ABSTRACT

A New System for Catalytic Asymmetric Epoxidation

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This thesis concerns the catalytic asymmetric synthesis of epoxides. An introduction highlights the utility of chiral epoxides in asymmetric synthesis. The important methods that have been developed towards the construction of this influential functional group are also described.

The second chapter is dedicated to our efforts to synthesise chiral organic catalysts for asymmetric epoxidation. The first part of this chapter starts with the investigation of chiral imines and the corresponding oxaziridines, followed by positively charged systems that include: Transient iminium species, formamidinium and oxazolinium salts, acyclic aldiminium and cyclic ketiminium salts as precursors to the electrophilic oxaziridinium entity.

The remaining part of this chapter deals with the synthesis of enantiopure dihydroisoquinolinium salts as catalysts for asymmetric epoxidation. The most successful appear to be those with a chiral residue which is attached to the exocyclic carbon-nitrogen bond. An enantiomeric excess of 73% is obtained for the epoxidation of *trans*-stilbene.

This is a new catalyst motif previously unreported, and is readily accessed in virtually two steps. Multigram quantities of a wide variety of catalysts proved easy to obtain since, the developed route does not involve chromatography at any of the stages, is rapid and inexpensive. Aminoalcohols derived from chiral aminoacids and terpenes, were also successful as catalyst precursors and thus, a significant library of mediators was prepared. Due to the catalytic system being rather unexplored, a full optimisation study was undertaken to establish which factors and to what extent influnce the enantioselectivity of the process. The synthesis of catalysts from chiral isochromans and other cyclic benzylic ethers of different size and nature was also investigated. This chapter concludes with a few suggestions for future researchers in this area.

The third chapter is the experimental section and is dedicated to the methods of synthesis and characterisation of the compounds mentioned in the previous chapter. More than fifty of these are novel compounds.

X-Ray reports regarding the crystallographic represantation of the structure of selected compounds are provided in the first appendix. Additional NMR data are provided in the second appendix.

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"Ψυχαιον σπηνθηρα δυσιν κρασας, νω και νευματι θειο, ομονοιαις τε, εφ οις τριτον, ερωτα αγνον συνδετικον παντων επιβητορα σεμνον, εθηκεν."

ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
AcOH	acetic acid
$[\alpha]_D$	specific optical rotation at the sodium line
aq.	aqueous
Ar	aryl
BINAP	binaphthalene
BINOL	binaphthol
BITET	bitetralene
Bn	benzyl
Boc	tertiary butoxycarbonyl
b.p.	boiling point
^{n}Bu	normal butyl
^{t}Bu	tertiary butyl
°C	degrees Celsius
c	concentration
CASH	camphor-sulfonyl-hydrazone
cat.	catalyst (catalytic amount)
CDI	carbonyl diimidazole
cm^{-1}	wavenumber
conc.	concentrated
CPI	camphor-phosphinoyl-imine
δ	chemical shift
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
de	diastereoisomeric excess
DET	diethyl tartrate
DIPT	diisopropyl tartrate
DMF	dimethyl formamide
DMSO-d_6	dimethyl sulfoxide (deuteriated)
ee	enantiomeric excess
EtOH	ethanol
hfc	hexafluorobutyrylcamphorate
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
g	gram(s)

IR	infra red
J	coupling constant
LDA	lithium diisopropylamide
M	molar
MCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	megahertz
mmol	millimole(s)
mL	millilitre(s)
m.p.	melting point
m/z	mass to charge ratio
NCA	N-carboxyanhydride
NMR	nuclear magnetic resonance
Nu	nucleophile
n.O.e.	nuclear Overhauser effect
Pd/C	palladium on charcoal
Ph	phenyl
PhIO	iodosylbenzene
ppm	parts per million
^{i}Pr	isopropyl
psi	pound per square inch
quat.	quaternary
R	alkyl
RAMP	(*R*)-1-amino-2-(methoxymethyl)-pyrrolidine
salen	salicylideneaminato ligand
S_N2	nucleophilic substitution (bimolecular)
S_N1	nucleophilic substitution (unimolecular)
TBAF	tetrabutylammonium fluoride
TBHP	tertiary butyl hydroperoxide
TfO	trifluoromethanosulfonate
THF	tetrahydrofuran
TLC	thin layer chromatography
TPP	triphenyl phosphine
w/v	weight per volume

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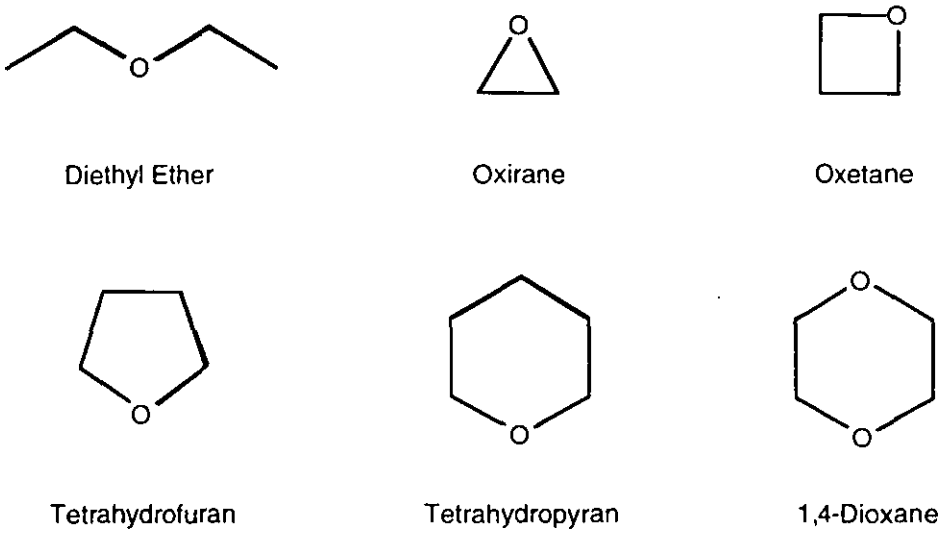
CHAPTER 1

INTRODUCTION

1.1 Epoxides, general considerations.

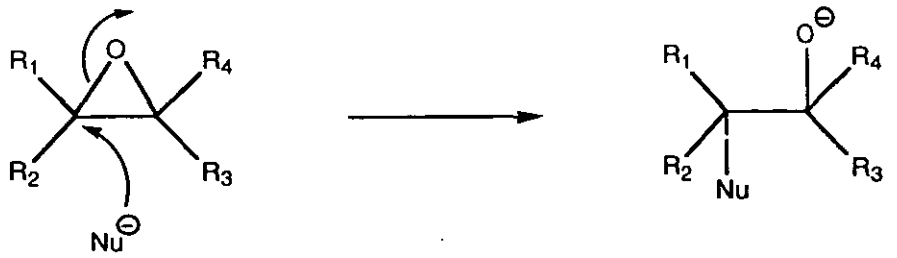
Epoxides, also known as oxiranes, constitute a special class of the family of cyclic ethers. These reactive heterocycles consist of a three membered ring containing two carbon atoms and one oxygen atom. Non-cyclic and cyclic ethers of greater sizes than four membered rings, such as diethyl ether, tetrahydrofuran and 1,4-dioxane, are normally unreactive, and for this reason they have found use as solvents in organic chemistry.



Scheme 1: Members of the family of ethers.

In large contrast, oxiranes are particularly reactive molecules and have long been regarded as remarkably versatile intermediates in synthetic organic chemistry. The reactivity exhibited by the epoxides is inherent in the strain associated with the three membered ring, where the angles between the carbon-carbon-oxygen and carbon-oxygen-carbon bonds are closer to 60° rather than 109° that is expected for tetrahedral carbon or oxygen atoms. Therefore, most reactions concerned with the epoxide functionality involve ring opening of the heterocycle, the relief of that strain being the driving force.

The addition of nucleophiles to epoxides to form 1,2-disubstituted products is one of the most well studied reactions in organic chemistry.[1-7] Epoxides can be ring opened by a variety of nucleophiles. These include oxygen compounds (water, alcohols, phenols), nitrogen compounds (amines, derivatives of amines, azide, isocyanates), acids (hydrogen halides, hydrogen cyanide, sulfonic acids, carboxylic acids), sulfur compounds (sulfides, thiols, thiophenols thioacids), and various carbon nuclephiles.



Scheme 2: Ring opening of epoxides is a facile process due to the relief of strain.

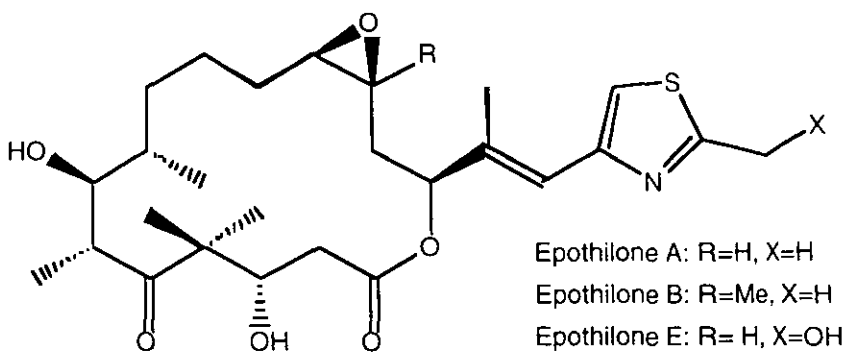
More importantly, these reactions can occur in either neutral, basic or acidic media. The products are usually the corresponding alcohols.

This property of epoxides, namely to react with substantially diverse reagents under a variety of conditions, establishes them as important molecules not only in organic chemistry but also in biological systems.

1.2 Epoxides in natural products and biological systems.

Oxiranes are widely distributed in nature and are of biochemical and biosynthetic/mechanistic interest.[8]

The epothilones are a growing class of naturally occuring antitumor agents,[9-11] whose importance is clearly reflected in the increasing number of publications reporting approaches to their total synthesis,[12-17] analogue construction,[18,19] and biological activity.[19,20] Their name is derived from the three key functionalities present: epoxide, thiazole and ketone (Scheme 3).



Scheme 3: The epothilones display remarkable cytotoxicity against leukaemic cells.

Although, in such polyfunctional systems, a single functional group is not usually responsible for the observed biological activity, epothilone B was more

efficient against lymphoblastic leukaemic cells than the de-oxy derivative (the analogue without the epoxy oxygen atom). Epothilone B treatment was also the most effective against the same type of cells that had survived treatment with taxol, vinblastine or etoposide.[19] This makes epothilone B the most active anti-cancer drug discovered to date.

The epoxide functionality is also present in various antibiotics such as caspimycin,[21,22] one of the few natural compounds which contain the perhydroindacane core (Figure 1).

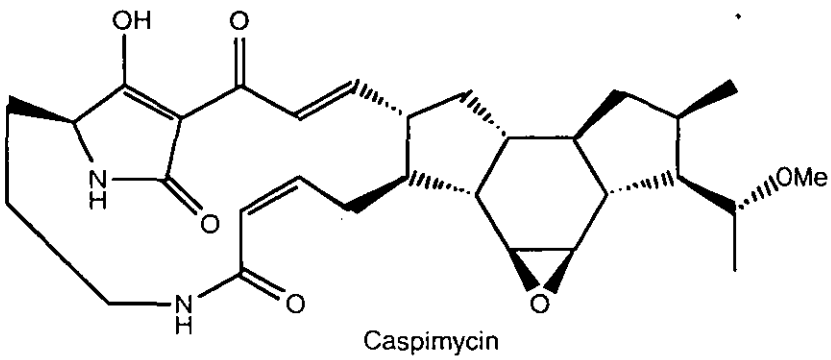
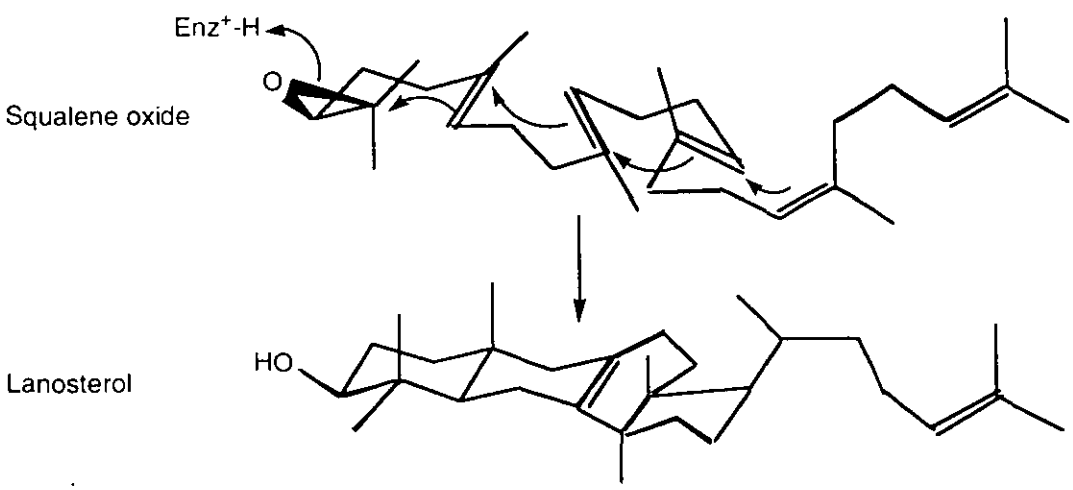


Figure 1: Caspimycin is another natural product which contains the epoxide functionality and has significant biological properties.

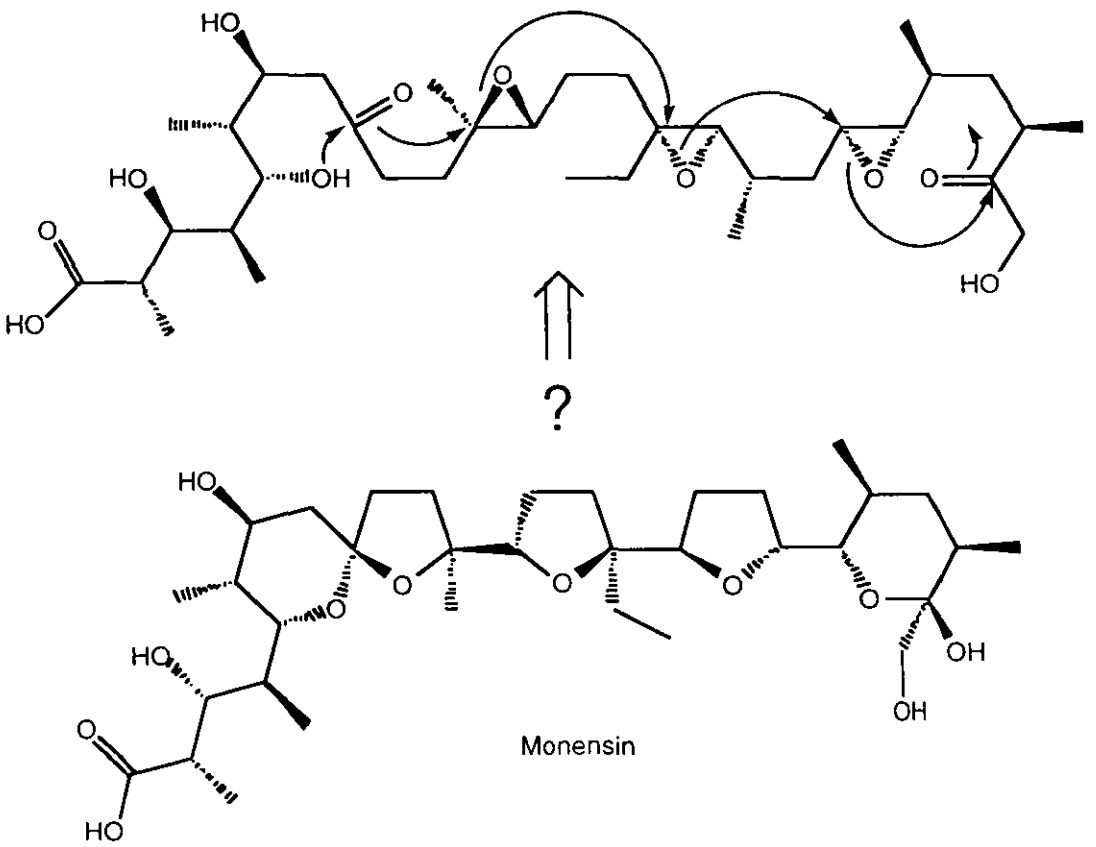
Squalene oxide (upper molecule in scheme 4) offers another example on the importance of the oxirane functionality in nature.



Scheme 4: Squalene oxide is the precursor to steroids.

The synthesis of lanosterol (Scheme 4) is thought to proceed through tandem cyclisation of the unsaturated moieties in squalene oxide, with concomitant ring opening of the epoxide followed by a series of charge migrations.[525,526] Lanosterol is probably the exclusive precursor of cholesterol and other steroid hormones including testosterone, progesterone, oestrone and cortisone.[23,24]

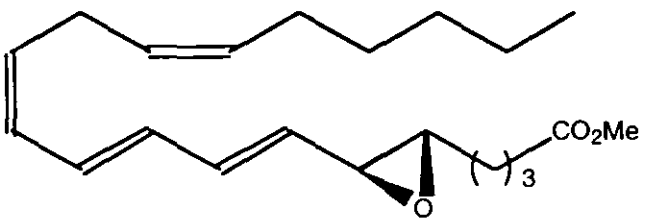
The biosynthesis of monensin,[25] has also been proposed to take place through a similar pathway from the appropriate intermediate(s) (Scheme 5).[26]



Scheme 5: Monensin is thought to be accessed by a tandem ring opening/polycyclisation reaction of the appropriately positioned epoxides.

For a long time it has been known that the ultimate carcinogenic metabolites of polycyclic aromatic hydrocarbons are the corresponding tetrahydrodiol epoxides,[27,28] and that an allene oxide is the precursor to preclavunone A.[29] Recent reports on the action of oxiranes within organisms revealed that epoxides react not only stereospecifically but at specific sites. These sites were identified as the N-7-guanine in human DNA and the N-terminal valine in human haemoglobin.[30,31] Furthermore, leukotriene A (LTA) is the biogenetic precursor of the leukotrienes

LTC, LTD and LTE, which are important natural mediators of allergic asthma (Scheme 6).[32] An epoxide is one of the two functionalities present in the antibiotic fosfomycin (Scheme 6).[33]

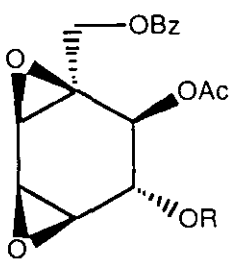


Leukotriene A_4 methyl ester (LTA_4)

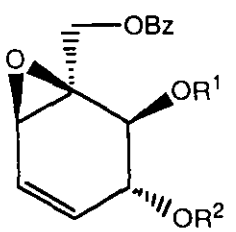
Fosfomycin

Scheme 6: Biologically active molecules that contain the epoxide functionality.

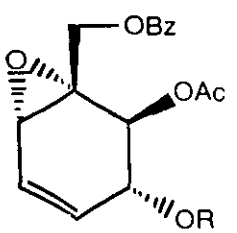
Naturally occurring cyclohexane epoxides have also attracted considerable attention due to their unusual structures and biogenesis. (+)-Crotepoxide and (+)-boesenoxide are members which possess a *bis*-epoxide functionality (Figure 2). The former was shown to display tumour-inhibitory activity against Lewis lung carcinoma in mice and Walker intramuscular carcinosarcoma in rats.[34]



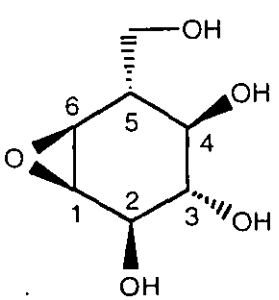
(+)-Crotepoxide: R= Ac
(+)-Boesenoxide: R=Bz



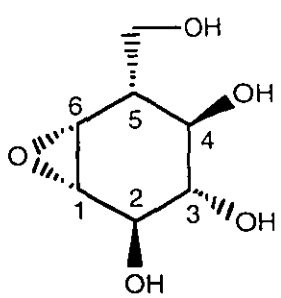
(+)-β-Senepoxide: R^1= R^2= Ac
(+)-Pipoxide: R^1= H, R^2= Bz



(−)-Senepoxide: R= Ac
(+)-Tingtanoxide: R= Bz



(1R,6S)-Cyclophellitol



(1S,6R)-Cyclophellitol

Figure 2: Naturally occuring cyclohexane based epoxides. The *bis*-epoxides are unusual.

At roughly the same time, (+)-pipoxide and (–)-senepoxide were isolated and shown to exhibit tumour-inhibitory, antileukaemic and antibiotic activity (Figure 2).[35,36] Recently, two additional members of this family, (–)-tingtanoxide and (+)-β-senepoxide were discovered (Figure 2).[37] In addition, (1*R*,6*S*)-cyclophellitol and (1*S*,6*R*)-cyclophellitol have been demonstrated to be potent β-D- and α-D-glucosidase inhibitors respectively, presumably due to the structural resemblance to β-D- and α-D-glucose.[38,39] The increased interest in these compounds as therapeutic agents is reflected in the recent efforts towards their total syntheses.[40,41]

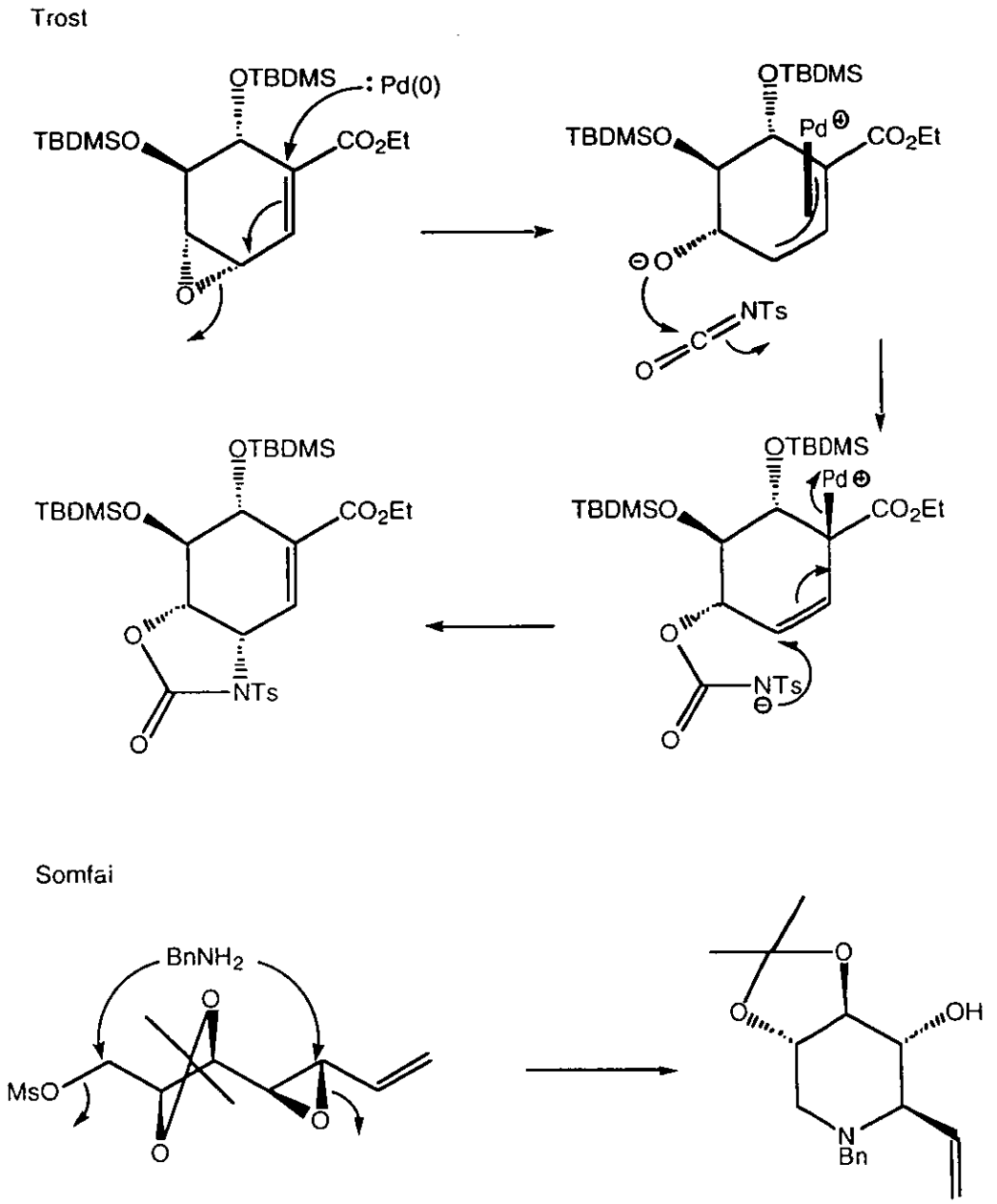
1.3 Epoxides as chiral building blocks.

No attempt will be made to cover all possible types of reactions to which epoxides can be subjected. Their usefulness as key intermediates in the construction of complicated and synthetically challenging molecules is well recognised.[42,43] As approximately 2000 articles have been published in the last four years (1994-1998) concerning the use of epoxides in organic transformations and biological studies, only representative reactions of epoxides will be mentioned. The context of these will be particularly focused on the most recent advances of epoxide chemistry in chiral systems because of the increasing demand for such compounds in the pharmaceutical, agrochemical and food industries.

No reaction of epoxides has been more thoroughly studied and used in synthesis than the nucleophilic ring opening of the fundamental heterocycle. It is generally agreed that this reaction follows an S_N2 mechanism with a backside attack on an epoxide carbon, resulting in Walden inversion at this centre. Normally, inversion occurs even in an acidic medium, arguing against an S_N1 mechanism with a free carbonium intermediate. Retention of configuration has been observed in some cases and this topic has been reviewed.[44]

However, a recent and particularly interesting example is that described by Trost, in the reaction of an α,β-unsaturated, cyclic epoxide with N-tosylisocyanate in the presence of palladium(0). The introduction of the nitrogen atom with retention of configuration viadouble inversion at the epoxide carbon was a key step in the synthesis of (+)-valienamine. Part of Trost's synthesis is depicted in scheme 7.[45]

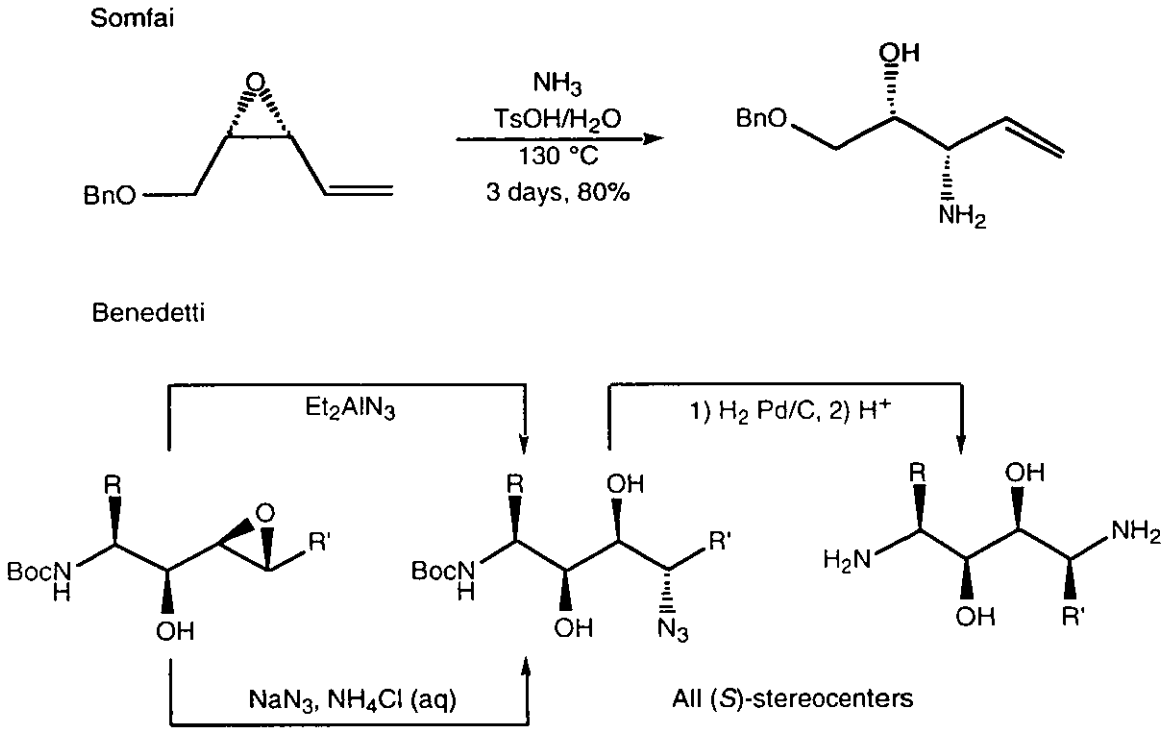
The closely related vinyl epoxides react normally however, to give products of inverted configuration at the attacked epoxide carbon. They also exhibit a high propensity to react with a variety of nucleophiles at the allylic epoxide carbon. This property of vinyl epoxides was successfully exploited by Somfai in the synthesis of (+)-deoxynojirimycin (Scheme 7).[46] The alternative mode of cyclisation to give the five membered ring was not observed.



Scheme 7: Ring opening of epoxides with overall retention and inversion of configuration.

The reaction between enantiopure epoxides and nitrogen nucleophiles to provide the important chiral building blocks 1,2-aminoalcohols, is a well established synthetic protocol. For primary 1,2-aminoalcohols, the ammonolysis of epoxides in liquid or aqueous ammonia is used, but it is usually slow even for the more reactive vinyl epoxides (Scheme 8).[47] More commonly, a buffered aqueous solution of sodium azide is employed followed by hydrogenation of the azido alcohol. A

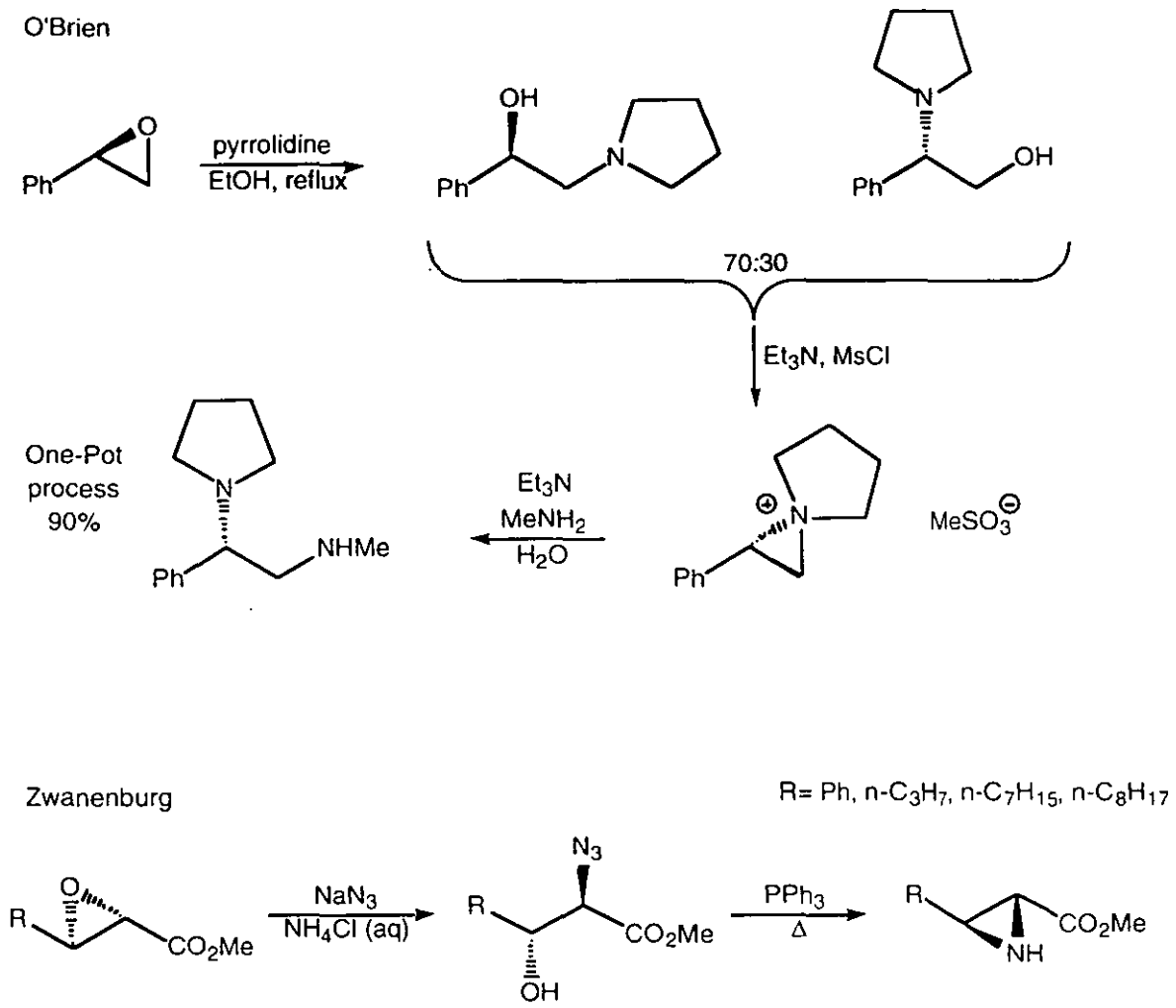
significant improvement in this area is the use of diethylaluminium azide, which also activates the epoxide ring by coordination to the epoxide oxygen, due the Lewis acid character of the aluminium reagent.[48] Routine hydrogenation of the 1,2-azidoalcohols furnishes the primary 1,2-amino alcohols (Scheme 8).



Scheme 8: Synthesis of chiral 1,2 aminoalcohols from epoxides.

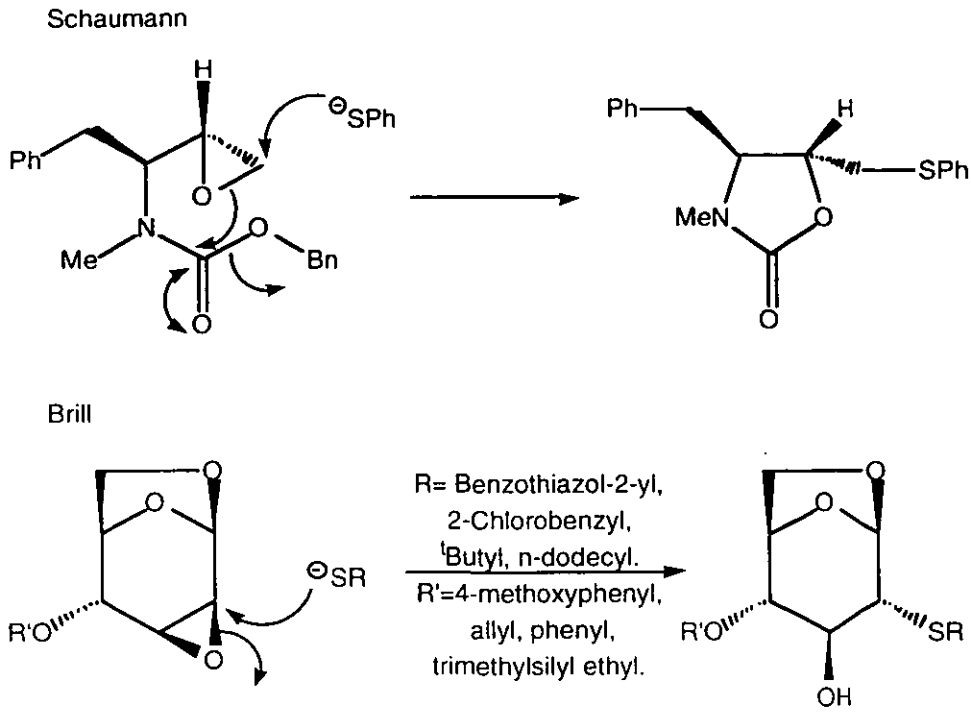
1,2-Diamines can also be prepared from epoxides by ring opening with a secondary amine followed by conversion of the hydroxyl moiety into a good leaving group. For example, mesylation of the alcohol leads to spontaneous intramolecular formation of an aziridinium intermediate which can be quenched with a primary amine (Scheme 9).[49]

Epoxides can also be converted into aziridines their nitrogen analogues. Aziridines are accessed through reaction of the epoxide with sodium azide followed by treatment of the intermediate 1,2-azidoalcohols with triphenylphosphine. The latter reaction is thought to procced *via* the Staudinger iminophosphorane intermediate (Ph_3P=N-), and gives aziridine with inversion at both former epoxy carbons (Scheme 9). This type of stepwise aziridination has been developed by Zwanenburg for the preparation of aziridines of α,β-unsaturated esters,[50,51,52] and by Somfai for the preparation of α-vinyl aziridines.[46]



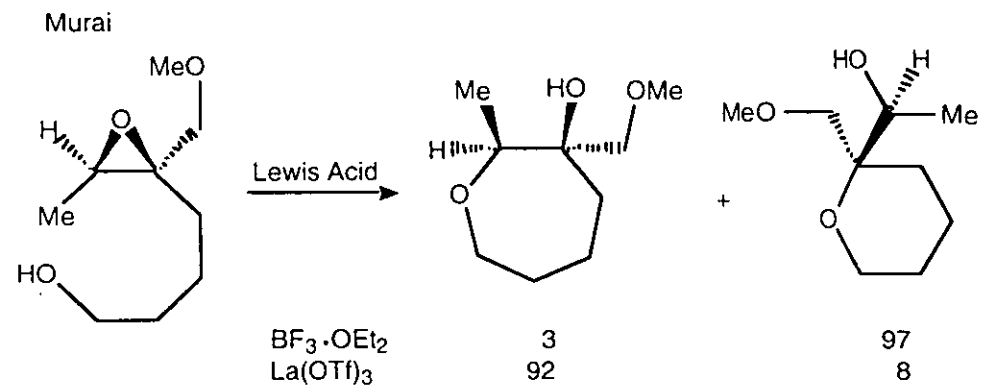
Scheme 9: Epoxides as precursors in the asymmetric synthesis of 1,2-diamines and aziridines.

Sulfides have also been used to induce ring-opening of epoxides with a great deal of regiocontrol. The examples provided by Schaumann on the synthesis of versatile chiral building blocks containing sulfides,[53] and the preparation of sulfur analogues of (–)-levoglucosan by Brill,[54] are classic entries in this area (Scheme 10). Interesting examples of reactions of sulfur and oxygen nucleophiles with 1,4-pentadiene-*bis*-epoxide were recently reported by Jung in the synthesis of L-2', 3'-dideoxyisonucleosides.[55]



Scheme 10: Regiospecific nucleophilic attack of thiols in the ring opening of epoxides.

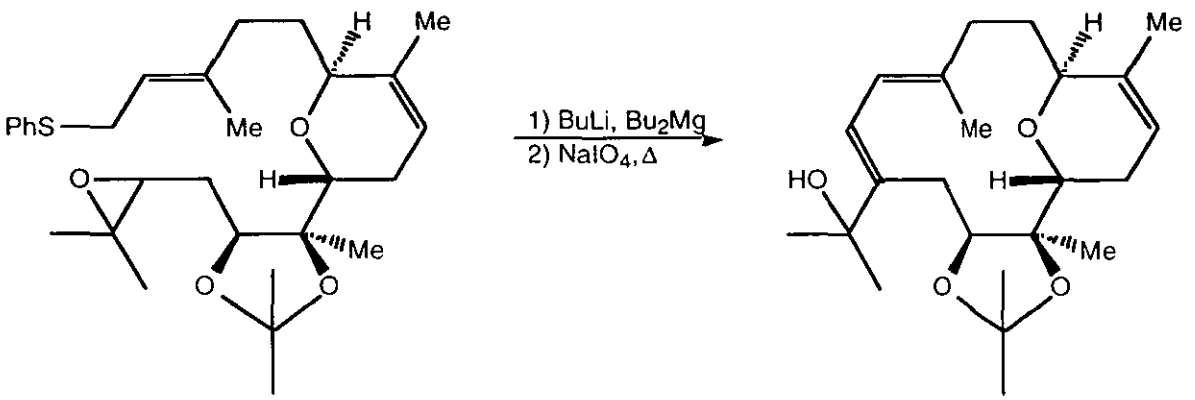
Oxygen nucleophiles are more commonly employed in the ring-opening of oxiranes in the presence of a Lewis acid. Styrene oxide was converted to the corresponding 1,2-hydroxyether (monoprotected diol) when treated with methanol in the presence of cerium(IV) triflate.[56] Intramolecular variants of this process have also been described and used for example by Murai for the formation of medium sized ring ethers (Scheme 11).[57]



Scheme 11: Synthesis of medium size rings by ring opening of epoxides with oxygen nucleophiles.

The choice of the Lewis acid appears to be crucial in determining which epoxide carbon is attacked and therefore the ring size of the product. For example, boron trifluoride etherate strongly favours formation of the cyclic ether with the smallest possible size, by an *exo* type of cyclisation, while the *endo* cyclisation pathway, which leads to higher ring sizes, is promoted by lanthanum(III) triflate possibly due to the larger co-ordination sphere involved.

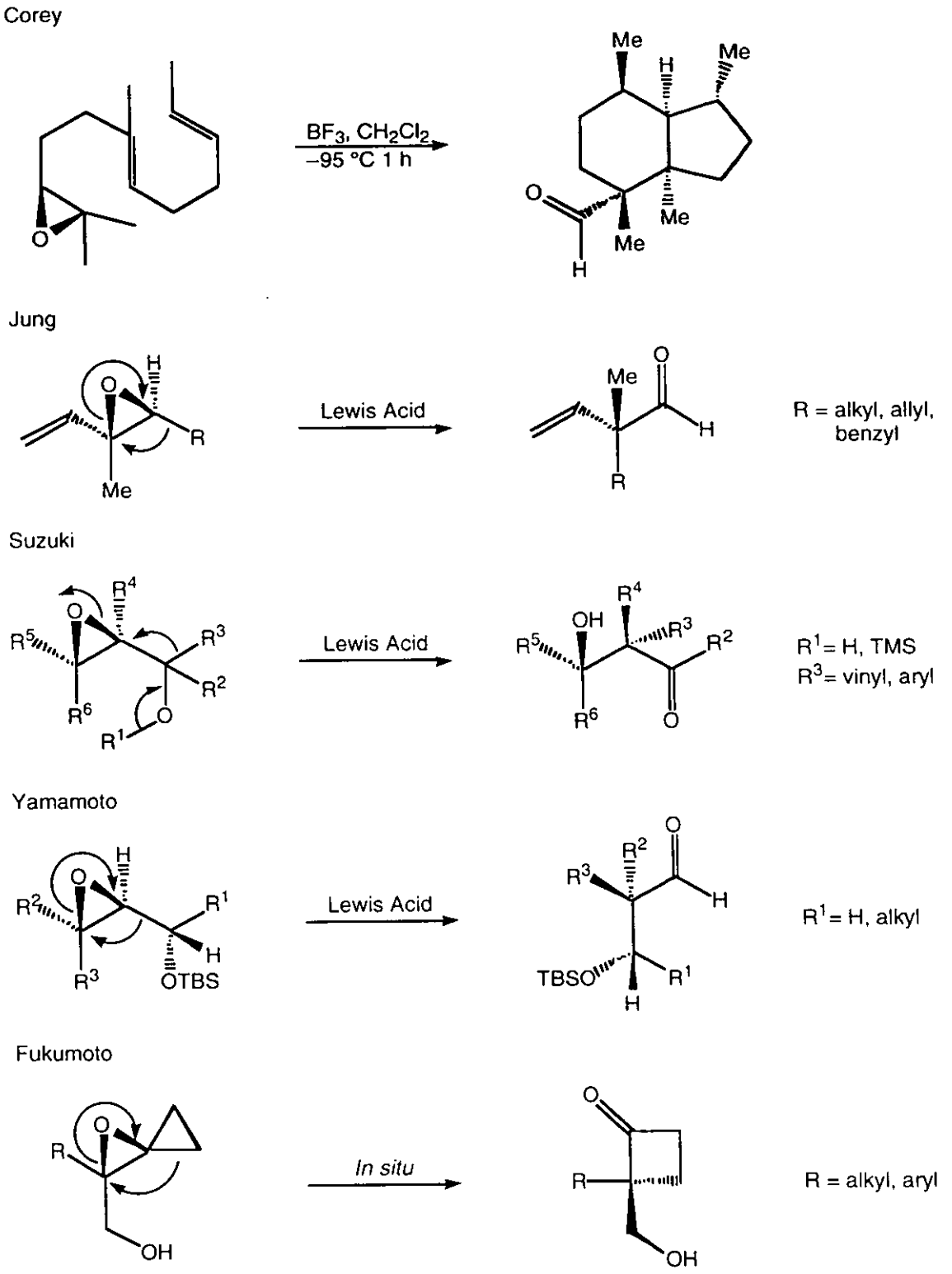
Nakata



Scheme 12: Construction of macrocycles *via* epoxide ring opening.

This method of medium size ring construction has been successfully applied to natural products synthesis in Nakata's approach to methyl sarcophytoate.[58] A carbanion was used as the internal nucleophile to access the 14-membered ring diene unit, needed as one of the components for a Diels-Alder reaction, in 76% yield (Scheme 12). Epoxide-mediated cyclisations are not always straight forward however. For example, Corey has reported a "remarkably complex and unpredictable cyclisation and rearrangement reaction of cations derived from unsaturated epoxides".[59] The carbonyl compounds obtained when these substrates are subjected to Lewis acids appear to be the end products of a series of group and charge migrations across the carbon skeleton (Scheme 13).

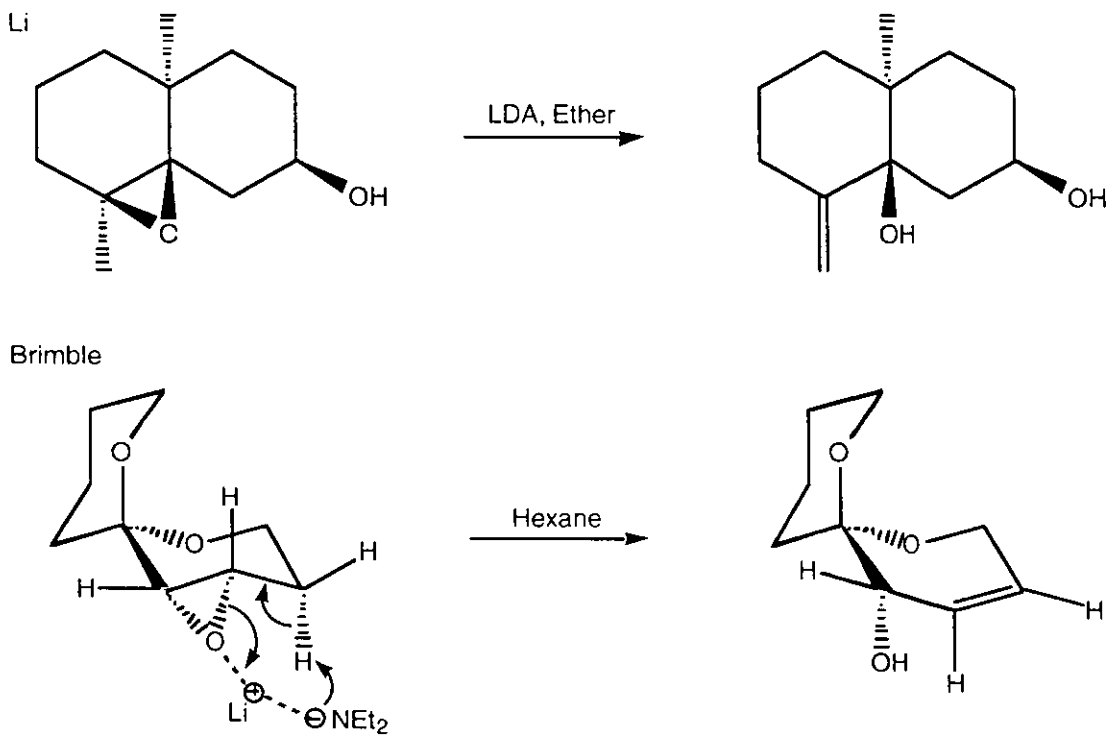
This work of Corey is nonetheless a special case. In general, rearrangements of epoxides to carbonyl compounds are not only very common but also allow predictability as to which substituent or group of substituents will migrate.[60] Such rearrangements have been thoroughly studied and can be subdivided into four groups: the Jung,[61] Suzuki,[62] Yamamoto,[63] and Fukumoto[64] variants (Scheme 13). In addition, all of these epoxide rearrangements have been used in the preparation of chiral intermediates for natural product synthesis.



Scheme 13: Synthetically useful rearrangements of epoxides.

The synthetic value of the rearrangements of epoxides to carbonyl compounds has received increased attention lately, and new methods have been developed to allow further reactions of the new carbonyl groups to take place *in situ*.[65,66]

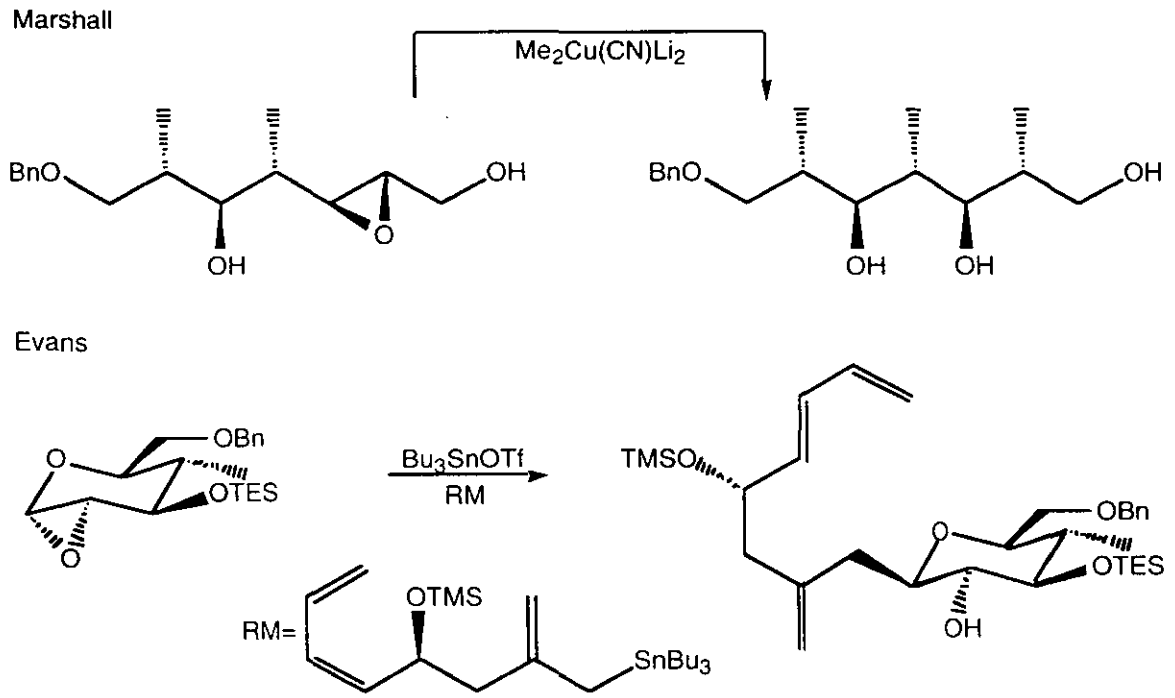
Two of the most common rearrangements of epoxides are the Payne rearrangement (see below under Sharpless asymmetric epoxidation), and their transformation into allylic alcohols. Upon treatment with base, one of the *syn*-β-protons, with respect to the epoxide oxygen, is abstracted followed by concerted ring opening of the oxirane. This reaction has been regularly employed to access chiral secondary or tertiary allylic alcohols. Recent examples of this rearrangement have been described by Li in the synthesis of (–)-4,10-*epi*-5β,11-dihydroxyeudesmane,[67] and by Brimble in the synthesis of oxygenated analogues of 1,7-dioxaspiroacetals which displayed herbicidal activity (Scheme 14).[68]



Scheme 14: The rearrangement of epoxides to allylic alcohols.

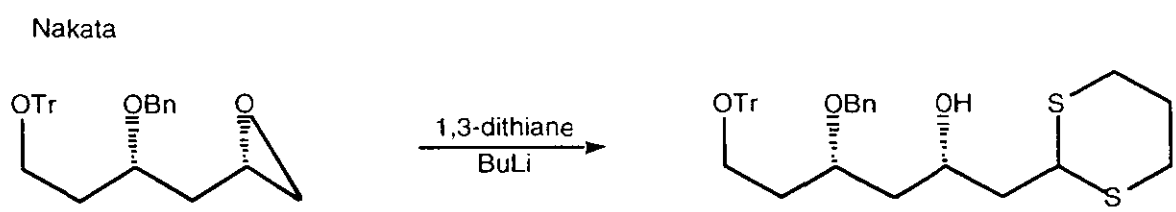
The ring opening of oxiranes with organometallic reagents is usually slow in the absence of a Lewis acid. The most common activators used are copper(I) salts, with the corresponding homocuprates or higher order cuprates being the active species.[69] In this reaction, the diversity tolerated in the nature of the carbon

nucleophile, allows the structure to range from simple alkyl to vinyl and branched allyl species. Marshall used the cuprate methodology to synthesise the C7-C16 and C21-C27 subunits present in zincophorin and rifamycin-S respectively (Scheme 15).[70] These entities were difficult to access otherwise, for example with reiterative aldol reactions. Evans found that allylic carbon nucleophiles work best when tributyltin triflate is used as the Lewis acid, and has used this technology to access the C39-C51 fragment of altohyrtin C (Scheme 15).[71]



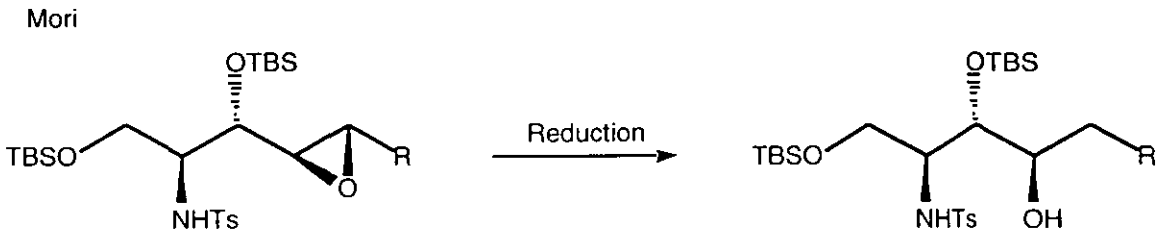
Scheme 15: Ring opening of oxiranes with organometallic reagents.

Nakata's approach to altohyrtins (spongistatins) was also based on ring opening of an epoxide with a carbon nucleophile (Scheme 16).[72] In this case, 2-lithio-1,3-dithiane was employed to attack the oxirane intermediate with excellent regiocontrol, thus allowing access to β-hydroxycarbonyl compounds.



Scheme 16: Epoxide ring opening with 1,3-dithiane, an acyl anion equivalent.

Reducing agents such as lithium metal, lithium aluminium hydride, DIBAL, tributyltin hydride and Red-Al™ can also be used for ring-opening of epoxides.[68,73] The resulting products are saturated alcohols which may not be accessible with the same degree of regiocontrol by hydroboration/oxidation of the parent alkene. This strategy was employed by Mori to access various types of phytoshingosines (Scheme 17), which are key intermediates in the synthesis of KRN7000, penazetidine A, and penaresidines A and B. All four of the latter natural products belong to the family of shingosine analogues.[74]



Scheme 17: Epoxide ring opening with reducing agents affords the saturated alcohol.

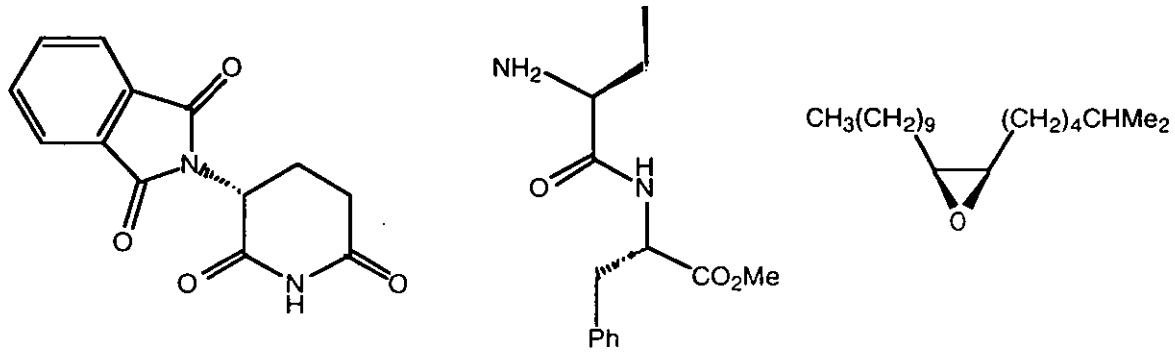
Among numerous other recent developments in epoxide chemistry, interesting advances include: the ruthenium(III) catalysed conversion to 1,3-dioxolanes,[75] the bismuth(III) and titanium(IV) catalysed conversion to thiiranes,[76,77] the use of epoxides as precursors to γ-spirolactones,[78] and the regio- and stereospecific ring opening of propargylic epoxides.[79]

The futher elaboration of epoxide chemistry is however beyond the scope of this discussion.

1.4 Asymmetric synthesis of epoxides.

Nature produces a variety of chiral compounds, examples of which include amino acids, carbohydrates and nucleotides. Larger systems that consist of such building blocks, for example enzymes, are chiral but may also possess intrinsic chirality due to their arrangement in space. The most celebrated example is the helix of DNA. In general, biological systems recognise the members of a pair of enantiomers as different compounds and consequently, different responses are realised. The sad case of thalidomide is well known. One of the enantiomers, (*R*), is a sedative while the other (*S*), is a teratogen (Figure 3). Unfortunately this drug was introduced to pregnant women in the racemic form. An example from the food industry, is the commercial sweetener aspartame which is a simple dipeptide (Figure 3). Sweetness is associated only with the isomer derived from the L-amino acids.

Disparlure is the gipsy moth pheromone responsible for the attraction of male to female species, and hence for the reproduction of the species (Figure 3). Minute concentrations of the natural enantiomer can be readily detected by the male species, while the unnatural enantiomer is not detected even when 10^6 times more concentrated samples are used.



(*R*)-Thalidomide Aspartame Disparlure

Figure 3: Enantiomers are recognised as different compounds by the invariably chiral receptors in biological systems.

Accordingly, as receptors are invariably chiral, public perception and associated legislation in the fields of pharmaceuticals, agrochemicals, and food additives demand single enantiomers. Because of this, there has been an explosive development in the field of asymmetric synthesis.

Enantioselective synthesis may be accomplished by resolution, separation of diastereoisomers, special chromatographic separation of enantiomers, or asymmetric synthesis. The latter may be achieved by chiral auxiliary methods or with chiral starting materials. More importantly, *catalytic* asymmetric synthesis is the most elegant and challenging approach and offers significant advantages over the other methods since a large number of stereogenic centers can be created by the use of a small amount of non-racemic catalyst. Catalytic asymmetric synthesis has also significant economic advantages over stoicheiometric methods (chiral reagents, auxiliaries and starting materials), in large scale syntheses.

Enantiopure epoxides are very important chiral building blocks because two stereogenic centers are associated with this functionality. As discussed above, these versatile heterocycles readily undergo stereo- and regiospecific ring opening, leading to a large variety of chiral products. It is therefore not surprising that a great deal of effort from laboratories around the globe has been, and continues to be,

dedicated to the asymmetric synthesis of oxiranes. As approximately 400 articles concerning the development of new, or modification of older, chiral epoxidation methods have been reported within the last four years (1994-1998), no attempt will be made to describe all of the approaches made. The chemical literature coverage here is particularly focused on catalytic asymmetric processes for the synthesis of epoxides, although some interesting aspects of stoicheiometric epoxidation methods are also discussed.

1.4.1 Peroxyacids.

The most common and simple method for the formation of oxiranes is the epoxidation of alkenes by peroxyacids (peracids). This reaction was first reported by Prileschajew in 1909.[80] The peroxy oxygen in the intramolecularly hydrogen bonded peracid is very electrophilic, and is attacked even by poor nucleophiles such as olefins. Consequently, the more electron rich the olefin the faster the epoxidation reaction. The transition state was initially described as planar or "butterfly".[81] Recent calculations however, have shown that the spiro transition state is energetically more favoured[485] (Figure 4), (see also below in dioxirane mediated epoxidations). The oxygen transfer step is concerted and stereospecific. Namely, both carbon-oxygen bonds are formed simultaneously and the geometry of alkene is retained in the epoxide product. That is, *cis* olefins give *cis* epoxides and *trans* olefins give *trans* epoxides.

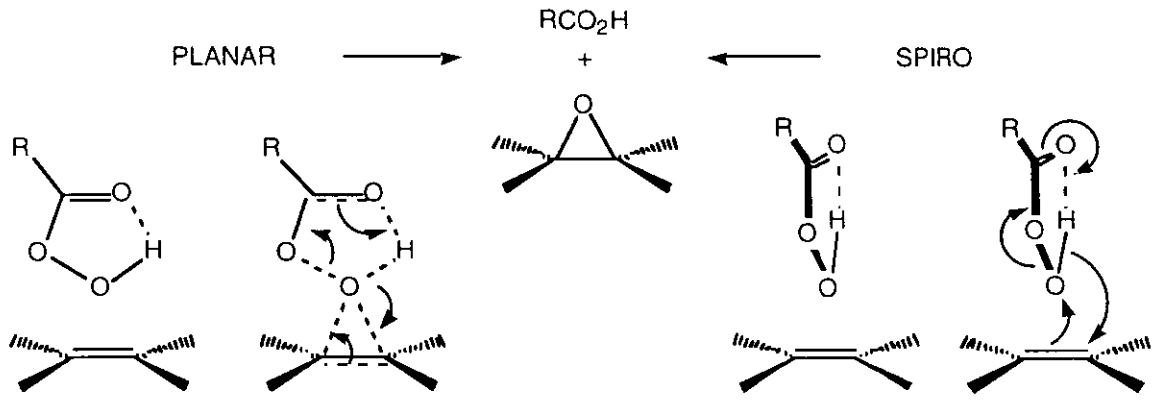
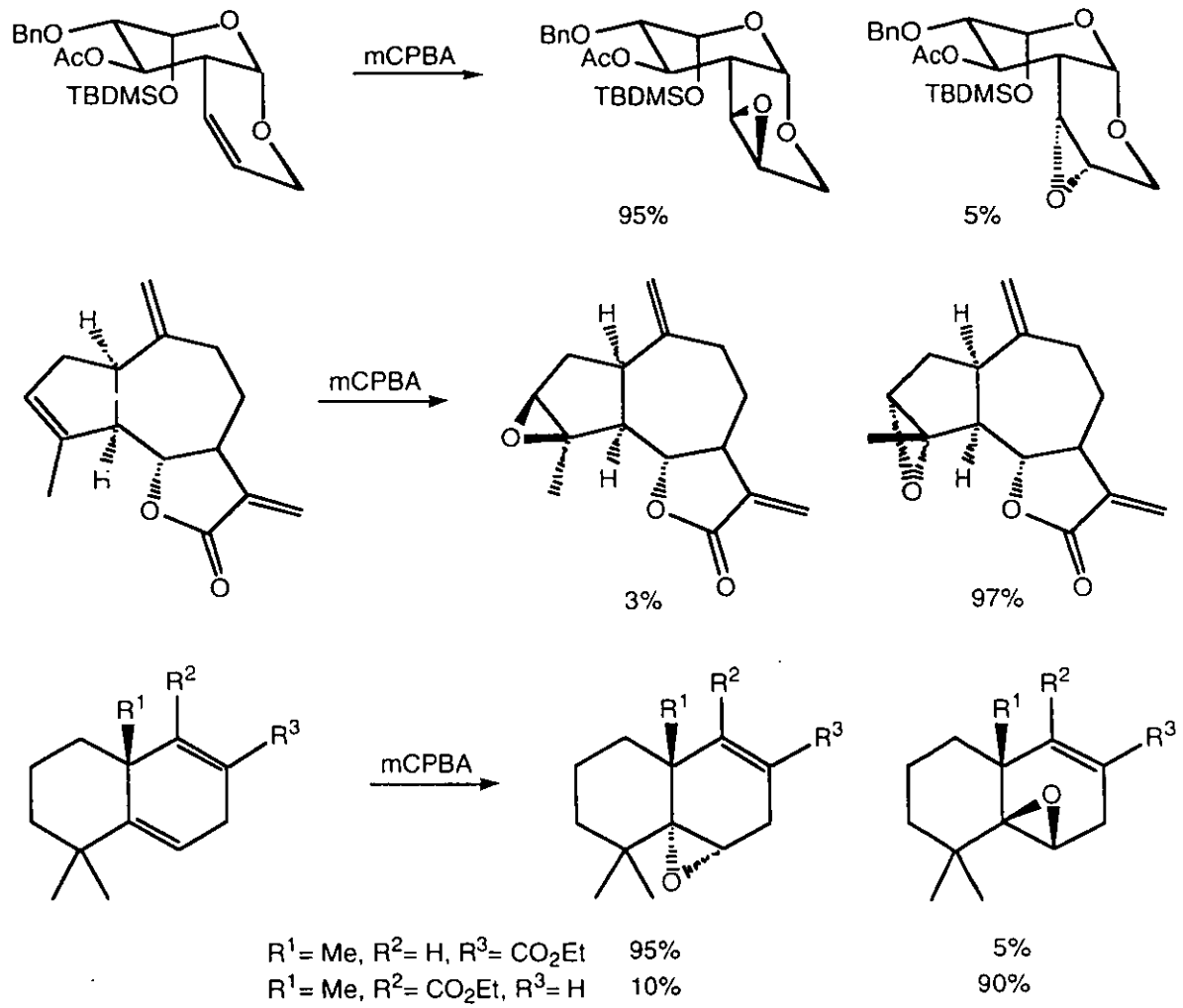


Figure 4: The planar and spiro transition states in the oxygen transfer from peracids to alkenes.

The peracid most often used for epoxidations is *meta*-chloroperoxybenzoic acid (mCPBA). When the two enantiotopic faces of an alkene are equally accessible to the oxidant, a racemic mixture of the corresponding enantiomers of the epoxide is

obtained. It is desirable however to control the reaction such that epoxidation occurs preferentially at one of the enantiotopic faces of the alkene. Since mCPBA is not chiral and therefore cannot discriminate between the two enantiotopic faces of the olefin, in this case asymmetric epoxidation can only be achieved when the alkene substrate bears directing groups. In this type of substrate, one of the faces of the double bond is shielded by a sterically demanding group, or there is a substituent which can interact electronically with the peracid, for example by means of hydrogen bonding (Scheme 18). This type of asymmetric synthesis is termed "substrate controlled".

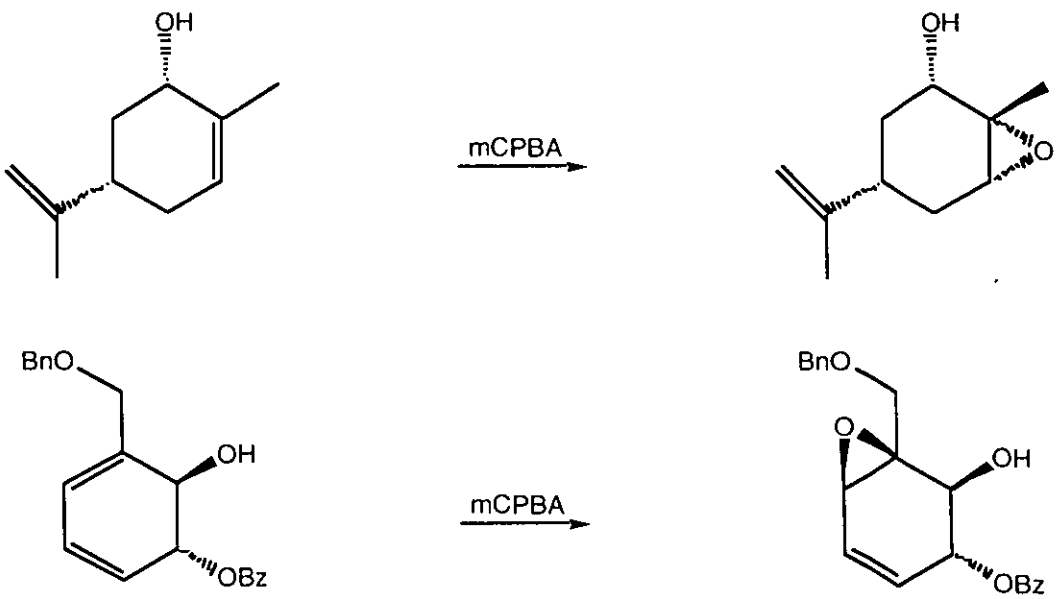


Scheme 18: Substrate controlled asymmetric epoxidations using the non-chiral oxidant mCPBA.

For example, double bonds which are part of fused ring systems are epoxidised stereoselectively at the more accessible concave face (Scheme 18).[82,83] In

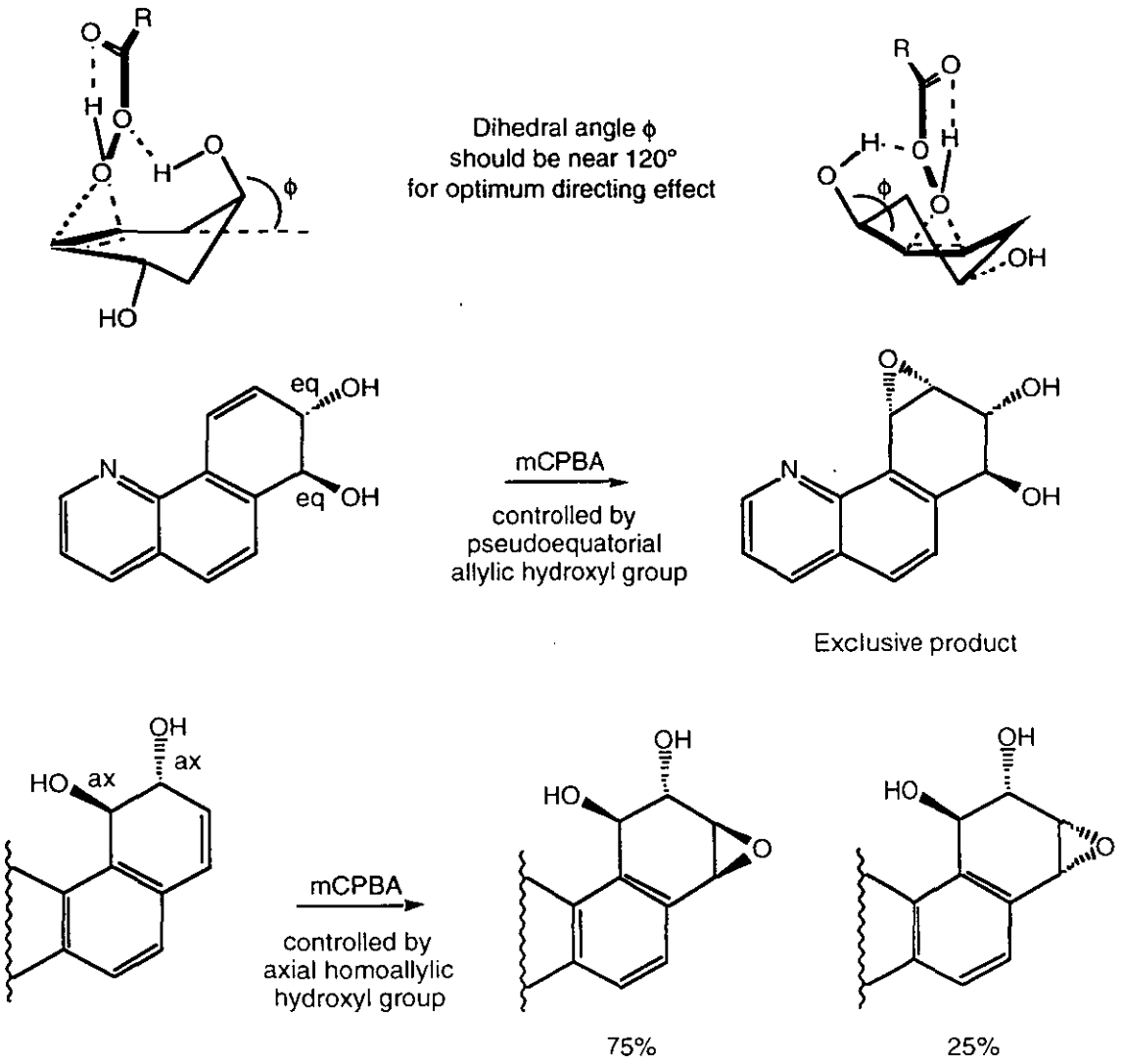
cases where a bulky group is present near the alkene, epoxidation takes place preferentially *anti* to that substituent (Scheme 18).[84]

Substrate controlled asymmetric epoxidations with non-chiral oxidants such as mCPBA can also be realised when chiral allylic alcohols are used as substrates. The hydroxyl group is able to participate in hydrogen boding with the peracid, and therefore direct the oxygen transfer to the alkene.[85] The product is usually the *syn* epoxide with respect to the reactive conformation of the hydroxyl group. Henbest and Wilson were the first to show that, in the absence of severe steric interference, cyclohex-2-en-1-ols are epoxidised stereoselectively by organic peracids to yield predominately *cis*-epoxyalcohols.[86] The epoxidation of (+)-carveol and 1,2-dihydrophenols are typical examples in this area (Scheme 19).[87,88]



Scheme 19: Cyclohex-2-en-1-ols give almost exclusively *syn*-epoxyalcohols.

However, for larger ring sizes (e.g. cyclooct-2-en-1-ol), epoxidation with peracids gives mainly the *trans*-epoxyalcohols.[89] The pseudoequatorial hydroxy group is more effective than the pseudoaxial in directing epoxidation. This is because the ideal hydrogen bonded transition state is attained when the dihedral angle in the O–C–C=C moiety is 120°.[90] According to this suggestion, homoallylic hydroxy groups can also direct epoxidation but only when they occupy axial positions (Scheme 20).[91,92]

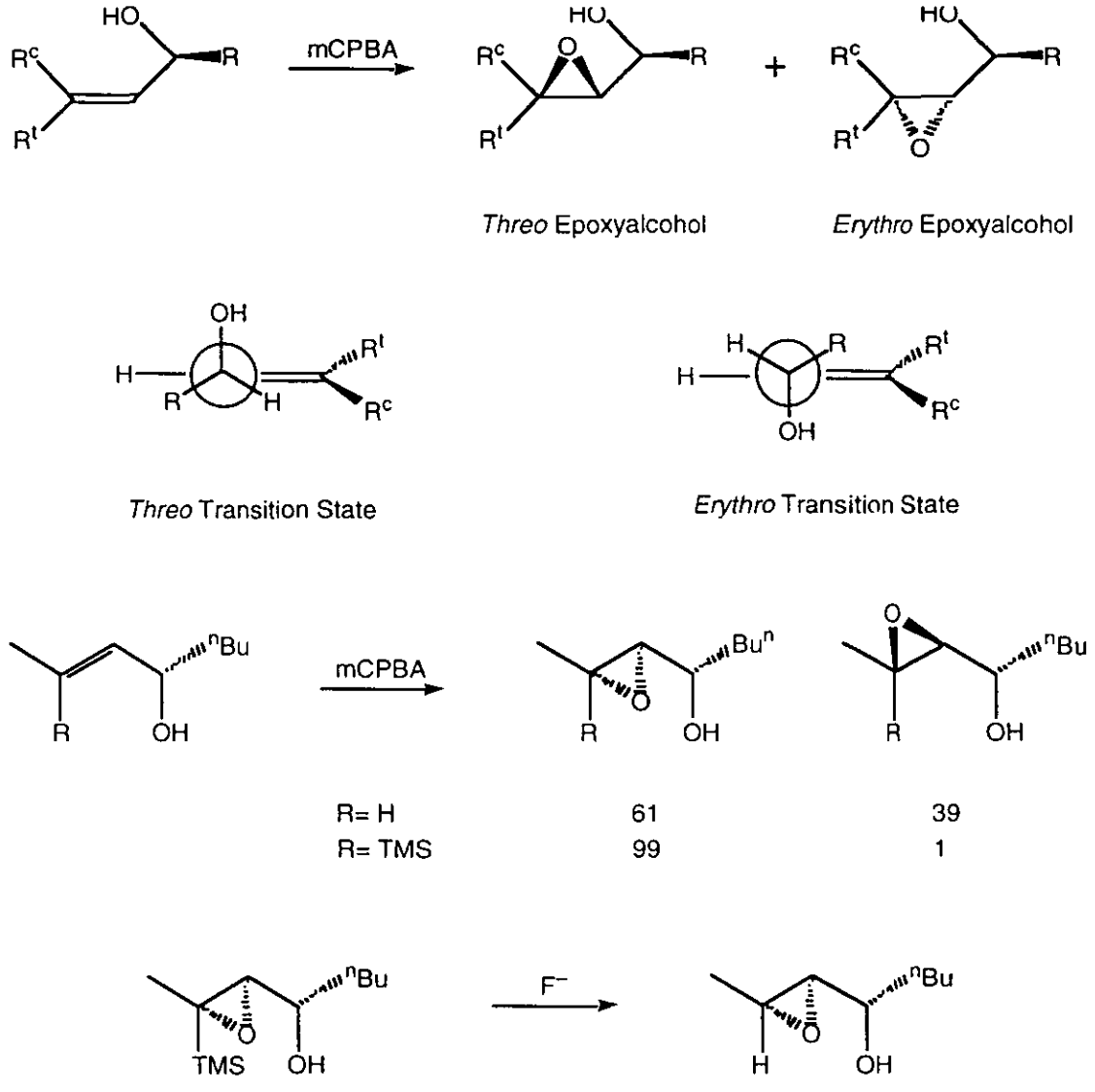


Scheme 20: Directing effects of allylic and homoallylic hydroxyl groups.

Besides the hydroxy group, carbamates,[93] ethers,[94] ketones,[95] and amides[96] are also capable of directing the epoxidation by peracids, provided that they are appropriately positioned within the cyclic alkene substrate.

With acyclic alkene substrates the situation is different. Epoxidation of simple primary allylic alcohols by achiral peracids is not enantioselective unless there are stereogenic centres present in the substrate. Epoxidation of secondary allylic alcohols can furnish the diastereoisomeric *threo*-and *erythro*-epoxyalcohols. The relative amounts of these products are dependent upon the steric interactions between the substituents in the *threo* and *erythro* transition states respectively (Scheme 21).[97] Examination of the rotamers in question reveals that when both R and R^c are alkyl groups, steric interactions destabilise the *erythro* transition state.[98] Indeed, high *threo*

selectivity is observed in the epoxidation of secondary allylic alcohols with trisubstituted or *cis*-disubstituted double bonds.[99,100] When R^c is simply a hydrogen, steric interactions also favour the *threo* transition state, but the destabilisation of the *erythro* rotamer is not sufficient to allow great diastereoselectivity to be observed.[101] Thus *trans*-disubstituted or monosubstituted secondary allylic alcohols are epoxidised with poor selectivities by organic peracids. This effect has been used to synthesise 2,3-epoxyoctan-4-ol with excellent stereoselectivity by using the trimethylsilyl substituted allylic alcohol (Scheme 21).



Scheme 21: The direction of epoxidation exhibited by acyclic allylic alcohols.

mCPBA epoxidation, followed by treatment with fluoride anion, furnished the desired product, which could not be obtained with the same degree of stereocontrol directly from the corresponding oct-2-en-4-ol (Scheme 21).[101] This sequence has been used extensively for the preparation of similar epoxyalcohols.[102]

Because mCPBA is shock sensitive and can detonate, it has been replaced on several occasions by cheaper and safer peroxyacids such as magnesium monoperoxyphthalate (MMPP), peracetic acid, trifluoroperacetic acid, 4-nitroperbenzoic acid and, more recently, 5-hydroperoxycarbonylphthalimide.[103]

With simple, prochiral, unfunctionalised alkenes, peroxyacid epoxidation affords racemic mixtures of epoxide products. For this reason organic chemists since at a very early stage investigated chiral organic peracids. The first asymmetric epoxidation was reported by Henbest in 1965, who used the chiral peroxy acid (+)-peroxycamphoric acid but the enantioselectivities obtained were of the order of 1.0-2.4% ee for a variety of substrates.[104,105] Pirkle later demonstrated that the oxidant Henbest had actually used contained two topological isomers (1 and 2 in Figure 5). He then in turn purified and used (+)-peroxycamphoric acid (1 in Figure 5) for asymmetric epoxidation, but the enantioselectivities of the afforded epoxides were only 1.5-2.0 times greater than those obtained by Henbest with the mixture of oxidants.[106]

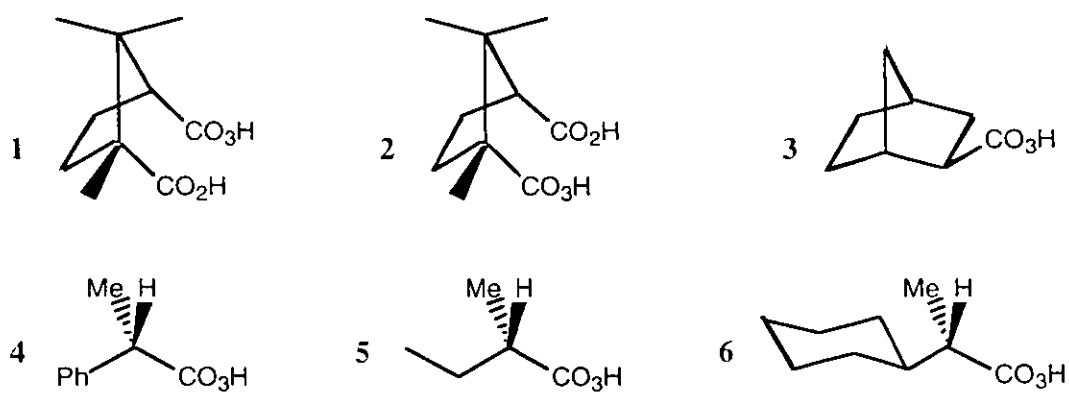
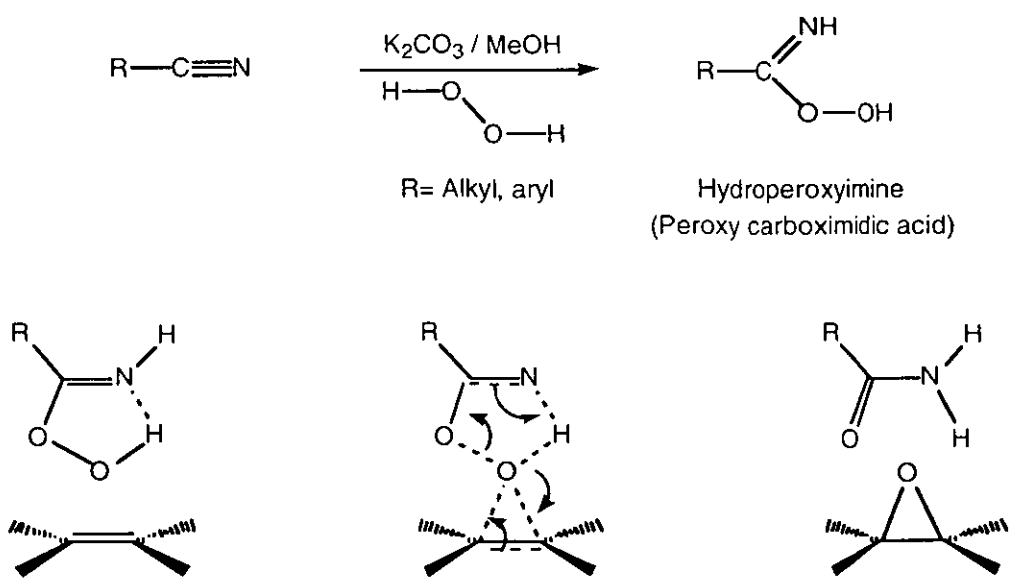


Figure 5: Chiral peracids that have been used in asymmetric epoxidation.

Since then, various other chiral peroxyacids have been tested with very limited success (3-6 in Figure 5).[107,108] The poor enantioselectivities obtained with such systems is usually attributed to the location of the chiral centre which is considered to be too remote from the site of oxygen transfer.

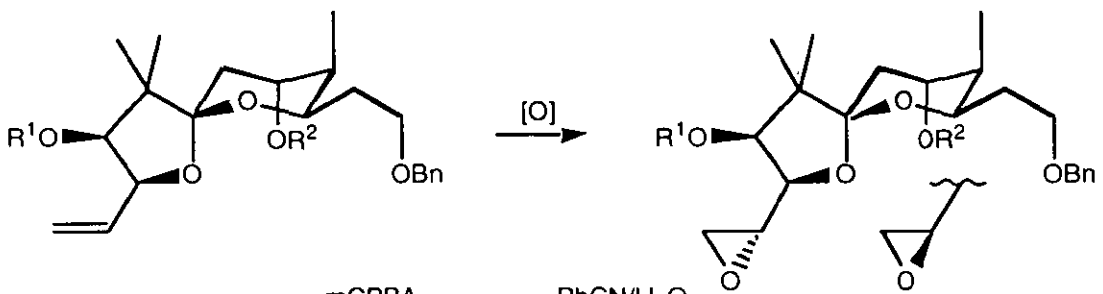
1.4.2 The Payne epoxidation and related processes with organic oxidants.

Hydrogen peroxide is a particularly attractive oxidant in organic transformations due to its low cost. In addition, the corresponding reduced product that is formed during the oxidation process is simply water, which is obviously environmentally friendly. However, hydrogen peroxide does not epoxidise alkenes directly because of the low nucleophilicity of the π-electrons in the carbon-carbon double bonds. Therefore, the peroxy entity must be activated by means of converting hydrogen peroxide into a more electrophilic species. Payne first reported that alkenes present in an alkaline solution of hydrogen peroxide and a nitrile are epoxidised smoothly and in good to excellent yields.[109,110] It is thought that the reaction proceeds through a hydroperoxyimine which is the addition adduct resulting from nucleophilic attack of hydroperoxide on the nitrile carbon, but this intermediate has never been isolated. In the absence of substrate, the hydroperoxyimine (or peroxy carboximidic acid) disproportionates to give the corresponding primary amide and molecular oxygen, and this process constitutes the Radziszewski reaction.[109] In the presence of an olefin the reactive intermediate is intercepted, and epoxidation occurs, with the primary amide (hydrated nitrile), being the only side product of the reaction. The transition state for the oxygen transfer step presumably resembles that described for the epoxidation of alkenes by peracids but no definite proof exists. The reaction is stereospecific (retention of alkene geometry) (Scheme 22).



Scheme 22: The Payne epoxidation of alkenes. The nitriles most often used are acetonitrile and benzonitrile.

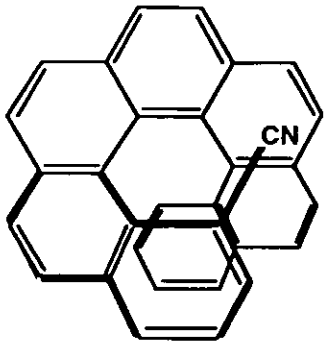
Although hydroperoxyimines are structurally related to peroxyacids in the sense that the carbonyl moiety is replaced with the isoelectronic N-H iminyl unit, significant differences in stereoselectivities are sometimes observed during epoxidation reactions.[111,112] A recent example is the epoxidation of the intermediate vinyl substituted spiroketal required in the synthesis of calyculins A and B by A. B. Smith.[113] mCPBA epoxidation occured with poor selectivity and favouring the undesired diastereoisomer even in the presence of a variety of directing groups. Selectivities with the Payne epoxidation system were not only markedly better, but the desired diastereoisomer could be obtained with the appropriate protecting/directing groups (Scheme 23).



	mCPBA	$PhCN/H_2O_2$
	α:β (yield)	α:β (yield)
R^1= H, R^2= BPS	1:4 (71%)	1:18 (86%)
R^1= PMB, R^2= H	complex mixture	9.5:1 (89%)

Scheme 23: Payne versus mCPBA epoxidation of a terminal double bond with directing groups.

From very early on, this methodology was recognised as an important epoxidation protocol and attempts were made to introduce chiral nitriles as asymmetric epoxidising agents.[114,115] As with the chiral peracids however, these efforts never yielded chiral epoxides of greater optical purity than 10%, probably for the same reasons:[116] The chirality of the oxidant is associated with a carbon atom relatively remote from the oxygen transfer site. The only exception is a nitrile derived from heptahelicene. Helicenes are very large molecules and are intrinsically chiral due to the helical arrangement of the fused aromatic rings. 2-Cyanoheptahelicene was reported to epoxidise *trans*-stilbene and α-methylstyrene under the classical Payne conditions, with absolute enantiocontrol.[117] The use of helicenes in asymmetric epoxidation however, has not been further elaborated, presumably due to the difficulty of synthesis of helicenes in enantiomerically pure form (Scheme 24).[118]



Scheme 24: 2-Cyanoheptahelicene is the only nitrile reported to epoxidise prochiral alkenes with excellent stereocontrol under the Payne epoxidation conditions.

A similar system for alkene epoxidation based on hydrogen peroxide involves activation of the oxidant with diimides. The corresponding intermediate is a hydroperoxyamidine which after oxygen transfer is converted to the N,N'-disubstituted urea.[119,521,522] Since the hydroperoxy moiety is also planar in this system, the prospects of developing chiral diimides as chiral epoxidising agents seem bleak.

With the failure of chiral peracids and hydroperoxyimines to afford decent enantioselectivities, researchers have concentrated on compounds where the hydroperoxy moiety is attached to a tetrahedral carbon or sulfur atom.[120] In these cases, the oxygen transfer step takes place nearer the stereogenic centre. Rebek and McCready reported a number of such chiral derivatives which included α-hydroperoxy ethers, acetals, and amines, derived by action of hydrogen peroxide on acetals, orthoesters, and imines respectively.[121] These species however have not been isolated and tentative representations are given in figure 6. The results were once more disappointing. Secondary α-hydroperoxyamines were dehydrated under the reaction conditions to the corresponding oxaziridines.

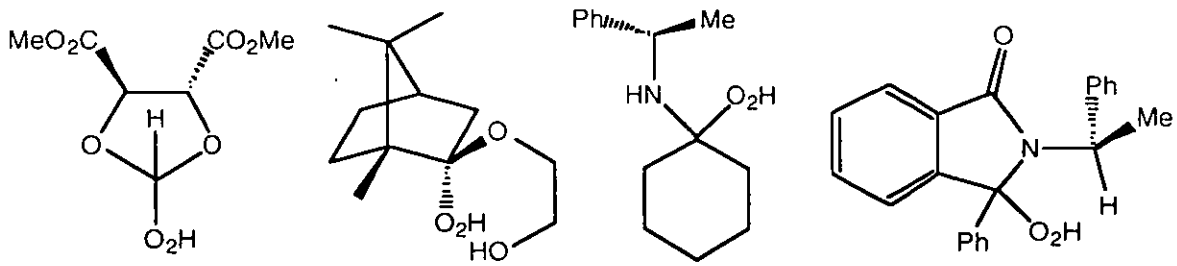
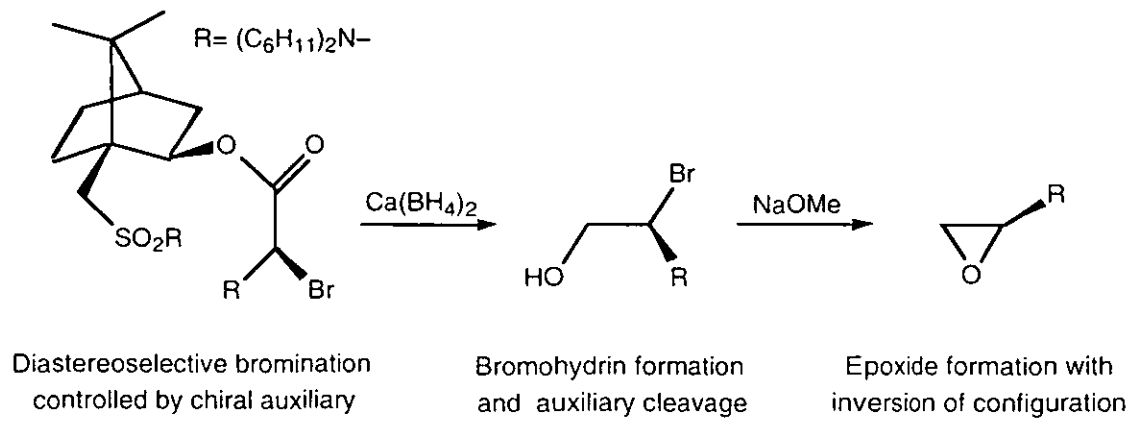


Figure 6: Some of the α-hydroperoxy intermediates tested by Rebek for asymmetric epoxidation.

1.4.3 Epoxides from halohydrins and related precursors.

Epoxides can be obtained from halohydrins upon treatment with base.[122] Halohydrins are in turn prepared from alkenes by exposure to halogenating agents in dilute aqueous solution.[123] Usually chloro- or bromohydrins are employed, but iodohydrins have also attracted attention recently.[124] Starting from alkenes, this is overall a two-step sequence of epoxide formation and thus is at clear dissadvantage over the one-step epoxidation methods.

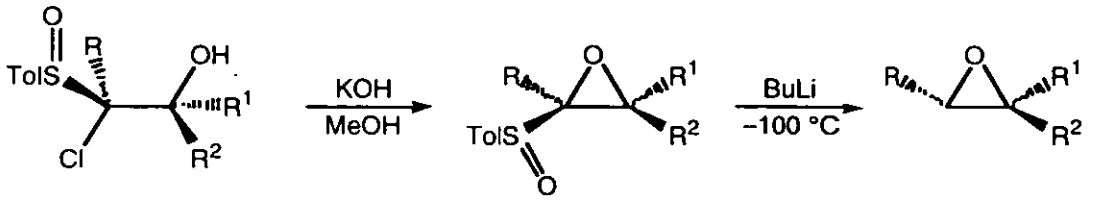
It follows that chiral halohydrins can give rise to chiral epoxides. The intramolecular cyclisation occurs in an S_N2-like fashion, and therefore the chiral epoxides are obtained with retention of configuration at the carbon atom bearing the hydroxyl group, but with inversion at the carbon atom bearing the halogen atom. In order to access non-racemic epoxides from prochiral alkenes, enantiocontrol is required during the bromohydrin formation step. One way to achieve this is to perform an asymmetric halogenation on a substrate with a latent hydroxyl group. This synthetic protocol has been employed by Oppolzer, who achieved asymmetric halogenation of esters by the use of a chiral auxiliary derived from camphor. Reduction of the ester linkage furnished the halohydrin free from the chiral auxiliary and upon treatment with base the desired epoxide was isolated with excellent enantiomeric excess (Scheme 25).[125]



Scheme 25: Oppolzer's stepwise approach to enantipure terminal epoxides.

A more popular approach has been to control the stereochemistry of the hydroxyl bearing carbon by means of nucleophilic attack of α-halocarbanions on carbonyl compounds.[126] In several cases, the stereocontrol of the nucleophilic addition has been controlled by auxiliaries derived from enantiopure sulfoxides.[127,128,129] Exposure of these halohydrins to base generates epoxides which

are detached from the chiral sulfoxide by treatment with butyl lithium.



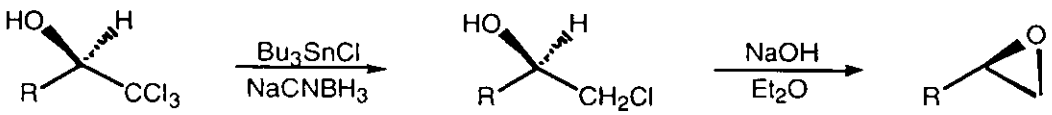
Sulfoxide controlled addition of carbanion to carbonyl compound

Epoxide formation with inversion of configuration

Cleavage of chiral auxiliary

Scheme 26: Stepwise approach to enantiopure epoxides based on chiral sulfoxides as auxiliaries.

