ALKALOIDS AS CATALYSTS FOR ASYMMETRIC SYNTHESIS

by

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Dedication

To Fiona.

Declaration

I, Douglas B. Taylor, hereby certify that this thesis has been composed by myself, it is a record of my own work and has not been accepted in partial or complete fulfilment of any other degree or professional qualification.

Signed ..... Date 7/5/93

I was admitted to the Faculty of Science of the University of St. Andrews under Ordinance General No. 12 on 1st October 1989 and as a candidate for the degree of Ph.D. on 1st October 1990.

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I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate to the Degree of Ph.D.

Signed ..... Date 11th May 1993

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Acknowledgements

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Finally, I thank the SERC for their financial support.

Lecture Courses

The following is a statement of the lecture courses attended during the period of research; Organic Research Seminars (3 years attendance); Asymmetric Synthesis, Dr R. A. Aitken; Pharmaceutial Chemistry, Dr R. A. Aitken and Dr A. R. Butler; Unusual Oxides and Sulphides of Carbon, Dr R. A. Aitken; Case Studies in Mechanistic Chemistry, Dr A. R. Butler; Advanced Topics in Bioinorganic Chemistry, Dr D. T. Richens; Chemical Carcinogenesis, Dr C. Thomson; Oils and Lipids, Prof. F. D. Gunstone.

ABSTRACT

The cinchona alkaloids, dihydroquinine, dihydroquinidine, dihydrocinchonine and dihydrocinchonidine have been evaluated as chiral bases for the generation of ethoxycarbonylnitrene by α–elimination from the Lwowski precursor ethyl *N*–*p*–nitrobenzenesulphonoxycarbamate. While the nitrene is successfully generated, the enantioselectivity observed in its addition to 1–methylcyclohexene is disappointing, with values never greater than 5% e.e. Sparteine has also been examained for this reaction. Variation in the concentration of the reactants, and the nature of the nitrene have been examined in detail.

The quaternary ammonium salts derived from dihydrocinchona alkaloids have been used as catalysts for asymmetric phase transfer catalysed reaction of ethoxycarbonyl nitrene with 1–methylcyclohexene. Again although the aziridine is produced, the e.e. values obtained are not high enough to be synthetically useful. Changing to 1–phenylcyclohexene as the substrate led to insertion rather than additon of the nitene.

Both cinchona and morphine alkaloids have been evaluated as base catalysts for ring opening of cyclohexene epoxide with water, methanol and acetic acid. Mixtures of products were usually formed with no useful enantioselectivity.

Finally the morphine alkaloids dihydrocodeine, oxycodone, dihydrothebainone and buprenorphine have been evaluated as catalysts for the asymmetric ring opening of a tricyclic anhydride and a tetracyclic epoxyanhydride with methanol, reactions in which the cinchona alkaloids have previously been found to be highly effective. In the former case the resulting diacid monoester had low e.e. but in the latter, useful selectivity was achieved, suggesting that further studies on the use of the morphine alkaloids for reactions of this type may be worthwhile.

CONTENTS

EXPERIMENTAL

DISCUSSION

INTRODUCTION

A. Asymmetric Synthesis And The Alkaloids

Asymmetric synthesis has become one of the most important areas of chemistry in recent years. With chiral molecules playing an important role in biological systems it has become important for both the pharmaceutical industry (as thalidomide demonstrated) and the agricultural industry.

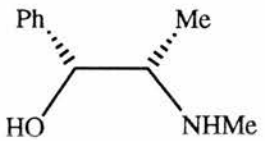
Japp[1] in a published lecture stated that 'only asymmetry can beget asymmetry'. This is the principal that governs asymmetric synthesis: if an enantioselective reaction is to occur then a chiral molecule must be present. There are four possible ways of achieving this.

The first method is to perform a transformation on a chiral molecule so that a new stereogenic unit is formed and chirality is retained during the reaction. The second method involves attaching a chiral auxiliary to a substrate, carrying out a transformation, and then removing the auxiliary from the product. Both these methods have the disadvantages of needing large amounts (molar equivalents) of chiral starting material, and several reaction steps before a chiral product is reached.

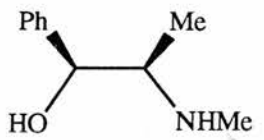
The third method is to use a chiral reagent to carry out the transformation and the fourth method is to use a chiral catalyst. The advantages of these last two methods are that the transformations can be carried out in one easy step, and in the case of chiral catalysts, a small amount of chiral material can carry out several transformations. It is in these last two methods particularly that the alkaloids have proved to be useful sources of chirality.

The three most popular types of alkaloid to have been used are ephedrine, the cinchona alkaloids, and sparteine. Some of the others that have been used are brucine, strychnine, and morphine, but the high toxicity of these alkaloids makes them less attractive.

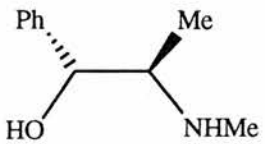
The simplest and most widely used of the alkaloids is ephedrine (**1–4**). Both enantiomers and diastereomers are readily available, and as a result both enantiomers of the product may be obtained by using the appropriate ephedrine.



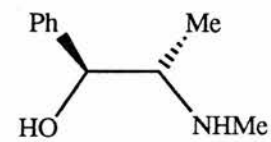
1 (–)–(1R,2S)–Ephedrine



2 (+)–(1S,2R)–Ephedrine

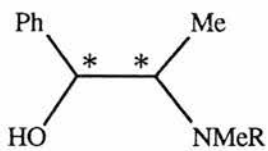


3 (1R,2R)–Pseudoephedrine

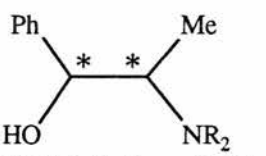


4 (1S,2S)–Pseudoephedrine

To get the best selectivity ephedrine is usually used in its *N*–alkylated (**5**) or *N*,*N*–dialkylatednorephedrine form (**6**). The added bulk and the dual functionality of the nitrogen and oxygen atoms gives the molecule the ability to interact with other molecules so as to impart its asymmetry.



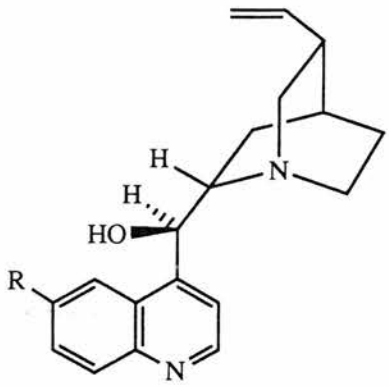
5 *N*–Alkylephedrine



6 *N*,*N*–Dialkylnorephedrine

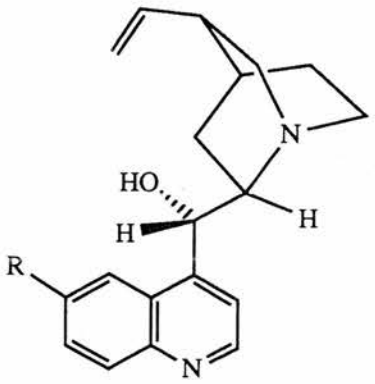
The cinchona alkaloids[2] **7–10** are much larger molecules with the same amino alcohol functionality as ephedrine. The group consists of two pairs of diastereomers quinine–quinidine, and cinchonine–cinchonidine. Although their relationship is diastereomeric, around the active amino alcohol site their relationship is enantiomeric. This has the effect of making both product enantiomers readily available by using the appropriate alkaloid. The

diastereomeric nature of the different alkaloids then shows up as differences in the enantioselectivities of the products.



7 (8S,9R)–Quinine (R=OMe)

9 Cinchonidine (R=H)



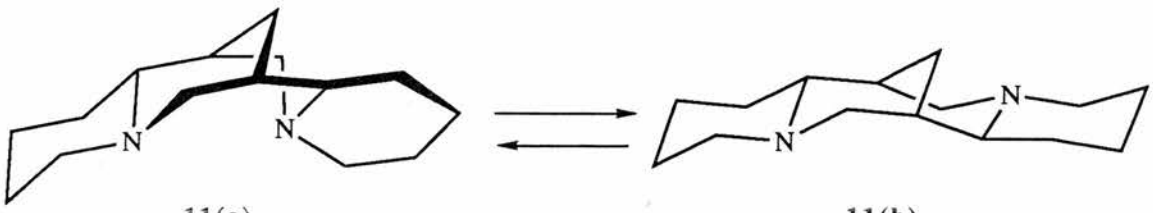
8 (8R,9S)–Quinidine (R=OMe)

10 Cinchonine (R=H)

The unique structure of the cinchona alkaloids makes them ideal to be used as catalysts. The vinyl group is an ideal handle to modify or attach the alkaloid to a polymer backbone. The quinuclidine ring portion acts as aliphatic hydrocarbon bulk. The nitrogen of the quinuclidine acts as a base. The stereogenic nature of C**8** and C**9** leads to enantioselectivity. The hydroxyl group can form hydrogen bonds, bond with metals, and can also be modified. The quinoline portion of the molecule acts as aromatic bulk and can also be polarised to form charge transfer complexes. Finally the nature of the R group can have an effect on the steric and polar influence of the catalyst. To sum up, the aliphatic and aromatic bulk around the C**8**–C**9** bond, along with all the Van der Waals interactions that can occur, can lead to high enantioselection when these molecules are used as catalysts.

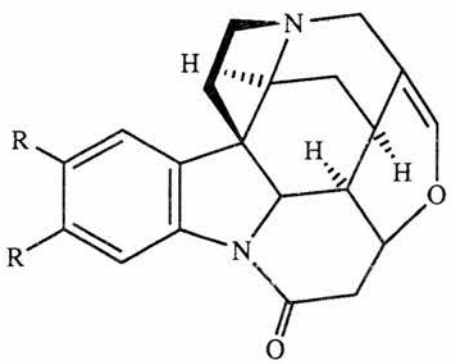
Sparteine **11** is a diamine that can exist in two conformations. It has been suggested that an equilibrium could exist between the two conformations, however from a model of the structure it is not easy to see how the molecule can flip between the two structures. Sparteine is obviously not as complex a

molecule as the cinchona alkaloids and so the possibilities for its interaction with other molecules are limited. Its main use is as a bidentate ligand bonding to metals like lithium and magnesium.



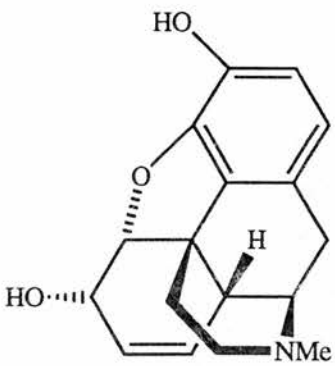
11(a) **11(b)**

Some of the other alkaloids that have been used are listed below. These alkaloids are usually more toxic than those discussed previously. They are of varying structure types , all with a sterically hindered amine function.

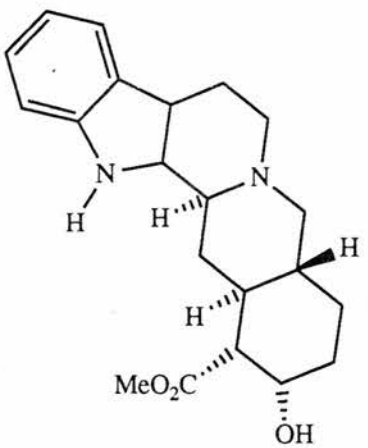


12 Strychnine (R=H)

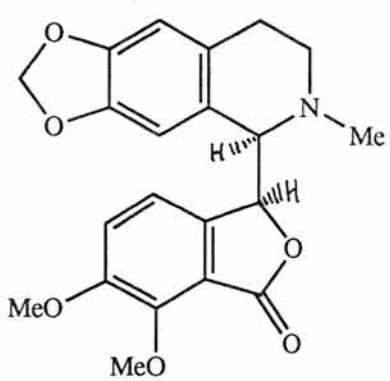
13 Brucine (R=OMe)



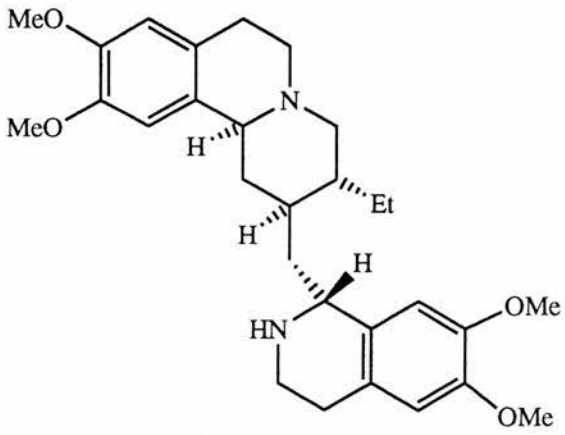
14 Morphine



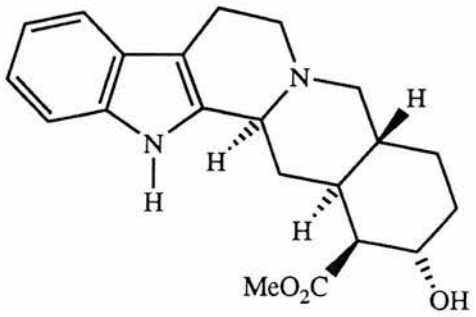
15 Yohimbine



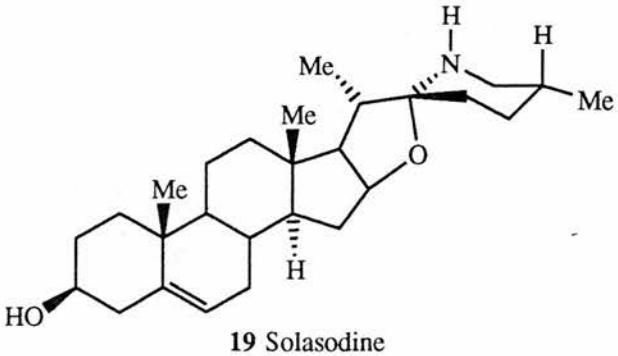
16 Narcotoline



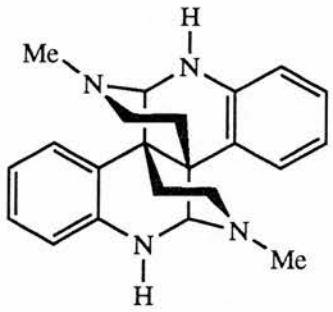
17 Emetine



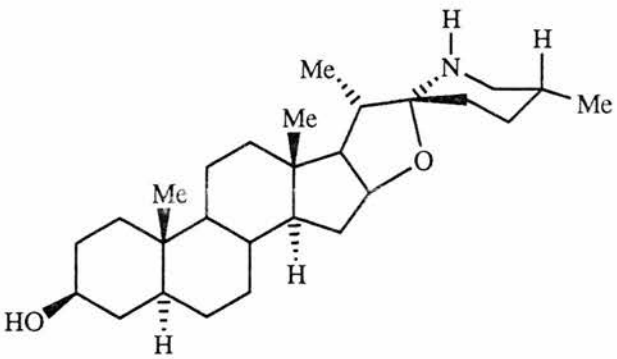
18 Corynanthine



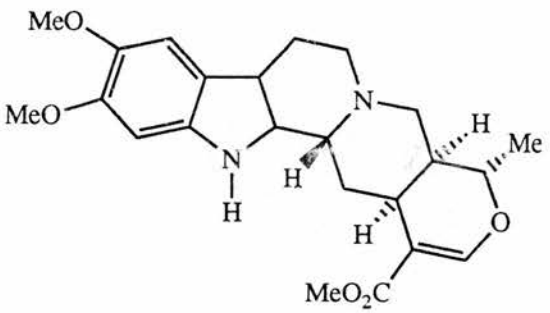
19 Solasodine



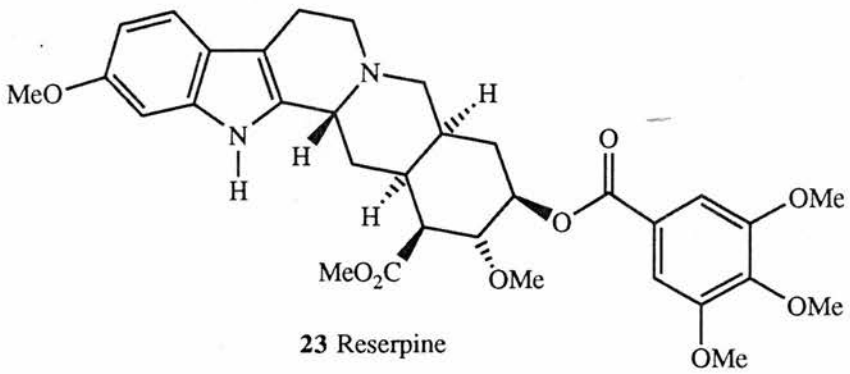
20 Calycanthene



21 Tomatidine

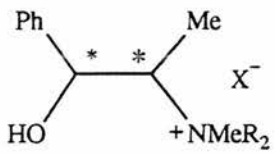


22 Reserpiline



23 Reserpine

The alkaloids can be *N*–alkylated to form quaternary ammonium salts. Such salts are useful as phase transfer catalysts and this extends the range of reactions that the alkaloids can catalyse. The three types mentioned earlier ephedrine, the cinchona alkaloids and sparteine have also been *N*–alkylated and the salts **24–26** used as phase transfer catalysts.



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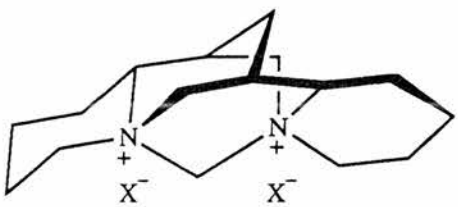

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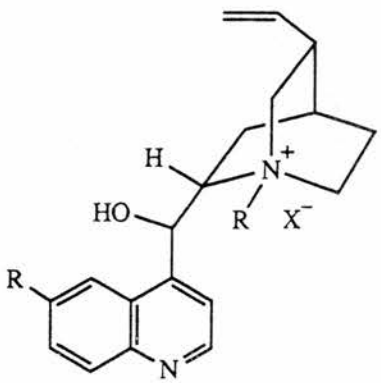
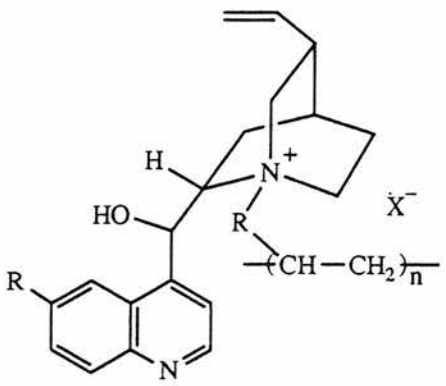


26

The alkaloids can also be bound to a polymer backbone. Both ephedrine and cinchona alkaloids have been used in this way. The ephedrine was bound to the polymer by *N*–alkylation **29** and the cinchona either by *N*–alkylation **27** or through the vinyl group **28**. The polymer bound catalysts have the advantage that they can be easily removed from a reaction mixture and reused.



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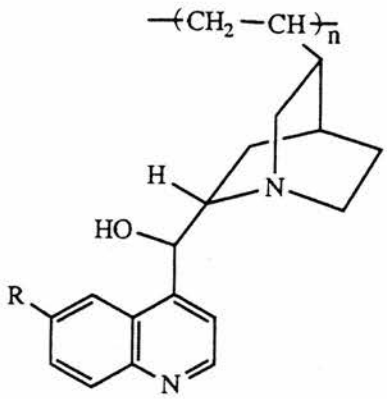

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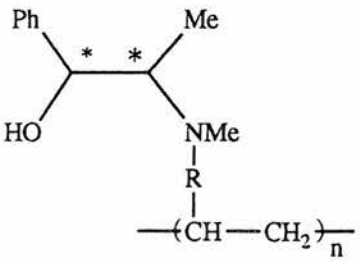


29

B. Carbon Carbon Bond Formation

Carbon–carbon bond forming reactions are of fundamental importance to organic synthesis. This is because they are the method used to build up organic molecules. To be able to carry out these reactions with enantiocontrol is, then, an important goal in asymmetric synthesis. Much work has been carried out on such reactions and the alkaloids have proved to be useful sources of chirality.

1. Organometallic Alkylations

The enantioselective addition of organometallic compounds to aldehydes produces optically active secondary alcohols. Such compounds are components of many biologically active compounds and are also useful for liquid crystals.

They are also important as synthetic intermediates for various functionalities. This then makes the reaction one of the most important reactions in asymmetric synthesis.[3]

One of the first alkaloid catalysed organometallic reactions to be carried out was the addition of Grignard reagents to aldehydes in the presence of sparteine to produce optically active alcohols. The reaction however only produced low selectivity. Reacting ethylmagnesium bromide with benzaldehyde in the presence of sparteine produced *(R)*–1–phenylpropan–1–ol with 22% e.e.[4] This was the best result obtained and selectivites were usually less than 10%.

The reaction of dialkylzinc compounds with aldehydes is rarely used in organic synthesis. This is because the reaction is slow and side reactions can occur. However Mukaiyama reported[5] that the presence of chiral β–amino alcohols accelerated carbon–carbon bond formation. The ephedrine and cinchona alkaloids both have the β–amino alcohol functionality and are a good source of chirality.

(a) Alkylation of Aromatic Aldehydes by Dialkylzincs

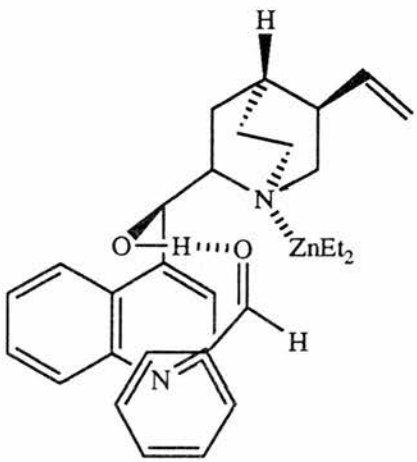
Wynberg[6] was the first to report the alkaloid catalysed addition of diethylzinc to benzaldehyde. The alkaloids used were the cinchona alkaloids.

The quinine catalysed reaction gave 1–phenylpropanol with 92% yield and 68% e.e., and an improvement on this was achieved when *o*–ethoxybenzaldehyde was alkylated to give 1–(*o*–ethoxyphenyl)propanol with 72% yield and 92% e.e. On the basis of his results Wynberg concluded the following.

The configuration of the alkaloid at **C8–C9** determines the configuration of the product. The difference in e.e. between the opposite configurations i.e. between quinine **7** and quinidine **8** was explained by the difference in orientation of the vinyl group. Thus the vinyl group plays some part in the

reaction mechanism, and this was demonstrated by the dramatic drop in e.e. when dihydroquinine was used to catalyse the reaction. A big drop in the e.e. when acetylquinine was used as the catalyst suggests that the hydroxy group at C**9** plays an important part in the reaction mechanism.

The increase in e.e. when *o*–alkoxybenzaldehyde was used appeared to be the result of steric effects rather than electronic effects since the 2,6–dimethoxy compound gave no improvement in e.e. These conclusions then led Wynberg to propose the transition state **30**



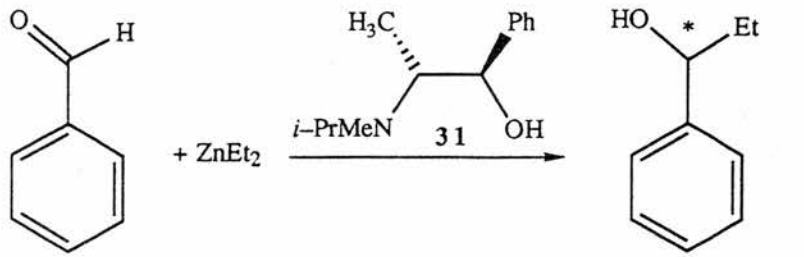
30

This transition state explains the above result and also gives the correct absolute configuration for the product. However studies on the mechanism of the same reaction using ephedrine suggest the formation of a zinc alkoxide species.[3] This would also explain the above result. The only thing that is unclear in the first case is the role played by the vinyl group.

Buono[7] made an interesting discovery about the effect of temperature on the cinchona alkaloid catalysed reaction. The results showed that increasing the reaction temperature while decreasing the reaction time resulted in higher e.e.s. This is the opposite effect from most other asymmetric reactions where colder temperatures and longer reaction times result in higher e.e.s.

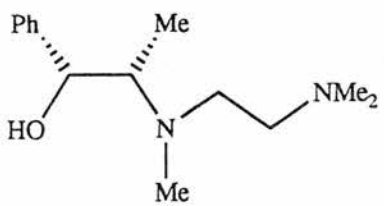
The work carried out with the cinchona alkaloids then prompted Chaloner[8] to report her work on the corresponding ephedrine catalysed reactions. Chaloner showed that the reaction of diethylzinc with benzaldehyde could be catalysed by *N*–alkylated ephedrines to produce optically active alcohols. Selectivities of up to 80% e.e. were achieved when *N*–isopropylephedrine **31** was used as the catalyst.

Chaloner[9] then went on to optimise this reaction by varying the diethylzinc to benzaldehyde ratio. This showed that when a large excess (4x) of diethyl zinc was used enantioselectivities of up to 95% could be achieved.

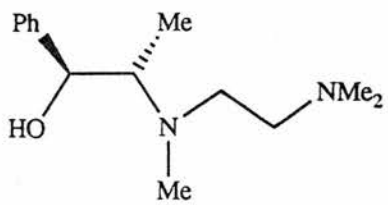


99.8%, 95% e.e.

It was reported by Corey and Hannon[10] that the lithium salt of (1R,2S)–*N*–[2–(dimethylamino)ethyl]ephedrine **32** catalysed the reaction of diethylzinc with benzaldehyde to afford (R)–1–phenylpropanol with 90% e.e. When the (1S,2S)–psuedoephedrine **33** was used as the catalyst, (S)–1–phenylpropanol was obtained with 91% e.e. This showed that the configuration in the catalyst governs the configuration of the product.

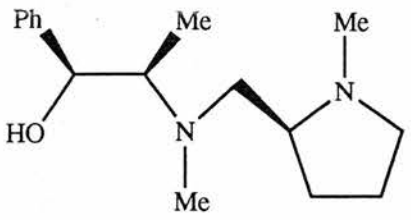


(1R,2S)–**32**

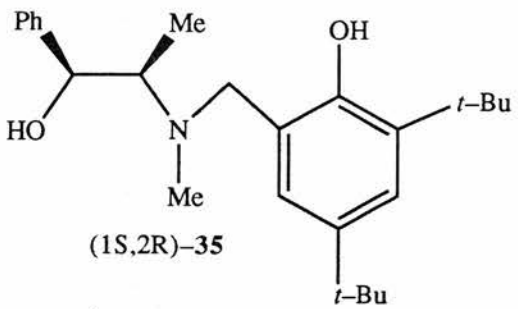


(1S,2S)–**33**

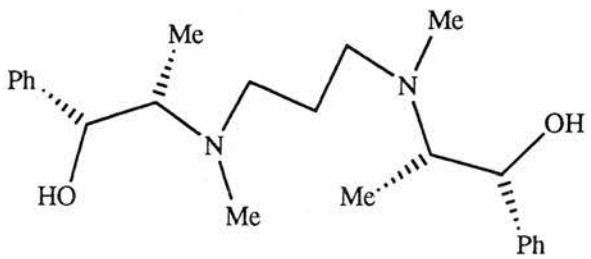
The lithium salt of chiral catalyst **34** gave (S)–1–phenylpropanol with 95% e.e.[10] Another catalyst used was the phenol derivative of psuedoephedrine, **35** which gave (S)–1–phenylpropanol with 86% e.e.[11] Saoi[12] and his coworkers made the C_2 symmetric diaminodiol **36** from ephedrine. The dilithium salt of **36** catalysed the reaction to produce (R)–1–phenylpropanol with 85% e.e.



(1S,2R)–**34**

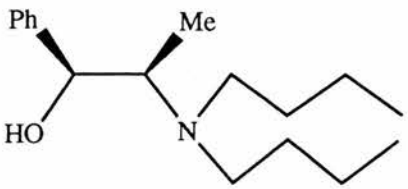


(1S,2R)–**35**

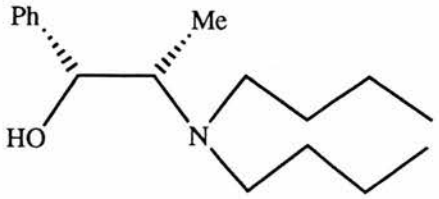


36

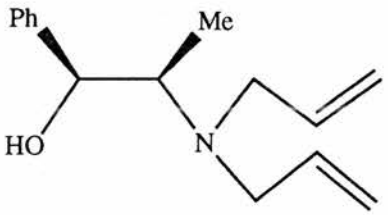
The *N,N*–dibutylnorephedrines **37** and **38**, which have been found to be efficient catalysts for the addition of diethylzinc to aliphatic aldehydes, were also found to be effective catalysts for the addition reaction to aromatic aldehydes. The reaction of diethylzinc with benzaldehyde in the presence of **37** gave (S)–1–phenylpropanol with 100% yield and 90% e.e.[13] The norephedrines **39** and **40** were also found to be effective catalysts for this reaction.[14]



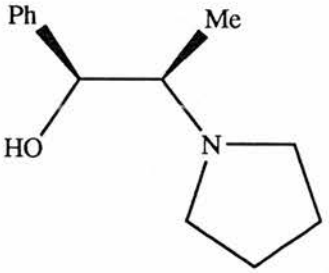
37 (1S,2R)–(-)–DBNE



38 (1R,2S)–(+)–DBNE

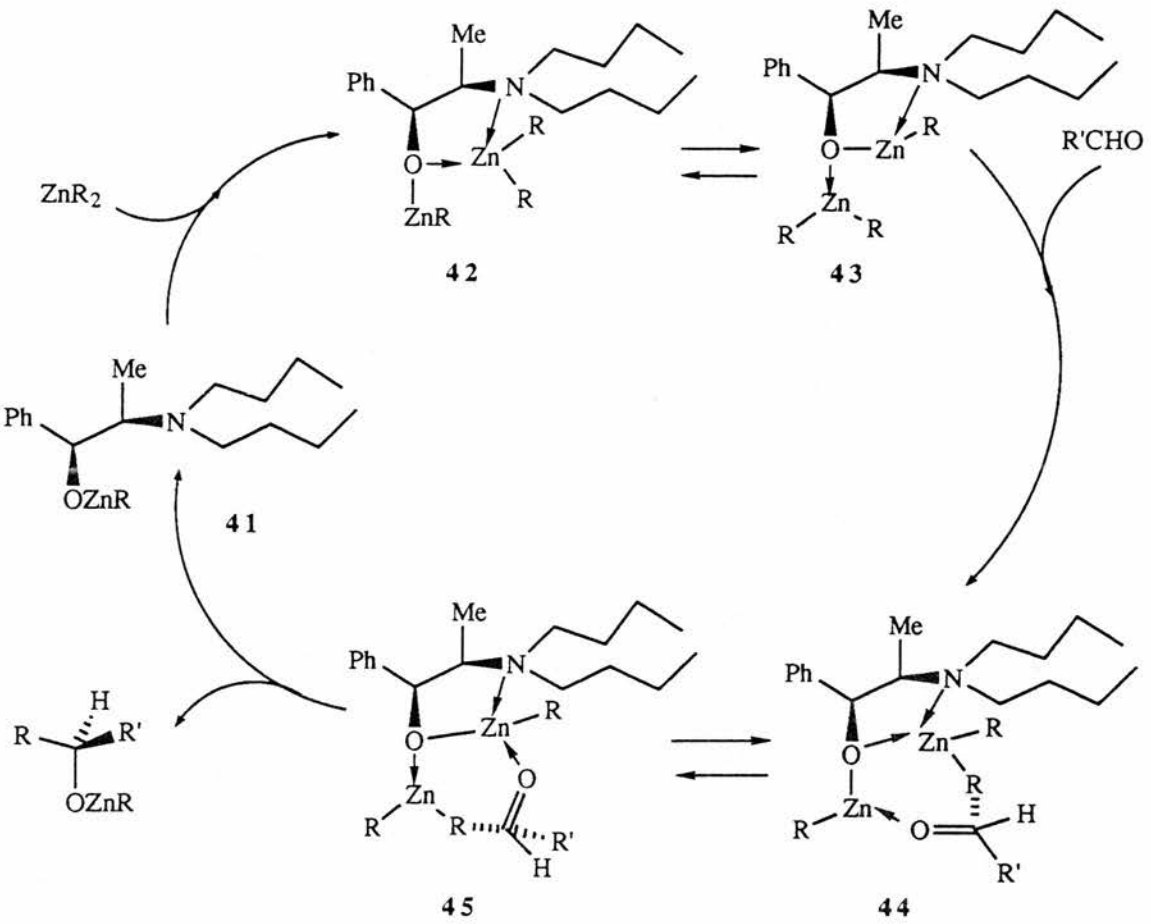


(1S,2R)–**39**

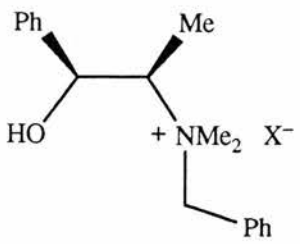


(1S,2R)–**40**

Soai[14] has tentatively proposed a mechanism for the reaction. The zinc alkoxide **41** which forms initially will be able to form complexes **42** and **43** with further dialklylzinc. Reaction of these complexes with aldehyde then leads to the possibility of two six–membered transition states, **44** and **45**, with the bulk of the *N*–alkyl group playing an important role in the selectivity of the reaction. Too bulky a group leads to the inhibition of the six–membered transition state. Adding an excess of diethylzinc then ensures the formation of complexes **44** and **45** leading to enantioselection in the reaction.



Soai[15] has also used the chiral quaternary ammonium salts of the ephedrines to catalyse this reaction. Reacting benzaldehyde with diethylzinc in the presence of **46** afforded (S)–1–phenylpropanol with 90% yield and 74% e.e. This was achieved when hexane was used as the solvent so that the catalyst was in the solid state. When DMF was used as the solvent the catalyst was in solution and no e.e. was observed. This is a rare example where the solid state catalyst is more effective than the solution state catalyst. The reason for this is that the DMF strongly solvates the ammonium cation and this disrupts the chiral complex which would form.



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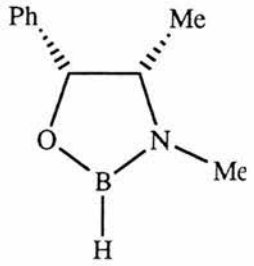
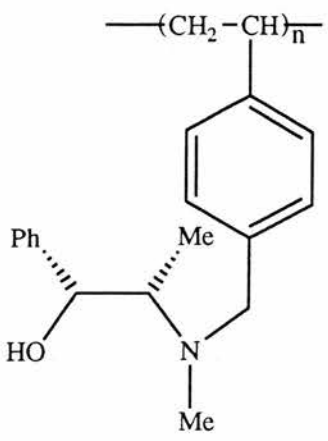


47

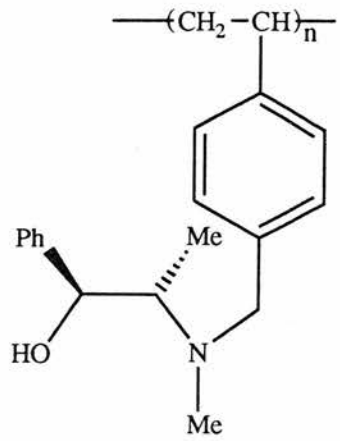
The chiral oxazaborolidine **47** is an effective catalyst for the addition of diethyl zinc to benzaldehyde to afford (R)–1–phenylpropanol with 95% e.e.[16] When the boron was replaced by aluminium, lithium or zinc the e.e. dropped dramatically. What makes boron superior to the other metals is the shorter bond lengths between boron and ephedrine.

In general polymer supported chiral catalysts have given low to moderate selectivities in carbon–carbon bond forming reactions. However polymer supported ephedrine catalysts have proved to be effective in the reaction of diethylzinc with aldehydes.

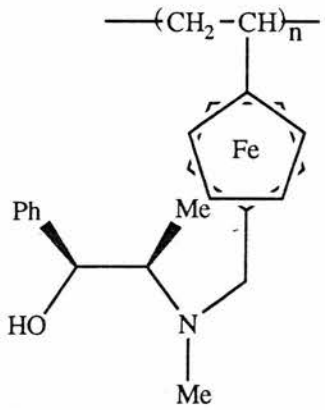
The reaction of diethylzinc with benzaldehyde in the presence of polymer supported ephedrine **48** afforded (R)–1–phenylpropanol with 89% e.e.[17] The catalyst was recovered and reused without any loss of activity. The selectivity, although not as good as that for the homogenous ephedrine catalysed reaction, is still high. However when pseudoephedrine derived polymer **49** was used, this afforded (S)–1–phenylpropanol with only 44% e.e. Despite this poorer selectivity, this reaction shows that as before the configuration at C**1** of the catalyst determines the configuration of the product.



