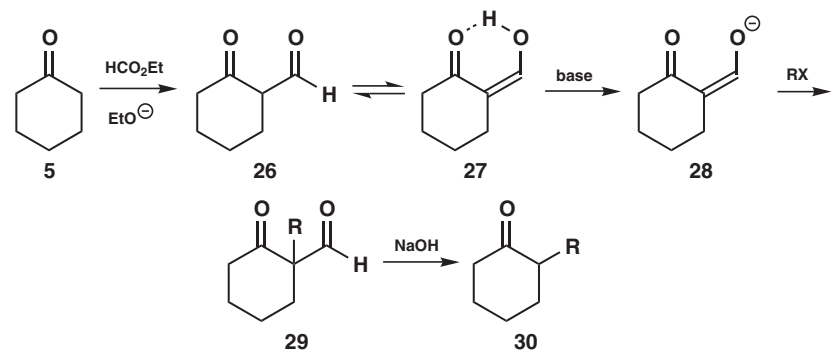
The new enone **15** condenses in turn in a second Michael addition with the keto-ester **16** under equilibrating conditions to form, presumably, intermediates like **17a** and/or **17b**. This gum is not isolated but hydrolysed and decarboxylated to give the steroid intermediate **18**.



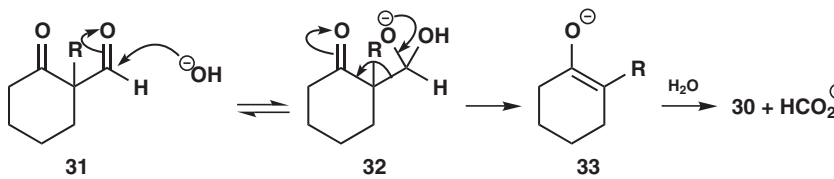
This sequence illustrates the use of enolates from 1,3-dicarbonyl compounds in Michael reactions: they are useful too in alkylations, aldol condensations (Knoevenagel conditions), and reactions with epoxides, as in the synthesis[3] of **20**. Nowadays they tend to be used if they are readily available, or if the disconnections suggest their use, as in the building of **11** into **18**. Examples include the diketone **11** and the six-membered equivalent both used in steroid synthesis, acetoacetates **16** and **19** and the keto-lactones **20**, malonic acid **21** and its esters, "Meldrum's acid" **22**, a very enolisable malonate derivative,[4] and the keto-ester **25** formed via its stable enolate **24**, by the cyclisation of the diester **23**, an intermediate in nylon manufacture. The compounds **11**, **16**, **19**, **20**; R=H, **21**, **22**, and **25** are all available commercially.



The 1,3-dicarbonyl approach is not suitable for aldehydes as the final destruction of the dicarbonyl relationship usually means that the aldehyde itself is sacrificed, as in the sequence **26** to **30** used in the alkylation of ketones.[5]

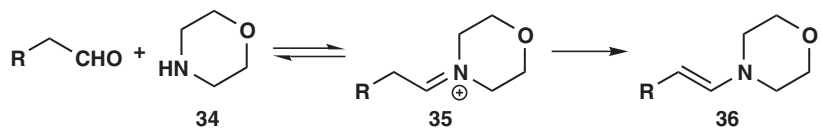


When the position between two carbonyl groups is blocked, attack by a nucleophile **31** occurs at the more electrophilic of the two (an aldehyde if there is one) cleaving **32** the 1,3-dicarbonyl system.

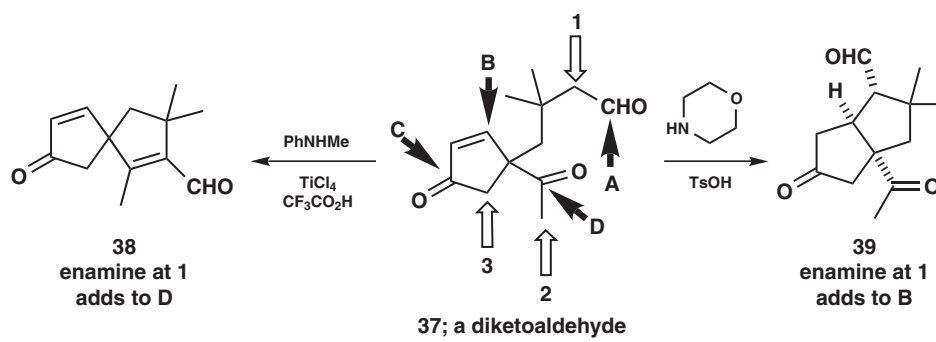


Enamines and Aza-Enolates

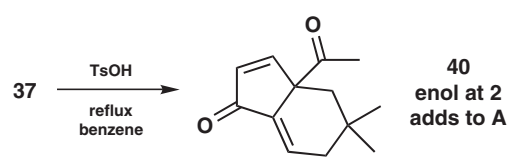
One specific enol equivalent that works very well for aldehydes is an enamine. Secondary amines such as Me_2NH, Et_2NH, pyrrolidine, piperidine, or morpholine **34** add cleanly to aldehydes to give enamines **36**. These relatively stable nitrogen analogues of enols react well with reactive alkyl halides, such as α-carbonyl halides, and in Michael additions. They were considered in chapter 2 and only a few extra examples will be given here.



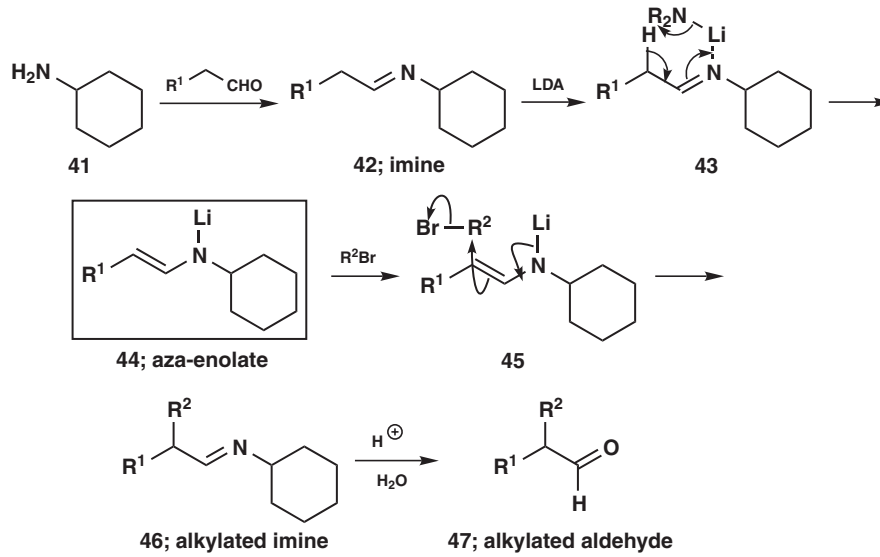
The diketo-aldehyde **37** has four electrophilic carbon atoms (A-D) and three positions for enolisation (1-3). Cyclisation could occur in twelve different ways. Three can be regioselectively realised by different conditions.[6] With morpholine catalysis, the aldehyde forms an enamine which does a Michael addition on the enone (B) to give **39**. Enamine formation with PhNHMe also gives the aldehyde enamine, but this time it does an aldol condensation with the simple ketone (D) to give **38**.



Finally, acid catalysed reaction gives the expected thermodynamic product **40**. All three products involve the aldehyde: the enamines select for d^2 behaviour of the aldehyde while acid catalysis brings it in as an electrophile (a^1). You cannot expect to achieve such control in all examples, but it is clear that enamines have something special to offer as aldehyde specific enol equivalents.



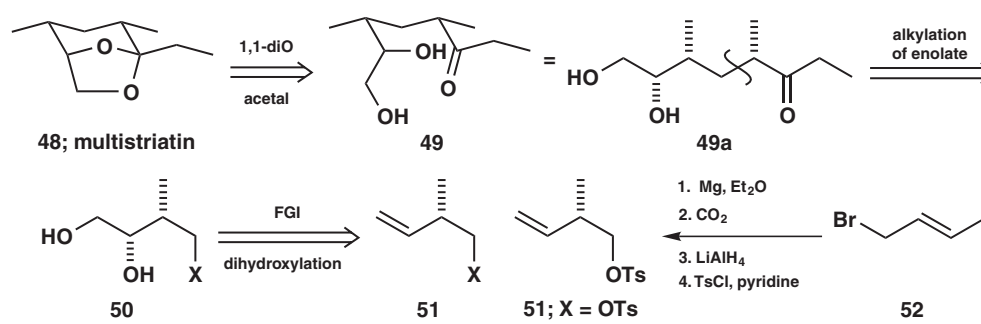
Alkylation with simple alkyl halides is generally a poor reaction with enamines. Alkylation often takes place on nitrogen instead of carbon, and Stork and others[7] have developed the aza-enolates to remedy this deficiency. A primary amine, usually cyclohexylamine, combines with an aldehyde to form an imine **42**. Treatment with LDA **43** gives the lithium derivative, the analogue of a lithium enolate, known as an azaenolate **44**. These intermediates are alkylated reliably at carbon **45** with most primary, and even with secondary alkyl halides, to give the alkylated aldehyde **47** after hydrolysis of the imine **46**.



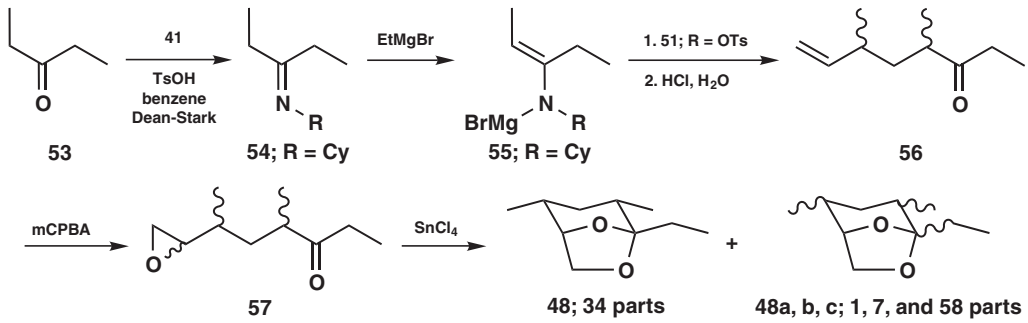
The synthesis of multistriatin

Dutch elm disease is a fungal disease, carried by elm bark beetles, which devastated the elm populations of many parts of the world in the 1970s. The beetles assemble at a suitable elm tree on the call of a pheromone containing, among compounds derived from the tree, one charactacteristic of the beetle itself, multistriatin **48**. The stereochemistry of this compound was deduced by the synthesis of the various possible isomers as so little natural product was available.[8] We shall use three of these syntheses to illustrate the application of aza-enolates to alkylation reactions.

Multistriatin **48** is an acetal formed from the keto-diol **49**. Disconnection **49a** next to one of the branchpoints reveals the enolate of a symmetrical ketone (Et_2CO). This will have to react with an alkylating agent **50** whose 1,2-diol could be masked if it were made from an alkene **51**. This is doubly attractive as the alkene **51** is available by known chemistry from **52**.

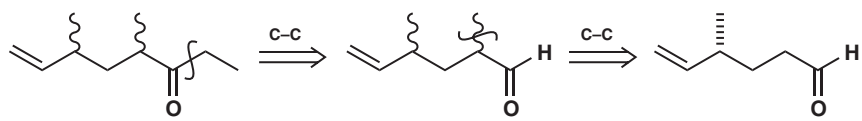


For the alkylation step, Silverstein[9] chose the magnesium derivative **55** of the aza-enolate of **53** and cyclohexylamine **41**. Reaction with the toluene sulfonate **51**; X=OTs gave inevitably a mixture of diastereoisomers of the enone **56**. It turned out not to be necessary to make the diol as the epoxide **57** could be directly transformed into multistriatin **48** with a Lewis acid catalyst (**48** and **57** are isomers). This method produced all four diastereoisomers and the all equatorial compound **48** was identical with natural multistriatin.



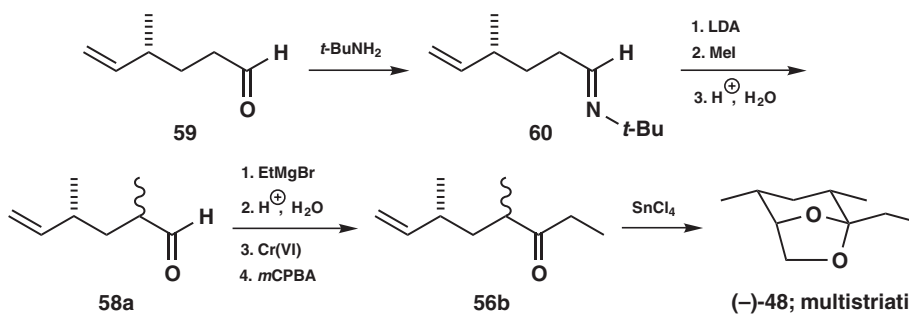
53 **54; R = Cy** **55; R = Cy** **56** **57** **48; 34 parts** **48a, b, c; 1, 7, and 58 parts**

Synthetic optically active compound was needed to check the absolute configuration of the natural product, and disconnection of the intermediate **56a** to the aldehyde **58** was chosen as **59** could be made from natural (+)-citronellol.



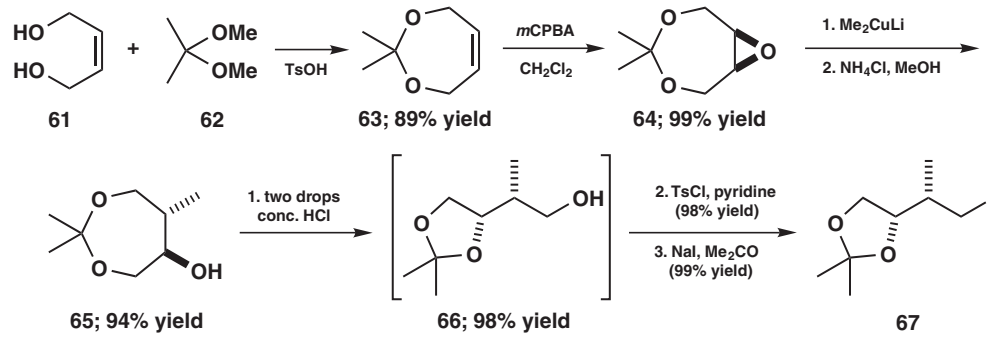
56a **58** **59**

For the alkylation step, the lithium derivative of the *t*-butyl imine **60** gave a good yield, but of course a mixture of diastereoisomers. The rest of the synthesis[10] is straightforward and gave a mixture of compounds from which the correct enantiomer of multistriatin was isolated in 53% yield. It emerged from this synthesis that the chiral centre next to the ketone could be epimerised to the correct configuration during acid-catalysed cyclisation of the final intermediates.

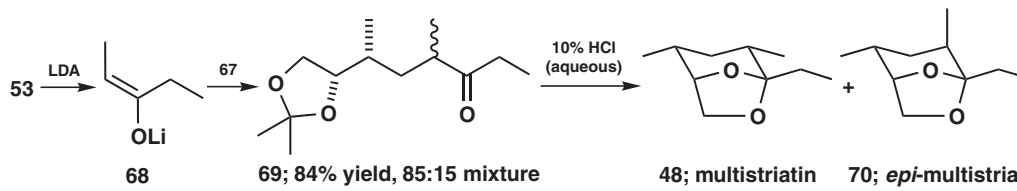


59 **60** **58a** **56b** **(–)-48; multistriatin**

All that is needed is a more controlled synthesis of the two other chiral centres, and one such started from the available *cis* butenediol **61**. Protection as an acetal **63**, epoxidation **64**, and epoxide opening with a cuprate (chapter 8) gave the correct diastereoisomer of **65**. This undergoes an acid-catalysed acetal rearrangement from the less stable seven to the more stable five-membered ring **66**, and a suitable leaving group (iodide) is introduced **67**. Every step goes in very high yield.



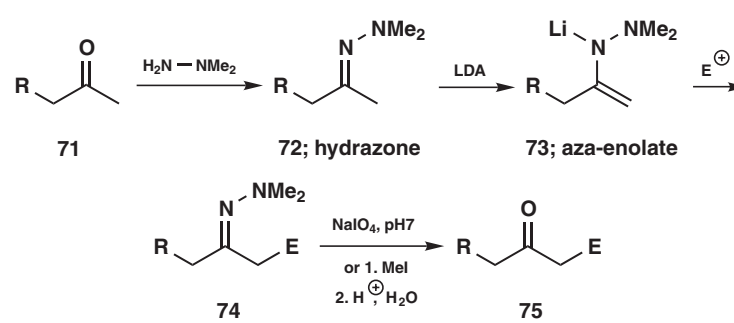
This time the lithium enolate **68** of **53** was used to give, after equilibration of the centre next to the ketone, a stereoselective synthesis of racemic multistriatin.[11] The yield in the final step was 98% of an 85:15 mixture of **48** and **70** separated by chromatography.



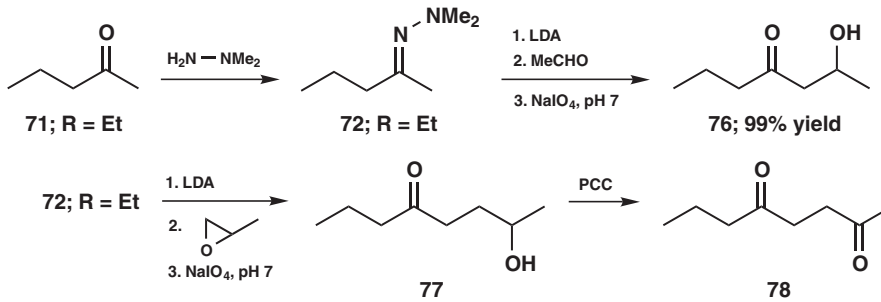
It would be a fair summary of the present situation to say that lithium enolates of ketones or esters are now usually preferred to aza-enolates for nucleophilic alkylation, but that lithium derivatives of cyclohexyl or *t*-butyl imines are preferred for the nucleophilic alkylation of *aldehydes*. We shall treat lithium enolates later, along with the equally popular silyl enol ethers, but there is one more nitrogen derivative which should come first.

Metallated hydrazones

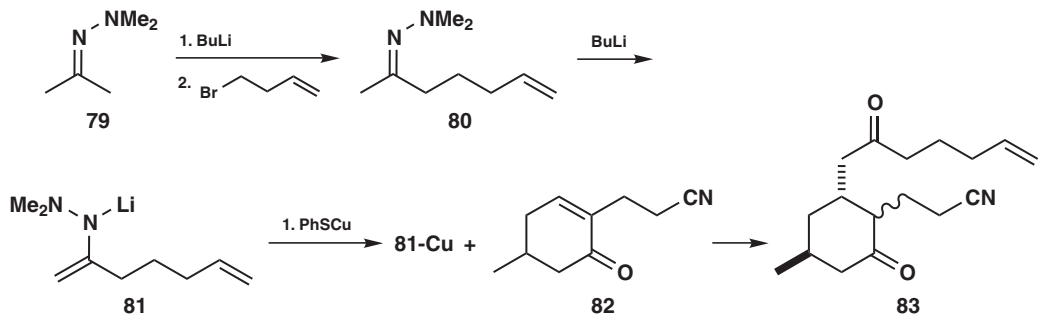
Various derivatives of aldehydes and ketones are used to make stable crystalline compounds for purification and identification, chiefly oximes and substituted hydrazones, and it was inevitable that they should also be tried out as sources of d^2 reagents. Only the *N,N*-dimethylhydrazones have emerged as important reagents. Dimethyl hydrazine gives *E*-hydrazones, e.g. **72** from unsymmetrical ketones **71** with the NMe_2 group *cis* to the methyl group.[12] Lithium derivatives **73** can be made with LDA or BuLi and these react with electrophiles (E^+) to give a new bond to the methyl group **74**. The products are formed as stable hydrazones and must be worked up under oxidative conditions, or by alkylation and hydrolysis, to restore the carbonyl group **75**.



Clean reaction occurs with enolisable aldehydes or ketones to give aldol products, e.g. **76** and with epoxides to give products **77** with a 1,4-relationship between the functional groups. The oxidative work-up affects neither secondary alcohol, but these can of course be oxidised with Cr(VI) if a diketone **78** is wanted.

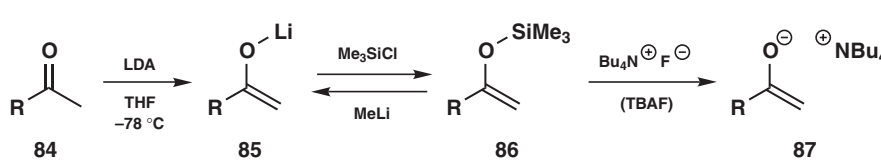


Alkylation and Michael addition also occur, and these are illustrated together in Heathcock's synthesis of lycodine intermediates. The dimethylhydrazone of acetone **79** can be alkylated to give **80**. The hydrazone is retained while the lithium derivative is again formed. Though the new hydrazone **80** must intially have the *Z* configuration, its lithium derivative **81** can rotate to the *E* configuration while lithium is exchanged for copper so that a Michael addition to the enone **82** can be carried out. The product **83** has the expected *anti*-1,3 relationship due to axial attack, but no stereoselectivity was found on protonation next to the ketone.[13]

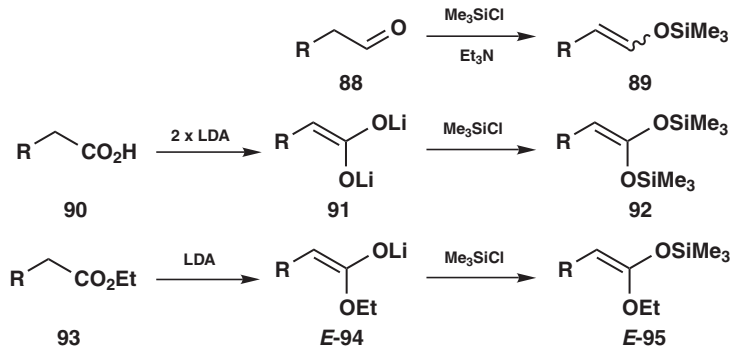


Lithium Enolates and Silyl Enol Ethers

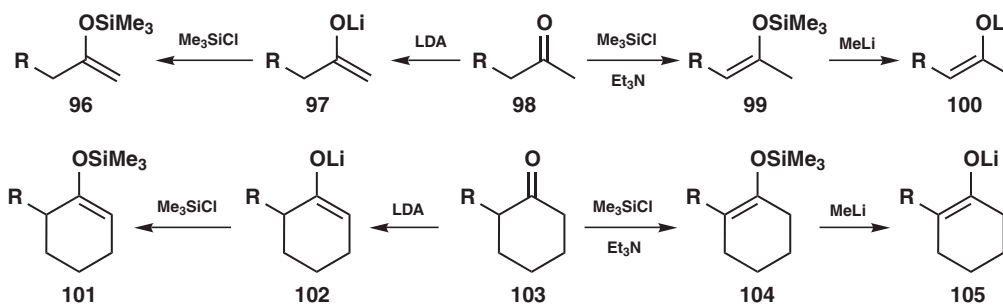
Lithium enolates **85** and silyl enol ethers **86** are probably widest in application in modern organic synthesis. The basic rules of selectivity were laid down in chapters 2-4 where many examples were given. We shall simply summarise the position and add some extra versatility from chapters 5-9. These two methods must be taken together because easy interconversion means that a way of making one is a way of making another. In addition, the silyl enol ethers **86** are a source of "naked" enolates **87** when fluoride is used to remove silicon in the absence of a metal cation. Tetra-alkyl ammonium fluorides such as TBAF ($Bu_4N^+ F^-$) are usually used.



Aldehydes **88** do not form stable lithium enolates as the aldol reaction is too fast, but they form stable silyl enol ethers **89** under equilibrium conditions. Acids **90** can be transformed into either type of derivative: the dilithium enolate **91** or the ketene silyl acetals **92**. Esters give predominantly *E*-lithium enolates and silyl enol ethers, e.g. 65:15 *E:Z* -**95**; R=Me. Amides rarely give satisfactory enolates.

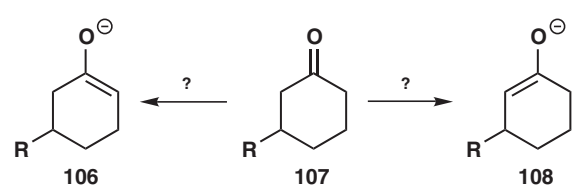


With ketones we come to the problem of regioselectivity, and the situation from chapter 3 is that methyl ketones **98** and ketones with one primary and one secondary alkyl group, particularly cyclic ketones such as **103** give the less substituted lithium enolate **97** or **102** by kinetically controlled deprotonation with LDA, and the more substituted silyl enol ether **99** or **104** on silylation under equilibrium conditions. Either derivative (lithium enolate or silyl enol ether) may be used to make the other, e.g. **96** and **100**.

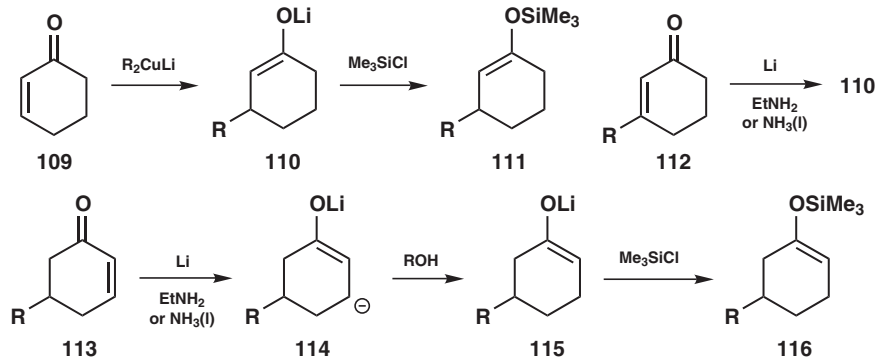


Specific enolates by conjugate (Michael) addition

After our discovery of Michael additions of lithium cuprates to enones in chapter 9, we are also now able to make specific enolates **106** and **108** of unsymmetrical ketones whose branchpoint is the β rather than the α atom, such as 3-alkyl cyclohexanones **107**. That is, providing we don't try and make them from the ketone itself.



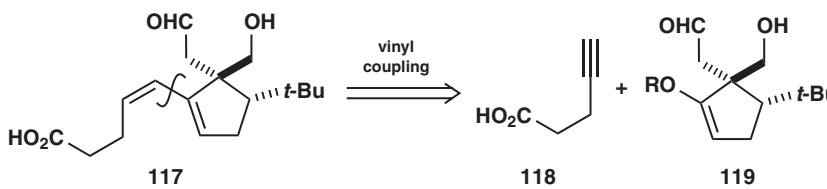
Addition of R_2CuLi to cyclohexenone **109** gives the lithium enolate **110** and hence the silyl enol ether[14] **111**. It is not so obvious how to make the alternative enolates, but reduction of enones with Li in liquid ammonia or in a simple amine such as Et_2NH gives the lithium enolate by the Michael addition of hydrogen.[15] Two electrons are added to the enone to give the unstable dilithium derivative **114**. One molecule of a weak acid (usually *t*-BuOH or water) is present which protonates the more unstable of the two anions to give the lithium enolate **115**. This means that enone **112** is an alternative source of **110** and **111**.



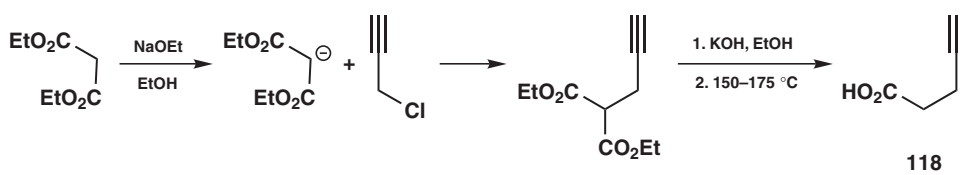
Since we know many methods to make enones with complete regioselectivity (chapter 5) we are equipped to make both specific enolates of any unsymmetrical ketone, though not necessarily *from* the ketone itself. It is of course a strategic advantage to have methods which make carbon-carbon bonds on the way to specific enolates as these methods are more versatile and more likely to be convergent.[16]

An intermediate in Corey's ginkgolide synthesis

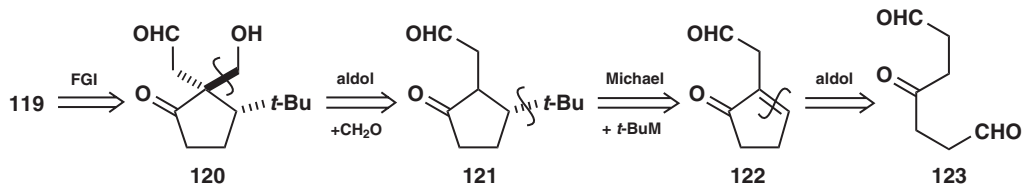
A few examples should make modern approaches plain. In Corey's ginkgolide synthesis he needed the intermediate **117** and decided to make it by coupling two vinyl derivatives (see chapters 11 and 20), the one derived from a triple bond **118** and the other an enol derivative of a cyclic ketone **119**.



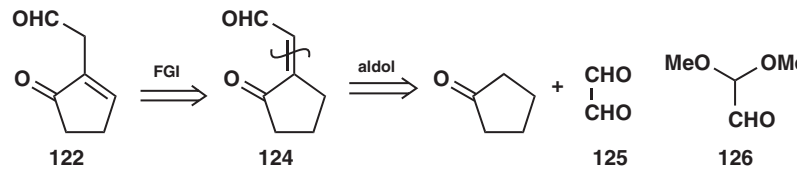
The first **118** was made by alkylation of a malonate ester followed by hydrolysis and decarboxylation in the traditional way. With no problems of regio- or stereo-selectivity there is something to be said for methods easily carried out on a large scale.



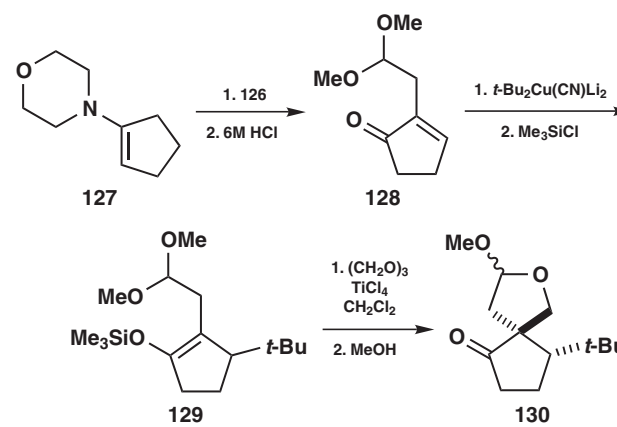
The second **119** clearly came from the ketone **121** and this looks like an aldol product from CH_2O and a specific enolate of the ketone **121**. This ketone is substituted at only one α-atom, so regioselective enolisation would be possible. But there are problems of chemoselectivity (the other CHO group) and stereoselectivity and a Michael addition approach on the enone **122** looked more promising. Aldol disconnection of **122** seems to have uncovered an excellent symmetrical intermediate **123** which can cyclise only to give **122**.



Corey evidently did not want to work with a keto-dialdehyde **123** and preferred to consider the aldol disconnection on the alternative enone **124** (the double bond will readily move into the ring). This reveals a symmetrical dialdehyde **125**, but this is too reactive to be used and Corey preferred the half-protected compound **126**.



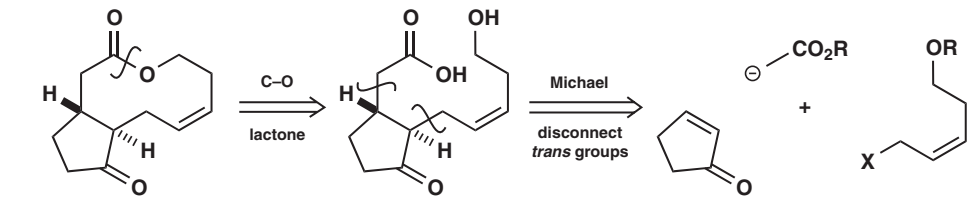
The morpholine enamine **127** of cyclopentanone ensured a clean aldol reaction and strong HCl put the double bond into the ring to give **128**. Cuprate addition and trapping by silylation gave the specific enol equivalent **129** which reacted with formaldehyde polymer under the usual Lewis acid catalysis to give **130**, which is **120** protected as an internal acetal. The electrophile (CH_2O) added to the opposite face of the enol to the one occupied by the *t*-butyl group.[17]



A synthesis of jasmine ketolactone

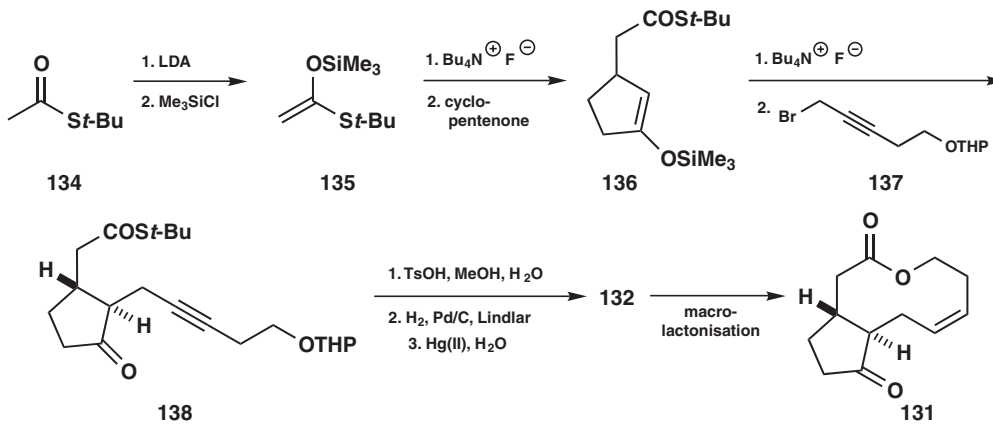
The synthesis of the macrocyclic lactone **131** found in jasmine flowers illustrates the use of "naked" enolates. Lactone disconnection to **132** and the usual Michael-based three-component

disconnection reveals cyclopentenone, an acetate enolate equivalent, and a *Z* allylic halide **133** with an OH group which will have to be protected.



131; jasmine ketolactone **132** **133**

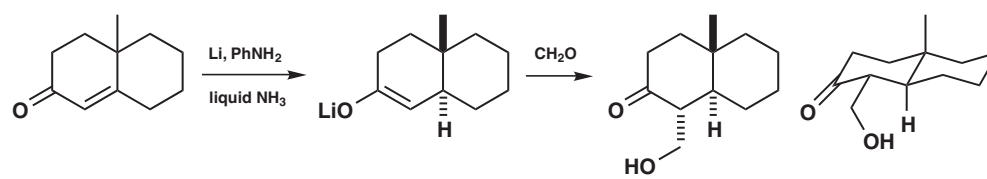
The *t*-butylthiolester **134** provides the silyl enol ether **135** as the acetate enolate equivalent and adds to cyclopentenone with fluoride catalysis to give the silyl enol ether **136**. Release of the naked enolate and alkylation with the alkyne **137** gives **138** which has the correct *anti* stereochemistry and can simply be transformed into the hydroxy acid.[18] The final cyclisation demands special methods we shall meet in chapter 43.



134 **135** **136** **137**

138 **131**

When the enolate is formed by reduction of an enone, the first chiral centre is created by protonation and is often under thermodynamic control. Thus the steroid intermediate **139** is reduced to the *trans* decalin **140**. Reaction with an electrophile (here CH_2O) occurs on the *same* side as the added proton as the group that was already there (the other ring in **140**) is bigger than the added hydrogen atom. The conformational drawing **141a** shows that the CH_2OH group is equatorial and may also have equilibrated by enolisation.[15]



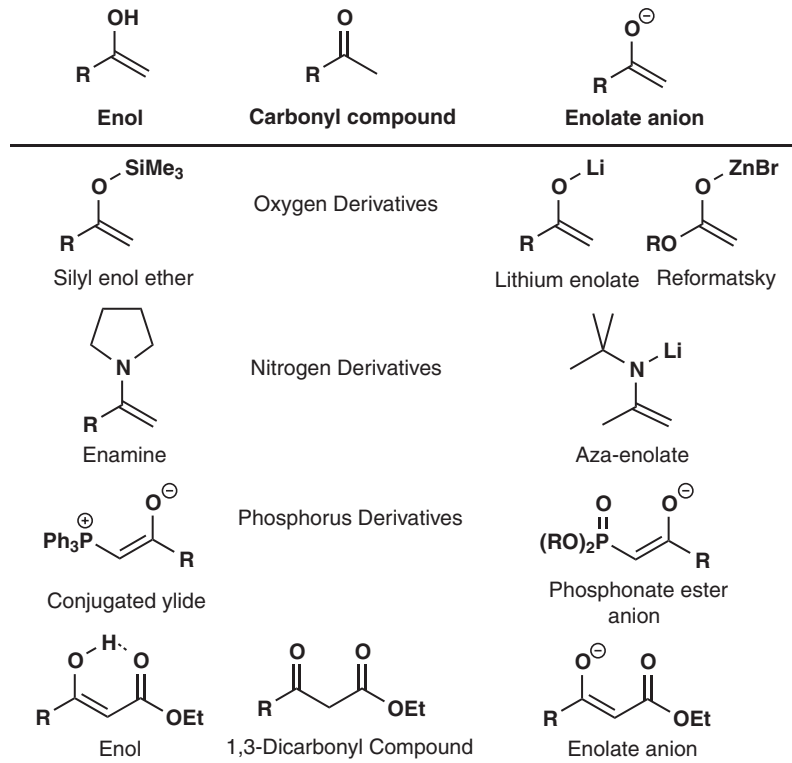
139 **140** **141** **141a**

Tables of Enol Equivalents and Specific Enolates

Table 1 lists the simplest enolates. The less reactive enol-like compounds on the left and the more reactive enolate like compounds on the right. The headings reflect this but you should be aware by

now that the simple enols and enolate anions shown there cannot be prepared and isolated but are normally used in equilibrium with the carbonyl compound.

In general terms the reagents on the left are good at conjugate addition while those on the right are reactive enough to be alkylated. All react with simple carbonyl compounds in aldol and Claisen ester reactions.

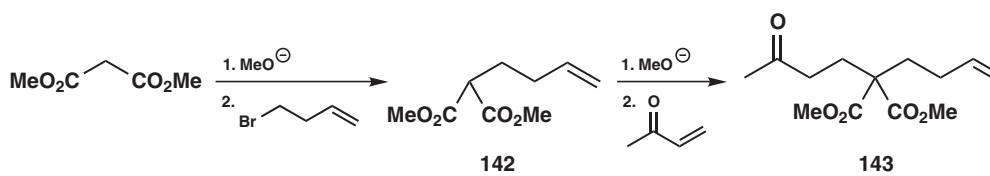


Modern Use of Specific Enolate Equivalents

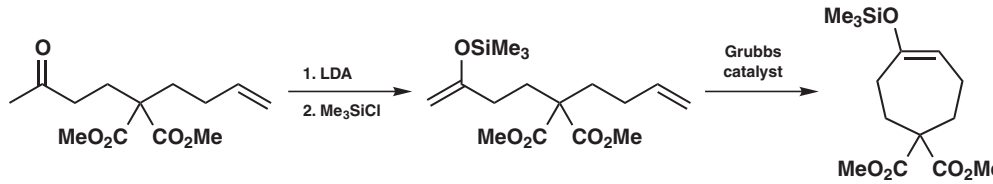
So which specific enolates are in normal use today? The answer is simple - all of them! We shall end this chapter with a few examples to make the point.

Malonates, lithium enolates and silyl enol ethers in one synthesis

In a study of ring closure by metathesis (chapter 15) to produce specific enol equivalents from cyclic ketones, Shibasaki[19] decided to use enolates from malonates to make the many starting materials quickly. For example, alkylation followed by conjugate addition gave starting material **143** in two steps.

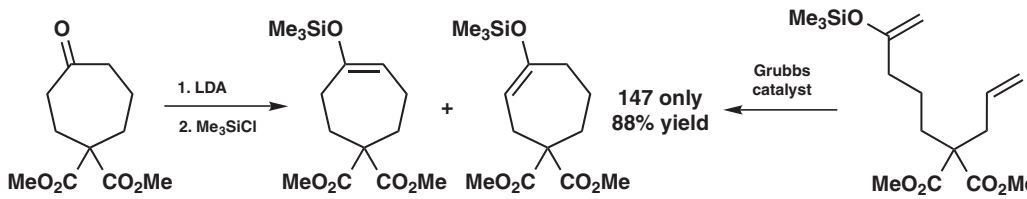


This was converted into the kinetic lithium enolate and then into the silyl enol ether **144**. Metathesis with the Grubbs catalyst (you will meet this properly in chapter 15) gave the cyclic silyl enol ether **145** in 99% yield.



143 **144** **145**

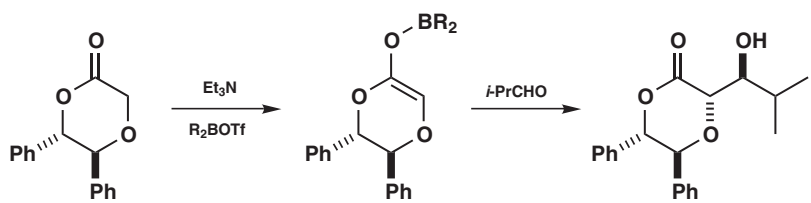
If the unsymmetrical cyclic ketone **146** was treated with LDA and Me_3SiCl, some of the same silyl enol ether **145** was formed but as 30% of a mixture with the alternative **147**. This could also be prepared by metathesis from the unsaturated compound **148**, prepared in a similar way. This is surely the best way to produce specific enolates of (though not from) unsymmetrical cyclic ketones. This study shows how an old method (malonate), modern methods (lithium enolates and silyl enol ethers) and very modern methods (metathesis) can be used in cooperation to produce excellent results.



146 **145 (30%)** **147 (70%)** **148**

Other metal enolates

Later in the book, when we deal with asymmetric enolate reactions, boron enolates will be very important. A simple example[20] of an aldol reaction with a boron enolate, prepared from the ester **149** and a boron triflate using an amine as base, shows why. The boron enolate **150** could be prepared with a weak base and reacts with the aldehyde without catalysis to give essentially one diastereoisomer of the aldol **151** in good yield. If the titanium enolate (prepared with $TiCl_4$ and an amine) was used, both the yield and the stereoselectivity were worse. In other circumstances enolates of titanium and other metals are very successful.

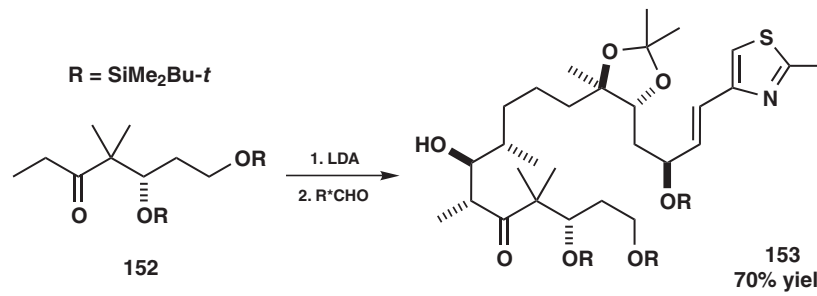


149 R = cyclohexyl **150** **151; 86% yield**

Coupling large fragments with metal enolates

Even reactive lithium enolates can be used to couple complex fragments burdened with extensive functionality and stereochemistry. Mulzer's work on epothilones[21] combined the lithium enolate

of the ketone **152** with an aldehyde in an aldol reaction to give a 70% yield of the epothilone analogue **153**.



152 **153** **70% yield**

The product **153** is formed in good yield and stereoselectivity though the aldehyde (whose structure you can easily deduce from that of **153**) has an enolisable chiral centre and various other functional groups and stereogenic centres. Specific enolates are vital reagents for the 21st century.

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General references are given on page 893

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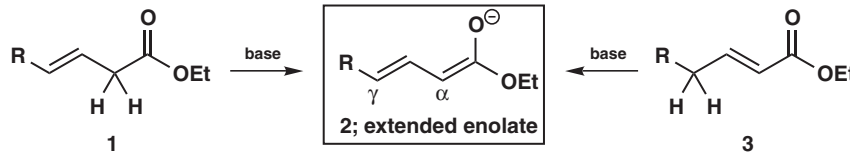
11 Extended Enolates

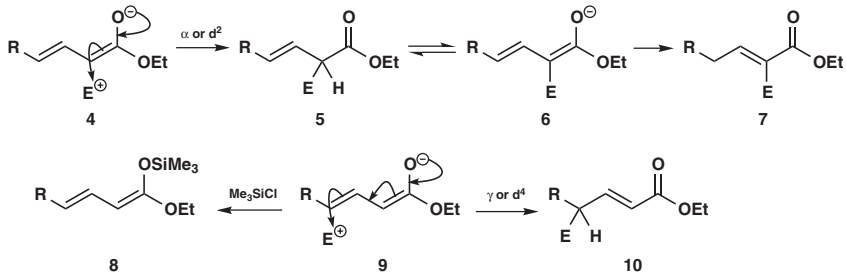
Introduction: *The extended enolate problem*

The extended enolate problem[1] is easily stated but not so easily solved. If an unsaturated ester **1** is treated with base, a conjugated enolate **2** is formed. The conjugated ester **3** can form the same enolate **2** by loss of one of the marked protons. This intermediate **2** is an *extended enolate*, extended by conjugation into a double bond and interesting because a new dimension of versatility is added to its reactions. Enolates normally have to choose between reaction at oxygen or carbon, but the extended enolate may also choose at which carbon to react. This chapter is about the reasons for that choice.



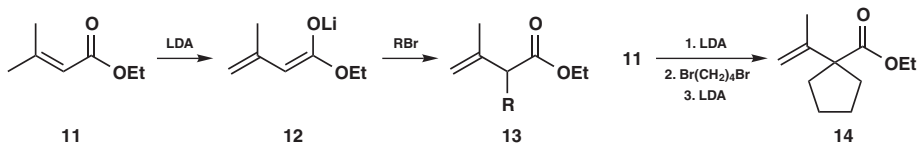
The two possibilities are traditionally known as α and γ. Reaction in the α position **4** as a d^2 reagent gives unconjugated ester **5** which may become conjugated[1] by α to γ proton transfer via extended enolate **6**. Reaction in the γ position **9** as a d^4 reagent gives conjugated **10** directly. The remaining possibility – reaction at oxygen – is realised by silylation to give the extended silyl enol ether **8**.

Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

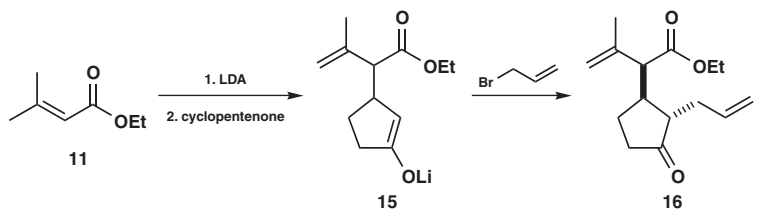


Kinetic and thermodynamic control

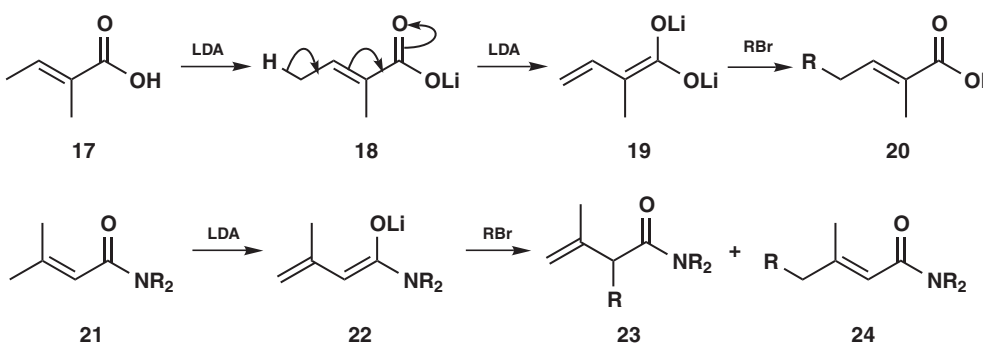
The kinetic site for reactivity is the α position, where the coefficient of the HOMO is larger,[2,3] but reaction at the γ position gives the more stable conjugated product. Ester **5** is the kinetic product and **7** and **10** are thermodynamic products. Early experiments[4] soon revealed that reactive lithium enolates such as **12** were alkylated almost exclusively with kinetic control at the α position, making synthesis of rings **14** possible by double alkylation.[5]



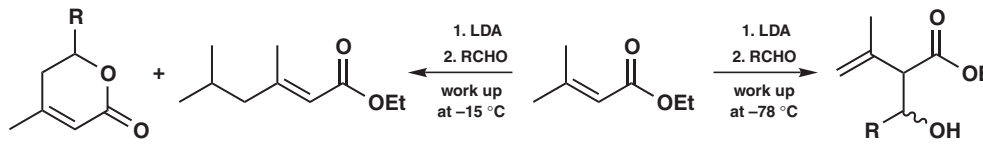
Even Michael addition occurred at the same (α) site and the resulting specific enolate **15** can be alkylated with the stereoselectivity expected for three-component reactions from chapter 9 (*anti* addition of the new groups). The product **16** was used by Oppolzer in his synthesis of khusimone.[6]



The dilithium derivatives **19** of carboxylic acids **17** are much more inclined to alkylation at the γ position[7] to give **20** though α-alkylation is by no means uncommon,[8] while extended enolates **22** of amides such as **21** occupy a midway position, ratios of **23**:**24** varying from 67:33 to 98:2 for different R groups. In both these last two examples the metal can be exchanged for copper to improve γ-selectivity, as it seems copper favours conjugate addition both for nucleophiles and for electrophiles.[9]



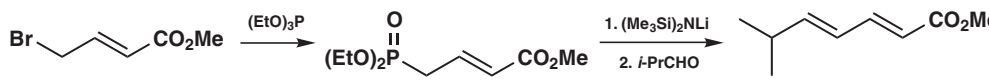
Alkylation is essentially irreversible, so thermodynamic products are difficult to make, but the aldol reaction is reversible, and the proportion of reaction at the γ position of ester **11** and acid **17** derivatives in aldol reactions increases both with temperature and time. Hence the α-aldol **27** is the product with the extended enolate of ester **11** if the reaction is worked up at low temperatures. At higher temperatures the γ-aldols **25** and *E*-**26** are the only products,[10] the lactone **25** coming from cyclisation of *Z*-**26**.



Z-25 *E*-26 11 27

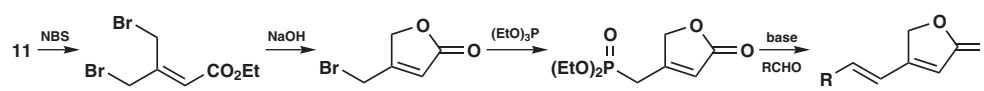
Wittig and Horner-Wadsworth-Emmons Reactions

A device for getting extended enolates of esters to combine with aldehydes and ketones in the γ position is to use a Wittig approach. The bromo-ester **28** is commercially available. Reaction with a trialkyl phosphite gives the phosphonate ester **29** that gives dienes such as **30** with aldehydes.[11] Phosphonium salts can also be used.[12]



28 29 30; 97:3 *E.E:Z,E*

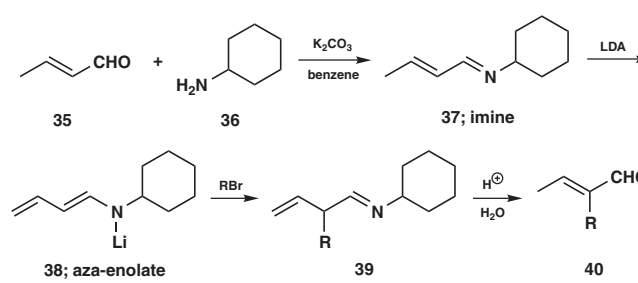
Other γ-bromoesters such as **31** can be made by radical bromination[13] with NBS (this too is a γ reaction!) and used in similar Horner-Wadsworth-Emmons reactions. It does not matter if some reaction occurs at the γ position of **29** or **33** as the Wittig elimination cannot occur on such an intermediate and it reverses. The products of these 'aldol' reactions are dienes **30** and **34** and are usually made for use in Diels-Alder reactions. We shall return to this subject later in this chapter.



31 32 33 34

Extended Aza-Enolates

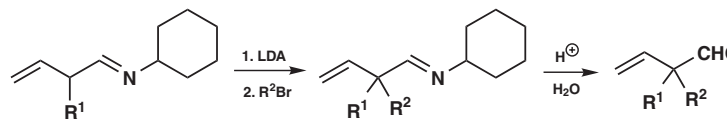
Aldehydes present special problems as usual. For alkylations in the α-position, the aza-enolates discussed in chapter 10 are the best. The cyclohexylimine **37** can be made in 82% yield from crotonaldehyde[14] and its lithium derivative **38** reacts cleanly at the α-position with alkyl halides[15] to give the non-conjugated imine **39**.



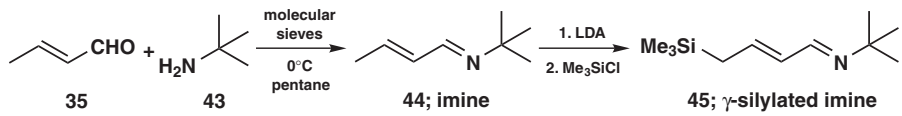
35 36 37; imine

38; aza-enolate 39 40

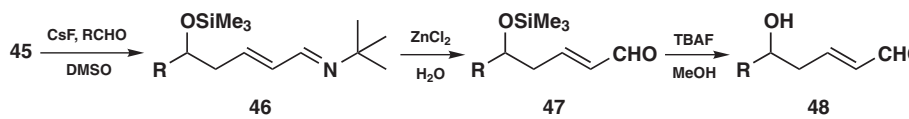
There is naturally a problem in hydrolysing **39** to the unconjugated aldehyde as the double bond tends to move into conjugation to give **40** unless the α-position is blocked **42** by two alkylations.[15]



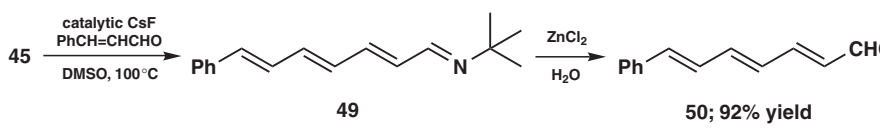
Aldol reactions also occur with these intermediates **38** though α,γ mixtures are often formed.[16] Silylation of *t*-butyl imines occurs reliably in the γ-position and this is one of the best ways to control aldol reactions with extended enolates.[17]



Treatment of **45** with an aldehyde RCHO at room temperature with catalytic CsF to remove the silyl group creates low concentrations of free extended enolate that react in the γ-position with the new aldehyde to give the imine **46**. This can be converted into the true γ-aldol **48** by hydrolysis and removal of the silyl group.

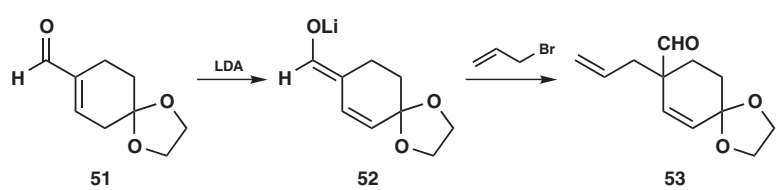


Under more vigorous conditions (100 °C) the dienal is formed in good yield and it is even possible to combine two enals to form a trienal, e.g. **50**, regiospecifically.



Extended Lithium Enolates of Aldehydes

Extended lithium enolates of conjugated aldehydes are more stable than those of simple unconjugated aldehydes, and can be used particularly where there is a branch at the α-position as in the vernolepin intermediate **53** which can be made by alkylation of the lithium derivative[18] **52**. You will notice that the ketone in **51** is protected, an obvious precaution against enolisation, and it is impressive that the enolate-acetal in **52** does not fragment.

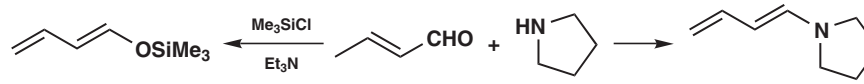


Summary: α-Alkylation of Extended Enolates

To summarise: α-alkylation of extended enolates of esters, acids, and aldehydes with alkyl halides or Michael acceptors can be accomplished reliably by kinetic methods. These reactions are particularly suited to producing quaternary centres between C=O and C=C functional groups. Aldol reactions are not so reliable, but can be controlled by temperature in some cases, and by Wittig approaches in others. We now need to look at ways of getting reaction at the γ-position.

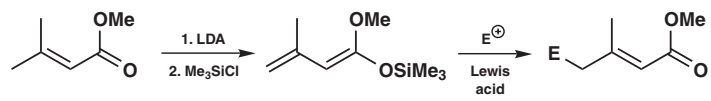
Reaction in the γ-Position

The most obvious methods of activating the γ-position would involve enamines[19] and silyl enol ethers.[20] These are the more stable of the various specific enol equivalents (chapter 10) and thus are more suited to thermodynamic control. Extended enamines **55** are easy to make and are excellent electron-rich dienes for the Diels-Alder reaction but react in the α-position with most alkylating agents.

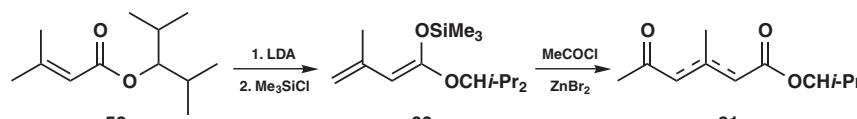


54 **35** **55**

Silyl enol ethers from aldehydes **54** and esters **57** are reagents that give clean reaction at the γ-position with a variety of electrophiles **58**. Acylation occurs under Friedel-Crafts conditions, and the crowded esterifying group $(i\text{-Pr})_2CH$ in **59** ensures that reaction occurs entirely at the γ-position. The product is a mixture of double bond positional isomers **61** as both are conjugated with one of the carbonyl groups.

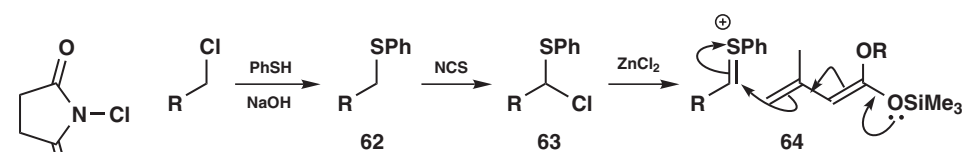


56 (cf. 11) **57; 93% yield** **58**

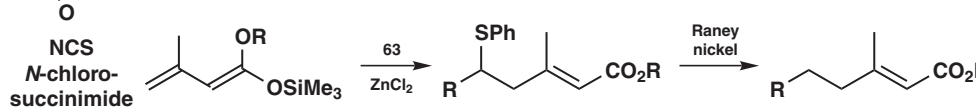


59 **60** **61**

It is more difficult to make alkylation reversible but Fleming and Paterson achieved this by using a PhS group to stabilise even a primary cation.[21] An alkyl halide is converted into a sulfide **62** and then into a chlorosulfide **63** with *N*-chlorosuccinnimide (NCS) by the Pummerer reaction. These compounds **63** react with Lewis acids to give sulfur-stabilised cations that react in the γ-position **64** with silyl enol ethers **65** to give **66**.

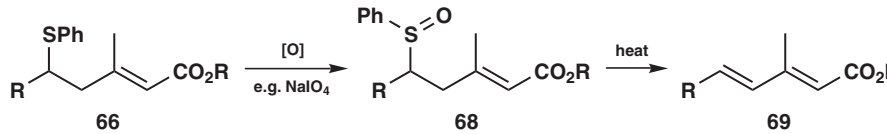


NCS ***N*-chloro-succinimide** **62** **63** **64**

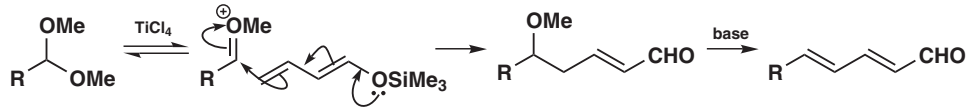


65 **66** **67**

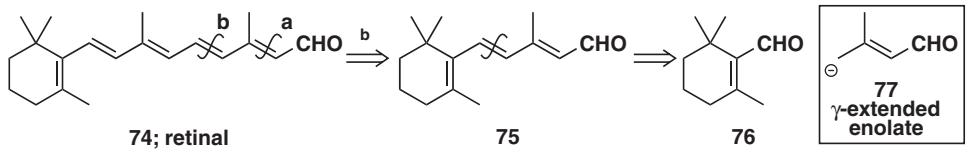
The PhS group may be removed in two ways: reductively with Raney nickel to give **67**, the product of γ-alkylation of **65** with the alkyl halide, or oxidatively by thermal decomposition of the sulfoxide **68** (chapter 32) to give the new double bond in **69**, the product of an extended aldol reaction, like the ester **30**.



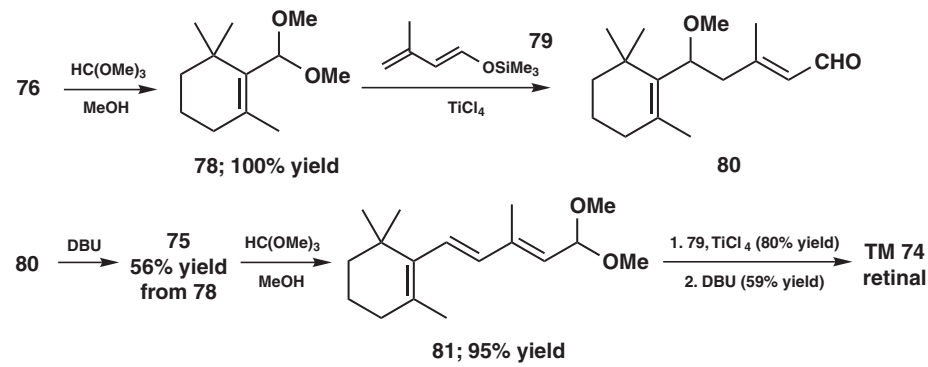
The true extended aldol reaction, the combination of an extended enolate in the γ-position, with an aldehyde or ketone, can best be realised by combining a silyl enol ether **54** with an acetal **70** under Lewis acid catalysis.[20] The Lewis acid, usually $TiCl_4$, catalyses the formation of the oxonium ion **71** which adds in the γ-position to the silyl enol ether [cf. **64**] to give the adduct **72** from which the remaining OMe group can be removed with base to give the dienal **73**, the extended aldol product.



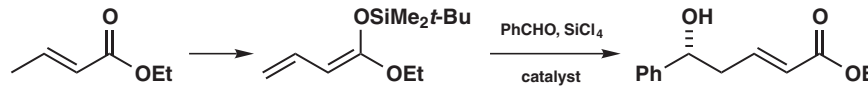
An excellent example is the synthesis of the visual pigment retinal **74**. An aldol disconnection **74a** is possible but four sequential aldols would be needed. But only two extended aldol disconnections **74b** and **75** are needed and both require the same extended enolate[22] **77**.



The starting material is natural β-cyclocitral **76**, converted to its methyl acetal **78**. The extended enolate **77** is best realised as the silyl enol ether **79** and reaction with **78** followed by base gives the trienal **75**. Repetition of the three steps gives all *E* retinal **74**. The two extended aldol reactions go in excellent yield with total regioselectivity, only the base-catalysed eliminations with DBU are disappointing.



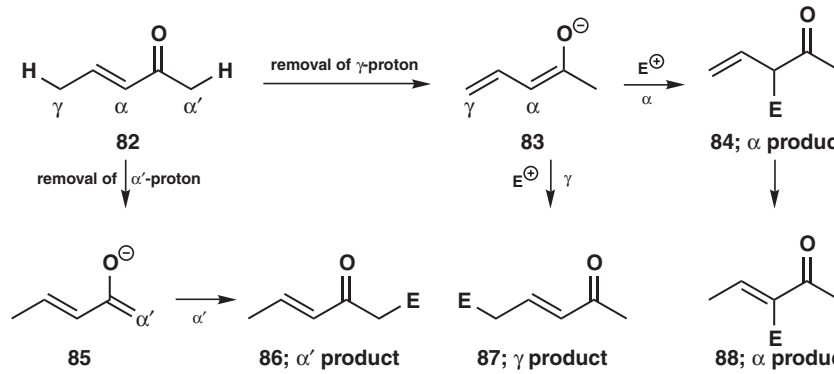
Recent developments include an asymmetric version of the aldol reaction in the γ-position. The silyl enol ether **82** from ethyl crotonate reacts with aldehydes in the presence of the Lewis acid $SiCl_4$ and an asymmetric catalyst (see the paper if you are interested in the structure of this complex catalyst) to give a high yield of the 'aldol' product **83**. The γ:α ratio is >99:1 and the product **83** is virtually enantiomerically pure.[23]



ethyl crotonate **82** **83; 89% yield**

Extended Enolates from Unsaturated Ketones

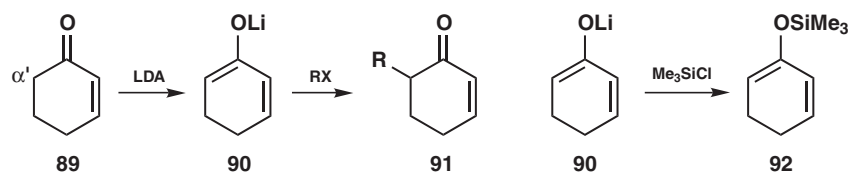
With ketones **82** a further dimension of regioselectivity is present. The extended enolate **83** can be formed in the same way by the loss of the γ-proton, and it can react in either the α or the γ positions to give conjugated **87** or **88**, or unconjugated **84** products. But the ketone may also be able to enolise on the other side of the carbonyl group, usually called the α′ position, to give a new enolate **85** which can react at the α′ position to give another conjugated product **86**. There are four possible products in all. The kinetic and thermodynamic factors governing the regioselectivity of the reactions of the extended enolate are as before, but the enolisation itself is now also subject to such factors. The protons in the α′ position are more acidic than those in the γ position and so **85** is the kinetic enolate, while the linearly conjugated extended enolate **83** is the thermodynamic enolate rather than the cross-conjugated and therefore less stable enolate **85**.



82 **83** **84; α product**

85 **86; α′ product** **87; γ product** **88; α product**

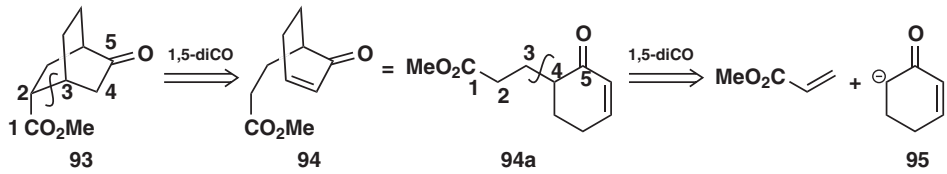
Kinetic enolisation and reaction at the α′ position are easy to control by lithium enolates. Hence cyclohexenone reacts with LDA to give the enolate **90** which is alkylated at the α′ position to give **91** but silylated on oxygen[24] to give **92**, much as expected for simple lithium enolates (chapter 2).



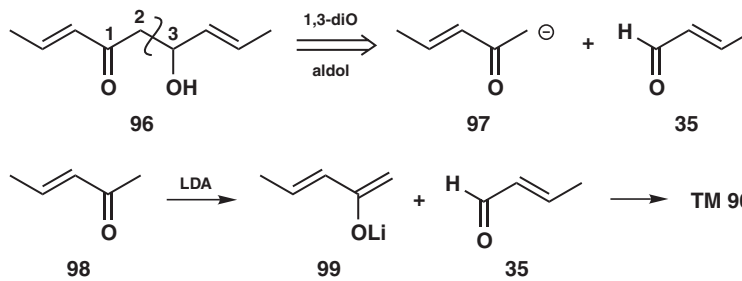
89 **90** **91** **90** **92**

A spectacular example is the synthesis of the bicyclic keto-ester **93**. Two consecutive Michael disconnections reveal the α′ extended enolate of cyclohexanone **95** and methyl acrylate. The synthesis is even easier: kinetic enolisation of cyclohexenone with LDA and reaction with methyl

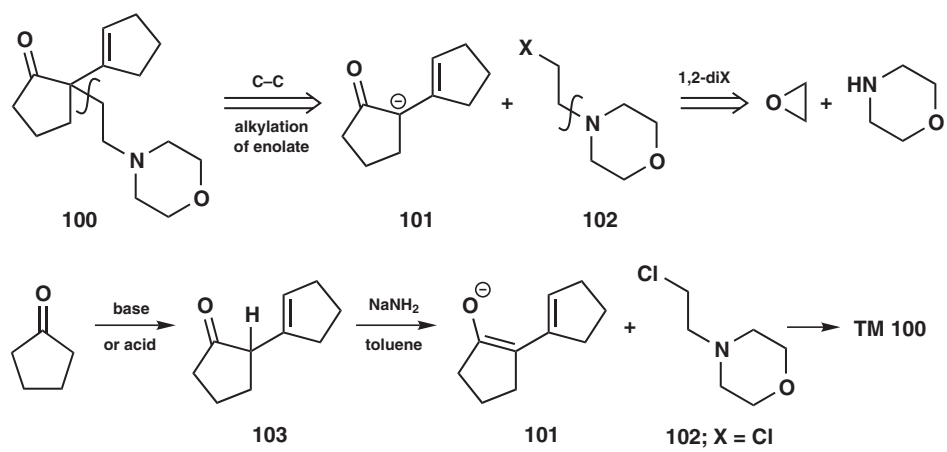
acrylate gives the cage ketone **93** directly in 90% yield.[25] Reaction of cross-conjugated lithium dienolates such as **95** with Michael acceptors tends to give Diels-Alder adducts (see below) and this may be the mechanism of the addition.



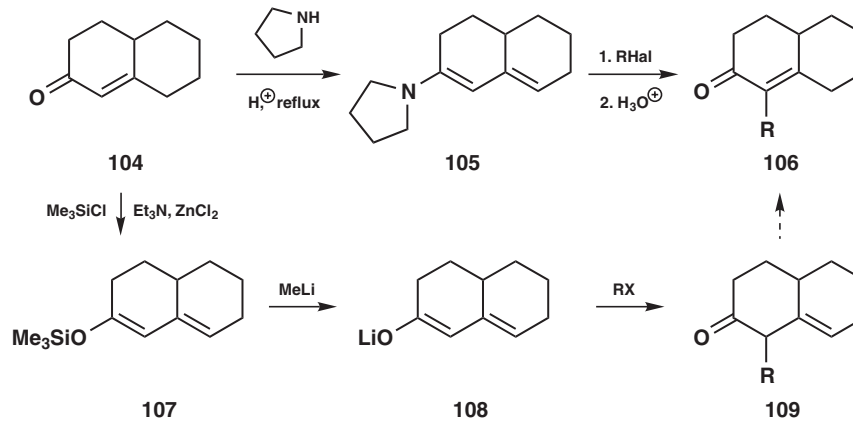
Extra selectivity is needed in the synthesis of the open chain compound **96**. This is clearly an aldol, but analysis reveals the need for two forms of regioselectivity in that an α´ extended enolate **97** is required to add 1,2 to a conjugated aldehyde **35**. Fortunately aldehydes tend to prefer 1,2 to 1,4-addition (chapter 9), especially with hard nucleophiles such as lithium enolates, and this synthesis works as planned.[26]



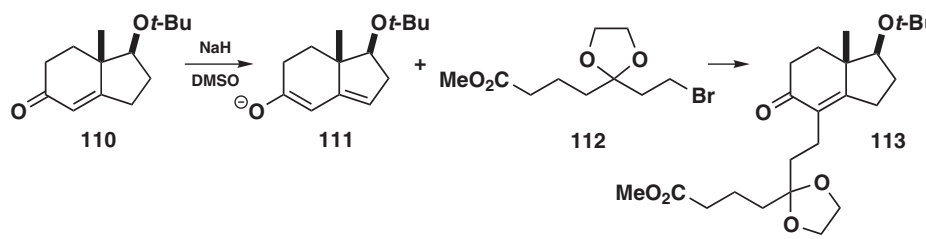
Under more equilibrating conditions such as alkoxide bases in alcohol solution or amide bases in liquid ammonia, enolisation occurs to give the extended enolate **83** which is then alkylated in the α-position by alkyl halides. At first this seems the most difficult combination to achieve: thermodynamic enolisation followed by kinetically controlled addition of an electrophile, but it is in fact a common result achieved with a variety of bases. Examples include the synthesis of pentethylcyclanone **100**, an anti-tussive drug, by alkylation of the enone **103**, the aldol dimer of cyclopentanone. Disconnection at the branchpoint to the available alkyl halide **102**; X = Cl requires α-alkylation of the extended enolate **101** derived from the cyclopentanone aldol dimer[27] **103**. This is easily achieved by sodium amide in toluene.[28]



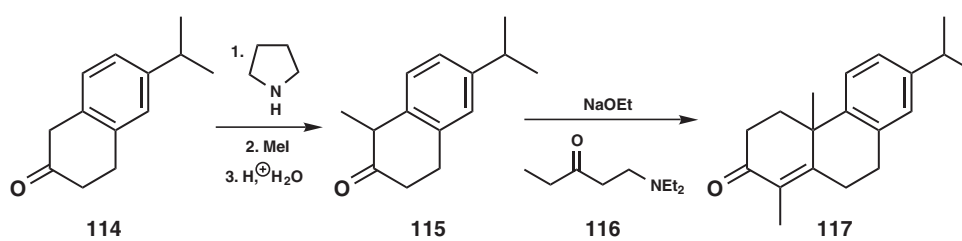
Reaction in the α- or γ-positions (i.e. from the extended enolate) is again best controlled by enamines or silyl enol ethers, both being formed under equilibrating conditions.[20,29] Enones such as **104** give the enamine **105** and the silyl enol ether **107** from which the lithium enolate **108** can be made. Both these intermediates give α-alkylated products **106** or **109**. Direct reaction of **104** with LDA would of course give the α´ lithium enolate.



Alkylation of the lithium enolate **108** occurs in the α-position to give **109**. This may remain unconjugated, but in the next example **113**, became conjugated.[30] Aza-enolates and hydrazones achieve α-alkylation too.[31] Reaction in the γ-position of silyl enol ethers requires the same methods as were used for aldehydes and esters above.

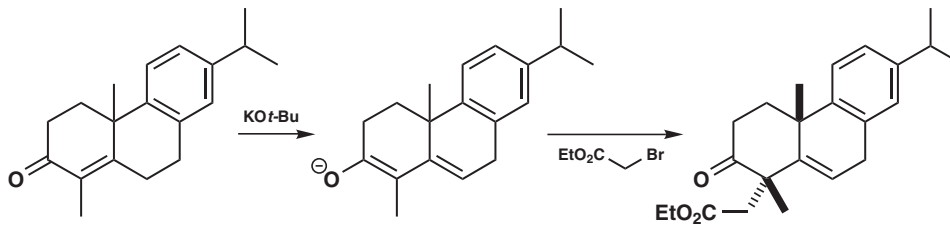


A good example of enolate control comes in Stork's synthesis of abietic acid.[32] The first two reactions each involve regioselectivity of enolates in the formation of **115** and **117**.



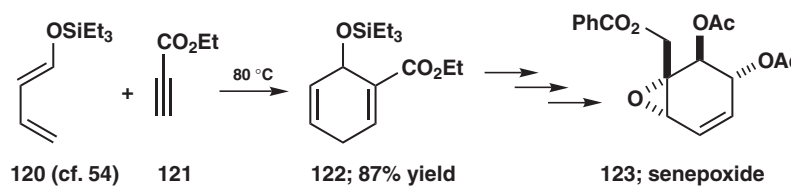
The next stage requires formation of an extended enolate **118** and its reaction with ethyl bromoacetate. Reactions of enolates with α-bromoesters are not normally recommended as the basic enolates may remove the rather acidic proton between the ester and the bromine atom. The extra conjugation in the extended enolate makes it significantly less basic and this reaction goes

cleanly in the α-position and on the opposite face to the axial methyl group. The rest of the synthesis is described in Fleming, *Selected Organic Syntheses*.[33]

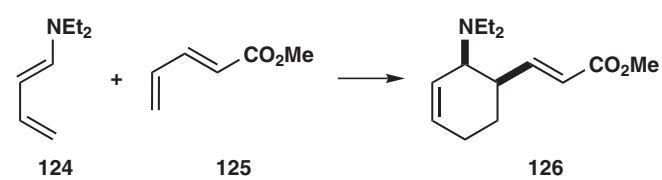


Diels-Alder Reactions

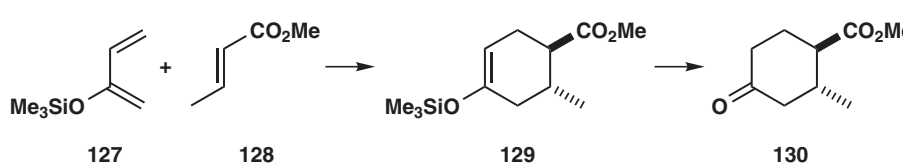
The extended enolates themselves as well as the enamines and the silyl enol ethers derived from them are all good electron-rich Diels-Alder dienes showing excellent regioselectivity in reactions with electron-deficient dienophiles. Thus extended silyl enol ethers such as **54**, **60**, and **92** are also 1-substituted butadienes.[34] A typical reaction is the cycloaddition of **120** with the alkyne **121** to give a single regioisomer of the adduct **122** in high yield. This compound was used by Schlessinger[35] in his synthesis of senepoxide **123**.



Enamines such as **55** are even more reactive[19] and **124** reacts regiospecifically with the unsaturated ester **125** to give a single regio- and stereo-isomer of **126** while no 1-RO butadiene will do so.

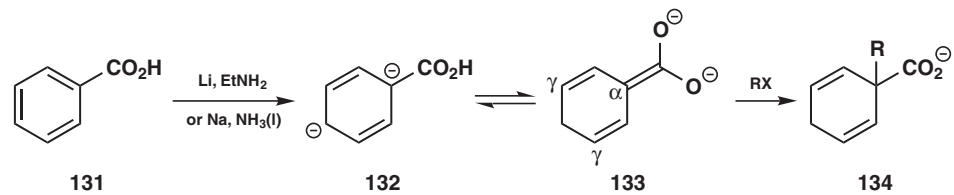


The 2-silyloxybutadienes derived from the α´ enolates such as **127** are in some ways even more interesting.[20] They add equally well to dienophiles such as **128** with the expected "para" regioselectivity, but the products are now specific enol equivalents of cyclic ketones: it would be difficult to make **129** from **130** in any other way.

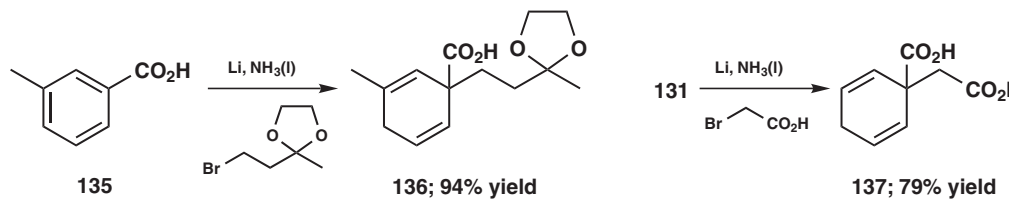


Extended Enolates from Birch Reductions

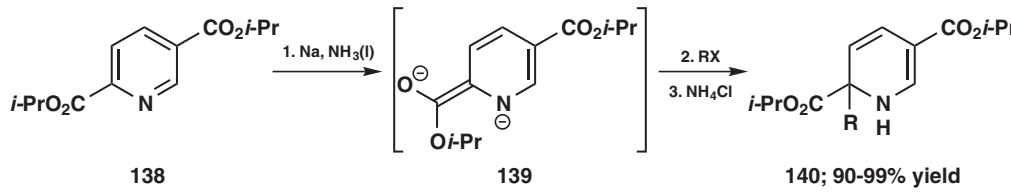
Simple Birch reduction of benzoic acid **131** gives initially an intermediate that can be represented as dianion **132**. Proton transfer from CO_2H to the less stable of the two anions gives the enolate **133** that you will recognise as a (doubly) extended enolate with one α- and two γ-positions. Alkylation occurs at the α-position to give **134**. This is a useful way to construct a quaternary centre on a six-membered ring: the two remaining alkenes can be further developed in many ways.[36]



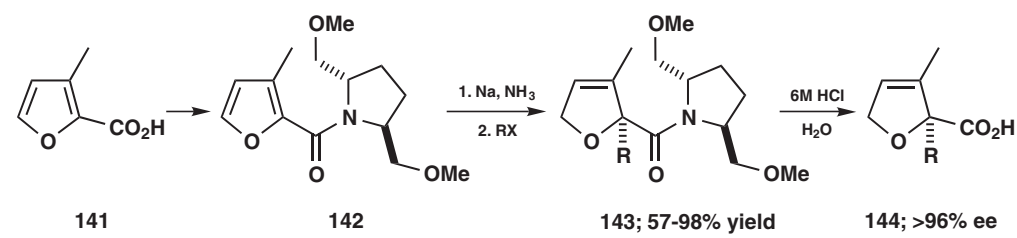
Functionalised alkyl halides can be used and substitution on the benzene ring is all right. Here are two examples giving the protected ketone **136** and the diacid **137** in good yields.[37]



Birch reduction of aromatic heterocycles is equally rewarding if more challenging mechanistically. The pyridine diester **138** is reduced to an intermediate that could be drawn as **139**. Both anions are extended enolates but one has the charge delocalised onto the nitrogen atom and so is less reactive than the other. Alkylation occurs at the α-position[38] to give **140**.

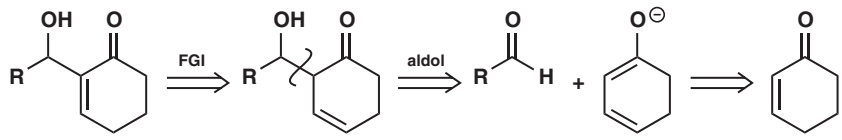


Asymmetric versions of the Birch reduction are now appearing (chapter 28) and a C_2 auxiliary attached to the furoic acid **141** allows Birch reduction and alkylation between the ring oxygen atom and the carbonyl group to give, after hydrolysis, enantiomerically pure acids[39] **144**.

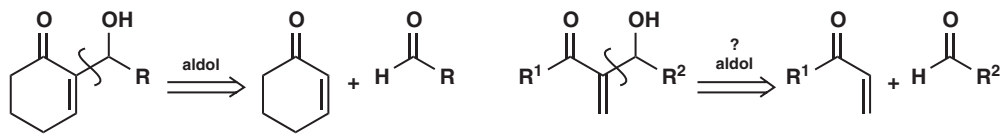


The Baylis-Hillman Reaction

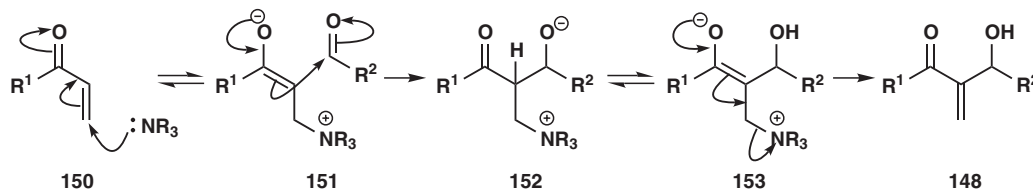
The disconnections for the aldol reaction in the α-position on an extended enolate would be something like this: first move the alkene from conjugated **145** to unconjugated **146** so that aldol disconnection gives the extended enolate **147** derived from the enone **89**. This chemistry demands at least one hydrogen atom in the γ-position of the enone **89** so that formation of the extended enolate **147** is possible. That hydrogen is of course replaced when the conjugated product **145** is formed from **146**.



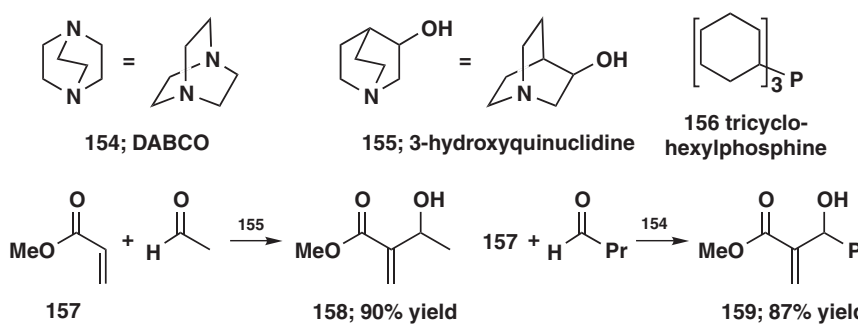
We might prefer the simpler disconnection **145a** as this gives the starting materials directly. But supposing the aldol product **148** has no γ-hydrogens? No extended enolate can be formed from the enone **149**, the reaction is impossible and it appears that the disconnection is meaningless.



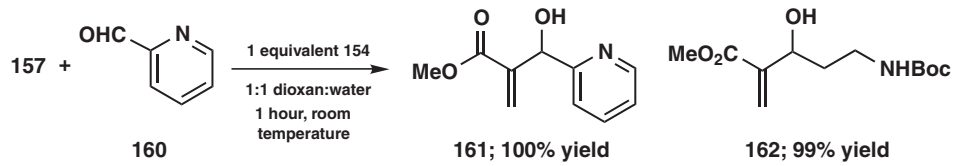
Fortunately this is not so and the Baylis-Hillman reaction[40] allows an escape from these problems. The enone is mixed with the aldehyde and a catalyst, usually a tertiary amine or phosphine, is added. The catalyst need not be basic as its role is reversible conjugate addition **150**. This gives the enolate, as we saw in chapter 10, that does the aldol addition **151**. The product **152** forms a new enolate that eliminates **153** (E1cB) the catalyst to give the product **148**.



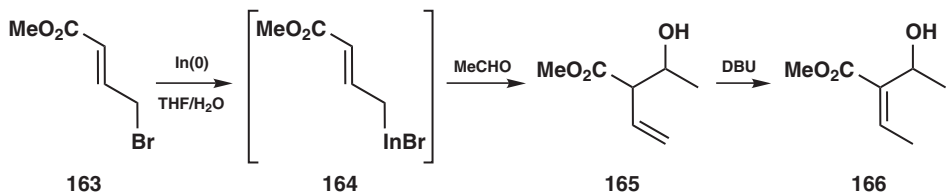
The best catalysts are usually DABCO **154** or hydroxyquinuclidine **155** among amines and tricyclohexylphosphine **156**. Efforts continue to find effective asymmetric catalysts.[41] Examples with acrylates, enolisable aldehydes, and the amine catalysts are **158** and **159**.



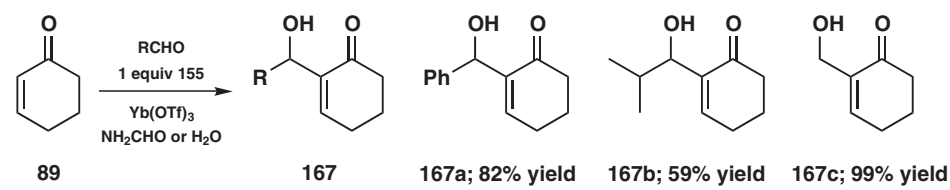
Recent developments to make the reaction more efficient have included using stoichiometric amine in mixed organic aqueous solvents and a notable success was achieved with aromatic aldehydes to give e.g. **161** and enolisable aldehydes to give e.g. **162** in high yields under mild conditions.[42]



Though some of these reactions use enolisable aldehydes, none uses enolisable Michael acceptors so the question of competition of this α′ reaction with extended enolisation proper has not arisen. One alternative approach uses an indium-mediated reaction of the γ-brominated ester **163** with aldehydes to give either non-conjugated **165** or conjugated **166** α′-products.[43]

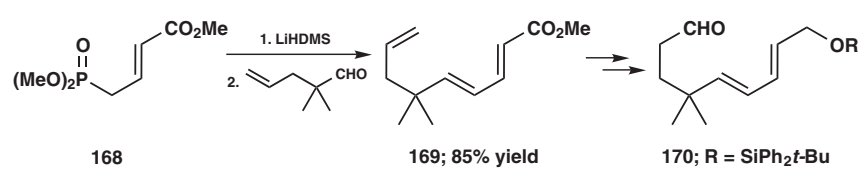


One genuine case where the enone can form both normal (α′) and extended enol(ate)s is cyclohexenone **89**, the compound we used to introduce this section. Recent results show that Baylis-Hillman reaction with this enone gives good yields of Baylis-Hillman products **167** providing stoichiometric **155** is used in solution in water or formamide (NH_2CHO) with $Yb(OTf)_3$ catalyst. The aldehydes can be aromatic **167a**, aliphatic **167b** or even formaldehyde **167c** most easily used in aqueous solution. Under these conditions the reaction is quite fast.[44]

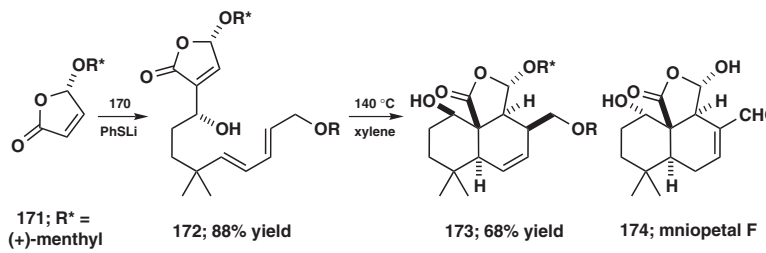


The Synthesis of Mniopetal F

We conclude with two synthesis that include both γ- and α′-selective extended enolate chemistry.[45] The first is of of mniopetal F. The Horner-Wadsworth-Emmons reaction of **168** (cf. **29**) prepared by γ-bromination of an extended enol with the appropriate aldehyde gives the triene **169** with good (>20:1) *E:Z* selectivity and of course total γ-selectivity. This is converted into **170**.



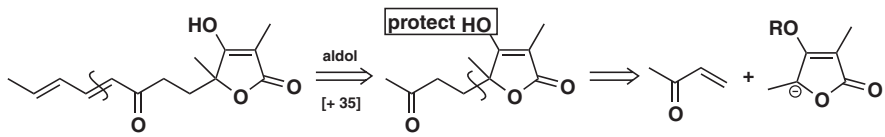
A Baylis-Hillman reaction with the chiral butenolide **171** goes in excellent yield and stereoselectivity with LiSPh as the catalyst. Sulfur is of course good at conjugate additions. The product **172** is clearly destined for a Diels-Alder reaction and the product **173** is nearly ideal for conversion into mniopetal F **174**.



171; R* = (+)-menthyl **172; 88% yield** **173; 68% yield** **174; mniopetal F**

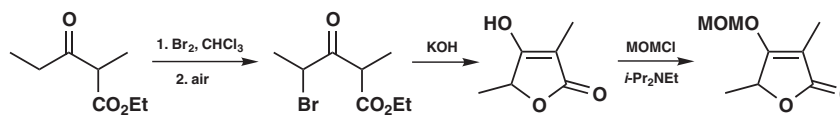
A Synthesis of Vertinolide Using α´ and γ-Extended Enolates

A recent synthesis of the natural tetronic acid vertinolide **175** illutrates several aspects of extended enolate chemistry. An enone disconnection suggests an aldol reaction between the methyl ketone **176** and crotonaldehyde **35**. The ketone **167** might be made by conjugate addition of a reagent for the γ-extended enolate **178** to butenone[46] **177**.



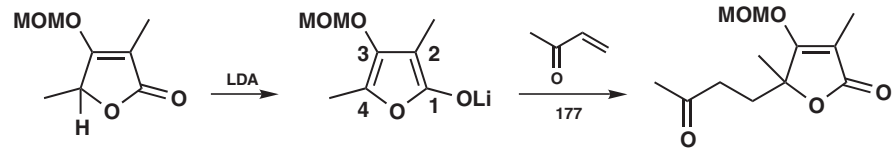
175; vertinolide **176** **177** **178; d^3 synthon γ-homoenolate**

The tetronic acid **181** is easily made by bromination of the ketoester **179** and treatment of **180** with KOH. Protection with the MOM group ($MeOCH_2$-) gives **182** from which an extended enolate might be made.



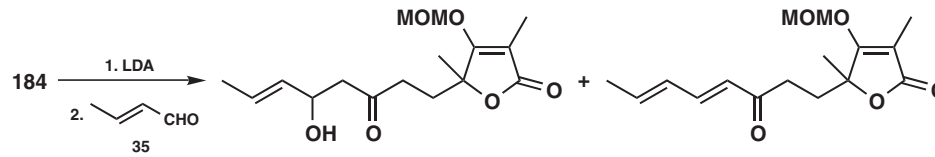
179 **180** **181; 67% from 167** **182; 99% yield**

Treatment of **182** with LDA gives the lithium enolate **183**. This is an unusually interesting extended enolate. It has an obvious α-position at C2 but we want reaction to occur at the γ-position C4. The complexity arises from the other two oxygen atoms. The ring oxygen makes C2 and C3 both nucleophilic and the MOMO group makes C4 nucleophilic as all these connections are enol ethers. Finally the ring is a furan. The enolate is therefore very stable and thermodynamic control a possibility. In the event, conjugate addition occurred with butenone **177** at C4 as hoped and in good yield to give **184**.



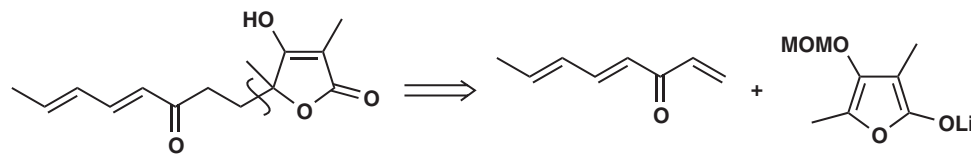
182 **183** **184; 75% yield**

The aldol reaction of **184** with crotonaldehyde **35** was rather unsatifactory as a mixture of aldol **185** and dienone **186** was formed. The aldol could be converted into the enone with basic alumina but the yield was only 61%. An alternative was needed.



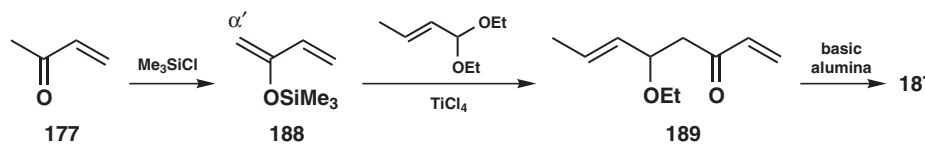
185; 63% yield **186; 24% yield**

Since the conjugate addition of the extended enolate **183** works so well, an attractive alternative is to disconnect the whole side chain and attempt conjugate addition of **183** to the trienone **187**. There is an obvious problem of regioselectivity with **187**.



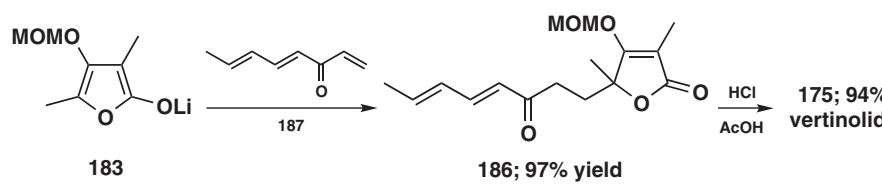
175a; vertinolide **187** **183**

The trienone **187** could be made by Lewis acid catalysed addition of the α′ silyl enol ether **188** from butenone **177** to the diethyl acetal of crotonaldehyde and elimination with basic alumina.



177 **188** **189**

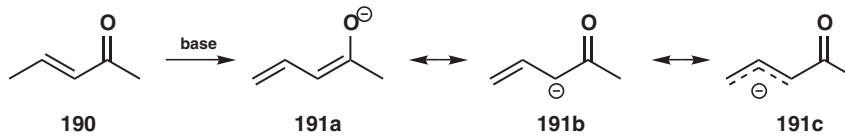
Conjugate addition of the γ-extended enolate **183** to the trienone **187** went in excellent yield and gave the complete skeleton of vertinolide in one step. Deprotection gave the natural product in a remarkably short and efficient way.



183 **186; 97% yield**

Conclusion: Extended Enolate or Allyl Anion?

We have considered a variety of related intermediates in this chapter as extended versions of enolate ions **191** and as dienes. Another legitimate way to consider them is as acylated allyl anions **191c**, and this leads us to the next chapter where we consider how to use allyl anions in synthesis.



190 **191a** **191b** **191c**

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General references are given on page 893

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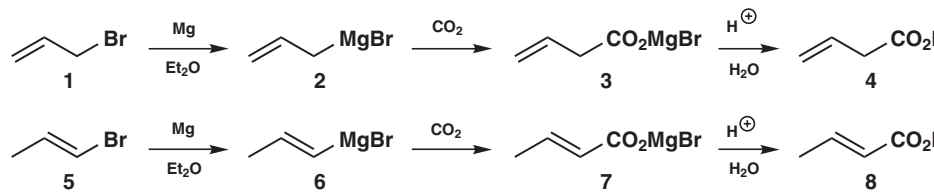
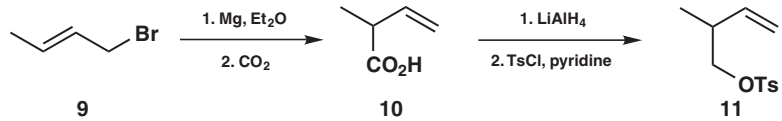
12 Allyl Anions

Introduction: Allyl Grignard Reagents

A Grignard reagent **2** can be made from allyl bromide **1** and it reacts cleanly with electrophiles such as carbon dioxide to give the unconjugated acid **4**. So also do vinyl halides such as propenyl bromide **5**, giving the conjugated acid **8**. It is important that you understand the difference between these two series. When the halide is directly attached to a double bond **5** we have a very unreactive vinylic halide and a well-behaved Grignard reagent **6**. We have already used these intermediates in chapter 5 and we shall meet them in more detail in chapter 16. When the halide is joined, not directly to the double bond, *but to the atom next door* we have a reactive allylic halide **1** and a badly behaved Grignard reagent **2**. Controlling the behaviour of allyl anions and metal derivatives is the subject of this chapter.

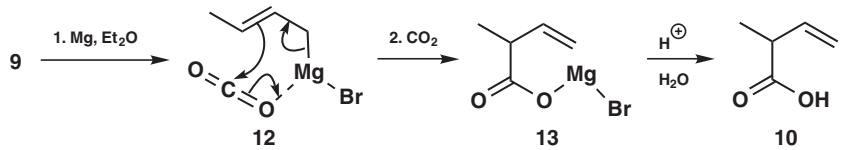


So what exactly is wrong with allyl Grignard reagents? Even if they are symmetrical **2**, yields tend to be low as the allyl metal bond cleaves easily to give relatively stable allyl radicals that may dimerise or polymerise. When the allyl group is unsymmetrical **9** reaction often occurs at the "wrong" end of the allyl system, here to give the acid **10** and eventually the tosylate **11** needed in chapter 10 for the synthesis of multistriatin.



9 **10** **11**

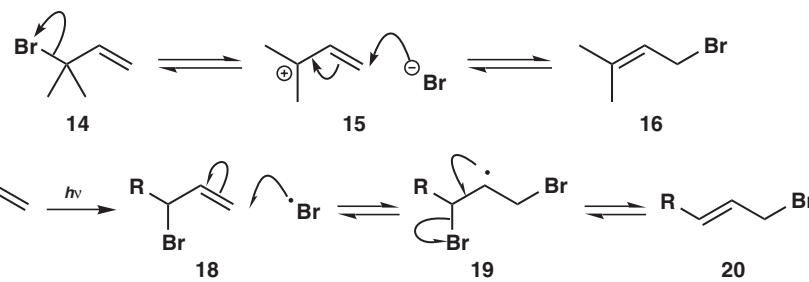
The reaction may occur through a six-membered cyclic transition state **12** that directs the electrophile to the other end of the allylic system. This is bad enough, but worse is to come.



12 **13** **10**

The [1,3] allylic shift

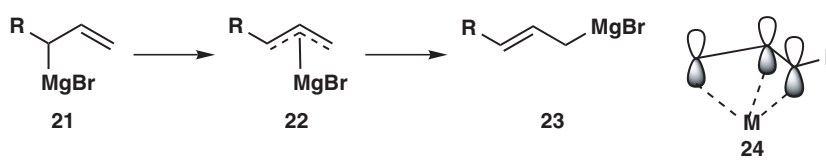
Very few allylic derivatives are stable: only H, C, O, N, Si, and F are secure from a [1,3] shift. Halogens may move from one end to the other of the allylic system by an ionic pathway via the delocalised allylic cation **15** or by a radical chain pathway via the dibromoalkyl radical **19**. These are both equilibrium reactions and the dominant component is the one with the more heavily substituted double bond **16** or **20**.



14 **15** **16**

17 **18** **19** **20**

Metals such as Li or Mg may move by way of the η^3 allyl complex **22** from one end **21** to the other **23** of an allylic system. This η^3 allyl complex has the metal sitting roughly at the middle of the triangle formed by the three carbon atoms of the allyl system, and at right angles to them, so that the orbitals of the metal may overlap with all three p-orbitals of the allyl group **24**. This becomes a stable compound rather than an intermediate when M is a transition metal.

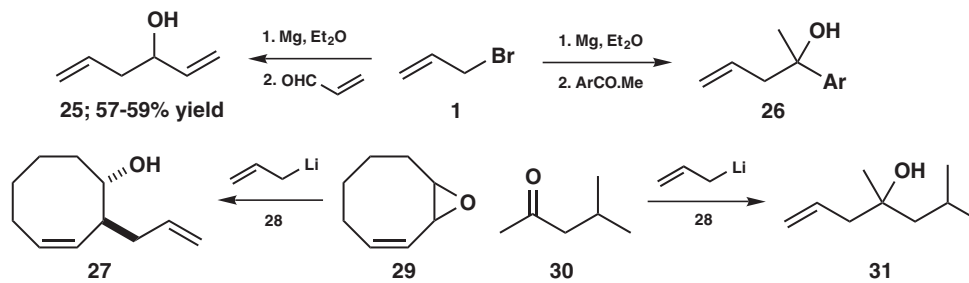


21 **22** **23** **24**

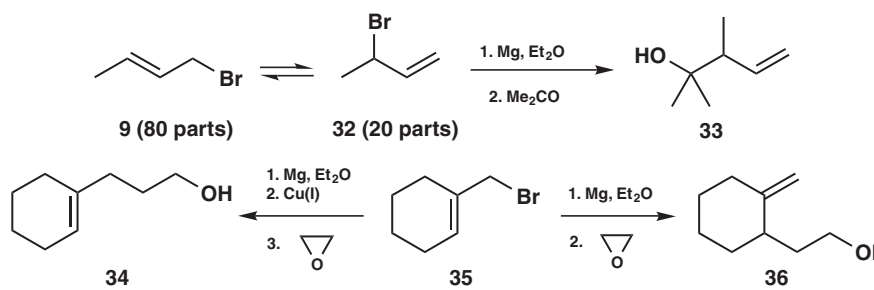
If neither the halides nor their metal derivatives have a stable structure, how can we expect to control their reactions? Things are not quite as bad as that. The bromides and chlorides are stable at low temperatures in the absence of Lewis acid catalysts or radical generators. The Grignard reagents often react cleanly to give the less substituted double bond isomer, presumably by the type of process shown in **12**. We shall be seeing methods to control transition metal allyls and allyl silanes which make these intermediates valuable reagents in synthesis, and you should finish this chapter in a confident mood without fear of fluxional allyl compounds.

Allylic Lithiums and Grignard Reagents

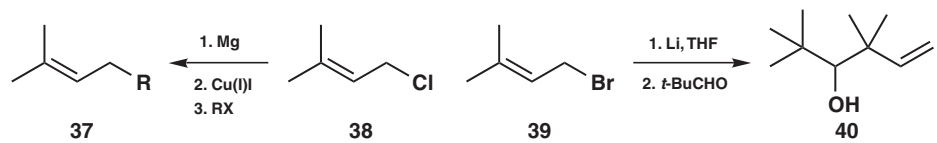
Before looking at alternative solutions, let us review the situation with allyl Grignards and allyl lithiums. Allyl Grignard **2** has a lower basicity than propyl Grignard and it reacts well with aromatic ketones to give tertiary alcohols **26** without much enolisation.[1] Reactions with conjugated enones and enals occur by direct (1,2) rather than Michael (1,4) addition, as in the reaction with acrolein[2] to give **25**. Allyl-lithium **28** also gives reasonable yields with enolisable ketones, as in the adduct[3] **31**. The reaction of allyl-lithium with the epoxide **29** to give the *anti* adduct **27** illustrates regioselectivity as well as stereospecificity.[4] Reaction at the allylic end of the epoxide occurs because of the superior reactivity of allylic electrophiles in the S_N2 reaction.



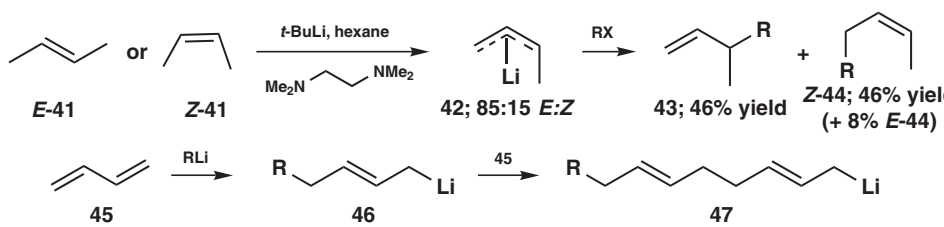
Turning to unsymmetrical allyl derivatives, the halides **9** and **32** are usually used as an 80:20 mixture. Both give the same Grignard reagent that reacts with CO_2 to give **10** and with aldehydes and ketones with the same regioselectivity[5] to give alcohols such as **33**. Another unsymmetrical allylic halide, existing only in the form **35** with the trisubstituted double bond inside the six-membered ring, reacts with ethylene oxide at the more substituted end to give the alcohol **36**. Presumably these unsymmetrical allylic Grignard reagents prefer the form with the more highly substituted double bond and react via a six-membered cyclic transition state such as **12**. In some cases the regioselectivity can be reversed by exchanging Li or Mg for copper. The allylic Grignard derived from **35** gives only the alternative alcohol **34** when Cu(I) salts are added before the epoxide.[6]



The unsymmetrical copper allyl derived from prenyl halides **38** and **39**, the basic unit from which terpenes are constructed, can be alkylated at the less substituted end to give unrearranged **37**, though the corresponding Grignard reagent gives a mixture of products.[7] The corresponding lithium derivative, made from prenyl bromide **39**, reacts with aldehydes with the reverse regioselectivity.[8] The copper derivatives are probably η^3 allyls and react at the less hindered end, as do the nickel allyls soon to be discussed.

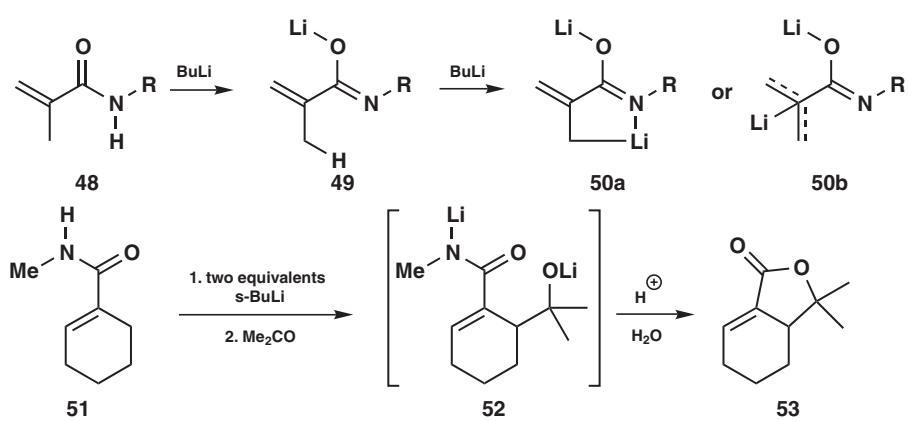


The extra delocalisation in an allyl anion might tempt one to make lithium allyls by removal of a proton from an alkene. This approach is not generally very successful. Either *E* or *Z*-but-2-ene **41** can be deprotonated, but *t*-BuLi is needed as well as the lithium chelating agent TMEDA (Me_2NCH_2-CH_2NMe_2). The lithium allyl prefers the *Z* configuration **42** but gives a mixture of regio and stereoisomers **43** and **44** on alkylation.[9] Nor is it possible to make useful lithium allyls by addition of, say BuLi, to butadiene **45** as the resulting allyl lithium **46** adds to another molecule of butadiene to give another allyl lithium **47** and polymers are formed.[10]

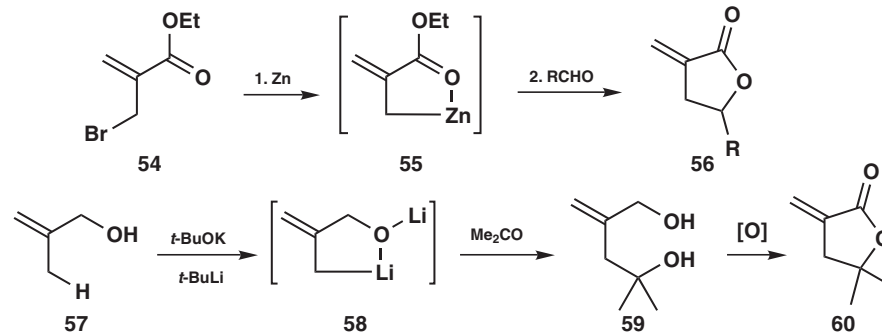


Allylic lithiums with C-2 substituents

One way in which allyl lithiums can be made by direct deprotonation is when the allyl system has a substituent not at one end but in the middle, and when the substituent is of the kind we used in chapter 7 for directing aromatic lithiation. The simplest examples are amides such as **48** that react with two molecules of BuLi to give a dilithium derivative[11] often represented as an allyl complex **50b** though it is probably a lithium σ-complex **50a**. These amide derivatives react with aldehydes and ketones to give lactones,[12] e.g. **53** via adducts such as **52**.

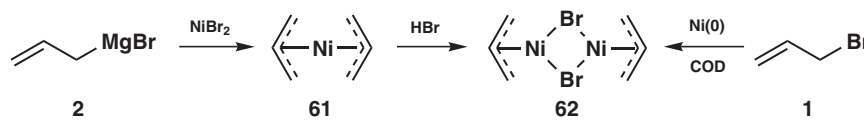


Similar compounds **56** can be made[13] from zinc derivatives of bromoesters **54** and even the simple alcohol[14] **57** gives the diol **59** and hence another *exo*-methylene lactone **60** by oxidation.

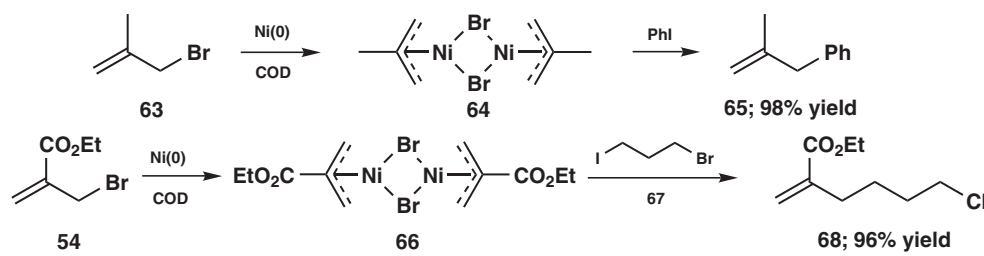


Allyl Nickel Complexes

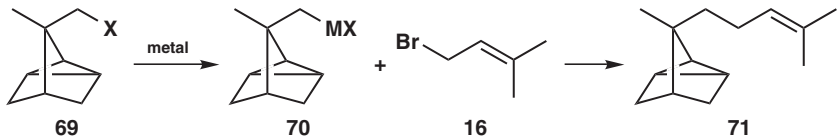
Perhaps the most useful of the η^3 allyl complexes (cf. **24**) are the π-allyls of nickel.[15] The simplest type **61** are rather unstable and form the bromide-bridged complex **62** on treatment with HBr. These are stable compounds officially complexes of Ni(I) but better regarded for our purpose as dimers of η^3 complexes of allyl anions and Ni(II), much as allyl Grignard reagents **2** can be regarded as σ-complexes of allyl anions and Mg(II). Direct exchange of Mg(II) for Ni(II) gives the unstable complexes **61**, but the stable dimer **62** can be made by oxidative insertion of Ni(0), as its cyclo-octa-1,5-diene (COD) complex, into allyl bromide **1**.



These π-allyls of nickel are prone to give allyl dimers, but the more stable complexes **62** are useful for coupling with alkyl halides, the allyl group of **62** acting as an allyl anion equivalent. That this is not an S_N2 reaction, but a coupling on the nickel atom, is clear because even aryl halides react successfully. Almost all the published examples involve substituted allyl groups, particularly in the 2-position. Thus the 2-methylallyl complex **64** couples with alkyl iodides or iodobenzene to give adducts, e.g. **65** in excellent yield. There is good selectivity for iodides against other halogens: thus the complex **66**, derived from **54**, displaces only iodide from **67**, again in excellent yield.[15]

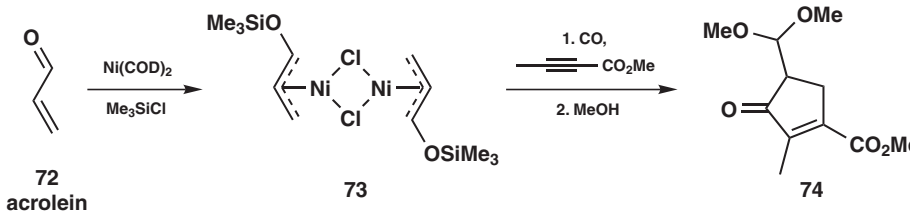


Unsymmetrical allyl complexes react almost exclusively at the less substituted end of the allylic system. Santalene **71** has been prepared from **69** and **16** in two ways. Coupling the Grignard reagent **70**; MX = MgBr with **16** gives 20% yield[16] while the allyl nickel complex **70**; MX = NiI couples with **16** in 95% yield.[17] This is a major development from the allyl derivatives of Mg and Li, which tend to react at the more substituted end of the allyl system, and are in any case less well behaved than the nickel complexes.

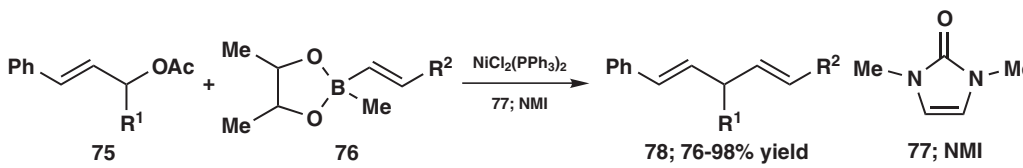


Alkylation and a cyclopentenone synthesis

Modern developments have included allyl groups functionalised at the ends, particularly those derived from silylated enals such as **72**. The application shown here creates a cyclopentenone **74** by combination of the allyl nickel **73** with an alkyne and CO rather in the style of the Pauson-Khand reaction (chapter 6).[18]

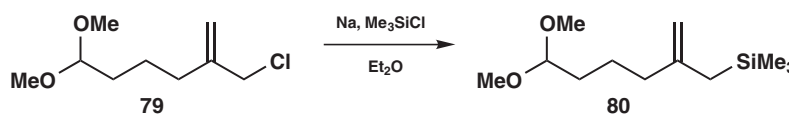


This last example succeeds partly because nickel catalyses the union of the three reagents in the second step. Similar things happen in the combination of nickel allyls with zinc borates **76**. The allyls are derived from unsymmetrical allylic acetates **75** and react at the end remote from the phenyl group (R^1 is an alkyl group and R^2 is an aryl or alkyl group).[19]



Allyl Silanes

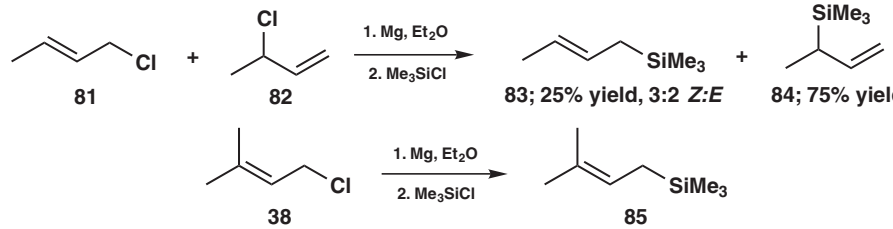
The most useful of all allyl anion equivalents are the allyl silanes.[20] This is because it is easy to make them regioselectively, because they do not undergo allylic rearrangement (silicon does not do a [1,3] shift) and because their reactions with electrophiles are very well controlled: addition always occurring at the opposite end to the silicon atom. Symmetrical allyl silanes can be made from allyl-lithiums or Grignards by displacement of chloride from silicon. A useful variant is to mix the halide with a metal, e.g. sodium, and Me_3SiCl in the same reaction, rather after the style of the silicon acyloin reaction,[21] as in the synthesis of the acetal **80**.



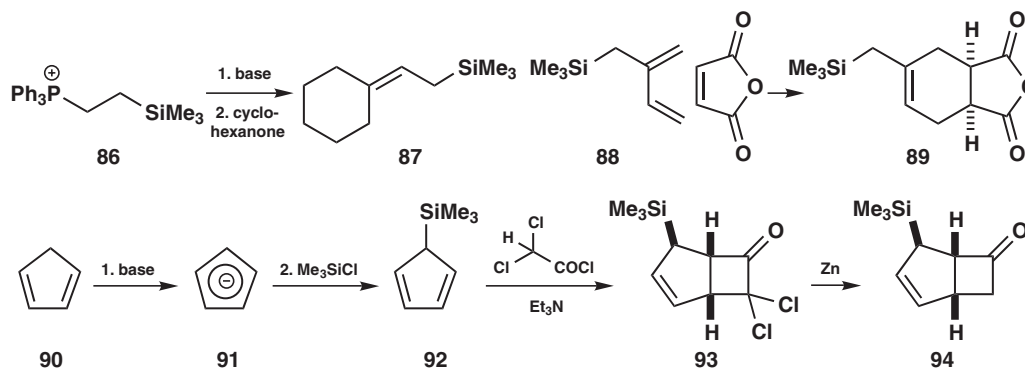
Synthesis: silylation, Wittig, and cycloaddition reactions

Syntheses of unsymmetrical allyl silanes from Grignard reagents are subject to the usual regioselectivity problems. The mixture of halides **81** and **82** gives a mixture of Grignard reagents,

see **21** and **23**, from which a mixture of allyl silanes **83** and **84** can be made.[22] However, this mixture can be converted[23] into the thermodynamic product (**83**, as a mixture of *E* and *Z* isomers) by TBAF (Bu_4NF) at 100 °C as the fluoride ion is a nucleophilic catalyst, attacking the silicon atom with excellent chemoselectivity. More highly substituted allyl halides like **38** give only the less substituted allyl silane[24] **85**. This may seem a disadvantage, but it is quite the reverse as you will see.

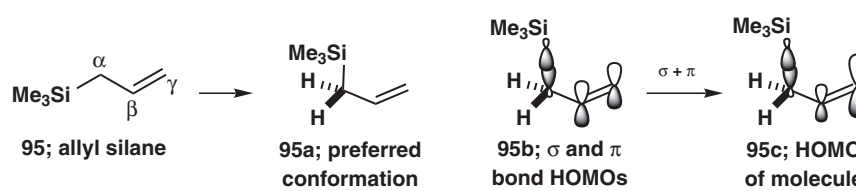


One reliable method for getting the silicon on the less substituted end of the allylic system is the Wittig approach of Seyferth.[25] The unsubstituted reagent **86** reacts well with ketones to give allyl silanes of the type **87**. Alternatives depend on cycloaddition reactions: 1-trimethylsiclylbutadiene **88** gives Diels-Alder adducts, e.g. **89** with maleic anhydride. Direct silylation of the cyclopentadienyl anion **91** gives **92**, one of the few substituted cyclopentadienes which is useful in cycloadditions. A 2+2 cycloaddition with dichloroketene[26] gives the cyclobutanone **93** which can be dechlorinated with zinc. Both **93** and **94** are allyl silanes.[27]

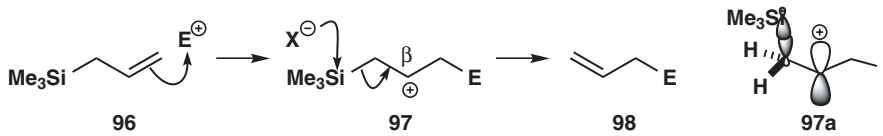


The stabilisation of cations by silicon

Even if silicon chemistry is new to you, you should by now have a picture of stable compounds with C-Si bonds and selective reaction with fluoride. You are already familiar with silyl enol ethers as nucleophilic enolate equivalents and allyl silanes resemble these in many ways. The missing link is the β-silyl effect. A Si atom stabilises a cation in the β-position by overlap of the populated and relatively high energy C-Si σ-orbital with the empty p orbital of the cation. This overlap is already present in the preferred conformation **95a** of the allyl silane **95** as an anti-bonding interaction **95b** between the C-Si σ-orbital and the π orbital of the double bond. The resultant molecular orbital (the new HOMO) **95c** increases the nucleophilic reactivity of the carbon atom in the γ-position.

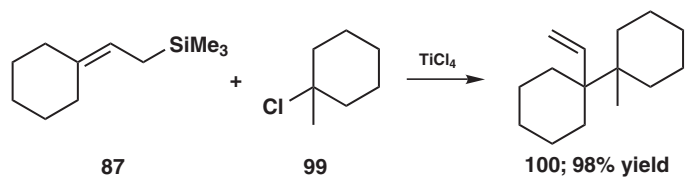


Electrophilic attack on an allyl silane therefore occurs **96** away from the silicon to give the stabilised cation. A nucleophile, particularly an oxygen or halogen nucleophile such as MeOH or Cl^-, attacks the silicon atom selectively **97** and removes it to give the allylic product **98** in which the electrophile has added regiospecifically to the far end (from Si) of the allyl silane. The β cation **97a** is stabilised by a bonding overlap between the filled C–Si σ-orbital and the empty p-orbital of the cation. This is σ-conjugation or hyperconjugation.

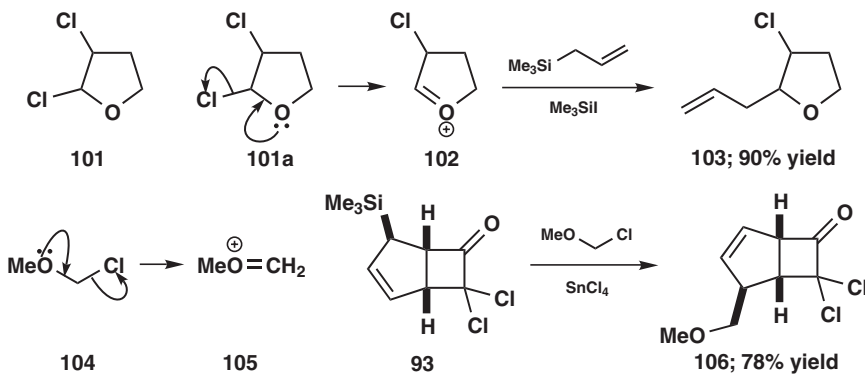


Reactions: alkylations, reactions with epoxides and aldehydes, conjugate additions

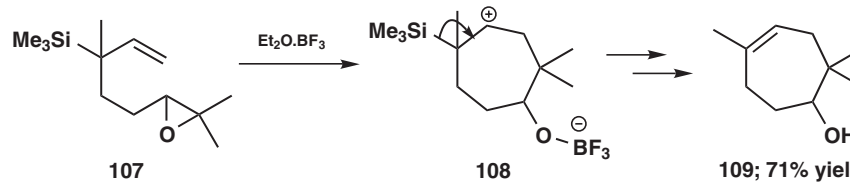
The range of electrophiles is very large.[20] Alkylation with tertiary alkyl halides, e.g. **99**, and Lewis acid catalysts allows the synthesis of molecules with two adjacent quaternary centres,[28] such as **100** from **87**.



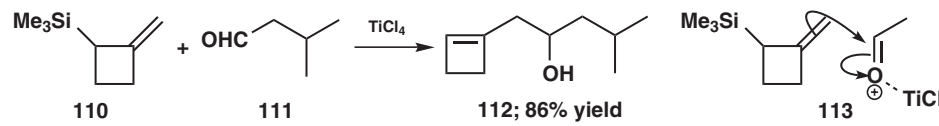
The best alkylating agents are those which give the most stable cations: only the halide next to oxygen in **101**, which can give **101a** the oxonium ion **102**, reacts with allyl silane[29] to give **103**. That the reaction involves regiospecific attack at the end of the allyl system away from silicon is shown by the oxonium ion **105** and **93** which also react stereoselectively on the outside of the folded bicyclic structure.[30]



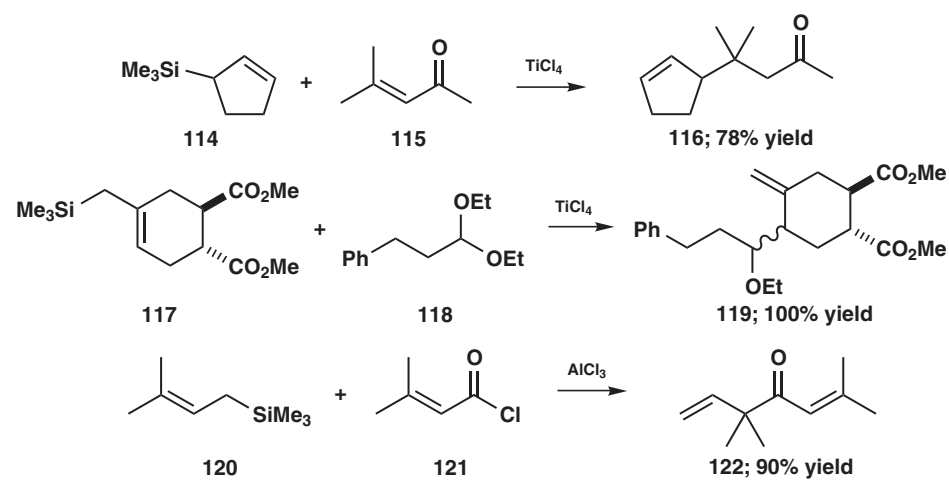
Epoxides generally react at the more substituted end, even in intramolecular *endo*-like reactions such as the cyclisation of **107**, as this gives the more stable cation.[31] The allyl silane must capture the epoxide in **107** as it opens and it must do so faster than the familiar rearrangement of epoxides under the same conditions (BF_3).



There are many regiospecific reactions with aldehydes and ketones, such as the four-membered ring example **110** which gives an addition to the aldehyde **111** very like the aldol reaction with a silyl enol ether (and even uses the same catalyst, $TiCl_4$) to give the unsaturated alcohol[32] **112** - presumably the key step is **113**.

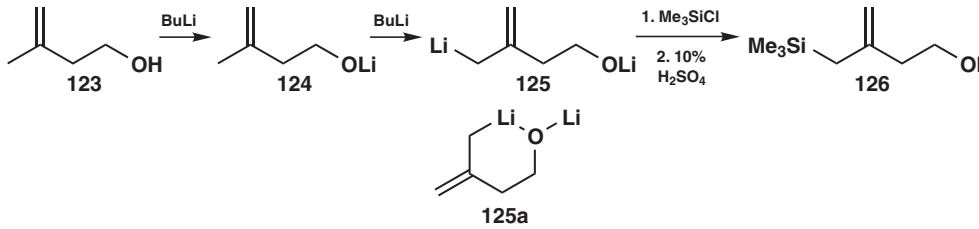


Additions to enones, e.g. **115** generally occur in the Michael sense giving δ,ε-unsaturated enones[33] such as **116**. Acetals **118** can replace aldehydes in additions with allylic transposition[34] as in **117** to **119** and acylation occurs with acid chlorides as in the synthesis of the terpene artemisia ketone **122** from two C_5 units with at least a passing resemblance to the biosynthesis of this irregular terpene.[20,35]

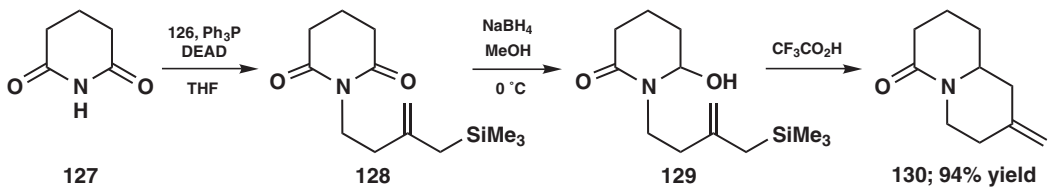


Heterocyclic synthesis with allyl silanes

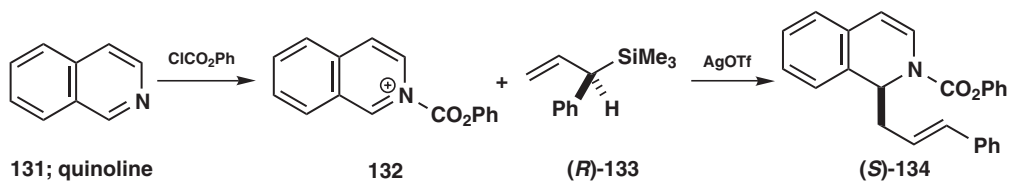
Two aspects of allyl anion chemistry are combined in the synthesis of bicyclic lactams by Gramain and Remuson.[36] Treatment of the unsaturated alcohol **123** with BuLi initially forms the lithium alkoxide **124** and then the allyl lithium **125**, possibly better represented as **125a**. The proton is removed only from the methyl group rather then the internal CH_2 group. Reaction with Me_3SiCl and careful acidic workup gives the allyl silane **126**.



The allyl silane **126** is coupled with the imide **127** by a Mitsunobu procedure and one of the carbonyl groups is reduced to give the alcohol **129**. Treatment with CF_3CO_2H now cyclises the allyl silane to give a new heterocyclic ring **130**.

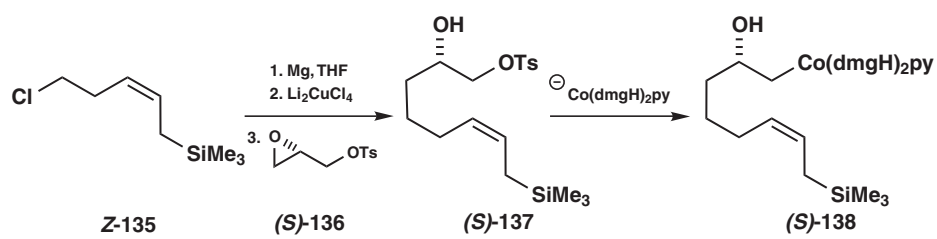


More recent developments with allyl silanes have included the use of single enantiomers such as (*R*)-**133** that adds in a Mannich-style reaction to give (*S*)-**134** with about 95% enantioselectivity.[37]

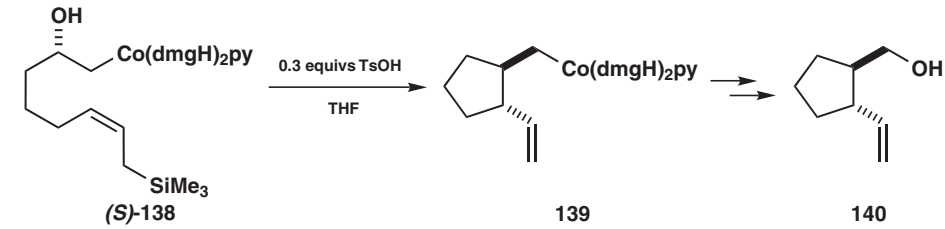


Reactions with Co-stabilised cations

More exotic electrophiles include cobalt-stabilised cations derived the alcohol (*S*)-**138** made by a sequence of reactions that shows the stability of allyl silanes to bases. The cuprate from *Z*-**135** adds to a single enantiomer of the epoxide (*S*)-**136** and the tosylate in the product (*S*)-**137** is displaced by a Co(I) anion to give the intermediate (*S*)-**138** as a stable orange solid.[38]

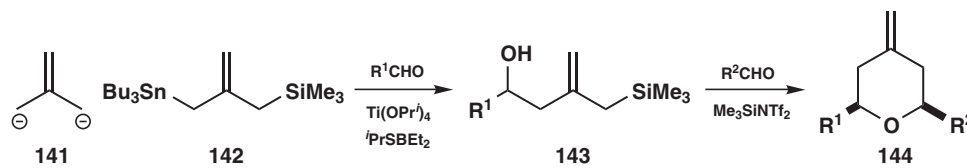


In acid solution, cobalt creates a π-stabilised cation at the site of the OH group that cyclises onto the allyl silane with the expected regioselectivity and excellent enantioselectivity. The nature of the cation stabilisation and the removal of the cobalt are discussed in the workbook. The structure of this group '$Co(dmgH)_2py$' is explained in the workbook.

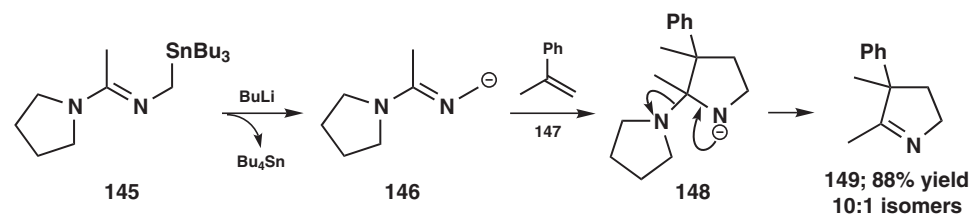


An Allyl Dianion? The Role of Tin in Anion Formation

The prospects of inventing a reagent for the dianion synthon **141** might look remote but the reagent **142**, both an allyl silane and an allyl stannane, does the job.[39] Reaction with one aldehyde occurs at the end occupied by tin and the second, using a different Lewis acid, at the end occupied by silicon. The result is a tetrahydropyran **144** with 2,6-syn substituents, both being equatorial.

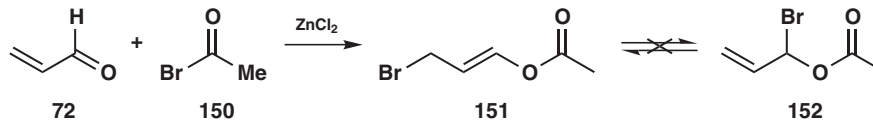


A commoner role for tin is to sacrifice itself in the formation of allyl anions (or allyl lithiums) with BuLi. The 'allyl' (it has a nitrogen atom in the backbone, so strictly an 'aza-allyl') tin **145** reacts with BuLi to form Bu_4Sn and the allyl anion **146** that adds to the styrene **147** in a 1,3-dipolar cycloaddition to give the amide ion **148** that eliminates pyrrolidine to give the imine **149**. The imine **149** is formed as a 10:1 mixture of positional isomers.[40]

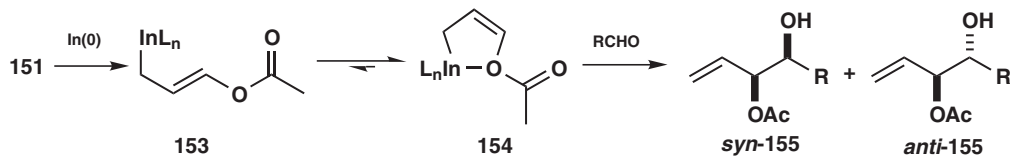


Halide Exchange with Chelation: Indium Allyls

The problem with forming allyl metal derivatives by exchange of zerovalent metal with halide ions is that we often cannot be sure where the halide ion is and never sure where the metal is because of rapid [1,3] shifts, cf. compounds **21** and **23**. If the allylic system has a substituent that chelates with the metal then only one derivative is likely to be formed. We need a halide at one end of the allyl group and a chelating substituent at the other. Just such compounds can be made by acylation of acrolein **72** in the presence of zinc chloride. No [1,3] shift of Br will occur as the alkene much prefers to be disubstituted and conjugated with oxygen **151** rather than unconjugated and terminal **152**.

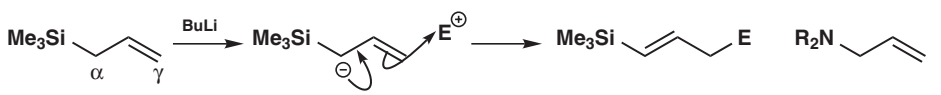


Whichever isomer (positional or geometrical) of the indium allyl is first formed (e.g. **153**) is unimportant as equilibration leads to the stable chelated version **154** that reacts with aldehydes to give, as expected, reaction at the other end of the allyl system from the metal.[41] The product **155** is formed as a *syn*/*anti* mixture but the *syn* isomer can predominate by as much as 90:10. You may wonder why indium was used. The usual reason for indium is that its organic derivatives are stable in water but here the more important point is the low reactivity of allyl indiums.

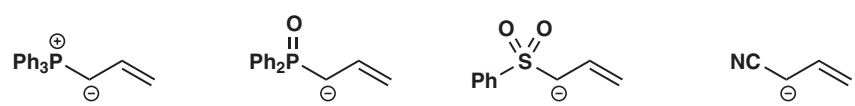


Allyl Anions by Deprotonation

In the next chapter we shall see that allyl anions made from allyl silanes **95** by the removal of a proton still react in the γ-position **156** but retain the silyl group in the form of a vinyl silane **157** and are reagents for the d^3 synthon, the homoenolate ion. Though the Me_3Si group is electron-donating it is also anion stabilising. Other electron-rich but anion-stabilising groups such as amines **158** also form anions that react in the γ-position.

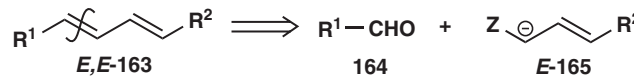


Allyl anions with electron-withdrawing and anion-stabilising functional groups form anions much more easily and then react (mostly) in the α-position. There are many examples of this sort of substituent including extended enolates (chapter 11), and allyl anions stabilised by phosphonium **159**, phosphonate **160**, sulfone **161**, and cyanide **162** functional groups. All of these prefer to react in the α-position (at least kinetically) and we shall explore some of these.

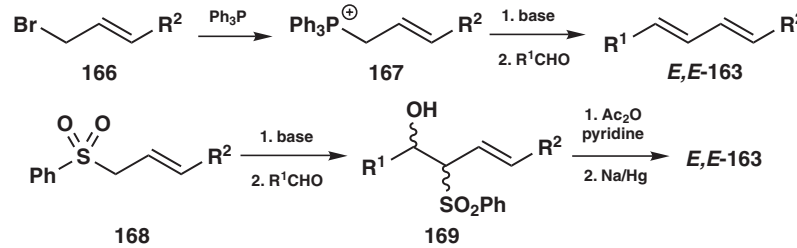


The synthesis of all-trans dienes

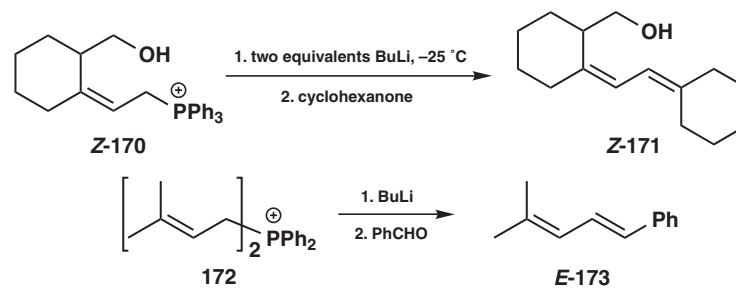
We shall finish this chapter by considering two ways to achieve condensation between an allyl anion and an aldehyde (or ketone) in the synthesis of dienes **163**. The reagent **165** is an allyl anion stabilised by a heteroatom (Z) that can be lost with the OH group after addition to R^1CHO.



The best candidates are phosphonium salts (Z = Ph_3P^+) **167**, using the Wittig reaction, and sulfones (Z = $PhSO_2$) **168**, using the Julia reaction,[42] as we shall see in chapter 15. Wittig reagents are easily made from allylic halides, substitution usually occurring at the less hindered end, and react with aldehydes at the site next to the Ph_3P^+ group since elimination of Ph_3PO can occur only if this regioselectivity is observed (c.f. the similar solution to the γ-extended enolate problem, chapter 11).

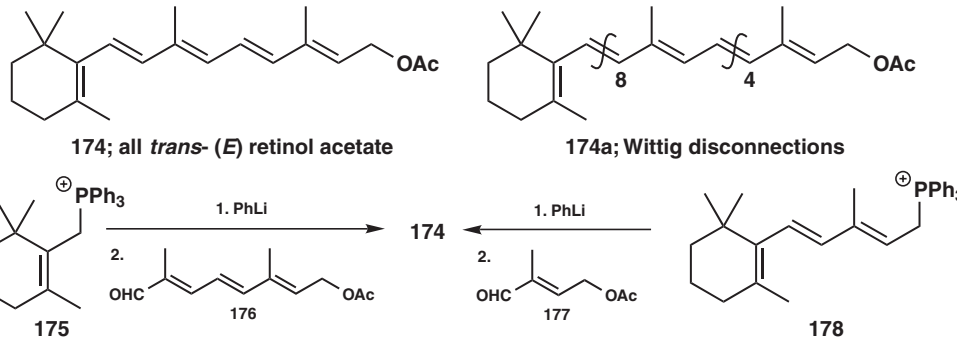


These ylids are classified as "semi-stabilised" or of "intermediate" reactivity, and their stereoselectivity may be poor.[43] If the stereochemistry of the double bond in the ylid (from **167**) is *E*, this is generally retained in the product, but if it is *Z*, as in the ylid derived from **170**, low temperatures are needed to stop rotation at the allyl ylid stage. At −25 °C less than 5% *E*-**171** is formed in the synthesis of vitamin D metabolites.[44] The stereochemistry of the new double bond is generally not well controlled, 1:1 ratios of *E:Z* are not uncommon, but Vedejs finds that phosphonium salts such as **172** with two phenyl and *two* allyl groups give good yields of *E*-dienes[45] such as **173**.

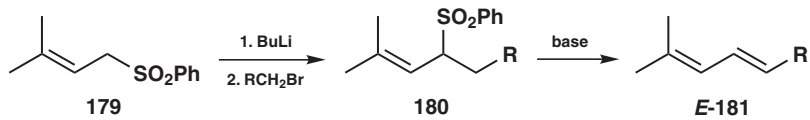


The synthesis of all-trans retinol

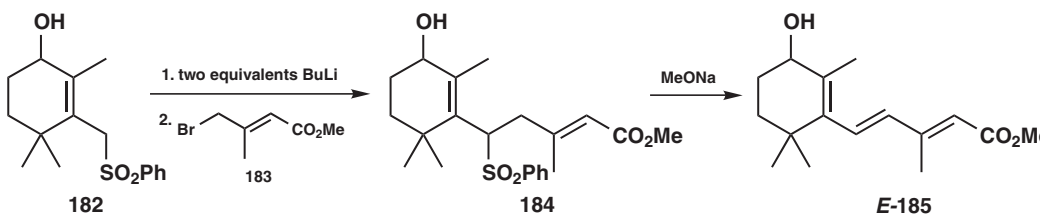
If *E,E* dienes like **163** are wanted, then such Wittig reactions are ideal as the mixed products can be equilibrated to the *E,E* diene by addition of small amounts of radical generators such as iodine or PhSH. The commercial (BASF) synthesis of Vitamin A involves all *trans* retinol **174** that can be made from two different allylic ylids derived from **175** and **178** with the appropriate aldehydes **176** and **177**. In both cases *E,Z* mixtures are formed, but equilibration with iodine gives **174** with an all *E* side chain.[46] A different synthesis of such compounds appeared in chapter 11.



Direct α-alkylation of anions of allylic sulfones **179** gives products **180** from which $PhSO_2^-$ can be eliminated with mild base (MeONa) to give *E*-dienes **181**. The more usual condensation of sulfones with aldehydes is not necessary and those adducts **169** may eliminate to give vinyl sulfones instead of alkenes.[47]



As part of a synthesis of sesquiterpenes, the sulfone **182** and the allylic halide **183** were coupled (allylic electrophile as well as allylic nucleophile!) to give a mixture of diastereoisomers of **184** that gave the triene **185** on elimination.[48] Note that the new double bond is exclusively *E*.



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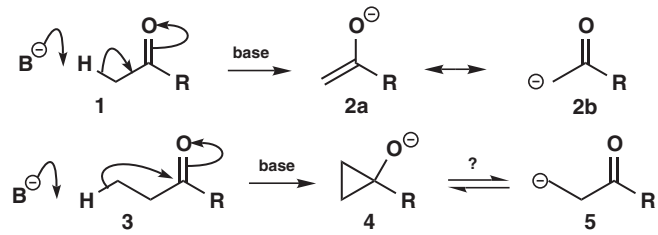
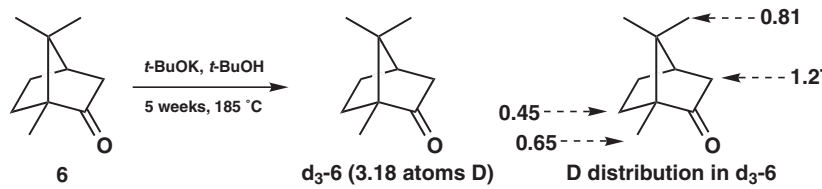
13 Homoenolates

Introduction: *Homoenolisation and homoenolates*

Enolisation **1** involves the removal of the α-proton from a carbonyl compound to form an enolate ion **2**. *Homo*enolisation involves the removal of a β-proton **3** to form the homoenolate ion **4** or **5**. Both the enolate and the homoenolate can be represented as carbanions, but whereas the enolate version **2b** is merely a different way of representing a single delocalised structure, the homoenolate **5** is a different compound from the cyclopropane **4**. No literal examples of homoenolates **5** are known so they have the status of synthons which may be represented in real life by reagents derived from cyclopropanols **4** among many other possibilities.[1]

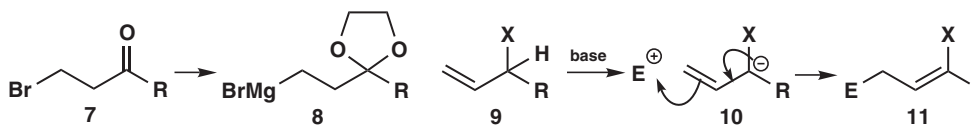


Direct homoenolisation of a carbonyl compound with base is not of much practical use. Ketones blocked in the α-position do exchange with deuterium in base, but after five weeks in *t*-BuOK/*t*-BuOD at 185 °C only 3.18 atoms of deuterium had been incorporated into camphor **6** with the distribution shown. The two sites for homoenolisation were responsible for only 0.65 and 0.45 atoms, in contrast to 1.27 atoms at the α and 0.81 at the γ atoms.[2]



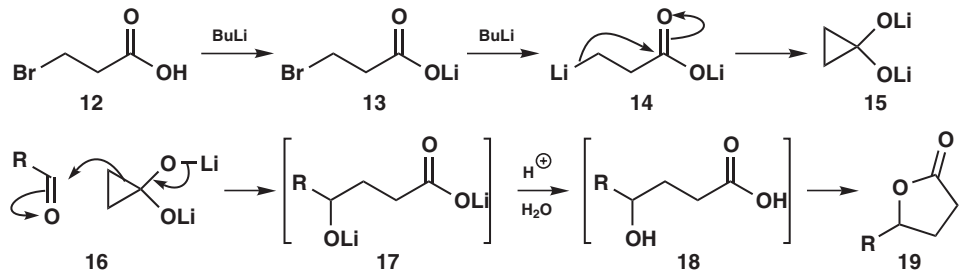
Summary of strategies

Useful synthetic methods therefore rely on reagents which have been devised to represent the d^3 synthon or homoenolate **5** in reactions and there are three important classes of these. The cyclopropane or direct approach uses reagents such as **4**. Hoppe's 'defensive strategy' uses a nucleophile created at C3 that is neither stabilised nor destabilised by a protected carbonyl group as in the Grignard reagent **8**. Hoppe's 'offensive strategy' uses an allyl anion with a heteroatom (X in 9) at one end.[1] This strategy has 'many problems' or rather many conditions that must be fulfilled. The heteroatom must help to stabilise the anion, the anion must react in the γ-position **10** (chapter 12), and it must be possible to hydrolyse the product **11** to a carbonyl compound.

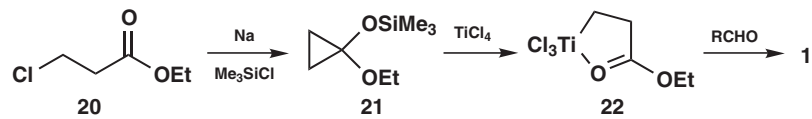


Three-Membered Ring Homoenolate Equivalents (The 'Direct' Strategy)

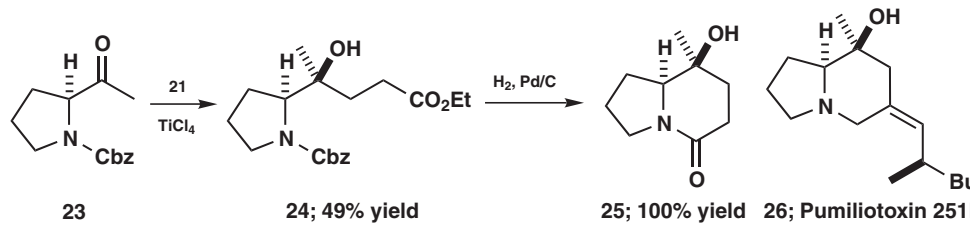
Perhaps the only true homoenolates used in synthesis are derived by metallation of derivatives of 3-haloacids. The acids themselves **12** give lithium 3-halocarboxylates **13** and hence by metallation the homoenolate which probably exists as **15**, an analogue of the dilithium enolates of carboxylic acids (chapter 2). Reaction **16** with aldehydes or ketones gives γ-lactones **19**, by a 'homoaldol' reaction via γ-hydroxyacids **18**, common products from addition of acid homoenolates to carbonyl compounds.[3]



Ester homoenolates can be made from 3-chloroesters **20** with sodium in the presence of Me_3SiCl which traps them as the cyclopropyl silyl ethers[4] **21**, analogues of silyl enol ethers, in a step reminiscent of the acyloin condensation.[5] Reaction with aldehydes and ketones again gives γ-lactones **19** and Kuwajima has shown that the titanium homoenolate **22** is a true intermediate in this reaction.[6]

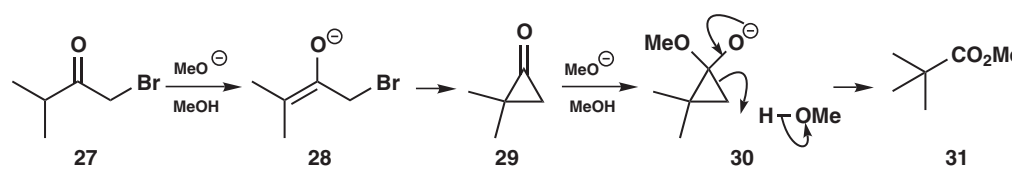


Addition of this homoenolate to the ketone **23**, a single enantiomer derived from natural proline, gives the tertiary alcohol **24** with high stereoselectivity.[7] Removal of the Cbz protecting group leads to spontaneous cyclisation to give **25**, an intermediate on the way to the neurotoxin pumiliotoxin 251D **26**.

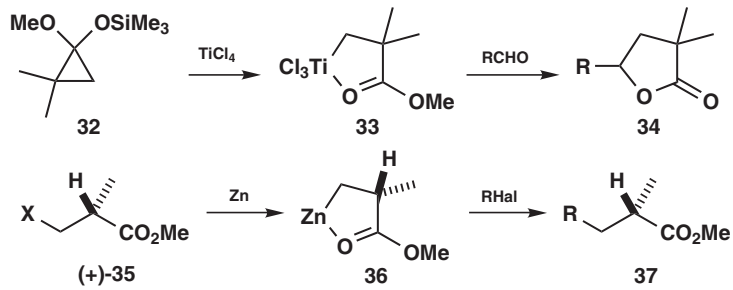


Unsymmetrical cyclopropane homoenolates

There is an obvious difficulty if the cyclopropane ring is unsymmetrically substituted and our best guideline here is the last stage of the Favorskii reaction,[8] e.g. **27** to **31**, where a cyclopropoxide ion is protonated **30** at the carbon atom giving the better anion, usually at the less substituted carbon.

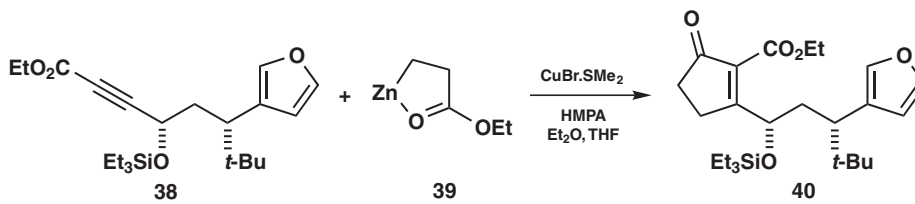


Opening the corresponding silyl ethers **32** with $TiCl_4$ also usually occurs at the less substituted atom to give the homoenolates[6] **33** and hence the lactones **34**. This regioselectivity means that a chiral centre next to the carbonyl group **35** can be preserved during the formation of esters **37** by alkylation of a zinc homoenolate[9] which may have the structure **36**.



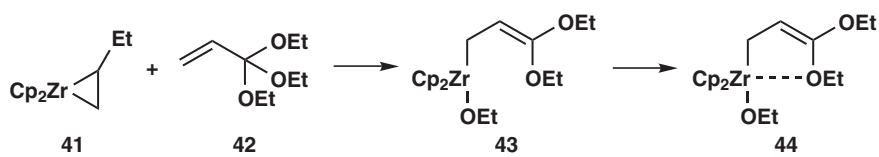
Conjugate addition of zinc homoenolates

The simple zinc homoenolate **39**, derived from **21** with $ZnCl_2$ and ultrasound, does a conjugate addition to the acetylenic ester with Cu(I) catalysis to give a new cyclopentenone **40**, an intermediate[10] on the way to gingkolide B. The stereochemistry of **38** is not affected by the reagent.

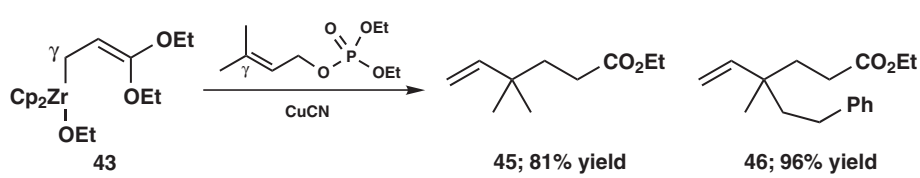


Zirconium homoenolates

Zirconium ester homoenolates **43** or **44** can be prepared from the triethyl orthoacrylate **42** with the zirconocene complex of but-1-ene **41** (Cp means cyclopentadiene). These resemble the zinc and titanium species we have been discussing but are not derived from cyclopropanes.[11]

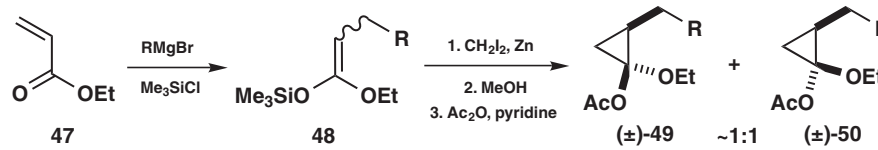


In the presence of CuCN, these homoenolates react with acid chlorides to make γ-ketoesters but their forte is reaction with allylic phosphates. Prenyl diethylphosphate gives **45** in good yield and the more highly substituted product **46** is formed in near quantitative yield. These are impressive results: both reagents react through the γ-carbon: the homoenolate **43** where the Zr is and the allylic phosphate where the phosphate isn't.

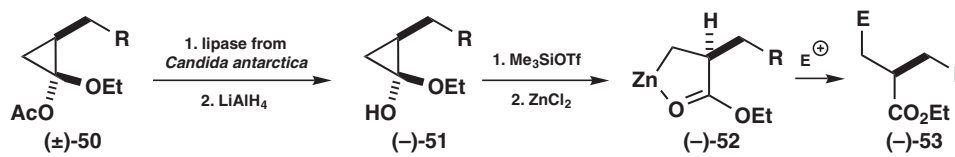


Enantioselective cyclopropane homoenolates

Recent developments in the cyclopropane approach to homoenolates have emphasised enantioselectivity.[12] Racemic mixtures of acetals of cyclopropanones can be prepared by Simmons-Smith cyclopropanation of silyl ketene acetals. Silicon-promoted conjugate addition (chapter 9) of Grignard reagents to acrylate esters **47** gives mixtures of *E/Z* isomers of the silyl ketene acetals **48**. Cyclopropanation and exchange of the silyl group for an acetate gives a roughly 1:1 mixture of *syn* and *anti* cyclopropanes **49** and **50**, easily separated by chromatography.

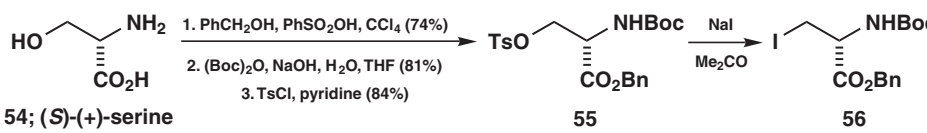


Kinetic resolution (chapter 28) of each diastereoisomer with a lipase gives single enantiomers of the hemiacetals **51** and hence the zinc homoenolates **52**. Various electrophiles (E in **53**) gave enantiomerically pure (>99% ee) adducts where E = H, allyl or imine.[13]

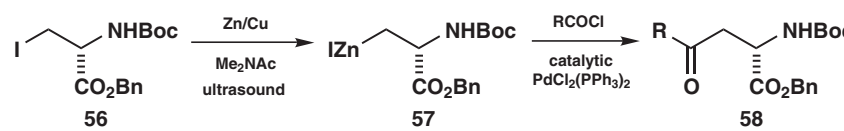


An enantioselective amino acid homoenolate

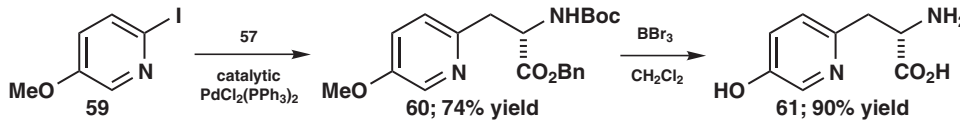
An important use of enantiomerically pure homoenolate equivalents is the synthesis of other α-amino acids from serine. Natural (*S*)-(+)-serine **54** is protected on both its amino and carboxyl groups and the OH group turned into a leaving group **55**. Displacement with iodide gives the starting material **56** with no loss of optical activity.[14]



Treatment with zinc/copper couple activated by ultrasound in dimethylacetamide gave the zinc homoenolate **57** stabilised by chelation to either the ester or the carbamate. Acylation with acid chlorides and Pd(0) catalysis gave the enantiomerically pure γ-oxo-amino acids **58** in good yield.

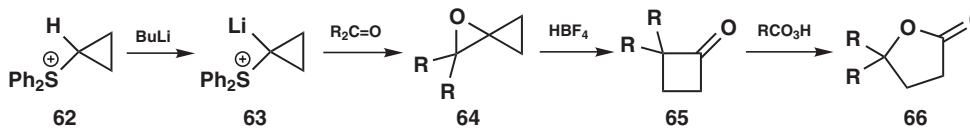


Arylation with ArI and palladium catalysis is also possible and forms the key step in an asymmetric synthesis of the antibiotic azatyrosine.[15] This differentiating antibiotic has anti-cancer potential. Coupling **57** with the pyridine **59** gave **60** and removal of the methyl protecting group gave azatyrosine **61**.

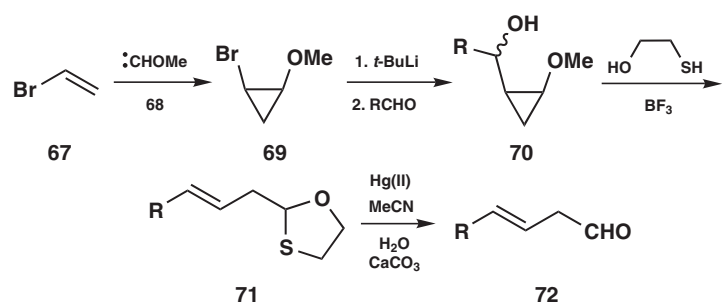


Homoenolate equivalents from three-membered rings

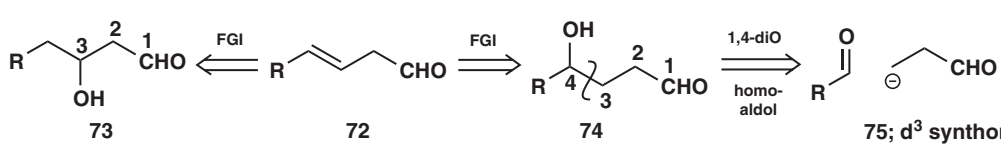
Other three-membered ring compounds have been used to achieve the result of homoenolate attack on ketones, the most important being Trost's cyclopropyl sulfur compounds and Corey's cyclopropyl ethers. Attack of the sulfonium ylid[16] **63** on a ketone gives the usual epoxide[17] even though it is an oxaspiropentane **64**: this rearranges to the cyclobutanone **65** in acid. Baeyer-Villiger rearrangement involves migration of the more highly substituted carbon atom[18] to give the lactone[19] **66**, the result of ester homoenolate addition to the ketone R_2CO.



Corey's method[20] relies on metal exchange with the bromocyclopropane **69** prepared by carbene addition. The extra stabilisation of cyclopropyl anions (chapter 8) makes both this lithium derivative and the ylid **63** more easily handled. Addition to aldehydes or ketones gives mixtures of adducts **70** [it turns out that none of the stereochemistry of **69** or **70** matters] which fragment under Lewis acid catalysis to give the thioacetal **71**. Careful hydrolysis releases the 3,4-enal *E*-**72**, the product of a homoaldol reaction with an aldehyde homoenolate and RCHO and a difficult compound to make as the double bond moves into conjugation very easily.



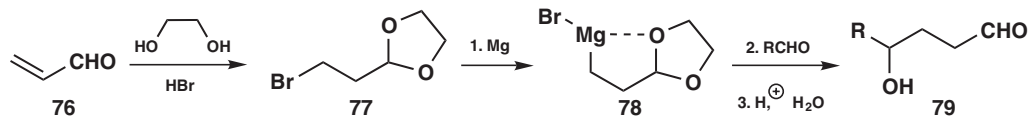
The disconnections for this homoaldol are not obvious. Just as a conjugated (α,β-unsaturated) enal is derived from an aldol, we can consider deriving this unconjugated (β,γ-unsaturated) enal **72** from a hydroxyaldehyde. We might initially prefer FGI to **73** as the 1,3-relationship is easy to make. But **73** will dehydrate to the conjugated (α,β-unsaturated) enal. Instead we must set up a 1,4-diO relationship **74** so that we can disconnect to an aldehyde RCHO and the homoenolate **75** of propanal.



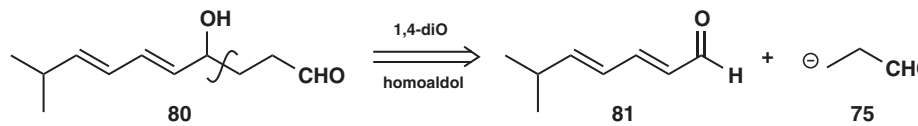
The Defensive Strategy: d³ Reagents with Protected Carbonyl Groups

Acetals

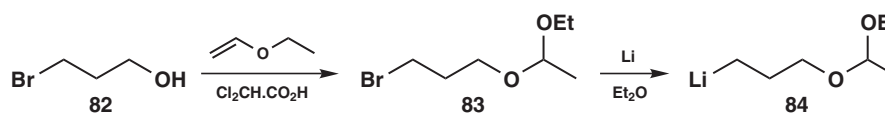
Conceptually the simplest of all the homoenolate equivalents, organometallic reagents such as the Grignard **8** could be regarded as avoiding the problem. This is unfair and a better way to look at them is to regard their synthesis as reversing the polarity of unsaturated carbonyl compounds. Unsaturated aldehydes and ketones can be converted into bromoacetals such as **77**, and Büchi and Wuest[21] used the Grignard reagent derived from **77**, that may have the chelated structure **78**, in their synthesis of nuciferal as long ago as 1969.



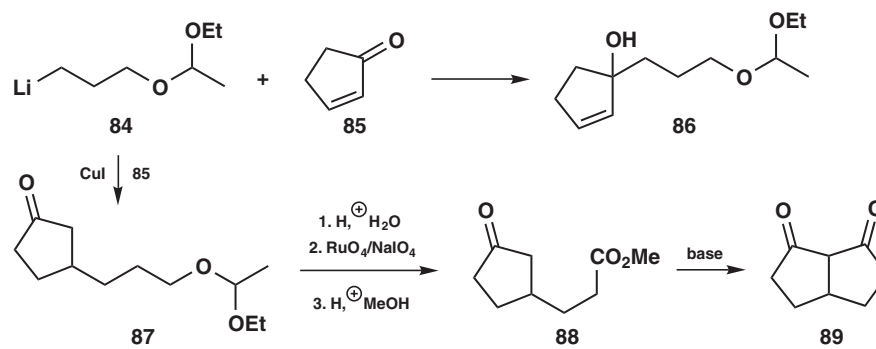
Roush used this reagent in his synthesis of dendrobine[22] for which he needed the unsaturated hydroxyaldehyde **80**. Disconnection next to the OH group reveals the dienal **81** and the homoenolate synthon **75**. The dienal can be made by consecutive aldol reactions or using extended enolate chemistry (chapter 11). Reaction between the Grignard reagent from **77** and the aldehyde **81** in THF gave >95% of **80**. Similar reagents are available at the ketone oxidation level.[23]



For both the alcohol and the carboxylic acid oxidation levels, the best organometallic reagent is probably the very simple protected lithium derivative **84** introduced by Eaton.[24] Easily made from available bromopropanol **82**, the acetal **83** gives the stable (because of chelation by one or both acetal oxygen atoms?) lithium derivative **84** by oxidative insertion.

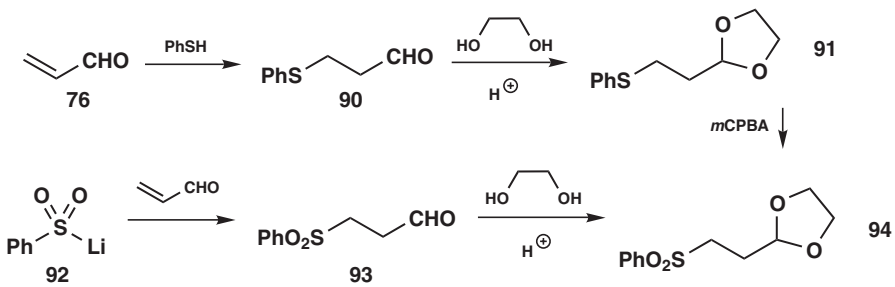


Addition to aldehydes, ketones, and enones occurs cleanly at the carbonyl group, e.g. to give **86**, but the copper derivative adds to enones in the expected Michael sense (chapter 9) to give 1,6-dicarbonyl compounds such as **88** after oxidation. Cyclisation to **89** completes a cyclopentannelation sequence (chapter 6).

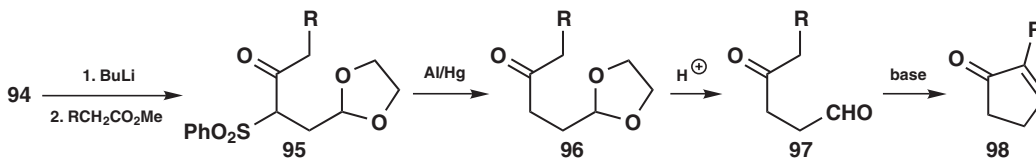


Sulfones

Possibly more popular are the protected sulfones[25,26] such as **94**, again easily made by Michael addition at either the sulfide or sulfone[27] oxidation state as sulfur nucleophiles are excellent Michael donors.

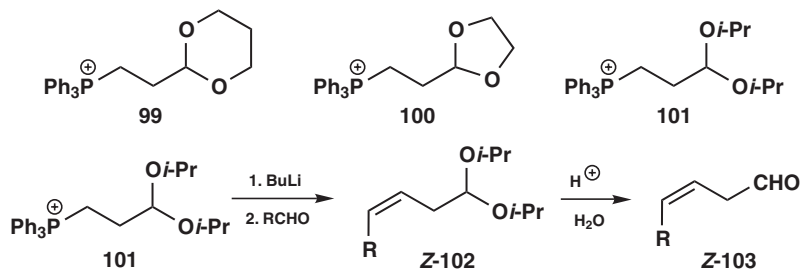


Lithium derivatives of these sulfones can be alkylated with alkyl halides or epoxides,[28] and acylated with esters to give the ketones **95** from which the sulfonyl group can be removed with aluminium amalgam. Deprotection and cyclisation provides a synthesis of cyclopentenones **98** (cf. chapter 6).[26]



Phosphonium salts

The corresponding phosphonium salts[29] **99**, **100**, and **101**, made from the bromoacetals, can be used in Wittig reactions to give *Z*-acetals such as **102**. It is difficult to hydrolyse the acetal without isomerising the geometry or the position of the double bond, but non-cyclic acetals such as **101** satisfactorily give *Z*-alk-3-enals[30] **103**.

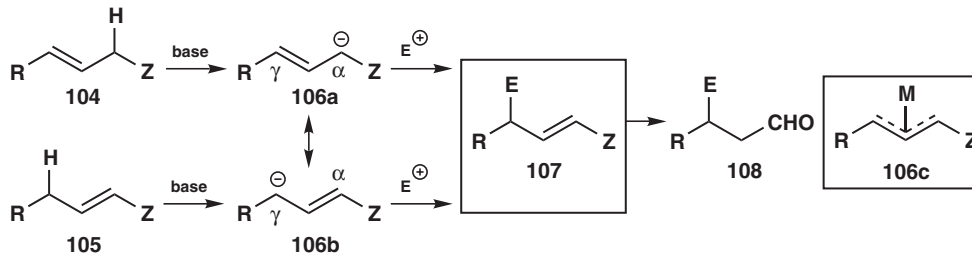


The Offensive Strategy: Heteroatom-Substituted Allyl Anions

Regioselectivity

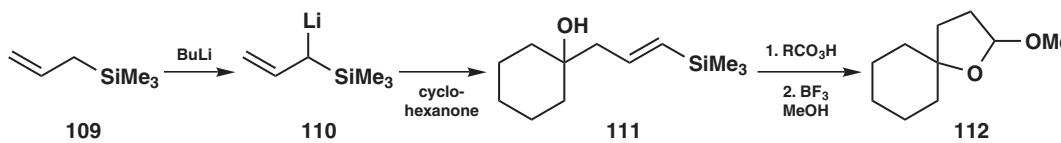
Allyl anions with a heteroatom at one end **106**; Z = OR, NR_2, etc, can act as homoenolates providing certain conditions are met. The anion must be easy to make from **104** or **105**, it must react reliably at the γ-position with a range of electrophiles E^+ to give only the vinyl derivative

107, and that vinyl derivative must be easily hydrolysed to a carbonyl compound. It turns out[1] that these conditions are generally fulfilled when Z = NR_2, SiR_3, OR, or SR, though the substituent(s) R do also matter. If M is a transition metal, the π-allyl complex **106c** may be the best representation of the allyl 'anion.'

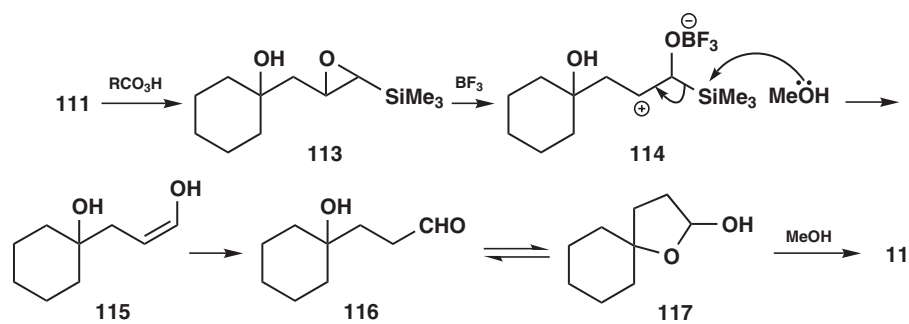


Anions of allyl silanes

Lithium derivatives of allyl silanes react in the γ-position with alkyl halides, epoxides, and carbonyl compounds. The lithium derivative **110** of allyl silane **109** gives only the γ-adduct **111** with ketones.[31] Vinyl silanes such as **111** are usually converted into carbonyl compounds via epoxides which rearrange with Lewis acid catalysis and loss of silicon to give protected versions of ketones or aldehydes **112**.



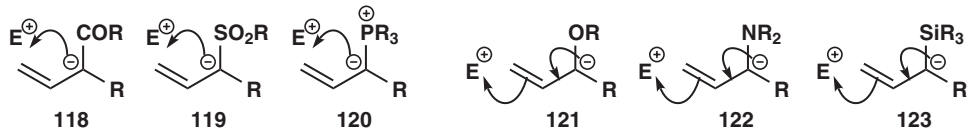
The reaction may involve the formation of the β-silyl cation **114** (chapter 12) or in this case participation by the OH group may be involved. In any case the final product is a protected version **112** of the 3-hydroxyaldehyde **116**.



Anions of allyl sulfides

Anions of allyl sulfides have been quite widely used but their regioselectivity is unpredictable and the vinyl sulfides **107**; Z = SR resulting from γ-addition are difficult to hydrolyse.[32] Anions of allyl ethers are more difficult to prepare, but generally better behaved.[33] A study of such anions led Still to propose that allyl anions with very anion stabilising substituents Z = COR **118**, SO_2Ph **119**, $^{+}PPh_3$ **120** etc, react α with all electrophiles, those with moderately anion-stabilising substituents

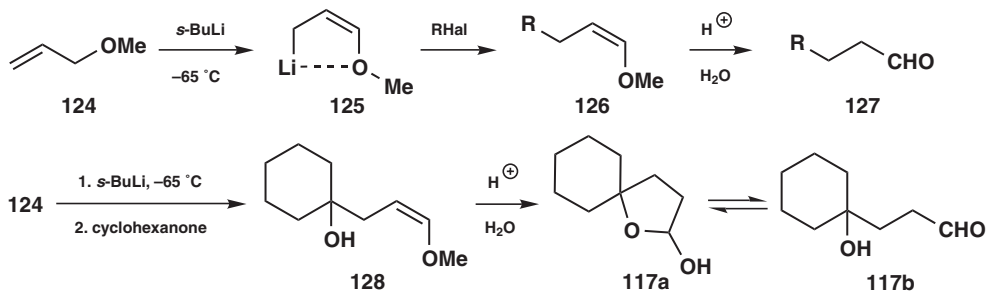
react α (or where the metal is) with alkyl halides but γ (or where the metal isn't) with carbonyl compounds, and those with anion destabilising substitutents Z = OR **121**, NR_2 **122**, or $SiMe_3$ **123**, react γ with all electrophiles.[34] A wide selection of these anions appears in Hoppe's review.[1]



118 **119** **120** **121** **122** **123**

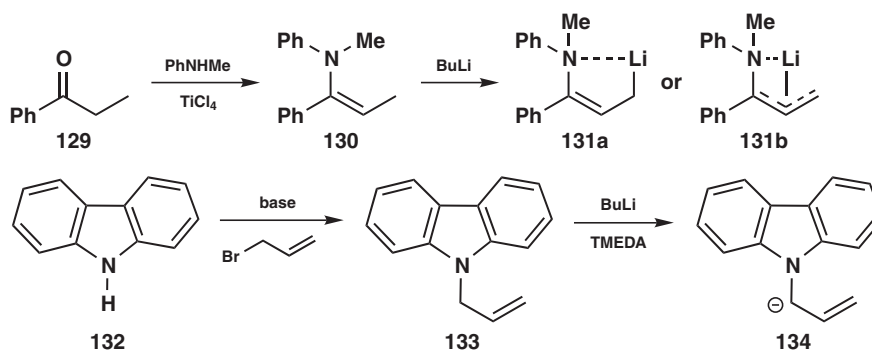
Anions of allyl ethers

Allyl ethers **124** clearly belong in the last category and their lithium derivatives **125** react both with alkyl halides, to give **126**, and carbonyl compounds, to give **128**, with the correct regioselectivity for them to act as homoenolate equivalents. The *Z*-alkene in both products **126** and **128** suggests the chelated structure **125** for the allyl-lithium. Acidic hydrolysis releases the carbonyl group **117b**, in the form of a hemiacetal **117a** from the carbonyl adduct **128**. These allyl ethers **124** need strong base to remove the not very acidic proton and must be lithiated at low temperature to avoid the Wittig rearrangement.[33]



Anions of allyl amines

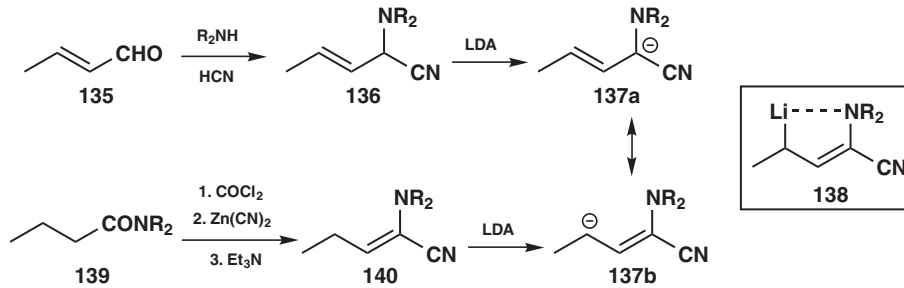
Anions derived from enamines or allyl amines have been widely explored and are among the best homoenolate equivalents. Enamines **130** from PhNHMe and aldehydes[35] or aryl ketones[36] **129** can be deprotonated with BuLi to give lithium allyls **131**, as can the corresponding allyl amines.[37] The anion of carbazole **132** reacts on nitrogen with allyl halides and the products **133** can be converted to lithium derivatives **134** with BuLi in the presence of chelating agents such as TMEDA. The representations **131a**, **131b** and **134** are alternatives.[38]



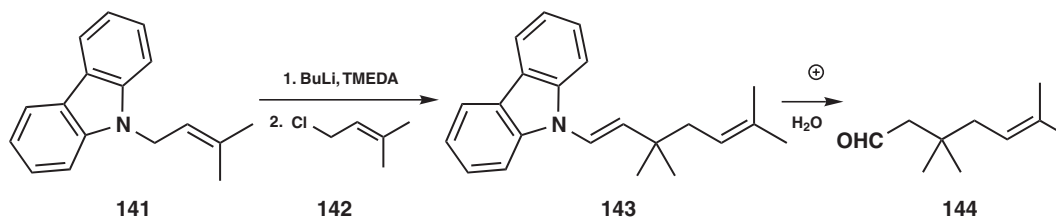
129 **130** **131a** **131b**

132 **133** **134**

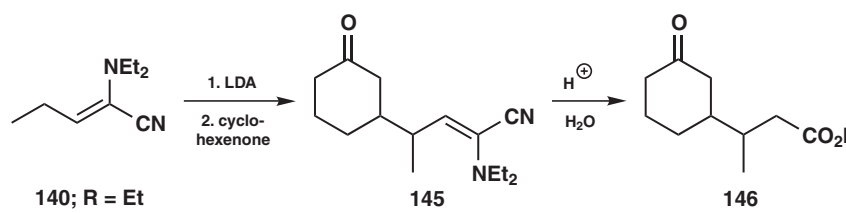
Amino-nitriles[39] **136** can be made directly from unsaturated aldehydes in the first stage of the Strecker reaction and deprotonated with LDA. The same allyl-lithium derivatives **137** can be made from saturated amides[40] **139** via the vinyl isomer **140** of **136**. All these lithium allyls, maybe **138** is the best representation, react as homoenolates.



The lithium derivative from the unsymmetrical allylic carbazole **141** reacts with the unsymmetrical allyl chloride **142** to give **143**. The starting material was made from carbazole **132** and **142** so this allyl electrophile has reacted twice at its *less* substituted end, but the nucleophilic homoenolate from **141** has reacted at its *more* substituted end, because that is γ-addition relative to the nitrogen atom.[38,39] Hydrolysis of the resulting enamine *E*-**143** gives the aldehyde **144**.

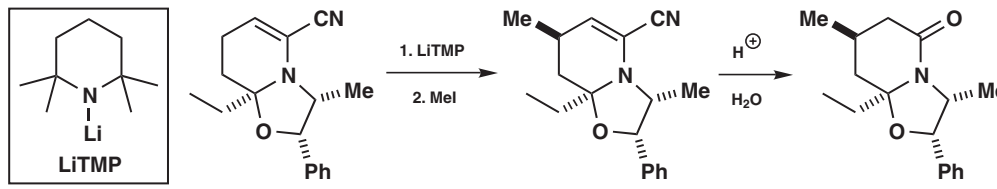


We shall see in chapter 14 that saturated amino nitriles are good d^1 reagents and the unsaturated versions **140** are good d^3 reagents, particularly effective at Michael addition. The lithium derivative from **140**; R = Et gives conjugate addition to cyclohexenone and hence the keto-acid **146** with a 1,6 relationship between the two carbonyl groups. The reconnection strategy[41] is not suitable for this compound as it is impossible to put a double bond between the two carbonyl groups. Lithium derivatives of allyl amines are homoenolates of aldehydes or ketones while lithium derivatives of unsaturated amino-nitriles are homoenolates of acids.

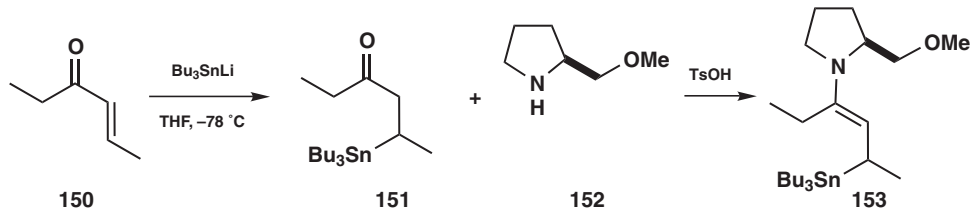


Asymmetric allylic amines

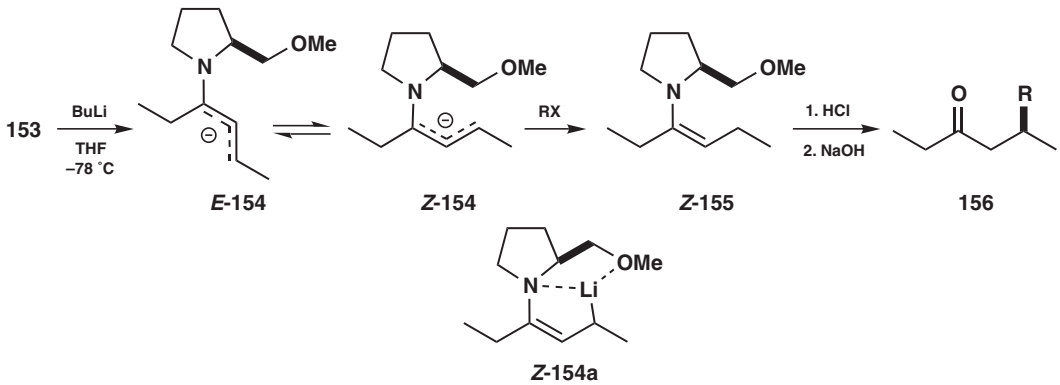
In this style too, asymmetry has become a major concern.[42] An asymmetric version **147** of this homoenolate was made from natural *nor*-ephedrine and could be alkylated stereoselectively using lithium tetramethylpiperidide (LiTMP) as base. The product could be hydrolysed to the bicyclic amide[43] **149**.



An open chain example[44] **153** of asymmetric homoenolates from allylic amines uses the proline derivative **152** and the β-stannyl ketone **153** made by conjugate addition of Bu_3SnLi to the enone **150**.

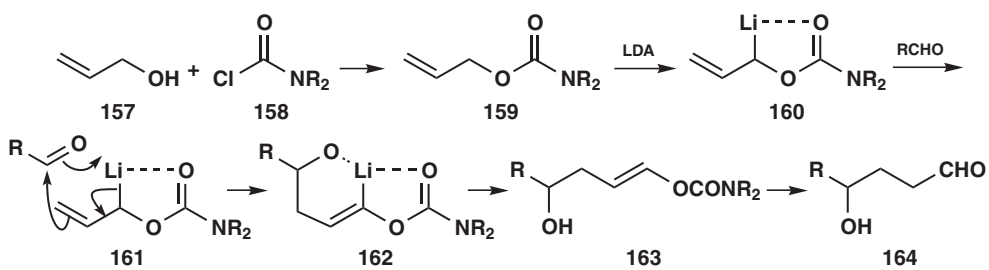


The lithium derivative of **153** can equilibrate to the chelated isomer *Z*-**154** that reacts cleanly in the γ-position with alkyl and allyl halides to give, after hydrolysis of the initially formed enamine **155**, the ketones **156** with generally good enantiomeric excess. Structure *Z*-**154a** shows the chelation in the lithiated intermediate best.



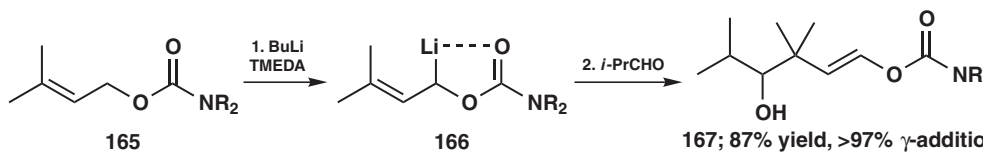
Allyl Carbamates

The most sophisticated homoenolate equivalents, and the first to allow some control over stereochemistry, are the lithium derivatives **160** of allyl carbamates **159** introduced by Hoppe.[1] They are particularly valuable for reaction with an aldehyde or a ketone in a homoaldol reaction.



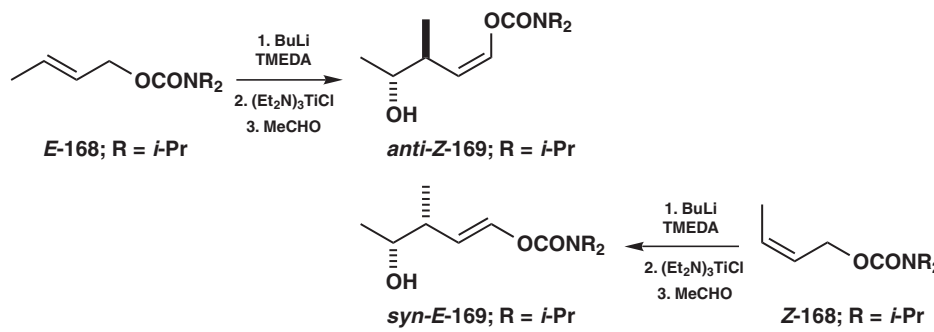
Though anions of allyl ethers, the extra functionality allows regiospecific heteroatom-directed lithiation **160** in the manner of chapter 7. Hence reaction of **160** with an aldehyde goes through a six-membered cyclic transition state **161** to give the enol derivative **163** and hence the γ-hydroxyaldehyde **164**.

We described some anions of allylic amines as γ-lithiated species **131a** and **154** that reacted in the γ-position. Here the position of lithiation is α **160** but that too ensures good γ-selectivity even when the γ-position is disubstituted **165** and the aldehyde is branched. Both the yield of **167** and the selectivity are excellent.[40]

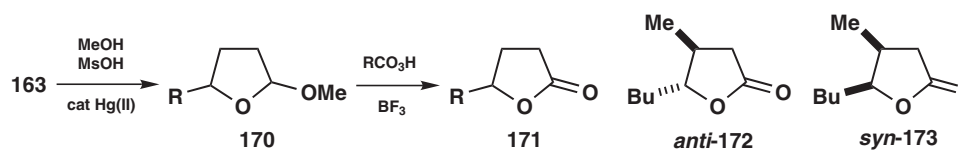


Stereoselectivity in the homoaldol reaction

Because of the cyclic transition state, stereoselectivity in the manner of stereoselective aldol reactions (chapter 4) is found, that is the geometry of the double bond in **168** determines the stereochemistry of the homoaldol product **169**, providing that lithium is exchanged for titanium or aluminium. That *E*-**168** gives *anti*-**169** and *Z*-**168** gives *syn*-**169** is not surprising, but the geometry of the resulting enol derivatives is. Fortunately it is irrelevant to the final product.



The final hydrolysis is not trivial: an Hg(II) catalyst is necessary to give acetals **170** that can be oxidised to lactones **171**. By this means both *syn* and *anti*-**172**, the *quercus* lactones from oak bark,[45] can be made stereoselectively in 87% and 90% yields respectively.



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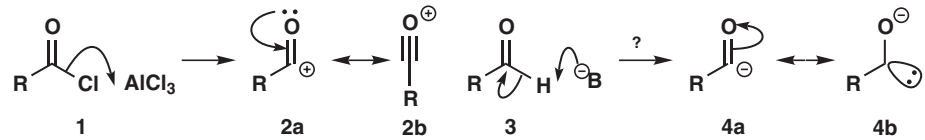
14 Acyl Anion Equivalents

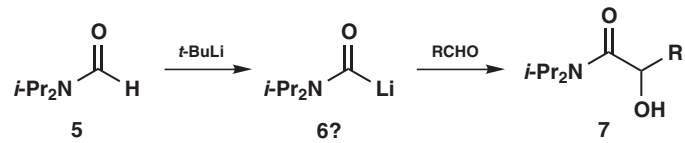
Introduction: *Acyl Anions?*

The acyl cation **2a** or acylium ion **2b** is a familiar intermediate in the Friedel-Crafts reaction. It is easy to make (acid chloride + Lewis acid **1**) and it can be observed by NMR as it expresses the natural reactivity pattern of the acyl group. The acyl anion by contrast has *umpolung* or reverse polarity.[1] One might imagine making it from an aldehyde by deprotonation **3** and that it would be trigonal **4a** or possibly an oxy-carbene **4b**. Such species are (probably) unknown and their rarity as well as their potential in synthesis has led to many synthetic equivalents for this elusive synthon. The acyl anion, the d^1 synthon, is the parent of all synthons with umpolung[2] and should perhaps have been treated before the homoenolates dealt with in the previous chapter.

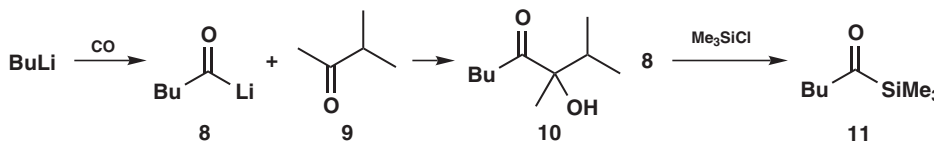
Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren



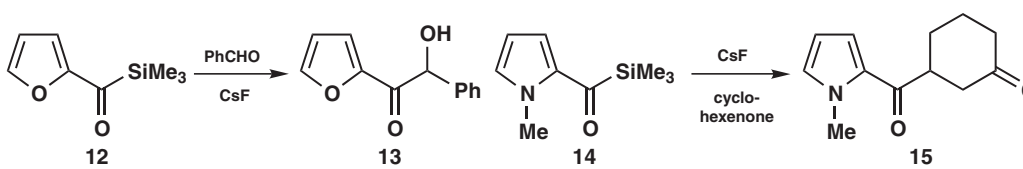
There are a few examples of carbonyl compounds losing a proton from the CHO group in strong base, though they are not aldehydes. The tertiary amide **5** gives a lithium derivative with *t*-BuLi, perhaps **6**, that adds to aldehydes to give **7**, the result of addition of an acyl anion to the aldehyde.[3]



There are two approaches to lithium derivatives of aldehydes, though neither starts from the aldehydes themselves. Carbonylation of primary alkyl-lithiums gives an intermediate,[4] probably **8**, that adds to aldehydes or ketones, e.g. **9**, to give hydroxyketones **10** and can be silylated to give the acyl silane **11**.



Alternatively the Me_3Si group may in turn be removed from the acyl silanes **11**, **12** or **14** with CsF to give possibly the acyl anion itself, or at any rate a species which adds to aldehydes and ketones in the same way,[5] and even does Michael reactions to give e.g. **15**.

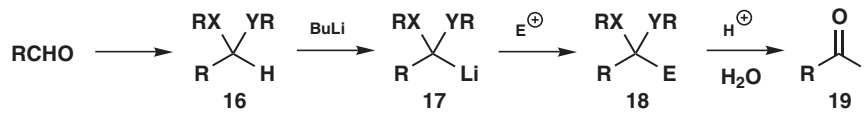


Acyl Anion Equivalents: *d*^{1} *Reagents*

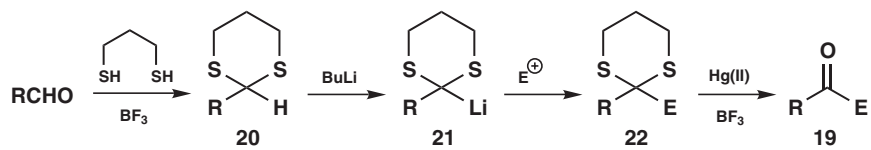
The yields in these reactions are not wonderful and most syntheses planned with acyl anion or d^1 synthons are realised with one of the reagents we are about to describe rather than with acyl-lithiums. Things may change as understanding of these rather reactive intermediates develops. There are three main types of acyl anion equivalent: reagents which can be considered as modified acetals, that is *protected* aldehydes, *masked* carbonyl compounds such a nitroalkanes, and substituted vinyl-lithiums. The rest of this chapter will be devoted to these reagents.

Modified Acetals as Acyl Anion Equivalents

Any acetal-like derivative **16** of an aldehyde can be used as an acyl anion equivalent providing the atoms X and Y stabilise an anion so that the lithium derivative **17** (or even the anion itself) can be formed, and providing that the product **18** of addition to an electrophile can be hydrolysed to a carbonyl compound. There is usually a conflict between these two requirements: thus acetals **16**; X = Y = O are very easily hydrolysed but do not in general form lithium derivatives. Often one substituent is chosen to stabilise the anion (S, CN, etc) while the other is chosen to help the hydrolysis (O, N, etc).

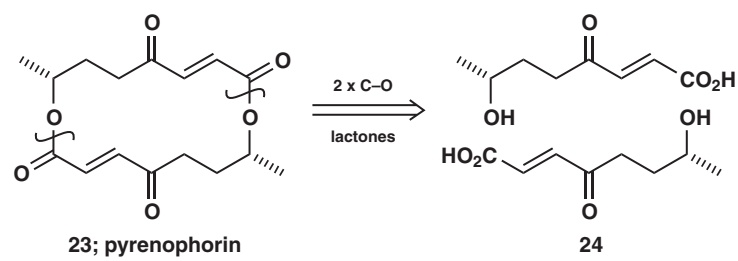


Dithians **20** illustrate this approach and have been remarkably popular considering the problems in their use. They can be made from aldehydes with propane-1,3-dithiol and Lewis acid catalysis. They are deprotonated with BuLi and react with alkyl halides, epoxides, and carbonyl compounds (E^+) to give **22** and hence **19** after hydrolysis. The hydrolysis is by no means easy: there are many methods and this alone should warn us that none is very good.[6]

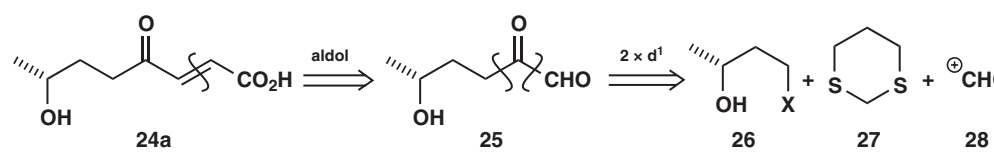


An asymmetric synthesis of pyrenophorin

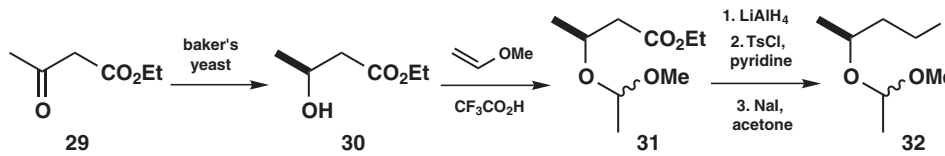
A synthesis of pyrenophorin using dithian shows how it works. The target **23** is a macrocyclic (16-membered ring) dilactone and disconnection of the ester linkages reveals two identical halves **24**: pyrenophorin has C_2 symmetry.[7]



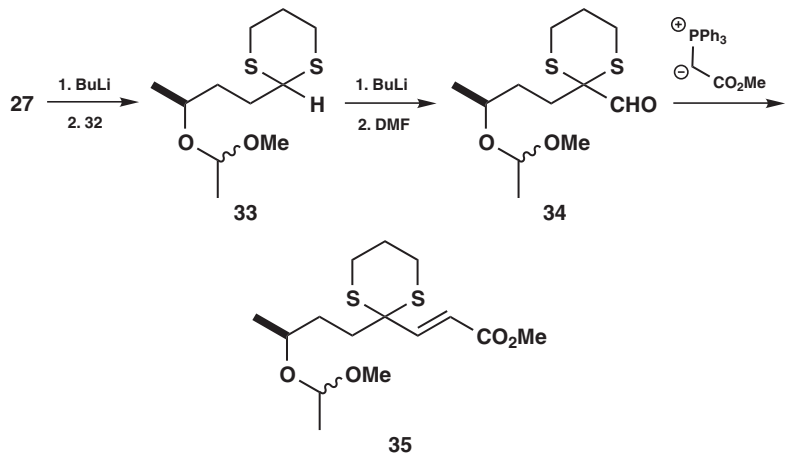
The enone **24** could be made by an aldol or Wittig approach from **25**. This contains unhelpful 1,2 and 1,4 relationships and the strategy is to ignore these and disconnect either side of the ketone, imagining it as a d^1 reagent used twice. The electrophiles would be one enantiomer of an alkylating agent **26**, probably with the OH group protected, and a reagent for the formyl cation **28**.



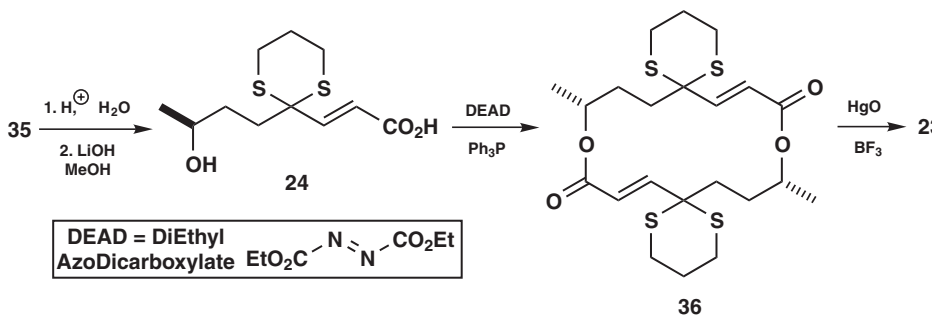
An optically active reagent **32** for the left hand fragment can be made by asymmetric reduction of ethyl acetoacetate with ordinary baker's yeast (see chapter 29), protection of the OH group as a mixed acetal **31**, reduction of the ester and conversion of the new OH group into an iodide **32**.



Alkylation of dithian itself **27** with the iodide **32** establishes the 1,4-diO relationship in **34** and this new dithian can be acylated with DMF (Me_2NCHO). The carbon skeleton of half pyrenophorin **35** is completed by an *E*-selective Wittig reaction with a stabilised ylid.



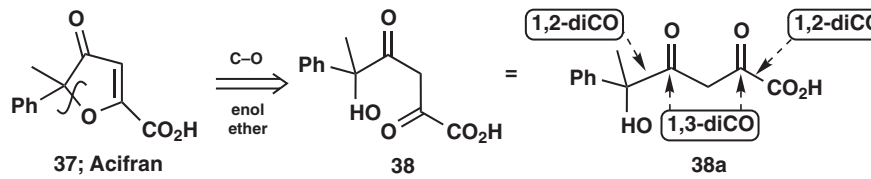
Removal of the two protecting groups leaves the dithian in place and it is left there while the macrocyclisation is completed with a Mitsunobu reaction. Notice that this esterification occurs with inversion so only now is the correct stereochemistry in place. Finally the dithian is hydrolysed with Hg(II) and BF_3.



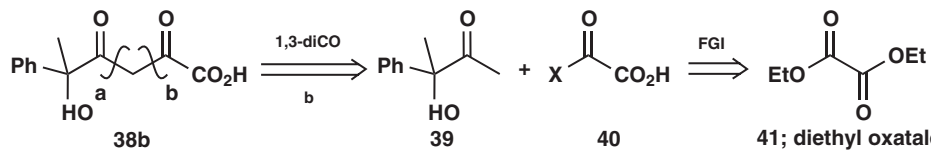
The synthesis of a drug using a dithian as an acyl anion equivalent

The anti-antihyperlipoproteinemic drug acifran **37** is a simple heterocycle whose structure can best be understood after disconnection of the enol ether.[8] The carbon framework **38** contains a

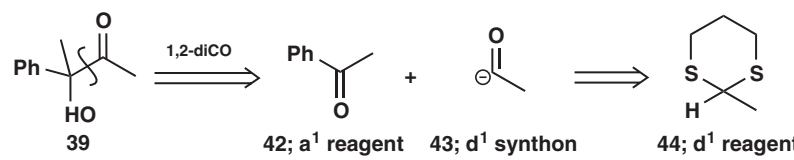
remarkable number of relationships: two 1,2- and one 1,3-diCO relationships **38a** as well as two 1,4-diCO and a 1,5-diCO.



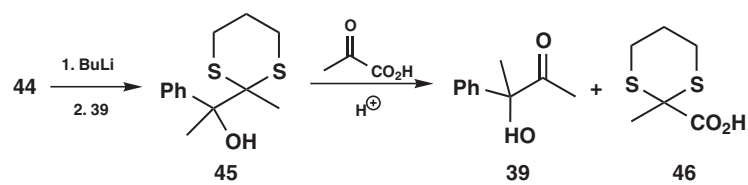
We prefer odd-numbered to even-numbered disconnections and of the two possible 1,3-diCO **38b** is better as it gives an enolisable ketone **39** and the unenolisable, symmetrical and very electrophilic diethyl oxalate **41**.



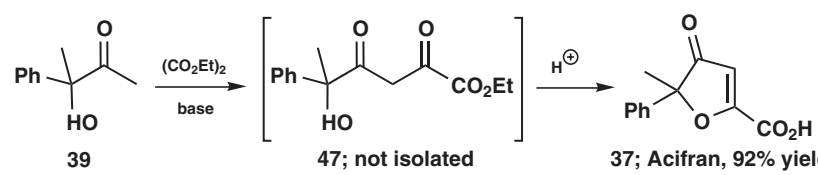
The α-hydroxyketone **39** could be made from attack of a d^1 reagent on the rather enolisable ketone PhCOMe **42**. The reagent chosen for the d^1 synthon **43** was again a dithian **44**.



The synthesis starts simply with the coupling of the lithium derivative of **44** with **39** but takes a novel turn when a dithian exchange with pyruvic acid is used to remove the dithian from **45**. The keto group in pyruvic acid is unstable, being next to another carbonyl group, while that in **39** is stable. Dithian exchange removes this instability by forming the pyruvic acid derivative **46**.

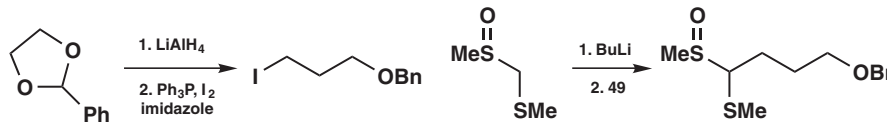


The rest of the synthesis is straightforward: no protection is needed in the favourable Claisen ester condensation to give **47** and the formation of the enol ether, being intramolecular, requires only heating with acid. This treatment also hydrolyses the remaining ester.

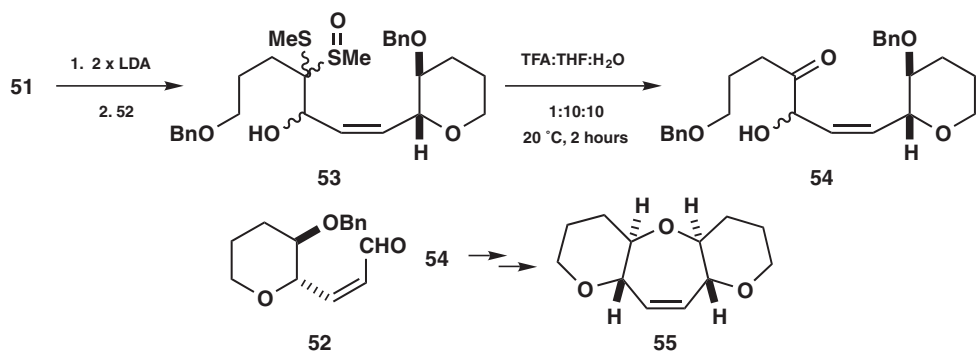


Dithioacetal monoxides

Recent developments have tried to remedy the difficult hydrolysis of the dithian. The monosulfoxides of dithioacetals are better at stabilising anions and more easily hydrolysed. They can be prepared by alkylation of the parent compound **50** with a suitable alkyl halide, e.g. to give **51**.[9]



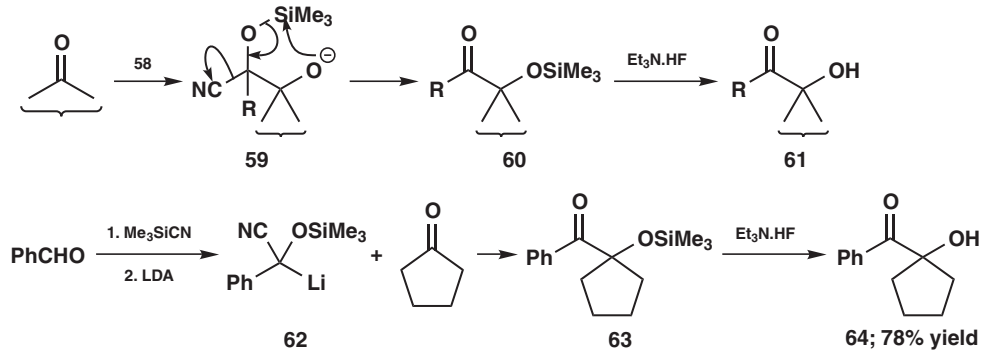
The lithium derivatives are prepared with LDA and add to most electrophiles. Only direct addition occurs to the sensitive *Z*-enal **52** to give a mixture of diastereoisomers **53** from which the dithioacetal is easily removed under mild conditions to give the ketone **54**. The product **54** was converted into the symmetrical triether[10] **55**.



Protected Cyanohydrins of Aldehydes

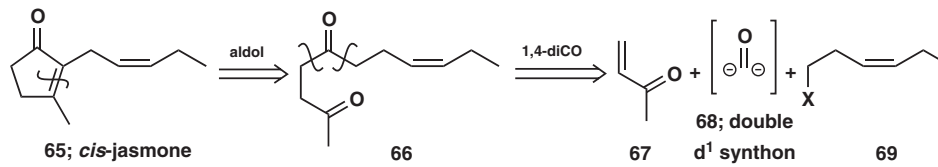
Unsymmetrical d^1 reagents of this kind, i.e. **16**; X ≠ Y, are best represented by the various cyanohydrin derivatives. Cyanohydrins themselves have an acidic H on the free OH group, but silylated cyanohydrins[11] **57**, formed with Lewis acid[12] or crown ether[1] catalysis, lack this acidic proton and give lithium derivatives **58** with LDA.

These lithium derivatives **58** react with many electrophiles but are particularly suited to aldehydes and ketones as the developing oxyanion captures the Me_3Si group **59** with loss of the CN group making this a much easier hydrolysis than that of a dithian. Treatment with fluoride then gives the hydroxy-ketone **61**. An example is the coupling of the d^1 reagent **62** from benzaldehyde with cyclopentanone to give the α-hydroxyketone **64** in a respectable 78% yield from benzaldehyde.

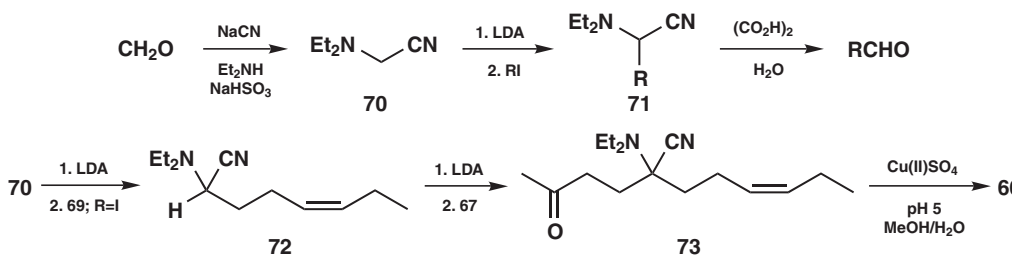


Amino nitriles are useful for conjugate addition

For d^1 reagents which will add Michael fashion to any unsaturated carbonyl compound, amino-nitriles are best. They were invented by Stork[13] for this very purpose and used in his *cis* jasmone **65** synthesis. This TM has perhaps been more synthesised than any other, though its simple structure and obvious enone disconnection to **66** make it a rather uninspiring choice these days. The 1,4-diketone **66** does indeed cyclise to **65** presumably under thermodynamic control, and the double disconnection **66** [cf. the disconnection of pyrenophorin **23**] requires a d^1 reagent that will react with enones **67** in the Michael sense and with alkyl halides **69**.

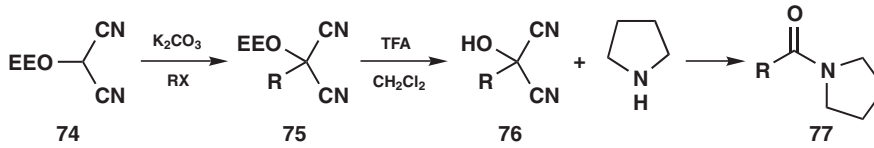


The amino nitrile **70** is simply and cheaply made (90% yield) and does react with alkyl halides.[14] Aldehydes are easily released from **71** with aqueous oxalic acid. After a second alkylation or Michael addition an even milder method of hydrolysis, aqueous Cu(II) salts at near neutrality, releases diketones such as **57**. Cyclisation in base gives *cis*-jasmone[13] **65**.

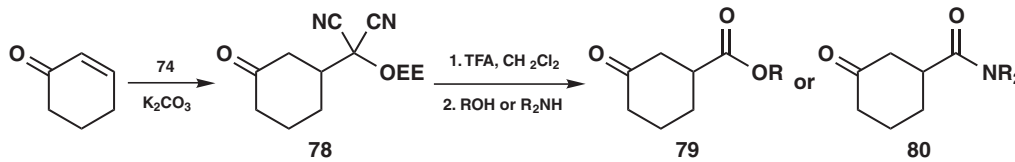


Acyl anion equivalents of the ester d^1 synthon $^-CO_2R$

At the ester oxidation level the best d^1 reagent is probably Yamamoto's $ROCH(CN)_2$. This reagent **74** (EE = EthoxyEthoxy) is easily prepared and reacts with alkyl halides using only the mild base K_2CO_3. Hydrolysis of the protecting group and displacement with a secondary amine gives the amides[15] **77**. Reaction with tosylimines gives amino acids.

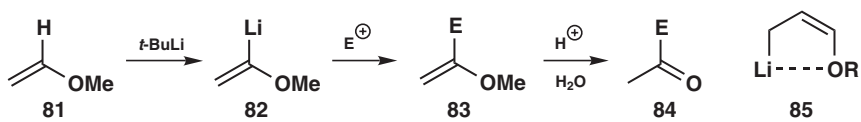


Since the anion is so stable, it reliably does conjugate additions and provides a simple route to γ-keto acid derivatives.[16] The initial adducts **78** can be worked up with either alcohols or amines to give γ-keto-esters **79** or γ-keto-amides **80**.



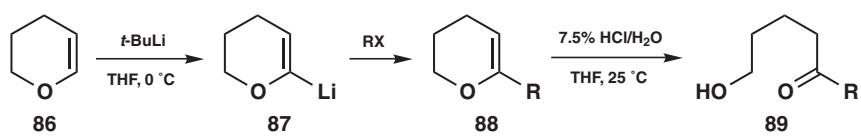
Methods Based on Vinyl (Enol) Ethers and Enamines

Just as anions of allyl derivatives can be homoenolate equivalents (chapter 13) so anions of vinyl derivatives can be acyl anion equivalents. Vinyl (or enol) ethers can be lithiated reasonably easily, especially when there is no possibility of forming an allyl derivative, as with the simplest compound **81**. The most acidic proton is the one marked and the vinyl-lithium derivative **82** reacts with electrophiles to give the enol ether of the product[17] **84**. However, *tertiary* butyl lithium is needed and compounds with γ-CHs usually end up as the chelated allyl-lithium **85**. These vinyl-lithium compounds add directly to conjugated systems but the cuprates will do conjugate addition.[18]

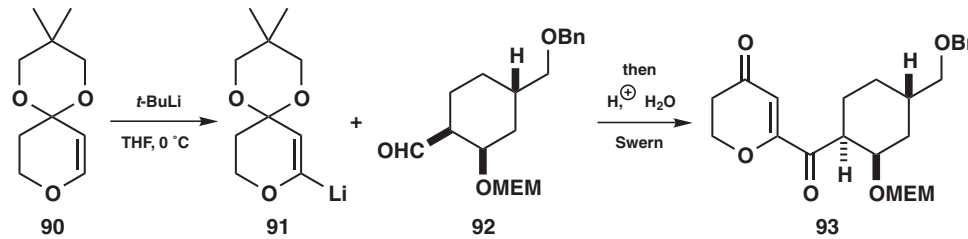


Lithium derivatives of cyclic vinyl ethers

Cyclic vinyl ethers such a dihydropyran **86** form stable lithium derivatives **87** probably because isomerisation to structures like **85** is impossible. Reaction with electrophiles such as alkyl halides gives adducts, e.g. **88**, and hydrolysis under very mild conditions reveals the carbonyl group[19] **89**.

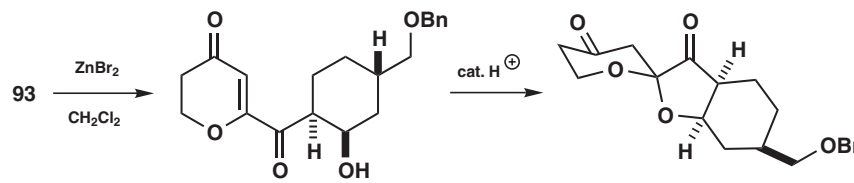


These reagents, usually with further functionalisation, have been widely used. Smith's synthesis of phyllanthoside involved the coupling of the lithium derivative of **90** with the aldehyde **92** and the exposure of one protected ketone to give **93** having two exposed ketones and one concealed as an enol ether.[20]



90 91 92 93

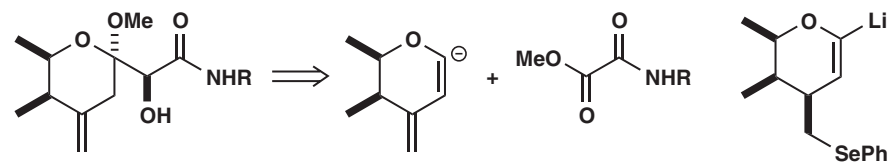
The hidden carbonyl group is more apparent after the removal of the MEM protecting group **94** and formation of the acetal **95** in acid solution. One diastereoisomer of the spirocyclic compound **95** is formed in 71% yield.



94 95; 71% yield

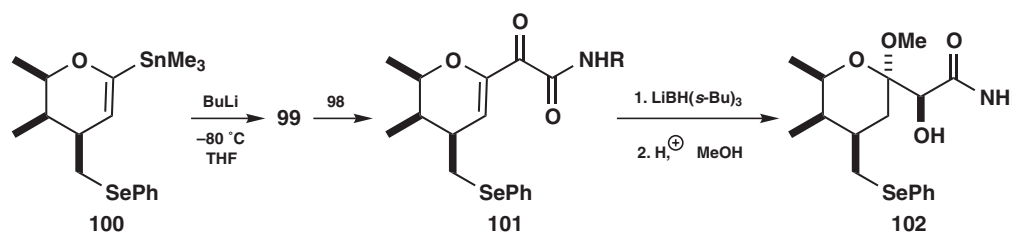
The synthesis of pederin and related anti-tumour agents

The group of antitumour agents related to pederin have a common structural feature **96** of a functionalised tetrahydropyran attached through an amide linkage to a variety of complex amines. In his successful syntheses of these compounds, Kocienski[21] chose to disconnect next to the ring and use a reagent **99** for the d^1 synthon **97** that would be acylated by the oxalyl derivative **98**.



96; pederin antitumour agents 97 98 99

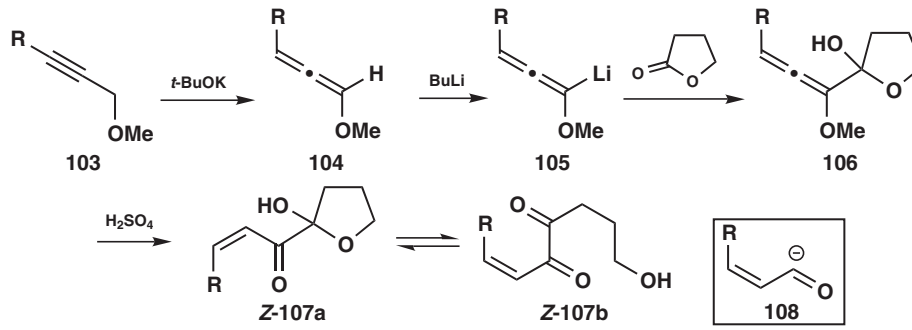
The lithium reagent **99** was prepared from the stannane **100** - one advantage being that n-BuLi is strong enough to do the job. Addition to the ester **98** gave the ketone **101** and reduction and acetal formation gave the complete structure **102** from which the alkene **96** could be revealed by oxidation and selenoxide elimination (chapter 33). This synthesis looks very easy but the complicated amines 'RNH_2' were very difficult to make.



100 101 102

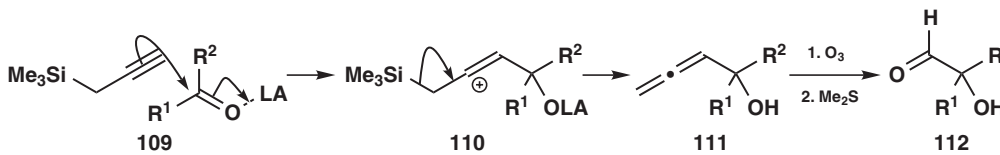
Lithium derivatives of allenyl ethers

Allenyl ethers similarly have no γ-protons so allyl anions cannot be formed. The allenyl ethers **104** are readily made from propargyl ethers **103** and are lithiated next to oxygen **105**. Reaction with lactones gives adducts **106** that decompose in acid to the hemiacetal **107a** of the 1,2-diketone **107b**. The conjugated alkene has the *Z*-configuration as the enol ether in **106** prefers protonation on the side away from the R group. The allenyl lithium **105** is a reagent for the synthon[22] **108**.

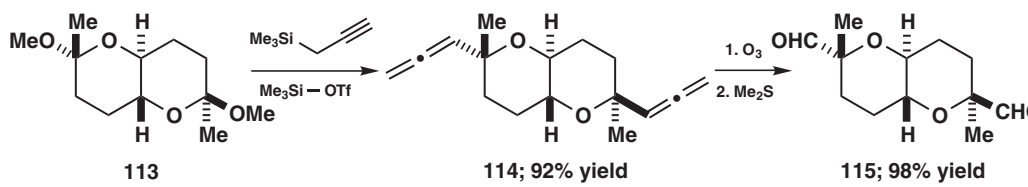


Oxidative Cleavage of Allenes

Another way that allenes can be used to provide an acyl anion equivalent is by the Lewis acid catalysed addition of propargyl silanes to electrophiles **109** followed by oxidative cleavage of the allene. The intermediate vinyl cation **110** is stabilised by the silicon β-effect (chapter 12) and loss of the Me_3Si group gives the allene **111**. Oxidative cleavage of the sensitive allene reveals that it has acted as a reagent for the formyl anion.



In their synthesis of hemibrevetoxin, Nelson[23] converted the centro-symmetric acetal **113** into the dialdehyde **115** by this method. Yields of the bis-allene **114** and of the final product were excellent. Note that the acetal **113** acts as a suitable electrophile as the Lewis acid (Me_3SiOTf) removes the OMe group to give an oxonium ion intermediate.

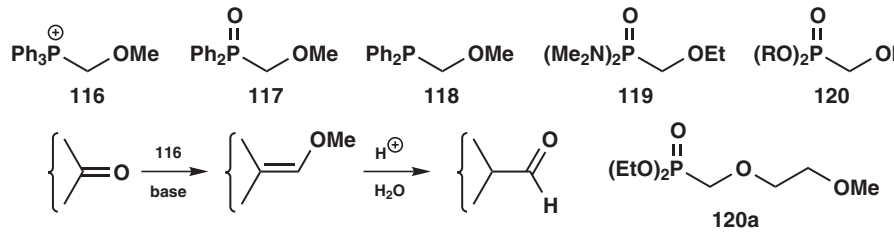


Vinyl Ethers and Enamines from Wittig-Style Reactions

Vinyl ethers

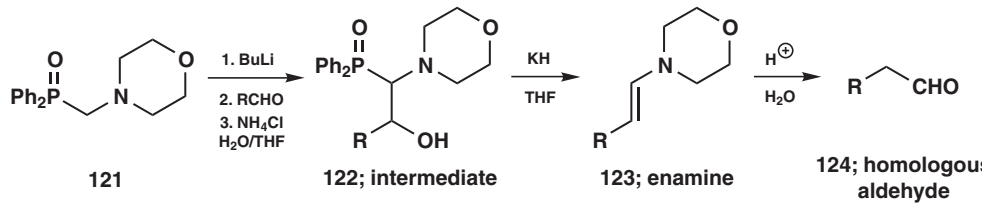
More general methods depend on Wittig reactions with functionalised ylids. The ylid[24] from **116** and the lithium derivatives of **117-120** all react with aldehydes and ketones to give enol ethers that can be hydrolysed to chain-extended aldehydes. Yields with the ylid from **116** are not always wonderful and the phosphonate ester **120a** with a chelating substituent generally does better.[25]

In very crowded cases the lithium derivative of the phosphine **118**, though it must be made with *s*-BuLi, is the most reactive.[26]

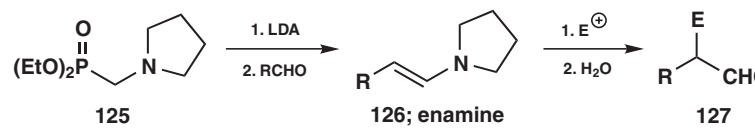


Enamines

Lithium derivatives of amino substituted phosphine oxides, such as the morpholine **121**, give adducts **122** on reaction with aldehydes that eliminate with a potassium base to give enamines **123** in excellent yields: 90–99% for R = Ar and 63–83% for R = alkyl. These are easily hydrolysed to the homologous aldehydes[27] **124**.

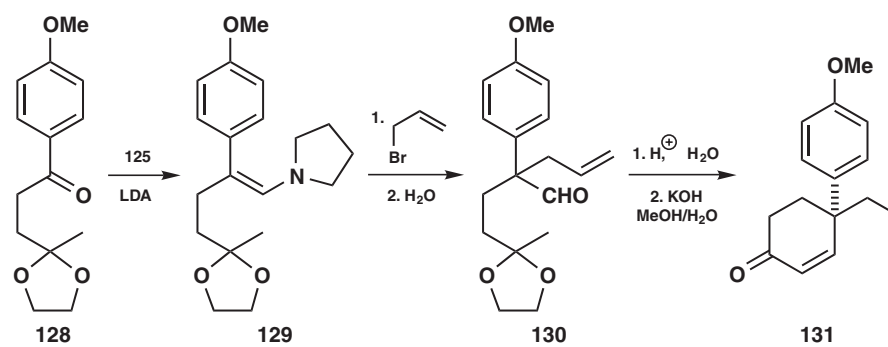


The pyrrolidine phosphonate **125** does much the same thing in one step but the real virtue of these methods is that the enamines **123** and **126** are reactive enough to combine with various electrophiles, particularly allylic halides, α-halo-carbonyl compounds and Michael acceptors (see chapter 10) to give substituted homologous aldehydes or ketones[28] **127**.



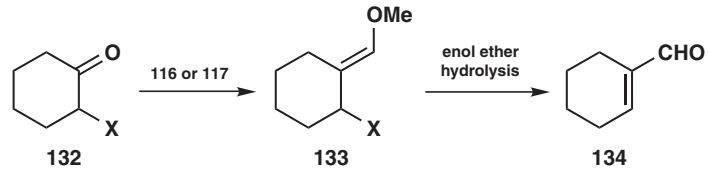
A synthesis of O-methyljoubertiamine

This method has been applied to a synthesis of the alkaloid *O*-methyljoubertiamine. Reaction of the lithium derivative of **125** with the part-protected diketone **128** gave an enamine **129** that was immediately allylated to create the quaternary centre in **130**. Deprotection and cyclisation completed the cyclohexenone[28] **131**. A discussion of the strategy and further details of this synthesis are in the workbook.

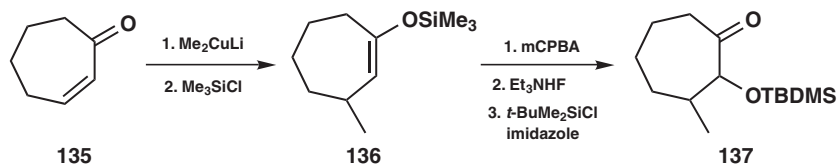


Synthesis of enals by functionalised Wittig reagents

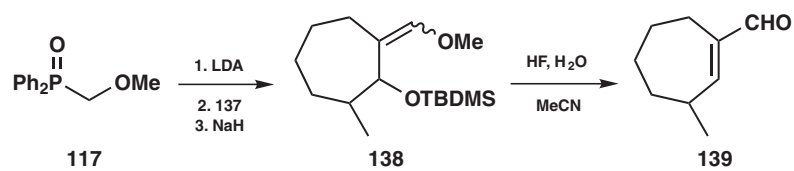
If there is a leaving group in the β-position of the carbonyl starting material **132** during homologation by the methoxymethyl reagents **116** or **117**, it is lost during the hydrolysis of the enol ether product **133** to form an enal **134**.



The leaving group X may be only an OH group, inserted by hydroxylation of a silyl enol ether **136** (chapter 33) formed by conjugate addition of a silyl cuprate (chapters 9 and 10) to an enone **135** and protected by the robust silyl group TBDMS (*t*-$BuMe_2Si$-) **137** for reaction with the lithium derivative of **117**.

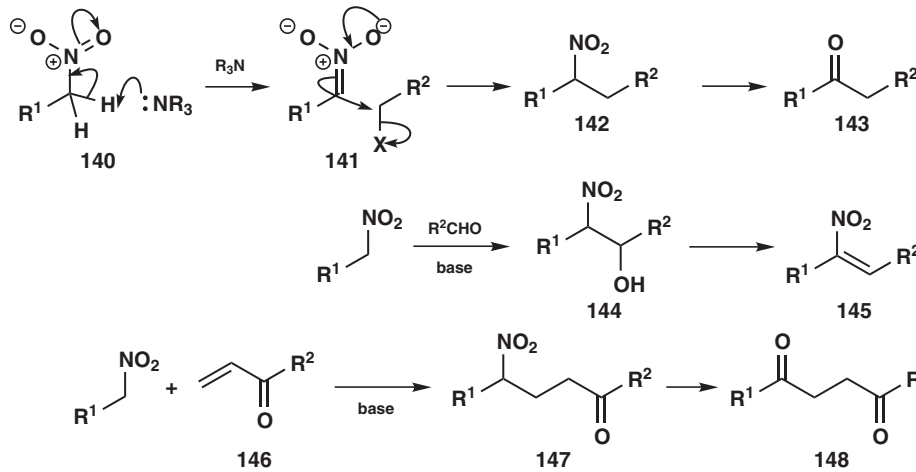


The lithium derivative of **117** gives an adduct from which the phosphinate can be removed with NaH. Hydrolysis of the enol ether **138** with HF in aqueous acetonitrile gave the enal, e.g. **139** in around 50% overall yield.[29] The overall strategy is conjugate addition of a nucleophilic alkyl group followed by direct addition of a nucleophilic CHO group. An alternative uses a sulfur leaving group (X = SPh in **132**) and the ylid from **116** to achieve the same result. The final hydrolysis requires Hg(II) to remove the sulfur.[30]

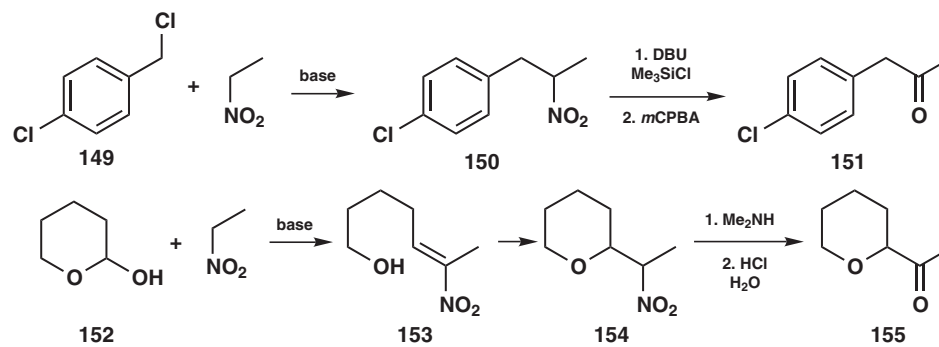


Nitroalkanes

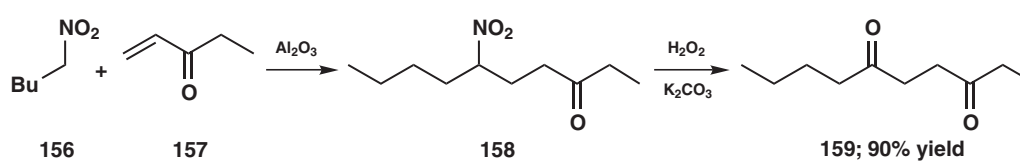
The problem with many acetal-style d^1 reagents is often that there is barely enough stabilisation for the "anion". This problem is easily solved with the nitro group as it has enough anion-stabilising ability by itself, about the same as two carbonyl groups in fact. Using only weak bases such as tertiary amines (Hünig's base *i*-Pr_2NEt is popular) nitroalkanes react **141** with many electrophiles such as alkyl halides, aldehydes or ketones, and unsaturated carbonyl compounds to give products such as **142**, **144**, **145** or **147**. For a long time the problem with the nitro group was rather the eventual conversion to a carbonyl group, e.g. **142** to **143**, but there are now many reagents for this reaction at the aldehyde, ketone, or acid oxidation levels.[31] The examples which follow illustrate some of these.



Alkylation solves the awkward problem of how to make aryl ketones of the pattern **151**, awkward because the Friedel-Crafts reaction doesn't work with this substitution pattern. Alkylation of a nitroalkane with the benzylic halide **149** does work well and the product **150** can be oxidised to the ketone[32] **151**. Reactions with aldehydes work even with masked aldehydes[33] like dihydropyran to give **154** and hence the ketone **155** with a 1,2-substitution pattern after hydrolysis.[34] More vigorous conditions give nitroalkenes **145** from aldehydes and these will be very useful later as a[2] reagents.

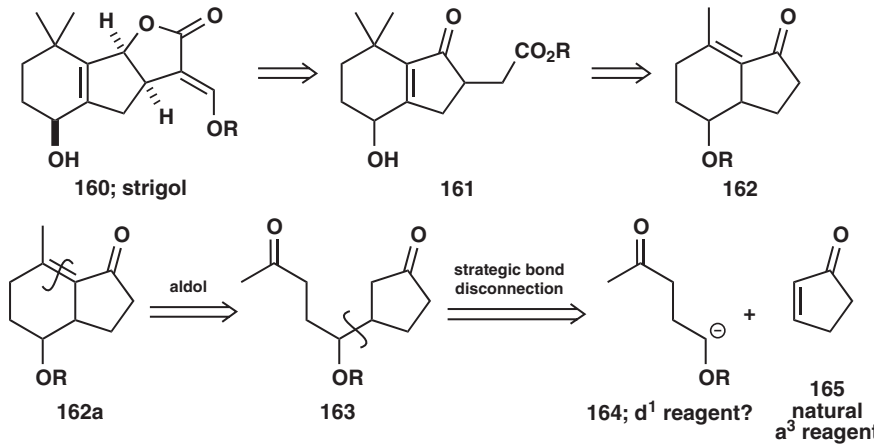


Michael additions go particularly well with nitroalkanes with catalytic base because the first formed enolate is more basic than the nitroalkane. Diketones, e.g. **159**, keto-aldehydes and keto-acids can all be made by this route and the two steps can be combined in one using alumina to catalyse the Michael addition (**158** is not isolated) and an oxidative work-up to release the ketone.[34]

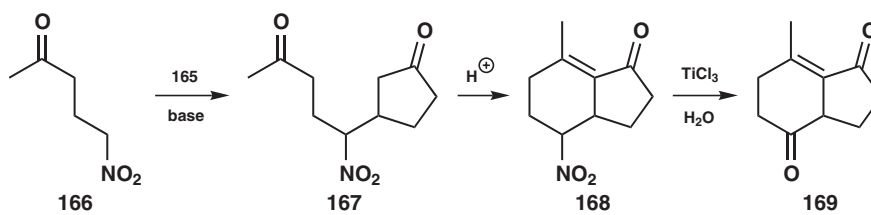


A synthesis of strigol using nitroalkanes

When Raphael wanted the key intermediate **162** for his synthesis of strigol **160**, the aldol disconnection **162a** revealed the need for the diketone **163** and hence by disconnection of a very strategic bond, the d^1 synthon **164**.

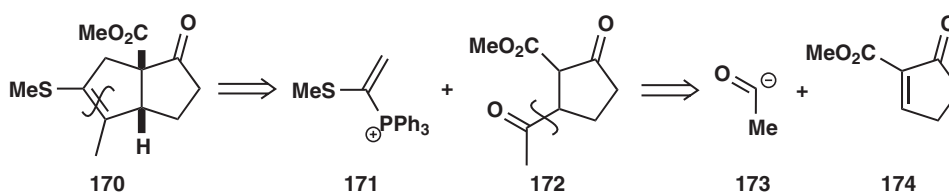


The nitroketone **166**, though at the wrong oxidation level, is an ideal reagent for this purpose as it is not necessary to protect its ketone during the Michael addition. Conversion of the nitrocompound **168** into the ketone **169** with $TiCl_3$ illustrates the generally preferred method for this reaction.[35]

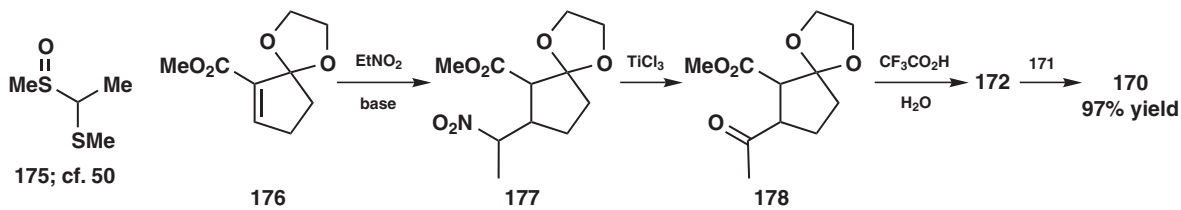


Synthesis of mono-protected diketones

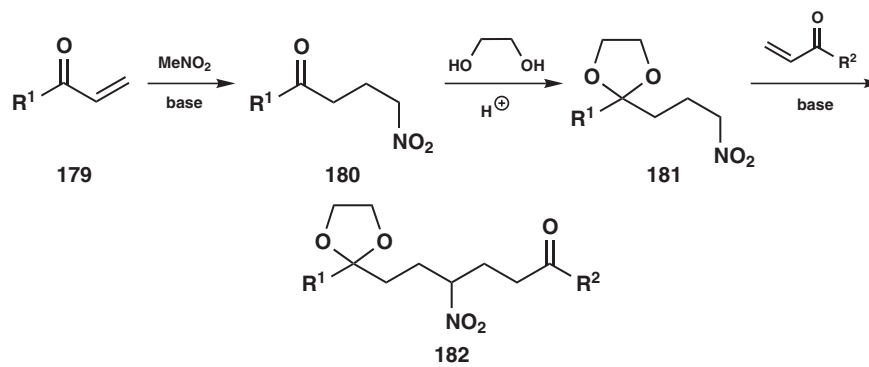
The nitro group can solve the problem of making a diketone with one of the ketones protected. When Hewson wished to make a series of natural products from the key intermediate **170** using his reagent **171** he needed the diketoester **172**. Disconnection of a strategic bond reveals the possibility of adding a d^1 reagent to the unsaturated ketoester[36] **174**.



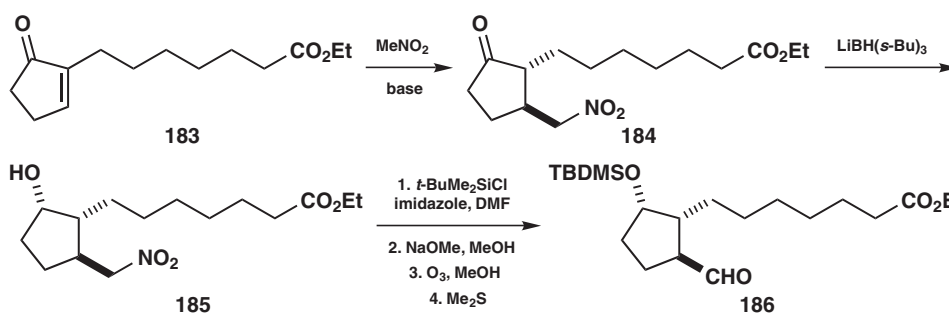
Attempts with various reagents showed that the ketoester was inclined to polymerise unless it was used as its acetal **176** and that acetal style reagents for the d^1 synthon **173** such as **175** gave poor results. The solution was to use nitroethane to give **177** having each keto group masked in a different form. Conversion of nitro group to ketone was better with $TiCl_3$ than other reagents. The diketoester was formed as a single (*trans*) isomer which gave an excellent yield of **170** with the reagent **171**.



Alternative and more general approaches to partly protected diketones include the Michael addition, protection, Michael addition sequence **179** to **182** and the Michael addition reduction sequence **183** to **186**. The first provides a molecule **182** containing three ketones: one free, one protected as an acetal, and one masked as a nitro group. The acetal can be removed in dilute acid without hydrolysing the nitro group and the nitro group can be converted to a ketone without disturbing the acetal,[31,34] e.g. with H_2O_2 and K_2CO_3.

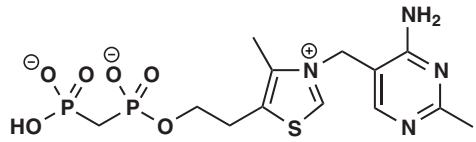


The second has been used to make prostaglandins from the intermediate aldehyde **186**. Note the stereochemistry: the obvious *trans* arrangement of the two substituents in **184** after the Michael addition and the approach of the bulky reducing agent L-selectride® Li(*s*-Bu_3BH) from the opposite face to the nearer and larger of the two substituents. Finally, a reductive workup (Me_2S) is needed after the oxidation of nitro to ketone with ozone.[37]

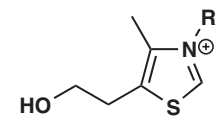


Catalytic Methods: The Stetter Reaction

The useful Stetter reaction[38] is biomimetic - the idea and the reagent came from the coenzyme thiamine pyrophosphate **187**. Removing unnecessary substituents left the core of the thiazolium species **188** where R is usually benzyl (catalyst a) but can be various other primary alkyl groups.



187; thiamine pyrophosphate

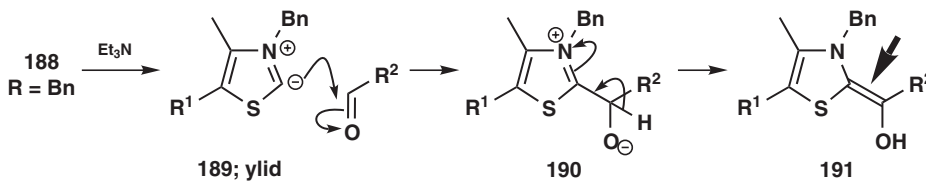


188; Stetter thiazolium salts

catalyst a:
R = CH_2Ph
(benzyl)

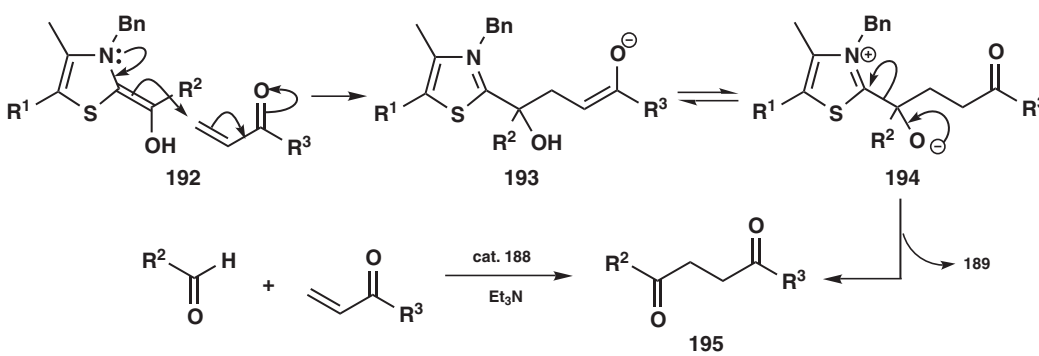
others (b-d)
R = Me, Et
$(CH_2)_2OEt$

Reaction with an aldehyde starts by the removal of a proton with quite a weak base (usually a tertiary amine) to give the ylid **189** in which the negative charge is stabilised partly by electrostatic interaction (the ylid) and partly by the sulfur atom. Nucleophilic attack on the aldehyde gives **190** which can transfer a proton from C to O to give uncharged **191**.



189; ylid **190** **191**

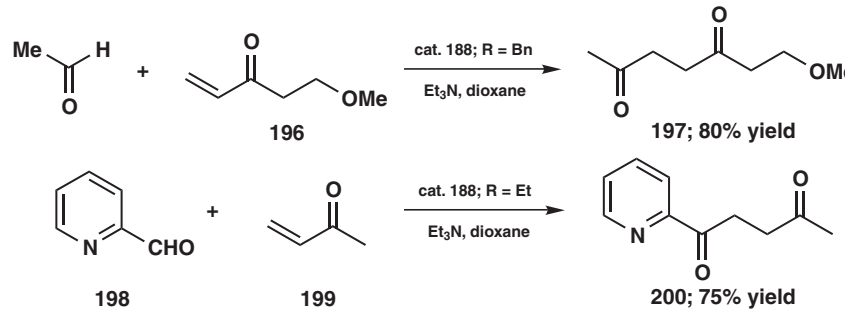
This is a strange compound. The exocyclic (arrowed) alkene is an enol at one end but an enamine and a vinyl sulfide at the other. All three atoms, O, N, and S, have lone pairs making this a very electron rich alkene. The nitrogen atom dominates so that conjugate addition **192** to enones works well. The product **194** loses the catalyst **189** to give a 1,4-diketone **195**. The reaction is simplicity itself: the aldehyde, enone, catalyst and weak base (usually amine or sodium acetate) are heated in ethanol.



192 **193** **194**

195

Examples include enolisable aldehydes adding to enolisable enones to give e.g. **197**, and an impressive range of aromatic and heterocyclic compounds as either component. The pyridine **200** is formed in only 12% yield if sodium cyanide is used as catalyst.[38]



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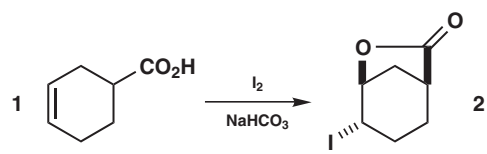
Section C:
Carbon–Carbon Double Bonds

15 Synthesis of Double Bonds of Defined Stereochemistry

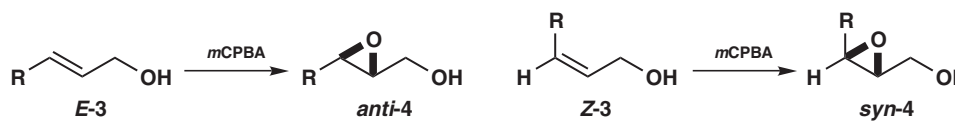
Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

Introduction: *Alkenes: framework or functional groups?*

The carbon-carbon double bond (olefin or alkene) is a structural feature on the border of framework and functionality. Unlike the carboxylic acid in **1** it is *inside* the skeleton of the molecule and involves no atoms except carbon and hydrogen. It has no polarity and yet it has the potential of producing highly polar functionality at two carbon atoms in a single reaction, as in the iodolactonisation to give **2** from **1**.

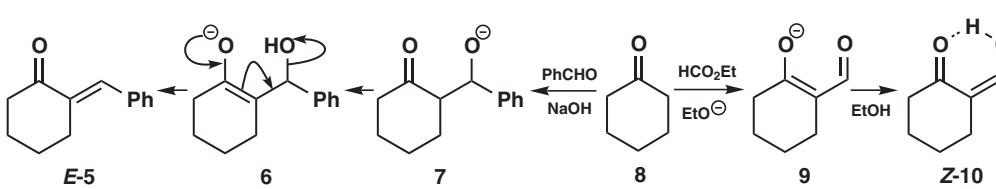


In the same reaction stereochemistry may be generated: two stereogenic centres are in fact produced in this reaction and in the epoxidation of **3**. The sense of the stereochemistry produced in these reactions depends critically on two factors: the inherent stereoselectivity of the reactions (*anti* in the iodolactonisation and *syn* in the epoxidation) and the geometry of the alkene. Inside a six-membered ring of **1** the alkene must of course by *cis* or *Z*. In the open chain allylic alcohol **3** it can be *E* or *Z* depending on the method of synthesis. This chapter explores ways to control the stereochemistry of alkenes as an essential preliminary to the control of three-dimensional stereochemistry in chapter 25 where you will meet a method to make single enantiomers of **4** from the alkenes in *E*- and *Z*-**3**.



Control of Alkene Geometry by Equilibrium Methods

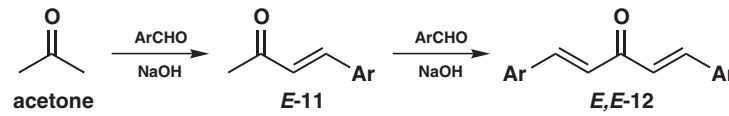
In many reactions there is an equilibrium between reactants and products so that only the more stable of the two alkenes is produced. In the Claisen ester condensation of cyclohexanone **8** with ethyl formate, the true product under the conditions of the reaction is the stable enolate **9** and this is reversibly protonated on workup to give the more stable H-bonded enol of the ketoaldehyde *Z*-**10**. In the aldol reaction between the same ketone and benzaldehyde, the initial product **7** gives the enolate **6** and dehydration is reversible: only the more sterically favourable *E* isomer of **5** is formed. Note that it is irrelevant that the aldol **7** is a mixture of diastereoisomers: all stereochemistry is lost in the formation of the enolate **6**. In later parts of this chapter a more specific relationship between 3D and 2D stereochemistry will be established.



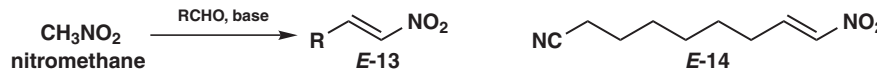
Some examples from other chapters

There are very many reactions which routinely give *E*-alkenes as the more stable product. You will already be aware of many of them and there are many scattered around the other chapters in this book. We shall simply give a few more examples here and a list of cross references to other examples.

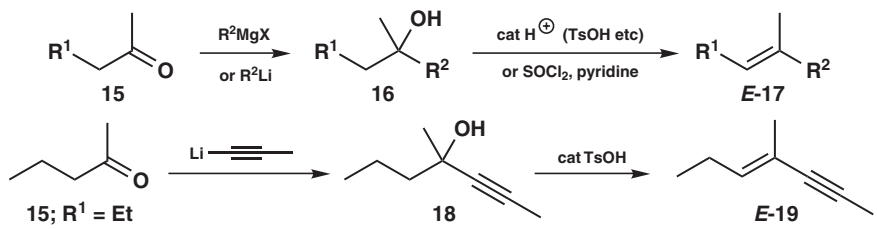
1. Aldol reactions followed by dehydration, e.g. enones *E*-**11** and *E,E*-**12**. We shall meet *E, E*-**12**; Ar = Ph later as a useful ligand for palladium.[1]



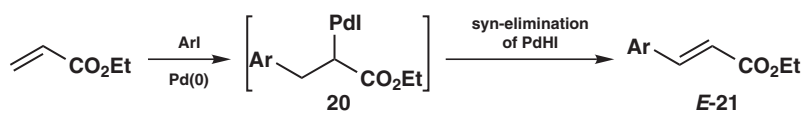
2. The base-catalysed condensation of nitromethane with aldehydes to give nitroalkenes *E*-**13** (the Henry reaction). One example *E*-**14** was used in a Corey prostaglandin synthesis.[2]



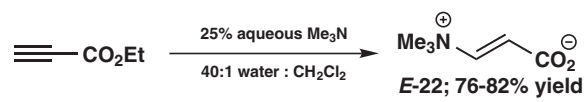
3. Dehydration of tertiary alcohols **16** formed by the addition of organo-metallic species to ketones **15**. An example is from Corey's erythronolide synthesis where dehydration of **18** gives only the *E*-enyne[3] **19**.



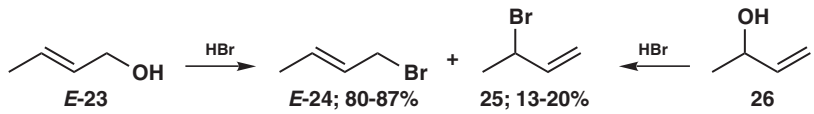
4. The Heck reaction with α,β-unsaturated carbonyl compounds. The intermediate Pd(II) σ-complex **20** eliminates PdHI in a *cis* fashion and prefers to give the *E*-alkene **21**.



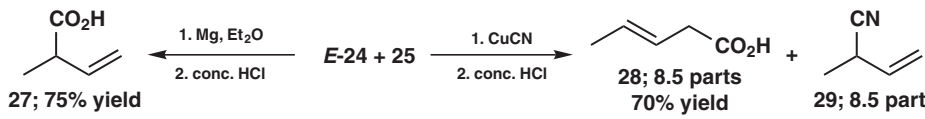
5. Nucleophilic addition to α,β-unsaturated alkynes under equilibrating conditions. This example comes from a recipe in *Organic Syntheses* where a good yield of crystalline *E*-**22** is reported.[4]



6. Equilibration of allylic alcohols, halides etc *via* an allyl cation. Whichever alcohol **23** or **26** is used as starting material, treatment with HBr gives the same equilibrium mixture of all *E*-**24** and **25**. No doubt any *Z*-**24** has also equilibrated to *E*-**24**.



7. Formation and equilibration of allylic metal derivatives such as those from the allylic bromides **24** and **25** we have just made. Reaction of the Grignard reagent with CO_2 gives only **27** but displacement of bromide with cyanide leads to the isomeric acid *E*-**28** both in good yield.[5]



A More Detailed Look at The Principles

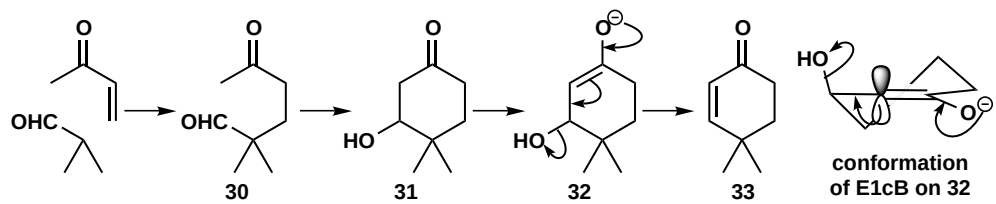
This simple picture hides a number of principles which we shall need to explore in this chapter. In outline we can distinguish these cases:

1. Only one alkene is possible. This is usually a cyclic *cis* alkene.
2. The two alkenes are in equilibrium and the *trans* alkene is formed.
3. The *cis* alkene is formed stereoselectively.
4. The *trans* alkene is formed stereoselectively.
5. The reaction is stereo*specific*. The geometry of the alkene depends on the mechanism of the reaction and the stereochemistry of the starting material.

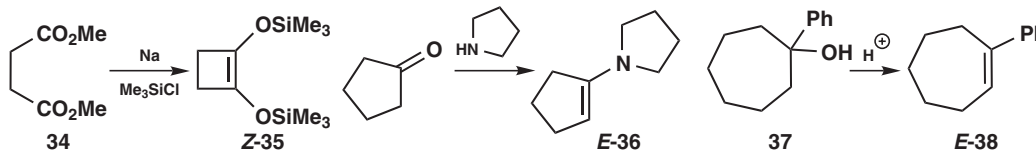
Case 1: Only one alkene is possible. This is usually a cyclic cis alkene

We shall deal with all the cases and explain the principles behind them. We need spend no time on case 1. Alkenes in 3- to 7-membered rings must be *cis* as the *trans* alkenes cannot be formed. Medium rings from 8-membered upwards can form *trans* alkenes but they are less stable. Only from (about) 12-membered rings upwards is the *trans* alkene the more stable isomer.

This simple Robinson annelation (chapter 5) produces a *cis* cyclohexene **33** because that alone is possible. The step in which the double bond appears is the E1cB elimination **32** at the end. The enolate will always have one lobe of the p-orbital shown in the conformational diagram correctly aligned to expel the hydroxide leaving group and form the *cis* alkene.



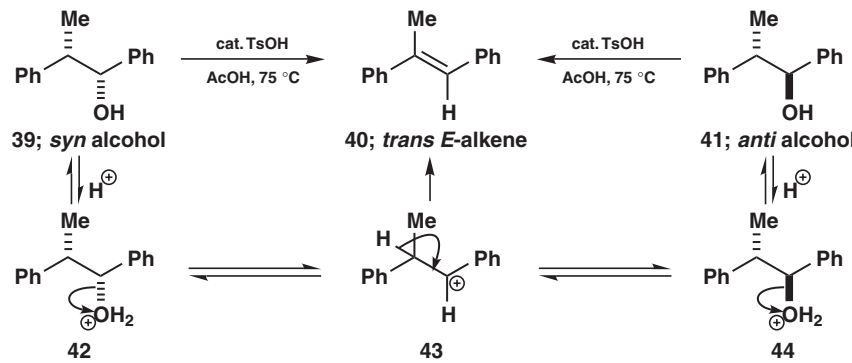
Each of the following reactions gives exclusively the *cis* (actually *E* or *Z* as shown) alkenes **35**, **36**, and **38** for the same simple reason: *trans* alkenes cannot exist in four-, five- or seven-membered rings. The reactions are from other chapters of the book.



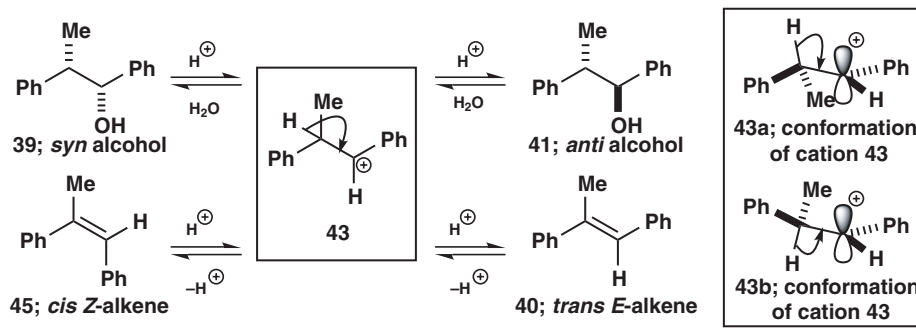
The first reaction is the silicon-directed acyloin the second is simple enamine formation from chapter 2 and the third reaction is a simple E1 elimination. The same reaction will start off our next section concerning alkenes in equilibrium.

Case 2: The two alkenes are in equilibrium and the trans alkene is formed

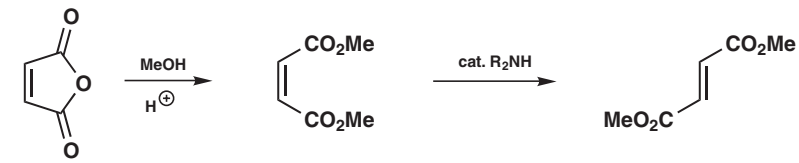
We can go back in time to some very famous work by Cram which led him to deduce his famous rule.[6] Reaction of either diastereoisomer of the (racemic) tertiary alcohol **39** with acid gives the same mixture of alkenes in which the *trans* alkene *E*-**40** predominates (>50:1) to a very great extent. The elimination is E1 *via* the tertiary carbocation **43**.



Each alkene can be made stereospecifically (the synthesis of the *Z*-isomer **45** is given later in this chapter) and treatment of the *cis* alkene **45** under the same acidic conditions also gives the *trans* alkene **40**. The alkenes are in equilibrium *via* the stable tertiary carbocation **43**. The cation has two conformations **43a** and **43b** that can eliminate to give the *E*-alkene **40** and free rotation about the central σ-bond in this relatively long-lived intermediate **43** ensures that one of these conformations is accessible from all possible starting materials.

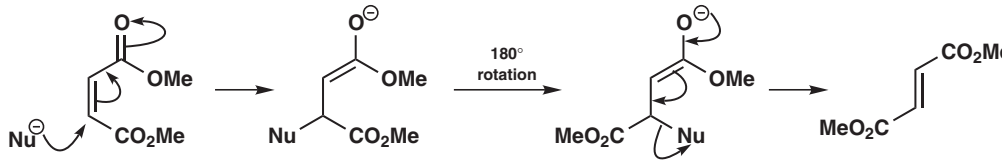


Such perfect cases of equilibration are rare. Another important one concerns equilibration by Michael addition to conjugated alkenes. A classic case is the preparation of maleate **47** and fumarate **48** esters from (the necessarily *Z*-) maleic anhydride **46**. Simple treatment with methanol in acidic solution gives the liquid maleate **47** as expected. It is unusual for *cis* and *trans* alkenes to be given different names: maleic and fumaric acids were named before their relationship was understood.



46; maleic anhydride | **47; dimethyl maleate b.p. 204-205 ˚C** | **48; dimethyl fumarate m.p. 103-104 ˚C**

Slowly in solution crystals are formed and these are the more stable fumarate ester. The process is enormously accelerated by adding a trace of an amine and must occur by reversible Michael addition of the amine or even of traces of methanol or any other stray nucleophile.[7]



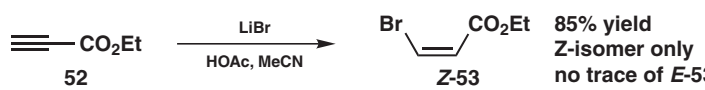
49 **50** **51** **48**

Once again a long-lived intermediate - the enolate ion **50** - allows free rotation about the central σ-bond and the elimination of the catalyst from a more favourable conformation **51** leading to the *E*-alkene **48**. The same process occurs during the dehydration step following aldol reactions which occurs by an E1cB mechanism with the same sort of intermediate (e.g. formation of *E*-**5**, *E*-**11** and *E,E*-**12**). This process is so easy that it is actually very difficult to make *cis* alkenes conjugated to the more reactive electrophilic groups such as aldehydes.

Case 3: The cis alkene is formed stereoselectively

You might think that this case would be very rare. Why should any reaction *choose* to form the less stable *cis* alkene? There are only a few simple cases, it is true, but there is one extremely important more complex case too. So important is this case that it is the first choice alkene synthesis in most people's mind. We shall look first at the simple *Z*-selective reactions.

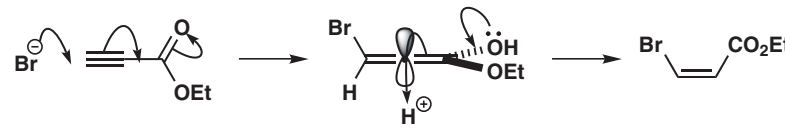
We can start with a Michael addition. This sounds crazy as we have just explained that Michael addition leads to rapid equilibration. However, Michael addition to triple bonds may not. One remarkably simple case is the addition of LiBr in weakly acidic solution to a triple bond conjugated to an ester **52**.



52 | ***Z*-53** | **85% yield Z-isomer only no trace of *E*-53**

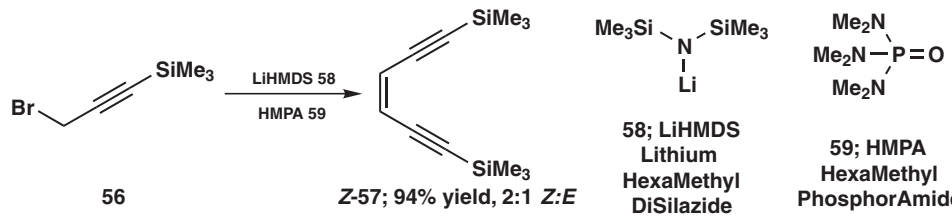
Only the *Z*-alkene **53** is formed. The difference here is in the structure of the enol intermediate **55**. There is no free rotation. Instead the two cumulated (allene style) double bonds are held rigidly

at right angles to each other. Protonation occurs on the lobe of the p-orbital away from the bromine atom **55** and the *Z*-alkene **53** results. This is clearly kinetic control.[8]



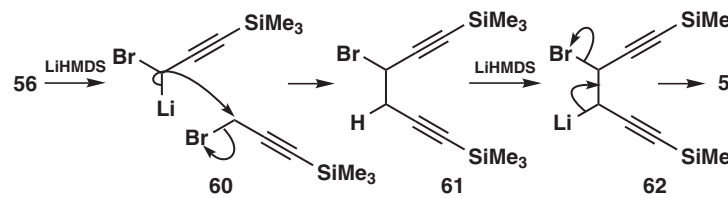
54 **55** ***Z*-53**

A more remarkable case is the formation of predominantly *Z*-enediyne **57** during the base catalysed dimerisation of the propargyl bromide **56**. This is important as well as remarkable as the enediyne antibiotics contain this structural feature which has to be *Z* for biological activity.[9]



56 ***Z*-57; 94% yield, 2:1 *Z:E*** **58; LiHMDS Lithium HexaMethyl DiSilazide** **59; HMPA HexaMethyl PhosphorAmide**

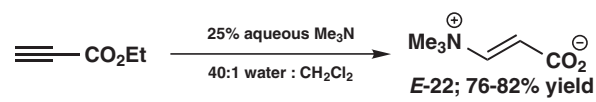
You might say that the selectivity is "only" 2:1 but in truth it is remarkable that the reaction is *Z*-selective at all. In practice 60% *Z*-**57** can be isolated by chromatography. The obvious mechanism is the formation of a lithium derivative, S_N2 coupling **60**, and base-catalysed E2 elimination **62**.



60 **61** **62**

For this mechanism to deliver *Z*-**57** the conformation (or even configuration?) of the intermediate must favour **62** which looks rather unlikely. However, the reaction *does* give predominantly *Z*-**57**. Maybe the two long thin alkynes actually attract rather than repel one another **62a**. The original authors offer a different (carbenoid) explanation but without much conviction.

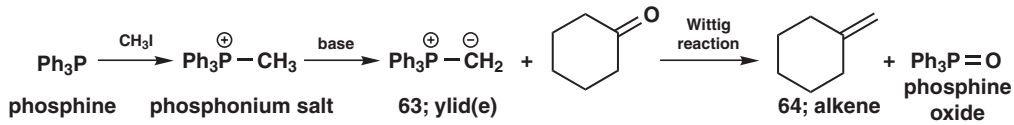
These examples both concern triple bonds. But please do not think that all reactions of alkynes are *Z*-selective. A salutary lesson is hidden in another volume of *Organic Syntheses* in a nucleophilic addition to the same alkyne as in our first example. Evidently under these polar hydrophilic conditions equilibration occurs by reversible protonation.[10]



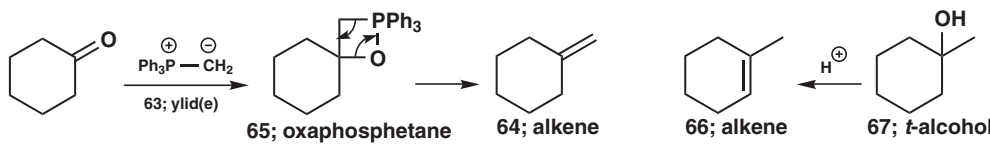
***E*-22; 76-82% yield**

The Wittig Reaction

Now to the great *Z*-selective alkene synthesis. The Wittig reaction. Along with the Diels-Alder and the aldol reactions this is one of the most important reactions of all time. You probably have an idea of the basic reaction:

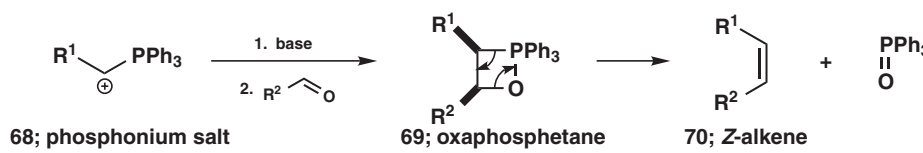


We have chosen this example to illustrate the first virtue of the Wittig reaction: you know where the alkene will be in the product **64**. Even if, as here, it is less stable than some other possibility (the endocyclic alkene **66** that would be formed by dehydration of the tertiary alcohol **67**), the new alkene must be between the carbon atoms formerly occupied by the phosphonium ylid and the carbonyl group. This is because the last step is the regiospecific decomposition of a four-membered ring (an oxaphosphetane) **65**.



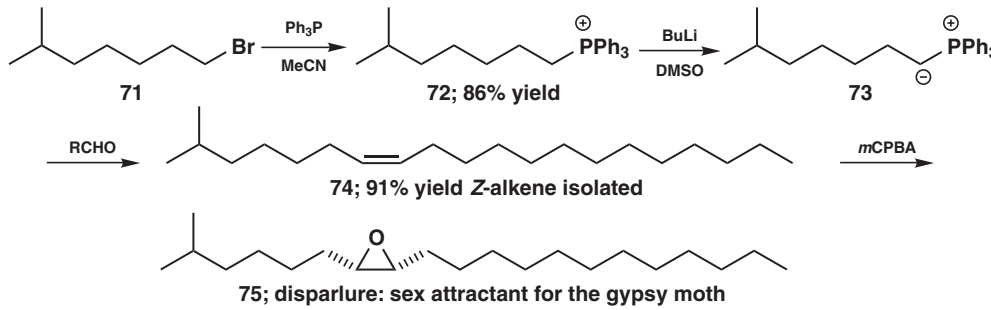
The last step of the Wittig reaction is stereospecific

This regiospecificity has stereochemical consequences too. The geometry of the alkene product **70** is not decided in the elimination of $Ph_3P{=}O$ from the oxaphosphetane **69**. If this step is a concerted *cis* elimination then the **stereochemistry of the oxaphosphetane is faithfully reproduced in the alkene product**. Here is an example:

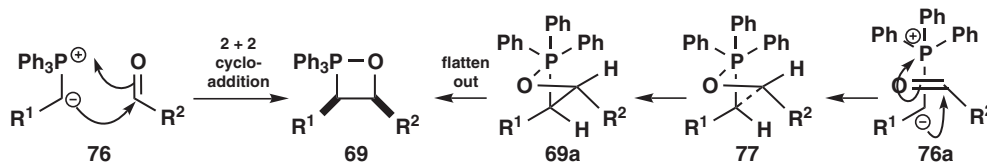


The Z-selective Wittig reaction with simple ylids

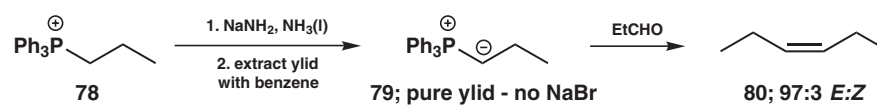
If the *syn* oxaphosphetane **69** is favoured, the *Z*-alkene **70** must be formed. And it is! The formation of the oxaphosphetane is *syn* selective and the elimination step is stereospecific. The selectivity varies, but with R=Alkyl it is usually quite good. Here is an example - the synthesis of the sex attractant **75** of the Gypsy moth. This is the epoxide of a long chain *cis* alkene ***Z*-74** easily made by a Wittig reaction with excellent *Z*-selectivity.[11]



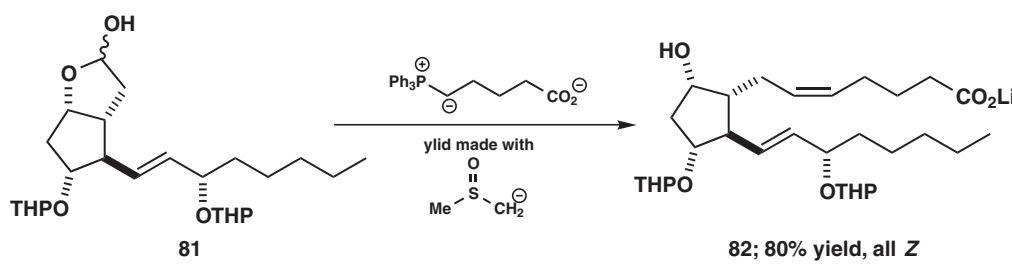
This reaction is obviously of the greatest significance. Yet the detailed mechanism of the formation of the oxaphosphetane is not agreed. No previous intermediates have been isolated and one of the two main contenders is a one-step mechanism **76**. This mechanism has the advantage of a believable explanation for the stereoselectivity. A 2+2 cycloaddition must have an antarafacial component - it must be a $_{\pi}2_{s} + _{\pi}2_{a}$ reaction **76a**.



As the two components approach each other at 90° **76a**, the two substituents keep out of each other's way **77** and so, when you flatten out the four-membered ring **69a**, they end up on the same side **69**. Part of the evidence for this mechanism is that salt-free ylids give the highest *Z*-selectivity.[12] Normal preparations of ylids by treatment of, say, a phosphonium bromide with BuLi, have a molecule of salt (here LiBr) inevitably present. But not this way:

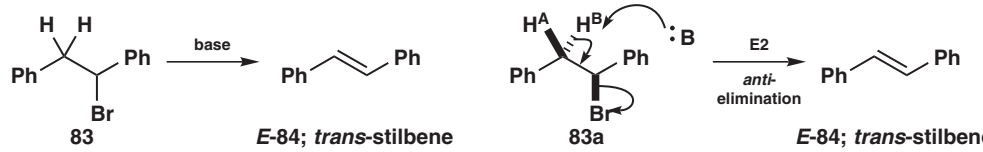


This procedure was used in the synthesis of the upper chain of a prostaglandin **82** (see chapter 6) where the stereochemistry is related to the biological activity.[13] Note that the aldehyde is tied up as a hemiacetal in the starting material **81** (see chemoselectivity chapter) and that the "salt-free" ylid is actually a carboxylate anion made with sodium derivative of DMSO in DMSO. As you will see in the next section, not all Wittig reactions are *cis* selective - those of stabilised ylids are *trans* selective.



Case 4: The trans alkene is formed stereoselectively

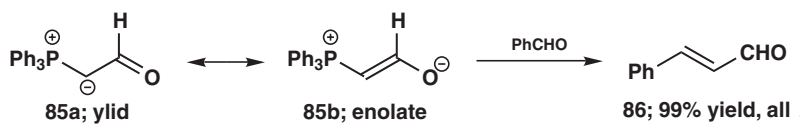
Many E2 reactions fit into this category. A simple base-catalysed elimination of an alkyl bromide will normally give the *E*-alkene because there are two diastereotopic hydrogen atoms which could be lost and the one which gives the *E*-alkene is lost more quickly because that transition state has the lower energy. This is a kinetic effect on a reaction in which the transition state resembles the product.



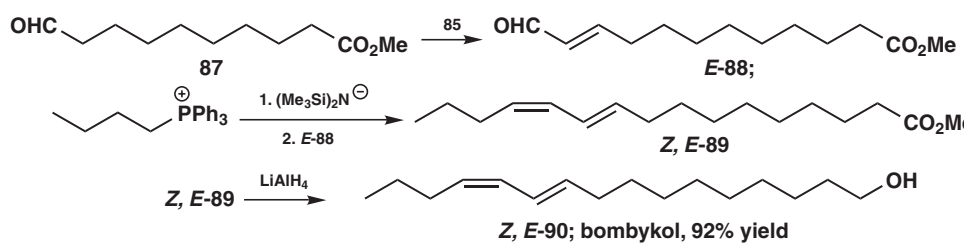
The same arguments apply to most E1cB reactions (see **32**) where there are two conformations of the enolate during elimination - one leading to the *Z*- and the other to the *E*-alkene. The second is preferred in acyclic compounds as it gives the more stable transition state.

The *trans*-Selective Wittig Reaction

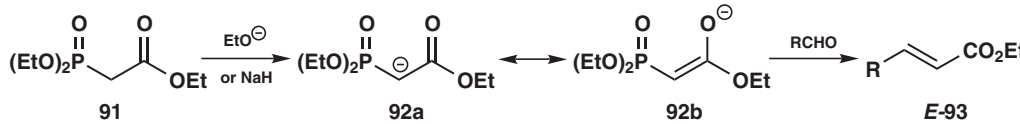
Simple phosphonium ylids give *Z*-selective olefination. Ylids in which the carbanion is stabilised not only by the P^+ atom but also by a conjugating group, particularly a carbonyl group, give *E*-selective reactions. The extra stabilisation is delocalisation of the enolate kind **85b**. This simple example **85** with an aldehyde group is a stable ylid which can be prepared in and even recrystallised from water and is available from Aldrich. It reacts with aldehydes and ketones to give *E*-enals[14] **86**.



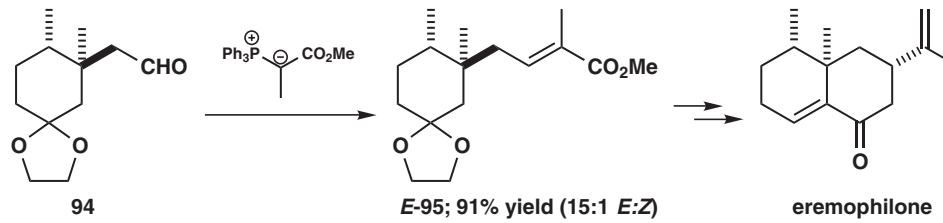
A sequence using this reagent **85** followed by a Wittig reaction with an unstabilised ylid is a good route to *E,Z*-dienes that are often found as insect pheromones. This sequence was used in the synthesis of bombykol **90**, the pheromone of the silk worm moth[15] *Bombyx mori*. The first Wittig gives less than 5% *Z*-**88** and the second, using a salt-free ylid, less than 3.5% *E,E*-**89**.



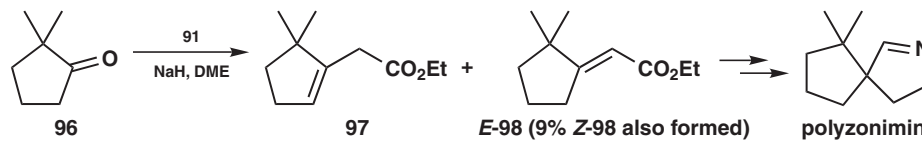
The extra stabilisation makes the ylid rather unreactive and phosphonate esters **91** are often used instead of phosphonium salts in these reactions. Treatment with a base (NaH or RO^- is often used, BuLi will certainly not do) gives an inherently more reactive enolate anion **92** rather than an ylid. These Horner-Wadsworth-Emmons reagents (HWE as we shall call them, though they go under many other names) react with ketones as well as aldehydes and the product is normally the *E*-alkene[16] **93**.



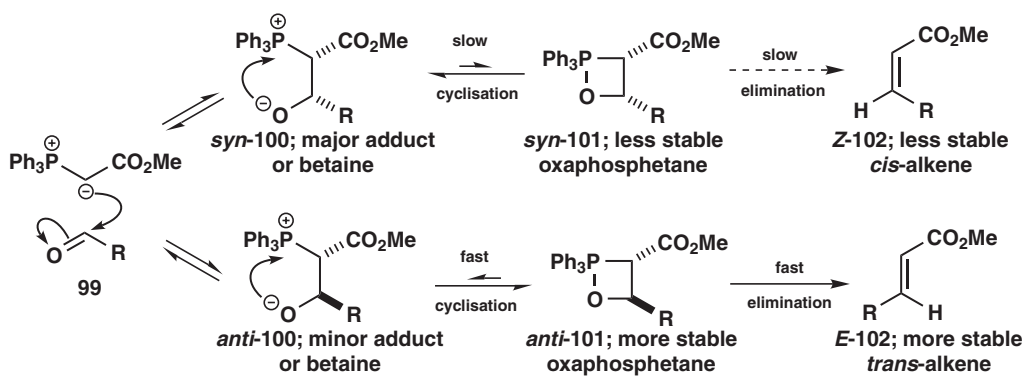
Here are two examples - one with an ylid and an aldehyde and one with a phosphonate ester and a ketone. Both give esters of conjugated unsaturated acids and both give the *E*-isomer. The first gave an excellent yield of *E*-**95** with good selectivity (15:1) even though the new alkene is trisubstituted. It was used in the synthesis of the terpene eremophilone.[17]



The second gave the trisubstituted alkene *E*-**98** (together with 9% of the *Z*-isomer) and this was used to make the interesting millipede compound polyzonimine.[18]



So what makes the dramatic difference between these reactions and those of the unstabilised ylids? Well, again there is no agreement, but we offer one explanation. Supposing the reaction is again stereoselective in favour of the *syn* oxaphosphetane **101**, but this time the reaction can reverse as the starting ylid (or carbanion) is so much more stable. The more abundant *syn*-**100** cyclises to *syn*-**101** more slowly than does the less abundant *anti*-**100** to *anti*-**101** and, in turn, *anti*-**101** eliminates more rapidly than *syn*-**101**.

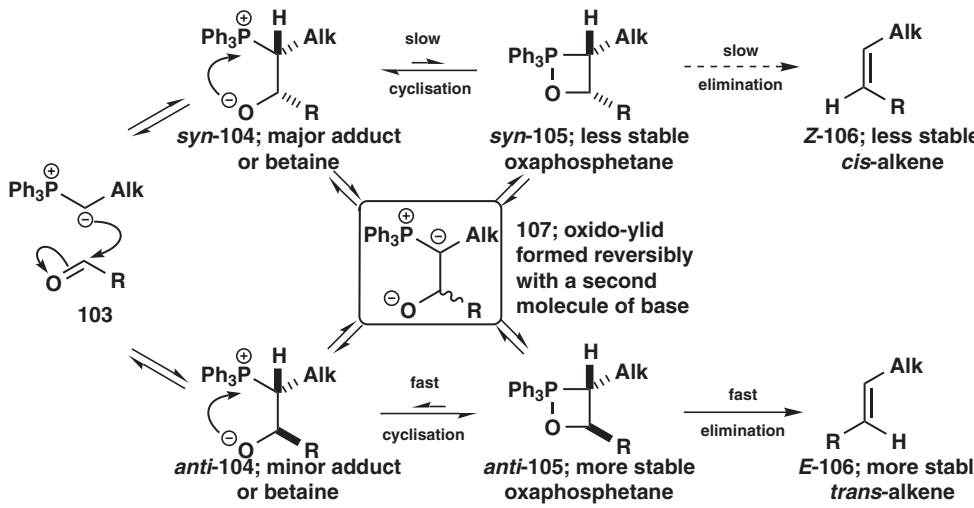


This is more than just an explanation of the *trans* selectivity. It is an alternative (many would say the correct!) mechanism for the Wittig reaction. We shall not enter the debate about whether the "adduct" (or betaine) **100** is a true intermediate. There is no doubt that the oxaphosphetane **101** is a true intermediate. This explanation is more convincing because it also allows us to explain the reactions in the next section.

Crossing the Stereochemical Divide in the Wittig Reaction

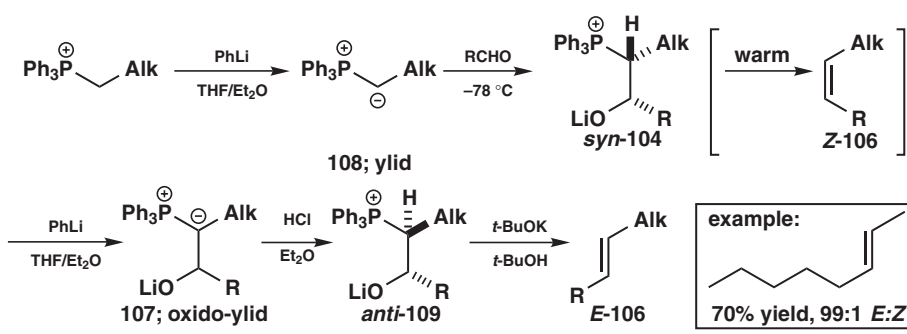
The Schlosser modification

The Wittig reaction is so powerful that we should like to cross into the forbidden zones - to make *E*-alkenes from non-stabilised ylids and to make *Z*-alkenes from stabilised ylids. Both are possible. The stability of the two oxaphosphetanes just considered gives us a clue as to how to accomplish the first of these. Schlosser argued that if we could equilibrate the two series *without going back to the starting materials* we could cross from the kinetically favoured *syn* betaine or oxaphosphetane to the more stable *anti* series. He did this by carrying out the reaction at low temperature and treating with a second molecule of base before the elimination occurred. The oxido-ylid **107** can be formed from both diastereoisomers of either the betaine **104** (if it is an intermediate) or oxaphosphetane **105**. Reprotonation preferentially gives the more stable *anti*-**104** or **105** and hence the *E*-alkene **106** on warming.

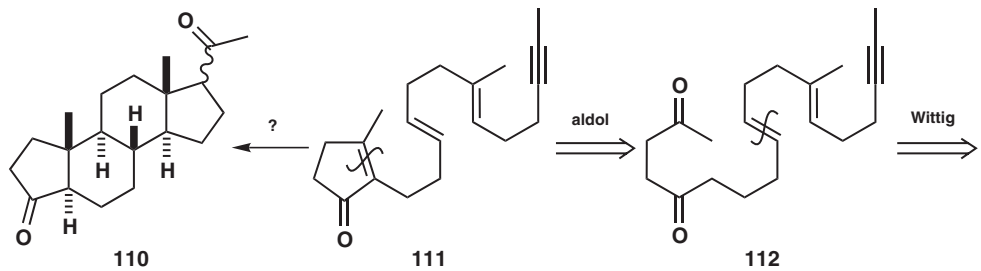


As an example, the synthesis of oct-2-ene by the normal Wittig procedure gives an 80:20 *Z:E* mixture. By the Schlosser modification, set out in detail below, virtually pure (99:1) *E*-oct-2-ene is formed in good yield in a one-pot process. Notice the low temperature used when the aldehyde is added. This is necessary to avoid completion of the Wittig. After epimerisation with a second molecule of PhLi, the oxido ylid **107** is acidified to give the alcohol *syn*-**109** that eliminates quickly with a potassium base.[19]

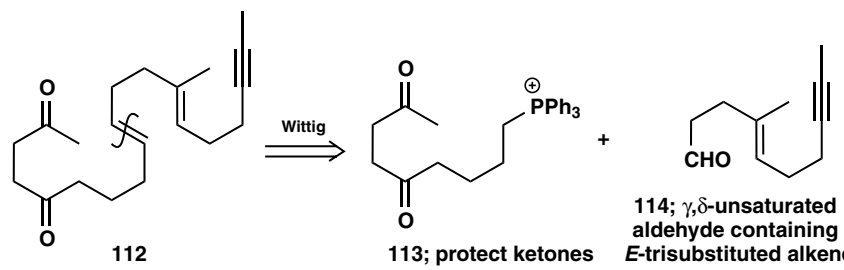
The Schlosser-Wittig Sequence for making simple *E*-Alkenes



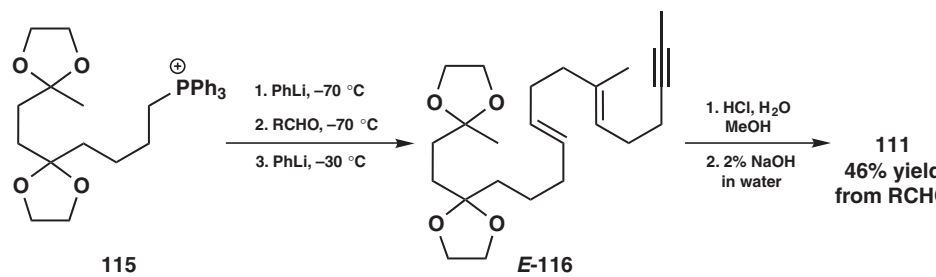
A more serious example is from Johnson's biomimetic polyolefin cyclisation. He wished to make the polyene **111** for potential cyclisation to **110**, a 5-6-6-5 ring system analogous to the natural steroids. After the obvious aldol disconnection, it is best to disconnect the *trans*-alkene **112** in the middle of the molecule.



This requires a Schlosser modification of the Wittig reaction and in theory the CHO and PPh_3 groups could be placed on either fragment. There is, as we shall soon see, a strong reason for wishing to make the trisubstituted *E*-alkene by a [3,3]-sigmatropic rearrangement that gives an alk-4-enal and so this is the preferred analysis:



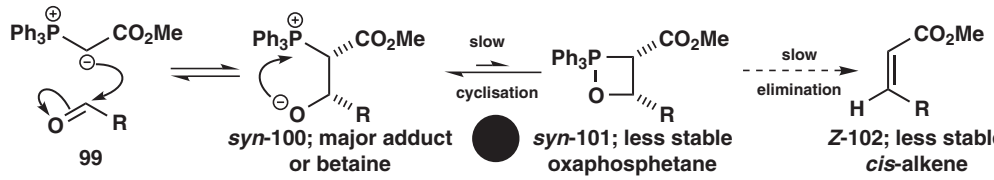
The Wittig reaction was carried out by the Schlosser method - the ylid was generated with PhLi and the aldehyde added at low temperature (−70 °C). A second equivalent of PhLi was added and the intermediates allowed to equilibrate at −30 °C. Elimination of $Ph_3P{=}O$ occurred under these conditions to give the *E*-alkene. Deprotection and aldol condensation gave the cyclopentenone in a very impressive 46% yield over the five steps from the original aldehyde.



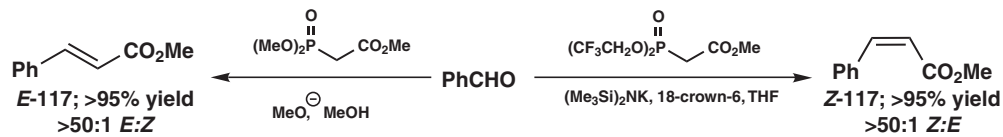
Notice the control inherent in the aldol cyclisation. One from four possible enolates attack one of two carbonyl compounds. This is clearly thermodynamic control under these weakly basic conditions (chapter 5?). The more highly substituted alkene (here tetra-substituted) and the most stable possible ring (i.e. 5- not 3- or 4-membered) is formed. The geometry of the alkene is of course controlled by the ring.[20]

Conjugated Z-alkenes

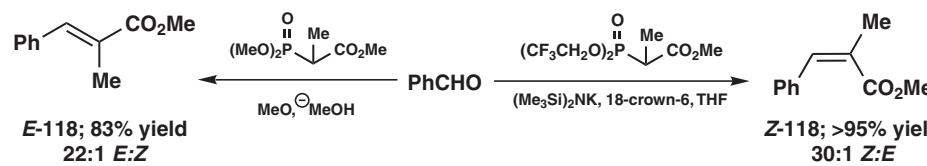
A typical Horner-Wadsworth-Emmons synthesis of a conjugated alkene would involve a phosphonate ester **92** and an aldehyde and would be extremely *E*-selective for *E*-**93**. This selectivity relies on the reversal of the reaction leading to the major adduct **100**, so if we want to make this reaction *Z*-selective, we have to make the cyclisation of the major adduct faster. The black spot marks where the acceleration is needed. Once the *syn*-oxaphosphetane **101** is the major (or only) product, the *Z*-alkene **102** must be formed as the elimination is stereospecific.



This problem was solved by Still and Gennari with strongly electron-withdrawing groups (CF_3CH_2O-) on the phosphorus atom. Nucleophilic attack at phosphorus is speeded up and the reaction becomes *Z*-selective. Conditions have been chosen to get the best *Z*-selectivity and we can contrast the two results with the same aldehyde.[21]



Amazingly, this reaction works well when trisubstituted alkenes are needed - one of the few methods which does - and we can summarise that situation in a similar picture.

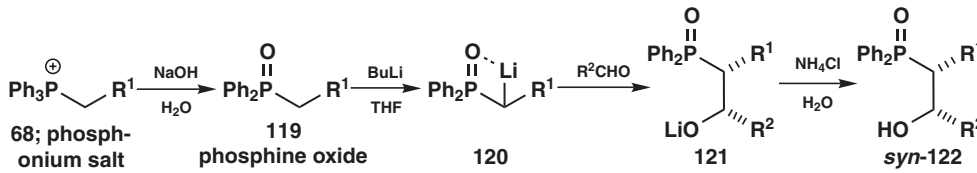


Stereocontrolled Reactions

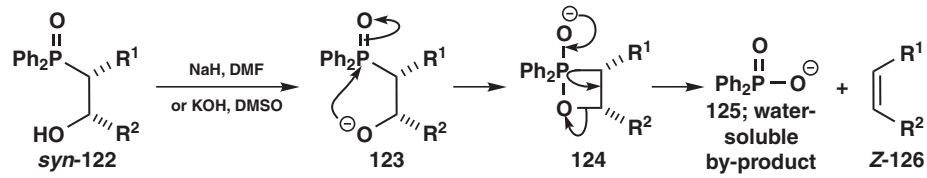
These two versions of the HWE are close to stereochemical control: the formation of either isomer (*E* or *Z*) at will from (more or less) the same starting materials. The next two reactions achieve this aim. By purification of Wittig-type intermediates the stereospecific elimination gives a single isomer of the alkene.

The Horner-Wittig reaction with phosphine oxides

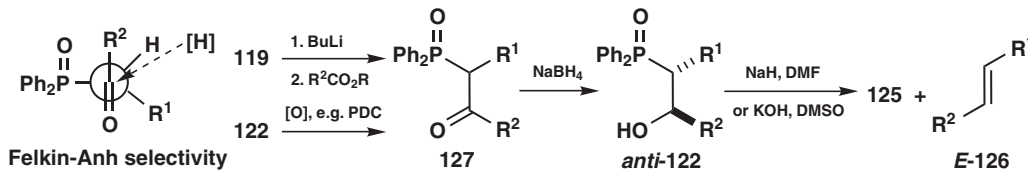
Treatment of a phosphonium salt **68** with aqueous base instead of the anhydrous bases used in the Wittig reaction leads to a stable phosphine oxide **119**. The lithium derivative **120** contains a genuine C–Li bond and reacts stereoselectively with aldehydes to give stable adducts **121** that in turn gives the highly crystalline alcohols *syn*-**122**, easily purified by crystallisation and, if necessary, chromatography.[22]



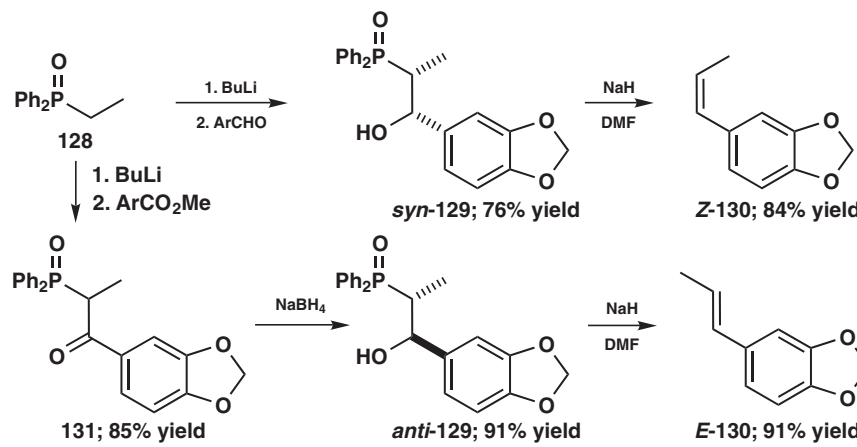
When one pure diastereoisomer of **122** is treated with a sodium or potassium base, a Wittig-style elimination occurs on the anion **123** via the four-membered ring **124**. The stereochemistry of **122** is not affected by this reaction so *syn*-**122** must give *Z*-alkene **122**. The by-product is water-soluble $Ph_2PO_2^-$ rather than the sometimes difficult to remove Ph_3PO formed in the Wittig reaction.