Corey has also demonstrated that enantiopure terminal epoxides can be accessed from α-trichloromethylketones.[130] This author has developed chiral oxazoborolidines which were shown to catalyse reduction of this type of ketones with excellent enantiocontrol. Catalytic reduction of the trichloromethyl group to the monochloro compound followed by treatment with aqueous base or DBU furnishes enantiomerically pure monosubstituted epoxides. This method however is applicable only for terminal epoxides (Scheme 27).



Enantioselective reduction of the thrichlomethyl ketone

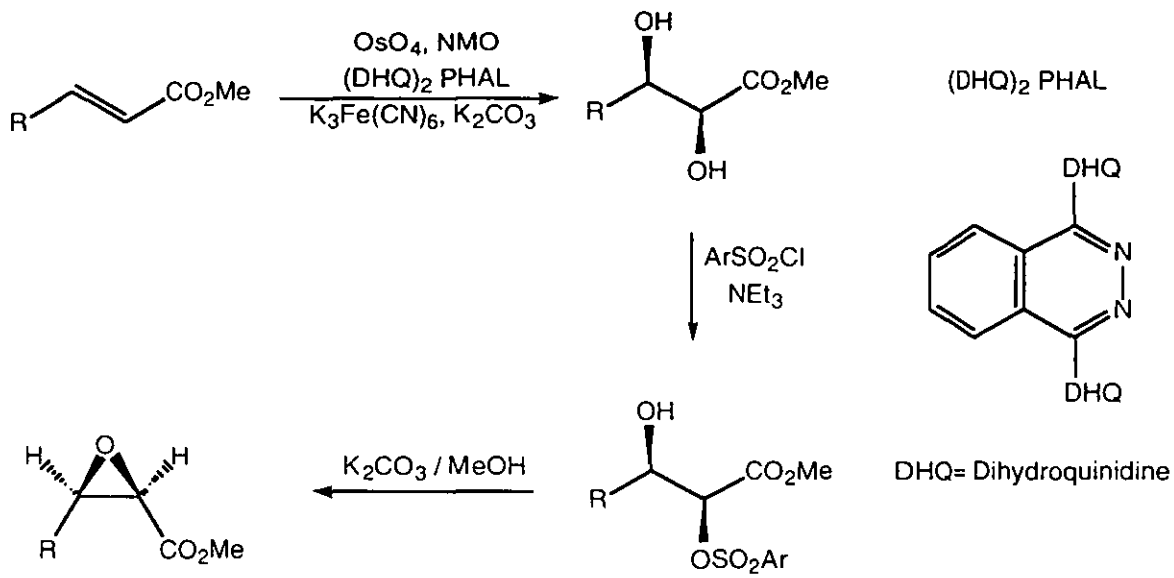
Halohydrin formation by selective dechlorination

Epoxide formed is monosubstituted

Scheme 27: Corey's approach to chiral monosubstituted epoxides *via* enantioselective reduction.

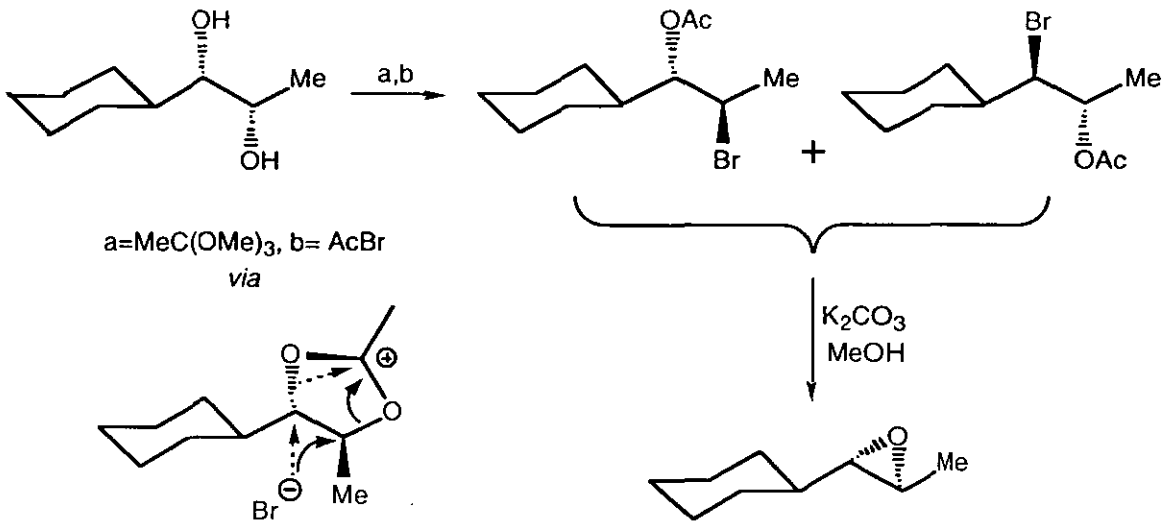
A more elegant approach towards the stereocontrolled introduction of the hydroxyl group is the Sharpless catalytic asymmetric dihydroxylation.[131,132] In this process, alkenes are used as the substrates. In addition, the reaction is catalysed by osmium tetroxide in the presence of a chiral ligand derived from an alkaloid of the quinine group and N-methyl morpholine oxide (NMO) as the stoicheiometric oxidant. Although osmium tetroxide is very toxic, 0.2 mol% suffices to catalyse the reaction, and hence this process has a clear advantage over the stoicheiometric methods described above. In this reaction, olefins are converted into the corresponding *syn*-diols with good to excellent enantiomeric excesses for selected

classes of substrates. Regioselective monotosylation of the diol followed by exposure to aqueous base cleanly produces epoxides with inversion at the tosylated carbon atom.[133] Therefore, using this sequence *trans*-epoxides are obtained from *cis*-alkenes and *cis*-epoxides from *trans*-alkenes. The example in scheme 28 describes the stepwise formation of an epoxy ester, but the method is applicable to a broad range of simple and functionalised olefins.[134]



Scheme 28: Stepwise enantioselective epoxidation with inversion of olefine stereochemistry using the Sharpless asymmetric dihydroxylation protocol.

Alternatively, treatment of the diol with trimethyl orthoacetate in the presence of acetyl bromide affords the corresponding acetoxybromides with inversion at the halogenated carbon atom.[135] The acetoxy group is then hydrolysed to the parent hydroxy group, which, under the reaction conditions, displaces the halogen to generate the oxirane with inversion of configuration at that carbon atom. Overall, the stereochemistry of the starting alkene and diol is retained in the epoxide product through double inversion.[136] When trimethylsilylchloride is used instead of acetyl bromide, the acetoxychlorides are the afforded intermediates.[137,138] The formation of the acetoxyhalides is thought to proceed through initial formation of the corresponding 2-methoxy-1,3-dioxolane (Scheme 29). The added electrophile assists the departure of the methoxy group to generate the intermediate 1,3-dioxolan-2-ylium species which is then ring opened by the halide. The latter step is not always regiospecific but that is inconsequential due to the double inversion in the overall process.[136]



Scheme 29: Stepwise enantioselective epoxidation with retention of olefine stereochemistry using Sharpless asymmetric dihydroxylation protocol.

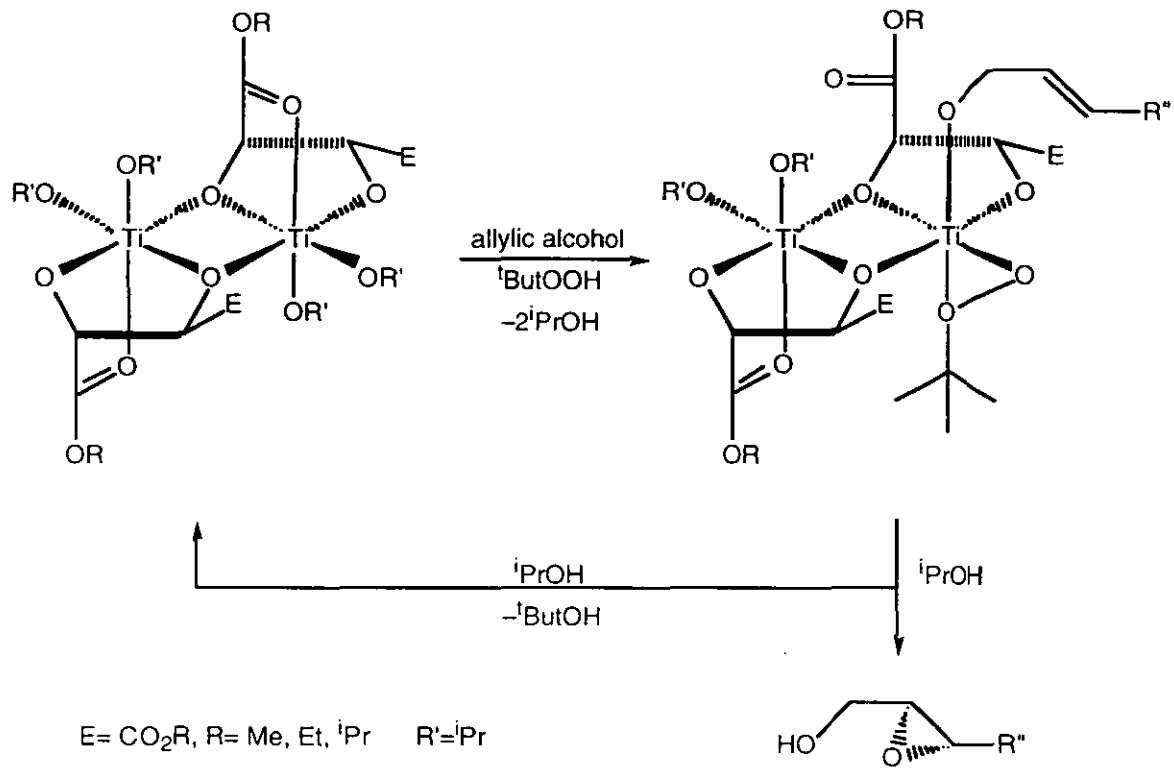
In cases where the original dihydroxylation of a substrate does not proceed with satisfactory enantioselectivity, tethering of the substrate to a chiral auxiliary has also been employed, for example in the synthesis of epoxyangelate.[139]

1.4.4 The Sharpless catalytic asymmetric epoxidation of allylic alcohols.

Following the first asymmetric epoxidation by Henbest in 1965, high levels of asymmetric induction remained unaccomplished for 15 years until Katsuki and Sharpless reported a system for the asymmetric epoxidation of allylic alcohols. This method involved a titanium(IV) alkoxide, an chiral tartrate ester, and tertiary-butylhydroperoxide (TBHP) and furnished 2,3-epoxylalcohols in good yields and with enantiomeric excesses of usually greater than 90%.[140]

The Sharpless asymmetric epoxidation of allylic alcohols has become one of the most influential reactions in asymmetric synthesis and has established itself as one of the most important discoveries in chemistry this century.

The success of this method depends on the presence of the hydroxyl group of the allylic alcohol which coordinates to the metal and therefore binds the molecule to the chiral complex (Scheme 30). The latter activates the oxidant and controls the delivery of oxygen to the substrate preferentially to one of the two enantiotopic faces of the alkene. The hydroxyl group also enhances the rate of reaction and provides selective epoxidation of the allylic olefin in the presence of other types of double bonds.

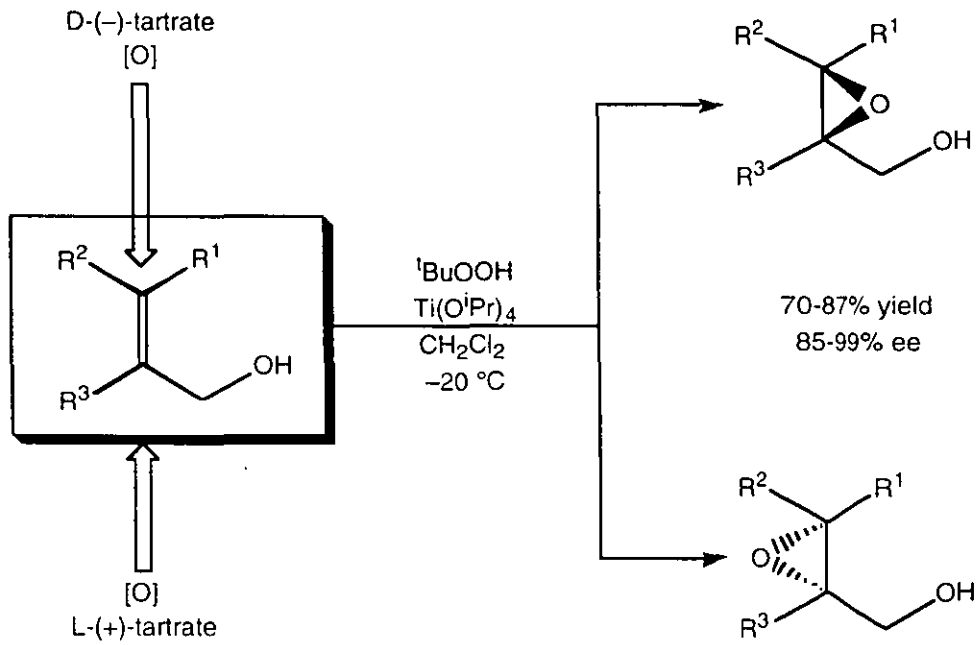


Scheme 30: The allylic hydroxyl group is essential in ensuring proximity of the double bond to the chiral site.

The reaction was shown to proceed catalytically with respect to the titanium tartrate complex and complete epoxidation of the most reactive allylic alcohols was achieved with only 5-10 mol% of the active complex. The level of enantioselectivity was similar to that obtained when a stoicheiometric amount of the complex was used. With less reactive alcohols however, stoicheiometric quantities were used until 1986. Then, an important improvement was made. Sharpless found that the catalytic reaction is enhanced dramatically in the presence of molecular sieves, and nearly all types of allylic alcohols were epoxidised completely with only 5-10 mol% of the catalyst.[141,142] The molecular sieves remove adventitious water from the reaction mixture and therefore prevent its coordination to the catalyst and displacement of the chiral ligand. The advantages of the catalytic reaction include easier isolations, milder conditions and increased yields for sensitive epoxyalcohols. In the stoicheiometric process, several of the epoxyalcohol products were unstable under the reaction conditions presumably due to the mild Lewis acidity of titanium alkoxides which could catalyse the ring opening of the desired oxiranes.[143,144] In the catalytic version these problems are minimised, and application of *in situ*

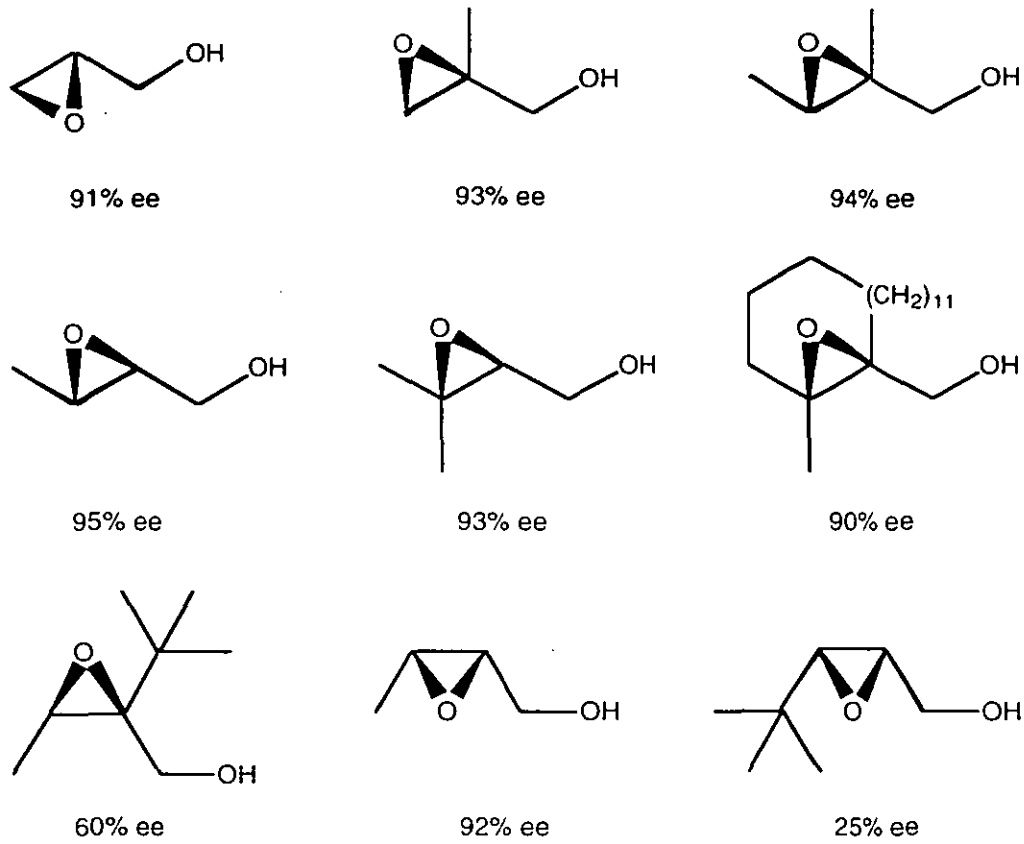
derivatization of the product is also possible.[145,146] This has proved particularly important for the isolation of unstable or water soluble epoxyalcohols which could now be converted *in situ* into the corresponding tosylates, 3,5-dinitrobenzoates or trityl ethers, and isolated as such.[142,147,148] Furthermore, these crystalline derivatives of substrates for which epoxidations did not proceed with high enantioselectivities, could be recrystallised in some cases to enantiopurity.[142,146,149]

One of the major advantages of the Sharpless asymmetric epoxidation of allylic alcohols is the capability to produce either enantiomer of the desired epoxyalcohol at will, simply by choosing the D or L form of the commercially available tartrate esters. The other powerful feature is the ability to predict the stereochemical outcome of the process for a given type of chiral tartrate ester. For prochiral primary allylic alcohols, this relationship is depicted in scheme 31. To date this model has never failed.



Scheme 31: The stereochemical course of the reaction can be unambiguously predicted.

Nearly all types of prochiral primary allylic alcohols are epoxidised with high enantiomeric excesses. The Achilles' heel of this method is realised upon increasing the degree of branching or the steric demand of the substituent *cis* to the hydroxymethyl moiety (R^1 in scheme 31).[150] Representative examples are given in scheme 32.[150-156]

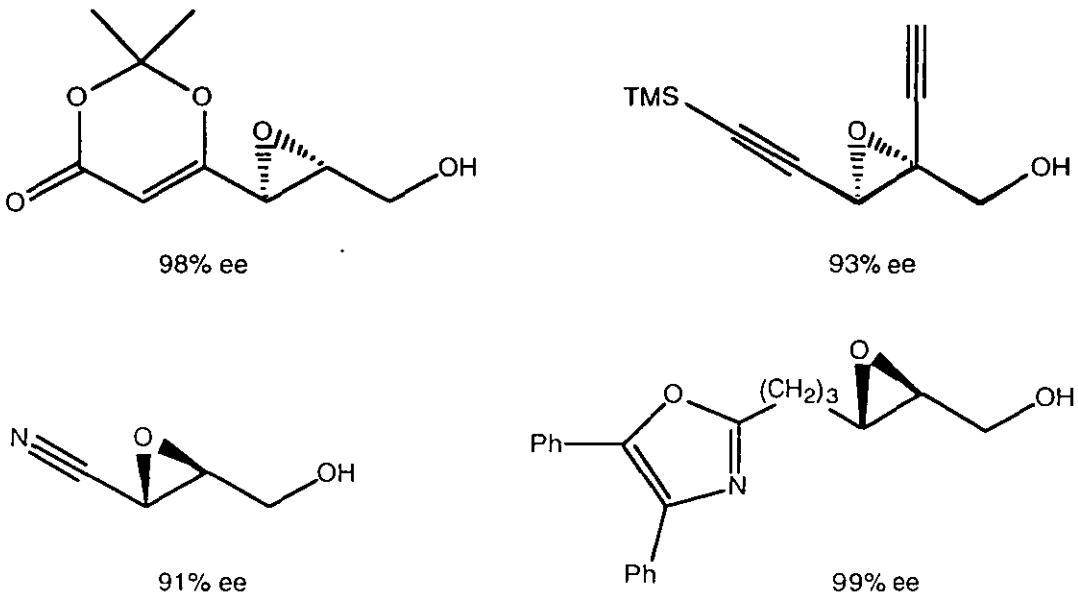


Scheme 32: Prochiral primary allylic alcohols are epoxidised with excellent enantioselectivity using the titanium tartrate protocol. The exceptions are few and can be predicted.

In the Sharpless asymmetric epoxidation of allylic alcohols, the substrate acts as a ligand, and thereby proximity of the double bond to the chiral oxygenating complex is secured. In the absence of the allylic hydroxyl group, no reaction occurs. Although this aspect introduces substrate specificity, it also renders the process chemo- and regiospecific. Namely, with substrates that contain several carbon-carbon double bonds in addition to the allylic alcohol, it is only the latter moiety which is epoxidised.[140,157]

Another important feature of this catalytic process is its tolerance of other functional groups that may be present in the substrate. This remarkable chemoselectivity allows epoxidation of heavily functionalised molecules to proceed under mild conditions without formation of side products. In particular, ethers,[158] acetals,[159] esters,[160] carbonyls,[161] sulfonamides,[162] nitriles,[163] urethanes,[164] triple bonds,[165] heterocycles (except for furfuryl alcohol),[166] silyl groups,[167] and other functionalities and protecting groups are unaffected in this process. Examples are given below (Scheme 33).[168-171] Exceptions arise when nucleophilic substituents are

appropriately positioned so that intramolecular ring opening of the newly formed epoxide becomes favourable.[172,173,174] Incompatible groups are carboxylic acids, thiols, phosphines, and most phenols and amines.[175]



Scheme 33: The Sharpless asymmetric epoxidation tolerates a broad range of functional groups.

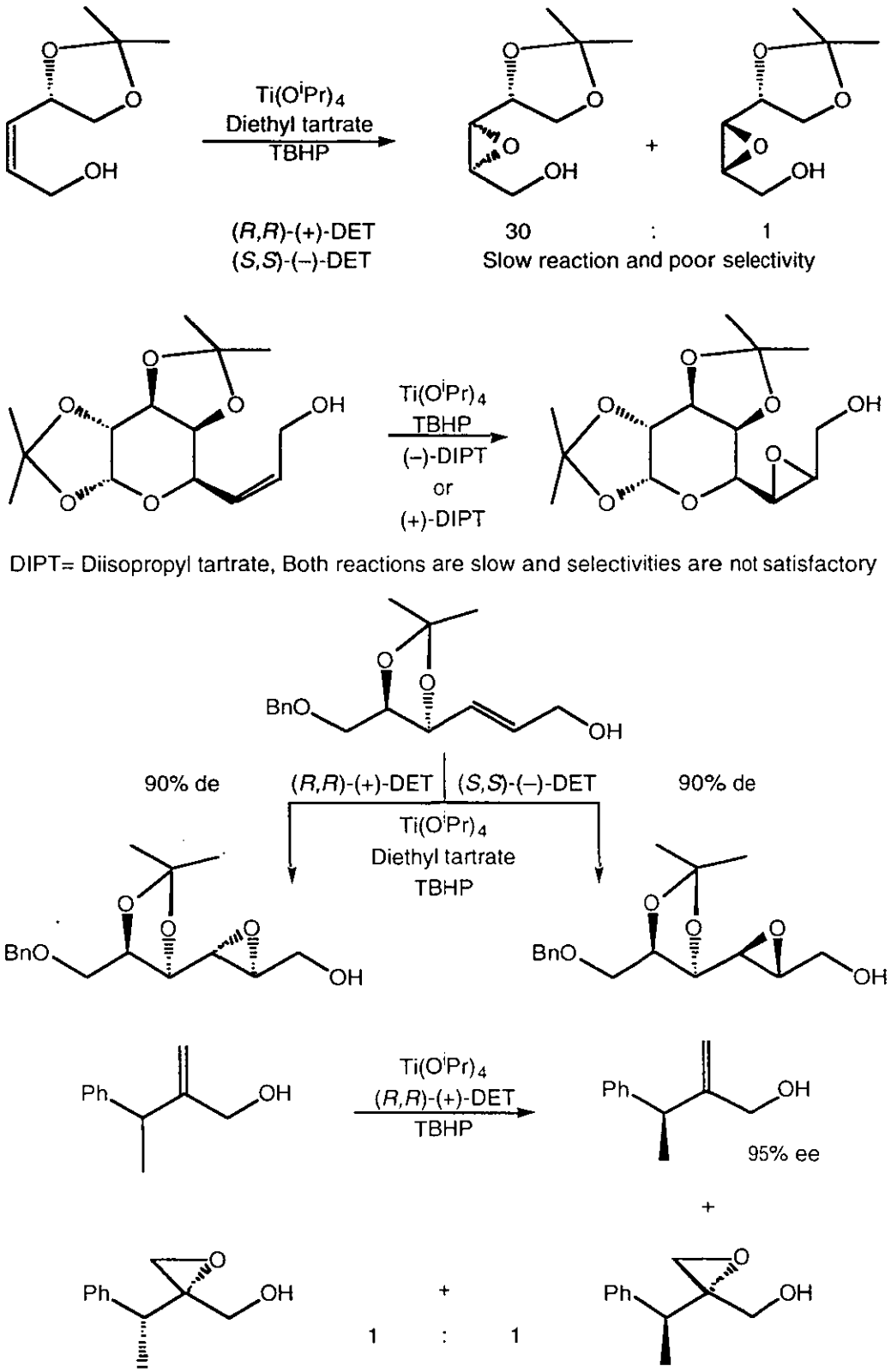
The Sharpless procedure uses at least 5 mol% of catalyst. If less than that is used, the enantioselectivities and reaction rates drop dramatically. In turn, the catalyst must be prepared with titanium isopropoxide and the dialkyltartrate in 1:1.2 stoicheiometry. More than 20% excess of the chiral ligand with respect to the metal retards the reaction rate, while less than the recommended amount also has a deleterious effect on the enantioselectivity.[142] In one of the modifications of the Sharpless procedure, tartramides were used as the chiral ligands in place of the esters.[176] Intrestingly, with this additive, *cis*-α-hydroxymethylstilbene was epoxidised in 82% ee when the stoicheiometry of metal-to-ligand was 2:1, but with reverse stereochemistry and 93% ee when the same chiral auxiliary was used at 2:2.4 metal-to-ligand stoicheiometry. Similar results have also been observed whith other chiral ligands and/or different stoicheiometries. In these cases, different species are thought to act as the catalysts, where in the case of tartramides conformational effects have also been invoked.[143,176,213] Reversal of enantioselectivities is also observed when the catalyst is prepared from diisopropyl tartrate and dichlorotitanium(IV) diisopropoxide in 1:2 stoicheiometry, instead of titanium(IV) isopropoxide.[143,214]

In a similar modification of the Sharpless epoxidation, other chiral diols have been used as ligands, but few of them were as successful as the classical tartrates.[177] The use of polymer-supported tartrate esters has also been investigated, but the enantioselectivities obtained with this variant were not as great as those afforded with the traditional method.[178]

So far only prochiral primary allylic alcohols have been discussed. The story is somewhat different with chiral substrates. The titanium tartrate catalysed epoxidation is sensitive to existing chirality in the substrate. The level of sensitivity depends on the bulkiness and polarity of the substituents as well as on the location and absolute configuration of the stereocentre.[179] If the chirality of the ligand matches that of the substrate the epoxyalcohol can be obtained with high diastereoisomeric excess, while, in the mismatched case, slow reactions and poor diastereoselectivities are realised (Scheme 34).[158] There have been cases where the intrinsic chirality of the substrate overrides the influence of both enantiomers of the chiral catalyst (Scheme 34).[180] However, in the majority of the cases with chiral primary allylic alcohols, the effect of the chiral catalyst wins over the intrinsic chirality of the substrate, and both diastereoisomers of the epoxyalcohol can be accessed with high selectivity (Scheme 34).[181]

For racemic mixtures of chiral substrates, one of the enantiomers reacts or binds to the chiral catalyst faster than its antipode, and hence kinetic resolution is realised. The difference in rates may be sufficient such that at 50% conversion, only one enantiomer of the chiral allylic alcohol has been epoxidised, and therefore the unreacted enantiomer can be obtained with high enantiomeric purity. In addition, if the epoxidation of the faster reacting antipode also proceeds with high enantiofacial control (matched chirality with catalyst), then both epoxyalcohol and unreacted allylic alcohol are obtained with high de's and ee's respectively. Due to the intrinsic chirality of the substrate however, the de of the epoxyalcohol may not always be great,[182] while the ee of the unreacted substrate may be high for certain types of substrates and poor for others.[183,184] The difference in the reactivity exibited by the two enantiomers of the substrate, may be enhanced with bulkier tartate esters (e.g. dicyclohexyl) but in the representative examples given in scheme 34 the diethyl or diisopropyl derivatives were used.

Neither chiral or prochiral tertiary allylic alcohols are very good substrates for the Sharpless asymmetric epoxidation because they react slowly under these contitions. This is thought to be due to the stong attachment of the tertiary alkoxy residue of the substrate to the titanium complex.[185]



Scheme 34: Epoxidation and resolution of chiral primary allylic alcohols.

Chiral secondary allylic alcohols constitute a rather special class of substrates because the chiral titanium tartrate catalyst is particularly sensitive to the existing stereogenic center at the carbon bearing the hydroxyl group. Because of the additional substituent near the coordination sphere of the metal complex, one of the enantiomers usually matches the steric requirements of the chiral site better than its antipode. It has been observed that secondary allylic alcohols of (*S*)-configuration react much more rapidly with (*R,R*)-(+)-dialkyl tartrates than their antipode (Figure 7, center, $R^1 \neq H$, $R^2 = H$), and give the *erythro* epoxyalcohol almost exclusively. Epoxidation of the antipode of that allylic alcohol (Scheme 41, center, $R^1 = H$, $R^2 \neq H$) with the same tartrate ester is not very selective because of unfavourable steric interactions with the chiral ligand, and mixtures of the *threo* and *erythro* epoxyalcohols are usually obtained.

The same trend appears when an enantiopure secondary allylic alcohol is treated with either chiral form of the titanium tartrate complex. It follows that for an optically pure, chiral secondary allylic alcohol the *erythro* epoxide can be prepared with good diastereoselectivity from the matched case of chiral ligand and substrate (top left and bottom right in Figure 7, Scheme 35).[186]

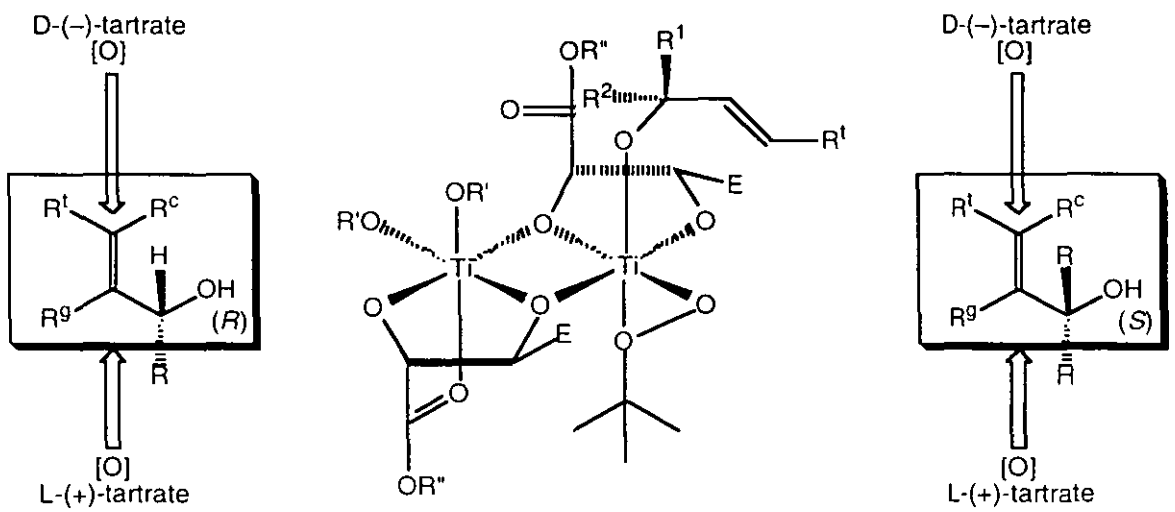
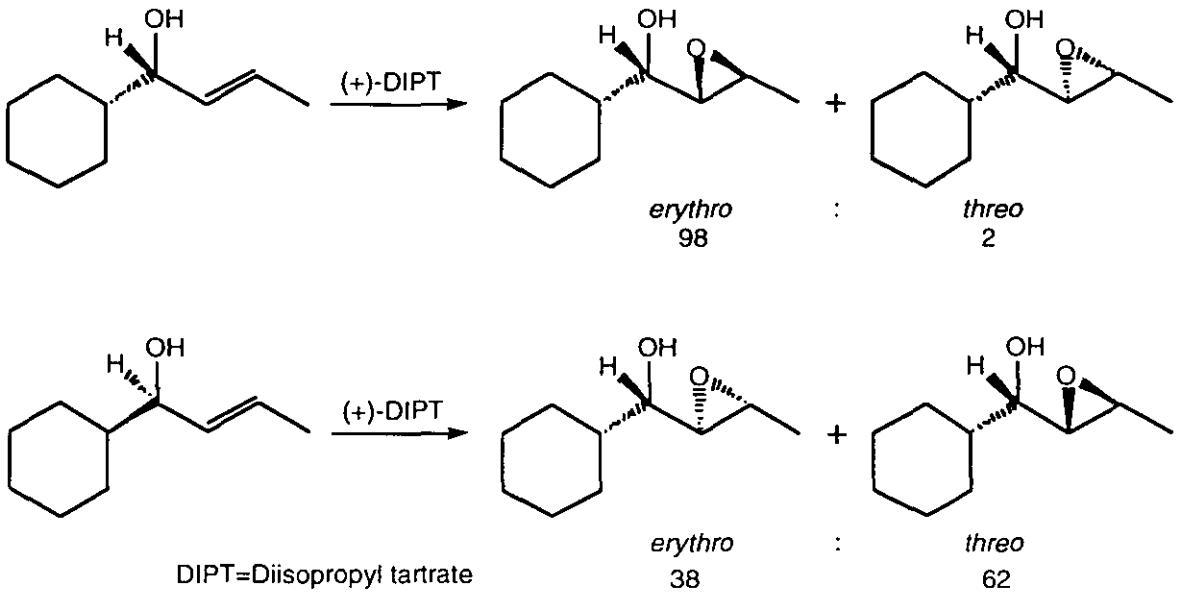
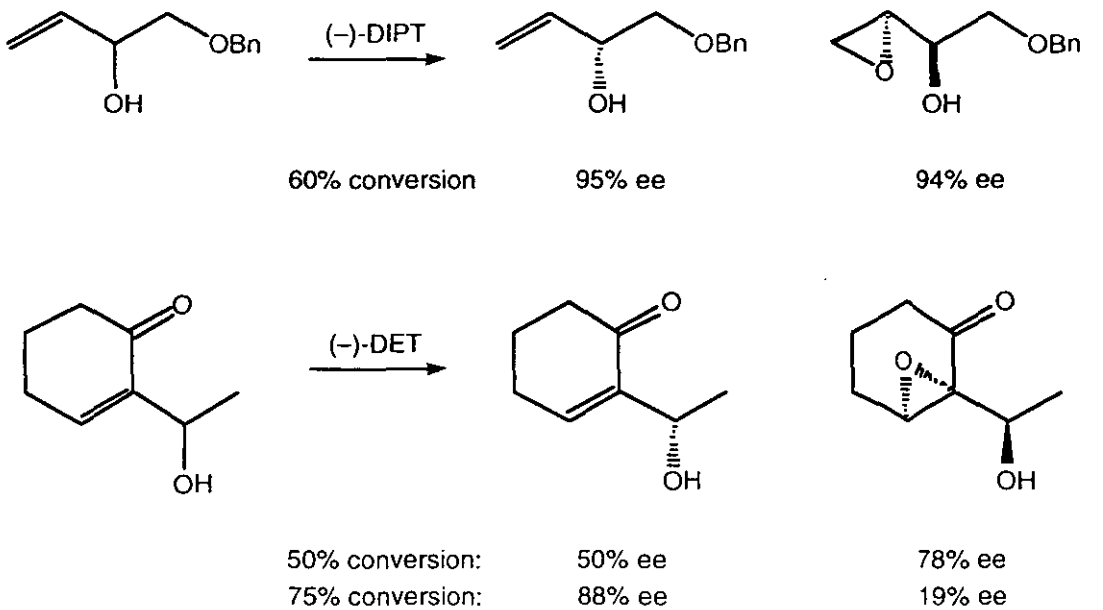


Figure 7: Steric hindrance of the substituent R^2 at the stereogenic carbon atom, greatly influences the asymmetric epoxidation of secondary allylic alcohols.



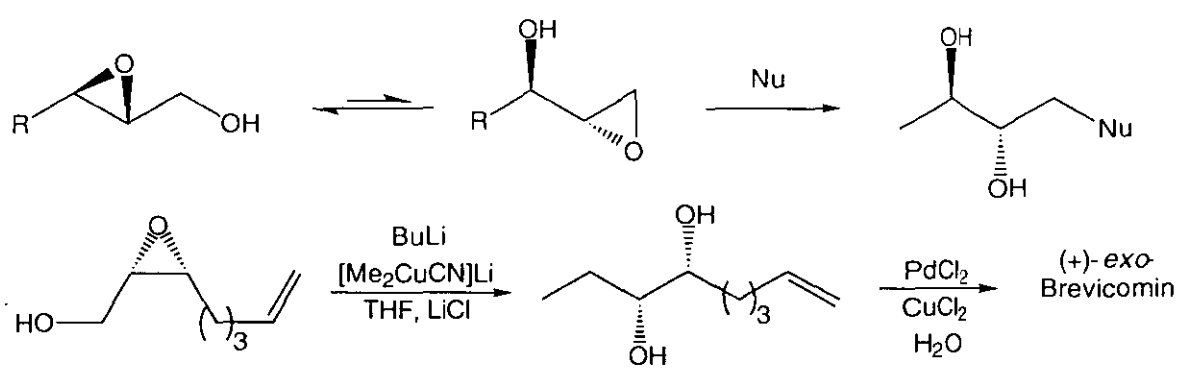
Scheme 35: *Erythro* epoxyalcohols can be obtained with high selectivity from the Sharpless asymmetric epoxidation of enantiomerically pure secondary allylic alcohols.

Due to this difference in reactivity of enantiomeric secondary allylic alcohols, the Sharpless procedure is very good for the kinetic resolution of their racemates. Theoretically, for good resolutions, the relative rate of epoxidation for the two enantiomers should be between 50 and 100. The actual values observed in this process are between 15 and 700.[187,188] Like all resolutions, the maximum yield is limited to 50%, which in this case is accomplished by using approximately half an equivalent of oxidant (TBHP) with respect to the substrate. The general predictive model as outlined in figure 7 can also be used to determine the stereochemical outcome of the epoxidation/resolution, which in most cases correlates well with that observed for the epoxidation of primary allylic alcohols (Scheme 31).[189] The substituent effect is similar to that found in primary allylic alcohols, with the *trans* substituted being the best, and those with a bulky *cis*-substituent being the worst, substrates respectively. In general, with the other types of substrates, slightly poorer selectivities are obtained compared with the primary allylic alcohols. For the best substrates, there have been several reports where both the oxygenated product and the unreacted starting material were obtained with excellent de's and ee's respectively.[190-192] This is not always the case however. In some cases, resolution of the secondary analogues favours the unreacted allylic alcohol rather than the epoxy derivative due to formation of diastereoisomers, but that is highly substrate dependent (Scheme 36).[193-195]



Scheme 36: Kinetic resolution of racemic secondary allylic alcohols using the Sharpless reaction.

Interestingly, this synthetically undesirable aspect of the Sharpless process can be easily overcome *via* the Payne rearrangement.[196] This rearrangement of 2,3-epoxyalcohols provides an indirect route to epoxides of secondary or tertiary allylic alcohols with high enantiomeric purity. In some cases these are isolable, while in others they are generated as reactive intermediates and trapped *in situ* (Scheme 37). In this reaction, 2,3-epoxyalcohols are rapidly equilibrated with 1,2-epoxyalcohols under alkaline conditions. Deprotonation of the primary hydroxyl group generates the corresponding alkoxide which intramolecularly ring opens the adjacent di-, tri-, or tetrasubstituted enantiopure epoxide with inversion of configuration, to afford the secondary or tertiary alcohol with a terminal epoxide.



Scheme 37: The Payne rearrangement-epoxide ring opening sequence.

The process is reversible and the equilibrium ratio is highly dependent on the substrate but usually favours the primary 2,3-epoxyalcohol.[197] However, because terminal epoxides are considerably less hindered and therefore more reactive, it is possible to trap the rearranged product by means of ring opening with an added nucleophile.[184,198,199] The example shown in Scheme 37 demonstrates the approach of Page and co-workers through a Payne rearrangement towards the synthesis of (+)-*exo*-brevicomin.[523,524] Thus the Sharpless asymmetric epoxidation-Payne rearrangement-epoxide ring opening sequence is a powerful synthetic tool to access 1-substituted-2,3-diols which are useful chiral building blocks.[202] This synthetic protocol has also been successfully applied in the asymmetric synthesis of sugars.[200] Recently this methodology has been applied in the enantioselective synthesis of chromanols whose skeleton is found in naturally occuring bioactive compounds.[201]

Finally, homoallylic alcohols are inferior substrates than allylic alcohols for the Sharpless reaction.[203] In general, as the distance between the hydroxyl group and the double bond increases, the asymmetric induction drops sharply. Usually enantiomeric excesses for these epoxy alcohols range between 20 and 50%. Interestingly, the stereochemistry of the epoxide is opposite to that observed for allylic alcohols.

In summary, the Sharpless asymmetric epoxidation of allylic alcohols has become one of the cornerstones of asymmetric transformations. The reaction itself is substrate specific, but the great versatility of 2,3-epoxy alcohols is beyond question. Furthermore, the importance of this method is reflected in the fact that it has been industrialised by ARCO Chemical Company for the manufacture of both enantiomers of glycidol; an attractive chiral building block.[204] A variety of natural products and synthetic intermediates have been accessed by what is considered to be one of the most reliable and influential processes in organic chemistry. Tetronasin (ICI M139603),[205] two diastereoisomers of 11-hydroxy-12,13-epoxy-octadecadi-7,9-enoic acid,[206] squalene oxide and dioxides,[207] FR900482,[208] isostatin,[209,210] preswinholide A,[211] all eight L-hexoses,[200] amphoteronolide B,[212] and amphotericin B,[212] are just a few examples where this methodology has been applied. The popularity of this method also arises from the commercial availability of the required catalyst precursors (either enantiomer of various tartrate esters, titanium alkoxides), and organic peroxides. Although this protocol is the best for the asymmetric synthesis of 2,3-epoxy primary alcohols, there are also inherent limitations. In many cases preparation of diastereoisomeric epoxyalcohols from chiral substrates is not very selective. The reaction is very successful for the resolution of racemic mixtures of chiral allylic alcohols, but depending on the

substrate, may favour the unreacted starting material rather than the epoxide. Tertiary allylic alcohols are poor substrates. The enantioselectivities drop sharply as the spacing of the hydroxyl group from the double bond increases and no epoxidation occurs in the absence of such a coordinating group in the vicinity of the double bond.

1.4.5 Metalloporphyrins as epoxidation catalysts.

Despite the success of the Sharpless procedure in the asymmetric epoxidation of allylic alcohols, the achievement of high enantioselectivities in the epoxidation of alkenes bearing no functionality to precoordinate to the catalyst, remains a challenging problem. It is difficult to obtain high enantioselectivity in the asymmetric epoxidation of unfunctionalised alkenes, because only the steric and electronic properties of the substrate can influence the stereochemical course of the reaction. However, the asymmetric epoxidation of simple olefins is particularly important and has received significant attention, because the range of readily available substrates could be very broad.

Interest in the transition metal porphyrin complexes in oxo-transfer catalysis arose from Groves' discovery that Fe(III) porphyrin complexes are models for cytochrome P-450 monooxygenase.[215] In 1983, Groves and Meyers described the first example of catalytic asymmetric epoxidation of simple olefins mediated by chiral porphyrin complexes (Figure 8).[216]

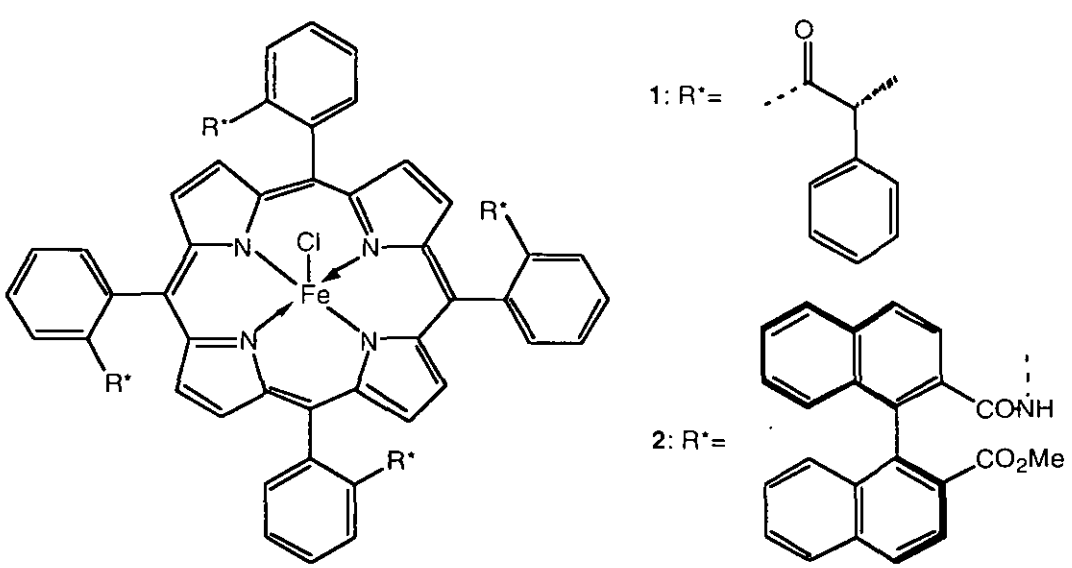
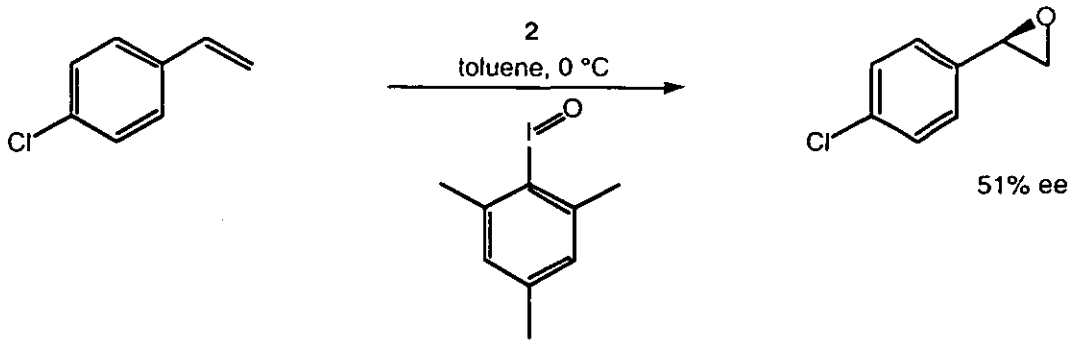


Figure 8: Two of the first chiral porphyrins used by Groves for alkene epoxidation.



Scheme 38: One of Groves' first catalytic asymmetric epoxidation of simple alkenes using metalloporphyrin 2 in scheme 44.

Oxidation reactions were carried out with catalysts 1 and 2 in Figure 8 and iodosylmesitylene as the stoicheiometric oxidant (Scheme 38). The enantioselectivity of these catalysts were low to moderate, and *cis*-olefins exhibited higher reactivity than their *trans* analogues. The best substrates proved to be styrenes, and an enantiomeric excess of 51% was obtained for 4-chlorostyrene (Scheme 38). Groves next examined iron and manganese metalloporhyrins with a "double strap" derived from binaphthyl, but the improvements were not great.[217]

Since then, very diverse chiral porphyrin complexes have been synthesised and tested, but save for certain types of substrates, enantioselectivity has never reached high levels.[218] Notable systems are those developed by Naruta,[219,220] Collman,[221] and Inoue.[222] One of Collman's first catalysts was a manganese(III)-porphyrin complex with a single strap linking two opposite *meso* positions, a feature that renders the two faces of the porphyrin complex sterically inequivalent (Figure 9). This system was designed so that an external bulky ligand (3,5-ditertiarybutyl phenol) could block the more accessible face, and therefore oxidation of the metal centre, and consequently of the substrate, would take place in the chiral cavity under the strap (Figure 9). Initial results were however disappointing (styrene oxide was obtained with 13% ee), and this was explained in terms of the size of the cavity being too large to allow maximum steric communication.[221] This has been an acceptable rationalisation, because Inoue's monostrapped manganese(III)-metalloporphyrin with N-ethyl imidazole as the external ligand, exhibited better enantioselectivities (indene oxide with 58% ee), possibly due the shorter strap spanning one face of the metalloporphyrin (Figure 9).[222]

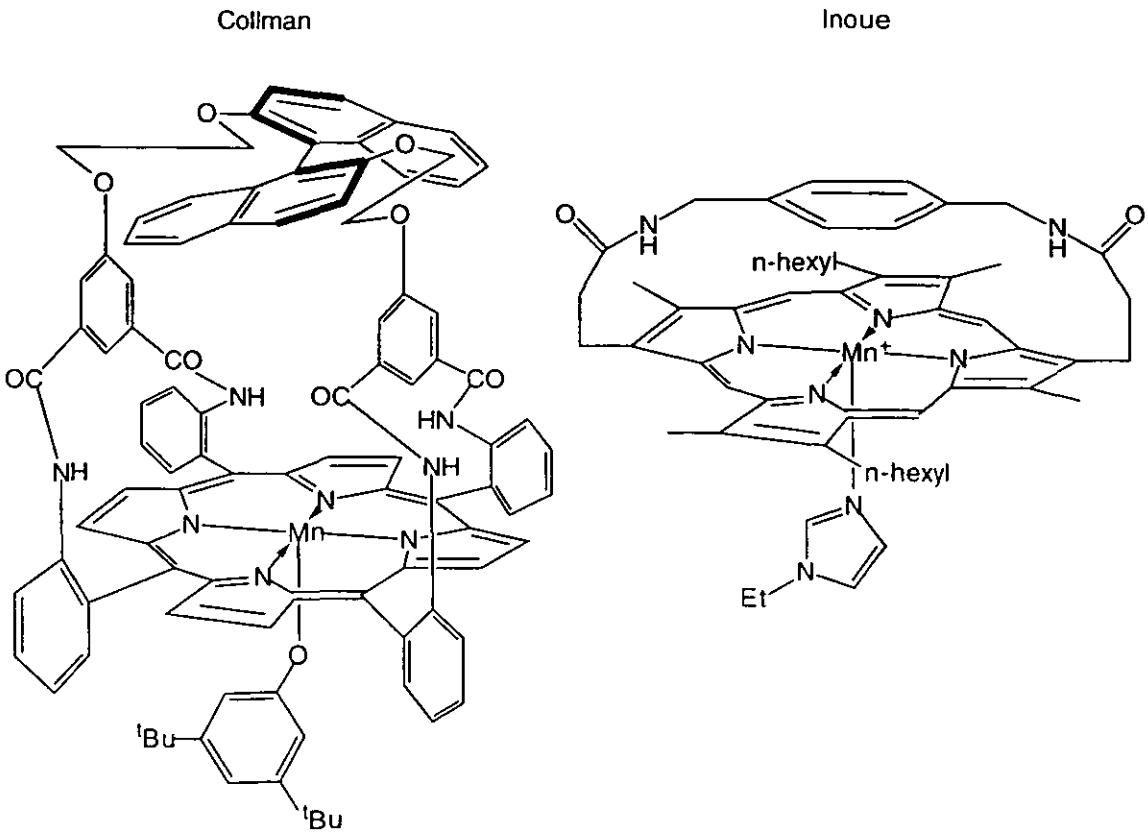


Figure 9: Manganese(III) porphyrin complexes that have been used as chiral epoxidation catalysts by Collman and Inoue respectively.

More recently Collman reported the synthesis and testing of a new class of chiral porphyrins where adjacent *meso* positions are linked through straps derived from threitol (Figure 10).[223] The best catalyst in terms of enantioselectivity had the threitol-derived straps at the same face of the porphyrin and were joined by an additional linker *via* a diacetal moiety. Therefore, it is the latter linker which spanned one of the faces of the porphyrin. The optimum stereochemistry at the acetal carbon atoms was found to be that shown in Figure 10, giving overall a C2 symmetrical system. The enantioselectivities exhibited by these systems proved sensitive to the external ligand. Thus 3,5-ditertiarybutyl phenol, pyridines and imidazoles with small substituents were ineffective in forcing the reaction to take place in the chiral cavity. However, when 1,5-dicyclohexyl imidazole was used (at the correct concentration), significant enantioselectivities were obtained for styrenes and *cis*-aryl alkenes (69-88% ee), but not for *trans*-aryl, alkyl or *cis*-alkyl substituted olefins. These results were obtained with iodosylbenzene as the oxidant. Attempts to replace this reagent with sterically less demanding (hydrogen peroxide, bleach), or bulkier

(iodosylmesitylene, TBHP) oxidising agents led to inferior enantioselectivities. It has been postulated that small oxidising agents may replace the external ligand and promote oxygen transfer processes at the least hindered face of the complex. Similarly extremely bulky oxidising agents may not fit in the chiral cavity and may also compete with the external ligand for the less hindered face.[223]

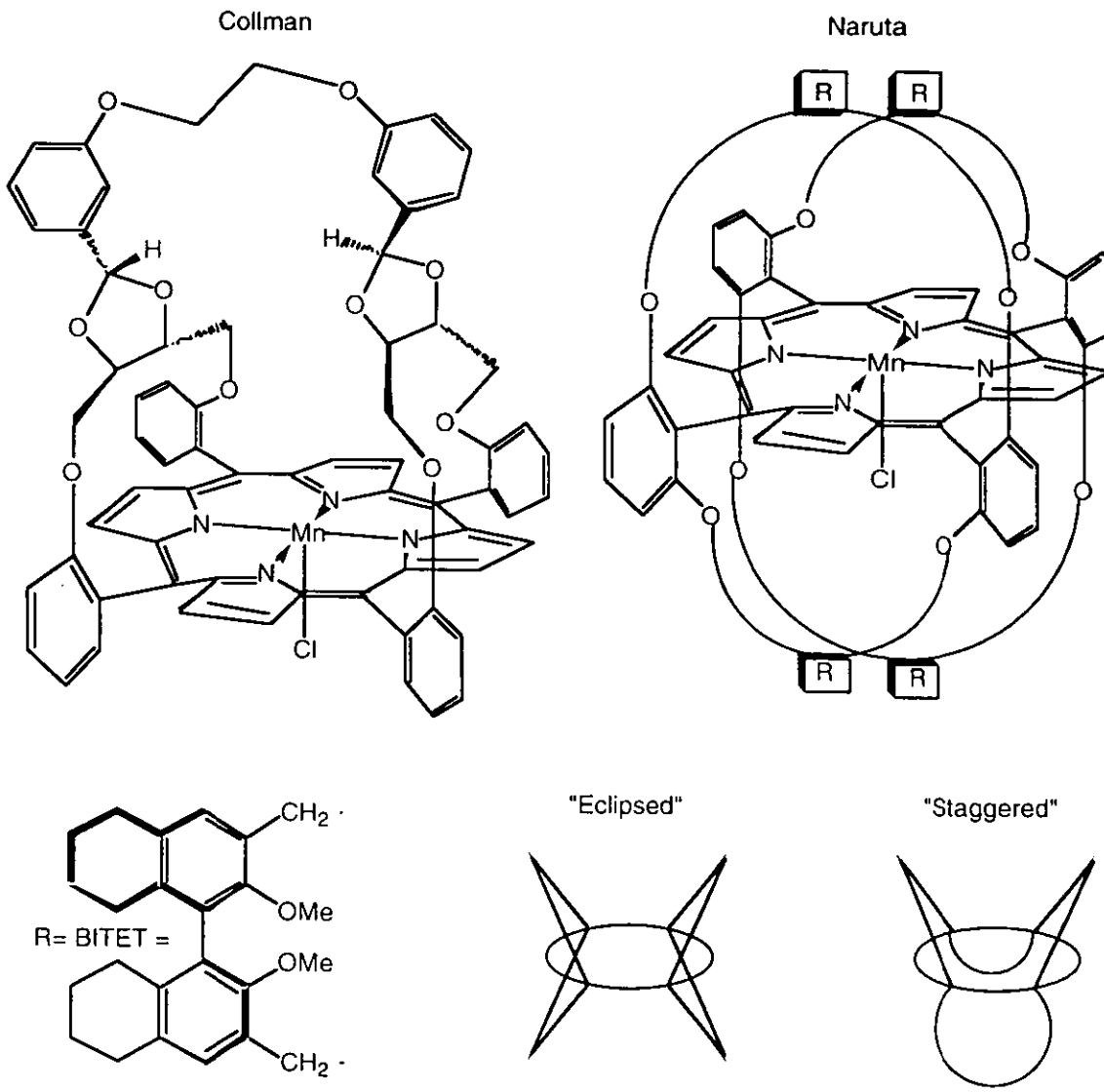


Figure 10: Collman's latest catalyst and Naruta's multistraped "eclipsed" metalloporphyrin.

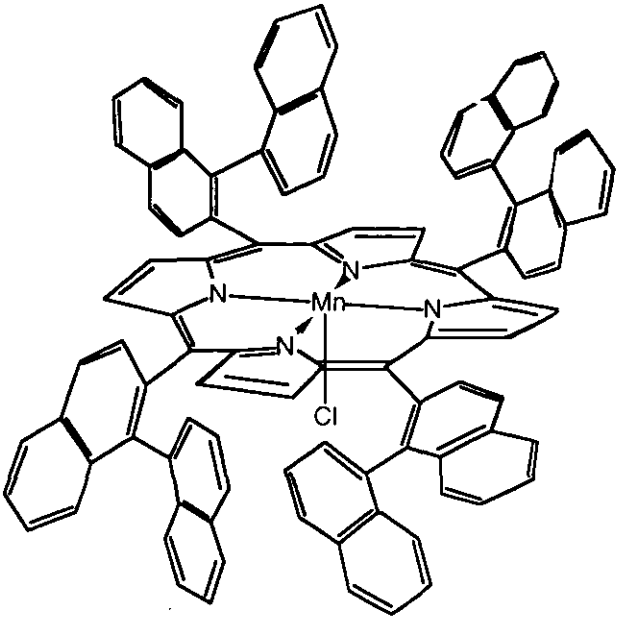
In Naruta's catalyst,[219,220] straps also link adjacent *meso* positions of the porphyrin core, but they exist at both sides of the porphyrin plane (Figure 10). The chiral linkages, which in this case do not span the faces of the metalloporphyrin, are derived from binaphthyl (BINAP) or bitetraline (BITET or bitetrahydronaphthalene)

units respectively. Although the latter entities are C2 symmetric, the resulting structure, which contains four of these species, is of D2 symmetry and two topological isomers can be realised: The "eclipsed" and the "staggered" (Figure 10). Preliminary results showed that the BITET derived catalyst imparted superior asymmetric induction than the BINAP analogue in the epoxidation of unfunctionalised olefins, presumably due to the greater bulk associated with the former linker. Naruta used the "eclipsed" form of the BITET-derived catalyst in the catalytic epoxidation of simple alkenes, and also attempted a correlation of the electronic properties of the substrate with the enantioselectivities observed.[220,224] This author found that electron deficient alkenes were epoxidised with higher enantioselectivities than their electron rich analogues, again with styrenes being the best substrates. For example, 4-nitrostyrene was epoxidised with 89% ee,[220] while 4-methoxystyrene oxide was obtained with poor enantiomeric excess. Naruta later reported that the same "twin coronet" iron(III)-metalloporphyrin could catalyse the asymmetric epoxidation of 3,5-dinitrostyrene with 96% ee, which is the highest reported for metalloporphyrin-mediated asymmetric epoxidations.[224]

The potential applicability of chiral metalloporphyrin complexes as epoxidation catalysts appears to be compromised by several problems. These systems are obtained by multistep syntheses in extremely low overall yields, and the enantioselectivities obtained in asymmetric epoxidation are usually moderate. In addition, these catalysts tend to be unstable under the reaction conditions,[225] and with the exception of Naruta's catalyst, low turnovers of epoxidation reactions have been realised with the systems descibed above. This is considered to be due to decomposition of the chiral porhyrin moiety by means of cleavage and/or oxidation of the chiral linkages under the reaction conditions.[225,231] The latter may also be the reason for the decreased enantioselectivity observed with several systems for the oxygen transfer step as the reaction progresses,[221] and to limit catalyst degradation, substrates are typically employed in large excess relative to the oxidant, typically 10-100:1.

An important step towards overcoming catalyst decomposition was achieved by O'Malley and Kodadek.[226] These researchers realised that electron releasing groups on the aryl substituents at the *meso* positions of the metalloporphyrin promote sensitisation of the system towards oxidative degradation. However, for systems with electron withdrawing groups or simple aryl substituents at the positions in question, catalyst stability and activity are increased substantially. This concept had also been previously demonstrated by Meunier, albeit for achiral metalloporphyrins.[227]

O'Malley and Kodadek



Halterman

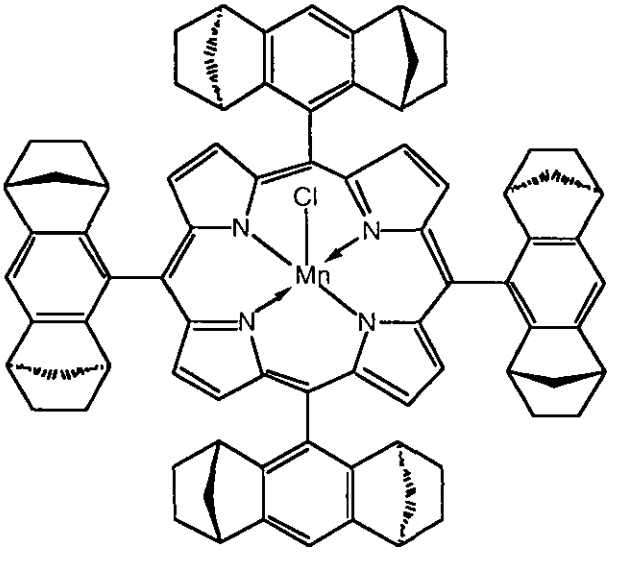


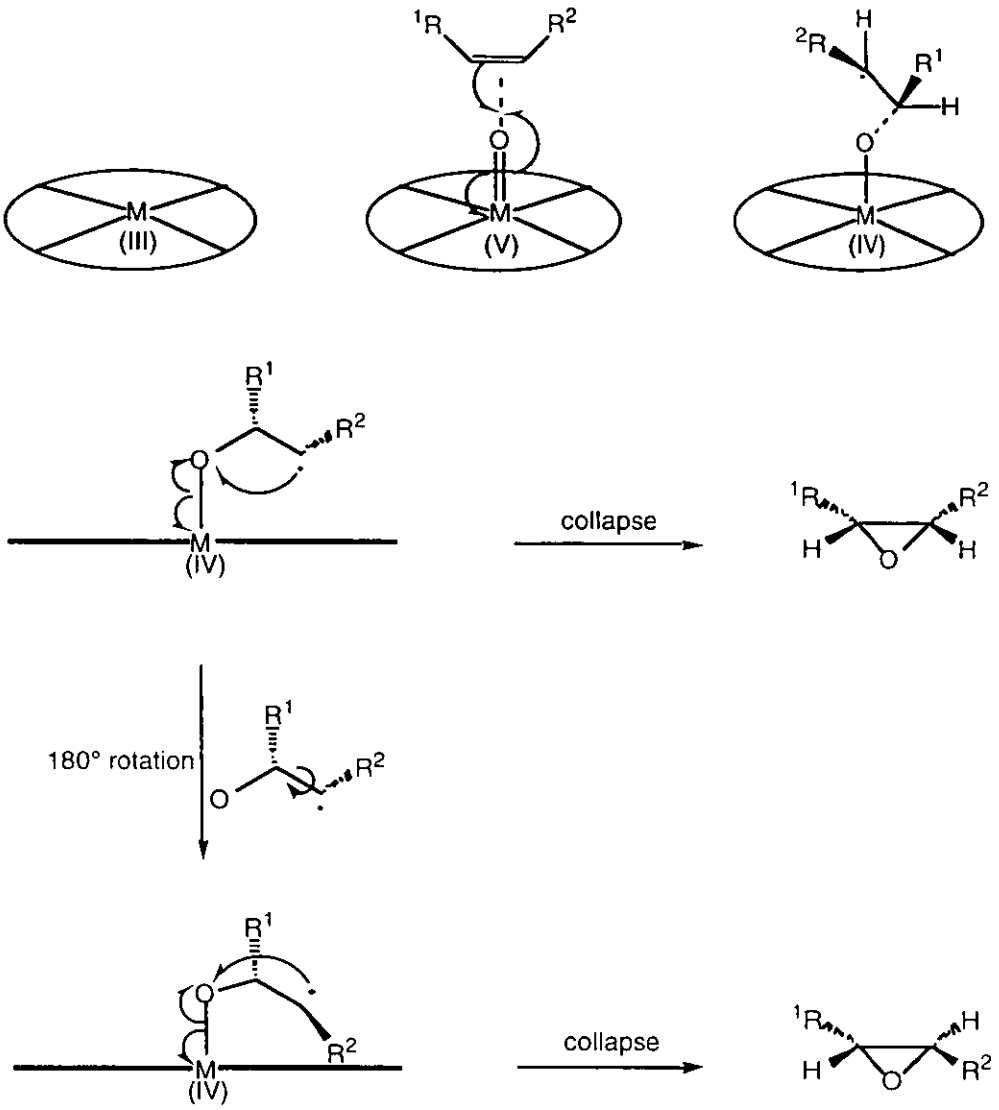
Figure 11: Catalysts developed by O'Malley and Kodadek, and Halterman respectively

The catalyst developed by O'Malley and Kodadek has BINAP groups attached to the *meso* positions ("chiral wall" porphyrin, Figure 11 upper structure), and its robustness is reflected in the catalytic asymmetric epoxidation of simple alkenes with greater than 3000 turnovers.[226] The enantioselectivities obtained with this catalyst, however, are only moderate.

High catalyst turnovers (>2000) are also obtained with the first D4 symmetric manganese(III) metalloporphyrin reported by Halterman (Figure 11, lower structure).[228] The four C2 symmetrical substituents are derived from the corresponding aldehyde which in turn was synthesised by a double Diels-Alder reaction between cyclopentadiene and benzoquinone. As usual with these systems, best enantioselectivities were obtained for styrenes or *cis*-substituted alkenes, with up to 76% ee for *cis*-β-methyl styrene. *Trans*-β-methyl styrene oxide was also isolated from the same reaction mixture with 34% ee.[229,230]

The scrambling of the original olefin geometry is not uncommon in catalytic epoxidations mediated by porphyrin complexes of iron, manganese and ruthenium(III). A widely accepted rationale is depicted in scheme 39.[231] Oxidation of the metal(III) centre, initially produces the corresponding oxo-complex (M=O), which is electrophilic by virtue of the high oxidation state (V) of the metal atom. A single electron transfer from the double bond of the alkene to the oxygen, then relayed to the metal, produces a radical and a carbon-oxygen bond with the latter atom still attached on the metal atom which is now reduced to oxidation state IV.[231-234] The possible fates of this radical intermediate depend upon its stability (substituents), and the identity of the metal ion involved.[235-237] Collapse at this stage to form a second carbon-oxygen single bond, generates the epoxide with retention of the original stereochemistry of the double bond, with concomitant release of the metal atom in the original oxidation state (III). Alternatively, a 180° rotation around the bond joining the formerly olefinic carbon atoms followed by collapse of the radical on the oxygen atom and release of the reduced metal, affords the epoxide corresponding to the geometric isomer of the original substrate (Scheme 39). For steric reasons the epoxide corresponding to the *cis* substrate predominates, particularly at high reaction temperatures.[216,231]

Although no definite direct proof of these reactive species has been provided, products that may arise from alternative reaction pathways of the radical intermediate can be isolated. Several have been identified as carbonyl compounds resulting from oxidative cleavage and/or migration of protons α- to the radical centre.[224] In addition, this model explains the increased enantioselectivities obtained with electron deficient alkenes, because the initial electron transfer from such substrates is unfavourable and therefore a slower and more selective process is observed.[223-225, 231]



Scheme 39: Proposed mechanism for the catalytic asymmetric epoxidation of simple alkenes mediated by chiral metalloporphyrins. The bold line represents the plane of the chiral porphyrin.

Recently, Gross reported developments in catalytic asymmetric epoxidation using (carbonyl)-ruthenium(II) and dioxoruthenium(VI) metalloporphyrins.[231,238] In an attempt to combine two of the most successful approaches, Gross used the D2 symmetry of the strap motif developed by Naruta,[224] but the chiral straps he used were synthesised from the same threitol units employed by Collman.[223] Gross compared the ruthenium complexes derived from the new porphyrin ligand with the corresponding manganese(III) and iron(III) catalysts. Interestingly, these novel metalloporphyrins, despite sharing many similarities with the systems described previously, exhibited enantioselectivities that showed little sensitivity to the external

pyridine or imidazole ligands. In addition the dioxoruthenium(VI) derivative imparted higher asymmetric induction than the (carbonyl)-ruthenium(II) analogue in the epoxidation of a variety of substrates, thus ruling out the conversion of the latter into the former under the reaction conditions. While nearly all of the above authors used dichloromethane as the epoxidation solvent, Gross obtained poor enantioselectivities under the same conditions. When benzene or toluene were used as the solvent however, a significant increase in enantioselectivities was observed, but only for the best substrates for metalloporphyrins, namely styrenes and *cis* substituted alkenes (with up to 73% ee for 4-fluorostyrene with the iron complex). These results were obtained with iodosylbenzene as the stoicheiometric oxidant, but it was quickly established that for the ruthenium complex the enantioselectivities were sensitive to the nature of the oxidant. The highest values were obtained when iodosyl benzene was substituted for 4-methylpyridine oxide, but the yields of the epoxides were very poor. More importantly, these systems were so robust under the improved reaction conditions that more than 6000 catalytic turnovers could be achieved, and this is the highest reported value for porphyrin chemistry. With the increased catalyst stability at hand, Gross used the substrates in stoicheiometric amounts with respect to the oxidant and in a thousand fold excess with respect to the catalyst.

Similar reaction profiles were also described by Berkessel for a (carbonyl)-ruthenium(II) metalloporphyrin using Halterman's D4 symmetric ligand.[239] Berkesel also observed increased enantioselectivities but decreased yields using pyridine oxides as the stoicheiometric oxidant, and the beneficial effect of aromatic solvents. As expected, the enantioselectivities for the epoxidation of aliphatic terminal or *trans*-disubstituted olefines were poor, but up to 77% ee was achieved for dihydronaphthalene oxide. In general, slightly higher enantioselectivities were obtained than those found by Halterman for the corresponding manganese complex using bleach as the stoicheiometric oxidant.

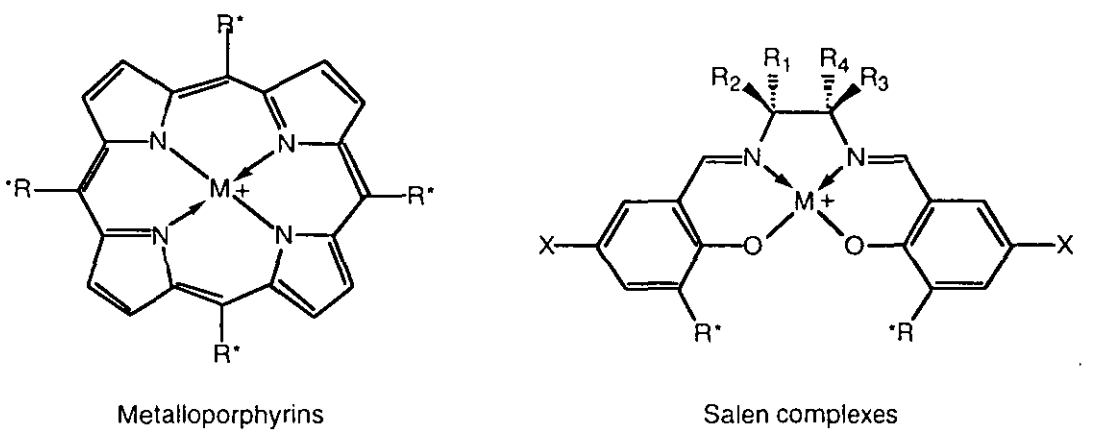
Recent developments in this area include the use of ruthenium(III) and manganese(III) metalloporphyrins in the catalytic epoxidation of simple alkenes mediated by cheaper oxidants such dioxygen and hydrogen peroxide.[240,241]

In summary, asymmetric epoxidation catalysed by metalloporphyrins is only successful for a few substrates. The problem of catalyst degradation and low turnovers has only recently been overcome, but without great improvements in the enantioselectivities for the vast majority of substrates. The multistep synthesis of these catalysts invariably affords poor yields of the active complexes, and thus their synthetic utility is drastically limited.[242,243] Related systems that are easily accessed

and exhibit superior efficiency and enantioselectivity have been developed and offer an attractive alternative. These are described below.

1.4.6 The Jacobsen epoxidation method.

"Chiral salen complexes possess several structural and chemical features in common with porphyrins that render them appealing templates for chiral catalyst design"[218] (Figure 12). Achiral salen complexes were first shown to catalyse the epoxidation of unfunctionalised alkenes by Kochi,[244,245] Burrows,[246] and Nishinaga.[247] In contrast to metalloporphyrins, salen complexes are not completely planar, and can bear asymmetric centres at the tetrahedral carbons atoms near the metal/reaction site (Figure 12). This is the key feature for the origin of the improved asymmetric induction observed in the catalytic epoxidation mediated by salen complexes.[248,249]



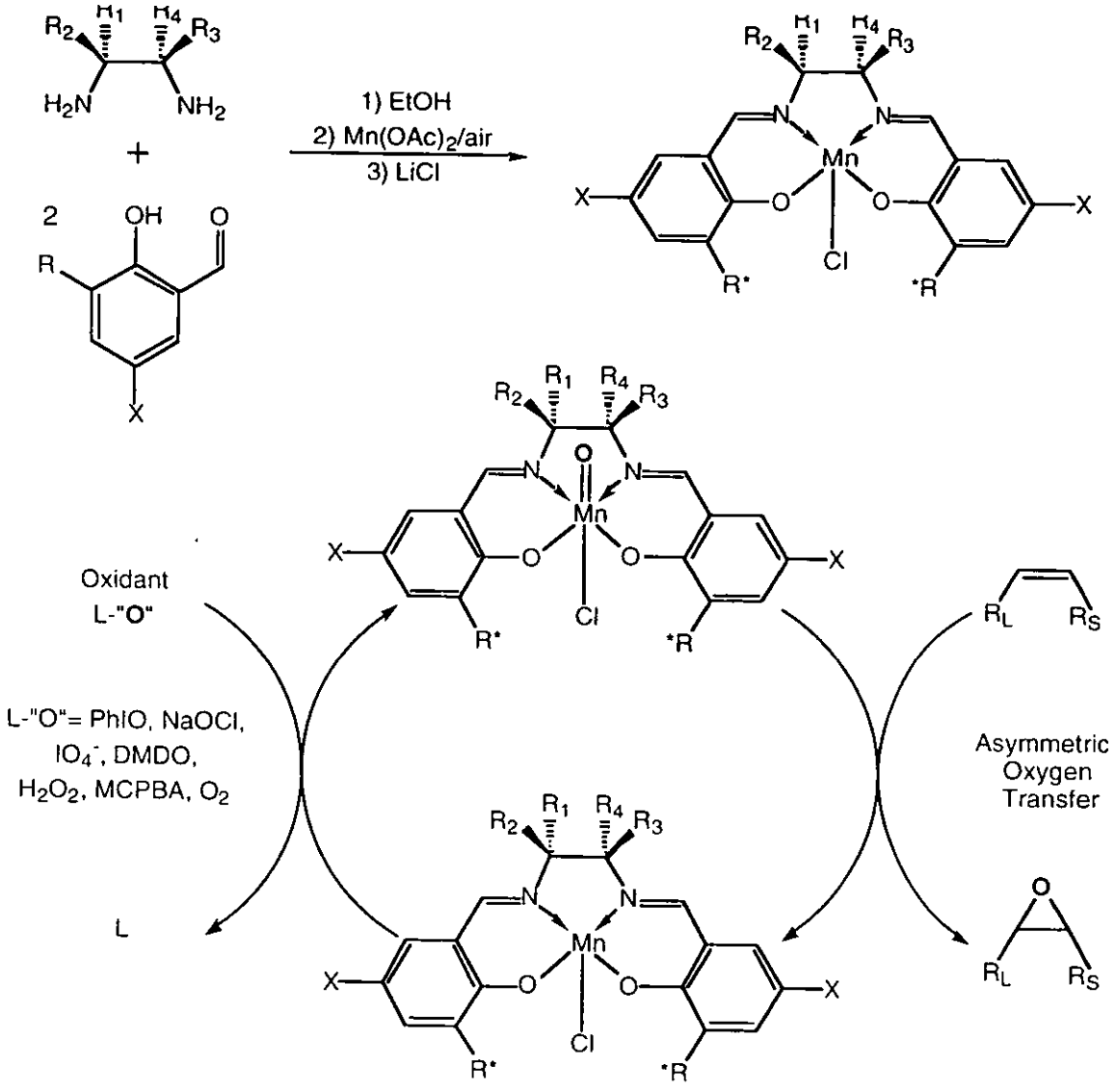
Metalloporphyrins Salen complexes

Figure 12: Salen complexes allow incorporation of chiral substituents nearer the reaction site in comparison to metalloporphyrins.

Furthermore, unlike the porphyrin analogues, the synthesis of salen complexes (salicylideneaminato ligand or salicylaldehydediimine) from chiral diamines and salicylaldhehydes is simple, rapid and, in most cases, a high yielding process (Scheme 40). Because salen ligands are easily accessible, extensive libraries of these catalysts were prepared, and screened in a short period of time.[218]

By far, the most remarkable developments in this area have been independently described by Jacobsen and Katsuki who between them have synthesised more than 120 chiral salen complexes to date. Using this methodology, ligands derived from chiral 1,2-diamines (1,3- and 1,4-diamines have been employed less frequently), and substituted salicylaldehydes which may also be chiral, are

complexed to transition metals, to give salen complexes (Scheme 40). These are excellent catalysts for asymmetric epoxidation, but generally, manganese complexes display superior selectivities and turnovers than catalysts derived from other metals.[218]



Scheme 40: Synthesis and application of chiral manganese(III) salen complexes in the catalytic asymmetric epoxidation of unfunctionalised alkenes.

Epoxidations are usually carried out with 1-10 mol% of the chiral manganese(III) salen complex and 1 or 2 equivalents of a stoicheiometric oxidant. Iodosylbenzene, which is the standard oxidant with metalloporphyrins can be replaced by the cheaper and environmentally friendly sodium hypochlorite (bleach)

in this method.[250] Dioxiranes,[251,252] periodates,[253] peracids,[254,255] hydrogen peroxide,[256-259] and molecular oxygen in combination with a sacrificial aldehyde can also be used.[260-263] With the latter three oxidants however, addition of an external donor ligand is indispensable, probably because the coordination of the axial ligand accelerates the cleavage of the oxygen-oxygen bond. The solvents most commonly used are acetonitrile, dichloromethane or dichloroethane, but fluorinated solvents, such as fluorobenzene, are preferred when molecular oxygen or air are used as the oxidants.[255,258,260]

One of the first catalysts developed by Jacobsen was the manganese salen complex derived from the chiral 1,2-diphenylethylene diamine and salicylaldehyde, but that displayed negligible enantioselectivities in the asymmetric epoxidation of unfunctionalised alkenes (Figure 13, R=X=H).[218,264] In order to explain the poor selectivities, Jacobsen postulated that the substrate approached from the side of the flat aromatic rings opposite the chiral ethylene bridge (Figure 13, Path B). This suggested that introduction of bulky groups *ortho* to the phenolic moiety (positions 3, 3') should hinder this mode of approach and therefore direct the incoming alkene towards the chiral residue (Figure 13, enhancement of Path A)

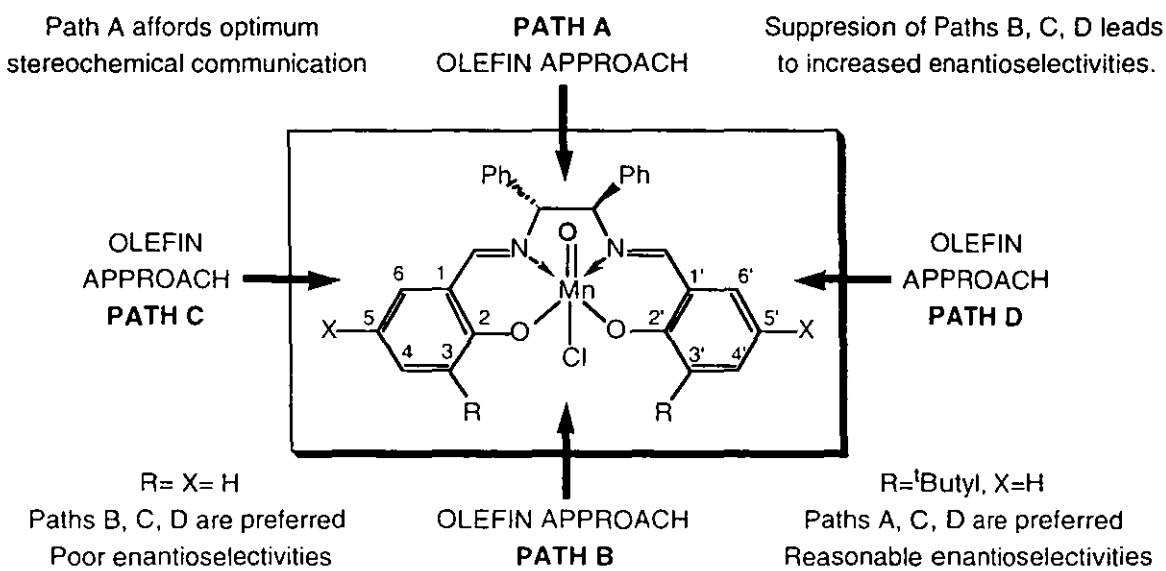


Figure 13: Modes of approach of the alkene substrate to the oxo-complex according to Jacobsen.

Indeed, introduction of tertiary butyl groups at those positions resulted in dramatic increases in enantioselectivities (30-94% ee) for a variety of *cis*-disubstituted alkenes, including some functionalised alkenes such as acetals of cyclic enones and α,β-unsaturated esters.[218,264]

Replacement of the phenyl groups in the parent diamine with the bulkier mesitylene or naphthyl groups resulted in slower reaction rates, decreased enantioselectivities, and increased by-product formation. Furthermore, manganese salen complexes derived from the conformationally more rigid *trans*-1,2-diamino-1,2-dimethylcyclohexane and a variety of substituted salicyldehydes afforded only moderate enantioselectivities.[265] However, it was observed that that the sense of asymmetric induction was opposite from that anticipated on the basis of Path A according to the model depicted in Figure 13. Jacobsen then realised that the substrate may competitively approach the active site from the sides of the complex along the trajectory *para* to to the phenolic moiety (Figure 13, Paths C and D). Indeed, derivatives with substituents at the 5, 5' positions exhibited significant influence on the selectivity of the process (Figure 13, X≠H).[218,265] Jacobsen also discovered that the ability of the catalyst to impart high asymmetric induction was also highly dependent upon the electronic properties of the chiral ligand. Thus, introduction of the electron-donating and bulky tertiary butyl group at the 5, 5' positions (*para* to to the phenolic moiety), and use of *trans*-1,2-diaminocyclohexane as the chiral diamine, led to the most successful salen complex-catalyst developed by Jacobsen to date. Enantioselectivities reported with this manganese complex for *cis*-disubstituted alkenes were typically between 85 and 98% ee (Figure 14).[218,265] Similar results are obtained with the triisopropylsiloxy derivative.

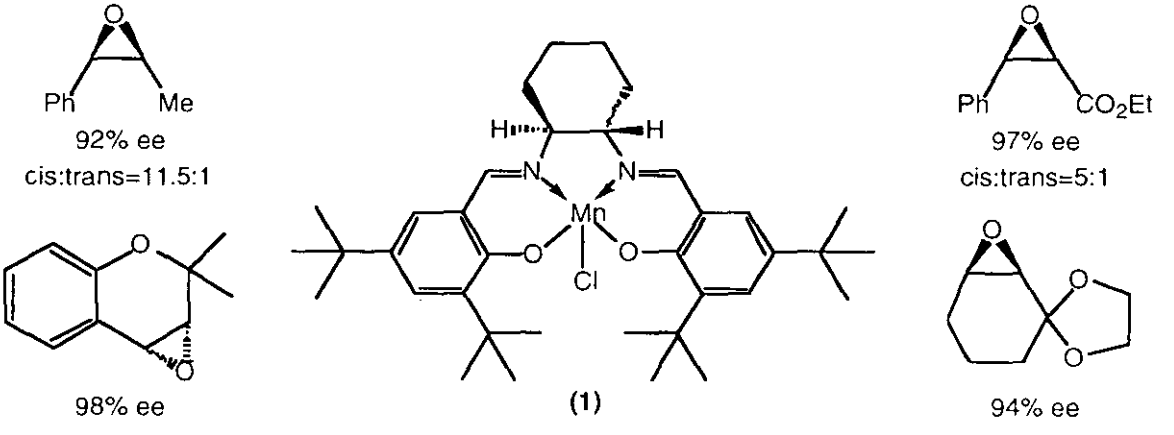
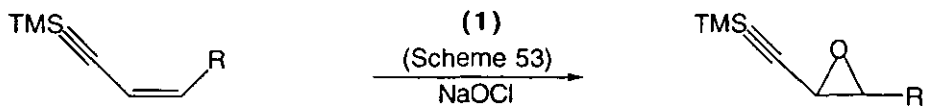


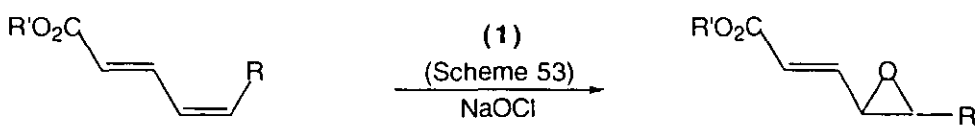
Figure 14: Jacobsen's most successful catalyst for the asymmetric epoxidation of *cis* alkenes.

Despite the high enantioselectivities, there is an Achilles' heel to this method: scrambling of olefin geometry in the epoxides of acyclic *cis* disubstituted alkenes. As with the manganese(III) porphyrin complexes, the metal centre is responsible for the formation of radical intermediates which lead to the observed mixture of

diastereoisomeric epoxides, and thus the transformation is not stereospecific. The extent of degeneration of olefin geometry in the oxygenated product depends heavily upon the substituents in the original alkene.[218,266] In general, isolated *cis*-dialkyl substituted double bonds react in a concerted fashion with complete retention of the alkene stereochemistry, to give the corresponding *cis* epoxides. The conjugated *cis*-analogues however, are believed to react by an electron transfer process, which gives rise to radicals, and therefore scrambling of double bond stereochemistry becomes inevitable. The *cis/trans* ratio is usually greater than 1 for *cis*-disubstituted-aryl alkenes (Figure 14), but less than 1 for alkyl substituted enynes and dienes (Scheme 41).[267] The latter is also the case even when the corresponding *trans*-olefins are used as the substrates.[268]



R	epoxide ratio *cis/trans*	ee *cis*	ee *trans*
Me	1:2.5	48	90
Ph	1:1	35	35
Cyclohexyl	1:5.2	64	98



R	R'	epoxide ratio *cis/trans*	ee *cis*	ee *trans*
Me	^{t}Butyl	1:7	14	66
n-C_5H_{11}	Et	1:9	—	87
CH_2OTBDMS	Et	1:7.3	—	83

Scheme 41: Asymmetric epoxidation of conjugated *cis* alkenes with Jacobsen's catalyst.

In addition, when dienes are used as substrates, regioselectivity issues also arise. With alkyl substituted *cis,trans* dienes the *cis* double bond reacts faster, but gives the *trans,trans* monoepoxide as the major product (Figure 15).[268] When one of the double bonds of the diene is conjugated to an electron withdrawing group, it is

the more electron rich double bond, not directly conjugated to the electron deficient group, that is preferentially epoxidised regardless of being *cis* or *trans*, but the reaction also gives mixtures of *cis* and *trans* epoxides (Figure 15).[268] The stereochemistry of the unreacted double bond is not affected. The *cis/trans* ratio of the monoepoxidised diene ranges from 1:1 to 10:1, and generally the *trans* products are obtained with superior enantioselectivities.[267,268] In contrast, in the mixture of epoxides obtained from isolated double donds, the *cis* products are obtained with higher enantioselectivities.

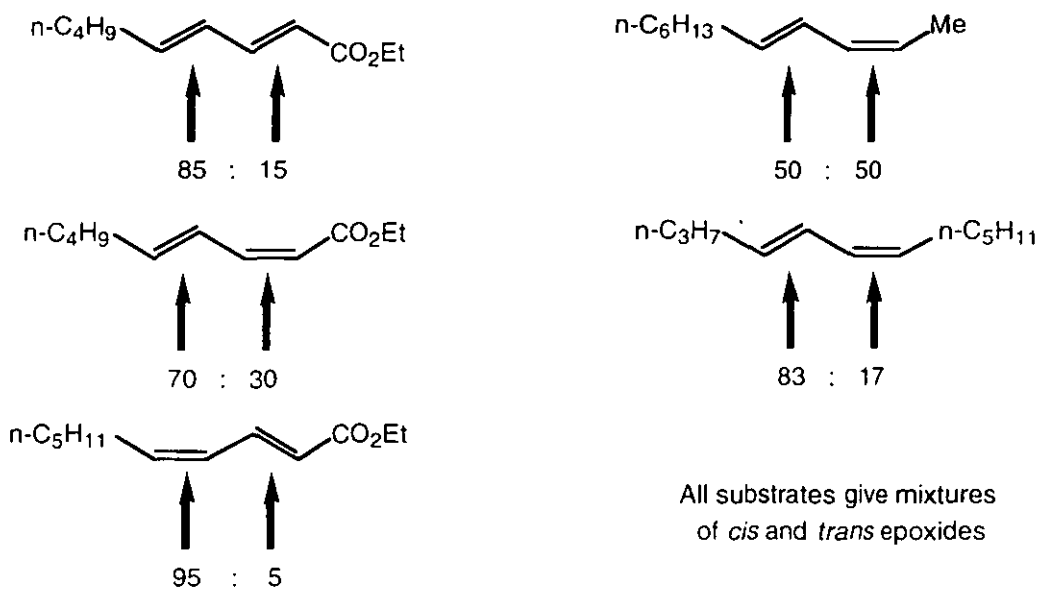


Figure 15: The regioselectivity in the asymmetric epoxidation of acyclic dienes with Jacobsen's catalysts is heavily dependent on the substrate.

In 1994, Jacobsen reported that quaternary ammonium salts could influence the *cis/trans* ratio of epoxides obtained during the oxidation of acyclic 1,2-disubstituted alkenes.[269] In particular, chiral ammonium salts derived from cinchona alkaloids were shown to promote epoxidation of certain substrates with greater than 9:1 *cis/trans* ratio, but these additives do not influence the enantioselectivity of the reaction which is solely determined by the chiral ligand.[269] The effect of the additive is however, not equally successful for all types of substrates, and the nature of interaction with the catalyst remains unclear.

Jacobsen has also investigated the effectiveness of chiral manganese(III) salen complexes in the asymmetric epoxidation of tri- and tetrasubstituted alkenes. High enantioselectivities are obtained in the epoxidation of the former category of alkenes

(85-95% ee) using the same catalyst that was developed successfully for the epoxidation of *cis*-disubstituted double bonds, but similar selectivities were obtained with a range of other ligands.[270] Several catalysts were also tested in the asymmetric epoxidation of tetrasubstituted olefins, but there did not seem to be a superior catalyst for all types of substrates examined.[271] Generally, enantioselectivities are high for chromene derivatives (75-97% ee) but significantly less for dihydronaphthalene and stilbene derivatives (7-65% ee).[271]

The series of catalysts developed by Katsuki focus on a chiral residue attached at the aromatic carbon *ortho* to the phenolic group (3, 3' positions).[272-278] These derivatives are also good epoxidation catalysts, but the best systems are those that possess substituents with axial chirality rather than asymmetric centers at the 5, 5' positions.[279-282] These are synthesised from a BINAP precursor that contains the 2-hydroxyarylaldehyde moiety, equivalent to the salicylaldehyde component (Figure 16). In comparison to Jacobsen's catalyst, the Katsuki systems exhibit similar enantioselectivities for *cis*-alkenes but afford greater enantioselectivities in the epoxidation of *trans*-olefins (66 vs 25-33% ee for *trans*-stilbene oxide.[277,282]

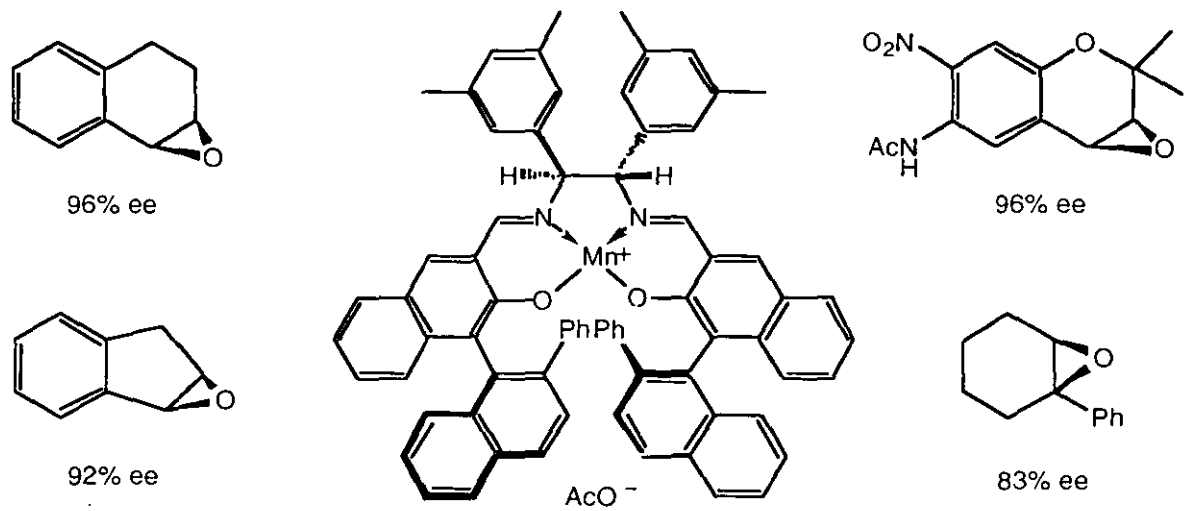


Figure 16: Katsuki's catalyst also mediates asymmetric epoxidation of alkenes with high enantioselectivities.