48



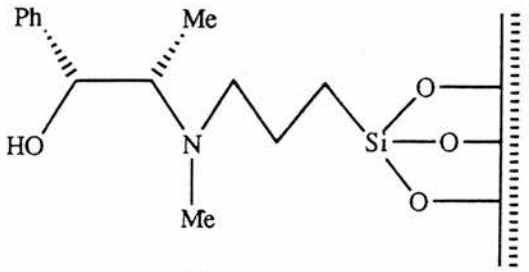
49



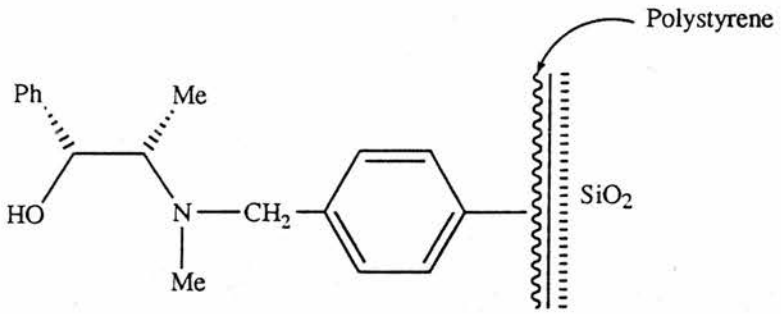
50

A chiral polymer **50** possessing the *N*–ferrocenylephedrine moiety catalysed the reaction to afford (S)–1–phenylpropanol with 72% e.e.[18]

Chiral *N*–alkylatednorephedrines have been immobilised on silica gel or alumina **51** using a silane coupling reagent (3–chloropropyl)–trimethoxysilane.[19] Reacting diethylzinc with benzaldehyde in the presence of **51** afforded (R)–1–phenylpropanol with 59% e.e. in the case of alumina and 37% e.e. in the case of silica. Ephedrine immobilised on silica gel coated with polystyrene **52** has also been used to catalyse the reaction, and this gave (R)–1–phenylpropanol with 56% e.e.[19] Although only moderate selectivities were obtained, these are the first examples of such catalysts in carbon carbon bond forming reactions.



51

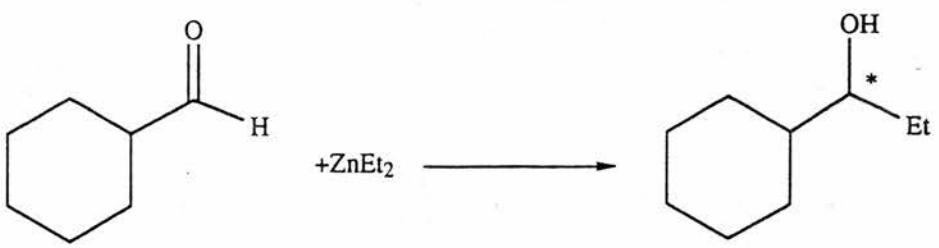


52

(b) Alkylation of Aliphatic Aldehydes

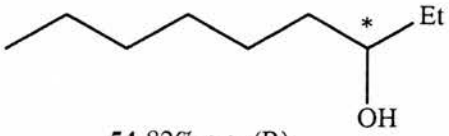
Aliphatic aldehydes have proved to be harder to alkylate with only moderate selectivities being achieved initially. This is presumably because of the loss of the stereoelectronic effect of the aryl groups.

Initially Chaloner used *N*–isopropylephedrine to catalyse the reaction of diethylzinc with cyclohexane carboxaldehyde. Using 1 equivalent of diethylzinc gave alcohol **53** with 0% e.e., using 4 equivalents of diethylzinc gave the (R)–**53** with 97% e.e.[9]

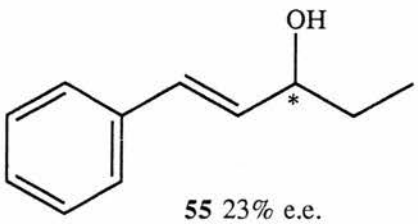


53

Chaloner was also able to synthesise **54** from heptanal with 82% e.e. and **55** with 23% e.e. from cinnamaldehyde.

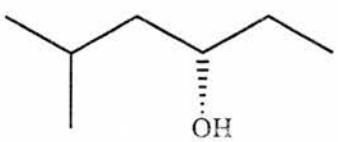


54 82% e.e. (R)

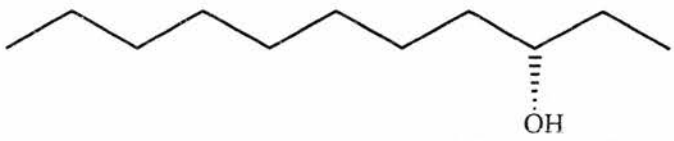


55 23% e.e.

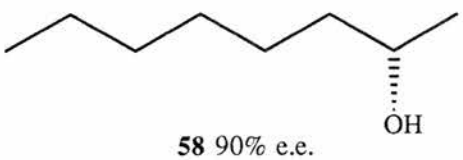
The reactivity of various *N,N*–dialkylnorephedrine derivatives was investigated by Saoi.[14] The best catalyst was found to be *N,N*–dibutylnorephedrine (DBNE) **37/38**, smaller and larger alkyl groups both gave lower selectivities. Reacting isopentanal with diethylzinc in the presence of DBNE afforded (S)–5–methylhexan–3–ol **56** with 93% e.e. Alcohols **57**–**62** were also similarly obtained with high selectivities.



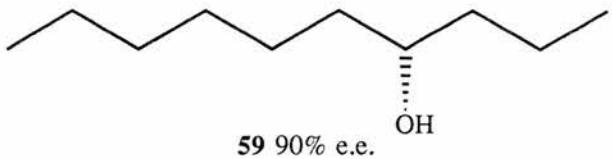
56 93% e.e.



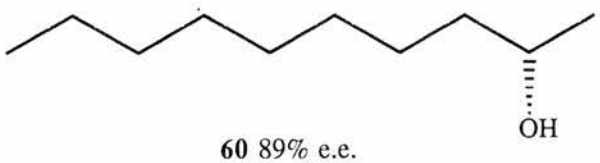
57 87% e.e.



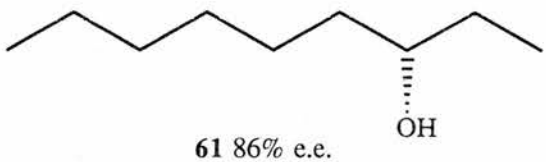
58 90% e.e.



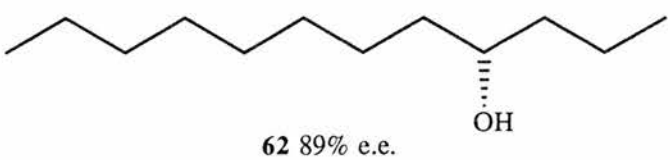
59 90% e.e.



60 89% e.e.



61 86% e.e.

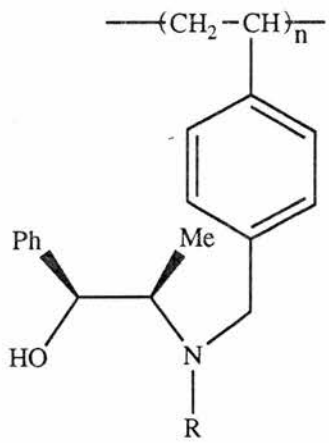


62 89% e.e.

(1S,2R)–*N*,*N*–Diallylnorephedrine **39** and (1S,2R)–1–phenyl–2–(1–pyrrolidinyl)propanol **40** were also found to be effective catalysts.[14] Both catalysed the addition of diethylzinc to heptanal to afford (S)–nonan–3–ol with 88% e.e. and 95% e.e., respectively.

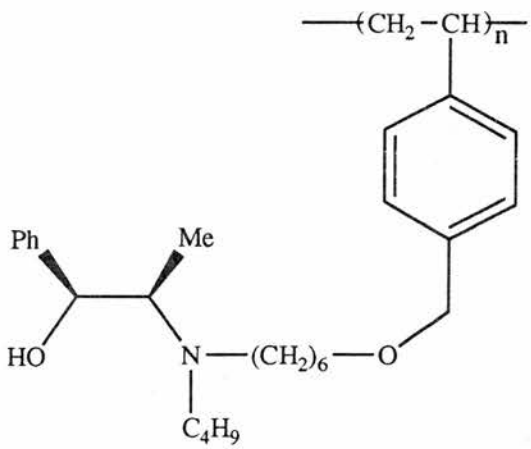
The chiral oxazaborolidine **47** catalysed the addition of diethylzinc to hexanal to afford (R)–octan–3–ol with 52% e.e.[16] Compared with DBNE this catalyst was clearly not very effective for the addition of diethylzinc to aliphatic aldehydes.

Polymer supported ephedrines have also proved to be useful catalysts for the addition of diethylzinc to aliphatic aldehydes. The polymer **63**, initially used for the reaction, proved to be an ineffective catalyst giving only low e.e.s. However, simply changing to **64** showed that an improvement in the selectivity could be achieved. Reacting heptanal with diethylzinc in the presence of **64** gave nonan–3–ol with 60% e.e.[20]



63 R=Me

64 R=Et



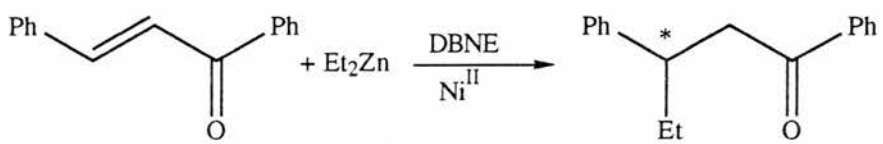
(1S,2R)–**65**

The polymer supported ephedrine **65**, which has a spacer group between the polymer and the norephedrine, proved to be the best polymer bound catalyst for the addition of diethylzinc to aliphatic aldehydes giving e.e.s of up to 75%.[21] The catalyst was easily recovered and reused with no loss of

activity. The high selectivity of this catalyst was thought to be due to the spacer group which may give the ephedrine more freedom to form a chiral complex with diethylzinc.

(c) Michael Addition of Diethylzinc

The reaction of dialkylzincs with α,β–unsaturated ketones in the presence of a chiral catalyst can yield synthetically useful optically active β–substituted ketones. The reaction can be catalysed by nickel complexes and adding ephedrine to the nickel can then give a chiral catalyst. No characterisable nickel complex has been isolated, however adding DBNE to nickel acetylacetonate produces an effective catalyst *in situ*. This was then used to catalyse the reaction of chalcone **66** with diethylzinc to afford (R)–**67** with 45% e.e.[22]



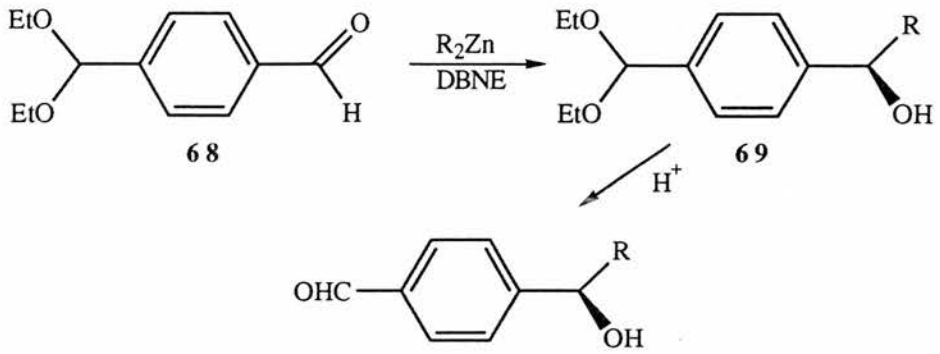
66 **67**

An improvement in the selectivity was made by adding an achiral ligand to the nickel as well as the DBNE. The most effective chiral catalyst for the Michael addition of diethylzinc was found to be a mixture of DBNE, 2,2'–bipyridyl, and nickel acetylacetonate. This catalysed the reaction of chalcone **66** with diethylzinc to afford (R)–**67** with 90% e.e.[23]

(d) Synthesis of Optically Active Hydroxyaldehydes

Optically active hydroxyaldehydes and hydroxyketones are important synthetic intermediates. Soai[24] recognised that chiral compounds such as **70**–**72** were potential building blocks for the formation of liquid crystals.

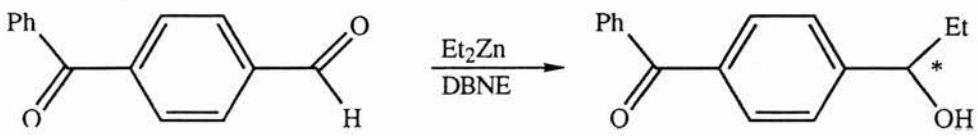
Reacting the acetal **68** with dialkylzinc in the presence of DBNE gave the alcohol and then acid hydrolysis during work up gave the hydroxy aldehydes **70–72** with up to 94% e.e.



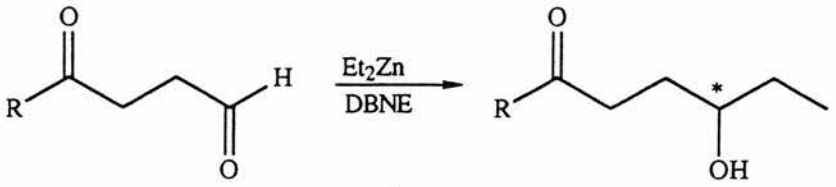
68 **69**

70 R=Me 74%, 88% e.e.
71 R=Et 76%, 94% e.e.
72 R=*n*–Bu 60%, 91% e.e.

In a similar way optically active hydroxyketones could be readily synthesised from compounds containing a ketone as well as an aldehyde carbonyl group.[13] Organozinc compounds are very unreactive towards ketones and so the organozinc compound will only react with the aldehyde carbonyl. Using this method hydroxyketone compounds **74**, **76** and **77** were synthesised with up to 99% chemoselectivity and with 91% e.e.



73 **74** 99%, 91% e.e.



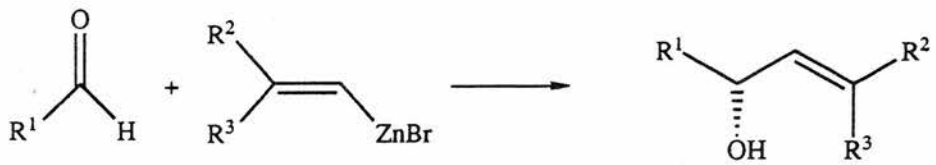
75

76 R=Ph 52%, 87% e.e.
77 R=$PhCH_2CH_2$ 47%, 81% e.e.

(e) Synthesis of Allyl and Alkynyl Alcohols

Optically active allyl and alkynyl alcohols are important synthetic intermediates in the synthesis of natural products and biologicaly active molecules. The addition of diethylzinc to α,β–unsaturated aldehydes is one possible method for synthesising optically active allyl alcohols. DBNE has proved to be an efficient catalyst for this reaction giving allyl alcohols with up to 82% e.e.[25]

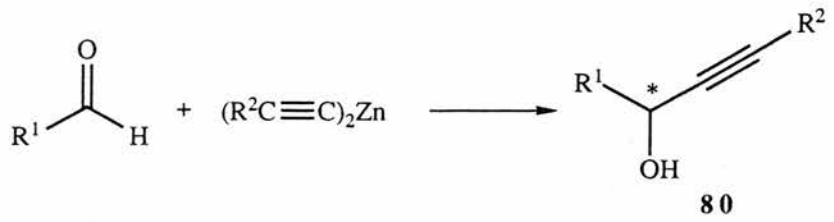
Another method is to add vinylzinc to aldehydes in the presence of a chiral catalyst. The lithium salt of *N*–methylephedrine was found to be an effective catalyst for this reaction. Reacting E–propenylzinc bromide with 3,3–dimethylpropanal in the presence of a stoichiometric amount of catalyst gave **79** with 98% e.e.,[26] while reaction of the *Z*–isomer with benzaldehyde proceeded in 86% e.e. to give **78**.



78 R^1=Ph, R^2=H, R^3=Me 68%, 86% e.e.
79 R^1=*t*–Bu, R^2=Me, R^3=H 48%, 98% e.e.

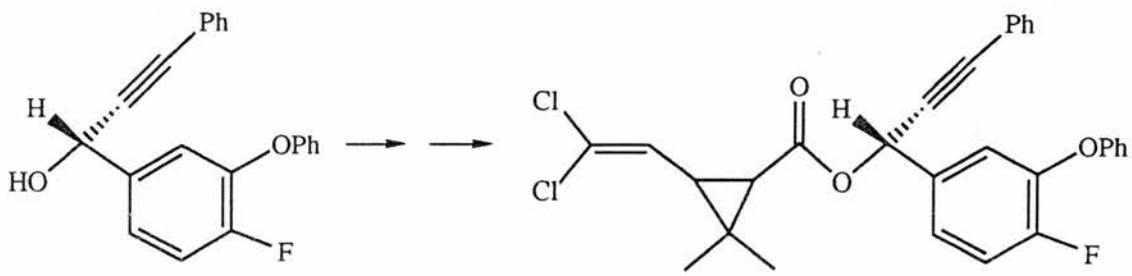
Similarly to the allyl alcohols, there are two possible ways to synthesise optically active alkynyl alcohols **80**. The first method is to add alkynylzinc reagents and DBNE was found to catalyse the reaction with only moderate

e.e.s of 10–43%.[27] The most efficient catalyst was found to be the lithium salt of *N*–methylephedrine which catalysed the reaction with up to 88% e.e.[28]



80

Tombe used this method to prepare alcohol **81** with 81% e.e.[28] and the product can then be converted to **82** which is an insecticide with a low toxicity to fish.



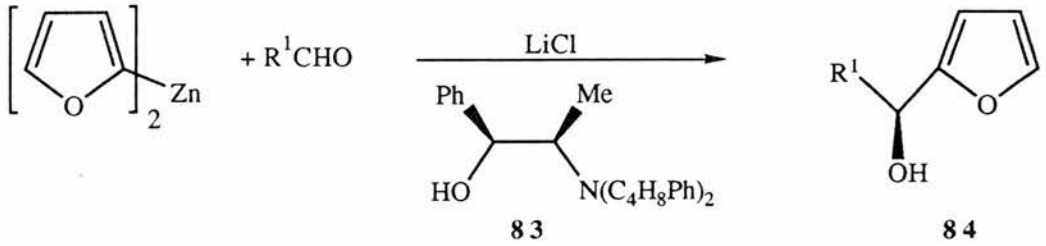
81 **82**

The second method for the synthesis of these alcohols is to add dialkylzinc reagents to alkynyl aldehydes. However the alkaloid catalysts have not been very successful for this reaction giving e.e.s of only 21%.[27]

(f) Asymmetric Synthesis of Furyl Alcohols

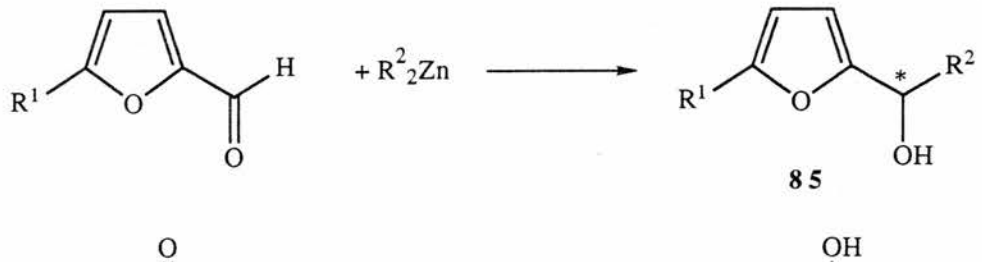
Substituted furans have gained importance as multifunctional building blocks and their preparation in chiral form can be useful in the synthesis of natural products and biologically active compounds. There are two possible pathways to such compounds using dialkylzincs. A furylzinc can be added to an aldehyde or an alkylzinc can be added to a furyl aldehyde.

Carrying out the reaction by adding difurylzinc to aldehydes using (1S,2R)–*N*,*N*–di(4–phenylbutyl)norephedrine **83** gave good optical yields of up to 73% e.e.[29] Difurylzinc was prepared in situ from furyllithium and zinc chloride and the presence of lithium chloride increased the enantioselectivity of the reaction. This is thought to be due to the chelation effect of lithium with the furan oxygen.



83 **84**

The reaction of dialkylzincs with furylaldehydes can be catalysed by quinine with up to 60% e.e. and DBNE with up to 93% e.e.[30] Different furyl alcohols have been synthesised including the 3–substituted example **86** with 94% e.e.[31]



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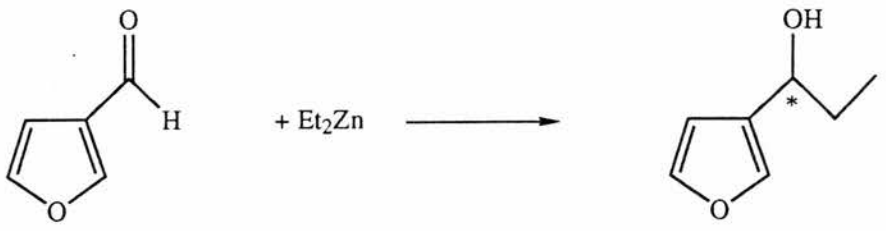
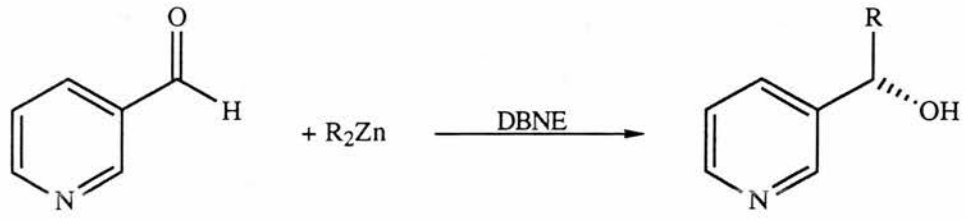


86 52%, 94% e.e.

(g) Synthesis of Optically Active Pyridyl Alcohols

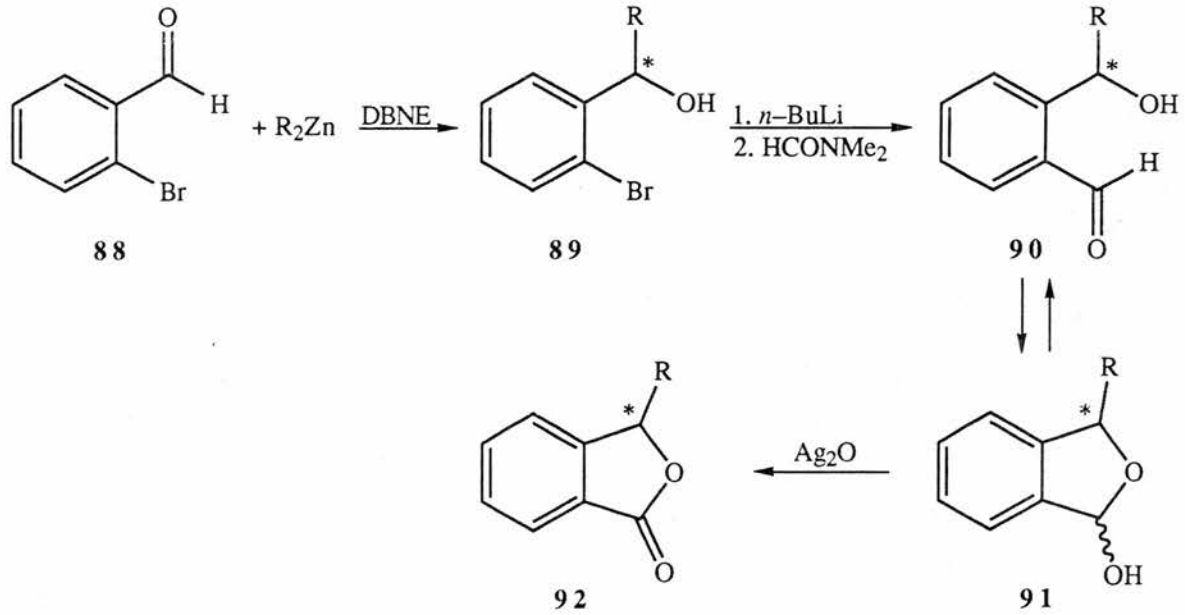
DBNE catalysed the reaction of dialkylzincs with 3–pyridinecarboxaldehyde to give optically active alcohols with up to 86% e.e.[32]



87

(h) Synthesis of Optically Active 3–Alkylphthalides

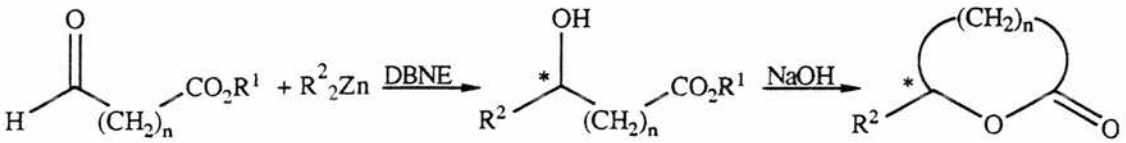
Optically active 3–alkylphthalides are substances present in natural products such as celery oil. Such compounds can be synthesised by the addition of dialkylzincs to **88** in the presence of DBNE to give chiral alcohols **89**. A few simple reaction steps then lead to the optically active phthalide **92** with up to 90% e.e.[33]



88 **89** **90** **92** **91**

(i) Synthesis of Optically Active Hydroxy Esters and Lactones

Optically active lactones are important molecules for the synthesis of pheromones. DBNE catalysed the addition of dialkylzinc to **93** to give optically active alcohols **94** which can be easily converted to lactones **95** with up to 95% e.e.[34]



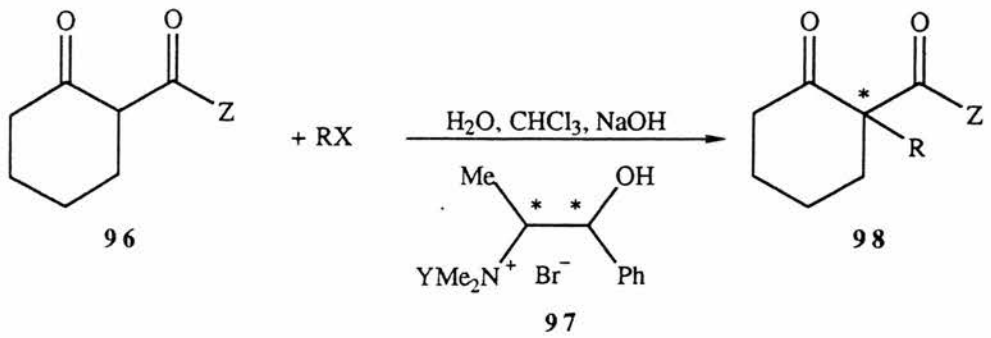
93 **94** **95**

2. Enolate Alkylations

Alkylation reactions may be carried out on enolates and an important method of producing these is to react a ketone with sodium hydroxide solution in the presence of a phase transfer catalyst. The enolate formed may then react with an alkyl halide to produce a carbon–carbon bond. The chiral phase transfer catalysts (PTC) derived from the alkaloids have been used with great effect in such reactions.

(a) Alkylation with Alkyl Halides

The first phase transfer alkylation of enolates using alkaloid PTCs was reported by Fiarid.[35] In the reaction of **96** with alkyl halides he used the quaternary ammonium salts derived from ephedrine **97** as the chiral PTCs.

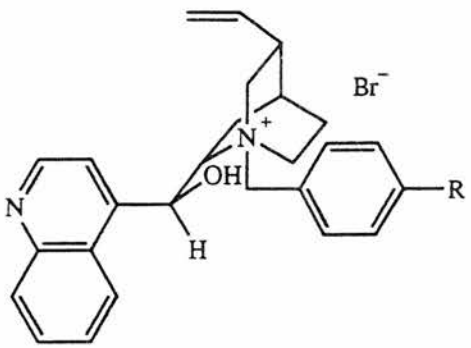


96 **97** **98**

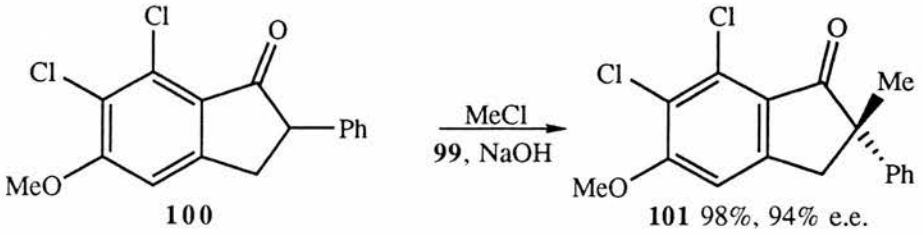
It was claimed that this reaction produced **98** in up to 15% ee. This, however, has been disputed as most of the optical activity observed was due to compounds produced by the decomposition of the catalyst.

The quaternary ammonium salts derived from the cinchona alkaloids were found to be much more effective catalysts for the addition of alkyl halides to enolates.

Hughes and Dolling of Merck Sharpe and Dohme found that *N*–benzylcinchoninium bromide **99** catalysed the reaction of **100** with methyl chloride to afford indanone **101** with 94% e.e.[36]

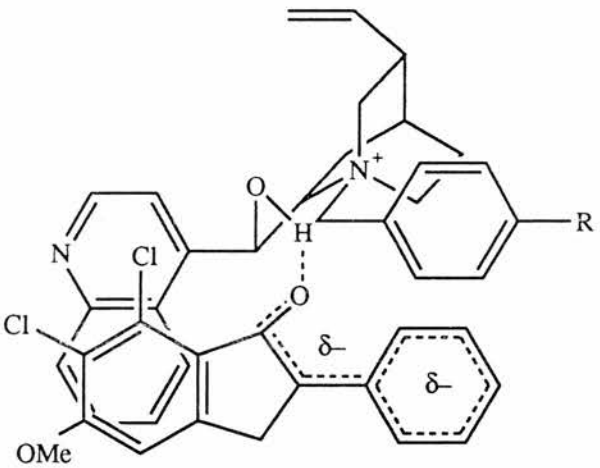


99 R=OMe, Me, H, F, Cl, CF_3.



100 **101** 98%, 94% e.e.

The reaction mechanism has been studied quite extensively.[37] Some points of note are that nonpolar solvents such as toluene produced better results than polar solvents, and the enantioselectivity of the reaction increased with higher dilution, increased sodium hydroxide concentration, faster agitation and lower temperatures. The catalyst concentration had little effect on the enantioselectivity, but it did control the rate of the reaction.



102

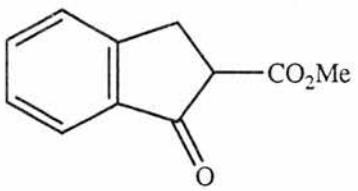
The high enantioselectivity observed in the reaction can be explained by the unique transition state **102** formed between the indanone and the catalyst. The conformation of the catalyst is such that the benzyl group and the quinoline ring are orientated away from each other so that there is an 'aromatic plane'. The formation of the indanone anion results in polarisation of the indanone in such a way that it can lie flat along the 'aromatic plane' of the catalyst. A hydrogen bond can form between the hydroxyl group of the

catalyst and the keto oxygen of the indanone locking the indanone in position. This means that the methyl chloride can only add from one side of the indanone to give the (S) enantiomer of the product.

(b) Michael Addition Reaction of Enolates

Enolate anions, such as those used above, can react in a Michael fashion with α,β–unsaturated ketones. The diketo compounds produced can then undergo a Robinson annulation to produce cyclic compounds. To ensure that only one enolate anion can form, substituted ketones were used. If an acidic α–hydrogen is left after the Michael addition reaction this can lead to racemisation or further addition reactions.

It was Wynberg who first reported the use of cinchona alkaloids to catalyse the addition reaction of the anions of various acidic organic compounds **103–109** to methyl vinyl ketone **111**.[38] Although all of these ketones reacted with **111** to produce optically active products none of the optical yields were determined.



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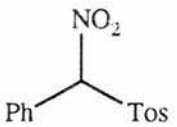

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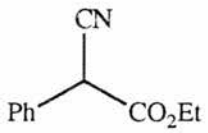

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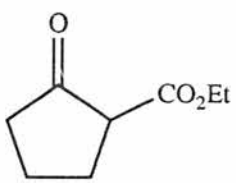

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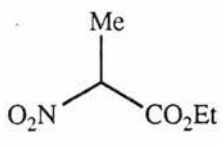

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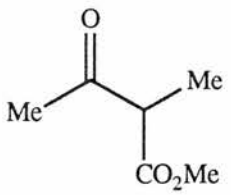

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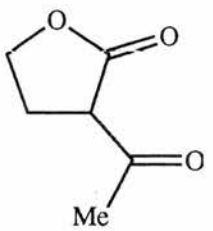
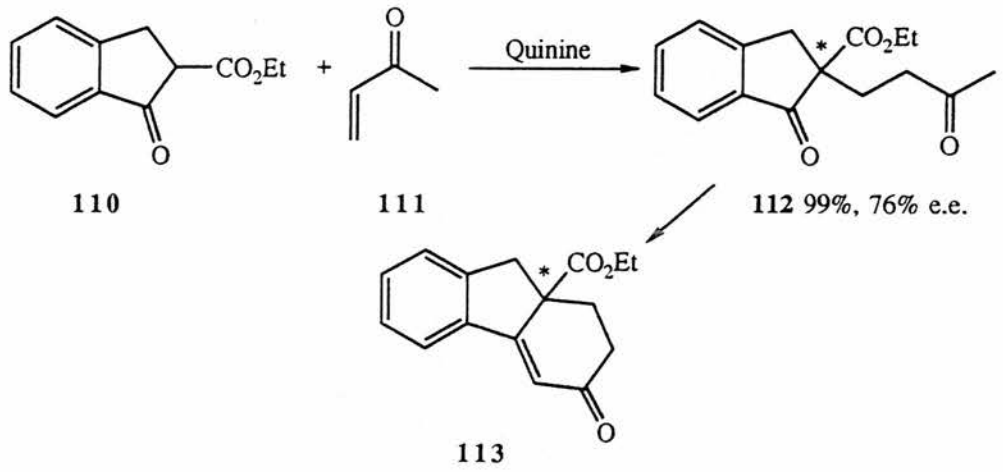
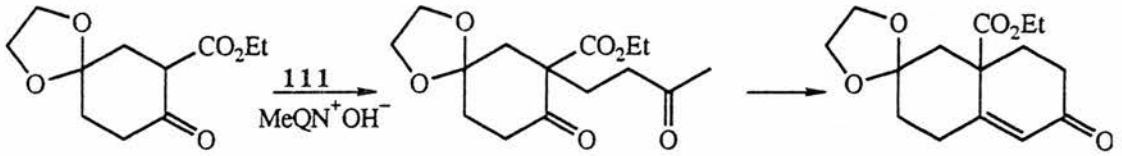


109

Wynberg then went on to show that **110** can be added to **111** in the presence of quinine to produce **112** with 76% e.e.[39] The reaction of **114** with

111 in the presence of N–methylquininium hydroxide afforded (S)–**115** with 25% e.e. The quaternary hydroxide was used because it was found that quinine was not a strong enough base to form the enolate anion.



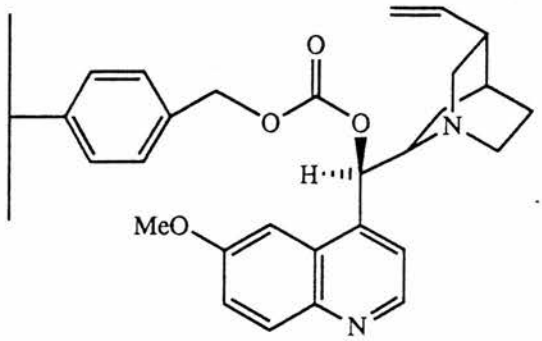


114 **115** 100%, 25% e.e. **116**

In both the above reactions the product of the Michael addition underwent a Robinson annulation to produce optically active bicyclic ketones.

Several different polymer bound alkaloids have been used to catalyse the Michael addition reaction. These catalysts produced optically active products with low to moderate e.e.s.

Wynberg[40] copolymerised the cinchona alkaloids with polystyrene through a linkage with the hydroxy or methoxy group of the alkaloid to produce catalysts **117–119**. These catalysed the Michael addition with e.e.s of up to 11%.



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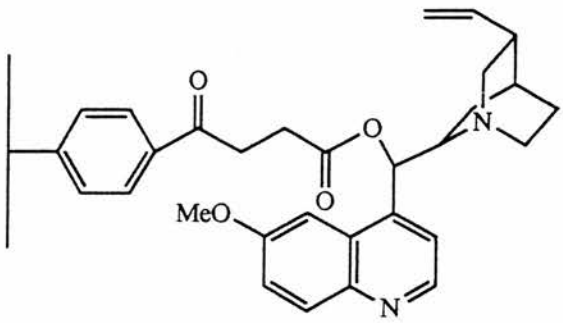

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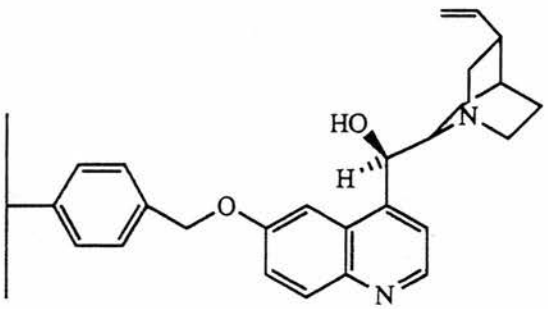

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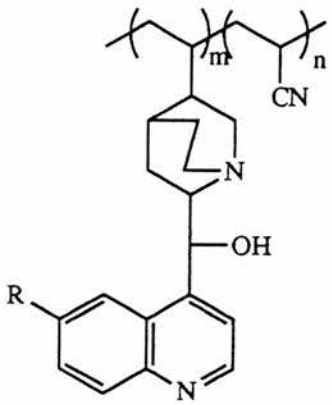

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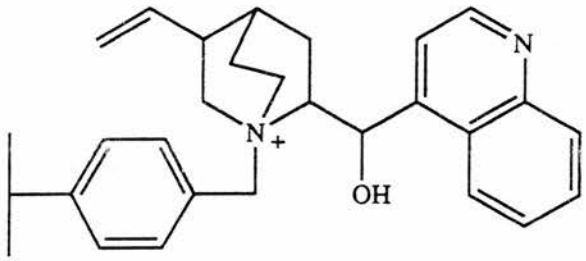


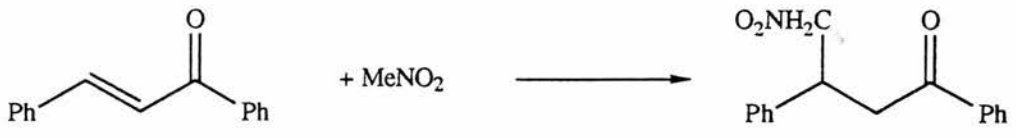
121

Kobayashi[41] copolymerised the alkaloids with acrylonitrile through the vinyl group on the alkaloid to produce catalyst **120**. This left the active part of the molecule unaltered. The reaction of ketones with **111** in the presence of quinidine–acrylonitrile copolymer gave optically active products with up to 48% e.e. The quinine–acrylonitrile copolymer gave e.e.s of up to 30%.