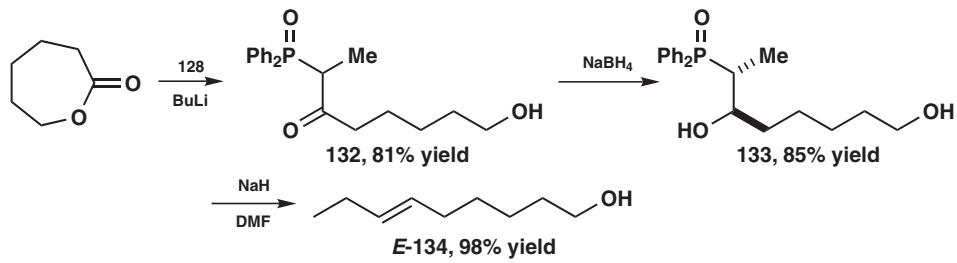
If the *E*-alkene is required, reduction of the ketones **127**, prepared by acylation of **119** or by oxidation of mixtures of isomers of **122**, with $NaBH_4$ in alcoholic solution gives *anti*-**122** selectively. Stereospecific elimination then gives exclusively *E*-**126**. The reduction is controlled by Felkin-Anh selectivity (see chapter 21).



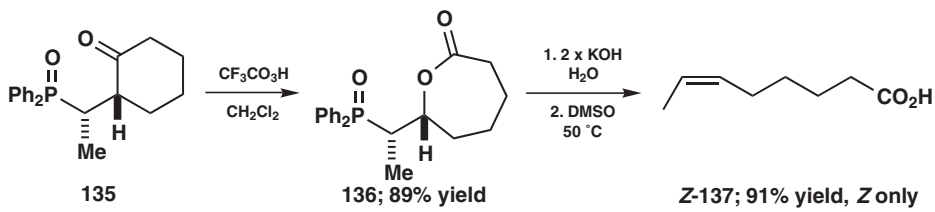
A simple example is the stereochemically controlled synthesis of the two isomers of isosaffrole **130** from the phosphine oxide **128**. Two steps give *Z*-**130** in 64% yield while three steps give *E*-**130** in 70% yield. It is a matter of judgement whether the inevitable sacrifice of yield in a two- or three-step process is worth the formation of single geometrical isomer rather than the mixture obtained from the one-step Wittig or HWE reaction.[23] More complex molecules formed by the Horner-Wittig reaction include brevetoxin[24] A and the immunosuppressant[25] FK506.



The intermediate **122** is a stable compound and can be made by any chemistry that gives simple alcohols. Acylation of **128** with a lactone gives the hydroxy ketone **132** and reduction gives the *anti*-diol **133** in excellent yield. Elimination gives pure *E*-**134**, a pheromone of the Mediterranean fruit fly.

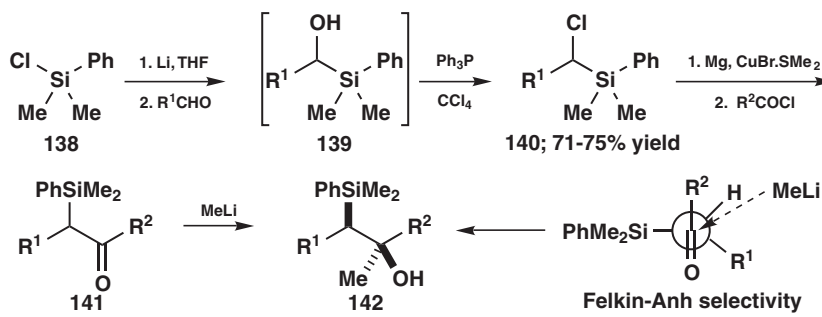


The γ-ketone **135** can be made by reaction of **128** with cyclohexene oxide followed by oxidation. Baeyer-Villiger rearrangement gives mostly (24:1) the lactone **136** with the right regiochemistry for elimination after hydrolysis to give[26] only *Z*-**137**.

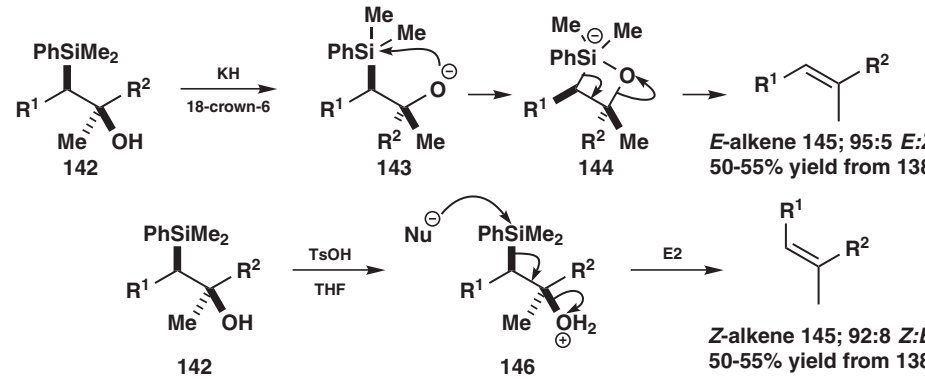


The Peterson reaction

This silicon analogue of the Wittig reaction has the advantage of two alternative stereospecific elimination mechanisms.[27] Providing you can make the silicon-containing alcohols (and there's the problem!) as single diastereoisomers, you can get either *E*- or *Z*-alkene from either one. The best example is probably Barrett's synthesis of trisubstituted alkenes[28] The silyl-lithium derived from **138** is converted into the ketone **141** by straightforward steps. Reaction with MeLi is stereoselective (see Felkin-Anh explanation) to give the alcohol **142** with the silyl and OH groups *syn*.

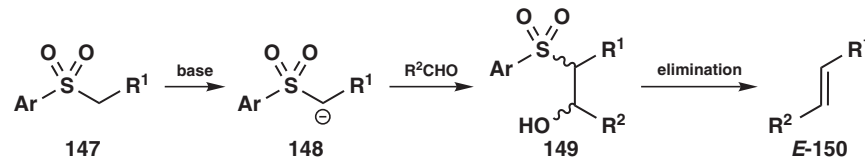


Elimination in base goes through the Wittig-style intermediates **143** and **144** and is *syn*-specific to give *E*-**145** while elimination in acid follows an E2 mechanism with an *anti* arrangement of silyl and OH groups to give *E*-**145**.

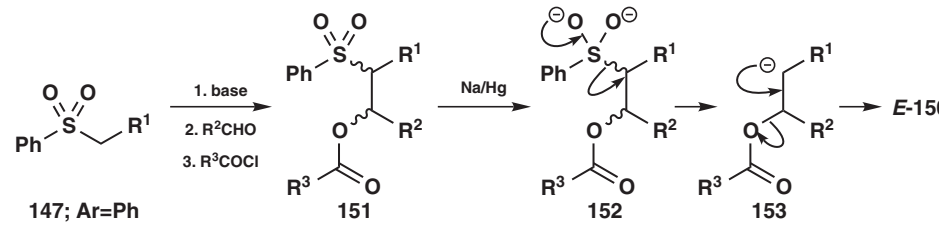


Stereoselective Methods for *E*-Alkenes: The Julia Reaction

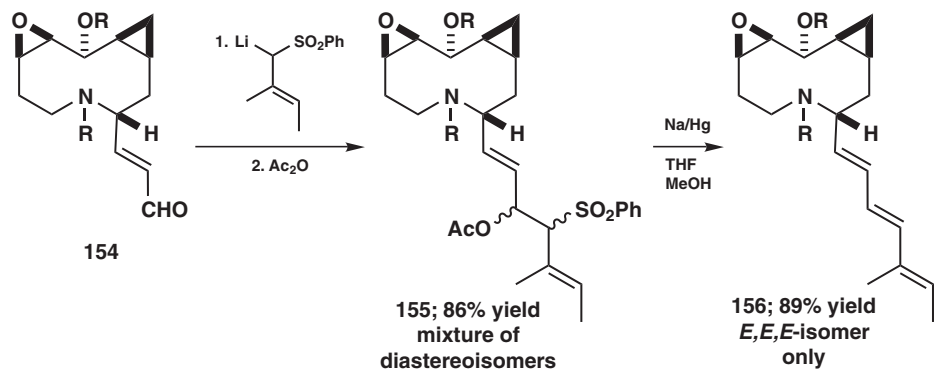
The Julia olefin synthesis is rather like the Wittig reaction with a sulfone instead of a phosphonium salt but with one other important difference: the elimination step is stereoselective and both diastereoisomers of the intermediate can give the same isomer of the alkene. Treatment of the sulfone **147** with a strong base gives the anion **148** (or a metal derivative) that combines with an aldehyde to give a diastereomeric mixture of adducts **149**. Elimination by various methods gives, in open chain compounds, mostly *E*-**150** but, in cyclic compounds, mostly the *Z*-alkene.[29]



Originally the phenylsulfone **147**; Ar=Ph was used and the adduct was acylated then treated with dissolving metal (e.g. sodium amalgam) to bring about a reductive elimination by electron transfer. Addition of two electrons to **151** gives the dianion **152** that breaks down to the carbanion **153** or something like it - at any rate without stereochemistry - and so to the alkene.

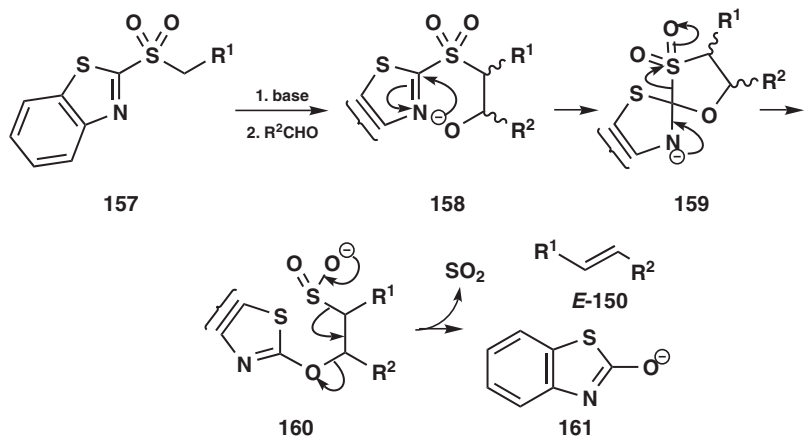


An advanced example of this simple approach was used by Danishefsky in the synthesis of the antibiotic indolizomycin.[30] This example illustrates the compatibility of the Julia olefination with many sensitive functional groups. The enal **154** was combined with the lithium derivative of an allylic sulfone and the adduct acylated to give a mixture of isomers of the adduct **155**. Elimination with sodium amalgam gave a good yield of the *E,E,E*-triene **156**. [The 'R's are protecting groups.]

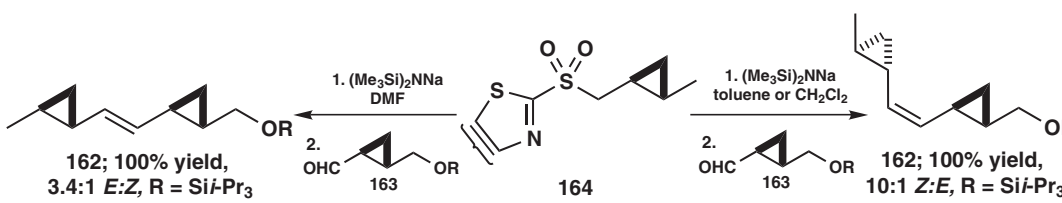


Modified Julia reactions

Recent developments emphasise the convenience of replacing the three step (Marc) Julia reaction by one-step procedures using reagents **147** in which Ar is a heterocycle. Thus (Sylvestre) Julia used a benzothiazole **157**. The adduct **158** with an aldehyde decomposes by fragmentation of the spiro compound **159** without the need for any further reagents to give SO_2, the alkene **150** and the benzothiazole **169**. The benzene rings are omitted from **158–160** for clarity.[31]

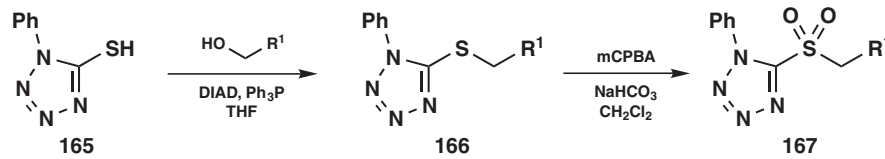


This method was greatly improved by Charette's observation that the hexamethyldisilazide bases (Li, Na or K) and careful choice of solvent made either *E*- or *Z*-selective alkene synthesis possible without the side reactions found in the original method.[32] Starting from the benzothiazole **164**, either *E*- or *Z*-**162** could be made in high yield and good selectivity by choice of solvent alone. Both partners in this modified Julia reaction are enantiomerically pure cyclopropanes and this method led to no destruction of either stereochemistry or the three-membered rings. This method was used to make a single enantiomer of a natural product containing six cyclopropane rings: details are given in the workbook.

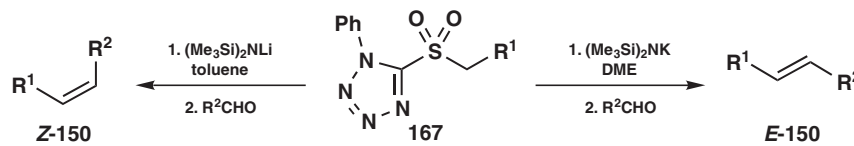


The Kocienski modification of the Julia reaction

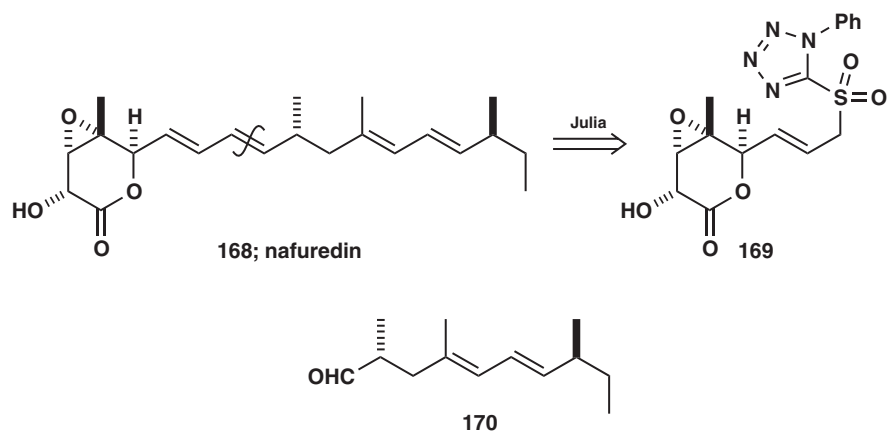
The best version of the Julia olefin synthesis (so far) is probably that introduced by Kocienski.[33] It uses *N*-phenyl tetrazolyl sulfones **167** easily prepared from the available thiol **165** by a Mitsunobu reaction with a simple alcohol followed by oxidation.



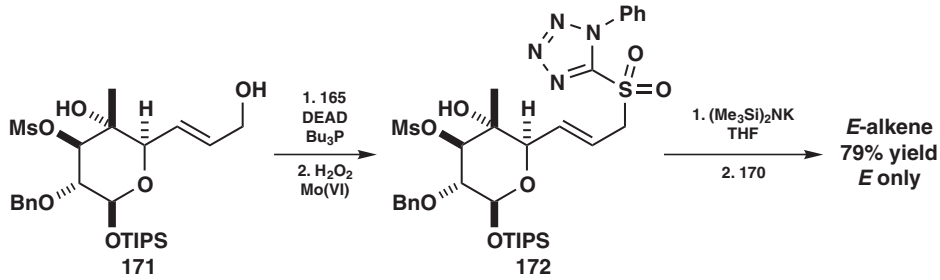
The reaction uses hexamethyldisilazide bases and is again sensitive to solvent. Polar solvents (dimethoxyethane, DME, is the best) and $(Me_3Si)_2NK$ give high *E*-selectivity (usually >95:5 *E:Z*) while non-polar solvents (toluene is the best) with $(Me_3Si)_2NLi$ give moderate *Z*-selectivity.



A recent application is the synthesis of the anti-parasitic agent nafuredin **168** by Omura's group.[34] Nafuredin has four alkenes in the side chain but disconnection near the middle of the molecule is strategically best. As with the Wittig, there is a choice where to put the sulfone and the aldehyde. The sulfone **169** can be easily made from an allylic alcohol. No doubt some of the functional groups in **169** will have to be protected.



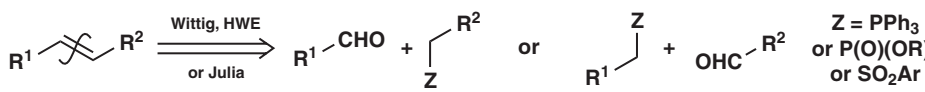
The asymmetric aspects of the syntheses of **169** and **170** appear in the workbook. The other three alkenes were made by *E*-selective Wittigs with stabilised ylids or HWE reactions. The sulfone **172** for the Julia reaction was prepared from **171**, in turn prepared from glucose and gave the corresponding *E*-alkene (a modified version of **168**) in excellent yield and perfect *E*-selectivity.



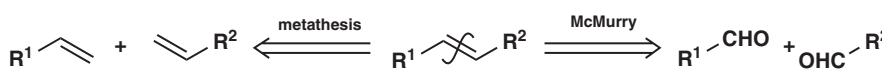
Direct Coupling of Carbonyl Compounds and Alkenes

Carbonyl compounds: the McMurry reaction

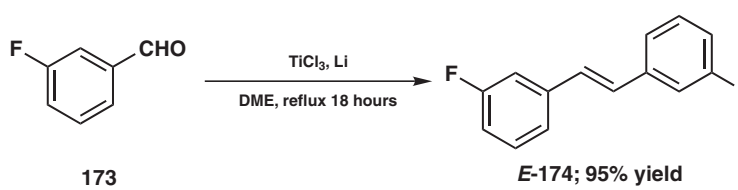
The disconnections for the Wittig, HWE, and Julia reactions are at the double bond with the starting materials being a carbonyl compound and a P or S functionalised alkyl group. There is a choice about which component has which functional group.



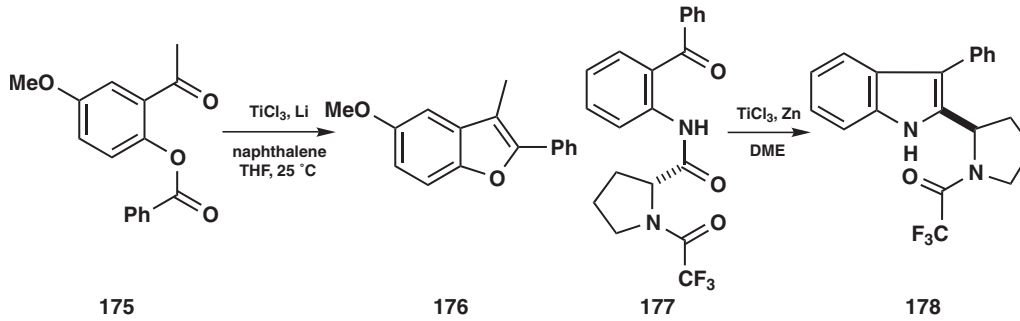
We now turn to two reactions, the McMurry and metathesis, that have the same disconnection but both reagents have identical functional groups: carbonyls for the McMurry and alkenes for metathesis. These methods have the advantage of simplicity but there are obvious problems of selectivity.



The McMurry[35] uses low-valent titanium to couple two carbonyl groups together and works very well when the two compounds are the same: the symmetrical stilbene *E*-**174** can be made in 95% yield and in almost perfect (99.92:0.04 *E:Z*) *E*-selectivity from 3-fluorobenzaldehyde **173**. The low-valent titanium is produced by reduction of Ti(III) with lithium metal.[36]

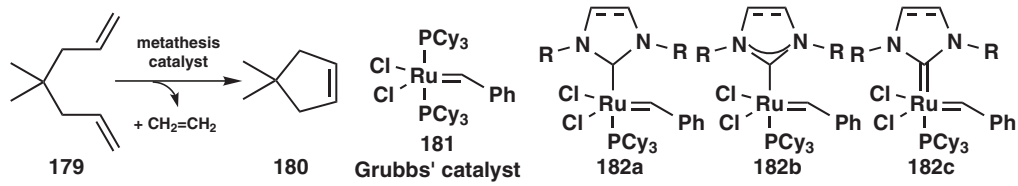


If the reaction is intramolecular two different carbonyl groups can be coupled unambiguously and these two examples show that esters[37] **175** and amides[38] **177** can be used to make benzofurans **176** and indoles **178**.

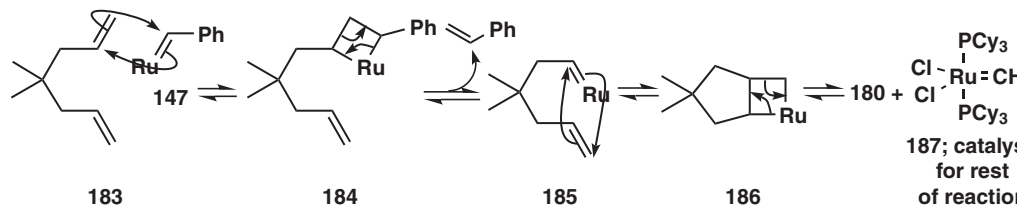


Alkenes: olefin metathesis

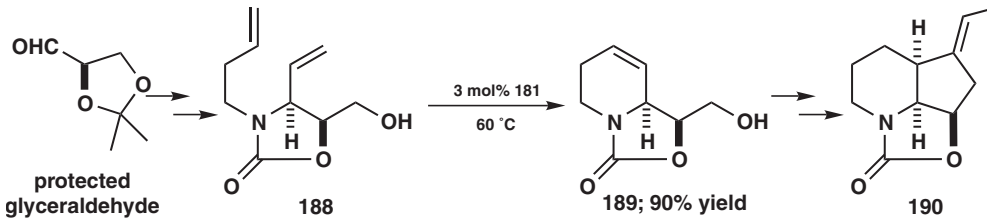
Metathesis is now one of the most important ways to make alkenes. And yet practical catalysts for metathesis were reported only in the 1990s and the reaction[39] was largely limited to cyclic alkenes such as **180**. Though there are many metathesis catalysts, by far the most important are the two Grubbs ruthenium carbene complexes **181** and **182**. They are not the most active catalysts but they are stable and easy to use and compatible with a wide range of functional groups. The simpler **181** is obviously a carbene complex and is usually called 'Grubbs' catalyst'. The more active complex **182** ('second generation Grubbs') replaces one of the tricyclohexyl phosphines with a heterocycle. In these diagrams the dotted line shows that there may or may not be a double bond on the other side of the ring. Otherwise the diagrams **182a-c** show three different ways of drawing the same compound. The first **182a** has the advantage of simplicity but wrongly suggests that there is a hydrogen atom on the ring where the Ru atom bonds. The other two **182b,c** show more clearly that the heterocyclic ring is also a carbene-like ligand.



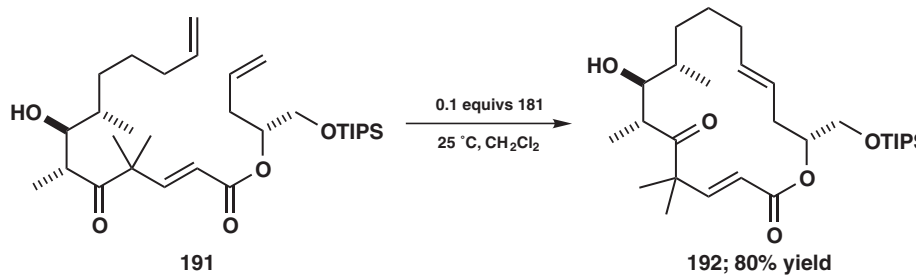
The mechanism of the reaction involves a series of [2 + 2] cycloadditions **183** and **185** and cycloreversions **184** and **186**. The first cycle (**183** to **185**) is different from the main reaction in that the other product is styrene and the catalyst then changes to the methylene complex **187**. The reaction goes from left to right as the other product is gaseous ethylene.



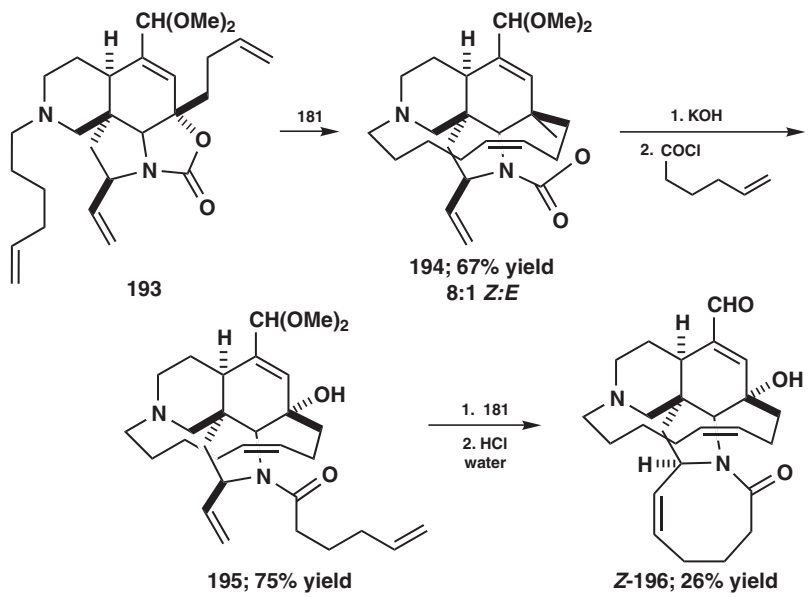
A simple example is the synthesis of analogues of the antibiotic and antifungal streptazolin by Cossy.[40] Enantiomerically pure diene carbamate **188**, prepared from the chiral pool (see chapter 23 and the workbook for this chapter) was treated with the Grubbs' catalyst to form the six-membered ring **189** required for (−)-4,5-dihydrostreptazolin **190**. This metathesis product inevitably contains a *Z*-alkene.



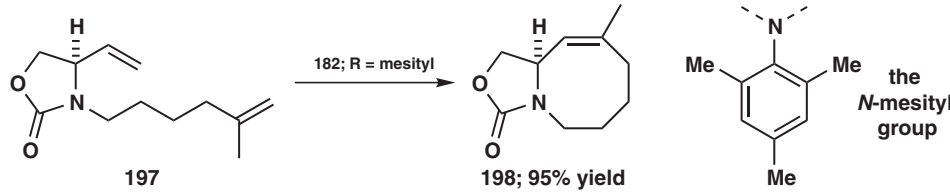
Metathesis is excellent for the formation of medium- and large rings. In the synthesis of epothilones K. C. Nicolaou[41] used the Grubbs catalyst to close the 16-membered ring lactone **192** from the open chain ester **191** in good yield under mild conditions. The most obvious way to prepare **192** is to make an open chain hydroxy-acid and cyclise by lactone formation. The metathesis cyclisation generally works better.



The very complex natural product ircinal A *Z*-**196** has difficult *Z*-alkenes in the eight-membered ring and in the 'frill' round the molecule's waist. Both have been inserted by metathesis with good *Z*-selectivity.[42] The starting material **193** has three alkenes but only two metathesise to give the 13-membered cyclic frill **194**. The final metathesis to close the eight-membered ring is obviously difficult and the yield is poor.



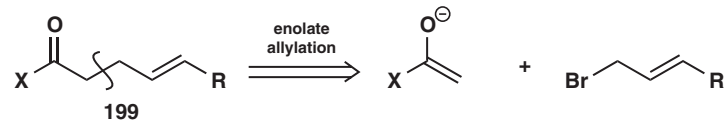
A much simpler heterocyclic eight-membered ring[43] **198** was successfully closed in 95% yield with the second generation Grubbs catalyst **182**; R = mesityl [this is the catalyst with the double bond]. This example shows that trisubstituted alkenes can be made by metathesis too.



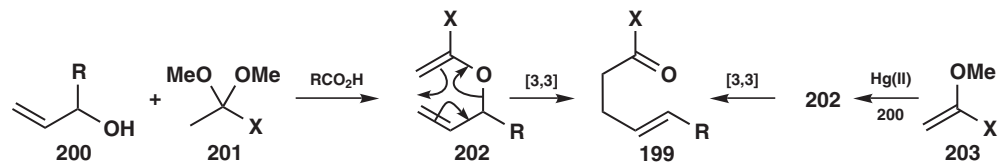
Stereoselective Methods for *E*-Alkenes

[3,3]-Sigmatropic rearrangements

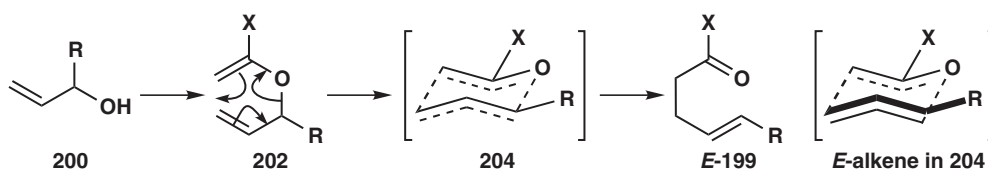
We said a few pages back that there was a strong reason for making a trisubstituted *E*-γ,δ-unsaturated carbonyl compound **111** by a [3,3]-sigmatropic rearrangement and we have come now to the section of the book where we look at this reaction more closely. The disconnection is of the α,β bond in a γ,δ-unsaturated carbonyl compound **199**.



We call this disconnection "enolate allylation" because we want to alkylate an enolate ion with an allyl halide. We have already discussed (chapter 19) the regioselectivity problems inherent in reactions of allyl derivatives and you should recall that we want to react at the correct (less substituted) end of the allyl system and we want to make an *E*-alkene. The solution is to use a [3,3]-sigmatropic rearrangement. This is the reaction sequence:

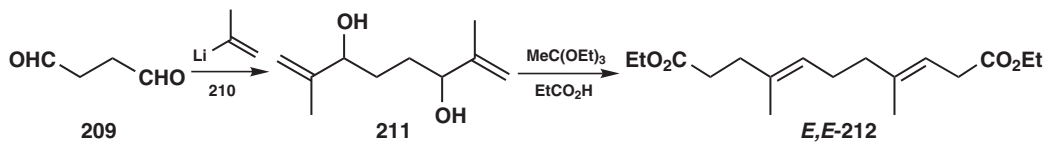


Instead of an allylic halide, which can equilibrate all by itself, we use a regiochemically stable allylic alcohol **200**. This is combined with an acetal **201** under proton catalysis or with a vinyl (enol) ether **203** under Hg(II) catalysis to give the key vinyl allyl ether **202**. These compounds rearrange on heating as the mechanism shows **202** to give the *E*-γ,δ-unsaturated carbonyl compound **199**. A C–C single bond replaces a C–O single bond (a bad bargain this) and the reaction is driven by the replacement of a C=C double bond by the more stable carbonyl group. These reactions can be carried out at the aldehyde (X=H), ketone (X=R), ester (X=OR) or amide ($X=NR_2$) oxidation level just by choosing the correct starting material.

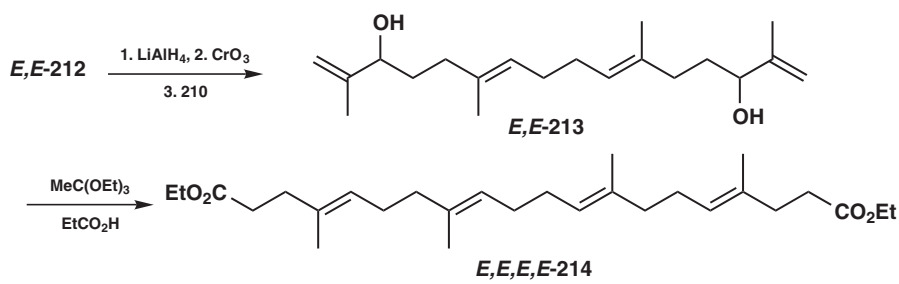


Because the [3,3] sigmatropic rearrangement turns the allylic system inside out we must use the 'wrong' allyl alcohol **200** to make **199**. The *E*-selectivity is a result of a chair-like transition state **204** in which the substituent R prefers an equatorial position. The second diagram of the transition state marks the *trans* arrangement of the three bonds involved. These rearrangements are among the most *E*-selective reactions known.[44] The selectivity is still good even when a tri-substituted alkene **208** is being made, providing that a large substituent is in the equatorial position **207**.

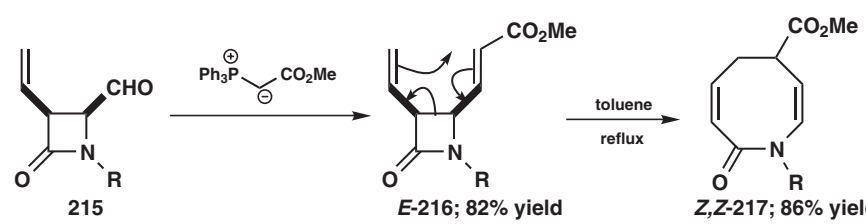
An excellent illustration is Johnson's synthesis of squalene[45] by a series of double [3,3] rearrangements. Reaction of a dialdehyde **209** with propenyl lithium **210** gives a double allylic alcohol **211** that undergoes a double rearrangement at the ester oxidation level with an orthoacetate [$MeC(OEt)_3$].



Reduction of the esters in the product **212** to aldehydes allows the whole process to be repeated twice more. The complete skeleton **214** has four new alkenes and yet contains over 90% of the *E,E,E,E* isomer.

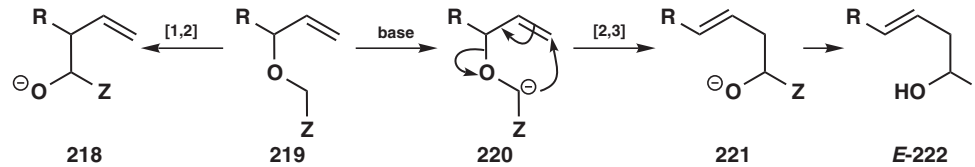


This method too gives *Z*-alkenes if they are in a ring. The β-lactam **215** can be converted into the *E*-alkene **216** by a Wittig reaction and hence by a [3,3] sigmatropic rearrangement into the eight-membered heterocycle **217** containing two new *Z*-alkenes.[46] The discerning reader will notice that this is quite a different reaction from the last. That was an oxy-Cope (or Claisen-Cope) driven by the formation of a carbonyl group. This is the Cope itself with all carbon atoms in the (necessarily boat shaped) cyclic transition state. The driving force is the loss of the strained four-membered ring.

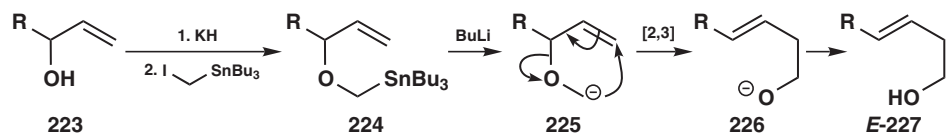


[2,3]-Sigmatropic rearrangements: The Wittig rearrangement

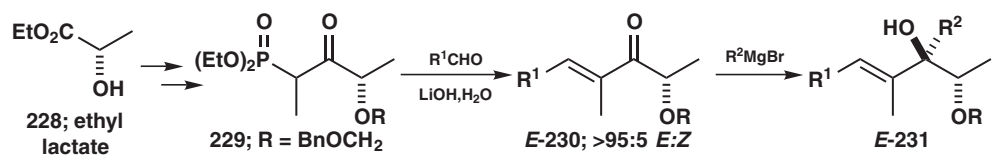
Derivatives of allylic alcohols such as **219** may rearrange in base to the homoallylic alcohols **222** with the creation of a new alkene. The reaction is a [2,3]-sigmatropic rearrangement of the anion **220** and works best when the group Z is anion-stabilising otherwise there may be competition with the original Wittig rearrangement to give the alcohol derived from **218**. Both these products are more stable than the carbanion **220** because they are oxyanions. The reaction of **220** to give **221** is best called the [2,3]-Wittig rearrangement and is *E*-selective as the group R prefers a (pseudo-) equatorial position in the half-chair transition state.[47]



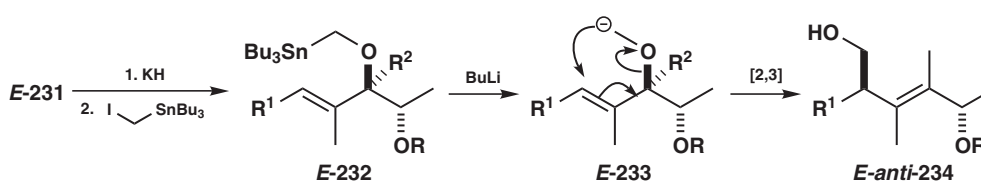
The problem of what to do with the usually unwanted anion-stabilising group Z is solved in the Wittig-Still rearrangement by using the R_3Sn group that sacrifices itself to form the anion. Alkylation of the allylic alcohol **223** and treatment with BuLi initiate the rearrangement **225** to give the unsubstituted *E*-allylic alcohol **226**. There are many examples.[48]



Most of the examples in this chapter have been disubstituted alkenes, a few have been trisubstituted, but none so far has been tetrasubstituted (except cyclic alkenes) as this is the most difficult case of all. One solution[49] starts with ethyl lactate **228** and uses a HWE reaction on the enantiomerically pure phosphonate **229** to make the *E*-enone **230** with very high selectivity. Chelation-controlled addition of a Grignard reagent gives the stereochemically pure allylic alcohol **231**. Chelation control is explained in chapter 21.



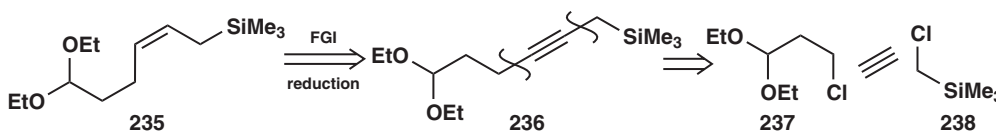
Alkylation of the free OH provides the substrate **232** for the Wittig-Still rearrangement **233**. The new tetrasubstituted alkene **234** is almost entirely *E* (>95:5 in most cases) and the migrating CH_2O group is transferred across the top face of the allylic system as drawn. The [2,3]-sigmatropic rearrangement is suprafacial.



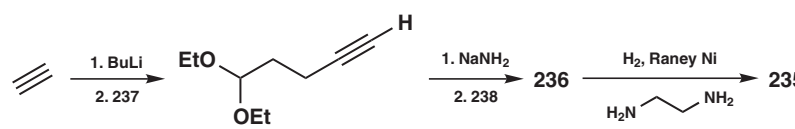
There are many sigmatropic rearrangements and all are *E*-selective in open chain compounds but can give *Z*-alkenes if the structure of the compound demands it. In this way they resemble the McMurry reaction and olefin metathesis. Many such reactions are used to transmit three-dimensional stereochemistry rather than for *E/Z* control in alkenes.

Reduction of Alkynes

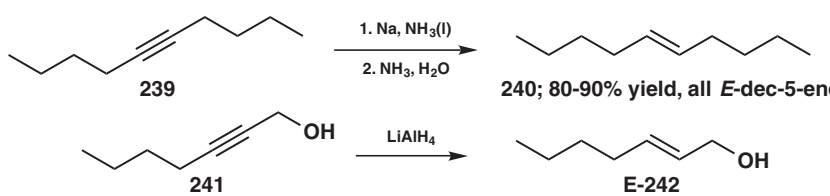
You will already be aware that *cis*-alkenes can be formed by catalytic hydrogenation of alkynes. This example illustrates how acetylene, a double-ended nucleophile, can be used to build the skeleton of a *Z*-allyl silane **235** of the type used in chapter 12. The disconnection **236** is next to the 'alkene' (now an alkyne) rather than across it.



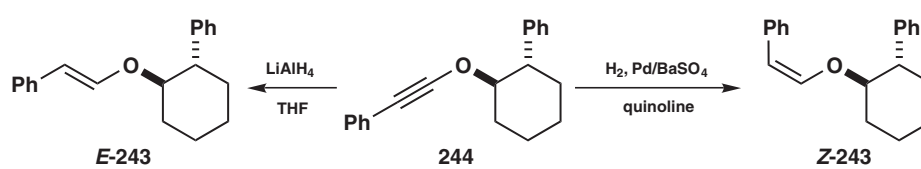
The synthesis is straightforward except that the normal Lindlar catalyst is not used, Raney nickel being preferred in this case.[50]



Reduction of alkynes with sodium in liquid ammonia produces *E*-alkenes as you will be aware though the reduction of functionalised alkynes with $LiAlH_4$ is perhaps more common nowadays. Here are simple examples of both methods: the $LiAlH_4$ reduction will be discussed in the next chapter.



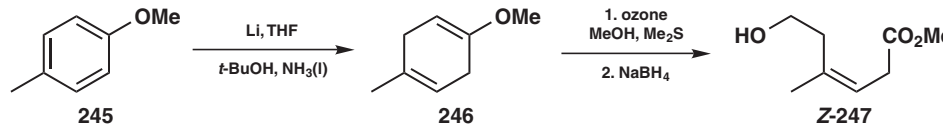
In an important paper making enantiomerically enriched amines by 1,3-dipolar cycloadditions, Denmark[51] made both isomers of the vinyl ether **243** from the alkyne **244**. Lindlar reduction gave pure *Z*-**243** while $LiAlH_4$ reduction gave pure *E*-**243**.



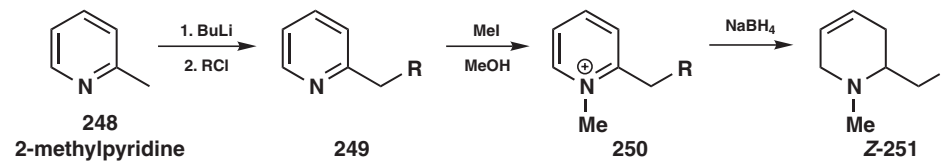
Stereospecific Methods for *Z*-Alkenes

Using cyclic compounds

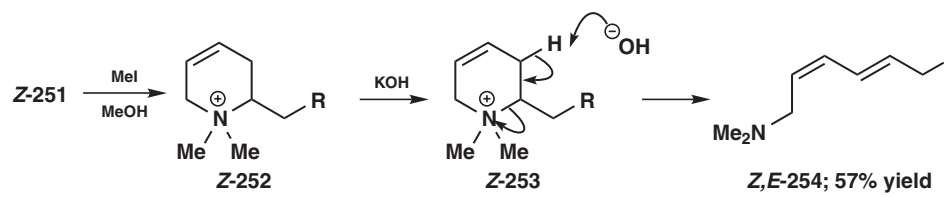
In a smaller ring (<8 membered) an alkene must have the *Z*-configuration. Cleavage of another bond in such a ring must leave the *Z*-alkene intact. We shall look at oxidative cleavage of Birch reduction products, elimination in a nitrogen heterocycle and hydrolysis of lactones. Birch reduction of aryl ethers **245** leaves two non-conjugated alkenes **246**: the enol ether is much more nucleophilic and so is more easily cleaved by ozone. Corey[52] used this strategy to make trisubstituted alkene **247**.



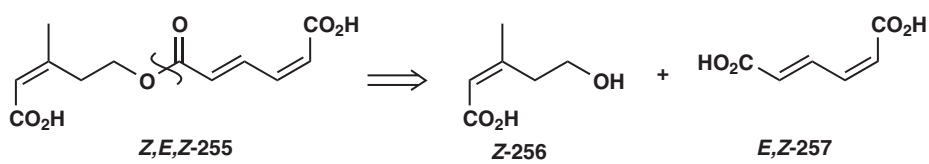
Simple pyridines, such as 2-methylpyridine **248**, can be alkylated and reduced to leave just one necessarily *Z*-alkene **251** not conjugated with nitrogen.



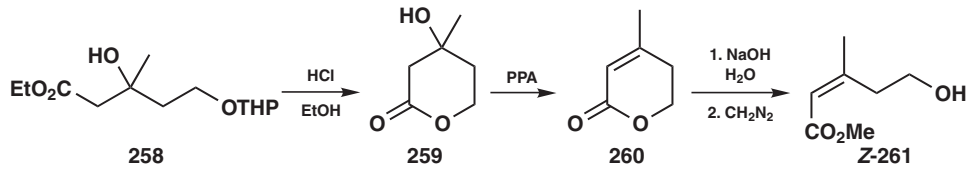
Further alkylation and elimination **253** gives an open chain diene **254**. The second alkene is formed stereoselectively with *E* geometry.[53]



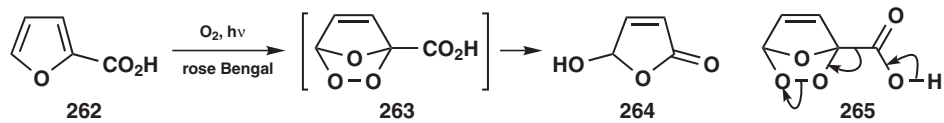
White needed the diacid ester *Z,E,Z*-**255** for his synthesis of the anti-leukaemia compound verrucarin.[54] It must clearly be made from the components *Z*-**256** and *E,Z*-**257** though there are obvious selectivity problems in getting the right ester from compounds with three different CO_2H groups.



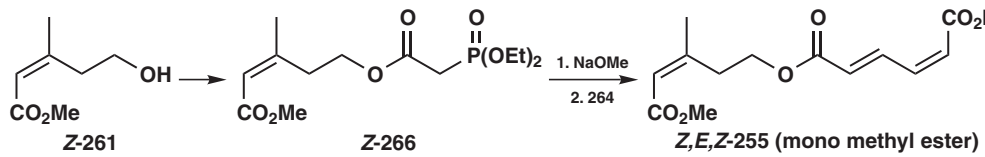
The *Z*-acid **256** was made from a lactone. Dehydration of the tertiary alcohol in the open chain compound **258** would give the *E*-alkene but after cyclisation to the lactone **259** dehydration with polyphosphoric acid (PPA) must give *Z*-**260**. Careful hydrolysis and methylation gives *Z*-**261**, the methyl ester of *Z*-**261**.



The *Z*-alkene in the other half **257** was made from a furan **262**. Cycloaddition with singlet oxygen (rose Bengal is a dye that sensitises the conversion of normal triplet oxygen to the singlet) leaves one necessarily *Z*-alkene in the five-membered ring **264**. One possible mechanism for the decarboxylation of the cycloadduct **263** is given **265**.



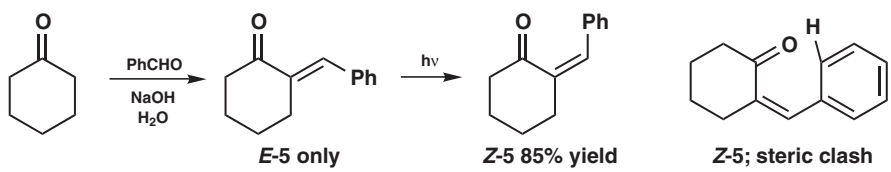
The two halves are coupled by an HWE reaction to put in the easiest double bond - the conjugated *E*-alkene. The alcohol *Z*-**261** is converted into an ester *Z*-**266** that reacts directly with the hemiacetal **264** using two equivalents of base to give the ester of *Z,E,Z*-**255** in 84% yield. Note that this method also keeps the acids distinct.



Interconversion of *E* and *Z* Alkenes

Photochemical isomerisation to the Z-isomer

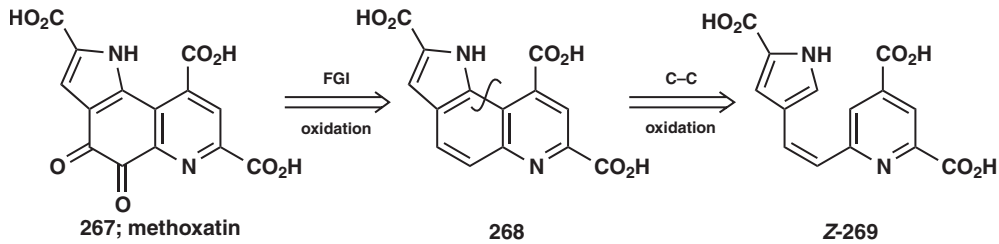
A simple approach to a difficult alkene might be to make whatever mixture results from the easiest synthesis and convert it stereoselectively into one isomer or, with more precise control, to make the wrong isomer, if that is easier to make, and convert that stereospecifically into the other. A simple example is the enone *E*-**5** made by an aldol condensation. It is easy to see why *E*-**5** is the thermodynamic product: there is a steric clash in the Z-isomer between the carbonyl oxygen and one of the ortho-Hs on the benzene ring.



Shining light on the pure *E*-**5** isomerises it completely[55] into *Z*-**5**. The excited π,π* state of the enone **5** has one electron in the π* orbital allowing free rotation about the alkene. But why should it prefer the less stable *Z*-isomer? Photochemical reactions are determined not by thermodynamic stability but by light absorption. More stable *E*-**5** is planar and conjugated and absorbs light more efficiently and at higher wavelength but *Z*-**5** cannot be planar and absorbs light less efficiently and at a shorter wavelength than does *E*-**5**. Irradiation at a higher wavelength converts all *E*-**5** into *Z*-**5**.

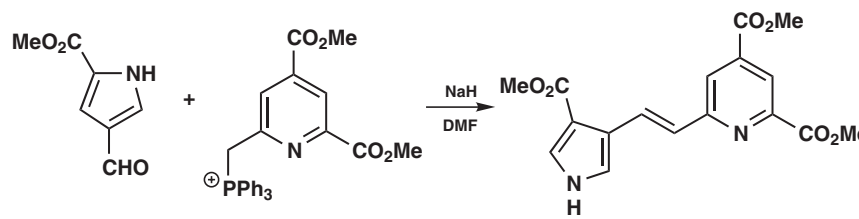
A synthesis of methoxatin

Methoxatin **267** is a bacterial co-enzyme that allows the oxidation of methane to more useful one-carbon compounds. The 1,2-dione in the middle ring is the powerhouse of the molecule and can be made from the simpler aromatic compound **268** by oxidation. Oxidative cyclisation of the *Z*-alkene **269** might give **268**.



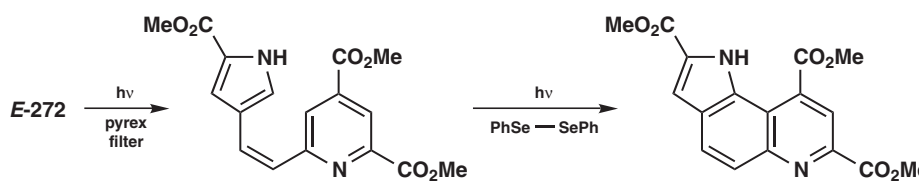
267; methoxatin **268** ***Z*-269**

Making **272** from the aldehyde **270** and the Wittig reagent **271** proved easy once all the carboxylic acids were protected as methyl esters but gave mainly *E*-**272** as either of the possible ylids is stabilised. Clearly this isomer cannot cyclise so isomerisation to *Z*-**272** was necessary.[56]



270 **271** ***E*-272; 84% yield, >95% *E***

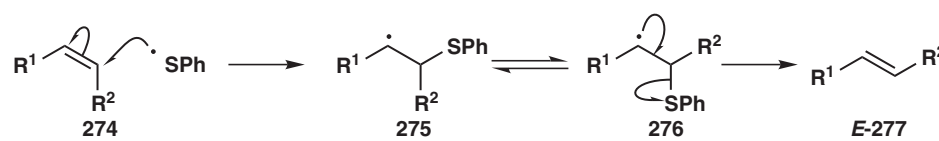
Brief irradiation with UV light through a pyrex filter (to remove short wavelength light) in the presence of diphenyldiselenide (PhSe – SePh) gave the trimethyl ester of **268** by isomerisation to *Z*-**272** and oxidative cyclisation.



Z*-272; 100% yield, 100% *Z **273**

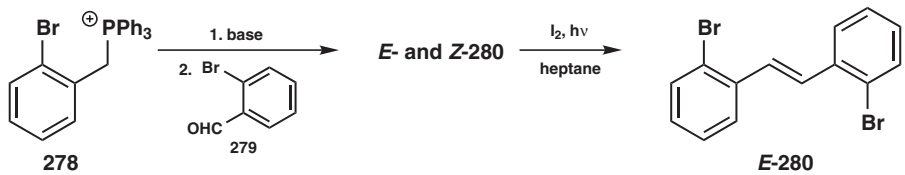
Radical isomerisation to the E-isomer

Relatively stable radicals such as I•, PhS• or Bu_3Sn• add to alkenes **274** and then drop out again. PhS• radicals are easily made by AIBN treatment of thiophenol (PhSH) or simply by refluxing the alkene with PhSH without any precautions to remove oxygen. If the intermediate **275** has a long enough life it can rotate and equilibrate thermally to the *E*-alkene **277**.

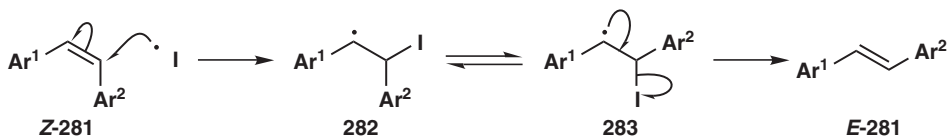


274 **275** **276** ***E*-277**

Stilbene formation by the Wittig reaction usually gives a mixture (here 7:3 *Z*:*E*) of *E*- and *Z*-isomers **280**. Irradiation of a heptane solution containing a small amount of iodine in sunlight isomerises the mixture to the *E*-stilbene **280** which crystallises from solution in 68% yield.[57]

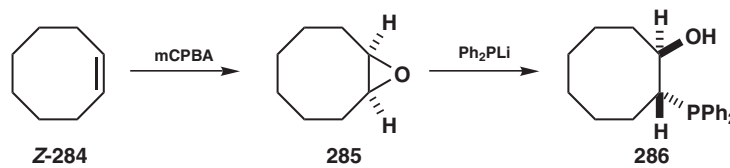


The mechanism is the same: iodine absorbs the sunlight (the solution is purple) to give I• radicals that add to the alkene **281** to give a long lived radical **282** that rotates before ejecting the I• radical. There is an example of the use of the Bu_3Sn• radical in the next chapter.

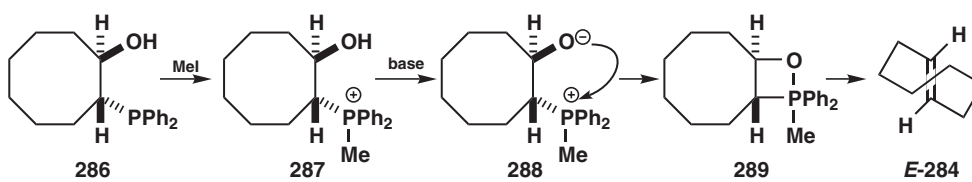


Stereospecific Interconversion of *E* and *Z*-isomers

Some isomers of alkenes are particularly difficult to make and a stereospecific method is required. Fortunately there is a good one. *Cis*-cyclo-octene *Z*-**284** is easy to make by elimination and is available commercially. The epoxide **285** is made without change of stereochemistry and opening this epoxide with the very nucleophilic Ph_2PLi ensures one inversion in the formation of the phosphine **286**.



The phosphine **286** is easily alkylated to provide the Wittig intermediate **287** that eliminates in the usual stereospecific manner via the oxaphosphetane **288** and must therefore give the strained *trans*-cyclo-octene *E*-**284**, the smallest *trans* cycloalkene that is stable. It is also chiral.[58]



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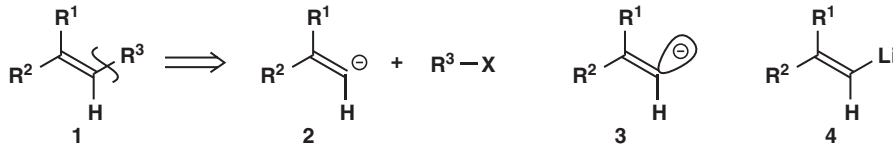
16 Stereo-Controlled Vinyl Anion Equivalents

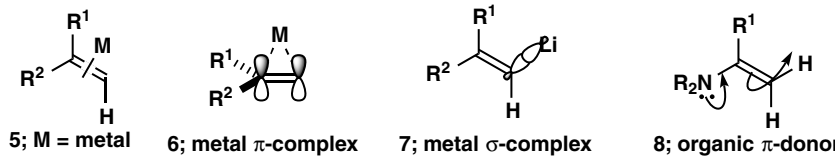
Introduction: Reagents for the Vinyl Anion Synthon

Fresh from the discussion in chapter 15 on stereo-controlled alkene synthesis, did you notice that we avoided one disconnection entirely? We never considered combining a vinyl anion **2** with a carbon electrophile. This chapter concerns reagents for the vinyl anion synthon and particularly those that allow control over the stereochemistry of the double bond in the product. Please notice from the start that we mean vinyl anions where the nucleophilic group is in the plane of the alkene **3**. This means that we shall chiefly be discussing vinyl metals such as vinyl-lithiums. These are metal σ-complexes **4** with the metal atom also in the plane of the alkene.

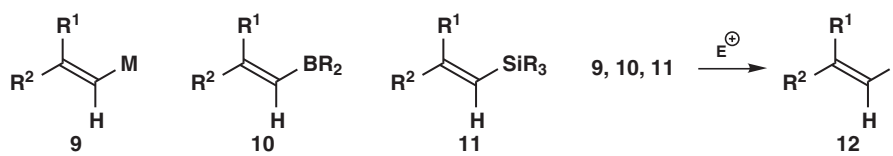
Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren



We shall not be using metal π-complexes **5** where the metal sits at right angles to the alkene plane **6**. These are very important compounds and have their role to play in synthesis but they do not have the right properties to act as reagents for the vinyl anion synthon. Nor shall we be using the familiar organic reagents such as enamines **8** that act as π-donors at the same atom. The problem here is the same - though electrophilic attack occurs at the correct atom, it occurs at right angles to the alkene plane and stereochemistry is difficult to control. Instead we shall be describing vinyl metal σ-complexes **7**.



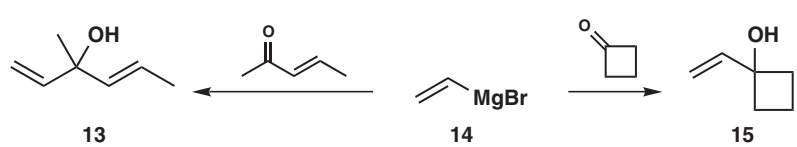
Stereochemical information is built into reagents **9** that have a nucleophilic vinyl-metal bond in the plane of the alkene. This bond already has a stereochemistry - it is *cis* to R^1 and *trans* to R^2 - and this information can be passed to the products providing that the reaction with electrophiles is stereospecific. In most of the methods in this chapter vinyl metals **9**; M = Li, Mg, Cu, Sn, Al, Zr, or compounds closely related to them such as vinyl boranes **10** or vinyl silanes **11**, react with electrophiles E^+ with retention of configuration **12**.



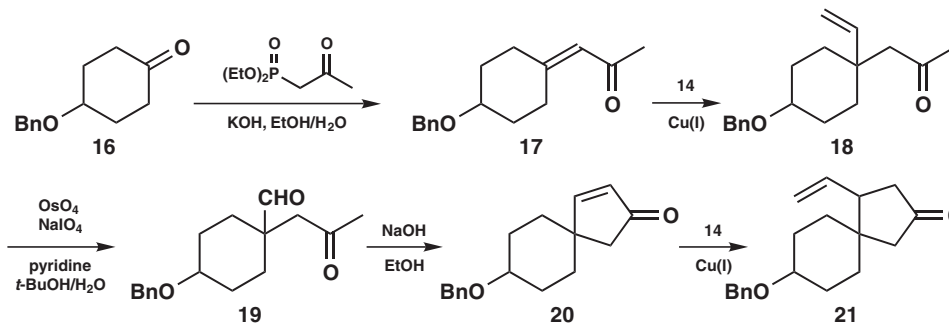
This reaction will be useful only if we are able to prepare these compounds with a fixed (*E* or *Z*) configuration. The first part of the chapter concerns the preparation and reactions of simple vinyl metal derivatives and we shall then progress to a study of stereochemistry.

Vinyl-Lithiums

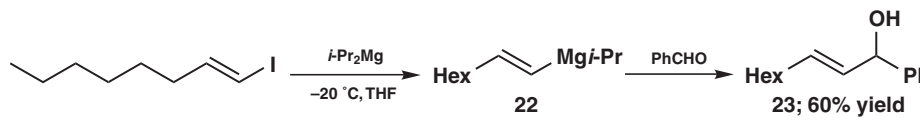
Unsubstituted vinyl-lithium and vinyl Grignard **14** reagents can be made directly from the halide by oxidative insertion of Li(0) and Mg(0). Vinyl-lithium is available as a 2M solution in THF from Alfa and vinyl magnesium bromide, which must be prepared in THF, is available in THF from Aldrich. These are quite stable σ-complexes because alkenyl anions are more stable than saturated alkyl anions. They add as nucleophiles to carbonyl groups, e.g. cyclobutanone to give **15** and prefer direct to conjugate addition with enones to give e.g. **13**. We have already used them in enone synthesis (chapter 5).



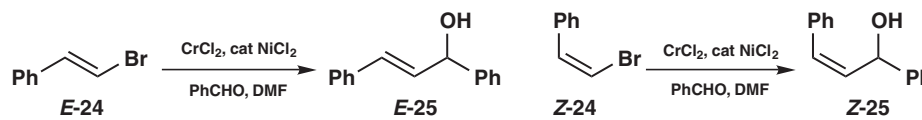
Both the Grignard reagent **14** and vinyl-lithium can be converted into copper derivatives by exchange with Cu(I) halides. Two Cu(I)-catalysed conjugate additions of vinyl Grignard to enones start one of Corey's gibberellin syntheses.[1] In the absence of Cu(I) the vinyl Grignard reagent **14** adds directly to the carbonyl groups of **17** and **20**.



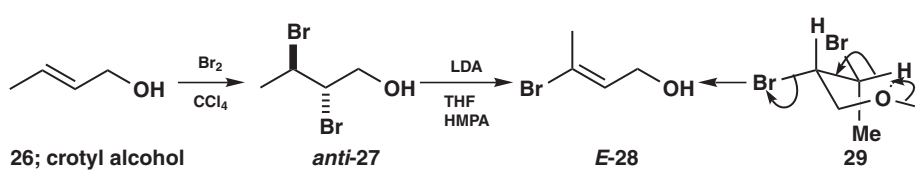
The extra stability of vinyl Grignard reagents is clearly shown by Knochel's preparation of **22** by exchange with i-Pr_2Mg. Notice that the alkenyl group is transferred rather than the alkyl group to benzaldehyde and that both metallation and reaction with the aldehyde occur with retention of configuration.[2]



A few substituted vinyl halides are available, such as *E*- and *Z*-1-bromopropene, and a few can be made with stereochemistry. Both *E*- and *Z*-1-bromostyrene have been used in stereospecific additions to benzaldehyde with Cr(II) and catalytic Ni(II) as the metals.[3] The synthesis of these isomers from cinnamic acid is described in the workbook.



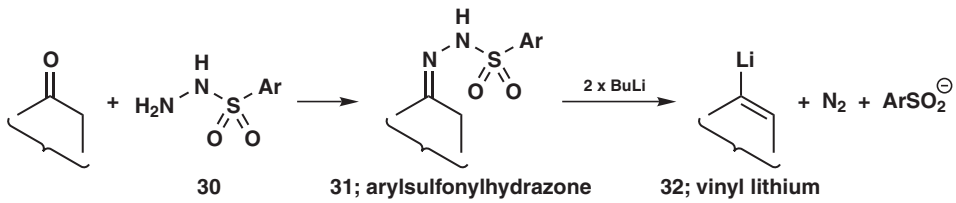
A few more vinyl halides can be made stereospecifically by halogenation and base-catalysed elimination. One example is the vinyl bromide *E*-**28** available by stereospecific *trans* bromination of crotyl alcohol **26** followed by stereospecific elimination.[4] Various regioselectivities are available in the elimination reaction so the formation of that particular alkene is in a way more surprising than the stereopecificity of the reaction. Presumably the bromine atoms increase the acidity of nearby Hs (H-2 and H-3 in *anti*-27) so that one or other of the vinyl bromides will be formed. One explanation is an intramolecular elimination through an *anti-peri*-planar transition state in a chair like conformation using OLi as an internal base **26**. It can reach H-3 in a five-membered cyclic array.



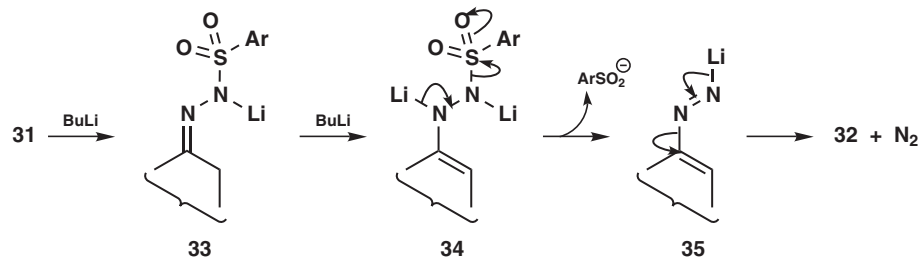
This type of approach is inevitably limited and we need to look at more general methods of making alkenyl-lithiums since these can be converted into all the other reagents we might need.

Vinyl-Lithiums from Ketones: The Shapiro Reaction

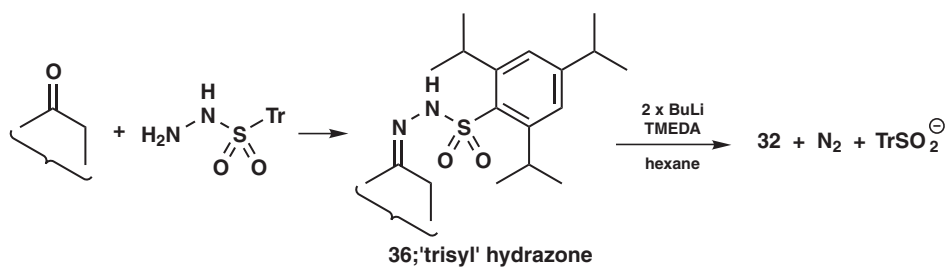
This extraordinary reaction converts a ketone into a vinyl-lithium **32**. First an aryl sulfonyl hydrazone **31** is made by the obvious condensation with the aryl sulfonyl hydrazine **30**. Treatment with two equivalents of butyl-lithium gives the vinyl-lithium.[5]



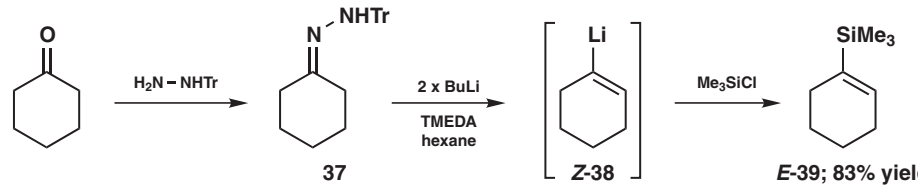
The first equivalent of butyl-lithium removes the rather acidic NH proton to give **33** and the second forms an aza-enolate **34**. It may sound difficult to get two lithium atoms into the same functional group but the necessary sulfonyl group is very electron-withdrawing. Two β-eliminations now occur. The more reactive aza-enolate N−Li bond expels arylsulfinate anion to create an N=N double bond **35**. Note that this is not the usual arylsulf**o**nate ($ArSO_3^-$) containing S(VI) but the lower oxidation state aryl sulf**i**nate ($ArSO_2^-$) containing S(IV). Though not such a good leaving group as sulfonate, it is still good. The remaining N−Li bond now lacks any stabilisation from sulfur and so can initiate the second β-elimination. The main driving force for this reaction is the formation of a molecule of nitrogen. The lithium atom is forced to migrate from nitrogen to carbon to form a vinyl-lithium **32**.



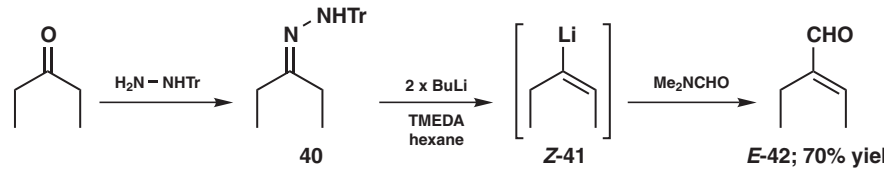
Practically, it is important that the aryl group has no *ortho* hydrogen atoms as competing *ortho*-lithiation (chapter 7) may interfere with the reaction. The favoured aryl group is 2,4,6-tri-isopropyl-phenyl or 'trisyl' shown in the hydrazone **36**. Hydrocarbon solvents such as hexane and addition of ligands for lithium such as TMEDA allow the reaction to go with maximum efficiency.



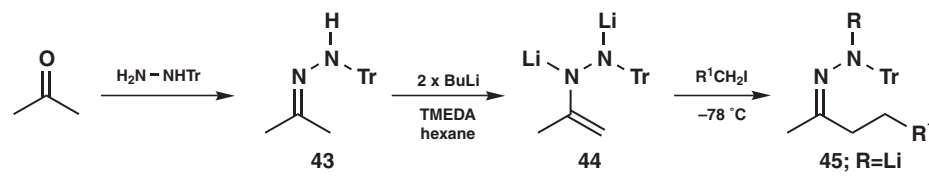
The vinyl-lithium may be combined directly with the carbon electrophile such as an alkyl halide or a carbonyl compound, or converted into another vinyl derivative such as the silane for later development. Many common examples use cyclic ketones. Cyclohexanone gives the *Z*-vinyl-lithium[6] **38** (Li has a *lower* priority than C) and hence the *E*-vinyl silane **39** (Si has a *higher* priority than C) in good yield on trapping with Me_3SiCl.



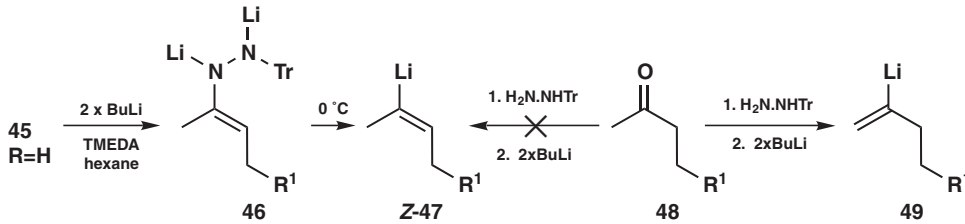
This example has stereochemistry of a sort, but the other isomer is impossible. If the ketone is unsymmetrical, the double bond prefers to go into a methyl group **49**, as one would expect for kinetically controlled aza-enolate formation (chapter 3), so no stereochemistry can be developed there. With symmetrical open-chain ketones, the lithium atom prefers to sit *trans* to the chain giving the *Z*-vinyl-lithium[6] **41**. Reaction with an electrophile, such as DMF, occurs with retention of configuration giving the *trans* product *E*-**42** (this is usually the *E* isomer as the electrophile usually has higher priority than saturated C!).



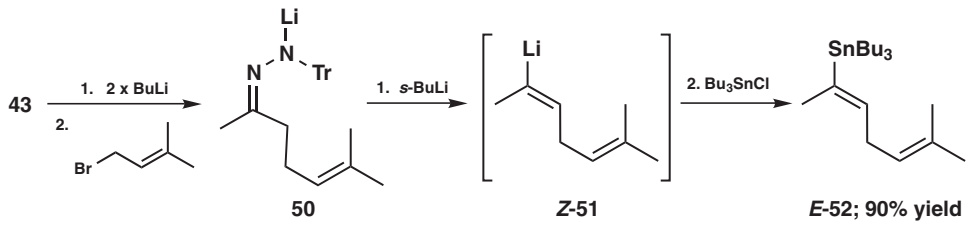
This process is obviously of limited value as the two side chains in the product will always differ by only one carbon atom. There is a way round this difficulty. If acetone trisylhydrazone **43** is converted to the dilithio derivative **44** and alkylated at low temperature, the monolithio-product **45**; R = Li is stable. You may have noticed that we have always drawn the hydrazone with the NTr group on the same side as the double bond. This is no coincidence. When alkylation occurs this configuration of the C=N bond is maintained.



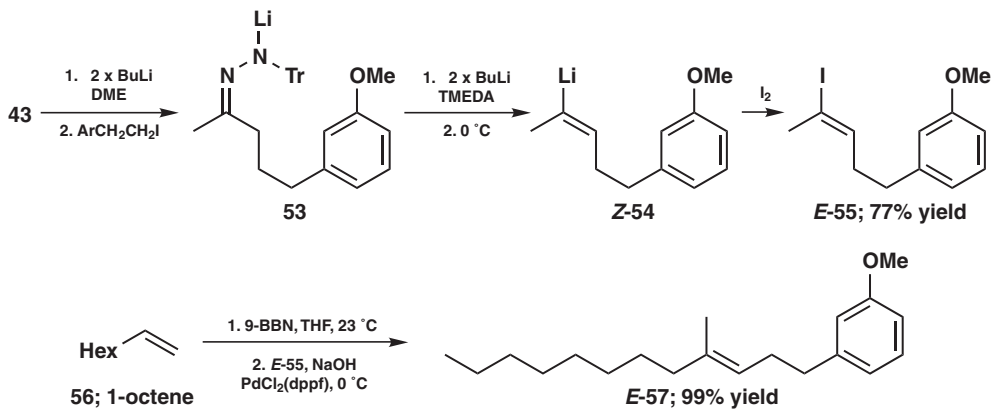
It appears that the lithiation site is determined by the geometry of the C=N bond. When a second (third?) lithiation is induced, it occurs on the same side as the first - and this is now the *more* crowded side **46**. The regiochemistry is determined by the C=N bond but the stereochemistry remains as before. When the Shapiro reaction is allowed to go to completion, by warming to 0 °C, the unsymmetrical *Z*-vinyl lithium *Z*-**47** is produced. This is the isomer that cannot be made by the Shapiro reaction from the methyl ketone **48**.



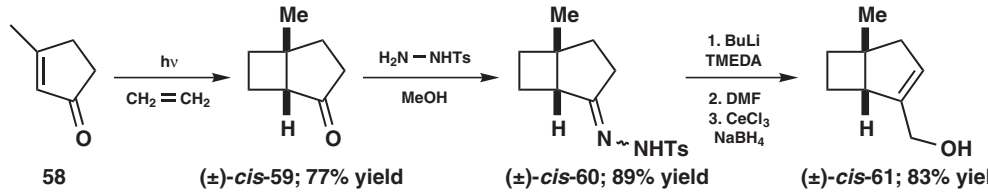
It can be quenched with electrophiles in the usual way. In this example prenyl bromide is the first electrophile giving the stable lithiated hydrazone **50**: the Shapiro reaction gives *Z*-**51** trapped as the vinyl stannane[7] *E*-**52**. The vinyl silane **39** and stannane **52** products from these reactions can be used to make more elaborate alkenes with control over geometry as we shall see later.



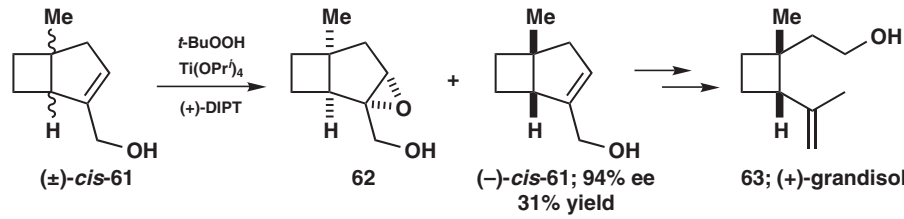
One recent application (that also introduces the next section) is to quench the vinyl-lithium *Z*-**54** with iodine and use the vinyl iodide *E*-**55** in a Suzuki coupling[8] (chapter 18) with a vinyl borane made by hydroboration of an acetylene.[9]



A recent application involving a kinetic resolution (chapter 28) led to an asymmetric synthesis of the cotton boll weevil pheromone grandisol. Photochemical addition of ethylene to the cyclopentenone **58** gives the racemic ketone **59**. The Shapiro reaction using simply tosylhydrazine works well and is completely regioselective in favour of the alkene not at the bridge. Trapping with DMF and Luche reduction gives the allylic alcohol **61**. Attempts to make **61** by other methods gave much worse yields.[10]



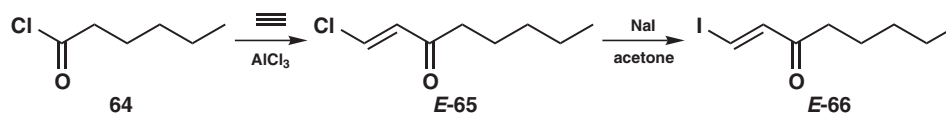
Kinetic resolution (chapter 28) using the Sharpless asymmetric epoxidation with L-(+)-di-isopropyl tartrate (chapter 25) removed the unwanted enantiomer as the epoxide **62** and left the required enantiomer (−)-**61** for transformation into (+)-grandisol **63**.



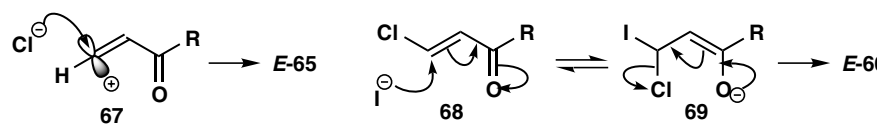
The Shapiro reaction is important and useful but it is limited. We need to explore next a method with a wider scope - vinyl metals made from alkynes. The trick here is to add two things on the same side of the triple bond - typically one is a metal and the other a hydrogen atom or an organic fragment such as an alkyl group.

The Aliphatic Friedel-Crafts Reaction

The application of the aliphatic Friedel-Crafts reaction (chapter 5) to alkynes is a stereoselective approach to vinyl-lithiums that forms a bridge between the Shapiro reaction and the next section-hydrometallation. Acid chlorides **64** react with alkynes under Lewis acid catalysis to give E-β-chloroenones *E*-**65** stereoselectively. The chlorine can be replaced by more reactive iodine by conjugate substitution.[11]

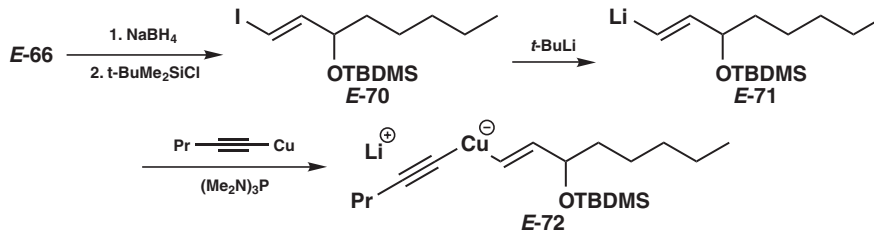


Both these reactions are stereoselective. Chloride prefers to add *anti* to the ketone in the linear vinyl cation intermediate **67**. Rotation of the σ-bond in the enolate intermediate **69** in the conjugate substitution allows loss of chloride to give either the *E*- or the *Z*-vinyl iodide **66**.

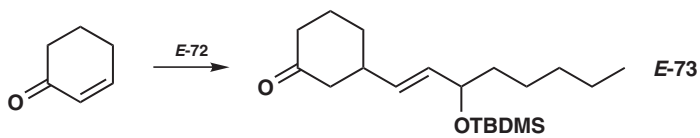


This compound *E*-**66** could be metallated with lithium directly but it would then destroy itself by reaction with its own keto group so reduction and protection first gives the silyl ether *E*-**70**. This vinyl iodide was converted into a vinyl-lithium *E*-**71** and then into a vinyl cuprate *E*-**72** for

conjugate addition. We shall have more to say about these reactions below but note at this stage that both occur with retention of configuration at the alkene.



Conjugate addition to cyclohexenone occurred very efficiently to give *E*-**73** in 80% yield. It can be argued that both ends of the alkene in this product were linked to the rest of the molecule by vinyl anion additions to electrophiles.[12]

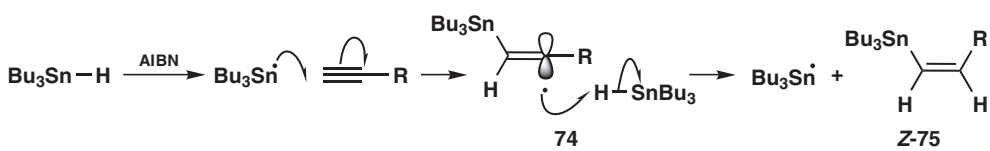


Hydrometallation of Alkynes

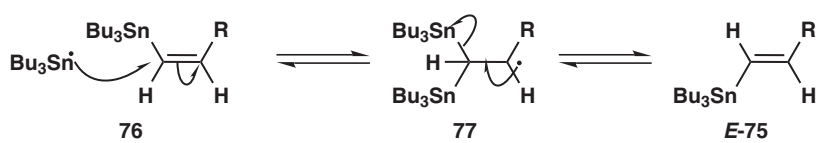
There are broadly three groups of metals that do this reaction. Some such as tin hydrides do so by a radical mechanism, boron and silicon by hydroboration-style reactions, and transition metals such as zirconium by π-complex formation. We shall take them in that order.

Hydrostannylation of terminal alkynes

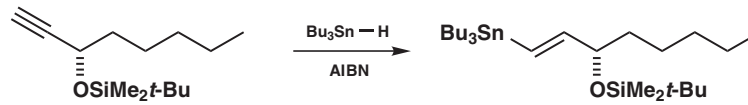
Tin hydrides readily form radicals. Typically Bu_3SnH reacts with AIBN to give tin radicals that add to alkynes at the unsubstituted end to give the more substituted vinyl radical. The vinyl radical captures a hydrogen atom **74** from another molecule of Bu_3SnH to produce another tin radical and complete the chain. The other product is a vinyl stannane *Z*-**75**. Here is the complete scheme:



This reaction shows a remarkable stereoselectivity. The kinetic product is the *Z*-alkenyl stannane *Z*-**75**. This is easily explained by arguments similar to those we used in chapter 15. The vinyl radical is on a linear (sp hybridised) carbon and reaction with a large reagent like Bu_3SnH occurs preferentially on the less hindered side **74**. This gives the *Z*-alkene *Z*-**75**. If the reaction is carried out at higher temperatures or with an excess of Bu_3SnH the *E*-alkenyl stannane *E*-**75** becomes the product. This is obviously the thermodynamic product and equilibration occurs by repeated addition **76** and loss **77** of Bu_3Sn• radicals to the vinyl stannane.



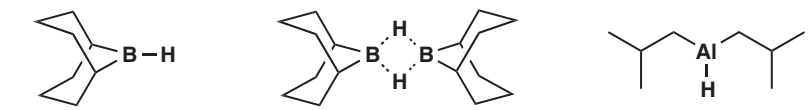
This example of the commoner thermodynamic route was used by Corey[13] in the synthesis of prostaglandins as described below.



78 ***E*-79**

Hydroboration and Hydroalumination of Alkynes

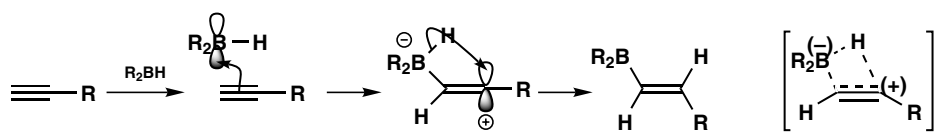
Boron and aluminium are group three (13) elements so their hydrides R_2BH and R_2AlH are dimers e.g. **81** linked by hydrogen bonds. Two useful compounds are 9-BBN **80** (9-BoraBicyclo[3.3.1]-nonane) and DIBAL **82** (Di-IsoButylALuminium hydride, also known as DIBAH). Because of their large alkyl substituents these compounds are reasonably stable and can be bought. In solution they are in equilibrium with their monomeric forms which are active hydro-boration and -alumination reagents for triple bonds. The monomers **80** and **82** are trigonal with an empty p-orbital on the B or Al atom.



80; 9-BBN monomer **81; 9-BBN dimer** **82; DIBAL monomer**

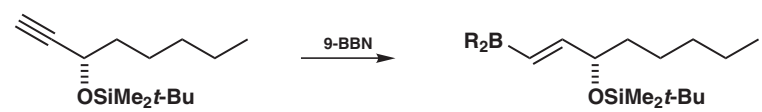
Hydroboration of alkynes

They react with terminal alkynes by electrophilic addition of the empty p-orbital to the unsubstituted end of the triple bond **83**. The intermediate would then be the more substituted vinyl cation **84**. It is easier to draw this mechanism with R_2BH than with the full structure for 9-BBN. The intermediate **84** is not fully formed before hydride transfer begins so that the reaction is semi-concerted and the transition state is something like **86**. The result is a regioselective and stereospecific *cis* hydroboration of the triple bond to give the *E*-vinyl borane **85**. The intermediate **84** is quite like the radical intermediate in hydrostannylation but the difference is that hydrogen transfer is intramolecular and stereospecific in hydroboration.



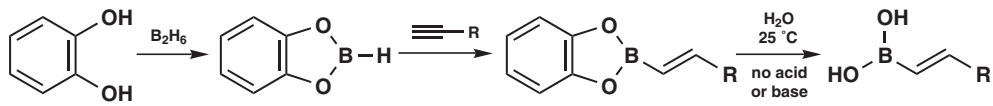
83 **84** **85** **86**

Here is a simple example in the field of prostaglandin synthesis where 9-BBN was used on a protected optically active propargyl alcohol.[12] The starting material is identical to the alkyne **78** that we reacted with Bu_3SnH above and the result is the same - *cis* hydrometallation with the metal atom at the terminus. However that was a thermodynamically controlled stereoselective radical chain reaction while this is a kinetically controlled stereospecific electrophilic addition to give the vinyl borane *E*-**87**.



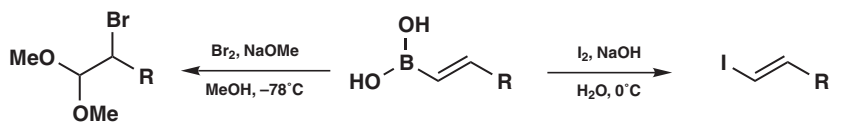
78 ***E*-87**

Of recent years, boronic acids $RB(OH)_2$ have become important in Suzuki couplings (chapter 18) and they too can be made by hydroboration of alkynes. Catechol borane[14] **89** is prepared from catechol **88** and diborane - a typical reaction of boranes with acidic OH groups to give stable B–O bonds - and is available commercially as a solution in THF. Hydroboration of an alkyne with catechol borane shows the usual regioselectivity and stereospecificity to give a terminal *E*-vinyl boronate ester[15] **90** and hydrolysis of the ester under very mild conditions[14] (room temperature, no acid or base) gives the boronic acid[16] **91**. We shall see later that you can argue whether these compounds can be considered as vinyl *anion* equivalents, but it seems sensible to discuss their preparation at this point.



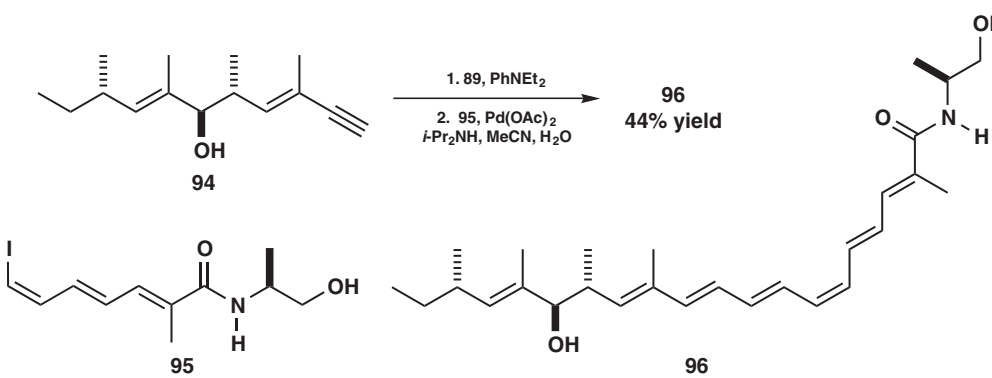
88; catechol **89; catechol borane** ***E*-90** ***E*-91; boronic acid**

Treatment with iodine gives the *E*-vinyl iodides **93** stereospecifically and quantitatively. There is no doubt that these intermediates act as vinyl anion equivalents after exchange of the iodine for a metal. With bromine in methanol, protected 2-bromo aldehydes **92** are formed in good yield.[16]



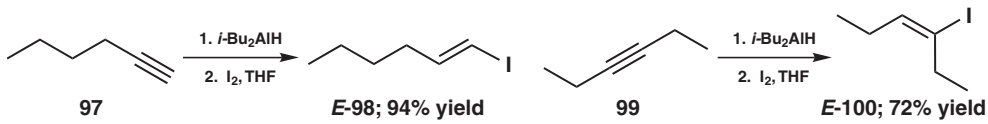
92; 90-94% yield ***E*-91; boronic acid** ***E*-93; 100% yield**

A dramatic example of this technique is the last step of Heathcock's synthesis of myxalamide A **96**. Hydroboration of the alkyne **94** with catechol borane gives the *E*-vinyl borane and this is combined with the *Z*-vinyl iodide **95** in a palladium-catalysed Suzuki coupling to give the natural product **96** with every alkene correct.[17]



Hydroalumination of alkynes

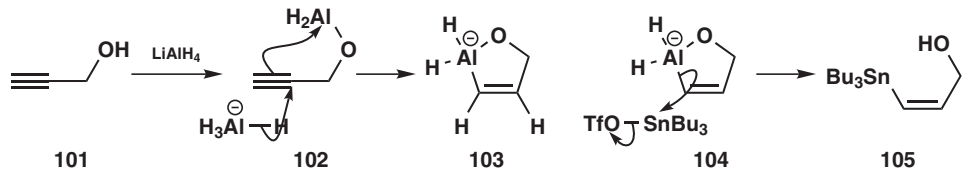
Reactions of terminal alkynes with DIBAL are very similar - *syn* addition leads to the *E*-vinyl alane and hence, by exchange with iodine or bromine, to *E*-vinyl halides.[18]



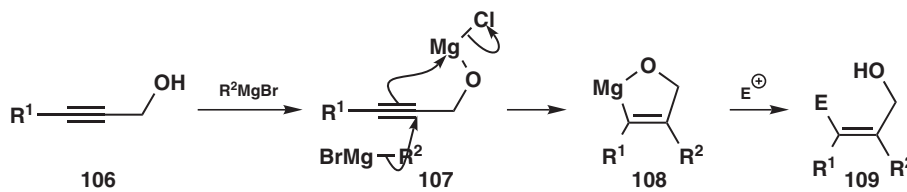
97 ***E*-98; 94% yield** **99** ***E*-100; 72% yield**

Hydroalumination of propargyl alcohols

Reduction of acetylenes does not usually occur with $LiAlH_4$ but reduction of propargyl alcohols **101** with $LiAlH_4$ occurs through a cyclic aluminium σ-complex **103** and is well controlled stereochemically. If the σ-complex **104** is trapped with an electrophile such as halogens or Bu_3SnOTf, a simple *Z*-vinyl derivative, e.g. **105** results with a useful OH group for further development.[19] The kinetic route to *Z*-vinyl stannanes above is a radical reaction and more difficult to control so it is just as well that there is a good route to a simple *Z*-vinyl stannane by a non-radical reaction.

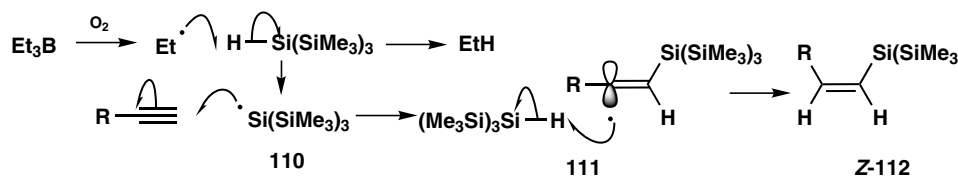


A similar process occurs with Grignard reagents.[20] Though this is strictly carbometallation, the subject of the next section, it is very similar mechanistically to the reduction with $LiAlH_4$. One magnesium atom guides a second Grignard reagent into the alkyne **106** to form the metallocycle **108** and hence, by reaction with, say, halogens, derivatives **109** with R^1 and R^2 *cis* (*E* or *Z* depending on priorities!). Two molecules of $LiAlH_4$ or R^2MgBr are needed and the intermediates **103** and **108** are vinyl anion equivalents.



Hydrosilylation

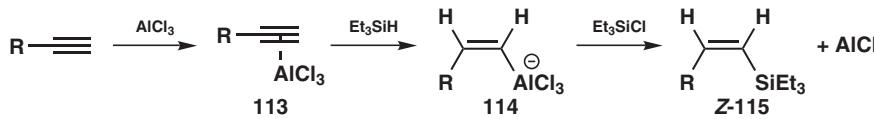
The reaction of alkynes with R_3SiH can take place by three different mechanisms: radical, ionic catalysed by Lewis acids, and ionic catalysed by transition metals.[21] The radical method is best with tris(trimethylsilyl) silane, a reagent introduced originally to take toxic tin out of radical chemistry. Promoted by Et_3B in the presence of oxygen the stable radical **110** adds to the alkyne to give the linear radical **111** that collects a hydrogen atom from another molecule of tris(trimethylsilyl) silane to complete the cycle. As in the formation of vinyl stannanes **75** the large reagent delivers hydrogen *anti* to the large $Si(SiMe_3)_3$ substituent.[22] Typical *Z:E* selectivity is >20:1. The products **112** can be converted into *Z*-vinyl bromides by reaction with bromine in CH_2Cl_2 at 25 °C.



Hydrosilylation of alkynes catalysed by Lewis acids

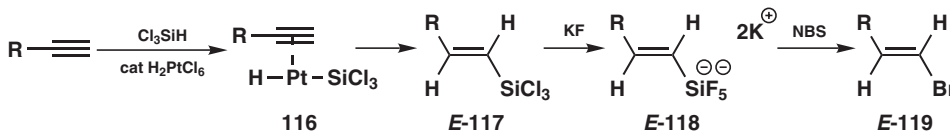
Lewis acid-catalysed addition of Et_3SiH (Me_3SiH cannot be used as it is unstable) also gives the *Z*-vinyl silane **115**. This is *trans* addition to the alkyne and probably occurs by 'H^-' transfer to the

π-complex **113** followed by electrophilic substitution of the 'ate' complex **114** with retention of configuration. The substituent R can be alkyl or aryl and can have an alkyloxy functionality.[23]

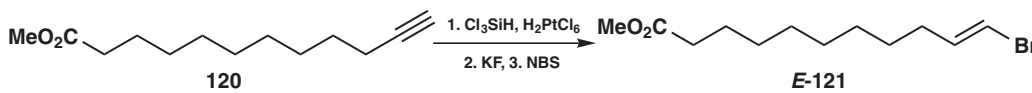


Hydrosilylation of alkynes catalysed by transition metals

The commonest combination here is trichlorosilane with H_2PtCl_6 as catalyst. *Cis* addition of the silane is preferred, probably *via* a metal complex such as **116**, giving the *E*-vinyl silane **117**. The $SiCl_3$ group is not easily replaced but the dianion **118** formed with KF reacts cleanly with NBS to give the *E*-vinyl bromide **119** with retention of configuration.[24]

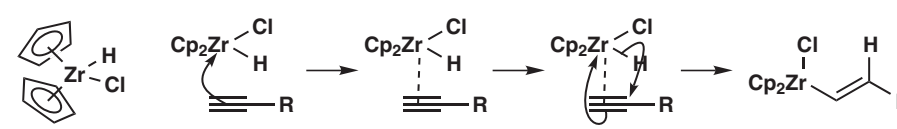


R can be alkyl or aryl and can carry various functional groups such as the ester in **120**. The vinyl bromide *E*-**121** is formed in 68% yield and is >95:5 *E:Z*. However other transition metals may give the *Z*-vinyl silane as is the case with Et_3SiH and an Ir(I) catalyst.[25] Yet other transition metals give the opposite regioselectivity as with Et_3SiH and a Ru(I) catalyst.[26] The best advice is to use conditions already determined by reliable workers.

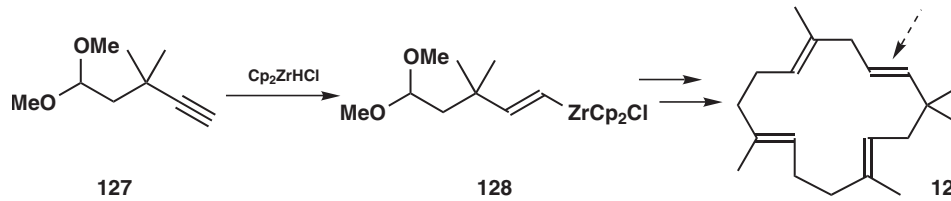


Hydrozirconation

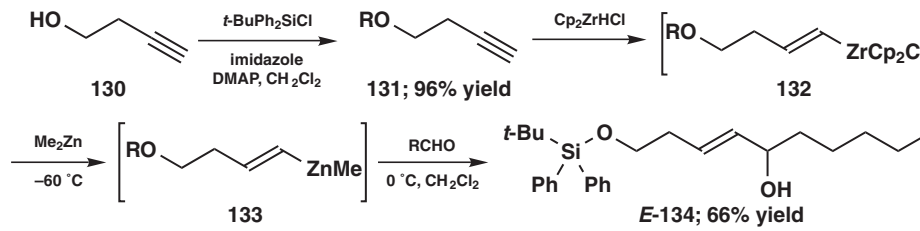
Among transition metals, zirconium is the most important for hydrometallation of alkynes. The available 16 electron complex Cp_2ZrHCl (Cp = cyclopentadienyl) **122** (zirconocene hydrochloride) adds stereoselectively *syn* to alkynes to give the *E*-vinyl zirconium species **126**. The initial interaction is the donation of two electrons by the triple bond **123** to make the reasonably stable 18-electron π-complex (or η^2-complex) **124**. Typically for a transition metal π-complex, a ligand is now transferred from the metal to one end of the π-bond **125** while the metal itself forms a stable 16-electron σ-complex at the other **126**. The H transfer is intramolecular so the metal and H atoms must add to the same side of the triple bond. The zirconium atom transfers the least stable anion among its ligands. This is obviously H^- as Cl^- is much more stable. The metal prefers to take the terminal position because the resulting σ-complex is more stable as it is a σ-complex of the less-substituted carbanion.[27]



Here is an example from the McMurry flexibilene synthesis quoted in chapter 1. An alkyne **127** with a protected aldehyde group reacts with Cp_2ZrHCl to give a vinyl zirconium complex **128** which is coupled to a palladium-allyl complex in the next step. The *E* double bond so produced is present with the same *E* configuration in the final product. It is marked **129** with an arrow in the diagram.[28]



Exchange of the zirconium for zinc allows addition to carbonyl compounds. A free alcohol group, as in **130**, must be protected and the zirconium in the initial product **132** replaced by zinc before the aldehyde is added to give the allylic alcohol **134**. Both reactions occur with retention of configuration.[29]



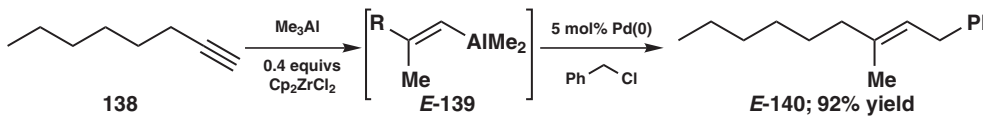
Carbo-Metallation

Some of the metals we have been discussing can be used for the simultaneous *cis*-addition of an alkyl or aryl group and a metal to an alkyne.[30] This process is called carbometallation and involves particularly Li, Mg, Al, Cu, and Zn.

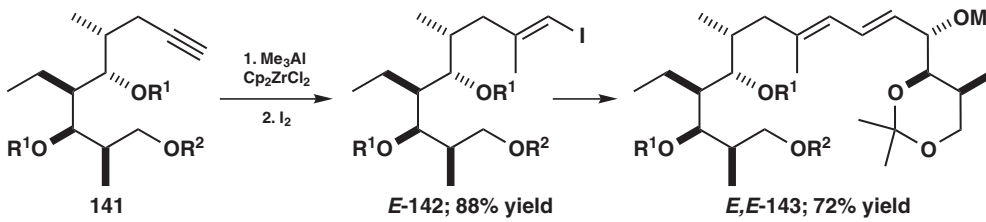
Carboalumination

Trialkyl aluminiums are not reactive enough to add to alkynes but do with catalysis particularly from Cp_2ZrCl_2. In reaction with Me_3Al, the methyl and the $AlMe_2$ groups are added to the same side of the triple bond to give an unstable alkenyl aluminium *E*-**136** that is reacted immediately with an electrophile to give the product *E*-**137** with retention of configuration.[31] The mechanism is uncertain but almost certainly involves transfer of a methyl group from zirconium in a π-complex such as **135** with a number of chloride ligands on one or both metals, or even between them.[32]

Palladium-catalysed coupling of such an intermediate *E*-**139** with benzyl chloride gives the trisubstituted alkene *E*-**140** as the only product in high yield.[33]



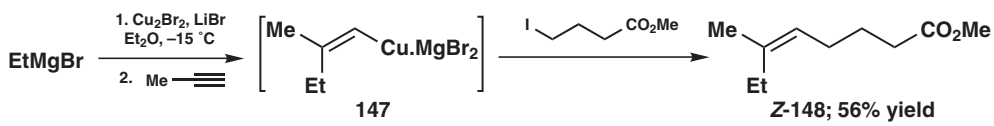
A recent application to the synthesis of the macrolide antibiotic concanamycin used carbometallation of the alkyne **141** to give the vinyl iodide *E*-**142** followed by a palladium-catalysed coupling with a vinyl stannane, also created from an alkyne, to give the diene[34] *E,E*-**143**.



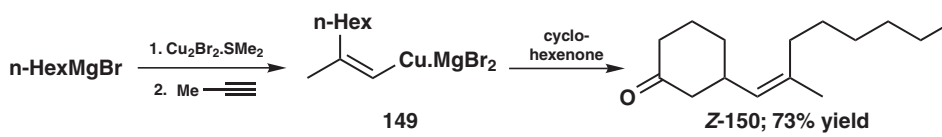
Carbocupration

Various organo-copper compounds carry out carbocupration of alkynes without any extra catalyst. The reagents may be RCu (usually with some ligand such as Me_2S), Grignard reagents with added Cu(I), or any of the more complex cuprates also used in conjugate addition (chapter 9). *Cis* addition is the rule with the metal ending up on the terminal carbon atom[35] *E*-**145**.

The electrophile (E in *E*-**146**) can be an alkyl halide, acid chloride, conjugated carbonyl compound and so on. A simple example illustrating the use of a functionalised alkyl halide, produces the *Z*-alkene **148** as the larger group is added by carbocupration.[36] Addition in the reverse order would have given *E*-**148**.

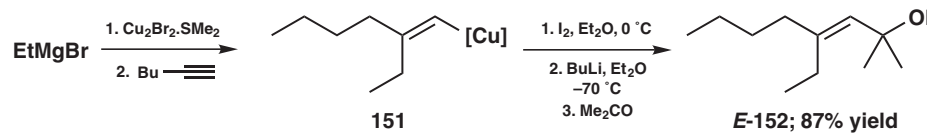


We expect vinyl copper derivatives to be best at conjugate addition but we are disappointed at the few enones that react satisfactorily. Carbocupration of propyne with n-hexylcopper gives the intermediate **149** that adds to cyclohexenone with retention of the *Z*-configuration to give the conjugate addition product[37] **150.** With open chain enones results are not so good.



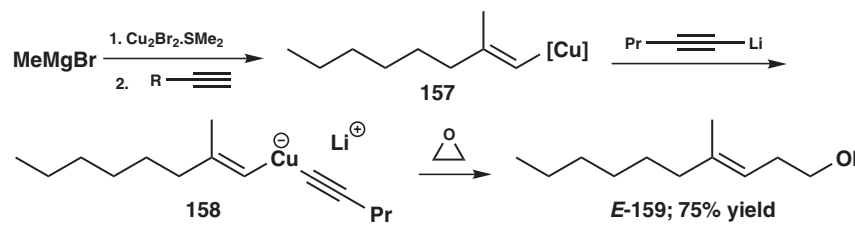
Reactions of Vinyl Sn, B, Al, Si, and Zr Reagents with Electrophiles

So far we have given an assortment of ways these vinyl metals might be used in synthesis as vinyl anion equivalents. Now it is time to consider their reactions in more detail. One of the commonest ways, and certainly the most obvious way in which they act as vinyl anions, is to transform them into vinyl-lithium reagents. This can be done directly or via halogenation. After carbocupration, exchange with iodine and then lithium gives a vinyl-lithium that reacts cleanly with enolisable aldehydes and ketones to give allylic alcohols, e.g. *E*-**152**, all with retention of configuration.[38]

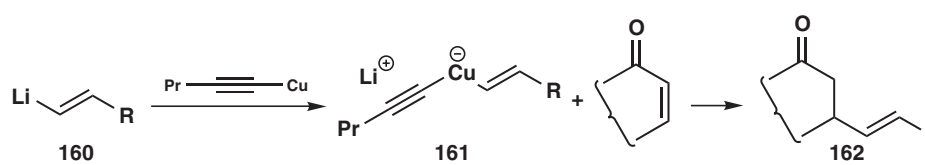


Treatment of vinyl Sn, B, or Al compounds with BuLi results in effective addition of Bu^- to the metal to form a hypervalent anion such as **154**. These are often referred to as "ate" complexes. The analogy is with the names of anions such as sulf*ate* or carbon*ate*. You are already familiar with the copper analogues, usually called cupr*ates*. Lithium now replaces tin at the vinyl group **155** to form a vinyl-lithium derivative *E*-**156**. The reaction is an electrophilic substitution at carbon - the lithium atom attacks the C-Sn bond and does so with retention of configuration.

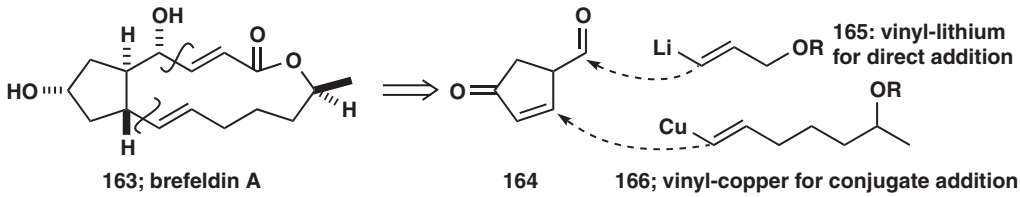
Vinyl copper derivatives such as **157** do not react with epoxides but transformation of the vinyl copper into a cuprate by the addition of pentynyl lithium gives a cuprate that preferentially transfers the vinyl group (the *less* stable anion is transferred from copper) to ethylene oxide to give the homoallylic alcohol[39] *E*-**159**. Note that **157** has the opposite stereochemistry to **149**.



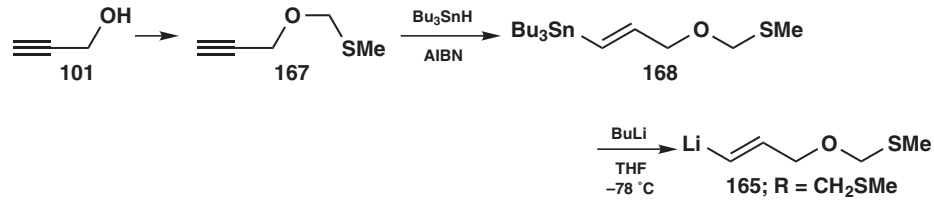
A lithium atom may also be replaced by copper to make a cuprate **161**. As in the previous example, using pentynyl copper ensures that no vinyl group is wasted. Such cuprates are superior to simple copper derivatives in conjugate addition to give **162** with enones. All these reactions happen with retention at the vinylic carbon.



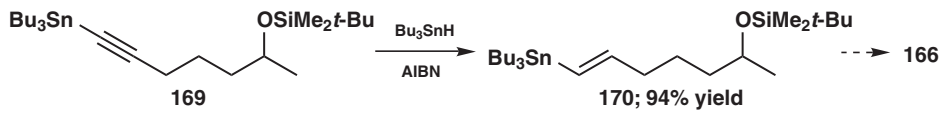
An excellent illustration of both these types of vinyl anion equivalent appears in Corey and Wollenberg's synthesis[40] of the antibiotic brefeldin A **163**. This interesting molecule has two *E*-alkenes, one attached to a hydroxyl group as an allylic alcohol, and so accessible by direct addition of a vinyl lithium **165** to an aldehyde, and one in a 1,3-relationship with an alcohol and so accessible in theory by conjugate addition of a vinyl copper (or cuprate) **166** to the simple double electrophile **164**. Each OH group must be protected.



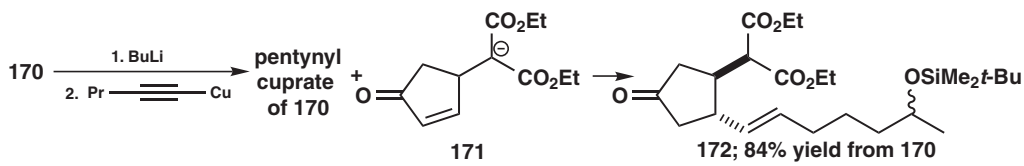
Each vinyl metal reagent was prepared by thermodynamic hydrostannylation of the corresponding alkyne.[41,42] The simpler lithium derivative **165**; R = CH_2SMe came from the protected propargyl alcohol **167**.



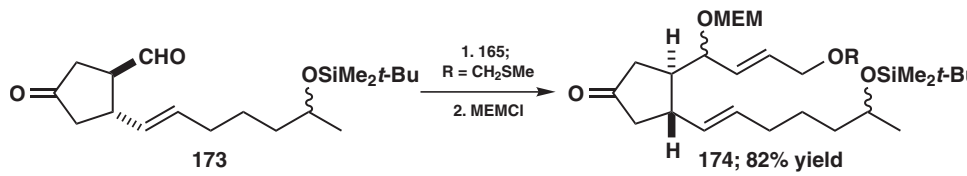
The vinyl stannane **170** for the copper derivative came from another protected alcohol **169** by a similar route but the protecting groups were made quite different so that they could be removed selectively.



The vinyl stannane **170** was converted into the vinyl-lithium and then the vinyl cuprate as described for **161** and added to the enolate anion of **171**. Notice the protection of the malonate ester group in **162** by deprotonation with sodium hydride. The product **172** is all *anti* across the five-membered ring and all *E*, but there is of course no control at the remote stereogenic centre on the side chain.

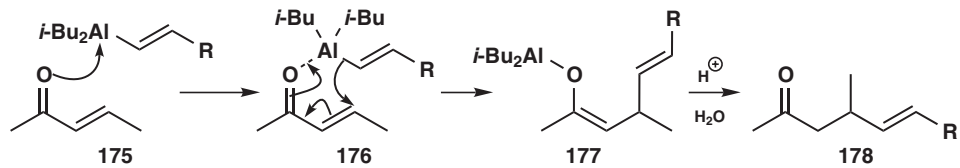


Functional group manipulation now gives the aldehyde **173** ready for addition to the vinyl-lithium reagent **165**. The product was trapped as the MEM (methoxy-ethoxy-methyl-) derivative **174** in a very high yield but without any stereoselectivity. Fortunately, Corey already knew how to control the stereochemistry at the two OH groups by oxidation to ketones and stereoselective reduction so the synthesis could be completed.

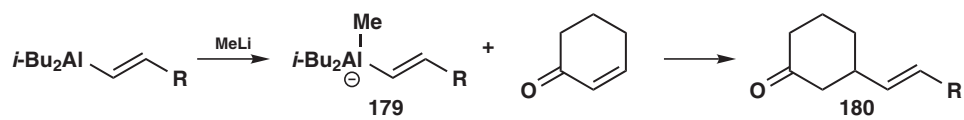


Reactivity of vinyl alanes

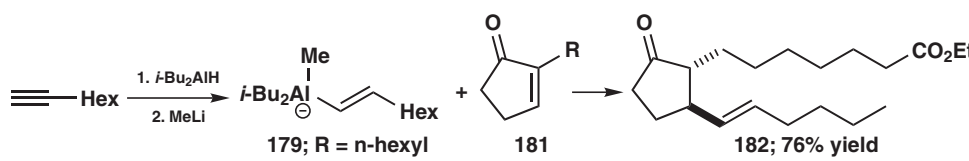
Vinyl aluminium compounds also carry out conjugate additions and illustrate well the difference in reactivity between vinyl alanes and the related "ate" complexes. If the enone can adopt the s-*cis* conformation, as in **175**, a cyclic mechanism is possible in which aluminium both acts as a Lewis acid and delivers the vinyl nucleophile. Notice that the *E*-vinyl alane leads to the *E*-γ,δ-unsaturated ketone **178** as this is again an S_E2 reaction at the vinyl carbon.[32]



If the enone cannot adopt the s-*cis* conformation, it is necessary to convert the vinyl alane into an "ate" complex **179** before conjugate addition. Conjugate addition now occurs to s-*trans* enones, such as cyclic enones, to give the *E*-γ,δ-unsaturated ketone **180** after aqueous work-up. Notice that this time the most stable anion is transferred - the choice is between Me, *i*-Bu, or vinyl. Aluminium is not a transition metal and simply releases the most stable anion as there must be some negative charge on the group being transferred.

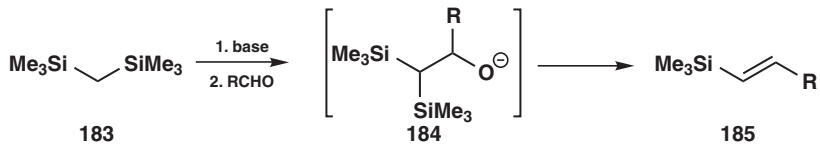


We have already seen examples of cuprates being used in stereochemically controlled conjugate additions to cyclopentenones and similar results can be achieved with ate complexes of vinyl alanes prepared by hydroalumination of alkynes to give e.g. **179**; R = hexyl and hence the *anti*-*E*-product[43] **182**.



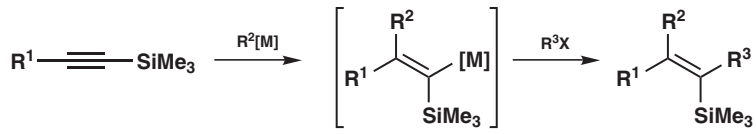
Preparation of vinyl silanes

We have seen that vinyl silanes can be prepared by hydrosilylation of alkynes by three different mechanisms giving good control over geometry of these inevitably terminal vinyl silanes. Vinyl silanes are stable compounds and can be isolated, unlike most of the vinyl metals we have seen so far, and other ways of making vinyl silanes allow the more-or-less controlled synthesis of mono- or trisubstituted compounds with reasonable control over selectivity. These include the Peterson reaction with two $SiMe_3$ groups on the same carbon atom **183** and, more relevant to this chapter, reactions of vinyl lithiums with silyl chlorides.[44]



183 184 185

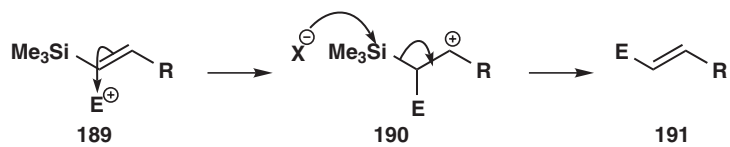
Hydrometallation or carbometallation of alkynyl silanes **186** is easier because of the presence of the silicon atom as the metal prefers to be at the silylated end of the resulting alkene **187**. Trapping these intermediates with electrophiles allows the stereochemically controlled synthesis of almost any vinyl silane **188**. The metal can be Li, Mg, Al, or Cu and both **187** and **188** are single geometrical isomers (whether *E* or *Z* depends on priorities of M and the various R groups).[30]



186 187 188

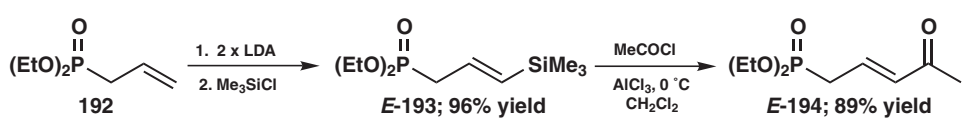
Reactions of vinyl silanes

Vinyl silanes resemble alkenes in reactivity: they combine with reactive electrophiles such as bromine without catalysis but need Lewis acid catalysis for reaction with carbon electrophiles. Reaction usually occurs **189** at the silyl end of the alkene so that the intermediate **190** enjoys the β-silyl stabilisation of the carbocation. The silyl group is removed by a nucleophile, usually a halide ion.[45]



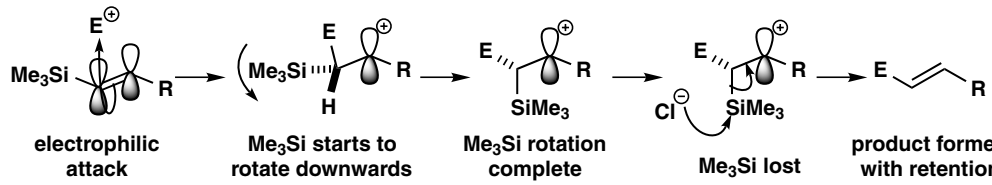
189 190 191

If the electrophile also benefits from Lewis acid catalysis, as in the aliphatic Friedel-Crafts reaction, good yields of products are generally found. The anion of the allyl phosphonate **192** can be silylated to give the vinyl silane **193** and this reacts in turn with the classical combination of acetyl chloride and $AlCl_3$ to give the enone *E*-**194** that can be used in HWE reactions to make dienones[46] (chapter 15).

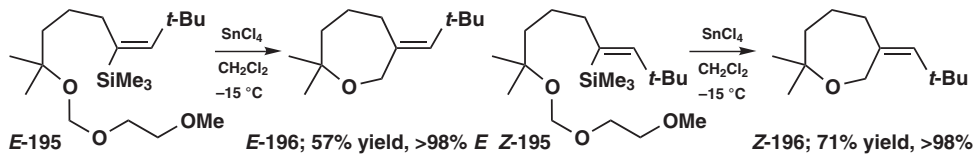


192 *E*-193; 96% yield *E*-194; 89% yield

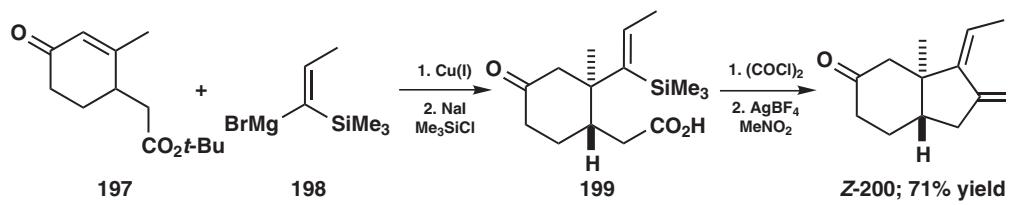
The conversion of **193** to **194** occurs with retention of configuration. Many such reactions give only the more stable of the two possible products, depending on the lifetime of the β-silyl cation **190**. In favourable circumstances the reaction is stereospecific with retention. The initial attack of the electrophile occurs on either face of the alkene by interaction with the π-bond. As the new C−E bond is formed the Me_3Si group starts to rotate away from the electrophile as the C-atom becomes tetrahedral. This rotation continues until the C−Si bond is parallel with the empty p-orbital on the other carbon atom and then stops. Loss of the Me_3Si group gives the product with retention of alkene geometry.



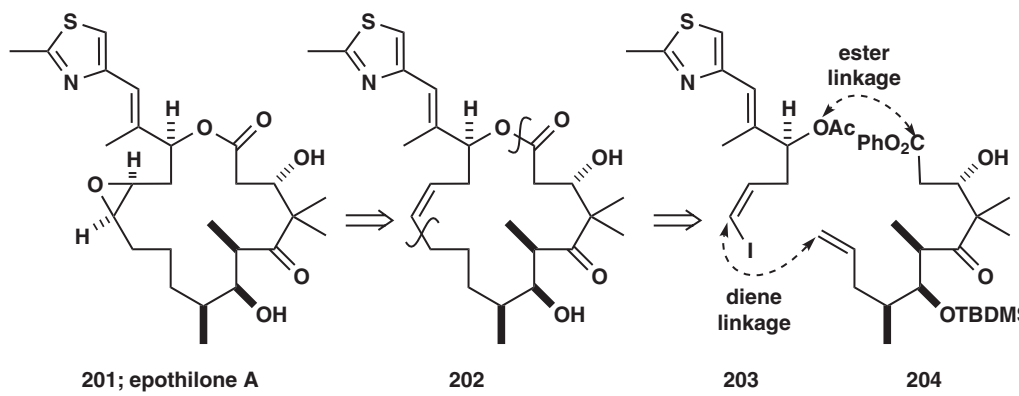
Of course, if the intermediate cation, stabilised by the β-silyl cation effect, has a lifetime long enough to allow rotation about the C−C bond, the stereochemical information is lost. Clear-cut examples with retention are often intramolecular and the most valuable are those that create an exocyclic alkene. A famous example is the cyclisation of the two acetals *E*- and *Z*-**195** with $SnCl_4$ as the Lewis acid to give reasonable yields of the oxepanes **196** with complete retention of configuration at the exocyclic alkene.[47]



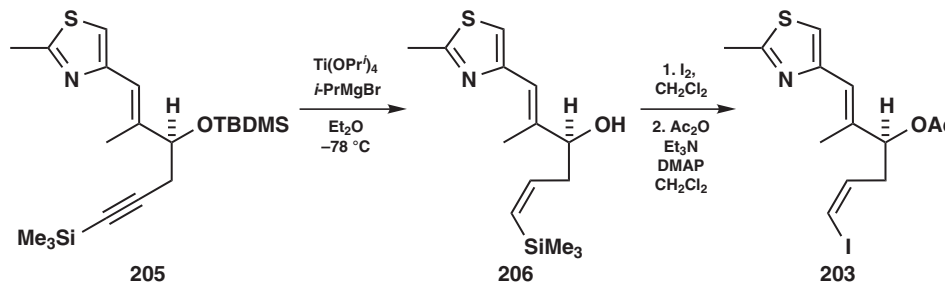
The lifetime of the key intermediate can sometimes be controlled by choice of Lewis acid. Copper-catalysed conjugate addition of the vinyl Grignard reagent **198** to the enone **197** gives the *anti* adduct **199** as expected. Intramolecular Friedel-Crafts reaction of the corresponding acid chloride with $AgBF_4$ as this Lewis acid gave only the less stable *Z*-enone **200** but other Lewis acids such as $TiCl_4$ gave *E*/*Z* mixtures.[48]



Even replacement of silicon by a humble halide can be important in complex syntheses. The epothilones, e.g. **201**, are anti-cancer compounds of some promise. Chemoselective epoxidation of intermediate **202** is possible and Shibasaki decided to disconnect at the obvious ester and the far less obvious diene requiring a C−C bond to be made stereoselectively between two alkenes[49] **203** and **204**.



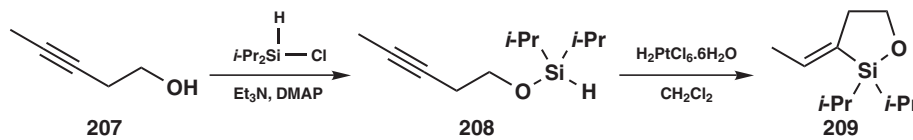
Each half of the molecule was made as a single enantiomer by catalytic asymmetric synthesis. We are concerned with the vinyl iodide **203**. The obvious reduction of **205** with DIBAL failed and instead hydrotitanation gave the *Z*-vinyl silane **206**. Replacement of Me_3Si with iodine was regio- and stereospecific giving only the *Z*-vinyl iodide in 59% yield.



205 **206** **203**

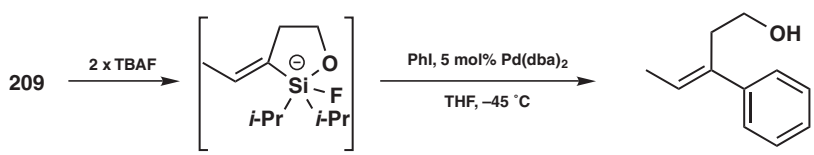
'Ate' complexes from vinyl silanes

As we have seen with *E*-**118**, 'ate' complexes with two negative charges on silicon are possible and so it should come as no surprise that one fluoride ion can be added to most silyl groups to give an 'ate' complex with just one negative charge. These complexes now have a C−Si bond of greater nucleophilicity than the π-bond and so behave like the other vinyl metals in this chapter. Silylation of the alcohol **207** with a silyl halide having a Si−H bond opens the way for Pt-catalysed intramolecular hydrosilylation (cf. above) to give only the *E*-vinyl silane[50] **209**.



207 **208** **209**

Addition of fluoride (as TBAF, the salt Bu_4NF) gives the 'ate' complex **210** that couples with aryl and alkenyl halides to give a single isomer of a trisubstituted unsaturated alcohol, e.g. **202**, with retention at the alkene.



210 ***E*-211; 88% yield**

The scope of vinyl metals as sources of nucleophilic vinyl groups is very great. As well as the expected electrophiles such as halogens, alkyl and acyl halides, aldehydes and ketones, unsaturated carbonyl compounds and epoxides, they also combine with aryl and alkenyl halides with palladium catalysis. The usual stereochemical course is retention at the vinyl group. It is necessary to decide whether the vinyl metal is reactive enough or whether it must first be transformed into an 'ate' complex. Since most of these vinyl metals can be converted into each other with retention, this is an unusually versatile group of reagents.

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General references are given on page 893

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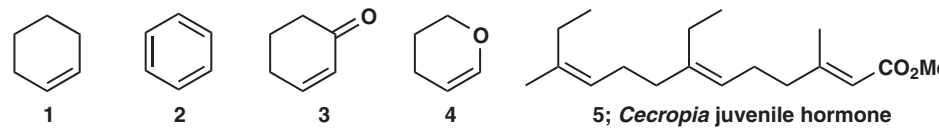
17 Electrophilic Attack on Alkenes

Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

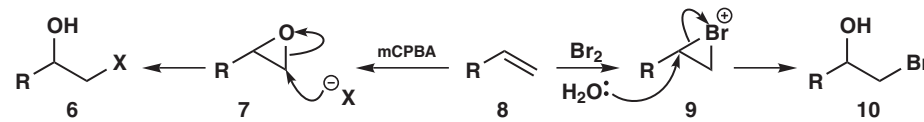
Introduction: *Chemo-, Regio-, and Stereoselectivity*

The last two chapters have been concerned with making alkenes of known stereochemistry. An important reason for wanting to do this is that alkenes have unusual potential as starting materials for making polyfunctional compounds with control over all aspects of selectivity.



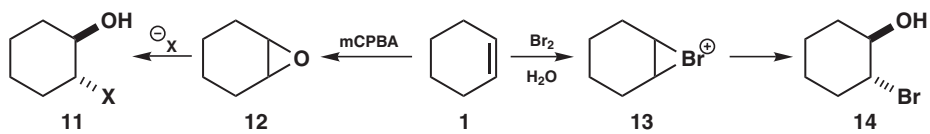
1 **2** **3** **4** **5; *Cecropia* juvenile hormone**

Chemoselectivity is often easy to control in alkenes because the alkene is a "weak" functional group. It does have inherent reactivity with electrophiles such as bromine but when another functional group, whether electron-donating or electron-withdrawing, is conjugated to the alkene, the reactivity is normally dominated by the other functional group. Compounds 2–4 would normally not be described as alkenes but as benzene, an enone, and an enol ether. But they are all alkenes. You will already know many reactions that would happen with one of these compounds and not at all with another. The triene **5** has three alkenes in the same molecule and we shall want to react just one and not the others. Chemoselectivity.



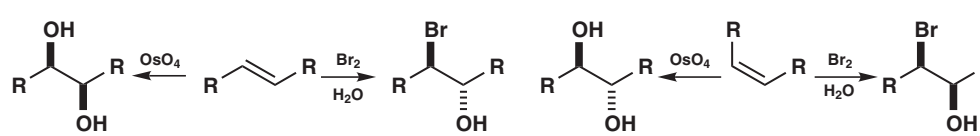
6 **7** **8** **9** **10**

Regioselectivity usually arises when an unsymmetrical electrophile attacks an unsymmetrical alkene. Familiar examples would be the action of bromine water or peroxyacids on a terminal alkene **8**. The intermediate bromonium ion would be attacked by water at the *more* substituted end **9** and the epoxide by a nucleophile at the *less* substituted end **7**.



11 **12** **1** **13** **14**

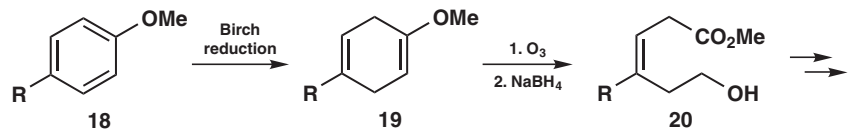
Stereoselectivity comes from a stereospecific *syn* or *anti* addition to an alkene of fixed and known geometry. These last reactions, applied to cyclohexene, lead to *anti* bromohydrin **14** while epoxidation occurs stereospecifically and *syn*. It doesn't matter which *end* of the epoxide **12** or bromonium ion **13** is attacked by the nucleophile: *anti* addition occurs in both cases since inversion is demanded by the mechanism of the S_N2 reaction. Cyclohexene must be *Z* but in open chain compounds *syn* addition to the *E*-isomer would lead to the same diastereoisomer of the product as *anti* addition to the *Z*-isomer. In this chapter we explore more advanced versions of these reactions in which usually several types of selectivity will be combined and show how they are used in synthesis.



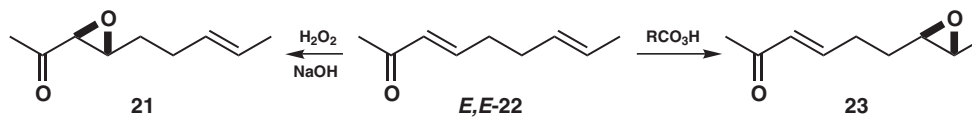
***syn*-15** ***E*-16** ***anti*-17** ***anti*-15** ***Z*-16** ***syn*-17**

Chemoselectivity

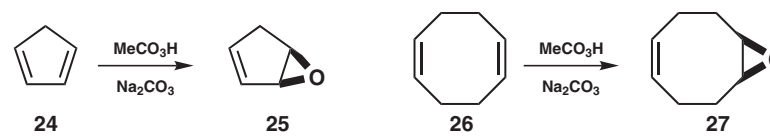
The commonest form of chemoselectivity involves the preferential attack of electrophiles on electron-rich alkenes as in the ozonation of a Birch reduction product **19** used in chapter 15 to make a *Z*-alkene *Z*-**20**; R=Me and hence *Cecropia* juvenile hormone **5**.



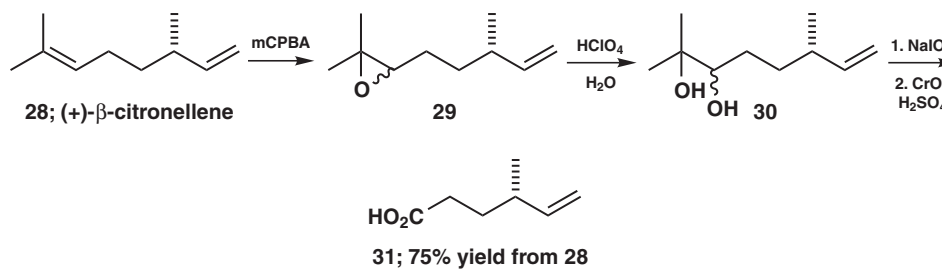
The alkene that is attacked is an enol ether and is much more nucleophilic than the other simple alkene. Similarly nucleophilic reagents attack only alkenes that are conjugated with an electron-withdrawing group. Chemoselective epoxidation is usually straightforward. The peracid epoxidation is stereospecific: the alkene **22** is *E* and so the epoxide **23** is *trans* (or *anti*). The other epoxidation is stereoselective as it is a two stage process and gives the more stable *trans* (or *anti*) epoxide **21** by choice. There is an example later in the synthesis of vernolepin.



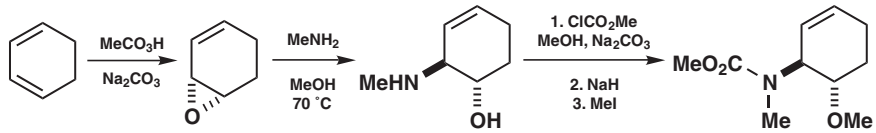
There is often no difficulty either if the two alkenes are the same, whether conjugated or not, as some reactions will stop cleanly after one alkene has reacted. A conjugated diene is more nucleophilic (higher energy HOMO) than a simple alkene so the first product, e.g. **25** is a less nucleophilic alkene than the starting material. The monoepoxide of cyclopentadiene **25** can be made by direct epoxidation of cyclopentadiene itself **24** provided that the solution is buffered with sodium carbonate to prevent the acid by-product ($MeCO_2H$) from decomposing **25**. Cyclo-octa-1,5-diene **26** can also give the mono-epoxide **27** cleanly. The difference in reactivity is less here - probably only about a factor of two - there are two equal double bonds in the diene and only one in the epoxide - and this approach is less reliable.[1]



Even if the only difference between the two alkenes is the number of substituents, that can be enough for some reactions. If the substituents are simple alkyl or aryl groups, then the more highly substituted alkene will be the more nucleophilic. This is enough to allow the epoxidation of the trisubstituted alkene in citronellene[2] **28** while leaving the monosubstituted alkene intact and provide a source of the optically active acid **31** for Nicolaou's synthesis of rapamycin.[3]

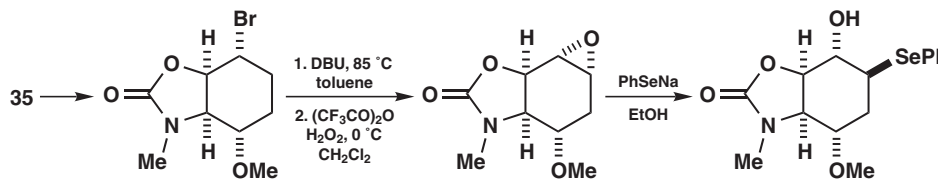


The synthesis of the aglycone (the bit without the sugar) fortamine **44** of the antibiotic fortimicin A illustrates this sort of chemistry perfectly. Selective epoxidation of cyclohexadiene **32** gives a good yield of monoepoxide **33** if the reagent is buffered. Nucleophiles, such as $MeNH_2$ attack at the allylic centre as the S_N2 reaction is accelerated by the alkene to give the *anti*-amino alcohol **34**. The amino group is acylated and the OH group methylated ready for the next step.



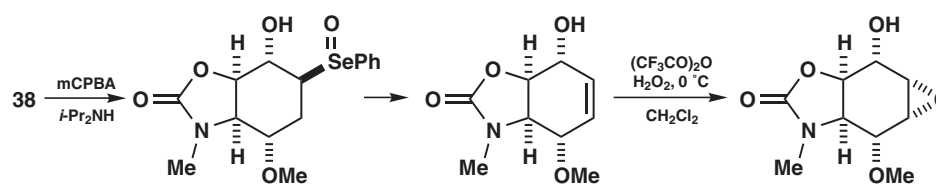
32 **33; 84% yield** **34; 99% yield** **35; 88% yield**

We shall discuss the conversion of **35** into **36** later in the chapter. Elimination and epoxidation stereoselectively produces the epoxide **37** on the outside (*exo*-face) of the folded alkene. Nucleophilic opening with $PhSe^-$ gives the *trans*-diaxial product (chapter 21).



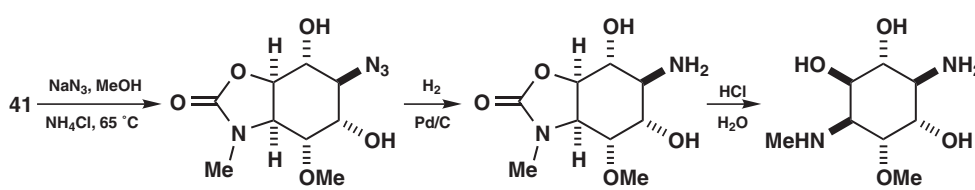
36; 86% yield **37; 89% yield** **38**

Oxidation to the selenoxide **39** and thermal elimination (chapter 32) produces a new alkene **40** that forms an epoxide **41** on the outside face again. At this point every carbon atom in the six-membered ring is functionalised, five oxygen-based and one nitrogen, and this all started with symmetrical cyclohexadiene. Each functional group was selectively introduced from an alkene.



39 **40; 94% from 37** **41; 62% yield**

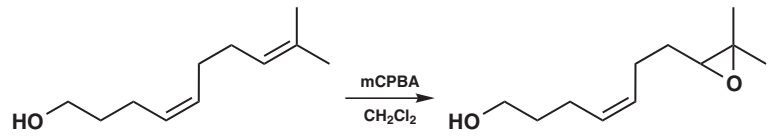
Now the epoxide **41** was opened regioselectively and stereospecifically with azide ion to give the *trans* di-axial product **42** that was reduced to the amine **43**. The synthesis of fortamine **44** was completed by the removal of the protecting carbamate.[4]



42 **43; 92% yield** **44; 99% yield**

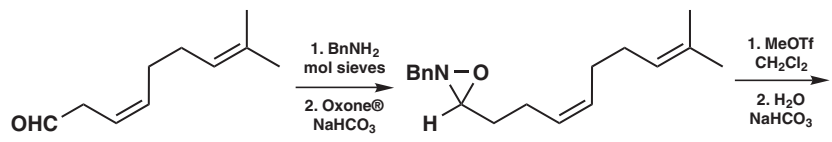
Controlling Chemoselectivity

In view of the last example, you should not be surprised that the non-conjugated diene **45** reacts with mCPBA at the more highly (tri-) substituted alkene to give the epoxide **33** in good yield.[5]

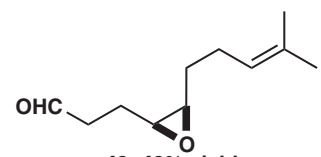


45 **46; 75% yield**

Chemoselective reaction at the cis-disubstituted alkene is more difficult. One solution is to deliver the reagent intramolecularly through a favourable 5/6 membered ring. The alcohol **45** is converted into the aldehyde **47**. Oxidation of the derived imine with the commercial reagent Oxone® ($KHSO_5.KHSO_4.K_2SO_4$) gives the oxaziridine **48** in yet another chemoselective oxidation. Methylation at nitrogen makes the oxaziridine electrophilic at oxygen and intramolecular epoxidation takes place.

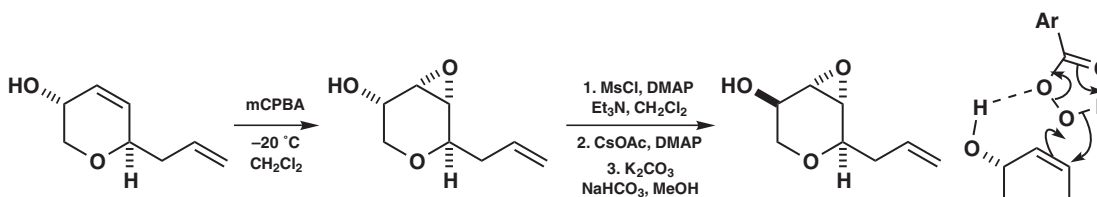


47 **48; 47% yield**



49; 48% yield

It is not necessary for the reagent to be covalently bound to the substrate for intramolecular epoxidation. Hydrogen bonding of peroxy acids or hydroperoxides, often with a co-ordinating metal such as $VO(acac)_2$, delivers the reagent to well situated alkenes.[6] This can achieve chemo- and stereoselectivity. Epoxidation of the dienol **50** with mCPBA gives a good yield of the epoxide **51** with only 15% of the *bis*-epoxide. They tried $VO(acac)_2$/*t*-BuOOH first but it gave mainly enone.[7]

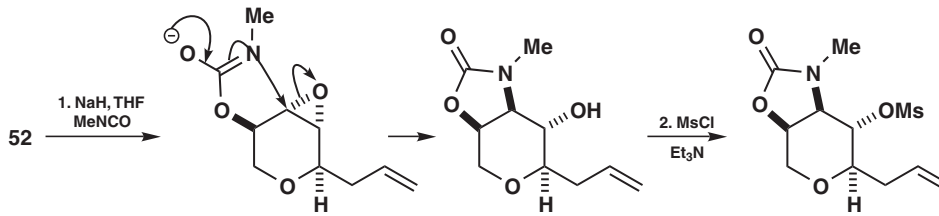


50 **51; 73% yield** **52; 83% yield** **53**

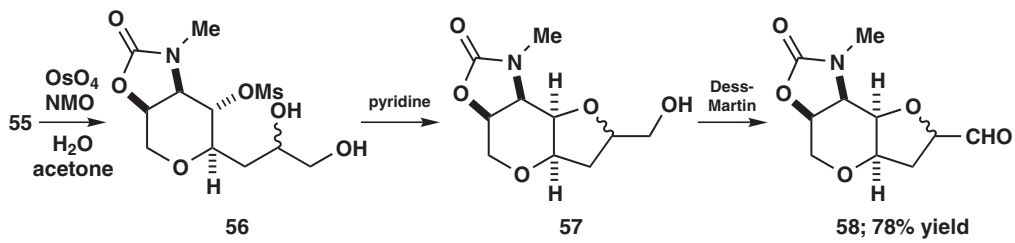
The intramolecular delivery of the reagent by some intramolecular mechanism such as the one in the margin is confirmed by the exclusive *syn* relationship between the OH group and the epoxide in **52**. The hydrogen bond between the OH group and the peracid makes the electrophilic oxygen atom of mCPBA more reactive and guides it in to the bottom face of the molecule as

drawn. Epoxidation of the other alkene would involve an unfavourable medium-ring transition state. In fact the *trans* relationship **53** was required so the OH group was inverted.

Regiospecific opening of the epoxide was also achieved by intramolecular delivery of the nucleophile. The alcohol **52** was converted into the reactive intermediate **53** with methyl isocyanate. Cyclisation can occur only to the nearer end of the epoxide (5-*exo-tet*) to give **54**. The stereochemistry is already correct for the S_N2 inversion on the epoxide **53**. The free OH group is turned into a good leaving group by mesylation without isolation of **54**.

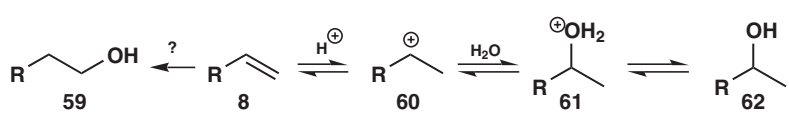


Finally the remaining alkene is dihydroxylated with catalytic OsO_4 and stoichiometric *N*-methylmorpholine (NMO) as oxidant to give the diol **56** that cyclises to the THF **57** stereospecifically. The aldehyde **58** was used to make (−)-dysiherbane.



Regioselectivity

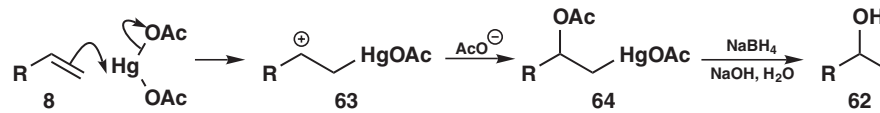
Epoxidation and dihydroxylation have become even more important in recent times as asymmetric versions have been developed and widely used. These are the subject of a special chapter (chapter 27) and do not have intrinsic regioselectivity. In this section we shall discuss the hydration of alkenes and how to reverse the normal regioselectivity of the reaction by hydroboration. These reactions *do* have regioselectivity and are used in organic synthesis as is a related electrophilic addition, iodolactonisation, that we shall deal with later in this chapter. The hydration of an alkene **8** - literally the addition of water - might occur with either regioselectivity to give the primary **59** or secondary **62** alcohol. If the reaction were a simple acid-catalysed addition, the secondary alcohol **62** would be expected as the secondary cation **60** would be an intermediate and the alcohol **62** is sometimes called the Markovnikov product. In fact the reaction does not usually occur just by treating alkenes with acidic water and special methods must be developed for both regioselectivities.



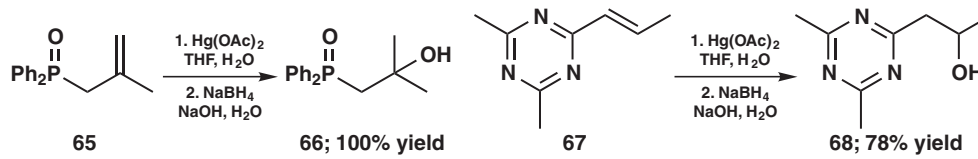
'Markovnikov' Hydration

Mercuration-reduction

The proton is not a good electrophile for an alkene - it is too hard. Some metal ions are much better soft electrophiles and mercury, as Hg(II), is outstandingly good. Addition of mercury (II) salts, usually the acetate but the oxide and sulfate are also used, to alkenes **8** gives regioselective addition *via* the cation **63** with the mercury adding to the less substituted end of the alkene. This stage, the formation of **64**, is oxymercuration. Reduction in alkaline solution removes the mercury, hydrolyses the ester and releases the secondary alcohol **62**. The complete process is Brown's mercuration-reduction method (Vogel, page 545, calls it oxymercuration-demercuration, take your choice) for the hydration of alkenes.[8] The radical mechanism for the removal of mercury is discussed in the workbook.

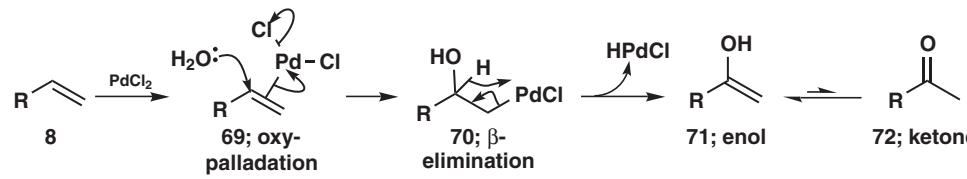


The reaction is surprisingly tolerant of other functional groups. The tertiary alcohol 66 is formed in 100% yield on a 5 gram scale by this method[9] and the electron-withdrawing triazine ring in **67** makes the secondary *alkyl* cation more stable than the alternative.[10] In spite of these virtues, this method has fallen out of favour as it requires stoichiometric toxic mercury.



Wacker oxidation

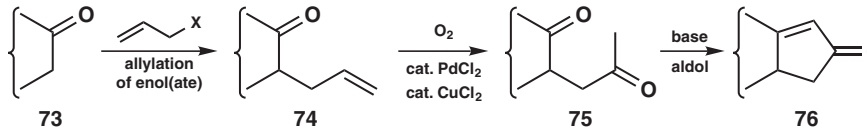
Wacker oxidation[11] provides a way to add water to an alkene **8** and oxidise the product to a ketone **72** all in the one step using oxygen under palladium (II) catalysis. The key to the difference between these two superficially rather similar sequences lies in the great tendency for palladium to undergo β-elimination **70**. Oxypalladation **69** gives an unstable alkyl-palladium σ-complex which decomposes at once to regenerate the double bond.



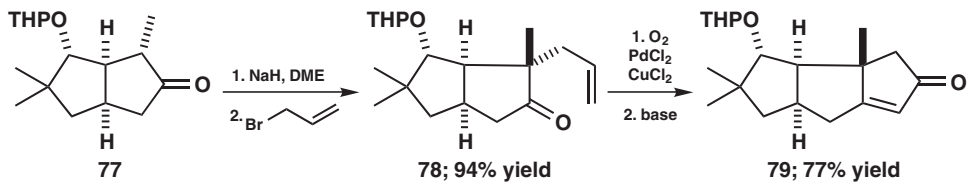
The palladium is released as HPdCl - still Pd(II)- but this decomposes rapidly to Pd(0) to end the cycle. In practice Pd(0) is reoxidised to Pd(II) with catalytic Cu(II) and the stoichiometric oxidant, O_2, oxygen itself, regenerates the Cu(II). The Wacker process is run on a large scale in industry to make simple carbonyl compounds but does find some use in the laboratory.

It obviously has no stereoselectivity but the regioselectivity is as expected for oxymetallation: water adds to the more substituted centre.

This reaction is part of a useful cyclopentannelation sequence. Allylation of ketones is among the easiest alkylations: subsequent Wacker oxidation and cyclisation creates a new five-membered ring **76**. This is the α-acyl cation strategy discussed in chapter 6, though this version of it was not mentioned.



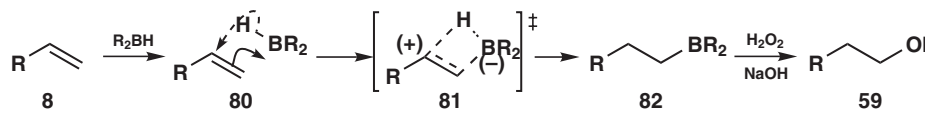
An illustration that demonstrates stereoselectivity as well comes in Ikegama's synthesis of coriolin.[12] Allylation of the sodium enolate of cyclopentanone **77** gives one diastereoisomer of the precursor **78** for a Wacker oxidation and cyclisation to give the tricyclic intermediate **79**.



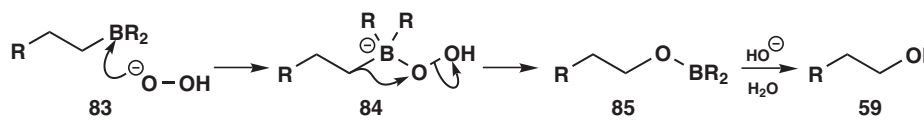
Hydroboration: 'Anti-Markovnikov' Hydration of Alkenes

Mechanism, regio- and stereoselectivity of hydroboration

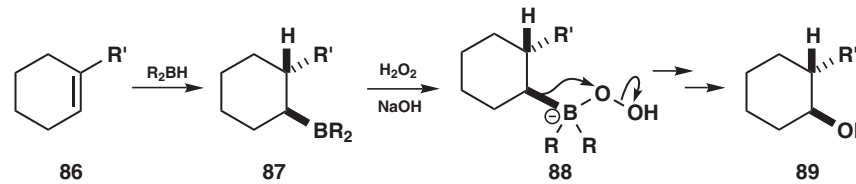
Reversing the Markovnikov regioselectivity calls for hydroboration.[13] We discussed hydroboration of alkynes in the last chapter and many of the same principles apply here. The reaction is a *syn* addition of R_2B-H to an alkene in which the boron bonds to the less substituted end of the alkene. The same sort of hydroborating agents are used – such as 9-BBN –and the mechanism is similar. The most important interaction is between the full π orbital of the alkene (HOMO) and the empty p-orbital on boron (LUMO) **80**, but the reverse interaction between σ(B−H) and π*(alkene) also comes into play as the reaction proceeds. The result is *syn* addition via a transition state **81** with some positive charge on carbon and some negative charge on boron.



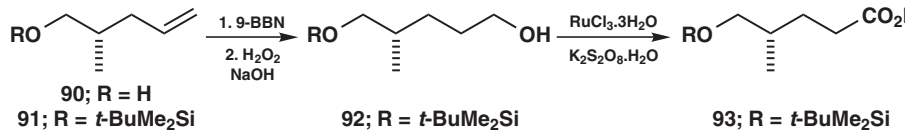
These alkyl boranes are not used as precursors for alkyl-lithiums but more usually oxidised to alcohols **59** with alkaline H_2O_2. This reaction involves nucleophilic attack by $HO-O^-$ anion on boron **83** followed by alkyl migration from boron to oxygen **85**.



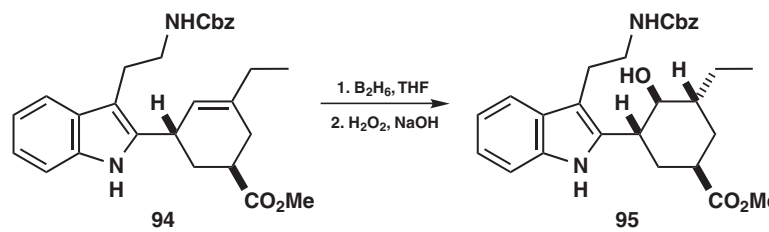
The stereochemistry of all these steps is important. The hydroboration is a *cis* addition of H and BR_2 displayed clearly by the product **87** from the cyclic alkene **86**. The addition of HOO^- to boron obviously involves no change in stereochemistry at carbon. The migration step **88** goes with retention of configuration as the filled s orbital of the C−B bond is used and the last step involves nucleophilic attack by HO^- on boron so there is again no change in stereochemistry at carbon. The overall result is retention at the stereogenic centre during the oxidation to give **89**.



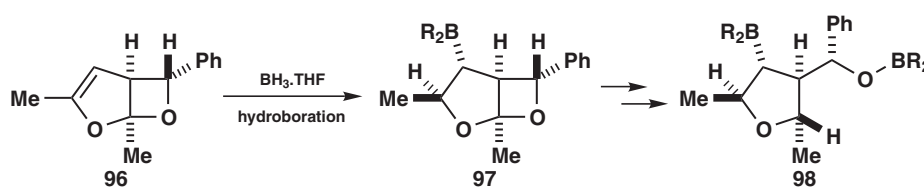
A simple example is the oxidation of an alkene to a carboxylic acid **93** in Evans' synthesis of cytovaricin. The alkene had been put in by allylation and the optically active unsaturated alcohol **90** was first protected **91** and then subjected to hydroboration and oxidation. Protection before the second alcohol appeared prevented impossible chemoselectivity problems.[14]



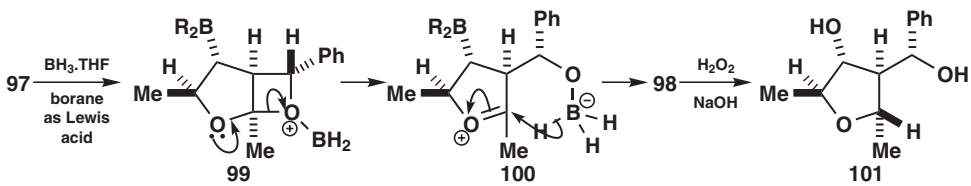
If the alkene has diastereotopic faces, the less hindered is normally attacked by the borane. A simple example occurs in Grieco's recent synthesis of the alkaloid ibogamine. The alkene **94** is a trisubstituted cyclohexene with two stereogenic centres in the ring. Hydroboration occurred with the expected regioselectivity on the top face of the alkene. This is the same face as the CO_2Me group, but the opposite face to the nearer and larger indole substituent. The alcohol **95** was the only product formed and was isolated in 68% yield. Simple reactions led to ibogamine.[15]



A more complex example with stereochemistry comes from Schreiber's asteltoxin synthesis.[16] Hydroboration of the bicyclic acetal **96** with borane itself occurs on the underside of the folded bicyclic molecule to give **97**. But this is not the end of the story. The product of the hydroboration is the THF **98**.



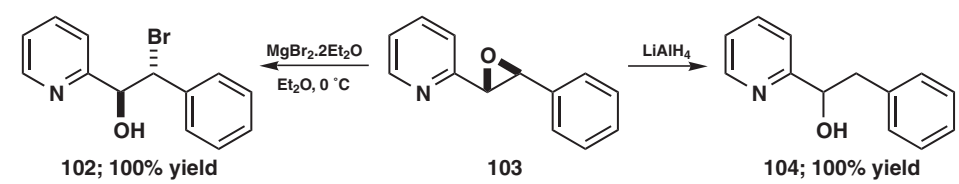
Borane was used to achieve a cunning reduction of the acetal in the same reaction mixture by acetal opening **99** followed by intramolecular hydride transfer **100** so that a single diastereoisomer of the borane/borate **98** was formed. Only now is the borane oxidised with alkaline hydrogen peroxide and the new alcohol **101** is formed as expected with retention of configuration. Three new stereogenic centres (the old acetal centre could not be counted as a permanent stereogenic centre) are formed in this sequence. We shall return to hydroboration later as a way of making carbon-carbon bonds.



Alternative Approaches to the Synthesis of Alcohols from Alkenes

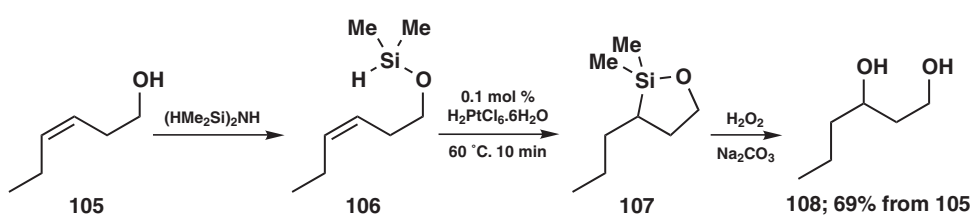
Regioselective reduction of epoxides

In view of the difficulties inherent in all these methods, others have been developed from epoxides and by intramolecular delivery of reagents. These methods are not so general as those we have described so far and we shall quote just two approaches. The unsymmetrical diaryl epoxide **103**, easily made by the sulfonium ylid method [details in workbook] reacts with nucleophiles as the benzylic centre rather than the centre next to the pyridine ring. Reduction with $LiAlH_4$ gives just the alcohol **104** while reaction with $MgBr_2$ gives just one bromohydrin **102** both in quantitative yield. It is possible that metals such as Mg, Al, or Li coordinate the pyridine nitrogen and epoxide oxygen atoms.[17]

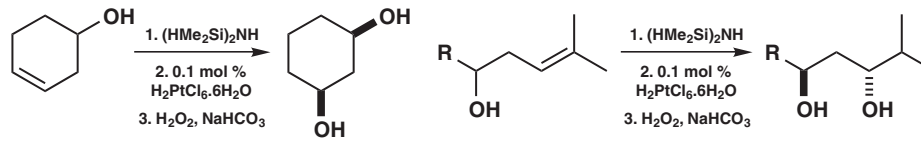


Intramolecular hydrosilylation

A hydrosilylation approach with the silicon being delivered intramolecularly from an OH group in **106** is also regioselective.[18] Catalysis by H_2PtCl_6 efficiently gave the heterocycle **107** and an oxidation of the C−Si bond (cf. the similar reaction on boranes above) gave one regioisomer of the diol **108**.



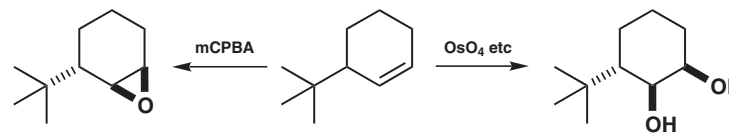
There is good stereoselectivity with cyclic chiral alcohols such as **109** (>100:1) but the more flexible achiral compounds such as **111** are not so good. In both cases the OH group delivers the Si−H from the same face but **111** can adopt a different conformation.[19]



109 **110; 73% yield** **111; R = n-C_5H_{11}** **112; 72% yield**

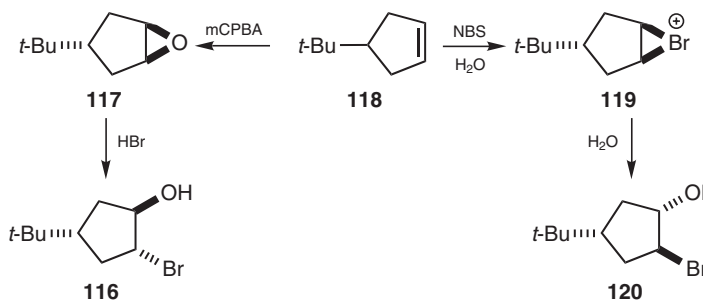
Stereoselectivity

Electrophilic attack on alkenes is normally stereospecifically *syn* (as in hydroboration) or *anti* (as in bromination). In this section we consider stereoselective aspects of these reactions. In the simplest cases, the two faces of the alkene are diastereotopic because of some stereogenic centre elsewhere in the molecule. Reaction will then occur on the less hindered face opposite the substituent already present. In favourable cases, where the substituent is large and close to the alkene, the selectivity may be high.



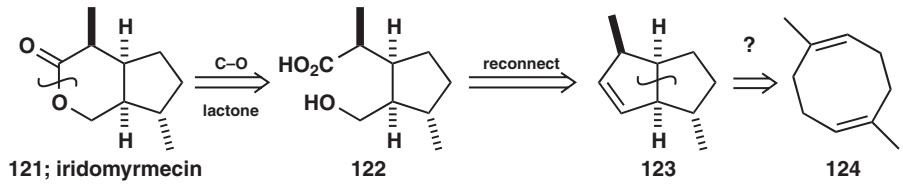
113 **114** **115**

Corey took advantage of the availability of specific *syn* and *anti* additions to make the two possible diastereoisomers of a bromohydrin by different methods. In each case the initial attack occurs *anti* to the *t*-butyl group and the second reagent, the nucleophile, adds from the other face. The order of events decides which product is formed.[20]

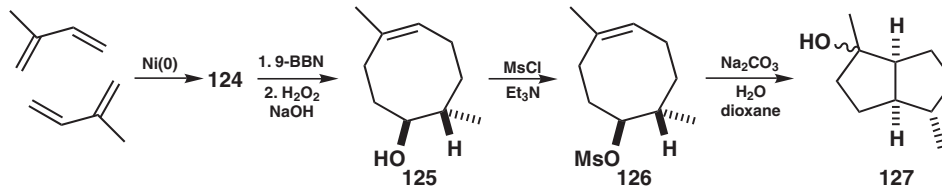


117 **118** **119** **116** **120**

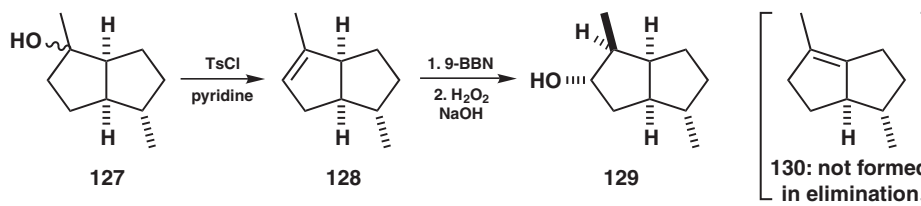
For a more complex example, we turn to Whitesell's synthesis of iridomyrmecin[21] **121**, a compound from the Argentine ant *Iridomyrmex humilis*. This compound is a bicyclic lactone with four stereogenic centres. Opening the lactone reveals the basic skeleton **122**. This skeleton has a 1,5-diO relationship and one might consider Michael additions at this point, but Whitesell noticed something more fundamental. If the two functionalised atoms were reconnected, the skeleton **123** has some symmetry. The substitution pattern of the two methyl groups in the two five-membered rings is the same, though the stereochemistry is different and an oxidisable double bond is required in one ring but not the other. It might be possible to make the compound from a symmetrical cyclo-octadiene **124**.



The synthesis of such eight-membered rings by the nickel-catalysed dimerisation of butadienes, is used here with 2-methylbutadiene. The regio-selectivity and stereo-specificity of the hydroboration of symmetrical **124** are as expected for a trisubstituted alkene. Conversion of the alcohol **125** into a good leaving group **126** made it reactive enough to carry out electrophilic addition on the other alkene. In aqueous solution, the final nucleophile was water and the product a mixture of diastereoisomers of the tertiary alcohol **127**.

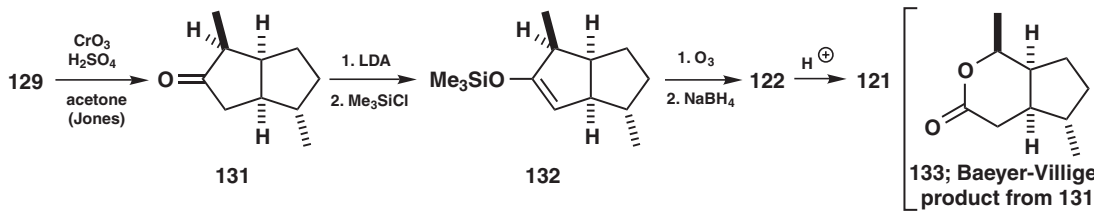


For the transannular reaction to occur, the molecule must fold inwards. In fact medium rings are normally folded like this anyway. The regioselectivity of the electrophilic cyclisation of the alkene gives as normal the more substituted cation. Inversion of course occurs at the mesylate centre and the ring junction has to be *cis* as 5/5 ring fusion would be very strained it were *trans*. The third stereogenic centre does not matter. Elimination of the tertiary alcohol **127** (TsCl, pyridine) preferentially gives the alkene **128** away from the ring junction. This is mainly to avoid flattening out the stable folded fused five-membered rings, but the tri-substituted alkene **128** may also be preferred to the alternative tetra-substituted alkene **130**. Now a second hydroboration introduces the required oxygen functionality in the left hand ring **129**. The regiospecificity is as expected and the borane (9-BBN again) adds stereoselectively to the less hindered lower face of the molecule. This is because of the folded rings. They are folded *upwards* (the ring junction hydrogens are *down*) and so the lower surface is outside the fold. It is very difficult to get inside these folded molecules, particularly with a large reagent like 9-BBN.



The left hand ring must now be cleaved and so the alcohol is converted to a ketone **131**. The obvious Baeyer-Villiger reaction will give the wrong cleavage product **133** as the *more* substituted group migrates from carbon to oxygen in these rearrangements. Stereospecificity is fine - the rearrangement goes with retention- but the regioselectivity is wrong. The problem is solved by ozonolysis of an enol derivative. Kinetic lithium enolate formation (chapter 3) and trapping with

Me_3SiCl gives a stable silyl enol ether **132**. Silyl enol ethers are of course alkenes too and can be oxidised by ozone. Reductive work-up is necessary not only to prevent the H_2O_2 by-product from oxidising the aldehyde but also to reduce it to the alcohol *in situ*. Acid-catalysed lactonisation of **122** finally gives iridomyrmecin **121**.



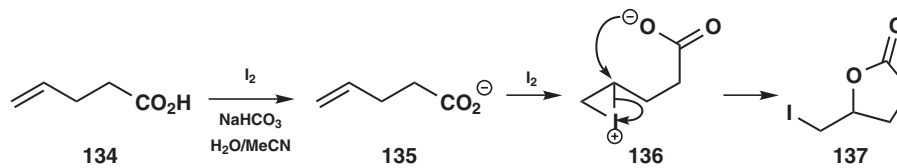
This synthesis involves four electrophilic attacks on alkenes - two hydroborations, one alkylation by a mesylate, and one ozonolysis. This is possible - even though the starting material had only two alkenes - because one of the alkenes is recreated three times. You will have noticed that each time it reappears, it moves round the structure so that electrophilic attack followed by double bond (re-)creation enables the formation of several new bonds as well as the introduction of new functionality.

Now that we have introduced all three kinds of selectivity in the context of electrophilic attack on alkenes, we shall look at some ways to control selectivity by special devices. In the examples which follow it is more convenient to treat the three selectivities together as they are often interdependent.

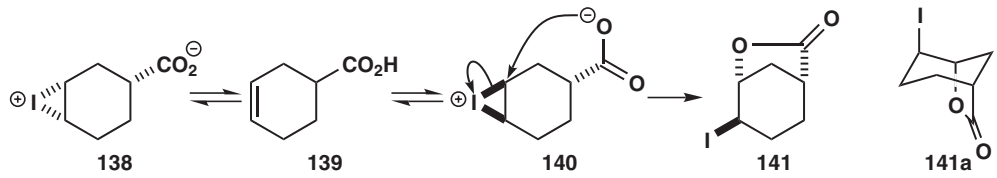
Selectivity by Intramolecular Interactions

Halolactonisation

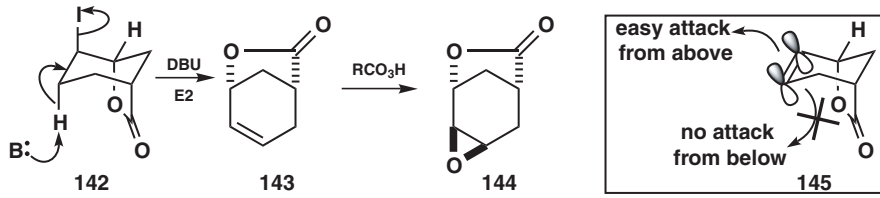
We have seen several instances of regio- and stereochemical control by intramolecular delivery of a reagent. This approach reaches its apogee when the reagent is tethered with a covalent bond to the alkene. The most important of these reactions is iodolactonisation or, more generally, halolactonisation.[22] Reaction of an unsaturated acid **134** with iodine in aqueous $NaHCO_3$, to ensure that the acid is present as its anion **135**, gives an iodolactone **137** with virtually complete control. Iodine attacks the double bond and the regioselectivity is normal - the nucleophile, the carboxylate anion, attacks the more highly substituted end of the iodonium ion **136**.



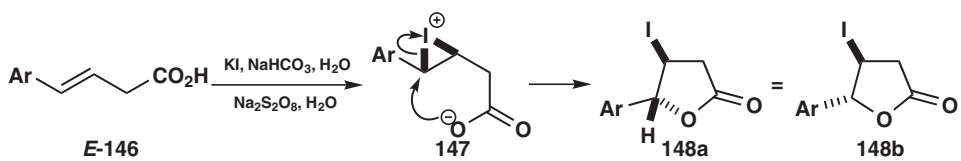
However, if the alkene is symmetrically substituted, the nucleophile attacks the nearer end of the iodonium ion as it is easier for it to achieve the 180° angle necessary for the S_N2 reaction. This automatically leads to stereoselectivity as well. Perhaps the most famous examples come from Diels-Alder adducts such as **139**. The carboxylate anion can reach only the same face of the six-membered ring to which it is already attached (a *trans* ring junction is impossible with this bridged ring). This means that only the *anti* iodonium ion **140** can cyclise and the *syn* iodonium ion **138** must revert to starting materials. The iodolactone **141** has a 1,3-diaxial bridge **141a**.



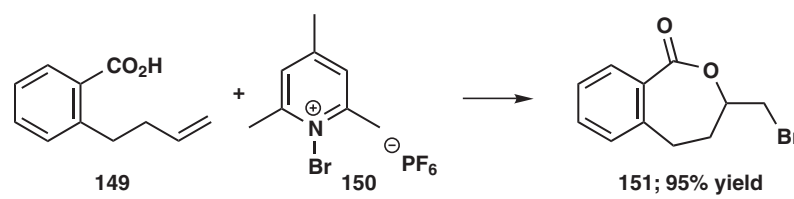
This result has further implications. An elimination using the bicyclic amidine DBU can occur only on one side of the iodine atom **142** as this is the only way to get H and I *anti-peri*-planar for the E2 reaction. The alternative H atom is equatorial. Electrophilic attack on this new alkene **143** must occur from the side opposite to the lactone bridge which, because it is diaxial, effectively blocks the alkene on one side **145**. Epoxidation **144** again provides a good illustration.



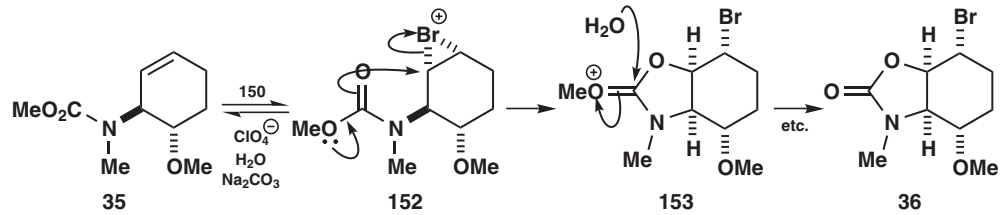
If the lactone produced might be either four- or five-membered, then the five-membered ring is usually preferred as this reaction is under thermodynamic control.[23] A series of aryl lactones was prepared in this way using KI and an oxidising agent as the source of iodine. Attack on either enantiotopic face of the alkene *E*-**146** gives an iodonium ion which cyclises by the rather awkward mechanism **147** needed to make the five membered ring **148**. Note that the stereochemistry of the alkene survives the one inversion. Preparation of the starting materials involves chemistry we met in the last chapter so it is reviewed in the workbook.



If the choice is between a seven- and an eight-membered lactone, the seven-membered ring **151** is preferred to the medium sized ring as in a recent series of experiments[24] using the collidine-Br^+ reagent **150**.

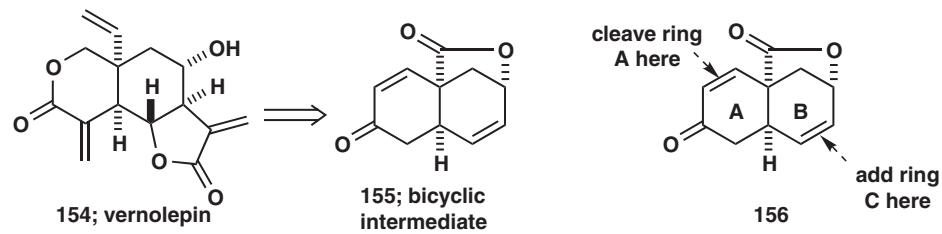


We can now return to the conversion of **35** to **36** mentioned earlier in the chapter. This is a bromolactonisation using a carbamate ester as the free acid would be unstable. The reagent is nearly the same as **150**; only the perchlorate salt is used instead in aqueous base. The ester group attacks the bromonium ion **152** to give the oxonium ion **153** that is hydrolysed under the conditions.[4]

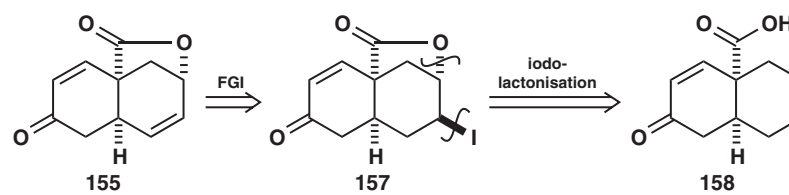


The synthesis of vernolepin

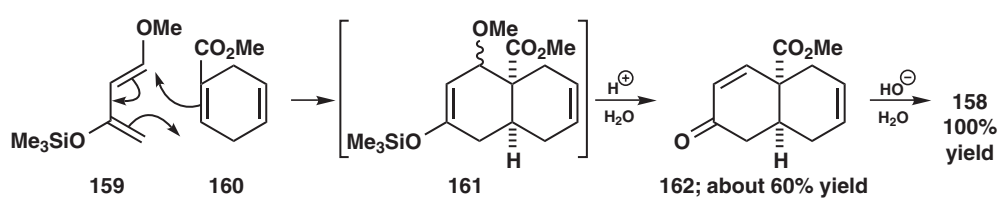
In his synthesis of the anti-tumour compound vernolepin, Danishefsky[25] used this very style of chemistry to great effect. Vernolepin **154** has just one carbocyclic ring and two lactone rings, but the synthesis was planned around an intermediate with two carbocyclic rings **155** so that all the stereochemistry could be controlled. You can see that the three stereogenic centres in the intermediate are correct, that there is a double bond in ring A **156** that might be cleaved oxidatively and another in ring B where the third ring is to be added.



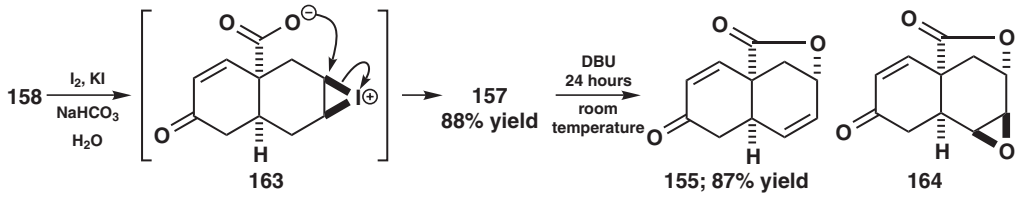
We shall discuss the synthesis of the intermediate **155**. The combination of a double bond and a lactone in ring B looks as though it could come from an iodolactonisation and elimination. We can draw the disconnections for these steps to reveal a possible starting material **158**.



This unsaturated acid was made by a Diels-Alder reaction, but not the one you might have expected. Danishefsky invented a special diene 'Danishefsky's diene' **159** for the introduction of enone functionality in the Diels-Alder reaction and here you see an application. The Diels-Alder adduct **161** is a silyl enol ether with a leaving group in the β-position and it hydrolyses easily to the enone **162**.

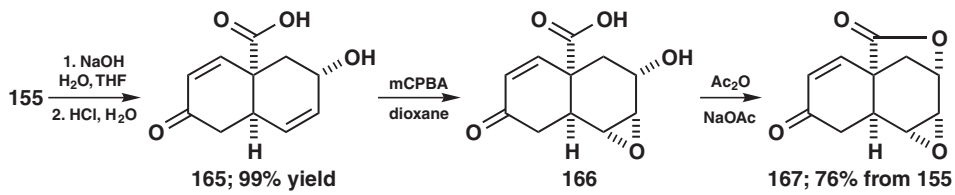


Note the chemoselectivity between the two alkenes in the cyclohexadiene **160**. This is the expected selectivity as Danishefsky's diene, with two electron-donating substituents is obviously electron rich and prefers to react with the electron-deficient alkene. The next two steps are the planned iodolactonisation and elimination with the usual reagents. There is chemoselectivity here too as iodine will attack the more nucleophilic double bond in **158**, regioselectivity in that the carboxylate anion attacks the nearer end of the alkene **163**, and stereoselectivity in that the anion can reach only the bottom face of the alkene.

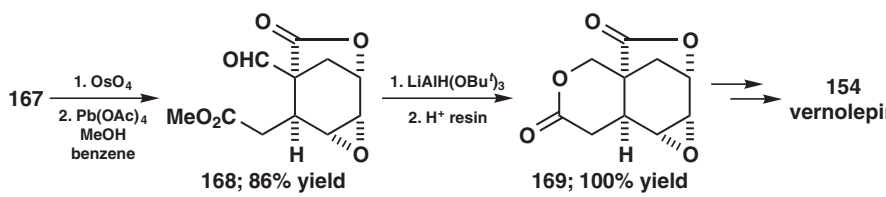


Now the time has come to react one of the alkenes and not the other. The reaction chosen was epoxidation as we could expect only the more nucleophilic non-conjugated alkene to be attacked by mCPBA. Direct epoxidation of the lactone **155** gave only the epoxide **164** with the correct chemoselectivity but the wrong stereoselectivity. The lactone bridge directs the peracid to the top face of the alkene.

But if the lactone is first hydrolysed, there is an OH (and CO_2H) group on the lower face of the molecule to deliver the peracid to the same face. This is a clear demonstration of the positive nature of this type of stereoselectivity as the lower face of the molecule is the more crowded. The last step closes the lactone again.



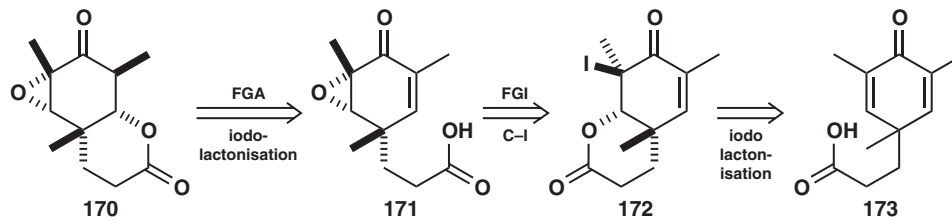
Now that the more nucleophilic alkene is no more, the less nucleophilic one can be oxidised and ring A converted into a lactone **169**. The rest of this synthesis is equally interesting but is outside the scope of this chapter. It has to start with some chemoselective reaction on the two lactones in **169** as described in the workbook.



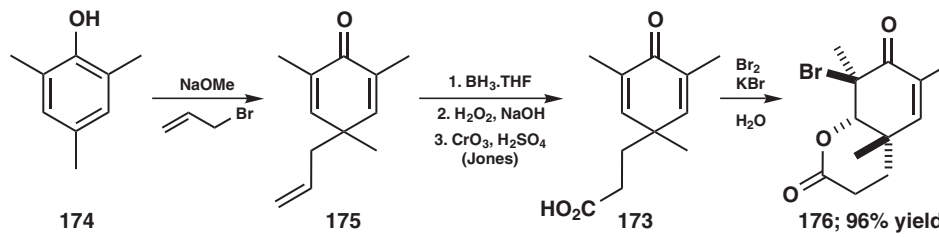
Halolactonisation in the synthesis of erythronolides

A remarkably clever combination of hydroboration and successive halolactonisations gave a vital intermediate in Corey's synthesis[26] of erythronolide B. Compound **170** was required with its five

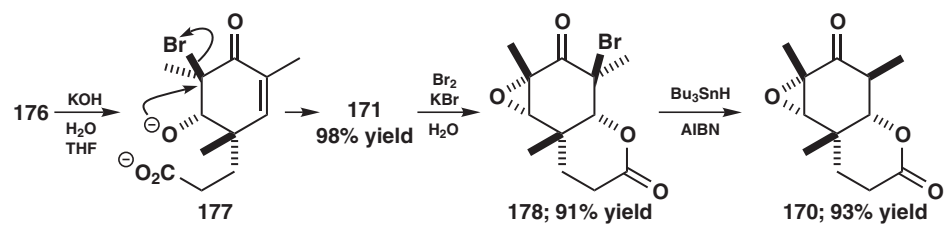
stereogenic centres around a six-membered ring. Corey realised that both sides of the ring could be developed by halolactonisations with the same carboxylic acid, used twice, once on each alkene.



The starting material **173** is drawn without stereochemistry because it is not chiral! The symmetry in this dienone means that it does not matter which alkene reacts first as they are the same. You may also have noticed that the stereochemistry of the methyl groups on the double bonds comes out wrong in both reactions, but, as we shall see, this does not matter. The starting material can be made from a simple phenol **174** by *ipso*-allylation and then hydroboration. The hydroboration is of course regioselective and attacks the electron-rich alkene rather than the enone system. The alcohol produced was further oxidised by Jones reagent without isolation. Now we are ready for the first bromolactonisation.



This reaction goes in a wonderful yield in spite of the rather unreactive enone. Maybe this is why the more aggressive bromine was preferred to iodine. The acid can be delivered only to the bottom face of the ring as it is tethered to that face and the bromine must therefore add to the top face. The next stage was to hydrolyse the lactone in base. The oxyanion released closed spontaneously onto the neighbouring bromide **177** to form an epoxide **178** with inversion. With that inversion, the stereochemistry is correct. This sequence of halolactonisation, hydrolysis and closure to an epoxide has been used in many syntheses to get one particular diastereoisomer of an epoxide. Now that the molecule is unsymmetrical and while it has a free carboxylic acid, it was resolved so all future diagrams show a single enantiomer. The next step was bromolactonisation on the other side to give **170**.

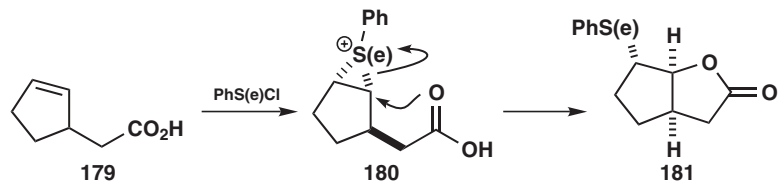


This also worked very well with all the usual selectivities and the bromine atom was removed with Bu_3SnH to give mostly the correct diastereoisomer as the hydride approaches the enolate

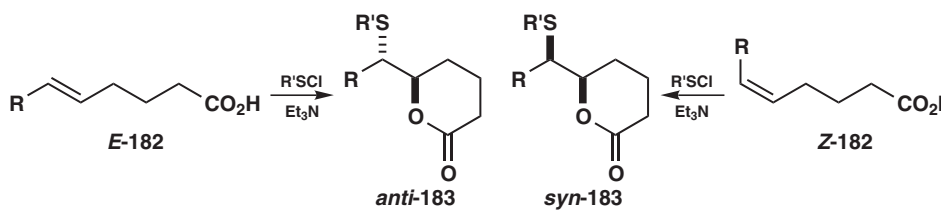
radical intermediate to give mostly an equatorial methyl group. We shall stop our analysis here but the full story is told in *Classics in Total Synthesis*, page 173 ff.

Sulfenyl- and Selenenyl-Lactonisation

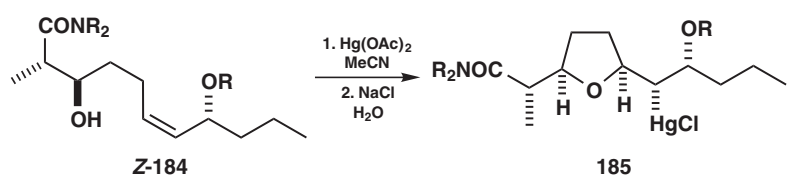
Halolactonisation works well because bromine and iodine form three-membered ring intermediates when they attack an alkene. Sulfur (II) and selenium (II) electrophiles form even better defined intermediates of this kind and similar cyclisation reactions occur with impressive control over selectivity.[27] A simple example would be the formation of the bicyclic lactone **181**. As the carboxylic acid is tethered to the five-membered ring, it can cyclise only to the intermediate with S(e) on the other face **180**. The mechanism is similar to that of iodolactonisation and the stereochemical points are the same. The products are useful for the generation of radicals as Bu_3SnH removes a PhSe group and leaves a radical behind while oxidation and elimination leaves a new alkene (chapter 33).



We can use sulfenyl-lactonisation to illustrate the stereospecificity of the process when the alkene differs in geometry. Rokach[28] has shown that the geometrical isomers of the unsaturated acid *E*- and *Z*-**182** give the correct diastereoisomers of the lactones from *anti* addition of Cl and R'S.

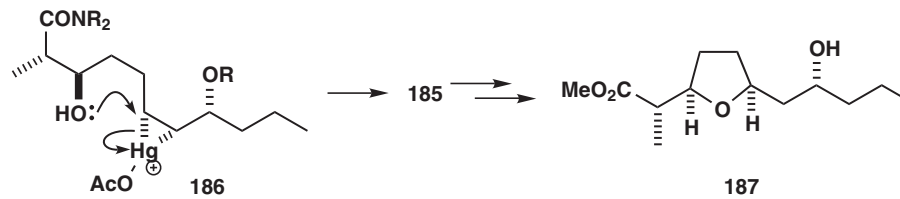


Returning to a reaction we met right at the start of this chapter will illustrate that the regio- and stereochemistry of many different electrophilic reactions with alkenes can be controlled by intramolecular nucleophiles. The mercuration of the *cis* alkene ***Z*-184** leads to a 6:1 ratio of diastereoisomers of a cyclic ether **185** by a related trapping of the intermediate by the internal OH group.



This is impressive because attack on the *cis* alkene **186** has to occur on the bottom face to lead to the product **185** and this line is hindered by the allylic OR group. Notice that the regiochemistry is

determined by the proximity of the OH group to one end of the alkene and that the stereochemistry of the alkene survives (with an inversion) in the product. The HgCl group is removed by reduction and the product converted into a building block **187** for the pammamycins, naturally occurring macrolides.[29]

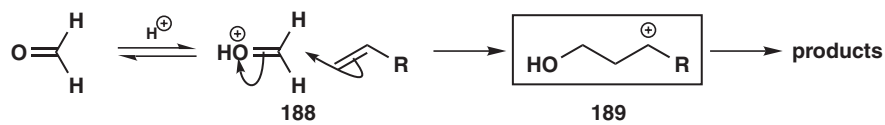


We shall end this chapter with three ways to make carbon–carbon bonds by electrophilic attack on alkenes. Though useful, they are not as important as the functionalisation reactions we have discussed so far, but they are each special in their own way. The first two, the Prins reaction and hydroboration revisited, use one-carbon electrophiles.

The Prins Reaction

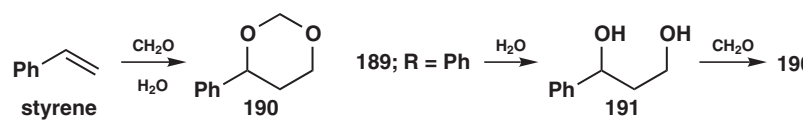
The original Prins reaction

This is a "forgotten" reaction of remarkable scope which can sometimes give useful molecules very difficult to make by any other means.[30] The electrophile is formaldehyde (or occasionally another reactive aldehyde) in acid solution and the first step is straightforward - normal "Markovnikov" addition **188** gives the more stable cation **189**, the key intermediate in a Prins reaction.

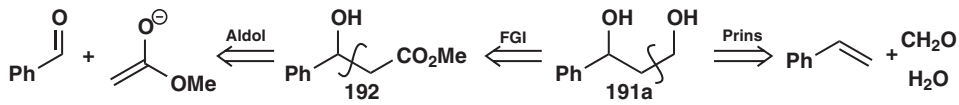


A number of things can happen now depending on the structure of the alkene and counterion of the acid. Direct cyclisation is not usually one of them as that would give an oxetane, a four-membered cyclic ether. Formaldehyde is often used as the 37% aqueous solution "formalin" (used to preserve biological specimens) and then there is then plenty of water around.

One good example is the reaction of styrene with two molecules of formaldehyde to give an acetal **190** in 100% yield with a solid acidic resin as catalyst.[31] Resuming the mechanism where we left off, presumably water adds to the cation to give a diol **191** which cyclises with another molecule of formaldehyde. There are other possibilities as this reaction gives a stable six-membered ring with an equatorial phenyl group and is probably under thermodynamic control.

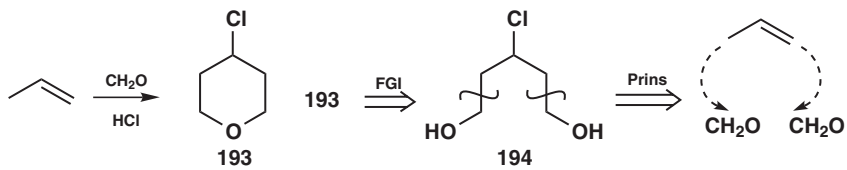


The true product is the 1,3-diol **191**, of which the product actually formed **190** is the formaldehyde acetal, and the disconnection should be contrasted with the aldol route **192** to the same product as a different carbon-carbon bond is formed.

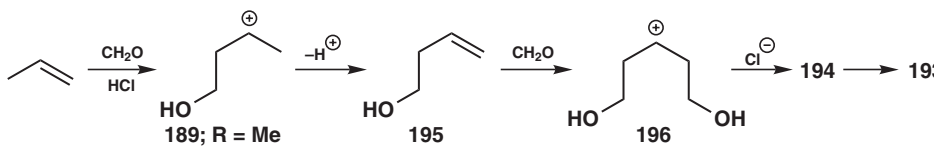


The formation of tetrahydropyrans by the Prins reaction

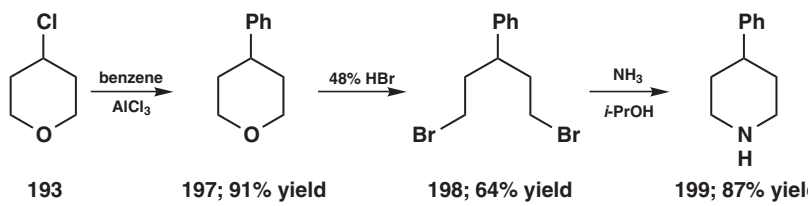
Aliphatic alkenes also undergo the Prins reaction and a well-conducted example is with propene, formaldehyde and HCl. The product is 4-chloro-tetrahydropyran in good yield.[32] This compound presumably arises from the cyclisation of another diol **194** and that clearly comes from one molecule of propene and two of formaldehyde. What is different from the last example is that the two molecules of formaldehyde must have been added to opposite ends of the original propene.



We can now reconstruct the reaction mechanism. The first cation **189**; R=Me is formed as before, but in the absence of water elimination must reform an alkene **195** on the other side before a second molecule of formaldehyde is added. The HCl used provides a chloride ion to intercept the second cation **196**.

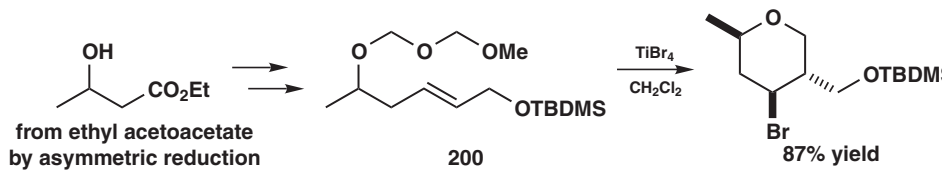


This product (4-chlorotetrahydropyran, 4-Cl-THP) **193** may not look very useful but the chlorine atom can be converted into a nucleophilic Grignard reagent or used in a Friedel-Crafts reaction to give **197** while the ether ring may be cleaved to give a doubly electrophilic unit **198**. One useful application is the synthesis of 4-phenyl piperidine **199**, a structural unit found in medicinal compounds.



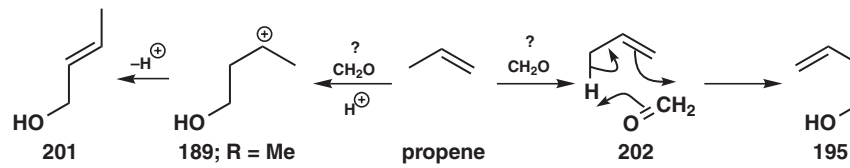
The disconnections corresponding to this chemistry are remarkable as the molecule is built up quickly from very simple starting materials. In this application, **193** acts as a pentyl 1,3,5-trication synthon!

A more modern version[33] of these reactions uses a Lewis acid (TiX_4) and a pre-formed acetal **200** of a homoallylic alcohol to make the same products. Asymmetric reduction (chapter 26) of ethyl acetoacetate gives the starting hydroxyester as either enantiomer. Yields are much higher and control is exerted in making the protected homoallylic alcohol **200**.

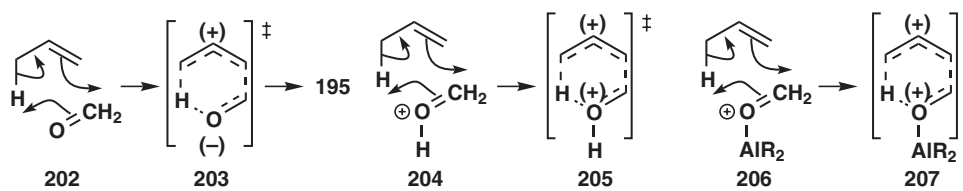


The oxo-ene mechanism

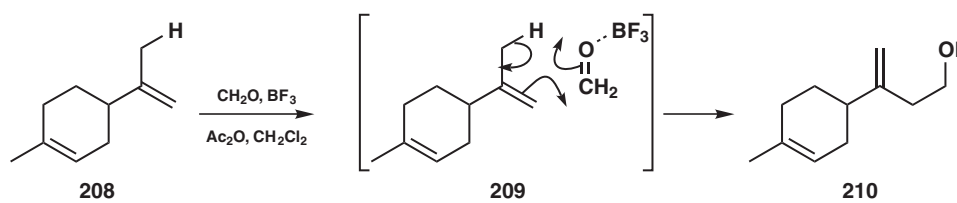
Returning to the mechanism of 4-Cl-THP **193** formation. When the cation **189** loses a proton to form an alkene, why should it lose that proton to make a terminal alkene? Surely the proton from the other side would be lost preferentially to give the more stable alkene **201**? One solution to this dilemma is to make the loss of the proton and the addition of formaldehyde concerted **202**.



The first step **202** is now a pericyclic reaction. It looks like a cycloaddition, though it involves a hydrogen transfer as well. It is in fact a carbonyl (or 'oxo-') "ene" reaction. It is like a Diels-Alder cycloaddition in which a C–H bond has replaced one of the double bonds in the diene and a C=O group is the dienophile. Many Prins reactions are probably carbonyl ene reactions. In his excellent review[30] in *Comprehensive Organic Synthesis*, B. J. Snider says "The (carbonyl) ene reaction and the Prins reaction are not mechanistically distinct". Though this step is pericyclic, it is very polar and the transition state **203** no doubt contains partial charges. It is therefore stabilised and the reaction accelerated by protic acids **205** and Lewis acids **207**.

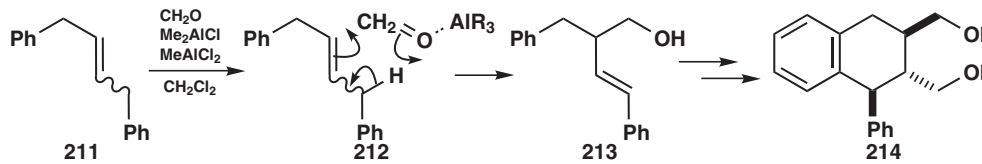


Snider has found dialkyl aluminium halides to be excellent catalysts for this reaction and they can be used to stop the reaction after the first step. This is a real advance in the Prins reaction that otherwise tends to give a mixture of products by multiple addition of the aldehyde and intervention by various nucleophiles. A simple example is the addition of formaldehyde to the terpene limonene **208** catalysed by BF_3. A single monoadduct **210** is formed in good yield.[34] This must be a Lewis acid catalysed carbonyl ene reaction on the external double bond **209**. Notice the excellent chemoselectivity in that the internal alkene is not attacked and the excellent regioselectivity in that hydrogen atoms at four other sites might have taken part in the reaction, but do not.

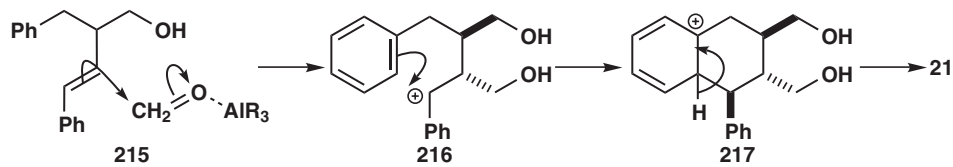


Stereoselectivity in the Prins reaction

Snider's synthesis of the aryl lignan skeleton is an example with stereochemistry.[35] Either geometrical isomer (*E* or *Z*) of the starting material (1,4-diphenylbut-2-ene) was combined with formaldehyde and a mixed catalyst of $MeAlCl_2$ and Me_2AlCl. The all *anti* cyclised product **214** was formed in 40-50% yield. The first step must be a carbonyl ene reaction **212**. It doesn't matter which way we write this as the molecule is symmetrical and we know that the stereochemistry is irrelevant.

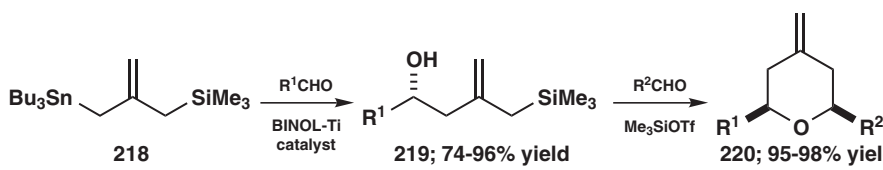


The next step is a simple electrophilic attack by another molecule of formaldehyde on the alkene - in other words a simple Prins reaction **215** - showing the regioselectivity we expect to produce the secondary benzylic cation **216**. The second molecule of formaldehyde has added onto the opposite side from the first. The resulting cation is perfectly placed for an intramolecular Friedel-Crafts alkylation **216** of the benzene ring. This is again a stereoselective reaction giving the more stable *anti* diastereoisomer **214**. This sequence involves three successive C−C bond-forming reactions and the stereochemistry is simply controlled by the preference for the more stable *anti* product.



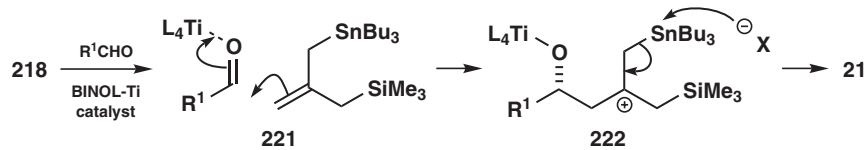
Double Prins reactions: use of Sn and Si to control cation formation

One problem with the original Prins reaction was uncertainty in the fate of the cation **189**. Recent advances have used the chemistry of allyl tins and silanes explored in chapter 12. For example addition of aldehydes to reagent **218** with a chiral catalyst formed from BINOL (chapter 26) and $Ti(O\textit{i}\text{-}Pr)_4$ gave the allyl silane **219**. This in turn reacted with a second aldehyde using an achiral Lewis acid to give the THPs **220**. Yields are very high, enantiomeric excess almost perfect (90-96%) and various aromatic, enolisable aliphatic and functionalised aldehydes can be used in both steps. Control expressed in the isolation of the stable intermediate **219** means that the two aldehydes need not be the same.[36]

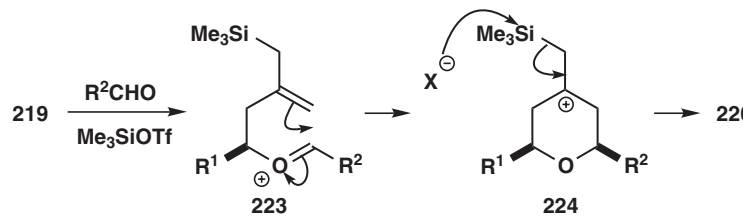


The first step **221**, whether you call it a Prins reaction or not, gives a cation **222** stabilised by both silicon and tin (chapter 12). Nucleophilic attack on tin is preferred (tin is lower down the

periodic table) and that gives the product. The presence of both silicon and tin stabilise the cation while the tin decides its fate. There is no need to invoke an oxo-ene mechanism. The *absolute* stereochemistry is decided by the chiral catalyst: you are not expected to see how.



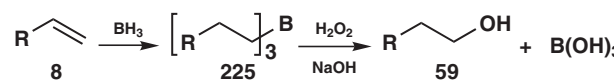
The second Prins reaction goes through the oxonium ion **223** to give the final product. Again the nucleophile is an allyl silane **223** and the second intermediate is a cation stabilised by the silicon β-effect. The *relative* stereochemistry is decided in the second reaction and **220** has the favoured diequatorial conformation.



Hydroboration as a Way to Make Carbon-Carbon Bonds

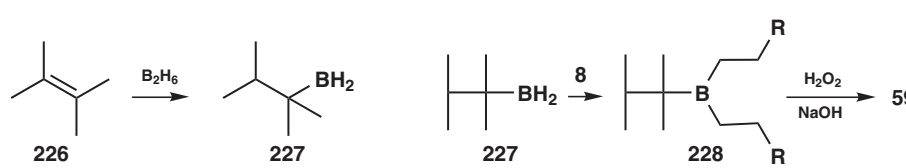
Carbonylation of Alkyl Boranes

Earlier in this chapter we discussed the oxidation of boranes with hydrogen peroxide. When borane itself was used, the reaction was quite unambiguous. The trialkylborane **225** is the first product and when it is oxidised any of the three identical alkyl groups may migrate first to oxygen.



Eventually all three will migrate and three molecules of alcohol will be formed.

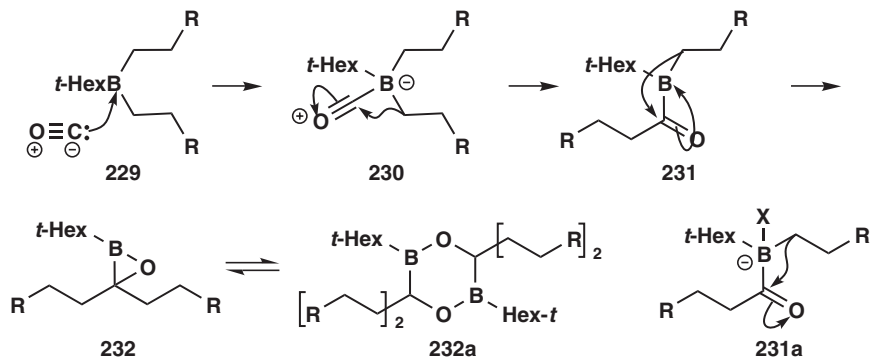
Borane is supplied as its THF, R_3N, or Me_2S complex or generated *in situ* from BF_3 and $NaBH_4$. But substituted boranes must be prepared. We met 9-BBN, the most popular dialkyl borane, in chapter 16 and used it earlier in this chapter. The most popular monoalkyl borane is "thexyl" borane whose pet name simply means *t*-hexyl borane and whose *t*-hexyl group is often represented as a large letter H. These are obviously bulky boranes and give sterically enhanced regioselectivity in hydroboration of mono substituted alkenes **8**. They are both used in the synthesis of alcohols **59**. These reactions will be successful providing that the newly introduced alkyl group migrates to oxygen in preference to the *t*-alkyl group in **228** here or the cage structure in 9-BBN adducts.



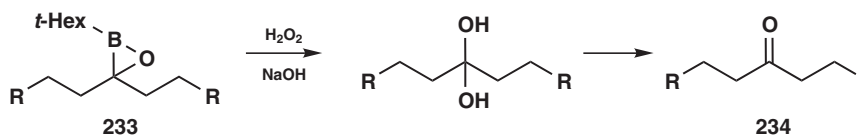
The rule most people know is that "the group best able to support a positive charge" migrates best. This rule applies to cationic rearrangements like the Baeyer-Villiger where the transition state for the migration has a positive charge. In these boron "ate" complex rearrangements, the transition state has a *negative* charge and the rule is reversed.[37] It might be an exaggeration to say that the group "best able to support a negative charge" migrates as alkyl groups *de*stabilise negative charges, but the migration order is primary>secondary>tertiary. The group which destabilises the negative charge least migrates best. In the case of 9-BBN, other secondary alkyl groups migrate better than the bicyclononane group because bridgehead atoms migrate worse than ordinary groups. If a bridgehead atom migrates, the whole cage must distort.

Carbon monoxide

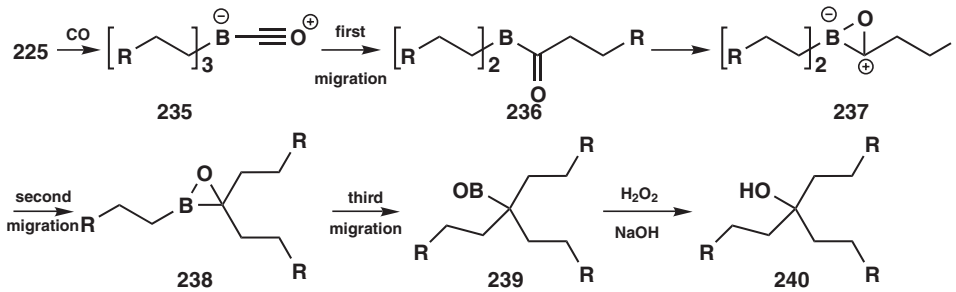
Armed with this essential information, we can look at C−C bond-forming processes. A famous example is the formation of ketones with carbon monoxide.[38] The first step is addition of CO **229** and then boron to carbon migration **230** of the primary alkyl group. For the transfer of the second alkyl group an "ate" complex **231** must be formed again, and a nucleophile, usually based on oxygen, is added to the very unstable ketoborane **230** and a second alkyl group is driven across **231** to give a more stable hydroxyborane **232**, the product at this stage.



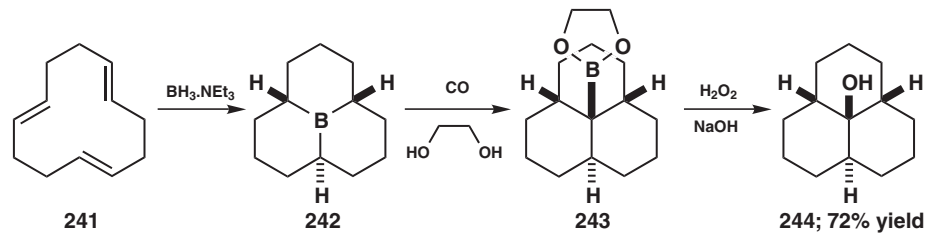
The final step is the usual oxidation with alkaline hydrogen peroxide. Both groups on the boron **232** are now tertiary so an excess of oxidant must be used to drive both across to oxygen. The products are *t*-hexanol and the hydrate of the ketone **234**. This doesn't affect the ketone synthesis, only the by-product.



If all three groups on borane can migrate, as in normal trialkyl borane, tertiary alcohols are the products. Three migrations from boron to carbon go via the unstable ketone **236** and epoxide **238** to the relatively stable *t*-alkyl boron derivative **239** that is oxidised to the *t*-alcohol **240**. A *t*-alkyl group must migrate here as there is no alternative.

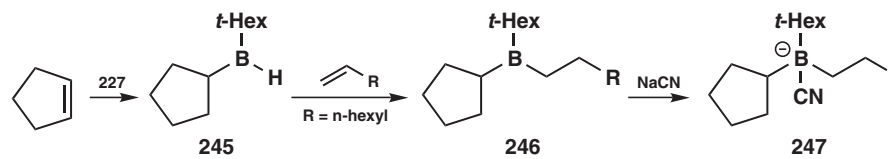


A dramatic example is the synthesis of the alcohol **244** by the literal insertion of a CO unit into the triene **241**. Heating **242** at 200 °C for six hours after hydroboration equilibrates positional and stereochemical isomers and shows how stable the trialkyl borane is. Glycol is added as the nucleophile so that the stable heterocycle **243** equivalent of **239** can be purified as a crystalline compound. All three B to C migrations go with retention of configuration.[38]

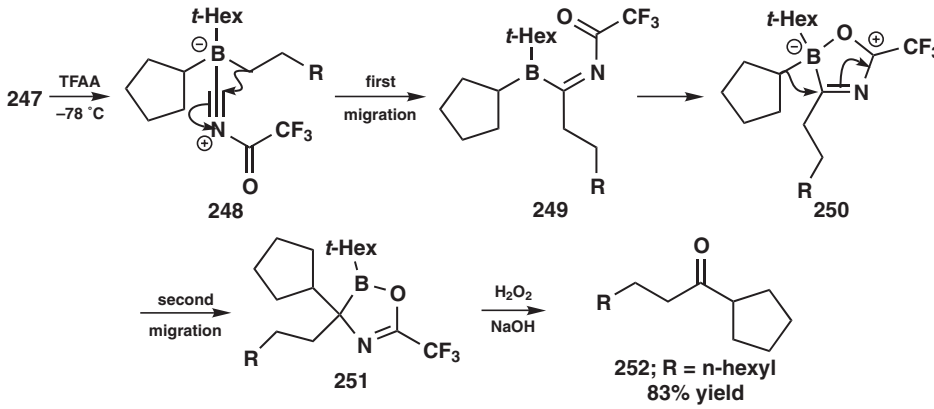


Ketone synthesis using cyanide ion

Not everyone wants to use carbon monoxide and a more convenient, though equally deadly, one-carbon reagent is cyanide ion. This does not require the high pressures often needed to make CO react.[39] Cyanide forms stable "ate" complexes **247** with boranes and we shall use two different alkenes to illustrate this possibility. Thexyl borane **227** is essential for reaction with two different alkenes and it is better to use the more hindered alkene first. These precautions lead to a more selective reaction with the first alkene.

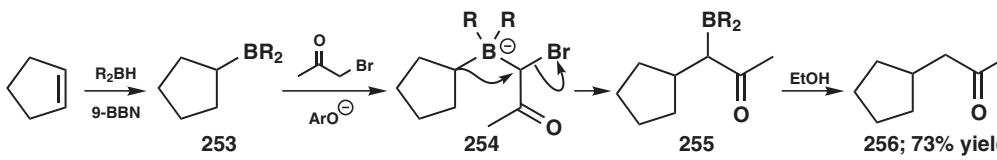


The "ate" complex **247** has an obvious resemblance to the CO complex **230** but the nitrogen atom is less electron-withdrawing than the oxygen atom as it lacks the positive charge so the cyanide complex is less prone to rearrangement. Acylation with trifluoroacetic anhydride leads to B to C migration of the primary alkyl group **248**. This new borane **249** looks stable but the amide group can cyclise onto the boron to regenerate an "ate" complex **250** and initiate migration of the secondary alkyl group. Oxidation of this quite stable heterocycle **251** causes the usual migrations and replaces all B−C bonds by B−O bonds. The final organic product is a ketone **252**. Notice that the first formed borane had primary, secondary and tertiary alkyl groups on it so this sequence illustrates well the order of rearrangements.



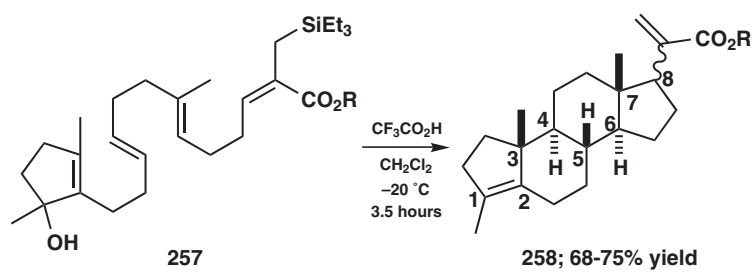
Reactions with α-halo-carbonyl compounds

Any nucleophile that contains a leaving group on its α-atom could in principle be used to initiate rearrangement of alkyl boranes. A simple way to make C−C bonds is to use the enolate of an α-halo-carbonyl compound.[40] The favoured reagent is 9-BBN (R_2BH) and primary or secondary groups can be migrated in preference to that cage structure. The best base for creating the enolate is the very hindered 2,6-di-*t*-butylphenoxide and B to C migration occurs on the 'ate' complex with displacement of bromide **254**. The 9-BBN is removed from the product simply with ethanol.



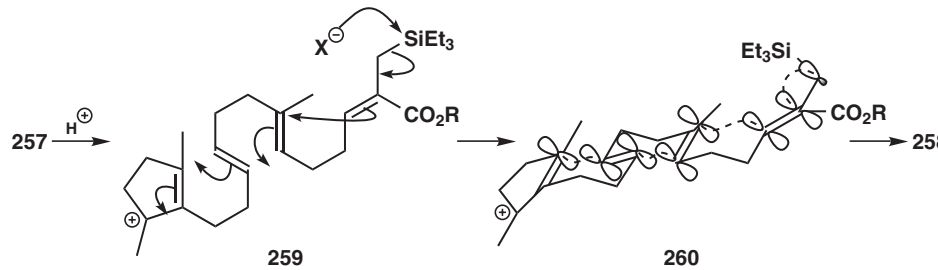
Polyene Cyclisations

In these remarkable reactions, a series of electrophilic attacks on a bank of alkenes e.g. **257** is initiated by an electrophile. Each alkene adds to its neighbour until the bank is exhausted and essentially complete chemo-, regio- and stereo-selectivity is achieved. These reactions were discovered by W. S. Johnson[41] and the idea came from nature where steroid synthesis is accomplished by very similar reactions. The main problem is terminating the sequence regioselectively and here allyl silanes (chapter 12) are most effective.

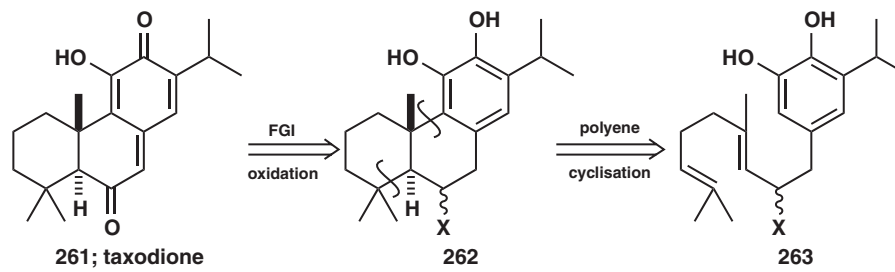


The mechanism involves the formation of an allylic cation **259** from the tertiary alcohol **257** and the electrophilic attack on each alkene in turn until the allyl silane is reached when loss of the Et_3Si group to the β-silyl cation terminates the reaction. Chemoselectivity is determined simply

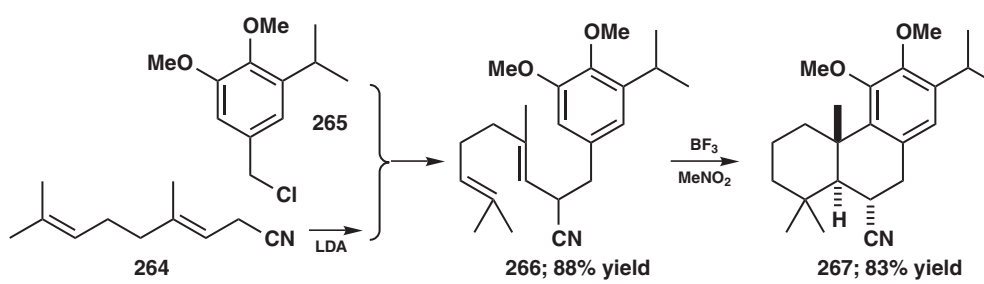
by the proximity of the right alkene. Regioselectivity comes from the way the molecule folds up **260** so that each new ring is already in a chair as it is formed. Stereo*specificity* - the relationship between centres 4 and 5 and between centres 6 and 7 - comes from the two central alkenes reacting in a concerted fashion so that their *trans* geometry becomes *trans* 3D stereochemistry in the product. Stereo*selectivity* - the relationship between centres 3 and 4 and between centres 5 and 6 - is again determined by the way the molecule folds.



This may look like a rather specialised method but the biomimetic inspiration applies to much simpler compounds. Taxodione **261** is an antitumour compound from the swamp cypress *Taxodium distichum*. It has an extended quinone-like enone system and two *trans* fused six-membered rings. Livinghouse[42] realised that the extended quinone might be derived by oxidation of a simpler aromatic compound **262** where "X" is an oxidisable group. He then saw a possible polyolefin cyclisation in which a tertiary cation derived from a simple alkene **263** starts the reaction and the aromatic ring terminates the sequence.

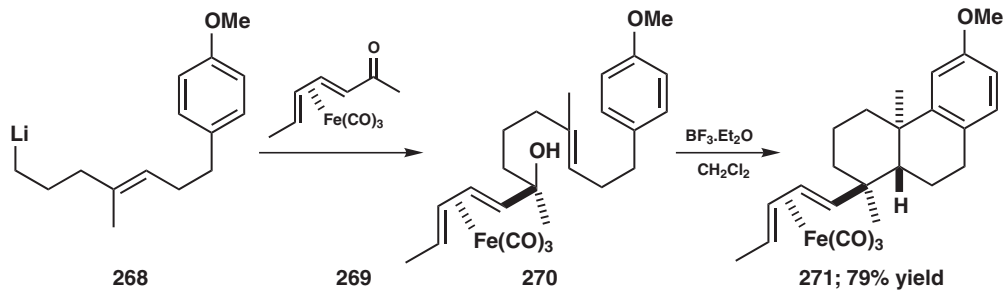


The unknown "X" now assumes a different role. If it is both oxidisable and anion stabilising, it can be used to build the molecule by a simple alkylation reaction. This disconnection is more or less in the middle of the molecule, both starting materials **264** and **265** will have to be prepared, and so the synthesis will be very convergent. The choice for "X" was cyanide and the phenolic OH groups were protected as OMe groups. The cyclisation was accomplished with BF_3 in $MeNO_2$ and gave a very good yield indeed of **267** with complete control over stereochemistry - even the cyanide centre was controlled as the CN group goes equatorial.



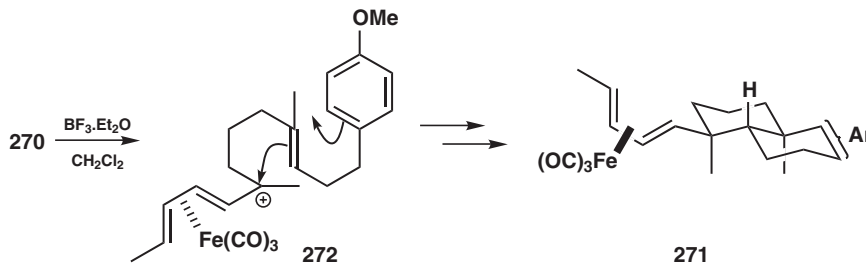
The remaining steps are trivial except for the conversion of the cyanide to a ketone. This was achieved by oxidising the lithium "enolate" of the cyanide. The methyl groups were removed from the phenols with BBr_3 and the final oxidation to the extended quinone was done with oxygen adsorbed onto silica. The whole synthesis took only seven steps and gave a remarkable overall 21% yield.

Recent developments include asymmetric polyene cyclisations but also include new ways to initiate cyclisations. Iron tricarbonyl stabilises pentadienyl cations and its complexes with dienes are chiral. Addition of the achiral lithium derivative **268** to the chiral complex **269** gives the polyene precursor **270** that cyclises with Lewis acid to give a single diastereoisomer of the bicyclic compound[43] **271**.



268 **269** **270** **271; 79% yield**

The Lewis acid removes the OH group from the alcohol **270** to give the $Fe(CO)_3$-stabilised cation **272** that initiates the cyclisation. The product is formed with the large iron diene complex in the equatorial position.



272 **271**

Looking Forwards

We have spent some time in this chapter looking at the diastereoselectivity of some very important reactions. We shall be returning to the most important of these in chapter 25 where we discuss two of the most important reactions of the century - asymmetric versions of epoxidation and dihydroxylation by osmium. These developments were possible only because of the selectivities already established by the work described in this chapter and the selectivities we have discussed will be important in many syntheses.

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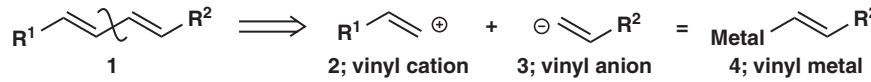
18 Vinyl Cations: Palladium-Catalysed C−C Coupling

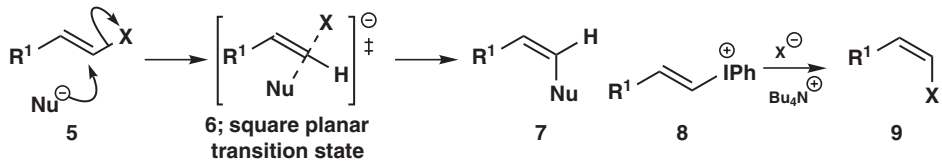
Introduction: Nucleophilic Substitution at sp^2 Carbon does NOT Occur

If you want to make a diene one obvious place to disconnect is between the two alkenes **1**. Though this has a pleasing symmetry, one of the synthons must be a vinyl cation **2** and the other a vinyl anion **3**. We have already met stereochemically controlled reagents for the vinyl anion synthon such as vinyl metals **4** (chapter 16) and all we now need is a good reagent for the vinyl cation. That is the subject of this chapter. First we need to examine why you can't just use a vinyl halide and expect to get substitution of the halide ion.

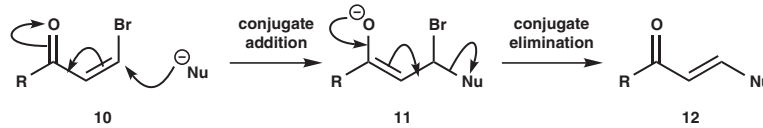
Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren



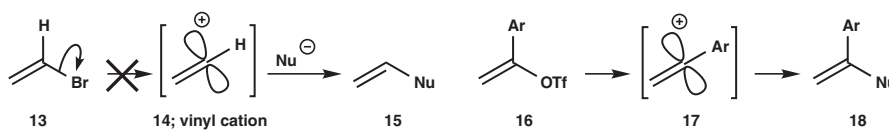
Nucleophilic substitution of unactivated vinyl halides is a rare reaction.[1] The S_N2 reaction at a trigonal sp^2 carbon atom **5** is generally thought to be unknown. It is puzzling that this innocent looking reaction should be impossible: could it be that the transition state, which would have to contain square co-planar carbon **6**, is too high in energy? Recent work[2] suggests the PhI may be displaced from vinyl iodonium salts **8** by halide nucleophiles with inversion of configuration (*E*-**8** gives *Z*-**9** with inversion) but it remains to be seen if this is a useful reaction in synthesis.



Nucleophilic substitution at trigonal carbon is known by the addition-elimination mechanism **10** where an enolate intermediate **11** is formed and the negative charge is deposited on an electronegative atom such as oxygen. This is conjugate substitution and you will see the analogy with nucleophilic aromatic substitution. There is no need for stereospecificity in the two-step process and we might expect *Z*-alkenyl halides **10** to give *E*-enone products **12**.



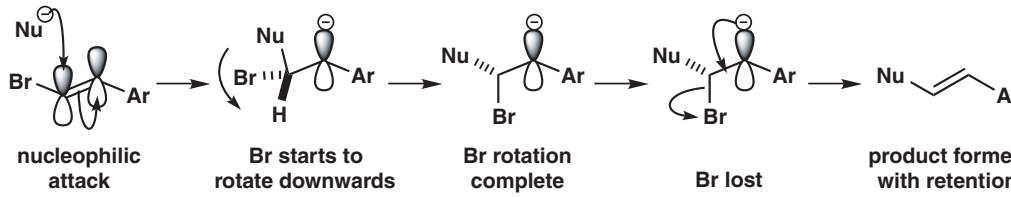
The third possibility is an S_N1 reaction with a vinyl cation as intermediate. This is unlikely when we are dealing with vinyl bromide itself **13** as the cation **14** would be very unstable. Notice that the vinyl cation would be a linear species with an empty p-orbital. Such cations are known when they are stabilised by conjugation **17** and the leaving group is excellent, such as triflate (OTf = $CF_3SO_2O^-$ in **16**) but these S_N1 reactions are rarely used in synthesis.



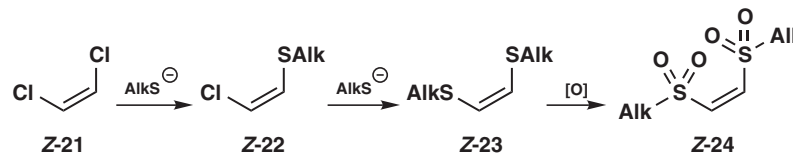
Stereospecificity in the addition-elimination mechanism

By far the most important of all these mechanisms is addition-elimination. The carbanion intermediate must be stabilised by a group Z such as Ar, COR, CN, RSO, or RSO_2. The reaction then becomes a conjugate substitution as **10** to **12**. It appears there that, if the intermediate **11** has a lifetime longer than bond rotation, only the more stable of the two products (*E* in this case) will be formed. However, there are quite a few cases where the first step is rate-determining and the intermediate has a very short lifetime indeed. These reactions go with retention of configuration. An important example is the replacement of halides by thiolate nucleophiles[3] in 2-bromo styrenes **19**.

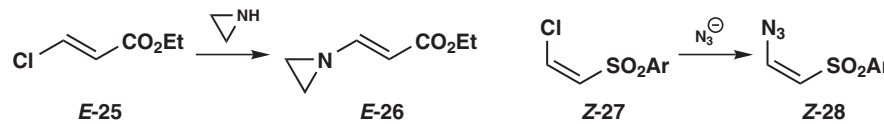
The explanation resembles that for the retention of stereochemistry in the reaction of vinyl silanes with electrophiles (chapter 16). To make this clearer, we have drawn the diagrams as nearly the same as those in that chapter as possible. It does not matter which surface of the alkene is attacked by the nucleophile as long the bromine atom continues to rotate in the same direction. Once it reaches the vertical it can be eliminated by the carbanion and the result is retention (<5% of the other isomer).



The reaction even goes twice if there are two leaving groups (chloride in this case **21**) and the products can be oxidised to the more stable sulfones **24**. It is more impressive with the *Z*-isomer.

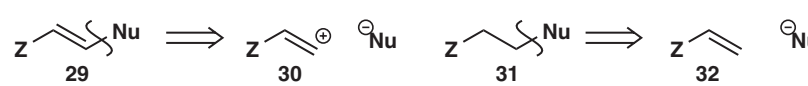


Other systems that allow stereospecific substitution with retention include ester-activated chloride displacement by an amine (**25** to **26**) and sulfone-activated chloride displacement by azide (**27** to **28**). The choice of *E*- or *Z*-isomers is arbitrary as each gives >98% retention.[1] The reactions shown so far do not include carbon nucleophiles.



Towards Carbon Nucleophiles and Vinyl Cation Equivalents

The subject of this chapter is how we can achieve reaction of nucleophiles with vinyl electrophiles such as vinyl halides. We cannot easily make S_N1 or S_N2 reactions happen at sp^2 carbon atoms but we can make the products of those unfavourable reactions by other reactions in which the same bond is formed. We want to be able to use carbon nucleophiles. We also want to control the stereochemistry of the double bond in the product. This is the disconnection we want to achieve **29**:

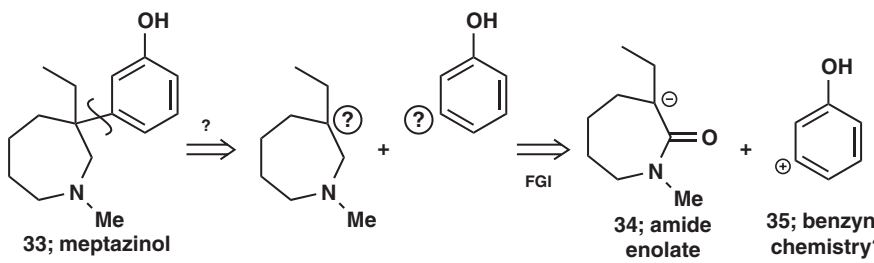


You may think that we already know how to do this by conjugate or Michael addition where Z is an anion-stabilising group. These reactions do add nucleophiles to double bonds but the

intermediate is an enolate and the double bond disappears in the product so that the disconnection is **31** and the alkene **32** is a reagent and not a synthon. We would be happy with conjugate addition as a solution to the problem if the double bond could be restored in the product. We shall first consider some conventional solutions to the problem such as conjugate substitution and conjugate addition with the restoration of the double bond and then move on to more important modern solutions mostly based on palladium chemistry.

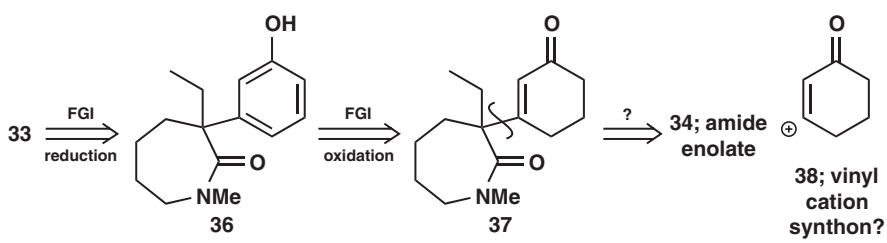
Vinyl cation equivalents

We shall start with a pharmaceutical example, the Wyeth analgesic Meptazinol[4] **33**. This compound has a seven-membered ring amine attached through a quaternary carbon atom to a *meta*-hydroxy benzene ring. The greatest simplification would undoubtedly arise by disconnection of the strategic bond joining the two rings. But the functionality is all wrong for this. Hydroxy groups direct *ortho* and *para* and the nitrogen cannot help to activate the required carbon on the seven-membered ring. Changing the functionality of the amine to an amide makes a lot of sense as a correctly placed carbonyl group activates the right carbon atom and amides can be converted into amines by reduction. However this will require the use of a nucleophilic enolate **34** at what is to become the quaternary carbon atom and so forces us to use an equivalent of an aryl cation **35**: this route was beautifully realised by the use of benzyne chemistry and this is described in the workbook.

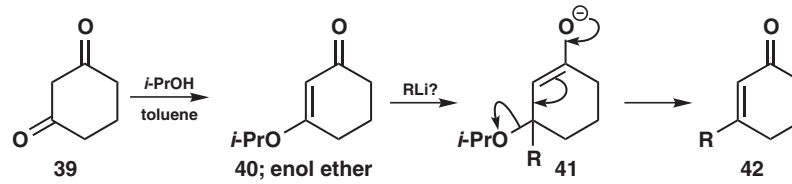


Conjugate Substitution

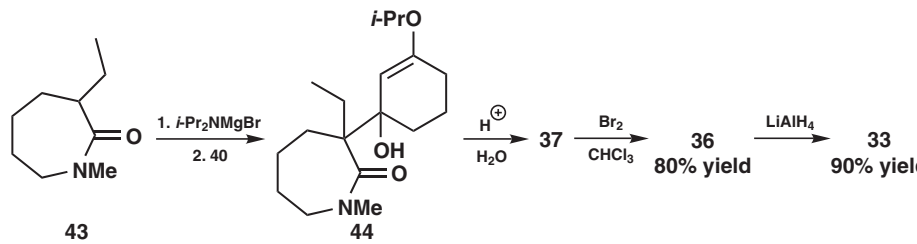
More relevant to this chapter is the realisation of a vinyl cation strategy which was in fact chosen as the development route for the product. Adjusting the oxidation state of the benzene ring reveals a promising enone **37** and requires a reagent for the vinyl cation synthon **38**.



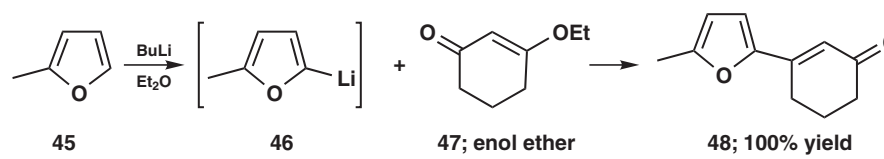
The best way to derive a reagent for the synthon **38** is to insert a leaving group at the vinylic position. The enol ether **40**, easily prepared from the 1,3-diketone **39** turns out to be ideal as we can envisage conjugate substitution by the amide enolate **34**.



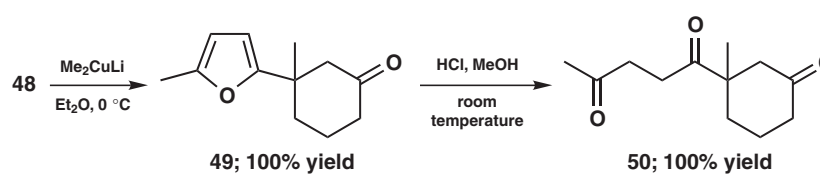
Addition of the magnesium enolate of the amide followed by acidic work-up gave the amido-enone in one step with the double bond still present in the ring. Notice that direct addition of the enolate to the carbonyl group **41**, rather than the conjugate addition envisaged, actually occurred. This doesn't matter as the enol ether **40** has a symmetrical carbon skeleton. The synthesis was completed by an oxidation of the enone ring with bromine to give the benzene ring in **36** and a reduction of the amide to give meptazinol itself.



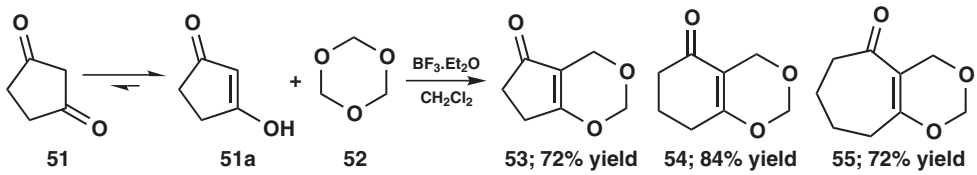
The nucleophile does not have to be an enolate: *ortho*-lithiated aromatics (chapter 7) work well as in this sequence used in the synthesis of sesquiterpene lactones. 2-Methyl furan **45** is lithiated in the one remaining α-position **46** and it adds to the ethyl equivalent of **40** to give the enone **48** in quantitative yield.[5]



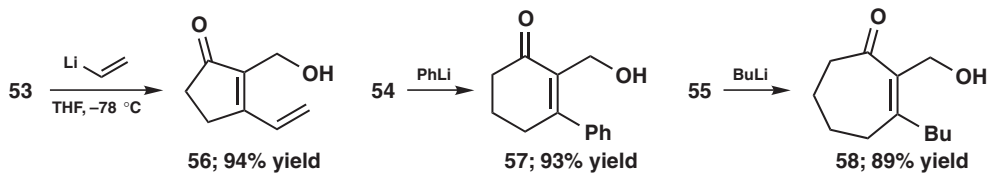
The further development of **48** is interesting. Conjugate addition of Me_2CuLi creates a quaternary centre **49** and acid hydrolysis of the furan releases the triketone **50** used to make sesquiterpene lactones. The yields in these three steps are amazingly good.



Substituted versions of these reagents retain the symmetry of **40** and **47**. One interesting type is prepared by a Prins reaction of the diketone **51** with trioxan **52**, the trimer of formaldehyde.[6] The six- **54** and seven-membered **55** compounds are easily made in the same way.

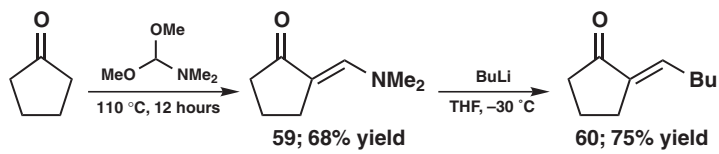


Reaction with organo-lithium compounds works well with all three examples: one molecule of formaldehyde is lost but a CH_2OH group is retained in the products **56**, **57**, and **58** from addition of vinyl, phenyl, and butyl lithium. This chemistry was used to make bertyodionol.[7]

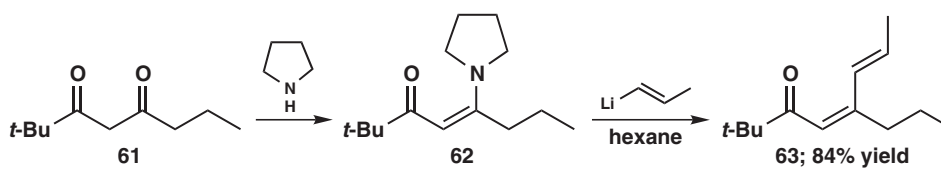


Unsymmetrical 1,3-dicarbonyl compound derivatives

For unsymmetrical versions do not start from the diketone. One way is to start from a monoketone and react with an amide acetal (like those used in Claisen rearrangements, chapter 15). Thus cyclopentanone gave the enaminoketone **59** that reacts with BuLi to give the enone **60**. There is no doubt here that the nucleophile has added in a conjugate fashion.[8]

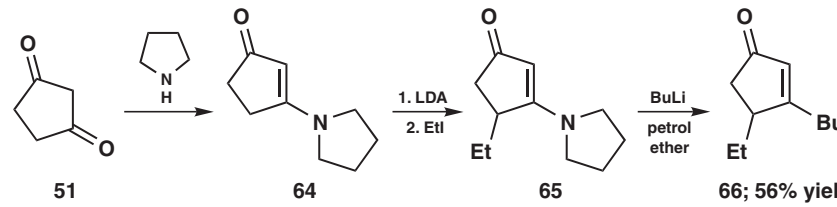


The same intermediates **62** can be formed from diketones and amines, particularly pyrrolidine, and react well with organolithium compounds. The newly added RLi replaces pyrrolidine in good yield providing that a hydrocarbon solvent is used. The yields of dienyl ketones such as **63** are very good.[9]

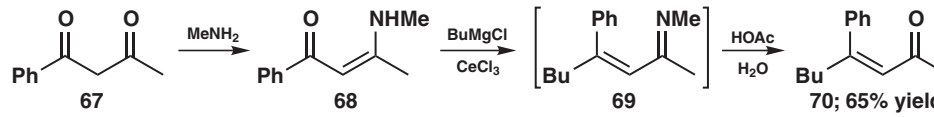


Unsymmetrical enaminones

It is obviously easier to prepare symmetrical enaminones such as **64** by this method but these can be 'desymmetrised' by enolate alkylation to give, say, **65** before conjugate substitution leads to the final product **66**. The yields are reasonable for a three-step process and the middle step gives the product **65** of γ-alkylation of an extended enolate (see chapter 11).

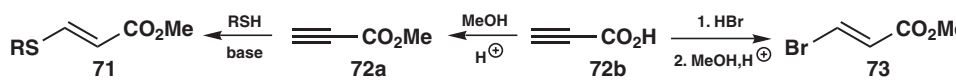


The reverse regioselectivity is realised by cerium-catalysed addition of Grignard reagents to enamino ketones **68** formed with primary amines.[10] The structure of the product shows that direct addition to the carbonyl group has occurred: the Ce atom presumably delivers the butyl group through chelation to nitrogen. There is reasonable stereochemical control: the newly introduced group goes *trans* to the carbonyl group in the product **70**.

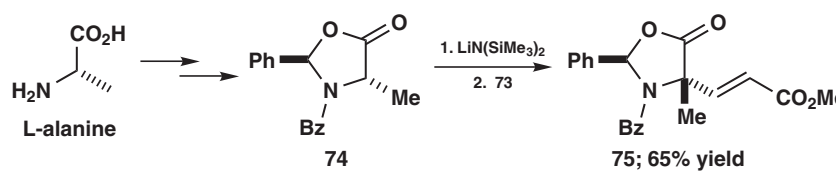


Conjugate Addition to Alkynes

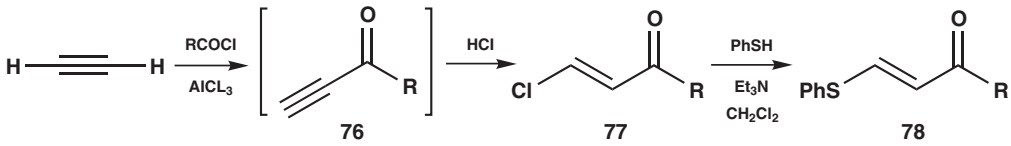
Conjugate addition alone gives a vinyl derivative if the electrophile is an alkyne. We have seen examples of this in chapter 15 where, for example, halides and thiolate nucleophiles gave substituted alkenes such as **71** and **73** from **72** as the *E*-isomers under equilibrating conditions. The bromoester **73** is easily made from the acetylenic acid **72b** and esterified afterwards.[11] These compounds will now prove useful as vinyl cation equivalents as conjugate substitution on **71** and **73** is generally more successful than conjugate addition to **72**, at least with carbon nucleophiles. We are not concerned here with the related carbometallation of alkynes described in chapter 16 as the products are formally vinyl *anion* equivalents. However, as we shall see later in this chapter, the distinction is blurred in Pd-catalysed couplings.



So lithium enolates react with the halide **73** by conjugate substitution. The lithium enolate of the enantiomerically pure heterocycle **74** prepared from natural alanine gives one diastereoisomer of *E*-**75** in reasonable yield. After further manipulation the heterocycle was hydrolysed to give cyclopropanes that are glutamate antagonists.[12]

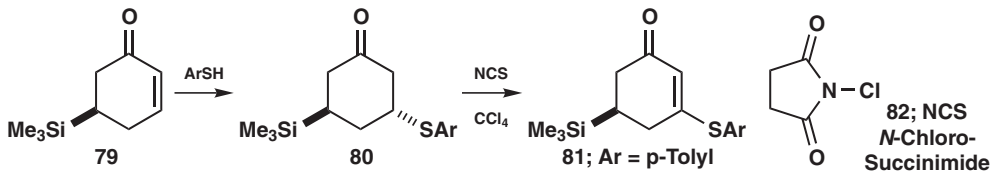


The corresponding ketones **76** can be made by aliphatic Friedel-Crafts reactions between an acid chloride and acetylene using $AlCl_3$ as catalyst. Under these conditions chloride adds to the acetylenic ketone to give the β-chloroenone **77** directly. These compounds are converted into the sulfides **78** by conjugate substitution[13] and are used as vinyl cation equivalents in the next section.

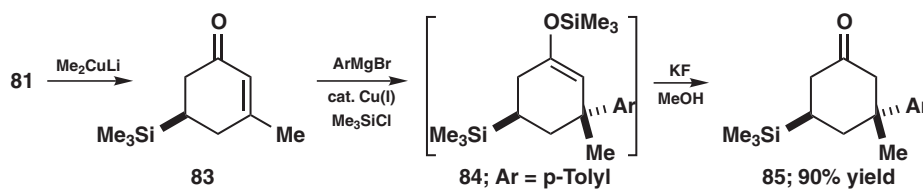


Sulfur-based leaving groups

The sulfur compounds like **71** can be made by conjugate addition not only to alkynes but also to enones, e.g. **79**, by using the Pummerer oxidation of the products **80** with *N*-chlorosuccinimide (NCS) **82** to give a β-thio-enone **81** not accessible by conjugate addition to an alkyne.

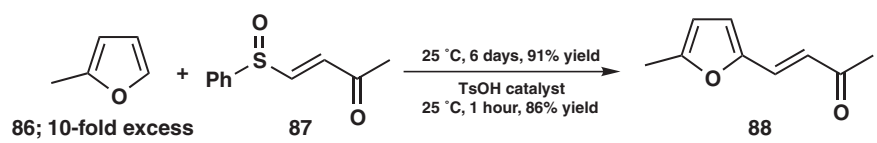


While organo-lithium compounds add directly to the carbonyl group of **81**, cuprates carry out a conjugate substitution to give the enone **83**. Now a conjugate *addition* gives the ketone **85**. It is necessary to use Cu(I) catalysis and silyl trapping (see chapter 9) to make this conjugate addition work but it gives good yields. The group added *second* (here *p*-tolyl) ends up *trans* to the Me_3Si group on the other side of the ring.[14] And what is the Me_3Si group there for? That is explained in the workbook.

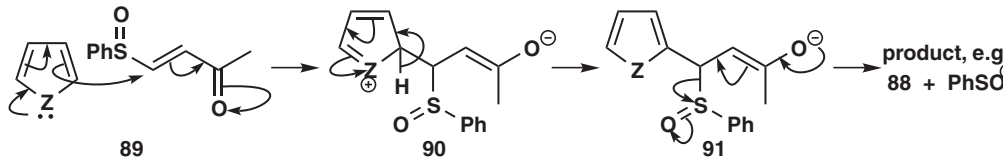


Sulfoxides and sulfones

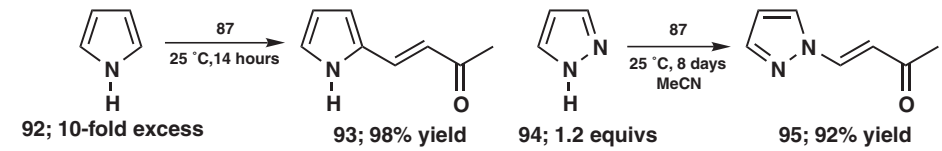
One advantage of sulfur chemistry is that reagents can be used at three oxidations levels: sulfide **80**, sulfoxide and sulfone. The enones with the more highly oxidised sulfur atoms are more electrophilic and need less reactive nucleophiles. Thus the sulfoxide **87** reacts with unactivated pyrroles and furans, e.g. **86** with or without acid catalysis.[15]



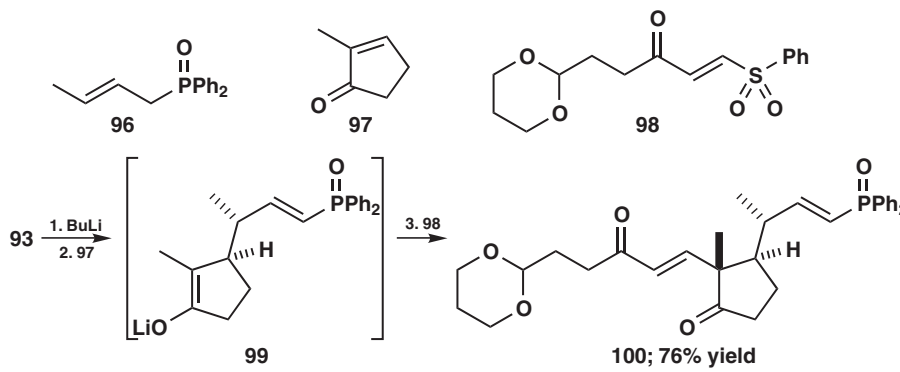
The nucleophiles **89**; Z = O or NR react by normal electrophilic aromatic substitution: both the addition **89** and the expulsion of the leaving group **91** are faster with PhSO instead of PhS. In the acid catalysed reactions the intermediates **90** and **91** would be enols rather than enolates.



vThe more reactive pyrrole **92** needs a shorter time while imidazole and pyrazole **94** react much faster but through nitrogen. All these reactions go in remarkably high yield.

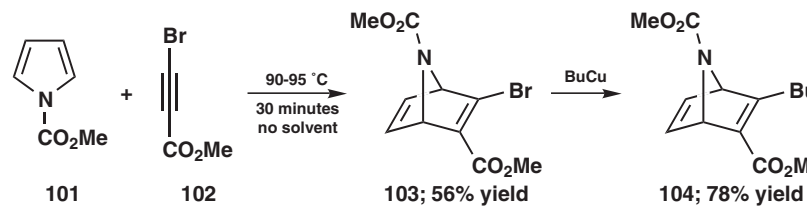


The sulfone **98** allows a tandem (chapter 36) sequence of remarkable selectivity. The lithium derivative of the allylic phosphine oxide **96** (see chapter 12) adds to the enone **97** to give the lithium enolate **99** trapped by the sulfone **98** to give the complex product **100** in 96% yield: the only imperfection in stereochemical control is 3% of the *Z*-vinyl phosphine oxide.[16]



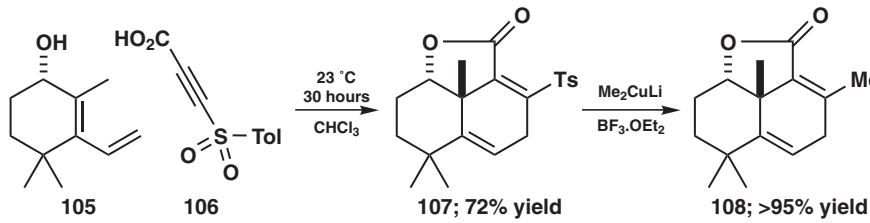
The Diels-Alder Reaction on β-Bromo and β-Sulfonyl Alkynes

An alternative to conjugate addition to alkynes is the Diels-Alder reaction that gives the required β-substituted alkenes without conjugate addition. Thus the deactivated pyrrole **101** reacts quite well with the activated haloalkyne ester **102** to give the bicyclic compound **103** having the right arrangement of Br and CO_2Me to allow conjugate substitution. Alkyl copper reagents are best and give good yields of compounds such as **104** used in a synthesis of epibatidine.[17]



The more elaborate diene **105**, prepared by enantioselective reduction of the corresponding ketone, (chapter 26) reacts with the β-tosyl alkyne acid **106** to give a good yield of one regio- and

stereo-isomer of the lactone **107** having the leaving group in the right position for replacement with a nucleophile. A methyl group was needed for the synthesis of forskolin and Me_2CuLi was the best reagent.[18]

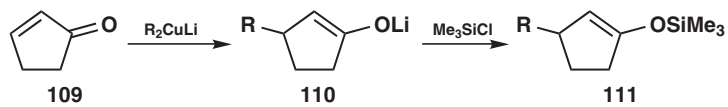


Choice of leaving group

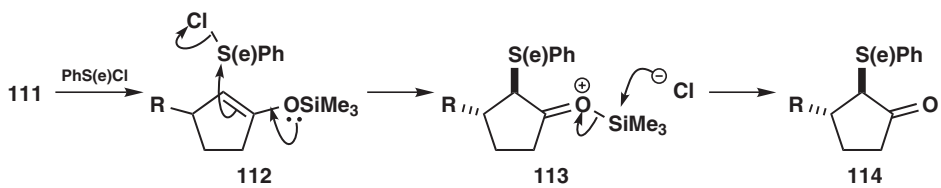
You will notice that simple organo-lithium and copper compounds as well as lithium enolates are used in these conjugate substitution reactions. If the leaving group is a halide, there is a danger of transmetallation with RLi (though not with lithium enolates) and organo-copper compounds are safer. With leaving groups such as NR_2, OR, or sulfur in various oxidation states, there is essentially no danger of transmetallation as oxidative insertion into the strong C-N, C-O, or C-S bonds is rare, and simple RLi can be used.

Modified Conjugate Addition

The double bond can be restored after a conjugate addition to an electrophilic alkene if the enolate intermediate **110** is trapped as a silyl enol ether **111** and then combined with a sulfur or selenium electrophile which is later eliminated. Organocuprates are ideal nucleophiles for this process as the intermediate enolate can be trapped as a silyl enol ether and reacted directly with PhSCl or PhSeCl.

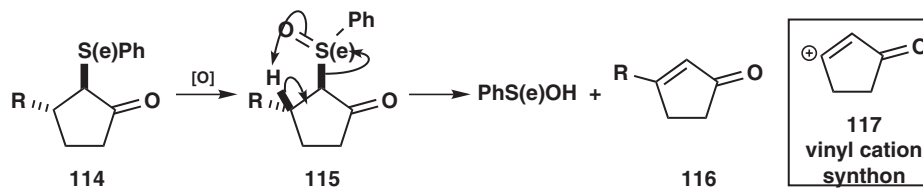


This method of making specific enolate equivalents we met in chapter 9. Reactive electrophiles like PhSCl and PhSeCl react rapidly with the silyl enol ether **111** to give the 2-PhS(e)-ketone **114**. Addition is to the face of the ketone not blocked by the alkyl group on C-2.



Oxidation of the sulfur or selenium atom to the sulfoxide or selenoxide stage allows thermal elimination to take place by a cyclic mechanism **115**. Because the PhS(e) group is *trans* to the alkyl group it must be *cis* to the hydrogen atom at C-2 and so *cis* elimination is possible. The selenoxides are unstable and decompose spontaneously but the sulfoxides usually need heating. The double bond is put back in its original position **116** so the strategy of the sequence is addition

of an alkyl anion to a β-enone cation synthon **117**. This chemistry is discussed in more detail in chapter 33 under 'oxidation of enolates'.

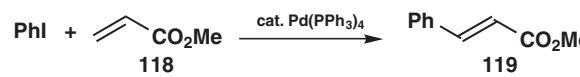


A more general solution to the problem is to change the nucleophile from an organo-lithium or copper species to an organo-palladium compound and this leads on to the Heck reaction.

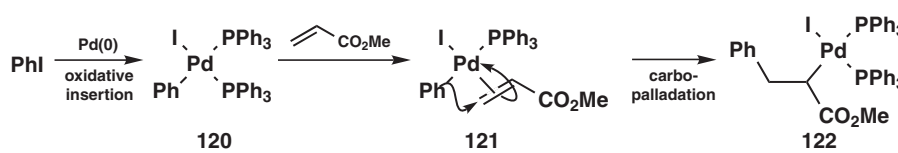
The Heck Reaction

General description

We have discussed palladium chemistry in chapter 8 where there was a brief description of palladium σ-complexes. In this chapter we shall see the results of adding palladium σ-complexes to unsaturated carbonyl compounds. Michael addition occurs but the palladium leaves the intermediate in such a way that the original alkene is restored.[19] We shall take a simple example first – the addition of iodobenzene to methyl acrylate.

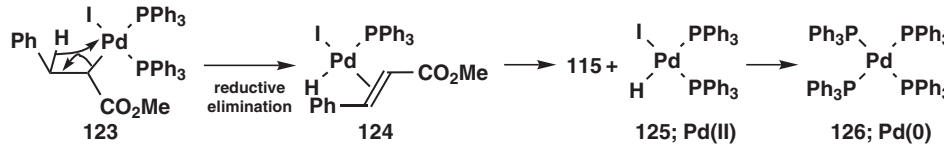


The first step is oxidative addition of the Pd(0) species to iodobenzene. This is called oxidative addition because the Pd atom adds between the benzene ring and the iodine atom and is oxidised from Pd(0) to Pd(II) **120**. The mechanism is described in chapter 8. Next the alkene forms a π-complex **121** with the palladium atom. The π-bond is a two-electron ligand and it makes sense for it to displace one of the two-electron phosphine ligands. However, we should emphasise that it is not always possible to be precise about which other ligands are present on the palladium atom in these reactions. Now the nucleophilic attack occurs. The palladium atom transfers its phenyl ligand to one end of the double bond and attaches itself to the other as a σ-complex **122**. This is like a phenyl anion doing a Michael addition to the alkene which is made even more electron deficient by complexation to Pd(II). This view explains the regioselectivity of the addition as "Ph^-" would certainly attack the more electron-deficient end of the alkene and the Pd would prefer to form a σ-complex to the more carbanion-like enolate position. However, you can view it as a coupling reaction on the surface of the metal if you like.



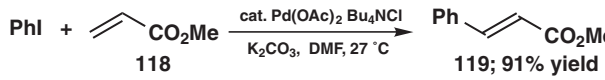
Palladium alkyl complexes are inherently unstable because of β-elimination. We saw this in action in the discussion on hydrogenation in chapter 8. The palladium atom leaves with a hydrogen

atom from C-3 of the ester **123** and the σ-complex **122** reverts to a π-complex **124** with the product. The product is freed if the palladium (II) atom drops out of the π-complex as **125**: it can lose HI and revert to Pd(0) ready for the next cycle. During the reactions Pd is present in all the complexes as Pd(II) but it enters and leaves the cycle as Pd(0).



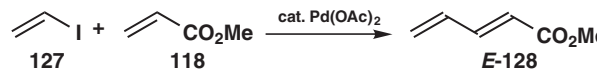
The stereochemistry of the double bond in the product is a result of the stereoselective β-elimination of palladium - this reaction could give either the *E*- or the *Z*-cinnamate but the reaction is reversible and the *E*-cinnamate is more stable.

This sort of Heck reaction is normally done in a more convenient way. Though Pd(0) really starts off the cycle, Pd(II) is involved and $Pd(OAc)_2$ [or $(Ph_3P)_2Pd(OAc)_2$] is a more convenient reagent than $Pd(PPh_3)_4$. This same product can be made in excellent yield under very mild conditions without any phosphine at all.[20] An explanation of the necessary reduction of Pd(II) to Pd(0) is in the workbook.

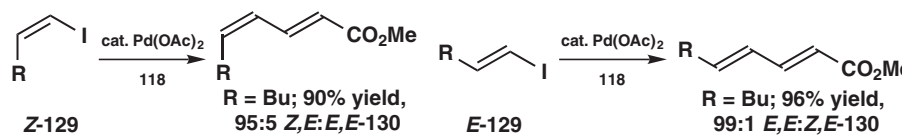


Scope and limitations of the Heck reaction: synthesis of dienes

Because of β-elimination of palladium, this reaction cannot be used with most alkyl halides. However, vinyl halides are fine as their palladium σ-complexes do not undergo β-elimination to give alkynes. Here is a simple example.



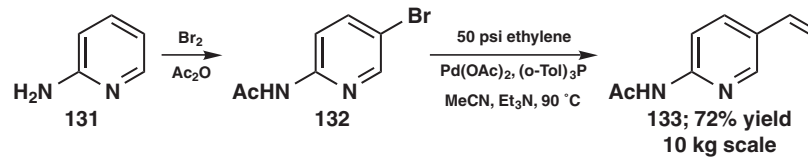
The mechanism is the same as before with vinylPdI replacing PhPdI. The *E*-alkene is again produced under thermodynamic control. But what happens if the vinyl iodide has some stereochemistry? Then there is stereospecificity in the formation of this alkene: *Z*-vinyl iodides **129** give *Z*-alkenes and *E*-vinyl iodides give *E*-alkenes stereospecifically with retention. In chapter 16 we discussed this sort of reaction - replacement of halide by metal or of metal by metal at a trigonal carbon atom normally occurs with retention. This reaction can give *E,E*- or *Z,E*- dienes **130** but not E, *Z*- or *Z,Z*-dienes.[20]



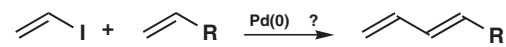
As we have drawn the products, the right hand double bond is formed stereoselectively under thermodynamic control, and can be *E* only, while the left hand double bond is formed stereospecifically with retention from the original vinyl halide and can be *E* or *Z*.

The Heck reaction with electron-rich alkenes

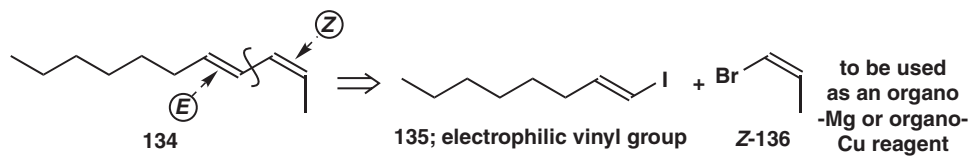
The obvious limitation of this reaction so far is in the electrophile as we have suggested naturally electrophilic enones as ideal partners for aryl or vinyl palladium σ-complexes. In fact, complexation with palladium makes all alkenes electrophilic and nucleophilic addition can in principle occur to a simple alkene while it and the nucleophile are both bound to the palladium atom. Such reactions are known for aryl halides. Even ethylene itself does satisfactory Heck reactions and its reaction with the bromopyridine **132** is the basis for a large scale process leading to a drug.[21]



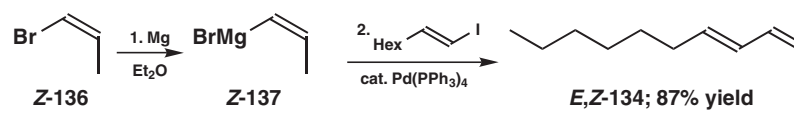
In practice, with vinyl halides, three regioselective problems arise - which alkene is to act as the electrophile, which end of the alkene is attacked by the nucleophile, and which way does the β-elimination occur?



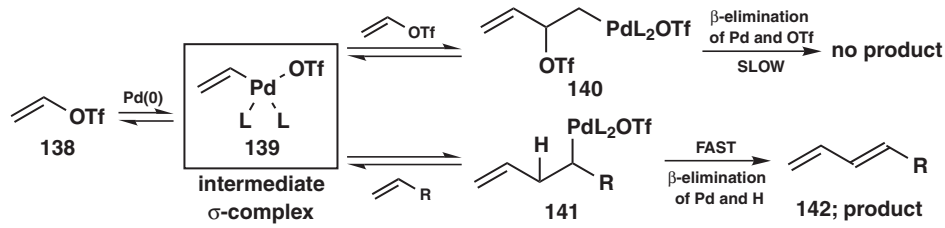
These problems may be avoided by making an organometallic compound [often of Cu(I) or Mg(II)] from the halide intended to become the palladium σ-complex and to use another vinyl halide as the electrophile. Palladium prefers to take out a halide rather than a hydrogen atom in the β-elimination step and all three problems disappear. In the synthesis of this *E,Z*-diene **134**, we prefer to use a Pd σ-complex for the *Z*-alkene part **136** and a vinyl iodide **135** for the *E*-alkene.



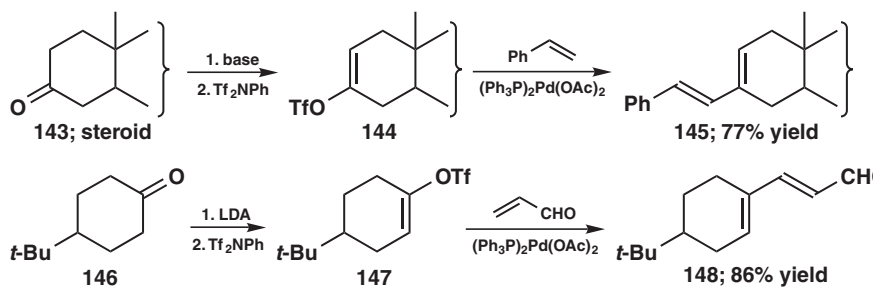
The Grignard reagent from *Z*-1-bromopropene combines with *E*-1-iodo-octene with catalytic $Pd(PPh_3)_4$ to give the pure *E,Z*-diene in 87% yield. The Mg and Pd exchange by transmetallation as Mg forms stronger bonds to oxygen.[22]



This solution takes the method outside the scope of the Heck reaction which is better realised with vinyl triflates **138** [Triflate = OTf = OSO_2CF_3]. These can be made into palladium σ-complexes but do not function as electrophiles since the β-elimination of Pd and OTf is a poor reaction. The small amount of Pd σ-complex **139** formed in solution adds both to the alkene and the remaining vinyl triflate but β-elimination leads rapidly to product, releasing Pd(0) for the next cycle, from only intermediate **141**.

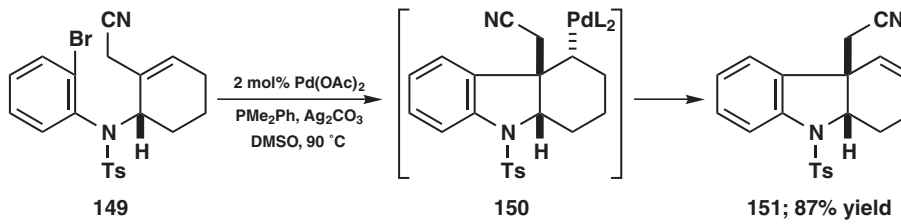


Vinyl triflates, which are of course enol triflates, such as **144** and **147**, can be made directly from ketones **143** and **146**, and react with electron-deficient, conjugated, and electron-rich alkenes. Here are just two examples giving dienes **145** and **148** in good yield.

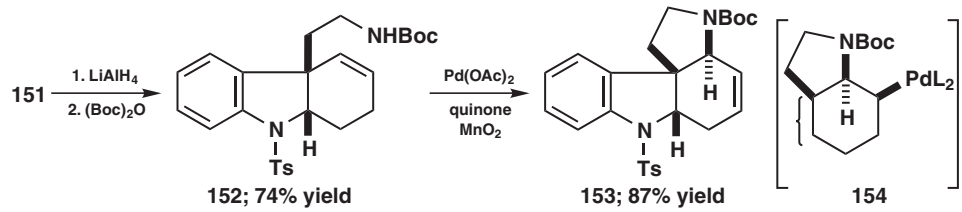


A synthesis of strychnine

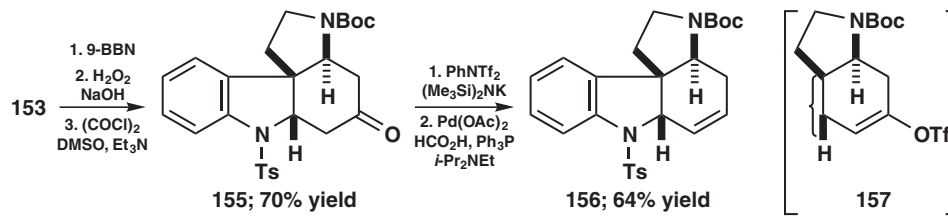
Rapid development in the Heck reaction has made it one of the most important of all modern methods. A dramatic example is a recent synthesis of strychnine by M. Nakanishi and M. Mori.[23] This synthesis illustrates the intramolecular Heck reaction particularly well, showing examples of regioselectivity in attack on the alkene and in formation of the new alkene. The synthesis starts with a Heck reaction on enantiomerically pure **149**. Attack occurs on the nearer end of the alkene to give **150** that cannot eliminate to reform the same alkene as there are no H atoms left and the alkene **151** must be formed. The stereochemistry is controlled by the short tether linking the aryl bromide and the alkene.



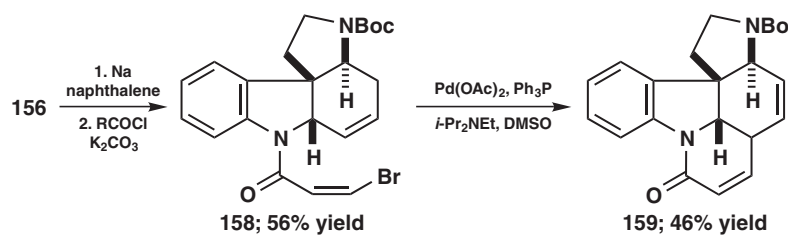
The second ring is closed by an amido-palladation reaction. The nitrile in **151** is reduced to a primary amine and protected with a Boc group. Reaction with Pd(II) allows nucleophilic attack by the amide on the nearer end of the alkene and β-elimination again pushes the alkene round the ring **153**, this time because there is no syn H atom in the intermediate **154** at the site of addition. Palladium is released as Pd(0) but this reaction needs Pd(II) so the quinone and MnO_2 are there to carry out the required oxidation.



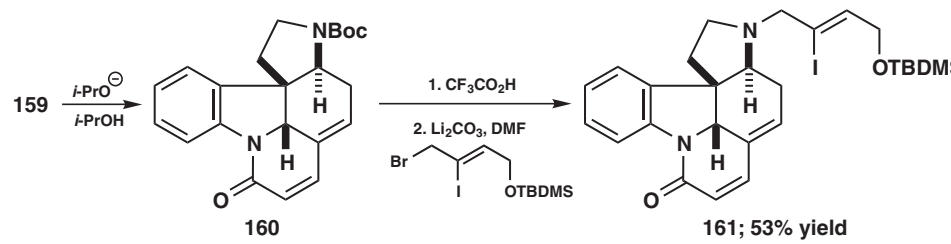
Now the alkene must be moved yet one more time around the ring to prepare the way for another intramolecular Heck reaction. Hydroboration (chapter 17) of **153** is regioselective because of the large N-Boc group and Swern oxidation completes the insertion of the ketone **155**. Reduction and elimination use another palladium-catalysed reaction. Conversion to the triflate **157** is followed by Pd-catalysed transfer hydrogenation, the H atom coming from formic acid HCO_2H.



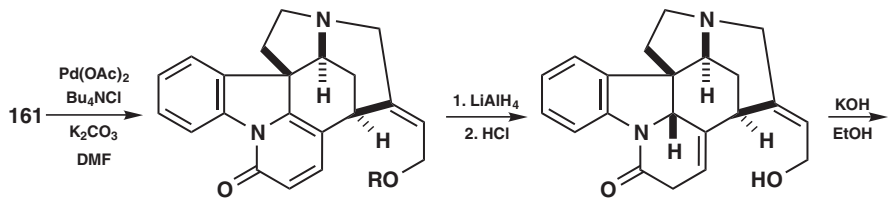
The molecule is now prepared for the next Heck reaction by reductive removal of the Ts group from nitrogen and acylation with *Z*-3-bromoacryloyl chloride to give **158**. Intramolecular Heck reaction closes the ring **159** in reasonable yield and with the correct and expected regioselectivity. The stereochemistry of the new centre is irrelevant as it will disappear. The double bond is moved back round the ring one place! In this reaction we see a β-bromo unsaturated acid derivative providing the nucleophile for the Heck reaction rather then the electrophile for conjugate substitution.



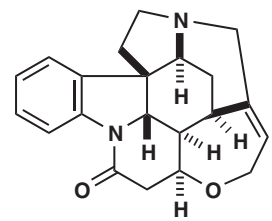
The double bond is moved into conjugation **160** with base and the side chain for the last Heck reaction is added by deprotection at nitrogen and alkylation with an allylic bromide to give **161**. Notice that the allylic bromide reacts rather than the vinylic iodide as this reaction is not catalysed by palladium.



Now the Heck reaction can be induced to close the ring **162**. In this case the vinyl iodide forms the palladium derivative and the regioselectivity of the attack is at the δ-position of the dienone mainly because of the tether. The closure of the last ring was already known and the synthesis of strychnine **164** complete. This synthesis uses three Heck reactions and two other palladium-catalysed reactions.



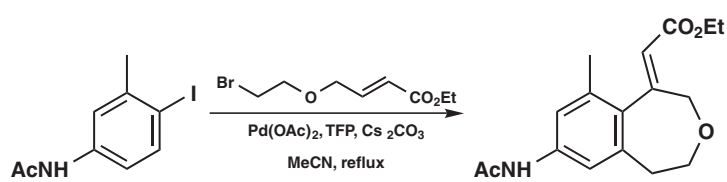
162; R = TBDMS, 48% yield **163; 44% yield**



164; strychnine

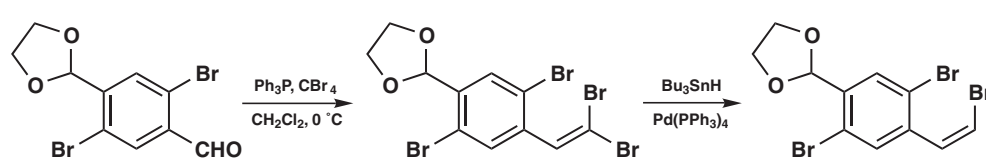
Recent developments in the Heck reaction

The big difference between the Heck reaction and those couplings to follow in the next section is that only one of the alkenes is marked with functionality (halide, triflate): the other is a simple alkene and loses a hydrogen atom during the Heck process. This sounds like a disadvantage where regioselectivity is concerned but some recent examples should convince you that the Heck reaction is very important indeed. So the Heck reaction can be combined with a Pd-catalysed *ortho* alkylation of an aromatic halide **165** to give benzoxepines **166** in excellent yield even with an unprotected amide on the ring.[24]



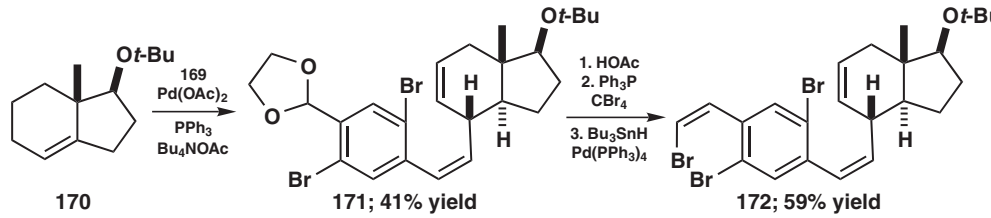
165 **166**

A bonanza of Heck reactions was used by Tietze[25] in the synthesis of cephalostatin analogues. Corey-Fuchs reaction on the aldehyde **167** gives the alkene **168** from which the trans Br atom is stereoselectively removed by Pd-catalysed tin hydride reduction to give the *Z*-vinyl bromide **169**. This reaction is discussed below under Stille coupling.

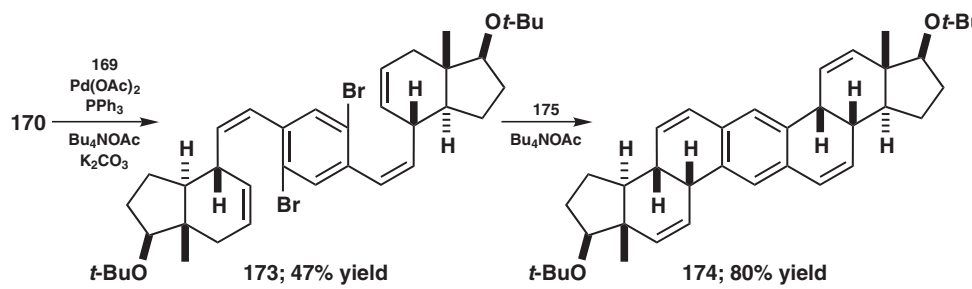


167 **168; 80% yield** **169; 98% yield**

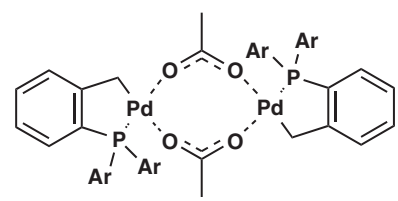
Heck reaction with the enantiomerically pure bicyclic alkene **170** gives the new C–C bond **171** with retention at the vinyl bromide, stereoselective introduction of two new stereogenic centres, and relocation of the alkene since *cis* elimination of palladium is required. Repetition of the first two reactions after deprotection of the other aldehyde gives a new *Z*-vinyl bromide **172** ready for the next Heck reaction.



Now a second Heck reaction between the newly formed vinyl bromide **172** and the same alkene **169** gives the C_2-symmetric compound **173** with all the same selectivity. Notice that vinyl bromides are more active in the Heck reactions than the aryl bromides present **169** and **172**. However, when there are no more vinyl bromides left, the two aryl bromides do take part in a double intramolecular Heck reaction. Two more stereogenic centres are introduced and the alkene moves one place further round the ring. A special catalyst **175** is needed for this reaction that goes in excellent yield.



This synthesis involves two Pd-catalysed reductions and four Heck reactions all using $Pd(OAc)_2$ except the last. The yields are not always wonderful, but the synthesis is made very short and selective by the repeated Heck requirements.



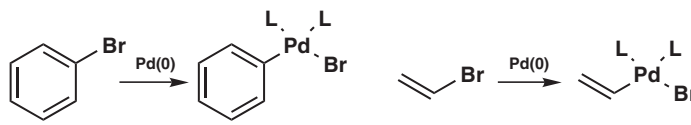
Sp^2–sp^2 Cross-Coupling Reactions by Transmetallation

Halide and triflate leaving groups are also involved with palladium catalysis in the most general of all these reactions with vinyl electrophiles. These use a main group rather than transition metal, chiefly boron or tin, in stoichiometric amounts to mark one molecule as nucleophilic and then

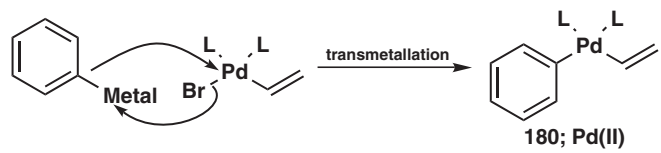
transfer that group to the palladium atom by a transmetallation. Combination with an aryl or vinyl halide or triflate completes the synthesis.
We can write a general scheme for this class of reaction in four stages:

1. Preparing the organometallic (usually boron **176** or tin **177**) compound by various methods from the intended nucleophile.

2. Oxidative addition of catalytic palladium (0) to the aryl or vinyl halide or triflate.

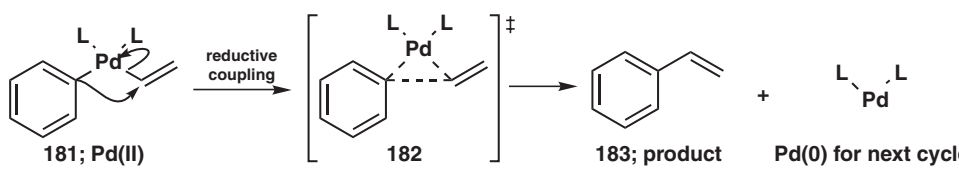


3. Transmetallation to give a Pd-C bond **180** and a B-(or Sn-) halide (shown with an aryl 'nucleophile' and vinyl 'electrophile').



The arrows on the transmetallation step are intended to indicate which group joins to which rather than a mechanism. We have seen other transmetallation reactions of this sort - Li exchanged for Cu or boron or tin for example in chapter 16 in particular. They may well go through a four-centred transition state in which the aryl group (in this case) is bonded to both metals and the halide also. Organometallic mechanisms are not always known in detail.

4. Coupling on Pd to make the new C−C bond and to release the Pd(0) for the next cycle.

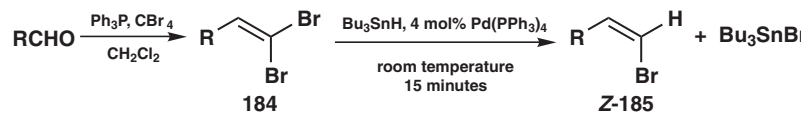


We have described the two components in the coupling as "nucleophilic'' and "electrophilic''. These words are intended to help you make sense of the reactions and should not be taken literally. Of course, when the two groups, vinyl, aryl or whatever, are both bound to the palladium atom, neither is nucleophilic or electrophilic (unless one of them is an unsaturated carbonyl compound) and their combination is a coupling reaction. The coupling occurs through a three-membered transition state **182** and there may be some involvement of the p-orbitals on the carbon atoms joined to palladium.

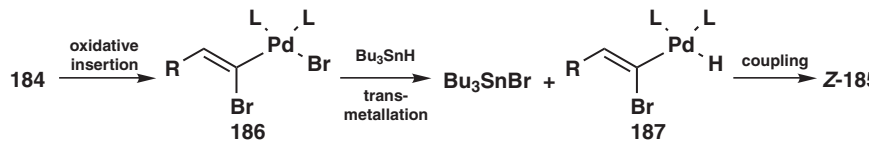
The designation "intended as the nucleophile" is helpful when considering the origin of the fragments. When making a disconnection with an sp^2-sp^2 cross-coupling in mind, one has to decide which molecule is to form the palladium σ-complex and that one is "intended as the electrophile". If these labels do not help, discard them.

Stille coupling

When an organotin compound is the nucleophile, the coupling is called Stille coupling after J. K. Stille of Colorado State University, the inventor.[26] In chapter 15 we saw how organo-tin compounds are sources of radicals, but with palladium catalysis the reaction changes. We shall start with an example which may look trivial but is very important for this chapter. Reaction of readily prepared 1,1-dibromoalkenes **184** with tributyltin hydride under Pd(0) catalysis gives *Z*-1-bromoalkenes **185** with high stereoselectivity.[27]

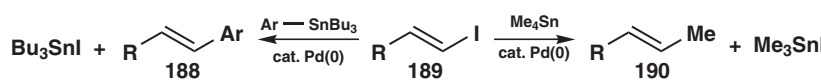


The reaction starts with stage 2 (stage 1 is already done as we can buy the 'organometallic' Bu_3SnH): oxidative insertion of Pd(0) into the less hindered of the two C-Br bonds of the dibromoalkene, that is the one *trans* to R to give the Pd(II) σ-complex **186**. Notice that palladium is again strongly influenced by steric hindrance. Stage 3 is transmetallation – the palladium gets the H atom and the tin gets the Br atom **187**. Most reactions of Bu_3SnH end up with tin exchanging the weak Sn−H bond (~310 kJ/mol) for the much stronger Sn−Br bond (~380 kJ/mol). Stage 4 is the coupling of the vinyl group and the H atom - stereospecifically with retention.

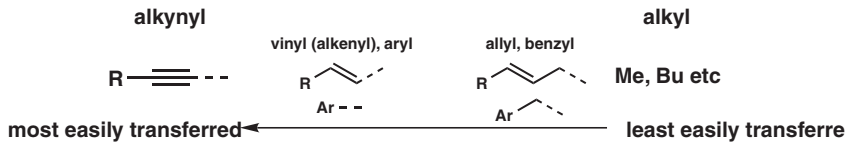


Palladium is released as Pd(0), ready for the next cycle. The relevance of this reaction to the subject of this chapter is that we have already used, and will use again, *Z*-bromoalkenes for the stereospecific synthesis of dienes. This is one way to make them.

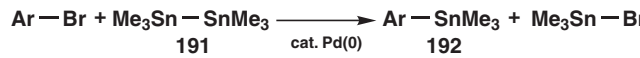
Carbon-carbon bonds can be made from palladium-catalysed reactions of vinyl bromides, iodides **189** or triflates with any organotin compounds which cannot undergo β-elimination after transfer to palladium. These include vinyl, methyl, allyl, benzyl, and aryl groups. This raises the question of which group is transferred from a tin atom in such reactions. With tetramethyl tin there is no choice, the methyl group being transferred to give **190** but aryl groups are transferred in preference to alkyl, giving **188**.



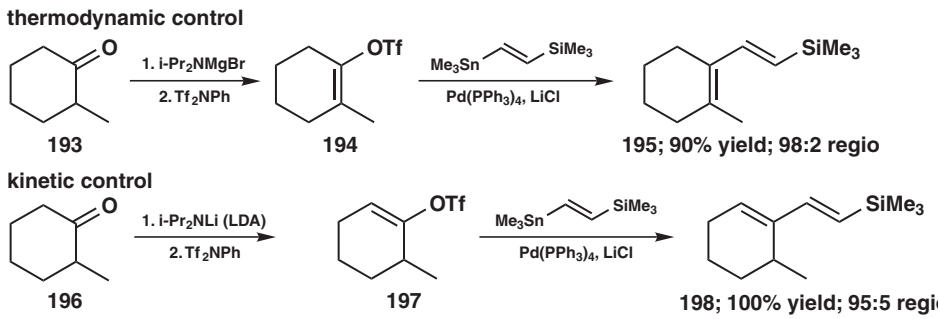
When we want to transfer a group from tin we do not want to waste three of them. The rule is that tin transfers the best *anion* to palladium (strengthening our view that the organotin compound is the nucleophile). Alkynyl groups are transferred best and the order for other groups is roughly as below.



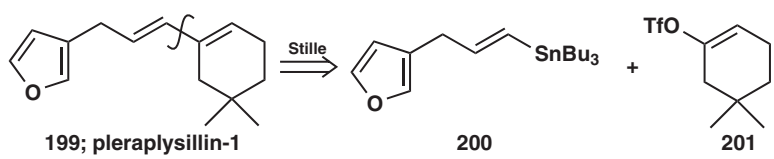
The exact order doesn't matter. What is important is that aryl, vinyl, allyl and benzyl are all transferred more easily (and that means much more easily) than butyl or methyl. If we use a Bu_3Sn– or an Me_3Sn– group, we can be sure that no butyl or methyl groups will be transferred. A neat example is the preparation of aryl tin compounds **192** from aryl halides by Stille coupling. How is that possible? If one tin is to be transferred to carbon, another must pick up the halide so we need two tin atoms joined together – hexamethylditin **191** is the reagent.



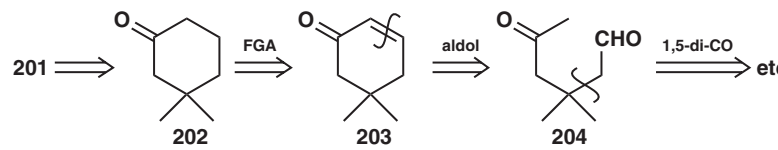
If the electrophile is a vinyl triflate, it is essential to add LiCl to the reaction so that the chloride may displace triflate from the palladium σ-complex. Transmetallation takes place with chloride on palladium but not with triflate. This famous example illustrates the similar regioselectivity of enol triflate formation from ketones to that of silyl enol ether formation discussed in chapter 3. Kinetic conditions give the less **198** and thermodynamic conditions the more highly substituted **195** triflate.



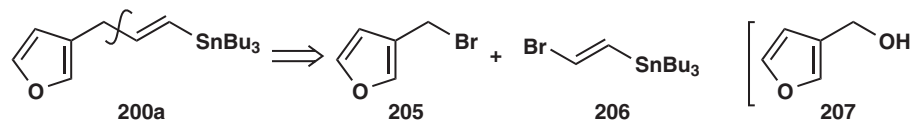
Now let us look at a complete synthesis.[28] The natural product pleraplysillin-1 **199** is found in a marine sponge and in the nudibranch (a kind of apparently defenceless shell-less mollusc) that eats it. It has a defensive role - the nudibranch is "rapidly rejected as a food source by carnivorous fish".[29] Pleraplysilin-1 has a diene joined to a furan at the difficult 3-position. Disconnection between the two double bonds suggests a vinyl triflate **201** from a cyclic alkene, as we can make that regioselectively from the corresponding ketone, and a vinyl stannane from the furan half **200**.



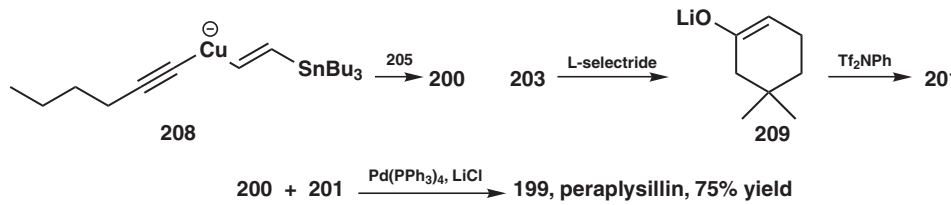
The enol triflate comes from regiospecific reduction of the enone (chapter 3) which can be made by a Robinson annelation.



3-Substituted furans are awkward to make but 3-hydroxymethylfuran **207** is available commercially and is converted into the corresponding bromide **205** with PBr_3 in pyridine. Alkylation of a vinyl cuprate with this reactive alkyl bromide was used here.



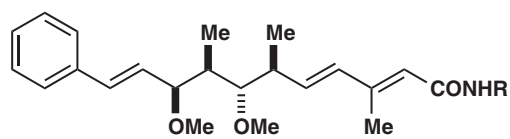
The synthesis is summarised below. Note the use of a hexynyl group on the cuprate **208** - the rule for cuprates is the opposite of the rule for stannanes - the *less* stable anion is transferred first. The coupling requires LiCl and is then very efficient.

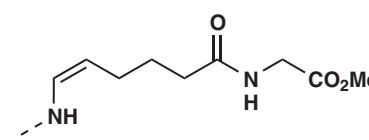


The synthesis is convergent, very short, and gives just the one regiochemical and geometrical isomer of the diene. Another peraplysillin-1 synthesis is described in the workbook.

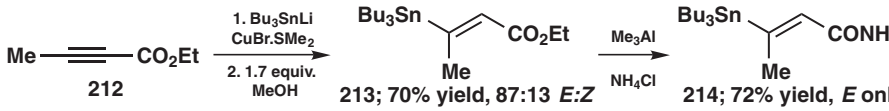
Recent developments in Stille coupling

Because Stille coupling uses stoichiometric tin to control the regioselectivity, one might expect it to become rather less popular as concern over the environmental effects of toxic tin grows. In fact it is as popular as ever, particularly in laboratory syntheses. Two recent syntheses of crocacins both use the reaction to make the diene system. Crocacin C is a primary amide **210** while crocacin D has the more complicated side chain **211**. The rest is the same.

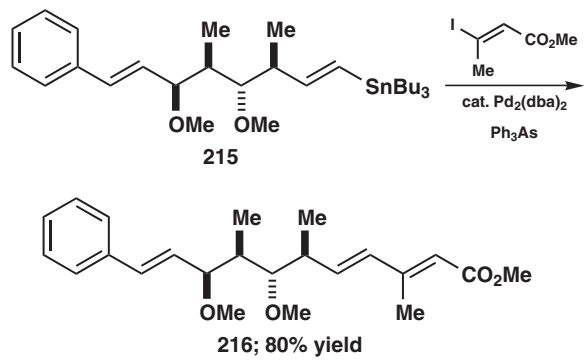




Both syntheses made the bond between the two alkenes by a Stille coupling. One put the tin on the amide part by a Cu(I) catalysed conjugate addition of Bu_3SnLi to the acetylenic ester **212** and Weinreb amide formation. Coupling this vinyl stannane with a single enantiomer of the iodide derived from the rest of the molecule gave crocacin C in good yield. The synthesis of the iodide uses an asymmetric aldol reaction and is described in the workbook.[30]

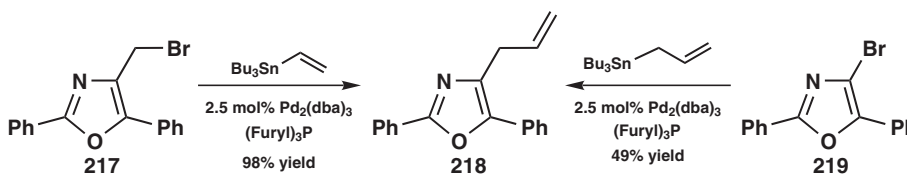


The other synthesis[31] had the tin on the larger part of the molecule **215**. This starting material was also made by an asymmetric aldol reaction and the vinyl stannane was introduced by a special reaction described in the workbook. This is perhaps the more obvious way to do the coupling with the electrophilic halide combining with the vinyl stannane but these syntheses show that the Stille coupling is versatile.

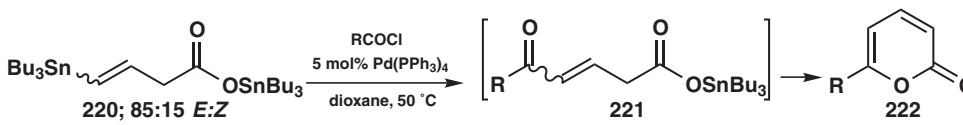


Variations in Stille coupling

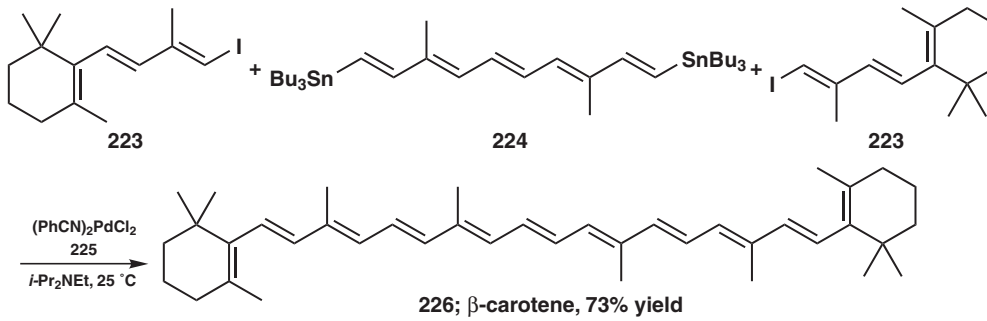
Other reasons for the continuing popularity of the Stille are the range of functional groups compatible with the reaction and the variety of structures that can be incorporated into either component. The allyl isoxazole **218** can be made either from vinyl or allyl-tributyltin using either **217** or **219** It turns out that vinylation of **217** gives a better yield.[32]



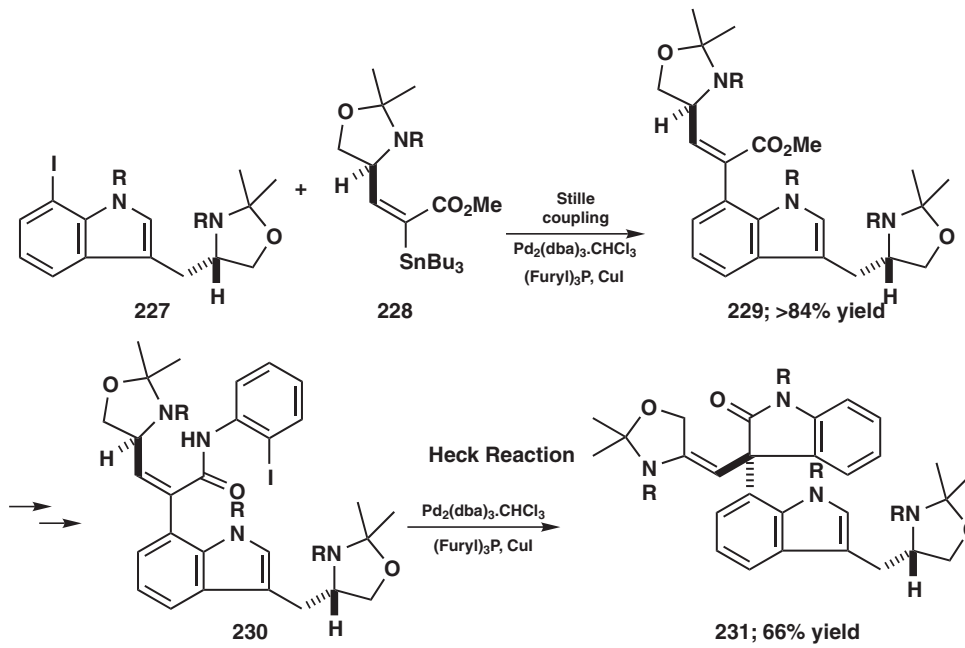
The 'electrophile' can include reagents such as acid chlorides, leading to acylation **221** and cyclisation to pyrones[33] **222** or bromo-quinones with similar reagents **220** leading eventually to chromenes.[34]



Double Stille couplings are valuable for symmetrical compounds like β-carotene **226**. The symmetrical bis-tributylstannyl-pentaene **224** is coupled at both ends to the iodo-triene **223** in one step with catalyst **225** to give an excellent yield of β-carotene **226** with full control over *E/Z* stereochemistry.[35]

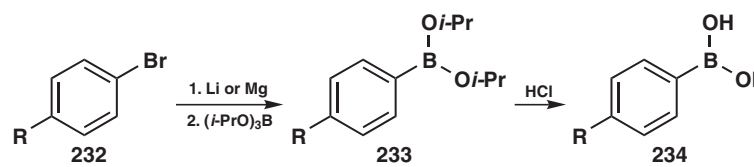


The synthesis of the complex anti-leukemia compound asperazine **231** uses a series of palladium-catalysed reactions including a Stille coupling and a Heck reaction as well as a palladium-catalysed hydrostannylation. This is an asymmetric synthesis as the starting materials are made from serine and tryptophan. We summarise only the key steps but the full description is worth reading.[36]

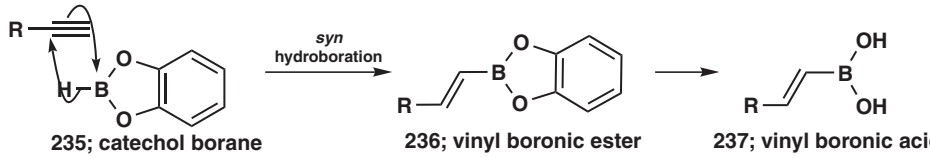


Suzuki coupling

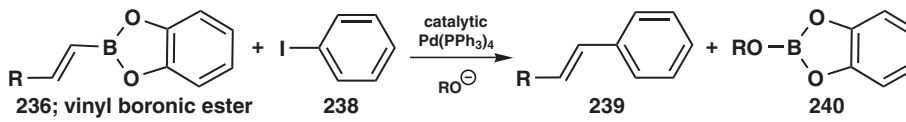
In the Suzuki coupling[37] the trialkyltin functional group on the "nucleophilic" partner in the coupling reaction is replaced by a boronic acid **234**. These stable compounds are easily made from simple organometallic compounds and boronic esters **233** followed by hydrolysis.