Higher selectivities in the epoxidation of *trans*-disubstituted olefins can also be obtained with a chiral chromium salen complex according to a recent report.[283] However, the same problems of *cis/trans* isomerisation during the epoxidation process are also at work with Katsuki's catalysts. As with the systems developed by Jacobsen, Katsuki's chiral manganese(III) salen complexes are also capable of

imparting high asymmetric inductions in the epoxidation of trisubstituted alkenes, typically between 83 and 99% ee.[284] In comparison, high enantioselectivities are obtained with both systems for specific classes of alkenes, but Jacobsen's salen complexes are synthetically easier to access.

The mechanism of the Jacobsen epoxidation reaction has been a point of controversy over the years and is yet not fully understood. Two aspects of this reaction have been of particular interest to the two pioneers in this area Jacobsen and Katsuki. First, the exact mode of approach of the olefin to the active site, and secondly the mechanism of the oxygen transfer step. Understanding these aspects is of prime importance in order to design more selective catalysts. As mentioned previously, Jacobsen supports approach of the olefin substrate towards the active site of the complex along a trajectory above the chiral bridge joining the two nitrogen atoms, with the smaller substituent nearer to the axial hydrogen atom (Figure 17).[218,266]

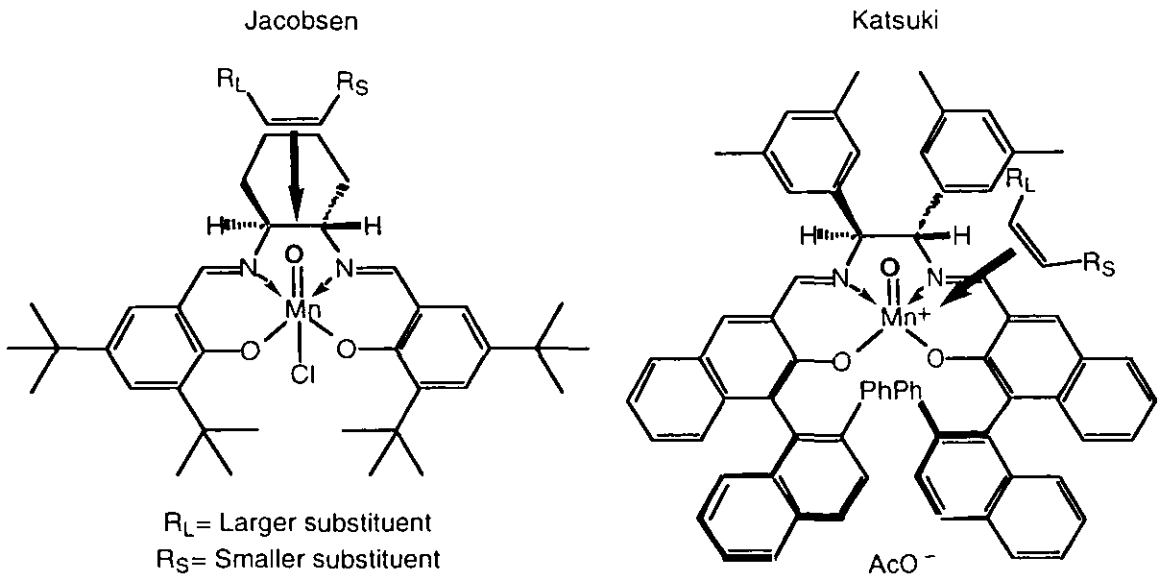
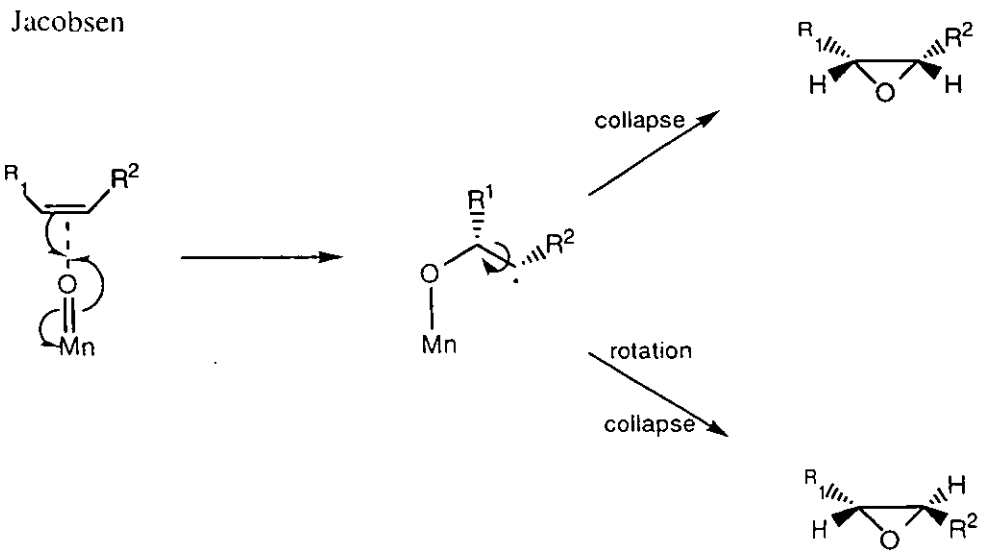


Figure 17: The models of olefin approach to the oxo complex as supported by Jacobsen and Katsuki respectively.

Katsuki favours the approach along one the nitrogen-metal-oxygen diagonals from the nitrogen end, due to π–π interactions, and argued that Jacobsen's model is not consistent with the influence of the 3, 3' substituents on the enantioselectivities.[285-287] In Jacobsen's systems however, in addition to these substituents there are bulky groups *para* to the phenolic entity which hinder the mode of approach supported by Katsuki, whose ligands lack those substituents. In

addition, in several cases higher enantioselectivities are obtained with the Jacobsen system despite the absence of the additional stereogenic centers. In contrast, Katsuki has demonstrated that a salen complex derived from an achiral diamine, but with asymmetric units *ortho* to the phenolic oxygen atoms, affords reasonable asymmetric induction in the epoxidation of *trans* olefins.[288] Nevertheless, because the two authors have constructed their models in reference to different complexes, strict comparison cannot be made,[289] but either model can explain to some degree the stereochemical outcome of the epoxidation reaction depending on the catalyst used.

Due to the similarity between manganese(III) salen and porphyrin complexes, a similar mechanism was proposed to be in operation during the epoxidation process by Kochi, in his work with achiral salen complexes.[244,245] The existence of the radical intermediate described above for the metalloporphyrin-catalysed reaction is widely accepted because it explains the *cis/trans* partitioning of the epoxide products (Scheme 42). The point of controversy has been how this intermediate is formed.



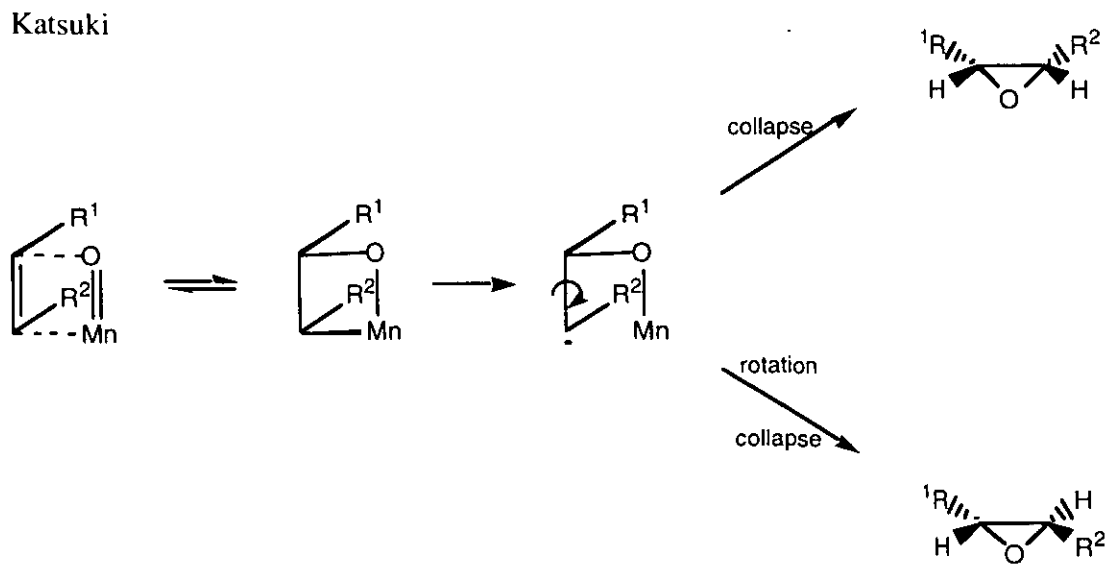
Scheme 42: Jacobsen supports the same mechanism proposed for the epoxidation catalysed by manganese(III) porphyrins.

Jacobsen supports oxidation of the metal(III) to the oxo metal(V) complex, followed by an irreversible electron transfer directly from the substrate on the oxygen atom, to give the intermediate radical. The latter is partioned between collapse to the epoxide and rotation/collapse to the diastereoisomeric epoxide (Scheme 42).[290]

The relative rate of each collapse pathway depends upon the substituents at

(Scheme 42).[290]

The relative rate of each collapse pathway depends upon the substituents at the carbon bearing the radical, which is stabilised by aryl, alkenyl and alkynyl groups. It follows that the *cis/trans* ratio of the epoxide products depends upon the half-life of the intermediate, which is prolonged for conjugated substrates.[218] Simple alkyl substituents which cannot stabilise this intermediate collapse quickly to the product largely with retention of the existing geometry, giving overall the profile of a concerted process.[291] Katsuki obtained non-linear Eyring plots for the asymmetric catalytic epoxidation of dihydronaphthalene and other substrates, and suggested the presense of a reversibly formed intermediate. Reversible formation of a metallaoxetane species followed by homolytic cleavage of the carbon-manganese bond generates the radical in question (Scheme 43).[286,292,293] The partitioning of the latter between collapse and rotation/collapse depends, as in Jacobsen's proposal, on the substituents of the starting alkene.



Scheme 43: Katsuki supports that reversible formation of a metallaoxetane species precedes and gives rise to radical intermediate.

Jacobsen in turn, questioned the validity of this interpretation of the data because the effect was greatest for dihydronaphthalene oxide, which is known to undergo efficient kinetic resolution by a secondary oxidation pathway.[294,295] In addition, the variations in ee's were too small, and several important experimental details were missing. Jacobsen repeated the study to determine the relationship between ln[enantiofacial selectivity] and the reciprocal of temperature for four

substrates over a large temperature range and obtained linear Eyring plots.[295,296] Linear Eyring plots suggest that the reaction proceeds *via* the irreversible formation of an intermediate,[297] in accord with the direct electron transfer from the alkene to the oxo complex. Extensive studies have also proved the importance of the added external ligand on the yield, rate of the reaction,[244,245] enantioselectivity, and the *cis/trans* ratio of the diastereoisomeric epoxides produced (where applicable).[254,275,297] Such effects can only be realised if the external ligand is actually coordinated to the metal centre during both the generation of the oxo complex and the oxygen transfer step. This leaves no available coordination sites for the formation of the metallaoxetane species. Even from a steric point of view, the formation of the latter also seems difficult. To accomodate the observation that diastereoisomeric epoxides are generated from *cis*-aryl olefins, the aryl substituted olefin terminus would have to bind to the Mn centre in closest proximity to the plane defined by the ligand in the metallaoxetane intermediate.[295]

An independent approach was recently reported by Norrby and Åkermark who examined the epoxidation of 1-phenyl-1-vinylcyclopropane, and the *cis* and *trans* 1-cyclopropyl-1-phenylprope-1-nes, with the racemic form of Jacobsen's catalyst (manganese (III) complex with the diimine derived from *trans*-1,2-diaminocyclohexane and 3,5-di-*tert*-butylsalicylaldehyde).[298] The cyclopropyl entity is a well known radical trap that has also been used by Jacobsen.[291] Therefore, if a radical was formed at the benzylic position α- to the cyclopropyl group, ring opened products would be observed. Interestingly, ring opened products were indeed obtained, but their proportion depended highly upon the combination of oxidant and solvent. In general, when the epoxidation was carried out in the two phase system of dichloromethane and a buffered solution of sodium hypochlorite, little or no ring opened products were observed, while iodosylbenzene in benzene invariably affords ring-opened products. The authors interpreted these observations by invoking the metallaoxetane intermediate, and supported this rationale by computer calculations.[299] However, no mention of the effect of the added external ligand was made in this study, although its importance in this reaction is well established.[300,301] In fact, both Jacobsen and Katsuki have recently synthesised salen ligands with a pendant coordinating group (Figure 18, pyridine N-oxide and carboxylate respectively).[295,302] The manganese(III) complexes of these have been shown to be excellent catalysts for the asymmetric epoxidation of alkenes in the absence of any external ligand.

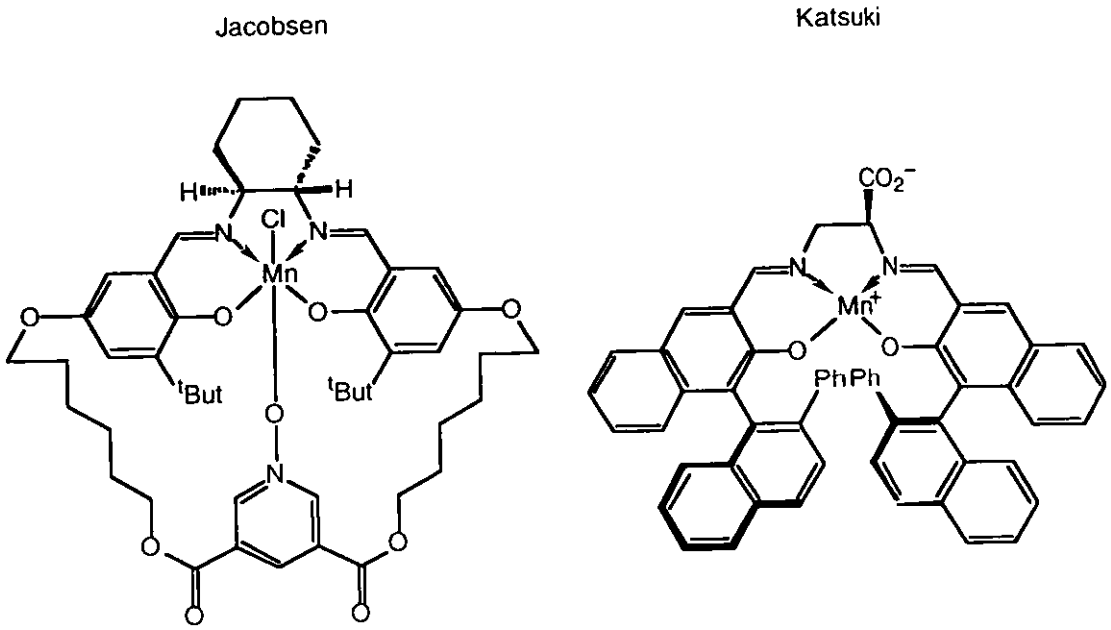


Figure 18: Chiral manganese(III) salen complexes with pendant coordinating groups

Jacobsen has also established that the more electron rich the ligand the better the enantioselectivities of the oxygen transfer to the substrate.[303] The Hammett plots of the observed enantioselectivities for three different olefins gave linear correlations, with the σ_p values of the substituents para to the phenolic group of various ligands.[295,296] Additionally, the correlation between the logarithm of enantiofacial selectivity and the σ_p values of the same substituents in the epoxidation of indene at various temperatures revealed an isokinetic point.[296] The observation of an isokinetic relatiosliip is generally taken as evidence that the reaction parameter being varied (in this case temperature), affects only one type of interaction in the system.[304] Electron donating substituents on the ligand may stabilise the high-valent manganese(V) oxo complex, and therefore attenuate its electrophilicity. The substrate perhaps reacts in a slower and more selective fashion with the milder oxidant.[296] Katsuki also examined the electronic effect of the substituents in his systems but he obtained lower enantioselectivities for some substrates when ligands with electron donating groups were used.[286,305] The study was however carried out for a catalyst that is effectively derived from a binaphthalene precursor, so the effect of the ligand substituent was examined for what would be in the Jacobsen catalyst a vinylogous position.

Because Jacobsen and Katsuki have worked with different salen ligands strict quantitative comparisons cannot be made. In truth, the mechanism of this important

reaction seems to be influenced by several parameters in addition to the nature of the ligand and substrate. The manganese(V) oxo complex has never been isolated, but its existence was confirmed recently by electro-spray tandem mass spectrometry.[306] Only the chromium oxo complex and its adduct with pyridine oxide have been isolated, and their X-ray analysis determined that their structures are square pyramidal and octahedral respectively, with the chromium ion slightly off the plane defined by the salen ligand and towards the axial oxygen atom.[245] Katsuki has also argued that the manganese derivatives may not be planar, but folded, with each half of the salen ligand in a skew arrangement to one another.[302] There is no evidence for such a conformation, but computer calculations render it possible. In contrast, Jacobsen has showed by X-ray analysis that both the Mn(III) salen complexes and their adducts with external ligands are consistently square planar.[290,295]

In 1997, Katsuki reported an interesting solvent effect for chiral chromium(III) salen complexes which was consistent with a change in mechanism from non-polar solvents (toluene) to polar solvents (acetonitrile).[307] Generally, the enantioselectivities of the epoxidations mediated by chiral manganese(III) salen complexes are not sensitive to solvent effects. This is indicative of a process involving radical intermediates, because they are not charged and therefore not heavily solvated. Katsuki proposed that, in polar solvents, the chromium complexes promote epoxidation *via* a different species (probably not radicals) from that involved in the manganese(III) based systems.[307]

Other developments of the Jacobsen system include: Kinetic resolution of racemic alkenes,[308,309] immobilisation of the catalyst on a polymer support[310,311] and polydimethylsiloxane membranes,[312] optimisation studies,[313,314] epoxidation of dienyl sulfones,[315] resolution of allenes,[316] kinetic hydrolytic resolution of racemic terminal epoxides,[317-319] and the desymmetrisation of *meso* epoxides by asymmetric ring opening with thiols, carboxylates, and azide.[320-322]

Finally, Jacobsen's catalyst has been used for the asymmetric epoxidation of an alkene intermediate in the synthesis of leukotriene methyl ester (LTA_4),[268] CDP840, an important inhibitor of phosphodiesterases,[323] the antihypertensive agents cromakalim and EMD-52,692,[324] and in the synthesis of (+)-teretifolione B by kinetic resolution.[308]

In summary, unlike the porphyrin systems, the enantioselectivities obtained with the chiral salen complexes can be up to 96%. In addition, a wider range of substrates can be used in comparison to the metalloporhyrin systems. Nevertheless, the complication which arises with these systems, is the lack of stereospecificity.

Furthermore, with the exception of *cis* disubstituted alkenes there does not seem to be a superior catalyst for other types of olefins. The ease of synthesis however, and tuning of the electronic and steric properties of the salen ligands may make the Jacobsen method one of the most popular for the asymmetric epoxidation of simple alkenes.

1.4.7 Other metal and Lewis acid-catalysed epoxidation reactions.

Nowadays, because of the success of the Sharpless and Jacobsen methods, titanium and manganese are the metals most commonly associated with systems of catalytic epoxidation. However, a number of other metal-ligand combinations have been studied over the years in order to develop catalysts for the epoxidation of various alkene substrates.

For example, Sharpless had shown that the catalytic epoxidation of allylic alcohols could be achieved by achiral vanadium(V) or molybdenum(VI) complexes and organic hydroperoxides with high regio- and stereoselectivity.[325,326] Sharpless later used a chiral hydroxamic acid derived from campholic acid as ligand for this process, and obtained enantioselectivities between 5 and 50% ee in the asymmetric epoxidation of prochiral primary allylic alcohols (1 in Figure 19).[327] The use of a chiral hydroxamic acid derived from proline afforded 80% ee in the epoxidation of α-phenylcinnamyl alcohol.[90] Sharpless supported that the mechanism of the vanadium catalysed epoxidation appears to proceed *via* the oxo-complex, which is then further coordinated with the oxidant and the substrate in similar fashion to that described earlier for the titanium tartrate process.[327] However, a number of alternative mechanisms have been proposed over the years depending on the vanadium species actually used as catalysts.[328] Berkessel has recently reported a chiral ligand that was used in the TBHP/vanadium(V) or nickel (II) catalysed epoxidation, albeit with poor results.[329]

Oshima has reported that the epoxidation of allylic alcohols may be mediated by aluminium tertiary butoxide and TBHP.[330,357] Diastereoselectivities were in many cases greater and usually of the opposite configuration from those obtained using the archetypal vanadium catalyst $VO(acac)_2$.[325]

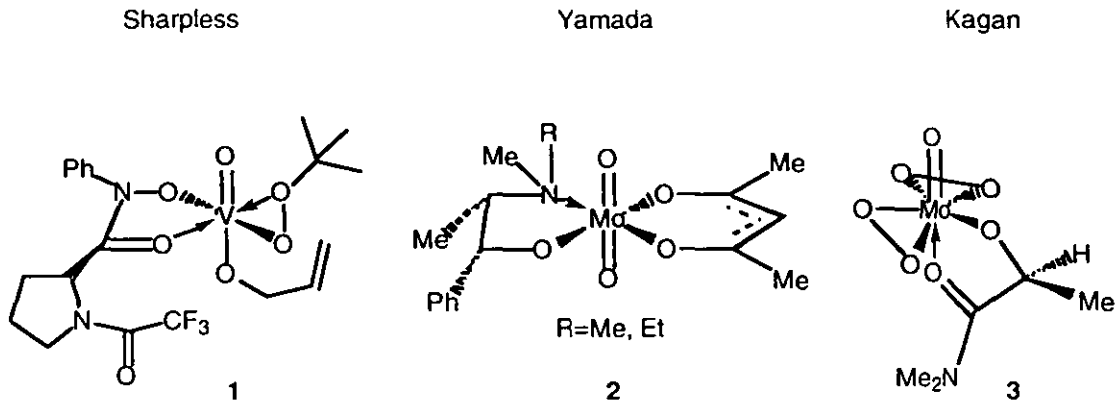
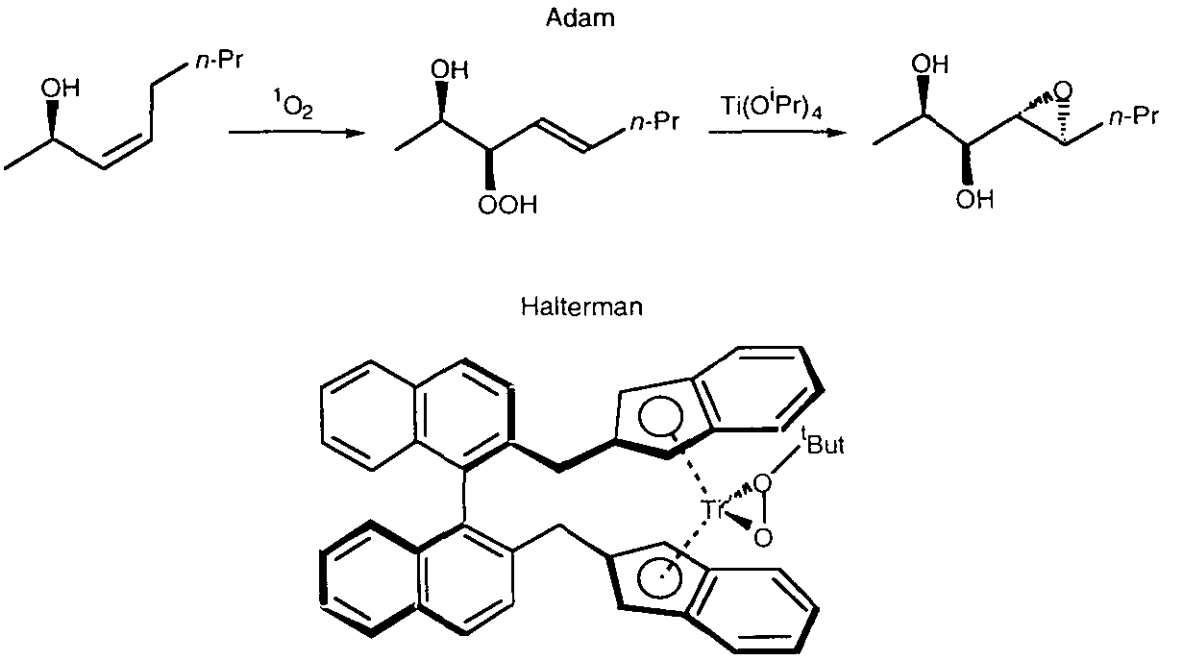


Figure 19: Some of the first chiral vanadium and molybdenum complexes developed for catalytic asymmetric epoxidation.

The vanadium catalysed epoxidation is not as successful for simple olefins as it is for allylic alcohol substrates. In contrast, catalysis by molybdenum complexes is faster and works better for unfunctionalised alkenes,[331,332] but is less effective for allylic alcohols.[333] Chiral molybdenum complexes that have been employed in the asymmetric epoxidation of alkenes have met with limited success. Yamada used [N-alkylephedrine-dioxomolybdenum(acac)] complexes and afforded up to 33% ee (2 in Figure 19),[334] while similar results were reported for the prolinol analogue.[335] Lower enantioselectivities were obtained when TBHP/dioxomolybdenum(acac)$_2$ was allowed to mediate epoxidation of simple alkenes in the presence of chiral sugar derivatives.[336] Kagan has used a complex derived from a chiral amide and diperoxo-oxomolybdenum·HMPA (3 in Figure 19), and obtained up to 35% ee in the epoxidation of low molecular weight alkenes.[337] Optimisation of this process through a ligand and additive variation approach, has led to improved results in certain cases.[338-340] The mechanism for the dioxomolybdenum complexes and the oxomolybdenum diperoxy species-catalysed epoxidations has been the subject of many discussions (especially for the latter type of catalysts).[328] Nevertheless, the mechanism of the molybdenum-catalysed epoxidation of allylic alcohols seems to parallel that involving vanadium complexes, but none of the above processes can compete with the titanium tartrate procedure.

An intramolecular variant of the Sharpless catalytic asymmetric epoxidation of allylic alcohols has been described by Adam. In this reaction, an allylic alcohol is photooxygenated (ene reaction) to furnish the α-hydroxy allylic hydroperoxide, which, upon treatment with titanium isopropoxide, epoxidises the alkene entity intramolecularly without the use of an external oxidant (Scheme 44).[341-343] The

product obtained is the diol epoxide. Adam has also found that the epoxidation of allylic alcohols occurs faster with 1,2-hydroperoxy alcohols than with TBHP, and has used several such derivatives as the oxidants in the Sharpless process. Diastereoselectivities ranged from 52 to 90% de.[344] Halterman has described a method for asymmetric epoxidation based on a chiral titanium-cyclopentadienyl complex, but low to moderate enantioselectivities were observed (Scheme 44).[345]



Scheme 44: Adam's procedure for the synthesis of epoxydiols and Halterman's catalyst.

Reactions related to the Jacobsen method have also been reported.[259] Bolm has introduced a new ligand for the manganese(III) catalysts used in the epoxidation of simple alkenes, that is based on a chiral 1,4,7-triazacyclononane (Figure 20). Despite the structural differences between this and the salen ligands, the usual problems of *cis/trans* epoxide partitioning were also observed. The enantioselectivities obtained in the epoxidation of *cis*-β-methyl styrene were 55 and 13% ee for the *trans* and *cis* epoxides respectively (in 7:1 ratio). A chromene substrate was epoxidised with 40% ee.[346] Other macrocyclic ligands have also been complexed with iron(III) and nickel(II) by Hopkins and Burrows respectively (Figure 20). These complexes were used for asymmetric epoxidation with iodosylbenzene as the stoicheiometric oxidant, but almost complete absence of asymmetric induction was observed.[347-349] It has been postulated that the active oxidising agents in these systems may involve free radicals that are not coordinated to the chiral complex.[350]

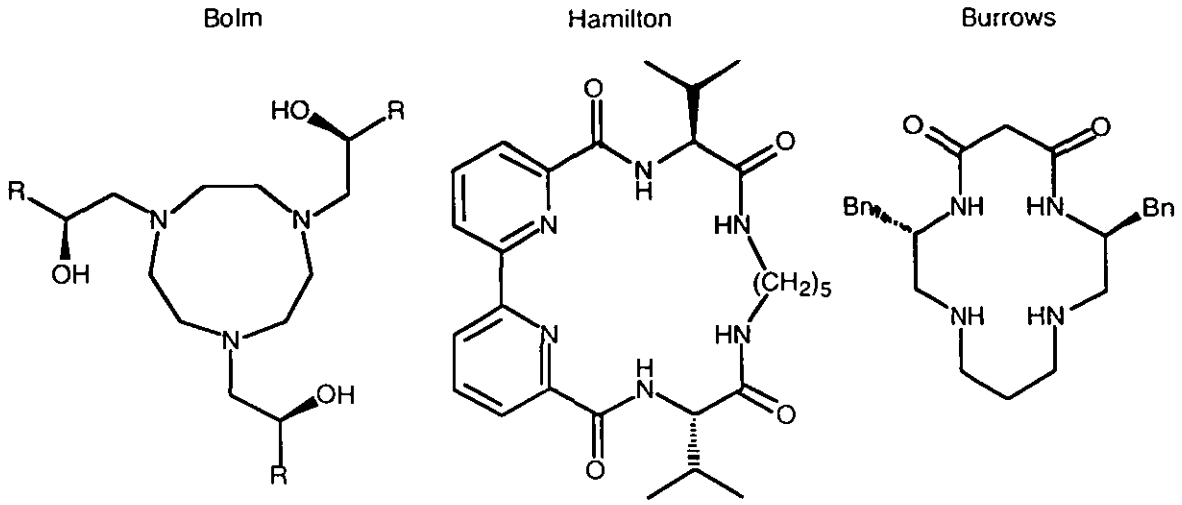


Figure 20: Chiral macrocyclic ligands developed for the Mn(III), Fe(III) and Ni(II) catalysed asymmetric epoxidation respectively.

Ozaki has tested cobalt(III) complexes of chiral tetradentate ligands but low enantioselectivities (0-17% ee) were observed in the epoxidation of styrene with iodosylbenzene as the stoicheiometric oxidant (Figure 21).[351]

Recently, Pfaltz reported a method of catalytic asymmetric epoxidation mediated by a ruthenium chiral complex.[352] The ligand involved was a tetradentate C2 symmetric oxalamide which is readily available from 2-(2-aminophenyl)oxazolines (Figure 21). The stoicheiometric oxidant used was sodium periodate which is commonly employed with ruthenium trichloride in the oxidative cleavage of C–C double bonds. Indeed, significant amounts of benzaldehyde were found in the reaction mixture of *trans*-stilbene epoxidation. The ratio of epoxide to oxidative cleavage products was found to be highly dependent on the substituent(s) of the chiral ligand (Figure 21). The valinol derived-oxalamide was the best of those tested, affording (1:1) benzaldehyde and *trans*-stilbene oxide in 62% ee when *trans*-stilbene was used as the substrate. Chiral ligand/Ru(III)/$NaIO_4$ catalysis in asymmetric oxygen transfer has been reported previously,[353,354] but the enantioselectivities are inferior to those obtained with the Pfaltz system.

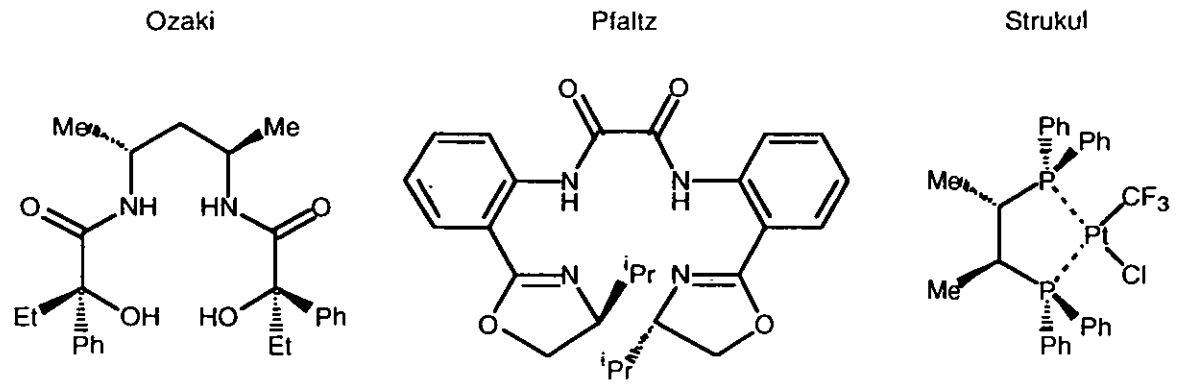
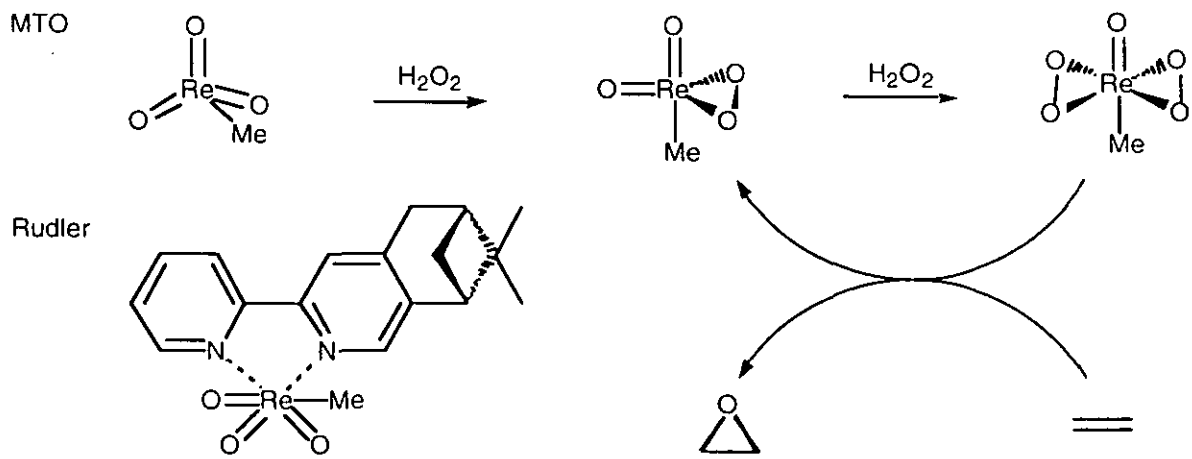


Figure 21: Chiral ligands for the Co(II) and Ru(III) catalysed asymmetric epoxidation. The Pt(II) complex is particularly successful in the epoxidation of terminal olefins.

The asymmetric epoxidation of terminal aliphatic olefins has been a challenging task in this area. The most successful catalyst to date for the epoxidation of these type of substrates was reported in 1987 by Strukul, and involves a platinum/chiral diphosphine complex (Figure 21).[356] Hydrogen peroxide was used as the stoicheiometric oxidant and the epoxidation of propene and oct-1-ene, was achieved with enantioselectivity of 41% ee. The exact mechanism of the oxygen transfer however, has been a point of controversy.

Remarkable advances have been recently made by Sharpless in the catalytic epoxidation of simple olefins mediated by methyltrioxorhenium (MTO) and hydrogen peroxide as the stoicheiometric oxidant (Scheme 45).[358]

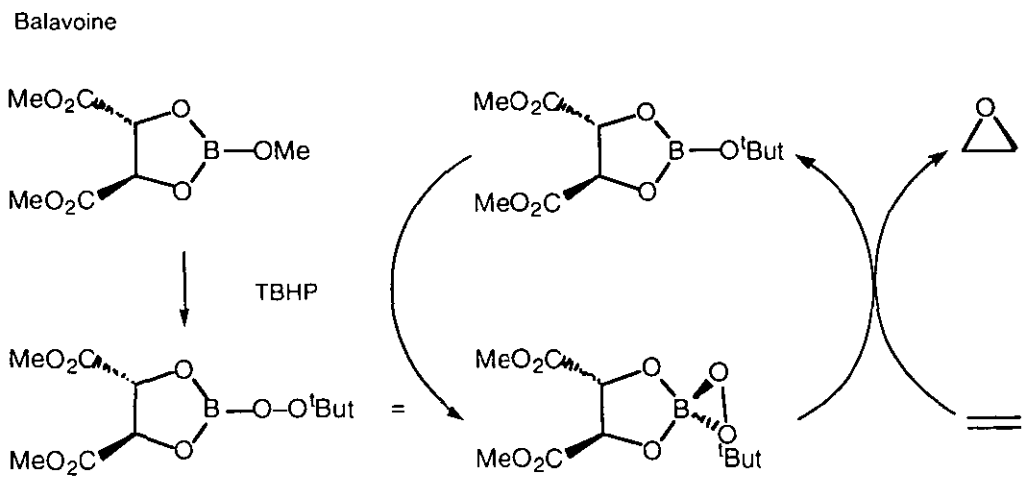


Scheme 45: The MTO method is very successful in the catalytic epoxidation of simple alkenes.

Although this reaction has been known since 1989, there were significant

problems with ring opening of the epoxide product under the reaction conditions.[359-362] Sharpless reported that these problems could be overcome by addition of pyridine (12 mol%).[363] In 1998, Nakajima reported the beneficial effects of bipyridine N-oxide on the rate and yield of the catalysed oxygen transfer.[364] The range of substates that can be used in this process is extremely broad, and excellent yields of the corresponding epoxides can be obtained within 2-24 hours using just 0.5 or 1 mol% of MTO.[365,366] The active oxidising agent is thought to be a diperoxo complex (Scheme 45).[367] Rudler has used an MTO complex with a chiral bipyridine, but no asymmetric induction was observed in the catalytic epoxidation process (Scheme 45).[365]

Asymmetric epoxidation has also been catalysed by Lewis acids that are not derived from transition metals. In 1993 Balavoine reported an asymmetric epoxidation method that was mediated by a chiral borate and TBHP as the stoicheiometric oxidant (Scheme 46).[368] The reaction times required were rather long (18-30 hours) and the enantioselectivities generally ranged between 6-22% ee, but *trans*-stilbene oxide was obtained with 51% ee.



Scheme 46: Catalytic asymmetric epoxidation mediated by chiral borates.

Catalytic asymmetric epoxidation methods that utilise molecular oxygen as the stoicheiometric oxidant continue to be of interest because of the attractive economics of the reagents. Kureshy has reported several systems based on complexes of Ru(II), Ru(III), Mn(III), and Co(II) with chiral Schiff bases.[369-374] More recently the same author described the catalytic aerobic enantioselective epoxidation of simple alkenes with molecular oxygen in the presence of isobutyraldehyde, catalysed by Ni(II) complexes with symmetrical and non-symmetrical chiral Schiff

bases.[375] The best ligand of those tested appeared to be a C2 symmetric ligand derived from 1,2-diphenyl-1,2-ethylenediamine which afforded indene oxide with 41% ee (Figure 22). Higher yields but lower enantioselectivities were obtained for long chain aliphatic alkenes.

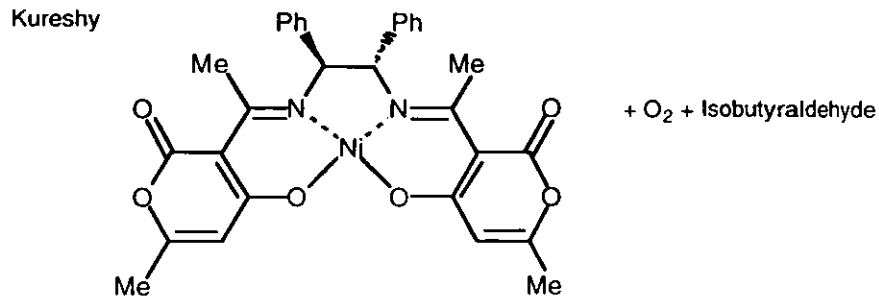


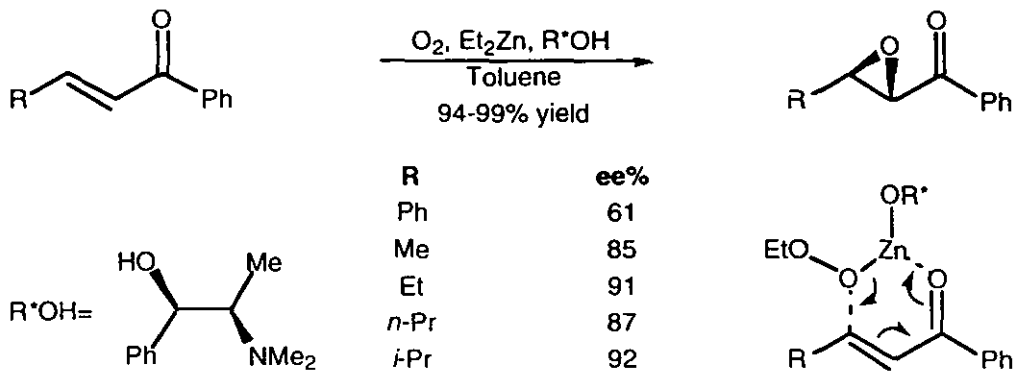
Figure 22: The latest of catalysts described by Kureshy for the catalytic aerobic asymmetric epoxidation of simple alkenes.

All of the methods described above deal with the asymmetric epoxidation of simple or electron-rich alkenes which act as nucleophiles at an electrophilic oxygenated species. Until recently, high enantioselectivities in the catalytic asymmetric epoxidation of electron-deficient alkenes could only be achieved by the method of Juliá which is discussed in more detail below.

In 1996 Enders reported an interesting method for the asymmetric epoxidation of *trans*-1,3-disubstituted enones.[376] The reaction employs molecular oxygen as the stoicheiometric oxidant, which, in the presence of diethyl zinc and a chiral alcohol (N,N-dimethylpseudoephedrine), forms a chiral alkoxy(ethylperoxy)zinc species (Scheme 47). The latter forms complexes with enones through the carbonyl moiety, and the peroxy entity delivers the oxygen to the substrate in a the fashion of an oxa-Michael addition (Scheme 47). The lowest enantioselectivity was observed for the transformation of chalcone to chalcone oxide (61% ee), while the epoxides of related substrates were obtained with 82-92% ee. The reaction is attractive on economic grounds because of the inexpensive reagents involved, but it is still a stoicheiometric process.[377]

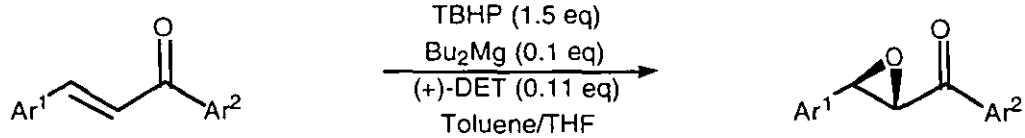
In 1997 Jackson reported a catalytic process for the asymmetric epoxidation of *trans*-1,3-diarylenones employing dibutylmagnesium, diethyl tartrate and TBHP as the stoichiometric oxidant (Scheme 47).[378] The reaction probably proceeds though coordination of both the chiral ligand and the substrate to the *tert*-butylperoxomagnesium species.

Enders



R	ee%
Ph	61
Me	85
Et	91
n-Pr	87
i-Pr	92

Jackson



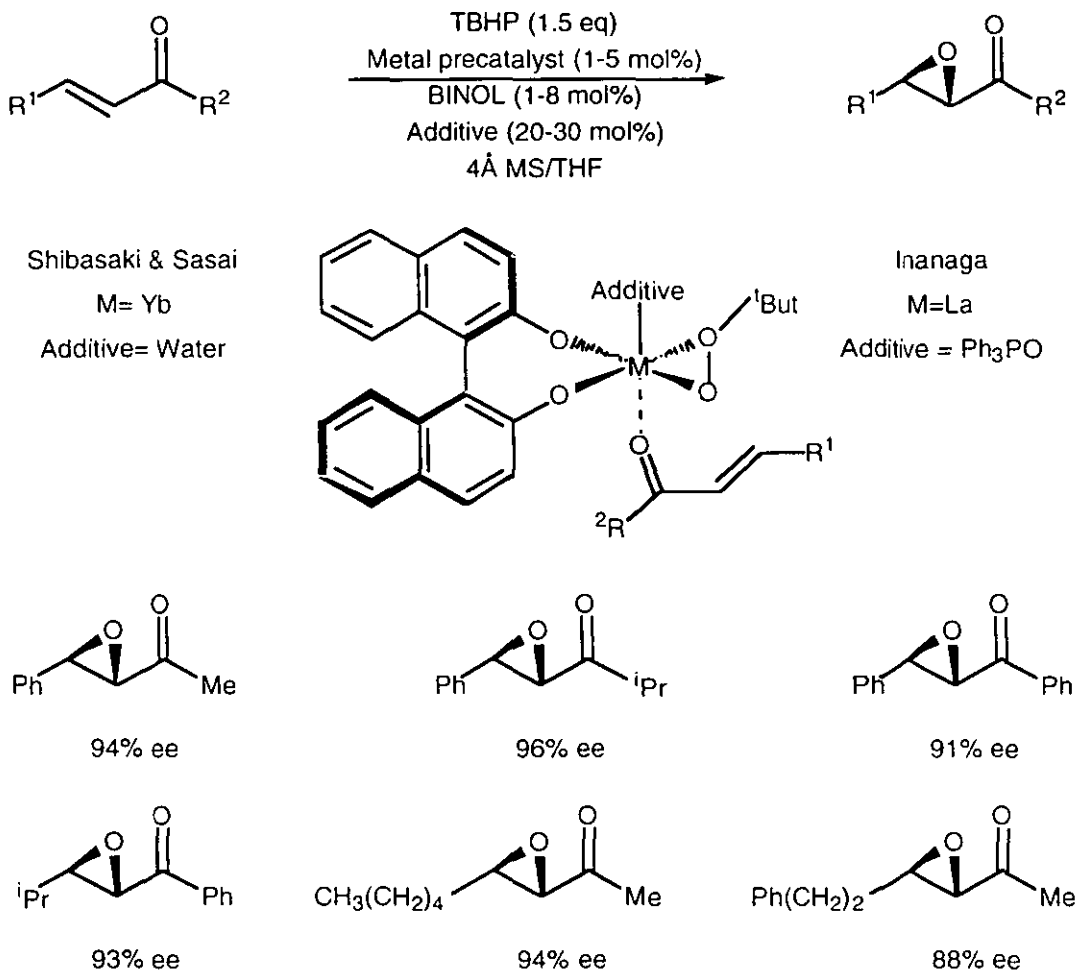
Ar^1	Ar^2	ee%
Ph	Ph	94
Ph	*p*-MePh	87
Ph	2-naphthyl	92
p-ClPh	Ph	81
p-MePh	Ph	84

Scheme 47: The methods developed by Enders and Jackson for the epoxidation of enones.

As described above for the Enders system, intramolecular addition of the peroxy entity in a Michael fashion furnishes the epoxyketone with concomitant release of tertiary butanol. The reaction is catalytic in the chiral ligand and dibutyl magnesium (10 and 11 mol% respectively). The enantioselectivities obtained in the epoxidation of chalcone-related substrates are between 81 and 94% ee, but the yields of the epoxyketones are usually moderate (36-61%). However, both enantiomers of the desired epoxyketone can be accessed because both enantiomers of DET are readily available.

A breakthrough in the catalytic asymmetric epoxidation of enones has recently been achieved by Shibasaki and Sasaki who used lanthanide/BINOL complexes as the chiral catalyst and TBHP or cumene hydroperoxide (CMHP) as the stoicheiometric oxidant (Scheme 48).[379] In particular, the ytterbium complex

appeared to be the best in terms of ee, yields and rate in the epoxidation of *trans*-1,3-disubstituted enones, while the lanthanum analogue offered similar ee's but decreased rates of conversion. Interestingly, for high enantioselectivities to be realised, the addition of a small amount of water or molecular sieves seemed indispensible. The water is thought to modify the chiral enviroment around the catalyst by acting as an external ligand, but the exact nature of the active species is largely unknown.[380] A tentative structure is depicted in Scheme 48. Enantioselectivities for the epoxidation of a wide range of substrates ranged between 83 and 94% ee.[381]



Scheme 48: This method is perhaps the best for the catalytic asymmetric epoxidation of enones.

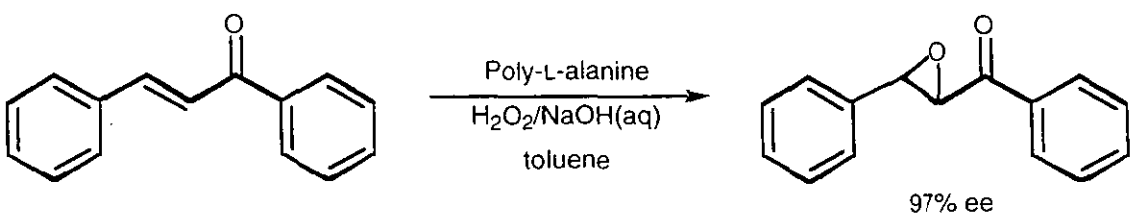
Improved results were reported recently by Inanaga who studied several other additives and found that triphenyl phosphine oxide had the most beneficial effect on the enantioselectivity of the process (Scheme 48).[382] Thus α,β-unsaturated

ketones can be epoxidised with 87-96% ee within 1-12 hours depending on the substrate, by the lanthanum/BINOL complex in the presence of molecular sieves and the additive, in THF at ambient temperature. As in the case of the Shibasaki system, the excact identity of the species formed upon addition of the additive is remains unknown.

More importantly, all of the reagents required in these processes are commercially available, and either enantiomer of the desired epoxyketone can be accessed readily. The method of Shibasaki and Sasai is complemented by the system of Inanaga, and together they provide a versatile methodology in the asymmetric synthesis of epoxyketones. These processes exhibit the broadest generality in the catalytic asymmetric epoxidation of enones, since excellent enantioselectivities can be obtained even for substrates that are unsuitable for the Juliá reaction (Scheme 48).[381,382]

1.4.8 The Juliá process and related reactions in asymmetric epoxidation.

In 1980 Juliá reported that synthetic polypeptides could be used in the catalytic asymmetric epoxidation of α,β-unsaturated ketones (Scheme 49).[383] Chalcone oxide was obtained in 97% ee from a triphasic system of toluene, water, and polyalanine in the presence of hydrogen peroxide and sodium hydroxide. Peptides are generally insoluble in water, organic solvents, or most mixture of these, but the triphasic system seemed essential for high asymmetric inductions. In the absence of water, no reaction takes place.[384] In this reaction, polyalanine exhibited superior performance than the corresponding polymer derived from glutamic acid, and, the polymeric nature of the catalyst was vital for the reaction to proceed with high asymmetric induction.[383-385] This was taken as evidence that the surface of the polypeptide is probably involved in the reaction and therefore the polymer acts as a phase transfer catalyst.



Scheme 49: Juliá's catalytic asymmetric epoxidation of chalcone was a landmark discovery.

High enantioselectivities are usually obtained when the peptide contains at

least 10 units of the aminoacid although longer polymer chains of 30 amino acid residues have been shown to be advantageous in some cases.[384,386] The identity of the aminoacid unit present in the peptide is one of the most important parameters of the catalytic system. Results from the early work of Juliá suggested that polyalanine, poly-L-leucine, and poly-L-isoleucine, are better catalysts than polyvaline and polyphenylalanine.[386] A variety of other oxidants, such as mCPBA and tertiary butyl hydroperoxide, have been tested, but the results were inferior to those obtained under the classical conditions (hydrogen peroxide/sodium hydroxide system).[384]

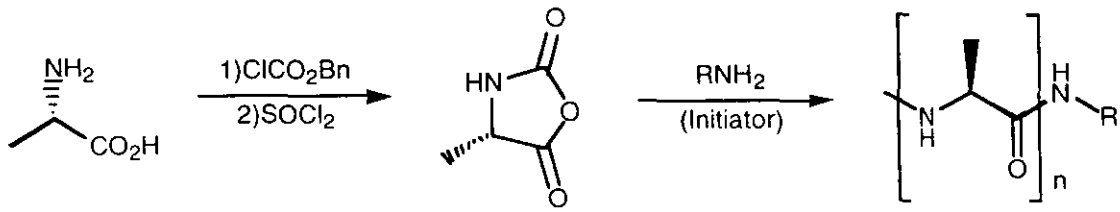
The polypeptide can be recovered and reused, but both conversion and asymmetric induction decrease with repeated isolation/usage. This is due to the alkaline conditions of the reaction which degrade/hydrolyse the amide linkages of the polymer/catalyst.[383,384] The efficiency of the recycled catalyst is usually better when the original peptide is of long chain length and is derived from an amino acid with a bulky substituent such as poly-L-leucine.[386] This imparts hydrophobicity to the polymer and therefore enhances its resistance to hydrolysis.

The nature of the organic solvent is also of prime importance. The reaction profiles are poor when in hydrocarbon solvents (hexane), while aromatic (toluene) and halogenated solvents (carbon tetrachloride) appear to be the organic media of choice. Furthermore, when a water-miscible organic solvent such as methanol, was used, the resulting biphasic system afforded racemic product.[388] This suggested that hydrogen bonding between the substrate and the polypeptide is important for asymmetric induction. Support for this rationale was gained by the use of a peptide derived from proline whose linkages consist of tertiary amides and therefore, the N-H entities which are essential for hydrogen bonding, are absent.[388] Not surprisingly, the results obtained with this polymer were very poor in terms of enantiomeric excess and conversion. It has been argued however, that the ineffectiveness of derivatives which lack the N-H moiety may be due to a different secondary structure.[388] It has been proposed that the best results in the asymmetric epoxidation of enones are obtained with polyleucine and polyalanine because of these polymers exhibit an enhanced tendency to form α-helical structures due to hydrogen bonding.[386]

The concept of the helical structure, perhaps provides a rationale for the requirement of at least 10 amino acid units in the polymers, in order to obtain high asymmetric induction, (the chain is then long enough to form a distinct helix). X-ray powder diffraction showed that there is some degree of order in the structure of the hydrogen-bonded peptides,[389] but such polymers may predominantly adopt a β-sheet structure.[390]

The mechanism of the Juliá epoxidation reaction however, is still unclear. It has been postulated that the hydrophobic polymers/phase transfer agents may promote a stabilising environment for the hydrophobic substrate, and therefore accelerate the reaction. Surface studies on these polypeptides during the epoxidation process support the suspected phase transfer effect, and that the reaction site may be associated with a monolayer.[391]

The synthesis of the polypeptides employed in the Juliá reaction involves a polymerisation process of the appropriate amino acid unit, which is often used as its N-carboxyanhydride (NCA).[392] The latter is conveniently prepared in one step from the amino acid precursor and is generally crystalline and easy to purify. Polymerisation of this derivative can be initiated by either the use of a humidity tank or by reaction with a suitable amine, diamine. The best results in the epoxidation reaction are obtained with polymers that are prepared with simple diamines as the initiators in the polymerisation reaction.[387] The reaction begins by nucleophilic attack of the initiator on the carboxyanhydride moiety with concomitant release of carbon dioxide and generation of the primary amine of the original aminoacid precursor (Scheme 50).



Scheme 50: Synthesis of polypeptides using the aminoacid-NCA method.

However, the nature of the groups attached at the O and N ends of the polymer do not exert sigificant influence on the activity of the catalyst.[388] The average length of the polyamino acid formed is greatly influenced by the purity of the reagents and the mole percentage of the initiator used.[393] Reliable results are usually obtained with initiators that are more nucleophilic that the amino group generated on the polymer chain.[392] The synthesis, however, of polymers of more than 20 amino acid units is not always reproducible because the amino group terminus becomes increasingly more hindered as the reaction proceeds due to the developing secondary structures of the inter- and intramolecularly hydrogen-bonded polymer chain.[392] The extensive characterisation of these catalysts is often

limited due to the extreme insolubility of the polymers in conventional solvents,[394] but information regarding molecular weight distribution can be obtained with the use mass spectroscopy.

The Juliá process can be easily performed at 0 °C and for a long time it has been the method of choice for the epoxidation of *trans*-1,3-diarylenones. The weakness of this methodology is that it is extremely substrate specific for the chalcone type of molecules or closely related substrates. Enones with enolisable α-protons are usually poor substrates but advances with this type of substrates have been recently made and will be discussed later. Examples of 1,3-diaryl-2,3-epoxyketones and related substrates that have been synthesised with this method are illustrated in figure 23 below.[384,388,389,395]

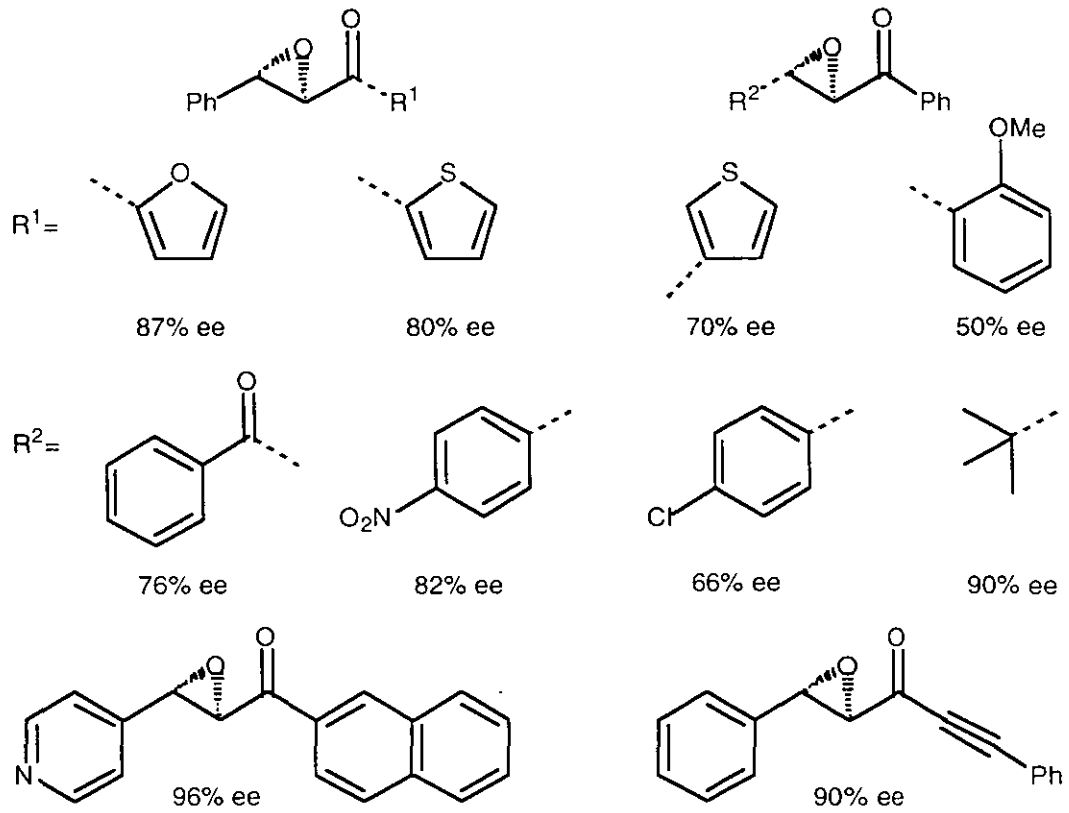


Figure 23: Juliá asymmetric epoxidation of substituted chalcones and related substrates

One of the attractive aspects of the Juliá process is the use of hydrogen peroxide as the stoicheiometric oxidant which is inexpensive and environmentally friendly. In addition, under the alkaline conditions nucleophilic, oxidisable groups such as sulfides are not affected and therefore excellent chemoselectivity is usually observed (Figure 24).[395] The regioselectivity of the Juliá process is demonstrated in

the epoxidation of fully conjugated dienones which are monoepoxidised exlusively at the double bond adjacent to the carbonyl group.[387] However, other types of electron deficient, conjugated double bonds are poor substrates for this reaction (Figure 24).[384,286,394,396]

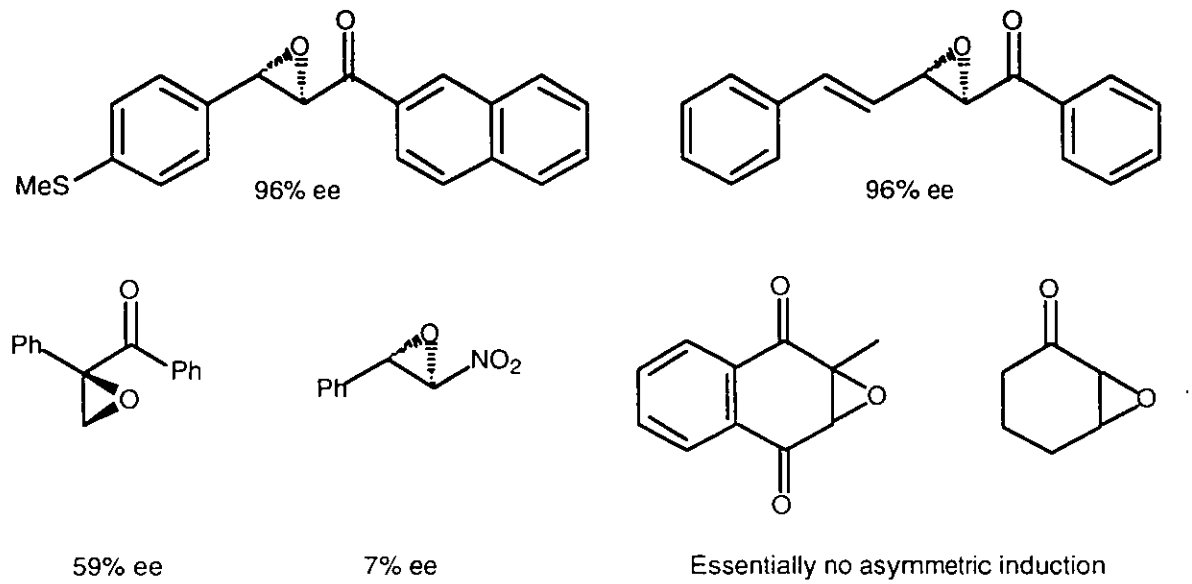


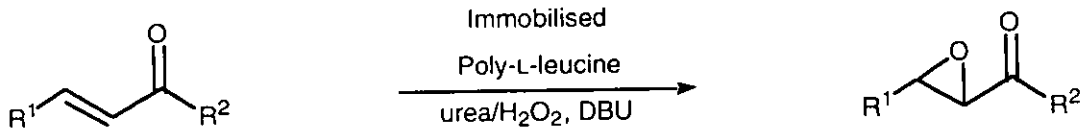
Figure 24: The Juliá process exhibits remarkable chemo- and regioselectivity but high enantioselectivities are obtained only for substrates structurally related to chalcone.

In addition to the narrow range of substrates suitable for the Juliá process there are also problems associated with long reaction times, oxidant decomposition, and the difficult work up of the three phase mixture. Furthermore, the size of the polypeptides used in this process, is usually comparable with the pore size of conventional filter devices, and therefore problems arise on attempts to isolate the catalyst from the reaction mixture.

Early attempts to overcome these difficulties have been reported by Juliá and Colonna, who synthesised a polymer-bound polyalanine derivative by reaction of (poly)alanine-NCA with a hydroxy-functionalised polystyrene.[388] The tethered polymer exhibited similar catalytic activity with the non-supported version of the original polyamino acid in the epoxidation process. In 1990 Itsuno reported another system of polymer-supported polyamino acids of various chain lengths and demonstrated their use in the Juliá reaction.[397] The immobilised derivatives were synthesised through reaction of alanine and leucine NCAs with a benzylamine-loaded cross-linked polystyrene, and the best results in terms of catalyst activity were obtained with the polymer-bound polyleucine that contained approximately 30

amino acid residues. Using this chiral phase transfer catalyst in the traditional three phase system (toluene, water, polymer supported polyleucine), enantioselectivities between 76 and 99% ee were obtained for a range of monosubstituted chalcones. The polymer-supported catalyst appeared to be quite robust under the reaction conditions as it was isolated and reused 12 times with no loss of asymmetric induction. Related polymer-supported polyaminoacids were then developed, but exhibited inferior stability under the strong alkaline conditions.[398]

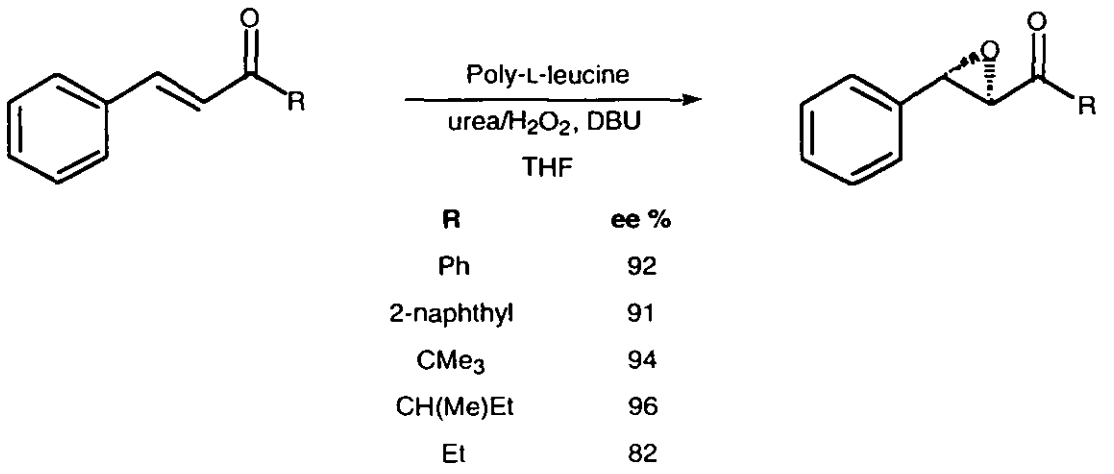
Roberts has recently showed that the asymmetric epoxidation of chalcone can be catalysed by polyaminoacid derivatives under non-aqueous conditions, thus greatly simplifying the work up of the reaction.[399-401] The improved technology involves the use of urea-hydrogen peroxide complex in THF, in the presence of an organic base (DBU) and immomolised poly-L-leucine (Scheme 50).



R^1	R^2	ee %
Ph	Ph	95
PhCH=CH-	2-naphthyl	95
Ph	Me	83

Scheme 51: The Juliá process mediated by immobolised poly-L-leucine under anhydrous conditions.

Under these conditions, reaction of chalcone derivatives and related substrates provided the corresponding epoxides in 70-99% yield and 83-95% ee within 30 minutes. Roberts has also reported the results obtained for the epoxidation of several substrates which included some enolisable enones, mediated by unsupported polyleucine under the improved/anhydrous conditions (Scheme 52).[402,403] Roberts' modifications in conjuction with the recent advances in polymer supported aminoacids have provided some solutions to the problems of long reaction times and isolation of catalyst and product in the Juliá reaction (Scheme 52).[404]



R	ee %
Ph	92
2-naphthyl	91
CMe_3	94
CH(Me)Et	96
Et	82

Scheme 52: Roberts' improved conditions offer simpler work up and reduced reaction times in the Juliá reaction.

The Juliá process has been employed several times in the construction of chiral building blocks such as 2,3-epoxyalcohols,[405,399] α-hydroxy ketones,[406] and flavanols,[407,408] by appropriate manipulation of the carbonyl or heterocyclic entity of the epoxyketone products. The Juliá process coupled with the Baeyer-Villiger oxidation provides a powerful tool for the synthesis of epoxy esters.[409] This sequence has been used in the synthesis of therapeutic agents such as a β-amino-α-hydroxy acid residue which constitutes a side chain of taxol,[401] the leukotriene antagonist molecule F104353,[393,408] the blood pressure lowering agent diltiazem,[392] and other biologically active compounds.[403]

In summary, the Juliá process offers an attractive method for the catalytic asymmetric epoxidation of chalcone derivatives. However, the synthetic utility of this method is limited, largely due to the failure to epoxidise other types of enones and conjugated electron-deficient olefins with reasonable enantioselectivities. The availability of polypeptides derived from unnatural amino acids may also be limited for large scale epoxidations, since in the Juliá reaction the substrate to catalyst ratio is usually 1:1 (w/w). The problems initially encountered with long reaction times, work-up and stability of the catalyst have recently been in part overcome by the efforts of Roberts and other research groups. Whether these modifications will render this methodology competitive enough with the alternative and more general methods of Shibasaki and Inanaga, still remains to be seen.

The asymmetric epoxidation of the chalcone type of substrate has also been accomplished by other types of chiral phase transfer catalysts.[410-413] Wynberg pioneered the use of chiral ammonium salts, and obtained chalcone oxide with 55%

ee using alkaline hydrogen peroxide as the stoicheiometric oxidant and a quinine derived quaternary ammonium salt as the chiral phase transfer catalyst (Figure 25).[414-416] Comparable results were obtained with other oxidants such as sodium hypochlorite (bleach), but interestingly, the configuration of the major enantiomer of chalcone oxide obtained with the latter oxidant was opposite to that obtained with hydrogen peroxide.[417] Wynberg's catalyst was also used in the epoxidation of a quinone derivative with anhydrous TBHP as the stoicheiometric oxidant and the corresponding epoxide was obtained in 78% ee.[418,419] The preferred solvent and base for these reactions are toluene and sodium hydroxide (powdered if anhydrous conditions are employed).

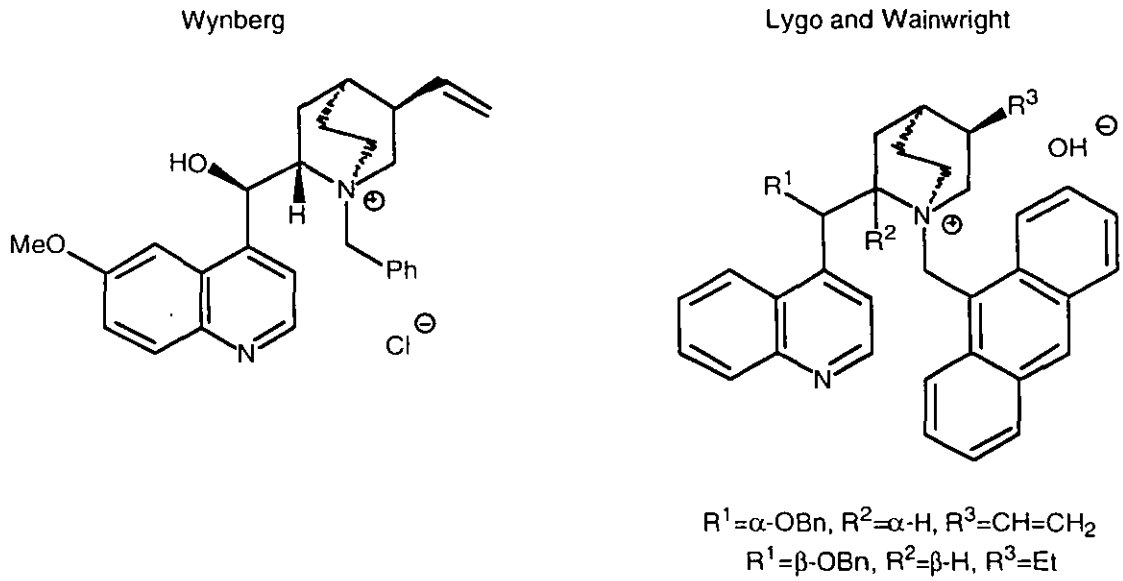


Figure 25: Quinine derived phase transfer catalysts for the asymmetric epoxidation of enones.

More recently, Lygo and Wainwright re-examined the effect of the structure of the quinine derived ammonium salt on the enantioselectivity of the process.[420] Optimisation of various quinine derivatives led to superior catalysts for the asymmetric epoxidation of 1,3-diarylenones and some substrates with aliphatic substituents. Although the latter reacted considerably more slowly than the former type of enones, the enantioselectities for the substrates tested ranged between 69 and 89% ee. More importantly, in each case the enantiomeric epoxide could be accessed with similar enantioselectivity by the use of diastereoisomeric quinine derivative (Figure 25).[420]

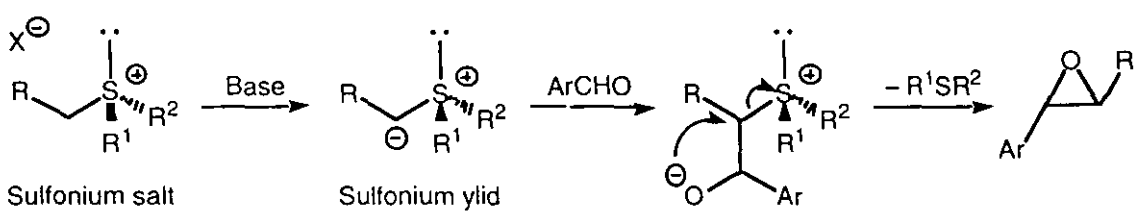
Related processes that have been described, involved the use of cyclodextrins as chiral phase transfer agents for the asymmetric epoxidation of enones.[421] In the

epoxidation of chalcone and cinnamaldehyde however, low enantioselectivities were observed using either hydrogen peroxide or bleach as the oxidants, and either α- or β-cyclodextrin.[421,422] Attempts to improve the enantioselectivities by modification of the hydroxyl groups present in the cyclodextrins have so far been unsuccessful.[423] The highest enantioselectivity (48% ee), using this class of chiral phase transfer catalyst, has been reported in the epoxidation of substituted benzoquinones using TBHP as the stoicheiometric oxidant.[424]

1.4.9 Chiral sulfur ylids in asymmetric epoxide formation.

The reaction between sulfur ylids and carbonyl compounds to furnish epoxides was first reported by Johnson in 1961.[425] Since then, this method has been extensively developed, and modified to provide an entry in the arsenal of synthetic chemists for the asymmetric synthesis of epoxides.[426] Sulfonium ylids have become by far the most popular mediators of this type although related reagents have been employed and are described below.

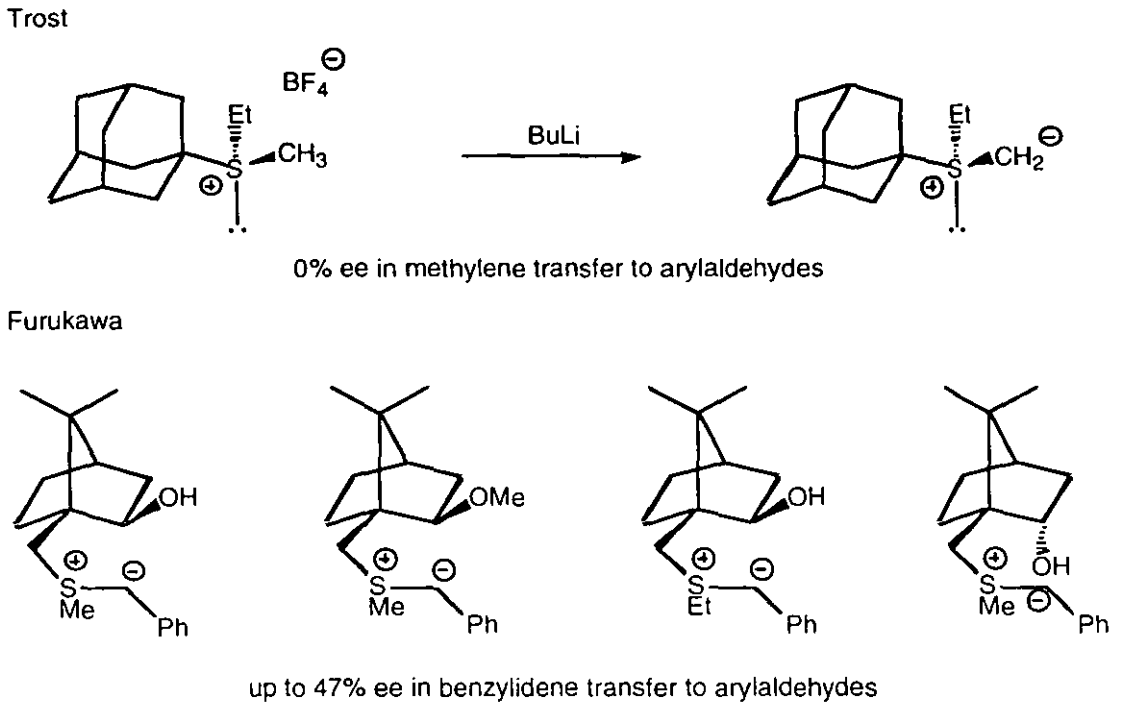
In this reaction, the nucleophilic sulfur ylid, generated from deprotonation of the appropriate sulfonium salt, attacks the electrophilic carbon atom of a carbonyl compound (usually an aldehyde) and generates an alkoxide. For sulfonium ylids, this step is usually irreversible, but intramolecular ring closure by attack of the alkoxide on the former nucleophilic carbon atom generates an epoxide with concomitant release of the related sulfide (Scheme 53).



Scheme 53: Epoxide formation by alkylidine transfer to carbonyl compounds from sulfur ylids.

The first attempt to prepare non-racemic epoxides from a chiral sulfonium ylid was made by Trost in 1973, who used an enantiomerically pure adamantane derivative (Scheme 54).[427] Upon deprotonation, the methylated ethyl-adamantyl sulfide was shown to transfer the methylene group to substituted benzaldehydes, but the afforded styrene oxides were of negligible optical purity. Trost investigated if this outcome was due to inversion at the chiral tetrahedral sulfur atom but found that the ylid was configurationally stable. It later became evident that had Trost used

the sulfonium benzylid instead of the methylid, significant enantioselectivities could have been observed in the resulting stilbene oxides.



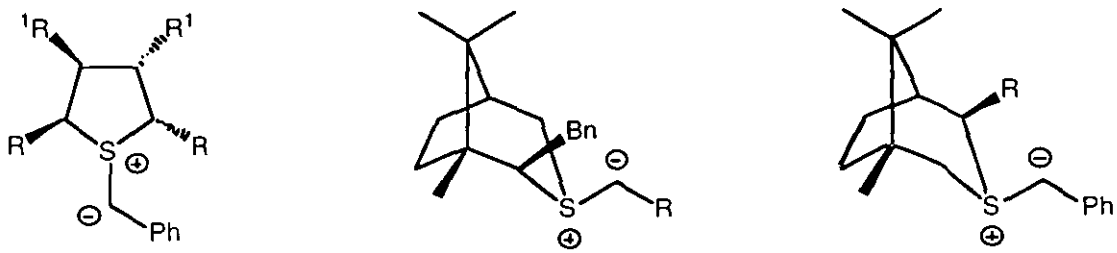
Scheme 54: First Trost and then Furukawa used chiral sulfur ylids for epoxide formation.

16 Years later Furukawa reported the first successful epoxidation mediated by chiral sulfonium ylids.[428] These were derived from camphor, and promoted benzylidene transfer to benzaldehyde to form exclusively *trans*-stilbene oxide with up to 47% ee (Scheme 54). Furukawa successfully accessed the oxirane products in one pot by allowing the chiral sulfides to react with benzyl bromide and benzaldehyde in stoicheiometric amounts under alkaline conditions, thus preparing both the chiral sulfonium salt and the corresponding ylid *in situ*. When sub-stoicheiometric amounts of sulfides were used however, the yield of the epoxide products was low.

Durst considered that the low level of enantioselectivity may be due to formation of diastereoisomeric sulfonium ylids by non-selective alkylation (benzylation) at either prochiral lone pair of electrons at the sulfur atom. Durst designed and used C2 symmetric cyclic sulfides to generate chiral sulfonium benzylids which in turn reacted with a range of substituted benzyldehydes (Figure 26).[429,430] Rewardingly, reaction with 4-nitrobenzaldehyde afforded the corresponding *trans*-4-nitrostilbene oxide with 83% ee. Durst later reported a more

enantioselective process through the use of chiral sulfonium ylids derived from (+)-camphoric acid (Figure 26).[431] As already mentioned for the Trost system, methylene transfer with these terpene derived ylids was also unselective, but enantioselecivities were up to 96% ee for benzylidene transfer to benzaldehydes. Although the parent sulfides are not C2 symmetric, a single and configurationally well-defined diastereoisomeric sulfonium salt and consequently benzylid is produced upon benzylation due to steric and conformational effects (Figure 26).

Durst



R= CH_2OBn, R^1= H
R= CH_2OBn, R^1= OBn
R= H, R^1= OTBDMS

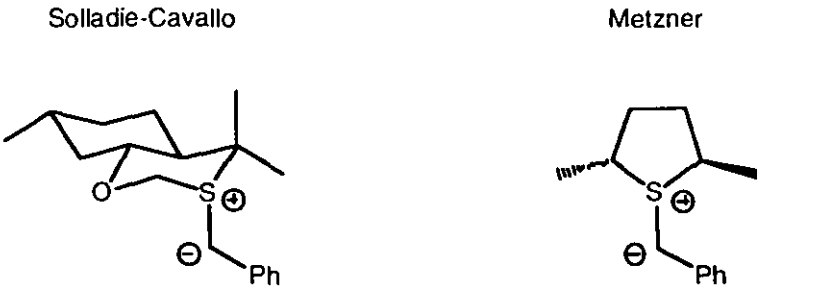
R= Ph, *p*-ClPh, H

R= Bn, ^iPr, H

up to 96% ee in benzylidene transfer to arylaldehydes

Figure 26: Durst's chiral sulfonium ylids have been among the most successful in asymmetric epoxide formation by benzylidene transfer to aromatic aldehydes.

Solladié-Cavallo then reported a highly enantioselective benzylidene transfer to aryl aldehydes mediated by a sulfur ylid derived from pulegone.[432] This was the first example of a sulfur ylid derived from a chiral 1,3-oxathiane. The latter heterocycle, was part of a bicyclic terpenoid structure (Figure 27). Using this precursor, the alkylation and consequently ylid formation is diastereospecific, presumably due to the anomeric effect.[433] Treatment of this ylid with substituted benzaldehydes and sodium hydride in dichloromethane furnished the corresponding *trans*-stilbene oxides with 97.8-99.9% ee.[434] The same research group also used the novel 1,3-oxathiane-derived ylid in the asymmetric transfer of other aryl-methylene groups to formaldehyde, thus gaining access to terminal monosubstituted epoxides. They also used this methodology to prepare successfully two (*R*)-β-andrenergic compounds.[435]



100% de and 97.9-99.9% ee

30-86% de and 86-94% ee

in benzylidene transfer to aldehydes

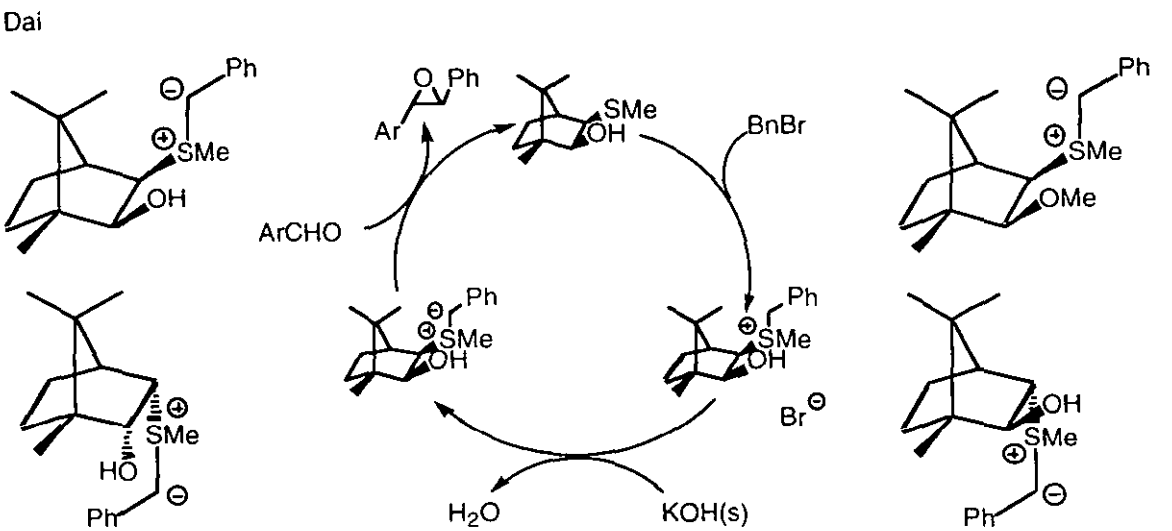
Figure 27: Chiral sulfonium ylids developed by Solladié-Cavallo and Metzner respectively.

More recently, Metzner and Julienne described asymmetric epoxidations using 2,5-dimethylthiolane, a new C2 symmertic symmetric sulfide (Figure 27).[436] Although similar in structure with Durst's original mediators, it can be prepared easily in two steps rather than five. The *in situ* prepared S-benzyl sulfonium salt was successfully used under alkaline conditions in benzylidene transfer to aldehydes. After some optimisation, the optimum solvent system for high enantioselectivities appeared to be acetonitrile/water. With this mediator, *trans*-stilbene oxides are formed from substituted benzaldehydes with high enantioselectivities (84-90% ee), but small amounts of *cis*-stilbene oxides (4-8%) are also formed. The problem of diastereoselectivity becomes more severe when aliphatic aldehydes are used as substrates (30% de for cyclohexane-carboxaldehyde), but the enantioselectivities are also high (94 and 82% ee for *trans*- and *cis*-1,2-cyclohexyl-phenyloxirane respectively. The reaction times allowed for this process are slow (2 days at ambient temperature), but the ease of preparation of the chiral sulfide, despite the cost, is at clear advantage over the methods described above.

A number of other related sulfonium ylid-mediated epoxidations have been reported, but have shown limited success.[437] All of the methods discussed above, however, are stoicheiometric with respect to the chiral sulfide, and their long term synthetic utility was questioned from the early days by Furukawa.[428]

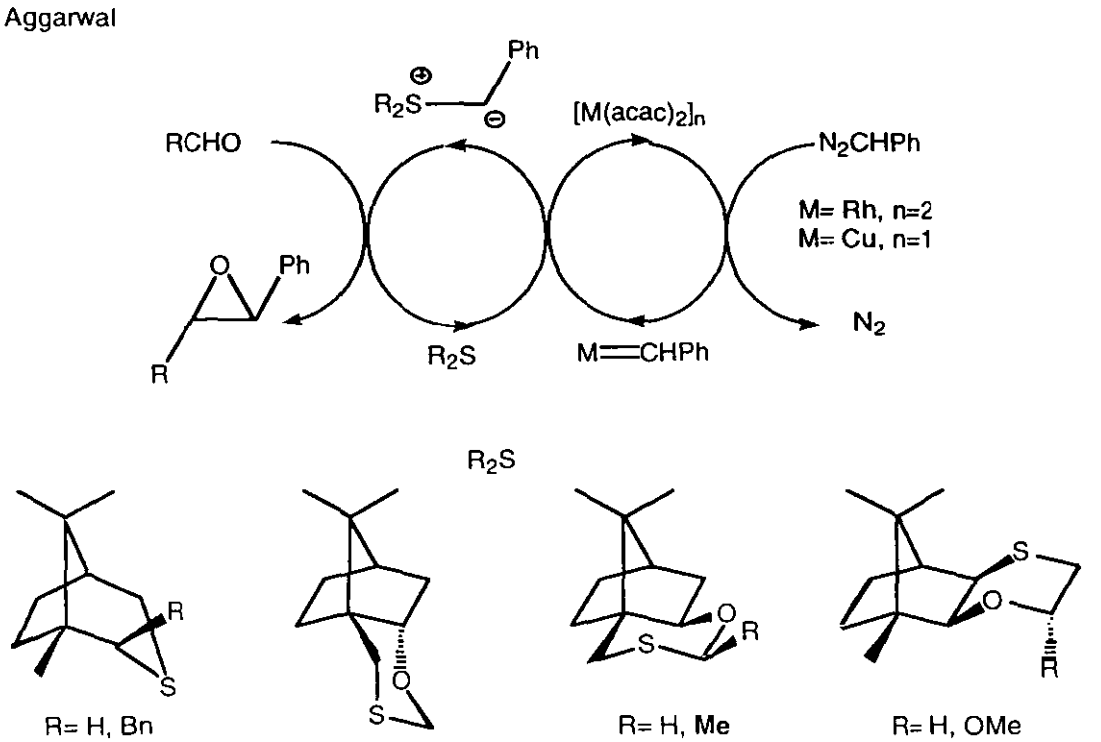
A breakthrough in this area was achieved by Dai who succeeded in modifying the sulfur ylid-mediated epoxidation to proceed catalytically.[438] This author reported the synthesis of 1,2-oxygenated thioethers and sulfonium salts from camphor (Scheme 55). In the stoicheiometric reaction, the corresponding benzylids (derived from methylation of the benzylthioether) were shown to mediate

benzylidene transfer to benzaldehydes with enantioselectivities up to 96% ee. In the catalytic reaction however, the enantioselectivity for the same substrate was lower (60% instead of 96% ee), presumably due to the different method of generation of the ylid (*via* benzylation of the methylthioether), which probably occurs with less diastereocontrol (Scheme 55). In this catalytic process, the formation of the sulfonium salt seemed to be the rate determining step. Addition of silver salts enhanced the electrophilicity of benzyl bromide and therefore the rate of the reaction. Under these conditions however, only a few sulfonium salts could be prepared successfully and, in general, the catalytic version of this reaction is problematic when benzyl halides are involved.



Scheme 55: Dai first developed the catalytic asymmetric epoxidation by sulfur ylides.

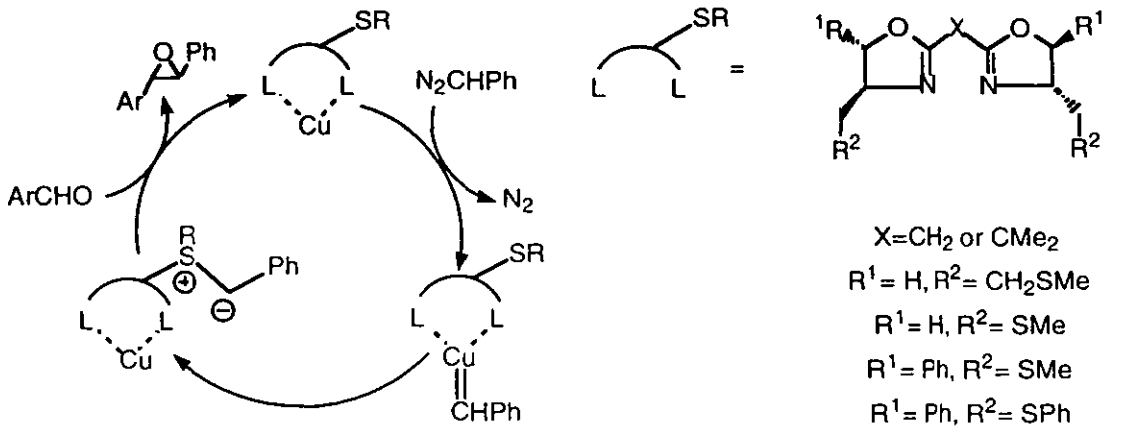
Deprotonation of sulfonium salts is not the only method to prepare sulfonium ylids. An alternative method is the reaction between a sulfide and metal carbenoid (usually rhodium or copper) which gives the ylid directly in one step.[439-441] This approach was investigated by Aggarwal who achieved the preparation of stilbene oxides by combining two catalytic processes in one pot.[442,443] Thus, catalytic formation of a metal carbenoid by reaction of the appropriate metal complex and a diazocompound, was coupled with catalytic sulfur ylid formation from the metal carbenoid and a (chiral) sulfide (Scheme 56). The plethora of reagents required in this process initially led to significant problems of side product formation, but these were overcome by careful optimisation of the reaction conditions. In particular, the purity of the metal complex precursor was vital for the correct function and outcome of the coupled catalytic reactions.[444]



Scheme 56: Aggarwal's catalytic process for asymmetric benzylidene transfer to aldehydes.

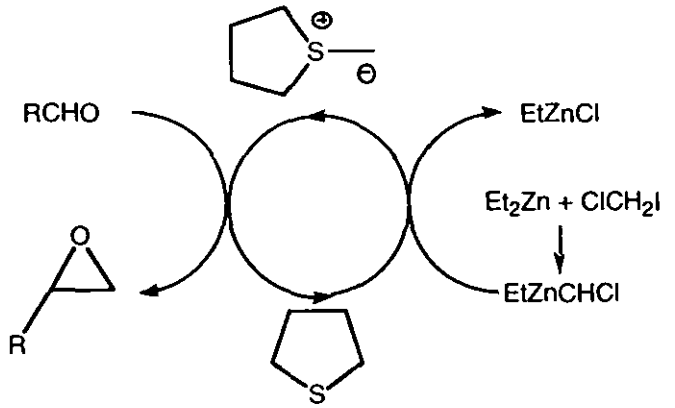
Several chiral sulfides were tested with varying success,[443] among which was one of Durst's camphoric acid-derived sulfides.[445] In this process the best results to date were obtained with a tricyclic acetaldehyde thioacetal derived from camphor sulfonic acid (Scheme 56, in bold).[445,446] Good to excellent diastereo- and enantioselectivities were observed for benzylidene transfer to aromatic and conjugated aldehydes (92:8-98:2 ratio of *trans*- to *cis*-stilbene oxides and 68-93% ee). However, as with the related processes described above, the diastereoselectivity is dramatically lowered when aliphatic aldehydes are used as substrates (7:3 ratio of *trans*- to *cis*-1,2-cyclohexyl-phenyloxirane from cyclohexanecarboxaldehyde).[426,444] Decreased diastereo- and enantioselectivities were obtained for stilbene oxides when some camphor-derived 1,4-oxathianes were used as the chiral ylid precursors in this reaction (Scheme 56).[447] Aggarwal has also attempted to reduce the complexity and atom economy of the double catalytic process by employing a copper complex with a chiral ligand (mainly bis-oxazolines) which possessed pendant sulfide groups (Scheme 57).[448] Therefore, reaction of the chiral metal complex with phenyl diazomethane produces the corresponding copper carbenoid which in turn reacts intramolecularly with the pendant sulfide to generate the chiral sulfonium ylid.

Several such bifunctional catalysts were prepared, but the enantioselectivities observed in this combined approach for benzylidene transfer were very low (0-14% ee) (Scheme 57).



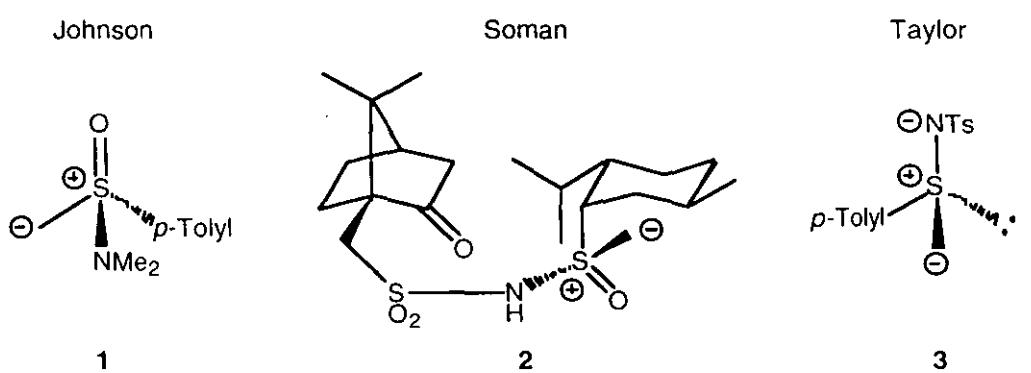
Scheme 57: Aggarwal's bifunctional catalyst for asymmetric benzylidine transfer to aldehydes.

From the early work of Trost and Durst it became obvious that this methodology is not appropriate for the preparation of terminal epoxides by methylene transfer to aldehydes from sulfonium ylids, regardless of the method used for the preparation of the latter. Recently, Aggarwal reported an alternative approach for the generation of sulfonium methylids from reagents traditionally associated with the Simmons-Smith cyclopropanation reaction.[449] In this process chloroiodomethane is treated with diethyl zinc to furnish a zinc carbenoid which then reacts with a sulfide (tetrahydrothiophene), to generate directly the sulfonium methylid (Scheme 58). The latter transfers the methylene entity to the aldehyde present in the reaction mixture and therefore terminal epoxides are realised in good yield. The reaction appeared to be successful for both aromatic and aliphatic aldehydes with little formation of side products that would be expected to form in the presence of the reactive organozinc reagents and Lewis acids based on that metal. In addition, no cyclopropanation products are observed for unsaturated aldehydes. The process is not however catalytic since two- to threefold excesses of all other reagents are required with respect to the aldehyde substrate (Scheme 58). Low diastereoselectivities are realised with chiral substrates, and the reaction has not been modified into an asymmetric process.