Hodge[42] copolymerised the cinchona alkaloids using polystyrene joined to the alkaloid through the quinuclidine nitrogen producing a quaternary

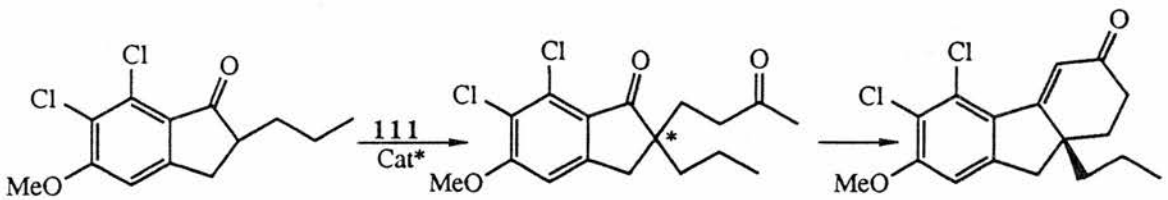
ammonium salt **121**. This catalysed the reaction with low selectivities of up to 30% e.e.

Wynberg reported[43] the first phase transfer Michael addition reaction using the alkaloids as PTCs. The best result obtained was when nitromethane was added to **66** in the presence of *N*–methyl–*N*–benzylephedrinium bromide and potassium fluoride to give **122** with 26% e.e.



66 **122** 50%, 26% e.e.

Conn and coworkers at Merck Sharp and Dohme found[44] that the quaternary ammonium salts of the cinchona alkaloids could catalyse the addition of **123** to **111**. Reacting **123** with **111** in the presence of [*p*–(trifluromethyl)benzyl]–cinchoninium bromide produced **124** with 80% e.e. They were then able to carry out a Robinson annulation to produce optically active tricyclic ketone **125** which is a potential drug candidate.

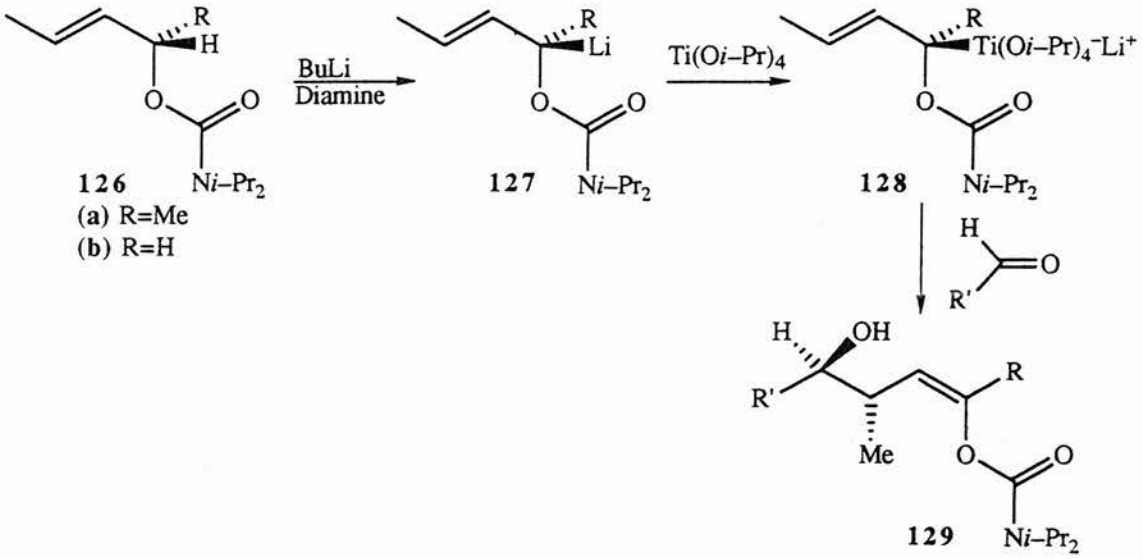


123 **124** 95%, 80% e.e. **125**

(c) Deprotonation

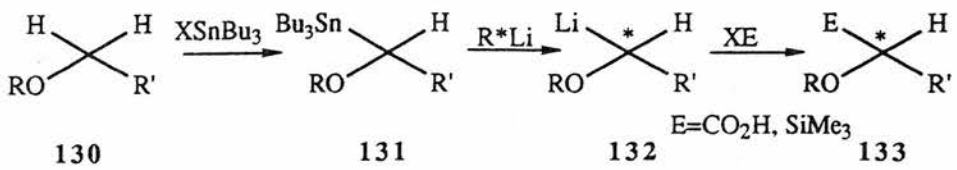
Enantiomerically pure carbamates such as **126a** can undergo deprotonation with lithium amides to produce **127** with retention of configuration. A metal exchange with titanium then produces **128** which can

react with aldehydes with retention of configuration and enantiofacial differentiation.



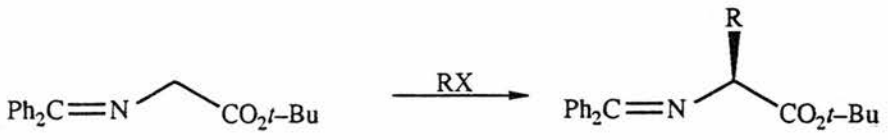
However when the same reaction is carried out on compounds **126b** no chirality exists in the starting compound and so chirality has to be introduced to the reaction. One way of doing this is to use a chiral lithium reagent such as sparteinyl lithium. Carrying out the reaction using this reagent gave **129b** with up to 95% e.e.[45]

A similar problem exists in the deprotonation of **130** with the added problem that butyl lithium does not react directly with **130**. To overcome these problems the sterically hindered compound **131** was made, a metal exchange with sparteinyl lithium gave **132**. Reacting **132** with carbon dioxide or TMS–chloride gave **133** with up to 96% e.e.[46]



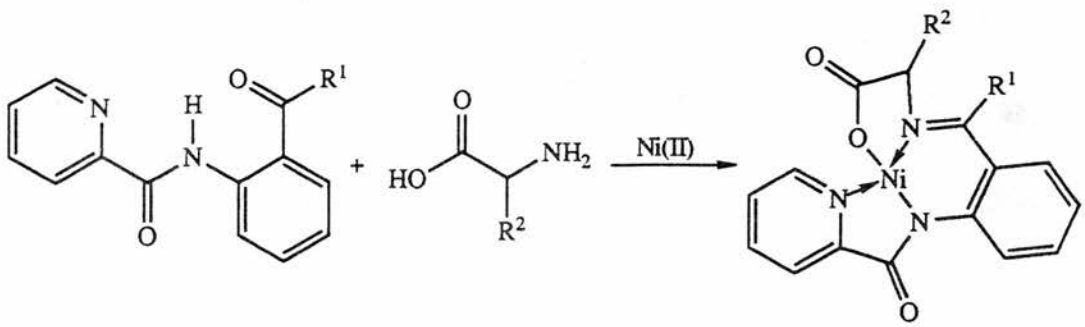
3. Synthesis of Amino Acids

An asymmetric synthesis of amino acids has been carried out by the phase transfer production of an anion followed by the addition of an alkyl halide. O'Donnell reported[47] that compound **134** could be alkylated under phase transfer conditions by various alkyl halides. Using the quaternary ammonium salts of the cinchona alkaloids as PTCs gave products **135** with up to 66% e.e. A recrystallisation, followed by removal of the protecting groups, gave amino acids with 50% overall yield and >99% e.e.



134 **135**

Another approach to the synthesis of amino acids was to form nickel complexes **136**. Such complexes can then undergo asymmetric phase transfer catalysed alkylation reactions with alkyl halides or acrylonitrile and using the quaternary ammonium salts of the cinchona alkaloids as catalysts. This produced amino acids with low e.e.s of up to 13%.[48]

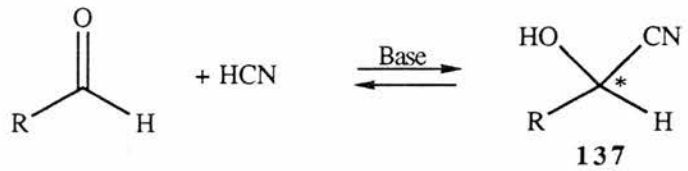


136

4. The Cyanohydrin Reaction

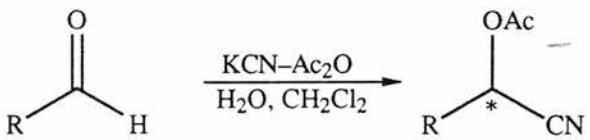
4. The Cyanohydrin Reaction

The reaction of hydrogen cyanide with aldehydes in the presence of a base yields cyanohydrins **137**. Bredig and Fiske[49] were the first to use the cinchona alkaloids as base catalysts to produce optically active cyanohydrins. However only low enantiomeric selectivity was observed. This was due to the instability of the cyanohydrins formed which may decompose or racemise. The best selectivities were obtained by Prelog and Wilhelm[50] who reacted cinnamaldehyde and hydrogen cyanide in the presence of the cinchona alkaloids and diethylamine. They determined the stereoselectivity by extrapolating to zero time to obtain up to 25% e.e.



137

Julia[51] tried the cyanohydrin reaction under phase transfer conditions using *N*–dodecyl–*N*–methylephedrinium bromide and *N*–benzylcinchoninium chloride as catalysts. Although the products were isolated as the more stable acetates **138** only small rotations were observed (<1°) for various aldehydes. The ephedrine salt gave slightly better rotations than the cinchona alkaloids.

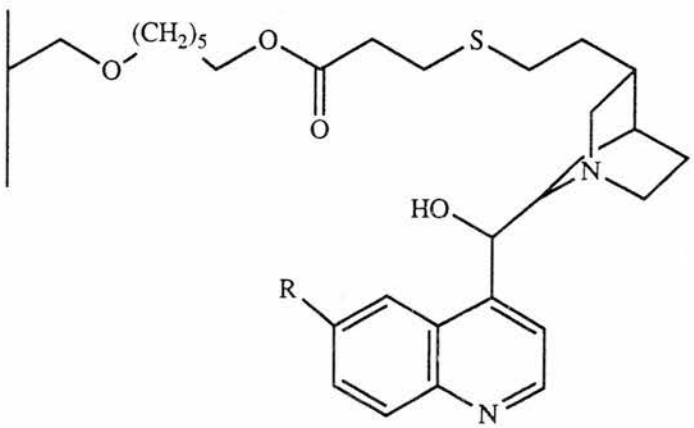


138

In order to obtain high optical yields of stable cyanohydrin acetates, Oda[52], used a combination of alkaloid catalysis and lipase catalysed resolution

in a one pot method. As well as the cinchona alkaloids brucine was also used. Brucine produced only low yields of cyanohydrins which were optically inactive, but the cinchona alkaloids were the best catalysts giving e.e.s of up to 75% for aliphatic aldehydes.

Polymer bound alkaloids have also been used in the alkaloid–lipase cyanohydrin reaction. Two different polymers have been used, a direct alkaloid–acrylonitrile copolymer and one with a spacer group **139** between the polymer backbone and the alkaloid. In both cases the polymer backbone was bound to the vinyl group of the alkaloid. Both were found to be effective catalysts giving the product with up to 92% e.e.[52] They could also be reused with no loss of activity.



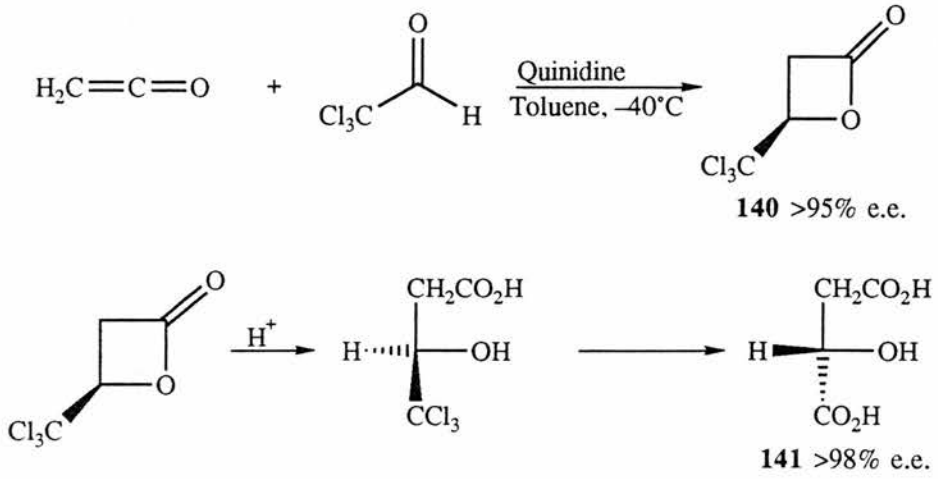
139

5. Cycloaddition Reactions

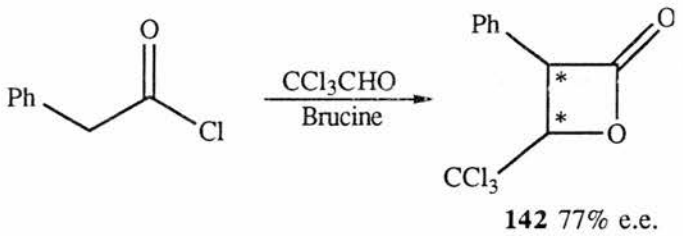
In the presence of base ketene will undergo a [2+2]–cycloaddition reaction with chloral to produce β–lactones. Wynberg used the cinchona alkaloids as bases in this reaction to produce optically active β–lactones **140** with greater than 98% e.e.[53]

It was found that the ketene first acylates the alkaloid so that the actual catalyst is the alkaloid ester. It has also been shown that hydrolysis of the β–

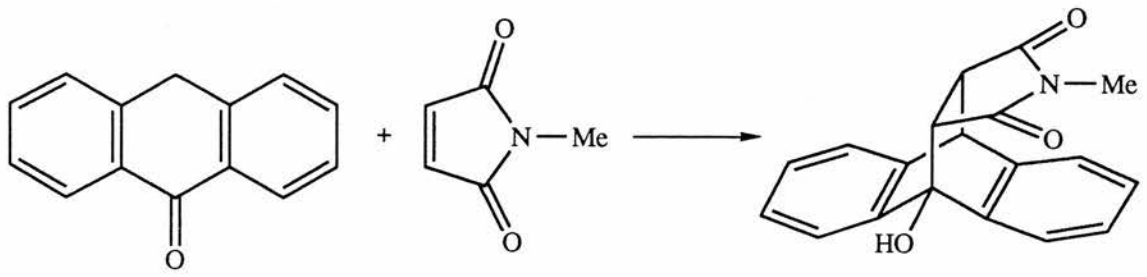
lactones produces malic acids **141** with inversion of configuration and excellent selectivity. The reaction has been carried out on a wide range of aldehydes to produce both product enantiomers with high selectivity.



It has also been shown that the reaction can be catalysed by brucine to produce e.e.s of up to 77%.[54]

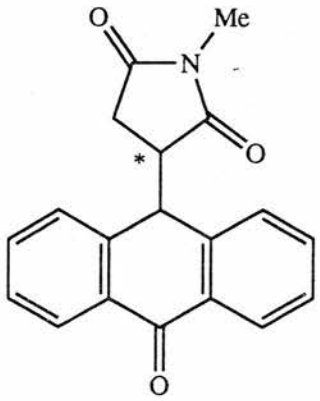


In the presence of base, **143** undergoes a Diels Alder reaction with *N*–methylmaleimide **144** to produce **145**. Kagan showed that the alkaloids can catalyse the reaction to produce optically active product.[55] The best result obtained was when the reaction was carried out at –50°C using quinidine as the catalyst to produce **145** with up to 61% e.e. Ephedrine also catalysed the reaction to produce **145** with up to 17% e.e.



143 **144** **145**

When the reaction was carried out under phase transfer conditions using *N*–benzylquininium chloride as the catalyst, the Michael adduct **146** was formed with 16% e.e.



146

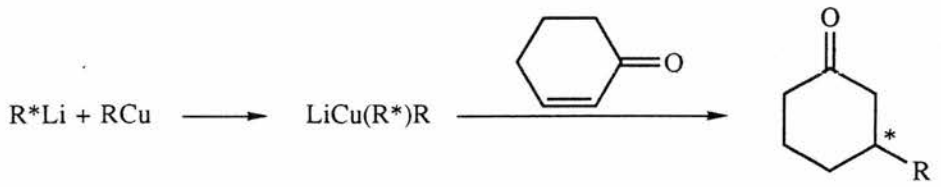
6. Asymmetric Conjugate Addition

Organometallic reagents may undergo addition to α,β–unsaturated substrates to produce a new carbon–carbon bond. The organometallic reagents may be altered by adding chiral ligands so that an asymmetric addition reaction occurs.

Table 1

Alkaloid	Substrate	R	% e.e.
Cinchonidine	**66**	Me	34(S)
Cinchonine	**66**	Me	0
Corynanthine	2-cyclohexenone	Ph	0
Tomatidine	"	"	0
Yohimbine	"	"	20(S)
Solasodine	"	"	10(R)
33	2–cyclopentenone	Et	77(R)
Emetine	2–cyclohexenone	Ph	40(R)
Ajmaliene	"	"	10(R)
Calycanthine	"	"	0
Reserpine	"	"	10(S)
Reserpiline	"	"	10(S)

Reagents such as the lithium organocuprates have been used in this way. Adding chiral lithium compounds, such as lithium–alkaloids, to organocuprates results in an asymmetric alkylating agent **147**. Several alkaloids have been used in this reaction and the results are listed in Table 1.[56]



147 **148**

Low to good selectivities have been obtained for the reaction. The best alkaloid to use was the ephedrine derivative which gave 77% e.e. The high

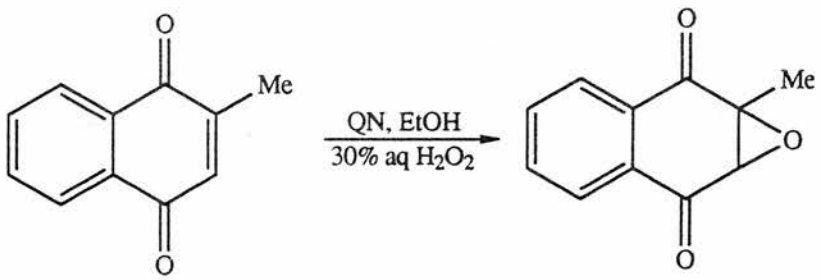
selectivity produced by this alkaloid was thought to be due to an intermediate where both the oxygen and the nitrogens are coordinating to the lithium.

C. Oxidations

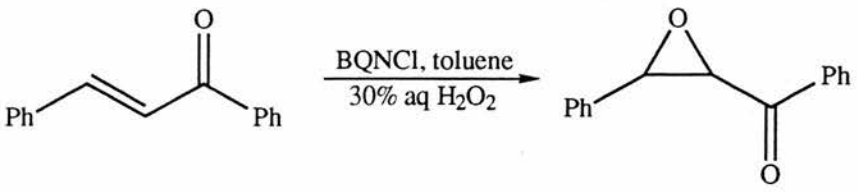
1. Epoxidation

Epoxides are important intermediate molecules both in biological metabolic processes and organic synthesis. Their asymmetric synthesis is then an important goal for organic chemists. This is demonstrated by the degree of interest shown in the reaction since Wynberg published the first asymmetric epoxidation.[57]

Wynberg found that reacting quinone **149** with hydrogen peroxide in the presence of quinine gave the epoxide **150** in good yield, but with no appreciable stereoselectivity.[57] However when the reaction was carried out under phase transfer conditions significant stereoselectivity was observed. Reacting chalcones **66** with hydrogen peroxide in a two phase system using cinchona alkaloid salts as the PTC gave the epoxide **151** with up to 55% e.e.[57]



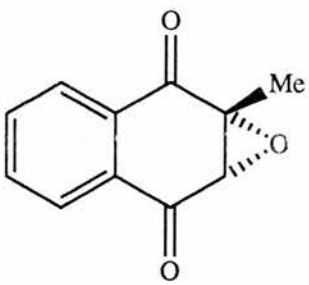
149 **150**



66 **151**

The chalcones,[58] quinones,[59] and cyclohexenones[2] have all been successfully epoxidised under these reaction conditions. Three reagents have been found to carry out the epoxidation, 30% hydrogen peroxide, *t*–butylhydroperoxide, and 28% sodium hypochlorite. The hydrogen peroxide produces the opposite enantiomer from the other two reagents.

The quinone **149** was epoxidised under phase transfer conditions using hydrogen peroxide to give vitamin K_3 **152** with a low e.e.[57] However this was the first asymmetric synthesis of this compound which plays an important role in prothrombin biosynthesis.[60]

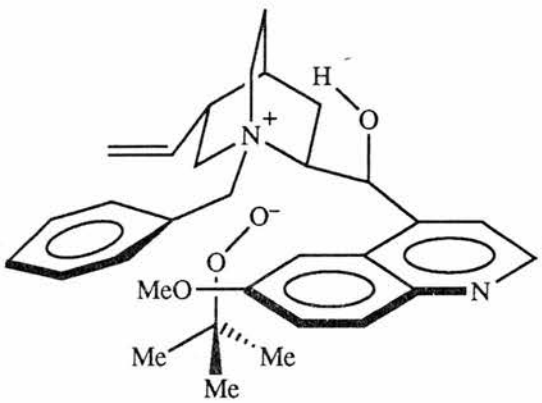


152 (2R,3S)–(–)–Vitamin K_3

Cyclohexenones were not oxidised by hydrogen peroxide, except for 4,4–dimethylcyclohexenone which gave optically active epoxide. The other cyclohexenones examined gave water soluble decomposition products. However a successful asymmetric epoxidation of 2–cyclohexen–1–one was carried out using *t*–butylhydroperoxide, *N*–benzylquininium chloride and sodium hydroxide as the base. This gave the epoxide with 20% e.e.[2]

Ephedrine and polymer bound ephedrine salts have also been used to catalyse this reaction,[61] however the cinchona alkaloids were found to be the most effective catalysts.

A mechanism for the reaction has been proposed,[2] although the lack of kinetic data makes it dubious. If we assume a tight ion pair between the peroxide anion and the alkaloid **153**, and also hydrogen bonding between the ketone and the hydroxyl group on the alkaloid, this then leads to two transition states, **154** and **155**, which lead to the two enantiomers. In transition state **155** the quinuclidine ring of the alkaloid is blocking the double bond from the peroxide and so **154** is favoured.



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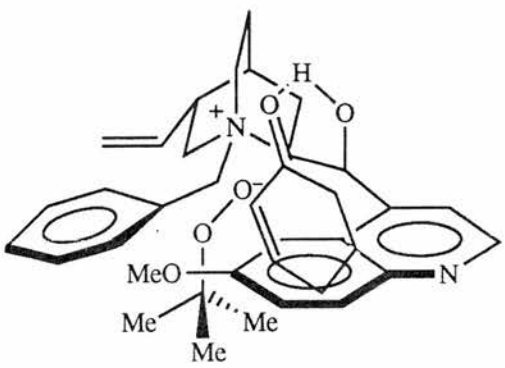

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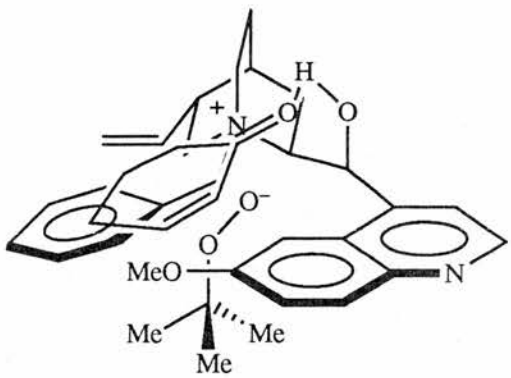
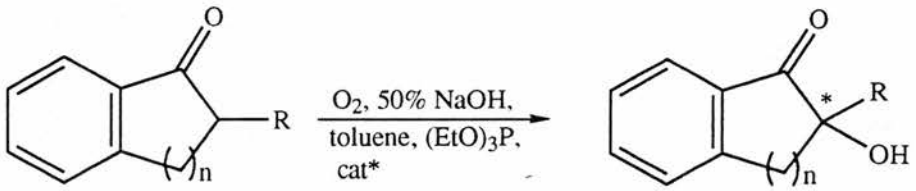


155

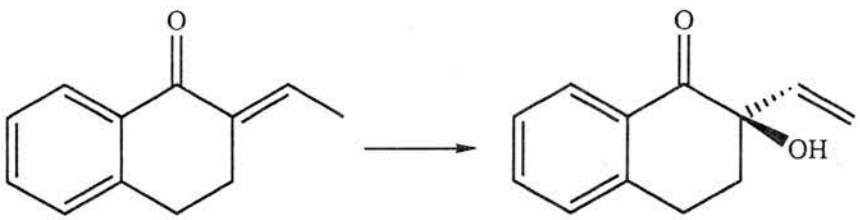
2. Oxidation using Molecular Oxygen

An unusual procedure for the formation of optically active α–hydroxy ketones has been reported by Shiori.[62] Ketones **156** were reacted with molecular oxygen in a two phase system using the alkaloid salts as chiral phase transfer catalysts. This resulted in the formation of α–hydroxy ketone **157** with greater than 90% yield and up to 79% e.e. A range of different catalysts were used with the cinchona derived catalysts proving to be the most effective.



156 **157**

The α,β–unsaturated ketone **158** reacted under the same conditions to give the α–hydroxy ketone **159** with good yield and moderate e.e.



158 **159** 73%, 55% e.e.

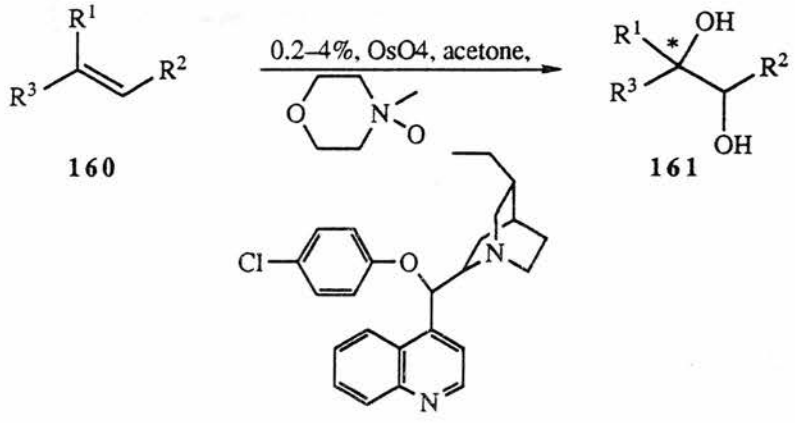
3. Asymmetric Dihydroxylation

(a) Simple Alkenes

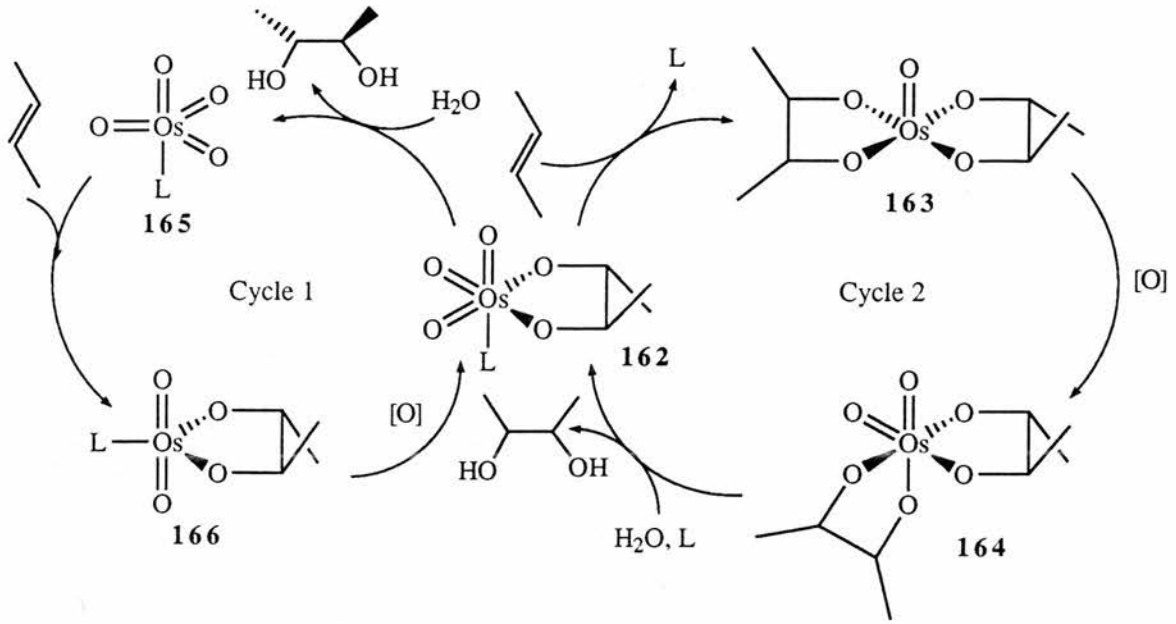
The most effective method for adding two hydroxyl groups to an alkene is the osmium dihydroxylation reaction which gives syn addition of the

hydroxy groups. This was carried out asymmetrically in a stoichiometric way by Sharpless as early as 1980[63] using the cinchona alkaloids. Although the reaction was very reliable and selective, the expense and toxicity of osmium meant that a catalytic system would be much better. The development of such a system by Upjohn using *N*–methylmorpholine *N*–oxide, which could be accelerated by the addition of tertiary amines, led Sharpless to develop a cinchona–osmium tetroxide catalytic system.

The initial reaction procedure reported[64] in the literature gave diols **161** with moderate to good selectivities. The best results were obtained for the dihydroxylation of the styrenes and stilbenes, and it seemed that the reaction would be limited to these compounds.



While investigating the mechanism of the reaction Sharpless discovered two catalytic pathways.[65] The key intermediate in these pathways is **162** which when hydrolysed by water produces a chiral diol. However it may also react with another molecule of alkene displacing the chiral ligand to form **163**. Oxidation and then hydrolysis of **163** then leads, with poorer selectivity, to products of the opposite enantiomer from first cycle.

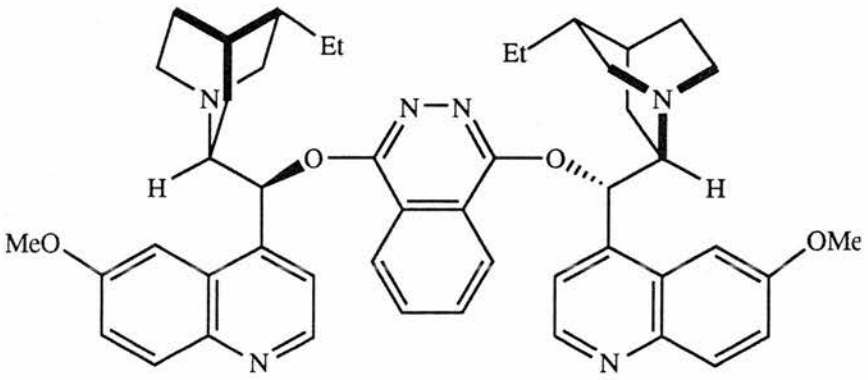


When the alkene was added slowly to this system, the second cycle was suppressed. This led to an improvement in selectivity and also led to aliphatic alkenes being hydroxylated with moderate to good e.e.s.[66]

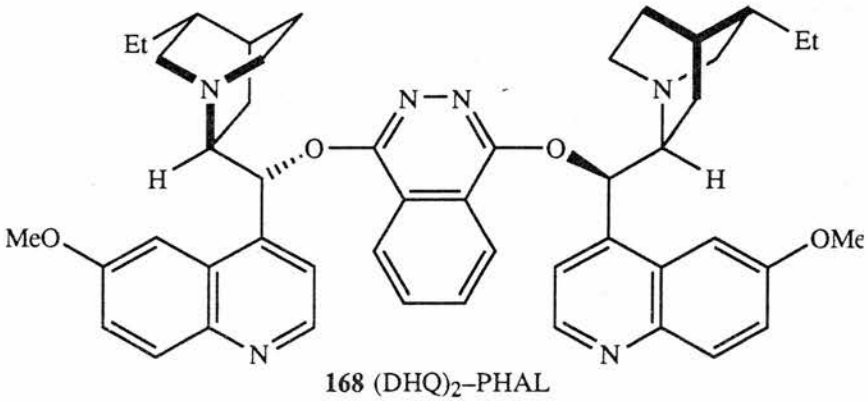
Another improvement was made when the *N*–methylmorpholine *N*–oxide was replaced by potassium ferricyanide as the oxidant,[67] and the acetone by *t*–butanol as the solvent. This led to a two phase *t*–butanol–aqueous potassium ferricyanide/carbonate system which appeared to suppress the second cycle completely. The dihydroxylation of stilbene under these conditions gave the corresponding diol with 99% e.e. and dec–5–ene gave the corresponding diol with 74% e.e. The mechanism of this reaction is still being investigated as it is not clear whether the new oxidation system does not oxidise **163** to **164** or if a different catalytic cycle is present.

Sharpless' most recent work has led to the best improvement yet in the reaction. The formation of the quinine and quinidine dimers **167** and **168** with a phthalazine bridge has led to e.e.s of greater than 99%.[68] Also the addition of methanesulphonamide in the dihydroxylation of nonterminal alkenes has led to an improvement in the rate of reaction. The

methanesulphonamide enhances the rate of osmate ester hydrolysis which is the rate determining step for the dihydroxylation of nonterminal alkenes.



167 $(DHQD)_2$–PHAL

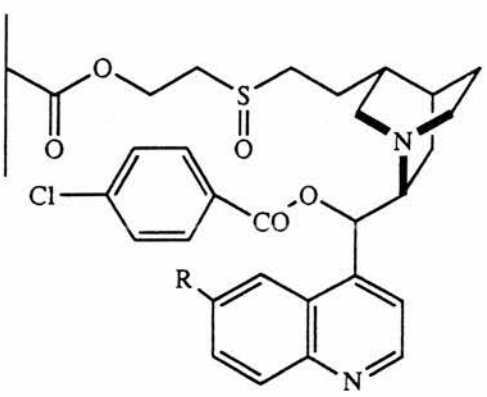


168 $(DHQ)_2$–PHAL

Sharpless has taken a reaction that initially had some limitations and developed it into into an excellent method for the asymmetic dihydroxylation of alkenes. All the different types of alkene can now be hydroxylated with either enantiomer being accessible with good selectivity.

Various polymer bound alkaloids have been found to be useful catalysts for the dihydroxylation reaction. Sharpless has synthesised several alkaloid–acrylonitrile copolymers[69] with and without spacer groups. The direct acrylonitrile–alkaloid copolymer, with no spacer group, was found to catalyse the reaction slowly and gave low selectivities. This was due to the alkaloid being too close to the polymer backbone. Using the polymers that have spacer

corresponding diol with 93% e.e.[69] Potassium ferricyanide was found to improve the selectivity of the reaction, and the polymers could be reused with no loss of activity.



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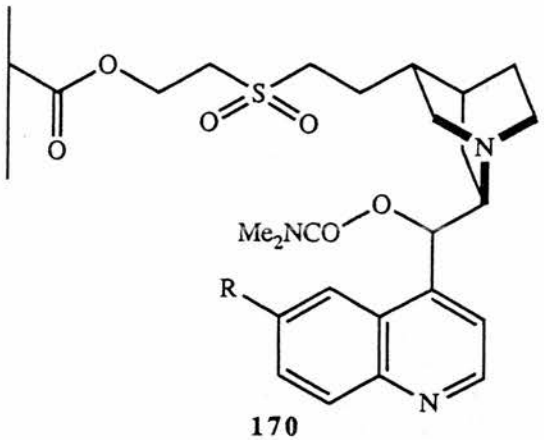

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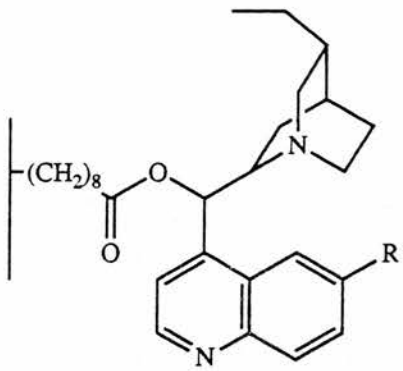
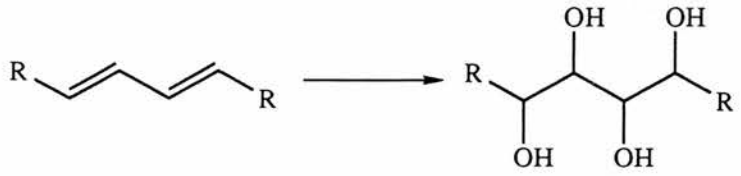


171

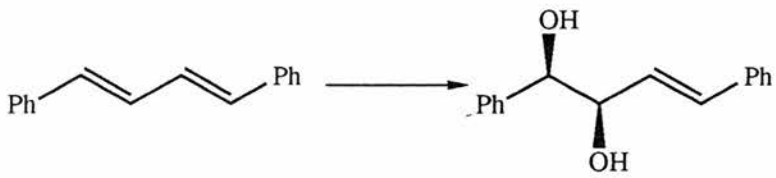
(b) Dihydroxylation of Dienes

Dihydroxylation of dienes under the original conditions gave the tetrols **172.**[70] Very little selectivity was observed either chemoselectivity, between the double bonds, or stereoselectivity, between the enantiomers.