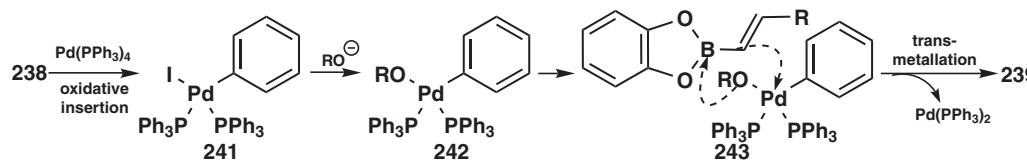
A standard way to make vinyl boronic acids **237** is to hydroborate an alkyne with catechol borane[38] **235** and again hydrolyse the ester products **236**. The empty orbital of the boron atom attacks the electron-rich terminus of the alkyne where is the larger HOMO of the π-bond. One detailed example[39] includes Suzuki coupling to *Z*-styryl bromide. Another diester group commonly used in the Suzuki coupling is derived from pinacol - examples appear later.



There are many other ways of making boronic acids and you are referred to Suzuki's review[37] for a full discussion. A Suzuki coupling would occur if one of these boron compounds **236** was combined with an aryl or vinyl halide or triflate in the presence of Pd(0) and an oxy-anion.

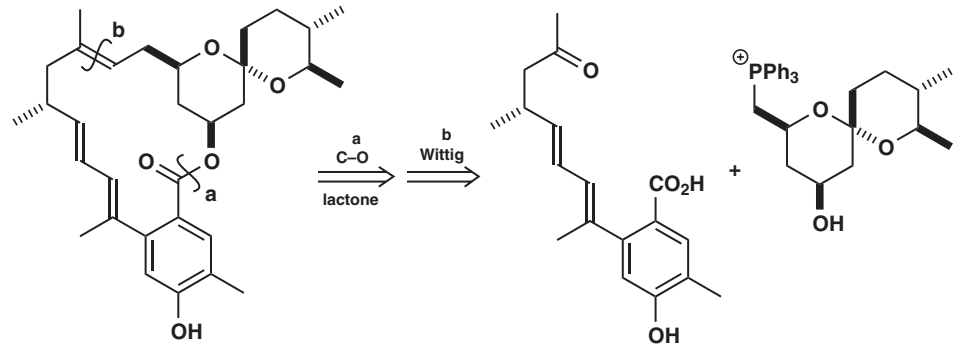


The first step in a Suzuki coupling is the formation of the vinyl or aryl boron derivative and this we have already discussed. The second step is the oxidative insertion of Pd(0) into the other partner in the coupling reaction, here iodobenzene **238**. This σ-complex **241** forms without the oxyanion. It is in the third step, the transmetallation reaction **243**, that the oxyanion is necessary. Boron is barely a metal and it forms strong B−O bonds. It will not exchange its organic group with the palladium atom unless it gets an oxygen atom in return.

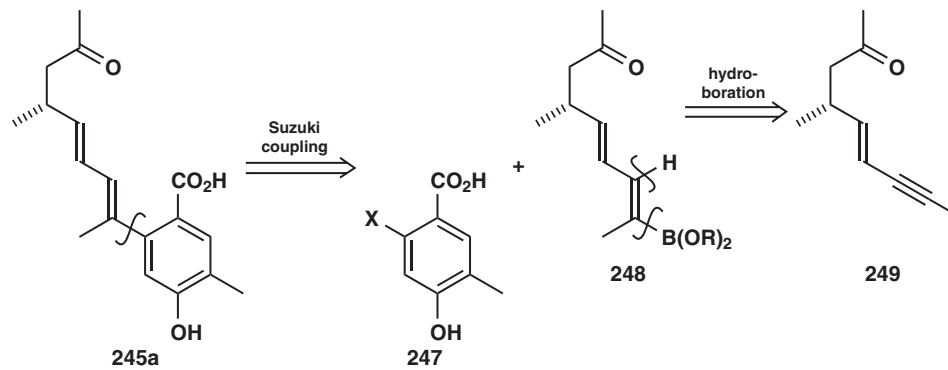


The dotted arrows on the transmetallation step **243** show only what joins to what and are not intended as a serious mechanism. Indeed a better mechanism might involve addition of RO^- to the boron atom *before* transmetallation. This process can be used to couple aryl to aryl, vinyl to vinyl, and aryl to vinyl (either way round!). As boron compounds are much less toxic than tin compounds, the Suzuki coupling is often preferred industrially. Because each partner in the coupling reaction is marked in a different way – one with a boron atom and one with a halide – we can be sure that we shall get cross coupling reactions only.

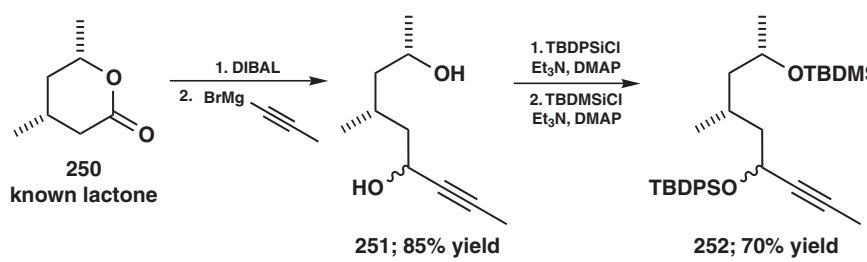
When the bond between the two sp^2 centres is in the middle of the molecule, the disconnection becomes very attractive strategically. Markós milbemycin synthesis[40] illustrates this point well. Milbemycins belong to a family of anti-parasitic agents and milbemycin β3 **244** is one of the simplest. Disconnection of the macrocyclic lactone **a** reveals a continuous carbon skeleton with an aromatic ring conjugated to a diene and one isolated alkene. Markó next decided to disconnect the isolated alkene **b**, having in mind a Wittig reaction with **246** on the ketone **245** and it is this ketone we are going to analyse in detail.



Removing the aromatic ring from the diene makes good sense once we know about Suzuki coupling as it allows us to build the two halves of the molecule separately. There is a free choice as to whether we put the boron atom on the diene or on the aromatic ring, but Markó put it on the diene because he planned to make the vinyl boronate **248** by hydroboration of an alkyne **249**. Note the protection of the phenol and the carboxylic acid as methyl ether and ester respectively.

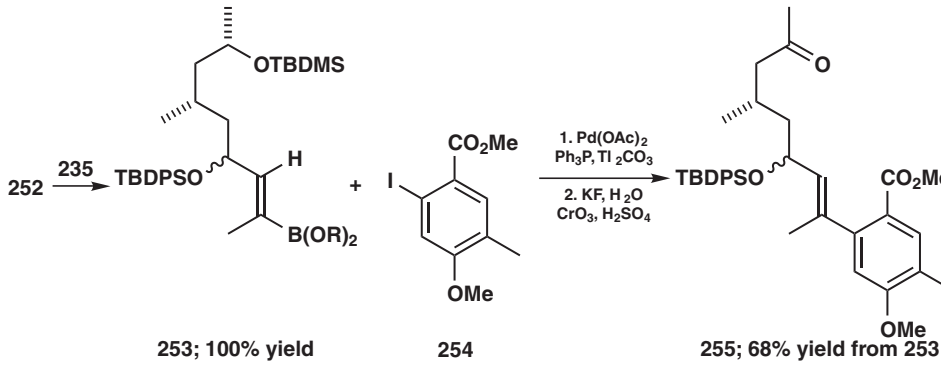


No doubt joining the alkyne to the alkene could also have been done by a coupling reaction in the coordination sphere of a metal but an alternative is to imagine the alkene as coming from the dehydration of an alcohol **251**. This allows disconnection to the known lactone **250**. The synthesis of the alkyne uses DIBAL for partial reduction and the differential protection of the two OH groups by more or less hindered silyl groups.

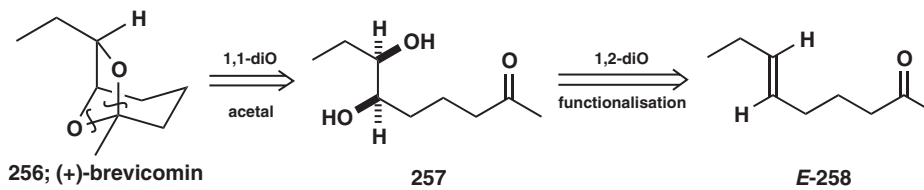


Hydroboration of the alkyne **252** with catechol borane **235** is regioselective for steric reasons and the resulting *E*-vinyl boronate **253** couples with the iodo-benzene **254** under palladium catalysis.

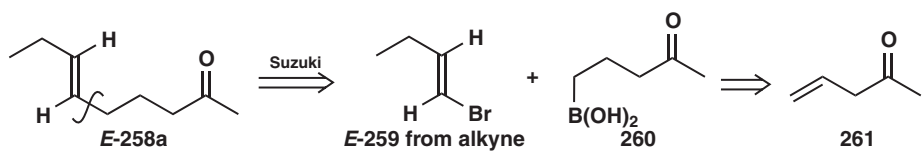
The coupling was followed, without isolation, by a Jones oxidation to give the required protected hydroxyketone. Half of milbemycin β3 had been assembled with good stereochemical control thanks to Suzuki coupling.



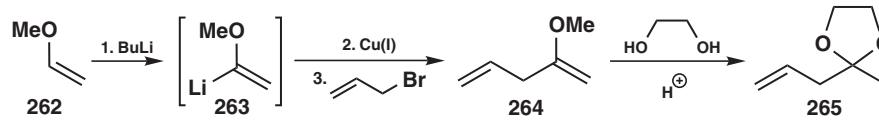
All the examples we have chosen so far have been of aryl and vinyl nucleophiles with no possibility of β-elimination when they are transferred to palladium before coupling. With Suzuki coupling it is possible to use saturated alkyl boranes in combination with vinyl halides and get coupling products in good yield. An example is the preparation[41] of *exo*-brevicomin **256**, the aggregation pheromone of the Western pine beetle *Dendroctonus brevicomis*. Almost all syntheses, including this one start with the unravelling of the acetal to reveal a ketodiol **257**. The 1,2-diol is *syn* as drawn and can be made diastereoselectively by *cis* dihydroxylation of an alkene of the same configuration, that is *E*-**258**. The reagent normally used in this reaction is OsO_4 with various catalysts. In chapter 25 you will see that this reaction can be made to produce just one enantiomer of the *syn* diol.



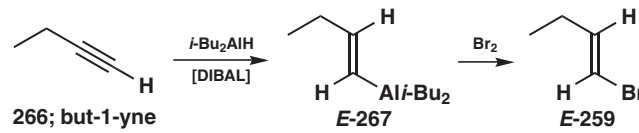
Using a Suzuki disconnection, we intend to add an alkyl boronic acid **260** to an *E*-vinyl bromide **259** (from but-1-yne) and the boronic acid will come from hydroboration of a simple alkene **261** rather than an alkyne.



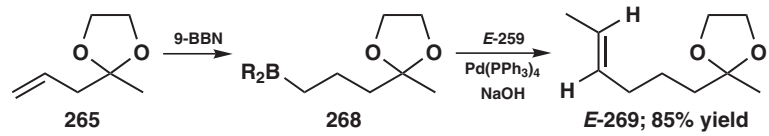
Each stage of this synthesis uses interesting reactions. The unsaturated ketone was made by allylation of a d^1 equivalent – a methoxyvinylcuprate from **263** and it was necessary to protect the ketone as the acetal **265** during the rest of the reactions.



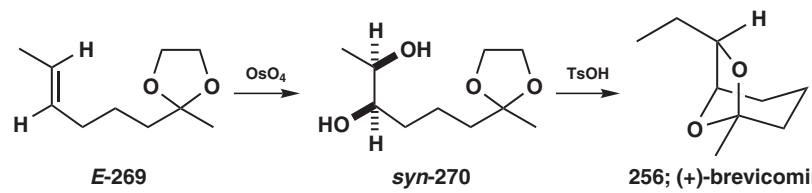
The *E*-butenyl bromide **259** was made by hydroalumination and bromination of but-1-yne **266**. Hydroalumination occurs stereospecifically *cis* (chapter 16) **267** and electrophilic replacement of aluminium by bromine occurs with retention at the sp^2 centre.[42]



Hydroboration of the unsaturated ketone was carried out with the very hindered borane 9-BBN and the alkyl borane **268** was coupled with the vinyl bromide **259** without isolation using Pd(0) as catalyst and NaOH to force the transfer of the alkyl group from boron to palladium. The pure *trans* (*E*-) coupled product **269** is formed in 85% yield so coupling must be faster than β-elimination in this case.



Asymmetric dihydroxylation with OsO_4 gave the *syn* diol **270** which was deprotected and cyclised with toluene-*p*-sulfonic acid (TsOH) catalysis in over 90% yield to complete this short and interesting stereochemically controlled synthesis of *exo*-brevicomin **256** in 65% yield from allyl bromide.

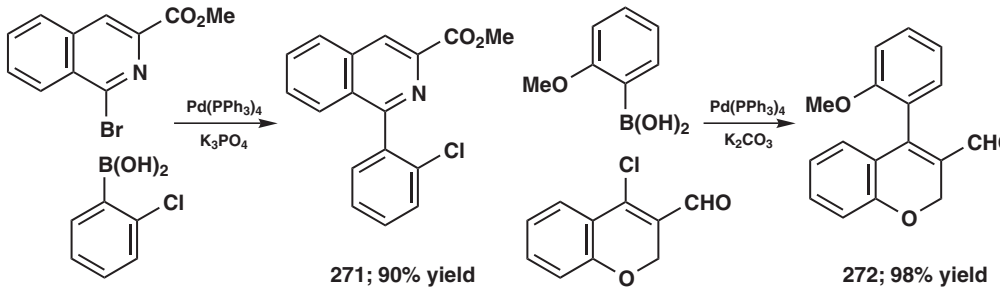


Recent developments in Suzuki coupling

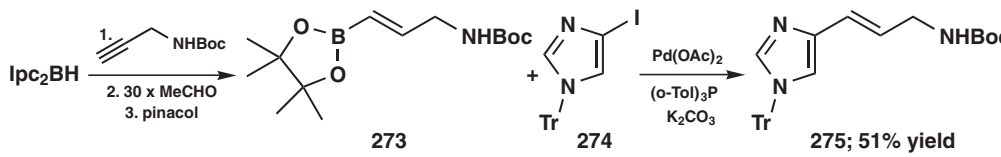
You will have realised that the Suzuki coupling is the best of those we have mentioned. It is regiospecific as the positions for coupling are marked, one with a boronic acid and one with a halide. It does not use toxic tin. It can be used for all the aryl, heteroaryl, vinyl, benzyl and other groups that Heck and Stille use and in addition it can be used for saturated alkyl boronic acids with β-hydrogen atoms without β-elimination. It is not surprising that it is very widely used and we give a few representative examples.

Direct coupling of aryl with heteroaryl compounds works well with *o*-Cl and *o*-MeO groups on the phenylboronic acid in coupling with isoquinolines or coumarins. In the first case **271** it was

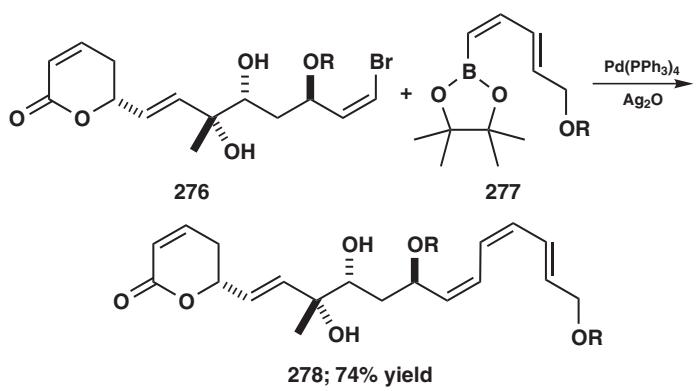
necessary to have a bromine (rather than a chlorine) atom on the isoquinoline to ensure chemoselectivity as there is a chlorine atom on the boronic acid.[43] In the second **272** a chlorine is all right but this is an easier reaction as it is like conjugate substitution.[44]



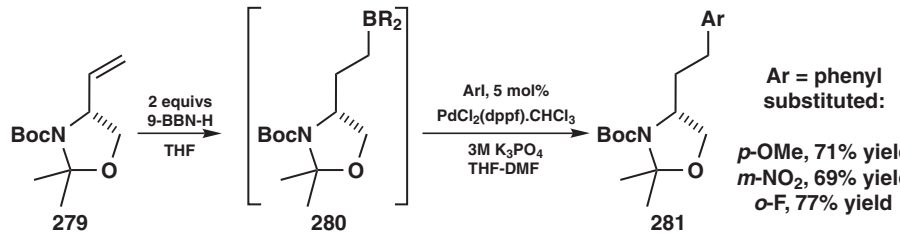
Heterocycles are also coupled to vinyl boronic acids and these can be made by hydroboration of alkynes. This example[45] shows the compatibility with functionality such as the NHBoc group in **273**.



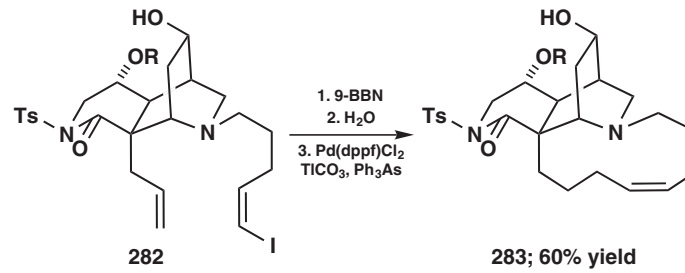
Direct coupling of two vinyl groups remains an important job for the Suzuki reaction. In their synthesis of the antibiotic (+)-fostriecin, Reddy and Falck[46] coupled the *Z*-vinyl bromide **276** with the *Z*-boronic ester **277** to make the triene **278** with *Z,Z,E*-alkenes. Free OH groups obviously do not interfere.



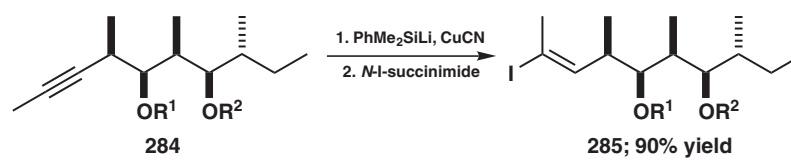
The most distinctive contribution of the Suzuki to modern methodology is the coupling of alkyl boronic acids, formed by hydroboration of alkenes, to vinyl and aryl halides.[47] The simple mono-substituted alkene **279** reacts with 9-BBN followed by Suzuki coupling with aryl iodides to give products **281** in good yield regardless of the nature or the position of the substituents.[48]



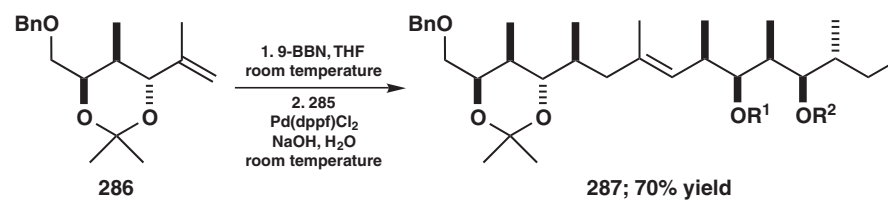
Intramolecular coupling of a *Z*-vinyl iodide and a saturated alkyl chain in **282** creates a new 11-membered ring **283** providing the 'ansa' bridge in Danishefsky's synthesis[49] of xestocyclamine A. The yield in the formation of this difficult medium ring and the toleration of functionality are both impressive.



The coupling of two enantiomerically pure fragments to form an alkene of fixed geometry in the centre of ebelactone allows a convergent synthesis.[50] One fragment, the vinyl iodide **285** is ultimately derived from a coupling between a chiral aldehyde and a chiral allyl boronate but more immediately by silyl-cupration of an alkyne **284** and iodination.



The other fragment, the alkene **286** originates in an Evans' aldol reaction (chapter 27) and is coupled to **285** by hydroboration and Suzuki reaction. The yield is very impressive, as is the stereocontrol over the new centre next to the acetal. The full synthesis appears in the workbook together with some stereochemical explanations.



Summary

The palladium-catalysed reactions with alkenyl, aryl, and heteroaryl halides or triflates as one partner ('electrophilic') and alkenes (Heck), aryl or vinyl stannanes (Stille) or aryl, vinyl and even alkyl boronic acids (Suzuki) as the other ('nucleophilic') partner provide a synthetic method of astonishing power and versatility. These reactions are only just starting to be explored and great things are expected of them.

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General references are given on page 893

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19 Allyl Alcohols: Allyl Cation Equivalents (and More)

This chapter analyses the problems associated with allylic electrophiles and the unique usefulness of allylic alcohols in their solution. The preparation and other chemistry of allylic alcohols is here too.

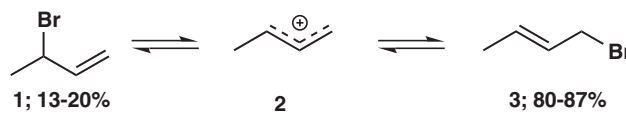
Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

Part I – Introduction

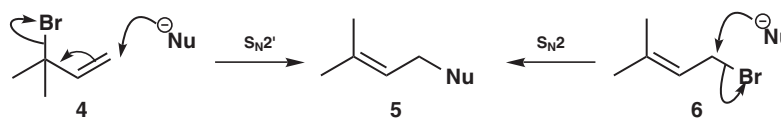
The Problem of the [1,3]-Shift

Nucleophilic attack on unsymmetrical allylic halides

At the start of chapter 12 (Allyl Anions) we discussed briefly the general problem that faces any use of allylic derivatives in synthesis. Many of them are not stable with respect to the [1,3]-shift or allylic rearrangement. The bromides **1** and **3** are in equilibrium under most conditions: in polar solvents they equilibrate via the allylic cation **2** to give mostly the compound **3** with the more highly substituted alkene.[1]



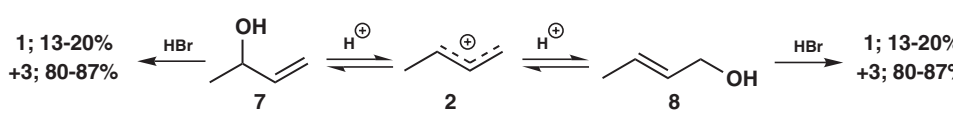
This does not prevent the use of allylic bromides in synthesis. As nucleophiles may attack an allylic derivative from either end of the allylic system, there is a further opportunity to get the product with the more highly substituted double bond. You will probably know that prenylation of nucleophiles, particularly enolates, gives overwhelmingly the prenyl derivative **5**. The primary allylic halide **6** (prenyl bromide) reacts by the S_N2 reaction while the tertiary halide **4** reacts by the S_N2' reaction.



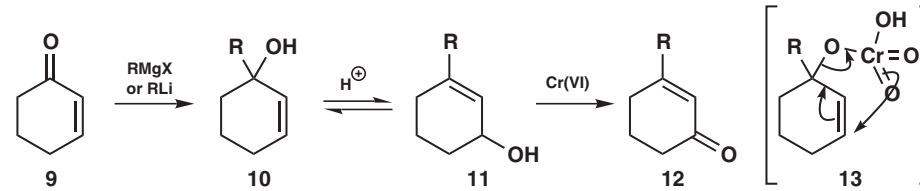
This chapter is about ways to get greater control over processes like these. It concerns ways to make allylic derivatives react at the more substituted end to give the less stable product, ways to control allylic substitution when both possible products have equal numbers of substituents on the alkene and ways to control the stereochemistry. The key reagents in this chapter are allylic alcohols. Though these do equilibrate in acid solution, under other conditions they are stable and they are easily prepared regio- and stereospecifically by many ways. Strictly 'allyl' refers to the prop-2-enyl group CH_2=CH-CH_2- though nowadays it usually means any group next to an alkene but not directly attached to it. We shall use 'allylic' rather than 'allyl' for that meaning though the distinction is on the way out.

Rearrangement and stability of allylic alcohols

The mixture of **1** and **3** can be made by treatment of either alcohol **7** or **8** with HBr. Under these strongly acidic conditions equilibration between the alcohols as well as between the allylic bromides occurs through the allylic cation **2**.



This can be useful when oxidation of an equilibrating alcohol is carried out in acidic conditions, say with a Cr(VI) reagent. The first formed alcohol **10** cannot be oxidised but the rearranged alcohol **11** can. This rearranged alcohol might be formed via an allylic cation or it might be by [3,3]-sigmatropic rearrangement of the chromate esters **13**.



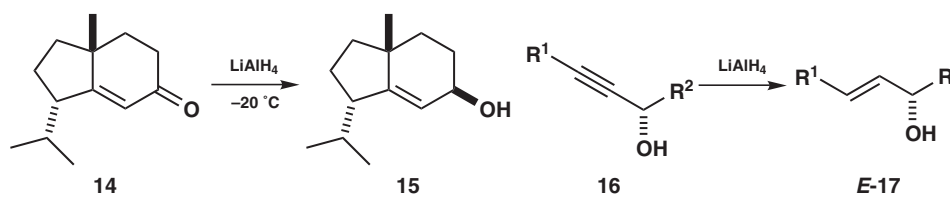
Under other conditions such as base or ionic solvents or radical formation, 1,3-shifts do not occur either with the alcohols themselves nor with simple derivatives like carboxylate esters. They are therefore ideal for use as specific allylic electrophiles except for the fact that OH^- is a terrible leaving group and simple nucleophilic displacements on allylic alcohols are unknown. Special chemistry will be needed.

Part II – Preparation of Allylic Alcohols

Traditional Methods

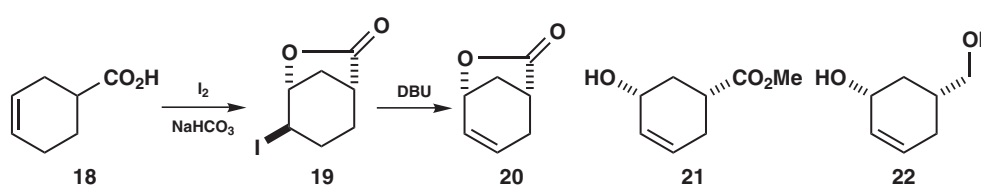
Reduction of enones prepared by the aldol or Wittig reactions

Types of reactions we meet elsewhere in the book include the reduction of α,β-unsaturated carbonyl compounds prepared by the aldol or Wittig reactions. The cyclic enone **14**, prepared by a Robinson annelation is reduced regio- and stereo-selectively by $LiAlH_4$ to the allylic alcohol[2] **15**. The reduction of acetylenic alcohols **16**, prepared by addition of metallo-alkynes to aldehydes, also with $LiAlH_4$ is *E*-selective (chapter 15) giving the allylic alcohol[3] *E*-**17**.



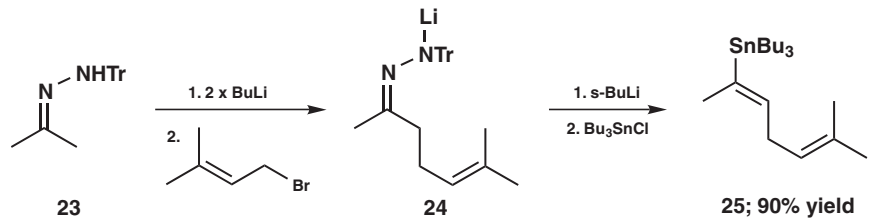
Elimination on or reduction of iodolactonisation product

Slightly more unusual is the elimination and hydrolysis or reduction of iodolactonisation products **20** (chapter 17). Elimination replaces the alkene but in a different position **20** and cleavage of the lactone bridge[4] by methanolysis gives **21** or by reduction gives **22**. As we get on to the reactions of allyl alcohols you will see how these and other methods are used to make particular compounds.

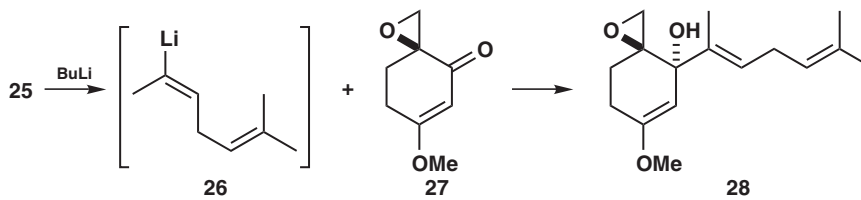


Addition of vinyl metals to aldehydes and ketones

Addition of vinyl metals to aldehydes and ketones (chapter 16) also allows control over stereochemistry. The stereospecific vinyl anion equivalent **24** is one we made in chapter 16 by the Shapiro reaction. We repeat this scheme because it uses prenylation of a hydrazone aza-enolate to make the starting material for the vinyl-tin compound **25**.

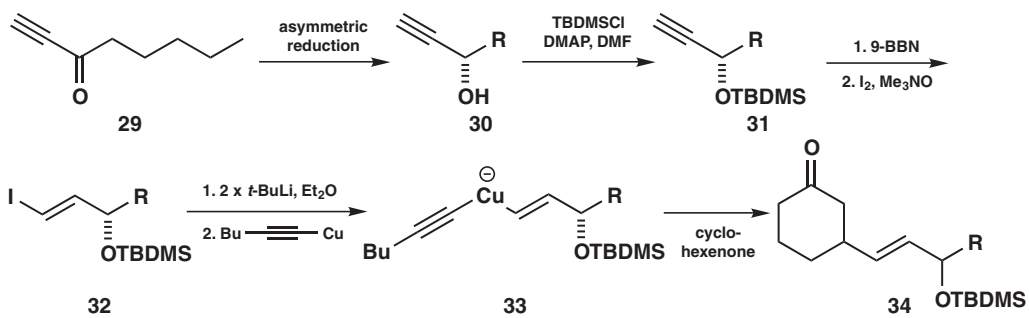


Conversion of the vinyl tin **25** to the vinyl lithium **26** and coupling with the keto-epoxide **27** gives one diastereoisomer of the allylic alcohol **28** (17:1), used in a synthesis of ovalicin.[5] Notice that the vinyl-lithium **26** is one geometrical isomer and that it attacks the carbonyl group of **27** on the same face as the oxygen atom of the epoxide. This looks like chelation control.



Reduction of acetylenic alcohols made by addition of alkynes to aldehydes or ketones

Conjugate addition of the complete allylic alcohol fragment is possible with the mixed cuprate reagents **33** prepared by asymmetric reduction (chapter 26) of acetylenic ketones **29** to give the alcohols **30**, protection as a silyl ether **31** and hydroboration-iodination. Lithiation and reaction with hexynyl copper (I) gives the mixed cuprate **33** from which the less stable anion is transferred selectively to an enone.[3] This approach has been widely used in the synthesis of prostaglandins.

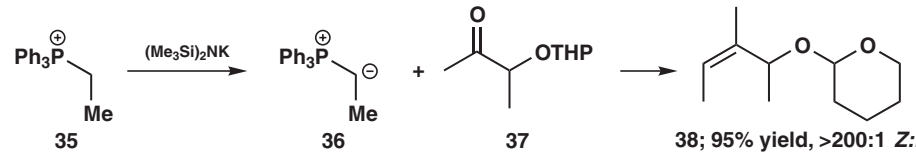


Wittig examples

Two simple examples of an *E*-selective Wittig reaction followed by reduction of the carbonyl group giving allylic alcohols with full control over double bond geometry are given in chapter 15 and the following section in that chapter on *Z*-selective Wittig variants shows how Wittig-style reactions followed by reduction can be used to give *Z*-allylic alcohols. The methods used to make enones

in chapters 2-4 and summarised in chapters 5 and 6 are also methods to make allylic alcohols as reduction with anionic reducing agents (e.g. $NaBH_4$ or $LiAlH_4$) is usually regioselective.

One special case with a non-stabilised Wittig reaction is the remarkably *Z*-selective reaction[6] with THP-protected α-hydroxyketones **37**. These are among the most *Z*-selective Wittig reactions known and it is the influence of the α-OTHP group that is decisive. The product **38** is of course a protected allylic alcohol. In chapter 33 we shall see how to make these α-hydroxyketones stereo- and regiospecifically.



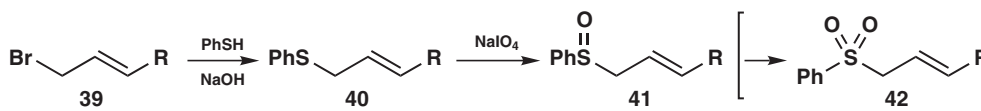
35 **36** **37** **38; 95% yield, >200:1 *Z:E***

All these methods give allylic alcohols regiospecifically, that is with the OH group and the alkene in predictable positions. They are often stereoselective for the alkene and may also be enantioselective as we shall see later. Provided the allylic alcohol is kept away from strong acid, its structure is more secure than that of most allylic compounds.

Allylic Alcohols by [2,3] Sigmatropic Shifts

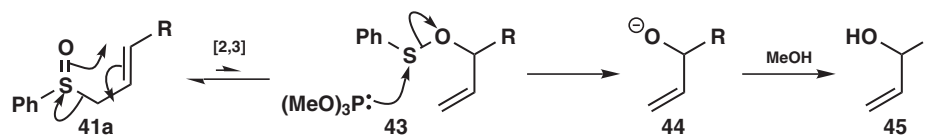
Sulfoxide and sulfonium ylids: Regio- and stereochemical control

We shall be using [2,3] sigmatropic shifts in the reactions of allylic alcohols so this section is an introduction to that as well as describing perhaps the most tightly controlled method for making allylic alcohols. Allylic sulfides **40** are easily oxidised chemoselectively with reagents such as sodium periodate to the corresponding sulfoxides **41**. More powerful oxidants tend to form the sulfone **42**.



39 **40** **41** **42**

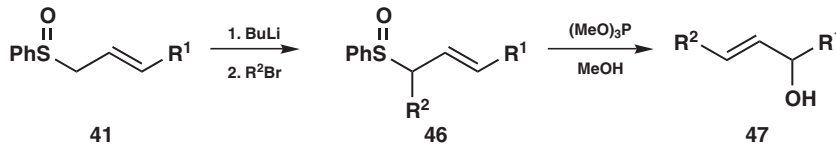
These allylic sulfoxides **41** are in equilibrium with a sulfenate ester **43** by a [2,3]-sigmatropic rearrangement **41a**. It is not usually possible to detect the sulfenate ester by NMR so there must be less than about 3% of it, but it can be trapped by various nucleophiles that like to attack sulfur. These 'thiophiles' include secondary amines, thiolate anions and, most important, phosphite esters. The reaction is carried out in a protic solvent (usually the alcohol already present in the phosphite ester) and a rearranged allylic alcohol **45** is formed.



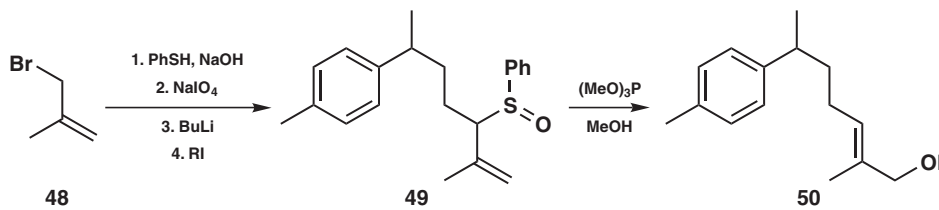
41a **43** **44** **45**

Since the original preparation of the allylic sulfide involved nucleophilic attack on an allylic halide **39**, the more stable allylic sulfide - the one with the more highly substituted alkene **40** - is formed and this is inevitably and usefully transformed into the less stable allylic alcohol **45**. The reaction is more useful still because the intermediate allylic sulfoxide **41** may be alkylated before rearrangement and this gives the unsymmetrically substituted *E*-allylic alcohols **47**. These reactions

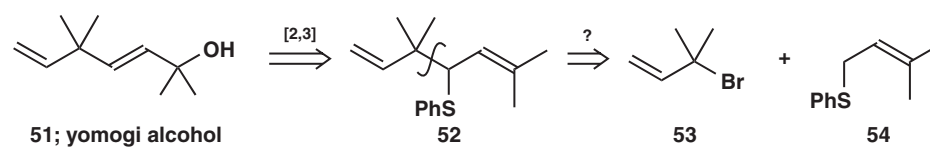
are exceptionally *E*-selective and we shall delay an explanation of this stereoselectivity until we have discussed the use of such allylic alcohols in [3,3] sigmatropic rearrangements later in the chapter.



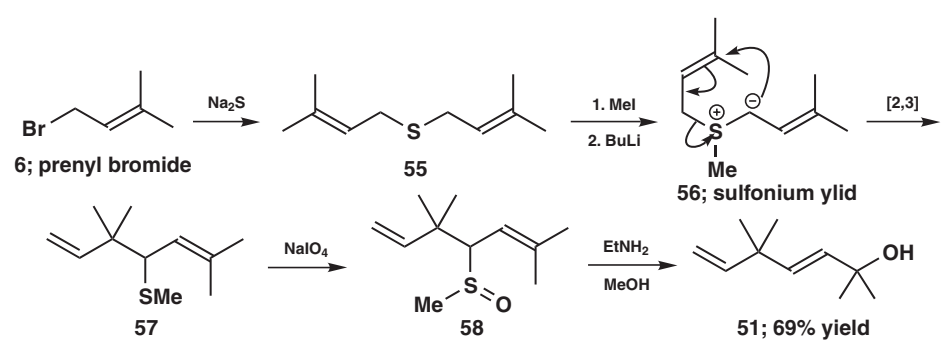
An example is the synthesis of nuciferal by David Evans and group.[7] Symmetrical allylic halides like 'methallyl' bromide **48** can give only one product on reaction with nucleophiles. Alkylation of the sulfoxide with a large alkyl iodide gives the allylic sulfoxide **49**. The [2,3] sigmatropic rearrangement gives a single geometrical isomer of the primary allylic alcohol **50**: the corresponding aldehyde, formed in 99% yield on oxidation of **50** with MnO_2 is the natural product nuciferal. Both regio- and stereochemical control are complete.



These [2,3] sigmatropic rearrangements on sulfur compounds are not restricted to sulfoxides as they occur equally with sulfonium ylids. A good example showing both is the synthesis of yomogi alcohol **51**, an irregular monoterpene. Reversing the [2,3] sulfoxide rearrangement gives an allylic sulfide **52** that we should like to make by alkylation of the simple prenyl sulfide **54** with the allylic halide **53**. However, we know that won't work: the alkylation will occur at the less hindered end of the allylic halide.

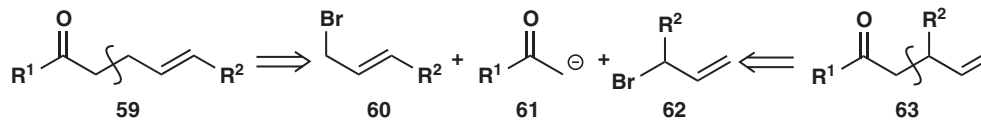


The solution is surprising. Evans deliberately made the wrong doubly allylic sulfide **55** and rearranged it twice to give yomogi alcohol. At first the sulfur atom must be alkylated (therefore adding a phenyl group is not suitable and a methyl group is used instead). Then the first [2,3] rearrangement (on the sulfonium ylid) **56** gives the right skeleton **57** and the second (on the sulfoxide **58**) gives the target molecule. In this reaction, the older thiophile $EtNH_2$ was used.[8]

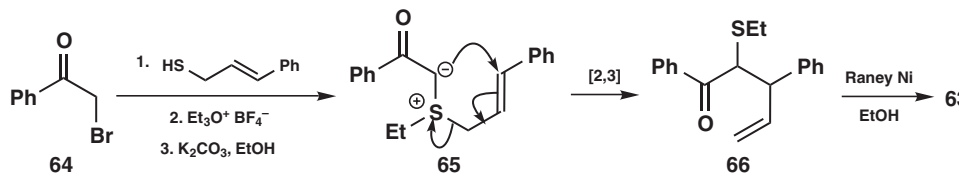


[2,3] Sigmatropic shifts in the allylation of ketones

The allylation of ketones is a simple reaction. Most of the specific enol equivalents described in chapters 2-6 react well with allylic halides. Disconnection of the γ,δ-unsaturated ketone **59** to the enolate **61** and the allylic halide **60** is trivial and the reaction of, say, an enamine will occur at the less hindered primary centre to give **59**. However, supposing the target molecule is the isomeric ketone **63**. The same disconnection gives the isomeric allylic bromide **62** which will almost certainly give the alternative product **59** by reaction at the less hindered end of the alkene.

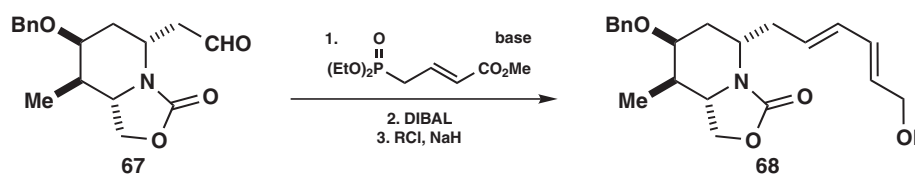


One solution is a [2,3] sigmatropic rearrangement of a sulfonium ylid. A stable allylic thiol reacts cleanly with an α-haloketone **64** to give a sulfide and hence the sulfonium salt after ethylation. Only a weak base is need to make the ylid **65** as this is also an enolate. Notice the regioselectivity here: the alternative ylid would also be stabilised but only by an alkene. The [2,3] shift joins the allylic fragment to the enolate of the ketone and at the same time turns it inside out. This automatically produces the more difficult product **63** after desulfurisation with Raney nickel. We shall see alternative solutions to this problem later in the chapter.[9]

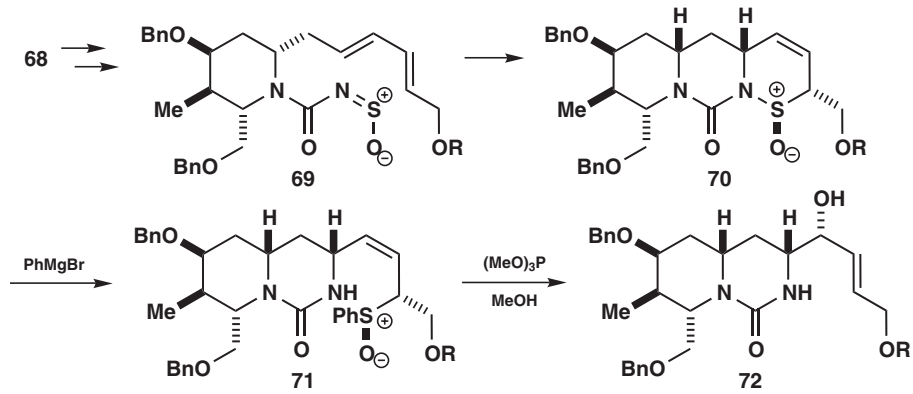


Recent applications

The preparation of the allylic alcohol **68** by Horner-Wadsworth-Emmons reaction followed by reduction illustrate how this method is compatible with varied functionality and stereochemistry.



The diene alcohol derivative **68** is used to prepare the starting material **69** for an intramolecular hetero-Diels-Alder reaction to give a new heterocyclic ring **70** that can be cleaved with phenyl Grignard to release a sulfoxide **71** for the preparation of a new allylic alcohol **72**. Notice that the stereochemistry of the sulfoxide is shown and that there is complete control over 2D and 3D stereochemistry. The allylic alcohol **72** was used in Weinreb's synthesis of toxins[10] produced by fresh water blue-green algae.

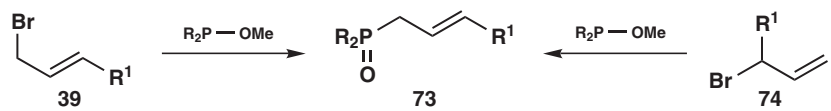


Part III – Reactions of Allylic Alcohols

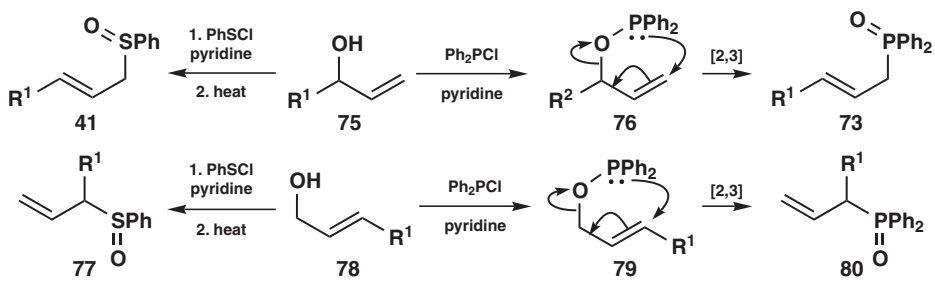
[2,3] Sigmatropic Rearrangements

Reminder of the conversion to allylic sulfoxides

You saw in the last section that the preparation of allylic sulfides by displacement of, say, a halide from an allylic system is likely to give the more stable allylic sulfide whichever allylic halide is used and that the corresponding allylic sulfoxides are made by oxidation of the sulfide. The same is true of phosphorus compounds **73** used in chapter 15 to make dienes of fixed configuration. If R = OR, **73** is an allylic phosphonate for the Horner-Wadsworth-Emmons reaction but if R = Ph, **73** is a phosphine oxide for the Wittig-Horner reaction.

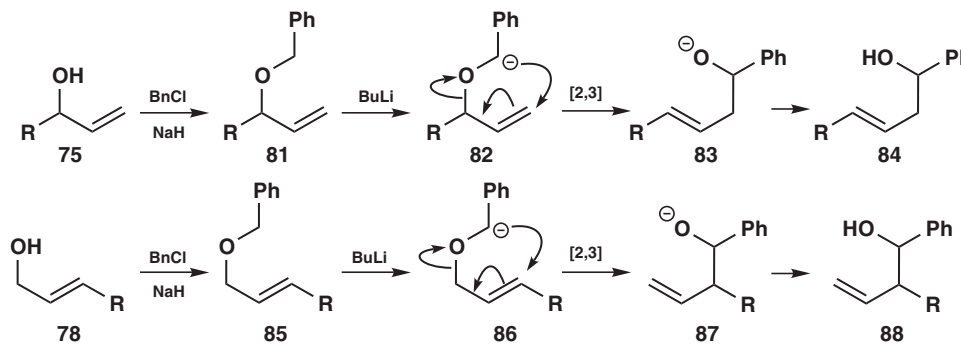


The specific preparation of either phosphine oxide **73** or **80** can easily be carried out from the appropriate allylic alcohol. The reaction is like the one we saw for the preparation of allylic alcohols from allylic sulfoxides but the [2,3]-sigmatropic rearrangements **76** and **78** run only in this direction with phosphorus.[11] It is also the preferred direction with sulfur. Since allylic alcohols **75** and **78** are stable to the allylic rearrangement, each alcohol gives specifically one allylic phosphine oxide **73** or **80** or allylic sulfoxide **41** or **77**. This is the theme for most of the rest of the chapter.

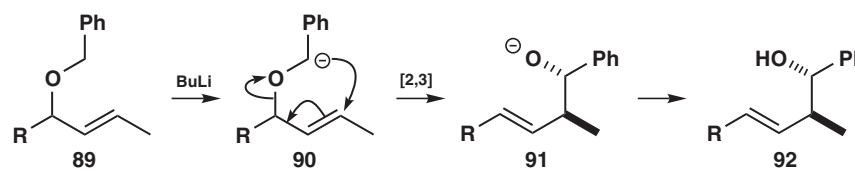


The [2,3] Wittig rearrangement

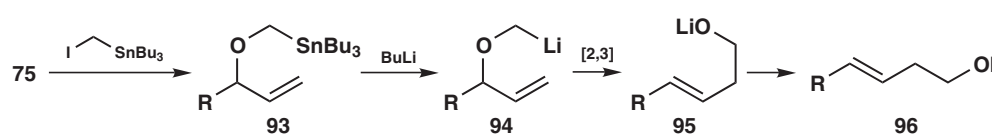
Ethers of allylic alcohols also undergo a [2,3] sigmatropic rearrangement. The driving force is the conversion of an unstable C-Li compound into a stable O-Li compound. These intermediates are often described as anions and in some cases may be so - it is certainly easier to draw the mechanism of the [2,3] shift that way. The commonest ethers used are benzylic **81** and **85** so that the proton to be removed has some acidity. Again a specific product **84** or **88** is formed from each isomer of the allylic alcohol **75** or **78**. The original allylic alcohols are transformed into homoallylic alcohols. This rearrangement **82** and **86** is often called the [2,3]-Wittig rearrangement.[12]



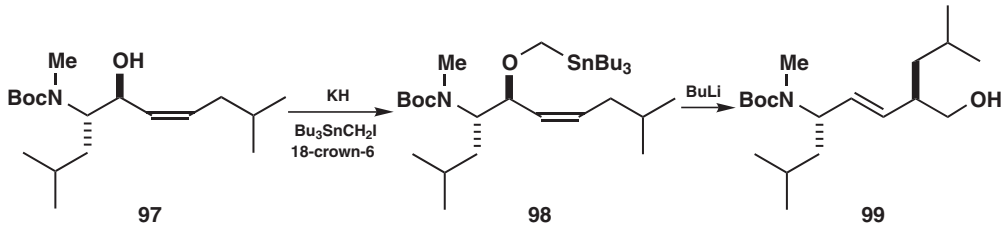
There is good, if somewhat substrate-dependent, stereoselectivity when there is a substituent at the end of the alkene in the starting material. The *E*-ether **90** gives almost exclusively (98%) the stereochemistry shown in the product.[13] The transition state has a 'half-chair' conformation.[14]



In this form the reaction is limited as an anion-directing substituent such as phenyl is needed and this group is incorporated into the structure. A more general approach is to provide an R_3Sn group **93** that can be replaced by lithium even if there is no other substituent at all on the carbon atom. This variation is often known as the Wittig-Still rearrangement.[15]

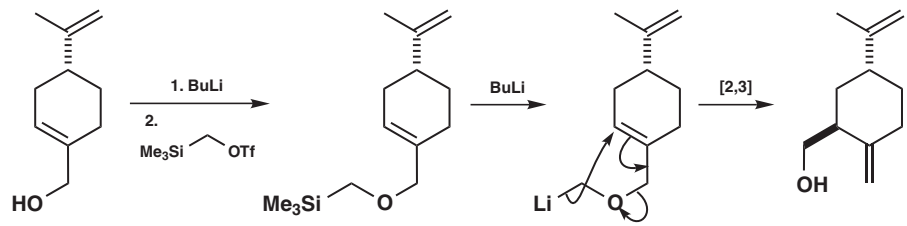


This approach has been applied to the synthesis of peptide isosteres, compounds that have the same shape as peptides but lack the amide link. In this case **99** it is replaced by an *E*-alkene. The starting material **97** is made from the natural amino acid leucine and the Wittig-Still [2,3] shift on **98** rearranges this into an *E*-alkene flanked by two chiral centres **99**.



97 **98** **99**

The migrating group passes suprafacially across the *Z*-alkene but appears to invert because the skeleton must be redrawn to show the *E*-alkene. This is an elegant way of transforming relatively easy to control 1,2 stereochemistry into more remote 1,4 stereochemistry.[16] There is another example of the conversion of 1,2- into 1,4-stereochemistry at the end of this chapter. Not everyone is happy with stoichiometric toxic tin, but an alternative is available in the silicon compounds such as **101**



100; natural (*R*)-(+)-perilla alcohol **101** **102** **103**

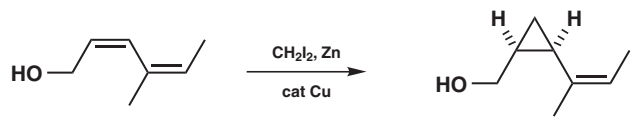
Alkylation of the allylic alcohol **100** with the silyl alkyl triflate gives an ether **101** from which the Me_3Si group can be removed with BuLi. The new substituent (CH_2OH) in **103** must be axial as it has to overlap with the p-orbitals of the alkene as it moves.[17]

Reactions with Electrophiles

This section is mainly about the role of the OH group in directing reagents (mostly electrophiles) to one face or other of the alkene. This does not strictly fit with the title of the chapter but these reactions are important and this seems to be the logical place for them.

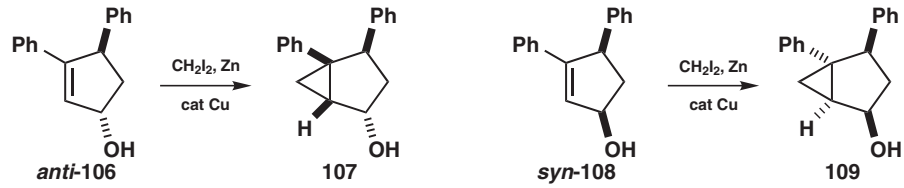
The Simmons-Smith cyclopropanation reaction

In its most general form the Simmons Smith reaction[18] is the addition of a carbenoid to an alkene to form a cyclopropane. The reagent is an organometallic compound made from a gem-dihalide and zinc usually with catalysis from a more active metal such as copper or silver, and probably has a structure such as ICH_2ZnI. It is best known with allylic alcohols as the OH group directs both the regio- and stereochemical outcome. In the simple diene *Z,Z*-**104**, only the allylic alcohol forms a three-membered ring even with an excess of the reagent and does so stereospecifically.[19]

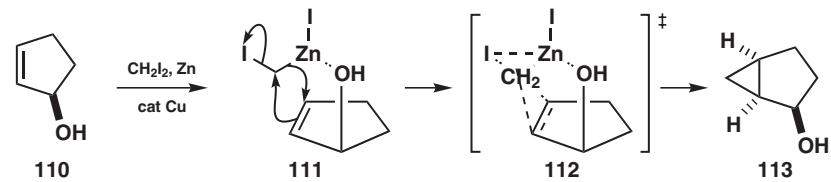


***Z,Z*-104** **105**

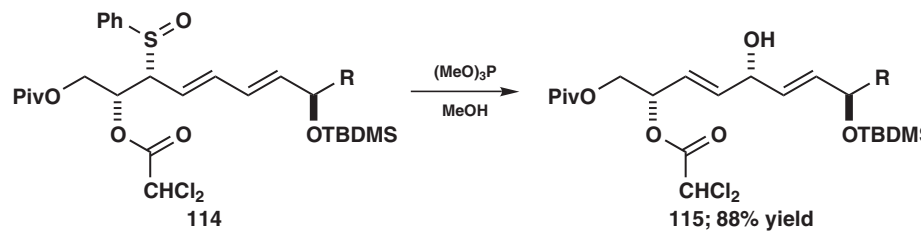
When the OH group is on a chiral centre the faces of the alkene become diastereotopic and the face *syn* to the OH group is preferred. These two diastereoisomers *anti*-**106** and *syn*-**108** show clearly that this is chelation control and not mere steric hindrance as the cyclopropane ring is formed on the same side as the OH group regardless of the position of the benzene ring.[20]



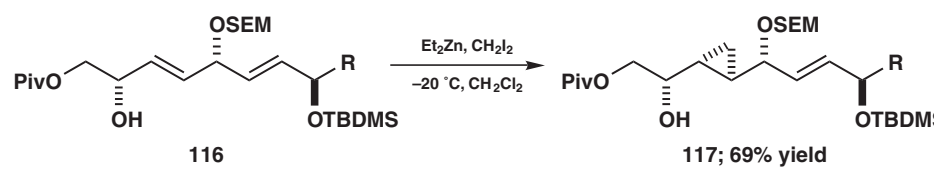
The zinc atom probably coordinates to the OH group and delivers the CH_2 group in a mechanism such as **111**. It appears that the iodine atom is simultaneously transferred to the metal so that the transition state is something like **112**. At all events, the new ring is formed on the *syn* face to the OH group **113**. These diagrams have been stripped of the benzene rings for clarity.



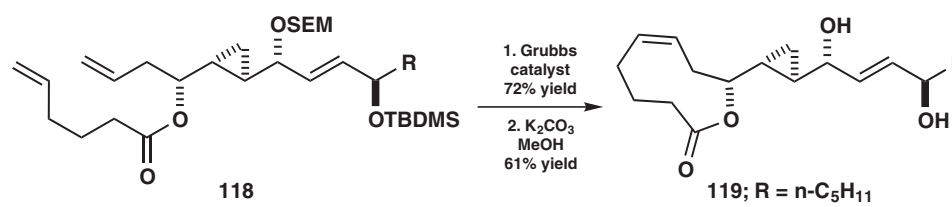
The many recent publications affirm the importance of this reaction in modern synthesis. Tanaka and Takemoto's synthesis of the marine metabolite halicholactone uses a sulfoxide route to the allylic alcohol **115**. Notice the suprafacial [2,3]-sigmatropic rearrangement and that the OH group ends up in the middle of the diene. Attempted cyclopropanation of **115** gave a poor yield of a mixture of products.[21]



It was necessary to exchange protecting groups so that there was only one allylic alcohol **116** and to use a modification of the Simmons-Smith reaction with Et_2Zn and CH_2I_2 to get a good yield of one diastereoisomer of the cyclopropane **117**.

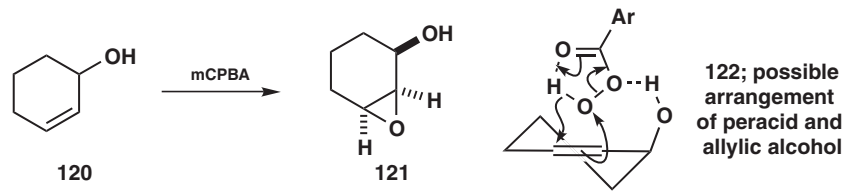


Further transformations gave a precursor **118** for a ring-closing olefin metathesis using the Grubbs catalyst described in chapter 15. This gave the unsaturated nine-membered lactone required and deprotection revealed halicholactone **119**. The solution to the regioselectivity problem of cyclo-propanation with three OH groups and three alkenes embedded in the skeleton of **119** is elegant.



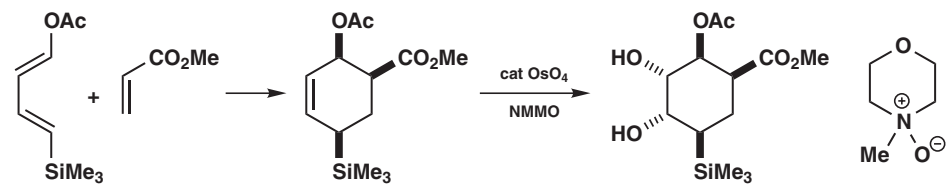
Stereochemically controlled epoxidations

Many epoxidising agents, notably mCPBA and *t*-BuOOH/$VO(acac)_2$, are capable of bonding to the OH group of an allylic alcohol. Epoxidation then occurs more readily on allylic alcohols and on the same side of the alkene as the OH groups, rather in the style of the Simmons-Smith reaction. The stereochemical outcome is easiest to see in cyclic allylic alcohols. Thus the cyclohexenol **120** gives the *syn* epoxide **121** cleanly with mCPBA via the conformation **122** in which the axial OH delivers the reagent to the same face of the alkene.



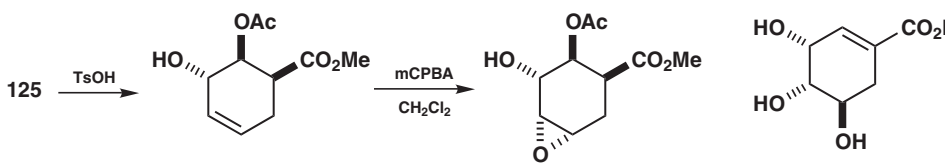
120 121

A good illustration of many aspects of this chemistry comes from Koreeda's synthesis of shikimic acid.[22] The silyl diene **123** adds cleanly to methyl acrylate to give essentially one isomer of the adduct **124** (9:1). Dihydroxylation with catalytic OsO_4 and the stoichiometric oxidant NMO (*N*-methylmorpholine-*N*-oxide) occurs on the opposite face to all three substituents. The alkene **124** is an allylic acetate but this group has no attractive interaction with the reagent.



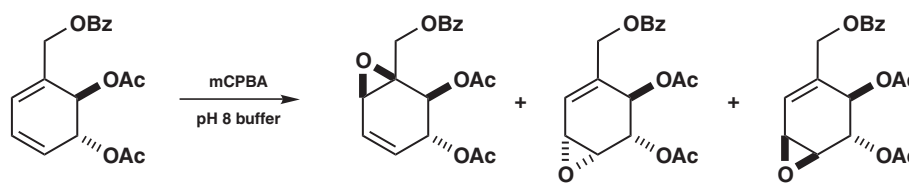
123 124; 72% yield 125; 96% yield NMO

A Peterson elimination, necessarily in acid solution as the OH and $SiMe_3$ groups are *anti* (see chapter 15) gives a new alkene **126** that is allylic to the remaining OH group. Now epoxidation with mCPBA occurs on the face of the alkene *syn* to the OH group to give **127**.



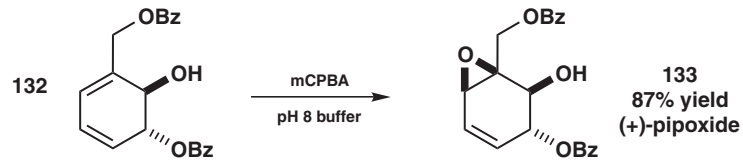
126; 98% yield 127; 91% yield shikimic acid

An example showing both regio- and stereoselectivity occurs in Ogawa's synthesis of pipoxide.[23] Epoxidation of the diene **128**, with no free OH groups, gave a mixture of epoxides in low yield with very poor regio- and stereoselectivity.

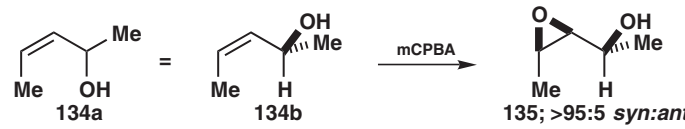


128 129; 19% yield 130; 24% yield 131; 14% yield

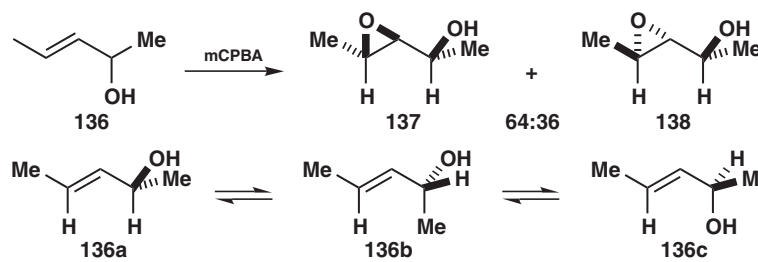
By contrast, the diene **132** with one free OH group gave a single epoxide in excellent yield. Epoxidation has occurred only at the allylic alcohol and only on the same side as the OH group despite the crowded nature of the alkene. This product **133** is the plant metabolite pipoxide.



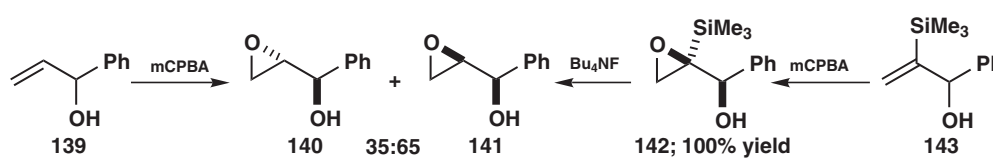
The stereoselectivity with non-cyclic allylic alcohols is more complicated. The molecules tend to adopt a Houk conformation (chapter 21) with a hydrogen atom in the alkene plane and the OH group above or below. If the reagent is guided in by bonding to the OH group, *syn* epoxidation results. This is the case with allylic alcohols with a trisubstituted or a *cis*-disubstituted alkene **134** since there is then a group in the plane of the alkene favouring the Houk conformation **134b** since whichever group on the chiral centre sits in the alkene plane must eclipse the *cis* substituent.[24]



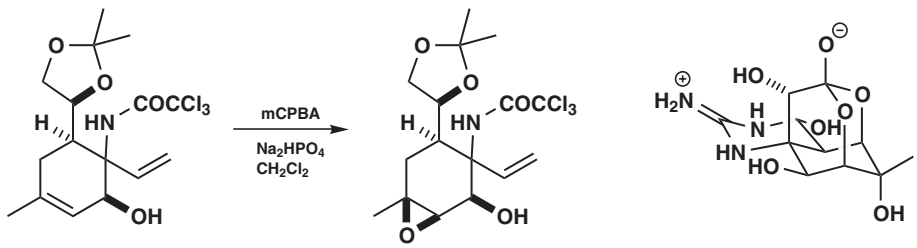
However, *trans*-disubstituted alkenes are in general not epoxidised so selectively. In the simplest case with two methyl groups **136**, the selectivity is about 2:1 *syn:anti* as the three conformations **136a**, **136b**, and **136c** are about equally favourable since whichever group on the chiral centre sits in the alkene plane needs eclipse only the *cis* hydrogen atom.



Even mono-substituted allylic alcohols **139** that generally give very poor diastereoselectivity can give good results if the steric interactions are boosted by a Me_3Si group **143**. The Me_3Si group pushes the Ph and OH groups out of the plane and favours the Houk conformation so that stereoselectivity is complete[25] **142**. The Me_3Si group can be removed with retention of configuration by fluoride ion. These more complex cases really fit into chapter 21 where you will see other examples of the Houk conformation in action.[26]



Fortunately the synthesis of complex molecules is likely to involve the epoxidation of more rather than less crowded allylic alcohols. An outstanding recent example is Isobe's synthesis[27] of 11-deoxytetrodotoxin **146**, one of the metabolites of the notoriously poisonous Japanese *fugu* (puffer fish). Epoxidation of the allylic alcohol **144** gave an almost quantitative yield of one regio- and stereo-isomer of the epoxide **145**. The mCPBA reagent was buffered with phosphate but that explains only the survival of the acetal: the lack of epoxidation at the other alkene is remarkable as it has an allylic relationship with the rather acidic NH group.



144 **145; 96% yield** **146; 11-deoxytetrodotoxin**

Regio- and Stereocontrolled Reactions with Nucleophiles

We now return (at last!) to the original theme of the chapter: how can we add allylic electrophiles to other molecules with control over all the aspects of allylic systems we have been considering? We need to control:

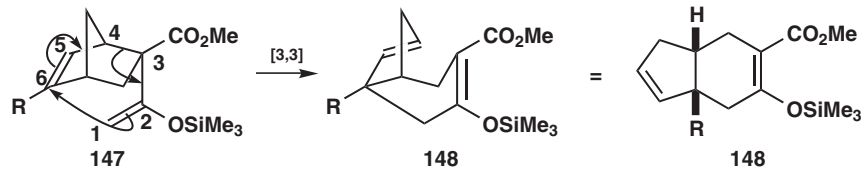
- Which *end* of the allylic system is attacked (regioselectivity)
- Which *face* of the allylic system is attacked (stereoselectivity)
- The geometry of the alkene in the product (stereoselectivity)

Among the methods available for these reactions, two have gained prominence: the use of Claisen-style [3,3]-sigmatropic rearrangements for the selective allylation of enolates and the more general reactions of palladium allyl cation complexes.

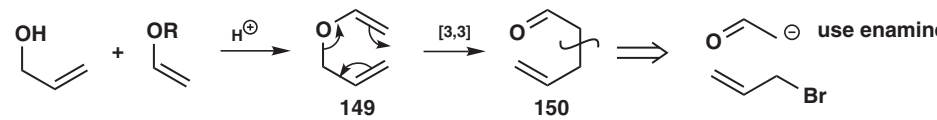
Claisen-Cope rearrangements

The Cope rearrangement is a [3,3]-sigmatropic reaction of a 1,5-diene to give another 1,5-diene. The reaction may be degenerate or there may be some reason for the reaction to go one way or the other such as relief of strain or development of conjugation. The Claisen version of the Cope rearrangement has a built-in direction finder. An oxygen atom in the carbon chain becomes a carbonyl group in the product and a C=O bond is significantly more stable than a C=C bond.[28]

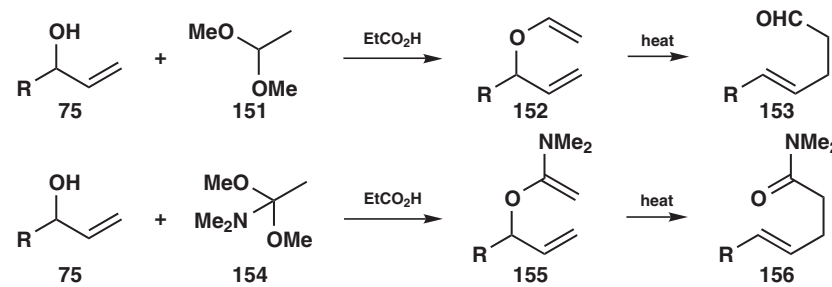
Corey[29] used a Cope rearrangement **147** in one of his syntheses of gibberellic acid. This reaction is driven both by the release of strain (the fused bicyclic product **148** is less strained than the bridged bicyclic starting material) and by development of conjugation. But the Cope is difficult to use and there is no general synthesis of appropriate starting materials.



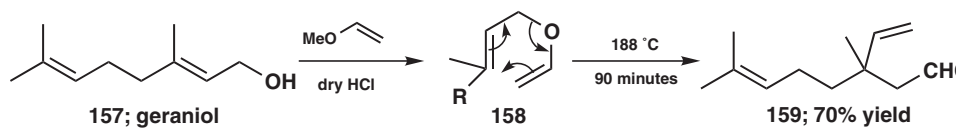
The Claisen-Cope rearrangement is much easier to use. The starting material is an allyl vinyl ether **149** that can be made from an allylic alcohol. The product looks as though it might have been made by the allylation of an enol(ate) and the same disconnection **150** does for both. In this simple case, the product could equally well be made from an enamine of acetaldehyde and allyl bromide but you should by now realise that more complicated examples need a lot of control.



The starting materials are made from the allylic alcohol **75** by exchange with either an acetal **151** or a vinyl ether. Though acid catalysis is needed for this reaction, it must not be strong enough to cause isomerisation of the allylic alcohol so carboxylic acids such as propionic ($EtCO_2H$) are strong enough. Derivatives of aldehydes **152**, ketones, acids, and amides **155** can all be used. Here are examples of an aldehyde **153** and an amide **156**.

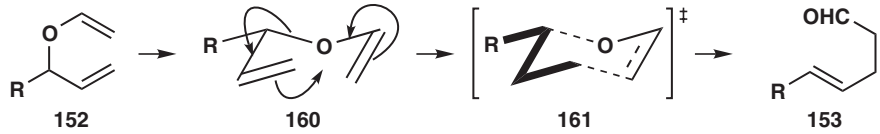


Regiocontrol is easy to explain: the allyl part of the molecule is turned inside out (or back to front if you prefer) with the new C–C bond being formed at the other end of the alkene from the OH group **158**. Since the easier allylic alcohol to make is the one with the more highly substituted alkene (e.g. geraniol **157**) it is actually easier to make the more 'difficult' allylated product.[30]

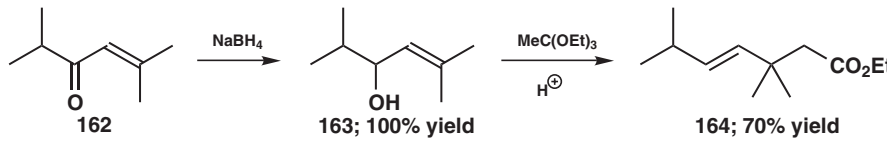


The stereochemistry of the alkene needs a little more explanation. The transition state for the reaction is a six-membered ring and it prefers a chair-like conformation with the substituent R in an equatorial position **161**. This gives an *E* alkene in the product and these reactions, like the [2,3]

shifts we have already seen, are very *E*-selective. The heavy bonds in the transition state **161** show the *trans* arrangement of the alkene that is being formed.



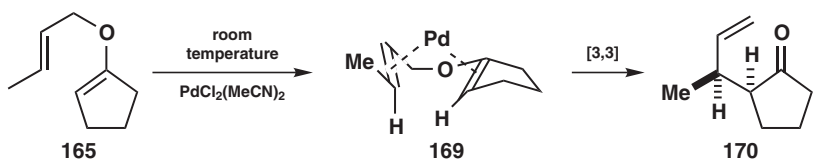
An example of the formation of an ester of an *E*-4,5-alkenoic acid **164** comes in a synthesis of chrysanthemic acid by Ficini and her group.[31] Reduction gives the allylic alcohol **163** and [3,3] Claisen rearrangement with triethyl *ortho*-acetate gives the product **164** in one step.



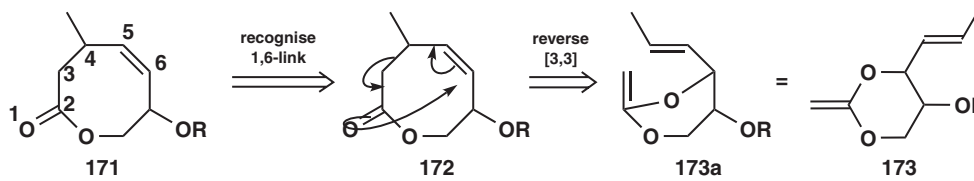
Stereochemistry in the Claisen-Cope rearrangement

Control over the geometry of the allylic ether portion of the starting material is easy - just use the appropriate allylic alcohol. Control over the vinyl ether is more difficult as that alkene is created in the exchange reaction. If the vinyl ether is cyclic, the problem disappears. The allyl vinyl ether **165**, made from cyclopentanone and the allylic alcohol but-2-en-1-ol **8** rearranges with catalysis by 2,6-dimethylphenol into one diastereoisomer of the allylated product[32] **168**. The stereoselectivity is easily predicted by the chair transition state **167**.

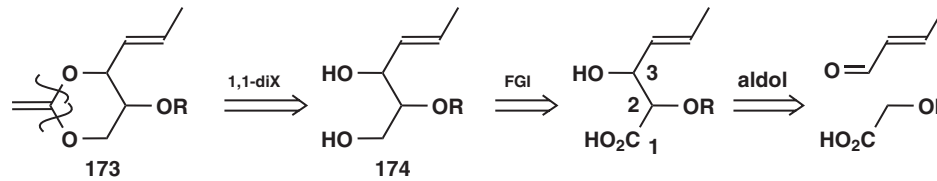
If a Pd(II) catalyst is used instead the other diastereoisomer **170** is formed. Presumably Pd coordinates to both alkenes and holds the molecule in a boat conformation **169** during the reaction. In both cases the more difficult regiochemistry is achieved with the bonus of stereochemical control.



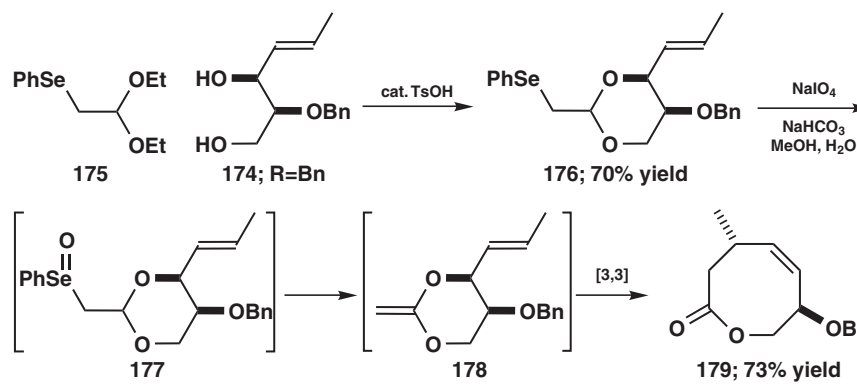
The easiest way to find the Claisen-Cope disconnection is to reverse the reaction. First you must recognise that this is worth doing and the simplest clue is to look for a piece of skeleton with two terminal π-bonds (alkene or carbonyl), the ends being 1,6-related. Here is a difficult example that makes an eight-membered ring **171** and also illustrates a different way to make the enol ether.[33] Reversing the [3,3] looks awkward **173a**, but redrawing the structure **173** makes it look much better.



This particular enol ether is also an acetal (a ketene acetal) so we should be able to make it from the diol **174**. This has 1,2- and 1,3-diO relationships and we much prefer to disconnect the 1,3 as we can then use some sort of aldol reaction.

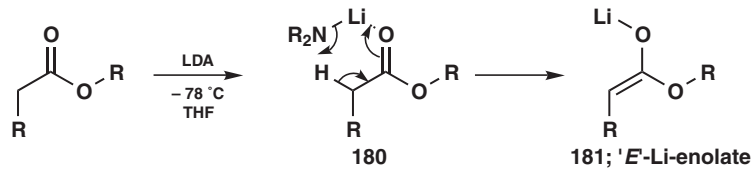


There are also stereochemical considerations here and Holmes used the Evans asymmetric aldol reaction (chapter 27) to make the starting material **174**; R=Bn. The formation of any allyl vinyl ether reagent involves no change in the stereochemistry of the allyl alcohol - this is acetal exchange at the vinyl ether or acetal centre. The enol ether was added in masked form as a selenium compound **175** (chapter 32) as selenoxides eliminate at room temperature. The stereochemistry is developed directly from that in **177** as it transforms during the [3,3] shift.

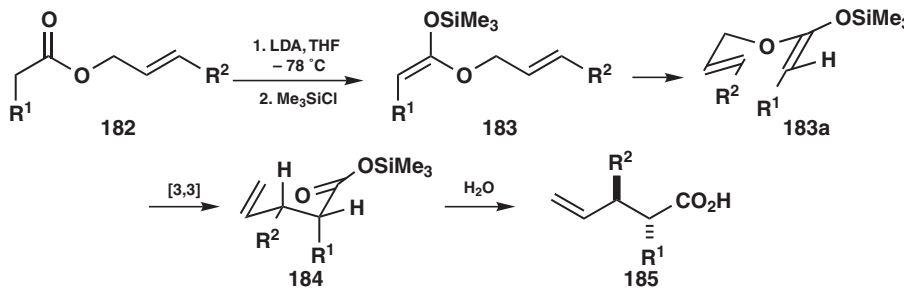


The Claisen-Ireland rearrangement

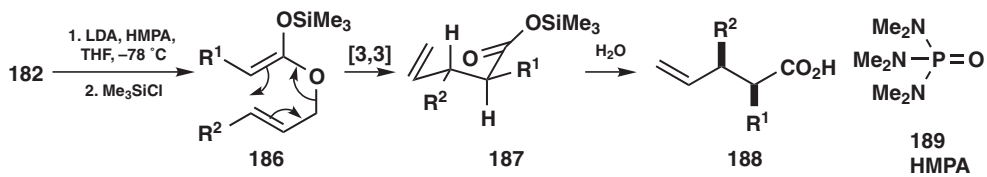
One special application comes when silyl enol ethers of allylic esters provide the starting material: this is known as the Claisen-Ireland reaction. Esters normally form *E*-enolates **181** with LDA at low temperature. Because the *E/Z* nomenclature depends on the hierarchy of the substituents it is particularly ridiculous when applied to enol derivatives of esters. A lithium enolate (Li < C) would have the opposite stereochemical label from a silyl enol ether (Si > C) so a uniform scheme is adopted whereby the metal – O bond always has priority over the other. The mechanism **180** may remind you of the reasons for this - they are discussed in more detail in chapter 4.



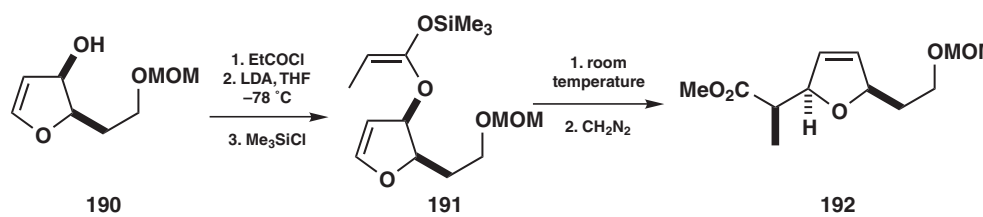
This is true also of allylic esters **182** so that the geometry of both alkenes involved in the Claisen-Cope rearrangement can be controlled if the lithium enolate is trapped by silylation to give **183**. Drawing the rearrangement in the chair conformation **183a** → **184** gives a predictable diastereoisomer of the product **185**.



Ireland also discovered a remarkable way to form the *Z*-enolate.[34] All that was necessary was to add HMPA (HexaMethylPhosphorAmide **189**) to the solvent in making the lithium enolate. This excellent (though also dangerously carcinogenic) ligand for Li reverses the stereochemistry to give the more stable *Z*-silyl enol ether **186** and hence the opposite stereochemistry of the product **188**.

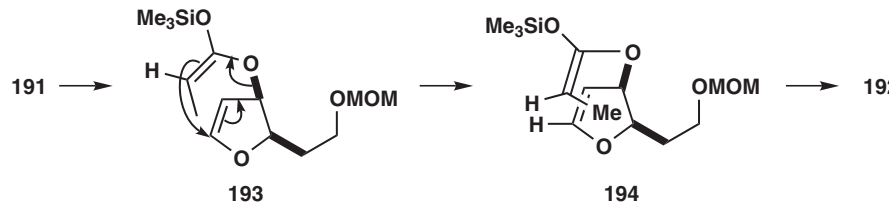


Most of the complex polyether antibiotics made using this reaction have actually used cyclic allylic alcohols and with them a boat-like conformation is preferred in the Claisen-Ireland rearrangement. A simple example is the dihydrofuran **190**, prepared as a single enantiomer from a sugar (in chapter 23 we shall call this a 'chiral pool' strategy). Acylation and *E*-selective silyl enol ether formation **191** followed by Claisen-Ireland rearrangement gives one diastereoisomer of the product[35] **192**.



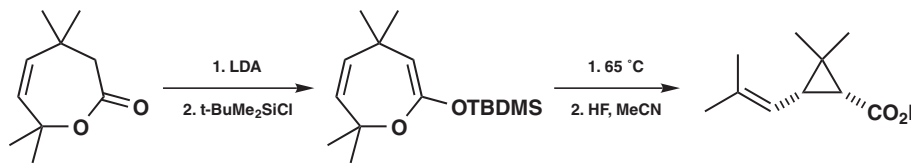
The observed stereochemistry requires the enol ether to be transferred suprafacially across the top face of the five-membered ring **193** (this fixes the stereochemistry at the new centre on

the ring) with the bulk of the side chain away from the ring in a boat-like arrangement. The stereochemistry of the centre on the side chain is determined by the geometry of the enolate: this *E*-enol ether has the methyl group over the heterocyclic ring **194**.

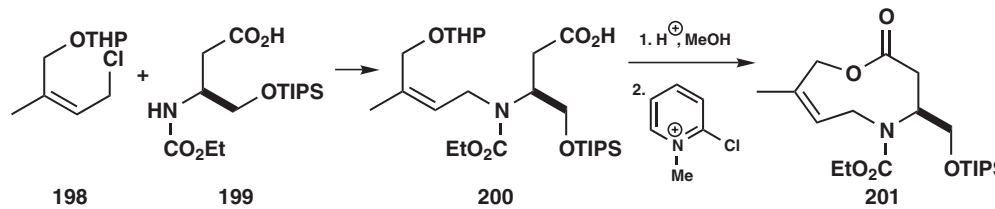


This result in particular should warn you that the choice between a chair- and boat-like transition state is narrow. In general open-chain compounds prefer the chair and cyclic compounds the boat but do not rely on it! In spite of this apparent disadvantage the Ireland version of the Claisen rearrangement is one of the most widely used ways to set up complicated molecules. Ireland himself has used it to make a catalogue of polyether antibiotics with the monensin synthesis being perhaps the most remarkable. These syntheses are beyond the scope of this book but are worth reading.[36]

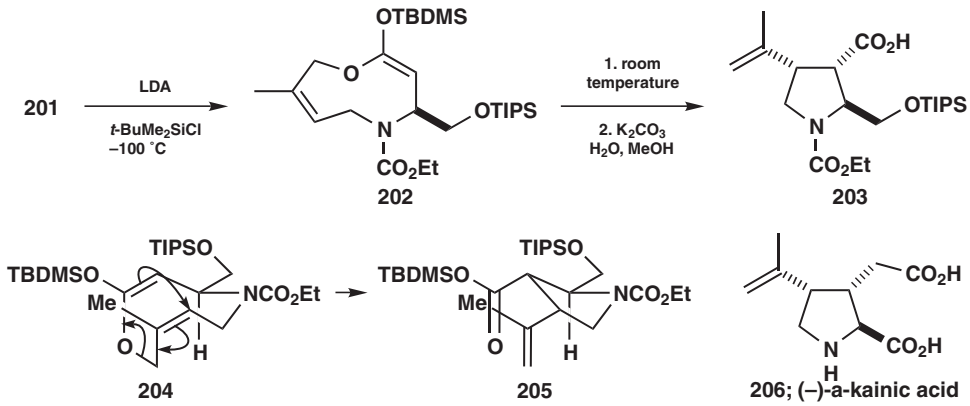
When both alkenes (allyl and vinyl ether) are inside a ring the stereochemical problems are much simplified. The reaction inevitably leads to ring contraction and a simple example is Funk's synthesis[37] of chrysanthemic acid **197** from the seven-membered lactone **195**. The silyl enol ether **196** rearranges to *cis*-chrysanthemic acid in very high yield. A chair transition state is impossible in this restricted molecule.



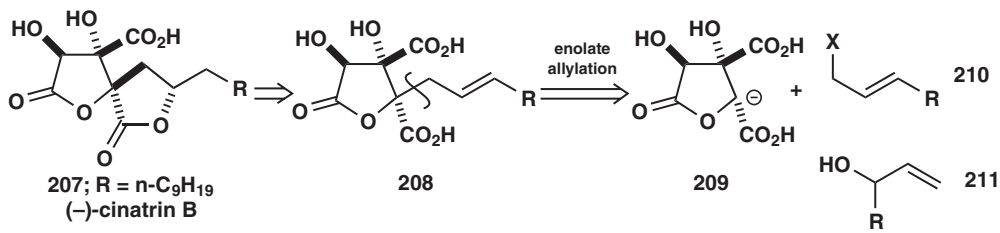
Knight's synthesis of (−)-α-kainic acid provides a heterocyclic example.[38] The starting material for the Claisen rearrangement is made from natural aspartic acid coupled to an allylic chloride **198** with a protected allylic alcohol **200** also present. Deprotection and lactonisation gives the nine-membered nitrogen-containing lactone **201**.



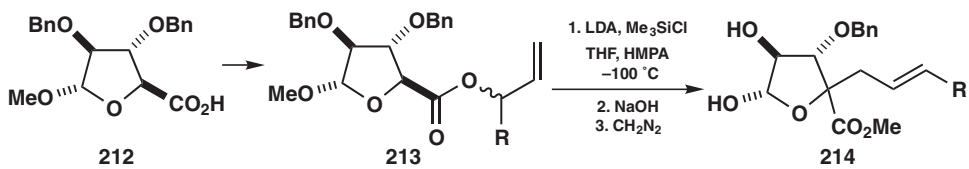
Formation and trapping of the lithium enolate gave only the *E* silyl enol ether **202** (that is with a *cis* alkene in the ring). As this is a cyclic enol ether, a boat-like transition state is expected and the formation of a single diastereoisomer of **203** confirms that this is true. Diagrams **204** and **205** should clarify the conformation of the molecule as it reacts, the mechanism, and the stereochemistry of the product. The product was converted into kainic acid **206** in a few steps.



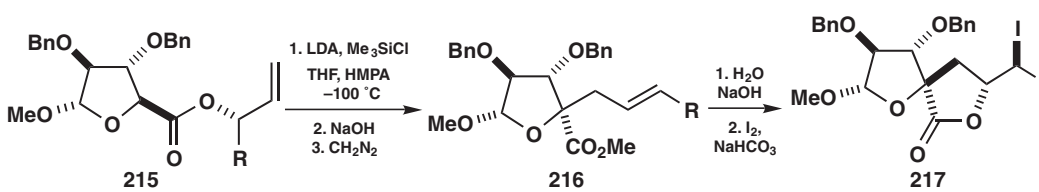
Recent developments in this important reaction have helped to reveal the relationship between 2D and 3D stereochemistry. The synthesis of the phospholipase inhibitor cinatrin B **207** illustrates a serious stereochemical problem.[39] Cinatrins have spiro-fused lactones. Each ring contains chiral centres and the spiro C-atom is also chiral. It is very difficult to relate stereochemistry between such orthogonal rings. The second lactone might be added by cyclisation onto an alkene such as **208** and that could arise from allylation of an enolate **209**. Clearly some protection will be needed.



The starting material **212** was chosen as it was available from natural arabinose and contains enough functionality for the purpose. Esterification with racemic alcohol **211** gave a mixture of esters **213**. This does not seem to matter as that centre is destroyed in the Claisen-Ireland rearrangement giving **214** but this compound was formed as a 43:57 mixture of diastereoisomers.



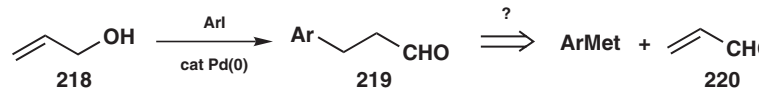
Use of the enantiomerically pure alcohol **211** revealed a surprising stereospecificity. One enantiomer **215** gave (mostly) the required diastereoisomer **216** and hence the iodolactone **217** having the right stereochemistry at the spiro centre and at the lactone centre in the new ring. Removal of iodine, selective oxidation and addition of a d^1 reagent gave (−)-cinatrin B.



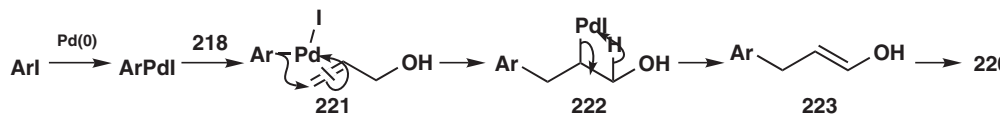
The scope of the Claisen-Cope rearrangement is very great but you have been given enough mechanistic and stereochemical detail to unravel all but the most difficult. The disconnection is always simple - the reaction corresponds to an allylation of an enolate and, providing you remember to turn the allylic system inside out, you will find the starting materials. All that remains is to identify which method to use and how to control the stereochemistry. Oh, and you also have to make the starting materials!

Pd-catalysed reactions of allylic alcohols

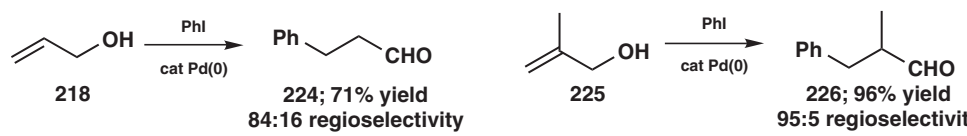
In the last chapter we introduced the Heck reaction as a way to add nucleophiles to electrophilic alkenes. The details of the mechanism are discussed there. The reaction also occurs with allylic alcohols **218** and is a good way to make carbonyl compounds, particularly aldehydes, **219** as the alternative conjugate addition of an organometallic compound to an enal often shows poor regioselectivity (chapter 9).



Formation of the aryl palladium (II) complex ArPdI by oxidative insertion is followed by π-complex formation and transfer of the aryl group from palladium to the alkene **221**. Then β-elimination **222** gives the enol **223** of the product. The other ligands on palladium are omitted.

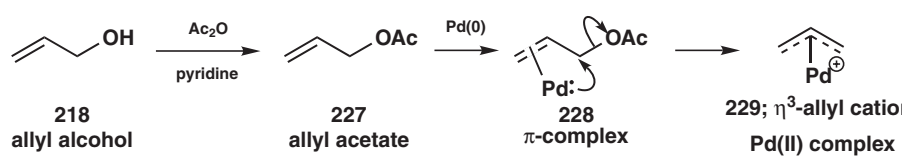


The regioselectivity is not as good with allylic alcohols as it is with unsaturated carbonyl compounds as there is only a steric preference for transfer of the aryl group to the end of the alkene. Examples **224** and **226** show how this can be improved with extra substitution.[40]

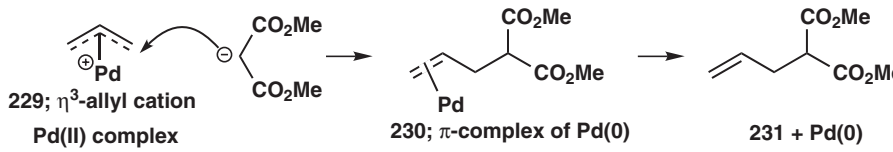


Pd-allyl acetate complexes

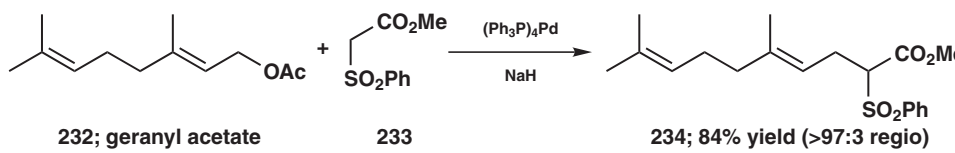
Allylic alcohols **218** can be converted into their acetates **227** by standard methods, e.g. Ac_2O/pyridine or DMAP, without any allylic rearrangement. Reaction with Pd(0) gives initially a π-complex **228** but this loses acetate as the Pd atom donates a pair of electrons to form an η^3 allyl cation complex **229** of Pd(II).



These allyl cation complexes **229** are electrophilic and react with a variety of nucleophiles, most notably with the stabilised enolates of β-dicarbonyl compounds such as malonates. The immediate product is again a π-complex of Pd(0) **230** but there is now no leaving group so the Pd(0) drops off and is available for a second cycle of reactions. Though the reaction strictly requires Pd(0), the more convenient Pd(II) compounds are often used with phosphine ligands. Reduction to Pd(0) occurs either because the phosphine is a reducing agent or by oxypalladation and β-elimination.



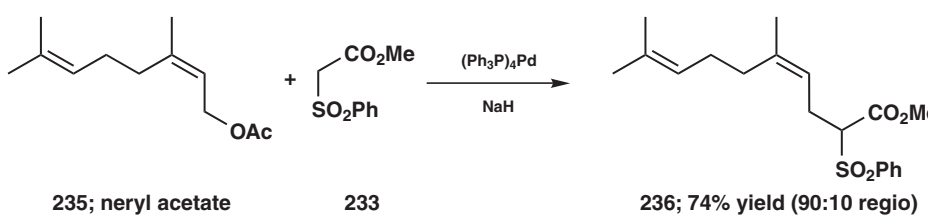
The allyl cation complex has the Pd(II) atom at right angles to the allyl plane and more or less in the middle of the triangle. It has therefore lost regiochemistry as the same complex would be formed by either regioisomer. Simple versions of the reaction are still useful - geranyl acetate **232** reacts only at the alkene that is part of the allylic acetate and gives mostly the product of attack at the less hindered end of the allyl cation.[41] When malonate is the nucleophile, the regiochemistry is 9:1 in favour of attack at the terminal carbon. With the sulfone **233**, the reaction is totally regioselective.



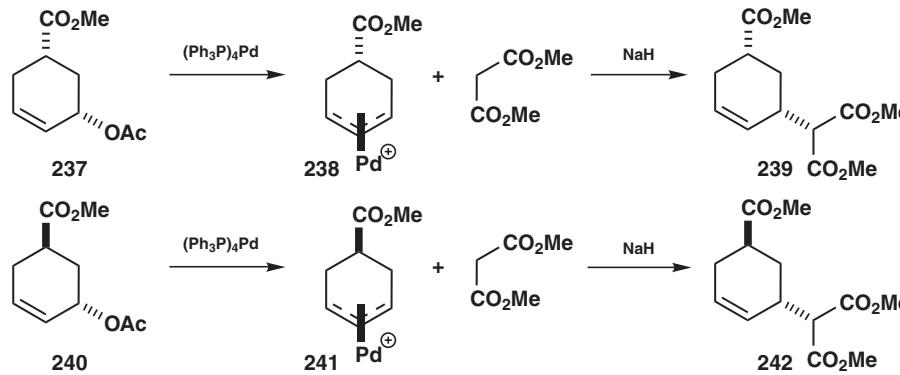
You will appreciate that CO_2R groups may be removed from these various products by hydrolysis and decarboxylation. The sulfones can be removed by reduction, for example with sodium amalgam in ethanol - this is 'dissolving metal' reduction and works by electron transfer in the style of a Birch reduction.

Stereochemistry of Pd-allyl cation complexes

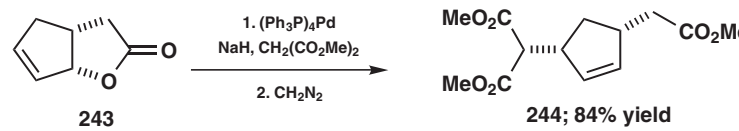
The most important aspect of this chemistry is its stereoselectivity. The stereochemical integrity of the alkene in the starting material may be preserved. This is not surprising with the geranyl acetate just described but is also the case with the *Z*-isomer neryl acetate **235**. The regioselectivity is less (90:10, attack at the terminus being favoured) but the major product contains only the *Z*-alkene present in the starting material. There is no rotation at any stage in the reaction.



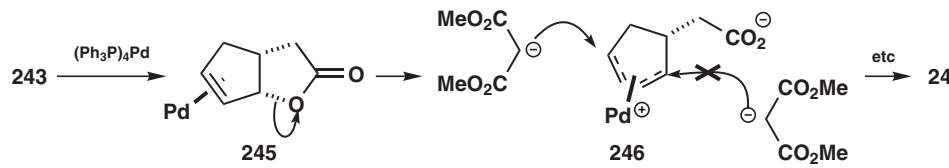
In three dimensions the reaction is stereospecific with retention by double inversion. The palladium approaches the alkene from the opposite face to the leaving group and the nucleophile approaches from the opposite face to the palladium. This is clearly shown by reaction of the two diastereoisomers **237** and **240** with malonate. [**Note**: These compounds are of course racemic and attack at either end of the achiral η^3 allyl cation complexes **238** or **241** would give racemic material anyway.]



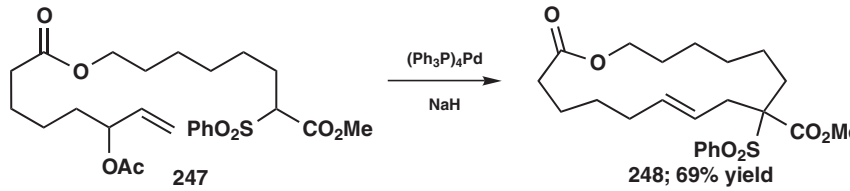
The combination of stereo- and regiochemistry can be very powerful. The lactone **243** reacts with malonate esters to give one regio- and stereoisomer of the triester product[41] **244**.



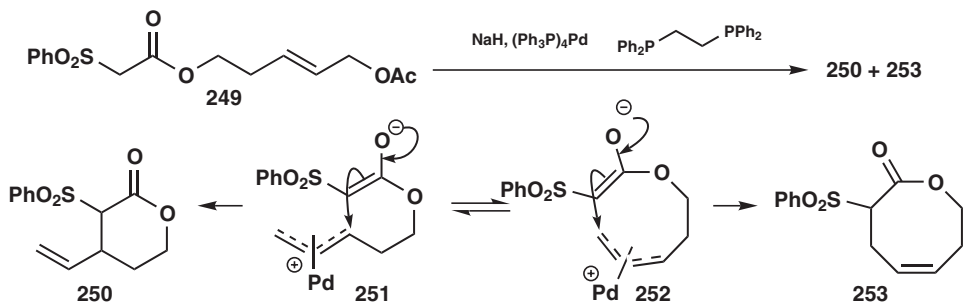
The palladium forms a π-complex **245** from the top face of the alkene, opposite the carboxylate leaving group. The nucleophile then adds from the opposite face to the palladium. The η^3 allyl cation complex is unsymmetrical and the nucleophile adds at the less hindered end. The selectivity is very marked in both steps because the starting material is a folded molecule and the palladium much prefers to add to the *exo* face of the alkene. The nucleophile has to add from the same face as the CH_2CO_2- side chain so it prefers addition to the end of the complex as far from this side chain as possible **246**.



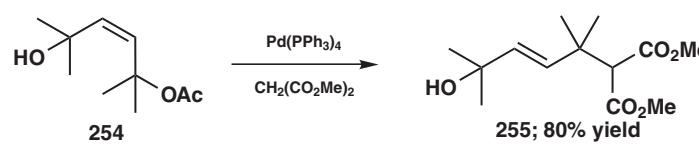
When the reaction is intramolecular, the question of ring size may affect both the regiochemistry and the stereochemistry of the alkene. In general, we might expect smaller or larger rings to be preferred to medium rings (8-13 membered) and it is obviously impossible to have an *E*-alkene in, say, a seven-membered ring. So it is not surprising that the 16-membered 'large' ring **248** is formed from **247** by attack at the end of the allylic system and with complete *E*-selectivity. This is a good way to make macrolides (large ring lactones).[42]



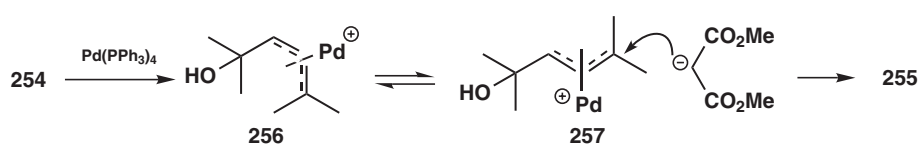
However, the formation of the eight-membered ring **253** with a *Z*-alkene from the *E*-allylic acetate **249** with only a trace (6%) of the six-membered ring **250** was described by Trost[42] as a 'shocking preference for cyclisation to the eight-membered ring'. Clearly the geometry of the η^3 allyl cation complex can change during the reaction and this seems to be particularly the case for intramolecular reactions. The initially formed η^3 allyl cation complex **251** can cyclise either to the six-membered ring or to the very unstable *E*-isomer of the eight-membered ring. Rotation to the other η^3 allyl cation complex **252** must be faster than this cyclisation and the new complex can cyclise to either product.



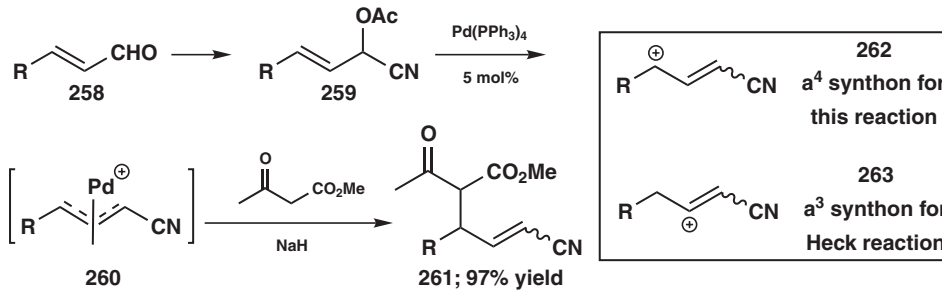
The regioselectivity of the addition is affected by functionality. In another synthesis of chrysanthemic acid, Ficini[43] combined the monoacetate of the *cis* (*Z*)-alkene diol **254** with malonate to give only the *trans* (*E*)-adduct **255** in 80% yield.



Evidently *cis/trans* isomerisation of the η^3 allyl cation complex is faster than addition. The regioselectivity is remarkable. Either the steric hindrance of Me_2COH next to the alkene is worse than that of the tertiary centre that is actually attacked or the OH group electronically discourages nucleophilic attack as it does in simpler S_N2 reactions. We shall see a related regioselectivity in the reactions of diene monoxides in the next section.

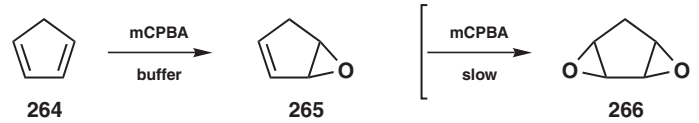


Conjugating and electron-withdrawing groups such as CN or CO_2R make the remote end of the allyl cation complex more electrophilic. The CN substituted compounds **259** are easily made[44] by acetylating the cyanohydrins of enals **258**. Superficially this might look rather like a Heck reaction but the nucleophile is added in a different position. These complexes are reagents for the a^4 synthon **262** having *umpolung* while the Heck reaction gives products from natural conjugate addition (a^3 **263**). The product **261** is formed as an *E/Z* mixture: if an ester group (CO_2Me) is the activating group, only the *E*-isomer is formed.

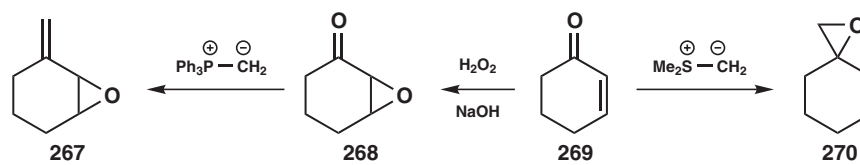


Pd and monoepoxides of dienes

A clever variation on the reactions of allylic acetates is the palladium-catalysed reaction of monoepoxides of dienes with nucleophiles. These monoepoxides can be made in two chief ways. If the diene is symmetrical **264**, epoxidation of one of the alkenes occurs more rapidly than the epoxidation of the monoepoxide because the HOMO (ψ_2) of the diene is higher in energy and therefore more nucleophilic than the HOMO (π) of an alkene. It is simply necessary to buffer the epoxidation reagent as these monoepoxides **265** are sensitive to acid (chapter 17).

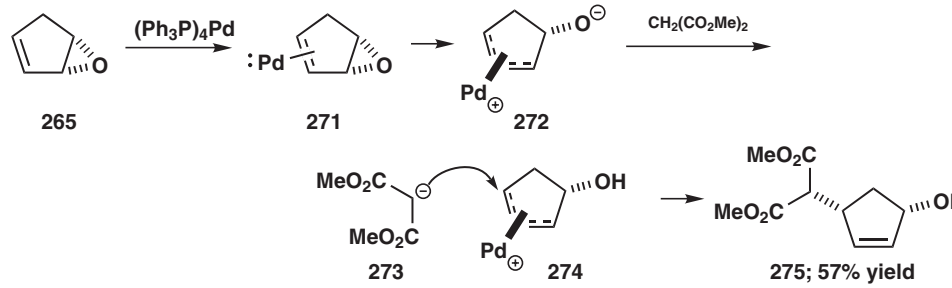


If the diene is unsymmetrical, particularly if the monoepoxide of the less substituted and therefore less nucleophilic alkene is wanted, alternative methods are required. The enone **269** provides both epoxides **270** and **267**. The sulfur ylid route converts the enone directly to one epoxide while base-catalysed epoxidation followed by a Wittig reaction provides the other.

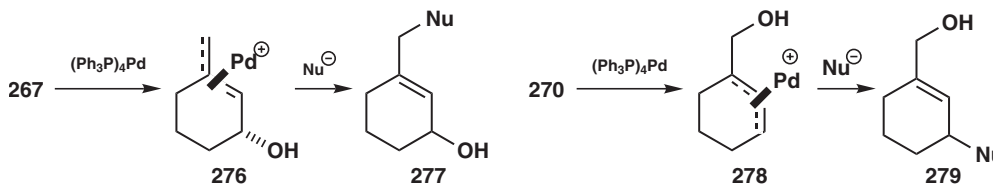


Reaction of these epoxides with Pd(0) follows the pattern of the allylic acetate reactions. The epoxide oxygen atom is the leaving group but the alkoxide intermediate is basic enough to deprotonate nucleophiles such as malonates without added base. With cyclopentadiene monoxide **265**, one regio- and stereoisomer **275** is formed.[45] The palladium adds to the opposite side of the

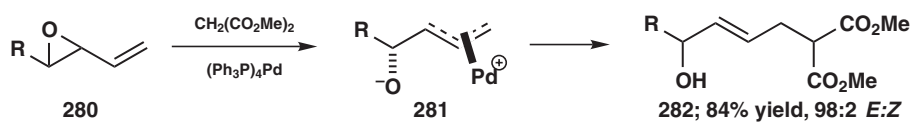
ring to the epoxide and the nucleophile adds to the opposite side to the palladium and at the end of the allyl cation away from the OH substituent **274**, as you should by now expect.



In general, substitution occurs at the less hindered end of the allyl cation and, unlike the cations formed from allylic acetate, these cations are never symmetrical - one end always has the nearby OH group that was the oxygen atom of the epoxide. The two isomeric epoxides **267** and **270** also give isomeric products though there is no stereochemistry here.

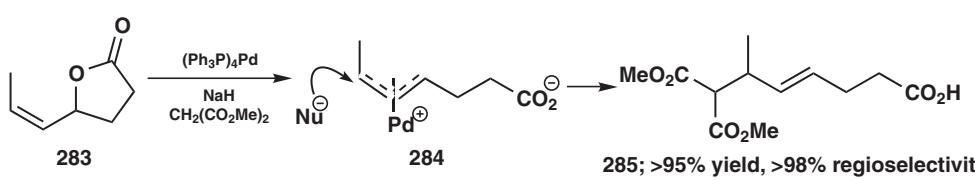


In the simplest cases of open chain epoxides with terminal alkenes,[46] reaction is predominantly at the end of the chain and the product is overwhelmingly the *E*-isomer.

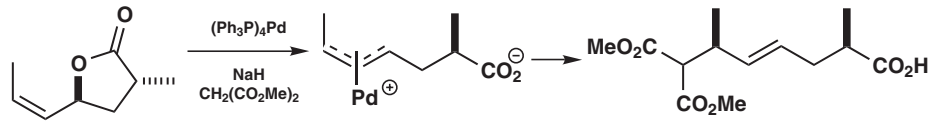


The control of remote chirality

Allylic carboxylates and epoxides give the opportunity to control stereogenic centres that are not next to one another and may be as far apart as a 1,4-relationship across a *trans* alkene. There is an example of a similar problem solved by a [2,3] sigmatropic rearrangement earlier in this chapter. In particular vinyl lactones such as **283** have special uses. Trost[47] first checked the regiochemistry of the reaction with lactone **283**. This forms the usual η^3 allyl cation complex **284** that reacts with the enolate at the end further from the carboxylate group. The alkene moves along the structure and emerges in the *E* configuration **285** corresponding to the conformation of the lactone.

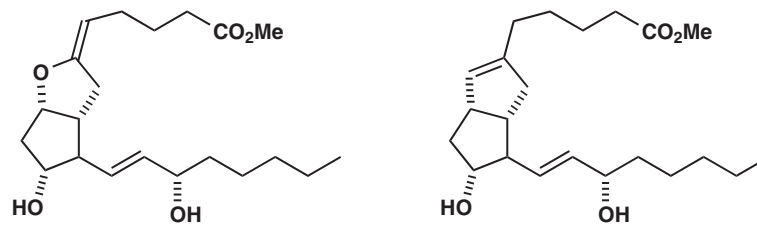


Now for the stereochemistry. If a single diastereoisomer of the methylated lactone **286** is reacted under the same conditions with the same nucleophile, a single diastereoisomer of the product **288** is formed in excellent yield. Because the stereogenic centres are so far apart, it was difficult to tell one diastereoisomer from the other and Trost explains carefully how this was done.



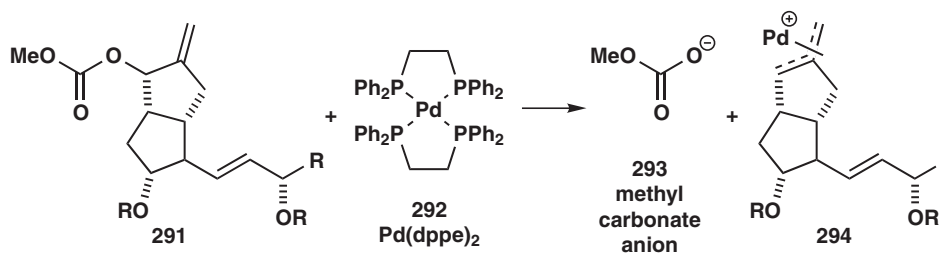
286 **287** **288; 90% yield >98% regioselectivity**

These reactions are also used industrially. The Japanese company Teijin Ltd. uses the reaction of a stable carbanion with an allylic carbonate to make a stable analogue **290** of prostacyclin (PGI_2) for use in the treatment of diseases of the circulatory system. Prostacyclin itself **289** is an enol ether and is too labile for medicinal use.[48]



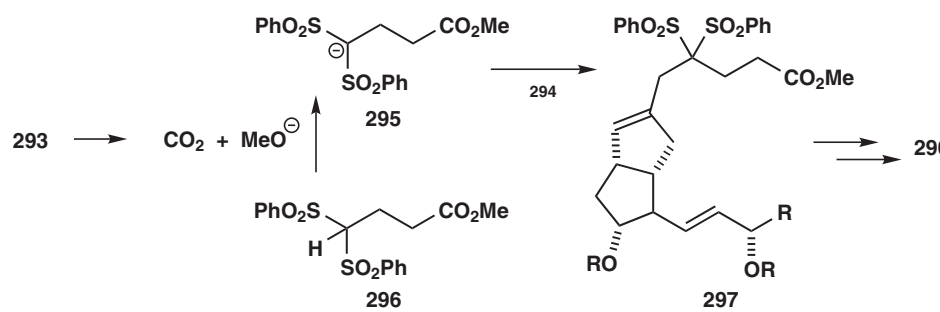
289; PGI_2 or prostacyclin **290; Teijin's isocarbocyclin**

The reaction starts with an allylic carbonate **291** that gives the usual η^3 allyl cation complex **294** with Pd(0) though the ligand is the less usual chelating diphos **292** ($Ph_2PCH_2CH_2PPh_2$). The leaving group is a carbonate anion **293**.



291 **292 Pd(dppe)$_2$** **294**

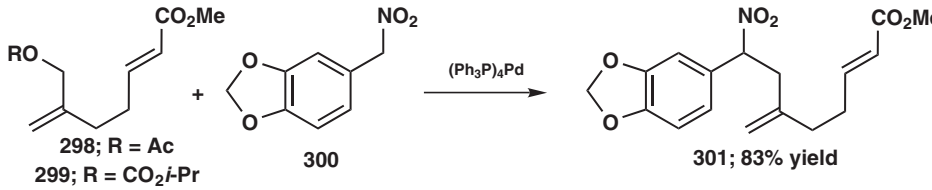
The carbonate anion loses CO_2 to give methoxide ion which, like the anion released from a diene monoepoxide, is basic enough to deprotonate the nucleophile, a bis-sulfone **296**. The anion from this **295** adds to the less hindered end of the allyl cation complex **294**. The product **297** has the skeleton of the prostacyclin analogue and the sulfones simply need to be removed by reduction.



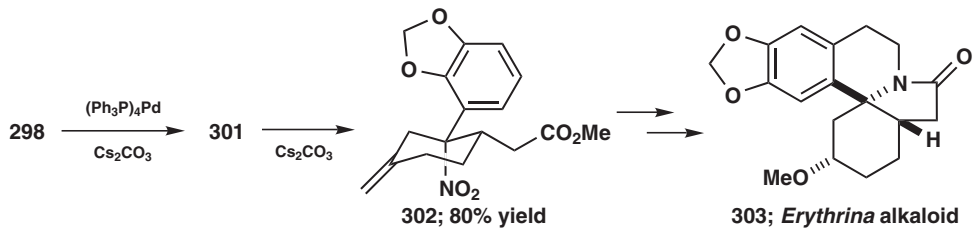
295 **296** **297**

Recent developments

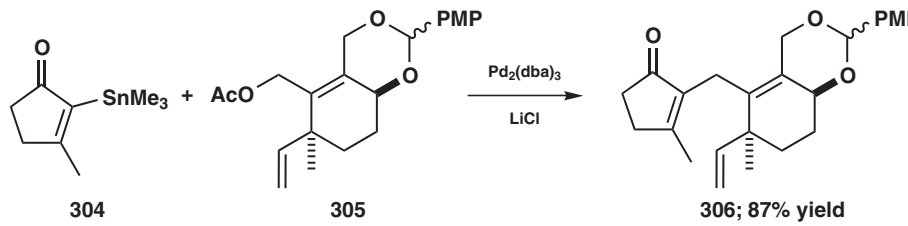
The palladium-catalysed coupling of allylic esters with carbanions has now been extended to include other reactions. The allylic carbonate **299** couples with the nitro compound **300** to give the expected product **301** in good yield.



But if the acetate **298** was used the additional base required (here Cs_2CO_3) catalysed a further intramolecular conjugate addition of the nitro-stabilised anion to the unsaturated ester to give a new six-membered ring **302** with good stereoselectivity. This compound was converted into the *Erythrina* alkaloid[49] **303**.



Since vinyl stannanes (chapter 18) couple with electrophiles under catalysis by Pd(0), it makes sense to create the electrophile by the palladium-catalysed reactions of allylic acetates in the same pot.[50] The vinyl stannane **304** reacts cleanly with the more complex allylic acetate **305** with 0.2 equivalents of Pd(0) to give the triene **306** in good yield.[51]



Summary

The chemistry of allylic alcohols and their derivatives is remarkably rich. They can be used to add allyl groups to other molecules with good regio- and stereochemical control. The methods in this chapter, particularly the palladium-catalysed reactions and the sigmatropic rearrangements, should allow you to make many otherwise difficult target molecules.

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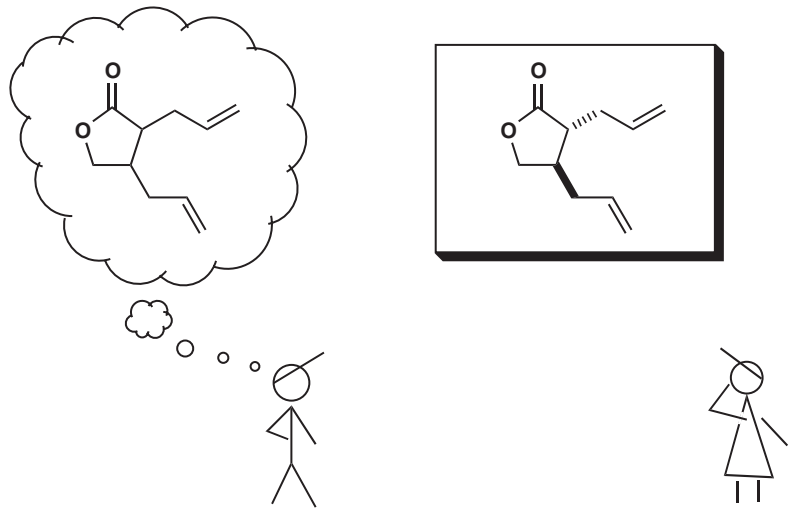
Section D: Stereochemistry

20 Control of Stereochemistry – Introduction

Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

Introduction

Stereochemistry denial



This chapter is – and the next ten chapters are – about stereochemistry. Nobody these days would question the importance of stereochemistry. But inexperienced undergraduates – and, it has to be said, some practising organic chemists – who are faced with a synthesis which involves a little stereochemistry often *ignore* the stereochemical aspect, and focus entirely on the bond-forming side of things. It is not hard to see why somebody might suffer from this 'Stereochemistry Denial'. Stereochemistry isn't easy; it complicates matters and is probably the most difficult aspect of organic chemistry for most chemists. One need only look in the literature from the early part of the 20th Century to see syntheses where compounds were produced as diastereomeric mixtures, where the fact that they were mixtures was of *no* concern to the authors, and where the final relative stereochemistry of the product was not known, and, at the time, could not have been. That was then. Not any more.

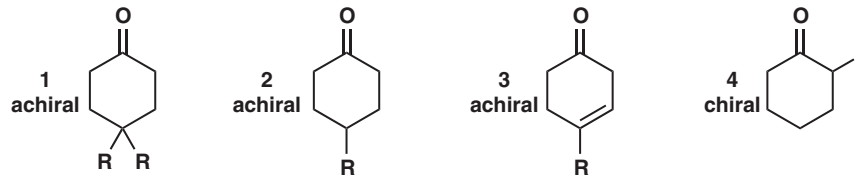
In this chapter we introduce the language of stereochemistry and some of the concepts that are used in later chapters within this section and also in the rest of the book. If you are unfamiliar with some of the finer stereochemical points, then this chapter could well be a 'baptism by fire'. Don't be put off – come back to any difficult parts of this chapter after some of the others in this Section (chapters 21–31).

Before coming to the first section, it is worth pointing out that we assume you know: what an enantiomer is, what a racemate is, what is meant by relative stereochemistry and what is meant by absolute stereochemistry.[1] We also assume you know the term enantiomeric excess.[2]

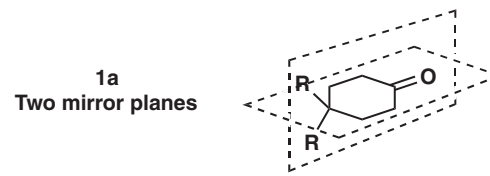
The Words We Use

Four ketones

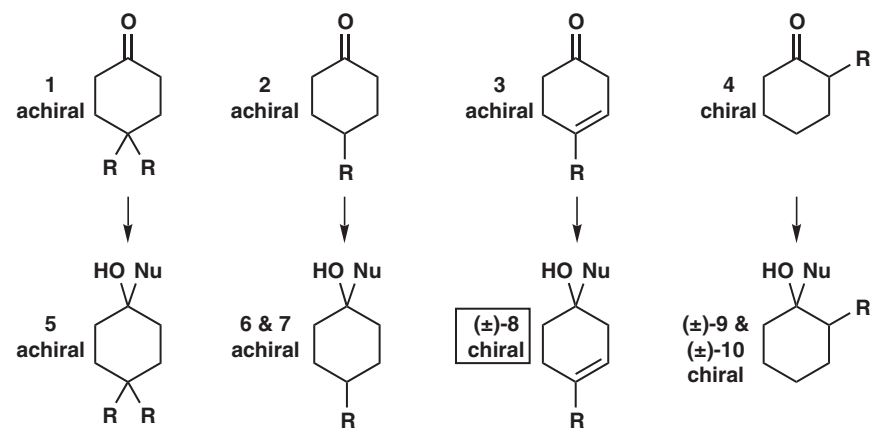
Consider the four ketones **1** – **4**. The first three are achiral but the last is chiral and racemic.



If we just imagine the six membered rings to be flat for a moment (they are not of course but it doesn't matter for our purposes) then the first molecule has two mirror planes running through it – one is in the plane of the paper and the other is a right angles to the paper **1a**. The next two molecules, **2** and **3**, each have one mirror plane. The last ketone **4** has no mirror planes and has a single stereogenic centre.

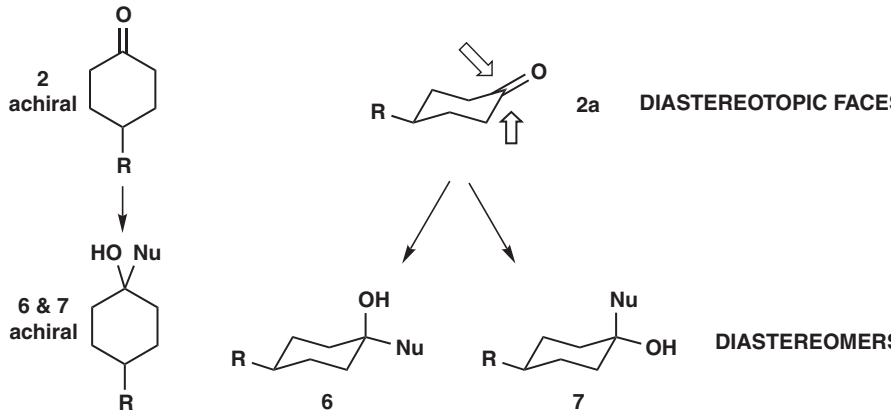


Now let us consider a reaction of each of these ketones with a nucleophile, Nu^-. In every case, an sp^2 centre is replaced by an sp^3 centre to give alcohols **5** to **10**.



Diastereomeric and diastereotopic

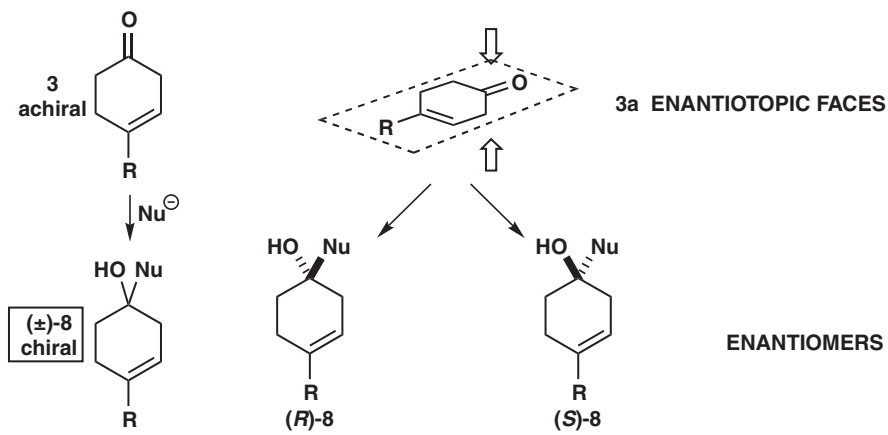
We will come back to ketone **1**. With ketone **2**, there are two possible products **6** and **7**. The nucleophile could attack the ketone from one face or from the other **2a**. Only the top face is on the same side as the R group. The two possible products from the reaction are diastereomers and so the two faces of the ketone are *diastereotopic.*



A similar situation arises with ketone **4**. Attacking the carbonyl on one face leads to one diastereomer while attack on the other face leads to another. Hence the faces are diastereotopic. The ketone **4** is chiral and racemic so the two diastereomers **9** and **10** will also be racemic.

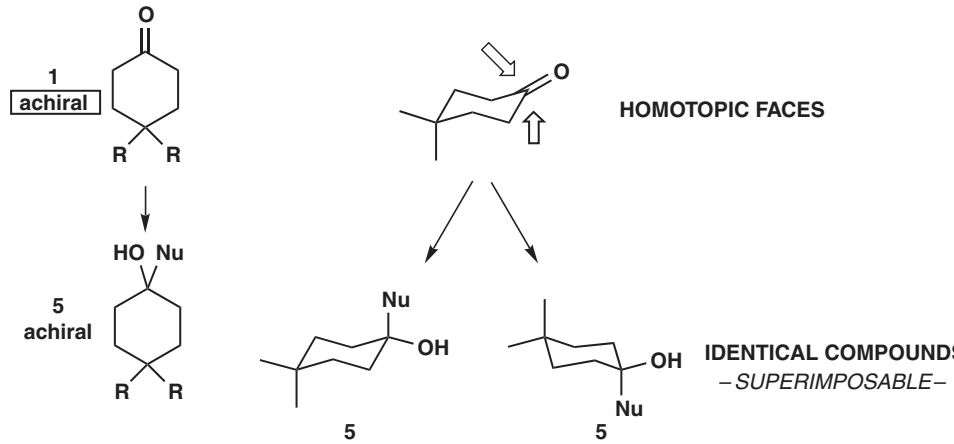
Enantiomers and enantiotopic

Like ketone **2**, ketone **3** can give two possible products and the nucleophile could attack the ketone from one face or from the other. However, this time, the two lines of attack lie on either side of the mirror plane that runs through ketone **3a**. The two products are enantiomers and the two faces of the molecule are thus enantiotopic. This reaction was the only reaction that started with an achiral material but gave a chiral product. Because a reaction of ketone **3** leads to chiral products we can also describe ketone **3** as prochiral.



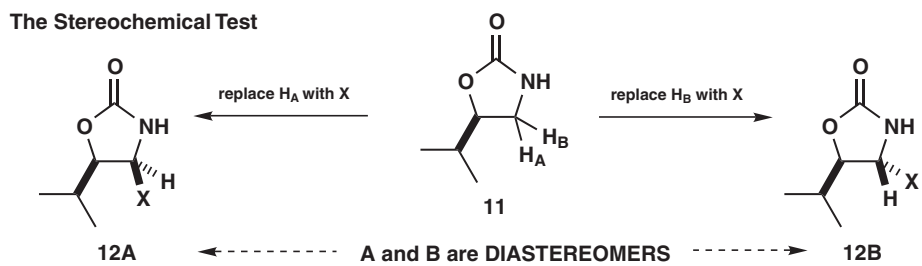
Homotopic

With ketone **1**, it doesn't matter at all which side of the molecule is attacked. The exact same compound **5** results and there is no possibility of different enantiomers or diastereomers. The compounds are superimposable. The two faces of the molecule are homotopic.



How to decide if two groups are homotopic, enantiotopic or diastereotopic

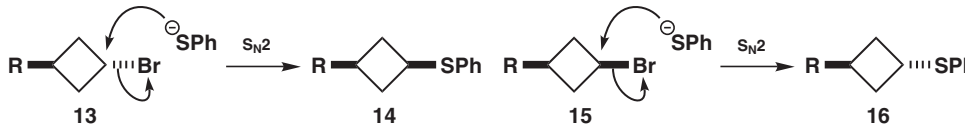
There is a test you can do to decide. It always works. First, substitute one of the groups you are interested in with something else – which we will call **X** – to give a new molecule **A**. Now, instead, substitute the other group you are interested in with **X** to give you a second molecule **B**. Now decide upon the relationship between your two new molecules **A** and **B**. If they are enantiomers of one another then the two groups must have been enantiotopic. If they are diastereomers of one another then the two groups must have been diastereotopic. And if the two molecules you end up with are exactly the same – by which we mean that one can be superimposed upon the other – then the two groups must have been homotopic.



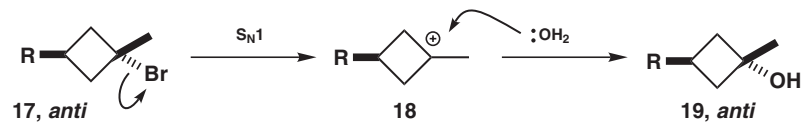
In the example above, the two protons H_A and H_B in oxazolidinone **11** are replaced in turn to give two new molecules **12A** and **12B**. This replacement gives us *diastereomeric* products — the protons themselves in the oxazalidinone (H_A and H_B) are therefore *diastereotopic*. In an NMR spectrum we would expect protons H_A and H_B to have different chemical shifts. We could have looked at other aspects of oxazolidinone **11** – the stereochemical relationship between the two methyl groups for example.

Stereoselectivity and stereospecificity

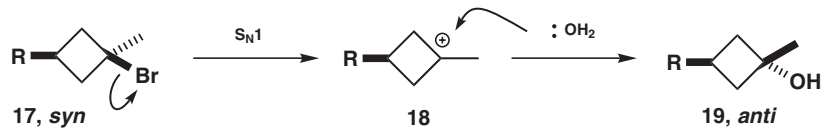
Stereospecificity. Let us state at the outset that stereospecificity is *not* just perfect stereoselectivity. This is a very common misconception. There is a difference between 100% stereoselectivity and stereospecificity. The reaction from **13** to **14** proceeds by an S_N2 mechanism. The nucleophile, PhS^-, attacks from behind the leaving group and so, of course, the reaction proceeds with inversion. This happens whether the molecule likes it or not. It is forced by the mechanism to give a specific product from a specific starting material. A stereospecific reaction conveys the idea that the other diastereomer will yield the opposite result: **15** must give **16**.



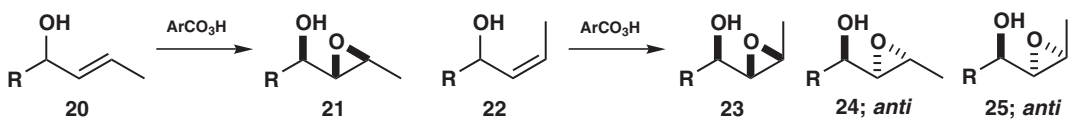
Stereoselectivity. To continue with similar examples – in a stereoselective reaction the molecule *selects* a particular reaction pathway for some reason. That reason might include steric hindrance, kinetics or thermodynamics but the molecule isn't forced by mechanism to react one way only. In the reaction of **17**, which proceeds by S_N1 rather than S_N2, the intermediate cation **18** may be attacked from either side by a nucleophile (there is no longer the necessary inversion we see with S_N2). Attack occurs selectively from the less hindered face of the cation **18**.



With stereoselectivity, there is the distinct possibility that different isomers will give the *same* product. The intermediate cation **18** is the same whether that starting material is *syn* **17** or *anti* **17** and must give the same product **19**.



There are plenty of reactions that contain both stereoselective and stereospecific components. One reaction might also be regioselective and even chemoselective and it is important to be able to dissect a reaction into these different selectivity components. An example concerns the two epoxidation reactions of **20** and **22**.

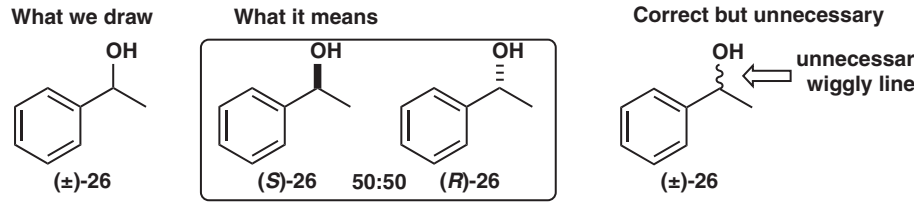


These reactions contain stereoselective and stereospecific components. The starting materials **20** and **22** are chiral and racemic and the faces of the double bonds (in both cases) are diastereotopic. Epoxidation is stereospecific since there is only one extra atom in the epoxide it *must* react with the two carbon atoms on the same side if the reaction is concerted. But, with allylic alcohols the reactions are also stereoselective since the OH will form a hydrogen bond with the peracid and hence deliver the oxygen *syn* to the alcohol. It could in principal react to give the *anti* product but it is not possible to make (as the major product anyway) the *anti* isomers **24** and **25** by this method. Another example of a reaction that has both stereoselective and stereospecific components appears in the pumiliotoxin synthesis in Chapter 21.

The Structures We Draw

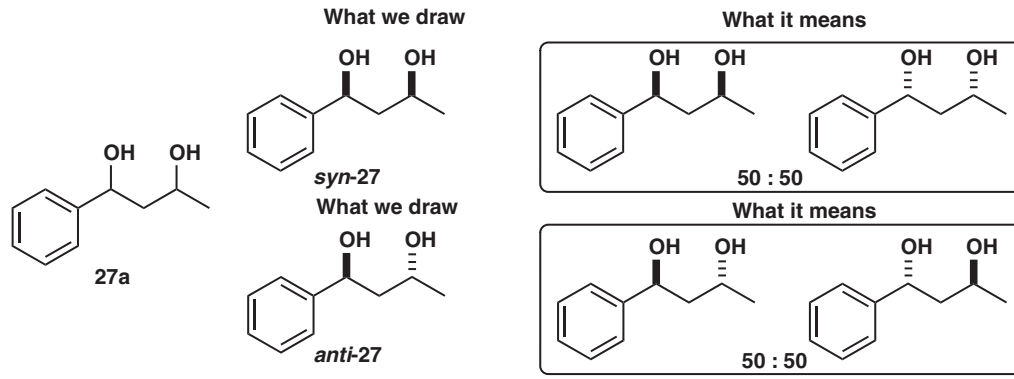
Racemates with one chiral centre

If the compound **26** is a racemate with only the one chiral centre then the bonds are best drawn as ordinary straight lines. This implies a racemate – that there are equal amounts of the two enantiomers (*S*)-**26** and (*R*)-**26**. There is no need to draw a wiggly line, for instance.



Racemates with two chiral centres

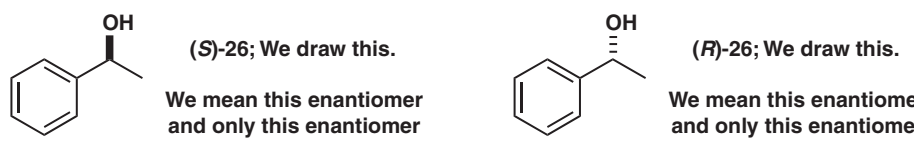
Now things are more complicated. This is because, whether we have racemates or not, we need to specify relative stereochemistry. The *syn* diol **27** contains two chiral centres. We have to draw in stereochemistry because we need to define which diastereomer we are concerned with. It is, however, racemic. Similarly, what we draw with the *anti* diol is *anti*-**27**.



Interestingly, this is the point at which many chemists bail out of stereochemistry. Somehow, even the thought of relative stereochemistry becomes all too much (a bit like the character in the cartoon). Such a person would draw this diol as **27a** which might mean anything. It really is worth taking the time to think about what the stereochemistry is and drawing it in.

Optically pure compounds with one chiral centre

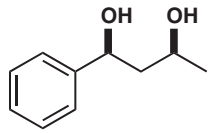
We can now draw the compound **26** as we mean it. There is no ambiguity.



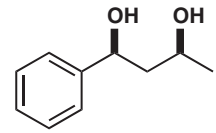
Optically pure compounds with two chiral centres

Now if we draw *syn*-**27**, we would like it to mean only that enantiomer. But now comes the difficulty. How do we distinguish this diagram from the one we used for the racemic compound? They both look the same. Sadly there is no easy answer to this and with two chiral centres it is ambiguous but for a start we can label the drawing (±)-*syn*-**27** if racemic. Sound advice is to spell it out on your

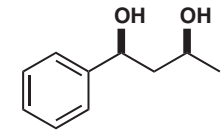
diagrams. Write (±) under the racemic compound and 'optically pure' under the optically pure one, or else label it (*S,S*)-**27** or (+) or whatever is right.



***syn*-27**



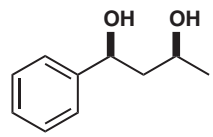
(±)-*syn*-27



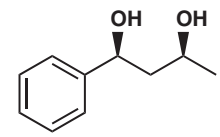
optically pure *syn*-27

Sophisticated diagrams

An attempt has been made to fix this ambiguity and to use 'blocks' for relative stereochemistry (±)-*syn*-**27** and 'wedges' for absolute (*S,S*)-*syn*-**27**. And this would be quite a good system if every body did it, but they don't. Sadly, for the moment at least, this extra level of complexity is not widely accepted and cannot be relied upon.



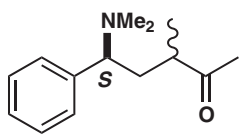
(±)-*syn*-27



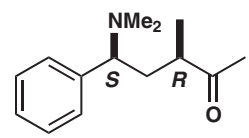
optically pure *syn*-27

Wiggly lines and two chiral centres

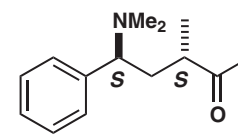
A wiggly line can mean several things. It can simply mean that both configurations are present, though as we saw above, it is not necessary with a racemic mixture. Suppose that we have only the *S* configuration of the amine **28** at the benzylic site.



28



(*S,R*)-28



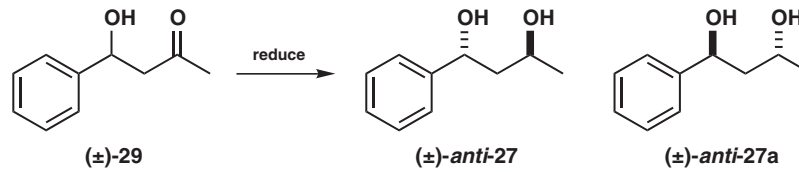
(*S,S*)-28

This diagram **28** could mean several things —

i) Both diastereomers (*S,R*)-**28** and (*S,S*)-**28** are present (though not necessarily in equal amounts).
ii) There is only one diastereomer but we don't know which one it is.
and it might even mean —
iii) We don't care. (Because, say, of reactions to follow that make it unimportant).

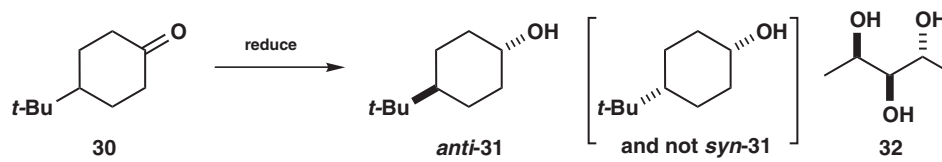
Racemates with one chiral centre which react to give a racemate with two

Consider a racemate with one chiral centre such as **29**. We do not define the stereochemistry since there is only one centre. Note that the bond is not bold or hashed or even wiggly. If we reduce this in a stereoselective reaction so that *anti*-**27** results then we draw in the relative stereochemistry. Even though the product is a racemate, and we've added the '±' symbol to avoid any confusion, we must define the relative stereochemistry. Of course, we could equally have drawn the other enantiomer **27a**.



Achiral diastereomers

You do not need chirality to make definition of the stereochemistry essential. If there are two possible diastereomers stereochemistry needs to be defined. This is the case where the achiral ketone **30** is reduced to the achiral alcohol **31**. Even though both starting material and product are achiral – there is stereochemistry to be addressed, say *anti*-**31** is formed and not *syn*-**31**.

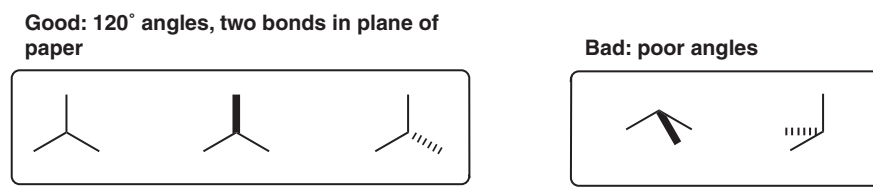


We've gone on about how important it is to always draw in the stereochemistry but we will end this section with one last point—beware of adding *too much* stereochemical information. Later in this chapter is a subsection on *Unhelpful Drawings* under **Popular Misconceptions**. Triol **32** is an example of a compound drawn with too much stereochemical information.

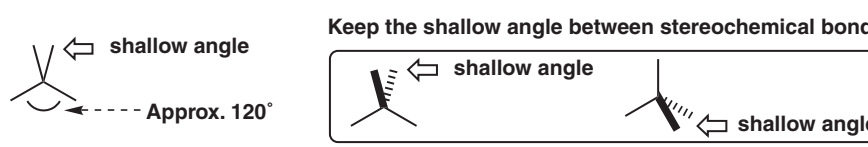
The Fundamentals of Stereochemical Drawings

Drawing tetrahedra

We've all got into trouble from time to time when drawing stereochemistry. Most often it happens when we are standing in front of a group of people. A few simple, and probably entirely obvious, guidelines might help. As far as possible, try to keep two bonds in the plane of the paper. You cannot get more than two tetrahedral bonds in the plane at a time but it is certainly possible to draw structures with fewer and such drawings rapidly become very messy. If you need to draw only three bonds then keep them at 120° to one another.

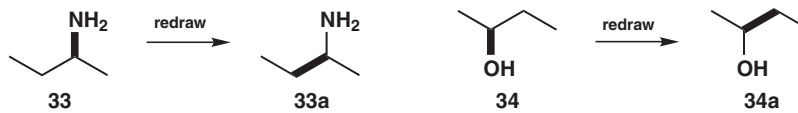


If you need to draw all four bonds then draw the third and fourth bond with a shallow angle between them. If you need to indicate stereochemistry, keep the shallow angle between the thick and hashed bonds. The other two are in the plane of the paper.

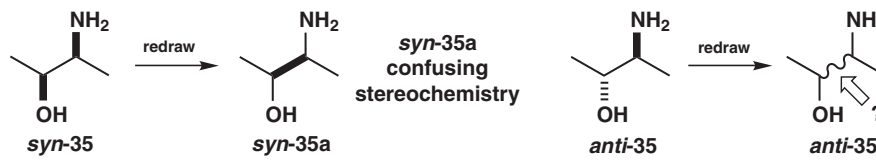


Drawings to avoid

There are many. One of the most confusing is to use a stereochemical bond (ie a hashed or a bold bond) between two stereocentres. For example, amine **33** and alcohol **34** can be drawn without confusion in several ways two of which are shown below.



The potential confusion arises when we have two stereogenic centres next to one another. The first depiction of aminoalcohol **35** makes perfect sense but the redrawn form is starting to get confusing. Which centre does the bold bond refer to?



In fact, we can work out the stereochemistry in the second drawing of **35**. If we look at each centre in isolation and consider the bold bond to both then it works. But this is rare and works here because we happen to have *syn*-**35**. How we would redraw *anti*-**35** in a similar way? Would we use a bold or a hashed bond to do it? There is no good answer. The best thing to do is follow these two guidelines—

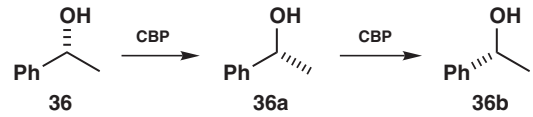
i) Keep the main chain of the molecule in the plane of the paper. This means that stereochemical bonds will not appear in the main chain of the molecule.
ii) Do not use stereochemical bonds between two stereocentres. This will ensure the same.

Mental manipulation of tetrahedra

Over the next few chapters it will often be necessary to redraw tetrahedra in different ways. You need to become proficient at this. We introduce two manipulations that will take you a long way. We will start by looking back at the trivial manipulation we just did with amine **33**. There is nothing new here but we've invented the terms **CBP** and **GSR** to help you. Imagine a single enantiomer of the amine **33**. We would not normally draw in the hydrogen but we've done it in the box just to remind you where it is. We know with tetrahedra that only two bonds can be in the plane of the paper at any one time. The first manipulation we encounter simply changes which bonds are in the plane. This is something you very often have to do in reaction schemes. We shall simply call this manipulation a "Change of Bonds in the Plane" or a **CBP**.

Notice that if we start with one of the bonds coming out of the paper then one of the bonds is *always* coming out of the paper (but remember, you are not allowed to swap groups). If you are

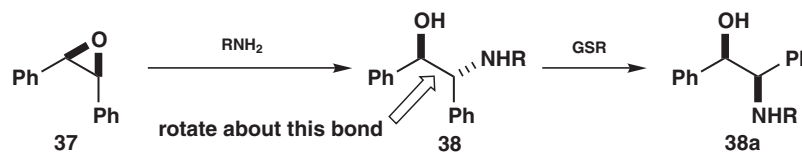
not convinced by this, make a tetrahedral model and leave the final hydrogen off the back. The result leans like a (static) spinning top on its side and if you hold two bonds in the plane then the other one pops up. The reverse is true too of course—if one of the groups is pointing away from us then one must always be pointing away. See what happens when we do a **CBP** as with alcohol **36** below.



No groups swap location when we perform a CBP. Now we meet the second type of manipulation we shall call a "Group Swap by Rotation" or a **GSR**. If we *do* swap the location of two groups then we must do so by rotating about one of the bonds **33c** and, as a consequence, we move from one thick bond to one hashed bond **33d** (or from one hashed bond to one thick bond).

You shouldn't use these devices without understanding how they work. If necessary use models to satisfy yourself that you understand how it works. Amaze yourself at how easy it is. If up until now you have been a stereochemical denialist and work among other denialists then learning these basic skills will earn you instant awe and respect at the flipchart!

Imagine the ring opening of *cis*-stilbene oxide **37** by an amine in an S_N2 reaction. The product is the amino alcohol **38**. Redrawing this **38a** so that we have the longest chain in a zig-zag is easy by application of a GSR to the right hand portion of the molecule. Note that we have not drawn any structure with a hashed or thick line between two chiral centres. In this sequence the question of absolute stereochemistry does not arise as *cis*-stilbene oxide **37** has a plane of symmetry and is therefore achiral.



Stereochemical Descriptors

This is a short section to describe what the various stereochemical descriptors mean. There are several in common usage and we assume you know what *R* and *S* mean. The more antiquated terms include *d* and *l* and D and L. Antiquated they may be but their use is still common and you need to, or at least ought to, know what they mean.

d, l

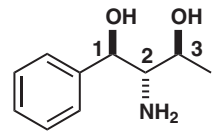
These were once used to indicate the sign of optical rotation. So, *d* for dextrorotatory and *l* for levorotatory. These have been replaced by (+) and (−) respectively.

d, l

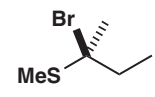
These are used mostly for carbohydrates and amino acids. The terms are obsolete and come from a time when the configurations of lots of chiral compounds relative to each other were known but the absolute configuration was not. D-(+)-Glyceraldehyde is taken as the standard. Enantiomerically pure compounds that could be related to D-(+)-glyceraldehyde by a series of reactions or degradations were labeled D [or L if they related to L-(+)-glyceraldehyde]. Without going into details, an amino acid is L if the amino group is on the left in a Fischer projection which has the carboxylate at the top. They are smaller than normal capitals.

R, S**

These are a sensible way to describe relative stereochemistry of racemic compounds. Suppose we have a compound **39** with three asymmetric centres. We know that we have only one diastereomer. The enantiomer drawn could be called (1*R*, 2*S*, 3*S*)-1,3-dihydroxy-2-aminobutylbenzene. But the enantiomer, (1*S*, 2*R*, 3*R*)-1,3-dihydroxy-2-aminobutylbenzene will also be present. To indicate that both are there we could either call it (1*RS*, 2*SR*, 3*SR*)-1,3-dihydroxy-2-aminobutylbenzene or (1*R**, 2*S**, 3*S**)-1,3-dihydroxy-2-aminobutylbenzene.



39



(*S*)-40

r, s

These are a bit more complicated but important terms and are discussed in '*Pseudoasymmetric Centres*' below.

Re, Si

These two terms are in common usage and refer to which face of a flat functional group such as a carbonyl. The faces will either be enantiotopic or diastereotopic. They are very commonly used terms and easy to understand if you already understand *R* and *S*. If the decending priority of the groups define a clockwise motion then the face being viewed is the *Re* face. Similarly, an anticlockwise motion indicates that the *Si* face is being viewed. One thing to remember here is that whether a face is *Re* or *Si* has *nothing* to do with whether the resulting compound is *R* or *S*. If it were, then *Re* and *Si* would have to also depend upon the priority of the incoming group.

re, si

These are often, mistakenly, used for *Re* and *Si* but, in a way, they are to *Re* and *Si* as *r* and *s* are to *R* and *S*. In other words they concern the formation of pseudoasymmetric centres from sp^2 centres. And we shall just leave it at that as they are not encountered very frequently. If you want to know more, have a look in Eliel's book on Stereochemistry.

(+), (−)

These simply refer to the direction of rotation of polarised light. Unlike *R* and *S* which are determined by configuration, their determination is entirely empirical. In other words, although we know that hypothetical compound **40** has the *S* configuation, we have no idea whether it is (+) or (−) and will not know until we put it into a polarimeter.

lk, ul

These might be called 'derivatives' since they are further removed from the stereochemical information than *R* or *S*. As such they are less useful since they need more 'decoding' to get back to the actual structure. They are used for compounds with adjacent chiral centres. They are easy enough to understand – a compound with two *R* chiral centres (or one with two *S* chiral centres) is a *lk* (*lk* for 'like') compound whereas a compound with one *R* and one *S* centre would be *ul* (*ul* for 'unlike'). Although this has the advantage of being unambigous, it does not convey a pictorial

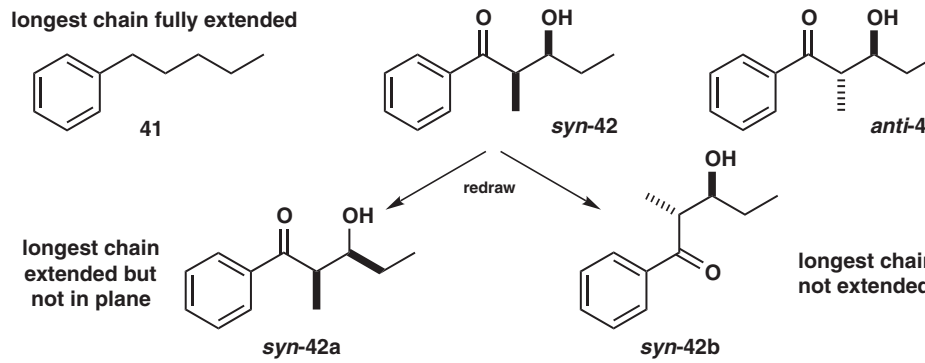
image at all. Since organic chemists think with structures, *ul* and *lk* is considered by many not to be helpful. For a more transparent device, see *syn* and *anti* below.

l, u

These are related to *lk* and *ul* but, instead of describing the relationship between two chiral centres, they describe the relationship between a prochiral centre and the resulting chiral centre. A situation where a *Re* face gives after reaction, an *R* centre is *l* (and *Si* face giving *S* centre) but *Re* face giving *S* centre is *u* (and *Si* giving *R*).[3] They are not used very commonly.

syn, *anti*

We use these routinely in this book. Once a molecule has been drawn in the standard way with its most extended chain **41** then if the two groups concerned are on the same side of the molecule it is *syn* and if they are on the opposite side then they are *anti*. This is illustrated with the aldol products *syn*- and *anti*-**42**.

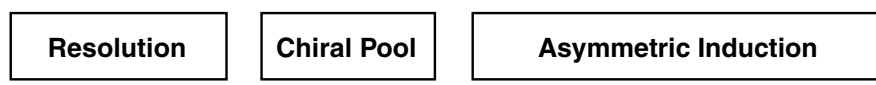


The advantage (or disadvantage depending on your point of view!) with *syn* and *anti* is that they always need a picture to go with them. Compound **41** shows the skeleton of **42** with the longest chain in its most extended form (zig-zag). Aldol *syn*-**42a** shows *syn*-**42** redrawn but with the zig-zag chain not being kept in the plane and *syn*-**42b** with the longest chain not extended. Neither of these is as good as *syn*-**42** but it might well be necessary to draw some compounds like this (if there is a macrocyclic ring for example we might have no choice). Something drawn in the way of **42b** would then look like *anti* rather than *syn*. There are no rules according to atoms priorites etc – the picture is king. It is also fast to go from name to picture and no 'decoding' is needed.

If you take one thing away from this section it should be that **any name or stereochemical description should be tied firmly to a clear stereochemical diagram** drawn on the lines we have suggested. Everybody will then know what you are talking about.

The Next Ten Chapters

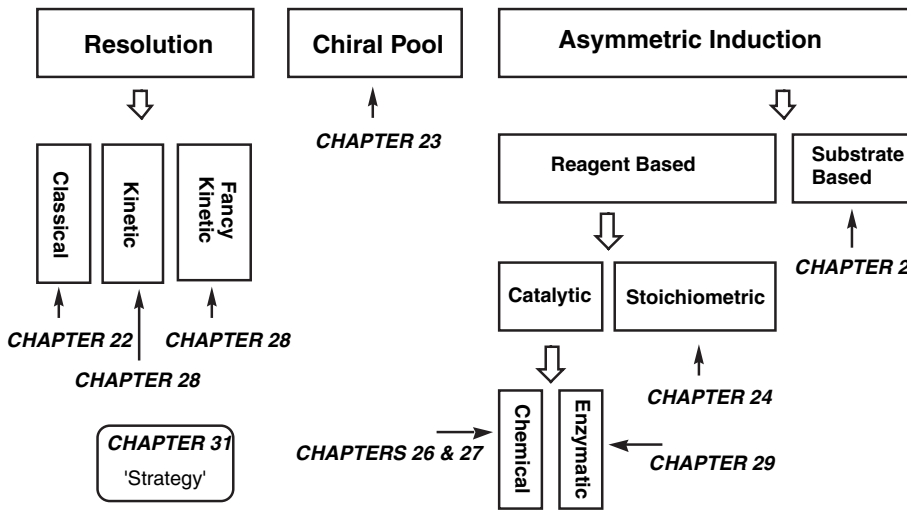
The next ten chapters are all to do with stereochemistry. The next chapter and Chapter 30 concern *relative* stereochemistry and its control. All the other chapters are concerned with asymmetric synthesis and the different strategies that can be employed. The different strategies can be broadly divided into three groups. These are resolution, chiral pool and asymmetric induction.



These main groups can be subdivided as shown below. This diagram shows not only the structure of the field asymmetric synthesis but how they are arranged in this book. Resolution, for instance divides into 'Classical', 'Kinetic' and what we call 'Fancy Kinetic' which means dynamic kinetic

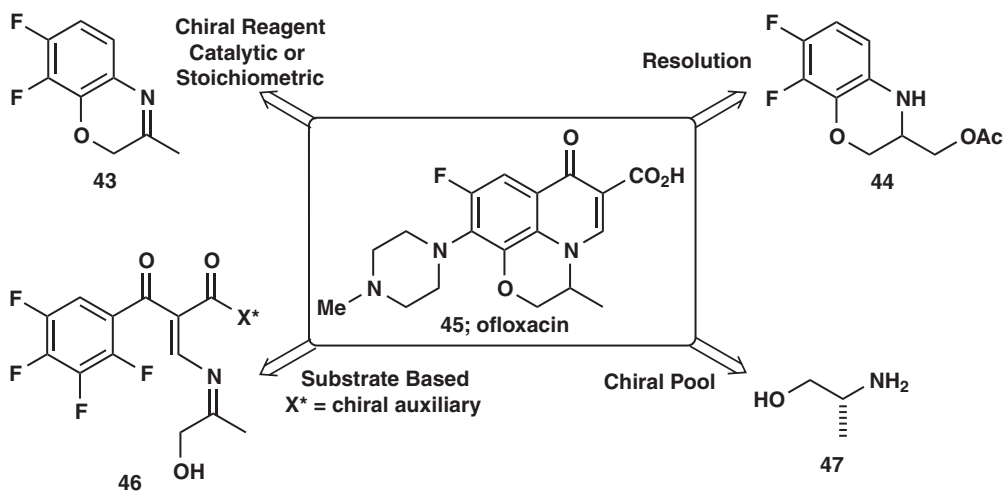
resolutions and all the complicated stuff. All the resolution subdivisions involve the separation of enantiomers. Classical resolution includes methods like the formation of diastereomeric salts whereas in a kinetic resolution enantiomers may be separated because one reacts faster than the other.

Some of the subgroups can be divided further so reagent-based asymmetric induction divides into catalytic and stoichiometric methods and even these may subdivide. Some of the subdivisions are so important that they have entire chapters dedicated to them and others even have several chapters devoted to them. For instance, we devote two chapters to catalytic asymmetric induction (or three if you count enzymes) – one for C–O and C–N bond forming reactions and one for C–H and C–C bond forming reactions. Although it looks as if there are clear divisions between the topics it is, of course, not that simple and one chapter will refer to another. Finally, Section D rounds up with a chapter on Strategy of Asymmetric Synthesis. The other chapters are self explanatory.



Division of Topic and Chapters in Section D.

Many enantiomerically pure compounds can be made by a variety of strategies. Several conceivable strategies for the synthesis of the quinolone antibiotic ofloxacin **45** are shown below. The molecule contains only one chiral centre and this may be introduced as a fragment from the chiral pool **47** or by the resolution of a key intermediate **44** or indeed the final product.[4] A synthesis developed[5] for the preparation of racemic ofloxacin which incorporates racemic aminoalcohol (±)-**47**, could in principle



be turned into an asymmetric synthesis.[6] Alternatively an achiral intermediate **43** could be asymmetrically reduced or a chiral auxiliary could be attached **46** to direct an asymmetric reduction.[7] The application of different strategies means that several compounds show up in more than one chapter.

Stereochemical Analysis

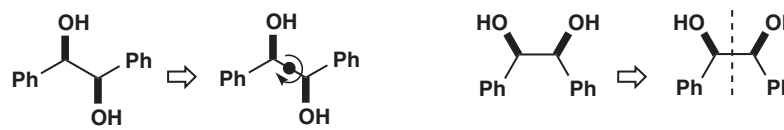
Stereochemical analysis is a formal descripton of the stereochemical aspects of molecules and their reaction. In many ways it is simply a formalisation of what chemists do anyway and is not dissimilar to retrosynthetic analysis. But clarity is vital and clarity can be achieved only by using the stereochemical words we have just met.

Stereochemical analysis uses stereochemical words to describe the properties of molecules and of reactions. It uses words of symmetry and it avoids ambiguous words. The word 'same' means different things to different people and depends upon the context. One chemist might describe two enantiomers as being the 'same' because they have the same structure whereas another chemist concerned with asymmetric synthesis might well describe them as 'different'. 'Different' is not much better but by using the word 'enantiomer' we know where we are. We have divided the analysis into nine steps but, as we shall see, you will often feel you don't need all of them.

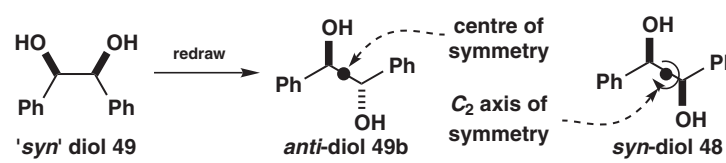
Stereochemical words	*Properties of molecules*		*Properties of reactions*
	• Diastereotopic	Diastereomer	• Stereoselective
	• Enantiotopic	Enantiomer	• Enantioselective
	• Homotopic	Homomer	• Stereospecific
	• Chiral	Achiral	
	• Racemic		

Step No. 1

Look for symmetry in the starting material. Identify axes, planes or (less commonly) centres of symmetry. For example, diol **48** has a axis of symmetry whereas diol **49** has a plane. Diol **48** is C_2 symmetric and chiral; **49** is achiral.



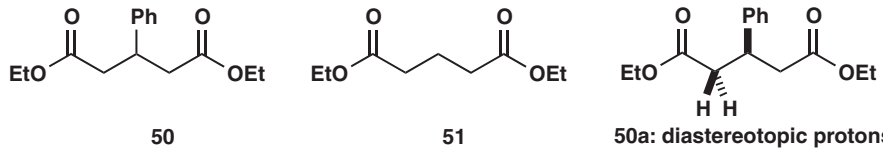
A word of warning straight away – be careful about how the molecule has been drawn (especially if you have previously suffered from stereochemistry denial!). Redrawing the apparent *syn* diol **49** reveals the *anti* relationship between the hydroxyl groups **49b**. The plane of symmetry is no longer evident. In fact, the molecule has a *centre* of symmetry in this conformation. Diol **49** is achiral however we draw it. Normally, our priority should be for planes and axes before we start thinking about centres.



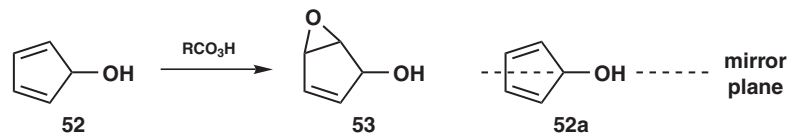
Step No. 2

Identify relationships within the molecule. For example, once you have identified a plane of symmetry in a molecule, you might decide that two ester groups are enantiotopic. 'Enantiotopic' is

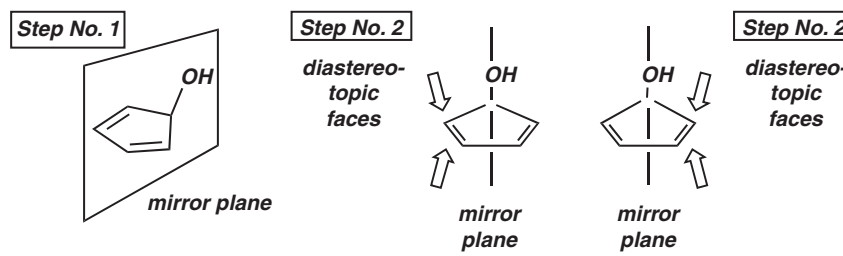
the relationship. Make sure, by looking back at *Enantiomers and Enantiotopic* if necessary, why the ester groups in **50** are enantiotopic while those in **51** are homotopic. Imagine being at a party where no relationships were revealed – you would not know who is whose brother, sister, husband or wife. It would be unfortunate to be without information of that kind (especially) if you were a bit of a gossip. Relationships count and, just because a girl has a sister, it doesn't stop her from having a brother too. So don't stop your analysis once you have identified one relationship—be exhaustive. We have identified that the ester groups in **50** are enantiotopic, but we might also notice that the two protons at the α-position are diastereotopic **50a**. One is on the same side as the phenyl group and one is not.



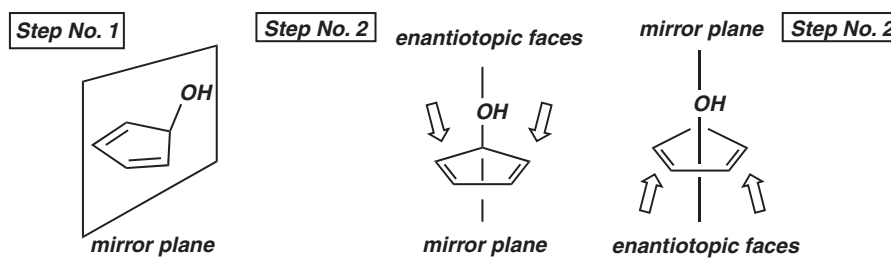
We shall now examine the epoxidation of the doubly allylic alcohol **52** to show how steps 1 and 2 give insight into the possible stereochemical outcome of this reaction. We shall assume that mono epoxidation is possible. The five-membered ring is flat and the two bonds to the epoxide oxygen must of course be on the same side of the ring. Step 1, *looking for symmetry in the starting material*, reveals one symmetry element - a mirror plane through the OH group at right angles to the ring **52a**. The molecule is achiral.



Step 2, *identifying relationships within the starting material*, is more revealing. The two alkenes are reflected in the mirror plane so they are enantiotopic. But the top and bottom faces of the ring are diastereotopic - one is on the side of the OH group and one is not. So it is possible for any epoxidising agent to choose either the top or bottom faces by steric hindrance or by bonding to the OH group.

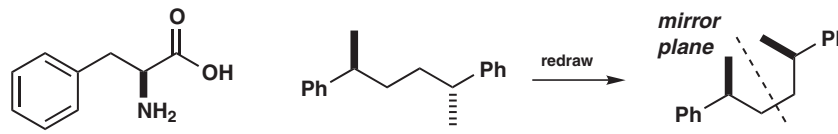


But the choice between the two enantiotopic top faces or the two enantiotopic bottom faces would produce a single enantiomer, and that would require the introduction of asymmetry, probably from the reagent.



Step No. 3

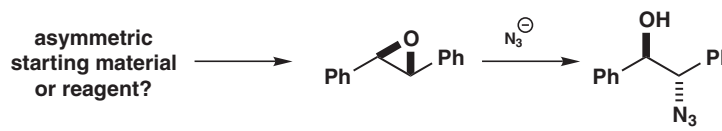
Decide whether or not the molecule is chiral (not to be confused with step number 4). The amino acid **54** is clearly chiral (whether or not it is racemic of course). A cursory glance at compound **55** may fail to expose that it is *not* chiral. Compound **55** in fact contains a centre of symmetry (rather more difficult to spot) but redrawing **55** as **55a** exposes a mirror plane within the molecule. Either way, it cannot be chiral.



54 **55** **55a**

Step No. 4

If the molecule *is* chiral, decide whether or not it is enantiomerically pure. You will often have to know more about the reaction than is evident in the scheme. For instance, *trans*-stilbene oxide **56** is always chiral but may or not be racemic. It is not evident in the scheme below and it could easily be either. It all depends how it was made. If only achiral starting materials and reagents were used, the epoxide **56** must be racemic. If asymmetry was present somewhere, it may be a single enantiomer. But had we put optically pure stilbene oxide **56** into the reaction then we could expect to get an optically pure product **57** at the end. Amino acid **54** is likely to be enantiomerically pure anyway (as are other compounds from the chiral pool) and if we were in any doubt it has been drawn as a single enantiomer. In other situations we need to know the context to be sure.



56 **57**

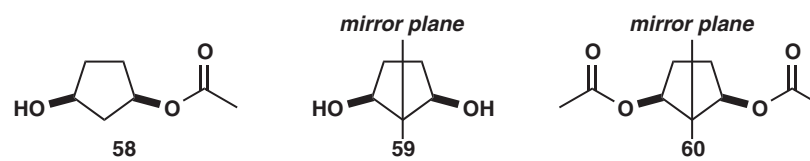
These first four steps are the most important. They are not the whole story and it may be necessary to go through the next five steps as well. Experience will show you if they are needed and enough experience may allow you dispense with this formal analysis.

Step No. 5

Identify the source of chirality and indicate the chiral centres or axes. You may feel this is unnecessary but it doesn't hurt to draw a ring around a chiral centre or draw in the symmetry plane with a coloured pen.

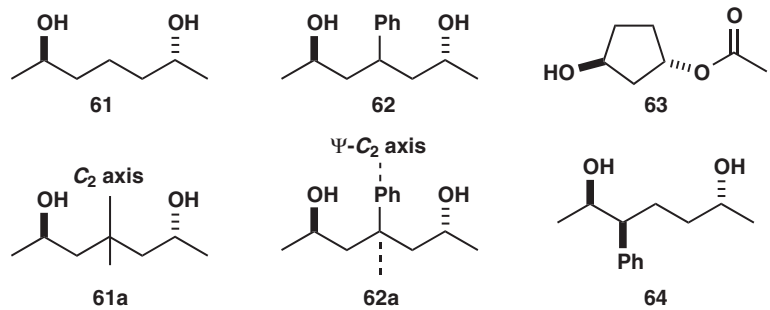
Step No. 6

Look for more subtle symmetry relationships. These might be where molecules are only just short of symmetry or where a small change in the molecule could increase its symmetry. For example, we could raise the level of symmetry of the ester **58** by either hydrolysing it to give the diol **59** or by esterification of the remaining hydroxyl group to give the diester **60**. It can often be instructive to notice this sort of thing if only as a warning.



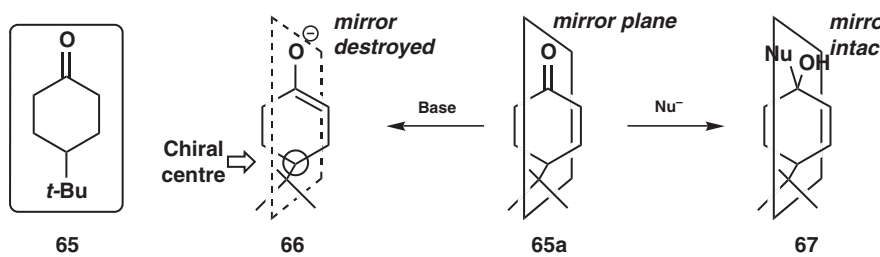
58 **59** **60**

A completely different issue, but another where we are just short of some symmetry, is that of the pseudo-C_2 axis. The diol **62** has a pseudo-C_2 axis (Ψ-C_2) – removal of the phenyl group would give us the genuine article **61** and **61a**. Note that this term is applied to compounds where the disruptive element is on the axis itself (or rather where this axis *could* be) because it is only here that the substituent will be non-stereogenic. Hence we describe **62** as pseudo-C_2 but not **63** or **64**. The pseudo-C_2 phenomenon is very real but there are those who do not like the name. There is a movement to rename it pro-C_2. We hope this movement gathers momentum. It is a better description (akin to prochiral) and is without the negative connotation of 'pseudo'.



Step No. 7

Decide how the reaction influences symmetry. Is symmetry created, destroyed or even left unchanged? If a molecule contains a mirror plane, for instance, and the new bonds are made within the mirror plane we can expect the symmetry element to be retained. However, attack at one side or other of the mirror plane will naturally destroy it. Ketone **65** has mirror plane that slices through the ring **65a**. The mirror plane contains the carbonyl and the central carbon of the *tert*-butyl group. If we attack the carbonyl with a nucleophile, the nucleophile will have a line of attack that is within the mirror plane and the resulting alcohol **67** will retain the mirror plane. This is not the case if we make an enolate **66**. The proton must be removed from one side or the other and this will destroy the mirror plane. Notice that when this happens a chiral centre is formed where the *tert*-butyl group connects to the ring.



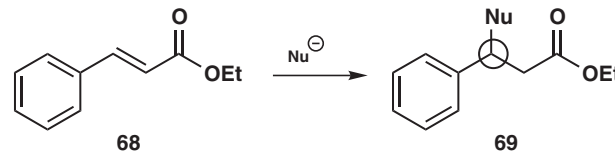
Step No. 8

Is there an asymmetric aspect to the reaction? Are we, for instance, attacking one of two enantiotopic groups selectively?

Step No. 9

How does the product differ to the starting material? If necessary, apply step numbers 1 to 6 to the product too. It might be worth explicitly stating the 'obvious' that, in the very simple conjugate

addition of a nucleophile to ethyl cinnamate **68**, we started with an achiral planar material but the product **69** is chiral *and racemic*.



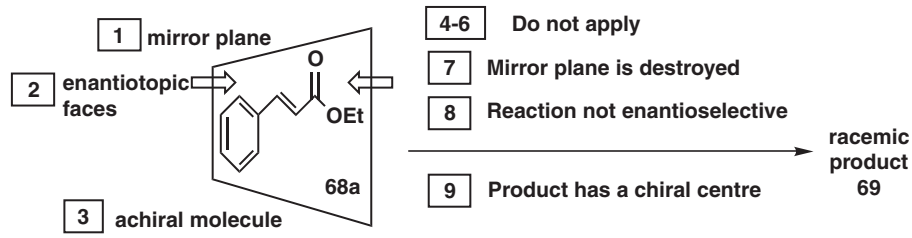
68 69

Summary

So then, to summarise, here are the nine steps of stereochemical analysis —

1. Look for symmetry in the starting material
2. Identify relationships within the molecule
3. Decide whether or not the molecule is chiral
4. Decide whether or not it is enantiomerically pure
5. Identify the source of chirality and indicate the chiral centres or axes
6. Look for more subtle symmetry relationships
7. Decide how the reaction influences symmetry
8. Identify any asymmetric aspect to the reaction
9. Consider how the product differs to the starting material. Reapply steps 1 to 6.

Applying these nine steps to the simple nucleophilic conjugate addition to a cinnamate ester **68**, we can summarise our findings.



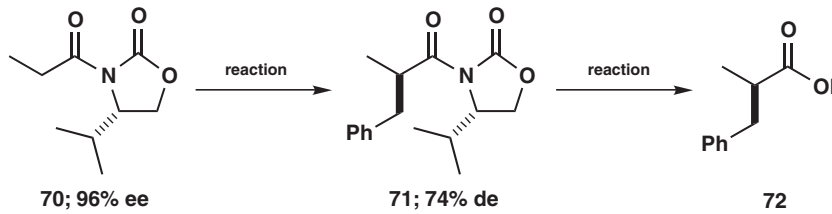
Some Principles

In this section we look at the influence of some numbers on the outcomes of reactions.

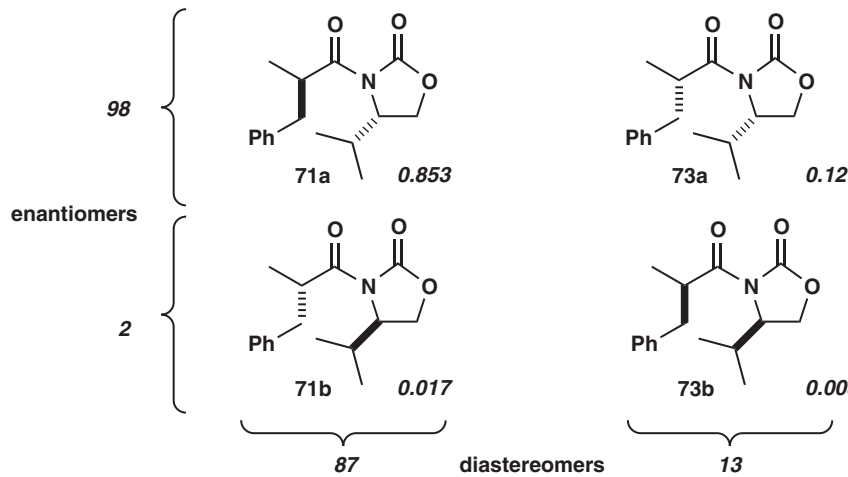
Chiral auxiliaries

In Chapter 27 (Substrate Based Strategy) we shall meet the use of chiral auxiliaries. If you ask someone what properties a good chiral auxiliary should have you will get all the usual suspects – cheap, both enantiomers available, easy to put on, easy to take off, effective at induction etc. However, there is one property that gets very little attention. After the reaction the diastereomers should be *separable*. Suppose we have a chiral auxiliary **70** with an enantiomeric excess of 96% which reacts

to produce the product **71** in 74% diastereomeric excess. What is the ee of the product **71**? If the product were hydrolysed *without* separating the two diastereomers of **71** what would be the enantiomeric excess of the liberated acid **72**? If the two diastereomers *were* separated before hydrolysis what would be the ee of the liberated acid **72**? Try to work the answers out for yourself before you look at the answers.



The answer to the first question is easy. The ee of **71** is 96%. The ee of the 'wrong' diasteromer (which we'll call **73**) is also 96%. The answer to the second question is a bit surprising. It is 71% ee. The best way to explain this is to draw out all four possibilities. A 96% ee means we will have 98% of one enantiomer **71a** and 2% of the other **71b**. And a 74% de means that we will have 87% of one diastereomer **71** and 13% of the other **73**. The ratio of **71a** to **71b** will be 98 to 2 as will the ratio of **73a** to **73b** (keep your attention on the stereochemistry in the ring here – this will not change regardless of the reactions going on nearby).



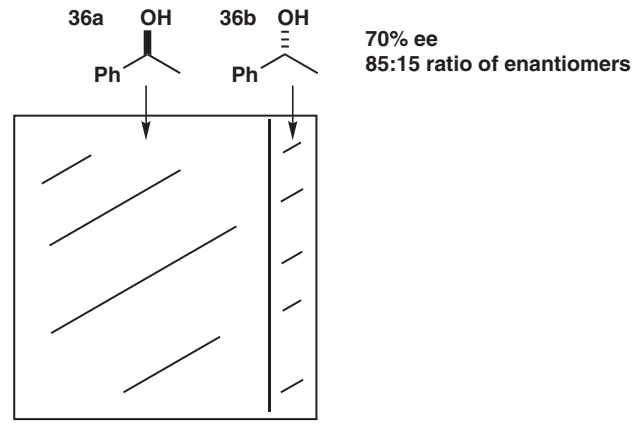
The ratio of **71a** to **73a** is 87 to 13 but the same is true with the other enantiomer in the reaction so the ratio of **71b** to **73b** is also 87 to 13. The relative amount of each of the four structures can then be determined. For example, the proportion of **71a** is $0.98 \times 0.87 = 0.853$. If the compounds are not separated before hydrolysis then everything will be included. One enantiomer of the acid **72** will result from **71a** and **73b** ($0.853 + 0.003 = 0.856$) and the other from **73a** and **71b** ($0.127 + 0.017 = 0.144$). The ee is $0.856 - 0.144/0.856 + 0.144 =$ **71.2%**. This might surprise you as it is lower than either the de or the ee of the reaction!

It is a different story if the diastereomers are separated first. In this case both **73a** and **73b** will have been thrown away. The ee is therefore $0.853 - 0.017/0.853 + 0.017 = 96\%$. This is an important lesson. It shows how important separating the diastereomers is. As long as you can do

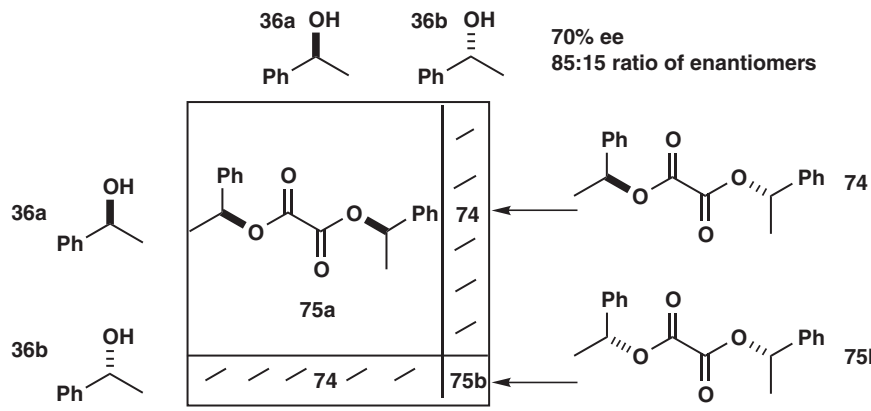
this, your de could be 0% (which would mean your auxiliary was a resolving agent) and you could still get an ee of 96% or whatever the ee of the auxiliary was. This brings us to the next point, your ee will only be as good as the ee of the auxiliary, so get 100% if you can.

The Horeau principle

We saw above how two numbers conspired to lower the quality of the product. In this next example the reverse happens. We want to improve the ee of **36**. Suppose we have alcohol **36a** and its enantiomer **36b** in an 85:15 ratio, an ee of 70%. We'll represent this by the area in the box.

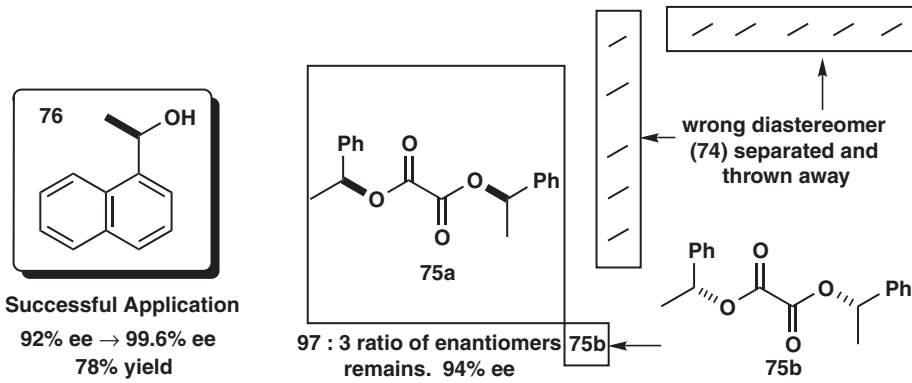


If the alcohol is reacted with oxalyl chloride then two molecules of alcohol react with each molecule of oxalyl chloride. Two diastereomers result. One has enantiomers **75a** and **75b** and the other is achiral **74**. Assuming the molecules react statistically (and there is no chiral recognition) then the proportion of **75a** should be $0.85 \times 0.85 = 72.25\%$. Here's where the method works – most of the unwanted enantiomer gets incorporated into the other diastereomer **74** ($2 \times 0.85 \times 0.15 = 25.5\%$). Only a small amount of the enantiomer of **75b** is produced ($0.15 \times 0.15 = 2.25\%$).



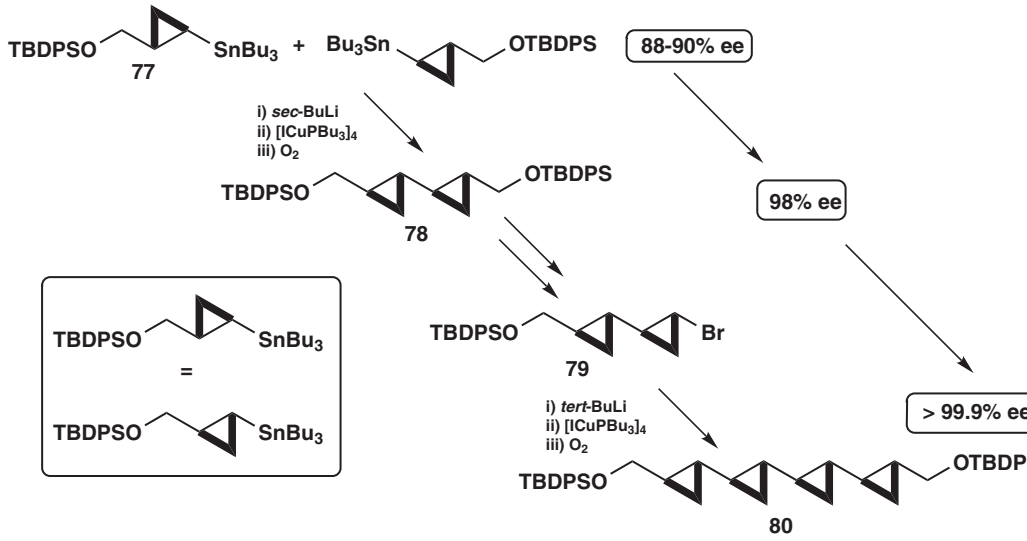
The diastereomer **74** is removed to leave **75a** and the small amount of **75b** in a ratio of 97:3. If these esters are cleaved then we have the alcohol **36** with an ee of 94% which is quite an

improvement. This is done at the expense of yield of course as some of the alcohol we wanted was thrown away in diastereomer **74**.



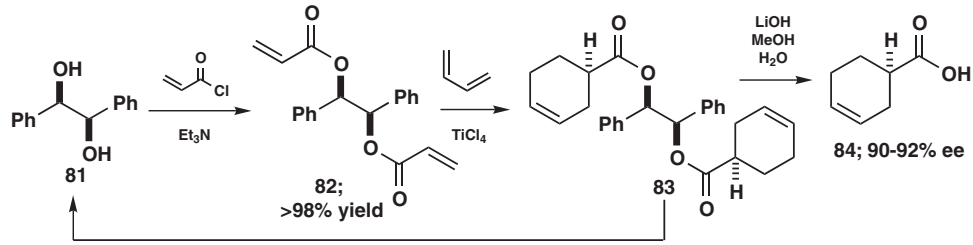
This method was successfully used[8] to improve the enantiomeric excess of alcohol **76** from 92% ee to 99.6% ee. The combination of substrates that are already of quite good enantiomeric excess to give a product of even better ee is not uncommon and is sometimes referred to as the Horeau Principle.[9]

On the way to the antibiotic FR-900848, an intermediate with four contiguous cyclopropane rings **80** was required.[10] Cyclopropane **77** was made in 88–90% ee. Dimerisation of **77** yields a product of 98% ee for the same reasons as outlined above – if the correct enantiomer of one compound combines with the wrong one of the other then a different diastereomer is produced and removed, thus removing the wrong enantiomers. Only on the rare occasions that two wrong enantiomers combine do they form the enantiomer of **78** and slip through the net to the next round. Dimerisation of **79** improves the ee again, this time to >99.9%.



The authors of the above work specifically mention the Horeau principle but its operation is often less explicit. Take for example the production of acid **84** which can be produced in 90–92% ee by the reaction of optically pure diester **83** of hydrobenzoin **81** in a Diels-Alder reaction.[11]

Since two asymmetric reactions are going on the ee of the product will be enhanced (so long as the diastereomer of **83** is separable and removed the auxiliary is forgiven if it only gets it wrong once – it has to get it wrong twice for the wrong enantiomer to find its way through). The acid is cleaved from the hydrobenzoin which is recycled. Acid **84** was needed in part of a synthesis of FK-506. In fact the authors say that the 90–92% ee material is formed from the reduction of the *crude* cycloadduct **83**. In which case the Horeau principle cannot be operating as we intimate above unless the authors somehow *inadvertently* purified their cycloadduct without realising during, for example, the filtration through silica.



You might like to work out what the selectivity is in each cycloaddition reaction. To give you a clue, look back at the graphical diagrams used for diester **84/85** and think about using square roots. We shall see this sort of double reaction to enhance selectivity again in Chapter 28. One reaction is a kinetic resolution and the reagent reacts twice. On the second pass it removes the small amount of the wrong compound that was formed the first time round.

Popular Misconceptions

Misuse of words

'Chiral'. For the purist, this is an especially irritating misuse. A worker who has been using racemic stilbene oxide is about to move onto using enantiomerically pure stilbene oxide. He describes the enantiomerically pure stilbene oxide as 'chiral stilbene oxide' or more probably, in the abreviated colloquial language of the lab as 'my chiral compound'. Racemic stilbene oxide is no less chiral than optically pure stilbene oxide and so 'chiral stilbene oxide' says no more than 'stilbene oxide'. 'Chiral' is sometimes used in this way even by experienced and distinguished chemists!

'Chiral Synthesis'. For the same reason as above, a reaction that features racemic materials is no less chiral than one with optically pure materials. It should not, therefore, be refered to as a 'chiral synthesis': 'asymmetric synthesis' is a better term.

'Racemic Synthesis'. We've heard many people object to this term but we really don't know why. If you can have an asymmetric synthesis, then why can't you have a racemic synthesis? The objection runs along these lines - 'it is the *compounds* that are racemic and not the *synthesis* and so it should not be refered to as a racemic synthesis'. We suppose so, but the same is true for asymmetric synthesis isn't it? Presumably we should not have a 'comfortable armchair' since it is the person who sits in the armchair who is comfortable and not the armchair itself but we would be allowed to have a 'warm house' since the house is indeed warm. Objections to 'racemic synthesis' are dogmatic in that they deny the transferred epithet (as in comfortable armchair) which is a common feature of English.

'Homochiral'. Is sometimes used to mean 'optically pure' and both the authors have used it this way. But this use to mean optically pure should probably be avoided since 'homochiral' has another meaning; if two molecules have the same absolute stereochemistry they can be said

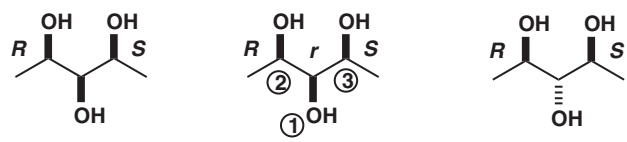
to be homochiral. Hence if we say 'those two aminoacids are homochiral' then we have two different meanings depending on how we are using 'homochiral'. 'Enantiomerically pure' is unambiguous.

Chiral centres and stereogenic centres

There has been a move away from describing something as a 'chiral centre'. The argument is that a centre, a point, cannot be chiral. Instead it is refered to as a stereogenic centre. If you replace your 'chiral centres' with 'stereogenic centres' you will be on safe ground but you should be aware that they are not necessarily the same thing. In the way that all elephants are mammals but not all mammals are elephants so all chiral centres are stereogenic centres but not all stereogenic centres are chiral ones. The dimethylcyclohexanes **85** and **86** illustrate a simple case. Neither compound is chiral as they both contain a mirror plane. There are no chiral centres. However, changing the configuration of the carbon atom where the methyl joins the ring in **85**, gives a different (achiral) diastereomer **86**. The centres are thus stereogenic (as they give rise to other stereoisomers) even though they are not chiral centres.

Pseudo-asymmetric centres

We can continue with the above theme but things start to get a bit more complicated. Consider the triol **87**. It is not chiral and might be described by many as a *meso* compound. We'll come back to this compound but for now look at the central carbon atom. This is not a chiral centre and not an asymmetric centre. You can see this if you try to decide whether it has an *R* or *S* configuration. You immediately run into trouble because two of the groups on either side are the same (enantiotopic). This means we cannot give one a greater priority than the other as we usually would.



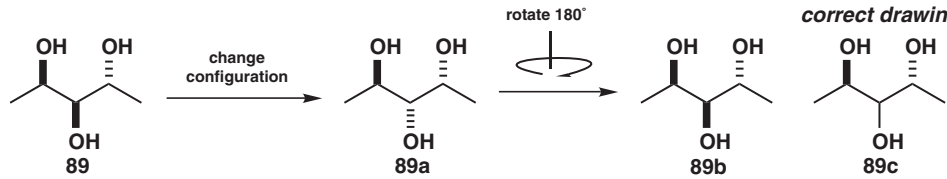
87 **87a; *(R, r, S)*** **88; *(R, s, S)***

It is, in fact, *r* (note lower case). In this situation the group with the *R* configuration is given greater priority than the one with *S*. Those priorites in **87a** would mean an *R* configuration if it were a real chiral centre but since it isn't we call it *r*. If we change its configuration (to *s*) we get a different *meso* diastereomer **88**. In other words we get another achiral compound. Whatever we do with that centre we get achiral diastereomers so it can scarcely be asymmetric—it is not an asymmetric centre. However, when we change the configuration we do get different diastereomers so it is certainly stereogenic (gives rise to stereochemistry). So we see, something can be a stereogenic centre without being a asymmetric, or chiral, centre. Such centres are sometimes referred to as pseudoasymmetric centres. In a detailed and highly cited paper, Mislow points out

that chirotopicity (something that is chirotopic is in a chiral environment) and stereogenicity are conceptually distinct. The centres above could be referred to as achirotopic (because the molecule is not chiral they are not in a chiral environment) and stereogenic centres.[12]

Unhelpful drawings

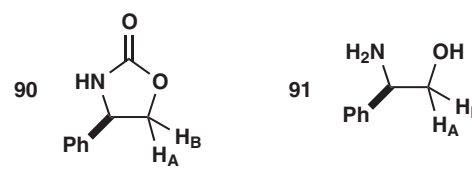
Let's look at a diastereomer **89** of the triol **87** that we have just met. Again we focus on the central carbon. Imagine trying to make the diastereomer of **89** by changing the configuration at the central atom (**89** changes to **89a**). We now rotate **89a** by 180° and find that **89b** is identical to **89**. Whatever we do with the central OH (whether we have it coming forwards or going backwards) makes no difference at all. In other words there is no stereochemical information at all. Triol **89** should be drawn **89c** with an ordinary bond to the central OH.



This lack of stereochemistry is typical of substituents that lie on a pseudo-C_2 axis and compound **60** was drawn correctly without stereochemistry to the central phenyl group. However, the central substuent does disrupt the C_2 axis that would otherwise be there. Consider the two hydroxyl groups on the left and right of the molecule. One of them will be on the same side of the molecule as the central hydroxyl and one will not. The hydroxyl groups on the left and right of the molecule are diastereotopic whereas they would be enantiotopic if the central hydroxyl were not there (because they would be related by the C_2 axis)

Bond rotation

The misconception is that if a bond rotates fast enough, protons interchanging position by that rotation will be the same. For example, we have already discussed diastereotopic protons in molecules like **90**. The diastereotopic nature of the protons H_A and H_B is quite obvious here because it is clear that one will be on the same side of the five-membered ring as the phenyl group and the other will not be.

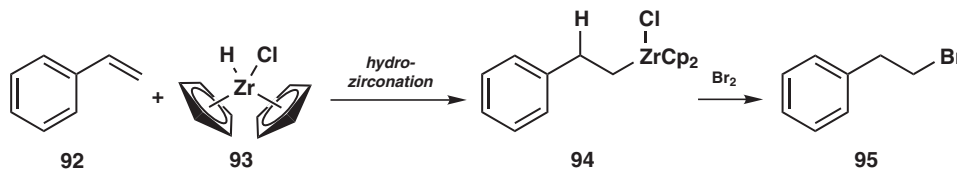


The protons in **91** are diastereotopic too. We can see this easily with the diastereotopicity test we have discussed earlier. Nevertheless, there is sometimes a misconception that, because we now have bond rotation, they are equivalent. After all, with **91** (unlike **90**) we can swing proton H_B into the position occupied by H_A and vice versa. But the rotation itself, changes the environment too – putting H_B where H_A was also puts the OH in a different place, so H_B does not experience

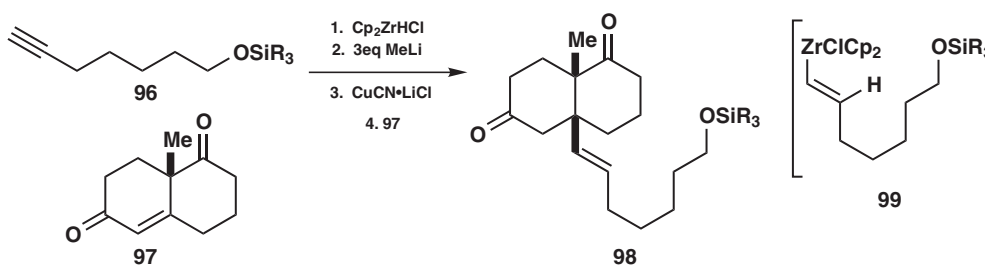
the environment that H_A did. Rotating the bond faster will not help as the environment will be changed at exactly the same rate! As a dog cannot catch its own tail so we cannot get away from the diastereotopicity.

Stereospecificity revisited

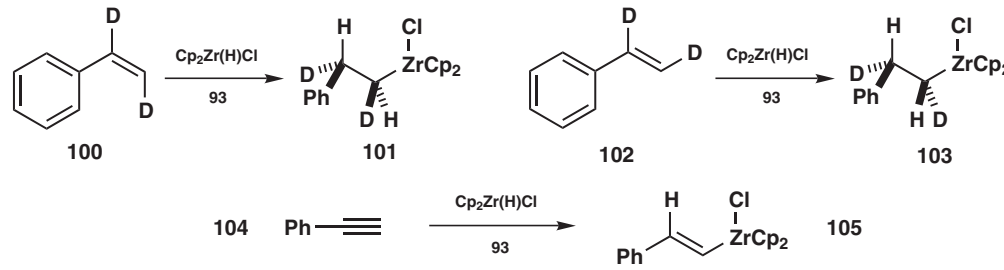
If you find yourself in a group of organic chemists and the conversation seems to be flagging a bit, try throwing in the word 'stereospecific' and before you know where you are you will find yourself in the middle of a lively debate about what the word means. We have already established in the earlier section that stereospecificity is not merely 100% stereoselectivity and we won't look at that again here, but there are other issues for chemists to argue about. The situation is nicely illustrated by the reactions of the Schwartz reagent [$Cp_2Zr(H)Cl$] **93**. This reacts across alkenes by hydrozirconation to give a species **94** with a carbon–zirconium bond. This bond can be cleaved by adding water (which adds a proton to the carbon as we would expect with an organometallic) or electrophiles such as halides. It can be a very useful reaction.



In one example alkyne **96** is activated by hydrozirconation. The zirconium is in the terminal position **99**. The two Cp rings are quite big and so it is usual for the zirconium to add preferentially to the less hindered end of the triple (or double) bond. This is the regioselective aspect of the reaction and not what concerns us here. Transmetallation to the organolithium and again with Cu(I) gives the cuprate and this cuprate does a conjugate addition to the double bond of an enone that looks suspiciously Robinson annelation-derived.[13] Before we move on, notice that the double bond has a *trans* geometry – we shall come back to this.



Now then, the hydrogen and zirconium are added from the same side of the molecule at the same time. If we have a molecule of styrene that is deuterated we can detect this. If we start with the *trans*-dideuterated styrene **100** we get one diastereomer **101**. But if we start with the *cis*-dideuterated styrene **102** we get the other diastereomer of product **103**. It is a similar story with a substrate with a triple bond. With phenylacetylene **104**, addition of hydrogen and zirconium occur from the same side. Thus after reaction of the organozirconium species we have a *trans* double bond as we observed with **98** and **99**.



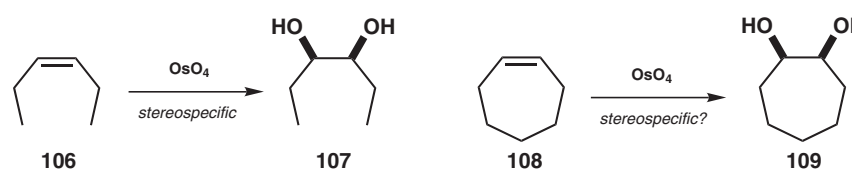
Some chemists would argue that the reactions of the double bonds are stereospecific, but the reaction of the triple bond is not. Their argument is that, for a reaction to be stereospecfic, a specfic diastereomer of starting material must lead to a specfic diastereomer of product and this implies that there is an alternative diastereomer of starting material which would give the alternative diastereomer of product. BUT, since the actylene has no diastereomer, this cannot be stereospecific.

Other chemists would argue that this is a load of rubbish and that both are examples of stereospecificity. We should be concerned with the *mechanistic* element of the reaction. We want to know how the *zirconium complex reacts*, and this is what the stereospecificity refers to; delivery of hydrogen and zirconium to the same side of a multiple bond. The first group of chemists would probably come back with the argument that in order to probe the mechanism in the first place you need two diastereomers of starting material and how can we be sure that the reaction with the triple bond goes by the same mechanism – and so on. Perhaps we should mention that Schwartz himself describes the addition across a triple bond as stereospecific.[14]

The definition used by Eliel[15] says that something is stereospecific when 'starting materials differing only in their configuration are converted to stereoisomerically distinct products'. He goes on to talk about changing the catalyst instead of the substrate and to discourage the meaning 'highly stereoselective.' This definition embraces the meaning of stereospecificity in the double bond scenario but not its extension to the triple bond. This denies the mechanistic spirit of the word stereospecific. To return to an ordinary S_N2 reaction of, say, an alkyl halide with an unspecified nucleophile. We know S_N2 reactions always go with inversion and that an S_N2 reaction is stereospecific. The reaction goes with inversion because the antibonding orbital is populated as the reaction proceeds and there is no other option. Is this stereospecific because it is defined by the population of the antibonding orbital AND because there is another enantiomer of alkyl halide for us to consider or is it just because the antibonding orbital defines the process exactly?

This is turning into a bit of a soap box but we would suggest that it is more instructive to use the latter definition. Thus the different stereospecific outcomes from different starting material isomers is a *consequence* of stereospecificity of the reaction and not the other way round.

Perhaps the madness of needing to have another diastereomer of a starting material in order for a reaction to be stereospecific is more obvious in the next example. Heptene **106** may be dihydroxylated stereospecifically to give **107**. But the reaction of cycloheptene **108** would not be a stereospecific reaction because there is no such thing as a *trans* cycloheptene. Clearly this is crazy – both reactions are stereospecific. But see what your friends think.



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General references are given on page 893

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15. *Eliel*, page 1008.

21 Controlling Relative Stereochemistry

Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

Open Chain Chemistry - with Chelation Control
Grignards
Zinc borohydride
Open Chain Chemistry - in its Most Genuine Form
Felkin control over reactions of nucleophiles with carbonyl compounds
Role of electronegative substituents
The Houk conformation for reactions of alkenes with electrophiles
Allyl silanes

Note Before We Start: We assume you already know about conformational control in making new chiral centres and about folded molecules preferring to react on the convex or *exo* face. You are referred to *Clayden* chapters 33 and 34 for a basic treatment of this material.

Introduction

Most of the compounds we shall be looking at in this chapter will be in racemic form. We are concerned only with the control of relative stereochemistry and not with the control of absolute stereochemistry. However, many of the reactions have been developed into asymmetric versions. It is certainly true that many of the reactions have been employed within asymmetric synthesis – that is, where the *asymmetric* part has come from elsewhere and this idea will be revisited in Chapter 30. If we are to concern ourselves simply with relative stereochemistry then, for there to be any stereochemical relationship, we must have at least *two* chiral centres. If there is no chirality in the starting materials this means that two chiral centres must form in one reaction and if there is only one new chiral centre that forms in the reaction then there must have been a chiral centre already in one of the starting materials.

Some sort of 'cyclic aspect' is usually a feature of good stereocontrol. This aspect might be in the form of a cyclic transition state or perhaps in the generation of a genuinely cyclic compound but in any case a cyclic aspect is associated with fewer degrees of freedom – or less floppiness – in whatever system we are considering which usually means better control. Without trying to be exact, the cyclic aspect of reactions broadly decreases down the series –

- Formation of cyclic compounds *via* cyclic transition states
- Reactions of cyclic compounds
- Cyclic intermediates
- Formation of acyclic compounds *via* cyclic transition states
- Open chain stereochemistry

Each of the above topics can be looked at either with no pre-existing chirality, or with a chiral element already in one of the molecules.

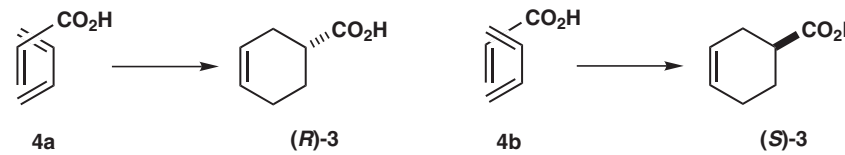
Part I – No Chirality in Place at the Start

Formation of Cyclic Compounds via Cyclic Transition States

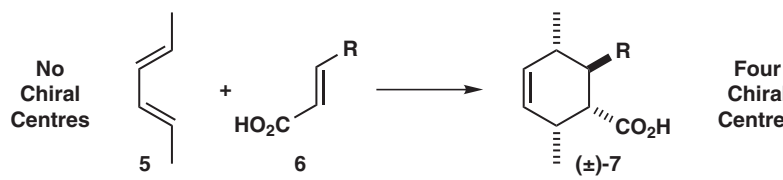
Cycloadditions

Cycloadditions are supremely powerful when it comes to the controlled formation of many stereogenic centres. The stereochemistry of the products can be the result of many different stereochemical aspects. Though strictly this example does not have a place in this chapter (because relative stereochemistry is not generated), it is instructive.

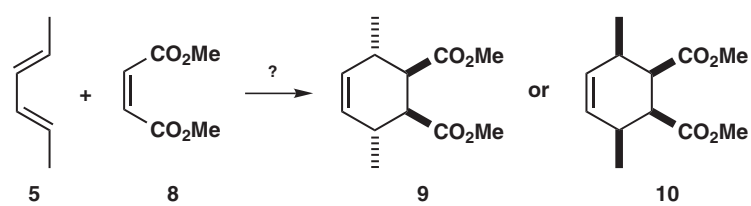
This is a straightforward Diels-Alder reaction. The product is the racemic acid **3**. The faces of the dienophile **2** are enantiotopic – if the diene attacks from one face **4a** we get one enantiomer (*R*)-**3** and the other (*S*)-**3** if it attacks from the other **4b**. However, it doesn't matter at all which face of the diene **1** reacts. Its faces are homotopic.



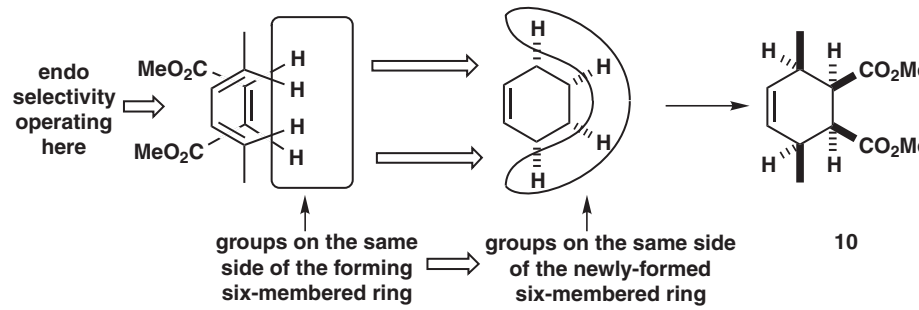
The Diels-Alder reaction is, of course, an excellent way of introducing several new chiral centres at once. The *E,E*-diene **5** and unsaturated acid **6** can be expected to give the adduct **7**. Note that we move from no chiral centres in the starting material to four chiral centres. The product is racemic (±)-**7** since we have made no effort to make a single enantiomer.



The selectivity in the above reaction comes from two sources. Firstly there is the stereospecific aspect. This demands that stereochemistry in the starting materials shows up in the products. That is, the *trans* relationship between R and CO_2H in the unsaturated acid **6** shows up in the product **7** as a *trans* relationship. The same stereospecific dictat ensures that the two methyl groups of the diene **5** end up on the same side in the product. This is less easy to see with a diene, but we would expect the methyl groups to be *trans* to one another in the product only if we instead started with the *E,Z*-diene. Secondly, there is the stereo*selective* aspect to the reaction - often referred to in this context as *endo* selectivity. We will not go into *why* this happens here[1] but with normal *endo* selectivity, the electron-withdrawing group of the dienophile will prefer to be close to the electron-rich diene. When **5** reacts with **8**, we know that the two methyl groups must be on the same side of the molecule and that the two CO_2Me groups must be on the same side of the molecule. But two structures **9** and **10** answer this specification. Which is formed?

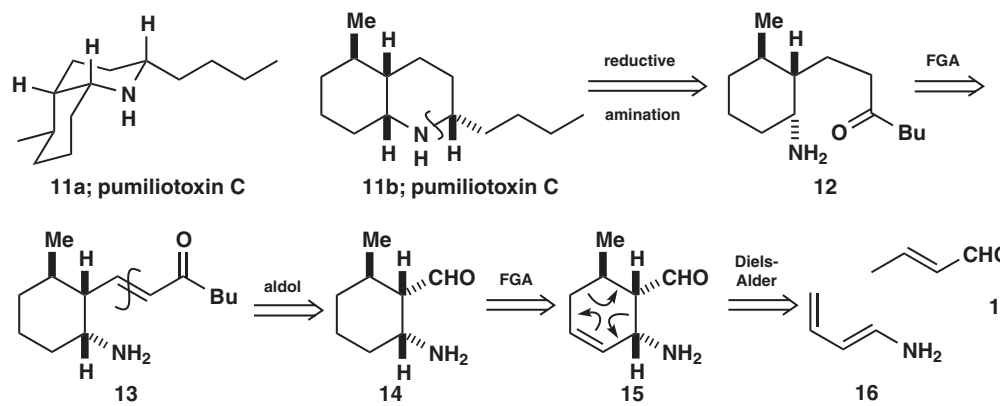


Predicting the stereochemical outcome of a Diels-Alder reaction is easy once you know the likely transition state. The trick is to identify all the groups that are on the same side of the six-membered ring. The figure below shows one way to do this with the bonds on the right hand side exaggerated and placed in a box. Once the new six-membered ring has been made then these groups stay on the same side. In this case all the hydrogen atoms are on the same side: the product is **10**.

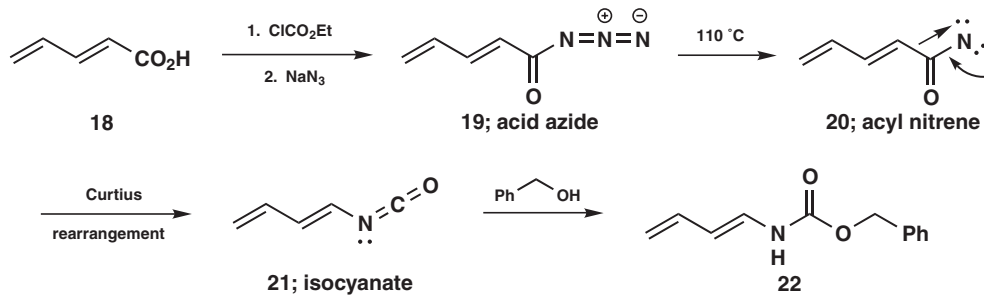


Many Diels-Alder reactions have both stereospecific and stereoselective aspects. It is as important as ever at this point not to confuse perfect stereoselectivity with stereospecificity. So, let's look at a real example. Pumiliotoxin C **11** (a toxin from a tropical frog) contains four chiral centres and in the following synthesis, three of them were controlled by a Diels-Alder reaction.[2] The retrosynthetic analysis is quite instructive.

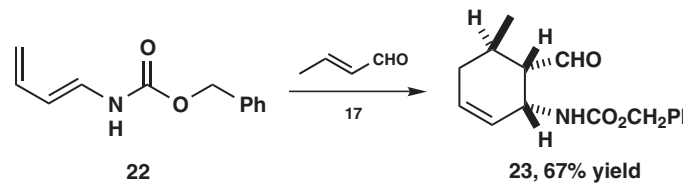
The first disconnection **11b** (reductive amination) takes no consideration of the chirality at all – we will worry about this later. We already have a six membered ring and it now contains *all* the chirality. The introduction of double bonds by FGA is used to considerable effect in this retro-synthesis. The first new alkene allows us to do an aldol disconnection **13** that not only removes a carbon chain but also reveals an electron-withdrawing group on the six-membered ring **14**. This is, of course, one vital component of the Diels-Alder reaction. The next FGA puts in the double bond that allows us to do the retrosynthetic Diels-Alder step **15**.



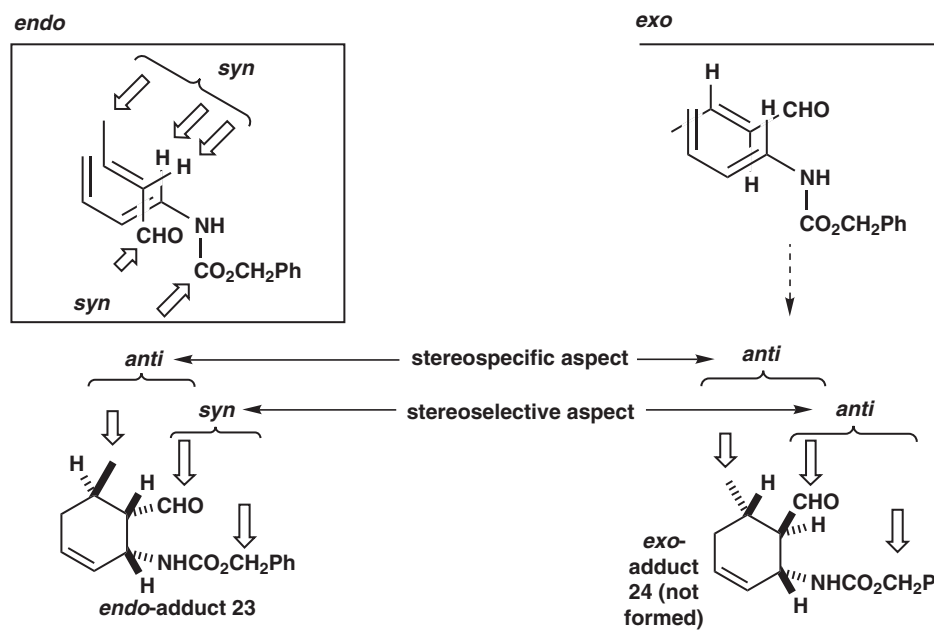
The *trans* relationship between the methyl group and the aldehyde **15** must be preserved in the unsaturated dienophile **17**. The other component (the primary enamine **16**) will clearly not be a stable compound and something will have to be done about that in the forwards route. The reagent used for enamine **16** is carbamate **22** which is made[3] from unsaturated acid **18**.



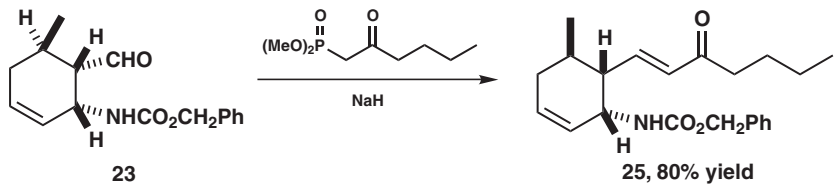
We are now ready for the key step in the sequence which is the reaction of the carbamate **22** with the unsaturated aldehyde **17** to give the Diels-Alder adduct **23**.



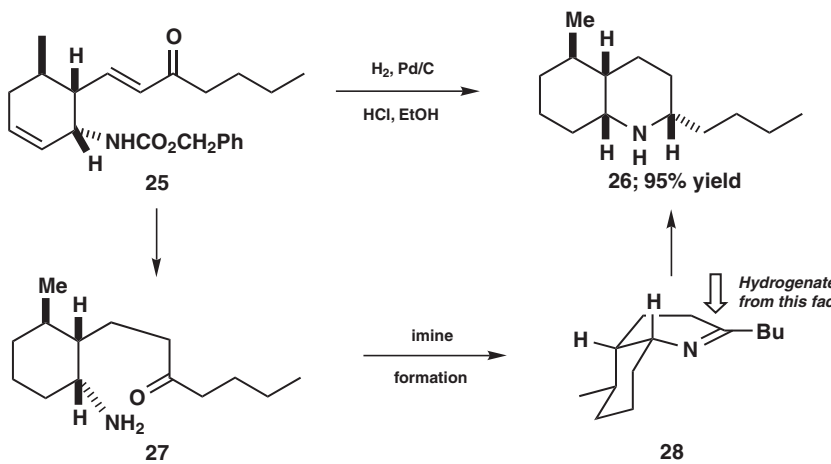
This adduct **23** contains three of the four stereocentres and we should look a little more carefully at the reaction that has just occurred. The two molecules **22** and **17** could have approached each other in two ways which correspond to *endo* and *exo* selectivity. In the *endo* case, on the left, giving **23**, the *anti* relationship between the methyl group and the formyl group stems from the *trans* geometry of crotonaldehyde and is stereospecific. The *syn* relationship between the formyl group and the carbamate comes from the *endo* selectivity in the transition state and is stereoselective. Had the two components of the cycloaddition chosen to come together in the alternative *exo* way (on the right) then there would have been an *anti* relationship here and **24** would have been formed.



We have now discussed the main point of interest but we may as well finish off the synthesis. Reaction of the aldehyde **23** with a phosphonate salt gives the unsaturated compound **25**. This is the Horner-Wadsworth-Emmons reaction described in chapter 15. Notice that the compound has two double bonds that we do not actually want – they were there to aid the synthesis and have now done their job.



The final step is hydrogenation which removes both of these unwanted double bonds. But the hydrogenation does much more than this! For a start the nitrogen is deprotected **27** and exercises its nucleophilic muscles once the α,β-unsaturation has been removed (it cannot reach the ketone until this happens). The result is the imine **28** which can *also* be hydrogenated. Now the final stereocentre is introduced. The imine **28** is hydrogenated from its less hindered face. This is an example of a folded molecule reacting on its convex face. There are several examples of diastereoselective reactions on folded molecules in chapter 17.



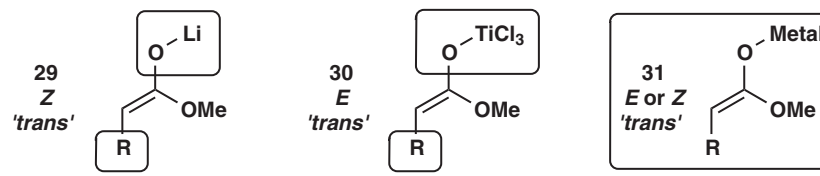
Formation of Acyclic Compounds *via* Cyclic Transition States

Stereoselective aldol reactions

From a stereochemical point of view, aldol reactions can provide us with another one of those *fiat lux* moments – stereochemistry appears to spring from nothing. As in the Diels-Alder reaction, the stereochemistry comes from two places. Firstly, there is the geometry of the starting materials and secondly, there are choices that are made in the transition state (remarkably like the Diels-Alder reaction in fact). Let us focus on the geometry of the starting materials—whether enolates have a *cis* or a *trans* geometry.

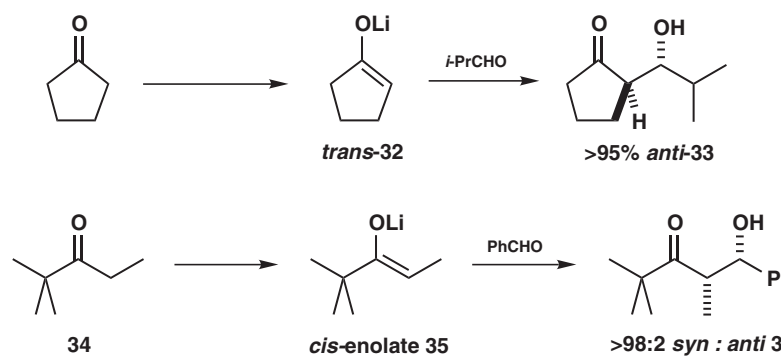
Nomenclature

Just before we go any further we need a quick note on nomenclature. We see below a lithium enolate **29** and a titanium enolate **30** of an ester. By definition, the lithium enolate **29** contains a *Z* double bond (lithium is lighter than carbon) whereas the titanium enolate **30** contains an *E* double bond (titanium is heavier than carbon). But to call one *E* and the other *Z* is plainly crazy. The important thing, as far as we are concerned, is that the substituent R is *trans* to the reactive oxygen. In order to avoid confusion we shall refer to *both* of these as *trans* enolates regardless of the metal **31**. This is not universally done (some chemists will be outraged by such simplicity) but is what we shall be doing in this book.



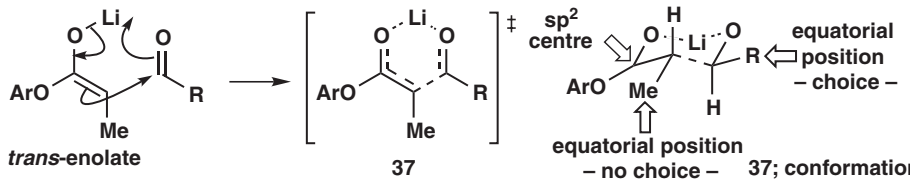
Early work

The pioneering work of Dubois[4] showed that *trans* enolates **32** of cyclopentanone react to give selectively *anti* aldol products **33**. The enolates have to be *trans* because the substituent is locked into a ring. Heathcock showed that ketone **34** (note in particular the *tert*-butyl group on the left) gave the *cis* enolate **35** and mostly *syn* products[5] **36**.

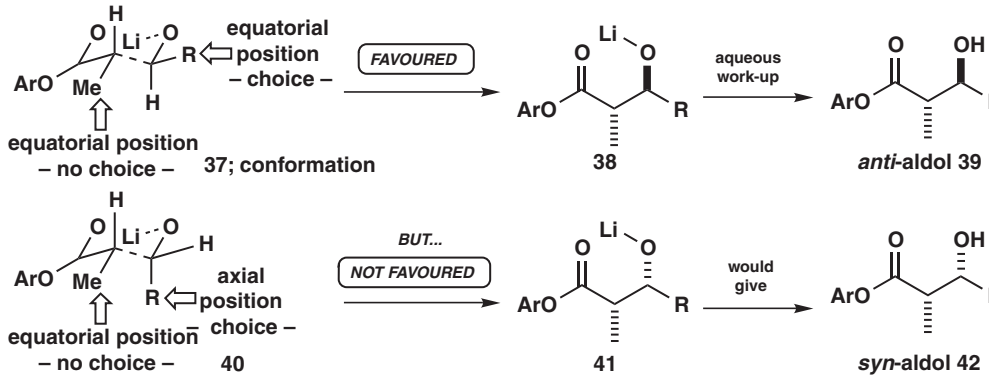


The transition state model

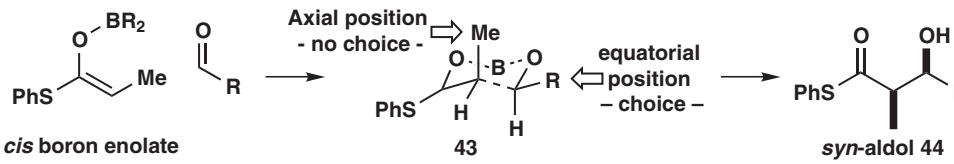
So, *trans* enolates give *anti* aldol products whereas *cis* enolates give *syn* aldol products. Why? The enolate and the electrophile fit together in the transition state into a six-membered ring. Chemists often refer to the model as the 'Zimmerman-Traxler' transition state.[6] The six-membered ring is in a chair conformation. Consider the reaction of some aldehyde RCHO with a *trans* lithium enolate. The lithium, the oxygen atom, adjacent carbon atom and nucleophilic carbon atom of the enolate react via the six-membered ring transition state **37**. The methyl group *must* go into an equatorial position as it is *trans* to the oxygen atom of the enolate and is forced into this position. Finally, there is one sp^2 centre (ArOC) that stays as an sp^2 centre from start to finish.



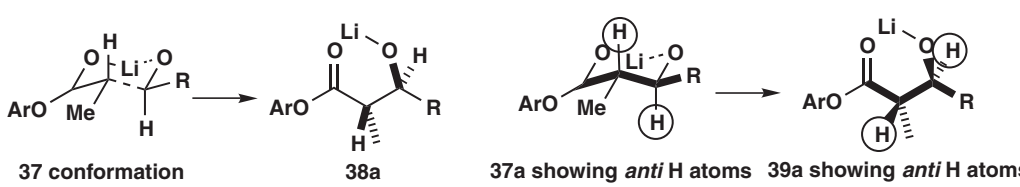
The R group of the aldehyde, however, can *choose* to take up an equatorial position **37** or it could fold round the other way and go into the axial position **40**. The favoured conformation **37** gives the *anti*-aldol **39** while the disfavoured conformation **40** would give the *syn*-aldol **42**.



What about *cis* enolates? Consider this time the reaction of a boron enolate. As the lithium was in the six-membered ring last time so the boron atom is this time. Now the methyl group of the enolate is forced to adopt the axial position **43** but the aldehyde still chooses to have its R group in the equatorial position. The result is a *syn* aldol product **44**.

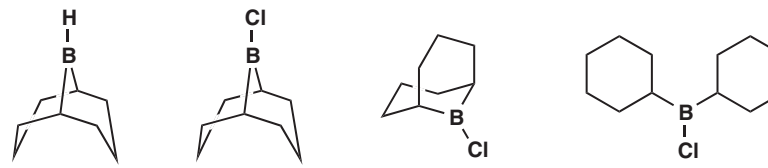


If it is not obvious to you how the six-membered transition states gives rise to the stereochemistry in the aldol products then read on. The trick is to identify the carbon zig-zag in the six-membered transition state that corresponds to the zig-zag in the open chain compound. The way we drew the chairs allows for easy mental transfer of the stereochemistry. Firstly the conformation **37** giving rise to compound **38** is redrawn **37a** but with the hydrogen atoms on the stereocentres emphasised. Now notice the front part of the six-membered ring – the zig-zag is highlighted in bold. The hydrogen atoms are quite clearly *anti* to one another and will be *anti* to one another on the zig-zag in the final molecule **39a**. In this molecule forward bonds are shown by wedges. The absolute stereochemistry indicated in the transition state is the same as that in the final product (satisfy yourself that this is the case) but note that the zig-zags kink in opposite directions – we still have a little bit of work to do in making the mental transfer.



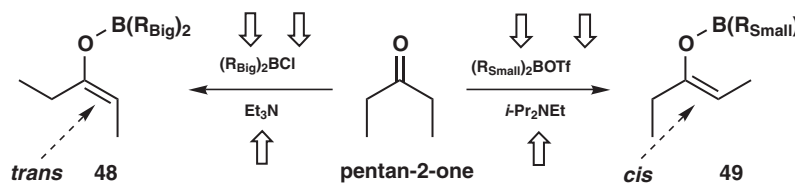
Getting control – ketones

It is all very well knowing what enolates give rise to what aldol products, but this is not much use unless we can *choose* to have *cis* or *trans* enolates. Clearly with cyclopentanone there is no option but to form a *trans* enolate. But with an acyclic ketone we will need a little more care. Boron enol ethers provide an answer. Two common boron reagents used are 9-BBN chloride **46** (derived from 9-BBN **45**) and another is dicyclohexylboron chloride **47**. Other reagents include the corresponding triflates. There are also the chiral boron reagents that we shall meet later chapters.

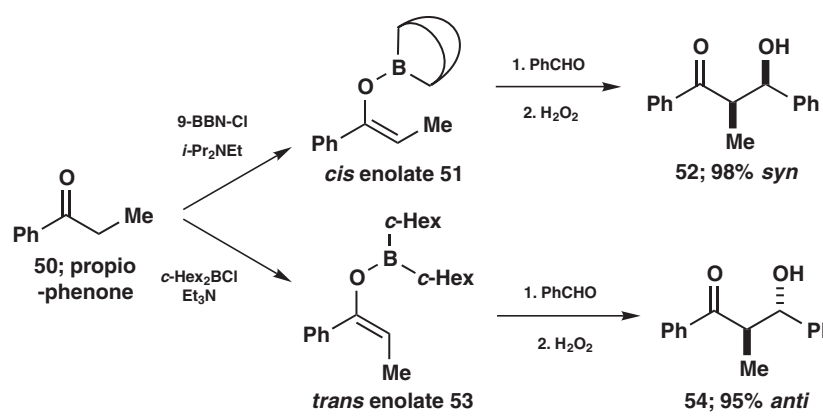


45; 9-BBN **46; 9-BBN-Cl** **46; 9-BBN-Cl** **47; *c*-Hex$_2$B-Cl**

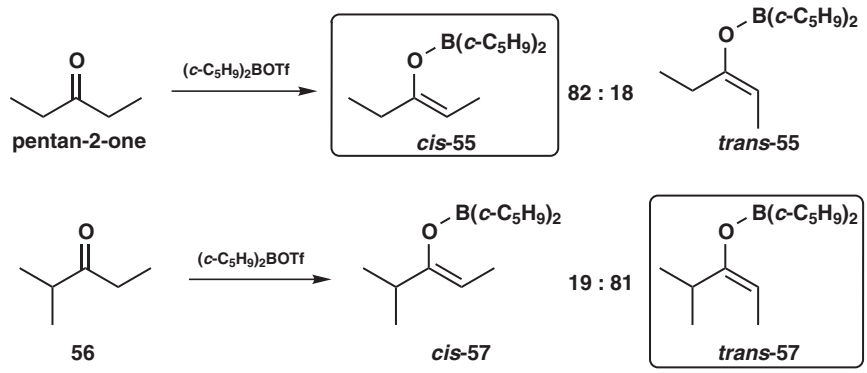
Amazingly, different combinations of base, alkyl groups, and leaving groups on the boron give different enolate geometries. Broadly speaking, *cis*-enolates **49** are obtained by having a small alkyl groups on boron (like butyl), a good leaving group (triflate) and a more bulky neutral base (like *i*-Pr$_2$NEt). In contrast, *trans*-enolates **48** are obtained with sterically demanding alkyl groups on boron (like cyclohexyl), a less good leaving group (chloride) used in combination with a small neutral base (Et$_3$N).[7] The methodology to obtain *trans*-enolates selectively[8] was later in coming. We will avoid explanations about *why* these combinations work but suggestions are available.[9,10]



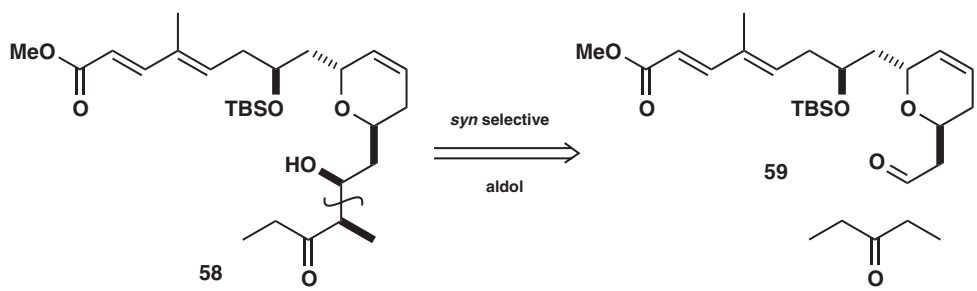
Interestingly, although the 9-BBN group looks like a large group, it (like dibutyl) is often complementary to a dicyclohexyl boronyl system. Since the groups on the boron are 'tied back' it probably has fewer steric demands than one might initially imagine but also 9-BBN enolates readily undergo equilibration.[11] Although the leaving group is important,[12] even keeping boron's leaving group the same and varying the nature of the alkyl groups can have dramatic effects.[8] The reaction of propiophenone can thus be varied to give either *anti* **54** or *syn* **52** aldol products.



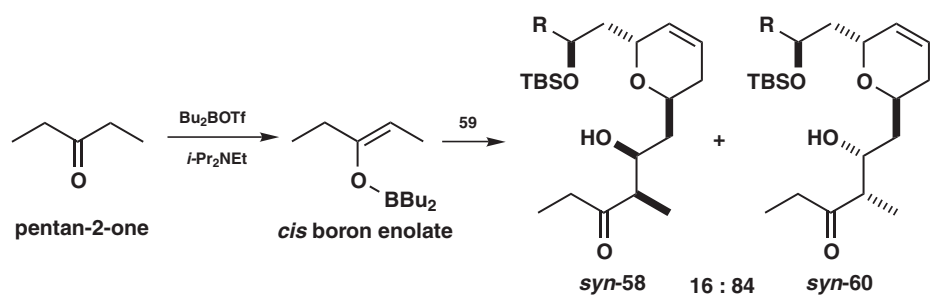
But is isn't as simple as this. The stereochemistry of the enolisation depends also on the group on the other side of the carbonyl (phenyl in the above case). So, for example, while pentan-2-one gives mostly *cis* boron enolate **55**, branched ketone **56** give mostly *trans*.[13] The aldol reaction is immensely complicated as there are so many variables. However, all the fundamentals from *cis* and *trans* enolates to double stereodifferentiation can be found in a review by Heathcock.[14]



Ester **58** is a key intermediate in a synthesis concerned with swinholide A.[15] We can see that two of the stereocentres could be controlled through the use of a *syn*-selective aldol.

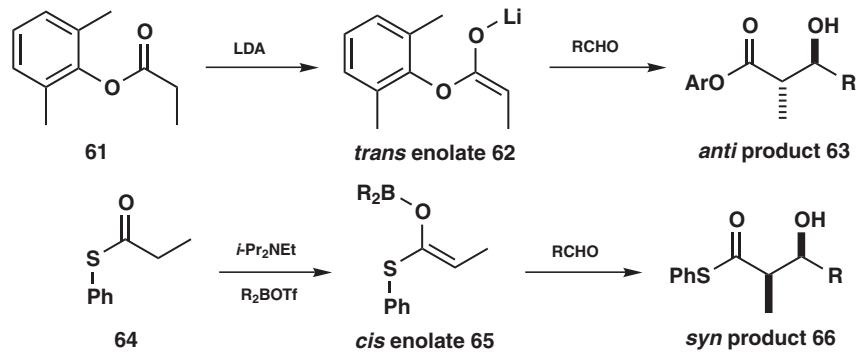


Indeed, the forwards reaction uses a boron triflate and a bulky base of the type we have seen in order to make the *cis* boron enolate and achieve exactly this control. There are, of course, *two syn*-aldol products possible here, **58** and **60**, by virtue of the chiral centres present in the aldehyde fragment, and both do indeed form (in a 16:84 ratio). Trying to achieve selective formation of one of these *syn* diastereomers rather than the other *syn* diastereomer is beyond the scope of this chapter, even though that too is relative stereocontrol. It is complicated because it involves enantiomerically pure reagents in combination with the enantiomerically pure aldehyde and a match/mismatch issue. These issues are explored more fully in Chapter 30. Examples include combinations of chiral or achiral aldehydes with both achiral and chiral boron reagents.

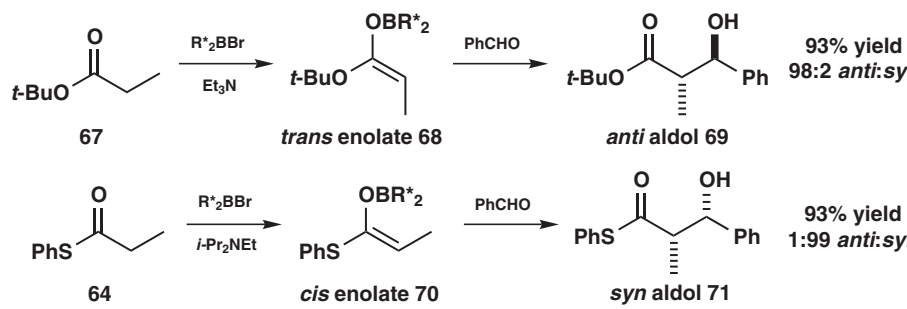


Getting control – esters

With esters there is yet another variable that may be used – the nature of the esterifying alcohol. In fact, we saw the enolates resulting from esters **61** and **64** earlier in the chapter when we were discussing the transition states. The ester may have a hindered aromatic component[16] **61** or be a thioester **64** instead of an ester.

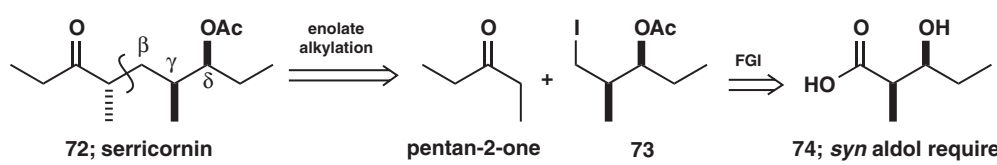


Corey used an ester and a thioester in combination with an optically pure boron reagent in order to control both relative and absolute aldol stereochemistry.[10] The optically pure boron reagent was busy with the absolute control (the details belong in chapter 27 but **69** was 94% ee and **71** 97% ee by virtue of the chiral boron reagent).

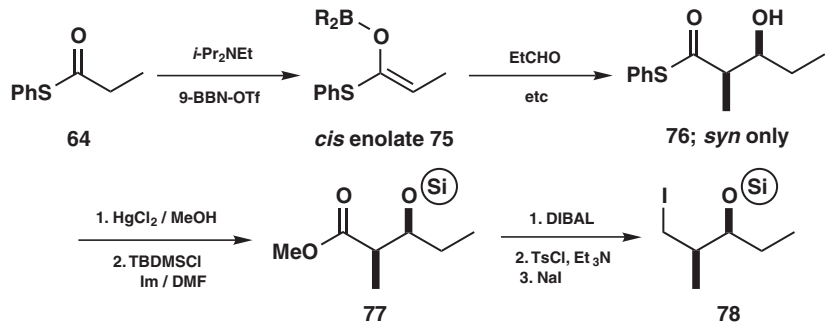


The advantage with esters is that once the stereocontrol has been achieved, the alcohol or thiol component of the ester may be replaced with something else entirely. That something else may not contain a heteroatom at all as we shall see in the next illustration. Serricornine **72** is a sex pheromone for the cigarette beetle and synthetic serricornine is used in the control of the beetle.

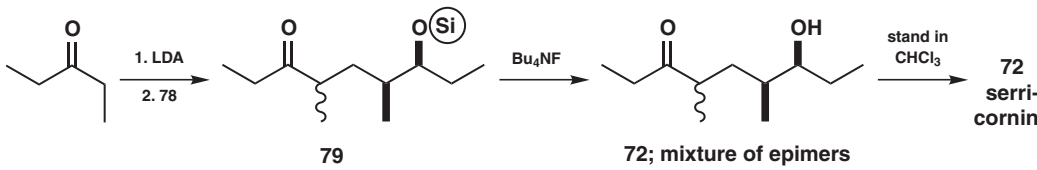
We are interested in this instance in the stereochemistry between the γ- and δ-positions. To use aldol chemistry here would require a carbonyl at the β-position and it is conspicuous by its absence. We shall have to put it in. Disconnection **72** of serriconin and FGI leads to an acid **74** which is looking a little more like the kind of substrate we need for an aldol reaction.



The synthesis starts with the thioester **64** to get the *cis* boron enolate **75** we need for the *syn* product. Once the adduct **76** has been made, the sulfur has done its work and can be removed. Transesterification with MeOH and $HgCl_2$ and straightforward steps lead to iodide **78**. Once this iodide has reacted with the enolate of pentanone, there will be no trace of the carbonyl that originally allowed the aldol chemistry to be performed.



One noteworthy step is the control of the final chiral centre. You will have noticed that we did not worry about the stereochemistry at the α-position at all. Natural serricornine readily epimerises at that position and so the workers knew they could leave nature to sort that out later. After deprotection of **79** the mixture epimerised to serricornine **72**. This synthesis by Baker and Devlin was used as the basis for their enantioselective synthesis of serricornine. To intrigue you, something other than PhS was used and this something could also be removed and was a chiral auxiliary.[17]

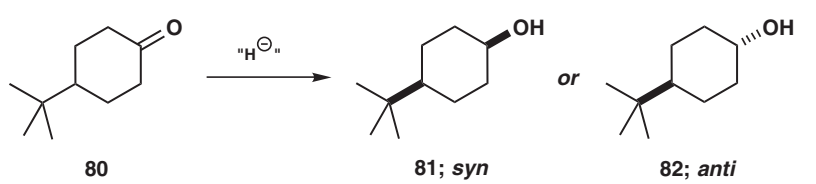


Reactions of Cyclic Compounds

Conformational Control with Six-Membered Rings

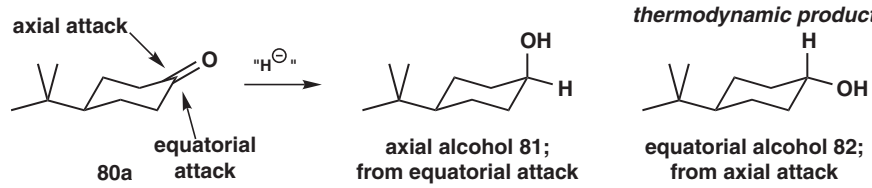
Addition of nucleophiles to cyclic ketones

Cyclic compounds have fewer degrees of freedom than their acyclic counterparts and this means that not only can we expect a higher level of control, but the resulting stereochemistry is easier to visualise. So reduction of the achiral ketone **80** could lead to the *syn* alcohol **81** or the *anti* alcohol **82**. The question is which do we get and why?



In fact, either can be achieved by using different reducing agents[18] but let us first look at the issues concerned in conformational terms. Attack on the carbonyl group **80a** will either be

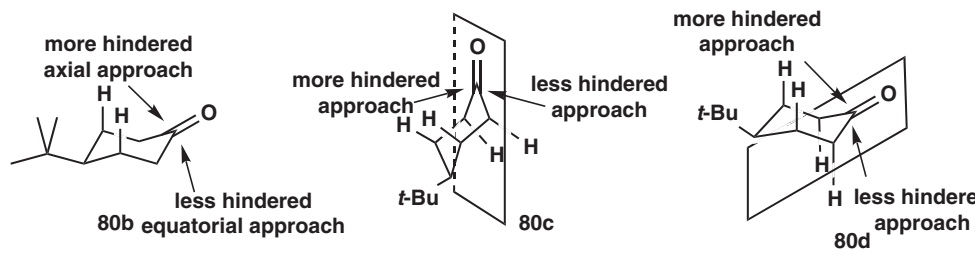
axial or equatorial leading to the two alcohols **81** and **82** Note that both **81** and **82** are *achiral* molecules—achiral molecules with stereochemistry.



Reducing Agent			
Li, NH_3, ROH	1	:	99
$NaBH_4$	7	:	93
L-Selectride	96.5	:	3.5

The product with the equatorial hydroxyl group **82** will certainly be the thermodynamic product because both of its substituents are in the equatorial position. Let's look at what reagents yield what products. The combination of Li in NH_3 will generate solvated electrons. The reducing agent is an electron. We will come back to this in a minute but for now notice that it is highly selective at producing the diequatorial compound. Conversely L-Selectride®, $LiBH(s\text{-}Bu)_3$, is highly selective at producing the other diastereomer.[19] At lower temperatures or with an even bulkier reducing agent >99.5% **81** is formed.

There is stereochemical control in this reaction but we must be clear about one thing – the tertiary butyl group is NOT responsible simply by steric hindrance. It is too far away to be of any direct consequence. Its function is to lock the conformation of the ring. It is the *ring itself* that provides the steric hindrance. Structure **80b** shows that the there will be steric hindrance from the axial protons on the ring. Another way to look at this is to consider the plane of the ketone **80c/d**. Some of you will find the 'right and left' distinction of **80c** easier to grasp and some the 'top and bottom' distinction of **80d**. Either way you should see that on one side is the rest of the ring while on the other side there are merely two protons.



We can explain the result with the L-Selectride quite easily. It is a very large reagent and will thus approach from the less hindered side to give the compound with the axial OH. The result with the Li in NH_3 takes a little more explaining. Small things are less affected by steric issues than large things. Some of us know from experience that while closing doors and windows is a very effective way of keeping cats out of your house, mice will get in through the tiniest of holes. Trying to block the holes up is simply a waste of time – they will find a way in! Similarly, while large reducing agents can be expected to respond to steric hindrance, small ones, if they are influenced at all, will be influenced by other things.

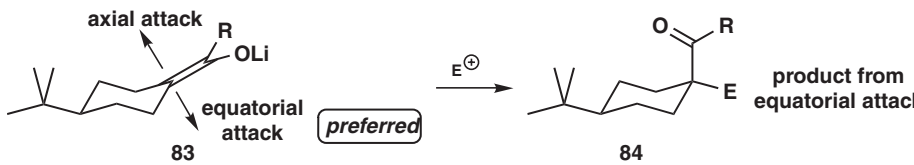
With this in mind we should look back to the result with the electron (Li in NH_3). This is the smallest reagent that can be! It will take no notice of steric constraints whatsoever but may well

be influenced by other things. If the extra stability of the thermodynamic product shows up in the transition state of the reaction then we would expect this reaction to go faster. This is clearly what is happening with the electron. Although that appears to wrap it up, it may be that this argument is simplest, largely because the transition state is probably more like the starting material than the product and there are other factors at work.[20]

Summary (whatever the explanation): large reagents add equatorially and small ones add axially providing that the thing being added is smaller than the thing already there.

Reactions of exocyclic enolate

The above concerns an electrophilic centre in a six membered ring. The reverse would involve a nucleophilic centre in a six membered ring. If anything the chemistry is now more straightforward and is not so influenced by the size of the electrophile. With the exocyclic enolate **83**, equatorial attack is preferred.[21] But if the enolate is too reactive then there is little selectivity.



In this section we are not concerned with chirality being in place before the reaction but there is an additional warning here. Even if a molecule does have a chiral centre in it, it may be that this centre has nothing whatever to do with the stereocontrol observed. Consider the two unsaturated ketones below. One of them **85** is chiral, one of them **86** is not.

In both cases, a nucleophile will come in across the unsaturated side of the molecule. The two chiral centres at the bridgeheads of the chiral molecule **85** have nothing to do with this. The only consequence of the chiral centres will be that the product will be a chiral diastereomer whereas (with the achiral ketone **86**) the product will be an achiral diastereomer.

Part II – Chirality in Place from the Start

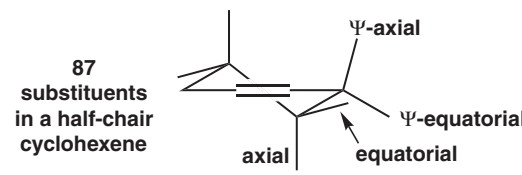
Using one chiral centre to control another

Reactions of Cyclic Compounds: Conformational Control

The half-chair

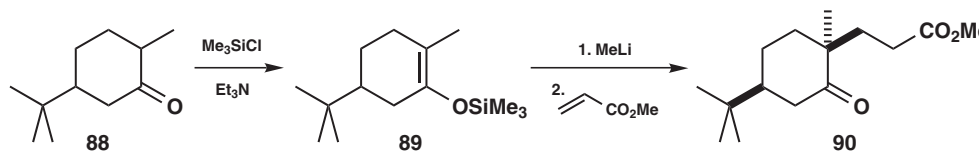
The first concept that needs to be introduced here is the half-chair. Assuming you know how to draw the chair form of a cyclohexane, then the half-chair is a way to describe cyclohexene. One half of the normal chair has been flattened – hence the term 'half-chair'.

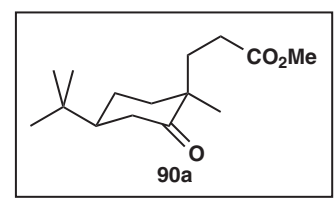
The usual way to draw a half-chair is with the double bond at the front of the six-membered ring **87**. The two carbons that are furthest away from the double bond are less perturbed from their chair-like arrangement and the substituents are axial and equatorial. Those next to the double bond are not genuine axial or equatorial substituents and occupy what are called the 'pseudo-axial' and 'pseudo-equatorial' positions. Pseudo is indicated by a 'Ψ' symbol. We shall see in the next section how a half-chair can develop into a chair.



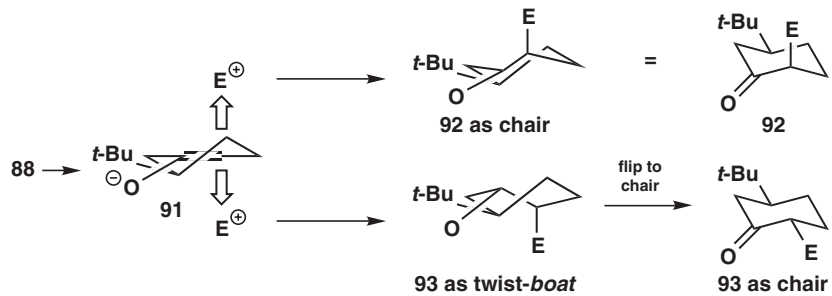
Reactions of endocyclic enolates

The ketone **88** reacts with Me_3SiCl and base to give the more substituted silyl enol ether **89**. This has only one chiral centre and that is at the point where the *tert*-butyl group joins the ring. The silyl enol ether **89** is turned into a reactive lithium enolate by the application of MeLi. This enolate then reacts with the methyl acrylate to give **90** with the stereochemistry as shown.[22] If the tertiary butyl group is in the equatorial position, which is to be expected, then the new group has been installed in an axial position **90a**. It is this that needs to be explained.





We need to consider how the conformation of the half-chair changes as it reacts. Enolate **91** is drawn as a half-chair with the tertiary butyl group at the back of the molecule in an equatorial position. If the electrophile attacks from the top face then, as a bond forms to the electrophile and the sp^2 hybridisation changes to sp^3, a chair **92** starts to take shape (for clarity, we've omitted the carbonyl double bond in the conformational diagram). We see that the electrophile occupies an axial position. However, if the electrophile attacks from below, then a twist boat **93** starts to develop instead. If this boat were flipped into a chair, the new electrophile would be in the equatorial position.[22]

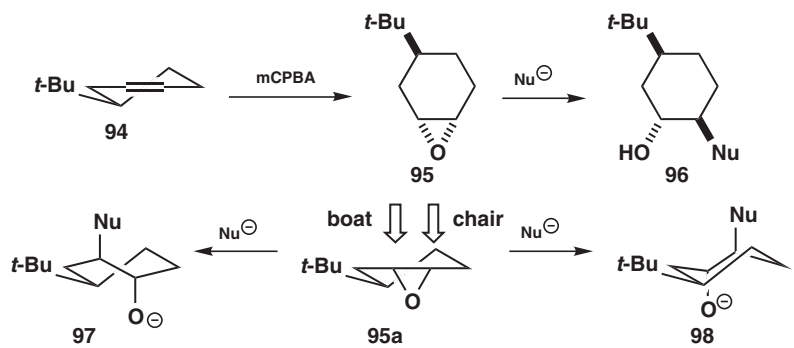


So attack on one side leads to an axial substituent whereas attack on the other leads to an equatorial substituent (but only after the ring flips). Boats are, of course, much less favourable than chairs and so axial addition is the usual outcome as the chair is formed during the reaction and not afterwards. We shall refer back to this as the normal development of a half-chair.

Summary: If the starting material is *not* a chair (it might be a half chair), the most important thing is to get a chair. The question of whether groups go equatorial or axial is less important. On the other hand, if the starting material is already a chair (it might be ketone **80**), the most important question is whether groups or reagents are in equatorial or axial positions.

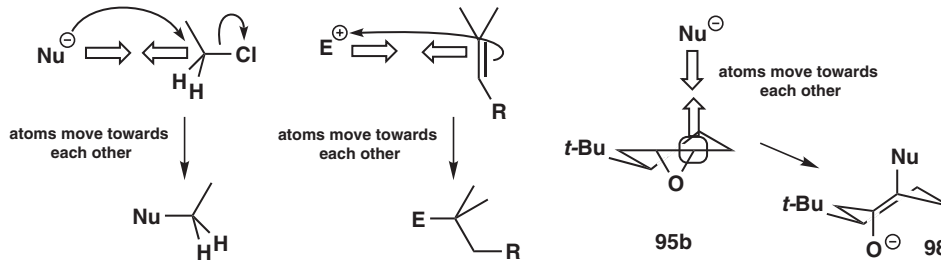
Opening epoxides

We can look at how epoxides are opened in a similar way. The flattening of the six membered ring by the strain of the three membered ring **95a** is not dissimilar to the flattening caused by a double bond **94**. We can attack the end of the epoxide **95** (with generic nucleophile, Nu^-) that leads to a chair **98** rather than the end that leads to a twist-boat **97**. Compound **96** is the *trans*-di-axial product as both Nu and OH occupy axial positions.



Atoms move towards each other when a bond is made

When you think about the development of a half-chair into a chair it is important to remember that atoms move *towards* each other as they form a bond. This sounds like rather an obvious statement but there is subtle psychology at work – although chemists rarely make the mistake when the half chair is the *nucleophilic* component, it seems all too easy to think absent-mindedly of an attacked electrophilic carbon atom in a half-chair retreating *away from* the incoming nucleophile – and this is *not* the case. The atoms move towards each other.

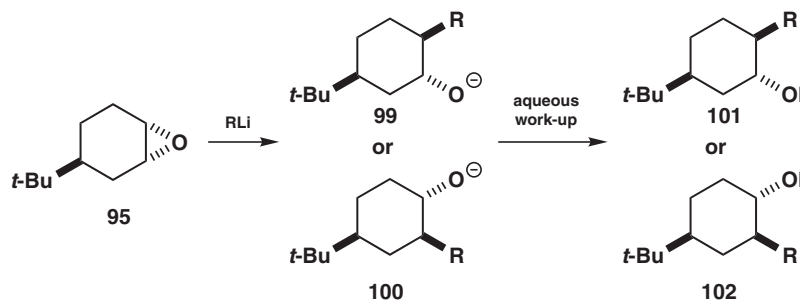


Microscopic reversibility

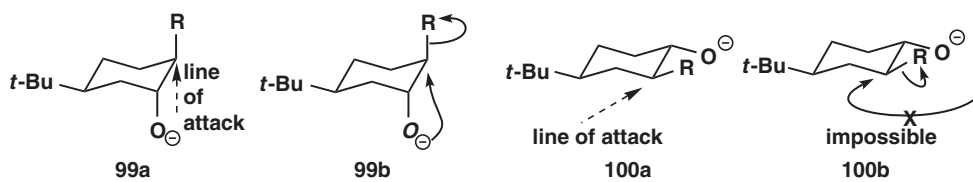
Another way to look at the opening of epoxides uses the principal of microscopic reversibility. Microscopic reversibility is all about considering a reaction in reverse like watching a piece of film run backwards. You would expect the film running backwards to be the exact reverse of the film running forwards. A clown receiving a custard pie from the left of his face, will have it removed to the left of his face. We would never expect that, in reverse, it would disappear off to the right! The same is true of reactions – as then run forwards, so shall they run backwards. At every step of the way (frame by frame) they will be identical.

The justification for this is that a reaction running forwards will run along the lowest energy pathway. Hence it will run back that way too. If there were a lower energy pathway on the way back then the forwards reaction would have found it and used it too! The lowest pass between two valleys is the same whichever way one is travelling. Why should we bother with this? For the simple reason that it is sometimes easier to consider a reaction in the reverse sense – easier to see the orbitals concerned, the stereochemistry involved, the conformation necessary or whatever.

We will stick with the epoxide **95** we used in the half-chair analysis above and react it with RLi. Since the nucleophile is organometallic the reaction is not reversible. We should be clear about this point — the reaction does *not* have *to be* reversible to use a microscopic reversibility argument. The two conceivable products **101** and **102** are drawn (assuming S_N2 reaction).



We now draw the conformational diagrams **99a** and **100a** of the intermediates and consider the reverse reaction that would lead back to the same epoxide **95**. In the reverse reaction, the alkoxide would have to come in behind the R group and displace it.



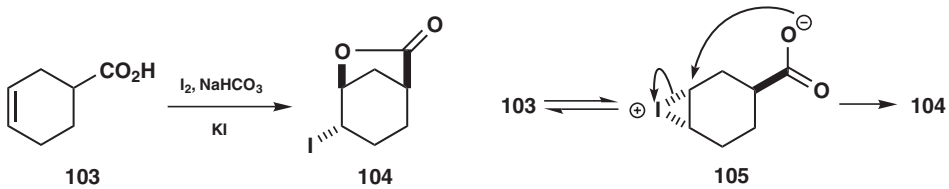
In one case this is clearly possible **99** and in the other it is not **100**. And if R^- cannot be displaced by O^- then the forwards reaction cannot happen either. So, once again, the diaxial product is the product we would expect. It is not really necessary to get too involved with orbitals here as the alignment (or lack of it) is very evident. But if we wanted to we could think of this from an orbital point of view. The σ* of the C–O bond is populated when the epoxide is opened and goes into forming the lone pair on oxygen and the C–R σ-bond. They would have to realign to turn back into their former selves in the reverse reaction too.

Summary: Opening cyclohexene oxides with nucleophiles gives the *trans*-di-axial product.

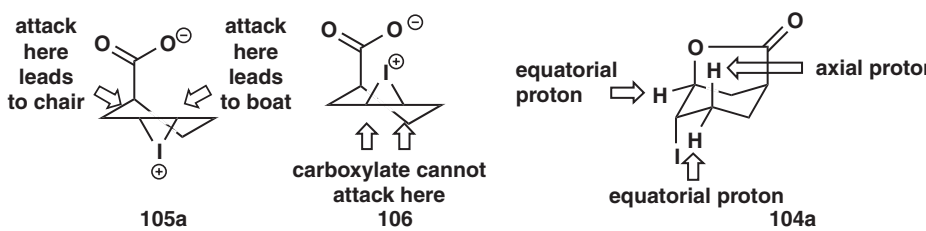
Formation of a Cyclic Intermediate

Iodolactonisation

A stable cyclic intermediate can be a good way to control stereochemistry. The idea is often to create stereochemistry in forming the ring and cleave the ring later with the stereochemistry already in place. Treatment of acid **103** with iodine yields the iodolactone **104**. This must take place by an intramolecular version **105** of the reactions we have just been discussing.[23] This reaction was also discussed in chapter 17.



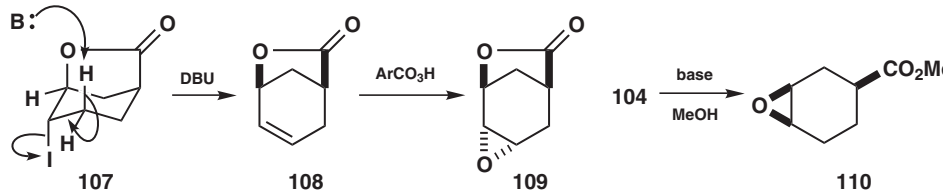
This reaction is worth looking at in a little more detail. It depends upon formation of an intermediate species, the iodonium ion **105**. There is nothing to stop the diastereomeric iodonium ion **106** from forming but cyclisation with the carboxylate ion cannot occur and, since the reaction is reversible, the reaction will run back to the unsaturated acid **103** and try again. The two alternative iodonium ion conformations with equatorial CO_2^- groups cannot cyclise until the chain flexes to put the CO_2^- axial.



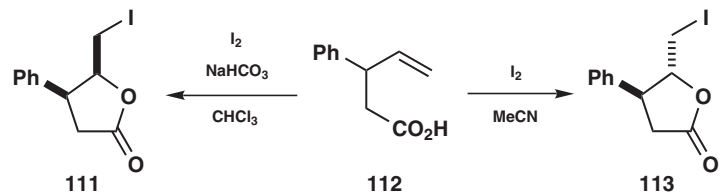
The iodonium ion that does react cyclises **105** to give a chair **104a** and not a boat. The 1,3- lactone bridge must be diaxial - another reason why the CO_2^- group must be axial for cyclisation to occur. We can also see that the product **104** has the *trans*-diaxial relationship between the iodine and the CO_2^- group we are familiar with from the opening of epoxides.

The iodolactone **104** can be elaborated. Once again we should look at the compound from a conformational point of view **104a**. There is only one proton in an antiperiplanar relationship to the axial iodine atom and so elimination will occur with this proton **107**. When it comes to reaction of the new double bond in **108**, stereoselectivity will be dominated by the lactone bridge which

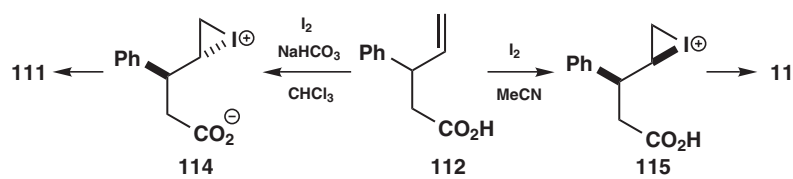
will provide a barrier to incoming reagents. So, epoxidation leads to the oxygen being introduced on the underside of the ring to give epoxide **109**. On the other hand, if the lactone bridge is first opened a different epoxide **110** is formed.



Just before we continue let's have a look at the reagents used in the iodolactone formation. The iodine is obviously needed but notice the weak base, $NaHCO_3$. This will deprotonate the acid (making it more nucleophilic) and make the reaction faster. Only one product is possible from **103** but in some cases the presence or absence of base leads to different products. The example **103** is probably the most straightforward – we start with a ring to aid the control of another one. Things become more complicated when we form iodolactones from open chain compounds The hexenoic acid **112** can give two different iodolactones[24] **111** and **113**.



In one reaction base is used and in the other it is not. When base is *not* used the product is the thermodynamic *trans* lactone **113** whereas with base then the kinetic *cis* lactone **111** is formed. The decision about stereochemistry is made when the iodine first attacks the double bond. But this is not the end of the story. Once again we might expect addition of I_2 to be reversible (which means that the decision is not yet irrevocable) and so the selectivity will be down to *which* of the iodonium ions **114** or **115** cyclises. The influence of the base might be to change the rate determining step of the reaction. With a more reactive nucleophile to hand (carboxylate instead of carboxylic acid) we could imagine that the iodonium ion **114** would not have any time to equilibrate before nucleophilic attack occurs.

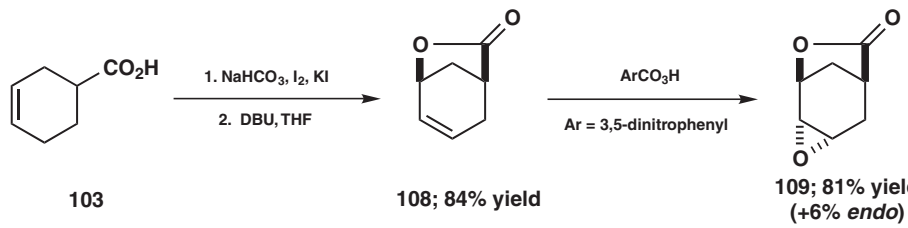


Predicting stereochemistry

It tends to be easier to predict the stereochemistry of thermodynamic products and in general, thermo-dynamic control give good diastereoselection. With six-membered rings the bulkier substituents will end up *trans* if they are substituted in a 1,2 pattern and *cis* if they are 1,3-related (this is presuming there is some element of *choice* of course). With five membered rings then the substituents need to be 1,2-related if there is to be diastereoselection and then they will end up *trans*.[25]

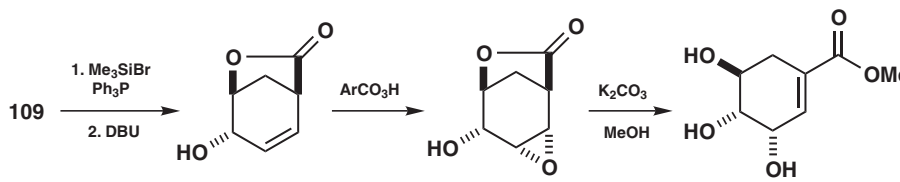
Application of an iodolactonisation reaction

(±)-Methyl shikimate **116** has been made using a strategy with iodolactonisation at its heart.[26] Note that shikimate has three chiral centres. Interestingly, these three centres are controlled in the synthesis by a centre that is finally destroyed. The first steps are iodolactonisation of **103** and subsequent elimination and epoxidation to give **109** as described above.



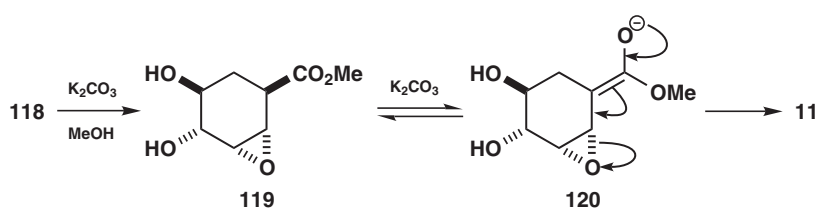
103 **108; 84% yield** **109; 81% yield (+6% *endo*)**

Epoxide **109** is opened with Me_3SiBr (Ph_3P-catalysed) and another elimination with DBU gives the allylic alcohol **117**. The epoxidation that follows is controlled in a couple of ways. Firstly, the axial alcohol can direct the reagent (the same peroxyacid used to make **109**) to the bottom face of the six-membered ring which is also the less hindered side of the molecule (opposite the lactone bridge) **118**. The synthesis is completed with basic methanolysis of the lactone **118** to give racemic methyl shikimate **116**.



117 **118; 85% yield** **116; 98% yield**

The last step in this reaction (the methanolysis) warrants a little more discussion as there is quite a lot going on—the epoxide has gone and a new double bond has appeared. The first step is merely the methanolysis to give ester **119** but, under the basic reaction conditions, the ester can be deprotonated to form enolate **120** which spontaneously opens the epoxide to give our target material. Note that the stereochemical information at the α-position – the only chiral centre in the starting material **103** – is lost with the deprotonation and never comes back.

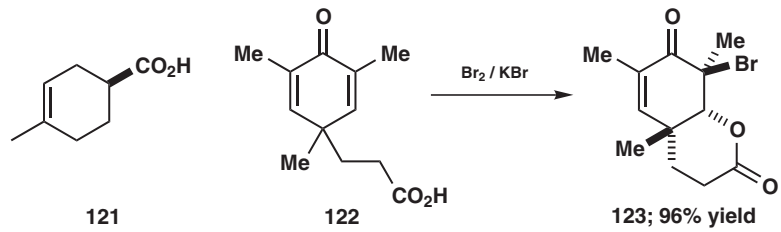


119 **120**

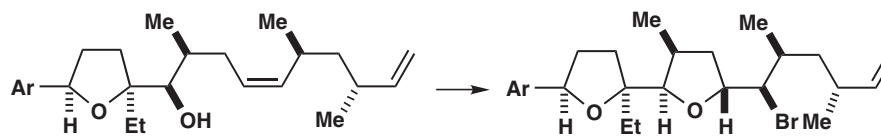
Variations on this theme

There are several reactions that have a similar flavour to iodolactonisation.[27] That is, where an intramolecular nucleophile attacks an electrophilic site that is derived from a double bond. The most

obvious cousin must be the *bromo*lactonisation. Acid **121** was subjected to bromolactonisation in the first stage in the synthesis of a pheromone component.[28] But for a more complicated substrate, bromolactonisation was used in Corey's synthesis[29] of erythronolide B. Dienone **122** was reacted with bromine and KBr to give bromolactone **123** in 96% yield. In fact, a few steps later, *another* bromolactonisation was done which featured the other double bond.



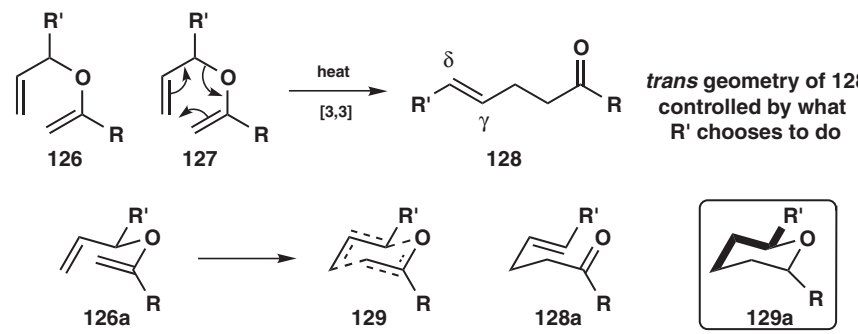
Other varieties of this sort of reaction include bromoetherification (where the nucleophilic component is an alcohol rather than a carboxylic acid). Kishi[30] used this reaction to form one of the tetrahydrofuran rings **124** to **125** in his synthesis of Monensin but he used NBS instead of bromine as the source of electrophilic bromine.[31]



Formation of an Acyclic Compound *via* a Cyclic Transition State

Claisen rearrangement

The Claisen rearrangement[32] converts an allyl vinyl ether **126** into a γ,δ-unsaturated carbonyl compound **128**. This is already useful simply because it is a good way to make γ,δ-unsaturated carbonyl compounds but we are interested in the additional stereoselective aspects of the reaction. This is a [3,3]-sigmatropic reaction **127**.

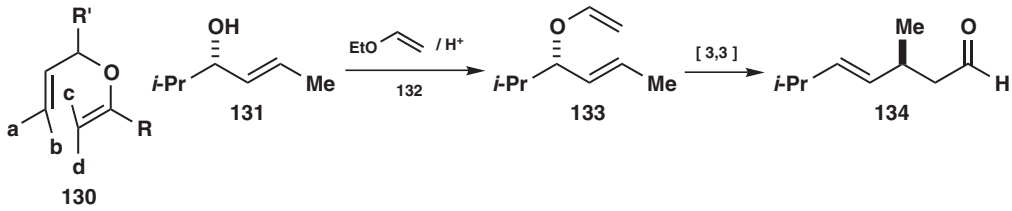


At first sight it may appear that this reaction is not going to be terribly useful stereo-chemically. For instance, in the above scheme we start with one chiral centre and end with none at all. However, it should be noted, before we start to make the chemistry any more complicated, that the *trans* geometry of the double bond is controlled by what R' chooses to do in the transition state **129**.

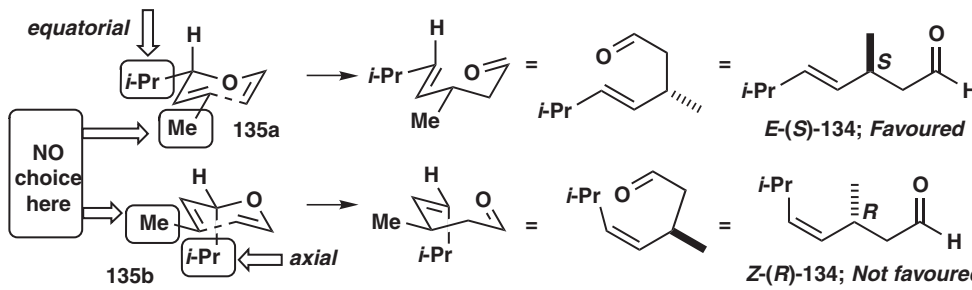
The choice is reminiscent of what we have seen with the aldol reaction – where the electrophilic aldehyde chooses to place its R group equatorial. Here too, R' chooses the equatorial position. The equatorial positions in cyclohexane are always parallel to one of the existing bonds within the cyclohexane ring **129a**. The relationship between that bond and the substituent R' is already *trans* before **126a** and during the reaction **129**. So, a *trans* double bond results. This reaction is discussed in chapter 15.

We can make the situation much more complicated because substituents can be introduced to both of the double bonds **130**. Of all the substituents R' and a-d, R' is the only one that has any choice—the others just have to do what they are told.

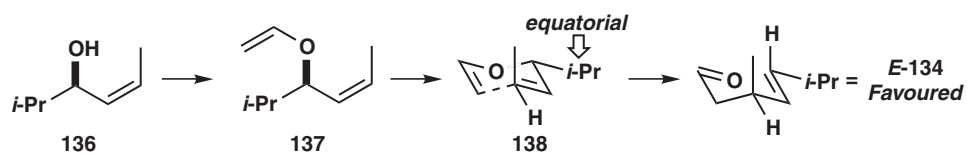
Allylic alcohol **131** reacts with enol ether **132** to give an allyl vinyl ether **133** which is ripe for rearrangement. As it happens, **133** is optically pure and contains a *trans* double bond.



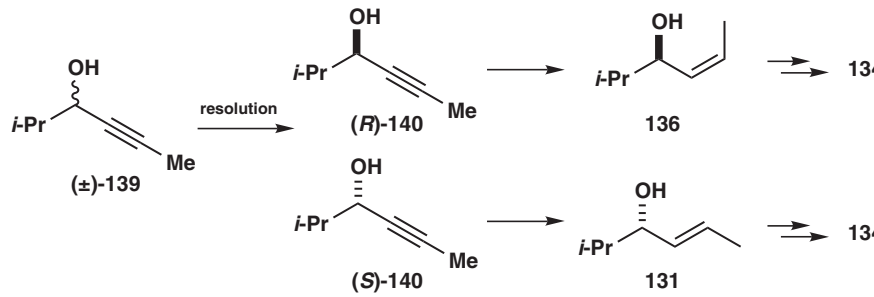
The two options for rearrangement are that the isopropyl group can choose whether it adopts an axial **135b** or an equatorial **135a** position in the transition state.[33] The methyl group has no choice at all – it has to be in an equatorial position because it is attached to the *trans* double bond involved in the reaction. The product from **135a** contains a *trans* double bond and an *S* configured carbon atom while the product from **135b** has a *cis* double bond and the *R* configuration.



The product ***E*-134** resulting from the equatorial isopropyl group is the one that is favoured. Note that the chiral centre we started with has been destroyed and a new chiral centre has been introduced. This process is sometimes known as 'chirality transfer'. Interestingly, if we start with the other absolute stereochemistry *and* the other bond geometry **136**, the outcome is the same.[34] So, *cis* compound **137** also gives aldehyde **134**.

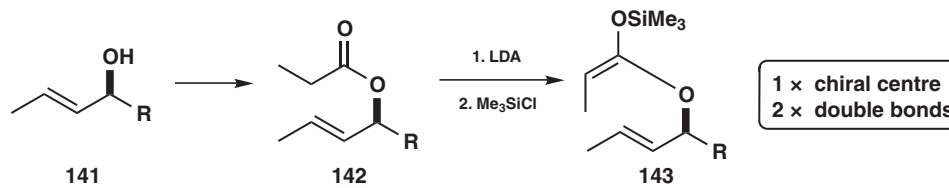


To the shrewd operator, this can be quite a handy trick since it provides a way of using *both* enantiomers, from a resolution say, to give the *same* enantiomer of product.

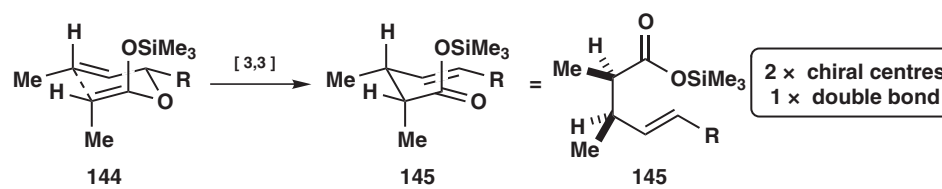


The Ireland-Claisen rearrangement

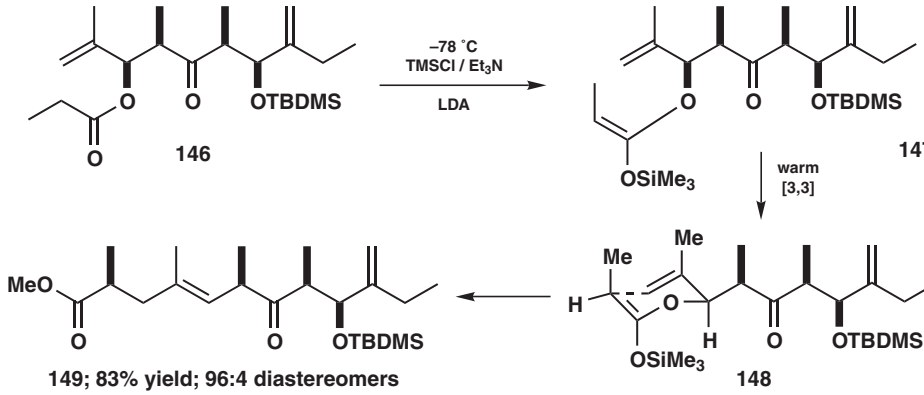
There are many variations on this Claisen theme. Take, for instance the Ireland-Claisen reaction[35] where an enol ether of an ester (a silyl ketene acetal) **143** is used instead of the simple vinyl group in the standard Claisen reaction. The double bond geometry can be controlled by the enolisation process. In this example **143** we have one chiral centre and two double bonds before the reaction. Once again, the R group has choice but the substituents on the double bonds do not.



Following the reaction we have two chiral centres and one stereochemically controlled double bond **145**. Note that the chiral centre that was in place at the start has been destroyed but its chiral essence has not — it is reborn in the two new chiral centres in **145**.

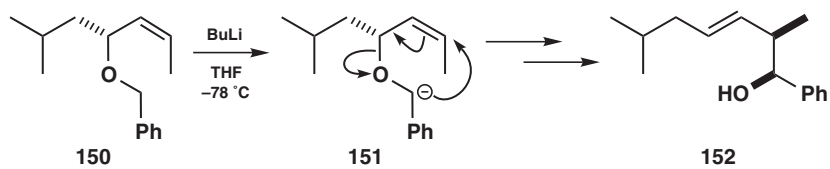


An Ireland-Claisen reaction was employed by Hulme and Paterson in their synthesis of the ebelactones.[36] Interestingly, the synthesis featured an unprotected ketone **146**. This nice piece of chemoselectivity probably relied upon the conditions of the enolisation process as well as the steric congestion around the ketone. The enolisation reaction used an *in situ* trapping by having a mixture of Me_3SiCl and Et_3N together with the ester before the LDA was added. The *cis* silyl enol ether (or '*E* silyl ketene acetal' if you prefer) **147** resulted and following rearrangement and hydrolysis the *E*-ester **149** was isolated in 83% yield and 96:4 diastereomeric ratio.



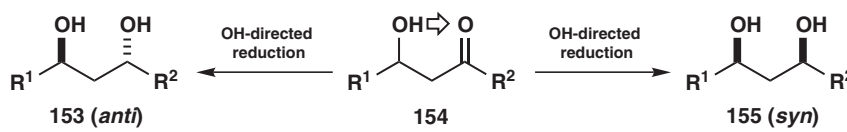
With all this talk of chair transition states it is easy to think that the outcomes of Claisen reactions and their friends are easy to predict. Beware however, because they can occasionally proceed through a boat transition state if the substituents make the chair too unfavourable.

A related reaction is the [2,3] Wittig rearrangement.[33, 37] This goes *via* a five-membered transition state – we shall not go into any more detail about that – but it too is a useful reaction both for making homoallylic alcohols and because of the stereocontrol that can be achieved in the process. Allylic ether **150** gives[38] only the diastereoisomer shown of alcohol **152**. The [2,3]-sigmatropic rearrangement **151** creates an *E*-alkene at the expense of a *Z*-alkene and two new chiral centres at the expense of one. The immediate product of the [2,3]-shift is an oxyanion instead of a carbanion.



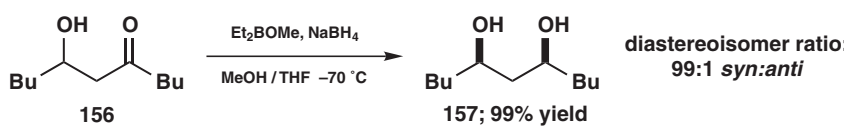
Stereoselective Reduction of β-Hydroxy Ketones

We shall look in this section at two methods to reduce β-hydroxy ketones **154**. One method gives the *anti* product **153** whereas the other gives the *syn* **155**. In both cases, the existing chirality at the carbinol carbon is dictating the reagent's performance.

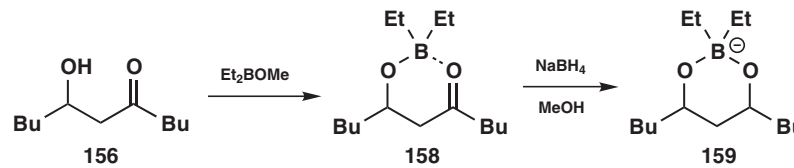


Syn selective reductions

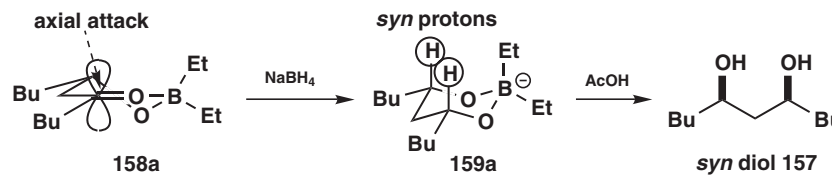
The overall process involves a stoichiometric reducing agent which is plain old $NaBH_4$ and another boron species Et_2BOMe. We shall see in a minute that it is the job of this second boron species to hold the β-hydroxy ketone **156** in a ring as the reduction proceeds.[39]



But first consider the yield of the reaction. It is 99%. What is more, the diastereoselectivity is 99:1. If you work in a lab yourself, you might reflect on how many of *your* reactions go in 99% yield with such high selectivity. It really is a very good reaction indeed and this is how it works. Under the reaction conditions the cyclic intermediate **158** is formed. Methoxide has been displaced from Et_2BOMe and one of the carbonyl lone pairs also gets in on the act and binds the boron in place. Reduction of **158** gives another boron chelate **159**.

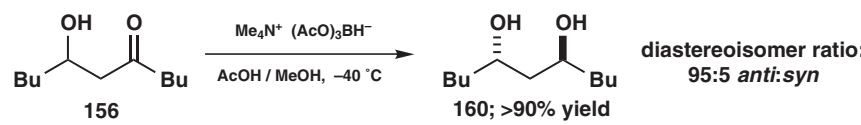


We have two sp^2 centres in the ring (the carbonyl) and so have a half-chair **158a**. We already know from this chapter that half-chairs, by axial attack, develop into chairs. Axial delivery of hydride from $NaBH_4$ gives **159a**. Note the two hydrogen atoms in the resulting chair **159a**. In your mind, highlight the zig-zag of the carbon chain from one butyl group to the other to reveal that the two hydrogen atoms are on one side of the chain and the two oxygen atoms on the other side. The stereochemistry is in place. All that remains is to remove the boron to liberate the diol *syn*-**157**. This hydrolysis is done with acetic acid.

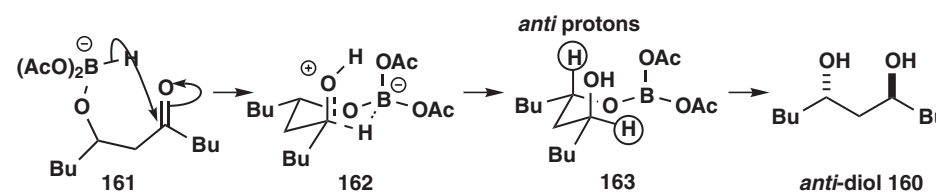


Anti selective reductions

Boron reagents are used once again in the *anti* selective reduction but this time one reagent does all the work. Again, a look at the overall reaction reveals a reaction of the same calibre.[40]

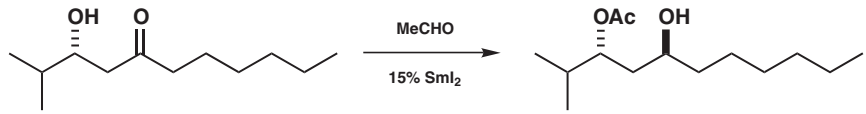


Once again it's the hydroxy group that starts things off by binding to the boron **161**. But this time the hydride is delivered internally to the carbonyl group through a chair transition state **162**. The hydrogen atom forms part of the ring with the carbonyl oxygen axial and the butyl group equatorial. Again, highlight the carbon chain in your mind and notice the substituents on it **163**. This time the two hydrogen atoms (and the two oxygen atoms) are on *opposite* sides of the chain.



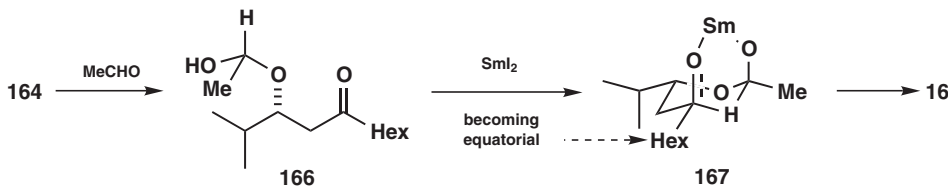
The Evans-Tishchenko reduction

Another way to produce 1,3-diols in an *anti*-selective reaction also starts with a β-hydroxy ketone. The reaction is catalysed by samarium iodide but the stoichiometric reducing agent is acetaldehyde which ends up as the acetate ester in the product **165**.



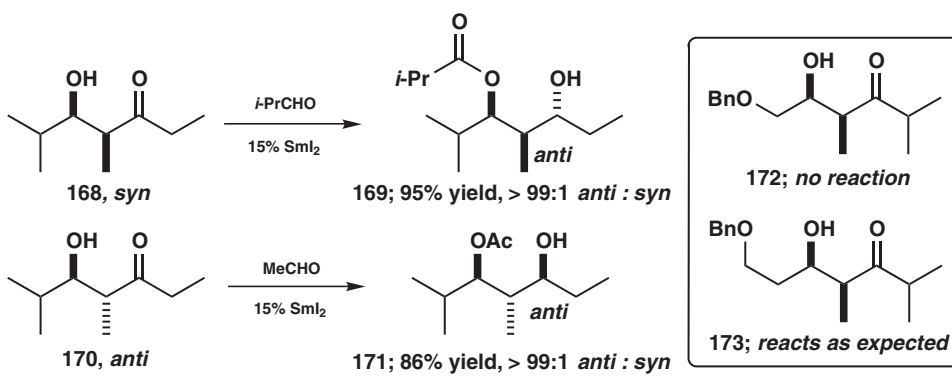
164 **165; 96% yield > 99:1 *anti : syn***

The overall reaction gives the ester **165** and not, as we might expect, a diol or an acetal. The alcohol **164** reacts with acetaldehyde to form a hemiacetal **166**. It is the hydrogen on this hemiacetal that is delivered as a hydride to reduce the neighbouring carbonyl but only after a Sm chelate **167** is formed. Compare this transition state **167** with **162** where trisacetoxyborohydride donated the hydride ion. They are very similar: both transfer a hydride *via* a six-membered cyclic transition state. In **162** the boron holds the two oxygens in a ring while in **167** it is samarium.[41]



166 **167**

The selectivity (>99:1) is astounding but made all the more impressive when we see that substrates with other chiral centres react very selectively too. So, both *syn* and *anti* β-hydroxyketones **168** and **170** give excellent *anti* diastereoselection. But this reaction can be as fickle as frustrated chemists rather expect – compound **172** does not react at all under these conditions while compound **173** reacts as expected.



168, *syn* **169; 95% yield, > 99:1 *anti : syn***

172; *no reaction*

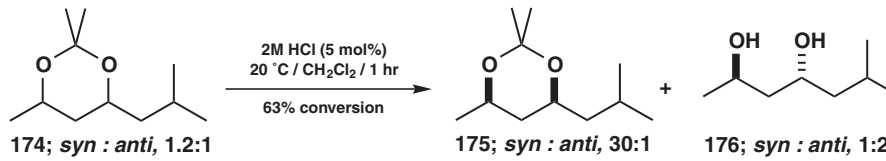
170, *anti* **171; 86% yield, > 99:1 *anti : syn***

173; *reacts as expected*

Kinetic diastereoselection of 1,3-diols

While we are on the subject of *anti* and *syn*-1,3-diols, there is a very useful reaction that allows their separation by means of reaction rather than, say, chromatography. The reaction is a kinetic diastereoselection. With a kinetic resolution, one enantiomer of substrate reacts faster than the

other. With a kinetic diastereoselection, one diastereomer of substrate reacts faster than the other. As with a kinetic resolution, the quality of the material that is left behind improves as the reaction is taken to greater levels of completion. Acetals **174** were made from a mixture of the corresponding *anti* and *syn* diols. The acetals are hydrolysed with dilute acid and then the reaction is stopped prematurely by the addition of base. The *anti* diastereomer hydrolyses more quickly to produce the *anti* diol **175** while the *syn* acetal **176** is left behind.[42]

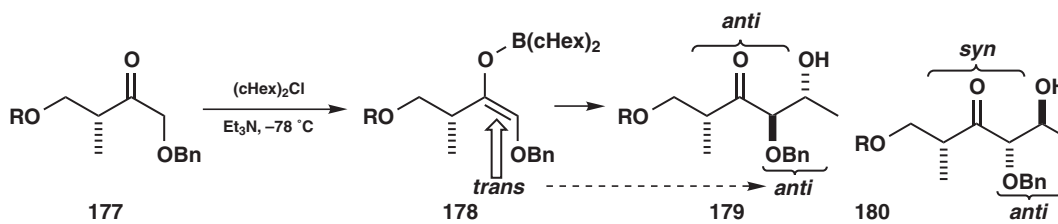


174; *syn : anti,* 1.2:1 **175; *syn : anti,* 30:1** **176; *syn : anti,* 1:2**

Aldol revisited

Finally we'll have a quick look at how combinations of these methods have been applied. In the aldol reactions we have looked at so far there has been no chirality at the start. Both the aldehyde and the enolate have been achiral species that have reacted in a stereoselective way to give a particular diastereomer. With the aldol reaction there is a lot of opportunity to introduce aspects of chirality. The enolate could be chiral as could the aldehyde. In addition to this, the whole reaction could be mediated by a chiral catalyst. Although chiral enolates are most commonly associated with asymmetric methods (most famously the method of Evans in Chapter 27) it is important to remember that the components could just as easily be chiral and *racemic.* The diastereoselectivity that allows the Evans's chemistry to work with optically pure materials will operate whether the auxiliary is optically pure *or not.*

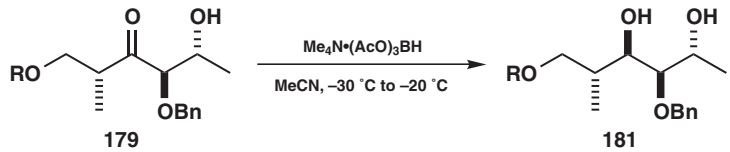
In the next example, the chiral ketone happens to be optically pure but it is still an example of relative stereocontrol. We shall see more of relative stereocontrol with optically pure materials in Chapter 30. We saw in the Diels-Alder reaction that different features of reactivity are responsible for different aspects of resulting stereochemistry — geometry of starting materials, stereospecificity of reaction and *endo* selectivity all have their part to play. Ketone **177** is reacted with a boron chloride to give boron enolate **178**. Significantly, this is a *trans* enolate which means we can expect an *anti* relationship from the aldol reaction which we do indeed see **179**.



177 **178** **179** **180**

However, another *anti* relationship also appears in the product. The *trans* enol was not responsible for this but the existing chiral centre was. Assuming that the *trans*-boron enolate will give its *anti* relationship come what may, the two possible diastereo-mers were the *anti*, *anti* **179** and the *syn*, *anti* **180**. One chair transition state leads to one and another chair to the other.

If you would like to know more about how the existing chiral centre makes its influence felt then you are directed to the paper[43] and a suggestion for transition states.[44] For now we continue with the manipulations. The new hydroxyl group that has been formed in the aldol reaction can be used to direct a stereoselective reduction of the ketone in the way that we have already seen. So, β-hydroxyketone **179** is reduced to diol **181**.



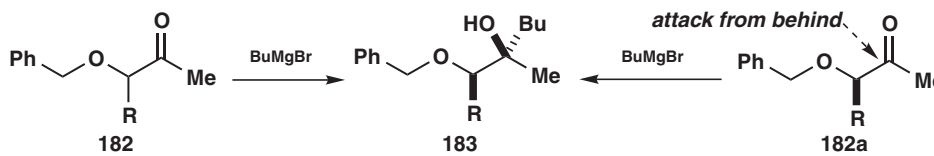
179 **181**

We now have four chiral centres. Three of them are new and put in place relative to the starting chiral centre. Since that was optically pure we have an optically pure product. Diol **181** is an intermediate on the way to a fragment of Spongistatin 1 – a chain extension, asymmetric dihydroxylation and stereoselective intramolecular Michael addition all feature on the way there.[43]

Open Chain Chemistry - with Chelation Control

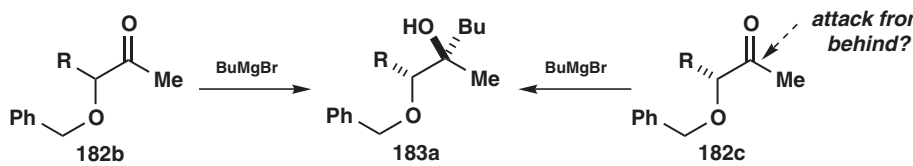
Grignards

When students first encounter stereochemistry, there is a tendency for them to justify stereochemistry based upon the way the compounds happen to have been drawn. So, when asked to explain why ketone **93** reacts with BuMgBr to give mostly diastereomer **94** the answer is easy. Why yes, obviously the butyl group comes in on the less hindered side of the carbonyl **182a** which is the one opposite the R group.