Scheme 58: A Simmons-Smith variant for the synthesis of racemic terminal epoxides.

Chiral aminosulfoxonium ylids have also been employed in the asymmetric synthesis of epoxides.[450] The first example of an aminosulfoxonium methylid was described by Johnson in 1968, but low optical yield of styrene oxide was observed in the methylene transfer to benzaldehyde (20% ee) (1 in Figure 28).[451,452] Although not fully explored, mechanistic studies have indicated that aminosulfoxonium ylids are configurationally stable, and the low enantioselectivity in methylene transfer is attributed to the reversibility of the initial attack on the carbonyl carbon atom.[453,454] In contrast, the same nucleophilic addition is usually irreversible in the case of sulfonium ylids.



Up to 20,86 and 70% ee in the methylene transfer to aldehydes and ketones respectively

Figure 28: Other types of sulfur ylids used in the asymmetric synthesis of epoxides.

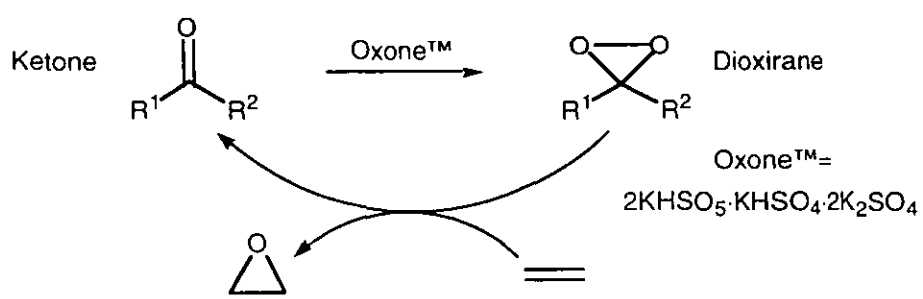
Promising results for the asymmetric synthesis of terminal epoxides have been reported by Soman in the stoicheiometric reaction of chiral sulfoximine anions with aldehydes and ketones.[455,456] The most successful of these methylene transfer mediators was a menthol-camphor hybrid sulfoximine anion (2 in Figure 28), which,

upon treatment with acetophenone, produced α-methyl styrene oxide with 86% ee. In a related process, teminal epoxides with 20-70% ee were obtained by methylene transfer to aldehydes and ketones from a chiral sulfimide anion developed by Taylor (3 in Figure 28).[457] Diastereoselective formation of epoxides that involves reaction between achiral sulfur ylids or equivalent reagents and chiral aldehyde/ketone substrates (substrate controlled), are beyond the scope of this discussion.[426,458,459]

In summary, the chiral sulfur ylid method for asymmetric epoxide formation remains of limited synthetic utility. This is because only benzylidine transfer to aromatic aldehydes to give stilbene oxides occurs with a high degree of enantio- and stereocontrol. Most other types of epoxides, particularly aliphatic ones, cannot be obtained in high yields and enantioselectivities by the chiral sulfur ylid approach.

1.4.10 Catalytic asymmetric epoxidation by chiral dioxiranes.

Dioxiranes are cyclic organic peroxides, whose unsual reactivity stems from the strain associated with the three membered ring and the relatively weak O–O bond.[460-462] They are readily attacked even by poor nucleophiles such as olefins, at one of the electrophilic oxygen atoms, and therefore constitute a class of powerful oxidising agents (Scheme 59).[463-467]



Scheme 59: Dioxiranes are an important class of oxidants based purely on organic molecules.

Dioxiranes are generated *in situ* by action of potassium monoperoxysulfate ($KHSO_5$, active ingredient in Oxone™) on ketones usually in acetonitrile or dimethoxyethane solvent.[468,469] Dioxiranes have also been studied as reagents for epoxidation which can be catalytic with respect to the parent ketone (Scheme 59).[470-473] In this context, several chiral ketones have been examined as catalysts for asymmetric epoxidation, but until recently the enantioselectivities obtained with these systems were only up to *ca.* 20% ee. Examples of such preliminary approaches based on simple chiral ketones have been described by Curci and Marples (Figure

29).[474-476]

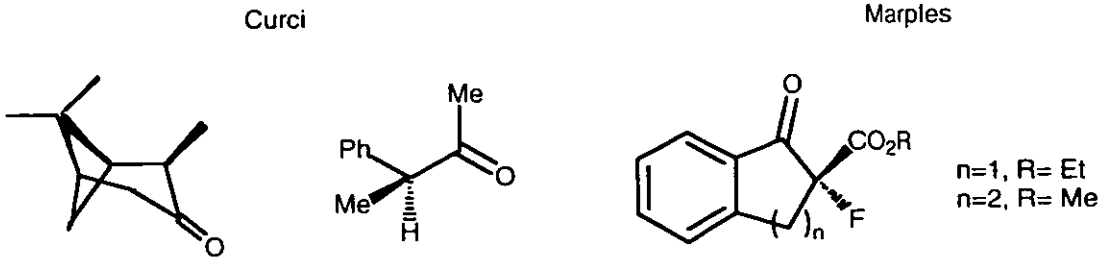


Figure 29: Chiral ketones that were examined by Curci and Marples respectively as dioxirane precursors in the asymmetric epoxidation of alkenes.

In 1996 however, Yang reported asymmetric epoxidation of unfunctionalised alkenes by a C2 symmetric ketone through the corresponding dioxirane species.[477] The chiral ketone was derived from BINAP and exhibited enantioselectivities between 5 and 50% ee under stoicheiometric conditions in the epoxidation of standard substrates and 87% ee in the epoxidation of *trans*-4,4'-diphenylstilbene. Yang extended the list of substrates by including other *para*- substituted stilbenes and used catalytic amounts of the chiral carbonyl compound (10 mol%).[478] These substrates were epoxidised with higher enantioselectivities (50-76% ee). The effect on enantioselectivities was then tested for a range of substituents in the original C2 symmetric ketone, and the most successful mediators appeared to be those with a bromo- and 2-(1,3-dioxanyl)- substituent *ortho*- to the ester linkages (Figure 30, in box).[479] For very hindered alkenes, such as *trans*-4,4'di*tert*-butylstilbene, enantioselectivities of up to 95% ee were achieved (Figure 30). Yang also used a chiral ketone derived from carvone to examine the electronic influence of remote substituents with respect to the carbonyl group acting as the dioxirane precursor.[480] Optimisation of the catalyst structure (72-89% ee for *trans*-stilbene oxide) was then followed by investigation of the electronic properties of the substrate with respect to the enanantioselectivities observed. In general, the more electron rich the substrates, the faster and the more selective is the asymmetric oxygen transfer.

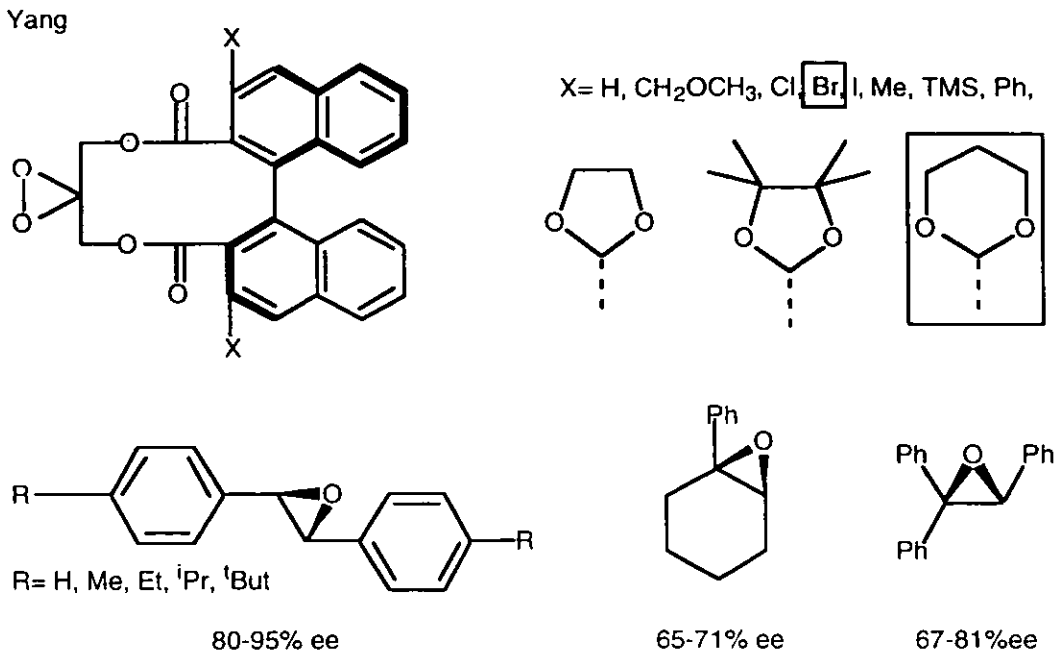


Figure 30: Results obtained with Yang's C2 symmetric ketones.

In addition, the observed configuration in the non-racemic epoxides obtained could be rationalised in terms of the spiro transition state (Figure 31), while the alternative planar transition state (Figure 31) becomes unfavourable on steric grounds, at least for *trans* olefins.[481-483] The spiro transition state is now universally accepted as the mechanism in operation during this oxygen transfer process not only by theoretical and computational studies,[484-486] but also by independent experimental results discussed below.

Figure 31: Possible transition states during the oxygen delivery from dioxiranes to alkenes.

In 1997, Song also reported preliminary results for catalytic asymmetric epoxidation using C2 symmetric ketones.[487] Only *trans*-stilbene and *trans*-β-methylstyrene were tested, and the corresponding epoxides were obtained with 59

and 29% ee respectively. These results were obtained using a hydrobenzoin derived ketone (Figure 32). In the same year, Adam disclosed results of asymmetric epoxidation mediated by yet another two C2 symmetric ketones derived from mannitol and tartaric acid (TADDOL).[488] The latter derivative (Figure 32) proved to be the best catalyst, and afforded enantioselectivities between 65 and 80% ee. The highest enantioselectivities were obtained at optimum pH 10.5.

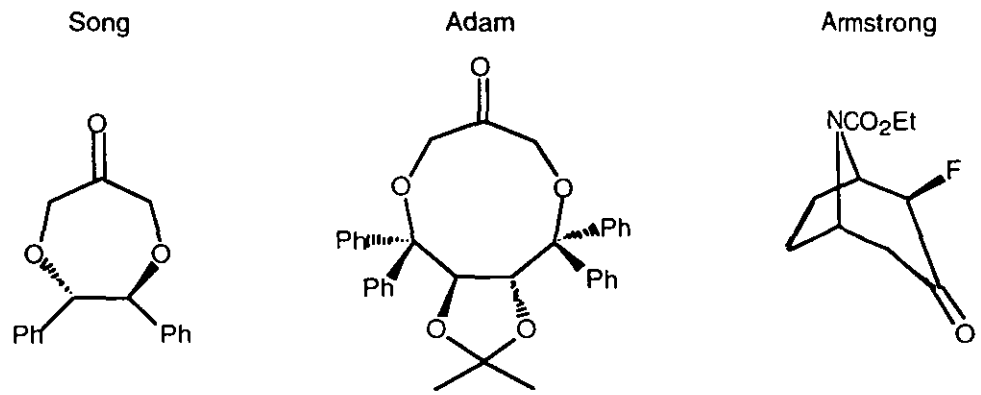


Figure 32: Ketones that have been used as precursors to chiral dioxiranes by Song, Adam, and Armstrong respectively.

The following year, Armstrong reported that a tropinone-derived α-fluoroketone (Figure 32) was a good mediator for the catalytic asymmetric epoxidation of simple olefins, through the corresponding dioxirane.[489] The ketone, although difficult to access, exhibited enantioselectivities in the range of 69-83% ee for various substrates, while styrene was epoxidised with 29% ee. Interestingly, the electron-deficient double bond in *trans*-methylcinnamate was epoxidised successfully with 64% ee. Armstrong not only invoked the spiro transition state to rationalise the stereochemical outcome of the epoxidation reaction but also introduced a new feature. It was argued that the α-fluoro group exerts a stabilising and directing effect by interacting with the olefinic proton in the substrate during the transition state of oxygen transfer.[489] This argument is similar to that used by Yang in the study of the electronic effects of remote substituents on the transition state, where the olefin was shown to experience a built up of positive charge (consistent with nucleophilic attack of the substrate on the electrophilic dioxirane).

A breakthrough in this area was achieved recently by Shi, who reported excellent enantioselectivities in the epoxidation of a wide range of olefins using the dioxirane of the chiral ketone 1 (Figure 33).[490] The catalyst is easily accessible from

fructose in two synthetic steps, and therefore is readily available on a large scale. Typical enantioselectivities obtained with this catalyst are between 80 and 95% ee. However, the chiral ketone decomposes under the reaction conditions (pH 7-8), presumably by a Baeyer-Villiger oxidative pathway, and a large excess of the mediator therefore had to be used (3 equivalents) with respect to the substrate.

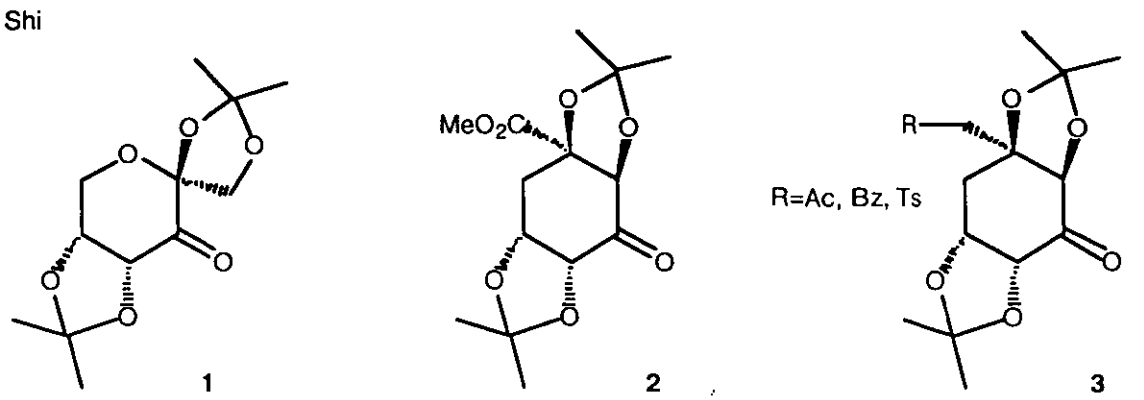
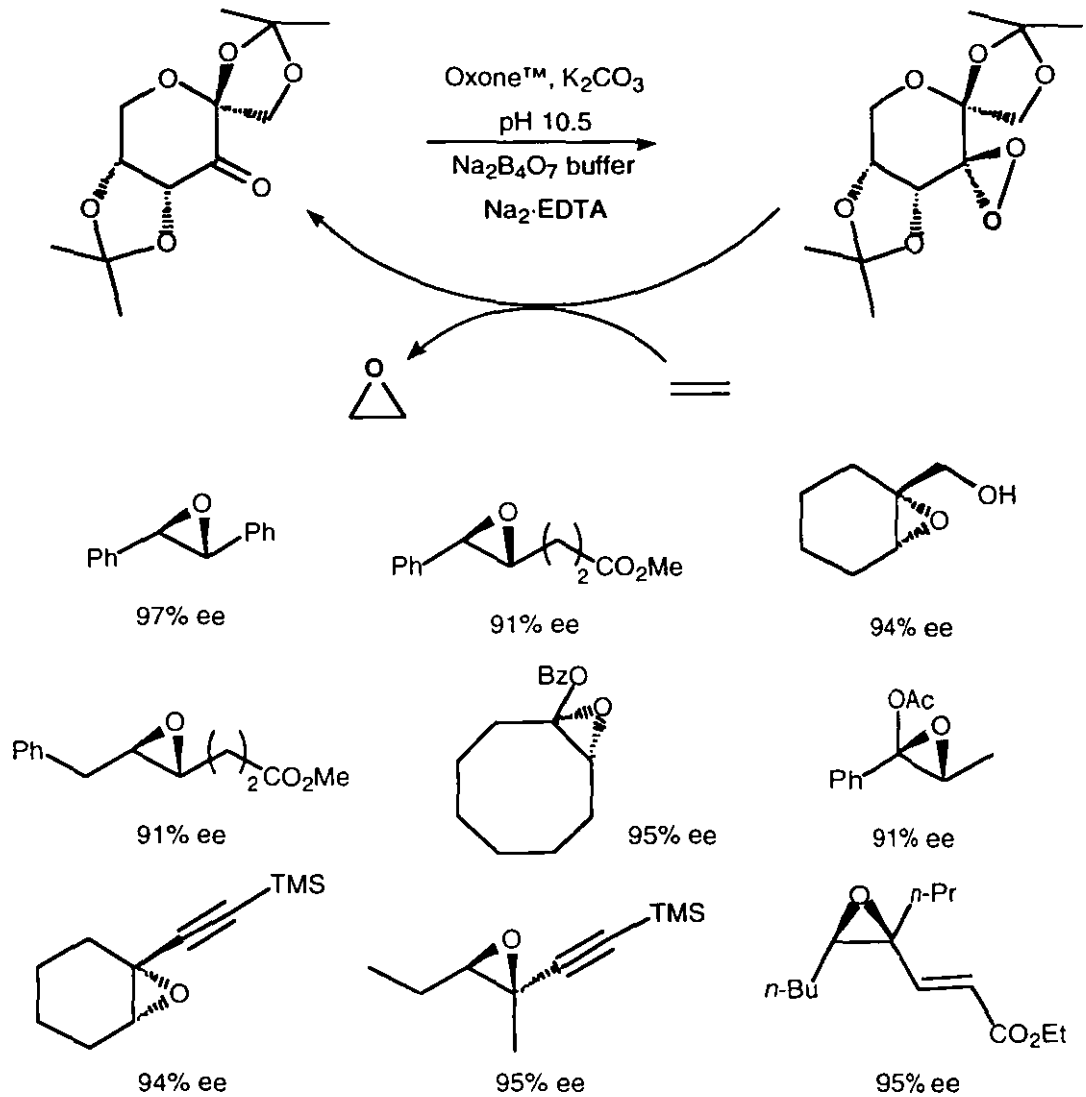


Figure 33: Chiral ketones developed by Shi as precursors to dioxiranes.

Shi then varied the reaction conditions, and found that the decomposition of the catalyst could be significantly suppressed if the reaction was carried out within a narrow pH window between 10 and 11.[491,492] Thus, under the improved conditions, 20 mol% of the chiral ketone was sufficient in order to access chiral epoxides in 65-95% yield.[491] More importantly, in the catalytic reaction slightly higher enantioselectivities were observed (91-97% ee) than in the stoicheiometric process. Several other related catalysts derived from quinic acid (2 and 3 in Figure 33) were tested, and imparted good asymmetric induction in the epoxidation of simple alkenes, but were not as successful as the fructose-derived ketone (1).[492] The synthetic utility of the reaction was quickly expanded by the successful asymmetric epoxidation of various hydroxyalkenes (90-94% ee),[493] enol ethers and enol esters (80-91% ee),[494] enynes (90-97% ee),[495] and conjugated dienes (90-97% ee), (Scheme 60).[496] With the latter type of substrates, monoepoxidation occurred with complete regioselectivity for most types of dienes tested, while for others the regioselectivity ranged from poor (1:1) to very good (14:1). There were also cases where the bis-epoxide was isolated as the major product.[496]



Scheme 60: Shi's system is successful for a wide range of alkene substrates.

In the epoxidation of silylenolethers the corresponding epoxides are not stable enough for isolation, and are converted into α-hydroxyketones upon work-up.[495] Adam has also used the same chiral ketone for the oxygenation of acyclic silyl enol ethers but the enantioselectivities are not as great with these substates.[497] The epoxides of enol esters are however stable and may be isolated.[495]

In the improved reaction conditions described by Shi, Na_2·EDTA was also included as a phase transfer catalyst. In fact, the epoxidation process does not seem to proceed satisfactorily in the absence of phase transfer catalysis.[498] This aspect of the dioxirane-mediated epoxidation has been thoroughly investigated by Denmark, who used keto-ammonium salts as catalysts (Figure 34).[499]

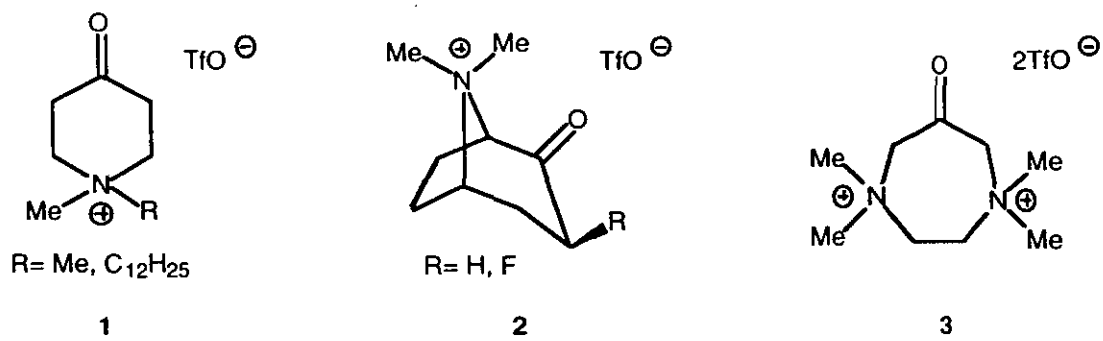


Figure 34: Denmark's keto-ammonium triflates act both as phase transfer catalysts and precursors to dioxiranes.

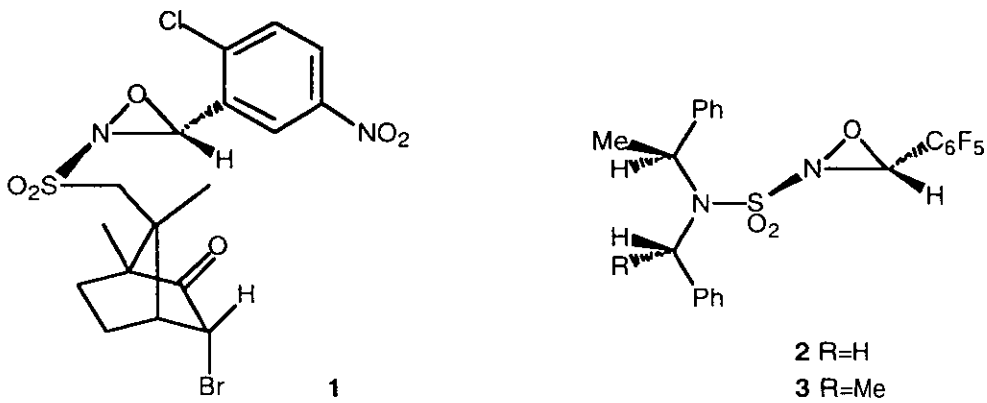
However, the potential for any ketone to mediate the epoxidation reaction involves both the ability to form the intermediate dioxirane and to transfer oxygen to the substrate. These criteria were not always met by several of the ketones/phase transfer catalysts prepared and tested by Denmark.[500] A tropinone derived α-fluoroketoammonium salt (similar to Armstrong's catalyst), was one of the best of those tested (2 R=F, Figure 34).[500] In contrast the non-fluorinated derivative (2 R=H, Figure 34) was a poor promoter for the reaction. The requirement of additional activation of the carbonyl group was quickly established and recently Denmark has reported a new class of catalysts (3 in Figure 34).[501] These are based on α,α'-bis(ammonium)ketones, and preliminary results have shown that a wide range of alkenes can be epoxidised in high yields (83-84%) within 2-20 hours. Chiral catalysts of this type can also be realised from optically active 1,2-diamines.[501]

1.4.11 Oxaziridines as reagents for asymmetric epoxidation.

Oxaziridines are the nitrogen analogues of dioxiranes and also act as oxygen transfer agents, albeit less reactive ones. Davis has shown that sulfonyl oxaziridines can epoxidise simple alkenes, but the reaction is significantly slower (3-12 hours at 60 °C) than for dioxiranes.[502] The oxygen transfer takes place with retention of configuration of the original olefin geometry and is therefore believed to be concerted. Although this is a stoicheiometric method, it appears attractive for sensitive substrates because epoxidations can take place under neutral conditions with no additional reagents.

Davis has also described examples of asymmetric epoxidation using chiral oxaziridines. The first such mediator tested was derived from bromocamphor (1 in Figure 35), but the enantioselectivities observed were low (up to 35% ee for *trans*-

stilbene oxide).[503] A chiral sulfonyl oxaziridine derived from (*S*)-(N-benzyl)-α-methylbenzylamine and pentafluorobenzaldehyde (2 in Figure 35), however afforded up to 65% ee in the epoxidation of *trans*-α-methylstilbene.[504] Improved results (greater than 90% ee for *trans*-α-methylstilbene oxide) were obtained with a sulfonyl oxaziridine that was based on a C2 symmetric amine (3 in Scheme 94), but the reactions were very slow (2 weeks at 60 °C).[505]



Scheme 94: Oxaziridines developed by Davis for stoicheiometric asymmetric epoxidation.

Davis favoured the planar transition state in his attempt to explain the stereochemical outcome of the epoxidation reactions,[506] and this was also supported by theoretical calculations.[507] According to Davis, this mechanism of oxygen delivery was also at work in the asymmetric oxidation of enolate anions by chiral oxaziridines which led to α-hydroxyketones with enantioselectivities of up to 95% ee.[508,509] Silyl enol ethers have also been reported to give epoxides when treated with oxaziridines but as mentioned above the instability of these compouds is too great to allow isolation.[510,467,495] To date, only Davis has reported successful isolation of α-silyloxy epoxides.[511] In the asymmetric oxidation of these substrates however Davis reported some enantioselectivity in the formation of the corresponding α-hydroxyketones (up to 11% ee).[511] As to why the delivery of oxygen to silyl enol ethers occurs with less enantioselectivity than to the corresponding enolates, is as yet unclear.

Oxaziridines are generally accessed by oxidation of the corresponding imines,[512,513] which are also produced upon oxygen transfer to substrates, but this system (oxaziridines/imine) has not yet succumbed to catalytic modification in asymmetric epoxidation. Interestingly, Davis has also reported the use of chiral sulfonyl oxaziridines in the asymmetric oxidation of sulfides to sulfoxides,[514] which

Page and co-workers have succeded in modifying to proceed catalytically.[515] The Page system involves a camphor derived sulfonyl imine as the mediator and hydrogen peroxide as the stoicheiometric oxidant.[516] It is possible that a related method can be developed for the catalytic asymmetric epoxidation mediated by an oxazirine/imine/oxidant system and therefore further research in this area is well justified.

1.5 Conclusions and research project design.

A concise description of the most successful chemical methods for asymmetric epoxidation has been presented. A crude classification of these would distinguish between those that employ metal complexes as mediators and those which are based purely on organic molecules. Asymmetric epoxidation mediated by biological and biomimetic systems has also been achieved with varying success,[42,517-520] but is beyond the scope of this discussion.

In truth, there does not seem to be a system which is applicable to all types of alkenes and enjoys generality. For example, the Sharpless epoxidation works specifically for allylic alcohols, the Jacobsen system is best for *cis*-aryl alkenes, the Shibasaki system and the Juliá process for enones, while the sulfur ylid method is successful only for stilbene oxides or closely related products. An exception to this rule may be the dioxirane system developed by Shi, but the whole of this methodology was reported while the research work to be discussed in the following chapters was in progress.

Intrigued by the oxidising properties of oxaziridines and based on our experience from the catalytic asymmetric sulfoxidation, we thought that it could be possible to modify the asymmetric epoxidation by chiral oxaziridines to proceed catalytically. Oxaziridines are also closely related to oxaziridinium salts, a lesser known reagent for asymmetric oxygen transfer which is discussed and investigated in greater detail in the following chapters.

The discussion that follows demonstrates how this research work has led to the development of a new system for catalytic asymmetric epoxidation.

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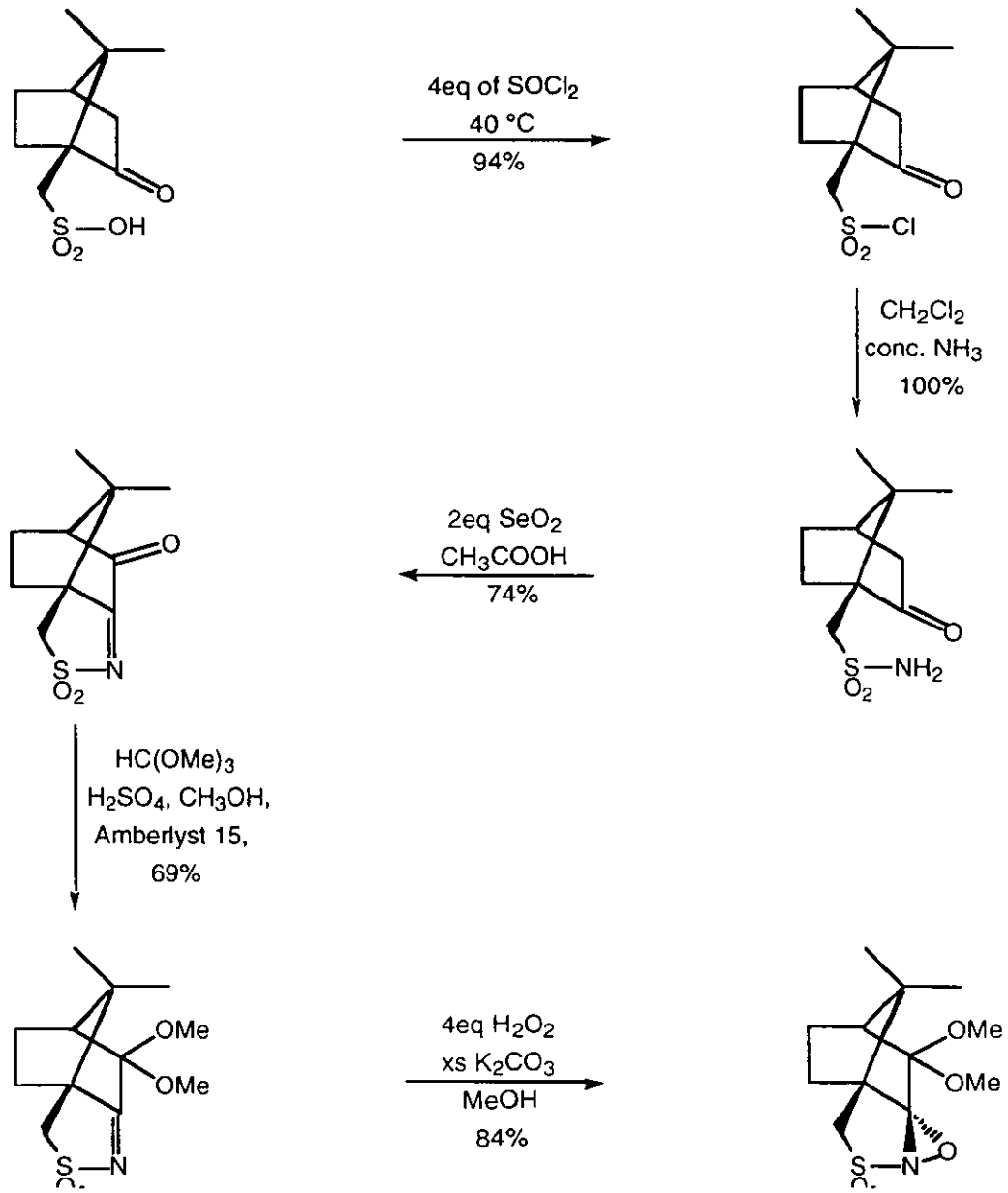
CHAPTER 2

RESULTS AND DISCUSSION

2.1 Chiral sulfonyl imines and oxaziridines.

In the search for new chiral oxidants for asymmetric epoxidation, 3,3-dimethoxy-camphorsulfonyl-2-oxaziridine was the first to be tested since it had performed well in the asymmetric oxidation of sulfides to sulfoxides. The reagent was synthesised as shown in Scheme 1.[1]



Scheme 1: Asymmetric synthesis of 3,3-dimethoxycamphor-10-sulfonyl-2-oxaziridine.

The overall synthetic sequence described in scheme 1 does not require

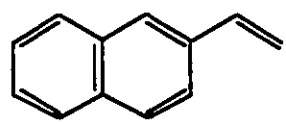
column chromatography at any of the stages.

Camphorsulfonyl chloride was treated with concentrated ammonia to yield the camphorsulfonamide, which in turn afforded the sulfonyl-2-imine by intramolecular condensation under Dean-Stark conditions. Oxidation of the imine with selenium dioxide furnished the 3-oxo-2-imine. However, it was found by preliminary work, that the two steps could be combined in one, if the sulfonamide was treated directly with selenium dioxide in acetic acid. The yield of this reaction is slightly lower than that obtained by the procedure which involves isolation of the intermediate imine but the economy in reagents and time is significant. The cost of the overall procedure can be further reduced by preparing the sulfonyl chloride from the substantially cheaper camphorsulfonic acid. Thionyl chloride was found to effect this transformation in nearly quantitative yield and thus it is superior than phosphorus pentachloride which has been employed previously in this reaction. The carbonyl group of the α-oxo-imine was converted to the dimethoxy ketal with trimethyl orthoformate, and finally treatment with hydrogen peroxide and potassium carbonate in methanol produced the diastereoisomerically pure camphor sulfonyloxaziridine. The five member ring containing the sulfonamido group can only be *cis*-fused to the terpenoid part of the structure; the *trans* isomer, that is the one with the oxygen occupying the *exo* position relative to the norbornyl-type framework, cannot exist for steric reasons.

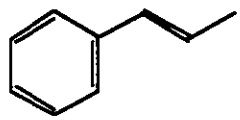
Davis has attempted alkene epoxidation with the 3,3-dihydro- and 3,3-dichlorocamphor-10-sulfonyl-2-oxaziridines without success.[2,3] The same author however, has reported that oxaziridines derived from saccharin or from substantially electron deficient aryl-aldimines could epoxidise simple alkenes.[4,5] In order to test the influence of substituents at the 3-position in the camphor systems, the 3,3-dimethoxy analogue was reacted with various alkenes under the same conditions employed by Davis;[4,5] namely refluxing chloroform (or benzene). Although this reagent oxidises sulfides to sulfoxides even at –20 °C, it failed in our hands to produce epoxides from the corresponding alkenes (Scheme 2). Thus, the electronic and steric influence of the methoxy groups did not improve the reactivity of the oxaziridine with less nucleophilic substrates, such as the olefins used.

The substantially more electron rich double bond of silylenolethers was considered next. 1-Trimethylsilyloxycyclohex-1-ene was allowed to react with camphor sulfonyloxaziridine under the same conditions as those used by Davis in a similar attempt to epoxidise these substrates,[6] and the reaction was monitored by TLC. After eight hours the consumption of the enol ether was complete but a polymeric material had been formed. At lower temperatures (40 °C), disappearance

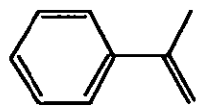
of the substrate was slower but the polymeric material was formed again.



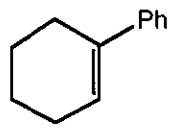
No reaction after 84 hours



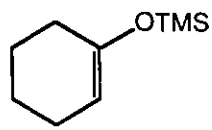
No reaction after 84 hours



No reaction after 48 hours



No reaction after 48 hours



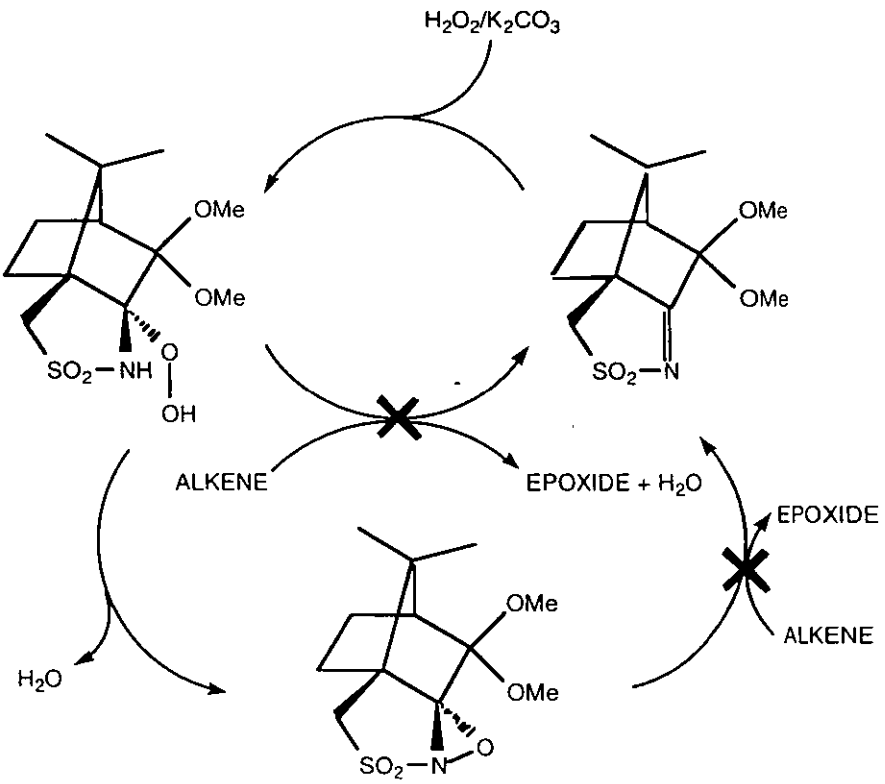
Polymeric material is formed

Scheme 2: The oxaziridine that affords best enantioselectivities in sulfide oxidation is inactive towards olefin epoxidation.

Inclusion of a Lewis acid (one equivalent of zinc chloride etherate) in this reaction, promoted the formation of the same undesired product in refluxing chloroform, while at ambient temperature the reaction proceeded at negligible rate. In all cases only partial disappearance of the oxaziridine was observed despite the complete consumption of the enol ether. Isolation of the unreacted oxaziridine indicated that the extent of the oxygen transfer reaction was of the order of 40 to 60% provided that only a small amount of this material was lost during work-up and isolation. Epoxy silyl enol ethers are unstable and prone to rearrangements,[6,7] but have been reported by Davis as isolable compounds.[8] Alternatively they can be hydrolysed to α-hydroxyl carbonyl compounds (Rubottom reaction).[9,10] Nevertheless, acidic work up of the crude reaction residue, followed by

chromatography, failed to furnish α-hydroxycyclohexanone.

Having established that sulfonyl oxaziridines are not electrophilic enough to epoxidise alkenes, attention was focused on hydroperoxyamines. These transient species are the addition adducts between hydrogen peroxide and imines.[11] It has been postulated that the hydroperoxyamine intermediate may transfer oxygen to the substrate before it dehydrates to the corresponding oxaziridine.[12,13] The next attempt towards a successful oxygen transfer process for simple alkenes, focused on hydroperoxyamines, generated *in situ* from electron deficient imines. This would also serve as an analogue of the nitrile mediated Payne epoxidation method which involves hydroperoxy imines as the active oxidising species.[14,15]



Scheme 3: Sulfonyl imines and oxaziridines do not mediate epoxidation of simple alkenes.

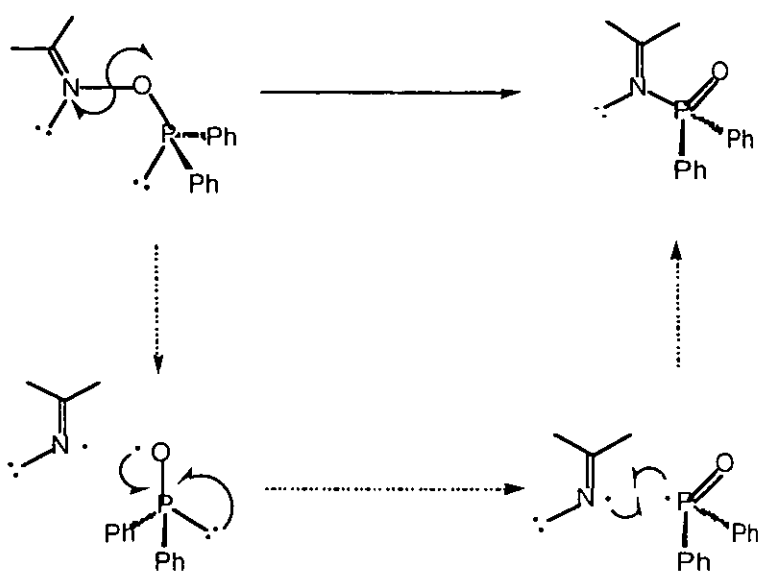
1-Phenylcyclohex-1-ene was treated with an equimolar amount of 3,3-dimethoxy-camphor-10-sulfonyl-2-imine and excess of alkaline solution of hydrogen peroxide, but no epoxidation was observed after 24 hours. This suggests that the hydroperoxyamine is not long lived or reactive enough to be intercepted by the substrate, but preferentially collapses to the corresponding oxaziridine. The latter

was the only product obtained from the reaction mixture (Scheme 3). This is in accord with the work of Page and co-workers who examined this system extensively, and found that in the presence of alkaline hydrogen peroxide, 3,3-dimethoxycamphor-10-sulfonyl-2-imine exhibited a higher tendency to produce the oxaziridine than the simple unsubstituted imine.[16]

To conclude, sulfonyl imines and oxaziridines are not potential mediators for alkene epoxidation and therefore further research was not focused on such systems.

2.2 Chiral phosphinoyl imines.

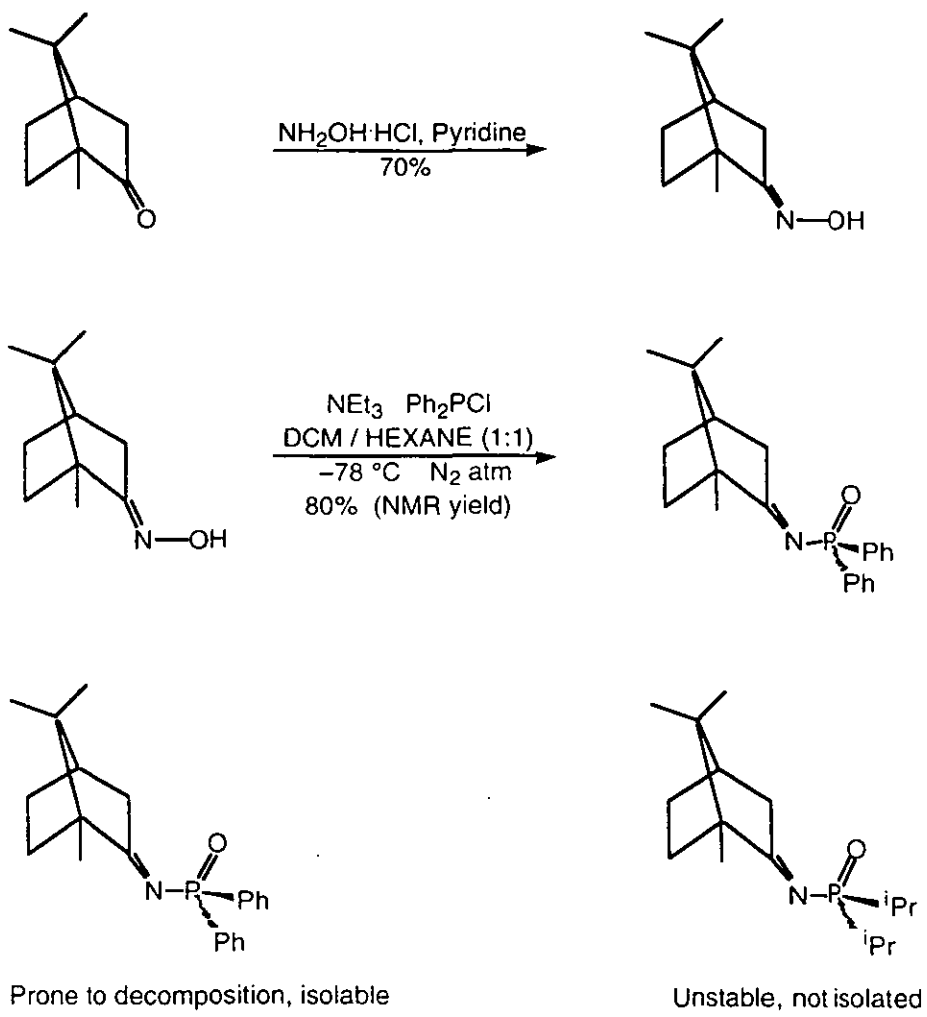
A different type of oxaziridine that has been used in the oxidation of both sulfides and alkenes is that based on the phosphinoyl group rather than the sulfonyl moiety.[17,18] These derivatives are expected to promote a more stereoselective oxygen transfer than their sulfonyl analogues, by virtue of the increased steric bulk associated with the phosphinoyl group.



Scheme 4: N-phosphinoyl imines derived from ketones can be prepared *via* their oximes.

The most practical route to phosphinoyl imines derived from ketones, is *via* the oxime according to the procedure developed by Krzyzanowska and Stec (Scheme 4).[19,20] The alternative method involves condensation of a ketone with diphenylphosphinic amide in the presence of a Lewis acid such as titanium(IV) chloride.[21] This method however, is not always reliable and therefore the two step procedure *via* the oxime is still the method of choice to date. Thus, camphor oxime[22]

was allowed to react with chlorodiphenyl phosphine and triethylamine at –78 °C to produce initially the O-phosphino-oxime which in turn, rearranged to the camphor N-phosphinoyl imine (Schemes 4 and 5). The NMR spectrum of the crude product suggested that the desired imine had been formed in 80% yield with unreacted oxime being the only impurity.

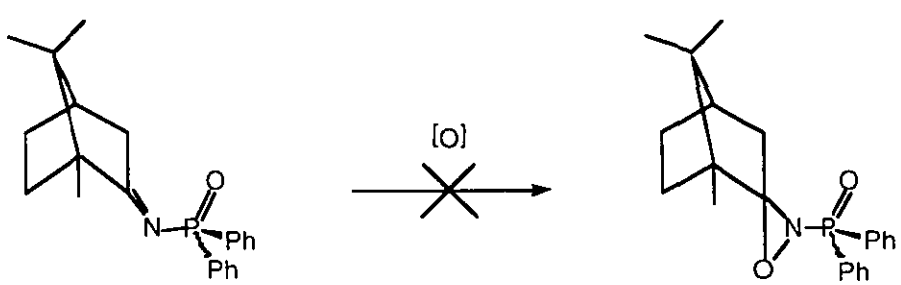


Scheme 5: Chiral phosphinoyl imines derived from camphor. The diphenyl derivatives are more stable and formed in higher yields.

The synthesis of the P,P-diisopropyl derivative was also attempted from the corresponding chlorophosphine. However, although the NMR spectrum of the crude product indicated that the desired derivative had been formed in 65% yield, it decomposed when subjected to column chromatography.

This is in accord with the report by Jennings who commented on the

derivatisation.[23] The same author found that phosphinoyl imines derived from aldehydes can be oxidised to the corresponding oxaziridines but only the mCPBA/potassium fluoride complex (1:2) proved efficient.[23] The mCPBA/KF complex was prepared according to the procedure reported by Camps who used this reagent for sensitive alkene epoxidation.[24] However the camphor phoshinoyl imine was found to be completely inert towards this oxidant regardless of the temperature and time allowed for the reaction. Basic hydrogen peroxide was also ineffective in carrying out the desired transformation, although sulfonyl oxaziridines were synthesised with this reagent. Inclusion of *p* -methyltolylsulfide in the reaction mixture did not result in the formation of the corresponding sulfoxide (within 24 hours), which would have probably been formed had the oxaziridine been produced. Attempted oxidation with Oxone™ in a two phase system (dichloromethane/water) resulted in hydrolysis of the phosphinoyl imine to camphor and diphenyl phosphinic acid. Trost[25] has developed an anhydrous source of Oxone™ in which the monoperoxy sulfate species is associated with the tetrabutylammonium ion as the counter-ion. This reagent has been used in the oxidation of sensitive compounds[26] but was also ineffective in producing the desired oxaziridine.



[O]: mCPBA/KF, mCPBA, OXONE™, Hydrogen peroxide/base, TBHP

Scheme 6: It is not yet clear whether the failure to oxidise camphor phosphinoyl imines is due to steric or electronic reasons.

In order to investigate the inertness of camphor phosphinoyl imines towards various oxidants, the structure of the diphenyl phosphinoyl imine was generated by computer simulation and studied. The optimised structure exhibits reasonable heat of formation, (stable); the bond lengths and bond angles de*via*te only slightly from those predicted for a tetrahedral phosphorus atom and an sp^2 hybridised nitrogen atom. However the carbon-nitrogen and phosphorus-oxygen double bonds are not

those predicted for a tetrahedral phosphorus atom and an sp^2 hybridised nitrogen atom. However the carbon-nitrogen and phosphorus-oxygen double bonds are not periplanar but in a skew type of arrangement at an angle of approximately 30°. This reduces the extent of conjugation between the two π-systems suggesting that the imino-carbon atom would not be as electrophilic as we had initially expected. More importantly, one of the phenyl groups seems to flank the *endo* face of the sp^2 carbon atom. It is well known for camphor derivatives that this is the only trajectory of approach for attack at the carbon atom in question. For example, in the reduction of camphor by lithium aluminium hydride, even the small hydride anion is delivered almost exclusively from the *endo* position to give the *exo* alcohol in 96% de.[27,28] The steric bulk of the geminal dimethyl group on the bridgehead carbon inhibits nucleophilic attack along the *exo* position. Perhaps the effect of the phenyl group mentioned above, in conjunction with the geometry of the rest of the structure, has a severe effect on the *endo* mode of attack by the various nucleophilic oxidants.

Finally, iodosobenzene, an electrophilic oxidant, was tested. This reagent was prepared from iodobenzene diacetate and sodium hydroxide in 88% yield.[29] An interesting reaction occurred when the crude phosphinoyl imine was treated with iodosobenzene in the presence of α-methylstyrene in dry dichloromethane. A product was formed rapidly according to TLC analysis even when the crude imine was present in small amounts. The production of the new compound did not increase with extended reaction times, but did so when more of the crude reagent was added. Traces of the new compound was isolated by column chromatography and it was identified as acetophenone, by comparison of the IR and NMR spectra with an authentic sample. It is not immediately obvious how this product was formed, but similar oxidative cleavages of alkenes have also been reported in epoxidation reactions.[84,85] A tentative assignment is through overoxidation and subsequent cleavage of the corresponding epoxide.

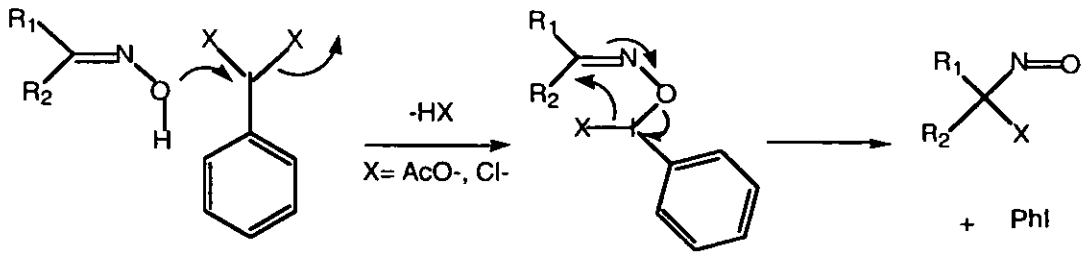
In order to test this hypothesis the reaction was repeated at lower temperatures, with styrene as the substrate, but the course of the reaction seemed unchanged by TLC analysis. The NMR spectrum of the crude product indicated that styrene oxide had been formed in small but detectable amounts. The low yields of benzaldehyde (*ca* 7%) and poor reaction profiles in all cases, even with the imine present in twofold excess, may be attributed to the poor solubility of iodosobenzene in the solvents used due to its polymeric nature,[30] or the steric demand of the camphor derivatives.

The explanation of these experimental facts is a challenging task, since the electron poor phoshinoyl imine was not expected to react with an electrophilic

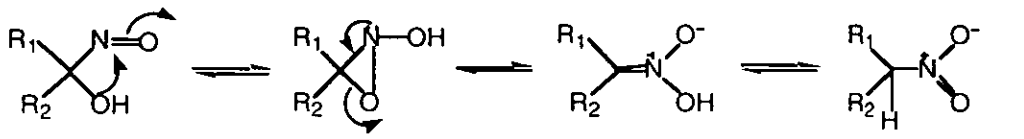
oxidant. It was therefore suspected that some impurities present in the crude imine might be responsible for the small amounts of the compounds obtained. In order to examine the validity of this statement, the crude diphenylphosphinoyl imine was subjected to column chromatography with the hope that it would not decompose as the diisopropyl derivative. Fortunately, a significant amount of the crude camphor phosphinoyl imine (CPI), survived the chromatography stage and it was thus obtained in a reasonably pure form. The experiment was repeated with stoicheiometric amounts of iodosobenzene, styrene and pure CPI but no reaction occurred. From the NMR spectrum of the crude CPI it was known that unreacted oxime was present, so the reaction was repeated with camphor oxime instead of the imine, and benzaldehyde was obtained in 32% yield. The aldehyde is also obtained in similar yields with cyclohexanone oxime, but the reaction proceeded to negligible extent with fenchone oxime.

All three oximes produced a green/blue colour on contact with iodosobenzene which in some cases persisted until the reaction ceased. It is beyond doubt that the oxime functionality is involved in this unusual oxygen transfer process. Corey,[31] and other research groups,[32] have also reported this colour change in reactions of oximes with related iodobenzene derivatives and assigned the blue colour to intermediates containing the nitroso functionality, (Scheme 7).

Following Corey's mechanistic analysis, the reaction between an oxime and iodosobenzene should produce a geminal hydroxy-nitroso adduct designated (A) in Scheme 7. This intermediate possibly reverts to the more stable nitro compound, presumably *via* the N-hydroxy oxaziridine, designated (B) in scheme 7. The latter may be able to deliver the oxygen to an alkene and the regenerated oxime can in principle be oxidised again (catalyst). As to how the epoxide (or the alkene) may react further to produce the carbonyl compound observed is still not clear.



For PhI=O the intermediate formed is thought to be (A)



Scheme 7: The reaction of oximes with iodine III compounds of the type $PhIX_2$.

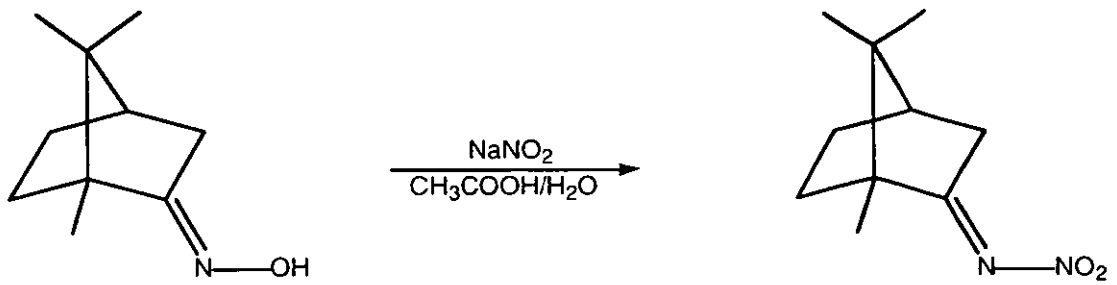
In order to test the validity of such a mechanistic proposal, a commercially available epoxide was subjected to the reaction conditions. However, styrene oxide was found to be stable in the presence of iodosobenzene in chloroform (ambient temperature) over a period of 48 hours. When cyclohexanone oxime was submitted to the reaction, the usual green/blue colour appeared, indicative of the formation of the nitroso species, but the epoxide was not intercepted by any reactive intermediate, and in fact the course of the reaction resembles that in which styrene oxide is excluded. From this reaction nitrocyclohexane was isolated in 17% yield, and the IR and NMR spectra were in accord with those obtained for a commercially available sample. Apparently, if it is formed, the geminal hydroxy-nitroso compound isomerises (possibly intramolecularly), to the nitro form, and hence a different intermediate must be invoked in order to account for the formation of the observed products when alkenes are present in the reaction mixture.

2.3 Chiral nitro imines.

In theory, more electrophilic oxaziridines are derived when groups of higher electron withdrawing capacity than the sulfonyl group, such as nitro and cyano, are attached to the nitrogen. Their synthesis would require reaction of carbonyl compounds with amines bearing the strong electron acceptor, followed by oxidation of the imine. There is however, an inherent problem in this synthetic approach. The strong electron acceptor diminishes the nucleophilicity of the amino group, and thus

the imines cannot be expected to be formed in significant yields.

Interestingly, camphor N-nitro imine can be prepared in one step in approximately 70% yield from camphor oxime when the latter is treated with sodium nitrite in acetic acid/water (Scheme 8).[33]



Scheme 8: Synthesis of camphor nitrimine.

Recrystallisation, however, lowered the yield dramatically, (25-40% isolated). The action of a nucleophilic oxidant is expected to produce the corresponding oxaziridine, at least as a reactive intermediate. Thus, a solution of the N-nitro imine in dichloromethane was treated with an alkaline aqueous solution of Oxone™ in the presence of 1-phenylcyclohex-1-ene and the reaction was monitored by TLC. After three hours, no sign of epoxide was evident. The only change in the reaction mixture was the disappearance of the nitro-imine. The latter is thought to have been hydrolysed to camphor which was isolated from the reaction mixture by column chromatography.

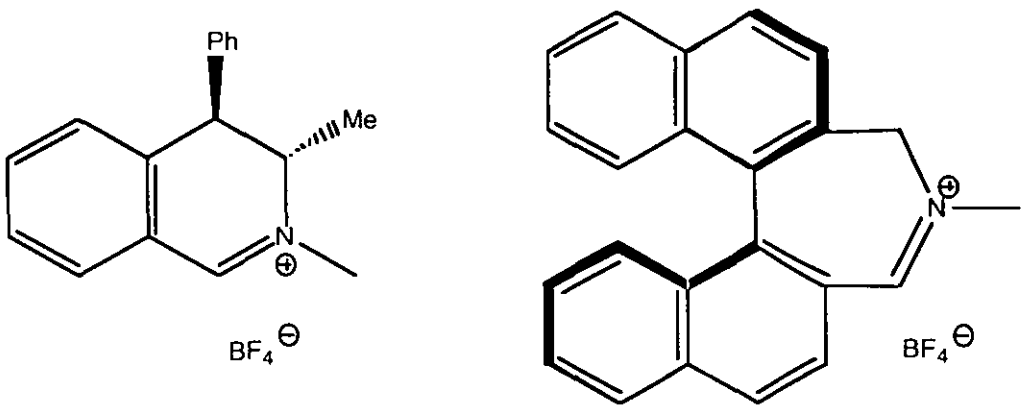
The results obtained with electron deficient imines did not encourage further consideration of these systems as potential mediators for catalytic asymmetric oxygen transfer to simple alkenes and therefore this approach was abandoned.

Davis has shown that although simple sulfonyl oxaziridines can oxidise sulfides to sulfoxides, they are ineffective in epoxidising olefins. The only type of oxaziridines which has been shown to be successful in epoxidising simple alkenes are benzene sulfonyl oxaziridines with a perfluorinated aromatic nucleus.[34,35] It seems that oxaziridines can be employed in alkene epoxidation only if their electronic properties are drastically modified.

2.4 Positively charged systems in oxygen transfer reactions.

The experiments described in the previous chapter lead to the conclusion that electron depleted imines and their corresponding oxaziridines are not potential mediators for alkene epoxidation. Although this approach has been successfully applied in the oxidation of sulfides, it fails with less nucleophilic substrates such as olefins. The reason for the apparent inertness of sulfonyloxaziridines towards alkenes may be associated with insufficient electrophilicity of the oxaziridine oxygen atom. In addition to the presence of more powerful electron withdrawing groups than the sulfonyl moiety, the electrophilicity of an oxaziridine moiety can be increased when a formal positive charge resides on the nitrogen.

In principle, alkylation of simple N-alkyl-oxaziridines, or oxidation of iminium salts, should generate oxaziridinium salts. Oxaziridinium salts were first reported as reactive intermediates in 1976.[36] However, these reagents have not received much attention prior to this work, and their oxidising properties towards alkenes have only recently attracted attention.[37-42]



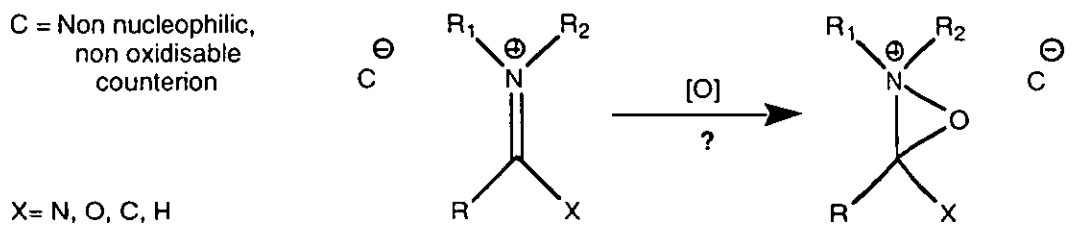
Scheme 9: The chiral iminium salts used by Hanquet and Aggarwal respectively.

It was Hanquet and Lusinchi who first examined the activity of oxaziridinium salts towards epoxidation,[43,44] and who first showed that iminium salts can catalyse alkene epoxidation with Oxone™ as the stoicheiometric oxidant.[45,46] These researchers also examined a chiral iminium salt (Scheme 9) in the catalytic process and showed that asymmetric oxidation of both olefins and sulfides could be accomplished. For example, stilbene oxide was obtained with 33% ee.[37] More recently, Aggarwal has used an enantiopure iminium salt derived from BINAP (Scheme 9), and has obtained 1-phenylcyclohex-1-ene oxide with 72% ee and stilbene oxide with 31% ee.[38]

Although the reported syntheses of these chiral iminium salts may be cumbersome (Hanquet's) and of significant cost (Aggarwal's), their proven ability to perform catalytic asymmetric alkene epoxidation, render further investigation of their chemistry well justified.

2.4.1 Design and synthesis of potential positively charged mediators.

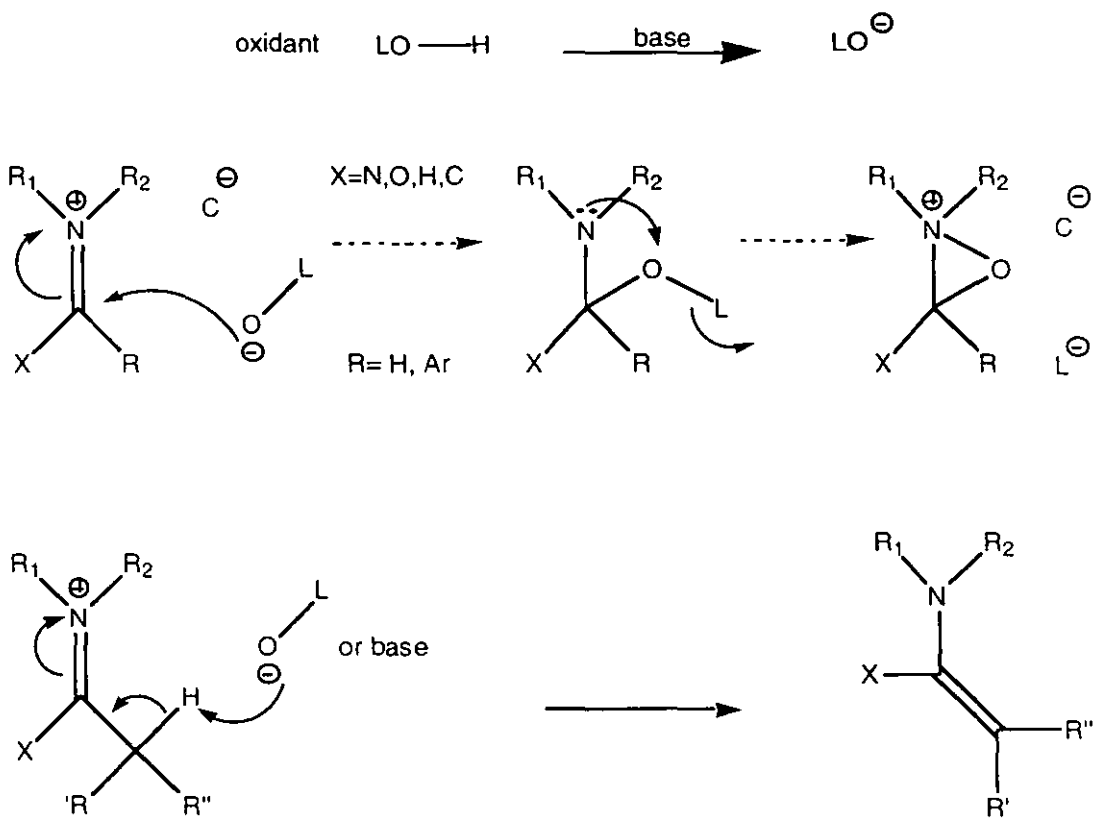
In principle, the oxaziridinium moiety can be accessed by a large variety of precursors. In theory any of the structures described below (formamidinium, oxazolinium and iminium salts) can give rise to the desired functionality if treated with the appropriate oxidant. Subsequent delivery of the newly incorporated oxygen atom to a nucleophilic substrate should regenerate the precursor, therefore rendering the reaction catalytic. However, the chemical behaviour of such species under oxidative conditions is absent from the literature, and hence a systematic investigation was warranted.



Scheme 10: Potential precursors to oxaziridinium salts.

A careful consideration of the organic salt precursor and the conditions to which it is intended to subject it, suggested several features which are vital for its correct function. Firstly, the counterion must be non-nucleophilic and non-oxidisable. A nucleophilic anion would engage the positively charged species in a non-productive equilibrium by forming the addition adduct, and consequently its concentration in the reaction mixture would be lowered. Furthermore, a nucleophile other than the substrate would compete for the electrophilic oxygen. Oxidisable anions that can be oxidised directly by the oxidant must also be excluded to ensure the oxidising agent is consumed in the desired way, that is in the generation of the oxaziridinium intermediate. Secondly, the nature of the groups designated R and X, in Scheme 10, determines the reactivity and stability of these systems. Under the alkaline, oxidative conditions required, α-hydrogens (with respect to the positively charged carbon atom) are not tolerated as they would give rise to enamines which are inactive in this type of process, (Scheme 11). Therefore, the groups R and X must

be either hydrogens or aryl substituents, or heteroatoms, (Scheme 10). Heteroatoms which can be oxidised should also be excluded as their oxidised derivatives often provide a good leaving group to be eliminated. For example in the case of X being sulfur, oxidation to sulfone and subsequent loss of sulfinate at the stage of the addition adduct is highly likely to occur (Scheme 11). Positively charged systems with tertiary carbon centres adjacent to the electron deficient carbon atom are prone to rearrangements, particularly migration, (orbitaly allowed 1,2 shift of substituents), and hence their correct function may be compromised.



Scheme 11: The nature of group R plays a decisive role in the chemistry of these organic salts under the reaction conditions in question.

It also follows from scheme 11 that the reaction is sensitive to the nature of the oxidant. The stoicheiometric oxidant must be one whose active oxygen is attached to a good leaving group. If this is not the case, the addition adduct would be stable, possibly unreactive, and the formation of the oxaziridinium moiety will be retarded or not take place at all. For example, comparison of the relative leaving group abilities of hydroxide, sulfate and chloride anions, suggests that hydrogen

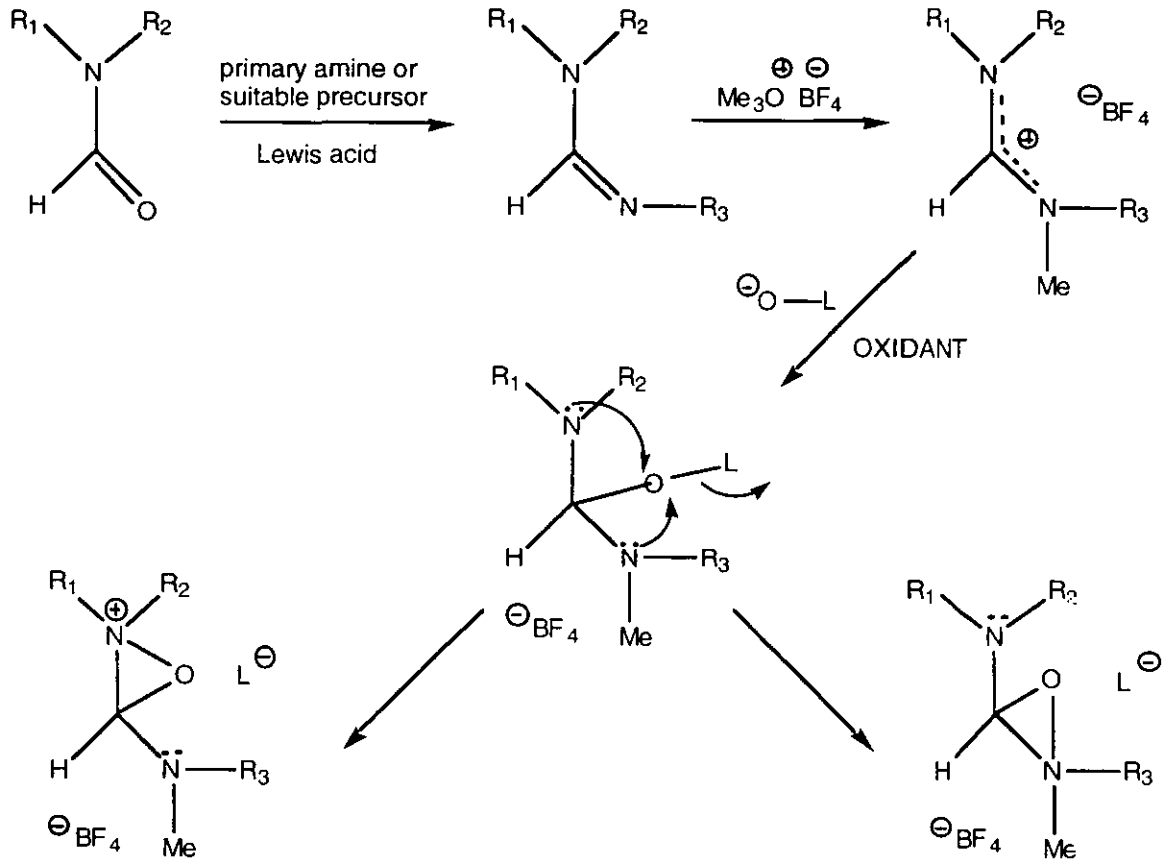
peroxide would not be as good an oxidant as Oxone™ or sodium hypochlorite, at least in this context (L=OH *vs* L=SO_4 or Cl in scheme 11).

From this preliminary theoretical analysis, it follows that the optimum structure of a potential precursor to oxaziridinium intermediates (iminium salt) should be derived from a secondary amine and an aryl aldehyde or a diaryl ketone. Alternatively, the condensation products between secondary amines and amides or esters of formic or aryl carboxylic acids should also prove promising precursors to oxaziridinium intermediates, (formamidinium and oxazolinium salts).

The synthesis of the systems designed above is discussed next according to the identity of the atom designated X in Scheme 10 and their behaviour under oxidative conditions is investigated.

2.5 Formamidinium salts (X=N).

These organic salts arise from quaternisation of formamidines and belong to the type of compounds described in Scheme 10 (R=H, X=nitrogen). There is, however, an inherent problem with this system. The second nitrogen atom present can also participate in an oxaziridinium functionality and hence two intermediates can, in principle, be formed (Scheme 12).



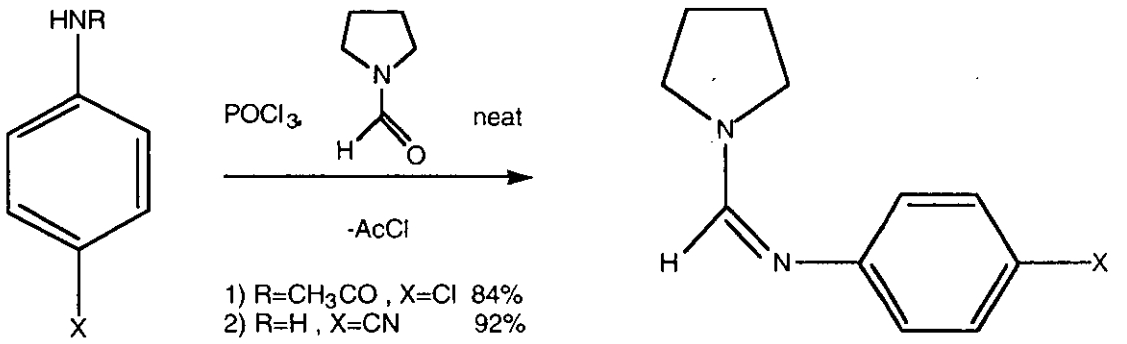
Scheme 12: The complication that must be considered when formamidinium salts are treated with the appropriate oxidant.

It might be possible to render only one heteroatom capable of producing the desired intermediate if the steric and/or electronic parameters of each nitrogen atom were modified appropriately.

Formamidinium salts are formed from formamidines, which in turn are the condensation products of formamides or the corresponding imidates and primary amines.[47] In the method of synthesis we employed, the acetamide of the amine was used instead and the condensation was mediated by phosphorus oxychloride, overall a high yielding process.[48] This method allowed control over the electronic

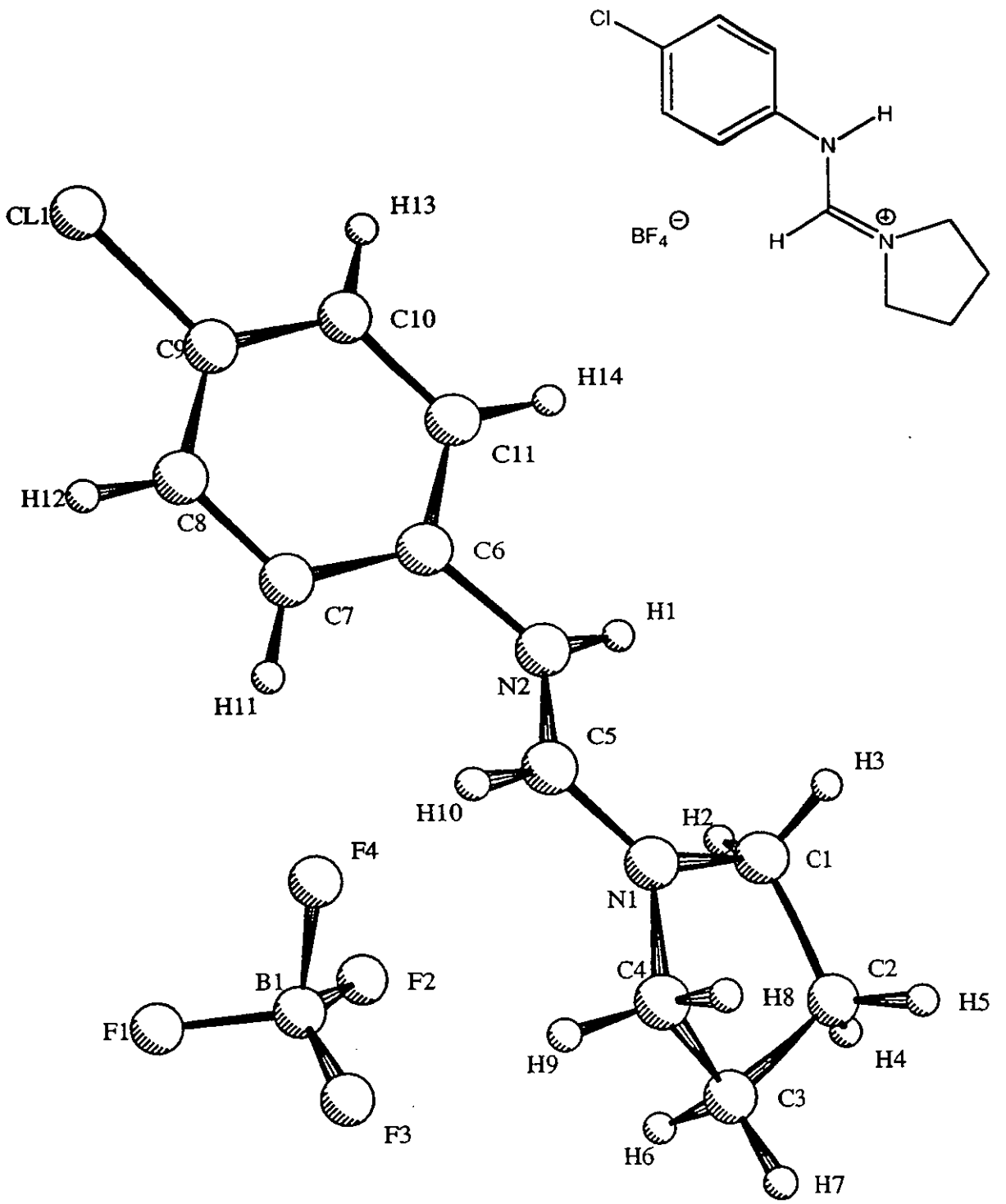
properties of the newly attached heteroatom as it was possible to use acetamides derived from 4-substituted anilines. Electron withdrawing groups on the aromatic ring should destabilise the positive charge developed on the anilinic nitrogen atom and therefore its participation in the oxaziridinium moiety would not be favoured on electronic grounds. Hence, only the dialkylated nitrogen may be electron rich enough to participate in the positively charged oxidising intermediate.

We found that amines attached to or in direct conjugation with strong electron withdrawing groups could be used directly in place of their acyl derivatives as they do not compete significantly with the dialkyl formamide for the Lewis acid (Scheme 14).



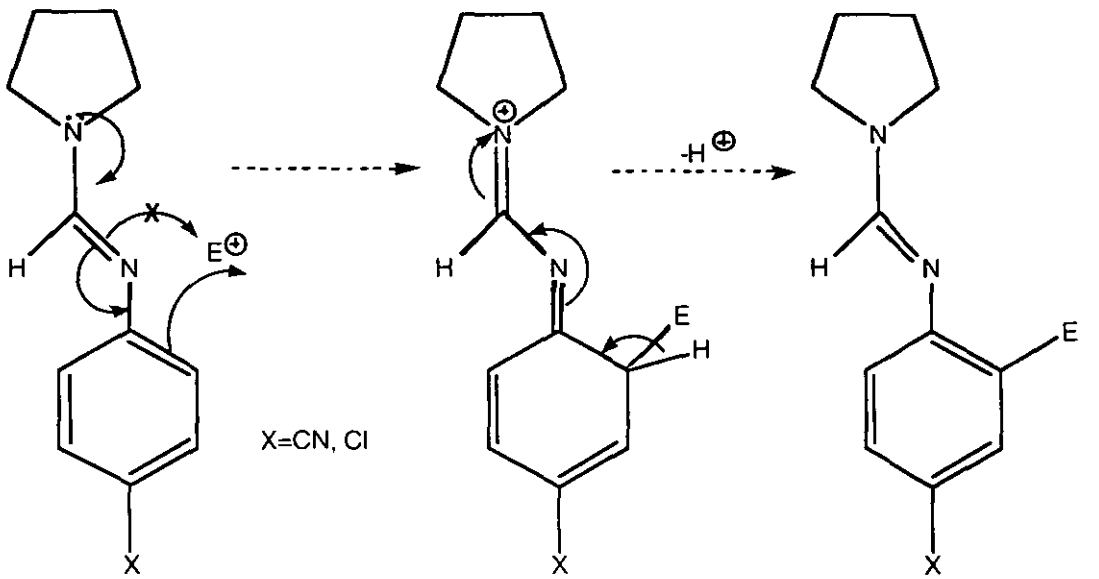
Scheme 13: Rapid and efficient method for the synthesis of formamidines.

Pyrrolidine carboxaldehyde was chosen as the starting material due to its structural resemblance to the commercially available formamide derived from proline; a potential precursor to chiral formamidinium salts. Although formamidine formation proceeds smoothly and in excellent yields, attempted quaternisation with trimethyloxonium tetrafluoroborate (Meerwein's reagent) failed. The only organic salt isolated was a small amount of the protonated formamidine whose X-ray structure was also obtained (Scheme 14). The crystallographic representation of the latter compound provided important information. First, the phenyl ring with the electron withdrawing substituent is twisted out of conjugation from the electron deficient amidinium moiety so that the positive charge is not destabilised. Secondly, the bonds of the formamidic carbon atom to both nitrogen atoms have the characteristics of double bonds and the N-C-N functionality is essentially planar.



Scheme 14: X-ray crystallographic representation of the protonated formamidine derived from 1-pyrrolidine carboxaldehyde and 4-chloroaniline.

Apparently the anilinic nitrogen is preferentially involved in the stabilisation of the positive charge rather than in conjugation with the aromatic nucleus or with both the phenyl ring and the amidinium moiety. This approach therefore does not appear to provide the discrimination required between the two heteroatoms.

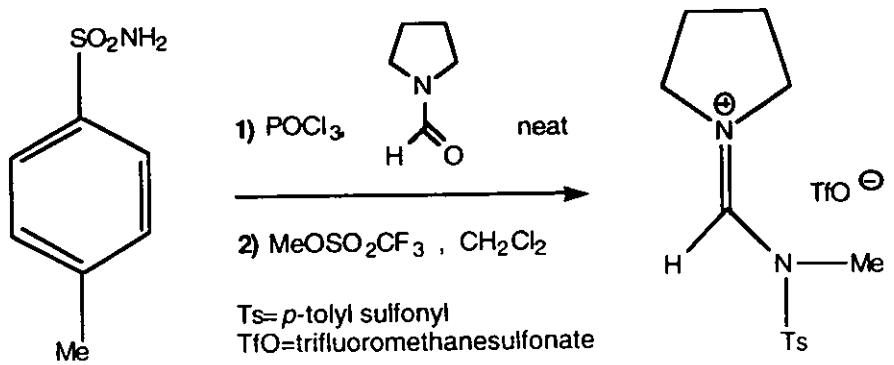


Scheme 15: Possible rationale for the generation of acid during the attempted methylation of formamidines.

It is not immediately obvious how the protonated formamidine arose but a rationalisation is given in Scheme 15. The explanation may lie in the high activating effect of the formamidine functionality towards the aromatic ring. Electron flow, from the two nitrogen atoms towards the electron withdrawing group, enhances the electron density at the *ortho* and *para* positions. The aryl ring is then sufficiently electron rich to react with the alkylating reagent at these positions. Elimination of a proton to restore aromaticity generates acid in the reaction medium. The formamidine moiety is basic enough to capture these protons. In order to test this mechanistic hypothesis, the pyrrolidine-N'-tosyl-formamidine was synthesised (Scheme 16).

The sulfonyl group attached to one of the nitrogen atoms suppresses its nucleophilicity, and hence the latter does not compete for the formation of the oxaziridinium intermediate. Additionally, since the formamidine moiety is not directly conjugated with the aromatic ring, methylation is anticipated to occur only at the sulfonyl nitrogen atom. These features are always at work since rotation of the phenyl ring does not influence the effect of the electron withdrawing group on

the formamidine functionality.



Scheme 16: A formamidinium salt that fulfils the requirements discussed in the design.

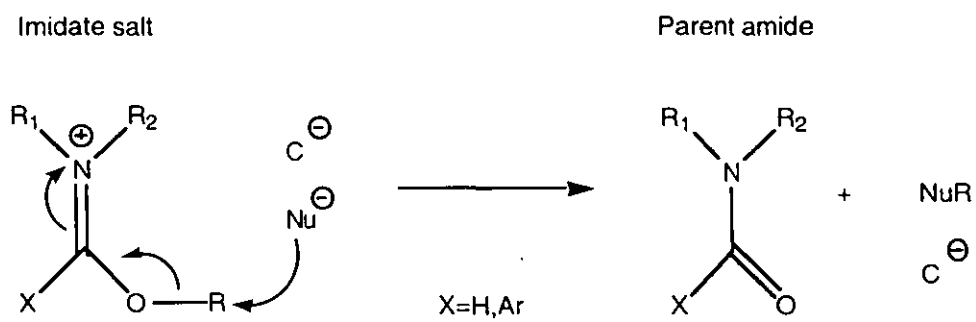
The yield for the formation of the pyrrole-N'-tosyl-formamidine is approximately 83 to 85%, while the quaternisation is almost quantitative, provided that enough time is allowed for the reaction (2-2.5 days) at ambient temperature, and that an excess of the methylating agent (2.5 equivalents of methyl triflate) is used. Interestingly, the reaction with trimethyloxonium tetrafluoroborate is significantly slower. The successful quaternisation of this derivative suggests that the anilinic derivatives reacted in a different way and the analysis of this problem was reasonably good. Finally, this organic salt was tested for its catalytic activity. Under the conditions previously employed by Hanquet[36] and Aggarwal[37] (Oxone™, sodium bicarbonate and the substrate, in acetonitrile/water at 0 °C), no epoxidation was observed. Change of the substrate from α-methyl styrene to the more nucleophilic 1-phenylcyclohex-1-ene did not alter the outcome. In fact the organic salt appeared to be quite stable in the reaction mixture (TLC), and only after 24 hours had its depletion (possibly due to hydrolysis) proceeded to significant extent. This, however, was not accompanied by epoxide formation. Because in the original reports[36,37] the relative amount of water in the solvent system was not specified, the experiment was repeated with different proportions of water in the range of 1 to 50% with respect to acetonitrile. In all cases examined, no epoxide formation was detected with 1-phenylcyclohex-1-ene as the substrate. This suggests that the formamidinium salt tested is more stable than initially expected[49] and perhaps the role of the sulfonamido-nitrogen atom had been underestimated. These experiments seriously question further design of catalysts based on formamidinium salts.

2.6 Oxazolinium salts (X=O).

2.6.1. Design of potential mediators based on oxazolinium salts.

It is common knowledge that oxygen atoms are inferior at stabilising an adjacent electron deficient carbon centre than nitrogen atoms due to the increased electronegativity associated with the oxygen atoms. Therefore, given the relative inertness of formamidinium salts, the obvious modification was to substitute one of the nitrogen atoms in the systems examined previously, with oxygen. The resulting compound is an imidate, and the corresponding quaternised structure is an imidate salt. The special class of imidates where both nitrogen and oxygen are part of a five (six) membered ring, is called oxazoline (oxazine); precursors to oxazolinium (oxazinium) salts. Chiral oxazolines, (or 4,5-dihydrooxazoles) and their salts have been used in asymmetric synthesis previously,[50-52] but not in the context described here. Oxazolinium salts provide an important candidate in the search of a suitable catalyst as they can possess all those vital features discussed earlier. In addition, the five membered ring makes them more resistant to hydrolysis when compared with their open chain analogues, the imidate salts.

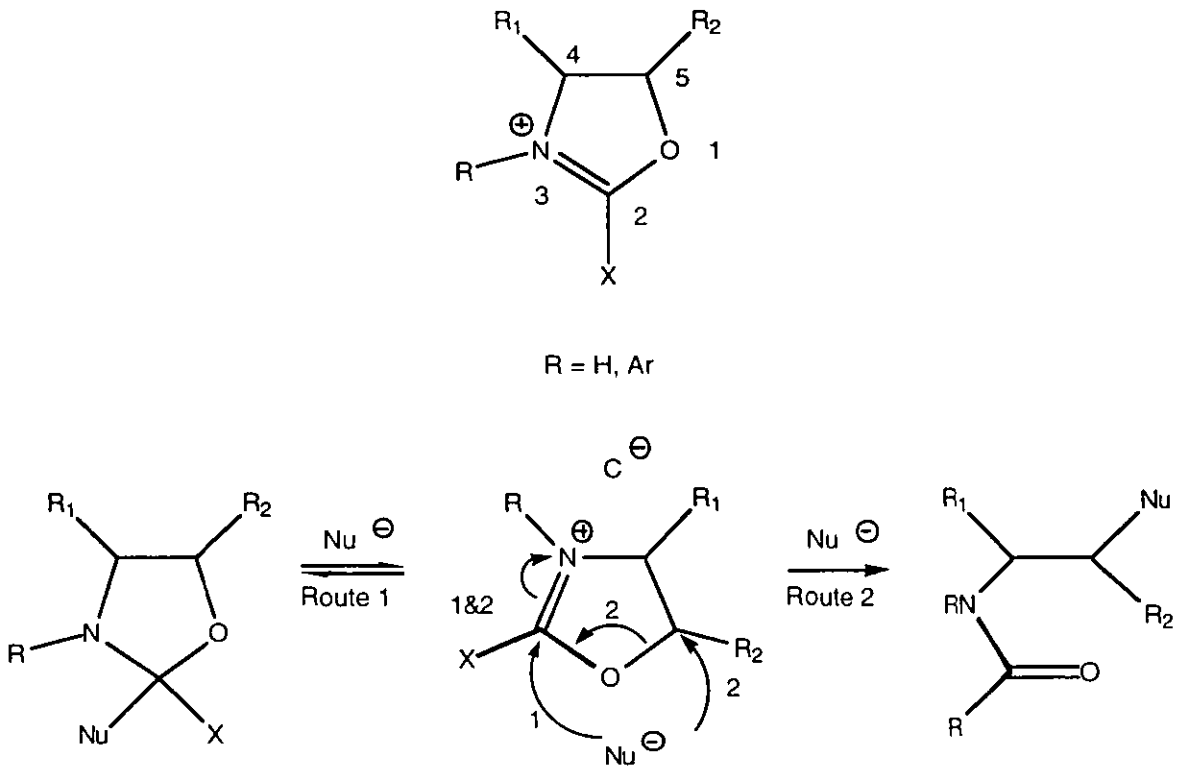
In 1964, Hünig carried out an extensive survey on organic salts and demonstrated their ambident electrophilicity.[53]



Scheme 17: The formation of the amide is favoured on thermodynamic grounds. Therefore imidate salts are not potential precursors to oxaziridinium intermediates.

In general, the predominant fate of ambident cations is highly dependent upon the substituents, identity of the heteroatoms involved in the stabilisation of the positive charge, the nature of the nucleophile, the solvent and finally the temperature. Imidate salts, (*i.e.* non-cyclic cases) are exclusively attacked by nucleophiles at the alkyl substituent of the oxygen atom in S_N2 fashion, to regenerate the parent amide.[54] In fact, such species have been demonstrated in the literature to act as powerful alkylating agents (Scheme 17).[55,56]

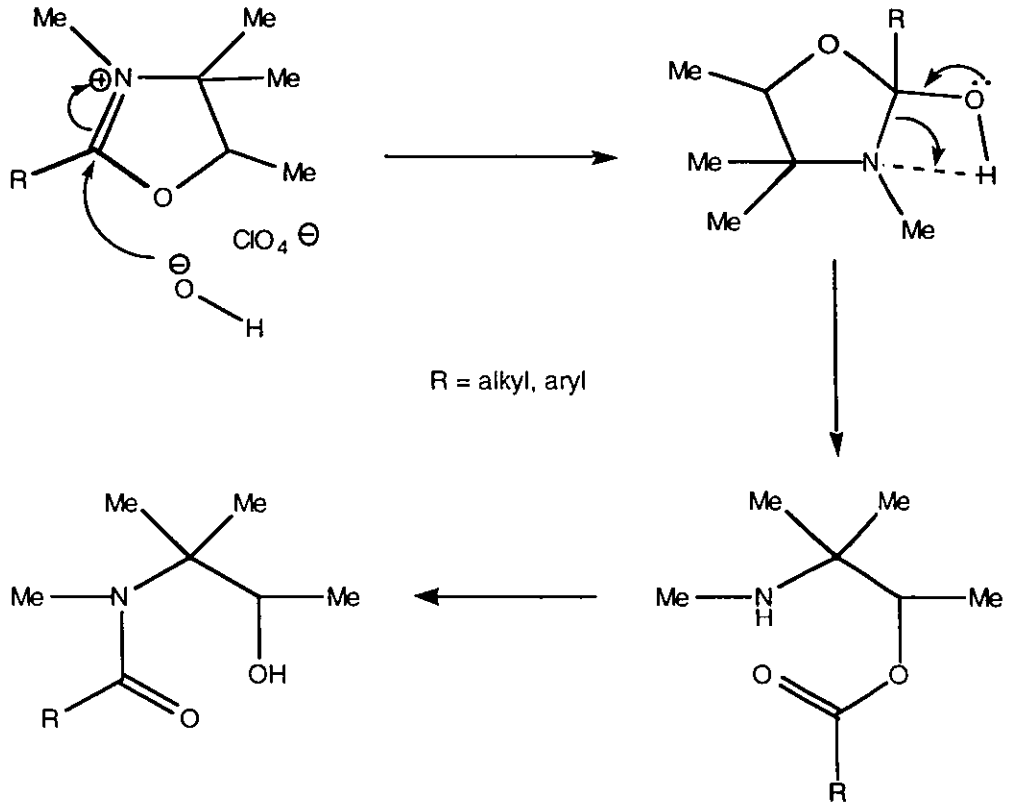
Oxazolinium salts react preferentially at the sp^2 positively charged carbon atom (C2), but they are also susceptible to nucleophilic attack (S_N2) at the sp^3 carbon attached to the oxygen atom (C5) (Scheme 18). Reaction at C2 is reversible, and the addition adduct is the kinetic product, also favoured at low temperatures.[57] When C2 has a hydrogen atom as the substituent, reaction at that centre is enhanced but with an aromatic substituent, due to the additional stabilisation of the positive charge, the alternative pathway to give the thermodynamically favoured amide, is preferred by the nucleophiles.[58,59]



Scheme 18: The ambident electrophilicity of oxazolinium salts as described by Hünig.

Almost invariably, the thermodynamic product (amide), arises when oxazolinium salts are subjected to nucleophiles. It is expected that the S_N2 reaction will be hindered when C4 is a secondary carbon, and thus reaction at C2 should predominate even when it bears a phenyl substituent. The above statement is also supported by the investigation carried out by Deslongchamps who examined the hydrolysis of various oxazolinium salts and observed that the initial products were the corresponding β-aminoacyloxy compounds.[60] The transfer of the acyl group onto the nitrogen atom to afford the thermodynamically favoured hydroxy amide is the final stage of the hydrolysis process. Deslongchamps neatly rationalised the

formation of the hydrolysis products, in terms of attack taking place by the nucleophile at C2 exclusively (Scheme 19).[60] Although this author emphasised the facile hydrolysis of these compounds, it should be noted that oxidants such as hydrogen peroxide and Oxone™ have not been tested with such systems, and may compete successfully with water because of their higher nucleophilic capacity due to the α effect.

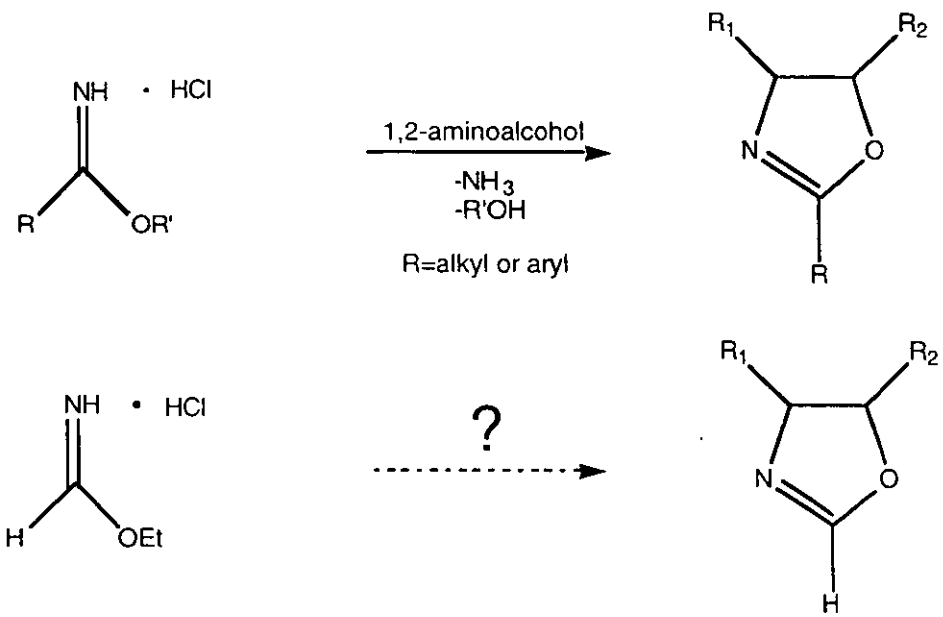


Scheme 19: Deslongchamp's rationale states that both the kinetic and thermodynamic products of the hydrolysis of oxazolinium salts arise from attack at C2.