172

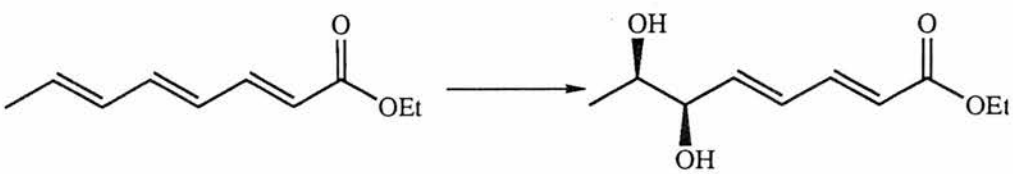
However when the reaction was repeated under the new conditions with $K_3Fe(CN)_6$ and using $(DHQD)_2$–Phal **167** as the catalyst both chemo– and stereoselectivity were observed. The dihydroxylation of 1,4–diphenylbutadiene gave the corresponding diol **173** with 99% e.e.[71]



173 84%, 99% e.e.

Several dienes were hydroxylated under these conditions and the following points noted. Tetrols, if formed, were only formed in trace amounts. In unsymmetrical conjugated dienes dihydroxylation occurred preferentially at the more electron rich double bond. *E* double bonds were dihydroxylated in preference to *Z* and trisubstituted double bonds were dihydroxylated in preference to terminal double bonds.

A conjugated triene **174** has also been dihydroxylated. This gave the corresponding diol **175** with 95% e.e.[71]

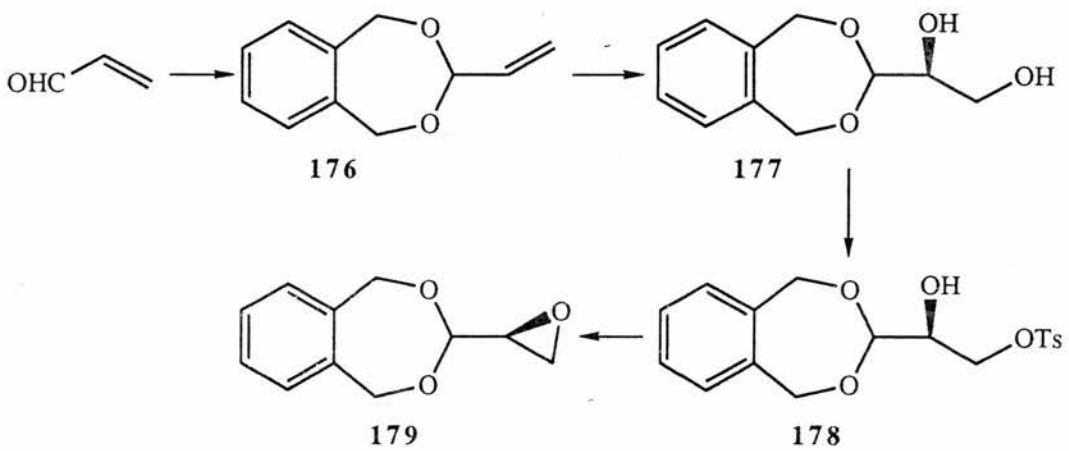


174 **175** 93%, 95% e.e.

(c) Asymmetric Dihydroxylation of Acrolein

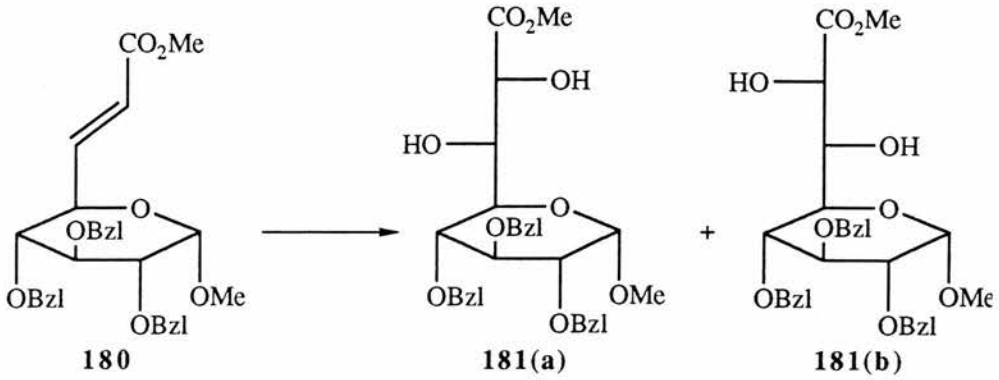
Enantiomerically pure derivatives of glyceraldehyde are important building blocks for the synthesis of a variety of biologically active molecules. The synthesis of stable and easily handled derivatives is an important goal in organic chemistry.

Sharpless has used his dihydroxylation reaction to hydroxylate **176** to produce the chiral glyceraldehyde equivalent **177** with 97% e.e.[72] after recrystallisation. This can be converted into another glyceraldehyde equivalent **179** with 97% e.e. in a few simple steps.

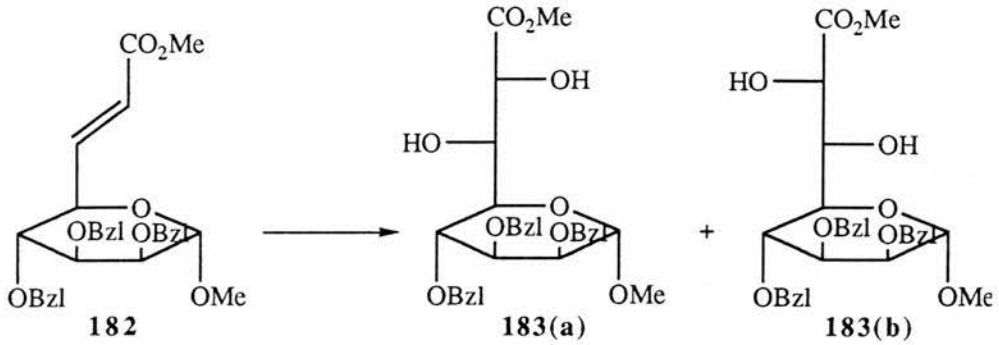


(d) Dihydroxylation in Carbohydrate Synthesis

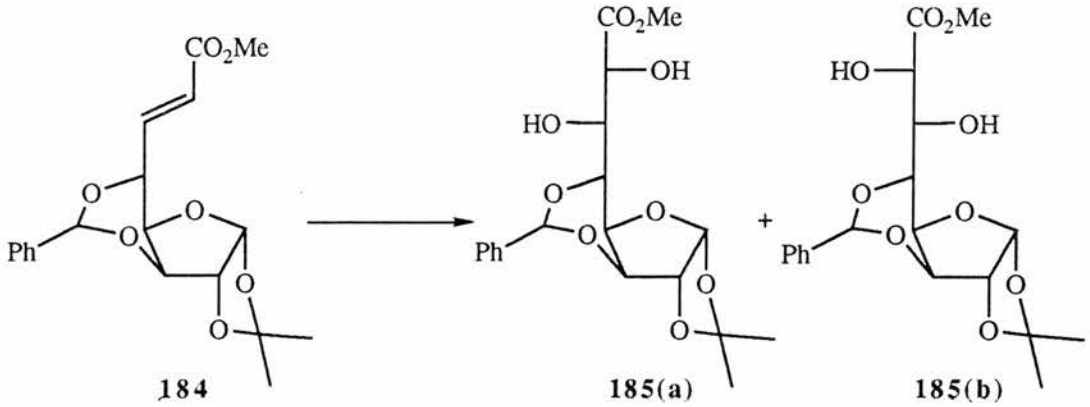
Brimacombe and McDonald[73] have used the Sharpless dihydroxylation to great effect in the synthesis of sugar molecules **181**, **183** and **185**. In each of the reactions that they tried an improvement in the d.e. was achieved when the alkaloid catalysed reaction was used. The reaction was carried out under Sharpless' original reaction conditions and so further improvements in the selectivity should be possible.



OsO_4 only 10.3:1
OsO_4 H_2QD 1.34:1
OsO_4 H_2QN 20.5:1



OsO_4 only 7.4:1
H_2QD 3.45:1
H_2QN 15.9:1

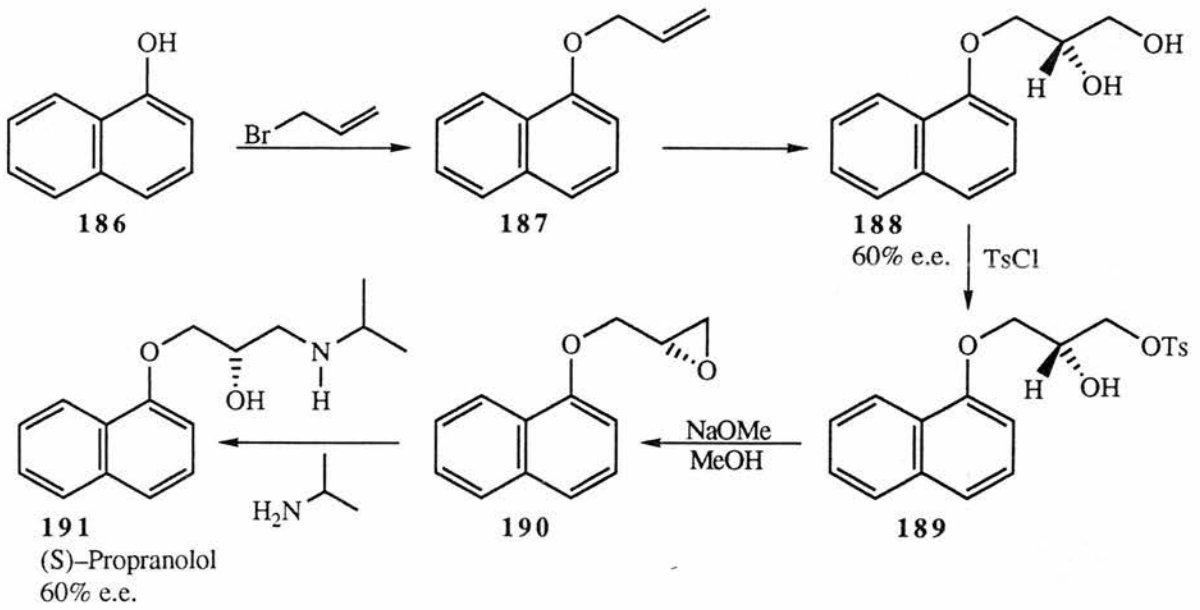


OsO_4 only 1:2.15
H_2QD 1:5.3
H_2QN 1:1.6

(e) Synthesis of Optically Active β–Blockers

Compounds like **191** have been used, in their racemic form, as β–blockers for a number of years. With increasing concern about the safety of

racemic drugs, and the possibilty of new legislation banning their use, an asymmetric synthesis of such molecules is needed.

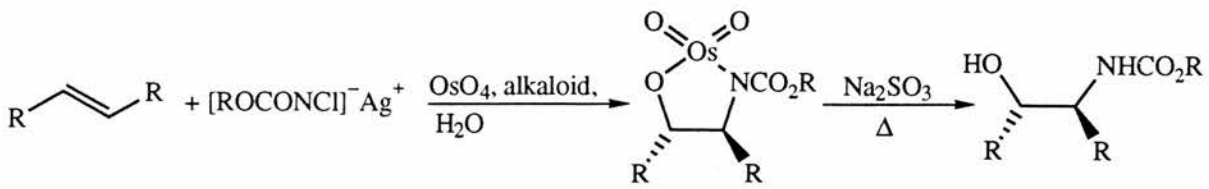


Rao[74] has developed such a synthesis using the Sharpless dihydroxylation reaction. The allyl ether **187** was dihydroxylated using the improved Sharpless reaction conditions with potassium ferricyanide to give the diol **188** with 60% e.e. Making the epoxide **190** and then ring opening it with an amine gave the *β*–blocker **191**.

4. Hydroxyamination

The reaction of osmium tertroxide in the presence of **192** with an alkene produces vicinal hydroxcarbamates **194**. Hassine[75] realised that the alkaloids could be used, in a similar way as in the dihydroxylation reaction, to produce an asymmetric hydroxyamination. Carrying out the reaction on *Z*–stilbene using dihydroquinine produced the corresponding hydroxyamine **194** with 100% e.e. The hydroxyamination of unsymmetrical alkenes produced

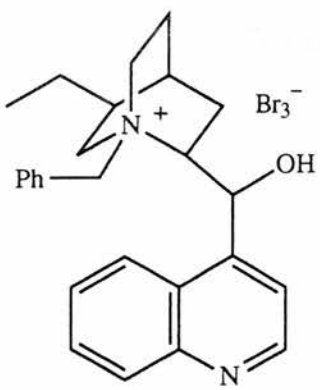
aminoalcohols with low selectivities because of the possibility of diastereomers.



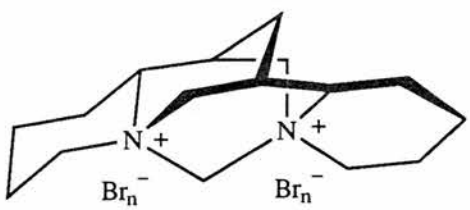
192 **193** **194**

5. Halogenation of Alkenes

In an attempt to produce chiral vicinal dibromo compounds Belluci[76] has used brominated alkaloids, such as **195** and **196**, as brominating agents. The cinchona alkaloid derivatives **195** brominated cyclohexene to give optically active 1,2–dibromocyclohexane. The 1,2–dibromocyclohexane had optical rotations of up to –8.4°, however no e.e.s were determined.



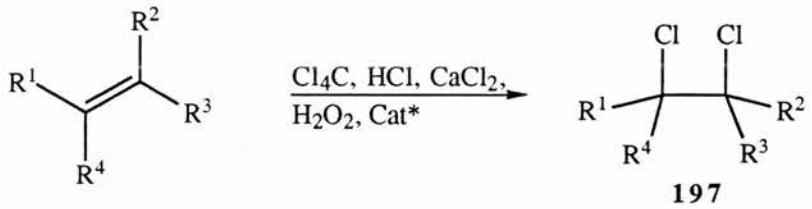
195



196
n=1–3

The sparteine derived reagents **196** brominated cyclohexene to give 1,2–dibromocyclohexanes with rotations of up to +16°. Again no e.e.s were determined.

Julia[77] has used a phase transfer chlorination reaction to produce optically active dichloro compounds **197**. Using *N*–benzyl–*N*–dodecylephedrinium bromide and *N*–benzylcinchonium chlorides as the phase transfer catalysts gave optically active dichloro compound with rotations of up to +0.48°. The e.e.s of the products were not determined.

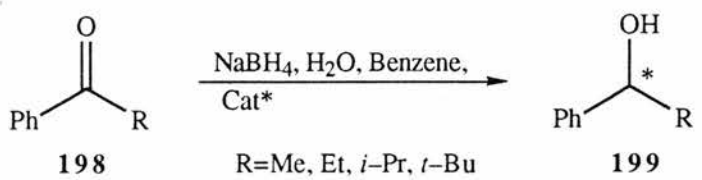


197

D. Reductions

1. Borohydride Reductions

The reaction of sodium borohydride with ketones to produce secondary alcohols may be carried out under phase transfer conditions. A number of the alkaloid ammonium salts have been used in this context. It was found by Colcunnia[78] that hindered ketones **198** could produce optically active alcohols. Unhindered ketones, such as octanone, gave no optical activity. Using the *N*–alkylephedrinium bromides as the catalyst gave e.e.s of up to 14% in the reduction of phenyl *t*–butyl ketone.



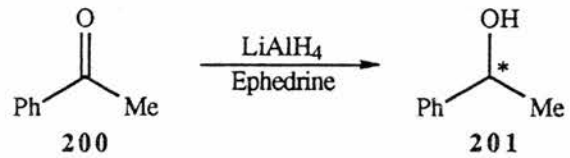
198 R=Me, Et, *i*–Pr, *t*–Bu **199**

The best catalyst was found to be *N*–benzyldihydroquininium chloride. Reacting phenyl *t*–butyl ketone with sodium borohydride in the presence of this catalyst gave the corresponding alcohol with 32% e.e.

2. Lithium Aluminium Hydride Reductions

Lithium aluminium hydride may also be modified with chiral reagents to produce chiral secondary alcohols.

Adding *N*–methylephedrine to lithium alumium hydride produces a reagent useful in the asymmetric reduction of ketones and α,β–unsaturated ketones. The reduction of acetophenone **200** using this reagent afforded the corresponding alcohol **201** with 84% e.e.[79] The reduction of α,β–unsaturated ketones gave optical yields of up to 98% e.e.

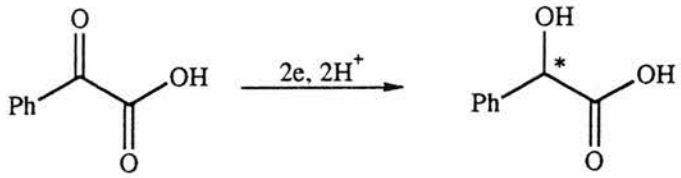


200 **201**

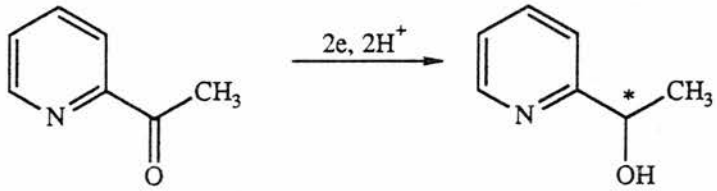
3. Electrochemical Reduction

Various double bonds may be reduced by electrochemical means. It has also been found that it is possible to absorb molecules on to the electrode surface which may affect the electochemical reduction. One such method involves the absorption of alkaloids on to a mercury electrode[80] to produce an asymmetric reduction. This procedure has been used to reduce ketones, cyano, alkene, and also halogenated compounds. The alkaloids that have been used are cinchona, ephedrine, yohimibine, strychnine, brucine, narcotine, emetine, sparteine, and morphine.

The electrochemical reduction of ketones by an ephedrine–mercury electrode gave low e.e.s. The electrochemical reduction of acetophenone in the presence of *N,N*–dimethylephedrinium bromide gave 1–phenylethanol with 16% e.e.[80] Similar reduction of **202** in the presence of strychnine gave (–)–(R)–**203** with 19% e.e., brucine gave (–)–(R)–**203** with 11% e.e.[80] None of the other alkaloids gave any significant selectivity. The reduction of 2–acetylpyridine **204** gave (+)–(S)–**205** with 48% e.e. when strychnine was used and (+)–(S)–**205** with 27% e.e. when brucine was used.[80]

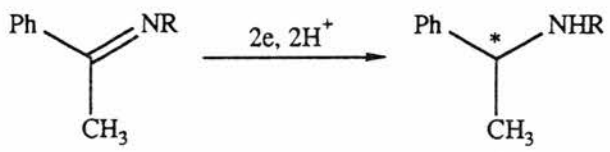


202 **203**



204 **205**

The reduction of **206** in the presence of (1R,2S)–*N*–methylephedrine gave the (S) amine **207** with 8% e.e.[80]



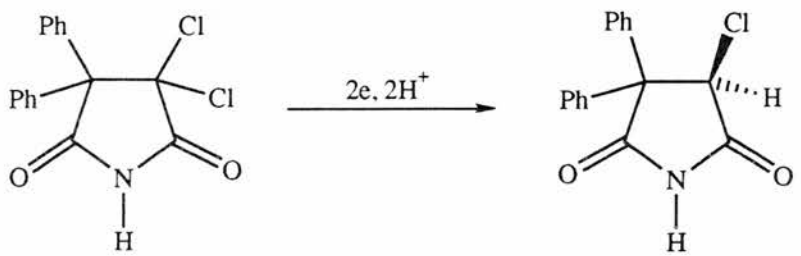
206 **207**

The electrochemical reduction of 4–methylcoumarin in the presence of sparteine gave (R)–4–methyldihydrocoumarin with 17% e.e. The other

The electrochemical reduction of 4–methylcoumarin in the presence of sparteine gave (R)–4–methyldihydrocoumarin with 17% e.e. The other alkaloids gave selectivities of up to 12% e.e. apart from brucine which showed no selectivity. Narcotine gave (S)–4–methyldihydrocoumarin with 15% e.e.[80]

The electrochemical reduction of 1,1–dibromo–2,2–diphenylcyclopropane in the presence of emetine gave (R)–1–bromo–2,2–diphenylcyclopropane with up to 42% e.e. The alkaloids strychnine and brucine also showed selectivites giving the (R) isomer with up to 32% e.e.[80]

The electrochemical reduction of **208** has been carried out in the presence of emetine, yohimbine and strychnine. All these alkaloids showed selectivity, strychnine giving (–)–**209** with 26% e.e.[81] which was the best result.



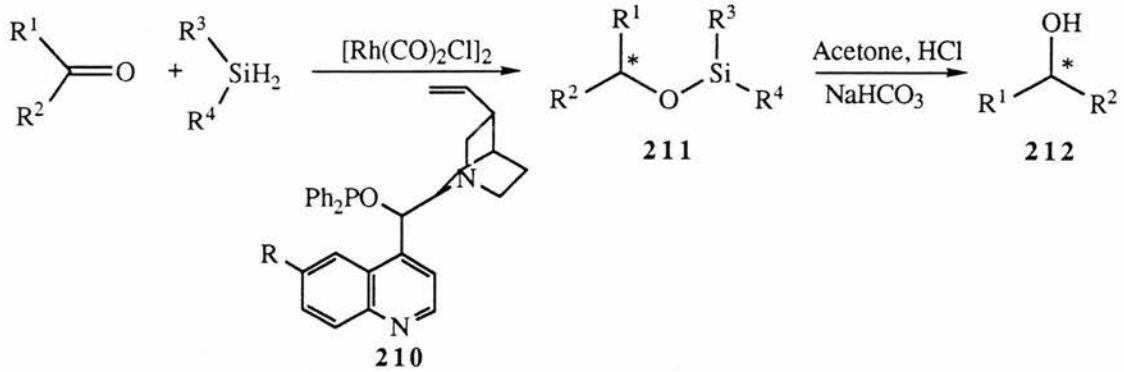
208 **209**

The selectivities of the electrochemical reductions were found to vary with pH, potential difference, temperature and solvent, and the optimum conditions were different for each reaction.

4. Hydrosilylation

Buono[82] has developed an asymmetric hydrosilylation reaction using rhodium catalysis. By making the phosphinite ester of the cinchona alkaloids **210**, he was able to produce chiral bidentate ligands for the rhodium catalyst.

Using this ligand–catalyst combination both aryl and alkyl ketones were reacted to produce optically active alcohols **212** with up to 58% e.e. This is the first report of a cinchona–phosphorus ligand and work is being carried out to see what other reactions it is useful in.

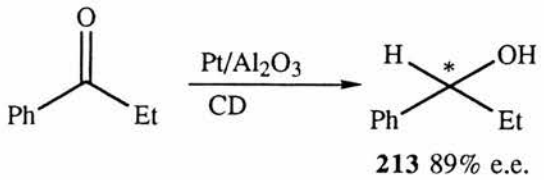


5. Hydrogenation

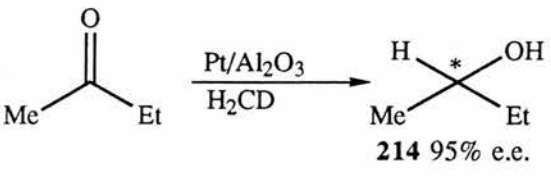
Hydrogenation is a very useful way of carrying out functional group interconversion and a wide range of double bonds can be hydrogenated. An asymmetric hydrogenation reaction is then a good way of introducing asymmetry into a molecule. Hydrogenation reactions are usually carried out using heterogeneous metal catalysts. The metals in such catalysts may be modified by adding chiral ligands such as the alkaloids. This produces an asymmetric hydrogenation catalyst.[83]

(a) Hydrogenation of Carbonyl Compounds

The hydrogenation of carbonyl compounds has proved to be the most successful of the alkaloid catalysed hydrogenation reactions perhaps because it has been the most widely studied.

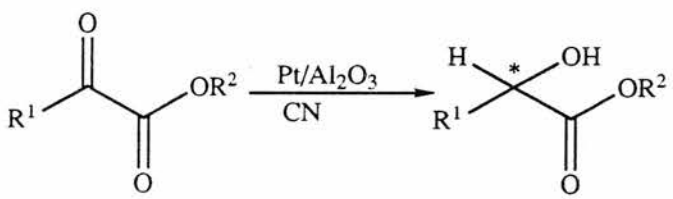


213 89% e.e.



214 95% e.e.

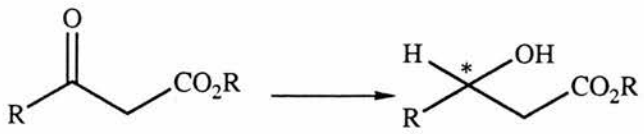
The catalyst system used is platinum on alumina to which the cinchona alkaloids have been added. The hydrogenation of simple ketones such as butan–2–one produced **214** with selectivities of up to 95% e.e. The α–ketoesters have also been hydrogenated using the platinum–alkaloid catalyst to give **215** with up to 90% e.e.[83]



215

It has been found that, as well as all the solvent effects, the effect of catalyst structure plays an important role. Small changes in the alumina, platinum or alkaloid can have a dramatic effect on the selectivity of the reaction.

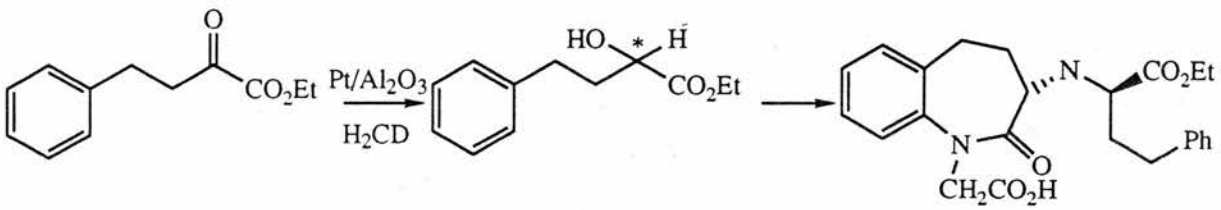
The hydrogenation of β–keto esters was not as successful producing **216** with low selectivities of 5% e.e.[83] Better catalysts have been developed for this reaction.



216

(b) Synthesis of Benazerpil

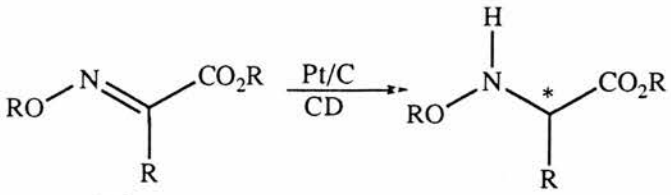
The hydrogenation of α–ketoesters has been used in the synthesis of benazerpil **219** which is an angiotensin–converting enzyme inhibitor. The α–ketoester **217** was hydrogenated to produce **218** with 80–85% e.e. This was then converted, after several steps, into benazerpil **219**.[83]



217 **218** 80–85% e.e. **219** Benazerpil

(c) Hydrogenation of CN

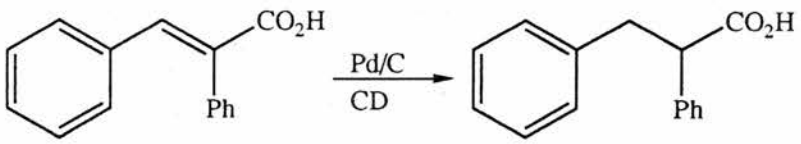
A platinum on charcoal catalyst modified by the cinchona alkaloids has been used to hydrogenate **220** to produce **221** with 15% e.e. A palladium on charcoal catalyst modified with cinchonidine has also been used to produce **221** with 10% e.e.[83] Although these selectivities are low, there is no good asymmetric catalyst for this reaction so these results are significant.



220 **221**

(d) Hydrogenation of Alkenes

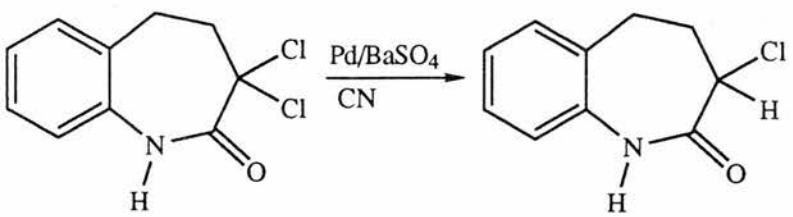
A palladium on charcoal catalyst modified by the cinchona alkaloids has been used to hydrogenate alkenes. In the presence of such a catalyst the hydrogenation of **222** produced **223** with 30% e.e.[83] However better catalysts have been developed for this reaction.



222 **223** 30% e.e.

(e) Hydrogenation of CCl

A palladium on barium sulphate catalyst modified with cinchonine has been used to reduce the carbon–chlorine bond. The hydrogenation of **224** using this catalyst produced **225** with 50% e.e. A platinum–barium sulphate catalyst has also been used to give the same product with 25% e.e.[83]



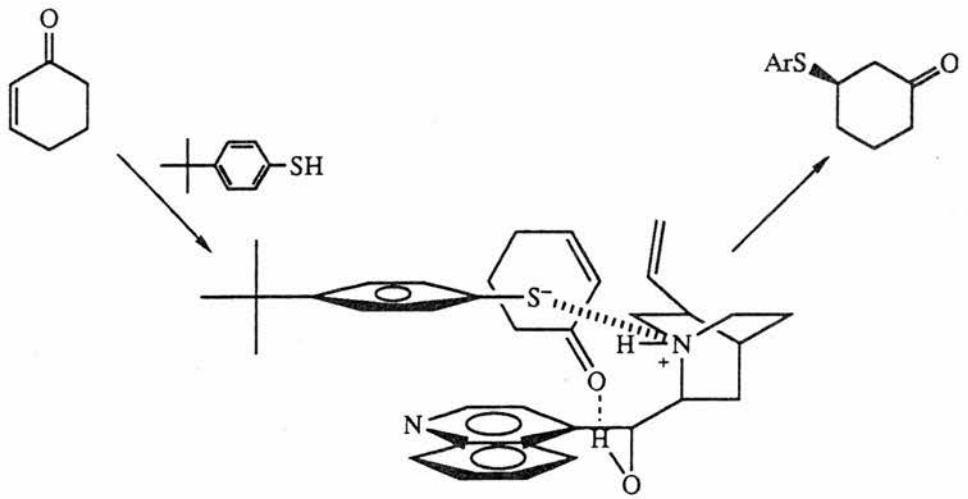
224 **225** 50% e.e.

E. Thiol Addition Reaction

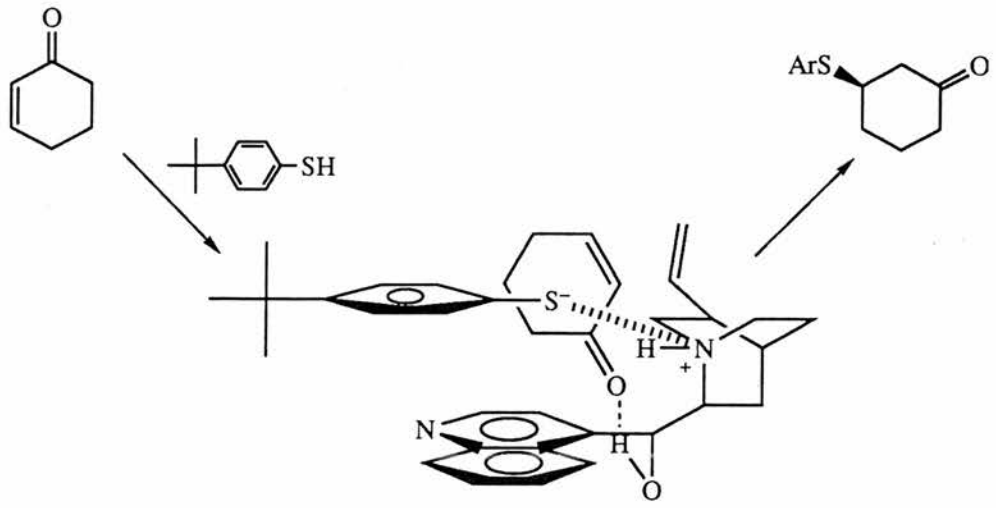
1. Simple Addition to Enones

Thiophenols may be added to electron poor alkenes such as α,β–unsaturated ketones to produce β–thiosubstituted ketones. This reaction may be catalysed by the cinchona alkaloids to produce optically active products. The reaction has been carried out using several thiophenols and several α,β–unsaturated ketones to give optical yields of up to 80%.

Wynberg[84] has proposed a mechanism for the reaction with the formation of transition state **226**. Quinine's low energy conformation is as shown in the transition state. A tight ion pair forms between the thiophenol and the quinuclidine nitrogen. The cyclohexenone is hydrogen bonded to the hydroxyl hydrogen. The other transition state which can form is the one where cyclohexenone lies the opposite way, but this leads to an unfavoured interaction between the C5 and C6 of the cyclohexenone and the quinuclidine portion of the alkaloid. Increasing the bulk at C5 and C6 of the cyclohexenone led to the highest selectivity.



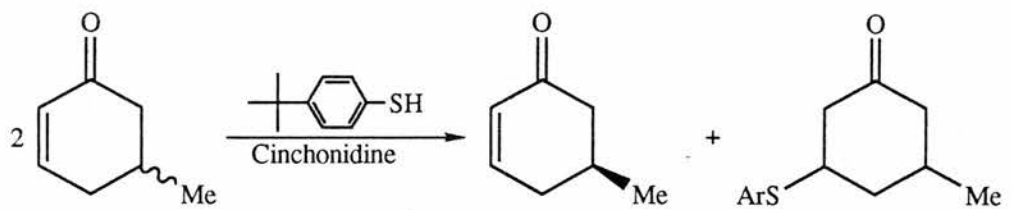
226



226

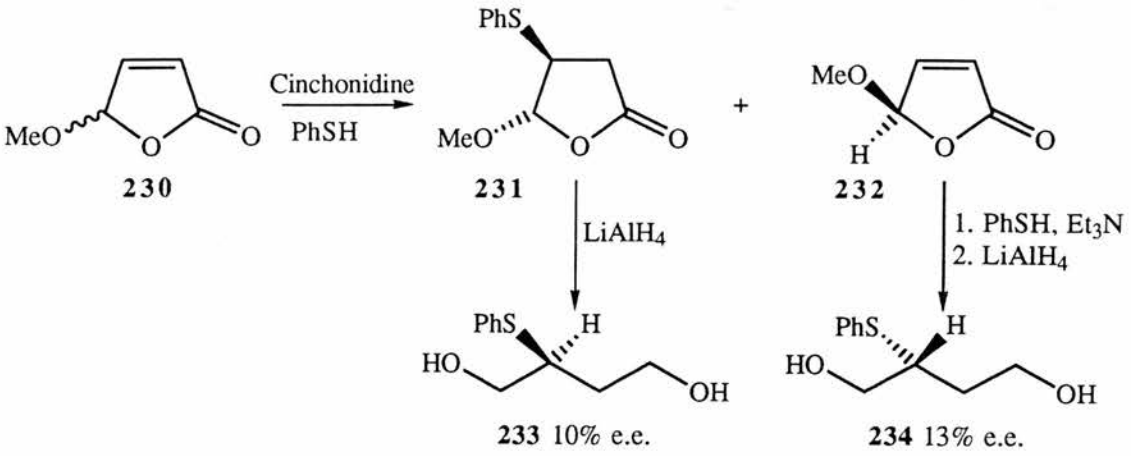
2. Kinetic Resolution

The thiophenol addition reaction can be used to resolve racemic α,β–unsaturated ketones. Thus if racemic 5–methylcyclohexenone **227** is reacted with *p*–(*t*–butyl)thiophenol, (S)–5–methylcyclohexenone **228** can be recovered from the reaction mixture with 59% e.e.[2]



227 **228** 59% e.e. (S) **229**

The products of the resolution reactions can then be used to synthesise other compounds. For example the diols **233** and **234** produced from the kinetic resolution of **230** can be converted into optically active 3,4–epoxybutanol.[85]

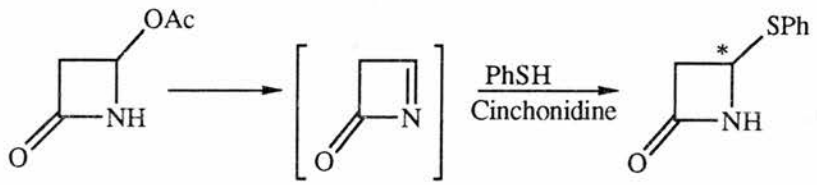


230 **231** **232**

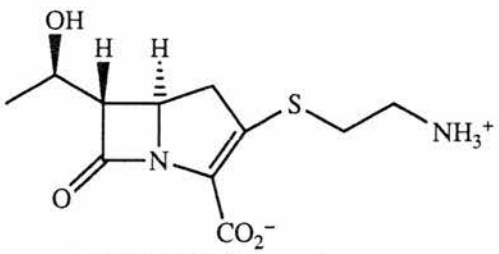
233 10% e.e. **234** 13% e.e.