182 **183** **182a**

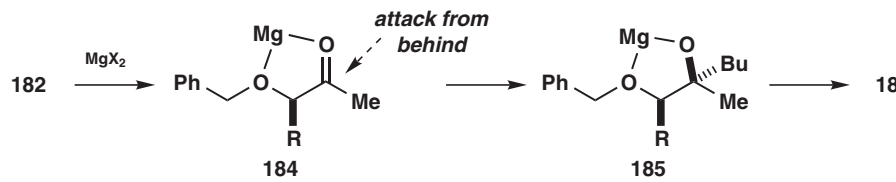
But of course, the exact same question could be asked with the structures merely drawn in an alternative conformation **182b** and **183a**. Sticking with the same enantiomer we now find that attack still occurs from behind even though that is now from the same side as the R group.



182b **183a** **182c**

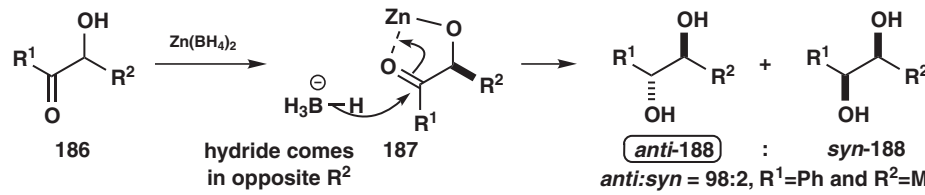
Something, somewhere must be controlling the conformation to give control of stereochemistry and just drawing the molecules in a convenient way is going to give the right answer only by chance. Chelation is the answer. In the example we've just seen, it is the magnesium of the Grignard that is doing the work. Both the oxygen atoms bind to it to lock the conformation of the

molecule **184**. The butyl group does indeed attack the ketone from the less hindered side (opposite the R group) and now we have a reason why.

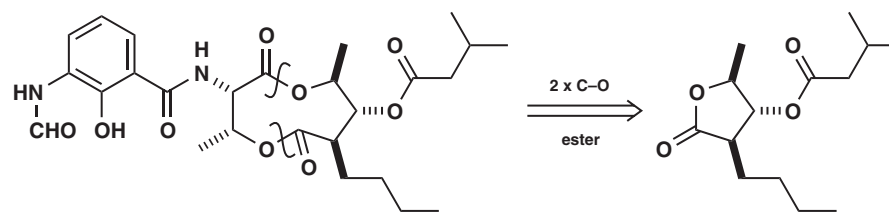


Zinc borohydride

Chelation control of this kind is commonly exploited in reduction and a favourite reagent is zinc borohydride[45] [$Zn(BH_4)_2$]. As with the Grignard, we need a second oxygen atom to do the binding. It works well with α-hydroxyketones **186**. Generally speaking, the *anti* diastereomer will be favoured. We can draw a conformation where the oxygen atoms are on the same side of the molecule both bound to the zinc **187**. The hydride will then be delivered from the less hindered side of the molecule. If R^1=Ph and R^2=Me, the ratio *anti:syn*-**188** is 98:2.



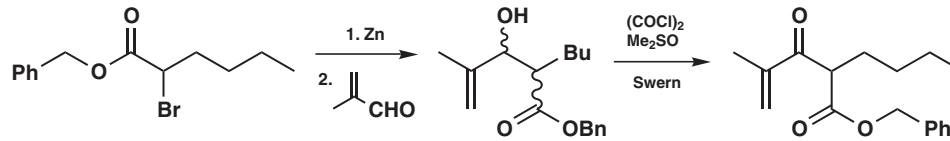
A similar sort of thing can be achieved with β-ketoesters where the major product is the *syn* diastereomer as we shall see in the example given below. Interestingly, $Zn(BH_4)_2$ does not generally work very well with β-hydroxyketones. But there are other very powerful methods available for that sort of transformation which we have see already. Both the reduction of a β-keto ester and an α-hydroxy ketone are put to use in the synthesis of racemic blastmycinone[46] **190** – a key fragment of blastmycin **189**.



189; (±)-blastmycin

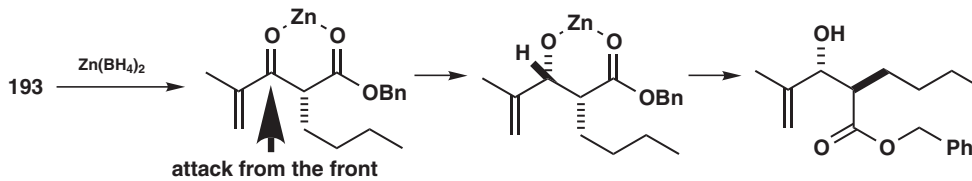
190; (±)-blastmycinone

The synthesis of blastmycinone begins with a Reformatsky reaction. Although the resulting allylic alcohol **192** is a required intermediate, it is formed in this reaction without any stereocontrol. The alcohol **192** is oxidised in a Swern reaction to the enone **193** only to be resurrected in the next reaction but this time with stereocontrol.



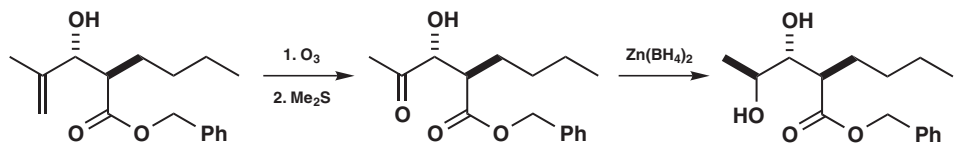
191 192 193

The ketone **193** is reduced with $Zn(BH_4)_2$ via the chelate **194**. In the enantiomer drawn, the hydride attacks the molecule on the opposite side from the butyl group. After hydrolysis of the zinc chelate of the product **195** the molecule is drawn as we have drawn it before **196** but in the reacting conformation **194** both the oxygen atoms are on the same side of the molecule because they are chelating the zinc atom.



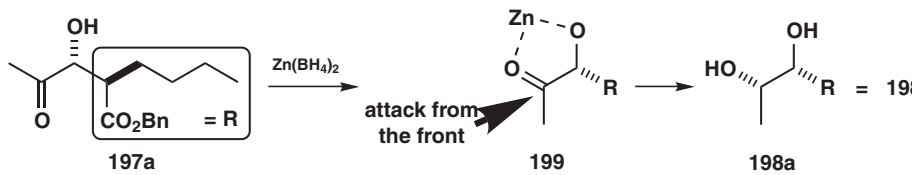
194 195 196

The first new stereocentre is thus taken care of. Next another carbonyl is revealed **197** by ozonolysis of the double bond. We are now in a position to introduce with control the second stereo-centre using the one we have just made!



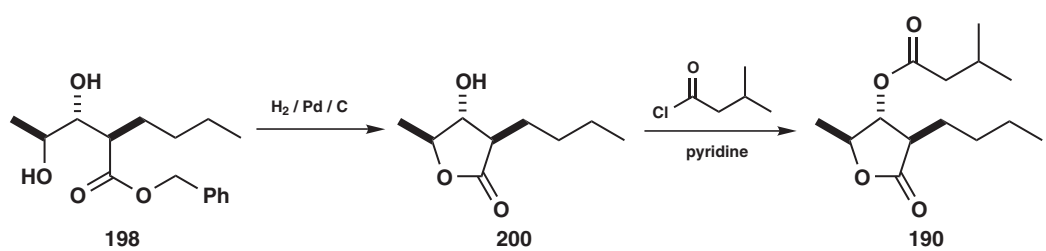
196 197 198

This time chelation is with the ketone and the hydroxyl group **199**. The chelate **199** is drawn without the ester group for clarity and note (once again) that the oxygen atoms are on the same side because they chelate the zinc atom and that attack occurs opposite the side chain.



197a 199 198a

The benzyl group is removed by hydrogenation which leads, by spontaneous ring closure, to the lactone **200**. The synthesis is completed by esterifying the remaining hydroxyl group.



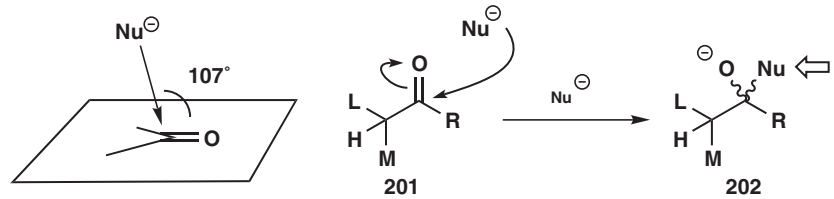
198 200 190

Open Chain Chemistry - in its Most Genuine Form

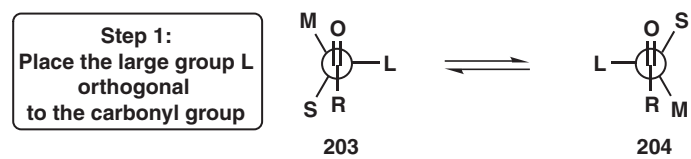
The most genuine form of open chain chemistry has no chelation to hold things in rings. But there must be something controlling the conformation or there would be no control. We look at two examples – the addition of nucleophiles to acyclic ketones and the addition of electrophiles to alkenes.

Felkin control over reactions of nucleophiles with carbonyl compounds

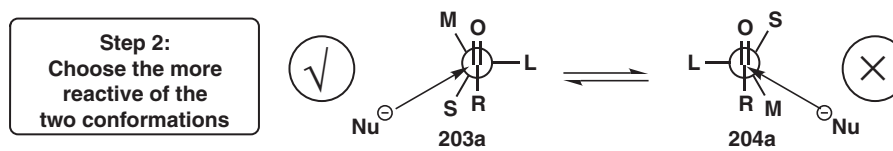
We need to consider firstly the line of attack nucleophiles use in approaching carbonyl groups. The nucleophiles come in to the C=O bond at an angle close to the tetrahedral angle of 109° and not just at 90°. We shall see that this is significant. This is often referred to as the Bürgi-Dunitz trajectory from the work by Bürgi and Dunitz who found an angle of 107° from crystal structures where a nitrogen atom approached a carbonyl group.[47] Theoretical values are not wildly different.[48] Imagine nucleophilic attack **201** on a carbonyl compound with a stereogenic centre next door. We will call the groups L (for large) and M (for medium). The hydrogen can be S (for small). What influence will the old chiral centre have on the newly forming chiral centre?



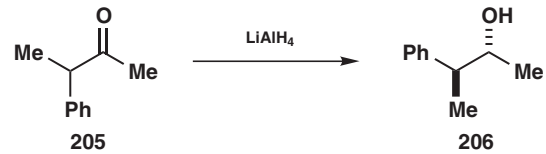
We view the molecule from the carbonyl carbon down towards the chiral centre which gives us a useful (Newman) projection of the molecule. The most comfortable conformation for the molecule is with the larger group being at 90° to the carbonyl functional group. The two rotamers with this conformation are **203** and **204**.



The nucleophile will come in opposite the large group and it would rather come in alongside the small group **203a** (which is often a hydrogen atom) than alongside the medium group **204a**. We see now why 107° is significant. The model indicates that, as far as the nucleophile is concerned, there would be no difference between the rotamers if the nucleophile came in at 90° as it would come in between (rather than alongside) the M and S group.

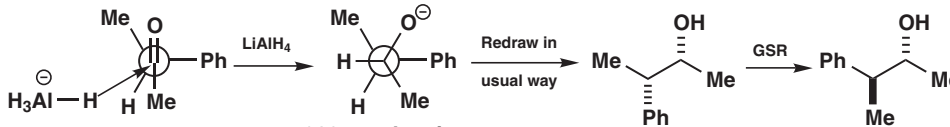


Consider then, the reduction of ketone **205** with $LiAlH_4$. Unlike some of the reductions we have seen so far in this chapter, there are no coordinating sites in the rest of the molecule for chelation control of any kind. The result of the reduction is alcohol **206** complete with stereocontrol.



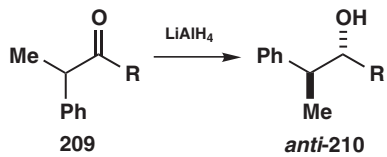
205 206

And now the explanation. The phenyl group is the largest group and sits at 90° to the carbonyl. Attack is alongside H **207**. When working through the stereochemistry it is helpful to draw the result with a Newman projection before drawing the molecule in the standard way. In redrawing we have then performed a GSR (Chapter 20) to reveal that we have *anti* **206**.



207 208; product in Newman Projection 206a *anti*-206

The selectivity improves if the group adjacent to the carbonyl is increased in size.[49] Diastereoselectivity can be further improved by lowering the temperature. The 98% (i.e. 49:1) selectivity that is observed when R=*tert*-Bu is increased to 99.8% when the temperature is lowered from 35 °C to −78 °C.

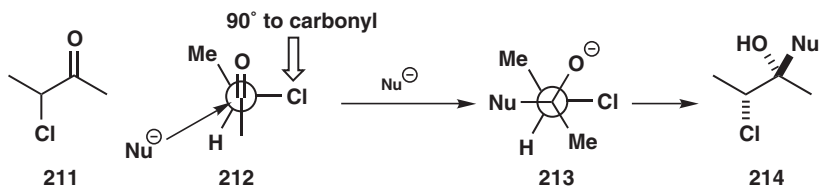


209 *anti*-210

R	Me	Et	*i*-Pr	*t*-Bu
***anti : syn* ratio**	**2.8:1**	**3.2:1**	**5:1**	**49:1**

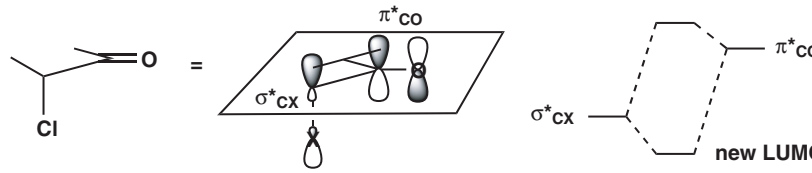
Role of electronegative substituents

Another thing to consider is the role of electronegative substituents. These can interact with the carbonyl in an electronic way (as opposed to steric). They too have a tendency to sit at 90° to the carbonyl. So the α-chloroketone **211** reacts with nucleophiles **212** to give the adduct **213** and hence the alcohol **214** with the nucleophile *anti* to the OH group.



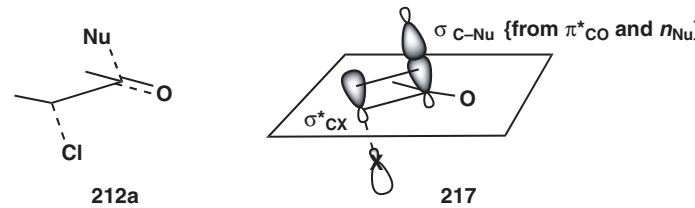
211 212 213 214

The explanation for this depends upon the interaction of orbitals and there are a couple of ways of looking at this. One way is to think of the π^*_{CO} orbital interacting with the σ^*_{CX} orbital to give an even lower antibonding orbital[50] **216**. This overlap can occur only if the orbitals are correctly aligned **215** and this will occur when the substituent is at 90° **211a**. There are no electrons in this orbital of course, so the benefit from the overlap will only occur once the nucleophile starts to feed in electrons.



211a **215** **216**

The other argument (or the other part of the same argument) applies when the nucleophile has already started to attack **212a**. The σ-bond between the nucleophile and the carbonyl carbon is partly formed (σ_{C-Nu}). Once again, this can overlap with the σ^*_{CX} orbital **217** to lower the energy a bit further.[51] The angles of the orbitals are slightly different because the attack has started.

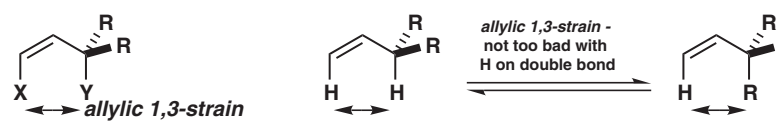


212a **217**

These explanations talk about the position of the electronegative atom just before the reaction happens or as the reaction is happening (and are thus concerned with the ground state or the transition state of the reaction). The electronegative atom may or may not be at 90° in the ground state but who cares – it is where it is when the reaction is happening that counts!

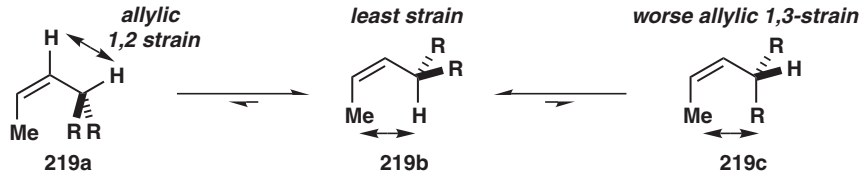
The Houk conformation for reactions of alkenes with electrophiles

The Houk conformation depends upon allylic 1,3 strain so we will look at this first.[52] The strain we are concerned with is between substituents on the double bond with substituents at the allylic position. They will be in the same plane for the strain to be present **218**. When the substituent on the double bond is merely a proton, the allylic 1,3 strain is not too bad between the proton and a larger group. About 25% of the conformations will have the proton and the substituent in the same plane **218b** but the rest will have two hydrogens in the plane **218a**.

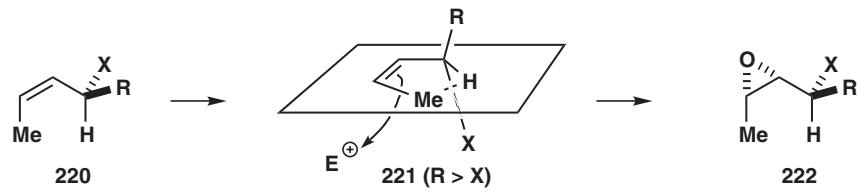


218 **218a; 75%** **218b: 25%**

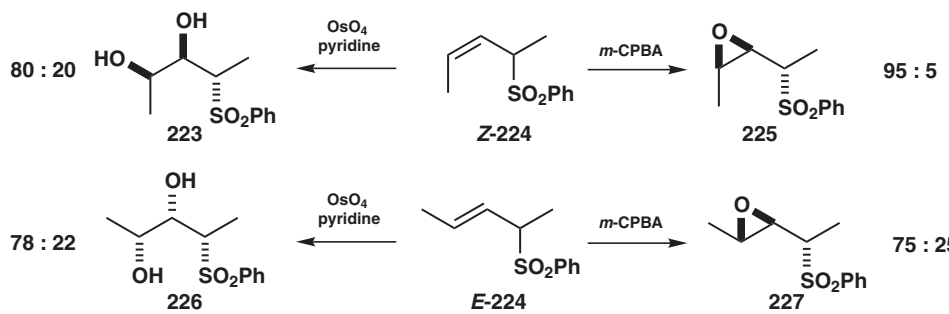
This changes significantly when the substituent on the double bond is something larger. Even with a methyl group then the only significant conformation **219b** will have the proton eclipsing the methyl group. And, just in case you are wondering, the methyl group will *not* prefer to stagger itself between the two larger groups **219a**. This is because it would result in allylic-1,2 strain on the other side of the molecule. Allylic-1,2 strain is very bad news, worse than allylic 1,3-strain, even between two protons. Conformations **219b** and **219c** have no 1,2-strain but **219c** has worse allylic 1,3-strain than **219b**. Since we have only one significant conformation, this is the only one we need to consider for reactions. It is known as the Houk conformation.



If R is larger than X in **220** we can expect electrophilic attack on the double bond to occur opposite R **221**. If the electrophile were a peroxyacid, the product would be the epoxide **222**.

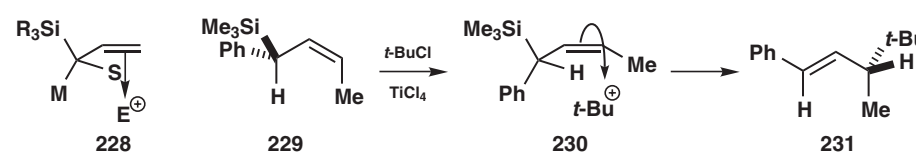


Epoxidation of the *cis* allyl sulfone ***Z*-224** gives the stereochemical outcome we would expect from a Houk conformation.[53] The selectivity with the *trans* compound ***E*-224** is less good – also as we would expect. Things are rarely quite so simple as this of course and dihydroxylation of the same substrates gives rise not only to reduced selectivity but a reversal in stereoselectivity **226**.

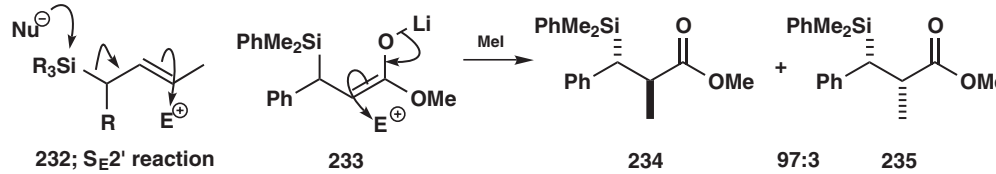


Allyl silanes

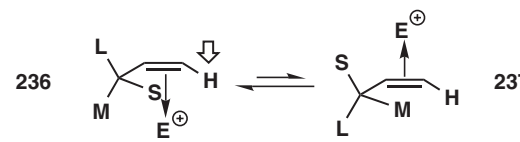
The steric interactions that go into controlling the Houk conformation can be reinforced by electronics in the case of allyl silanes (or other σ-donors instead of silicon).[54] The silicon substituent is large and also electron donating. We have already learned about β-cations being stabilised by silyl groups. From a Houk point of view we can expect electrophiles to react as shown in **228**. The small group (S) is in the plane of the double bond and the large group (L) is usually the silyl group. Hence reaction of **229** leads to **231** by attack of the electrophile (*t*-Bu^+) on the opposite side to the Me_3Si group in the Houk conformation **230** (an example of chirality transfer) and the usual loss of silicon from the β-cation.



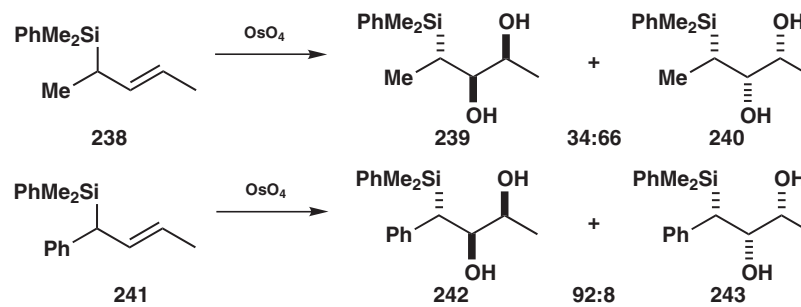
Reaction with electrophiles can be by S_E2' reaction **232** as in the last example but the other end of the double bond can react if it is part of, for example, an enolate **233**. Reaction of **234** is an example of the latter and highly stereoselective.



If the group on the double bond is merely a proton **236** then it is possible for the medium group to move into the plane **237** so long as the medium group is itself quite small (typically a methyl group). Although this **237** would not be the major conformation, it allows the electrophile to react alongside the small group.



For large electrophiles, which clearly have difficulty coming in alongside the medium group, this selectivity is observed and illustrated by the reaction of **238** with OsO_4 (large) to give mostly **240**. However, once the medium group is made a bit larger (Ph instead of Me) there is a return[53] to the selectivity expected by **236**. The reactivity depicted in **237** is not expected if the double bond has anything larger than a proton *cis* to the chiral centre – the allylic strain would be too great.



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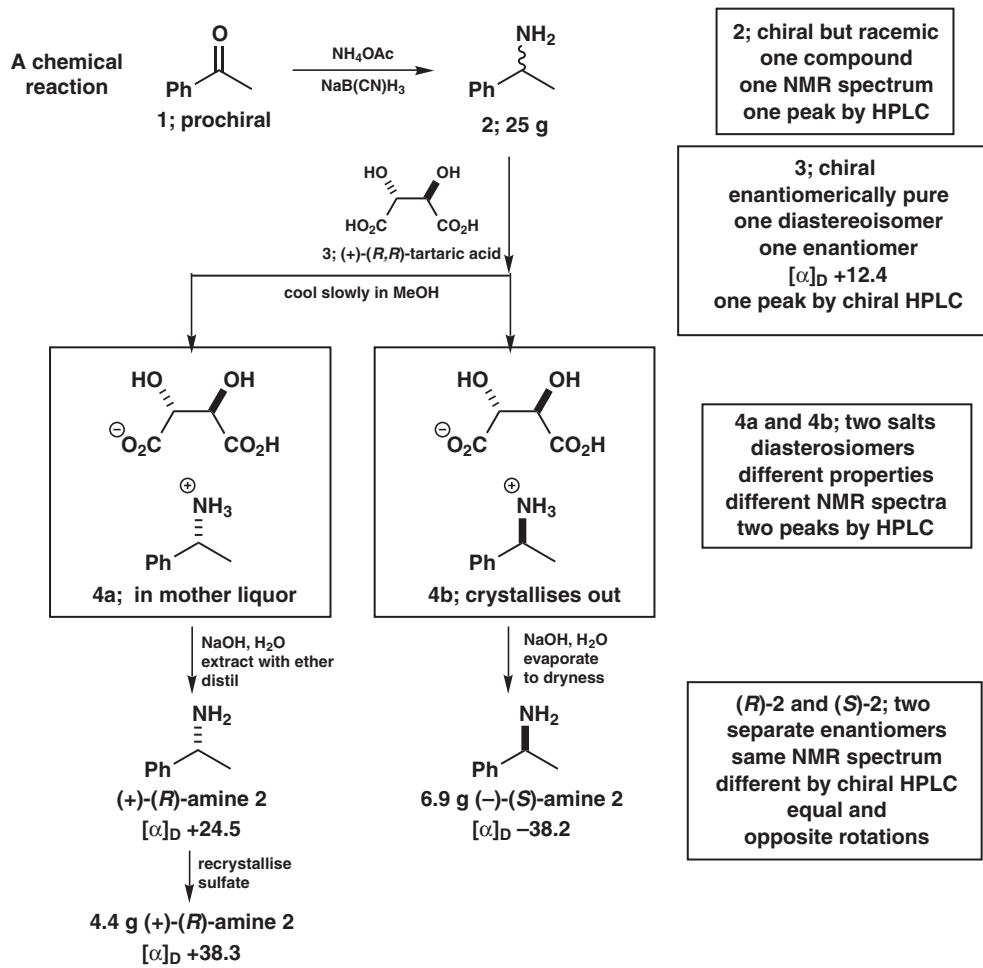
22 Resolution

Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

Resolution

Introduction and an example (1-phenylethylamine)

Resolution is the separation of a racemic compound into its right and left handed forms. In the world at large it is an operation we carry out whenever we sort chiral objects such as gloves or shoes. Simply inserting your right foot into any shoe tells you at once whether it is a left or right shoe: the combination of right foot and right shoe has different physical properties (it fits) to the combination of right foot and left shoe (it hurts). Resolution also needs a "right foot", a single enantiomer of a resolving agent which we combine with the racemic compound to form a 1:1 mixture of diastereoisomers. These will probably have different physical properties so that any normal method of separation (usually crystallisation or chromatography) separates them; removal of the resolving agent then leaves the optically active target molecule. We shall begin with a classical resolution - almost *the* classical resolution.[1]



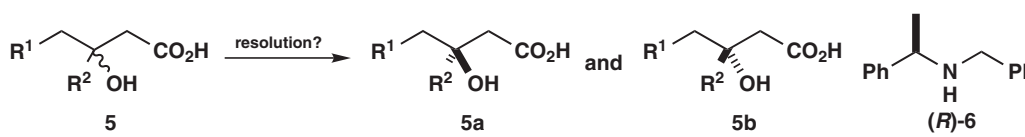
The amine **2** is made by a chemical reaction - the reductive amination of ketone **1**. The starting material **1** and the reagents are all achiral so the product **2**, though chiral, *must* be racemic. Reaction with one enantiomer of tartaric acid **3** forms the amine salt **4**, or rather the amine *salts* **4a** and **4b**. Examine these structures carefully. The stereochemistry of tartaric acid **3** is the same for both salts but the stereochemistry of the amine **2** is different so these salts **4a** and **4b** are diastereoisomers. They have different physical properties: the useful distinction, discovered by trial and error, is that **4b** crystallises preferentially from a solution in methanol leaving **4a** behind in solution. Neutralisation of **4b** with NaOH gives the free amine (*S*)-**2**, insoluble in water and essentially optically pure.

Crystallisation doesn't remove all of **4b** from solution so the mother liquor contains mostly **4a** with some **4b**. This is clear when the solution is neutralised and the free amine **2** isolated from it by distillation. The rotation has the opposite sign to that of (*S*)-**2**, but is smaller. Recrystallisation of the sulfate salt brings the rotation to the same value as that of (*S*)-**2**, but with the opposite sign and we have a sample of pure (*R*)-**2**. You may feel that we have laboured this very simple resolution but it is important that you understand this process before continuing not only this chapter but all this section - chapters 22–31. The amine **2** is itself an important compound as you will see in the next section.

Choice and Preparation of a Resolving Agent

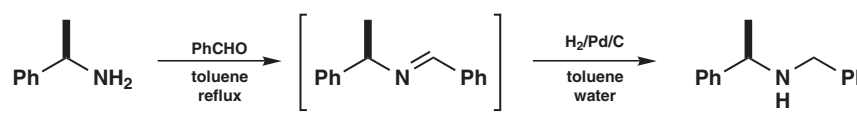
Resolving a hydroxy-acid on a large scale

Chemists at Parke-Davis have been making hydroxy acids of the general structure **5** in their development of an HIV protease inhibitor and they sought a method of resolution that would give them both enantiomers.[2] The obvious resolving agent would be a single enantiomer of some kind of amine so that a salt would be formed between the resolving agent and the carboxylic acid **5**. This would be the reverse of the resolution we have just seen. They tried many amines including **2**, but the best by far was **6**. The salts between **5** and **6** were easily crystallised, the separation of the diastereoisomers was straightforward, and the yield and % ee of the recovered **5** was excellent.



5 **5a** **5b** (*R*)-**6**

Now a difficulty emerged. They wanted to carry out the resolution on a large scale but enantiomerically pure **6** is expensive. The solution was to make it themselves from previously resolved cheap **2**. The obvious route is reductive amination using benzaldehyde and the only danger is racemisation of the intermediate imine **7**. They found that the imine **7** did not racemise as it was prepared in toluene but that some racemisation took place when $NaB(CN)H_3$ was used for the reduction. The solution was to use catalytic hydrogenation and they prepared 53 kg batches of optically pure **7** in 98% yield by this method and used that to resolve the hydroxy acid **5**.

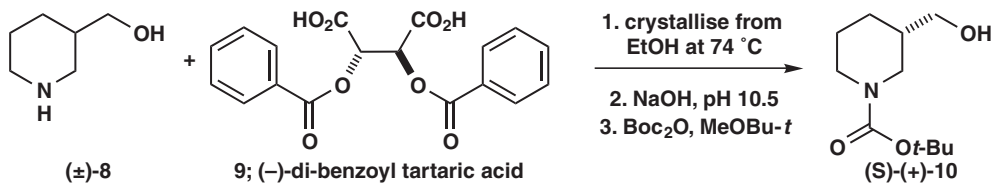


(*R*)-(+)-**2** imine **7** (*R*)-**6**

The preparation of **6** is not a resolution but the starting material **2** was prepared by a resolution and enantiomerically pure **6** was used in a resolution. This sequence of identifying the best resolving agent and then preparing it from a resolved starting material is standard practice. You will meet the lithium derivative of compound **6** in chapter 26 as a chiral reagent. In the past many racemic acids were resolved using toxic alkaloids such as strychnine. Nowadays simple amines such as **2** or **6** are preferred. **Top Tip:** If you need to resolve an acid, try first amine **2** or some derivative of it such as **6**.

Resolving a hydroxy-amine on a large scale

The Bristol-Meyers Squibb company wanted the simple heterocycle **8** for the preparation of a tryptase inhibitor. As **8** is an amine, tartaric acid was the first choice for a resolving agent. It again turned out that a modified version of the first choice was the best. Tartaric acid is so good at resolutions that simple variations, such as the dibenzoate ester **9**, often work well.



(±)-8 9; (–)-di-benzoyl tartaric acid (S)-(+)-10

In this instance, the exact proportions of the resolving agent and **8** and the purity of the crystallisation solvent were important in getting good results.[3] After one crystallisation, the ee of the salt was about 50% but this improved by 10-15% with each recrystallisation and reached >99% after five recrystallisations. By then the yield had dropped to 30% from a theoretical maximum of 50%. For the next stage in their synthesis, they really needed the Boc derivative (*S*)-(+)-**10** so the salt was directly converted to **10** in >99% ee on a 50 g scale. You will see later in this chapter that an enzyme can be used to do the same resolution.

These two examples, **5** and **8**, show that with two functional groups in a molecule it is better to choose the one that can form a salt (here CO_2H and R_2NH) rather than the OH group as it would be necessary to make a covalent compound to use that group.

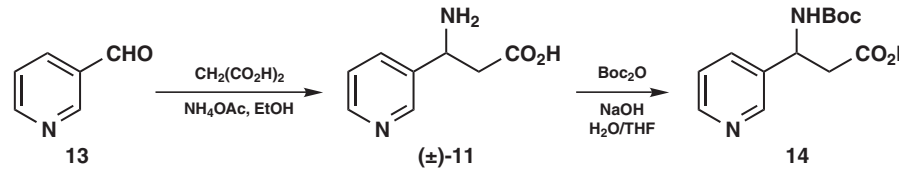
Resolving an amino-acid on a large scale

Other companies (Cilag AG and R. W. Johnson) required the pyridine-containing β-amino acid **11** or, to be more accurate, the ester dihydrochloride[4] **12**. This combination of acidic and basic functional groups offers a wide choice of resolving agents.

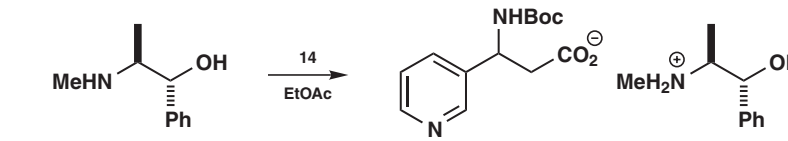
11 12

The synthesis of the racemic compound is interesting and relevant. The simple aldehyde **13** could be combined with ammonia and malonic acid all in the same operation to give racemic **11**.

One of the functional groups now should be protected so that the other can be used for the resolution and the amine was blocked with a Boc group to give **14**.

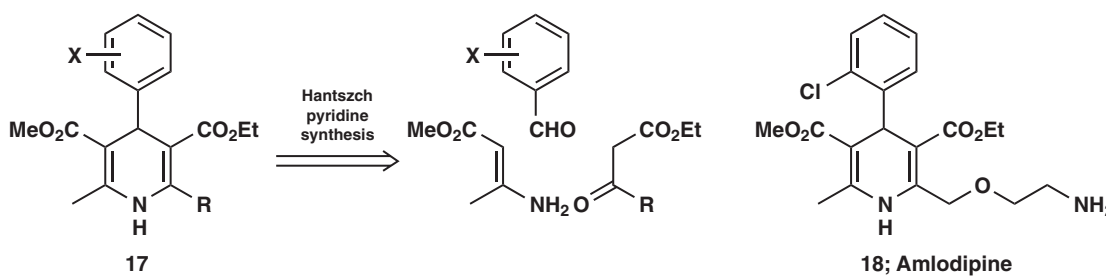


The best resolving agent was also a bifunctional compound, the natural amino alcohol ephedrine **15**. Mixing **14** with ephedrine in warm ethyl acetate gave an immediate precipitation of the salt **16**. The crude salt already had an ee of around 90% but one recrystallisation again from ethyl acetate gave pure salt **16** in 42% yield and >98% ee. Conversion to **12** required merely neutralisation (NaOH) and reaction with HCl in MeOH to remove the Boc group and make the methyl ester. The product **12** was isolated on a large scale in 82% yield with >98% ee. This is a spectacularly successful resolution.

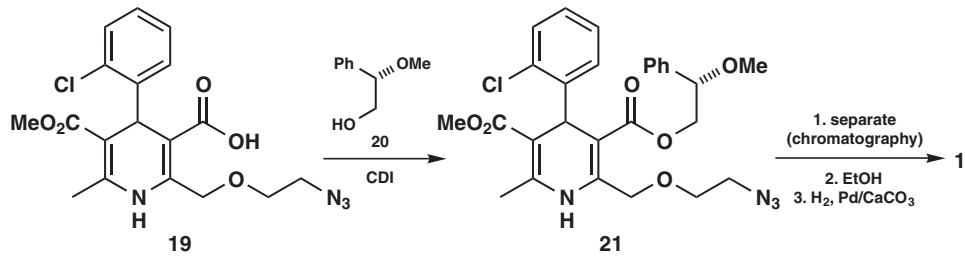


Resolution via covalent compounds

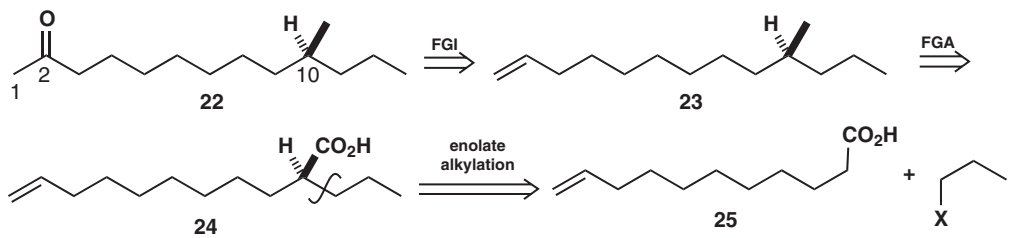
The calcium channel blocking dihydropyridine drugs **17**, used in the important field of heart disease and easily prepared by the Hantszch pyridine synthesis, are chiral but 'only just.' The molecule does not quite have a plane of symmetry, because there is a methyl ester on one side and an ethyl on the other and because R may not be Me. An important example is amlodipine **18**, a best seller from Pfizer, and this is more asymmetrical than some. Nevertheless resolving these compounds is difficult.



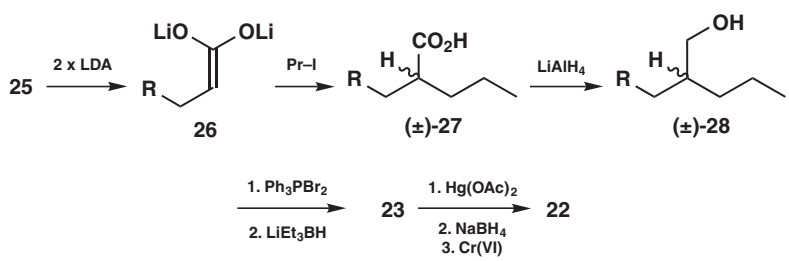
The method published by Pfizer[5] relies on the formation of an ester **21** of an intermediate carboxylic acid **19** with the alcohol **20** derived from available mandelic acid and the separation of the diastereoisomers by chromatography rather than crystallisation. We can assume that the classical crystallisation of diastereoisomeric salts was not successful. Removal of the ester was simplified as a transesterification. CDI is carbonyl-di-imidazole.



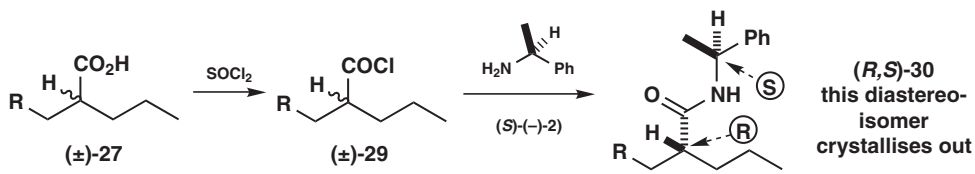
The second example of resolution via a covalent compound also involves a decision about when to resolve. Ketone **22** is the pheromone of the southern corn rootworm. It has the one functional group and one stereogenic centre in a 1,9 relationship. Disconnection was guided by the long distance between the ketone and the stereogenic centre and by the availability of undecenoic acid[6] **25**. The ketone is changed to an alkene and the 10-methyl group to CO_2H to allow disconnection to a readily available starting material **25**.



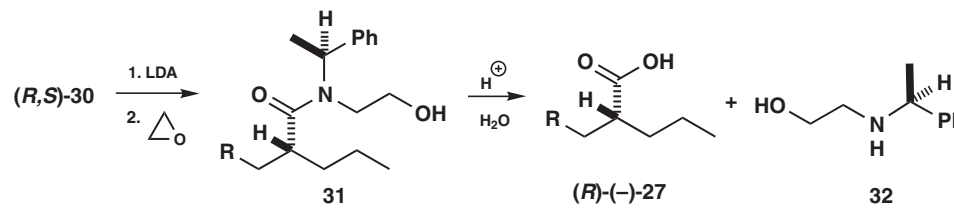
We need to add a propyl group to the di-lithium derivative **26** (chapter 2), reduce the CO_2H group to CH_3, and convert the alkene into a ketone by the mercuration-reduction sequence described in chapter 17.



The CO_2H group also helps resolution. Amide formation with the amine (*S*)-(−)-**2** gave the amide **30** - a likely crystalline derivative. It is of course impossible to predict with certainty which compounds will crystallise, and particularly which diastereoisomer will crystallise. It turns out that (*R,S*)-**30** crystallises out, leaving (*S,S*)-**30** in solution. Recrystallisation purifies this diastereoisomer until it is free from the other.



The resolving agent must now be removed by hydrolysis of the amide. This is a risky business as enolisation would destroy the newly formed stereogenic centre, and a cunning method was devised to rearrange the amide **30** into a more easily hydrolysed ester by acyl transfer from N to O. The rest of the synthesis is as before. By this means the alcohol **28** was obtained almost optically pure, <0.4% of the other enantiomer being present. No further reactions occur at the newly formed stereogenic centre, so the absolute chirality of **22** is as shown.



Advantages and Disadvantages of the Resolution Strategy

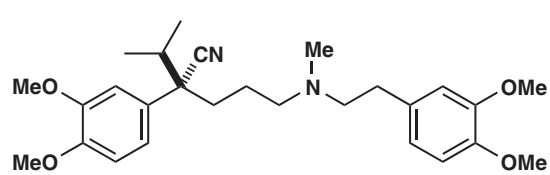
These examples expose the main weakness of the resolution strategy: the maximum yield is 50% as half the chiral molecule **2**, **6**, **8**, **11**, **19**, or **24** must be the wrong enantiomer. In addition, extra steps are needed to add and remove the resolving agent and, in the removal of the resolving agent, racemisation is a danger. There are advantages too: in principle you get both enantiomers of the target molecule so if you are making a chiral auxiliary, or don't know the structure of a natural product, or want to investigate the relationship between biological activity and stereochemistry, all situations where having both enantiomers is a distinct advantage, resolution may be the best strategy. You can minimise the disadvantages by resolving as early as possible: that way there is least waste of time and materials. In favourable cases you can neutralise either or both disadvantages, as we shall see soon. The maximum yield may be made 100% if the wrong enantiomer can be recycled. Some extra steps may be avoided if no covalent compound is formed at all.

However, the fact remains that, even in the 21st century, most drugs that are sold as single enantiomers are manufactured by resolution. When you see a paper about the preparation of a single enantiomer that has in its title words like 'practical' 'expedient' or 'efficient' you may guess that resolution is going to be used. This situation will change. Asymmetric methods, the subjects of chapters 26–28, particularly the catalytic methods, gain in efficiency and ease of operation every year and are likely to become steadily more important.

When to Resolve

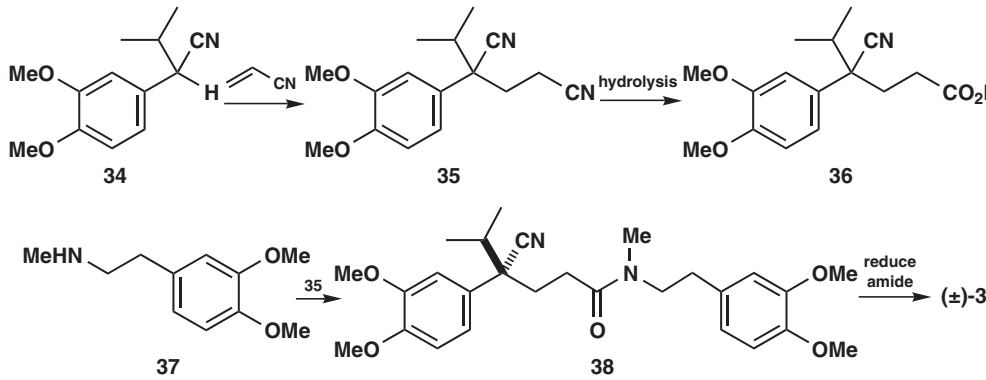
General rule: resolve as early as possible

Verapamil **33** is used in the treatment of cardiovascular disease. An asymmetric synthesis by the resolution strategy would normally be planned around a synthesis of the racemic compound and the important decision would be: when do you resolve?



33
verapamil

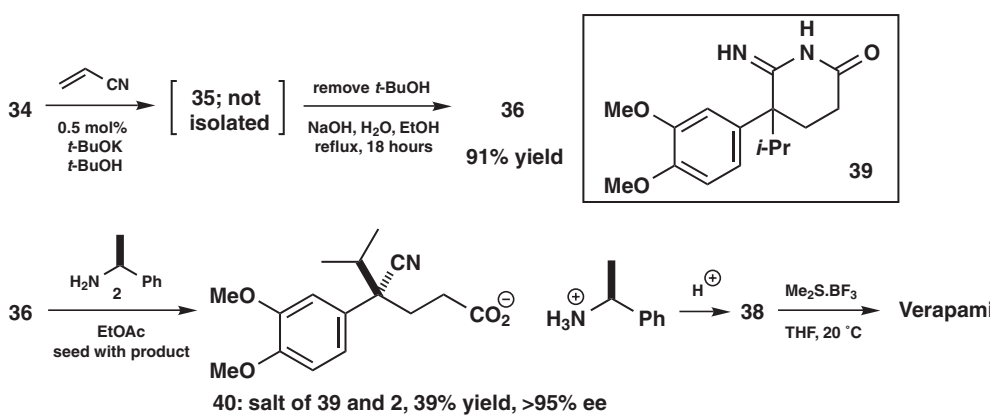
The most satisfactory answer is 'as early as possible'. If the starting material can be resolved then nothing is wasted. If the final product is resolved then half of the starting material, the reagents, energy, time and so on is wasted. And probably more than half; for few resolutions produce even close to 50% yield of the wanted enantiomer. Here is the outline racemic synthesis of verapamil without distracting details - where would you resolve?



These are the questions you should ask, and the answers in this case:

1. What is the first chiral intermediate?
   Answer: the starting material **34**.
2. Is it a suitable compound for resolution?
   Answer: No doubt it could be resolved, though a nitrile is not particularly convenient, but the chiral centre is immediately destroyed in the next reaction. No.
3. Which is the first intermediate that can be conveniently and safely resolved?
   Answer: The carboxylic acid **36**. It has a very helpful functional group and the chiral centre, being quaternary, is secure from racemisation.
4. Do any reactions occur later in the synthesis that might racemise the molecule?
   Answer: No. The one chiral centre is unchanged in the rest of the synthesis.

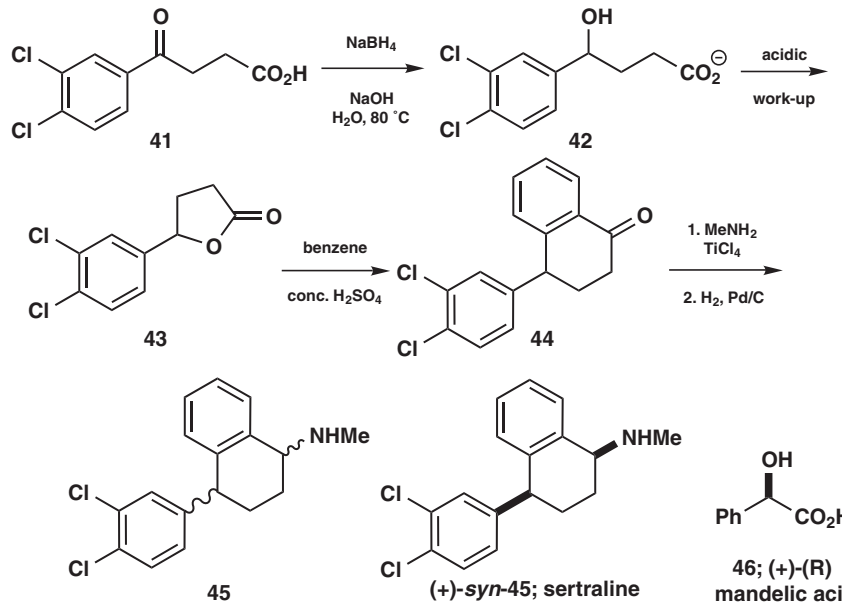
We already have a good idea how to resolve a carboxylic acid by making a salt with an enantiomerically pure amine. In this case the first amine you think of, phenylethylamine **2**, works very well. Here is the asymmetric synthesis, carried out on a 50–100 g scale at Celltech.[7] The hydrolysis of the dinitrile **35** is chemoselective because the intermediate **39** is formed. The salt with **2** crystallises in good yield (39% out of a possible 50%) and in excellent ee.



40: salt of 39 and 2, 39% yield, >95% ee

Resolution of Diastereoisomers

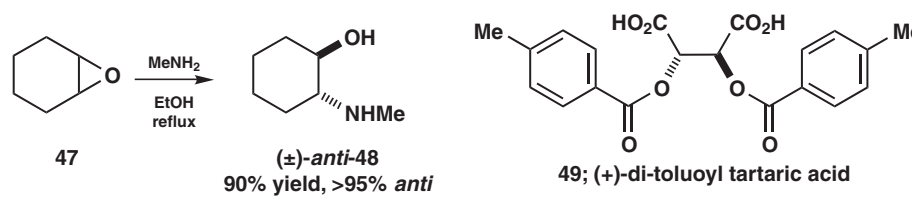
When the compound itself contains more than one chiral centre the question of diastereoisomers takes precedence over that of enantiomers. Resolution is normally performed on the wanted diastereoisomer rather than on the mixture. In the case of sertraline **45**, an anti-depressant that affects serotonin levels in the brain, the active isomer was not known when both diastereoisomers were prepared by a unselective route.[8] The starting material **41** was made by a Friedel-Crafts reaction between 1,2-dichlorobenzene and succinic anhydride.



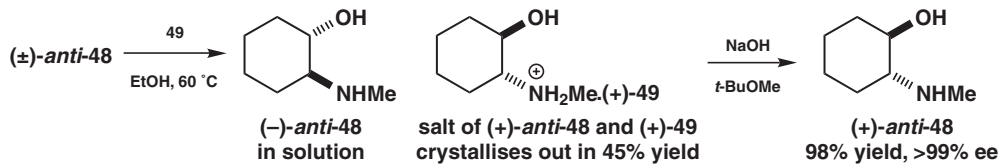
Separation of the *syn* and *anti* diastereoisomers by crystallisation of the HCl salt revealed that it was the *syn* diastereoisomer that was active and the reductive amination of **44** could be controlled to give 70% *syn*-**45**. The diastereoisomers of **45** were separated before the resolution. There is no point in resolving any earlier compound in the synthesis as even more material would be wasted in the reductive amination step. Natural (−)-(*R*)-mandelic acid **46** was a good resolving agent for **45** and 50% of the material derived from **44** could be isolated as the active (+)-*syn*-(1*S*,4*S*)-**45**.

Resolution of compounds made as diastereoisomeric mixtures

It may be possible to prepare the correct diastereoisomer, assuming that this is known, by stereoselective synthesis and avoid the problem. The *anti* isomer of the amino alcohol **48** can be prepared from cyclohexene oxide **47** in high yield and with minimal contamination (<3%) of the *syn*-diastereoisomer.[9]

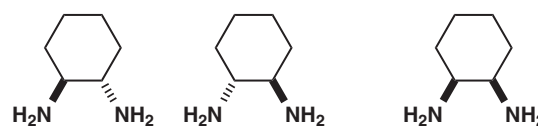


Resolution with tartaric acid **3** required up to seven recrystallisations to get pure material and by that time the yield was only 8%. Di-*p*-toluoyl tartaric acid **49** (cf **9** used earlier) was spectacularly better when used in the right proportions (4:1 **48:49**). The solubility of the required diastereoisomer as the salt of one molecule of (+)-**49** with two molecules of (+)-**48** was very much less than that of (+)-**49** with two molecules of (−)-**48** so that merely mixing **48** and (+)-**49** in the right proportions in ethanol at 60 °C for twenty minutes, cooling, and filtering off the crystals gave a 45% yield in >99% ee. Neutralisation with NaOH and extraction with *t*-BuOMe gave pure (+)-**48**.

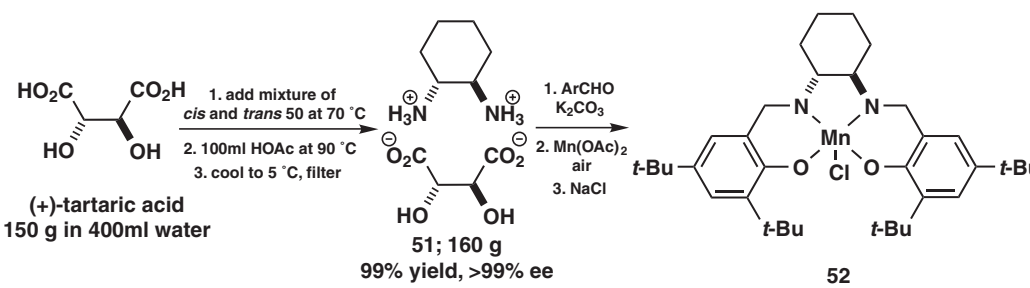


The synthesis of Jacobsen's Mn(III) epoxidation catalyst by resolution

Possibly the easiest resolution known is of the related *trans* diaminocyclohexane **50**, used to make the catalyst for Jacobsen's asymmetric epoxidation (chapter 25). It is not even necessary to separate the diastereoisomers first and this is a big advantage as the commercial mixture of about 40:60 *cis* and *trans*-**50** costs about one tenth of the pure racemic *trans* and about one hundredth of the resolved *trans* isomer. You can usually tell if a commercial product is made by resolution as the two enantiomers cost about the same.

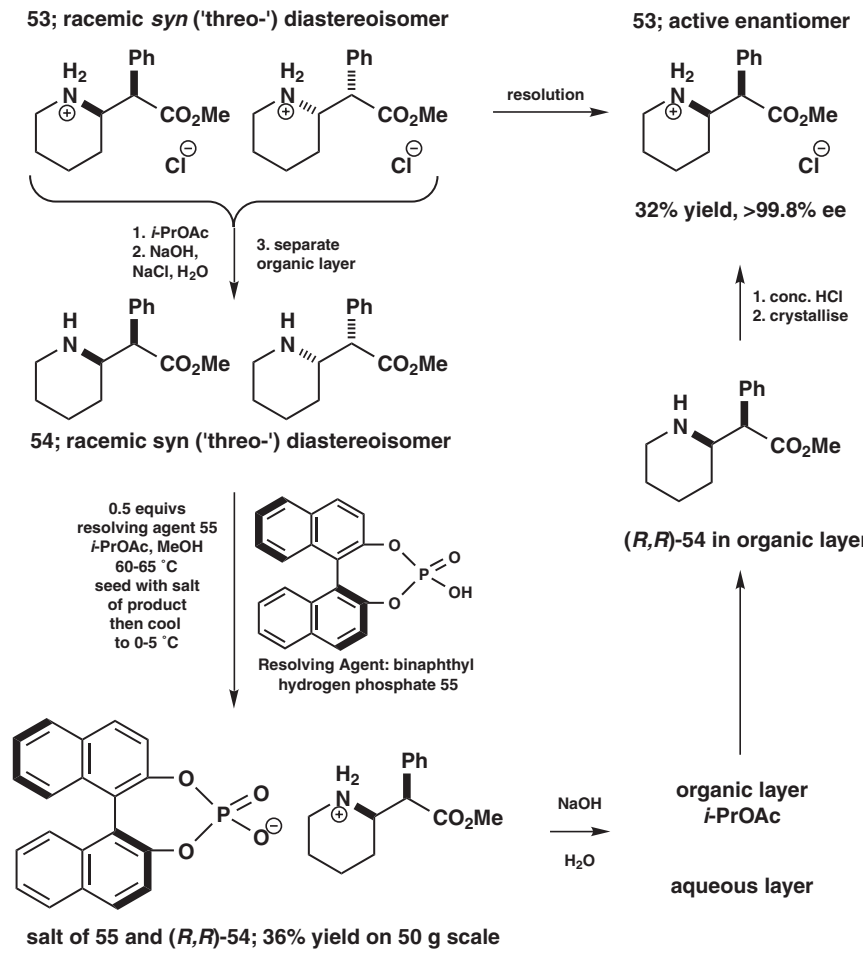


The resolving agent is tartaric acid: 150 g are dissolved in water in a litre beaker. Then 240 ml of the mixture of isomers of **50** is added at 70 °C followed by 100 mls acetic acid at 90 °C and the solution cooled to 5 °C. The pure salt **51** separates out in 99% yield - that is 99% of all that enantiomer originally present - and with 99% ee. This is almost incredibly good. Though the free *trans*-diamine **50** can be isolated from this salt, it is air-sensitive and it is better to make the chiral catalyst **52** directly from the salt as shown. The yield is better than 95% and the catalyst **52** can be made in multi-kilogram quantities by this resolution.[10]



Resolution with half an equivalent of resolving agent

Since only half the compound (the maximum amount of either enantiomer) crystallises out, it may seem extravagant to use a whole equivalent of resolving agent and in some cases the resolution is much better with only just enough to crystallise one enantiomer, as with **48**. A case in point is methylphenidate[11] **53**. The HCl salt of racemic *syn* **53** is marketed as 'Ritalin' for treatment of children with ADHD (attention deficit hyperactivity disorder). The resolving agent is unlike anything we have seen so far: an axially chiral BINOL-derived cyclic phosphate **55**. If the right amount is added to a solution of **54** to crystallise just one enantiomer a very good yield (38% out of 50%) of the salt can be isolated on a 50 g scale. Separation is now easier as one enantiomer is a salt and the other a neutral compound: simple solvent/solvent extraction is used. The active enantiomer, (*R,R*)-**53**, can be isolated in an overall yield of 32%.

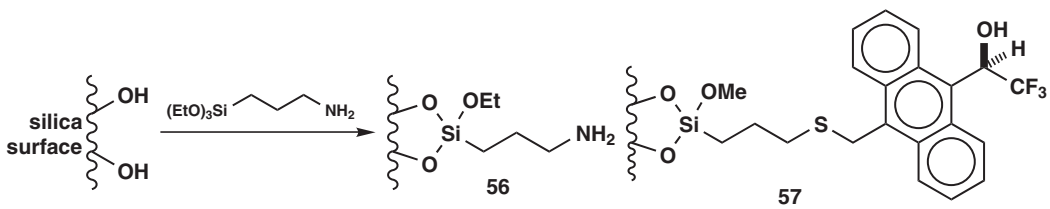


It is not possible to give a comprehensive guide to the essentially practical skill of classical resolution in this book. You are referred to the papers we quote and also to Eliel and Wilen, chapter 7, pages 297 to 441 for a fuller account. We must move on to other styles of resolutions particularly those that do not involve the separation of specially prepared diastereoisomers.

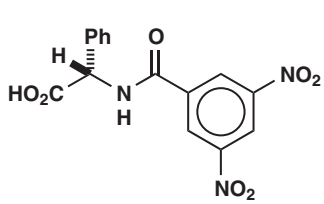
Physical Separation of Enantiomers

Chromatography on chiral columns

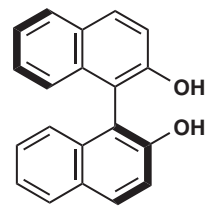
One good way to separate enantiomers physically is separation on a chiral chromatography column. There are now many of these available[12] usually consisting of silica functionalised with a linker such as a 3-sulfanyl- or 3-amino-propylsilyl group **56** to which are attached enantiomerically pure groups such as the covalently bound anthryl alcohol **57**. Separation occurs when suitable racemic compounds are passed down the column, usually in hexane containing about 10% *i*-PrOH. This method is one of the best ways to assess the enantiomeric purity of a compound and ees are routinely measured using chiral columns.



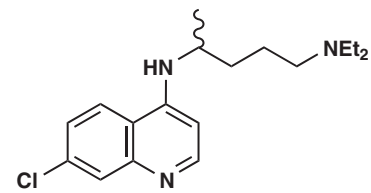
A column loaded with the amide **58** that is held in place merely by hydrogen bonds and electrostatic forces is used preparatively to resolve the important axially chiral binaphthol[13] **59**. You will meet compounds of this type as reagents and ligands in chiral catalysts in chapters 24–26.



58

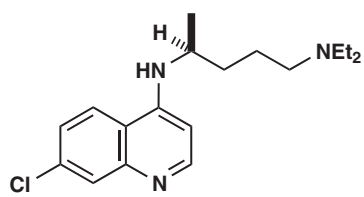


59; binaphthol

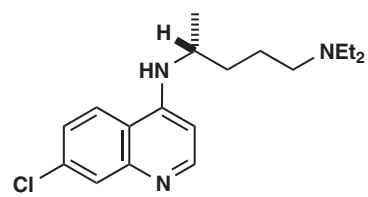


60; chloroquine

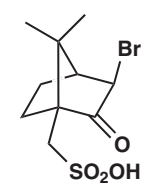
The anti-malarial compound chloroquine **60** is a salutary case. For many years it was thought that both enantiomers were equally active against the parasites that transmit malaria. This was because the only optically active samples available (rotations +12.3 and −13.2) were obtained by conventional resolution with bromocamphor sulfonic acid **61** and were of low purity.



(+)-(*S*)-chloroquine 60
$[\alpha]_D$ +12.6



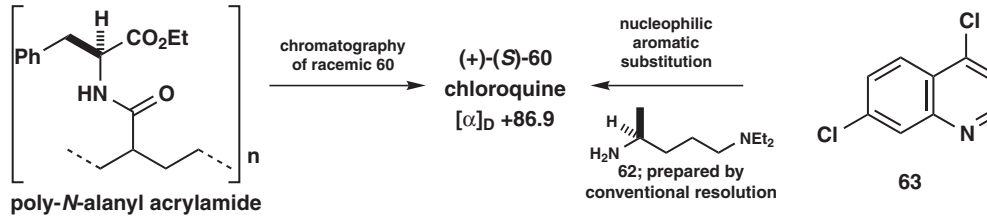
(–)-(*R*)-chloroquine 60
$[\alpha]_D$ –13.2



61; bromo-camphor sulfonic acid

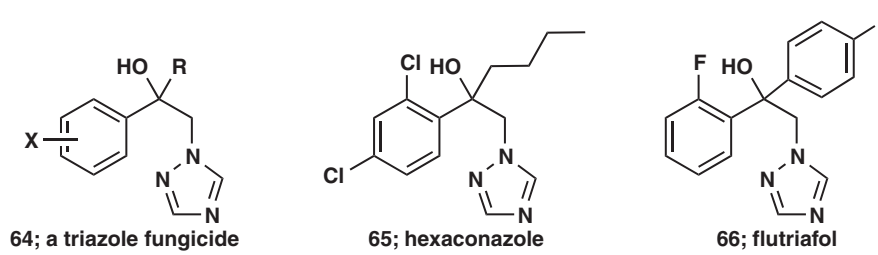
When the racemic compound was resolved on a poly-*N*-alanylacrylamide column, samples of rotation +86.9 and −86.9 showed not only that the (+) isomer of **60** was more active against

malaria, but that it also had fewer toxic side-effects. The active enantiomer is now made from the dichloroquinoline **63** and the enantiomerically pure diamine **62** prepared by conventional resolution.

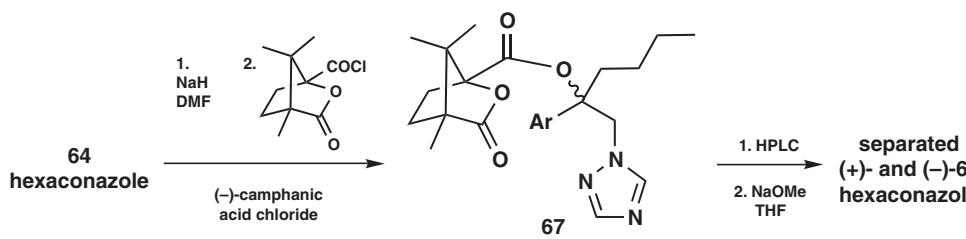


Resolution of triazole fungicides by HPLC

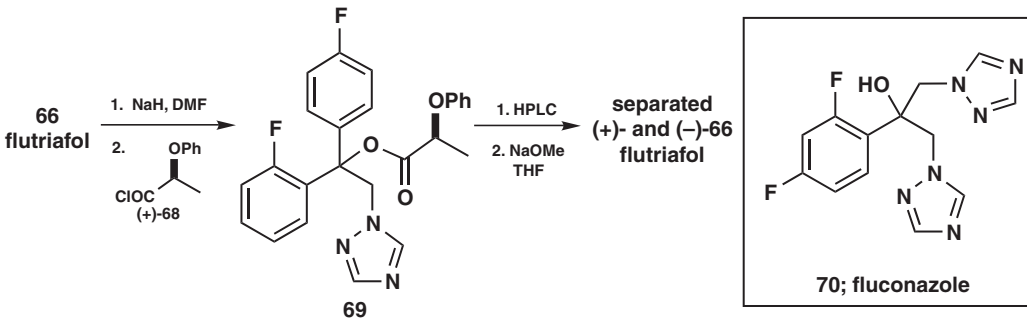
The triazole fungicides of general structure **64** such as hexaconazole **65** and flutriafol **66** are a rare case of human and plant medicine using similar compounds. They were initially used as racemates but it was soon essential to discover the active enantiomers. Conventional resolution by crystallisation of diastereomeric derivatives proved difficult.



The solution was to make the usual sort of diastereoisomers by acylation with camphanic acid chloride and to separate them by standard (not chiral) HPLC on Dupont 'Zorbax' columns. Only 60 mg was separated at a time but that was enough to accumulate grams of material. The craft needed in such separations is best illustrated by the solvent composition needed for good separation of **65**. You must use 918:80:2 of $F_3C\text{-}CCl_3$, MeCN, and Et_3N. The (−) isomer was biologically active.[14]

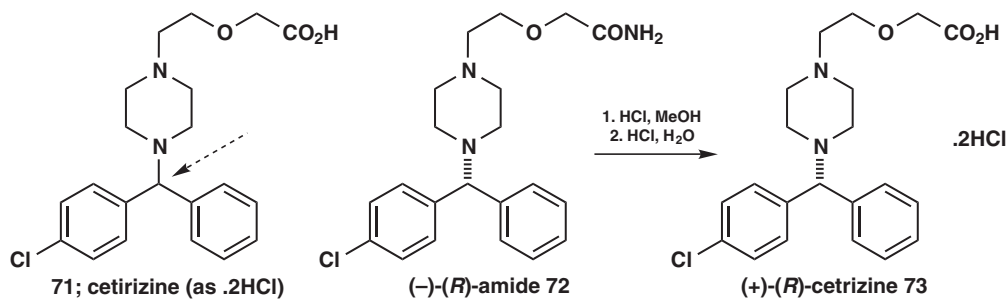


If you need any more convincing, applying the same method to flutriafol **66** gave the camphanic esters as before but now no separation could be achieved even with HPLC. Esters **69** of a different acid **68** could be separated on the same column but using 1:1 CH_2Cl_2/EtOAc as eluent. You will not be surprised to know that fluconazole **70** is now a leading fungicide in this area. It is not chiral.



A commercial drug separation by chiral HPLC

Cetirizine **71**·2HCl is an antihistamine marketed as Zyrtec. It has a 'low grade' chiral centre (arrowed) - the molecule is chiral only because one of the benzene rings has a *para*-chloro substituent. It is very difficult to resolve cetirizine or to synthesise it asymmetrically. One company, Sepracor Inc., whose business is making single enantiomers, found that the related amide **72** could be separated by chiral HPLC on Chiral Technologies 'Chiralpak AD' columns: the two enantiomers having very different retention times (4.8 and 8.8 minutes). They could separate nearly 40 g of racemic material with one injection and, by repeated injections, could easily separate 1.6 kg of (−)-(*R*)-**72** with 99.8% ee. The separate enantiomers were converted to cetirizine in two steps and the (+)-(*R*)-enantiomer **73** found to be biologically active.[15]

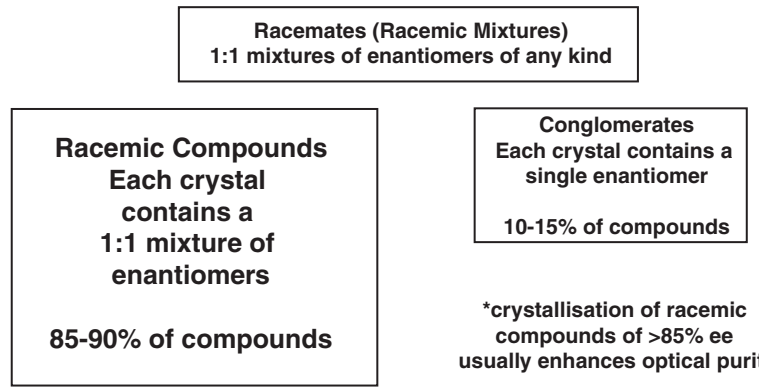


Chiral HPLC is the method of choice for analysing enantiomers and determining % ee. It can be used preparatively. In either application it is best to consult an expert when choosing columns and solvents.

Differential Crystallisation or Entrainment of Racemates

Conglomerates and racemic compounds

Most chiral compounds crystallise as racemic crystals, each crystal containing equal numbers of right and left handed molecules, and cannot be separated by crystallisation. Some racemates, unfortunately only about 15% of those known, crystallise as "conglomerates" or "racemic compounds"; that is each crystal consists only of one enantiomer though the crystalline mass contains equal numbers of right and left handed crystals.[16] You may recall that Pasteur[17] did the very first resolution by picking out right and left handed tartrate crystals by eye. If a saturated solution of such a compound is seeded with crystals of one enantiomer (usually quite a lot is needed: 5–25% by weight), that enantiomer may crystallise out first in the process known as *differential crystallisation* (or sometimes as *entrainment*).



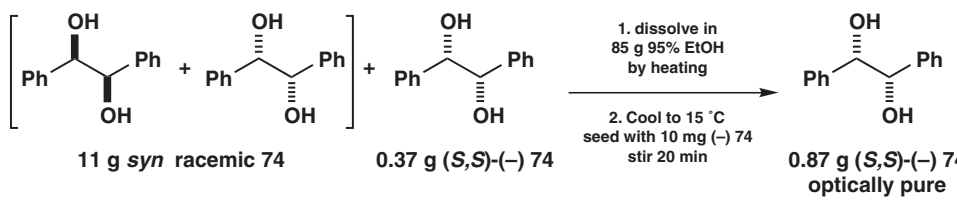
Conglomerates can be recognised by a number of features:

1. The m.p. of the racemate is the same as that of the single enantiomer
2. The IR spectrum of the solid racemate is the same as that of the single enantiomer
3. The racemate is more soluble than either enantiomer in a chosen solvent.

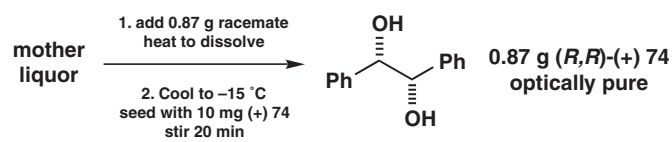
There is no guarantee that a given group of molecules nor any derivatives of them will provide conglomerates but there are some well known cases, thus with α-amino acids, certain known derivatives, such as the *N*-acetyl amides, generally crystallise as conglomerates. We shall give some examples to show how the method works.

Typical procedure for differential crystallisation (entrainment)

cis-Stilbene diols form conglomerates. A solution of 11 g racemic *cis* stilbene diol **74** and a small amount (usually about 5–10%, here 0.37 g) of (−)-**74** in hot ethanol is cooled and seeded with 10 mg (−)-**74**. After 20 minutes 0.87 g pure (−)-**74** has crystallised out. The excess of the one enantiomer is less soluble than the racemate but the yield is only about twice as much as the amount of pure enantiomer added in the first place.

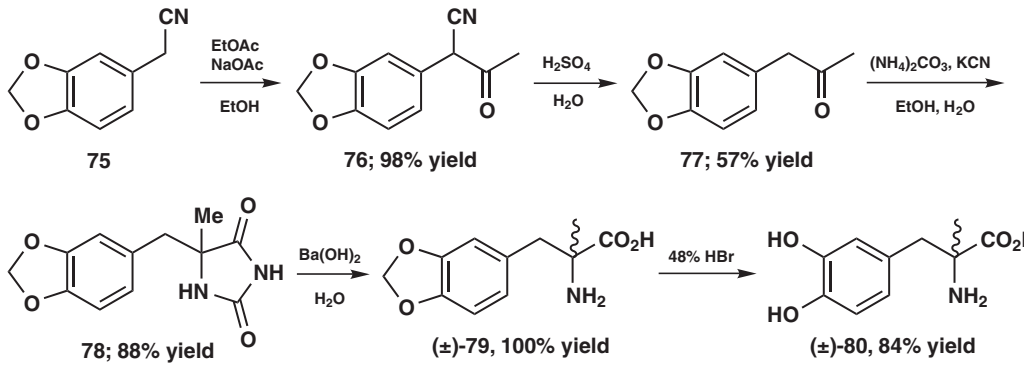


The solution is now enriched in the other enantiomer so we replace the lost racemate by adding another 0.87 g heating and cooling as before but seeding with the other enantiomer (+)-**74**. We get about 0.87 g of (+)-**74** crystallising out. And so on. After fifteen cycles 6.5 g (−)-**74** and 5.7 g (+)-**74**, each 97% ee, had been separated. This compound is more efficiently prepared by asymmetric dihydroxylation (chapter 25).

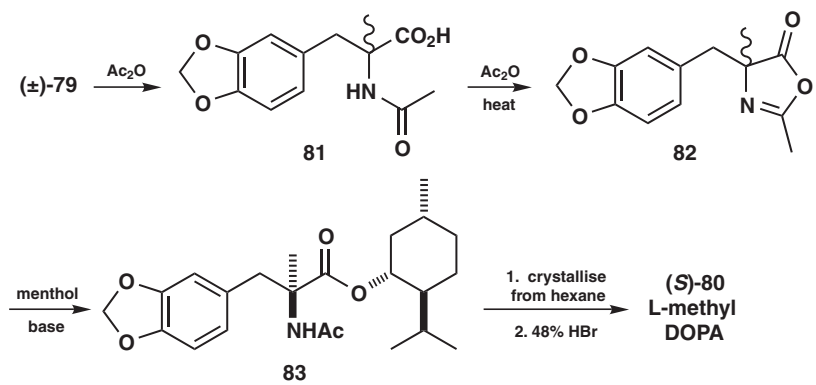


Conventional resolution of L-methyl DOPA

The aromatic amino acid L-methyl DOPA (Di Hydroxy PhenylAlanine) **80** is used to make an anti-hypertensive compound. Synthesis by the Strecker method clearly requires the aromatic ketone **77**, and the synthesis follows the pattern below.[18] The intermediates and final product have been resolved in various ways.

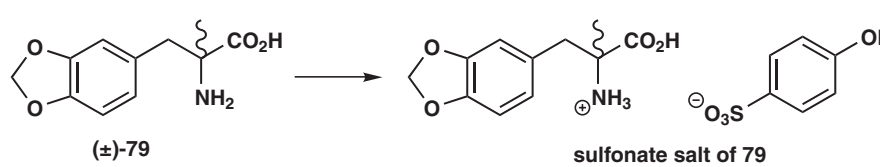


The synthesis of L-methyl DOPA **80** by the Strecker reaction was straightforward and of course produced racemic material. A conventional resolution by crystallising the menthyl ester **83** from hexane and hydrolysis of acetal, ester and amide in 48% HBr (note that no racemisation by enolisation can occur) gives good yields.[19]



Resolution of L-methyl DOPA by differential crystallisation

Careful study of m.p./composition diagrams and infra red spectra revealed that aryl sulfonate salts of aromatic amino-acids may form conglomerates, and **79** has indeed been purified by differential crystallisation. Batches of racemic salt are seeded with about 20% by weight of pure L-**79**. This gives a yield of about 40% of pure L-**79**. This is again about twice the original excess of the single enantiomer. The mother liquor is rich in D-**79**, so seeding with that enantiomer gives a similar yield of pure D-**79**, and the process can be repeated.[20]

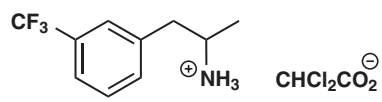


Finding a differential crystallisation approach to fenfluramine

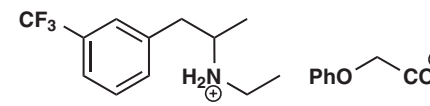
The anorectic drug fenfluramine **85** is made by the alkylation of the simpler amine **84**. Either compound could be resolved and, though a classical resolution of the camphoric acid salt of fenfluramine was known, chemists at Rouen were determined to achieve better results by differential crystallisation.[21]

84 **85; Fenfluramine**

Just how determined you will see. They looked at salts of both amines with 'about fifty' achiral acids of which eight proved to be conglomerates, three for **84** and five for **85** (this is about what would be expected - about 10%). Of these eight, two could not be separated by crystallisation because one salt **86** had crystal facets that acted as seeds for the *other* enantiomer while the conglomerate of another **87** was unstable and easily reverted to a racemic compound.

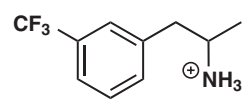


86; salt of 84 with chloracetic acid

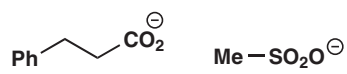


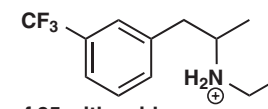
87; salt of 85 with phenoxyacetic acid

That left six candidates, two for **84** and four for **85**. All six salts could be separated by crystallisation as we have described giving alternately one enantiomer and then the other but the best were the salts of **85** with the two arylacetic acids. You may feel that this heroic effort, though successful, is rather discouraging.

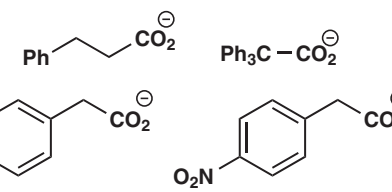


salts of 84 with acids:





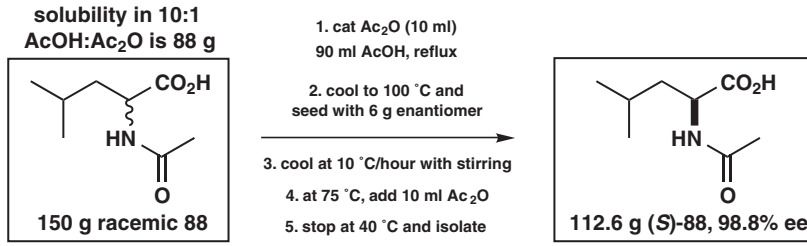
salts of 85 with acids:



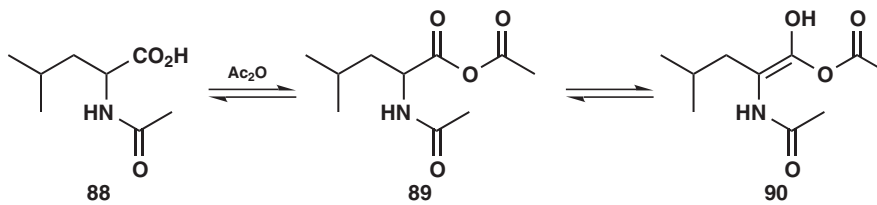
Resolution with Racemisation

Resolution of amino acids by differential crystallisation with racemisation

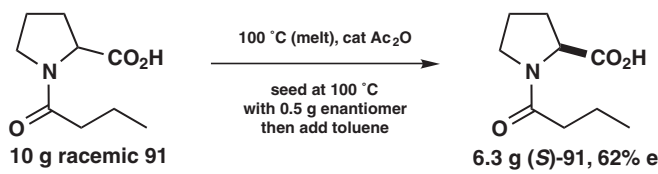
The separation of the enantiomers of most amino acids can be achieved by differential crystallisation of their *N*-acetyl derivatives, such as that of leucine. Racemic *N*-acetyl leucine **88** is dissolved in the right solvent mix cooled and seeded with 4% by weight of natural (*S*)-**88**. Pure (*S*)-**88** crystallises out in good yield.[22]



In fact your suspicions may have been aroused by the quantity of material put in. We started with 150 g racemic **88**, that is 75 g of each enantiomer and we seeded with 6 g of (*S*)-**88** making 81 g of (*S*)-**88** altogether. But the yield of pure crystalline (*S*)-**88** was 112.6 g - too much! Clearly the other enantiomer is somehow being converted into the enantiomer that crystallises. The clue is the addition of that extra Ac_2O at step 4. This forms a mixed anhydride **89** that racemises by enolisation **90** and crystallisation can continue.

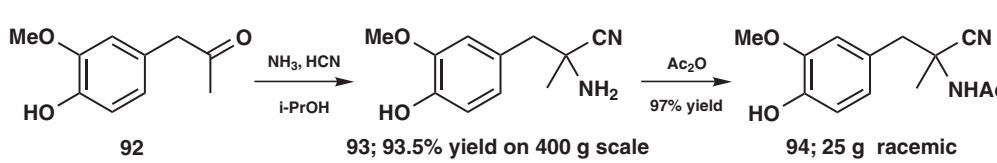


Sometimes these differential crystallisations with racemisations are very easy to do. Racemic *N*-butyroyl proline **91** gives a good yield of one enantiomer in moderate ee just by melting the racemic compound with catalytic acetic anhydride and seeding with one enantiomer. Further crystallisations improve the ee. The yield is 6.3 from 10.5 g or 60% of the total material. This process is clearly a great improvement on simple differential crystallisation both in simplicity of operation and because it is no longer necessary to alternate the isolation of enantiomers.

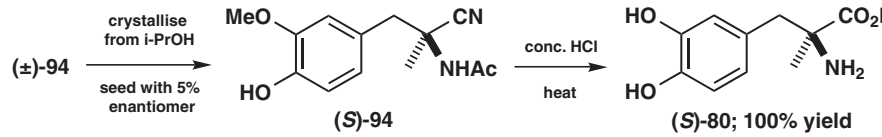


Differential crystallisation and racemisation when enolisation is impossible

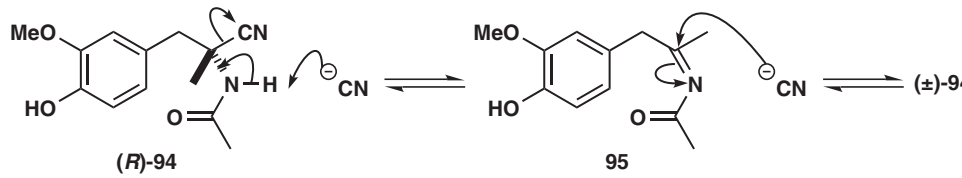
We return to the asymmetric synthesis of L-DOPA noting that it is an amino acid that cannot racemise by enolisation as it has no proton between the NH_2 and CO_2H groups. We again use the Strecker reaction - the only change is a minor alteration of phenolic protecting groups. The Strecker synthesis gave a good yield of the amino-nitrile **93** that could be converted into L-DOPA **80** with conc. HCl. Unfortunately no derivatives of **93** could be separated by differential crystallisation.



When the *N*-acetyl derivative of the intermediate **94** was crystallised from isopropanol with seeding a good yield of enantiomerically pure L-DOPA could be crystallised out. Treatment of the residue from the mother liquor with NaCN in DMSO led to complete racemisation and the differential crystallisation could be repeated.[23]

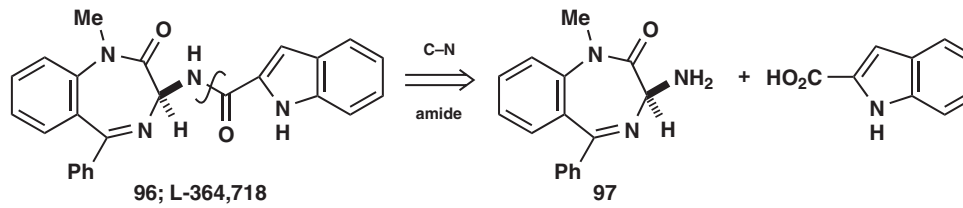


This racemisation is a separate chemical reaction from the crystallisation but one cycle gave 63% yield of L-DOPA of 100% ee. Evidently the cyanide is lost from **94** by elimination and readdition **95** gives racemic **94**.

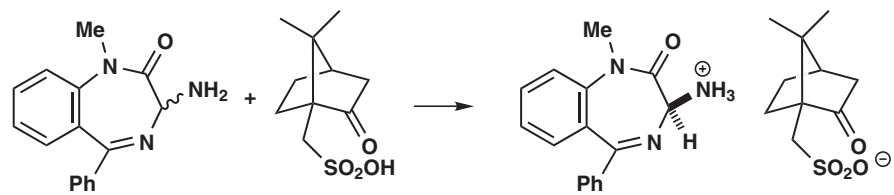


Kinetic resolution with racemisation

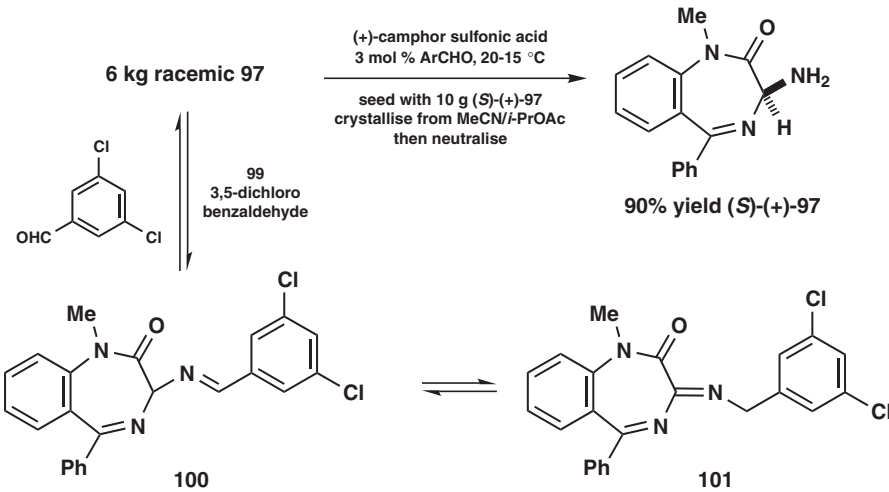
Amine (*S*)-(+)-**97** is needed for the synthesis of a gastrointestinal hormone antagonist, Merck's cholecystokinin antagonist **96**, by acylation with indole-2-carboxylic acid.



The racemic compound is available by methods used (*Disconnection Textbook*, page 250) for the closely related benzodiazepines like diazepam, used in the treatment of depression. The one stereogenic centre is next to a primary amine, and the compound forms a crystalline salt with camphor sulfonic acid **98** (cf. **61**). The maximum yield is 50%, but the amine (*S*)-**97** can be released from the salt simply by neutralisation.[24] This is a classical resolution by crystallisation of diastereoisomers.

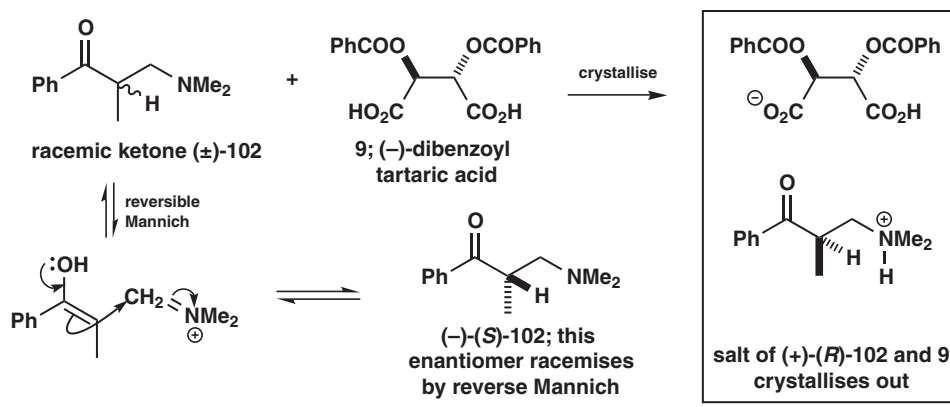


A remarkable improvement happens if the salt is crystallised in the presence of 3,5-dichlorobenzaldehyde **99**: 90% optically active salt crystallises out. Clearly the non-crystalline enantiomer is racemising via the still chiral imine **100** by imine exchange with achiral imine **101**.

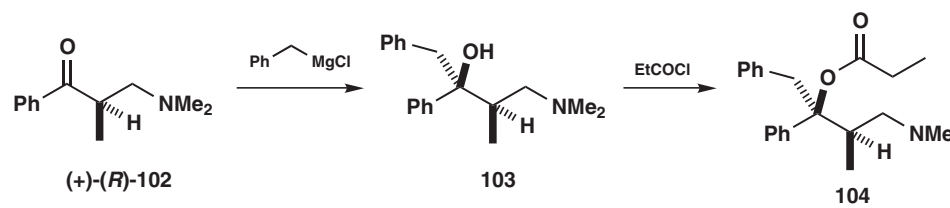


Other methods of racemisation during resolution: the Mannich reaction

Even more complicated reactions can be used to racemise during a resolution. The amino ketone **102** is needed for the synthesis of the analgesic and useful asymmetric reagent (see chapter 24) DARVON. Classical resolution with dibenzoyl tartaric acid **9** succeeds in crystallising the (+) enantiomer and racemising the mother liquors by reverse Mannich reaction.[25]

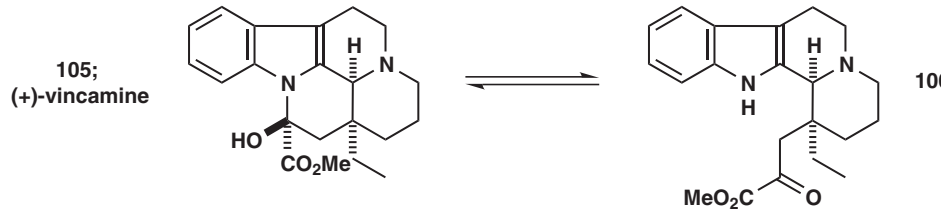


The enantiomerically pure ketone (+)-(*R*)-**102** can be converted to DARVON **104** by a chelation controlled diastereoselective addition of benzyl Grignard and acylation. Using the other enantiomer of **9** gives the other enantiomer (−)-(*S*)-**104** which is called NOVRAD.

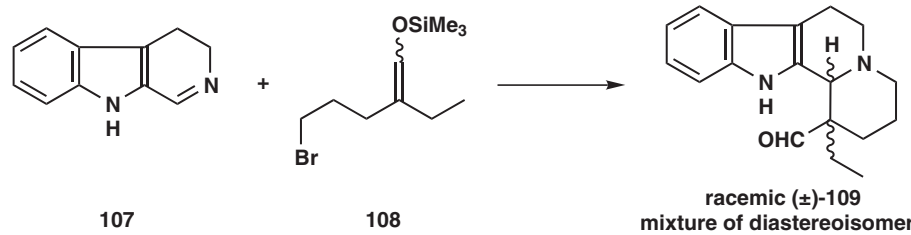


A case where two stereogenic centres are equilibrated in one step, and a third in another occurred in Oppolzer's synthesis[26] of (+)-vincamine **105**, a natural alkaloid used for the treatment of cerebral insufficiency in man. It has three stereogenic centres, but one of them epimerises at

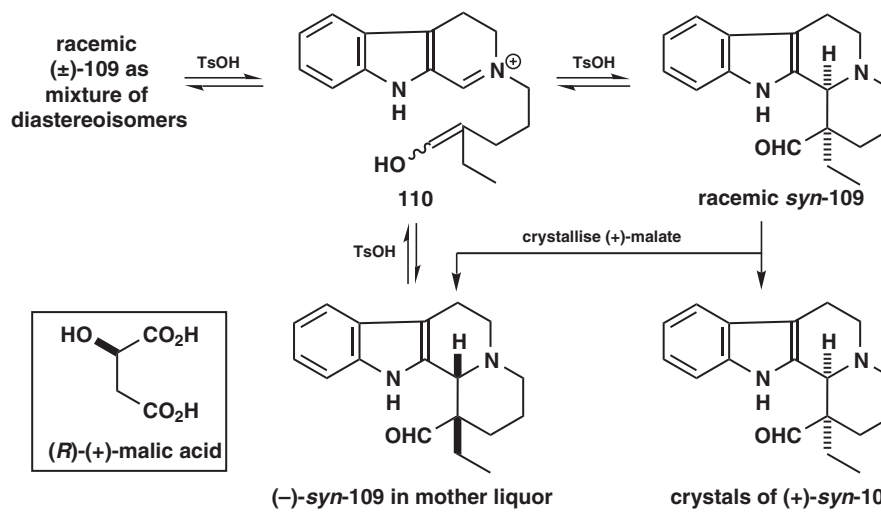
room temperature by equilibration with the ketone **106** so need not be controlled - it equilibrates in nature too, so it will automatically be correct.



Earlier in the synthesis the heterocycle **107** was combined with **108** to give an advanced intermediate **109** as a mixture of diastereoisomers. As both starting materials are achiral **109** is also racemic.

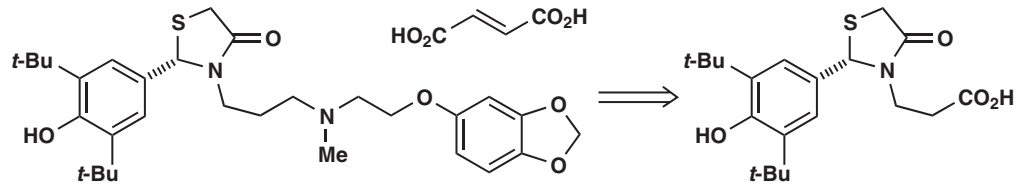


Heating the mixture of isomers of **109** with TsOH equilibrates the diastereoisomers so that the required more stable *syn* (H and Et *syn*) diastereoisomer of **109** crystallises out. Treating this with (+) malic acid leads to crystals of the natural enantiomer (+)-*syn*-**109**. Both the unwanted *anti*-diastereoisomer and the unwanted enantiomer can be equilibrated again with TsOH. This cannot be enolisation as there are no α-hydrogens and is presumably equilibration by reversible Mannich reaction as **110** lacks either stereogenic centre and so epimerises both!



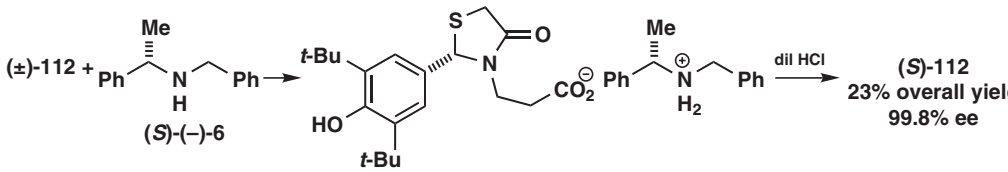
Resolution with racemisation in the manufacture of a drug

Resolution with racemisation is used in the manufacture of the cardioprotective drug CP-060*S* **111** by the Chugai Pharmaceutical company.[27] The drug itself can be resolved with some difficulty but as it is made from the simpler carboxylic acid **112** this looks a better bet.



(*S*)-111; CP-060*S* as hydrogen fumarate 112

The resolving agent for the acid **112** is the simple amine **6** that we discussed at the start of this chapter. A 27% yield of the salt of (*S*)-(−)-**6** with the required (*S*)-**112** with ee >99% was crystallised from *i*-PrOH/*i*-Pr_2O. This is not a good recovery but they preferred to sacrifice yield to near perfect ee as the mother liquor was racemised by treatment with NaOH in water at room temperature. The resulting solution had <1% ee – the one time when low ee is a good thing – and was used in the next resolution.



salt of (*S*)-112 and (*S*)-(–)-6; 27% yield, >99% ee

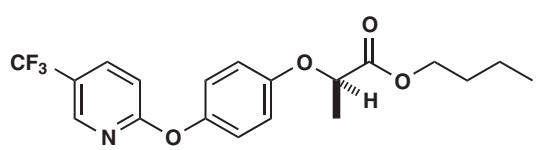
You are fortunate if you can find a way to resolve and racemise in the same solution but, in theory, any reversible reaction such as the important Diels-Alder or aldol reactions could do the job so this method has wider application than might appear at first sight.

Kinetic Resolution with Enzymes

Enzymes as resolving agents

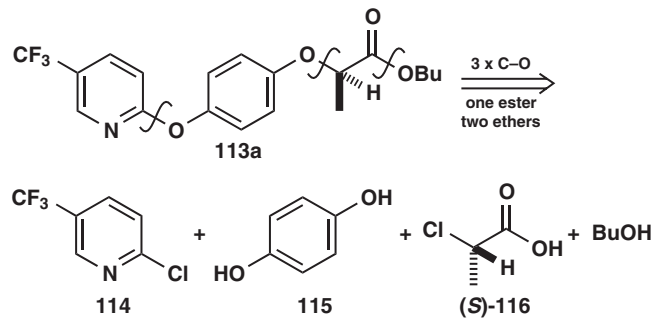
There is a chapter soon (29) about enzymes as reagents in organic synthesis, but they are also widely used in industry as resolving agents. The basis of this application is the enantioselectivity of enzymes. They react with only one enantiomer of a racemic mixture and can be used to create the wanted enantiomer or destroy the unwanted. A process in which one enantiomer reacts and the other does not is called a *kinetic resolution* (chapter 28) since the resolution depends on the rates of two competing reactions. The result is that instead of separating enantiomers or even diastereoisomers, one is separating two compounds of different structure that also happen to belong to the two opposite stereochemical series.

Zeneca market a herbicide for broad leaved crops, Fusilade[28] (fluazifop butyl) **113**. This is a carboxylic ester with two ether linkages, one between two aromatic rings.

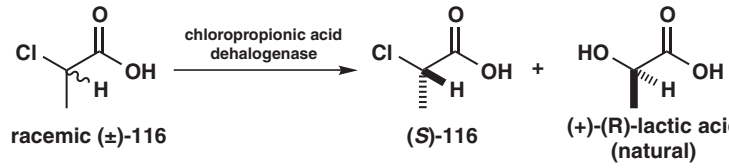


(*R*)-113
Fluazifop Butyl
"Fusilade"

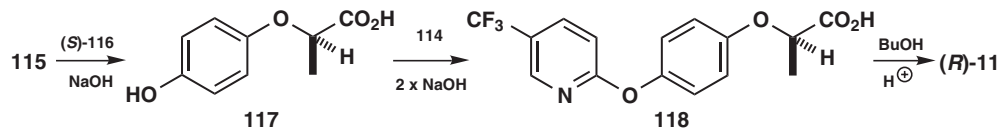
Disconnection of the ethers **113a** is guided by our mechanistic knowledge that nucleophilic substitution is possible on alkyl halides, and on 2-halo-pyridines such as **114**, but not easy on halobenzenes.



The only chiral intermediate is the chloroacid **116** which Zeneca manufacture as a racemic compound. They use the enzyme chloropropionic acid dehalogenase to destroy the unwanted isomer by conversion to lactic acid. It is easy to separate these two compounds as they are not even isomers.

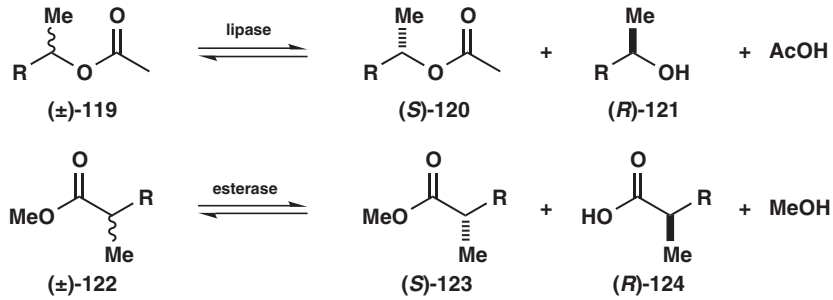


It is important to follow the fate of stereogenic centres made early in a synthesis and they have established that the nucleophilic substitution of **115** with **116** to give **117** goes with inversion and not, as happened to amino acid derivatives in chapter 23, with unexpected retention. The active product is therefore the (*R*)-**113** enantiomer shown.



Kinetic resolution by ester hydrolysis with enzymes

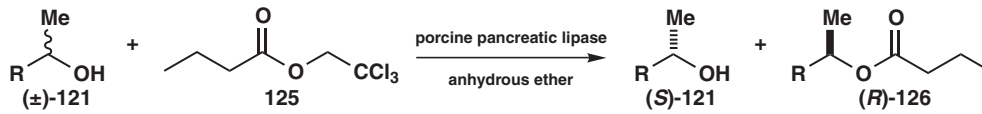
By far the commonest reaction used in kinetic resolution by enzymes is ester formation or hydrolysis. Normally one enantiomer of the ester is formed or hydrolysed leaving the other untouched so one has the easy job of separating an ester from either an acid or an alcohol. There are broadly two kinds of enzymes that do this job. Lipases hydrolyse esters of chiral alcohols with achiral acids such as **119** while esterases hydrolyse esters of chiral acids and achiral alcohols such as **122**. Be warned: this definition is by no mans hard and fast! If the unreacted component (**120** or **123**) is wanted, the reaction is run to just over 50% completion, to ensure complete destruction of the unwanted enantiomer, while if the reacted component (**121** or **124**) is wanted it is best to stop short of 50% completion so that little of the unwanted enantiomer reacts.



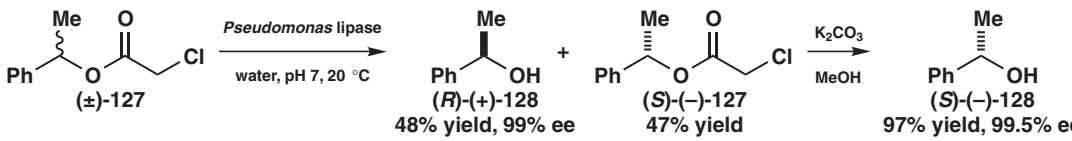
There is an inherent problem with either type of enzyme as the reactions are reversible. One way to make the reaction run in the direction of ester formation is to use a non-aqueous solvent (you may be surprised that enzymes function in, say, heptane, in which they are insoluble, but lipases do). One way to make the reaction run in the other direction is to make the alcohol component an enol so that, on hydrolysis, it gives the aldehyde or ketone and does not reverse.

Resolutions of secondary alcohols by lipases

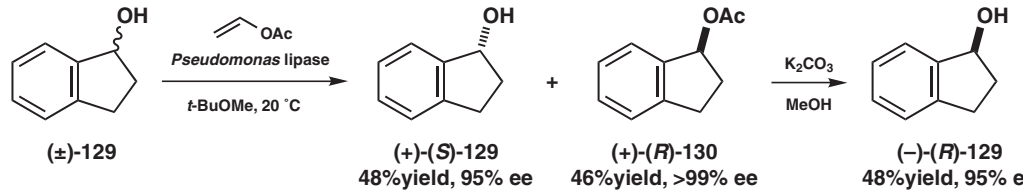
Simple secondary alcohols **121** (R = alkyl or aryl) are enantioselectively esterified by the reactive trichloroethyl ester **125** using porcine pancreatic lipase in anhydrous ether. The products, one enantiomer of **121** and the other enantiomer of the ester **126**, are both formed in >90% ee, and are easily separated from each other and from the insoluble enzyme.[29]



The reaction occurs in the reverse direction in aqueous buffer (pH 7, 20 °C) using a lipase from *Pseudomonas* spp. The reactive chloroacetates, e.g. **127**, give the best results with nearly quantitative yields of (*R*) alcohol **128** and (*S*) ester **127** separated by flash chromatography on a 250 g scale. The ester (*S*)-**127** was easily hydrolysed to the (*S*) alcohol **128** without racemisation.[30]

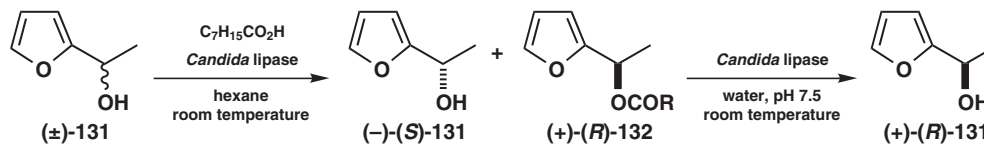


The same enzyme catalyses the esterification of racemic **129** in non-aqueous solution with vinyl acetate. The released alcohol is CH_2=CHOH, the enol of acetaldehyde: it immediately forms acetaldehyde which self condenses and is removed from the equilibrium. The enzyme is filtered off, the enantiomerically pure alcohol (*S*)-**129** and acetate (*R*)-**130** separated by flash chromatography, and the ester hydrolysed to the alcohol without racemisation. Either method (esterification or hydrolysis) gives both enantiomers of a range of secondary alcohols.[31]

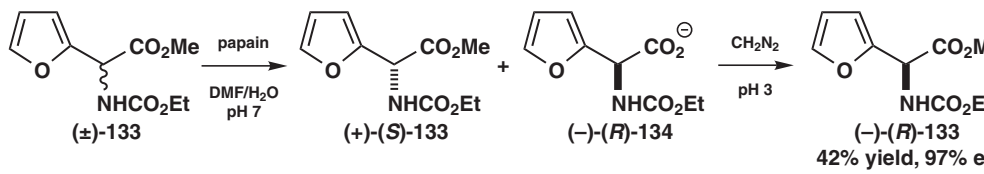


Kinetic resolution with proteolytic enzymes

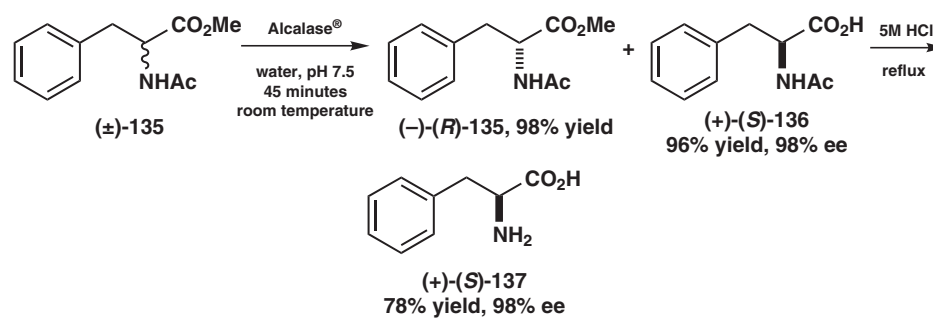
The simple furan alcohol **131** is successfully resolved[32] with a lipase from *Candida cyclindracea* and you should note that the same enzyme is used to form the octanoate **132** and, under different conditions, to hydrolyse it to the pure alcohol (+)-(*R*)-**131**.



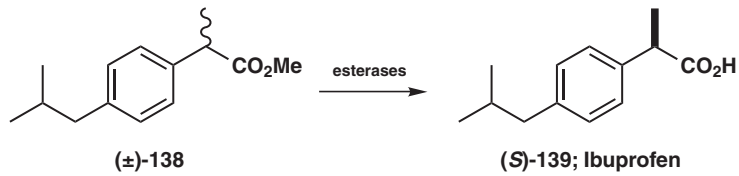
However, the closely related amino acid **133** was not a substrate for either lipase (from pigs or *Candida*) but could be resolved with the proteolytic enzyme papain. This acted as an esterase, hydrolysing the methyl ester rather than the amide. Note that this kinetic resolution produces a single enantiomer of the carboxylic acid rather than the alcohol and that separation of **134** from **133** is very easy as the free acid can be extracted from organic solvents by aqueous base in which it is soluble as the anion.



Perhaps the ideal enzymatic resolution is that of phenylalanine **137** by the proteolytic enzyme subilopeptidase, marketed as Alcalase® acting as a lipase on the ester amides **135**. The reaction stops after one enantiomer is consumed: the yields and ees of the two products are close to 100%. The amide (*S*)-**136** can be hydrolysed directly to natural phenylalanine (*S*)-**137**. The unnatural (*R*)-**135** can of course be hydrolysed to the arguably more valuable (*R*)-**137** but it can also be racemised by NaOMe in MeOH for the next cycle of reactions.[33]

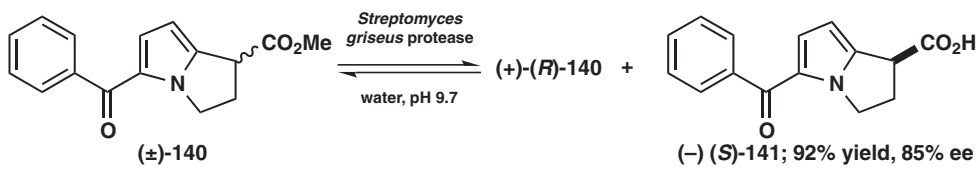


More recently acids have been resolved with enzymes cloned and over-expressed in their own organisms, such as an esterase from *Bacillus subtilis* that resolves ibuprofen methyl ester **138** to give ibuprofen **139** of 99% ee. A range of anti-inflammatory arylpropionic esters, including **138**, could also be resolved with a cell-free extract from *Pseudomonas fluorescens* showing that purified enzymes are not essential.[34]



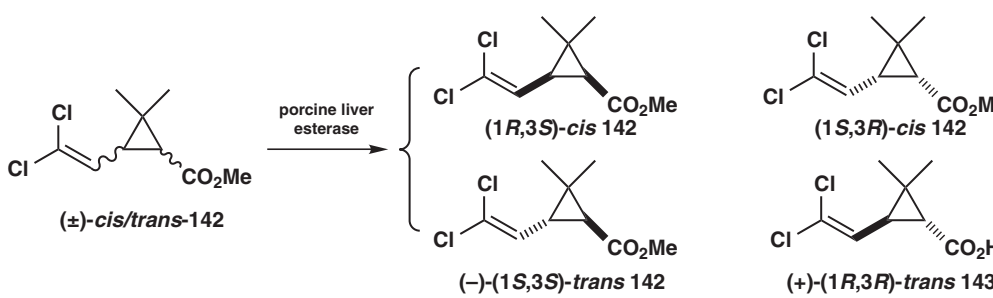
Kinetic resolution with racemisation using proteolytic enzymes

In all these enzymatic resolutions so far the maximum yield of one enantiomer is of course 50% and only in the last example have we seen the recycling of the other enantiomer. However in the resolution of esters **140** of the anti-inflammatory drug ketorolac **141**, the easily enolised ester **140** racemises in moderately basic conditions and, after a survey of four lipases and four proteases, one was found[35] that hydrolyses the ester **140** enantioselectively at pH 9.7. The product of the reaction is (−)-(*S*)-ketorolac **141** in 92% yield but only 85% ee. One recrystallisation improves this to 94% ee.



Kinetic resolution on diastereoisomeric mixtures

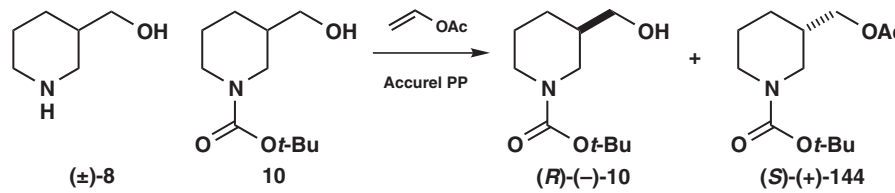
Derivatives of chrysanthemic acid such as (1*R*,3*R*)-permethrinic acid **143** are in demand for the manufacture of highly specific insecticides that do not persist in the environment. Mixtures of the esters **142** are easy to make and contain various proportions of the *cis* and *trans* diastereoisomers. Pig liver esterase accepts only the *trans* esters as substrates so complete hydrolysis gives the unchanged *cis* esters and hydrolysed but poorly resolved *trans* acids. At 50% conversion, kinetic resolution of the *trans* esters occurs.[36]



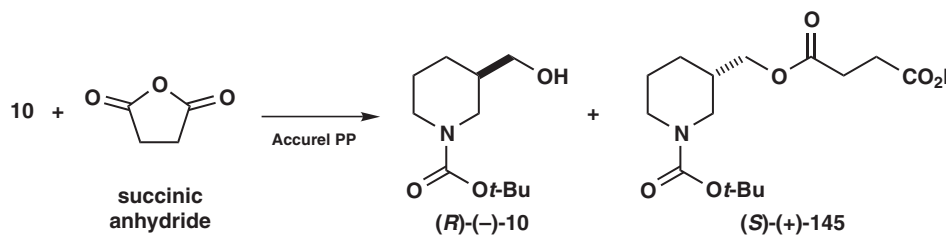
At 50% conversion, the product contains three esters, the two *cis*-**142**s and the (1*S*,3*S*)-*trans* ester together with a little (1*S*,3*S*) -*trans* acid and all of the (1*R*,3*R*)-permethrinic acid **143**. The ratio of these last two is 10:90 but one recrystallisation from petrol gives (1*R*,3*R*)-permethrinic acid **143** in 98% ee. This approach works for several different cyclopropane-based carboxylic acids in much the same way.

Comparison between enzymatic and classical resolution

Earlier in this chapter we described the resolution of the piperidine **8** by classical resolution. The Bristol-Meyers Squibb company also investigated an enzymatic resolution.[3] Various esterases and lipases had been used before on various derivatives of **8** but none was efficient. Two methods were successful. Accurel PP, a lipase immobilised on polypropylene, resolved the N-Cbz derivative **10** to give 46% yield of (*R*)-(−)-**10** with 99.4% ee. Unfortunately this is not the wanted enantiomer and the ester (*S*)-(+)-**144** could be isolated only by chromatography.

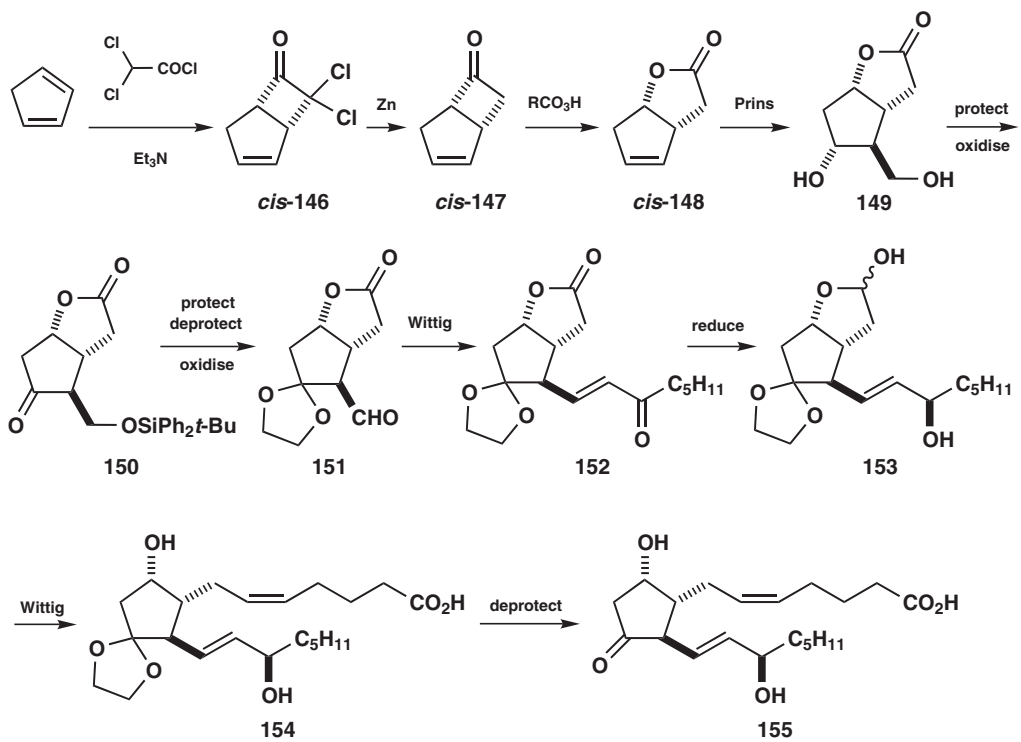


The separation problem was solved by esterifying racemic **10** with succinic anhydride. The (*R*)-ester **145** now has a free carboxylic acid group and can be separated simply by extraction with weak base ($NaHCO_3$) without any chromatography. The ester is easily hydrolysed to (*S*)-(+)-**10** which was obtained in 32% overall yield (maximum 50%) and 98.9% ee. They do not say whether they prefer this resolution to the classical version with dibenzoyl tartaric acid but both are good.

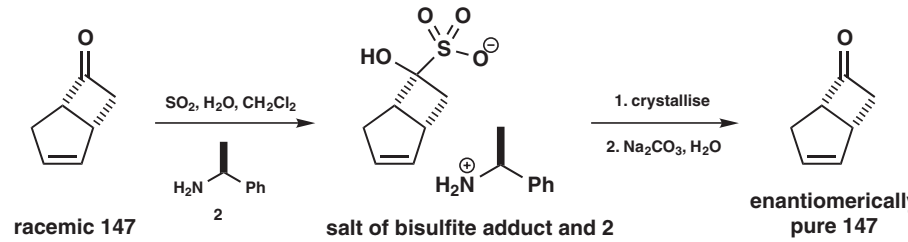


Asymmetric Synthesis of Prostaglandins with many Chiral Centres

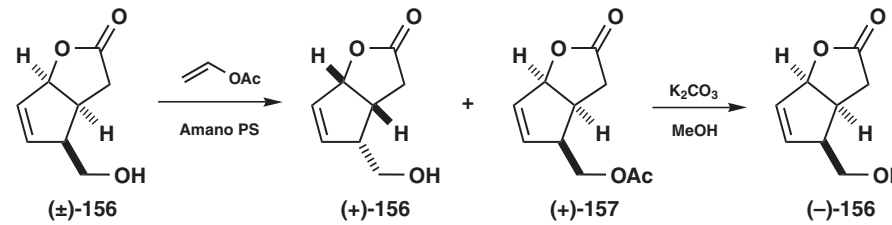
We end with a stereochemically involved synthesis of a prostaglandin **155**. The racemic synthesis is summarised below - each compound is a single diastereoisomer and all from **146** to **155** are chiral but all are racemic as the synthesis starts with achiral materials. There are 14 steps in the synthesis and the final product **155** contains four chiral centres.[37] If we want a single enantiomer, where should we resolve?



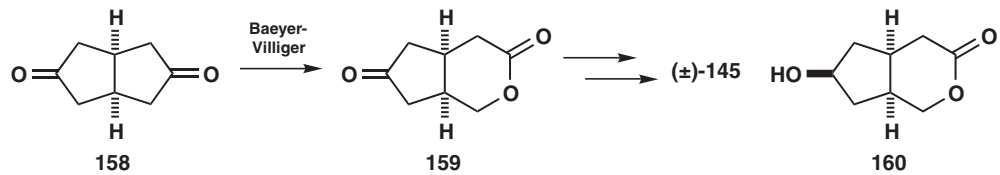
The obvious answer is as early as possible. The first chiral intermediate is **146** and that already has two chiral centres. The first intermediate with a useful functional group is **149** with its two alcohols. The chemists at what was then Glaxo (now GlaxoSmithKline) chose an ingenious resolution of the stable ketone **147**. Because this is a strained ketone it forms a stable adduct with bisulfite and that could be resolved as a salt with our old friend 1-phenylethylamine **2**. The bisulfite compound reverts to the ketone **147** on treatment with base and the resolution was complete.



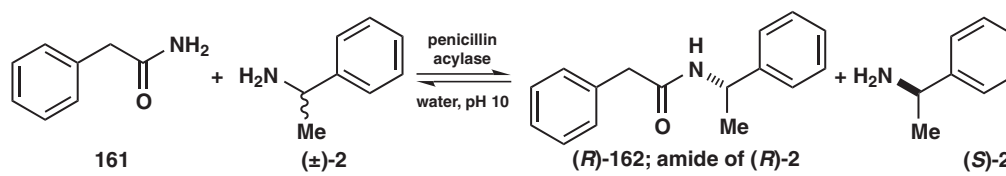
More recently enzymes have been used to resolve related intermediates also used in prostaglandin synthesis.[38] Acylation with vinyl acetate catalysed by twelve lipases was tried and the best was 'Amano PS' from *Pseudomonas cepacia*. At 55% conversion the alcohol (+)-**156** was obtained in 40% yield and 91% ee and the acetate (+)-**157** in 78% ee. This low enantiomeric purity could be enhanced to 95% by hydrolysis to (−)-**156** and reacetylation with the enzyme. Note that the alcohol and acetate of the same series have opposite signs of rotations.



It should not be assumed that all these adventures are successful. The same workers attempted to resolve the first chiral intermediate **159** in the synthesis of **156** by acylation of the related alcohol **160** with the same range of lipases but with only very limited success.[39] The ee of **160** was 34–66% with the various enzymes. Neither could **160** be resolved with chiral HPLC. You may see that it is asymmetric in the ring remote from the alcohol.



Returning to the resolution of amines, an enzymatic acylation of racemic amines in aqueous solution by a penicillin acylase (enzymes used in industry in the synthesis of penicillins) from *Alicaligenes faecalis* has recently been reported.[40] The best acylating agent is the amide **161** of phenylacetic acid. There is a big advantage here. Unlike the ester formations and hydrolysis we discussed earlier, no amide exchange occurs with simple amides like **161**. The amide (*R*)-**162** was formed in 45% yield and 98.5% ee. Once it has been separated from free (*S*)-**2**, it can be hydrolysed to free (*R*)-**2** with the same enzyme! This automatically perfects the ee.



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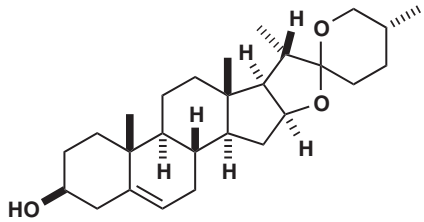
23 The Chiral Pool — *Asymmetric Synthesis with Natural Products as Starting Materials* —

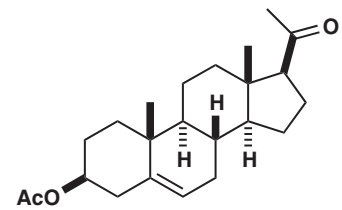
Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

Introduction: The Chiral Pool

The chiral pool is that collection of available natural products considered cheap enough to use as starting materials for organic synthesis. The chiral pool strategy is the incorporation of part or all of one of these compounds into the target molecule.[1] Chiral pool compounds were used as resolving agents (chapter 22) and derivatives of them will be used as reagents (24), catalysts (25 and 26) and chiral auxiliaries (27) and in this chapter we give the synthesis of many such compounds. There is of course no hard and fast definition of which natural products qualify for the chiral pool but our list appears at the end of the chapter. Most amino acids are cheap enough for anyone, and sucrose is one of the cheapest pure organic compounds anywhere, but if you plan the synthesis of a very active compound, say a prostaglandin, when only a few hundred grams *per annum* is needed, then a quite expensive compound becomes a suitable starting material. The Syntex headquarters is in Mexico City because R. E. Marker found that the Mexican yam *Dioscorea* could replace animals as a source of steroids since the vegetable "steroid" diosgenin **1** could be converted into optically active birth control ingredients[2] like pregnenolone acetate **2**.



1; diosgenin



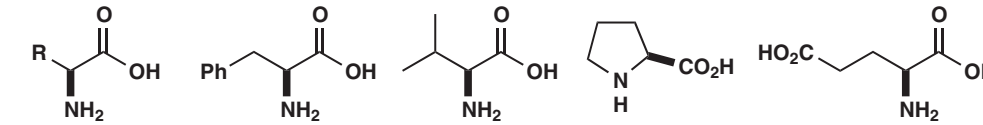
2; pregnenolone acetate

We shall introduce the chiral pool in the first half of this chapter, taking each type of natural product, such as the amino acids, in turn and give the key reactions that allow their use in synthesis. We shall illustrate this section with the synthesis of important resolving agents, reagents and catalysts for asymmetric synthesis, and chiral auxiliaries. We shall reveal that there is now what we shall call the 'new chiral pool' - compounds so easily made from natural compounds that they are readily (and often commercially) available. Then we shall look at syntheses of more complex targets, showing how the decision was made to use the chiral pool strategy.

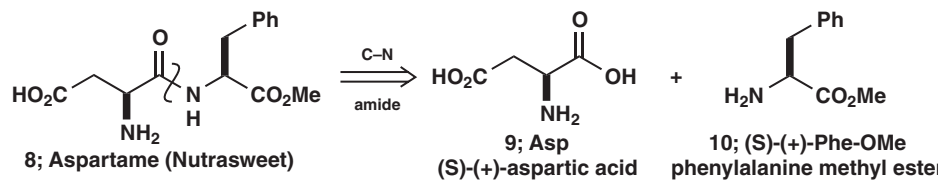
Part I – A Survey of the Chiral Pool

The Amino Acids

The α-amino acids found in proteins are widely available and reasonably priced - many indeed are cheap.[3] They have the general structure **3**, where R can be alkyl **4**, **5**, cycloalkyl **6** and functionalised alkyl **7** or aryl. They are all L, most are also *(S)* (all except cysteine and cystine), and some are (+) and some (−) as you would expect. Some are also available as the D enantiomer, usually more expensive, but the synthesis[4] of D amino acids (e.g. by enzymatic resolution, chapter 29) is making them cheaper. These examples **4**–**7** are very important.

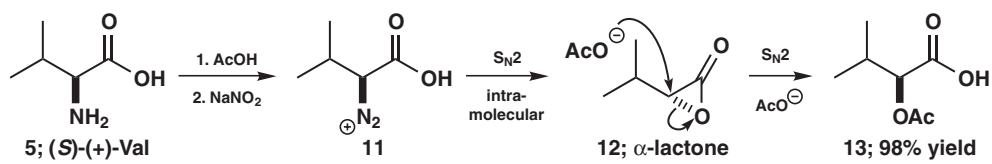


If you are manufacturing aspartame **8**, it is pretty obvious that you will use the natural amino acids Asp **9** and Phe **4**, modified only by turning Phe into its methyl ester **10**. Standard peptide coupling gives the artificial sweetener. However, to make more interesting compounds, the natural amino acids must be transformed by stereospecific reactions before they are incorporated.

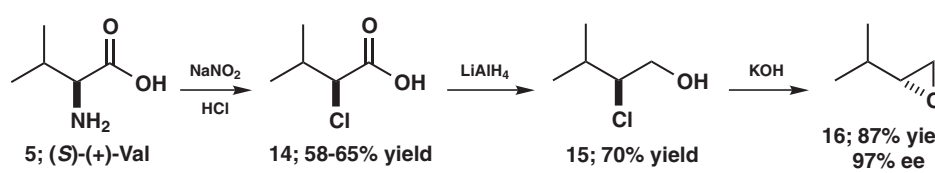


Important reactions of amino acids

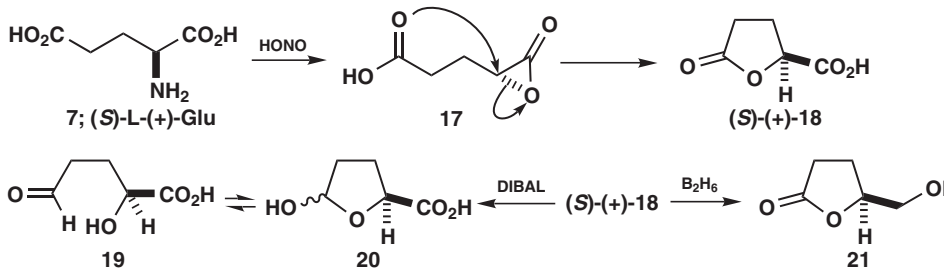
Diazotisation of amino acids gives diazonium salts such as **11** derived from valine **5**. This reaction obviously goes with retention as the chiral centre is not affected. The internal CO_2H group is the best nucleophile and displaces N_2^+ with inversion. Any nucleophile now opens the α-lactone **12** by S_N2 displacement at the alkyl centre, again with inversion to give **13** with overall retention from the original amino acid.[5] Most lactones react with nucleophiles at the carbonyl group but α-lactones react at saturated carbon as that relieves the strain of the 3-membered ring.



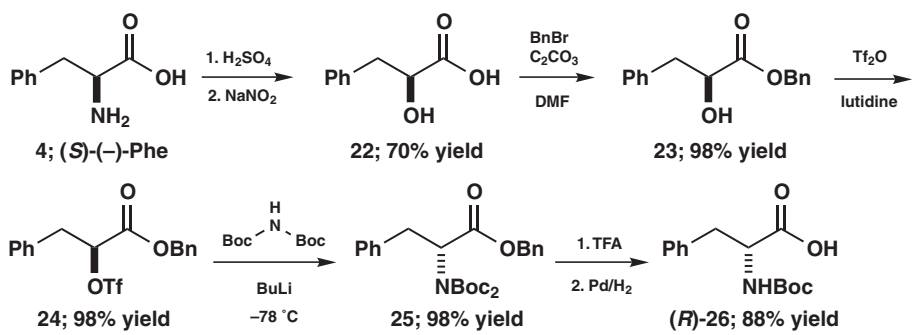
The same reaction works well with chloride as nucleophile to give **14** and, after reduction of the acid group and cyclisation of the alcohol **15**, the epoxide **16**. Such epoxides, made from many of the amino acids, now count as members of the new chiral pool. The diazonium salt **11** and the chloroacid **14** are susceptible to racemisation by enolisation and it is only after two distillations that the epoxide **16** has 97% ee. There are very detailed *Organic Syntheses* procedures for both these steps.[6]



Glutamic acid **7** has its own internal nucleophile: the diazonium salt initially cyclises to the α-lactone **17** which is then opened by the other CO_2H group to give the γ-lactone **18**. Selective reduction of either the lactone or the acid gives two useful intermediates[7] **19** and **21**.

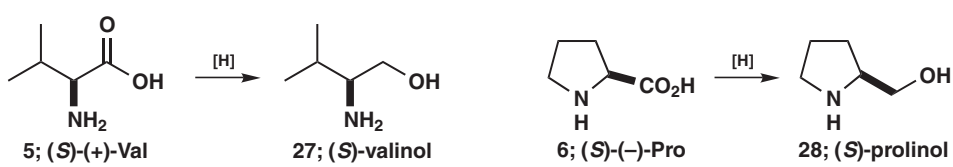


This type of reaction can be used to invert the natural series to give a rare and expensive (*R*)-amino acid. Phenylalanine **4** is converted into the hydroxyacid **22** with retention. Displacement of triflate from **24** with inversion and removal of the benzyl ester gives Boc-protected (*R*)-Phe **26**. In fact this method was used to make ^{15}N-(*R*)-Phe so the nitrogen nucleophile was labelled but it is the inversion that matters to us.[8]

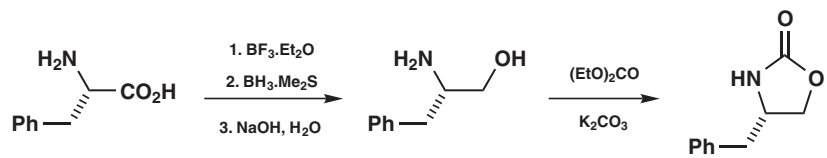


Reduction of amino acids

Reduction of the carboxyl group of the amino acids gives a range of amino alcohols, usually named after the parent acid such as valinol **27** and prolinol **28**. It is important that the reduction does not threaten racemisation. Various methods have been used such as $NaBH_4$ in acid solution[9] (no doubt producing borane *in situ*) and $LiBH_4$ with Me_3SiCl.[10]

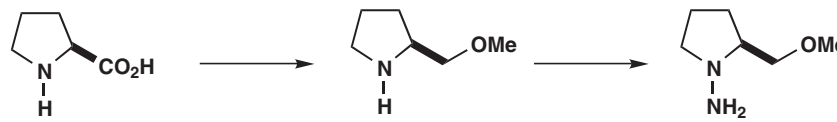


Valinol **27** and phenylalaninol **29** are used to make the Evans chiral auxiliaries used in asymmetric aldol reactions (chapter 27) and Evans prefers reduction with borane itself as its complex with Me_2S. The phenylalanine based auxiliary **30** is generally preferred as the compounds are more likely to be crystalline and can easily be made[11] on a 150 g scale.



4; (*S*)-(–)-Phe **29; 73-75% yield** **30; 78-79% yield**

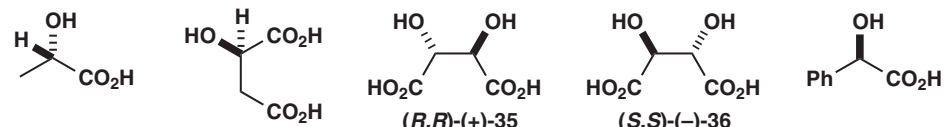
Prolinol methyl ether **31** is used in Enders's SAMP and RAMP chiral auxiliaries (chapter 27) and (*S*)-(−)-SAMP **32** can be made in 50–58% overall yield from (*S*)-L-(−)-proline on a 75 g scale.[12]



6; (*S*)-(–)-Pro **31** **32; (*S*)-(–)-SAMP**

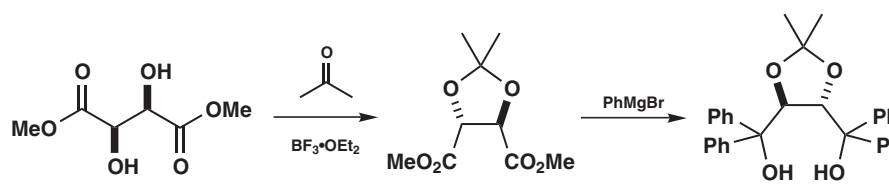
Hydroxy Acids

A few hydroxy acids are very cheap. (*S*)-(+)-Lactic acid **33** occurs in milk, (*R*)-(−)-malic acid in apples, and both enantiomers of the very important tartaric acid **35** and **36** are reasonably cheap. (+)-Tartaric acid **35** is usually called "natural" as it occurs in grapes, but (−)-tartaric acid **36** is natural too as it occurs in the West African tree *Bankinia reticulata*. The other enantiomers of malic and mandelic acids are commercially available and are not that much more expensive.



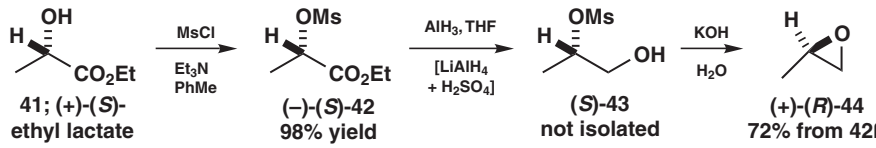
33; (+)-(*S*) -lactic acid **34; (–)-(*R*) -malic acid** **(*R,R*)-(+)-35 tartaric acid "natural"** **(*S,S*)-(–)-36 tartaric acid "unnatural"** **37; (*R*)-(–)- mandelic acid**

One of the most important specific applications of tartaric acid is the preparation of Seebach's TADDOLs, e.g. **40**. The dimethyl ester **38** is protected as the acetal **39** and reacted with four molecules of an aryl Grignard to give the TADDOL[13] **40**. All these compounds are C_2 symmetric and various TADDOLs have found applications as resolving agents, NMR additives, asymmetric catalysts and so on.[14] Some of these will feature later in the book.

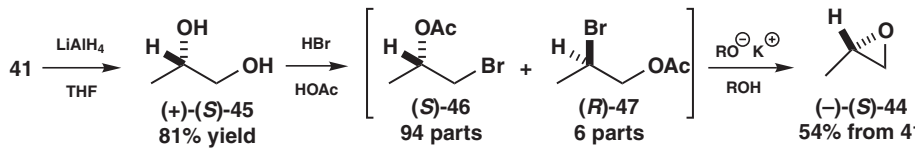


38; dimethyl tartrate **39; 77% yield** **40; TADDOL**

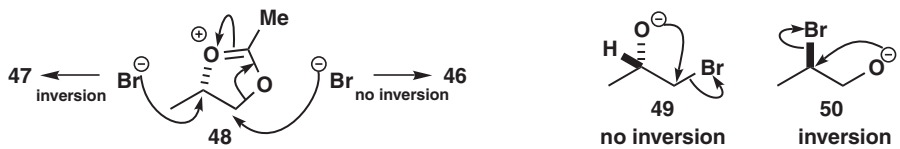
Both enantiomers of a member of the new chiral pool, propylene oxide **44**, can be made from lactic acid **33**. The idea is to reduce the acid and cyclise in two different ways. One is simple enough. Ethyl lactate **41** is mesylated, to turn the secondary alcohol into a leaving group **42**, and then the ester is reduced. Cyclisation uses the primary alcohol of **43** as the nucleophile in an internal S_N2 reaction so that inversion gives (*R*)-propylene oxide[15] **44**.



The second sequence starts with reduction of the ester to give the diol **45** with no change in stereochemistry. Reaction with HBr and HOAc gives an 89% yield of a mixture (94:6) of **46** and **47** which sounds like disaster. Not so as **46** and **47** react in different ways.



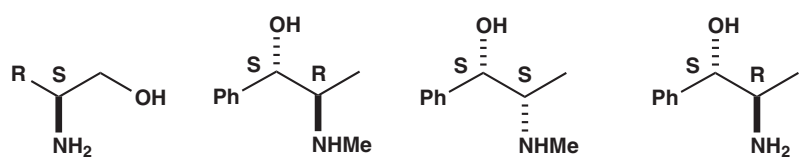
The HBr/HOAc reaction goes *via* the cation **48** that reacts either with or without inversion to give **46** or **47**. Treatment of the mixture with RO^- cleaves the ester to release the oxyanions **48** and **49** which cyclise to **44** without inversion **48** or with inversion **49**. The molecule either undergoes no inversion (*via* **46**) or two inversions (*via* **47**) and the result is retention.[16]



Malic acid **34** is useful for the simple functionalised skeleton it contains and so it is more likely to be incorporated into the target molecule than form part of a reagent. It will feature more in the second half of the chapter.

Amino Alcohols

The amino alcohols **51** derived from amino acids have been mentioned already. Amino alcohols available directly from nature are the ephedrine family: ephedrine **52**, its *anti*-diastereoisomer *pseudo*ephedrine **53** and *nor*ephedrine **54** lacking the *N*-methyl group. The enantiomers of these compounds are also available: (−)-**52** is about twice as expensive, (−)-**53** slightly (about 25%) more expensive, and (−)-**54** about the same price.



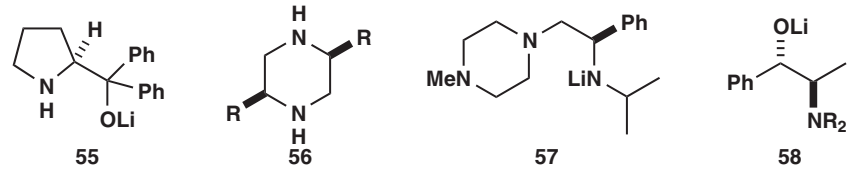
51; amino-alcohols from amino-acids

52; (1 *S*, 2*R*)-(+)-ephedrine

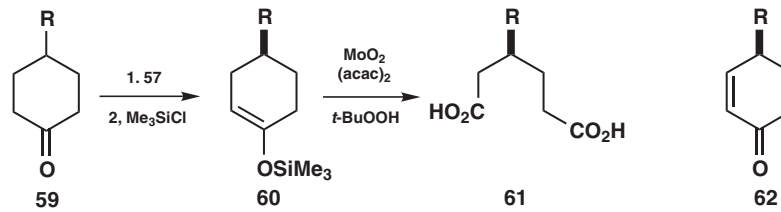
53; (1 S, 2S)-(+)-pseudoephedrine

54; (1 *S*, 2*R*)-(+)-norephedrine

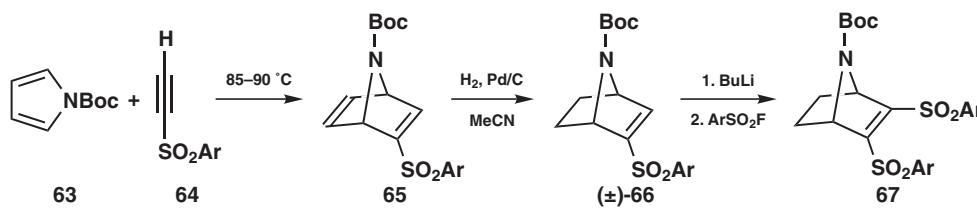
Derivatives of these aminoalcohols are used as bases for asymmetric deprotonation. There is more about this in the next chapter (asymmetric reagents) but we should note here that amino alcohols such as **55** and **58** or diamines such as **56** and **57** have been used successfully. Some, such as **55**, are derived from amino acids, others, such as **58**, are derived from the ephedrine family.[17]



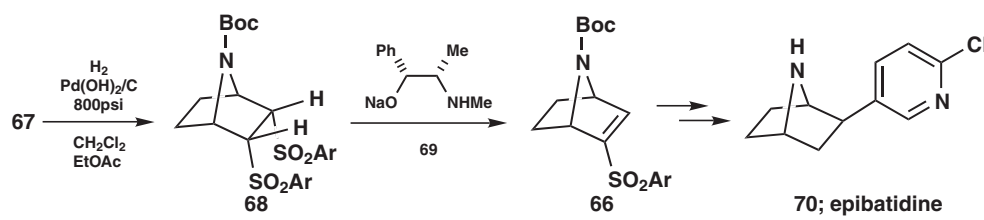
One useful reaction is the desymmetrisation of 4-substituted cyclohexanones **59** to give the silyl enol ethers **60** using the chiral base **57**. The chirality can be made more permanent by oxidative cleavage of the alkene to give the dicarboxylic acid **61**, or by Pd(II) oxidation (chapter 33) to the enone **62**.



A dramatic application was the asymmetric synthesis of epibatidine **70** by Simpkins.[18] Diels-Alder reaction of the deactivated pyrrole **63** with the alkynyl sulfone **64** gave the bicyclic core **65** of epibatidine. Selective reduction gave the compound **66** needed for epibatidine, but in racemic form. A directed lithiation (chapter 7) and sulfonation led to achiral *bis* sulfone **67**.

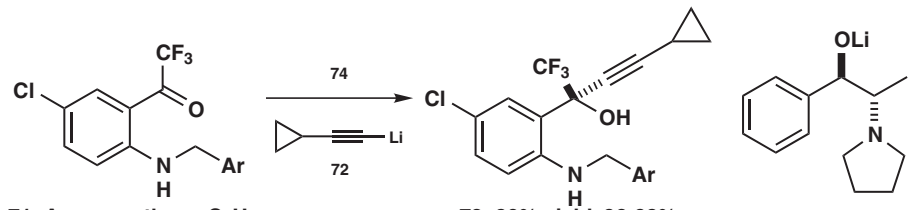


Catalytic reduction from the *exo*-face gave achiral **68** ready for desymmetrisation. Elimination with the chiral base (simply the sodium salt **69** of *pseudo*ephedrine **53**) gave a single enantiomer of **66** ready for conjugate addition of the pyridine and conversion into epibatidine **70**.



The same type of amino alcohol is used as ligand for various organo-lithium additions. *N*-Dialkylated *nor*ephedrines **58**, made by dialkylation of ephedrines,[19] are effective in catalysing the addition of lithium acetylides to carbonyl compounds.[20] This was particularly useful in Merck's

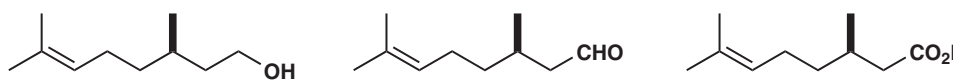
preparation of the anti-HIV drug efavirenz.[21] The ketone **71** was combined with the lithium derivative **74** and the lithium acetylide **72** (both made with BuLi) to give the adduct **73** in 96–98% ee improved to >99.5% by crystallisation.



71; Ar = *p*-methoxy-C_6H_4 **73: 80% yield, 96-98% e.e.** **74**

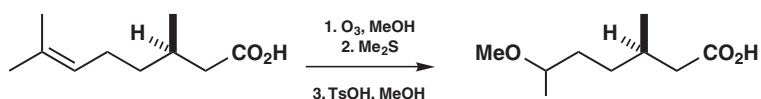
Terpenes

The molecules we have seen so far have usually been incorporated into the target molecule complete. There are two further and most important groups of larger molecules, the sugars and the terpenes, from which pieces are usually snipped out for incorporation. The simple monoterpenes (C_{10} compounds) citronellol **75**, citronellal **76**, and citronellic acid **77** are good examples. They are not cheap but both enantiomers are available, not always in excellent ee.



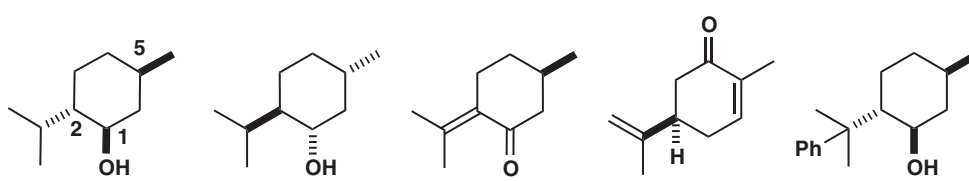
75; (*R*)-(+)-citronellol **76; (*R*)-(+)-citronellal** **77; (*R*)-(+)-citronellic acid**

These compounds are often used by oxidative cleavage of the alkene to give a C_7 unit with functionality at both ends, e.g. **78** from citronellic acid. Notice how the functional groups are carefully made different so that one end can be reacted selectively. This compound **78** was used by Mori in natural product synthesis.[22]



77; (*R*)-(+)-citronellic acid **78**

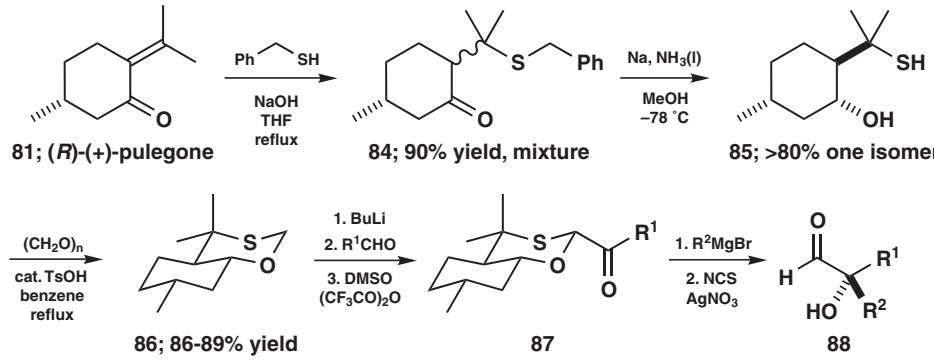
The cyclic monoterpenes are also very useful. Menthol **79** is very cheap and the ketones pulegone **81** and carvone **82** are moderately cheap. All are available as the other enantiomer, e.g. **80**. An important application is as a chiral auxiliary, the favourite being 8-phenylmenthol **83** made from pulegone,[23] see chapter 30.



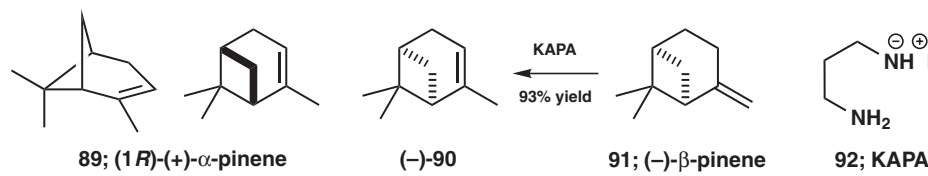
79; (1*R*, 2*S*, 5*R*) -(–)-menthol **80; (1*S*, 2*R*, 5*S*) -(+)-menthol** **81; (*R*)-(+)-pulegone** **82; (*R*)-(–)-carvone** **83; (–)-8-phenylmenthol**

Pulegone has also been used to make the chiral auxiliary **86** that acts as an asymmetric d^1 reagent. Conjugate addition of the thiol $PhCH_2SH$ gives a diastereomeric mixture of ketones **84** from which the single compound **85**, having all substituents equatorial, can be made by reduction.

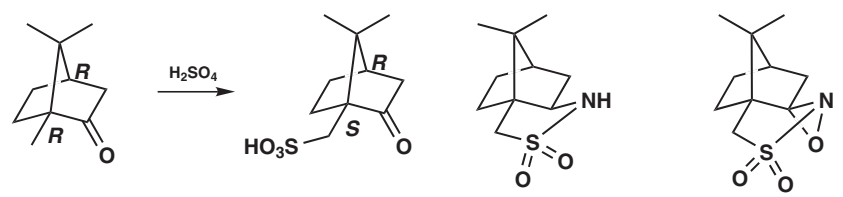
Formaldehyde introduces one carbon that is the d^1 centre in bicyclic **86**. A carbonyl group **87** is added by lithiation and reaction with an aldehyde followed by Swern oxidation. Nucleophiles add to this ketone from the front, i.e. opposite the sulfur rather than the oxygen atom, to give, after removal of the auxiliary, single enantiomers of the alcohols[24] **88**.



There are bicyclic monoterpenes too - α-pinene **89** and β-pinene **91** share a common skeleton with four- and six-membered rings but have the alkene in different places. There is a discussion in chapter 24 on the variable ee of α-pinene and it is better to make the (−)-enantiomer from the more reliable β-pinene **91** (99% ee) that can be isomerised with strong base ('KAPA') **92** in 93% yield to (−)-**90** without loss of ee. Many asymmetric reagents for reduction (chapter 24) and chiral auxiliaries for asymmetric aldol reactions (chapters 27 and 30) are based on α-pinene.[25]



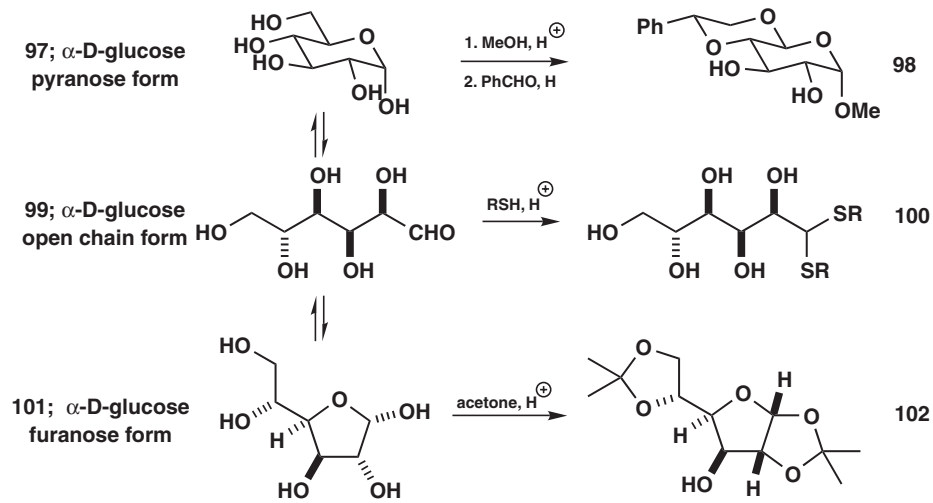
Camphor **93**, a bridged monoterpene with one six- and two five-membered rings is available in both enantiomeric forms and was used by Woodward in the synthesis of vitamin B_{12}. Sulfonation on camphor occurs on the bridgehead methyl group by a series of rearrangements described in the workbook. You will see in chapter 27 how Oppolzer's sultam **95** is used as a chiral auxiliary and in chapter 33 how oxaziridines such as **96** are used in asymmetric oxidation. Both are made from camphor-10-sulfonic acid **94**.



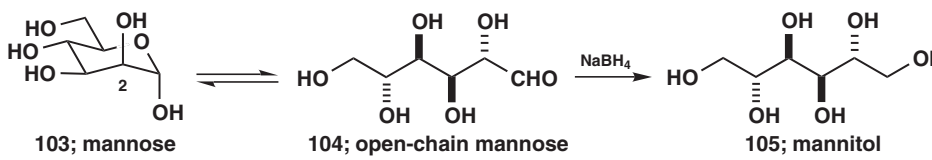
Carbohydrates - the Sugars

The sugars are generally both cheap and optically pure, and more compounds have been made from glucose **97** than any other member of the chiral pool. It is rare that a target molecule looks

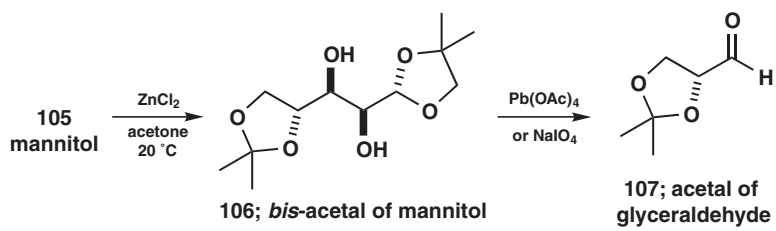
much like glucose, but by keeping in mind that glucose can exist in three forms, the normal pyranose **97**, the open chain **99**, and the furanose **101**, resemblances are easier to find. Each form may be trapped by suitable acetal formation: benzaldehyde prefers the pyranose form with all substituents (including the Ph group) equatorial except the anomeric OMe group, which prefers to be axial **98**. A thiol traps the free aldehyde **99** as the *bis*-alkylthioacetal **100**. Acetone prefers five-membered acetals from *cis* substituents, and so traps the furanose form **102**.



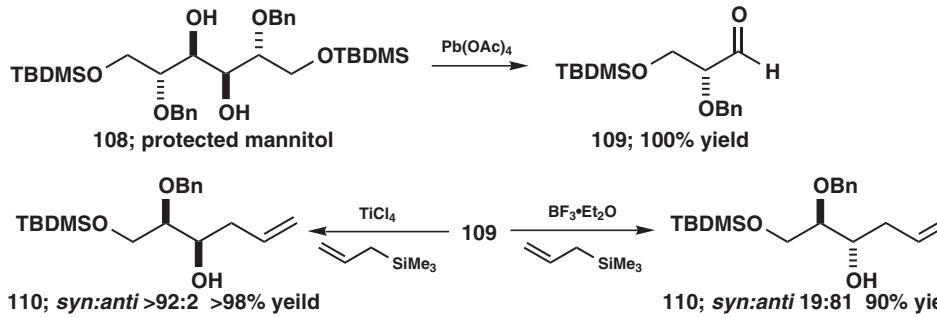
Mannose **103** resembles glucose closely except for the axial OH at C-2. This is a significant difference as the open chain form **104** makes clear: it is nearly C_2 symmetric and, on reduction, becomes so in the form of mannitol **105**.



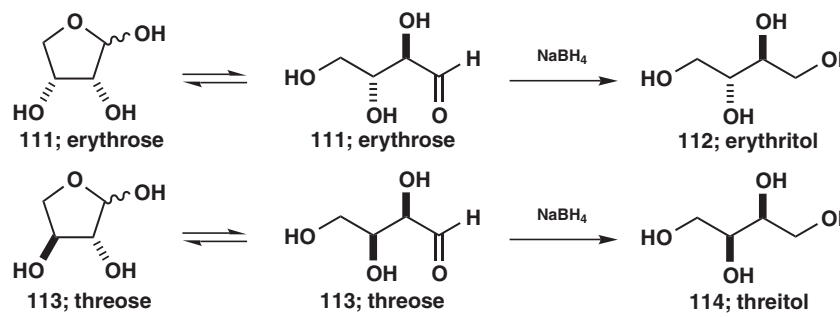
If mannitol is protected as the *bis*-acetal **106** (acetone prefers to form two acetals without stereochemistry rather than a single acetal in the middle - acetal formation is under thermodynamic control) and cleaved oxidatively, both halves give the same product - a protected form of the unstable D-glyceraldehyde[26] **107**.



An alternative sequence that gives 100% yield uses silyl and benzyl protecting groups **109**. This form of protected glyceraldehyde reacts with allyl silane to give **110** with good stereoselectivity that is dependent on the Lewis acid used as catalyst.[27] The products have been used in the synthesis of the immunosuppressant FK506 useful in transplant surgery.[28]



Glyceraldehyde, of which **107** and **109** are protected forms, is the only three-carbon sugar. There are two four-carbon sugars: erythrose **111** and threose **113**. Both exist in hemiacetal (furanose) and open chain forms and both are chiral but their symmetry properties differ. The tetrols formed by reduction of the aldehydes are *meso* erythritol **112** and C_2 symmetric threitol **114** having the same stereochemistry as tartaric acid **35**. Threose or threitol can be oxidised to tartaric acid. These sugars are the origin of the terms '*erythro*' and '*threo*' sometimes used to describe such diastereomeric relationships.

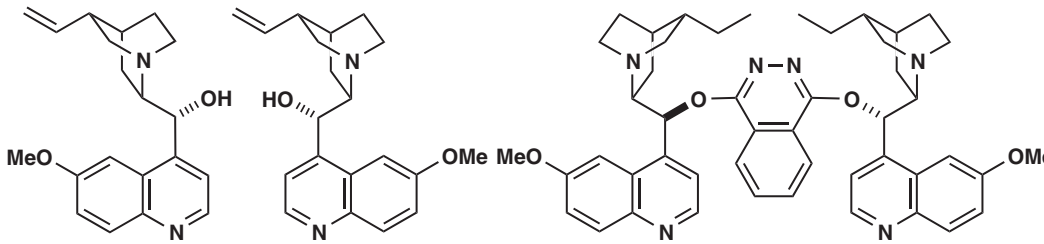


Threitol **114** has been used in many asymmetric syntheses, for example, the preparation of the C_2 symmetric *bis*-epoxide **117** by protection of the secondary and activation of the primary alcohols. Cyclisation of **116** could in principle give two fused four-membered rings, but three-membered rings are greatly preferred kinetically. The *bis*-epoxide **117** reacts with nucleophiles at the terminal carbons.[29]

The Alkaloids

These nitrogen-containing natural products, often with powerful biological properties, are not usually incorporated into target molecules. However, they are important in asymmetric syntheses as the foundations of many reagents and catalysts. Quinine **119** is familiar as an anti-malarial and an ingredient in tonic water. Quinine and its twin *cinchona* alkaloid quinidine **118** are referred to as *pseudo* enantiomers. Each occurs naturally as one enantiomer only but the two structures are nearly enantiomeric: only the vinyl side-chains disturb the symmetry and they act as enantiomers. The vinyl side-chains are reduced and two molecules of, say, dihydroquinine (DHQ) are joined

by a spacer such as phthalazine (PHAL) to form the catalyst $(DHQ)_2$-PHAL **120** that accelerates dihydroxylation of alkenes by OsO_4.



118; quinidine **119; quinine** **120; $(DHQ)_2$-PHAL**

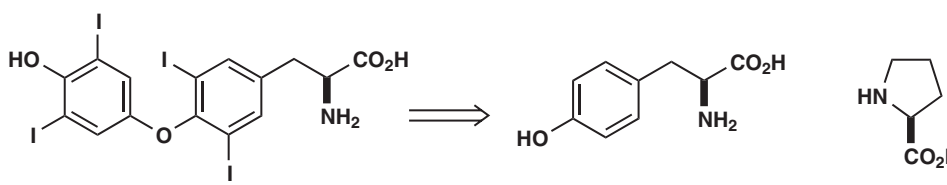
Other alkaloids such as brucine were used as resolving agents but their expense and extreme toxicity has made them unpopular and the availability of a range of amines (chapter 22), often made from the chiral pool, has made them unnecessary.

Part II – Asymmetric Syntheses from the Chiral Pool

Here we discuss syntheses of target molecules based on the chiral pool strategy using the same sequence of natural products as part 1. This time we discuss why the chiral pool strategy was chosen and try to demonstrate the particular value of each type of compound.

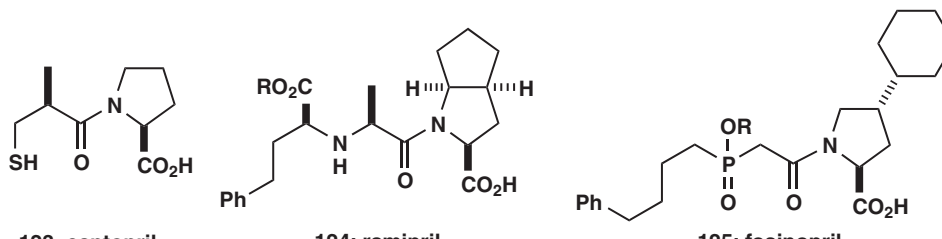
Amino Acids

With some targets the structure of an amino acid is immediately obvious. The thyroid hormone thyroxine **121** present in the thyroid gland contains the skeleton of the proteinaceous amino acid tyrosine **122** and can indeed be made from it.



121; thyroxine **122; tyrosine** **6; proline**

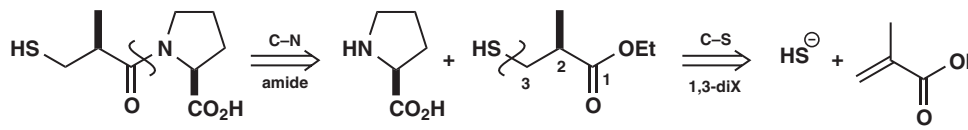
We have already met proline **6** and its structure is clearly contained in the Bristol-Meyers Squibb ACE inhibitor captopril **123**. In other cases the relationship is not so obvious. Other ACE inhibitors, also used to treat high blood pressure, such as ramipril **124** and fosinopril **125**, also contain the elements of proline but it is not obvious how we should use that observation.



123; captopril **124; ramipril** **125; fosinopril**

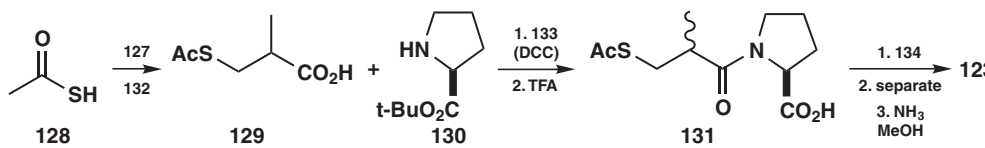
The synthesis of captopril

The first disconnection is easy **123a**: it is in the middle of the molecule, at the amide bond and reveals the molecule of proline **6**. The thiol acid **126** has a 1,3-relationship between SH and C=O and can be made by conjugate addition.



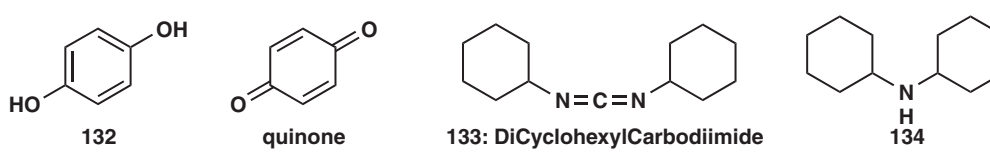
123a; captopril **6; proline** **126** **127**

Thiolacetic acid **126** is used as a reagent for nucleophilic SH (it is a carbonyl compound and the S atom is the nucleophile) and does the conjugate addition well. The racemic product **127** is coupled to protected proline **128** and the *t*-butyl ester hydrolysed to give a mixture of diastereoisomers of **129**. The salts of these can be separated and, after cleavage of the thiolester, the right isomer gives captopril. Proline acts as a resolving agent as well as providing half of the target molecule.



128 **129** **130** **131**

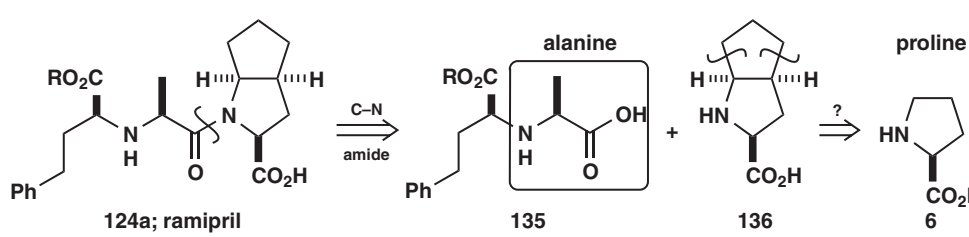
Three reagents deserve some comment. Quinol **132** is easily oxidised to quinone and protects the thiolacid **128** against disulfide formation. DCC **133** is a standard peptide coupling agent uniting free NH_2 and CO_2H groups by removing water to give dicyclohexylurea. The simple amine **134** is sufficient for separation by crystallisation during the resolution as the resolving agent (proline) is already present in the molecule and a crystalline salt is all that is needed. Making both diastereoisomers separately (each as a single enantiomer of course) established that **123** was several orders of magnitude more active than the other isomer.[30]



132 **quinone** **133: DiCyclohexylCarbodiimide** **134**

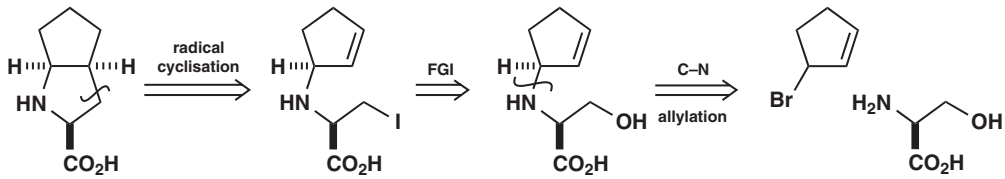
The synthesis of ramipril

Ramipril **124**, the Hoechst ACE inhibitor, is obviously more complicated. The first amide disconnection is the same and we can see the structure of alanine in the acid **135**. The amine **136** looks like proline but no reactions spring to mind to make the bonds corresponding to the disconnections.

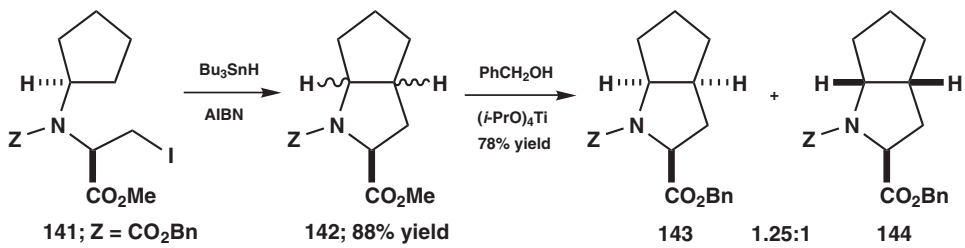


124a; ramipril **135** **136** **6**

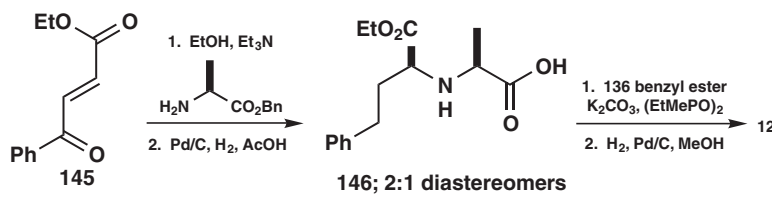
In practice **136** was not made from proline. Breaking open the other, more functionalised, ring **136a** is possible with the idea of a radical cyclisation onto an alkene **137**. FGI of hydroxyl for iodine reveals the elements of another amino acid, serine **140** and an allylic bromide **139**.



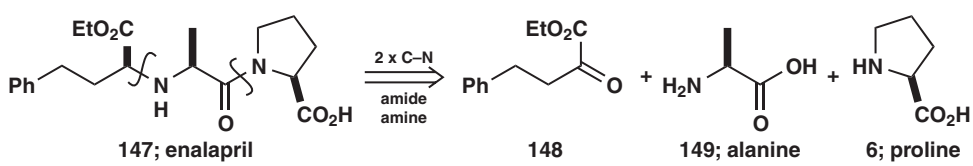
The key step in the synthesis was the radical cyclisation of **141** that gave an excellent yield of two diastereoisomers: both had *cis* ring junctions and the compounds could be separated after conversion to the *bis* benzyl esters **143** and **144**. Hydrogenation of **143** released **136**. Once again the chiral pool material (serine) acts both as starting material and resolving agent though here there was some selectivity (1.25:1) in favour of the right diastereoisomer[31] **143**.



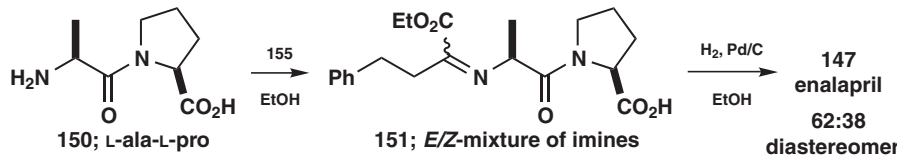
An ester of **136** is now used as resolving agent in coupling to the rest of the ramipril molecule. Conjugate addition of alanine to the ketoester **145** gives a 2:1 mixture of **146** and its diastereoisomer. Coupling with **136** allows separation of the right compound and hence completes the synthesis of ramipril.



The losses in yield when these semi-resolutions occur are not ideal and some ACE inhibitors are made with much better selectivity. Enalapril **147**, Merck's Vasotec, is easily disconnected to three simple pieces, proline **6**, alanine **149**, also part of ramipril, see **135**, and the keto-acid **148**, assuming we can make the amine by reductive amination.

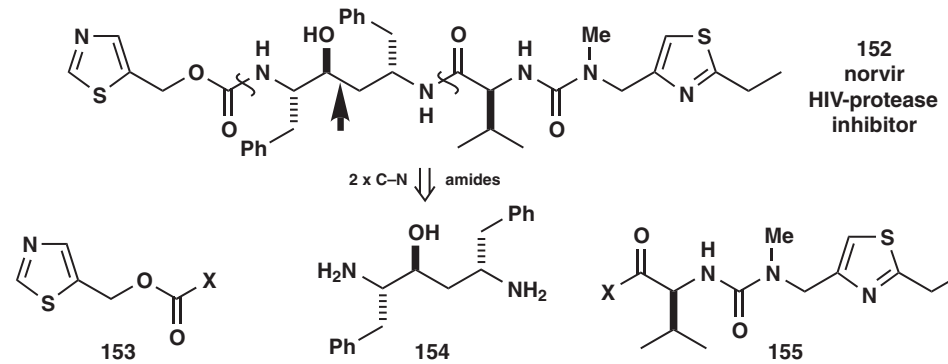


Normal peptide coupling (*N*-Boc-Ala with proline benzyl ester coupled with DCC and removal of the protecting groups) gives the dipeptide **150**. Formation of the imine **151** and reductive amination gives a 62:38 selectivity in favour of **147** providing that the reducing agent is hydrogen with Pd/C. Sodium cyanoborohydride gives almost 50:50. The maleate salt of **147** was separated by crystallisation.[32]

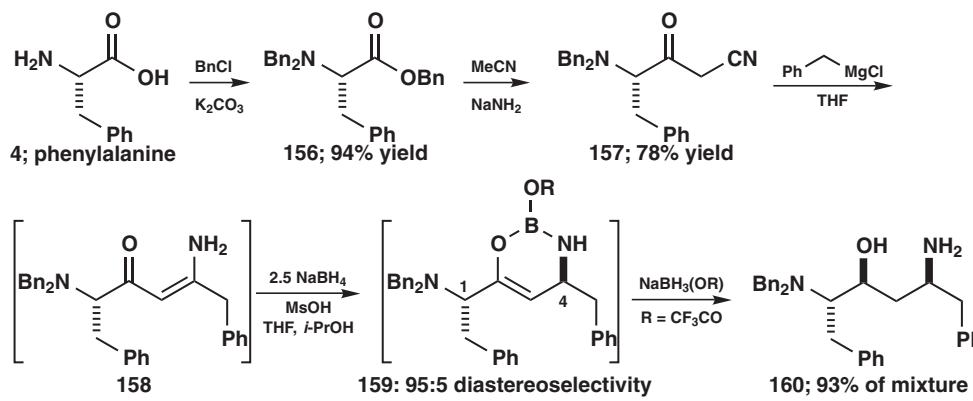


HIV-protease inhibitors

The HIV-protease inhibitors, probably the most successful drugs used to prevent HIV turning into AIDS, are all protein mimics with an unreactive C−C bond replacing an amide link. That bond is marked with a broad arrow in norvir **152**, Bristol-Myers Squibb's entry in this class. Amide disconnection reveals that the key central part of the molecule **154** looks like a phenylalanine dipeptide except that it has the C−C bond. So can we make **154** from phenylalanine **4**?



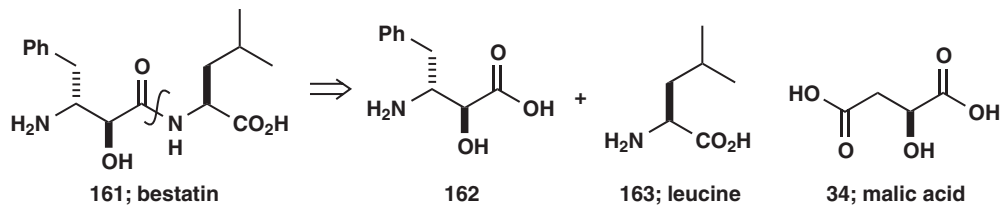
Phenylalanine **4** is protected with benzyl groups **156** and combined with the anion of acetonitrile to give **157**. Benzyl Grignard attacks the nitrile to give the enaminone **158** which is immediately reduced to the boron complex **159** that shows remarkably high 1,4-stereoselectivity (95:5). Still without isolation, reductive cleavage of **159** gives **160**, a protected version of **154**, again with excellent stereoselectivity.[33] The deprotected intermediate **154** is isolated in 60% yield from the enaminone **158** after debenzylation by Pd-catalysed transfer hydrogenation with ammonium formate.



Hydroxy-Acids

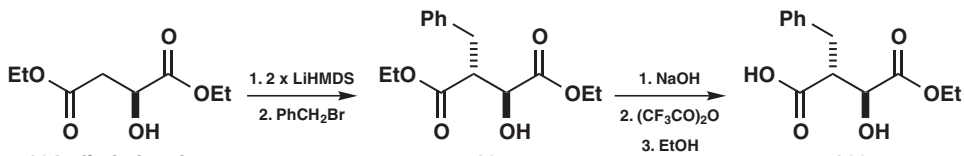
The synthesis of bestatin

The potent enzyme (aminopeptidase) inhibitor bestatin **161** provides another perfect bridge between the amino- and the hydroxy-acids. At first sight bestatin appears to be a dipeptide but only one of the components, leucine **163** is a normal α-amino acid. The other half **162** is a β-amino acid and also an α-hydroxyacid and that might give us the idea that malic acid **34**, with the same absolute configuration at the secondary alcohol, could provide a chiral pool starting material.



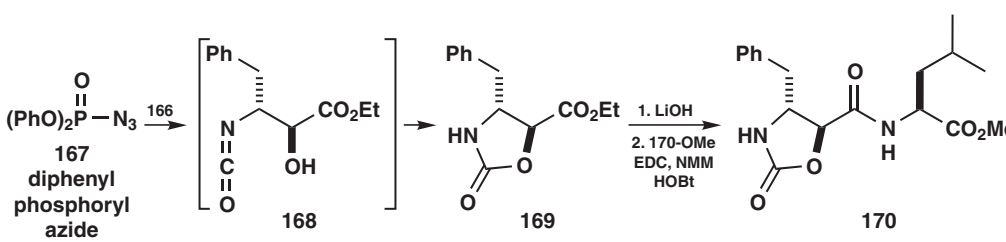
161; bestatin **162** **163; leucine** **34; malic acid**

First the benzyl group must be added. The di-lithium derivative of diethyl malate **164** is alkylated on the opposite side to the OLi group (chapter 30). Now the two ester groups must be distinguished. Reaction of the free diacid with trifluoroacetic anhydride and then with ethanol gives **166**. Presumably the two acids form a cyclic anhydride and the free OH forms an ester. Reaction with ethanol occurs at the more reactive (next to $OCOCF_3$) and less hindered (not next to benzyl) carbonyl group of the anhydride and the trifluoroacetyl groups fall off during work-up.



164; diethyl malate **165** **166**

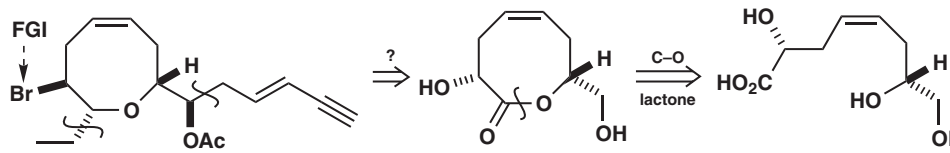
The free acid group is converted into an amine with diphenylphosphoryl azide **167**. A Curtius rearrangement with retention at the migrating group gives the isocyanate **168** which is captured by the OH group to give the cyclic carbamate **169**. Peptide coupling with leucine methyl ester using a water soluble carbodiimide (EDC), *N*-methyl morpholine (NMM) as base, and hydroxybenzotriazole (HOBt) as catalyst gives a slightly disguised form of bestatin **161** with all the stereochemistry correct.[34]



167 diphenyl phosphoryl azide **168** **169** **170**

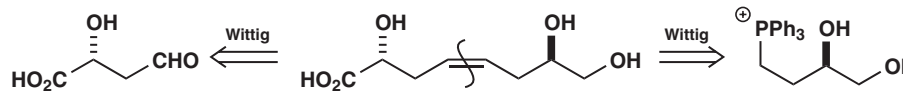
The synthesis of (+)-laurencin

Some molecules that can be made from the chiral pool give little hint of that when you first inspect their structures. It is only after the disconnection process had started that smaller fragments reveal a possible natural starting material. Laurencin **171** reveals its marine origin by the bromine atom and the eight-membered ring that is the heart of the molecule. Trimming off the side chains and writing a lactone **172** having the right sort of functional groups in the right places makes the problem much simpler and opening the lactone reveals a relatively simple open chain intermediate **173**.



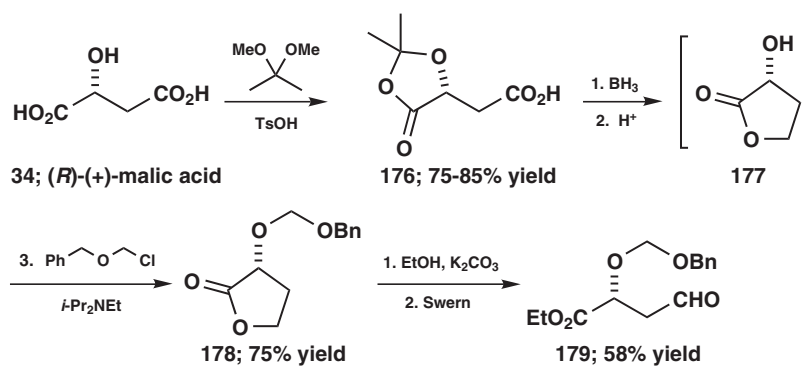
171; (+)-laurencin **172** **173**

Since there is a *cis* alkene in the middle of **173** a Wittig disconnection **173a** makes sense and the starting materials **174** and **175** turn out to be four-carbon units with functionality, mostly in the form of oxygen atoms, at C-1, C-2 and C-4. This is job description for malic acid and both compounds can indeed be made from (*R*)-(+)-malic acid[35] **34**.



174 **173a** **175**

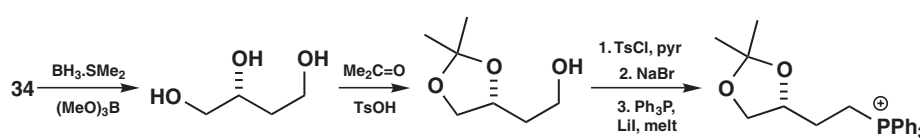
A protected version of the aldehyde **174** comes from acetal formation and reduction of the remaining CO_2H group. Acid catalysed hydrolysis of the acetal gives the lactone **177** that is protected as **178**. Hydrolysis and oxidation give **179** ready for the Wittig reaction.



34; (*R*)-(+)-malic acid **176; 75-85% yield** **177**

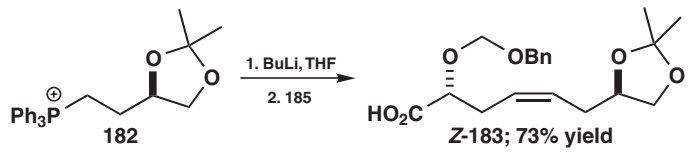
178; 75% yield **179; 58% yield**

The phosphonium salt **175** requires similar operations but malic acid **34** is reduced to the triol **180** before selective protection **181** leaves just one alcohol for conversion to tosylate, bromide and finally protected phosphonium salt **182**.



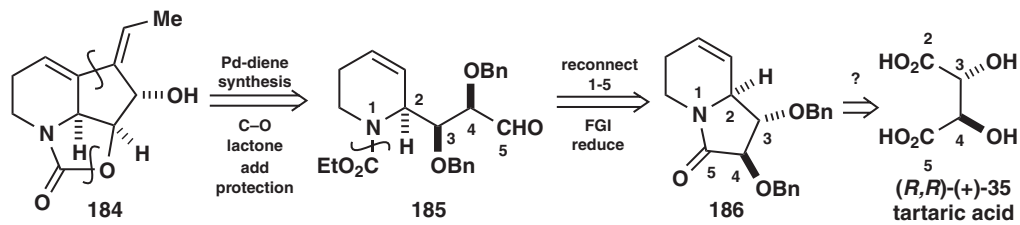
180; 98% yield **181; 82% yield** **182; 100% yield**

The Wittig reaction between the ylid formed from **182** with BuLi and the protected aldehyde **179** does indeed give the *Z*-alkene **183**, a protected version of **175**, ready for cyclisation and completion of the synthesis of laurencin. Notice how far apart (1,6-related) are the chiral centres in **183**. Making both independently from malic acid ensures that the right diastereoisomer, as well as the right enantiomer, results.

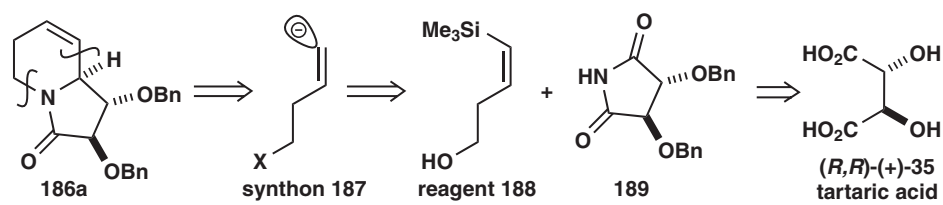


Streptazolin from tartaric acid

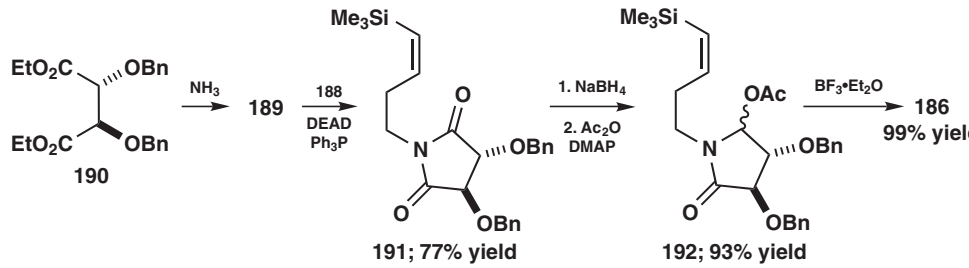
Streptazolin **184**, an antibiotic from a *Streptomyces* species, has a cluster of three rings, an awkward exocyclic alkene with geometry and three neighbouring chiral centres. There is no obvious chiral pool starting material. Disconnecting the lactone is obvious and we might be able to control the alkene geometry by the kind of Pd-catalysed coupling we met in chapter 18. This gives **185** from which we can remove the carbamate. The aldehyde can be reconnected to the nitrogen atom to give **186** - atoms 1 and 5 have been joined as an amide. Now the possibility emerges of making streptazolin from tartaric acid[36] **35**.



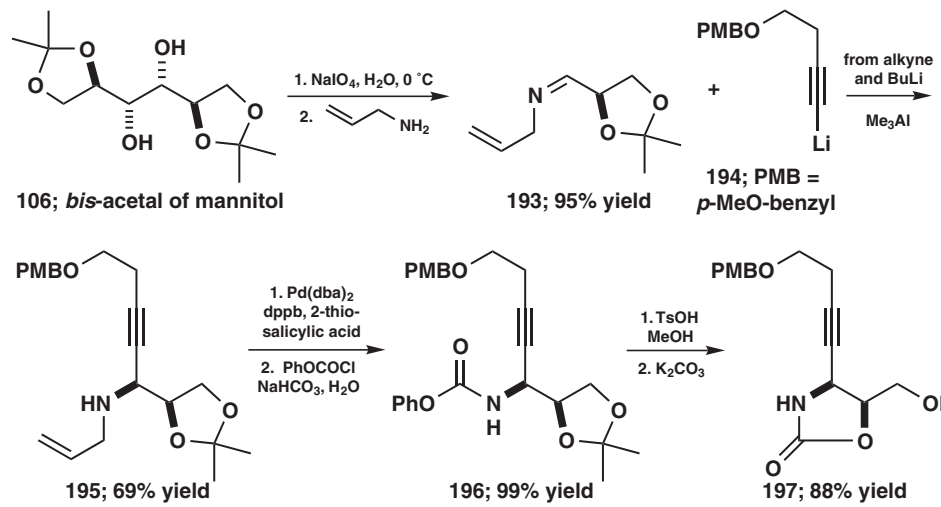
To get back to tartaric acid from **186** we must disconnect as in **186a** and the obvious synthon is **187** with the proviso that the nucleophilic end must control the geometry of the alkene. A vinyl silane is a good answer (chapter 18) with some leaving group at the other end **188** together with the imide **189** obviously derived from tartaric acid **35**.



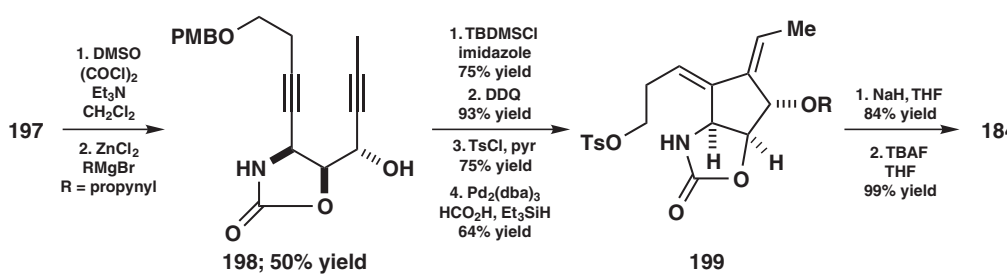
The imide **189** is easily made from protected tartaric acid **190** and the vinyl silane **188** coupled in a Mitsunobu reaction. Reduction of one of the carbonyl groups of the imide **191** may seem tricky but the molecule is C_2 symmetric so the two carbonyl groups are the same and once one is reduced the molecule is a much less reactive amide. The stereochemistry of the acetate in **192** does not matter as it disappears in the cyclisation to **186**. Notice that the alkene geometry is retained.



The next few steps including the vital palladium-catalysed cyclisation revealed a problem in this synthesis and it is continued in the workbook. An improved synthesis by Trost uses two alkynes in the cyclisation and the problems disappear. This starts from protected mannitol **106** and the oxidative cleavage is followed at once by imine formation **193**. Addition of the lithium derivative **194** goes with good selectivity (13:1 in favour of **195**). Adjustment of protecting groups and hydrolysis of the acetal leads to the key intermediate[37] **197**.



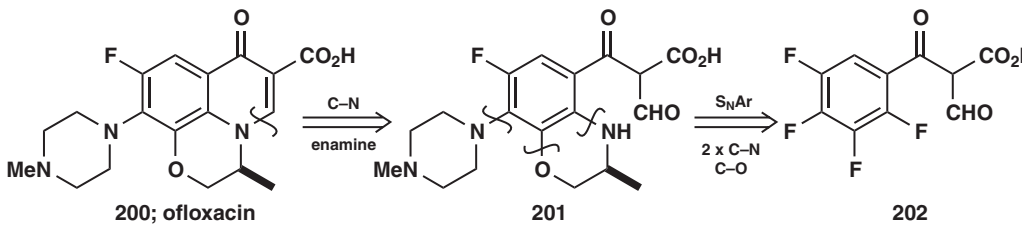
The second alkyne is introduced after oxidation to an aldehyde again with good selectivity (6:1 in favour of **198**). Protecting groups are added or adjusted before the Pd(0)-catalysed cyclisation gives both alkenes in **199** in the right place with the right geometry. The mechanism of the cyclisation was already established by Trost[38] and is discussed in the workbook. Cyclisation and deprotection gave streptazolin **184** in only 11 steps from the chiral pool.



Amino Alcohols

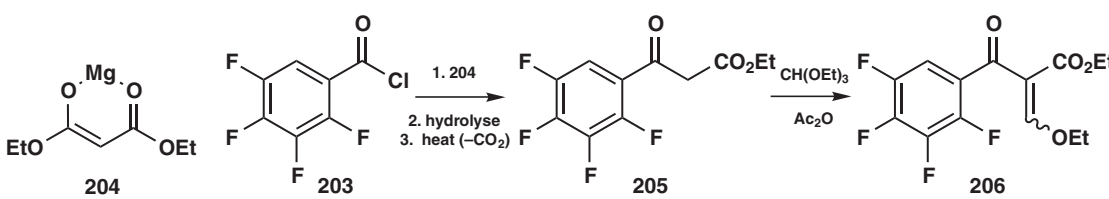
Synthesis of quinolone antibiotics

Quinolone antibiotics such as ofloxacin **200** are totally different from β-lactams, tetracyclines and so on and work in a different way. They offer some hope that resistance may be slow to appear. They all contain the 'quinolone' core: a benzene ring fused to a γ-pyridone. Most have various amine substituents and ofloxacin has a fluorine atom. Disconnection of the enamine reveals a benzene ring with a series of heteroatom substituents (N, N, O, F) and the one fluorine suggests that a series of nucleophilic substitutions might provide a synthesis.



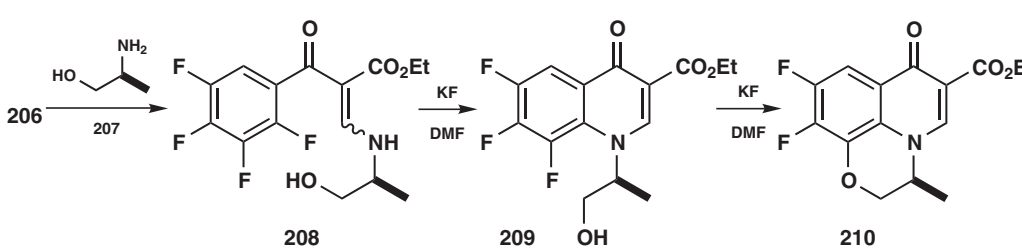
200; ofloxacin **201** **202**

The acid chloride of tetra-fluoro benzoic acid **203** acylated the magnesium enolate **204** of diethyl malonate to give **205**. The chelated magnesium enolate avoids *O*-acylation. Condensation with ethyl orthoformate puts in the masked aldehyde group and **206** is ready for a succession of aromatic nucleophilic substitutions.[39]



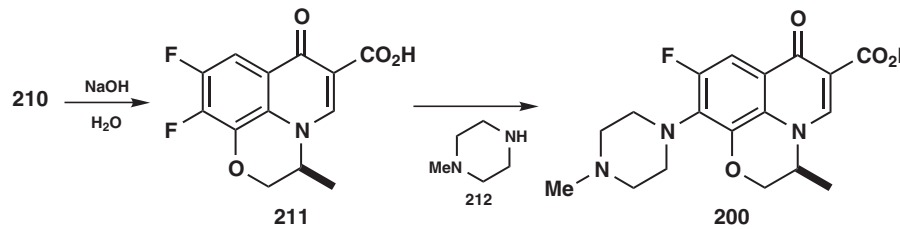
204 **203** **205** **206**

Reaction with the amino alcohol alaninol **207** from the chiral pool forms the enamine **208** and introduces the only chirality. The first two substitutions are controlled by the tether. The amine can reach only the *ortho* position to give the quinolone **209** and now the hydroxyl group can reach only the *meta* position to give **210**. The geometry of the enamine **208** means nothing as it is a conjugated enaminone and such double bonds rotate easily. The displacement of F by N to give **209** is activated by the carbonyl group but that of F by O to give **210** is not. The three fluorine atoms in the ring help and it is an intramolecular reaction.



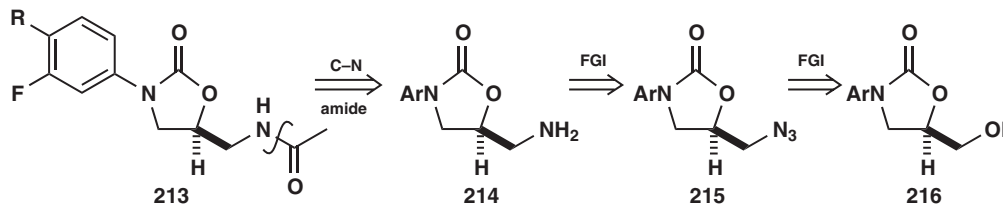
208 **209** **210**

That leaves just one nucleophile to introduce, the piperazine ring. After hydrolysis of the ester, *N*-methylpiperazine **212** displaces the fluorine *para* to the ketone and ofloxacin is formed. Amino alcohols are closely related to amino acids so this one example will be enough. The next group of antibiotics also look as though they might come from amino alcohols, but wait…

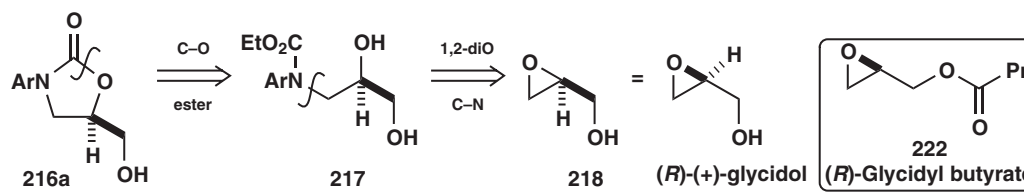


The oxazolidinone antibiotics

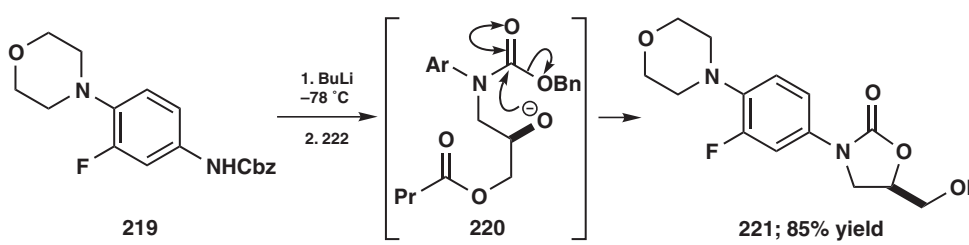
The oxazolidinones, general structure **213**, such as the Upjohn compound U100766, **213**; R = morpholine, are antibiotics that act by a different mechanism to all others. Amide disconnection takes us back through amine **214** and azide **215** to alcohol **216**.



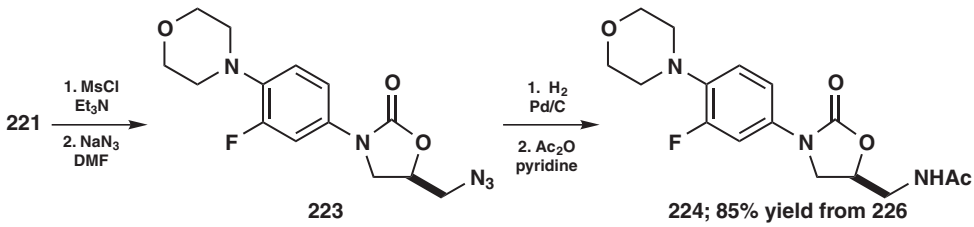
Opening the oxazolidinone ring reveals a three carbon chain with one functional group on each carbon atom **217**. Glycidol, available as either enantiomer, is an ideal starting material.



One of these antibiotics **224** was made by Upjohn from the Cbz-protected aromatic amine **219** and the ester **222** in place of glycidol. The lithium derivative of **219** attacks the epoxide releasing an oxyanion that attacks the Cbz group **220** releasing $PhCH_2O^-$ that in turn cleaves the butyrate ester and gives **221** in one pot and 85% yield.[40]

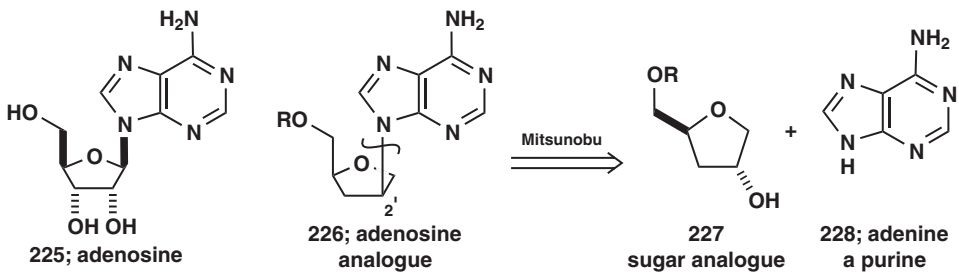


The synthesis is completed with mesylation and azide displacement to give **223** then reduction of N_3 to NH_2 and acetylation. This **224** is U100766, an antibiotic with a potency similar to that of vancomycin that might not stimulate resistance as quickly as β-lactams.[41]

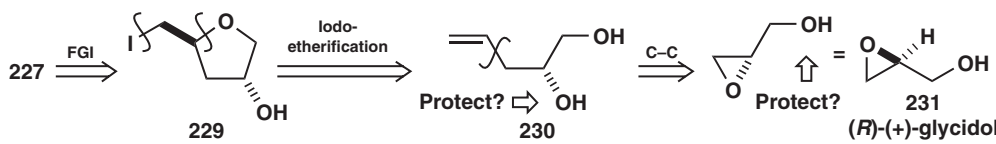


The synthesis of anti-viral nucleoside analogues

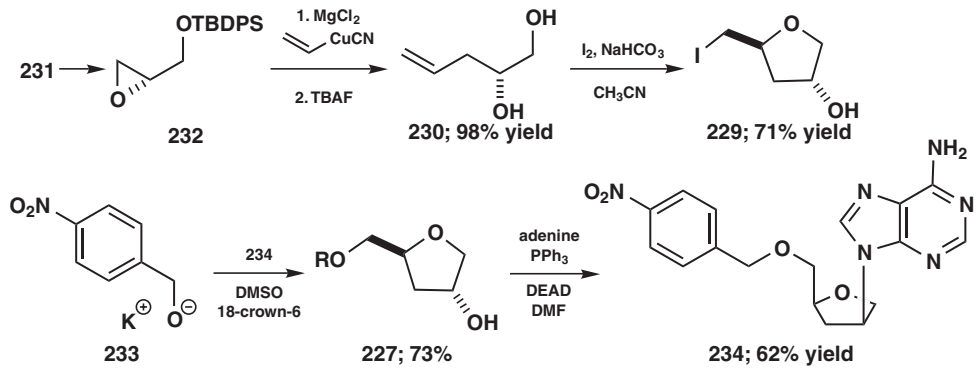
Many anti-viral compounds are analogues of the natural nucleic acid nucleosides such as adenosine **225**. This example **226**, known as (*S,S*)-iso-ddA (dda stands for di-deoxy-adenosine), has a severely modified sugar **227** but the purine, adenine **228**, is unaltered. The purine is attached to C-2′ instead of C-1′ making the molecule more stable and two of the OH groups have been removed. Coupling adenine to the modified sugar **227** needs a Mitsunobu process.[42]



Since **227** has a 1,2-diX relationship, one way to make it would be to change the terminal OR into I **229** and use an iodine cyclisation of the alkene **230**. That allows us to recognise a glycidol unit **231** by disconnection of the vinyl group.



It turns out that we need to protect only one of the hydroxyl groups: the primary OH of glycidol as a *t*-butyl diphenylsilyl ether **232**. The epoxide is opened by a vinyl cuprate and the iodoetherification occurs regio- and stereoselectively (no four-membered rings are formed and the *trans* stereochemistry of **230** is preferred). Iodide is displaced by the *p*-nitrobenzyloxide **233** and finally the Mitsunobu reaction with adenine goes on the right nitrogen atom to give **234**.

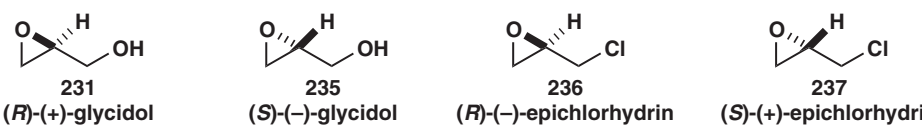


The New Chiral Pool

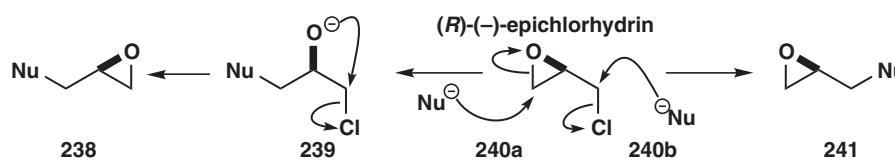
Glycidol as a chiral pool member

You may have felt that all this was out of place as glycidol is not available from natural sources. But both enantiomers are available quite cheaply by several processes such as Sharpless asymmetric epoxidation (chapter 25) and enzymatic hydrolysis of glycidol esters (chapter 29). We propose to elect glycidol and a number of other small molecules to the 'New Chiral Pool' as they now fill the same role as, say, the amino acids – cheap sources of enantiomerically pure small fragments of molecules that can easily be added to other fragments with predictable stereochemistry.

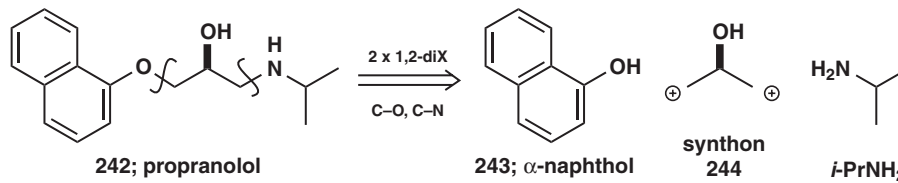
Whenever you require an electrophilic three-carbon fragment with functionality at all three carbons, glycidol **231** or **235** is a natural choice. But there's another, arguably even more useful reagent that does much the same thing – epichlorhydrin **236** and **237**.



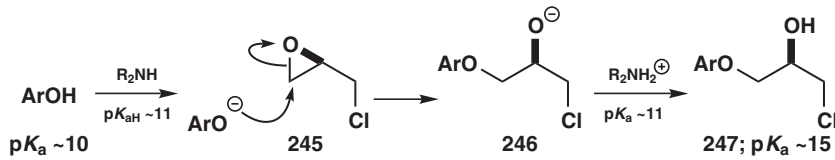
There is a complication: it is obvious that the terminal epoxide atom of glycidol is attacked by nucleophiles, but epichlorhydrin could be attacked at the terminal epoxide atom or at the CH_2Cl group. This matters a great deal: direct displacement of chloride **240b** gives one enantiomer of **241** but attack at the epoxide **240a** followed by cyclisation **239** gives the other **238**.



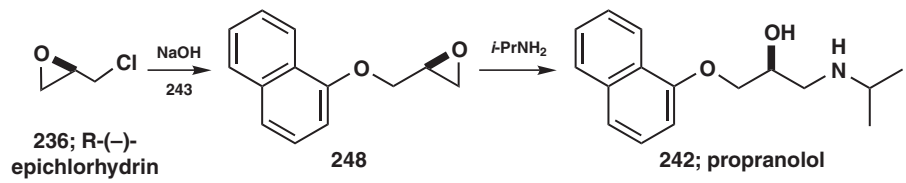
This sequence is particularly important in the synthesis of β-blockers such as propranolol **242**. Disconnecting α-naphthol **243** and *i*-$PrNH_2$ reveals a C_3-synthon **244**, electrophilic at both ends, that must be chiral. Epichlorhydrin is ideal.



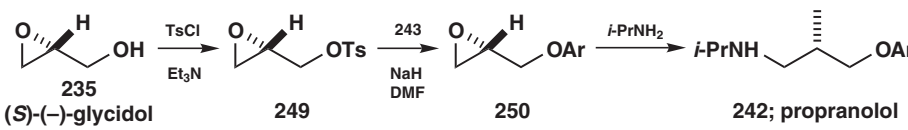
If we react epichlorhydrin with α-naphthol **243** and an amine, the amine (pK_{aH} about 11) will remove the proton from the phenol and that will attack epichlorhydrin **245** to give the alkoxide **246** that will remove a proton from the amine salt to give the intermediate **247**.



If we want to do the reaction in one step we must use a stronger base, such as NaOH, so that the intermediate **246** has a long enough lifetime to cyclise to the new epoxide **248** that will react with *i*-PrNH$_2$ to give propranolol.[43]

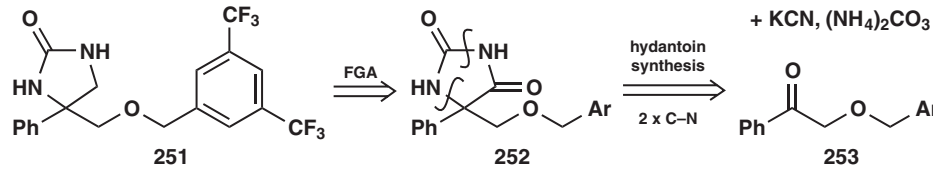


To make enantiomerically pure propranolol, it doesn't matter which way round the reaction goes as long as you know which and as long as it goes one way or the other. Glycidol **235**, easily made from mannitol, was made by Sharpless using asymmetric epoxidation (chapter 25) and converted into the tosylate **249**. This reacts with the anion of α-naphthol **243** at the CH_2OTs end and not at the epoxide end to give **250** and hence propranolol.[44] But we must use the other enantiomer, (*S*)-glycidol **235**, whereas we used (*R*)-epichlorhydrin **236**.

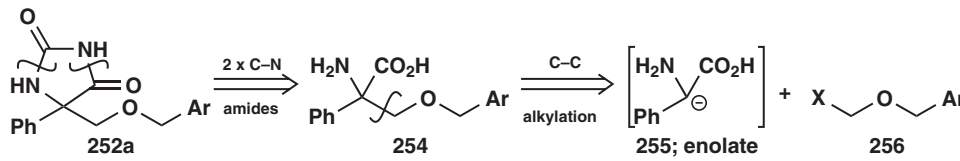


Phenylglycine as a chiral pool member

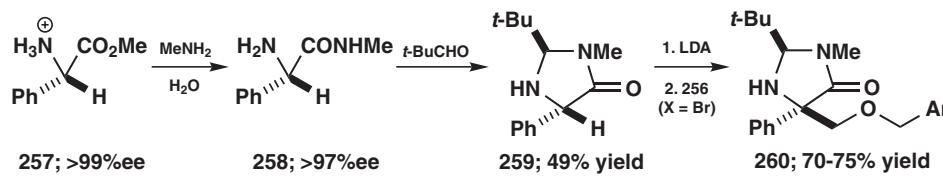
Phenylglycine doesn't occur in proteins but is available as either enantiomer. When Schering-Plough made the racemic drug **251** as an NK1 antagonist, the task was easy. Because a trusty hydantoin synthesis already existed, they mixed the ketone **253** with potassium cyanide and ammonium carbonate to get **252** and reduced out the spare amide carbonyl with $LiAlH_4$.



When they wanted a single enantiomer, this synthesis was useless. Where could chirality be introduced? Instead they disconnected the other two C−N bonds in the ring **252a** and worked their way back to the enolate of phenylglycine **255** and some alkylating agent **256**.

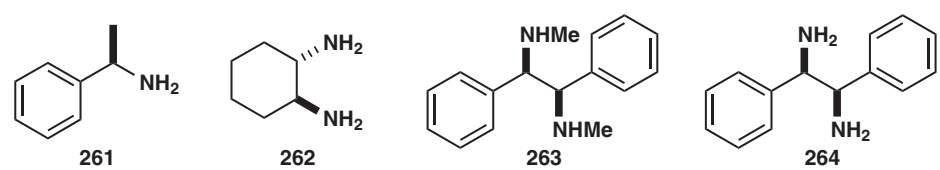


They did not know, of course, which enantiomer would be more active but it turned out that the methyl ester **257** was the right choice. Conversion to the amide **258** and aminal formation with pivalaldehyde **259** allowed control of enolate alkylation by Seebach's relay method (chapter 30). Hydrolysis of **260** and reaction with $ClSO_2NCO$ gave one enantiomer[45] of **251**.

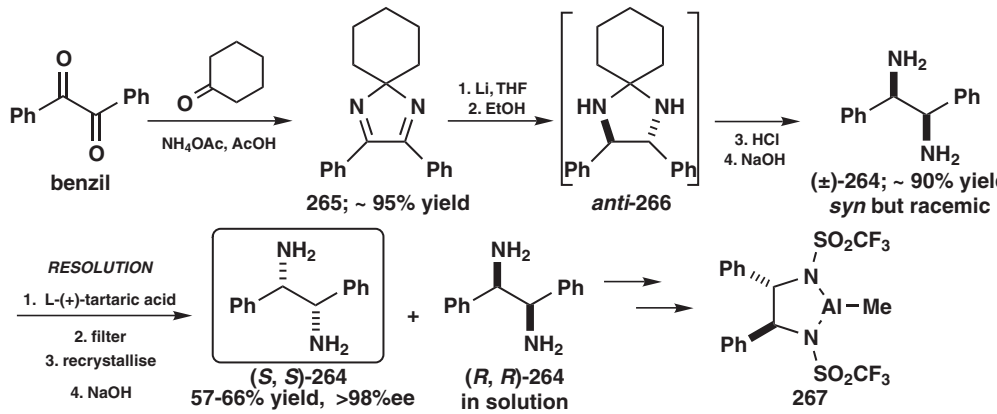


C_2 symmetric diamines as chiral pool members

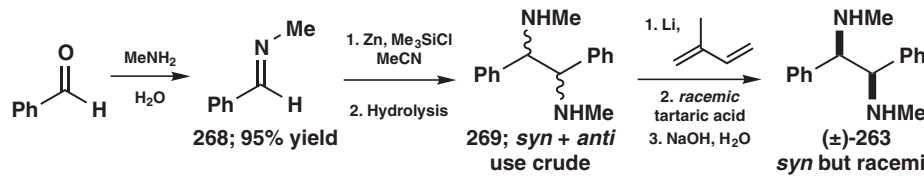
One mono-amine **261** and one diamine **262** were resolved in chapter 22 by the simplest of processes. They are joined in the new chiral pool by two closely related C_2 symmetric diamines, **263** and **264**, made by rather different procedures. Though we show only one enantiomer of these amines, both are available at about the same price as they are all made by resolution.



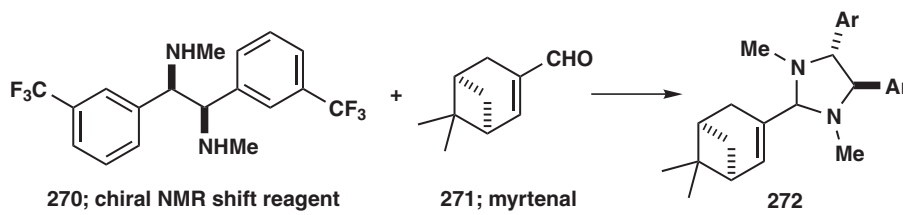
Diamine **264** is made from the α-diketone benzil by a simple but multiple cyclisation to give the heterocycle **265**. Stereoselective dissolving metal reduction gives *anti*-**266** and hence racemic **264** on aminal hydrolysis. Resolution with tartaric acid brings down crystals of the tartrate of one enantiomer. With L-(+)-tartaric acid, the salt with (*S,S*)-**264** is less soluble while (*R,R*)-**264** requires treatment with D-(−)-tartaric acid. One important application is the asymmetric Lewis acid[46] **267**.



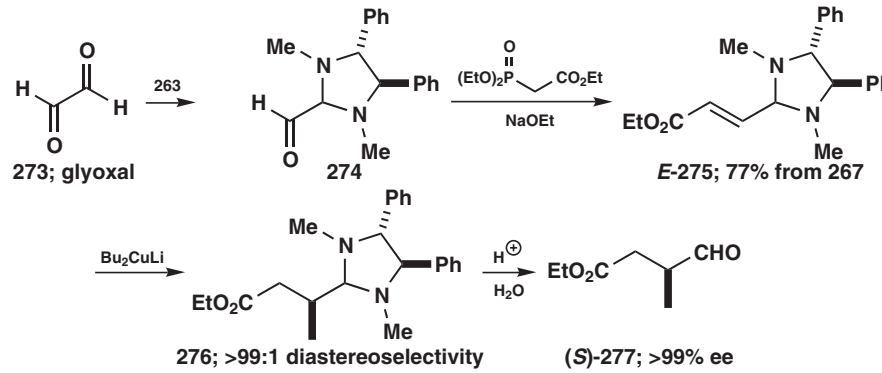
Diamine **263** is made by the radical (pinacol style) dimerisation of the benzaldehyde imine **268**. This gives a diastereomeric mixture equilibrated in favour of the *syn* isomer with lithium in isoprene and separated (51% yield) from the *meso* isomer by crystallisation with racemic tartaric acid.[47] Finally, (±)-**263** is resolved with a single enantiomer of tartaric acid giving 90% yield of either (*S,S*)-**263** or (*R,R*)-**263**, depending on which enantiomer of tartaric acid is used, in 99% ee. The isomer remaining in solution can be isolated with only slightly worse ee: 96%.



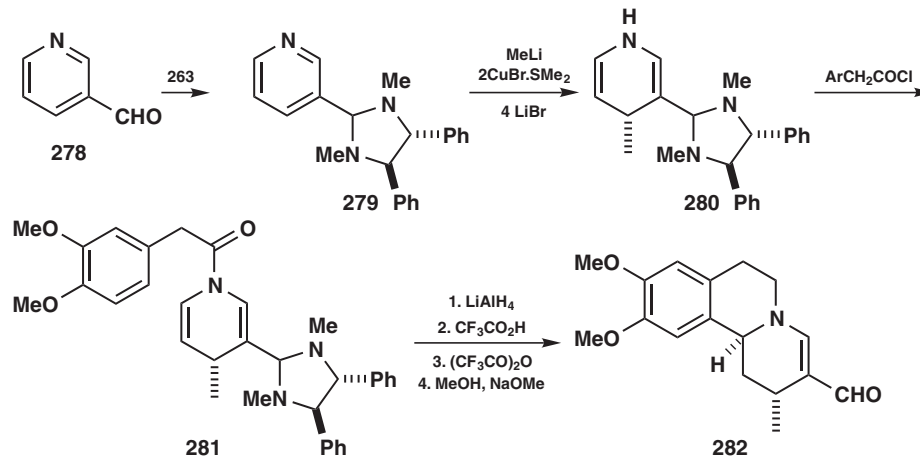
This diamine has had many uses. The *bis m*-trifluoromethyl compound **270** made in the same way from *m*-trifluoromethylbenzaldehyde, is a chiral NMR shift reagent that gives better spectra than the more traditional Eu-based shift reagents and allows the reliable determination of ee. Terpenes are notorious for low ees and the ee of myrtenal **271** was determined as 96% by formation of the aminal **272** and the measurement of its ^{19}F NMR spectrum.[48] The signals for the two diastereoisomers were easily distinguished and integrated even though the compounds were difficult to separate by chiral HPLC.



Compound **263** itself forms C_2-symmetric aminals and the one from glyoxal **273** is valuable in controlling nucleophilic attack on the remaining aldehyde group **274** or on electrophilic alkenes such as **275** formed in a Wadsworth-Horner-Emmons reaction (chapter 15). The aminal can be hydrolysed with acid in conditions that do not cause any racemisation even next to an aldehyde.[49]

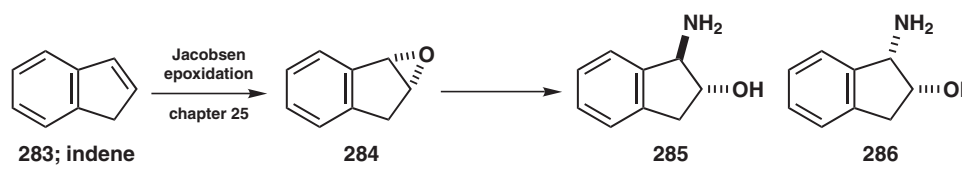


The aminal **279** with pyridine-3-aldehyde **278** adds cuprates in the 4-position with excellent stereoselectivity to give partly reduced pyridines **280** that are immediately acylated **281**. This example can be reduced and cyclised to the alkaloid **282** with two chiral centres under control.[50]

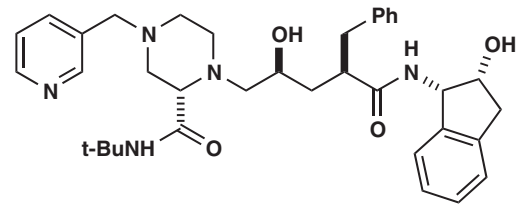


Amino-indanols

These may seem strange molecules to have a place in the new chiral pool but they were made on a vast scale by Merck in the synthesis of their HIV protease inhibitor crixivan (Indinavir). They both come from Jacobsen epoxidation of indene **283** (chapter 25): the *anti*-compound **285** by opening the epoxide **284** at the benzylic centre with azide ion.[51]

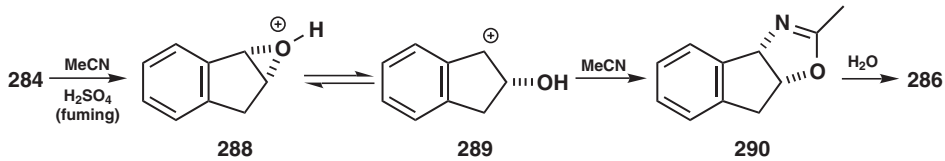


The *syn* compound **286** is more interesting. It was absolutely necessary for the synthesis of crixivan and is clearly visible at the right hand end of **287**. It is not a natural product.



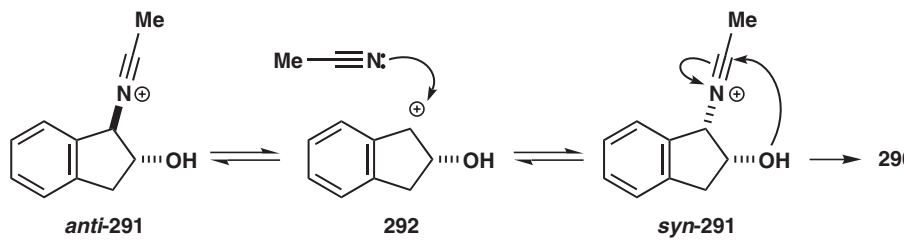
287
Merck's HIV-protease inhibitor crixivan (Indinavir)

Merck devised a synthesis that was so efficient that **286** is now available commercially (it was only a rumour that Merck would give it away free as they had so much) and has been used in asymmetric synthesis in many ways. The synthesis is described[52] in full by the Merck team in *Organic Syntheses*. The epoxide **284** is protonated by acid to give the cation **288** that captures acetonitrile in a Ritter reaction giving the heterocycle **290** that is easily hydrolysed to **286**.



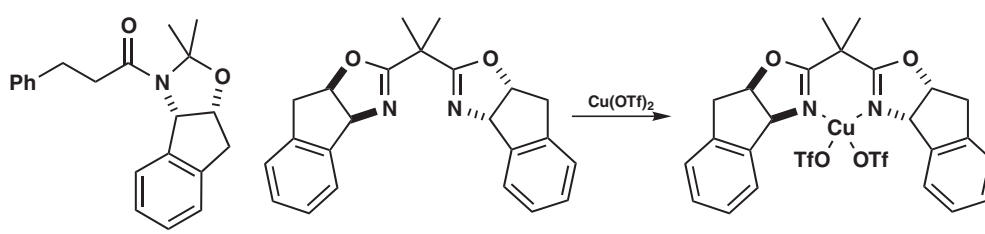
288 **289** **290**

The stereochemistry of this reaction looks all wrong. In fact the cation **289** prefers to capture acetonitrile **292** from the top side, opposite the OH group, to give *anti*-**291**. But this intermediate cannot cyclise and is in equilibrium with **292**. Only when *syn*-**291** is formed can cyclisation occur and the cations are removed from the equilibrium. Even the cyclisation that does occur looks bad enough but *5-endo-dig* reactions are all right.



***anti*-291** **292** ***syn*-291**

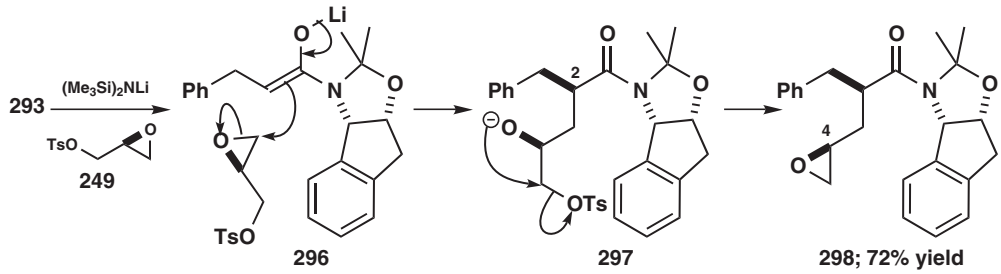
The amino-indanol **286** is the basis for many important asymmetric reagents such as the enolates derived from **293** and the metal complexes such as **295** derived from the dimer **294**. These are effective as catalysts for Diels-Alder reactions.[53]



293 **294** **295**

The synthesis of crixivan (Indinavir)

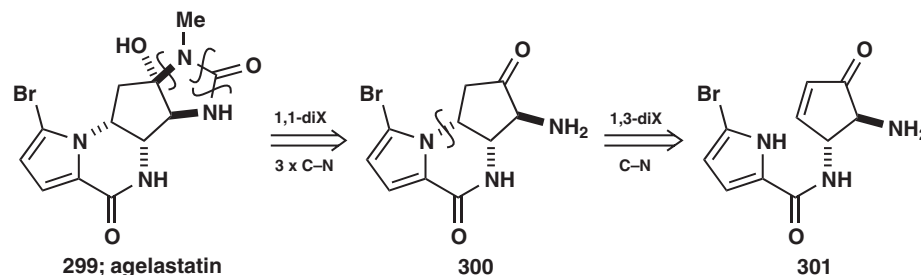
Further steps in this synthesis are interesting as the alkylation of the enolate of **293** with glycidol tosylate **249** puts in the next two chiral centres. Attack occurs at the epoxide end of the electrophile **296** and the stereochemistry at C-2 is controlled by the amino-indanol. The stereochemistry at C-4 is controlled by the electrophile and is again unchanged when the epoxide **297** is attacked by the piperazine nucleophile.[54] The remaining centre in crixivan is in the piperazine ring and this is secured by asymmetric hydrogenation (chapter 26). We have now explored both new and old chiral pool enough to look at a few syntheses without prejudging the starting materials.



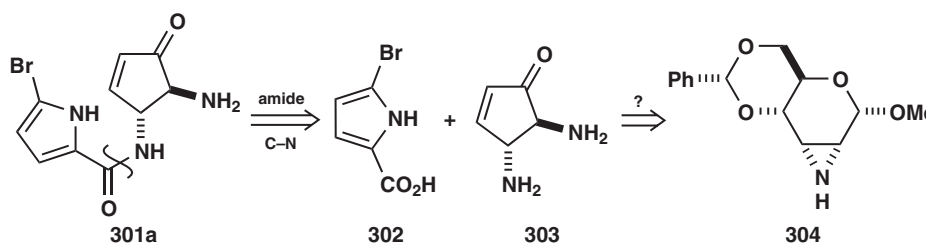
Conclusion: Syntheses from the Chiral Pool

The synthesis of agelastatin

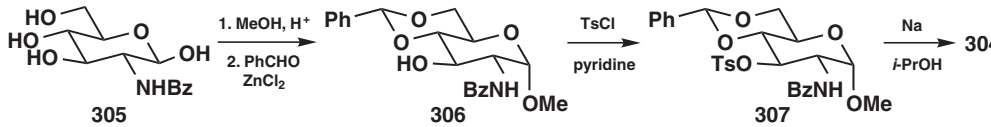
Agelastatin **299** is an interesting molecule partly because it is an anti-neoplastic and partly because of the massing of functionality around such a small frame. It contains a cluster of heteroatoms all having 1,1-diX relationships and removal of these reveals the basic carbon skeleton having a carbonyl group in a 1,3-relationship to the pyrrole nitrogen. Disconnection **300** with conjugate addition in mind reveals a much simpler compound **301** with just two neighbouring chiral centres.



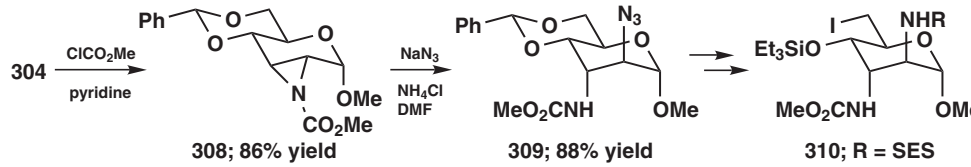
Disconnecting the amide **301a** isolates the five-membered ring containing both chiral centres **303**. It is not obvious whether this compound could be made from the chiral pool but literature search revealed a glucosamine derivative **304** that looked promising. Neither of your authors has detailed knowledge of the sugar literature, and neither author would have seen this possibility.



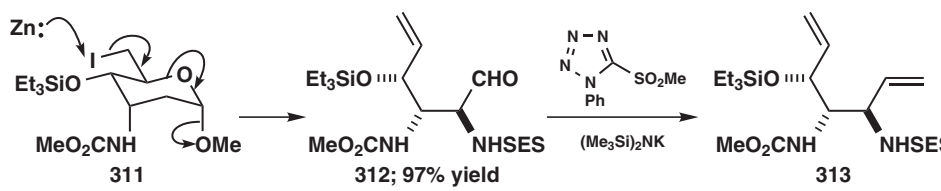
Glucosamine can be *N*-benzoylated **305** and protected as a methyl glucoside and a benzylidene acetal leaving just one OH free **306**. Tosylation of this free OH and treatment with base gives the three-membered ring[55] **304**.



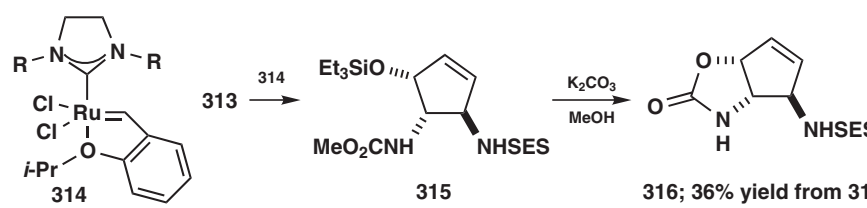
The synthesis of agelastatin from **304** is too long to describe in detail so we shall just pick out the most important stages. The *trans* relationship between the two nitrogen atoms in **303** was established by opening the *N*-acylated aziridine **308** with azide ion. The *trans*-diaxial product **309** is formed (chapter 21). Further functional group and protecting group manipulations (five steps) give **310**. The protecting group SES is $Me_3SiCH_2CH_2SO_2^-$, designed to be removed by fluoride ion.



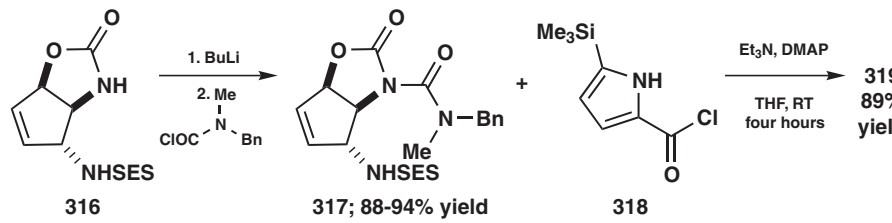
Now two critical steps. The iodide **310** is fragmented by zinc in aqueous THF **311** to give the unsaturated aldehyde **312** in astonishing yield. The mechanism **311** has the NHR group omitted for clarity: the loss of the MeO group may not be concerted with the rest. Though Wittig and Peterson failed, a Kocienski-Julia reaction (chapter 15) gave the diene **313** used immediately in the next step.



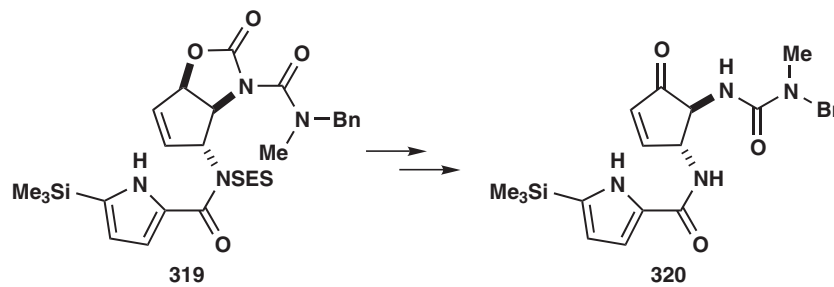
We hope you guessed that metathesis was used to close the five-membered ring. The modified Hoveyda-Grubbs catalyst **314** gave the best results and the product **315** cyclised to **316** after removal of the Et_3Si and CO_2Me protecting groups. This compound contains all the functionality and stereochemistry of **303**. So was it all worth it, just to use glucosamine from the chiral pool? Well, this was the first asymmetric synthesis.[56]



The final stages[57] are better seen if we turn **316** round to make it look more like **303**. Protection of the ring nitrogen **317** allowed acylation of the other nitrogen by the pyrrole **318** having Me_3Si in place of Br.

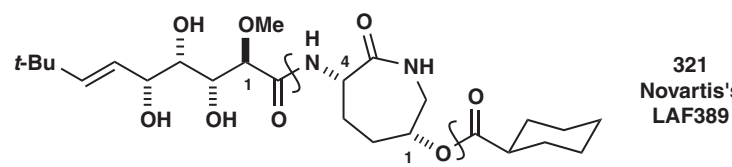


While **319** could be converted into the required enone **320**, no amount of trying allowed further progress with the synthesis. Conjugate addition occurred but other reactions followed. The answer was bromination. This gave a mixture of mono-, di-, and tri-brominated pyrroles but they all cyclised with Hünig's base to a mixture of protected **300** brominated in various places from which agelastatin was finally made.

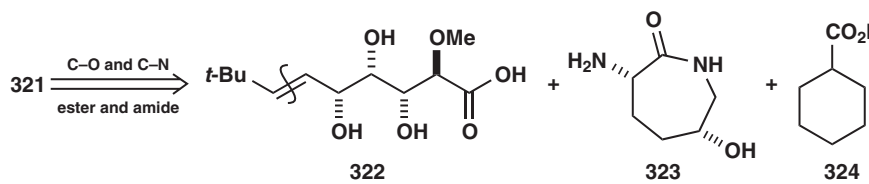


The synthesis of LAF389, a Novartis anti-cancer agent

The natural product bengamide B shows promising anti-cancer activity and Novartis have initiated a programme to synthesise the analogue LAF389 **321** on a large scale.[58] It contains a side chain with four contiguous chiral centres joined by an amide to a seven-membered ring heterocycle with two chiral centres.

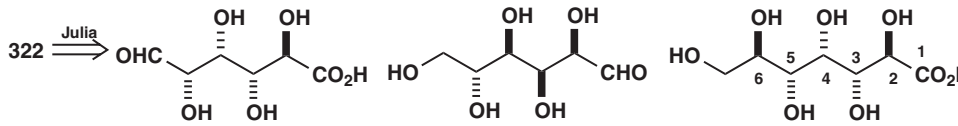


There is a 1,4-relationship both between the chiral centres on the ring and between those on the side chain and the nearer on the ring. This makes the ester and amide disconnections shown on **321** attractive giving three starting materials.

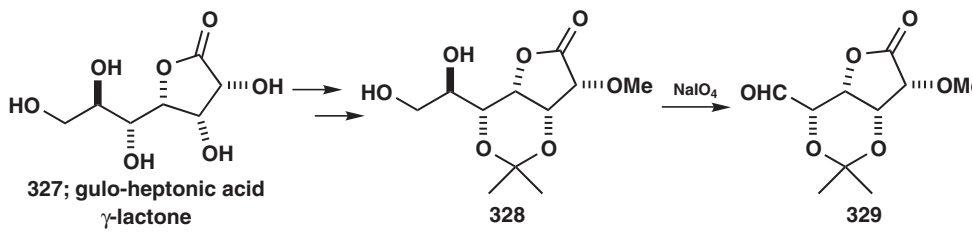


The side chain fragment **322** has the look of a sugar and, if the alkene is removed with a Julia reaction in mind (as it is an *E*-alkene, chapter 15), it has six carbon atoms with oxygen on each one **325**. Unfortunately two of the centres are not those in glucose **99**. However a C_7 sugar, the

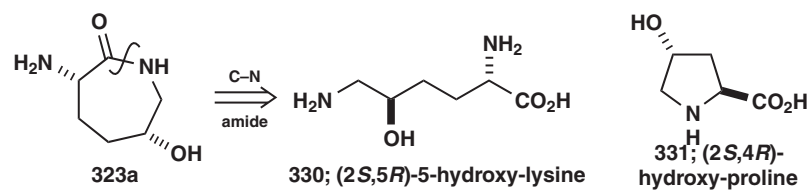
gulo-heptonic acid **326** is available. It has all the right stereochemistry at C-2 to C-5, only C-6 is unwanted but as it also has one too many carbon, that centre can be removed in making the aldehyde **325**. Again, a search of the sugar literature would be helpful.



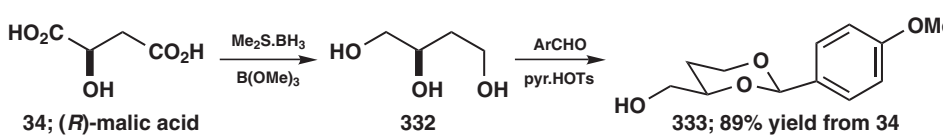
The acid **326** exists as the lactone **327** and can be selectively protected as **328** for oxidative cleavage by periodate to give **329**. The development synthesis was similar to the laboratory synthesis but in this step as in many others careful improvements were needed for it to be safe and effective on a large scale.



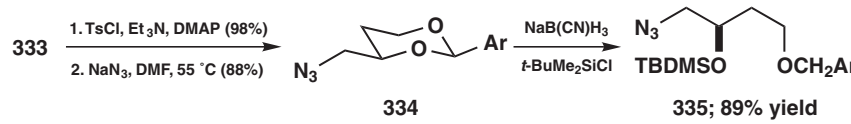
The other chiral component, the lactam **323**, is clearly a cyclised version of 5-hydroxy-lysine **330**. This and hydroxyproline **331** occur in the connective protein collagen. The hydroxy groups are added after the collagen is assembled but as they can be obtained by hydrolysis of collagen, they are members of the chiral pool.



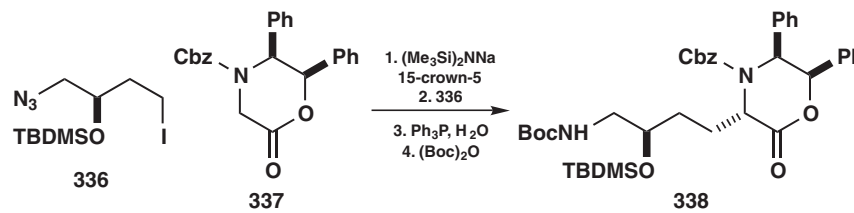
Hydroxyproline is abundant but hydroxylysine is not. Fortunately it can be made[59] from an abundant member of the chiral pool - malic acid **34**. Borane reduction gives the triol **332** and anisaldehyde gives the diequatorial acetal **333** under thermodynamic control.



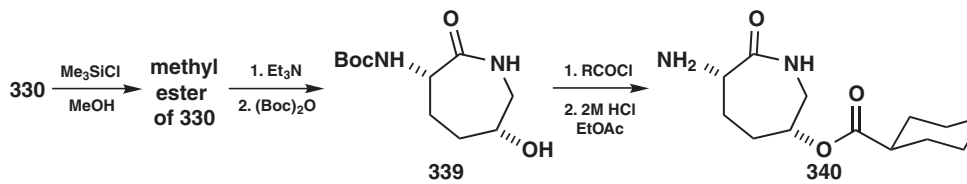
The free OH group can be converted into the azide **334** by the usual sequence. Now comes a critical step. The acetal is opened by reduction with remarkable (in their words 'unexpected') selectivity to give **335**. The key is to have a Lewis acid (a silyl chloride) present. If a proton is used, the opposite selectivity is achieved.



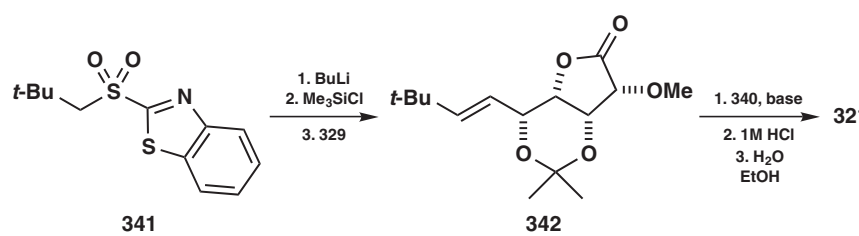
Now the terminal OH group can be deprotected, turned into a leaving group **336**, and used to alkylate an asymmetric glycine anion equivalent, the heterocycle **337**. The azide is then reduced and protected to give **338**, a protected version of **330**. The yield in the alkylation was 94% and only one diastereoisomer was detected.



The synthesis of **323** needed activation as the methyl ester for cyclisation to occur spontaneously. Protection of the primary amine was needed to get selective acylation of the alcohol to give **340**.



The final stages of the synthesis of LAF389 require only the combination of **340** with the Julia reagent **341** and deprotection and the synthesis of the drug molecule **321** from two different members of the chiral pool is complete.

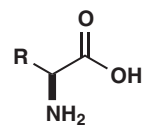


Part III – The Chiral Pool

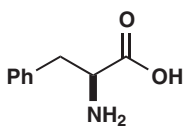
In the following tables the main members of the traditional chiral pool with our selection from the 'new chiral pool' are listed with the compound numbers given them in this chapter. The most accessible full listing is in Morrison[60] and the most comprehensive in Houben-Weyl[61] (this volume is in English). Valuable (and free) source books are the catalogues of chemical suppliers. These are the only way to find out prices as these change year-by-year.

The amino acids

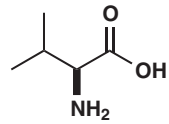
The proteinaceous α-amino acids are all available. They have the general structure **3** where R can be an alkyl group or a variety of substituted groups.[3,4] There are full listings in many textbooks.[62] Important members of this class described in the chapter include phenylalanine **4**, valine **5**, proline **6**, glutamic acid **7**, aspartic acid **9**, alanine **149** and leucine **163**. To these we add two functionalised amino acids, the thiol cysteine **343** and the amine lysine **344** with two heterocyclic amino acids, the imidazole histidine **345** and the indole tryptophan **346**.



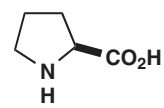
3; (L)-amino acids



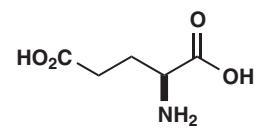
4; (*S*)-(–)-Phe
phenylalanine



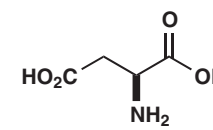
5; (*S*)-(+)-Val
valine



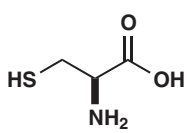
6; (*S*)-(–)-Pro
proline



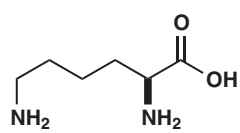
7; (*S*)-(+)-Glu
glutamic acid



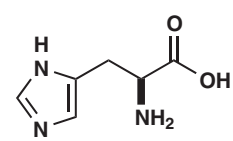
9; Asp
(S)-(+)-aspartic acid



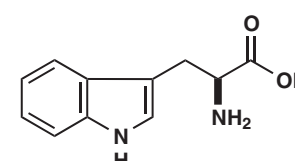
343; (*R*)-(+)-Cys
cysteine



344; (*S*)-(+)-Lys; lysine

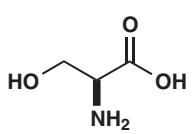


345; (*S*)-(–)-His; histidine

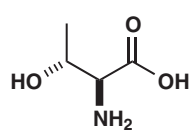


346; (*S*)-(–)-Trp; tryptophan

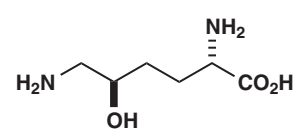
Hydroxyamino acids are useful because the OH group can be converted into a leaving group. We saw serine **138** earlier in the chapter. The other three have a secondary alcohol at a potentially useful chiral centre. Threonine **347** is found in normal proteins. The other two are present in collagen and the extra hydroxyl groups are added by oxidation after the protein is formed ('post-translational modification'). Hydroxyproline **331** is abundant, hydroxylysine **330** less so. We might also add synthetic phenylglycine as a new member.



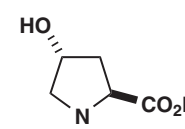
138; (*S*)-(+)-Ser
serine



347; (2*S*,3*R*)-(–)-Thr
threonine



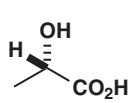
330; (2*S*,5*R*)-5-hydroxy-lysine



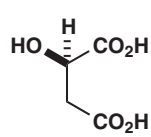
331; (2*S*,4*R*)-
hydroxy-proline

Hydroxy-acids

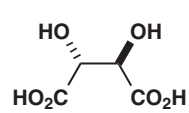
A few hydroxyacids are available: lactic **33**, malic **34**, tartaric in both forms **35** and **36**, and mandelic **37**.



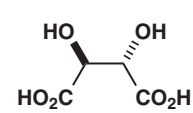
33; (+)-(*S*)
-lactic acid



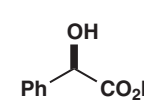
34; (–)-(*R*)
-malic acid



(*R,R*)-(+)-35
tartaric acid
"natural"

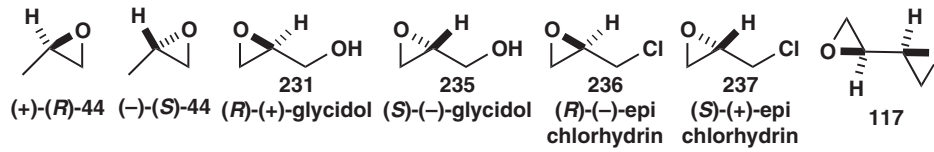


(*S,S*)-(–)-36
tartaric acid
"unnatural"



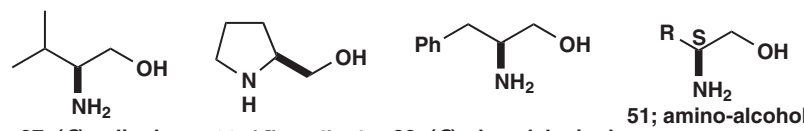
37; (*R*)-(–)-
mandelic acid

Derived from them and from other chiral pool members is a small collection of epoxides that are members of the new chiral pool: both enantiomers of propylene oxide **44**, of glycidol **231** and **235**, and of epichlorhydrin **236** and **237**, and the bis-epoxide **117**.

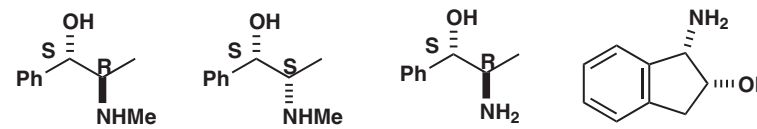


Amino alcohols

Reduction of amino acids (usually with borane) gives amino alcohols such as valinol **27**, prolinol **28** or phenylalaninol **30**: they have the general structure **51**.

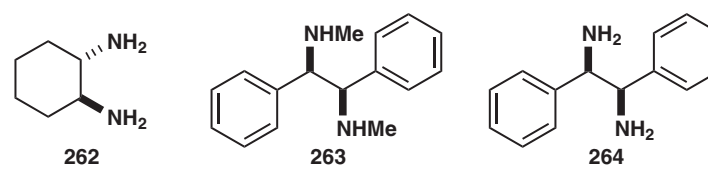


Other amino alcohols occur naturally, including the ephedrine family **52** – **54**. We can add the famous amino-indanol **286** to this collection.



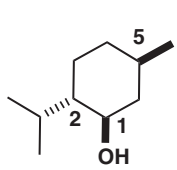
Diamines

These important compounds are all members of the new chiral pool and are all C_2 symmetric.

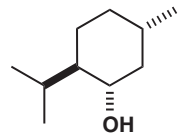


Terpenes

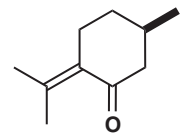
The variety of terpenes is great but they may not be available in high ee. Here is a selection: these are all monoterpenes (C_{10}) and may be linear, cyclic or bicyclic. We have included the new chiral pool members 8-phenyl-menthol **83** and camphorsulfonic acid **94**.



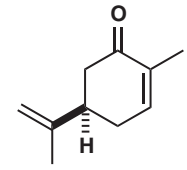
79; (1*R*, 2*S*, 5*R*) -(–)-menthol



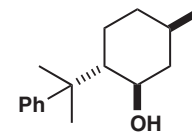
80; (1*S*, 2*R*, 5*S*) -(+)-menthol



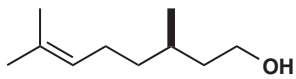
81; (*R*)-(+)-pulegone



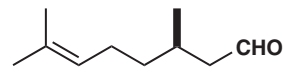
82; (*R*)-(–)-carvone



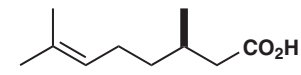
83; (–)-8-phenylmenthol



75; (*R*)-(+)-citronellol

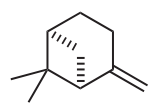


76; (*R*)-(+)-citronellal

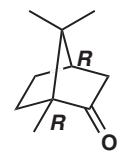


77; (*R*)-(+)-citronellic acid

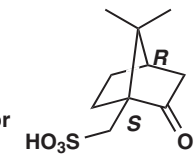
89; (1*R*)-(+) -α-pinene



91; (–)-β-pinene



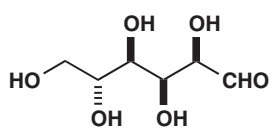
93; (+)-camphor



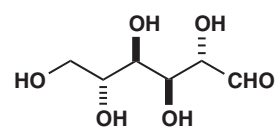
94; (+)-camphor-10-sulfonic acid

Sugars

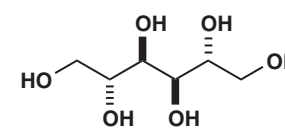
There is again a great abundance of sugars with every stereochemistry at every centre available at a price and their use in asymmetric synthesis is described in recent books.[63] The most important C_6 compounds are glucose **99** and mannose **104** and its reduction product mannitol **105**. The sugars are shown in their open chain forms so that the stereochemistry is clear. You are referred to the earlier parts of the chapter for the pyranose and furanose forms.



99; open chain α-D-glucose

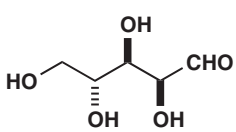


104; open-chain mannose

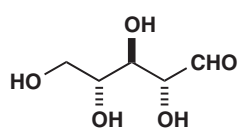


105; mannitol

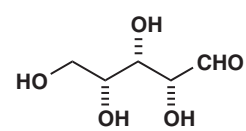
The C_5 sugars were not featured in the chapter but include arabinose, ribose and xylose. They each have corresponding alcohols among which beware that achiral xylitol is not much use in asymmetric synthesis.



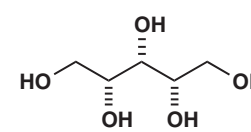
D-(–)-arabinose open chain form



D-(–)-ribose open chain form

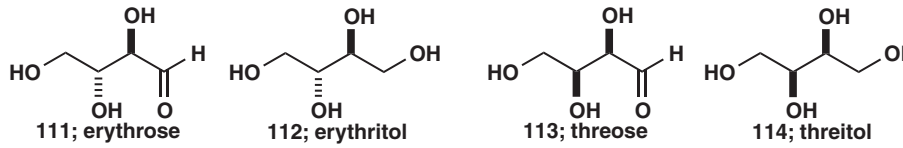


D-(+)-xylose open chain form

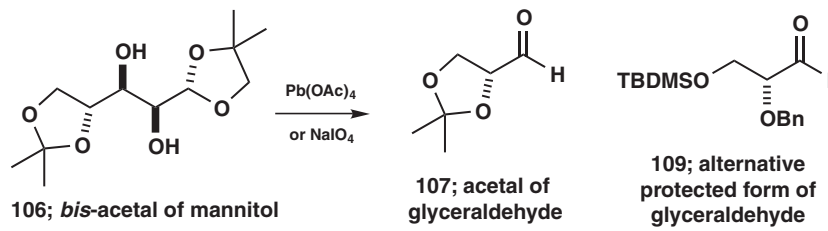


xylitol WARNING! achiral

The two C_4 sugars and their alcohols belong to the *erythro* or *threo* series. One alcohol **114** is C_2 symmetric (the bis epoxide **117** is made from it) but the other **112** is achiral with a plane (or a centre) of symmetry.



The only C_3 sugar is the rather unstable glyceraldehyde best used in a protected form such as **107** or **109** available from the oxidative cleavage of mannitol derivatives such as **106**.



Alkaloids

Not much used as building blocks for target molecules but invaluable for designing reagents and catalysts. See structures **118** and **119**.

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General references are given on page 893

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24 Asymmetric Induction I Reagent-Based Strategy

Introduction to Reagent-Based Strategy

So far we have used racemic compounds and resolved them (chapter 22) or started with enantiomerically pure materials (chapter 23). In the next four chapters we deal with the more demanding but ultimately more versatile and important creation of new stereogenic centres. Naturally the stereogenic centres are not really created: the chirality already exists and is *transferred* to the growing molecule from what may be called a *chiral auxiliary*: this process is called *asymmetric* (sometimes *chiral*) *induction*. In this chapter (reagent-based strategy) the chiral auxiliary is either part of the reagent or a chiral ligand on a metal. In the next two chapters it will be part of a chiral catalyst. In the fourth chapter, the chiral auxiliary is covalently bound to the growing molecule

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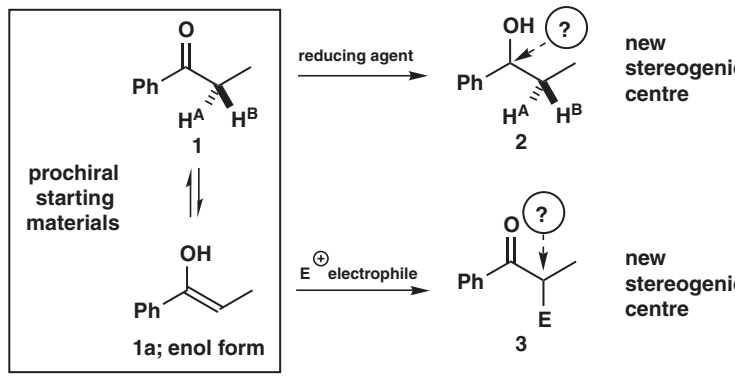
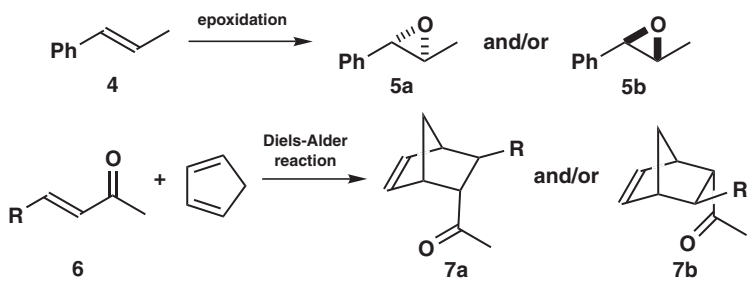
(substrate-based strategy) and so remains attached at the end of the reaction. Later in chapter 29 we shall discuss another kind of reagent - the enzyme.

A new stereogenic centre normally appears when a trigonal carbon atom becomes tetrahedral during a reaction (chapter 21). The unsymmetrical ketone **1** could be reduced to the chiral alcohol **2** or enolised and combined with an electrophile to give **3**. The starting material **1** is prochiral, and both the CH_2 and the C=O groups are prochiral centres. If one hydrogen atom, say H^A rather than H^B, is replaced by the electrophile E, a single enantiomer of **3** is formed. Similarly, if one face of the C=O group, say the one on our side of the paper, is attacked by the reducing agent, a single enantiomer of the alcohol **2** is formed. The two hydrogen atoms and the two faces of the carbonyl group are *enantiotopic*: you need to know your right from your left to tell them apart. An NMR machine, or an achiral reagent such as $NaBH_4$, cannot tell its right from its left, so H^A and H^B have the same chemical shift, and $NaBH_4$ gives an exactly 50:50 mixture of the enantiomers of **2**.

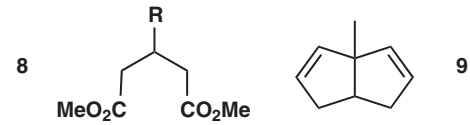


If we want to produce high yields of one enantiomer of **2** or **3**, we must use a reagent which *can* tell its right from its left, that is an enzyme or an asymmetric reagent with some built in mechanism for distinguishing two enantiotopic features. This is the subject of this chapter. Chapter 27 deals with the alternative strategy, making the Hs or faces of the C=O group *diastereotopic* so that achiral reagents *can* tell them apart.

Other trigonal carbons which can give rise to new stereogenic centres are simple alkenes undergoing electrophilic attack, e.g. epoxidation of **4**, and unsaturated carbonyl compounds **6** undergoing Diels-Alder reactions. These reactions may produce several stereogenic centres at once whose *relative* stereochemistry is controlled by the stereochemistry (*E* or *Z*) of the double bond, and by the *endo* selectivity of the Diels-Alder reaction.



We are concerned with the *absolute* stereochemistry of the product: does epoxidation give **5a** or **5b**? Does the Diels-Alder reaction give **7a** or **7b**? There is also a small group of prochiral tetrahedral carbon atoms with enantiotopic functional groups such as the diester **8** or the diene **9**. We shall meet examples of all these (and more!) in this chapter.



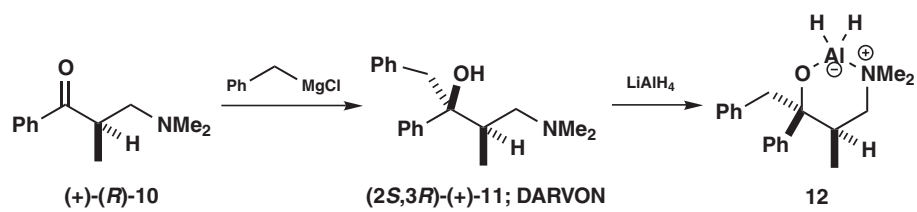
This chapter and the next two deal with two approaches. Asymmetric *reagents* are enantiomerically pure compounds used in stoichiometric amounts to make single enantiomers of the products. Asymmetric *catalysts* are enantiomerically pure compounds used in sub-stoichiometric amounts to catalyse the reaction of stoichiometric but achiral reagents to achieve the same result. You might think it would be easy to distinguish these approaches and often it is. However it can be difficult and broadly we shall describe stoichiometric compounds that transfer the odd atom to the final product as 'reagents' and compounds that are used in substoichiometric amounts and usually transfer no atoms to the product as 'catalysts'. In outline this chapter will deal with asymmetric reduction, asymmetric acids and bases, and asymmetric nucleophiles and electrophiles. Asymmetric oxidation will mostly be dealt with in chapter 25

Asymmetric Reduction of Unsymmetrical Ketones

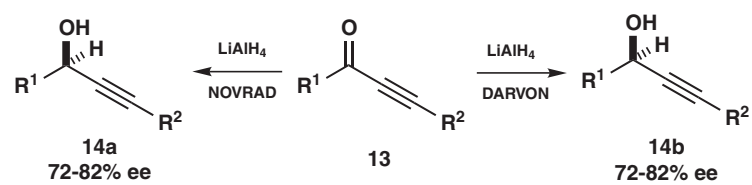
The reduction of unsymmetrical ketones such as **1** with achiral reagents $NaBH_4$ or $LiAlH_4$ gives racemic alcohols. The obvious way to make such a reduction asymmetric is to replace some of the H atoms around B or Al with ligands that form good bonds to boron or aluminium. This is usually done by reacting the achiral reagents with chiral diols or amino-alcohols.

Asymmetric boron or aluminium hydrides

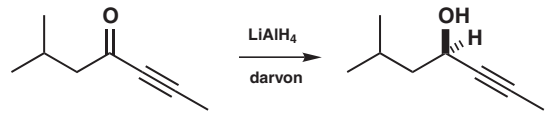
One of the earliest was the darvon complex of $LiAlH_4$. We saw in chapter 22 that both enantiomers of the amino-alcohol **11** (DARVON and NOVRAD) are available by resolution of the precursor **10**. DARVON **11** is also available as Chirald®. Reaction of DARVON **11** with $LiAlH_4$ replaces two hydrides with the OH and NMe_2 groups to give the reagent DARVON-H that presumably has the structure **12**.



This complex chiral hydride **12** reduces acetylenic ketones such as **13** with reasonable selectivity.[1] The other enantiomer of **14** comes from reduction of **13** with the enantiomeric reagent derived from NOVRAD. Note that the absolute sense of the induction in the reduction of **13** is the same with **12** and with the Alpine borane from (+)-α-pinene, below.

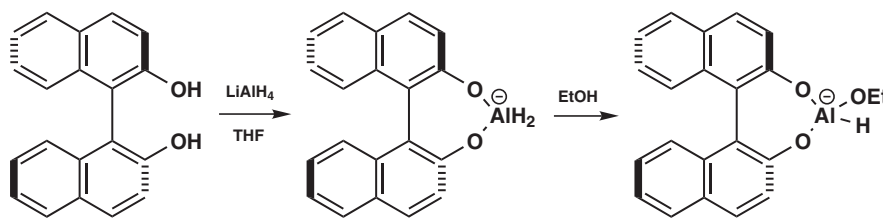


It is necessary for the two groups on the ketone to be sterically different and one of the best results is achieved with a linear acetylenic group on one side and a branched alkyl chain on the other. Even so the ee of this example is only 82% and newer reagents can improve on this.



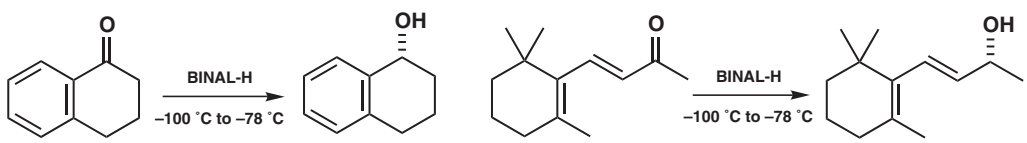
13; R^1= *i*-Bu, R^2= Me **14; R^1= *i*-Bu, R^2= Me**

A more successful development[2] was the reagent derived from $LiAlH_4$ and BINOL. Enantiomerically pure BINOL **15**, available as either enantiomer, is combined with $LiAlH_4$ to give **16** and then with a simple achiral alcohol such as ethanol. The reagent, known as BINAL-H, probably has structure **17**.



15 **16** **probable structure of 17; BINAL-H**

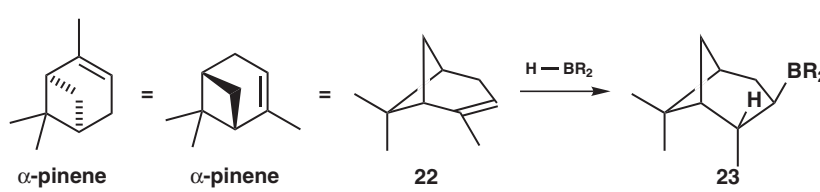
This is a better reagent in two ways. Acetylenic alcohols give higher yields and higher ees. The scope is also wider: though some contrast between the two sides of the ketone is still needed, simple ketones and, most usefully, α,β-unsaturated ketones work well. The reductions of α-tetralone **18** and ionone **20** illustrate the typical high yields and high ees.



18 **19; 91% yield; 87% ee** **20** **21; 87% yield; 100% ee**

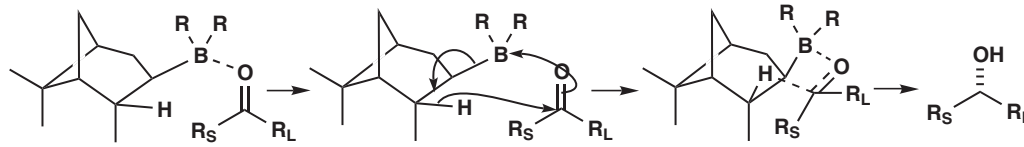
Asymmetric reduction by boranes

A different style of reduction comes with the use of trialkyl boranes derived from α-pinene. Hydroboration of α-pinene **22** occurs from the less hindered face away from the *gem*-dimethyl groups to give the tertiary borane **23** with the usual regioselectivity (chapter 17). The marked hydrogen atom is transferred from boron to carbon.[3]



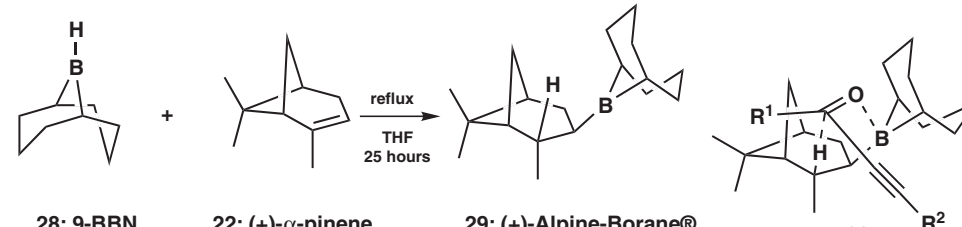
α-pinene **α-pinene** **22** **23**

On reaction with ketones, a bond is first formed between oxygen and boron **24** and then the same marked hydrogen atom is transferred **25** to the ketone through a tight six-membered cyclic transition state **26**. These reducing agents deliver a hydrogen atom from carbon rather than from boron. The larger group (R_L) on the ketone prefers to occupy an 'outside' position in the transition state **26** away from the pinene-derived cage leading to one enantiomer **27** of the alcohol.



24 **25** **26** **27**

An early success[4] was Midland's Alpine-Borane®, derived from 9-BBN **28** and α-pinene **22**. Hydroboration takes place from the less hindered side of the double bond, away from the *gem* dimethyl groups, to give alpine borane **29**. The reagent works well for acetylenic alcohols and the transition state **30** puts the acetylene in the 'outside' position.



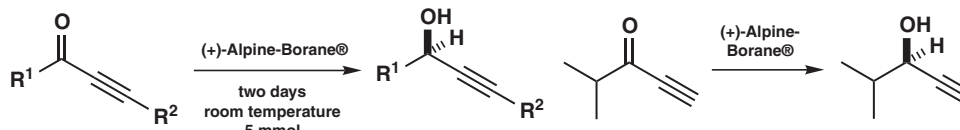
28; 9-BBN
0.5 molar THF solution

22; (+)-α-pinene
11 mmol

29; (+)-Alpine-Borane®
0.5 molar THF solution

30

The general scope of the ketones **31** is large and the results, especially for ee in the alcohol products **32**, are good. An example is the simple alcohol **34**. This enantiomer is the same as the one obtained from DARVON-H above.



31

32; 59-98% yield
77-100% ee

33

34; 78% yield
99% ee

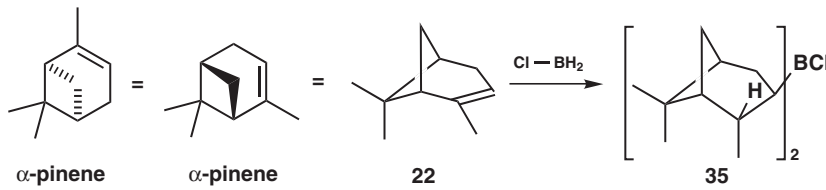
One advantage of this reagent is that both enantiomers of α-pinene **22**, the chiral auxiliary, are available from nature. Both enantiomers of Alpine-Borane® are available as THF solutions. However, the quality of natural α-pinene is erratic, and the table shows that you get what you pay for here as elsewhere. The prices are approximate relative prices to that of benzoic acid.

Table: Commercially Available α-pinene

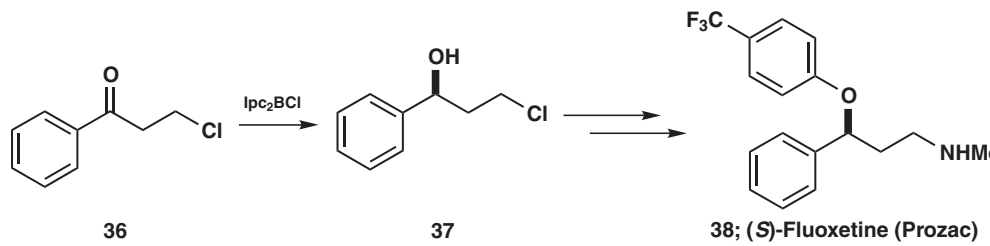
(1*R*)-(+)-α-pinene **22** rotation about +51.7 from *North American* conifer oils			(1*S*)-(−)-α-pinene rotation about −51.7 from *European* conifer oils		
$[a]^{21}D$	ee	price/100 g	$[a]^{21}D$	ee	price/100 g
+50.7	97%	240	−50.7	97%	235
	91%	22		87%	36
	0%	10		81%	8.4

Reduction of ketones with Ipc_2BCl (DIP-Chloride™)

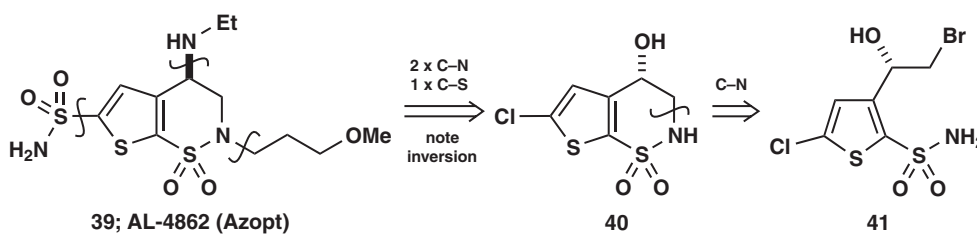
There are many other reducing agents derived from α-pinene and various boranes. It is worth referring to Brown's articles for details.[3] We shall describe just one of these[5] as it is rather different both sterically and electronically and seems to be the reagent of choice at the moment. Hydroboration of α-pinene with $ClBH_2$ occurs twice to give Ipc_2BCl **35** (strictly *B*-chloroisopinocampheylborane and available as DIP-Chloride™).



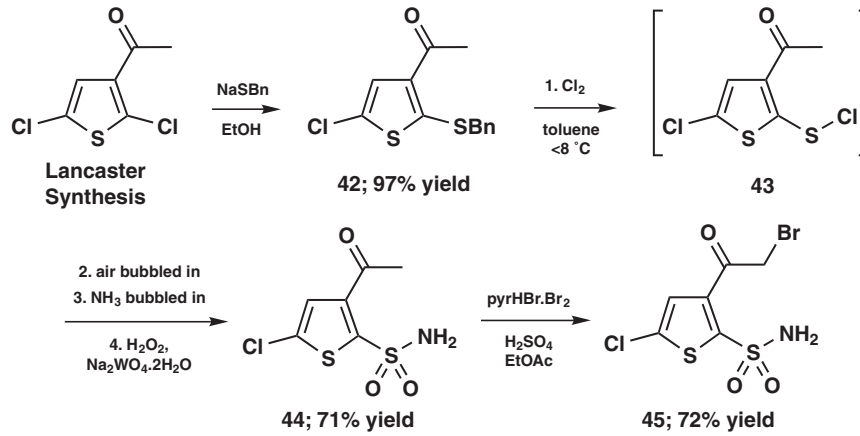
This borane has been used in the preparation of enantiomerically pure prozac,[6] *(S)*-Fluoxetine **38**. The simple ketone **36** is reduced to give the alcohol **37**, easily transformed into prozac **38**.



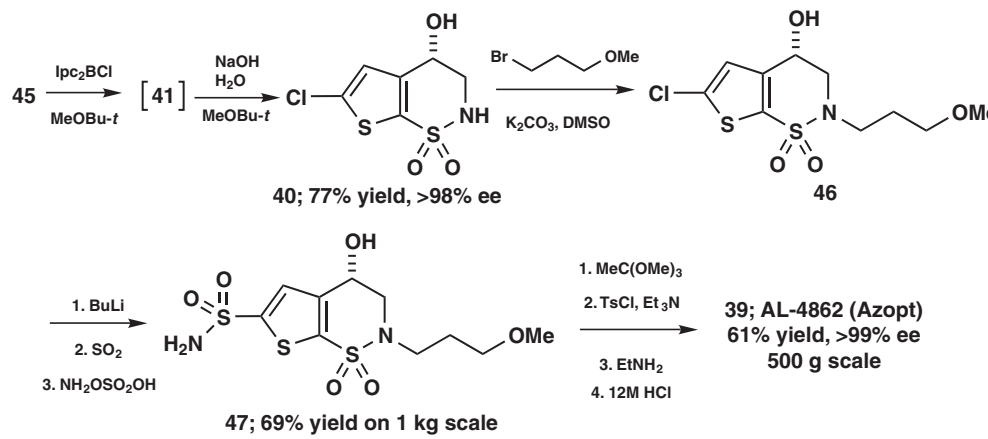
It is a mistake to dismiss these reagents as expensive academic toys not fit for serious chemistry as Ipc_2BCl has been used by Alcon Laboratories[7] in the large scale production of their glaucoma treatment Azopt **39**. Disconnection of most of the structural C–X bonds reveals the simple heterocycle **40** (note that inversion will occur when the EtNH group in **39** replaces the OH group in **40**). The saturated ring could come from cyclisation of **41** and either **40** or **41** could be made by enantioselective reduction of the corresponding ketones.



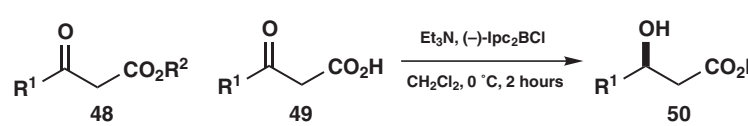
In fact they chose to make **41** by asymmetric reduction of the ketone **45** easily made from a thiophene available from Lancaster Synthesis.



The alcohol **41** was unstable and was cyclised immediately to **40**. The yield of enantiomerically pure **40** (>98% ee) from **45** was 77% on a 500 g scale. The only change to the newly introduced chiral centre is the inversion during the formation of the final product.



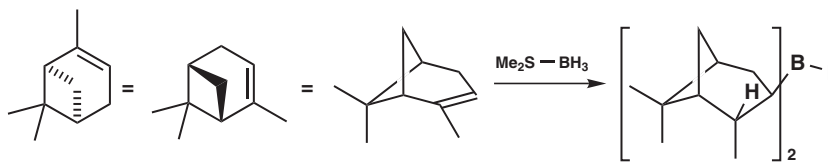
The functional groups in **45** clearly do not interfere with the reaction but some functional groups have a large effect. Reduction of β-keto-esters **48** gives poor yields and ees. By contrast the free acids **49** give alcohols **50** with high yields (87–92%) and very high ees (91 – >98%). Clearly the CO_2H group binds to the boron atom and cooperates with the Ipc group in delivering the H atom to one face of the ketone.[8] We shall return to these reagents under 'asymmetric electrophiles' when we discuss hydroboration of alkenes.



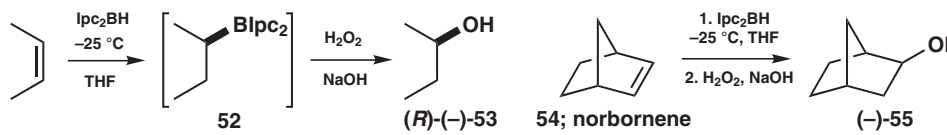
Asymmetric Electrophiles

Asymmetric hydroboration of alkenes

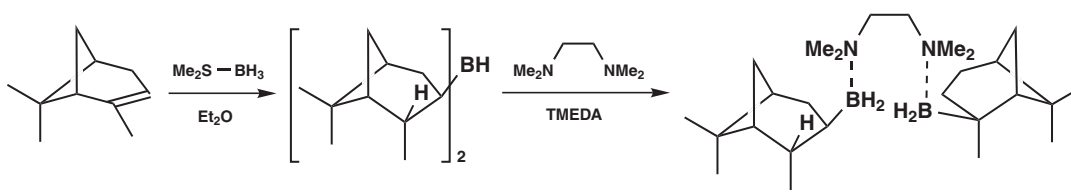
A hydroborating agent must have a free B–H bond and the obvious choice for asymmetric hydroboration is something derived from borane (BH_3 or B_2H_6) and α-pinene. The Me_2S-BH_3 complex reacts rapidly once with α-pinene, nearly as rapidly a second time to give good yields of Ipc_2BH **51**, but fails to react a third time. This is good news in a way as the reagent **51** is easy to prepare but is also a warning that it is unlikely to react with any hindered alkenes.[9]



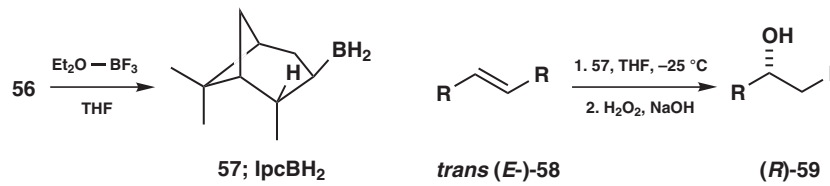
In fact, Ipc_2BH **51** reacts well with *cis*-disubstituted alkenes. Using crystalline Ipc_2BH **51** of 99.1% ee, *cis* butene gave (*R*)-(−)-2-butanol **53** of 98.1% ee in 73% yield and norbornene **54** gave *exo*-alcohol **55** of 83% ee in 63% yield. In this second case there is diastereoselectivity too. There are other examples in Brown's reviews.[3]



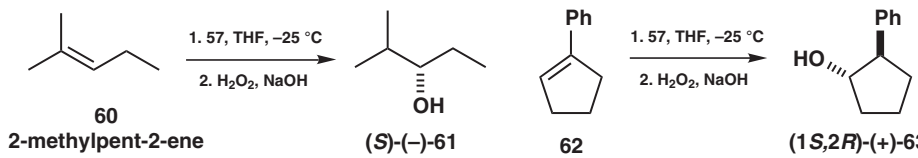
For more hindered alkenes the mono-substituted borane $IpcBH_2$ is better.[10] Direct hydroboration of α-pinene cannot be stopped after one hydroboration and gives Ipc_2BH **51** in good yield but the hydroboration is reversible. Adding TMEDA to a solution of Ipc_2BH **51** in ether precipitates the crystalline complex **56** of two molecules of $IpcBH_2$ and one of TMEDA. The yield is only 80% but if α-pinene of 94% ee is used, **56** crystallises with 100% ee.



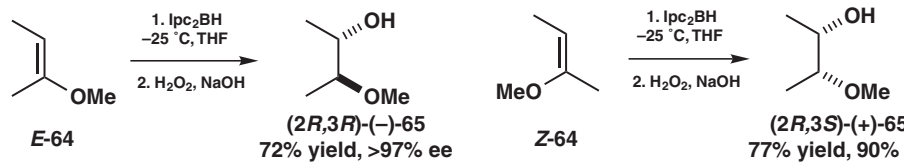
The reagent itself, $IpcBH_2$ **57** is released from the crystalline complex **56** by treatment with BF_3 in THF. TMEDA prefers to form a complex with the more electron-deficient BF_3: this crystallises leaving pure $IpcBH_2$ **57** in solution ready for hydroboration of alkenes. Reactions with simple *trans*-disubstituted alkenes **58** are reasonable: *trans* butene gives (+)-(*R*)-2-butanol of 73% ee in 73% yield.[11]



Trisubstituted alkenes - the type that do not react at all with Ipc_2BH - perform particularly well. Regioselectivity is usually excellent and the ees are generally better than those with simple *trans*-disubstituted alkenes. 2-Methylpent-2-ene **60** gives only 58% ee but the champion is 1-phenylcyclopentene **62** that gives 92% yield of the *anti* alcohol **63** in 100% ee. Brown[12] has improved on most of these ees by using modified 'pinenes' with larger bridgehead substituents but these 'pinenes' have to be prepared and the Ipc reagents retain their popularity.



More recently, the effects of functional groups on the alkene have been explored. Enol ethers are more nucleophilic than ordinary alkenes and the two enol ethers *E*- and *Z*-**64**, give good yields of different diastereoisomers of the half-protected diol **65**. Though **64** is a trisubstituted alkene, it reacts rapidly with Ipc_2BH with good enantioselectivity.[13]



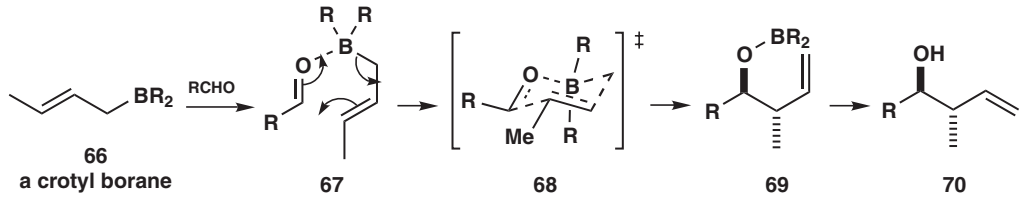
Asymmetric Nucleophilic Attack

This commoner type of reaction involves the attack of carbon or heteroatom nucleophiles onto carbonyl compounds, by direct or conjugate addition, and onto imines. Because we have just dealt with boranes we shall start with the reaction of allylic boron compounds with such electrophiles. You might strictly not call this nucleophilic attack.

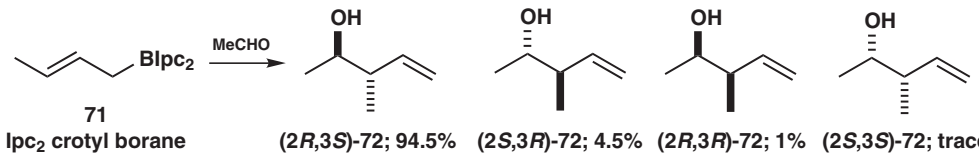
Transfer of Allylic Groups from Boron to Carbon

Reactions of chiral allylic boranes with carbonyl compounds

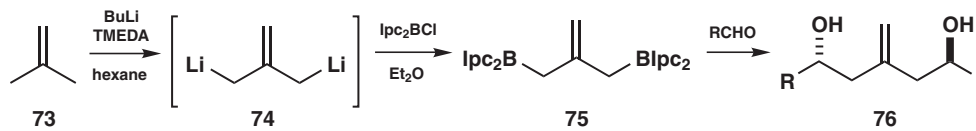
Simple alkyl boranes do not react with aldehydes and ketones but allyl boranes react rapidly because they can use a six-membered cyclic transition state **68** not unlike that of the Claisen rearrangement. The evidence for this is that the allyl group is rearranged in the product. In this example a crotyl borane **66** adds to an aldehyde to give *anti*-**70** since both R and Me prefer to be equatorial in the transition state **68**.



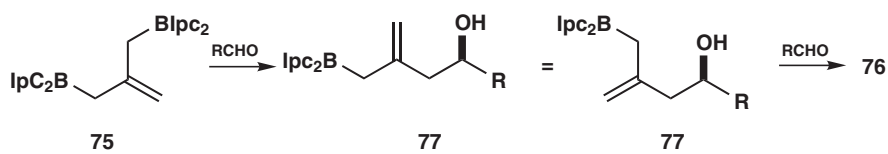
Allyl dialkyl boranes do this reaction, transferring only the allyl group as the mechanism **67** requires, so asymmetry can be introduced by replacing BR_2 with Ipc_2B to give **71**. In this specific instance, the reaction with acetaldehyde gives predominantly just one enantiomer (2*R*,3*S*) of the *anti*-diastereoisomer of **72** accompanied by some of the other *anti* enantiomer and traces of the *syn*-diastereoisomer.[3] The diastereoselectivity is therefore 99:1 and the ee 90%.



The allylic boranes can be made from allylic Grignard or lithium reagents with Ipc_2BCl **35** (used above in reductions). An interesting example is Barrett's synthesis[14] of the C_2-symmetric compounds **76**. The dilithium derivative **74** reacts with two molecules of Ipc_2BCl **35** to give the C_2-symmetric allylic double borane **75**, both Ipc groups having the same chirality. Reaction with an aldehyde gives the C_2-symmetric diols **76**.



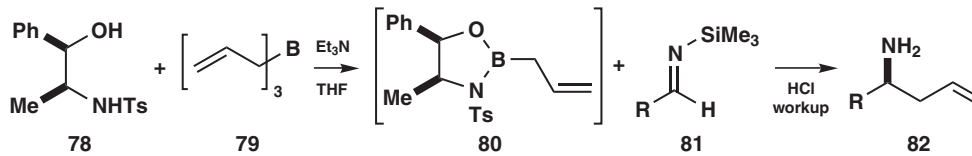
Various aliphatic and aromatic aldehydes can be used and either enantiomer of the metric diastereoisomer **76** can be made depending on the enantiomer of Ipc_2BCl used. Two allylic transfers occur, each with same sense of asymmetric induction and this is easier to see if **75** is redrawn and the intermediate **77** also redrawn before reaction. The ratio of the C_2 to the *meso* diastereoisomers is usually greater than 90:10 and the ees uniformly >95%.



Reactions of chiral allyl boranes with imines

Boranes other than those based on α-pinene are particularly useful in allylic transfer to imines to make single enantiomers of unsaturated amines. One good combination is an allylboron compound **80** complexed with an *N*-sulfonyl amino alcohol such as **78**, derived from nor-ephedrine (see chapter 23) with an *N*-silyl imine such as **81**. The unsaturated amines **82** are formed in good

yields[15] with ees around 90%. Brown has shown[16] that the water content of such reactions is critical - no reaction occurs in the complete absence of water!

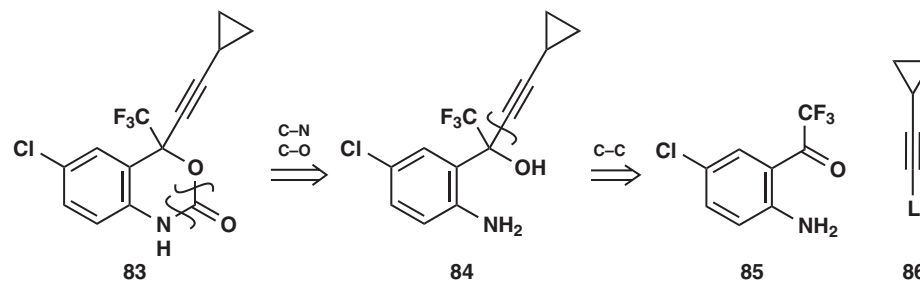


Asymmetric Addition of Carbon Nucleophiles to Ketones

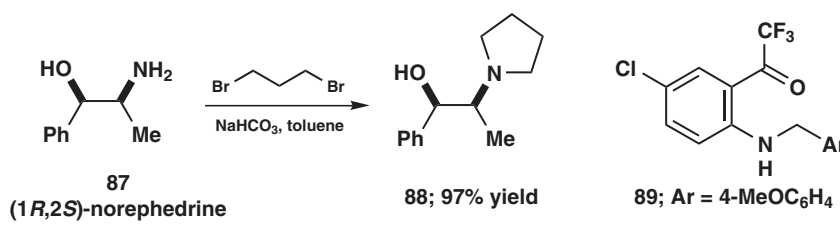
The chapters on asymmetric catalysis will describe catalytic versions of the reactions we are about to describe. Catalysis is a fundamentally more efficient way of asymmetric induction and we shall restrict our discussion here to cases where catalysis proved ineffective.

Addition of alkyl lithiums to ketones

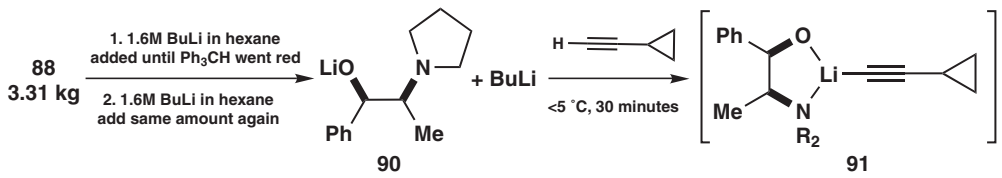
Merck's HIV-1 reverse transcriptase inhibitor Efavirenz **83** is one of the simplest anti-HIV drugs yet produced. The most straightforward synthesis[17] is based on closure of the amino alcohol **84** with some phosgene equivalent and the preparation of **84** by asymmetric addition of cyclopropyl-ethynyl-lithium **86** to the ketone **85**.



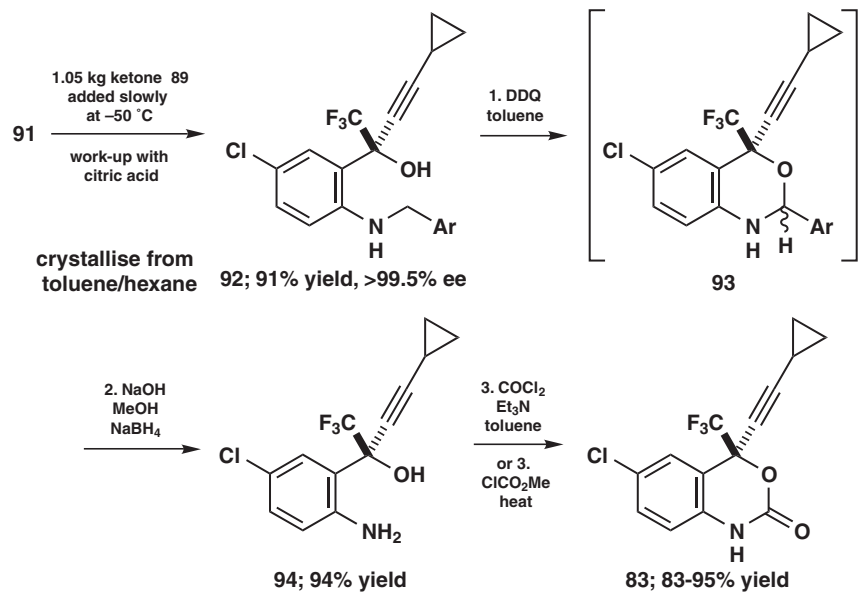
It was already known that amino alcohols of the kind we have just used **78** were good at this kind of asymmetric addition but this particular combination of an acetylenic nucleophile and an aryl trifluoromethyl ketone was uncharted territory. After some exploration, stoichiometric pyrrolidine alcohol **88** prepared by alkylation of norephedrine **87** from the chiral pool (chapter 23) proved the best and the ketone **85** had to be used as its *N*-4-methoxybenzyl derivative[18] **89**.



The conversion of ligand **88** into the reagent **91** required the specific conditions set out in the chart. Titration of BuLi against Ph_3CH produced the lithium alkoxide **90** with enough BuLi left over to make the lithium derivative **86** and the reagent **91** turned out to be a tetramer.[18]



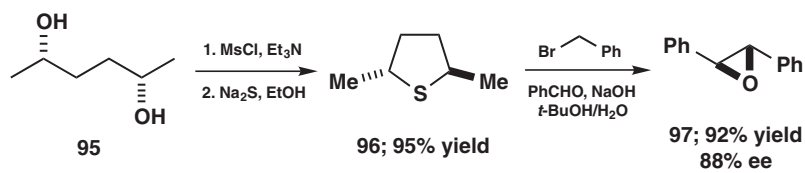
Addition of the reagent **91** to the modified ketone **89** also required exact conditions but all this care was rewarded with an excellent yield and an essentially perfect ee. The rest of the synthesis involves the oxidative removal of the protecting group via **93** and the closure of the cyclic carbamate to give **83**.



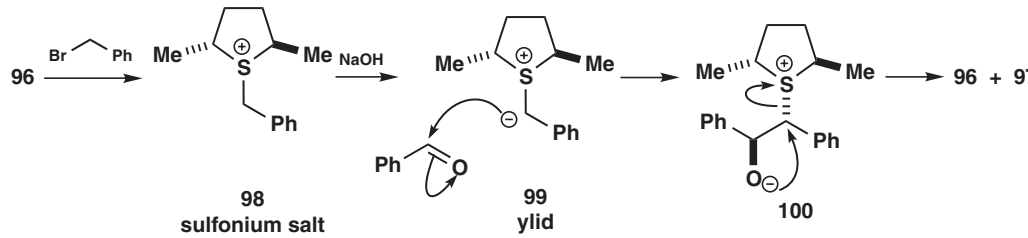
This one example reveals that it is usually necessary to find the right ligand for any direct addition of RLi or RMgX to a carbonyl group. If you are lucky you may find a catalytic method. If not, an amino-alcohol based stoichiometric method should be possible.

Asymmetric epoxidation with chiral sulfur ylids

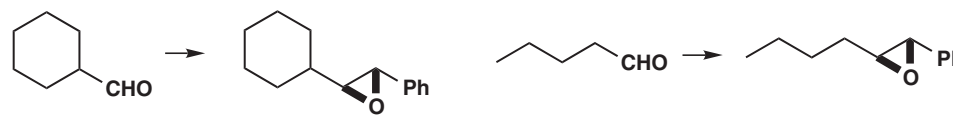
A very different type of chemistry occurs when sulfur ylids add to carbonyl compounds. Epoxides are formed and recent progress with chiral sulfur ylids allows good asymmetric induction in this reaction. The easily prepared C_2 symmetric sulfide **96** reacts with alkyl halides and then with aryl and alkyl aldehydes to give good yields of *trans* epoxides **97** with reasonable ees.[19]



The alkylation of the sulfide **96**, the formation of the ylid **99**, and the reaction with the aldehyde are all carried out in one operation. The sulfide is a good nucleophile for alkyl halides and forms the sulfonium salt **98**. This gives the ylid **99** with NaOH as a convenient base in aqueous *tert*-butanol. The ylid selectively attacks the aldehyde to give the betaine **100** that closes to the epoxide and releases the sulfide **96** for the next round.



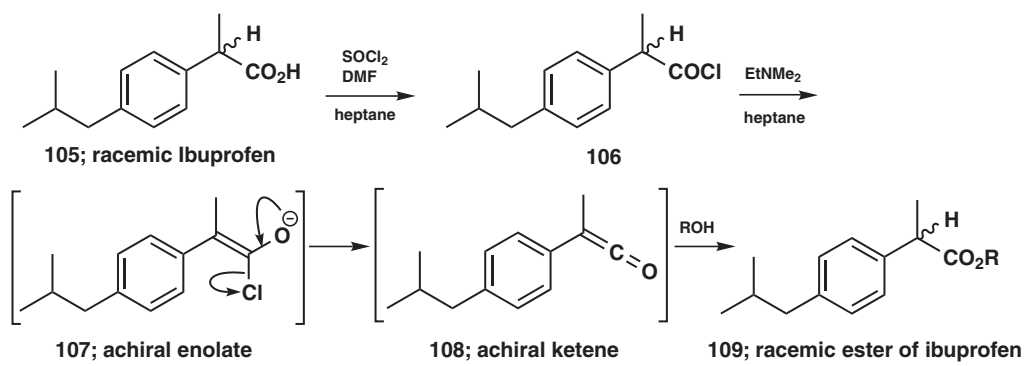
Enolisable aldehydes such as **101** or **103** do not give quite such good yields but the ees are still good and the diastereoselectivity in favour of the *trans* epoxides **102** and **104** is excellent. The secret of this method is the simple preparation of the reagent **96**. In the next chapters you will see that superior catalytic methods are available for asymmetric epoxidation of allylic alcohols and of *cis*-alkenes but they are less good for the *trans* disubstituted alkenes that would give **97**, **102**, or **104**. You will also see catalytic versions of sulfur ylid epoxidation.



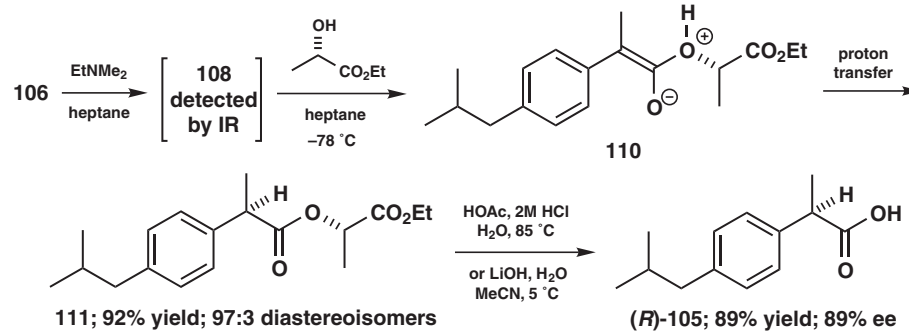
Asymmetric Nucleophilic Attack by Chiral Alcohols

Deracemisation of arylpropionic acids

Arylpropionic acids such as ibuprofen **105** are important NSAIs (non-steroidal anti-inflammatories). Only one enantiomer is active and some are administered as enantiomerically pure compounds through there is a problem with racemisation in the body by enolisation. This can be turned to advantage in 'deracemisation'. Weak bases are enough to convert the acid chloride **106** into an enolate that eliminates **107** to form the achiral ketene **108**. Addition of, say, ethanol then gives racemic esters **109**; R = Et of ibuprofen.