Therefore, the synthesis of oxazolinium salts with the structural properties mentioned above was the next target. Aminoalcohols derived from chiral aminoacids would not provide the ideal chiral building blocks since they give rise to oxazolines with a primary C5 centre which according to Hünig is susceptible to S_N2 attack. In contrast, norephedrine (1-phenyl-2-aminopropanol) derived oxazolines have a secondary C5, the key feature required, and it is available in both enantiomeric forms at a reasonable cost.

2.6.2 Synthesis of norephedrine derived oxazolines and oxazolinium salts.

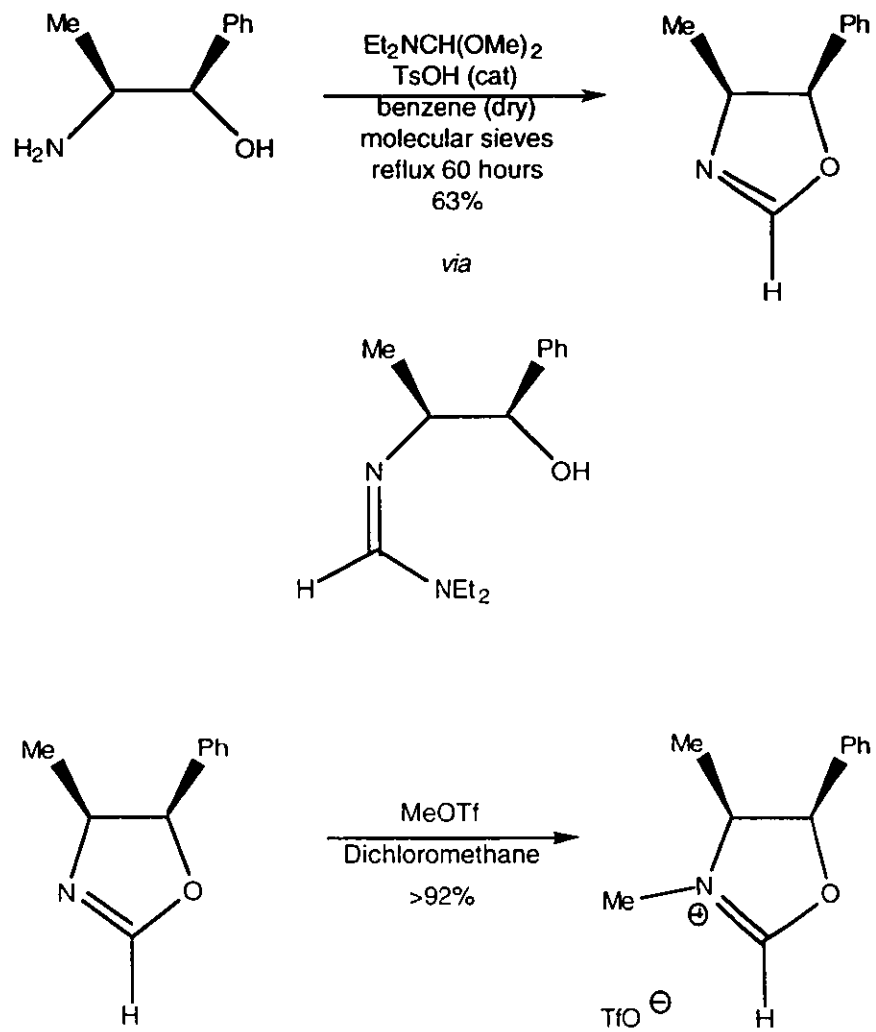
The method of synthesis is crucial since racemisation of the chiral carbon atom bearing the hydroxyl group is a problem with some of the methods reported in the literature, particularly in the one that involves condensation/cyclisation of a hydroxy amide.[61] Thorough literature search suggests that the method of choice is the condensation of the chiral amino alcohol with an imidate or an imidate salt (Scheme 20).[62] Since it is known that simple oxazolinium salts with a hydrogen substituent at C2 (refer to as 2H-oxazolinium salts) display better reactivity at the sp^2 carbon centre, their synthesis was targeted first. The only methodology available for the synthesis of 2H-oxazolines with C5 being stereogenic, was reported by Meyers and involves condensation of the amino alcohol with dimethyl formamide dimethyl acetal in dry benzene at reflux for 60 hours. Isolation of the oxazoline is brought about after column chromatography followed by distillation; overall a tedious procedure.[63]



Scheme 20: Imidates or imidate salts are among the most useful precursors of oxazolines.

Ethyl formimidate hydrochloride (a hydrogen cyanide derivative) has only recently become commercially available, and hence its role in the synthesis of 2H-oxazolines is unexplored (Scheme 20). The latter reagent was allowed to react with norephedrine in dichloromethane at room temperature or in dichloroethane at reflux for 24 hours. No reaction occurred in the first case and very little in the second one. Finally (4*S*,5*R*)-2H-3-methyl-4-phenyloxazoline was synthesised in 63% yield

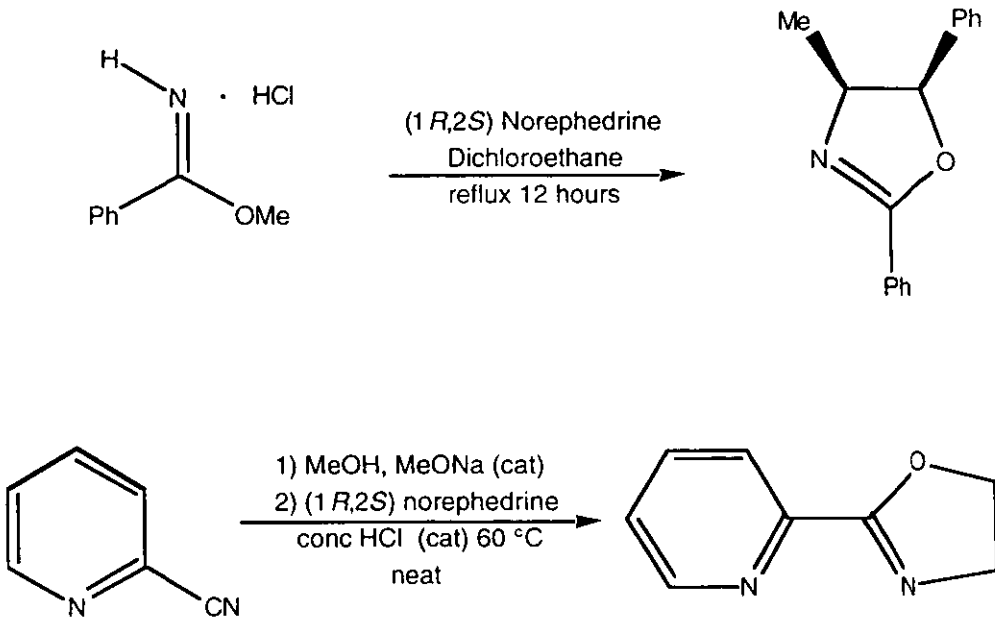
from (1*R*,2*S*) norephedrine, according to the method of Meyers as described above, and still remains the only method by which related 2H-oxazolines can be accessed.[61] Quartenisation with methyl triflate was almost quantitative (Scheme 21).



Scheme 21: The synthesis of the norephedrine derived 2H-oxazoline according to Meyers; the only procedure suitable for chiral compounds of this type.

This new organic salt was tested under the same conditions as those employed in the attempted oxidation using the formamidinium salt as mediator: 1 equivalent of Oxone™, 4 equivalents of sodium bicarbonate and 1 equivalent of the substrate (1-phenylcyclohex-1-ene), in acetonitrile/water at 0 °C, with catalytic amounts of the oxazolinium salt (10-20 mol%). The reaction was monitored by TLC analysis, which indicated that the organic salt disappeared quickly from the reaction mixture. This fact in comparison with previous results proves the greater reactivity

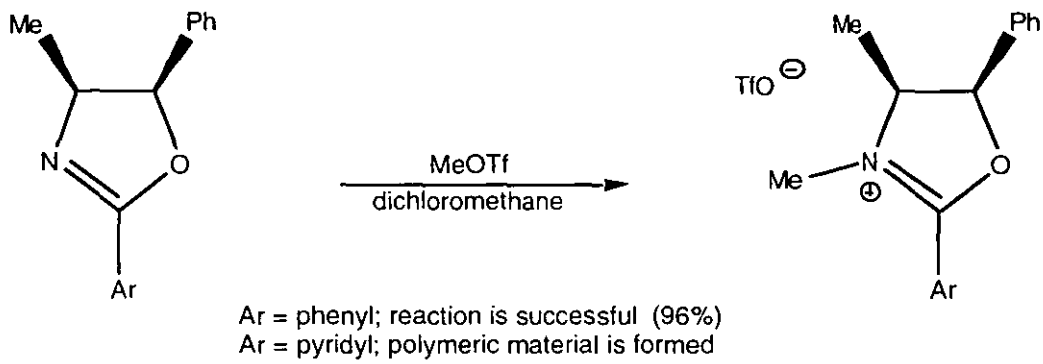
expected by the introduction of the oxygen atom, however, the desired reaction was not taking place. Because the most probable scenario is the hydrolysis of the oxazolinium salt, the proportion of water in the solvent system was reduced to minimum (a few drops). This rendered Oxone™ insoluble in the medium and no epoxidation was observed, although the organic salt was consumed. Lower reaction temperatures, higher proportions of the oxidant and catalyst (up to 50 mol%), had absolutely no effect on the course of the reaction. Phase transfer catalysis (tetrabutylammonium tetrafluoroborate), used in attempt to increase the concentration of Oxone™ in the reaction mixture, also met with failure. At this stage it was not clear whether this chemical behaviour was typical of oxazolinium salts or only of the 2H derivatives which display such a great tendency to hydrolyse/decompose due to the poor stabilisation of the positive charge.



Scheme 22: Synthesis of 2-phenyl and 2 pyridyl oxazolines derived from norephedrine.

In order to test a more stable oxazolinium salt, the 2-phenyl and 2-pyridyl substituted oxazolines also derived from norephedrine were synthesised (Scheme 22). The phenyl derivative was synthesised by treatment of methyl benzimidate hydrochloride with norephedrine.[64] The corresponding 2-pyridyl derivative was prepared in two steps from 2-cyanopyridine according to a literature procedure.[65] Treatment of 2-cyanopyridine with a catalytic amount of sodium methoxide (10 mol%) in methanol furnished the intermediate pyridyl imidate which was sufficiently pure to be reacted further. (4*S*,5*R*)-2-Pyridyl-4-methyl-5-phenyl

oxazoline was produced in good yield, but the corresponding salt could not be obtained by treatment with methyl triflate. Instead a polymeric material was isolated, presumably because the pyridine nitrogen atom, can also be methylated as well as attack the quaternised, electrophilic oxazolinium moiety. The attempt to block both nitrogens with excess of methyl triflate, and thus make a dicationic species was also unsuccessful. Again, polymeric material was formed. In contrast, the quarternisation of the 2-phenyl derivative proceeded smoothly, and the oxazolinium salt was isolated in excellent yield (Scheme 23).



Scheme 23: The corresponding salt of the 2-pyridyl derivative is prone to polymerisation presumably due to the presence of a nucleophilic nitrogen.

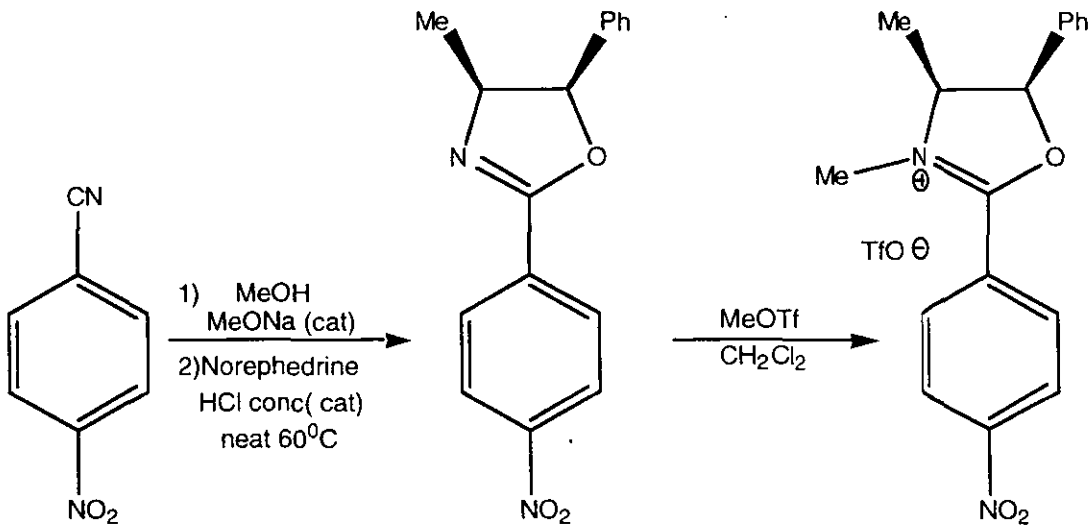
The 2-phenyloxazolinium salt was subjected to the same reaction conditions as the simpler, unsubstituted derivative (2H-oxazolinium salt), but, as in the previous case, no epoxidation was manifested with 1-phenylcyclohex-1-ene as the substrate. Modification of the amounts of water, catalyst, oxidant and identity of substrate had no effect whatsoever. Other oxidants such as hydrogen peroxide, tertiary butyl hydrogen peroxide, (TBHP), and bleach were also tested, with no generation of the epoxide product.

It is highly probable that with water being part of the solvent system the hydrolysis of oxazolinium salts occurs much more rapidly than the attack of the oxidant. This is unavoidable, because if water is excluded, Oxone™, the oxidant of choice, becomes insoluble.

In an attempt to avoid the sensitive nature of oxazolinium salts the previously unreported 2-(4-nitrophenyl)-4-methyl-5-phenyl oxazoline was synthesised in the same way as the 2-pyridyl derivative (Scheme 24). The X-ray crystallographic representation of this novel oxazoline is shown in scheme 25. The electron depleted double bond contained in this ring may serve as a precursor to an

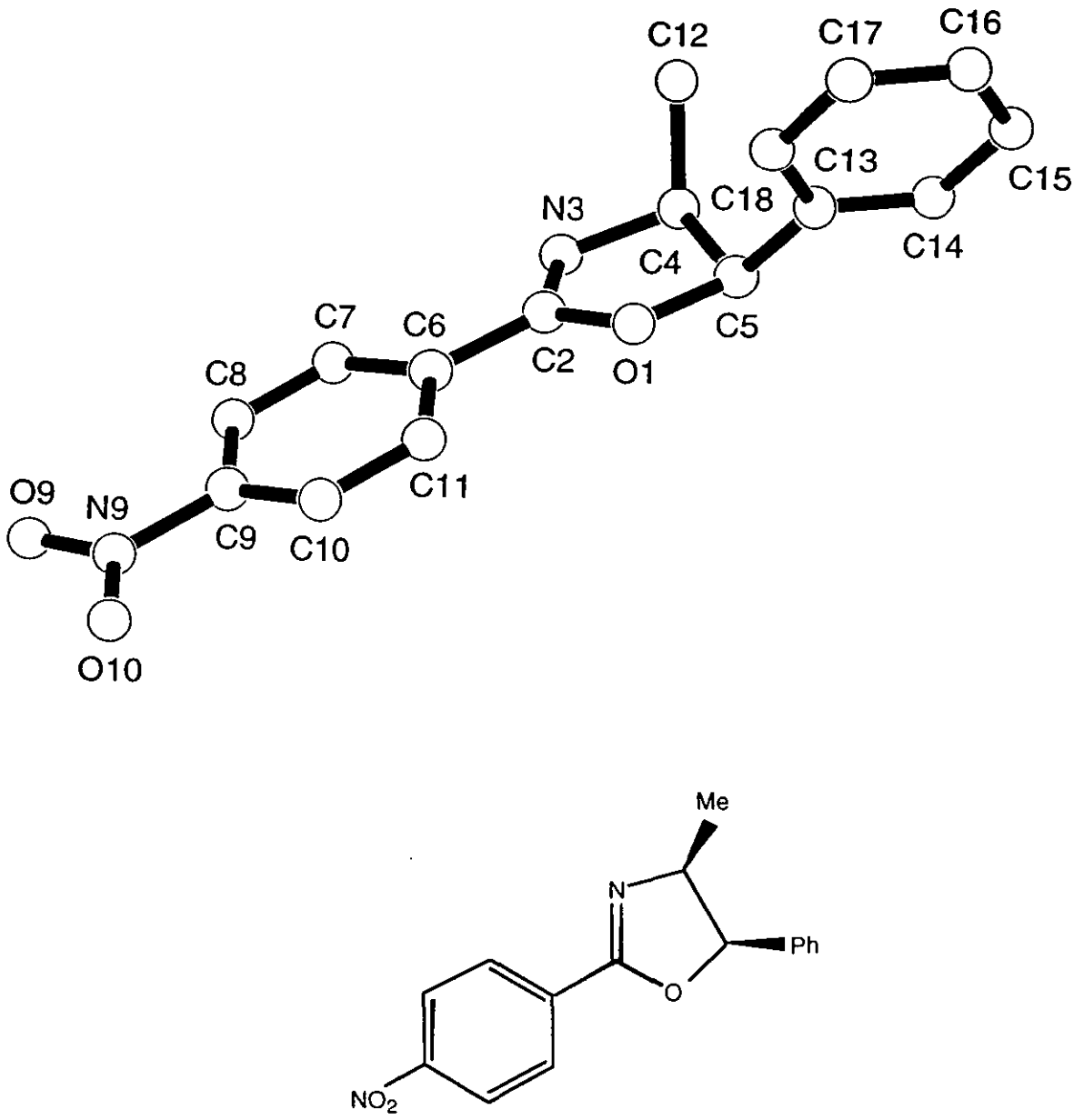
electrophilic oxaziridine. However, when this novel compound was treated with hydrogen peroxide in alkaline water/dichloromethane, it was recovered unchanged from the reaction mixture.

It is well established that oxazolines are not readily attacked by nucleophiles and this is why carboxylic acid derivatives are sometimes protected as such.[66] Similarly, this new derivative, despite the presence of the nitro group, was no exception. In line with the chemistry of oxazolinium salts, the quaternised product of the above oxazoline was also synthesised (Scheme 24).



Scheme 24: The latter two compounds were not found in the literature after an exhaustive search.

The quaternised 2-(4-nitrophenyl) derivative, also previously unreported, was expected to have substantial electrophilic capacity. It decomposes within hours when exposed to moisture as evidenced by the NMR spectrum of the compound, which shows that the partially hydrolysed form is present a freshly prepared sample of the oxazolinium salt under inert atmosphere. The crude salt was not subjected to the same conditions as the previous derivatives, since water would almost certainly degrade this compound. Instead it was treated with an anhydrous form of Oxone™ (active ingredient is $KHSO_5$), which was obtained by extracting an aqueous solution of Oxone™ and tetrabutylammonium hydrogen sulphate with dichloromethane; effectively, a cation exchange.



Scheme 25: X-ray crystallographic representation of the novel (4*S*,5*R*)-2-(4-nitrophenyl)-4-methyl-5-phenyloxazoline.

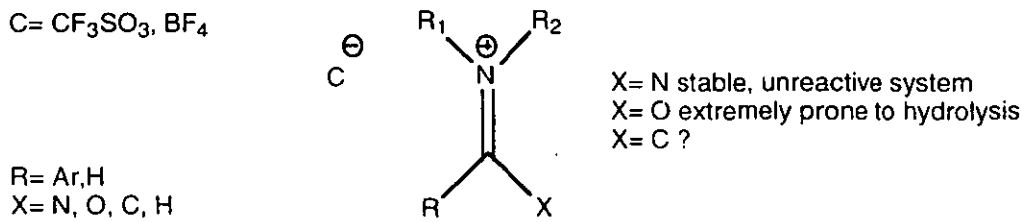
The crude salt was not subjected to the same conditions as the previous derivatives, since water would almost certainly degrade this compound. Instead it was treated with an anhydrous form of Oxone™ (active ingredient is $KHSO_5$), which was obtained by extracting an aqueous solution of Oxone™ and tetrabutylammonium hydrogen sulphate with dichloromethane; effectively, a cation exchange. Although this form of Oxone™ was developed and used by Trost in sulfur oxidation, there is no literature precedence for the use of this reagent as the stoicheiometric oxidant in epoxidation reactions.

The reaction was carried out in dry dichloromethane and with 1-phenylcyclohex-1-ene as the substrate. After 24 hours the reaction was ceased and worked up, but no 1-phenylcyclohex-1-ene oxide was isolated or observed by NMR spectroscopy.

This series of experiments demonstrated the inability of oxazolinium salts to catalyse oxygen transfer reactions to alkene substrates, and therefore further research on these systems was terminated.

2.7 Iminium salts.

The final case examined was that with no heteroatom but with a carbon atom attached to the positively charged moiety (Scheme 26). From a theoretical point of view this system should be more reactive than the corresponding formamidinium salts because the positive charge is not as well stabilised as with the additional α-nitrogen atom. This suggestion was put to the test.

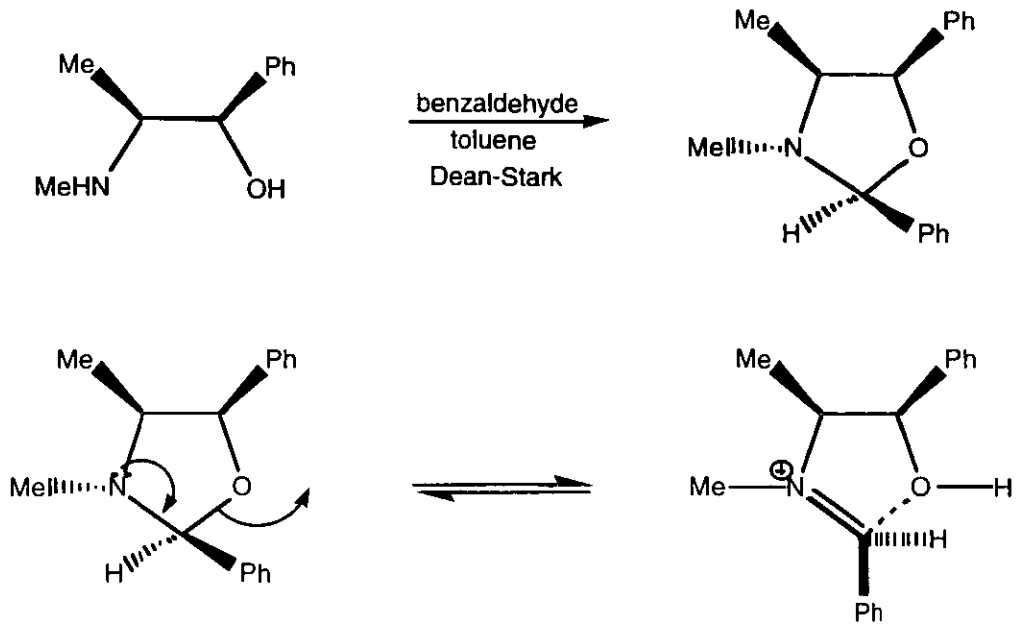


Scheme 26: With X=N, O too little reactivity or stability is obtained respectively. Could a carbon substituent balance the two effects?

2.8 Transient iminium species.

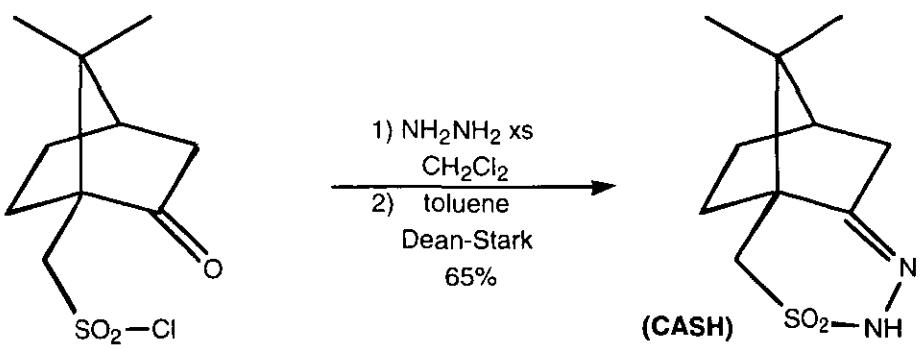
Before any formal iminium salts were examined, some intermediate cases were considered. In principle, a secondary amine condenses with an aldehyde to produce an iminium salt, provided that the conditions are appropriate to effect dehydration. With ephedrine, (chiral, secondary amino alcohol), the iminium salt formed initially is cyclised to the oxazolidine. Since there is evidence, mainly spectroscopic in nature, that there is an equilibrium between an oxazolidine and the corresponding iminium species (Scheme 27),[67,68,69] it may be possible to trap the desired moiety with a good nucleophile, (Oxone™). Since intramolecular cyclisation is quite facile, the iminium functionality generated *in situ* would be at least partially protected from hydrolysis in the form of the heterocycle.

The known derivative 3,4-dimethyl-2,5-diphenyl-oxazolidine, was prepared by the condensation of ephedrine and benzaldehyde in toluene under Dean-Stark conditions (Scheme 27). Examination of the NMR and IR spectra allowed unambiguous assignment of the stereochemistry at the former aldehyde carbon atom, in agreement with previous reports.[69] However, the compound was inert under the classical conditions employed earlier. Replacement of Oxone™ with TBHP and N-methyl imidazole as the base/proton relay afforded no products when 1-phenylcyclohex-1-ene was present. Acid catalysed promotion of the equilibrium was avoided because TBHP is incompatible with acids.



Scheme 27: The stereochemistry at the new stereogenic centre is under thermodynamic control.

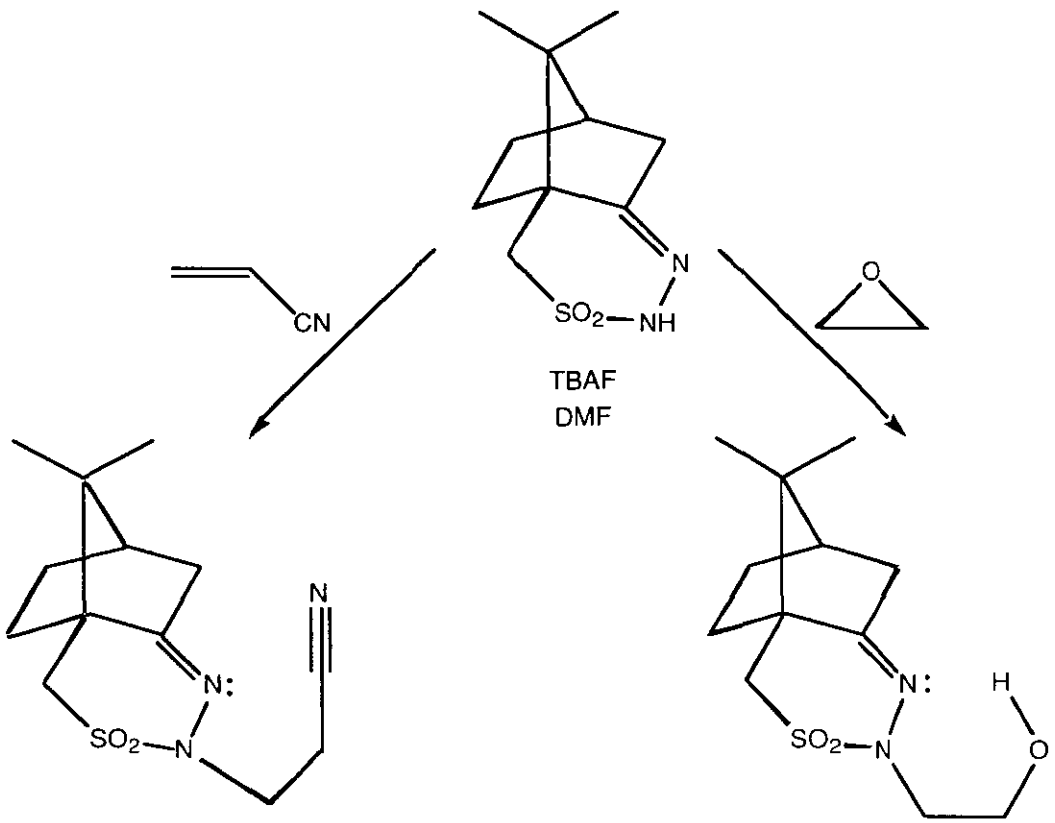
The cyclic camphor sulfonyl hydrazone (CASH), has been reported only once previously,[70] but derivatives of this interesting chiral, tricyclic structure are unknown, save for the N-methyl hydrazone derivative.[70] The method of synthesis reported here is easier and more efficient than the one described in the past. The improved procedure involves action of hydrazine on camphor sulfonyl chloride in dichloromethane followed by Dean-Stark cyclisation in 65% yield after recrystallisation from ethanol (Scheme 28).



Scheme 28: A new, simple and efficient route to camphor sulphonylhydrazone.

The proton attached to the nitrogen atom can be removed by weak bases

the resulting anion can be reacted with a wide range of electrophiles, including Michael acceptors. In this fashion, the N-ethyl alcohol and N-propionitrile derivatives were synthesised, from ethylene oxide and acrylonitrile respectively (Scheme 29). Optimum results for Michael additions were obtained when the hydrazone was allowed to react with the substrate in the presence of fluoride anions.[71] The yield for the Michael addition to acrylonitrile was highly dependant on the solvent polarity. DMF was found to be the solvent of choice (64% yield), while less polar solvents such as THF and chloroform provided decreased yields. The yield for the reaction with ethylene oxide is unoptimised, (28%), but as with the cyano derivative, the product was isolated without the use of chromatography.

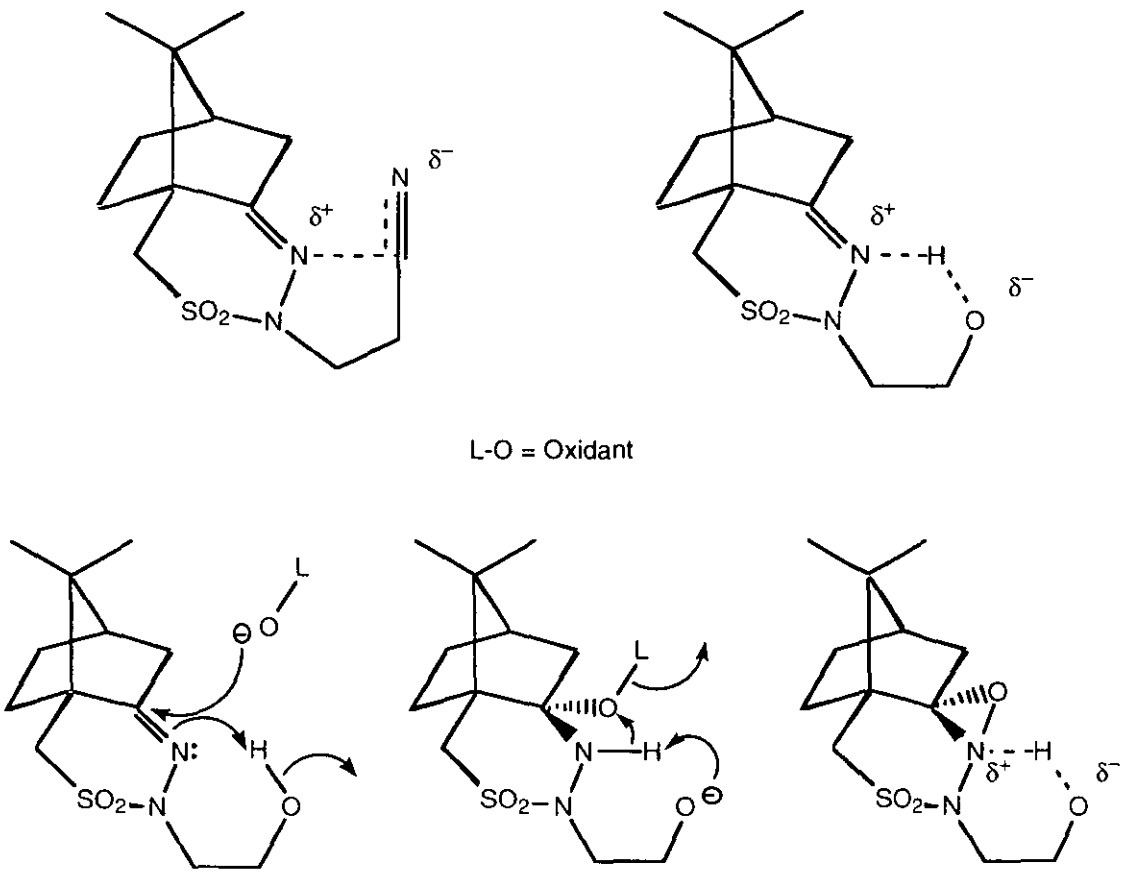


Scheme 29: Synthesis of novel derivatives of camphor sulfonylhydrazone.

The reason that these derivatives were selected is the presence of the electron deficient atom on the side chain; the nitrile carbon atom in the first case, and the proton of the hydroxyl group in the second.

These electron depleted atoms can interact with the sp^2 nitrogen lone pair of electrons, and consequently establish a five or six membered ring. This interaction

would generate a partial positive charge on the nitrogen atom which is part of the imine functionality (Scheme 30). The potential neighbouring group participation which is then set up can activate the carbon-nitrogen double bond towards nucleophilic attack, since an iminium salt character is partially established. Evidence for this intramolecular association, at least in the case of the hydroxy derivative, comes from the IR spectrum of the compound. The absorption characteristics of the oxygen-hydrogen bond correspond to an intramolecularly hydrogen-bonded species (sharp signal of medium intensity rather than broad) (Scheme 30).



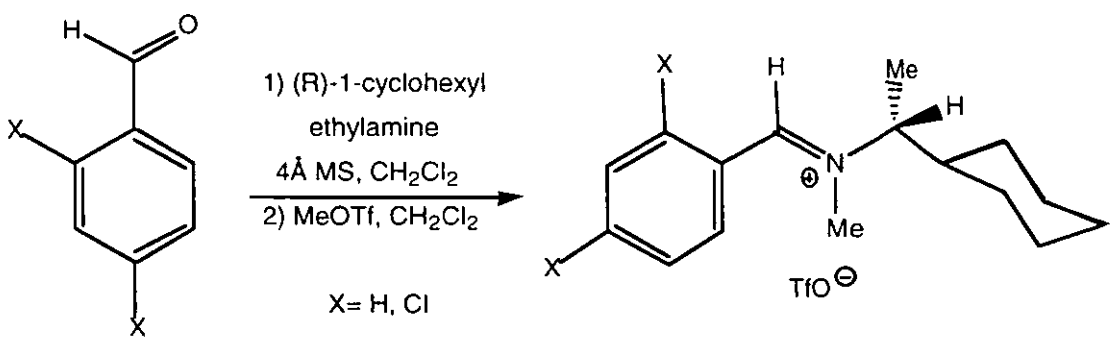
Scheme 30: The mechanism on which the design of these molecules was based on.

However, neither novel compound catalysed the epoxidation of 1-phenylcyclohex-1-ene, regardless of the oxidant used (hydrogen peroxide, Oxone™), and were recovered unchanged from the reaction mixture. Apparently, the desired reaction cannot be mediated by these transient iminium species, presumably due to their short life time.

To conclude, positively charged species which are formed either by transient iminium bonds or by partial quaternisation, (protonation) of imines are not potential mediators for catalytic epoxidation. Therefore systems with a formal positive charge on the imine nitrogen atom were targeted next.

2.9 Acyclic iminium salts.

Chiral imines can be accessed by condensation of primary amines and aldehydes when one of the reactants is optically active. As discussed previously, chiral, non-enolisable aldehydes cannot be accessed readily, but chiral amines are common and several are commercially available and hence this was the approach finally employed.



Schene 31: Combined yields for the two steps: X=H 81% , X=Cl 62%.

Condensation of (*R*)-1-cyclohexylethylamine with benzaldehyde or 2,6-dichlorobenzaldehyde in dichloromethane over molecular sieves, (modification of the method reported by Solladie),[72] furnished the two chiral imines in excellent yields. Subsequent quaternisation with methyl triflate in dry dichloromethane proceeded smoothly, and the corresponding chiral iminium salts were obtained in good yields, (Scheme 31). As expected, the NMR spectra of the iminium salts revealed only one geometric isomer present. The ^{1}H and ^{13}C NMR spectrums of the parent Schiff bases, suggest the presence of only one geometric isomer. For thermodynamic reasons, these are thought to be the ones with the nitrogen substituent and the aromatic ring in a *trans* relationship as it is usually the case with aromatic aldimines.[73] Quaternisation of the nitrogen atom, should in principle generate the iminium salt with the newly introduced methyl group *cis* to the aromatic substituent (retention of existing geometry of imine).

Treatment of these compounds (catalytic amounts, 0.1 equivalent) with an

aqueous alkaline solution of Oxone™ in acetonitrile in the precence of 1-phenylcyclohex-1-ene (one equivalent) afforded a product, (TLC), which in both cases turned out to be the corresponding aldehyde. Despite the adjustments made with the amount of water and the pH, which ranged between 7.5 to 10, the result did not change.

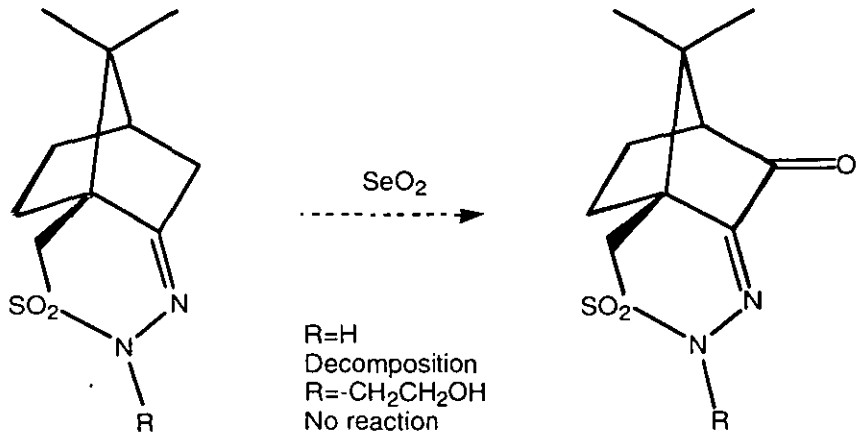
A few months after this investigation was carried out, Armstrong reported results from the catalytic epoxidation of alkenes mediated by acyclic iminium salts.[39] In this work, a range of substituted benzaldehydes was condensed with pyrrolidine, and the salts obtained were tested for catalytic activity. Again hydrolysis of the iminium salts was manifested, but this could be controlled primarily by addition of only a catalytic amount of water, and secondly by the substituent(s) on the parent aromatic aldehyde. Benzaldehyde and its 2,6-dichloro- analogue were two of the worst derivatives in terms of conversion; best being the 2-trifluoromethylbenzaldehyde derivative. The original intension in developing the pyrrolidine-based iminium salts was to encompass proline derivatives as potential chiral inimium systems for asymmetric epoxidation. However the latter derivatives proved very poor in imparting enantioselectivity in the catalytic oxygen transfer process.[74]

A second inspection of the iminium salts that have been already reported to mediate asymmetric oxygen transfer successfully to alkene substrates,[37,38,41] reveals a new key feature, perhaps the most important: They are cyclic (Scheme 9). Although, in principle, hydrolysis could still take place, the products (aldehyde and secondary amine), may, in principle, recombine to reform the iminium species which is eventually attacked by the oxidant. This intramolecular recombination probably ensures the survival of the active functionality. In the hydrolysis of open chain iminium salts, two distinct molecules are formed which do not recombine to any significant extent simply because of entropy reasons. In the cases of iminium systems which are bonded directly to a second heteroatom, hydrolysis of oxazolinium (or formamidinium) salts produces either an amine ester or a hydroxy amide (1,2-amine-amide). According to Deslongchamps observations,[60] these do not recondense to form the parent salt, presumably for thermodynamic reasons.

2.10 Cyclic iminium salts derived from ketones.

Our first attempt to synthesise a chiral, cyclic iminium salt was based on camphor sulfonylhydrazone, due to the simplicity of its preparation on a large scale. In line with the features identified as vital for the correct function of iminium salts in

the catalytic epoxidation reaction, the cyclic hydrazone with an α keto group was required for two reasons. Firstly the quaternised structure, (α-ketohydrazonium salt), would not have acidic protons, and secondly the adjacent carbonyl group should render the system more electrophilic.

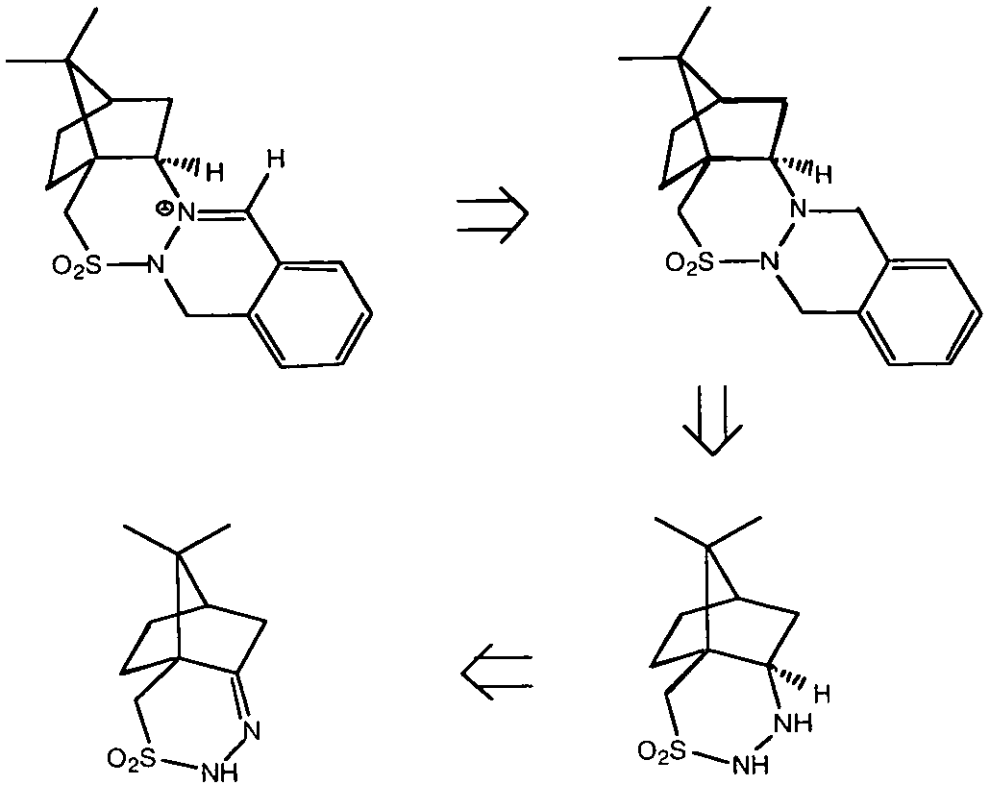


Scheme 32: The quaternised α-ketohydrazone was targeted as a potential catalyst.

However, the first marked difference in reactivity compared to the related sulfonyl imine was encountered when the cyclic hydrazone failed to be oxidised to the 3-keto derivative under the same conditions.[1] Treatment with selenium dioxide in refluxing acetic acid resulted in decomposition of the cyclic hydrazone (Scheme 32). This was also the case when the reaction was performed. At lower temperatures and when ethanol was used as the solvent, no reaction took place. In order to test whether this behaviour was due to the weak nitrogen-nitrogen bond or due to the labile N-hydrogen atom, the corresponding N-ethyl alcohol was subjected to the same oxidative conditions. This time no reaction was observed at all and the starting material was recovered almost quantitatively (Scheme 31). It is possible that the N-H bond was involved in other reaction pathways. The theoretical rationalisation for the inertness of this structure towards allylic oxidation could be based on the diminished acidity of its α-protons in comparison with the sulfonyl imine. It has been suggested that the first step in the selenium mediated allylic oxidation, is an *ene* reaction,[75] which proceeds faster when the migrating hydrogen atom is relatively acidic (lower activation energy). This is not the case though with our cyclic hydrazone, since the sulfonyl group is not in direct conjugation with the carbon-nitrogen double bond, as it is in the sulfonylimine.

An alternative cyclic iminium salt based on the chiral hydrazone was also

envisaged (Scheme 33, top left).

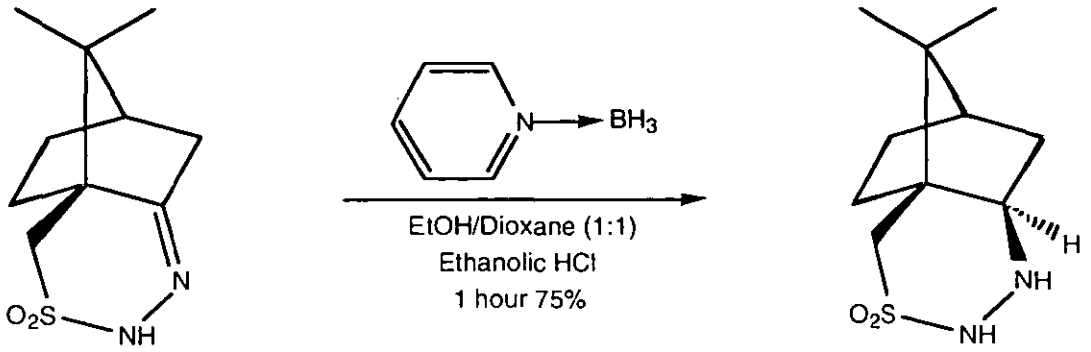


Scheme 33: Proposed retrosynthetic analysis for the synthesis of a chiral dihydrophthalazinium salt derived from camphor sulfonyl hydrazone.

The camphor derived dihydrophthalazinium salt (Scheme 33, top left) could be obtained by oxidation of the tetrahydrophthalazine moiety with ceric(IV) ammonium nitrate. This reagent has been employed previously in the oxidation of N-substituted tetrahydroisoquinolines to the corresponding-(dihydro- in most cases) -isoquinolinium salts with NO_3 as the counter-ion.[76] Reduction of the hydrazone to the cyclic hydrazide and subsequent treatment with 1,2-xylylene dibromide, should furnish the precursor required in the final step.

Kikugawa has developed the pyridine-borane complex, an air-stable and easy to handle diborane derivative which was shown to be very successful in the reduction of tosylhydrazones to tosylhydrazines.[77] Our camphor sulfonyl hydrazone was reduced with this reagent in 75% yield (Scheme 34). The ^{1}H and ^{13}C NMR spectra confirmed that only one isomer had been formed. As discussed in previous chapters, the stereoselectivity of the reaction stems from the geminal

dimethyl bridge which hinders the attack on the *exo* face of the sp^2 carbon atom, (Scheme 28). The expected *endo* delivery of the hydride was also confirmed by an X-ray structure of the product (Scheme 35).

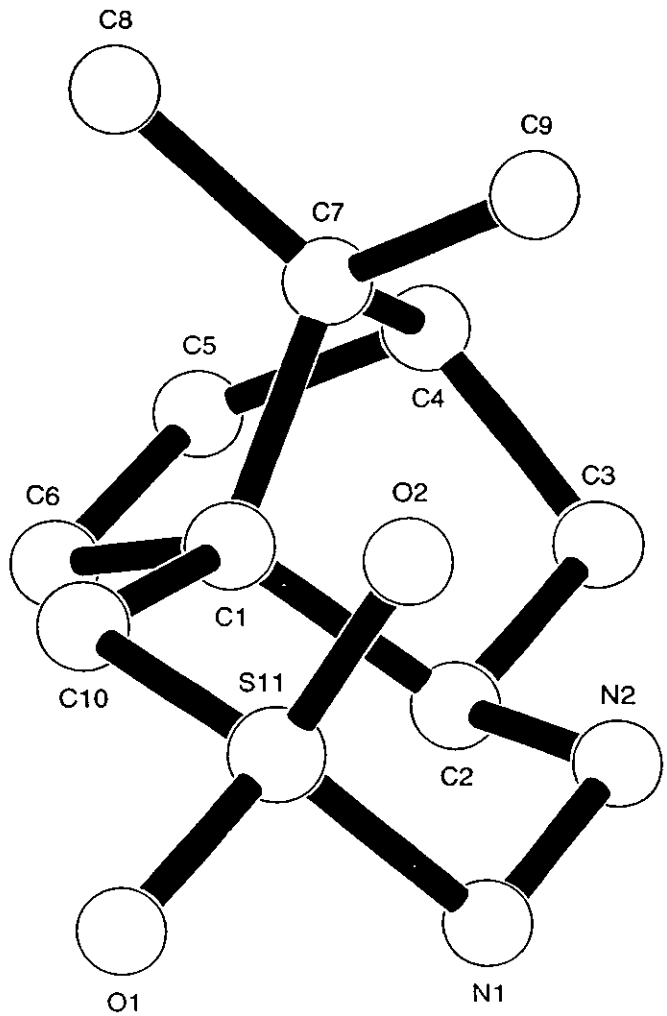


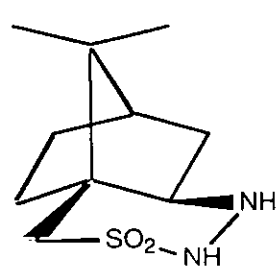
Scheme 34: Synthesis of the previously unreported cyclic hydrazine derived from camphor.

However, the resulting hydrazine failed to react with 1,2-xylylene dibromide in the fashion described in the retrosynthetic analysis under a variety of conditions, and thus, the precursor to the iminium salt could not be accessed.

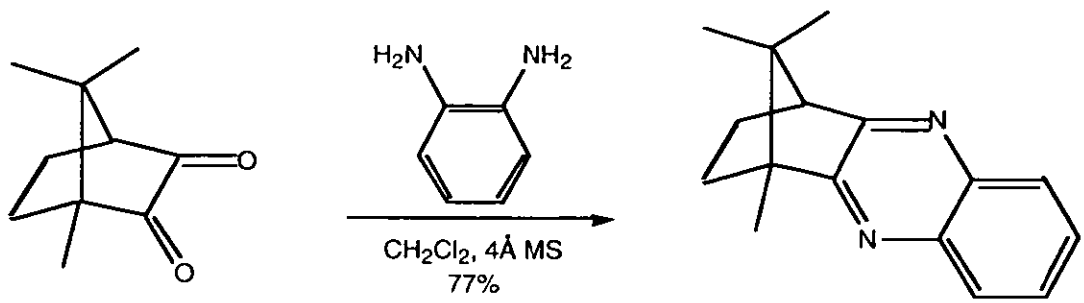
Further research was then focused on easily accessible chiral, cyclic iminium salts. A potential system which combines reactivity and stability is the previously unreported quinoxalinium cation derived from camphor quinone (Scheme 29). The latter is commercially available but can also be synthesised on a large scale easily.[78] It is well documented in the literature that condensation with 1,2-phenylenediamine furnishes the chiral quinoxaline,[79,80] but the conditions we employed have not been used previously (Scheme 36).[81]

Thus, equimolar amounts of 1,2-phenylene diamine and camphor quinone were allowed to react in dry dichloromethane over molecular sieves and produced the desired heterocycle as a yellow crystalline solid in 77% yield. Starting from camphor, this a two step synthetic sequence which does not involve column chromatography and can be easily carried out on large scale.





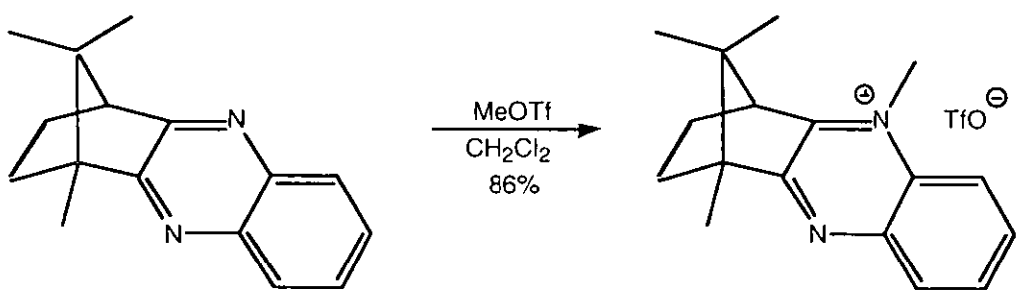
Scheme 35: X-Ray representation of the stucture of the tetracyclic 2-*exo*-camphor-10-sulfonylhydraz-1-ine.



Scheme 36: Similar camphor quinone derivatives have been reported previously.

The quaternisation of this optically active quinoxaline should take place firstly at the least hindered nitrogen atom that is the one *anti* to the bridgehead methyl group, although the dication was also a target. The expected stability of the cation(s) towards degradation is based on the the aromatic character of quinoxaline, while the reactivity should originate from the relative ease with which the aromaticity of one of the rings can be compromised and re-established in similarly fused aromatic systems.[82,199]

Quartenisation of the quinoxaline with one equivalent of methyl triflate produced a single product in high yield. Examination of the ^{1}H NMR suggested that this was the salt derived from methylation at the least hindered nitrogen atom, as expected (Scheme 37). The assignment was based on the signal of the bridgehead hydrogen atom which appears as a doublet at 3:95 ppm in contrast to 3.04 ppm in the parent neutral compound. The magnitude of the downfield shift suggests that the bridgehead proton is α- to the iminium moiety.

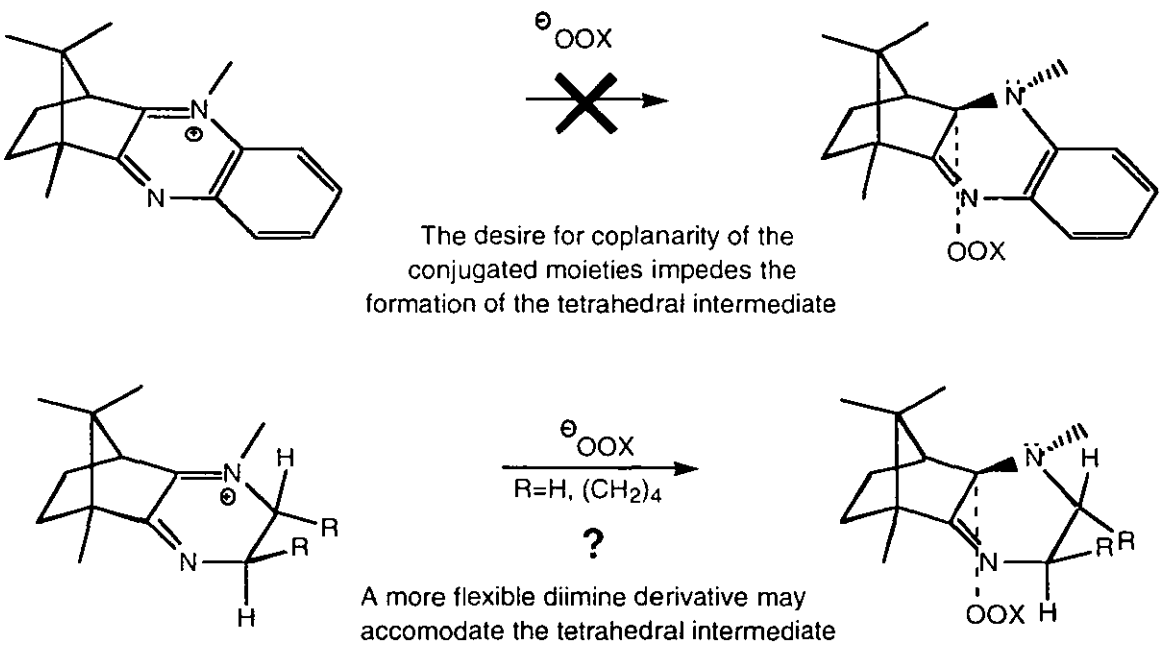


Scheme 37: A novel, camphor derived iminium salt.

Reaction of the heterocycle with a threefold excess of trimethyloxonium tetrafluoroborate, furnished a quantitative yield of the same mono-quaternised

compound without a trace of the dication being produced, presumably due to the steric interference of the bridgehead methyl group. The quinoxalinium salt is remarkably stable as no signs of decomposition have yet been detected after storage for more than a year, at room temperature in the presence of light and air. The organic salt was then tested under the same oxidative conditions employed previously (Oxone™), in the presence of 1-phenylcyclohex-1-ene, but no epoxide formation was observed. A rationalisation for the apparent inertness is a challenge to devise. This certainly does not stem from the aromatic character of the quinoxalinium salt, since very closely related organic salts derived from flavins, do react with hydrogen peroxide even in the absence of base to form α-hydroperoxy-amines.[82] These, after the transfer of one oxygen atom and loss of a water molecule, are regenerated; a process that clearly destroys the extended aromatic system temporarily.

Molecular modelling studies suggested that in our case, although the corresponding oxaziridinium salt is reasonably strain-free, and should in principle be formed, the energy of the transition state involved is too high to allow formation. Aromaticity is one factor but strain and inhibition of coplanarity become more important, at least in this case (Scheme 38).

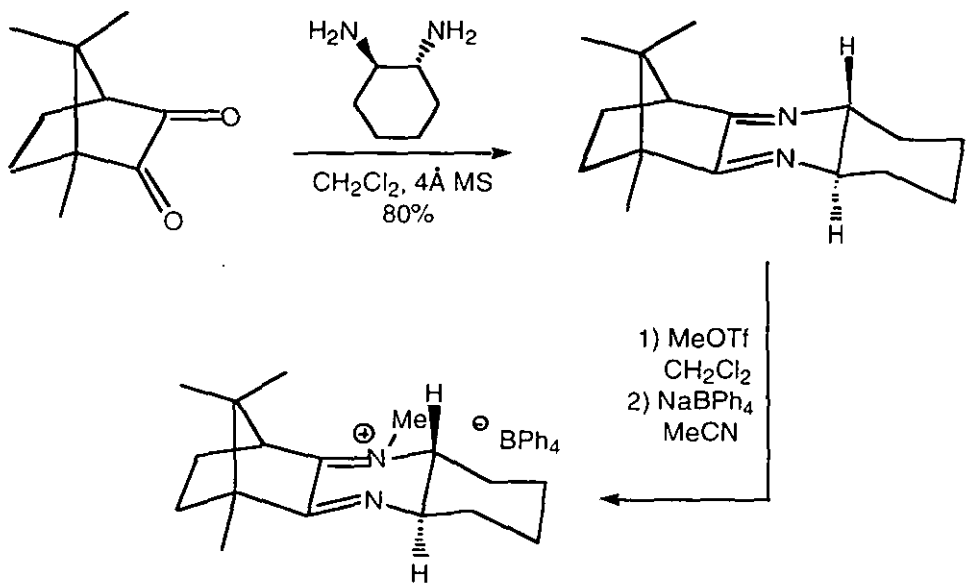


Scheme 38: Redesign of iminium salts derived from camphor diimines.

This may be rationalised as follows: The initial attack of the oxidant (Oxone™) on the iminium carbon produces the intermediate α-peroxysulfate-amine, in which both the methylated nitrogen atom and the carbon atom in question, participate now with sp^3 hybridisation. It is suggested that the high rigitity of the camphor skeleton can no longer accomodate the four interconnected sp^2 centres present in the intermediate, without severe distortion of the double bonds (Scheme 38).

Following this rationalisation, synthetic design was focused on camphor quinone derived diimines where the two nitrogen atoms are joined *via* an ethylene bridge of sp^3 carbon atoms. Regioselective methylation at one of the nitrogen atoms as with the previous system should produce a potential catalyst for asymmetric oxygen transfer. Due to the conformationally labile tetrahydropyridazine type of intermediate involved in the transition state, formation of the oxaziridinium species should not be impeded.

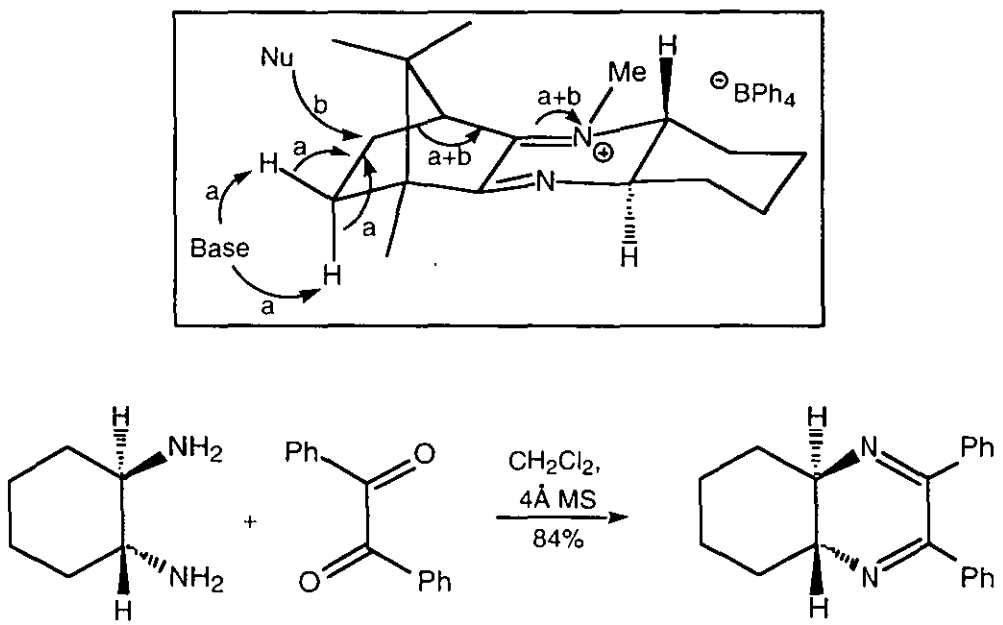
Initial attemps to synthesise the camphor diimine derived from ethylene diamine were unsuccessful. However, (1*R*,2*R*)-diaminocyclohexane readily condenses with camphor quinone in dichloromethane over molecular sieves to furnish the expected diimine in 80% yield (Scheme 39).



Scheme 39: Synthesis and possible decomposition pathway of a terpene derived iminium salt.

The latter compound is also regioselectively monoquaternised with methyl triflate, as the quinoxaline derivative, to produce the tetraphenylborate salt after anion exchange (Scheme 39). It is common knowledge that terpenoids rearrange

readily when a positive charge or significant electron deficiency is built up on the carbon atoms of the framework, and more than one product often arises.[83] Despite this, the iminium salt derived from camphor is isolable and does not degrade when handled and stored at room temperature. Nevertheless, this chiral iminium salt, (Scheme 39), although stable, failed to catalyse the epoxidation of 1-phenylcyclohex-1-ene under the previously employed conditions. In fact, it decomposed under the reaction conditions (a bright yellow oil was isolated, still of unknown identity), perhaps by a mechanism similar to the one found in the rearrangements of terpenes (box in Scheme 40).



Scheme 40: (Box) Possible decomposition pathways of terpene-derived ketiminium salts. (Below) An aromatic chiral diimine derived from benzil.

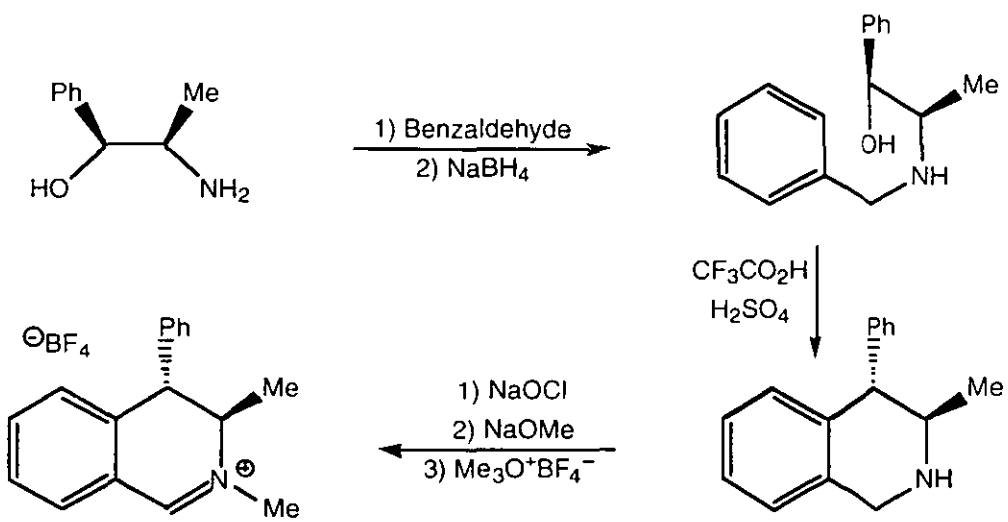
The last attempt to synthesise a more stable chiral ketiminium salt focused on aromatic precursors. Using the same conditions we employed earlier for the camphor derivatives, the diimine derived from benzil and (1*R*,2*R*)-1,2-diaminocyclohexane was obtained in good yield (Scheme 40). This compound however, failed to give the quaternised product upon treatment with methyl triflate. Instead, a complex mixture was obtained in several occasions.

After these findings, chiral ketiminium salts were not considered further as potential catalysts for asymmetric epoxidation.

2.11 Dihydroisoquinolinium salts.

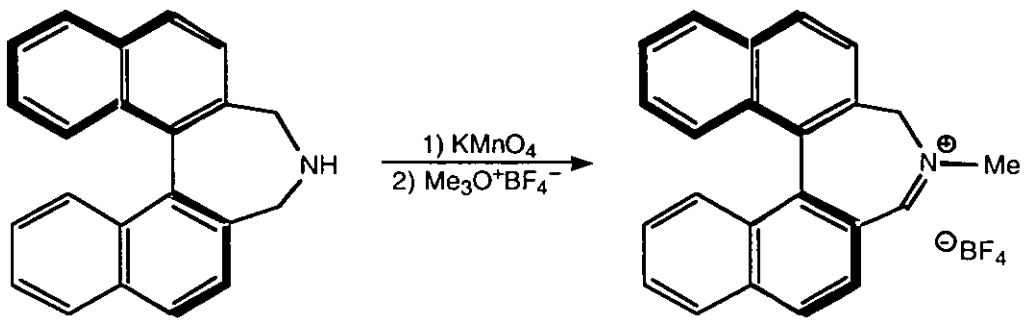
Preliminary experimentation revealed that cyclic, chiral iminium salts derived from ketones are inactive as mediators of asymmetric oxygen transfer to simple alkenes. To date, only Hanquet, Aggarwal and Page have reported successful iminium salts catalysts for the catalytic asymmetric epoxidation of unfunctionalised olefins.[37,38,41] Apparently, it was not a coincidence that the mediators used were based on chiral, cyclic iminium salts derived from aldehydes. The Hanquet and Aggarwal's catalysts were synthesised by quaternisation of the appropriate chiral cyclic aldimine with Meerwein's reagent, thus the exocyclic group attached to the nitrogen is invariably methyl or ethyl. Furthermore, these systems are very specific in nature and therefore the syntheses employed lack versatility.

The tetrahydroisoquinoline precursor of Hanquet's and Lusinchi's chiral iminium salt is obtained by an intramolecular Friedel-Crafts type of alkylation, which in turn is made from norephedrine. Overall, this is a five step synthesis for the iminium salt catalyst (Scheme 41). The success of the stereoselective cyclisation relies primarily on the relative ease with which the benzylic cation is formed. Secondly the steric hindrance between the phenyl and methyl groups, forces the two substituents *trans* to one another and at equatorial positions across the heterocyclic ring. It follows that other chiral aminoalcohol derivatives which do not possess these features may not be suitable precursors for this type of iminium salts.[162]



Scheme 41: The synthesis of Hanquet's and Lusinchi's chiral dihydroisoquinolinium salt.

Aggarwal's catalyst is even more of a special case. The cyclic aldimine precursor is obtained from bis(dibromomethyl)binaphthalene, an expensive starting material, and ammonia followed by oxidation (Scheme 42). It is obvious that this procedure cannot be used for the synthesis of a wide range of iminium salts.



Scheme 42: Synthesis of Aggarwal's BINAP derived iminium salt.

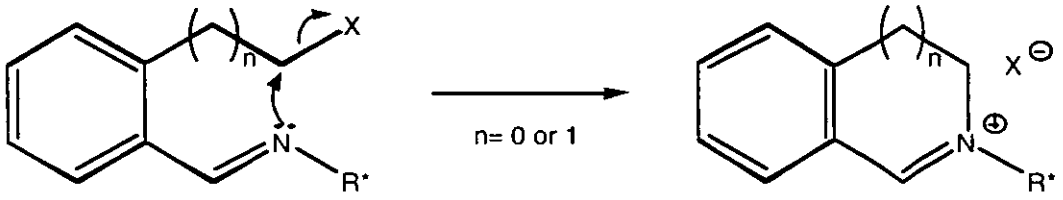
Hanquet and Lusinchi reported the asymmetric epoxidation of *trans*-stilbene with 33% ee both by subjecting the substrate in the catalytic reaction, (20 mol% of iminium salt), and by treatment with a stoicheiometric amount of the preformed oxaziridinium salt.[38] Aggarwal, however, tested several substrates and the results are summarised in table 1 below.

Substrate	Epoxide ee (yield)/configuration		
Styrene	8	(66)	-
trans-Stilbene	31	(71)	(*R*,*R*)
trans-a-Methylstilbene	45	(61)	(*R*,*R*)
1-Phenylcyclohex-1-ene	71	(80)	(*R*,*R*)
1-Methylcyclohex-1-ene	39	(80)	(1*S*,2*R*)

Table 1: The results obtained with the BINAP derived catalyst.

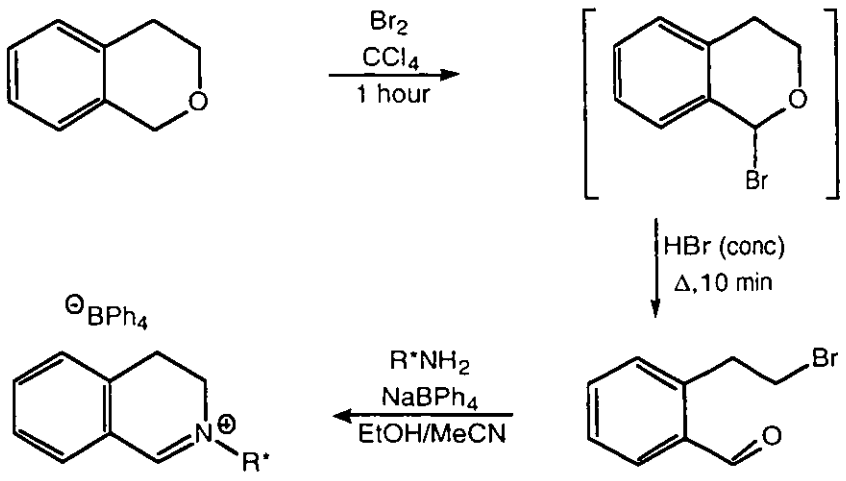
2.12 Catalyst design and synthesis.

The approach presented here towards the synthesis of this class of chiral heterocycles is entirely different in concept. Incorporation of the stereogenic centre on an exocyclic carbon atom through intramolecular quaternization of a chiral aryl imine, derived from a chiral amine, is relatively unexplored (Scheme 43).



Scheme 43: An alternative synthesis of chiral cyclic iminium salts.

The key intermediate, 2-(2-bromoethyl)benzaldehyde, was synthesised according to the procedure of Rieche and Schmitz (Scheme 44).[86] Typically, bromination of isochroman yields the expected 1-bromoisochroman which is isolated by distillation if required. Acidic hydrolysis of the initial product furnishes the desired intermediate in good yield (65%) which is also purified by distillation or chromatography. Nevertheless, the crude product (60-70% pure) can be reacted directly with the appropriate amine with almost equal success.



Scheme 44: A rapid and inexpensive route to active catalysts for asymmetric oxygen transfer.

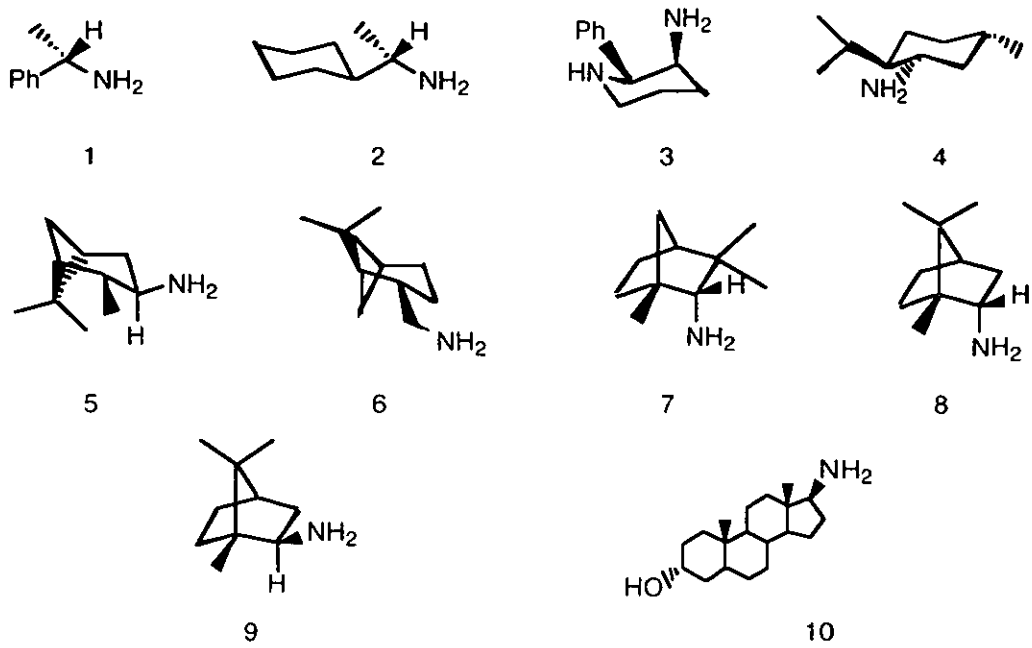
This method has proved invaluable for the screening of a wide variety of chiral amines and catalysts which was not feasible with the previous methodology. Furthermore, the overall process employed in the synthesis of the catalyst is rapid, inexpensive, involves simple synthetic steps, chromatography is not required and therefore it is easily scaled up. The reactions described below have been performed on 70 g scale without any difficulties .

2.13 Catalysts derived from simple primary amines.

Primary (chiral) amines react smoothly and rapidly with 2-(2-bromoethyl) benzaldehyde as depicted in Scheme 44, to furnish the corresponding dihydroisoquinolinium bromides. These organic salts, save for a few exceptions, are usually oils and difficulties were encountered on attempts to purify them by conventional methods.[87] This problem was solved by anion exchange by incorporation of one equivalent of sodium tetraphenylborate in the reaction mixture prior to work up.[88,89] The tetraphenylborate salts of these derivatives are all solids, with the degree of crystallinity varying with the alkyl group of the parent amine. As a consequence of a side reaction, the elimination of hydrogen bromide from the bromoethyl moiety of the precursor, the yields are generally between 30 and 60%. Substantially hindered amines give inferior conversions, typically of the order of 20-30%, presumably due to their tendency to act as bases rather than nucleophiles, as evidenced by the increased amounts of 2-vinylbenzaldehyde (and corresponding imine) observed. Nevertheless, the minute amounts required to catalyse the desired reaction more than compensate for the moderate yields and the cost of some of the chiral amines screened. Typically, for the epoxidation of 1-phenylcyclohex-1-ene on 0.42 g scale, less than 8 milligrams of most catalysts were used for quantitative conversions within 1 hour. Overall, the synthesis of the catalyst and the asymmetric synthesis of epoxides takes no longer than 8 hours.

The chiral primary amines that were initially employed as precursors to dihydroisoquinolinium salt catalysts for asymmetric epoxidation, are depicted in Scheme 45.[90]

Earlier reports of iminium salt-catalysed epoxidation did not provide experimental detail. Accordingly, reaction conditions were devised empirically and this approach was soon successful.



Scheme 45: Readily available chiral primary amines that served as catalyst precursors.

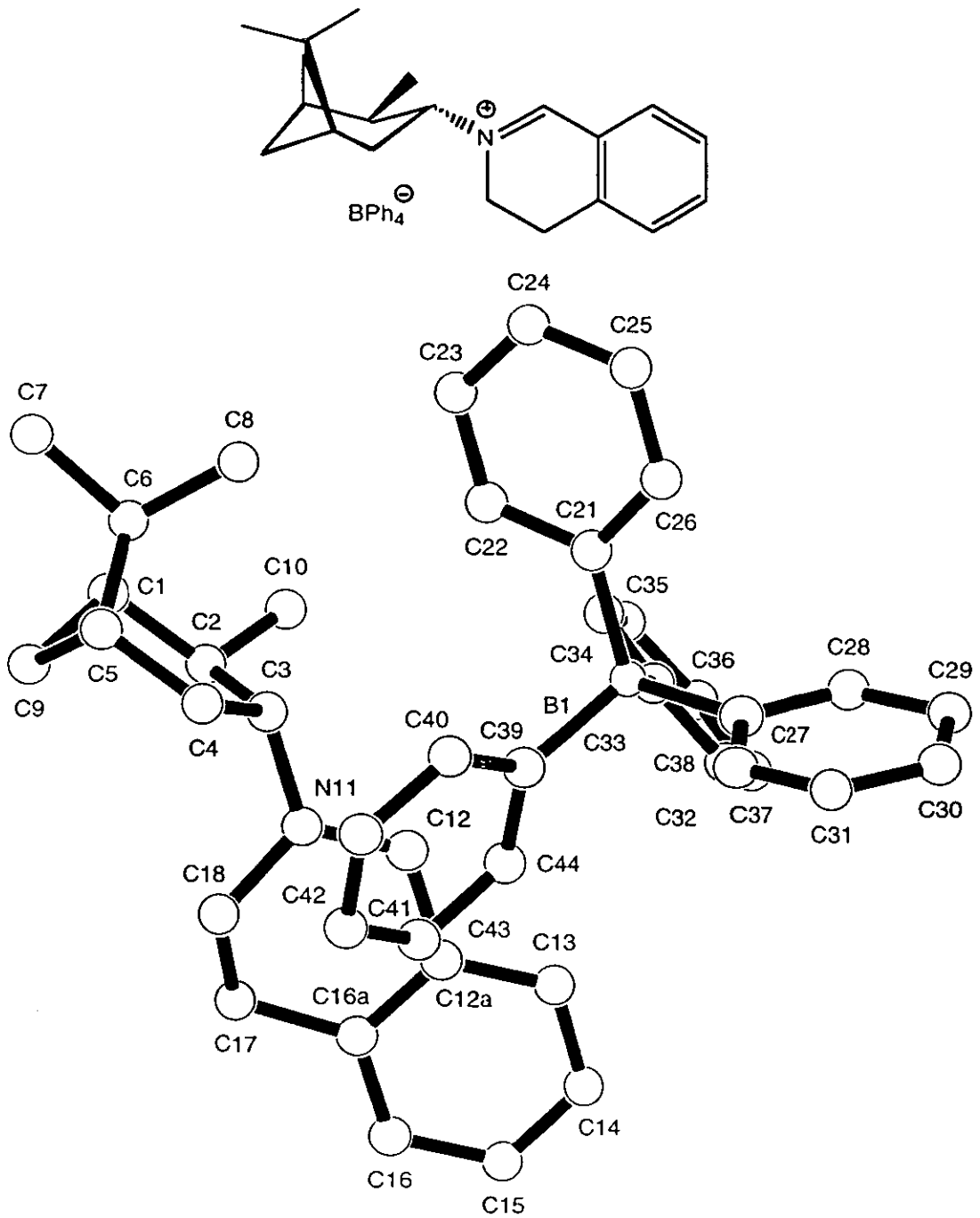
The results are summarised in table 2 and refer to the catalytic asymmetric epoxidation of 1-phenylcyclohex-1-ene at 0 °C in water/acetonitrile (1:2), using 0.5-5 mol% of the corresponding dihydroisoquinolinium salts, four equivalents of Oxone™ and eight equivalents of sodium carbonate.

With the first two and simplest entries, no chiral induction was observed and it became clear that a conformationally more defined and rigid system was required to impart reasonable enantioselectivities. The catalyst derived from 3-amino-2-phenylpiperidine, (entry 3), decomposes under the reaction conditions, hence the incomplete conversion, and is the only case where decomposition of the active species is observed. Since other mediators lack the piperidine moiety it is reasonable to assume that the nucleophilic nitrogen atom is involved in other reactions that interfere with the catalytic process. For example, nucleophilic attack at the iminium carbon produces an aminal which is probably catalytically inactive. Both camphor and menthyl systems gave disappointing ee's, although these are perhaps two of the most popular and selective systems upon which chiral auxiliaries and other chiral catalysts are based.[5,91-93]

Amine precursor	Catalyst load mol%	Epoxide yield	% ee / Configuration
1	5.0	54	0
2	5.0	70	0
3	1.0	39	25 (–)-(S,S)
4	0.5	63	19 (+)-(R,R)
5	0.5	68	27 (+)-(R,R)
6	0.5	66	12 (–)-(S,S)
7	0.5	45	32 (+)-(R,R)
8	0.5	60	18 (+)-(R,R)
9	0.5	58	8 (+)-(R,R)
10	0.5	47	14 (–)-(S,S)

Table 2: Screening of dihydroisoquinolinium salts derived from chiral amines whose entry numbers refer to previous scheme. Enantiomeric excesses were determined by NMR spectroscopy with (–)-Eu(hfc)$_3$ as the chiral shift reagent.

The factors which determine enantioselectivities remain unclear, since the myrtanyl system (entry 6), which has its stereogenic centres relatively remote from the reaction site, is more selective than the isobornyl system (entry 9). It is clear from the cases examined that increased steric hindrance near the reaction site is important, but is not the only key factor which governs enantioselectivity. For example, the fenchyl derivative, which is the most sterically demanding, gave the best enantioselectivity, albeit at the expense of the rate of the process, The N-(isopinocampheyl)dihydroisoquinolinium salt (Scheme 46), which has considerably less steric requirements is almost as selective as the fenchyl system.



Scheme 46: X-ray representation of the dihydroisoquinolinium tetraphenylborate derived from (−)-(1*R*,2*R*,3*R*,5*S*)-isopinocampheylamine. This catalyst exhibited one of the best reaction profiles and enantioselectivities in the catalytic asymmetric epoxidation of 1-phenylcyclohex-1-ene.

In addition, the N-(isopinocampheyl)dihydroisoquinolinium salt (Scheme 46), is significantly more selective than the camphor, menthyl and steroidal systems, (all of which have similar or higher steric demands), despite their similarity in the rate of conversion.

2.14 The reaction machinery.

A thorough examination of the reaction parameters was carried out in order to optimise the reaction conditions with respect to the enantioselectivity of the oxygen transfer to the olefin substrate. The isopinocampheylamine derivative exhibited, at least with 1-phenylcyclohex-1-ene, one of the best reaction profiles in terms of ee and rates. Furthermore, both enantiomeric forms of this chiral amine are commercially available. For these reasons it was chosen as the model catalyst upon which subsequent optimisation and mechanistic studies were based.

2.14.1 Effect of counterion.

Despite the failure to isolate the tetrafluoroborate salts by anion exchange of some of the iminium bromides prepared above, the isopinocampheylamine derived dihydro isoquinolinium salt proved quite successful in forming crystalline salts with a variety of counterions. Thus, in addition to the original tetraphenylborate, the corresponding tetrafluoroborate, hexafluorophosphate, perchlorate and periodate salts were also synthesised. The latter two were formed in better yields than their fluoride based analogues.

All of the salts were tested in the asymmetric catalytic epoxidation of 1-phenylcyclohex-1-ene in order to compare the enantioselectivities obtained. A catalyst loading of 5 mol% was used in 1:1 water/acetonitrile solvent in the presence of two equivalents of Oxone™ and four equivalents of sodium carbonate at 0 °C.

The enantioselectivities obtained exhibited an interesting trend. The periodate salt produced selectivities comparable to those obtained with the tetraphenylborate species (35% ee), while the fluoride based counterions afforded lower ee's (28%). The perchlorate salt furnished yet inferior enantiosectivities (20% ee). However, all of the salts invariably produced the same enantiomer of the corresponding epoxide (*R,R*), as the major component of the non-racemic product and the reactions were complete within the same time scale (45 minutes). Control experiments were also carried out to prove that both perchlorate, and more importantly periodate,[94] were not acting as oxidants towards both the substrate and the iminium salt under the reaction conditions.

Although differences in enantioselectivities observed are not large, they are reproducible, and they perhaps suggest the existence of the catalyst in the reaction medium as intimate ion pairs with the degree of intimacy dependent upon the relative polarisability of each counterion. Both tetraphenylborate and periodate are among the largest and more polarisable counterions known, and distortion of their electron cloud/density is therefore expected to occur with relative ease and to a sufficient extent that intimacy with the electron depleted carbon atom can be realised. The size of the species involved suggests that this coordinative type of interaction is likely to take place at the least hindered face of the iminium species and will therefore hinder the approching nucleophile. The oxidant is then expected to attack the opposite, counterion-free face. It follows that this rationale becomes more realistic with the more polarisable counterions where the difference in accessibility of the two faces of the iminium salt is therefore more pronounced. This interaction occurs to a lesser extent with the less polarisable tetrafluoroborate and hexafluorophosphate anions. Furthermore, coordination of these counterions via fluoride "bridges" between the iminium carbon atom and the phosphorus or boron can also be envisaged (the M-F-M "bridges" are known in inorganic chemistry, M= metal ion).[95,96] Perchlorate is one of the "hardest", *ie* least polarisable anions known. Its salts are entirely dissociated in solution and exist as individually solvated ions, not as intimate ion pairs. The perchlorate counterion cannot participate in the type of interaction described above and cannot therefore affect the stereochemical outcome of oxazidinium salt formation.

This concept is important and one of the features that render this catalytic reaction difficult to optimise. It is not one but two diastereoisomeric oxaziridinium salts that may be formed by attack of oxidant at *si* or *re* face of iminim species, and each may deliver the oxygen at either of the prochiral faces of the alkene sustrate with a degree of enantiocontrol.

2.14.2 Effect of the reaction stoicheiometry.

An increase in water to acetonitrile ratio is accompanied by an increase in the reaction rate. The effect is more pronounced when small amounts of catalysts are used. Thus, with the isopinocampheylamine derivative (0.5 mol%) the yield of 1-phenyl-cyclohex-1-ene oxide was approximately 30% after one hour at 0 °C when a 1:1 ratio of the two solvents was used but the yield was essentially quantitative at 2:1. Reducing the amount of Oxone™ and base by a factor of two, (one equivalent of Oxone, two equivalents of sodium carbonate), again resulted in incomplete

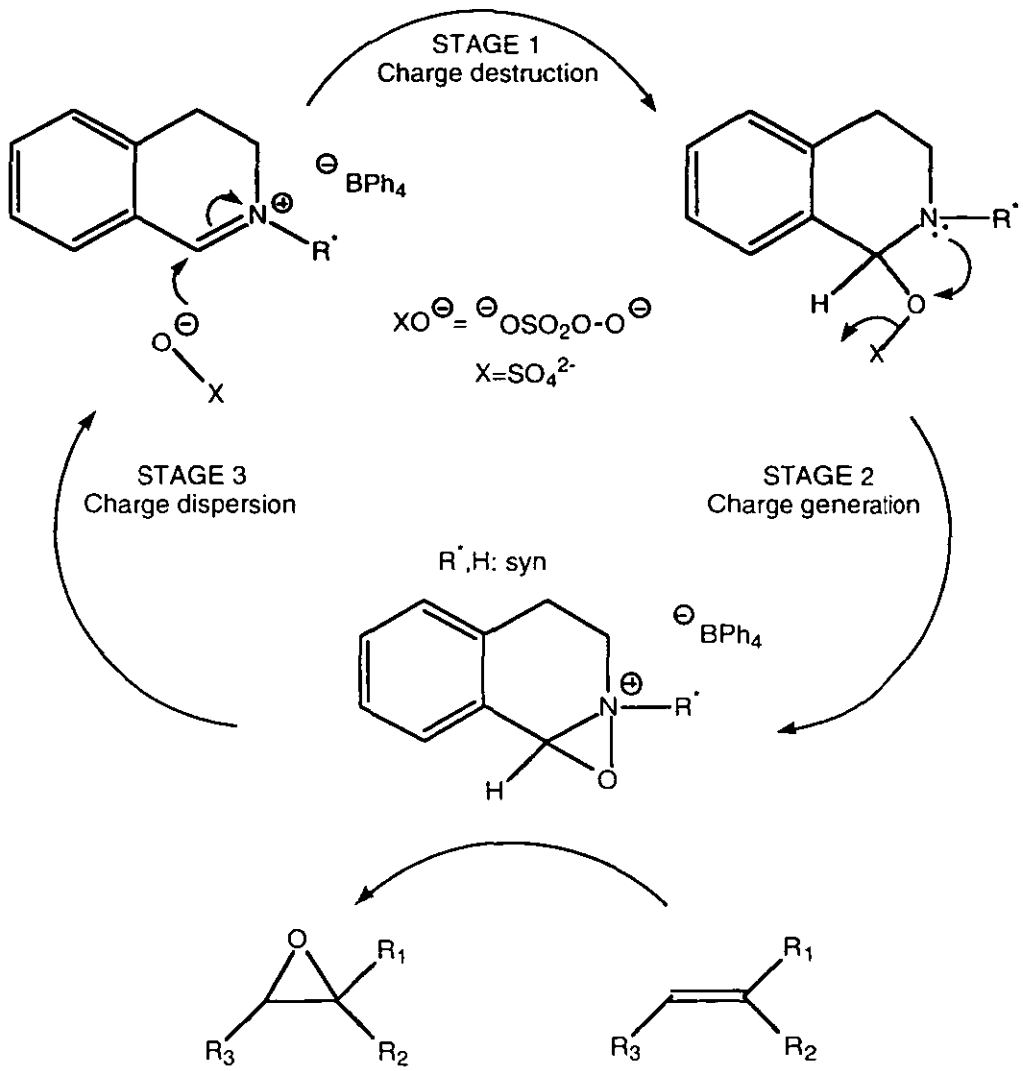
conversion after one hour in the improved solvent system. Reaction rates under more basic conditions (six equivalents of sodium carbonate) also decrease. In accord with previous reports, this may be caused by hydroxide anions attacking the iminium entity converting it into the corresponding hemiaminal,[200] or decomposition of Oxone™ itself under basic conditions.[97-101]

Higher catalyst loadings accelerate the rate of the reaction to such an extent that outweigh the effect of water content. Thus, when the water content was varied successively from 10 to 50 to 66 and finally to 90% in acetonitrile with 5 mol% catalyst loading (perchlorate salt), all reactions indicated complete consumption of 1-phenyl-1-cyclohexene within 20 minutes. It is perhaps remarkable that this change in solvent composition did not influence the enantioselectivity of the reaction. All reactions consistently produced 1-phenyl-cyclohex-1-ene oxide with 18-20% ee.

2.14.3 Mechanistic analysis and solvent effects.

A proposed mechanism for the catalytic asymmetric epoxidation of simple alkenes, mediated by chiral iminium salts, is depicted in Scheme 47.

The first stage of those described involves the formation of an adduct, formed by the nucleophilic attack of the oxidant on the iminium carbon atom. The iminium salt, however, can exist and react both as an intimate ion pair and as discrete species, the proportion of which is solvent, temperature and counterion dependent. Since R is chiral, the combined amount of the intermediate formed at the first stage should contain unequal amounts of the two possible stereoisomers at the newly created stereogenic centre. Overall, one effect of the first step is the destruction of the positively charged ion. This process proceeds faster and with lower selectivity in non polar solvents (low dielectric constant ε). It follows that in highly polar solvents the ionic species in question should be solvated and stabilised particularly well so that, any reaction pathway which leads to their neutralisation should be a higher energy, relatively unfavourable and slow process.[102] This suggests a more selective reaction in polar solvents with regard to the formation of the new chiral centre.



Scheme 47: Mechanistic analysis of the catalytic epoxidation cycle mediated by iminium salts.

The implications of such an effect are important because it is at this stage that the stereochemistry of the oxaziridinium salt is determined. The formation of the three membered ring can only take place so that the hydrogen atom and the chiral group designated R^* are *syn* related (formation of three and six membered rings fused in a bicyclic system in a *trans* relationship is impossible).

The generation of the positively charged oxidising species should now proceed faster in polar solvents,[102] but the rate of this transformation (stage 2) is inconsequential for the enantioselectivity of the overall process as the stereochemistry at both nitrogen and carbon atoms was determined at stage 1.

Finally (stage 3, Scheme 47), the delivery of the oxygen to the substrate is a

process in which charge dispersion occurs. That is a "hard" species with a localised charge (nitrogen), thus of high charge density, is transformed to a "softer" species where the charge is now delocalised (nitrogen, benzylic carbon atom and aromatic ring) hence the charge density decreases. As the polarity of the solvent decreases, processes that involve charge dispersion become slightly more favoured but not greatly so.[102] In this stage the chirality tranfer occurs from the chiral activated species to the substrate, thus, a slower reaction may also improve the enantioselectivity. Overall, the more polar the solvent system the slower the rate at which the transformations at stages 1 and 3 are realised, the higher the enantioselectivities.

An attempt was made to correlate reaction rates and the extent of asymmetric induction with the polarity of the water co-solvent as this could prove useful in the clarification of the reaction mechanism and features that control the enantioselectivity. For this reason the water co-solvents used were selected so that they differed both in nature and dielectric constant (ε, indicated by the values in brackets): dichloromethane (8.9), trifluoroethanol (26.7), acetonitrile (37.5) water (78.4) and formamide (111).[103]

The isopinocampheyl derived catalyst was employed (5 mol%) and tested in the catalytic epoxidation process using these co-solvents with water in 1:1 ratio. In order also to examine the counterion effect, the catalyst was tested both as its perchlorate and tetraphenylborate salts (20 vs 35% ee in acetonitrile).

The perchlorate salt exhibited an interesting trend. In trifluoroethanol, it mediated the epoxidation of 1-phenylcyclohex-1-ene within 30 minutes with quantitative conversion and 26% ee, while in dichloromethane the reaction was unusually slow, (50% conversion after three hours), but the ee of the epoxide was still increased to 33%. In formamide however there was no reaction. This was also the case for the tetraphenylborate salt. The lack of reaction in formamide regardless of the counterion involved perhaps suggests that the iminium species are far too well stabilised/solvated, and the possibility of an irreversible attack by the formamide cannot be dismissed. The tetraphenylborate salt mediated the same reaction in trifluoroethanol within the expected time scale (20-30 minutes) and with the same ee (26%). In the chlorinated solvent system however, no reaction was manifested even after three hours.

The difference in reactivity for both counterions with dichloromethane as the co-solvent perhaps reflects the poor miscibility of the two solvents, which may severely limit the availability of the inorganic oxidant in the organic phase. That the

perchlorate salt is more reactive in dichloromethane is perhaps due to the iminium salt itself acting as a phase transfer catalyst, with the perchlorate salt being the better due to its higher hydrophilicity. This rationale is in accord with Denmark's report on quartenary ammonium salts which were part of the structure of chiral ketones used in the asymmetric epoxidation of alkenes as dioxirane precursors.[100]

Water co-solvent 1:1	Dielecrtic constant ε	Perchlorate ee%	Tetraphenylborate ee%
$HCONH_2$	111.0	-	-
MeCN	37.5	20	33
CF_3CH_2OH	26.7	26	26
CH_2Cl_2	8.9	32	-

Table 3: Investigation of enantioselectivities obtained in iminium salt catalysed epoxidation as a function of the dielectric constant of the organic solvent and counterion.