3. Thiol Addition in Synthesis

Ikegami[86] has reacted 4–acetoxyazetidin–2–one **235** with thiophenol in the presence of cinchonidine to produce **237** with 55% e.e. This was then converted in 20 steps to (+)–thienamycin **238.**



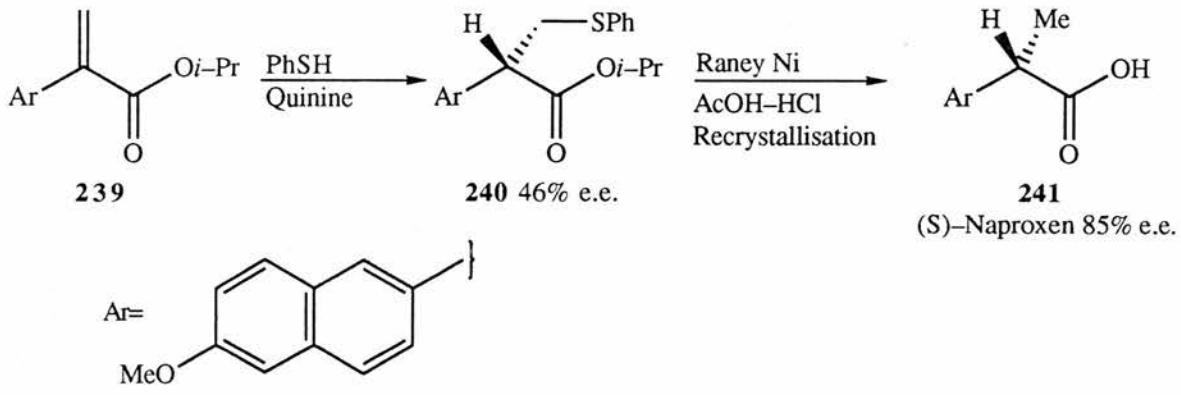
235 **236** **237** 55% e.e.



238 (+)–Thienamycin

Kumar[87] has used the thiol addition reaction to synthesise (S)–naproxen **241** which is an antiinflammatory agent. Reacting **239** with thiophenol in the presence of quinine produced **240** with 46% e.e. Removal of the thiophenol

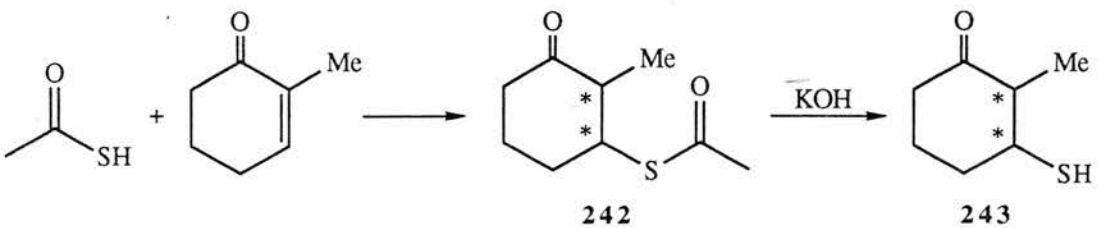
followed by acid–hydrolysis gave (S)–naproxen **241** with 72% overall yield and 45% e.e. After one recrystallisation the e.e. was improved to 85%.



239 **240** 46% e.e. **241** (S)–Naproxen 85% e.e.

4. Addition of Thiolacetic Acid

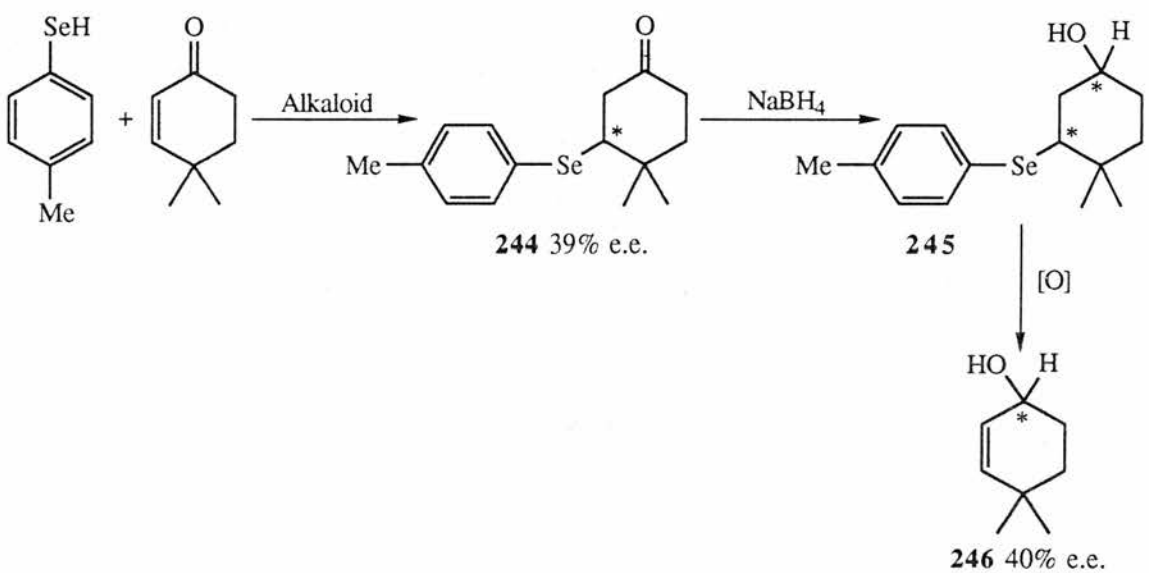
The thiol addition reaction does not lend itself to the preparation of thiols. Although thiolacetic acid additions are free radical reactions, it has been found that their addition to electron poor alkenes can be catalysed by a base. A possible route to the asymmetric synthesis of thiols would be the addition of thioacetic acid and then hydroloysis to give the thiol. The addition of thiolacetic acid to cyclohexenone in the presence of cinchonine gave **242** with 54% e.e.[88] Reaction of **242** with potassium hydroxide then gave the thiol **243**.



242 **243**

F. Selenophenol Addition

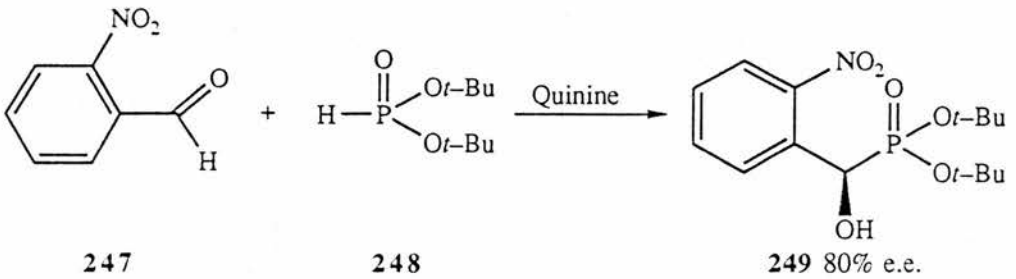
Under the same reaction conditions as those for thiophenol addition, selenophenols can also add to α,β–unsaturated ketones to give optically active selenides. The optical yields for the reaction are lower than those for thiophenol with e.e.s of up to 67%.[2] However the reaction is still a useful one and has been used to synthesise optically active α,β–unsaturated alcohols. The selenide **244** was first synthesised with 39% e.e. Reduction with sodium borohydride then gave the alcohol **245** and oxidation removed the selenium to give **246** with 40% e.e.[2]



G. Addition of Phosphorus

Phosphite esters can undergo a base catalysed addition to aldehydes. Wynberg[2] observed that quinine could catalyse the reaction 20 times more effectively than triethylamine and also produce optically active products.

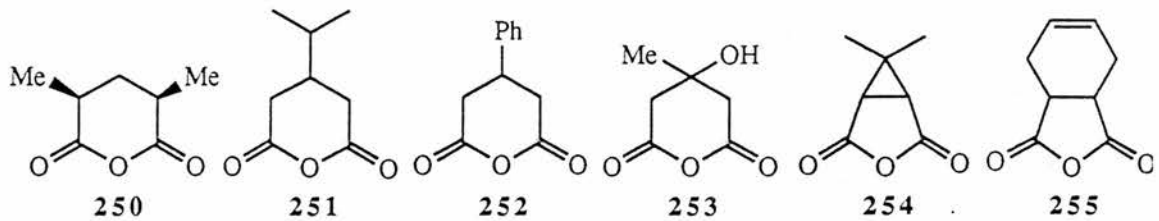
Reacting *o*–nitrobenzaldehyde **247** with phosphite ester **248** produced optically active phosphorus compounds **249** with up to 80% e.e.



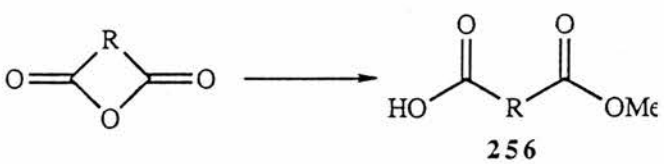
247 **248** **249** 80% e.e.

H. Asymmetric Ring Opening of Anhydrides

Oda[89] was the first to report the asymmetric ring opening of anhydrides. The anhydrides **250–255** were opened in the presence of methanol and alkaloid to give the corresponding ring opened half ester **256**. Using ephedrine as the catalyst gave only low ees of 9%. Using the cinchona alkaloids gave the half esters with up to 70% e.e.



250 **251** **252** **253** **254** **255**

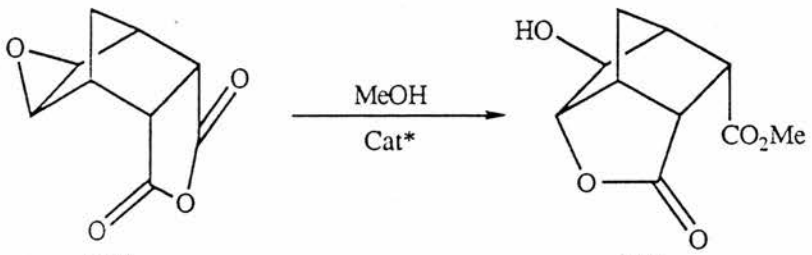


256

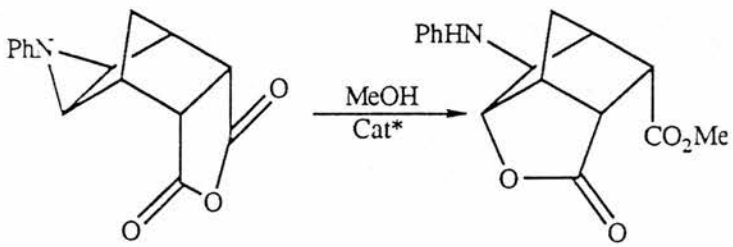
The selectivity of the reaction was found to be dependent on the solvent used, less polar solvents such as diethyl ether and toluene giving better results.

Also the concentration of reactants had an effect and by increasing the reaction concentration a better result was obtained.

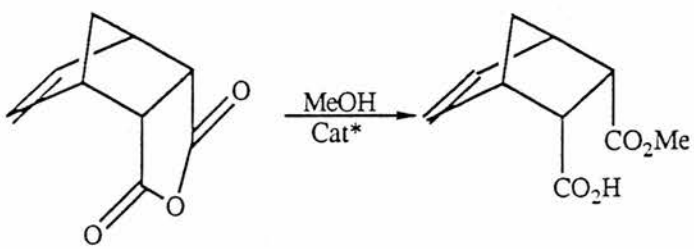
Our research group has carried out the same reaction on the bi– and tri–cyclic anhydrides to obtain the corresponding monoester or lactone in up to 90% e.e.[90,91] and quinine and quinidine were found to be the most effective catalysts.



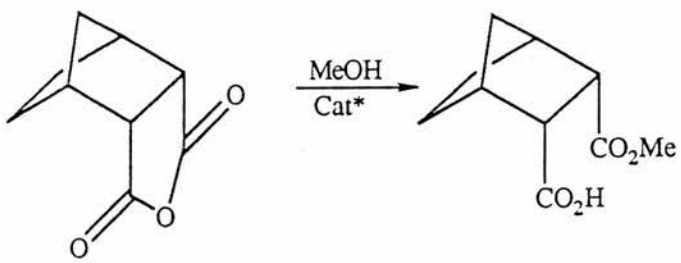
257 258



259 260



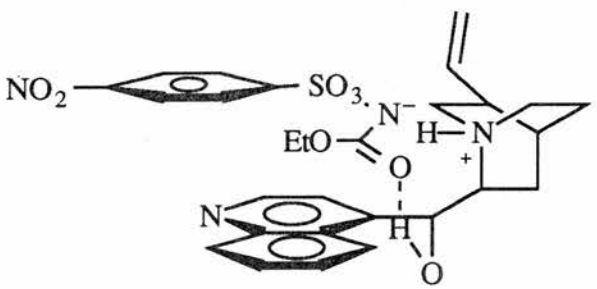
261 262



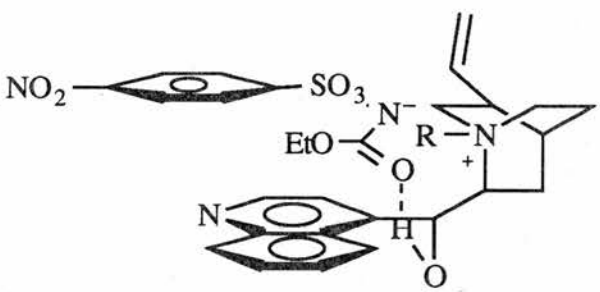
263 264

Programme of Research

As described earlier in the Introduction, the cinchona alkaloids have proved to be the most useful group of alkaloids for asymmetric synthesis. In many of the successful reactions they have been used to mediate base catalysed processes either in a homogeneous system or under phase transfer conditions. It therefore seemed worthwhile to examine the use of these alkaloids as bases for the generation of nitrenes by α–elimination and their subsequent addition to alkenes to form aziridines. Both the free bases in stoichiometric amount and the derived quaternary ammonium salts in the presence of e.g. Na_2CO_3 in a phase transfer system where they are only required as catalysts were worth investigating. The desired enantioselectivity relies on the formation of a complex **265** or **266** in which the incipient nitrene is held in the asymmetric environment of the alkaloid. For effective enantioselectivity this complex must be tightly bound together. The incipient nitrene can be bound to the alkaloid by π–π interaction between the aromatic rings present as well as the formation of the ion pair. If an aromatic ring is present in the alkene then it could be bound by π-π interaction.



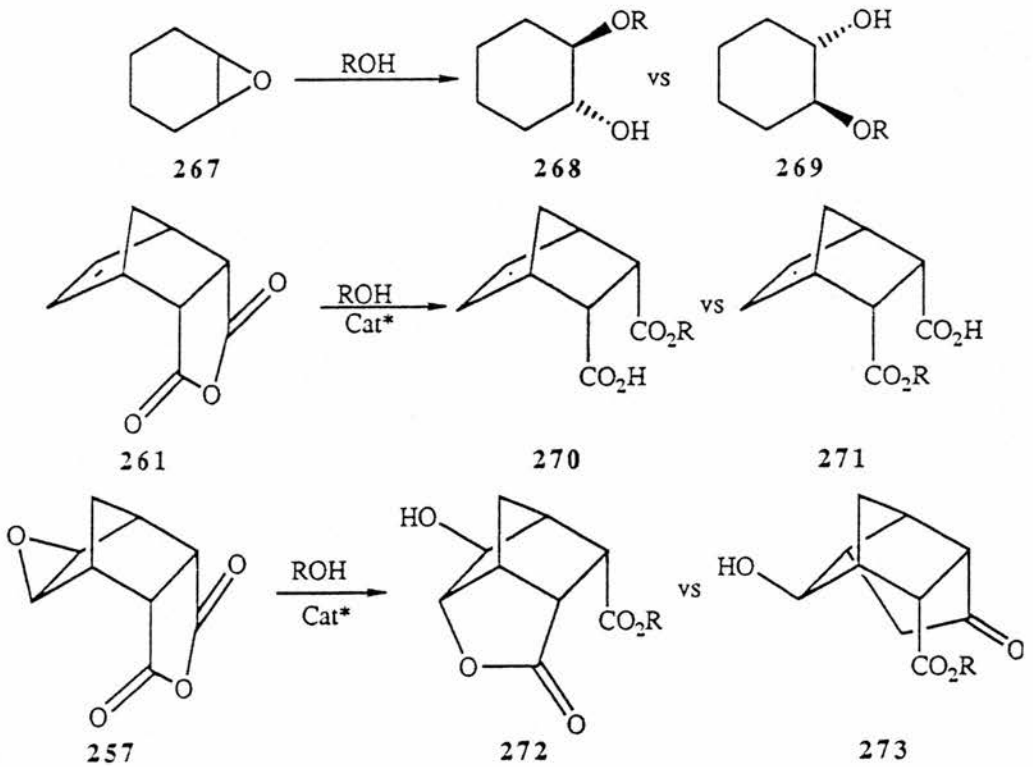
265



266

A second area of study involves the enantioselective reaction of achiral meso compounds. The opening of epoxides such as **267** with nucleophiles such

as water, alcohols and carboxylic acids can be catalysed by alumina, and the use of cinchona alkaloids for this reaction is of some interest. Both for this reaction and the opening of anhydrides such as **261** and **257** the use of morphine alkaloids as catalysts was to be examined. For the latter cases, the cinchona alkaloids had already proved to be efficient catalysts but the use of morphine alkaloids in this application has not been examined before, and promised to be of considerable interest.



EXPERIMENTAL

A Symbols and Abbreviations

mmol	millimoles
M	mol dm^{-3}
h,min	hours, minutes
NMR	nuclear magnetic resonance
δ	chemical shift in ppm
J	spin–spin coupling constant in Hz
s,d,t,q,m	singlet, doublet, triplet, quartet, multiplet
m/z	mass to charge ratio
ν_{max}	infrared absorbtion frequency in cm^{-1}
m.p.	melting point
b.p.	boiling point
CLSR	chiral lanthanide NMR shift reagent
e.e.	enantiomeric excess
d.e.	diastereomeric excess
PTC	phase transfer catalysis
petrol	petroleum ether 40/60

B Instrumentation and General Techniques

1. NMR Spectroscopy

(a) ^{1}H NMR

Routine spectra were obtained at 60MHz on a Varian EM–360 spectrometer and at 200MHz on a Varian Gemini 200. High resolution, and CLSR spectra were obtained at 300MHz on a Bruker AM–300 spectrometer operated by Mrs M. Smith and by the author.

(b) ^{13}C NMR

Routine spectra were obtained at 50MHz on a Varian Gemini 200 and high resolution spectra were obtained at 75MHz on a Bruker AM–300 spectrometer operated by Mrs M. Smith and the author.

All spectra were obtained from solutions in deuteriochloroform, except when stated otherwise, and chemical shifts are expressed in parts per million to high frequency of tetramethylsilane.

2. Infrared Spectroscopy

Spectra were obtained on a Perkin–Elmer 1420 ratio recording spectrophotometer. Solids were run as nujol mulls and liquids as thin films using matched sodium chloride cells. Spectra were calibrated with the polystyrene peak at 1603cm^{-1}.

3. Mass Spectrometry

Mass spectra were obtained on a Finnigan Incos 50 mass spectrometer and high resolution measurements were obtained on an AEI MS50 instrument, both operated by Mr C. Millar.

4. Elemental Analysis

Microanalyses for carbon, hydrogen, and nitrogen were carried out on a Carlo–Erba 1106 elemental analyser operated by Mrs S. Smith.

5. Melting Points

Routine melting points were determined using an Electrothermal melting point apparatus while melting points of new compounds were determined on a Reichert hot–stage microscope. All melting points are uncorrected.

6. Thin Layer Chromatography

This was carried out using 0.2mm layers of silica (Merck, Kieselgel $60F_{254}$) on aluminium sheets. The components were observed under ultraviolet light.

7. Column Chromatography

This was carried out using Fisons silica gel for chromatography (60–120 mesh).

8. Drying and Evaporation of Organic Solutions

Organic solutions were dried by standing over anhydrous magnesium sulphate and were evaporated under reduced pressure on a Büchi rotary evaporator.

9. Drying and Purification of Solvents

Commercially avaliable solvents were used without further purification unless otherwise indicated. Dry ether and dry toluene were prepared by the addition of sodium wire. Petrol refers to light petroleum, the redistilled 40–60°C boiling fraction being used for chromatography.

10. Optical Rotation

Optical rotation measurements were performed with an Optical Activity AA–1000 polarimeter operating at 589nm using a 5ml solution cell with a 10cm path length or a 1ml solution cell with a 20cm path length.

11. Chiral Lanthanide NMR Shift Reagents

The experiments were carried out at both 200 and 300MHz on standard NMR samples using tris[3–(heptafluoropropylhydroxymethylene)–(+)–camphorato]europium (III).

The enantiomerically enriched samples were run after the racemic analogues had been used to optimise the experimental conditions in each case.

C. Preparation of Carbamates

1. Preparation of ethyl *N*–hydroxycarbamate

A mixture of hydroxylamine hydrochloride (20.52 g, 0.30 mol), potassium carbonate (38 g, 0.275 mol), ether (150 ml), and water (2 ml) was cooled on ice. Ethyl chloroformate (27 ml, 0.28 mol), was added slowly. The reaction was warmed to room temperature and left to stir for 18h. The potassium chloride was removed by filtration. The filtrate was evaporated leaving an oil which was purified by Kugelrohr distillation to give ethyl *N*–hydroxycarbamate (24.47 g, 82%) as a colourless oil b.p. 105 °C, 1.5 mm Hg (lit.[92],113–116 °C, 3 mm Hg).

2. Preparation of benzyl *N*–hydroxycarbamate

A mixture of hydroxylamine hydrochloride (5.6 g, 81.2 mmol), sodium carbonate (12.5 g, 43.7 mmol), and water (37 ml) was stirred together while benzyl chloroformate (13.4 g, 78.4 mmol) was added slowly. The mixture was stirred for 18h, acidified, and the liberated oil extracted with ether. The solvent was evaporated and the remaining solid recrystallised from toluene to give benzyl *N*–hydroxycarbamate (11.81 g, 87%) as a colourless crystalline solid, m.p. 67–9 °C (lit.,[93] 65 °C).

D. Preparation of Nitrene Precursors

1. Preparation of ethyl *N*–*p*–nitrobenzenesulphonoxycarbamate **282**

To an ice cooled solution of ethyl *N*–hydroxycarbamate (15.17 g, 0.14 mol) in dry ether (200 ml) was added slowly *p*–nitrobenzenesulphonyl chloride (30.67 g, 0.14 mol). A solution of triethylamine (18.6 ml, 0.14 mol) in dry ether (20 ml) was added slowly and the mixture left to stir for 18h. The solution was filtered and evaporated leaving a yellow solid which was

recrystallised from toluene to give ethyl *N – p –* nitrobenzenesulphonoxycarbamate **282** (17.50 g, 44%) as pale yellow crystals m.p. 114–6 °C (lit.,[94] 116.4–116.8 °C).δ_H(60 MHz, $CDCl_3$) 1.15 (3H, t, J 7 Hz, CH_3), 4.15 (2H, q, J 7 Hz CH_2), 8.3 (5H, m, Ar, NH).

2. Preparation of benzyl *N–p–*nitrobenzenesulphonoxycarbamate **335**

A solution of benzyl *N*–hydroxycarbamate (10.84 g, 64.9 mmol) in dry ether (100 ml) was cooled in ice while *p*–nitrobenzenesulphonyl chloride (14.3 g, 64.4 mmol) was added slowly. A solution of triethylamine (9 ml, 64.9 mmol) in dry ether (10 ml) was added slowly and the mixture left to stir overnight. The precipitate which formed during the reaction was filtered off and the filtrate evaporated leaving a yellow solid which was recrystallised from toluene to give benzyl *N–p–*nitrobenzenesulphonoxycarbamate **335** (11.0 g, 48%) as a yellow crystalline solid m.p. 98–100 °C (Found: C, 47.3; H, 3.5; N, 7.9. $C_{14}H_{12}N_2O_7S$ requires C, 47.7; H, 3.4; N, 8.0%), ν_{max}(nujol) 3400(NH) and 1710(CO) cm^{-1}; δ_H (200 MHz; $CDCl_3$) 5.0 (2H, s, CH_2), 7.2 (5H, m, Ph), 8.1 and 8.2 (4H, AB pattern, J 10 Hz, Ar), and 8.9 (1H, s, NH).δ_C(50 MHz, $CDCl_3$) 69.3 (CH_2), 124.4 (Ar), 129.0 (2xAr), 129.4 (Ar), 131.2 (Ar), 134.4 (Ar), 139.0 (Ar), 151.4 (Ar), 155.9 (CO); m/z no M+, 186 (24%), 167 (20), 151 (15), 122 (15), 108 (64), 91 (100), 79 (61), 65 (30), 51 (33), 39 (26) and 28 (15).

E. Preparation of Alkaloids

1. Hydrogenation of alkaloids

(a) Hydrogenation of quinine

A mixture of quinine (5.57 g, 17.2 mmol), water (250 ml), conc. hydrochloric acid (5 ml) and palladium chloride (0.34 g, 1.9 mmol), was

stirred together in a hydrogen atmosphere until the required amount of hydrogen (385 ml) had been absorbed. The catalyst was filtered off through celite. Sodium hydroxide (2 M) was added slowly to the filtrate until all the dihydroquinine had precipitated. The precipitate was filtered, washed, dried, and recrystallised from toluene to give dihydroquinine **327** (5.03 g, 90%) as colourless crystals, m.p. 172–3 °C (lit.,[95] 172 °C).

(b) Hydrogenation of quinidine

Dihydroquinidine was prepared from quinidine (5.58 g, 17.2 mmol), water (250 ml), conc. hydrochloric acid (5 ml), palladium chloride (0.3 g, 1.7 mmol), and hydrogen (385 ml) by the same procedure that was used previously, to give dihydroquinidine **328** (4.65 g, 88%) as colourless crystals, m.p. 180–1 °C (lit.,[95] 169 °C).

(c) Hydrogenation of cinchonine

Dihydrocinchonine was prepared from cinchonine (4.51g, 15.3 mmol), water (250 ml), conc. hydrochloric acid (5 ml), palladium chloride (0.3 g, 1.7 mmol), and hydrogen (343 ml) by the same procedure used previously. The crude product was recrystallised from ethanol to give dihydrocinchonine **330** (4.25 g, 94%) as colourless crystals, m.p. 270–1 °C (lit.,[95] 268 °C).

(d) Hydrogenation of cinchonidine

Dihydrocinchonidine was prepared from cinchonidine (5.41 g, 18.4 mmol), water (250 ml), conc. hydrochloric acid (5 ml), palladium chloride (0.36 g, 2.0 mmol), and hydrogen (412 ml) by the same procedure used previously. The crude product was recrystallised from ethanol to give dihydrocinchonidine **329** (5.00 g, 92%) as colourless crystals, m.p. 241–2 °C (lit.,[95] 230 °C)

2. Preparation of free bases

(a) Preparation of sparteine **11** from sparteine sulphate

Sparteine sulphate pentahydrate (5.09 g, 12.1 mmol) was dissolved in sodium hydroxide solution, and the sparteine extracted with ether. The ether was evaporated and the residual oil purified by kugelrohr distillation to give sparteine **11** (2.69 g, 95%) as a colourless oil, b.p. 160 °C, 0.5 mm Hg (lit.,[96] 173 °C, 8 mm Hg).

(b) Preparation of buprenorphine **359** from buprenorphine hydrochloride

Buprenorphine hydrochloride (2.0 g, 4.0 mmol) was dissolved in sodium bicarbonate solution (1eq.), and the liberated buprenorphine extracted with ether. The ether was dried and evaporated to give buprenorphine **359** (1.7 g, 90%) as a colourless solid m.p. 205–6 °C (lit.,[97] 209 °C).

3. Preparation of quaternary ammonium salts

(a) Preparation of *N*–benzyldihydroquininium chloride **336**

A mixture of dihydroquinine (1.53 g, 4.7 mmol), benzyl chloride (1.21 g, 9.6 mmol), and ethanol (75 ml) was heated under reflux for 15hrs. The solvent was evaporated and ether was added to the oil. Scratching caused crystals to form which were collected to give *N*–benzyldihydroquininium chloride **336** (1.50 g, 70%) as pale pink crystals, m.p. 187–8 °C (lit.,[98] 202–3 °C).

(b) Preparation of *N*–methyldihydroquininium iodide **337**

A mixture of dihydroquinine (1.0 g, 3.07 mmol), ethanol, and methyl iodide (0.2 ml, 3.07 mmol) was stirred together at room temperature for 18h. The solvent was evaporated and the residual solid was recrystallised from

toluene to give *N*–methyldihydroquininium iodide **337** (0.98 g, 68%) as pale yellow crystals, m.p. 233–5 °C (lit.,[98] 233–5 °C decomp.).

(c) Preparation of *N*–methyldihydroquinidinium iodide **338**

A mixture of dihydroquinidine (4.16 g, 12.8 mmol), ethanol, and methyl iodide (0.8 ml, 12.8 mmol) was stirred together at room temperature for 18h. The solvent was evaporated and the residual solid was recrystallised from toluene to give *N*–methyl dihydroquinidinium iodide **338** (4.02 g, 72%) as pale yellow crystals m.p. 245–7 °C (lit.,[99] 242–3 °C).

(d) Preparation of *N*–methyldihydrocinchoninium iodide **340**

A mixture of dihydrocinchonine (0.78 g, 2.64 mmol), ethanol, and methyl iodide (0.16 ml, 2.64 mmol) was stirred together at room temperature for 18h. The solvent was evaporated and the residual solid was recrystallised from ethanol to give *N*–methyl dihydrocinchoninium iodide (0.74 g, 67%) as pale yellow crystals m.p. 263–5 °C (lit.,[100] 257 °C).

(e) Preparation of *N*–methyldihydrocinchonidinium iodide **339**

A mixture of dihydrocinchonidine (1.11 g, 3.75 mmol), ethanol, and methyl iodide (0.24 ml, 3.85 mmol) was stirred together at room temperature for 18h. The solvent was evaporated and the residual solid was recrystallised from ethanol to give N–methyldihydrocinchonidinium iodide **339** (1.05 g, 64%) as pale yellow crystals m.p. 236 °C (lit.,[101] 237–8 °C).

(f) Preparation of dihydrocodeine methiodide **343**

A mixture of dihydrocodeine (1 g, 3.32 mmol), ethanol, and methyl iodide (0.3 g, 4.8 mmol) was stirred together at room temperature for 18h until a precipitate formed. The precipitate was filtered off, washed with ether, and dried to give dihydrocodeine methiodide **343** (1.1 g, 75%), m.p. 256–7

°C (lit.,[102] 257°C), $[\alpha]_D$= -76.5° (c=0.2, H_2O); (Found: C, 51.1; H, 5.7; N, 3.1%. $C_{19}H_{26}INO_3$ requires C, 51.5; H, 5.9; N, 3.2).

(g) Attempted preparation of dihydrothebainone methiodide

A mixture of dihydrothebainone (1g, 3.32mmol), methyl iodide (0.3 ml, 4.8 mmol), and methylene chloride (10ml) was stirred together until a precipitate formed. The precipitate was filtered off and washed with ether. The precipitate was found not to be the methiodide salt. Using the product as a base resulted in iodine being evolved.

(h) Attempted preparation of oxycodone methiodide

A mixture of oxycodone (1 g, 3.17 mmol), methyl iodide (0.3 ml, 4.8 mmol), and methylene chloride (10 ml) were stirred together for 24h after which no precipitate had formed. The solvent was evaporated leaving a white solid which was found to be recovered oxycodone.

(i) Attempted preparation of buprenorphine methiodide

A mixture of buprenorphine (1 g, 2.14 mmol), methyl iodide (0.3 ml, 4.8 mmol), and methylene chloride (10 ml) was stirred together for 24hrs after which no precipitate had formed. The solvent was evaporated leaving a white solid which was found to be recovered buprenorphine.

F. Homogenous Aziridination

1. Aziridination using triethylamine

(a) Preparation of 7–ethoxycarbonyl–7–azabicyclo[4.1.0]heptane **312**

Ethyl *N*–*p*–nitrobenzenesulphonoxycarbamate (3.75 g, 12.9 mmol), and a mixture (125 ml) of cyclohexene (20%) and methylene chloride (80%) were

stirred together. A solution of triethylamine (1.75 g, 16.8 mmol) in the above mixture (25 ml) was added slowly. The reaction mixture was left stirring at room temperature for 24hrs. The solvent was evaporated, and the residual oil was partitioned between water and petroleum. The combined organic layers were washed with water, dried, and evaporated leaving a yellow oil which was purified by kugelrohr distillation to give 7–ethoxycarbonyl–7–azabicyclo[4.1.0]heptane **312** (1.12 g, 48%) as a colourless oil, b.p. 95 °C, 0.5 mm Hg (lit.,[103] 68 °C, 1.25 mm Hg). δ_H(8 0MHz, $CDCl_3$) 1.3 (3H, t, J 7 Hz, CH_3), 2.0 (8H, m, 4xCH_2), 2.7 (2H, broad s, CH) and 4.25 (2H, q, J 7 Hz, CH_2).

(b) Preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313**

The above compound was prepared by the same procedure used previously using ethyl *N–p*–nitrobenzenesulphonoxycarbamate (3.12 g, 10.8 mmol), 1–methylcyclohexene (3.66 g, 31.9 mmol), triethylamine (1.92 g, 19 mmol), and methylene chloride (270 ml). Kugelrohr distillation gave 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** (0.53 g, 28%) as a colourless oil, b.p. 100 °C, 0.5 mm Hg (lit.,[104] 120–2 °C, 17 mm Hg).δ_H(300 MHz, $CDCl_3$) 1.35 (3H, t, J 7 Hz, CH_3), 1.5–2.0 (8H, m, 4xCH_2), 2.4 (1H, t, CH), and 4.2 (2H, q, J 7 Hz, CH_2).

(c) Preparation of 1–ethoxycarbonyl–2–ethyl–3–methylaziridine **314**

The above compound was prepared by the same procedure used previously using ethyl *N–p*–nitrobenzenesulphonoxycarbamate (3.31 g, 11.4 mmol), *cis*–pent–2–ene (1.30 g, 18.6 mmol), triethylamine (2.40 g, 2.83 mmol), and methylene chloride (150 ml). This gave 1–ethoxycarbonyl–2–ethyl–3–methylaziridine **314** (0.13 g, 7%) as a colourless oil, b.p. 50 °C, 20

mm Hg. δ_H(80 MHz, $CDCl_3$), 1.25 (11H, m, 3xCH_3 and CH_2), 2.3 (2H, m, 2xCH) and 4.25 (2H, q, J 7 Hz, CH_2).

(d) Attempted preparation of 1–ethoxycarbonyl–2–methyl–2–phenylaziridine **315**

The above compound was prepared by the same procedure used previously using ethyl *N–p*–nitrobenzenesulphonoxycarbamate (4.04 g, 13.9 mmol), α–methylstyrene (10 ml, 77 mmol), triethylamine (2.61 g, 25.8 mmol), and methylene chloride (150 ml). The resulting product was a mixture of several compounds that could not be separated.

(e) Attempted preparation of 1–ethoxycarbonyl–2–methyl–3–phenylaziridine **316**

The above compound was prepared by the same procedure used previously using ethyl *N–p*–nitrobenzenesulphonoxycarbamate (3.23 g, 11.1 mmol), β–methylstyrene (6 ml, 46 mmol), triethylamine (1.50 g, 14.9 mmol), and methylene chloride (150 ml). The resulting product was a mixture of several compounds that could not be separated.

2. Aziridination using the alkaloids

(a) Attempted preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo [4.1.0]heptane **313**

Dihydroquinine (3.31 g, 10.2 mmol), 1–methylcyclohexene (5 ml, 42 mmol), and methylene chloride (25 ml) were stirred together at room temperature. A mixture of ethyl *N–p*–nitrobenzenesulphonoxycarbamate (3.28 g, 11.3 mmol), 1–methylcyclohexene (2 ml, 16.9 mmol),and methylene chloride (50 ml) was added slowly. The reaction mixture was then stirred at room temperature for 18h. The solvent was evaporated and petroleum added

causing a precipitate to form. The precipitate was filtered off and the filtrate evaporated. The residual oil was purified by column chromatography (silica gel 60–120 mesh, ether:petrol; 1:1) to give 6–(ethoxycarbonylamino)–1–methyl cyclohexene **332** (0.33 g,.16%) as colourless crystals, m.p. 43 °C (lit.,[104] 43–6 °C). δ_H(300 MHz, $CDCl_3$) 1.3 (3H, t, CH_3), 1.75 (9H, m, CH_3, and 3xCH_2), 1.95 (1H, s, CH), 4.1 (2H, q, CH_2), 4.6 (1H, s, NH), 5.55 (1H, s, CH). δ_C(75 MHz, $CDCl_3$) 14.7 (CH_3), 18.5 (CH_3), 20.9 (CH_2), 25.1 (CH_2), 30.1 (CH_2), 49.0 (CH_2), 60.7 (CH), 126 (CH), 133.4 (C), and 156.3 (CO).

(b) Preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** using dihydroquinine **327**

A mixture of dihydroquinine (3.30 g, 10.1 mmol), 1–methylcyclohexene (5 ml, 42 mmol), and methylene chloride (10 ml) was stirred together while ethyl *N–p*–nitrobenzenesulphonoxycarbamate (2.90 g, 10 mmol) was added slowly. The reaction mixture was left stirring at room temperature for 3h. The solvent was evaporated and hexane added to the residual oil which caused a precipitate to form. The precipitate was filtered off and the filtrate evaporated. The residual oil was purified by column chromatography (flash silica gel,ether:petrol;1:1) to give 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** (0.67 g, 37%), $[\alpha]_D$=+0.55° (c=1, CH_2Cl_2). The NMR was the same as that in F.1.(b).