Asymmetric induction would in theory be possible if a chiral alcohol were used in the last step[20] and, amazingly, providing α-hydroxy-esters or lactones are used, can actually be realised.[21] The elimination is followed by infra red until the ketene is completely formed (2,100 cm^{-1}) and then the asymmetric oxygen nucleophile is added in heptane at −78 °C. The best reagents are (*S*)-(−)-ethyl lactate and (*R*)-(+)-pantolactone **112** from the chiral pool - they give opposite enantiomers with excellent ees. In this case *R*/*S does* give a good indication of chirality as the functional groups are virtually the same. The induction takes place on the protonation of the enolate rather than the addition of the alcohol. Ethyl lactate gives the ester **111** in a 97:3 ratio of diastereoisomers that becomes 89% ee on hydrolysis to **105**. Even under the very mild hydrolysis conditions shown, some racemisation occurs during hydrolysis.



The other enantiomer (*S*)-**105** comes from reaction with (*R*)-(+)-pantolactone **112** in rather better ee - evidently the hydrolysis of the ester **113** is faster and occurs without racemisation. In both cases, rather precise conditions are necessary. This should be seen as both a warning and an encouragement.

Conditions for asymmetric induction by attack of homochiral alcohols on ketenes

Same **solvent** and **catalyst** used for synthesis and reaction of ketene:

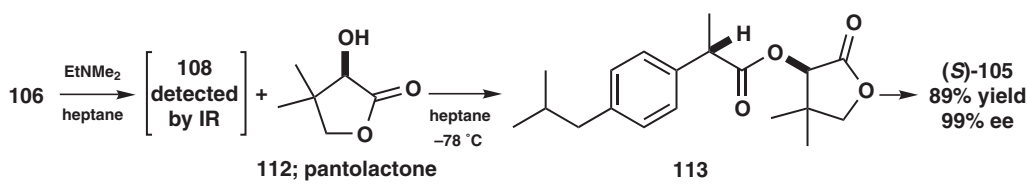
Solvent: Heptane best, toluene all right, polar solvents no good.

Catalyst: Me_3N and *N*-Me-pyrollidine best, Et_3N and *i*-Pr_2NEt all right.

Temperature unimportant: only 7% decrease in ee at room temperature *cf.* −78 °C.

Dilution critical: 90% ee. at 1M; 97.2 ee at 0.02M.

Work-up: treat with aqueous AcOH to cleave any anhydride formed.

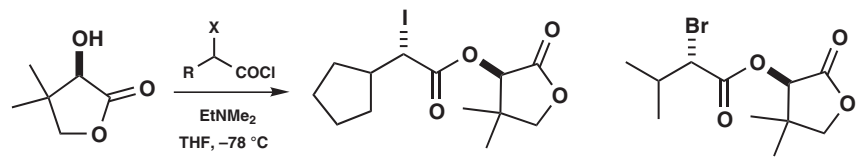


Deracemisation of α–halo acids

The same reagent (*R*)-(+)-pantolactone **112** gives good results with α-halo acids that are good precursors for many other compounds such as α-amino acids by nucleophilic displacement. The α-halo acid chlorides **115** are prepared directly from the simple acids **114** and treated with the same tertiary amine $EtNMe_2$ used above to give the unstable ketenes **116** and hence the esters **117** by reaction with (*R*)-(+)-pantolactone[22] **112**.

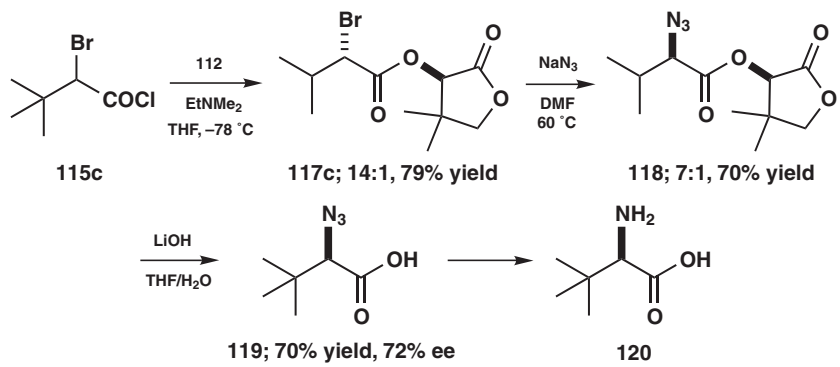
114 115 116 117

It is best not to isolate the ketene but to add a solution of the acid chloride **115** in THF to a mixture of (*R*)-(+)-pantolactone **112** and $EtNMe_2$ also in THF at −78 °C. R is always alkyl and X can be Br or I. The esters **117** are isolated as mixtures (7:1 to 19:1) of diastereoisomers: two examples follow.



112 117a; 19:1, 73% yield 117b; 8:1, 78% yield

It is essential that the ketene is formed: reaction of the acid chlorides **115** with (*R*)-(+)-pantolactone **112** also gives the esters **117** but as a 1:1 mixture of diastereoisomers. A useful application is the preparation of unusual amino acids such as **120** by S_N2 displacement of halide with azide and reduction of the azido group. It is best to hydrolyse the ester at the azide stage **118** to reduce racemisation but even so some does occur both in the azide displacement and in the hydrolysis.

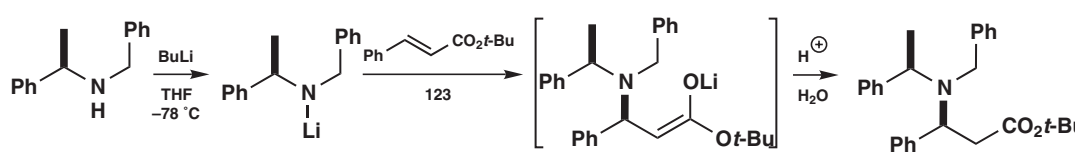


115c 117c; 14:1, 79% yield 118; 7:1, 70% yield

119; 70% yield, 72% ee 120

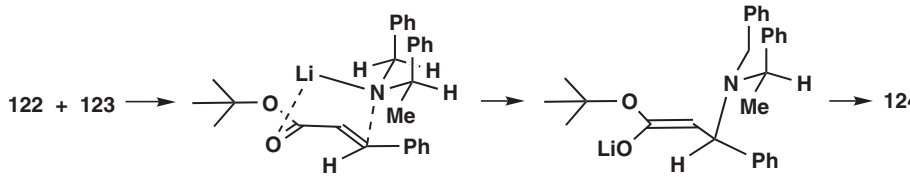
Asymmetric Conjugate Addition of Nitrogen Nucleophiles

The work of Steven Davies[23] at Oxford has made conjugate addition of nitrogen nucleophiles a reliable and useful reaction. The essential reagent is the amine **121**, prepared on a large scale by resolution (chapter 22). This amine does not react with unsaturated esters like **123** but the lithium derivative **122** adds in a conjugate fashion to give the ester **125** via the enolate **124**.

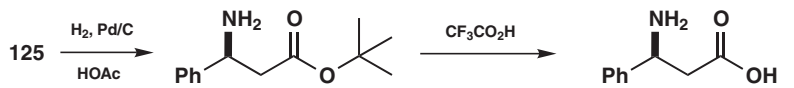


121 122 124 125; 92% yield; 95% de

Here at last some explanation can be offered. The lithium derivative **122** forms a Li–O bond to the carbonyl group of the ester **123** in its best 's-*Z*' conformation and the nitrogen atom adds to the conjugate position 'like a butterfly settling on a leaf' **126** to give the lithium enolate **124** in the same conformation **124a**.



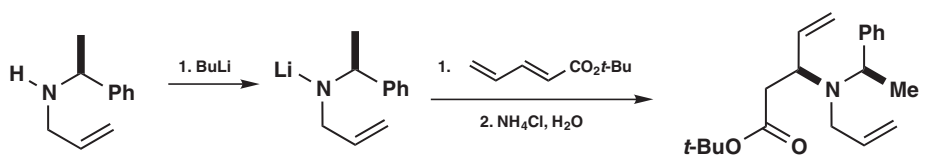
The two benzyl groups on the nitrogen atom can be removed by hydrogenation – remarkably the third benzylic bond to nitrogen is not cleaved - and the *t*-butyl ester hydrolysed in acid solution to give 'β-phenylalanine' **128** in good yield and ee. The reagent **122** has supplied just one nitrogen atom to this final product **128** and no recycling of **121** is possible. Fortunately **121** is very easy to make.



127; 84% yield **128; 100% yield; 95% ee**

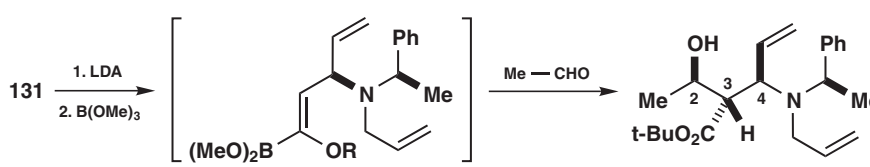
An asymmetric synthesis of thienamycin

In this sequence valuable chemical information is discarded. Not only is **124** a specific enolate, it has a specific geometry ('*Z*' lithium enolate). This information can be used in a tandem style of reaction described in chapter 36. We shall continue with an alternative. Replacing the benzyl group in **121** with an allyl group **129** and adding to a dienoate ester (*t*-butyl sorbate) gives the product **131** from regioselective addition[24] at C-3.



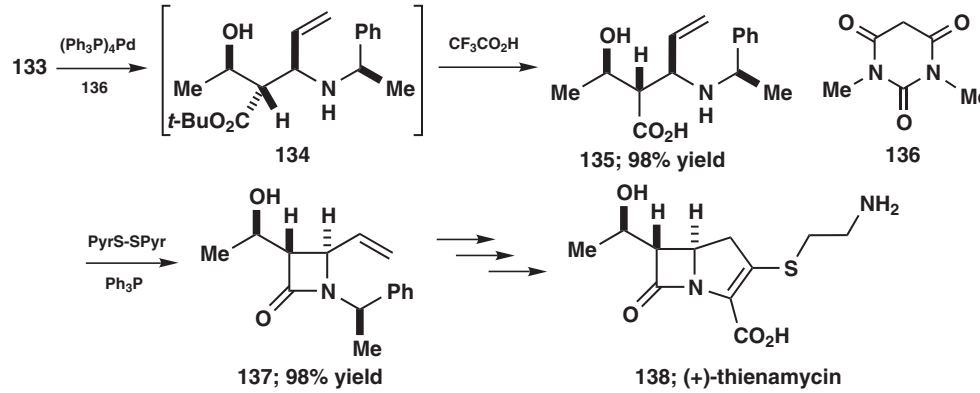
129 **130** **131; 87% yield, 99:1 diasts**

This ester **131** forms the usual '*E*'-enolate with LDA that can be trapped as the boron enolate **132**. Reaction with acetaldehyde gives, as expected, an *anti* aldol (chapter 4). The major product is **133** in a 91:9 ratio with the other *anti* aldol. This diastereoisomer can be isolated in 75% yield. The absolute stereochemistry is decided by the chiral centre already in place in **132** - it remains as C-4 in **133**. The next centre along (C-3) is controlled by C-4 and the relative stereochemistry of C-3 and C-4 is controlled by the geometry of the enolate.



132; '*E*' boron enolate **133; 75% yield**

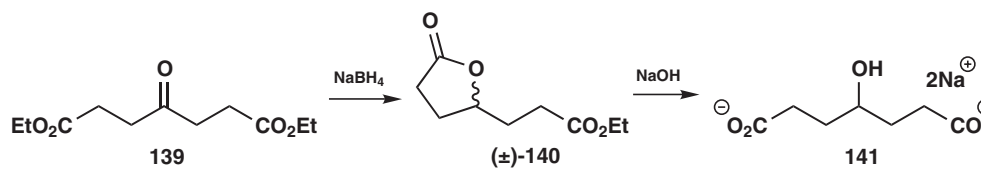
This compound was used in an asymmetric synthesis[25] of the antibiotic thienamycin **138**. The *N*-allyl group was removed with Pd(0) catalysis to give **134** and the *t*-butyl ester hydrolysed to give the redrawn acid **135**. Cyclisation by the pyridyldisulfide reagent gave the β-lactam core **137** of the antibiotic **138**.



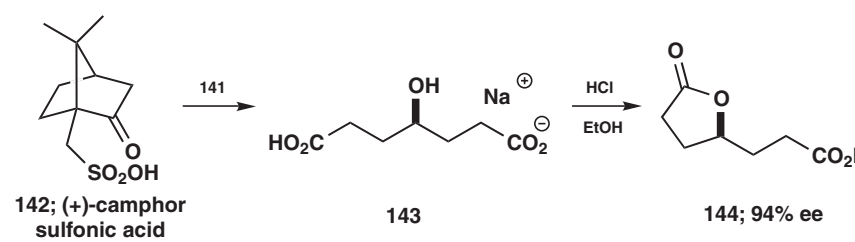
Asymmetric Protonation

Enantioselective lactonisation of achiral hydroxy diacids

Reduction of the achiral ketodiester **139** gives the racemic lactone **140**. Hydrolysis of both ester groups then gives the again achiral hydroxydicarboxylate **141**. This compound is prochiral and the two CO_2^- groups are enantiotopic. If one could be protonated selectively by an enantiomerically pure acid, one enantiomer of the monoacid would be formed. This sounds like an improbable event.



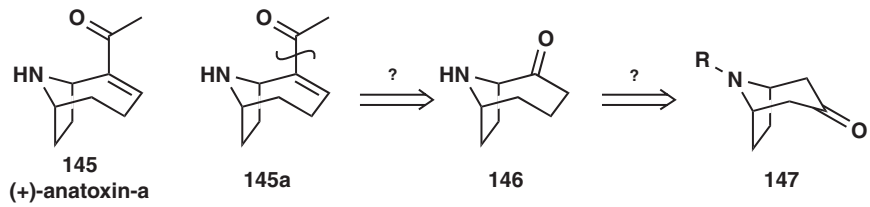
As you may guess, it does work. Camphor sulfonic acid **142** (used in chapter 22 as a resolving agent) protonates just one of the carboxylate anions and cyclisation then gives the lactone[26] **144** in remarkably high ee (94%). The two carbonyl groups are now different enough to be developed separately.



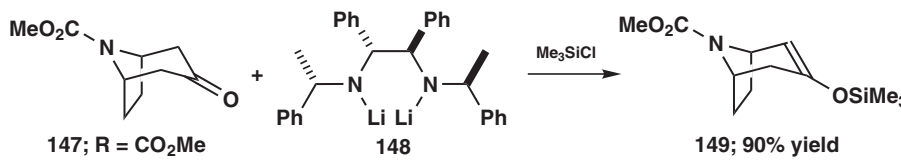
Asymmetric Deprotonation with Chiral Bases

A more widely used method is deprotonation to make, say, an enolate, with one enantiomer of a base. The base must form a close association with the substrate and that usually means a lithium

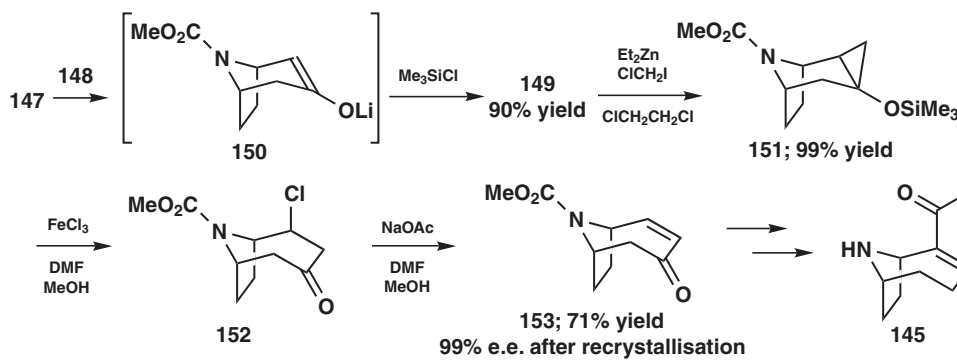
amide. You may object that a planar enolate is not intrinsically chiral, but desymmetrisation of a symmetrical ketone is ideal. Simpkins' synthesis of anatoxin **145** is a good example.[27] This highly toxic compound (known as 'sudden death factor') is the model for potentially useful pain killers. Simpkins wanted to make it from readily available tropinone derivatives **147**.



A lot of work has to be done. A carbon atom needs to be added and the ketone moved round to allow addition of a d^1 reagent. But this is an attractive strategy because tropinone is achiral and enolate formation desymmetrises the molecule. It was not easy to find the right base. In the end the C_2-symmetric double base **148** gave the silyl enol ether **149** in good yield, and, as we shall see later, good ee.

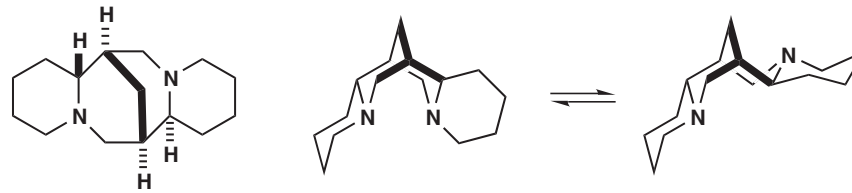


Clearly the lithium enolate **150** must be formed asymmetrically and is trapped by Me_3SiCl to give the silyl enol ether **149**. Simmons-Smith-style cyclopropanation adds the extra carbon and the product **151** is cleaved with Fe(III) to give the enone **153**. This is not the same as **146** but has an electrophilic carbon in the right place. The enone **153** is crystalline and can be obtained optically pure for conversion to a single enantiomer of anatoxin **145**. Further details are in the workbook.

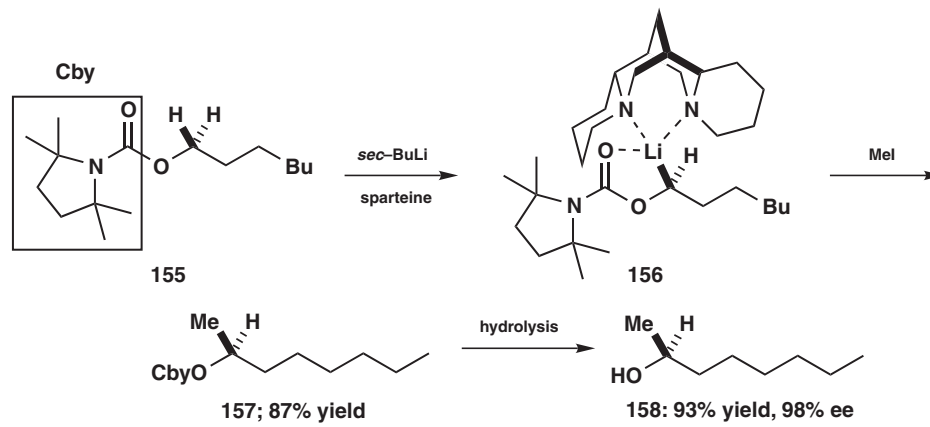


Asymmetric deprotonation with sparteine

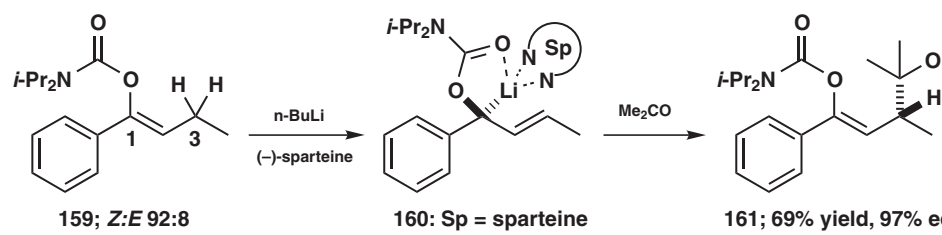
By far the most popular asymmetric deprotonation uses sparteine as a ligand for lithium.[28] Sparteine **154** is a bicyclic alkaloid from lupins and gorse and has two nitrogen atoms that can, in one favourable conformation **154a**, chelate a lithium atom. In spite of appearances, it is not (quite) C_2-symmetric and only one enantiomer is available.



A simple application is the asymmetric alkylation of carbamates **155** of cyclic amines. Removal of one of the diastereotopic protons from **155** gives a more stable sparteine chelate **156**. This is not an enolate but has a C–Li bond stabilised by coordination to the carbonyl group. Alkylation occurs with retention of configuration to give, after hydrolysis, one enantiomer of the secondary alcohol[28] **158**.

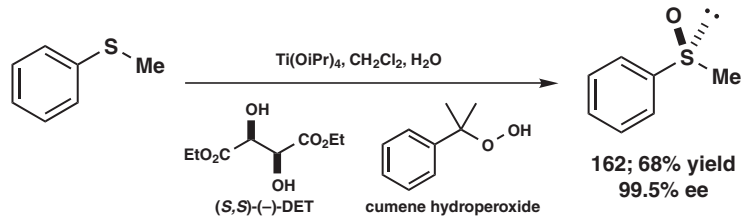


Hoppe has extended this work to d^3 reagents **159** (homoenolates - see chapter 13 for achiral versions) by the addition of a double bond.[29] Lithiation occurs at C-1 by removal of one of the enantiotopic protons at C-3. Aldol reaction with acetone occurs at C-3 of the complex **160** as expected for a homoenolate (chapter 13) giving a single enantiomer of the homoaldol product **161**. All these reactions use an excess of sparteine.

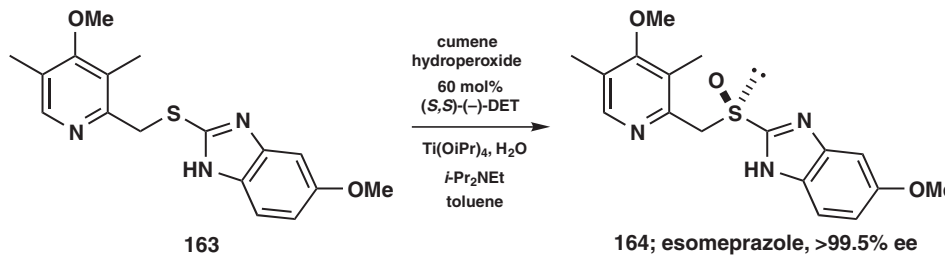


Asymmetric Oxidation

The most important example of stoichiometric asymmetric oxidation is probably the titanium-catalysed conversion of sulfides into sulfoxides by cumene hydroperoxide in the presence of stoichiometric diethyl tartrate. A simple example is the efficient asymmetric synthesis of methyl *p*-tolyl sulfoxide **162**, an important starting material for much sulfoxide-controlled asymmetric synthesis.[30]



The very important anti-ulcer drug omeprazole is a sulfoxide and is invariably made by oxidation[31] of the sulfide **163**. AstraZeneca workers have reported[32] that the same mixture gives the enantiomerically pure drug **164**, to be marketed as esomeprazole, in good ee. An important difference is that the asymmetry comes from only 60 mol% of tartrate and they were able to get 91% ee with only 4% tartrate. We are entering the more efficient realms of catalysis - the subject of the next two chapters.



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25 Asymmetric Induction II Asymmetric Catalysis: Formation of C–O and C–N Bonds

Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

Introduction: *Catalytic methods of asymmetric induction*

In the previous chapter we discussed various reagent-based strategies for the enantioselective formation of chiral centres. The next two chapters are also concerned with reagent-directed strategy but with an important difference. The source of asymmetry is used in a much lower concentration: it is a catalyst. We may put in a few milligrams of an optically active compound and get out grams or even kilograms of enantiomerically pure product. This chapter concerns the formation of C–O and C–N bonds, the next the formation of C–H and C–C bonds.

We dedicate a large part of this chapter to two very important, and extraordinarily useful, enantioselective methods – catalytic asymmetric epoxidation (AE) and catalytic asymmetric dihydroxylation (AD). Impressively, *both* these methods were developed by Professor Barry Sharpless's research group and are therefore often referred to as the Sharpless epoxidation and the Sharpless dihydroxylation. Both are examples of ligand-accelerated catalysis.

Part I – Sharpless Asymmetric Epoxidation

There are many asymmetric epoxidation reactions but none is as reliable or has been as widely used as the Sharpless Asymmetric Epoxidation[1] (AE), the subject of this section, and the Jacobsen epoxidation, the subject of a later section in this chapter.[2]

The AE method

The Sharpless epoxidation converts a prochiral allylic alcohol **1** into a chiral epoxy alcohol **2** and gives that epoxy alcohol with a very high enantiomeric excess.

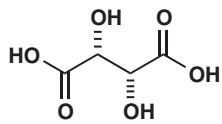
1 **2**

There is a great deal of flexibility allowed within the framework of this reaction – the substituents on the starting material can vary a great deal and the double bond can be *E* or *Z*. However, there is one restriction and that is that the substrate must be an *allylic* alcohol. If it isn't the reaction will not work because, as we shall see, the hydroxyl group plays a crucial role in the reaction. The reagents used are an oxidising agent (usually, *tert*-butyl hydroperoxide *t*-BuOOH, but other

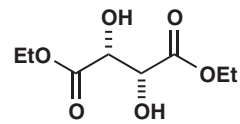
hydroperoxides can be used), a catalyst, and – for the asymmetric induction – a chiral and enantiomerically pure ligand. There is an *Organic Synthesis* procedure for a typical case.[3]

The ligands

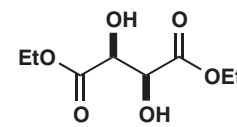
The ligands used are the dialkyl tartrates. Most commonly, the diethyl or diisopropyl tartrates are used. Diethyl tartrate is often abbreviated to DET, diisopropyl tartrate to DIPT and dimethyl tartrate to DMT.



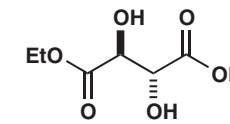
3; (*R*,*R*) L-(+)-tartaric acid



4; (*R*,*R*) L-(+)-DET



5; (*S*,*S*) D-(–)-DET



6; *meso*-DET

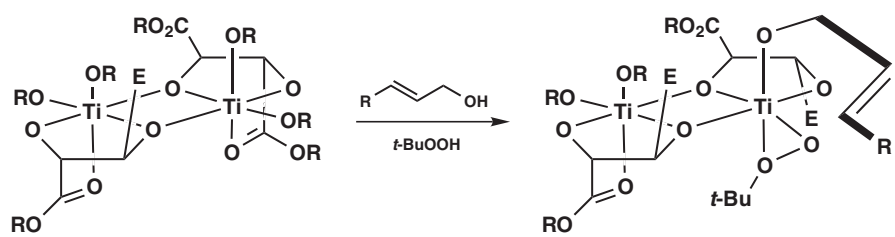
Importantly, both enantiomers of tartaric acid are available. However (and also importantly) one is very much more expensive than the other. The cheap one is L-tartaric acid **3** and is often referred to as 'natural' tartaric acid. It is about 35 times cheaper than the 'unnatural' D-tartaric acid though, in fact, there is nothing unnatural about this acid at all – it too comes from natural sources. The ethyl **4**, **5** and *iso*-propyl esters of both enantiomers are also available. These are the enantiomers of C_2 symmetric DET, the other diastereoisomer, *meso*-DET **6** is achiral. The ligand can be used catalytically providing that molecular sieves are added.[4]

The catalyst

The metal at the heart of the active catalyst is titanium. This holds everything together—the tartrate ligand, the substrate (the allylic alcohol) and the oxidant *tert*-butyl hydroperoxide *t*-BuOOH. The structure of the catalyst before substrate or ligand binding is thought to be as shown in the figure below. There are two titanium atoms and two unsymmetrically bound tartrate units.

Catalyst structure

The most likely structure of the catalyst is based on X-ray structures of related compounds and reinforced by calculations.[5] It is dimeric with two Ti atoms, two tartrates and four alkoxides. We show one of two degenerate structures. When the catalyst combines with the allylic alcohol and the hydroperoxide, the same titanium atom takes both and only one diastereotopic face of the alkene is presented to the active oxygen atom.

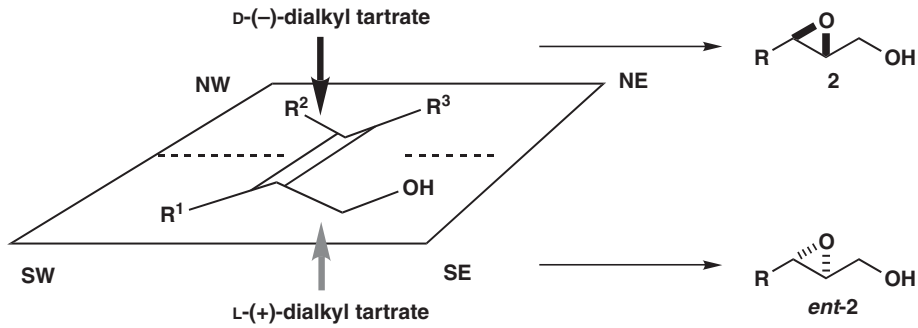


Likely catalyst structure
E = CO_2R

Proposed 'loaded' catalyst structure
E = CO_2R

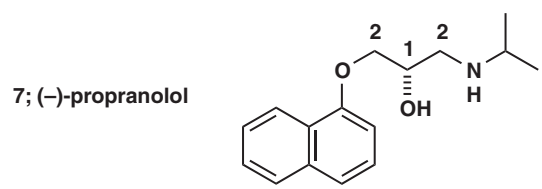
The mnemonic device

The absolute configuration of the epoxide product depends upon the enantiomer of the tartrate ligand that is used. The empirical observation is very reliable—when the allylic alcohol is drawn with the carbinol carbon in the SE quadrant as in the figure below, the L-tartrate directs attack of the oxygen atom from the oxidising agent *t*-BuOOH to the bottom face of the olefin while the D-tartrate directs it to the top.

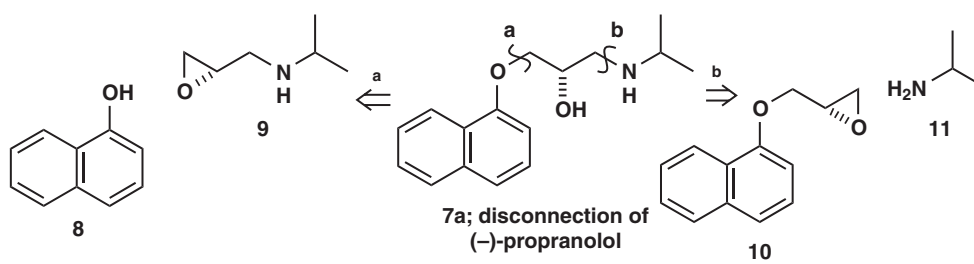


The synthesis of propranolol

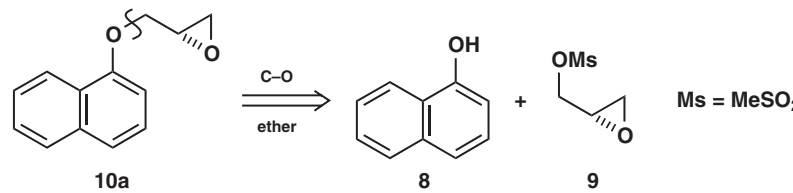
Propranolol **7** is a β-blocker. Let's consider how it could be disconnected. The first thing to notice is that there are two 1,2-related functional groups. We have an ether and an alcohol on the left-hand side of the molecule and, on the right, a 1,2-aminoalcohol.



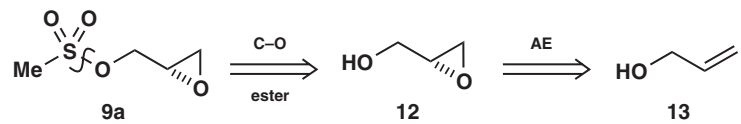
Because we have an alcohol in the *middle* of the molecule, we can imagine disconnections **7a** or **7b** that rely upon the attack of a nucleophile on the terminal position of an epoxide. Notice that there is only one chiral centre in this molecule.



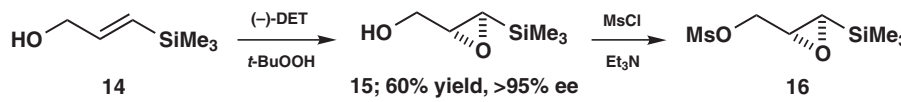
Either disconnection **a** or **b** would be fine. However, the way it was done[6] involved disconnection **b**. The next disconnection is akin to **a** in that it uses α-naphthol **8** as the nucleophile.



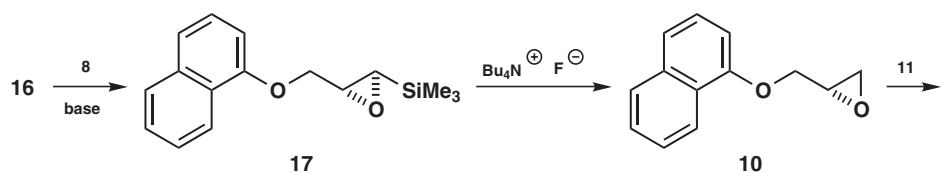
Mesylate was chosen as the leaving group and the epoxy mesylate **9** could be made from the corresponding alcohol **12** and that, in turn, from allyl alcohol **13** by Sharpless epoxidation.



In fact, allyl alcohol **13** was not used at the start of this synthesis because low ees result if there is no substituent on the alkene *trans* to the alcohol (R^2 in the mnemonic should be something other than H). It is much better here to add a removable group and so the silyl alkene **14** was used instead of **13**. The silyl group allowed the isolation of the epoxy alcohol **15** in a much higher yield than was possible using allyl alcohol itself and the ee of **15** was >95%. The alcohol was converted to a mesylate **16**.



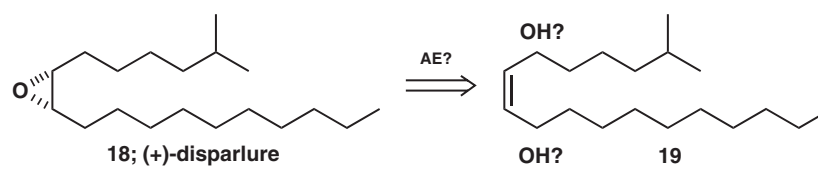
The mesylate was then displaced using sodium naphthoxide made from **8** with base. The silyl group is not wanted in the final product and was removed with TBAF (tetrabutylammonium fluoride, $Bu_4N^+ F^-$). Finally the epoxide **10** was opened with isopropylamine **11**. This synthesis depends on regioselective opening of an epoxide at the less substituted end.



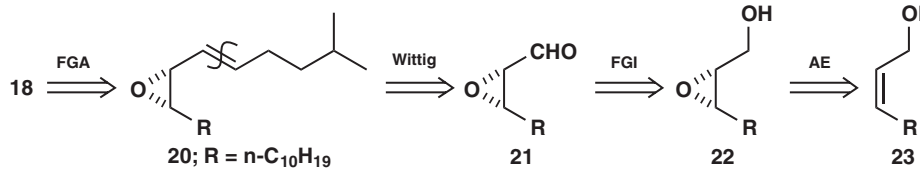
Modification after Sharpless Epoxidation

Oxidation after Sharpless epoxidation

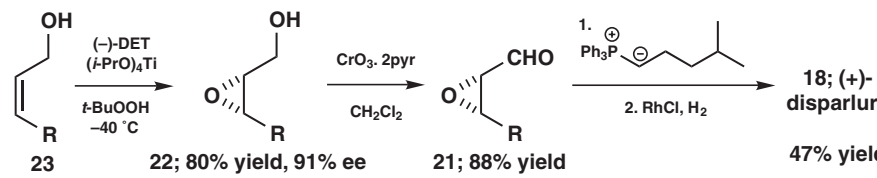
Disparlure **18** is the sex attractant of the gypsy moth. The only functional group in disparlure is the epoxide and we need an alcohol somewhere if the stereoselective introduction of this group is to be done by AE. Our disconnection strategy[7] is dominated by that thought – an alcohol must be introduced somehow at one of the allylic carbons in **19**.



It is best to add the OH group in a reaction that allows a helpful disconnection so an alkene was introduced (Functional Group Addition) to give the vinyl epoxide **20**. The double bond can be disconnected by a Wittig reaction. Although we might expect a mixture of double bond geometries using the Wittig reaction it doesn't matter here—this double bond is going to be removed anyway. Aldehyde **21** could come from alcohol **22** which is the product from an AE reaction on the *Z*-allylic alcohol **23**. The geometry of *this* alkene must be controlled and fortunately *Z*-allylic alcohols are easily made by partial reduction of alkynes (chapter 15).

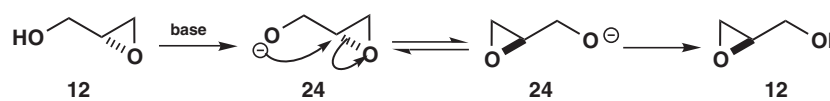


The (*Z*)-allylic alcohol **23** was epoxidised at −40 °C to give **22** in 91% ee and 80% yield. Sharpless[7] says 'The crystallinity of the epoxy-alcohol **22** greatly simplifies its isolation (no chromatography needed.)'. Oxidation, Wittig reaction and hydrogenation of the alkene complete the synthesis of (+)-disparlure **18** that did indeed attract the moths.

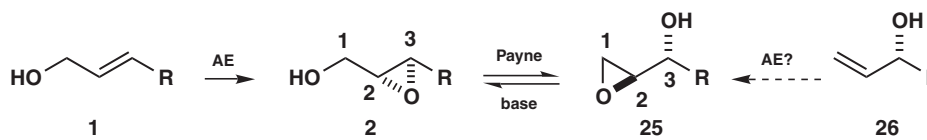


The Payne rearrangement

The products of a Sharpless epoxidation, such as epoxides **12**, **16**, or **22**, are potentially unstable in base as the anion of the alcohol can attack the epoxide **24** in the Payne rearrangement. This is easily seen with the simplest compound **12**. It doesn't and we have rather given the game away by the compound numbers. The OH groups in the right hand and in the left hand compounds **12** are homotopic. Sharpless made the definitive statement of this in his propranolol synthesis.[6]

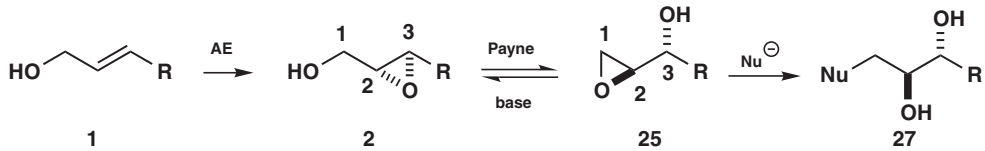


If the carbon skeleton is unsymmetrical **2** the danger is different: the Payne rearrangement gives a mixture of two products **2** and **25**. There are now three places where a nucleophile might attack: C-3 in **2**, C-1 in **25**, and C-2 in both but with different stereochemical outcomes. We much prefer to make **1** rather than **26** by AE as **26** is already chiral and the AE reaction would be a kinetic resolution.

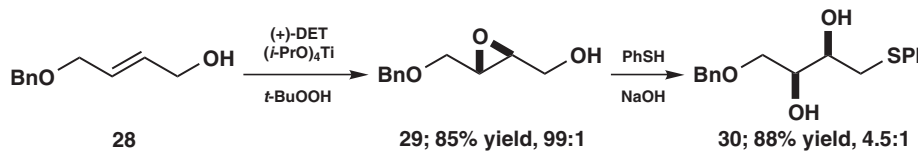


Of the two compounds **2** and **25**, the more substituted epoxide **2** is the more stable and therefore the more abundant. But the mixture reacts with nucleophiles preferentially at the least substituted

carbon, that is C-1 in **25**. The minor component of the mixture **25** gives the major product **27**. So AE on **1** can be used to make products from **2** or **25** according to the reaction conditions.

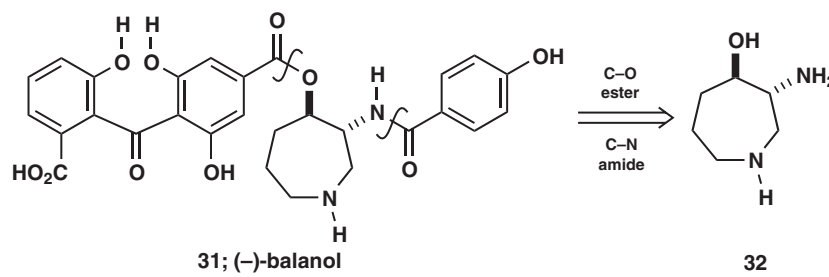


Our illustration comes from Sharpless's sugar syntheses.[8] The mono benzyl ether **28** responds well to AE and reaction of the epoxide **29** with PhSH in basic solution gives mostly (4.5:1) the product **30** of the Payne rearrangement.

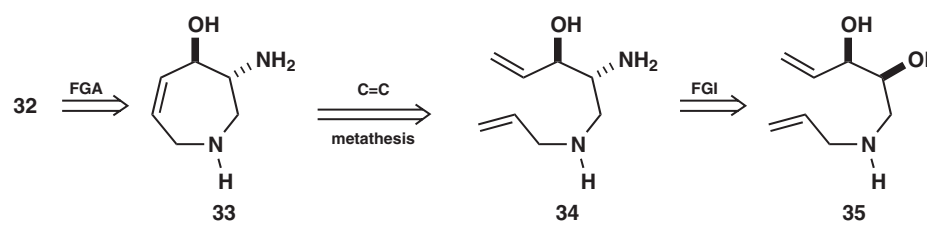


Asymmetric Induction at the Allylic Alcohol Centre: AE is *anti*-Selective

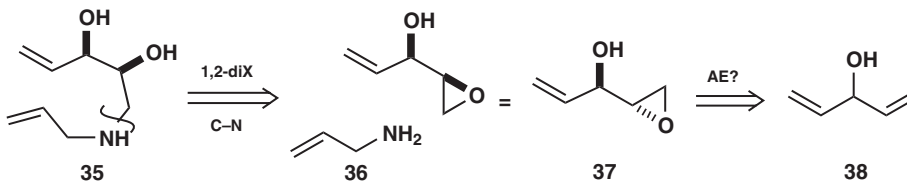
It is possible to make the CH(OH) centre of the allylic alcohol asymmetric by an AE reaction. This is a kind of symmetry breaking, It is well illustrated by Fürstner's synthesis of the only interesting piece **32** of the natural product (−)-balanol **31**: a potential lead for development of protein kinase inhibitors.[9] The two disconnections are trivial.



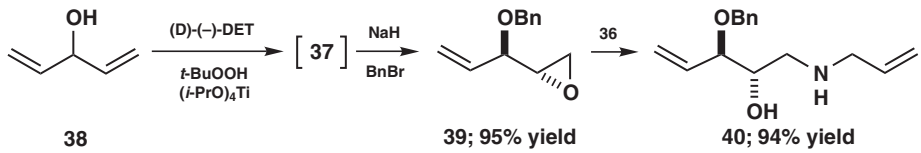
It does not look initially as if the cyclic amine **32** can easily be made by AE. However, the two substituents on the seven-membered ring are *anti* and could come from an epoxide opening. The key idea is to make the seven-membered ring by olefin metathesis (chapter 15). An alkene must again be added and Fürstner placed it so as to make the alcohol allylic **33**. Reversing the metathesis gives a non-cyclic starting material **34**. Now he removed one of the amines and replaced it by a second OH group to give **35**.



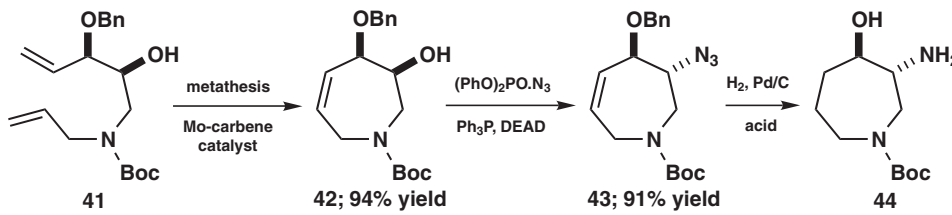
Disconnection of a 1,2-diX relationship gives allyl amine **36** and an epoxide **37** that might be made by AE. The starting material is indeed an achiral allylic alcohol **38** but it has two alkenes. They are in fact enantiotopic and AE will probably be able to discriminate between them. A more difficult question is what will be the stereochemistry of the alcohol in **37** as it becomes a stereogenic centre during the AE reaction. It turns out (by experiment) that AE has *anti*-selectivity: the catalyst delivers the epoxide oxygen to the opposite face to the OH group. This is surprising because both oxygen atoms are Ti-bound. But inspection of the loaded catalyst structure above shows that a substituent (here vinyl) on the allylic alcohol would prefer to be on the opposite face of the alkene to that attacked by *t*-BuOOH when both are bound to Ti. The symmetry aspects of this reaction are discussed in more detail in chapter 28.



'Unnatural' D-DET was needed to get the right absolute stereochemistry and **37** was not isolated but protected as a benzyl ether **39** before reaction with allylamine gave the carbon chain of **35**. Conversion of OH into NH_2 now required inversion.

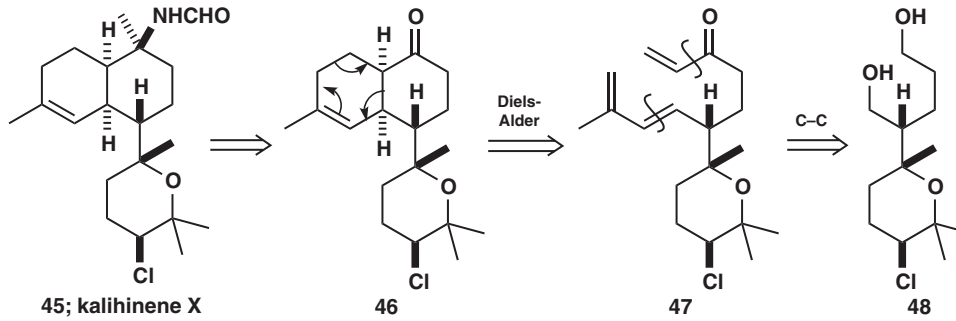


After *N*-Boc protection, metathesis worked very well to give doubly protected **42** and inversion with diphenylphosphoryl azide under Mitsunobu conditions gave the azide **43**. This order of events allowed a triple reduction - of the alkene, the azide and the benzyl group - in one step and Boc-protected **44** could then be used in the synthesis of balanol itself.

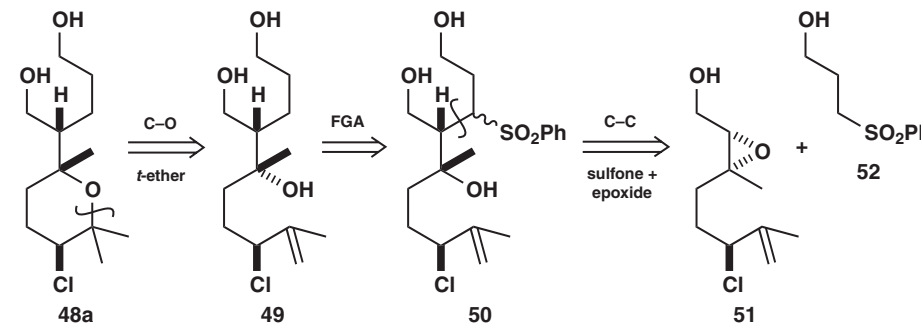


No Asymmetric Induction from Remote Allylic Alcohol Centre: Reagent Control

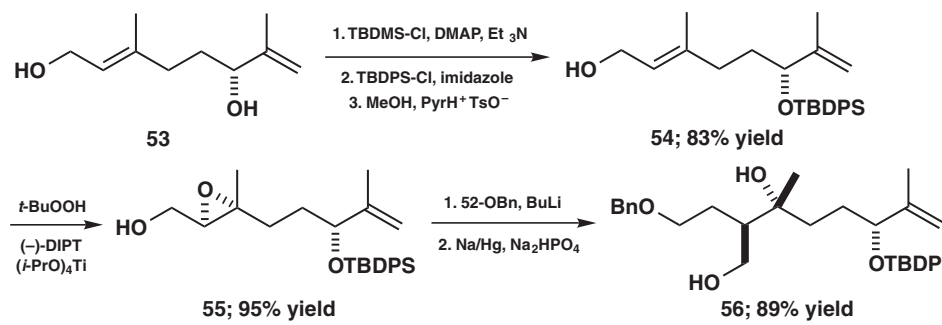
If there is already a chiral centre in the molecule that has already been controlled by asymmetric synthesis, the AE reaction will ignore it if it is far enough away. Yamada's synthesis[10] of the biologically active diterpenoid **45** illustrates this and demonstrates control when nucleophiles attack an unsymmetrical epoxide. Preliminary disconnections with a Diels-Alder in mind took the chemists back to the diol **48**.



The tetrahydropyran ring **48** has a tertiary carbon joined to oxygen **48a** and this C–O bond can be made by addition of an alcohol to an alkene. Addition of an anion-stabilising sulfone **50** allows a C–C disconnection back to the epoxide **51** that does look like an AE product except for the allylic chloride.



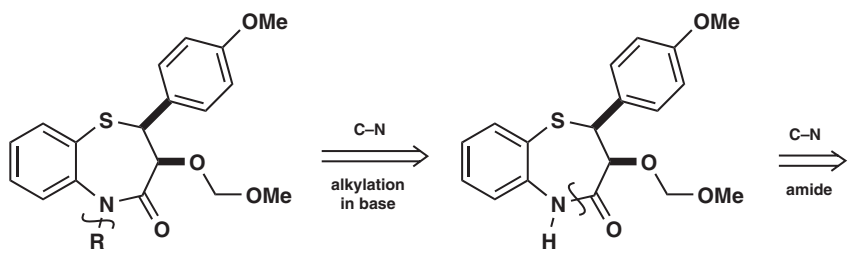
The substrate chosen for the AE reaction was the *bis* allylic alcohol **53** having the same carbon skeleton as **51** but with an inverted alcohol replacing the chloride. This was a strange choice as one of the allylic alcohols must be protected and there remains the question of the influence of the stereogenic centre on the AE reaction. Protection was easy: silylation with *t*-$BuMe_2SiCl$ (TBDMSCl) occurred only on the primary alcohol, silylation with *t*-$BuPh_2SiCl$ (TBDPSCl) could be forced onto the one remaining OH and selective methanolysis of the less hindered silyl group gave **54**. The AE reaction was, as expected, regioselective for the allylic alcohol but most significantly was highly reagent controlled (10:1 in favour of **55** over the other diastereomer). Reaction with the lithium derivative of the sulfone **52** gave **56** which could be converted into **51** by acetylation of the two OH groups, desilylation and Mitsunobu-style inversion of the alcohol with Ph_3P and CCl_4. These reactions are discussed in the Workbook.



Should the starting material **53** be enantiomerically pure? Yes, as there is virtually no kinetic resolution. The asymmetric centre in **53** is evidently too far from the alkene that reacts by AE to have more than a minor effect on the stereoselectivity. Enantiomerically pure alcohol **53** was already available from asymmetric reduction (using CBS, see chapter 26) of the corresponding enone. Sharpless epoxidation does have limitations but it is supremely practical.

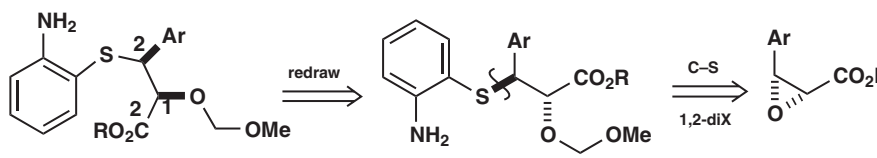
Asymmetric Synthesis of Diltiazem

Diltiazem is a calcium channel blocker used in the treatment of angina and hypertension. The active compound is the (+) enantiomer of the *cis*-diastereoisomer **57**. The side chain (R = $Me_2NCH_2CH_2$- in **57**) can be added by alkylation of **58**. The amide is an obvious disconnection.



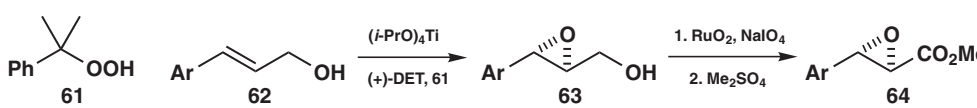
57; (+)-*cis* diltiazem **58**

The intermediate **59** has two 1,2-diX relationships but only one can reasonably be derived from an epoxide and redrawing **59a** to show the *anti*- stereochemistry between S and O that would result from opening an epoxide unfortunately reveals an epoxide **60** from a *cis* unsaturated ester.



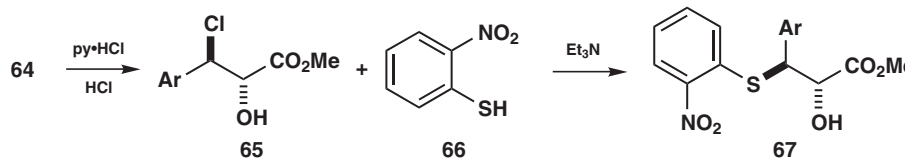
59 **59a** **60**

We need an allylic alcohol if we are to use AE and we much prefer a *trans* allylic alcohol. So two inversions will be needed. The epoxide **63** was made in excellent yield and ee provided cumyl hydroperoxide **61** was used as the oxidant. Oxidation gave the required ester **64**.



61 **62** **63** **64**

Now for the first inversion. It turns out that nucleophilic attack by chloride ion occurs next to the electron-rich aromatic ring rather than next to the ester. The thiol **66** was used so that the thiolate anion could be made with a weak base, and the required regio- and stereochemistry is in place **67**. The rest of the synthesis[11] is in the Workbook. We shall be seeing other syntheses of diltiazem later in this chapter that use other asymmetric methods.

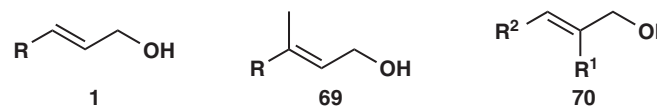


Summary of Sharpless Epoxidation

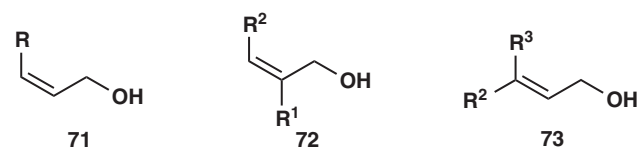
This exceptionally accommodating reaction can be made to work for most kinds of allylic alcohol but there are some general guidelines that we shall summarise here:

1. The substrate must be an allylic alcohol such as **1**. The next best is a homoallylic alcohol **68** but then the reaction is slow and the ees generally poor.

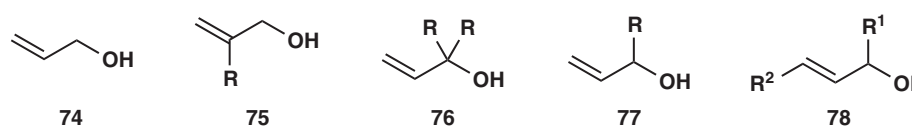
2. The best results come with terminal allylic alcohols that have *E*-alkenes with some substitution such as **1**, **69**, and **70**.



3. Allylic alcohols with *Z*-alkenes (that is an alkyl group *cis* to the OH group **71** – **73**) generally give poor results. The mnemonic device above shows that the fit is poor.



4. Terminal alkenes other than allyl alcohol itself are not much use. The epoxide from one achiral type **75** is very susceptible to nucleophilic attack and the Payne rearrangement, while the other achiral type **76** gives poor ees. The chiral compounds **77** and **78** belong to the realm of kinetic resolution (chapter 28).



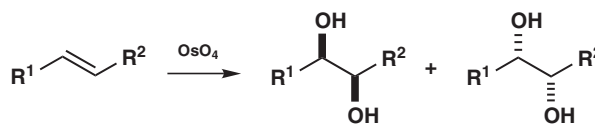
Part II – Sharpless Asymmetric Dihydroxylation

The Sharpless dihydroxylation reaction (AD) is arguably the most important discovery in organic chemistry of the 20th century. There is no question that asymmetric synthesis is at the forefront of modern synthetic organic chemistry. And the most impressive asymmetric methods are those which are *catalytic*. The Sharpless epoxidation achieved this and more. But those methods that

combine high enantiomeric excesses and high catalyst turnover with activity over a broad range of substrates become supremely useful when they are simple to perform and require no fancy solvents, temperatures or other rigorously controlled conditions. The Sharpless Asymmetric Dihydroxylation (AD), an asymmetric version of the familiar dihydroxylation of alkenes with osmium tetroxide, is such a method.[12] As testimony to their ease of use, both the Sharpless epoxidation and the Sharpless dihydroxylation have now found their way into undergraduate laboratory practicals.

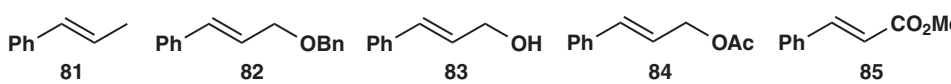
The AD Method

Professor Barry Sharpless[13] wrote, 'It reacts only with olefins and it reacts with all olefins (slight poetic licence here)' The "It" is, of course, osmium tetroxide which reacts with those olefins to give 1,2-diols.[14] It does so stereospecifically, introducing the two hydroxyl groups on the same side of the flat double bond **79** to give the *syn* diastereoisomer **80**. In addition to this stereospecificity, in the presence of an appropriate ligand, osmium tetroxide may react with olefins enantioselectively, attacking one or other of the two enantiotopic faces to give **80** or *ent*-**80**.



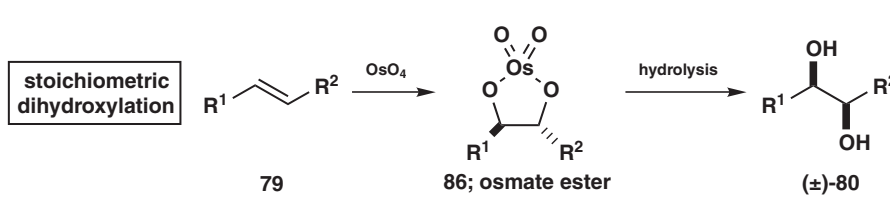
The reaction has been developed by Sharpless[15–18] and others[19] from one which required a stoichiometric amount of prohibitively expensive osmium tetroxide to one where as little as 0.002 mol% of osmium may be used.[13] What is more, the former method performs a racemic transformation whereas the latter yields essentially optically pure diols.

Look at that quote again. The variety of substrates that can be used is enormous and even for an asymmetric reaction, no other functionality is required. Of the five compounds illustrated below, only the allylic alcohol **83** forms a suitable substrate for the Sharpless epoxidation but all are suitable for the asymmetric dihydroxylation (AD) reaction.

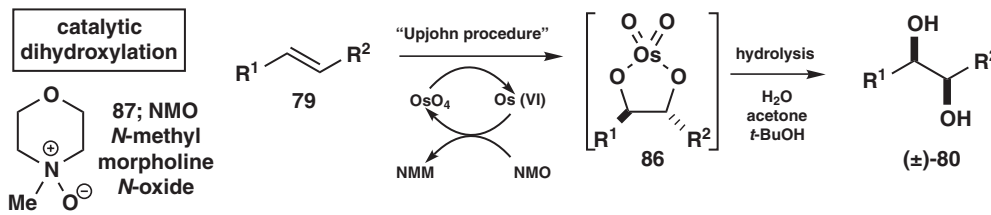


It is certainly appropriate for us to describe here some of the important aspects of Sharpless dihydroxylation methodology. This background is essential to chemists who do, or are thinking about doing, the reactions. However, a detailed discussion of, for instance, the *mechanism* of the reaction, or the explanations behind the origin of the enantioselectivity, are beyond the scope of this book and so, where this sort of thing is described at all, it is done mostly from an empirical standpoint.

Some history. The development of the current state of the art makes an interesting story. The reaction of osmium tetroxide with olefins was discovered[14] in the 1930s. The reaction first gives an osmate ester **86**. This ester is a stable species but can be hydrolysed to yield the diol **80**.

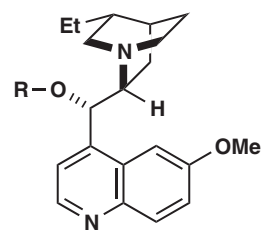


Osmium tetroxide is very expensive and very toxic which made using it quite unattractive. For a long time, many people who used osmium tetroxide to convert olefins to diols—and this was long before *enantioselective* dihydroxylations came on the scene—used the Upjohn procedure.[20] This process used *catalytic* amounts of osmium tetroxide, NMO (*N*-methylmorpholine *N*-oxide) **87** as the stoichiometric oxidant, and one solvent phase. The solvent was water, acetone and *tert*-butyl alcohol. The osmate ester **86** was hydrolysed under these conditions and the osmium (VI) species was reoxidised to OsO_4 by NMO.

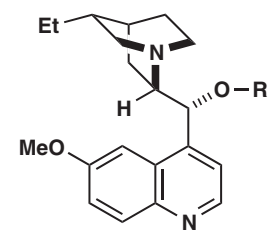


The ligand

The simplest asymmetric ligands that were used, and from which all of the state-of-the-art ligands are derived, were esters of either dihydroquinidine **88** or dihydroquinine **90**. Sharpless first developed a stoichiometric process using these ligands but many years passed before the *catalytic* asymmetric dihydroxylation was achieved when the ligands were added to the standard Upjohn process.[15] The two cinchona alkaloids (and their ester ligands **89** and **91**) are not, in fact, enantiomers, but diastereomers. The absolute configurations of the centres in one complement those in the other at all but one centre – where the ethyl group joins the quinuclidine unit – and so they function as enantiomers. Cinchona is pronounced sink*own*er: "Named by Linnæus after the countess of Chinchon, who, when vice-queen of Peru, was cured of a fever by Peruvian bark, and afterwards brought a supply of it into Spain" according to the Shorter Oxford English Dictionary.



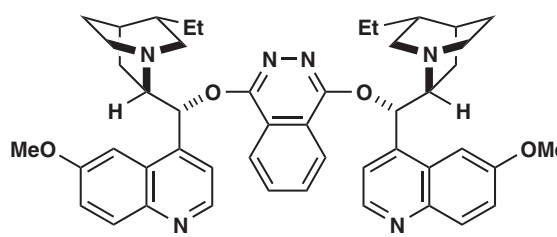
88; dihydroquinidine (R = H) (DHQD)
89; (R = *p*-chlorobenzoyl)



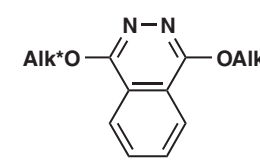
90; dihydroquinine (R=H) (DHQ)
91; (R = *p*-chlorobenzoyl)

92; quinuclidine (achiral)

These ligands were superseded with the development of the phthalazine (PHAL) ligands in which *two* cinchona alkaloid units are connected together. The two most widely used ligands are the phthalazine ligands $(DHQD)_2$-PHAL **93** and $(DHQ)_2$-PHAL and these are used in the two commercially available asymmetric dihydroxylation mixes – AD-mix-α and AD-mix-β.

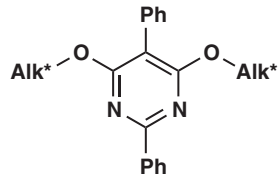


93; $(DHQD)_2$-PHAL

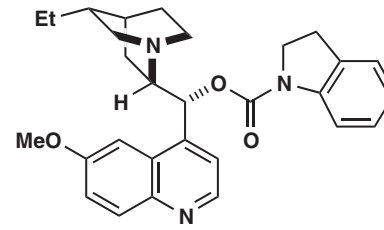


94; phthalazine ligands
$(DHQ)_2$-PHAL or $(DHQD)_2$-PHAL
simpler representation

The diphenylpyrimidine (PYR) **95** and the indoline (IND) substituted ligands **96** are other types. The indoline ligands contain just the one alkaloid unit. The three different ligand types (PHAL, PYR and IND) are suitable for different types of olefin.

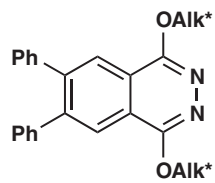


95; diphenylpyrimidine ligands (DHQ)$_2$-PYR or (DHQD)$_2$-PYR simple representation

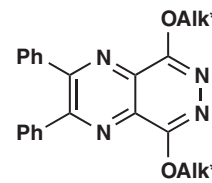


96; (DHQIND)

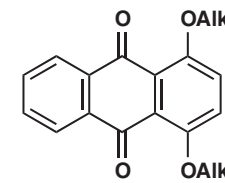
More recently discovered ligands[21] include the diphenylpyrazinopyridazine (DPP) **98** and anthraquinone (AQN) **99** ligands as well as the diphenyl analogue of the phthalazine ligands (DP-PHAL) **97**.



97; diphenylphthalazine (DP-PHAL) ligands



98; diphenylpyrazinopyridazine (DPP) ligands



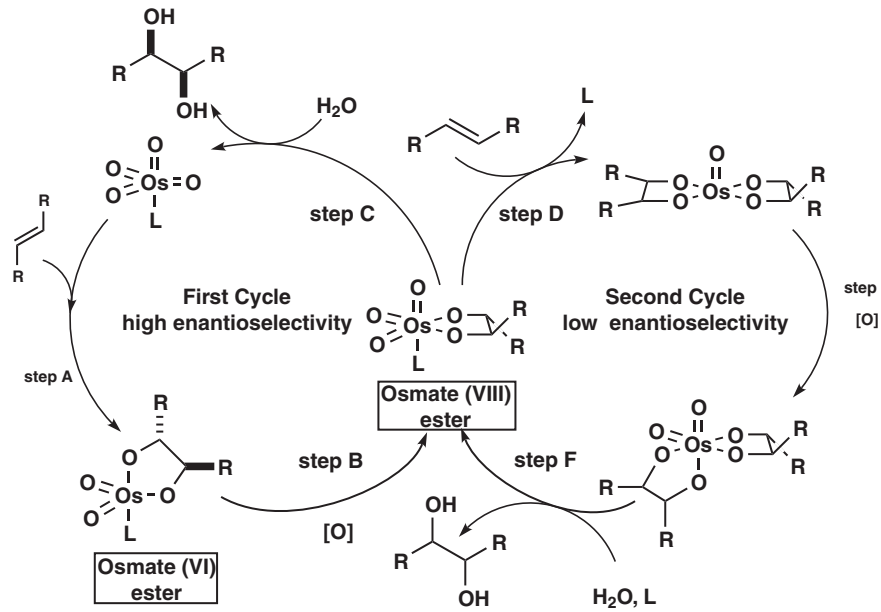
99; anthraquinone (AQN) ligands

Solvent dependence

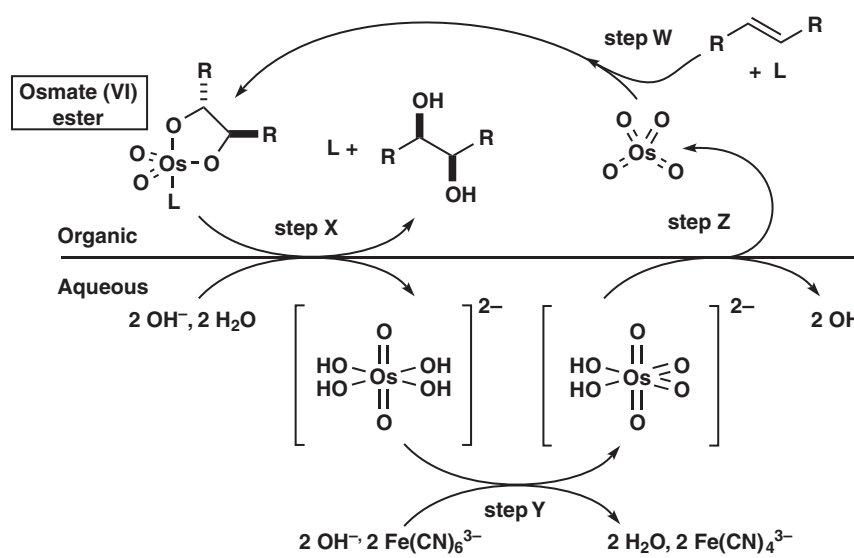
There are two solvent systems commonly used for dihydroxylations. The first involves just one phase and consists of either water and acetone[22] or water, acetone and *tert*-butyl alcohol.[14] The second, and more modern, solvent system is a two phase mixture and consists of water and *tert*-butyl alcohol. The impact that the two phase system has on enantioselectivity is profound. This is because it prevents the deleterious 'second cycle' which can otherwise occur. In fact, the single phase method *is* still used for certain applications including multiple dihydroxylations.

The catalytic cycle

One of the problems encountered in the development of the AD reaction was a second cycle.[23] The first cycle is the same as the cycle we saw in the Upjohn procedure with one modification. It is possible for the osmium in the osmate (VI) ester to become oxidised *before* hydrolysis to form an osmate (VIII) ester. If this species simply hydrolyses to diol and OsO_4 then there is no problem but otherwise this is where the trouble starts. In the second cycle the osmate (VIII) ester reacts with *another* olefin instead of being hydrolysed. It does so with low enantioselectivity (and sometimes in the opposite sense to the first cycle) which results in the poorer enantiopurity of the product (step D rather than step C below). One way round this is to keep the olefin concentration as low as possible which can be done by adding the olefin slowly.[22,23] Although slow olefin addition resulted in a profound improvement in enantiomeric excess, it was inconvenient and no way near as effective as the alternative which was to alter the conditions. The use of two phases makes it impossible for the second cycle to occur.[19,24]



Before the osmate (VI) ester, resulting from the addition of olefin and osmium tetroxide, can react with a second olefin it has to be reoxidised (step B). With two phases, the osmate ester and olefin are in the organic layer and the oxidant [$Fe(CN)_6^{3-}$] is in the aqueous layer. Hence the osmium cannot be oxidised while it is in the form of the osmate (VI) ester to an osmate (VIII) ester. Only after the osmate ester has hydrolysed may the osmium enter the aqueous phase and be reoxidised for another cycle (step Y).[12] It is critical that the reaction mixture is biphasic. Just using a water/*tert*-butyl alcohol solvent system is not enough because these two solvents can be miscible. It was demonstrated[24] that stoichiometric osmylation of styrene in 1:1 *tert*-butyl alcohol/water, a homogeneous reaction, gave a product with 58% ee. That same stoichiometric reaction performed in the presence of either $K_3Fe(CN)_6$ or potassium carbonate led to a 74% ee. These salts stop the water and *tert*-butyl alcohol mixing. The addition of K_2CO_3 is essential. Although it may be partially replaced with $NaHCO_3$ for base-sensitive materials the AD reaction fails to turn over with its complete omission.[12,24]

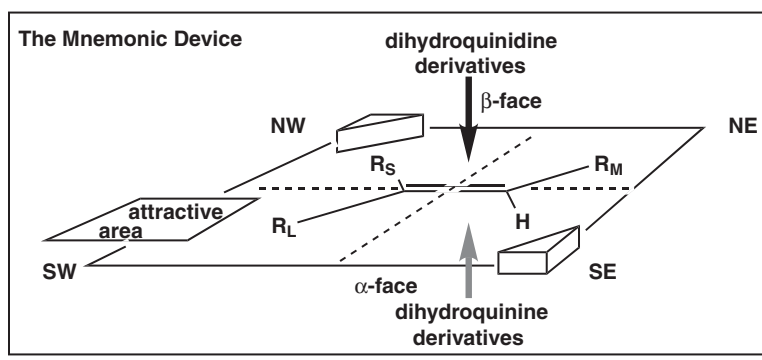


Methanesulfonamide

Another key development was the discovery that methane-sulfonamide $MeSO_2NH_2$ accelerated the rate of hydrolysis of the intermediate osmate ester (not to be confused with the rate of the addition of osmium tetroxide to the olefin). Reaction times can be reduced by as much as 50 fold. After 3 days at 0 °C in the absence of methanesulfonamide, *trans*-5-decene had been only 70% converted to the corresponding diol but the diol was isolated in a 97% yield after just 10 h at 0 °C in the presence of methanesulfonamide. This improvement means that reactions can be run at 0 °C instead of room temperature. However methanesulfonamide *slows down* the reaction of *terminal* olefins. It is thus omitted from such reactions.[16]

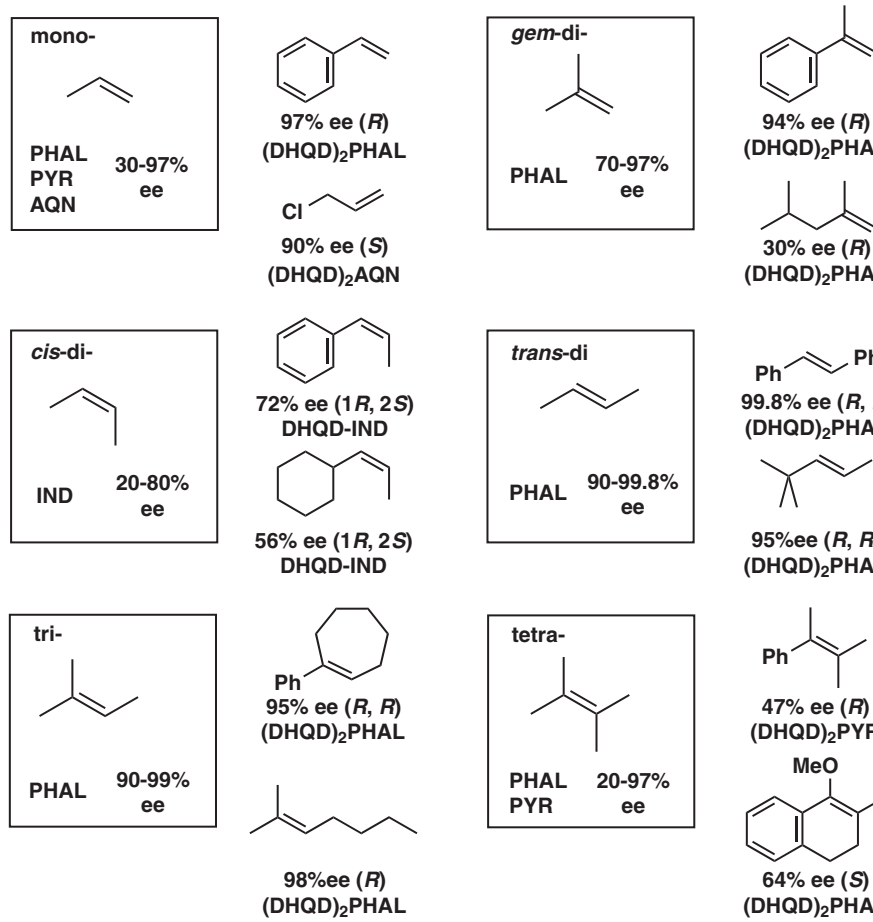
Substrate Dependence and the Mnemonic Device

In order to predict facial selectivity, Sharpless and co-workers invoke a mnemonic device.[25] To an approaching olefin, the greatest steric constraints are presented by the NW, and to an even greater extent, the SE quadrants. The SW and NE quadrants are more open and, in addition, the SW quadrant contains what is described as an "attractive area". The attractive area is particularly well suited to accommodate flat aromatic groups. The olefin positions itself according to the constraints imposed by the ligand and is dihydroxylated from above (β-face), in the case of dihydroquinidine derivative, or from below (α-face) in the case of dihydroquinine derivatives. The commercially available AD-mix-α and AD-mix-β are chosen according to this mnemonic.



Inspection of this mnemonic illustrates why stilbene is such a good substrate for these ligands: its two aromatic portions can align nicely with two-fold degeneracy into the ligand pocket with only hydrogen atoms in the sterically demanding areas. In contrast, we can see why *cis* alkenes make such poor candidates – one of the substituents will *have* to be in a sterically demanding area. Of all the alkene classes,[25] the *cis*-di-substituted alkenes are the least good. They need a unique ligand - the indoline substituted alkaloid[18] **96** and even then enantiomeric excesses rarely exceed 80%. The figure below outlines the ligands that Sharpless recommends for each of the six olefin classes. Five of the six work very well with either PHAL or PYR. The AQN ligands are particularly suited to allylically substituted terminal olefins[21] and the PYR ligands are good for sterically congested olefins.

Recommended ligands for different classes of alkenes

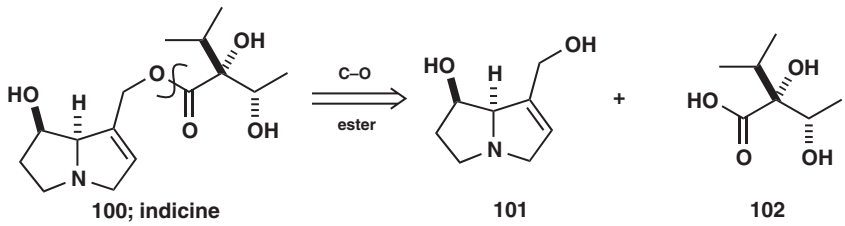


Applications of the Sharpless AD Reaction

That was the background. And now we look at the application of the AD reaction. First of all we look at a few retrosyntheses before moving on in the section *dihydroxylating with more than one double bond* to consider the more complicated issues. It is often easy to spot when a Sharpless AD strategy might be used if there are two hydroxyl groups in the target molecule which are 1,2-related.

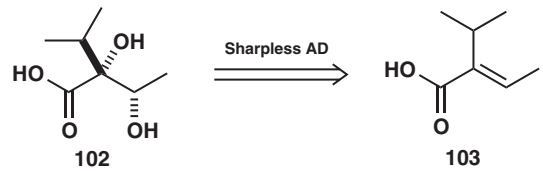
The synthesis of indicine

Indicine **100** is an alkaloid which has antitumour activity but hepatic toxicity.[26] The molecule clearly consists of two enantiomerically pure chunks which we would like to separate in our retrosynthesis. What is more, those two portions are conveniently connected by an ester linkage making the first disconnection very easy.



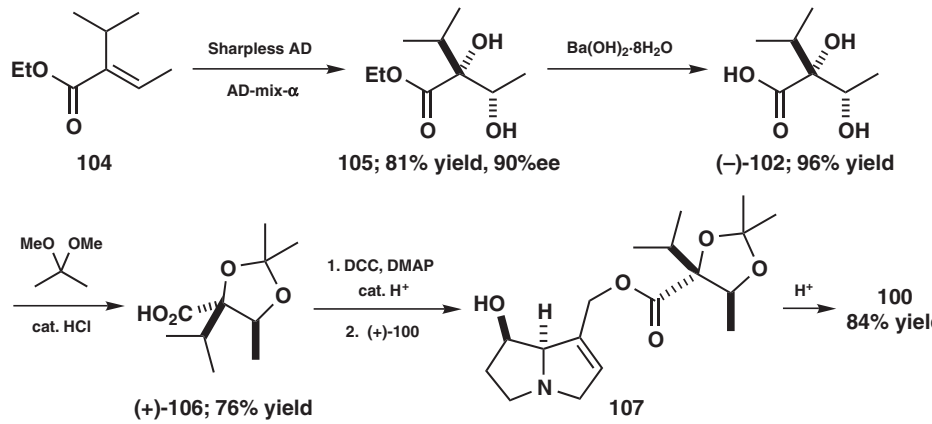
100; indicine **101** **102**

We shall not concern ourselves with the whole synthesis of (+)-retronecine **101** at this stage but just with the diol **102**. Diol **102** comes from the corresponding alkene by Sharpless AD.



102 **103**

The substrate for the Sharpless AD was, in fact the ethyl *ester* **104** of the α,β-unsaturated acid **102**. This was dihydroxylated using AD-mix-α and then the ester **105** was hydrolysed using barium hydroxide. Before the resulting acid was coupled with alcohol **101**, the diol functionality was protected as an acetal **106**. The coupling was performed using DCC and DMAP and the protecting group was removed under acidic conditions to give indicine **100**.



104 **105; 81% yield, 90%ee** **(–)-102; 96% yield**

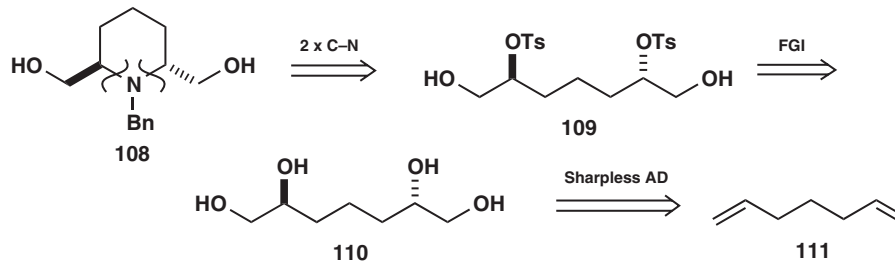
(+)-106; 76% yield **107**

When fitting olefin **104** into the pocket provided by the mnemonic device we notice that the isopropyl group and the ester function in olefin are of similar size. As a result, we might expect the ee to be low and yet 90% is achieved.

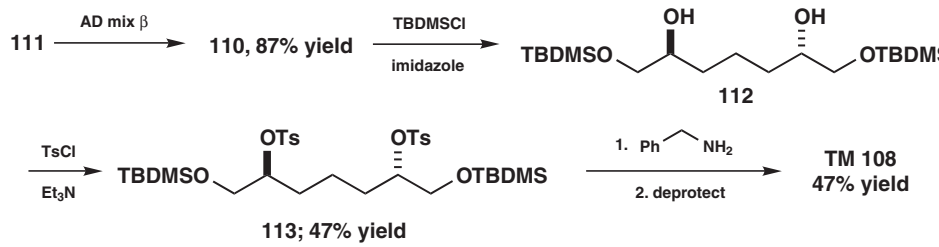
The synthesis of a C_2-symmetric piperidine

When we think about retrosynthesis, two 1,2-related oxygen atoms, each on stereogenic carbon atoms, as in **100**, may scream to be 'retro-dihydroxylated' but it is harder to spot where the strategy may be useful if there is only one oxygen atom or where heteroatoms are not even 1,2-related. Consider, for instance, the C_2-symmetric 2,6-disubstituted piperidine[27] **108**. We notice for a start that the two oxygen atoms are most certainly not 1,2-related. At best they are 1,5. Both the oxygen atoms are 1,2-related to the nitrogen atom however. Two carbon – nitrogen bonds can be disconnected at once to give the tosylated tetraol **109**. We are going to have to think about protection

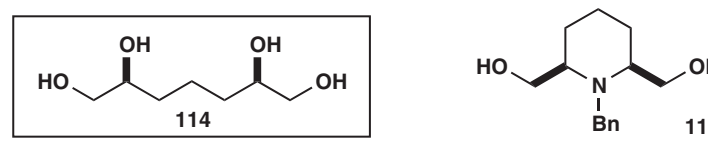
because the secondary alcohols are the ones that need to be tosylated – we will worry about that in the forwards synthesis. As the tetraol **110** is C_2 symmetric it could be made by *bis* dihydroxylation of diene **111** using the *same* asymmetric ligand.



Diene **111** was dihydroxylated using AD-mix-β to give the C_2 symmetric tetraol **110** and its *meso* diastereomer **114** in a combined yield of 87%. The primary hydroxyl groups are selectively protected using TBDMS chloride and imidazole – otherwise they would react with tosyl chloride. The secondary alcohols are then activated with tosyl chloride to yield **113** and *meso* isomer in 47% yield from the tetraol. Reaction with benzylamine yields the target material **108** in 47% and the unwanted *meso* amine **115** in 30% yield.

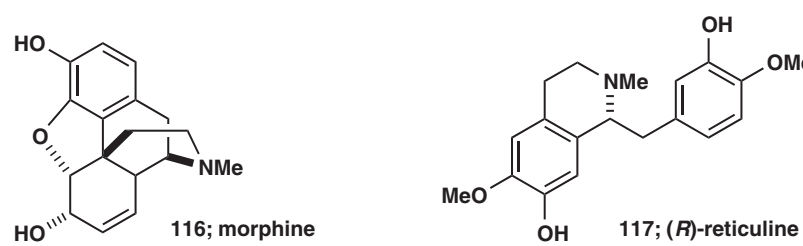


Take particular note that two hydroxylations are done on the same substrate **111** at the same time. We will not dwell too much on this here, but from the point of view of enantiomeric excess this is an aspect of asymmetric methodology that can be very useful. See **Double Methods** in chapter 28.

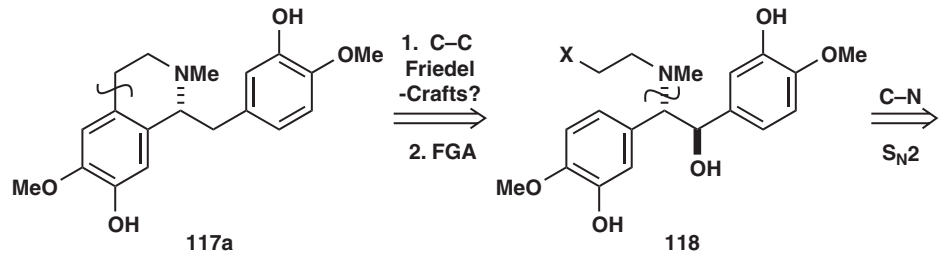


The synthesis of the alkaloid reticuline

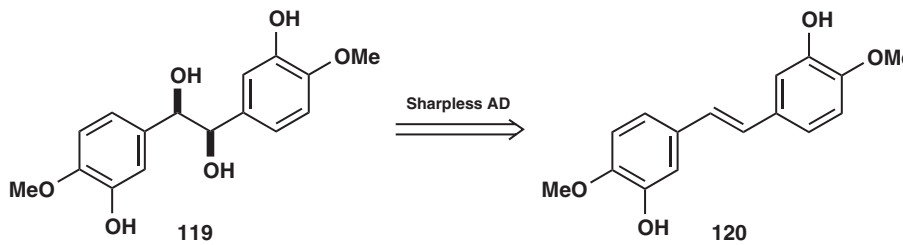
If it is difficult to spot where a product results from a dihydroxylation because there is only *one* oxygen in the product then it must be even more difficult to spot when there are none. Reticuline **117** is a natural product which can be used in the synthesis of morphine **116**.



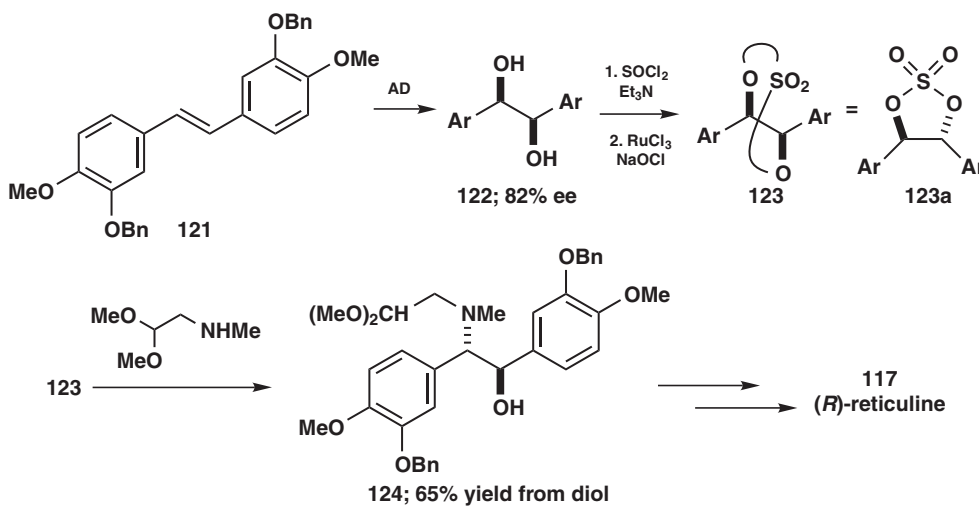
We will come onto the stereochemistry in just a moment but first we can simplify the structure by disconnecting the six-membered amine ring. We should be able to make this C–C bond **117a** using a Friedel-Crafts reaction. Right, we notice that there is no oxygen functionality involved in reticuline's one chiral centre. If we are to use a Sharpless AD reaction then the first thing to do is to put in some oxygen functionality.



The C–N bond of the amine can now be disconnected **118**. If we imagine that it was introduced by an S_N2 displacement, then we invert that stereocentre and introduce an oxygen-based leaving group to give the diol **119**. Now we have the sort of compound that we are looking for! We can instantly see that this comes from the corresponding stilbene **120**. Notice that the hydroxyl groups in **120** are homotopic and that the diol **119** is C_2 symmetric.

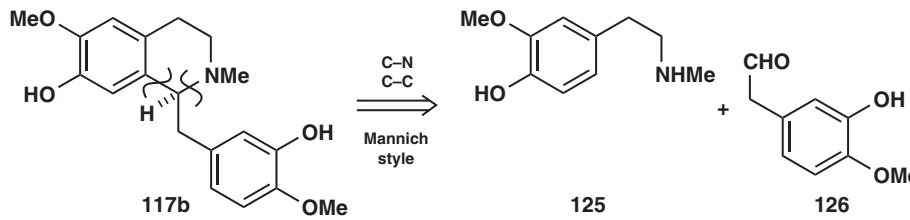


The stilbene **121** (which is dibenzylated **119**) is dihydroxylated to yield diol **122** in 82% ee and 88% yield. This diol needs to be activated. It is reacted with $SOCl_2$ to yield a cyclic sulphite which is oxidised to cyclic sulphate **123**. This is redrawn as **123a**. Both cyclic sulphites and cyclic sulphates are very useful synthetic building blocks with, of course, *two* electrophilic carbon atoms.[28] The two benzylic oxygen atoms here are homotopic so attacking either benzylic position will yield the same enantiomer of product. In fact a protected aminoaldehyde was used as nucleophile as this makes the cyclisation easier.[29] This and the deprotection steps are given in detail in the Workbook.



Note that to keep a straight carbon chain in our drawing of the cyclic sulfate **123a** we need to draw the two S–O bonds in a very curvaceous way **123**. This technique is often used to keep emphasis on the *syn* nature the two hydroxyl groups of diols when the diols are converted to cyclic sulfates or acetals.

The disconnection we used to plan the synthesis of reticuline is rather unusual. Reticuline is often drawn in a way **117b** that is rotated clockwise by 60° from the way drawn above **117a**. The disconnections are more often a C–C disconnection between the aromatic ring and an imine resembling the Mannich reaction as the imine is formed by the attack of an amine **125** on an aldehyde **126**. This is an easy reaction to carry out but it forms two bonds and a chiral centre all in one step and is difficult to make asymmetric. Because we wanted to use AD, we needed a different disconnection.



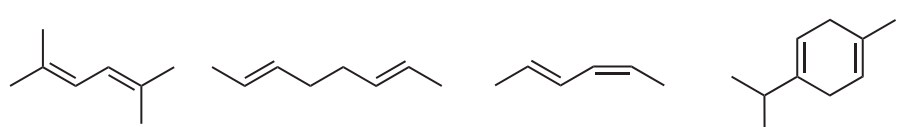
Dihydroxylating Compounds with More than One Double Bond I—Regioselectivity

Here we think about *which* double bond will be dihydroxylated if a molecule contains more than one. We postpone the question of how one already dihydroxylated double bond influences the diastereoselectivity in the dihydroxylation of a second double bond until the next section.

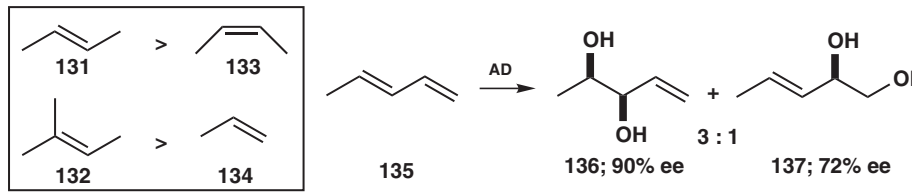
If there is more than one double bond in a molecule then, unless we have something like a symmetrical diene, there will be a question of regioselectivity. Predicting that regioselectivity can be a bit of a minefield and you need to know what you're doing.[12] In this section we will deal with some of the simpler guidelines. The Workbook deals with some of the more subtle rules and finer methods. We start with dienes.

Dienes

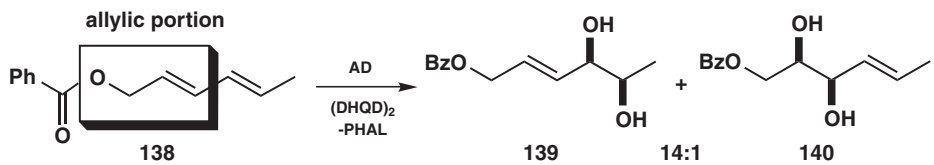
With two double bonds only, we need to worry about two main things – whether or not they are conjugated to each other, and whether or not they are equivalent from a symmetry point of view **127** – **130**. A substrate may contain two double bonds which are – because they are related by a symmetry element that makes them so – equivalent. Then they may be conjugated or not. The double bonds may, of course, be different electronically and/or sterically. For the sake of strategy we must have some idea how one double bond reacts in the presence of another. For the moment we will concern ourselves only with monodihydroxylation of dienes and outline a few guidelines. Guidelines are not rules. For a given substrate, the *Guidelines* may support each other or they may conflict with one another. In the latter case, predicting what will happen can be a bit tricky!



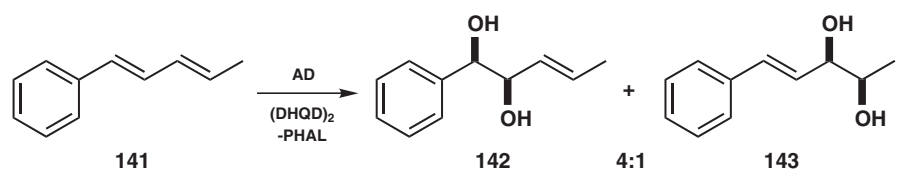
Guideline One. – Double bonds which are *trans*-di- **131** or tri- **132** substituted react faster than those which are either *cis*-di- **133** or *mono*- **134** substituted. The simple diene **135** reacts regioselectively at its *trans* double bond when it is dihydroxylated using $(DHQD)_2PHAL$ as the ligand.



Guideline Two. – Electron-rich double bonds react in preference to more electron-deficient double bonds. You can see that this is partly responsible for *Guideline One* but the principle extends beyond this. The benzoate ester **138** contains two *trans* double bonds but one is evidently much more reactive than the other. The double bond on the left is part of an allylic ester and is deactivated by the electron-withdrawing benzoate group.

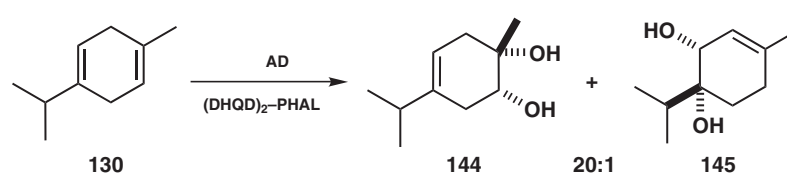


Guideline Three. – In a conjugated system, the double bond that reacts will be the one that leaves the most conjugated system behind. This means that the double bonds at the end of a conjugated system are the more reactive. Conjugated diene **141** has one 'end' only because the benzene ring is included in the conjugated system but is not reactive. It is perhaps worth noting that in a simple conjugated system – like, for instance, octatetraene – the highest HOMO coefficient and the highest LUMO coefficient will both be on the terminal carbon.



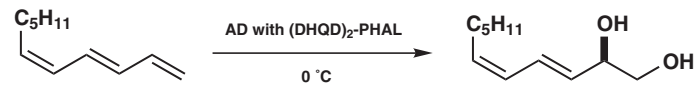
This guideline predicts that dihydroxylation of the diene **141** would give the diol **142** as the main product.[30] This is indeed the case but, as we shall see, this selection is easy to overturn. In this case, if the bulk of the aromatic ring is increased then the selectivity is reversed.

Guideline Four. – Other *Guidelines* being equal, the least hindered double bond will react preferentially.[30] Thus **130** gives mainly **144**.



When guidelines combine or compete

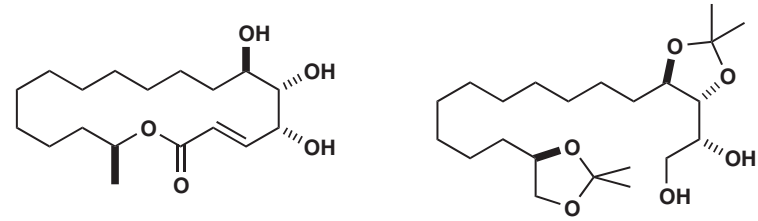
Combinations of these simple systems can be seen. Triene **146** has three different sorts of double bond—a *cis*, a *trans* and a terminal double bond. Which of these will react preferentially? Two of the guidelines come into play here. We have a conjugated system and so we would expect one of the double bonds at the end of that system to react by *Guideline Three*. However, *Guideline One* tells us that double bonds which are *trans*-di- substituted are more reactive than those which are either *cis*-di or mono- substituted. So maybe the triene reacts in the middle! The answer is, in fact, that it reacts at the right hand end. Conjugation is more important than alkyl groups.[30]



146 **147**

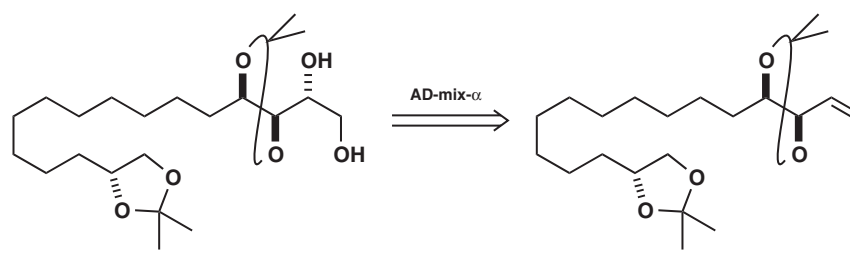
A synthesis of aspicillin

In the synthesis of (+)-aspicilin **148**, a lichen macrolide, by Sinha and Keinan[31] all the chiral centres were introduced using the AD reaction. An intermediate in the synthesis of this compound was compound **149**.



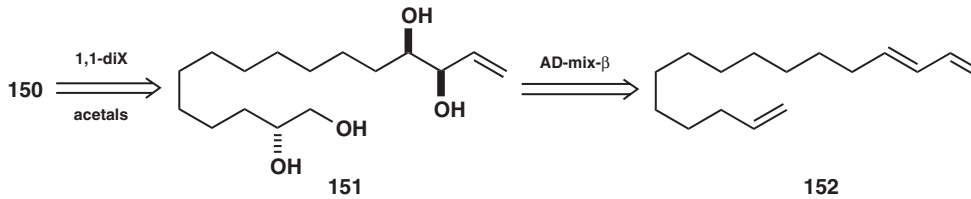
148; (+)–aspicilin **149**

If we draw the carbon backbone of **149** in a slightly straighter fashion **149a** it's easier to see the retrosynthetic step that follows. This means that we are forced to draw the acetal **150** in the same distorted way that we used with cyclic sulfates. We can install the diol at the end of the molecule using AD-mix-α.

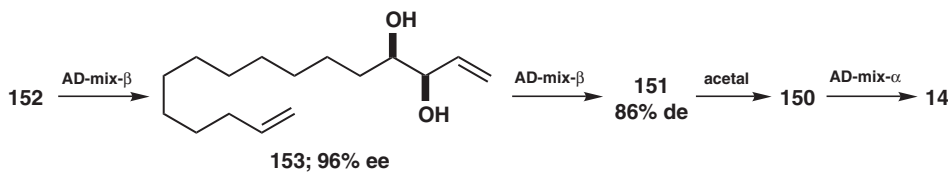


149a **150**

We can then remove both of the acetal protecting groups to reveal the tetraol **151**. The stereochemistry of both the diols in **151** demands the use of AD-mix-β on **152**.



It is when we look at the synthesis in the forward direction that we see just how clever it is. We react triene **152** with AD-mix-β and there are three double bonds which *could* react. There are two terminal double bonds and one *trans* double bond. *Guideline One* would suggest that the first double bond to react would be the *trans* one to give product **153**. Sinha and Keinan[31] who thoroughly investigated the dihydroxylations of this triene, found that this was indeed the case. The diol forms with a 96% enantiomeric excess. We are then left with two terminal double bonds. Which of these will react? In a conjugated diene, the dihydroxylation of one double bond reduces the reactivity of the second one considerably. Hence the second dihydroxylation yields mostly **151** which is formed with an 86% diastereomeric excess. The tetraol is protected before we react the final double bond with, *this* time, AD-mix-α.

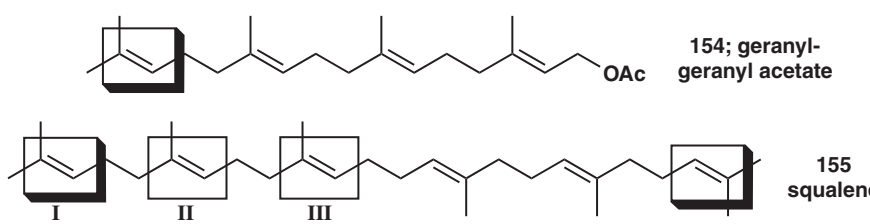


This synthesis uses *both* enantiomeric asymmetric dihydroxylation reactions. They are used successively to exploit the regioselectivity dictated by the inherent relative double reactivities. For certain substrates this makes the asymmetric dihydroxylation a tremendously powerful reaction.

Designer ligands to improve selectivity

It is also possible to select our regioselectivity by the synthesis of 'designer' ligands. Corey[32] has synthesised a ligand which provides superior selectivity for some substrates. One difference is that, rather than having the methyl ether of the quinoline ring we find in quinine, it has a 4-heptyl ether. The idea is that this further sterically encumbers the ligand.

One might imagine that regioselectivity in the case of either geranyl geranyl acetate **154** (with four double bonds) or squalene **155** (with six double bonds - notice the symmetry here) would be a tricky business.



It is. If squalene **155** is mono-dihydroxylated with OsO_4 using $(DHQD)_2PHAL$ as the ligand, the three double bonds I, II and III react in a ratio of 2.4:1.8:1.0. If no ligand is present *at all* they react in a ratio of 1:1:1 but with Corey's ligand, reaction of double bond I and the sum of the reactions of II and III give a product ratio of 8:1.

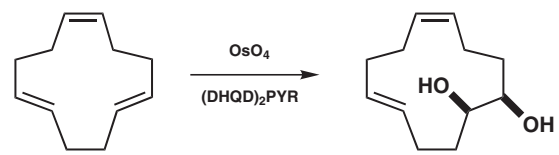
Dihydroxylating Compounds with More than One Double Bond II—Diastereoselectivity

There are two main issues here. Firstly, if one of two double bonds has reacted, does the remaining one become more or less reactive than it was in the first place? Secondly, how does the stereochemistry of the first dihydroxylated double bond influence the stereochemistry of subsequent reactions?

The factor that has the biggest influence - at least on the first of these questions - is the solvent system that is used. Up until now we have been looking at the regioselective *mono*dihydroxylation of substrates containing more than one double bond. The solvent system that we have used has been the biphasic *tert*-butanol and water system.

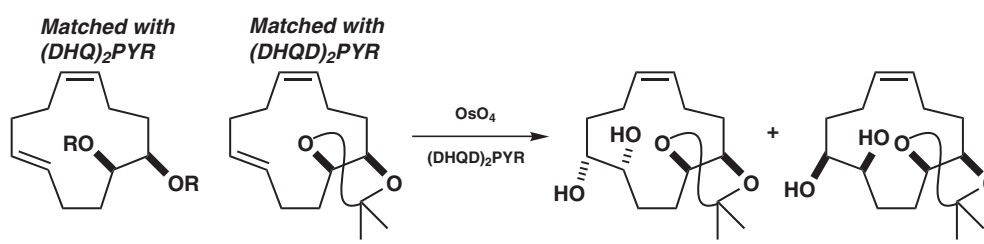
Advanced dihydroxylation strategy

Just have a look at cyclododecatriene **156**. It has twelve carbon atoms, two *trans* double bonds and one *cis* double bond. This compound, with its three double bonds, presents us with all sorts of opportunities.[33] The first thing to realise is that the *trans* double bonds will react with OsO_4 more quickly than the *cis* double bond. In fact, *both* the *trans* double bonds will react before the *cis* double bond. We can dihydroxylate **156** to give us the diol **157**. A better ee is obtained (94%) when this reaction is allowed to go to completion because the minor enantiomer is removed by kinetic resolution. The phenomenon of enantiomeric enhancement by kinetic resolution and the idea of match/mismatch in the context of a diol substrate with AD reagents are explored in Chapter 28.



156 **157; 84% yield, 94% ee**

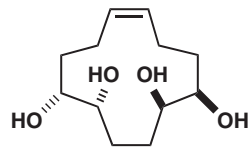
There is clearly an option for further dihydroxylation. The diol can be protected and how we protect it depends on the dihydroxylation we want to do next. It turns out that the disilyl ether **158** is matched with $(DHQ)_2PYR$ whereas dioxolane **159** is matched with $(DHQD)_2PYR$. Hence we may, by judicious protection, maximise subsequent stereoselectivity. Obviously, the disilyl ether of the enantiomer of **157** would be matched with $(DHQD)_2PYR$ and the enantiomer of dioxolane **159** with $(DHQ)_2PYR$.



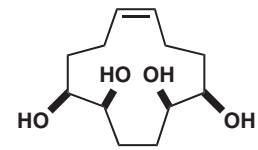
158; R = TBDMS **159** **160** **99:1** **161**

The major product from the dihydroxylation of **159** is the partially protected tetraol **160**. If this were deprotected it would form the C_2 symmetric tetraol **162**. Note that **162** results from two

successive treatments of dodecatriene **156** with OsO_4 in the presence of $(DHQD)_2PYR$. If we wanted to make tetraol **163** – which is achiral – we would be advised to use diether **158** and treat it with OsO_4 and $(DHQ)_2PYR$ before deprotection. This chemistry is explored in the Workbook.



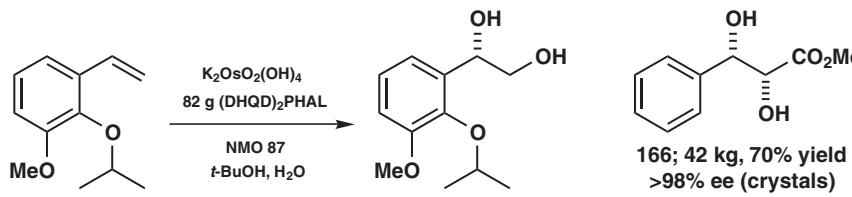
162



163

Scaling Up the Asymmetric Dihydroxylation

This important reaction has been applied on a large scale by the pharmaceutical industry. The amplification of chirality from small amounts of catalyst and the minute amounts of osmium make it very attractive but the expense of $K_3Fe(CN)_6$ and the difficulty of removing it from the reaction mixture on a large scale suggest using NMO instead. The by-product is then the simple amine *N*-methylmorpholine that can simply be extracted in the workup as can the ligand. The first of these examples was a 2.5 kg reaction[34] while the second gave 42 kg of crystalline diol **166** in >98% ee from methyl *trans* cinnamate.[35]

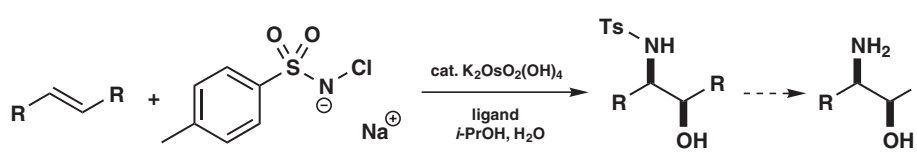


164 **165**

166; 42 kg, 70% yield
>98% ee (crystals)

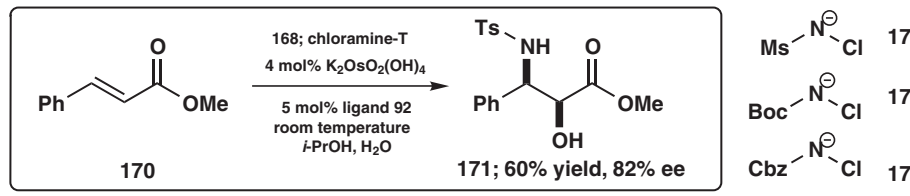
Part III – Aminohydroxylation

Not content with revolutionising the world of asymmetric synthesis with the catalytic asymmetric epoxidation reaction and the asymmetric dihydroxylation, Sharpless went on to develop the asymmetric aminohydroxylation[36] (AA). This is very similar to the dihydroxylation except one of the oxygen atoms is replaced with a nitrogen atom in the product **169**. This complicates matters because we may have the additional question of regioselection. You will now be familiar with all of the ingredients in the reaction – $K_2OsO_2(OH)_4$ is the source of OsO_4 although the reactive species in this reaction is not OsO_4 since one of those oxygen atoms has to go. The ligand is the familiar double cinchona ligand $(DHQD)_2$-PHAL **93** as is the mixture of alcohol and water (though isopropanol is used in this case) for the solvent. The one new component is the source of nitrogen. This is chloramine-T **167** (the sodium salt of *N*-chloro-*p*-toluenesulfonamide).[37] Here is a typical asymmetric aminohydroxylation reaction.

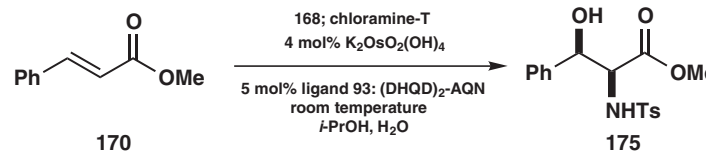


167; chloramine-T **168** **169**

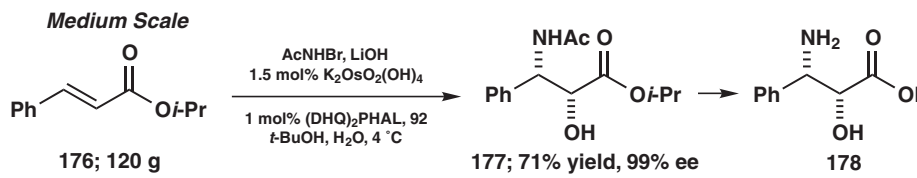
The reaction in the box below shows a typical AA with methyl cinnamate as the substrate. Methyl cinnamate **170** reacts in moderate yield and good, though not spectacular ee. Well never mind, this is a powerful transformation and not to be sneezed at. And from a practical point of view, it is often the case that the resulting amino alcohols can be recrystallised to very high ee. Note the regioselection in the reaction. With a cinnamate (or other α,β-unsaturated carbonyl compound) we have a nicely differentiated double bond which, in the absence of symmetry, is much better than two ends of a double bond that are only *slightly* different. We find the nitrogen atom bound to what was the more electrophilic end of the double bond **171**. This is a handy mnemonic for the selectivity with a standard ligand – the more nucleophilic nitrogen atom binds to the more electrophilic end of the double bond (though, of course, it is only a mnemonic and not any sort of explanation). Three alternative nitrogen sources are **172** – **174** (but there are plenty more). While chloramine-T **167** and *N*-chloromethylsulfonylamide **172** are added to the reaction as salts, the carbamate salts (BocNClNa **173** and CbzNClNa **174**) are prepared *in situ* from the carbamates.



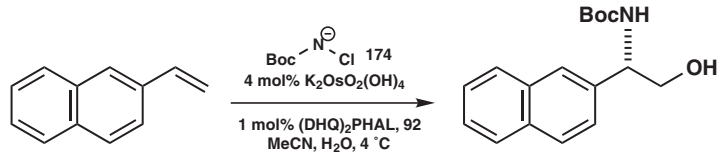
Incredibly, changing the ligand to $(DHQD)_2$-AQN **94** gives us the opposite regioselection (regioisomer **175**) and yet the ee is similar to that obtained with $(DHQD)_2$-PHAL and the same enantiotopic side of the double bond attacked.



The reaction also scales up nicely[38] – using *N*-bromoacetamide this time – and in a reaction that was 630 times larger than Sharpless' standard mmol scale reaction, 120g of isopropyl cinnamate was reacted to give acetamide **177**. The yield is good and the ee excellent. Hydrolysis of both the ester and the amide give (2*R*, 3*S*)-3-phenylisoserine **178** which is a precursor to one of the side chains of Taxol.® The β-amino alcohol function is found in many biologically active compounds and this catalytic reaction will be attractive to process research groups.



Many of the application of AA have used conjugated alkenes but simple, even mono-substituted alkenes such as **179** can be used providing there is some definite difference between the ends - here with this naphthalene compound **180** between no substituent and an aromatic ring. The synthesis of lactacystin using AA is described in chapter 31.

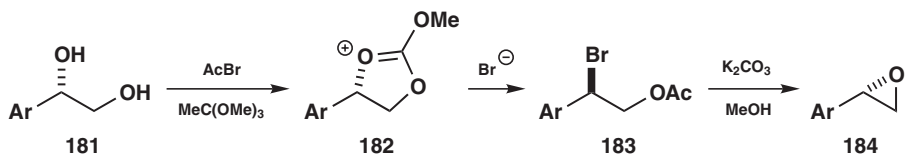


179 **180; 70% yield, 98% ee**

Aminohydroxylation is the least well developed of the methods in this chapter but in many ways the most promising. Research continues. We shall now return to epoxidation as this is an alternative route to unsymmetrically substituted derivatives.

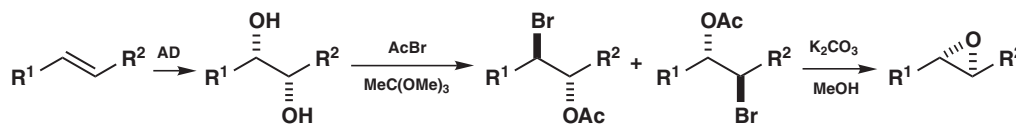
Part IV – Converting 1,2-Diols into Epoxides

We have already seen how cyclic sulfates such as **123** can be converted into amino alcohols that might have been made by amino hydroxylation. The conversion of 1,2-diols, made by the AD reaction, into epoxides has been very widely used. A combination of acetyl bromide and an orthoester gives a bromoacetate via an oxonium ion **182**. The ion is formed with retention, bromide opens it with inversion at the benzylic centre, and epoxidation in base inverts it again. The net result is retention.[39]



181 **182** **183** **184**

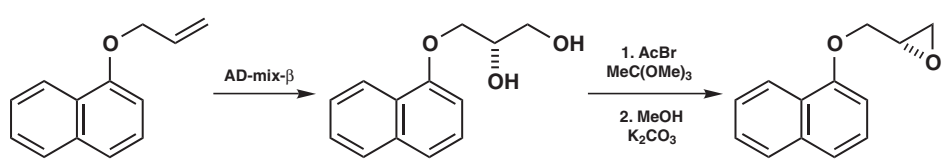
It seems at first that regioselectivity is going to be a problem with diols such as **79** but this is not the case. A mixture of bromoesters **185** and **186** is indeed formed but both give the same epoxide **187** in base as each centre undergoes either no change or a double inversion. The result is again retention at both atoms and we have made the epoxide **187** from the alkene **79** asymmetrically.[40]



79 ***ent*-80** **185** **186** **187**

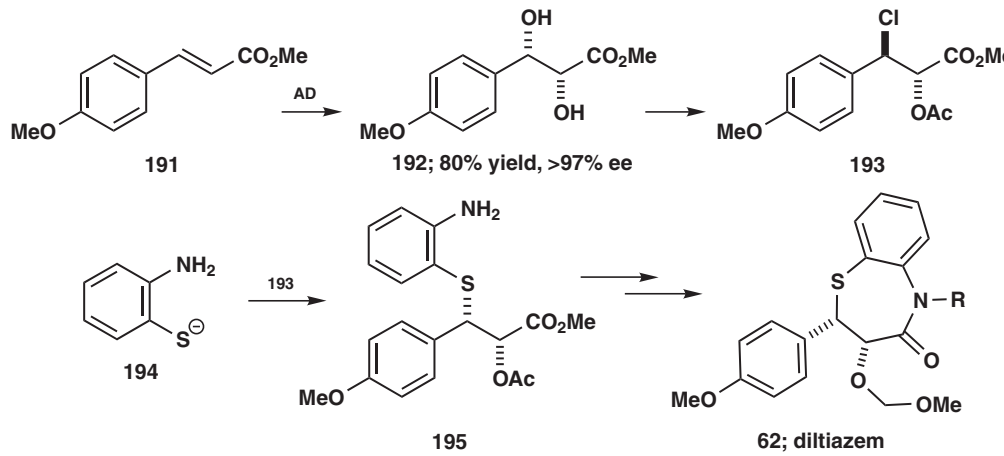
Applications of the AD to epoxide transformation: propranolol and diltiazem

We return to two compounds we made earlier by the AE reaction: propranolol **7** and diltiazem **67**. In both cases the synthesis is easier as we do not have to start with an allylic alcohol. The synthesis of propranolol[41] uses the allyl ether **188** that gives the diol **189** with good ee in the AD reaction for a monosubstituted alkene. Transformation to the epoxide **190** shows no loss of ee. Reaction with *i*-$PrNH_2$ was already known to give propranolol **7**. This is a very short synthesis from easily made starting materials.



188 **189; 90% yield, 91% ee** **190; 92% yield, 91% ee**

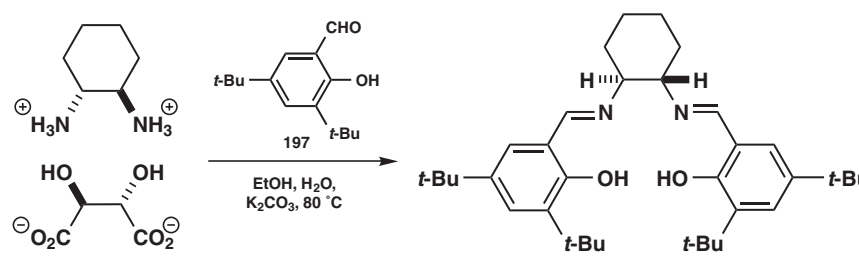
The synthesis of diltiazem[42] starts with the cinnamate that was actually used to make the allylic alcohol **62**, the substrate for the AE route described above. No special extra inversion is required here if the intermediate **193** is used as the electrophile rather than the epoxide derived from it. Again, this is shorter and simpler than the previous synthesis.



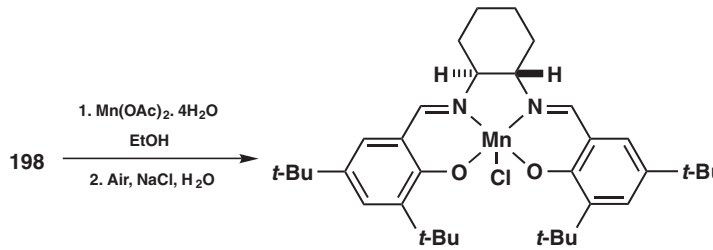
However, it would be better if we had an asymmetric epoxidation that, unlike AE, did not require any particular functionality. We do: it is the Jacobsen epoxidation, the third of the great triumvirate of catalytic reactions in this chapter.

Part V – Jacobsen Epoxidation

The catalyst in this type of epoxidation is a salen, that is a compound derived from a salicylaldehyde and a diamine.[43] One of the best is **198**, made from the substituted salicylaldehde **197** and the tartrate salt of the C_2 symmetric diamine **196** that results from a very simple resolution (chapter 22). There are others: they are all C_2 symmetric salens made from C_2 symmetric diamines and have large groups on the two benzene rings.

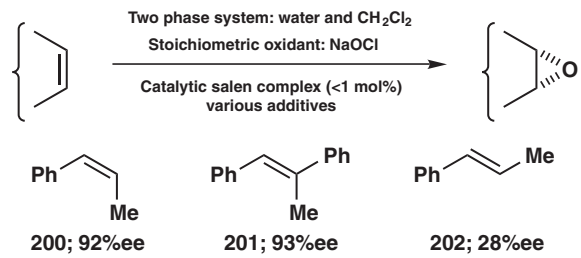


The active catalyst is a Mn(III) complex **199** of the salen used at 1 mol% or less. The stoichiometric oxidant is bleach (NaOCl) and again a two-phase system (CH_2Cl_2 and water) is best. Various additives such as pyridine-*N*-oxides improve performance.



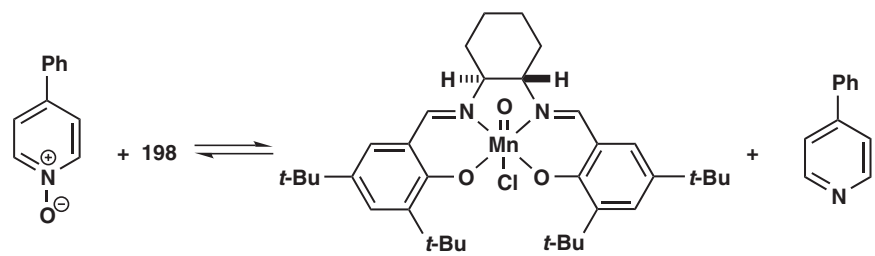
199; 95-99% yield

The Jacobsen method gives very good results with *cis*-alkenes, including cyclic alkenes, and trisubstituted alkenes. But is not so good with *trans* alkenes. Typical ees for these three classes of alkenes are shown for **200** to **202**.



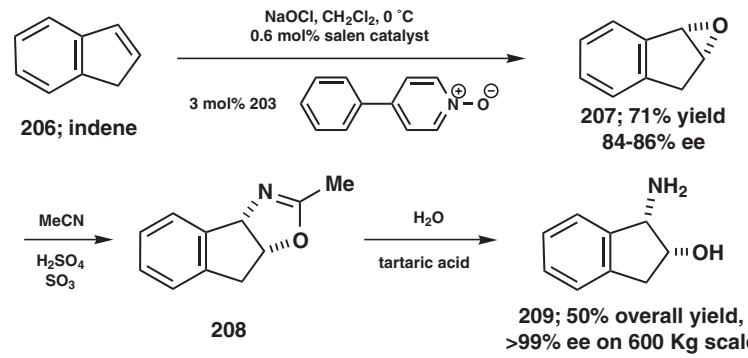
200; 92%ee **201; 93%ee** **202; 28%ee**

It is believed that the active complex is a Mn(V) oxo-species[44] **204** that is in equilibrium with the Mn(III) complex **199**. The oxidation of **199** to **204** can occur with NaOCl but is much quicker if a pyridine *N*-oxide such as **203** transmits oxygen atoms from NaOCl to **199**. The pyridine **205** is then re-oxidised to **203** with NaOCl. In the active complex **204** the oxygen atom is held above (or below - the ligand is C_2 symmetric) the diamine that is the source of the asymmetry.

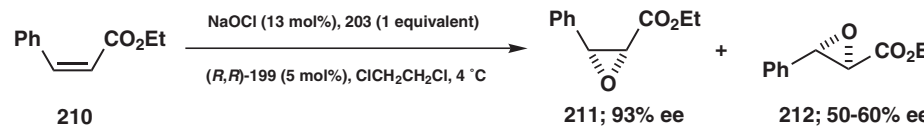


203 **204** **205**

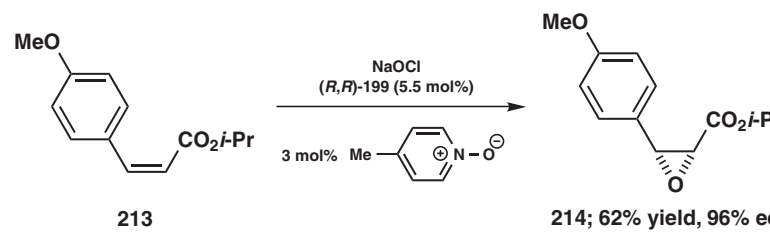
Perhaps the most famous Jacobsen epoxidation is that of indene **206** used in the synthesis of the amino-indanol[45] **209**. The anti-AIDS drug Crixivan incorporates **209** which is also a cheap chiral auxiliary in its own right.



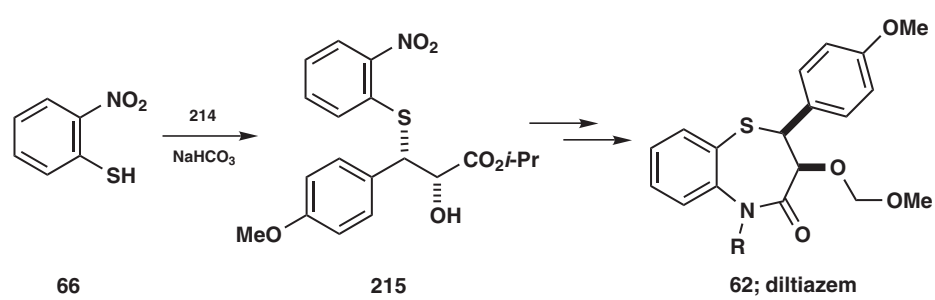
Another important application is the asymmetric epoxidation of *cis* cinnamate esters **210**. They are poor substrates for AD and the allylic alcohols derived from them by reduction are poor substrates for AE. Jacobsen epoxidation gives epoxides in good yield (>90%) but not all is the *cis*-epoxide **211**. There is some leakage to the *trans* epoxide **212** a typical ratio of **211**:**212** being 5:1. The *cis* epoxide is formed in excellent ee but the *trans* epoxide in only moderate ee.



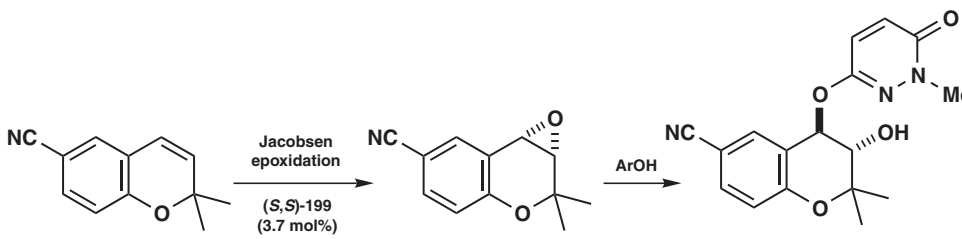
Electron-donating groups on the benzene ring improve the *cis*:*trans* ratio and *iso*-propyl esters improve the ee. This make for a simple synthesis of diltiazem **62**: a compound we have already made by AE and AD. Epoxidation of **213** gives a reasonable yield of nearly enantiomerically pure *cis*-epoxide **214** (only 10% of the *trans* epoxide is formed).



The epoxide is opened regioselectively with the anion of the nitrobenzene thiol **66** and the rest of the synthesis is essentially as described earlier (reduction, cyclisation, addition of substituents to O and N).



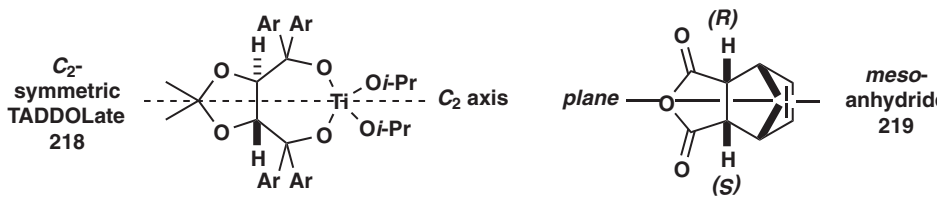
Other improvements include the development of more sterically hindered ligands[46] and changes in oxidant to *m*CPBA and NMO to give efficient asymmetric synthesis of monosubstituted epoxides.[47] The asymmetric epoxidation of dimethylchromenes such as **216**, a previously problematic task, is easy with Jacobsen epoxidation and these epoxides such as **217** have been used to make calcium channel antagonists **218**.



216 **217; 96% yield, 97% ee** **218; 85% yield, 97% ee**

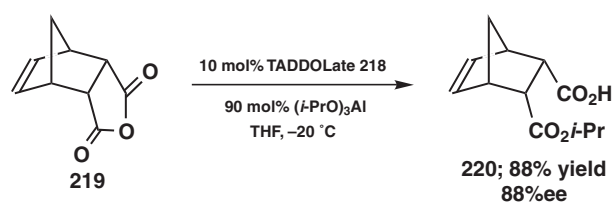
Part VI – Desymmetrisation Reactions

So far we have looked largely at substrates which are flat achiral objects that have chiral centres introduced by means of a reagent. Desymmetrisations are slightly different. Molecules which are desymmetrised tend to be of a *meso* type. That is, they are achiral because they have a mirror plane and the sides of the molecule contain left and right handed portions **219**. This is in contrast to the C_2 axis present in many catalysts such as the TADDOLate **218**. Desymmetrisations are powerful because there may be several chiral centres embedded in an *achiral* molecule which suddenly become much more useful in the newly formed chiral molecule. There are a large variety of symmetrical substrates that have been enantioselectively desymmetrised[48] and we look at a few of the more important classes.



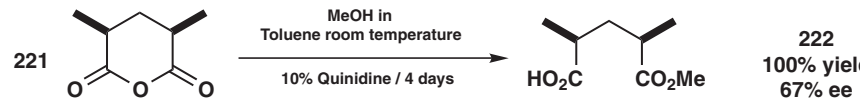
Opening anhydrides

For example, acid anhydride **219** is achiral and the molecule can be drawn above to highlight the mirror plane running through it. It has an *R* and an *S* chiral centre, one on either side of the mirror. The anhydride can be cleaved with $Al(O\textit{i}\text{-}Pr)_3$ in a reaction catalysed by a titanium TADDOLate **218**. The resulting ester[49] **220** is formed in 88% yield and 88% ee.

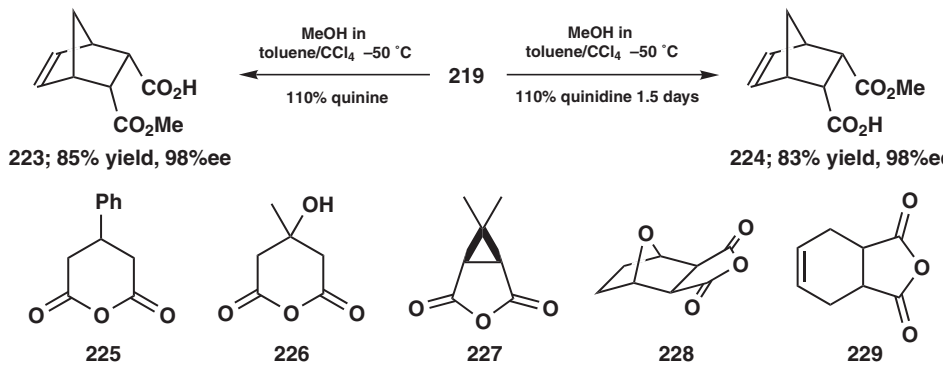


219 **220; 88% yield 88%ee**

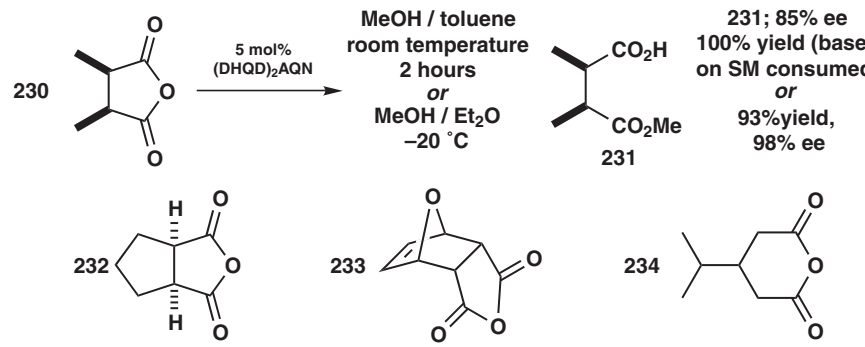
We have seen much of quinine and quinidine in this chapter alone. They are among those 'privileged structures' which seem to turn up time and again as being useful for asymmetric reactions. Oda[50] had found that 10% of guinidine would catalyse the opening of anhydride **221**. The trouble was that the ee of the ester **222** was modest (67%) and the reaction took 4 days.



Bolm[51] was able to improve matters by piling in the quinine (so that over an equivalent was used – 110%) which enabled the reaction of anhydride **223** to be done at a lower temperature (giving a better ee) in a mere 1.5 days. The pseudo-enantiomer quinidine could also be used to give ester **224**. A range of rings **225** to **229** works.

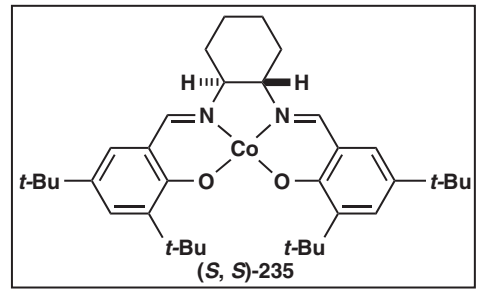


But matters were really significantly improved by Chen *et al*.[52] If one cinchona alkaloid works, what about the double cinchona alkaloid ligands that are used in the asymmetric dihydroxylation reactions? Amazingly, these ligands work really well for desymmetrisations of anhydrides such as **230.** Only 5% of catalyst is needed and they can be done at room temperature or −20 °C for better enantiomeric excess. Once again a range of anhydrides can be used **232**–**234**.

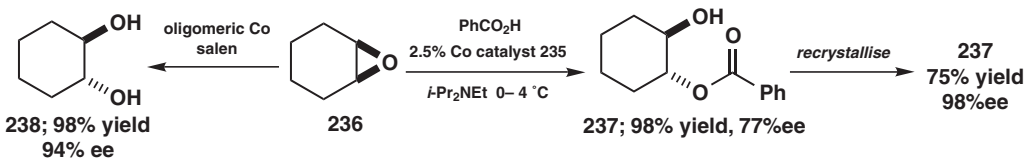


Opening epoxides

Another privileged structure is the salen complex we have already seen as the catalyst **199** for Jacobsen epoxidations. Here the equivalent cobalt complex **235** is used to catalyse the opening of an achiral epoxide.[53]



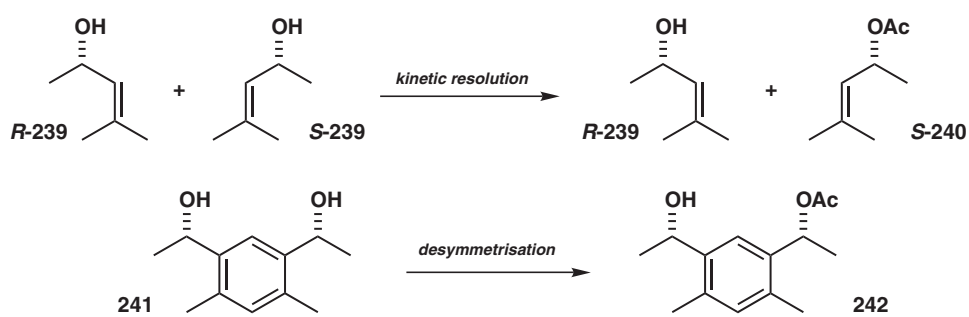
Cyclohexene oxide **236** is opened with benzoic acid catalysed by 2.5% of the cobalt salen complex **235** to give the asymmetric half ester **237**. Although the ee is only 75% this is improved by recrystallisation to 98% ee. Epoxides on other ring sizes can also be opened enantioselectively.



The (very useful) hydrolysis of cyclohexene oxide **236** to give the C_2 symmetrical diol **238** is difficult with the standard Co salen **235**. However, this reaction can be achieved in high yield and enantiomeric excess with a special oligomeric form of the salen.[54] The oligomeric form simply contains several salen complexes connected together in each molecule. This has enhanced reactivity for certain reactions. Reactions which proceed exceptionally well with a dimeric form of the catalyst are believed to make use of two active sites and thus benefit from the entropic advantage of having them both in the same species.[55]

Comparison of desymmetrisation and kinetic resolutions

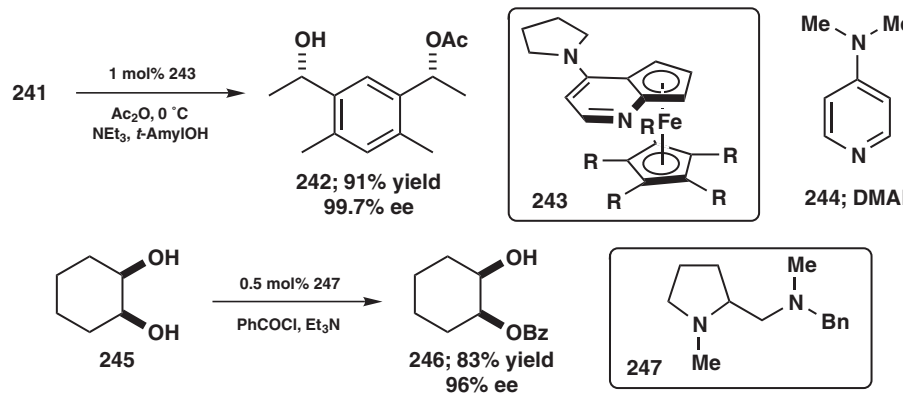
As we shall see further in Chapter 28, a kinetic resolution is the more rapid reaction of one enantiomer of starting material over the other. In the absence of anything fancy (like a dynamic kinetic resolution) they are limited to 50% yield of product (or starting material). But because a desymmetrisation starts with one achiral molecule (instead of a pair of enantiomers) this limitation is removed as are other complications we face in kinetic resolutions such as the build up of the wrong enantiomer which makes selectivity more difficult. However, it is worth noting that desymmetrisation and kinetic resolutions are brothers in the stereochemical world.



Consider, for example, a hypothetical kinetic resolution of enantiomers (*R*) and (*S*)-**239** by esterification of one of them. Compare this to the esterification and desymmetrisation of diol **241**. In many ways, a desymmetrisation is a kinetic resolution but with the two enantiomers joined together in the same molecule. The features that make a reagent work well in a desymmetrisation, may well make it work in a kinetic resolution. Indeed, in **Double Methods** in Chapter 28 we see that this is the case.

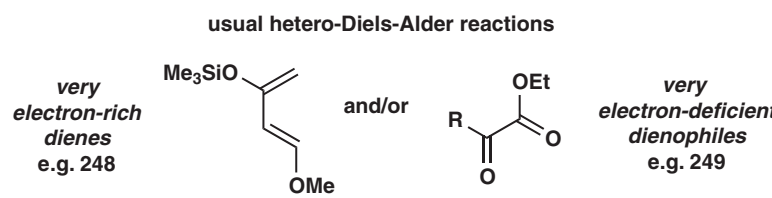
Mono esterification of diols

Diol **241** is very enantioselectively acylated with 1% of Fu's chiral[56] version **243** of DMAP **244**. The enantiomeric excess is a staggering 99.7% ee. Other, rather less fancy, chiral nucleophilic catalysts[57] have been used very effectively including pyrrolidine derivative **247** for the asymmetric benzoylation of **245**.



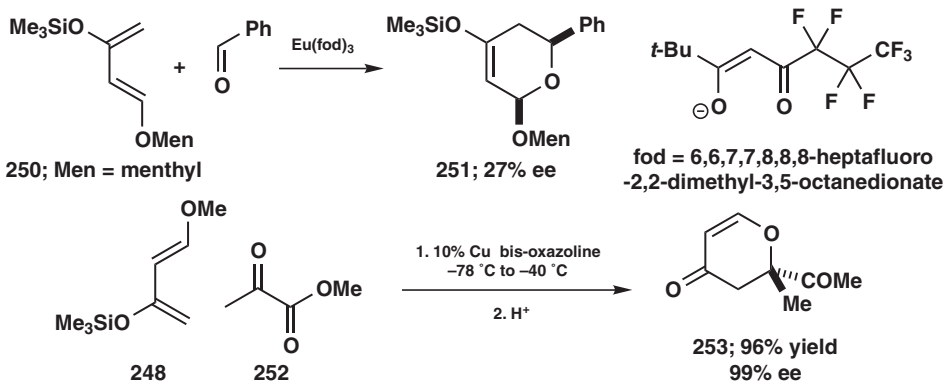
Part VII – Hetero Diels-Alder Reactions

Hetero-Diels-Alder reactions are not as straightforward as ordinary Diels-Alder reactions. In an ordinary (normal electron demand) Diels-Alder reaction we are accustomed to having an electron-rich diene and an electron-deficient dienophile. In asymmetric catalysis, early successes with a hetero-Diels-Alder reaction[58] typically needed a *very* electron rich diene, such as Danishefsky's diene **248**, or *very* electron deficient dienophiles like a glyoxylate **249**.

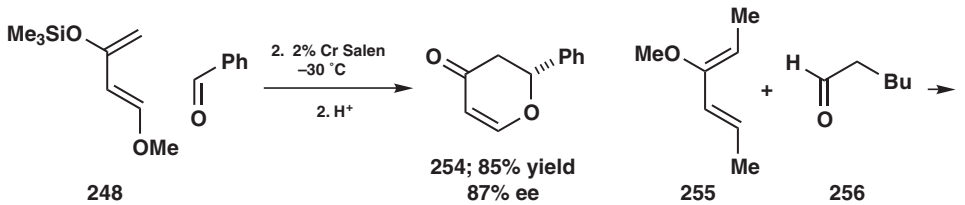


In the example below with a modified Danishefsky's diene[59] **250**, the asymmetry comes from a menthyl auxiliary while the reaction is catalysed by a europium complex. The ee (determined on a subsequent fragment) is a modest 27% but can be dramatically improved by using an

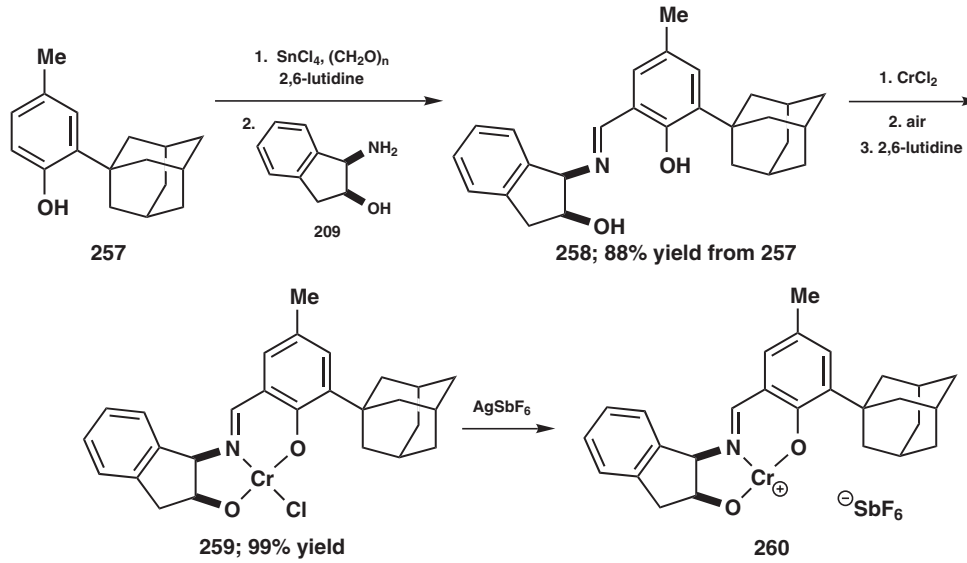
optically pure catalyst, $Eu(hfc)_3$, in the reaction together with the auxiliary. Excellent yield and enantiomeric excess have been achieved using a copper catalyst featuring a bisoxazoline ligand[60] but again we see a very electron-rich diene **248** coupled with a very electron-deficient dienophile **252**.



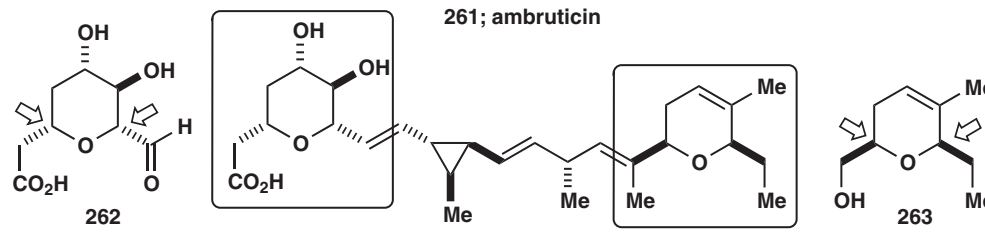
A further complication is whether the HDA reactions *really* proceed by a pericyclic mechanism or whether they are *stepwise* reactions (aldol then cyclisation). Both are conceivable and possible.[61] The salen complexes like those of Co **235** or Mn **199**, but this time with chromium at their heart, catalyse the reaction of Danishefsky's diene and benzaldehyde.[62] The yield and ee are excellent and the reaction works with a variety of aldehyde dieneophiles and, although the ee's are not always spectacular, the products can sometimes be recrystallised to high ee. The question of [4+2] versus aldol-then-cyclisation is also addressed. The intermediate compound that would be expected from the aldol reaction was found *not* to cyclise under the reaction conditions which indicates that the [4+2] mechanism is active.



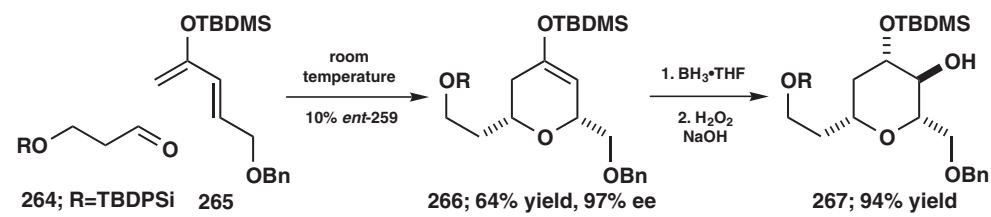
This is all very well but what about using dienes which are more typically electron rich (with one oxygen substituent instead of two) **255** in combination with normal aliphatic aldehydes **256**? A catalyst that could achieve this would be very useful. One solution is a modification of the chromium salen complex which replaces half the salen with an adamantyl group and the other half with *cis*-aminoindanol **209**. The synthesis of this complex **258** is straightforward since commercially available compounds **257** and **209** are combined in high-yielding reactions and the complex itself is impressively enantioselective.[58] The hexafluoroantimonate catalyst **260** was more enantioselective than the corresponding chloride **259**.



The application of this catalyst is nicely illustrated in a synthesis of ambruticin.[63] Ambruticin **261** is an antifungal compound. The tetrahydropyran on the left hand side of the molecule and the dihydropyran on the right both contain two stereogenic centres which could be controlled in a hetero Diels-Alder reaction via **262** and **263**.

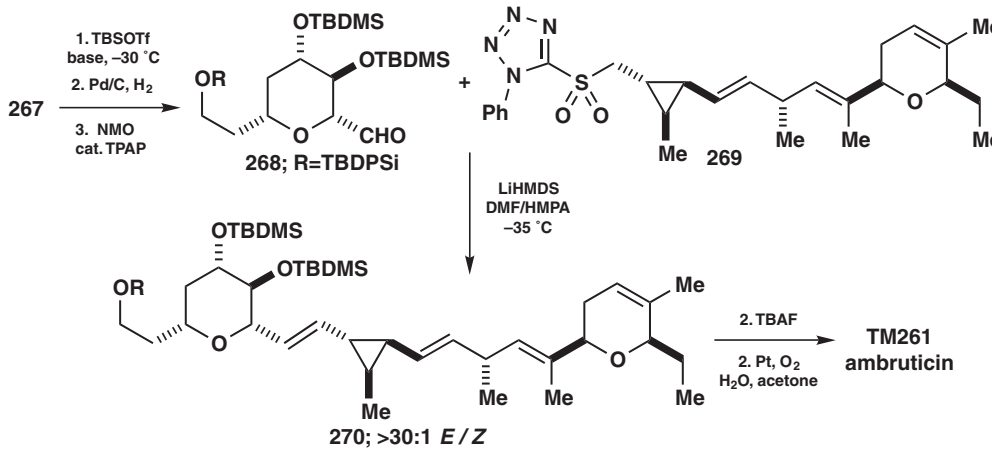


The first HDA reaction is between aldehyde **264** and diene **265** at room temperature. The diene is reasonably electron rich and the aldehyde an ordinary aliphatic. Note that there are no stereocentres that arise merely from stereospecific reactions of the substrates. The pyran is formed in 97% ee and the subsequent hydroboration is regio- and diastereoselective to give alcohol **267** as a single diastereomer. The other pyran ring (for the right hand side of ambruticin)



is made in a very similar manner but using the other enantiomer of catalyst **259**. This time the yield was 87% and the ee >99%!

Several other interesting reactions are employed in the synthesis including an asymmetric cyclopropanation and an asymmetric hydroformylation but we'll end by highlighting the Kociénski-Julia olefination. Rather than employing the ordinary sulfone of the Julia reaction[64] or the one-pot (Sylvestre) Julia method[65] which employs benzothiazolyl sulfones, the Kociénski variant[66] uses a tetrazole substituted sulfone **269** (chapter 15). The key advantage over the benzothiazolyl sulfone being that the aldehyde and sulfone do *not* need to be premixed before the addition of base. The *E*/*Z* selectivity by using LiHMDS in DMF/HMPA is very good at >30:1 but with NaHMDS in THF the *E*/*Z* selectivity is reversed to 1:8. A lithiated tetrazolesulfone sporting a *tert*-butyl



(as opposed to the phenyl group seen here) is even more stable.[67] Returning to the synthesis of ambruticin – deprotection and oxidation of **270** gave the final product **261**.

Catalytic reactions look like the best bet for the future of asymmetric synthesis. In the next chapter you will see how C– H and C–C bonds can also be made by catalytic asymmetric reactions. The only limitation at the moment is the relatively small number of reactions that have been developed. Some of those you have met in this chapter – Sharpless AE and AD and Jacobsen epoxidation – are among the best.

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26 Asymmetric Induction III Asymmetric Catalysis: Formation of C–H and C–C Bonds

Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

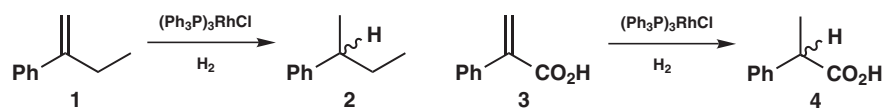
Introduction: Formation of C–H and C–C Bonds

The last chapter was mostly about the asymmetric introduction of functionality using catalytic reagents. The first part of this chapter concerns the modification of the carbon skeleton, or of existing functional groups, by asymmetric catalytic reduction, usually by hydrogenation with Rh or Ru catalysts. The second part is more varied: metals are again used for some reactions but there are also examples of an exciting modern approach: organic catalysis. New C–C bonds are formed by a variety of reactions ranging from cyclopropanation through Robinson annelation to alkene metathesis. All are asymmetric. A valuable general reference for this chapter and the last is Ojima's book[1] *Catalytic Asymmetric Synthesis.* It contains a useful list of ligands and their acronyms on pages 801-856 just before the index.

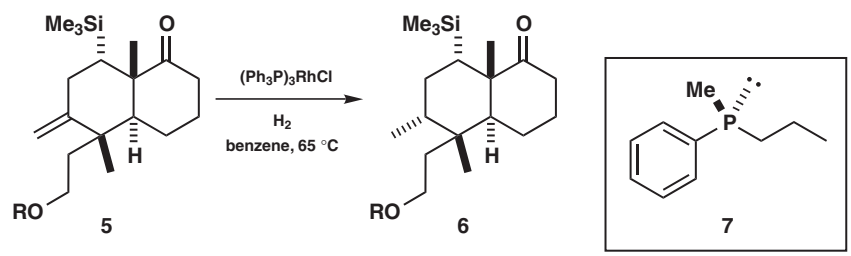
Part I – Asymmetric Formation of C–H Bonds

Introduction: Catalytic hydrogenation with soluble catalysts

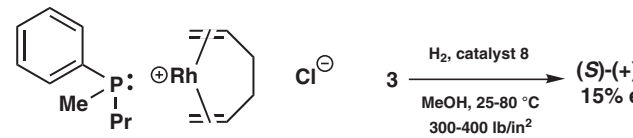
Catalytic hydrogenation using hydrogen gas and insoluble palladium catalysts such as Pd/C will be well known to you already. This story starts with the invention of Wilkinson's catalyst, the Rh(I) phosphine complex $(Ph_3P)_3RhCl$ that can be used for catalytic hydrogenation in organic solvents such as benzene. It catalyses the reduction of simple alkenes such as **1** or conjugated alkenes such as **3** to give (racemic) products **2** and **4** having new chiral centres.[2]



Hydrogenation using Wilkinson's catalyst is still used for diastereoselective reduction as in the transformation of the functionalised enone **5** into the ketone **6** with high diastereoselectivity.[3] Other (homogeneous or heterogeneous) catalysts were less effective.



Horner[4] at Mainz in Germany and Knowles[5] at the Monsanto works in the USA realised at more or less the same time (1968) that if Ph_3P were replaced by an enantiomerically pure phosphine such as **7**, asymmetric induction might accompany the reduction. Unsymmetrical phosphines are enantiomerically stable, unlike the corresponding amines, as pyramidal inversion is much slower with P than with N. The phosphine was not available in high enantiomeric purity but Horner made compound **2** in 8% ee while Knowles made compound **4** in 15% ee. Such results would be scorned today but they were the first.

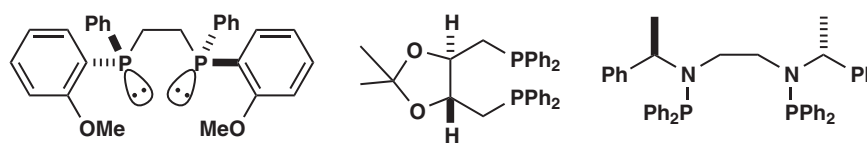


Catalyst 8: 69% 'optical purity'

Hydrogenation with C_2-Symmetrical *bis*-Phosphine Rhodium Complexes

C_2 symmetric ligands (DIPAMP, DIOP, PNNP)

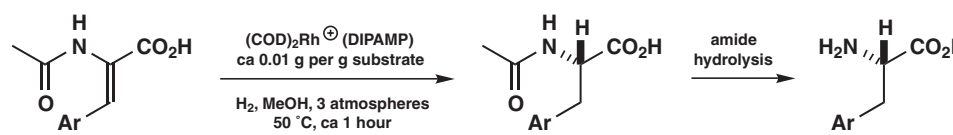
The real breakthrough came when Kagan[6] realised that only one of the three phosphines in Wilkinson's catalyst was displaced by the alkene substrate - alkenes, like phosphines, are two electron donor ligands. If the remaining two phosphines were linked together to form a more rigid chiral ligand, results should be much better. There is now a large selection of such catalysts, usually having C_2 symmetry, some chiral at both phosphorus atoms such as DIPAMP **9**, some chiral in the backbone such as DIOP **10**, derived from tartrate and Kagan's first successful catalyst, or PNNP **11**, derived from α-methylbenzylamine and chiral in the side chain.[7]



9; (*S,S*)-(+)-DIPAMP **10; DIOP** **11; PNNP**

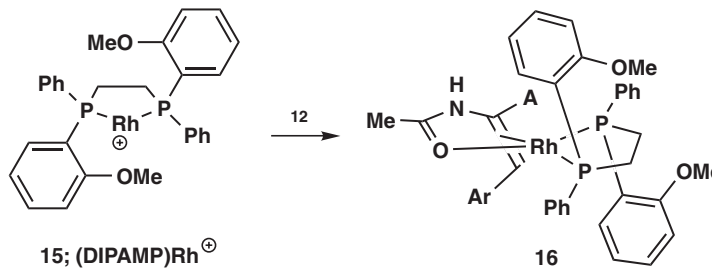
Reduction of 2-acylamino acrylates to give aminoacids

One of the most famous examples is a general synthesis of aromatic amino acids **14**, both natural like phenylalanine **14**; Ar = Ph, and unnatural. The easily prepared *N*-acyl enamines **12** are hydrogenated in methanol catalysed by the rhodium-DIPAMP complex, to give the saturated amides **13** in almost perfect ee. Hydrolysis releases the amino acid **14**. This process was discovered by Knowles at Monsanto.



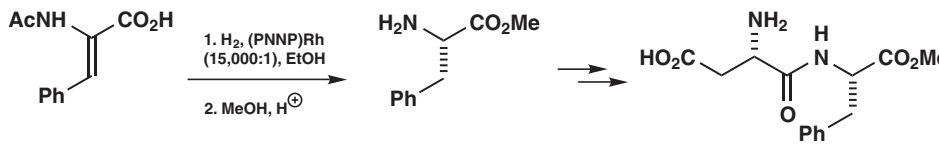
12 **13; 96-100% ee** **14; 96-100% ee**

Though it is often difficult to say exactly how asymmetric induction occurs, the complex probably adopts a C_2 symmetric conformation **15** allowing the enamine to bind to the rhodium both at the alkene and at the amide group **16**. Transfer of hydrogen from Rh to the bound alkene gives **13**. The enantiotopic alkene faces in **12** become diastereotopic by complexation with the chiral catalyst.



15; (DIPAMP)Rh⊕ **16**

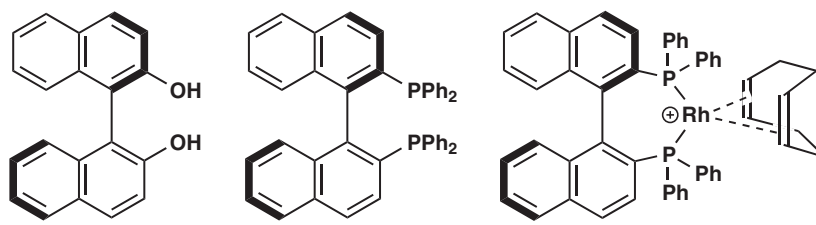
Phenylalanine is manufactured for incorporation into the sweetener Aspartame™ (nutrasweet) **18** by a process using PNNP **11**. This has the advantage that even lower catalyst loadings are possible and a high pressure is not needed.



12; Ar = Ph **17; Ph-OMe; 83% ee crystallise to 97% ee** **18; aspartame**

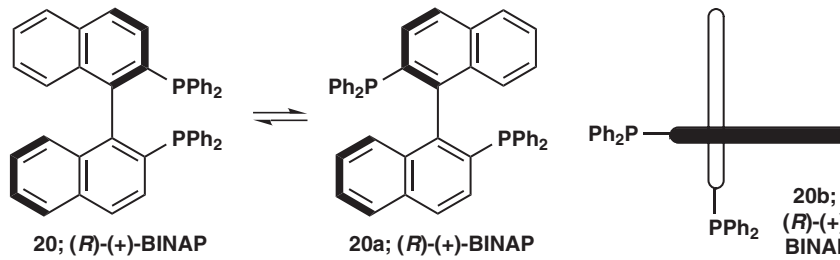
Hydrogenation with C_2-Symmetrical BINAP Rh and Ru Complexes

The first place in catalytic hydrogenation nowadays is taken by Rh or Ru complexes of BINAP. This ligand has axial chirality as the naphthalene rings cannot rotate past each other. These compounds were developed by Noyori, who with Knowles and Sharpless received the 2001 Nobel prize for their contributions to asymmetric synthesis. BINAP **20** is usually made from BINOL **19** and either **19** or **20** can be resolved. Rhodium complexes similar to those we have met include a molecule of cyclooctadiene and, as these are Rh(I) compounds, a counterion, often triflate **21**. Both enantiomers of BINAP are available commercially.[8]



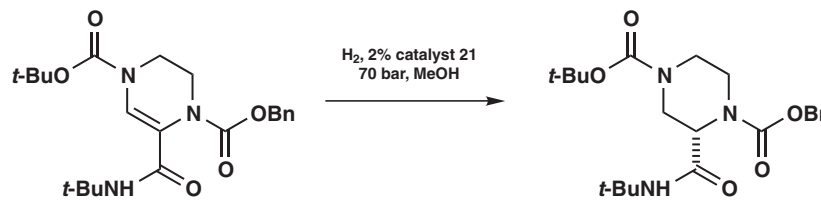
19; (*R*)-(+)-BINOL **20; (*R*)-(+)-BINAP** **21; [(*R*)-(+)-BINAP(COD)Rh]OTf**

Though BINAP is almost always represented as **20**, it is important to realise that **20a** is an equally good representation. The two naphthalene rings are not co-planar and can rotate by less than 90° around the bond joining them. The true structure is more like **20b** (seen looking along the bond joining the two naphthalenes).



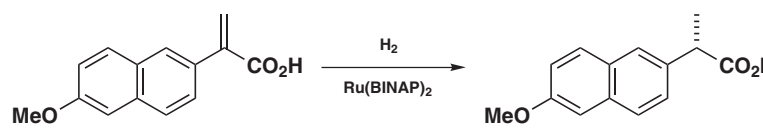
20; (*R*)-(+)-BINAP **20a; (*R*)-(+)-BINAP**

Rhodium complexes of BINAP can be used in much the same way as those we have just seen. In the synthesis of the Merck HIV protease inhibitor crixivan an enantiomerically pure piperazine **23** essential for activity was prepared by reduction of an *N*-acyl enamine **22** with 2% of catalyst **21**. Though the catalyst loading is relatively high, the essentially perfect yield and enantiomeric purity of the product make this worthwhile.[9]



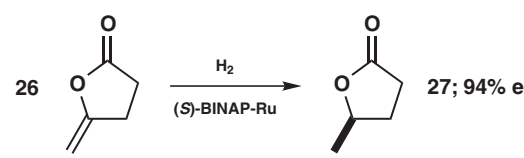
22 **23; 96% yield; 99% ee**

The achievements of the Noyori group using ruthenium BINAP catalysts are extensive and remarkable. Simple alkenes are reduced whether conjugated or not: the very efficient synthesis of the analgesic and anti-inflammatory naproxen **25** from an unsaturated acid **24** resembling **1** is a good example.



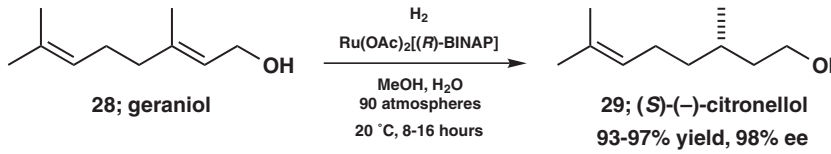
24 **25; Naproxen: 97% ee**

The presence of functionality does not disturb these excellent results. The cyclic enol ester **26** is cleanly reduced without reduction of the lactone.



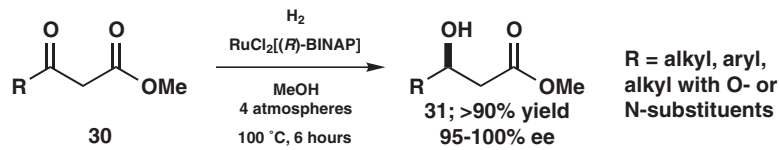
27; 94% ee

Reduction of geraniol **28** shows remarkable chemoselectivity: only the allylic alcohol is reduced to give citronellol **29** of higher enantiomeric excess than that found naturally. The catalyst is used at 7 mol%: that means 3 mg/g of geraniol. The catalyst must have acetate as the counterion or it is not so chemoselective.[10] You will see an alternative synthesis of the other enantiomer of citronellal shortly.

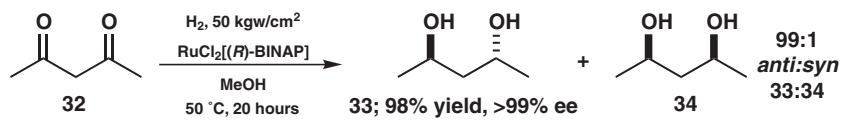


Asymmetric Hydrogenation of Carbonyl Groups

It is more difficult to hydrogenate carbonyl groups than alkenes as the C=O group is considerably more stable thermodynamically than the C=C bond. Asymmetric hydrogenation of ketones with Ru-BINAP catalysts is possible, though increased pressure and higher temperatures are usually needed. Hydrogenation of β-ketoesters **30** is a general reaction giving good yields and excellent chemo- and enantio-selectivity.[11]

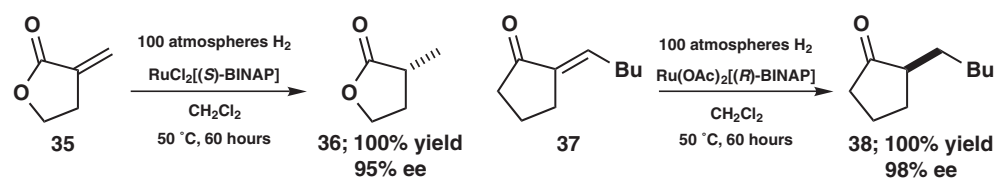


Both carbonyl groups of β-diketones **32** are reduced and the two reductions are independently enantioselective in the same sense so that the chiral (C_2 symmetric) product **33** predominates by 99:1 over the *meso* compound **34**. This makes symmetrical 1,3-diols such as **33** readily available.[12] Elsewhere you will meet methods that use one centre to induce another in a 1,3-relationship, maybe by diastereoselective reduction - this is a quite different strategy.

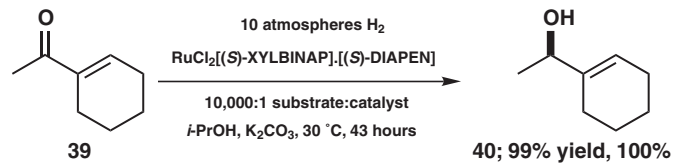


Regioselective asymmetric hydrogenation of enones

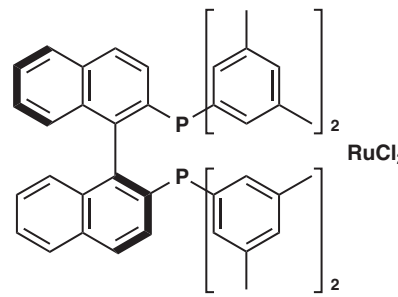
The situation is different when both C=C and C=O groups are present in the same molecule. We have seen the rather special case of the enol ester **26** and the usual result with conjugated enones is also that reduction of the alkene is preferred. High pressures are needed but good enantiomeric excess can be achieved with unsaturated lactones **35** and ketones **37**. The lactone needs the $RuCl_2$ catalyst but the ketone gives better results with the corresponding acetate.[13] Notice that use of each enantiomer of BINAP gives a different enantiomer of the product **36** or **38**.



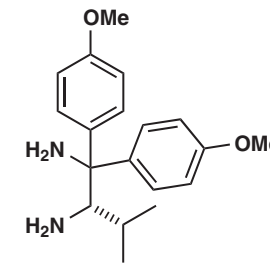
When asymmetric reduction of the ketone of an enone such as **39** is wanted, the catalyst must be further modified[14] by using the very crowded BINAP derivative XYLBINAP **41** and the diamine additive DAIPEN **42**. The results are then excellent but this example makes the point that it is essential to follow closely related examples when attempting the asymmetric reduction of any but the simplest alkene.



39 **40; 99% yield, 100% ee**



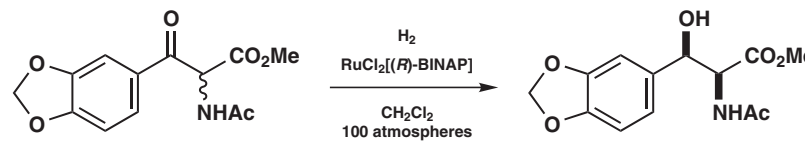
41; (*S*)-XYLBINAP



42; (*S*)-DAIPEN

Asymmetric reduction of ketones with kinetic resolution

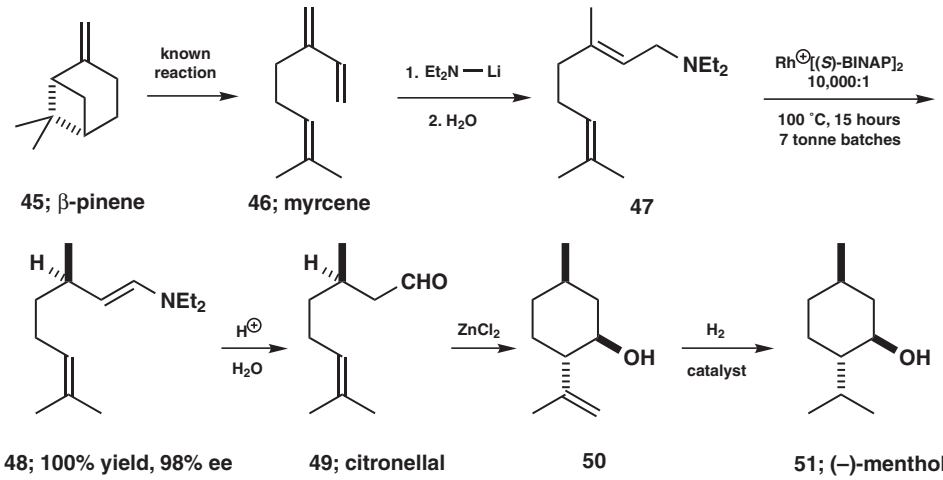
Since β-keto-esters enolise rapidly and extensively, dynamic kinetic resolution is possible in which one enantiomer is reduced more rapidly than the other.[11] By this means two chiral centres may be developed simultaneously especially when there is an *N*-acetyl substituent on the middle atom as in **43**. The synthesis of unusual functionalised amino acids related to threonine becomes straightforward. A fuller discussion of dynamic kinetic resolution appears in chapter 28.



43 **44; 99:1 syn:anti, 94% ee**

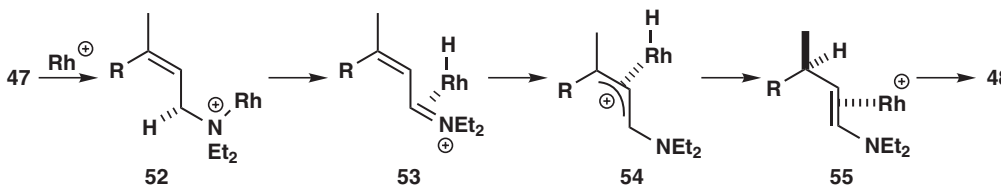
A Commercial Synthesis of Menthol

One of Noyori's most remarkable achievements is a commercial synthesis of (−)-menthol **51** used since 1983 by the Takasago International Corporation on a scale of thousands of tonnes a year. This and related processes are discussed in detail by S. Akutagawa and K. Tani in chapter 3 of Ojima's *Catalytic Asymmetric Synthesis*. The process is summarised here:

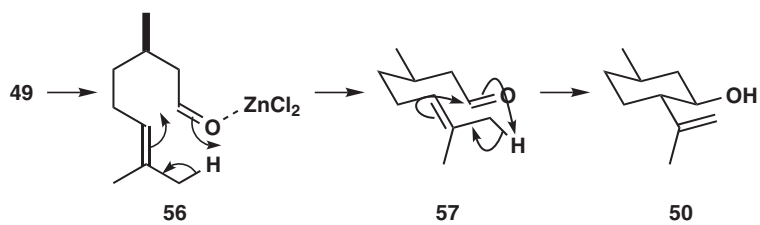


Noyori's synthesis of menthol by Rh^+-catalysed [1,3]H shifts

Various natural terpenes, including β-pinene **45**, can be used to make myrcene **46**. Addition of lithium diethylamide to the diene portion of **46** gives the achiral allylic amine **47**. Now comes the asymmetric catalytic process: a [1,3]H shift rather than a hydrogenation giving the enamine **48** easily hydrolysed to citronellal of higher enantiomeric purity than can be found naturally. The [1,3]H shift probably involves complexation of Rh to the nitrogen atom **52**, removal of hydrogen to create an imine complex **53**, transformation to an allyl cation Rh complex **54**, rather like the Pd complexes we met in chapter 19, and replacement of the original H atom to give the enamine **55**, more stable because of conjugation than the original allylic amine **47**. The decisive moment is the selection of one of the enantiotopic H atoms (marked in **52**) so that the Rh atom occupies the lower face of **53**–**55** and returns the H atom to that same face.

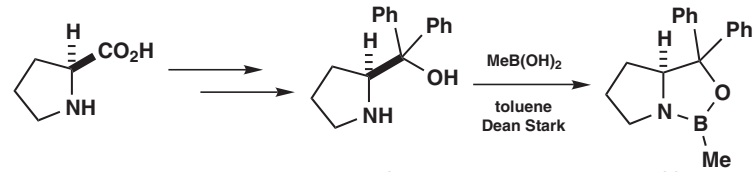


The rest of the synthesis involves a Zn(II)-catalysed oxo-ene reaction **56** going through a chair transition state **57** to put all the substituents equatorial in the product **50** and thus create the relatively remote two remaining chiral centres. A classical hydrogenation gives the iso-propyl group. Menthol itself is in great demand but Takasago also find a market for the other terpene intermediates such as citronellal.



Corey's CBS Reduction of Ketones

Among the very few worthwhile methods for catalytic reduction that do not depend on hydrogenation is Corey's CBS[15] reagent **60**, derived from proline **58** by protection and addition of phenyl Grignard, giving the bulky amino-alcohol **59**. This is converted into the stable crystalline boron compound **60**.

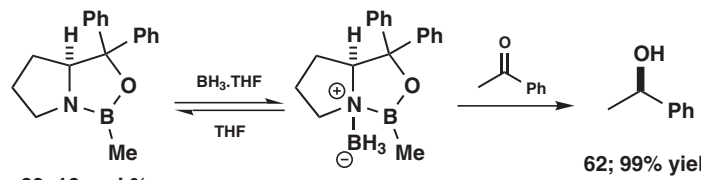


58
(*S*)-L-(–)-proline

59

60

Even this method is only semi-catalytic as usually about 10-15% of the reagent **60** is used with stoichiometric borane, to give **61** which reduces simple ketones with high enantioselectivity to give **62**. The advantage of this method is that reduction of carbonyl groups is the favoured reaction and takes place under mild conditions - not the situation with hydrogenation.

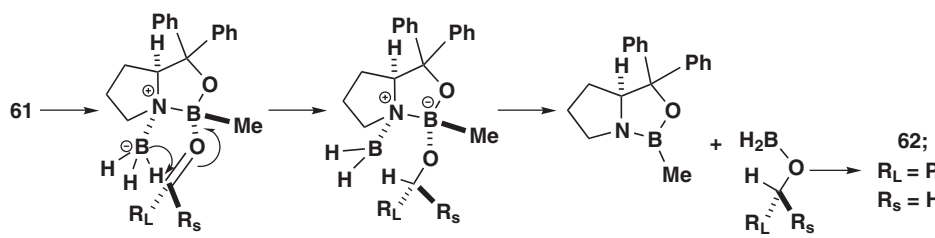


60; 10 mol %

61

62; 99% yield
96.5% ee

This **61** is a genuine chiral borohydride, but presumably relies on complexation of the ketone oxygen by the other boron atom **63**. In general, high enantioselectivity on acyclic substrates requires a rigid complex such as **63** to stop the substrate rotating. It is obviously no use ensuring delivery of H from, say, the top face of the molecule if the molecule is rotating and the "top" face is continually changing. Intramolecular transfer of hydride gives the boron ester **65** of the product **62** and returns the catalyst **60** ready for reaction with another molecule of borane.



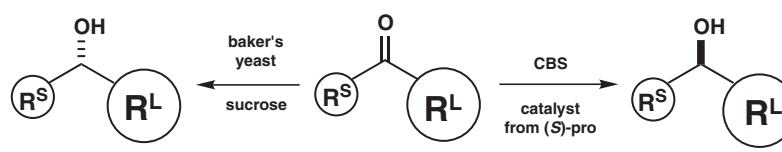
63

64

60

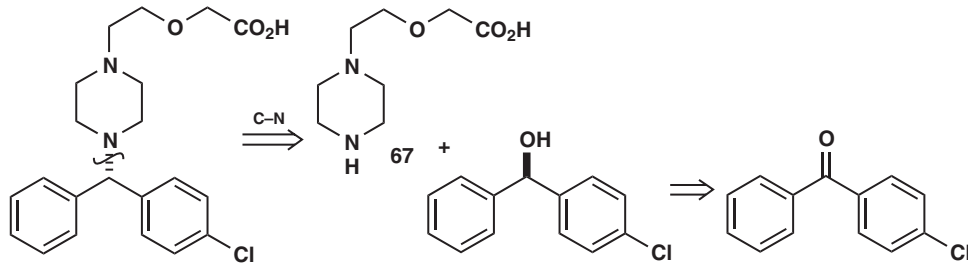
65

The general rule is expressed in **65** using R_L and R_s to show the large and small substituents on the ketone. Proline is naturally and cheaply available only as one enantiomer so it is interesting to note that this most general of asymmetric ketone reductions generally gives the opposite enantiomer to the most general of enzymatic reductions, that with baker's yeast. (see chapter 29)

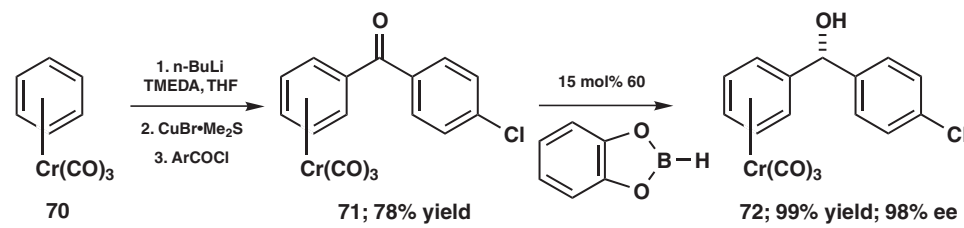


A synthesis of the H_1 blocker cetirizine

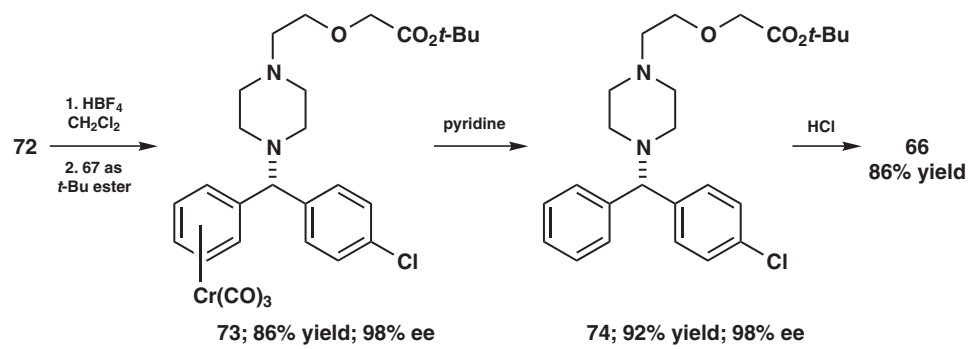
The synthesis of the H_1 blocker cetirizine **66** is an interesting application of this reagent. Cetirizine can obviously be made by substitution on some derivative of one enantiomer of the alcohol **68** by the piperazine **67**. Asymmetric reduction of the ketone **69** might provide **68** but the difference in size between the two substituents is altogether insufficient for asymmetric induction.



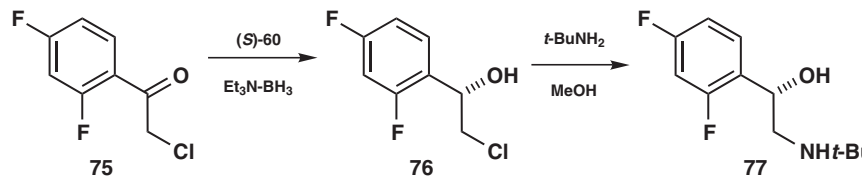
Corey's solution[15] was to make one of the aromatic rings much larger than the other by complexation with $Cr(CO)_3$ **70**. This is a very large substituent as the three CO molecules stretch out linearly from the Cr atom. To get full value from this substituent, he used it to direct lithiation and acylation to give the ketone **71** with one ring definitely much larger than the other and reduction with the CBS reagent **60** using catechol borane as the stoichiometric reducing agent gave the alcohol **72** in excellent yield and ee.



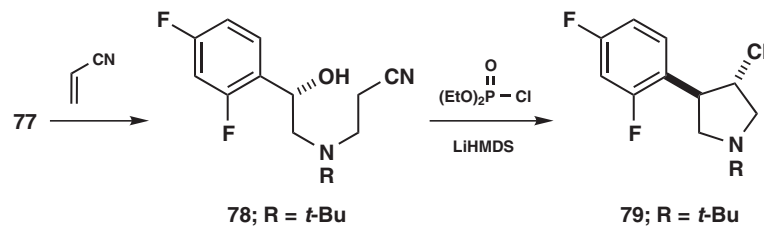
You may have noticed that this appears to be the wrong enantiomer for cetirizine. Not so as the $Cr(CO)_3$ has a final job to do. It stabilises cations and this substitution is likely to occur by the S_N1 mechanism as the doubly benzylic cation is so stable. Treatment of **72** with HBF_4, a strong acid with a non-nucleophilic counterion, creates the cation. The $Cr(CO)_3$ sits on one side of this planar system and preserves its chirality. The nucleophile attacks on the face not occupied by $Cr(CO)_3$ and the substitution occurs with retention.



Nowadays much less catalyst is needed. This is particularly important in large scale syntheses as of the intermediate needed by Merck[16] for the drug intermediate **79**. The starting material is ketone **75** easily made by a Friedel-Crafts reaction. Reduction using only 0.5% CBS catalyst **60** gave alcohol **76** of 98.9% ee. Even with only 0.1% **60**, the ee of the product **76** was still 94.2%.



The synthesis continued with displacement of Cl by an amine, actually via an epoxide, to give **77**, conjugate addition of acrylonitrile **78** and ring closure with inversion and high stereoselectivity at the nitrile centre.



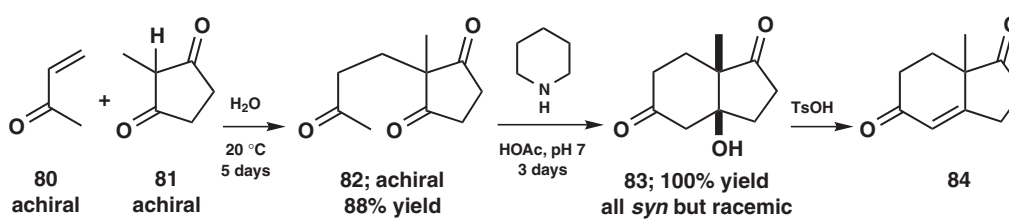
Part II – Asymmetric Formation of C–C Bonds

Metal complexes remain with us in the formation of C–C bonds, indeed a wider variety of metals as Al, Co, Cu, Mo, Ru, Ti and Zn all have parts to play in a wide variety of reactions. But we must also introduce a new type of catalyst – the simple organic compound – and we must start with organic catalysis as it is involved in some of the same reactions as the metal complexes.

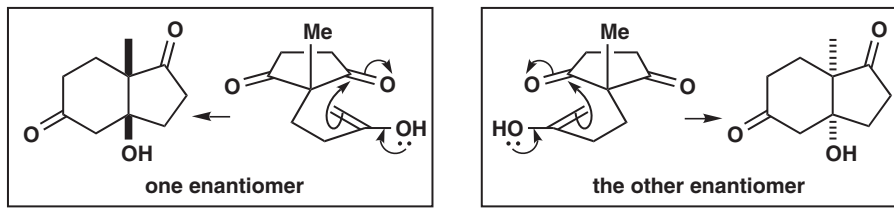
Organic Catalysis

The Robinson annelation

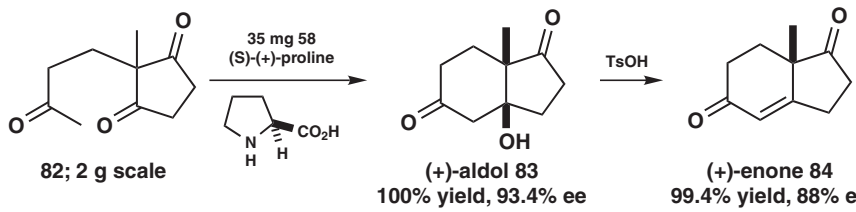
Pride of place here must go to the asymmetric Robinson annelation, discovered as long ago as 1974, but not appreciated at the time for the landmark that it undoubtedly was.[17] The normal Robinson annelation (text chapter 36) is first a Michael addition to produce an achiral triketone **82** which cyclises when the enol of the methyl ketone adds, aldol fashion, to the *syn* face of either of the other ketones to give **83**, and hence the enone **84**, the north east corner of a steroid.



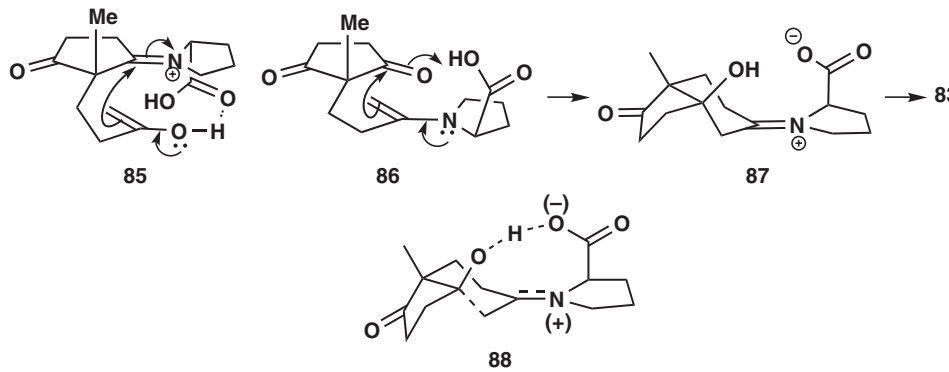
The top and bottom faces of the five-membered ring in **82** are diastereotopic and the intramolecular reaction selects the *syn* face. But the two ketone groups in **82** are enantiotopic. If the enol attacks the right hand ketone one enantiomer of **83** is formed while if it attacks the left hand ketone, the other enantiomer is formed.



The reaction is normally catalysed by weak acids and weak bases, such as piperidine and acetic acid. Replacing these with a catalytic (50:1) amount of proline **58** led to optically active **83** in an astonishing 93.4% ee and 100% yield. Dehydration gave the enone **84** with some loss of ee (by reverse aldol?), but recrystallisation from ether gave 100% ee.



The chiral auxiliary must obviously be involved intimately with the cyclisation, perhaps by forming an imine **85** or an enamine **86**, so that only the enantiomer **83** of the cyclisation mechanism applies. In both these proposals, the free CO_2H group of proline interacts by hydrogen bonding with a ketone or OH group. Explanations involving two molecules of proline have now been discredited and the most recent explanation[18] is that the enamine mechanism **86** is correct with that step as the rate determining step, closely followed by addition of water to the iminium ion **87**. The transition state has a chair-like central portion **88**.

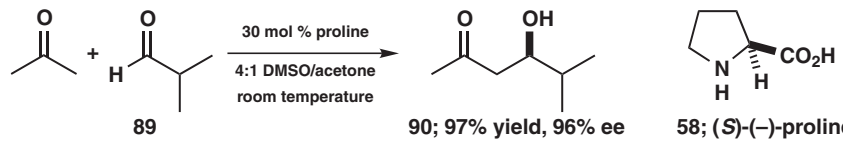


Proline is now recognised as a first class chiral auxiliary, having a rigid structure and a high grade stereogenic centre carrying contrasting sterically and electronically demanding substituents.

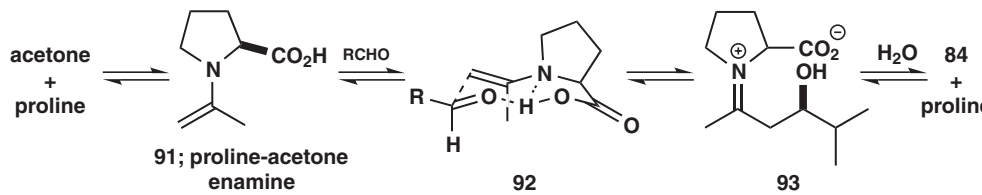
This was an extraordinary result when it was published in 1974 as it was well ahead of its time. It is still one of the best asymmetric reactions with catalytic amounts of a chiral reagent. An example of an asymmetric Robinson annelation using stoichiometric 'catalyst' is in the workbook.

The proline-catalysed aldol reaction

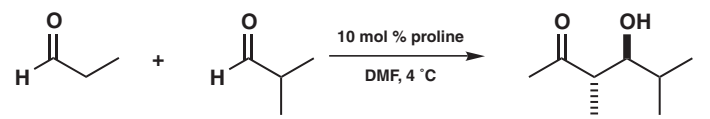
The asymmetric Robinson annelation relies on an intramolecular aldol reaction to create the new chiral centre. More recently List[19] and MacMillan[20] have used proline **58** to catalyse intermolecular aldol reactions with nearly as good results. Acetone and isobutyraldehyde **89** can be condensed to give a single enantiomer of the aldol **90** in excellent yield and ee providing 30% proline is used as catalyst.



Acetone, the component that must enolise, is present in large excess but the achievement is considerable. The reaction involves formation of the proline enamine of acetone **91** which then attacks the aldehyde through a chair-like transition state **92** held together by the acidic proton of proline's carboxylic acid. This gives the imine salt **93** hydrolysed to the product with regeneration of proline. The intermediates are like those in the Robinson annelation: enamines and imines. Organic catalysis with amines relies on equilibria between these intermediates and carbonyl compounds.

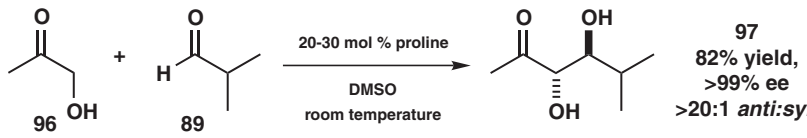


At the moment the limit is reached when both components in a crossed aldol reaction are enolisable aldehydes. One is indeed propionaldehyde **94** - a compound notorious for self-condensation - that reacts cleanly with isobutyraldehyde **89**. However, it is necessary to add the propionaldehyde slowly by syringe pump. The aldol **95** is produced in very high yield considering the similarity of the two aldehydes but the most amazing aspect is the very high diastereo- and enantioselectivity.[20]

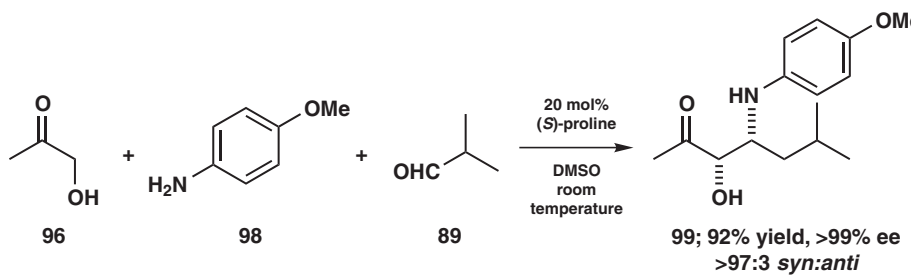


Reactions with hydroxy-acetone

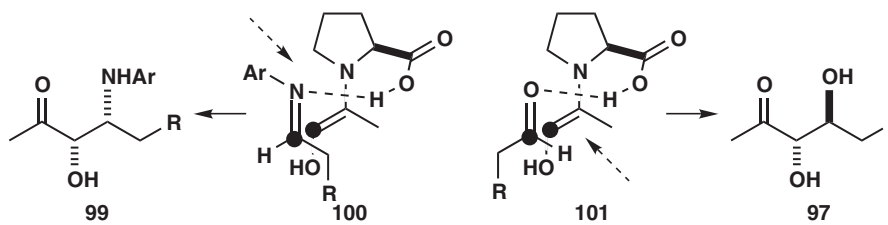
It turns out that one of the best ketones for these asymmetric crossed aldol reactions is hydroxyacetone **96**. Combination with isobutyraldehyde **89** gives an aldol that is also an *anti*-diol **97** with almost perfect selectivity.[21] The proline enamine of hydroxyacetone is evidently formed preferentially on the hydroxy side. You will recall from chapter 25 that asymmetric synthesis of *anti*-diols is not as easy as that of *syn* diols.



Hydroxyacetone **96** is a reagent in an even more remarkable reaction: the asymmetric direct three-component Mannich reaction. It is combined with an aromatic amine **98** and the inevitable isobutyraldehyde **89** with proline catalysis to give a very high yield of a compound **99** that might have been made by an asymmetric amino-hydroxylation. The proline enamine of hydroxyacetone, must react with the imine salt formed from the amine and isobutyraldehyde. This is a formidable organisation in the asymmetric step.

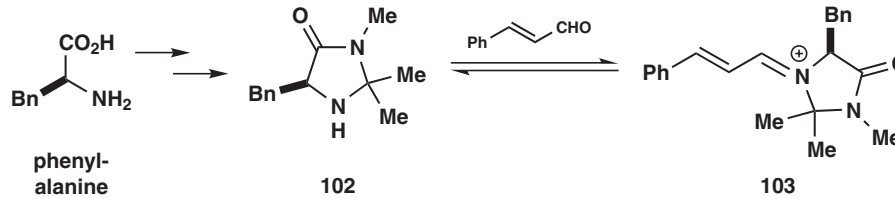


There is something different here. The absolute stereochemistry at the OH group (the one that comes from hydroxyacetone) is the same in **99** as it was in **97** but the relative stereochemistry is different: *anti* in **99** but *syn* in **97**. The electrophile (ketone in **97** or imine in **99**) must approach the proline enamine in different ways. List's suggestion is that the large *N*-aryl group prefers to keep away from the rest of the molecule in the transition state **100** leading to **99** but that the side chain on the aldehyde is more important in the transition state **101** leading to **97**. The dotted arrows in **100** and **101** show where that clash would come and the black dots mark the atoms that join to form the new bond. There is a review of the catalytic asymmetric aldol reaction that includes material from other chapters.[22]

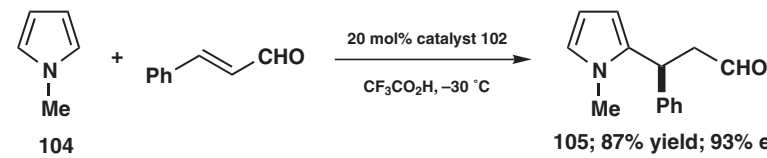


Conjugate addition

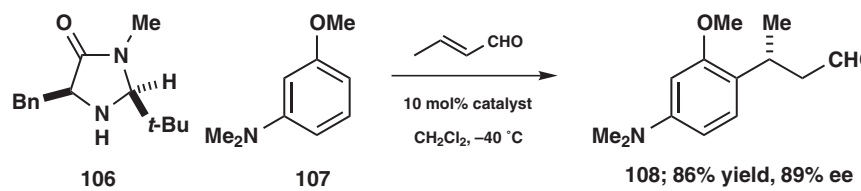
α,β-Unsaturated carbonyl compounds also reversibly form iminium salts with secondary amines and that offers opportunities for asymmetric conjugate addition and, as we shall soon see, asymmetric Diels-Alder reactions. The pioneer in the development of modern organic catalysis has been Dave MacMillan[23] at Berkeley and he reported the asymmetric conjugate addition of heterocycles such as pyrroles to enals catalysed by the amine **102** prepared from phenylalanine. The amine forms an iminium salt **103** reversibly and this salt is more electrophilic than the enal.



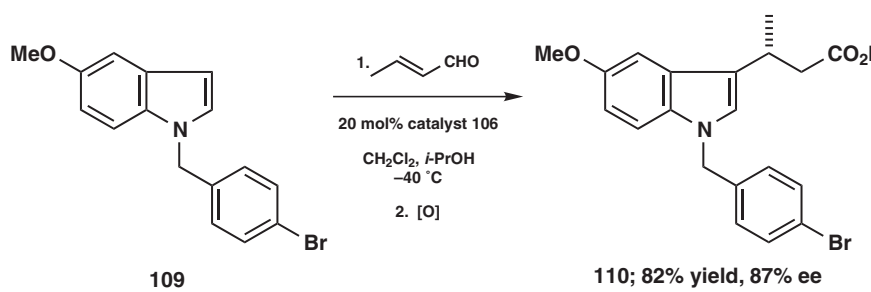
When *N*-methyl-pyrrole **104** is the nucleophile, clean conjugate addition occurs at its α-position with good ee in the product. Conjugate addition is normally a problem with aldehydes (chapter 9) so both regio- and enantioselectivity are impressive. The catalyst loading is quite high but clearly the catalyst can detach itself quickly enough from the first formed adduct to maintain a concentration of **103** large enough to swamp the slower reaction of **104** with the enal.



A new catalyst **106**, also derived from phenylalanine but with extra chirality, is needed for conjugate additions to crotonaldehyde. Nucleophilic benzene rings such as **107** react with good regio- and stereoselectivity[24] in the same sense as **105**.



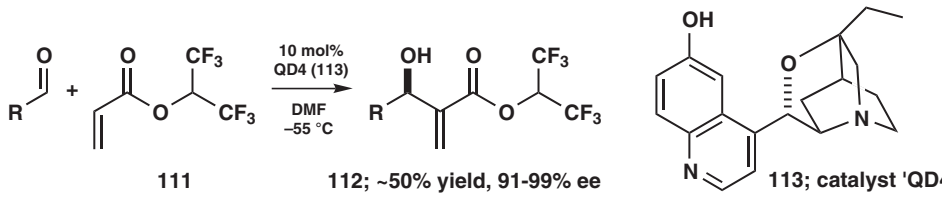
This method has been applied to the synthesis of a COX-2 inhibitor **110**, one of a new generation of analgesics under development by the Merck company. This requires conjugate addition to the 3-position of an indole **109** and the same catalyst is used.[25]



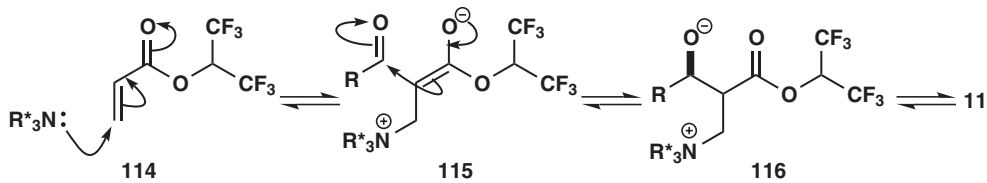
Catalysed asymmetric Baylis-Hillman reactions

Other reactions are possible with iminium salts derived from α,β-unsaturated carbonyl compounds. The Baylis-Hillman reaction (chapter 18) also uses conjugate addition as a first step and we shall deal with that immediately. Much more work has been done on the Diels-Alder reaction: that will follow. The Baylis-Hillman reaction between an electrophilic α,β-unsaturated carbonyl compound and an

electrophilic aldehyde is catalysed by tertiary amines and lowish yields are generally acceptable as so much is achieved in a one-pot reaction. The obvious source of asymmetry is a chiral amine catalyst but only recently has the right amine and the right α,β-unsaturated carbonyl compound been identified.[26]



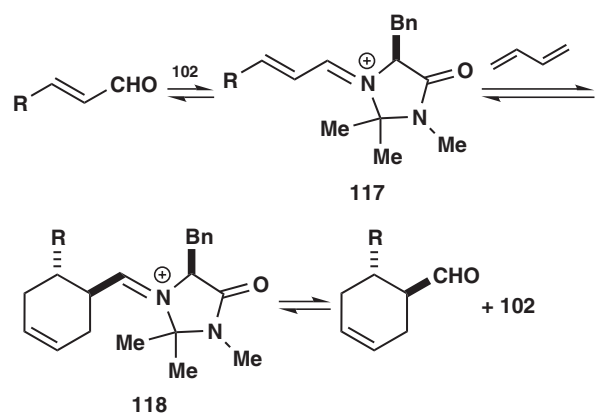
The unusual catalyst **113** must add to the unusual ester **111** in a reversible conjugate addition **114** to give the enolate that adds to the aldehyde in the asymmetric step **116**. The bicyclic amine must be placed close to the carbonyl group of the aldehyde: Hatakeyama suggests an H-bonding interaction with the OH group on the quinoline ring of the catalyst. Finally, elimination of the catalyst launches a second cycle. The next few years are likely to see considerable development here.



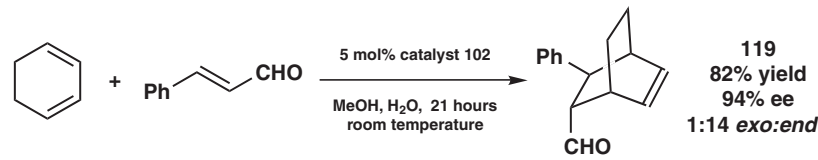
Catalysed Asymmetric Diels-Alder Reactions

Organic catalysis

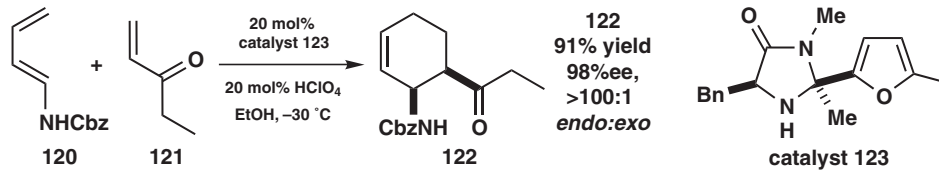
This is an important area with many available methods. We shall look first at organic catalysis and then change to catalysis by metal complexes. The same type of intermediate **117** used for conjugate addition is clearly also suitable for Diels-Alder reactions with the same proviso: it must be more reactive then the α,β-unsaturated carbonyl compound as that too can do Diels-Alder reactions. And of course the first formed product **118** must hydrolyse rapidly to release the catalyst **102**.



An early example was the reaction between cyclohexadiene and cinnamaldehyde catalysed by the phenylalanine-derived amine **102** to give the *endo* adduct **119** with good selectivity of all kinds.[23]



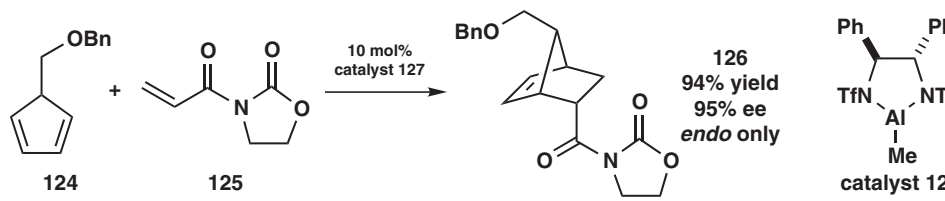
More recent developments include the refined catalyst **123** with extra bulk and an extra chiral centre. This catalyses reactions between functionalised dienes such as **120** and acyclic enones such as **121**. The very high yields, ees, and *endo:exo* selectivity of the product **122** compensate for the 20% catalyst loading. It is very difficult to get high ees in Diels-Alder reactions with acyclic ketones and you will see in the next section why this catalyst is successful.[27]



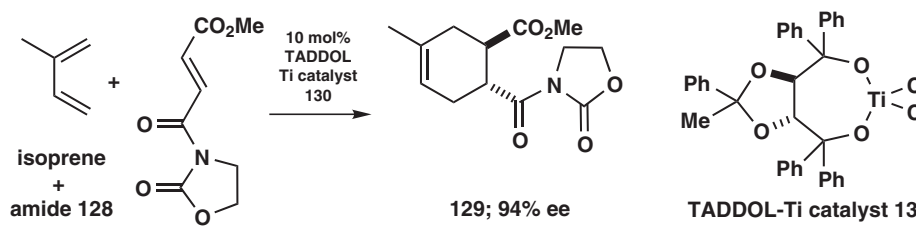
Diels-Alder reactions catalysed by metal complexes

C_2-Symmetric Lewis acid catalysis

The best results before organic catalysis were with amides **125** and Lewis acid catalysts based on Al, Ti, and Cu(II) with C_2-symmetric ligands. Corey's aluminium complex **127** derived from the diamine whose resolution was described in chapter 22 works well with substituted cyclopentadienes **124** and the product **126** was used in prostaglandin synthesis.[28] There are three aspects of stereoselectivity in this reaction: which diastereotopic face of **124** is attacked? (that *anti* to the CH_2OBn group), is the product *exo* or *endo*? (*endo*) and which *endo* product is formed, **126** or its enantiomer? Only for the last question is asymmetric catalysis necessary, though Lewis acid catalysis of any kind enhances *endo/exo* selectivity.

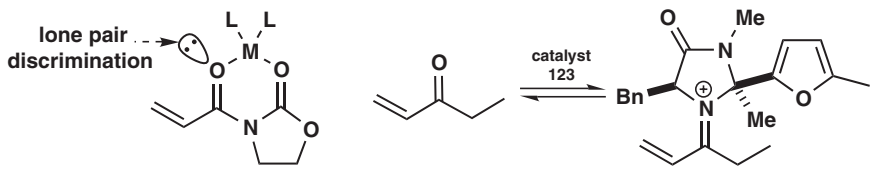


Seebach's TADDOL auxiliaries, derived from tartrate (chapter 23), combine well with Ti(IV) to make an effective Lewis acid catalyst **130** for Diels-Alder reactions. The reaction of isoprene with the doubly activated amide dienophile **128** gives one adduct **129** in good yield.[29] Polymer supported versions of this catalyst are available.



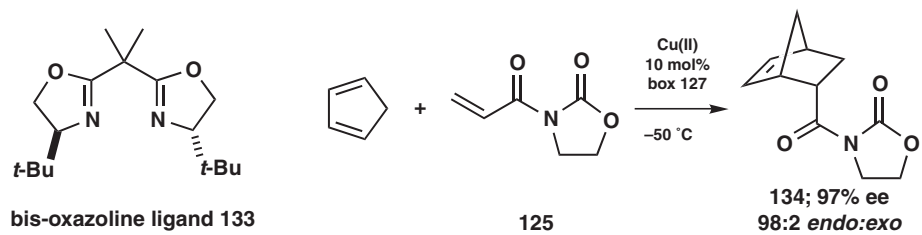
Origins of enantioselectivity in catalysed Diels-Alder reactions

You may be wondering why these dienophiles **125** and **128** have a heterocyclic ring attached to the carbonyl group. Later in chapter 27 you will see that chiral versions of this oxazolidinone are essential for other Diels-Alder reactions. But this ring is not chiral and its role is to chelate the metal **131**. By this means the two lone pairs on the ketone oxygen atom are distinguished and the asymmetry of the catalyst activates one face of the alkene rather than the other. Such a distinction is not possible for a ketone such as **121** and that is why organic catalysts such as **123** are much more effective. The iminium salt **132** shows the same kind of shape as the complex **131**. In both these diagrams **131** and **132** the orientation of the alkene cannot be stated for certain.

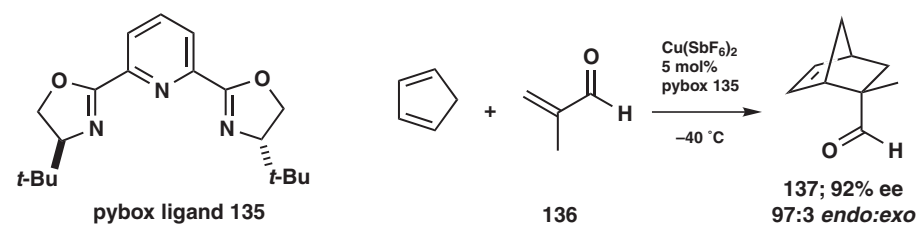


Box and pybox catalysts in asymmetric Diels-Alder reactions

Another important group of ligands for metal-catalysed reactions are based on oxazolines derived from amino acids. Evans[30] has used the bis-oxazoline or 'box' ligands in Cu(II)-catalysed Diels-Alder reactions. Ligand **133** is derived from the unnatural amino-acid *tert*-leucine and, complexed with $Cu(OTf)_2$, catalyses Diels-Alder reactions of the same dienophile **125** with various dienes. The best counterions are triflate (OTf) and SbF_6.

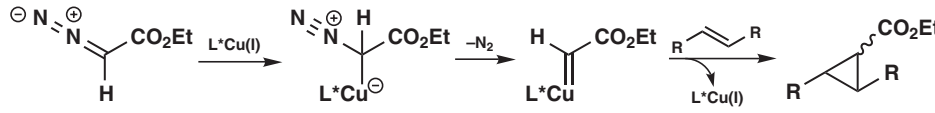


The more highly chelating pybox ligands such as **135**, also prepared from *tert*-leucine, catalyse Diels-Alder reactions even with aldehydes such as **136**. Now the counterion really must be the very non-nucleophilic SbF_6. In these examples diastereo- (*endo*/*exo*) and enantioselectivity are excellent.[31]

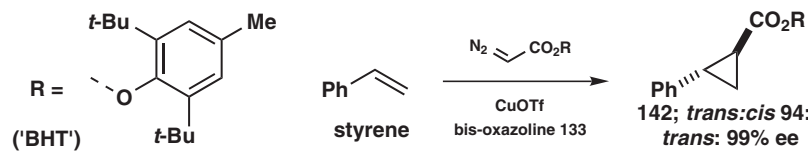


Cyclopropanation

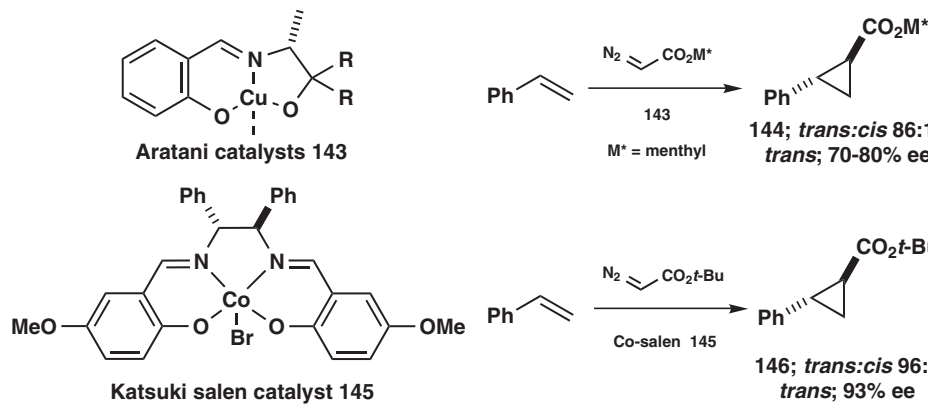
Historically one of the first asymmetric methods to be explored, cyclopropanation came of age[32] with box and salen ligands on Cu(I). Diazo compounds, particularly diazoesters **138**, react with Cu(I) to give carbene complexes **140** that add to alkenes, particularly electron-rich alkenes to give cyclopropanes **141**. The reaction is stereospecific with respect to the alkene - *trans* alkenes giving *trans* cyclopropanes - and reasonably stereoselective as far as the third centre is concerned. Any enantioselectivity comes from the chiral ligand L*. You have already seen the Ru carbene complexes are intermediates in olefin metathesis (chapter 15).



A good test case is styrene. With the box ligand **133** the best diazoester is the acetate of 'BHT', 2,6-di-*t*-butyl-4-methylphenol. This gives excellent diastereoselectivity and near perfect ee in the *trans*-cyclopropane[30] **142**.

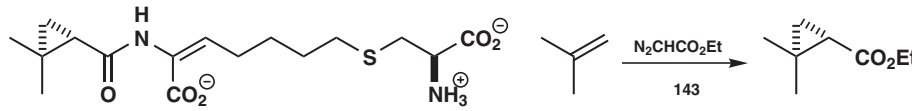


The early salen-type catalysts **143** of Aratani gave moderate results when menthyl diazoacetate was used,[32] but more modern versions, such as the salen-Co catalyst **145** of Katsuki[33] are much more impressive. You saw such catalysts in the last chapter under Jacobsen epoxidation.



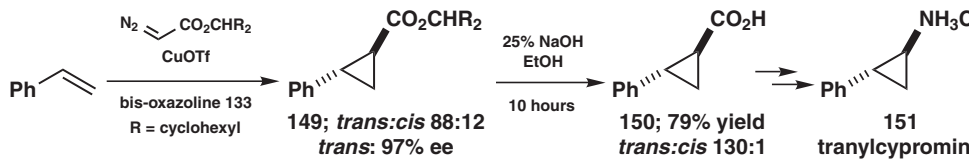
Application to the synthesis of medicinal compounds

Cilastatin **147** is used to increase the potency of β-lactam antibiotics. It is manufactured commercially by asymmetric cyclopropanation of isobutylene with ethyl diazoacetate catalysed by the Aretani Cu(I) complex **143** that is more effective with this trisubstituted alkene than with styrene.[34]



147 148; 92% ee

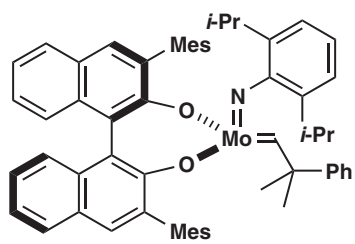
The antidepressant tranylcypromine **151** was made using the Evans box ligand **133**. A different bulky ester **149** gave good ee but only moderate diastereoselectivity.[35] The *trans* diastereoisomer hydrolyses faster than the *cis* so the free acid was essentially pure *trans*. Further reactions including a Curtius rearrangement with retention gave tranylcypromine **151**.



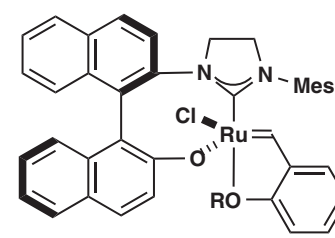
149; *trans:cis* 88:12
trans: 97% ee
150; 79% yield
trans:cis 130:1
151
tranylcypromine

Asymmetric Alkene Metathesis

Metal carbene complexes are also involved in metathesis (described in chapter 15). Exchange of carbene complexes with alkenes via a metallacyclobutane releases volatile alkenes such as ethylene with the formation of new alkenes. Ring closing metathesis is particularly favoured but normally leads to no new chiral centres. The simple Mo and Ru carbene catalysts described in chapter 15 cannot of course be used to induce asymmetry but a new generation of asymmetric Schrock **152** and Grubbs **153** catalysts can create asymmetry if a choice between two enantiotopic alkenes is offered.[36]

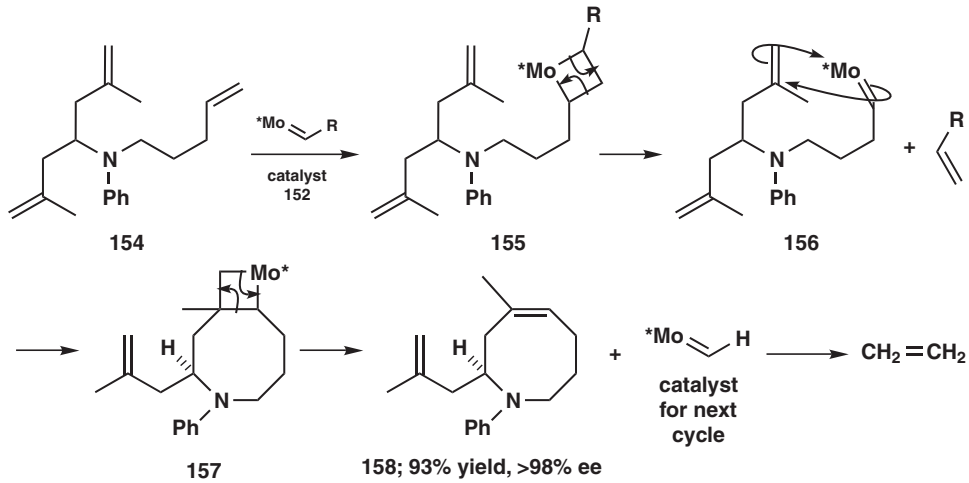


152; Asymmetric Schrock

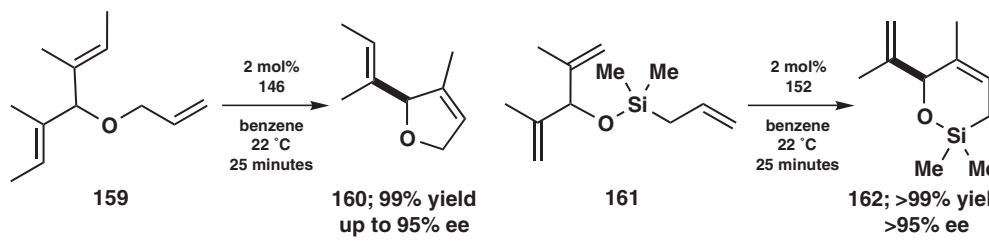


153; Asymmetric Grubbs

As we largely discussed Grubbs Ru catalysts in chapter 15 we shall redress the balance by using examples of the Mo catalyst **152**. The necessary parts of the substrate are (a) a monosubstituted alkene so that metathesis starts there and (b) a choice between two at least disubstituted enantiotopic alkenes for the second stage in the metathesis. So the amine **154** forms first the metallacyclobutane **155** and hence the new carbene complex **156** that can choose between the remaining two alkenes. In this case it does so very well indeed to give a high yield of the eight-membered cyclic amine **158** as a single enantiomer. The conditions are mild: 2 mol% of **152** in benzene at 22 °C for 25 minutes. Other than the solvent, all is fine.



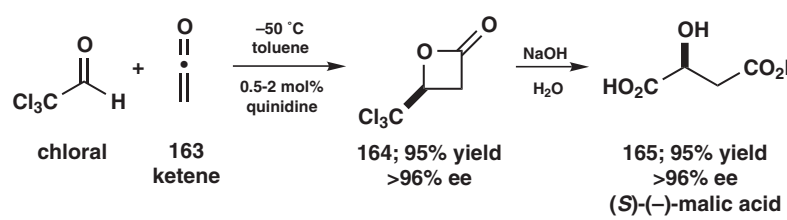
Examples of oxygen heterocycles include the five-membered ring **160** and the six-membered ring **161**. It may seem at first sight that the obligatory extra alkene in all the products is a disadvantage but this is a useful functional group that can be used to develop functionality or can simply be oxidised to a carbonyl group. It is generally more reactive than the alkene embedded in the ring. The silicon compound **162** can also be cleaved at both Si – O and, if necessary, Si – C bonds to give an open chain compound.



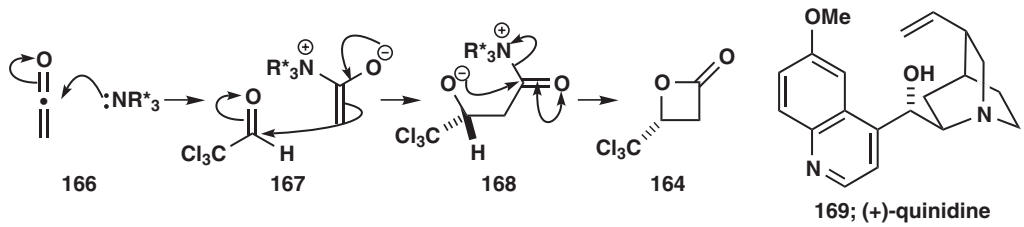
Asymmetric Pericyclic Additions to Carbonyl Groups

2 + 2 Ketene cycloadditions

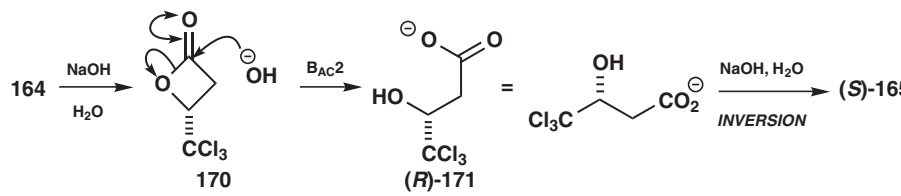
In chapter 25 you met the 'pseudoenantiomers' quinine and quinidine when their dihydroderivatives were used in Sharpless asymmetric dihydroxylation. The cinchona alkaloids themselves are used to catalyse a 2 + 2 cycloaddition of ketene to chloral in an important industrial process.[37] Chloral reacts with ketene **163** from a generator in the presence of quinine or quinidine to give the β-lactone **164**. Catalysis by quinine gives the other enantiomer. Hydrolysis opens the lactone ring and hydrolyses the CCl_3 group to CO_2H to give either enantiomer of malic acid **165**.



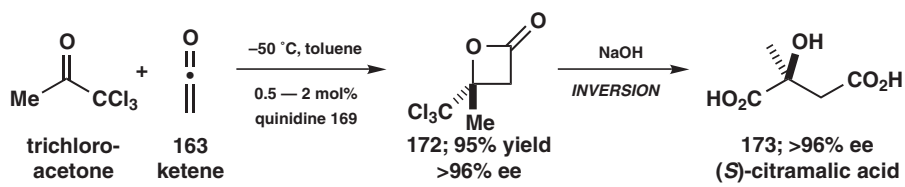
This is probably not strictly a 2 + 2 cycloaddition but an addition of the chiral amine **169** to the ketene **166** to give a chiral enolate that adds to chloral in the step that induces asymmetry **167**. Ring closure **168** gives the lactone **164** and regenerates the quinidine for the next cycle.[38]



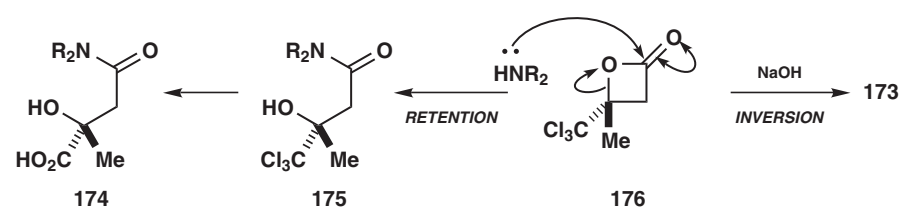
The mechanism of the hydrolysis both of the lactone and of the CCl_3 group by hydroxide must be understood to interpret the stereochemistry.[39] Whereas simple β-lactones tend to react at sp^3 carbon by an S_N2 reaction ($B_{Alk}2$) as that releases ring strain in the slow step, the CCl_3 group slows down the S_N2 reaction and lactone **164**, like most lactones, is attacked at the carbonyl group by hydroxide ion **170**. The configuration at the chiral centre is retained in this step. The hydrolysis of the CCl_3 group in **171** to CO_2H however occurs with inversion at the chiral centre - the details of this reaction are in the workbook. The other enantiomer (*R*)-(+)- of malic acid thus joins the new chiral pool (chapter 23).



Reaction with trichloroacetone is similarly high-yielding and enantioselective giving the β-lactone **172** and after hydrolysis with inversion, (*S*)-citramalic acid **173**. Again, quinine gives the other enantiomer.

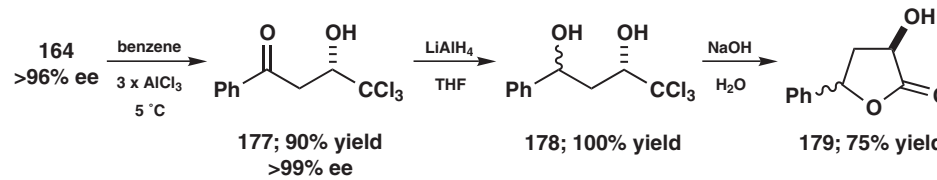


Hydrolysis of both lactones **163** and **172** by hydroxide ion occurs with inversion during the conversion of the CCl_3 group to CO_2H. Weaker nucleophiles clearly attack the carbonyl group **176** to make available a series of derivatives such as the amides **174** and **175**.

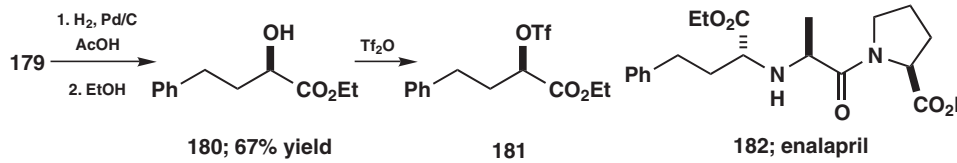


Synthesis of enalapril

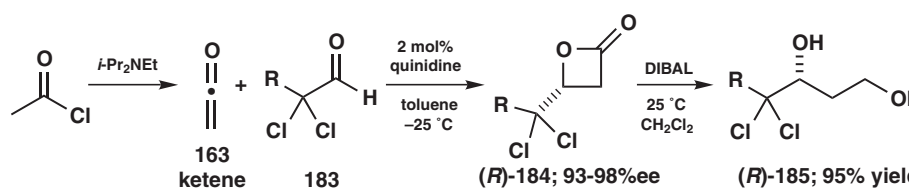
The ACE (Angiotensin Converting Enzyme) inhibitors are a group of important drugs that reduce high blood pressure and help to prevent strokes and heart attacks. One is enalapril **182** that can be made from the β-lactone **164**. A Friedel-Crafts acylation (note that attack at the carbonyl group is preferred) gives the ketone **177** reduced to the diol **178** and hence to the lactone **179** both as single enantiomers of mixtures of diastereoisomers.[40]



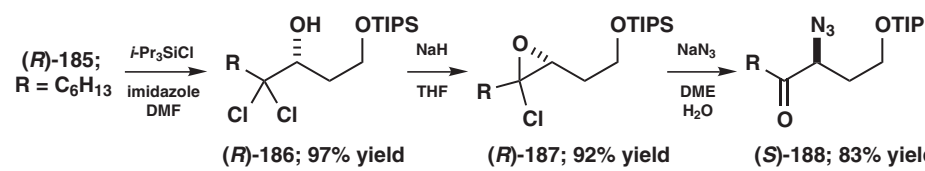
Catalytic hydrogenation of the benzylic C–O bond in **179** removes the second chiral centre and the hydroxy-ester **180** is prepared for coupling to an enantiomerically pure amine by conversion to the triflate **181**. The coupling goes with inversion to give enalapril[41] **182**.



Recent developments extend the asymmetric β-lactone formation to dichloroaldehydes **183** with formation of the ketene **163** by elimination on acetyl chloride rather than from a ketene generator. A mixture of the aldehyde **183**, Hünig's base and 2 mol % quinidine **169** is treated with acetyl chloride to give the β-lactones **184** in good yield (40–85%) and excellent ee. Reduction with DIBAL gives the diol **185** with the two chlorine atoms intact.[42]

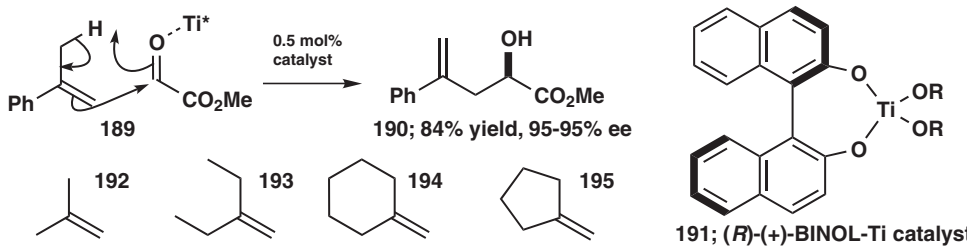


Among various further developments, the formation of the azido ketone **188** is especially promising. It also illuminates aspects of the mechanism of the hydrolysis of **157** and **165**. The closure of the epoxide **187** and its opening by azide ion with inversion and the exposure of the carbonyl group **188** by loss of chloride all also occur in the hydrolysis of the CCl_3 group in **157** and **165** (see workbook).



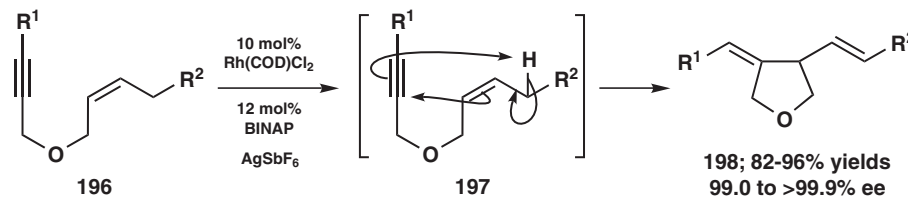
Carbonyl ene reactions

The carbonyl ene reaction is between a similarly reactive aldehyde and an alkene rather than a ketene. Glyoxalate esters and chloral are typical of the carbonyl compounds involved. Asymmetric versions rely on Lewis acid catalysts similar to those used in Diels-Alder reactions based on Ti and Al among other metals.[43] A simple example is the formation of **190** from methyl glyoxalate and an alkene **189** catalysed by 0.5 mol% of a BINOL-Ti complex **191**. Other alkenes that react well are **192** - **195**.



Alder ene reactions

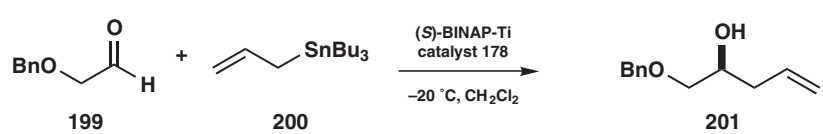
The original ene reaction, invented by Alder, was between an alkene such as **192** and a dienophile - that is a conjugated unsaturated carbonyl compound. If the reaction is intramolecular, the alkenes need not be specifically activated by conjugation but they must be clearly distinct in reactivity. Xumu Zhang and group[44] have recently reported asymmetric tetrahydrofuran syntheses using the BINAP Rh(I) catalyst **21** so successful in hydrogenations. A *Z*-allyl propargyl ether **196** reacts with this Rh catalyst in an ene reaction that corresponds to the tortured mechanism **197**. The substituents R^1 and R^2 can be a range of alkyl, aryl, and functionalised groups. No absolute stereochemistry is given but each enantiomer of BINAP produces a different enantiomer of **198**.



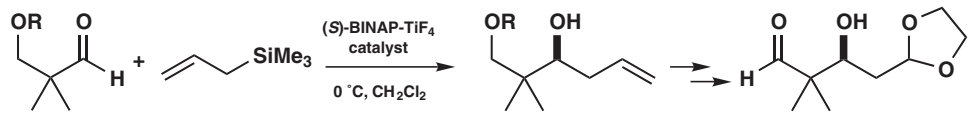
Nucleophilic Additions to Carbonyl Groups

Allyl metals

Closely related to the previous section is the asymmetric addition of allyl stannanes to aldehydes. The catalyst is the same and the main difference is that an R_3Sn group is lost instead of a proton. This has the advantage that there is no ambiguity about the position of the alkene in the product. An example is the addition of an allyl group to the functionalised aldehyde **199**. Complexation of either or both oxygen atoms to the Ti is indicated.[45]



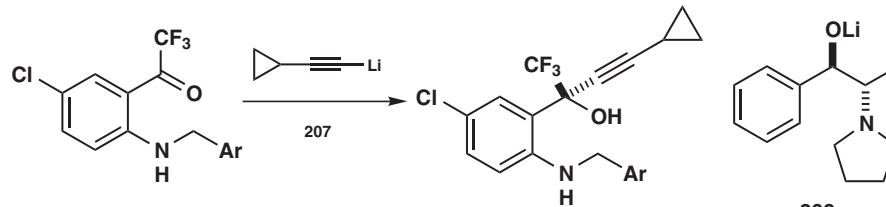
Recent improvements include the replacement of the toxic tin reagent **200** with the allyl silane[46] **203**. Addition to the alkoxyaldehyde **202** gives **204** that can be transformed into the half-protected dialdehyde **205**.



202 **203** **204; 97% yield, 91% ee (97% after recrystallisation)** **205**

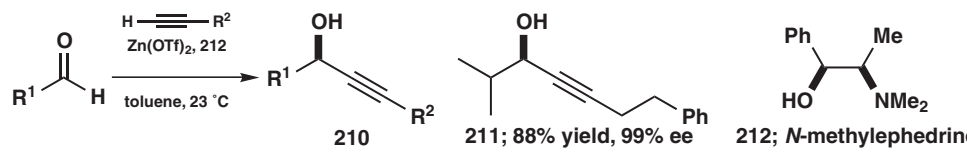
Alkynyl metals

Ideally it should be possible to add organo-Li and Grignard reagents to prochiral aldehydes and ketones with a chiral catalyst to give alcohols in good enantiomeric excess. This is difficult since the *uncatalysed* rate of addition is so high. It is possible to add the less reactive lithium acetylides such as **207** to ketones in the presence of stoichiometric lithium derivatives of amino alcohols such as **209**, analogues of ephedrine. The product **208** is used in the asymmetric synthesis of the Merck anti-HIV compound Efavirenz.[47]



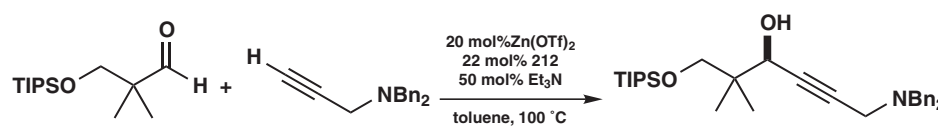
206; Ar = 4-MeOC$_6$H$_5$ **208; 80% yield, 96-98% e.e.** **209**

Among the best catalytic versions of such reactions are Carreira's additions of alkynyl zinc reagents to carbonyl compounds.[48] Organo-zinc reagents are very much less nucleophilic than organo-Li or Mg compounds so the rate of the uncatalysed reaction is small. The catalysts are again amino alcohols related to ephedrine (such as *N*-methylephedrine **212**) and a big advantage is that no separate step is needed to create the alkynyl zinc reagent as the acetylene, $Zn(OTf)_2$ and the amine do the trick. With stoichiometric catalyst **212** the reaction is general for propargyl alcohols **210** such as **211** and the toluene used as solvent need not be completely dry.



210 **211; 88% yield, 99% ee** **212; *N*-methylephedrine**

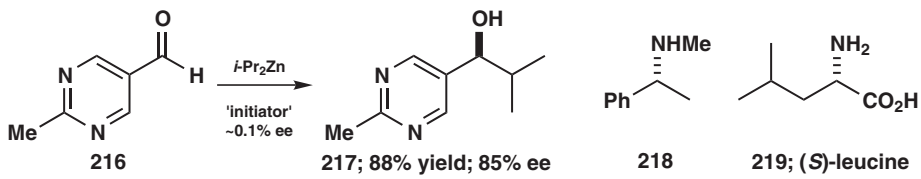
The catalytic reaction, using admittedly 20 mol% $Zn(OTf)_2$, 22 mol% catalyst **212**, and 50 mol% Et_3N, is successful with a variety of functionalised aldehydes and acetylenes such as **213** and **214**. Though toluene is used as solvent, in fact no solvent is necessary.[49]



213 **214** **215; 80% yield, 95% ee**

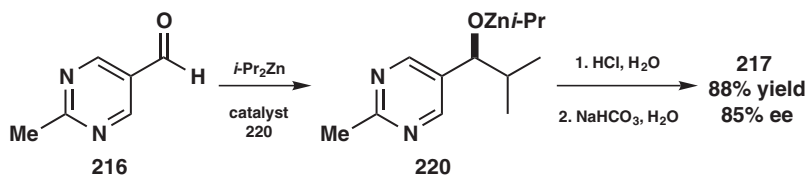
Addition of alkyl organo-zinc reagents

Though not so general as the reactions we have just seen, the catalysed addition of dialkyl zincs to certain aldehydes sets a new standard for catalysis that needs some explaining. Dialkyl zincs add to the pyrimidine aldehyde **216** under catalysis from amino alcohols, amino acids such as leucine **219**, hydroxy acids, and simple secondary alcohols or amines such as **218** to give enantiomerically enriched alcohols **217**. Plain sailing so far, except for the extraordinary range of catalysts.



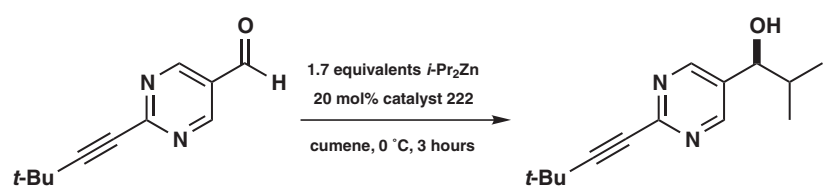
216 **217; 88% yield; 85% ee** **218** **219; (*S*)-leucine**

The strange thing is that catalysts of low enantiomeric excess, even as low as 0.1% ee, induce asymmetry of a much higher order (here 95%). This 'asymmetric amplification' is particularly intriguing since ees of about 0.1% can be produced by irradiating racemic leucine with circularly polarised light. The true catalyst in these reactions is the zinc alkoxide **220** of the *product*. The 'initiators' as they are better known, such as leucine, merely create a small amount of this true catalyst.[50]



216 **220**

This is easily demonstrated in what Soai calls 'practically perfect asymmetric autocatalysis' with the special aldehyde **221** using 20 mol% of the previously prepared product **222** as catalyst and enough *i*-Pr_2Zn to allow for the conversion of the catalyst to the zinc alkoxide. There is considerable amplification: if the catalyst **222** has 5.5% ee, the product (also **222**) is 70% ee. But if enantiomerically pure catalyst is used, the yield and the ee of the product are practically perfect. Each molecule of catalyst produces five molecules of itself as product. The amplification factor is six and if the whole of the product is used in a second reaction with five times as much aldehyde a second batch of **222**, 36 times as much, is the product.[51]

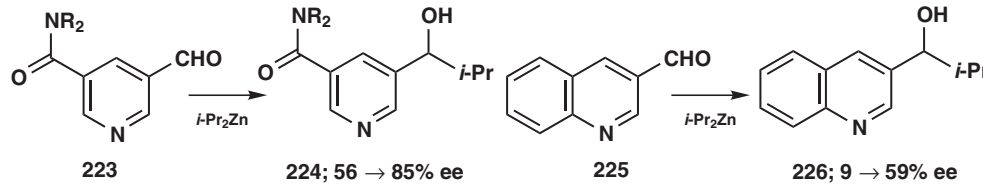


221

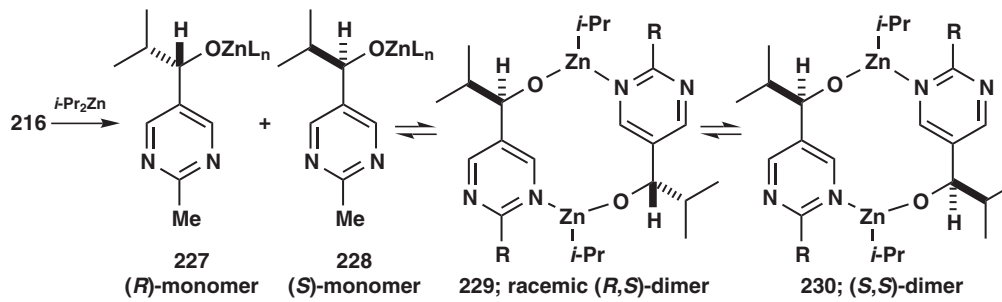
5.5% ee catalyst - - → **222; >99% yield; 70% ee**

>99.5% ee catalyst → **222; >99% yield; >99.5% ee**

So how are we to explain such remarkable results? The key point is that all the aldehydes must have a pyrimidine **216**, **221**, pyridine **223**, or quinoline **225** ring joined to the carbonyl group and the heterocyclic nitrogen must be *meta* to the aldehyde.

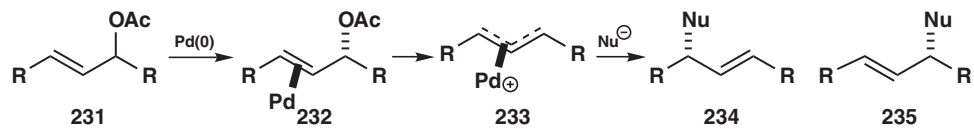


Non-linear relationships between ee of catalyst and ee of product require some dimeric species. Suppose the true catalyst, the zinc derivative of the product, forms dimers. There are two diastereoisomers of these, a *meso* dimer **229** and a homochiral dimer **230**. If the *meso* dimer is more stable than **230** it will absorb all the minor enantiomer **227** leaving only the major enantiomer **228** to catalyse the reaction. Of course, it could be the homochiral dimer **230** that is the active catalyst as the dimers have spare coordination sites on zinc. This phenomenon is described in more detail in an excellent paper.[52]



Palladium Allyl Cation Complexes with Chiral Ligands

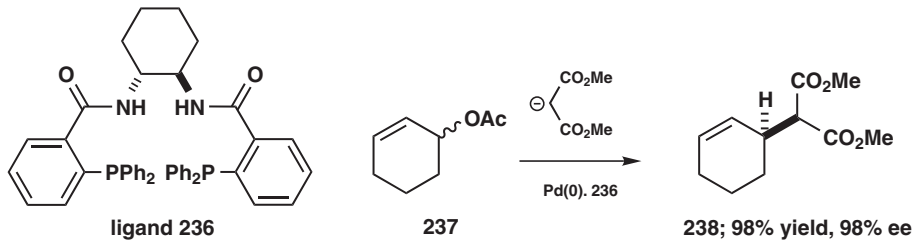
In chapter 19 we discussed the uses of palladium allyl cation complexes as electrophiles. We established that Pd(0) adds to the opposite face of the allylic system to the leaving group **232** to form an η^3 cation complex **233** and that the nucleophile attacks from the opposite face to the Pd so that the two inversions lead to retention. We established that regioselectivity and diastereoselectivity can be well controlled. If this seems unfamiliar we suggest you read the relevant section of chapter 19 before proceeding.



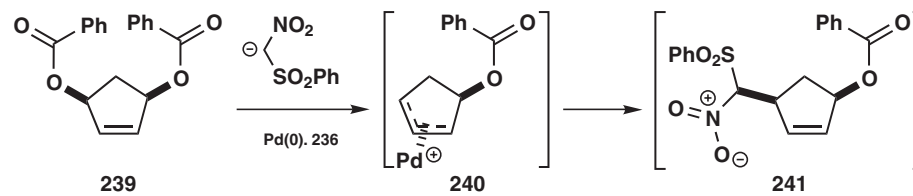
What is new here is that attack of the nucleophile on the complex **233** can lead to asymmetric induction in a number of ways. For example either enantiomer **234** or **235** could be formed from the symmetrical complex **233**. This involves attack at one enantiotopic end of the allylic system rather than one enantiotopic face and in this sense rather resembles the ring closing step (**82** → **83**) in the asymmetric Robinson annelation. Though essential early work[53] was done on the symmetrical complex **233**; R = Ph, we shall concentrate on more recent results.

Trost established[54] that the ligand **236** was the best for many of these reactions. Thus racemic allylic acetate **237** gives a symmetrical allylic cation complex like **233** and the ligand directs the

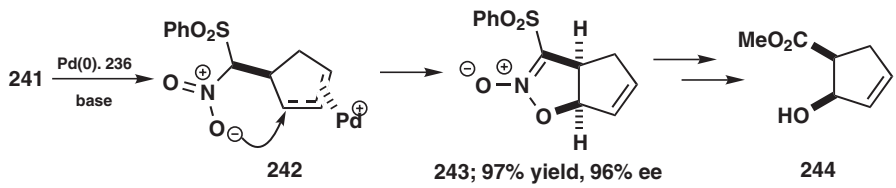
malonate nucleophile to one end only to give **238**. High ees are achieved only if the counterion is large - $(Hexyl)_4N^+$ being the best.



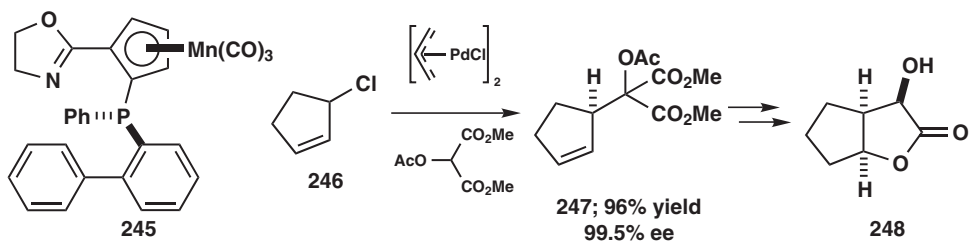
Desymmetrisation of bis allylic esters such as **239** adds another dimension. Asymmetry is already introduced in the η^3 cation complex **240** by selection of one of the enantiotopic benzoates as leaving group. Attack of the nucleophile occurs on the same side as the other benzoate, as that is the side opposite the Pd atom and so there is strong regioselectivity for the site away from the second benzoate. Since the first formed product **241** is still an allylic benzoate, further reaction is possible.



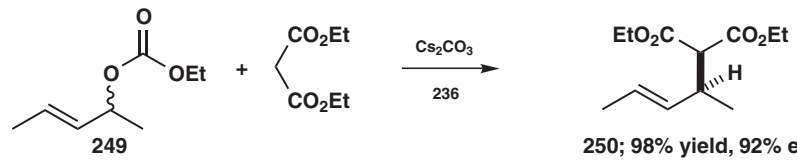
Cyclisation of the intermediate **241** in the same pot closes the five-membered ring **243** leading to **244**, an intermediate in the synthesis of the anti-viral drug carbovir. Both stereo- and regioselectivity are controlled by the short tether.[55]



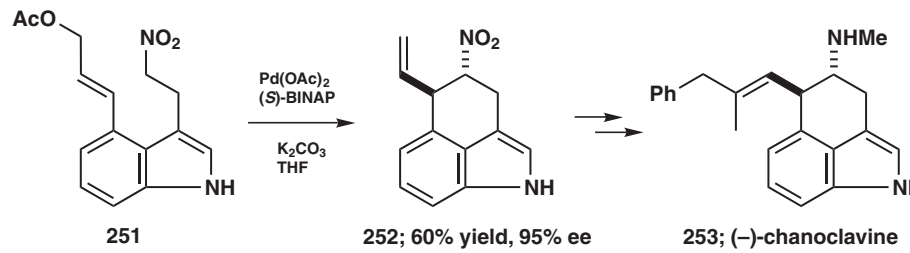
Catalyst **236** is by no means the only one to achieve such results. Helmchen[56] uses the manganese-containing monophosphine **245** for alkylation of malonates with racemic allylic chloride **246** to give the adduct **247** that is used in the synthesis of the lactone **248**.



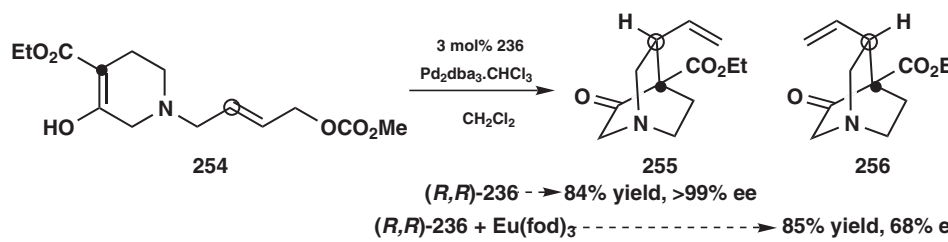
Enantioselectivity with open chain compounds is more difficult but Trost uses ligand **236** for the simplest of these: the symmetrical allylic carbonate **249** (note the different leaving group: CO_2 is lost, see chapter 19) with malonate anions formed with $CsCO_3$. However, this is the best result from a variety of different open chain allylic carbonates.[57]



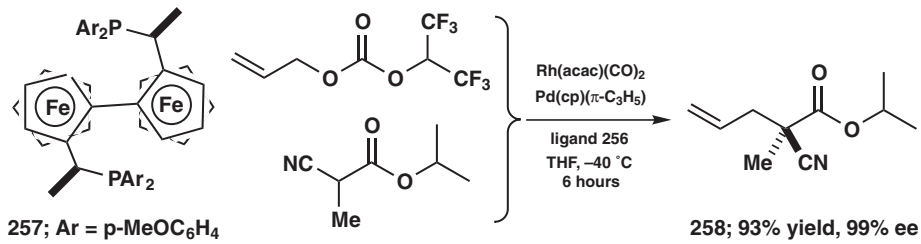
Intramolecular reactions generally give excellent results. Allylation of the nitroalkane portion of the indole **251** closes the six-membered ring of the ergoline alkaloids such as chanoclavine **253**. Genet's study of various ligands revealed that BINAP provided the best results.[58]



More recently, Trost has developed[59] a clean way to form the difficult bicyclic core of the *cinchona* alkaloids with good diastereo- and enantioselectivity using his favourite ligand **236**. Chirality is developed at both ends of the new bond: at the allylic carbon (marked with an empty circle) and at the former enol carbon (marked with a black blob). The two diastereoisomers of the product **255** and **256** form the core of the quinine alkaloids. They have the same absolute stereochemistry in the bicyclic core but the stereochemistry of the vinyl group is different. There is a strong match/mismatch effect: (*R,R*)-**236** gives 4.6:1 diastereoselectivity in favour of **255** and excellent ee while (*S,S*)-**236** gives 8:1 diastereoselectivity in favour of **256** and poor ee.



Controlling enantioselectivity at the enol centre alone can be achieved with special reagents and a very complex catalyst. An allylic carbonate with a fluorinated esterifying group allylates a prochiral enolate derived from *i*-propyl cyanopropionate catalysed by Pd, Rh, and the chiral Fe 'TRAP' ligand **257**, gives excellent results. The explanations for these last two examples are complicated and you are referred to the papers if you want to know more.[60]



Summary

This is a very big and growing subject. There are many catalytic reactions, such as the phase-transfer catalysed alkylation of enolates, that we have no space to discuss here. That particular one is treated in the workbook.

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General references are given on page 893

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55. B. M. Trost, L. Li and S. D. Guile, *J. Am. Chem. Soc.*, 1992, **114**, 8745.
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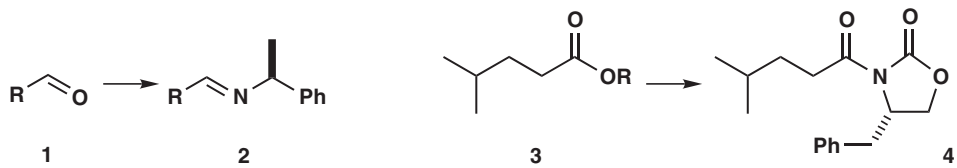
27 Asymmetric Induction IV Substrate-Based Strategy

Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

Introduction to Substrate-Based Strategy

In the last few chapters we have started with a prochiral molecule having enantiotopic features: the faces of an alkene for instance - and differentiated these faces with enantiomerically pure reagents or catalysts. In this chapter we explore the alternative approach. The enantiotopic faces are transformed into diastereotopic faces by the covalent attachment of a chiral auxiliary. It seems inevitable that this auxiliary must be stoichiometric but you will even see that 'catalytic' substrate methodology is starting to emerge. It also seems inevitable that two extra reactions will be needed: the attachment and the removal of the chiral auxiliary. In spite of this, one of the most important methods of asymmetric synthesis, centred around Evans's amino acid-based chiral auxiliaries, uses this approach.



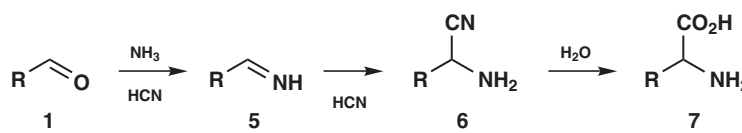
Thus the faces of the carbonyl group in the aldehyde **1** are enantiotopic but after attachment of a chiral amine they become diastereotopic in the imine **2**. The faces of the enolate of the ester **3** are enantiotopic but those of the enolate of the amide **4**, after attachment of the Evans phenylalanine-derived oxazolidinone, are diastereotopic.

You may notice something else that is different in this chapter. It is much easier to offer reasonable explanations for substrate-style asymmetric induction because we have a better idea of the conformation the compound adopts during the reaction as the configuration of the product is a guide.

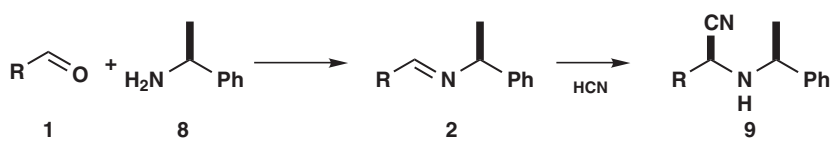
Chiral Carbonyl Groups

The asymmetric Strecker reaction

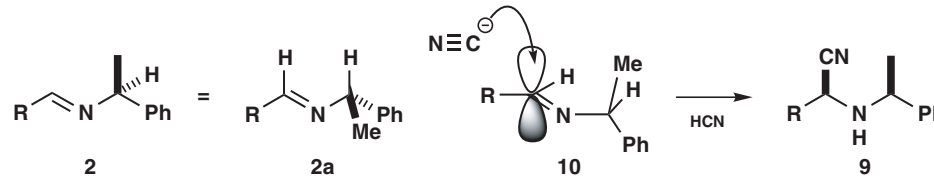
The Strecker reaction is a way to make α-amino acids **7** from aldehydes **1** with cyanide and ammonia. Cyanide adds to the unstable imine **5** to give the stable amino nitrile **6** that can easily be hydrolysed to the inevitably racemic α-amino acid **7**.



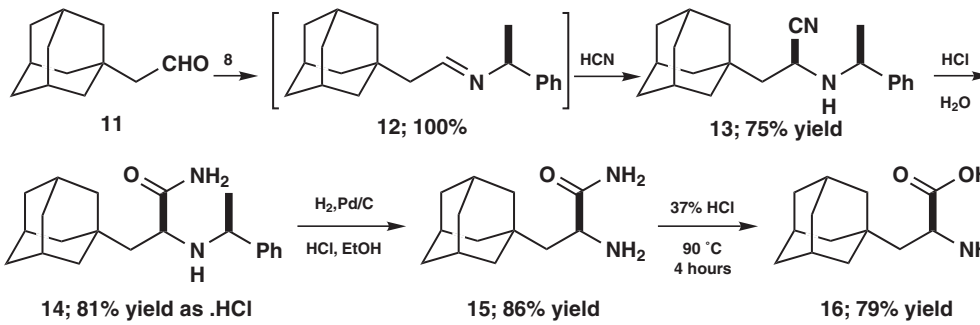
One asymmetric Strecker reaction[1] uses the enantiomerically pure amine **8**, available as both enantiomers since it is easily prepared by resolution (chapter 24), as a way to make the imine **2** have diastereotopic faces. Cyanide addition is reasonably diastereoselective giving mainly the amino nitrile **9**.



The most likely explanation is that the imine prefers a Houk-style conformation **2a** with the two marked H atoms in the plane and the cyanide adds **10** to the face of the C=N bond opposite the larger phenyl group.

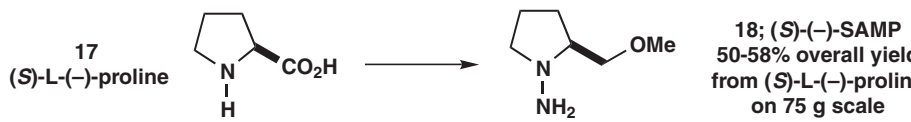


An advantage of the substrate-based strategy is that the chiral auxiliary is still attached to the molecule after the induction reaction and so the product, **9** in this instance, can be purified as one diastereoisomer before the chiral auxiliary is removed. An example of the asymmetric Strecker reaction in practice is the synthesis of the 'fat' amino acid **16** having an adamantyl group to increase solubility in fats and hence permeability to cell membranes.[2] After purification of the amino nitrile **13** hydrolysis gives the amide **14**, hydrogenation removes (and sadly destroys) the chiral auxiliary, and a final hydrolysis gives the 'fat' amino acid **16**.

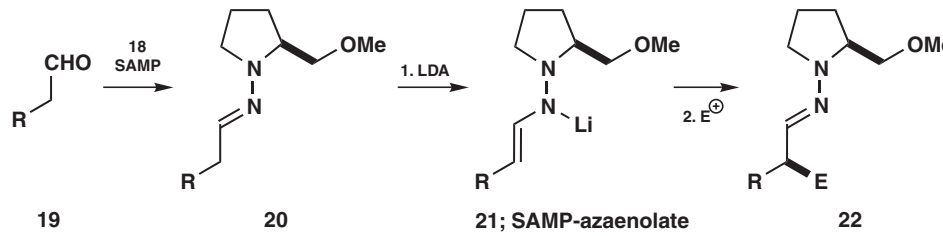


Chiral Enolates from Imines of Aldehydes: SAMP and RAMP

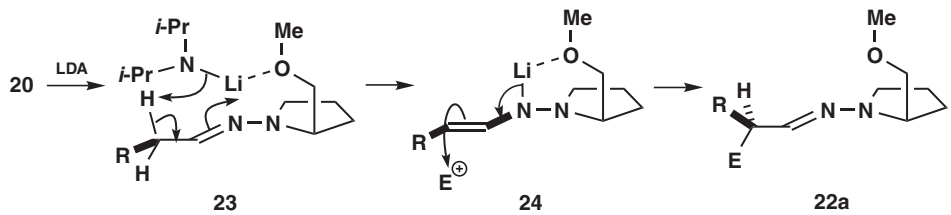
Aza-enolates derived from imines were introduced in chapter 10. It is easy to see that imines from chiral amines might well be used to make aza-enolates that would react asymmetrically with electrophiles. Among the most famous examples are the hydrazones SAMP and RAMP derived by Enders from proline.[3] The starting material derived from natural (*S*)-(−)-proline **17** is called SAMP **18** and the one derived from unnatural (*R*)-(+)-proline is RAMP. The reactions of the two are identical except that they lead to products of opposite chirality.



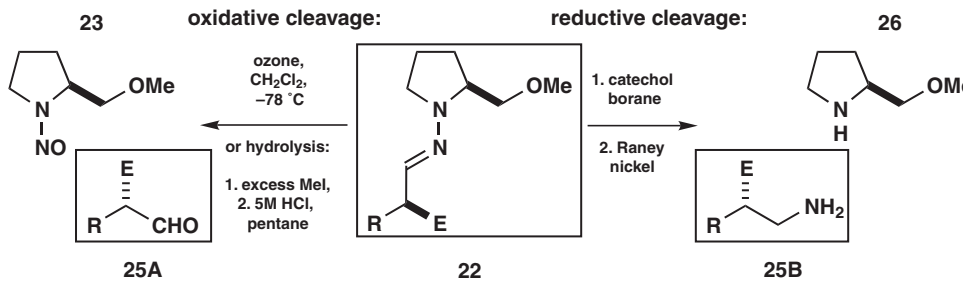
Imines **20** formed from SAMP and enolisable aldehydes prefer an *E*-configuration across the C=N bond. Lithiation gives the aza-enolate **21** also with the *E*-configuration derived from the preferred *conformation* of **20**. Reaction with an electrophile gives mostly the diastereoisomer **22**.



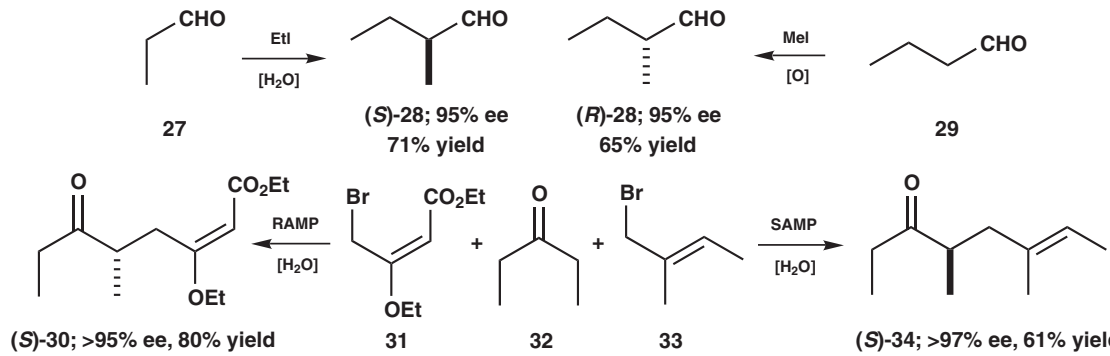
The side chain OMe group is essential for the asymmetric induction as it complexes the lithium atom of LDA so that only one of the diastereotopic protons is removed **23** and holds the aza-enolate in one configuration **24** with Li bonded both to N and to O. Electrophilic attack then occurs *anti* to the lithium atom on the unhindered face of the aza-enolate **24** to give the product in the same conformation **22a**.



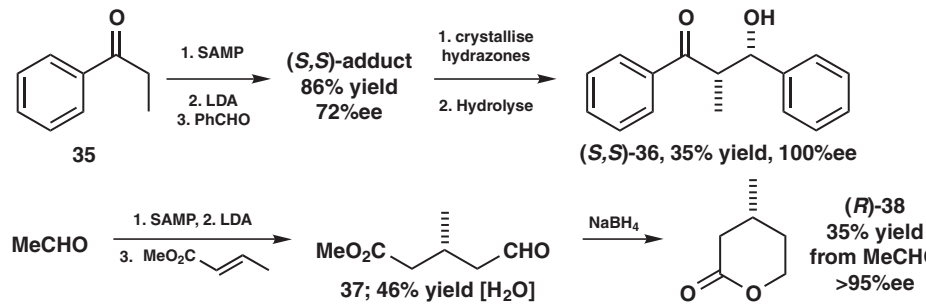
This is an excellent and popular method but removal of the chiral auxiliary is rather difficult and must be carried out oxidatively to produce the aldehyde product **25A**. The chiral auxiliary emerges as the *N*-nitroso compound **23** and this can be recycled. An alternative is alkylation (MeI) and acidic hydrolysis. Reductive removal gives the amine **25B** and an intermediate **26** in the synthesis of SAMP.



The electrophile E^+ can be an alkyl halide or sulfate, an aldehyde to give aldol products, or an α,β-unsaturated ester when conjugate addition is preferred. Examples from simple alkylation show that the alkyl halide can be primary alkyl, allylic **33**, and even an α-bromoester or γ-bromo-α,β-unsaturated ester **31**. The original carbonyl compound that forms the chiral imine with SAMP or RAMP can be an aldehyde **27** or **29**, a ketone (symmetrical **32** or blocked on one side **35**), or an enone. Only the reagents and products are shown with oxidative [O] or hydrolytic [H_2O] workup. Notice that SAMP is used for the formation of either enantiomer of **28** by using different starting materials but that RAMP is used to enter the other enantiomeric series from **32**.



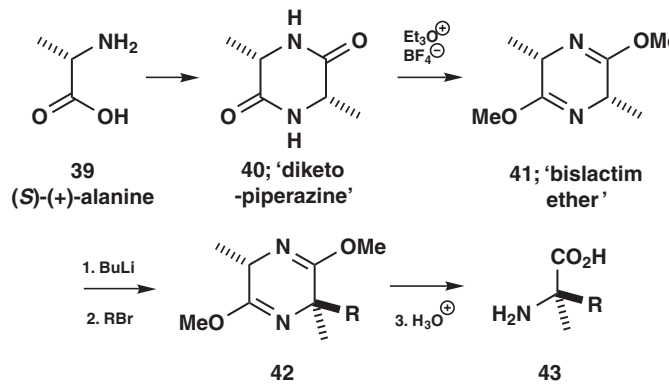
Reactions with aldehydes give *syn*-aldol products **36** in moderate ee but the hydrazones are crystalline so, at the expense of yield, ee can be raised to 100%. Conjugate addition gives good ees but moderate yields and the first formed products, e.g. **37**, can be converted into useful lactones, e.g. **38**.



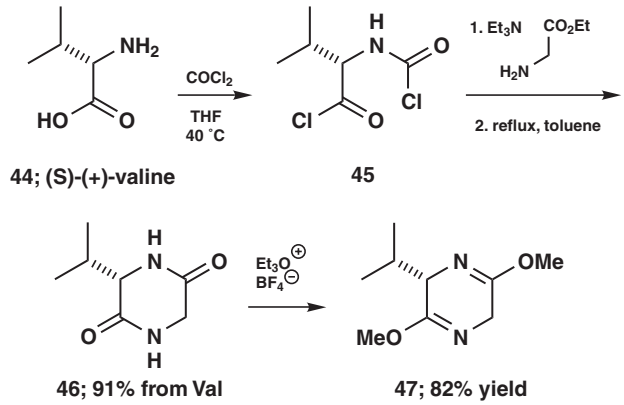
Chiral Enolates from Amino Acids

Schöllkopf's bislactim ethers

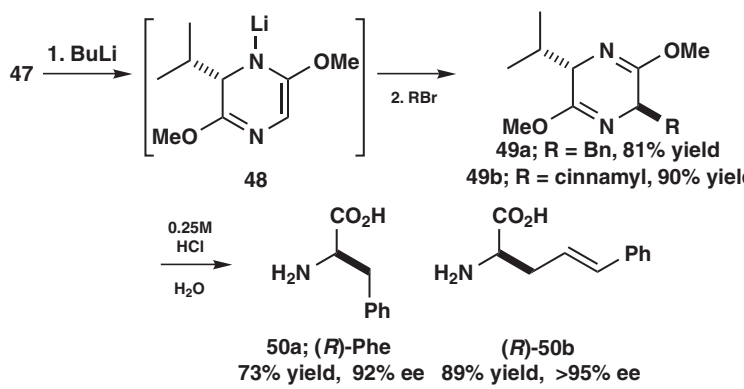
A simpler way to restrict the conformation of an enolate is to confine it in a heterocycle and an important group of chiral enolates come from various derivatives of amino acids. The first successful such compounds were Schöllkopf's 'bislactim ethers' **41** derived from the diketopiperazines **40** formed when an amino acid such as alanine **39** condenses with itself.[4] Treatment of **41** with butyl lithium creates a lithium enolate on one position in the ring: the methyl group in the other position keeps the chirality intact. Alkylation occurs selectively on the opposite side to the remaining methyl group **42** and hydrolysis releases a new tertiary amino acid **43** and one of the original alanines.



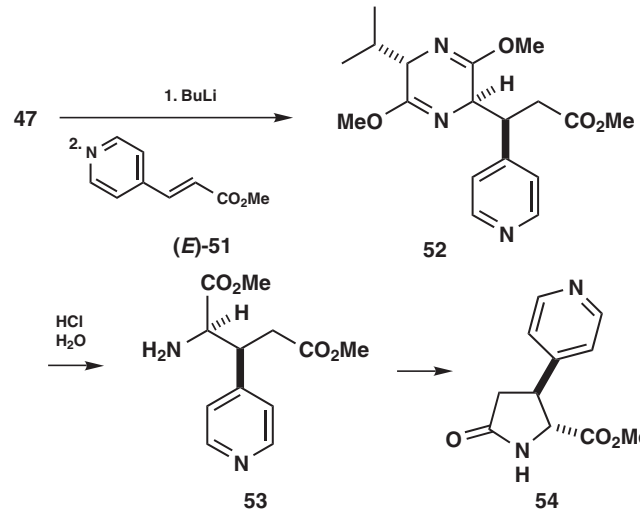
A better version **47** has a larger isopropyl group, derived from valine **44**, to differentiate the faces on the enolate, and no substituent at the enolate site. The starting material **46**, prepared from valine **44** and glycine, is commercially available, as is its *R*-isomer and the derived bislactim ether **47**.



Treatment with BuLi generates chemoselectively the lithium enolate of the less substituted lactim and electrophiles attack the face opposite the branched isopropyl group. Selectivity is good: the purified diastereoisomers can be isolated in over 80% yield and hydrolysis requires only dilute aqueous acid as these are easily protonated imines. These examples show a benzylic and an allylic halide. The first **50a** is unnatural (*R*)-phenylalanine and the second **50b** is an unnatural amino acid.

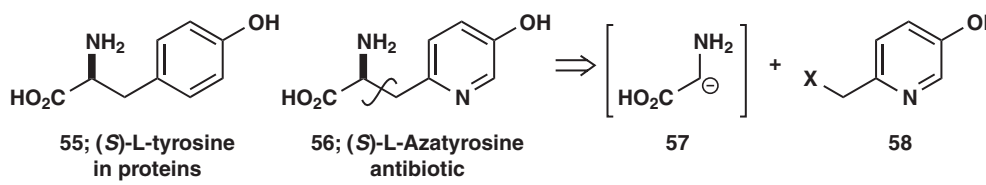


Conjugate addition is also possible with α,β-unsaturated esters and the interesting pyridine derivative (*E*)-**51** gives a 90% yield of the conjugate addition product **52** that is 95% one diastereoisomer. Purification and hydrolysis gives the substituted proline derivative **54** *via* the amino acid **53**. Many variations of this theme have been played with different electrophiles.

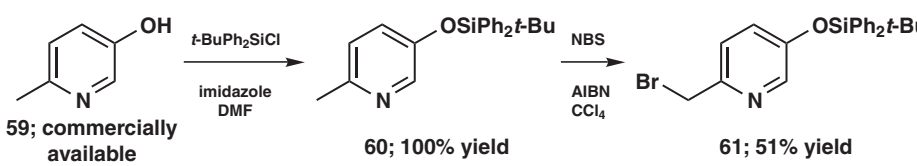


Other chiral glycine enolates: Williams's method

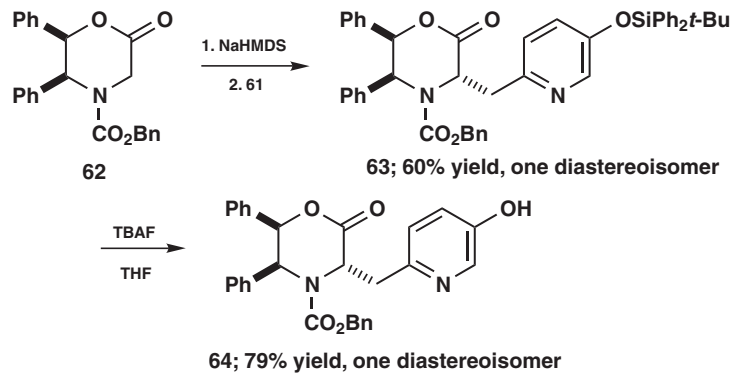
Continuing the theme of pyridine in amino acids we take (*S*)-azatyrosine **56** as an example of Williams's chiral glycine enolate equivalent.[5] The only difference between tyrosine **55** and aza-tyrosine **56** is the nitrogen atom in the benzene ring yet the one is an amino acid found in protein and the other an antibiotic. The most appealing approach to aza-tyrosine is the alkylation of some asymmetric equivalent of glycine enolate **57** and, probably, a protected version of **58**.



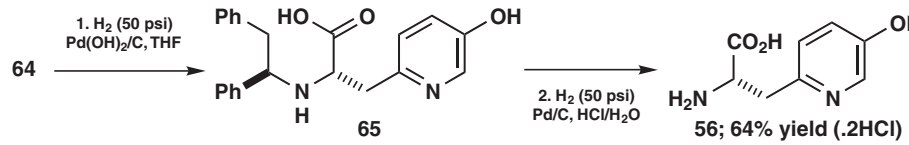
The unusual amino acid **56** has been synthesised[6] by alkylation with the silylated bromide **61** prepared from commercially available **59**. You might notice the radical bromination step giving only moderate yields.



The chiral glycine equivalent **62** is available from Glytech Inc., Fort Collins, Colorado. Its sodium enolate reacts with **61** to give a reasonable yield of one pure diastereoisomer of **63** from which the silyl group is easily removed to give **64**.

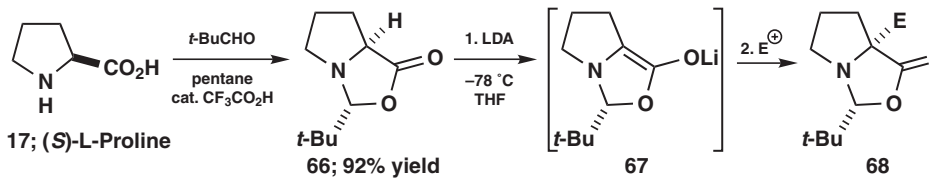


Removing the chiral auxiliary is more tricky. One hydrogenation cleaves both benzylic C–O bonds and releases **65**. This is not isolated but hydrogenated under stronger catalysis in acidic solution to cleave the benzylic C–N bond and release aza-tyrosine **56** as its dihydrochloride. The chiral auxiliary is destroyed in this process.



Seebach's relay chiral units

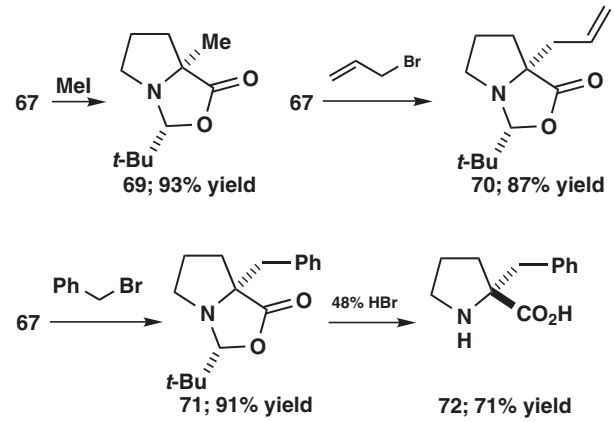
Probably the most important and useful of all these amino acid-based chiral enolates are those of Seebach.[7] The simplest is made from proline **17** simply by forming the *N,O*-acetal **66** with pivaldehyde (*t*-BuCHO). The lithium enolate **67** is alkylated diastereoselectively with various electrophiles E^+ to give one diastereoisomer of **68**.



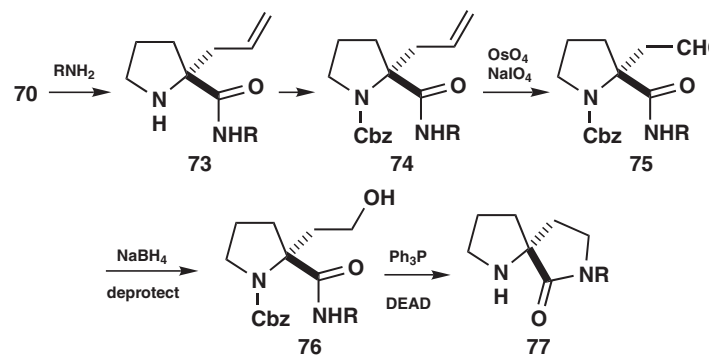
There is a lot to explain here. It looks very odd that *syn*-**66** is preferred and even more so that alkylation of the enolate **67** occurs on the same face as the undoubtedly large *t*-butyl group. Both these issues matter as the original chiral centre in proline is destroyed in **67** and only the newly introduced chiral centre in **66** retains the stereochemical information from proline. This centre acts as a relay for the stereochemical information. Others call this a 'memory' effect. The acid-catalysed formation of the *N,O*-acetal **66** is under thermodynamic control (acetal formation is reversible) and the conformation **66a** shows that the molecule folds about the necessarily *cis* ring junction and the *t*-butyl group prefers to be on the outside (or *exo*- face).[8] The enolate **67** has a flattened conformation **67a** (probably more flattened than this!) and its alkylation is under kinetic control. Attack is preferred on the outside, *exo*-face. Note that this happens to restore the original configuration at the ex-proline chiral centre.

66 66a 67a 68a

The examples below show that alkylation with a variety of groups gives good yields of the purified diastereoisomers shown (**69**–**71**). The last example **71** shows that hydrolysis gives the alkylated proline **72**. As these are tertiary amino acids, there is little chance of racemisation.



Alkylated prolines can be incorporated into synthetic peptides as mimics for the β-turn found in the conformation of folded proteins. One such compound[9] combines a spirocyclic proline derivative **77** with tyrosine. The allyl group in **74** is oxidatively cleaved to give **75** and eventually coupled to the nitrogen atom of the amide in **76** by a Mitsunobu reaction.

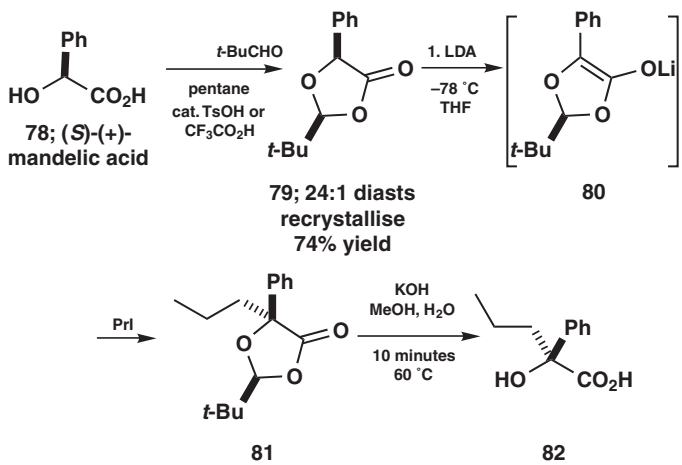


Chiral Enolates from Hydroxy Acids

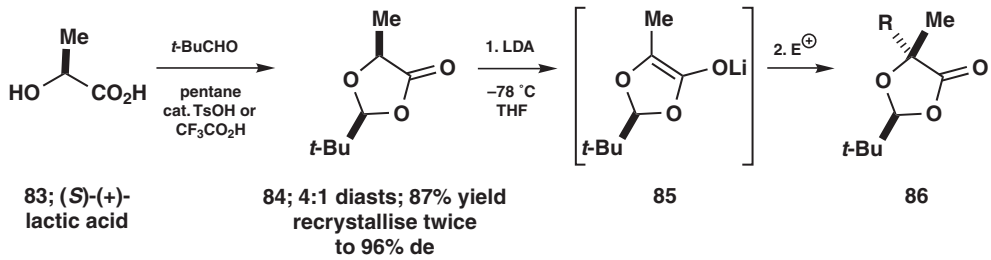
Seebach's relay chiral units

Even more famous is Seebach's related chemistry on hydroxy acids[10] such as lactic and mandelic acids from the chiral pool (chapter 23). Mandelic acid **78** gives the *cis* pivaldehyde acetal **79** in 74% yield after a recrystallisation to remove a small amount of the *anti* isomer. The lithium

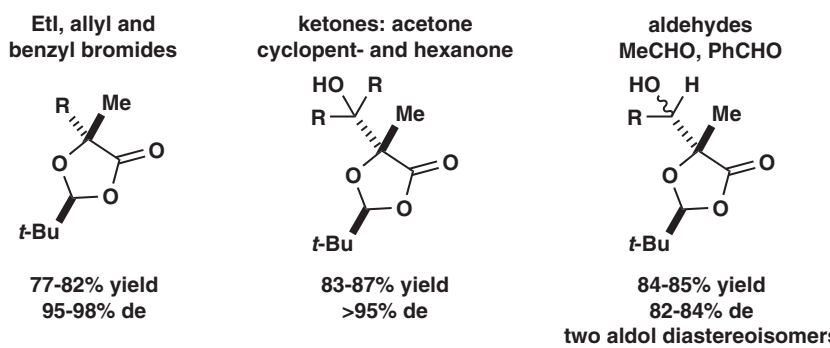
enolate **80** reacts on the side opposite the *t*-butyl group to give **81**. As with the amino acids, the original chirality is restored. Hydrolysis gives the new hydroxy acid **82**.



Lactic acid **83** does much the same thing though the stereoselectivity in forming the initial acetal **84** is not so good - as might be expected with the smaller methyl group.



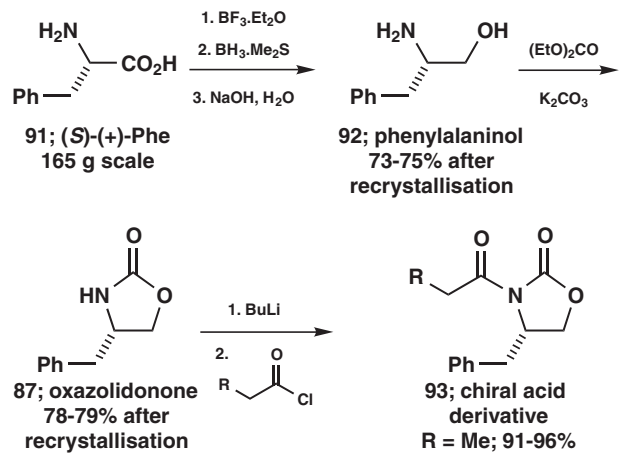
The scope and diastereoselectivity of reactions with various electrophiles are shown below. The only weak point is the poor diastereoselectivity in aldol reactions with aldehydes. These methods have been widely used as they are robust and reliable. Nevertheless the methods we have so far described for chiral enolates are less significant than the Evans chiral oxazolidinones in the next section.



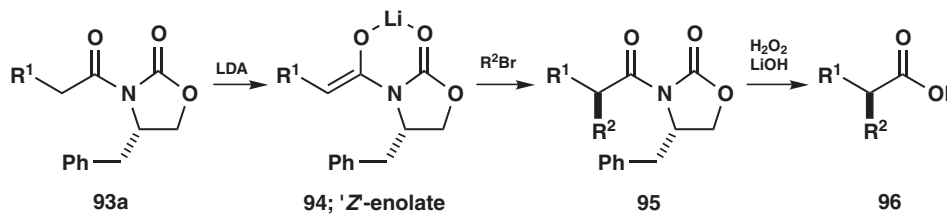
Chiral Enolates from Evans Oxazolidinones

The main Evans oxazolidinones are **87/88**, derived from phenylalanine, and **89/90**, derived from valine. All are available at a price - higher naturally for the unnatural *R*-isomers. Generally **87/88** are preferred as most of their derivatives are crystalline so that purification of diastereoisomers is easier.[11]

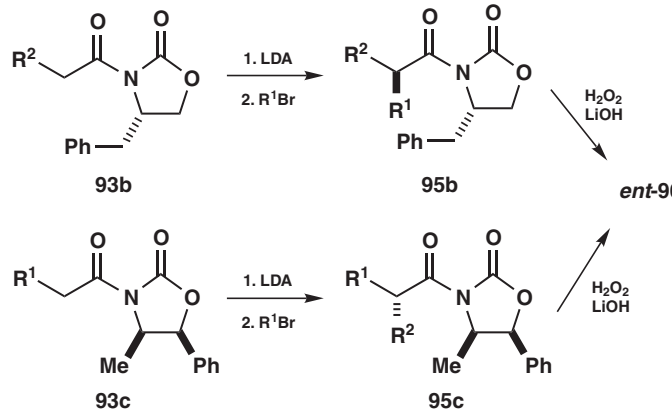
The preparation of each is easy and this is the route to **87/88** as described by Evans[11] in *Organic Syntheses*. Reduction of the free acid **91** with the borane-dimethylsulfide complex is easy if smelly and the rest is straightforward. The same auxiliary **87** can be used with any acid: acylation with the acid chloride gives the chiral derivative **93** ready for enolate formation.



The benzyl group has three jobs to do: (i) force conformation **93a** with R^1 *anti* to N, (ii) Make the 'cis' or '*Z*' enolate **94** selectively from this conformation, and (iii) direct the electrophile to the top face of the enolate to give **95**. Chapter 4 reveals the reason why this enolate is called *Z*. Cleavage of the product **95** to give the free acid **96** is best done with LiOOH made from H_2O_2 and LiOH. This is the best nucleophile for attacking the '*exo*' carbonyl without epimerisation through enolisation.

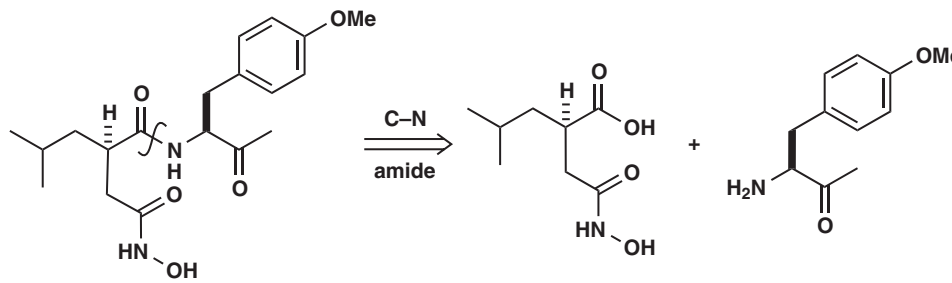


If the other enantiomer is wanted, two strategies are available. Either the alkyl groups can be added in the reverse order, if this is mechanistically reasonable, or the oxazolidine **93c** can be constructed from *nor*-ephedrine from the chiral pool (chapter 23). Hence both enantiomers of **96** can be made in good yield and high ee.

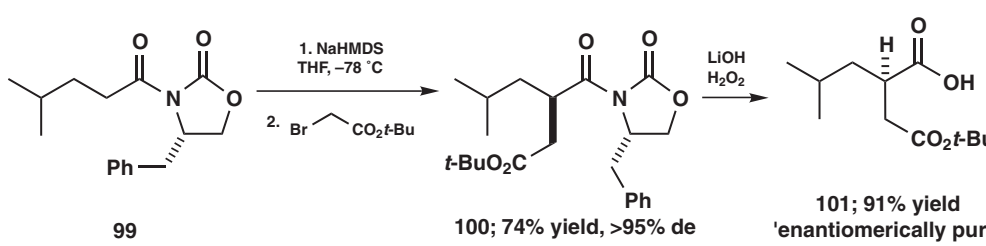


Application of asymmetric alkylation with Evans auxiliaries

Modern treatments for arthritis includes inhibition of the collegenase enzymes that attack connective tissue in the affected joints. One such is the peptide analogue **97** clearly made from a tyrosine derivative and the unusual carboxylic acid **98** also containing a hydroxamic acid. This unusual functional group can be made from a carboxylic acid so the target is a diacid derivative of **98** with the two acids distinguished in some way.



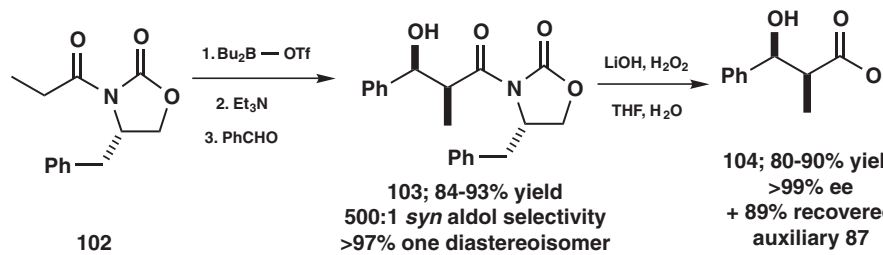
The Evans alkylation method is ideal for this compound.[12] The phenylalanine-derived auxiliary **87** is acylated to make the starting material **99**. The sodium enolate is alkylated with *t*-Bu bromoacetate to give **100** with the expected stereoselectivity. *Exo*-cleavage gives **101** that has one free CO_2H group and one protected as a *t*-Bu ester. This was used to make **98**.



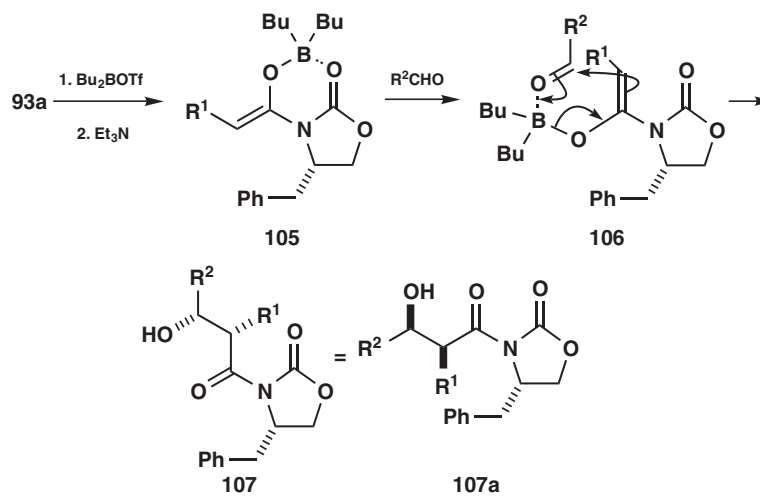
Aldol Reactions with Evans Oxazolidinones

The syn aldol reaction with boron enolates

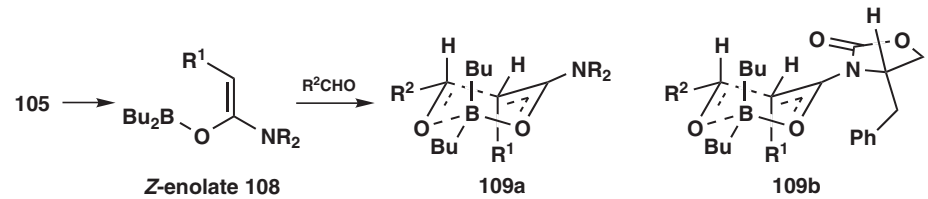
The boron enolate of the starting material **102** reacts with an aldehyde such as PhCHO to give **103** with excellent selectivity: the induction from the oxazolidinone to the methyl group is near perfect and the relative stereochemistry of the aldol[11] is >500:1. Hydrolysis gives the hydroxy-acid **104** in nearly 100% ee and recovered auxiliary **87**.



The stereochemistry is more tricky to understand than that of the alkylations. Aldol reactions of the lithium enolates such as **94** are nowhere near so stereoselective as either alkylation or boron-mediated aldols. The key point is that lithium can coordinate to four different atoms at a time whereas a Bu_2B group has only two spare coordination sites. The *Z*-boron enolate **105** is formed but coordination of the incoming aldehyde to the boron atom displaces the oxazolidinone C=O group and the left hand half of the molecule rotates about the C–N bond by 180° to give **106**. Why it should do this is open to question. Evans suggests that there is better (longer) conjugation as a result. Aldol reaction through a six-membered cyclic mechanism **106** gives **107**, more usually drawn as **107a**.

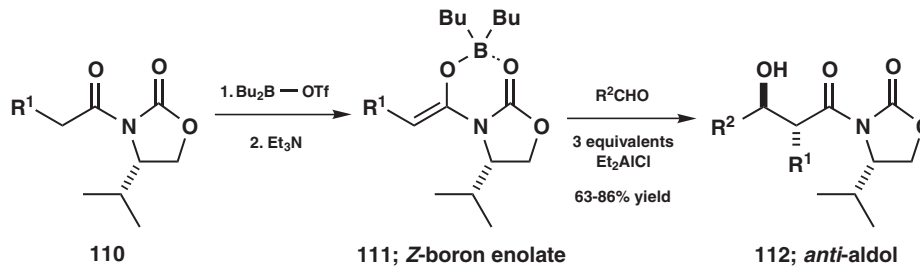


The stereochemistry of the aldol step **106** results from the chair-like conformation of the transition state **109a** with R^1 forced to be axial because it comes from the *Z*-enolate **108** and R^2 choosing to be equatorial (see explanation of simple *syn*/*anti* aldols in chapter 21). The absolute stereochemistry comes from the blocking of the lower face of the enolate by the benzyl group of the chiral auxiliary **109b**.

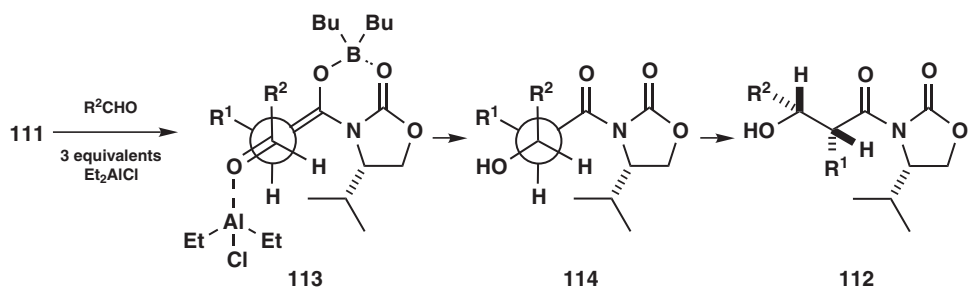


Anti *aldols by Lewis acid-catalysed reactions with Evans oxazolidinones*

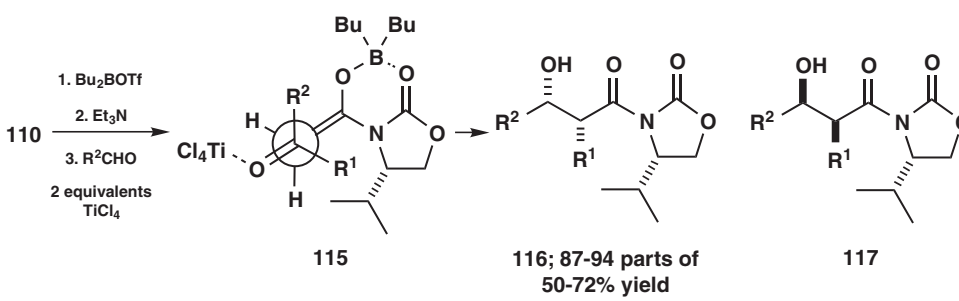
Though either enantiomer of a *syn*-aldol can be made by using the right auxiliary in an Evans aldol reaction the *anti* aldols cannot be made this way. The addition of a Lewis acid catalyst transforms the situation.[13] Using the valine-derived chiral auxiliary **89**, the same *Z*-boron enolate **111** is used but the aldehyde is added in the presence of a threefold excess of the Lewis acid Et_2AlCl. The product is predominantly one enantiomer of an *anti*-aldol **112**.



Instead of complexing to the boron atom, the aldehyde prefers the Lewis acid and the 'open' or 'extended' transition state **113** leading to the stereochemistry shown in a Newman projection as **114**. In fact, as well as the *anti*-aldol **112**, both enantiomers of *syn*-aldols are formed in small amounts - around 5% of **116** and traces of **117**.



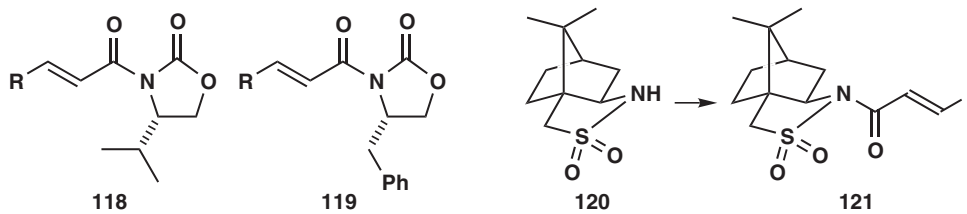
With a 'smaller' Lewis acid ($TiCl_4$) a slightly different 'open' or 'extended' transition state **115** is preferred leading predominantly to one *syn*-enantiomer **116**. These variations on aldol reactions with the Evans auxiliaries allow the synthesis of almost any enantiomer in good yield.