The fact that both the perchlorate and tetraphenylborate salts produced the epoxide with 26% ee in trifluoroethanol is at first sight odd since the other parameters were kept constant, and in order to investigate further this apparent insensitivity of the counterion, the periodate salt was also tested in this solvent. Interestingly, the latter catalyst also furnished the epoxide with 26% ee. This may result from the formation of the trifluoroethoxide anion in all three cases. The results from this study are summarised in table 3.

2.14.4 Effect of temperature.

The effect of this parameter on the reaction is also difficult to study over a wide range, partly due to the solubility and instability of Oxone™ in alkaline conditions,[97-101] which increases at higher temperatures, and partly due to the freezing point of water. When the solvent system used was of high acetonitrile to water ratio, the reaction at –8 °C was sluggish as the solubility of the inorganic oxidant and base in water is dramatically decreased at that temperature.

However, given that a high water content in the solvent system does not adversely affect the enantioselectivities and also speeds up the reaction, the oxidation was repeated using an increased proportion of water in the solvent system (water/acetonitrile=3:1). Surprisingly, oxidation of 1-phenylcyclohex-1-ene mediated by the isopinocampheylamine derived dihydroisoquinolinium salt (5

mol%), produced, within 45 minutes with complete consumption of the starting material, the corresponding epoxide in slightly improved yield. The enantioselectivity was virtually the same as that obtained at 0 °C (*ca* 36% ee). In order to double check on the apparent insensitivity of the reaction selectivity with temperature, the oxidation was also conducted at lower catalyst loading. Thus, with 0.5 mol% of the same catalyst, the selectivities exhibited at 0 and –10 °C were again essentially the same (26-28% ee).

In the absence of the cooling bath, the temperature of the reaction mixture reaches up to *ca* 34 °C perhaps due to the exothermicity of the neutralisation of Oxone™ by the base (sodium carbonate), and ambient temperature is then slowly attained. When the oxidation was repeated over this temperature range (27-32 °C), negligible conversion to the epoxide was detected after one hour. This unexpected failure of the catalysed process may be due to the instability of the oxaziridinium species or of Oxone™ at higher temperatures.

Indeed, in catalytic processes for asymmetric alkene epoxidation where Oxone™ is used as the stoicheiometric oxidant, (e.g. mediated by oxaziridinium salts and dioxiranes), reactions performed above 0 °C are rare.[38,41,104-107]

2.14.5 Effect of catalyst loading.

Catalyst loading was expected to be an important parameter in the reaction system. The relationship depicted in Figure 1 was obtained for the isopinocampheyl derivative with 1-phenylcyclohex-1-ene as the substrate and indicates that both selectivity and rate increase when larger amounts of catalyst are incorporated in the reaction. When 5 mol% of catalyst is employed the reaction proceeds to completion within 15-20 minutes.

For the same substrate, quantitative conversions can be accomplished within one hour using less than 0.5 mol% of the catalyst; this is believed to be unprecedented for iminium salts involved in such a reaction.

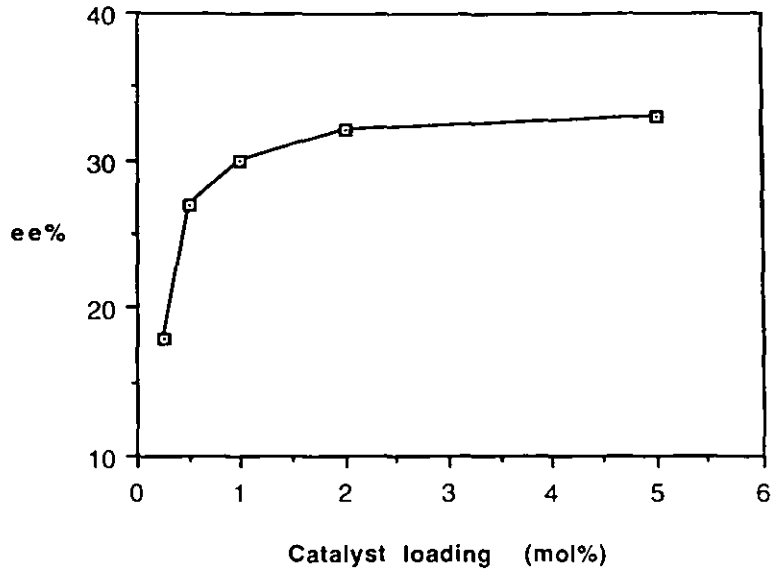


Figure 1: The catalyst used is the one derived from isopinocampheylamine (entry 5 of Table 1). Enantioselectivities refer to the epoxidation of 1-phenylcyclohex-1-ene at 0 °C in 1:1 acetonitrile/water. All runs produced quantitative conversions except the one performed with 0.25 mol% of the catalyst.

2.14.6 Effect of concentration.

The concentration of the substrate in the reactions descibed above was approximately 2M. When the concentration was increased by a factor of 2.5, to *ca* (5M), a detrimental effect on the reaction rate was observed and the enantioselectivity was dramatically decreased too.

Dilution of the original reaction mixture by a factor of 2.0 (to *ca* 1M), had no significant extent on the reaction rate or the selectivity. Thus, when 0.5 mol% of the isopinocampheyl based catalyst was used, in reactions of 5 and 1M concentrations, 1-phenylcyclohex-1-ene oxide was obtained in 25% yield and 18% ee under the former conditions but in 54% yield and 25% ee under the latter (67% yield and 27% ee at 2M).

2.14.7 Effect of substrate.

Aggarwal's BINAP based iminium salt provided 71% and 31% ee for the epoxidation of 1-phenylcyclohex-1-ene and *trans*-stilbene respectively.[38] Hanquet's system provides *trans*-stilbene oxide with 33% ee.[37]

Catalysis by our own systems as described above, seems to follow a different pattern regarding the substrate-enantioselectivity relationship (Table 4).

The isopinocampheylamine derived catalyst was tested with several aryl alkenes as substrates alkenes in acetonitrile/water (2:1) at 0 °C. In contrast to the system of Aggarwal *trans*-stilbene is the best substrate of those studied.[41] *Trans*-stilbene oxide was obtained with 73% ee which is the best result reported for catalytic asymmetric epoxidation mediated by iminium salts to date.

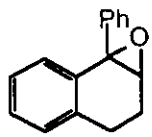
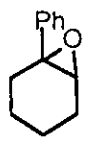
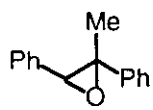
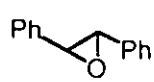
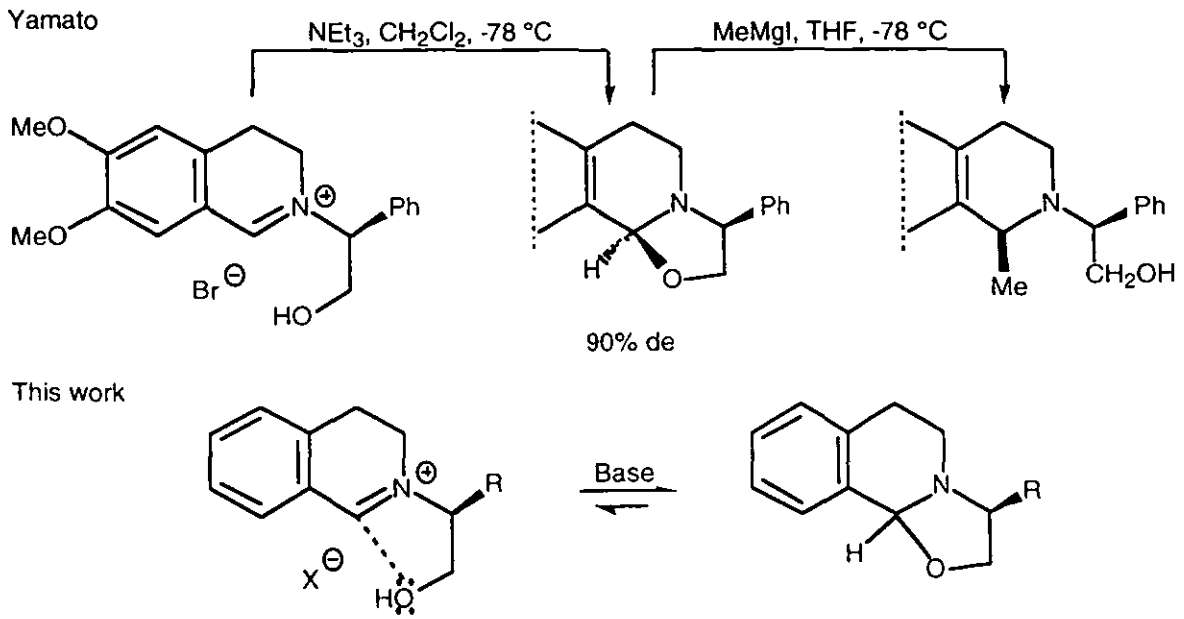
Epoxide	ee % / Configuration	Isolated yield %
	63 (–) -	73
	40 (+)-(R,R)	68
	15 (+)-(R,R)	72
	68 (73)* (+)-(R,R)	75 (78)*

Table 4: Preliminary screening of some unfunctionalised olefines in the catalytic asymmetric epoxidation process using 5 mol% of the isopinocampheylamine derivative; *values in brackets correspond to results obtained with 10 mol% of catalyst.

2.15 Catalysts derived from 1,2-aminoalcohols.

Functionalised iminium salts have not been tested as catalysts for asymmetric epoxidation of simple alkenes. The cyclocondensation products that may be obtained from reaction of 2-(2-bromoethyl)benzaldehyde and 1,2-aminoalcohols give rise to dihydroisoquinolinium salts with a pendant hydroxyl group.

There has been one report of a related system which was cyclised stereoselectively to the corresponding oxazolidine after treatment with base. In turn, the new heterocyclic compound reacted in stereoselective fashion when subjected to nucleophilic attack to furnish the ring opened product (Scheme 48).[108] Similar stereoselective ring opening reactions of oxazolidines have also been reported.[109-111]



Scheme 48: The ring opening and closure of oxazolidines is under thermodynamic control.

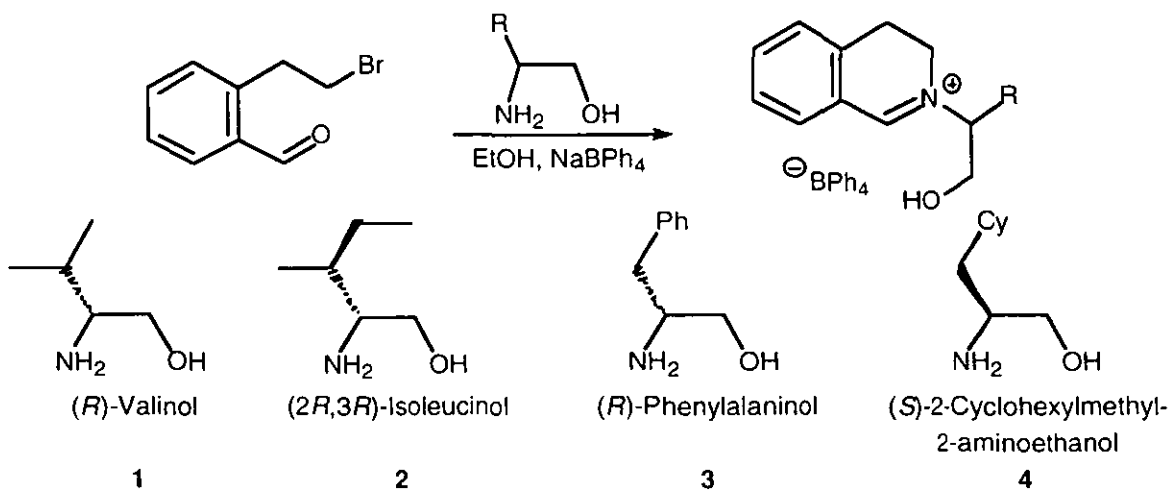
Following speculation that the hydroxyl residue in the latent catalyst might direct the nucleophilic attack of the oxidant preferentially at one of the faces of the iminium moiety, several readily available chiral aminoalcohols were tested as catalyst precursors.

The resulting dihydroisoquinolinium salts with pendant hydroxyl group are expected to exist in equilibrium with the corresponding oxazolidines under the alkaline reaction conditions (Scheme 48). The chemical behaviour of these systems is discussed in more detail below in three groups according to the degree of substitution of the carbon bearing the hydroxyl group.

2.15.1 Chiral aminoalcohols with primary hydroxyl group.

Members of this class of aminoalcohols are almost invariably derived by reduction of chiral aminoacids. Reaction of the aminoalcohols with 2-(2-bromoethyl)benzaldehyde, as described previously for the simple amines, furnished the desired dihydroisoquinolinium salts. Under these conditions the hydroxyl moiety does not attack the iminium carbon to produce the bicyclic oxazolidine unless the salt is treated with base.

The corresponding salts of the amino alcohols depicted below (Scheme 49), were synthesised without difficulty, but unfortunately all of these derivatives produced almost racemic 1-phenylcyclohex-1-ene oxide when subjected in the catalytic reaction.



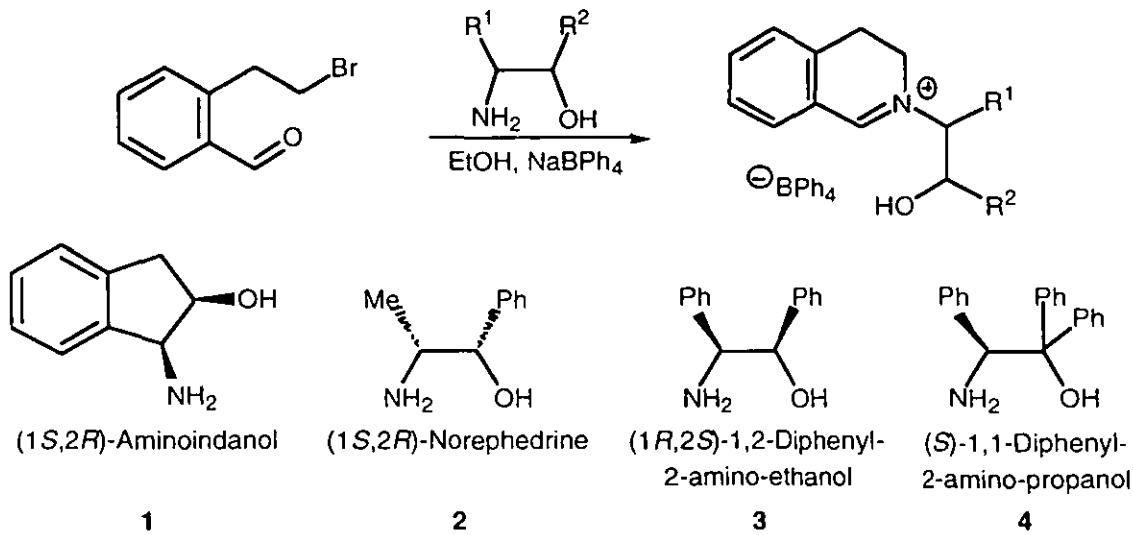
Scheme 49: Chiral aminoalcohols with primary hydroxyl group used as catalyst precursors.

Disappointingly, the presence of the additional stereogenic centre adjacent to the nitrogen atom in the isoleucinol derivative (2 in Scheme 49), is inconsequential in the enantioselectivity of the process.

Another interesting feature of these novel catalysts was that the rate of the catalytic process was slow compared to that exhibited by the mediators without a pendant hydroxyl group. We believe that this is due to the equilibrium being established between the iminium salt and the corresponding oxazolidine which is not expected to be catalytically active. The latter is thought to be the predominant component under the alkaline conditions employed in the reaction.

2.15.2 Chiral amino alcohols with secondary or tertiary hydroxyl groups.

The dihydroisoquinolinium salts derived from the aminoalcohols depicted in Scheme 50 were prepared under the usual conditions by reaction with 2-(2-bromoethyl)benzaldehyde. Interestingly, the bromide salt of the norephedrine derivative precipitated directly and no anion exchange was carried out. Testing of these derivatives revealed that when the hydroxyl group resides on a stereogenic secondary carbon atom there is a dramatic increase in enanioselectivity compared with the cases where this is primary.



(1*S*,2*R*)-Aminoindanol (1*S*,2*R*)-Norephedrine (1*R*,2*S*)-1,2-Diphenyl-2-amino-ethanol (*S*)-1,1-Diphenyl-2-amino-propanol

1 **2** **3** **4**

Scheme 50: Commercially available amino alcohols with a secondary hydroxyl group. The stereogenic carbon atom bearing the hydroxy residue is important in asymmetric induction.

For example, the norephedrine derived dihydroisoquinolinium salt (2 in Scheme 50) catalysed oxygen transfer to 1-phenylcyclohex-1-ene with enantioselectivity of the order of 30% ee, while the 1,2-diphenyl related derivative furnished the same epoxide with 24% ee. Disappointingly, the aminoindanol derivative not only imparted negligible asymmetric induction during the process but was the most ineffective of all those tested as far as the rate of the catalytic oxidation is concerned.

The results obtained with the norephedrine-derived dihydroisoquinolinium bromide with several aryl alkene substrates are presented in table 5.

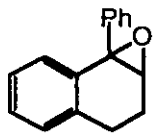
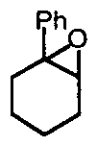
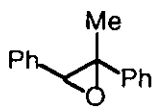
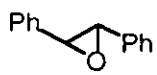
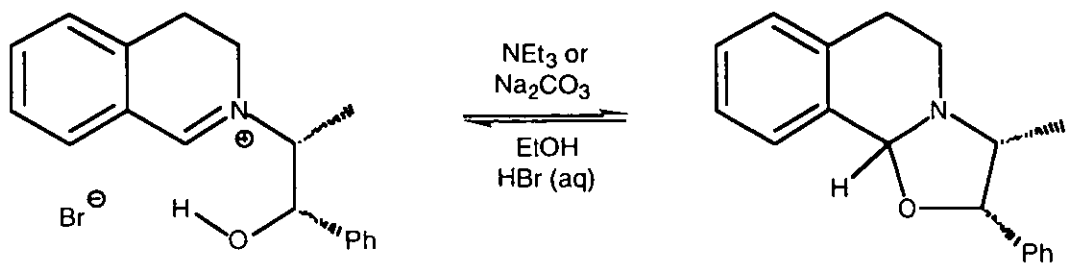
Epoxide	ee % / Configuration	Isolated yield %
	33 (+) -	61
	30 (+)-(R,R)	64
	20 (+)-(R,R)	57
	12 (+)-(R,R)	45

Table 5: Selectivities obtained in the catalytic epoxidation process with 10 mol% of the norephedrine based catalyst in 2:1 acetonitrile/water.

As described above, for catalysts derived from simple primary amines, 0.3 mol% suffices in order for the reaction to proceed to quantitative conversion within one hour. 5 mol% of the catalysts with a secondary hydroxyl group however is usually required, while for those with a primary hydroxy group approximately half that amount is needed (2.5 mol%). The difference in reactivity between the latter two classes may well correlate with the leaving group ability of the corresponding alkoxides: Secondary alkoxides are stronger bases and therefore inferior leaving groups so affecting the equilibrium between the iminium salt and the oxazolidine.

In order to prove that the oxazolidine was formed reversibly under the reaction conditions, the organic salt derived from norephedrine was dissolved in dry dichloromethane and treated with three equivalents of triethylamine at ambient temperature.[108] After approximately one hour the ring closed compound was obtained in almost quantitative yield (97%) as a mixture of diastereoisomers at 1:4.5 ratio (Scheme 51). The ratio was determined by comparison of the integrals of the signals due to the oxazolidine proton(s) at the carbon attached to the two

heteroatoms. The same result was obtained with a kinetic base, sodium carbonate, in a two phase system (Scheme 51). At 0 °C, the ratio of the two diastereoisomers changed only slightly from 1:4.5 to 1:5.0. Lowering the reaction temperatures to –55 °C resulted in a profound increase in the stereoselectivity of the ring closing process, as the ratio of the two diastereomers was then 1:10.



Scheme 51: The ring closure to the oxazolidine is fast and unselective under the conditions examined.

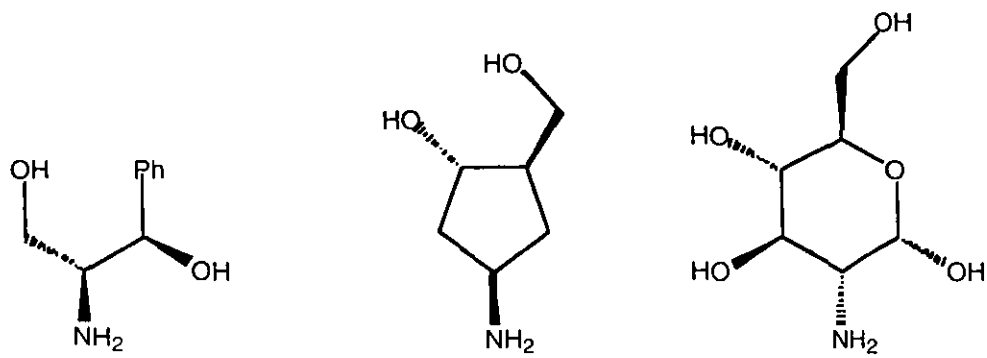
These experiments suggest that this reaction is under thermodynamic control. In fact, it is well documented in the chemical literature that ring opening of oxazolidines is reversible and that stereospecific formation of these heterocycles can be achieved by prolonged heating at high temperatures.[67]

It is reasonable to assume that the poor enantioselectivities obtained with the norephedrine derived catalyst may stem from the modest stereoselectivity observed in the formation of the corresponding oxazolidine. Consequently, this is translated into poor ability of the chiral residue to direct the oxidant efficiently to one of the diastereotopic faces of the iminium moiety. Finally, the mixture of the norephedrine derived oxazolidines was exposed to an ethanolic solution of hydrobromic acid and the precipitated parent dihydroisoquinolinium salt was reisolated in good yield (62%). Prolonged exposure (reaction mixture allowed to stand overnight) increased the yield (81%).

At the other end of the spectrum, the dihydroisoquinolinium salt derived from 1,1-diphenyl-2-amino propanol, which contains a tertiary hydroxyl group, could not be isolated. The signal expected for the iminium proton (*ca* 8.5-9.1 ppm) was absent in the NMR spectrum of the crude product, although most of 2-(2-bromoethyl)benzaldehyde had reacted (diminished intensity of aldehyde proton signal at *ca* 10.15 ppm). In addition, the IR spectrum of the crude reaction product(s) showed negligible absorption at 1650 cm^{-1}, the frequency of the iminium

functionality, suggesting strong preference of such systems to exist in the oxazolidine form. Acidic work up also failed to precipitate the salt by ring opening of the oxazolidine.

2.16 Catalysts derived from aminopolyols.



(1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol

1

(1*S*,2*R*,4*S*)-4-amino-2-hydroxy methylcyclopentanol

2

α-D-Glucosamine

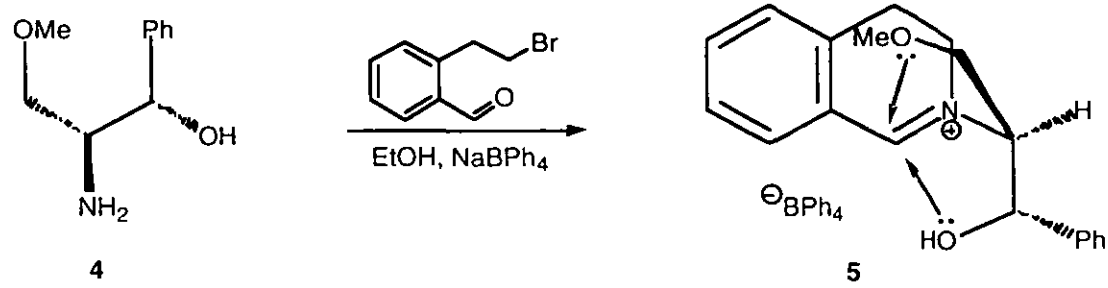
3

Scheme 52: Possible catalyst precursors with more than one hydroxyl group.

2-Amino-1-phenyl-1,3-propanediol (1 in Scheme 52) is an aminodiol which is structurally related to norephedrine in that in the place of the methyl group α to the nitrogen atom there is a carbinol. In order to gain insight into the effect of such a structural change on the enantioselectivity of the catalytic process, the preparation of the dihydroisoquinolinium salt derived from this aminodiol, was attempted. It was however quickly discovered that when more than one hydroxyl group is present in the same molecule of the amine catalyst precursor (2,3 in Scheme 52),[112] the corresponding dihydroisoquinolinium tetraphenylborates fail to materialise from the reaction mixture.

There is a readily available derivative of the aminodiol in question, with the primary alkoxy group protected as its methyl ether (4 in Scheme 53). This derivative unlike the parent molecule, did react cleanly with 2-(2-bromoethyl)benzaldehyde under the usual reaction conditions, to produce the corresponding dihydroisoquinolinium salt, albeit in low yield. The precipitation of the salt proved unusually problematic; evidently the introduction of the second oxygenated functionality deprives the salt of some crystallinity.

Unfortunately, this compound (5 in Scheme 53) exhibited no catalytic activity, perhaps because both faces of the iminium salt are shielded towards nucleophilic attack by the oxidant. Although in terms of rate it was expected to be inferior than the norephedrine derivative due to the presence of the methoxy group, which can also hinder one of the faces of the iminium species by coordination, its complete lack of reactivity was hardly anticipated.

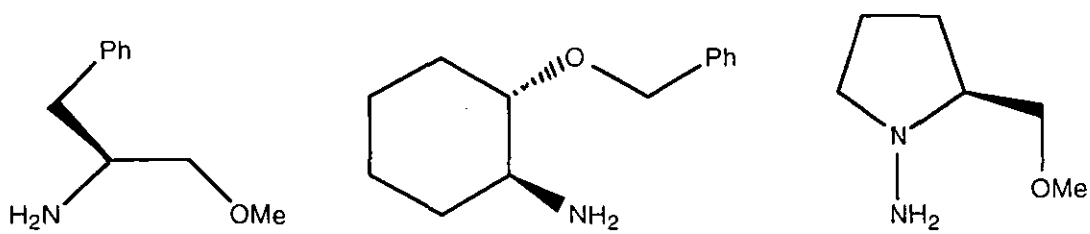


4 5

Scheme 53: The strong chelating effect deprives the iminium species from its reactivity.

2.17 Catalysts derived from aminoethers.

Protection of the hydroxyl group in the aminoalcohol series, as an alkyl or silyl ether, would create a new class of potential catalyst precursors. We felt that these would still have the advantage of potential for directing the oxidant but should react much faster than the hydroxy analogues due to their inability to form the corresponding inactive oxazolidines.



(S)-Phenyl alaninol methyl ether

(1*S*,2*S*)-2-benzyloxy cyclohexylamine

RAMP

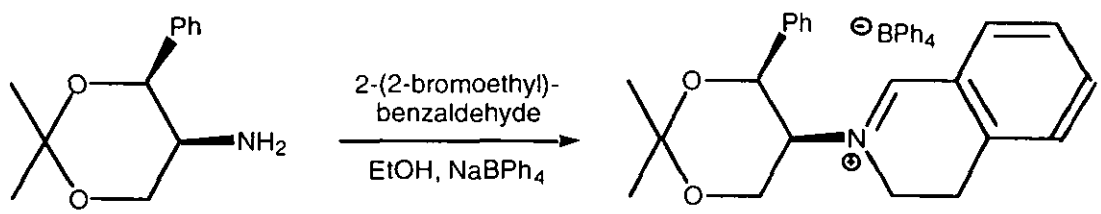
Scheme 54: Selected chiral amino ethers which served as precursors of iminium salts.

Initially, three amino ethers were selected: The first was the methyl ether derived from phenylalanine (Scheme 54). The dihydroisoquinolinium salt was prepared under the usual conditions but like its parent molecule it furnished virtually racemic 1-phenylcyclohex-1-ene oxide.

The second amino alcohol derivative bears a substantially larger benzyl ether (Scheme 54), also formed the corresponding iminium salt in good yield. When subjected under the usual catalytic conditions for oxygen transfer, 1-phenylcyclohex-1-ene oxide was isolated in good yield but with less than 5% ee. These experiments suggest that the size of the ether moiety is much less important in these systems than the exact nature and structure of the chiral carbon skeleton on which the primary amino group resides.

The third aminoether tested is the RAMP hydrazine derived from prolinol (Scheme 54).[113] In this case attack of the ethereal oxygen atom at the iminium carbon atom would result in a six membered ring structure rather than five as in the previous examples. The hydrazonium salt was isolated in good yield, but proved inactive as catalyst for asymmetric epoxidation under a variety of conditions.

Subsequently, a precursor with additional type of oxygen functionality was also tested. The condensation product between acetone and the 2-amino-1-phenyl-1,3-propanediol, 5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane, reacted smoothly with 2-(2-bromoethyl)benzaldehyde to furnish the corresponding dihydroisoquinolinium salt in greater than 75% yield (Scheme 55). The acetal group was unaffected by the acid generated in the ethanolic reaction medium.

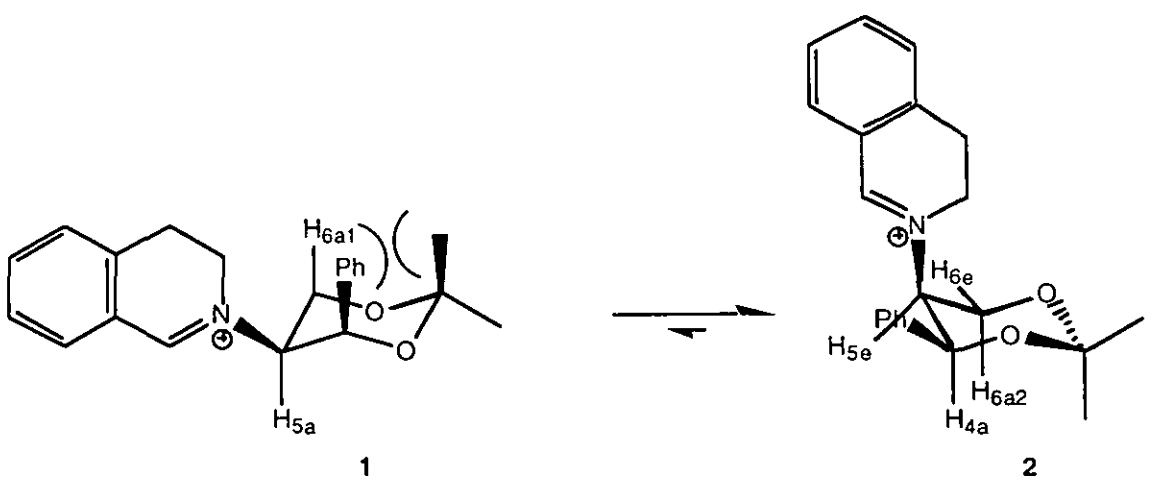


Scheme 55: Synthesis of the novel chiral dioxane derived dihydroisoquinolinium salt.

In this system, unlike the ones examined previously, the oxygenated portion of the structure would be expected not to participate in coordination with the iminium species. An important feature is that the stereochemical relationship of the nitrogen atom with the phenyl group is *syn*. This implies that either the phenyl or the isoquinoline group must be axial.

Despite the comparable size of the two substituents, NMR spectroscopy suggests the presence of only one conformer at ambient temperature. This conclusion is drawn from two observations: First, all the proton signals are sharp and the coupling constants corresponding to each of the protons at the 1,3-dioxane

ring are consistent with chair conformation 2 in scheme 56 ($JH_{6a2}H_{5e}$, $JH_{4a}H_{5e}$ *ca* 3 Hz). This is also in accord with previous reports regarding 5-axially-4-equatorially-disubstituted-2,2-dimethyl-1,3-dioxane rings.[114] If there had been significant amounts of other conformers rapidly equilibrating, or conformation 1 alone, larger (average) values of coupling constants for the 1,3-dioxane ring protons would have been expected due to the diaxial disposition of protons H_{6a1} and H_{5a} in scheme 56 (theoretically $JH_{6a1}H_{5a}$ *ca* 7-10Hz). Secondly, in the ^{13}C NMR spectrum, the geminal methyl groups appear at 17.98 and 28.68 ppm (axial and equatorial respectively). This is also consistent with conformation 2 in scheme 56 according to Evans report on 1,3-diol acetonides.[115,116]



Scheme 56: NMR spectroscopy indicates the existence of only one conformer at ambient temperature.

A more careful inspection and analysis of the conformers reveals that there is a reason why conformer 2 in scheme 56 might be expected to be the thermodynamically favoured one. When the phenyl group is axial (1 in Scheme 56) the structure is destabilised by several 1,3 diaxial interactions. That of the aromatic ring and the axial hydrogen (H_{6a1}), and, more importantly, one of the methyl groups of the anomeric carbon atom. In contrast, when the isoquinolinium group is axial (2 in Scheme 56) there are no such interactions, as the equivalent 1,3-positions are occupied by oxygen atoms and the axial methyl group is in an *anti* relationship with the heterocycle.

In order to gain some evidence about the suspected conformational preference, a variable high temperature NMR experiment was conducted in

deuteriated dimethyl sulfoxide (DMSO-d_6). As indicated above, the NMR spectrum of this organic salt at ambient temperature suggested only one conformer present due to the lack of the appearence of a second set of resonances or broad signals.

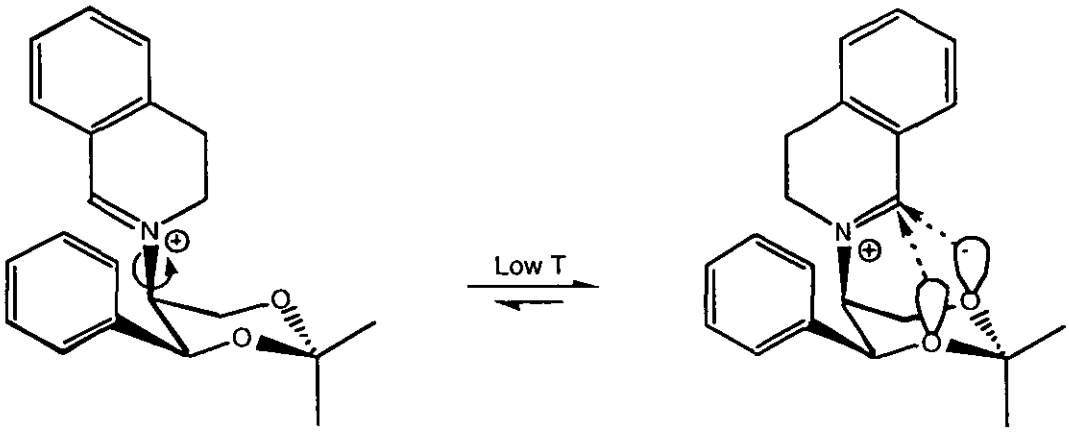
Examination of the spectra obtained between 35 and 85 °C clearly showed that there was no change in the appearance or in the chemical shifts of the resonances (except for the HDO resonance), and therefore no conformational changes occur across this temperature range. It was only from 95 to 105 °C that broadening of the signals was observed as a coalescence point was reached (Appendix 2). This would suggest that the conformational barrier to rapid interconversion between the two conformers is high.

Due to the high melting point of DMSO-d_6 the low temperature NMR expreriment was conducted in deuteriated acetonitrile (MeCN-d_3). This experiment revealed a second coalescence point at approximately –20 °C (Figure 2), and caused broadening of the signals corresponding to the dimethylene moiety of the dihydroisquinolinium substituent. This may be associated with a rotational barrier around the bond joining the 1,3-dioxane ring and the nitrogen atom since the signals corresponding to the protons of the 1,3-dioxane ring are hardly affected.

In conformer/rotamer 4 (Scheme 57), there are two axially oriented lone pairs of electrons (one from each oxygen atom), and the planar iminium functionality may orientate itself near the electron-rich regions. This is a stabilising interaction that favours this rotamer/conformer and impedes rotation of the dihydroisoquinolinium entity (Scheme 57). We believe that this interaction becomes more important at lower temperatures where there is less available energy for conformational/rotational changes.

This is also supported by single crystal X-ray analysis of the structure obtained for this organic salt (Figure 3), which may also suggest possible overlap between one the lone pairs of oxygen atom 1 (HOMO) and the iminium double bond (LUMO).

Free rotation around the nitrogen atom–1,3-dioxane ring (chair conformation, 1 in Scheme 57) at ambient temperature, is also supported by n.O.e studies carried out in deuteriated acetonitrile at 25 °C (Appendix 2). How this effect may influence the asymmetric induction imparted by this compound in the catalytic process, is discussed below.



3 4

Scheme 57: Perhaps the coalescense that occurs at –20°C is indicative of the electrostatic interaction between the iminium moiety and the lone pairs of the oxygen atoms.

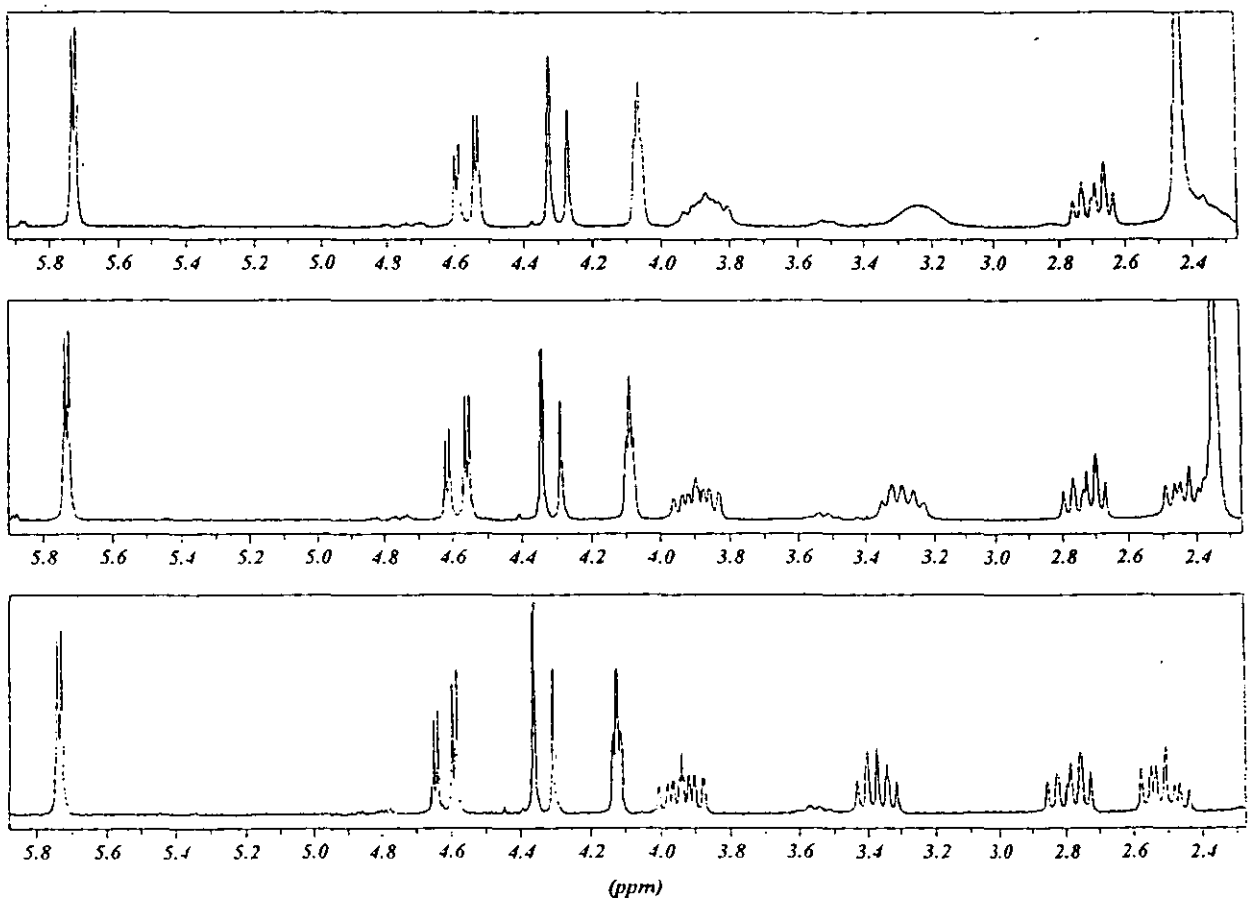
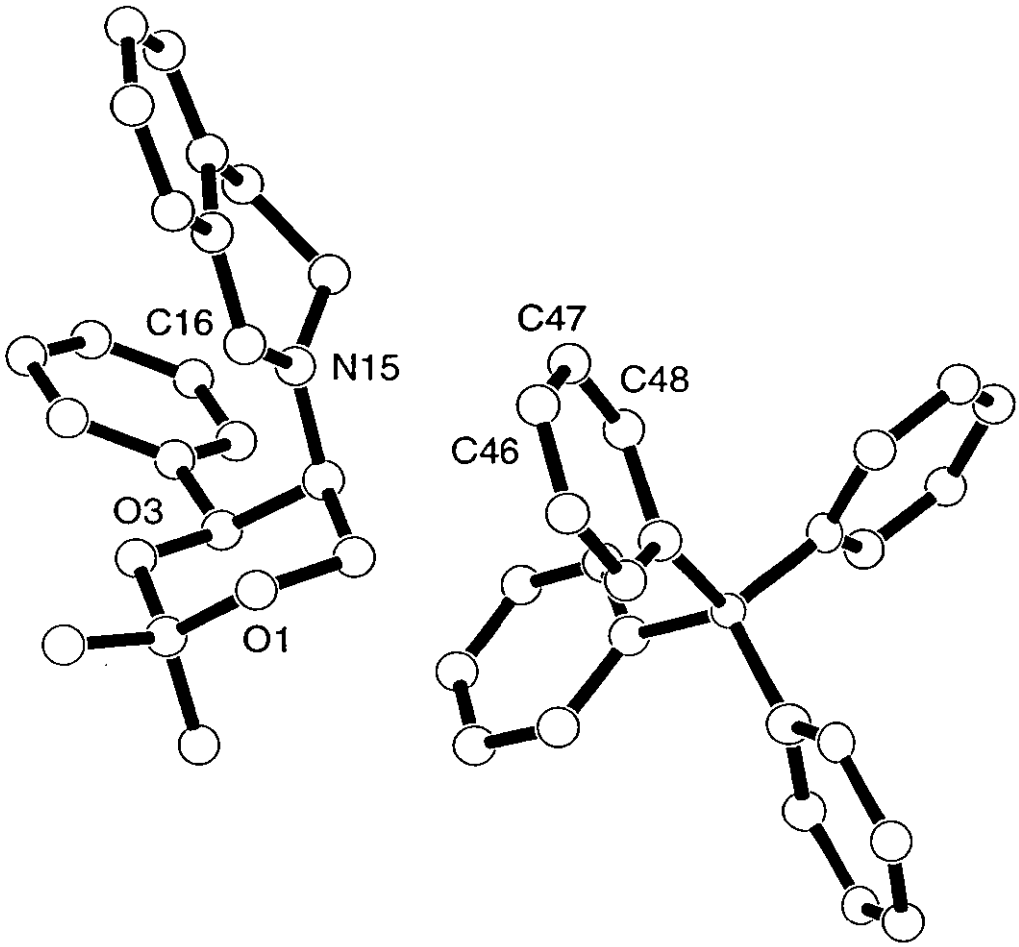


Figure 2: Low temperature NMR experiments conducted in MeCN-d_3 at -20, -10, and 0 °C (from top to bottom respectively), suggest a barrier to conformational/rotational changes at low temperatures that may be due to intramolecular electrostatic interactions.



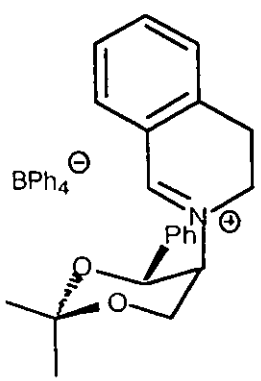


Figure 3: X-ray representation of the dihydroisoquinolinium salt derired from (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane. It is clearly shown that the isoquinolinium group is axially orientated and the iminium carbon points near oxygen atom 1.

This novel compound was tested in the catalytic asymmetric epoxidation of simple alkenes, and the results are summarised below in table 6. Preliminary examination of these results suggests that it is the least substrate specific iminium salt catalyst discovered to date.

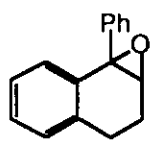
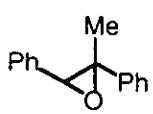
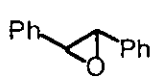
Epoxide	ee % / Configuration	Isolated yield %
	50 (–) -	64
	40 (–)-(S,S)	55
	47 (+)-(R,R)	52
	43 (+)-(R,R)	48

Table 6: Results obtained in the epoxidation of simple alkenes mediated by 5(*S*)-(N-dihydroisoquinolinium)-2,2-dimethyl-4(*S*)-phenyl-1,3-dioxane.

2.18 Comparison between simple and functionalised iminium salt catalysts.

The investigation next carried out concerned the performance of the most successful catalysts with a larger variety of substrates. In particular, comparison between the isopinocampheylamine derived catalyst and that prepared from 5-amino-2,2-dimethyl-4-phenyl-(1,3)-dioxane, could provide insight into the role of the oxygenated portion of the latter mediator.

The results obtained with the 1,3-dioxane derived catalyst show that this mediator is dramatically less substrate specific than the terpenoid or any other derivative previously tested.

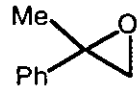
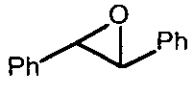
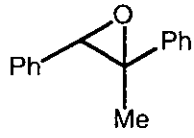
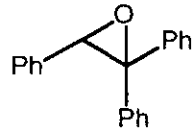
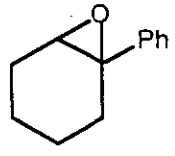
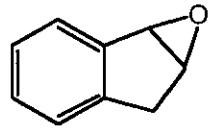
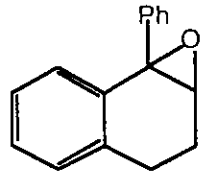
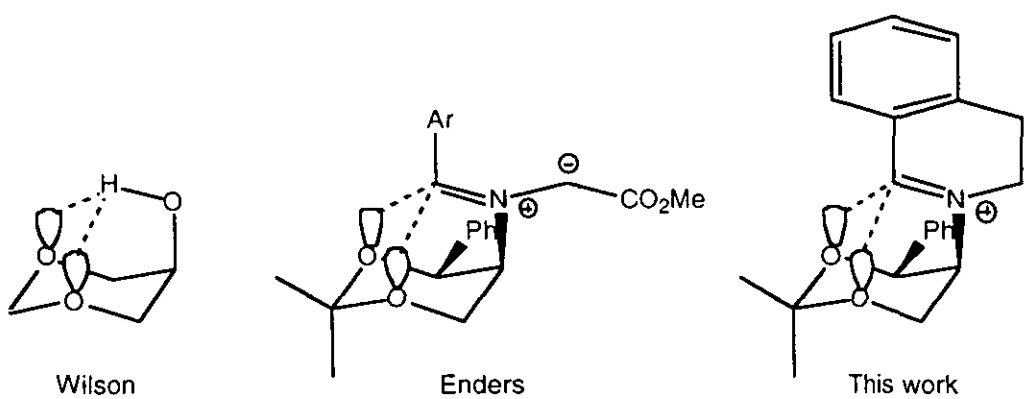
Catalyst precursor:	(–)-Isopinocampheylamine	(+)-5-Amino-2,2-dimethyl-4-phenyl-1,3-dioxane
Epoxide	Isolated Yield % (ee) % / Configuration	Isolated Yield % (ee) % / Configuration
	68 **(8)**-(+)-(*R*)	64 **(20)**-(+)-(*R*)
	73 **(68)**-(+)-(1*R*,2*R*) 75 **(73)**-(+)-(1*R*,2*R*) †	48 **(43)**-(+)-(1*R*,2*R*)
	72 **(15)**-(+)-(1*R*,2*R*)	52 **(47)**-(+)-(1*R*,2*R*)
	43 **(5)**-(+)-(*S*)	54 **(58)**-(+)-(*S*)
	68 **(40)**-(+)-(1*R*,2*R*) †	55 **(40)**-(–)-(1*S*,2*S*)
	34 **(3)**-(+)-(1*S*,2*R*)	52 **(17)**-(+)-(1*S*,2*R*)
	73 **(63)**-(–)- –	64 **(50)**-(–)- –

Table 7: Runs were conducted with 5 mol% of catalyst loading in water/acetonitrile (1:1) with 2 equivalents of Oxone™and 4 equivalents of sodium carbonate at 0 °C. † 10 mol% was used.

The results shown in table 7 refer to the epoxidation of simple alkenes at 0 °C using Oxone™ as the stoicheiometric oxidant in water/acetonitrile (1:1).

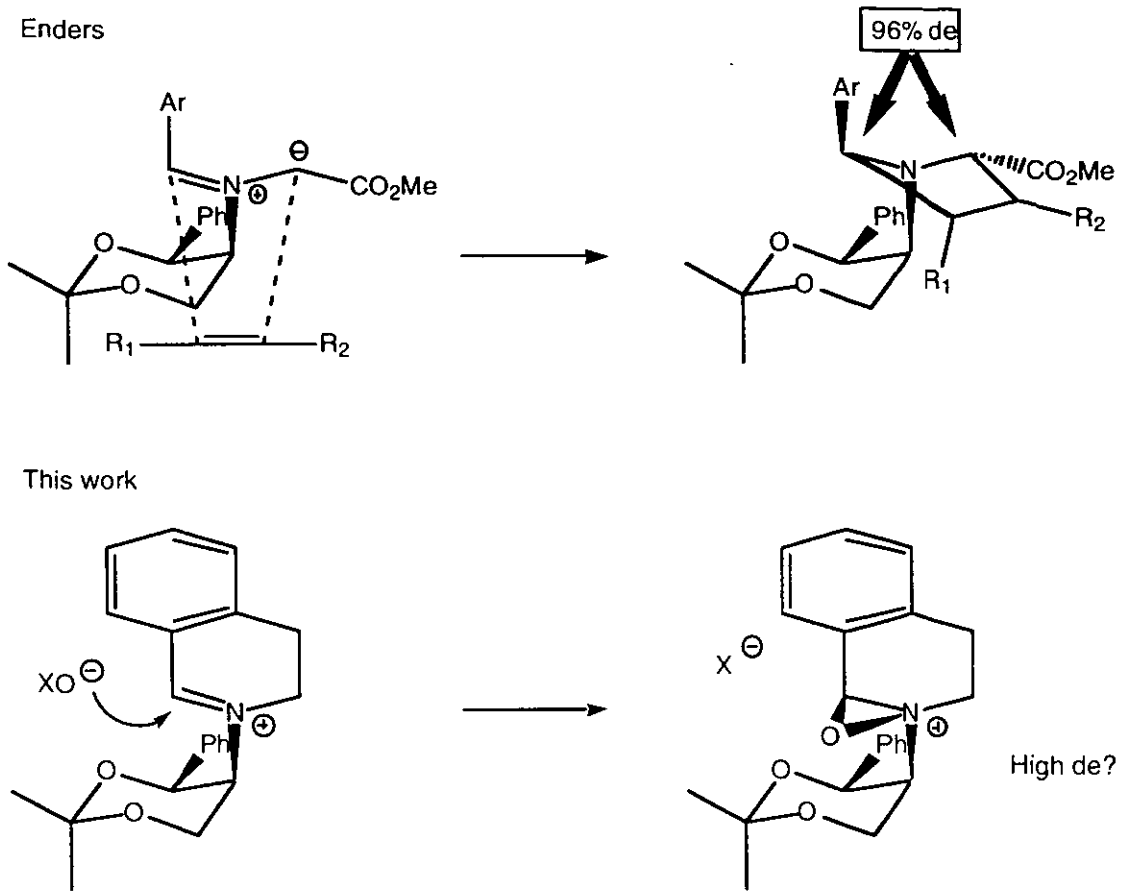
Interestingly, the enantioselectivities obtained with the dioxane based catalyst are less sensitive to catalyst loading than those obtained with the isopinocampheylamine derivative. Thus, the subsubstrates tested furnished the corresponding epoxides with almost identical ee's when 5 or 10 mol% of the catalyst was employed.

We believe that the success of the dioxane based catalyst may partly stem from the high conformational rigidity. The strong preference of these systems to exist in such a conformation has been documented in both theoretical and experimental context in the chemical literature.[117-120]



Scheme 58: Electrostatic interactions serve as stabilising forces of these conformations.

In the prefered conformation as shown in scheme 58 and confirmed by the X-ray structure, the phenyl substituent hinders the attack of the oxidant at the rear face of the iminium moiety where the proximal face is accessible to nucleophiles. This arrangement is likely to produce only one of the two possible diastereoisomeric oxaziridinium intermediates and therefore enantioselectivity losses may only arise from the oxygen transfer to the substrate. This rationalisation of minimum enantioselectivity leakage for the overall process is also supported by the work of Enders in a closely related system. Enders investigated the asymmetric synthesis of pyrrolidines *via* 1,3-dipolar cycloadditions using an azomethine ylid derived from 5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane.[120] The stereoselectivities obtained from these reactions with a variety of dipolarophiles (typically 96% de) are easily explained when the same type of reactive conformer is invoked (Scheme 59).

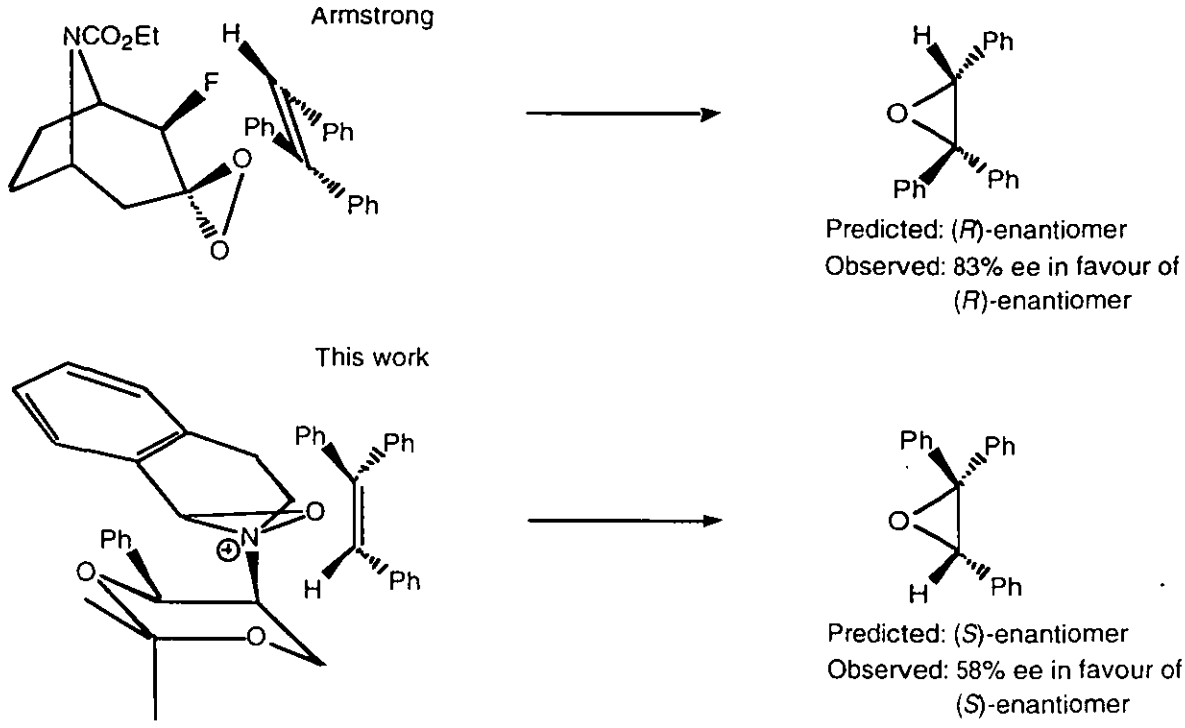


Scheme 59: The success of the dioxane derivative in catalytic asymmetric epoxidation may lie in the almost exclusive formation of one diastereoisomeric oxaziridinium intermediate.

The well-defined conformation which may lead to improved enantioselectivity in the catalytic epoxidation process mediated by the dioxane derivative is absent from the dihydroisoquinolinium salt derived from isopinocampheylamine. Consequently, rotation around the bond between the nitrogen atom and the chiral auxiliary may result in both diastereotopic faces of the iminium moiety to become susceptible to nucleophilic attack by the oxidant. Therefore, substantial enantioselectivity leakage for the overall process may occur.

Another possible reason for the superior consistency of the dioxane derivative could be the interaction between one of the oxygen atoms with an olefinic hydrogen atom during the transition state. This rationale was first put forward by Armstrong who investigated the epoxidation of simple alkenes mediated by the dioxirane derived from a chiral α-fluoroketone.[121] Armstrong suggested that the high enantioselectivities in the epoxidation reaction as well as the

configuration of the oxirane products may be explained on the basis of an electrostatic interaction between the fluorine substituent and an olefinic proton. This interaction is based on the build up of positive charge on the olefinic carbon atom(s) during the oxygen transfer.[122] Following this argument, we can also predict the stereochemical outcome of the epoxidation process catalysed by iminium salts (Scheme 60).



Scheme 60: The proposed transition state for asymmetric epoxidation mediated by oxaziridinium salts which takes into account heteroatom interaction during oxygen transfer.

It therefore appears that the heteroatom interaction has a dramatic influence on the enantioselectivity of the overall process. This is perhaps, one reason why the isopinocampheylamine derivative which lacks the additional heteroatom, mediates epoxidation of triphenyl ethylene with less than 5% ee.

The transition states shown in Scheme 60, have been constructed according to the spiro model. In the spiro transition state the alkene approaches the oxaziridinium moiety in such a way that the axis of the carbon-carbon double bond is perpendicular to the carbon-nitrogen bond axis (Scheme 61). In the alternative transition state, the planar, the two components approach one another in such a way that these axes are parallel to one another and in the same plane (Scheme 61).

Scheme 61: Geometrical approaches between the substrate and the reactive intermediate.

Davis has been one of the few authors to favour the planar transition state during oxygen transfer from oxaziridines to alkenes and enolate anions.[4,34,123] The spiro transition state is now widely accepted as the mechanism in operation during both dioxirane and oxaziridine mediated epoxidation, and is also supported by recent theoretical and computational studies.[124,125]

To conclude, the success of the dihydroisoquinolinium salt derived from 5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane in being the least substrate specific iminium salt-catalyst discovered to date, may lie in the intramolecular heteroatom interaction. In fact, this catalyst is a member of a new family of dihydroisoquinolinium salts which contain more functionality than those reported prior to this work. Nevertheless, the catalyst derived from isopinocampheylamine is the most successful to date in terms of imparting the highest level enantioselectivity of any reported iminium salt in catalytic asymmetric epoxidation.

2.19 The combined approach.

In the search for the catalyst that would mediate catalytic asymmetric epoxidation with high enantioselectivities, we attempted to identify features present in previously tested systems that influenced positively the asymmetric induction. The results obtained with the most successful and structurally diverse dihydroisoquinolinium salts were compared and a new line of approach was created.

2.19.1 Design and synthesis of new catalyst precursors.

The results obtained from our preliminary screen of chiral amines indicated that some of the catalysts based on terpenoid systems were the most effective of those tested as far as the asymmetric induction to the substrate is concerned. From the aminoalcohol series, it was also demonstrated that the hydroxyl group can influence the stereochemistry with which the intermediate oxaziridinium ion is formed. The results obtained from the norephedrine derived catalyst, whose molecular complexity and size are far lesser than the terpene-based analogues, exemplify the importance of the pendant chiral alcohol. In addition, from the enantioselectivities exhibited by the dioxane derivative it could also be inferred that the presence of a group of high steric demand α to the nitrogen atom may be of major importance in the asymmetric induction of the process. The identification of these independent and autonomous features, prompted the belief that a catalyst derived from a system which combines two or all three of these characteristics may deliver epoxides of increased enantiomeric excesses from the catalytic reaction.

One way to associate the amino and hydroxyl groups in 1,2-relationship within a structure, in conjuction with high steric demand in the vicinity of nitrogen, is to incorporate the two functionalities on a terpenoid carbon skeleton. The first synthetic approach towards the construction of the desired difunctional compounds involved the manipulation of the carbonyl group so frequently present in terpenes.

The synthesis of terpenoid 1,2-aminoalcohols is discussed below according to the method used to generate the amino group. In addition, further classification of catalyst precursors is used within each method, according to the order of substitution on the carbon atom bearing the hydroxyl group, (primary, secondary and tertiary).

2.20 Amines from oximes.

2.20.1 Pendant tertiary hydroxyl group.

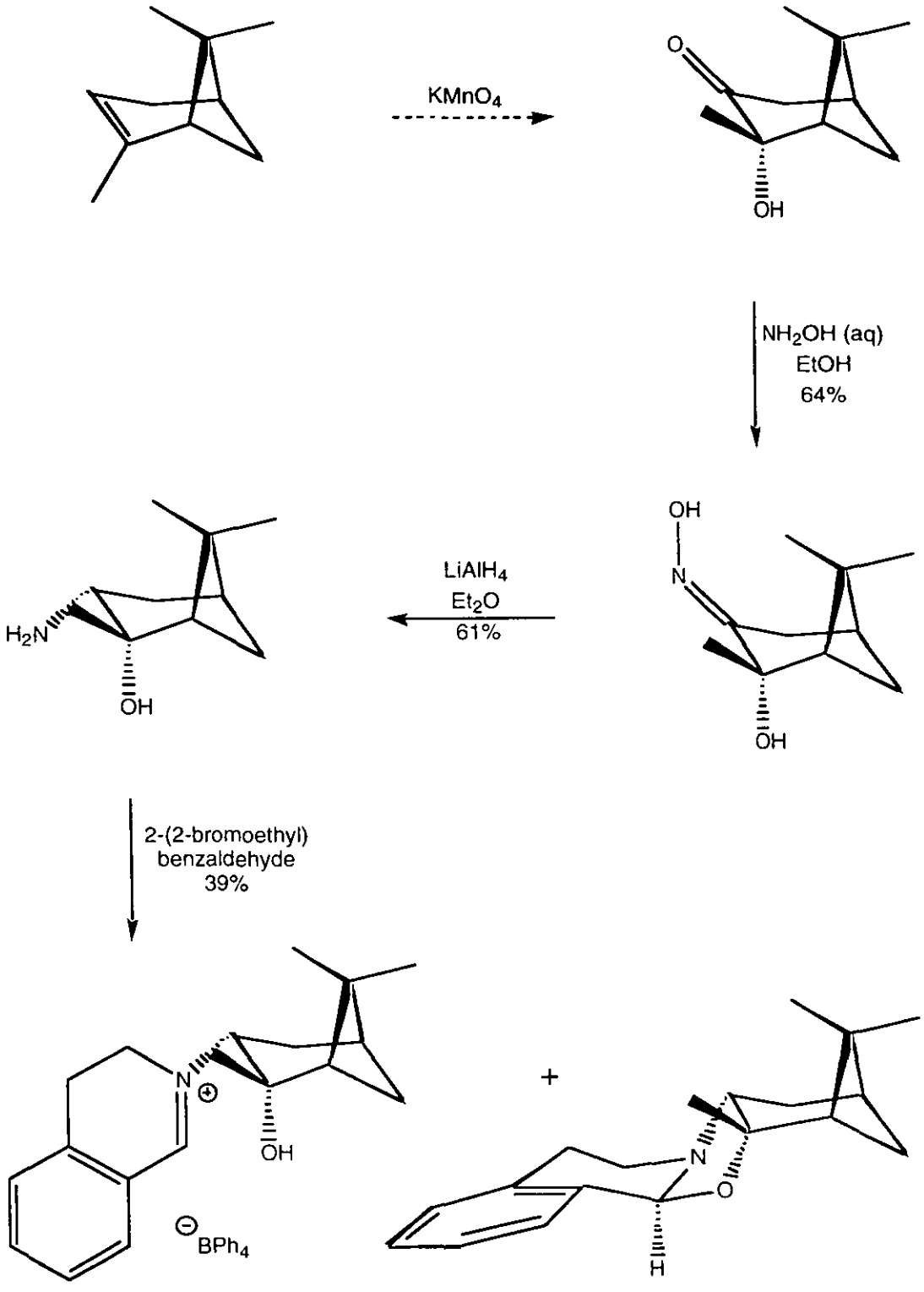
The first terpenoid ketone considered was 2-hydroxy-3-pinanone which possesses the correct 1,2-relationship between the two functionalities. Both enantiomers of this optically active starting material are commercially available. In addition, it is easily accessed on large scale, *via* permanganate oxidation of pinene in one step (Scheme 62).[126,127]

The desired *cis-endo*-3-amino-2-hydroxypinane was synthesised in two steps by oxime formation followed by reduction with lithium aluminium hydride (Scheme 62).[128] Intrestingly, the hydride delivery takes place at the most hindered face of the carbon-nitrogen double bond perhaps due to complexation of both the tertiary hydroxyl group and nitrogen atom with the reducing agent to form a five membered ring. This can only be *cis* fused with the cyclic terpenoid skeleton. Reaction of this aminoalcohol with 2-(2-bromoethyl) benzaldehyde followed by the usual anion exchange furnished a solid which consisted of two components (Scheme 62). These were unambiguously identified by NMR spectroscopy as the desired dihydro isoquinolinium salt and one of the corresponding oxazolidines in a 3:1 ratio. As previously suspected, with pendant tertiary alcohols, intramolecular ring closure is not only inevitable but also irreversible (See 2.15.2). Incorporation of significant amounts of trifluoromethane sulfonic acid failed to alter the ratio of the two components even in polar solvents such as dimethyl sulfoxide and acetonitrile, which favour the existence of the charged species.

This derivative also served to test the previous hypothesis that catalysts derived from 1,2 amino alcohols with tertiary hydroxyl groups, are relatively inert as catalysts in our system due to irreversible oxazolidine formation. When this system was subjected to the catalytic process only traces of 1-phenylcyclohex-1-ene oxide were produced even after prolonged reaction times (8 hours).

This clearly demonstrates the validity of the hypothesis stated earlier and provides evidence for the existence of the catalyst in equilibrium with the corresponding oxazolidine under alkaline conditons. This equilibrium heavily favours the latter, because ring opening of the oxazolidine would require the tertiary alkoxide to act as a leaving group.

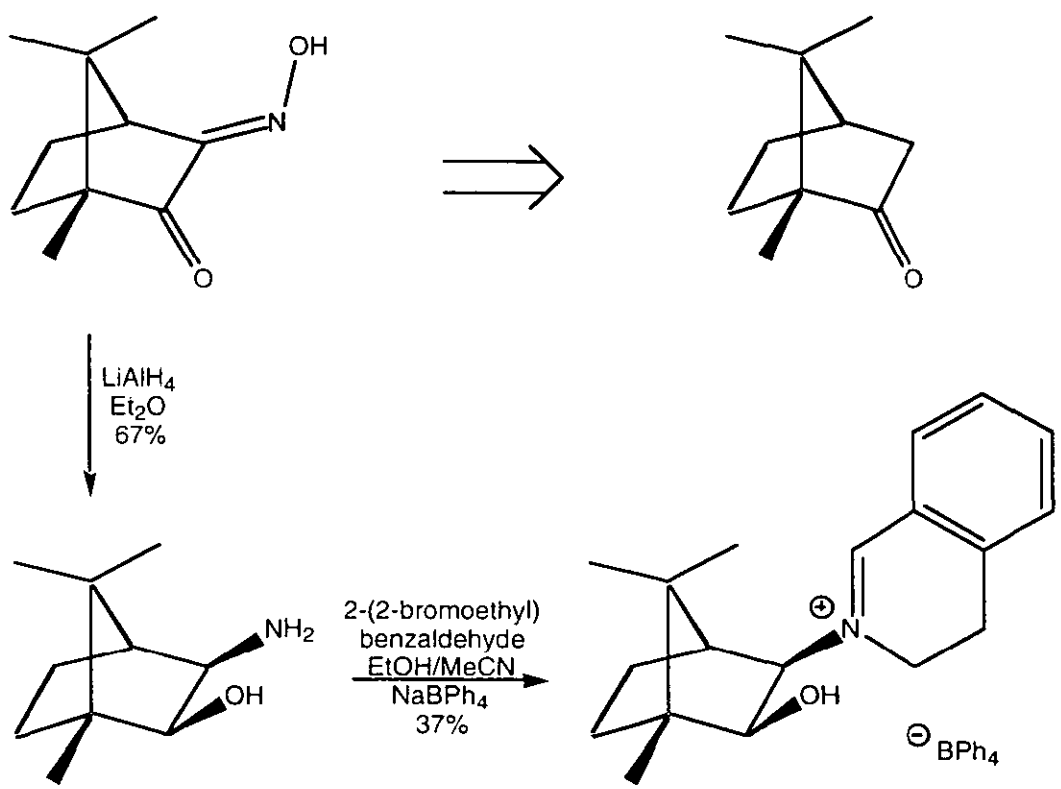
In the light of this finding, further research was focused on catalysts with pendant secondary or primary hydroxyl groups.



Scheme 62: Synthesis of 3-amino-2-hydroxypinane, (2-hydroxy-isopinocampheylamine), and the corresponding iminium salt, which exist in equilibrium with one of the possible oxazolidines.

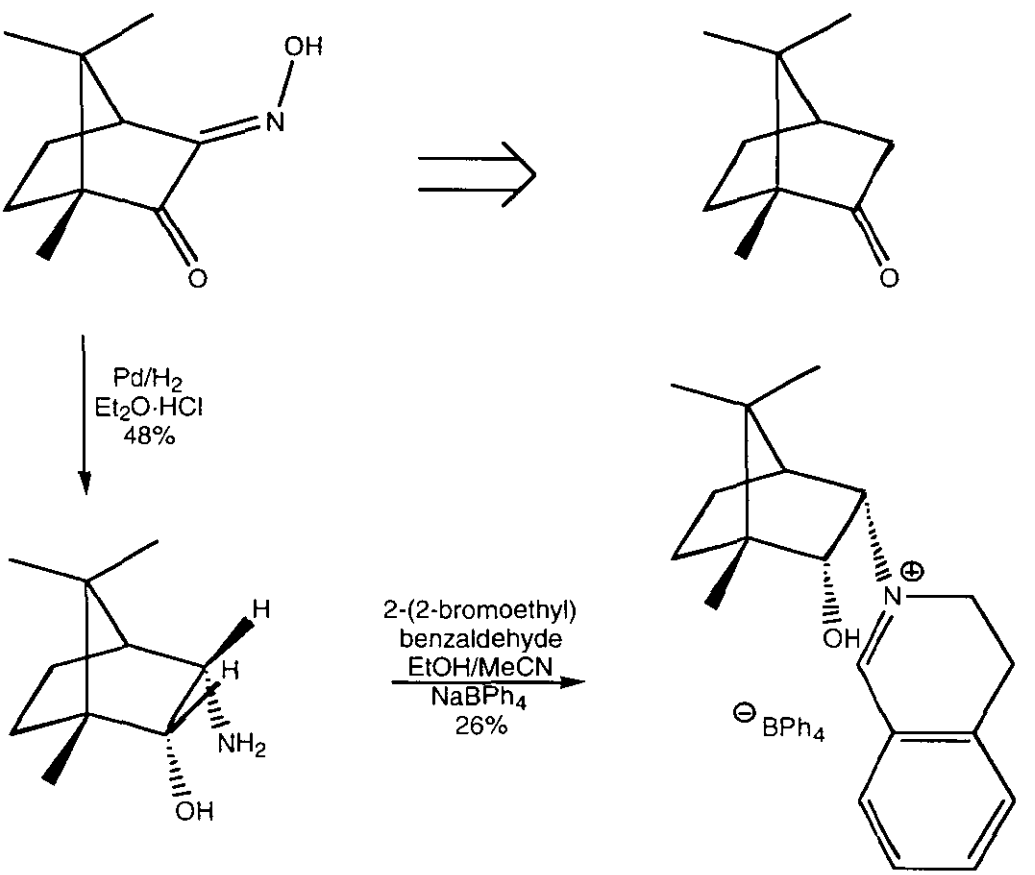
2.20.2 Pendant secondary hydroxyl group.

Using the same synthetic methodology, it was possible to envisage the preparation of 1,2-aminoalcohols derived from camphor as potential catalyst precursors. Thus, when the commercially available camphor quinone monoxime was treated with an excess of lithium aluminium hydride, the corresponding (*cis-exo*)-3-amino-2-borneol, was furnished as expected from *endo* hydride attack, in greater than 70% yield (Scheme 63).[129-131] Again, the precursor is available in large quantities since it is easily accessible from camphor in two steps. As described earlier selenium dioxide oxidation of camphor furnishes camphor quinone almost quantitatively even on a 100 g scale.[78] Treatment of the 1,2-diketone with hydroxylamine, selectively produces the monoxime from reaction at the least hindered carbonyl group.[132,133] Routine treatment of *cis-exo*-3-amino-2-borneol with 2-(2-bromoethyl)benzaldehyde gave access to yet another novel chiral dihydroisoquinolinium salt (Scheme 63) which was tested for its activity in the catalytic process at 5 mol% loading.



Scheme 63: Synthesis of the iminium salt derived from *cis-exo*-3-amino-2-borneol.

The epoxidation process was carried out as normal with 1-phenylcyclohex-1-ene as the substrate in the presence of Oxone™ and sodium carbonate in water/acetonitrile (1:1), at 0 °C. In contrast with the pinane derivative, the camphor analogue exhibited remarkable activity towards the catalysis of asymmetric epoxidation of this substrate. The rate of the catalytic reaction, as well as the yield of the epoxide produced with this catalyst, are comparable with those manifested by iminium salts lacking the hydroxyl group. However, the enantioselectivity imparted in the epoxidation of 1-phenyl-1-cyclohexene did not exceed 10% ee.

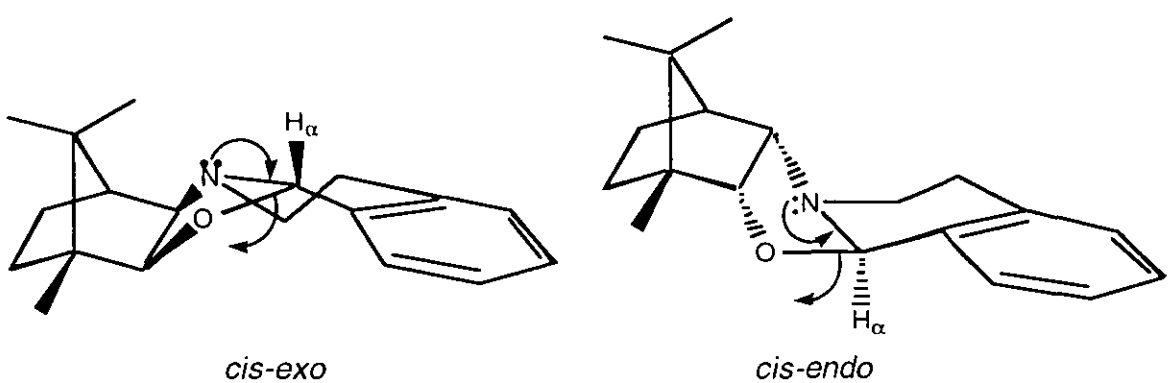


Scheme 64: Synthesis of the iminium salt derived from *cis-endo*-amino borneol.

In order to examine the influence of the geminal dimethyl moiety and possibly identify the cause for the low enantioselectivity observed, the *cis-endo*-3-amino-2-borneol was synthesised (Scheme 64). The latter amino alcohol was accessed by hydrogenation of camphor quinone monooxime in the presence of a catalytic amount of palladium on activated charcoal and ethereal hydrogen chloride as the solvent.[129] The *cis-endo*-3-amino-2-borneol also proved a successful catalyst

precursor as it furnished the expected dihydroisoquinolinium salt when condensed with 2-(2-bromoethyl)benzaldehyde (Scheme 64). The new derivative was tested (5 mol%), for catalytic activity in the epoxidation process with 1-phenylcyclohex-1-ene as the substrate undrer the usual conditions. In comparison with the first aminoborneol examined, the *cis-endo* derivative reacts more slowly but still catalyses the reaction to completion. As with the *cis-exo* analogue however, the enantioselectivity was extremely poor (<5% ee).

The difference in rate of the two catalytic reactions can easily be interpreted in terms of the relative proximity of the geminal dimethyl bridge. This bulky part present in both *cis-exo* and *cis-endo* diastereoisomers seriously affects the unavoidable equilibrium in which the iminium salt is engaged with the corresponding oxazolidines (Scheme 65). In the *cis-exo* compound the sterically demanding group interacts unfavourably with the pseudo axial hydrogen manifested in the ring closed form (H_α in Scheme 65). This unfavourable interaction is far more severe for the alternative oxazolidine. Such interaction is absent from the tricyclic oxazolidine derived from the *cis-endo* compound, and consequently more of the latter component, which is catalytically inactive, may be present in the alkaline reaction mixture.



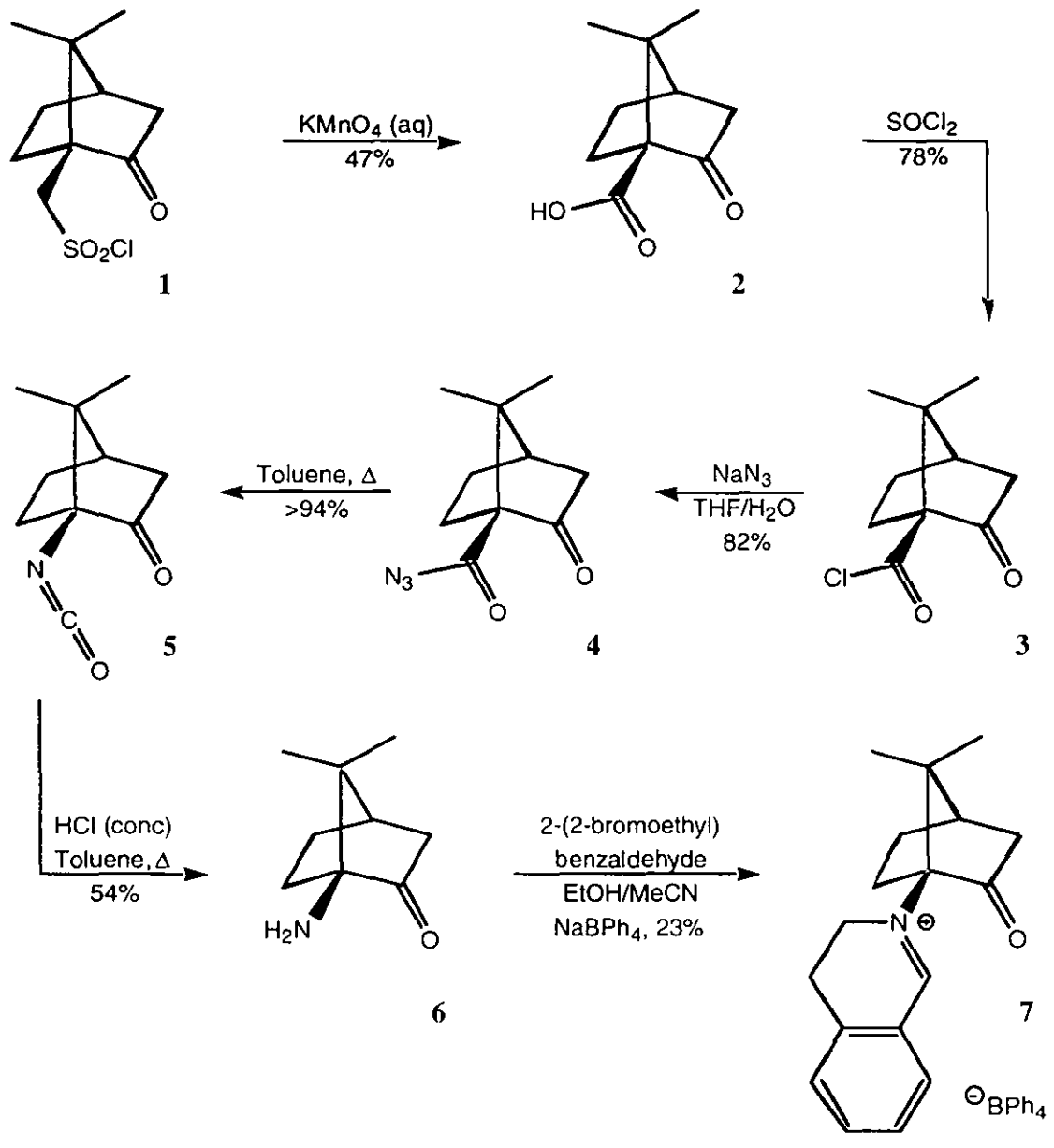
Scheme 65: Ring opening of both oxazolidines relieves the strain of the multicyclic compounds.

In both diasteroisomers however, one of the faces of the iminium functionality is flanked by the alkoxy group while the other is relatively exposed. It appears probable that the result of this arrangement is that the oxidant attacks almost exclusively at the unhindered side to produce the oxaziridinium salt. Thus, although the reactive intermediate is probably formed stereospecifically, the absence of a sterically demanding group at the vicinity of the oxygen transfer site

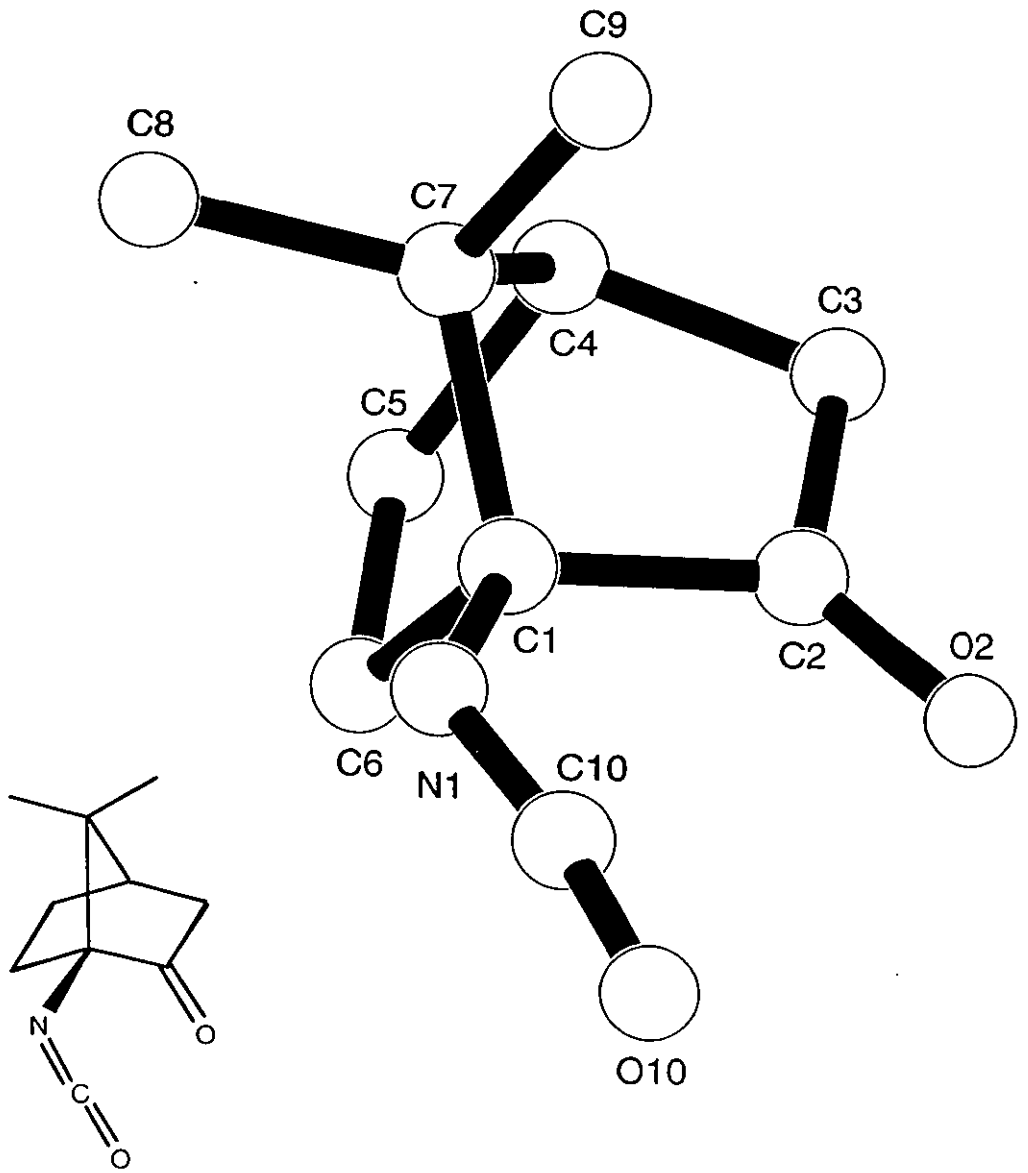
previously not examined in our study. Except from the increased bulk and rigidity associated with the tertiary carbon, the target molecule also bears a pendant carbonyl group which can be easily converted into the secondary alcohol. It was thought that the combination of these two features could have a beneficial effect on the stereochemical course of the catalytic oxygen transfer process.

The starting material for the synthesis of aminoapocamphor is camphor sulfonic acid, (1 in Scheme 68), which is oxidised by permanganate to ketopinic acid (2 in Scheme 68). This reaction rarely proceeds in greater than 40% yield but can be carried out reproducibly on 100 g scale according to a literature procedure.[134] Exposure of the carboxylic acid in thionyl chloride as the solvent produced the ketopinic acyl chloride (3 in Scheme 68) which was treated with an excess of sodium azide to furnish the desired precursor for the Curtius rearrangement (4 in Scheme 68). The acyl azide isolated was found to be contaminated by significant amounts of the isocyanate (5 in Scheme 68), whose X-ray structure analysis was also obtained (Scheme 69). The rearrangement product is undoubtedly produced during the evaporation of toluene (b.p. 110 °C) used at the extraction stage.[135] Attempts to obtain the acyl azide in pure form, involved extraction from the aqueous medium with solvents of lower boiling point (THF, diethyl ether, light petroleum), but without success. This is not however a serious problem because the isocyanate is the precursor to aminoapocamphor and therefore the Curtius rearrangement of the crude acyl azide was carried out in boiling toluene. Thus, the isocyanate was obtained in almost quantitative yield, after approximately two hours. Subsequent portions of the isocyanate were obtained by direct thermolysis of the toluene solution obtained from extracting the acyl azide without isolation/purification of the latter. The rearrangement proceeded with retention of stereochemistry at the migrating centre, rendering this method a powerful synthetic tool for the construction of chiral nitrogen compounds at a tertiary carbon centre.[136] Subsequent hydrolysis of the chiral isocyanate with concentrated hydrochloric acid in toluene/water furnished optically pure aminoapocamphor (6 in Scheme 68).[137] The new chiral amine was condensed in the usual way with 2-(2-bromoethyl)benzaldehyde and furnished after anion exchange the expected dihydroisoquinolinium tetraphenylborate, albeit in low yield (7 in Scheme 68). The new catalyst was tested (5 mol%) in the catalytic asymmetric epoxidation of phenyl cyclohexene and the epoxide was successfully isolated, but the enantioselectivity was very poor (<5% ee). It is clear that the role of the keto group was overestimated, as it does not seem to interact with the iminium moiety presumably due to the decreased nucleophilicity of this type of oxygen functionalitiy. The

absence of this interaction combined with the modest steric demand of the carbonyl group does not promote stereoselective oxidation of the iminium salt. Furthermore, this may allow the alkene to approach relatively unrestricted hence causing the compromised enantioselectivities.



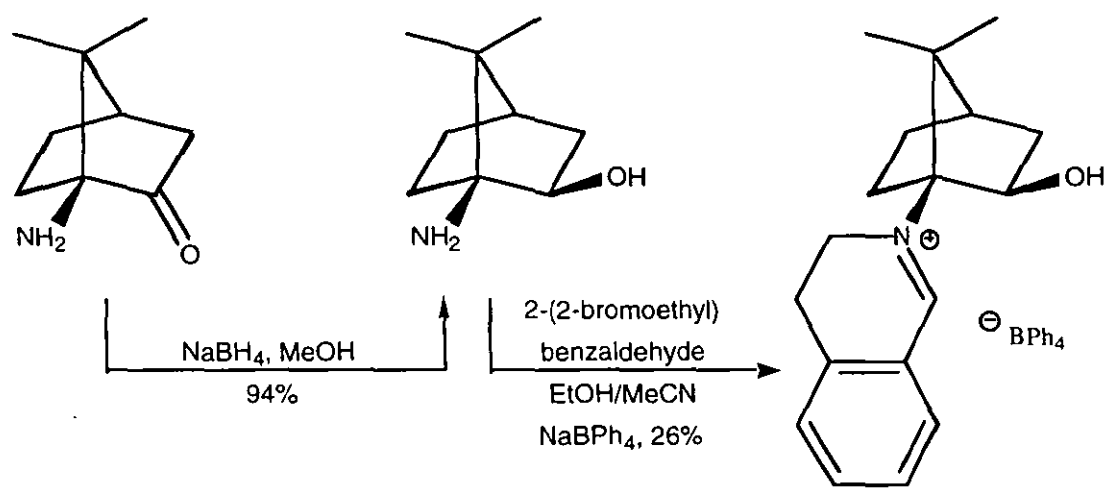
Scheme 68: Synthesis of the dihydroisoquinolinium salt derived from aminoapocamphor.



Scheme 69: Single crystal X-ray analysis of aminoapocamphor isocyanate.

2.21.2 Pendant secondary hydroxyl group.

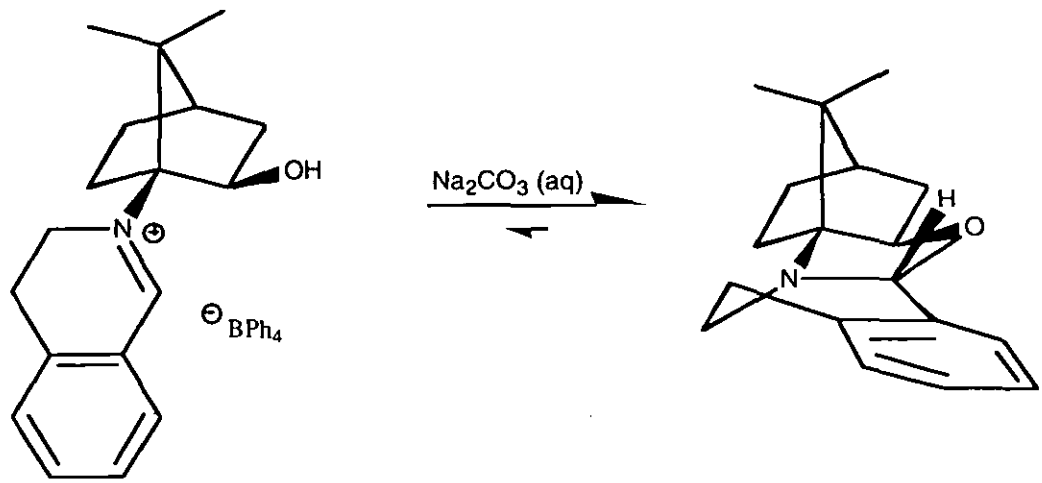
Nevertheless aminoapocamphor can easily be reduced to the corresponding 1,2-aminoalcohol.[135] We had already established, from the examination of dihydroisoquinolinium salts derived from simpler 1,2-aminoalcohols, that the hydroxyl group exhibits neighbouring group participation and therefore positively influences the enantioselectivity of the epoxidation process. Thus, reduction of the chiral ketone with sodium borohydride in methanol gave the *exo*-aminoapocamphol, as expected from *endo* hydride attack, in almost quantitative yield (Scheme 70). The corresponding dihydroisoquinolinium tetraphenylborate was produced upon treatment of the aminoalcohol with 2-(2-bromoethyl)benzaldehyde and anion exchange (Scheme 70), but as with the related amino ketone, the yield of the chiral heterocycle was low. However only small amounts of the organic salt are required in the catalytic reaction, and despite the seven step synthesis, chromatography is not required at any of the stages.



Scheme 70: Synthesis of amino apocamphol and its related dihydroisoquinolinium salt.

The new organic salt was tested for activity at 5 mol% catalyst loading with 1-phenylcyclohex-1-ene as the usual model substrate. Surprisingly, the catalytic reaction was exceedingly slow even at 10 mol% of catalyst loading. After two days, the epoxide was isolated in 18% yield and 22% ee. It seems likely that the diminished reaction rate stems from the equilibrium in which the iminium salt is engaged with the corresponding oxazolidine (Scheme 71). Inspection of the structure resulting from the intramolecular ring closure reveals that there are no unfavourable

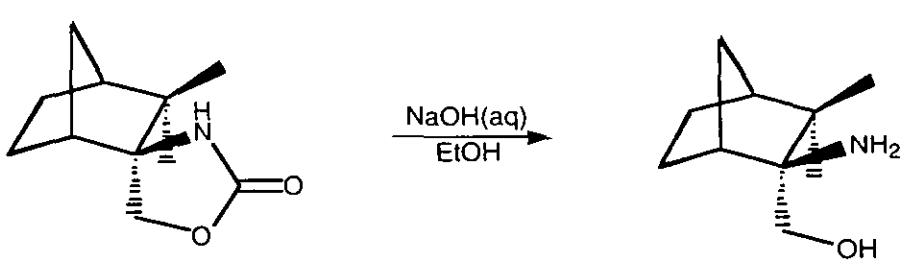
interactions which can sterically accelerate the ring opening of the oxazolidine as was the case with the *cis-exo* aminoborneol derivative.



Scheme 71: The tetracyclic oxazolidine may be too stable and therefore act as a catalyst sink for this dihydroisoquinolinium salt.

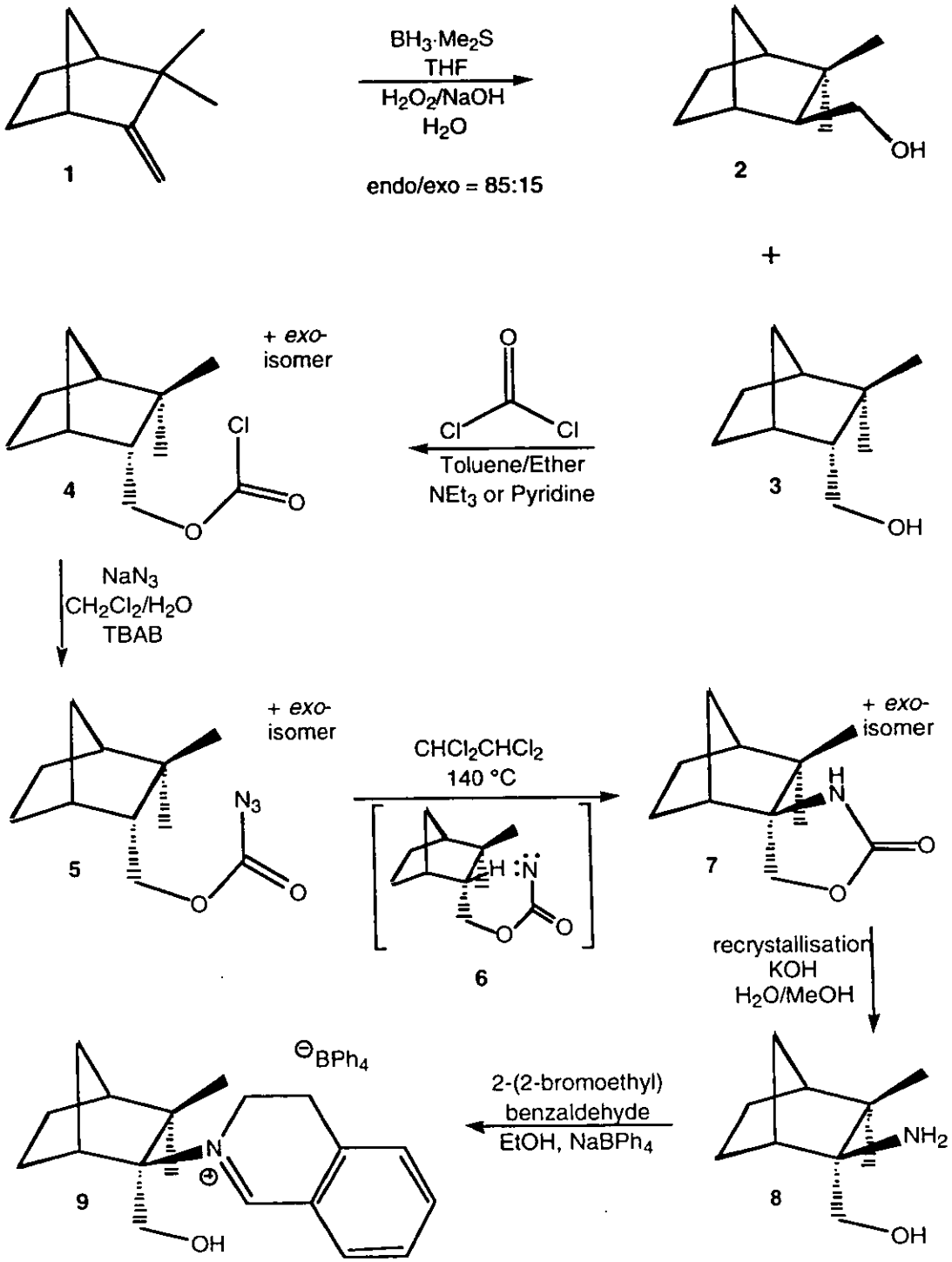
2.22 Amines from nitrene insertion (pendant primary hydroxyl group).