(c) Preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** using dihydroquinidine **328**

The above compound was prepared by procedure 2(b) using 1–methylcyclohexene (5 ml, 42 mmol), dihydroquinidine (3.28 g, 10.1 mmol), methylene chloride (10 ml), and ethyl *N–p*–nitrobenzenesulphonoxycarbamate (2,92 g, 10.1 mmol) to give 7–ethoxycarbonyl–1–methyl–7–

azabicyclo[4.1.0]heptane (0.46 g, 25%), 5% e.e. (^{1}H NMR with Eu(hfc)$_3$). The NMR was the same as that in F.1.(b).

(d) Preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** using dihydrocinchonine **330** (low concentration)

The above compound was prepared by procedure 2(a) using 1–methylcyclohexene (4 ml, 33.9 mmol), dihydrocinchonine (3.71 g, 12.5 mmol), methylene chloride (85 ml), ethyl *N – p –* nitrobenzenesulphonoxycarbamate (2.98 g, 10 mmol), and with chromatography using flash silica gel. This gave 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** (0.47 g, 26%), $[\alpha]_D$= +0.2° (c=3.2, CH_2Cl_2). The NMR was the same as that in F.1.(b).

(e) Preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** using dihydrocinchonine **330** (high concentration)

The above compound was prepared by procedure 2(b) using 1–methylcyclohexene (5 ml, 42 mmol), dihydrocinchonine (3.24 g, 10.9 mmol), methylene chloride (10 ml), and ethyl *N–p–*nitrobenzenesulphonoxycarbamate (2.90 g, 10 mmol). This gave 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** (1.25 g, 68%), $[\alpha]_D$= -0.2° (c=1, CH_2Cl_2), $[\alpha]_D$= -0.1° (c=2, CH_2Cl_2). The NMR was the same as that in F.1.(b).

(f) Preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** using dihydrocinchonidine **329**

The above compound was prepared by procedure 2(b) using 1–methylcyclohexene (4 ml, 33.9 mmol), dihydrocinchonidine (2.97 g, 10.0 mmol), methylene chloride (10 ml), and ethyl *N – p –* nitrobenzenesulphonoxycarbamate (2.87 g, 9.9 mmol). This gave 7–

ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane (0.21 g, 11.7%), 5% e.e. (^{1}H NMR with Eu(hfc)$_3$). The NMR was the same as that in F.1.(b).

(g) Preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** using sparteine **11** (low concentration)

The above compound was prepared by procedure 2(a) using 1–methylcyclohexene (4 ml, 33.9 mmol), sparteine (2.97 g, 12.4 mmol), methylene chloride (85 ml), ethyl *N*–*p*–nitrobenzenesulphonoxycarbamate (2.93 g, 10.1 mmol), and flash silica gel. This gave 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** (0.70 g, 38%), $[\alpha]_D$=0.0° (c=1, CH_2Cl_2). The NMR was the same as that in F.1.(b).

(h) Preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** using sparteine **11** (high concentration)

The above compound was prepared by procedure 2(b) using 1–methylcyclohexene (4 ml, 33.9 mmol), sparteine (2.52 g, 10.8 mmol), methylene chloride (10 ml), and ethyl *N*–*p*–nitrobenzenesulphonoxycarbamate (2.91 g, 10 mmol). This gave 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** (0.30 g, 16%), $[\alpha]_D$=0.0° (c=1, CH_2Cl_2). The NMR was the same as that in F.1.(b).

G. Phase Transfer Aziridination

1. Using benzyltriethylammonium chloride

(a) Preparation of 7–ethoxycarbonyl–7–azabicyclo[4.1.0]heptane **312**

A mixture of benzyltriethylammonium chloride (0.27 g, 1.2 mmol), ethyl *N*–*p*–nitrobenzenesulphonoxycarbamate (2.84 g, 9.79 mmol), cyclohexene (2.07 g, 25 mmol), methylene chloride (300 ml), and sodium bicarbonate

solution (20 ml) was stirred together for 4h. The organic layer was separated, washed with water, dried and evaporated. The residual oil (1.59 g) was purified by Kugelrohr distillation to give 7–ethoxycarbonyl–7–azabicyclo[4.1.0]heptane **312** (0.85 g, 51%). The NMR was the same as that in F.1.(a).

(b) Preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313**

A mixture of benzyltriethylammonium chloride (0.64 g, 5 mmol), 1–methylcyclohexene (1.33 g, 13.8 mmol), ethyl *N – p –* nitrobenzenesulphonoxycarbamate (2.89 g, 9.97 mmol), methylene chloride (100 ml), and sodium bicarbonate solution (20 ml) was stirred together for 18h. The organic layer was separated, washed with water, dried and evaporated. The residual oil was purified by column chromatography. Kugelrohr distillation on the first fraction gave 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** (0.24 g, 13%). The NMR was the same as that in F.1.(b).

(c) Attempted preparation of 7–ethoxycarbonyl–1–phenyl–7–azabicyclo[4.1.0]heptane

A mixture of benzyltriethylammonium chloride (0.5 g, 2.20 mmol), 1–phenylcyclohexene (1.58 g, 10 mmol), methylene chloride (10 ml), and sodium bicarbonate solution (20 ml) was stirred together while ethyl *N–p–* nitrobenzenesulphonoxycarbamate (2.86 g, 9.86 mmol) was added slowly. After the reaction mixture had stirred for 3h the organic layer was separated ,washed with water, dried, and evaporated. The remaining oil was chromatographed on silica gel and two fractions were collected. The first fraction gave 1–phenylcyclohexene. The second fraction after Kugelrohr distillation gave 1–phenyl–6–ethoxycarbonylaminocyclohexene **342** (0.51 g,

21%) as a white crystalline solid m.p. 95 °C (lit.,[105] 96° C). δ_H(200 MHz, $CDCl_3$) 1.2 (3H, t, CH_3), 1.7 (6H, m, 3xCH_2), 2.2 (1H, m, CH), 4.0 (2H, q, CH_2), 4.6 (1H, s, NH), 6.4 (1H, t, CH) and 7.3 (5H, m, Ar). δ_C (50 MHz, $CDCl_3$) 14.3 (CH_3), 17.5 (CH_2), 25.6 (CH_2), 29.8 (CH_2), 45.9 (CH_2), 60.4 (CH), 125.5 (Ar), 126.9 (Ar), 128.1 (Ar), 129.1 (Ar), 136.5 (CH), 139.4 (C) and 155.7 (CO).

2. Aziridination Using Chiral Phase Transfer Catalysts

(a) Attempted preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo [4.1.0]heptane **313** using *N*–benzyldihydroquininium chloride **336**

N–benzyldihydroquininium chloride (0.46 g,1.1 mmol), 1–methylcyclohexene (1.13 g, 11.8 mmol), ethyl *N* – *p* – nitrobenzenesulphonoxycarbamate (2.92 g, 10.1 mmol), methylene chloride (300 ml), and sodium bicarbonate solution (20 ml) were stirred together for 4h. The organic layer was separated, washed with water, dried, and evaporated. Ether was added to the residual oil causing a precipitate to form which was filtered off. The filtrate was evaporated leaving a yellow solid which was found to be ethyl*N*–*p*–nitrobenzenesulphonoxycarbamate. The experiment was repeated using sodium carbonate solution and sodium hydroxide solution with the same result.

(b) Preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo [4.1.0]heptane **313** using *N*–methyldihydroquininium iodide **337**

A mixture of *N*–methyldihydroquininium iodide (0.52 g,1.1 mmol), 1–methyl cyclohexene (1.13 g, 11.8 mmol), ethyl *N* – *p* – nitrobenzenesulphonoxycarbamate (2.89 g, 9.97 mmol), methylene chloride (100 ml), and sodium bicarbonate solution (20 ml) was stirred together for 18h. Water was added and the organic layer separated, washed with water,

dried and evaporated. Ether was added to the residual oil and with scratching a precipitate formed. The precipitate was filtered off and the filtrate evaporated. The remaining oil was chromatographed on silica gel (ether:petrol, 1:1). Kugelrohr distillation of the first fraction gave 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** (0.18 g, 10%) as a colourless oil, $[\alpha]_D$=+1.35° (c=1.1, CH_2Cl_2). The NMR was the same as that in section F 1(b).

(c) Preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo [4.1.0]heptane **313** using *N*–methyldihydroquinidinium iodide **338**

A mixture of *N*–methyldihydroquinidinium iodide (1.34 g, 2.9 mmol), 1–methyl cyclohexene (2 ml, 16.9 mmol), methylene chloride (60 ml), and sodium bicarbonate solution (20 ml) was stirred together while a mixture of ethyl *N*–*p*–nitrobenzenesulphonoxycarbamate (3.05 g, 10.5 mmol), 1–methylcyclohexene (2 ml, 16.9 mmol), and methylene chloride was added slowly. The reaction mixture was then left to stir for 18h. Water was added and the organic layer was separated, washed with water, dried and evaporated. Petrol was added to the residual oil and with scratching a precipitate formed. The precipitate was filtered off and the filtrate was evaporated. The residual oil was chromatographed on silica gel (flash silica, ether:petrol, 1:1). Kugelrohr distillation gave 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** (0.93 g, 51%) as a colourless oil, $[\alpha]_D$=+0.33° (c=3, CH_2Cl_2). The NMR was the same as that above.

(d) Preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo [4.1.0]heptane **313** using *N*–methyldihydrocinchoninium iodide **340**

The above compound was prepared by the same procedure used previously using *N*–methyldihydrocinchoninium iodide (4.56 g, 10.4 mmol), 1–methyl cyclohexene (4 ml, 33.9 mmol), methylene chloride (85 ml), sodium

bicarbonate solution (20 ml), and ethyl *N – p –* nitrobenzenesulphonoxycarbamate (3.21 g, 11.1 mmol). The product was chromatographed on silica gel (70–130 mesh, ether:petrol, 1:1). Kugelrohr distillation on the first fraction gave 6–(ethoxycarbonylamino)–1–methylcyclohexene (0.66 g, 32%) and 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** (0.24 g, 13%), $[\alpha]_D$=0.0° (c=2, CH_2Cl_2). The NMR was the same as that above.

(e) Preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo [4.1.0]heptane **313** using *N*–methyldihydrocinchonidinium iodide **339**

The above compound was prepared by the same procedure used previously using *N*–methyldihydrocinchonidinium iodide (4.11 g, 9.4 mmol), 1–methyl cyclohexene (4 ml, 33.9 mmol), methylene chloride (85 ml), sodium carbonate solution (20 ml), and ethyl *N–p*–nitrobenzenesulphonoxycarbamate (2.89 g, 10 mmol). The product was chromatographed on silica gel (flash silica, ether:petrol, 1:1). Kugelrohr distillation on the resulting oil gave 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** (0.87 g, 48%), $[\alpha]_D$=+0.46° (c=2.6, CH_2Cl_2). The NMR was the same as that above.

3. Aziridination using chiral phase transfer catalysts at high concentrations

(a) Preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo [4.1.0]heptane **313** using *N*–methyldihydroquininium iodide **337**

A mixture of *N*–methyldihydroquininium iodide (1.26 g, 2.69 mmol), 1–methylcyclohexene (4 ml, 33.9 mmol), methylene chloride (10 ml), and sodium carbonate solution (20 ml) was stirred together while ethyl–*N–p*–nitrobenzenesulphonoxycarbamate (2.93 g, 10.1 mmol) was added slowly. The reaction mixture was stirred together for 2–3h. The organic layer was separated, washed with water, dried and evaporated. The residual oil was

chromatographed on silica gel (flash silica, ether:petrol, 1:1). Kugelrohr distillation of the first fraction gave 7–ethoxycarbonyl–1–methyl–7–azabicyclo[4.1.0]heptane **313** (0.47 g, 25%), $[\alpha]_D$=+1.75° (c=1, CH_2Cl_2). The NMR was the same as that above.

(b) Preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo [4.1.0]heptane **313** using *N*–methyldihydroquinidinium iodide **338**

The above compound was prepared by the same procedure used previously, using *N*–methyldihydroquinidinium iodide (1.00 g, 2.14 mmol), 1–methylcyclohexene (4 ml, 33.9 mmol), methylene chloride (10 ml), sodium carbonate solution (20 ml) and ethyl *N*–*p*–nitrobenzenesulphonoxycarbamate (3.09 g, 10.7 mmol). This gave 7–ethoxycarbonyl–1–methyl–7–azabicyclo [4.1.0]heptane **313** (0.36 g, 15%), $[\alpha]_D$=+0.64° (c=2, CH_2Cl_2). The NMR was the same as that above.

(c) Preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo [4.1.0]heptane **313** using *N*–methyldihydrocinchoninium iodide **340**

The above compound was prepared by the same procedure used above, using *N*–methyldihydrocinchoninium iodide (1.09 g, 2.33 mmol), 1–methylcyclohexene (4 ml, 33.9 mmol), methylene chloride (10 ml), sodium carbonate solution (20 ml) and ethyl *N*–*p*–nitrobenzenesulphonoxycarbamate (2.83 g, 9.8 mmol). This gave 7–ethoxycarbonyl–1–methyl–7–azabicyclo [4.1.0]heptane **313** (0.58 g, 32%) 5% e.e. (^{1}H NMR with $Eu(hfc)_3$). The NMR was the same as that above.

(d) Preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo [4.1.0]heptane **313** using *N*–methyldihydrocinchonidinium iodide **339**

The above compound was prepared by the same procedure used above, using *N*–methyldihydrocinchoninidium iodide (1.09 g, 2.33 mmol), 1–

methylcyclohexene (4 ml, 33.9 mmol), methylene chloride (10 ml), sodium carbonate solution (20 ml) and ethyl *N*–*p*–nitrobenzenesulphonoxycarbamate (2.81 g, 9.69 mmol). This gave 7–ethoxycarbonyl–1–methyl–7–azabicyclo [4.1.0]heptane **313** (0.20 g, 7%) 5% e.e. (^{1}H NMR with Eu(hfc)$_3$). The NMR was the same as that above.

(e) Preparation of 7–ethoxycarbonyl–1–methyl–7–azabicyclo [4.1.0]heptane **313** using dihydrocodeine methiodide **343**

The above compound was prepared by the same procedure used above, using dihydrocodeine methiodide (0.5 g, 1.66 mmol), 1–methylcyclohexene (4 ml, 33.9 mmol), methylene chloride (10 ml), sodium carbonate solution (20 ml) and ethyl *N*–*p*–nitrobenzenesulphonoxycarbamate (3.0 g, 10.3 mmol). This gave 7–ethoxycarbonyl–1–methyl–7–azabicyclo [4.1.0]heptane **313** (0.10g, 5%), $[\alpha]_D$=+1.0° (c=0.3, CH_2Cl_2). The NMR was the same as that above.

(f) Preparation of 6–(ethoxycarbonylamino)–1–phenylcyclohexene **342** using *N*–methyldihydroquinidinium iodide **338**

The above compound was prepared by the same procedure used above using *N*–methyldihydroquinidinium iodide (1.05 g, 8.3 mmol), 1–phenylcyclohexene (1.16 g, 10.2 mmol), methylene chloride (10 ml), sodium carbonate solution (20 ml) and ethyl *N*–*p*–nitrobenzenesulphonoxycarbamate (2.90 g, 10 mmol). This gave 6–(ethoxycarbonylamino)–1–phenylcyclohexene **342** (0.24 g, 10%), $[\alpha]_D$=+4.0° (c=0.3, CH_2Cl_2). The NMR spectra were the same as G 1(c).

H. Opening of Epoxides

1. Preparation of epoxides

(a) Preparation of cyclohexene oxide **348**

Following a literature method[106] a mixture of cyclohexene (8.0 g, 97.6 mmol), anhydrous sodium carbonate (19 g), and methylene chloride was stirred together while peracetic acid (20 ml of a 33% solution in acetic acid,) was added slowly. After the reaction mixture had stirred for 3h it was poured onto water. The organic layer was separated, dried, and evaporated. Kugelrohr distillation on the remaining oil gave cyclohexene oxide **348** (5.6 g, 58.5%) b.p. 60 °C, 20 mm Hg (lit.,[107] 131.5 °C, 760 mm Hg). δ_H(200 MHz, $CDCl_3$) 1.3 (4H, m, 2xCH_2), 1.8 (4H, m, 2xCH_2) and 3.0 (2H, m, 2xCH).

(b) Preparation of 2,3–epoxybicyclo[2.2.1]heptane

The above compound was prepared by the same procedure used previously using norbornene (5.71 g, 60.7 mmol), sodium carbonate (28 g), and peracetic acid (10 ml of a 33% solution in acetic acid). Kugelrohr distillation gave 2,3–epoxybicyclo[2.2.1]heptane (4.1 g, 61%) as a white crystaline solid m.p. 122 °C (lit.,[108] 122–4 °C). δ_H(60 MHz, $CDCl_3$) 1.4 (6H, m, 3xCH_2), 2.5 (2H, m, 2xCH) and 3.1 (2H, m, 2xCH).

2. Base catalysed opening of epoxides

(a) Attempted preparation of cyclohexane–1,2–diol

A mixture of cyclohexene oxide (1.0 g, 10.2 mmol), benzyltriethylammonium chloride (0.25 g, 1.10 mmol), methylene chloride (20 ml) and sodium carbonate solution (20 ml) was stirred together overnight. The organic layer was separated, washed with water, dried and evaporated. The residual oil was found to be unchanged cyclohexene oxide.

The reaction was repeated using *N*–methyldihydrocinchoninium iodide as the phase transfer catalyst, but there was no reaction.

The reaction was also repeated using sodium hydroxide, and also sodium bicarbonate as the base. there was no reaction in either case.

(b) Preparation of cyclohexane–1,2–diol using quinine

A mixture of cyclohexene oxide (1.14 g, 11.6 mmol), quinine (1.04 g, 3.2 mmol), and dry ether (50 ml) was stirred together for 4d. The reaction mixture was washed with dilute hydrochloric acid, water, then dried and evaporated. The resulting oil (0.59 g) contained *trans*–cyclohexane–1,2–diol **351**,[109] *cis*–cyclohexane–1,2–diol **352**,[109] and cyclohexene oxide. δ_H(200 MHz, $CDCl_3$), 1.3 (m, CH_2), 1.8 (m, ring CH_2), 3.1 (s, epoxide CH), 3.5 (m, *cis*–alcohol CH) and 3.7 (m, *trans*–alcohol CH).

(c) Preparation of cyclohexane–1,2–diol using alumina and quinine *(7)*

A mixture of cyclohexene oxide (1.06 g, 10.8 mmol), dry alumina (10 g), quinine (3.15 g, 9.72 mmol), and dry ether (50 ml) was stirred together for 4d. The reaction mixture was washed with dilute hydrochloric acid, sodium carbonate solution, water, then dried and evaporated. The remaining oil was found to be a mixture of *trans*–cyclohexane–1,2–diol **351**, *cis*–cyclohexane–1,2–diol **352**, and cyclohexene oxide by ^{1}H NMR as above.

3. Opening of epoxides using methanol and a base

(a) Attempted preparation of 2–methoxycyclohexanol **350** with quinine

A mixture of cyclohexene oxide (1.00 g, 12.2 mmol), quinine (0.60 g, 1.85 mmol), methanol (1.76 g, 55 mmol), and dry ether (50 ml) was stirred together for 4d. The reaction mixture was then washed with dilute hydrochloric acid, sodium carbonate solution, water, then dried, and evaporated. The remaining oil was found to be unreacted cyclohexene oxide.

The reaction was repeated using dry alumina instead of quinine and also under reflux conditions. However no reaction occurred.

(b) Preparation of 2–methoxycyclohexanol **350** with alumina *(5)*

A mixture of cyclohexene oxide (5.21 g, 63.5 mmol), toluene, methanol (25 ml), and alumina (100 g) was heated together under reflux for 6h. The alumina was filtered off through celite and the filtrate was evaporated. Crystals formed from the remaining oil (0.59 g), these were collected and shown to be 2–methoxycyclohexanol **350** (0.20 g, 2.4%). δ_C(75 MHz, $CDCl_3$) 24.0 (CH_2), 24.2 (CH_2), 28.5 (CH_2), 32.3 (CH_2), 56.4 (CH_3), 73.6 (CH), and 85.0 (CH).

(c) Attempted preparation of 2–methoxycyclohexanol **350** with quinine and alumina

A mixture of cyclohexene oxide (1.10 g, 11.2 mmol), quinine (3.38 g, 12.0 mmol), dry alumina (10 g), methanol (4 ml), and dry ether (30 ml) was stirred together for 4d. The alumina was filtered off through celite and the filtrate was washed with dilute hydrochloric acid, sodium bicarbonate solution, water, then dried, and evaporated. The resulting oil was found to be a mixture of *cis*– and *trans*–cyclohexane–1,2–diol. The NMR was the same as before.

(d) Attempted preparation of 1–hydroxy–2–methoxybicyclo[2.2.1]heptane

A mixture of 2,3–epoxybicyclo[2.2.1]heptane (0.25 g, 2.3 mmol), methanol (1 ml), dry alumina (15 g), and dry ether (50 ml) was stirred together for 4d. The alumina was filtered off through celite and the solvent evaporated. The resulting oil was found to be the starting epoxide. The reaction was repeated under several different conditions, but no reaction was found to occur.

4. Opening of epoxides using acetic acid and base

(a) Preparation of 2–acetoxycyclohexanol **349**

A mixture of cyclohexene oxide (1.02 g, 12.4 mmol), quinine (1.28 g, 3.95 mmol), acetic acid (5 ml), and dry ether (50 ml) was stirred together for 7d. The reaction mixture was washed with dilute hydrochloric acid, water, sodium carbonate solution, then dried and evaporated. The remaining oil was found to be cyclohexene oxide with a trace of 2–acetoxycyclohexanol (small peaks <1% in the carbon NMR spectrum consistent with the product).

(b) Preparation of 2–acetoxycyclohexanol **349** using alumina

A mixture of cyclohexene oxide (0.53 g, 6.46 mmol), acetic acid (1.04 g, 17.3 mmol), alumina (19 g), and dry ether (50 ml) was stirred together for 4d. The alumina was filtered off through celite and the filtrate evaporated. The remaining oil was found to be cyclohexene oxide with a trace of 2–acetoxycyclohexanol present.

(c) Preparation of 2–acetoxycyclohexanol **349** using alumina under reflux *(1)*

A mixture of cyclohexene oxide (0.62 g, 6.5 mmol), toluene (100 ml), acetic acid (5 ml), and alumina (26 g) was refluxed using a Dean and Stark apparatus for 3h. The alumina was filtered off through celite and the filtrate evaporated. Kugelrohr distillation then gave 2–acetoxycyclohexanol **349** (0.50 g, 49%) as colourless crystals m.p. 39 °C (lit.,[110] 39–40 °C). δ_H(200 MHz, $CDCl_3$) 1.3 (4H, m, **4-5**CH_2), 1.7 (2H, m, **3**CH_2), 2.05 (2H, m, **6**CH_2), 2.1 (3H, s, CH_3), 3.2 (1H, s, OH), 3.55 (1H, m, CH), and 4.6 (1H, m, CH). δ_C(300 MHz, $CDCl_3$) 20.8 (C**4**), 23.25 (C**5**), 23.32 (CH_3), 29.4 (C**3**), 32.5 (C**6**), 71.6 (C**2**), 77.4 (C**1**), and 170.9 (CO).

(d) Preparation of 2–acetoxycyclohexanol **349** using quinine under reflux *(2)*

A mixture of cyclohexene oxide (1.04 g, 12.7 mmol), toluene (100 ml), acetic acid (2 ml), and quinine (3.54 g, 10.9 mmol) was refluxed using a Dean and Stark apparatus for 3h. The reaction mixture was washed with dilute hydrochloric acid, sodium carbonate solution, water, then dried and evaporated. Kugelrohr distillation on the remaining oil gave 2–acetoxycyclohexanol **349** (0.04 g, 2%). The NMR was the same as above.

(e) Preparation of 2–acetoxycyclohexanol **349** using quinine and alumina under reflux *(3)*

A mixture of cyclohexene oxide (1.06 g, 10.8 mmol), toluene (100 ml), acetic acid (5 ml), alumina (20 g), and quinine (3.47 g, 10.7 mmol) was refluxed using a Dean and Stark apparatus for 3h. The alumina was filtered off through celite and the filtrate was washed with dilute hydrochloric acid, sodium carbonate solution, then dried and evaporated. Kugelrohr distillation on the remaining oil gave 2–acetoxycyclohexanol **349** (1.24 g, 67%), $[\alpha]_D$=0.0° (c=2, CH_2Cl_2). The NMR was the same as above.

(f) Preparation of 2–acetoxycyclohexanol **349** using quinine and dry alumina *(4)*

A mixture of cyclohexene oxide (1.16 g, 11.8 mmol), dry ether (20 ml), acetic acid (5 ml), dry alumina (10 g), and quinine (3.67 g, 11.3 mmol) was stirred together for 3d. The alumina was filtered off through celite and the filtrate was washed with dilute hydrochloric acid, sodium carbonate solution, then dried and evaporated. Kugelrohr distillation on the remaining oil gave a mixture of cyclohexene oxide, *cis*–, and *trans*–cyclohexane–1,2–diol, and 2–acetoxycyclohexanol **349** as determined by ^{1}H NMR.

(g) Attempted preparation of 1–hydroxy–2–acetoxybicyclo[2.2.1]heptane *(5)*

A mixture of 2,3–epoxybicyclo[2.2.1]heptane (1.30 g, 11.8 mmol), acetic acid (5 ml), alumina (25 g), and toluene (100 ml) was refluxed using a Dean and Stark apparatus for 24h. The alumina was filtered off through celite and the filtrate washed with sodium carbonate solution, dried and evaporated. The remaining oil was found to contain several different rearranged compounds.

I. Ring Opening Of Aziridines

(a) Preparation of 2–ethoxycarbonylaminocyclohexanol

A mixture of 7–ethoxycarbonyl–7–azabicyclo[4.1.0]heptane (1.73 g, 9.45 mmol), quinidine (3.35 g, 10.3 mmol), dry alumina (10 g), and dry ether (30 ml) was stirred together for 4d. The alumina was filtered off through celite, the filtrate was washed with dilute hydrochloric acid, sodium carbonate, water, then dried and evaporated. The remaining solid was recrystallised from toluene to give 2–ethoxycarbonylaminocyclohexanol (0.67 g, 41%) as a colourless crystalline solid, m.p. 95–96 °C (lit.,[111] 72 °C) $[\alpha]_D$=+0.78° (c=1.6,CH_2Cl_2). δ_H(200 MHz, $CDCl_3$) 1.25 (3H, t, **Et**CH_3), 1.35 (3H, m, **4–5**CH_2), 1.75 (3H,m, **3–4**CH_2), 2.2 (2H, m, **6**CH_2), 3.6 (1H, m, **2**CH), 3.8 (1H, m, **1**CH), 4.15 (2H, q, **Et**CH_2), and 5.45 (1H, s, OH). δ_C(50 MHz, $CDCl_3$) 16.6 (**Et**CH_3), 24.2 (**4**C), 25.2 (**5**C), 32.8 (**3**C), 36.0 (**6**C), 56.5 (**2**C), 60.8 (**Et**CH_2), 63.0 (**1**C), and 156.3 (CO).

(b) Preparation of 1–acetoxy–2–ethoxycarbonylaminocyclohexane **354** *(8)*

A mixture of 7–ethoxycarbonyl–7–azabicyclo[4.1.0]heptane (1.91 g, 10.4 mmol), quinidine (3.46 g, 10.7 mmol), dry alumina (10 g), acetic acid (5 ml) and dry ether was stirred together for 3d. The alumina was filtered off through celite, the filtrate was washed with dilute hydrochloric acid, sodium carbonate, water, then dried and evaporated. Kugelrohr distillation gave an oil

which partially crystallised after a few days. The crystals were found to be 2–ethoxycarbonylaminocyclohexanol (0.39 g, 22%) and the remaining oil (0.84 g) was found to be a mixture of 6–ethoxycarbonylaminocyclohexene and 1–acetoxy–2–ethoxycarbonylaminocyclohexane **354**.

J. Ring opening of anhydrides

(a) Preparation of *endo*–bicyclo[2.2.1]hept–5–ene 2,3–dicarboxylic acid monomethyl ester **262** using buprenorphine **359**

A mixture of *endo*–bicyclo[2.2.1]hept–5–ene 2,3–dicarboxylic acid anhydride (1.67 g, 10.7 mmol), buprenorphine (0.6 g, 1.28 mmol), dry toluene (60 ml), and methanol (0.96 g, 30 mmol) was stirred together for 48h. The toluene was evaporated and the remaining oil dissolved in methylene chloride. The solution was washed quickly with dilute hydrochloric acid, dried and evaporated. The remaining white solid was recrystallised from ether to give *endo*–bicyclo[2.2.1]hept–5–ene–2,3–dicarboxylic acid monomethyl ester **262** (1.63 g 78%), $[\alpha]_D$= –0.69° (c=1.08, CH_2Cl_2). δ_H(200 MHz, $CDCl_3$) 1.1 and 1.7 (2H, AB pattern J=5 Hz, **7**CH_2), 3.15 (2H, m, **2,3**CH_2), 3.35 (2H, m, **1**, **4**CH), 3.6 (3H, s, CH_3), 6.25 (2H, m, **5,6**CH), and 9.75 (1H, s, CO_2H).

The NMR of the α–phenylethylamine salt did not show two clearly resolved methyl signals. The e.e. was determined from the rotation to give e.e.=54%.

(b) Preparation of *endo*–bicyclo[2.2.1]hept–5–ene 2,3–dicarboxylic acid monomethyl ester **262** using dihydrocodeine **357**

The above compound was prepared by the same procedure used previously, using *endo*–bicyclo[2.2.1]hept–5–ene 2,3–dicarboxylic acid anhydride (1.73 g, 11.1 mmol), dihydrocodeine (1.0 g, 3.32 mmol), methanol (0.96 g, 30 mmol), and dry toluene (60 ml). This gave *endo*–

bicyclo[2.2.1]hept–5–ene 2,3–dicarboxylic acid monomethyl ester **262** (1.66 g 76%), $[\alpha]_D$= +0.094° (c=1.1, CH_2Cl_2). The NMR was the same as that above.

The NMR of the α–phenylethylamine salt showed two methyl signals at δ3.486 and 3.495 with a ratio of 1.1 to 1 to give e.e.=5%.

(c) Preparation of *endo*–bicyclo[2.2.1]hept–5–ene 2,3–dicarboxylic acid monomethyl ester **262** using oxycodone **358**

The above compound was prepared by the same procedure used previously using *endo*–bicyclo[2.2.1]hept–5–ene 2,3–dicarboxylic acid anhydride (1.78 g, 11.4 mmol), oxycodone (1.0 g, 3.17 mmol), methanol (0.96 g, 30 mmol), and dry toluene (60 ml). This gave *endo*–bicyclo[2.2.1]hept–5–ene 2,3–dicarboxylic acid monomethyl ester **262** (1.57 g 70%), $[\alpha]_D$= –0.69° (c= 4.2, CH_2Cl_2). The NMR was the same as that above.

The NMR of the α–phenylethylamine salt did not show two clearly resolved methyl signals. The e.e. was determined from the rotation to give e.e.=54%.

(d) Preparation of *endo*–bicyclo[2.2.1]hept–5–ene 2,3–dicarboxylic acid monomethyl ester **262** using dihydrothebainone **360**

The above compound was prepared by the same procedure used previously using *endo*–bicyclo[2.2.1]hept–5–ene 2,3–dicarboxylic acid anhydride (1.71 g, 11.0 mmol), dihydrothebainone (1.0 g, 3.3 mmol), methanol (1.0 g, 31.3 mmol), and dry toluene (60 ml). This gave *endo*–bicyclo[2.2.1]hept–5–ene 2,3–dicarboxylic acid monomethyl ester (1.94 g 90%), $[\alpha]_D$= +0.15° (c= 4.2, CH_2Cl_2). The NMR was the same as that above.

The NMR of the α–phenylethylamine salt showed two methyl signals at δ3.489 and 3.497 with a ratio of 20 to 16 to give e.e.=11%.

(e) Preparation of *endo*–bicyclo[2.2.1]hept–5–ene 2,3–dicarboxylic acid monomethyl ester **262** using quinine

The above compound was prepared by the same procedure used previously using *endo*–bicyclo[2.2.1]hept–5–ene 2,3–dicarboxylic acid anhydride (1.67 g, 10.7 mmol), quinine (1.20 g, 3.70 mmol), methanol (0.64 g, 20 mmol), and dry toluene (60 ml). This gave *endo*–bicyclo[2.2.1]hept–5–ene 2,3–dicarboxylic acid monomethyl ester **262** (1.67 g 80%), $[\alpha]_D$= +1.08° (c= 4.2, CH_2Cl_2). The NMR was the same as that above.

The NMR of the α–phenylethylamine salt showed two methyl signals at δ3.490 and 3.498 with a ratio of 14 to 36 to give e.e.=44%.

(f) Preparation of *endo*–bicyclo[2.2.1]hept–5–ene 2,3–dicarboxylic acid monomethyl ester **262** using cinchonine absorbed on alumina

A mixture of *endo*–bicyclo[2.2.1]hept–5–ene 2,3–dicarboxylic acid anhydride (1.76 g, 11.3 mmol), cinchonine–alumina (10 g), methanol (1 g, 31.2 mmol), and dry toluene was stirred for 48h. the alumina was filtered off through celite and the filtrate evaporated. The remaining oil was dissolved in methylene chloride, washed quickly with dilute hydrochloric acid, dried, and evaporated. The remaining solid was recrystallised from ether to give *endo*–bicyclo[2.2.1]hept–5–ene 2,3–dicarboxylic acid monomethyl ester **262** (0.98 g, 44%). The NMR was the same as that above.

The NMR of the α–phenylethylamine salt showed two methyl signals at δ3.459 and 3.468 with a ratio of 37 to 25 to give e.e.=19%.

(g) Preparation of 9–methoxycarbonyl–2–oxatricyclo[3.3.0.$1^{4,7}$]nonan–8–ol–3–one **258** using oxycodone **358**

The above compound was prepared using the same procedure as J(a) using *endo*–5,6–epoxybicyclo[2.2.1]heptane–2,3–dicarboxylic acid anhydride (1.0 g, 5.6 mmol), oxycodone (1.0 g, 3.2 mmol), methanol (0.98 g, 30.6

mmol), and toluene (60 ml). This gave the crude product (0.5 g, 43%) which by the NMR still contained some alkaloid. The chiral shift experiment was carried out successfully on this crude mixture, the CH_3 singlet being shifted from δ3.7 to give two signals at δ3.985 and 4.055 with a ratio of 2.5 to 3.7 to give e.e.=9.7%.

(h) Preparation of 9–methoxycarbonyl–2–oxatricyclo[3.3.0.$1^{4,7}$]nonan–8–ol–3–one **258** using dihydrocodeine **357**

The above compound was prepared by the same procedure used previously using *endo*–5,6–epoxybicyclo[2.2.1]heptane–2,3–dicarboxylic acid anhydride (1.03 g, 5.7 mmol), dihydrocodeine (1.0 g, 3.3 mmol), methanol (0.96 g, 30 mmol), and toluene (60 ml). This gave the crude product (0.22 g, 18%) which by the NMR still contained some alkaloid. The chiral shift experiment was carried out successfully on this crude mixture, the CH_3 singlet being shifted from δ3.7 to give two signals at δ4.084 and 4.146 with a ratio of 4.7 to 3.7 to give e.e.=10%.

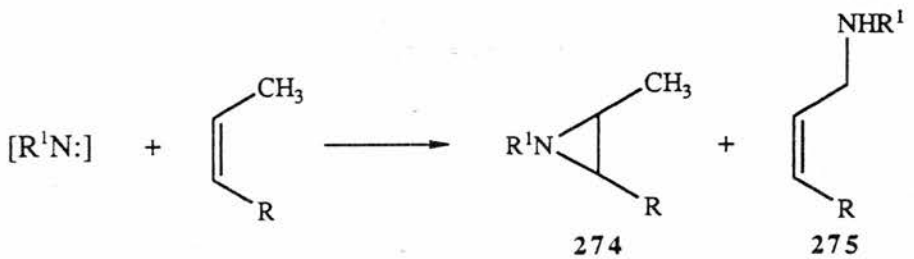
(i) Preparation of 9–methoxycarbonyl–2–oxatricyclo[3.3.0.$1^{4,7}$]nonan–8–ol–3–one **258** using dihydrothebainone **360**

The above compound was prepared by the same procedure used previously using *endo*–5,6–epoxybicyclo[2.2.1]heptane–2,3–dicarboxylic acid anhydride (1.0 g, 5.6 mmol), dihydrothebainone (1.0 g, 3.3 mmol), methanol (0.95 g, 29.7 mmol), and toluene (60 ml). This gave the crude product (0.51 g, 43%) which by the NMR still contained some alkaloid. The chiral shift experiment was carried out successfully on this crude mixture, the CH_3 singlet being shifted from δ3.7 to give two signals at δ3.958 and 4.010 with a ratio of 7.5 to 5.4 to give e.e.=9.7%.