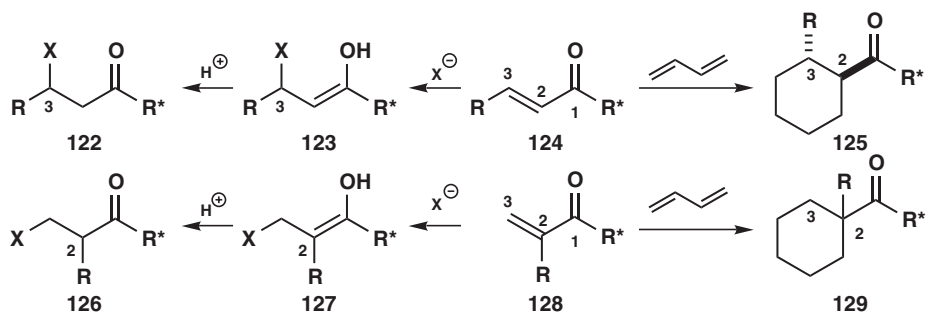
Chiral Auxiliaries

Asymmetric aldol, conjugate addition, and Diels-Alder reactions compared

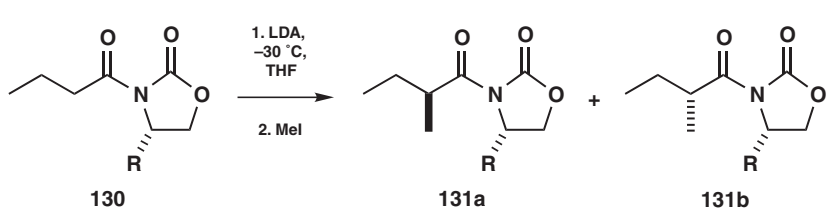
Since conjugate (Michael) addition and Diels-Alder reactions use α,β-unsaturated carbonyl compounds, asymmetric versions of these reactions could use the auxiliaries that we have seen in aldol reactions in the form of **118** and **119**. Diels-Alder reactions work very well with these unsaturated amides and also with amides **121** derived from Oppolzer's chiral sultam[14] **120**, prepared simply from camphorsulfonyl chloride.



There are other considerations than mere analogy. If R* represents some chiral auxiliary, a Diels-Alder reaction on **124** gives a product **125** with two new chiral centres, one, at C-2 in exactly the same place as in the aldol products such as **107**. Michael (conjugate) addition to **124** on the other hand gives a compound **122** with only one new chiral centre (C-3) one atom further away from the chiral auxiliary. Another substitution pattern **128** still creates a new chiral centre at C-2 in the Diels-Alder adduct **129** but this time Michael addition does the same. However, the new centre is not created in the conjugate addition step, as that gives the enolate **127**, but in the protonation of **127**, an inherently less well controlled and probably reversible step. We shall therefore consider Diels-Alder reactions first and tackle the more troublesome Michael additions in the next section.

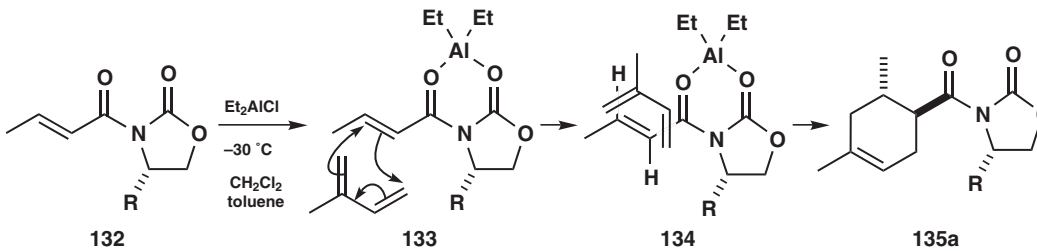


A study of the substituents on the oxazolidinone ring revealed that the highest diastereoselectivity in methylation of the lithium enolate of **122** was achieved when R = *t*-Bu. The normally used auxiliaries, with R = *i*-Pr and Bn respectively, performed less well, but the compound with R = Bn was the best compromise between availability and selectivity.[15]

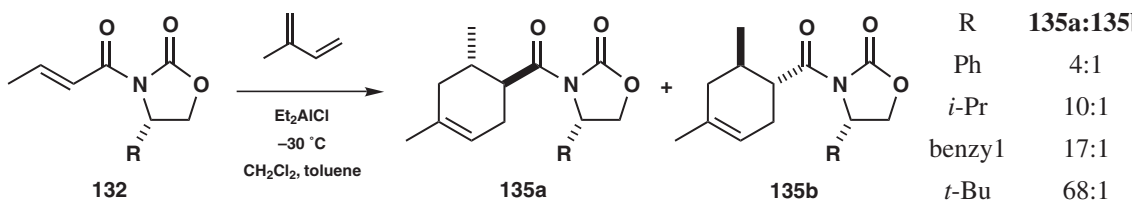


R	**131a:131b**
Ph	2:1
i-Pr	6:1
benzy1	20:1
t-Bu	>100:1

The Diels-Alder reaction with the analogous compound **132** needs Lewis acid catalysis and shows the expected regioselectivity **135**. The predicted stereoselectivity is *endo* addition to the face of the diene opposite group R **133** to give the diastereoisomer **135a**.



The isomer **135a** is indeed favoured and the actual results for the four compounds are remarkably like those for the alkylation. The minor product **135b** has the *anti* stereochemistry across the new six-membered ring but these two centres have the opposite stereochemistry relative to that of the chiral auxiliary. The message is that, in most cases, R = benzyl is the sensible choice but that if it performs poorly there ought to be a big improvement with R = *t*-Bu.

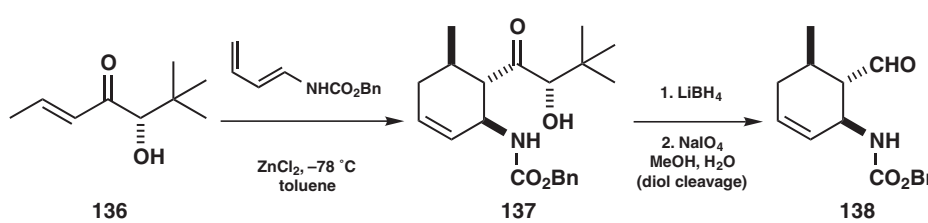


R	135a:135b
Ph	4:1
i-Pr	10:1
benzy1	17:1
t-Bu	68:1

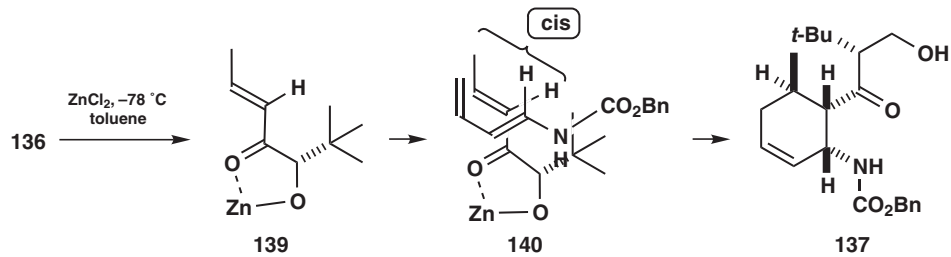
The Asymmetric Diels-Alder Reaction

Introduction

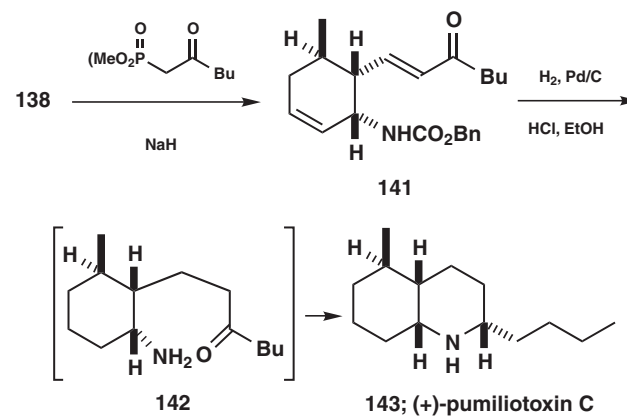
Most asymmetric Diels-Alder reactions have the chiral auxiliary attached to the dienophile as in the example we have just seen.[14] One of the earliest was the blocked α-hydroxyenone[16] **136** that cyclises with electron-rich dienes to give adducts such as **139** and was used in a synthesis of pumiliotoxin **143** based on that of Overman.[17] The weakness here is the cleavage of the auxiliary requires reduction to a diol and periodate cleavage with the inevitable destruction of the auxiliary.



This time the Lewis acid is $ZnCl_2$ and this holds the chiral dienophile in a fixed conformation **139**. Reaction through the *endo* arrangement **140** gives one enantiomer of the product **137** in 67% yield and >99% ee.

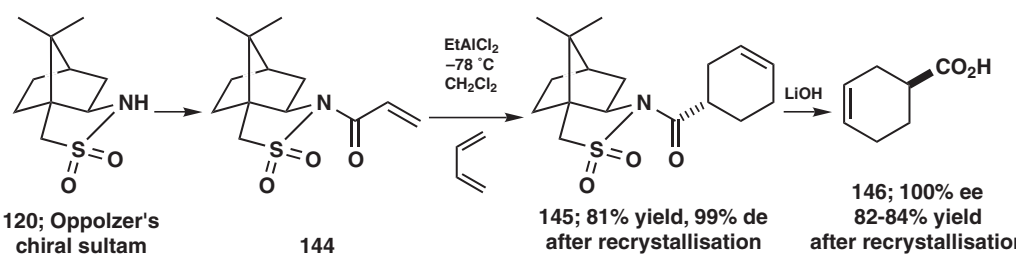


The rest of the synthesis of pumiliotoxin is straightforward involving a Horner-Wadsworth-Emmons olefination (chapter 15) and a hydrogenation that accomplishes reductive amination and the control of another chiral centre. This synthesis is also discussed in chapter 21.

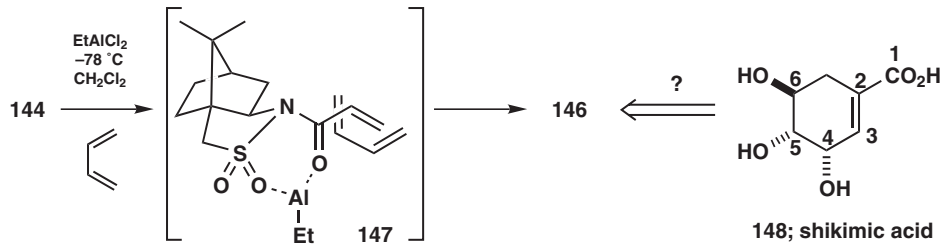


Diels-Alder reactions with Oppolzer's chiral sultam

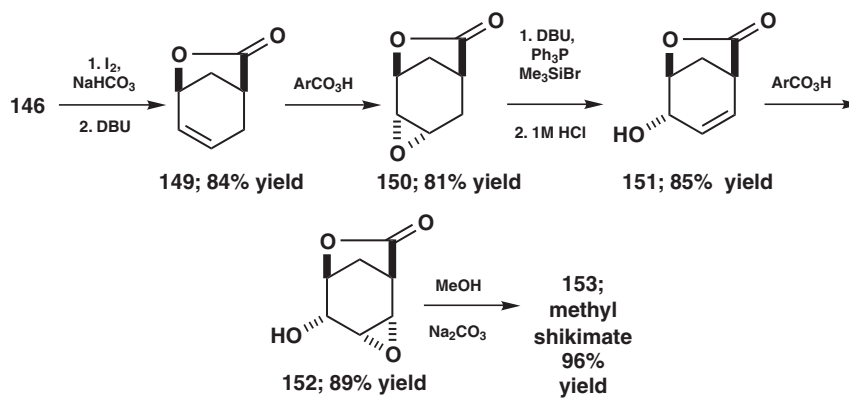
Oppolzer's chiral sultam **120** is easily converted to the amide **144** with α,β-unsaturated acid chlorides and reacts with dienes with the Lewis acid $EtAlCl_2$ as catalyst. The adduct **145** is essentially a single compound and LiOH hydrolysis gives the simplest of all Diels-Alder adducts **146** as a single enantiomer in good yield.[18]



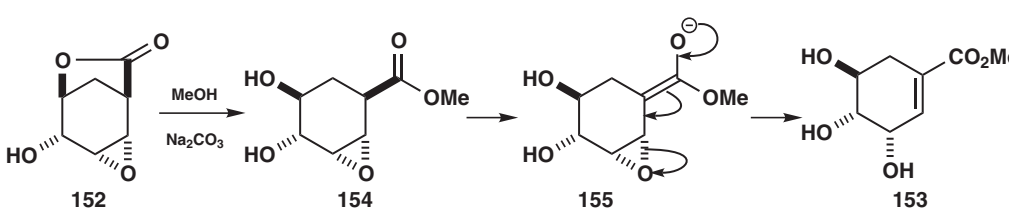
The Lewis acid holds the acylated sultam in conformation **147** and the diene approaches from the less hindered lower face away from the camphor cage. As both enantiomers of camphor are available, either enantiomer of Diels-Alder adducts can be prepared in this way. This one **146** was used in an asymmetric synthesis of shikimic acid **148**, the biological precursor of aromatic rings.[19]



Only relative stereochemistry (chapter 21) now needs to be controlled and an iodolactonisation followed by elimination gives **149**, epoxidation and elimination **151**, a second epoxidation and then simple treatment of **152** with basic methanol gives the methyl ester **153** of the target molecule.

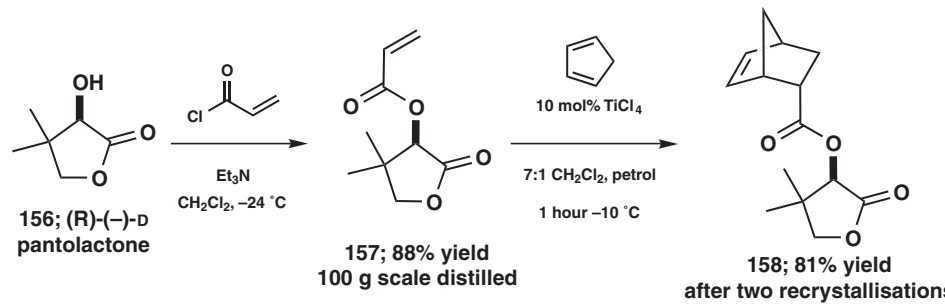


The mechanism of the last step is interesting. The lactone **152** cannot form an enolate as it would be at a bridgehead but after methanol has opened the lactone to give **154**, the enolate **155** can form and immediately fragments. Notice that the original chiral centre, introduced in the asymmetric Diels-Alder reaction, is destroyed in this step after it was used to control the formation of the three OH groups. This synthesis is also discussed in chapter 21.

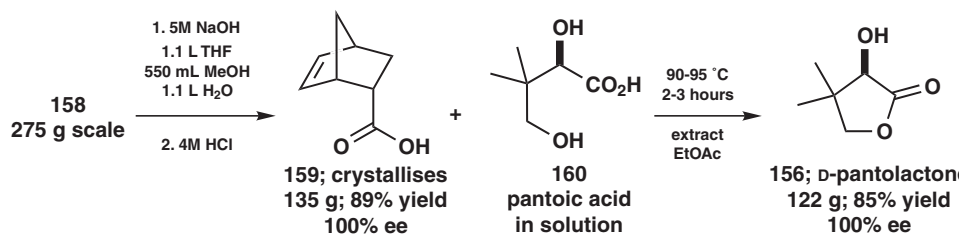


Diels-Alder reactions with pantolactone as chiral auxiliary

We saw pantolactone **156** acting as a reagent in chapter 26. Here it esterifies an unsaturated acid to control a Diels-Alder reaction. It has two main advantages. It is easy to use on a large scale and it is easily removed from the product. The simple acrylate derivative **157** reacts with cyclopentadiene to give essentially pure (by HPLC) adduct **158** in 81% yield after two recrystallisations.[20]

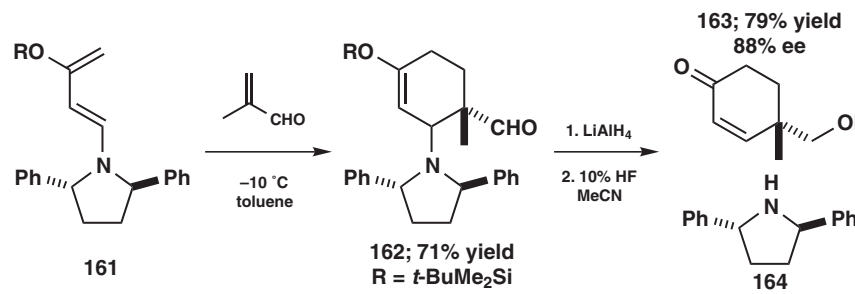


Hydrolysis is simpler than those we have seen before and the separation of the crystalline Diels-Alder adduct **159** from the soluble pantoic acid **160** simplicity itself. Acidification then recreates the chiral auxiliary **156** for the next reaction.

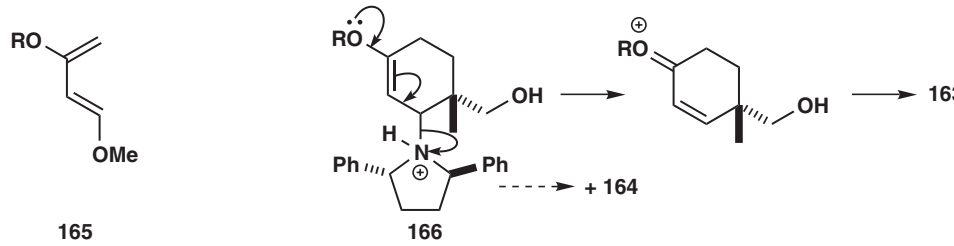


Chiral auxiliaries attached to the diene

Most asymmetric Diels-Alder reactions have the chiral auxiliary attached to the dienophile as an ester or an amide. There is no such obvious place to attach an auxiliary to a diene but the chiral analogue **161** of Danishefsky's diene has a C_2 symmetric amine **164** attached as an enamine. Cycloaddition without a Lewis acid gives good selectivity in the formation of adduct[21] **162**. Reduction and hydrolysis releases the enone **163** in reasonable ee.

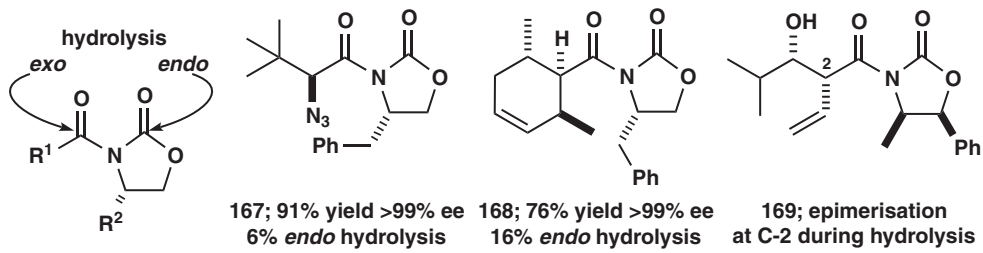


Danishefsky's diene **165** reacts with the same dienophile to give racemic **163**. The hydrolysis of the adduct is much the same in both cases but protonation of the nitrogen atom **166** is easier.

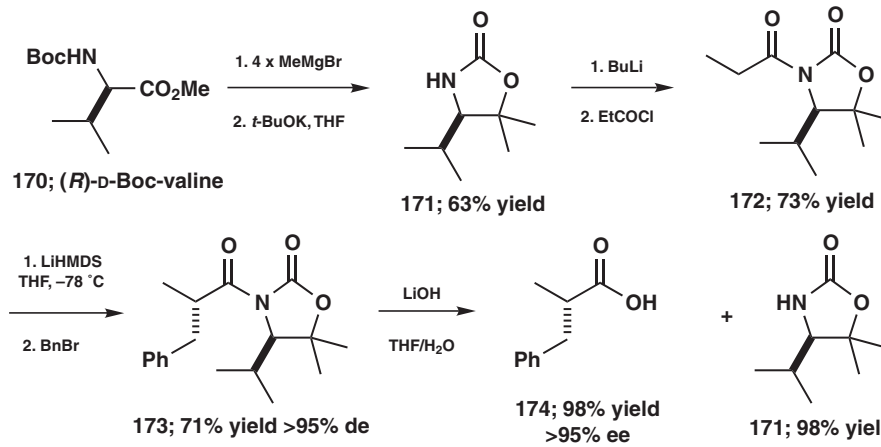


Improved Oxazolidinones: SuperQuats

In spite of the excellence of all these auxiliaries in their various fields, the oxazolidinones remain the most widely useful. And they, like many of the others, still cause problems in the vital step of hydrolysis to remove the chiral auxiliary. Here are three examples[22] where hydrolysis is carried out with the standard reagents: 4–8 equivalents of 30% H_2O_2, then 2 equivalents LiOH in 3:1 THF:H_2O. The first two examples give significant amounts of unwanted *endo* hydrolysis while the last is partially epimerised at C-2.



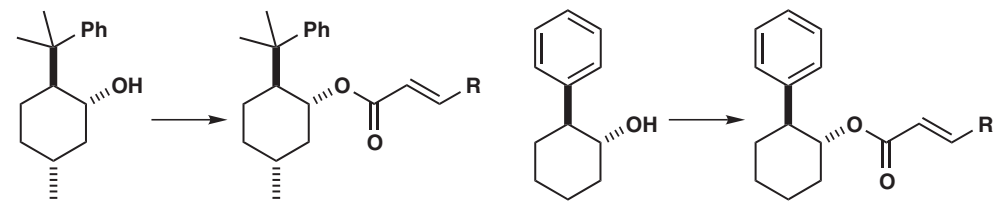
One solution is to make the oxazolidinone ring more resistant to hydrolysis by packing it with substituents. Among the best examples are the 'SuperQuats' developed by Steve Davies at Oxford.[23] Valine (the unnatural isomer in this case) is used to construct an oxazolidinone with two geminal methyl groups **171**. We show a simple alkylation of the lithium enolate: note the high yield of both the final product after hydrolysis **174** and the chiral auxiliary **171** ready for recycling. There is no *endo* hydrolysis nor epimerisation.



Asymmetric Michael (Conjugate) Additions

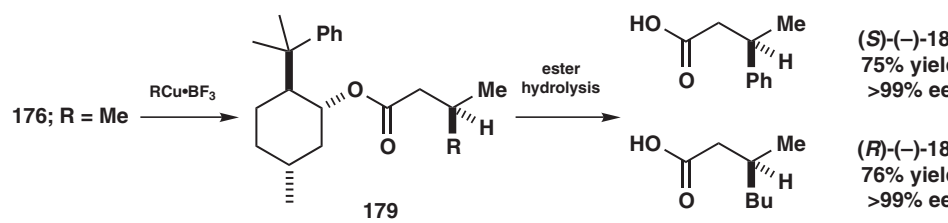
Michael additions with 8-phenylmenthyl esters of unsaturated acids

Though some of the auxiliaries we have been discussing will initiate asymmetric Michael additions, there are two that are particularly effective and we shall discuss mainly those. The first is based on a cyclohexane ring with an equatorial OH and an aromatic blocking group. The most famous is 8-phenylmenthol **175**, made from the natural terpene pulegone[24] (chapter 23) though later discoveries have shown that much simpler auxiliaries, even the bare bones **177** can work quite well.[25]



175; 8-phenyl-menthol **176** **177** **178**

Conjugate additions of organocuprates as their BF_3 complexes ($RCu{\bullet}BF_3$) add with good stereo-selectively to **176**; R = Me even though the nearest stereogenic centre in **176** to the one being created has a 1,5 relationship, evident in the product **179**. Two examples, **180** with an aryl and **181** with an alkyl nucleophile, show high selectivity >99% ee in both cases.[26] Other nucleophiles such as amines and thiols also give good results.[27]

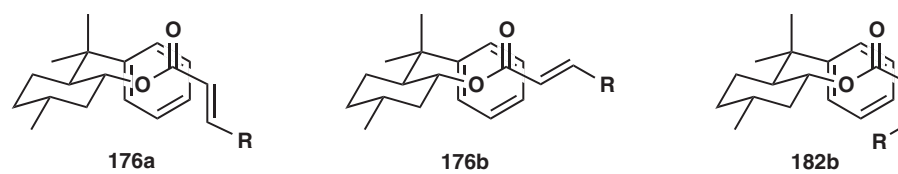


179

(*S*)-(–)-180
75% yield
>99% ee

(*R*)-(–)-181
76% yield
>99% ee

This and many other results, including the much lower diastereoselectivity when the *cis* alkene is used, suggest that π-stacking between the alkene and the benzene ring means that the conformation of **176** in reaction is **176a** rather than **176b**. The same conformation with the *cis*-alkene **182b** would be destabilised.

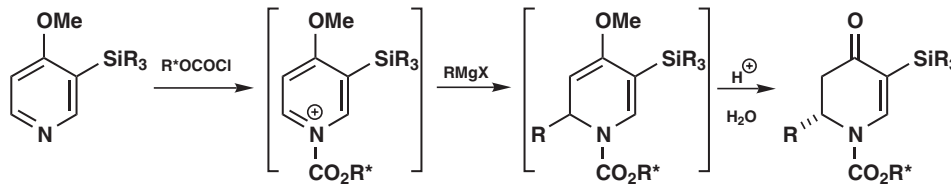


176a **176b** **182b**

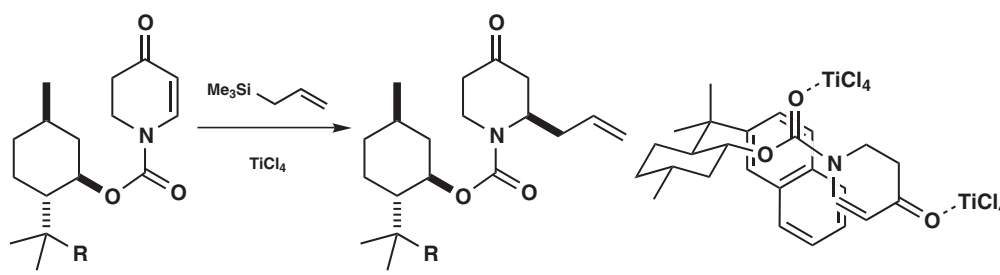
The same auxiliary gives high enantioselectivity in Diels-Alder reactions[28] with cyclopentadiene and butadiene - it gives good yields of **146** used in a synthesis of sarkomycin.[29] In a later section of this chapter you will see it used in asymmetric Birch reduction.

Chiral auxiliaries attached elsewhere in asymmetric Michael additions

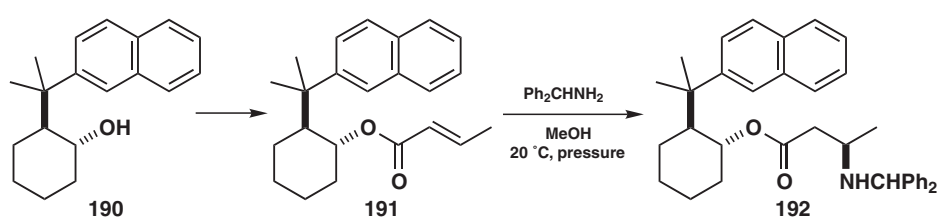
Cyclic α,β-unsaturated carbonyl compounds cannot have a chiral auxiliary attached in the same way. We shall illustrate the many ingenious solutions to this problem with two heterocyclic examples. Both also show the effects of modifications of 8-phenylmenthol. The first is a pyridinium salt **184** and the chiral auxiliary is attached through an ester group to the nitrogen atom of the parent pyridine **183**; R_3Si = TIPS, *i*-Pr_3Si. Addition of a Grignard reagent to the less hindered carbon atom next to N^+ gives the enol ether **185** and hence the enone **186** on workup.[30] Though many variations in the group R* were tried, the best results were with 8-phenylmenthyl itself (R*OH = **175**).



The second is a dihydropyridone with the chiral auxiliary also attached to nitrogen[31] through an ester group **187**. The nucleophile is an allyl silane, requiring Lewis-acid catalysis for reaction (chapter 12). The chiral auxiliary is attached to the opposite end of the electrophilic enone system this time but at about the same distance from the prochiral electrophilic carbon. Though **187**; R = Ph gave quite good results (92:8 in favour of **188**), much better results were achieved with **187**; R = 2-naphthyl (97:3) suggesting that some conformation such as **189**, with good π-stacking making for a very hindered face of the enone, is responsible.

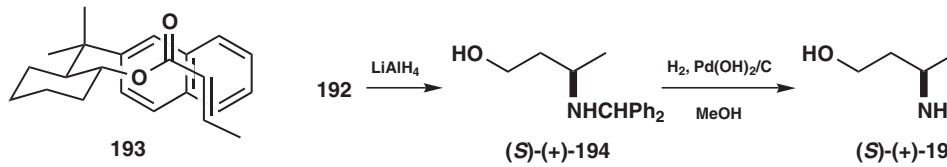


The simpler auxiliaries we mentioned at the start of this section are effective in the addition of amines under pressure to crotonates. Of many auxiliaries tried, the simple *trans* cyclohexanol carrying a β-naphthyl substituent on a tertiary carbon, was the most effective.[25]



The preferred conformation for the reaction is **193** with excellent π-stacking: the nucleophile adds from the front as drawn. These chiral auxiliaries are easily made as either enantiomer so

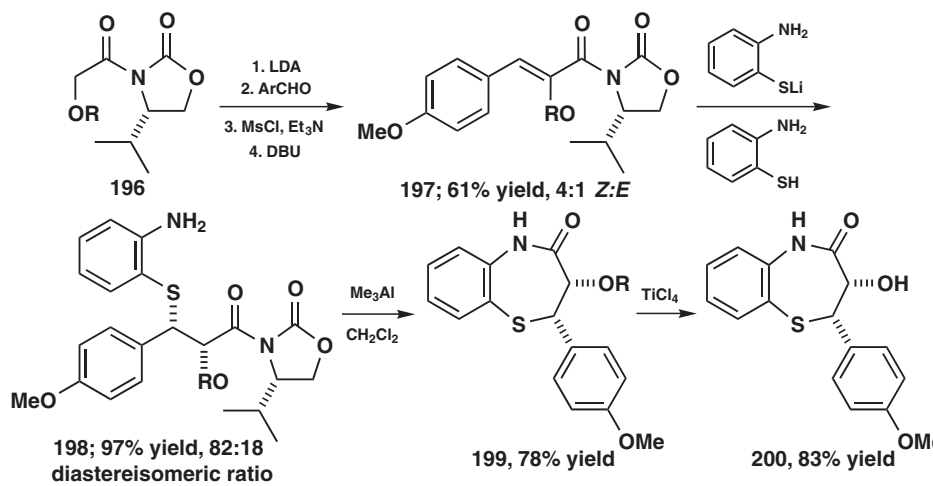
both series can be entered. The chiral auxiliary and protecting group can be removed reductively to give the simple amino alcohol (*S*)-(+)-**195** and this sequence is complementary to the Davies chiral amine addition to unsaturated esters discussed in chapter 26.



Other Chiral Auxiliaries in Conjugate Addition

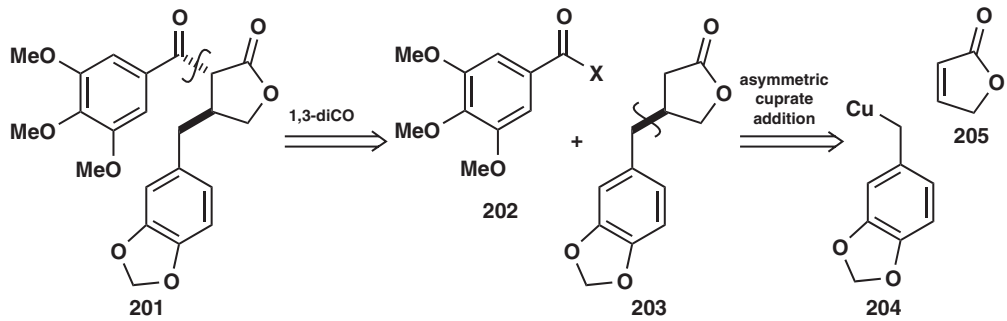
The Evans oxazolidinones

The original Evans auxiliaries have been used in a synthesis of the heart drug (+)-diltiazem **200** based on asymmetric conjugate addition of a sulfur nucleophile. The enone **197** was prepared by an aldol condensation with valine-derived **196** and anisaldehyde. This gave a 4:1 mixture of *Z* and *E*-**197** but fortunately both isomers reacted with an excess of *ortho*-aminobenzene thiol and base to give about the same ratio of diastereoisomers of the adduct **198**. Cyclisation with Me_3Al removed the chiral auxiliary and diltiazem **200** then needs only the removal of the protecting group.[32] This is a rare example of successful asymmetric Michael addition to a trisubstituted alkene.

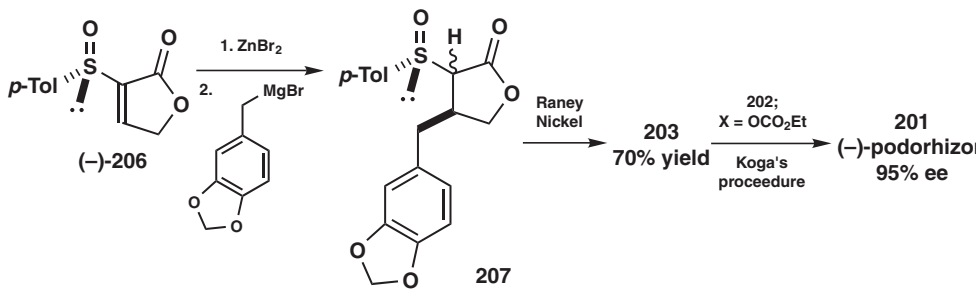


Chiral sulfoxides

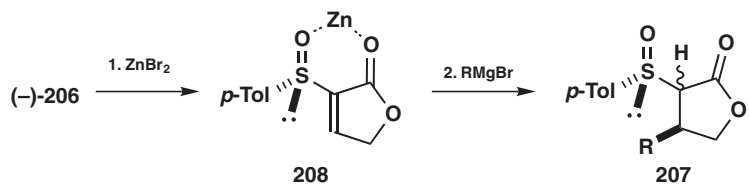
Cyclic enones or unsaturated lactones inevitably have a fixed conformation (s-*trans*), but the chiral auxiliary cannot be attached to the carbonyl group. Chiral sulfoxides can be attached directly to the double bond (cf. enone synthesis strategy of chapter 5) and have been used chiefly by Posner[33] based on work by Solladié[34] in asymmetric Michael additions. Any sulfur-based functional group can be removed reductively with Raney nickel. Posner[35] has used this strategy in the synthesis of the anti-tumour lignan (−)-podorhizon **201**. Acylation of the lactone **203** with **202** would give podorhizon and **203** could be made by asymmetric Michael addition of **204** to the achiral butenolide **202**. But where can the chiral auxiliary be attached?



The answer is at carbon as a sulfoxide **206** to make the butenolide chiral and to enhance the electron deficiency of the alkene, so that a Grignard reagent will do instead of a cuprate. After the sulfoxide is removed and the acylation complete, podorhizon is formed in good yield and 95% ee.



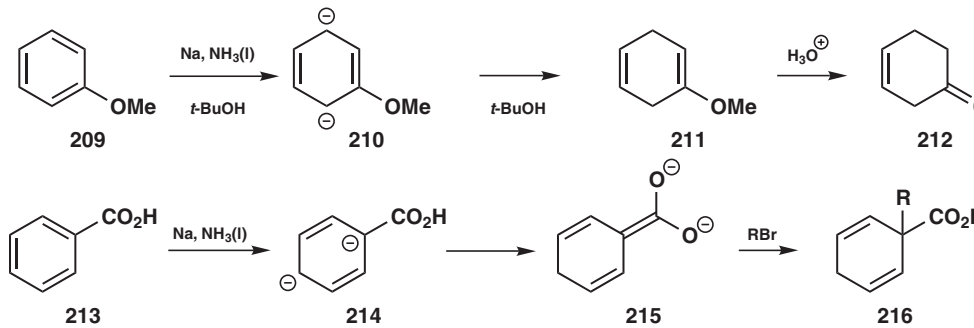
A Lewis acid is needed to hold the sulfoxide in a fixed conformation **208**: addition then occurs to the face of the alkene occupied by the lone pair and opposite to the aryl group.



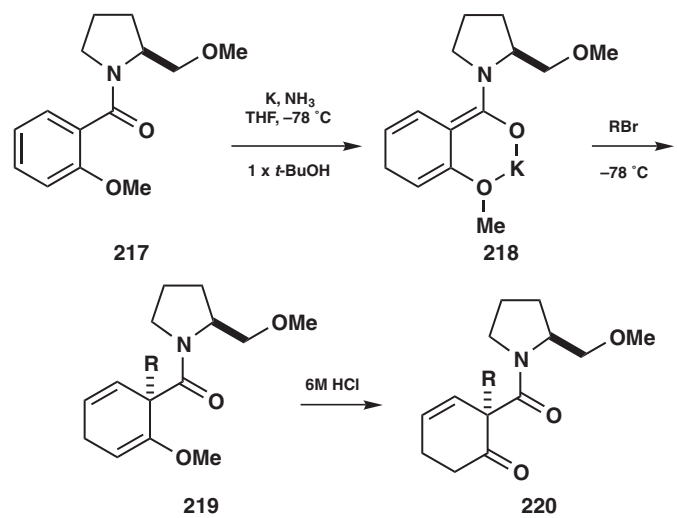
Asymmetric Birch Reduction

Birch reduction of benzene

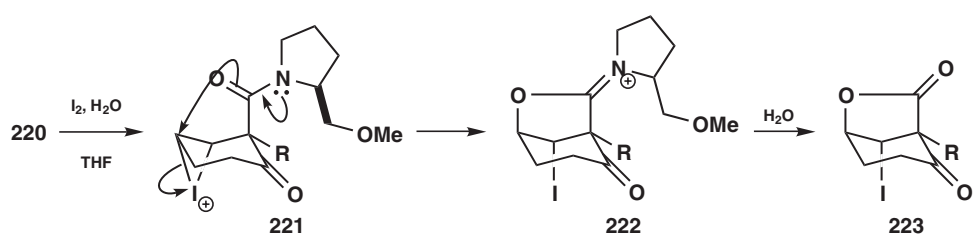
The normal Birch reduction is most interesting when applied to aromatic ethers **209** or acids **213**. The addition of two electrons may make a dianion in which the charges keep away from the ether **210** but conjugate with the acid **214**. Protonation of **210** gives the enol ether **211** and hence the non-conjugated enone **212**. The dianion **214** has a proton which transfers to the less stable anion leaving the enolate **215** that can be alkylated to give **216**. None of these compounds is chiral and there appears to be little scope for asymmetric induction.



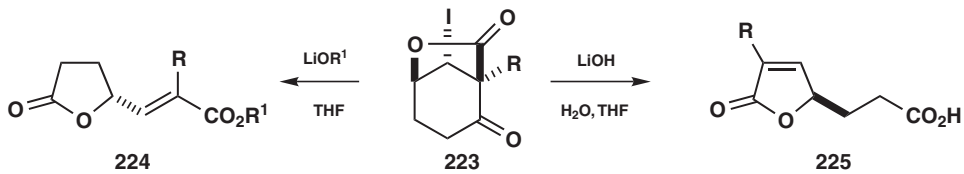
Schultz's remarkable work combines ether and acid in the same molecule and adds a chiral auxiliary (the same proline derivative **26** used in SAMP) to the acid.[36] Both enantiomers of the starting material **217** are available from Aldrich at about the same price. Birch reduction with potassium in ammonia gives the chelated intermediate **218** that is alkylated on the face opposite the CH_2OMe side chain to give **219** and hence **220** by hydrolysis of the enol ether.



An interesting version of iodolactonisation is used to remove the chiral auxiliary from **220**. Iodine attacks the alkene with participation of the amide oxygen atom **221** to give a salt **222** that hydrolyses to the iodolactone **223** with recovery of the auxiliary **26** if required.

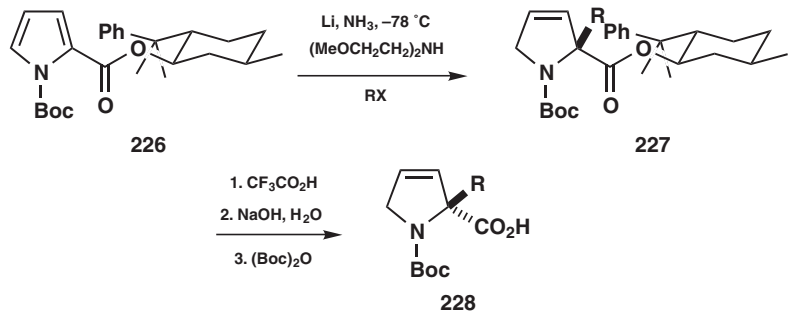


The iodolactone **223** can be fragmented in two different ways by different reagents to give the lactones **224** or **225** that bear little resemblance to the original benzene ring.



Asymmetric Birch reduction of heterocycles

8-Phenylmenthol is the auxiliary in an asymmetric Birch reduction of pyrroles by Donohoe[37] Lithium in ammonia does the reduction and the enolate is trapped with various alkyl halides. Hydrolysis of the esters **227** releases the enantiomerically enriched (78–90% ee) dihydropyrroles **228** in good yield. Furans give similar products with a C_2 symmetric amine as auxiliary. This should become a general route to a variety of heterocycles.



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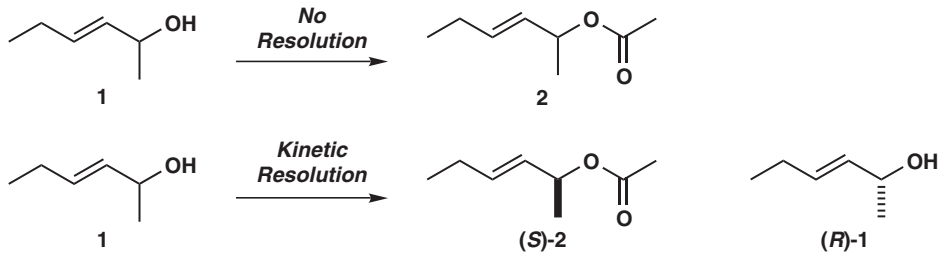
28 Kinetic Resolution

Resolution is the separation of enantiomers. We have seen resolution before in Chapter 22. A kinetic resolution is a resolution which works simply because, under the right conditions, one enantiomer of a racemic mixture reacts *faster* than the other.[1]

Types of Reactivity

With a kinetic resolution, the substrate will already have a chiral centre. The question comes down to how much notice the reaction conditions take of this chirality. So for instance, allylic alcohol **1** could be acylated. Both enantiomers react at the same rate and the reaction pays no attention at all to the chiral centre. For a kinetic resolution to operate, that chiral centre would have to demand attention so that one enantiomer reacted and the other did not.

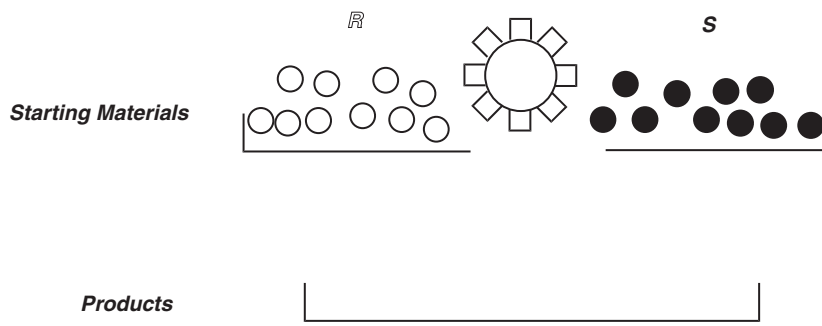
Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren



The reactions above illustrate another point. This simple acylation of a racemic alcohol can be turned, in principle, into a kinetic resolution. We shall see several reactions we have encountered in this book that also can be involved in kinetic resolutions. The above reaction did not create any *extra* chiral centres but that too is possible – even quite common – and naturally adds to the complexity of the reactions.

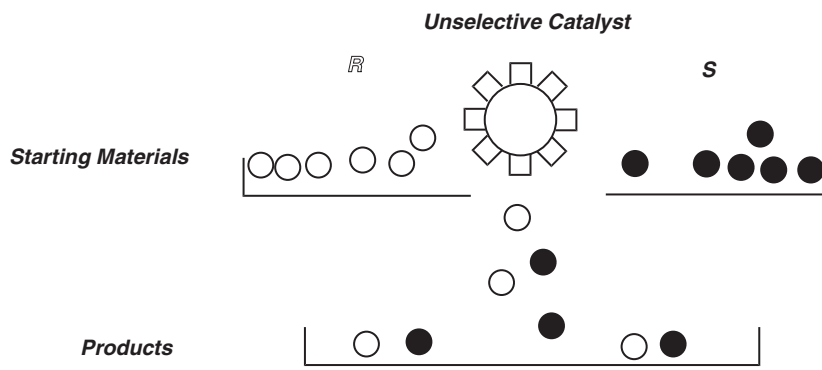
The Water Wheel

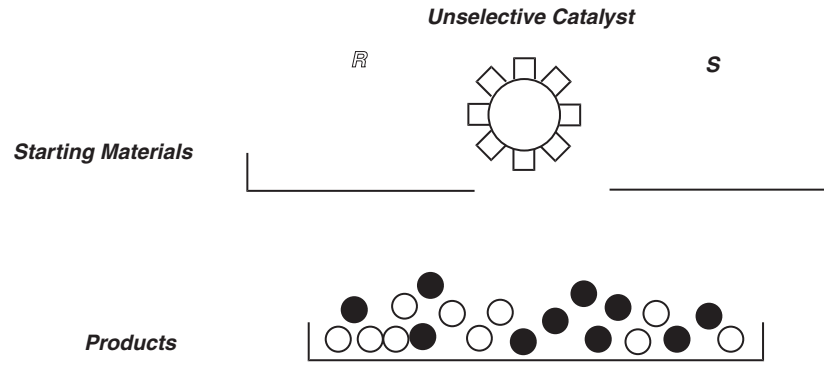
A good visual depiction of kinetic resolution is a water wheel image. Imagine a tray containing black and white balls which have to run through the water wheel in order to get to the tray underneath The black and white balls represent *R* and *S* enantiomers and moving through the wheel is a transformation that yields the products in the tray underneath. This visualisation will also allow us to explain one of the more subtle and crucially important aspects of kinetic resolution—the degree of completion.



An unselective wheel

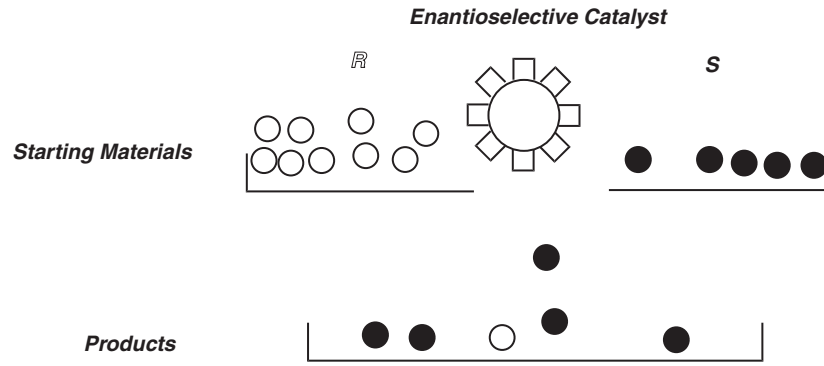
With an unselective wheel, the balls just flow randomly through the wheel and we get a 50/50 mix black and white products and, similarly, the starting materials are consumed in an unselective way.



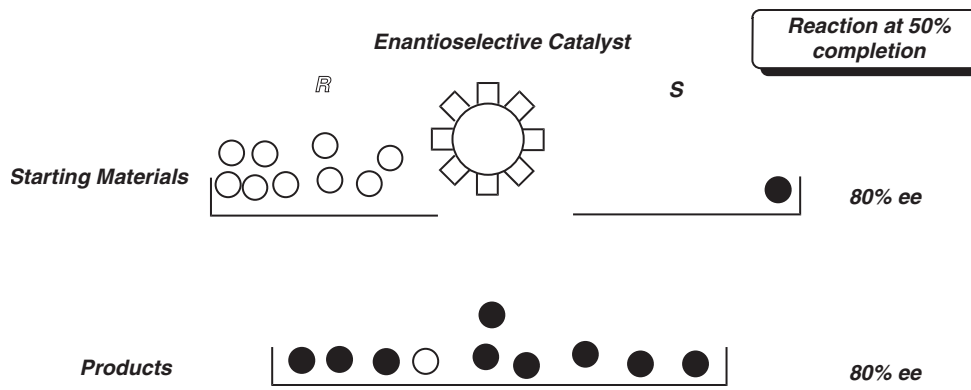


A selective wheel

Imagine now a wheel which is selective for the black balls and prefers to let them through. The result is a product that is rich in black balls and a starting material that becomes increasingly rich in white balls. The wheel is not perfect, however, and occasionally lets a white ball through.

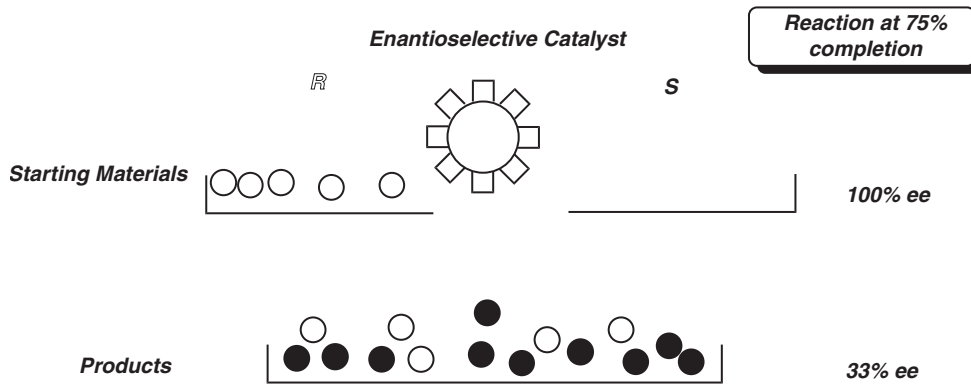


It is instructive to look at *how* rich the products and starting materials are in black and white balls as the reaction proceeds. When the reaction is 50% complete we have 80% ee of product and 80% ee of starting materials. One of the white balls has made it through to the product.



It is a crucial feature of kinetic resolutions that if we want a very good enantiomeric excess in our starting materials then we will have to run the reaction past 50%. It is typical with kinetic resolutions

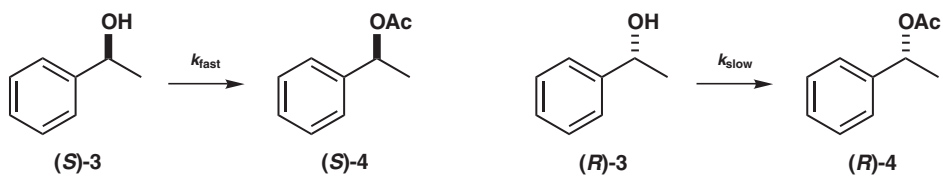
to find that the best quality material is *what is left behind*. If we continue to 75% completion then we can see that all of the black balls have been consumed and the remaining starting material has 100% ee. This is at the cost of the ee of the product of course which has fallen to 33% ee.



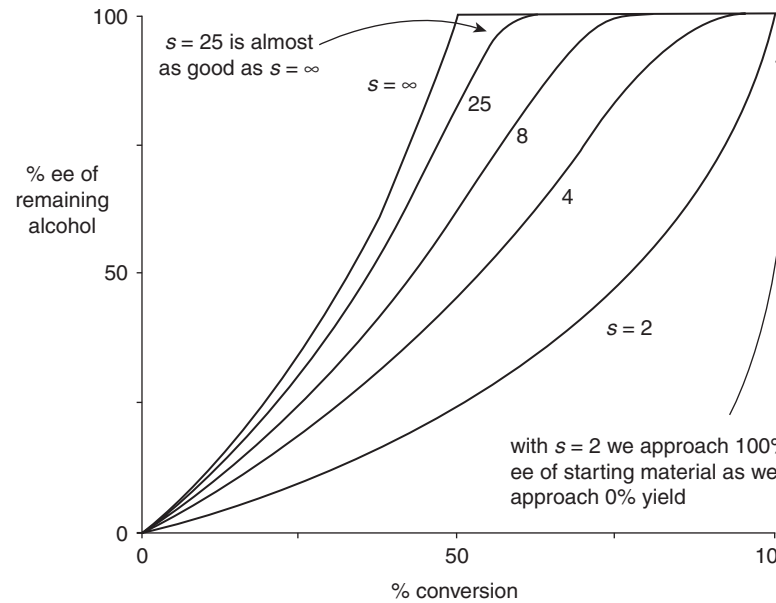
Keep this in mind. When you see a starting material with 98% ee in a paper, look to see how much conversion was needed to leave this sort of quality behind. If only 51% conversion was needed it is excellent, but if the workers needed to run the reaction to 90% conversion, then there can only be at most, 10% of this quality starting material – not so good! We look at this in more detail in the next section.

S Values, Equations & Yields

With the water wheel it is not merely a question of one enantiomer reacting and the other one not. It is, rather, a question of one reacting *quickly* (k_{fast}) and the other reacting *slowly* (k_{slow}). We will see much more of something called the '**s** value' later. This is the selectivity factor and is quite simple: $\mathbf{s} = k_{fast} / k_{slow}$ or, in other words, the relative rate. Consider two enantiomers of an alcohol being enantioselectively acetylated by some means. One reacts fast and one more slowly.



The graph shows several plots which show the % ee of the remaining alcohol **3** against the % level of conversion.[2] This graph would be valid for any standard kinetic resolution. The perfect kinetic resolution where $k_{fast} / k_{slow} = \infty$ obviously gives 100% ee of the remaining alcohol at 50% conversion but it is instructive, and quite amazing, to note that the curve for $k_{fast} / k_{slow} = 25$ is *nearly as good*. It is possible to get nearly 100% ee of starting material even when k_{fast} / k_{slow} is as low as two, but the yield would be approaching 0% because the reaction has to be run until there is hardly any starting material left.[3]



Other symbols used in the realm of kinetic resolution include *C*, the level of conversion where $0 < C < 1$. In a classical kinetic resolution where one enantiomer reacts faster than the other and the other is left behind then the following equation is true.[4] This equation is important as relates three crucial factors—conversion, ee and selectivity.[5]

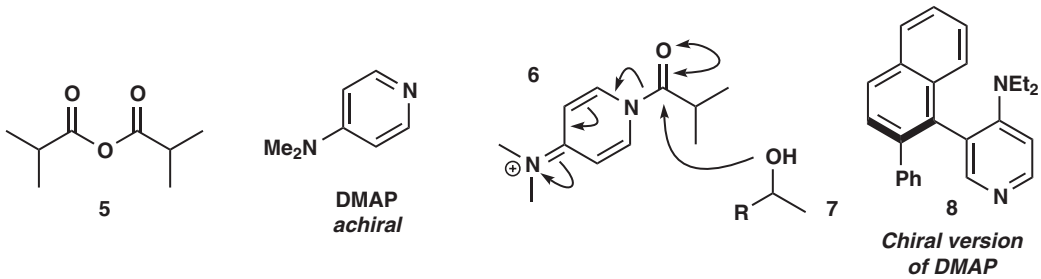
$$S = \frac{\ln[(1-C)(1-ee)]}{\ln[(1-C)(1+ee)]} \qquad \frac{ee}{ee'} = \frac{C}{1-C}$$

The second equation tells us what we already know about kinetic resolutions from the graphical 'water wheel' description—in other words, you can't have it all! A good ee means that you will have to compromise on yield and vice versa. But the better your **s** value, the less severe those compromises need to be. Ee' is the enantiomeric excess of the product and ee is the enantiomeric excess of the remaining starting material. Remember that although the ee of starting material will increase as a reaction proceeds, the ee of the product must go down once conversion exceeds 50%.

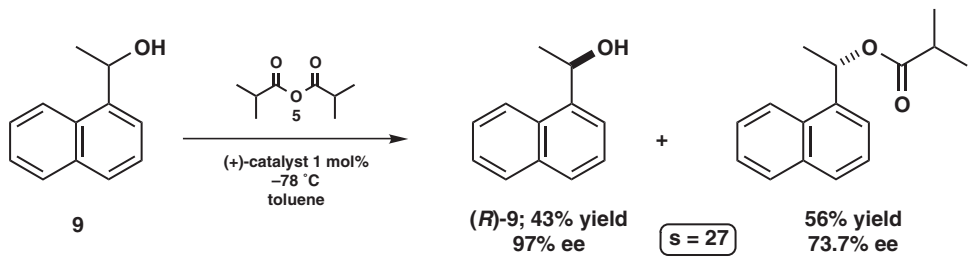
Standard Kinetic Resolution Reactions

Chiral DMAP

Let us return to the reaction we mentioned at the very start of the chapter – the reaction of a chiral alcohol to form an ester. DMAP is used to catalyse the acylation of alcohols reactions by nucleophilic catalysis.

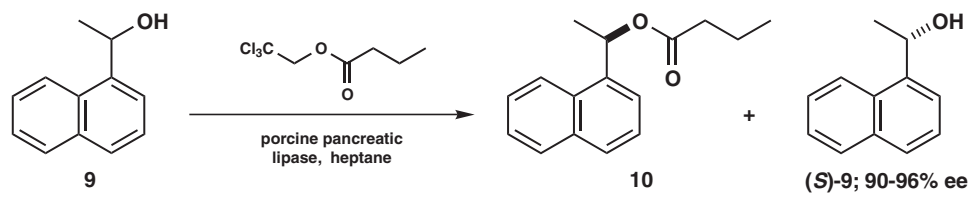


DMAP itself is achiral but a chiral version would make the achiral reactive intermediate **6** chiral. Since the alcohol **7** reacts with this species, there is the possibility that one of the alcohol enantiomers will react more quickly than the other and there will be a kinetic resolution. All that needs is for a chiral version of DMAP to be developed. Because DMAP has two planes of symmetry, this takes some doing. One way that was developed by Spivey *et al.* was to use an axis of chirality.[6] One plane of symmetry is removed because a naphthyl ring is attached on one side and not the other while the chiral axis differentiates the back and front faces of the pyridine ring **8**. For the esterification of **9** the **s** factor was 27 which means good levels of ee in both the starting material and the product should be possible. Indeed 97% ee of the starting material can be achieved at around 56% conversion.



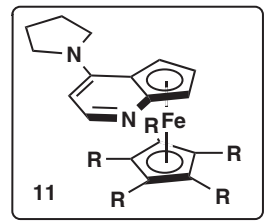
An important consideration with any catalysed asymmetric reaction is the rate of the background reaction. In other words, the reaction of the isobutyryl anhydride **5** with the alcohol *without* the catalyst. This reaction will generate racemic material and so clearly it has to be slow (relative to the asymmetric reaction) if asymmetric catalysis is to be effective.

The same alcohol **9** was kinetically resolved by Heathcock using porcine pancreatic lipase.[7] There

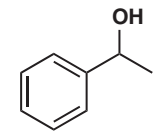


is a striking contrast between the conditions used in the two reactions. The enzymatic reaction is conducted at 60 °C and takes several days! The reactive enantiomer is esterified. Heathcock reveals that the *S* alcohol that remains at the end of the reaction contains 2–5% of the *R* enantiomer. This is upgraded by two recrystallisations to >99.5% ee.

Another chiral DMAP **11** has been developed by Fu.[8] This contains neither a chiral centre nor an axis of chirality and is probably best described as having planar chirality. The **s** factor was improved from 14 to a very useful 43 simply by changing the solvent and reaction temperature The references contain useful sample experimental procedures.[8, 9] Several alcohols including **12**–**15** have been resolved with this but in looking at the ees, remember to note the conversion necessary to achieve them. Clearly the acetylene **15** was more difficult to resolve.[9]

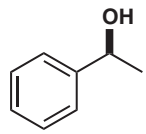


11

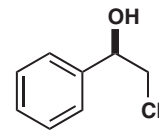


With Ac_2O and Et_3N

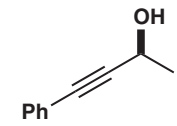
2% catalyst room temp. Et_2O	1% catalyst 0 °C *t*-amylOH
s = 14	**s = 43**



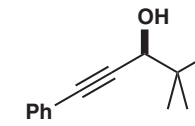
12
99% ee at
55% conversion



13
98% ee at
56% conversion



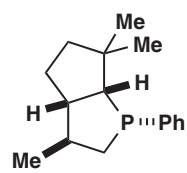
14
96% ee at
58% conversion



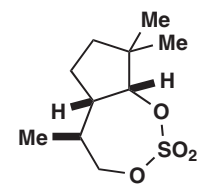
15
95% ee at
86% conversion

While we are on the subject of chiral DMAP it is worth noting that even phosphines[10] can be used to catalyse acylation reactions and some of the **s** values that can be achieved are quite spectacular. The phosphines are bicyclic compounds **16** and **18**. The nature of the phosphine is very important and the focus of the work was not on enantiomeric excess but rather the all-important **s** value.

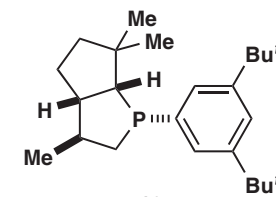
The synthesis of **16** starts using a lactate derivative and makes cunning use of a lithium-binding chain to achieve the selectivity required in producing intermediate **17**.[11] The even better catalyst **18** was prepared from the same key intermediate **17**.



16

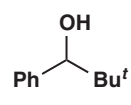


17

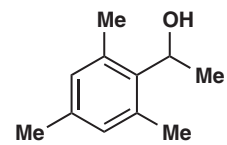


18

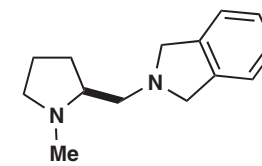
The reaction catalysed by **16** was an esterification with benzoic anhydride and the best kinetic resolution obtained (**s** = 67) with benzylic alcohol **19** was at – 40 °C. A value of 67 is very good for a kinetic resolution. However, exceptional results were obtained using phosphine **18**. This catalyst is effective with a variety of alcohols and conditions. The best result was obtained with **20**, Ac_2O and, crucially, catalyst which had been recrystallised to >99.9% ee. In this instance **s** = 390!



19



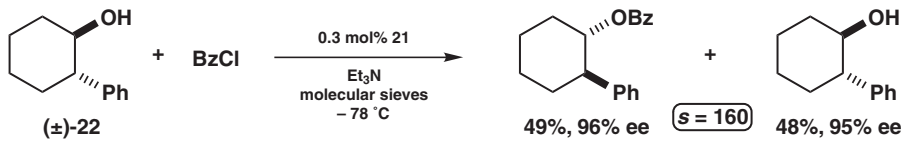
20



21

Vedejs points out that with these high **s** values, the importance of the enantiomeric excess of the catalyst becomes very important.[12] For example, an **s** value of 145 obtained with catalyst with an ee of 99.6% is expected to improve to **s** = 204 with catalyst of 100% ee. With **s** values lower than 40 the effect is much less significant.

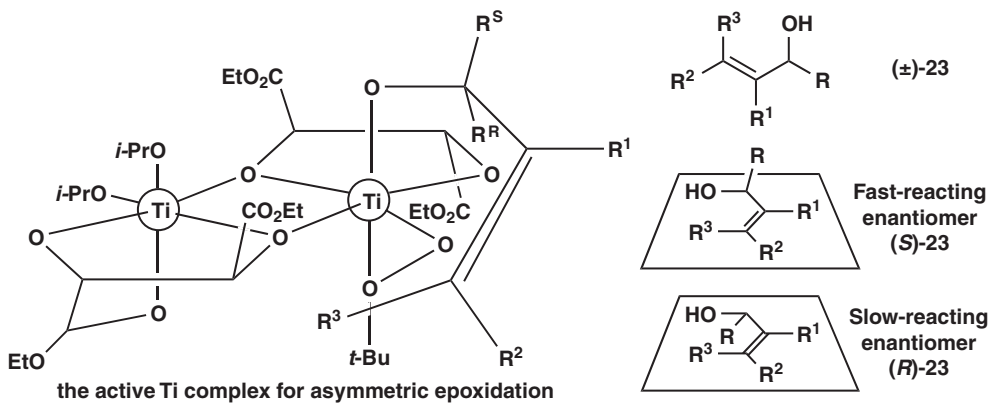
The Fu and Vedejs catalysts are excellent and work with a range of substrates but good kinetic resolutions can be achieved even with some very simple chiral diamines. A catalyst derived from proline **21** was used at low temperature and low loading to resolve the secondary alcohol **22** very effectively.[13] The use of the proline-derived catalysts has been extended to some primary alcohols.[14]



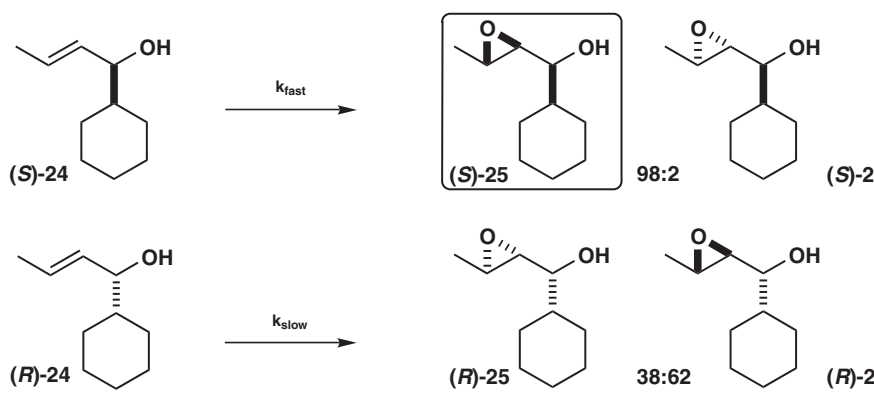
Epoxidation reactions

Perhaps the most famous and widely used kinetic resolution is the Sharpless epoxidation of allylic alcohols[5, 15] – a reaction we encountered[16] in Chapter 25. This is where matters become marginally more complicated than the simplest kind of kinetic resolution because we are introducing *more* chiral centres to the molecules in addition to exploiting the ones that are already there.

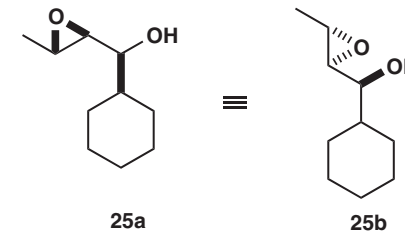
The tartrate complex is the same as the one we have previously encountered in chapter 25. Two enantiomers of allylic alcohol can form two diastereomeric reactive complexes with the single enantiomer of titanium complex. This is illustrated below with, in this instance, the chiral centre at the carbinol carbon of the allylic alcohol. The general allylic alcohol **23** is arranged with the double bond reaching round to the hydroperoxide ready for reaction. In one of the diastereomeric complexes the R group clashes sterically with the titanium complex. In the other complex the R group is able to occupy uncongested space. Not surprisingly, the enantiomer of allylic alcohol **23** that must react via the congested complex is the slow-reacting enantiomer.



A compound which is nicely illustrative of this reaction (and often cited) is allylic alcohol[17] **24**. With L-(+)-diisopropyl tartrate this alcohol has a fast-reacting (*S*) and a slow-reacting (*R*) enantiomer but what is not addressed in the above diagram is that, in principle, both enantiomers could give two different diastereomers **25** and **26**.



With the fast-reacting enantiomer there is good diastereoselection in this reaction too and the main product is **25** in a 98:2 ratio. The slow-reacting enantiomer is less selective giving a 38:62 ratio. It is not uncommon for allylic alcohols in this context to be drawn in a different orientation – **25a** is merely an alternative drawing of **25b**. How *much* faster the fast reaction is depends on the nature of the catalyst. The selectivity increases from dimethyl- to diethyl- to diisopropyl tartrate from 19 to 36 to 104.[18]



25a **25b**

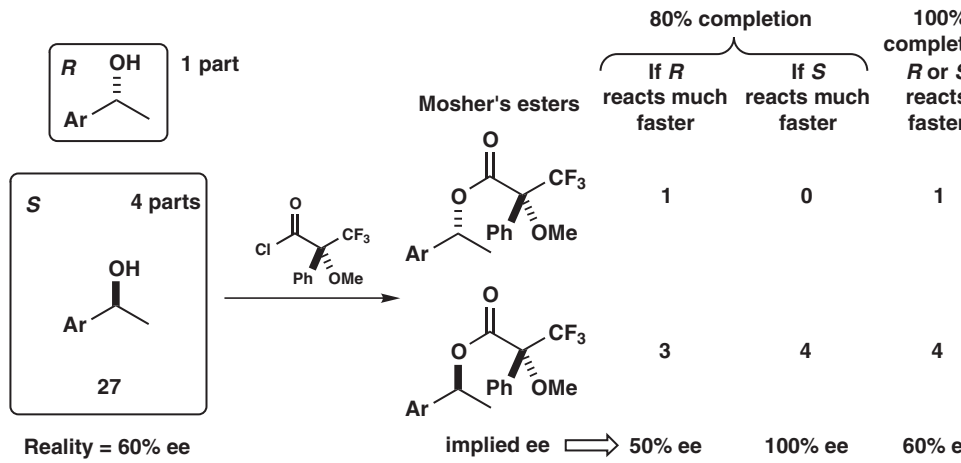
Before the dihydroxylation reaction burst onto the asymmetric scene, asymmetric epoxidation and associated kinetic resolutions were possibly the most popular methods of producing single enantiomers simply because they worked so well. The epoxidation could, for example, be used reliably in undergraduate laboratories.

We will see Sharpless epoxidation reactions in the **Double Methods** section towards the end of the chapter. Interestingly, Sharpless' other famous asymmetric method – dihydroxylation – has *not* found widespread use in kinetic resolution. This is probably because the AD is just too powerful or, to be anthropomorphic, too wilful. In other words, it is not sensitive to the chirality of the substrate and charges ahead and reacts with both enantiomers. That is not to say there are not examples of kinetic resolution with dihydroxylation,[19] but they are more rare. However, the dihydroxylation is even more useful and much more general than the kinetic resolution of allylic alcohols by asymmetric epoxidation and was discussed in Chapter 25. A slightly complicated case of kinetic resolution of alcohols by asymmetric dihydroxylation is in the **Double Methods** section.

Epoxides are a familiar sight in the world of kinetic resolutions. As well as being made by kinetic resolution, racemic epoxides can themselves be the substrates in a kinetic resolution. For example, the use of cobalt-salen complexes – something we shall see again in the dynamic kinetic resolution section – can be used to mediate the formation of enantiomerically pure oxazolidinones.[20] Enzymes can be used to react with one enantiomer of epoxide.[21] And enzymes are a good way to kinetically resolve compounds and can work under surprising conditions – supercritical CO_2 for example.[22]

Unwanted kinetic resolutions

Something to watch out for is unwanted kinetic resolutions. An example is found in the determination of enantiomeric excess by making derivatives like Mosher's esters using an optically pure reagent. Consider the following. An alcohol **27** has been made in 60% ee – four parts *S* alcohol to one part *R* alcohol – but the ee has not yet been determined. Suppose that a reaction to make Mosher's esters is done to 80% completion and that the *R* alcohol reacts very much faster than the *S*.

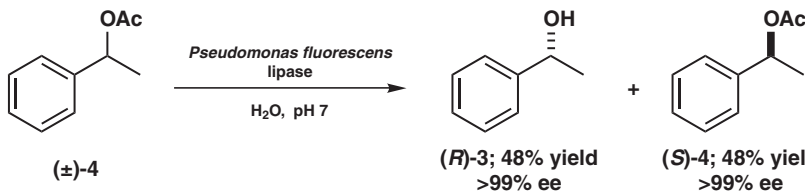


The result would be three parts *S* alcohol (now incorporated into the ester) to one part *R*. The implied ee is 50%. Perhaps worse is the case if the *S* enantiomer reacts very much faster. We would have four parts *S* alcohol to no parts *R* and the implied ee would be 100%!

It is crucial that the reaction is taken to 100% completion so that every last bit of the starting alcohols show up in their derivatives. That way the 4:1 ratio is maintained and the real ee uncovered.

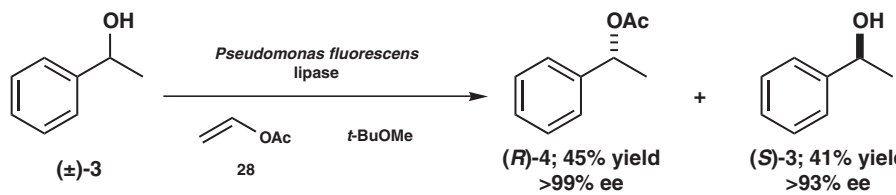
Enzymes

The whole of the next chapter (Chapter 29) looks at enzymes and their application. Nevertheless, it is worth examining a simple case here in the context of kinetic resolution. The selectivity of enzymes is often so good that the reaction can be run to 50% completion so that the enantiomeric excess of both the product *and* the unreacted starting material is excellent. Lipase from *Pseudomonas fluorescens* will hydrolyse one of the enantiomers of the acetate **4** very effectively in water at



neutral pH. Hence the (*R*)-enantiomer of alcohol **3** is produced in 48% yield and >99% ee while the unreacted enantiomer is left behind in 48% yield and >99% ee too!

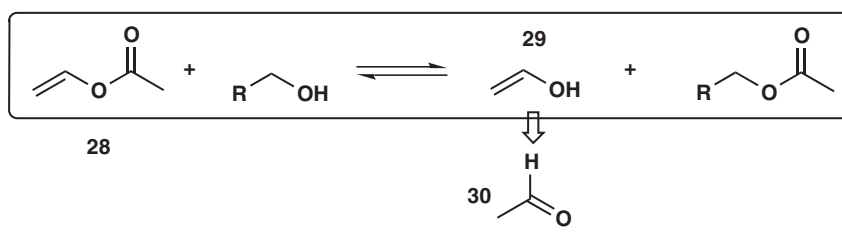
It is the (*R*)-enantiomer that reacts. So if we started with racemic *alcohol* (instead of racemic



acetate) and ran the reverse reaction using the same enzyme, then the molecule that would be left behind would be the (*S*)-enantiomer of alcohol **3**. This does indeed work.[23]

Interestingly, we can thus make *either* enantiomer of alcohol using the same enzyme. However, the yields and ees show us that the reverse reaction is not quite so good. The use of vinyl acetate as the acetylating agent is a common trick and cunning because the displaced vinyl alcohol **29** does not hang about but tautomerises into acetaldehyde **30** – thus removing it from the equilibrium and helping to drive the reaction forwards. The one drawback is that the increasing concentration of acetaldehyde is detrimental to the reaction (presumably by reducing the activity of the enzyme).

Pseudomonas is found in the section below on Dynamic Kinetic Resolutions. We will meet *Pseudomonas fluorescens* again in the next chapter where we also see enzymes in kinetic resolutions with racemisation of starting material (dynamic kinetic resolution).



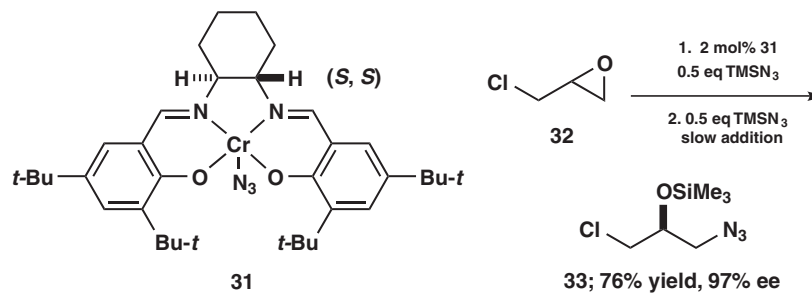
Dynamic Kinetic Resolutions

The biggest problem with a kinetic resolution is that, even with the best selectivity and thus product with 100% ee, your yield is limited to 50%. The unwanted enantiomer goes to waste. A dynamic kinetic resolution (DKR) gives us the opportunity to raise this theoretical maximum to 100%. In the simplest DKR, the starting material is racemised under the reaction conditions but only one of the enantiomers then goes on to react. The continual racemisation of starting material ensures that the unwanted enantiomer never builds up. This racemisation has an added bonus when it comes to selectivity. With a standard kinetic resolution, in becomes increasingly tricky for the reagent or catalyst to be selective for the desired enantiomer as we approach 50% completion because there is so much of the unreacted, undesired material competing for its attention. With a DKR, since there is no such build up, it is less difficult for a reagent to be selective at the end of the reaction.

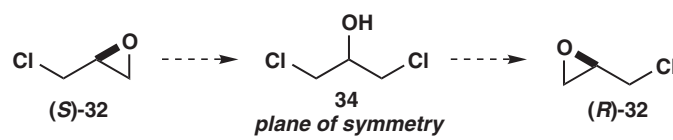
In Chapter 22 we saw resolution with racemisation applied to the synthesis of L-364,718. That could have been described as a dynamic resolution or possibly even a dynamic thermodynamic resolution but *not* a dynamic *kinetic* resolution as it did not depend on one enantiomer reacting faster than the other. Rather it depended on the thermodynamic stability of one crystalline form over the other.

Reaction of epichlorhydrin

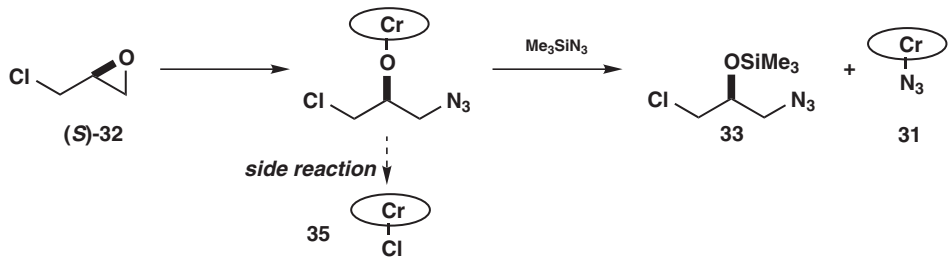
Racemic epichlorhydrin **32** can be dynamically kinetically resolved using a salen chromium complex **31**. The enantiomeric excess of the product **33** is excellent at 97% and the yield 76%.[24]



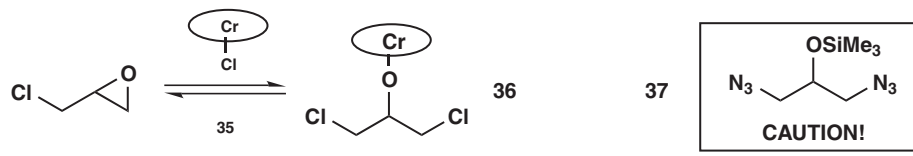
On first inspection of the reaction scheme it looks as though the epoxide is opened with azide and the process mediated by the chromium complex. But this would be a standard KR and give us a maximum yield of 50% – something else must be going on to interchange the two enantiomers of epichlorhydrin. Imagine epichlorhydrin opened by a chloride ion. We would have a species with a plane of symmetry **34** and formation of the epoxide on the other side of the molecule would transform one enantiomer into another.



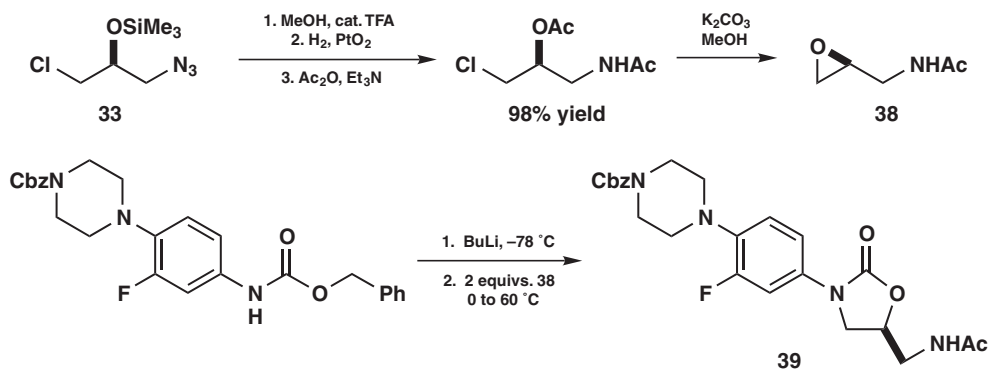
Something akin to this happens in the reaction above. In the normal course of events the azide complex **31** reacts with epichlorhydrin to give an intermediate which reacts with $TMSN_3$ to regenerate the reagent and silylate the oxygen. But there is a side reaction which generates the chloride salen complex **35**.



It is this complex which can add to epichlorhydrin and, in a reverse reaction that may happen from either side, racemise it **36**. Note that under the reaction conditions the azide half of $TMSN_3$ adds quickly but the Me_3Si half slowly – the reactive enantiomer of epichlorhydrin is there to be had at the start but must be made by continuous racemisation in the second part of the reaction. A potential by-product from these reactions is the double azide **37** which the authors think looks suspiciously explosive.

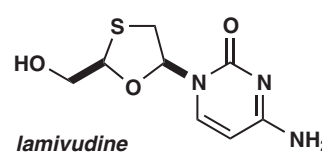


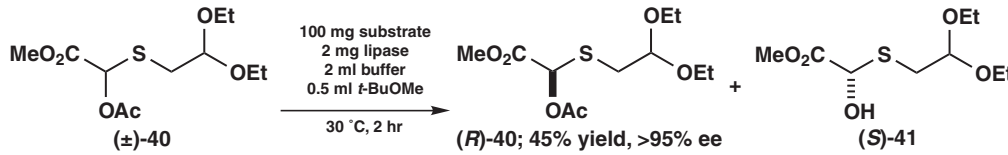
The azide **33** is readily transformed into the convenient reagent **38** which has been incorporated into a final intermediate **38** in the synthesis of the oxazolidinone antibiotic **39**.[24]



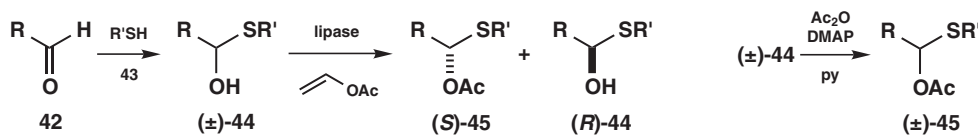
α-*Acetoxysulfide*

A synthesis of lamivudine in optically pure form requires the use of α-acetoxysulfide (*R*)-**40**.[25] This can be produced in optically pure form by a kinetic resolution using the lipase from *Pseudomonas fluorescens*. This enzyme hydrolyses the enantiomer that we do not want and leaves behind the one that we do. The authors investigated a range of sulfide side chains and the acetal **40** that is used in the synthesis of lamivudine worked perfectly.[26] The solvent is important. The use of chloroform instead of *t*-BuOMe gives low ees in the opposite sense.

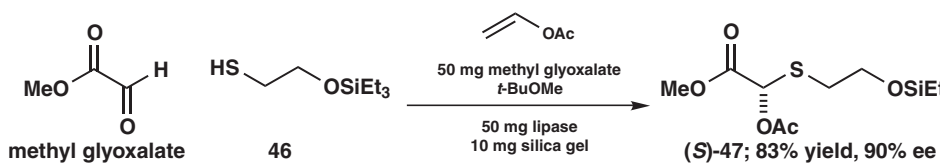




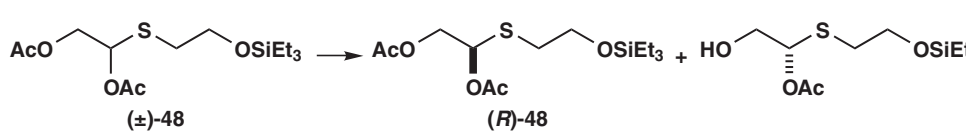
This is the result of kinetic resolutions that we have come to expect and although the selectivities are excellent (ee $>$ 95%) the yield can never be more than 50%. In order to get more than 50% we would need to recycle the unreactive enantiomer.



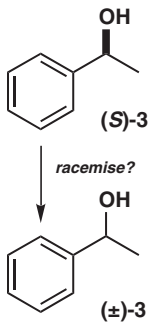
Racemic α-acetoxysulfides **45** can be made by the addition of a thiol **43** to an aldehyde **42** followed by acetylation of the resulting hydroxyl group with Ac_2O.[27] The idea that the lipase from *Pseudomonas fluorescens* might be used to mediate the acetylation instead, using vinyl acetate as the stoichiometric reagent, to give (*S*)-**45** works. But we have still not achieved a *dynamic* kinetic resolution. We would need to return the unacetylated material (*R*)-**44** to starting materials for this to happen. However, it was found that hemithioacetals decomposed during column chromatography on silica to give the starting thiol **43** and aldehyde **42**. This led the workers to the idea of adding silica to the reaction mixture to promote reformation of the starting aldehyde and thiol. It worked.[27] In the presence of silica gel the yield is substantially greater than 50% because the wrong enantiomer of the intermediate hemithioacetal can return to starting materials.



Several thiols were looked at with **46** being one of several that gave high ee of product. Overall the enantioselectivities for the acetylation reactions are slightly higher than those for the hydrolysis reactions which the authors suggest is due to greater conformational rigidity of the enzyme in organic rather than in aqueous solvents. You may have noticed that since this reaction is concerned with the esterification of the (*S*)-enantiomer rather than the hydrolysis of the (*S*)-enantiomer we generate the (*S*)-acetate **47** and sadly not the one that is actually needed for the synthesis of lamivudine! The authors went on to use *Pseudomonas fluorescens* for the hydrolysis of diacetate **48** (a standard kinetic resolution reaction) to give a key intermediate of the correct enantiomer (*R*)-**48**. In this case a primary acetate is hydrolysed.[28]

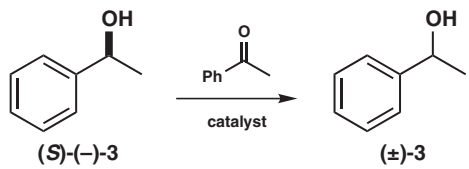


Enzymes and metals together



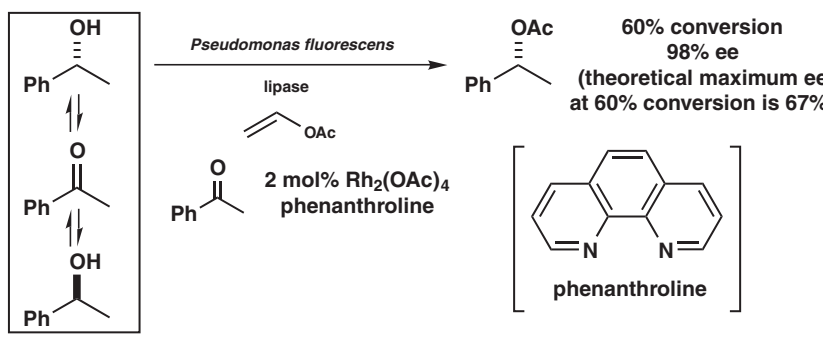
In the above example, an enzyme for the kinetic resolution was combined with silica to provide the dynamic part of a dynamic kinetic resolution. The role of the silica is to racemise the hemithioacetal that does not get acetylated. The racemisation of most alcohols is unlikely to be so straightforward. Consider *sec*-phenethylalcohol **3**; how would we racemise this? Silica is unlikely to do the job.

Williams was in the unusual position for a worker in asymmetric synthesis of trying to find a catalyst that was good at racemisation.[29] An ingenious solution is to use the transfer hydrogenation of acetophenone. If (*S*)-alcohol can be the hydrogen source for the reduction of acetophenone then, so long as there is no enantioselection of any kind, the products will be regenerated acetophenone (from the optically pure alcohol) and racemic alcohol from the achiral acetophenone. Numerous catalysts were investigated including those based on iridium and ruthenium. Two results with aluminium and rhodium are shown below.

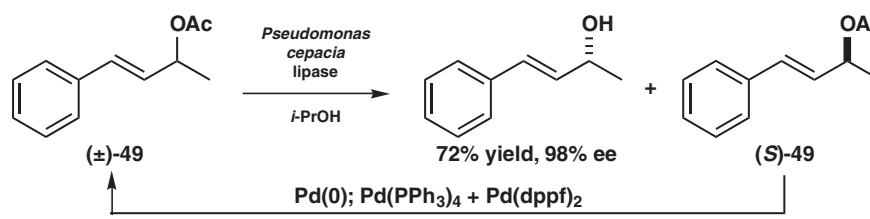


catalyst	yield, ee
20 mol% Al(OPr-*i*)$_3$	80% 0%ee
3 mol% $Rh_2(OAc)_4$ + KOH + phenanthroline	73% 0%ee

The racemisation process was then combined with enzymatic kinetic resolution. The overall picture can be seen below.[29] Racemisation is going on in the box and the lipase from *Pseudomonas* converts the (*R*)-enantiomer of alcohol into its acetate. At 60% conversion the product has 98% ee. The 60% may not seem all that impressive but in a standard kinetic resolution, the *maximum* ee that is possible at 60% conversion (product therefore contains 50% of one enantiomer and 10% of the other) is 67%. Another result gave 76% ee at 80% conversion. The maximum ee of product at this conversion with a kinetic resolution is a mere 32%!

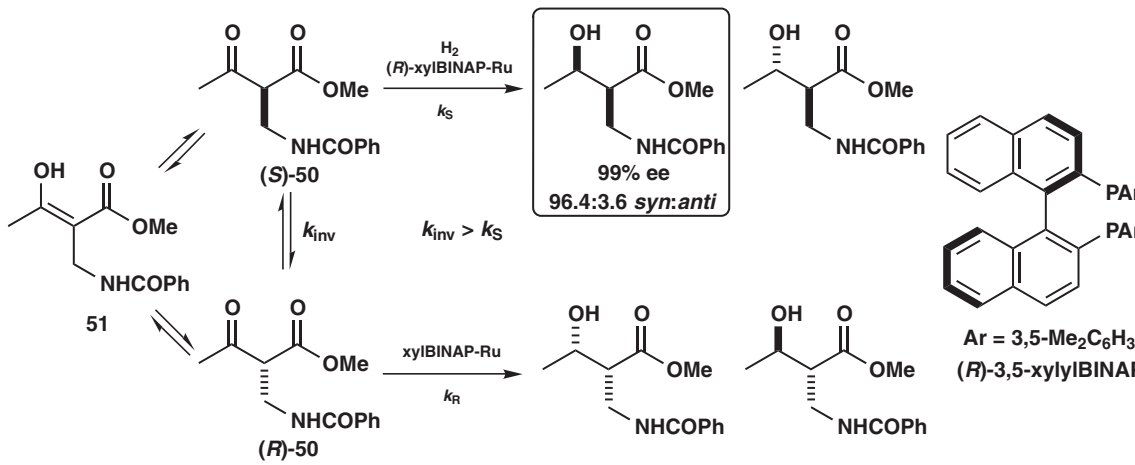


Lipases have also been combined with palladium catalysts to provide the dynamic aspect of the kinetic resolution.[30] In the example below the unreacted allyl acetate (*S*)-**49** is racemised. The formation and reactions of Pd-allyl cations are discussed in chapter 18.



Hydrogenation

Something that we have not addressed is the *rate* at which racemisation occurs relative to the rate of the kinetic resolution. Clearly if the rate of racemisation is too slow, there will be a build up of the less reactive enantiomer. For the best selectivity the starting materials should remain racemic which means that the rate of racemisation must be faster than the fast kinetic resolution reaction. This is the case in the hydrogenation of β-ketoester **50**.[31] Racemisation is fast and occurs via the enol **51**. The product has 99% ee. Most of the impurity is the wrong diastereomer but nevertheless the *syn*:*anti* is a healthy 96.4:3.6. The ligand on the ruthenium is a slightly modified version of BINAP. The phenyl rings of ordinary BINAP are replaced with xylyl rings.



Parallel Kinetic Resolutions

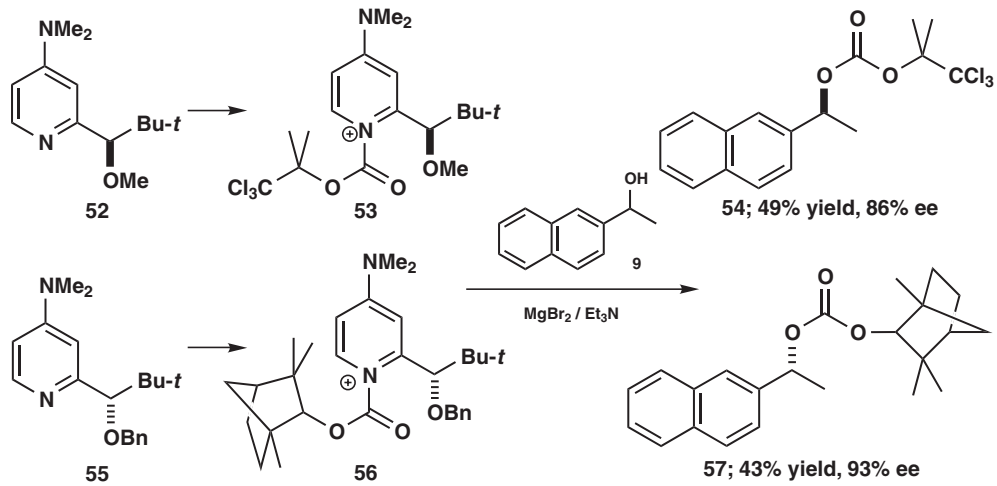
Kinetic resolutions are a bit like a big tin of assorted sweets at Christmas with an aunt who likes to eat the blue triangles. Initially, she has an easy time finding the blue triangles and eating them up—*delicious*. But as time goes on, those blue triangles become more scarce and thus harder to find amongst the red squares etc. Similarly, a reagent selecting an enantiomer from a racemic mixture finds it hard and harder to find the enantiomer it wants. Really what we need is an uncle who eats those red squares.

Alternatively, think back to the image at the start of the chapter with the black and white balls for another analogy. Remember that the wheel is selective for white balls. Towards the end of the reaction, there are hardly any white balls left and the wheel, which doesn't have perfect selectivity anyway, will find it increasingly hard to pick them out. And if all the white balls have gone, then the wheel, if it continues reacting, will be forced to react with the black balls. This is all bad news for selectivity. If there were another water wheel which was selective for black balls (but delivered them to a separate container) then the concentration of black balls would not increase.

With a parallel kinetic resolution, one enantiomer reacts to give one product while the other reacts to give something else. The main advantage is that the increasingly steep uphill struggle is removed since the concentration of the desired enantiomer does *not* decrease relative to the one that is not wanted. The one that is not wanted is being reacted too – but to give something else. Ideally they should both react at a similar rate.

One way to make sure that two enantiomers of starting material react at an equal rate is to use a racemic reagent. But, of course, this is totally useless as we shall just get a racemic

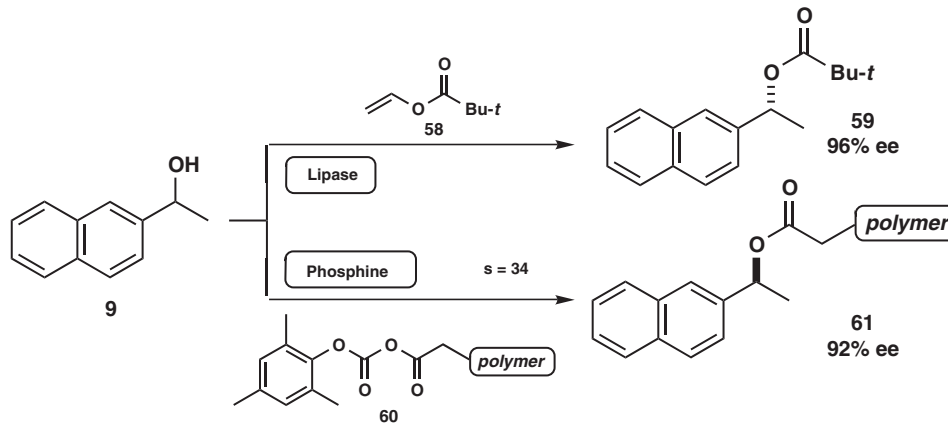
product at the end! However, with a reagent that is *nearly* racemic, as it were, we can achieve parallel kinetic resolution. What we mean by 'nearly racemic' should become clear and such a method was illustrated by Vedejs.[32] The reagent is a chiral form of DMAP which has already been acylated. Note that the reagent is, in fact *two* optically pure reagents that are almost enantiomers of one another. The idea is that one reagent will react with one enantiomer of material and the other with the other and that the products *will be separable*. Each pseudo-enantiomer of reagent (**53** and **56**) delivers a different acyl group so that the 'enantiomers' are different compounds and can be distinguished. Additionally, the trichlorobutyl protecting group can be removed with zinc and acetic acid to give the alcohol (*S*)-**9** and leave the fenchyl carbonate **57** intact.



The main advantage of parallel kinetic resolution is that the selectivity value, **s**, need not be nearly so high to get good results. With a standard kinetic resolution, we would need **s** = 200 in order to obtain both 50% of starting material and product with 96% ee. A parallel kinetic resolution needs **s** = 49 to obtain the same results (there are two **s** values in a parallel kinetic resolution—one for each reaction, we assume here that they are equal). However, we can see that it is quite a business designing a parallel kinetic resolution and for many applications it simply would not be worth the bother if the **s** value is good.

With a parallel kinetic resolution, the two reactions should not interfere with one another. In the example above, both reactions were acylations but the use of stoichiometric reagents meant that the right acylating group was attached to the right enantiomer. Even here, Vedejs does not rule out a small amount of leakage between the paths (once the chiral DMAP is liberated it can get in on the act with the other pathway). A PKR becomes more difficult if, in addition to the reactions being related, they are also catalytic.

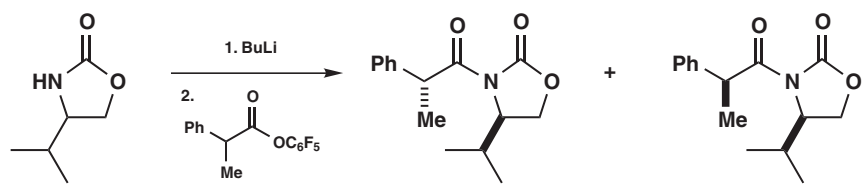
In the example below, one enantiomer of compound is acylated by a lipase and the other by a phosphine-catalysed process.[10, 33] We want the lipase to catalyse the reaction between vinyl pivalate **58** and the *R*-alcohol, and the phosphine to catalyse the acylation of the *S*-alcohol using the polymer-bound anhydride **60**. But, the lipase must not use the polymer-bound anhydride or the wrong enantiomer of alcohol will end up polymer-bound. Similarly, the phosphine must not react with the vinyl pivalate. Fortunately, the phosphine does not react with the vinyl pivalate and the lipase, which is insoluble, cannot interact with the polymer bound material. Also, the lipase will be kept away from the potentially damaging *P*-acylphosphonium intermediates. The conditions are described as a 'Three-Phase System'. The three phases are the solution phase and the two separate insoluble phases of the polymer bound anhydride and the cross-linked lipase.



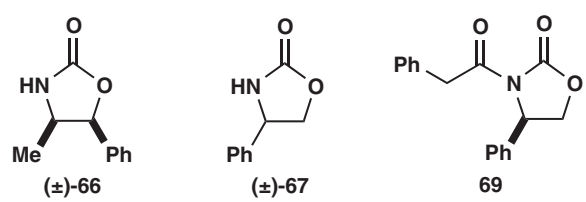
The **s**-values for the lipase route and the phosphine route were not the same, but this is less important than the rates of enantiomer consumption being equal. Hence the relative amounts of lipase and phosphine were adjusted so that the rates of enantiomer consumption were equal. At the end of the reaction, one enantiomer of alcohol is bound to the polymer and the other has formed an ester in solution. They may be separated by filtration. Both reactions have products of higher ee's than predicted for the simple kinetic resolution reactions at 50% conversion. Note that really quite different reagents were used to react with the two enantiomers.

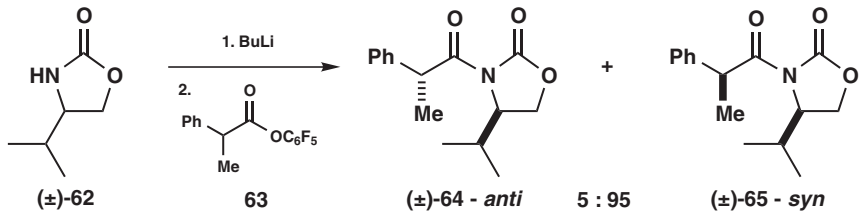
If you have got the idea by now that parallel kinetic resolutions are a complicated business then the next example will show just how simply they can be achieved. Eames set about using different (pseudo-enantiomeric) Evans' auxiliaries to resolve an ester.[34] However, the 'auxiliaries' are nothing of the sort in this reaction. On each side of the reaction, an enantiomerically pure oxazolidinone is reacted with a racemic ester **63** which is to be resolved. A crucial foundation to the work was to establish which chiral oxazolidinones show good selectivity. This was done with racemic oxazolidinones and racemic substrate. Using racemic oxazolidinone exposes the diastereoselectivity of the reaction without the complication of the concentration of the substrate enantiomers varying as the reaction proceeds. It also mimics the environment of the parallel kinetic resolution itself.

Hence it was found that while valine-derived oxazolidinone **62** and phenylglycine-derived **67** gave good selectivity (for the *syn* diastereomer) norephedine-derived **66** did not.



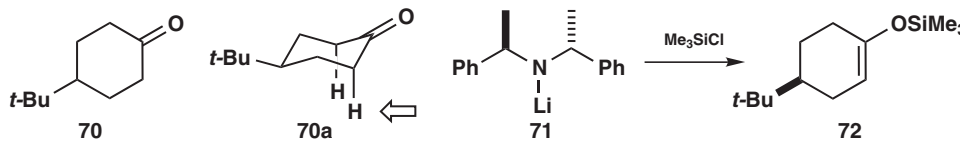
For the parallel kinetic resolution itself, (*S*)-**62** and (*R*)-**67** were used together with racemic ester **63** in an efficient and readily achieved kinetic resolution. Despite the similar appearance of **64** and **68** they could be separated. It is worth pointing out that the major *syn* products are complimentary to the *anti* products to be expected from a standard alkylation of an oxazolidinone like **69**.



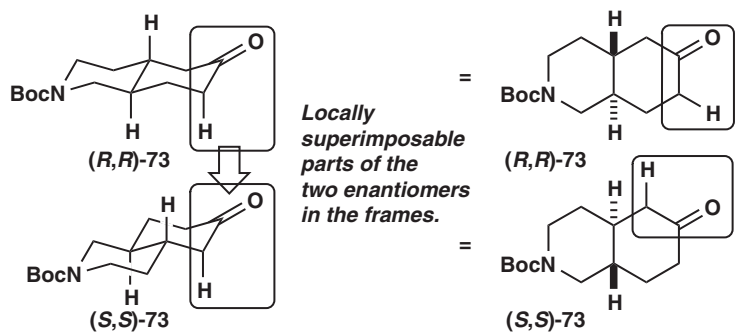


Regiodivergent resolutions

Initially this sort of thing looks like one of those academic fancies that will not actually be of any use to a medicinal chemist working at the coal face of pharmaceutical production. But don't give up just yet, later we come onto applications to regioselectivity in steroid chemistry. In this next example, one enantiomer of substrate reacts with the optically pure base in one way and the other enantiomer in another – hence the 'divergence'. Before we get started with the reaction, the substrate needs careful stereochemical analysis.

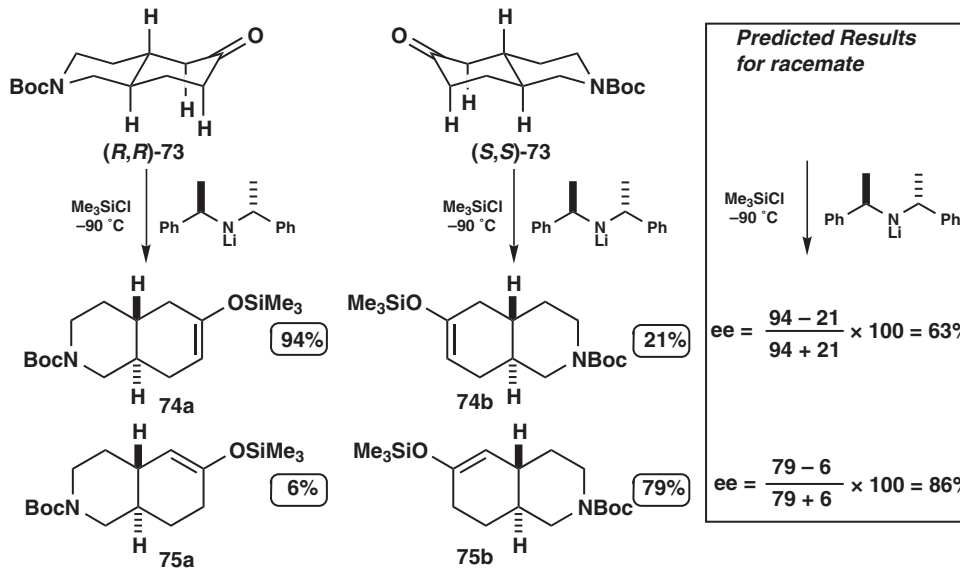


With achiral ketone **70**, an optically pure base **71** chooses between one enantiotopic proton and another to make the enolate enantioselectively. The choosing goes on *within* the compound – there is no enantiomer of the starting material. However, things are a little more complicated when we move to a racemic substrate. The protons on either side of the carbonyl of ketone **73** are not enantiotopic but diastereotopic. The enantiomeric proton can be found in the other enantiomer of compound. We might imagine, therefore, in a straightforward situation, that a chiral base would deprotonate one enantiomer of starting material and ignore the other completely. Thus we would have enantioselection and all would be well. With ketone **73** it is not quite so simple.

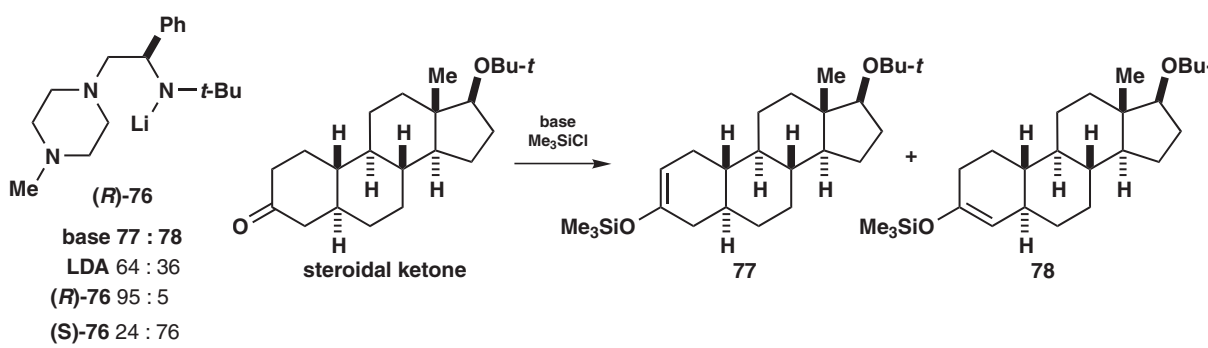


We know that enantiomers cannot be superimposed. However, if we compare (*R*,*R*)-**73** and its enantiomer, we can see that a crucial *part* of each molecule *can* be superimposed. This local congruence in the molecules can be exploited. It is this region that is attractive to the chiral base and it corresponds to different parts in each enantiomer. Thus we can expect the regioselection of one enantiomer to be different from that in the other.

When a single enantiomer of (*R*,*R*)-**73** was reacted with base **71**, a 94:6 ratio of the regioisomeric enol ethers **74** was generated. When the other enantiomer (*S*,*S*)-**73** was reacted with the same base **71** then the preference for the regioisomers was the other way round at 21:79. These numbers are not 6:94 as well because the molecule also has an inherent preference for which position it would like to be deprotonated. For the sake of simplicity we shall ignore this modest match/mismatch issue and move on. So, the question then is what would we expect to see if we had started with racemic **73**. Regioisomer **74** would be generated in 94 parts from one enantiomer and in 21 parts from the other. We would therefore expect the ee to be 63%. Meanwhile, the other regioisomer **75** is generated in 79 parts from one enantiomer **75b** and only 6 parts from the other **75a** so we can expect an ee of 86%. The ees determined experimentally when racemic **73** was used were 60% and 83%. The relative amounts of **74** and **75** we can expect would be (94+21): (6 +79)= 58:42. Experimentally[35] it was 55:45.



Broadly, what has been achieved here is one enantiomer reacting to give one product and the other enantiomer reacting to give the regioisomeric product. Hence the term - regiodivergent resolution. This is really another example of a parallel kinetic resolution. The implications are of more general use, of course, than the rather specialist example given here. Consider for instance the reaction of the optically pure steroidal ketone. Deprotonation with LDA and quenching with TMSCl gives a mixture of the two enol ethers **77** and **78** with moderate selectivity. Before we move on to using a chiral base in this situation, it is worth noting that the use of an achiral base, LDA, has uncovered an inherent preference (in a kinetically controlled reaction) of the molecule itself – this was something we ignored with ketone **73** but which was clearly present too.[36] Anyway, by making use of an optically pure base, we can either improve the selectivity or overturn the molecules' preferences. Both of these options are useful.



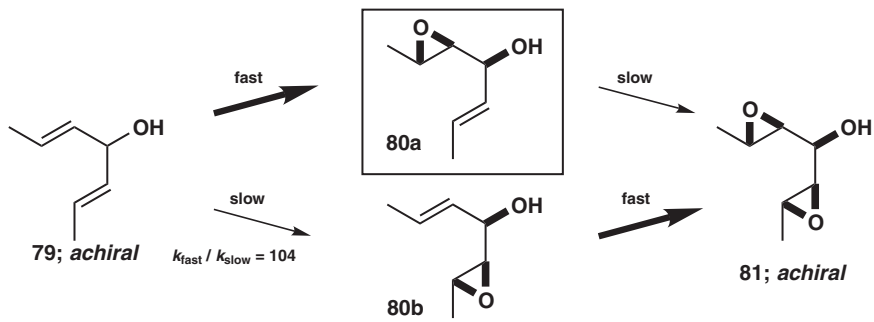
Double Methods

If a selective process can be applied *twice* then we might expect the quality of the resulting material to be very high. In the next example, the selective process is applied first to produce mostly a single enantiomer. When applied the second time, it removes the small amount of the wrong enantiomer that was produced the first time round! In Chapter 25 we mentioned that desymmetrisations and kinetic resolutions were brothers. Both are used in each of the examples below.

Desymmetrisation then kinetic resolution

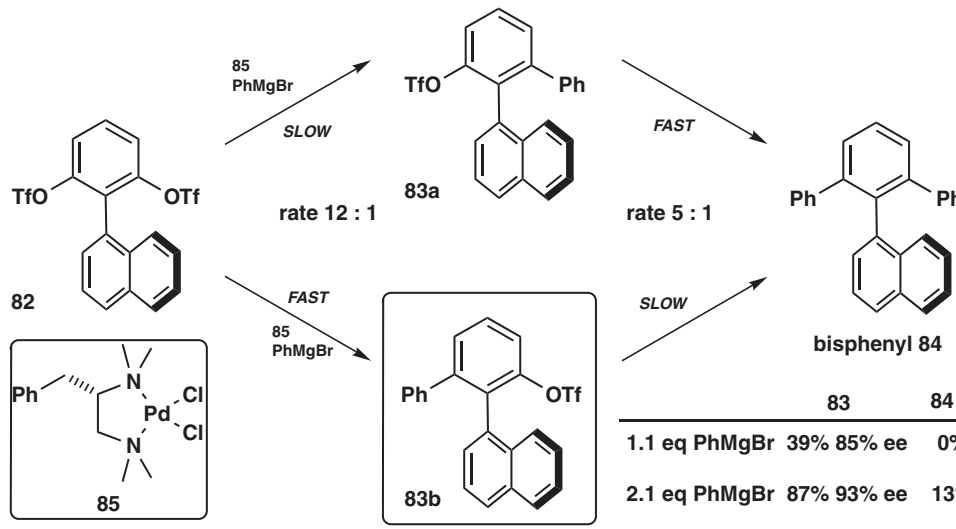
The doubly allylic alcohol **79** is reacted under Sharpless epoxidation conditions.[37] Selectivity is good because k_{fast}/k_{slow} is high at 104. This first reaction is not a kinetic resolution because we are not resolving anything and, indeed, the starting material is achiral (and prochiral). This first reaction produces mostly enantiomer **80a** with a little of enantiomer **80b**. With such good selectivity we would expect good ees even after the first round and so we do. At 50% conversion we have a 48% yield of **80a** and already excellent ee of 99.4%.

The second reaction converts each enantiomer **80a** and **80b** into the same double epoxide **81**. Here is the key to the enhancement process – the double bond that the reagent found more attractive in the starting material **79** (and hence reacted with fast) is the one that remains *unreacted* in product **80b**. Hence we might expect this undesired product **80b** to react faster than **80a** to give the double epoxide. At 99% conversion, the yield of **80a** is 93% and the ee 99.96%. The reference contains plenty of the maths behind this rather complicated process.[37]



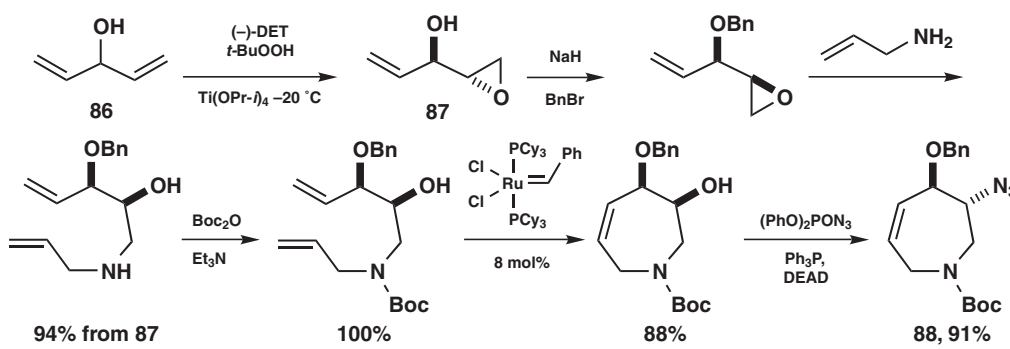
If the enhancement of enantiomeric excess did not impress you much (though it should, 99.96% *is* very difficult to achieve in one go!) perhaps an example where the ee is a bit lower after the first round will make the point more effectively. The bistriflate **82** contains a biaryl bond with restricted rotation so that replacing one of the triflates with something else will give us a chiral molecule (**83a** and **83b** are enantiomers). As above, the first reaction is a desymmetrisation and the second reaction a kinetic resolution upon the products from the first. Both reactions are palladium mediated cross-couplings of an aryl triflate and phenyl Grignard.

An optically pure palladium complex **85** catalyses the formation of a biaryl bond and selects between the two enantiotopic triflates. The selectivity is less good than the example above with the fast reaction only 12 times faster than the slow reaction for the first stage. We would expect that the best enantiomeric excess in a *product* that could be obtained with a rate ratio of 12:1 would be 85% ee [(12−1)/(12+1) × 100]. With a slight excess of PhMgBr we observe 39% of product **83** and an ee of 85%.



It is worth reiterating something here before we move on to the second reaction. With a kinetic resolution, the ee of a *product* is limited by the relative rates of the reactions. But the ee of the starting material left behind is *not* limited in this way. The ee can be increased by letting the reaction run a bit further to completion. There is a price to be paid in yield, of course, and you might find that to get your 98% ee you end up with only 2% yield but it can be done. In the second reaction (the reaction of **83a** and **83b**), the compound we want **83b** is one of the starting materials. The relative rates of reaction are quite poor at 5:1 but we already have a head start in ee anyway. The wrong enantiomer **83a** is eaten up in the second reaction With 2.1 eq we end up with an 87% yield of product in 93% ee with 13% of the doubly arylated product **84**.[38] If we wanted to increase this 93% further, we could run the reaction a bit further still.

These double methods look quite esoteric but they are more widespread than one might imagine. They need looking out for because they are sometimes not even noted by the authors of the work. In Fürstner's synthesis of (−)-balanol,[39] which we looked at in chapter 25, the chiral centres in the seven membered ring originate in a Sharpless asymmetric epoxidation (see chapter 25). We can see that the starting material **86** is a double allylic alcohol of the kind we saw earlier **79**. The enhancement of enantiomeric excess is certainly operating to give a product **87** of excellent ee. After a few manipulations, the opening of the epoxide with allyl amine and a ring closing metathesis, the key ring **88** has all the stereochemistry that it needs.



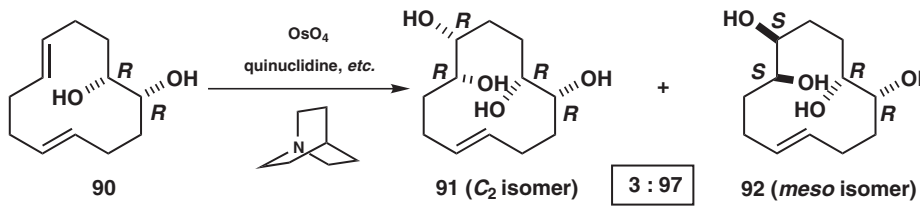
In the above examples enantiotopic reactive sites on either side of the compound were reacted before we moved onto more complicated matters. The next example is a variation on that theme

but this time we start with enantiotopic faces of a double bond. When triene **89** is reacted with OsO_4 and $(DHQD)_2PYR$ and allowed to go to a high level of completion then the product can be obtained enantiomerically pure. However, if the same reaction is stopped at low conversion then the enantiomeric excess of the product is only 95%.

89 **90**

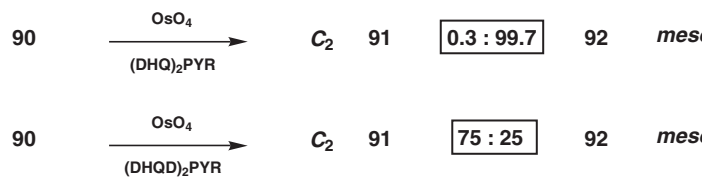
The explanation[40] is that there is a kinetic resolution going on—the minor enantiomer is being removed as the reaction proceeds. It reacts more quickly under the reaction conditions. We could leave the explanation at that but we shall not gloss over this point because it is worth consideration in a little more depth. In order to understand the nature of this process we need to know about the reactivity of diol **90**.

Both the chiral centres in diol **90** have the *R* configuration. We see perhaps the most revealing result when enantiomerically pure diol **90** is dihydroxylated with OsO_4 using an *achiral* ligand – quinuclidine. This is important because it tells us how the *substrate* likes to react with osmium tetroxide. There is a 3:97 product ratio in favour of the *meso* compound **92** rather than the C_2 symmetric compound **91**. In other words, the molecule with two *R* chiral centres prefers the reaction that leads to the formation of two new chiral centres of *opposite* configuration – *S*.

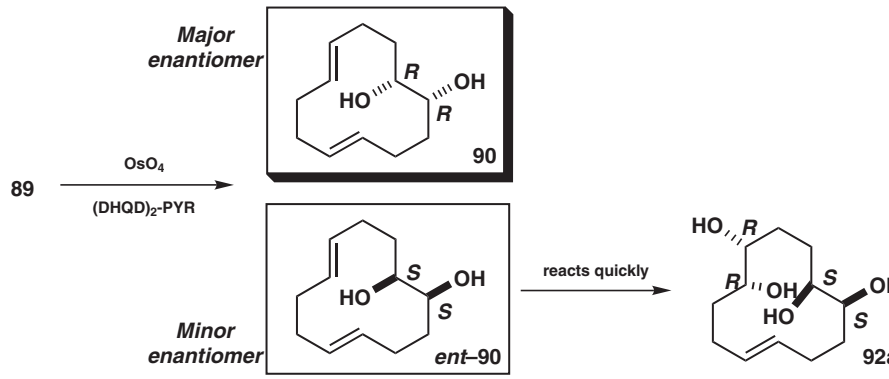


90 **91 (C_2 isomer)** **92 (*meso* isomer)**

So we see how the substrate likes to react but the reagents, of course, may have other ideas. The chiral ligand $(DHQ)_2PYR$ prefers to form two *S* chiral centres from a *trans* double bond of the kind we have in **90**. The diene **90** wants that too so we have the *matched* case and a high selectivity of 0.3:99.7.



However, $(DHQD)_2PYR$, the pseudo-enantiomer of $(DHQ)_2PYR$ (see chapter 25), would prefer to form two *R* chiral centres. The substrate and reagent are in competition here—the mismatched case. The selectivity is turned over to 75:25 in favour of the C_2 symmetric product **91** this time. So the reagent wins but not outright; there is still much of the *meso* diastereomer formed. Now we can return to the original question which concerns the reaction of triene **89**.



Triene **89** reacts to form the diol **90**. A small amount of the enantiomeric diol, *ent*-**90**, is also formed. The crucial point is that this minor product is matched with the reagent and is reacted away, and quickly, to the tetraol **92a** (**92a = 92** but is drawn in a different way). The major product **91** is mismatched with the reagent and reacts more slowly. The first dihydroxylation (of **89**) is the fastest of all three.

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General references are given on page 893

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29 Enzymes: Biological Methods in Asymmetric Synthesis

Preliminary note on biological methods

This chapter concerns methods totally different from anything else in this section. It is mainly about enzymes as catalysts but also deals briefly with whole organisms. These methods are outside

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the experience of most organic chemists and we urge you to study the literature thoroughly before attempting any of them. Fortunately there are books dealing both with laboratory and commercial practice, including three particularly good ones.[1]

Introduction: Enzymes and Organisms

Good and bad features of enzymes as catalysts

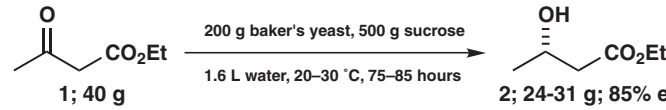
Whether you use isolated enzymes or whole organisms, you are really employing one or more enzymes as catalysts in chemical reactions. Enzymes are the most refined catalysts in existence. They are usually highly specific: catalysing the reaction of only one compound at a specific reaction site with defined stereochemistry including enantioselectivity. They bring about almost incredibly large rate accelerations - 10^9 to 10^{12} is commonplace. They do so in reactions in dilute aqueous solutions at 37 °C and at low concentrations. They do all this with inherently inefficient catalytic mechanisms - general rather than specific acid and base catalysis - that are successful because the protein binds the substrate so that the reagents (such as coenzymes, if any, or water) and the catalytic groups are in exactly the right positions to exert maximum synergistic effects. No wonder that organic chemists use them as catalysts in organic reactions.

So why are chemical reagents rather than enzymes used for most reactions? Each enzyme virtue may be a vice in organic synthesis. High specificity is disastrous: who would want a reagent that would reduce just one ketone enantioselectively, however efficient it might be? Alongside large rate accelerations go small turnovers and long reaction times. Living things want to produce small amounts of many different compounds at a trickle over days or even years. Chemists want tonnes of compounds in a few hours. We don't want to use low concentrations in water. We are not restricted to general acid or base catalysis: NaOH at 100 °C hydrolyses esters by specific base catalysis much faster than the fastest enzymes. And the binding is a problem too: enzymes have molecular weights of tens or hundreds of thousands so that even 1 mole % catalyst might weigh more than the substrate!

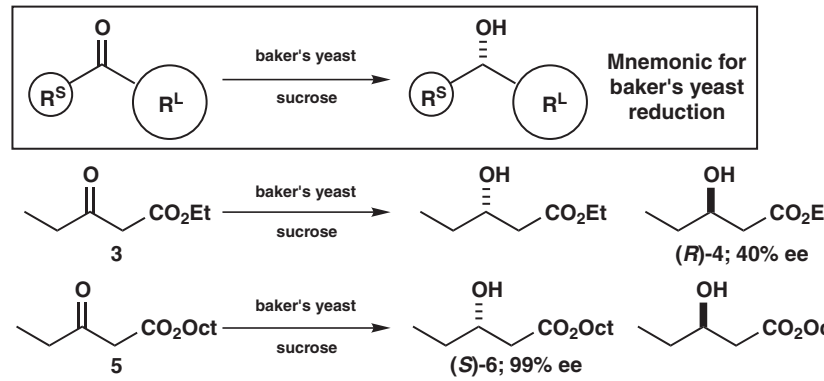
Now the boot is on the other foot - why should chemists use enzymes? This chapter will show that many enzymes are not very substrate specific and will for example reduce a large variety of ketones with essentially perfect enantioselectivity. Some of these enzymes catalyse reactions that are essentially impossible with chemical reagents. Some can be used in organic solvents at high temperatures. Practically they may be easy to use once someone else has worked out the details and, if they are immobilised on polymers, for example, they can be used again and again with a trivial workup since the starting material gives the product and nothing else. Genetic engineering allows simple organisms such as *E. coli* to promote, say, enantioselective Baeyer-Villiger oxidations of ketones. As with all synthetic methods, enzymes are used in some reactions with great success and are to be avoided in others. Their use will grow both in the laboratory and in the manufacturing plant.

Organisms: Reduction of Ketones by Baker's Yeast

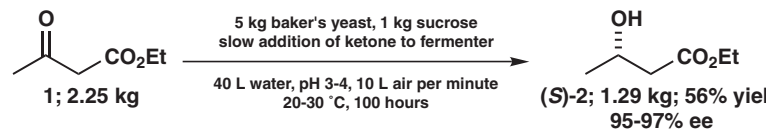
The ordinary yeast used by bakers in their bread making is a valuable organism for the enantioselective reduction of unsymmetrical ketones.[2] It is particularly efficient at the reduction of β-keto-esters such as ethyl acetoacetate **1**. An *Organic Synthesis* procedure[3] reveals that the true reagent is sucrose, which provides just one H atom, that plenty of yeast is required, and that 3–4 days are needed to make 20–30 g product **2** in only 85% ee.



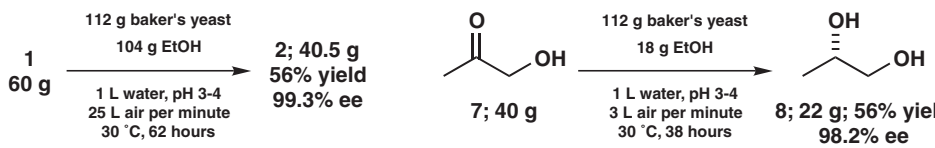
The mnemonic for these reductions is based on the size of the two groups on the ketone. In this case **1** the 'large' group is CH_2CO_2Et and the 'small' group Me. With the keto-ester **3**, though the 'small' group still appears to be Et rather than CH_2CO_2Et, in fact the other enantiomer (*R*)-**4** is produced in low ee. The solution in such cases is the make the ester group very large, octyl being a popular choice **5**. Now we get (*S*)-**6** in good ee.



On a large scale, slow addition of the ketone and good aeration are essential to cut the reaction time and then kilos of **1** can be reduced in excellent ee in only 3-4 days.[4] Under these conditions, each kg of product requires 1.8 kg ethyl acetoacetate **1**, 3.9 kg yeast, and 3.5 kg sucrose.

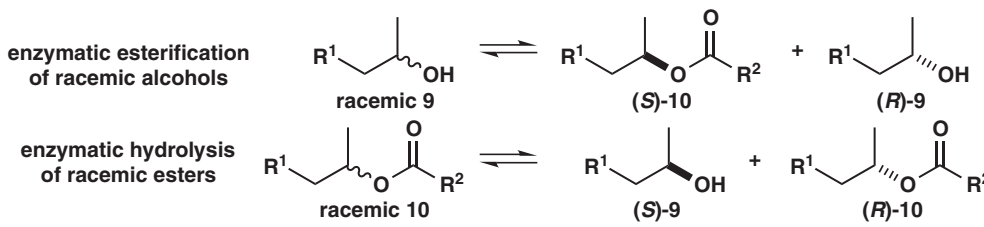


On a large scale, smaller quantities of materials can be used if the sucrose is replaced with ethanol. Since the yeast is an organism there are other enzymes present and EtOH is converted enzymatically into the coenzyme NADPH, the true reducing agent, produced from sucrose in the reductions above. Aeration is again crucial and a bubble column reactor is used. Ethyl acetoacetate **1** is again efficiently reduced and so is hydroxyacetone **7** to give the useful diol[5] **8**.

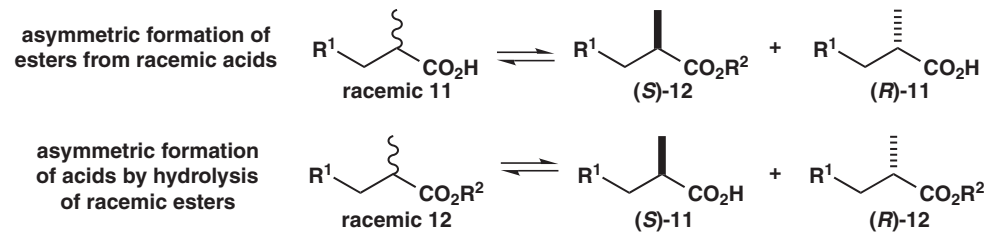


Ester Formation and Hydrolysis by Lipases and Esterases

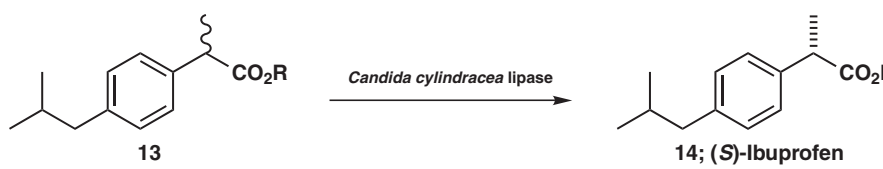
Lipases and esterases are enzymes that hydrolyse esters in one direction or make them in the reverse direction. A wide variety of such enzymes is commercially available and you are advised to seek a close analogy before choosing one or another.[6] If the alcohol **9** is the interesting part, these enzymes can be used to provide enantiomerically enriched alcohol or ester by either reaction.



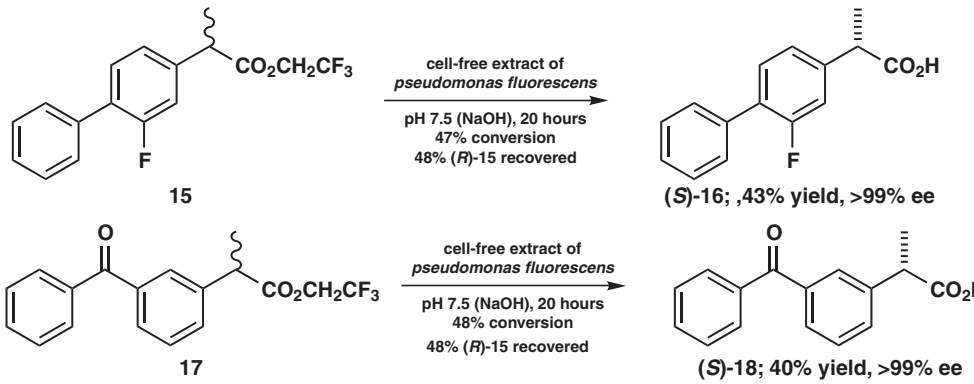
On the other hand if the acid is the interesting part then the same two types of reaction can be carried out to produce enantiomerically enriched esters or acids as required. Both these reactions are equilibria. Both are also kinetic resolutions (chapter 28) and it is not usually possible to get both products in high ee. The key statistic is the rate ratio ('E') of hydrolysis or esterification of the two enantiomers. Since the molecules we shall be using are not natural substrates of lipases, the *E* value will vary considerably but, as you know from chapter 28, it does not need to be very large for acceptable results. This 'E' is often called k_S/k_R in chemical kinetic resolution and called the '**s** value' in chapter 28.



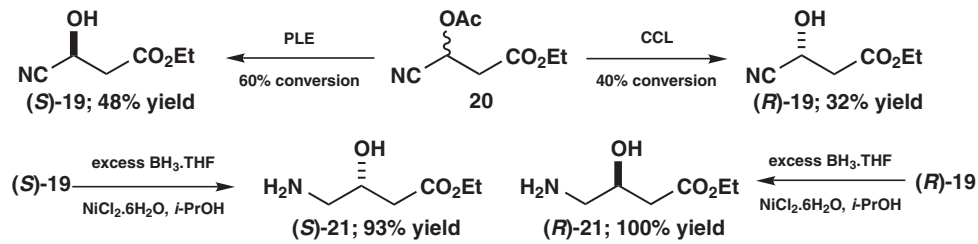
Important examples of this last type are the 2-aryl propionic acids, widely used as anti-inflammatory drugs. The active enantiomer of ibuprofen **14** can be formed by hydrolysis of esters **13** with the lipase from *Candida cylindracea*. The natural enzyme gives $E = 10$ but if it is refolded by precipitation from solution in 1:1 EtOH/Et_2O with sodium cholate the *E* value rises to >100. The unnatural substrate **13** fits the refolded enzyme better than it fits the native enzyme.[7]



Typical kinetic resolutions of the arylpropionic acids are those of flurbiprofen **16** and ketoprofen **18** with a cell-free extract of *Pseudomonas fluorescens*. Note the special ester (trifluoroethyl) selected for maximum efficiency and how successful that is: perfect ee in the hydrolysed products at close to 50% conversion.[8] The unreacted esters **15** and **17** can of course be racemised by enolisation and added to the next resolution.

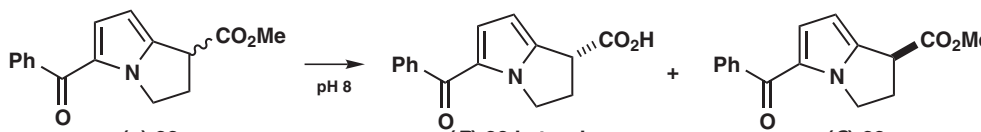


In some cases two different enzymes may show opposite enantioselectivities. The lipase from *Candida cylindraceae* (CCL) and the esterase from pig liver (PLE) do so with racemic cyanohydrins[9] such as **20**. Note that the acetate is hydrolysed rather than the ethyl ester. Each enantiomer may be reduced in high yield to a single enantiomer of the amine **21**. The literature value for the rotation of this compound is $[\alpha]_D$ 20.8 and the measured value for (*S*)-**21** was −20.9 and for (*R*)-**21** was +20.6. Though this is not usually a reliable method of assessing enantiomeric purity, it is quite convincing here. Later in this chapter you will meet an alternative way to make the same sorts of compounds using different enzymes.



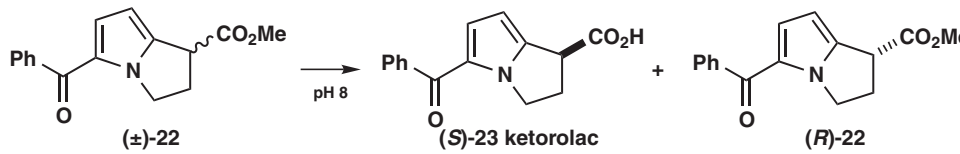
Kinetic resolution with racemisation

Clearly the efficiency of these reactions is improved if the starting material is racemising under the reaction conditions (see dynamic kinetic resolution in chapter 28). Ketorolac **23**, another aryl propionic acid, has an acidic proton and its esters racemise at slightly alkaline pH (9-10). Is it possible to find an enzyme system that will operate in this pH range? First a lipase had to be found that would do the hydrolysis of the ester **22** in the right sense. A selection of lipases gave the wrong enantiomer (*R*)-**23** except for porcine pancreatic lipase but that gave low ees.



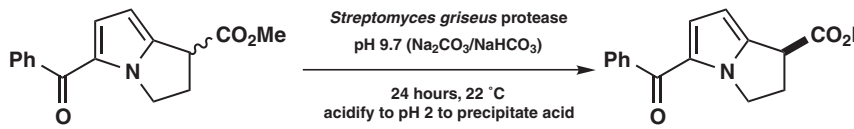
(±)-22	(*R*)-23 ketorolac	(*S*)-22
Lipase from *Mucor meihei*	94% ee	90% ee
Lipase from *Pseudomonas spp.*	90% ee	93% ee
Lipase from *Candida cylindracea*	74% ee	94% ee
Porcine Pancreatic Lipase	(*S*) 32% ee	(*R*) 4% ee

A selection of proteases did much better giving the right isomer of ketorolac (*S*)-**23** in good yield and ee and one, the protease from *Streptomyces griseus*, did exceptionally well. This was at pH 8 - the normal pH for the enzyme.



Protease from *Aspergillus saitoi*	**96% ee**	**80% ee**
Protease from *Bacillus subtilis*	**96% ee**	**62% ee**
Protease from *Aspergillus oryzae*	**70% ee**	**>96% ee**
Protease from *Streptomyces griseus*	**>96% ee**	**>96% ee**

With the protease from *Streptomyces griseus* at pH 9.7 racemisation occurred at a reasonable rate and the enzyme still operated efficiently, giving (*S*)-**23** in good yield and only slightly reduced ee. One crystallisation gave 94% ee, acceptable for an anti-inflammatory.[10]



Enzymes versus whole organisms

We have discussed examples of pure enzymes - the lipases - and whole organisms - baker's yeast and before we continue it is worthwhile to pause and consider the relative merits of the two approaches. Many of these points will be elaborated in the rest of the chapter. There are other methods, as you will see, that fit neither of these descriptions exactly such as engineered micro-organisms that have a particular enzyme over-expressed. There will be examples of these later. Meanwhile here are the main points:

Cost: Pure enzymes are expensive while organisms such as yeasts are cheap. Individual cultures of microorganisms may also be expensive.

Scale: Very little pure enzyme or bacteria may be needed in contrast to the large quantities of yeast.

Specificity: A pure enzyme normally catalyses only one reaction while a living organism contains many enzymes and may catalyse many reactions.

Reagents: Pure enzymes normally need no more than pH adjustment though some, say enzymes that catalyse redox reactions, need expensive co-factors. These can normally be supplied by a second enzyme the recycles the co-factor. Organisms need feeding - this is cheap but may require a lot of material.

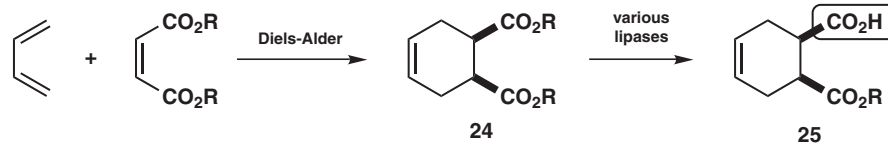
Work-up: Reactions with pure enzymes are clean to work-up though re-isolation of the enzyme will normally be preferred. Immobilised enzymes avoid this problem. The work-up of a reaction with a yeast is very messy indeed.

Waste products: None with an enzyme, lots with a yeast but at least they are environmentally friendly.

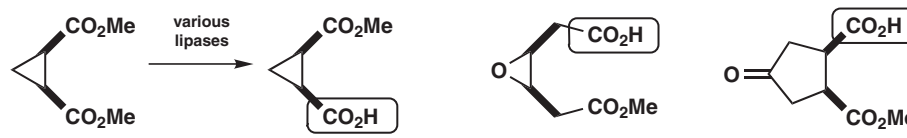
Desymmetrisation with lipases

These are hydrolyses of *meso* diesters rather than kinetic resolutions and can give quantitative yields of single compounds. The products are half acid, half ester and care must be taken to preserve this

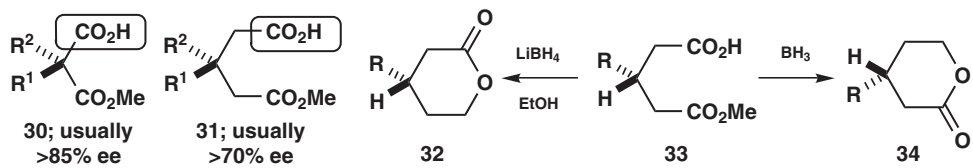
difference. One useful group is the Diels-Alder products such as those formed from butadiene and maleic esters **24**. Hydrolysis with various lipases[11] gives one enantiomer of the half ester **25**.



The results are sensitive to the esterifying alcohol ROH. If R = Me **26**, results are excellent (99% yield, >98% ee) but fall off as R gets larger. Even with R = Et things are significantly worse (67% yield, 27% ee) and with R = *i*-Pr they are hopeless (5% yield, 2% ee). It does not do to move too far away from the natural substrates. Three and five-membered rings also give good results: in each case the ester that is hydrolysed is marked - this is not always what one would expect - contrast **27** and **28**.

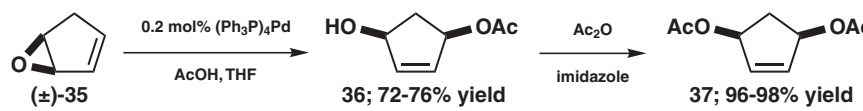


Another group of *meso* diesters are the acyclic compounds **30** and **31**. Pig liver esterase is good at forming the mono-ester **33** and this compound can be transformed by selective reduction into either **32** or **34**. These lactones are enantiomers so that either series may be entered from the same *meso* starting material.[12] In addition the precarious chirality of **33** is more secure in the lactones.

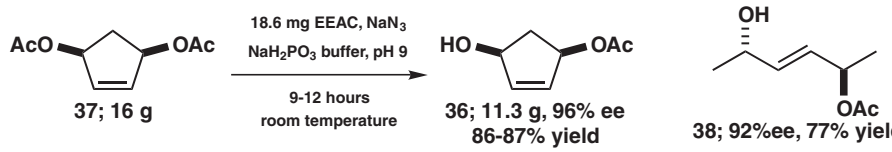


Immobilised enzymes in desymmetrisation

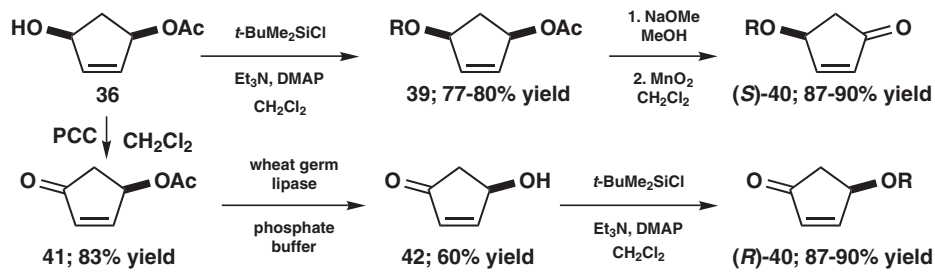
The starting material for the next desymmetrisation comes from an interesting reaction first described in chapter 19. The Pd-catalysed attack of AcOH on the mono-epoxide (±)-**35** gives the racemic monoester **36**. In order to convert this to a single enantiomer it is first made into the *meso* diester[13] **37**.



Now the acetyl cholinesterase from the electric eel (EEAC) efficiently desymmetrises the diacetate to give the enantiomerically pure monoester **36**. The enzyme can be used as a lyophilised powder or is available (from Sigma) immobilised on agarose beads. This form is easy to use and easy to isolate after the reaction. Other cyclic examples work well as does the most impressive open chain example **38** with an *E*-alkene.[14]

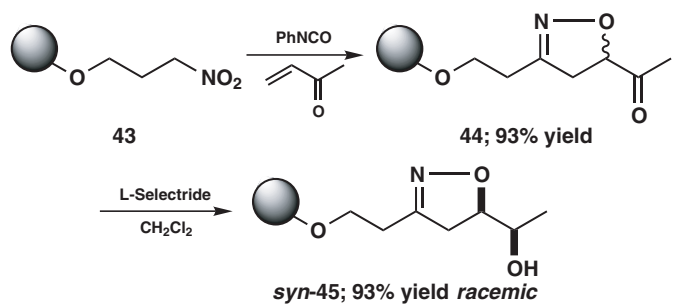


The product **36** can be converted by simple chemistry into either enantiomer of the enone **40** (R = TBDMS). Notice that another enzyme, this time a plant lipase, is used to hydrolyse the acetate **41** efficiently. There is no asymmetric induction in this step as **41** is already a single enantiomer.[15]

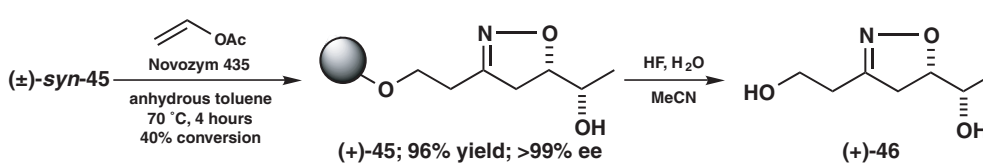


Polymer-supported reagents and enzymes

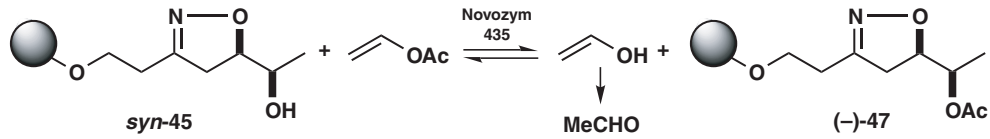
Polymer-supported enzymes have been combined with polymer-supported reagents in the synthesis of the bryostatins. The nitrone derived from the nitro compound **43** supported on a soluble aryl poly-ether polymer undergoes an efficient 1,3-dipolar cycloaddition with butenone to give the isoxazoline **44** and hence by reduction the racemic *syn* compound **45** required for the synthesis.[16]



The single enantiomer of **45** is produced by enantioselective acylation with vinyl acetate catalysed by Novozym 435, an immobilised lipase from *Candida antarctica* containing about 1% w/w enzyme on a macroporous polypropylic resin. You will appreciate that as both substrate and catalyst are on polymers, one at least must be soluble in the reaction mixture. The polymer is stripped from the substrate **45** with HF.

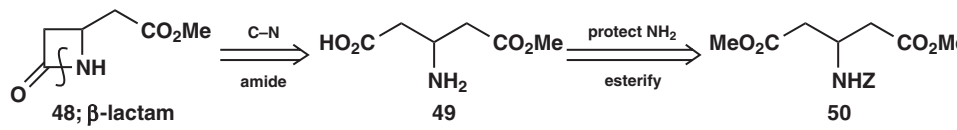


This is a kinetic resolution that works by enantioselective acylation of the unwanted enantiomer of the alcohol. The reaction is therefore an ester exchange and vinyl acetate is an efficient acetate transfer agent since the other product is 'vinyl alcohol' better known as the enol of acetaldehyde so the reaction is irreversible.

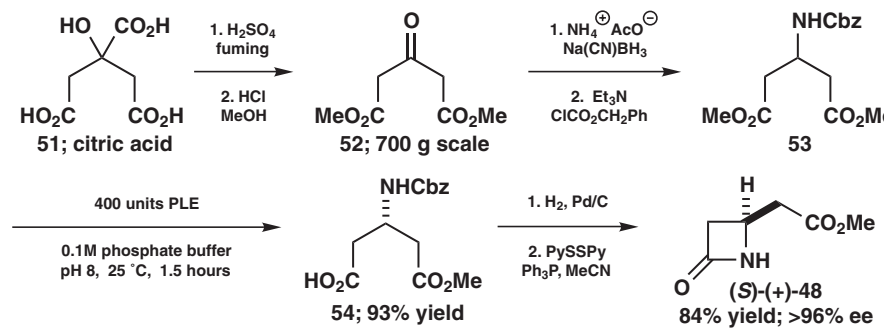


Effects of amines on lipases and esterases

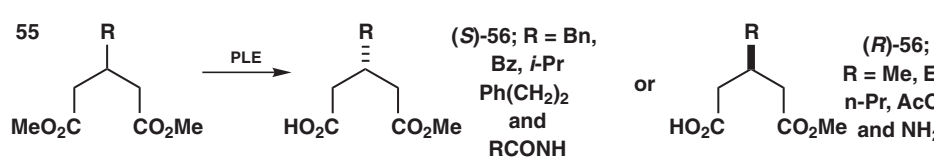
We end this section with two examples of the effects amines may have on esterase activity. The aggressive nitrogen nucleophile can obviously interfere with ester formation or hydrolysis. In designing a synthesis based on these enzymes we must find a symmetrical intermediate that might be desymmetrised. In the synthesis of the simple β-lactam **48**, simple disconnections led to the symmetrical amino-diester **50**, with the nitrogen atom protected.



Synthesis of a suitable substrate from citric acid **51** was straightforward[17] and Ohno[18] found that the Cbz-protected dimethyl ester **53** could be desymmetrised efficiently with pig liver esterase (PLE) or with even higher enantioselectivity, with the microbial enzyme from *Flavobacterium lutescens* (98% ee). The β-lactam **48** could be closed by the dipyridine-disulfide/Ph_3P method.

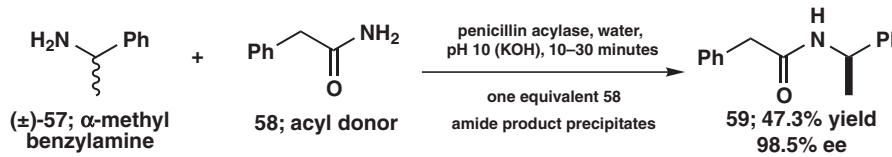


The selectivity of hydrolysis of this type of diester **55** (see also **31**) by PLE depends on the substituents. The two enantiomers of **56** are formed as shown with various degrees of ee and you will notice that there is no easily discerned system. Thus R = Pr and R = *i*-Pr give opposite enantiomers as do amides such as **53** and the corresponding free amine.[19]

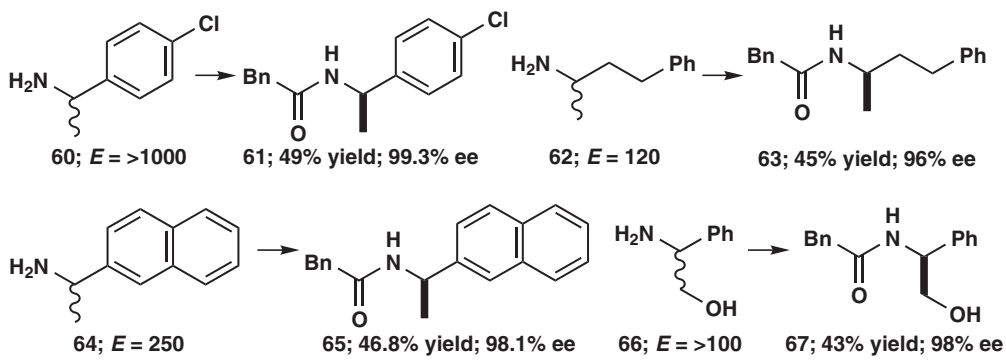


Other acylating enzymes

Amide formation and hydrolysis is of course also catalysed by enzymes and the recent report that the penicillin acylase from *Alcaligenes faecalis* catalyses an efficient kinetic resolution of racemic primary amines is very promising. A typical case is our old friend α-methylbenzylamine **57** (see chapter 22). One equivalent of an acyl donor **58** is needed and nearly 50% of the amide **59** can be isolated in excellent ee. The *E* value is 350 for this amine.[20]



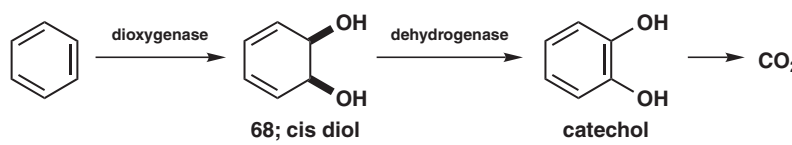
A selection of four amines shows the possible range. Some have aromatic substituents, some aliphatic and one **66** has an alcohol but no ester formation is observed. Though *E* varies from about 100 to over 1000, these numbers are all large enough to ensure excellent ee (see chapter 28) and the yields are all close to the maximum 50%. If the free amines are wanted, the same enzyme can be used to hydrolyse the amides. This process ensures essentially 100% ee as there is a further kinetic resolution in the hydrolysis.



Enzymatic Oxidation

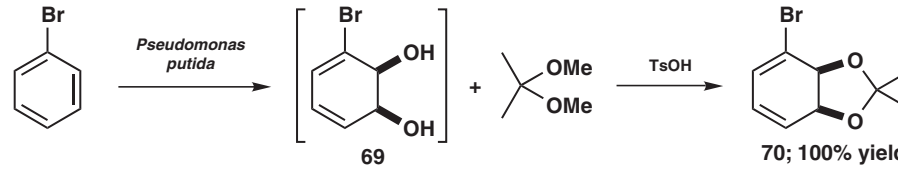
Asymmetric dihydroxylation of benzenes

When benzene falls on the soil it is processed (and so detoxified) by micro-organisms such as *Pseudomonas putida* by oxidation first to a diol[21] then to catechol and finally to CO_2. The diol **68** cannot be isolated as the dehydrogenase is too efficient but in 1970 Gibson discovered mutant F39D of *Pseudomonas putida* that lacks the dehydrogenase and produces the *cis* diol **68** in good yield.[21]



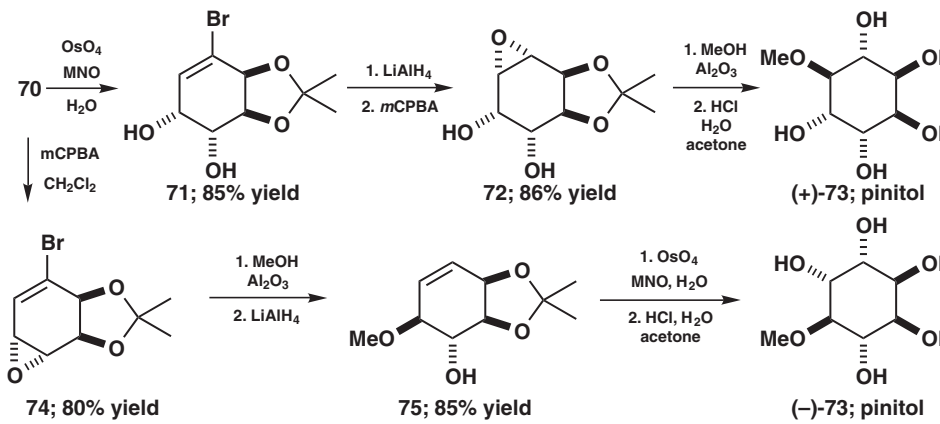
This mutant has been developed by Ley, Hudlicky and others into a practical method for the asymmetric oxidation of substituted benzenes to give the unstable diols best preserved as acetals. Even one substituent is enough to make the diol chiral and dihydroxylation normally occurs at

the 2,3-bond in the ring. Bromobenzene gives the diol **69** and hence the acetal **70** in 100% yield without isolation of the diol.[22]

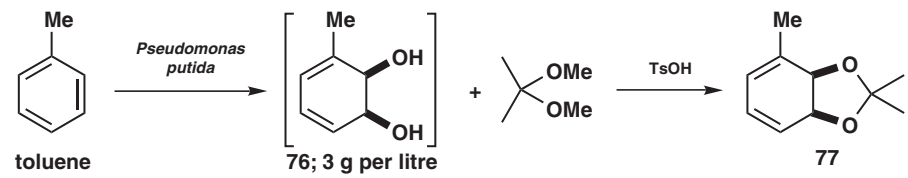


The practical details[23] are given in *Organic Syntheses*. One colony of *Pseudomonas putida* F39D from an agar plate is incubated in 50 mls broth at 30 °C for 24 hours with arginine to induce the dioxygenase enzyme for the substrate provided. This is added to 500 mls broth with 10 mls PhCl and arginine. The broth contains phosphate, K(I), Mg(II), Ca(II), molybdate, Fe(II), $N(CH_2CO_2H)_3$ as well as the trace metals Zn(II), Fe(II), Mn(II), Cu(II), Co(II), $Na_2B_4O_7$, and EDTA. Incubation at 30 °C for 48 hours gives the diol.

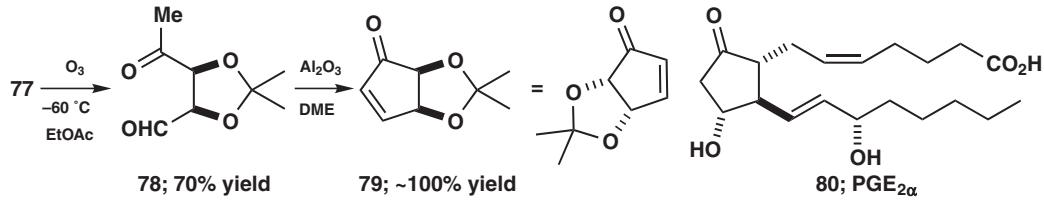
The acetonide **70** has been used to make both enantiomers of pinitol **73**. The rigid acetonide directs dihydroxylation or epoxidation to the bottom face of the ring to give **71** and **74**. The epoxide rings in **72** and **74** can be opened regioselectively with methanol to give the usual trans-diaxial products such as **75**. Carrying out the reactions in two different orders gives the two enantiomers[24] (+)-**73** and (−)-**73**.



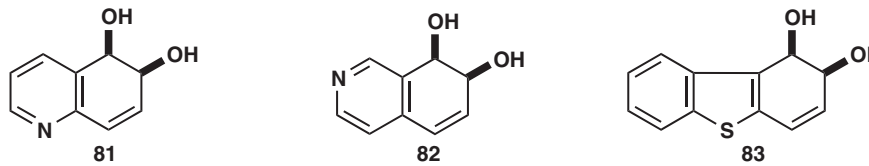
All monosubstituted benzenes react with the same regio- and enantio-selectivity whether the substituent is halogen, alkyl, alkenyl, CO_2H, CN, COMe, OMe or CF_3. Thus toluene gives the diol **76** that can be produced at 3g/litre in the broth described above. It is also a commercial product.



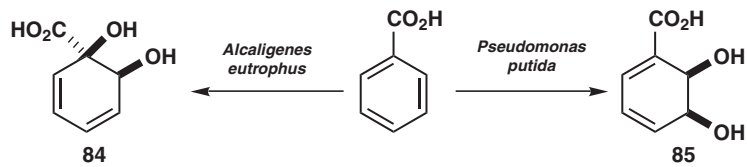
The acetonide **77** has been used in the synthesis of prostaglandins such as $PGF_{2\alpha}$ **80**. Once the aromaticity of the benzene ring is broken, further oxidation is easy and the diene **77** can be ozonised to the keto-aldehyde **79** that readily undergoes an intramolecular aldol to give the enone **79**. It is more obvious that **79** can be a precursor to **80** when it is redrawn to show the possibility of adding the side chains by conjugate addition and enolate trapping[22] (chapters 9 and 10).



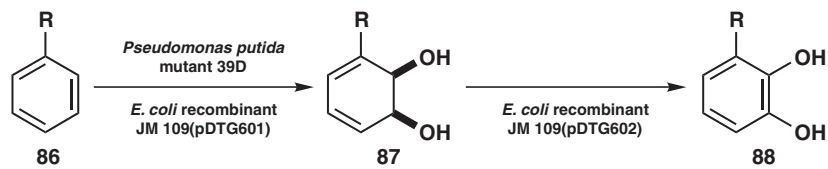
Dihydroxylation of quinoline, to give **81**, isoquinoline, to give **82**, and dibenzothiophene to give **83** are less predictable but in each case it is a benzene rather than a heterocyclic ring, and the 2,3-bond next to a carbon rather than a heteroatom that reacts.[25] The products are drawn to show the identity of the enantioselectivity.



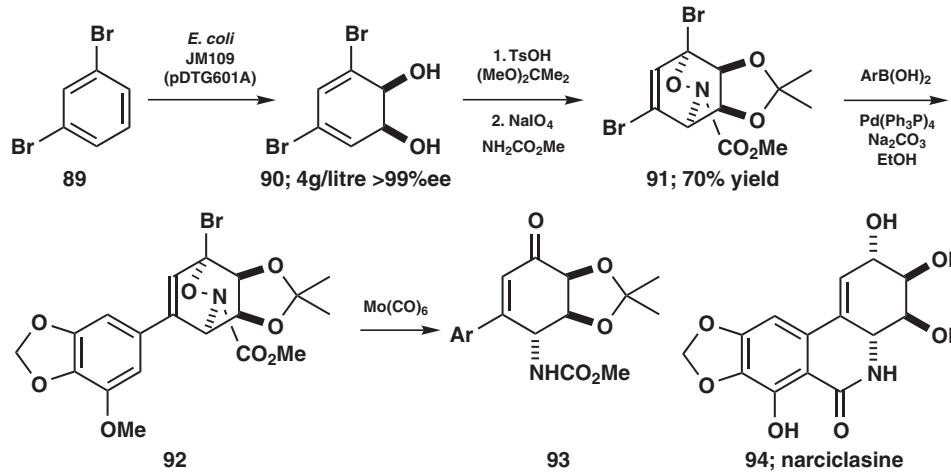
Other organisms may give different results: benzoic acid gives the expected diol **85** with *Pseudomonas putida* but reacts at the bond bearing the CO_2H group with *Alcaligenes eutrophus* to give[26] **84**.



Recent developments include the over-expression of the gene for the dihydroxylation and its transfer[27] into the common and easily grown organism *Escherischia coli* to form recombinant JM 109 (pDTG601A). This organism creates diols **87** from many monosubstituted benzenes more conveniently. The closely related recombinant organism carries out the rearomatisation to give **88**.

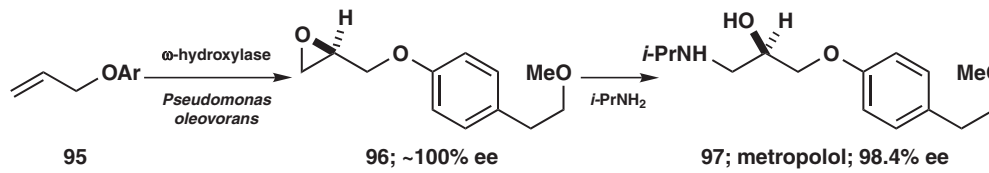


This method was used by Hudlicky in a synthesis of the alkaloid narciclasine. The diol **90** was trapped as the usual acetal and reacted as a diene with the nitroso ester MeO_2C-NO in a hetero-Diels-Alder reaction to give **91**. Suzuki coupling of the vinylic bromide with the right aryl boronic acid gave **92** and the N–O bond was reduced with $Mo(CO)_6$ to give the advanced intermediate **93** on the way to narciclasine[28] **94**.

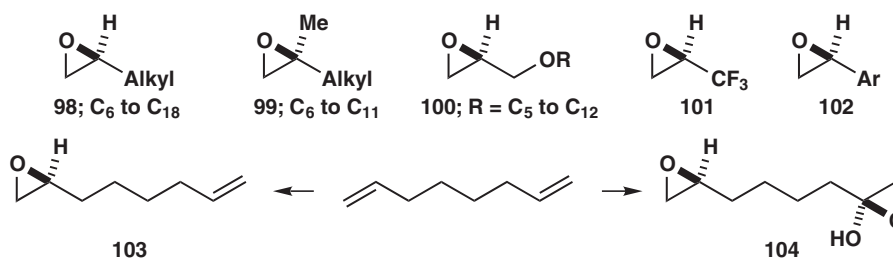


Epoxidation

There are all sorts of problems with epoxidation by micro-organisms and in general laboratory chemists prefer to use the Sharpless or Jacobsen epoxidations described in chapter 25. The ω-hydroxylase from *Pseudomonas oleovorans* does epoxidise aryl ethers of allylic alcohols with good selectivity and one product has been used in the synthesis of the β-blocker metropolol.[29] However the organism requires gaseous hydrocarbons as carbon sources and the epoxide products poison it.



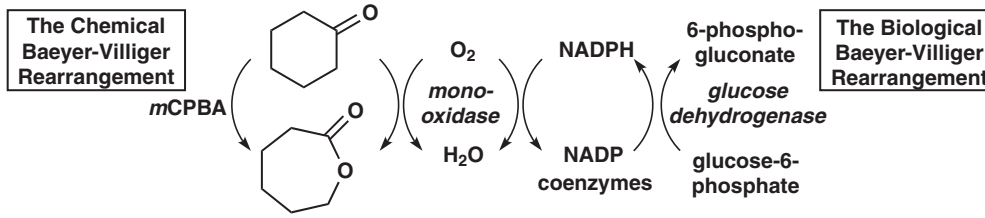
The Nippon Mining Company uses the soil micro-organism *Nocardia corralina* B-276 to produce a series of epoxides that are available commercially as single enantiomers. This micro-organism uses glucose as a carbon source and is not poisoned by the epoxides it produces. It also is very versatile as the selection **98** - **104** shows. The two epoxides **103** and **104** are especially notable as they are both made from hexa-1,5-diene.[30]



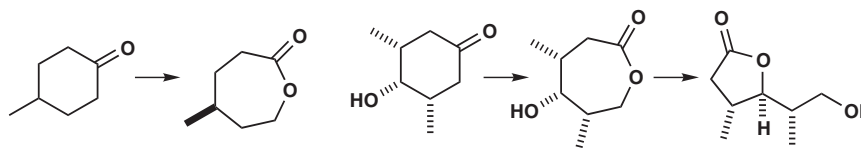
The Baeyer-Villiger reaction

The Baeyer Villiger reaction is an oxidation of ketones by peroxyacids that inserts an oxygen atom between the carbonyl group and the more substituted side of the ketone. The biological

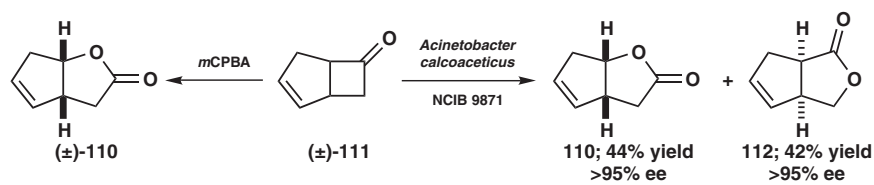
version does the same thing and is particularly interesting to us when it creates asymmetry from a symmetrical ketone. The enzymes are mono-oxidases that are coupled to the reducing enzyme glucose dehydrogenase.[31]



Examples include simple achiral ketones such as **105** and *meso* compounds with some stereochemistry[32] such as **107** that initially gives the seven-membered lactone **108** but this rearranges into the five-membered lactone **109**.

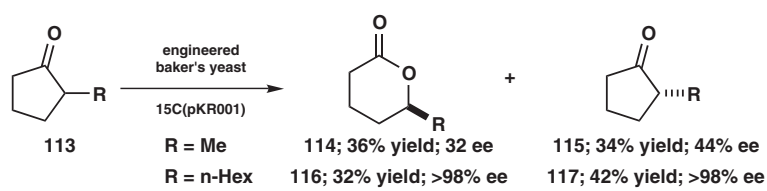


Nature has many surprises in the chemistry she does. One organism produces a scarcely credible result in the Baeyer-Villiger reaction. *Acinetobacter calcoaceticus* catalyses a kinetic resolution of the important bicyclic ketone **111**. The chemical reaction gives the expected lactone **110** with migration of the more highly substituted carbon atom. The biological reaction does indeed give one enantiomer of the same lactone but the remaining material is not unreacted **111**. Instead the other *regio*isomer **112** in the other enantiomeric series is formed in good yield and ee. Nature can accomplish reactions impossible to us, so far.[33] The latest news[34] on this reaction is that recombinant whole cells of *E. coli* expressing cyclohexanone mono-oxygenase are even more efficient.

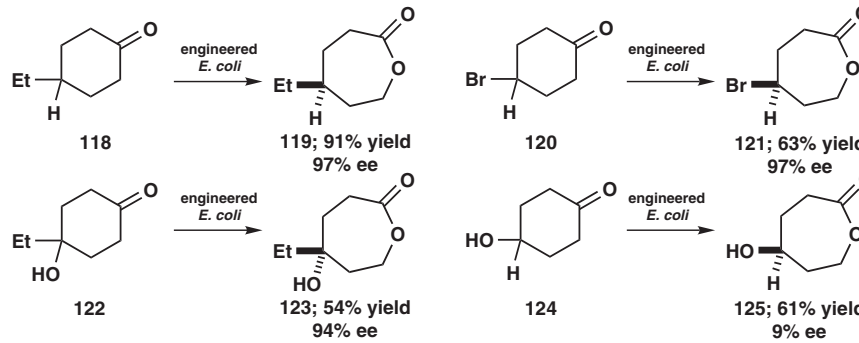


Baeyer-Villiger reactions with engineered baker's yeast

The mono-oxygenase from *Acinetobacter* sp NCIB 9871 can be cloned and expressed in the same baker's yeast that we met at the start of this chapter. This yeast carries out Baeyer-Villiger reactions and supplies its own NADPH from other enzymes in the yeast. A conventional kinetic resolution of cyclopentanones **113** gives single enantiomers of lactone and starting material.[35]



Whole cells of engineered *E. coli* BL21(DE3)(pMM4) desymmetrise cyclohexanones with substituents in the 4-position with variable results.[36] Simple mono-substitution **118** and **120** gives good results but the enzyme is very sensitive to hydroxyl groups giving a lower yield with the tertiary alcohol **122** and poor ee with the secondary alcohol **124**.

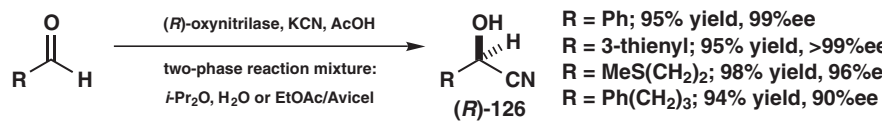


Nucleophilic Addition to Carbonyl Groups

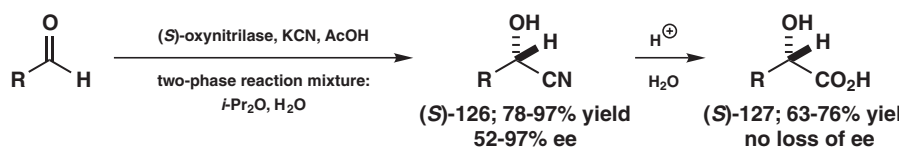
Asymmetric addition of cyanide to aldehydes

Oxynitrilase enzymes from various plants catalyse the addition of cyanide ion to aldehydes to give the cyanohydrins present in many plants. Amygdalin, the cyanohydrin of a trisaccharide, is perhaps the most notorious of these as it releases HCN from oil of bitter almonds and has been responsible for the death of people drinking old samples of the liqueur noyeau.[37]

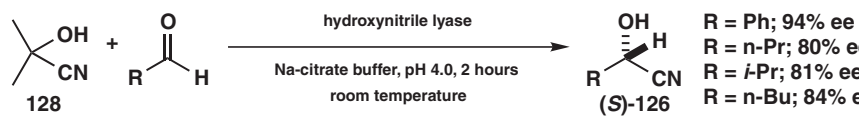
The (*R*)-oxynitrilase from the almond *Prunus amygdalis* has unusually low substrate specificity and gives good yields of a variety of cyanohydrins **126** providing that the reaction medium has two phases to inhibit the uncatalysed addition of HCN to the aldehyde.[38]



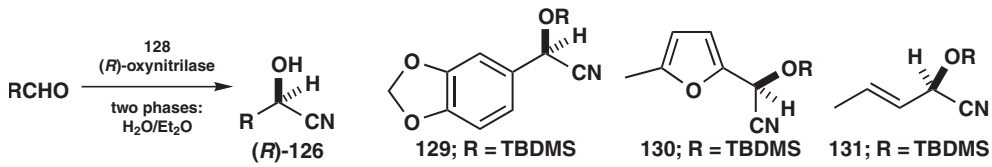
The (*S*)-oxynitrilase from *Sorghum bicolor* produces the other enantiomer but only from aromatic aldehydes.[39] The products can be directly converted into hydroxyacids **127** without loss of ee.



These two methods involve the potential release of toxic HCN during the reaction and a cleaner as well as a safer method is to use acetone cyanohydrin **128** as a cyanide transfer reagent. The enzyme from the Brazilian rubber tree *Hevea brasiliensis*, called a hydroxynitrile lyase, catalyses cyanohydrin formation from aliphatic as well as aromatic aldehydes.[40]

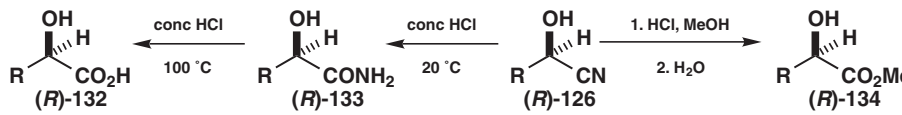


The commercial process run by Solvay Duphar, based on the work of van der Gen,[41] uses an aqueous extract of almond meal for (*R*)-**126** and the sorghum enzyme for (*S*)-**126**. Again a two-phase system (H_2O/Et_2O) is used and the rather unstable cyanohydrins, that may racemise by reversible loss of HCN, are stabilised by conversion to silyl ethers such as **129**–**131**. The last example shows that direct is preferred to conjugate addition.

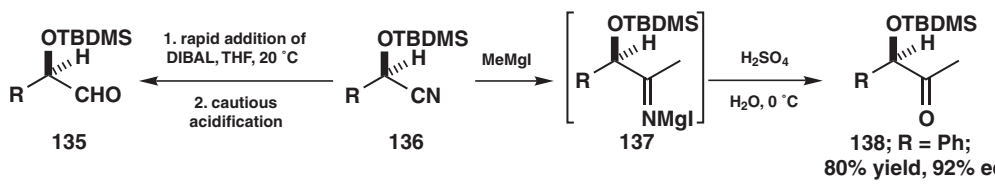


Products derived from cyanohydrins

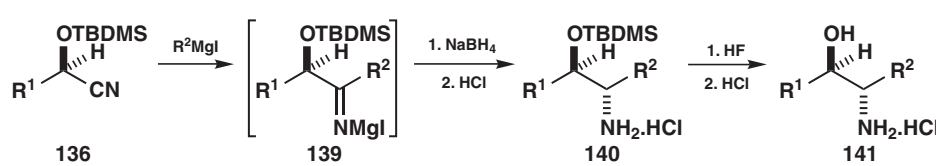
The obvious hydrolysis of the nitrile must be carried out carefully to avoid racemisation.[39,42] Two successful ways are direct conversion into esters **134** in acid solution or a two step process to the acids **132** *via* the much less easily racemised amides **133**.



Conversion to other carbonyl compounds is more tricky because of the increased likelihood of enolisation. The protected cyanohydrins **136** can be reduced to the aldehydes **135** with 1.5 equivalents of DIBAL and cautious acidification. The more stable ketones **138** are best made in two stages.[41] Additions of Grignard reagents gives the imine derivatives **137** that can be worked up in acid to give the ketones **133**.

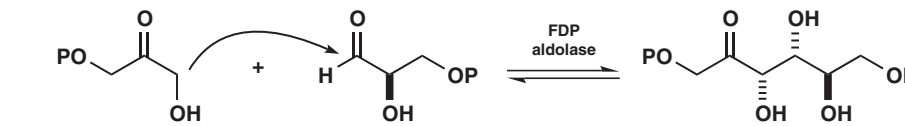


Secondary amines can be formed from the same starting materials **136** by tandem Grignard addition and borohydride reduction.[43] The reduction shows good Felkin-Anh selectivity (chapter 21) and the silyl group can be cleaved from the products **140**, as they are safe from racemisation, to give a range of amino alcohols **141**. Compounds like these can also be made by asymmetric amino-hydroxylation (chapter 25).



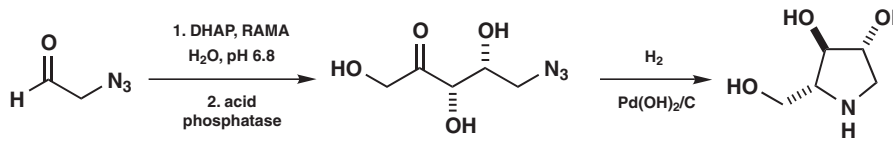
Enzymatically catalysed aldol reactions

The aldol reaction is extensively used in Nature as in the laboratory to make C–C bonds and some aldolases have been used in asymmetric synthesis. One of the most popular has been the fructose-6-phosphate aldolase[44] from rabbit muscle, familiarly known as RAMA. The enzymatic reaction combines the enol from dihydroxyacetone phosphate (DHAP) **142** with glyceraldehyde-3-phosphate **143** in a diastereo- and enantioselective aldol reaction. PO in these diagrams means phosphate.



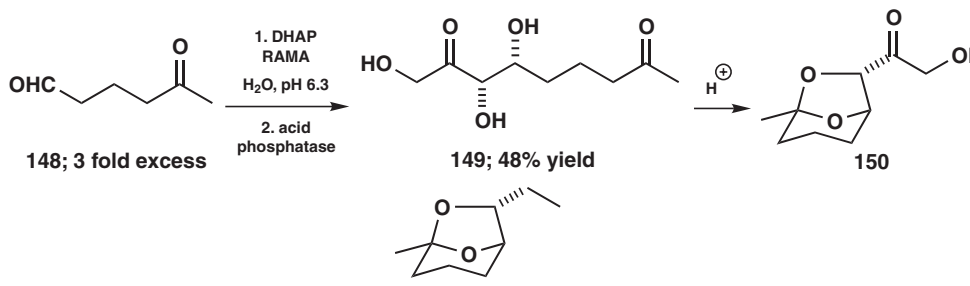
142; DiHydroxyAcetone Phosphate (DHAP) **143; Glyceraldehyde 3-phosphate** **144; Fructose 1,6-diphosphate**

The rabbit enzyme requires DHAP for the enol component but is more relaxed about the aldehyde. The azido-aldehyde **145** reacts cleanly with the formation of two new chiral centres **146** and the phosphate is removed by treatment with a second enzyme, a phosphatase.[45] Then reduction of the azide gives the trihydroxy pyrrolidine **147** with excellent control over a third chiral centre, less than 10% of the epimer being formed. The ees of the compounds are not easily determined from the published work.



145 **146; 78% yield** **147; 74% yield**

The insect pheromone *exo*-brevicomin **151** has been made this way using the ketoaldehyde **148** as the electrophile with DHAP as the usual enol component.[46] The reaction is entirely chemoselective: the ketone in **148** acts neither as enol nor electrophile. The product is a diol that one might think of making by an AD reaction (chapter 25). In acid solution it forms a cyclic acetal **150** having the skeleton of brevicomin. The rotation but not the ee of the brevicomin made this way is quoted.



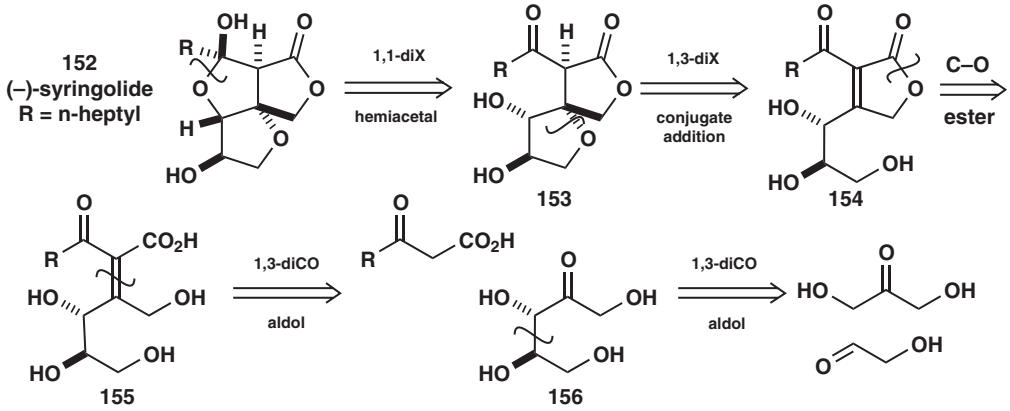
148; 3 fold excess **149; 48% yield** **150**

151; *exo*-brevicomin

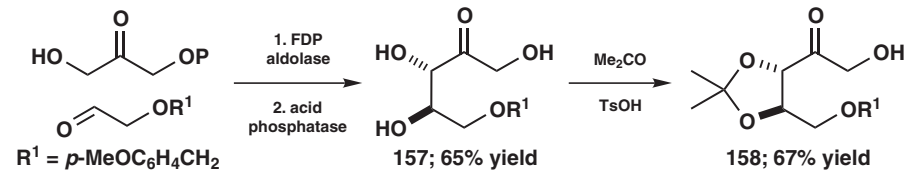
Synthesis of syringolide using an enzyme-catalysed aldol reaction

Syringolide **152** is a natural product that elicits an immune response from soyabeans. A series of straightforward disconnections leads back to a tetraol **156** that looks like an aldol product from

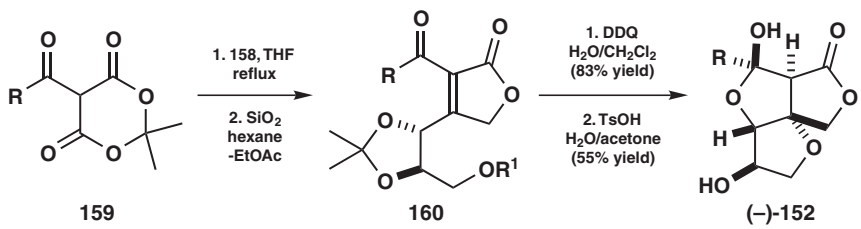
DHAP and a very simple aldehyde. Other than doubts about the geometry of the alkene in **155** and chemoselectivity with all the OH groups, it is a simply designed synthesis.[47]



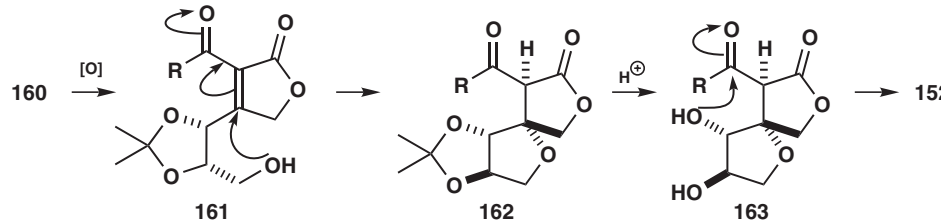
The solution to the chemoselectivity problem is minimal protection: a *p*-methoxybenzyl group for the hydroxyaldehyde and an acetal **158** for the diol unit in the product **157** of the enzyme-catalysed aldol reaction. The solution to the alkene geometry problem is going to be intramolecular trapping by the one remaining free OH group.



The Meldrum's acid derivative **159** was chosen to represent the keto-acid electrophile in reaction with the carbonyl group of **158**. One of the two carboxyl groups can be captured by the free OH group in **158** so that the geometry of the alkene is automatically correct in **160**. Removal of the *p*-methoxybenzyl group by oxidation and the acetonide with acid allows conjugate addition and hemiacetal formation to give (–)-syringolide **152** in one step from **160**.

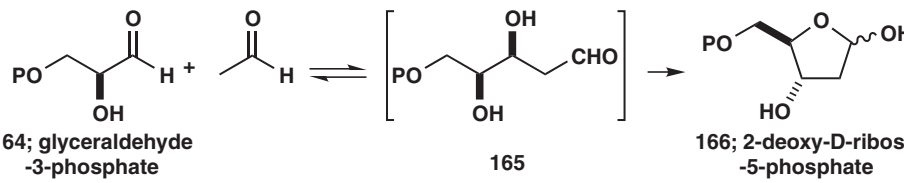


Three new chiral centres are created in this step. Removal of the *p*-methoxybenzyl group from **160** gives the free OH group that carries out conjugate addition **161**. It approaches the underside of the lactone as the five-membered acetal is planar and the CH_2OH group is already on the underside. Protonation of the enol product is under thermodynamic control and may change in the next reaction. Removal of the acetal gives two more free OH groups only one being able to add to the ketone **163** to give the hemiacetal in **152**. The stereochemistry of this centre is also under thermodynamic control and each addition ensures that each pair of five-membered rings have the more stable *cis* fusion in the final product **152**.

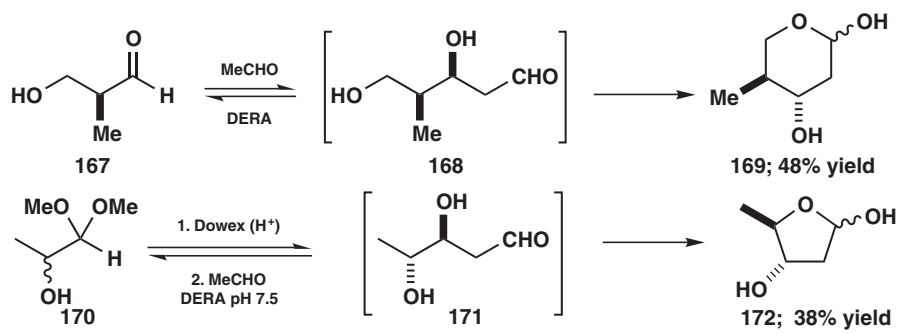


Engineered aldolase

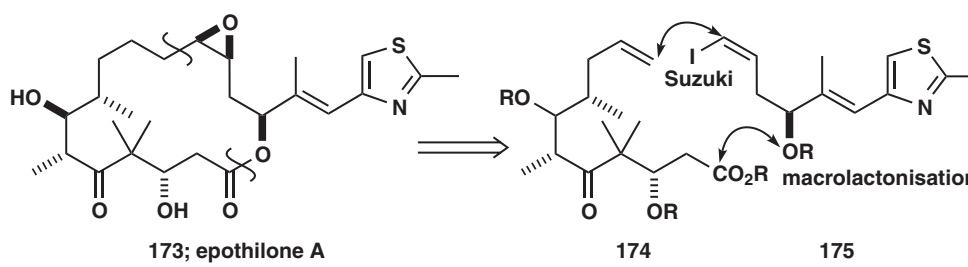
A different aldolase has been over-expressed in *E. coli* and used by Chi-Huey Wong in his synthesis of epothilones. It is 2-deoxyribose-5-phosphate aldolase (DERA) and the natural reaction is the condensation of acetaldehyde as enol with glyceraldehyde-3-phosphate **164** as electrophilic component to give an aldol product **165** that is trapped as a hemiacetal **166**.



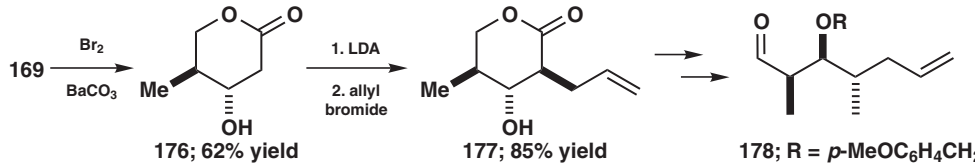
This enzyme is much less fussy than RAMA and will accept other enol components or electrophiles. In this case the β-hydroxyaldehyde **167** gives the six-membered cyclic hemiacetal **169** and the acetal **170** of unstable 2-hydroxypropanal gives one diastereoisomer of the aldol **171** by dynamic kinetic resolution and hence **172** in moderate yield.[48]



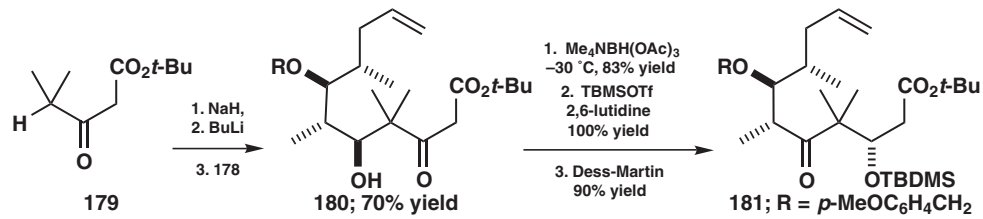
Both these products were used in the synthesis of epothilone A **173**. The disconnection of the lactone is simple but the other is less obvious. The epoxide must come from a *cis* alkene and that can be made by a Suzuki coupling of a borane derived from **174** and the *Z*-vinyl iodide **175**. As you will see, **174** was made from **169** and **175** from **172**, unlikely as it seems.



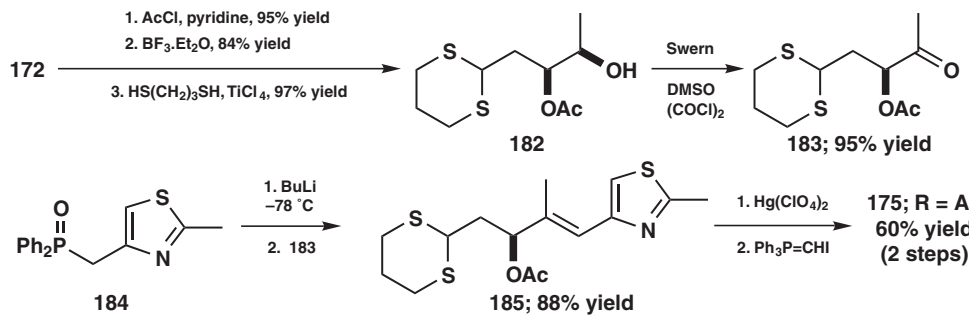
The hemiacetal **169** was first oxidised to the lactone **176** and the lithium enolate allylated with the expected stereoselectivity to give **177** and then, by a series of reactions described in the workbook, into the aldehyde **178**.



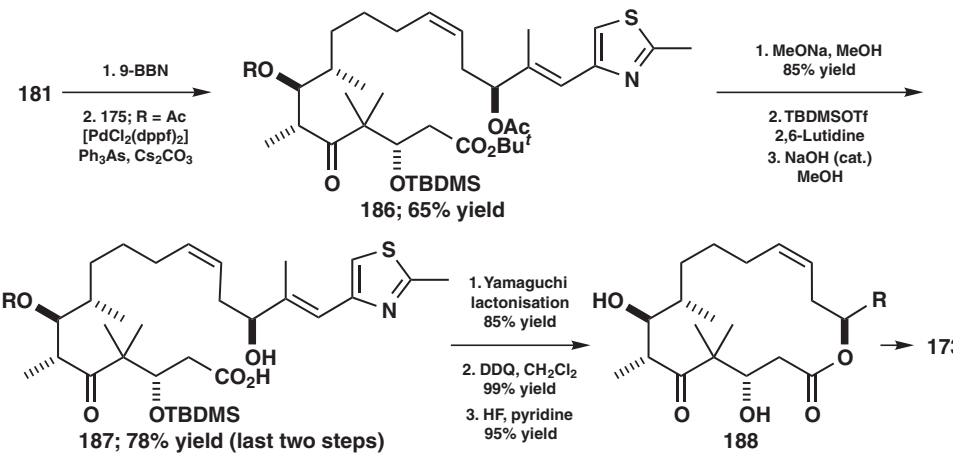
A stereoselective aldol reaction between the β-ketoester **179** at the less enolisable position and **178** creates the complete carbon skeleton of **174** with excellent stereoselectivity at the new OH group **180**. This OH group was used to control the stereochemistry of an Evans 1,3 reduction (chapter 21/30) before it was oxidised to the required ketone **181**: this is the same as **174** but has the protecting groups specified.



The other half was made from **172** by formation of the protected keto-aldehyde **183** followed by successive stereoselective Wittig-Horner and Wittig reactions to put in the two alkenes with control over stereochemistry. The Wittig-Horner is under thermodynamic control giving the trisubstituted *E*-alkene **185** while the Wittig is under kinetic control giving the *Z*-iodoalkene **175**; R = Ac (chapter 15).



The Suzuki coupling works very well - the moderate yield being offset by the degree of convergence achieved. Removal of the acetate and *t*-butyl ester groups allows a very efficient Yamaguchi lactonisation (see workbook) and then removal of all the remaining protection groups gives the *cis* alkene **188** that can be epoxidised stereoselectively by dimethyldioxirane though only in 45% yield to give epothilone A **173**. All the chiral centres in the final product, as well as some that were discarded en route, come from the original enzymatic aldol reaction.

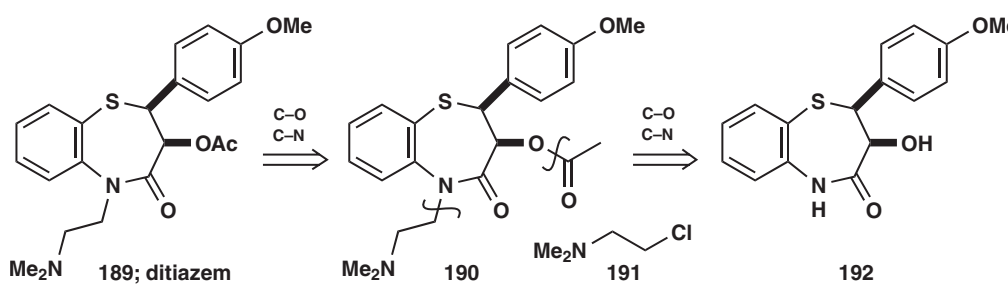


Practical Asymmetric Synthesis with Enzymes

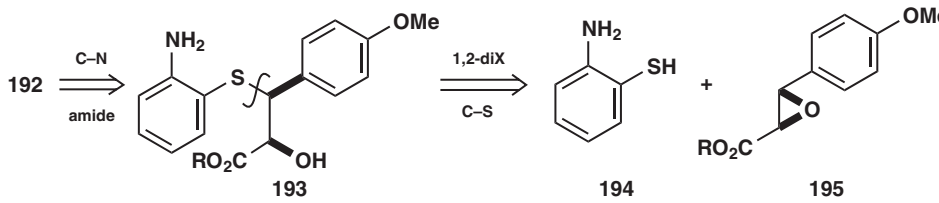
If you have reached this point in the chapter with the feeling that enzymes are all very well for the experts but that you are unlikely ever to use one, then this section is for you. Immobilized enzymes are now freely available from several companies and pharmaceutical companies use them on a large scale almost as a matter of routine. There are still problems of course and most asymmetric synthesis is not done with enzymes. In this section we set out to convince you that enzymes are practical reagents in organic solvents as well as in water and that practical minded chemists use them. An excellent review may convince you more.[49] Recently a whole issue of the journal *Organic Process Research and Development* (2002, **6**, issue 4, 420 ff.) was devoted to biocatalysis and the introductory article[50] makes the point too.

A calcium channel blocker: diltiazem

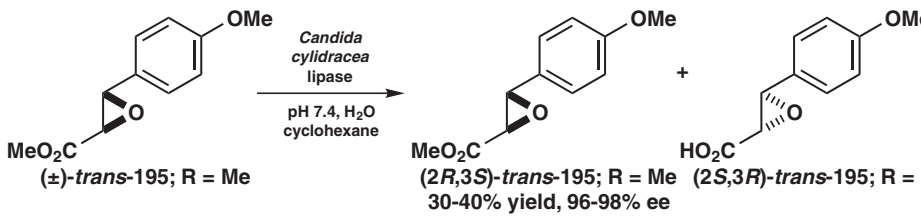
Calcium channel blockers, such as amlodipine introduced in chapter 22, are used to treat angina and hypertension. Diltiazem **189** was introduced by the Tanabe company in 1984 and is a simple derivative of the benzothiazepine **192** having two adjacent chiral centres on the heterocyclic seven-membered ring.



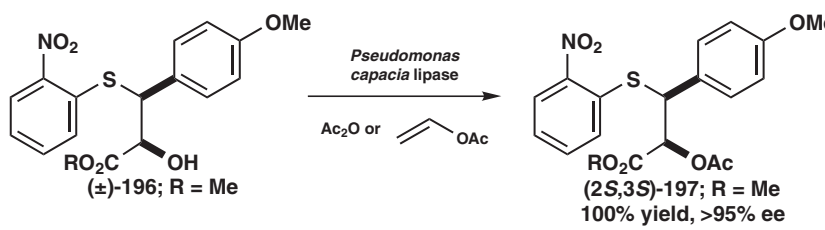
Disconnecting the ring amide reveals a 1,2-difunctionalised compound **193** that can be made by the nucleophilic opening of the epoxide **195** with the anion of the thiol **194**. To avoid chemoselectivity problems the corresponding nitro thiol is used. The chirality is already present in the epoxide which can be made by an asymmetric Darzens reaction or by Sharpless epoxidation. You may notice that the opening of the epoxide is, strangely a *cis* opening (see the workbook for details). Originally the resolution of an intermediate was used.[51]



Enzymatic methods use lipase catalysed reactions on epoxides **195** or the adducts such as **193**. Racemic *trans* methyl ester **195**; R = Me can be hydrolysed by *Candida cylindraceae* lipase using mixed solvents MeCN, CH_2Cl_2, or cyclohexane and water while no hydrolysis occurred in pure water. Cyclohexane gave the best results: the 'wrong' ester was hydrolysed while the 'right' one remained behind in the organic layer making separation simple. Ten grams could be turned over in 1.5 hours at room temperature.[52] Transesterification with chymotrypsin or lipases was less effective.

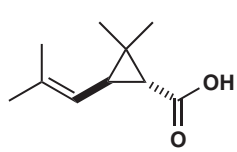


Acylation of the adduct **196** of *o*-nitrophenylthiol and the epoxide (±)-**195** with acetic anhydride or vinyl acetate in THF at room temperature catalysed by the lipase from *Pseudomonas cepacia* gave better results. Reactions with acetic anhydride are of course not possible in aqueous solution. The reaction took 2 days with Ac_2O and 7 days with vinyl acetate but the yields and ee were excellent. At 50% conversion, 100% yield of the acetate product **197** and the other enantiomer of the unreacted alcohol **196** can be isolated.[53]

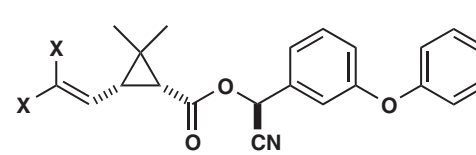


Insecticides based on chrysanthemic acid esters

The most important insecticides today are based on chrysanthemic acid: they are incredibly potent and can be used in small amounts only on the target pest. Chrysanthemic acid **198** is natural but the natural pyrethrin insecticides are too light sensitive to find much use. Chiral synthetic compounds such as cypermethrin **200** and deltamethrin **199** are used as single enantiomers.[54] They are based on the *cis* acid while natural chrysanthemic acid is *trans*.

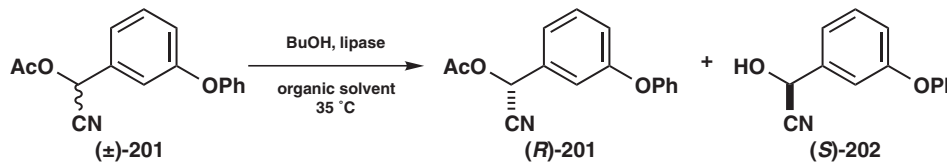


198; *trans*- chrysanthemic acid

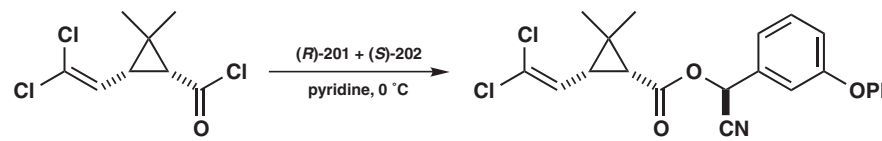


199; X = Br, (1 *R*,*cis*,α*S*)-deltamethrin
200; X = Cl, (1 *R*,*cis*,α*S*)-cypermethrin

The synthetic compounds are obviously esters of a cyclopropane carboxylic acid and a cyanohydrin **202**. Enantioselective transesterification of butanol and the acetate **201** of the cyanohydrin using immobilised lipases gives the required (*S*)-alcohol **202** and the unreacted enantiomer of the acetate (*R*)-**201** easily racemised with Et_3N. Reports using different lipases appeared at the same time: CHIRAZYME® L-6, the lipase from *Pseudomonas* immobilised on sephadex DEAE was used in *i*-Pr_2O and the racemisation carried out with Et_3N under reflux in the same solvent.[55]



Alternatively the Amano immobilised lipase P gave (*S*)-**202** in 49% yield and >99% ee with (*R*)-**201**. The mixture was separated by esterification with the chrysanthemic acid derivative giving the wanted ester and the easily separated unreacted acetate (*R*)-**201** racemised with Et_3N at 80 °C in toluene. The acid was prepared in only 86% ee so the alcohol (*S*)-**202** also acts as a resolving agent. Cypermethrin **200** is isolated in good yield and excellent diastereo- and enantiomeric purity after one recrystallisation.[56]

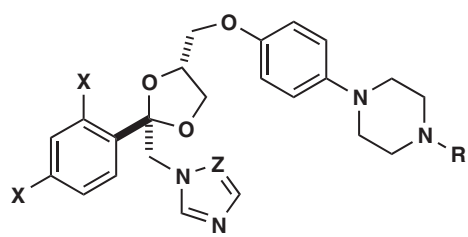


203; 86% ee

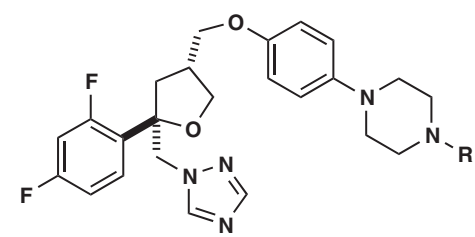
200; X = Cl, (1 *R,cis,*α*S*)-cypermethrin
82% yield, 99% de after recrystallisation

Anti-fungal triazole-containing tetrahydrofurans

A major breakthrough in modern medicine has been the discovery of effective anti-fungal compounds. One family such as ketoconazole **204** or saperconazole **205** has a dioxolan core carrying the active imidazole or triazole functionality. Schering-Plough have developed a new type having an apparently simpler tetrahydrofuran (THF) core such as **206**. This compound presents special problems for asymmetric synthesis.

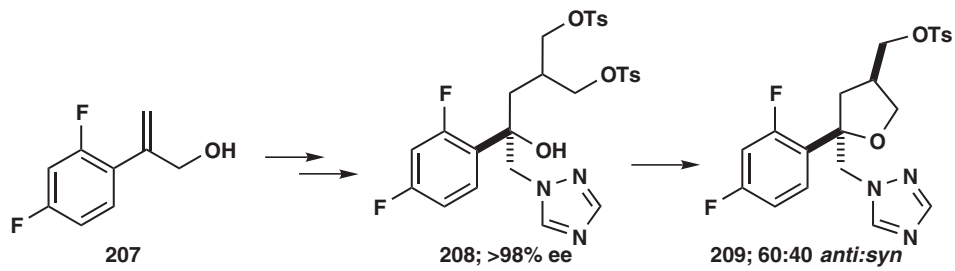


204; X = Cl, Z = CH, ketoconazole
205; X = F, Z = N, saperconazole

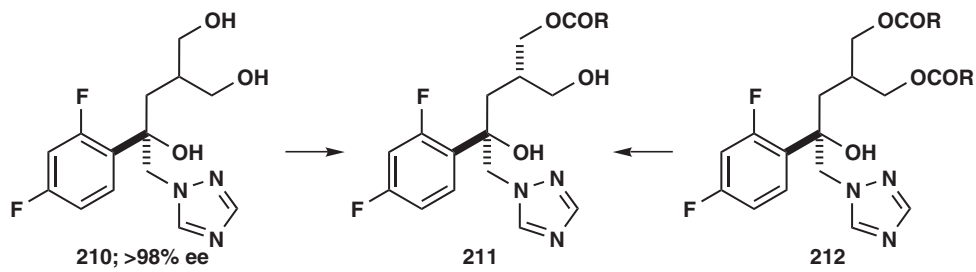


206; SCH51048, anti-fungal compound

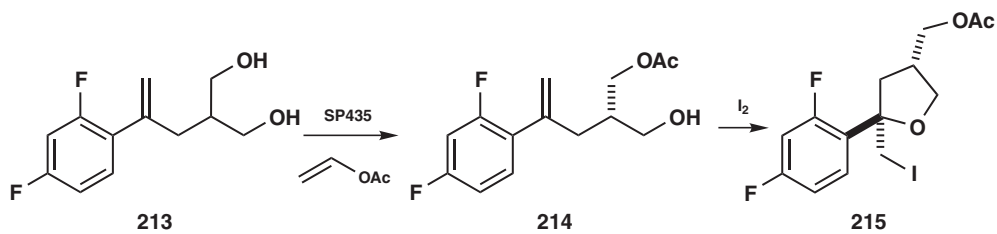
Initial attempts used the Sharpless epoxidation of the allylic alcohol **207** followed by addition of a carbon nucleophile and the triazole to give the ditosylate **208**. The two tosylates are diastereotopic but all attempts at cyclisation led to the anti THF **209** as the major product.



A more positive discrimination between the two primary OHs might be made if a reagent-dominated reaction were used and an enzyme is ideal for this job. Various lipases could be used either in the acylation of the triol **210** or in the hydrolysis of the diester **212.** In either case, the required monoester **211** could be formed in excellent ee. Novozyme (Novo Nordisk) SP 435 catalyses the monoacetylation of **210** in MeCN solution to give **211**; R = Me in 95% yield and 96.6% ee after only 55 minutes.

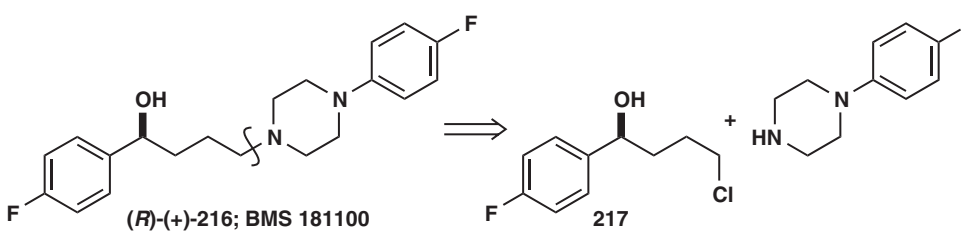


A simpler approach gave even better results. The prochiral diol **213** was cleanly monoacetylated by the same enzyme (98% yield, 98% ee) and iodo-etherification gave the required diastereoselectivity **215** with suitable functionality for the introduction both of the triazole and of the other side chain.[57]

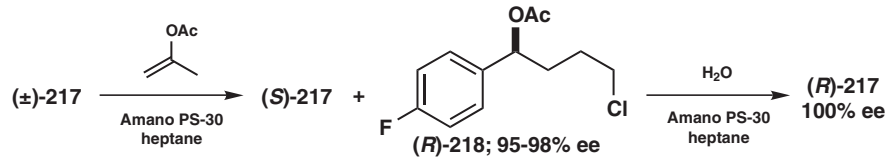


Bristol-Meyers Squibb anti-psychotic agent BMS 181100

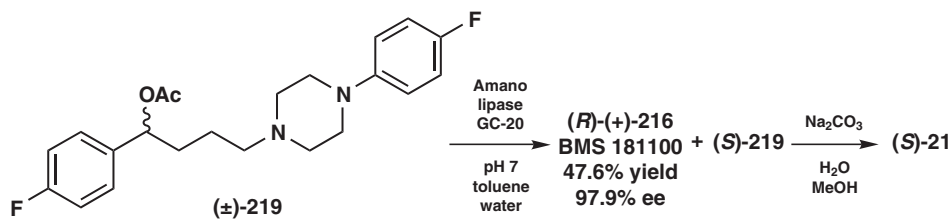
A related though simpler compound from Bristol-Meyers Squibb **216** is their anti-psychotic agent BMS 181100. It has two *p*-fluorophenyl groups joined through a C_4-piperazine linker containing a chiral secondary alcohol. The compound is easily made[58] by alkylation of an amine with the primary chloride **217**. There are two opportunities from enzymatic resolution.



Racemic **217** could readily be acetylated with isopropenyl acetate catalysed by the Amano lipase PS 30. The resolution was successful only in organic solvents and heptane was the best. Any water reduced both the rate of the reaction and the ee of the product. Acetylation occurred on the wanted (*R*) enantiomer **218** but the product could be hydrolysed to (*R*)-**217** with the same enzyme with added water. The reactions were carried out on a 100 g scale using 200 g of immobilised enzyme that could be filtered off and used again and again with little diminution in ee. This sounds like a lot of enzyme but it is a polymer-supported enzyme so the bulk is polymer.

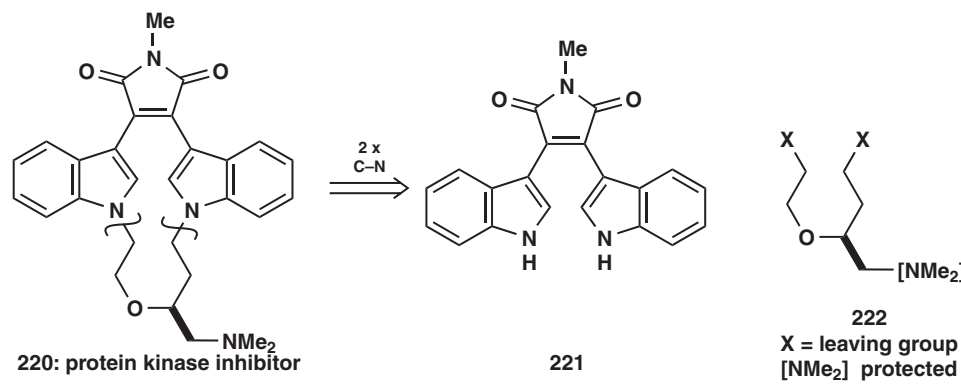


Alternatively, the acetate **219** of the final product (±)-**216** could be enantioselectively hydrolysed with another Amano lipase GC-20, chosen after a survey of fourteen enzymes. At this stage both enantiomers of the drug were needed for evaluation and the unreacted (*S*)-acetate could be hydrolysed to (*S*)-**215** without racemisation. Again organic solvent was necessary: *E* was 1 in pure water and maximum (>100) in toluene or CH_2Cl_2.



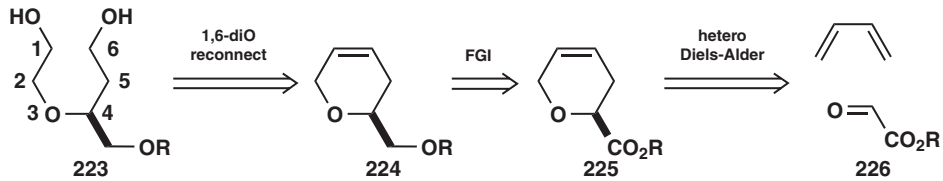
An Eli Lilly protein kinase inhibitor

Protein kinase inhibitors are in the news as cancer drugs but Eli Lilley have a saturosporinone analogue **220** to help diabetes patients overcome problems such as sight loss from retinopathy. The bis-indole portion **221** does not concern us but the chiral fragment **222** does.

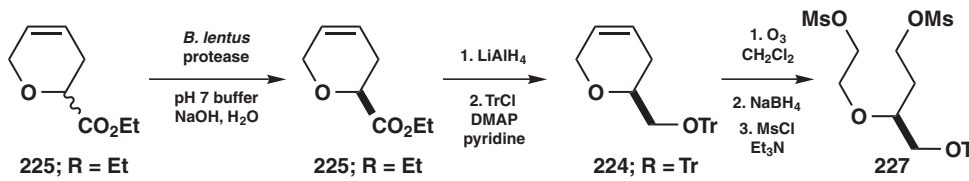


The near-symmetry of **222** suggests that writing OH or OR for the functionality **223** would be helpful. This reveals a 1,6 relationship between the two OH groups that might be made by oxidative cleavage of a cyclohexene **224**. This in turn could be derived from a Diels-Alder reaction

providing that the CH_2OR group is first replaced by a carbonyl group **225**. This ester might be resolved enzymatically.

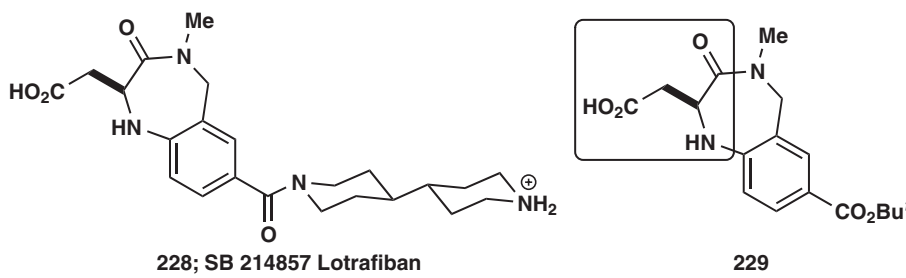


The commercial solution of ethyl glyoxylate **226**; R = Et in toluene was heated in an autoclave with butadiene to give the adduct **225**; R = Et in 50-60% yield, easily purified as the polymeric by-products are soluble in toluene. A survey of various enzymes and formulations showed that cheap aqueous *B. lentus* protease gave the best results. Only 90 mls of a 5% solution of the enzyme was needed to hydrolyse 150 g of **225**; R = Et in eight hours. Under these conditions *E* is 36.6 and 35–40% yield of (*S*)-**225**; R = Et having ee > 99.5% could be extracted with toluene. The free acid **225**; R = H remains in the aqueous layer. The trityl-protected bis-mesylate **227** was produced in good yield on a multi-kilogram scale with 96.7% ee and used to make the drug[59] **220**.



Lotrafiban: a GlaxoSmithKline drug to prevent blood clots

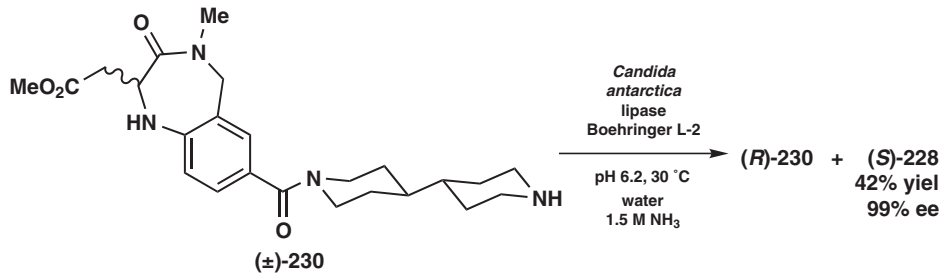
During the scale-up of an asymmetric synthesis of lotrafiban **228**, a drug for the prevention of thrombotic 'events', racemisation proved to be a problem. The synthesis used the chiral pool strategy (chapter 23), the fragment in the frame of the intermediate **229** being derived from aspartic acid.



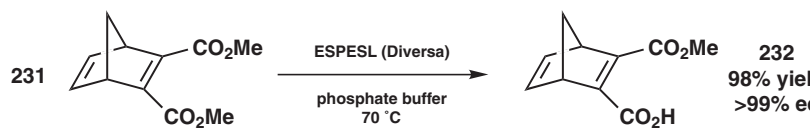
Since they already had a good synthesis of racemic ester, a late stage in the synthesis, an enzymatic hydrolysis looked a good bet. In the event hydrolysis with *Candida antarctica* lipase was superlative: hydrolysis gave only the required enantiomer and stopped cleanly at 50% conversion. Various supported versions were tried and the best was the Boehringer L-2 preparation in which the enzyme is covalently bound to a cross-linked resin making it stable in aqueous solution. In the pilot plant 76 kgm of racemic methyl ester **230** react in 2.5 hours with 6 kg of supported enzyme. Benzyl chloroformate in CH_2Cl_2 is added and the unreacted ester (*R*)-**230**,

now Cbz derivatised, remains in the CH_2Cl_2 layer (and is later recycled by racemisation) while the product is in the aqueous layer. The enzyme could be reused at least 100 times without loss of activity.[60]

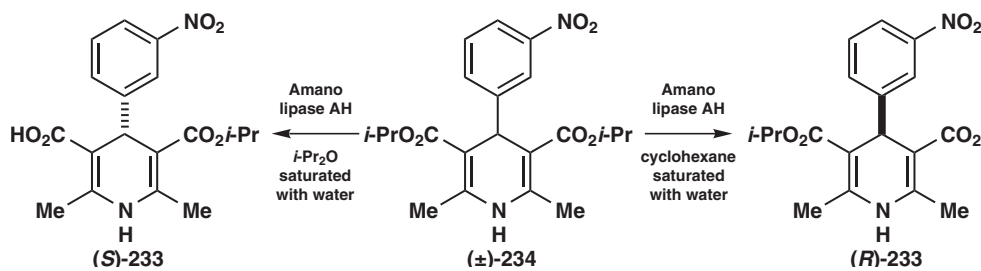
Two desymmetrisations



We end this chapter with two much simpler reactions - a couple of desymmetrisations - each special in their own way. The first is amazingly efficient, using a lipase/esterase from a thermophilic organism supplied as a recombinant protein by the Diversa corporation. The symmetrical Diels-Alder adduct **231** is rapidly and perfectly desymmetrised to the monoacid[61] **232** at 70 °C.



The second is even more remarkable. The amlodipine type of dihydropyridine drugs are chiral but only just so. In some cases the only distinction is a methyl ester on one side and an ethyl ester on the other. The symmetrical compound **234** can be easily made by the Hantzsch pyridine synthesis and desymmetrisation looks as good as anything in attempting an asymmetric synthesis. Work from the Amano company using their own lipase AH established, almost incredibly, that one enantiomer is formed in *i*-Pr_2O but the other in cyclohexane (both solvents are saturated with water).[62] One problem with enzymes is generally that they can give only one enantiomer. With an unnatural substrate in unnatural media this may not be the case!



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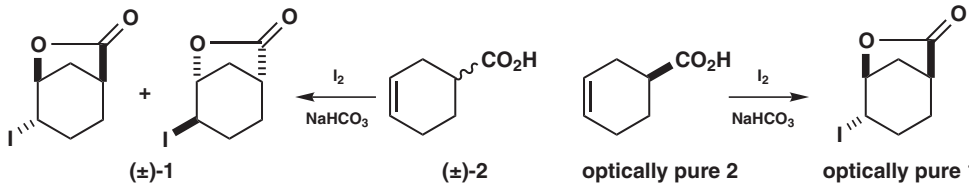
30 New Chiral Centres from Old — *Enantiomerically Pure Compounds & Sophisticated Syntheses* —

The Purpose of this Chapter

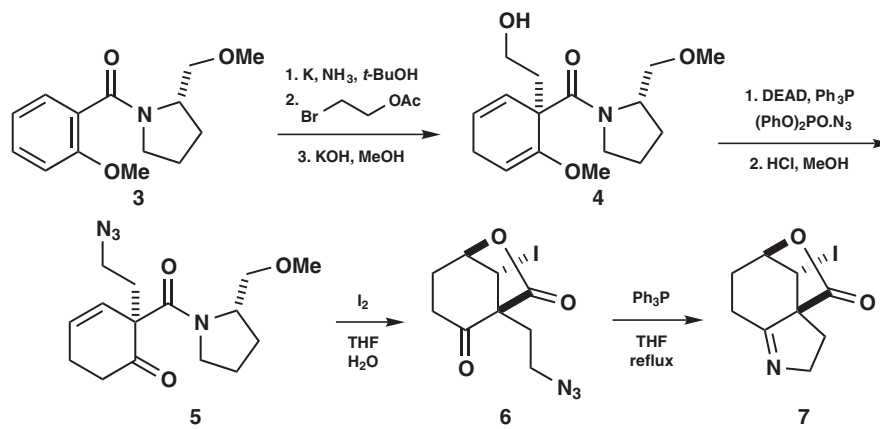
We have already seen in earlier chapters how one chiral centre can lead to another. We have seen this in the context of racemic compounds and in the context of optically pure ones. So for instance, new chiral centres are made when unsaturated acid (±)-**2** reacts to form the iodolactone **1**. If the acid **2** is racemic, both enantiomers of one diastereoisomer of the lactone **1** are formed but if **2** is optically pure, only one is formed. The existing chiral centre in **2** controls the two new ones in **1**. The relative stereochemistry in the racemic product (±)-**1** is exactly the same if we start with optically pure material.

Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

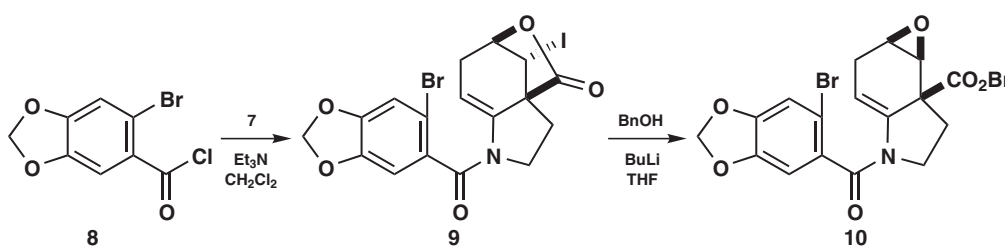


There is a clear overlap in concept between this chapter and chapter 21 but the purpose of *this* chapter is to explore how new chiral centres are made from old ones in some more sophisticated molecules, to look at some strategies we have not seen before, and to see how things are different when the starting material is a single enantiomer. We shall revisit the principles of chapter 21 so return there if you are in doubt about any of them. We shall use the asymmetric methods of chapters 22–29 and consider what advantage there is in having both substrate and reagent as single enantiomers. But first we shall look at an application of iodolactonisation in asymmetric synthesis.

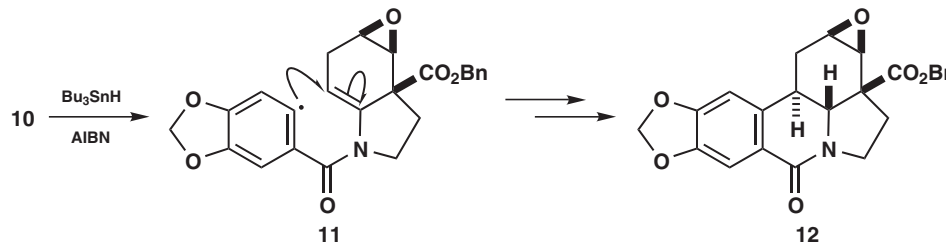
We pointed out in chapter 27 that Schultz's asymmetric Birch reduction can be developed with iodolactonisation to remove the chiral auxiliary and set up new chiral centres. Now we shall see how he applied that method to alkaloid synthesis.[1] The first reaction is the same as in chapter 27 but the alkyl halide is now specified: this gave diastereomerically pure acetate in 96% yield and hydrolysis gave the alcohol **4**. Mitsunobu conversion of OH to azide and enol ether hydrolysis gave **5**, the substrate for the iodolactonisation. Iodolactonisation not only introduces two new chiral centres but cleaves the chiral auxiliary, as described in chapter 27. Reduction of the azide **6** to the amine with Ph_3P leads to the imine **7** by spontaneous ring closure.



Acylation with **8** moves the imine to an enamine **9** and opening the lactone with the lithium alkoxide of benzyl alcohol gives the epoxide **10** ready for the key cyclisation.



This synthesis was designed around a radical cyclisation to close a six-membered ring and create yet another two new chiral centres. The radical may be induced either by Bu_3SnH or photochemically and cyclises in a 6-*endo-trig* manner from the top face of the enamine giving *cis* 5/6 and *trans* 6/6 ring junctions. The original six-membered ring that was the benzene ring in **3** now has five chiral centres. One was created in the original asymmetric Birch reduction but the other four were introduced two by two using iodolactonisation and cyclisation as diastereoselective reactions. Product **12** has the skeleton and most of the functionality of the lycorine alkaloids.



New Chiral Centres from Old

The starting materials in this chapter will already be single enantiomers and will have been made so by one of the methods we have discussed at length over the last eight chapters: Resolution (chapter 22), Chiral Pool (23), Asymmetric Reagents (24) Asymmetric Catalysis (25 and 26), Substrate-Based Strategy (27), Kinetic Resolution (28) or Enzymes (29). These strategies will be identified by chapter titles and you are invited to check back if such descriptions are obscure or to check the references for more detail.

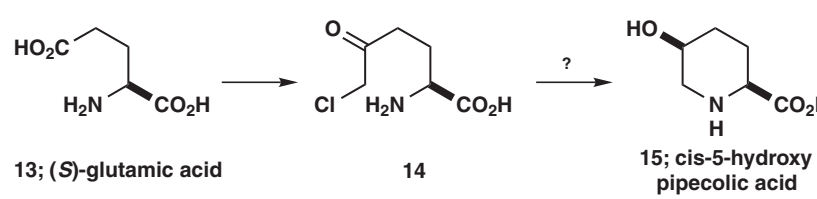
The starting materials will generally have one or two chiral centres and methods for transmitting this information across the molecule to form new chiral centres will be based on the discussion in chapter 21 and will involve:

- Use of Rings: preformed rings, conformational control, ring formation, folded molecules.
- Cyclic Transition States: chelation control, reagent delivery, rearrangements.
- Open Chain Stereochemistry: 1,2-control by Felkin-Anh and Houk transition states.
- More Distant Control: 1,3-, 1,4- and remote control.

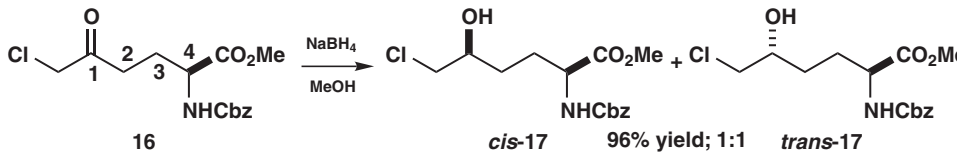
It will not be possible to separate these methods totally as many syntheses involve several of them sequentially or together but we shall usually introduce an area with a simple example to set the scene.

Creating New Chiral Centres with Cyclic Compounds

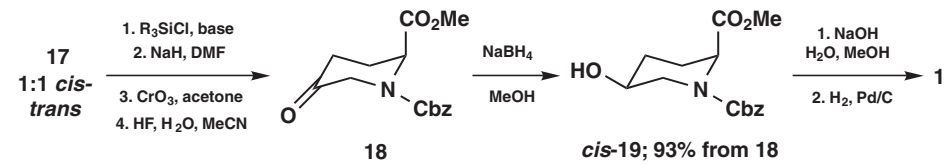
Rings have fewer conformations than open chains. This is as important in transmitting asymmetry as it was in chapters 20–29 in creating asymmetry. A simple illustration is Bailey's synthesis of *cis*-5-hydroxypipecolic acid **15** by a chiral pool strategy from natural (*S*)-glutamic acid **13**. Bailey's original idea was to cyclise the α-chloroketone **14** but this was not successful, even when NH_2 and CO_2H were protected.[2]



The corresponding protected alcohol **17** would cyclise but reduction of **16**, though giving a good yield, was totally non-stereoselective, giving *cis*- and *trans*-**17** in a 1:1 ratio. This is not surprising: drawn out as a straight chain compound **16** has a 1,4-relationship between the existing chiral centre and the prochiral carbonyl group. This is usually too far for effective induction.



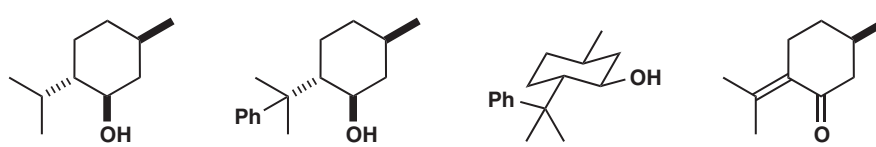
Cyclisation of the mixed (silylated) alcohols **17** and oxidation to the ketone **18** allowed a comparison between reduction of the open chain **16** and cyclic **18** ketones. Reduction of **18** gave just one diastereoisomer *cis*-**19** and so, after deprotection, the target molecule. Later improvements allowed a shorter route to **18** by rhodium-catalysed carbene cyclisation.[3]



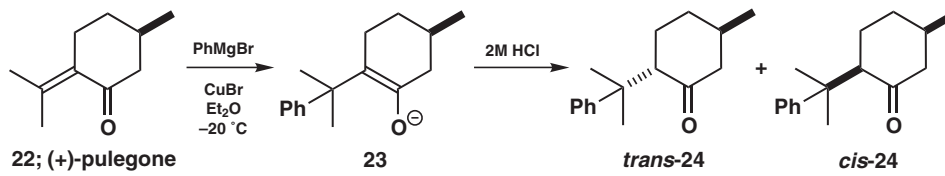
The high selectivity is due to the single conformation of **18** in contrast to the many conformations available for **16**. The CO_2Me group is axial to avoid eclipsing the planar Cbz group that is conjugated with the planar nitrogen atom. Reduction with the small reducing agent $NaBH_4$ gives, as usual, the equatorial alcohol **19**. Conformations of six-membered rings are particularly well defined but all rings have better defined conformations than the corresponding open chain compounds.

Conformational control

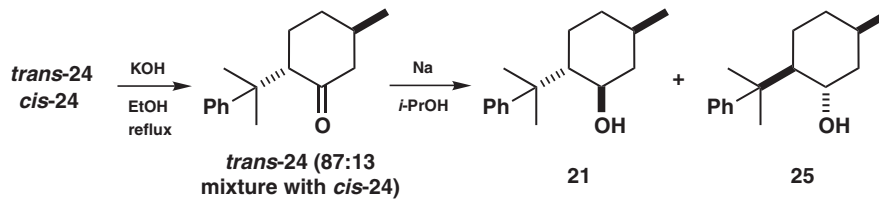
In chapter 27 we recommended 8-phenylmenthol **21** as a chiral auxiliary. The three chiral centres in 8-phenylmenthol are made by from the terpene pulegone **22** (chiral pool) having only one chiral centre. The new chiral centres have 1,3- and 1,4-relationships to the centre already present in pulegone and the key to their successful control is conformational analysis. 8-Phenylmenthol has all three substituents equatorial.



Copper-catalysed conjugate addition of PhMgBr to pulegone gives the enolate **23** with no new chiral centres but protonation gives a 55:45 mixture of the *cis*- and *trans*-ketones **24**. This is disappointing as we might have expected greater selectivity for the all-equatorial *trans*-**24**. In fact equilibrium was not achieved in acid and a separate treatment with KOH in ethanol under reflux converts the 55:45 mixture into an 87:13 mixture.[4]

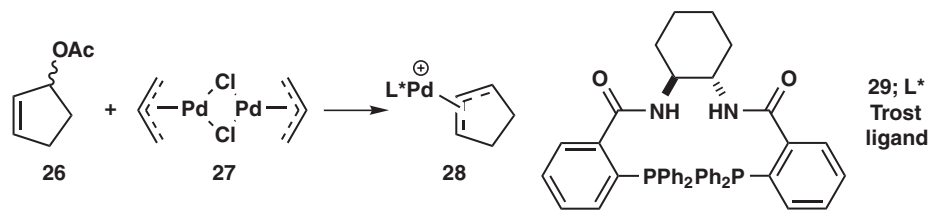


The mixture is reduced with sodium in *i*-PrOH to give the same proportions (87:13) of two alcohols **21** and **25**. This thermodynamically controlled reduction is totally stereospecific, giving the equatorial alcohol in both cases. Presumably the equilibration of the ketone **24** is less successful because the large $PhCMe_2-$ group eclipses the carbonyl group when it is equatorial. The two alcohols are easily separated as their chloroacetyl esters.

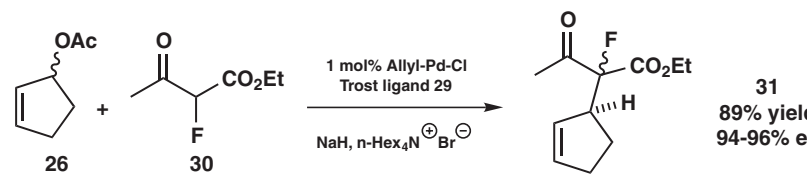


Cyclisation: ring-closing reactions

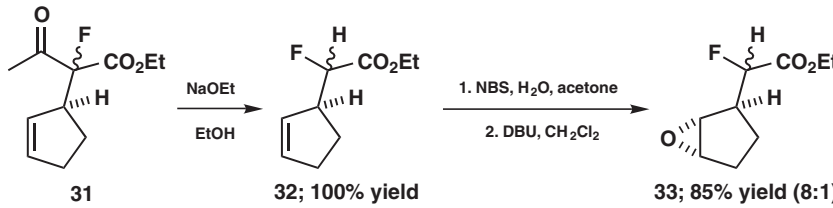
Schultz's lycorine **12** synthesis started with the creation of asymmetry (one centre) in one ring and built two other rings onto that ring by cyclisation reactions. This is a good strategy and can be applied to much simpler molecules such as Merck's anti-schizophrenia drug MGS002836. The first centre was introduced by asymmetric allylic alkylation of the palladium allyl cation complex **28** from the racemic acetate **26** using the Trost ligand **29** to provide the asymmetry.[5]



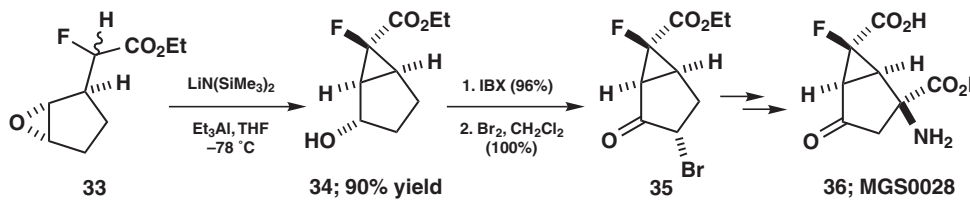
The nucleophile is the enolate anion from ethyl 2-fluoroacetate **30** formed with NaH in the presence of n-$Hex_4N^+Br^-$. The complex **28** would be achiral except for the ligand which directs the nucleophile to one end of the allyl cation on the opposite face to the palladium. With only 1 mol% of the catalyst up to 96% ee was achieved though only one centre in **31** is controlled.



This is not important as deacylation destroys that centre anyway **32**. Epoxidation followed: the best route was bromohydrin formation with NBS in water followed by elimination with DBU and gave an 8:1 selectivity for epoxidation on the opposite face to the substituent **33**.

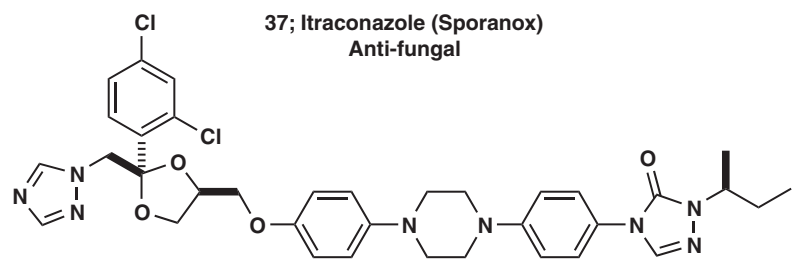


Now comes the critical cyclisation: treatment with a stronger base (LiHDMS) creates the prochiral enolate centre which cyclises onto the epoxide. The three centres on the ring are controlled: two are not involved and the third is stereospecifically inverted by the intramolecular S_N2. The new fluorinated centre on the three-membered ring **34** is controlled stereoselectively with the larger CO_2Et group on the outside (convex or *exo* face of the folded molecule - see below). Further reactions involve the oxidation of the alcohol **34**, bromination of the ketone, again on the outside of the folded molecule **35**, and introduction of an amino acid to give Merck's potential schizophrenia drug **36**. Each chiral centre was developed from the original asymmetric allylation.

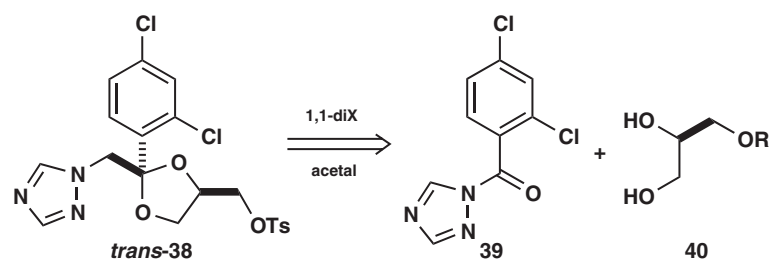


Thermodynamic control in formation of cyclic compounds

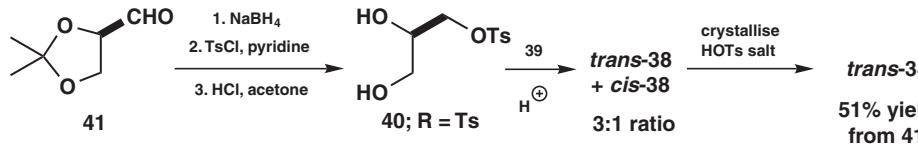
The rather complex anti-fungal compound itraconazole (Sopranox) **37** has two triazole rings each substituted with chiral units. They are very far apart and each must be made separately.[6]



Chemists at Sepracor appreciated that the left hand unit **38**, being an acetal, could be made only by the usual acetal formation from a ketone **39** and a diol **40**. Note that the diol is precariously chiral as if R = H, the compound has a plane of symmetry.

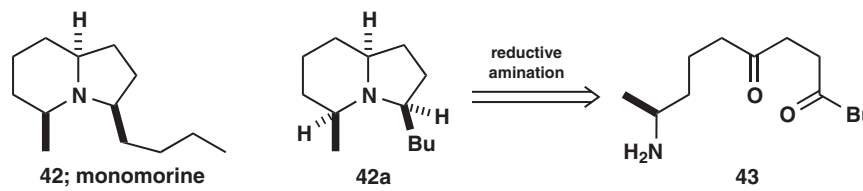


Diol derivatives **40** can be made from protected glyceraldehyde (chiral pool strategy) and the obvious choice for R is Ts so that the new C–O bond needed for itraconazole can be made by alkylation of the phenol. Reaction of the diol **40**; R = Ts with the ketone **39** in acid solution gave a mixture of *trans*- and *cis*-**38** in an acceptable 3:1 ratio. The preferred diastereoisomer has the benzene ring on the opposite side to the CH_2OH group. The triazole ring is further away and so less hindering. *Trans*-**38** can easily be separated from *cis*-**38** by crystallisation and the overall yield (51%) from **41** is excellent. *Cis*-**38** can of course be recycled as acetal formation is reversible: an advantage of thermodynamic control.

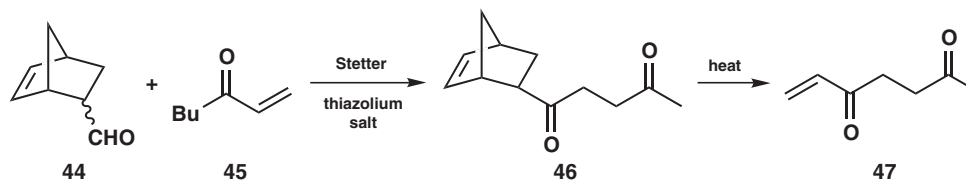


Cyclic intermediates

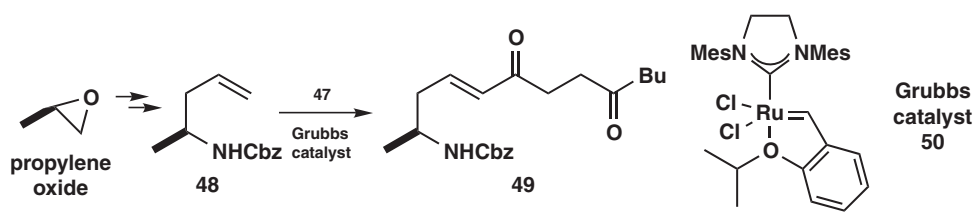
The conversion of prochiral centres in cyclic intermediates into fully blown chiral centres is a profitable way to transmit stereochemical information. The ant trail pheromone monomorine **42** when re-drawn so that we can see all three hydrogen atoms on the same surface of the molecule **42a**, is an ideal candidate for synthesis by reductive amination. One of the three centres must be made asymetrically and then the other two set up by reduction of imines formed from that amine and two ketones as in **43**.



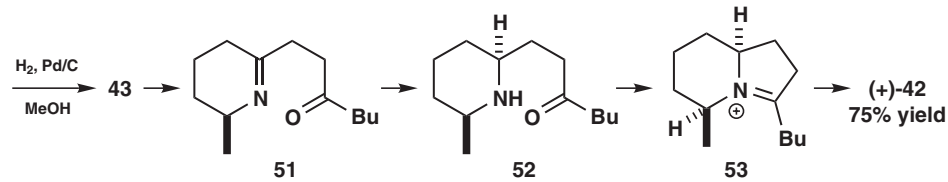
The synthesis we are going to describe is particularly ingenious. A Stetter reaction (chapter 14) with the Diels-Alder adduct **44** (it doesn't matter that this is racemic and a mixture of *exo/endo* isomers) and the enone **45** provides the 1,4-diketone in 85% yield and hence, by retro-Diels-Alder, the achiral enedione **47** in 81% yield.[7]



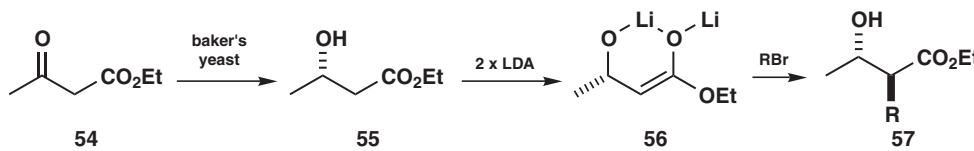
The amine **49**, made from one enantiomer of propylene oxide by simple reactions, is the source of the chirality. A cross-metathesis with **47**, using the Grubbs catalyst **50** gave a surprisingly excellent yield (89%) of the complete carbon skeleton **49** of monomorine.



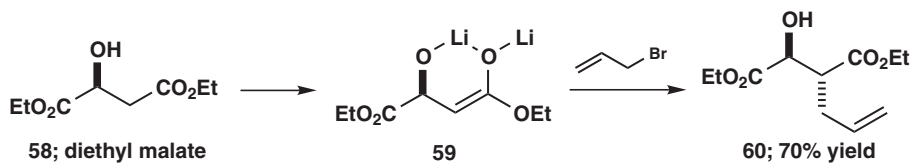
Catalytic hydrogenation of **49** produces monomorine in one step and in 75% yield. First the alkene must be reduced to give the molecule the flexibility to cyclise. Hydrogenation removes the Cbz group and the amine cyclises onto the nearer ketone to give the imine **51** which is reduced from the less hindered face opposite the Me group to give **52**. Now cyclisation to the second ketone produces the imine salt **53** and a second reduction from the same side gives (+)-monomorine. The first reduction of **51** is totally stereoselective but the second gives about 15% of the other epimer. Since the origin of the stereochemistry is only a methyl group, this is remarkably good.



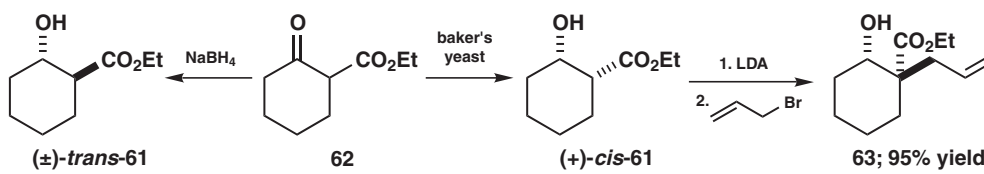
Other prochiral units that can be trapped in rings are enolates. One famous application is the alkylation of β-hydroxy acid derivatives available from the chiral pool (chapter 23), by asymmetric aldol reactions (chapter 27) and by asymmetric reduction of β-keto-esters either by catalytic hydrogenation (chapter 26) or by enzymes (chapter 29). Fráter found that the alcohol **55,** from the baker's yeast reduction of the ketoester **54**, formed the enolate **56** held in shape by chelation. Alkylation occurred on the top face.[8] This is not so much because the OH is down in **55** as that the methyl group is down in **56**.



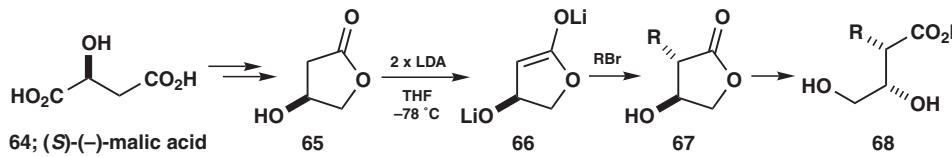
Seebach has done similar work with malic acid. A detailed account[9] of the allylation of the enolate **59** formed preferentially on the unsubstituted carbon atom with allyl bromide giving a 92:8 ratio of diastereoisomers **60** is in *Organic Syntheses*.



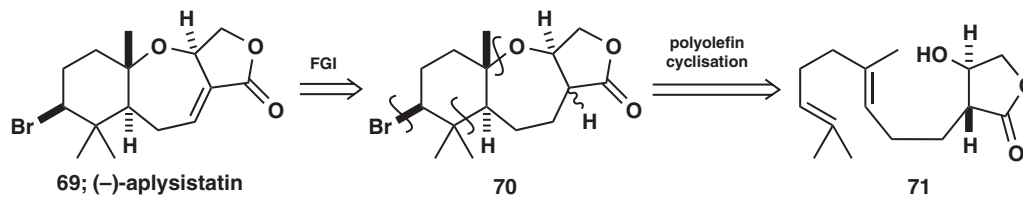
Fráter quotes an interesting example **62** where $NaBH_4$ reduction gave the all equatorial *trans*-**61** (racemic of course) while baker's yeast reduction gives one enantiomer of the *cis* compound **61** evidently by reagent controlled dynamic kinetic resolution (chapter 28). Allylation of the enolate of *cis*-**61** goes with the expected *anti* selectivity.[10]



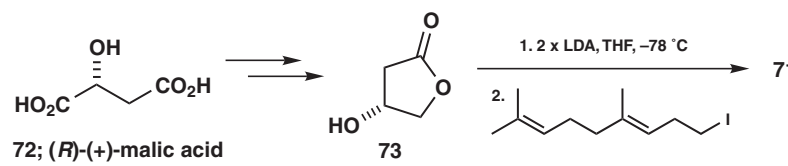
If the β-hydroxy acid derivative is a lactone, the chain is turned the other way and no chelation is possible. The lactone **65** can be prepared from malic acid **64** (either enantiomer) and the dilithium derivative **66** cannot be chelated. Instead the solvated (THF is the solvent) LiO group blocks the top face of the almost planar enolate. The selectivity is *anti* as before but when the chain is opened out **68** by hydrolysis of the lactone it is clear that the other diastereoisomeric relationship to that in **60** has been made.[11]



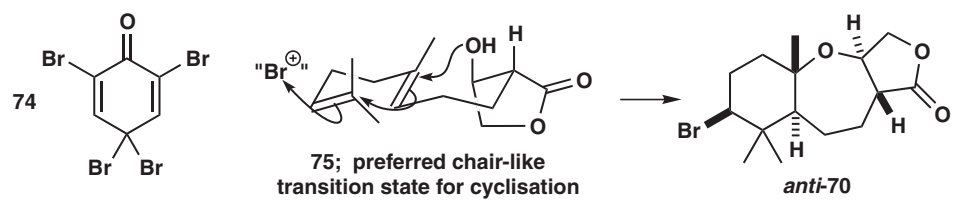
We shall illustrate this with Prestwich's synthesis[11] of the natural anti-cancer compound (−)-aplysistatin **69**. This interesting compound with a seven-membered cyclic ether and a bromine atom proclaiming its marine origin is probably made in nature by a polyolefin cyclisation and that strategy was used in the synthesis. The alkene must be removed **70** before the cyclisation can be reversed. The stereochemistry of the extra centre in **70** is unimportant until the realisation that it can be made by alkylation of a hydroxylactone **71** whose stereochemistry must be *anti*.



The (*R*)-(+)-isomer of malic acid **72** must be used and the lactone **73** is the enantiomer of **65**. The alkylating agent is the terpene derivative homogeranyl iodide and the selectivity is *anti* as expected. The yields in this synthesis are not wonderful but it is short and biomimetic.

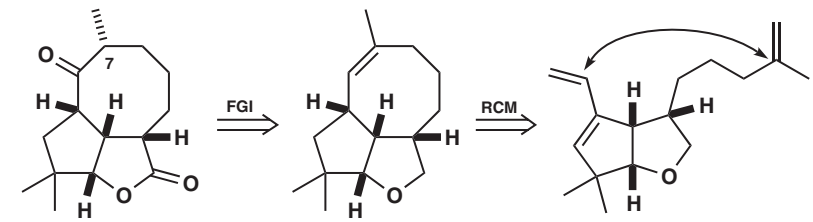


The cyclisation uses the convenient brominating agent **74** and the preferred conformation for cyclisation has an all chair arrangement of the side chain **75**. By this means the two chiral centres in **71** induce three more in **70**. The remaining double bond is introduced by selenium chemistry (chapter 33). In this process the chiral centre introduced by alkylation of **73** is destroyed but it has played its part in controlling the conformation **75**.



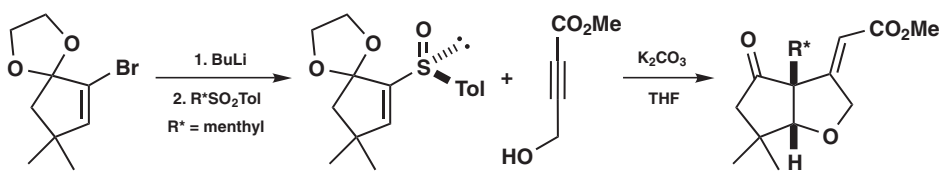
Stereochemical control in folded molecules

When two small rings are fused together, the molecule is folded rather like a half-opened book. When more rings are added, the molecule may adopt a bowl shape.[12] In both cases the molecule has a convex or *exo* face on the outside that reagents find easy to reach and a concave or *endo* face on the inside that is much more difficult to reach. Astericanolide **76** has two five- and one eight-membered rings and is bowl-shaped as all four hydrogen atoms at the ring junctions are on the same side. Paquette[13] decided to close the eight-membered ring by ring-closing metathesis (RCM, chapter 15) and so removed the ketone, the remote chiral centre (C-7) and the lactone carbonyl **77** as a preliminary. Disconnection gave **78** as the substrate for metathesis, the two arrowed carbons being destined for cyclisation.



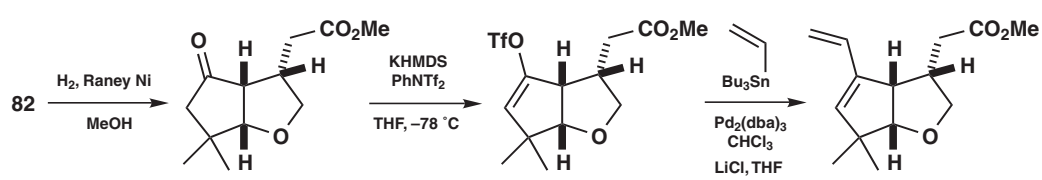
76; (+)-astericanolide **77** **78**

The 5/5 fused system in **78** is folded but has the side chain on the inside: it may be possible to force it inside by adding the hydrogen atom last. The synthesis starts with a vinyl-lithium reagent derived from **79** (chapter 16): reaction with a single enantiomer of menthyl *p*-tolylsulfinate gave the sulfoxide **80**. Michael addition of the propargyl alcohol **81** was not very efficient but could be persuaded to give one diastereoisomer of the adduct **82** in 38% yield. As we shall see in chapter 36, this sacrifice in yield is worthwhile when a tandem reaction occurs. Here Michael addition of the alcohol has been followed by Michael addition of the resulting anion to the acetylenic ester.



79 **80; 77% yield** **81** **82**

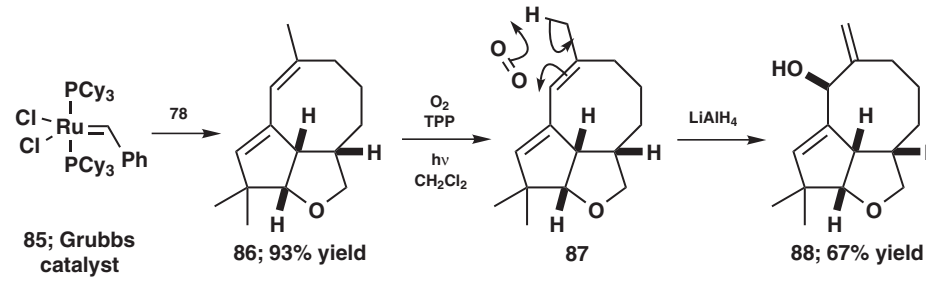
Hydrogenation with Raney nickel removes the chiral auxiliary and, as we had hoped, hydrogenates the alkene from the less hindered *exo*-face, pushing the side chain inside the folded molecule **83**. The ketone is converted into the only possible vinyl triflate for Stille coupling with a vinyl stannane to give the diene **84**.



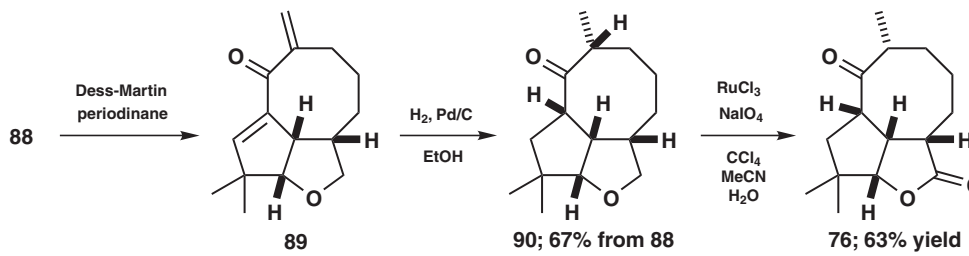
83; 88% yield **98% yield** **84; 98% yield**

The next few stages to produce the metathesis substrate **78** are straightforward and involve the creation of no new chiral centres. The metathesis was very successful with the original Grubbs' catalyst **85** and gave the cyclic diene **86**. Now the two carbonyl groups and the last two chiral

centres must be added. Porphyrin-sensitised (TPP = tetraphenylporphine) photochemical addition of singlet oxygen by an ene reaction **87** occurred also on the *exo*-face and gave, after reduction of the hydroperoxide, the doubly allylic alcohol **88**.

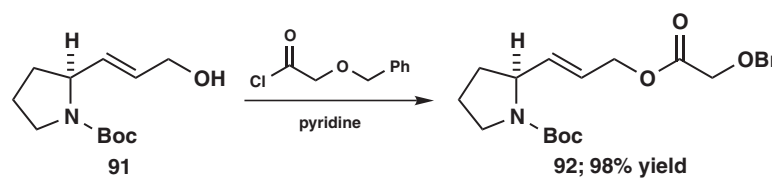


This new centre does not appear in the natural product **76**. It is oxidised to the ketone and both alkenes reduced catalytically, both hydrogen molecules being added from the *exo*-face to set up both chiral centres in one step. The THF is finally oxidised to the lactone with Ru(IV). After the initial Michael addition, controlled by the sulfoxide, every chiral centre depends on the folded or bowl-shaped molecule.

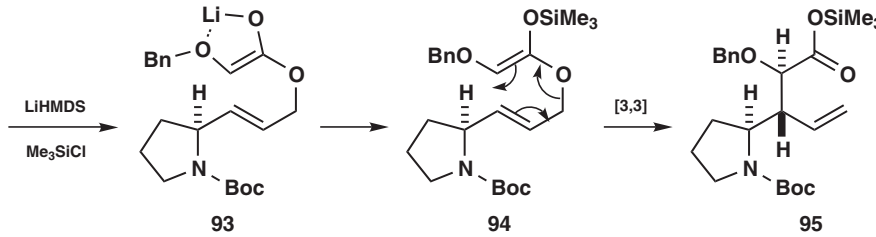


Stereochemical Transmission by Cyclic Transition States: Sigmatropic Rearrangements

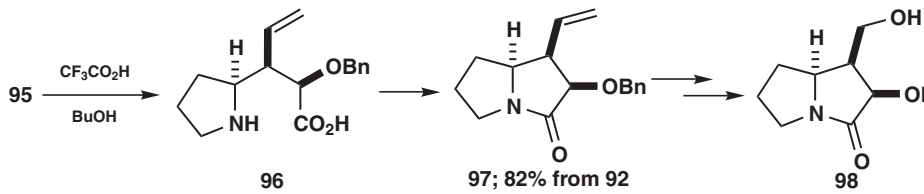
Rearrangements are more commonly used to move chirality around a molecule without actually creating new centres. That new centres can be made is illustrated clearly by Mulzer's Ireland-Claisen approach to indolizidine alkaloids[14] such as (−)-petasinecine **98** from proline (chiral pool). Proline is converted into the allylic alcohol **91** which is acylated to give the substrate **92** for an Ireland-Claisen rearrangement.



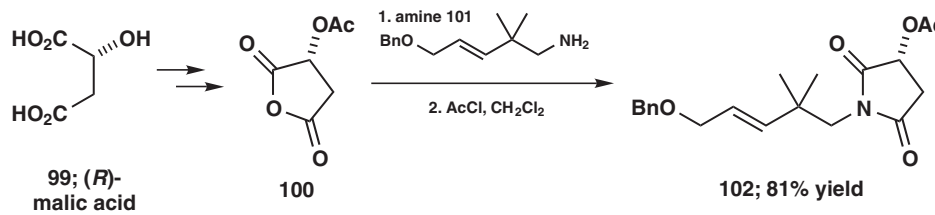
Treatment with LiHMDS [$LiN(SiMe_3)_2$] gives the *Z*-enolate **93** because of chelation and hence the silyl enol ether **94** that undergoes the [3,3] sigmatropic rearrangement to give one diastereoisomer of **95** with two new chiral centres both controlled by the original one from proline.



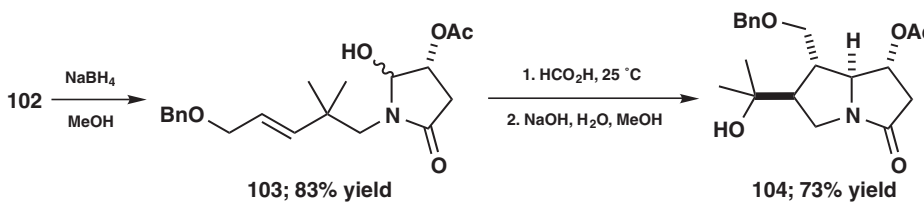
Removing the Me_3Si and Boc groups and redrawing the structure reveals the amino acid **96** that cyclises in acid solution to bicyclic **97** having the skeleton of the indolizidine alkaloids. Further steps lead to (−)-petasinecine **98**. This sequence looks involved but in fact only three intermediates are isolated: **92**, **96**, and one between **97** and **98**.



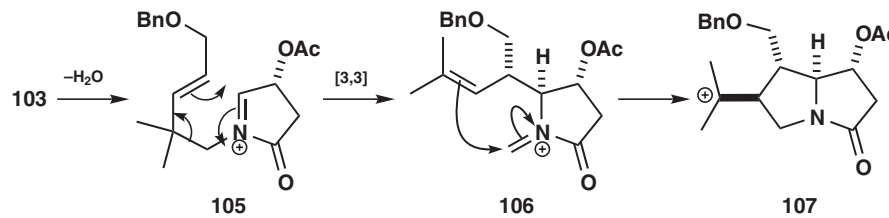
A more complicated example is the synthesis of (−)-hastanecine by Hart and Yang.[15] (*R*)-(+)-Malic acid **99** was used as a chiral pool starting material and converted into the anhydride **100** by straightforward steps. Reaction with the amine **101** gave the pyrrolidine **102**.



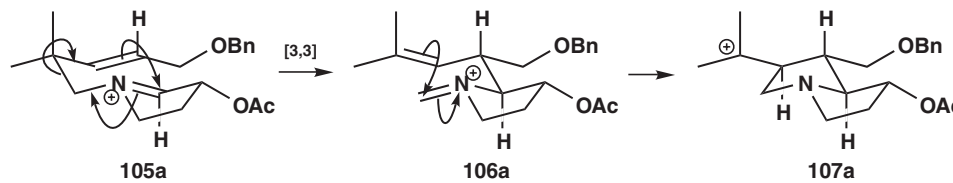
Reduction of the anhydride gave **103** with complete regioselectivity in favour of the carbonyl next to the acetate but without stereoselectivity. This doesn't matter as treatment with acid initiated a rearrangement - cyclisation sequence giving a the alcohol **104** after hydrolysis of its formate. This time there is complete stereoselectivity in the creation of three new chiral centres.



Loss of water from **103** gives the iminium salt that undergoes the [3,3]-sigmatropic rearrangement **105** to give **106** with two of the new chiral centres already fixed. An ionic cyclisation **106** fixes the third and the cation **107** picks up water to give **104** or formic acid to give its formate ester.

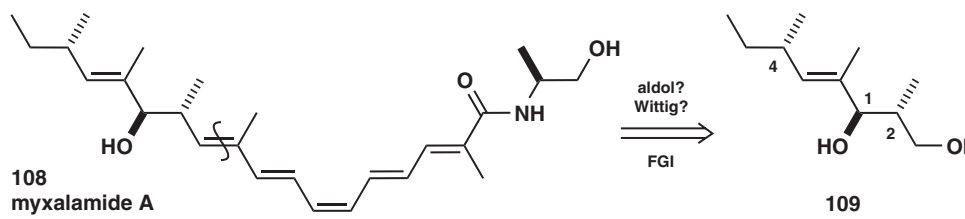


The stereochemistry of these steps is of course controlled by the original chiral centre derived from malic acid. The acetate prefers to adopt a pseudo-equatorial position in the cation **105** and the conformational drawings **105a–107a** show that a chair conformation for the [3,3] step with equatorial substituents gives the first two new chiral centres and a pseudo-equatorial position for the isopropyl substituent in the ionic cyclisation gives the third.

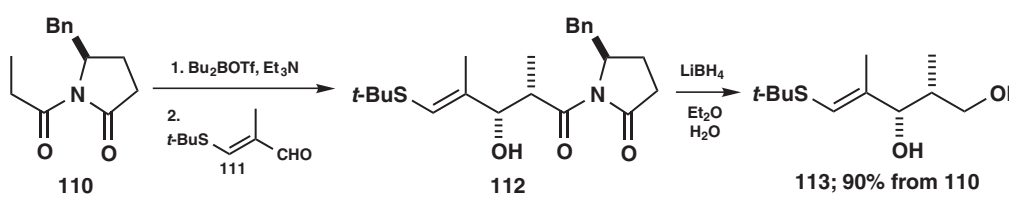


Mapp and Heathcock's synthesis of myxalamide A

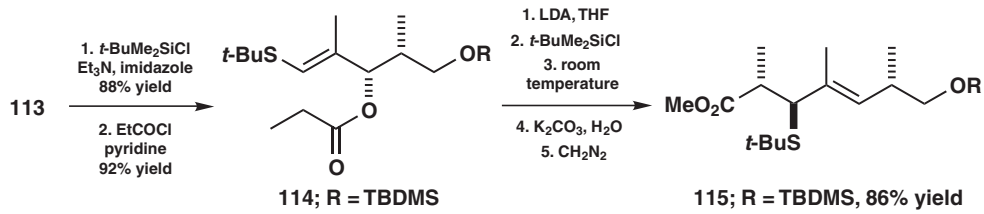
These [3,3]s and the related [2,3] sigmatropic rearrangements were used in the synthesis of the far more complicated anti-fungal and anti-viral myxalamide A **108**. At first sight the worst problem seems to be the chain of *trans* and *cis* alkenes dominating the structure. There is also some three-dimensional stereochemistry. At the right hand end is an amide of alaninol that will cause no problem but at the other end is a section with three chiral centres. This piece was disconnected at the first alkene and the necessary aldehyde functional group replaced by an alcohol **109** to avoid racemisation by enolisation. It is now clear that, while two of the chiral centres are adjacent, the third has a 1,4 relationship with the OH group and, worse, is separated by a *trans* double bond. At first sight it appears impossible to control this relationship. But look and wonder: a combination of [2,3] and [3,3] shifts succeeds.[16]



The synthesis started with an Evans' aldol between the phenylalanine-derived oxazolidinone **110** and the aldehyde **111**. Reductive cleavage of the *syn*-aldol **112** gave the diol **113** in excellent yield. This type of aldol reaction is discussed in detail in chapter 27. You may be impressed by the near perfect stereoselectivity but unimpressed that **113** is the wrong diastereoisomer. Look and wonder.

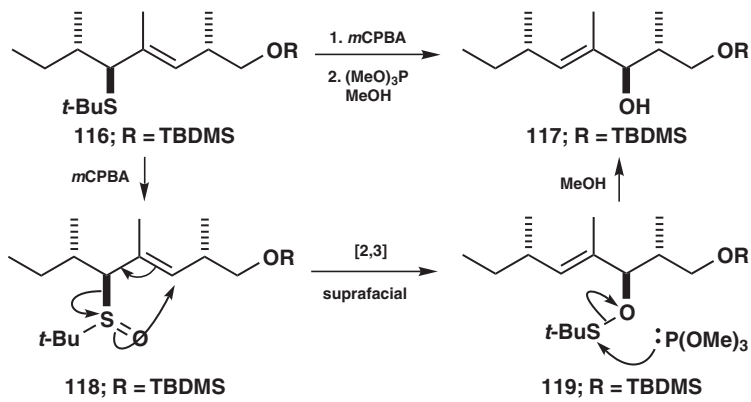


Protection of the primary and acylation of the secondary alcohol prepares the way for an Ireland-Claisen rearrangement. The *E*-enolate is produced and the [3,3] sigmatropic rearrangement transmits the chirality across the alkene to set up two new centres. The mechanism of the Ireland-Claisen rearrangement is described above **94** and occurs suprafacially across the backbone of the molecule through a chair-like transition state. We hope you agree both with the relative stereochemistry of the new centres and the *E* stereochemistry of the new alkene.



114; R = TBDMS **115; R = TBDMS, 86% yield**

The ester group is transformed into an ethyl group in simple fashion **116** and the position and stereochemistry of all the chiral centres corrected by an Evans-Mislow rearrangement. Oxidation to the sulfoxide **118** allows a [2,3] sigmatropic shift across the top face of the molecule giving an unstable sulfenate ester **119** from which sulfur is removed by a phosphite 'thiophile' to give the alcohol **117** with the correct *anti*-stereochemistry. The alkene returns to its original position and stereochemistry. The rest of the synthesis involves the construction of the polyene chain.[16]



116; R = TBDMS **117; R = TBDMS**

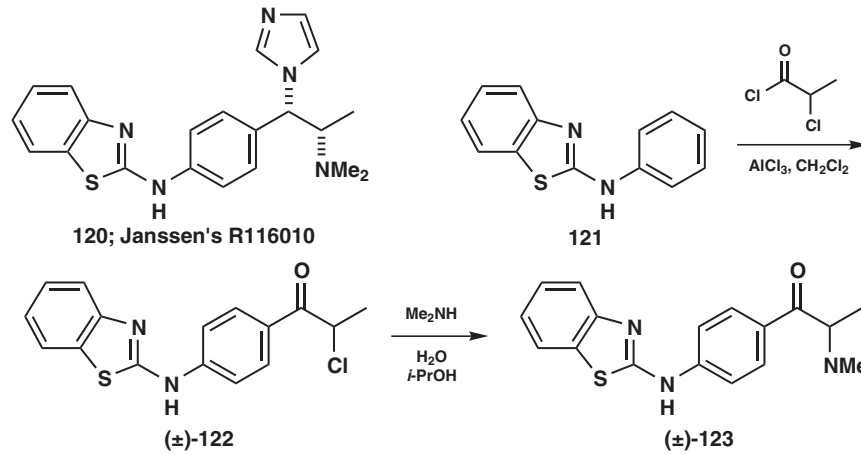
118; R = TBDMS **119; R = TBDMS**

Control of Open Chain Stereochemistry

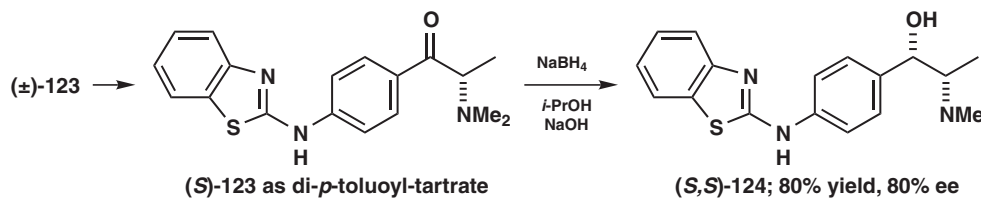
In chapter 21 we emphasise that the most reliable method of controlling one chiral centre by another in open chain compounds is by Felkin-Anh orbital control of nucleophilic attack on a carbonyl group next to a chiral centre. We shall start this discussion with that method and follow with the next most reliable - Houk control of electrophilic attack on alkenes also next to a chiral centre. These are of course both 1,2-control and we shall deal with that before discussing 1,3-, 1,4- and remote control.

Felkin-Anh control

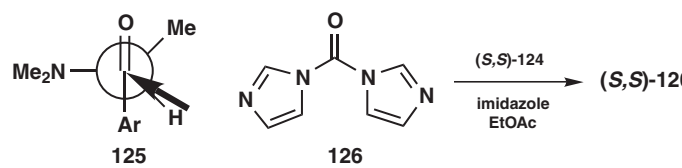
We start with simple but important example. The search for a manufacturing method for Janssen's anti-cancer drug **120** as one enantiomer of one diastereoisomer in high yield led to the racemic amino-ketone **123** easily made from **121** via a Friedel-Crafts acylation and a substitution with dimethyl amine.[17]



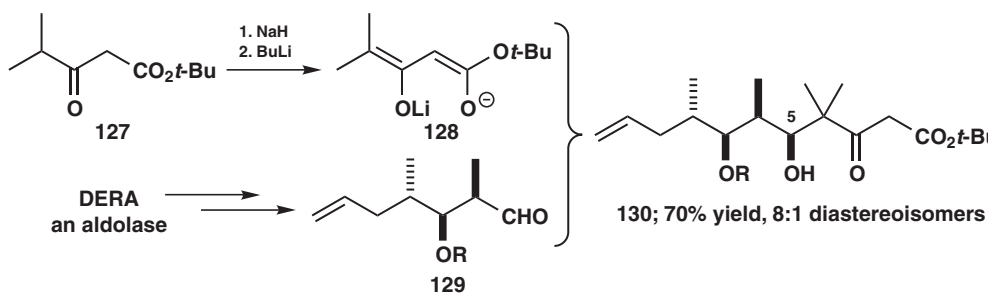
Dynamic kinetic resolution (chapter 28) of **123** with (+)-di-*p*-toluoyltartaric acid equilibrated the easily enolisable chiral centre and precipitated a 90% yield of the salt of the (*S*)-amine having 80% ee. Reduction with $NaBH_4$ in *i*-PrOH was very diastereoselective giving 99:1 *syn:anti*-**124**.



This is Felkin-Anh control: the NMe_2 group sits at right angles to the carbonyl group and nucleophilic hydride approaches at the Bürgi-Dunitz angle alongside the H atom **125**. The synthesis is completed by displacement of OH with an excess of imidazole using CDI (carbonyl-di-imidazole) **126** to activate the alcohol. Participation by the NMe_2 group is responsible for the retention of configuration.

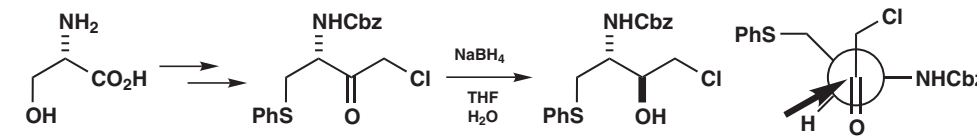


Even one methyl group can be enough to give reasonable Felkin selectivity. A vital step in Chi-Huey Wong's epothilone synthesis[18] is the addition of the double enolate **128** to a single enantiomer of the *syn,anti*-aldehyde **129** to give good diastereoselectivity (8:1) at the new chiral centre C-5. Though this is an aldol reaction of sorts, it is not a stereoselective aldol in the usual sense (chapter 3) but Felkin control in attack on the α-chiral aldehyde **129**.

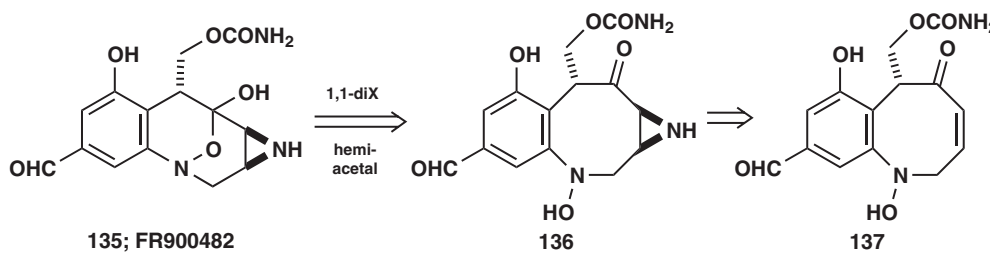


Since Felkin control has been well established in chapter 21, we shall simply give a couple of examples and two warnings before moving on to the less familiar Houk control. The first warning is that chelation control, particularly when metals such as magnesium are involved, may reverse the normal sense of induction. The second is that Felkin (or chelation) control cannot be guaranteed even when there is a large electron-withdrawing group next to the carbonyl group.

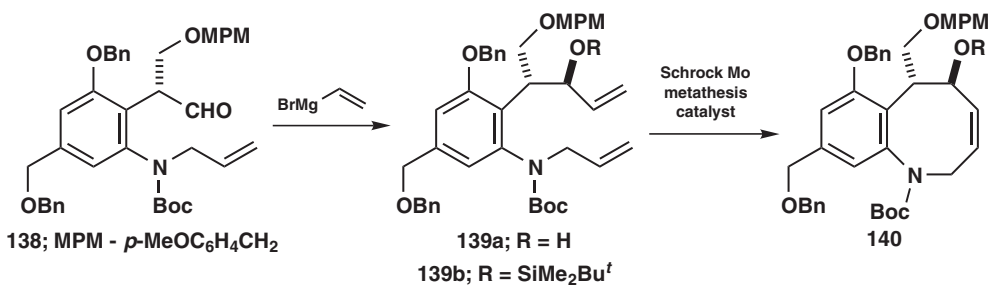
In the original synthesis[19] of the HIV protease inhibitor viracept by Aguron Pharmaceuticals the key intermediate **133** was made from serine (chiral pool) **131** *via* the simple ketone **132**. Reduction of **132** with $NaBH_4$ gave mostly the stereochemistry required **133**. The Felkin conformation is **134** with the large (and electronegative) NHCbz group orthogonal to the carbonyl group and nucleophilic hydride approaching alongside the small H atom. Yet the stereoselectivity is poor and this was not the route chosen for the manufacture of the drug.[20]



The anti-tumour antibiotic (+)-FR900482 **135** is particularly interesting as it contains a hemiacetal. Disconnecting this reveals an eight-membered ring with stereochemistry **136**. Martin[21] decided to make this ring by metathesis so that a protected version of **137** becomes an intermediate.

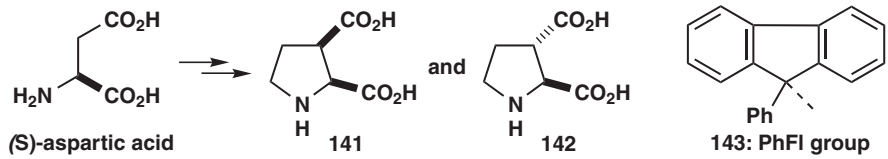


Now stereochemistry must be controlled in open chain chemistry. They were able to make a single enantiomer of **138** by desymmetrisation with a lipase (chapter 29). Reaction with vinyl Grignard gave one diastereoisomer of **139a** whose silyl ether **139b** underwent excellent metathesis with a Schrock Mo catalyst to give **140** and hence FR900482. They say disarmingly that 'the stereochemical outcome…may be rationalised either…(by)…chelation control or by the Felkin-Anh model'. Take your choice! It may appear that this new centre is unnecessary but it is in fact vital to control the formation of the aziridine.



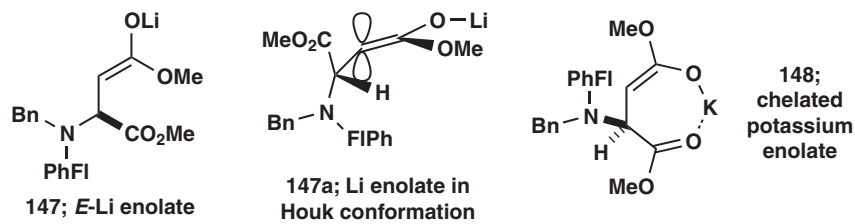
Houk control

Houk control concerns electrophilic attack on alkenes, enolates and the like. The alkylation of enolate **56** would be an example if it were not held in a ring by chelation. It can in fact be difficult to tell whether chelation is involved or not with many enolates and the outcome of the reaction may tell which. Chamberlin's asymmetric preparation of both pyrrolidine 2,3-dicarboxylic acids **141** and **142** from natural aspartic acid illustrates this perfectly. The key to the stereochemical control is the very large protecting group 9-phenylfluorenyl- **143** introduced by Rapoport.[22]

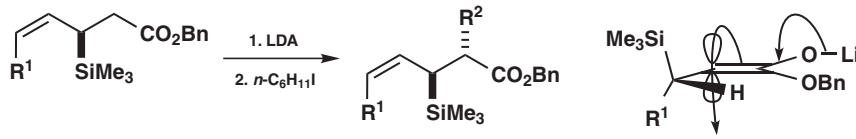


Aspartic acid is protected as the dimethyl ester **144** with the nitrogen atom carrying one benzyl group and one PhFl- group. Potassium or lithium enolates, made with K/LiN$(SiMe_3)_2$, were alkylated with allyl iodide. The lithium enolate gave a 23:1 mixture (96% yield) favouring *syn*-**145** but the potassium enolate gave a 10:1 mixture (94% yield) favouring *anti*-**146**. These were converted into **141** and **142** by ozonolysis, deprotection and reductive amination.

The lithium enolate is expected to have the *E*(enolate) configuration **147**. Chelation is impossible and it adopts the Houk conformation **147a** with the H atom on the inside eclipsing the π-bond. The enormous protected amine forces the allyl bromide to the opposite face. The potassium enolate prefers the chelated structure **148** and the same group directs the allyl iodide to the bottom face.



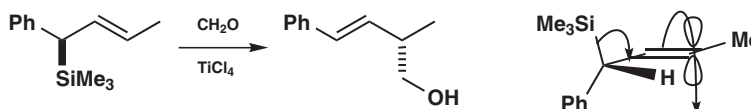
In these examples the sheer size of one of the groups controlled the transmission of stereochemical information. If the directing group is a silicon atom, electronic factors are important too.[23] Alkylation of the enolate from **149** was used in a synthesis of tetrahydrolipstatin.[24] There is no question of chelation here as no chelating group is present. The Houk conformation **151** of the lithium enolate has H inside and the Me_3Si group directs the alkylation to the bottom face.



149; R^1 = *n*-$C_{11}H_{23}$ 150; R^2 = *n*-C_6H_{11} 151

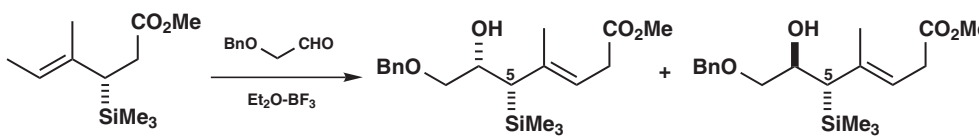
Reactions of allyl silanes with electrophiles

We shall see in this section that allyl silanes can direct the transfer of chirality through Houk conformations without the need to form an enolate. The typical reaction of an allyl silane with an electrophile (chapter 12) is at the remote atom of the alkene with loss of the silyl group. This transfers, but does not create, chirality. So the allyl silane **152** reacts with formaldehyde and a Lewis acid to give the homoallylic alcohol **153** with no loss of ee. The silyl group has gone, the alkene is transposed, and the sense of the S_E2' reaction is *anti*. All this is explained by the Houk conformation **154** with the C–Si bond able to interact with the alkene to raise the energy of the p-orbital and direct both the regio- and the stereoselectivity.[25]



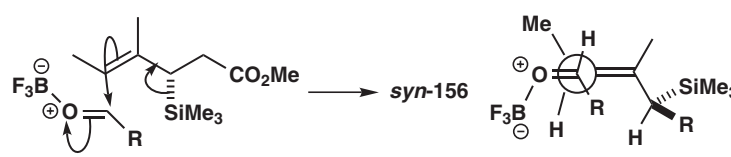
152; 85% ee 153; 86% ee 154

To create new chirality we need a prochiral electrophile. Single enantiomers of functionalised allyl silanes **155** are made by kinetic resolution with a lipase.[26] Reaction of **155** with an aldehyde and a Lewis acid gives the *syn* and *anti* homoallylic alcohols **156** and **157**.



155 *syn*-156 *anti*-157

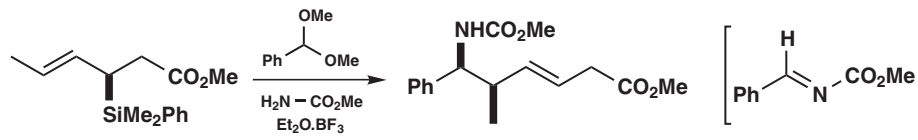
With BF_3, the *syn* product **156** predominates by 87:13 but with $MgBr_2$, the *anti* **157** is even more dominant (92:8). Both products have the same stereochemistry at C-5, determined by the Me_3Si group as in **154**. The mechanism **158** forces the electrophile to approach the alkene from the top face - opposite the Me_3Si group - but a detailed transition state such as **159** is needed to explain the new chiral centre at C-6. Panek suggests that **159** is the *anti-peri*-planar transition state and that $MgBr_2$ adopts a 'synclinal' transition state.



158 159

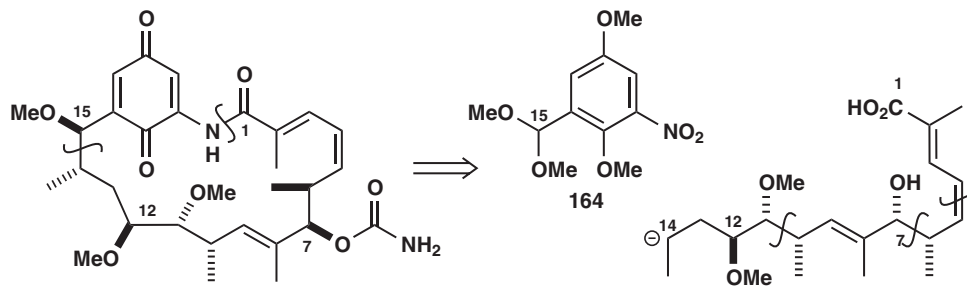
The electrophile, the substitution pattern, and the silyl group can all be varied: acetals and amines combine to form imines such as **162** under Lewis acid catalysis and these react in the same

way with allyl silanes such as **160** to give good yields of carbamates **161** with excellent stereoselectivity.[27]



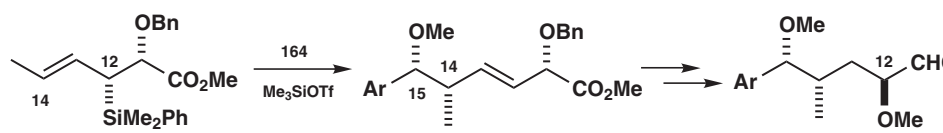
160 **161; 94% yield >30:1** **162**

An impressive application is the total synthesis[28] of the anti-tumour antibiotic (+)-macbecin I **163**. The amide disconnection is obvious and the decision to make the amino quinone from an aromatic nitro compound **164** sensible. Less obvious is the synthon **165** as the anion at C-14 could be an allyl silane but the further disconnections of **165** all correspond to allyl silane chemistry.



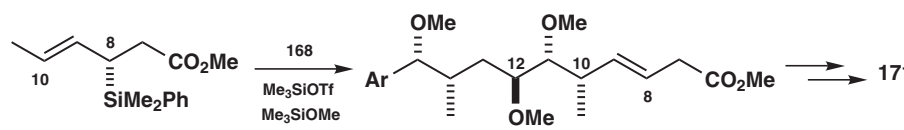
163; (+)-macbecin I **164** **165**

Three reactions of single enantiomers of allyl silanes were used to add each section of **165**. First the allyl silane **166** was coupled to the acetal **164** with Me_3SiOTf as the Lewis acid. The silyl group at C-12 controls the stereochemistry of both new chiral centres and the new alkene. The product is transformed into the aldehyde **168** for the next reaction.



166 **167** **168**

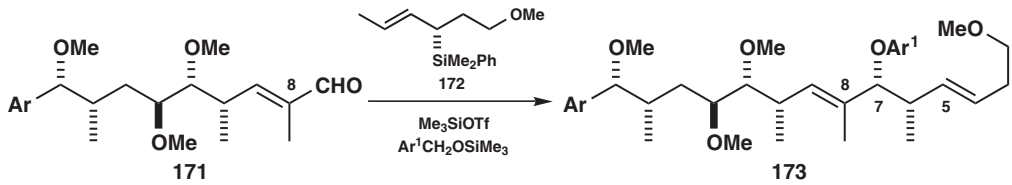
Now coupling to the simpler allyl silane **169** with the same Lewis acid but also with $MeOSiMe_3$ gives the new alcohol as its methyl ether **170**. Once again control is from silicon as the aldehyde has no neighbouring chiral centre to exert Felkin control. New chiral centres at C-10 and C-11 are created.



169 **170**

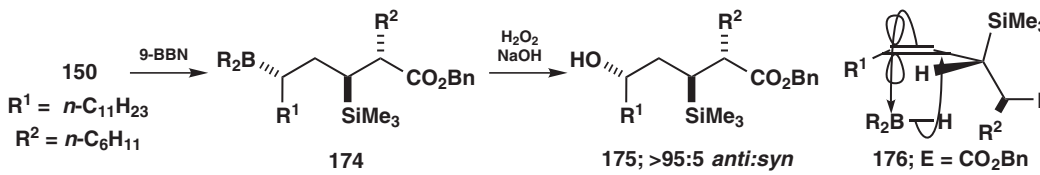
Again the product **170** is converted into an aldehyde **171** for the third allyl silane **172** reaction. This adds two more chiral centres by Houk control **173** and completes all seven chiral centres in the fragment **165**. The diene side chain is added but this involves no new chiral centres

and the synthesis of (+)-macbecin I **163** was completed by reduction, deprotection and amide formation.[28]

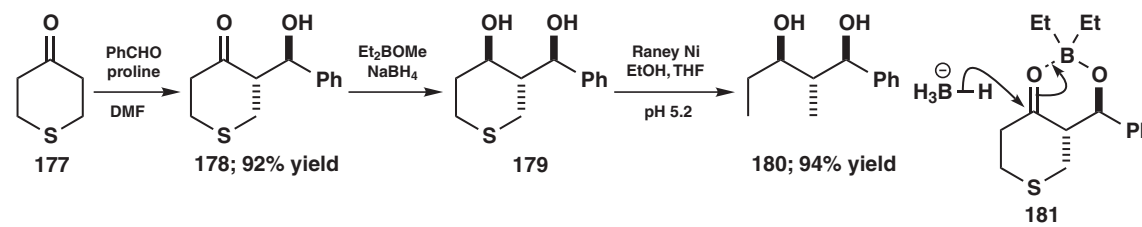


New chiral centres by 1,3-control

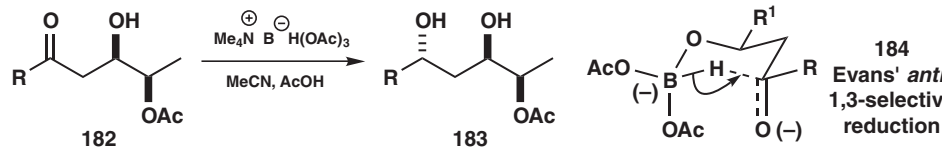
1,3-Control - the transmission of stereochemical information to the next-but-one carbon atom - is inherently more difficult than 1,2-control and almost impossible unless the molecule is held in some fixed conformation, usually by a ring (we shall not deal with that aspect as we have already discussed it at length), chelation, a cyclic intermediate, or a cyclic transition state. The next stage in the synthesis of tetrahydrolipstatin, the hydroboration of the alkene in **150** appears to involve 1,3-control in an open chain compound. However, the attack of 9-BBN on the alkene, which does indeed occur *anti* to the $SiMe_3$ group **174**, really occurs through a cyclic mechanism **176** involving 1,2 as well as 1,3-control. The B and H atoms add stereospecifically *cis* but stereoselectively *anti* to the $SiMe_3$ group.[24] The oxidation of the borane **174** to give the alcohol **175**, occurs stereospecifically with retention (chapter 17).



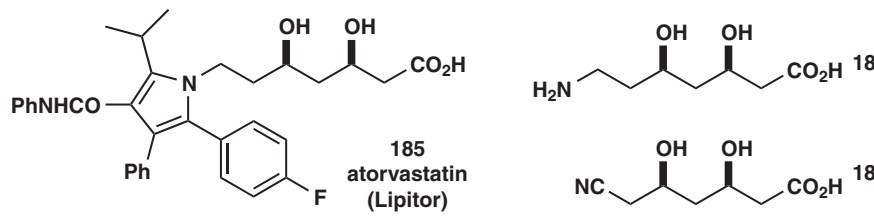
The proline-catalysed aldol reaction (chapter 26) of the heterocyclic ketone **177** with benzaldehyde gave the *anti*-aldol **178**. Reduction by the Prasad method (chapter 21) gave the *anti,anti*-diol **179** and so, by desulfurisation with Raney Ni, the *anti,anti*-diol **179**. The reduction could be controlled by the neighbouring chiral centre but the Prasad method uses 1,3-control by chelation with BEt_2 and external axial delivery of nucleophilic hydride from $NaBH_4$ **181**. This is 1,3-control via a cyclic intermediate.[29]



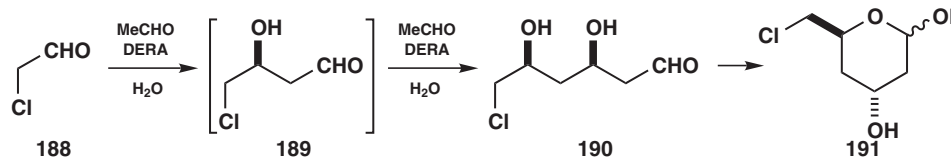
The alternative method of reduction of such hydroxyketones is the *anti*-selective Evans' intramolecular delivery of nucleophilic hydride through a cyclic transition state. In Janda's bryostatin synthesis, the diol monoester **182**, produced by kinetic resolution with an immobilised lipase (chapter 29) is reduced to the *anti*-diol **183** by acetoxy-borohydride. The hydride delivery is intramolecular through a chair transition state **184**. This is 1,3-control via a cyclic transition state (chapter 21).[30]



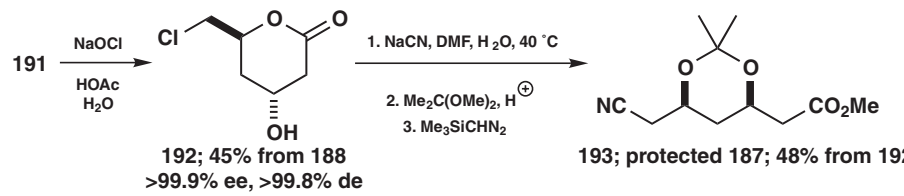
Apart from cases like these, we shall look for special methods to exercise 1,3-control. The importance of 1,3-control is immediately obvious from the structure of important cholesterol-lowering drugs like Lipitor (atorvastatin) **185**. The *syn*-1,3-diol is a challenge but might be made from the amine **186** or the nitrile **187**.



One successful approach is to use the enzyme DERA (chapter 29) to combine two molecules of MeCHO and one of $ClCH_2CHO$ in a double aldol reaction. Each aldol creates a new chiral centre: the first is controlled entirely by the enzyme but the second, using the chiral aldehyde **189** as the electrophile, could be affected by 1,3-control.[31] As might be expected for an enzyme-catalysed reaction, the catalyst dominates and the same stereoselectivity is found **190**. The product is isolated in the form of the lactol **191**.

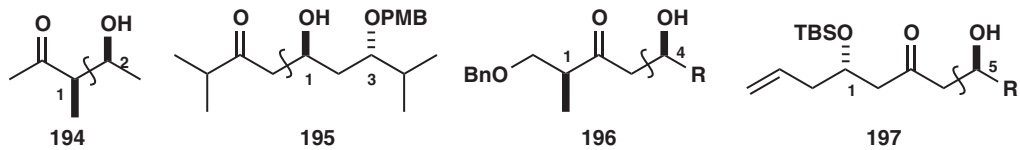


Transformation into a protected form of **187** is straightforward: oxidation with household bleach gives the lactone **192**, displacement with cyanide ion, acetal formation and esterification with trimethylsilyl diazomethane gives **193**. The synthesis of atorvastatin from **193** was already known. The next section discusses 1,3-control in non-enzymatic aldol reactions.



Aldol reactions

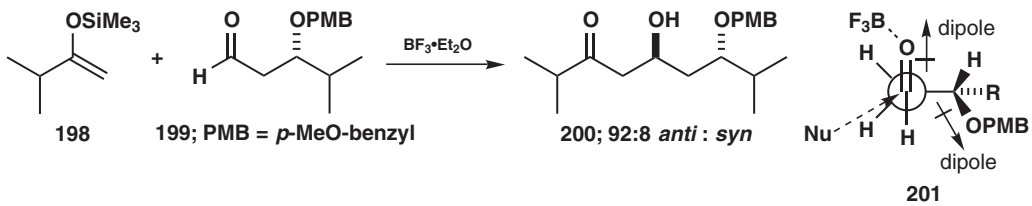
We have already seen how relative stereocontrol may be achieved in aldol reactions at the positions labelled 1 and 2 in **194** (chapters 4 and 27). One of these chiral centres is formed from the aldehyde electrophile and the geometry of the double bond of the enolate determined whether we got *anti* or *syn* geometry (chapters 4 and 21). The absolute stereochemistry at these centres could be controlled by a variety of methods (chapters 23–29), including the use of a chiral auxiliary (chapter 27).



Aldol reactions have become very much more sophisticated in the level of control that may be achieved. The types of control we are about to discuss do not depend upon double bond geometry. In each case from 1,3 **195** to 1,5-related stereocentres **197** the newly forming alcohol is one of the stereocentres and the other may be either in the incoming enolate fragment **196, 197** or already present in the aldehyde **195**. So the chiral centres are on either side of the ketone in **196** and **197** but both on the same side of the ketone in **195**.