In the search for new catalyst precursors, further design was focused on dihydroisoquinolinium salts derived from 1,2-aminoalcohols with pendant primary hydroxyl group. We thought that such a system could improve the enantioselectivity of the process without compromising the activity of the catalyst. The latter is based on the observation that catalysts derived from 1,2-aminoalcohols react faster when the hydroxyl group is primary, presumably because the equilibrium between the hydroxy iminium salt and the oxazolidine favours the former.



Scheme 72: Hydrolysis of Banks' oxazolidinone may provide a potential catalyst precursor.

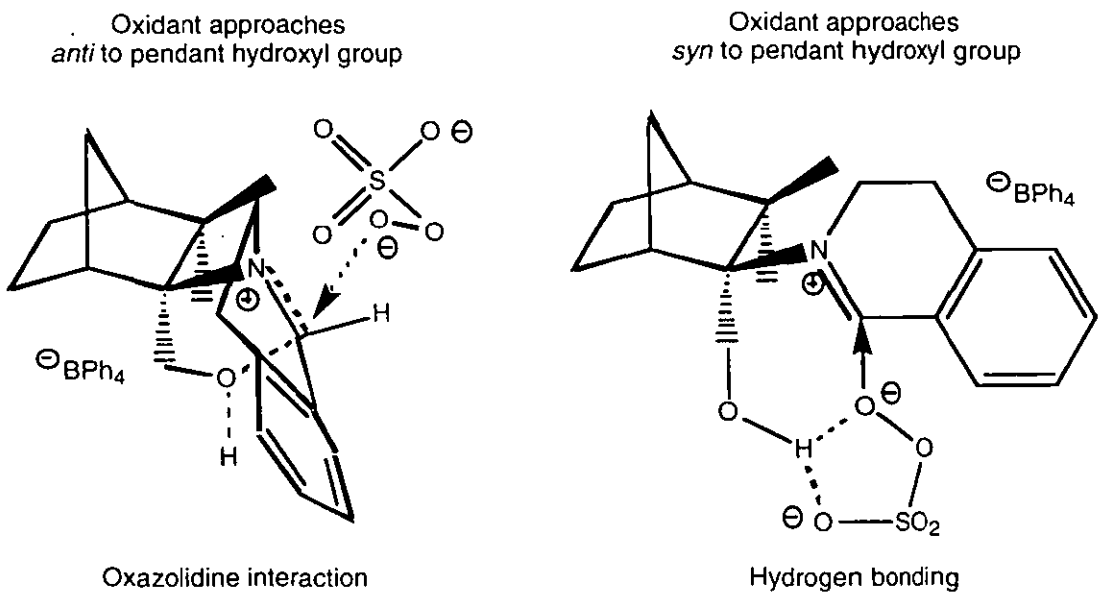
In 1994 Banks reported the synthesis of an oxazolidinone based on fenchone, by a route which does not involve the amino alcohol, but utilises a remarkable nitrene insertion reaction.[138] The hydrolysis of this oxazolidine to the corresponding aminoalcohol has been reported by Braslau (Scheme 72).[135] This aminoalcohol could serve as a useful catalyst precursor because of the pendant primary hydroxyl group. According to the literature procedure, the oxazolidinone is made from camphene (1 in Scheme 73), which is an attractive starting material as it is commercially available in both enantiomeric forms, and we therefore repeated the synthesis in order to access the desired catalyst precursor. Hydroboration/oxidation of camphene furnished a mixture of diasteroisomeric camphanols (*exo*/*endo* 15:85, 90% combined yield, 2 and 3 in Scheme 73),[138,139] The isomeric alcohols have been reported to be unseparable by column chromatography,[138,139] and the mixture of them was therefore treated with a threefold excess of phosgene to give the diastereoisomeric chloroformates in the same ratio and near quantitative yields (4 in Scheme 73).[138] Attempts to replace the highly toxic phosgene with di- or triphosgene and pyridine,[140] proved unsuccessful, as slower reactions, inferior conversions and more complex reaction mixtures were manifested. The mixture of chloroformates was then allowed to react with an excess of sodium azide in dichloromethane/water and thus convertion to the azidoformates, precursors of acyl nitrenes, was achieved (5 in Scheme 73). The mixture of diastereoisomeric acyl nitrenes was thermally generated from the azidoformates in a dilute solution, (1 or 2% w/v) of nearly boiling 1,1,2,2-tetrachloroethane (*ca* 140 °C), with concomitant gas evolution (nitrogen, 6 in Scheme 73). Interestingly, this reaction failed to to proceed at lower temperatures. The generated nitrenes, rapidly insert into the tertiary carbon-hydrogen bond to furnish the spiro oxazolidinones (7 in Scheme 73). The insertion step takes place with complete retention of stereochemistry at that centre,[140-142] and for this reason a singlet nitrene is thought to be involved in this type of process.[143,144] Triplet nitrenes (and carbenes) behave as diradicals, hence formation of the oxazolidinone would require abstraction of a hydrogen radical and formation of a new radical at the tertiary carbon atom. The latter intermediate would almost certainly cause scrambling of the stereochemistry at that centre before ring closure to the oxazolidinone occurs. According to Banks the only purification required in the entire process is a recrystallisation at this stage which affords the diastereomerically pure oxazolidinone from *endo* camphanol (Scheme 73),[138] the major product of the hydroboration/oxidation reaction.[138,139]



Scheme 73: A novel dihydro asoquinolinium salt is accessed by a nitrene insertion reaction.

The crude oxazolidinone (65% yield) was hydrolysed with aqueous potassium hydroxide in refluxing ethanol to give the corresponding 1,2-

aminoalcohol (8 in Scheme 73).[140] Without further purification, the latter was treated with 2-(2-bromoethyl)benzaldehyde in ethanol which, after anion exchange and one recrystallisation, afforded the diastereoisomerically pure dihydroisoquinolinium salt derived from 2-amino-*endo* camphanol (9 in Scheme 73). This novel dihydroisoquinolinium salt was then subjected to the usual conditions for catalytic oxygen transfer to alkene substrates. Once again, the outcome was unanticipated, as the new organic salt was completely inactive as catalyst for asymmetric epoxidation. Although initially disappointing, this was one of the most important results towards understanding the exact role of the hydroxyl moiety and ultimately the reaction mechanism. The inertness of the new compound cannot possibly arise from oxazolidine formation, as ring opening of the latter is a favourable process since it is derived from a primary alkoxy group. This was the very argument upon which the design and synthesis of this class of catalyst was based on.



Scheme 74: Possible directing effects of the pendant hydroxyl group.

Until this point, it had not been clear whether the neighbouring group participation effect by the hydroxyl moiety onto the iminium fuctionality directs the oxidant at the opposite face or it assists the oxidant to attack at the proximal face by means of hydrogen bonding (Scheme 74). More than fifteen aminoalcohol-derived catalysts have been tested successfully, but regardless of the order of the pendant hydroxyl group (primary, secondary and tertiary), any of the two mechanisms could have been in operation. The effect of steric hindrance on the other side of the

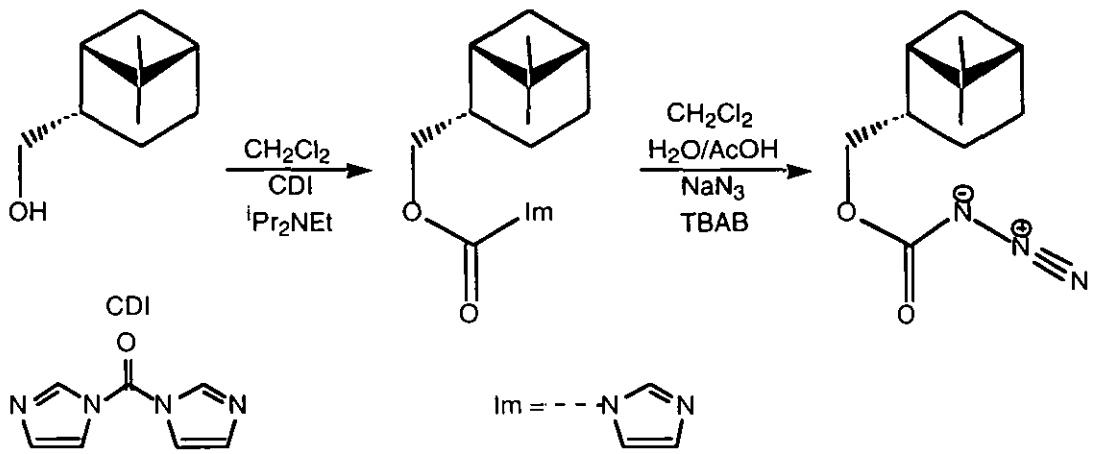
carbon-nitrogen double bond, in conjuction with the electronic effect of the pendant alcohol, had not been fully explored. The behaviour of the *endo*-camphanol-derived catalyst possibly suggests that the hydroxyl group promotes stereospecific oxidation of the iminium salt on the opposite face to which it co-ordinates. When this side of the iminium moiety is denied access by the presence of a sterically demanding group, no reaction takes place. In the case examined, the geminal dimethyl group renders the iminium moiety inaccessible to the oxidant and, despite the presence of the small carbinol group on the other side (Scheme 74), no reaction occurs.

With the stereospecific nitrene insertion successfully accomplished we thought that more derivatives of this type should be synthesised but of lesser steric demand in the vicinity of the nitrogen.

Hydroboration/oxidation of α-pinene affords a mixture of primary alcohols, both of which are commercially available as *cis* and *trans* myrtanol. Both primary alcohols could serve as precursors for pinane-derived acyl nitrenes which could ultimately lead to aminoalcohols, precursors of optically pure dihydroisoquinolinium salts. It was considered that if the synthetic sequence employed by Banks involved a safer but equally efficient alternative to phosgene it would be an advantage for the overall tranformation.

For this reason, carbonyl diimidazole (CDI) was tested as a substitute, and when reacted with *trans*-myrtanol in the presence of triethylamine in dry dichloromethane, the expected carbamate was isolated in quantitave yield in less than one hour (Scheme 75). This is already a previously unreported improvement of the process, since the reaction with excess phosgene takes more than four hours. Secondly, the product which slowly solidifies on standing is stable and can be stored indefinitely, in contrast with the very reactive chloroformate. The imidazole carbamate was then treated with an excess of sodium azide and a catalytic amount of TBAB (tetrabutylammonium bromide), but the starting material remained unconsumed even after prolonged reaction times. We decided to repeat the reaction under acidic conditions so that imidazole may be protonated and therefore converted into a better leaving group. Thus, small amounts of concentrated hydrochloric acid were found to promote the reaction but the yields of the azidoformate varied greatly with seemingly small changes in the amount of the acid incorporated. This chemical behaviour is indicative of a pH sensitive reaction and is explained in terms of competition between the nucleophilicity of the azide and the basicity of the unsubstituted imidazole nitrogen. The more acid is present, the higher the extent to which all basic species are protonated (both imidazole and

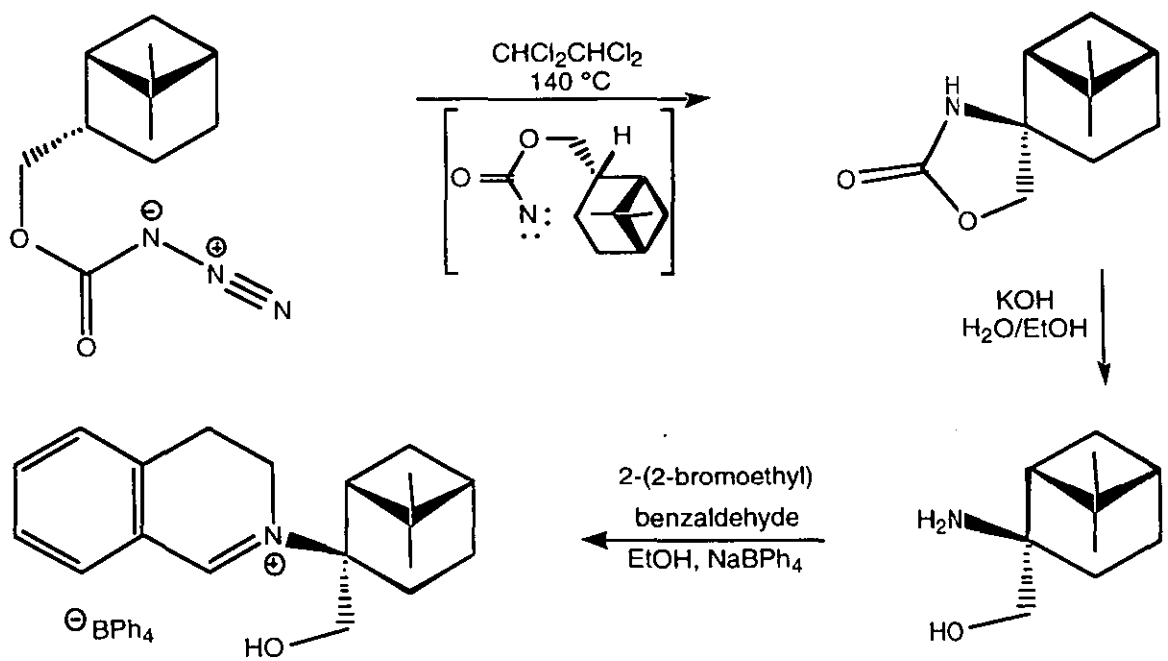
azide), and the more their nucleophilicity is compromised (azide). The converse is true under basic conditions. Such reactions proceed successfully within a narrow pH window, which is usually between 4 and 5. For this reason, acetic acid was used as the reagent of choice, and rewardingly the reaction proceeded smoothly to completion overnight (Scheme 75).



Scheme 75: Synthesis of *cis*-myrtanol azidoformate in quantitative yield in two steps.

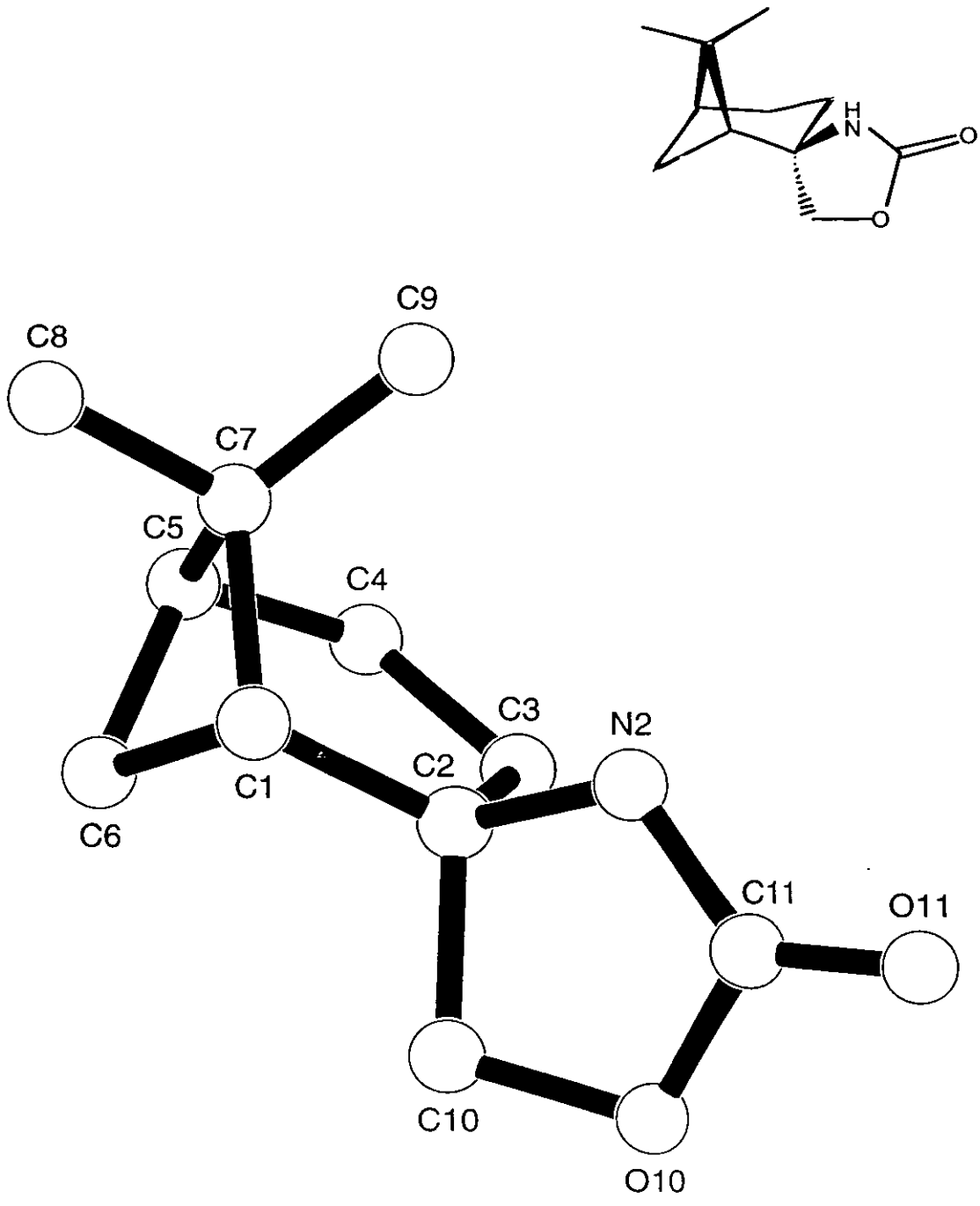
The azidoformate was then subjected to solution thermolysis in order to access the nitrene insertion product but in contrast to the previous two quantitative reactions the spiro oxazolidinone was isolated in a modest 32% yield. It is possible that the acyl nitrene is engaged in other C-H insertions to give other insertion products. For example, Banks has reported that several C-H insertion products are formed during the thermolysis of azidoformates derived from terpenes like camphor.[145] In the case of camphanol, there is only one C-H bond which can serve as the insertion site. This is due to the enhanced selectivity of the acyl nitrenes to insert into a tertiary carbon-hydrogen bond.[140-144,146] Furthermore five membered rings (oxazolidinones), are formed preferentially to the six membered analogues (oxazinones).[140] Although in theory the desired oxazolidinone should be the thermodynamically and kinetically preferred product, dropwise addition of a dilute solution of the azidoformate in boiling tetrachloroethane, as well as other attempts to optimise the reaction yield,[145] did not prove successful. However, the oxazolidinone (Scheme 76) could be isolated by precipitation upon addition of light petroleum, and its X-ray stucture was also obtained after recrystallisation (Scheme 77).

Hydrolysis of the oxazolidinone with aqueous potassium hydroxide in ethanol afforded the corresponding 2-amino-*trans*-myrtanol in 65% yield (Scheme 76) whose X-ray structure was also obtained (Scheme 78). This aminoalcohol was in turn reacted further with 2-(bromoethyl)benzaldehyde to furnish a novel and optically pure dihydroisoquinolinium salt (Scheme 76), albeit in poor yield (22%). It is worthy of mention that all intermediates in this synthesis as well as the final organic salt are new compounds, and no chromatography is necessary at any stage in their synthesis.

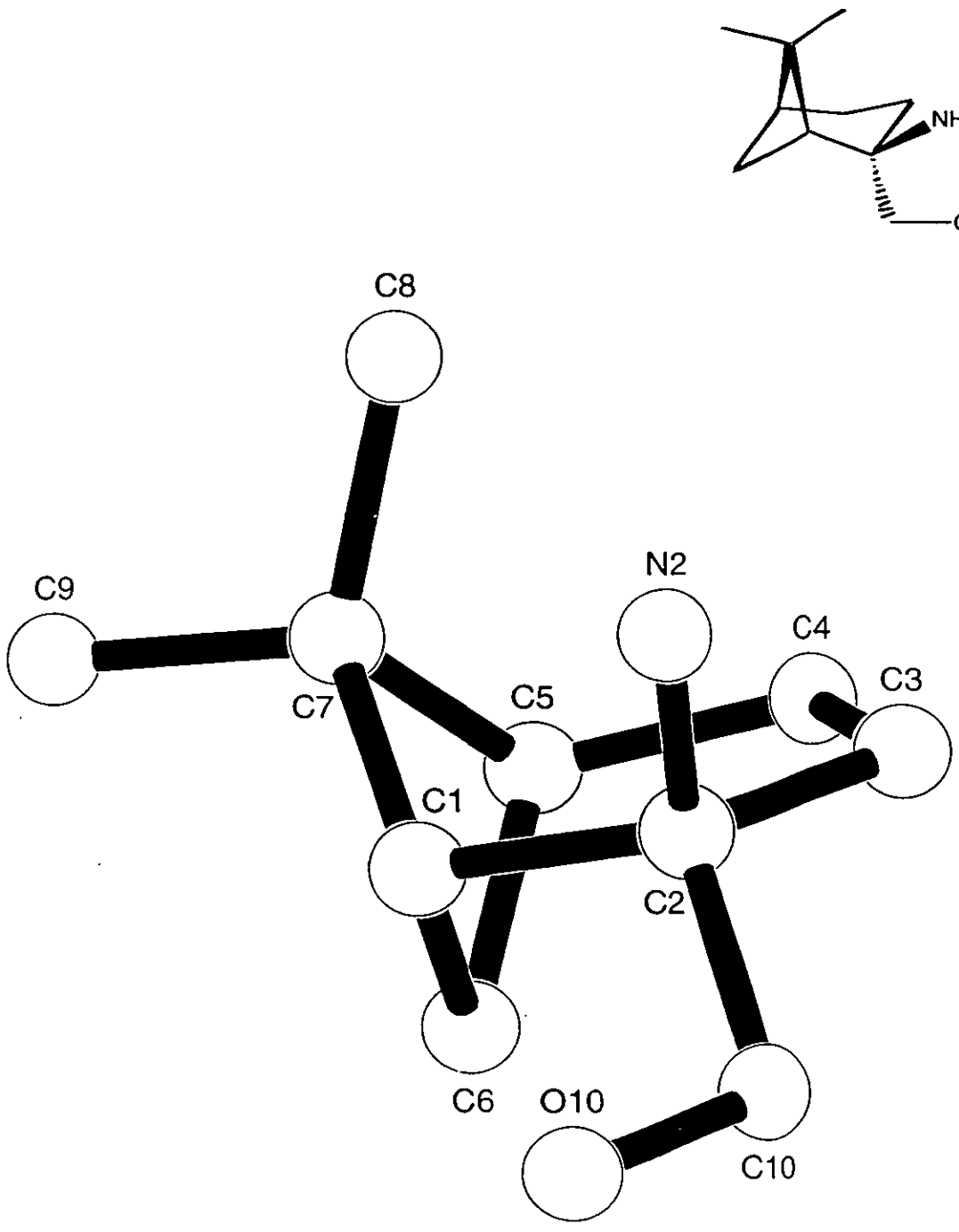


Scheme 76: Synthesis of the dihydroisoquinolinium salt derived from 2-amino-*trans*-myrtanol.

The new iminium salt was tested (5 mol%) in the catalytic asymmetric epoxidation under the usual conditions and was found to be one of the most active organic salts tested. In fact, it exhibited a clean reaction profile as well as one of the fastest conversions of 1-phenylcyclohex-1-ene to the corresponding epoxide (20 minutes), albeit with low enantioselectivity (27% ee).

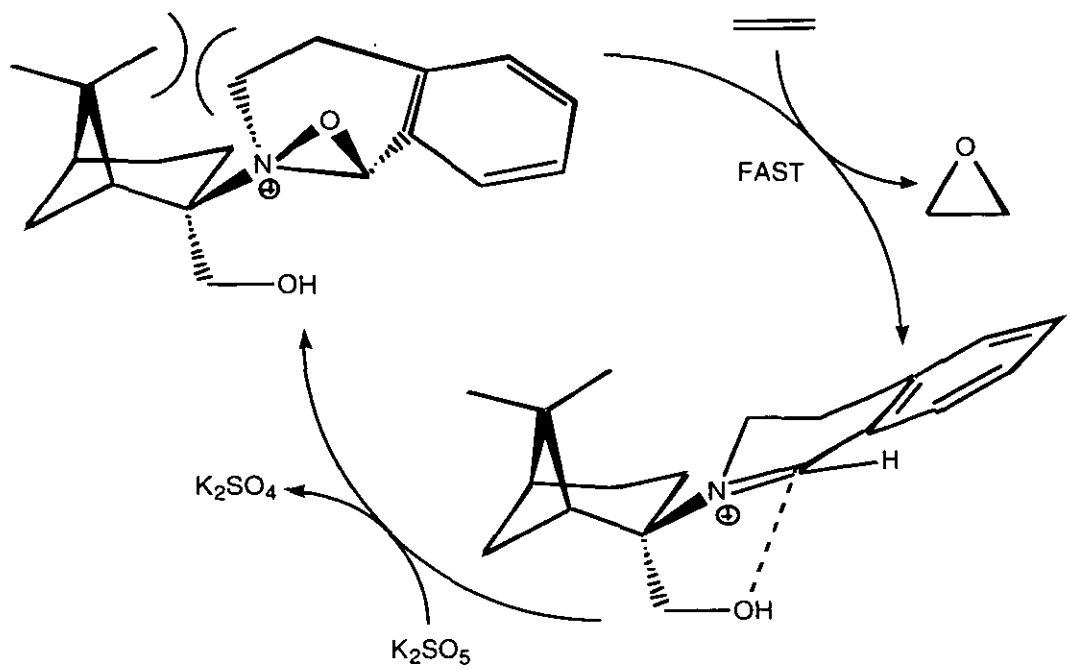


Scheme 77: Single crystal X-ray analysis of the oxazolidinone derived from 2-amino-*trans*-myrtanol. Interestingly this compound crystallises as its dimer due to hydrogen bonding.



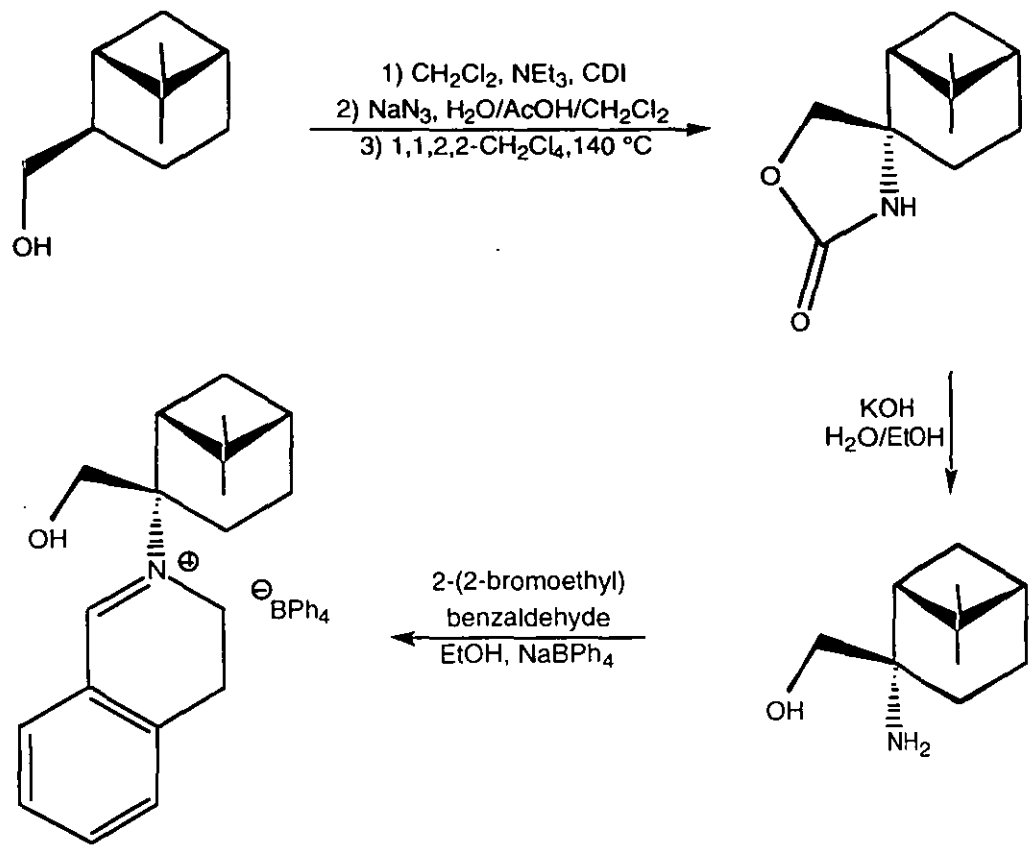
Scheme 78: Single crystal X-ray analysis of 2-amino-*trans*-myrtanol. This compound has not been reported previously.

As anticipated, oxazolidine formation from the primary alcohol is not a problem and we believe that the enhanced rate stems from steric acceleration due to the increased strain associated with the non-planar oxaziridinium salt which cannot be easily accomodated next to the dimethyl bridge. The result of this arrangement is an increased tendency to transfer the electrophilic oxygen even to poor nucleophiles, (alkenes) so that the structure can relax back to the original strain-free carbon-nitrogen double bond (Scheme 79). Such a high reactivity inevitably compromises the enantioselectivities observed.



Scheme 79: The enhanced reactivity of the dihydroisoquinolinium salt derived from 2-amino-*trans*-myrtanol may be attributable to steric acceleration.

Since pinane derivatives have been the most succesful among the terpenoid systems examined in imparting reasonable enantioselectivities,[41] examination of the substitution pattern across the bridged carbocycle may provide information for the optimum catalyst structure. Therefore the diastereoisomeric *cis* myrtanol was subjected to the same series of reactions in order to access the iminium salt with the pendant primary hydroxyl group, but with the geminal dimethyl bridge *trans* (*anti*) to the isoquinolinium moiety (Scheme 80).



Scheme 80: The nitrene insertion reaction is applied succesfully in the synthesis of the 2-amino-*cis*-myrtanol-derived dihydroisoquinolinium salt.

Employing the same synthetic protocol developed for the *trans*- isomer, the corresponding imidazole carbamate and azidoformate of *cis*-myrtanol were prepared in quantitative yields. The latter was subjected to solution pyrolysis in tetrachloroethane (140 °C), and the oxazolidinone was isolated in 50% yield (Scheme 80). The higher yield of the nitrene insertion reaction with the *cis*- derivative demonstrated the first difference in reactivity between the two diastereoisomers, and is satisfactorily explained on steric grounds. For the *trans*- isomer, the insertion step requires the electron-deficient nitrine intermediate to be situated between the geminal dimethyl bridge and the carbon-hydrogen bond which is to be cleaved. With such a high degree of order involved, the substrate/precursor is required to have low degrees of freedom (bond rotation and vibration in particular) in order for the specific geometry to be achieved. Therefore, substantially negative entropy of activation in the transition state is associated with the sterically crowded reaction site in the nitrene insertion reaction regarding the *trans*- isomer. In addition, this step

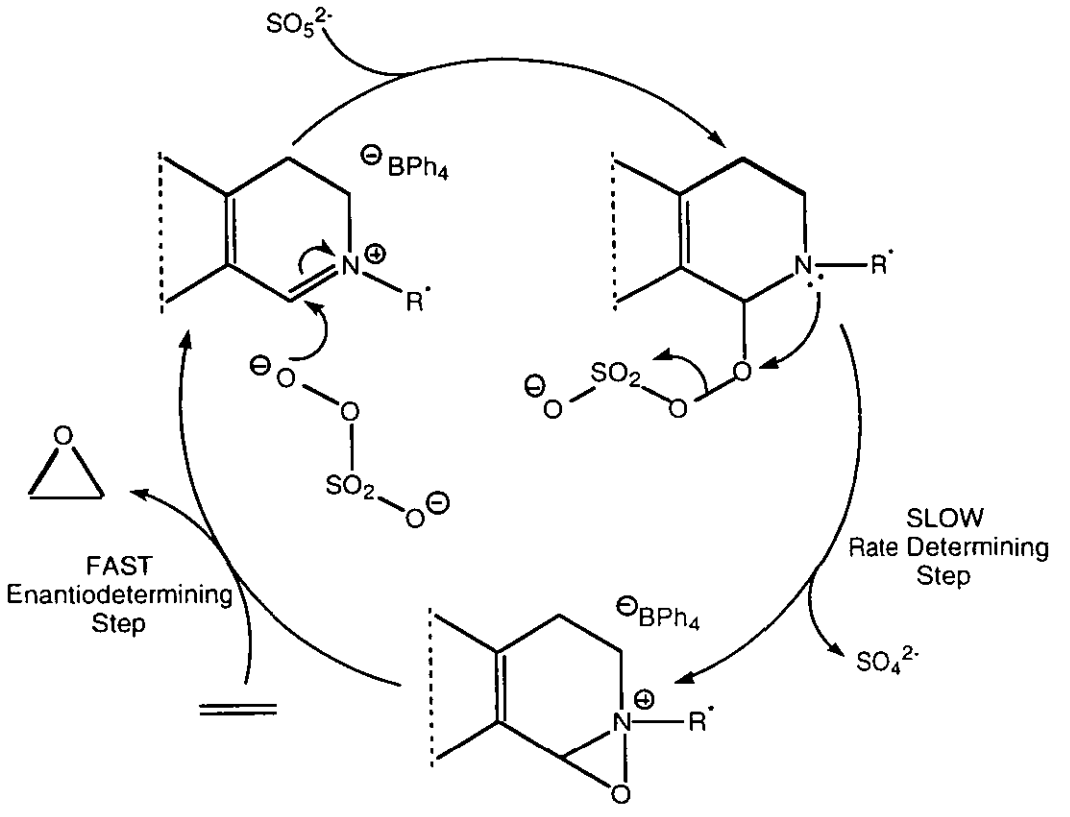
has to be performed at elevated temperatures in order for the nitrene to be generated. High temperatures increase the degrees of freedom in a given system (higher frequencies of bond rotation and vibration) hence the degree of disorder increases (more positive entropy). This is undesirable in the transition state of the nitrene insertion reaction of *trans*-myrtanol azidoformate, hence the low yield of the insertion product. In the case of the *cis*-isomer the carbon-hydrogen bond in question is not adjacent to the bulky group, and therefore the geometric requirements for the transition state are achieved with considerably less difficulty. Because less order is needed at the transition state, the reaction takes place more readily in the case of *cis*-myrtanol azidoformate than for the *trans*-isomer, hence greater yield of the corresponding oxazolidinone is obtained in the reaction time that the short-lived nitrene is present.

As in the previous cases of *endo*-camphanol and *trans*-myrtanol, the spiro oxazolidinone derived from *cis*-myrtanol is also formed exclusively with retention of configuration at the newly created stereogenic centre. Subsequent hydrolysis of the spirocyclic derivative furnished 2-amino-*cis*-myrtanol (Scheme 80) which afforded a novel and optically pure dihydroisoquinolinium salt when condensed with 2-(2-bromoethyl)benzaldehyde (Scheme 80). The yield for the latter reaction (33%) is greater than that obtained for the *trans*-diastereoisomer (22%), perhaps as a result of decreased steric hinderance in the vicinity of the amino group. In fact, low yields in this reaction are not uncommon when hindered primary amines such as 2-amino-*trans*-myrtanol are used as catalyst precursors (see 2.13).[41]

Interestingly, during the condensation between 2-amino-*cis*-myrtanol and 2-(2-bromoethyl)benzaldehyde the bromide salt precipitated out of the reaction mixture, an unusual event since this was observed on only one other occusion (norephedrine derivative). However, for comparison purposes, anion exchange was performed and the tetraphenylborate salt tested (5 mol%) in the catalytic process developed for the epoxidation of simple alkenes. Thus, 1-phenylcyclohex-1-ene was smoothly converted to the corresponding epoxide, but the enantioselectivity was poor (11% ee). 1-Phenyl-3,4-dihydronapthalene, *trans* stilbene and *trans*-α-methylstilbene all react considerably more slowly (up to 18 hours for the latter) than in the reaction catalysed by the iminium salt derived from 2-amino-*trans*-myrtanol. The enantioselectivities obtained with these three substrates were 14, 13 and 18% ee respectively. It is clear that the reaction profile of the process mediated by this catalyst is very different from that observed with the derivative from the *trans*-diastereoisomer, which afforded 1-phenylcyclohex-1-ene oxide in 67% yield after just 20 minutes and with greater ee. An important implication arises from these

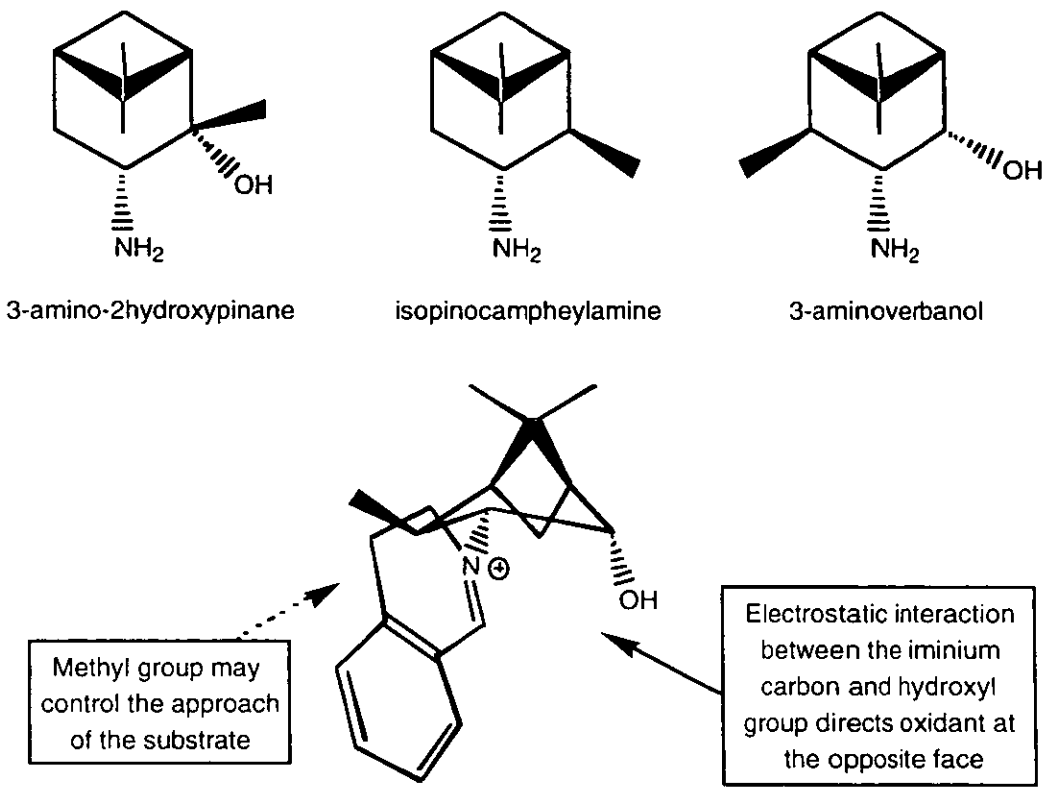
results: For this catalytic process, a slower reaction is not a pre-requisite of greater enantioselectivity as is the case with many other catalysed processes (e.g. Diels-Alder, palladium catalysed allylic substitution, Heck reaction).[147-149] This perhaps implies that the rate determining step (RDS) is not the enantiodeterming step during which the prochiral substrate is transformed into an optically active compound (Scheme 81). It is unlikely that the observed rate retardation stems from any tendency of the *cis*-myrtanol-derived catalyst to exist preferentially in the oxazolidine form, as this is unprecedented for catalysts with a pendant primary hydroxyl group and there are no significant steric interactions to alter this chemical behaviour.

It therefore appears that the rate determing step is the formation of the oxaziridinium moiety from the adduct initially formed from the generally faster reaction between the iminium functionality and Oxone™. This rationale is in accord with the mechanistic analysis carried out earlier (Scheme 81) (see 2.14.3).



Scheme 81: Slower reactions are not necessarily more enantioselective processes.

2.23 Amines from electrophilic nitrogen sources.



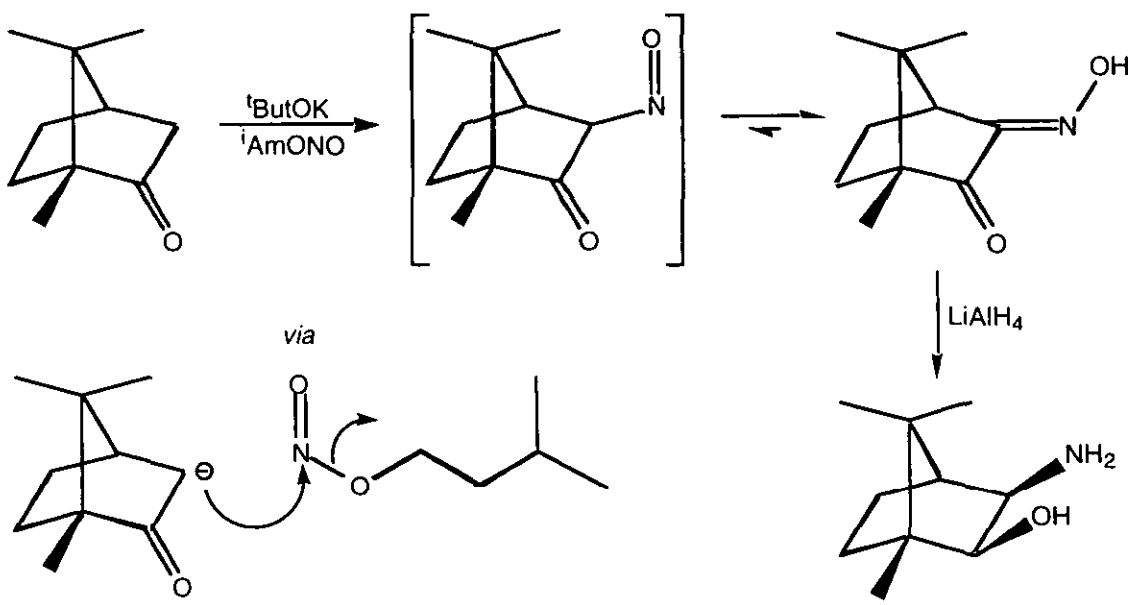
Scheme 82: 3-Aminoverbanol can serve both as probe for the optimum substitution pattern in pinane derivatives and as model for "flanked" amines as catalysts precursors.

The compound next targeted was *cis-endo*-3-aminoverbanol (Scheme 82) primarily due to its resemblance to isopinocampheylamine and *cis-endo*-2-hydroxy-3-aminopinane. Comparison of the results obtained from the corresponding dihydroisoquinolinium salts may lead to the optimum structure of the chiral residue on the amine component. Secondly, the aminoverbanol derivative offers a new system in terms of substitution pattern.

The amino group in this system is flanked by a hydroxyl group which can interact electrostatically with the iminium carbon, and a methyl group which may provide the steric hindrance required for enantioselective oxygen transfer. The overall effect is a pseudo-C2 symmetric system with the enantiotopic faces of the iminium salt electronically and sterically discriminated (Scheme 82).

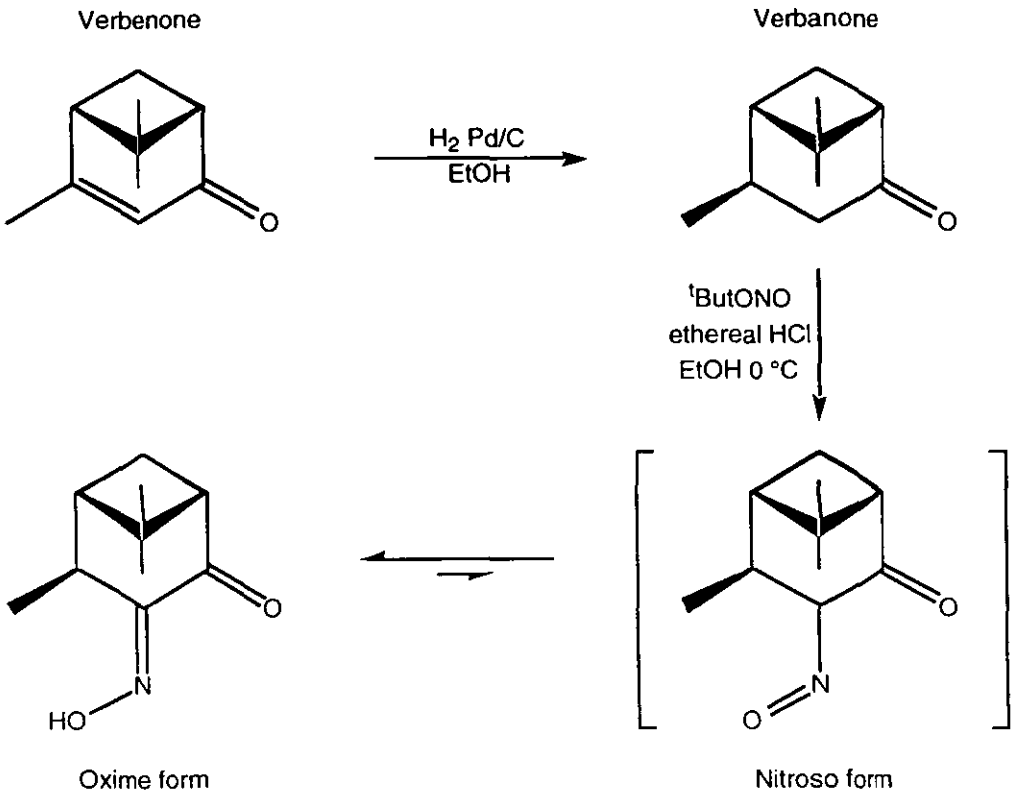
2.23.1 Amines from alkyl nitrites.

We thought that the desired amino alcohol could be accessed by amination of verbanone followed by reduction. Nitrites offer an attractive source of electrophilic nitrogen atom, and for this reason they have been used extensively in the synthesis of nitrogen containing molecules. For example the reaction between camphor-enolate and isoamyl nitrite furnishes the α-hydroxyimino-ketone (camphor quinone monooxime),[133] which can be reduced with lithium aluminium hydride to the corresponding 1,2-amino alcohol (Scheme 83).[129]



Scheme 83: Synthesis of *cis-exo*-2-amino-3-borneol by electrophilic nitrosation.

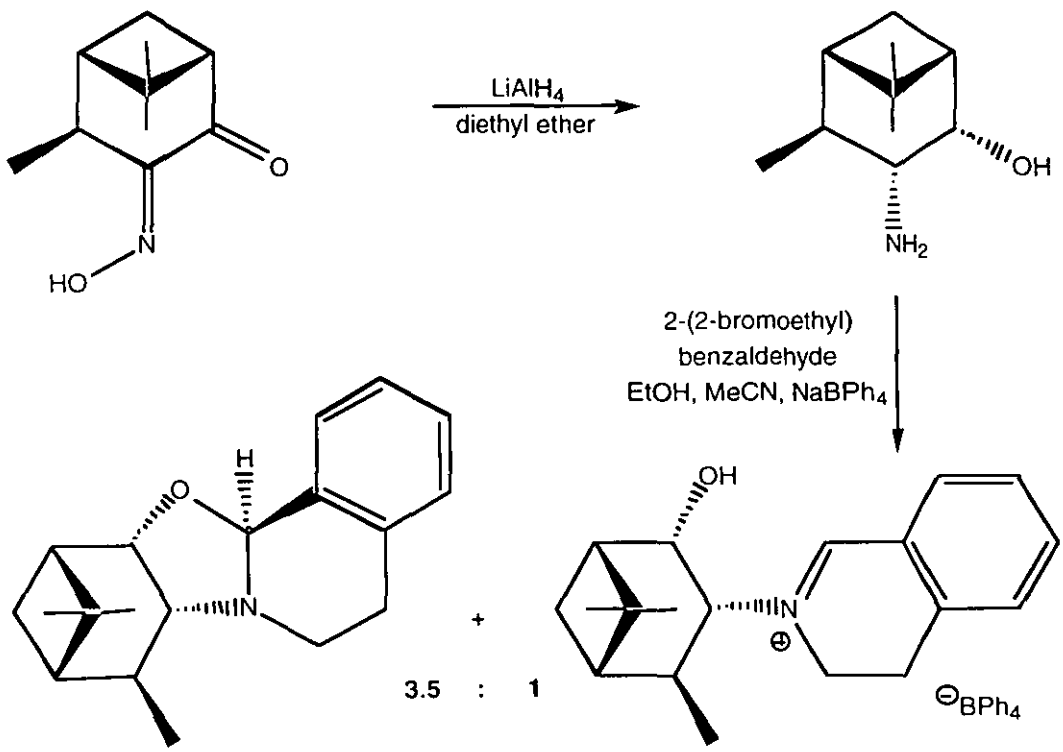
Verbanone was synthesised in one step from verbenone by palladium(0) catalysed hydrogenation in 84% yield (Scheme 84). It has been documented in the chemical literature that the hydrogenation of verbenone and related systems is stereospecific.[150,151] However, the starting material used, (–)-(1*S*)-verbenone, was only enantioenriched, (approximately 50% ee according to manufacturer). The enantiomerically pure form is not available, although several approaches towards the synthesis of this useful chiral building block have been described.[151-154] Verbanone of 91% ee has been reported to exhibit $[\alpha]^{20}_{D}$ –51.00 (c= 1.00, in $CHCl_3$),[151] while that obtained by us from hydrogenation of the available verbenone, exhibited $[\alpha]^{20}_{D}$ –26.40 (c= 1.00, in $CHCl_3$), suggesting an ee of approximately 47%.



Scheme 84: Synthesis of α-hydroxyiminoverbanone by nitrosation under acidic conditions.

The α-oximation of carbonyl compounds has been reported to be promoted by both bases and acids, where the nitrogen atom of the nitrite moiety is attacked by the enolate or the enol form respectively.[155-160] Verbanone was first treated with sodium methoxide in methanol in the presence of isoamyl nitrite, but no reaction occurred after 24 hours. Similarly, treatment of verbanone with potassium tertiary butoxide in THF in the presence of tertiary butyl nitrite also failed to produce the α-hydroxyimino ketone,[158] and thus, acid-mediated oximation was attempted next.[160] When dry ethereal hydrogen chloride was added to a solution of verbanone and tertiary butyl nitrite in ethanol, the reaction mixture turned blue. This is indicative of the intermediate nitroso compound (Scheme 84) which is formed by the reaction between the enol form of the ketone and tertiary butyl nitrite, with concomitant elimination of tertiary butanol. The nitroso species tautomerises under the acidic conditions to the thermodynamically more stable oxime form (Scheme 84). We found that for best yields of the oximated ketone, the hydrogen chloride solution should be added slowly so that the blue colour does not become intense. The

reaction is self-indicating, as a yellow solution is obtained when all of the ketone or nitrite has reacted. After work up, 3-hydroxyiminoverbanone (Scheme 84) is obtained as a brown oil which solidifies slowly into white crystals when taken up in ether and left to stand for several days.[161] Despite the colour change between the two states, (possibly *syn* and *anti* geometrical isomers regarding the oxime functionality), the crude material was examined by NMR spectroscopy and was shown to be reasonably pure. It was therefore used in the next step without further purification.



Scheme 85: Synthesis of 3-aminoverbanol and the related dihydroisoquinolinium salt.

Treatment of 3-hydroxyiminoverbanone with excess of lithium aluminium hydride in diethyl ether under reflux afforded the desired *cis-endo*-3-aminoverbanol (Scheme 85), part of which was purified as its hydrochloride salt.[161] No signs of formation of alternative diastereoisomers were observed. The crude amino alcohol was reacted with 2-(2-bromoethyl)benzaldehyde under the usual conditions to furnish a mixture of the expected dihydroisoquinolinium salt and one of the corresponding oxazolidines in 1:3.5 ratio in favour of the latter (Scheme 85). Exposure to trifluoroacetic acid failed to shift the equilibrium towards the side of the

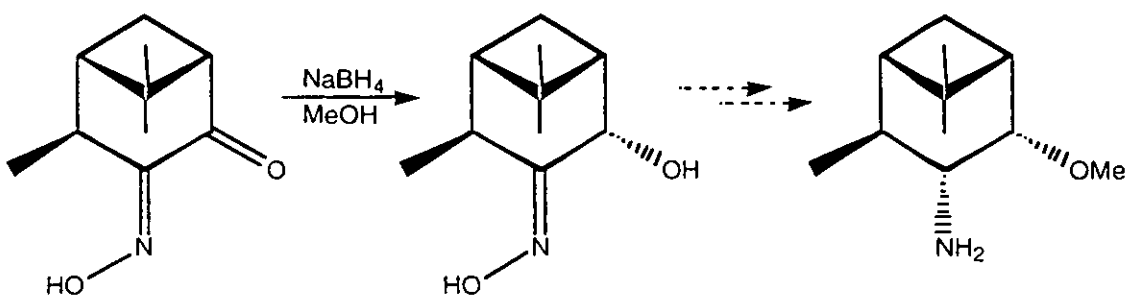
organic salt. The crude mixture was therefore subjected to the usual oxidative conditions (10 mol% with respect to the salt), with sodium carbonate and Oxone™ in acetonitrile/water (1:1), in the presence of 1-phenylcyclohex-1-ene, at 0 °C. The epoxidation of the model substrate proved unusually slow with this system and, unlike other cases, did not proceed to completion after 4 hours. From this reaction, 1-phenylcyclohex-1-ene oxide was obtained in 42% yield and 34% ee.

This is an intriguing result since the iminium salt used as the mediator for the oxygen transfer was only of 47-50% ee. In order to confirm this, the aminoalcohol was subjected to chiral HPLC analysis and the suspected value of 45-48% enantiomeric excess was confirmed. If there was a linear relationship between the enantiopurity of the catalyst used in the asymmetric oxygen transfer reaction and the enantiomeric excess of the epoxide obtained, this would suggest that a catalyst prepared from enantiomerically pure *cis-endo*-2-aminoverbanol would promote the epoxidation of 1-phenylcyclohex-1-ene with 71-76% ee. Enantiomeric excesses of this magnitude prove that the approach used towards the design of such catalysts was along the correct lines, and that a reasonable understanding of this complex reaction has been achieved. The above statement could be proved by preparing the catalyst from enantiomerically pure verbenone which in turn can be accessed from pinene.[152-154] The resumption of such a lengthy synthetic protocol was, however, discouraged by the moderate yield of 1-phenylcyclohex-1-ene oxide. In addition, when the dihydroisoquinolinium salt derived from 3-aminoverbanol was used to catalyse the epoxidation of 1-phenyl-3,4-dihydronaphthalene, no epoxide formation was observed after 24 hours. We believe that the effectiveness of this catalyst is compromised due to favourable formation of the corresponding oxazolidine(s), due to the rigidity of the pinane skeleton. As with the regioisomeric 2-hydroxy-3-aminopinane derivative, preference for the ring closed, neutral and inactive form is not only determined by the NMR spectrum of the crude product but is also reflected by the poor reaction profiles in the catalytic epoxidation process (see 2.20.1 and 2.21.2)

The obvious solution to this problem was to replace the catalyst precursor with 3-aminoverbanol methyl ether (previously unreported, Scheme 86), because such systems cannot form the inactive oxazolidine. Although oxygen methylation of primary aminoalcohols has been described by Meyers,[163-165] the method lacks generality and appropriate amine protection/deprotection steps are normally necessary.[165]

Chemoselective reduction of 3-hydroxyiminoverbanone to 3-hydroxyiminoverbanol (Scheme 86), followed by methylation and reduction of the

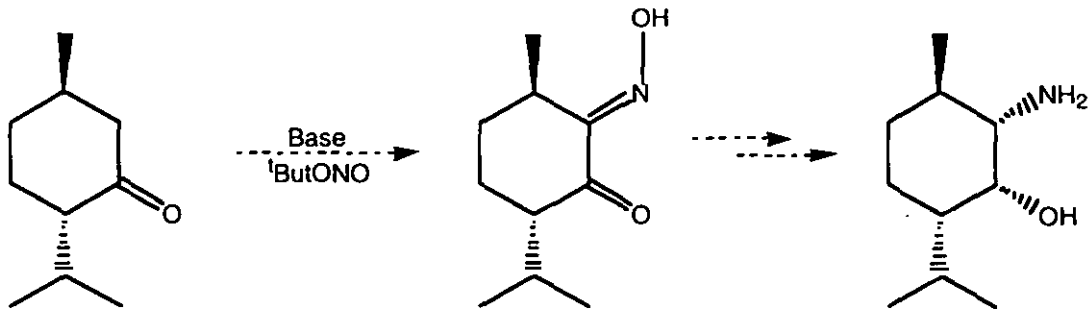
oxime, offered an alternative synthetic sequence. This method avoids concomitant methylation at nitrogen, while alkylation at both alcohol and oxime oxygen atoms, should not prove problematic because the latter moiety can also be reduced to the primary amine. The selective reduction of the keto group in the presence of the oxime was achieved with the use of sodium borohydride in methanol, and 3-hydroxyiminoverbanol was isolated in 61% yield without the use of column chromatography (Scheme 86).



Scheme 86: Chemo- and stereoselective reduction of 3-hydroxyiminoverbanone.

Disappointingly, and for reasons still unclear, treatment of the α-hydroxy-oxime with sodium or potassium hydride and methyl iodide in dry THF, failed to produce methyl ether or the methylated oxime. Instead, a complicated and unidentifiable mixture of products was obtained under a variety of conditions. Further efforts to access this compound were replaced by the design of similar systems which could be accessed by shorter synthetic sequences.

Having established that reasonable enantioselectivities are imparted when the isoquinolinium nitrogen is flanked by a hydroxyl and an alkyl group, further catalyst design was focused on similarly substituted systems. Menthone offered an attractive chiral building block due to the low cost, the ring structure, the alkyl substituents and the carbonyl moiety which was envisaged as a latent hydroxyl group. Electrophilic amination of the kinetic enolate of menthone, followed by reduction of the keto group, should furnish the appropriately substituted chiral amino alcohol. Because of the flexible cyclohexane sub-structure, it was expected that oxazolidine formation would not predominate as it is more difficult to achieve the appropriate transition state in systems with more degrees of freedom.



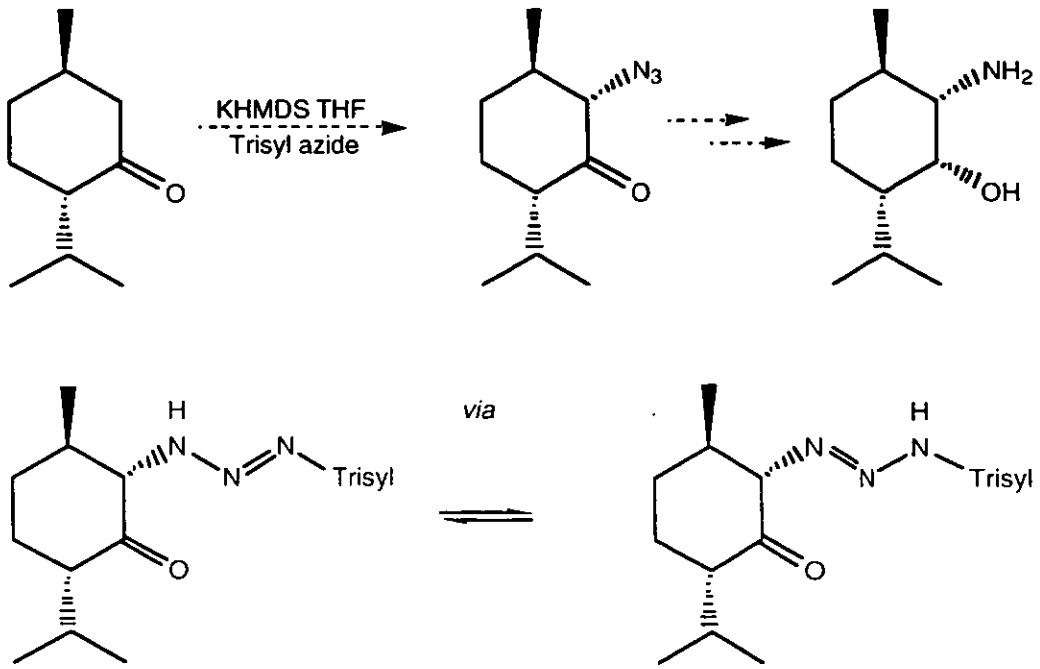
Scheme 87: First attempt towards the synthesis of 2-aminoneomenthol.

In order to achieve nitrogen incorporation specifically at the secondary carbon adjacent to the carbonyl group of menthone, the kinetic enolate of the chiral ketone was generated. Initially, oximation of menthone was attempted by treating the ketone with potassium tertiary butoxide and tertiary butyl nitrite in THF or tertiary butanol (Scheme 87),[158] but no reaction took place. The acid mediated reaction which was used in the case of verbanone, was not employed because both the thermodynamic and kinetic enol tautomers of menthone are generated under such conditions. Consequently, epimerisation at the carbon atom with the isopropyl substituent would almost certainly take place.

2.23.2 Amines from trisyl azide.

An alternative aminating agent is 2,4,6-triisopropylbenzene sulfonyl azide, commonly known as trisyl azide.[166] This azide transfer reagent was developed by Evans, who demonstrated that the terminal nitrogen is predominately attacked by potassium enolates, to furnish initially the carbonyl compound with the triazasulfonyl moiety attached to the α-carbon (Scheme 88). Upon heating or prolonged stirring, the sulphenate moiety is eliminated and the afforded product is the corresponding azide (Scheme 88).[166] The azide group transfer is expected to be stereoselective in our case due to the desire of the newly introduced substituent to occupy an equatorial position, across the menthone ring (substrate contolled).[167-170]

Following Evans' work, menthone was treated with potassium bis(trimethylsilyl)amide at –78 °C, followed by trisyl azide (Scheme 88). Almost complete consumption of the starting chiral ketone and the aminating agent was observed by TLC. After work up, the crude product was subjected to column chromatography and the major component of the reaction mixture was isolated.



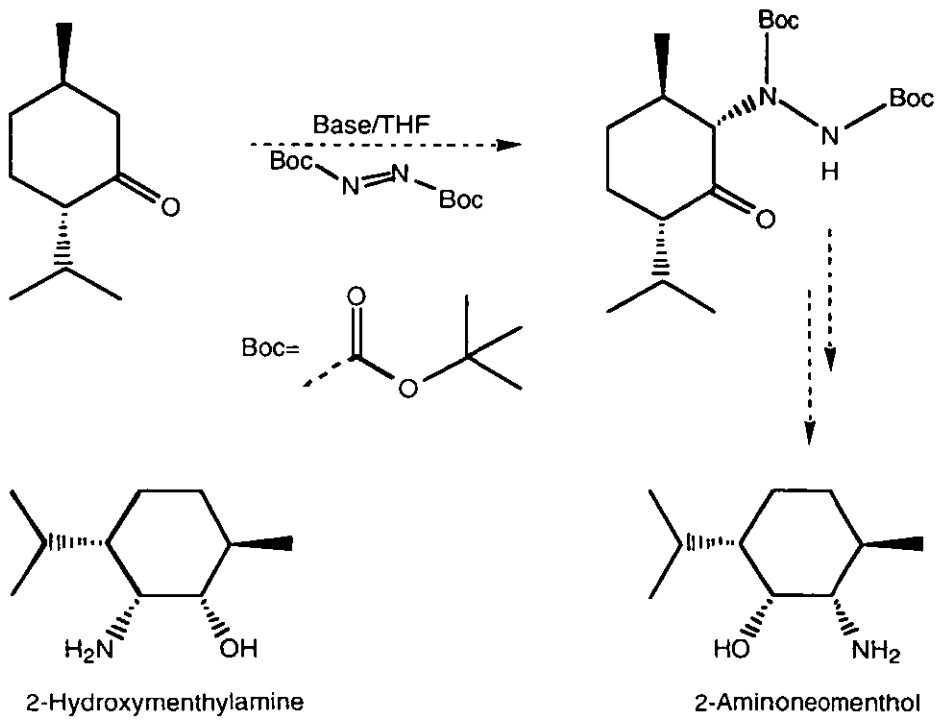
Scheme 88: Second attempt towards the synthesis of 2-aminoneomenthol.

However, the IR and NMR spectra did not allow unambiguous identification of the compound as the α-azidomenthone since aromatic residues were observed. The reaction was repeated with rigorously dried THF without effect on the reaction outcome. It is possible that in the case of menthone, the initial 1:1 adduct between the enolate and trisyl azide is not as labile as in the systems examined by Evans.[166]

2.23.3 Amines from ditertiary butyl azodicarboxylate.

The last source of electrophilic nitrogen tested was ditertiary butyl azodicarboxylate which has also been used by Evans for the preparation of amino acids.[171] This reagent behaves as a Michael acceptor when treated with carbon nucleophiles, by virtue of the electron depleted nitrogen-nitrogen double bond.[172,173] The resulting species is usually the substituted hydrazine with both of the nitrogen atoms protected as the tertiary butyloxycarbamates designated as Boc groups in scheme 89. Subsequent cleavage of the protecting groups with trifluoroacetic acid, followed by hydrogenolysis of the nitrogen-nitrogen bond,[171] is expected to furnish the desired α-aminomenthone (Scheme 89); the precursor to 2-aminoneomenthol (Scheme 89). Menthone was treated with ditertiary butyl azodicarboxylate after deprotonation with lithium diisopropylamide in THF at –78 °C, but a complex

mixture of products was obtained. The reaction was repeated with lithium and potassium bis(trimethylsilyl)amides, but column chromatography of the crude residues failed to provide the desired compound.

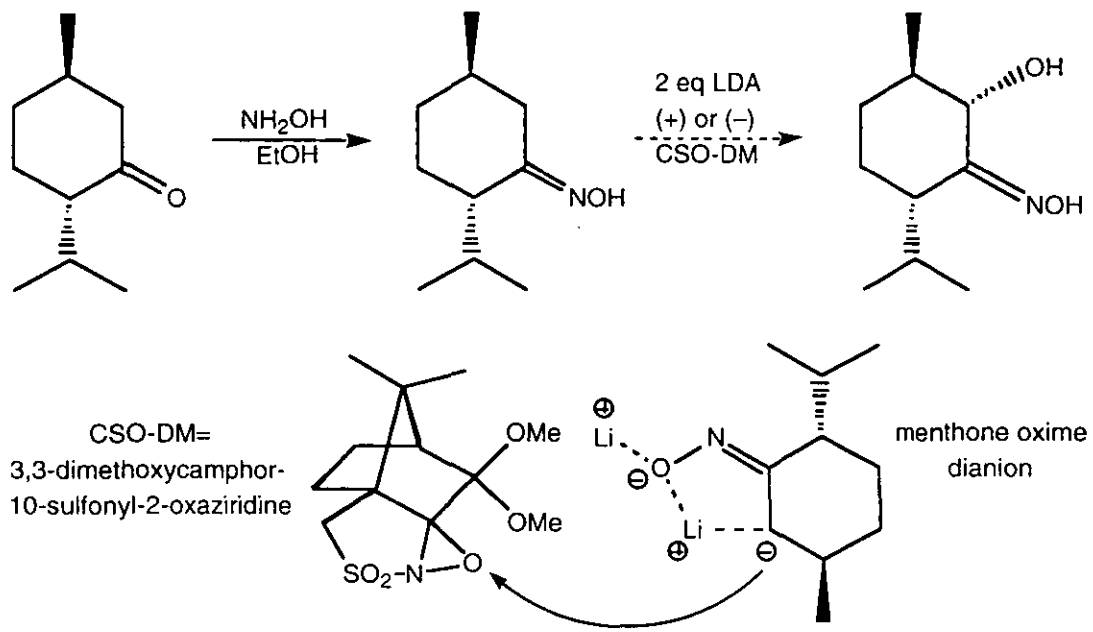


Scheme 89: Third attempt towards the synthesis of 2-aminoneomenthol.

In comparison to 2-aminoneomenthol, 2-hydroxymenthylamine (Scheme 89) has the positions of the amino and hydroxyl groups interchanged, but it also belongs to the series of catalyst precursors with the feature of the "flanked" amino group. Therefore the synthesis of this novel aminoalcohol was attempted next.

Since Davis has shown that simple sulfonyl oxaziridines can transfer the electrophilic oxygen to carbon nucleophiles such as enolates,[174,175] it was thought that α-hydroxy menthone could be accessed by this methodology. The carbonyl group of the chiral precursor can be easily converted to the oxime, which upon reduction should afford 2-hydroxymenthylamine. Discouraged by the performance of menthone enolate with various electrophilic nitrogen reagents, it was decided that the electrophilic oxaziridine should be treated with a much more reactive menthone enolate equivalent. Thus menthone was converted to the oxime which was treated with 2 equivalents of LDA in THF, at -78 °C to generate the dianion. The much more reactive dianion should be primarily oxygenated at the carbon

atom in the presence of 3,3-dimethoxycamphor-10-sulfonyl-2-oxaziridine. Several attempts to synthesise α-hydroxy menthone oxime using this route were unsuccessful, but it was possible to reisolate both chiral starting materials by column chromatography. In order to investigate whether there was a match or mismatch in the interaction of the two chiral components, both enantiomers of 3,3-dimethoxycamphor-10-sulfonyl-2-oxaziridine were tested with (–)-menthone oxime dianion (Scheme 90). Unfortunately though, in both cases, the oxygenated compound could not be observed or isolated after work up.



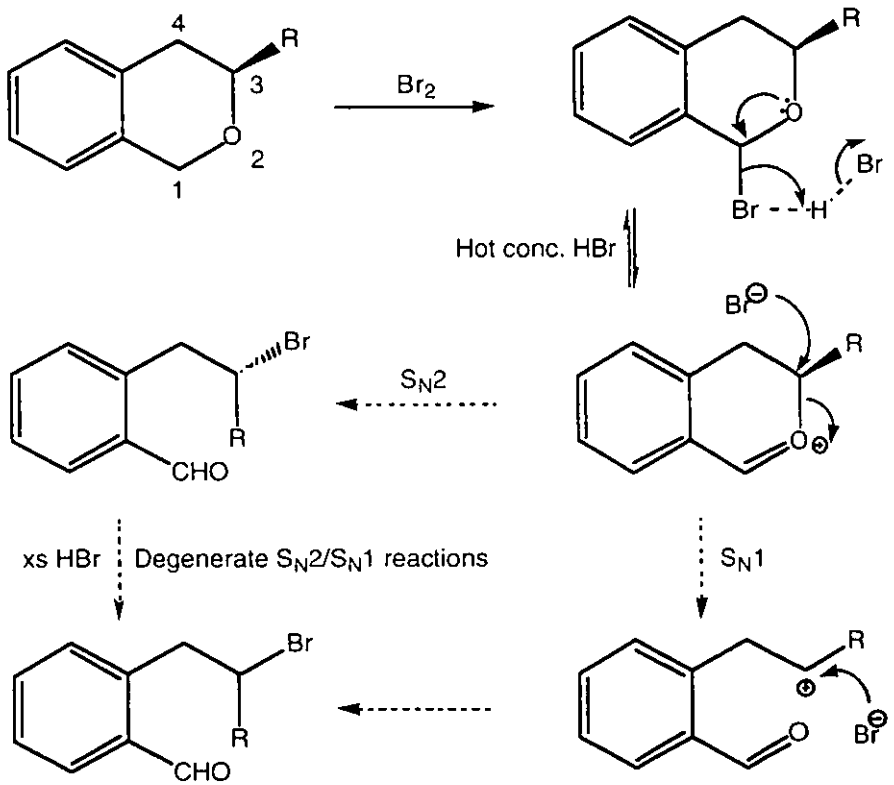
Scheme 90: Attempted synthesis of α-hydroxymenthone oxime.

2.24 The isochroman approach.

Having examined the effect of the chiral residue on the the amine and aminoalcohol precursors with regard to the enantioselectivity of the catalytic process, further research was focused on the 2-(2-bromoethyl)benzaldehyde component required for the construction of the dihydroisoquinolinium salt. We envisaged that the carbon chain which links the nitrogen atom of the iminium functionality with the aryl group could also bear stereogenic centres. These additional stereogenic centres may be stereochemically matched with those present on the chiral amine or aminoalcohol component, possibly resulting in a much more selective catalyst.

2.24.1 Design and analysis of synthetic aspects.

The design and synthesis of such chiral precursors, could, in principle, be based on the route employed previously for the construction of the unsubstituted 2-(2-bromoethyl)benzaldehyde. However, more careful analysis of the reaction conditions, mechanisms, and nature of the transformations involved, reveals that loss of stereochemistry may take place at some stages.

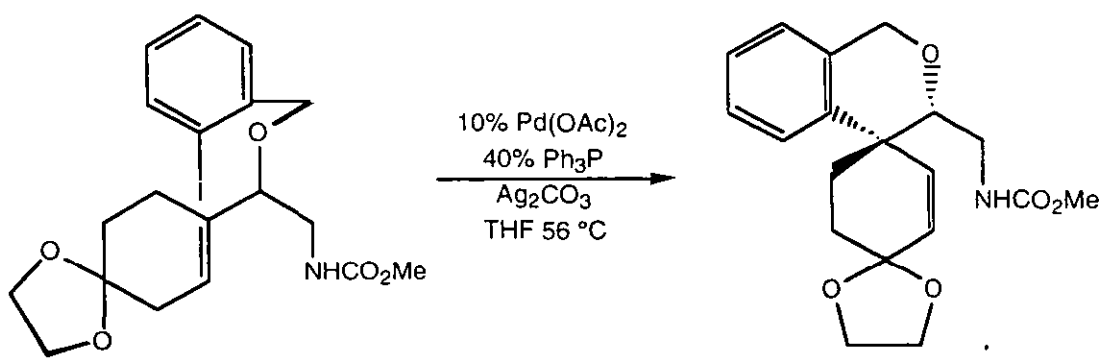


Scheme 91: 3-Substituted isochromans may not be suitable catalyst precursors.

For example, the ring opening of 1-bromoisochromanin refluxing concentrated hydrobromic acid, probably involves an S_N2 type displacement at the 3 position of the oxycarbenium species.

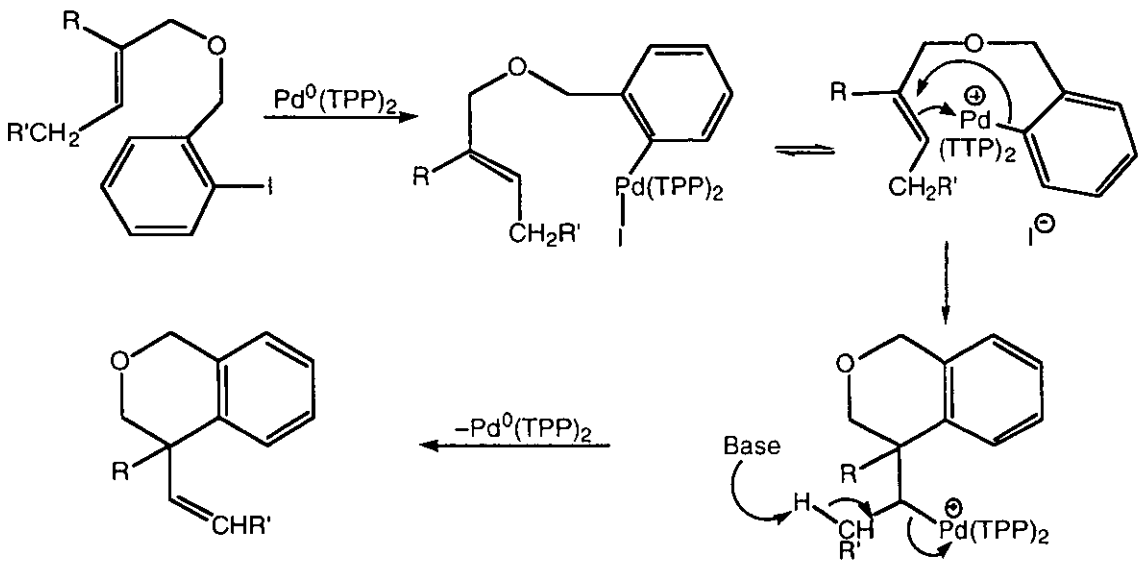
Branching at that position in order to introduce a chiral centre would result in a secondary carbon atom being involved in the ring opening process. S_N2 reactions at secondary carbon atoms are not only slower, but under strongly acidic conditions the S_N1 pathway starts to compete (Scheme 91). This results in loss of the stereochemistry at that position of the parent molecule. In addition, since bromide anions would be present in large excess, degenerate substitutions at the bromoalkyl moiety may also result in racemisation (Scheme 91). Alternative methods of oxidation/ring opening of isochromans have been considered,[176] but the same complications may arise. These render 3-substituted isochromans unsuitable precursors to enantiopure dihydroisoquinolinium salts, at least, with this methodology.

However, introduction of a stereogenic centre at the 4 position of isochroman is not expected to be affected by the reaction conditions associated with the bromination and subsequent ring opening. Isochromans are most commonly accessed by condensation of 2-phenethylalcohols with formaldehyde under acidic conditions.[177,178] In turn, for the chiral, 4-substituted heterocycle an enantiomerically pure 2-substituted-2-phenethyl alcohol is required. The latter can be synthesised by reduction of arylacetic acid derivatives.[179] Alternatively, it was thought that substituted isochromans may be accessed by 2-iodobenzyl ethers of chiral allylic alcohols by employing the Heck reaction. Indeed, this approach has been documented in the literature by Overman (Scheme 92),[180,181] Denmark,[182] and others in the synthesis of natural products.[183,184]



Scheme 92: The isochroman accessed by this Heck reaction was the key intermediate in Overman's synthesis of 6α-epipretazettine.

In order to avoid substituents at C3, a primary allylic alcohol was considered as the best precursor to a 4-substituted isochroman (Scheme 93). In addition, if the alcohol precursor is chiral there will probably be a good level of stereospecificity in the aryl group insertion step (substrate controlled). The ideal chiral primary allylic alcohol would be that which favours the exclusive formation of one diastereoisomer.



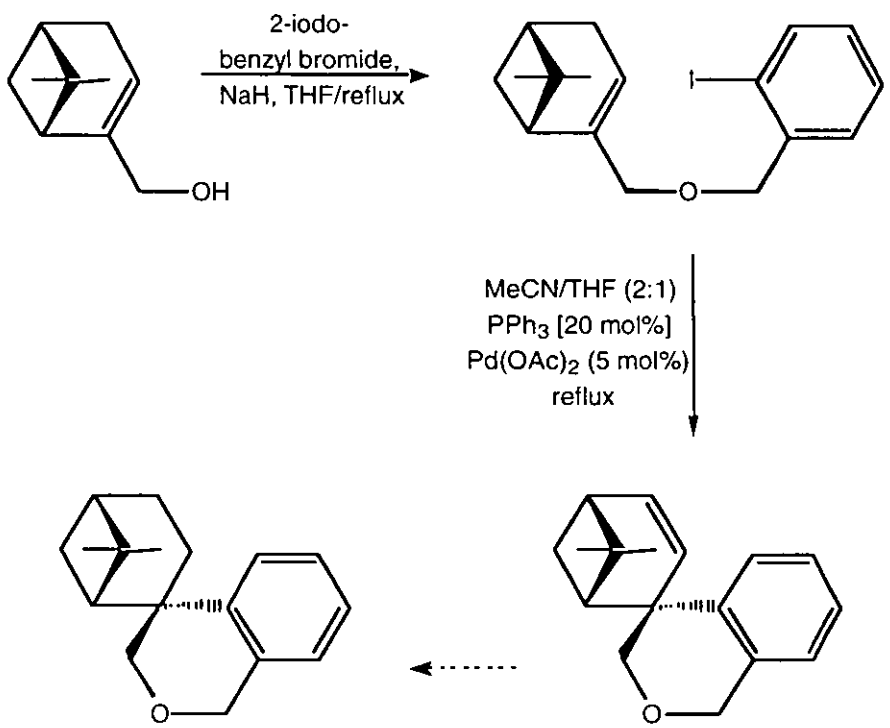
Scheme 93: Use of the Heck reaction in the construction of 4-substituted isochromans.

2.24.2 Synthesis of chiral isochromans.

In line with this methodology, myrtenol was chosen as a promising precursor to a pinene derived spiro-isochroman. Myrtenol was treated with sodium hydride and 2-iodobenzyl bromide in refluxing THF and was thus successfully converted into the corresponding iodobenzyl ether in excellent yield (Scheme 94). The palladium(0)-triphenyl phosphine (TTP) complex required for the Heck coupling was pre-formed by action of triphenyl phosphine on palladium(II) acetate in THF and the desired complex was obtained as a bright yellow solid suspended in the solvent. Overman and others have reported that silver salts promote the Heck reaction by means of removing the iodide anion from the coordination sphere of the palladium complex, and thus creating coordination sites for the substrate.[180,182] However, when the 2-iodobenzyl ether of the chiral allylic alcohol was introduced in the reaction mixture together with silver carbonate as the base, and brought to reflux, no reaction was observed by TLC analysis even after 24 hours. The difficulty of removing the silver residues in order to reisolate the starting material,

discouraged the use of silver salts. The reaction was repeated in THF with the same stoicheiometry of substrate/catalyst precursor/TPP (10:1:4), and triethylamine as the base (frequently used in Heck reactions), but no cyclised product was observed by TLC analysis.

The choice of solvent is considered to be one of the most important parameters for succesful Heck reactions.[182] Therefore the reaction was repeated in acetonitrile and although the palladium complex was successfully prepared, the iodo-alkene (viscous oil), was immiscible with acetonitrile. Therefore a co-solvent was necessary to introduce the substrate in the reaction mixture. Both THF and benzene were tested as co-solvents in the reaction and appeared beneficial for the formation of the desired spiro-isochroman (Scheme 94). The yield of the latter reaction after reflux for 24 hours, ranged between 54 and 63%, but this was not always reproducible.



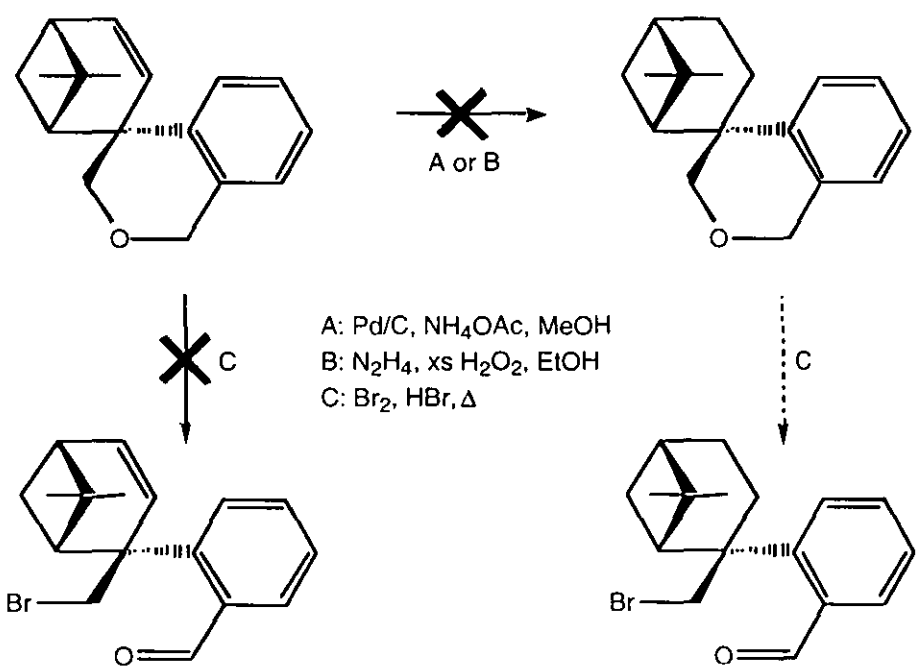
Scheme 94: Attempted synthesis of a chiral isochroman derived from (–)-myrtenol.

On the positive side, the reaction had produced only one diastereoisomeric isochroman as expected from the insertion of the aryl ring in the double bond from the face opposite to the geminal dimethyl group. Interestingly, and for reasons yet unclear, the spiro-isochroman gradually decomposes (hours), when left exposed to

air, but samples stored under nitrogen were suitable for use even after days of storage.

Since both the benzylic position and the double bond on the pinene skeleton are prone to bromination it was imperative to attempt the removal of the latter functionality. This proved a difficult task, because simple palladium catalysed hydrogenation could also lead to the cleavage of the benzylic ether.

Sajiki has reported that palladium-catalysed hydrogenation of unsaturated benzylic ethers in the presence of ammonium salts, such as formates or acetates, provided the saturated products with negligible signs of cleavage of the benzylic moiety.[185] This method seemed ideal for the construction of the saturated spiro-isochroman and was therefore attempted. Unfortunately though, when the substrate was subjected to palladium catalysed hydrogenation in the presence of either ammonium acetate or formate, no reaction was observed by TLC analysis. This was confirmed by NMR spectroscopy and may be due to increased steric hindrance in the vicinity of the double bond (Scheme 95).



Scheme 95: Attempted synthesis of a chiral 2-(2-bromoethyl)benzaldehyde.

The second attempt to hydrogenate the double bond selectively over the benzyl ether, involved the use of the reactive intermediate diimide since it has been shown to be extremely chemoselective towards carbon-carbon double bonds. This

may be prepared *in situ* in a number of ways,[186-189] but it was the method of Paquette which was ultimately used due to its simplicity.[186] Thus, exposure of the substate to a large excess of hydrazine hydrate and hydrogen peroxide in refluxing methanol, produced a bright yellow reaction mixture, indicative of the presence of diimide, (from oxidation of hydrazine). Despite that, no reduction of the double bond was observed by NMR spectroscopy on the isolated material (Scheme 95).

A third approach was then considered in order to produce a suitable saturated derivative for the subsequent bromination step. Hydroboration-oxidation of double bonds is a particularly reliable reaction, and, considering the steric demand in the vicinity of the unsaturated moiety, it should also prove regioselective. Treatment of the unsaturated spiro-isochroman with borane-dimethyl sulfide complex in hexane, followed by exposure to alkaline hydrogen peroxide, resulted in a particularly complex reaction mixture. Column chromatography afforded a small amount of a compound but the NMR spectrum did not allow unambigous assignment of the signals to the expected alcohol.

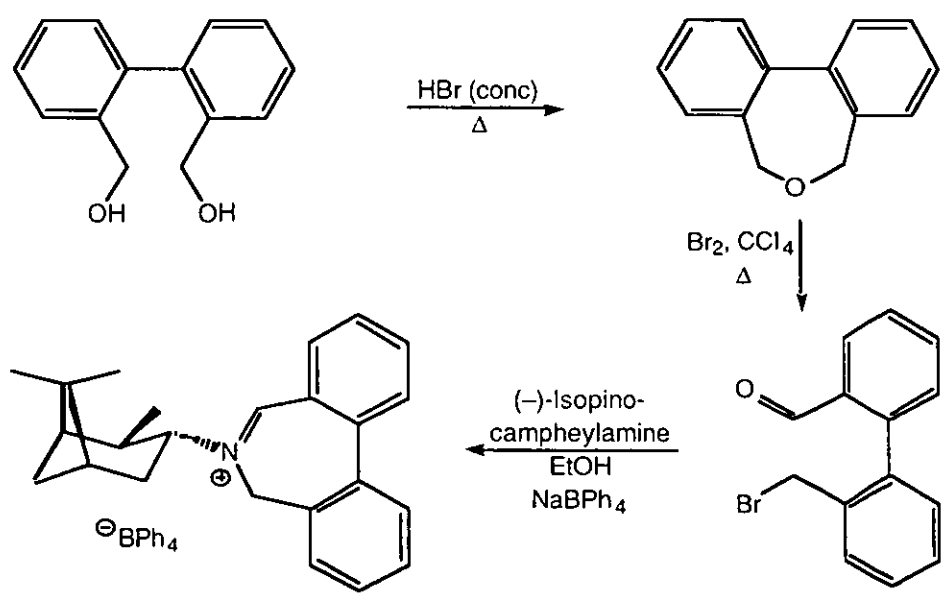
In a final (and more desperate), attempt, it was hoped that the unsaturated isochroman would react faster with bromine at the benzylic position rather than the double bond since the latter proved so unreactive in the previous cases. Thus, exposure of the substrate to a stoicheiometric amount of bromine in refluxing carbon tetrachloride, resulted in complete decolourisation of the bromine solution in less than an hour. The reaction was monitored by TLC which revealed incomplete reaction and a slight excess of bromine was required in order to observe complete consumption of the starting material. Exposure to hot, concentrated hydrobromic acid followed by the usual work up, afforded a foamy solid which was examined by IR and NMR spectroscopy. Dissapointingly, no aldehyde signals were observed as would have been expected had the bromination and ring opening of the isochroman occurred (Scheme 95). Instead, the NMR spectrum suggested that a complicated mixture of products had been formed in the bromination reaction of the unsaturated isochroman. This result rendered imperative the reduction of the unsaturated moiety in the pinene derived spiro-isochroman prior to bromination of the isochroman moiety, in order to access the chiral catalyst precursor.

The problematic synthesis of the saturated isochroman coupled with the capricious nature of the Heck reaction, compromised the effectiveness of this approach and alternative isochroman equivalents were sought.

2.25 Seven membered rings.

In principle, all cyclic benzylic ethers could act as precursors to bromoalkylbenzaldehydes, if subjected to the bromination/ring opening sequence, provided that functional groups that are susceptible to these reactions are absent. Dibenzoxepane (or 5,7-dihydrobenzoxepine), is a cyclic benzylic ether which provides an interesting candidate for this reaction sequence. This compound was synthesised from 2,2'-biphenyldimethanol according to a literature procedure,[190] by acid mediated dehydration/ring closure.[191-193] It was later found that the ether formation could have been effected by a Mitsunobu reaction, which has been recently employed for the synthesis of isochromans from the appropriate diols.[179]

Thus, exposure of 2,2'-biphenyldimethanol to hot, concentrated hydrobromic acid, afforded the cyclic ether as a white solid in 88% yield (Scheme 96). Subsequent treatment of this product with molecular bromine in carbon tetrachloride, followed by hot concentrated hydrobromic acid furnished the desired (2-bromomethyl-2'-carboxaldehyde)biphenyl as an extremely lachrymatory solid, in 59% yield (Scheme 96). It later proved that the final acid treatment was unnecessary since the bromooxepane initially formed, is not as stable as the six membered analogue, and the hydrogen bromide generated in the reaction is sufficient to effect the ring opening.

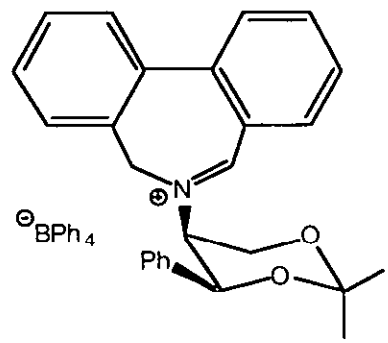


Scheme 96: Synthetic route to novel enantiopure dibenzazepinium salts.

Next, 2-bromomethyl-2'-biphenylaldehyde was treated with (–)-isopinocampheylamine in ethanol and after the usual anion exchange, furnished the corresponding chiral dibenzazepinium tetraphenylborate as a yellow solid in 42% yield (Scheme 96). The NMR spectrum of this novel organic salt at ambient temperature is difficult to interpret as it consists mainly of broad signals, and only when recorded at 80 °C in DMSO-d_6 allows unambiguous assignment. Although this property was absent from the ether and aldehyde derivatives, we believe that the sterically demanding chiral residue imparts restricted rotation around the biphenyl bond. In principle, these rotamers are diastereoisomeric and interconvertable, a feature that may positively influence the enantioselectivities of the asymmetric oxygen transfer process.

Therefore, the chiral azepinium salt was used as catalyst (10 mol%) in the asymmetric epoxidation of 1-phenylcyclohex-1-ene and *trans*-stilbene under the usual conditions. Overall, the azepinium salt derived from isopinocampheylamine exhibited inferior performance on enantioselective grounds, compared to the dihydroisoquinolinium salt with the same counterion and chiral residue on the nitrogen atom. The biphenyl derivative afforded 1-phenylcyclohex-1-ene and *trans*-stilbene oxides with 32 and 38% ee respectively while the corresponding dihydroisoquinolinium salt had furnished the same epoxides with 40 and 73% ee. However, both systems produced the same enantiomer (*R*,*R*) as the major component of the non-racemic product. This was the case for both epoxides prepared with the six membered ring catalyst.

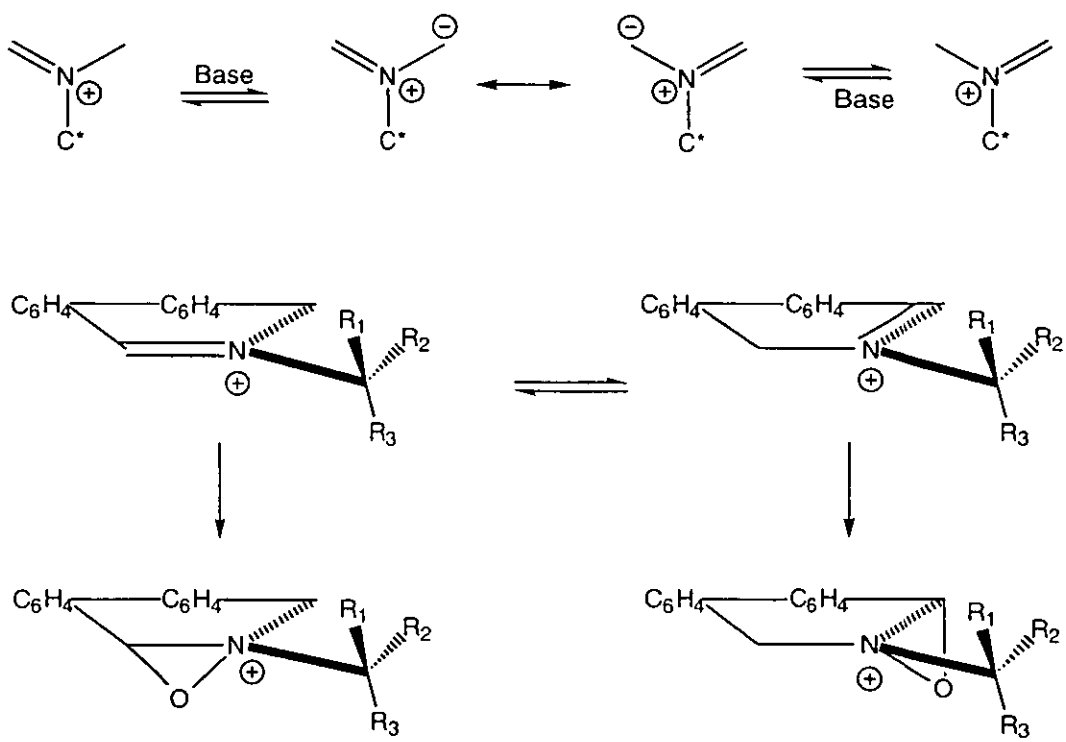
In order to examine further the effect of the dibenzo moiety on enantioselectivities, the azepinium salt from (4*S*,5*S*)-5-amino-4-phenyl-1,3-dioxane was also prepared and tested for catalytic activity (Scheme 97).[194]



Scheme 97: The dibenzazepinium salt derived from (4*S*,5*S*)-5-amino-4-phenyl-1,3-dioxane.