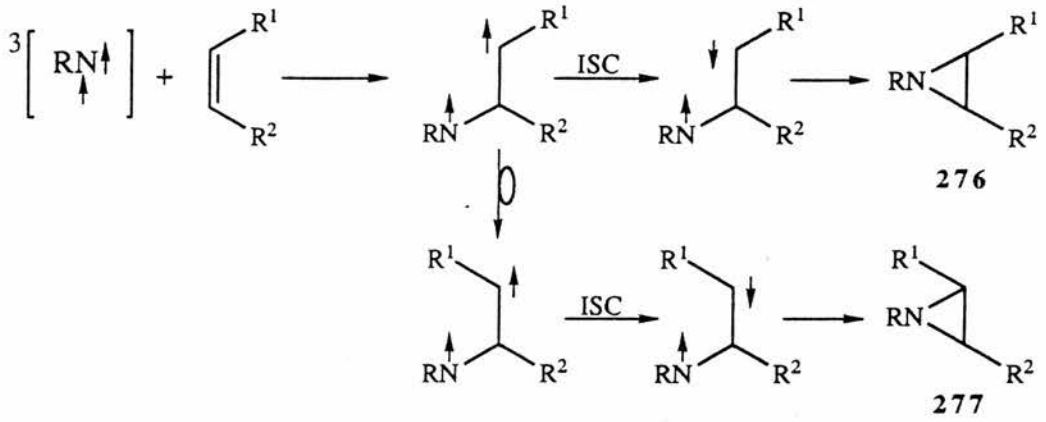
A. Asymmetric Aziridination

1. General Background

One of the most important methods for the formation of aziridines **274** is the addition reaction of nitrenes to double bonds. There are competing side reactions which can occur using this method, the main side reaction being nitrene insertion into a carbon–hydrogen bond to form an amine **275**. However this is usually a minor reaction as nitrenes are more reactive towards double bonds than carbon–hydrogen bonds.



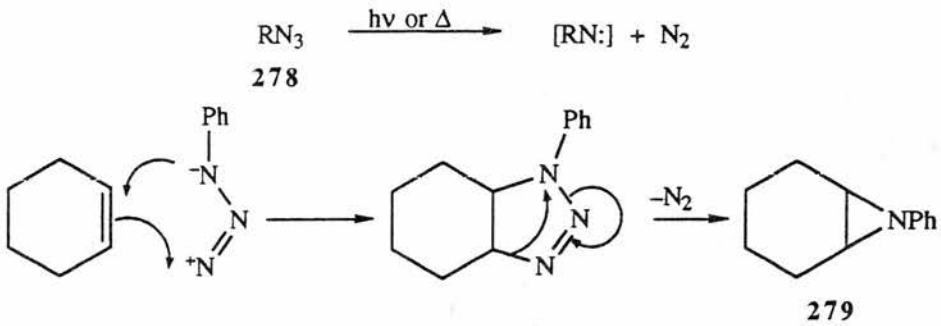
When using nitrenes their electronic state must be taken into consideration. The nitrene has two pairs of non–bonded electrons which gives rise to two possible electronic states: a singlet state where all the electrons are paired, and a triplet state where there are two paired electrons and two unpaired electrons. The singlet state reacts with alkenes with retention of configuration *i.e.* the *E*–alkene reacts to give the trans aziridine. In contrast the triplet nitrene reacts to give a mixture of isomers. This is because, for bond formation to occur, one of the electrons must change its spin and this process (intersystem crossing) is much slower than bond rotation allowing the formation of both cis **276** and trans **277** isomers.



There are several methods known for the formation of nitrenes and the most common ones are as follows.

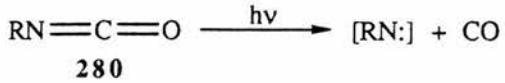
(a) From Azides

Azides **278** may undergo thermal or photolytic decomposition with loss of nitrogen to produce nitrenes which undergo addition or insertion reactions. Some care needs to be taken in assigning a nitrene as the intermediate in such reactions since azides can also undergo a [1,3]–dipolar cycloaddition reaction with alkenes which leads to the formation of aziridines via an intermediate triazoline. An example of this is the reaction of phenyl azide with cyclohexene which produces the aziridine **279** indirectly by the cycloaddition reaction.[112]



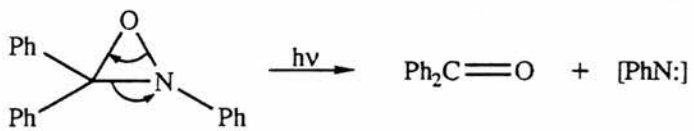
(b) From Isocyanates

The photolysis of isocyanates **280** leads to the formation of the nitrene and carbon monoxide. This reaction does not occur under thermal conditions.[113]



280

In a similar reaction oxaziridines **281** can undergo a photolytic decomposition reaction to produce nitrenes and carbonyl compounds.[114]

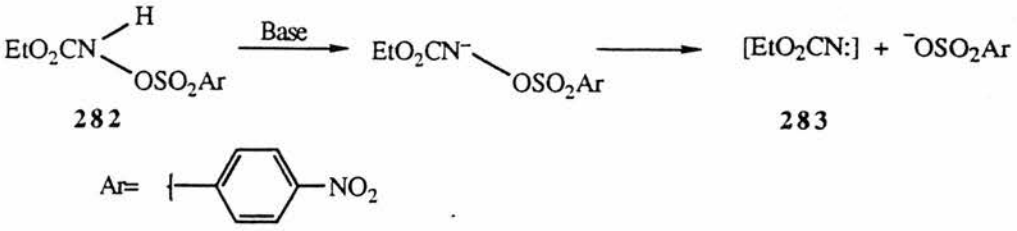


281

(c) From Nitrogen Anions: α–Elimination

Base induced α–elimination reactions can also produce nitrenes. This reaction may either proceed by the removal of the hydrogen by the base and then the subsequent loss of the leaving group, or it may be a concerted process.

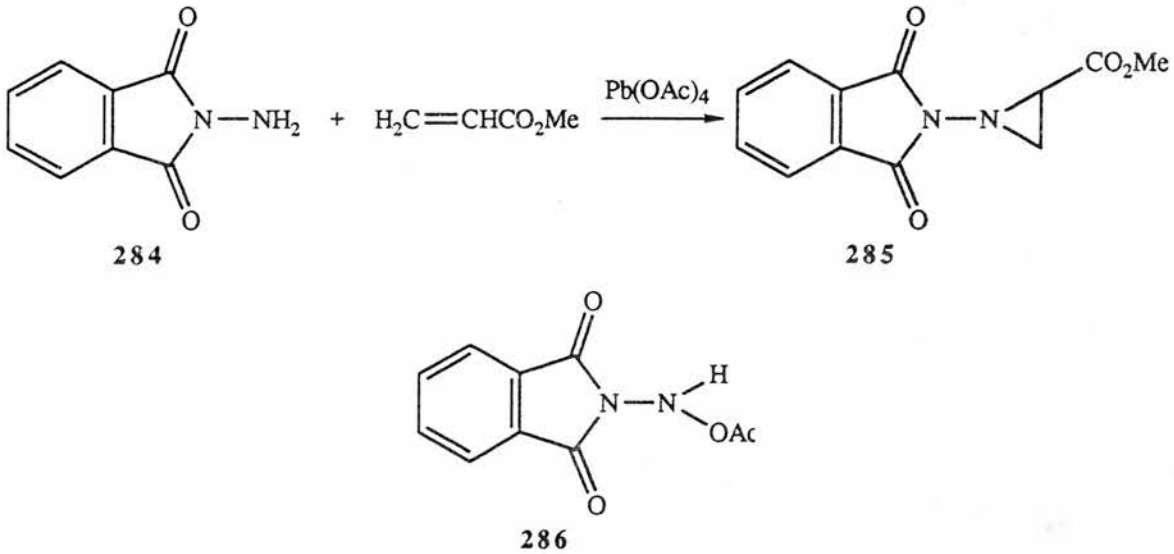
The best known example of such a reagent is the compound **282** developed by Lwowski which can undergo α–elimination to form ethoxycarbonylnitrene **283**.[115]



282 283

(d) Oxidative Routes

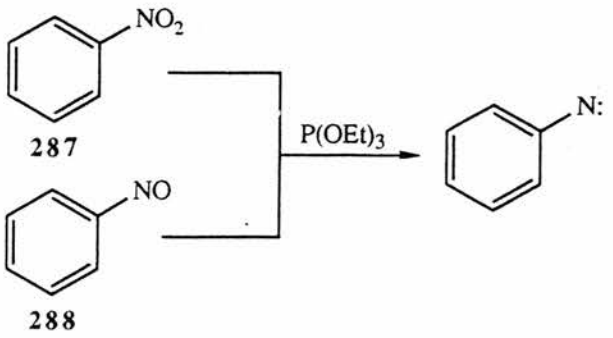
The oxidation of some amino groups is thought to produce nitrenes. For example the oxidation of *N*–aminophthalimide **284** by lead tetraacetate in the presence of alkenes produces aziridines **285** and this was thought to occur via a nitrene intermediate.[116] More recently Atkinson[117] has shown that the lead tetraacetate converts **284** into *N*–acetoxy compound **286** and this reacts to form the aziridine without a free nitrene being involved. Oxidation of **284** with other oxidising agents does however involve phthalimidonitrene.



284 285 286

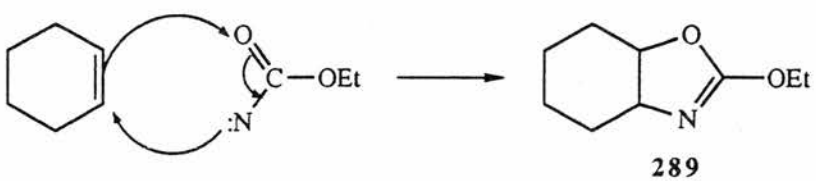
(e) Reductive Routes

Nitroso **288** and nitro **287** groups can be reduced by triethylphosphite to produce nitrenes. The nitrene that forms in this reaction may form a complex with the phosphorus making it more stable.[118]



The most studied of the above reactions is the formation of ethoxycarbonylaziridines either by the decomposition of azides or by α–elimination. These have then become some of the main routes for making aziridines.

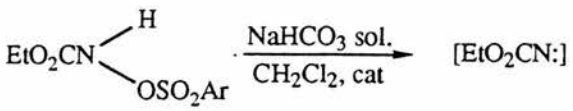
Lwowski[115] has studied the formation of this nitrene in detail. In his study the ethoxycarbonylnitrene was formed by decomposition of ethyl azidoformate and then reacted with cyclohexane, isopentane, cyclohexene, and benzene. These results were then compared with the results obtained when the same reactions were carried out using α–elimination as the nitrene generating method. This showed that there was the same product distribution for the two reactions thus establishing that for these reactions nitrenes are formed as the common intermediates. Lwowski also showed that ethoxycarbonyl nitrene reacts by nitrene addition and not as a [1,3]–dipole to give **289**.



289

Seno[119] showed that the base induced α–elimination reaction of Lwowski's compound **282** can also be carried out under phase transfer conditions. In this case Lwowski's compound was reacted with alkenes in the

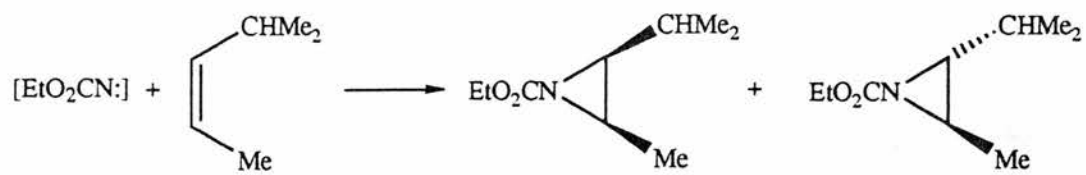
presence of sodium bicarbonate solution, dichloromethane and a catalytic amount of either quaternary ammonium or phosphonium halides.



282 **283**

Both Lwowski and Seno studied the electronic state of the nitrene in these reactions, Lwowski in the decomposition of azides and the homogeneous α–elimination reaction and Seno in the phase transfer reaction. Both came to the same conclusions.

The ethoxycarbonylnitrene has a triplet ground state, but it is intially formed in the singlet state. The singlet state reacts with retention of configuration while the triplet state does not. By studying the varation of *cis* **291** to *trans* **292** ratio in the product as a function of alkene **290** concentration it was established that, at high concentrations of alkene the singlet nitrene was reacting while at low concentrations the triplet nitrene was reacting. This showed that by having high concentrations of alkene the singlet nitrene could be trapped before it reverted to its ground state triplet. Thus stereocontrol could be achieved in the reaction.



283 **290** **291** **292**

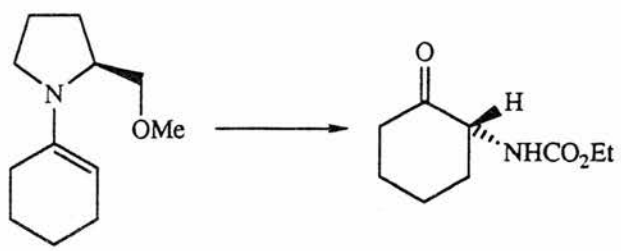
It has also been reported[120] that for certain alkenes containing a remote electron–withdrawing group, the phase transfer method gives the ethoxycarbonylaziridines in good yield while the homogeneous α–elimination

method is unsuccessful. This was attributed to selective favourable orientation of the substrates at the phase boundary in the former case.

2. Previous Work on Asymmetric Aziridination

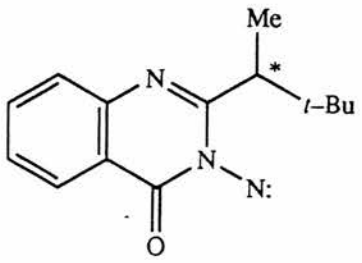
The asymmetric aziridination reaction has been little studied until recently. The original approaches to the asymmetric synthesis were to react nitrenes with chiral molecules containing a double bond or to react a chiral nitrene with an achiral molecule.

An example of the first method is the reaction of ethoxycarbonylnitrene with chiral enamine **293**. Hydrolysis then produced **294** in low yield but with 77% ee.[121]



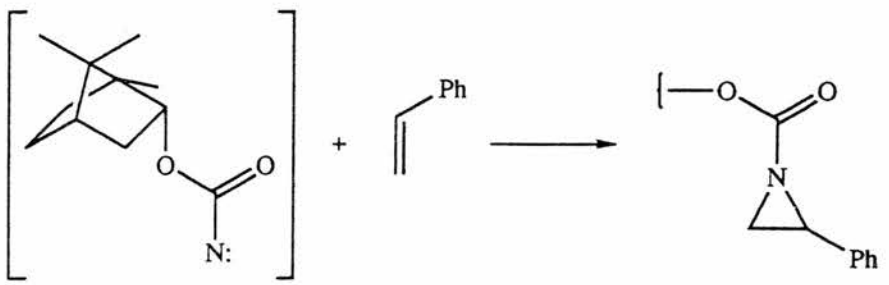
293 **294**

Atkinson[122] has developed chiral nitrenes such as **295** which on addition to achiral alkenes produce aziridines. Some success has been achieved using these reagents but only on certain alkenes which have favourable steric interactions. In general the stereogenic centre is too far removed from the reactive site to have any effect on the reaction.



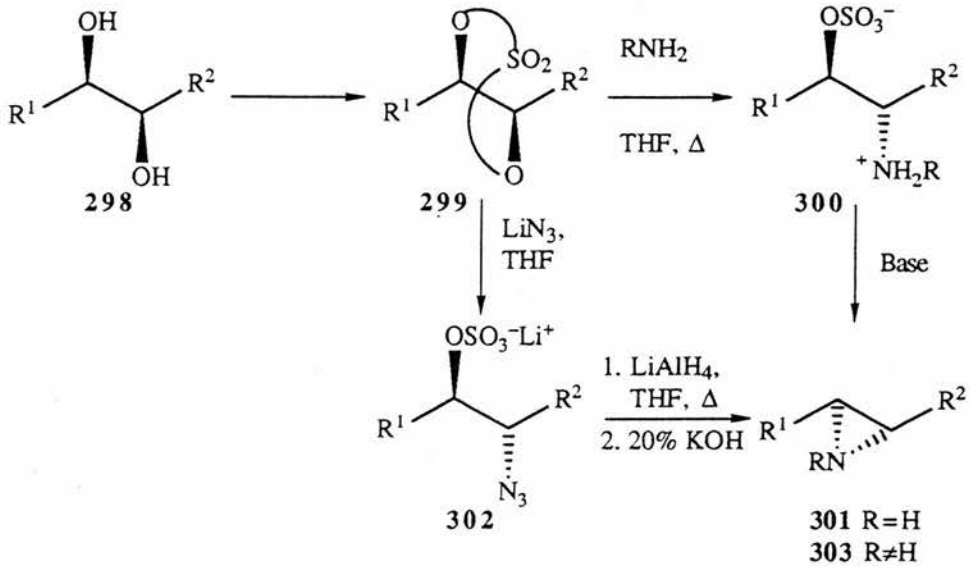
295

Other work[123] carried out more recently has involved the chiral nitrene **296** which reacted with styrene to produce the corresponding aziridine **297**. However no significant enantioselectivity was observed and again this was thought to be due to the remoteness of the stereogenic centres from the reactive site.

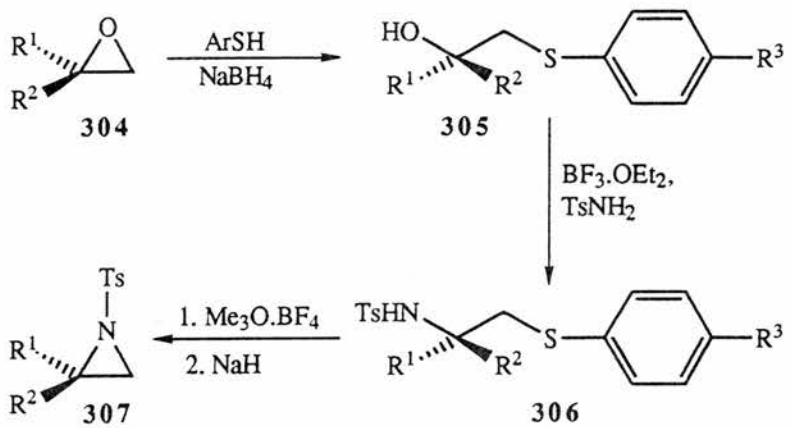


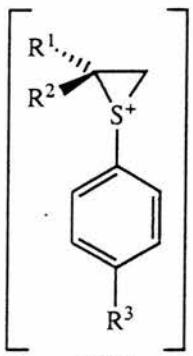
296 **297**

Two indirect synthetic routes to chiral aziridines have been published recently. The first was by Sharpless[124] who started from the chiral diols **298** produced by his asymmetric dihydroxylation reaction. The diols can be converted into a cyclic sulphate **299** with retention of configuration. Reacting the cyclic sulphate with lithium azide leads to the formation of azide **302** which can then be easily converted into a chiral aziridine **301**. Reacting the cyclic sulphate **299** with primary amine results in the formation of the *β*–amino sulphate **300** which can be converted into a chiral *N*–substituted aziridine **303**.



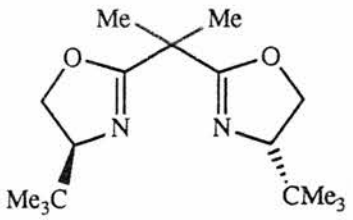
The second synthetic route[125] started from the chiral epoxides **304** which have become readily available due to the success of the titanium/tartrate method for their asymmetric synthesis. The chiral epoxides were opened by a substituted thiophenol to produce **305** with retention of configuration. The addition of *p*–toluenesulphonamide is the key step in the synthesis, retention of configuration at this stage being acheived by the anchiomeric effect of the arylthio group via intermediate **308**. Compound **306** was then converted, in two steps, into a chiral aziridine **307** with retention of configuration throughout the reaction.





308

The reactions that have been discussed so far are first and second generation methods of asymmetric synthesis and rely on the use of chiral starting materials. Until recently no one had produced a catalytic method for the formation of chiral aziridines. While our work was in progress Evans[126] has reported the first fourth generation synthesis. The chiral 4,4'–disubstituted bis(oxazolines), such as **309**, coordinated to copper were used as the chiral catalysts. The nitrene was generated from **310** which under the reaction conditions decomposes, in the presence of alkene, to give the aziridine **311**. Using this method the aziridine **311** was produced with 61% e.e.



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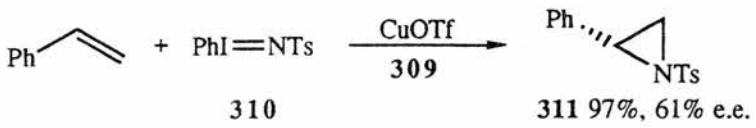
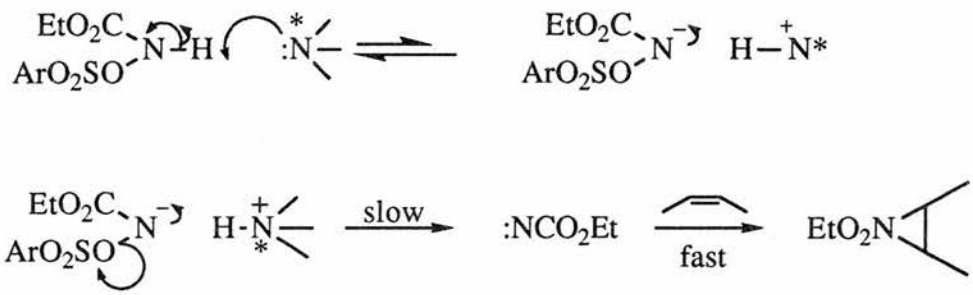


310 **311** 97%, 61% e.e.

3. Proposed Asymmetric Synthesis

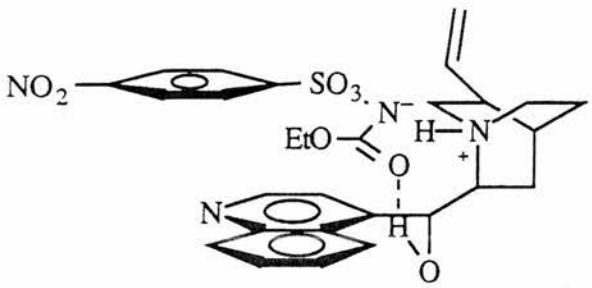
As described in the Programme of Research, our study has been directed towards the development of a catalytic route to chiral aziridines. Considering the alkaloid catalysed reactions discussed previously it was proposed that the alkaloids could produce enantioselectivity in the base catalysed aziridination developed by Lwowski.

In the reaction the base, here an alkaloid, removes a proton from the nitrene precursor to form an ion–pair with the alkaloid. This reaction is reversible with the equilibrium lying far to the left. The anion produced has a half life of 25secs[115] before it decomposes to the nitrene so this is presumably the rate determining step in the reaction. This is also the first nonreversible step in the reaction and thus the ion–pair formed is the crucial intermediate in the reaction for the transfer of chirality as enantioselectivity takes place in the first irreversible step.[127]



For effective enantioselectivity in the reaction the alkaloid must be bound tightly to the anion in the intermediate. There are several possible interactions that can ensure such a tight intermediate. There is the ionic interaction that exists in the ion pair which can be increased by using nonpolar solvents, such as methylene chloride, which will ensure that a tight ion pair exists. There are possible *H*–bonding interactions between the hydroxy group on the alkaloid and the carbonyl group on the precursor. The aromatic part of the precursor

could interact with the aromatic part of alkaloid. Such interactions have been shown to occur before in for example the thiophenol reaction discussed in the introduction.[84]



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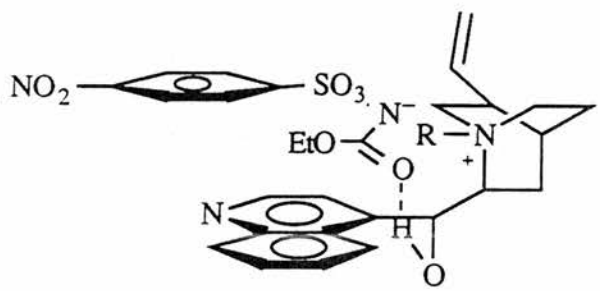
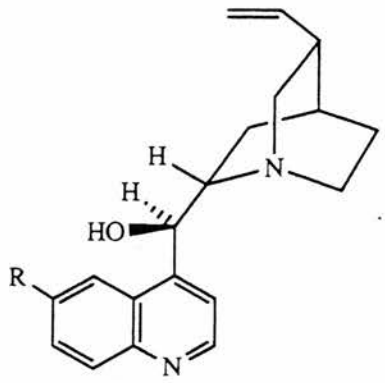


266

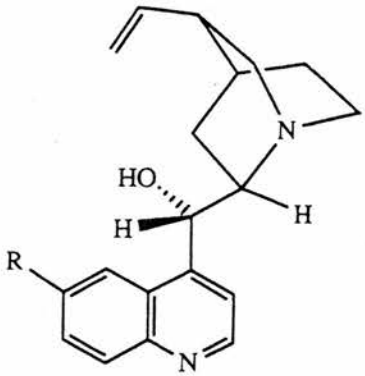
For a chiral aziridine to form the alkene must show a prefered interaction with this intermediate on one face of the double bond as opposed to the other and preferably also a more specific interaction of a substituent group of the alkene such as a phenyl ring which could interact with the aromatic part of the alkaliod.

The use of quaternary ammonium salts of the alkaloids as phase transfer catalysts is well documented. Thus using Seno's phase transfer procedure[119] for the α–elimination reaction a similar argument to the above could be made for this reaction and in this system there is the important advantage that the alkaloid can act as a catalyst for the basic action of for example bicarbonate. The ion pair **266** in this reaction will be held together at the phase boundary or in the organic phase ensuring a tight ion pair. The same *H*–bonding and aromatic interactions could be envisaged for the alkene and precursor.

The cinchona alkaloids **7–10** were thought to be the best alkaloids to use initially because of their well established ability to direct asymmetric reactions. The cinchona alkaloids have a vinyl group present which was hydrogenated to ensure that the nitrene did not react with the alkaloid.



7 (8S,9R)–Quinine (R=OMe)



8 (8R,9S)–Quinidine (R=OMe)

9 Cinchonidine (R=H)

10 Cinchonine (R=H)

4. Achiral Aziridination

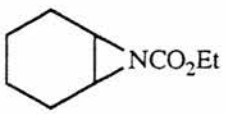
The initial reactions were carried out, using triethylamine as the base, in order to act as control reactions. This also allowed determination of which alkenes were best to use for the alkaloid catalysed reaction.

The reactions were carried out by adding 1 eq. of triethylamine to a stirred solution of Lwowski's compound in dichloromethane in the presence of excess alkene. The products were isolated by washing with water, evaporation and distillation.

From the results obtained (Table 2) it is obvious that 1–methylcyclohexene is the best prochiral alkene to use in the asymmetric reaction. This will give the best yield of aziridine.

Table 2

Alkene	Aziridine	Yield
Cyclohexene	**312**	48%
1–Methylcyclohexene	**313**	28%
cis–Pent–2–ene	**314**	7%
α–Methyl styrene	**315**	Insertion products
β–Methylstyrene	**316**	Insertion products



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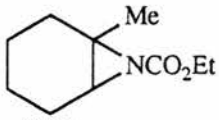

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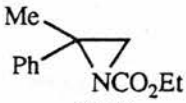


315

316

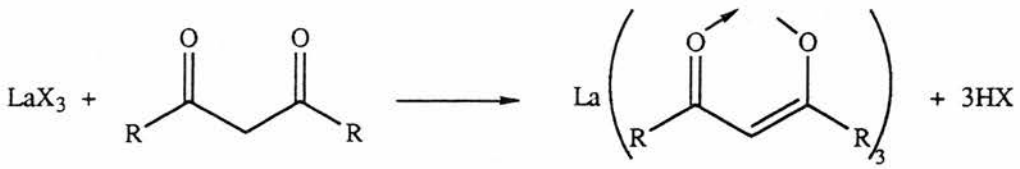
It was hoped that the methyl styrenes leading to **315** and **316** would be particularly useful alkenes to use as the phenyl group might interact favourably with the alkaloid. However only a mixture of insertion products, which could not be separated, was obtained from these reactions. This could be predicted from the literature as it has been reported[128] that styrene does not react with singlet nitrene to form an aziridine but prefers to react with triplet nitrene to form insertion compounds.

5. Determination of Enantiomeric Excess

Before describing the results of the asymmetric reactions a brief account of the methods used to determine the e.e. of the chiral aziridine products will be given.

(a) Chiral Shift Reagents

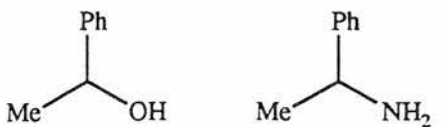
Chiral lanthanide shift reagents (CLSR) are hexacoordinate complexes of trivalent lanthanide metals with chiral 1,3–diketones **317**. The complexes are Lewis acids capable of forming weak association complexes with organic bases. The first reported[129] use of an achiral lanthanide shift reagent was in 1969 when the proton signals of cholesterol were shifted by tris–3–(dipivaloylmethanato)europium (III).



317 **318**

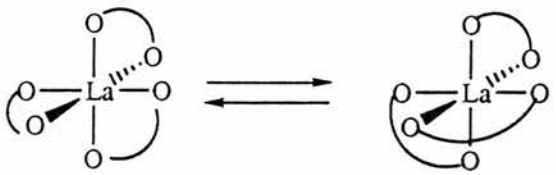
The interest of chemists was aroused by the report[130] of an induced shift ($\Delta\delta$) in the ^{1}H NMR spectrum. The magnitude of this $\Delta\delta$ was shown to be directly dependent on the distance of the proton from the alcoholic binding site of *n*–hexanol on complexation with this compound. The induced shift represented the difference between the normal ^{1}H NMR chemical shifts and the complex shifts $\delta^1(\Delta\delta+\delta^1=\delta)$ in ppm.

The first reported application of CLSR was in 1970 when Whitesides[131] and Lewis prepared tris–(3–pivaloyl–d–camphorato)europium (III) and produced different shifts ($\Delta\Delta\delta$) in the different enantiomers of racemic α–phenylethanol **319** and α–phenylethylamine **320** as well as the $\Delta\delta$ shift.



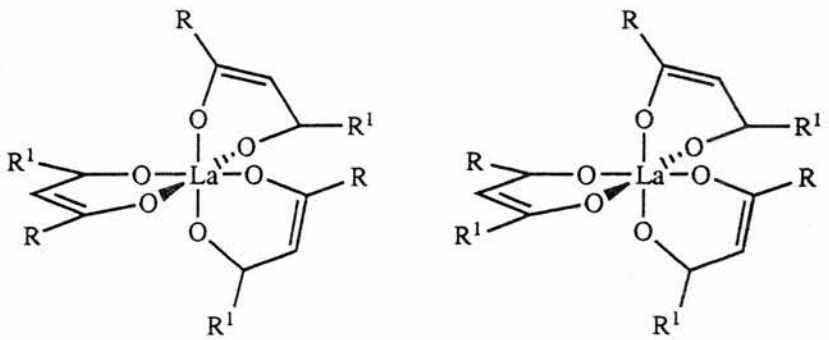
319 **320**

The structure of CLSRs have been investigated and they are known to exist in two isomeric forms **321** and **322** which interconvert too rapidly to be detected on the NMR timescale at –100°C.[132, 133]



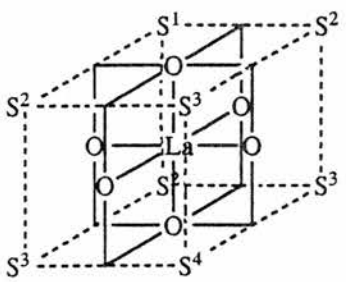
321 **322**

The chiral nature of the 1,3–diketone leads to the existence of cis and trans isomers **323** and **324** of each diasteromeric form.



323 **324**

The result of this property is the existence of 16 different potential donor binding sites, as each of the 4 diastereomeric CLSR isomers posses 4 potential donor binding sites. The structure is made even more complex by the



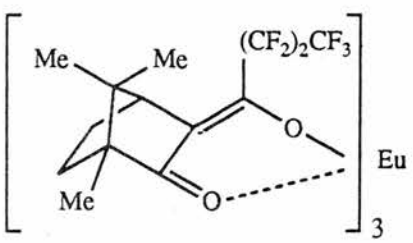
325

existence of donor CLSR complexes in more than a 1:1 ratio[134] which have been observed to exchange on the NMR time scale.[135] The above considerations do not normally affect the use of CLSR as the induced shift $\Delta\Delta\delta$ is the only factor of interest. The processes should however be kept in mind as they can generate misleading results if neglected.[134]

The mechanism of action of CLSRs was suggested to be two fold by McCreary and co–workers in 1974.[136] The first and dominant factor is the different stabilities of the diastereomeric complexes formed by the CLSR and a racemic mixture. This will cause the more stable collection of diastereomeric complexes to exhibit a larger induced shift than the less stable group. The second factor arises from the requirement that each diastereomer must form complexes of different geometry which implies different induced shifts through angular and distance factors. Both of the above factors operate and the exact contribution of each can not be evaluated due to the complex nature of the processes mentioned above.

(b) Chiral Shift Experiment on Aziridine **313**

The chiral shift reagent used to determine the e.e. of this chiral aziridine was tris[3–(heptafluoropropylhydroxymethylene)–(+)–camphorato]europium (III) derivative **326**.



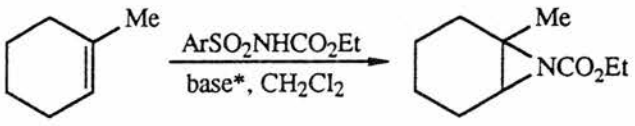
326

When 40% of the shift reagent was added to the racemic aziridine **313** the aziridine H was shifted from δ2.4 to δ4.4 and split into two equal size

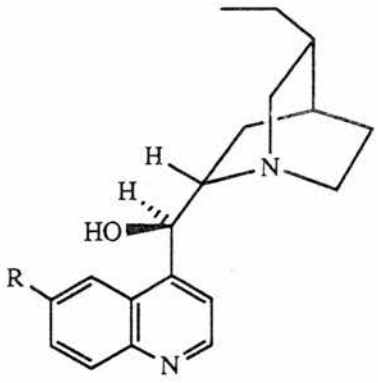
peaks. The methyl group signal was shifted from δ1.5 to δ2.4 and split into two equal size peaks. In the case of the chiral aziridines , the aziridine signal which was shifted to δ4.4 was used to determine the e.e. as this signal was the clearest.

6. Homogeneous Asymmmetric Aziridination

Taking account of the results above, the asymmetric aziridination reaction was carried out using 1–methylcyclohexene as the alkene and the dihydrocinchona alkaloids as bases. The components were stirred at room temperature in dichloromethane and after washing with water and evaporation the product was isolated by column chromatography.

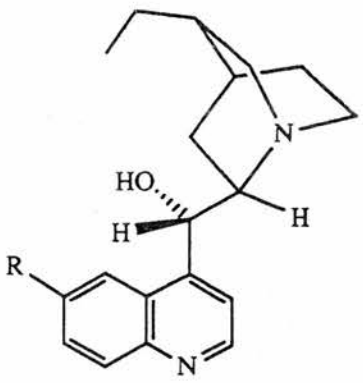


313



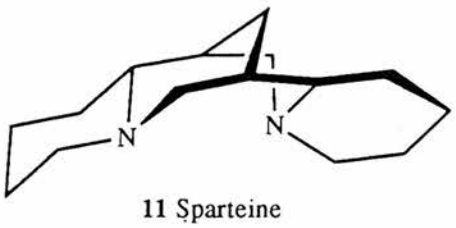
327 (8S,9R)–Dihydroquinine (R=OMe)

329 Dihydrocinchonidine (R=H)



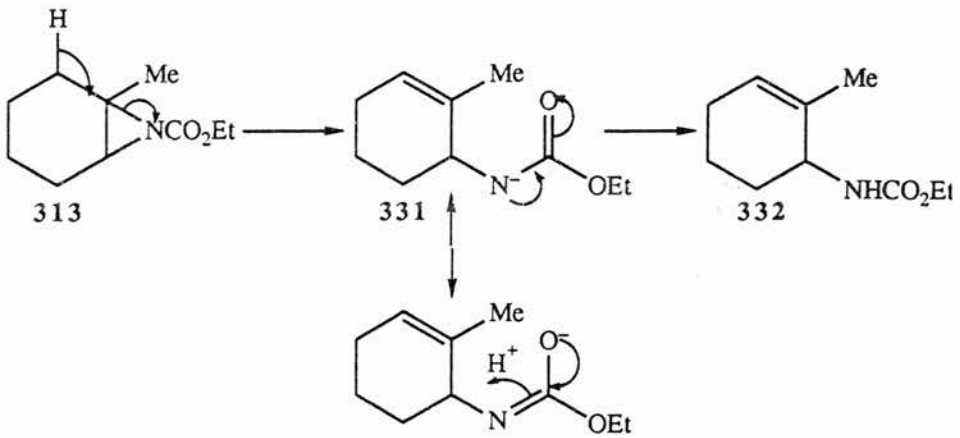
328 (8R,9S)–Dihydroquinidine (R=OMe)

330 Dihydrocinchonine (R=H)



11 Sparteine

All the reactions gave the aziridine as the main product until the batch of silica gel used for the column chromatography was changed, resulting in 6–ethoxycarbonylamino–1–methylcyclohexene **332** being produced. By taking the NMR before and after the column chromatography it was established that this was a result of a rearrangement ocurring on the column and not the product of an insertion reaction. This rearangement has been reported[102] by Takeuchi while looking at the acetic acid catalysed ring opening of aziridines. The rearrangement will be aided by the stabilising effect of the ester group. Using flash silica gel eliminated this rearrangement and produced only the aziridine as the main product.



The table of results (Table 3) shows that the yields of the reaction can vary quite considerably, but were generally about 20%. All the products showed some signs of optical activity, either a small rotation or a small difference in the NMR peaks of a chiral shift experiment.

Table 3

Base	Alkaloid /mmol	Alkene /mmol	282 /mmol	CH_2Cl_2 /ml	Yield of 313	Optical Rotation or e.e.*
327	10.1	42	10	10	37%	+0.55°
328	10.1	42	10.1	10	25%	5% e.e.
330	12.5	33.9	10	85	26%	+0.2°
330	10.9	42	10	10	68%	–0.2°
329	10	33.9	9.9	10	12%	5% e.e.
11	12.4	33.9	10.1	85	38%	0°
11	10.8	33.9	10	10	16%	0°

*Optical rotation values are estimated to be correct to ±0.05° and % e.e. values from chiral shift NMR experiments are estimated to be ±2%.