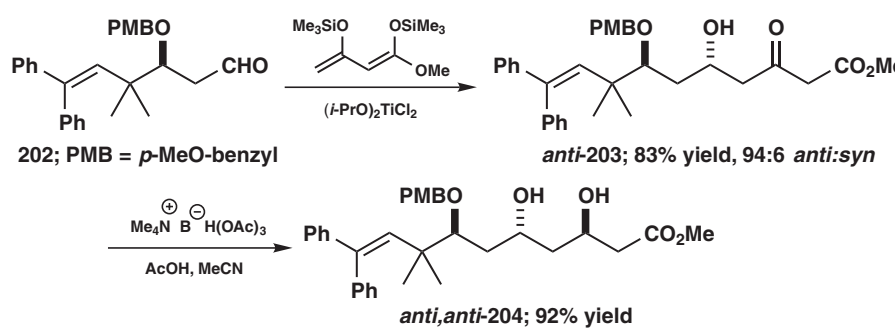
1,3-Anti induction

Good levels of 1,3-*anti* induction can be achieved with aldehyde **199** when it is attacked by silyl enol ether **198**. The aldehyde hydroxyl is the chiral centre and *p*-methoxybenzyl (PMB) is the best protecting group. Chelating Lewis acids (Ti, Li) are less effective than the combination of a silyl enol ether and BF_3 as the Lewis acid. The nature of the enol derivative is important and good selectivity is *not* achieved when an enol borinate is used.[32] We shall see in a moment that this lack of influence can be useful too.

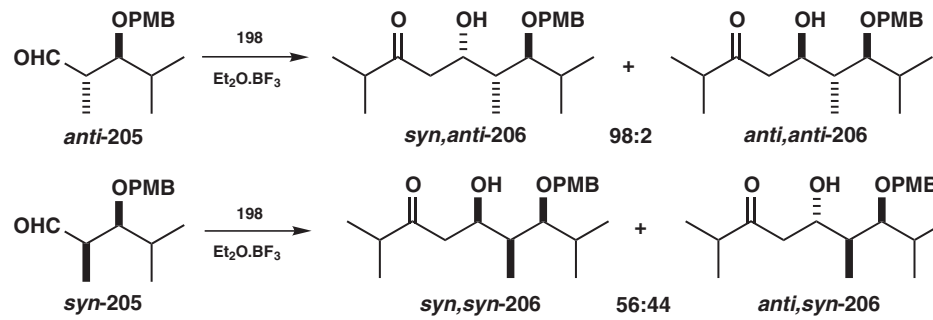


Evans suggests that an extended transition state is best with a Felkin-like orthogonal orientation of the chiral substituent to the carbonyl group. Conformation **201** shows an orientation in which the dipoles of the C=O and OPMB groups are as far apart as possible and with the nucleophile approaching alongside an H atom at the Bürgi-Dunitz angle. There are other possible explanations.[33]

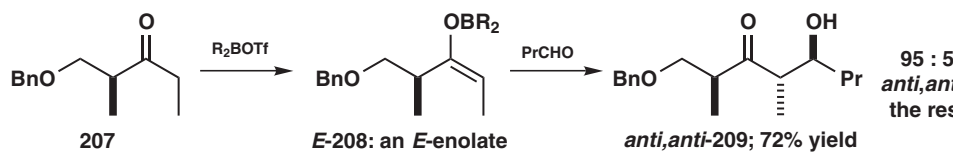
We referred above to a synthesis of bryostatin that contained a reduction controlled by a 1,3-relationship. Evans' synthesis[34] contains a 1,3-selective aldol as well as a 1,3-controlled reduction The aldehyde **202**, made by an asymmetric aldol reaction, was combined with the double silyl enol ether of methyl acetoacetate to give, as expected, the *anti*-aldol **203**. However, the only Lewis acid that gave this good result was $(i\text{-PrO})_2TiCl_2$ and not BF_3 thus emphasising the rather empirical aspect of this type of control. Evans's own 1,3-controlled reduction gave the *anti,anti*-triol **204** that was incorporated into bryostatin.



These aldols have all had just one chiral centre in the starting material. Should there be more than one, double diastereomeric induction produces matched and mismatched pairs of substrates and reagents, perfectly illustrated by the Evans' aldol method applied to the *syn* and *anti* aldol products **205** themselves derived from asymmetric aldol reactions. The extra chiral centre, though carrying just a methyl group, has a big effect on the result. The absolute stereochemistry of the OPMB group is the same in both *anti*-**205** and *syn*-**205** but the stereoselectivity achieved is very different. The matched case favours Felkin selectivity as well as transition state **201** but, with the mismatched pair, the two are at cross purposes. It is interesting than 1,2-control does not dominate in this case.[33]

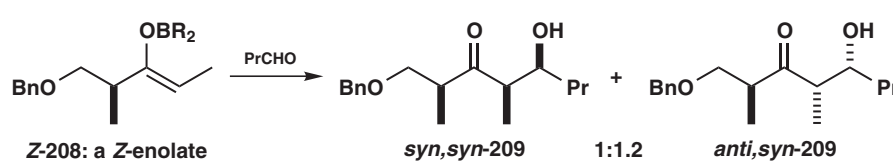


So far we have looked at the enolates of methyl ketones e.g. **198**. This has been deliberate in order to decouple these more remote selectivity issues from those of double bond geometry that we would also encounter if we were making enolates from, say, ethyl ketones such as **207**. In fact, although we have seen good selectivity, it is easier to obtain selectivity with the added congestion that arises with ethyl ketones. So, for instance the reaction of methyl ketone **198** leads to an *anti* selective product in a ratio of 94:6. Contrast this with the reaction of ethyl ketone **207** where there are four possible products rather than two and where the selectivity is 95:5 – the '95' being the major isomer **209** and the '5' being the *sum* of all the others! Note that the selectivity is observed without the use of chiral ligands.[35]

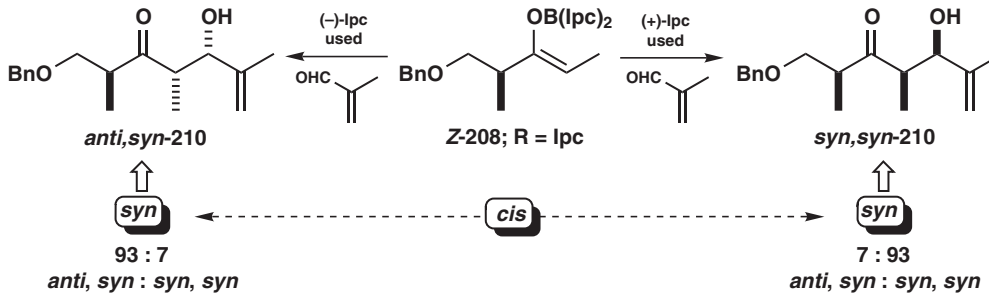


The *trans* double bond in **208** is responsible for the *anti* relationship between the alcohol and the adjacent methyl group. In fact, in a study with a variety of aldehydes, the most abundant of the three minor isomers also has that *anti* relationship. If we were to have a *cis* double bond in the enol borinate instead then we would expect to observe *syn* relationships here and that is exactly what happens. That is 1,2-control.

Now, whether this local *syn* arrangement is *anti* or *syn* to the more remote chiral centre in the enol borinate (1,3-control) can be controlled by the use of one enantiomer or other of a chiral boron reagent. The *cis* enol borinate with *achiral* boron reagent does not have much will of its own and leads to a 1:1.2 ratio of *syn*, *syn*: *anti*, *syn*.

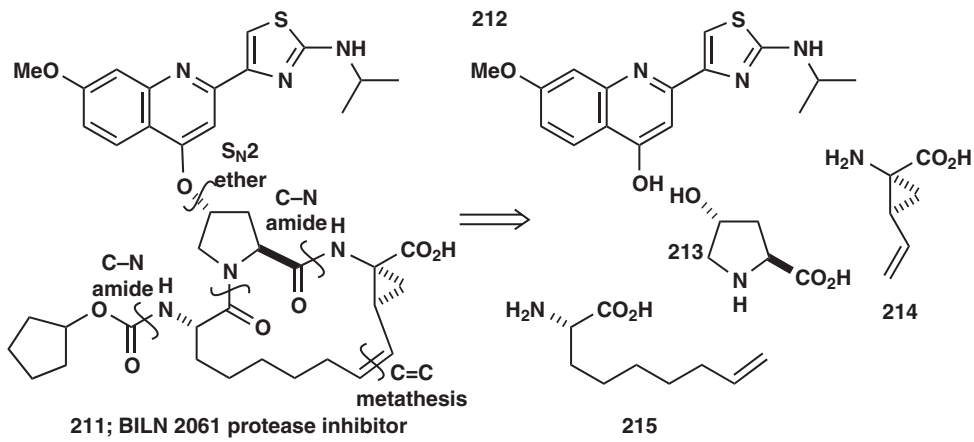


This is an advantage in that the enantiomers of Ipc (chapter 24) can exert their influence. Since both enantiomers of Ipc are available, we can make the diastereomers of the aldols **209** too using (+)- or (−)-$(Ipc)_2BOTf$ to make the boron enolates.[36] And of course if (+)-$(Ipc)_2BOTf$ gives *syn*,*syn*-**209**, (−)-$(Ipc)_2BOTf$ gives *anti*,*syn*-**209**.



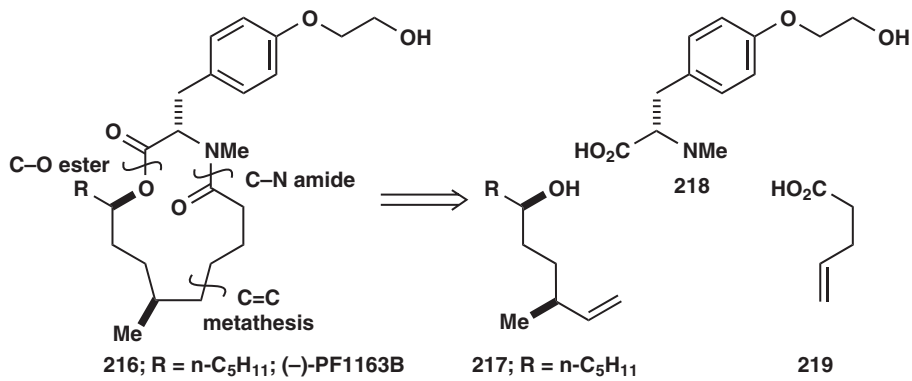
Introduction to 1,4- 1,5- and Remote Induction

Hepatitis C is the one that causes liver cancer and more effective treatments are urgently required. One approach is to discover specific protease inhibitors that should prevent replication of the virus. The Boehringer company[37] have found BILN 2061 **211** which they have made by the strategy outlined in **211**.

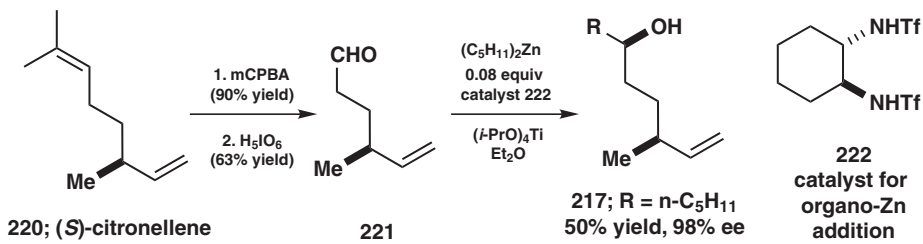


The achiral aromatic part **212** can easily be removed. The rest of the molecule has five chiral centres in three groups and the best strategy is to assemble each group separately. The amino acid fragment **215** can be made by asymmetric catalytic reduction (chapter 26). Hydroxyproline **213** is from the chiral pool and the cyclopropane **214** was made as a racemate and resolved. Linking these three fragments by stereospecific reactions (note that two inversions will be needed during ether formation with **212** to keep the *trans* arrangement across the ring) or by reactions that do not affect the chiral centres ensures that the final product has the correct absolute and relative stereochemistry.

Another popular strategy is to use a reagent-controlled reaction to add any further centres independently of those already present, trusting in the remoteness of the relationship to prevent any induction. A simple example is the anti-fungal agent (−)-PF1163B **216**, a compound from a *Streptomyces* species. Again a metathesis was added to the obvious disconnections (ester and amide) to give an amino acid fragment **218**, an achiral fragment **219**, and the interesting unsaturated alcohol **217** having a 1,4 relationship between the two chiral centres.[38]



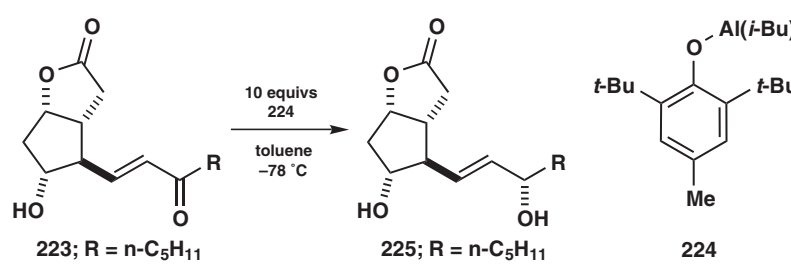
(*S*)-Citronellene **220** was available from the chiral pool so an oxidative cleavage gave the aldehyde **221** and the n-pentyl group could be added as an organozinc reagent by the method of Kobayashi[39] using the powerful C_2 symmetric catalyst **222**. The catalyst-dominated reaction ignores the chiral centre already present and gives excellent ee (98%).



These strategies are often chosen when relationships are 1,4- or more remote. In **211** and **216** the relationships between the groups of chiral centres are 1,4 at best. However, it is possible to control 1,4-relationships, and even a few that are more remote, by induction (that is stereoselective reactions) from existing centres and that is the concern of this part of the chapter. We shall first look at some relatively simple methods and then return to the aldol reaction.

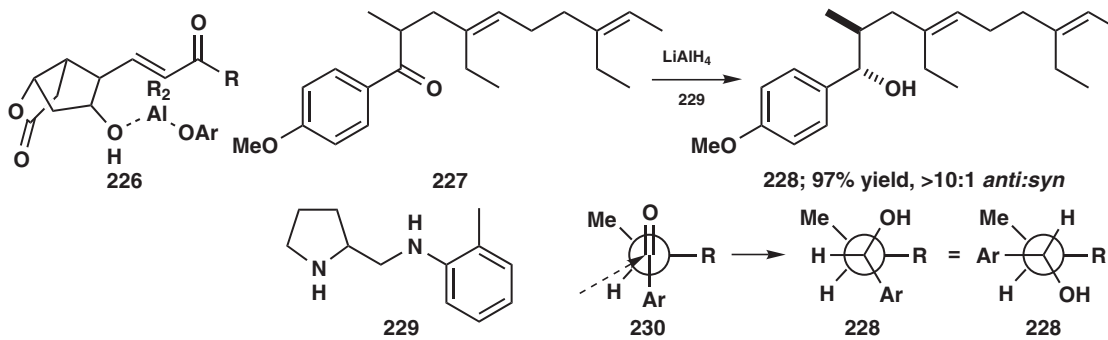
Remote control by substrate-controlled induction

There are probably more different reagents for reducing carbonyl groups than for any other reaction and some of these are very effective in controlling stereochemistry.[40] Many of these methods use reagent control but we are concerned with those that induce stereochemistry from an existing centre. The most famous example is the secondary alcohol in the prostaglandin side-chain. This is particularly difficult as the prochiral ketone in it is separated from the existing chiral centre by a *trans* alkene.[41] In the event,[42] the achiral reducing agent **224**, a bulky version of DIBAL, gave a 92:8 ratio of diastereoisomers of **225**.

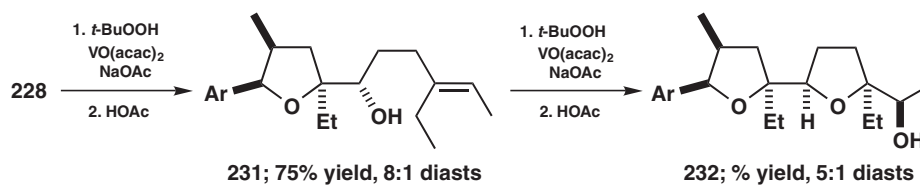


The requirement for such a large excess of **224** suggests that a second molecule binds to the OH group thus shielding one face of the ketone from reduction **226**. Though asymmetric reduction would now be preferred to this method it is remarkable that such a remote centre (and the OH is *five* atoms from the carbonyl group) exerts such a powerful effect.

A more typical early example is Kishi's polyether antibiotic syntheses using a sequence of epoxides made by controlled oxidation. The sequence starts with a somewhat similar reduction: $LiAlH_4$ with the diamine **229** reduces ketone **227** highly stereoselectively in a Felkin sense **230** to give almost exclusively *anti*-**228** which was resolved as a urethane (chapter 22) to give the enantiomer shown.[43]

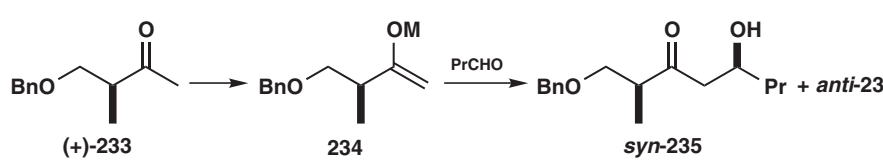


The hydroxyl group now directs the epoxidation of the nearer alkene using a vanadium directed delivery of *t*-BuOOH that gives an 8:1 selectivity. This resembles the last example being 1,4-control from OH though there is a nearer (1,3) chiral centre. The epoxide was not isolated but cyclised *in situ* to the THF **231**. This releases a new OH group that directs a second epoxidation and cyclisation with the same reagents to the *bis*-THF **232**. The stereochemistry of the THFs makes it clear that the OH is a 1,4-*syn* directing group for the epoxidations.

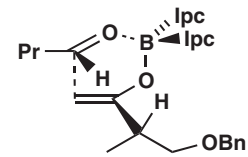


1,4 -Syn induction in the aldol reaction

When we discussed how *E*-enolates of ethyl ketones such as **207** gave 1,3-control in the aldol reaction, we noted that there was 1,4-control too. Paterson did the same reaction on the corresponding methyl ketones and found that the lithium enolate (M = Li in **234**) was unselective. The boron enolate with an achiral group 9 (M = dicyclohexyl-B) was selective giving 88:12 *syn:anti*-**235** in 84% yield but with a chiral group [M = (−)-$(Ipc)_2B$] the stereoselectivity was significantly better[35] (92:8).



This must be entirely 1,4- control. As these adducts **235** are barely distinguished by ^{13}C NMR and could not be separated even by HPLC, high diastereoselectivity is essential. One explanation is a Houk-like arrangement of the enolate but with methyl 'inside' (as the large groups on boron allow only H to be nearby) with the aldehyde arranged with Pr and BR_2 'trans' **236**.



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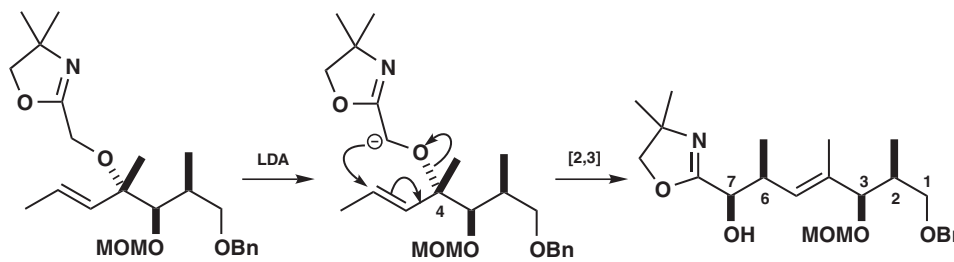
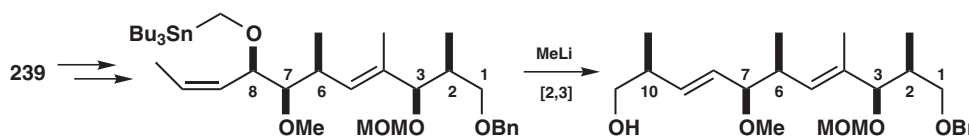
1,4-Control by sigmatropic shifts

Some pages back we described part of a synthesis of macbecin **163** by allyl silane chemistry. An alternative approach uses sigmatropic rearrangements to transfer and create new chiral centres.[44] The starting material gives a [2,3] Wittig rearrangement **238** after treatment with base. Centres 2 and 3 in the product **239** survive intact. Centre 6 is transposed from 4 by the rearrangement and centre 7 is created. The new alkene is *E* and all this is controlled by the chair-like transition state. This product **239** has two families of adjacent chiral centres 1,4-related across the new *E*-alkene.



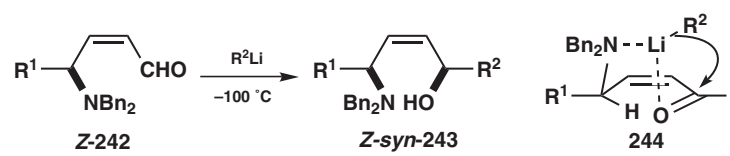
237 **238** **239**

Further transformations involving the Felkin style creation of a new chiral centre at C-8 allow a second [2,3]-rearrangement after the exchange of the Bu_3Sn group for Li. Another *trans* alkene is formed and the centre at C-8 transposed to C-10.



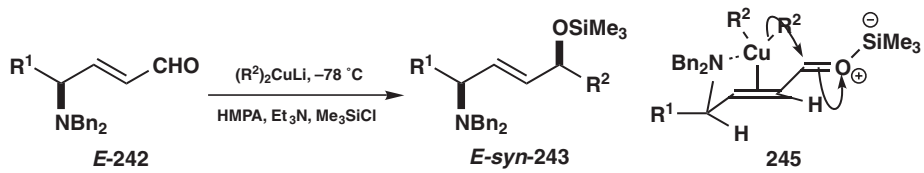
240 **241**

This strategy is generally more efficient than the direct creation of new centres by, for example, nucleophilic addition of organometallic compounds to carbonyl groups separated by an alkene from even such a powerful directing group as an amine. The *cis*-alkene *Z*-**242** reacts with a range of organolithiums (R^2 = alkyl or aryl) giving *syn*-**243** with usually >90:10 selectivity. Direct co-ordination of Li to the amino group in a Houk-like arrangement **244** explains this result.[45]



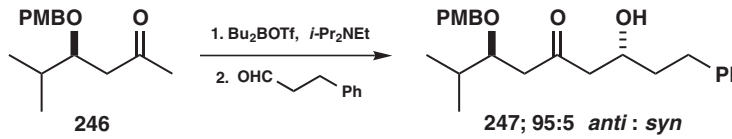
***Z*-242** ***Z-syn*-243** **244**

The *trans*-alkene *E*-**242** also gives reasonable stereoselectivity for the *syn* adduct *E-syn*-**243** but requires an organocuprate, HMPA in the solution, and the product must be trapped with Me_3SiCl to get between 80:20 and 90:10 selectivity. One possible explanation is that the alkene-Cu π-complex **245** bridges the longer gap between the amino group and the aldehyde.

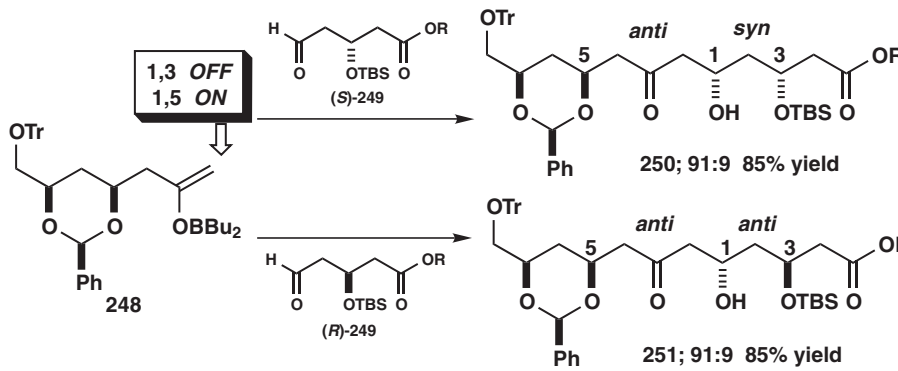


1,5-Induction by the aldol reaction

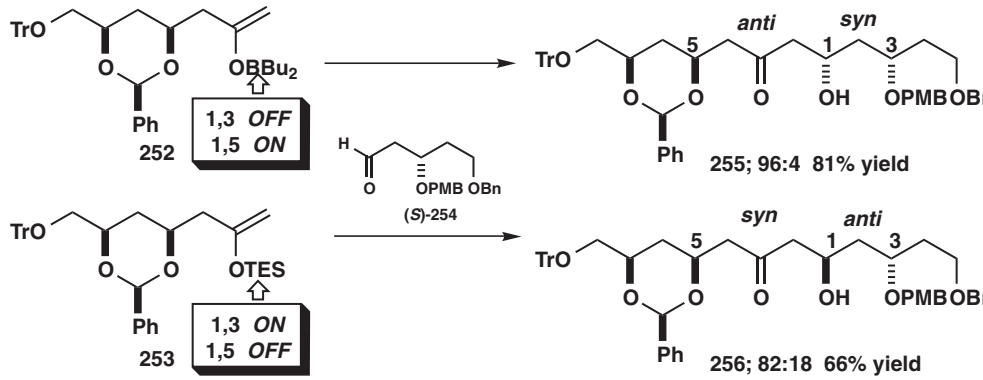
Highly 1,5-diastereoselective reactions can be achieved when the β-hydroxy group is present in the boron enolate of a methyl ketone such as **246** instead of the aldehyde. Notice that we already have a regioselectivity issue here – the $Bu_2BOTf/i\text{-}Pr_2NEt$ combination selectively reacts with the methyl group and not the methylene group. Reaction with dihydrocinnamaldehyde gives an aldol **247** with 95:5 *anti*:*syn* selectivity. In interesting contrast to the 1,3-diastereoselective aldols **200** above, silyl enol ethers give no 1,5-diastereoselectivity at all.[32] Selectivity can also be switched off by replacing the methoxybenzyl protecting group (PMB) with a silyl protecting group (TBDMS).



The non-selective reactions that result if boron enolates are used in the 1,3 case or if silyl enol ether are used for a 1,5 case means we can choose to switch off selectivity that might otherwise clash (mismatch). Boron enolate **248** combines with aldehyde (*S*)-**249** and, in another reaction, its enantiomer (*R*)-**249**. As we do not want the chirality of the aldehyde to be in control, boron enolates are what we need. The 1,5 *anti* relationship is controlled in both cases but the 1,3 *anti* or *syn* relationship develops by default and *not* by control.

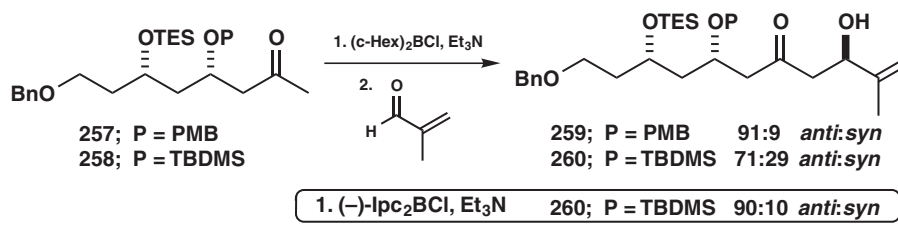


Alternatively we can combine the chiral nucleophiles **252** and **253** and a chiral aldehyde **254**, keeping the chiral aspects of the molecules the same in each reaction, but changing the nature of the enolate to suit us. Hence 1,5-induction operates when boron enolate **253** is used but 1,3-induction operates with the silyl enol ether **253**.



Note the strategy in these two schemes: one enantiomerically pure fragment is being combined with another enantiomerically pure fragment and, where they join, conditions are selected to determine which of these fragments controls the *new* chiral centre. This is a substrate-based strategy in all respects. One thing we have not done is to use an *external* chiral factor, such as a chiral boron reagent, and we will see this strategy now.

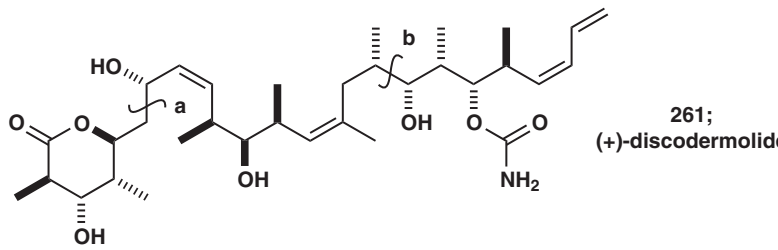
We have already mentioned that the use of a silyl protecting group is not effective for 1,5-*anti* induction. So, if the boron enolate from **258** reacts with methacrolein, the resulting selectivity (71:29) is not too bad – though not as good as with a benzyl protecting group **257**. An alternative method of obtaining good stereocontrol, if we want to keep silyl protection, is to introduce reagent control and replace the achiral boron chloride with (−)-Ipc_2BCl. This improves selectivity markedly with no drop in yield (which is 80% in both cases).



We have already collected some powerful tools for use in stereocontrolled aldol reactions, but we have not finished. We shall see now in Paterson's synthesis of (+)-discodermolide, how reagent control is used not to enhance the intrinsic substrate selectivity, but to overturn it. The aldol reaction is undoubtedly one of the most powerful ways of making carbon-carbon bonds and nature thinks so too. There are numerous natural products that are replete with 1,3 related oxygen functionality. Many of these are acetate or propionate-derived in nature. The methods detailed above developed from studies into the syntheses of these natural products. The manipulations of chiral ethyl ketones of this kind are of particular interest when it comes to natural products that are polypropionate-derived.

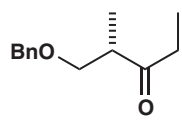
The Asymmetric Synthesis of (+)-Discodermolide

As one might expect, there are very many aldol reactions to be found in Paterson's synthesis[46] of discodermolide **261**. The synthesis involves 23 steps (in the longest linear sequence) and the overall yield is 10.3%. If we naïvely equate the yield with those 23 steps then we have an average yield in every step of around 90%. Several other groups are interested in the synthesis of discodermolide.[47,48]

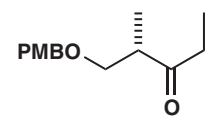


261;
(+)-discodermolide

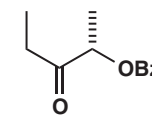
Although the molecule contains thirteen chiral centres, the synthesis starts with only three. They are ethyl ketones **262**, **263** and **264**. Discodermolide is retrosynthetically divided **261** into three sections and all of the chiral centres in each of these sections derive from one of the ketones. Ketones **262** and **263** differ only in the nature of the protecting benzyl group.



(*S*)-262

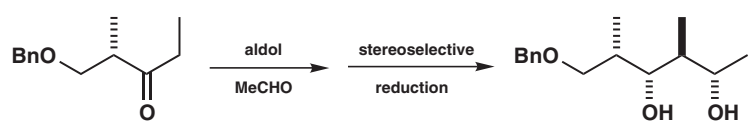


(*S*)-263



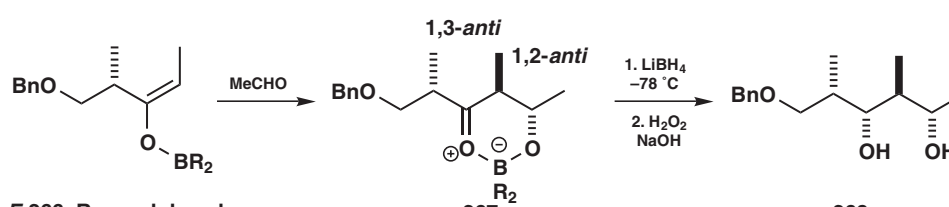
(*S*)-264

We shall not go through every detail of the synthesis – you are directed to the paper for that – but we will highlight three details. Firstly, there is the reaction of **262** which (in one pot!) is transformed into the advanced intermediate **265** in 86% yield and >97% diastereomeric excess. Secondly, there is the late-stage coupling of fragments (the C–C bond made is disconnection 'b' in **261**) and finally there is the overturning of selectivity by reagent control that we alluded to earlier.



(*S*)-262 **265; 86% yield, >97% ds**

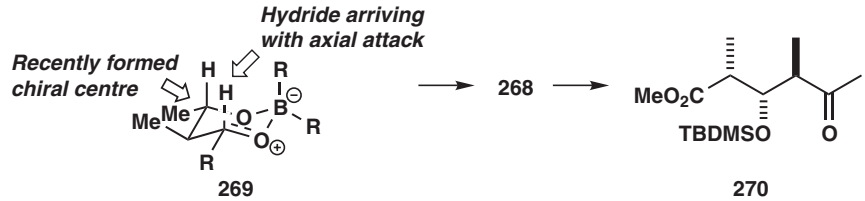
So, to kick off, ketone **262** is reacted to form *trans* boron enolate **266** that combines with acetaldehyde to give the intermediate **267**. The 1,2-*anti* stereocontrol comes from the enolate geometry and the chiral centre of the original ketone imposes the 1,3-*anti* control in the way we have seen already in this chapter. The intermediate **267** is reduced without working the reaction up and the boron removed to give **268**.



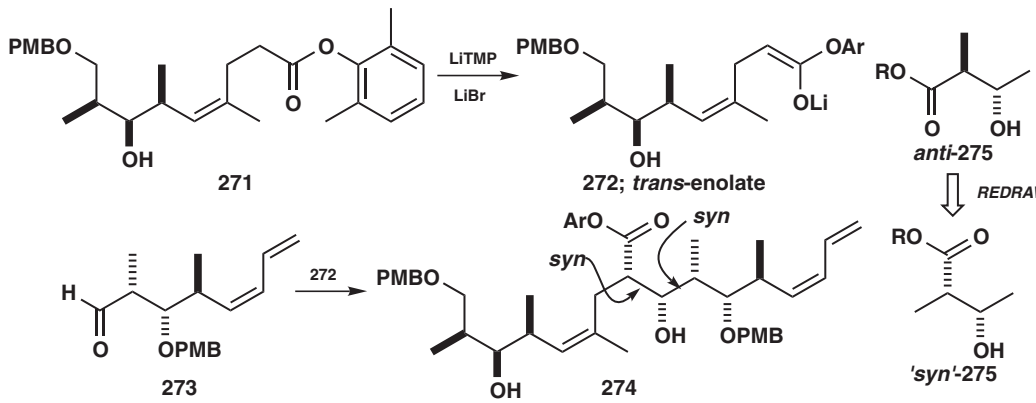
***E*-266; R = cyclohexyl** **267** **268**

The newly formed chiral centre bearing the alcohol in **266** determines the new 1,3-*anti* relationship that develops as the carbonyl is reduced by $LiBH_4$. Hydride attacks axially **269** (as in Chapter 21).

The alcohol that resulted from the aldol reaction is oxidised later (on the way to **270**) and so one chiral centre is destroyed after it has done its work.

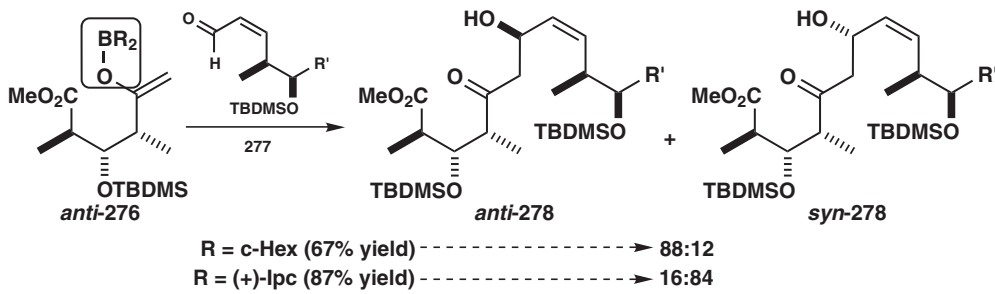


With all this boron enolate chemistry it is easy to forget some of the older enolate methods that are still available. The use of an ester containing a hindered phenolic group has been seen before in Chapter 21 to control the formation of *trans* enolates so that *anti* aldol products may be produced. It is used here to couple two fragments in just that way. Ester **271** reacts with the hindered base LiTMP (in combination with LiBr) to give *trans* enolate **272** which was combined with aldehyde **273** to give[49] the aldol adduct **274**.



The *syn* selectivity is controlled by the double bond geometry of the *trans* enolate **272** whereas the more remote aspects of the stereocontrol are controlled by the molecules themselves. Just a note at this point: we normally associate *trans* enolates with *anti* aldol products – the product observed is called *syn* only because of the way it is drawn, there is nothing unusual here **275**. The chiral centres in the enolate **272** are too remote to be effective and it is those in the aldehyde **273** that control the more remote aspects of stereochemistry. If we want to explain this selectivity, we need to have a reason for why one diastereotopic face of the aldehyde is attacked and not the other. As might be expected, the aldehyde reacts with Felkin-Anh selectivity as described earlier in this chapter.

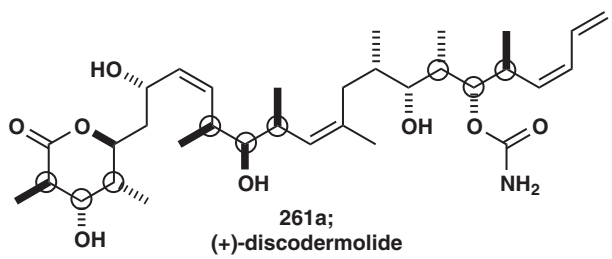
Our final highlight in the discodermolide synthesis is the use of reagent control to get what we want and not what the molecules want. The combination of enol borinate **276** and an aldehyde **277** featuring a *cis* double bond, led to the formation of aldols *anti*- and *syn*-**278**. A model study had shown that the inherent selectivity with these enals could be improved by the use of (−)-Ipc groups on boron instead of cyclohexyl but it is not the selectivity that was wanted. (+)-Ipc groups were able to turn around the selectivity *and* improve the yield of the reaction while they were at it.[50]

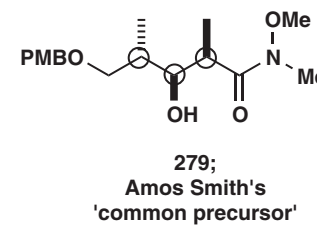


The tricky thing with a mismatched situation is that you do not know whether you will win (with reagent control) or whether the molecules will get their way (substrate control) but either way the result will be the product of a conflict. It is all the more impressive, therefore, when good levels of reagent control can be achieved in a mismatched situation.

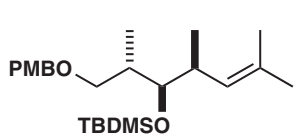
Making discodermolide on a large scale

Discodermolide is a promising anti-cancer drug and the Novartis company decided to blend the best parts of the published academic syntheses with their own ideas and make 60 grams of the compound for clinical trials. This was a decision necessitated by the very meagre supply from natural sources but a bold decision too as a large scale synthesis of such a complex molecule was without precedent. Discodermolide has three *Z*-alkenes and 13 chiral centres with, at first sight, no particular pattern. Smith noticed[47] that there were three repeating triads of centres marked with circles in **261a** and that each of these might be made from a 'common precursor' **279**.

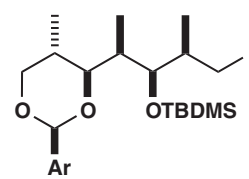




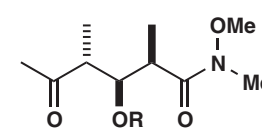
The Novartis company decided to use **279** as starting material for three fragments **280**, **281** and **282** and to use Paterson's aldol methodology (described above) to link them together and complete the synthesis.[51] In the event, they modified the original plan in many ways to make the synthesis practical. Key points were the production of **279** without chromatography, the conversion of **279** to **281** via all crystalline intermediates, a Suzuki coupling (chapter 18) and a Still-Gennari *Z*-alkene synthesis (chapter 15) and many other reactions already treated in this book.



280



281; R = *p*-MeOC$_6$H$_4$



282; R = TBDMS

Though improvements continue to appear, such as a revised route to the lactone portion,[52] and no doubt will continue to appear, this is a staggering achievement involving 43 chemists and you are particularly directed to the fifth paper in the series.[51] Commenting on the synthesis as a whole they say: 'The success of this project and its chemistry paves the way for other, perhaps even more complex, natural products to be prepared for early-phase clinical evaluations and sends a positive message to both the isolation and synthetic academic community and possibly other pharmaceutical companies that; "your work need not just be of academic interest" and it may be worth taking a few risks.'

Conclusion

Creating more chiral centres with enantiomerically pure rather than racemic starting materials is different in some important ways.

1. Remote diastereomeric relationships can be controlled by using enantiomerically pure components when it is impossible to control them by diastereoselective reactions.
2. Double diastereodifferentiation (using enantiomerically pure reagents and substrates) can enhance diastereoselectivity if we have a matched case, but can erode it if we have the mismatched case.
3. It is important to check the ee of the first product formed with extra chiral centres. There are three considerations here:

   (a) The starting material may racemise under the conditions of a reaction.
   (b) Coupling a starting material that is racemic or of low ee to an enantiomerically pure starting material may allow effective resolution of the product.
   (c) Once two or more chiral centres are in place, the enantiomeric purity of the molecule can be checked by ordinary NMR spectra as epimerisation leads to a diastereoisomer and simultaneous epimerisation of two or more centres without forming another diastereoisomer is unlikely (though not unknown).

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General references are given on page 893

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31 Strategy of Asymmetric Synthesis

This chapter examines the asymmetric synthesis of compounds that have been made by several different methods and assesses the factors that make one synthesis the most favourable. It also revises material from the rest of this section (chapters 20–30)

Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

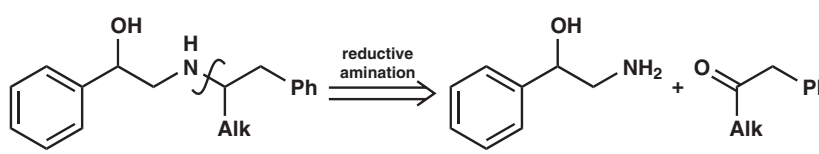
Strategies used in the synthesis of lactacystin, the β-lactone, and analogues
PS-519: A lactacystin analogue
A chiral pool synthesis of lactacystin from glucose
Chiral pool syntheses of lactacystin from amino acids
The reagent strategy: asymmetric epoxidation and asymmetric allylboration
Enzymes as reagents in the synthesis of lactacystin analogues
Syntheses of 3-hydroxyleucine by other strategies
A large-scale synthesis of lactacystin analogues using AD and an asymmetric aldol reaction

Introduction: Strategy of Asymmetric Synthesis

In the last seven chapters we have introduced the main approaches to the synthesis of single enantiomers. In this chapter we gather together those ideas and consider why anyone should choose one of these approaches rather than another. We shall look at simple and not-so-simple compounds that have been made by different routes. We shall examine why chemists rejected some of those routes and preferred others. Some compounds will be needed for laboratory syntheses on a small scale: others for commercial production on a large scale and different criteria will apply to these two situations. These are strategic considerations and the main point will be, as it always is, to get high yields in few steps with maximum selectivity. Here though the enantiomeric excess achieved by the different methods will also be important. We start with a very simple compound. More complicated molecules are considered in detail in Nicolaou and Sorensen, a book we highly recommend.

Part I – (*R*) and (*S*)-2-Amino-1-Phenylethanol

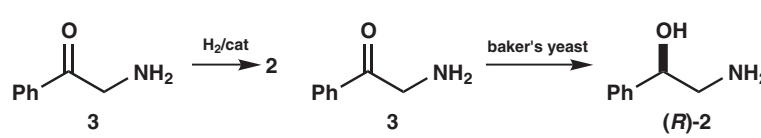
This simple compound **2** was needed by Novartis Pharma Inc. (Basel) for the preparation of a new class of anti-diabetic agents **1**. Both enantiomers were needed on a large scale to explore the relationship between stereochemistry and biological activity.[1]



1; anti-diabetic drugs **2; 2-amino-1-phenylethanol**

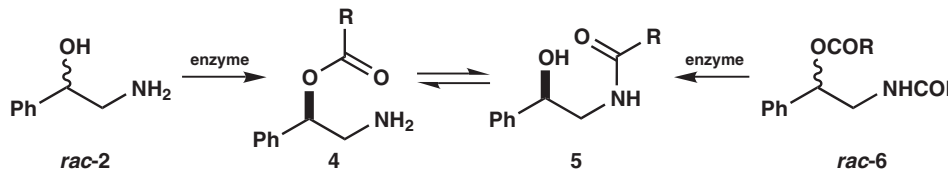
Methods rejected for development

The first step is to search the literature. Many methods had already been published but four of these were immediately discarded as being unsuitable for scale-up. Asymmetric reduction (chapter 26) of the amino-ketone **3** required ligands that were not available and would themselves have to be the subject of asymmetric synthesis. Then pressures greater than 50 atmospheres were needed to reduce the rather stable carbonyl group and even then ees were about 93% at best and usually much lower. Finally the turnover was slow so a lot of catalyst would be needed to make an efficient process. An alternative to chemical reduction would be baker's yeast (chapter 26). This gave only one enantiomer and required high dilution to be effective. Even then there was a very low throughput.



3 **3** **(*R*)-2**

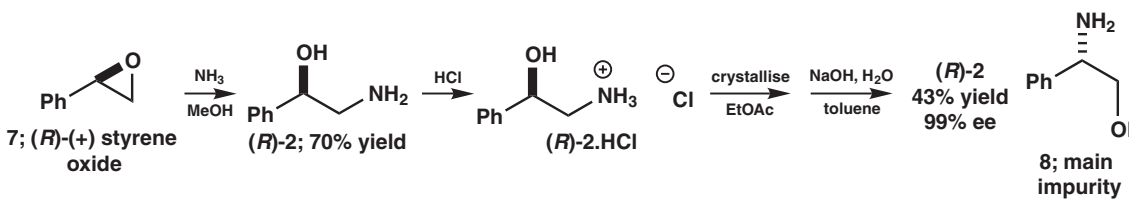
The racemic amino alcohol **2** was easy to prepare so one obvious choice is an enzyme-catalysed acylation or deacylation process (chapter 26). These worked reasonably well. Deacylation of the ester-amide **6** gave the amide **5** which was difficult to hydrolyse. Acylation gave the monoester **4** but this equilibrated rapidly with the same amide **5**. Both gave the same enantiomer of the amino alcohol and of course the maximum yield is only 50%.



Finally they rejected the crystallisation of a conglomerate. It was known that the salt between the amine **2** and *m*-aminobenzoic acid formed a conglomerate that could be crystallised with seeding of either enantiomer (chapter 22) but only from the rather expensive solvent THF. In any case the yield was only moderate and the ees too low to make this method worthwhile.

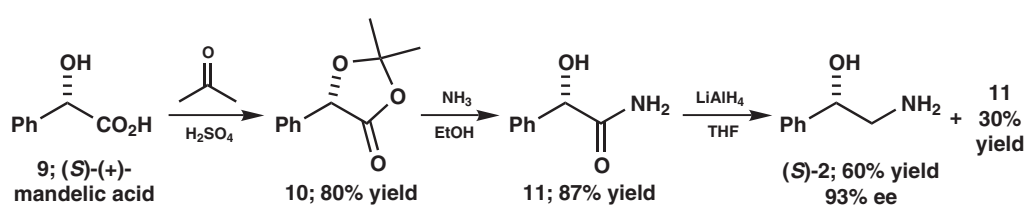
Methods considered for development and tried experimentally but rejected

Two methods were promising enough for serious consideration but were eventually rejected on practical grounds. They both amount to chiral pool strategies (chapter 25) though the first starting material, styrene oxide **7**, is not a natural product. Both enantiomers of **7** are commercially available.



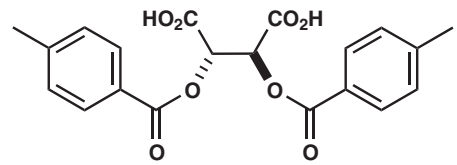
Treatment of styrene oxide with ammonia in methanol gave mostly (*R*)-**2** by nucleophilic attack at the less hindered end of the epoxide. However, some of the regioisomer **8** was formed by attack at the benzylic carbon and this proved difficult to remove. Crystallisation of the salt **2**.HCl and neutralisation gave the best samples (99% ee) of (*R*)-**2** but only in 43% yield and still contaminated with about 3.5% of the impurity **8**. This is not good enough.

Mandelic acid **9**, available as both enantiomers, was used to make the other enantiomer, (*S*)-**2**, for a change. The cyclic acetal ester **10** reacted with ammonia to give a good yield of the amide **11** but with significant racemisation. Worse, reaction with $LiAlH_4$ gave incomplete reduction even with a large excess of reducing agent so that the product, (*S*)-**2**, was contaminated with large amounts (about 30%) of unreacted amide **11**. Complete reduction could be achieved with a large excess of borane to give 90% (*S*)-**2**, without racemisation, but this is not practical for scale-up.



A successful large scale asymmetric synthesis by resolution

Initially resolution looked the least promising of all strategies. Resolution with tartaric acid was known but the best that could be done was a 3.7% yield of material with 63% ee. Trials with ten other acids gave better results, e.g.: (figures in brackets are ees after one recrystallisation) camphoric acid (38%), pyroglutamic acid (67%), Boc-alanine (69%). However the best resolutions were with acyl derivatives of tartaric acid and the very best was di-*p*-toluoyl tartaric acid (**12**; DPTTA). The salt from technical grade racemic **2** with DPTTA was crystallised from aqueous *iso*-propanol on 100 g scale giving eventually 80% yield of (*R*)-**2** with 99.8% ee. This has now been scaled up to 9 kg and is the method chosen for production.

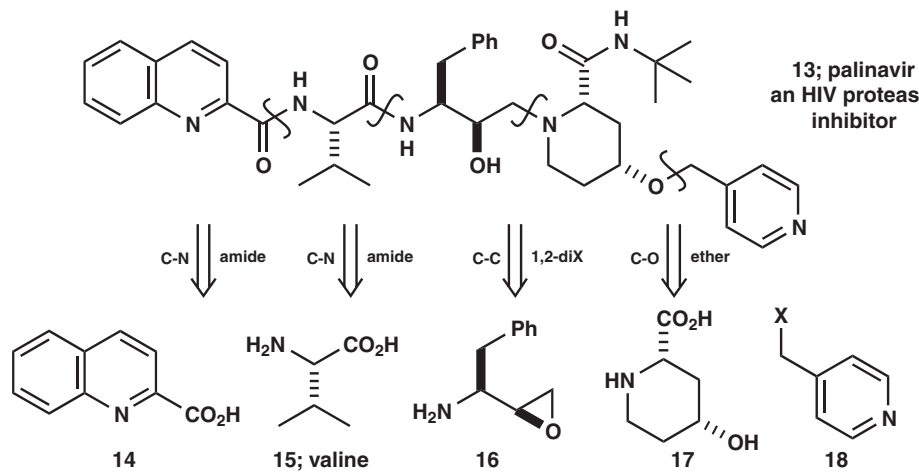


12; di-*p*-toluoyl tartaric acid (DPTTA)

Part II – (2*S*,4*R*)-4-Hydroxypipecolic Acid

A simple heterocyclic acid needed for an anti-HIV drug

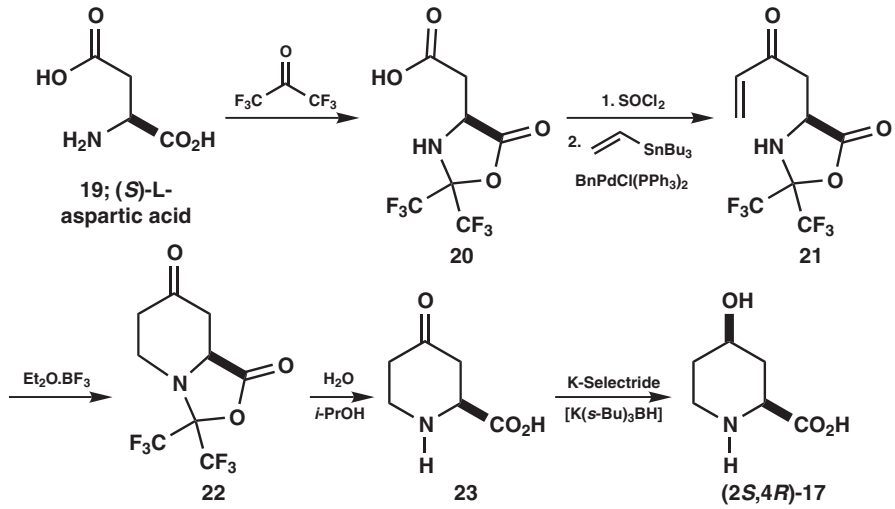
The HIV protease inhibitor palinavir **13** (from Bio-Méga/Boehringer, Québec) is a complex molecule that can be disconnected simply to five components. Two of these (**14** and **18)** are simple achiral aromatic compounds and two can be derived from the chiral pool (chapter 25): the amino acid valine **15** and an epoxide **16** derived from phenylalanine. The fifth **17** is the subject of this section. This compound has two chiral centres so we must first produce the right (*syn*-) diastereoisomer and then the right enantiomer.



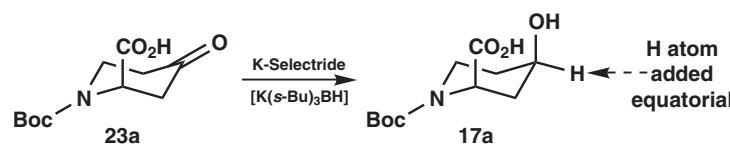
A chiral pool synthesis from aspartic acid

Though (2*S*,4*R*)-4-hydroxy pipecolic acid **17** is a natural product it cannot be obtained in sufficient quantity from nature. A chiral pool synthesis from aspartic acid **19** is known involving

a Pd-catalysed coupling of a vinyl stannane to an acid chloride.[2] This works well, but stoichiometric toxic tin is not acceptable in production.

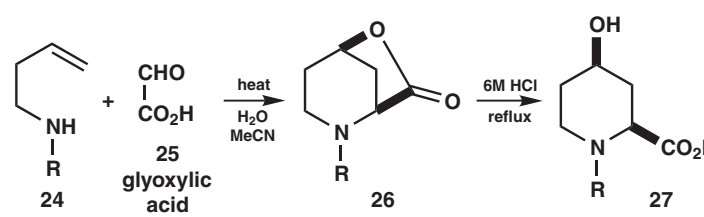


An important point from this synthesis is the transmission of chiral information (chapter 30) from the acid group in **23** to the OH group in **17** by reduction with the bulky reagent K-selectride. This sterically demanding reagent prefers an equatorial approach (chapter 21) and we can therefore deduce that the CO_2H group in **23** and both the CO_2H and OH groups in **17** are axial. The CO_2H group adopts an axial conformation in **23a** because the planar and conjugated (to N) Boc group would eclipse an equatorial CO_2H group. This information is vital for other syntheses.

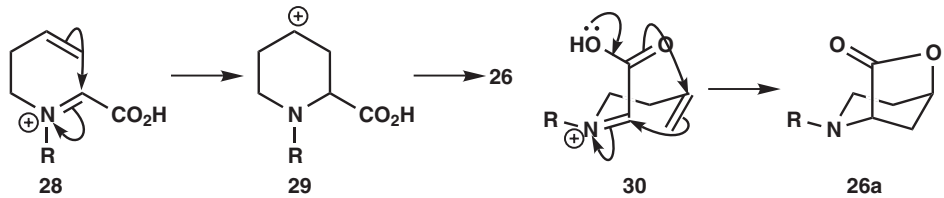


Choosing a new reaction to solve the stereochemistry problem

A simple reaction that creates both chiral centres in one step was already in the literature.[3] It is a cross between a Mannich and a Prins reaction involving the condensation of an unsaturated amine **24** with glyoxylic acid (**25**; available as an aqueous solution - fortunately the reaction works in water) to give a heterocyclic bridged lactone **26** with the right relative stereochemistry (but of course racemic).

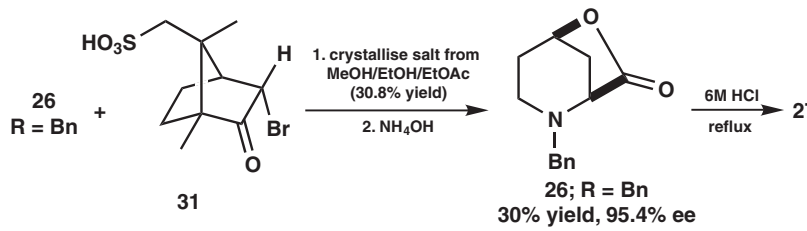


Presumably the aldehyde forms an iminium ion **28** with the amine and this is attacked by the alkene. One way to draw this would be **28** → **29** but it looks better to have concerted attack by the CO_2H group on the cation as it is formed **30**. At all events, the lactone **26** must have a 1,3-diaxial bridge **26a**.

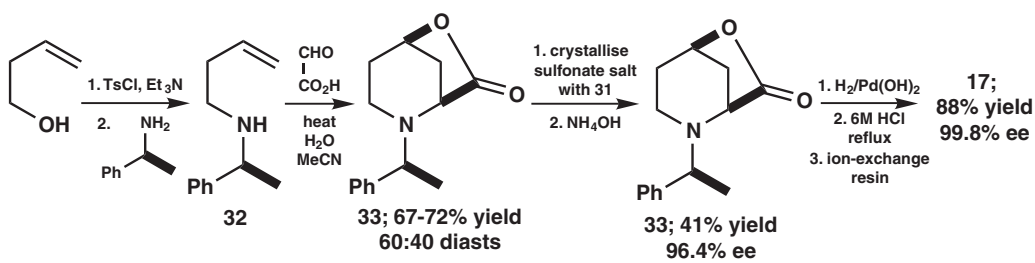


Making the new reaction asymmetric

The workers at Bio-Méga/Boehringer turned this promising reaction into an asymmetric synthesis.[4] They first tried resolution of **26** with R = benzyl as the group 'R' on nitrogen must be removable. The amine **24**; R = Bn could be made in only 41% yield - dialkylation was a problem. The new reaction with glyoxylic acid worked well and the lactone **26**; R = Bn could be resolved with a 55% amount (see chapter 22) of a bromocamphor sulfonic acid **31** but the yield was only 30% making it 12% overall from but-3-en-1-ol (see below) and the ee was not perfect (95.4%). However, they did find that the lactone could be hydrolysed to **27**; R = Bn without loss of stereochemical integrity.



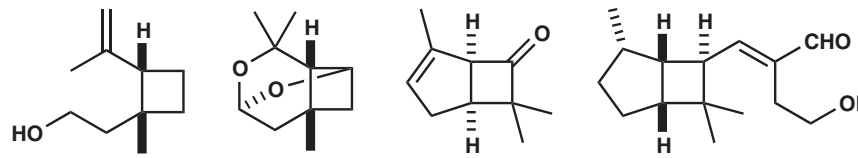
Their method of choice was part asymmetric induction and part resolution. The benzyl group was replaced by the chiral α-methylbenzyl group. This reduced dialkylation in the formation of the allylic amine **32** and allowed modest asymmetric induction in the formation of the lactone: **33** was 60:40 ratio of diastereoisomers. Crystallisation of the salt of **33** with the same sulfonic acid **31** completed the separation of one diastereoisomer and this gave **17** in good yield and essentially perfect ee. Note that the yield of pure **33** (41%) is actually quite good as the crude sample contained only 60% of the right diastereoisomer. The α-methylbenzyl group is removed by hydrogenation but its chirality is destroyed as it gives ethylbenzene. Recent work (discussed in the Workbook) at Chirotech leads to both enantiomers of both diastereoisomers.[5]



Part III – Grandisol and Some Bicyclo[3.2.0] Heptan-2-Ols

A bicyclic insect attractant used in agriculture

A modern approach to dealing with insect pests that wreck crops is to use specific attractants to lure the pest to its doom while offering no threat to beneficial creatures. Compounds such as grandisol **34** are not themselves toxic but they are irresistible to specific insect pests. Grandisol, marketed as 'grandlure', an attractant for male cotton boll weevils, is one of a family of unusual monoterpenes containing a four-membered ring. Others are lineatin **35**, an attractant for ambrosia beetles that bore into conifers, filifolone **36**, and raikovenal **37** (a sesquiterpene).

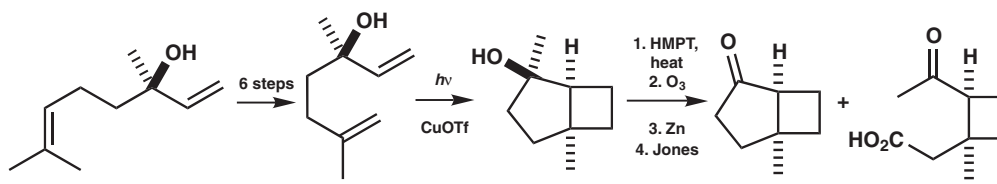


34; (+)-grandisol **35; (+)-lineatin** **36; (–)-filifolone** **37; raikovenal**

Chiral Pool Syntheses from Other Terpenes

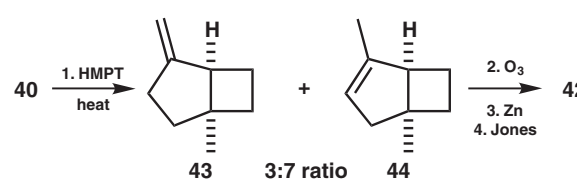
An attempt from linalool

This subject has recently been reviewed[6] and we shall concentrate on the different approaches to grandisol outlined in that review. Many of these approaches can clearly be used for the other compounds. An early approach was a chiral pool strategy from the simpler and commercially available terpene (*R*)-(−)-linalool **38**. Though this did not lead to a useful synthesis, it pointed the way to effective methods, particularly the Cu(I)-catalysed photochemical closure of the four-membered ring.



38; 3*R*-(–)-linalool **39** **40** **41** **3:7 ratio** **42**

The photochemical closure by a 2 + 2 cycloaddition of the two alkenes in **39** gave one diastereoisomer of **40**. The *cis* ring junction is inevitable and the rings fold so that the methyl group at the third centre is *exo* to the fold though the Cu(I) catalyst may be important for this. The bicyclic ring system in **40** makes it a useful precursor for compounds **35–37**. The next step is an unusual elimination catalysed by HMPT [$(Me_2N)_3P$]. The main product is the cyclic alkene **44** that gives the required intermediate **42** after ozonolysis but significant amounts of the *exo*-methylene compound **43** are also produced.

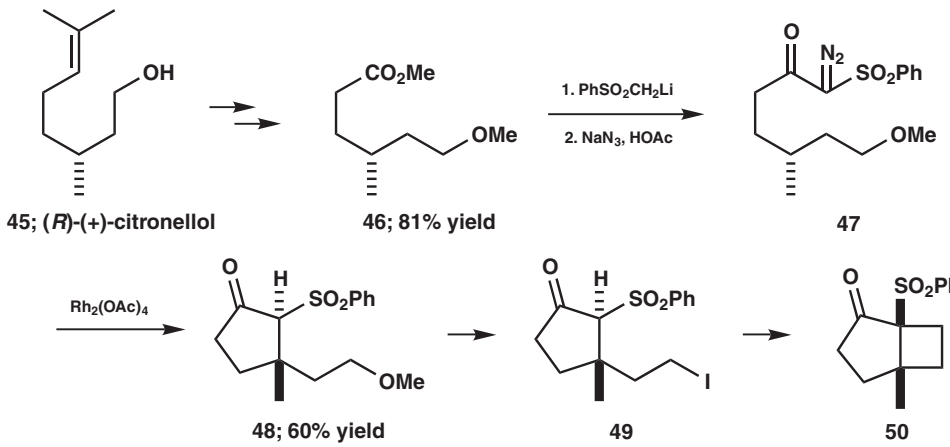


43 **3:7 ratio** **44**

What really makes this synthesis useless is that it would give the wrong enantiomer of grandisol (see the ring junction stereochemistry). While (*R*)-(−)-linalool is available in 100% ee, the (*S*)-(+)-enantiomer is both more expensive and available in only 64% ee.

An attempt from citronellol using carbene chemistry

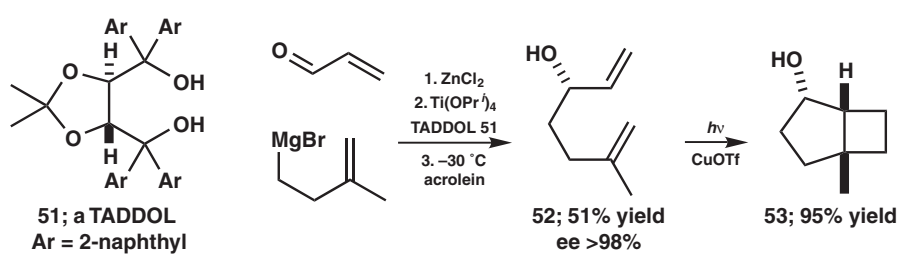
Citronellol **45** is a useful source of an isolated unfunctionalised chiral centre (chapter 23). It can be transformed into the ester **46** and then into the diazosulfone **47** by standard chemistry.[7] Now comes the interesting bit: an alternative to photochemistry for four-membered ring formation. Rhodium carbene complexes can be made from diazocompounds and insert into CH bonds, particularly if a five-membered ring can be formed. This one inserts into the chiral centre of **47** and does so with retention as expected. The centre might appear to be inverted because it is drawn differently in the two compounds. The chain is kinked *downwards* at the chiral centre in **47** but *upwards* in **48**. Conversion of the MeO group into a leaving group and cyclisation give the [3.2.0] bicyclic system with the right absolute stereochemistry but still having the sulfone attached. Compound **50** was converted into grandisol but the synthesis is very long (11 steps from **46**) and contains an elimination step like that in the previous synthesis (from **40**) but even less regioselective. Try again.



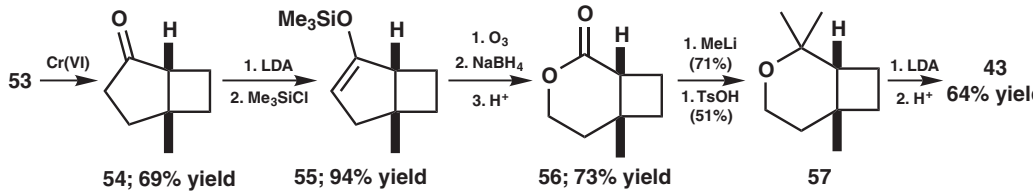
Asymmetric Synthesis

Asymmetric addition of an organo-zinc to an aldehyde

There are many examples of asymmetric addition of organo-metallic reagents to aldehydes (chapter 27) and the one that works here uses Seebach's TADDOL **51** as a ligand for zinc.[8] The TADDOL **51** is prepared from tartaric acid and used as its titanium (IV) complex to catalyse the addition of the organozinc compound to acrolein. After photochemical cyclisation in the presence of Cu(I), the bicyclic alcohol **53** was isolated in good yield and >98% ee.

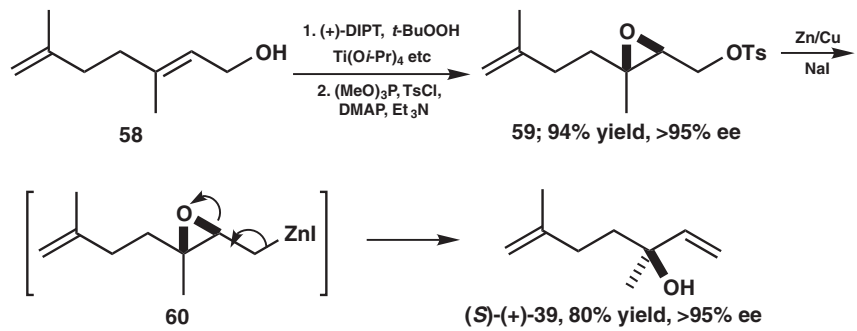


The remainder of the synthesis involved destruction of the original chiral centre from **52** and regioselective elimination. Several more steps were needed to give optically pure grandisol. The most interesting are the regioselective oxidation of the silyl enol ether **55** and the ingenious elimination that avoids formation of the *exo*-methylene compound **43** by an unusual base-catalysed elimination on a tertiary ether **57**. This process is too long for further development.



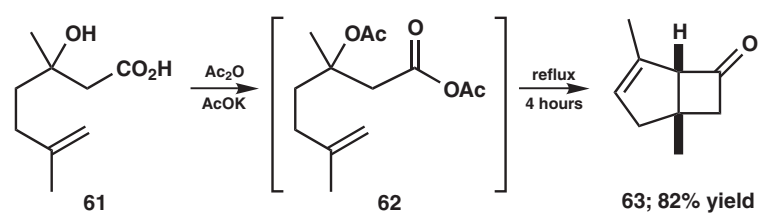
Synthesis by asymmetric dihydroxylation of a non-conjugated diene

Since the alcohol **39** is already known as a precursor for the wrong enantiomer of grandisol, an asymmetric synthesis of the right enantiomer would complete an efficient synthesis. The diene **58** is an ideal substrate for a Sharpless asymmetric epoxidation - reaction occurs only at the allylic alcohol (chapter 25). Two stage conversion of the OH into an iodide and treatment with zinc leads to an elimination **60** and the correct enantiomer of the tertiary alcohol **39** for conversion to grandisol.[9]



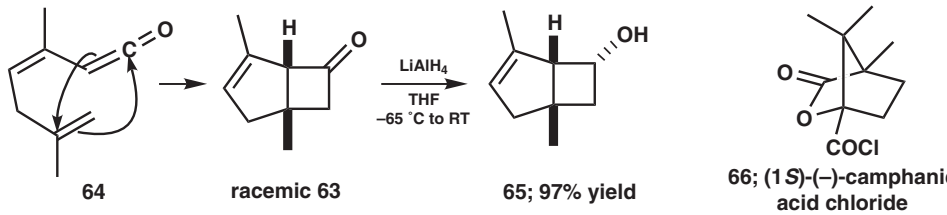
A Disappointment and a Resolution

All the methods so far described use either a photochemical cycloaddition or a transition metal carbene complex. Neither is well adapted to large scale production. The workers at Bologna[7] sought a new method. They found it in a thermal cycloaddition of a ketene and an alkene. The mixed anhydride **62** gave a single diastereoisomer of the bicyclic ketone **63** in 82% yield simply on heating. No UV light, no metals.



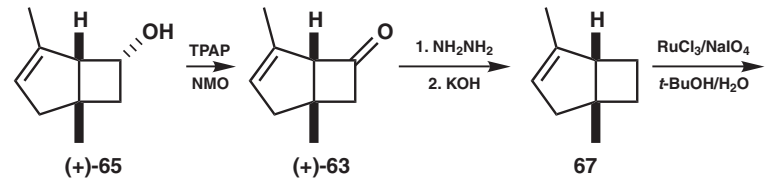
They then tried the same reaction on a single enantiomer of the alcohol **61** but to their great disappointment found only racemic product. It appears that this is indeed a 2 + 2 cycloaddition of the ketene **64** and this is an achiral molecule. However, reduction of the ketone with $LiAlH_4$ gave

only the *endo* alcohol **65** (the reagent approaches on the outside of the folded molecule) and this could be resolved efficiently with camphanic acid chloride **66**.



64 racemic 63 65; 97% yield 66; (1*S*)-(–)-camphanic acid chloride

The rest of the synthesis is straightforward but you should notice the catalytic Ru(III) oxidation used both on **65** and **67**, the periodate cleavage to replace ozonolysis in the formation of **68** and the Peterson reaction (chapter 15) used to make the alkene **69**. This method was used for the synthesis of quantities of both enantiomers of grandisol **34**.



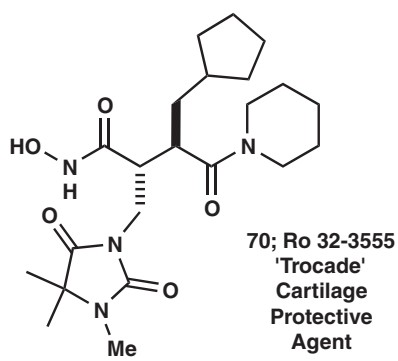
(+)-65 (+)-63 67

68; 71% yield 69; 81% yield (+)-34; 82% yield

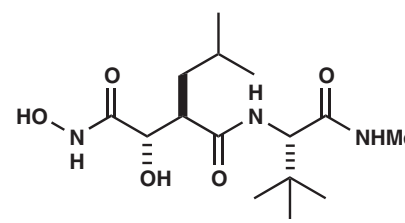
Part IV – Metalloproteinase Inhibitors

A group of compounds that protect cartilage from enzymatic degradation

Arthritis attacks all of us who live long enough. The stiffness in the joints arises because the collagen that lubricates them is eaten away by over-enthusiastic zinc-dependent enzymes known as metalloproteinases. One possible therapy for arthritis is inhibition of these enzymes by compounds such as 'Trocade' **70** and 'Marimastat' **71**.

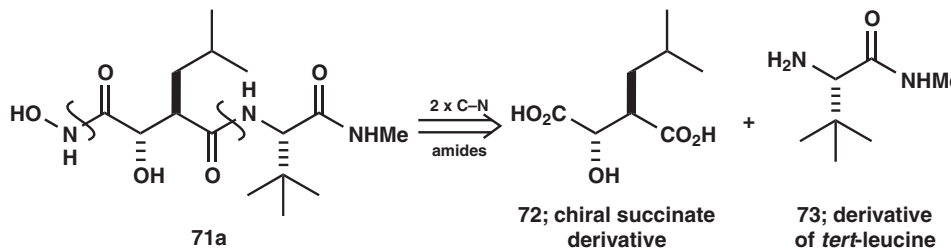


70; Ro 32-3555 'Trocade' Cartilage Protective Agent



71; BB-2516 'Marimastat' Cartilage Protective Agent

These drugs are clearly peptide mimics having a genuine amide portion to the right as drawn, a hydroxamic acid to the left and a core that binds zinc and acts as a transition state mimic for the peptide cleavage. They have a C–C bond instead of the amide linkage in the natural substrate so that the drug cannot be hydrolysed by the metallopeptidase. This is easily seen if we disconnect **71a** to show the amino acid *tert*-leucine **73** and a derivative of succinic acid (butanedioic acid) as the core **72**. A similar core is present in trocade **70**. We shall discuss the asymmetric synthesis of both core succinates.



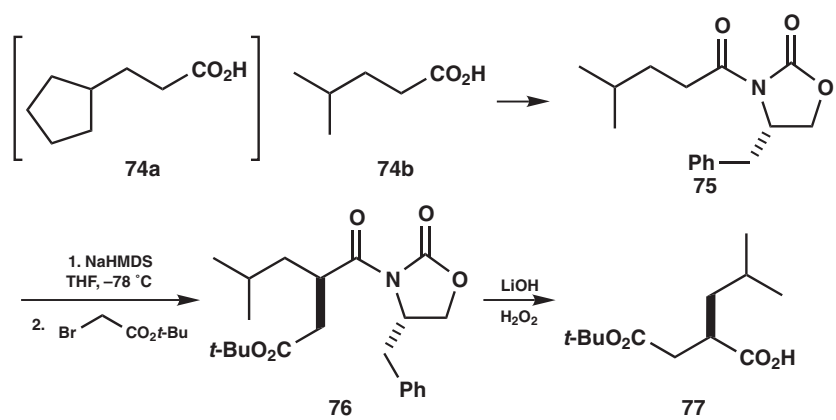
71a

72; chiral succinate derivative

73; derivative of *tert*-leucine

Asymmetric alkylation of Evans's chiral enolates

The succinate core can be prepared by alkylation of a simple carboxylic acid (**74a** or **b**) with a bromoacetate using the Evans oxazolidinone chiral auxiliary derived from phenylalanine (chapter 27). The branched alkyl group must be present in the substrate for alkylation and the second acid group added in the alkylation so that there is no competition between two carbonyl groups during enolate formation. After hydrolysis (91% yield) the alkylated succinic acid **77** has >95% ee. Notice that the two acid groups are differentiated by this procedure.[10]



74a

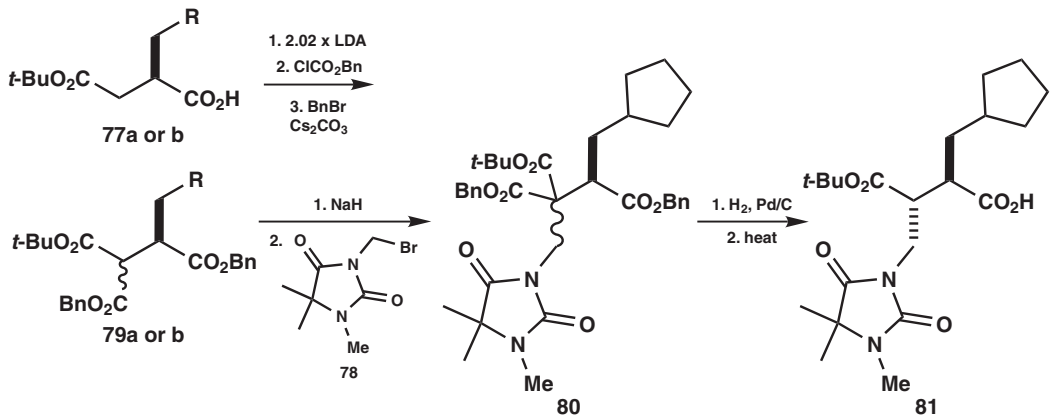
74b

75

76

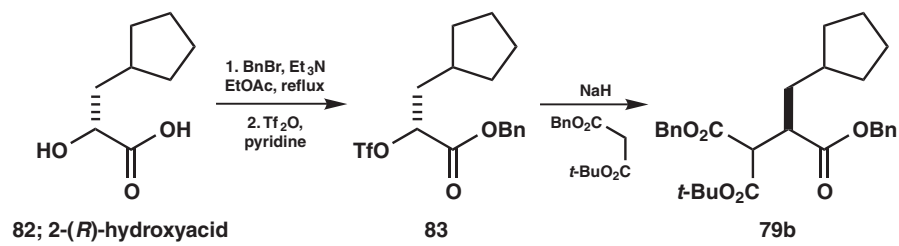
77

Direct alkylation of the enolate of **77a**; R = cyclopentyl with the alkyl halide **78** was not very diastereoselective so an alternative route was used to allow equilibration to the more stable isomer.[11] Carboxylation of the enolate gave **79a** and alkylation of this malonate gave a good yield of **80**. The benzyl esters were cleaved by hydrogenation and the malonate decarboxylated to give the required *anti* isomer of **81** in a 4:1 ratio with its *syn* diastereoisomer. Conversion into 'Trocade' is straightforward.

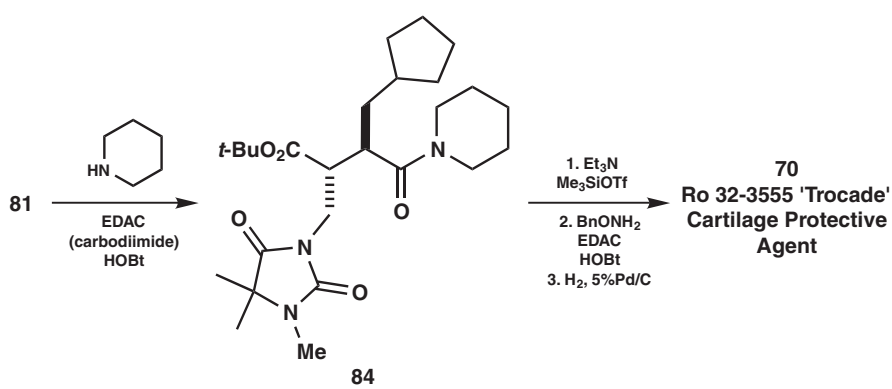


Asymmetric synthesis from an enantiomerically enriched hydroxy-acid

An alternative route to **79b** involved nucleophilic displacement from an enantiomerically pure hydroxy acid **82** with a malonate enolate. The OH group was activated as a triflate **83**. This method depends on the availability of optically pure hydroxyacid.[12] Notice that the 'wrong' enantiomer of **82** must be used as inversion occurs during the S_N2 reaction leading to **79b**.



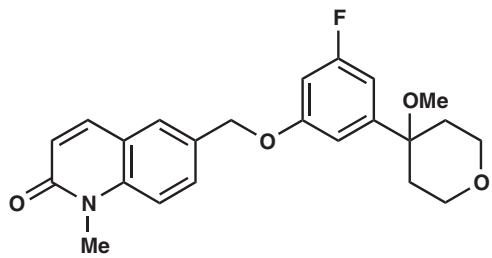
However intermediate **81** is made, the rest of the synthesis involves coupling the free acid to piperidine using a carbodiimide to give **84**, removing the *t*-butyl group to free the other acid, coupling that acid with a protected (*O*-benzyl) hydroxylamine and removing the protecting group.



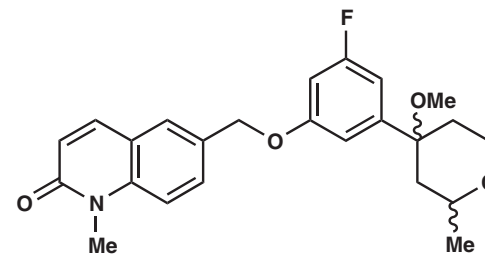
Part V – Conformational Control and Resolution: Kinetic or Not?

A tetrahydropyran that inhibits leukotriene biosynthesis

The leukotrienes are implicated in various inflammatory conditions such as rheumatoid arthritis and inhibiting their biosynthesis is potentially a useful therapy. Some time ago ICI (AstraZeneca now) found that some THPs (TetraHydroPyrans) inhibited the enzyme 5-lipoxygenase in the pathway to leukotrienes and they concentrated on achiral compounds such as **85** (known as ICI D2138). However it soon became clear that an extra methyl group, as in **86**, enhanced activity. This small change makes the molecule chiral by introducing two chiral centres. It was necessary to find which diastereoisomer (*syn* or *anti*) was more active and which enantiomer of that diastereoisomer was better.[13]

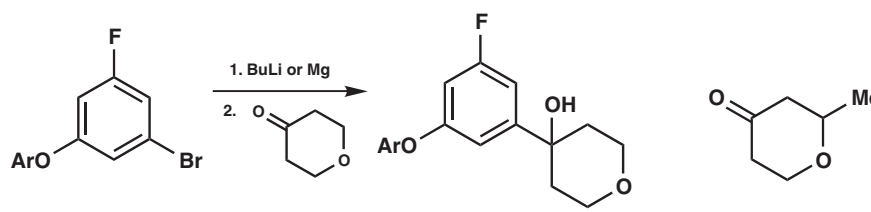


85; ICI D2138



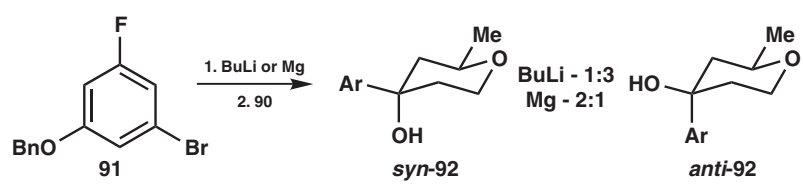
86

The synthesis of **85** had involved the addition of a suitable organo-Li or Grignard reagent made from **87** to the heterocyclic ketone **88** and it seemed sensible to adopt the same strategy for **86**. So two questions were asked: would it be better to start with a single enantiomer of **90** and what was the diastereoselectivity of RLi and/or RMgBr additions to **90**?



87 **88** **89** **90**

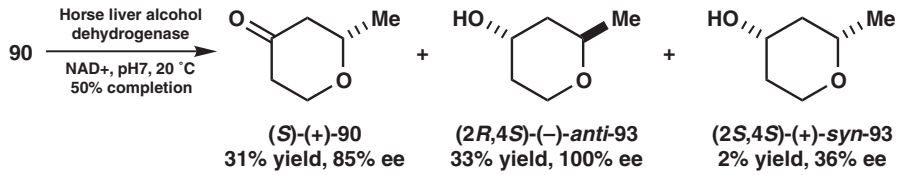
Answering the second question first, they found that the close relative **91** added to racemic **90** to give predominantly the *anti* diastereoisomer of **92** (3:1) while the Grignard reagent gave more of the *syn* isomer (2:1). The aryl-lithium prefers equatorial while the Grignard reagent prefers axial addition.



91 ***syn*-92** ***anti*-92**

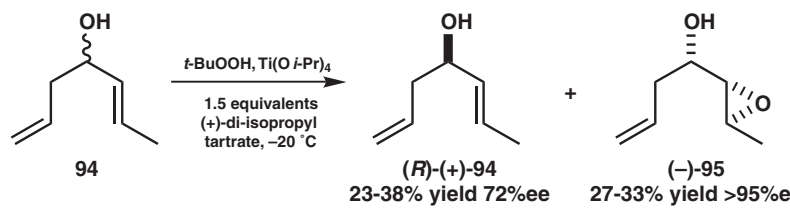
Asymmetric synthesis of 2-methyl-tetrahydropyran-4-one by kinetic resolution

Now it is worth making enantiomerically enriched **90**. One method already in the literature[14] involved reduction of racemic **90** with horse liver alcohol dehydrogenase. This is an enzymatic kinetic resolution (chapters 28 and 29) and at 50% reduction the products are 31% unreacted ketone **90** in good ee, 33% of one enantiomer of the *anti*-alcohol **93** in perfect (100%) ee, and a trace of the *syn*-alcohol **93**.

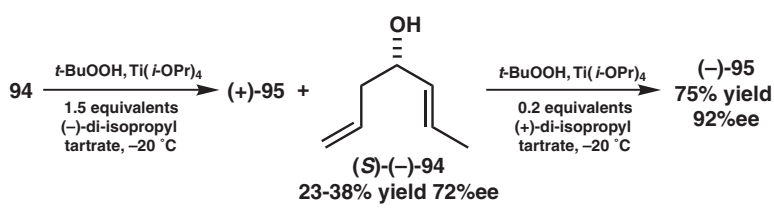


Oxidation of (−)-*anti*-**93** with PCC gave enantiomerically pure (+)-**92** and addition of the organo-Li or -Mg compounds would give the two diastereoisomers in this series. As you see the yield of enantiomerically pure **93** is only 33% and, as is often the case with a kinetic resolution, the unreacted ketone has a lower ee.

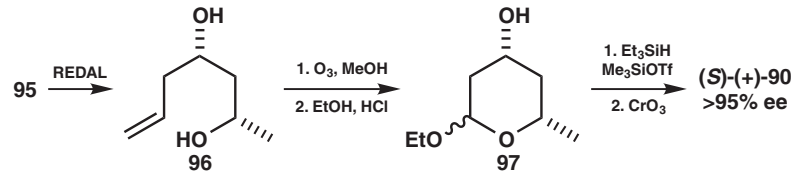
An alternative and more ingenious method gave all the stereochemical information required.[13] The racemic dienol **94** was subjected to Sharpless asymmetric epoxidation (chapter 25).[15] This is another kinetic resolution run to about 50% completion. Using an excess of di-isopropyl tartrate (DIPT, 1.5 equivalents) one enantiomer of the alcohol (*R*)-**94** remained (72% ee) and one enantiomer of one diastereoisomer of the epoxide **95** (>95% ee) was formed. Once again the unreacted starting material **94** has a lower ee than the enantioselectively formed product **95**.



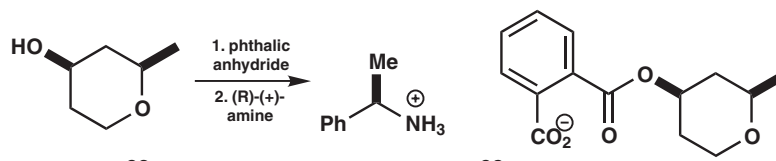
Alternatively, the 'wrong' enantiomer of DIPT was used to give the 'right' enantiomer of unreacted allylic alcohol (*S*)-(−)-**94** (of course also in 72% ee) and this was epoxidised using a catalytic amount (0.2 equivalents) of DIPT. This gave the 'right' enantiomer of the epoxide. By these means, good yields of both enantiomers of **95** could be formed and both could then be converted into the various stereoisomers of **86**.



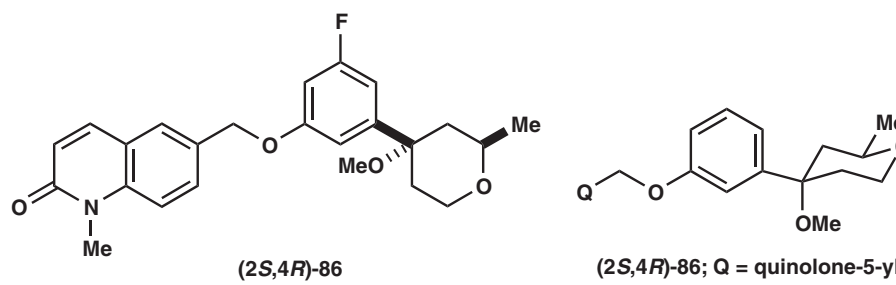
The epoxide **95** was reduced with REDAL [$NaAlH(OCH_2CH_2OMe)_2$] to give the diol **96**. Further simple chemistry gave the same (*S*)-(+) enantiomer of **90** as was left unreacted in the enzymatic kinetic resolution. This enantiomer was converted into the two tertiary ethers **86** in this series.



The other enantiomer (*R*)-(−)-**90** was obtained by resolution of racemic *syn*-**93** via the α-methylbenzylamine salt of the phthalate **98**. After chiral HPLC (chapter 22) the ester was hydrolysed and oxidation gave (*R*)-(−)-**90** from which the two remaining stereoisomers of **86** could be made.



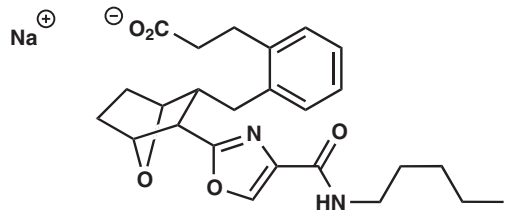
The purpose of this investigation was analytical rather than synthetic and it was established that the (2*S*,4*R*) enantiomer of **86**, one of the enantiomers with equatorial aryl and equatorial methyl groups, was the most potent compound.[13]



Part VI – Asymmetric Desymmetrisation of a Diels-Alder Adduct

Ifetroban sodium: a thromboxane receptor antagonist

Thromboxanes are human metabolites vital for blood clotting but too much of them is dangerous for patients with heart, lung, or kidney disease. They are also very unstable and the search for stable, orally available, thromoboxane antagonists at the Bristol-Meyers Squibb company revealed the useful compound ifetroban[16] sodium **99**. It contains three rings: an *ortho*-disubstituted benzene ring, an oxazole, and a bicyclic ether.

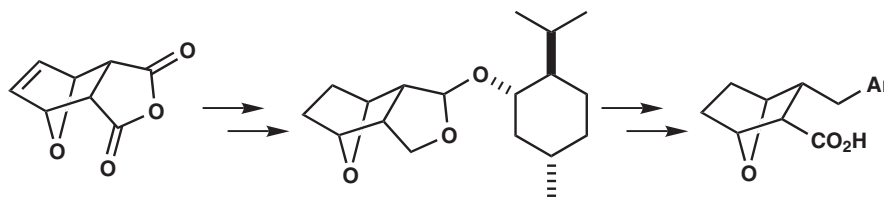


99
Ifetroban sodium

orally bioavailable thromboxane A2 receptor antagonist

A laboratory synthesis starting with a Diels-Alder reaction

The Diels-Alder reaction between furan and maleic anhydride is reversible and gives the more stable *exo*-adduct **100** (also commercially available). This compound contains the bicyclic ring system of ifetroban but is achiral and the key problem is to disrupt symmetry of the adduct **100** in a controlled way. The original synthesis used to make the drug[17] converted the adduct **100** into the menthyl acetal **101** as a single enantiomer in four steps and then into the carboxylic acid **102** in another six steps. This strategy amounts to a resolution as each menthol adduct could be isolated by crystallisation of a diastereoisomeric mixture in only about 30% yield.

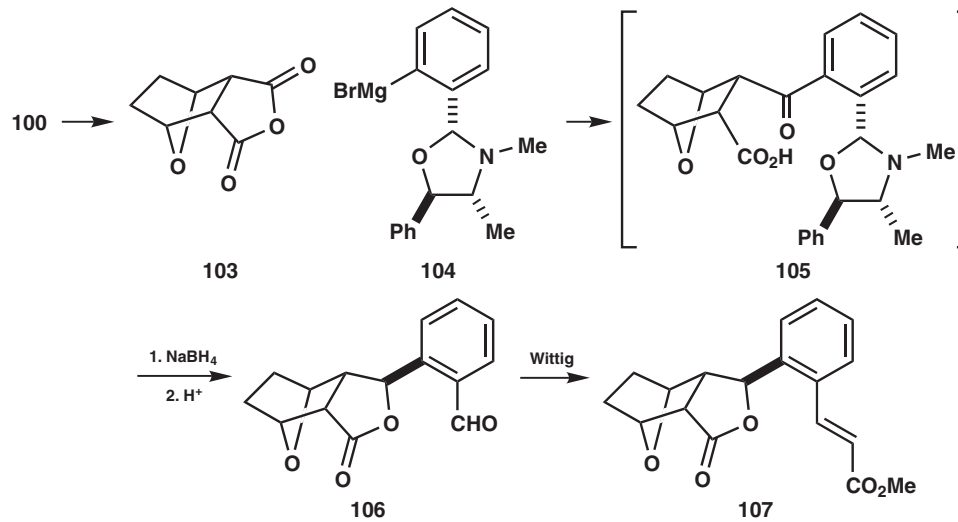


100 **101** **102**

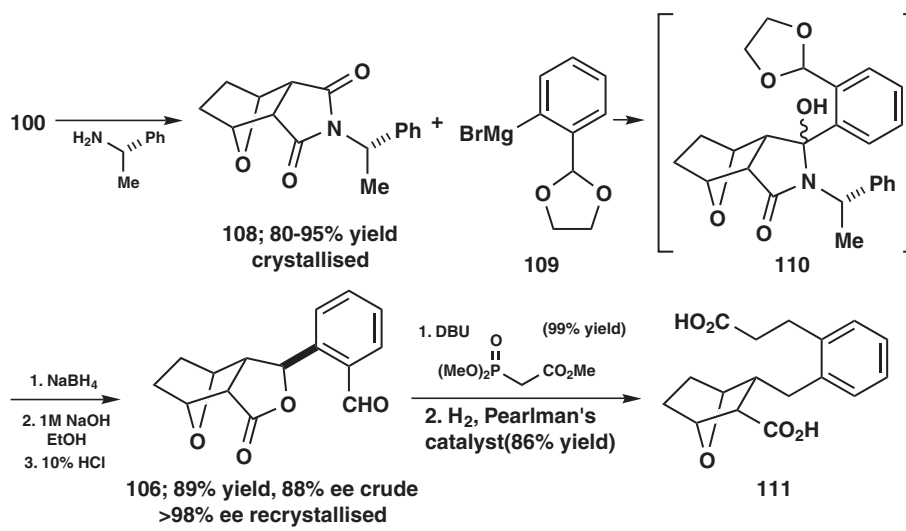
The problem with this synthesis is its great length (23 steps altogether) caused by the repeated changes of oxidation level of the functional groups. The overall yield is less than 3% but even so it was used to make some 20 kg of ifetroban sodium. As the compound became a more likely drug candidate, a more efficient synthesis was clearly needed.

Desymmetrisation of a symmetrical anhydride with a chiral Grignard reagent

Since the starting material for all syntheses of ifetroban is bound to be the achiral Diels-Alder adduct **100**, one good strategy is to desymmetrise this compound or the saturated version **103** with a chiral nucleophile. One that works is the oxazolidinone **104** derived from ephedrine.[18] [You have seen ephedrine used as a chiral auxiliary in chapter 27]. Reaction occurs predominantly at one of the enantiotopic carbonyl groups to give the keto-acid **105**. This is immediately reduced and the chiral auxiliary removed to give the lactone **106**. Though only one centre is marked, five new stereogenic centres are formed in **106**, one by the reduction and the others by desymmetrisation. The sequence is very selective, giving lactone **106** in 99.2% ee after recrystallisation. The aldehyde is used to add the side chain **107** by a Wittig reaction and the carboxylic acid is used to add the oxazole. The problem is that the yield is not very good. The lithium derivative of **104** gives only 50% yield and even the Grignard reagent gives 65% at best.



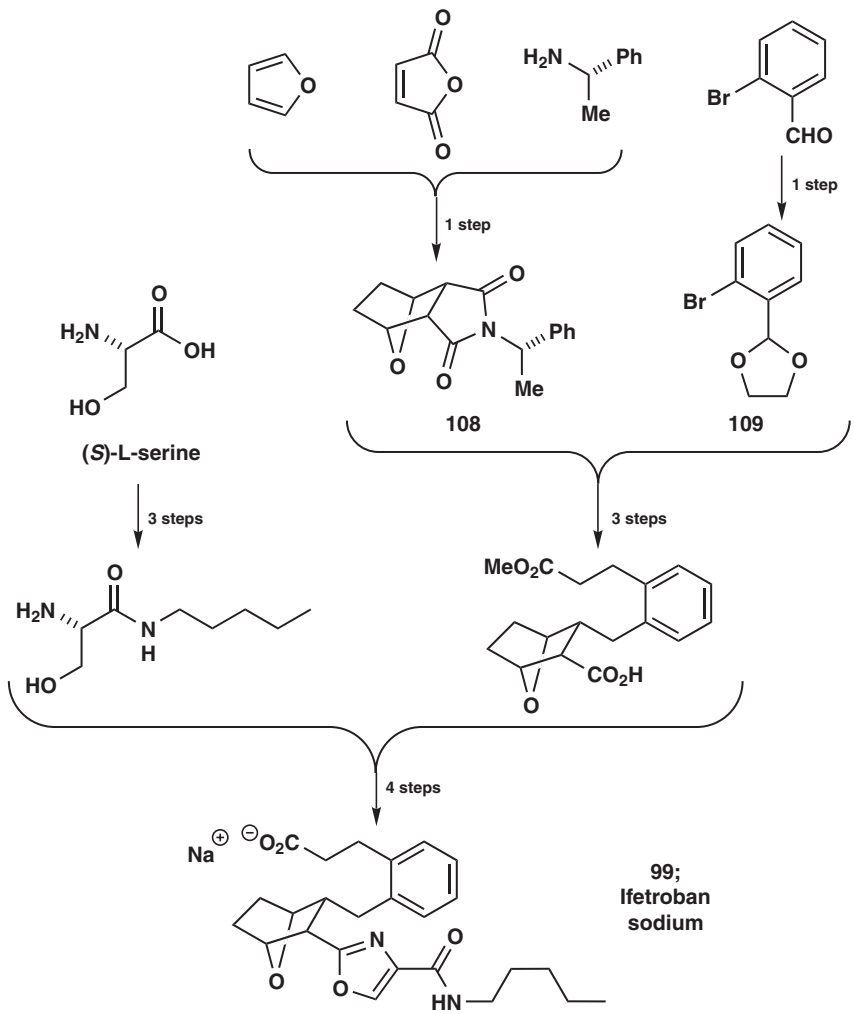
An alternative approach[17] is to attach a chiral auxiliary, (phenyl ethylamine, available by resolution, chapter 22, and used repeatedly in chapters 22–28, to the anhydride **100** in the form of a chiral imide **108**. This auxiliary is very close to the two carbonyl groups of the anhydride in **108** and directs the achiral Grignard reagent **109** to one of them to give adduct **110** immediately reduced and hydrolysed to the lactone **106**. One recrystallisation gives **106** in >98% ee. This time a Horner-Wadsworth-Emmons reaction (chapter 15) adds the side chain as a conjugated unsaturated acid reduced to the saturated side chain in **111**, a common intermediate in most syntheses of ifetroban. The formation of the oxazole and the rest of the synthesis is described by R. N. Misra and the Bristol-Meyers Squibb team.[16]



Laboratory and process routes compared

A simple comparison between the laboratory route used by the medicinal chemists and the route devised by the development chemists at Bristol-Meyers Squibb for the production of **99**

shows how important is this efficient asymmetric synthesis. The laboratory route used 23 steps and gave 3% overall yield with the asymmetry coming from a resolution. The process route, summarised below, has 12 steps, gives 28% overall yield and derives asymmetry from a substrate-attached chiral auxiliary. You may notice that the oxazole is assembled from the chiral pool (serine, see chapter 25) even though the chirality is lost: serine is just a convenient starting material.

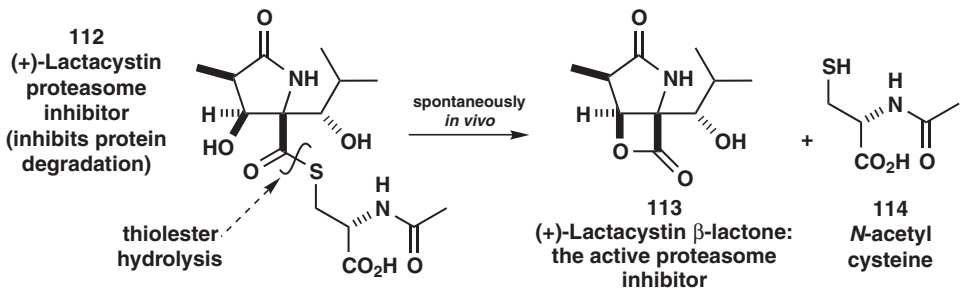


Part VII – Asymmetric Synthesis of a Bicyclic β-Lactone

Lactacystin: a natural proteasome inhibitor

Proteins in the human body have a limited lifetime. They are earmarked for degradation with a marker 'ubiquitin' and hydrolysed by proteasomes. Though this is a natural and necessary sequence of events it can get out of hand and proteasome inhibitors could provide treatments for heart diseases, asthma, and arthritis. Lactacystin **112** is a proteasome inhibitor from a soil micro-organism.

It works by the spontaneous hydrolysis of the thiol ester to give *N*-acetyl cysteine **114** and the true inhibitor, the β-lactone **113**. This β-lactone has been the target of many syntheses using diverse strategies and these form the last section of this chapter. Notice that the stereochemistry of the OH and CO groups in the β-lactone is the same as that in lactacystin itself since the β-lactone is both formed from **112** and reacts with **114** to give **112** by nucleophilic attack at the carbonyl group. The biology and chemistry of these compounds is summarised in an excellent review.[19] There are many syntheses - some very long - and we shall concentrate on the origin of chirality in each.

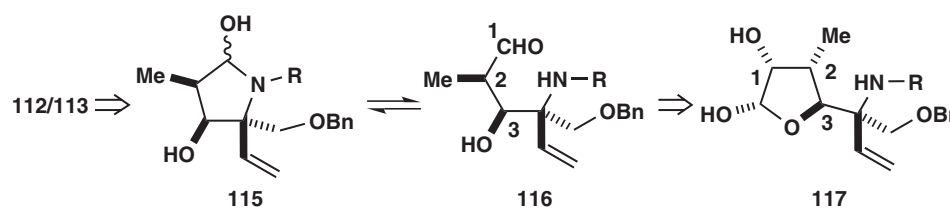


Strategies used in the synthesis of lactacystin, the β-lactone, and analogues

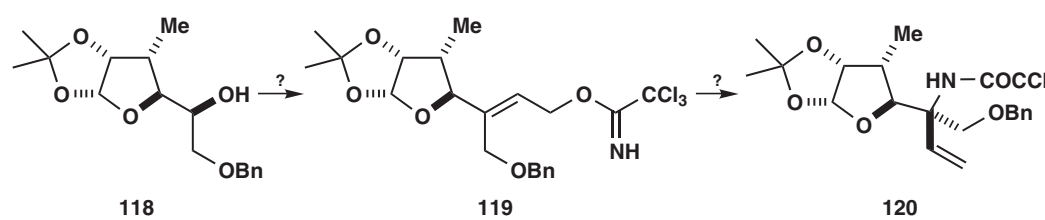
The thiolester portion is always derived from natural cysteine so there is a chiral pool element present in all syntheses. Because there are four consecutive chiral centres in the main portion of the molecule, just about every strategy has been employed by someone: more chiral pool, chiral reagents and catalysts, chiral auxiliaries attached to substrate or reagent, and sometimes combinations of these.

A chiral pool synthesis of lactacystin from glucose

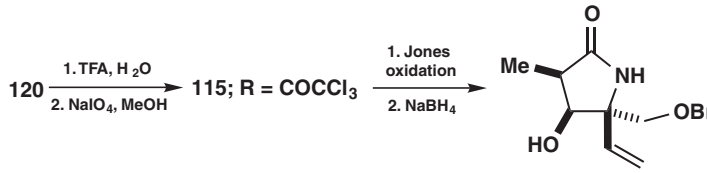
An early synthesis of lactacystin, not via the β-lactone, used glucose as starting material.[20] Disconnection to **115** (the vinyl group can be converted into CO_2H and the benzyl ether into CHO) gives a structure that can be redrawn as **116** and then, with incorporation of an extra C atom (to be removed in the synthesis by diol oxidation) derived from **117**.



It was already known that glucose could be converted into the cyclic ether **118** and a [3,3] sigmatropic rearrangement (Overman style, see chapter 19) on the allylic imidate ester **119** should give **120**, a derivative of **117**. The 'should' has to be there because it is not possible to forecast the stereochemical outcome with certainty.

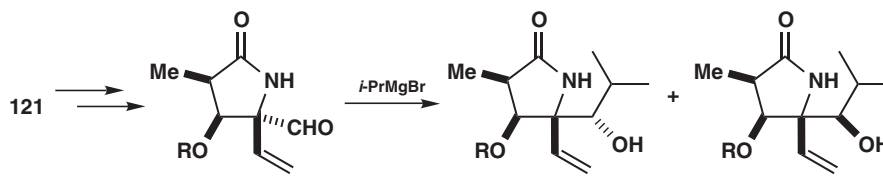


In the event, a 1:1 mixture of *E:Z* isomers of **119** gave a 4.8:1 mixture of **120** and its diastereoisomer at the new centre in 60% yield. This is a remarkable level of control but later syntheses do better. Deprotection, oxidative cleavage and cyclisation gave the pyrrolidine **121**.



121

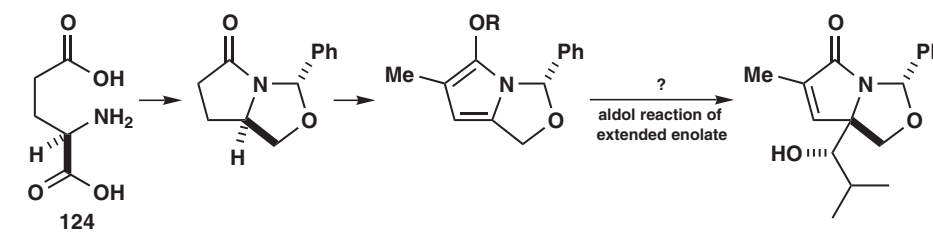
There was a further problem in the addition of *i*-PrMgBr to the aldehyde (R = *t*-BuMe$_2$Si-) derived from **121**. The chemo- and stereoselectivity were poor and the product contained 35% **123a**, 30% **123b**, and 21% alcohol from the reduction of **122**. Though the unwanted products could be recycled: **123a** by oxidation and re-reduction and the alcohol by oxidation to **122** it is clearly possible to do better.



122 **123a** **123b**

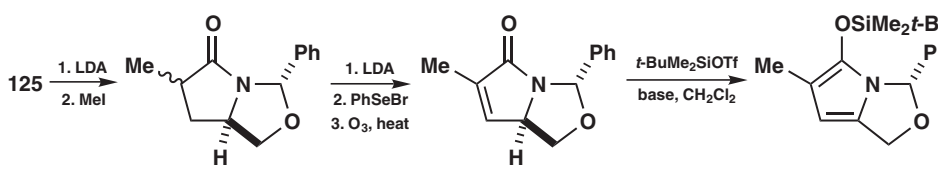
Chiral pool syntheses of lactacystin from amino acids

Amino acids are attractive starting materials for lactacystin and there are several published syntheses using this type of chiral pool strategy. Baldwin[21] used glutamic acid **124** with the idea of using the known Seebach-style intermediate **125** (chapter 24) with a relay chiral centre and destroying the original centre to give a pyrrole **126** that is also an extended enolate. An aldol reaction of **126** with *i*-PrCHO might be controlled to give the correct aldol product **127**.



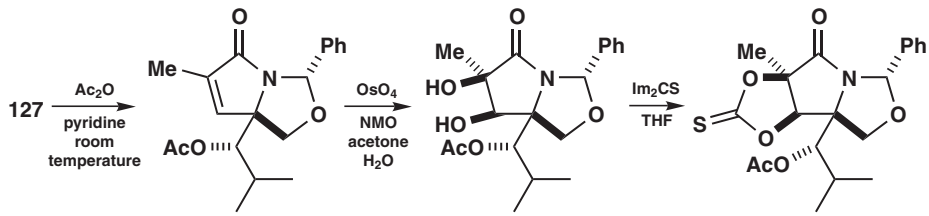
124 glutamic acid **125** **126** **127**

The conversion of **125** into the pyrrole **126** uses reactions from earlier chapters. Methylation is not stereoselective but that doesn't matter as selenenylation, oxidation, and elimination gives a single internal alkene – this chemistry will be explained in chapter 33. Now silylation destroys the original chiral centre from glutamic acid but keeps the relay centre.

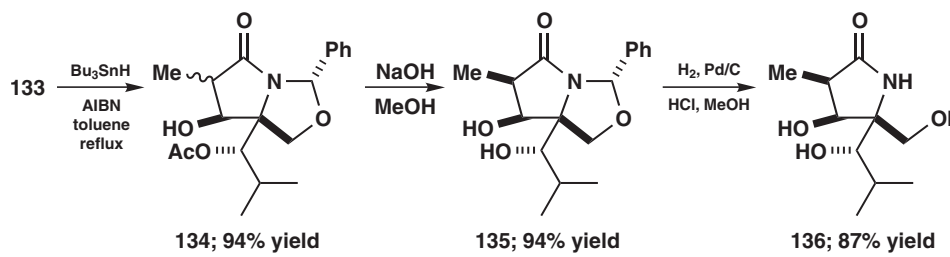


128; 95% yield **129; 79, 87% yields** **130; 89% yield**

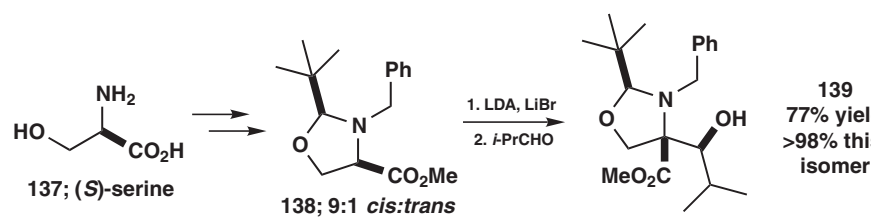
The aldol reaction proved difficult but a Lewis acid ($SnCl_4$) catalysed reaction at low temperature gave a 9:1 ratio of aldols in favour of **127** which could be isolated in 55% yield after chromatography. Notice that the aldehyde has added to the same face as that 'blocked' by the phenyl group, as we should expect from chapter 24. The alkene in **127** must now be removed, the remaining OH group introduced, and the last two chiral centres in the pyrrolidine ring controlled. These all present problems but the extra OH is the worst. Baldwin found an ingenious solution: two OHs were introduced *diastereo*selectively by a *racemic* dihydroxylation of the acetate **131**. The two OHs go on the right side, opposite the Ph and aldol groups, and the diol **132** is cyclised to the thiocarbonate **133** (Im = imidazole).



The thiocarbonate is used to get rid of the unwanted OH group in a radical reaction using Bu_3SnH to initiate a radical chain The methyl centre is epimerised in this operation but treatment with base gives the right diastereoisomer **135** and also hydrolyses the acetate. The original chiral auxiliary can now be removed by hydrogenation and **136** should be close enough to lactacystin for you to see that the synthesis can be completed.

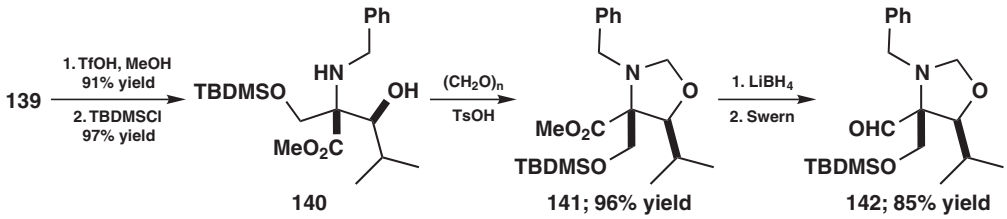


Corey's earlier synthesis[22] uses a related strategy from serine involving a Seebach-style relay chiral centre and two stereoselective aldol reactions. The aldol reaction with *i*-PrCHO is carried out first and the pyrrolidine ring assembled later with the second aldol reaction. Serine **137** is converted to the cyclic *t*-BuCHO derivative **138**. An aldol reaction with the enolate of **138** and *i*-PrCHO gives mostly the wanted aldol **139**. The aldehyde adds to the face opposite to the *t*-butyl group.

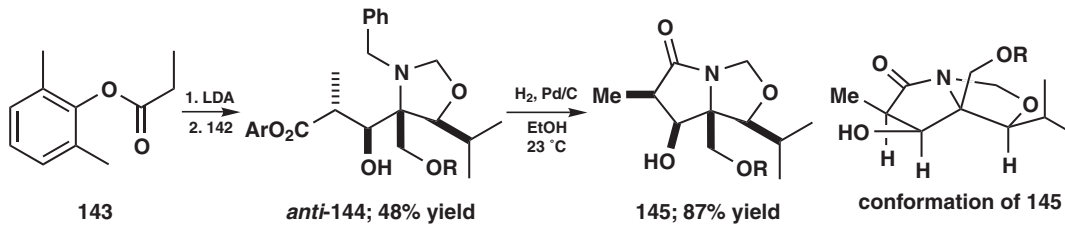


This oxazolidine ring is hydrolysed to give an open chain diol that can be selectively protected with the large *t*-$BuMe_2Si$ group **140**. Treatment with formaldehyde now gives a different oxazolidine

141 and hence the aldehyde **142** ready for the next aldol reaction. This aldehyde cannot be enolised so it is a good electrophile.

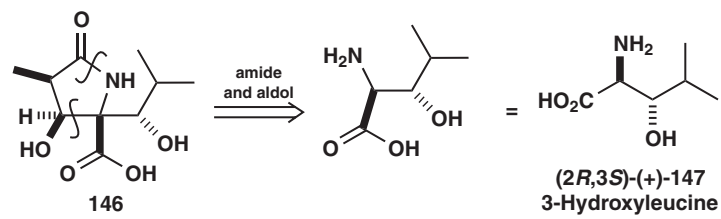


Heathcock's diastereoselective aldol method (chapter 4) gave the required *anti*-aldol **144** but only in low yield. Removal of the *N*-benzyl group allowed the amine to cyclise onto the aryl ester and the bicyclic compound **145** of fixed conformation is formed. Notice that all the substituents are on the outside (*exo* face) of the folded molecule (chapter 21). The further development of **145** into lactacystin can be found in the paper.[22]

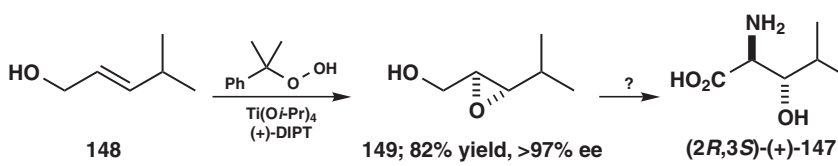


The reagent strategy: asymmetric epoxidation and asymmetric allylboration

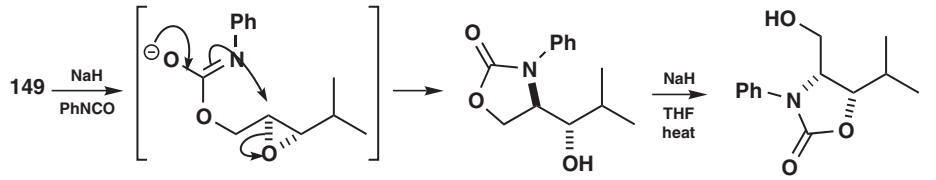
We move into approaches that are more sophisticated in several ways. The synthesis by Omura and Amos B. Smith[23] was partly inspired by the biosynthesis of lactacystin and partly by an attempt to make other diastereoisomers. Their key intermediate is the non-proteinogenic amino acid hydroxyleucine **147** and they were able to make both enantiomers of both diastereoisomers of this compound by asymmetric synthesis.



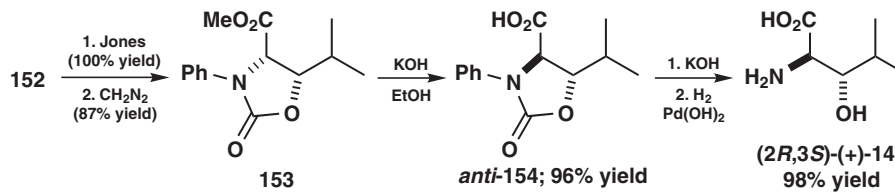
Sharpless asymmetric epoxidation (chapter 27) of the allylic alcohol **148** with cumyl hydroperoxide and (+)-di-isopropyl tartrate (DIPT) gave the epoxide **149** in excellent yield and enantiomeric purity. The other enantiomer could be made simply by using the other enantiomer of DIPT. The problem is now: how to react the epoxide regiospecifically with a nitrogen nucleophile?



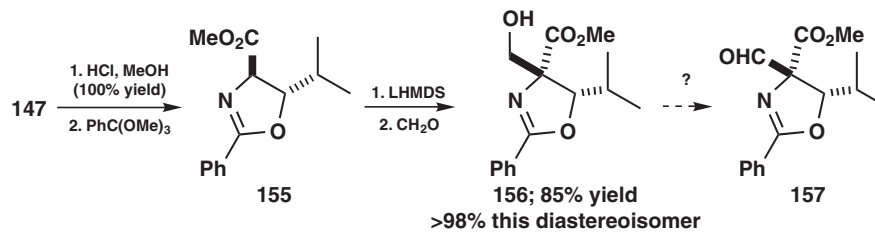
A cunning solution was to attach the nucleophile to the OH as an isocyanate and to use the anion **150** to react intramolecularly with the epoxide **149**. Initially the anion must cyclise to the nearer end of the epoxide to give **151** but even under the reaction conditions **151** starts to isomerise to **152**. This isomer **152** is not the alternative product from **150**: it is formed by attack of the secondary alcohol on the C=O group of **151**. Further treatment with NaH completes the isomerisation to **152**.



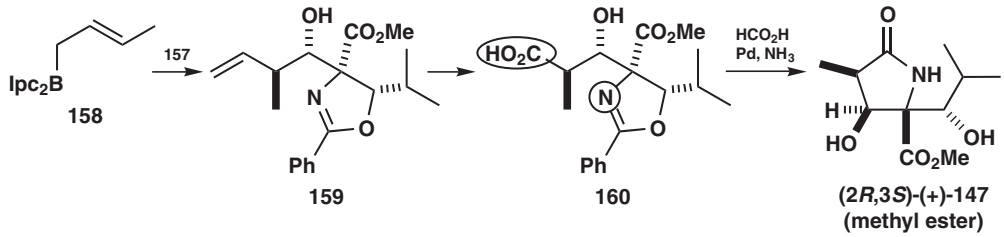
Oxidation and esterification give one diastereoisomer of protected 3-hydroxyleucine **153** and epimerisation in base gives another **154**. It is the latter that is required for the synthesis of lactacystin but either enantiomer of either diastereoisomer can be made by this sequence. The overall yield of natural 3-hydroxyleucine **147** is about 50% from the allylic alcohol **148**.



A few small changes give the oxazoline needed for the stereoselective aldol reaction with formaldehyde. There is no *syn/anti* aldol question here: the electrophile simply adds to the face of the more or less planar enolate opposite the isopropyl group. Now there was a severe difficulty in an apparently trivial reaction: oxidising the primary alcohol **156** to the aldehyde **157**. The advantage that the aldehyde is not enolisable is a disadvantage too as nucleophiles may attack and remove the CHO group. The problem was solved by careful choice of reagents (Moffat oxidation with DMSO, DCC and CF_3CO_2H). The aldehyde **157** was not isolated but used immediately in the next step.

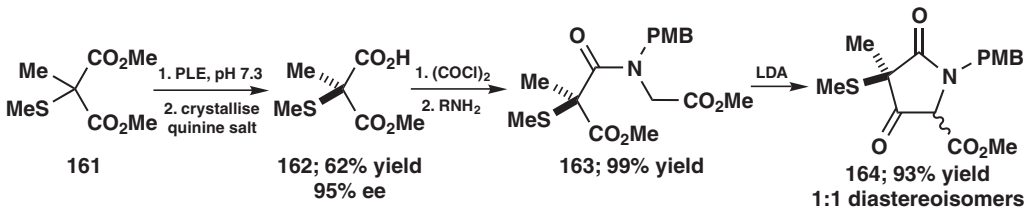


Brown's crotyl borane **158** (chapter 24) provides reagent control through a chair-like six-membered ring in the formation of **159**. Oxidation of the alkene (ozone with oxidative workup) gives the free acid marked in **160** and on removal of the benzylic group the freed amine (circled) cyclises to it to give the pyrrolidone required (**147** as its methyl ester). The synthesis can easily be completed from there.

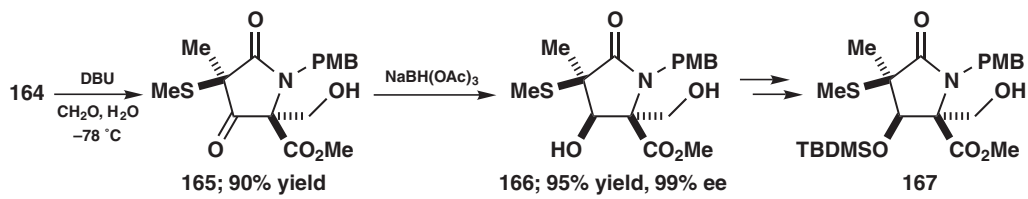


Enzymes as reagents in the synthesis of lactacystin analogues

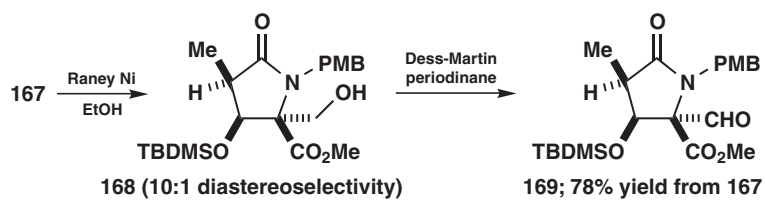
Many developments have come from Corey's laboratories in the lactacystin area since the synthesis described above.[24] One strategy we have not mentioned before is the use of an enzyme, pig liver esterase (chapter 29) in the selective hydrolysis of one of two enantiotopic ester groups in the malonate **161**. An MeS group is used to block enolisation and prevent racemisation of the product **162**. The mono ester **162** is initially formed in 67% ee improved by one crystallisation of the quinine salt to 95% ee. The pyrrolidine ring **164** is made in an unusual way by first forming the amide **163** and then cyclising the diester by carbonyl condensation. The new chiral centre in **164** is not controlled but disappears in the next step.



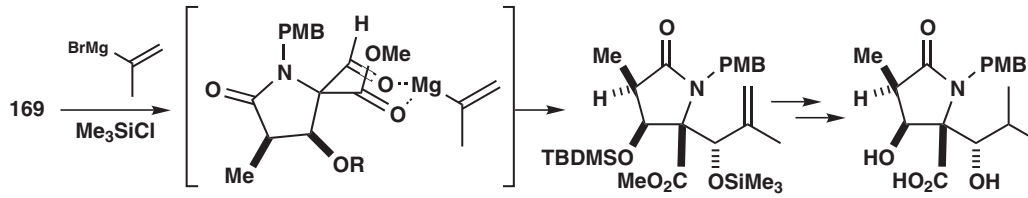
Now a remarkably simple aldol reaction with formaldehyde (compare **156** to **165**) needing only DBU as base gives mostly (9:1) the correct diastereoisomer **165**. Easier to explain is the stereoselective reduction of the ketone with acetoxy borohydride to give **166**: the primary alcohol replaces one of the acetates and directs the H atom to the bottom face of the ketone. Juggling the protecting groups gives **167** ready for the introduction of the remaining chiral centres.



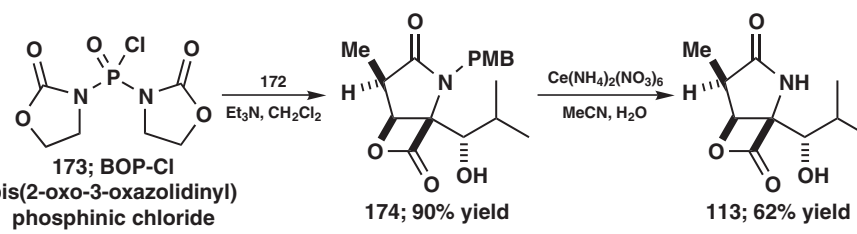
First, the MeS group was removed with Raney nickel giving the correct stereochemistry at the new centre in **168**. The stereochemistry actually comes from the protonation step and presumably arises because EtOH donates an H atom to the less hindered side of the desulfurised enolate opposite the OTBDMS group. Then oxidation with the Dess-Martin periodinane gives the vital aldehyde **169**.



In previous syntheses this last centre has usually been added in an aldol reaction and here too a carbon-carbon bond is made as the centre is introduced. But this time it is the addition of isopropenyl Grignard reagent in the presence of Me_3SiCl that is required to give **171**. The high stereochemical control suggests a chair-like intermediate **170** with both carbonyl groups coordinated to a magnesium atom and the isopropenyl group being transferred to the top face of the CHO group as drawn. Further adjustments lead to the hydroxyacid **172** which was, in this synthesis, transformed into the β-lactone **113** on the way to lactacystin **112**. The isoprop*en*yl Grignard was used as isopropyl Grignard annoyingly reduced the aldehyde rather than adding to it, as in the reaction of **122**.

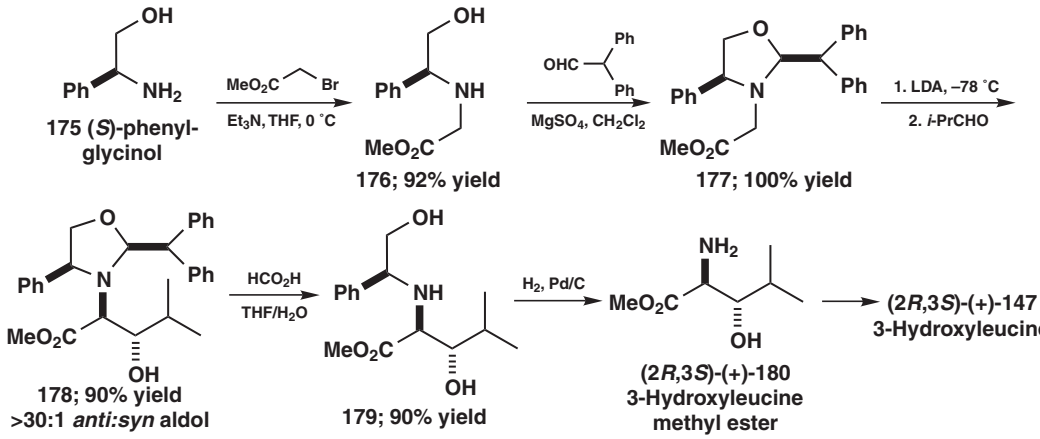


This synthesis includes the formation of the β-lactone using a phosphorus-based coupling reagent 'BOP-Cl' **173** bis(2-oxo-3-oxazolidinyl)phosphinic chloride. Notice the preferential formation of the fused rather than the spirocyclic β-lactone and that cyclisation occurs with retention so the phosphorus reagent **173** must activate the CO_2H group. The *p*-methoxybenzyl (PMB) group is removed by oxidation with Ce(IV) to give **113**. This approach from the enantiomerically pure **165** is ideally suited for the production of analogues and Corey has made many analogues to probe the origin of the biological activity.[24]

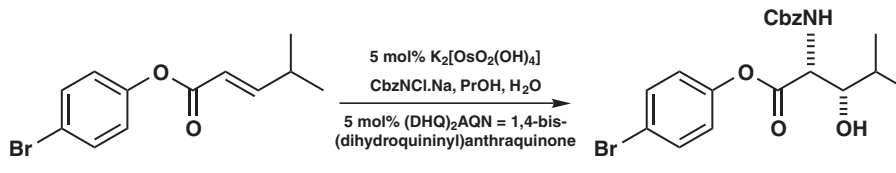


Syntheses of 3-hydroxyleucine by other strategies

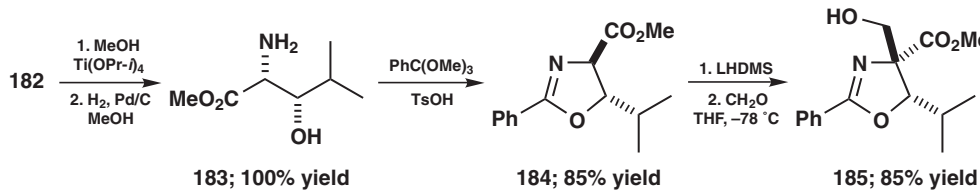
A leading group in lactacystin research is led by Panek at Boston University. They have produced two further approaches to a key intermediate, 3-hydroxyleucine **147**. One uses a chiral auxiliary strategy.[25] Phenylglycinol **175** is available as either enantiomer. It can be alkylated chemoselectively on nitrogen to give the amino ester **176**. Trapping this with Ph_2CHCHO produces the Seebach-style oxazoline **177** with a *cis* relationship between the old and the new (relay) chiral centres in 100% yield. The key step is a stereoselective aldol of the lithium enolate of **177** with *i*-PrCHO. Reaction occurs entirely on the face of the enolate opposite the two large groups (as drawn in **178**) and very much in favour of the *anti*-aldol product **178**. In this aldol reaction, the original chiral centre is not removed and the relay centre reinforces the stereoselectivity while holding the molecule in a fixed conformation. The rest of the synthesis is simply the removal of the various auxiliaries and protecting groups.



The other uses a catalytic process, Sharpless's aminohydroxylation[26] (chapter 25). By skilful choice of the esterifying group, the amino hydroxylation of the unsaturated ester **181** could be controlled to give the required regioisomer **182** in high ee after two recrystallisations from aqueous ethanol (it was initially 87%).

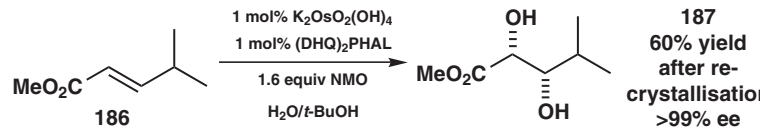


The methyl ester of the 'wrong' diastereoisomer of 3-hydroxyleucine **183** required merely deprotection of **182** and ester exchange best catalysed by Ti(IV). Incorporation into the oxazoline **184** prepares the way for the aldol reaction with formaldehyde that inverts the stereochemistry at the ester centre and leads to their lactacystin synthesis.[27]

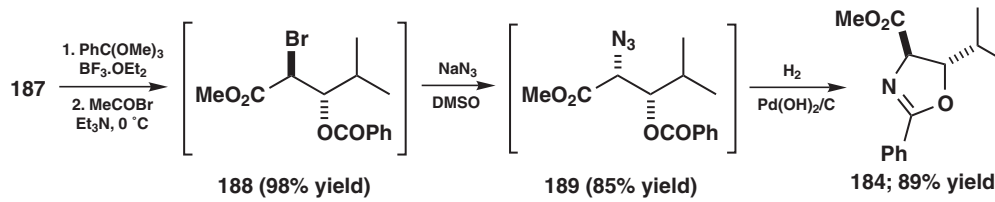


A large-scale synthesis of lactacystin analogues using AD and an asymmetric aldol reaction

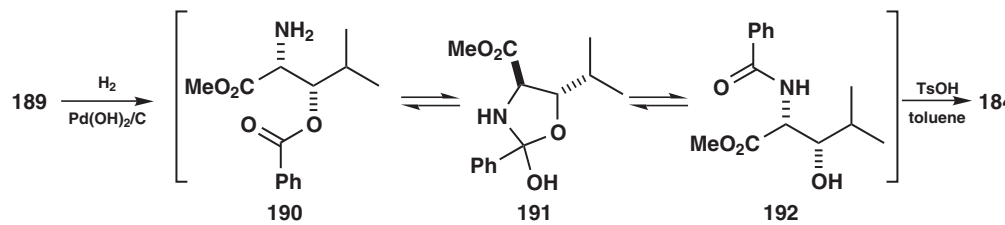
We end with a large scale synthesis by LeukoSite Inc. of Cambridge Mass.[28] designed to be used for analogues of natural lactacystin. They started with the asymmetric dihydroxylation (chapter 25) of the unsaturated ester **186** (cf. compounds **148** and **181**). This gave a 94% yield on a small scale with AD-mix-α but could not easily be adapted to a larger scale because of the excessive quantities of salts in over large volumes of solvent. They preferred a modification from Pharmacia-Upjohn at Uppsala using the organic re-oxidant *N*-methylmorpholine-*N*-oxide (NMO) instead of potassium ferricyanide, no potassium carbonate and a more concentrated solution.[29] This gave **187** in only 60% yield but >99% ee after two recrystallisations. All three Sharpless methods have now been used in lactacystin synthesis.



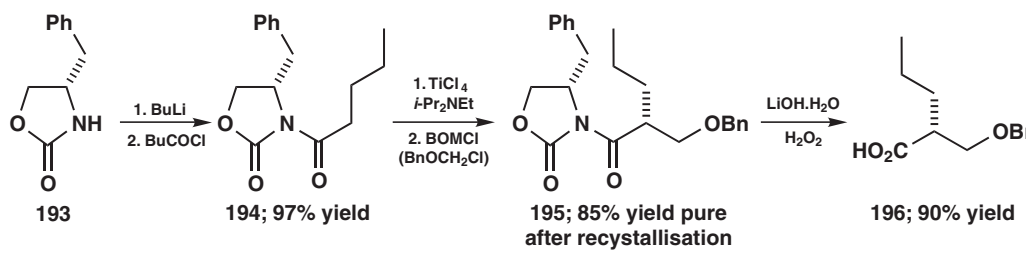
Now one of the two OH groups must be replaced by NH_2 with retention of configuration. This can be achieved by the *ortho*-ester method like that summarised in chapter 23 for propylene oxide. The intermediates **188** and **189** can be isolated but the process works better if **189** is hydrogenated to give the oxazoline **184** in 89% yield over the three steps. Note that the stereochemistry of **189**, and hence **184**, comes from a double inversion at the position α to the ester group.



The formation of **184** from **189** needs some explanation. Hydrogenation converts the azide into an amino group to give **190** and this is in equilibrium with **192** by transfer of the benzoyl group from O to N *via* the tetrahedral intermediate **191**. Dehydration of **191** gives the stable heterocycle **184**.

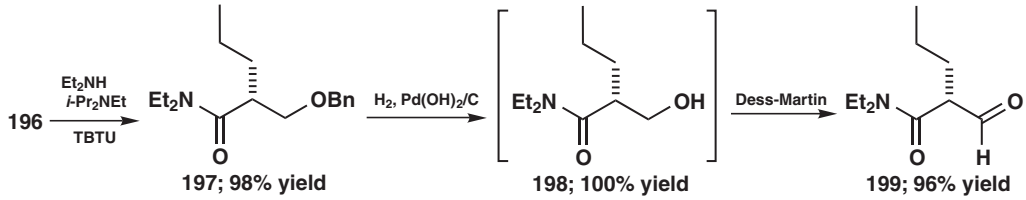


The oxazoline **184** provides an attractive approach to lactacystin as it is a protected form of 3-hydroxyleucine. The other half of the molecule was made in the LeukoSite synthesis by a very different method: the alkylation of an Evans' chiral auxiliary. This was chosen partly because they wished to vary the alkyl group on the pyrrolidone ring and we use the propyl compound as example. The phenylalanine derived oxazolidinone **193** (chapter 27) was acylated and then the titanium enolate of **194** was alkylated to give **195** with very high selectivity and the chiral auxiliary removed to give the simple acid **196**.

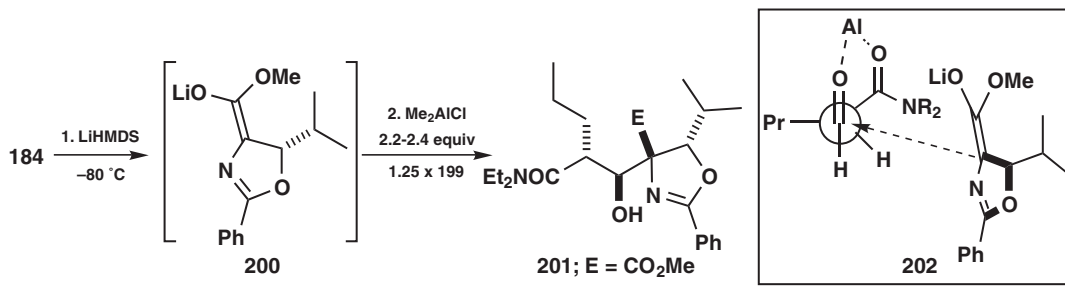


Coupling with Et_2N using TBTU [2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate], removal of the benzyl group and oxidation with the Dess-Martin periodinane

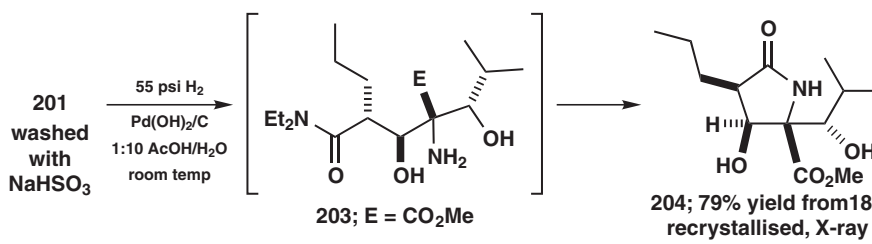
gave the aldehyde **199** in good yield. This sequence from **193** gave optically pure aldehyde **199** in 70% yield without any chromatography.



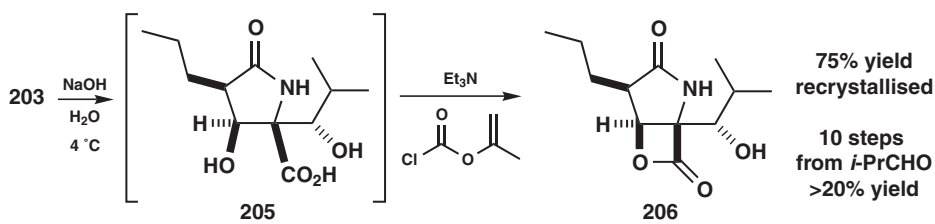
Now the two parts, **184** and **199**, must be linked in a controlled aldol reaction. The lithium enolate **200** reacts with the aldehyde in **199** in the presence of excess Lewis acid Me_2AlCl to give one diastereoisomer of **201** as the only product. Presumably the aluminium coordinates the tertiary amide and aldehyde oxygen atoms to hold the aldehyde in one Felkin conformation while it is attacked by the lithium enolate from one face only as sketched in **202**.



Any attempts to purify **201** by chromatography led to reverse aldol reactions and it was better not to isolate **201** but just to wash it with aqueous bisulfite before removing the oxazoline and allowing the amine **203** to cyclise to form the pyrrolidine **204**. An X-ray structure of **204** confirmed that the stereochemistry was correct.



Hydrolysis of the ester with NaOH and β-lactone formation gave the propyl analogue **206** of **113** in >20% yield from simple starting materials over ten steps.



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Section E:
Functional Group Strategy

32 Functionalisation of Pyridine

This chapter examines functionalisation strategy - the addition of functional groups to a pre-formed carbon skeleton. It revises previous sections in the context of some difficult reactions.

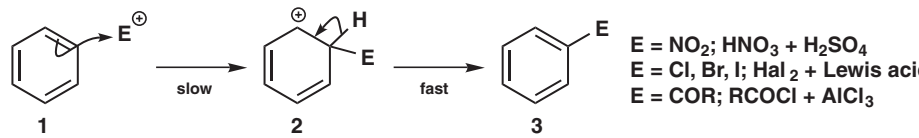
Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

Introduction

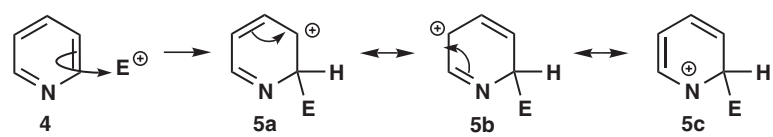
A theme of this section is making reactions work. Usually that means making reactions that already work quite well work much better. But we start with a reaction - electrophilic aromatic substitution on pyridines and related heterocycles - that doesn't really work at all. We shall see why not and how the reaction can be successfully realised. This involves some serious mechanistic thinking and questions of regioselectivity are vital to the solution. This is new chemistry with a great future.

Part I – The Problem

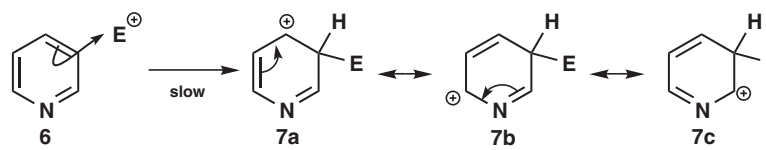
Because it is such a familiar reaction, it can be forgotten that attack by electrophiles on benzene **1** is difficult because it gives an intermediate cation **2** which has lost the aromaticity of the starting material. This is, after all, why Lewis acids are needed for many such reactions. The product **3** has regained aromaticity but this is no help to the rate-determining step, the attack of the electrophile and the formation of **2**. That the reaction occurs at all is because **2** is a delocalised pentadienyl cation and has some intrinsic stability as a cation. Successful electrophilic substitution of benzene by HNO_3/H_2SO_4, fuming H_2SO_4, RCOCl and $AlCl_3$, or halogens with various Lewis acids is also testimony to the extreme reactivity of these combinations of reagents.



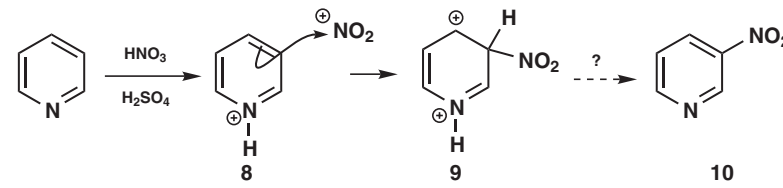
Pyridine has all the disadvantages of benzene plus some special ones of its own. Attack at the 2- or 4-positions **4** gives intermediate cations such as **5** which have part of the positive charge delocalised onto nitrogen **5c**. This would be no bad thing if the nitrogen atom were tetravalent like stable NH_4^+, but it is actually divalent like the unknown, electron-deficient, and presumably very unstable NH_2^+.



Attack at the 3-position **6** is not so bad as the intermediate cation **7** is no longer delocalised onto the electron-deficient nitrogen atom but is not as stable as the benzene intermediate **5** and the slow step is very slow because the HOMO of pyridine is lower in energy than the HOMO of benzene.

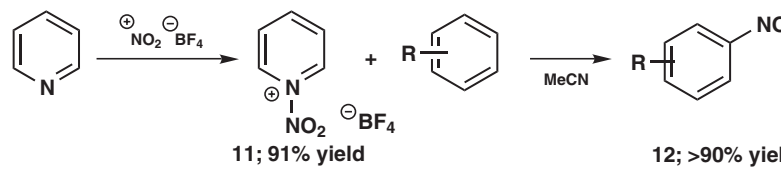


So far electrophilic attack on pyridines sounds only a bit more difficult than that on benzenes but there is worse to come. The reagents for nitration, halogenation and so on all require strong protic or Lewis acid catalysts and these go for the pyridine nitrogen atom first. Attempted nitration would have to occur on the cation **8**, making the intermediate an impossibly unstable dication **9**.

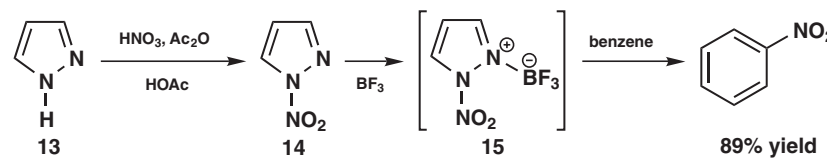


N-Nitro Heterocycles as Nitrating Agents

In fact, nitration of pyridine in the absence of protic or Lewis acid catalysts occurs at nitrogen.[1] The reagent has to be the rather unstable and moisture sensitive salt NO_2^+ BF_4^-. This is commercially available, though expensive. The product is also not very stable but can be isolated as the tetrafluoroborate salt **11** as BF_4^- is non nucleophilic. This compound **11** is itself a nitrating agent and can be used to nitrate benzenes (but obviously not pyridine) simply by mixing in acetonitrile. The products **12** have the usual substitution pattern for electrophilic substitution. Olah has called this process 'transfer nitration'.

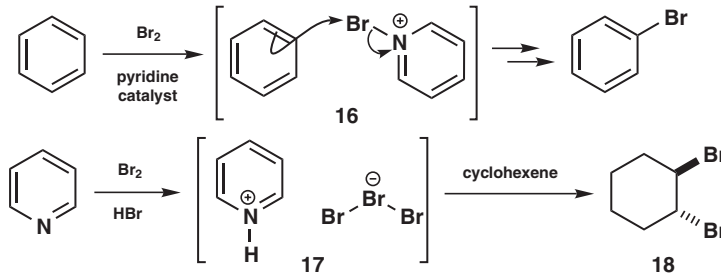


A better method for the same reaction (nitration of benzenes) is to use the product of nitration of pyrazole[2] **13**. When the nitration is carried out in the absence of strong acid, the product is the *N*-nitro compound **14**, a stable neutral molecule because a proton can be lost from the other nitrogen atom. This compound is stable but reacts with the Lewis acid BF_3 to give an intermediate **15** that nitrates benzene efficiently. It is probable that the *C*-nitration of pyrazoles also takes place via such an intermediate as **15**, see below.

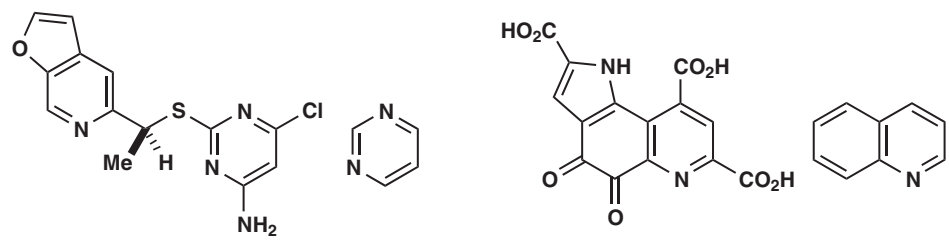


Pyridine can also be used as an efficient catalyst for the bromination of benzene (see *Vogel*, page 860) through reaction at the nitrogen atom **16** while the crystalline reagent pyridinium

bromide perbromide **17** is a convenient way of brominating alkenes. These are convincing illustrations that pyridine does not react with bromine at carbon.

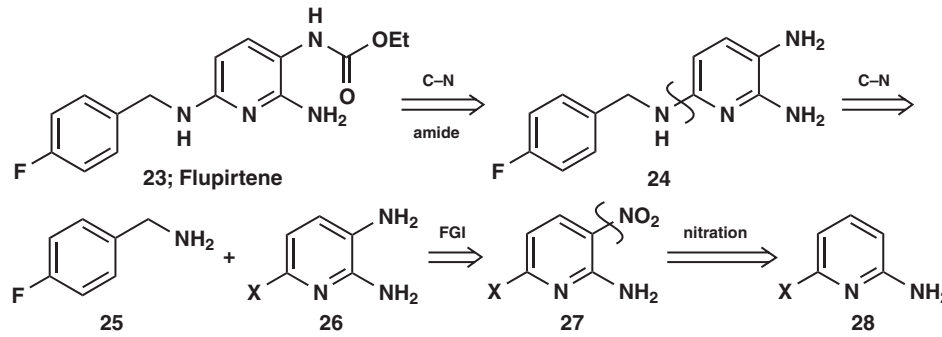


Direct electrophilic substitution of pyridines is not, in general, a useful reaction. Only 3-substitution is remotely possible as the intermediate **7** at least does not attempt to put the positive charges on the same atoms! The maximum yield of 3-nitro-pyridine by direct nitration is 5%, normally 3% is expected. If we want to carry out nitration on the pyridine ring, some means must be found better than normal electrophilic substitution. We shall now explore various ways in which this simple reaction can be achieved either by subterfuge or mechanistic ingenuity. The same remarks apply to other electron-deficient six-membered aromatic heterocycles such as pyrimidine **20** and quinoline **22**. Solutions to these problems are needed as many drugs and natural products contain these rings. The Pharmacia-Upjohn anti-AIDS drug PNU-142721 **19** contains pyridine and pyrimidine rings while the coenzyme methoxatin **21**, that allows bacteria to live off methane as their sole carbon source, contains an oxidised quinoline ring. All three rings are heavily substituted and preparation of these compounds needs regiochemically controlled substitution around the rings.

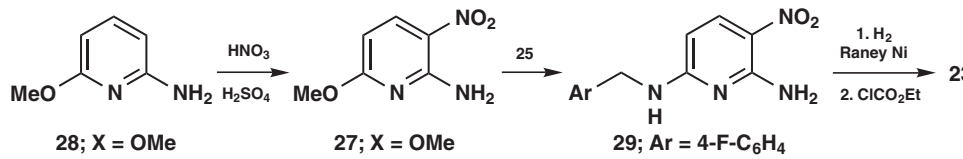


Part II – Traditional Solutions: Addition of Electron-Donating Substituents

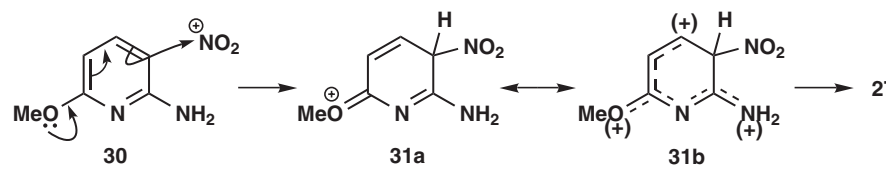
The analgesic Flupirtine **23** is a simple pyridine with three substituents at the 2, 3, and 6 positions. Removal of the amide shows the core **24**. The 4-fluorobenzylamine **25** could be added by nucleophilic substitution (easier in pyridines than in benzenes) and we shall delay the choice of the leaving group (X in **26**) for the moment. The only amino group we could conceivably add by nitration is the one in the 3-position so we might continue by FGI (reduction) and C−N disconnection **27**.



The nitro group will help the nucleophilic aromatic substitution so now we must choose the leaving group X in **27**. It need not be a good leaving group - the slow step in nucleophilic aromatic substitution is the addition of the nucleophile -so as long as X is a tolerable leaving group, it will do. It should promote electrophilic attack by NO_2^+ in the 3-position and **28;** X = OMe should be available commercially. Putting X = OMe fulfils all these conditions. Here is the synthesis.[3]

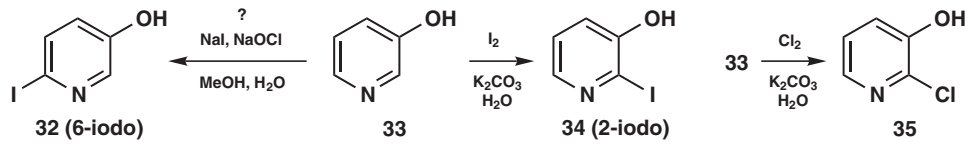


Nitration of **28**; X = OMe is successful because both electron-donating OMe and NH_2 groups activate the 3-position and the intermediate cation **31** is delocalised over both N and O atoms. We could have used lone pairs on either the OMe or NH_2 groups to draw the mechanism **30**. The reaction occurs in spite of the pyridine ring rather than because of it. The position of attack - C3 or C5 - is not easily predicted and searching the literature or trial and error is needed.

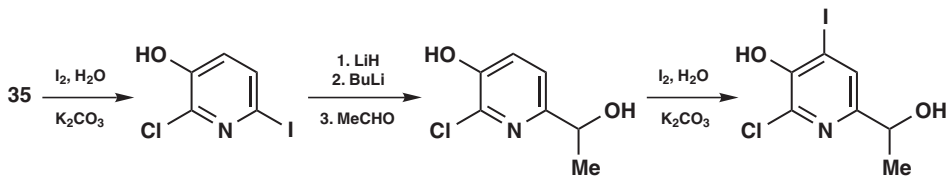


Regioselectivity in Electrophilic Substitution with Electron-Donating Groups

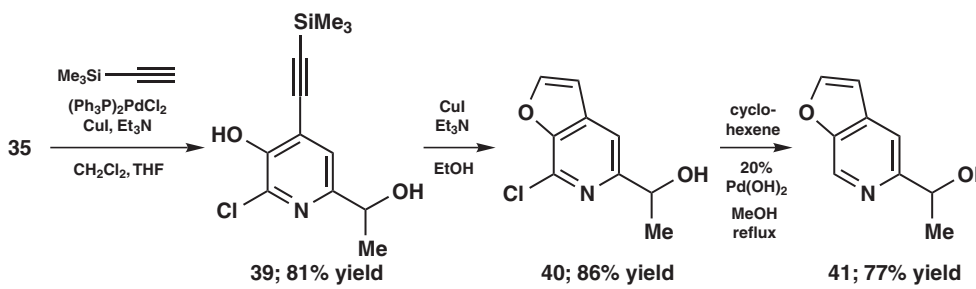
You might think that nowadays there would be no doubt about the results of such reactions as the nitration of **28** since NMR would quickly distinguish the possible products. This is not so as a notorious case shows. Though it was known that reaction of **33** with iodine in aqueous sodium carbonate gave the 2-iodo compound **34** in good yield, it was claimed in 1990 that a more complex reagent gave the 6-iodo isomer **32.** Reinvestigation showed that **34** was the only product though the alternative **32** could be formed in moderate yield at higher temperature. It was also known that chlorination gives the 2-chloro compound **35**. The preference for the site next to nitrogen (and therefore *para* to the OH group) may be due to steric crowding of the solvated oxyanion in water.[4]



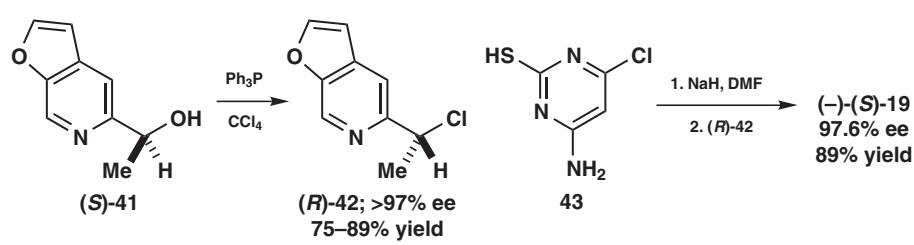
The synthesis of the drug PNU-142721 **19** required a series of electrophilic substitutions on 3-hydroxy pyridine[5] **33**. Iodination of the chloride **35** went in the previously inaccessible 6-position to give **36**. Now iodine-lithium exchange and reaction with acetaldehyde gave the secondary alcohol **37** and finally iodination gave the tetrasubstituted pyridine **38**. Each new substituent is added as an electrophile in a specific position. Only the acetaldehyde had no choice.



Installation of the furan ring requires two extra carbons provided by a Sonagashira coupling with trimethylsilyl acetylene to give **39**. Cu(I)-catalysed closure of the furan ring follows and now the role of the chlorine atom on the pyridine ring is revealed. It is there to block the most reactive position and, its job complete, it can now be removed by hydrogenation.

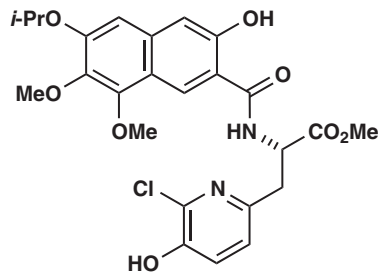


Completion of the synthesis of PNU-142721 **19** requires introduction of asymmetry and coupling with a pyrimidine thiol. Asymmetry was introduced in two ways. The alcohol **41** was enantioselectively acylated with trifluoroethyl butyrate catalysed by porcine pancreatic lipase (chapter 29) or else a Swern oxidation gave the ketone that could be enantioselectively reduced with (−)-Dip chloride (chapter 24). Clean inversion from (*S*)-**41** to the chloride (*R*)-**42** was achieved only with the Mitsunobu-like reagent Ph_3P/CCl_4. Finally, coupling with the thiolate anion of the pyrimidine **43** gave a second clean inversion.[5] One recrystallisation improved the ee of the drug **19** from 97.6% to over 99%.

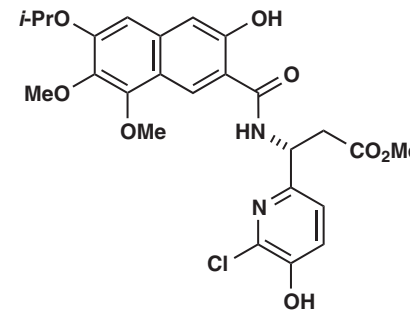


The Anti-Tumour Antibiotic Kedarcidin

Another incorrect structure was revealed by synthetic work aimed at structure **44**, alleged to be a part structure (the 'chromophore') of the antitumour antibiotic kedarcidin. The synthesis was successful but revealed that the structure was wrong as the compound is a β-amino acid and not an α-amino acid as had been assumed.[6]

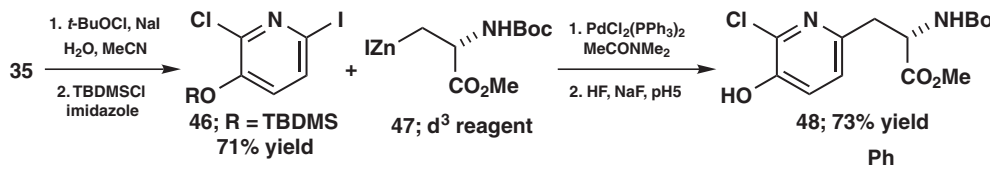


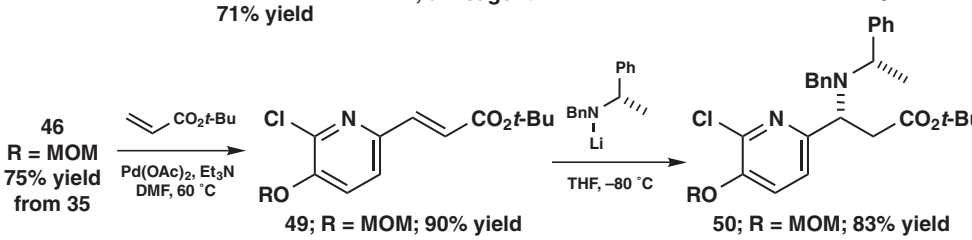
44; alleged kedarcidin chromophore (1993)



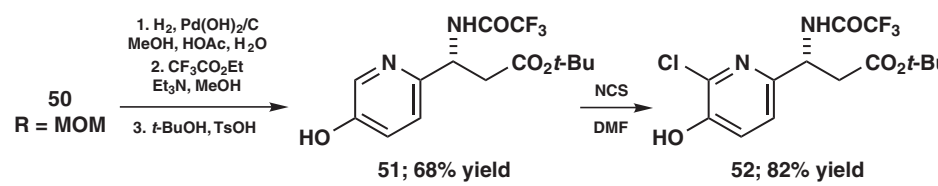
45; kedarcidin chromophore (1997)

The obvious compounds to make are the pyridine amines for coupling to the undisputed naphthalene fragment. Both were made from the same pyridine **35** that featured in the last section. Iodination and protection gave two iodo-pyridines **46**; R=TBDMS and MOM. The first was combined with Jackson's d^3 reagent **47** (chapter 13) in a Negishi coupling to give **48** and the second in a Heck reaction to give the unsaturated ester **49** to which Davies's chiral lithium amide (chapter 24) could be added to give a 97:3 ratio of **50** and its diastereoisomer.





Deprotection of **48** gave the amine needed for the synthesis of **44**: this proved not to be the natural product. The synthesis of the correct structure[6] **45** had a curious twist: removal of the benzyl groups from **50** resulted in dechlorination **51** and the chlorine was reinstated **52** with another electrophilic substitution having the same regioselectivity as that of **35**.

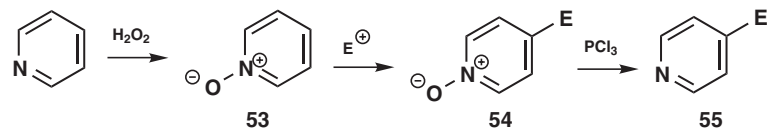


Halogenation and Metallation

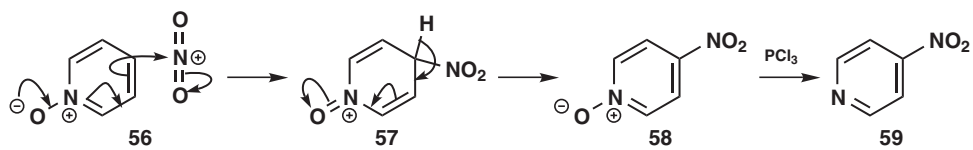
To summarise these last two examples: with even one electron-donating group on the pyridine ring, halogenation becomes a useful reaction. Metallation with lithium or palladium-catalysed couplings with alkenes (Heck), organo-zinc compounds, including those with β-hydrogens (Negishi), or boronic acids (Suzuki) make new C−C bonds while Buchwald-Hartwig chemistry makes new bonds to O or N atoms. These are obviously very versatile sequences.

Pyridine *N*-Oxides in Electrophilic Substitution

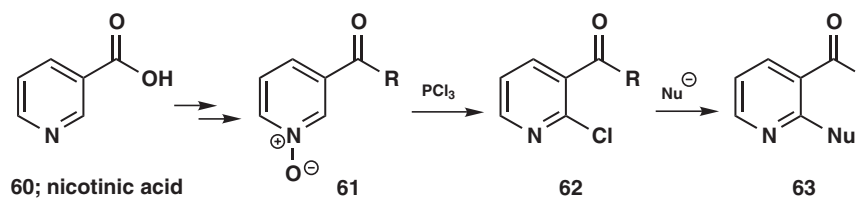
This is all very well if your target molecule happens to have electron-donating substituents on the pyridine ring, but what if it hasn't? The traditional solution is to use a pyridine *N*-oxide **53** which simultaneously blocks the lone pair on nitrogen and provides a strongly electron-donating substituent. Pyridines are easily oxidised to *N*-oxides with H_2O_2 (another instance of electrophilic attack at N) and the substituted *N*-oxides **54** are easily reduced back to the pyridines **55** with trivalent phosphorus compounds such as PCl_3.



Nitration can be carried out with the usual reagents and occurs in the 4-position (the 2- and 6-positions being sterically hindered by the solvated oxido group). The electrons from oxygen are used in the reaction **56** and the nitrogen atom retains its positive charge throughout but the intermediate **57** is only a *mono*-cation unlike **9**. This is a good synthesis of 4-nitropyridine **59**.

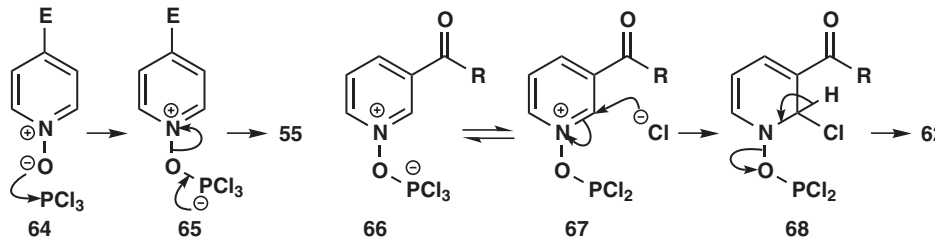


The deoxygenation of the product can be developed in synthetically useful ways. If there is an electron-withdrawing group at the 3-position and PCl_3 is used, deoxygenation is accompanied by chlorination at the 2-position **62**. This new chlorine is activated towards nucleophilic aromatic substitution both by its position on the pyridine ring and by the electron-withdrawing group at the 3-position and can be replaced by O, N, S, or P nucleophiles **63**. Pyridines such as **61** are easily made from available nicotinic acid, pyridine-3-carboxylic acid **60**.

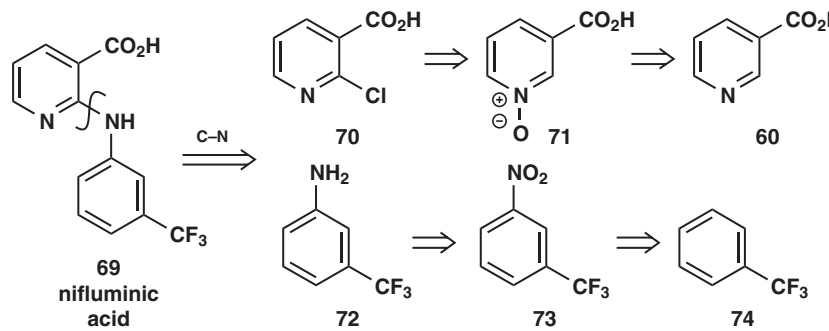


This result suggests that the initial interaction of the *N*-oxide with PCl_3 is nucleophilic attack by O^- **64**. The intermediate can then either lose $POCl_3$ **65** or add chloride. When nucleophilic attack

by chloride **67** occurs, it is the most electrophilic atom which is attacked - the one between the pyridine nitrogen and the electron-withdrawing group. Aromaticity is restored by the loss of a proton from the 2-position **68**. This is a sort of nucleophilic substitution occurring after electrophilic substitution. The leaving group (Cl_2PO^-) is not at the site of nucleophilic attack.

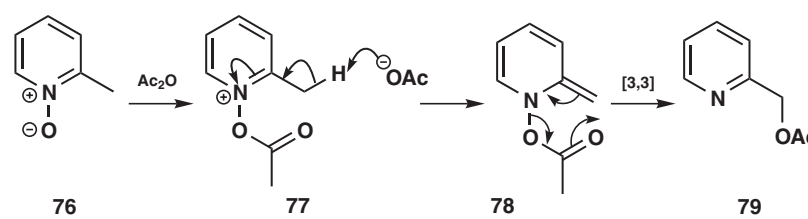


Good use is made of this chemistry in the synthesis of niflumic acid **69**, an analgesic with a pyridine ring. Disconnection of the C−N bond suggests a 2-chloropyridine **70** starting material easily derived from nicotinic acid **60** and a simple aromatic amine **72** available by functionalisation of trifluorobenzene **74**. **69** Is actually available as niflumic acid from Aldrich.

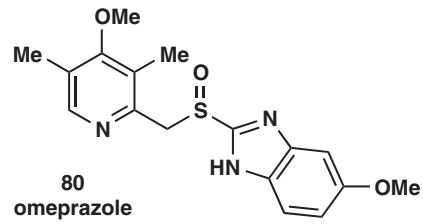


The only mild surprise in the synthesis is that the PCl_3 reaction turns the acid into an acid chloride **75** which must be hydrolysed before the amine is added, otherwise an amide would be formed.[7]

These *N*-oxides can also be used to functionalise side chains in pyridines **76**. The reaction is rather similar to the PCl_3 reaction in that acetic anhydride attacks the oxygen atom of the *N*-oxide and the released acetate ion can deprotonate **77** at an alkyl group in the 2-position. The resulting enamine **78** can sacrifice the weak N−O bond between the now neutral heteroatoms and form a much stronger C−O bond by a [3,3] sigmatropic rearrangement to give **79**.



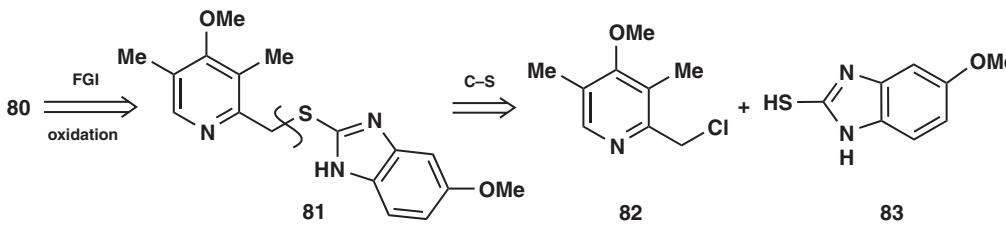
This chemistry, preceded by an electrophilic substitution on the *N*-oxide, finds a most important application in the synthesis of omeprazole, Astra(Zeneca)'s anti-ulcer drug and one of the best selling medicines of recent years. Omeprazole **80** is a sulfoxide and has a 2,3,4,5-tetrasubstituted pyridine linked through the sulfur atom to a benzimidazole.[8]



80
omeprazole

The sulfoxide **80** can be made from the sulfide **81** and an obvious C−S disconnection suggests two much simpler heterocyclic starting materials, a pyridine **82** and a benzimidazole **83**. It is the pyridine **82** which concerns us now.

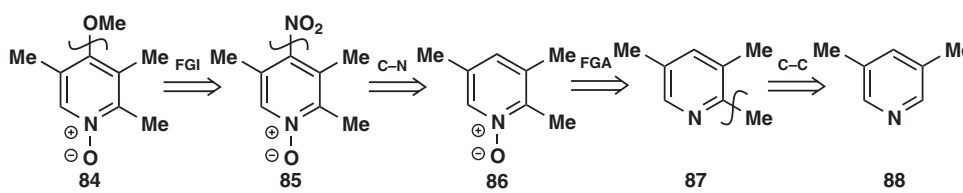
Omeprazole: Analysis 1



81 **82** **83**

Using the chemistry we have just described, the CH_2Cl group in the 2-position could be introduced by functionalisation of the trimethyl pyridine *N*-oxide **86** since only the methyl group in the 2-position should be affected. The group in the 4-position might be introduced by electrophilic attack on the *N*-oxide but there is no good reagent for "MeO^+" as we shall see in the next chapter. Nitration of the *N*-oxide **86** works well, however, and nucleophilic substitution is so good on pyridine *N*-oxides that this is a reasonable strategy.

Omeprazole: Analysis 2

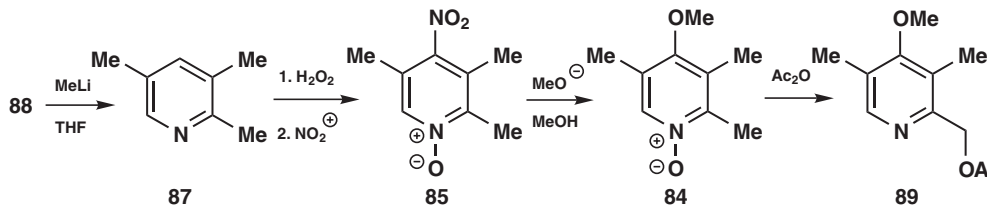


84 **85** **86** **87** **88**

3,5-Dimethylpyridine **88** is available and the methyl group in the 2-position can be added by the remarkable reaction in which MeLi appears to displace a hydride ion. It is not obvious that the nitration of **86** will occur in the 4- rather than the 6-position but O^- is a bigger substituent than it appears to be because of solvation. The published synthesis gives only "NO_2^+" as the reagent and does not say how it was formed.

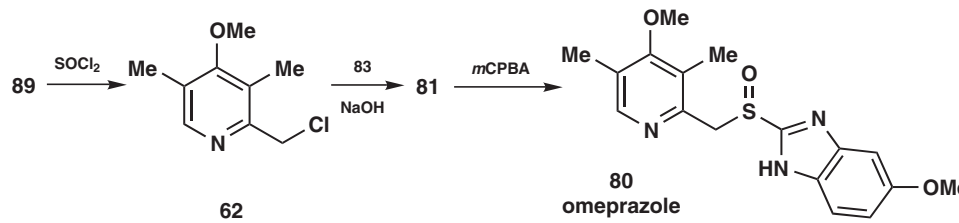
Omeprazole: Synthesis 1

The difficult nucleophilic displacement of the NO_2 group by methoxide must be carried out while the *N*-oxide is still present. The leaving group in this reaction is nitrite ion, NO_2^-, which is reasonably stable but you will recall that merely tolerable leaving groups are acceptable in a reaction in which the addition step is rate-determining providing that they accelerate that step. The nitro group certainly does that. The *N*-oxide has now completed its duties and functionalisation of the side chain (2-Me) by the acetic anhydride reaction follows to give **89**.



Acetate is not a good enough leaving group for an S_N2 displacement (note the difference between S_N2 and aromatic nucleophilic substitution) so it must be transformed into the chloride **82** before reaction with the thiolate anion of **58**.

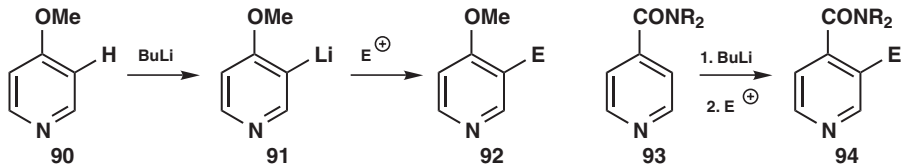
Omeprazole: Synthesis 2



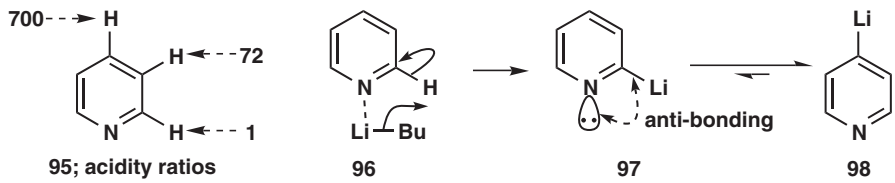
The final oxidation of achiral sulfide **62** to sulfoxide **80** with achiral *m*CPBA must of course produce racemic omeprazole. Omeprazole is actually a pro-drug - it is transformed enzymatically into the active compound - and in this process the chirality at sulfur is lost. The two enantiomers have nearly the same biological effects though the more readily absorbed (*S*)-omeprazole is now marketed as esomeprazole.

Ortho-Lithiation of Pyridines

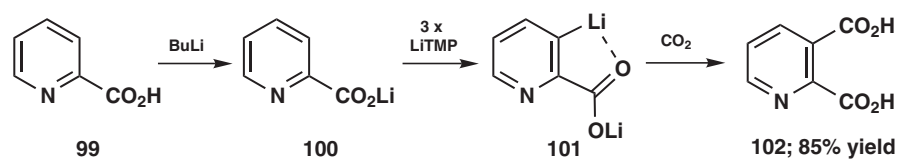
Halogenation and replacement of halogen (Br or I) by a metal is a useful way to extend the scope of electrophilic substitution on pyridines already having an electron-donating substituent (usually based on O or N). Another valuable way is *ortho*-lithiation (chapter 7), that is replacement of a hydrogen atom by lithium *ortho* to a similar substituent. The requirements are not quite the same. The substituent must be an *ortho*-director: it must acidify the *ortho* proton and/or direct the base (usually BuLi) to the *ortho* position. The simplest *ortho* directors are F and OMe but the best are oxazolines, amides, and carbamates. There are more details of these processes on benzene rings in chapter 7. If one of these groups is in the 4-position **90** or **93** lithiation **91** is unambiguous and any electrophile (E^+) that reacts with an aryl lithium reacts in the 3-position **92** and **94**.



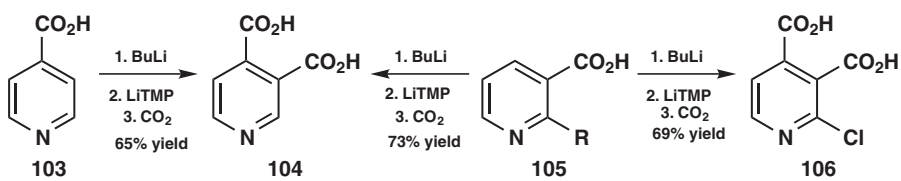
The relative acidities of the positions around the pyridine ring[9] without any assistance from an *ortho*-director are 700:72:1 for positions 4:3:2. It may seem odd that the position next to nitrogen is least acidic but the sp^2 lone pair on nitrogen has an antibonding interaction with the C-Li bond **97**. Though BuLi may be directed by the nitrogen **96** to C-2 the unstable product **97** soon equilibrates to the more stable C-4 Li derivative **98**.



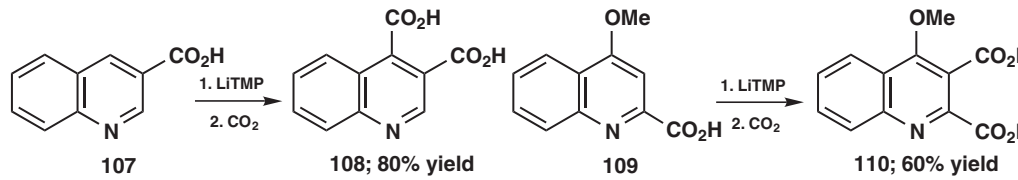
Regiospecificity demands *ortho*-direction. A surprisingly effective group is a carboxylic acid CO_2H that acts as its lithium derivative CO_2Li. One equivalent of BuLi is used to make this **100** from, say picolinic acid **99**, and three equivalents of LiTMP to make the C-Li derivative **101**. Reaction with electrophiles such as CO_2 or carbonyl compounds occurs at C-3 **102**.



Iso-nicotinic acid **103** must also react at C-3 but nicotinic acid **105**, R = H shows the regioselectivity expected from the relative acidity of C-1 and C-4 and gives substitution at C-4 whether C-1 is substituted **105**, R = Cl, or unsubstituted **105**, R = H. The same result is found for amides or oxazolines as *ortho*-directors.[10]

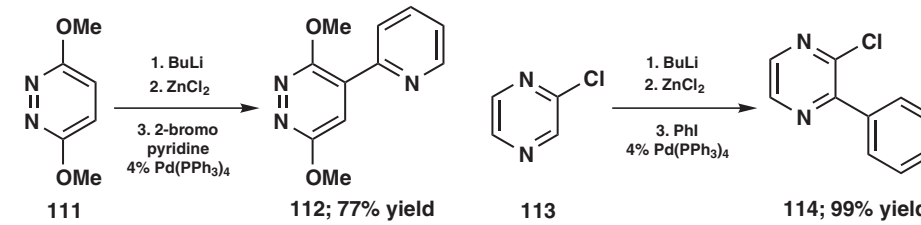


This behaviour also occurs with quinolines, e.g. **107** and **109**. BuLi cannot be used as it attacks quinolines as a nucleophile. This problem is also found with other heterocycles, particularly those with more than one heteroatom.[11]

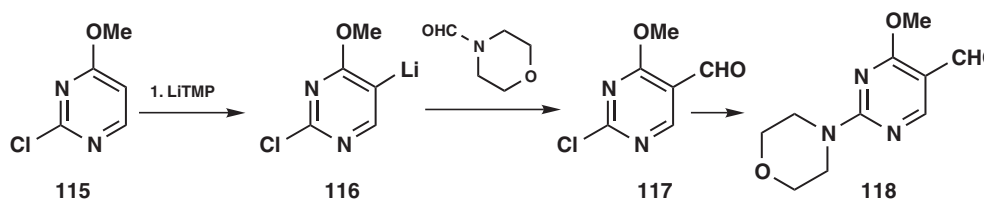


Diazines

The three diazines, pyridazine, pyrimidine and pyrazine, are metallated well providing there is good *ortho*-direction to prevent nucleophilic addition. The pyridazine (OMe as *ortho*-director) **111** and pyrazine **113** derivatives can be metallated[12] and their zinc derivatives coupled with aromatic rings (Negishi coupling) to give **112** and **114**. It is unusual to see Cl in **113** acting as such an efficient *ortho*-director.

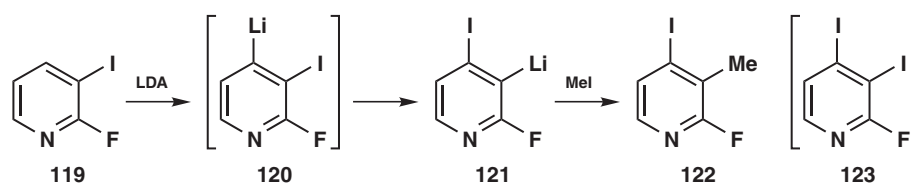


N-Formyl amines such as DMF make good electrophilic CHO donors and in reaction with the pyrimidine provide a tandem double coupling of electrophilic formylation followed by nucleophilic substitution by the released amine anion.[13] The OMe group is the *ortho*-director.

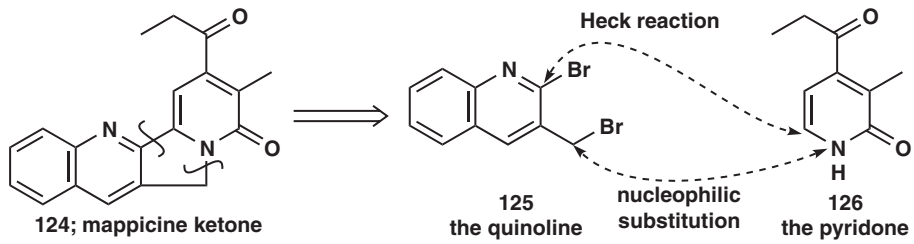


The Halogen Dance

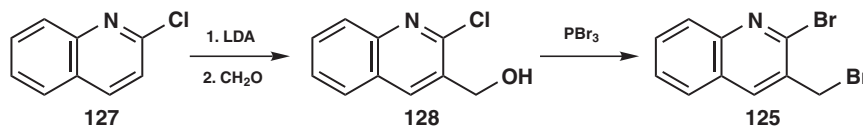
The iodo-fluoro-pyridine **119** is lithiated by LDA to give the only possible lithium derivative **120**. But iodine is a poor *ortho*-director and the compound equilibrates by the 'halogen dance' to put the Li atom next to one of the best *ortho*-directors: fluorine.[14] Presumably one molecule of **120** removes I from **119** to give **123** from which the 3-I atom is removed by another molecule of **120** initiating a chain.



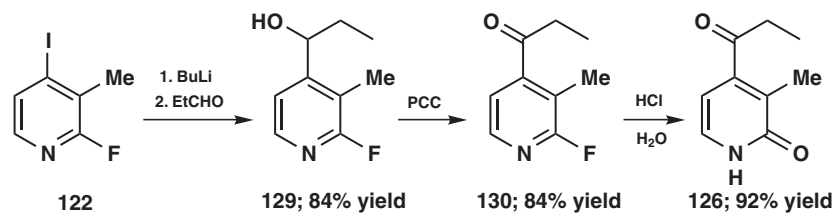
This product was used by Comins in his synthesis of mappicine. The antiviral alkaloid is the alcohol formed by borohydride reduction of mappicine ketone **124**. Strategic disconnections **124** split the molecule into a quinoline **125** and a pyridone **126** and correspond to a simple S_N2 and a Heck reaction. If the Heck reaction is performed last it will be intramolecular and hence regioselective.



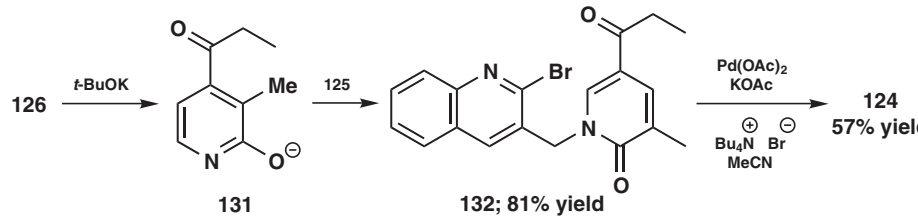
Each component is made by lithiation of a heterocycle. Chlorine-directed lithiation of the commercially available quinoline **127** goes at C-3 and reaction with formaldehyde gives the primary alcohol[15] **128**. Reaction with PBr_3 replaces both OH and Cl with Br to give **125**.



The pyridine **122** reacts with BuLi by I/Li exchange: capture of the lithium derivative with propanal and oxidation gives the ketone **130** in the heterocyclic equivalent of a Friedel-Crafts acylation. The fluorine atom that was originally present to initiate the halogen dance from **120** to **121** can now be hydrolysed to give the pyridone **126**.

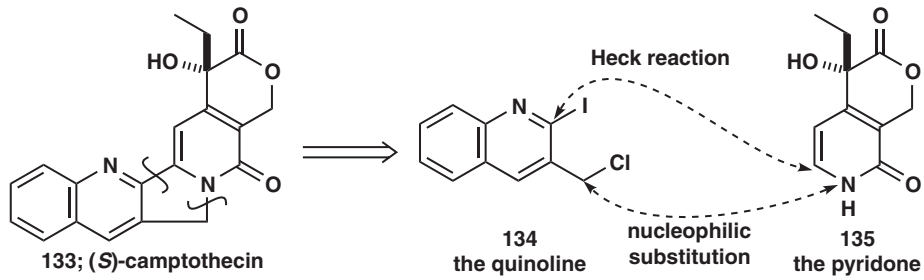


The quinoline **125** and the pyridone **126** are coupled by a base-catalysed S_N2 reaction. Formation of the anion of the pyridone ensures attack at nitrogen (chapter 35). It only remains to close the ring by a Heck reaction.[16]

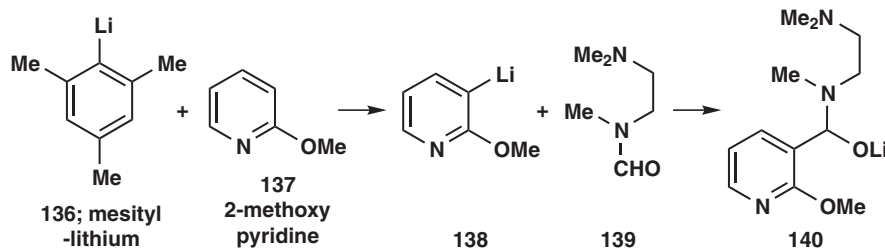


Tandem Double Lithiation: *The asymmetric synthesis of camptothecin*

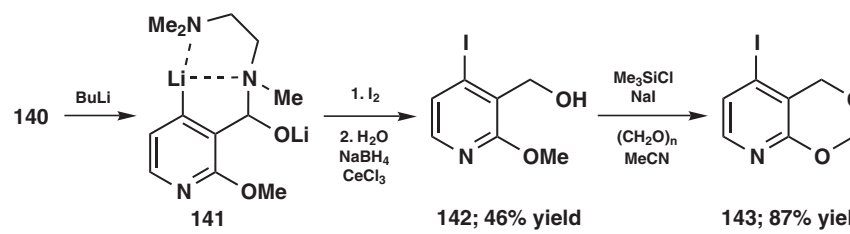
The closely related camptothecin **133** is more complicated because it is chiral. Close analogues (topotecan and irinotecan) are in use as anti-cancer drugs. As these compounds differ only by substitution on the quinoline, synthesis of the enantiomerically pure pyridone **135** is obviously of prime importance.



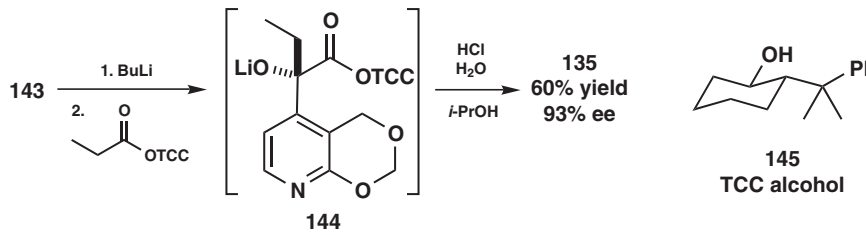
Comins' synthesis of **135** uses an ingenious double lithiation strategy. Treatment of 2-methoxy-pyridine **137** with the very hindered lithiating agent mesityl-lithium **136** gives clean *ortho*-lithiation **138**. Addition of Me_2NCHO would give the 3-aldehyde but Comins uses the *N*-formyl diamine **139** to give, before work-up, the lithium alkoxide **140** with the diamine still attached.



A molecule of BuLi is now guided to C-4 of **140** by the chelating diamine to give **141**. Reaction with iodine, reduction, demethylation and acetal formation give **143** in reasonable overall yield after a short sequence from **137**.

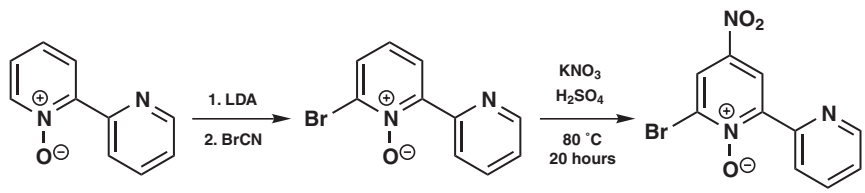


Now the asymmetric addition of the TCC **145** ester of 2-keto butyric acid (substrate strategy, see chapter 27) to the lithium derivative of **143**, prepared by I/Li exchange, gave the alkoxide **144** and hence, on work up in acidic solution, the pyridone[17] **135**. Coupling to the quinoline **134** was achieved by the same S_N2-Heck sequence used in the synthesis of **124**.

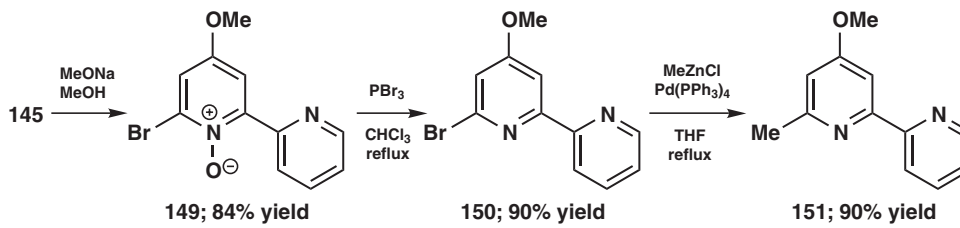


Tandem Lithiation of Pyridine *N*-Oxides and Nucleophilic Substitution

We have seen how pyridine *N*-oxides can be used to promote electrophilic oxidation at C-2,4, and 6. They also promote *ortho*-lithiation and nucleophilic substitution making them very versatile intermediates. This is well illustrated in Quéguiner's synthesis of the antibiotic caerulomycins. 2,2'-Bipyridyl, available as a ligand for many metals, is easily oxidised to its monoxide **146**. The synthesis starts with two electrophilic substitutions. Lithiation occurs *ortho* to the *N*-oxide: quenching with BrCN gives a good yield of the bromide **147** and a conventional electrophilic nitration occurs *para* to the *N*-oxide.



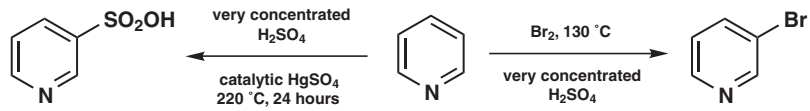
Next a nucleophilic substitution: the displacement of the poorish leaving group nitrite by methoxide to give **149**. The *N*-oxide had done its work so it is removed with PBr_3 and a Negishi coupling with MeZnCl completes the skeleton of the caerulomycins[18] **151**. Oxidation of the methyl group to an aldehyde with SeO_2 or phenyl seleninic anhydride gives caerulomycin E: its oxime is caerulomycin A.



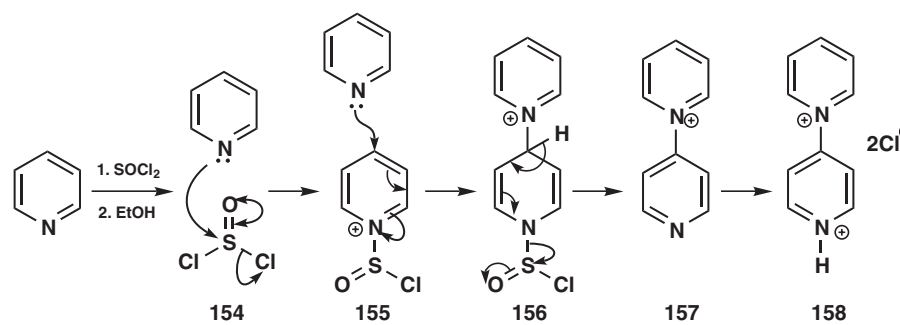
A limited use of direct electrophilic substitution combined with halogen/lithium exchange or *ortho*-lithiation allows us to make a variety of pyridines and quinolines. When the *N*-oxides are used as well, the scope is even wider. Nucleophilic substitution extends this still further. In the next chapter (33) we shall see that electrophilic oxygen can also be added to pyridines. What is missing is the direct formation of 3-substituted pyridines: this is dealt with in the next section.

Part III – Surprisingly Successful Direct Electrophilic Substitutions

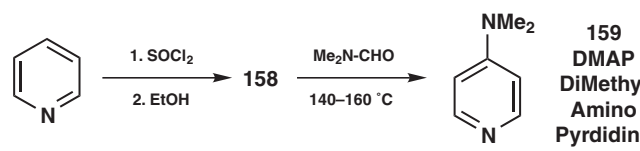
When, as in the omeprazole and caerulomycin syntheses, an *N*-oxide has a number of functions, it is worth building in this extra functionality. Only 4-substituted pyridines can be made from the *N*-oxide: the 3-isomers must be made available by direct electrophilic substitution on pyridines themselves and fortunately some direct methods do work, though it is not immediately clear why they do! Direct sulfonation[19] and bromination[20] both work well in very strong sulfuric acid, giving the 3-sulfonic acid **152** and 3-bromopyridine **153** in good yield.



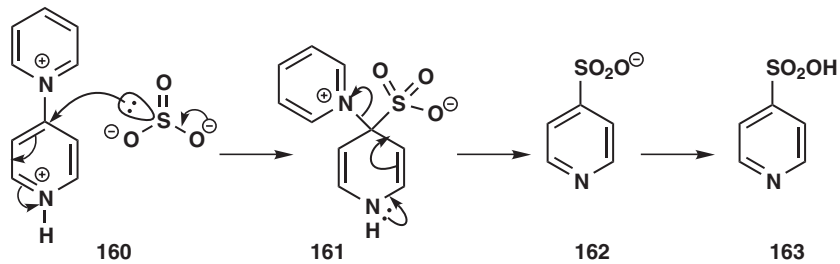
It seems strange that reactions are successful under very strongly acidic conditions when the pyridine will be completely protonated: one clue to this mystery is that "very strong sulfuric acid" is made by adding SO_3 to concentrated sulfuric acid. Another is the mechanism of an important reaction of pyridine with $SOCl_2$ which gives a double pyridinium salt[21] **158**. Initial electrophilic attack at nitrogen **154** is followed by nucleophilic attack by a second pyridine at the 4-position **155**. Loss of a proton **158** then re-aromatises the first pyridine and the remains of the $SOCl_2$ must disappear as SO(?) and chloride ions.



The final product **158** is useful because the pyridinium group can be displaced by nucleophiles. An important example is the reaction with DMF which gives[22] the acylation catalyst DMAP (pronounced 'D-map', 4-DiMethylAminoPyridine) **159**, and, presumably CO and HCl.



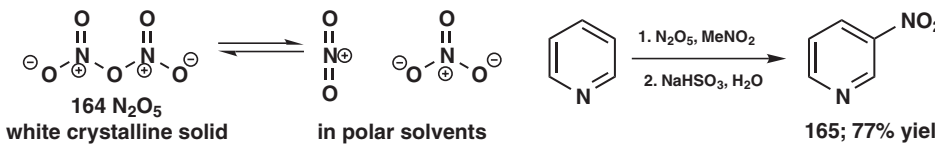
If the double salt **158** is heated with sodium sulfite (Na_2SO_3) in water, aromatic nucleophilic substitution **160** leads to the sodium salt of pyridine-4-sulfonic acid **162** or to the sulfonic acid itself **163** after acidification. These are nucleophilic substitutions following electrophilic attack at nitrogen.



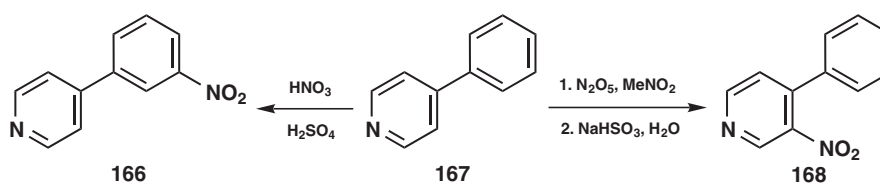
The products of many of the reactions in this section, e.g. **152**, **153**, and **163**, look as though they have been made by straightforward electrophilic substitution on the pyridine ring. But they haven't. In the next section we explore electrophilic substitutions that really work.

Part IV – Successful Nitration of Pyridine

We now come to the successful nitration of pyridines in the 3-position by an indirect procedure.[23] The reagent is N_2O_5, dinitrogen pentoxide, a kind of "nitric acid anhydride", a white crystalline molecular solid **164** that ionises in polar solvents such as nitromethane to NO_2^+ and NO_3^-. Treatment of pyridine with N_2O_5 in nitromethane followed by aqueous work-up with any of a variety of sulfites (SO_2, Na_2SO_3 or $NaHSO_3$) gives high yields of 3-nitro-pyridine **165**. The contrast with previous methods could hardly be greater. The maximum yield from direct nitration is 5% - here we get 77% of 3-nitro pyridine **165**.

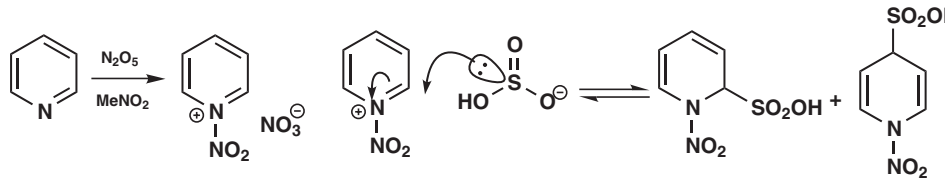


Reaction at pyridine is actually preferred to reaction at benzene - easily illustrated by the fate of 4-phenyl pyridine **167** under the two sets of conditions. Traditional nitration occurs only on the benzene ring **166** with the (presumably protonated) pyridine ring acting as a *meta*-directing deactivating substituent. With N_2O_5, nitration of the (presumably unprotonated) pyridine ring is preferred and occurs in the 3-position **168**.



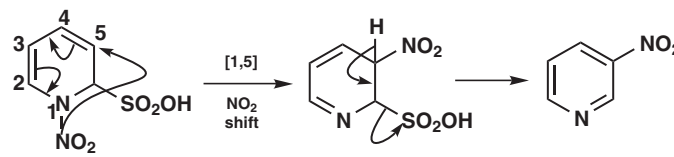
You may have partly guessed what is actually happening from the earlier parts of the chapter. Electrophilic attack occurs at nitrogen and the *N*-nitro pyridinium salt **169** is the product from the first stage. If the reaction is carried out at low temperature, this salt, similar to the fluoroborate **11** already known from the work of Olah, can be isolated.[24] The role of the bisulfite ion is as nucleophile. Attack actually occurs reversibly in the 2- and 4-positions but it is the former intermediate **171** that leads to the final product **165**. If bisulfite ion is added to the salt **169** in D_2O, the proton

NMR of compound **171** can be seen. You may already have guessed that the role of bisulfite was as a nucleophile, but what happens next?



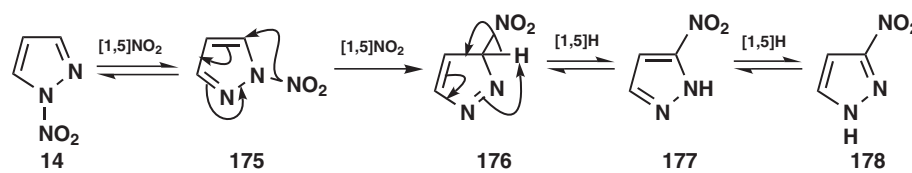
169 **170** **171** **172**

The bond between the nitro group and the pyridine nitrogen atom in **171** is a weak N−N σ-bond and it is advantageous for this to be transformed into a stronger C−N σ-bond. Intermediate **172** cannot easily achieve this but intermediate **171** can undergo a favourable [1,5] sigmatropic NO_2 shift **173**. Loss of bisulfite **174** then gives the product **165**.



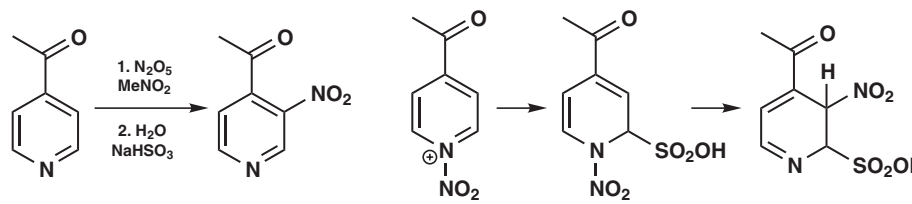
173 **174** **165**

The [1,5] sigmatropic shift may look unlikely at first but it should be compared with the [1,5] shifts familiar from cyclopentadiene chemistry. The nitro group passes suprafacially across the gap in the delocalised π-system of **173**. It is quite likely that the nitration of many pyrazoles goes through a similar sigmatropic rearrangement. If nitration occurs first at nitrogen **14**, the nitro group can then be transferred to carbon **175** (or to the other nitrogen atom!) by a [1,5]NO_2 shift to give **176** and this gives the product **177** by a [1,5]H shift. Even the tautomerism of pyrazoles, such as the interconversion of **177** and **178**, could be a [1,5]H shift.[25]



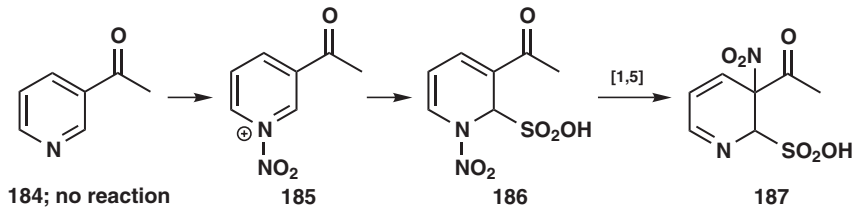
14 **175** **176** **177** **178**

This mechanism via **173** and **174** explains some puzzling results. Nitration of 4-acyl pyridines **179** occurs in excellent yield though electrophilic substitution would be disfavoured. Both the nucleophilic addition of $NaHSO_3$ (**181** to **182**) and the [1,5] shift (**182** to **183**) are probably accelerated by the presence of a ketone in the 4-position.



179 **180; 75% yield** **181** **182** **183**

No reaction at all occurs with 3-acyl pyridines[26] **86**. With this substitution pattern, we already know that nucleophilic attack occurs between the carbonyl group and the nitrogen atom to give **186** and hence **187** by a [1,5]NO_2 shift. No elimination of bisulfite would now be possible and this is a dead end.



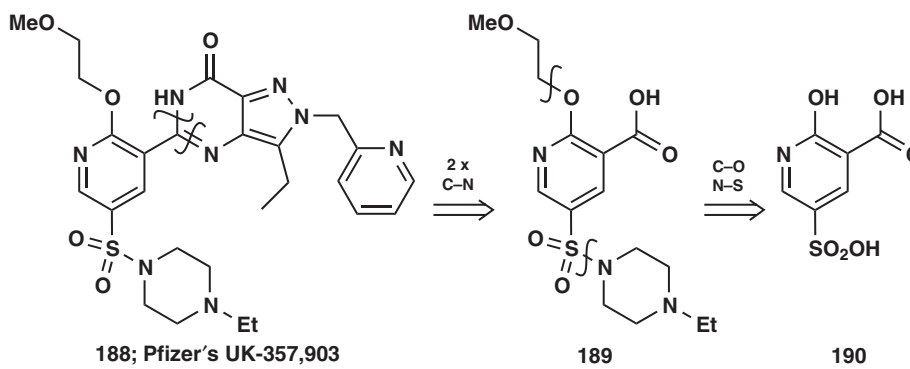
This work opens up important developments.

- Simple 3-nitro-pyridines and, by reduction, 3-amino pyridines are now readily available as starting materials.
- Nitration of compounds having pyridine and benzene rings can be controlled to give chemoselective reaction at either ring.

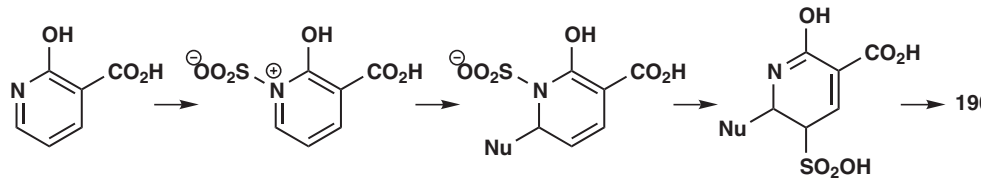
There will obviously be many applications in the future as the key reagent, N_2O_5, can be manufactured on a 100 tonne scale from N_2O_4 and nitric acid (HNO_3).

Sulfonation of Pyridines

Some reactions thought of as normal electrophilic substitution may in fact proceed by this mechanism. One example might be the sulfonation of 2-hydroxy-nicotinic acid used in the synthesis of a component[27] **190** of Pfizer's successor to Viagra **188**.

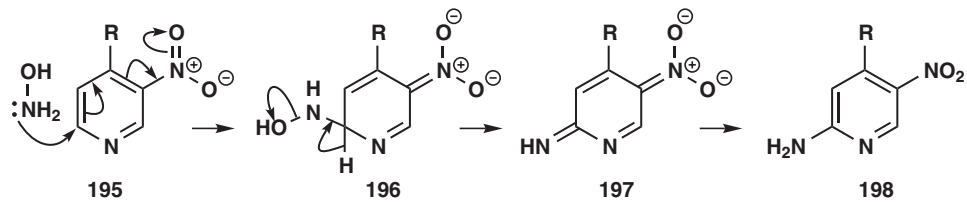


Sulfonation of 2-hydroxy-nicotinic acid **191** with sulfuric acid does not work but 30% oleum, that is sulfuric acid containing a 30% excess of SO_3, gives a 90% yield of **190**. This might easily occur by *N*-sulfonation **192**, addition of some nucleophile **193**, [1,5] shift **194** and elimination. Note that the position between CO_2H and N in **192** is blocked by the OH group so addition must occur on the other side in contrast to **184**. This compound will also be discussed in chapter 33.

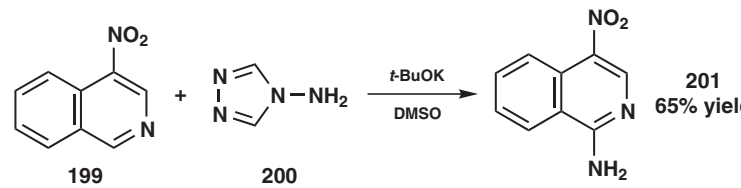


Extension by Vicarious Nucleophilic Aromatic Substitution

Vicarious nucleophilic substitution is the addition of nucleophiles carrying their own leaving group at an unsubstituted position on an aromatic ring. Since the Bakke nitration makes 3-nitropyridines available, reactions with amine nucleophiles X–NH_2, where X is a leaving group, at unsubstituted positions become possible.[28] One such nucleophile is hydroxylamine. Attack occurs next to nitrogen, but para to the nitro group **195**. Dehydration **196** and protonation of the anion **197** at the imine nitrogen gives the amine products **198**. A base (KOH is best) is also needed and R can be H, Alk, or Ar.

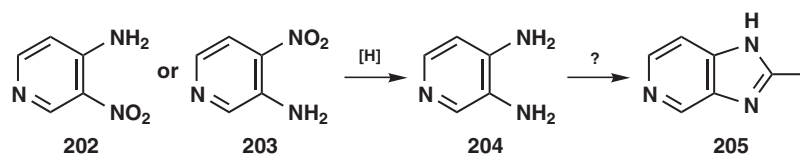


An alternative nucleophile is the amino-triazole **200** and this works better in some cases, notably the isoquinoline **199**. Amination again occurs *para* to the nitro group **201**.

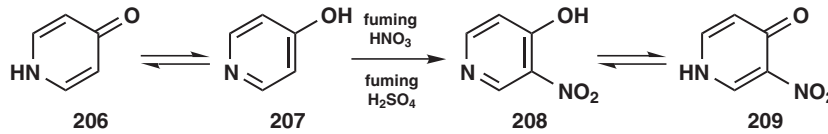


Synthesis of Imidazo[4,5-c]pyridines

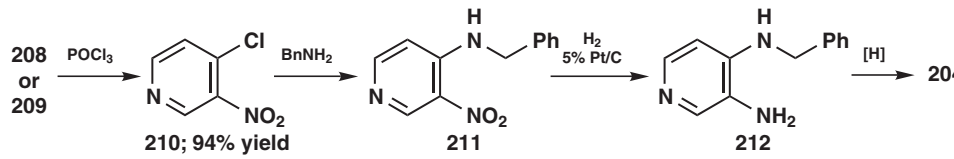
If, on the other hand, an amino group can be introduced *ortho* to the nitro group, reduction of **202** or **203** makes available the starting materials for fused heterocycles. One example is the synthesis of imidazo[4,5-c]pyridines **205** from diamino pyridines such as **204**.



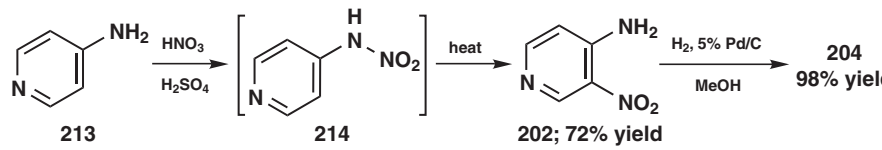
A published synthesis of 3,4-diaminopyridine[29] **204** starts with nitration of '4-hydroxypyridine' **207**. This is a difficult reaction in spite of the electron-donating OH group because the compound is mostly a pyridone **206**. Nevertheless a 74% yield of **208** can be achieved with a mixture of fuming nitric and sulfuric acids.



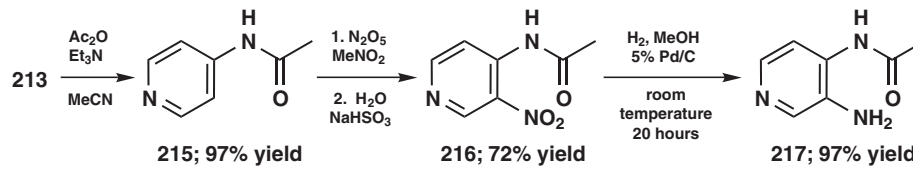
The product **208** may be as drawn or it too may be a pyridone **209** but in any case it reacts with $POCl_3$ to give the chloro-compound **210** and then by nucleophilic substitution with amines such as benzylamine to give, after reduction, the diamine **212** from which the benzyl group could be removed to give **204**.



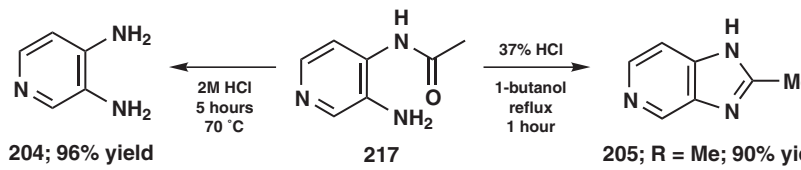
Another method[30] uses nitration of available 4-aminopyridine **213** to give unstable **214** and then by thermal rearrangement, the nitro compound **202** that can be reduced to **204** in good yield.



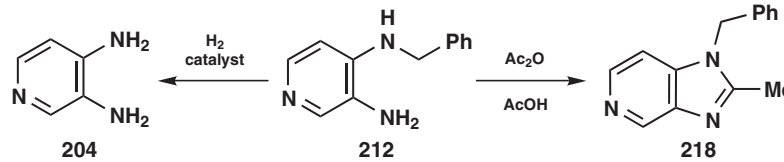
Neither of these methods is suitable for large scale production but the Bakke method[31] works well with a significant modification. The amino group in **213** must be protected as an amide **215** to prevent formation of **214**. Then nitration and reduction to give **217** (half-protected **204**) work very well.



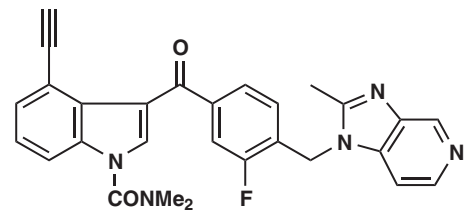
If the diamine **204** is wanted, hydrolysis of the amide in **217** is the answer. But if the more interesting imidazolo-pyridine **205** is wanted, acid catalysed cyclisation of the amine onto the amide gives the imidazole **205**; R = Me directly. Of course if R needs to be something else, the original acylation of **213** should be done with that anhydride $(RCO)_2O$.



The previous synthesis[29] ended at the half-protected diamine **212**. The *N*-benzyl group can of course be removed by hydrogenation to give **204** but cyclisation of **212** with an acid anhydride gives **218**, a part-protected version of **205**.

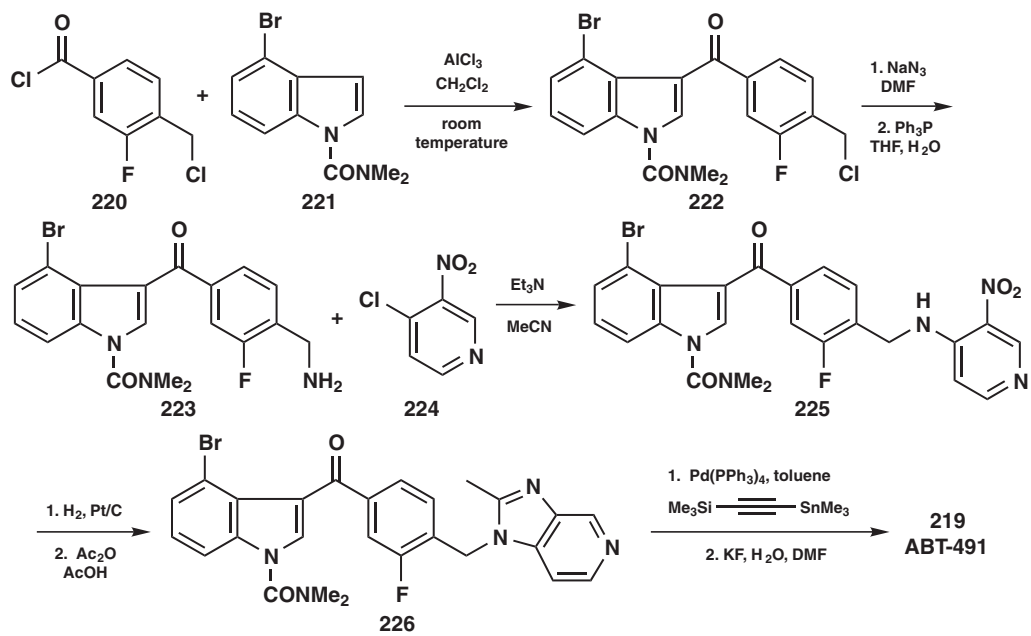


The type of molecule to be made from these compounds is illustrated by ABT-491, Abbott laboratories inhibitor[32] of platelet aggregation factor **219**. The imidazolo-pyridine segment is the very one we have been discussing (**205**; R = Me) with the added complication that the rest of the molecule must be added to one of the two nitrogen atoms of the imidazole and not to the other.



219
ABT-491
(Abbott
Laboratories)

The complete synthesis starts with a Friedel-Crafts reaction between a benzoyl chloride **220** and an indole **221**. Replacement of the chloride in **222** by an amino group is achieved by S_N2 with azide and reduction with Ph_3P. Nucleophilic substitution on the chloro pyridine **224** gives an intermediate **225** having imidazole connectivity problem solved. All that was needed was the correct nitro pyridine, easily made by Bakke nitration on 4-chloropyridine. The imidazole is closed by reduction and acetylation and a Sonigashira coupling inserts the acetylene. This is an impressively short and convergent synthesis with only one protecting group - the Me_3Si on the acetylene.

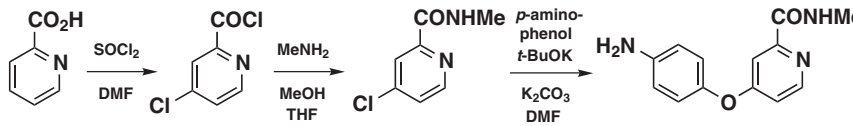


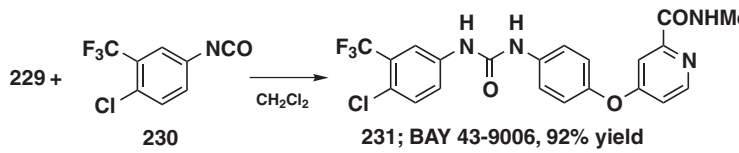
Part V – Applications

In this section we discuss the synthesis of various substituted pyridines by methods from earlier in the chapter and their applications in the synthesis of larger drug molecules.

The Baeyer anti-cancer drug BAY 43-9006

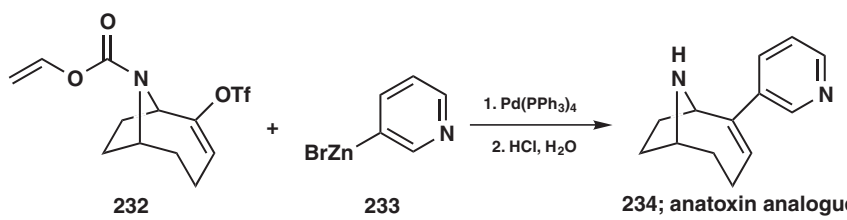
This relatively simple compound **231** requires the 4-Cl picolinic acid chloride **227** easily made in high yield by the $SOCl_2$ reaction described earlier. This has the advantage of simultaneously turning the acid into the acid chloride. Formation of the amide **228** and then the diaryl ether is followed by coupling with an isocyanate **230** to make the unsymmetrical urea **231**. This large scale synthesis is planned for manufacture.[33]





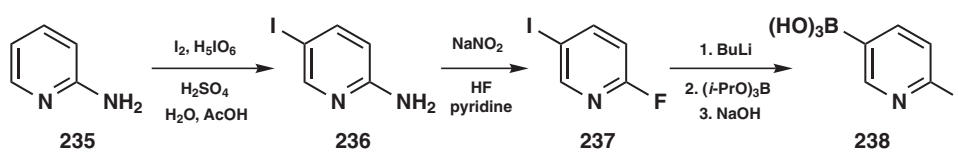
Anatoxin analogues

The heterocycles may be pyridine, pyridazine, pyrimidine (positional isomers) and the organo-zinc reagents **233** were made from the bromo-compounds. Six compounds such as **234** were made by Negishi coupling.[34]

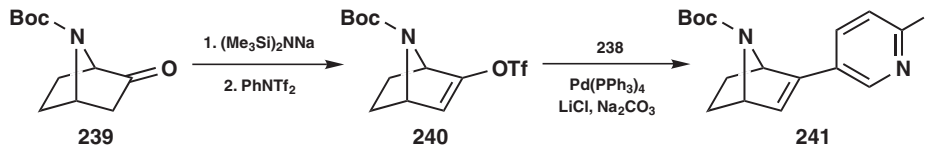


Epibatidine analogues (anti-smoking)

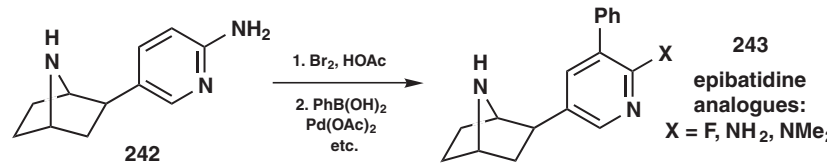
The starting materials were prepared by electrophilic and nucleophilic substitution on activated pyridines such as **235**. The essential boronic acid **238** needed lithiation.[35]



Suzuki coupling of such boronic acids with the triflate **240** of the protected ketone **239** gives bicyclic compounds such as **241** easily reduced to epibatidine analogues such as **242**.

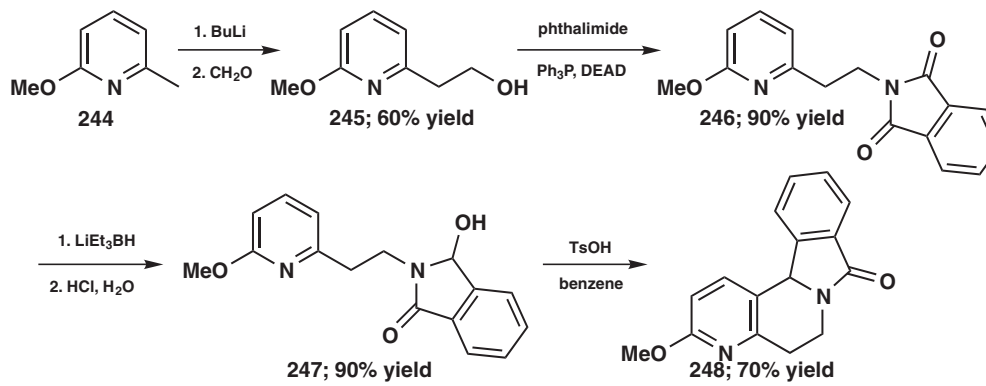


Alternatively, coupling of the boronic acid from **236** gives **242** that can be modified by electrophilic substitution afterwards and further Suzuki coupling used to give analogues[36]



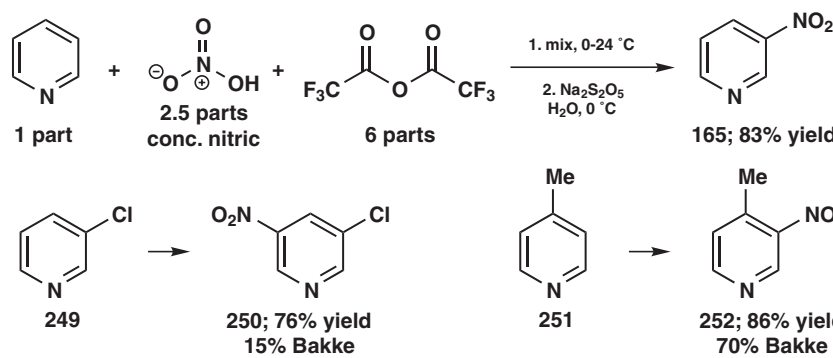
Polycyclic derivatives

Lateral lithiation of **244** and intramolecular electrophilic substitution with iminium ions derived from the partly reduced phthalimide **247** in acidic solution leads to the polycyclic derivatives[37] such as **248**. The 4-Me compound cyclises with some regioselectivity favouring *para* to OMe.



Katritzky's improvement of Bakke nitration

The main problem with the Bakke procedure is the need to prepare N_2O_5. Katritzky's group has avoided this by making N_2O_5 in situ from trifluoroacetic anhydride and nitric acid. Pyridine gives 83% yield of **165**, better than 77% by Bakke. Substituted pyridines such as **249** (76% rather than 15) and **251** (86% rather than 70) also give better yields, much better with **249**.



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33 Oxidation of Aromatic Compounds, Enols and Enolates

This chapter examines the addition of functional groups to aromatic rings and to carbonyl groups via enols or enolates. It revises previous sections.

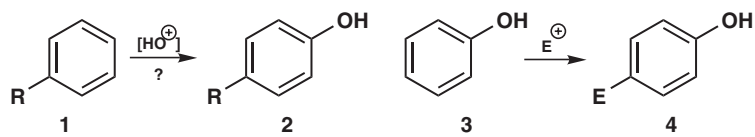
Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

Introduction

This chapter is also about functionalisation. But it deals with the addition of a difficult electrophile ('RO^+') to familiar nucleophiles: aromatic compounds, including the pyridines of chapter 32, and enols and enolates. As well as the difficulties of creating suitable reagents that control chemo- and regioselectivity, stereoselectivity and asymmetric induction are important.

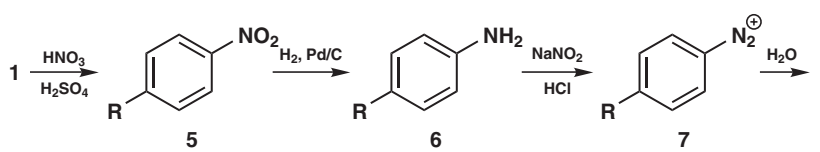
Part 1 – Electrophilic Substitution by Oxygen on Benzene Rings

The one large gap in electrophilic substitution reactions on benzene rings **1** is the absence of simple methods to introduce oxygen with an electrophilic reagent **2**. You were advised in the *Disconnection Textbook* (page 21) to have the oxygen atom present in the starting material **3** and achieve the same result by adding an electrophile **4**.

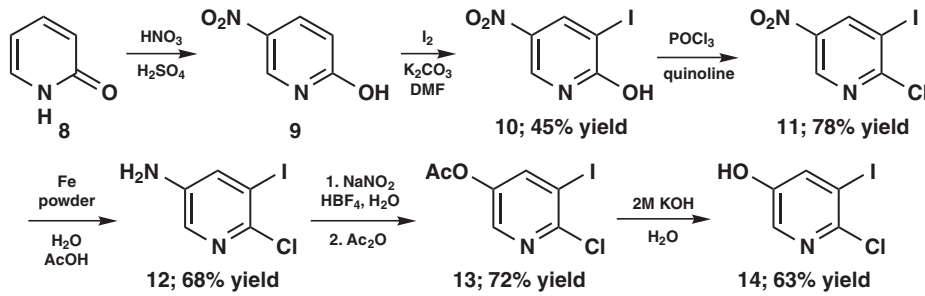


The Diazotisation Approach

The traditional approach was a nitration, reduction, diazotisation and hydrolysis sequence of four reactions. Though the OH group is actually added by a nucleophilic substitution on the diazonium salt **7** the nitrogen atom was originally added as an electrophilic nitro group **5**.

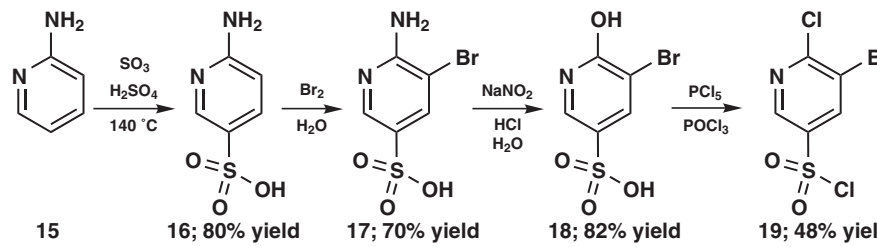


You might think such an apparently cumbersome approach is now no longer used but it is. In a synthesis of biologically active compounds related to epibatidine, the nitropyridine **9**, available by chemistry described in chapter 32, was converted into the key intermediate **14** by a sequence of reactions including the removal of the OH group already present and the introduction of a new one by diazotisation and so on.[1]

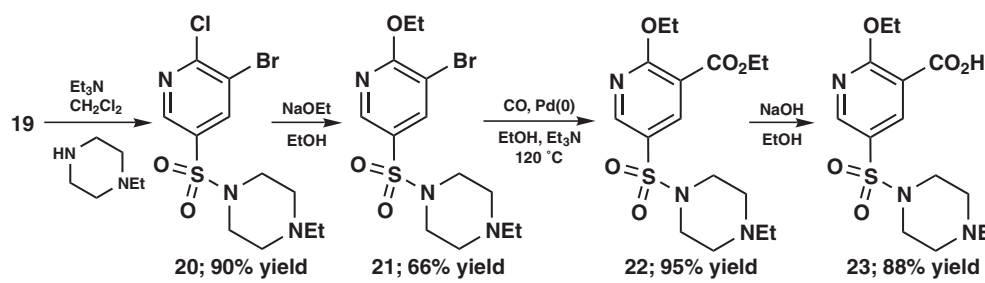


Synthesis of a successor to Viagra

In the large scale synthesis of the successor to Viagra described in the last chapter a short synthesis of the pyridine **23** replaced a much longer laboratory synthesis that used a similar sequence. The amino group in available 2-aminopyridine **15** directed sulfonation and bromination to give **17** and then, its work done, was replaced by the OH group **18**.

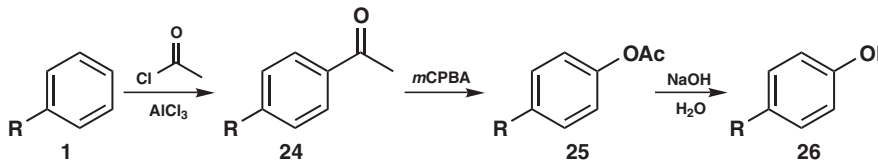


The conversion of the sulfonic acid to the sulfonyl chloride **19**, necessary for the formation of the piperazine amide **20**, also replaced the OH group by Cl. This was turned to advantage in introducing the OEt group by nucleophilic substitution before Pd(0)-catalysed carbonylation gave the carboxylic acid **23**. This eight step route[2] giving 11% yield, and containing a hazardous high temperature reaction with carbon monoxide, contrasts with the five step large scale route described in chapter 32 giving >50% yield.



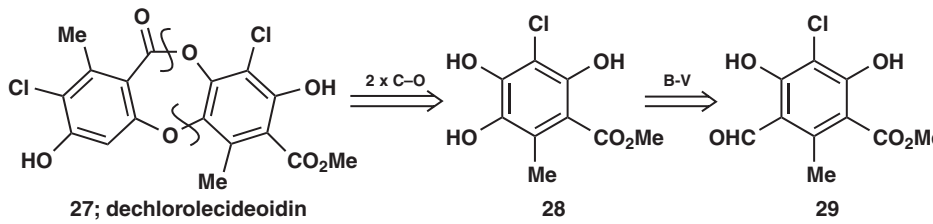
The Friedel-Crafts and Baeyer-Villiger Route

About the only simple way to introduce an oxygen atom by electrophilic substitution is to follow a Friedel-Crafts acylation of **1** using, say acetyl chloride to give **24**, with a Baeyer-Villiger oxidation with a peroxyacid. The aromatic ring will normally migrate in preference to the methyl group and the product **25** will be formed by the overall introduction of an acetate with the regioselectivity of an electrophilic substitution.

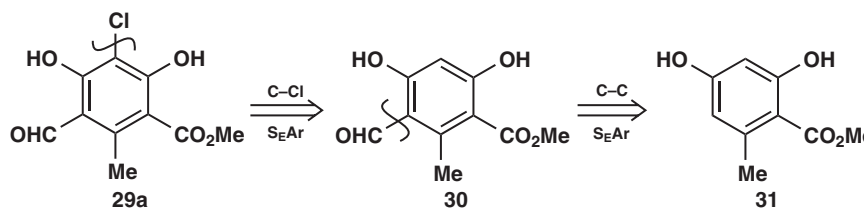


Avoidance by choice of oxygenated starting materials

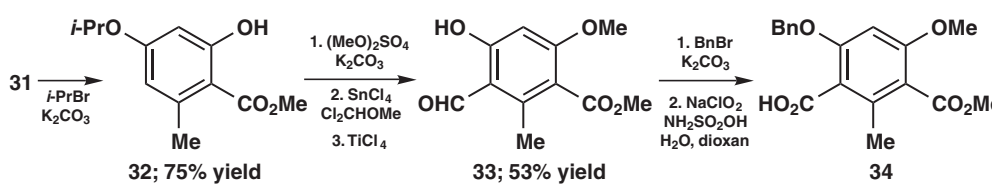
You are usually advised when making a complex aromatic compound to have any oxygen atoms (directly joined to the benzene ring) already present at the start. In their synthesis of the lichen metabolite dechlorolecideoidin **27**, McEwen and Sargent[3] chose the fully substituted benzene **29** as precursor for the right hand ring.



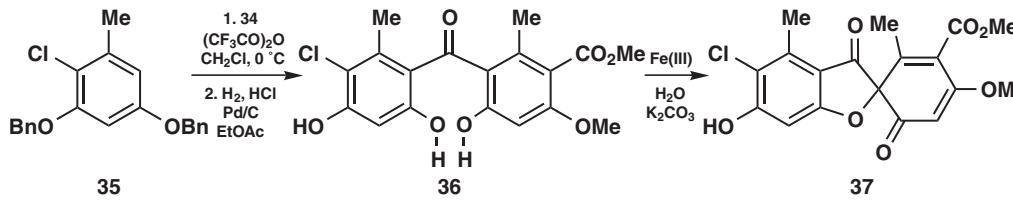
A search for available starting materials with both oxygen atoms present revealed methyl orsellinate **31** so the chlorine could be disconnected next to give **30**. Regioselectivity was confined to the formylation of **31** and they did indeed have difficulty with that step.



Methyl orsellinate **31** was differentially protected and formylated to give **33** after removal of the isopropyl group with $TiCl_4$. Benzylation and oxidation gave the benzoic acid **34** ready for a surprising conclusion to the synthesis.

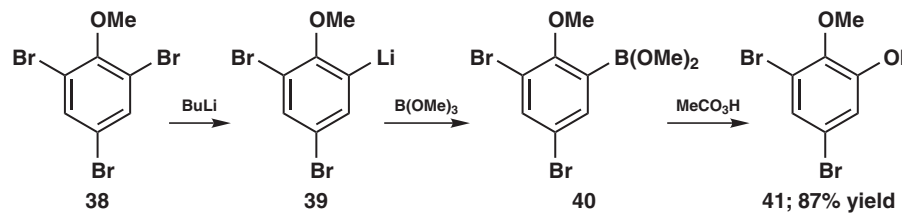


Friedel-Crafts acylation of **35** with **34** was brought about with trifluoroacetic anhydride and the benzyl groups removed to give **36**. The last oxygen was now introduced by an interesting oxidation with $K_3Fe(CN)_6$. The spirolactone **37** was formed in good yield and, on heating and removal of the OMe group, gave dechlorolecideoidin **27**. The interesting chemistry as well as the selectivity in this synthesis is explored in the workbook.

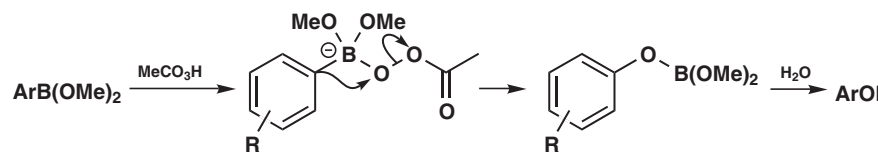


Oxidation through Lithiation and *Ortho*-Lithiation

Probably the best modern method for introduction of OH by electrophilic aromatic substitution is lithiation, reaction with a boronate ester, and oxidation.[4] These are the same boron compounds that are used in Suzuki coupling (chapter 18) and are made the same way. In this example, selective mono-lithiation by Br/Li exchange on available tribromoanisole **39** (easily prepared by bromination of anisole or phenol) occurs *ortho* to the MeO group and reaction of aryl-lithium **39** with trimethyl borate gives the boronic ester **40**. Peroxyacids such as peracetic acid are usually used for the final oxidation.



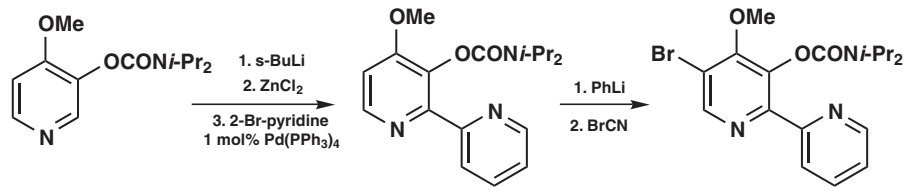
The oxidation is very similar to that used after hydroboration to make alcohols (chapter 17) and involves a migration of the aryl group from B to O as the weak O−O bond of the peroxy group is broken. It also closely resembles a Bayer-Villiger oxidation. The boronic acids are as good as the esters: PhMgBr reacts with $B(OMe)_3$ followed by 10% HCl to give $PhB(OH)_2$ oxidised without isolation to phenol[5] by H_2O_2 in 78% yield.



Hydroxylation of Pyridines by *ortho*-Lithiation

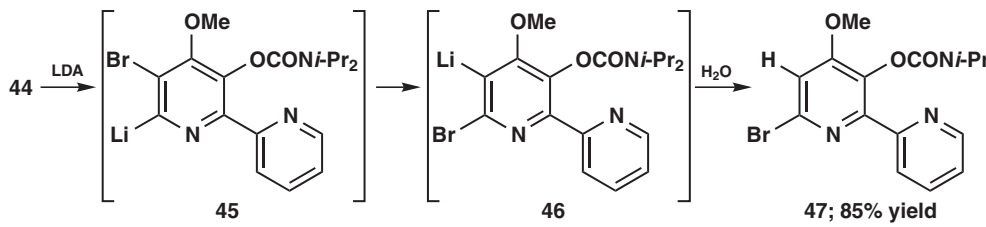
The basic *ortho*-lithiation strategy for electrophilic substitution on pyridines was explained in the last chapter. Now we need to explore the more powerful methods available when we add this boron-mediated oxidation. An example of control by *ortho*-lithiation in the synthesis of caerulomycin should reveal the possibilities. The pyridine **42** is lithiated in the 2-position because

an amide is a stronger *ortho*-director than a simple ether. Negishi coupling (chapter 18) of the Zn derivative with 2-bromo-pyridine gives the dipyridine **43** in good yield. A second *ortho*-lithiation must now occur at the 5-position and bromination gives **44**.



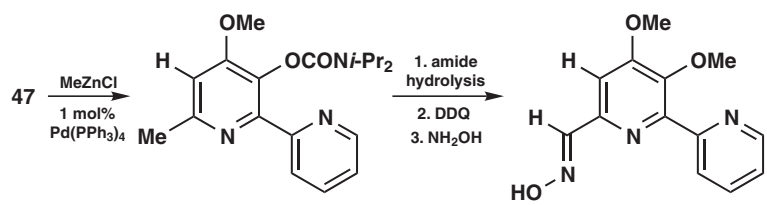
42 **43; 77% yield** **44; 81% yield**

Treatment of **44** with BuLi would lead to Br/Li exchange, but treatment with LDA lithiates the remaining position (C-6) on the ring **45** then the halogen dance (chapter 32) gives the more stable lithium derivative **46** with Li *ortho* to the OMe group. Protonation gives **47** in good yield.[6]



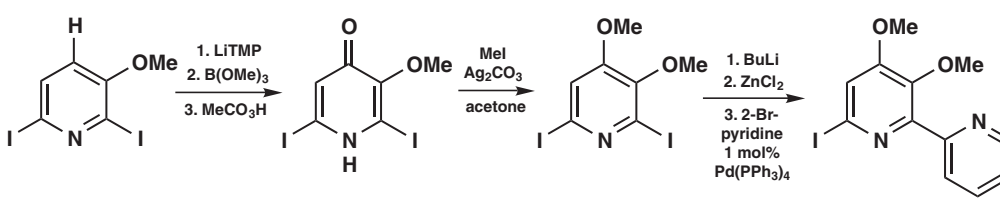
45 **46** **47; 85% yield**

Completion of the synthesis of caerulomycin C starts with a very efficient second Negishi coupling to give **48**, but then requires oxidation to an aldehyde, oxime formation, and removal of the original *ortho*-directing amide. The yield of **49** was unsatisfactory.



48; 100% yield **49; <10% yield**

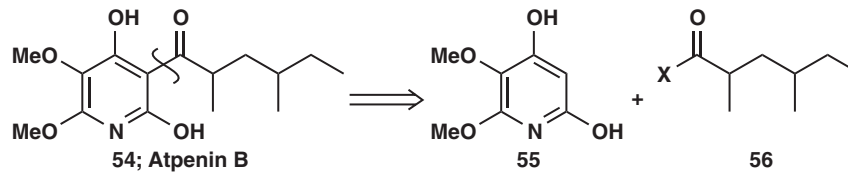
The successful sequence used the boron method to introduce one of the OMe groups and started with the di-iodo pyridine **50**. *ortho*-Lithiation with the very hindered LiTMP (lithium tetramethylpiperidide) to prevent I/Li exchange, reaction with a borate and oxidation gave the pyridone **51**. Methylation of the hydroxypyridine tautomer gave **52** and selective I/Li exchange of the iodine *ortho* to an MeO group followed by Negishi coupling gave the bipyridine **53**. The difference now is that a second I/Li exchange (BuLi - no choice now), reaction with DMF and oxime formation gave caerulomycin C **49** in good yield.[7]



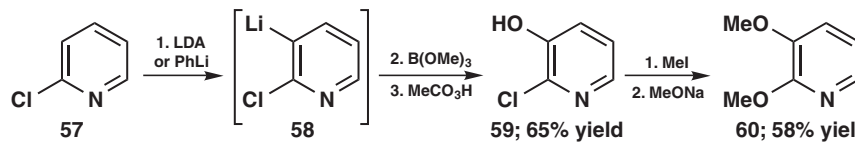
50 **51; 82% yield** **52; 65% yield** **53; 53% yield**

Synthesis of Atpenin B

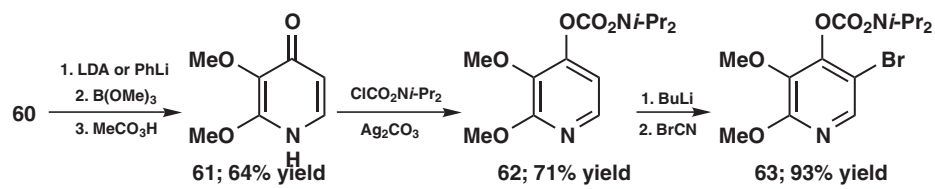
A dramatic example of this strategy is the synthesis of atpenin B **54** from 2-chloropyridine with the introduction of *four* oxygen atoms round the pyridine ring, three of them by electrophilic substitution. Far from being an 'impossible' reaction, electrophilic aromatic substitution by oxygen has become a favoured strategy. The first disconnection is easy: the alkyl side chain **56** can be added to the pyridine **55** by some kind of Friedel-Crafts acylation or via lithiation between two *ortho*-directors. This synthesis is on the cover of Clayden, *Organolithiums: Selectivity for Synthesis*, Pergamon, 2002.



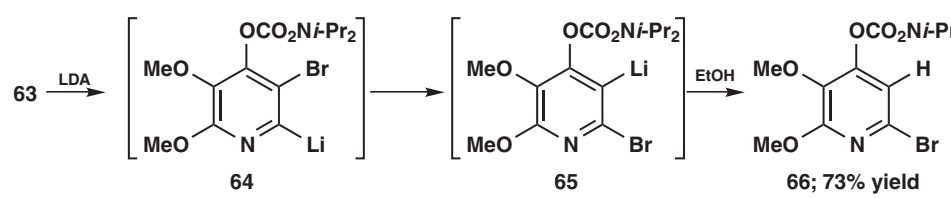
The 'clockwise' strategy chosen by Quéguiner and his group was to introduce the OH groups in turn from 2-chloropyridine **57** mainly by lithiation and reaction with a borate ester. With LDA or PhLi chlorine acts as an *ortho*-director **58** so the first OH group goes in easily **59**. Methylation and nucleophilic substitution by MeO^- puts in the two methoxy groups **60**.



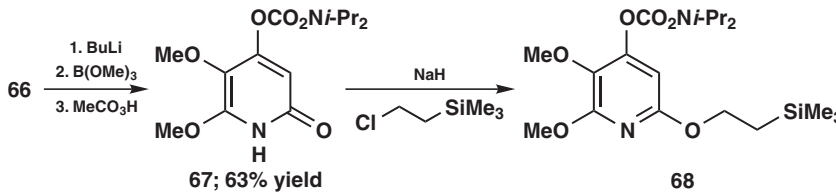
The third OH group can now be introduced in the same way **61**. The next stages are tricky as the fourth OH group is not on the next atom round the ring. The C-4 OH group must be made into a good *ortho*-director but not by MeO - a carbamate was chosen **62** - and some group must be placed at C-5 that can be used later to differentiate this position from C-6. Bromine was chosen **63**.



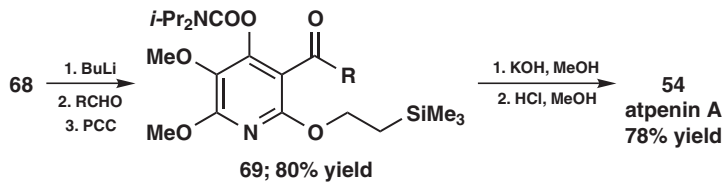
Now comes the clever bit. Lithiation of **63** with LDA occurs next to Br at the only remaining free position **64** but the 'halogen dance' (chapter 32) exchanges Br and Li so that Li is next to the excellent *ortho*-directing carbamate **65**. Protonation with EtOH gives **66** ready for introduction of the fourth and last OH group.



Lithiation with BuLi by Br/Li exchange and oxidation by the borate method inserts the C-6 OH group **67**. This is promptly protected as a labile 2-silylethyl ether **68** in readiness for the last lithiation and introduction of the side chain.

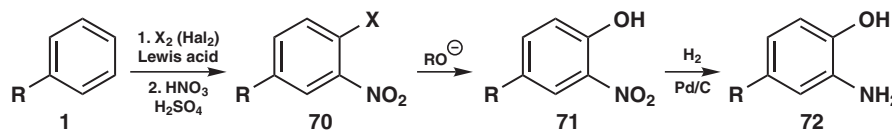


Lithiation promoted mainly by the carbamate and reaction with the required aldehyde **65** followed by oxidation turned out to be the best way to introduce the ketone. All that remained was to remove the two protecting groups and atpenin A **50** was formed in good yield.[8]



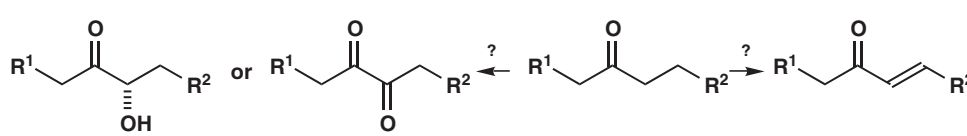
Introducing OH by Nucleophilic Substitution

This last sequence suggests that the introduction of OMe, or of course OH, could be done by displacement of activated halide. That is simple enough in a pyridine but is also possible in benzenes as halogens are *ortho, para*-directing and sequences such as **1** to **72** do a similar job.



Part II – Oxidation of Enols and Enolates

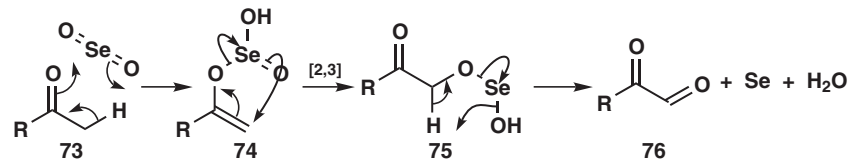
Since the carbonyl group is so important in synthesis and enolisation can now be well controlled (chapters 3-5, 10 and 11) it makes sense to prepare other molecules by controlled functionalisation of enols and enolates. As this involves replacement of hydrogen atoms by functional groups, these processes are all oxidations of some kind. We shall start with the introduction of a second carbonyl or hydroxyl group and progress to the introduction of an alkene, both being next to a carbonyl group already in the molecule. Two of the products have stereochemistry: asymmetry in the one and geometry (*E* or *Z*) in the other.



Direct Oxidation without Formation of a Specific Enol

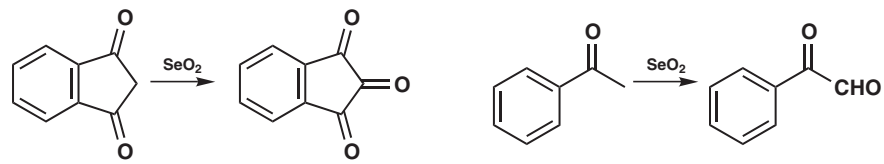
Selenium dioxide

Direct oxidation of carbonyls to 1,2-dicarbonyls can be carried out with selenium dioxide (SeO_2) though there are selectivity problems. The reaction starts with an 'ene' reaction **73** forming the enol derivative **74**. This undergoes a [2,3] sigmatropic shift **74** to form the C-O bond and loss of selenium and water **75** gives the final product **76**.



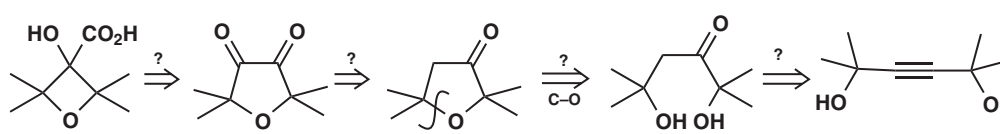
73 **74** **75** **76**

There is little control over enolisation as the enol derivative is formed in the first stage of the reaction. Two examples from Vogel[9] are the formation of ninhydrin **78** in poor yield and the more useful synthesis of the α-ketoaldehyde **80**. In both cases, enolisation has occurred at the only possible site.



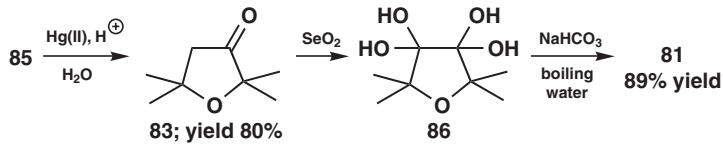
77 **78; 34% yield** **79** **80; 72% yield**

As an example we shall choose the cyclic 1,2-dione **82**. Ring contraction is a commonly used strategy for ring synthesis especially for the formation of five- from six-membered rings and three- from four-membered rings but is almost never used for the formation of four- from five-membered rings as the increased strain makes the reaction unfavourable. Nevertheless, the ring contraction of **82** to the acid **81** (by the benzilic acid rearrangement) did seem possible as the dione **82** is already strained. To test this idea, **82** had to be made. The chosen route was by functionalisation of the mono-ketone **83** as this could be made from the diol **84** and hence by hydration of the known adduct **85** of acetylene and two molecules of acetone.

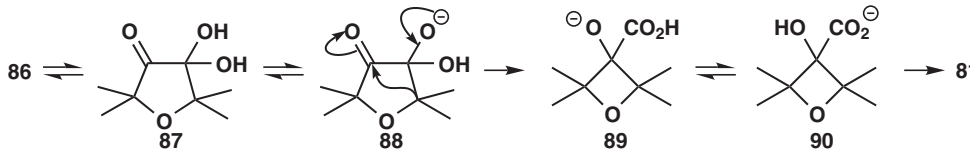


81 **82** **83** **84** **85**

Hydration of **85** catalysed by acid and Hg(II) gave the cyclic ether **83** directly[10] and oxidation with selenium dioxide gave the cyclic dione **82** which was stable as its crystalline dihydrate **86**. There is again no ambiguity of enolisation.

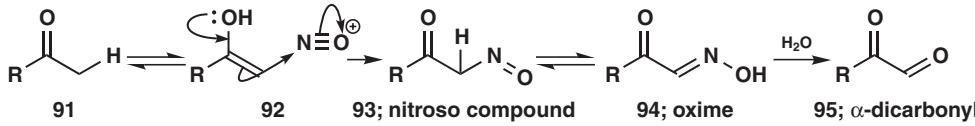


The ring contraction was surprisingly successful.[11] The best yields of **81** were with sodium bicarbonate though KOH can be used. Presumably only one ketone is necessary **87** for even such a weak base to promote the rearrangement from the monohydrate **88**. Under the reaction conditions the product is the stable carboxylate anion **90**.

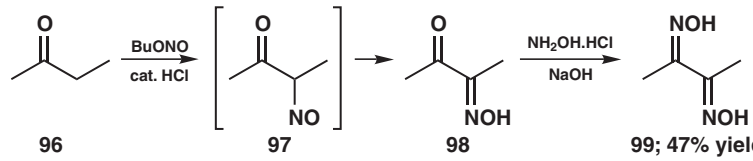


Nitrosation with nitrites

Another method is nitrosation with nitrous acid or, preferably, an alkyl nitrite in acidic solution. The enol of the carbonyl compound **91** reacts **92** with NO^+, formed from RONO in acid, to give the unstable nitroso compound **93** that tautomerises to the stable oxime **94**. If the dicarbonyl compound **95** is wanted, the oxime is easily hydrolysed.

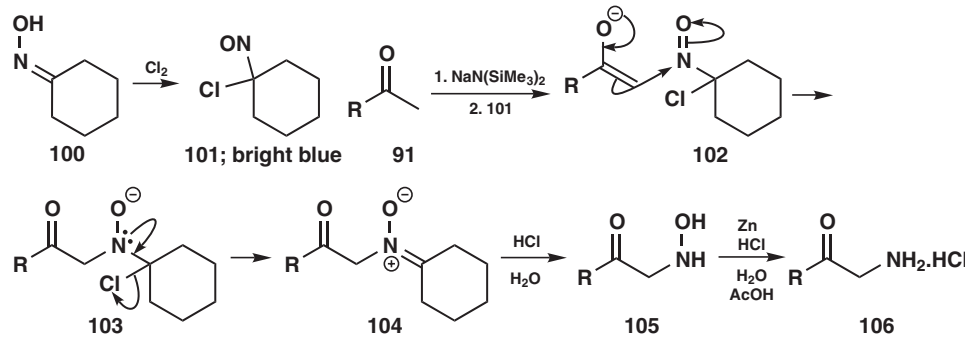


As the reaction is carried out in acidic solution, we can expect modest regioselectivity for enolisation on the more substituted side of the carbonyl group. An example from Vogel[12] is the oxidation of butanone **96** to give the monoxime **98** via the nitroso compound **97**. The dioxime (a useful ligand for metals) **99**, the diketone, or the monoxime **98** can be made by this route. Reduction of the oxines gives primary amines.

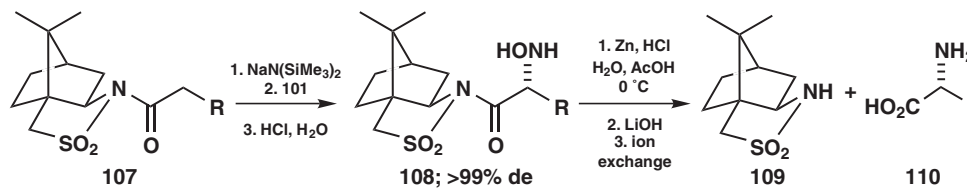


Nitrosation with stable nitroso compounds

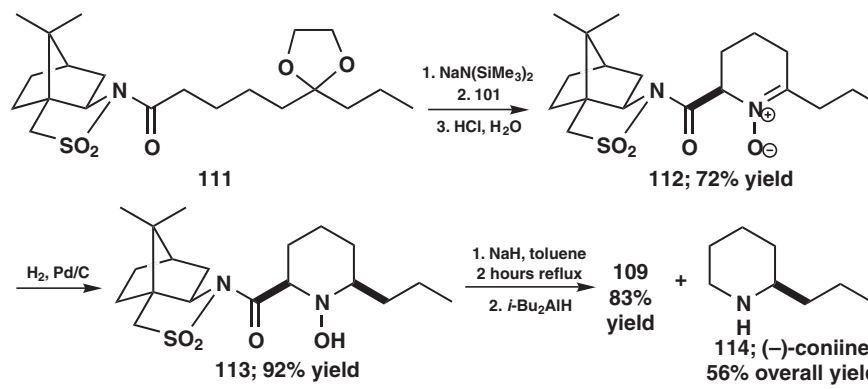
Nitroso compounds that cannot enolise are forced to keep the reactive N=O bond. Chlorination of the oxime **100** of cyclohexanone gives the bright blue α-chloro nitroso compound **101** stable enough to be isolated.[13] Enolates attack the nitroso group at nitrogen **102** to give, after elimination of chloride **103**, a nitrone **104** that can be hydrolysed to the hydroxylamine **105** and then reduced to the α–amino compound **106**, stable only as a salt.



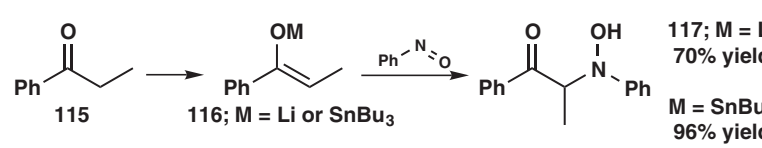
Oppolzer developed this chemistry into an asymmetric synthesis of α-amino acids **110** using enolates of amides **107** derived from his chiral sultam **109**. The hydroxylamines **108** are isolated in perfect diastereomeric purity which translates into high ees in the final products[14] **110**.



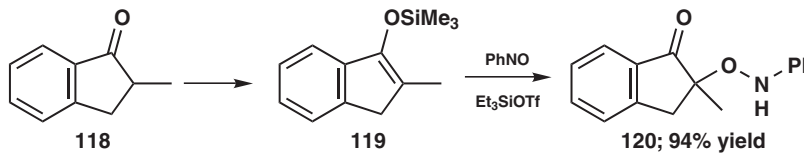
An ingenious application was in the asymmetric synthesis of coniine[15] **114**, the alkaloid in hemlock by which Socrates met his death. The sultam amide **111** incorporates a protected ketone so that acidic hydrolysis forms the cyclic nitrone **112** by capture of that ketone. Reduction and base-catalysed cleavage of the amide gives coniine **114**.



Much simpler, though not enantioselective, examples have been reported recently by Hisashi Yamamoto.[16] Lithium or tin enolates **116** react with nitrosobenzene to give good yields of hydroxylamines **117**.



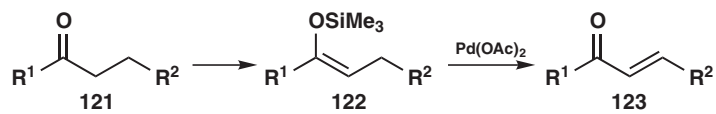
One interesting aspect of this reaction is that the acid-catalysed variant using silyl enol ethers **118** and Lewis acids provides a good way to oxidise the enol as the electrophilic end of the nitroso group switches to the oxygen atom. The product **120** is an N,O-disubstituted hydroxylamine. As the N−O single bond is rather easily cleaved reductively, this route promises to be a good way to make α-hydroxyketones.[17]



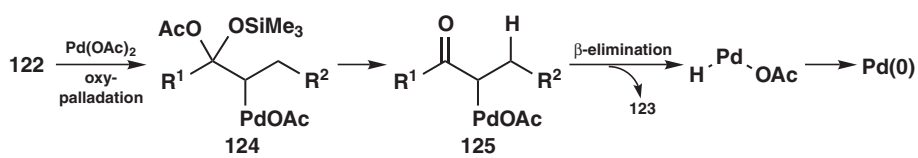
Indirect Oxidation with Formation of a Specific Enol: Enone Formation

Pd(II) oxidation of silyl enol ethers

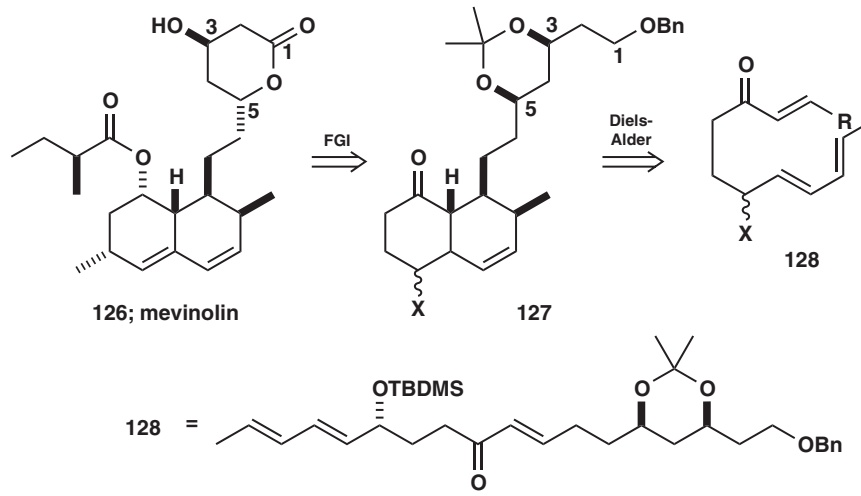
More regioselective methods are available if a specific enol equivalent (often the silyl enol ether **122**) can be used in the oxidation. These methods are usually used to introduce a conjugated alkene next to the carbonyl group. Oxidation of a silyl enol ether with Pd(II) does this job well.[18]



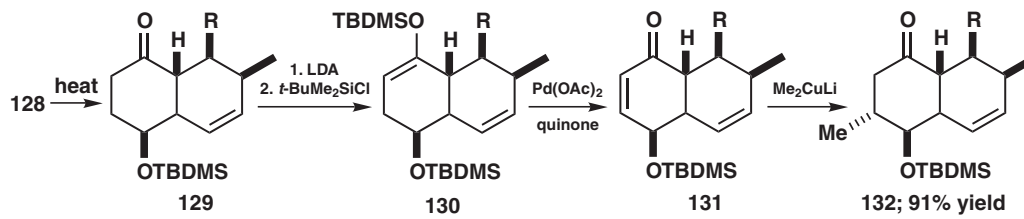
Regioselective oxy-palladation of the enol derivative gives **124** or **125**, either of which might lose palladium in a β-elimination that can only go one way. The problem is that the palladium comes out as Pd(0) but must go in as Pd(II) so the reaction is not intrinsically catalytic. The answer is to add a stoichiometric oxidant, such as a quinone, to complete the cycle.



An excellent example is the synthesis of mevinolin **126**, an HMG-CoA reductase inhibitor that lowers the cholesterol level, by Hirama and Iwashita.[19] Their idea was to use a Diels-Alder reaction to close both rings in one step and they therefore disconnected various peripheral fragments to leave the simpler ketone **127**. Reversing the Diels-Alder reveals **128** and the starting material was actually one diastereoisomer to ensure stereochemical control in the ring closure.

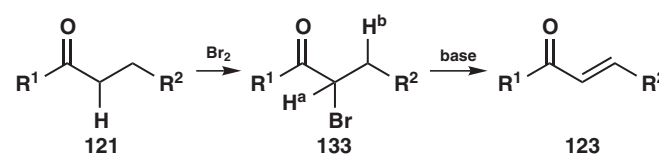


The Diels-Alder was successful[20] **129** but now the methyl group in the SW corner needs to be added by conjugate addition and that requires an enone. Oxidation of the silyl enol ether **130**, prepared by kinetic enolate formation with LDA, with catalytic $Pd(OAc)_2$ and benzoquinone as the stoichiometric oxidant gave the required enone **131** in 57% yield. Addition of Me_2CuLi was stereoselective to give **132** and the synthesis of mevinolin completed.



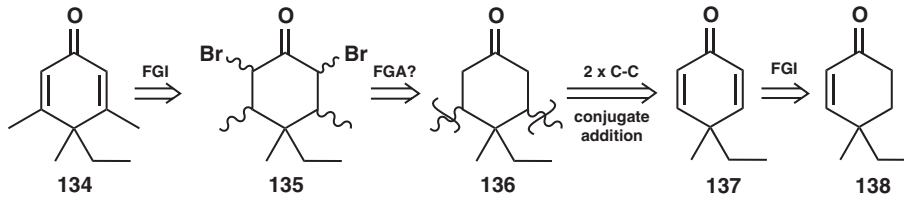
Bromination of enols in enone formation

The oldest but still occasionally useful method for enone formation from saturated ketones involves bromination and elimination of HBr from the bromoketone **133**. The problem here is that the proton to be removed (H^b in **133**) in the elimination is not the most acidic proton in the molecule: H^a is much more acidic.

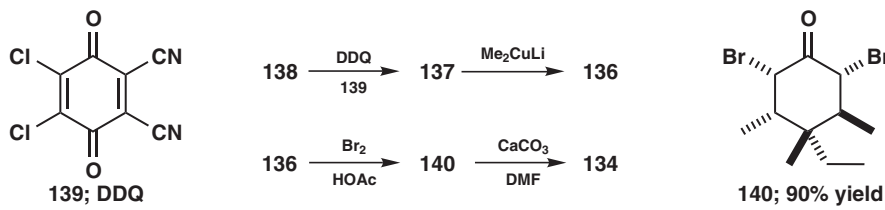


Nevertheless this method can work well if hindered or non-nucleophilic bases (such as DBN and DBU) are used. The dienone **134** was needed for a study of migrating groups in the dienone-phenol rearrangement.[21] The bold proposal was that double elimination from dibromoketone **135**

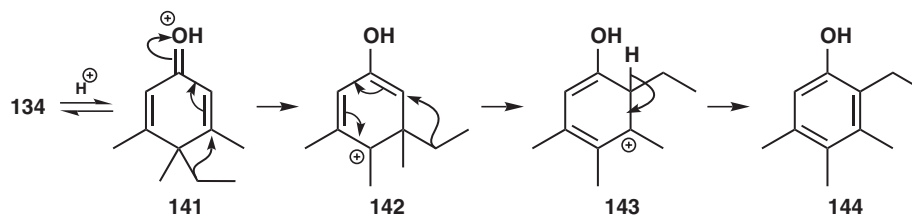
would allow the ketone **136** to be used and that this might in turn be made by double conjugate addition of a cuprate to dienone **137**. Direct oxidation by a quinone or SeO_2 would give this from the enone **138**, easily made by Robinson annelation.



The enone **138** could be oxidised to dienone **137** with the quinone DDQ **139**. Bromination of **136** rather surprisingly gave a single crystalline isomer **140** in 90% yield: NMR revealed the stereochemistry shown. The double dehydrobromination was carried out with calcium carbonate in DMF.

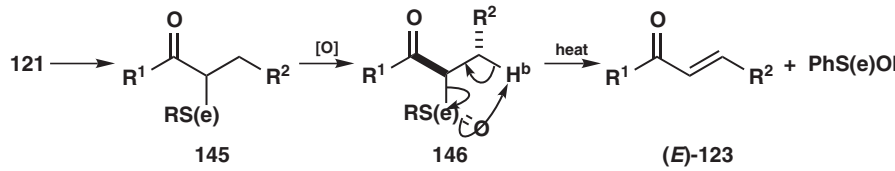


This synthesis was well worthwhile as the dienone-phenol rearrangement of **134** gave the phenol **144** showing that the ethyl group migrates better than methyl. The dienone rearranges to **142** and a second migration is needed before a cation is formed **143** that can give an aromatic compound by loss of a proton. In each rearrangement there is a choice between a methyl and an ethyl group.

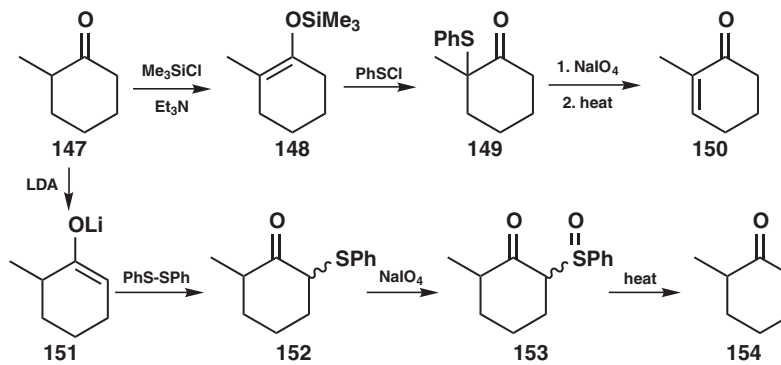


Sulfur and selenium compounds in enone formation

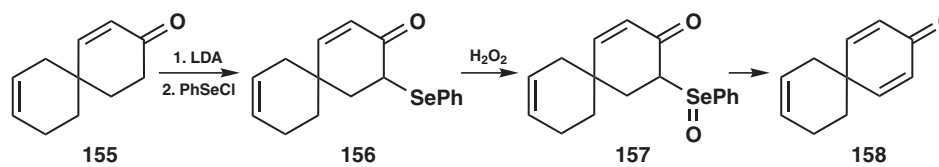
Probably the most popular method to introduce an alkene is by regioselective functionalisation with a sulfur or selenium reagent, oxidation, and elimination. The α-RS or α-RSe compound **145** is made by sulfenylation or selenenylation of a specific enol equivalent. Oxidation requires only mild reagents such as H_2O_2, and the elimination follows a cyclic *syn* mechanism **146** so the lack of acidity in H^b is unimportant. The elimination (a reverse ene reaction) is highly *E*-selective as the substituents R^1CO and R^2 prefer an *anti* conformation in the transition state. This resembles the high *E*-selectivity in the [3,3]-sigmatropic rearrangements discussed in chapter 15. S(e) means either Se or S.



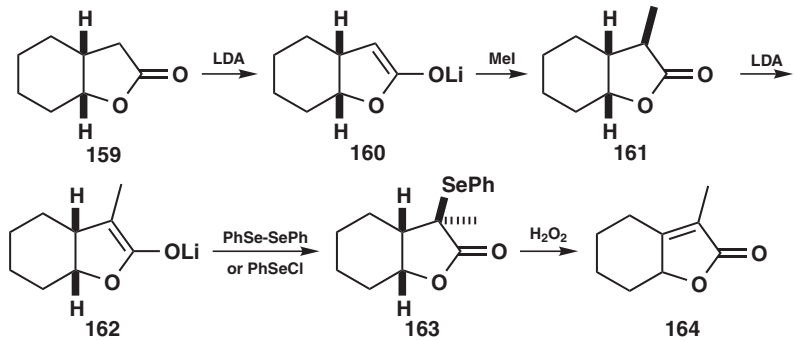
Sulfenylation of lithium enolates with PhS-SPh or of silyl enol ethers with PhS-Cl allows any α-PhS carbonyl compound to be made regioselectively, e.g. **149** and **152** from **147** (see chapter 5). Oxidation with sodium periodate gives the sulfoxide without over-oxidation to the sulfone, but elimination requires reasonably high temperatures (about 120 °C for MeSO but only about 50 °C for PhSO). Together with the unpleasant by-products, the results of disproportionation of unstable PhSOH, this has led to a preference for the selenium version of the reaction, though we must admit that the by-products are even more offensive.[22]



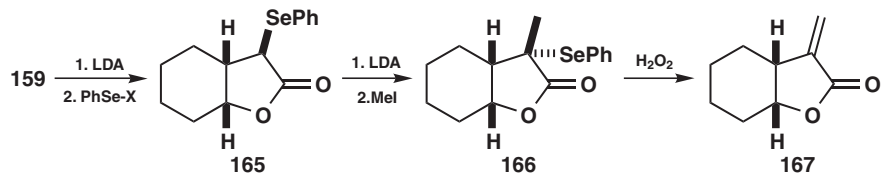
The selenium version of this reaction offers the advantages that over-oxidation is no problem and that the elimination of the selenoxides occurs at room temperature or below so that the oxidation and elimination normally occur as a single step.[23] A simple example is the preparation of another starting material **158** for a dienone-phenol rearrangement.[24] The lithium enolate of spirocyclic ketone **155** reacts with PhSeCl to give **156** and oxidation with H_2O_2 gives the dienone **158** directly, with the selenoxide **157** as an intermediate. The overall yield is 83%.



A general problem that is neatly solved by these methods is that of making exo-methylene lactones such as **167**. These compounds are cytotoxic and both carcinogenic and anti-cancer compounds are found in this class. If the *cis*-fused lactone **159** is converted into its lithium enolate **160** we have a classic case of a folded molecule and attack by an electrophile occurs on the *exo* face, that is the same face as the ring-junction hydrogen atoms. Methylation gives **161**. The lithium enolate of this molecule **162** again has a flat five-membered ring and a second electrophile also adds on the *exo* face, say to give **163**. In this compound the PhSe group and the ring junction H are *syn* to each other so elimination on the selenoxide tends to give the more stable but less interesting unsaturated lactone **164**.

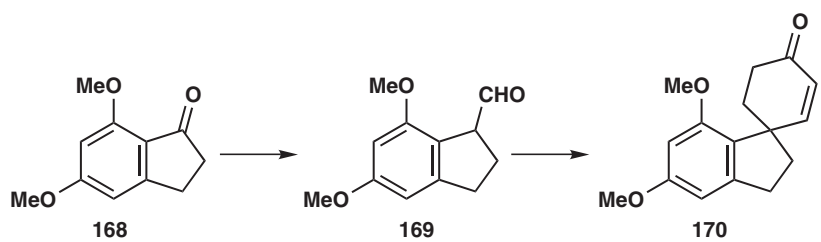


If we want the exomethylene lactone **167**, we must simply add the electrophiles in the reverse order.[25] The PhSe group is therefore *anti* to the ring junction H atom **166** and elimination on the selenoxide must give **167**.

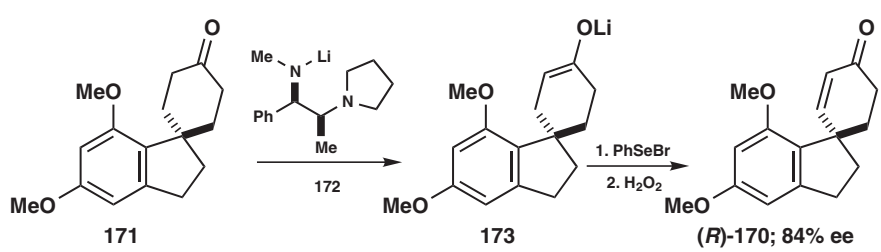


Asymmetric Synthesis of Cannabispirenones

The selenium oxidation can even be a source of asymmetry. Both enantiomers of cannabispirenones **170** occur naturally in different plants and the racemic enone is made in two steps from the achiral ketone **168**. You will see that **170** is chiral only by virtue of the alkene in the ring.

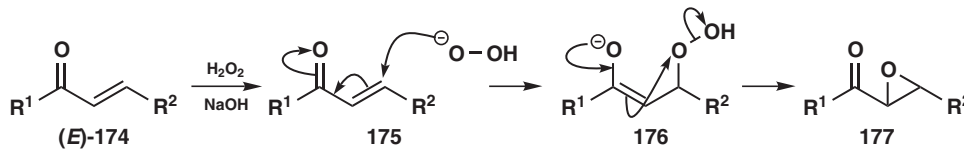


Hydrogenation of **170** gives the achiral saturated ketone **171** that can be desymmetrised by a chiral base. The lithiated diamine **172** gives mostly the lithium enolate **173** and hence, by addition of selenium and oxidative elimination, the enone (*R*)-**170**. Different bases give the other enantiomer.[26]

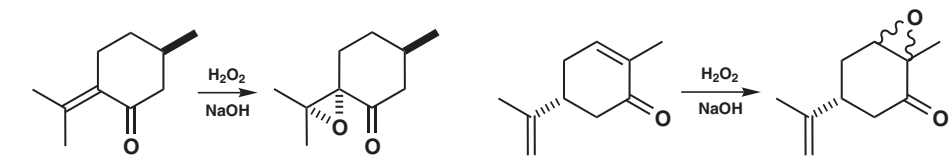


Oxidation of Enones: Epoxides and the Eschenmoser Fragmentation

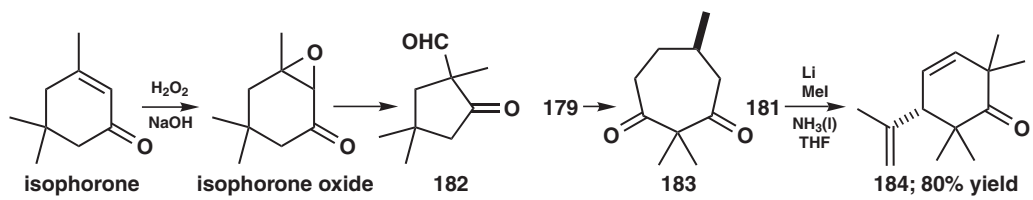
Once the enone is prepared, further oxidation becomes easier. The epoxide can be formed at the alkene with the nucleophilic oxidant H_2O_2/NaOH. The mechanism involves a discrete enolate intermediate **176** so the stereochemistry of the alkene is lost and *E*- and *Z*-enones **174** usually both give the *anti*-epoxide **177**.



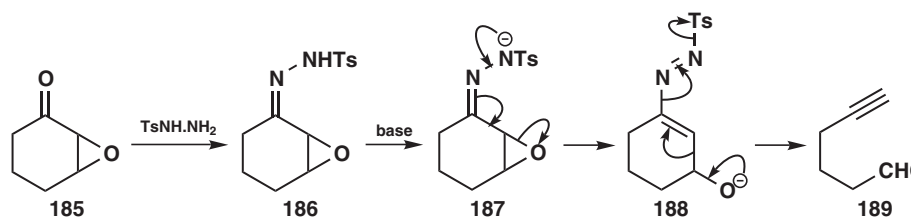
This reaction gives some stereoselectivity with pulegone **178** as the epoxide **179** is formed in an approximately 2:1 *anti:syn* ratio,[27] and chemo-selectivity as carvone **180** gives just one epoxide **181** as a mixture of diastereoisomers: the electron-rich alkene is not epoxidised.[28]



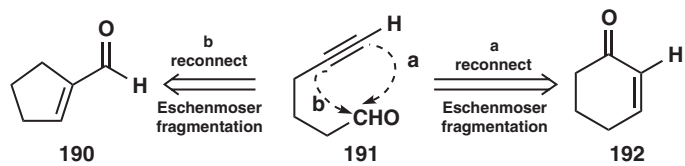
Further reactions on these compounds lead to other oxidised products in which the lack of stereochemical control in the epoxidation is unimportant, so, for example isophorone oxide rearranges with various catalysts to the cyclopentanone **182** (80% yield) while both isomers of pulegone oxide **179** gives the cycloheptadione[29] **183** (78% yield). Exhaustive methylation of the extended enolate produced by reduction of **181** gives **184** in good yield.[28]



The most dramatic of all these reactions is the Eschenmoser fragmentation[30] - a general route to alkynyl aldehydes **189** and ketones. The tosylhydrazone **186** of an epoxyketone **185** gives an anion on treatment with base that fragments once **187** to give an alkene and again **188** in the reverse direction **188** to give the alkyne.



The 'disconnection' corresponding to a fragmentation must of course be a reconnection and there is a choice here **191** when reconnecting the alkyne to the aldehyde **190** or ketone **192**. Whether you draw the intermediates or not you should get back to the same two enones as potential starting materials. In this case either method works and you may choose the enone you prefer, or that you find easier to make.



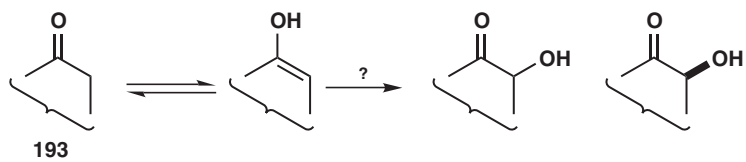
The rest of this chapter is about attempts to introduce electrophilic oxygen onto enolates. The option of acylation followed by Baeyer-Villiger rearrangement is not available as the starting materials themselves contain carbonyl groups and react with peroxy acids. The alternative solutions will lead us into interesting chemistry. We shall omit unreliable older solutions involving oxygen gas, $Pb(OAc)_4$ etc.

Part III – Electrophilic Attack on Enol(ate)s by Oxygen

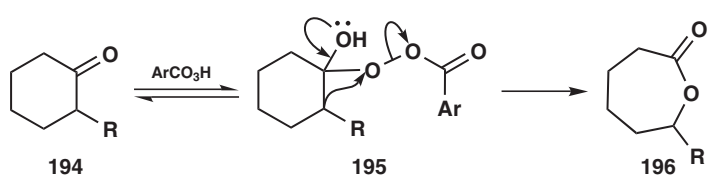
The Problem

Competition with Baeyer-Villiger rearrangement and oxidative cleavage

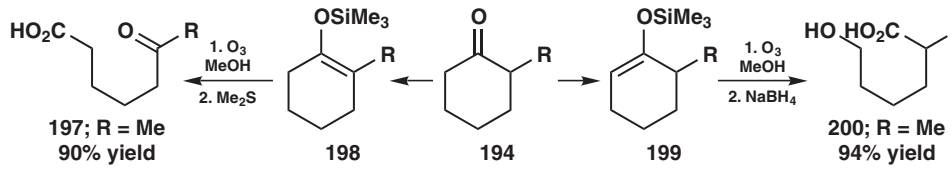
The idea is to be able to react a carbonyl compound **193** (or some specific enol derivative of it) with some reagent for the synthon "HO^+" so that a new C−O bond is formed on the next atom **192**. Sometimes no stereochemistry will be involved but we should also like to be able to create single enantiomers.



The most obvious thing to do is to react the carbonyl compound with a peroxyacid. After all, double bonds react to give epoxides and enols are more nucleophilic than double bonds. Unfortunately, peroxyacids are nucleophilic as well as electrophilic and form hemiacetals with carbonyl compounds which decompose by the C to O migration **195** known as the Baeyer-Villiger rearrangement.



Electrophilic oxygen is introduced at the carbon atom next to the old carbonyl group but the C−C bond linking these atoms is lost so the result is not α-hydroxylation. Oxidative cleavage of the enol alkene bond is going generally to be a problem in this section and is best illustrated by the useful ozonolysis of silyl enol ethers **198** and **199** of the same ketone **194**. The regiospecific formation of silyl enol ethers is described in chapter 3.

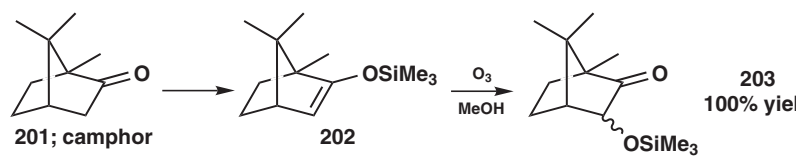


Reduction and cyclisation of ketoacid **197** would give lactone **196** while cyclisation of **200** would give the isomeric lactone. This second method is therefore controllable whereas in the Baeyer-Villiger rearrangement, only the more highly substituted group migrates. However, the Baeyer-Villiger does go with retention at the migrating group whereas there is no stereochemical control in the ozone reactions.

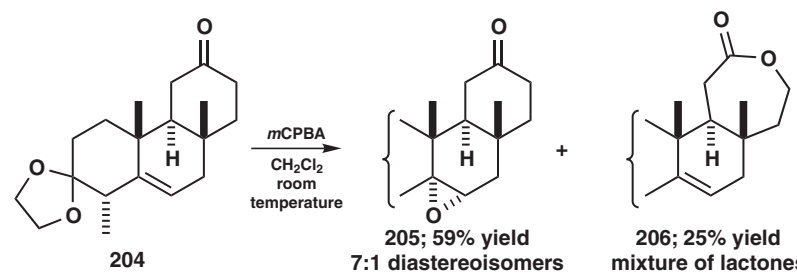
Unexpected Success with the "Obvious" Reagents

Unique successful hydroxylations with ozone and mCPBA

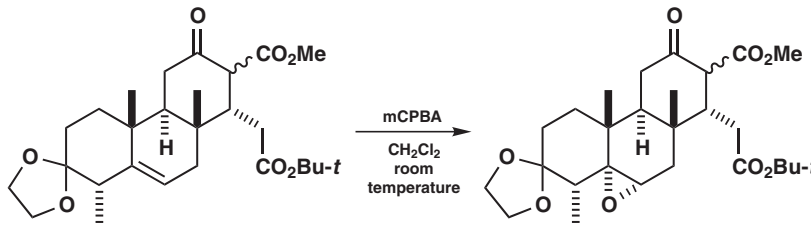
Two remarkable observations need discussion at this stage as they show that the two methods we have dismissed sometimes work. Attempted ozonolysis of the silyl enol ether **202** derived from camphor **201** gave instead a quantitative yield of the silyl ether of hydroxycamphor[31] **203**.



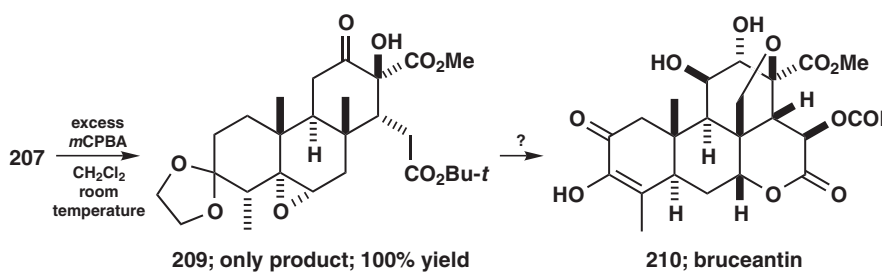
Though the product **203** is a mixture of diastereoisomers, it does at least show that even ozone sometimes attacks an enol as an oxygen electrophile. The second example is even more remarkable. Attempted epoxidation of the tricyclic ketone **204** gave a mixture of four compounds: two epoxides **205** in a 7:1 ratio from *m*CPBA attack at the alkene and two regioisomeric lactones **206** from the Baeyer-Villiger rearrangement of the ketone.



This compound was intended to be a model compound for a more complex ketone **207** to be used in the synthesis of the quassinoid natural products, some of which have anti-cancer properties, but, mindful perhaps of Woodward's dictum that the only reliable model compound is the enantiomer of the real thing[32] they tried the reaction with **207**. With one equivalent of *m*CPBA they got just one diastereoisomer of the epoxide.



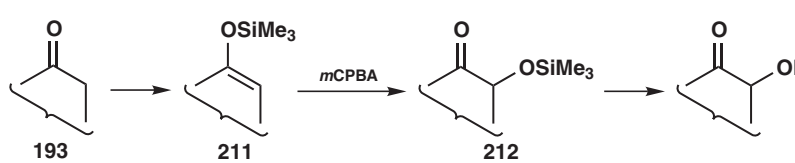
For the purposes of this chapter, the more exciting result was that treatment with an excess of *m*CPBA converted **207** into **209** in quantitative yield: epoxidation is totally stereoselective and hydroxylation has also occurred at the easily enolised position between the ketone and the ester to give a single diastereoisomer of the alcohol **209**. The stereoselectivities are remarkable enough but the mere fact the hydroxylation occurs so efficiently gives hope for the development of a more general method. Inspection of the structure of bruceantin **210**, the most promising of the anti-cancer quassinoids, shows just how valuable this reaction turned out to be. The difficult tertiary alcohol has been inserted in exactly the right place with the right stereochemistry.



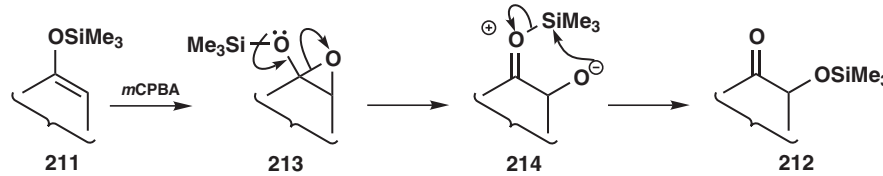
First Successful Method: Epoxidation of Silyl Enol Ethers (Rubottom Oxidation)

Method, mechanism, and isolation of intermediates

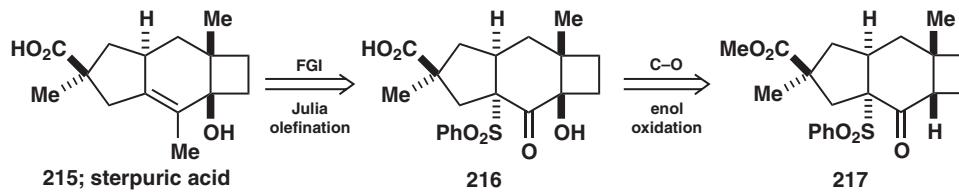
It is a small logical step from the last section to attempt the epoxidation of silyl enol ethers **211**. The result is slightly surprising: hydroxylation is successful but the product is the silyl ether **212** of the α-hydroxyketone.[33,34]



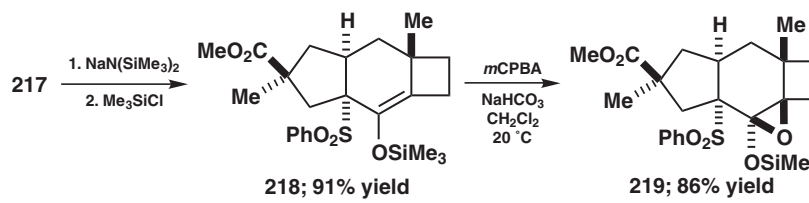
The immediate product is presumably the epoxide **213** which opens in acetal fashion to give **214** and transfers silicon intramolecularly to give **212**. The reaction **214** is formally a 5-*endo-tet* reaction and would not occur if carbon were being transferred. As silicon is the atom under attack, a pentacovalent *intermediate* can be formed and the requirement for a linear S_N2 transition state no longer applies.



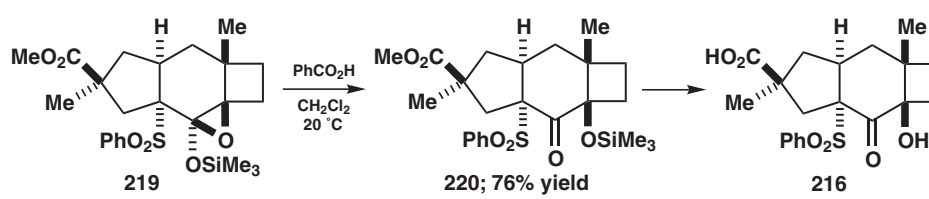
Support for this mechanism came from an unexpected quarter. In a synthesis of sterpuric acid **215**, Paquette planned to put in the alkene at the end by a Julia olefination.[35] Addition of MeLi to the ketone **216** and non-stereospecific elimination (chapter 15) looked a good strategy. The 1,2-relationship between OH and ketone in **216** is awkward and the decision was made to try a hydroxylation on the silyl enol ether of the parent ketone **217**.



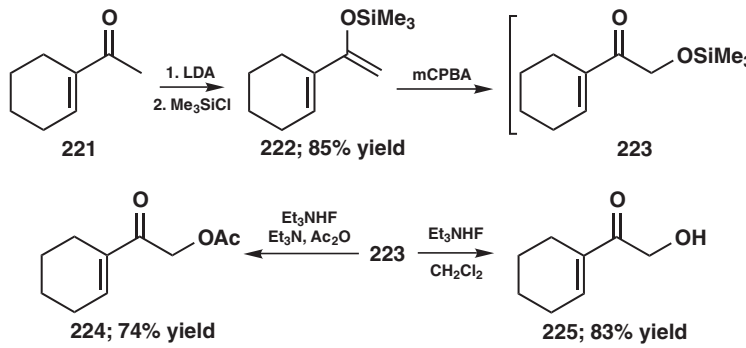
This decision was to have sensational results as treatment of the silyl enol ether **218** with buffered ($NaHCO_3$) *m*CPBA gave an 86% yield of a crystalline compound whose structure, determined by X-ray, was **219** - the first stable epoxide of a silyl enol ether had been isolated.



When the epoxide **219** was treated with even weak acid, or when the silyl enol ether **218** was epoxidised with unbuffered *m*CPBA, no epoxide could be found. Instead a 76% yield of the silyl ether **220** of the hydroxylated ketone **216** was formed. The stereochemistry of **220** is of course determined by that of **219** and the requirement for *cis*-fused four- and five-membered rings. Sterpuric acid **215** has the same stereochemistry.

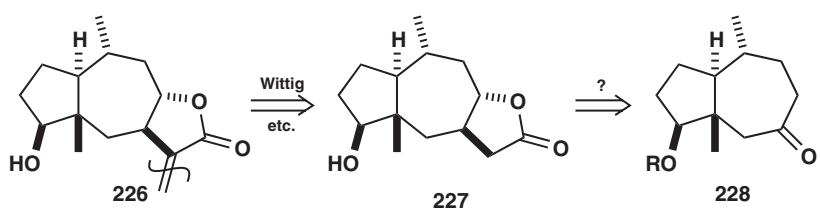


This approach can use the inherent regioselectivity of silyl enol ether formation (chapter 3) using kinetic or thermodynamic enolisation. Hence kinetic enolisation of enones (chapter 11) occurs on the α' side leading to 2-Me_3SiO-butadienes such as **222**. Epoxidation of this silyl enol ether gives the unstable silyloxy ketone **223** which can be desilylated by fluoride ion and hence transformed into the hydroxyketone **225** or acetoxy ketone **224**. These transformations are useful because the hydroxy ketones can be unstable[34] (see below).

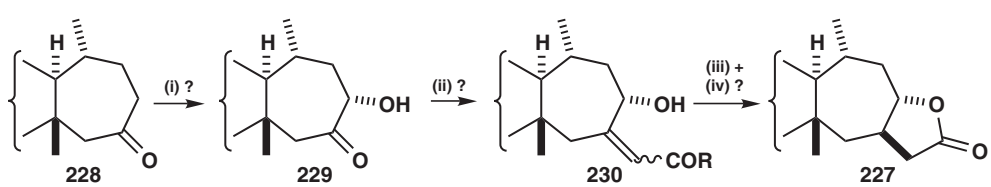


Chemo- regio- and stereoselectivity: synthesis of fused γ-lactones

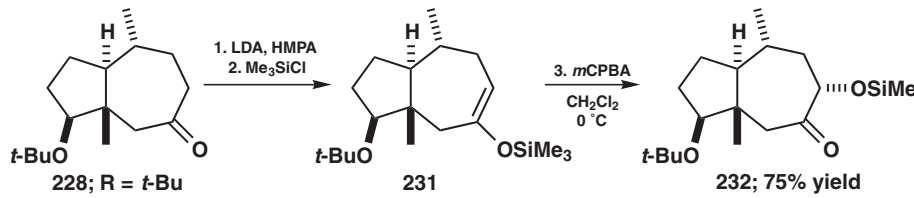
A dramatic example of selectivity comes in the approach to helenolides by Lansbury and Vacca.[36] Many sesquiterpenoids, such as **226**, have five-membered lactones fused onto larger rings and conjugation with an exomethylene group gives some anti-cancer properties. The exomethylene group can be added by Wittig and other reactions (see selenium chemistry earlier in the chapter). Lansbury and Vacca decided to explore the strategy of adding the lactone to a protected hydroxyketone having all the rest of the stereochemistry in place. They wanted methods for the disconnection **227** to **228**.



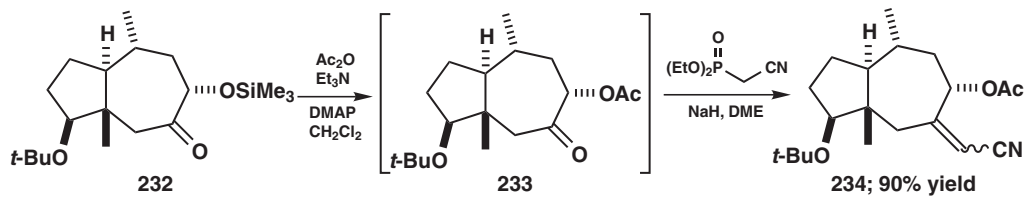
The idea was that the lactone **227** could come from **228** by the sequence: (i) stereo- and regioselective α-hydroxylation **229**, (ii) Wittig style reaction on the ketone to add the extra two carbon atoms **230**, (iii) stereoselective conjugate reduction of the double bond with the OH group directing the reagent to the bottom face of the alkene, and (iv) lactonisation.