There was a contradiction in the rotations observed in the two dihydrocinchonine mediated experiments. However when the concentration of the aziridine was varied, a variation in the rotation was also observed. This variation corresponds with the observed result i.e. at high concentration the rotation is more positive even changing its sign.

Table 4 Rotation of **306** as a function of concentration

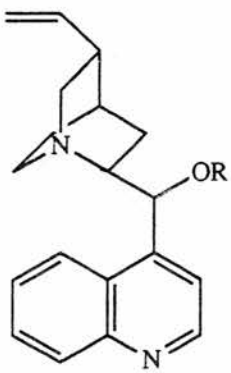
c	$[\alpha]_D$
3.2	+0.2°
2	–0.1°
1	–0.2°

Although rotations and differences in the chiral shift NMR were observed these differences are small and not really outwith the errors involved in these

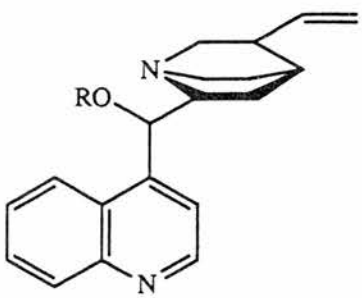
techniques. Therefore it cannot be said with any degree of certainty that chirality is being induced and even if there is some chirality transfer the values are so small that as a means of asymmetric synthesis it is not a viable reaction.

The results seem to suggest that the proposed transition state is either not being formed or does not have any influence on the nitrene addition reaction.

One thing that could have an influence on the selectivity obtained is the concentration of the reactants. These were varied as shown in the table but with little effect. Another thing that can influence the selectivity is the low energy conformation of the alkaloid. Wynberg[137] has studied the low energy conformation of the alkaloid in solution and has proposed two possible conformations: a closed conformation **333** where the quinoline portion is in front of the the nitrogen of the quinuclidine or an open conformation **334** where the quinoline ring is pointing away from it.



333 Closed

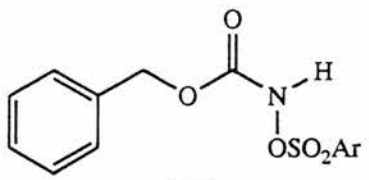


334 Open

Which conformation the alkaloid exists in depends on the R group. When the R group is acetyl the alkaloid is in the open conformation and when the R group is hydrogen the alkaloid is in the closed conformation. Therefore *O*–acetyldihydroquinine was used as the base so that both conformations of the alkaloid had been tried. This gave the same result as before so this factor was not influencing the reaction.

A completely different alkaloid was used as the base to see if the effect of structure plays a part in the reaction. However using sparteine as the base did not improve the selectivity of the reaction (Table 3).

Another way of improving the selectivity of the reaction is to increase the amount of steric bulk on the reactants. The new nitrene precursor **335** was synthesised and used in the reaction. However even with triethylamine this did not give the aziridine as the product but a mixture of other compounds.

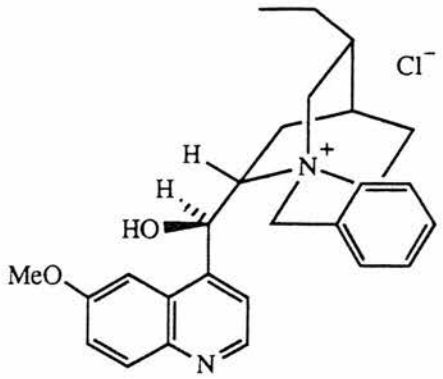


335

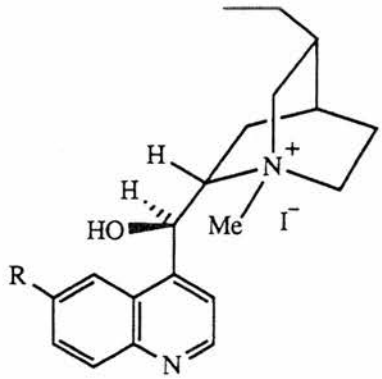
7. Phase Transfer Aziridination

The achiral reaction using benzyltriethylammonium chloride as the phase transfer catalyst was carried out on cyclohexene and 1-methylcyclohexene as a control reaction. Both alkenes produced the corresponding aziridine in 51% and 13% isolated yield respectively.

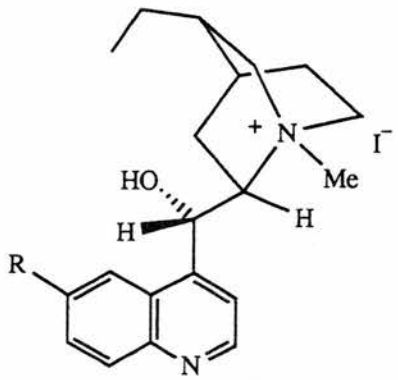
The reaction was now carried out under the phase transfer conditions reported by Seno using the hydrogenated salts of the cinchona alkaloids as catalysts. These were readily formed by simple reaction of the hydrogenated alkaloids with either methyl iodide or benzyl chloride.



336 Benzyldihydroquininium Chloride



337 Methyldihydroquininium Iodide (R=OMe)



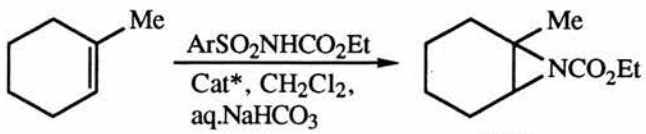
338 Methyldihydroquinidinium Iodide (R=OMe)

339 Methyldihydrocinchonidinium Iodide (R=H)

340 Methyldihydrocinchoninium Iodide (R=H)

The benzyldihydroquininium chloride salt **336**, used initially, gave no reaction when sodium bicarbonate, sodium carbonate, or sodium hydroxide were used as the bases. This was thought to be due to the alkaloid being too crowded with the bulky benzyl group preventing formation of an ion pair.

The methyl iodide salts **337–340** are less crowded molecules and they did produce the aziridine under the reaction conditions. The results show small optical rotations equivalent to about 5% e.e. The e.e. was either measured by rotation or chiral shift NMR. As in the homogeneous reaction the selectivities are not large enough to claim that chirality is being induced in the reaction.



313

Table 5

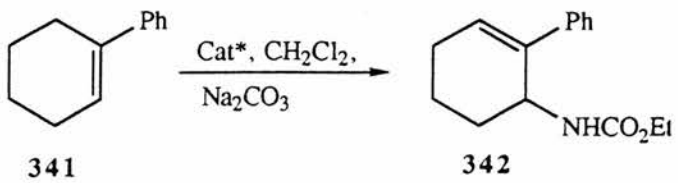
Catalyst	Cat Conc /mmol	Alkene conc /mmol	282 /mmol	CH_2Cl_2 /ml	Yield of 313	Optical rotation or e.e.*
337	1.1	11.8	10	100	10%	+1.35°
337	2.7	33.9	10.1	10	25%	+1.75°
338	2.9	33.9	10.5	120	51%	+0.33°
338	2.1	33.9	10.7	10	15%	+0.64°
340	10.4	33.9	11.1	85	13%	0°
340	2.3	33.9	9.8	10	32%	5% e.e.
339	9.4	33.9	10	85	48%	+0.46°
339	2.3	33.9	9.7	10	7%	5% e.e.

*See table 3.

To try and improve the selectivities of the reaction the concentration was varied, however this had no effect on the selectivities of the reaction.

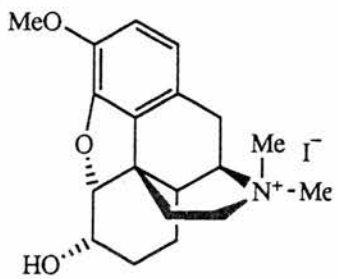
Another thing that might effect the selectivity of the reaction is the amount of steric bulk on the reactants therefore the reaction was carried out using 1–phenylcyclohexene **341** which might also introduce additional π interaction between the aromatic rings present. This gave the amine **342** as the major product of the reaction with no trace of the aziridine. From an NMR of the crude reaction mixture it could be seen that the amine **342** was the initial product of the reaction and not a product of rearrangement on the chromatography column as before. It is not clear if this is a product of insertion, as the substrate is not too dissimilar to styrene, or whether the

aziridine forms and then rearranges because of the extra strain in the molecule.



341 **342**

A different alkaloid was used to see if this would improve the selectivity of the reaction. The methyl iodide salt of dihydrocodeine was made **343** (the salts of dihydrothebainone, buprenorphine and oxycodone could not be made) and used as a phase transfer catalyst in the aziridination of 1–methylcyclohexene. Again no improvement was obtained in the selectivity.



343

During the course of our work another group published[123] a brief study involving addition of ethoxycarbonylnitrene to styrene and 1–methylcyclohexene using the PTC conditions with *N*–benzylcinchonidinium chloride as catalyst. As in our study no significant e.e. was achieved.

8. Conclusions

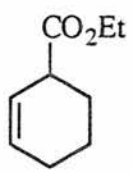
The asymmetric addition reaction of nitrenes to double bonds mediated by the alkaloids depends on the formation of a chiral transition state. This would then lead to the formation of one enantiomer in preference to the other.

Having tried several variables, concentration, steric bulk and catalyst structure, all with little success two possible conclusions can be drawn. Either the desired transition state is formed but does not induce a sufficient degree of selectivity in the reaction or the nitrene reacts with the alkene outwith the influence of the alkaloid i.e. the aziridination reaction occurs only once the free nitrene has diffused away from the alkaloid complex. Having tried several variables which might affect the transition state formed, with no improvement in the selectivity, we can probably conclude that the latter is the case.

To obtain an asymmetric reaction some method is needed to hold the reactants and alkaloid together. One such method might be to have a metal present. The cinchona alkaloids can easily be attached to metals by the vinyl group or the hydroxy group this would leave the nitrogen of the alkaloid free to catalyse the reaction.

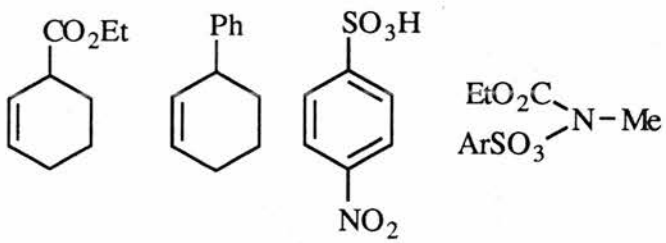
9. Further Work

In the reaction the problem appears to be the ability of the reactants to bind together in a tight transition state. Thus one possible area of further work is to use alkenes which contain a carbonyl group such as **344** which could *H*–bond to the alkaloid. Metal centres such as rhodium, which has been successfully used for carbene reactions, could be used to bring all the reactants together in a tight transition state.



344

A study could be carried out into the possible *H*–bonding interactions between the nitrene precursor and the alkaloid and also between the alkenes and the alkaloid. By mixing the alkaloids in solution with such compounds as and then studying the changes in the NMR, IR, and UV spectra, an idea of the interactions that are occurring could be achieved.



344 **345** **346** **347**

B. Ring Opening of Epoxides

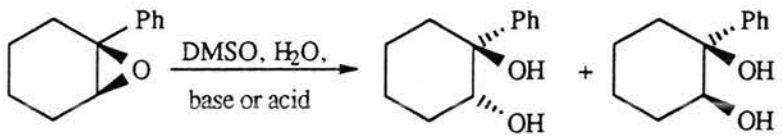
Epoxides are important intermediate molecules in organic chemistry and their formation and then ring opening can lead to several useful bifunctional molecules. To be able to carry out this reaction with stereocontrol is then an important goal for chemists.

1. Background

It is possible to hydrate epoxides directly with water using a high temperature of >100°. The reaction is highly dependent on the structure of the epoxide and lower temperatures may be used for certain epoxides.[138]

It is more usual to hydrate epoxides by using a base or an acid catalyst. Berti[139] has studied the base catalysed reaction and has found that the reaction is solvent dependent. It was found that the best solvent to use was DMSO which gave 60% hydrolysis in comparison with 10% hydrolysis when dioxane

was used. It was also found that some degree of stereocontrol could be achieved in the reaction by varying the DMSO concentration and the base used. When 85% DMSO in water was used with potassium hydroxide only the cis diol **350** was formed. In comparison the acid catalysed reaction gave the trans diol **349** when trichloroacetic acid was used.



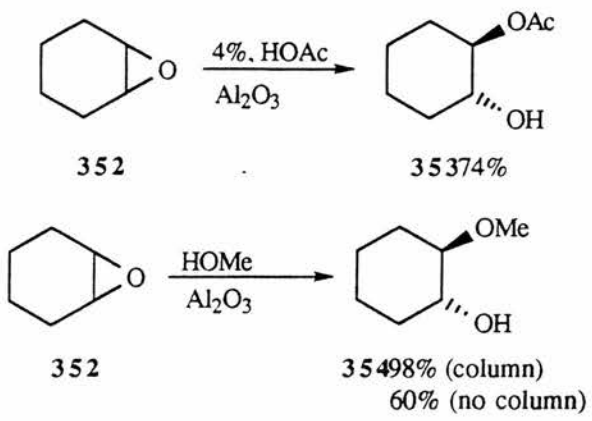
348 **349** **350**

The reaction depends on having the water, base and epoxide in the same phase therefore strong polar solvents are needed.

Epoxides can also react with alcohols or carboxylic acids to produce hydroxy ethers or esters **351** which are important molecules for the chemical industry. This reaction may be base or acid catalysed. It is possible to carry out the reaction at high temperature and pressure with no catalyst.

351

One of the most recent procedures for carrying out the base catalysed reactions has been reported by Posner[140]. In his procedure he uses the fact that organic molecules containing heteroatoms may be absorbed on to alumina which leads to the polarisation of the molecule as if the alumina was acting as a base. It would then be possible to bring reactant species together on the alumina thus creating a reaction under relatively mild conditions. Posner used this method to react epoxides with both alcohols and organic acids absorbed on alumina to produce **353** and **354**.



Posner[141] then went on to develop the reaction so that it could be carried out using a chromatography column packed with silica. In these reactions the epoxide reacts to give, exclusively, the cis product.

2. Asymmetric Ring Opening of Epoxides

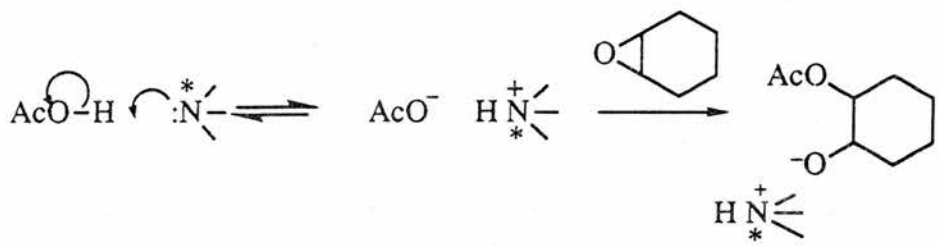
The only procedure reported so far on the catalytic asymmetric ring opening of epoxides is that of Belluci[142] who has used enzymes to open epoxides asymmetrically. Chiral epoxides can of course be ring opened with retention of configuration and this is the usual method for carrying out such reactions.

We thought that it might be possible to carry out the asymmetric ring opening of epoxides by using the chiral quaternary ammonium salts of the alkaloids as PTCs. The reaction was carried out using sodium bicarbonate, sodium carbonate and sodium hydroxide as the bases. However no reaction was observed presumably because of the need to keep the reaction in one phase as suggested by Berti.[139]

Posner[140] has shown that it is possible to react organic molecules which contain hetero atoms using alumina to polarise the heteroatom hydrogen bond. For example methanol can be used to open epoxide rings by absorbing the

methanol onto the alumina and thus polarising the molecule. The addition of an electrophile such as an epoxide would then lead to a reaction because of the alumina. Posner has applied this reaction with methanol, acetic acid and amines as the nucleophilic species.

We thought that it might be possible to use the alkaloids in place of the alumina to see if they could have the same polarising effect on the nucleophiles. In the reaction of methanol with the epoxide this would not be expected to work very well as the alkaloid is not a strong enough base to polarise the oxygen–hydrogen bond sufficiently to cause a reaction. However in the case of the acetic acid the alkaloid is capable of removing the more acidic proton and a reaction could occur. Enantioselectivity could then occur in the subsequent nonreversible stage of the reaction where the polarised group opens the epoxide ring. If a tight transition state occurs at this stage the enantioselectivity will occur.

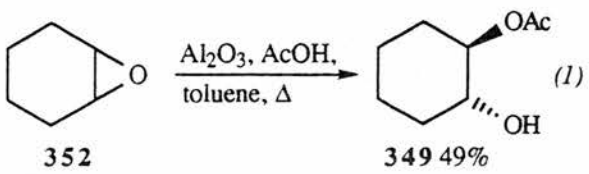


The interactions that can occur to ensure enantioselectivity are the formation of the ion pair and of *H*–bonding between the alkaloid and the epoxide.

Another possible way to introduce enantiocontrol is to absorb the alkaloid onto the alumina thus effectively creating a chiral alumina catalyst similar to those used in the hydrogenation reactions[83]. This combination of reactants may also lead to another possible mechanism whereby the alumina catalyses the addition of the alkaloid on to the epoxide ring as this has already been shown

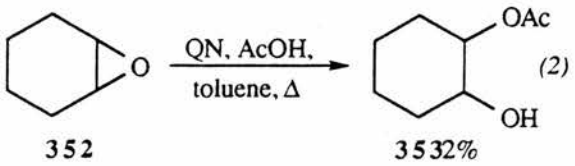
to occur for primary and secondary amines[140]. This however seems unlikely due to the steric bulk of the alkaloid.

Carrying out the reaction under the reported conditions using alumina, acetic acid and cyclohexene oxide initially gave no reaction. It was found that the reaction conditions needed to be dry before any reaction would occur. Thus cyclohexene oxide was heated under reflux with alumina and acetic acid using toluene as a solvent and Dean and Stark apparatus to remove water from the reaction. This produced **353** in 49% yield *(1)*. The trans configuration was assigned by comparison with the literature.[110]

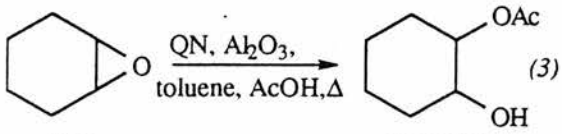


352 **349** 49% *(1)*

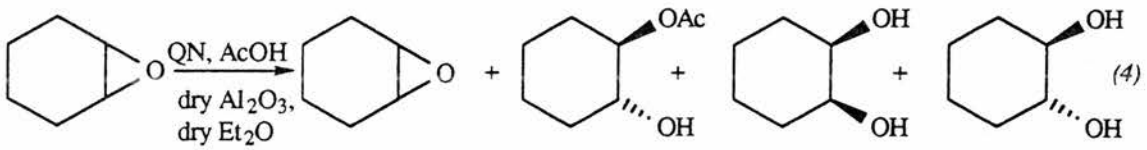
Replacing the alumina with quinine produced only a low yield of the product *(2)*. Carrying out the reaction using both alumina and quinine gave the best result for the reaction producing **353** in 67% yield *(3)*. However only a small rotation was observed. It was thought that this might be due to the high temperature used and so the reaction was repeated using dried alumina and dry ether at room temperature. This then gave a mixture of products. Not all the epoxide reacted and this was easily separated by distillation. This then left a mixture of cis **355** and trans **356** diols as well as the acetate **353** *(4)*. A small rotation was observed for the product mixture.



352 3532% *(2)*



352 35367% *(3)*

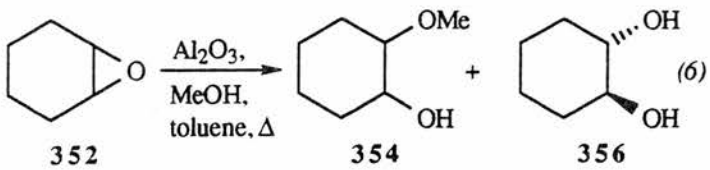


352 353 355 356 *(4)*

To increase the steric bulk of the reactant the reaction was carried out on norbornene oxide **357**. Boiling this epoxide with acetic acid and alumina in toluene while removing the water with the Dean and Stark apparatus for 24h produced only decomposition products of the epoxide *(5)* and no reaction was observed under less forcing conditions.

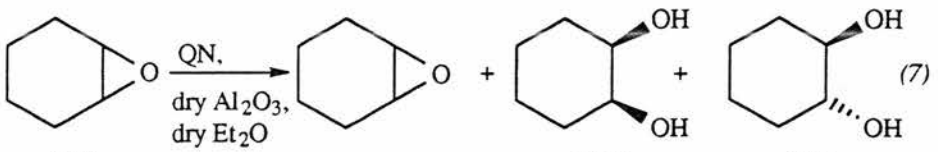
357 *(5)*

Reacting cyclohexene oxide with methanol, alumina and toluene under the Dean and Stark conditions gave a small amount of **354** and diol **356** *(6)*. No good method for the synthesis of **354** was found.



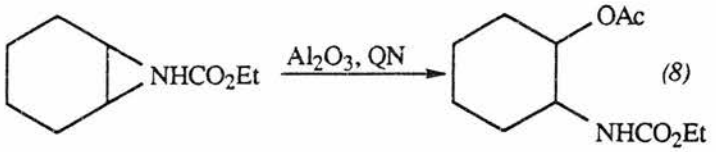
352 354 356 *(6)*

The unexpected formation of diols in the above reaction with acetic acid presumably by adventitious water led us to try our original idea of opening an epoxide to produce diols without adding water. Reacting cyclohexene epoxide with dry alumina and quinine gave a mixture of cis and trans diols with unreacted epoxide *(7)*. This gave no rotation which suggests that the rotation obtained in the acetic acid reaction was due to the acetate and not the diols.



352 355 356

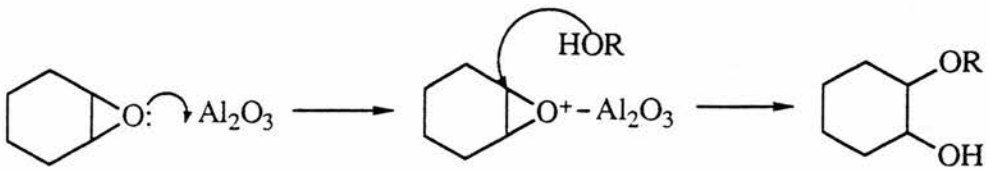
The reaction of acetic acid with achiral aziridine **312** catalysed by alumina and quinine produced a mixture of **358** and **312** with no selectivity. Methanol did not react with the aziridine under these conditions.



312 358

3. Further Work

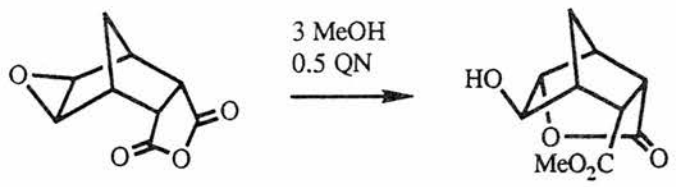
In the reaction one possible mechanism has not been discussed and that is the Lewis acid catalysed reaction. In this case the alumina polarises the epoxide by interaction with the oxygen rather than the alcohol as suggested by Posner. Nucleophilic attack by ROH then leads to ring opening. If this is the case then chiral Lewis acids might be worth investigating for this reaction.



C. Ring Opening of Anhydrides by Morphine Alkaloids

As described in the Introduction, the cinchona alkaloids have been by far the most widely used for asymmetric synthesis. In contrast the morphine based alkaloids have only been used in isolated cases. A number of non–toxic and readily available alkaloids of the morphine group were therefore evaluated as asymmetric catalysts.[143]

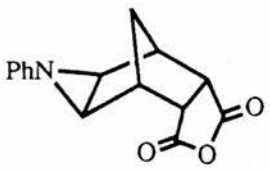
Previous work in this laboratory led to the development of an asymmetric ring opening of meso anhydrides to produce optically active mono esters of the diacid. As a result of these detailed studies effective procedures for the reaction of **257**, **259**, **261**, **263** and **359** were developed.[90, 91] These are summarised below:



257

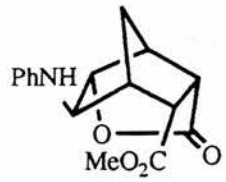
258(b) 57% 76% e.e. recrystalis'n 35% >99% e.e.

[Other enantiomer not available in high e.e.]



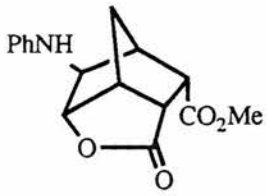
259

3 MeOH
0.5 QN

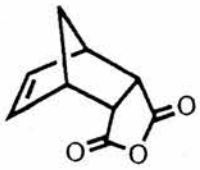


260(a) 74% 65% e.e.

3 MeOH
0.5 QD



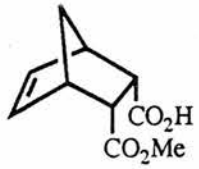
260(b) 95% 71% e.e.



261

[20g scale]

3 MeOH
0.5 QN

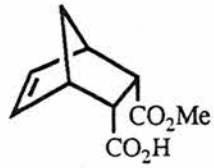


262(b) 88%
55% e.e.

recrystalis'n

48%
88% e.e.

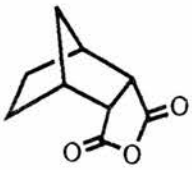
3 MeOH
0.1 QD



262(a) 97%
52% e.e.

recrystalis'n

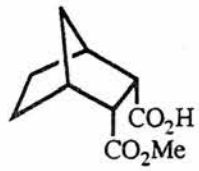
52%
93% e.e.



263

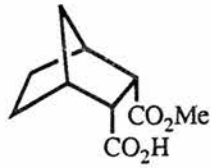
[0.5 equiv. catalysts
not examined]

3 MeOH
0.1 QN



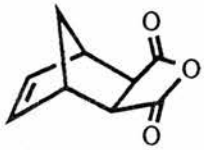
264(a) 82% 35% e.e.

3 MeOH
0.1 QD



264(b) 80% 44% e.e.

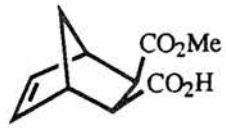
[Enantiomer enrichment
not examined]



359

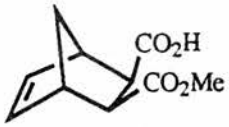
[20g scale]

3 MeOH
0.5 QN



360(a) 91% 58% e.e.

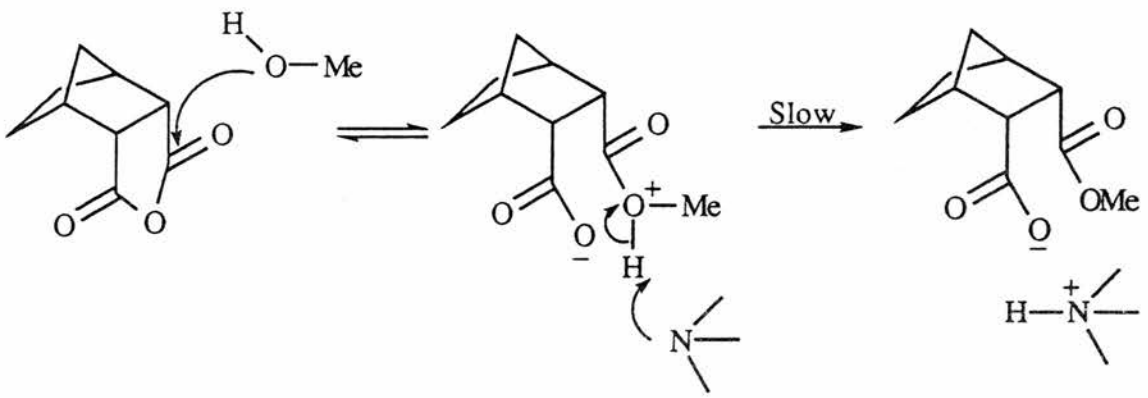
3 MeOH
0.5 QD



360(b) 88% 67% e.e.

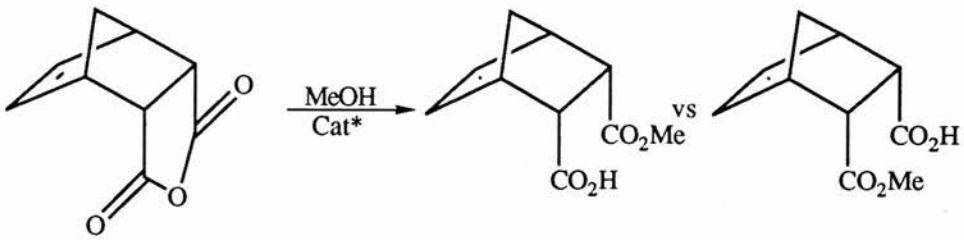
[Oils : enantiomeric enrichment not possible]

Studies by Oda carried out into the kinetics of the alcohol ring opening reaction have shown that the reaction proceeds via general base catalysis by the quinuclidine moitey. A possible mechanism for the reaction is then reversible nucleophilic addition of the methanol opening the anhydride. The next step is the general base catalysed removal of a proton. This step will be the rate determining step of the reaction. The transition state formed here will then be the important one for chirality transfer. The H–bonding along with the ion pair will ensure that a tight transition state is formed and that chirality transfer occurs. The final step in the reaction is the fast transfer of a proton from the alkaloid to the acid.



1. Opening of a Tricyclic Anhydride

One problem that existed with this reaction was the difficulty in separating and reusing the alkaloid. The best method for achieving this was to wash with dilute acid, but as the ester is acid sensitive this has to be done quickly . We thought that it would be possible to use the alkaloid–alumina system used previously so that the alkaloid could be filtered off with the alumina. Several solvent systems were used for this reaction but the alkaloid always stayed in solution.



261 **262(a)** **262(b)**

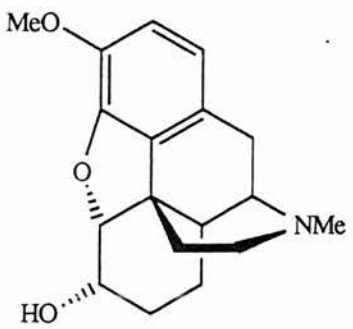
Table 6

Cat*	Optical Yield From Rotation	e.e. From Salt 365	Major Enantiomer
Quinine	85%	44%	**262(b)**
Cinchonine–Alumina		19%	**262(a)**
361	7%	5%	**262(a)**
362	54%		**262(b)**
363	54%		**262(b)**
364	12%	11%	**262(a)**

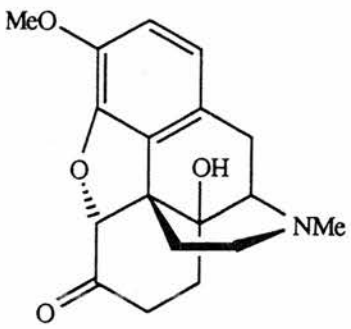
The optical yields of **262** were determined after recrystallisation which will have enhanced the optical yield. The recrystallisation was necessary to insure that all the alkaloid had been removed. The optical yield was calculated from the rotation by comparison with the known rotation of 1.27°[90].

The morphine alkaloids dihydrocodeine **361**, oxycodone **362**, buprenorphine **363** and dihydrothebainone **364** were also used in the reaction without the alumina to compare their results with those of the cinchona

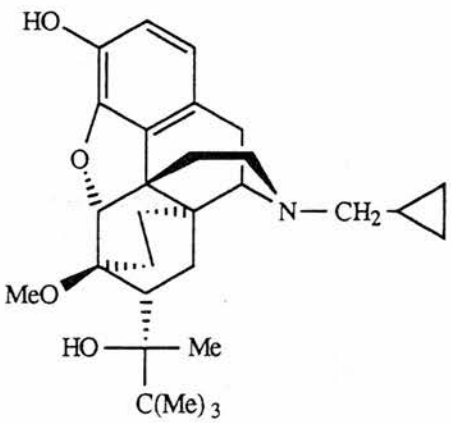
alkaloids. These alkaloids gave poorer selectivities although they all produced some enantioselectivity (Table 6).



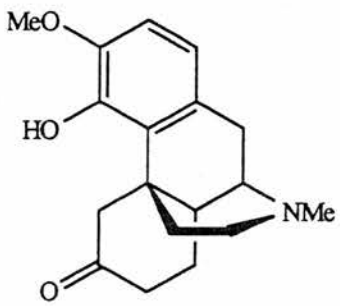
3 6 1 Dihydrocodeine



3 6 2 Oxycodone



3 6 3 Buprenorphine

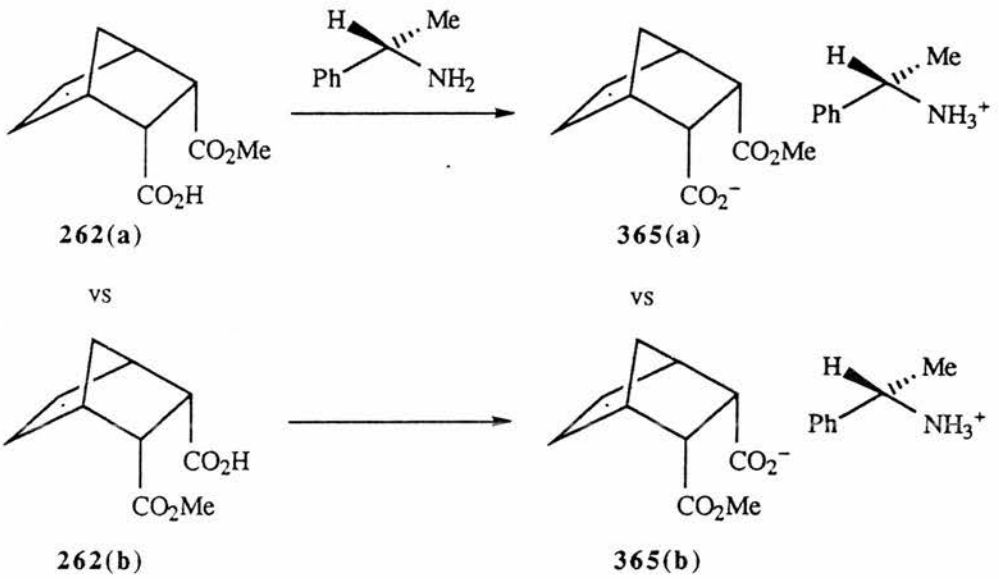


3 6 4 Dihydrothebainone

2. Determination of e.e. of **262** Using Diastereomeric salts

An important method for determing the e.e. of a compound is to convert the compound into a diastereomer. The diastereomers have different physical properties allowing the different amounts of each enantiomer to be determined. One method for determining the e.e. is to measure the difference in the NMR signals.

This technique was used to determine the e.e. of the monoester of the diacid **262**. The diastereomeric salt **365** was made from the acid group by reacting it with S–(–)–α–phenylethylamine.

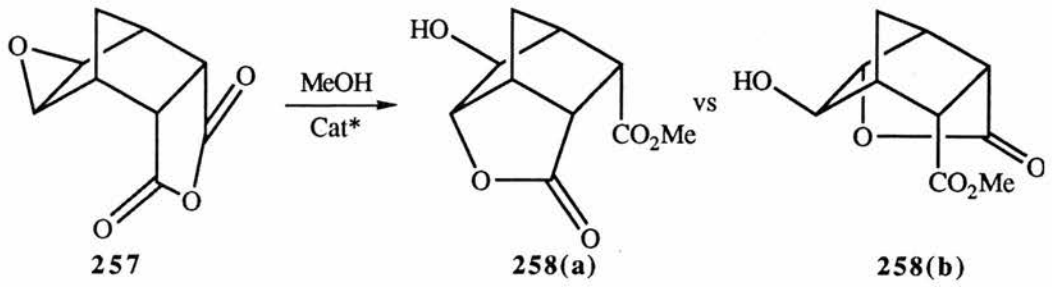


The diastereomeric salt showed two different peaks in the ^{1}H NMR for the methyl group protons.

3. Opening of a Tetracyclic Epoxy Anhydride

Another reaction that has previously been studied in this laboratory is the ring opening of a tetracyclic epoxy anhydride **257** to give the lactone **258** with up to 99% e.e.

The morphine alkaloids oxycodone **331**, dihydrocodeine **330** and dihydrothebainone **333** were assessed for this reaction to compare them with the cinchona alkaloids.



257 **258(a)** **258(b)**

The new alkaloids gave optical activities of up to 10% e.e. (Table 7) and this does not compare favourably with the cinchona alkaloids. However the reaction could be developed, as the reaction conditions used were the same conditions that were used for the cinchona alkaloids. One problem that arose from this was that not all the alkaloid could be removed from the product.

Table 7

Alkaloid	e.e	Major Enantiomer
362	9.7%	**258(a)**
361	10%	**258(b)**
364	9.7%	**258(b)**

One interesting feature of these results is that oxycodone gave the opposite product enantiomer to the other alkaloids.

4. Determination of the e.e. of **258**

The e.e. of lactone **258** was determined by chiral lanthanide shift reagent $Eu(hfc)_3$ which shifted the methyl hydrogen signal from δ3.6 to δ4.1 splitting it into two signals, one for each enantiomer. previous work done in the research group had assigned the higher frequency signal to enantiomer **258(a)** and the lower frequency signal to enantiomer **258(b)**. This then

allowed the configuration of the products obtained from the new catalysts to be assigned.

5. Further Work

The reactions of the morphine based alkaloids have given some interesting results. These reactions were carried out using the conditions developed for the cinchona alkaloids and so the reaction needs to be developed especially for the removal of the alkaloids.

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