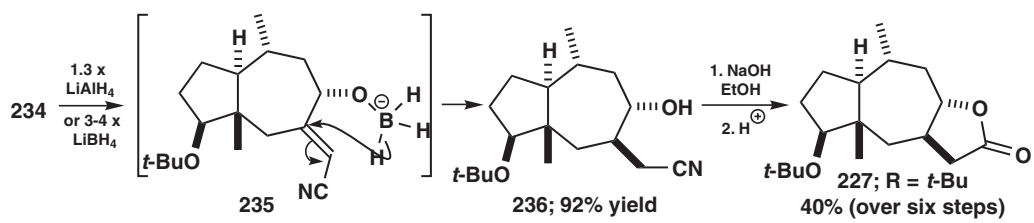
The reasons for the choice of reagent for each reaction are instructive. Epoxidation of a silyl enol ether was chosen for the hydroxylation for two reasons. It was known that the potentially difficult (the α-atom on both sides is primary) regioselectivity of enolisation of ketones **228** could be solved by using LDA and HMPA. The lithium enolate is formed away from the quaternary ring junction. Then epoxidation of related alkenes was known to go on the bottom face and the stereochemistry of the epoxidation determines the stereoselectivity of the hydroxylation **232**.



The unstable silyl ether in **232** was replaced by a more stable acetoxy ketone **233** which was not isolated. A Horner-Wadsworth-Emmons reaction was used for the Wittig-style olefination (chapter 15). A nitrile **234** replaced the carbonyl group in **230** as it was found easier to reduce nitriles in conjugative fashion.



The reduction step was stereoselective with either $LiAlH_4$ or $LiBH_4$. In both cases, the hydride reducing agent first cleaved the acetate ester and then an intermediate "ate" complex transferred hydride ion intramolecularly in a *cis* fashion **235** to the unsaturated nitrile to give the correct stereochemistry **236**. Finally cyclisation of the alcohol onto the nitrile to give the *trans* fused lactone **227** occurred in much the same way that nitriles are converted directly to ethyl esters with ethanol in acid solution. The overall yield of **227** was a respectable 40%.

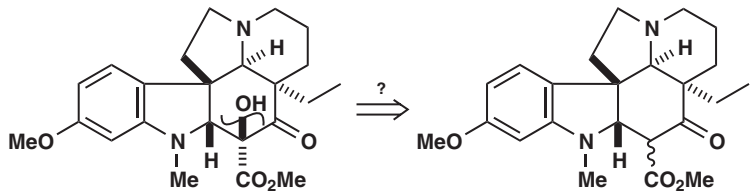


Hydroxylation of Amino-ketones via Silyl Enol Ethers

Synthesis of vinca alkaloids and model compounds

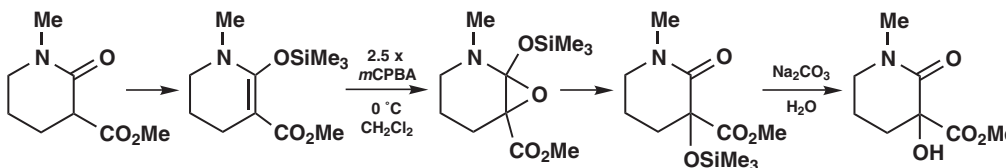
It would be a limitation of any of these methods if they could not be used with heterocyclic nitrogen compounds. This is a serious matter because amines are easily converted into *N*-oxides as we saw in the last chapter. The synthesis of the alkaloid vindoline **237** by Langlois raised this question.

Vindoline belongs to the *vinca* alkaloids, an important class of indole alkaloids whose dimers (such as vincadifformine) are anti-cancer compounds. The most difficult functionality in this compound is the tertiary α-hydroxyester and Langlois[37] proposed to make this by hydroxylation of the related keto-ester **238**.



237; vindoline **238**

There were two related questions of chemoselectivity to be answered here: would the amino groups in **238** be *too* reactive to survive the oxidation with *m*CPBA and would the rather stable silyl enol ether of the β-ketoester be reactive *enough* to be epoxidised? Langlois decided to conduct a trial experiment with the simple amino-β-ketoester **239** that contains all these features. If this is successful, there will still be the question of stereoselectivity. The silyl enol ether **240** was duly formed in the most stable position between the two carbonyl groups and epoxidation with an excess of *m*CPBA gave a good yield of the required α-hydroxyester **243** via the epoxide **241** and the silyl ether **242** which was desilylated in aqueous base without isolation.



239 **240** **241** **242** **243; 80% yield**

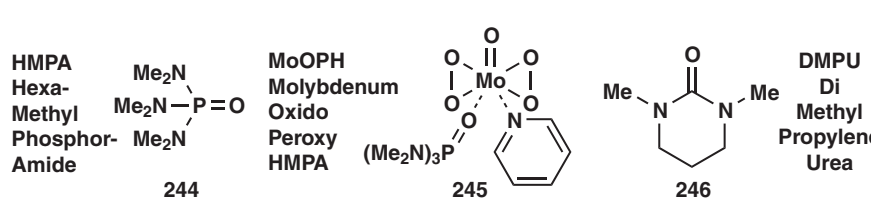
The same conditions were applied to the vindoline precursor **238** and the α-hydroxyester **237** was formed in an even better 89% yield as a single diastereoisomer with the hydroxyl group going in *syn* to the nearer ring junction hydrogen atom. This puts it on the *exo* face of the locally folded molecule. The synthesis of vindoline was completed from here.[38]

The epoxidation of silyl enol ethers is the oldest of the methods in this chapter but it works well and is still very much in use today. The reagents are simple and easy to use, rather unlike the one we are now going to meet.

Second Successful Method: Hydroxylation with MoOPH

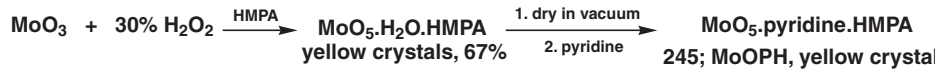
The reagent: hydroxylation of lithium enolates

MoOPH [pronounced "moof" and more correctly oxidoperoxymolybdenum(aqua)-(hexamethylphosphoric triamide)] is a molybdenum peroxide complex **245** that hydroxylates lithium enolates.[39]



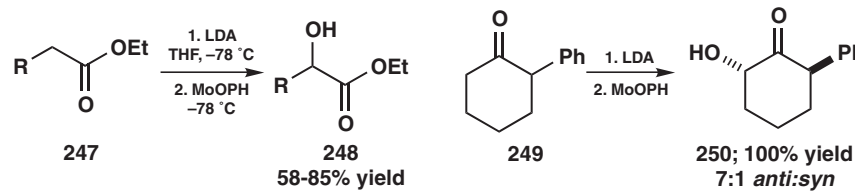
244 **245** **246**

It can be made by a simple process but unfortunately has to contain a molecule of carcinogenic HMPA **244** for stability. Versions with the safer DMPU **246** instead are not so effective. The crystals are best prepared just before use and are pale yellow when pure.[40]

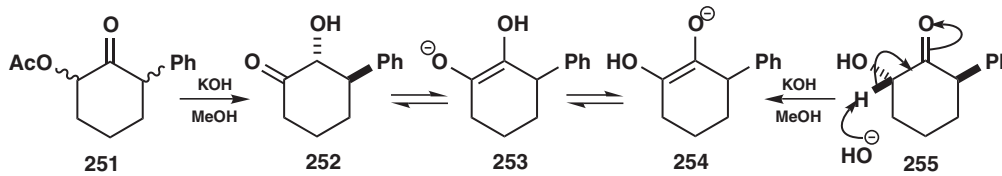


Stereoselectivity (substrate control)

In a typical reaction, the lithium enolate of the carbonyl compound **247** is prepared in the usual way and reacted with yellow MoOPH to give the hydroxylated product **248** and blue molybdenum compounds so that the reaction is self-indicating. The best feature of the method is that it uses lithium enolates since the regioselective preparation of these intermediates is much easier to control than that of other metal enolates. Hence 2-phenylcyclohexanone **249** gives a single regioisomer of the hydroxyketone **250** from kinetic enolisation with good stereoselectivity.

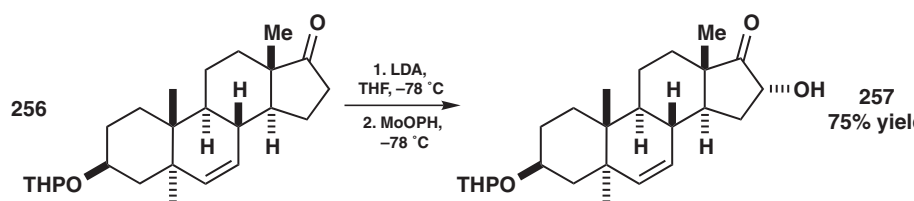


We have hinted in this chapter at the instability of some of these α-hydroxy carbonyl compounds and the hydroxylation of **249** unfolded some details of this problem. Compound **250** had been reported in 1960 from the hydrolysis of the ester **251** but the compounds produced by the two routes had different NMR spectra. The hydrolysis of the ester **251** actually gave a rearranged hydroxyketone **252**. The same product was formed on treatment of **250** with KOH. The instability arises if the carbon atom with the OH group also has a hydrogen atom and can therefore enolise **255**. The intermediate ene-diol (or its anion **254** or **253**) can re-protonate at either end of the double bond to give different ketones.

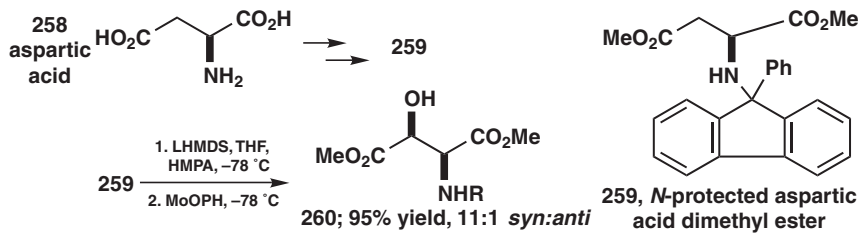


Hydroxylation of steroids and amino acids

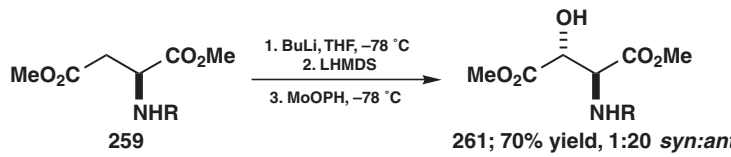
The message is that you should not treat α-hydroxy carbonyl compounds with base if they can enolise on the hydroxyl side. Because MoOPH is not an epoxidising agent, there is good chemoselectivity if the molecule also contains alkenes. This steroid example **256** shows that good yields and high stereoselectivity can be obtained.



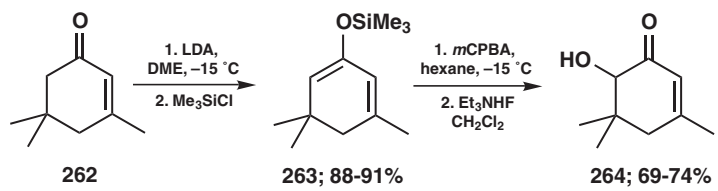
There is stereoselectivity here, as in the last example, and both are determined by the substrate, that is the molecule being hydroxylated. The reagent MoOPH is large and it attacks the less hindered side of the substrate under kinetic control. Some control can be achieved in the interesting hydroxylation of aspartic acid enolates.[41] The lithium enolate of the dimethyl ester of N-protected aspartic acid **259** gives high *syn* selectivity in hydroxylation next to only one of the two ester groups **260**.



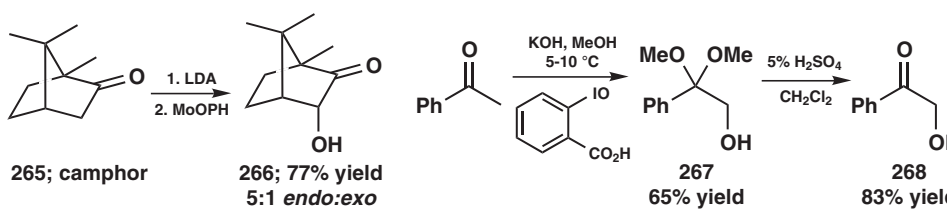
If **259** is first treated with BuLi and then turned into the lithium enolate and reacted with MoOPH, a good yield of the other diastereoisomer, *anti*-**261** is formed. The first result is probably hydroxylation opposite the very large NHR group in a Houk conformation of the enolate (chapter 21) while *anti*-selective hydroxylation probably results from chelation control.



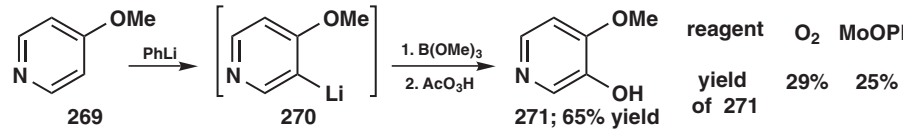
The popularity of MoOPH has waned with the discovery of the next type of reagents for hydroxylations. These *N*-sulfonyl oxaziridines should now probably be your first choice. In the 1986 volume of *Organic Syntheses* three recipes for hydroxylation of enolates stand side by side. Rubottom[42] describes the formation of the kinetic lithium enolate of the enone **262** and the oxidation of the silyl enol ether **263** with *m*CPBA to give the α' product **264** (see chapter 11 for the regioselectivity of such extended enolates).



Vedejs and Larsen[43] describe the preparation of MoOPH and the hydroxylation of the lithium enolate of camphor **265** to give a good yield of a 5:1 ratio of *endo:exo* alcohols **266** while Moriarty[44] gives an example of a method we have not discussed, the hydroxylation of potassium enolates with *o*-iodosobenzoic acid.



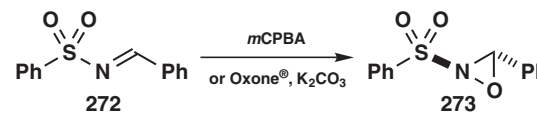
MoOPH is less effective than the boron method for oxidation of aromatic enolates too. In a similar comparison the pyridine **269** was lithiated and treated with oxygen, MoOPH, or the boronate sequence to give the hydroxypyridine **271**. The results are very clear.[45]



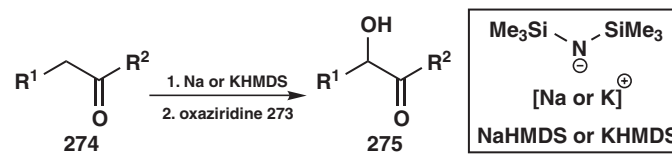
Third Successful Method: Hydroxylation with *N*-Sulfonyl Oxaziridines

The reagents and the mechanism

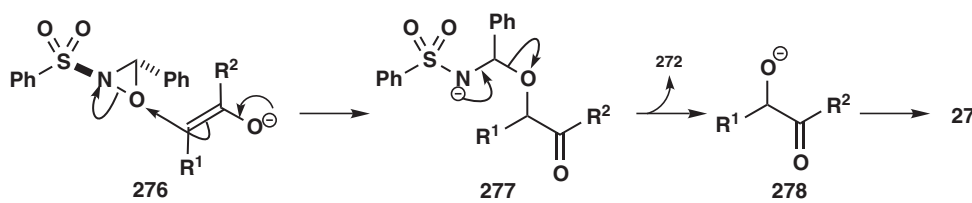
These reagents contain a three-membered ring made up of C, N, and O atoms - an oxaziridine. The nitrogen atom must be a sulfonamide (usually a benzene sulfonamide) and the carbon atom usually has some substituent. The simplest such reagent **273** is formed by epoxidation of *N*-phenylsulfonyl benzaldehyde imine **272** with mCPBA or Oxone®, a persulfate potassium salt $2KHSO_5.KHSO_4.K_2SO_4$.



This compound **273** is a single diastereoisomer and one of the two stereogenic centres is the nitrogen atom. Nitrogen normally inverts too quickly to be stereogenic but in a three-membered ring and with an electronegative substituent, inversion through the unfavourable trigonal nitrogen atom is very slow. It reacts with sodium or potassium enolates to give products of α-hydroxylation.[46]

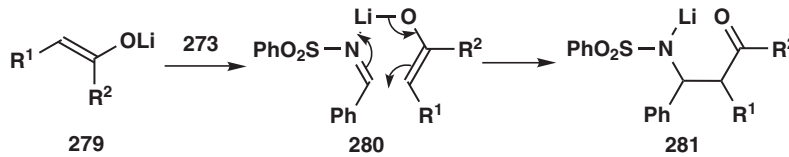


The enolate attacks the oxygen atom of **273** in an unusual S_N2 reaction at oxygen **276**. The leaving group is the sulfonamide anion, which is why a sulfonamide is necessary. The anion returns **277** to form the original imine **272** and ejects the anion **278** of the α-hydroxy-carbonyl compound **275**.



Hydroxylation of sodium and potassium enolates: side reaction with lithium

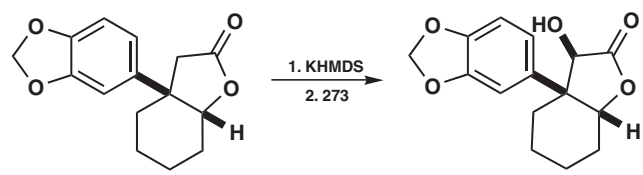
Lithium enolates **279** do give α-hydroxy-carbonyl compounds but there is a significant side reaction that is a kind of aldol reaction on the imine product **272** through a six-membered cyclic transition state **280** like those we used to explain the stereoselectivity of aldol reactions in chapter 4. Hence the Na or K disilazide bases NaHMDS or KHMDS are usually used.



279 **280** **281**

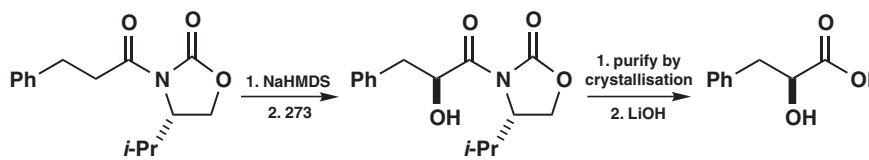
Substrate controlled stereoselectivity: asymmetric hydroxylation

Though the reagent **273** does have stereochemistry it does not transmit it to the product and the stereoselectivity of the reaction is under substrate control. Folded molecules like the lactone **282** react on the outside as expected to give the *exo*-product **283**.



282 **283**

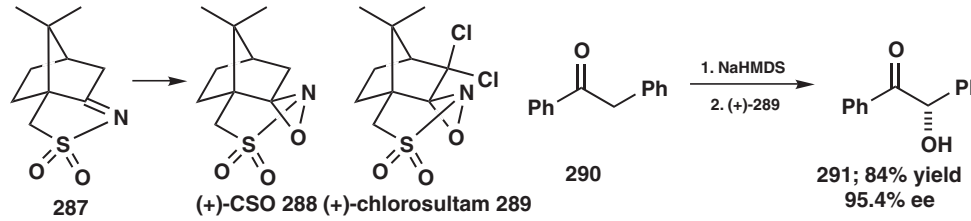
Good asymmetric induction occurs with the Evans valine-derived chiral auxiliary (as in **284**, see chapter 27) which reacts in alkylation style on the face of the enolate away from the *i*-Pr group. The products **285** give α-hydroxy-acids **286** on hydrolysis.



284 **285; 85% yield** **95:5 diastereoisomers** **286**

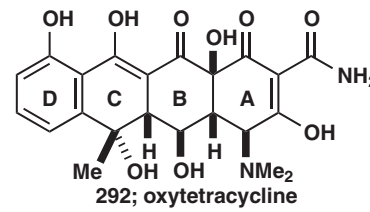
Asymmetric hydroxylation with camphor sultam derivatives

For asymmetric hydroxylation of enolates it is necessary to provide more permanent asymmetry than is found in **273**. The most successful reagents so far have been the (camphorsulfonyl) oxaziridines such as (+)-CSO **288**. Since both enantiomers of camphor are available and the formation of Oppolzer's chiral sultam (chapter 27) makes chemistry such as **265** → **287** familiar, these are reagents of some appeal. Derivatives with extra chlorine **289** or methoxy substituents are also available. Epoxidation of the imine **287** occurs exclusively on the lower face to give **288** and hence creates two new stereogenic centres (C and N in the oxaziridine ring) but it is the chirality of the bicyclic camphor system supported by the asymmetric position of the polar sulfone group that leads to successful induction. Hydroxylation of the simple ketone **290** with the chlorosultam **289** gives **291** with high ee.

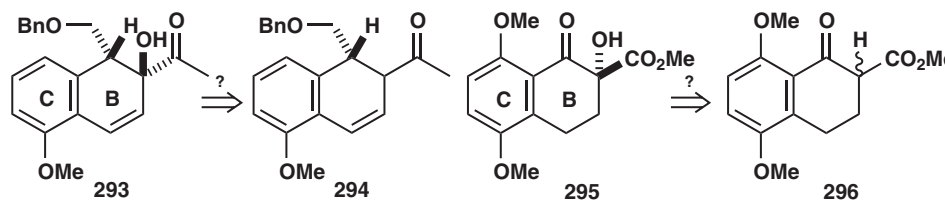


Asymmetric synthesis of tetracycline precursors

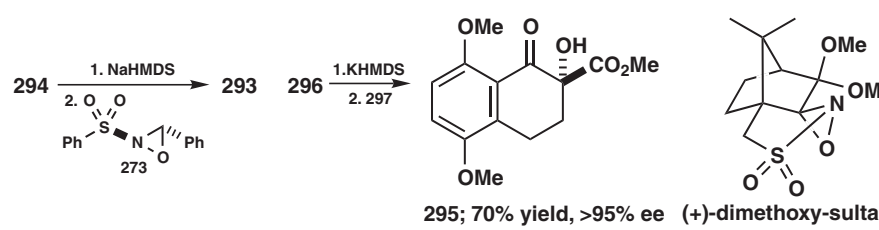
Strategies for producing optically active α-hydroxy-carbonyl compounds by hydroxylation with oxaziridines depend on whether enantio- or diastereo-selectivity is required. The synthesis of precursors for the antibiotic tetracyclines is a good illustration. These compounds, e.g. **292**, have four rings A-D, hence "tetracyclines". Ring D is usually aromatic but rings A–C have a variety of oxygenated functionality and stereochemistry. These two features come together at the A/B ring junction where there is a difficult tertiary α-hydroxy-carbonyl unit.



One strategy for tetracycline synthesis is to build a B/C precursor with suitable functionality for extension to ring A and with the tertiary α-hydroxy-carbonyl unit already in place. Two potential starting materials for different tetracyclines are **293** and **295** and both might be made by α-hydroxylation of enolates.

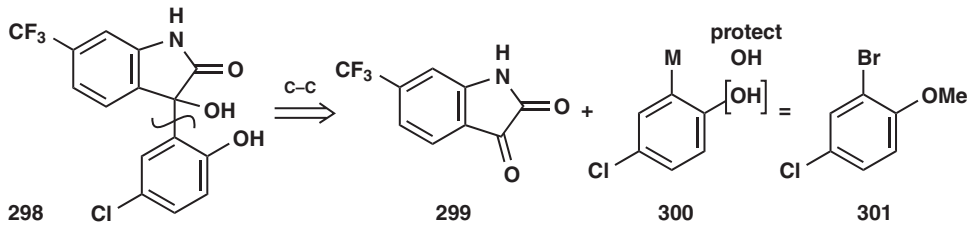


Both precursors **294** and **296** are chiral but the chirality of **296** lies at an enolisable centre between two carbonyl groups and the enolate, the intermediate in hydroxylation, is only prochiral. It makes sense therefore to use racemic **296** with the correct optically active sultam **297** to make **295** by asymmetric hydroxylation[47] but to use optically active precursor **294** with racemic sultam **273** in diastereoselective hydroxylation[48] (54% yield).

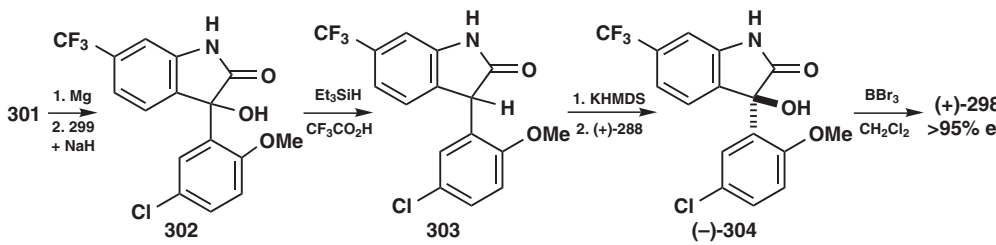


Synthesis of a calcium channel opening drug

The Bristol-Meyers Squibb calcium channel opener **298** can clearly be made by addition of some protected organometallic derivative **300** to the isatin **299**. In fact this is easily done with a Grignard reagent from **301** with an OMe group at the phenolic position. In the synthesis (below) a preliminary treatment of **299** with NaH was needed before addition of the Grignard reagent

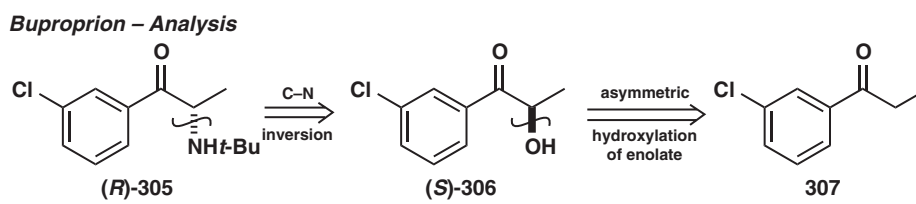


The chemists at B-MS were faced with the problem of determining the biological activity of both enantiomers of the drug. The availability of both enantiomers (from both enantiomers of camphor) of the Davies oxaziridine **288** made it worthwhile to remove the OH group from **302** and put it back again.[49] Protected **302** was reduced with Et_3SiH and TFA, a reagent that reduces alcohols that easily form cations, to **303**. Then this was enantiospecifically hydroxylated with each enantiomer of **288** to give, after deprotection with BBr_3, the two enantiomers of the drug **298**.

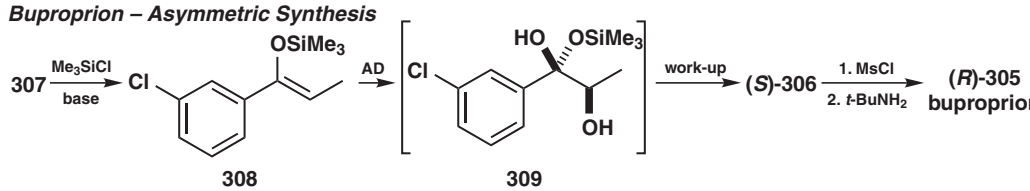


Asymmetric synthesis of buproprion

While a drug is being evaluated, it is necessary to prepare both enantiomers. When you know which enantiomer you want, you need an asymmetric (and preferably catalytic) synthesis. GlaxoSmithKline's anti-depressant drug buproprion[50] **305** provides an excellent example. This simple compound is needed as the (*R*)-enantiomer and can obviously be made by S_N2 displacement (with inversion) on some derivative of the (*S*)-alcohol **306**. Asymmetric hydroxylation of the enolate of the simple aryl ketone **307** should answer.



A chiral oxaziridine could have been used but the company prefers a catalytic method: the asymmetric dihydroxylation (chapter 25) of the silyl enol ether **308**. Presumably the diol **309** is formed but the hemiacetal collapses on workup and the mesylate of (*R*)-**306** allows displacement with *t*-$BuNH_2$ and the synthesis of buprion **307**.



Summary

Electrophilic substitution of pyridines (chapter 32) and the hydroxylation of aromatic compounds and enol(ate)s (this chapter) are now useful and flexible reactions that can be made to work on a variety of compounds with all the necessary selectivity. Functionalisation as a strategy - that is the removal of functionality during analysis - can be difficult to find during the disconnection process as one naturally tends to be thinking of making rapid progress in simplification by carbon–carbon disconnections. The secret is to keep it in the mind alongside the FGA strategy and ask the question: would this synthesis be easier if I either removed (functionalisation strategy) or added (FGA strategy) a functional group to the target molecule? A comprehensive review[51] of this topic appeared in 2003.

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General references are given on page 893

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34 Functionality and Pericyclic Reactions: Nitrogen Heterocycles by Cycloadditions and Sigmatropic Rearrangements

This chapter considers the effect of nitrogen atoms on Diels-Alder reactions, [3,3]-sigmatropic rearrangements such as the Aza-Cope, group transfer reactions such as the Alder Ene reaction and other pericyclic processes

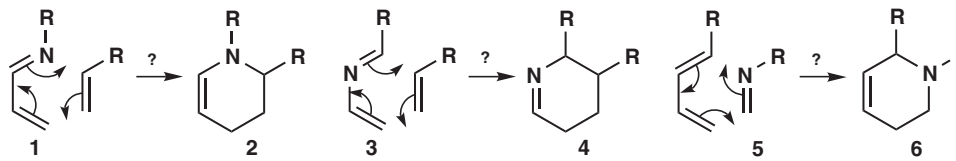
Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

Part I – Introduction

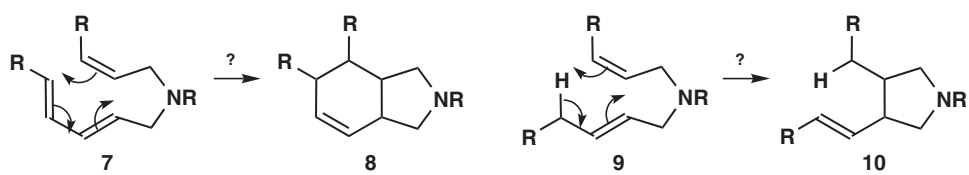
The Effects of Functionality on Pericyclic Reactions

Cycloadditions: The Diels-Alder and the Alder 'ene' reactions

Our understanding of pericyclic reactions is ultimately based on Woodward and Hoffmann's analysis of orbital symmetry. This chapter considers the consequences of inserting functionality into a pericyclic reaction so that the symmetry of at least one component is perturbed. For example, a nitrogen atom could be part of the diene in a Diels-Alder reaction in two ways: we could have a 1- or a 2- 'azadiene' (**1** or **3**). If the reaction is successful the product in both cases (**2** or **4**) would be a nitrogen heterocycle. Alternatively, we could use an imine **5** as the dienophile. Again, assuming that the reaction works, the product is a nitrogen heterocycle. In fact, as we shall see later, the influence of the added nitrogen atom is pernicious and none of these three reactions works very well with these simple compounds. This chapter will discuss what effects such functionality has on pericyclic reactions and how the difficulties can be overcome.[1]



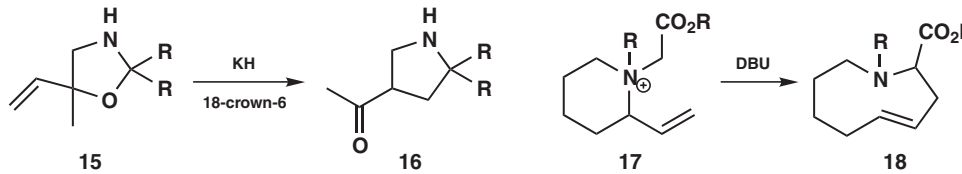
To limit the scope of the discussion and also to give it a useful synthetic focus, we shall consider only those reactions that lead to heterocyclic nitrogen compounds. These products may be aromatic but will more usually be partly saturated so there will be a good deal of stereochemistry and some asymmetric synthesis. We shall therefore also discuss reactions in which the nitrogen atom is not part of the pericyclic process as such but influences it strongly by being part of a tether. The regio- and stereo-selectivity in Diels-Alder reactions such as the cyclisation of **7** is largely controlled by the length and position of the tether so the functional group does influence the pericyclic process. The Alder 'ene' reaction **9** is a 'group transfer' reaction closely related to the Diels-Alder reaction but with a C–H bond in place of one of the alkenes in the diene. This reaction does not of itself close a ring so once again a nitrogen tether will be necessary if a heterocycle **10** is to be formed.



[3,3] and [2,3]Sigmatropic rearrangements: the aza Cope rearrangement

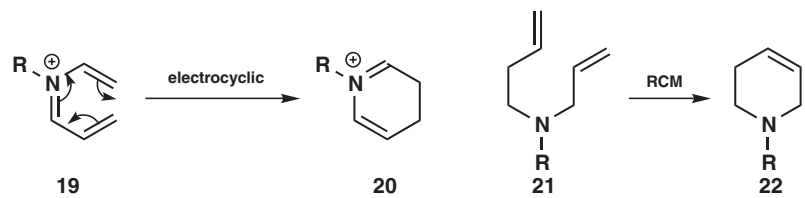
Typical [3,3] sigmatropic rearrangements include the Claisen and Cope rearrangements. The 'aza-Cope' is a [3,3] sigmatropic rearrangement with a nitrogen atom in one of two possible positions **11** or **13**. In neither case is a ring of any kind formed in this reaction but in both cases the product is a rather unstable imine and further ionic reactions may lead to heterocycles.

The tandem reactions in which the aza-Cope is followed by an ionic C–C bond-forming second step are often carried out on anions or cations. Here is an anionic example **15** to **16** we shall be discussing later in the chapter. Some of the most dramatic [2,3] sigmatropic rearrangements have been of nitrogen ylids undergoing ring expansion to give medium rings. We shall discuss the ring expansion of **17** to give a nine-membered cyclic amine **18** by [2,3] rearrangement of an ylid later.



Other pericyclic processes giving nitrogen heterocycles

The chapter ends with a rather miscellaneous collection of reactions such as one example of an electrocyclic ring closure **19** . There are more important examples of ring closing olefin metathesis (RCM) and other organometallic reactions such as the Pauson-Khand reaction and co-trimerisation.

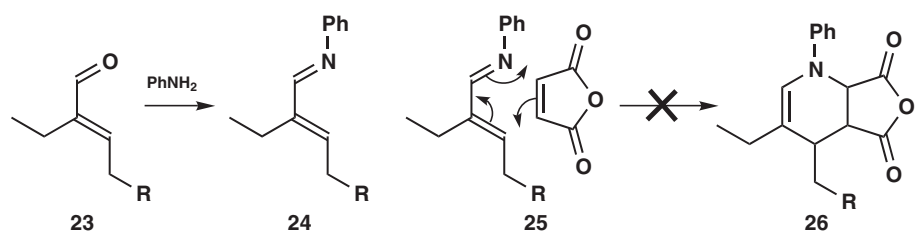


Part II– Cycloadditions to Make Nitrogen Heterocycles

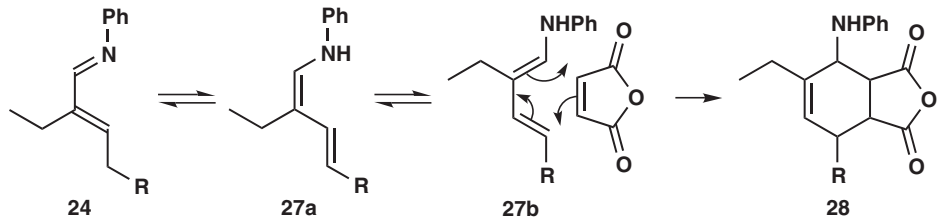
Diels-Alder Reactions with Azadienes

Problems with the Diels-Alder reactions with azadienes

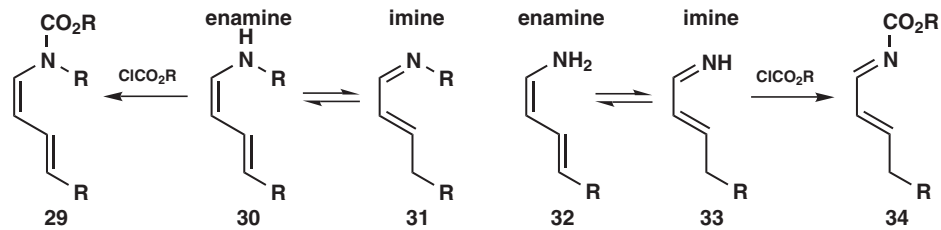
1-Azadienes **24** are easily made from amines and enals such as **23** . The Diels-Alder reaction of **24** with maleic anhydride looks very attractive **25** and you might expect **26** to be the product.



Unfortunately the nitrogen atom lowers the HOMO energy of the diene **24** and it is not a good match with the LUMO of maleic anhydride. Instead the imine **24** is in equilibrium with the enamine **27** and, in conformation **27b**, this has a high energy HOMO and so the product[2] of the reaction is **28**. The tautomerism between **24** and **27** may be especially easy as it can be drawn as a [1,5]H sigmatropic shift. This conflict between weakly electrophilic imines and their tautomers, the nucleophilic enamines, is one of the themes of this chapter.[1]



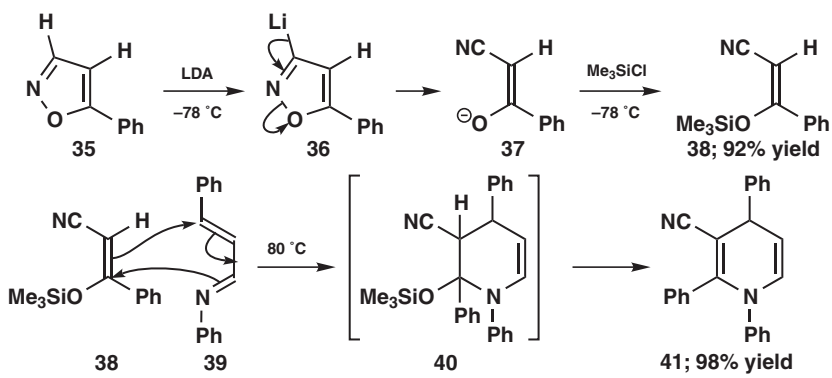
One solution to the imine/enamine equilibrium is to load the nitrogen atom with a removable acyl group. Popular choices are urethanes and sulfonamides. If the nitrogen atom is unsubstituted **32**, the imine **33** is favoured by conjugation but if the nitrogen is substituted **31**, it is forced to give the enamine **29**.



There is a further disadvantage in using simple Diels-Alder reaction of azadienes to make heterocycles. The products, e.g. **2** and **4** are themselves either imines or enamines and are inherently unstable and it is also necessary to stabilise them to make isolation of the heterocycle possible.

Stable 1-azadienes

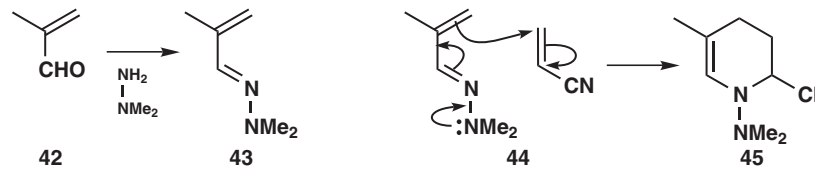
Among the few examples of simple 1-azadiene Diels-Alder reactions is a dihydropyridine synthesis using the stable azadiene **39** (prepared from cinnamaldehyde and aniline) with the dienophile **38** prepared from the isoxazole **35** by elimination. This is a reverse-electron-demand cycloaddition, the HOMO of the dienophile **38** combining with the LUMO of the azadiene **39** to give the cycloadduct **40** and hence the dihydropyridine **41** with complete regioselectivity and in very high yield.[3]



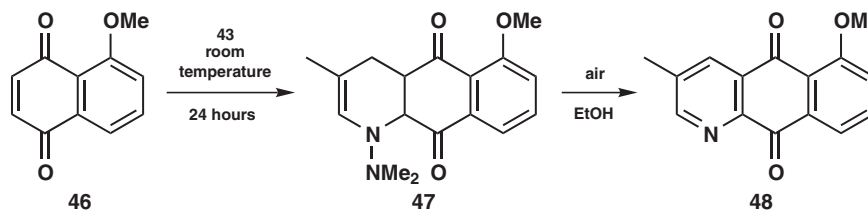
Other dienes, even cyclopentadiene, perform poorly with this dienophile **38** but the azadiene **39** that does so well here is a very special case. It is stabilised by the phenyl groups at both ends of the molecule and it cannot tautomerise into an enamine. More generally useful 1-azadienes must be stabilised by conjugating substituents that are definitely electron-donating or withdrawing so that the HOMO or the LUMO is unambiguously selected for cycloaddition.

Stable nucleophilic 1-azadienes (HOMO used in cycloadditions)

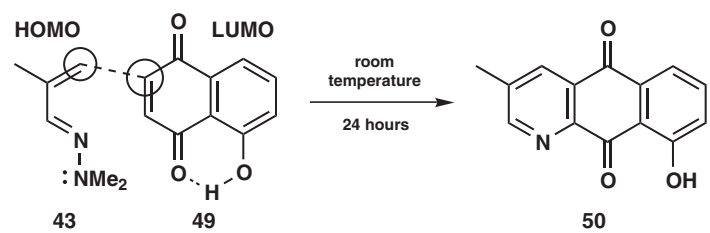
Ghosez used hydrazones **35** for this purpose. The regioselectivity shows that the NMe_2 group dominates the HOMO of the diene in reaction with the LUMO of dienophiles such as acrylonitrile. The arrows on the mechanism **44** show the nucleophilic end of the diene **43** interacting with the electrophilic end of acrylonitrile. The cycloaddition may or may not be concerted.[4]



Though the NMe_2 group can be reductively removed from **45**, it has generally been more valuable to convert the products into pyridines by elimination and oxidation. Reaction of the same diene **43** with the unsymmetrical naphthaquinone **46** gave a single regioisomer of **48** after treatment of the unstable adduct **47** with refluxing ethanol.[5]



If the substituent is OH instead of OMe, hydrogen bonding to one of the carbonyl groups of the naphthaquinone **49** reverses the coefficients in the LUMO and the opposite regioselectivity is found in the product **50**.

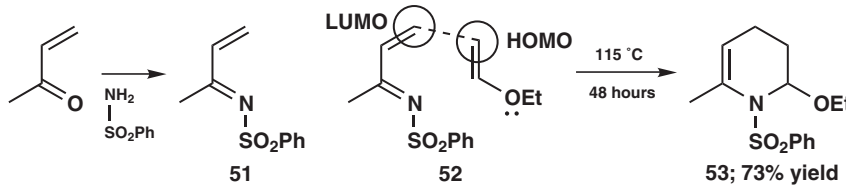


In all these examples the 1-azadiene is stabilised by being a hydrazone, but most published examples cannot tautomerise to enamines as they do not have proton-bearing substituents in the right position.

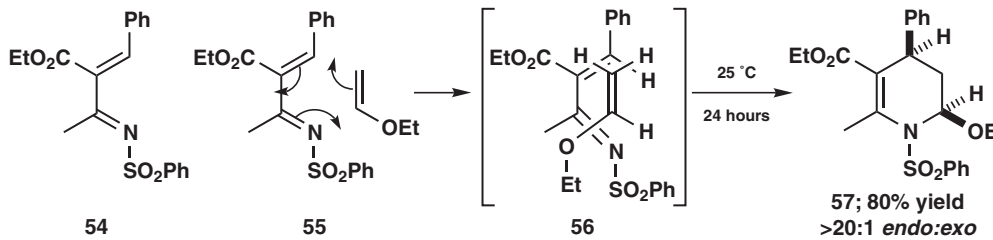
Stable electrophilic 1-azadienes (LUMO used in cycloadditions)

Sulfonamides are the most widely used electrophilic 1-azadienes, e.g. **51**, and they react with electron-rich dienophiles such as enol ethers in reverse electron demand Diels-Alder reactions.[6]

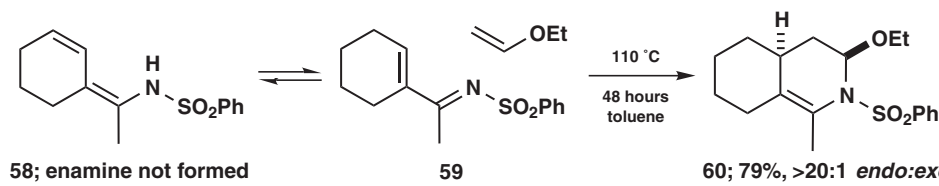
The LUMO of the diene **51**, activated by the imine, interacts **52** with the high energy HOMO of the enol ether to accelerate the reaction and determine the regioselectivity of the cycloadduct **53**.



Addition of another electron-withdrawing group to the azadiene (the ester in **54**) lowers the LUMO energy even more and the reaction **55** can now be run at room temperature (though pressure helps) with perfect regioselectivity **57** and good *endo:exo* stereoselectivity from the interaction of the OEt group with the back of the diene **56**.

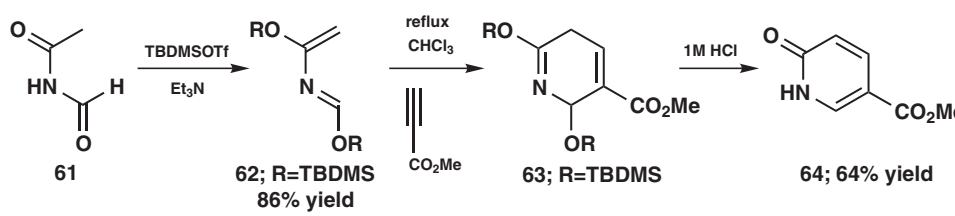


More impressively, azadienes, such as **59**, that could tautomerise to enamines **58** also give good yields of adducts **60** with high regioselectivity and *endo* stereoselectivity. 1-Azadienes are still not easy to use but enough methods are now available to make heterocycle synthesis by this route a practical proposition.

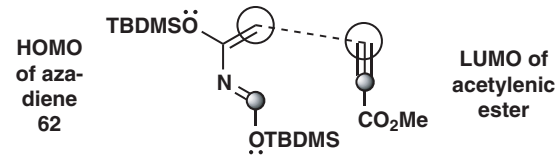


Diels-Alder reactions with 2-azadienes

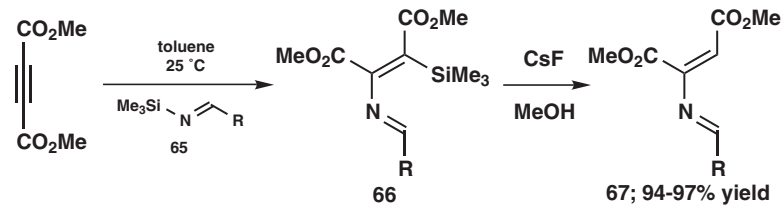
The same problems arise with 2-azadienes and Ghosez[7] has solved them by loading the dienes with strongly electron-donating or withdrawing groups. The imide **61** was doubly silylated to give a 2-aza-diene **62** that cannot tautomerise to an enamine. It adds regioselectively to an acetylenic ester to give a pyridone **64** after an acidic work-up that hydrolyses the silyl-imino ether of **63** and catalyses the aromatisation by loss of the other silyl ether.



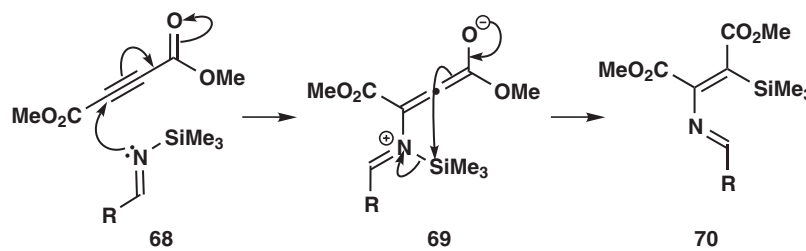
The regioselectivity of the addition is determined by the HOMO of the azadiene **62** which is dominated by the two electron-donating silyloxy groups. The nitrogen atom is almost irrelevant. The LUMO of the unsaturated ester is typical for any Diels-Alder reaction.



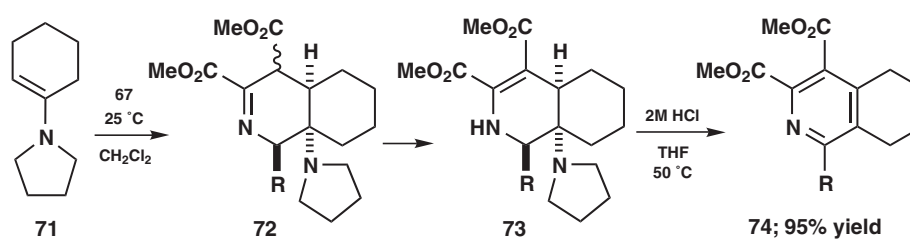
For a reverse electron-demand Diels-Alder with azadienes, Barluenga[8] reacted stable silylated imines **65** of unenolisable aldehydes (R = Ar or cinnamyl) with acetylene dicarboxylic esters to give the 2-azadienes **67**.



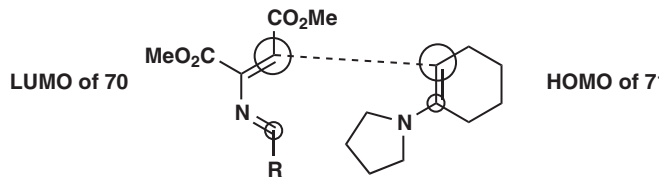
The imine nitrogen must attack the acetylene **68** and the resulting enolate desilylate the imine cation **69** to trap the diene as **70**. No tautomerism to an enamine is possible. This intermediate is desilylated with fluoride to give the diene **67** in remarkably good yield.



These dienes **70** have three electron-withdrawing groups, the imine and two esters, and react with electron-donating enamines, e.g. **71**, to give pyridines **74**, again in excellent yield, after an acidic work-up that tautomerises the initially formed imine **72** to the stable conjugated enamine **73** and then eliminates the amine used to make the enamine. The final oxidative aromatisation is spontaneous in air.

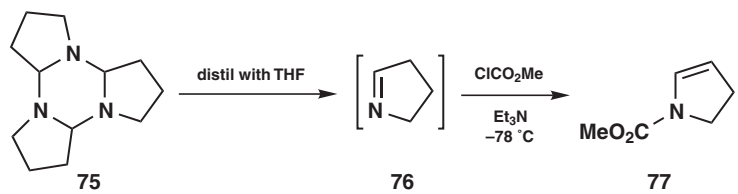


The regiochemistry of the cycloaddition is curious. The imine and the terminal ester groups direct to one end but the middle ester group dominates and directs the enamine to the other end. The diene LUMO evidently has its largest coefficient as shown, and seems again to ignore the imine, though whether this is a concerted cycloaddition or a two-step ionic reaction is uncertain.

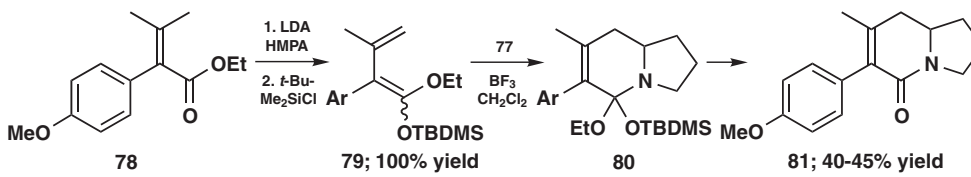


Diels-Alder Reactions with Imines

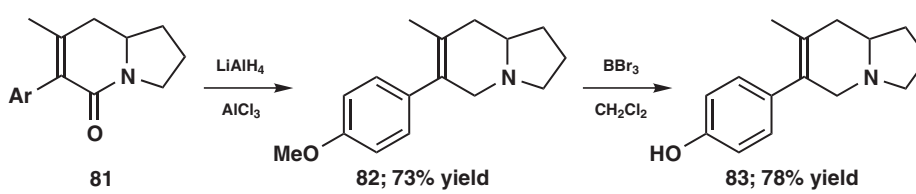
The other side of the coin is a Diels-Alder reaction between an ordinary diene and an imine.[9] Here the problem is the instability of the imine. An ingenious solution was found by Kraus[10] who distilled a THF solution of the trimer **75** into a flask cooled to −78 °C. The imine **76** was stable at that temperature and could be converted into the stable acylated enamine **77**.



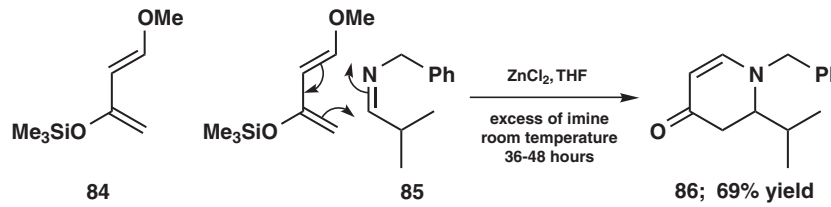
When Danishefsky[11] set out to synthesise ipalbidine **83**, a Diels-Alder reaction of this imine **77** was an obvious approach. To get efficient reaction, it was necessary to use a diene **79** activated by two electron-donating ethers and to activate the imine with a Lewis acid. The orientation of **81** is as expected from the LUMO of the imine reacting with the HOMO of the diene.



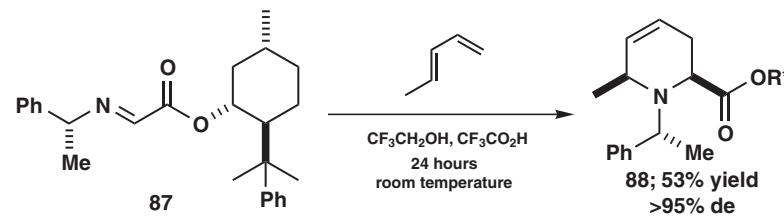
Conversion into ipalbidine **83** required reduction of the lactam **81** and demethylation of the aryl methyl ether **82**. Though the yield in the cycloaddition was poor, this is a short synthesis.



Even simple imines can be used if the diene is activated enough and Danishefsky's diene **84** is nucleophilic enough to combine with simple imines with Lewis acid catalysis. This example **85** could tautomerise to an enamine but the imine, especially as its $ZnCl_2$ complex, reacts better with such a nucleophilic diene.[12]

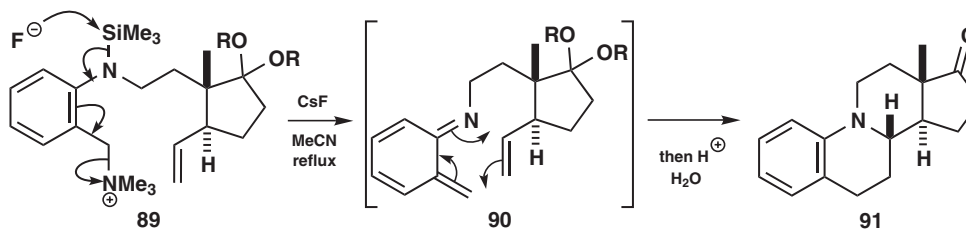


From the many examples of reactions with imines activated in various ways, we select the asymmetric synthesis of pipecolic acids by double diastereomeric induction using an activated imine **87** with two chiral auxiliaries - α-methylbenzylamine on the nitrogen atom and 8-phenylmenthol as esterifying group. Both these auxiliaries were discussed in earlier chapters (22 and 27). Acid-catalysed cycloaddition with normal dienes gives excellent asymmetric induction and reasonable yield. We show the matched case - the mismatched case is obviously worse.[13]



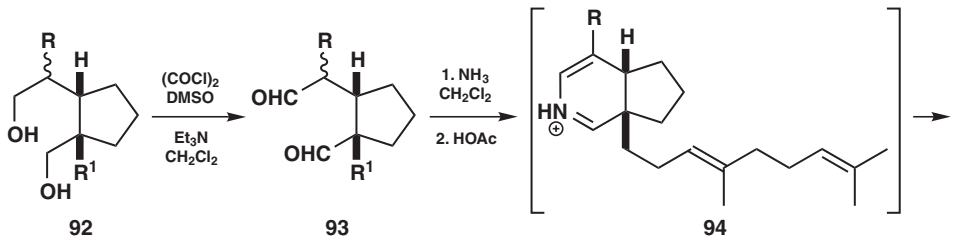
Intramolecular Diels-Alder Reactions with Azadienes

One sure way to make the hetero Diels-Alder reaction go well and with regio-and stereoselectivity is to make it intramolecular.[14] The highly reactive diene **90** is formed by elimination with fluoride ion from **89**. The cycloaddition is rapid because it restores aromaticity. The regioselectivity is as expected from HOMO of dienophile plus LUMO of diene but is probably controlled by the tether.[15] The stereochemistry certainly is: the azadiene is attached to the bottom face of the five-membered ring and is delivered to the bottom face of the dienophile to give the all-*trans* 'aza-oestrone' **91**.



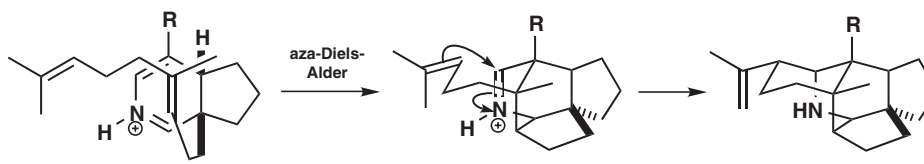
Heathcock has used a remarkable cascade of reactions, including an intramolecular Diels-Alder reaction of a protonated 2-aza-diene, in the synthesis of *Daphniphyllum* alkaloids. We give one example. The diol **92** gives the unstable dialdehyde **93** by Swern oxidation and hence the protonated

azadiene **94** by reaction with ammonia. As one of the aldehydes in **93** is joined to a quaternary centre and cannot form an enamine, only one such azadiene can be formed. But now that you can see the side chain 'R[1]', what happens to **94**? Several pericyclic reactions are possible.



92 93 94

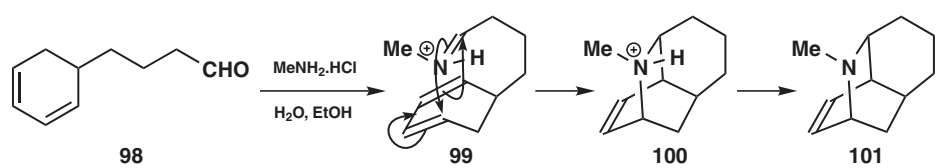
The product is the cage amine **97**. The azadiene must cycloadd to the nearer of the two unactivated alkenes in the conformation **95** (mechanism not shown for clarity). Though the regioselectivity is what we should expect from the HOMO of the dienophile and the LUMO of the protonated 2-azadiene, the short tether (two saturated carbon atoms) is probably responsible. It is certainly responsible for the stereochemistry as the tether delivers the dienophile to the top face of the diene.[16] The product **96** cyclises by addition of the remaining alkene to the immonium ion to give **97**. We shall see more of these tandem sequences later in the sections on sigmatropic rearrangements.



95 96 97

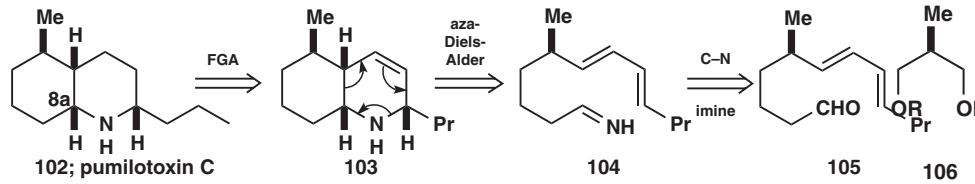
Intramolecular Diels-Alder Reactions with Imines

Simple imines give good yields of intramolecular Diels-Alder reactions providing always that the second ring formed is stable and that usually means five- or six-membered. Grieco has developed a simple method whereby an aldehyde, also containing a remote diene, is combined with an amine in acidic solution. The immonium ion cannot usually be isolated as cycloaddition **99** is rapid. A simple example **98** gives the tricyclic amine[17] **101**

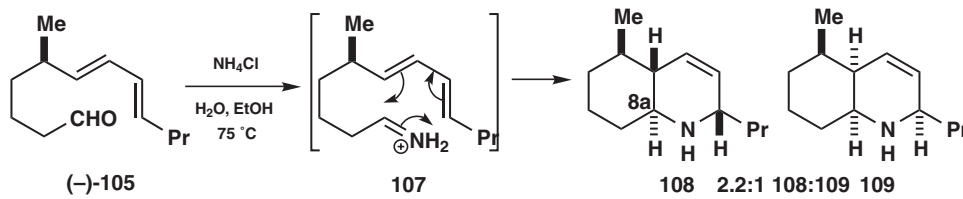


98 99 100 101

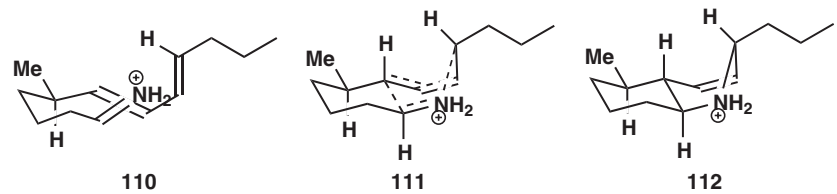
This reaction is obviously useful for the synthesis of hydroquinolines and compounds such as pumiliotoxin C **102**. The aza-Diels-Alder disconnection **103** requires a preliminary FGA. The required aldehyde **105** was made from the known enantiomerically pure **106**.



When the reaction was carried out by treating the aldehyde (−)-**105** with ammonium chloride, the cycloaddition took place under quite mild conditions (75 °C in aqueous ethanol) with complete regiochemical control but gave a mixture of two diastereoisomers **108** and **109** in a 70:30 ratio but none of the right isomer for the pumiliotoxin synthesis.[17] The major product **108** has three of the chiral centres correct but is epimeric with pumiliotoxin C **102** at C-8a. Grieco has used this reaction successfully for other alkaloids.[18]

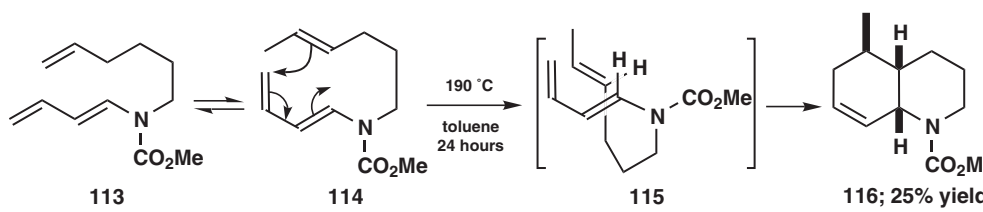


This result shows both the strengths and the weaknesses of such intramolecular aza-Diels-Alder reactions. The stereochemical outcome is controlled by the tether and such considerations as *endo/exo* selectivity matter very little. The molecule must fold **110** so that the preferred transition state **111** has the newly formed *carbo*cyclic ring (not the ring formed by the cycloaddition itself) in the best chair conformation **112**. The reaction is useful only if you want the stereochemistry it naturally gives.

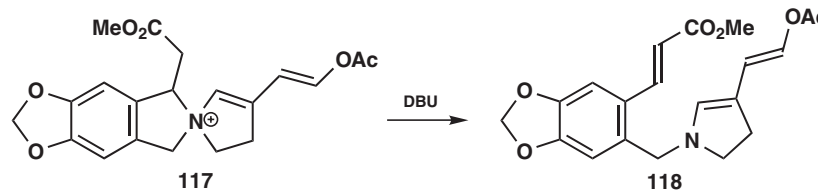


Intramolecular Diels-Alder Reactions with a Nitrogen Tether

The last example shows how intramolecular Diels-Alder reactions can produce two rings simultaneously. A simple Diels-Alder reaction (i.e. not 'aza') with a nitrogen atom in the tether simply switches the two rings round: now two new bonds in the carbocyclic ring are made by the cycloaddition while one of them also completes the heterocyclic ring. In simple examples both the regio- and stereochemistry is controlled by the tether: the carbamate-stabilised enamine **113** gives only the *cis* ring junction **116** via an *endo*-like transition state **115**. This time the relative stereochemistry *is* correct for pumiliotoxin C **102** though the yield is poor.[19]

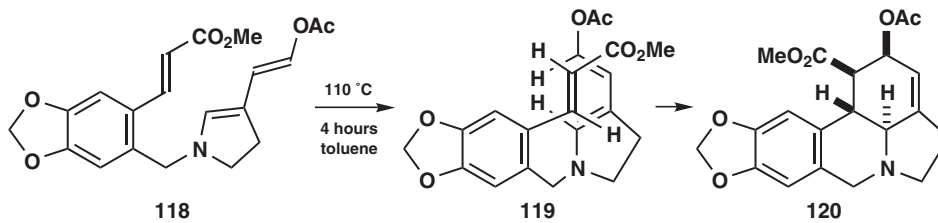


There are many examples of such reactions being used in synthesis. Often many new chiral centres are established in one step as in the lycorine synthesis of Boeckmann.[20] The starting material **118** is prepared by elimination on the spirocyclic ammonium salt **117** and contains no 3D stereochemistry.



117 118

Cycloaddition gives a single diastereoisomer of adduct **120** with four new chiral centres. The molecule **118** must fold **119** so that the ester group is indeed *endo* to the diene but that, and the regioselectivity, are mainly due to the very short tether - just one CH_2 group between two rigid rings. The product **120** is a late intermediate in a synthesis of lycorane.

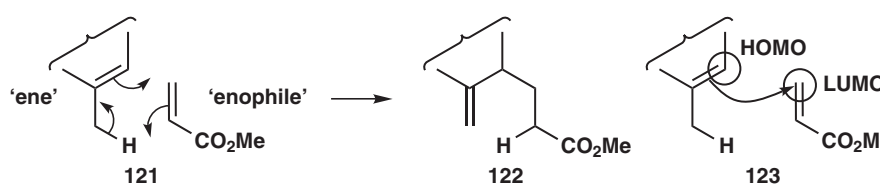


118 119 120

Part III – 'Ene' Reactions to Make Nitrogen Heterocycles

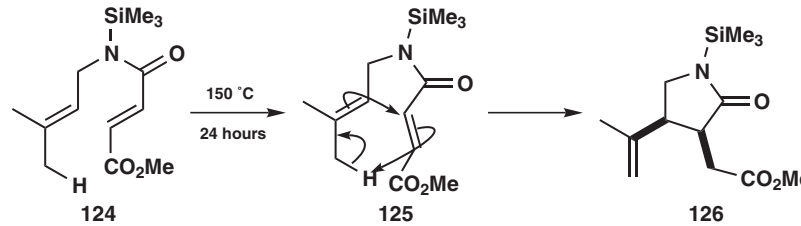
Intramolecular Alder 'Ene' Reactions with a Nitrogen Tether

The Alder 'ene' reaction is like a Diels Alder reaction in which one π-bond in the diene has been replaced by a C–H bond **121**. It does not therefore form a ring and does not fit easily into any of the three classes of pericyclic reaction (cycloaddition, electrocyclic, and sigmatropic). Since a hydrogen atom is transferred from one component to the other it is best described as a 'group transfer' reaction.[21] The regioselectivity is determined by the interaction **123** with the π-bond of the 'ene' (the HOMO) with the LUMO of the 'enophile.'



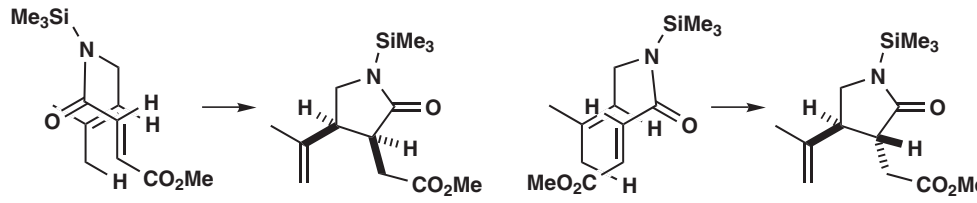
121 122 123

The 'ene' reaction forms a heterocyclic ring if the two components are tethered by a nitrogen atom. Simple examples described by Oppolzer and Snieckus show that there is some kinetic preference for the '*endo*' product. After 24 hours at 150 °C, the *syn* product **126** is the only one from the intramolecular 'ene' reaction[22] **125**.



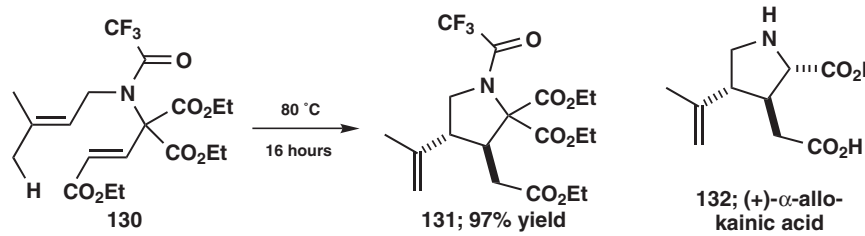
124 **125** **126**

If the reaction mixture, or compound **124** alone, is heated to >250 °C, the more stable *anti* isomer **129** is the only product. Though there are two carbonyl groups conjugated with the 'enophile' only the amide carbonyl can interact with the π-bond of the 'ene' so that the *endo* transition state **127** leads to the *syn* product **126**. The *exo* transition state **128** leads to the *anti* product **129** and equilibration is presumably by reverse 'ene' reaction.



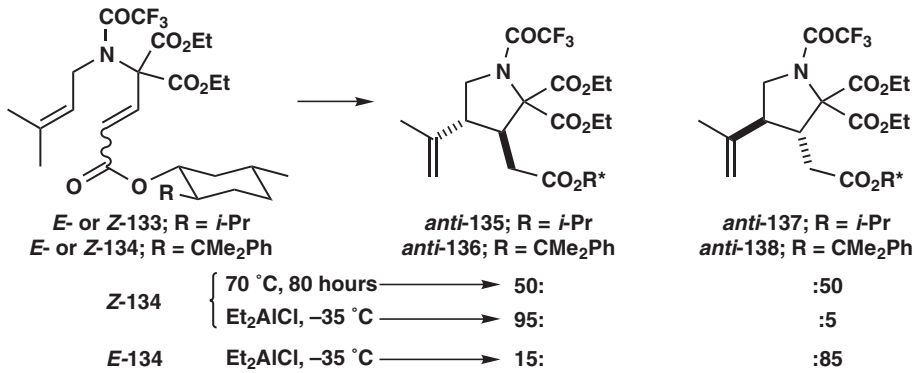
127 (*endo*) **126** **128 (*exo*)** **129**

If the carbonyl group responsible for the *endo* secondary orbital overlap is not there, as in **130**, the *exo* product **131** is formed at lower temperatures. This was just as well as the reaction was used to make allokainic acid **132** having the stereochemistry of **131**.

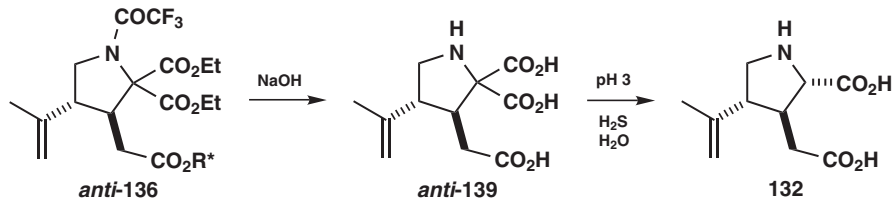


130 **131; 97% yield** **132; (+)-α-allokainic acid**

Recognising an 'ene' disconnection of this sort is not easy but the relationship between the π-bond and the carbonyl group in the product (**126**, **129**, or **131**) is a help. Of course the reaction could also be used to make saturated compounds by subsequent hydrogenation and then even that clue is no longer there. What makes this chemistry all the more useful is that an asymmetric version has been devised and used to make a single enantiomer of allokainic acid.[23] Initial results were not promising: the menthyl ester **133** gave *anti* **135** with less than 18% ee. However, the 9-phenylmenthyl ester **134** (see chapter 27) gave much better results. Regioselectivity and *anti*-stereoselectivity were unimpaired but asymmetric induction depended both on the geometry of the dienophile (*E* or *Z*-**134**) and the conditions. Thermal cycloaddition gave a 50:50 mixture of the two diastereoisomers *anti*-**136** and *anti*-**138** but with Lewis acid catalysis at lower temperatures a sensitivity to the geometry of the dienophile (*E* or *Z*-**134**) could be used to make either diastereoisomer and hence, after hydrolysis, either enantiomer of allokainic acid **132**.

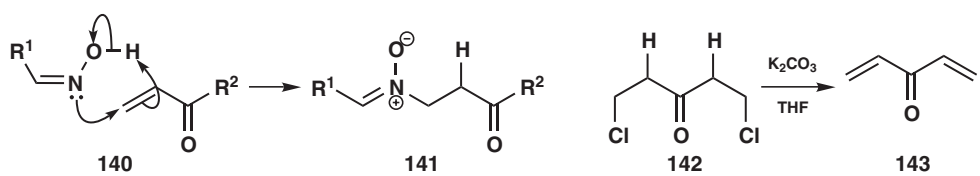


Natural (+)-α-allokainic acid **132** comes from *anti*-**136** by two simple steps in 73% yield. The stereochemistry of the final centre is under thermodynamic control.

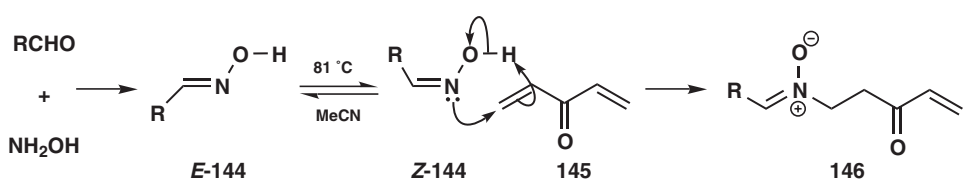


Intermolecular 'Ene'-style Reactions with Oximes

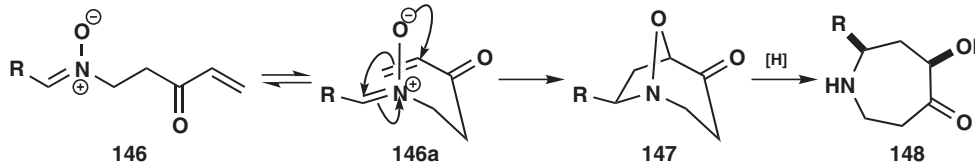
Nitrogen can be incorporated as an oxime into a different kind of 'ene' reaction that has been explored by Grigg and his group. The 'ene' component now bears no resemblance to a diene: one pair of electrons comes from the lone pair on nitrogen and the other from the OH bond of the oxime **140**. The enophile is a more conventional enone and the initial product is a nitrone **141**. No nitrogen heterocycle is formed in this step, but, if the enophile contains a second alkene, a 1,3-dipolar cycloaddition gives a bicyclic structure. The simplest reagent for this job is the rather unstable divinyl ketone (penta-1,4-dien-3-one, **143**). Fortunately this can be released from the dichloroketone **142** with base and distilled with the solvent THF into the reaction mixture.[24]



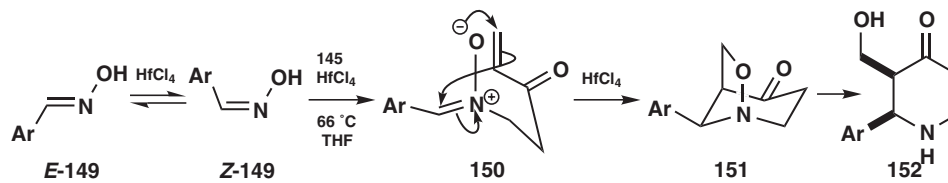
The oximes are easily made but only the *Z*-oxime reacts. The temperature must be high enough for the isomers to equilibrate. With alkyl oximes **144** this is easy enough: equilibration occurs at 81 °C in MeCN. The 'ene' reaction forms the nitrone **146** under the same conditions.



The 1,3-dipolar cycloaddition follows with the regiochemistry shown **146a** and the product is a bicyclic compound **147** with an N–O single bond that is easily reduced to give a seven-membered cyclic aminoketone **148** with stereochemistry.



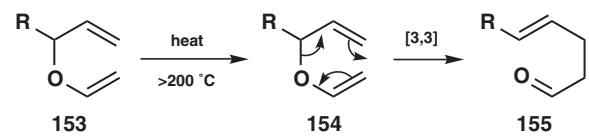
Oximes of aromatic aldehydes **149** do not equilibrate under these conditions but the Lewis acid catalyst $HfCl_4$ both allows oxime equilibration and reverses the regioselectivity of the 1,3-dipolar cycloaddition **150** so that the final product is a piperidine **152**. The regiochemical reversal is probably because the LUMO of the nitrone and the HOMO of the enone are used in **146a** but, by lowering the LUMO energy of the enone, $HfCl_4$ switches to the HOMO of the nitrone in **150**.



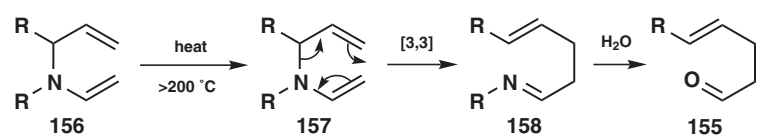
Part IV – [3,3] Sigmatropic Rearrangements

The 'Aza-Cope' Rearrangement

The aliphatic Claisen (or oxy-Cope) rearrangement is a familiar [3,3] sigmatropic rearrangement **154**, typically requiring temperatures of 200 °C or so. The reaction is driven by the formation of a carbonyl group **155**.

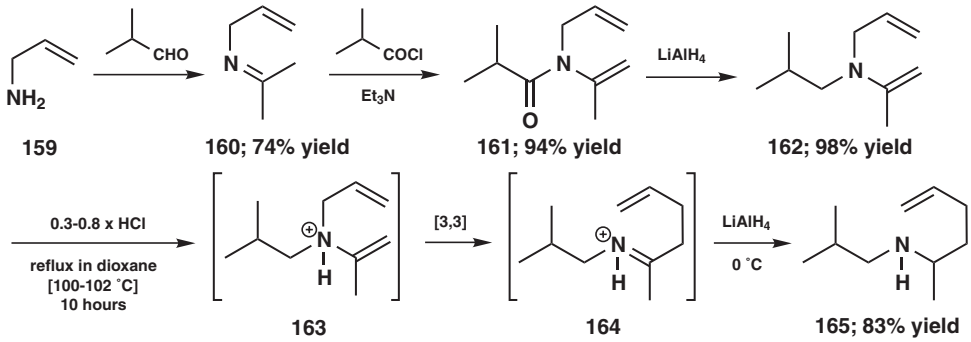


The 'aza-Cope' rearrangement **157** has no special name and, at first sight, no special utility as it requires at least as high a temperature and the products are imines **158** very easily hydrolysed to the products **155** of the Claisen rearrangement.

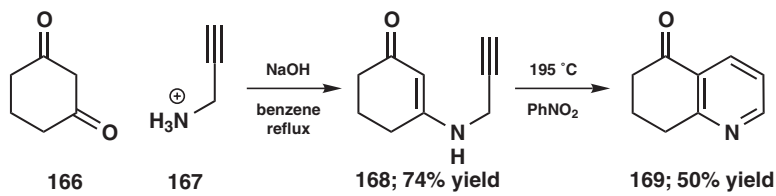


The reaction is of value only if the products can be trapped with the nitrogen still in place. Stille achieved this by (i) forming the starting materials by forcing the imine to enamine conversion

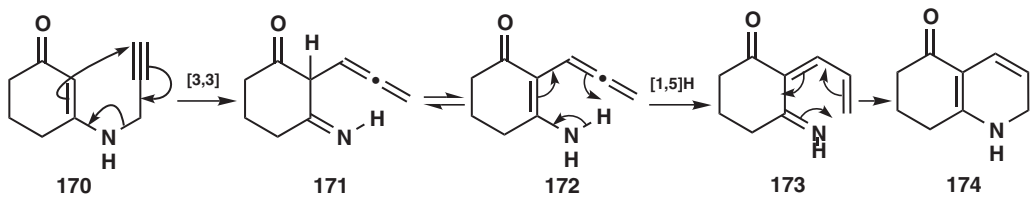
by acylation of the imine **160** followed by reduction **162**, (ii) accelerating the aza-Cope step by protonation of the amine **163**, and (iii) trapping the imine products **164** by a second reduction **165**. The enamine **162** can be isolated in 95% yield if the imine **160** is not isolated on the way.[25] Other catalysts also effective in reducing the temperature for the sigmatropic rearrangement from >200 to about 100 °C include $TiCl_4$, Me_3Al, and BF_3.



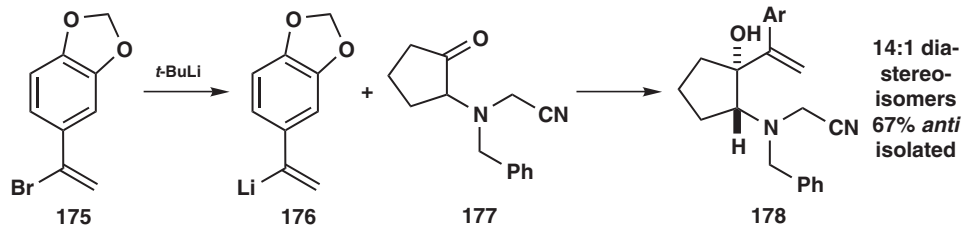
This sequence does not of course produce a nitrogen heterocycle. For that to happen we must have further reactions that make a second C–N bond. One of the earliest and most interesting is a pyridine synthesis[26] using a variety of pericyclic steps starting with propargyl amine **167** and a 1,3-diketone **166**.



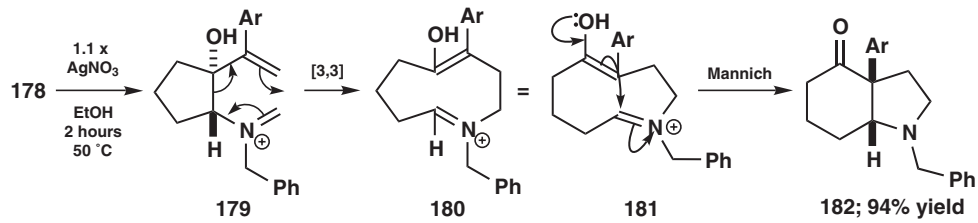
The stable enaminone **168** undergoes an aza-Cope reaction **170** at nearly 200 °C in nitrobenzene. It may seem odd that a linear alkyne should take part in such a reaction but in fact this is not unusual. The product is an allene **171** that undergoes tautomerism to the more stable enaminone **172** then a [1,5] sigmatropic H shift before cyclising to a dihydropyridine **174**. The cyclisation is formally a six electron disrotatory electrocyclic reaction **173**. The solvent $PhNO_2$ oxidises **174** to the pyridine **169**.



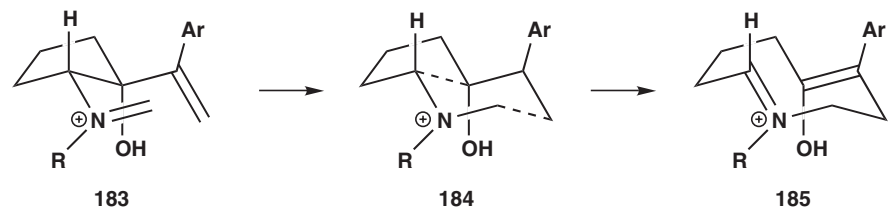
Though dramatic, this is an unusual example of such processes. Much more has been made of tandem aza-Cope and Mannich reactions, particularly by Overman. A typical sequence begins with the addition of a vinyl-lithium, e.g. **176**, to a protected α-aminoketone **177** to give, in this case, the product **178** from Felkin-like attack (chapter 21) on the side of the ketone *anti* to the amino group.[27]



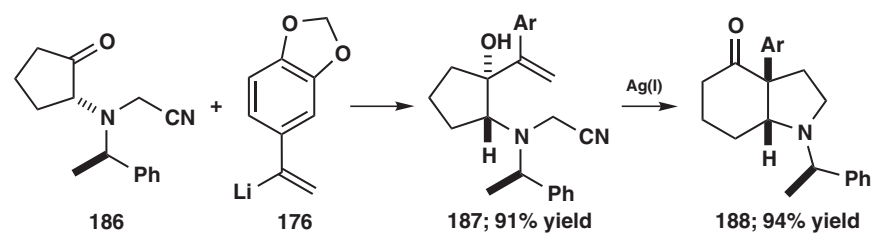
The cyanide group can be eliminated with silver(I) catalysis to give the starting material **179** for an aza-Cope rearrangement. The product **182**, however, has a new heterocyclic ring and has also rearranged. The old five-membered carbocyclic ring is now six-membered. The first step is indeed a [3,3] sigmatropic rearrangement on the immonium ion **179**. The product **180** is another immonium salt and is also an enol. Mannich cyclisation **181** gives the product **182**. This is the tandem aza-Cope (or azonia-Cope) rearrangement/Mannich ring closure sequence.



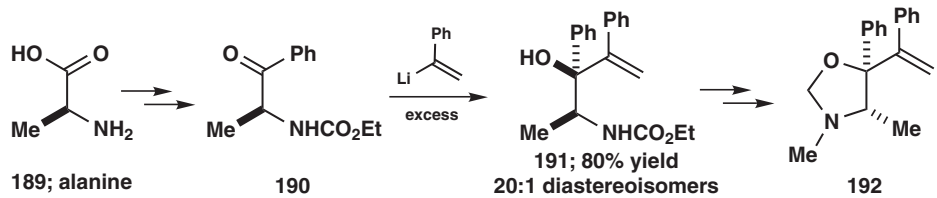
The stereochemistry can be predicted from the way the starting material **179** folds. Transition states for [3,3] sigmatropic rearrangements prefer a chair-like conformation, in this case **184**. The dotted bonds in **184** show that minimal change is needed to form the new σ-bond and break the old. The *anti* relationship between H and OH in **179** should be clear in **184**. The chair six-membered ring in **184** leads to the *syn* relationship between Ar and the same H in **185**.



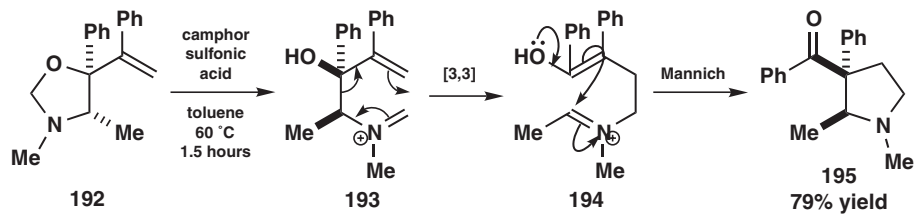
Such efficient transmission of stereochemical information suggest that asymmetric versions of this reaction should be possible. Using a single enantiomer of 1-phenylethylamine, a single enantiomer of the aminoketone **186** was prepared and converted into the starting material **187** for the aza-Cope reaction.[28] The tandem reaction sequence is the same as that for **178** to **182** but gives a single enantiomer of **188** in 94% yield and >99% ee.



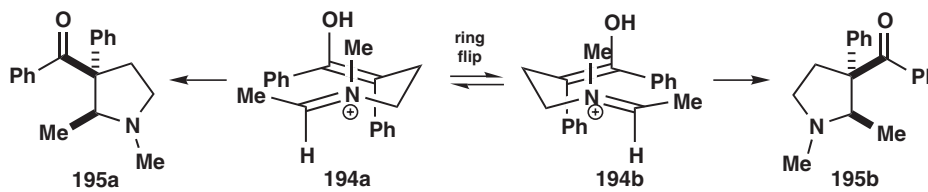
There is more to this chemistry than meets the eye. A simpler route to the [3,3] precursor, avoiding the need for stoichiometric silver, is set out in the chart below.



Treatment of **192** with acid releases the immonium salt **193** that undergoes the tandem aza-Cope/Mannich sequence. The final product is a single diastereoisomer of the substituted pyrrolidine **195**.



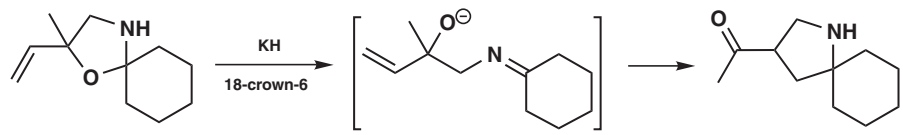
However, though **195** is a single diastereoisomer, it is completely racemic.[29] The intermediate **194** is achiral though it is formed in a chiral conformation **194a** that can give only one enantiomer **195a** of the product. The problem is that, if the intermediate **194a** is long lived enough for bond rotation, it may flip to the enantiomeric conformation **194b** that gives the enantiomeric product **195b**.



Racemisation occurs because the intermediate **194** is achiral and long lived enough for bond rotation. This does not apply to the corresponding intermediate in the previous example **185**. This compound is a cyclononadiene containing two *E*-alkenes. Such compounds are chiral and bond rotation is not possible because of the medium ring. Even if the chiral auxiliary is absent, a single enantiomer of **185** should, and does, rearrange to a single enantiomer of **182**.

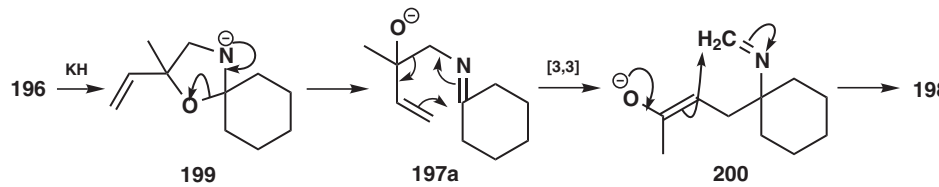
The Anionic 'Aza-Cope' Rearrangement

Alternatively, the aza-Cope rearrangement can be greatly accelerated by an oxyanion rather in the style of the Cope rearrangement itself. The N/O acetal **196**, easily prepared from cyclohexanone and an amino alcohol, undergoes a rearrangement in strong base to give the spirocyclic pyrrolidine[30] **198**.



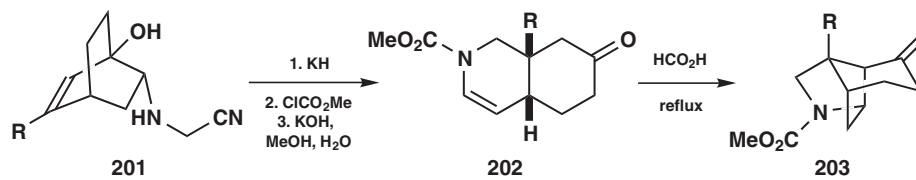
196 **197** **198**

The strong base removes the proton from the nitrogen atom and opens the ring **199** to give the starting material **197** for an anion-accelerated aza-Cope rearrangement at 25 °C in conformation **197a**. The product is an enolate, rather than the enols we have been seeing up to now, and it cyclises **200** in Mannich style onto the imine to give the anion of the product **198**.



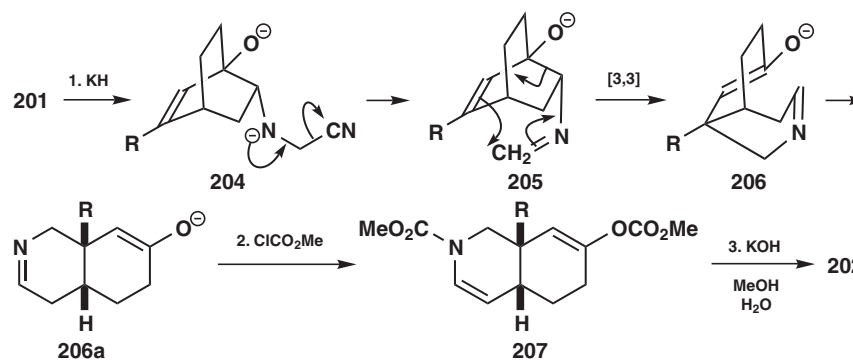
199 **197a** **200**

If the molecule is too rigid for the Mannich cyclisation to occur easily, it is possible to carry it out as a separate step. Overman's approach to gelsemine, a very difficult target, involves an anionic aza-Cope rearrangement on **201** and the trapping of the enolate.[31] The resulting ketone **202** is cyclised in acidic solution. Evidently the addition of the enol to the protonated imine goes better than the cyclisation of the enolate onto the neutral imine when the final product is as strained as **203**.



201 **202** **203**

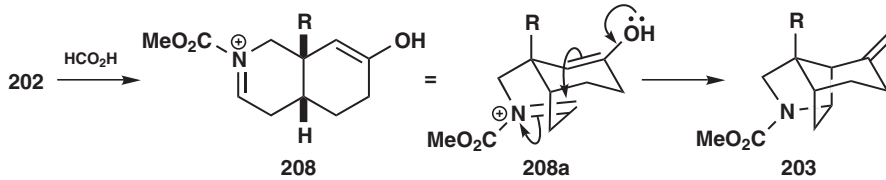
The first step is treatment of **201** with an excess of KH. Both the OH and the NH lose their protons and cyanide is eliminated **204** to give the starting material for the aza-Cope **205**. The product is initially formed in a twisted conformation **206** that opens out to give the simple *cis*-fused imine enolate **206a**. Trapping the enolate with $ClCO_2Me$ also converts the imine into the acylated enamine **207** and the enol ester is easily hydrolysed to give the ketone **202**.



204 **205** **206**

206a **207**

In formic acid, the enamine is protonated on carbon to give the very electrophilic immonium ion **208** which cyclises in conformation onto the enol **208a** in an intramolecular Mannich reaction to give the bicyclic skeleton **203** required for gelsemine.

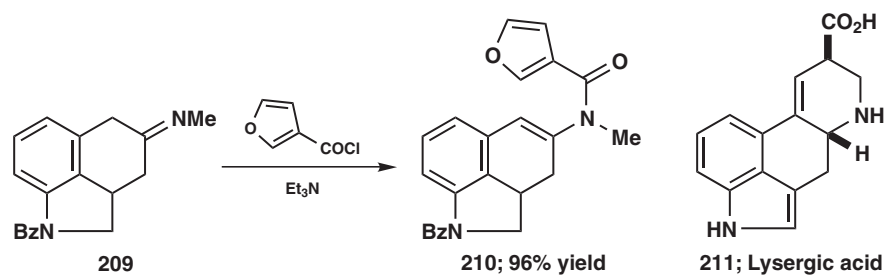


Part V – Other Reactions

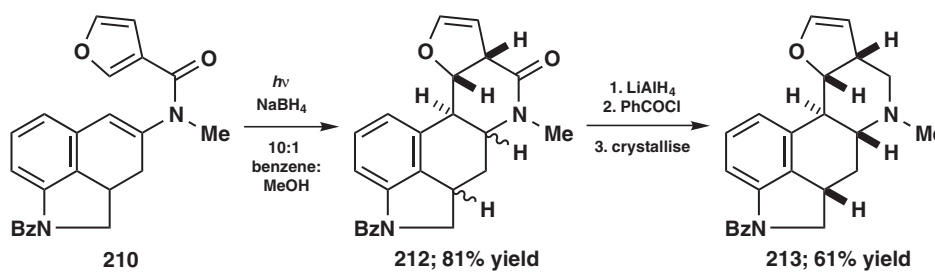
This part contains one genuine pericyclic reaction and a collection of near relatives that all give nitrogen heterocycles by the combination of various unsaturated molecules.

Electrocyclic Reactions

There are few useful examples of electrocyclic reactions giving nitrogen heterocycles and we shall give just one - a photochemical six electron electrocyclic reaction that closes a ring in a synthesis of lysergic acid **211**. The first step is the acylation of the imine **209** and its regioselective conversion into the more conjugated enamine[32] **210**.

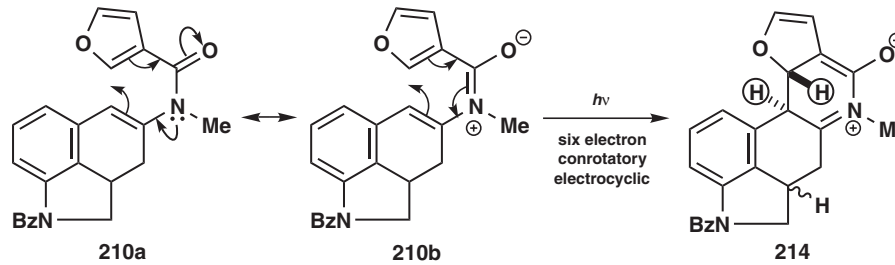


The electrocyclic step is a photochemical cyclisation of **210** under reducing conditions to give a mixture of diastereoisomers of **212** in about a 7:1 ratio. These were further reduced and the *N*-benzoyl group replaced to give a separable mixture of amines: the required diastereoisomer **213** was isolated in 61% yield.



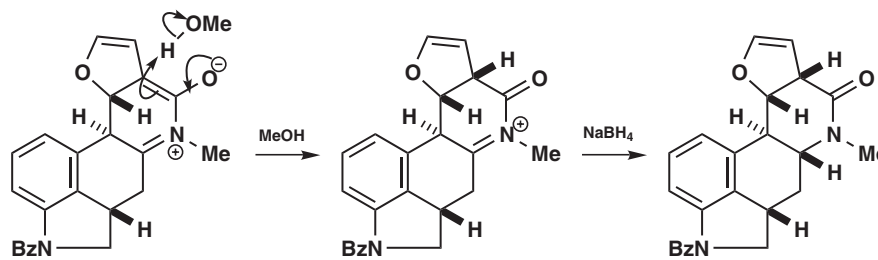
The electrocyclic step can be drawn on the amide **210a** but is perhaps more convincing when drawn on the delocalised version **210b**. In either case this is a photochemical six electron electrocyclic reaction and therefore *con*rotatory. This determines the *trans* stereochemistry at two of the

new centres in the product **214**: the ringed hydrogen atoms must both have rotated in the same sense (clockwise or anticlockwise).



210a **210b** **214**

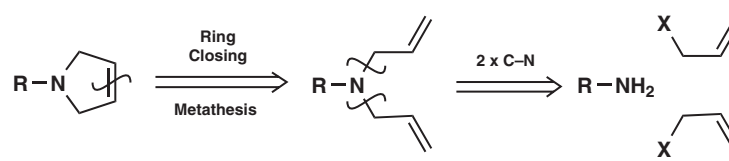
Under the reaction conditions, the enolate is protonated by methanol **215** to give the more favourable *cis* ring junction **216** and borohydride reduces the immonium group stereoselectively to give the major diastereoisomer **217** of the final product.



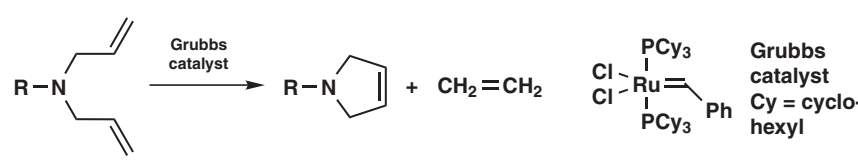
215 **216** **217**

Ring Closing Olefin Metathesis

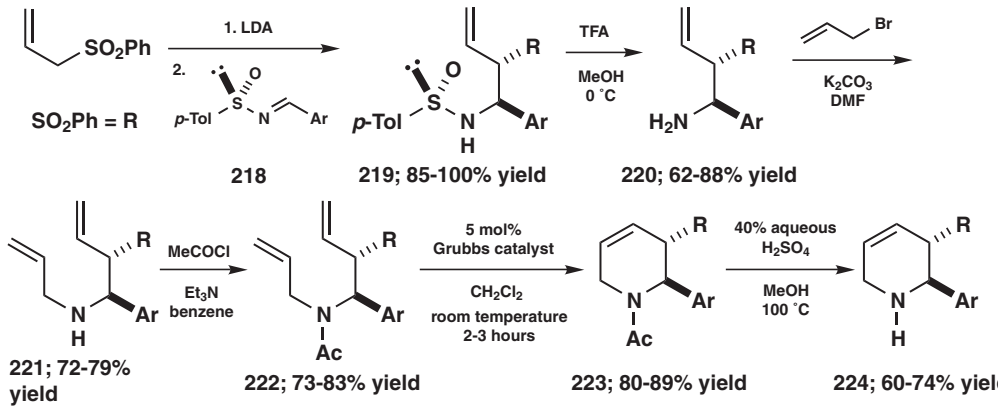
In principle ring closing metathesis (RCM, chapter 15) offers a simple route to unsaturated nitrogen heterocycles. The first disconnection is across an alkene inside the ring and normally two alkenes are created by the addition of a CH_2 group at each end. Further disconnection might have simple alkylation at nitrogen in mind. A special problems in making nitrogen heterocycles this way might well be complexation of the metal by nitrogen so the nature of R might be important.



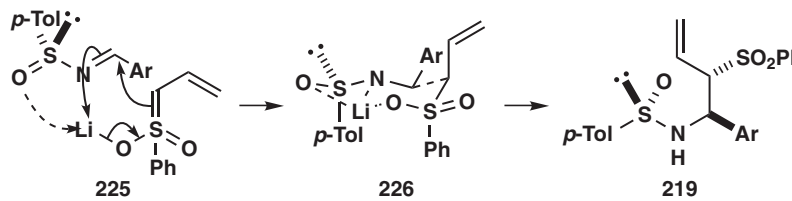
Though any group could be added in theory, the addition of a CH_2 group ensures that the other product will be gaseous ethylene so the thermodynamics are favourable. The Grubbs' catalyst (Cy = cyclohexyl) is greatly to be preferred because of its stability and wide scope. This is not strictly a pericyclic reaction but in concept it is very like a cycloaddition followed by a reverse cycloaddition.



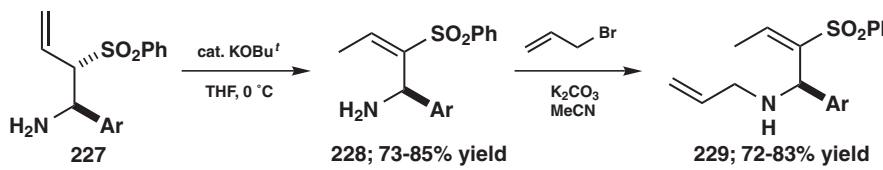
We shall discuss just the application of RCM to the asymmetric synthesis of pyrrolidine and piperidine derivatives. The asymmetry comes from an enantiomerically pure sulfinyl imine **218** that accepts a lithiated sulfone as nucleophile to give one diastereoisomer of adduct **219**; R = SO_2Ph. The chiral auxiliary is removed with acidic methanol and allylation on the nitrogen gave a potential RCM substrate **221**. In the event this compound failed to cyclise with the Grubbs' catalyst so the nitrogen was acetylated to make it a worse ligand. Now RCM was successful and the cyclic amide **223** formed in good yield. The amide can be hydrolysed quite easily to give the free amine **224** as a single enantiomer of the *anti* diastereoisomer.[33]



The stereoselectivity in the formation of **219** can be explained by a combination of the imine with the lithiated sulfone **225** in an intramolecular mechanism **225** with a chair transition state **226**. The vinyl group goes axial to avoid a clash with the large groups around the sulfone.

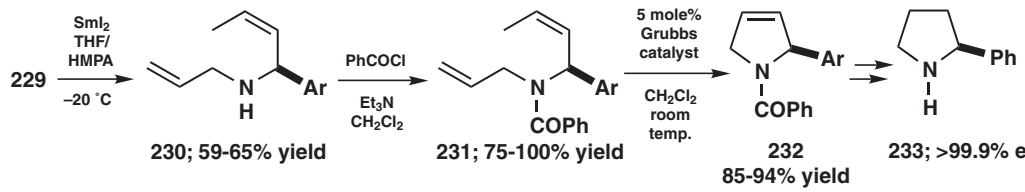


The synthesis of pyrrolidines demands first of all the movement of one of the alkenes closer to the nitrogen atom. This can be done by equilibration of the allyl sulfone in **227** to the more stable conjugated vinyl sulfone **228** with catalytic base. Then allylation at nitrogen gave a possible metathesis substrate **229**. In this series neither the amine **229**, nor the corresponding benzamide would undergo metathesis.



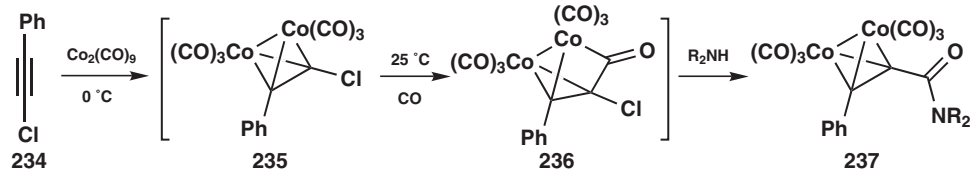
The problem is the sulfone. The trisubstituted alkene in **229** is too hindered. Reductive removal of the sulfone and acylation gave a good metathesis substrate **231** and hence the pyrrolidine

232. That the product was enantiomerically pure was demonstrated by chiral HPLC of the *N*-Boc compound and comparison of rotation with the known pyrrolidine **233**.

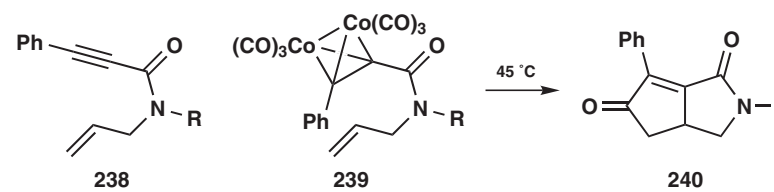


The Pauson-Khand Reaction

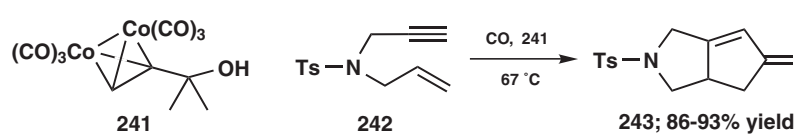
In chapter 6 we described the use of the remarkable Pauson-Khand reaction for the synthesis of cyclopentenones. If the components (CO, alkene and alkyne) are tethered by a nitrogen atom, a heterocycle will also be formed. The first stage in this process is to couple the cobalt carbonyl complex, e.g. **236**, of a halo-alkyne with an amine containing the alkene in the side chain. The best way to do this is to react **234** with $Co_2(CO)_9$ to give **235** and then **236** and to capture this complex with the amine without isolation of intermediates.[34]



If the secondary amine is an allylic amine, the complex **239** rearranges with the incorporation of a molecule of carbon monoxide (see chapter 6) to give the cyclopentenone **240** with simultaneous formation of a pyrrolidone. This might be easier to see when you realise that **239** is the Co complex of **238**. The yields are not wonderful (48–64%) but are reasonable for a reaction that does so much in one step.

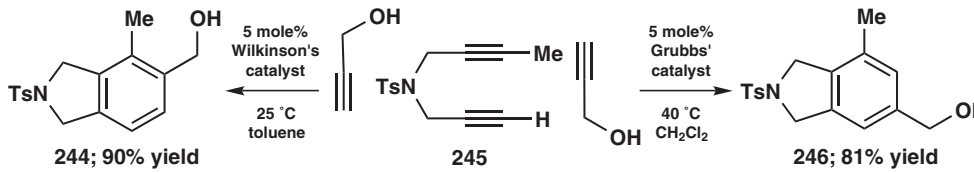


A recent *Organic Syntheses* procedure[35] describes a much higher yielding version using a cobalt complex formed from **241** by treatment with Et_3SiH and cyclohexylamine. Only catalytic amounts (5 mol%) are needed to cyclise the sulfonamide **242** to the pyrrolidine **243**.

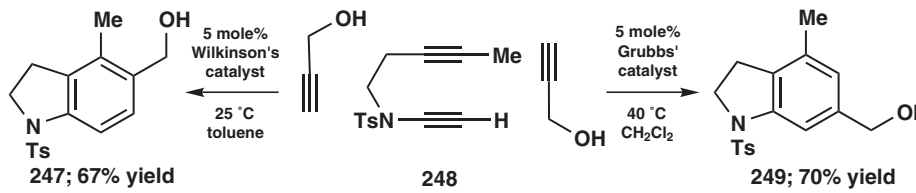


Metal-Catalysed Alkyne Trimerisation

In the same vein but more in the style of Vollhardt's co-trimerisation is a remarkable series of reactions that combine three alkynes. One is propargyl alcohol and the other two are tethered by a sulfonamide.[36] In the simple case **245**, trimerisation with the Grubbs' catalyst (see above) gives one positional isomer **244** of a benzo-pyrroline while Wilkinson's catalyst [$(Ph_3P)_3RhCl$] gives the other possible isomer **246**.



Even more remarkably, moving the nitrogen atom in the tether so that it is conjugated with one of the alkenes **248**, reduces the yield a little but doesn't alter the regioselectivity at all. The CH_2OH end of the propargyl alcohol reacts with the less hindered end of the amine when Grubbs' catalyst is used **249** but the other way round with Wilkinson's catalyst **247**. With Grubbs' catalyst the reaction is presumably a series of metatheses starting on the less hindered alkene. It is not yet understood how Wilkinson's catalyst reverses this selectivity.



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General references are given on page 893

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35 Synthesis and Chemistry of Azoles and other Heterocycles with Two or more Heteroatoms

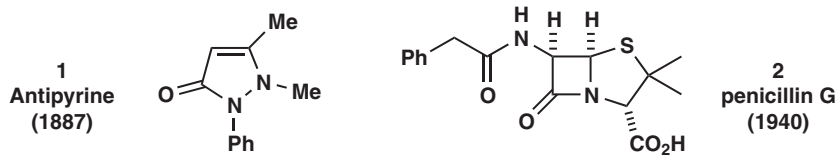
This chapter considers how aromatic heterocyclic compounds with two or more nitrogen (or other heteroatoms, chiefly O and S) atoms can be made. In particular it deals with the addition of new C-C and C-X bonds to previously prepared heterocycles of this kind.

Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

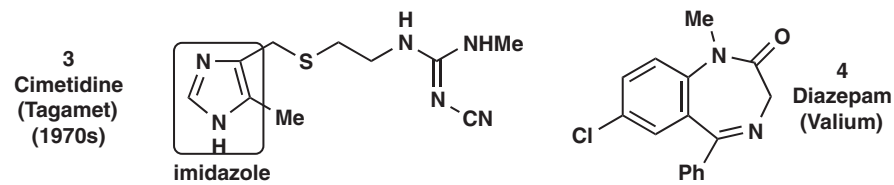
Part I – Introduction

Azoles: Heterocyclic Compounds with More than One Nitrogen Atom

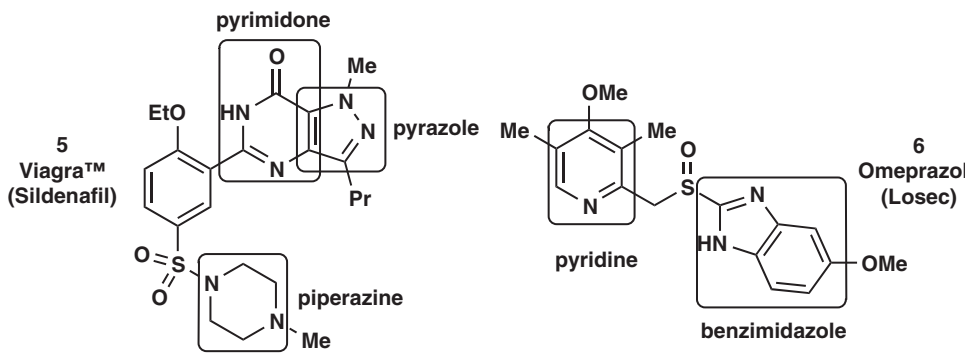
Most important drug molecules are heterocycles and most of those heterocycles contain more than one heteroatom yet the chemistry of these systems is neglected and even despised by many organic chemists.[1] A few examples should convince you that neglect of this area is quite unjustified for any serious organic chemist. The very first synthetic drug, antipyrine **1**, is an aromatic pyrazolone with two adjacent nitrogens in a five-membered ring. Perhaps the most famous drug of all, penicillin **2**, has a saturated five-membered ring with a nitrogen and a sulfur atom and of course the vital β-lactam used to disrupt bacteria cell wall synthesis.



In more modern times, the first successful anti-ulcer drug, cimetidine **3**, with its ability to block histamine synthesis in the stomach, is an imidazole and the classical anti-depressant valium **4** has a seven-membered ring heterocycle that is not (quite) aromatic.



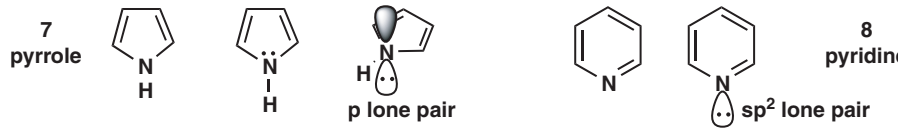
Coming more up to date, Viagra **5**, Pfizer's impotence treatment that hit the headlines at the end of the last century has three heterocyclic rings - a saturated piperazine and two aromatic rings that separately make a pyrimidone and a pyrazole and together imitate a purine. The most successful drug to date, Omeprazole **6**, is another anti-ulcer drug but with a unique action that inhibits the proton pump. It has a pyridine ring and a benzimidazole.



These rings are from four- to seven-membered, but five- and six-membered dominate. They may be saturated, partly saturated, or fully aromatic and they may contain one or more heteroatom. The heteroatoms may be nitrogen, oxygen, or sulfur but nitrogen dominates. In this chapter

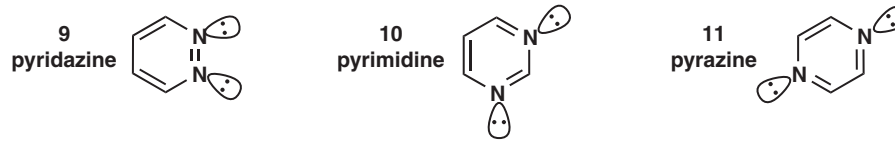
we shall be looking at the synthesis of five- and six-membered rings, mostly aromatic, and mostly containing two or more nitrogen atoms. The chemistry will be very varied.

It is worthwhile introducing these ring systems with a brief survey highlighting the main features of the various systems. All are based either on pyrrole **7** or pyridine **8**. The distinction between the two types of nitrogen atoms present in these rings is an extremely important part of understanding aromatic heterocyclic chemistry.

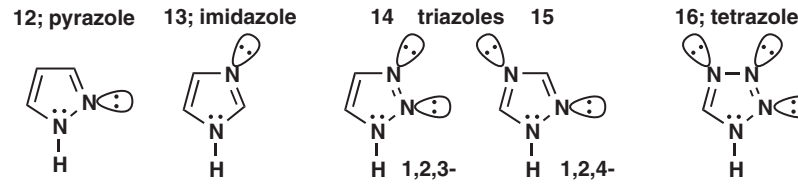


Pyrrole **7** has only two π-bonds so it needs the lone pair on the nitrogen atom to complete the aromatic sextet and the lone pair has to be in a p-orbital and delocalised round the ring. Pyridine **8** has three π-bonds so the lone pair on nitrogen is not needed. Besides, it is in an sp^2 orbital in the plane of the ring and cannot be delocalised as it is orthogonal to the p-orbitals in the ring. Pyrroles are therefore nucleophilic and react with electrophiles at nitrogen or at carbon while pyridines react with electrophiles only at nitrogen and the ring itself is electrophilic (chapter 32).

Adding an extra nitrogen atom (in thought only!) to the pyridine ring system creates three new heterocycles, pyridazine **9**, pyrimidine **10**, and pyrazine **11**, and in all three the extra nitrogen is of the pyridine type with localised lone pairs on both nitrogen atoms. These three heterocycles are more electrophilic and even less nucleophilic than pyridine.



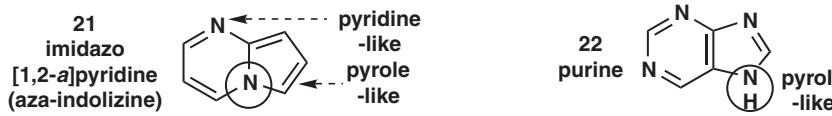
Adding more nitrogen atoms to pyrrole gives a series of diazoles **12** and **13**, triazoles **14** and **15** and tetrazole **16** but each has two π-bonds and so needs the lone pair of only one of the nitrogen atoms for aromaticity. Each extra nitrogen atom is of the pyridine sort with an sp^2 lone pair. These heterocycles become less nucleophilic as more nitrogen atoms are added. In the diagrams below, the pyrrole-like lone pairs are marked in the ring and the pyridine-like lone pairs in sp^2 orbitals outside the ring.



When sulfur or oxygen atoms are present in a five-membered ring, they provide the pyrrole-like lone pair and any nitrogen atoms are necessarily pyridine-like. The four most important systems are oxazole **17** and thiazole **18** with 1,3-related heteroatoms and isoxazole **19** and isothiazole **20** with an N-O or N-S bond.

With fused heterocyclic rings, the situation can be quite complicated but it is really necessary only to decide whether each nitrogen atom is pyrrole- or pyridine-like. You can count electrons in

each ring or in both rings together, whichever you prefer though in the case of the azaindolizine **21**, it is more convincing to count the ten electrons in the periphery as the pyrrole-like nitrogen belongs to both rings. The three unmarked nitrogens in the purine **22** are all pyridine-like.

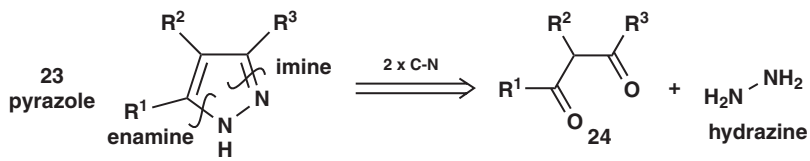


The rest of the chapter is divided into two parts. We shall first consider how the rings themselves may be formed and then how new bonds (either C-X or C-C) may be built onto a previously formed ring. Both methods are important.

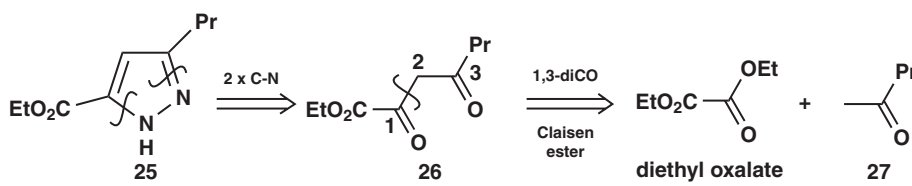
Part II – Building the Ring

a. The Simplest Disconnections

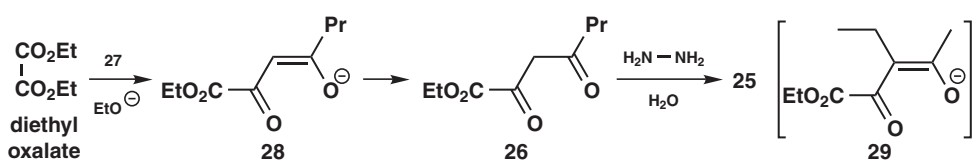
The first disconnection to be considered is breaking all the C–X bonds in the ring. This is an obvious strategy for a pyrazole since one C–N bond is part of an enamine and the other is an imine **23**. Both functional groups are made from amines and carbonyl compounds. Here hydrazine is the diamine that emerges from an easily made 1,3-dicarbonyl compound **24**.



An example is the pyrazole **25** needed for the synthesis of Viagra. Double C–N disconnection reveals a diketoester **26** with a convenient 1,3-diCO relationship that can be disconnected to a ketone **27** and unenolisable, reactive, and symmetrical diethyl oxalate.

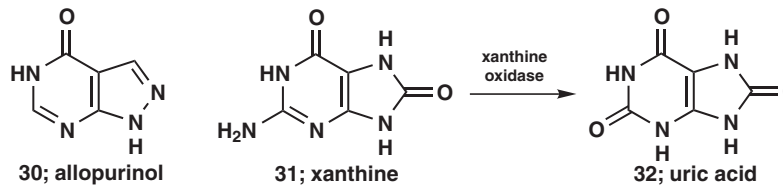


The Claisen condensation is regioselective because the most stable enolate **28** of the product **26** is formed under the reaction conditions and it is more stable than the alternative **29**. Reaction with hydrazine occurs at the two keto groups rather than at the less electrophilic ester.

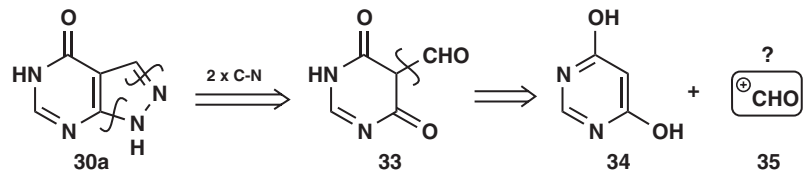


The synthesis of allopurinol

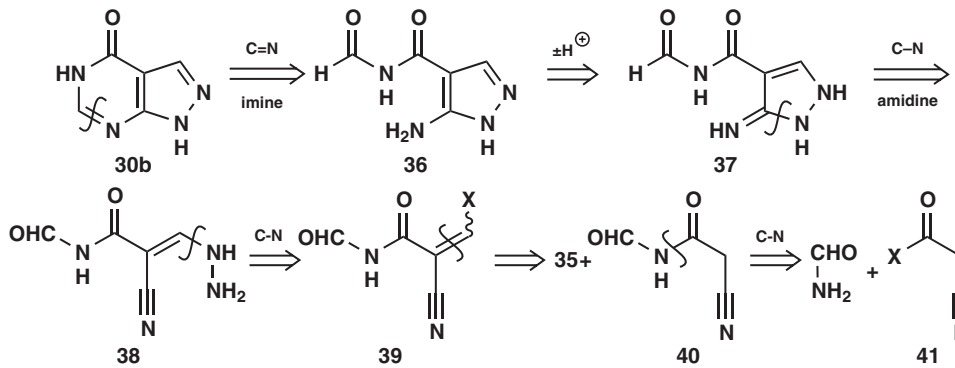
Many heterocycles were made by simple procedures of this kind and the syntheses were designed by breaking the molecule into reasonable pieces. Putting these aromatic molecules together generally relied on thermodynamics rather than kinetic selectivity. A good example is allopurinol **30**, a treatment for gout that works by inhibiting xanthene **31** oxidase and thus preventing the deposition of painful crystalline uric acid **32** in the joints. Allopurinol imitates purine **22**; the main change being the movement of a nitrogen atom in the right hand ring so that a pyrazole replaces the imidazole in purine.



Disconnection of hydrazine **30a** from allopurinol leaves a diamide with an extra aldehyde group **33**. Disconnection of that aldehyde leaves a simple and available symmetrical heterocycle that exists in the dihydroxy tautomer **34** and will require a one-carbon electrophile corresponding to the synthon **35**. We shall meet reagents for this synthon soon.

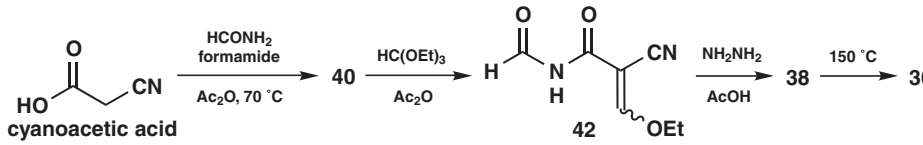


No doubt such a synthesis could be carried out. We might also explore the alternative disconnection of the six-membered ring. Opening up the amidine **30b** at first looks unpromising but tautomerism between **36** and **37** reveals an amidine and an excellent disconnection to a nitrile **38** from which hydrazine can be removed to give the much simpler **39**. Now we must use the same disconnection as **33** to give the same synthon **35** and the even simpler **40**.



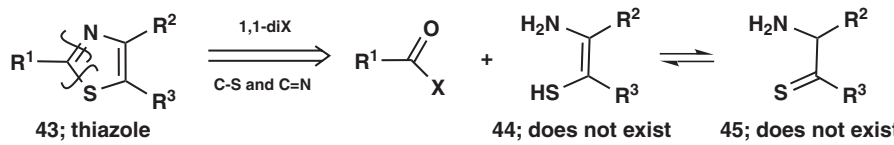
The synthesis is typical of old heterocyclic methods but has a delightful twist at the end. The one carbon electrophile corresponding to $^{+}$CHO is triethyl orthoformate $CH(OEt)_3$. The other starting materials are very simple: formamide, cyanoacetic acid, and hydrazine and the synthesis is very short. Intermediate **40** is crystalline but need not be isolated as 34 g of cyanoacetic acid can

be converted directly into 15 g of **42**. The twist is that the last reaction is carried out by heating the dry yellow crystalline **38** at 150 °C. No visible change occurs, but water is lost and the compound is entirely converted into allopurinol[2] **30**.

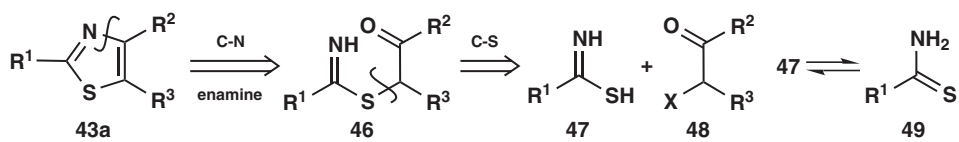


The synthesis of thiazoles

The most obvious disconnection (1,1-diX) of a thiazole **43** reveals an acid derivative but the other starting material **44** is an impossible compound requiring NH_2 and SH groups to be *cis* substituted on an alkene. Neither of these functional groups (primary enamine or thioenol) is stable and control of the geometry would also be impossible. The thiol **44** is also the thioenol of an α-amino thioketone **45**: these are equally unknown.

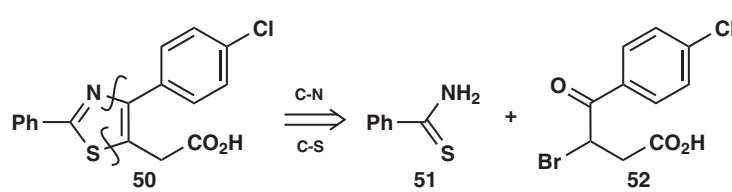


The most productive disconnection is to keep the two heteroatoms in the same starting material, recognising that this can be redrawn as a thioamide. We start by disconnecting the C–N bond **43a** of the enamine and then **46** the C–S bond to reveal a simple α-haloketone **48** and a compound **47** that may look strange at first but can be redrawn as a thioamide **49**.



The synthesis of thiazoles **43** adds an element of regioselectivity as the thioamide has soft (S; orbital controlled) and hard (N; charge controlled) nucleophilic sites and it is essential to differentiate equally clearly between the two electrophilic centres on the carbonyl part of the molecule. We need to know that a thioamide will react with an α-haloketone **48**; X = Cl, Br so that the hard nitrogen atom attacks the ketone and the soft sulfur atom attacks the saturated carbon atom. Thus the simple non-steroidal anti-inflammatory drug Fentiazac **50** is made from thiobenzamide **51** and the simple bromoketone **52**, made in turn by bromination of the ketoacid. The synthesis is just that.[3]

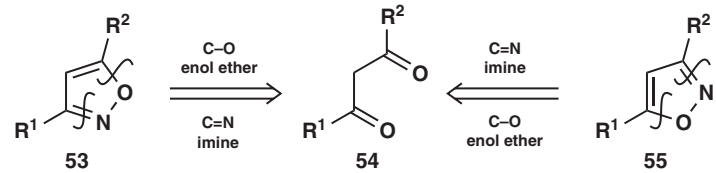
Fentiazac: Analysis



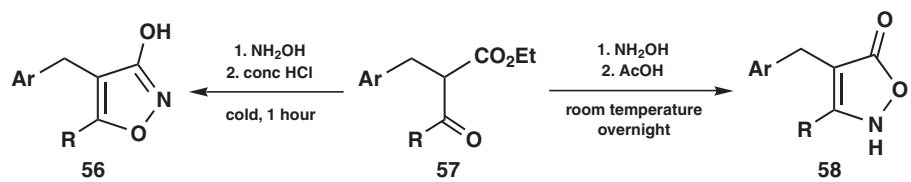
b. Routes to Isoxazoles

The synthesis of isoxazoles from dicarbonyl compounds

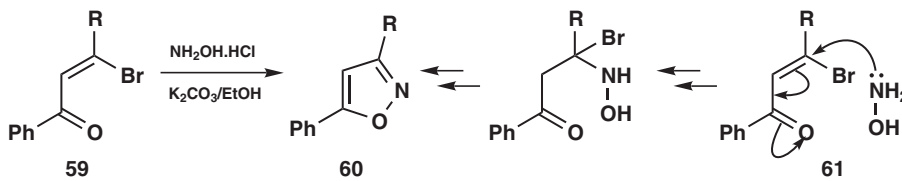
The disconnection of isoxazoles is easier because there is obviously a molecule of hydroxylamine (NH_2OH) waiting to be removed so that isoxazole **53** is 'obviously' made from 1,3-diketone **54** and hydroxylamine. That is all very well until we realise that we should also like to make isoxazole **55** from the same two starting materials!



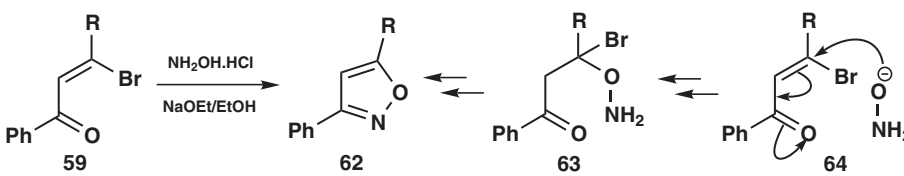
Regioselectivity is not so straightforward here. Both N and O are good nucleophiles for carbonyl groups. There has been some success in controlling the reaction by conditions. Thus chemists at Wyeth making 'glucose lowering agents for obese diabetic mice' reacted hydroxylamine with the ketoesters **57** in acetic acid at room temperature overnight to give mainly isomer **58** while in concentrated HCl at lower temperatures for shorter times, isomer **56** predominated. It looks as though **56** is the kinetic and **58** the thermodynamic product but the yield of either isomer was poor[4] (30–40% at best).



It is better to differentiate the two electrophilic sites more sharply. The bromoenones **59** give some regioselectivity at different pHs. Hydroxylamine is usually added as the crystalline hydrochloride and base is needed to release the free amine. Carbonate does this and with K_2CO_3 in EtOH, isoxazole **60** is the product. It appears that conjugate addition of the nitrogen atom **61** occurs first.[5]

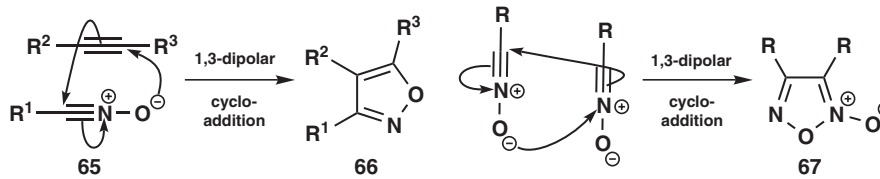


With the stronger base NaOEt in the same solvent, the isomeric isoxazole **62** is the main product. Presumably the hydroxylamine anion is the nucleophile and now the oxyanion does conjugate addition **64** in the first step. Attractive and rational though this method may be, the average yields of either isomer are only 25–50%. This type of approach relies too much on delicate choices between similar groups and a better way is needed.



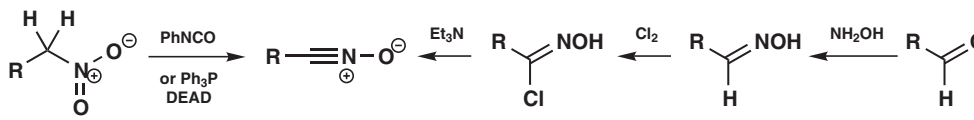
The synthesis of isoxazoles by 1, 3-dipolar cycloaddition

And this is it! Alkynes add to nitrile oxides in a concerted $_{\pi}4_s + _{\pi}2_s$ cycloaddition **65** to give an isoxazole **66** in one step.[6] The alkyne provides the two electrons and the nitrile oxide provides four (a lone pair on the oxyanion and one of the π-bonds in the alkyne). The nitrile oxide is an example of a '1,3-dipole' being nucleophilic at one end and electrophilic at the other. It provides the four π-electrons from three atoms. The alkyne is a 'dipolarophile'. You may guess that nitrile oxides are inherently unstable. In fact they do 1,3-dipolar cycloadditions on themselves to produce strange heterocycles **67** called furoxans. They must therefore be released in the presence of the dipolarophile and the dipolarophile must live up to its name and be better than the nitrile oxide at accepting the 1,3-dipole.



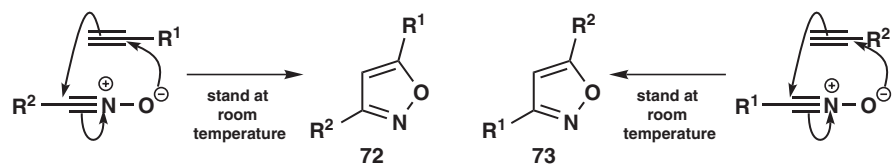
65 66 67

There are two good ways to do this. Dehydration of alkyl nitrocompounds **68**, either with PhNCO or with Ph_3P and DEAD (EtO_2C-N=N-CO_2Et) in a Mitsunobu elimination gives nitrile oxides **69**, as does the 1,3-elimination of HCl from chloro-oximes **70**. In the next section we shall show only the nitrile oxide but you should recall that it is generated in the reaction mixture by one of these reactions.



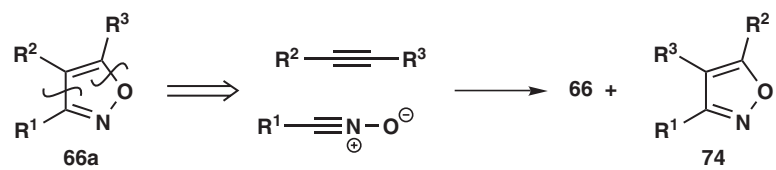
68 69 70 71

The problem of regioselectivity remains. Monosubstituted alkynes usually react cleanly using the HOMO of the alkyne and the LUMO of the nitrile oxide. The product is exactly that type of isoxazole (**72** or **73**) that was so difficult to make from dicarbonyl compounds and hydroxylamine. Here regioselectivity is controlled because the two substituents (R^1 and R^2) are on different reagents. Conditions are very mild.



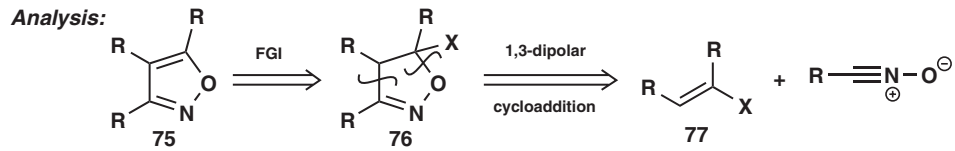
72 73

The disconnection for this reaction is extremely simple **66a** - just remove the nitrile oxide. However, if a fully substituted isoxazole is required, the disubstituted alkyne is no longer a satisfactory dipolarophile as it usually does not show enough regioselectivity.

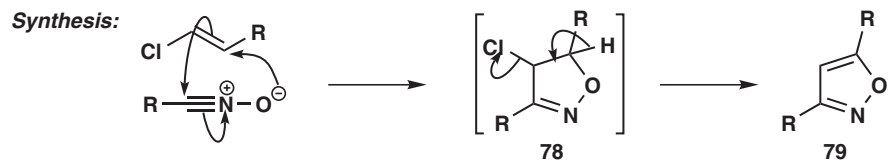


66a 74

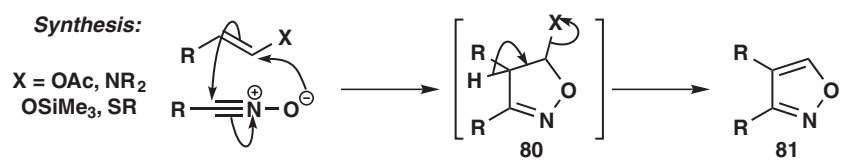
Better results are often obtained by using, as a latent alkyne, an alkene **77** with a substituent X that can be eliminated and that directs the regioselectivity of the cycloaddition. This means that a preliminary FGI on the isoxazole **75** (alkene to alkyl X) is required before the 1,3-dipolar disconnection **76**.



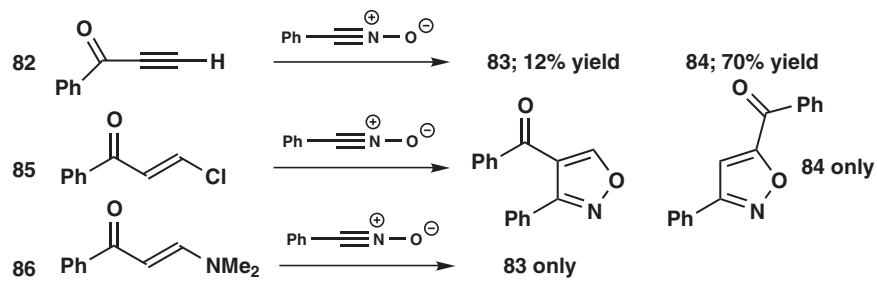
If X is electron-withdrawing, and the best example is X = Cl, the LUMO of the dipolarophile reacts with the HOMO of the nitrile oxide, i.e. O^- attacks the electrophilic end of the alkene, and the intermediate isoxazoline eliminates HCl **78** (not necessarily by an E2 reaction) to give the aromatic isoxazole **79**.



If on the other hand the substituent X is electron-donating, and various examples such as OAc, NR_2, $OSiMe_3$, or SR can be used, the regioselectivity is reversed with the HOMO of the dipolarophile attacking the LUMO of the nitrile oxide at the carbon end of the dipole. Elimination **80** gives the isomeric isoxazole **81**.



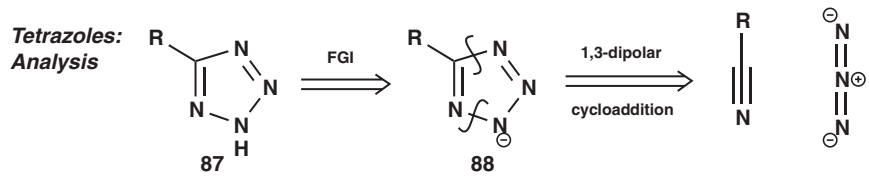
The three approaches can be compared with the same isoxazoles. 1,3-Dipolar cycloaddition with the alkyne **82** gives a mixture of regioisomers **83** and **84**. If the chloroalkene **85** is used instead, only **84** is formed while the enamine **86** gives **83** only.[7]



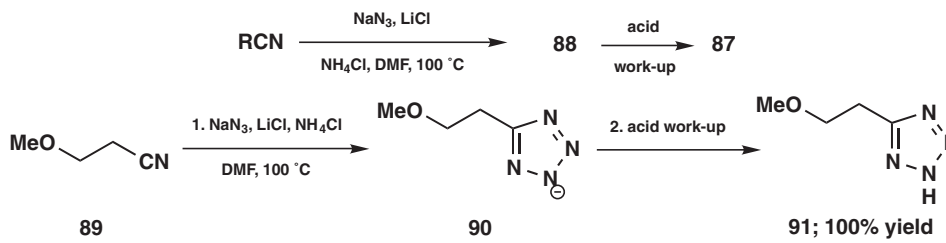
c. Tetrazoles

The synthesis of tetrazoles by 1, 3-dipolar cycloaddition

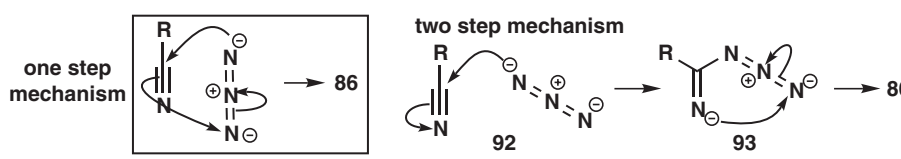
One group of heterocycles made almost exclusively by 1,3-dipolar cycloadditions is the tetrazoles **87**. They have four nitrogen atoms in the five-membered ring and therefore only one carbon atom and, inevitably, no C–C bonds. Tetrazoles are as acidic as carboxylic acids (pK_a about 5) and disconnection of the anion **88** into a nitrile and azide ion is the usual approach.



There are many ways to make the reaction work well, one of the most popular using sodium azide buffered with ammonium chloride with LiCl in DMF. The product is the tetrazole anion **88** and the tetrazole **87** is released on acidification. The example **91** shows that the yields are excellent and that functionality can be included in the side chain.[8]

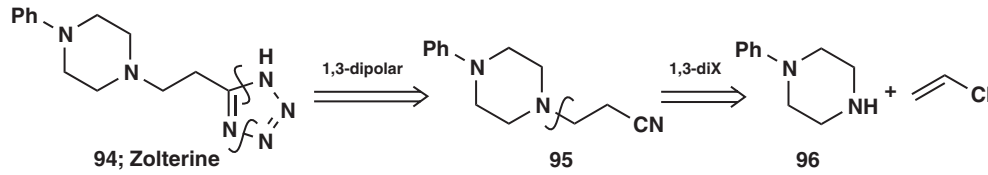


That the reaction occurs as expected between the HOMO of azide (which is, after all, an anion) and the LUMO of the electrophilic nitrile is confirmed by reactions with aryl nitriles ArCN with sodium azide. The yields are all close to quantitative but the reaction is faster when R is an electron-withdrawing group. Not everyone agrees that the reaction is concerted as the approach of the two linear molecules looks very hindered. However, a stepwise addition of azide ion **92** followed by cyclisation **93** looks, if anything, worse as two negatively charged atoms must attack each other in the cyclisation **93**. However, this too is pericyclic (electrocyclic) and not ionic.



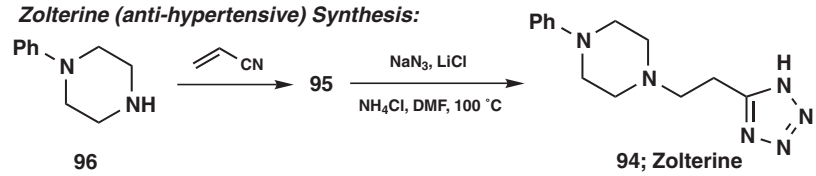
This disconnection should of course be followed by others as the need arises. Thus the antihypertensive zolterine **94** containing a second heterocyclic ring - a piperazine - can be made from nitrile **95** and that comes from conjugate addition of the piperazine to acrylonitrile.

Zolterine (anti-hypertensive) Analysis:



This synthesis was carried out using the method we have described and is short and unambiguous.[9]

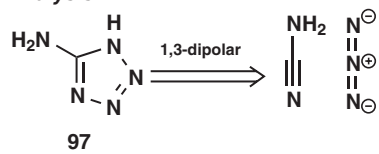
Zolterine (anti-hypertensive) Synthesis:



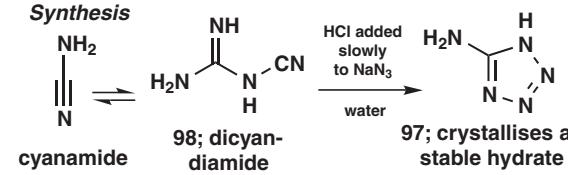
If there is functionality directly attached to the carbon atom of the tetrazole, a problem may seem to arise. Thus many drugs are made from 5-aminotetrazole **97** and our disconnection requires the unlikely looking molecule H_2N-CN. This is in fact 'cyanamide' available as a mixture with water and 'stabilisers' to prevent dimerisation to 'dicyandiamide' **98**. The dimer is 50 times cheaper and can be used in the 1,3-dipolar cycloaddition under slightly different conditions.[10]

Many Tetrazole Drugs Made from 5-Aminotetrazole

Analysis:

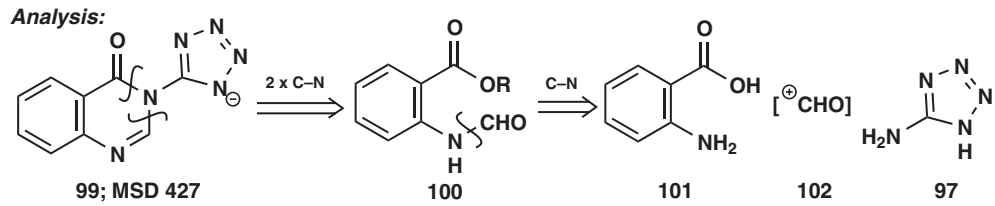


Synthesis

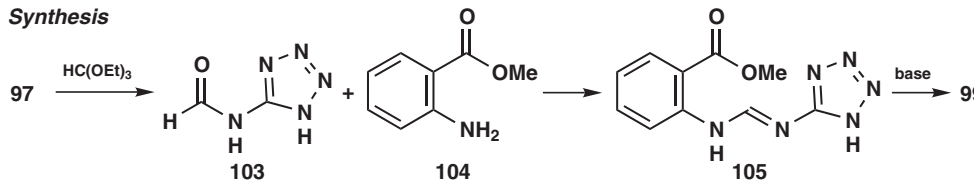


A good example of a drug made from aminotetrazole is Merrell Dow's anti-allergic agent MSD 427. You will notice that the drug **99** is actually the stable anion of the tetrazole. It makes sense to disconnect the aminotetrazole immediately to reveal the *N*-formyl derivative **100** of *o*-aminobenzoic acid (anthranilic acid) **101**.[11]

Analysis:



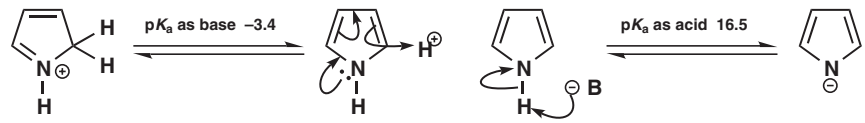
Another fragment is a one carbon electrophile we have shown as '$^{+}$CHO'. You will appreciate that the more heteroatoms there are in the ring, the more necessary it is to use small carbon fragments to make the rings. All that remains is to identify a reagent for **102** and to decide on the order of events. The reagent chosen was triethyl orthoformate $HC(OEt)_3$ and the synthesis was simplicity itself.



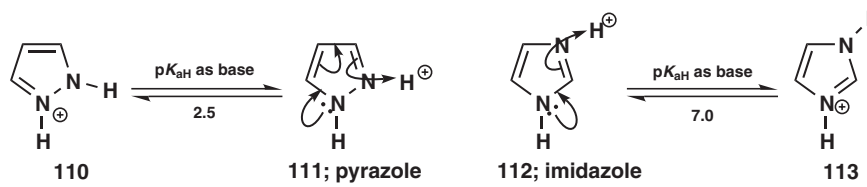
Part III – Disconnections Outside the Ring

a. N–C Disconnections: Azole Anions

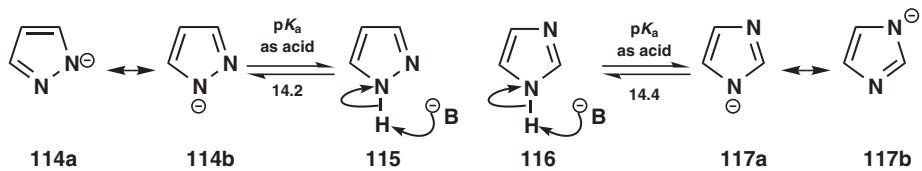
Though tetrazole is the most dramatic example of a stable anion from an azole, all the azoles show enhanced acidity when compared with simple cyclic amines.[12] Pyrrole (pK_{aH} −3.4) is a much weaker base than pyrrolidine (pK_{aH} +11.3) and it is protonated at carbon **107**, not at nitrogen, to give the de-aromatised ion **106** since the lone pair is delocalised round the ring. As an acid **108**, it is much stronger than simple amines since the anion **109** is aromatic, like the cyclopentadienyl anion, but more stable because of the electronegative nitrogen atom. Pyrrole is about as strong an acid as a tertiary alcohol, so bases that you might use to make *t*-BuO^-, such as NaH, are needed to make the anion.



Every additional nitrogen atom must be of the pyridine sort and this has the curious effect of increasing both the acidity and the basicity. There is another difference. Protonation now occurs on the pyridine-like nitrogen atom but both nitrogen atoms cooperate to deliver electrons in both pyrazole **111** and imidazole **112**. In this process the pyridine-like nitrogen atom becomes pyrrole-like and vice versa but this is merely formal as the cations **110** and **113** are symmetrically delocalised and the two nitrogen atoms are equivalent.

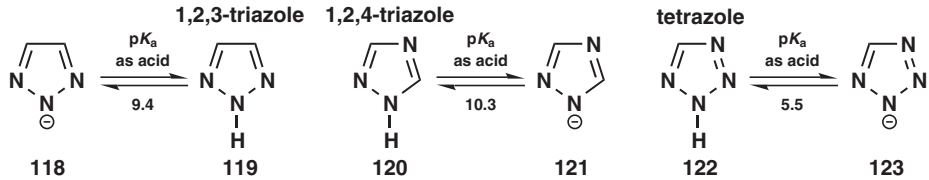


The action of pyrazole and imidazole as acids is simpler. In each case the anion (**114** or **117**) is aromatic, symmetrical, and more stable than the pyrrole anion because of the extra nitrogen atom. The two 'diazoles' pyrazole and imidazole are almost equal in acid strength.



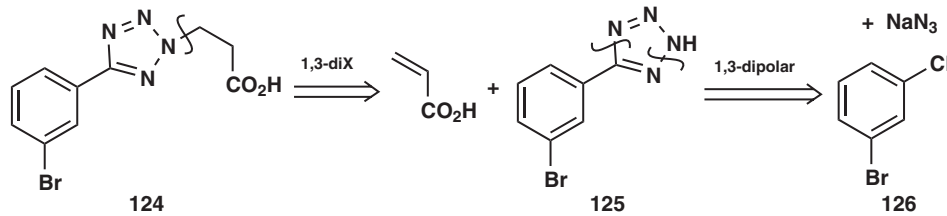
As we add (this is a thought process and not a chemical reaction) more nitrogen atoms the trend to greater acidity continues. The two triazoles **119** and **120** are stronger acids and, as we have seen,

tetrazole **122** is about as strongly acidic as carboxylic acids. All this information seems rather dull but it is essential to have a grasp of the trends when planning to make bonds to the nitrogen atoms of the azoles.

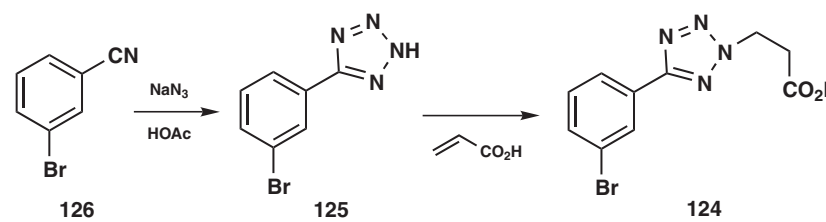


How to get reaction at nitrogen using azole anions

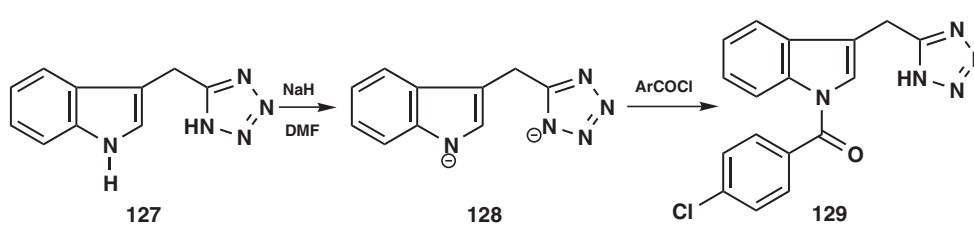
In a nutshell: if you want to make a bond to a nitrogen atom, use the anion. The simplest examples are tetrazoles. The anti-inflammatory broperamole is the piperidine amide of the acid **124** that has a 1,3-relationship that can be disconnected first to reveal a simple tetrazole **125** available by 1,3-dipolar cycloaddition.



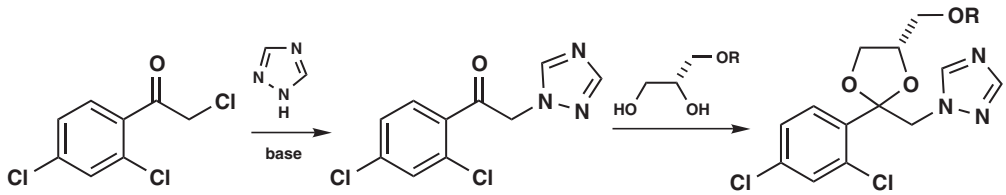
The tetrazole synthesis was done with azide and acetic acid and base-catalysed conjugate addition followed by treatment with $SOCl_2$, to make the acid chloride, and piperidine completed the synthesis.[13]



The indole-based drug **129** is clearly made by acylating an indole **127** and this was the last step in the synthesis, The problem here is chemoselectivity. The answer is the usual one of 'last in, first out'. The anion of the indole will be needed to ensure reaction at nitrogen but the anion of the tetrazole will be formed first. Two molecules of NaH make the dianion **128** and the less stable anion, that of the indole, reacts first.[14]

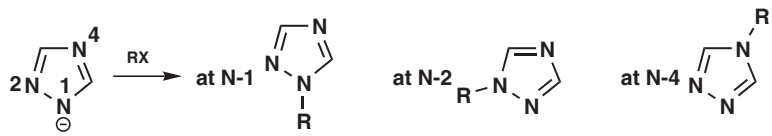


In many cases where azole anions are used, problems of regioselectivity arise too. There are many fungicidal drugs based on triazoles, usually 1,2,4-triazoles, and the anions of these compounds may have two different sites to react. The ketone **131** is made by alkylation of the triazole anion with the primary alkyl chloride[15] **130** and is the basis for many anti-fungal acetals **132**.



130 **131** **132; antifungal drugs**

The anion of 1,2,4-triazole **133** might be alkylated elsewhere. Reaction at N-1 or N-2 leads to the same product **134** but reaction at N-4 gives symmetrical **135** instead. It is not always easy to predict where reaction will occur but reaction at N-1 or N-2 is usually wanted and there is at least a 2:1 statistical factor in favour of this regioselectivity. We shall explore this question in the next section.



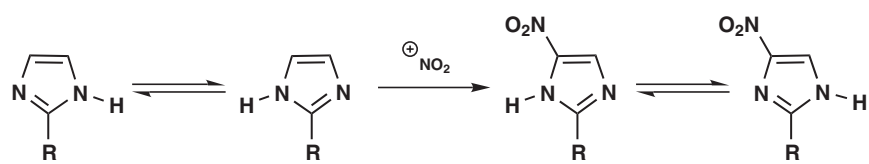
133 **134** **134** **135**

The problem of tautomerism in azoles

Any azole is a tautomeric mixture. That is not always obvious as, say, the two tautomers of imidazole itself are the same - they merely exchange protons in the way that a carboxylic acid does and this has no effect on reactions or synthesis.

tautomerism of imidazole **tautomerism of a carboxylic acid**

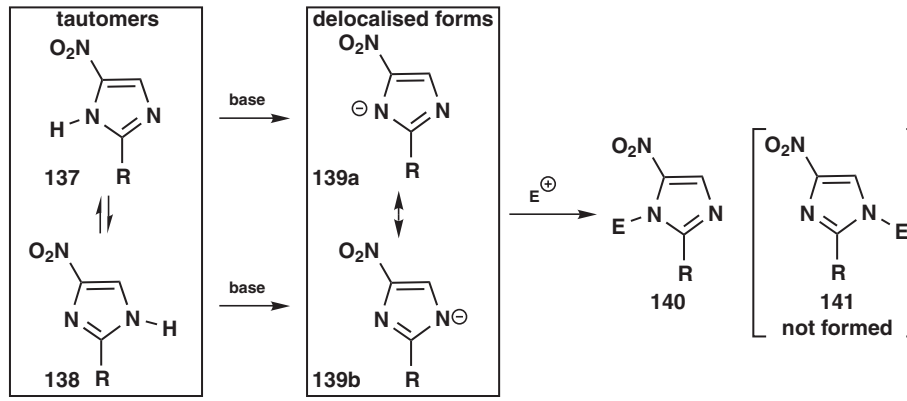
But as soon as there is substitution (anywhere except at the carbon atom between the two nitrogens **136**) the two tautomers become different and the sample contains both in equilibrium. Thus nitration of **136** gives a tautomeric mixture of **137** and **138**.



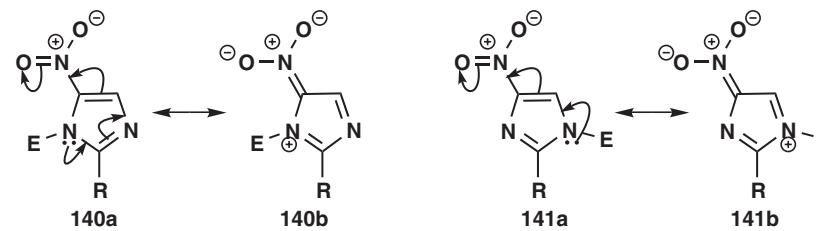
136a **136b** **137** **138**

There is no point in trying to separate these tautomers as each would rapidly equilibrate with the other. If the next reaction is intended to occur at one of the nitrogen atoms and so the anion is to be used, then all is well as both tautomers **137** and **138** give the same anion **139**. To be precise, the anion **139** is delocalised (**139a** and **139b** are just two different ways to draw the same anion) and protonation at either nitrogen atom gives one of the tautomers **137** or **138**. With such an

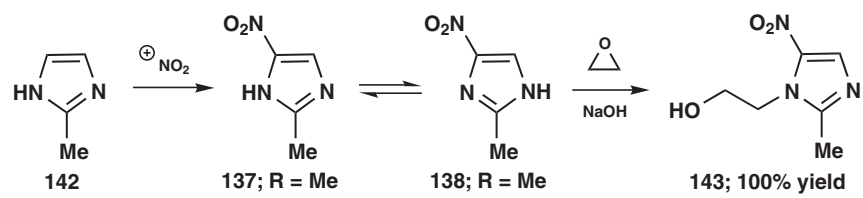
unsymmetrical anion, reasonable regioselectivity is to be expected, and the product on reaction of the anion **139** with an electrophile is isomer **140** rather than the other **141**.



Why should that isomer **140** be formed? The real reason is that the largest coefficient in the HOMO of the anion is at that nitrogen atom. This is not very helpful as it is not easy to work out quickly the distribution of coefficients in such molecules. Fortunately there is an easy way to find the answer. Look for the isomer of the product with the longest conjugated system between the pyrrole-like nitrogen and the functional group. Here the answer is clear-cut. The isomer formed **140** has conjugation from N lone pair to nitro group all round the ring as in **140a/b** while the other isomer **141** has that conjugation only round part of the ring **141a/b**.



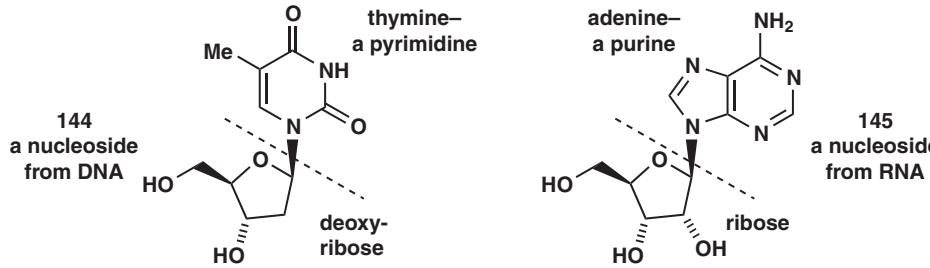
This chemistry is used in the synthesis of metronidazole[16] (Flagyl®) **143** a drug for the treatment of parasitic infections of the urinary tract. The substituent R is just methyl and the electrophile is ethylene oxide. The nitro group makes the imidazole NH in **137/8** even more acidic and NaOH is a strong enough base for the *N*-alkylation. The yield of **143** shows that regioselectivity is complete.



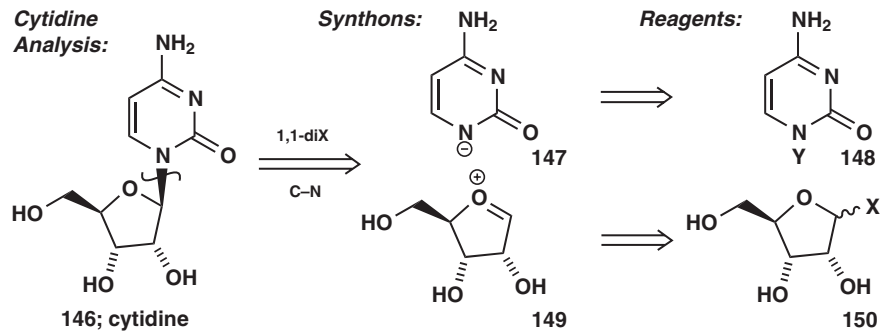
How to get reaction at nitrogen using silyl derivatives in acid solution

Not all reactions can be carried out in basic solution so we also need a method for adding electrophiles to heterocyclic nitrogen atoms in acidic solution. This is an important problem in nucleoside synthesis,

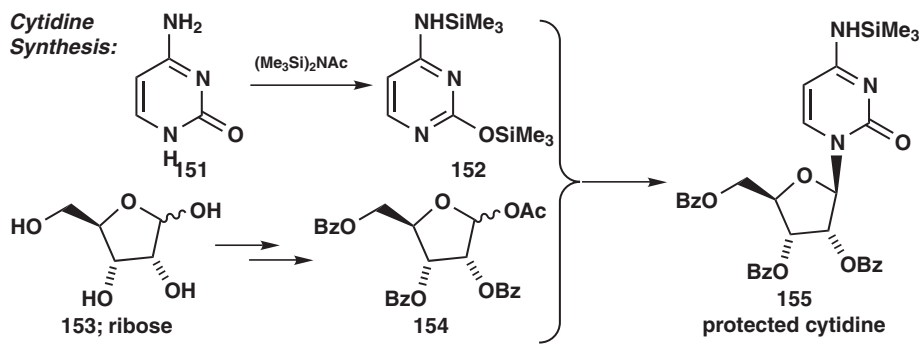
especially when modified nucleosides are needed for anti-viral compounds. A nucleoside consists of a 'base', a purine or a pyrimidine, joined through a nitrogen atom to a sugar. If the sugar is ribose we have an RNA-style nucleoside **145** and if deoxyribose, DNA-style **144**.



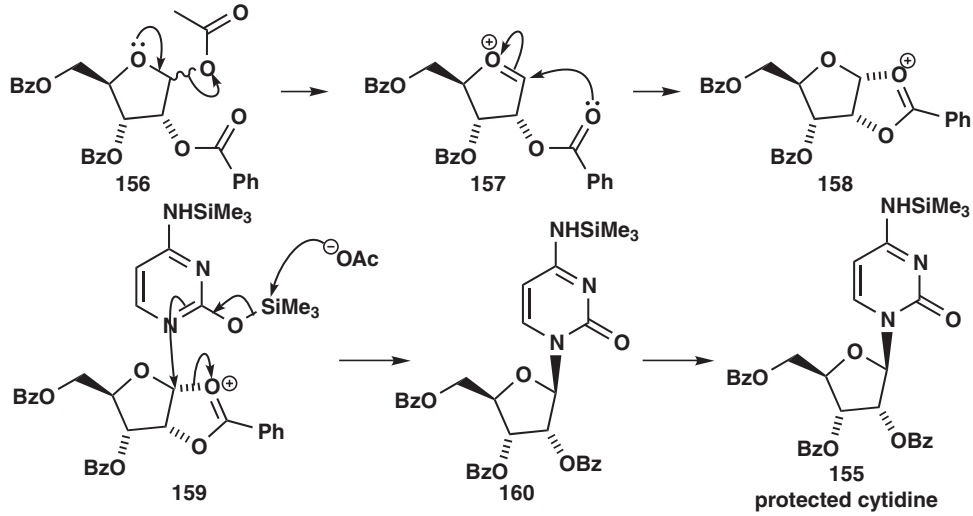
The obvious disconnection to make in any nucleoside is at the very strategic C–N bond between the two rings. Here is a proposed synthesis of cytidine **146**. It is also obvious to make the nitrogen a nucleophile **147** and the sugar the electrophile **149** by the addition of a leaving group **150**. The oxygen atom in the ring makes a cation at that position **149** rather favourable.



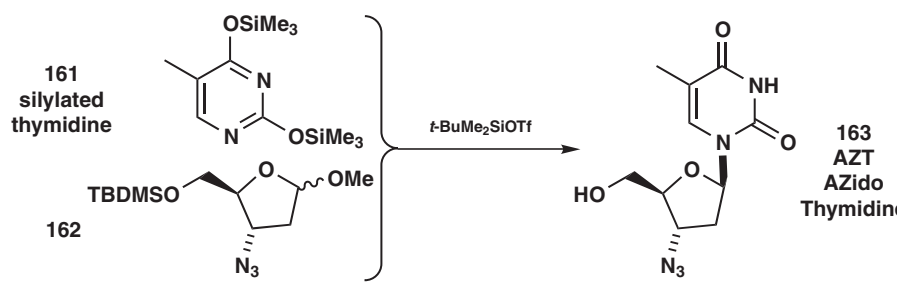
The leaving group on the sugar **150** could be a halide or acetate or even an alkoxide as we then would have an acetal. But these compounds will react in acidic rather than basic solution and so the problem is the structure of **148**: what can be Y? The answer is an $SiMe_3$ group, attached to the oxygen rather than the nitrogen and we have a famous silicon-directed nucleoside synthesis, the Vorbrüggen coupling.[17] The silyl group can be added in a number of ways and it will be important to protect all the OH groups.



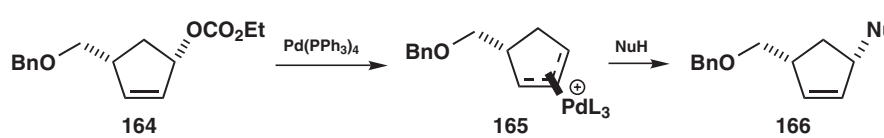
You may be surprised by the stereoselectivity of this coupling. The benzoate on the 2' position actually participates **157** after the acetate is lost **156** so that the silylated pyrimidine has to attack from the top face **159**. Silylated cytosine reacts rather like a silyl enol ether. This type of stereochemical control applies only to ribonucleosides and is more difficult to achieve without the 2' OH group.



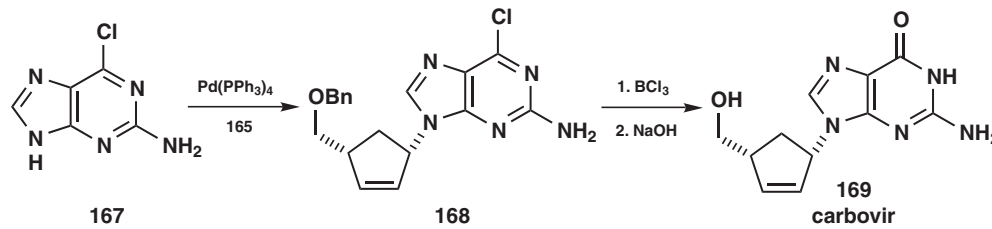
One synthesis of the important anti-viral drug AZT **163** (Azidothymidine, used in the treatment of HIV) shows this. The doubly silylated thymine **161** combines with the azido-sugar **162** under Lewis acid catalysis to give AZT after work-up. Only 33% of the required diastereoisomer **163** can be isolated and about the same amount of the other is formed.[18]



Other synthetic anti-viral compounds, such as carbovir **169**, lack the oxygen atom in the ring so that a route based on an S_N1 style stereoselective displacement appears impossible. Carbovir has a double bond in the ring however so that an η^3 palladium allyl cation complex allows regio- and stereo-selective displacement of an ester leaving group (chapter 19). The palladium attacks the alkene **164** from the opposite side to the leaving group to give **165**. The nucleophile then comes in from the opposite side to the palladium and at the end of the allyl cation farthest from the other substituent to give **166** with overall retention of configuration.



The starting material **164** can be made as a single enantiomer by the use of an oxazolidinone chiral auxiliary (chapter 27). Treatment with the chloropurine **167** catalysed by Pd(0) gave only the correct stereoisomer **168** in 63% yield - not a high yield but better than 33% - and deprotection and hydrolysis gave the guanine-derived carbovir[19] **169**.

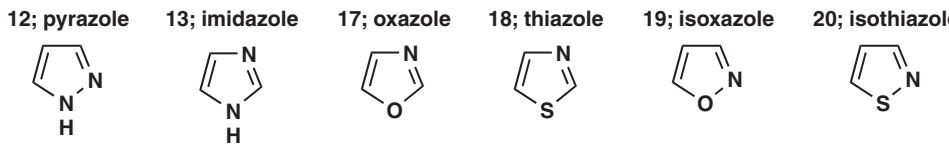


167 **168** **169** carbovir

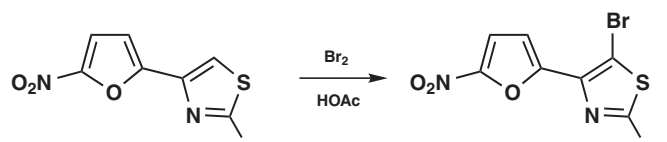
b. C–X Disconnections

Using electrophilic and nucleophilic aromatic substitution in five- and six-membered heterocycles. Chemo- and regioselectivity

Five-membered rings with two or more heteroatoms are usually good at electrophilic substitution as one of the heteroatoms must be either O or S or a pyrrole-like nitrogen atom any of which supply lone pair electrons. Pyrazole **12**, imidazole **13**, oxazole **17**, thiazole **18**, isoxazole **19** and isothiazole **20** are examples. Multiple substitution can be a problem but is less so than for pyrrole because there are fewer carbon atoms available and the pyridine-like nitrogen atoms deactivate the ring.

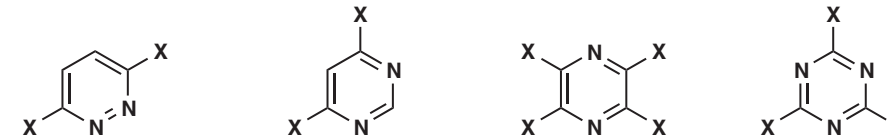


An example[20] is the antibiotic **171**. The nitro group on the furan ring of **170** was originally put in by nitration but now bromination is carried out in acetic acid. Furan is fundamentally more reactive towards bromine than the thiazole ring. However, the furan is deactivated by the nitro group while the thiazole is activated by the amino group. In fact bromination occurs exclusively at the one remaining position on the thiazole.

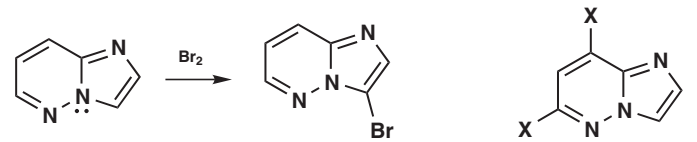


170 **171; 86% yield**

Six-membered rings with two or three nitrogens (they must all be pyridine-like) are very unreactive towards electrophilic attack but good at nucleophilic attack if there is any remotely feasible leaving group, even OR or better SR. The main ring systems are pyridazine, pyrimidine, pyrazine and triazine and the places where nucleophilic substitution occurs best are marked with an 'X'. We shall see examples of these reactions in the next section.

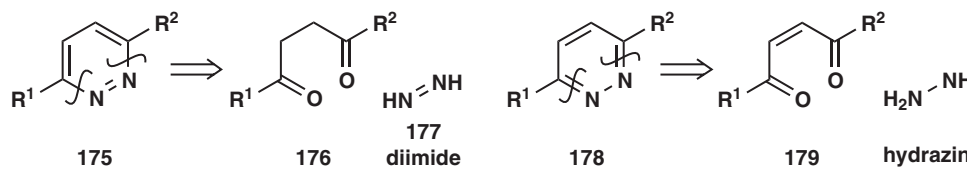


When there is a nitrogen atom common to two rings, one ring may be good at electrophilic and the other at nucleophilic substitution. In this example known as imidazo[1,5-*b*]pyridazine **172**, bromination occurs in the five-membered ring to give **173**, while nucleophilic substitution occurs if there are leaving groups X in the six-membered ring **174**. It is inevitable that the nitrogen common to both rings is of the pyrrole type and these systems are probably best considered as 10 electron aromatic compounds.

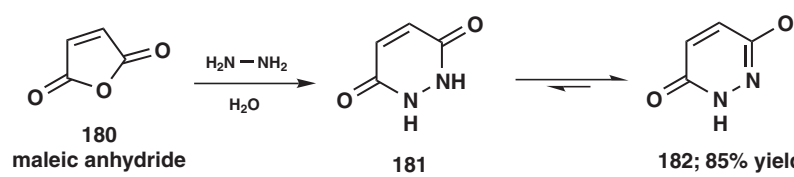


The synthesis of pyridazines

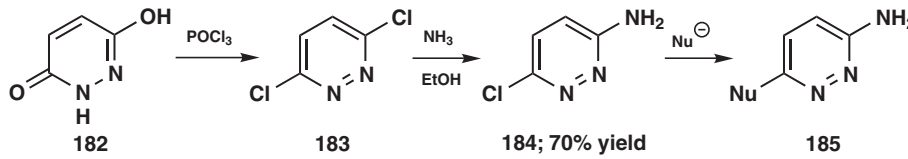
The 'most obvious' disconnection depends on which Kekulé form of the pyridazine you happen to draw. Disconnection of both C–N bonds reveals either **175** an encouraging 1,4-diketone **176** and a most discouraging molecule of diimide **177** or, by imine disconnection, **178** an encouraging molecule of available hydrazine and a rather discouraging *Z*-enedione **179**.



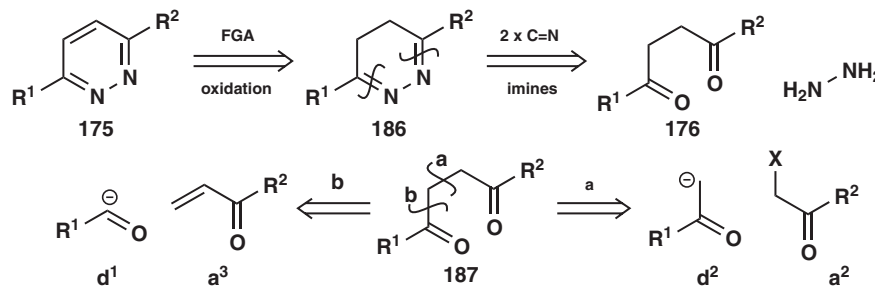
There is one useful case of the second disconnection. Maleic anhydride **180** has to have a *Z* alkene because of its cyclic structure. Reaction with hydrazine gives a diamide **181** that prefers to exist as **182** and is known as 'maleic hydrazide'.



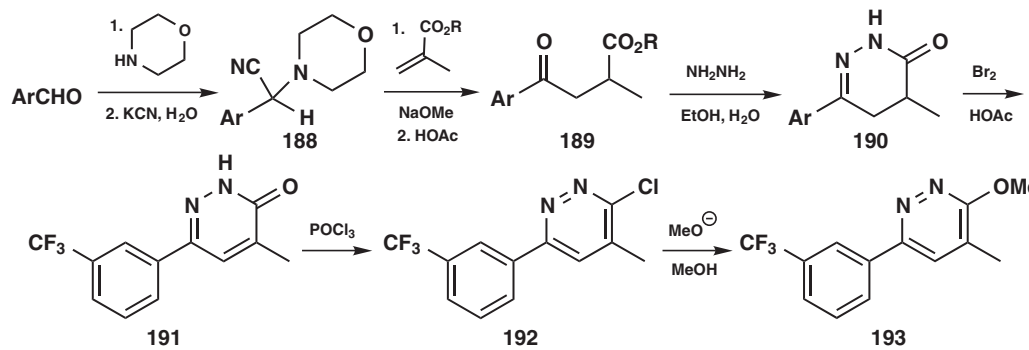
This product is useful because it gives the dichloride **182** with $POCl_3$. This compound reacts cleanly once with ammonia to give **184** and then again with any nucleophile, including amines under more vigorous conditions, to give **185**; Nu = NHR, OR, SR etc.[21]



A more general approach to pyrazines is based on an FGA strategy. Removal of the alkene also removes all the problems. Disconnection **186** of hydrazine gives the same simple 1,4-diketone **177** we saw before and the most obvious ways to make that **187** are the $d^1 + a^3$ or $d^2 + a^2$ strategies, both requiring some *umpolung.*



A simple example is the synthesis of Cyanamid's broad leaf herbicide **193** by the $d^1 + a^3$ strategy. *m*-Fluorobenzaldehyde combines with morpholine and cyanide to give the aminonitrile **188**. The marked proton is acidic because of the cyanide group. The anion is good at conjugate addition (these d^1 reagents were specifically designed by Stork for conjugate addition, chapter 9) and adds well to the methacrylate ester to give the 1,4-dicarbonyl compound **189**. Cyclisation with hydrazine and aromatisation with bromine gives the pyridazolone **191** and nucleophilic aromatic substitution by the $POCl_3$ and nucleophile (here methoxide) sequence gives the herbicide **193** in good yield.[22]

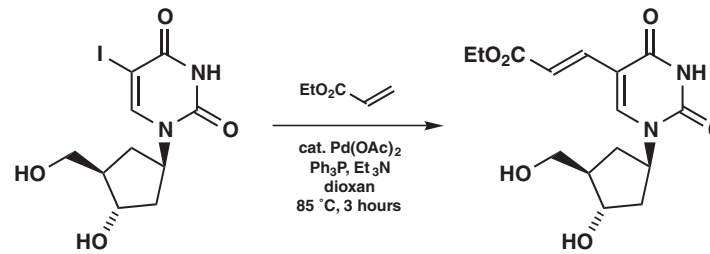


c. C–C Disconnections

The few reactions that work well with heterocycles. The Heck reaction, Friedel-Crafts acylation and a mention of lithiation

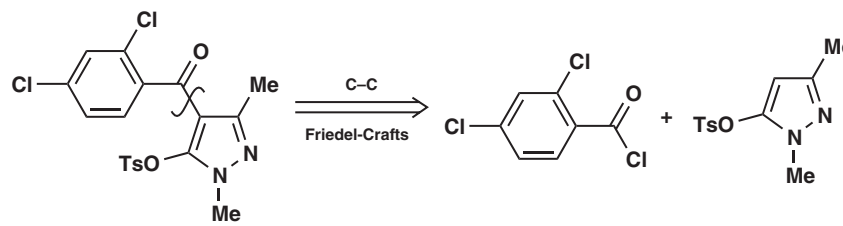
The ever-versatile Heck reaction (chapter 18) works well with most heterocycles providing one can put the halide or triflate in the right place on the heterocyclic ring. This example shows that an unprotected nucleoside **194**, made by iodination of deoxyuridine, reacts cleanly with ethyl acrylate

in a typical Heck reaction without any protection of the OH or NH groups in the nucleoside.[23] The reactions of nucleosides we have used so far have all required complete protection.



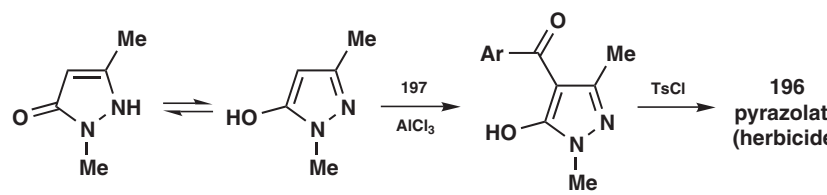
194 **195; 80% yield**

The Heck reaction makes a C–C bond and adds a highly functionalised fragment that can be elaborated into many other functional groups. The same is true of the Friedel-Crafts reaction that generally works well with azoles or other heterocycles able to do electrophilic substitution. As usual, it is best to have only one free position so that no regioselectivity problems arise. In the Heck reaction, the site of attack is marked by the iodine atom, but the Friedel-Crafts can occur at any free position. Our example is a pyrazole that acylates cleanly with Lewis acid catalysts to give eventually the herbicide pyrazolate **196**.



196; pyrazolate (herbicide) **197** **198**

It turns out that it is better to acylate the pyrazolone in a standard Friedel-Crafts fashion to give **201**. Whether you draw the pyrazole **200** as a pyrazolone **199** or not, there are plenty of electrons from one of the nitrogen atoms to activate the remaining free position in the ring. Subsequent tosylation fixes the molecule in pyrazole form as pyrazolate.



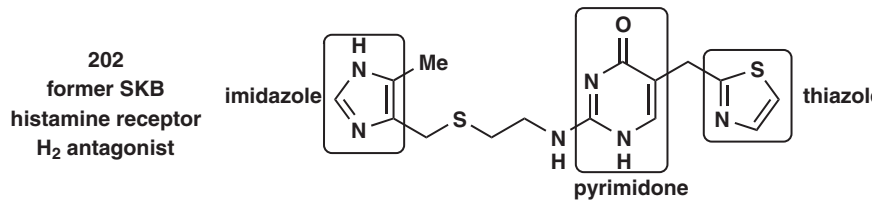
199 **200** **201**

d. Examples: an Anti-Ulcer Drug and Pentostatin

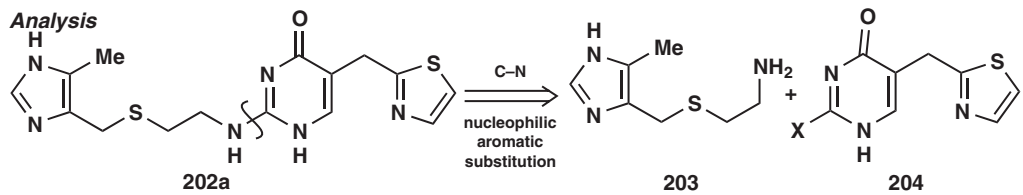
We give two examples: an anti-ulcer drug with three heterocyclic rings and an anti-viral and anti-tumour compound, pentostatin.

An isocytosine-based drug with three heterocyclic rings

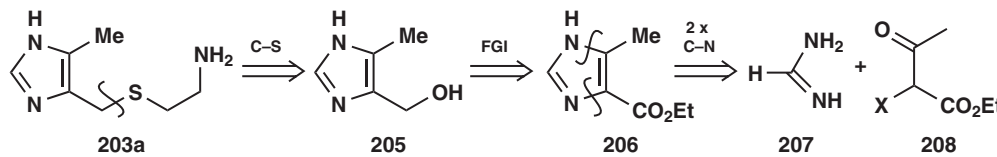
A series of anti-ulcer drugs such as cimetidine and ranitidine were the most successful drugs of all time when they first appeared. They work by inhibiting histamine action in the stomach. We shall look at a more modern version, a drug from what was then SmithKline Beecham, another H_2 receptor histamine antagonist[24] **202**. It is particularly appropriate for this chapter as it contains three heterocyclic rings with two heteroatoms each: an imidazole, a pyrimidone, and a thiazole and it allows us to revise material from other chapters as well as this.



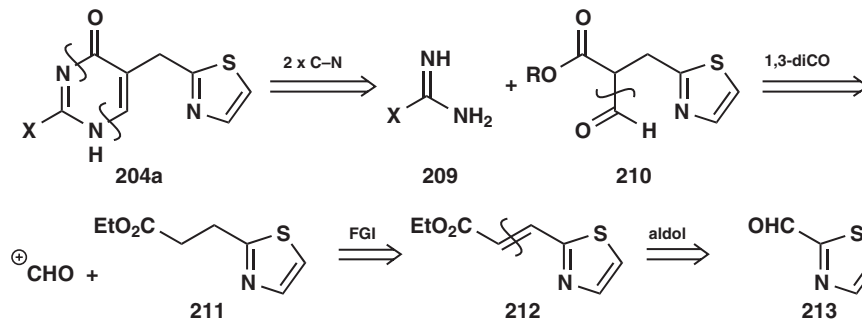
Strategically it is best to disconnect somewhere in the middle of the molecule and the ease of nucleophilic substitution on pyrimidones suggests the C–N bond *exo* to that ring **202a**. This gives us a relatively simple imidazole fragment **203** and a fragment with the other two rings **204**. The leaving group on the pyrimidone **204** (X) could be Cl but need only be as good as OMe.



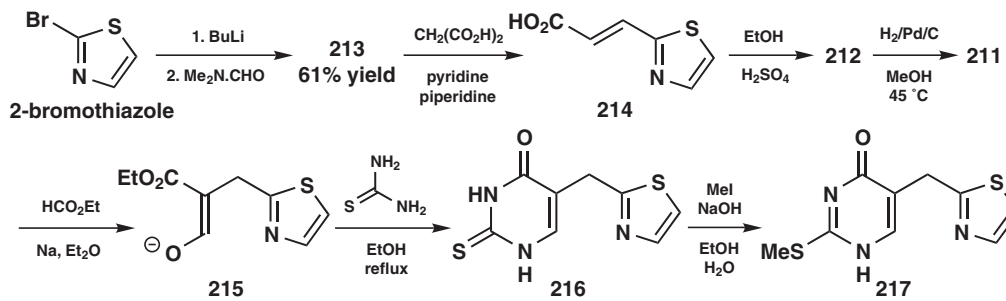
The imidazole **203** can easily be disconnected **203a** back to the simpler imidazole **205** and $H_2NCH_2CH_2SH$. You may forecast selectivity problems in the combination of unactivated **205** and the unprotected aminothiol, but wait. Alcohol **205** can be made from the ester **206** and that can be made from formamidine **207** and a suitably activated acetoacetate **208** (X is again a leaving group).



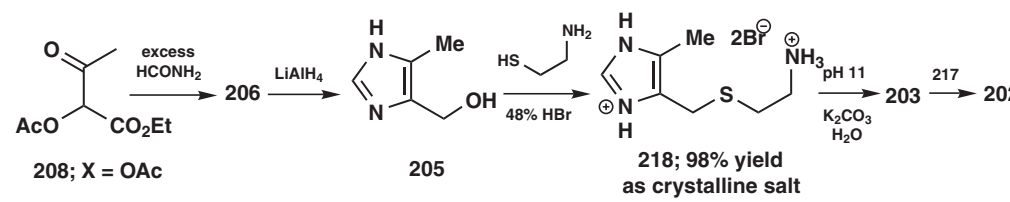
The remaining fragment can be disconnected **204a** at the six-membered ring by removal of some simple amidine derivative **209**. The remainder **210** has a 1,3-diCO relationship so a Claisen ester disconnection gives yet again a one-carbon electrophile and a simple ester **211**. This is best made from the unsaturated ester **212** and some sort of aldol reaction on **213**.



Now we must put the molecule together again. 2-Bromothiazole is available so lithiation and carbonylation with DMF gives **213** and an aldol (Knoevenagel) reaction with malonic acid gives **214** without a separate decarboxylation step. The best one-carbon electrophile is ethyl formate (HCO_2Et) and thiourea makes a suitable derivative of **209** for displacement.

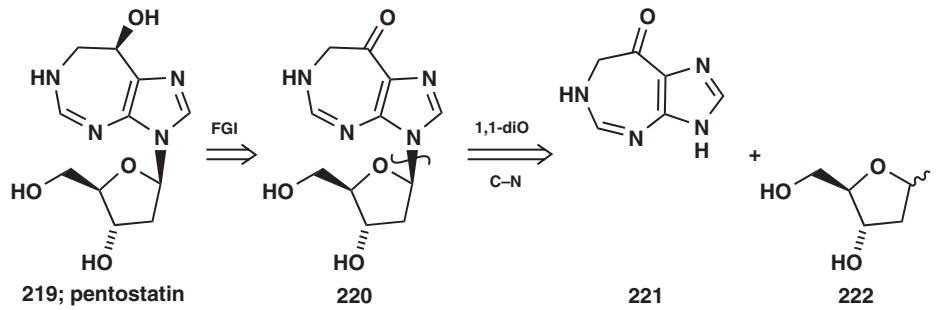


The other half starts with formation of the imidazole by the Bredereck reaction. The leaving group in **208** can be an acetate but more interestingly the nucleophile can be an excess of formamide $HCONH_2$. The alcohol **205** reacts selectively in strongly acidic solution with the aminothiol to give **218** without protection. After isolation as the HBr salt, **203** is liberated and reacted with **217** to give the complete molecule.

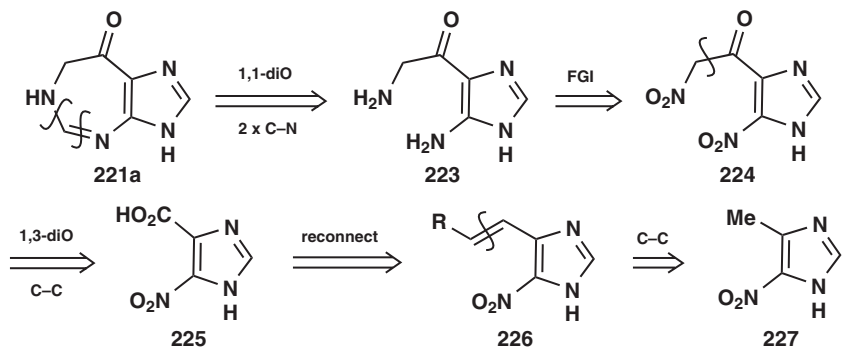


Pentostatin: an example with fused five- and seven-membered rings

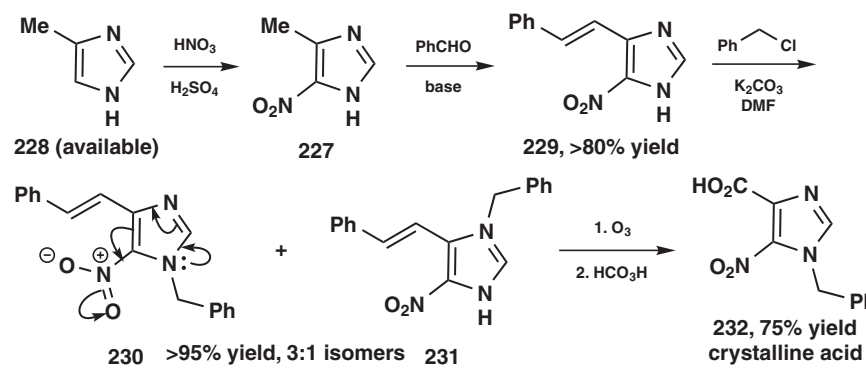
Pentostatin **219** is clearly a modified deoxynucleoside with a seven-membered ring instead of the normal six-membered ring of a purine.[25] It is simplest to remove the stereochemistry in the seven-membered ring by FGI of the alcohol to a ketone **220**. We can then disconnect the sugar, expecting to use the sort of chemistry earlier in the chapter, maybe a silyl derivative of the purine analogue **221** and a derivative of the sugar **222**, maybe with X = OAc.



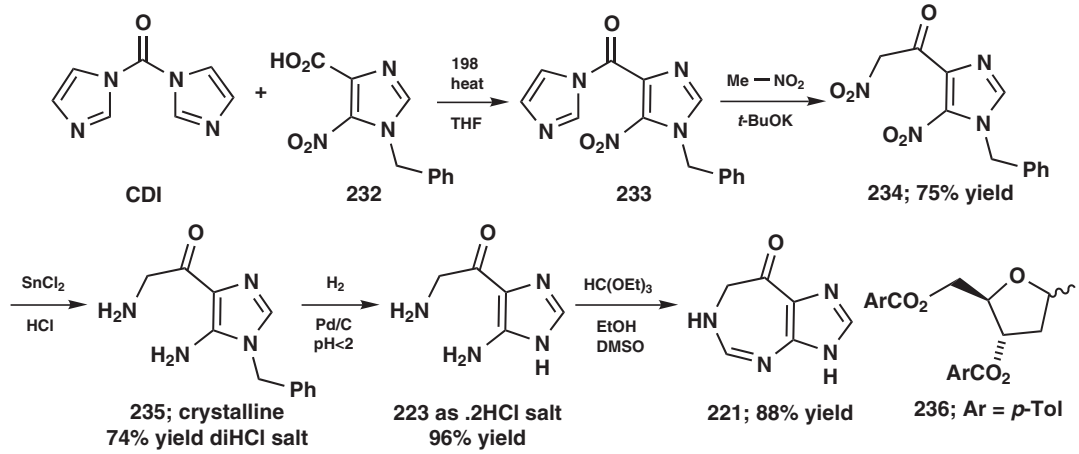
The sugar is available deoxyribose but the seven-membered ring heterocycle **221** must be made. Disconnection of the one atom electrophile from between the two nitrogen atoms reveals a diamine **223** that can be made by reduction of a dinitro compound **224**. Removal of nitromethane from **224** gives a simple nitroimidazole carboxylic acid **225**. Clearly the nitro group will be added by direct nitration but we can take advantage of its presence to reconnect an alkene **226** to the carboxylic acid with the idea of using the nitro group to activate the methyl group in **227**. Nitration of 4-methylimidazole would be expected to go where we want it as the only alternative, C-3, is between the two nitrogen atoms and less reactive to electrophiles.



The synthesis starts with the routine nitration of available **228** and the base-catalysed reaction of **227** with benzaldehyde to give **229** (**226**; R=Ph). It is necessary to protect this and benzylation in base gives predominantly the isomer **230** with the longest conjugated system. Ozonolysis (ozonation) reveals the stable crystalline carboxylic acid **232**. After deprotection, both isomers give **225**.



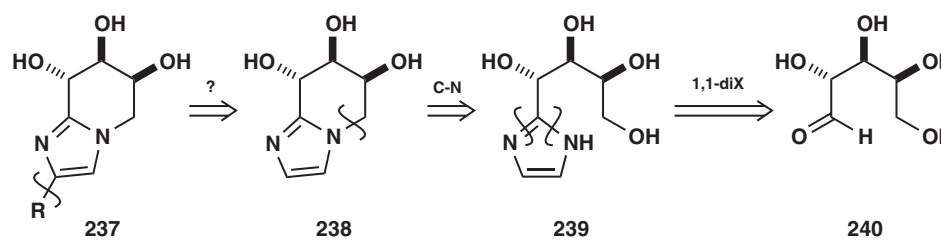
Now the seven-membered ring must be built up. Here an azole-based reagent, CDI, carbonyl di-imidazole proves invaluable. Reaction with **232** gives the acylimidazole **233** and this acylates the potassium 'enolate' of nitromethane in good yield to give **234** and hence, by reduction, the diamine **235**. The *N*-benzyl group can now be removed and the synthesis of the seven-membered ring is completed with the one-carbon electrophile $HC(OEt)_3$.



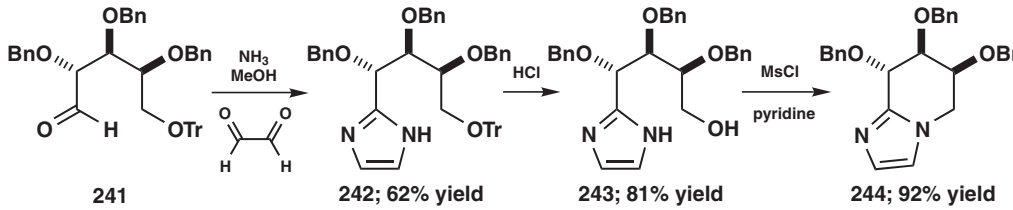
The rest of the synthesis follows the methods already discussed. The purine analogue **221** was silylated and coupled with the sugar derivative **236** to give a mixture of stereoisomers at the anomeric position. Deprotection and not very stereoselective reduction gave pentostatin.

A Designed Enzyme Inhibitor

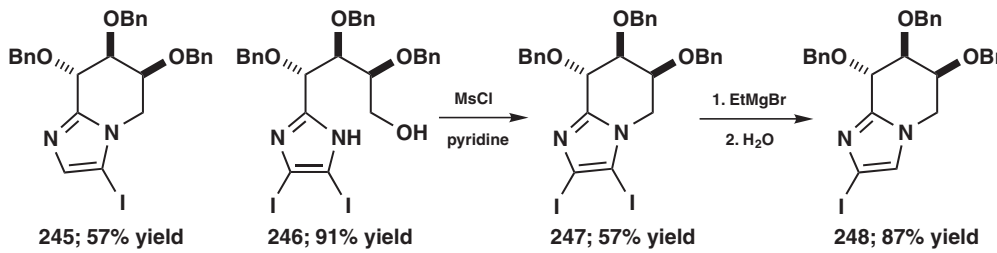
Modified sugars are important sources of new drugs. Imidazoles such as **238** are glucosidase inhibitors and Streith[26] and co-workers set out to develop more potent inhibitors by introducing substituents R into the basic structure. Modifying a core structure introduces diversity quickly from a single compound. The core structure **238** obviously comes from a sugar and the easiest way to remove the imidazole is to expose it **239** and then use an imidazole synthesis from an aldehyde **240** that is arabinose. How to add the substituent R regioselectively to **238** is not obvious.



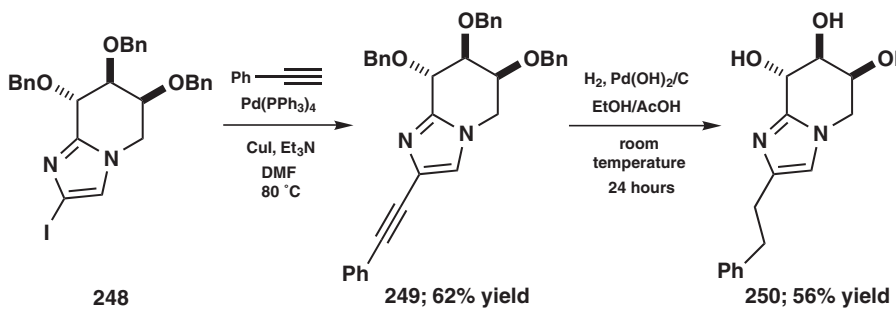
A protected form **241** of the aldehyde **240** was easily made from arabinose and the imidazole inserted with glyoxal and ammonia. Removal of the trityl group with HCl and cyclisation via the mesylate gave **244**, a protected version of **238**.



Now comes the moment of truth. Can **244** be functionalised regiospecifically? Though the imidazole portion is unsymmetrical, it is not a tautomeric mixture (in contrast to **136** and **137**). Iodination with NIS gives the wrong isomer **245**, the one with the longer conjugated system. The uncyclised imidazole **243** reacts twice to give **246** and hence by cyclisation and deiodination, **248**.



Each isomer can be combined with a variety of electrophiles using Mg or Pd as the metal to replace iodine by oxidative insertion, and the best inhibitor **250** was made by Sonagashira coupling of **248** to phenyl acetylene and reduction of **249** to the saturated compound.



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General references are given on page 893

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36 Tandem Organic Reactions

This final chapter examines a strategy – combining two or more distinct reactions in a single operation. The first reaction gives an intermediate, usually one difficult to make, that does a different reaction to make a product much larger than any starting material. Any type of chemistry may be used so this chapter also revises material from the earlier parts of the book.

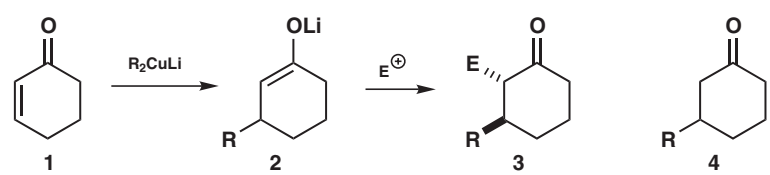
Organic Synthesis: Strategy and Control, Written by Paul Wyatt and Stuart Warren

Part I – Introduction

What are Tandem Reactions?

Short historical background

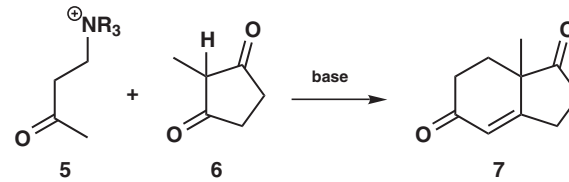
Tandem reactions[1] were originally any pair of reactions that followed one another in a single operation like the two people on a tandem. The most famous example still is conjugate addition followed by trapping of the specific enolate with an electrophile.[2] Addition of a lithium cuprate to the enone **1** gives the lithium enolate **2** and this combines with an electrophile to give the *anti* disubstituted ketone **3**. The point of making this a tandem process is that the enolate **2** could not be easily made from the parent ketone **4**.



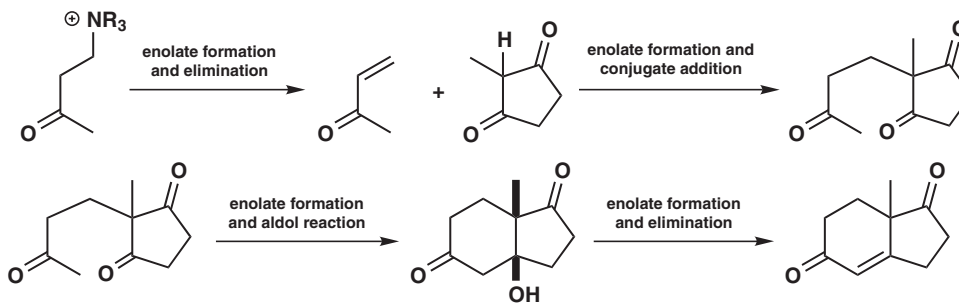
Since tandem reactions first appeared they have been given many diverse names such as cascade, consecutive, and coupled processes, domino reactions, interrupted polymerisation, one-pot, sequential and serial reactions, and tactical combinations. Some authors have tried to classify

tandem processes according to the lifetime of the intermediate, whether it is isolated, whether the two reactions follow spontaneously or need some intervention by the chemist and so on. It seems to us most helpful to call all these multi-step reactions carried out in one flask 'tandem reactions' and to prefer a discussion of their strategical significance to any attempt at a formal classification.

There is nothing new in reactions occurring in many steps all in the same pot. The Robinson annelation is a classic where conjugate addition and intramolecular aldol reactions follow each other without as break. An extreme example would be the reaction of a Mannich salt **5** with the 1,3-diketone **6** to give the enone **7** on treatment with base



Most chemists would consider that there are four separate steps in this reaction: elimination, conjugate addition, aldol reaction and dehydration. Mechanistically we should double this number as each step requires preliminary enolate ion formation.



Criteria for tandem reactions discussed in this chapter

In spite of all these steps, chemists do not usually consider the Robinson annelation a tandem reaction. This is partly because it is an old reaction but partly because each intermediate would, if isolated, give the same reaction as in the one-pot process. We shall describe as tandem reactions only those that have

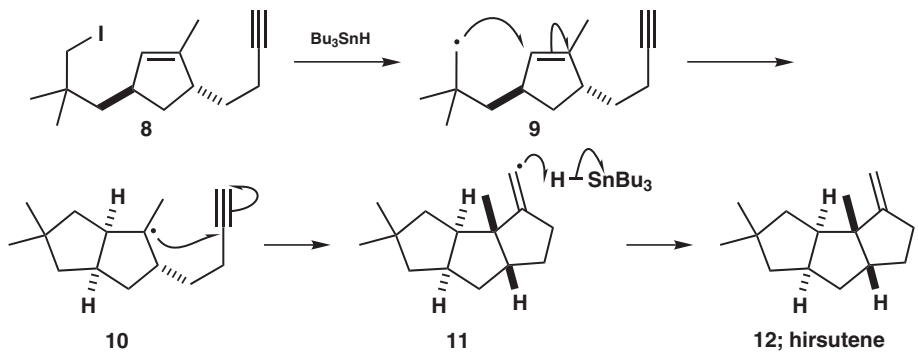
- At least two steps that form significant bonds (C–C or C–X)
- An intermediate produced in the first step that would be tricky to make otherwise.
- A second step that in some way depends on the first.
- Some advantage in running the steps in sequence such as regio- or stereoselectivity.
- Some degree of surprise in the way the reaction works (not entirely serious).

Tandem Reactions We Shall Not Discuss

Radical chain reactions

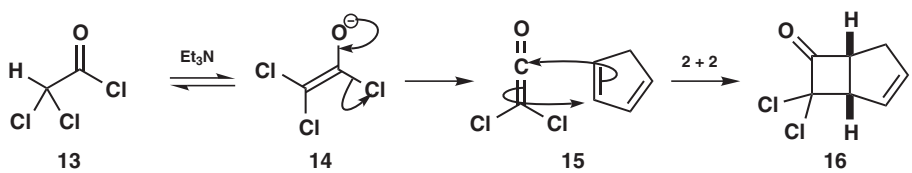
Some reactions that undoubtedly meet all these criteria we shall nevertheless exclude to restrict the chapter to a manageable size. Radical chain reactions, such as the synthesis of hirsutene **12**

by Curran, are tandem processes. The initial radical **9** cyclises first to a new tertiary radical **10** by a 5-*exo-trig* process and this in turn forms a second ring **11** by a 5-*exo-dig* cyclisation. Neither intermediate **10** nor **11** would be easy to make except by tandem reactions and there is excellent regio- and stereochemical control.[3]



Highly reactive intermediates

Nor shall we discuss reactions of highly reactive intermediates such as carbocations, carbanions, ketenes (such as **14**), or benzynes that are always prepared in the presence of the molecule with which they are to react. This 2 + 2 ketene cycloaddition **15** actually involves three steps but the ketene is very reactive and cyclopentadiene must be present when it is formed if a good yield of the important adduct **16** is to be had.



Polymerisation

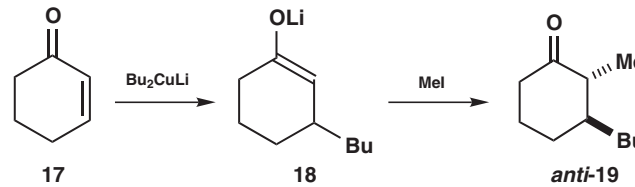
We shall not discuss polymerisation nor reactions that can be made to occur in one pot but are essentially independent processes except where there is an advantage in running them in tandem fashion. Since the most important aspect of tandem reactions is the nature of the intermediate after the first reaction, the first section has conjugate addition as the first step and explores the way a second reaction can use the enolate produced.

Part II – Conjugate Addition as the First Step

Simple Enolate Capture by Electrophiles

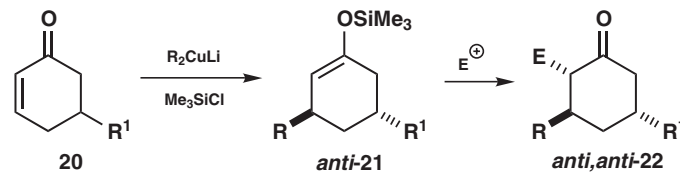
Anti *stereochemistry in six-membered rings*

Following our introduction, a simple example[4] of conjugate addition is a cuprate addition to cyclohexenone followed by trapping of the lithium enolate **18** with MeI to give the *anti* product **19**.



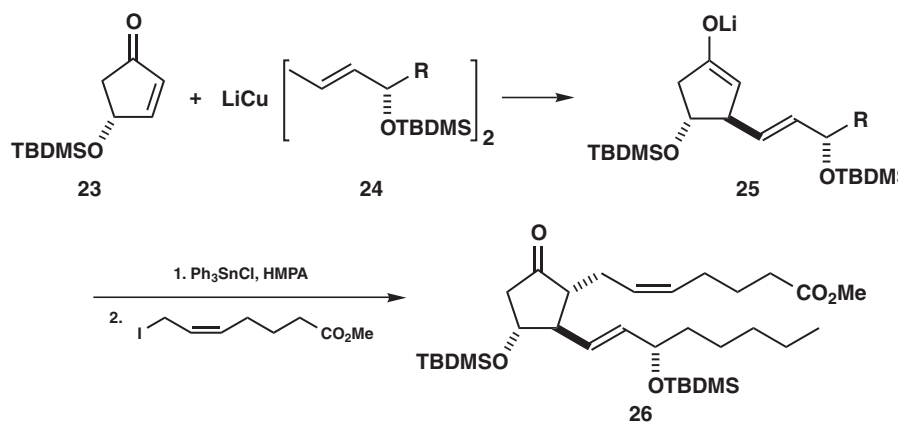
Conformational control from a chiral centre in the cyclohexenone

A more interesting situation arises with a substituent already on C-5 **20**. The cuprate then adds *anti* to that substituent (the intermediate is here trapped as a silyl ether *anti*-**21**) and trapping with electrophiles introduces a second *anti* relationship *anti, anti*-**22**. The stereoselectivity arises by axial attack both during the conjugate addition and on the enolate (chapter 21).



Remote stereochemical control in five-membered rings: prostaglandins

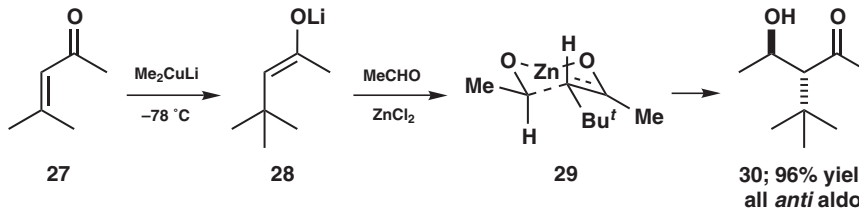
If the ring is not six-membered, conjugate addition occurs on the less hindered face, usually opposite any substituent. An example **26** in prostaglandin synthesis also makes the point that tandem reactions don't automatically solve all problems.[5,6]



Addition of the enantiomerically pure cuprate **24** to the enantiomerically pure cyclopentenone **23** occurs stereoselectively on the face of the enone **23** opposite the large silyl ether to give the lithium enolate **25**. Reaction with an electrophile would be expected to occur on the bottom face as the nearer (and larger) substituent is on the top face. And so it does, but it was not expected that the lithium had to be exchanged for a Ph_3Sn group to make the rather crowded enolate reactive enough for alkylation. The sequence round the ring is thus *anti*, *anti*. Notice that the allyl group is added as an electrophile (chapter 19) but the vinyl group is added as a nucleophile (chapter 16) in both cases with control over *E/Z* geometry. This is indeed, as Noyori calls his paper,[6] 'An Extremely Short Way to Prostaglandins.'

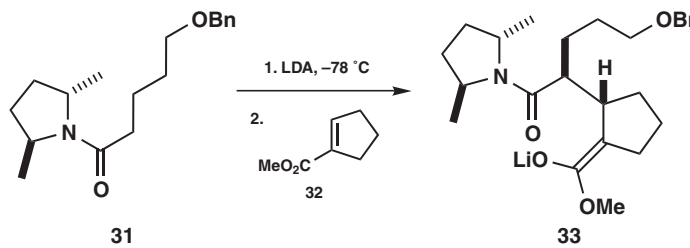
Regio- and stereochemical control in open chain compounds

Simple stereoselective aldol reactions (chapter 3) can also be controlled by tandem conjugate addition. Addition of Me_2CuLi to the simple unsaturated ketone **27** gives the lithium enolate **28**. It would be very difficult to produce this enolate from the parent ketone *t*-BuCO.Me with regio- or stereoselectivity. The cyclic transition state **29** with zinc replacing lithium then shows the way to the *anti*-aldol[7] **30**.

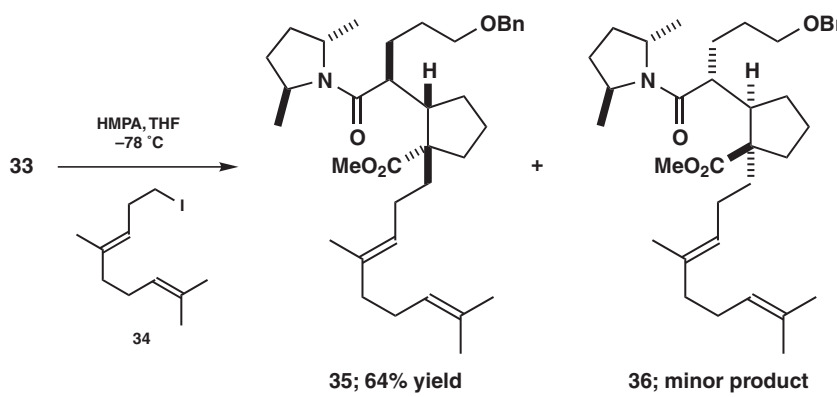


Asymmetric induction by a chiral auxiliary on the enolate

If no component has stereochemistry, asymmetric conjugate addition can be ensured by a C_2 symmetric chiral auxiliary attached to the enolate partner. Addition of the lithium enolate of the amide **31** to the unsaturated ester **32** gives the lithium enolate **33** with good stereochemical control at both the new centres.[8]



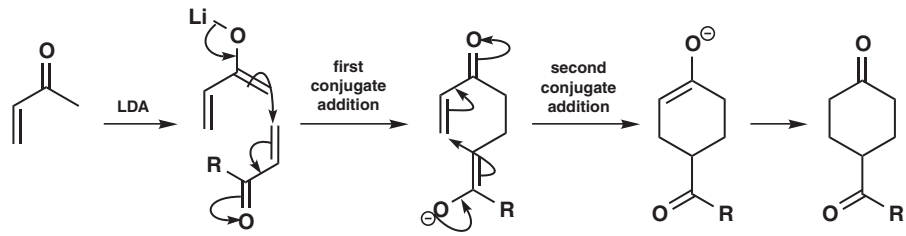
Alkylation with **34** now occurs to give mostly (11:1) the product **35** with the two new chains attached *trans* (*anti*-) to the five-membered ring. The yield is only moderate as is often the case in tandem reactions. The advantages of combining three substantial fragments regioselectively with the creation of three new stereogenic centres with absolute as well as relative stereochemical control outweigh this low yield. After all, no stepwise process is likely to give as much of **35**. The minor diastereoisomer **36** has the same relative stereochemistry as **35** in the new portion but, on amide hydrolysis, would give the other enantiomer of the product. Another way to put this is that the initial induction during the conjugate addition is imperfectly controlled but that the second step, the alkylation, is entirely stereoselective. See later for the next step.



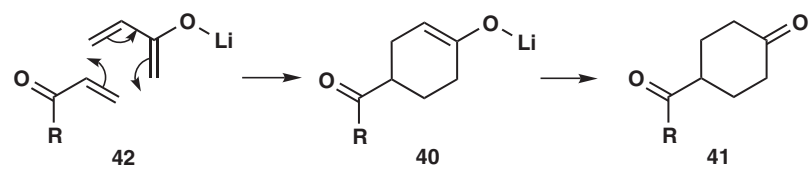
Tandem Michael-Michael Reactions: One Conjugate Addition Follows Another

Double Michael or Diels-Alder reaction?

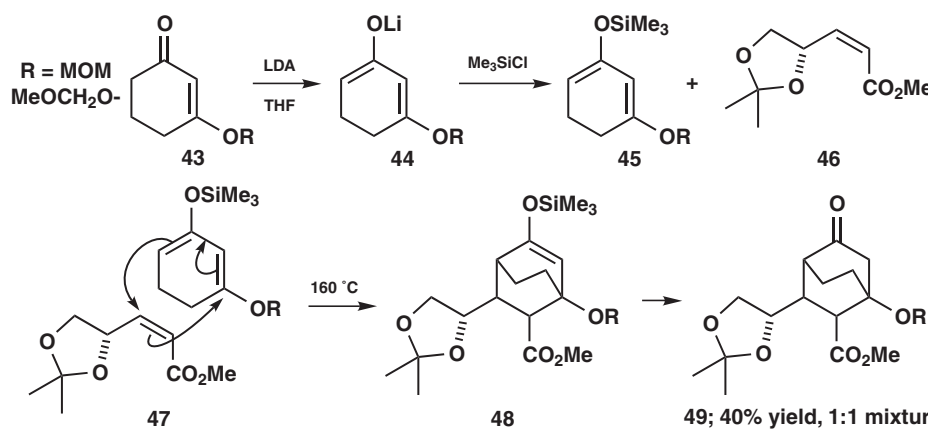
An important type of tandem reaction arises when both steps are conjugate additions (Michael reactions, chapter 9). The most widely used case is the conjugate addition **38** of a kinetic α' enolate from an enone **37** (chapter 11) to a second enone. The resulting enolate than adds back **39** to the first compound in a second conjugate addition. The product **41** contains a six-membered ring formed in the tandem process.



There is an alternative interpretation of this sequence: that the kinetic enolate does a Diels-Alder reaction **42** with the second enone. The regiochemistry is right: the more nucleophilic end of the enolate (higher energy HOMO) adds to the more electrophilic end of the second enone (larger coefficient in the LUMO). It is not possible to tell which mechanism is right in this example as there is no stereochemistry in the product and in any case this is a simplified example: most reported cases are much more complex.

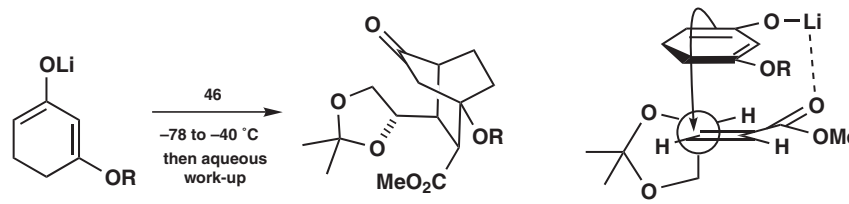


In one case the reaction was conducted as a genuine Diels-Alder reaction on the silyl enol ether **45** of the α'-enolate **44** to see what the result would be.[9] The Diels-Alder reaction **47** with the enantiomerically pure enoate ester **46** required 160 °C and gave a 40% yield of a 1:1 mixture of diastereoisomers of **49**.



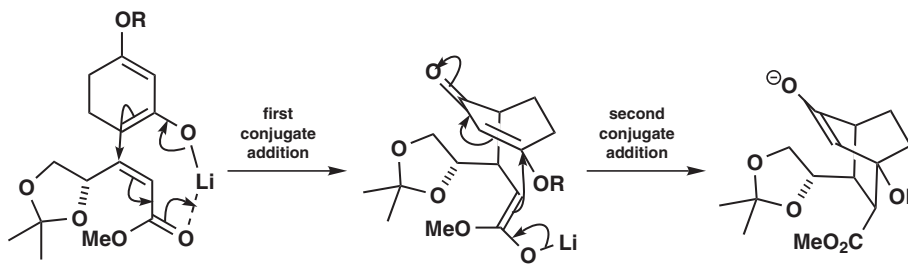
Stereochemical control in the double conjugate addition

The tandem Michael-Michael reaction gave a very different result. This time the lithium enolate **44** reacted with the unsaturated ester **46** at −78 to −40 °C and gave an 86% yield of a single adduct, *endo*-**49**. The most obvious conclusion is that the reaction does indeed go by a two-step mechanism, especially as the stereochemistry can be convincingly explained by lithium coordination to the two reagents **50**. There is just a possibility that it is a Diels-Alder reaction showing greater stereoselectivity because of the lower temperature.



44 ***endo*-49; 86% yield** **50**

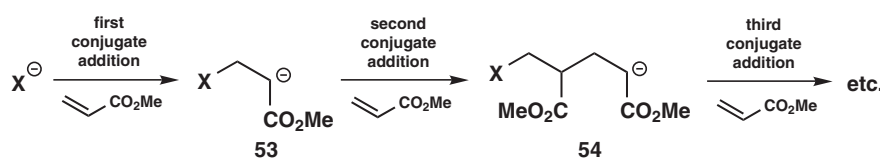
The stereochemistry is controlled by the first conjugate addition represented mechanistically as **50a** that gives the new lithium enolate in the right conformation for the second conjugate addition **51** giving the enolate **52** of *endo*-**49**. We shall assume that these reactions are tandem Michael-Michael additions for the rest of this section.



50a **51** **52**

Tandem Reactions as Polymerisation Terminated by Cyclisation

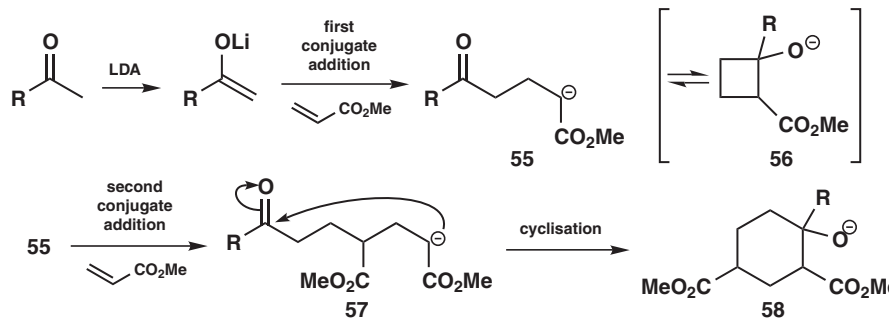
We have just seen how one conjugate addition can be followed by a second leading to a six-membered ring. If instead the product **53** of the first conjugate addition reacts with a second molecule of the Michael acceptor, this could be the start of polymerisation.



53 **54**

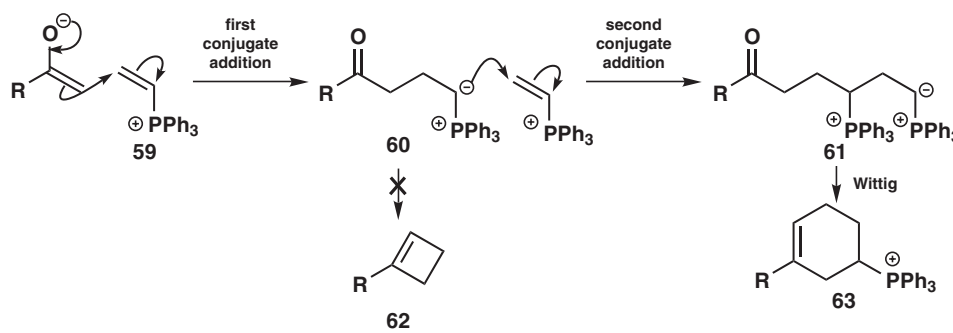
We lose interest in the polymerisation but imagine that the original nucleophile was the enolate of a carbonyl compound. Now the first two adducts have an alternative: they could cyclise.

It is not likely that **55** will cyclise as it would give a four-membered ring **56**, but **57** is very likely to cyclise to the six-membered ring **58**. If cyclisation is faster than the bimolecular addition of another Michael acceptor, the polymerisation will be interrupted and an efficient tandem process invented.

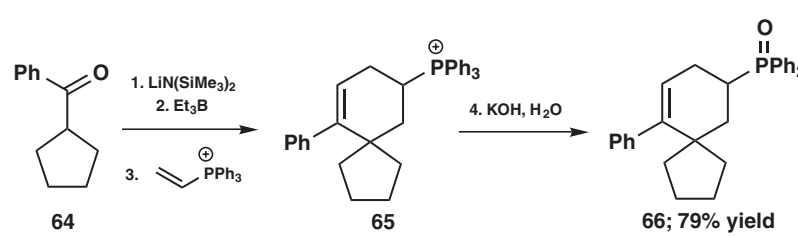


The 'MIMIRC' sequence with vinyl phosphonium salts

This is the basis of Posner's 'MIMIRC' (Michael-Michael-Ring Closure) sequences.[10] In the first example, the electrophile is a vinyl phosphonium salt **59**. The first adduct **60** could cyclise, by the Wittig reaction, only to a cyclobutene **62** so it prefers to add a second molecule of **59** but the next intermediate **61** cyclises to a six-membered ring **63**.

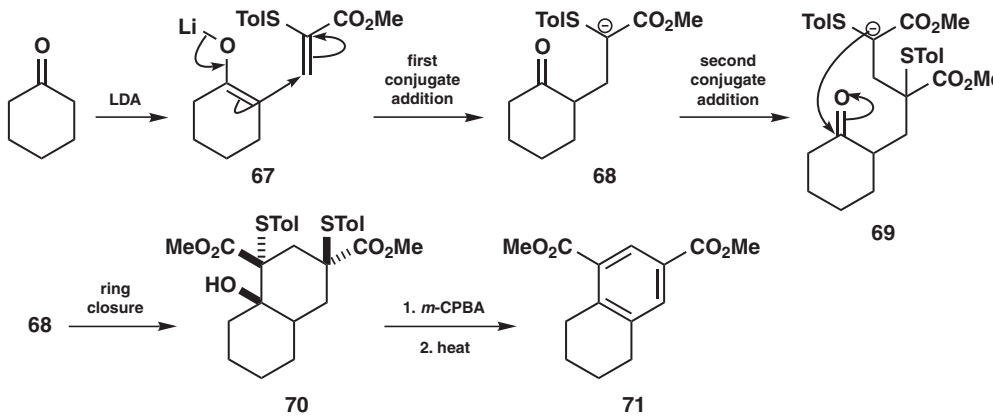


The final product **63** retains the Ph_3P^+ group from the first vinyl phosphonium salt **59** and in the example below, using a boron enolate, this was hydrolysed to the stable phosphine oxide[11] **66**. Note the creation of a quaternary carbon atom at a *spiro* centre.



Tuning the 'MIMIRC' sequence with different Michael acceptors

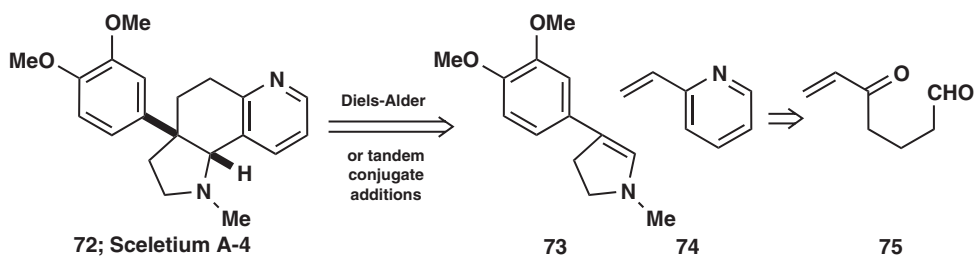
Fine tuning of the Michael acceptor led to better MIMIRC reactions. The combination of an ester group and an ArS at one end of the vinyl group is ideal.[12] The tandem product **70** is isolated as a single diastereoisomer in 55% yield, an average yield of 82% for the formation of each C–C bond. The ArS groups can be removed by oxidation to the sulfoxide and thermal elimination (chapter 33). Spontaneous dehydration gives the benzene ring **71**.



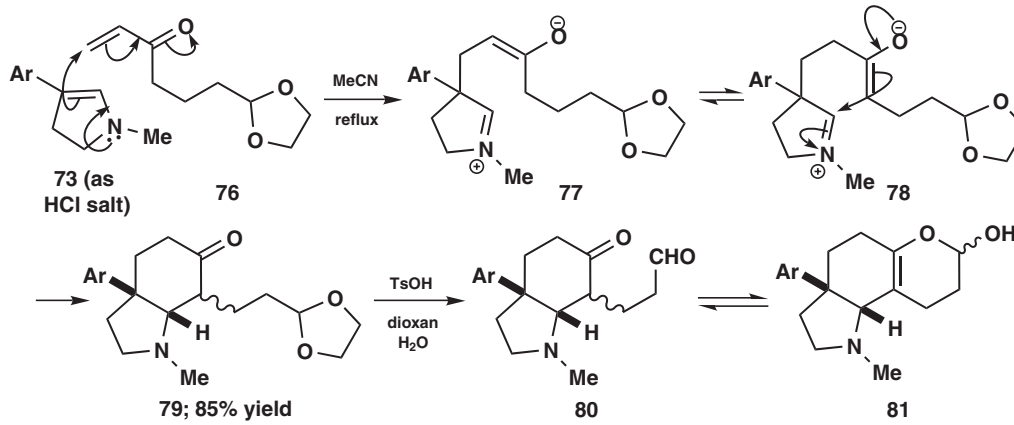
Heterocycles by Tandem Conjugate Additions

Tandem conjugate addition and Mannich reaction

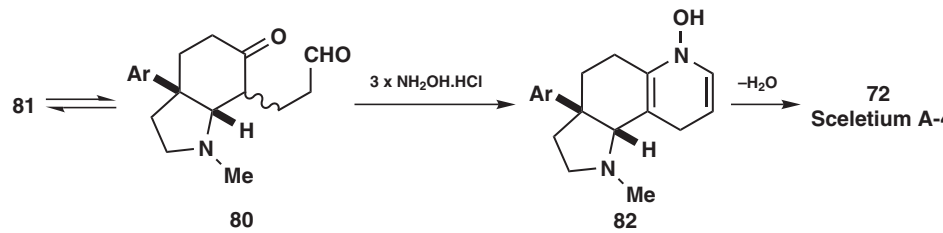
This type of sequence should be ideal for the construction of heterocyclic systems too. The *Sceletium* alkaloids have fused cyclohexane and pyrrolidine rings with a substituted benzene at the ring junction. Sceletium A-4 **72** also has a pyridine fused onto the cyclohexane ring. It looks as though tandem conjugate additions of the cyclic enamine **73** to the vinyl pyridine **74** might be a good synthesis of this compound but the vinyl pyridine is not electrophilic enough.



The answer is to use a protected form of the unsaturated ketoaldehyde **75** instead and build the pyridine afterwards.[13] The synthesis of the cyclic enamine **73** appears as a problem in the workbook. Conjugate addition of the enamine **73** gives one enolate **77** that equilibrates with the other **78**: cyclisation now gives **79**. Deprotection reveals the aldehyde **80** that exists as a mixture with the hemiacetal of its enol **81**. The 6/5 ring junction is formed preferentially *syn* while the third chiral centre is lost in equilibration with **81**.



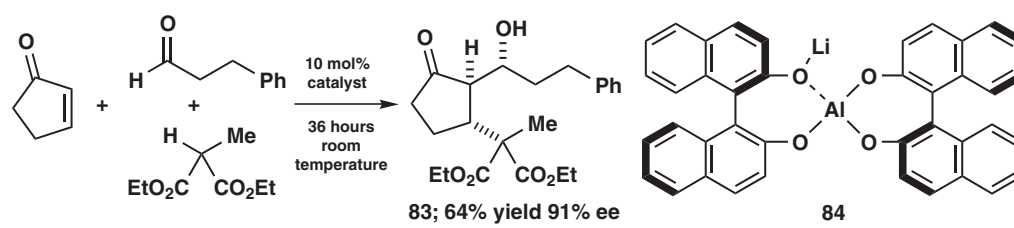
The mixture of **80** and **81** reacts with hydroxylamine in another tandem conjugate addition to give a heterocycle **82** that loses water to give Sceletium-A4 **72** in one step from the mixture.



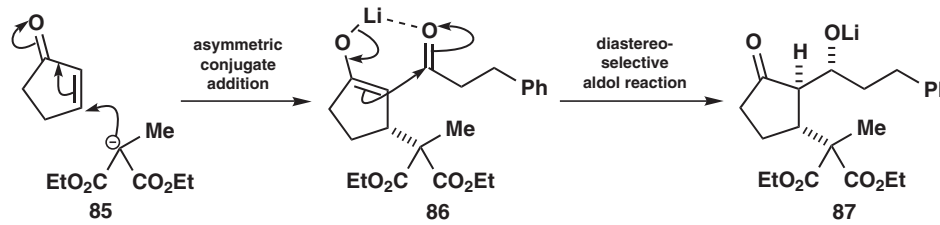
Tandem Conjugate Addition and Aldol Reaction

Tandem conjugate addition of enolates and aldol reactions

Other fates are possible for the enolate formed in the initial conjugate addition and an obvious possibility is an aldol reaction. With an asymmetric catalyst, the combination of three simple molecules leads to one enantiomer of one diastereoisomer of the tandem Michael-aldol product[14] **83**. The catalyst **84** is based on a BINOL Al complex (see chapters 25, 26). It can be drawn either as a lithium salt with an aluminium cation or, better, as a lithium aryloxide with a Lewis-acidic aluminium atom. This is better because both basic ArO^- and Lewis acidity are necessary for catalysis.

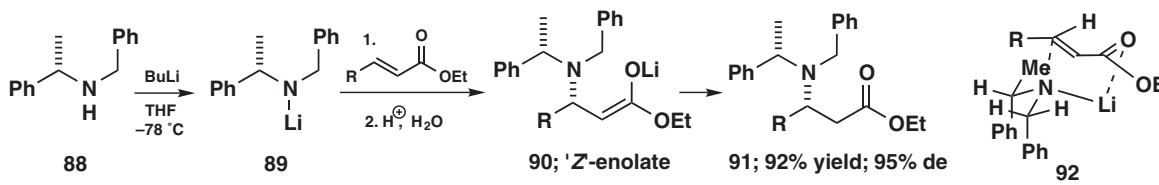


The conjugate addition **85** of the malonate to cyclopentenone creates asymmetry [exactly how is not known] in the enolate which accepts the aldehyde on the face opposite the malonate **86**. The stereochemistry of the third centre is determined by the necessarily *E*-enolate (chapter 4).

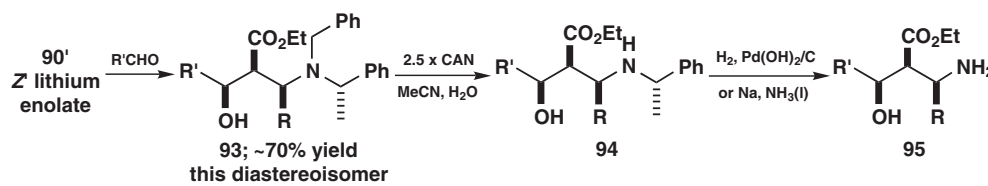


Tandem conjugate addition of chiral amines and aldol reactions

This more dramatic reaction starts with the simple conjugate addition of the Davies chiral version of LDA **89** to unsaturated esters first given in chapter 24. The lithium amide gives the *Z*-enolate of the product **90** and hence the adduct **91**. The transition state **92** gives the correct stereochemistry.[15]



The tandem aldol reaction simply involves adding an aldehyde to the lithium enolate before work-up. Since it is a *Z*-enolate we can expect a *syn* aldol. The '*Z*'-enolate **90** is indeed formed (we are drawing the molecules in a different way to make the aldol stereochemistry clearer) and it does give a *syn*-aldol with the added advantage that only one of the two possible *syn*-aldols **90** predominates. The two benzylic groups can be removed, the first with 'CAN', ceric ammonium nitrate, $Ce(IV)(NH_4)_2(NO_3)_6$ and the second by reduction, to give one enantiomer of **95.**



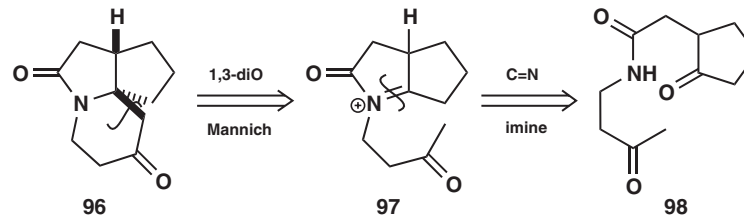
Part III – Intermediate is Unstable Imine or Enamine

Intermediate Would Be Formed by Amide Condensation

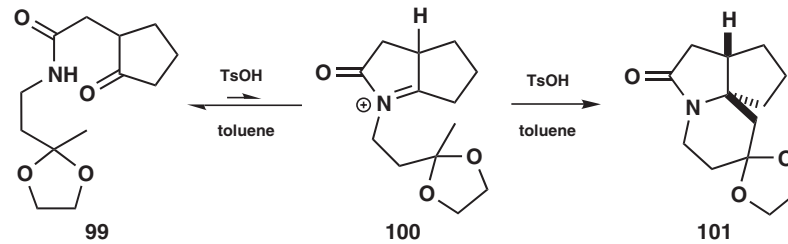
In this section we shall look at (mostly) heterocyclic syntheses where a vital intermediate is an unstable imine, iminium salt, or enamine that cannot be made stoichiometrically. The only way to use such an intermediate is to prepare it in low concentration as part of a tandem process in the presence of the third reagent. If the second step is fast enough, the unstable intermediate will be removed from the equilibrium and the process continues.

The synthesis of a tricyclic amine by tandem amide condensation and Mannich reaction

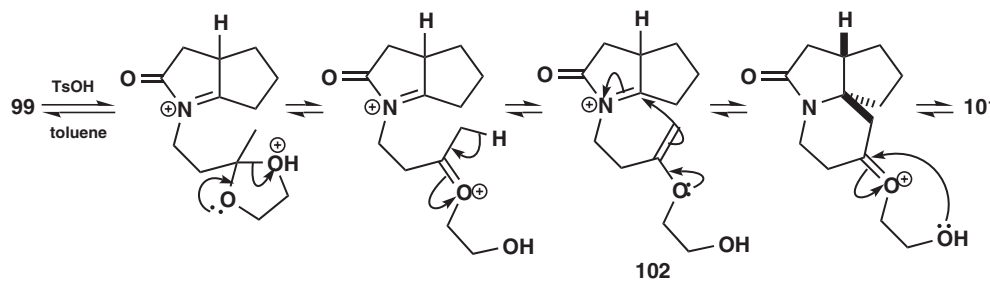
The tricyclic keto-amide **96** is at the core of the *Daphniphyllum* alkaloids. The 1,3-relationship between the nitrogen atom and the ketone suggests a Mannich disconnection and the intermediate iminium ion **97** is simply derived from the diketoamide **98**. However, the iminium ion would have to be formed by attack of the amide nitrogen atom on one of the ketones and this is an unfavourable reaction.[16]



A protected version **99** of **98** is easily made and the tandem sequence works well. The unstable iminium ion **100** is formed in low concentrations but cyclises under the acidic conditions to form **101**, the protected version of **96**.

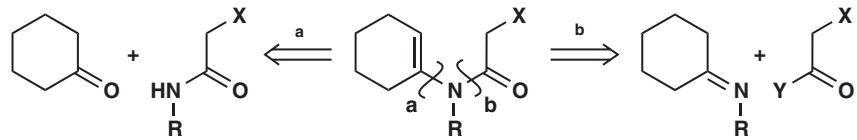


It is initially puzzling that it is not necessary to hydrolyse the acetal before the Mannich reaction. Under the acidic conditions, the acetal is in equilibrium with the enol ether and this is reactive enough to combine with the very electrophilic iminium ion **102**. The stereochemistry of the product is determined in this cyclisation step and simply ensures that the two five-membered rings are *cis* fused.



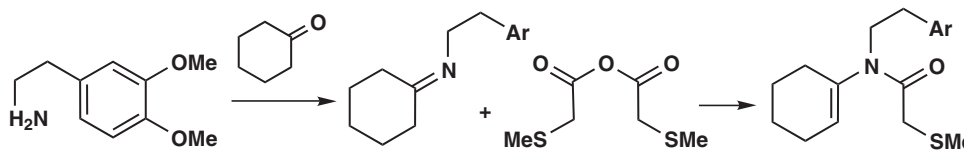
Alternatives to amide condensations: use of sulfur

Unsaturated amide **103** looks as though it should cyclise cleanly when the enamine on the left displaces the leaving group 'X'. But how are we to make **103**? Disconnection **a** is obvious but the amide nitrogen will not react with the ketone. Disconnection **b** is more promising. The imine nitrogen is not a good nucleophile but is a lot better than an amide while the acylating reagent can be made as active as we like.



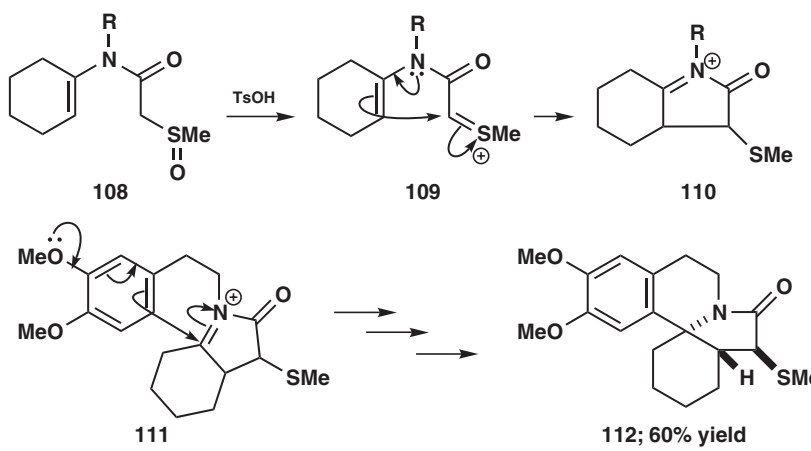
103

There was a hidden agenda here too. A second cyclisation onto an electron-rich benzene ring was planned to build up the skeleton of the Erythrina alkaloids and it occurred to Tamura[17] that a sulfide (X = SMe below) might control both cyclisations. Therefore the anhydride **106** was combined with an imine **105** already having the aromatic ring tethered to the nitrogen atom.



104 105 106 107

Simple displacement of SMe will not do for the first cyclisation as the SMe group must be preserved for the second cyclisation. Oxidation to the sulfoxide and cyclisation by the Pummerer rearrangement is the answer. The intermediate cation cyclises well **109** and creates a new cation **110** rather similar in style to **97**. The aromatic ring cyclises **111** to this cation. The stereochemistry is also well controlled. The 5/6 ring junction is *cis*, as expected since the two-carbon tether on the nitrogen delivers the aromatic ring to one face of the five-membered ring. The stereochemistry of the SMe group is not important as SMe will be reductively removed once it has done its work of controlling the cyclisations. The tandem aspect of this synthesis concerns the two successive unstable intermediates **109** and **111**.

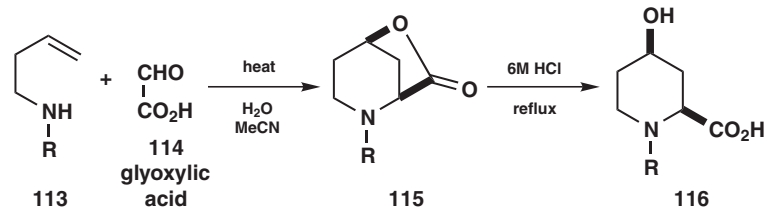


108 109 110 111 112; 60% yield

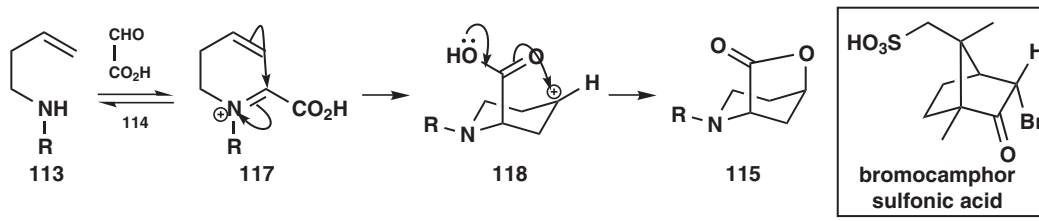
Asymmetric Tandem Methods Involving Unstable Imines etc.

An asymmetric synthesis of pipecolic acids

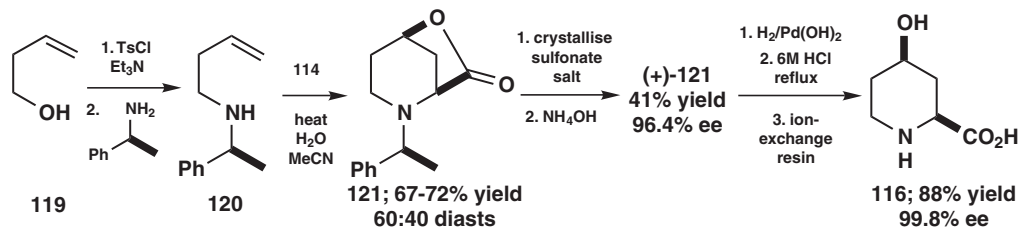
Even unactivated double bonds will cyclise onto reactive iminium salts as this synthesis of *cis*-4-hydroxy pipecolic acid **116**; R = H shows. This is like a Prins reaction but involves an iminium ion instead of an aldehyde.[18]



The stereochemistry comes from the intramolecular trapping of the intermediate cation **117** by the carboxylic acid to form a diaxial bridge. Hydrolysis of the lactone inevitably gives *cis*-**116**.

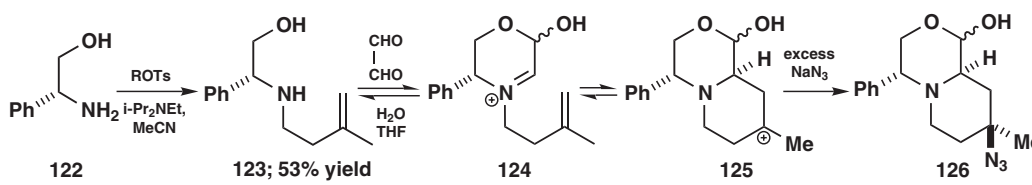


To make this an asymmetric synthesis, a chiral substituent was attached to the nitrogen atom **113**. The tandem reaction then gave a not very high selectivity (60:40 diastereoisomeric mixture) but the isomers could easily be separated by crystallisation of the salt of **115** with bromocamphor sulfonic acid. Removal of the α-methylbenzyl group and lactone hydrolysis gave the pipecolic acid **117** as a single enantiomer. This was needed for the synthesis of an HIV protease inhibitor.

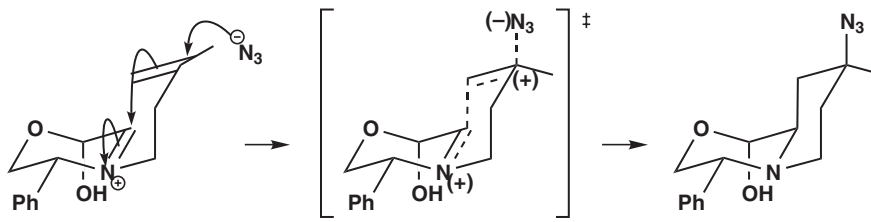


Intermolecular trapping of alkenes by iminium ions

It is surprisingly also possible to trap an external electrophile in this kind of sequence. The amino alcohol **122** from phenylglycine (chapter 23) was alkylated and the unsaturated amine **123** combined with glyoxal. This gives an equilibrating mixture of various cations such as **124** and **125**. If a large excess of a nucleophile such as azide ion is present, bicyclic products like **126** are formed in reasonable yield.[19]



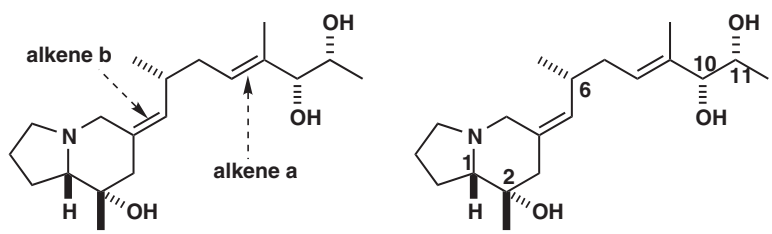
The cyclisation of the alkene onto the iminium salt must be concerted with the attack of the azide ion to some degree to account for the stereochemical control. Presumably the molecule folds as **127** and azide attacks at the back of the alkene through a transition state like **128**. In these diagrams the OH group is drawn in the anomerically more stable axial conformation.



127 **128** **126**

An Asymmetric Synthesis of (+)-Pumiliotoxin B

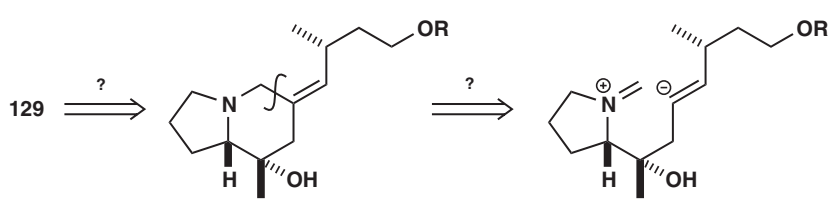
The family of pumiliotoxins, found in the poison-skinned frogs of South America, include pumiliotoxin B **129**. This polycyclic alkaloid has two alkenes: alkene **a** should be easy to control by Wittig or Peterson methods but alkene **b** is *exo* to a ring and there is very little difference between one side of the ring and the other. Some carefully controlled method will be needed. The stereogenic centres fall into three families: 1 and 2 are adjacent on the six-membered ring and should be simple. Centre 6 is entirely isolated and not functionalised. Centres 10 and 11 form a 1,2-diol and again should be simple to control. There is a three carbon spacer between each family and, if that were not bad enough, each spacer contains an alkene that holds the nearest chiral centres rigidly away from each other. The only reasonable approach is to make three separate enantiomerically pure pieces and join them together.



129; (+)-pumiliotoxin B **pumiliotoxin B: stereogenic centres**

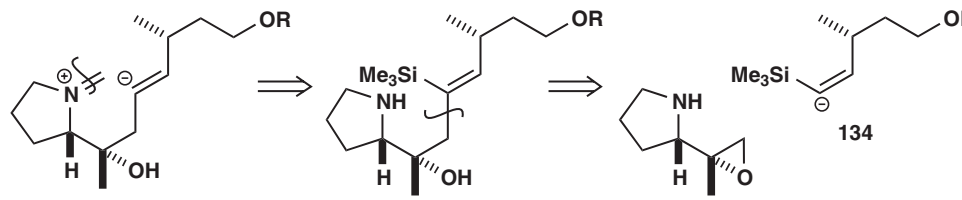
Retrosynthetic analysis

Disconnection at alkene **a** gives a fragment **130** with some functional group OR for the Wittig or Peterson reaction. There is a unique carbon atom between the nitrogen atom and alkene **b** so disconnection to an (unstable) iminium ion and a stereochemically controlled vinyl anion synthon **131** (chapter 16) was chosen by Overman,[20] who rather specialises in this kind of iminium ion.



130 **131**

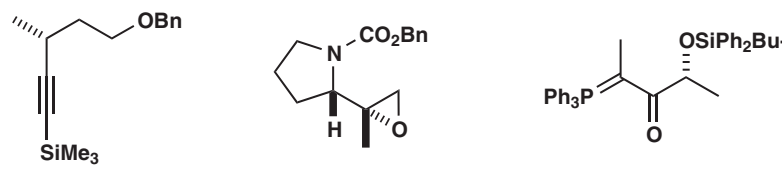
The reagent for the vinyl anion needs to be compatible with the conditions for imine formation and the choice fell on a vinyl silane **132**. The stereogenic centres in the ring can be controlled by an epoxide **133** in combination with some other vinyl silane reagent **134**.



131a **132** **133**

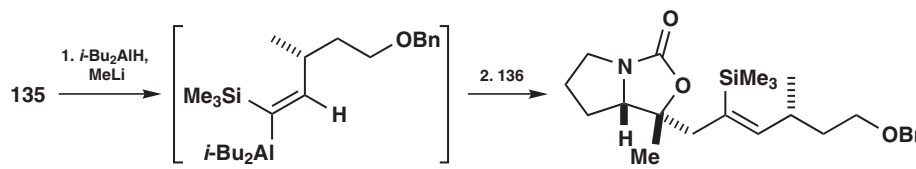
Three enantiomerically pure starting materials ensure remote stereochemical control

The synthesis is necessarily long and we shall concentrate on the tandem aspects. The three enantiomerically pure starting materials were the acetylenic silane **135** for C-6, prepared by resolution (chapter 22), the epoxide **136**, for C-1 and 2, prepared from proline (chiral pool strategy, chapter 23) and the Wittig reagent **137**, prepared from ethyl lactate (chiral pool again), for C-11.



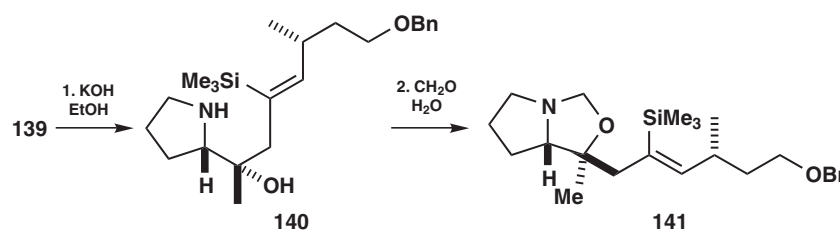
135 **136** **137**

Hydroalumination of the alkyne in **135** gave the *Z*-vinyl aluminium **138**. Treatment with MeLi gave the 'ate' complex that reacted with the epoxide **136** to give **139**. As the epoxide is opened, the oxyanion produced cyclises onto the Cbz group on nitrogen. This product was entirely *Z* and there was only a trace (<7%) of one other diastereoisomer.



138 **139; 77% yield, all *Z***

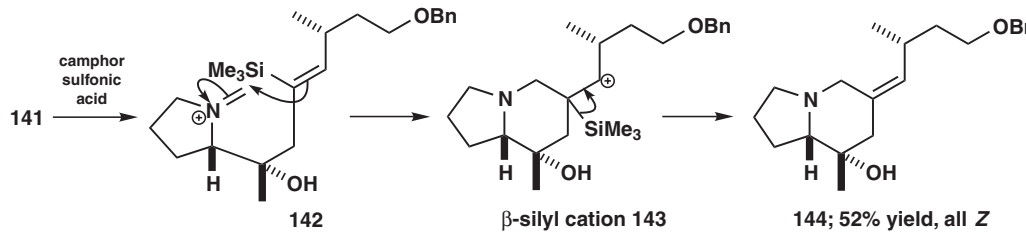
Hydrolysis of the carbamate in base released the unstable alcohol **140** that could be trapped with formaldehyde to give the new heterocycle **141**. This compound contains the extra carbon atom needed for the six-membered ring in pumiliotoxin B but this has yet to cyclise onto the vinyl silane



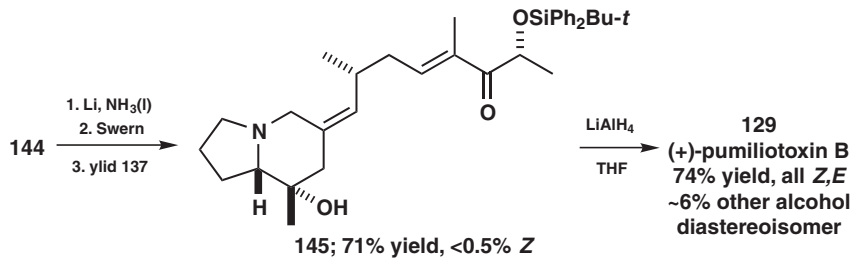
140 **141**

Tandem iminium ion formation and vinyl silane cyclisation

Now comes the critical moment. Treatment of **141** with acid (camphor sulfonic acid is used, not because it is enantiomerically pure, but because it is convenient) opens the heterocyclic ring to give the unstable iminium ion that cyclises onto the vinyl silane **142** to give the β-silyl cation **143** with retention of configuration at the alkene. The product **144** is formed in only moderate yield (52% from **141**) but contains no trace of the *E*-isomer.



Finally the benzyl group was removed, the primary alcohol oxidised to the aldehyde, and an *E*-selective Wittig reaction performed with the enantiomerically pure stabilised ylid **137**. No racemisation of either partner occurred and the product was almost pure *E* at the new alkene. Stereoselective reduction gave (+)-pumiliotoxin B **129** identical to the natural product in all respects, including biological effects.



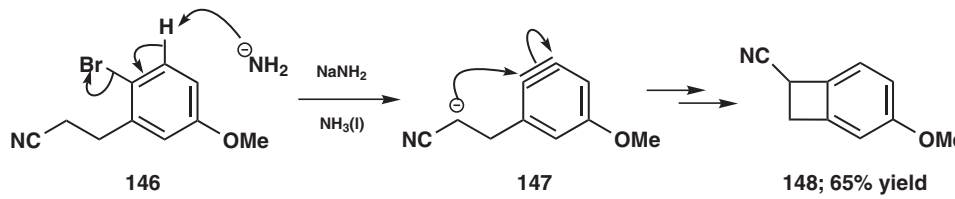
We have spent some time over this synthesis as it is a beautiful example of convergent use of enantiomerically pure starting materials brought together with a tandem Mannich/vinyl silane cyclisation at its core.

Part IV – Tandem Pericyclic Reactions

Pericyclic reactions are normally insensitive to conditions: they often require no acid or base catalysis and are 100% atom efficient with no by-products. There is no problem in running a sequence of pericyclic reactions whether cycloaddition, electrocyclic, or sigmatropic, and almost every combination has been tried. This section explores some of the more successful methods.

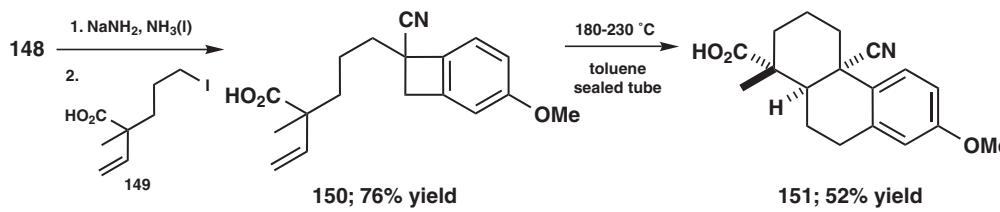
Electrocyclic Formation of a Diene for Diels-Alder Reaction

An early but important example of this style of tandem reaction is based on the benzocyclobutene **148**, easily prepared from the nitrile **146** by cyclisation of the benzyne[19] **147**.



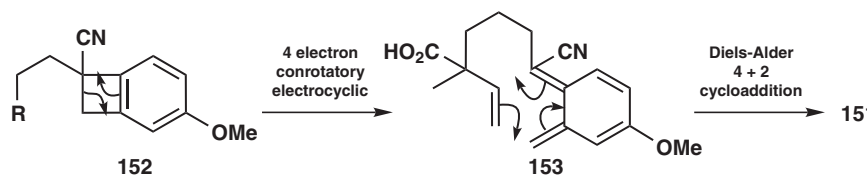
146 147 148; 65% yield

Alkylation with an unsaturated alkyl halide **149** gives an intermediate **150** ready for the tandem sequence. Simple heating at around 200 °C gives a single diastereoisomer of **151** with the creating of two new chiral centres and a typical tandem yield.



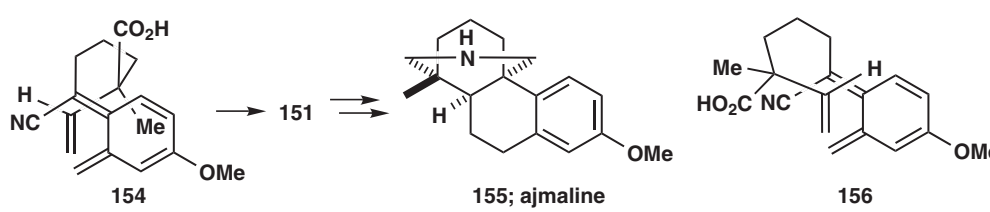
150; 76% yield 151; 52% yield

The cyclobutene ring first opens in an electrocyclic reaction **152**. This must be conrotatory as it is a four electron process but there is no stereochemistry at this stage. Then an intramolecular Diels-Alder cycloaddition **153** closes the new six-membered ring. This is a particularly favourable reaction as the formation of the alkene completes a benzene ring. It would not be possible to prepare such an unstable diene so a tandem process is necessary.



152 153

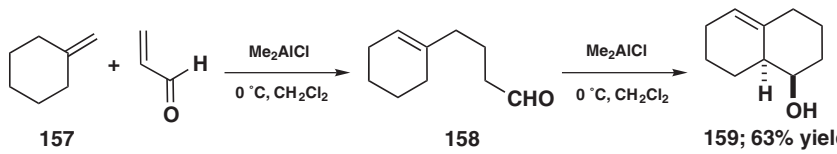
The stereochemistry suggests that the molecule folds up in the arrangement **154** with the methyl group on top of the benzene ring as that gives all three centres correct including the *cis* ring junction.[21] The reaction was designed as a route to ajmaline **155** and the bridging amine is formed from the necessarily *cis* CO_2H and CN groups. The alternative folding **156** would put CN and H *trans*. There is no *endo* overlap here as nothing is conjugated with the dienophile. Intramolecular Diels-Alder reactions need no *endo* overlap as the two components are already tethered.



154 155; ajmaline 156

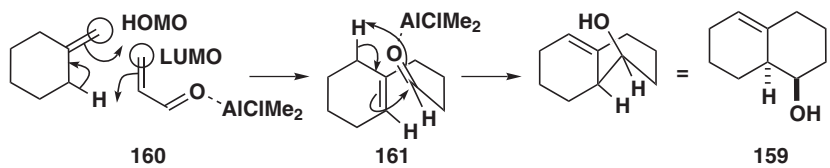
Tandem Ene Reactions

It is less common to find two pericyclic reactions of the same kind coupled together but the Alder 'ene' reaction and the oxo 'ene' reaction can both be catalysed by Lewis acids under the same conditions. A simple example is the combination of the exocyclic alkene **157** with acrolein. The intermediate unsaturated aldehyde **158** cyclises stereoselectively to form a new carbocyclic ring **159**. The intermediate **158** is perfectly stable so the tandem sequence is convenient rather than necessary.[22]



157 **158** **159; 63% yield**

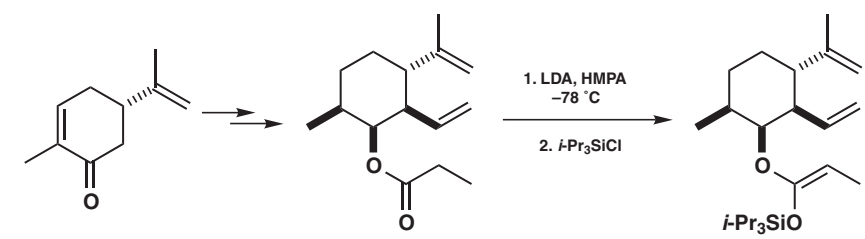
The first step is a straightforward ene reaction **160** with the LUMO of the aluminium complex of acrolein attracting the HOMO of the reactive alkene. The circles indicate the largest coefficient in each frontier orbital. The second step is an oxo-ene **161** with the oxygen atom of the aldehyde capturing the allylic proton. The stereochemistry of the product **159** suggests that the reactive conformation is **161**.



160 **161** **159**

Tandem [3,3]-Sigmatropic Rearrangements

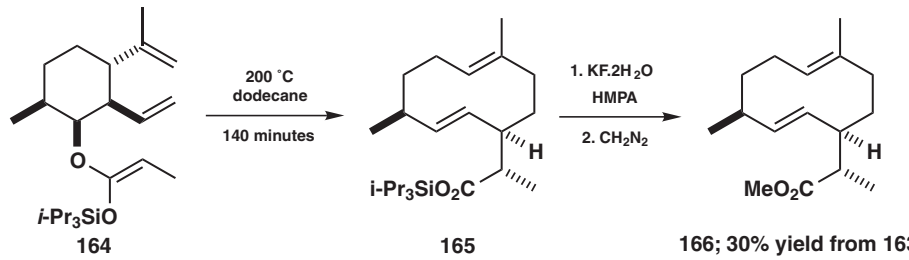
Cope rearrangements, the all-carbon [3,3]-sigmatropic rearrangements, often have no particular reason to go one way or the other. It may even be necessary in some syntheses to drive them in the direction they dislike. Such an example is the formation of a ten-membered ring (an unfavourable medium ring) from a six-membered ring.[23] The starting material **164** was prepared as a single enantiomer from (*S*)-(+)-carvone **162**.



162; (*S*)-(+)-carvone **163** **164**

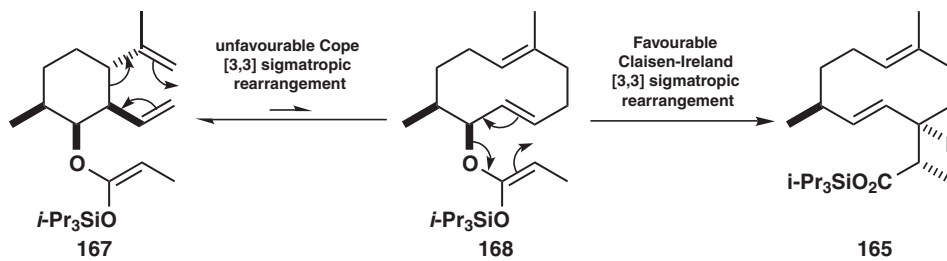
Heating this silyl enol ether **164** at about 200 °C gives the unstable silyl ester **165** isolated as the stable methyl ester **166** in 30% yield. This is obviously not a good yield but enough has been achieved to make the tandem process worthwhile. A ten-membered ring with two *E*-alkenes has

been formed. Two new stereogenic centres have been controlled relative both to each other and to what is now a remote centre - the isolated methyl group. Though the original centre on carvone has disappeared, three others have appeared.



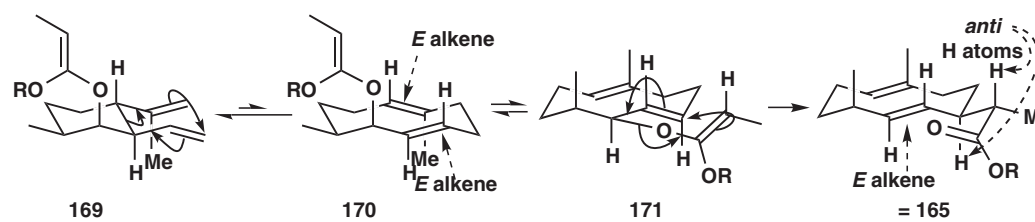
164 **165** **166; 30% yield from 163**

In detail, the first step is a Cope rearrangement - a [3,3]-sigmatropic rearrangement involving nothing but carbon atoms **167**. This step is unfavourable because it transforms a stable cyclohexane into an unstable *E,E*-decadiene. The product **168** is a minor component in the equilibrium. What drives the reaction forward is a favourable Claisen-Ireland rearrangement on the silyl enol ether **168**. This step is favourable because it creates a carbonyl group (the ester in **165**) at the expense of an alkene.



167 **168** **165**

The stereochemistry emerges from the reactive conformations of **165** and **168**. The most stable conformation **169** already has the two vinyl groups next to each other and the [3,3]-sigmatropic rearrangement can go through the favoured chair transition state to give the two *E*-alkenes in **170**. The substituents on each alkene are already *trans* to each other in **169**. Conformation **170** cannot do the next reaction but these ten-membered rings are very flexible and conformation **171** is just right. Again the *E*-alkene in **165** is already so arranged in **171** and the two new stereogenic centres develop without change from the *Z*-enol ether, the *E*-alkene, and the chair transition state for the Claisen-Ireland rearrangement **171**. This product was used to synthesise sesquiterpenes.

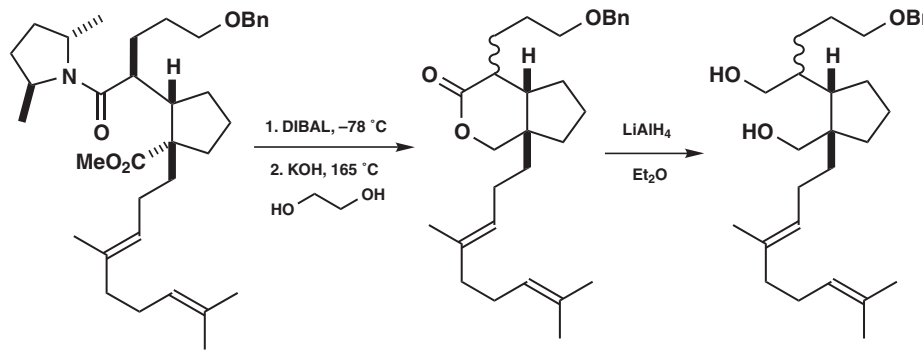


169 **170** **171** **= 165**

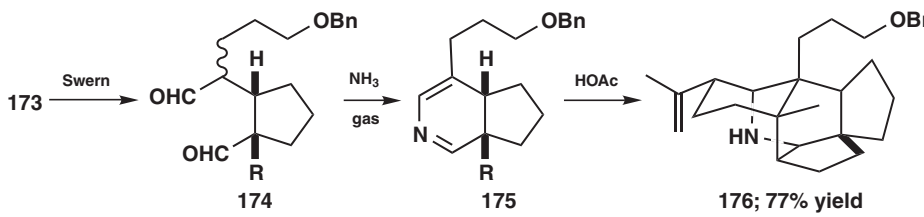
Tandem Aza-Diels-Alder and Aza-Ene Reactions

Completion of the synthesis of Daphniphyllum *alkaloids*

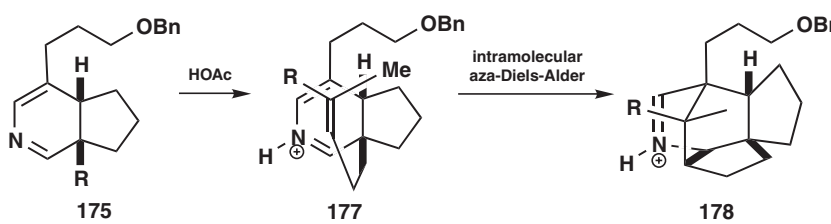
We left compound **35** as the product of a tandem conjugate addition/alkylation and promised further chemistry later in the chapter. In fact, **35** was used in another more remarkable tandem sequence involving two pericyclic reactions and the creation of a polycyclic *Daphniphyllum* alkaloid. The first few steps are straightforward and give diol **173** in good yield.[8]



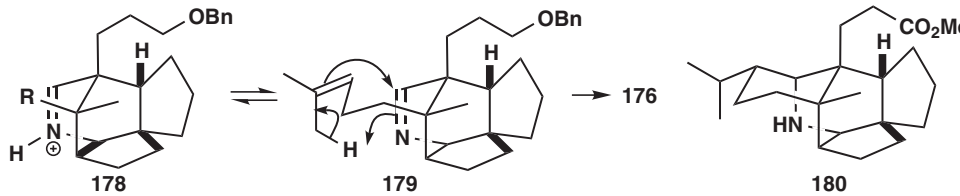
Now the excitement begins. The diol **173** is oxidised to a rather unstable dialdehyde **174** that is immediately combined with ammonia to give a dihydropyridine **175**. The chiral centre that was not controlled in the earlier sequence is lost in this step. This is again not isolated but treated with acetic acid. A series of reactions ensues - this is the second tandem sequence in this synthesis - and the molecule folds up to give **176**.



The first step is an aza-Diels-Alder reaction (chapter 34) with the (probably protonated) dihydropyridine **175** acting as the diene. Only the nearer of the two alkenes in the side chain can reach the aza-diene and it approaches from the top face (as drawn **177**) because it is tethered to the diene by that face. The tether determines both the regio- and the stereoselectivity of the reaction.



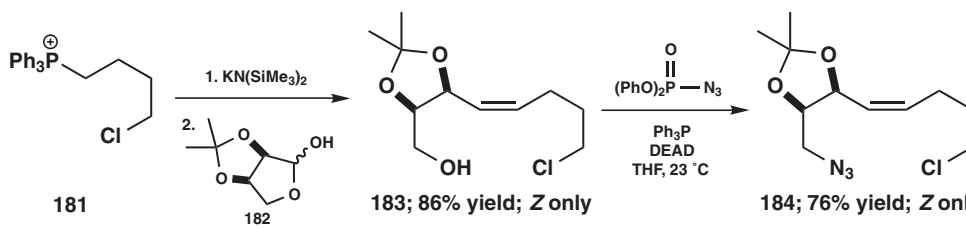
The second reaction amounts to an aza-ene reaction with the most remote alkene providing the 'ene' partner and the imine. The molecule folds up **179** to give a chair conformation in the developing six-membered ring and the product **176** is easily transformed into (−)-methyl homosecodaphniphyllate **180**.



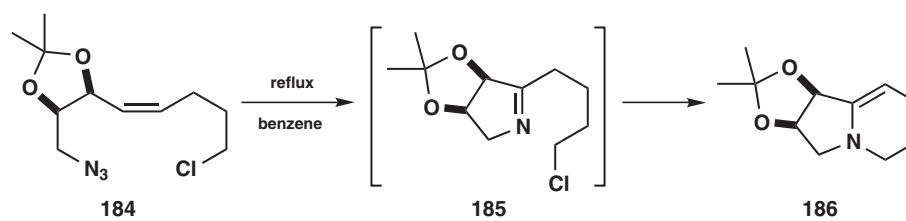
Tandem Reactions Involving 1,3-Dipolar Cycloaddition

Asymmetric synthesis of swainsonine

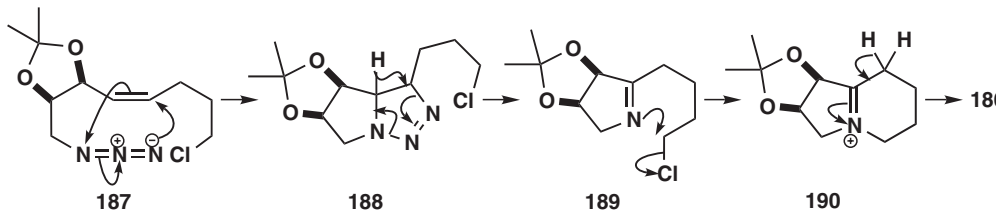
A commoner way to make heterocycles by pericyclic reactions is to use 1,3-dipolar cycloadditions. These often occur without catalysis and so are compatible with many other reactions. The starting material **182** for this asymmetric synthesis of swainsonine was derived from a natural sugar (chiral pool strategy, chapter 23). An exceptionally stereoselective Wittig reaction gave the *Z*-alkene **183** (chapter 15) and the alcohol was converted into the azide **184** with diphenylphosphoryl azide.[24]



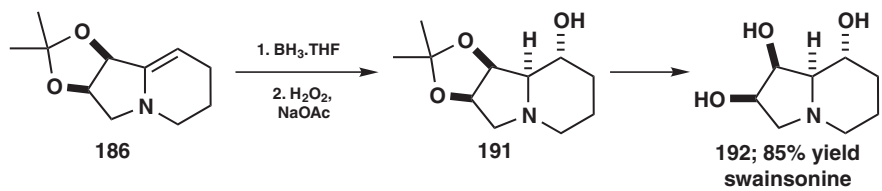
The tandem sequence occurs when the azide is heated in a hydrocarbon solvent. A 5/6 fused bicyclic ring system **186** is formed and the last reaction is known to be a simple cyclisation of the intermediate **185** (though this is not isolated) by nucleophilic displacement.



The first step is a 1,3-dipolar cycloaddition of the azide onto the unactivated alkene **187**. The regioselectivity of the cycloaddition (and no doubt also its stereoselectivity, though this is lost in the next reaction) is controlled by the short tether. The product **188** is not stable and rearranges, perhaps by the concerted H shift and loss of nitrogen shown, into **189** which promptly cyclises to give the product **186** by loss of a proton.

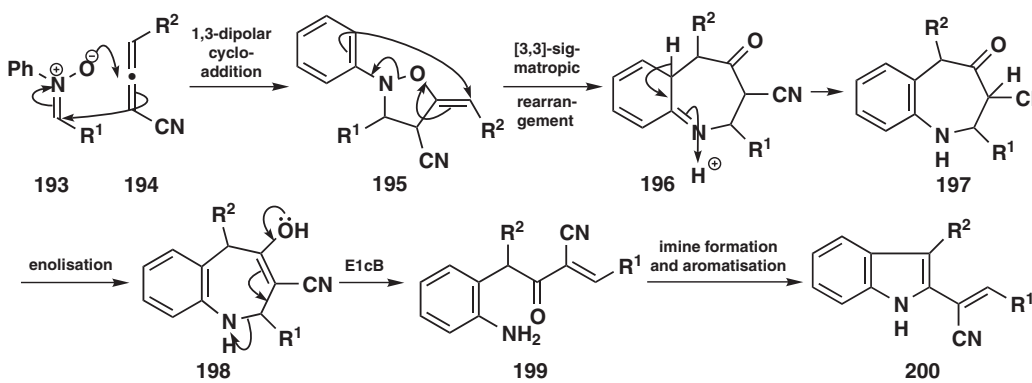


The stereochemistry needed for swainsonine **192** is introduced by hydroboration – borane adds to the face of the alkene opposite the acetal in **186** and the regioselectivity is determined by the nitrogen atom since the alkene **186** is an enamine.

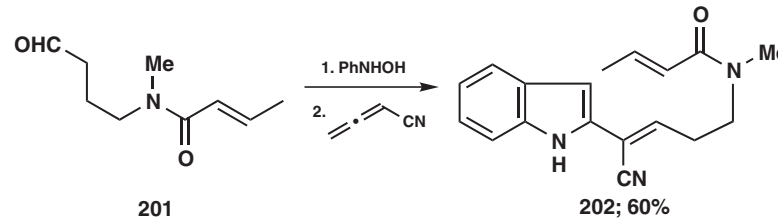


Tandem synthesis of 2-vinyl indoles

Now an extraordinary sequence starting with a 1,3-dipolar cycloaddition but containing at least seven reactions occurring sequentially. Reaction of PhNH.OH with an aldehyde R^1CHO gives the rather unstable nitrones **193** as the first step in the tandem sequence. The 1,3-dipolar cycloaddition with cyano-allenes **194** occurs regioselectively to give the unstable heterocycles **195** that immediately undergo a [3,3]-sigmatropic rearrangement that breaks the weak N–O single bond. Rearomatisation gives a benzo-azacycloheptanone **197** that eliminates the aromatic amine by an E1cB mechanism **198** to give an open chain amino enone **199**. This finally cyclises to the indole **200**. It is amazing that the molecule finds its way through this maze of reactions and even more amazing that the yields are quite good.[25]

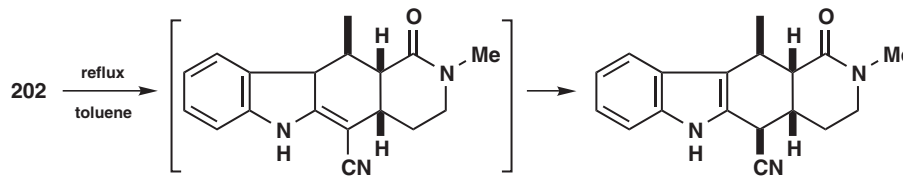


This sequence can be used to build polycyclic heterocycles very quickly from simple starting materials. Even enolisable aldehydes with extra functionality such as **201** can be used in the sequence; the more complex vinyl indole **202** is formed in very reasonable yield[25] (66%).



201 202; 60%

Clearly this indole **202** is destined for a Diels-Alder reaction and refluxing in toluene gives an excellent yield of one (*endo*-) diastereoisomer of the product **204**.



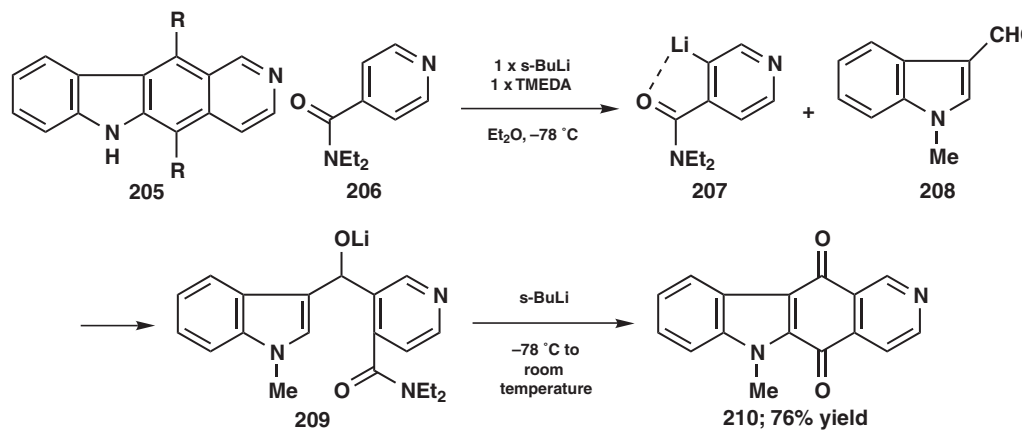
203 204; 80% yield

Part IV – Other Tandem Reactions Leading to Heterocycles

A Tandem Metallation Route to the Ellipticine Skeleton

As we move from pericyclic reactions to other processes, we can consider a tandem metallation route to the same basic skeleton, that of ellipticine **205**, the basis of some important drugs. The selectivity problem here is to relate the position of the two nitrogen atoms.

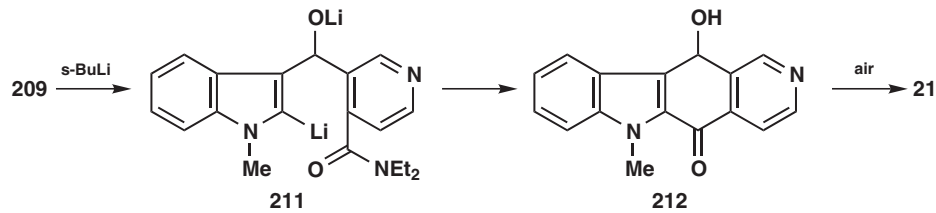
This process involves a straightforward directed *ortho* metallation (chapter 7) of the pyridine amide **206** and capture by the indole aldehyde **208**. Without work-up, the product **209** is lithiated again and the 'ellipticine quinone' **210** is formed in good yield.[26]



205 206 207 208

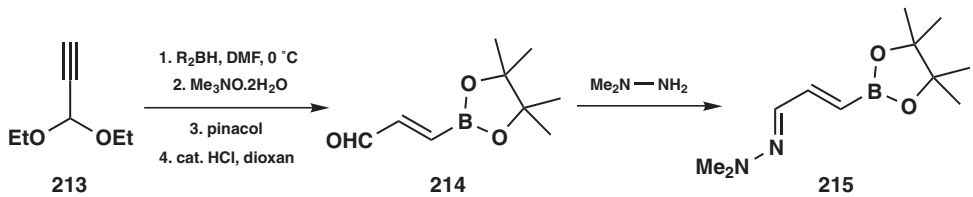
209 210; 76% yield

The second lithiation must occur preferentially on the indole to give **211** (the alternative is a second metallation on the pyridine ring). Cyclisation is by acylation and the product **212** oxidises in air to give the 'quinone' **210**.

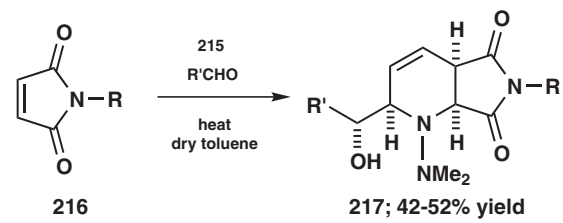


Tandem Aza-Diels-Alder and Allyl Boronate Reactions

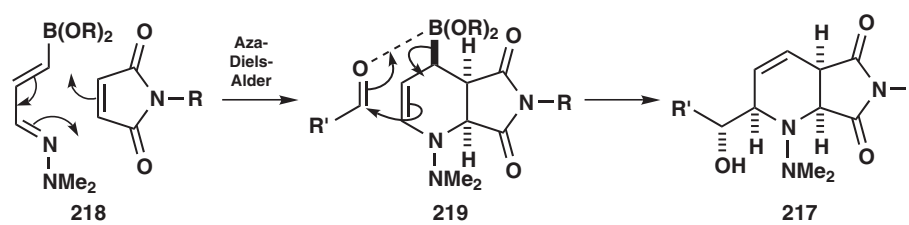
One last example of the aza-Diels-Alder reaction finishes this section. The diene **215** is a curious hybrid of a dienyl boronate and the sort of aza-diene we met in chapter 33 and is easily prepared by hydroboration of a suitable functionalised acetylene **213**.



Reaction with maleic imide **216** and an aldehyde gives a bicyclic product **217** with a new piperidine ring and four new stereogenic centres. The yield is around 50% - entirely acceptable in such a productive tandem process.[27]

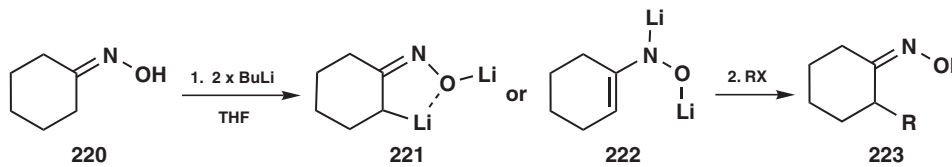


The first step is of course the aza-Diels-Alder reaction **218** with no regioselectivity but lots of stereochemistry. The *cis* ring junction in **217** comes from the *cis* alkene in maleimide and the *endo* transition state gives the remaining centre. The next step is an allyl boronate reaction **219** with the aldehyde. Coordination of the aldehyde oxygen with the boron ensures that the aldehyde is delivered to the top face and the aldol stereochemistry comes from the six-membered cyclic transition state. Snieckus comments that the reaction works well as a tandem process because the 4 + 2 cycloaddition is slower than the allyl boronate reaction so the unstable intermediate does not accumulate. This comment has more general application.

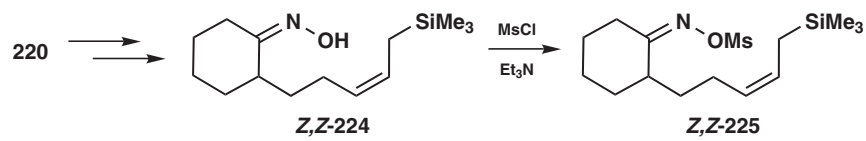


Tandem Beckmann Rearrangement and Allyl Silane Cyclisation

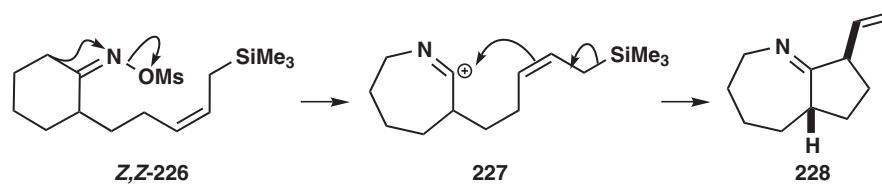
The Beckmann rearrangement[28] involves C to N migration of a group *anti* to the OH group on an oxime. Such a cation might be trapped by a carbon nucleophile such as an allyl silane (chapter 12) that is reactive but not destroyed under the Beckmann conditions. A condition for such a scheme would be a stereoselective way of making oximes and the answer is a directed metallation of a symmetrical oxime.[29] Lithiation of symmetrical cyclohexanone oxime **220** gives a lithium aza-enolate (**221** or **222**) that can be trapped with alkyl halides RX to give one isomer (*Z*-) of **223**.



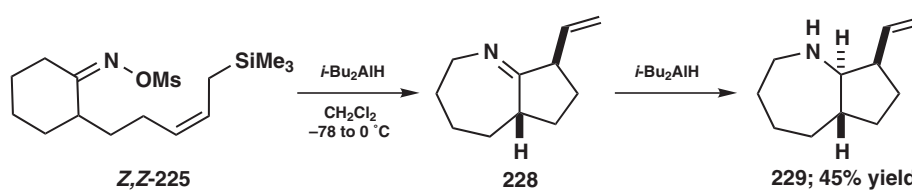
If the alkyl halide is a suitably functionalised allyl silane (*Z*-allyl silanes are easier to prepare) the product *Z,Z*-**224** can be activated by mesylation ready for the tandem procedure.[30]



Rearrangement of *Z,Z*-**226** now gives a cation **227** that reacts with the allyl silane to close a second ring. Attack occurs at the end of the alkene away from the silicon atom so that a β-silyl cation might be an intermediate.



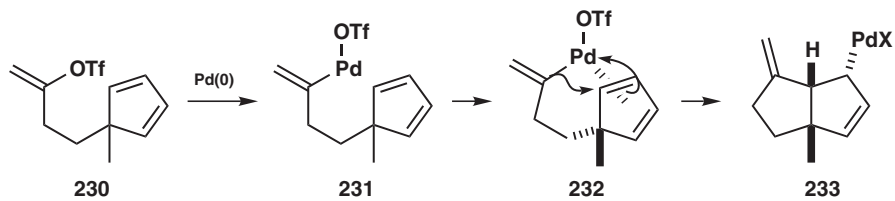
This product **228** is not very stable and the best conditions for the reaction turned out to be DIBAL (*i*-Bu_2AlH) in CH_2Cl_2. DIBAL acts first as a Lewis acid to initiate the rearrangement and then reduces the imine **228** stereoselectively to the stable amine **229**.



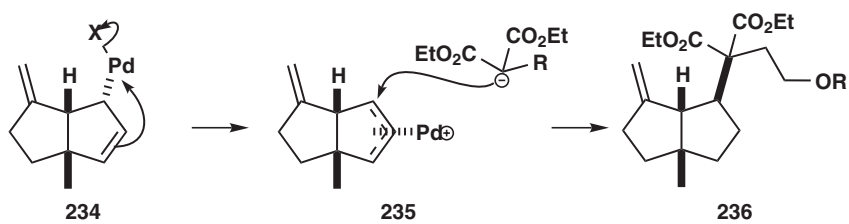
Part V – Tandem Organometallic Reactions

Tandem Asymmetric Heck and Pd-Allyl Cation Reactions

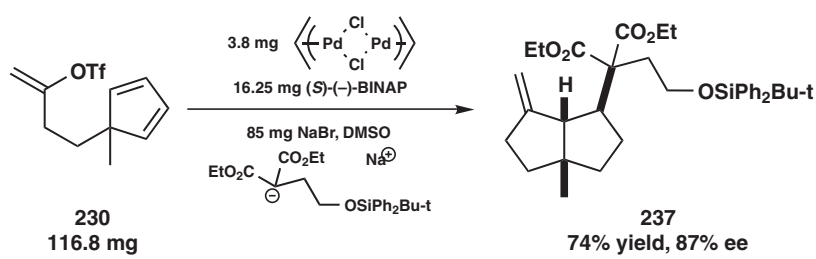
Two important palladium-catalysed methods are the Heck reaction (chapter 18) and nucleophilic attack on palladium allyl cation complexes (chapter 19). These two can be combined in a tandem process and, with a suitable chiral ligand, made asymmetric.[31] The first step is intramolecular Pd(0)-catalysed addition of a vinyl triflate to a cyclopentadiene. Oxidative insertion of Pd(0) into the vinyl triflate to give a palladium vinyl σ-complex **223** is followed by π-complex formation by this Pd(II) species. The short tether directs the Pd to the *cis* face of the flat ring. The Heck stage is completed by coupling **224** of the vinyl group to the nearer end of the old π-bond to make a new Pd(II) σ-complex **225**. Notice how convenient it is that the Heck reaction gives the Pd(II) complex needed to form the allyl cation while the loss of Pd(0) from the second step **226** provides the right oxidation state for the next Heck reaction.



Now the second alkene comes into play as **234** is really an allyl σ-complex that prefers to exist as an allyl η^3 cation complex **235**. If a suitable nucleophile, such as a malonate enolate, is present this will attack the allyl cation complex. It must attack from the opposite face to the palladium and prefers to attack next to the H atom rather than the Me group giving **236**.

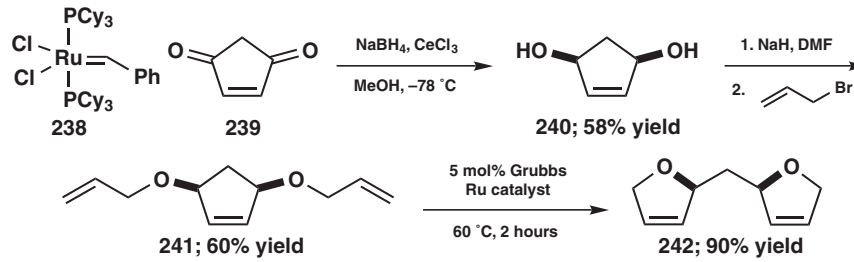


The starting material is not chiral and chirality first arises in the Heck reaction when the vinyl Pd complex can attack one of two enantiotopic alkenes in the diene. In the presence of catalytic BINAP, good asymmetric induction **237** can be achieved.

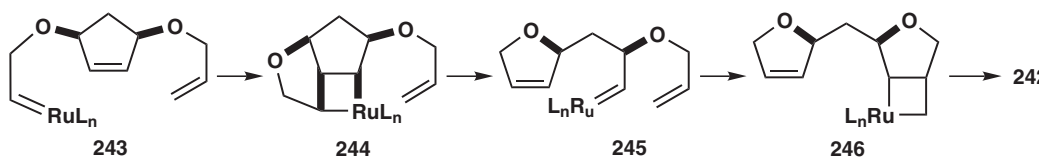


Tandem Ring-Closing and Ring-Opening Metathesis

With two identical groups it might seem that tandem reactions have little value. This ingenious double metathesis should convince you otherwise. The starting material **240** is made by Luche reduction (the Luche method prevents reduction of the alkene) of cyclopentenedione **239**. Allylation of both alcohols gives the symmetrical (*meso*) starting material **241** for the double metathesis with the Grubbs catalyst **238**. The symmetrical product **242** is formed in excellent yield.[32]

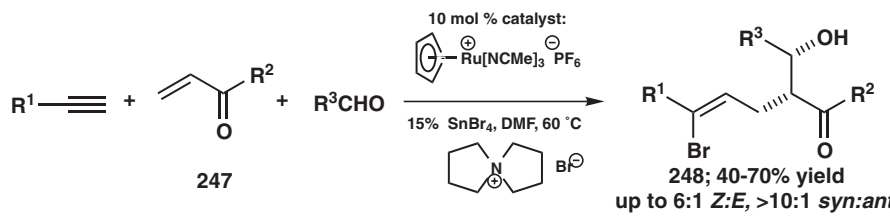


The metathesis starts with one of the less hindered allyl groups and it doesn't matter which you choose as the first intermediate will always be **243**. The Ru carbene complex can reach only the central alkene so it completes the metathesis with this to give **244** and then **245**. Now a second metathesis with the remaining allyl group gives the product **242** *via* **246**. The stereochemistry remains unaltered even though the molecule is opened up and put together again.

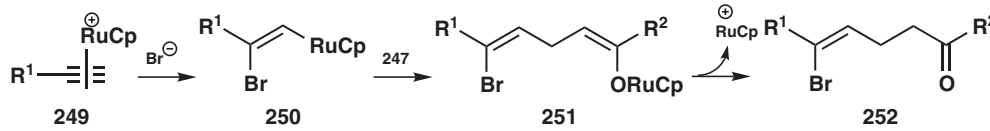


A Ru-Catalysed Four-Component Coupling

More recently, chemists seem to be able to invent multi-component reactions almost at will. An outstanding example is this four-component coupling catalysed by ruthenium. Three component, surely, do we hear you say? The fourth component is the bromide ion.[33]



The first step is the formation of an alkyne-Ru π-complex **249** that adds bromide ion, presumably transferred from Ru in view of the stereochemistry of **250**. Now the enone **247** and the vinyl-Ru complex **250** couple with retention of the stereochemistry of **250** and transfer of the Ru to oxygen to make a Ru-enolate. This is known to be true as work-up in the absence of the aldehyde gives the ketone **252**.



If the aldehyde is present, a Ru-aldol reaction gives a single geometrical and diastereomeric aldol product **248** and the Ru is lost as $CpRu^+$ so it can catalyse the next cycle. There are quite a few extra reagents needed to make the reaction go well: catalytic $Sn(II)Br_2$ and the curious spirocyclic ammonium salt. This latter is essential.

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