Disappointingly, the catalytic epoxidation with 1-phenylcyclohex-1-ene as the substrate was very slow, and the corresponding epoxide was obtained in only 17% ee.[195]

Apparently, poorer reaction profiles and enantioselectivities are observed when the dibenzoazepinium salt of a chiral amine is used as the catalyst instead of the dihydroisoquinolinium salt of the same precursor. We suspect that this behaviour may stem from a degenerate equilibrium *via* the ylid which can be formed under the alkaline conditions. This would allow the iminium moiety to be associated with both benzylic positions. If however, the rotation around the bond between the nitrogen atom and the chiral auxiliary is slower than this degenerate isomerisation, the two azepinium moieties will be diastereoisomerically related (Scheme 98). Provided that the chiral auxiliary promotes oxidation predominately at one of the prochiral faces of the iminium moiety, for example *syn* to the substituent designated R_3 in Scheme 98, formation of both diastereoisomeric oxaziridinium intermediates is likely to occur. In turn, this would result in poor enantioselectivity in the oxidation of the substrate (Scheme 98).



Scheme 98: The rationale for the low enantioselectivities obtained with azepinium salt-catalysts may lie in the formation of both diastreoisomeric oxaziridinium intermediates.

Some evidence for restricted rotation around the bond between the nitrogen atom and the chiral auxiliary follows from spectroscopy. The NMR spectra of both azepinium salts prepared exhibit broad signals at ambient temperature. This was not however, the case with the dihydroisoquinolinium salts prepared from the same chiral amines. In the case of the dibenzo derivatives, the benzylic protons next to the iminium bond are sufficiently acidic to promote formation of the ylid.[120,196-198] In addition, the resulted 1,3-dipole is reasonably stabilised by the biphenyl group. The analogous transformations are not expected to take place (at least not to the same extent) with the dihydroisoquinolinium systems due to the absence of the additional benzylic position adjacent to the iminium moiety. Consequently, the stability of the corresponding intermediates is not expected to be as great as in the dibenzo system.

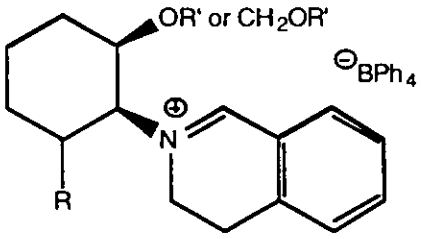
The poor versatility of this methodology towards the synthesis of novel iminium salt catalysts, and the decreased enantioselectivities obtained in the two cases examined, discouraged further attention on the isochroman approach.

This was the last attempt by the present author to synthesise a potential catalyst precursor and the search for more active and enantioselective catalysts, was continued by other researchers.

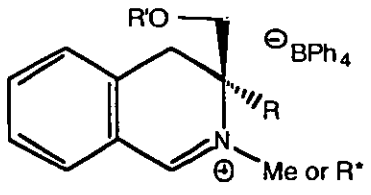
2.26 Optimum catalyst design.

The author evaluated the results obtained from this study and determined that the most promising approach towards the development of new catalysts is through the synthesis of dihydroisoquinolinium salts derived from "flanked" 1,2- or 1,3-aminoethers as described in 2.23. These derivatives may provide both steric and electronic discrimination between the prochiral faces of the iminium moiety, which may lead to stereospecific oxaziridinium ion formation and possibly improved asymmetric induction during oxygen transfer to the alkene substrate. This effect may be optimum when the aminoether entity is situated across a 6 membered ring due to conformational preferences.

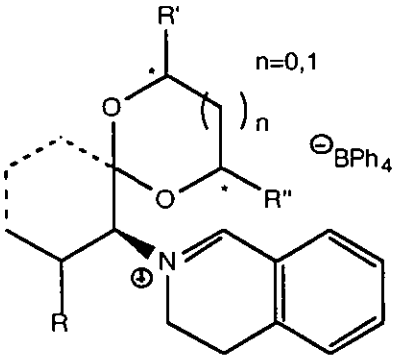
Good results were also obtained with the catalyst derived from (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane. If the "flanked" amine approach is successfully combined with chiral dioxane templates, then, access to novel and more enantioselective catalysts may be gained. Examples of such systems are shown in scheme 99.



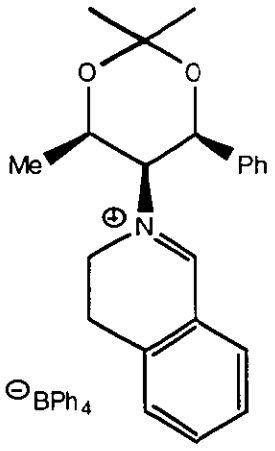
Activity may be compromised if
R larger than Me or R'=H



R= Bulky group
R' May be H



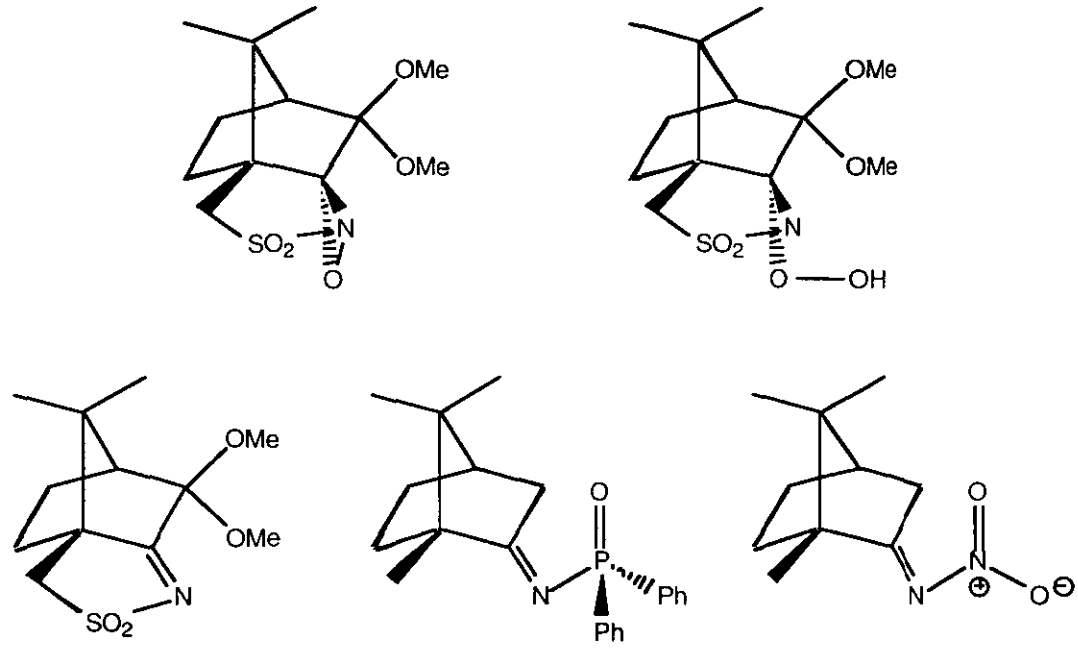
Pendant chiral
dioxalane or 1,3-dioxane



Scheme 99: Greater enantioselectivities may be obtained in the catalytic asymmetric epoxidation of simple alkenes with these dihydroisoquinolinium salts.

2.27 Conclusions.

This research project was concerned with the identification and synthesis of potential mediators for catalytic asymmetric epoxidation, based purely on organic compounds.

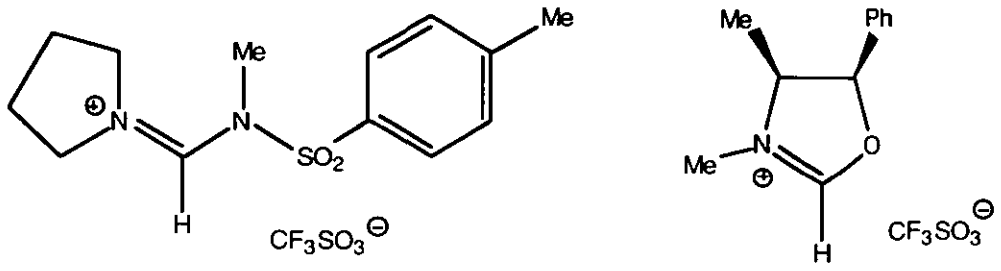


Scheme 100: An investigation of oxygen transfer from oxaziridines and hydroperoxyamines derived from simple N-sulfonyl, phosphinoyl, and nitro imines to alkenes was carried out.

We have demonstrated that asymmetric epoxidation cannot be accomplished with simple sulfonyl oxaziridines because the latter are not sufficiently electrophilic (Scheme 100). The parent sulfonyl imines are also incapable of mediating alkene epoxidation *via* the corresponding hydroperoxyamines. The same applies for other types of electron-deficient imines such as N-phosphinoyl and N-nitro imines (Scheme 100).

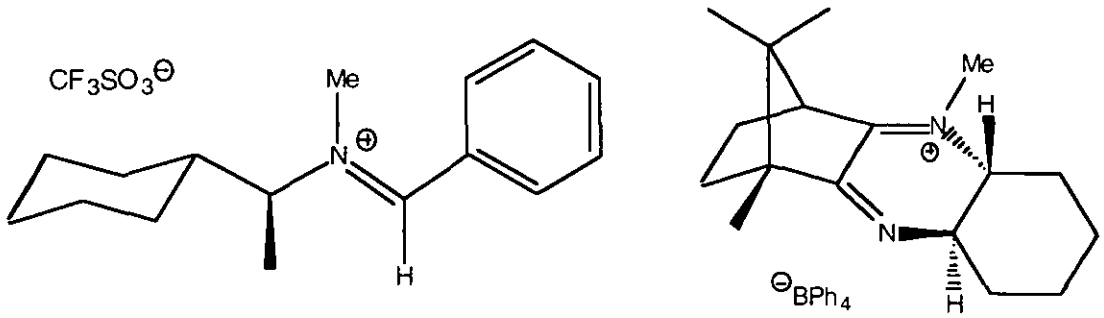
In the search for more electrophilic organic oxidants, we considered positively charged oxaziridines that may be prepared from iminium salts. For the first time, a systematic investigation was carried out on the chemical behaviour of a variety of positively charged systems containing the iminium moiety under oxidative conditions. This examination revealed that formamidinium salts are relatively inert to nucleophilic oxidants due to the sufficient stabilisation of the positive charge by the two nitrogen atoms (Scheme 101). In contrast, oxazolinium

salts exhibited a remarkable tendency to hydrolyse under the reaction conditions of choice (Scheme 101).



Scheme 101: Catalytic epoxidation mediated by oxaziridinium intermediates derived from formamidinium and oxazolinium salts was also examined.

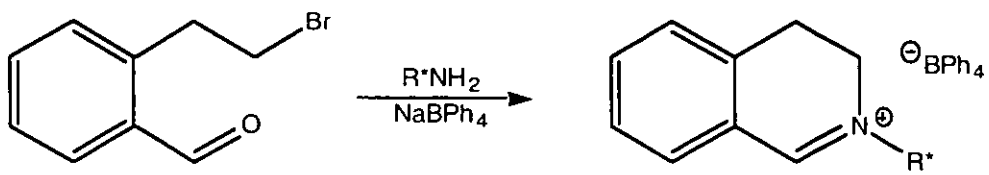
Acyclic iminium salts which are formed as transient species in various equilibria are not sufficiently long lived to be oxidised, and in turn promote epoxidation of olefins. Acyclic formal iminium salts derived from quartenised aldimines also appeared to be prone to hydrolysis, at least those derivatives studied (Scheme 102). In contrast, iminium salts derived from chiral terpenoid ketones were relatively unreactive or decomposed possibly *via* rearrangement of the terpene skeleton (Scheme 102).



Scheme 102: Salts derived from non cyclic aldimines or cyclic ketimines did not appear to be potential mediators for catalytic epoxidation *via* oxaziridinium intermediates.

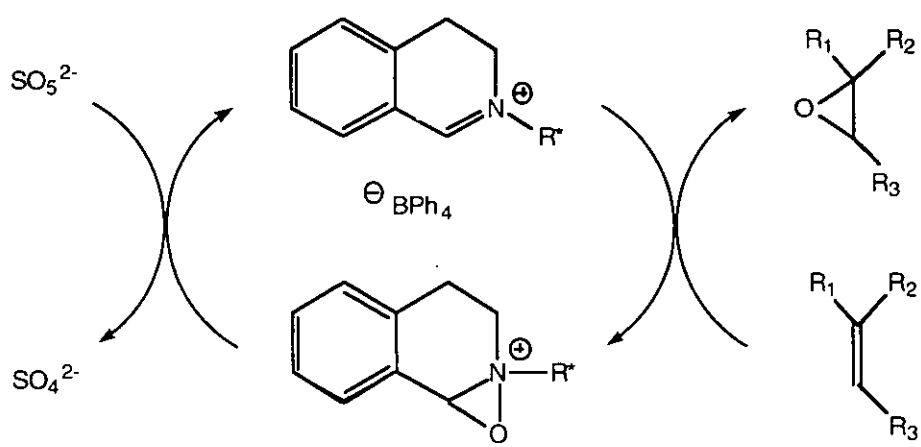
Following literature evidence that cyclic iminium salts derived from aldehydes may exhibit the desired balance between reactivity and stability, we developed synthetic sequence which allowed preparation of multigram quantities of chiral dihydroisoquinolinium salts. These systems have the chiral component resident on the exocyclic nitrogen substituent and had not been explored or tested

previously as mediators in catalytic epoxidation. Their preparation involves cyclocondensation of chiral primary amines and 2-(2-bromoethyl)benzaldehyde in turn prepared in one step from isochroman (Scheme 103). Due to the simplicity of the method, a respectable library of iminium salt catalysts was synthesised from readily available chiral amines, aminoalcohols, and aminoethers, and screened in a short period of time.



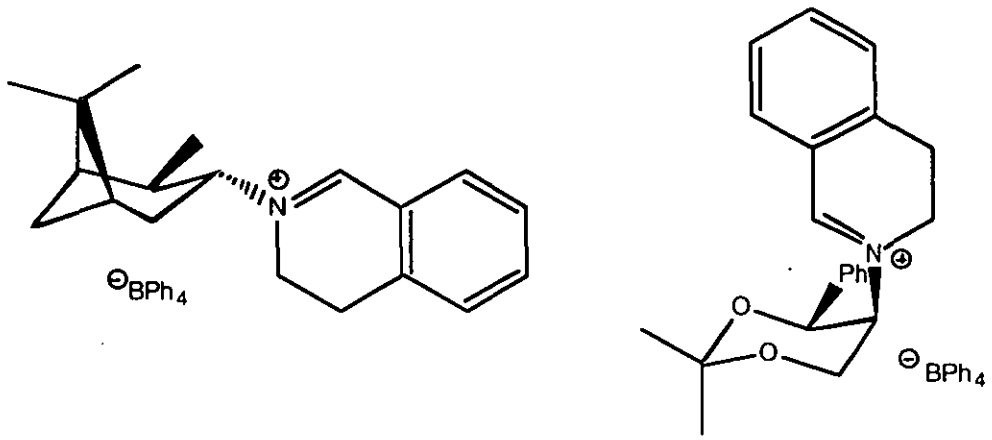
Scheme 103: A versatile synthetic route to chiral dihydroisoquinolinium salt was developed.

We found that catalytic asymmetric epoxidation of simple olefins could be accomplished within a few hours using just 0.30 mol% of these organic salts and Oxone™ as the stoicheiometric oxidant in acetonitrile/water (Scheme 104).



Scheme 104: We have developed a new system for catalytic asymmetric epoxidation.

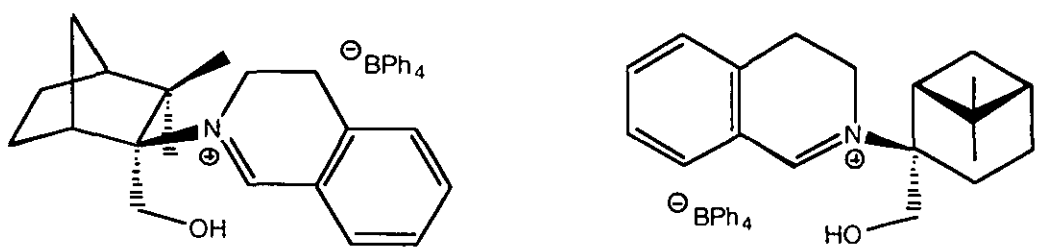
The best catalysts from this family of mediators appeared to be the derivatives of isopinocampheylamine and *syn*-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (Scheme 105). The first provided *trans*-stilbene oxide with 73% ee, the highest reported value for any epoxide prepared by iminium salt catalysis. The second mediator appears to be the least substrate specific iminium salt-epoxidation catalyst discovered to date. Generally enantioselectivities ranged between 40 and 58% ee for a variety of simple aryl alkene substrates.



Scheme 105: With these derivatives the best results were achieved in the catalytic asymmetric epoxidation of simple alkenes mediated by chiral iminium salts to date.

Optimisation of various reaction parameters such as catalyst loading, temperature, solvent system, concentration and counter-ion of the iminium species was also successfully carried out.

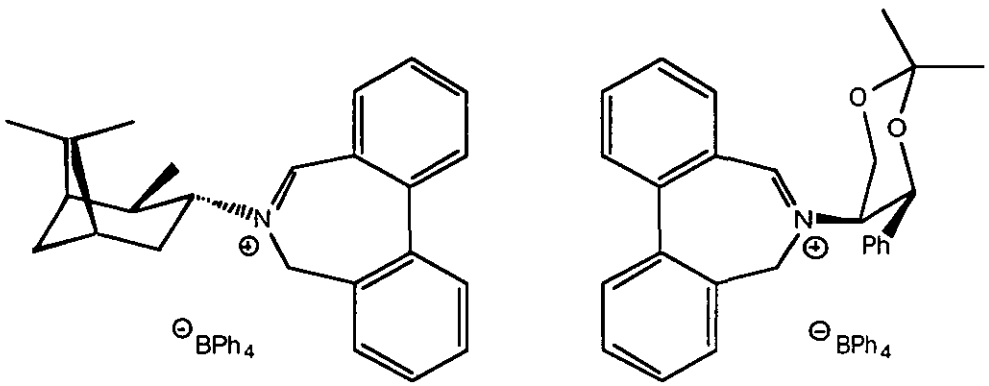
In the search for more enantioselective catalysts we synthesised a wider range of chiral dihydroisoquinolinium salts mainly derived from terpenoid aminoalcohols (Scheme 106), but these enjoyed limited success with respect to the enantioselectivities obtained for the epoxide products. We believe however, that from this study, valuable information was gained about the mechanism of the catalytic asymmetric epoxidation mediated by functionalised iminium salts.



Scheme 106: Novel dihydroisoquinolinium salts derived from terpenoid 1,2-aminoalcohols.

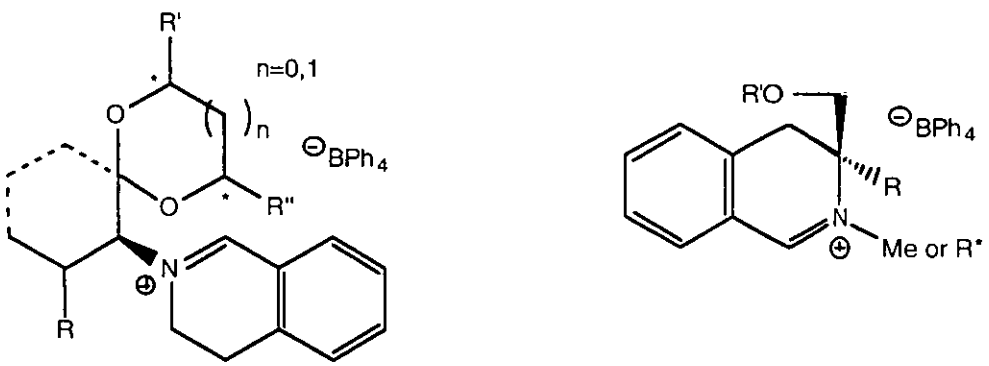
Attention was then focused on the other component used in the construction of the organic salt, namely the isochroman precursor of 2-(2-bromoethyl)benzaldehyde. The methodology employed to access suitably substituted bromoalkylbenzaldehydes as precursors to six and seven membered

cyclic iminium salts (Scheme 107), was only partially successful. The lack of availability of appropriate starting materials which could serve as precursors to chiral isochromans, and the generality of the chemistry involved, rendered this approach inferior to that which targets chiral, simple or functionalised amines as precursors to dihydroisoquinolinium salts.



Scheme 107: The effect of the size of the ring containing the iminium moiety on the enantioselectivity of the catalytic process, was also considered.

Finally, with the experience gained from this research work, the author suggested several systems that may serve as potential catalyst precursors and point of reference for future researchers in this area (Scheme 108).



Scheme 108: Better catalysts?

As a consequence of the findings published in this thesis, the catalytic asymmetric epoxidation of simple alkenes mediated by chiral iminium salts can no longer be considered as a methodology in its infancy.

CHAPTER 3

EXPERIMENTAL

3.1 Purification of reagents, compounds and solvents.

Commercially available reagents were used as supplied, without further purification, unless otherwise stated. Air and moisture sensitive compounds were stored in a desiccator over self indicating silica pellets, under a nitrogen atmosphere. charring

Flash chromatography was carried out using Merck 9385 Kieselgel 60-45 (230-400 mesh) and hand bellows to apply pressure to the column. Thin layer chromatography (TLC) was carried out on glass or aluminium plates coated with silica gel layer of 0.25 mm thickness, containing fluorescer. Compounds on this material were visualised by UV radiation at wavelength of 254 nm, or stained by exposure to an ethanolic solution of phosphomolybdic acid, (acidified with concentrated sulfuric acid), followed by charring where appropriate.

Light petroleum ether (b.p. 40-60 °C), was distilled from calcium chloride prior to use. Ethyl acetate was distilled over calcium sulphate or chloride. Dichloromethane was distilled over phosphorus pentoxide or calcium hydride. Tetrahydrofuran (THF), was distilled under nitrogen atmosphere from the sodium/benzophenone ketyl radical or from lithium aluminium hydride. Triethylamine and diisopropylethylamine were stored over potassium hydroxide pellets.

3.2 Preparation of glassware.

Highly air and moisture sensitive reactions were carried out using glassware that had been dried overnight in an oven at 240 °C. These were allowed to cool in a desiccator over self indicating silica pellets, under nitrogen atmosphere. The reactions were carried out under a slight positive static pressure of nitrogen.

3.3 Elemental analyses, optical rotation measurements and melting points.

Microanalyses carried out at the microanalytical laboratory of the Department of Chemistry, University of Liverpool were performed on a Carlo Ebra Elemental Analyser, while those carried out at Loughborough University were performed on a Perkin Elmer Elemental Analyser 2400 CHN.

Optical rotation values were measured with an Optical Activity-polAAar 2001 instrument, operating at λ=589 nm, corresponding to the sodium line, (D), at the temperatures indicated. The solvents used for these measurements were of spectrophotometric grade. The solutions for these measurements were prepared in volumetric flasks for maximum accuracy of the volume of the solvent used.

Melting points were carried out on a Electrothermal-IA 9100 and are

uncorrected.

3.4 Infrared and mass spectra (IR, MS).

Fourier transformed infrared absorption spectra were recorded on a Perkin Elmer FT-IR spectrometer Paragon 2001 instrument in the range of 4000-600 cm^{-1}. Solid samples were run as nujol mulls on sodium chloride discs or as thin films of their solution in dichloromethane. Liquid samples were run neat on sodium chloride discs.

Mass spectra carried out at Loughborough University were recorded on Cratos MS-80 or Jeol-SX102 instruments using electron impact (EI), ionisation technique. Electron spray mass spectrometry (ES), was carried out at the Glaxo-Welcomme Medicines Research Centre at the Stevenage site, using a Hewelett Packard Autoplatform instrument.

3.5 Nuclear Magnetic Resonance (NMR).

Proton nuclear magnetic resonance spectra, were recorded on the following NMR instruments: Bruker AC 200 Fourier transform spectrometer at the University of Liverpool, Bruker AC 300 at the GlaxoWellcome Medicines Research Centre at the Stevenage site, and Bruker AC 250 and Bruker DPX 400 at Loughborough University, operating at 200.10, 300.17, 250.13 and 400.13 MHz respectively. The experiments were conducted in deuteriated solvents with tetramethylsilane as the internal standard. Multiplicities were recorded as broad signals (br. s), singlets (s), doublets (d), triplets (t), quartets (q), quintets (quint), doublet of doublets (dd), doublet of triplets (dt), triplet of doublets (td), doublet of double doublets (ddd), and multiplets (m).

Carbon-13 nuclear magnetic resonance spectra were recorded on Bruker AC 250 and Bruker DPX 400 instruments at Loughborough University, operating at 62.86 and 100.62 MHz respectively. Normally the ^{13}C NMR spectrum for each compound was recorded in the same deuteriated solvent as that used for the ^{1}H NMR spectrum, unless otherwise stated. Tetramethylsilane or acetonitrile was used as the internal standard. DEPT, nOe and COSY analyses were recorded on a Bruker AC 250 and Bruker DPX 400 at Loughborough University.

Phosphorus-31 nuclear magnetic resonance spectra, were recorded on a Bruker AC 250 operating at 101.20 MHz.

3.6 Determination of enantiomeric excesses (NMR, Chiral HPLC).

Enantiomeric excesses were determined by either proton nuclear magnetic resonance, (^{1}H NMR), or by Chiral High Performance Liquid Chromatography, (Chiral HPLC).

The proton nuclear magnetic resonance spectra were recorded in deuteriated chloroform on Bruker AC 300 or Bruker AC 250 NMR instruments, operating at 300.17 and 250.13 MHz respectively, in the presence of *tris*-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), [(+)-Eu(hfc)$_3$], as the chiral shift reagent, and tetramethylsilane as the internal standard. Between 3 and 5 mol% of the chiral shift reagent was used, depending on the substrate and concentration of the solution used. In no case, however, did the total mass of the chiral shift reagent used in each of the ^{1}H NMR experiments exceed 10 mg due to the paramagnetic properties of europium(III), which may compromise data through line broadening.

The chiral columns used for the determination of enantiomeric excesses (ee), of non-racemic mixtures of chiral compounds by chiral HPLC, were Chiracel OD or Chiracel OJ on a TSP Thermo-Separating-Products Spectra Series P200 instrument, with a TSP Spectra Series UV100 ultra-violet absorption detector and a Cromojet Integrator. For the epoxides examined, the solvent system used was hexane/isopropanol (90:10), operating at a flow rate of 0.50 mL per minute, (pump pressure equivalent to 80-135 psi), with the UV detector set at 250 nm. Both solvents used for these measurements (hexane and isopropanol), were of HPLC grade.

3.7 Numbering systems.

The assignments of the proton and carbon-13 resonances have been made according to numbering systems. Some of the systems used are standard in chemical nomenclature but others were adopted by the present author in order that compounds derived from the same skeletal core retain the numbering of the parent compound. This was undertaken because according to IUPAC system, compounds derived from the same precursor often possess different numbering which is not convenient for comparison/recognition purposes.

3.7.1 Terpenes.

Carbon and hydrogen atoms from terpenes are numbered according to the standard system so that branched positions bear the smallest possible number. The carbon atoms which are at ring junctions are termed "bridgehead". For camphor, fenchone and camphanol systems (norbornyl frameworks), additional terminology

exists for the hydrogen atoms which are *syn* or *anti* to the bridge (*exo* and *endo* respectively) (Figure 4). Quaternary carbons are designated C quat. in the assignment. Similar standard numbering systems exist for pinene systems. Note that for verbanol derivatives the carbon bearing the methyl group is C4, in contrast to C2 in the related systems (Figure 4). This is because the carbon bearing the heteroatom takes precedence over the methyl-substituted carbon. The numbering system for menthyl derivatives is also standard (Figure 4).

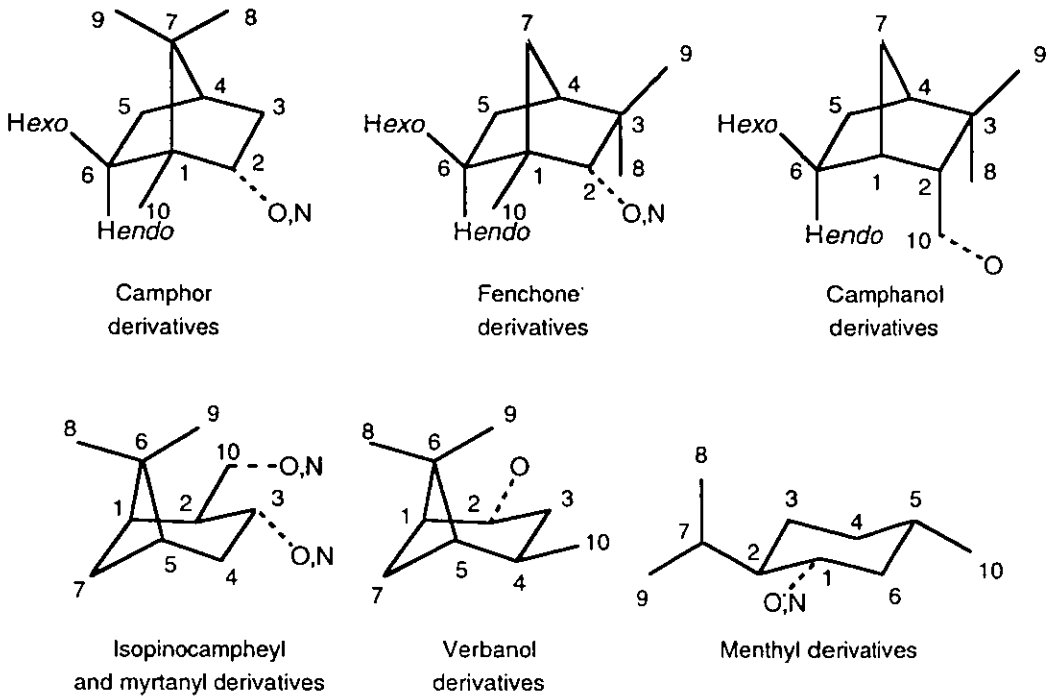


Figure 4: Numbering systems used for terpene derivatives.

3.7.2 Aromatics.

Aromatic systems are also numbered according to the standard protocol. Note that aromatic carbon atoms bearing a substituent are termed *ipso* and they are always quaternary (C arom. quat.) (Figure 5). All other aromatic carbon atoms which are attached to a hydrogen atom are termed C arom. (^{13}C spectra) or CH arom (^{1}H spectra). The dihydroisoquinolinium nucleus is also numbered according to a standard system and are designated *isoq1-10* (Figure 5). The same system applies for the tetrahydro- adducts of dihydroisoquinolinium salts derived from intramolecular cyclisation by nucleophilic attack of a neighbouring hydroxyl group. (Figure 5).

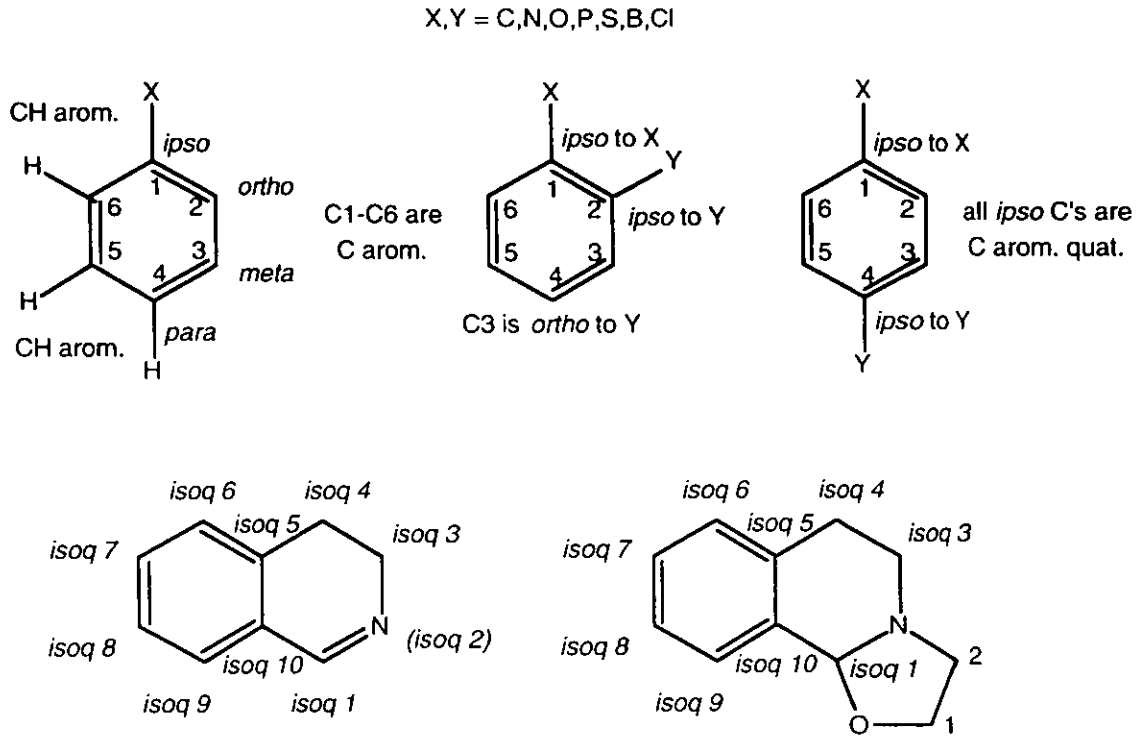


Figure 5: Numbering systems for various aromatic structures.

3.7.3 Miscellaneous.

Some of the systems described in this section that follows have been numbered empirically. In these, assignment of the hydrogen atoms has been made according to the substituents on the carbon atoms that they are attached to.

This method has been applied to systems where the fragment bearing the atoms in question (both carbon and hydrogen) can be recognised unambiguously by the description of the neighbouring groups, for example 1 in Figure 6.

Hybrid systems derived from terpenes are also numbered empirically. The terpene skeleton is numbered first, according to the appropriate system and numbers continue for the additional atoms of the molecule (2 in Figure 6).

For terpene-derived dihydroisoquinolinium salts, assignment has been made according to the appropriate system described for each of the distinct moieties (3 in Figure 6).

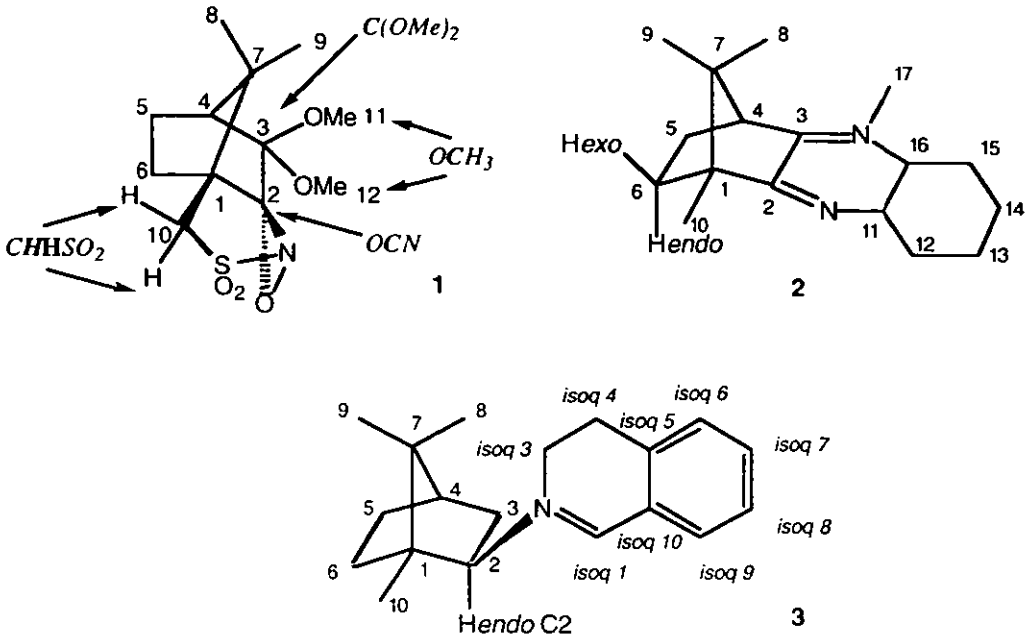
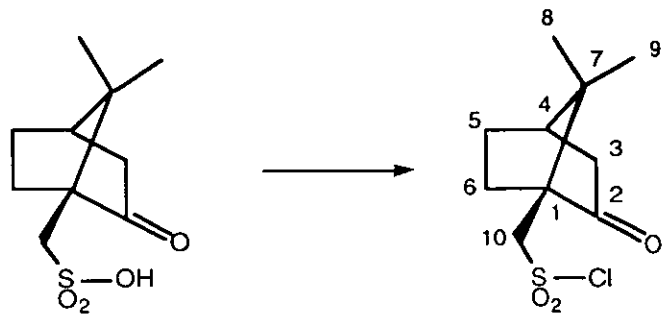


Figure 6: Empirical numbering and assignment systems used for complex derivatives.

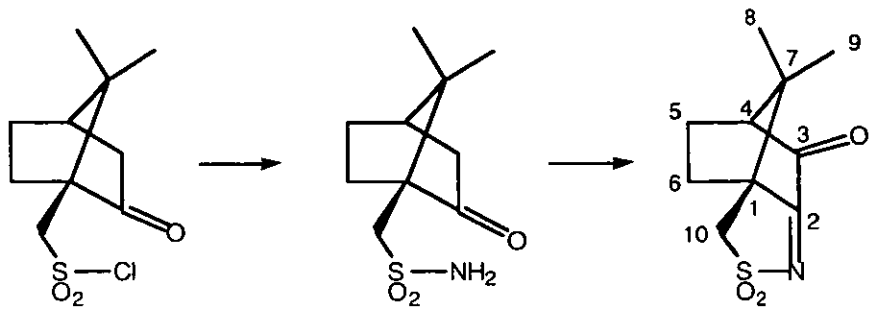
3.8 Individual experimental procedures and characterisation of compounds.

(+)-(1S,4S-)-(7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)-methanesulfonyl chloride:



(+)-(1S,4S)-Camphorsulfonyl chloride:[201,202] (1S)-(+)-Camphorsulfonic acid, (86.00 g, 0.37 mol), was heated to 40 °C (neat) in a two-neck 500 mL flask equipped with a reflux condenser and a drying tube ($CaCl_2$). Thionyl cloride, (108 mL, 176.18 g, 1.48 mol), was added *via* a dropping funnel over a period of 2 hours with stirring. Vigorous evolution of gas (HCl, SO_2) was manifested as the reaction proceeded. When the evolution of gas ceased, the reaction mixture was allowed to attain ambient temperature and stirred overnight. The resulting orange-yellow liquid is poured into ice cold water (500 mL) to hydrolyse the excess of thionyl chloride, and upon gentle stirring the sulfonyl chloride precipitated out of the aqueous phase. The product was quickly filtered and washed with more ice cold water and the bulk of water removed by suction filtration. The product was then dissolved in dichloromethane and dried over magnesium sulfate. Evaporation of the solvent afforded the crude camphor sulphonyl chloride, (88.21 g, 95%), which is sufficiently pure to be used without further purification; m.p. 63-65 °C; (lit. m.p. 65-66 °C)[201]. $[\alpha]^{20}_D$ +31.2 c=1 ($CHCl_3$), (lit. $[\alpha]^{20}_D$ +28.8 c=4.2 ($CHCl_3$)[202]); ν_{max}/cm^{-1} (nujol) 1741, 1414, 1280, 1170, 1047; δ_H ($CDCl_3$) (250 MHz), 0.93 (3 H, s, CH_3 at C8), 1.14 (3 H, s, CH_3 at C9), 1.46-1.54 (1 H, m, *exo* at C5), 1.74-1.82 (1 H, m, *endo* at C5), 1.99 (1 H, d, *J* 18.63 Hz, bridgehead H at C4), 2.07-2.19 (2 H, m, *endo* and *exo* at C6), 2.39-2.50 (2 H, m, CH_2 *endo* and *exo* at C3), 3.75 (1 H, upper portion of *AB* system, d, *J* 14.60 Hz, C*H*HSO_2 at C10), 4.30 (1 H, lower portion of *AB* system, d, *J* 14.59 Hz, C*H*HSO_2, C10). δ_C (62.5 MHz), 19.55 (CH_3, C8) 19.63, (CH_3, C9), 25.20 (CH_2, C5), 26.79 (CH_2, C6), 42.24 (CH_2, C3), 42.68 (CH, C4), 48.16 (C quat., C7), 59.61 (C quat., C1), 64.22 (CH_2, C10), 212.72 (C quat., C=O, C2); *m/z* 250; exact mass calcd for $C_{10}H_{15}ClO_3S$ 250.04304 found 250.04293.

(–)-(1*S*,7*S*-)-10,10-Dimethyl-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-ene-3,3,6-trione:

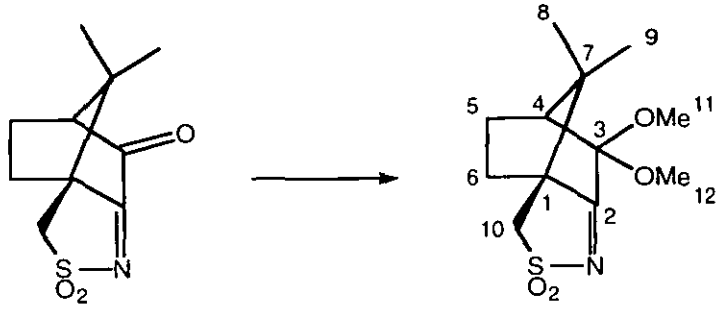


(–)-(1S,4S)-3-Oxo-10-camphorsulfonyl-2-imine:[204] (+)-camphorsulfonyl chloride, (20.05 g 80.00 mmol) was dissolved in 180 mL of dichloromethane and added in two portions via a 250 mL dropping funnel over a period of 30 minutes into 180 mL of commercially available concentrated ammonia solution (S.G. 0.88), cooled in an ice bath. The reaction mixture was stirred for two hours at the same temperature then transferred in a 500 mL separating funnel where the organic phase was separated and the aqueous was washed with dichloromethane (2x150 mL). The organic extracts were combined, dried over magnesium sulfate for 15 minutes, filtered and stripped of the solvent at a rotary evaporator. The (+)-camphorsulfonamide, 18.2 g, 98.7% yield, is of sufficient purity for subsequent reactions. Samples of improved purity can be obtained by recrystallisation from absolute ethanol.

To a solution of (+)-camphorsulfonamide (11.50 g, 46.12 mmol), in 400 mL of acetic acid, selenium dioxide (8.11 g, 73.01 mmol), was added and the reaction mixture was heated under reflux for 24 hours. The solution was filtered to remove the selenium remnants (toxic), and 600 mL of water were added followed by 250 mL of dichloromethane. The layers were separated and the aqueous phase was washed with more dichloromethane (2x250 mL). The combined organic extracts were dried over magnesium sulfate for 15 minutes, filtered, and the solvent was removed *in vacuo*. The resulted solid was recrystallised from absolute ethanol to give pure (–)-oxocamphor sulfonyl imine as a yellow crystalline solid 74%, m.p. 188-190 °C; (lit. m.p. 190-191 °C).[204] $[\alpha]^{20}_D$ –176.7 c=2.2 (acetone), (lit. $[\alpha]^{24}_D$ –178.5 c=2.2 (acetone)[204]); ν_{max}/cm^{-1} (nujol) 1750, 1640, 1330, 1160; δ_H ($CDCl_3$) (350 MHz), 0.99 (3 H, s, CH_3 at C8), 1.17 (3 H, s, CH_3 at C9), 1.79-2.12 (2 H, m, *exo* at C5 and C6), 2.19-2.38 (2 H, m, *endo* at C5 and C6), 2.79 (1 H, d, *J* 4.84 Hz, bridgehead H at C4), 3.25 (1 H, d, *J* 13.67 Hz, CH*H*-SO_2 at C10), 3.46 (1 H, d, *J* 13.65 Hz, C*H*H-SO_2, C10). δ_C (88.00 MHz), 18.34 (CH_3, C8) 20.13, (CH_3, C9), 22.23 (CH_2, C6), 27.93 (CH_2, C5), 44.64 (C quat., C7), 50.03 (CH, C4), 59.01 (CH_2, C10), 62.74 (C quat., C1), 183.51 (C quat., C=N, C2),

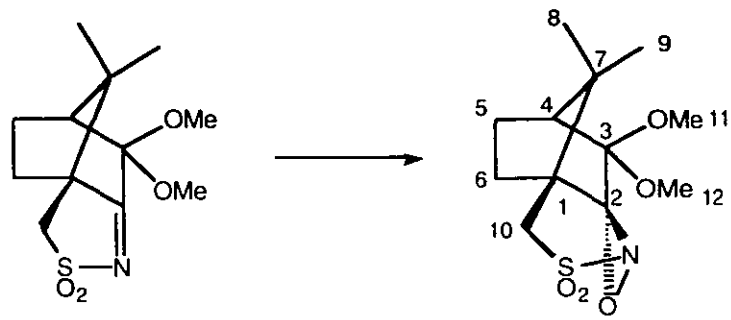
197.78 (C quat., C=O, C3); consistent with previous literature report.[204] *m/z* 245 [$M(NH_4)^+$]; exact mass calcd for cation $C_{10}H_{13}NO_3S$ 227.06161 found 227.06160. Found C, 52.74; H, 5.83; N, 6.13; $C_{10}H_{13}NO_3S$ requires: C, 52.86; H, 5.77; N, 6.16%.

(+)-(1*S*,7*S*-)-10,10-Dimethyl-6,6-di(methyloxy)-3λ⁶-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-ene-3,3-dione:



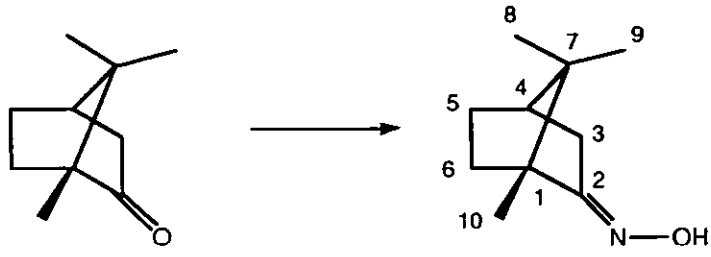
(+)-(1S,4S)-3,3-Dimethoxy-10-camphorsulfonyl-2-imine:[1,253,255] A solution of (–)-oxocamphor sulfonyl imine, (2.27 g, 10 mmol), in 25 mL of trimethyl orthoformate, 5 mL of methanol, 0.50 mL of concenterated H_2SO_4, and 0.50 g of Amberlist-15 ion-exchange resin was stirred and refluxed overnight. The room temperature solution was filtered, 20 mL of water was added and the mixture was extracted with dichloromethane (3x30 mL); the combined extracts were washed with 30 mL of water and dried ($MgSO_4$). Removal of the solvent afford a white solid which was purified by crystallization from absolute ethanol to give 2.6 g (95%) of the title compound; m.p. 186-188 °C, (lit. m.p. 186-187 °C)[253]. $[\alpha]^{20}_D$ +7.21 c= 3.6 ($CHCl_3$), (lit. $[\alpha]^{20}_D$ +7.30 c= 3.4 ($CHCl_3$)[253]); ν_{max}/cm^{-1} (nujol) 1620, 1340, 1160; δ_H ($CDCl_3$) (400 MHz), 1.00 (3 H, s, CH_3 at C8), 1.09 (3 H, s, CH_3 at C9), 1.80-2.40 (5 H, m, CH_2 of C5, CH_2 of C6 and bridgehead H at C4), 2.97 (1 H, d, *J* 12.03 Hz, CH*H*-SO_2 at C10), 3.16 (1 H, d, *J* 12.07 Hz, C*H*H-SO_2 at C10), 3.36 (3 H, s, OCH_3, C11), 3.47 (3 H, s, OCH_3, C12); δ_C (100 MHz), 20.46 (CH_3, C8), 20.53 (CH_3, C9), 20.63 (CH_2, C6), 29.25 (CH_2, C5), 46.01 (C quat., C7), 48.89 (CH, C4), 50.33 (OCH_3, C11), 50.55 (OCH_3, C12), 52.07 (C quat., C1), 64.27 (CH_2, C10), 103.00 (C quat., $C(OMe)_2$, C3), 188.73 (C quat., C=N, C2); consistent with previous literature report.[255] *m/z* (MH^+) 274; exact mass calcd for MH^+ $C_{12}H_{20}NO_4S$ 274.11130 found 274.11120. Found C, 52.94; H, 7.16; N, 5.02. $C_{12}H_{19}NO_4S$ requires: C, 52.73; H, 7.01; N, 5.12%.

(+)-(1S,6S-,8S-)-11,11-Dimethyl-7,7-di(methyloxy)-5-oxa-3λ⁶-thia-4-azatetracyclo[6.2.1.0^{1,6}.0^{4,6}]undecane-3,3-dione:



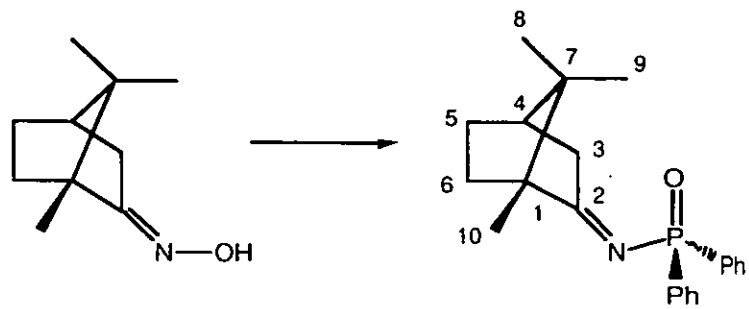
(+)-(1S,2S,4S)-3,3-Dimethoxy-camphor-10-sulfonyl-2-oxaziridine:[1,253,254] Potassium carbonate, (4.10 g, 29.70 mmol), was rapidly stirred in 20 mL of methanol at room temperature and 30% aqueous hydrogen peroxide, (3.35 mL, 1.01 g, 29.7 mmol), was added in one portion followed by (+)-3,3-dimethoxy-10-camphorsulfonyl-2-imine, (2.02 g, 7.30 mmol). The reaction mixture was stirred overnight then partitioned between saturated brine solution, (50 mL) and dichloromethane (100 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were washed with saturated $Na_2S_2O_3$ (10 mL) and water (30 mL) and dried over magnesium sulfate. Removal of the solvent afforded a white solid which was crystallized from absolute ethanol to give 1.41 g of the oxaziridine, 67% yield; m.p. 189 °C dec.; (lit. m.p. 189 °C).[253] $[\alpha]^{20}_D$ +94.1 c=3.40 ($CHCl_3$), (lit. $[\alpha]^{20}_D$ +91.3 c= 3.39 ($CHCl_3$)[254]); ν_{max}/cm^{-1} (nujol) 1354, 1165; δ_H ($CDCl_3$) (400 MHz), 1.06 (3 H, s, CH_3 at C8), 1.32 (3 H, s, CH_3 at C9), 1.75-2.30 (5 H, m, CH_2 of C5, CH_2 of C6 and bridgehead H at C4), 3.08 (1 H, d, *J* 12.02 Hz, C*H*H-SO_2 at C10), 3.29 (1 H, d, *J* 14.02 Hz, C*H*H-SO_2 at C10), 3.27 (3 H, s, OCH_3, C11), 3.34 (3 H, s, OCH_3, C12); δ_C (100 MHz), 20.45 (CH_3, C8), 21.62 (CH_3, C9), 28.07 (CH_2, C6), 29.31 (CH_2, C5), 45.11 (CH, C4), 47.42 (C quat., C7), 50.50 (OCH_3, C11), 50.78 (OCH_3, C12), 52.88 (C quat., C1), 54.57 (CH_2, C10), 97.59 (C quat., OCN, C2), 102.77 (C quat., $C(OMe)_2$, C3); consistent with previous report.[1,253,254] *m/z* (MH^+) 289; exact mass calcd for MH^+ $C_{12}H_{20}NO_5S$ 290.10622 found 269.10620. Found C, 49.89; H, 6.70; N, 4.82; $C_{12}H_{19}NO_5S$ requires: C, 49.81; H, 6.63; N, 4.89%.

(–)-(1*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one oxime:



(–)-(1R,4S)-Camphor oxime:[22,206-209] Hydroxylamine hydrochloride, (5.00 g, 72.00 mmol), was added to a solution of pyridine, (4 mL, 3.91 g, 49.46 mmol), in 50 mL of absolute ethanol, and the mixture was warmed until most of the salt was dissolved. (1*R*)-(+)-Camphor, (5.00 g, 32.80 mmol), was added and the reaction mixture is refluxed for 6 hours, then allowed to attain ambient temperature. The cool reaction mixture was stripped of most of the solvent, and 50 mL of ice cold water are added to the residue. This caused the precipitation of camphor oxime as white crystals which were filtered, dried under suction filtration and recrystallised from ethanol or methanol. If white needles crystallised out relatively fast more alcohol would be added (*ca* 10 mL) and the solution would be brought to boil to redissolve the solid. Slow cooling, affords 3.95 g of highly pure, crystalline camphor oxime as colourless square plates, 70% yield, m.p. 116-118 °C; (lit. m.p. 115-116 °C)[208]. $[\alpha]^{20}_{D}$ –51.50 c=0.52 (CH_2Cl_2); (lit. $[\alpha]^{20}_{D}$ –42.50 c=10 (EtOH)[209]); ν_{max}/cm^{-1} (nujol) 3293. 1684; δ_H ($CDCl_3$) (250 MHz), 0.82 (3 H, s, CH_3 at C8), 0.93 (3 H, s, CH_3 at C9), 1.04 (3 H, s, CH_3 at C10), 1.24 (1 H, dt, *J* 11.21, 4.97 Hz, *exo* at C6), 1.47 (1 H, dt, *J* 11.19, 5.02 Hz, *exo* at C5), 1.63-2.00 (3 H, m, *exo* at C3,*endo* at C5 and bridgehead H at C4), 2.12 (1 H, t, *J* 17.56 Hz, *endo* at C6), 2.49-2.68 (1 H, m, *endo* at C3), 6.19 (1 H, br. s, NOH); δ_C (62.50 MHz), 11.03 (CH_3, C8), 18.45 (CH_3, C9), 19.38 (CH_3, C10), 27.16 (CH_2, C5), 32.51 (CH_2, C6), 33.02 (CH_2, C3), 43.60 (CH, C4), 48.18 (C quat., C7), 51.70 (C quat., C1), 169.51 (C quat., C=N, C2); consistent with previous reports. *m/z* 167; exact mass calcd for $C_{10}H_{17}NO$ 167.13101 found 167.13120. Found C, 71.79; H, 10.19; N, 8.42; $C_{10}H_{17}NO$ requires: C, 71.81; H,10.25; N 8.37%.

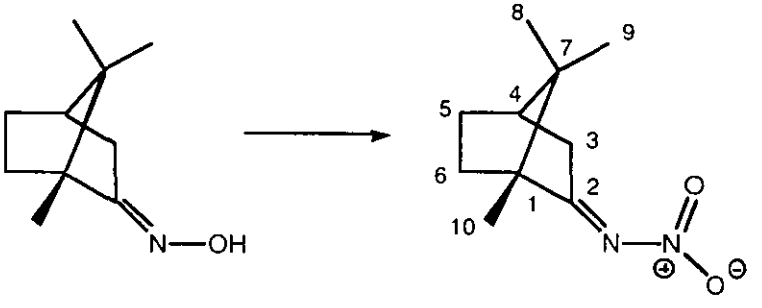
(–)-(1*R*,4*S*)-Diphenyl-*N*-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yliden)phosphinic amide:



(–)-(1R,4S)-Camphor-N-(diphenylphosphinoyl)-imine: This compound was prepared according to a modified procedure with respect to that reported originaly. Camphor oxime, (1.50 g, 8.97 mmol), was added to a solution of triethylamine, (0.91 g, 9.00 mmol), in 50 mL of dichloromethane/light petroleum ether (1:1) and nitrogen atmosphere was established. The solution was cooled to –78 °C and stirred for 30 minutes. Chlorodiphenylphosphine, (1.98 g, 8.97 mmol), was added rapidly in one portion and a copius amount of a white solid precipitated. The reaction mixture was stirred at the same temperature for 8 hours then allowed to attain ambient temperature overnight. The precipitated triethylammonium salt is removed by suction filtration and the solvents are evaporated under vaccuo, affording a yellow oil. Addition of dry petroleum ether (40/60) causes more salt to precipitate which is also removed by filtration. The solution was quickly washed once with saturated ammonium chloride solution and dried over sodium sulfate. Evaporation of the solvents gave 3.32 g of the crude product as a colourless oil, which is 80% pure by NMR, unreacted oxime being the only impurity. Due to the instability of the compound in acidic conditions, the crude product was chromatographed quickly on a short column of silica gel with 40% ethyl acetate in petrol as the eluent, to remove unreacted oxime. Then, the proportion of ethyl acetate was increased to 60% and furter elution furnished the phosphinoyl imine as a colourless oil. $[\alpha]^{20}_{D}$ –30.75 c=1.73, ($CHCl_3$), ν_{max}/cm^{-1} (neat), 3454, 3057, 2959, 1737, 1666, 1438, 1207, 1122, 895; δ_H ($CHCl_3$), (250 MHz), 0.7 (3 H, s, CH_3 at C8), 0.94 (3 H, s, CH_3 at C9), 1.09 (3 H, s, CH_3 at C10), 1.21-1.42 (2 H, m, *exo* at C6 and*exo* at C5), 1.70-2.02 (3 H, m,*exo* at C3, *endo* at C5 and bridgehead H at C4), 2.47 (1 H, dd, *J* 19.48, 2.70 Hz, *endo* at C6), 2.71-2.88 (1 H, m, *endo* at C3) 7.37-7.45 (6 H, m, arom.), 7.85-7.97 (4H, m, arom.); δ_C (62.50 MHz), 10.89 (CH_3, C8), 19.05 (CH_3, C9), 19.47 (CH_3, C10), 26.78 (CH_2, C5), 31.58 (CH_2, d, *J* 6.50 Hz, C6), 42.20 (CH_2, d, *J* 48.25 Hz, C3), 43.93 (CH, C4), 47.22 (C quat.,

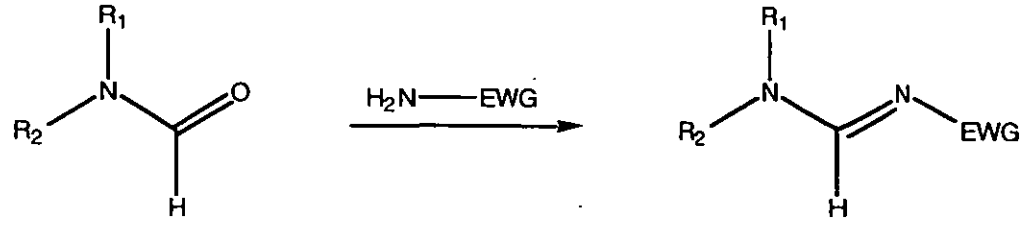
C7), 57.94 (C quat., d, *J* 76.30 Hz, C1), 128.05 (CH arom., d, *J* 3.90 Hz), 128.24 (CH arom., d, *J* 3.92 Hz), 131.05 (2xCH arom.), 131.10 (2xCH arom.), 131.28 (4xCH arom., m), 133.75 (C arom., quat., d, *J* 7.50 Hz, C-P), 135.77 (C arom., quat., d, *J* 7.50 Hz, C-P), 204.40 (C quat., C=N, d, *J* 43.05 Hz, C2); δ_P ($CHCl_3$), (101.20 MHz), 21.20 [$NPO(Ph)_2$];*m/z* 351; exact mass calcd for $C_{22}H_{26}NOP$ 351.17519 found 351.17579. Found C, 75.12; H, 7.51; N, 3.92; $C_{22}H_{26}NOP$ requires: C, 75.18; H, 7.46; N, 3.99 %.

(–)-(1*R*,4*S*)-1-oxo-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yliden)hydrazinium-1-olate:



(–)-(1R,4S)-Camphor-N-nitro-imine:[33] To a solution of (+)-camphor oxime (1.00 g, 6 mmol), in 30 mL of acetic acid, 15mL of 5% aqueous sodium nitrite was added, and the reaction mixture became yellow. The solution is left to stand for approximately 2 hours during which time the colour slowly disperses. When the reaction mixture became colourless, 30 mL of water were added and the white solid which precipitated was collected by filtration, 0.92 g. Recrystallisation from absolute ethanol gave 0.48 g of the pure nitrimine, 35% yield, m.p. 43 °C, (lit. m.p. 41-43 °C).[33] $[\alpha]^{20}_D$ –35.07 c=2.08, ($CHCl_3$), (lit. $[\alpha]^{20}_D$ –32.00 c=1, (dioxane)[33]); ν_{max} /cm^{-1} (nujol) 1647, 1571; δ_H ($CHCl_3$), (400 MHz), 0.90 (3 H, s, CH_3 at C8), 1.01 (3 H, s, CH_3 at C9), 1.07 (3 H, s, CH_3 at C10), 1.31-1.35 (1 H, m, *exo* at C6), 1.57-1.62 (1 H, m, *exo* at C5), 1.87-1.95 (2 H, m, *endo* at C5 and bridgehead H at C4), 2.05-2.07 (1 H, m, *endo* at C6), 2.69-2.75 (2 H, m, *endo* and *exo* at C3); δ_C (100 MHz), 10.74 (CH_3, C8), 19.00 (CH_3, C9), 19.75 (CH_3, C10), 27.08 (CH_2, C5), 31.93 (CH_2, C6), 35.50 (CH_2, C3), 43.767 (CH, C4), 49.20 (C quat., C7), 54.53 (C quat., C1), 189.83 (C quat., C=N, C2). *m/z* 196; exact mass calcd for $C_{10}H_{16}N_2O_2$ 196.12120 found 196.12086. Found C, 61.43; H, 8.23; N, 14.33; $C_{10}H_{16}N_2O_2$ requires: C, 61.20; H, 8.22; N, 14.27%.

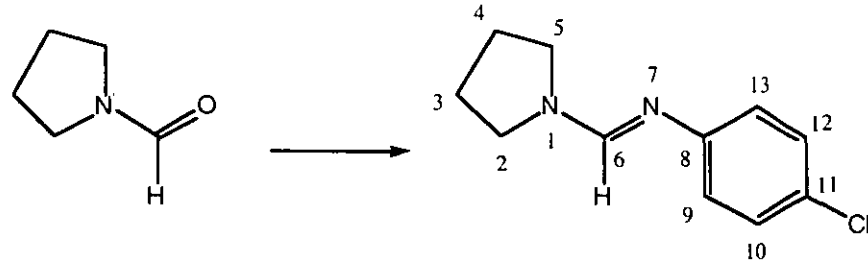
General procedure for the synthesis of formamidines:



This procedure involves acylated anilines as precursors,[48] but also works well for anilines conjugated to electron withdrawing groups. Similarly, primary sulfonamides are also successful pecursors.

The acylanilide (0.1 mol), is mixed with the dialkyl formamide (0.1 mol), and heated in the absence of solvent at 100 °C. Phosphoryl chloride (0.1 mol), is added dropwise to the mixture over a period of 30 minutes by means of a syringe pump with simultaneous distillation of the acyl chloride side product; (alkaline bleach trap in the case of free anilines or sulfonamides). When the addition is complete the mixture is heated for an additional hour and then allowed to cool to 60 °C. Water (50 mL) is added dropwise to the mixture which is then stirred for 30 minutes. 100 mL of 5M sodium hydroxide is added and the solution is extracted with toluene (2 x 25 mL). The combined organic extracts are dried over sodium sulfate and the solvent is evaporated.The residue is a brown oil (white solid in the case of sulfonamide) which slowly solidifies to a brown-yellow solid. The product is sufficiently pure, (95-97% by NMR), for further transformations. Purity can be impoved by recrystallisation from ethanol, (slow process, seeding is usually required).

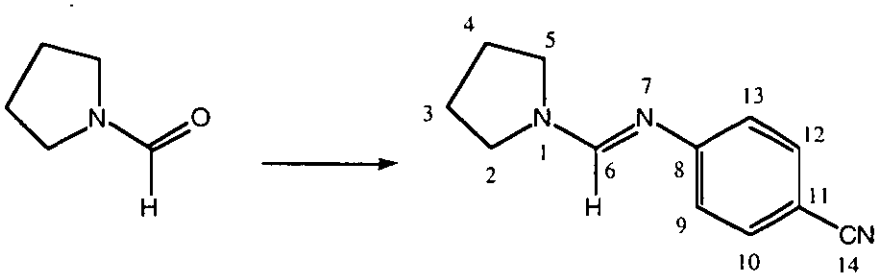
***N*-(4-chlorophenyl)-*N*-[(*E*)-1-tetrahydro-1*H*-pyrrol-1-ylmethylidene]amine:**



trans-Pyrrolidine-N'-(4-chlorophenyl)-formamidine: 84% yield, m.p. 71-73 °C. ν_{max} /cm^{-1} (nujol) 1632, 3293, 721; δ_H ($CHCl_3$), (300 MHz), 1.89-1.96 (4 H, m, 2xCH_2 at C3 and

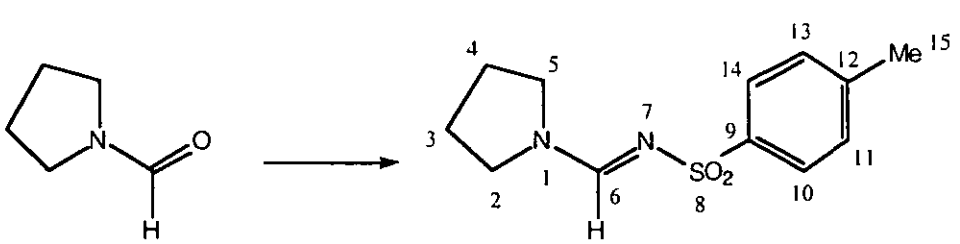
C4), 3.45-3.52 (4 H, m, 2xCH_2 at C2 and C5), 6.88 (2 H, d, *J* 8.24 Hz, arom., 2xCH at C9 and C13), 7.18 (2 H, d, *J* 8.24 Hz, arom., 2xCH at C10 and C12), 7.71 (1 H, s, NCH=N, CH at C6); δ_C (62.50 MHz), 24.82 (CH_2, C3), 24.86 (CH_2, C4), 45.26 (CH_2, C2), 48.67 (CH_2, C5), 122.27 (2xCH arom., C9 and C13), 127.17 (C arom., quat., *ipso* C–Cl, C11), 128.82 (2xCH arom., C10 and C12), 150.52 (CH, N–CH=N, C6), 150.78 (C arom., quat., *ipso* C–N, C8); *m/z* 208; exact mass calcd for $C_{11}H_{13}ClN_2$ 208.07672, found 208.07670. at C2 and C4

4-{[(*E*)-1-tetrahydro-1*H*-pyrrol-1-ylmethylidene]amino}benzene-1-carbonitrile:



trans-Pyrrolidine-N'-(4-cyanophenyl)-formamidine: 93% yield, m.p. 84-86 °C. ν_{max} /cm^{-1} (nujol) 2209, 1629; δ_H ($CHCl_3$), (250 MHz), 1.95-1.96 (4 H, m, 2xCH_2 at C3 and C4), 3.50-3.55 (4 H, m, 2xCH_2 at C2 and C5), 6.97 (2 H, d, *J* 8.40 Hz, 2xCH at C9 and C13), 7.77 (2 H, d, *J* 8.50 Hz, 2xCH at C10 and C12), 7.79 (1 H, s, NCH=N, CH at C6); δ_C (62.50 MHz), 24.63 (CH_2, C3), 25.08 (CH_2, C4), 45.46 (CH_2, C2), 48.99 (CH_2, C5), 104.43 (C quat., CN, C14), 119.93 (C arom., quat., *ipso* C–CN, C11), 121.63 (2xCH arom., C9 and C13), 133.12 (2xCH arom., C10 and C12), 150.84 (CH, N–CH=N, C6), 156.82 (C arom., quat., *ipso* C-N, C8); *m/z* 199; exact mass calcd for $C_{12}H_{13}N_3$ 199.11094, found 199.11090.

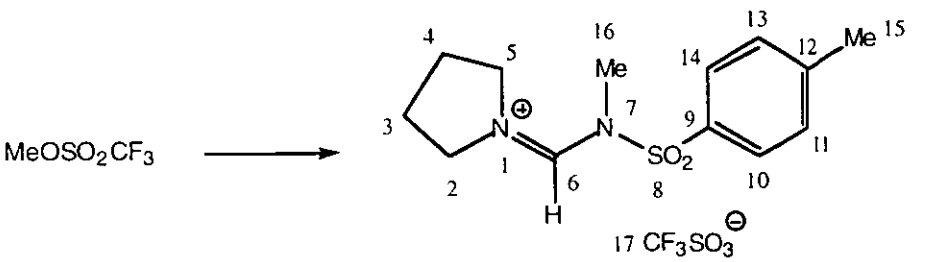
***N*1-[(*E*)-1-tetrahydro-1*H*-pyrrol-1-ylmethylidene]-4-methylbenzene-1-sulfonamide:**



trans-Pyrrolidine-N'-(4-tolylsulfonyl)-formamidine: 84% yield, m.p. 150-151 °C. ν_{max} /cm^{-1} (nujol) 1606, 1348, 1314, 1295, 1087; δ_H 1.89-1.95 (4 H, m, 2xCH_2 at C3 and C4),

2.39 (3 H, s, CH_3, C15), 3.43-3.60 (4 H, m, 2xCH_2 at C2 and C5), 7.24 (2 H, d, *J* 8.44 Hz, 2xCH at C10 and C14), 7.77 (2 H, d, *J* 8.24 Hz, 2xCH at C11 and C13), 8.31 (1 H, s, NCH=N, CH at C6); δ_C 21.38 (CH_3, C15), 24.27 (CH_2, C3), 24.93 (CH_2, C4), 46.34 (CH_2, C2), 49.86 (CH_2, C5), 126.45 (2xCH arom., C10 and C14), 129.20 (2xCH arom., C11 and C13), 139.89 (C arom. quat., *ipso* C–SO_2, C9), 142.24 (C arom. quat., *ipso* C–CH_3, C12), 155.73 (CH, N–CH=N, C6);*m/z* 252; exact mass calcd for $C_{12}H_{16}N_2O_2S$ 252.09324, found 252.09320.

1-({methyl[(4-methylphenyl)sulfonyl]amino}methylidene)-tetrahydro-1*H*-pyrrolium trifluoromethanesulfonate:

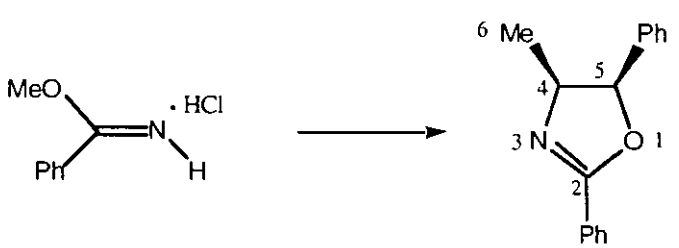


Pyrrolidine-N'-(4-tolylsulfonyl)-N'-methyl-formamidinium triflate: For the preparation of this compound see the general procedure for the synthesis of oxazolinium and formamidinium salts; 94% yield, m.p. 157-158 °C. ν_{max} /cm^{-1} (nujol) 1669, 1595, 1325, 1275, 1256, 1157; δ_H 1.99-2.13 (4 H, m, 2xCH_2 at C3 and C4), 2.40 (3 H, s, CH_3, C15), 3.41 (3 H, s, N–CH_3, C16), 4.00-4.12 (4 H, m, 2xCH_2 at C2 and C5), 7.38 (2 H, d, *J* 8.26 Hz, 2xCH at C10 and C14), 7.87 (2 H, d, *J* 8.42 Hz, 2xCH at C11 and C13), 8.63 (1 H, s, N=CHN, C6); δ_C 21.77 (CH_3, C15), 23.30 (CH_2, C3), 25.79 (CH_2, C4), 33.63 (CH_3, C16), 50.58 (CH_2, C2), 57.88 (CH_2, C5), 129.28 (2xCH arom., C10 and C14), 130.76 (2xCH arom., C11 and C14), 143.89 (C arom. quat., *ipso* SO_2, C9), 148.64 (C arom. quat., ipso CH_3, C12), 151.63 (CH, N=CH–N, C6) 178.23 (C quat. CF_3, C17); *m/z* (cation) 267; exact mass calcd for cation $C_{13}H_{19}N_2O_2S$ 267.11671 found 267.11697.

(–)-(4*S*,5*R*)-4-Methyl-5-phenyl-4,5-dihydro-1,3-oxazole:

(–)-(4S,5R)-4-Methyl-5-phenyl-oxazoline:[63] In a flask equipped with a soxhlet extractor containing 25 g of 4A molecular sieves, (1*R*,2*S*)-norephedrine, (5.00 g, 33.05 mmol), and DMF dimethyl acetal, (4.84 mL, 36.36 mmol), were dissolved and refluxed for 60 hours in dry benzene together with a catalytic amount of p-toluene sulfonic acid, (10 mg, 0.05 mmol). The reaction mixture was washed with 10% potassium bicarbonate (30 mL) and brine (30 mL), and dried over sodium sulfate. The solution was then concentrated and passed through a short column of silica gel with 30% ethyl acetate/hexane to remove residual formamidine. After evaporation of the solvents the residue was subjected to Kugelrohr distillation (150 °C at 6 mm Hg), to furnish 3.88 g of the oxazoline as a colourless oil, 73% yield. $[\alpha]^{20}_{D}$ –110.10 c=1.10, ($CHCl_3$) (lit. $[\alpha]^{20}_{D}$ –228)[63]; ν_{max} /cm^{-1} (neat) 1631 (ν_{CN}), 1098 (ν_{CO}); δ_H ($CDCl_3$), (400 MHz), 0.81 (3 H, d, *J* 7.00 Hz, CH_3, C6), 4.43-4.47 (1 H, m, CH at C4), 5.58 (1 H, d, *J* 10.03 Hz, CH at C5), 7.03 (1 H, s, N=CH–O, CH at C2), 7.22-7.38 (5 H, m, arom., 5xCH at Ph group); δ_C (62.50 MHz), 17.62 (CH_3, C6), 64.20 (CH, C4), 83.00 (CH, C5), 126.05 (CH arom., *para*), 127.86 (2xC arom., *ortho*), 128.22 (2xCH arom., *meta*), 128.54 (C arom., quat., *ipso* C at Ph ring), 153.85 (CH, N=CH–O, C2);*m/z* 161.

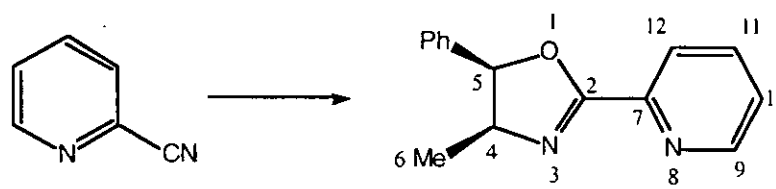
(–)-(4*S*,5*R*)-4-Methyl-2,5-diphenyl-4,5-dihydro-1,3-oxazole:



(–)-(4S,5R)-4-Methyl-2,5-diphenyl-oxazoline:[64,210] A solution of (1*R*,2*S*)-norephedrine, (5.00 g, 33.05 mmol), and methyl benzimidate hydrochloride (5.15 g, 30.03 mmol) in 80 mL of 1,2 dichloroethane was heated under reflux for 20 hours. After filtration

the solvent was removed by rotary evaporation. The residue was transferred on a silica column and eluted initially with dichloromethane to remove non polar impurities and subsequently with 50% ethyl acetate/petrol to furnish 4.83 g of the pure oxazoline as a colourless oil in 68% yield. $[\alpha]^{20}_{D}$ –156.47 c=2.08, ($CHCl_3$), ν_{max} /cm^{-1} (neat) 1651, 1099; δ_H ($CDCl_3$), (250 MHz), 0.90 (3 H, d, *J* 7.00 Hz, CH_3, C6), 4.64-4.70 (1 H, m, CH at C4), 5.77 (1 H, d, *J* 9.79 Hz, CH at C5), 7.25-7.52 (8 H, m, arom.), 8.04-8.08 (2 H, m, arom.); δ_C (62.50 MHz), 17.71 (CH_3, C6), 65.40 (CH, C4), 84.00 (CH, C5), 125.98 (2xCH arom.), 126.10 (2xCH arom.), 127.81 (CH arom.), 128.28 (2xCH arom.), 128.35 (2xCH arom.), 131.40, (CH arom.), 132.22 (C arom., quat., *ipso* Ph ring at C5), 137.15 (C arom., quat., *ipso* Ph ring at C2), 162.37 (C quart, N=C–O, C2); *m/z* 237.

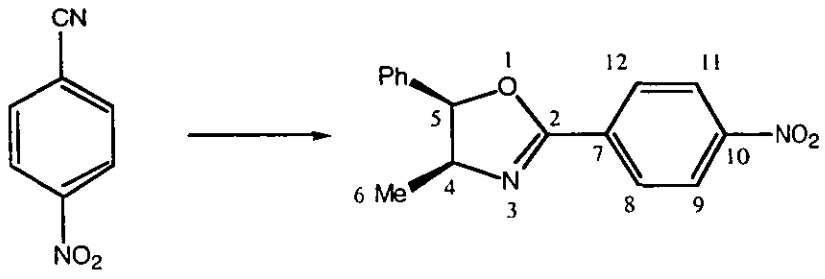
(–)-(4*S*,5*R*)-4-Methyl-5-phenyl-2-pyridin-2-yl-4,5-dihydro-1,3-oxazole:



(–)-(4S,5R)-4-Methyl-5-phenyl-2-(2-pyridyl)-4,5-dihydro-oxazole:[65,221] A solution of 2-cyanopyridine (5.2 g, 50 mmol) and sodium methoxide, (0.84 g of 25% solution in methanol, catalytic amount, 5 mmol) in methanol (100 mL) is stirred overnight at ambient temperature. Two drops of acetic acid are added to neutralise the base and the solvent is removed by evaporation to give the imidate as a yellow semi-solid which is reacted without further purification. The imidate and (1*R*,2*S*)-norephedrine, (8.32 g, 55 mmol, 1.1 eq) were heated neat (open flask) together with one drop of concentrated hydrochloric acid at 60 °C for 20 hours. The reaction mixture is occasionally flushed with nitrogen to remove the volatiles produced (methanol) especially towards the end of the reaction. The reaction mixture is then allowed to cool and 30 mL of tetrahydrofuran are added. Further cooling at –20 °C causes precipitation of the oxazoline which is collected by filtration as a colourless crystalline solid, 8.62 g, 73% yield, m.p. 138 °C (lit. m.p. 130 °C)[65]. $[\alpha]^{20}_{D}$ –369.02 c=2.00, ($CHCl_3$); ν_{max} /cm^{-1} (nujol) 1656, 1089; δ_H ($CDCl_3$), (250 MHz), 0.92 (3 H, d, *J* 7.00 Hz, CH_3, C6), 4.69-4.76 (1 H, m, CH at C4), 5.84 (1 H, d, *J* 9.91 Hz, CH at C5), 7.25-7.44 (6 H, m, arom., 5xCH at Ph group and CH at C12), 7.77-7.84 (1 H, m, arom. at C11), 8.07-8.10 (1 H, d, *J* 7.91 Hz, arom. at C12), 8.75-8.77 (1 H, d, *J* 4.61 Hz, arom. at C10); δ_C (100 MHz), 18.01 (CH_3, C6), 66.16 (CH, C4), 85.15 (CH, C5), 122.23 (CH

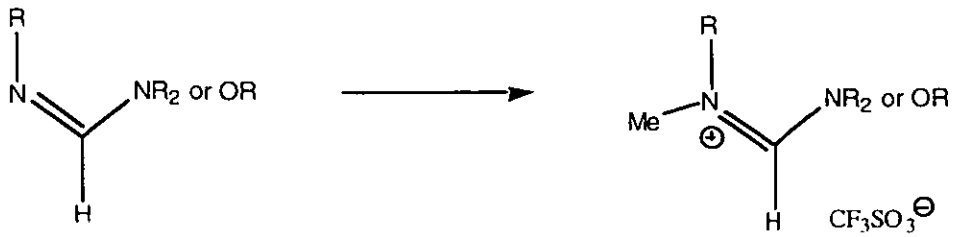
arom.), 124.33 (CH arom.), 126.82 (2xCH arom., Ph ring, *ortho*), 128.62 (CH arom.), 128.93 (2xCH arom., Ph ring, *meta*), 137.03 (CH arom.), 137.28 (C arom., quat., *ipso* Ph ring), 147.12 (C arom., quat., C7), 150.37 (CH arom.), 162.55 (C quat., N=C–O, C2); *m/z* 238; exact mass calcd for $C_{15}H_{14}N_2O$ 238.11060, found 238.11060.

(–)-(4*S*,5*R*)-4-Methyl-5-phenyl-2-(4-nitrophenyl)-4,5-dihydro-1,3-oxazole:



(–)-(4S,5R)-4-Methyl-5-phenyl-2-(4-nitrophenyl)-oxazoline: This was prepared from 4-nitrobenzonitrile, according to the procedure described above for the 2-pyridyl derivative; pale yellow solid, 68% yield, m.p. 180.5 °C. $[\alpha]^{20}_D$ –346.07 c=1.33, ($CHCl_3$); ν_{max} /cm^{-1} (nujol) 1648, 1596, 1518, 1093; δ_H ($CDCl_3$), (400 MHz), 0.94 (3 H, d, *J* 7.05 Hz, CH_3, C6), 4.70-4.78 (1 H, m, CH at C4), 5.85 (1 H, d, *J* 9.88 Hz, CH at C5), 7.26-7.43 (5 H, m, arom., 5xCH at Ph group), 8.23-8.33 (4 H, m, 4xCH at $C_6H_4NO_2$ group); δ_C (62.50 MHz), 15.98 (CH_3, C6), 64.36 (CH, C4), 83.15 (CH, C5), 122.01 (2xCH arom., Ph ring, *meta*), 125.97 (2xCH arom., Ph ring, *ortho*), 126.82 (CH arom., Ph ring, *para*), 127.74 (2xCH arom., at C9 and C11), 128.02 (2xCH arom., at C8 and C12), 134.84 (C arom., quat., *ipso* Ph ring), 138.31 (C arom., quat., C7), 148.06 (C arom., quat., C10), 159.67 (C quat., O–C=N, C2); *m/z* 282; exact mass calcd for $C_{16}H_{14}N_2O_3$ 282.10043, found 282.10040. Found C, 68.33; H, 5.00; N, 9.94; $C_{16}H_{14}N_2O_3$ requires: C, 68.08; H, 5.00; N, 9.92%.

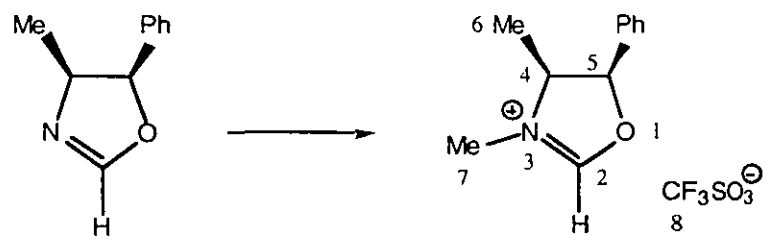
General procedure for the preparation of oxazolinium and formamidinium salts:



To an ice cooled solution of the oxazoline in dry dichloromethane (2 mL per

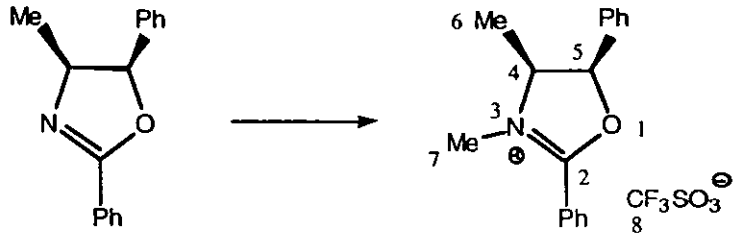
g), an equimolar amount of methyl triflate also in dry dichloromethane, is added slowly under nitrogen via a syringe. When the addition is complete the cooling bath is removed and the mixture is stirred overnight. The solution is concentrated to half its volume by rotary evaporation of solvent at temperature no greater than 30 °C. Upon slow addition of dry ether, the organic salt precipitated, collected by filtration and washed with additional dry ether. The salt is usually obtained in high yield and virtually pure. In the cases where the salt was obtained as oil, it seperated out of the solvents after the addition of ether and was isolated using a small separating funnel. Maceration of the oil with additional dry ether (vigorous stirring) followed by separation and drying of residual solvents under vacuum, improved purity.

(–)-(4*S*,5*R*)-3,4-Dimethyl-5-phenyl-4,5-dihydro-1,3-oxazol-3-ium trifluoromethanosulfonate:



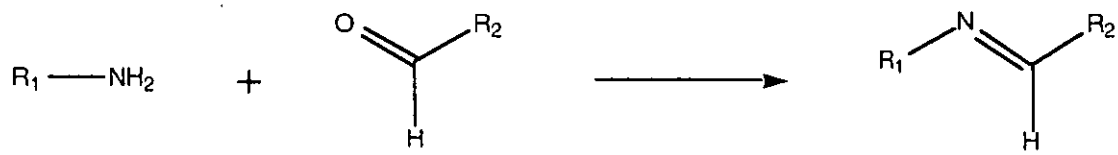
(–)-(4S,5R)-N,4-Dimethyl-5-phenyl-oxazolinium triflate: pale yellow oil; 93% yield. $[\alpha]^{20}_D$ –65.05 c=0.43, (CH_3CN); ν_{max} /cm^{-1} (neat) 1673, 1458, 1258, 1163, 1030, 638; δ_H ($CDCl_3$), (250 MHz), 1.00-1.04 (3 H, m, CH_3, C6), 3.52-3.56 (3 H, m, CH_3, C7), 4.85-4.89 (1 H, m, CH at C4), 6.53-6.58 (1 H, m, CH at C5), 7.29-7.31 (2 H, m, arom., *ortho*), 7.43-7.47 (3 H, m, arom, *meta* and *para*), 9.12 (1 H, s, O–CH=N, CH at C2); δ_C (62.50 MHz), 13.35 (CH_3, C6), 32.71 (CH, C4), 61.23 (CH_3, C7), 90.52 (CH, C5), 126.54 (2xCH arom., *meta*), 128.92 (C arom. quat., *ipso* Ph ring), 129.00 (2xCH arom.,*ortho*), 130.00 (CH arom., *para*), 165.59 (CH, O–CH=N, C2), 178.15 (C quat. CF_3, C8); *m/z* 176. Found C, 43.95; H, 4.32; N, 4.36; $C_{12}H_{14}NO_4S$ requires: C, 44.31; H, 4.34; N, 4.31%.

(–)-(4*S*,5*R*)-3,4-Dimethyl-2,5-diphenyl-4,5-dihydro-1,3-oxazol-3-ium trifluoromethanosulfonate:



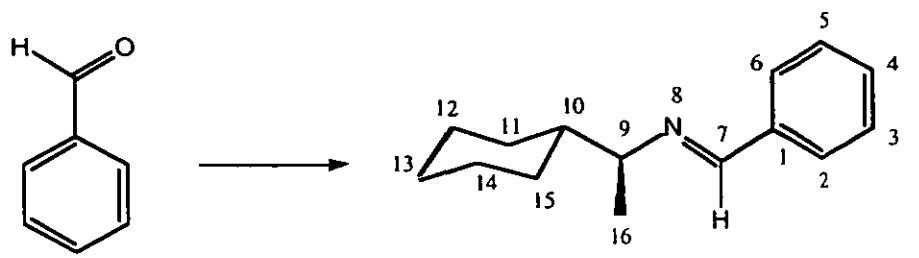
(–)-(4S,5R)-N,4-Dimethyl-2,5-diphenyl-oxazolinium triflate: White solid, 92% yield, m.p. 104 °C. $[\alpha]^{20}_D$ –47.22 c=1.86, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1656, 1602, 1029; δ_H (CD_3CN), (250 MHz), 1.11 (3 H, d, *J* 6.99 Hz, CH_3, C6), 3.60 (3 H, s, CH_3, C7), 5.16-5.23 (1 H, m, CH at C4), 6.70 (1 H, d, *J* 10.28 Hz, CH at C5), 7.26-7.98 (10 H, m, arom.); δ_C (250 MHz), 14.16 (CH_3, C6), 34.82 (CH, C4), 64.50 (CH_3, C7), 87.64 (CH, C5), 126.53 (2xCH arom.), 128.97 (2xCH arom.), 129.50 (2xCH arom.), 130.05 (CH arom.), 130.48 (2xCH arom.), 131.12 (C arom. quat., *ipso* Ph group at C5), 133.86 (C arom. quat., *ipso* Ph group at C2), 135.75 (CH arom.), 171.75 (C quat., O–C=N, C2), 178.82 (C quat. CF_3, C8); *m/z* (cation) 252; exact mass calcd for cation $C_{17}H_{18}NO$ 252.1388, found 252.1388; Found C, 53.60; H, 4.49; N, 3.45; $C_{18}H_{18}NO_4S$ requires: C, 53.86; H, 4.52; N, 3.49%.

General procedure for the preparation of aldimines:



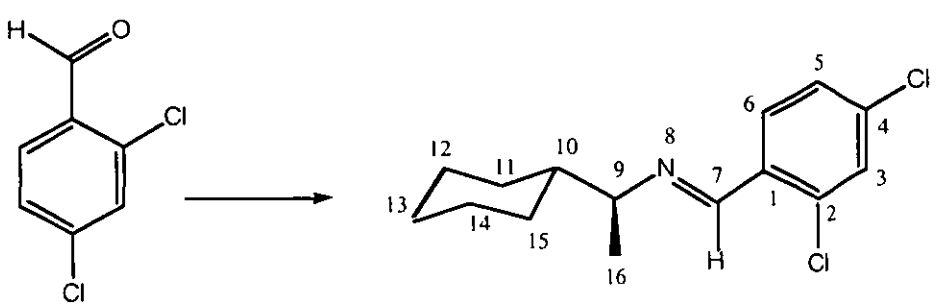
An equimolar solution of the aldehyde and primary amine in dry dichloromethane (1 g of aldehyde per 50 mL of solvent)[72] is left overnight over molecular sieves under nitrogen atmoshere. The sieves are removed by filtration and the solvent is evaporated in *vaccuo*. The products are obtained in almost quantitative yields and can be reacted further without purification as they are essentially pure.

(–)-(1*R*)-*N*-(1-cyclohexylethyl)-*N*-[(*E*)-1-phenylmethylidene]amine:



(–)-(1R)-cyclohexyl-ethylamine-trans-benzaldehyde imine: colourless oil; 91% yield. $[\alpha]^{20}_D$ –110.08 c=1.20, ($CHCl_3$); ν_{max} /cm^{-1} (neat) 1645, 1580; δ_H ($CDCl_3$), (250 MHz), 0.88-1.22 (2 H, m, from cyclohexyl group), 1.25 (3 H, d, *J* 6.45 Hz, CH_3, C16), 1.32-1.86 (9 H, m, from cyclohexyl group), 2.98-3.11 (1 H, quintet,*J* 6.54 Hz, CH at C9), 7.39-7.42 (3 H, m, arom., *meta* and *para*), 7.73-7.77 (2 H, m, *ortho*), 8.23 (1 H, s, HC=N, CH at C7); δ_C (62.50 MHz), [19.85 (CH), 26.20 (CH_2), 26.35 (CH_2), 26.54 (CH_2), 29,78 (CH_2), 29.91 (CH_2), all from cyclohexyl group, C10-C15 respectively], 43.68 (CH_3, C16), 71.90 (CH, C9), 128.00 (2xCH arom., *meta*), 128.42 (2xCH arom., *ortho*), 130.16, (CH arom., *para*), 137.00 (C arom. quat., *ipso* Ph ring), 158.50 (CH, HC=N, C7); *m/z* 215; exact mass calcd for cation $C_{15}H_{21}N$ 215.1673 and for MH^+ 216.1752; found for MH^+ 216.1752. Found C, 83.90; H, 10.04; N, 6.74; $C_{15}H_{21}N$ requires: C, 83.67; H, 9.83; N, 6.50%.

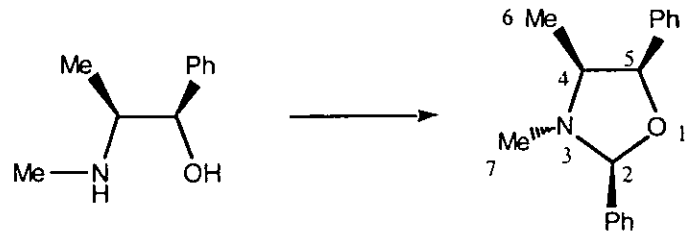
1-(*R*)-*N*-(1-cyclohexylethyl)-*N*-[(*E*)-1-(2,4-dichlorophenyl)methylidene]amine:



1-(R)-cyclohexyl-ethylamine-trans-2,4-dichlorobenzaldehyde imine: yellow oil; 81% yield. $[\alpha]^{20}_D$ –64.13 c=1.37, ($CHCl_3$); ν_{max} /cm^{-1} (neat) 1636, 1586, 858, 824; δ_H ($CDCl_3$), (250 MHz), 0.73-1.00 (2 H, m, from cyclohexyl group), 1.07 (3 H, d, *J* 6.43 Hz, CH_3, C16), 1.16-1.69 (9 H, m, from cyclohexyl group), 2.90-3.01 (1 H, quintet, *J* 6.49 6.48 Hz, CH at C9), 7.10 (1 H, dd, *J* 8.50 1.32 Hz, arom., CH at C5), 7.22 (1 H, d, *J* 1.58 Hz, arom., CH at C3), 7.85 (1 H, d, *J* 8.50 Hz, arom., CH at C6), 8.41 (1 H, s, CH at C7); δ_C (62.50

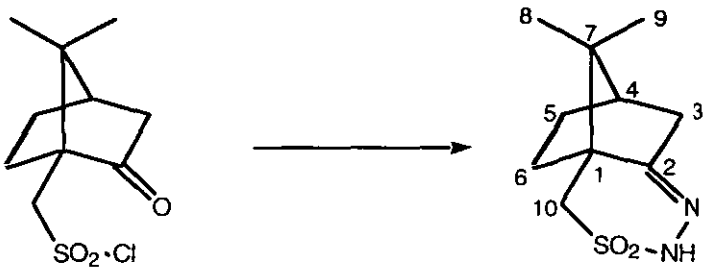
MHz), 19.75 (CH_3, C16), [26.15 (CH_2), 26.29 (CH_2), 26.48 (CH_2), 29,67 (CH_2), 29.80 (CH_2), 43.62 (CH), all from cyclohexyl group, C11-C15 and C10 respectively], 71.68 (CH, C9), 127.32 (CH arom., C6), 129.31 (CH arom.), 129.36, (CH arom.), 132.00 (C arom. quat., *ipso* C–Cl, C2), 135.10 (C arom. quat., *ipso* C–Cl, C4), 136.80 (C arom. quat., *ipso* C=N group, C1), 154.24 (CH, HC=N, C7); *m/z* 283; exact mass calcd for $C_{15}H_{19}Cl_2N$ 283.0894 and for MH^+ 284.09730; found for MH^+ 284.09730. Found C, 63.33; H, 6.71; N, 4.97; $C_{15}H_{19}Cl_2N$ requires: C, 63.39; H, 6.74; N, 4.93%.

(–)-(2*S*,4*S*,5*R*)-3,5-dimethyl-2,4-diphenyl-1,3-oxazolane:



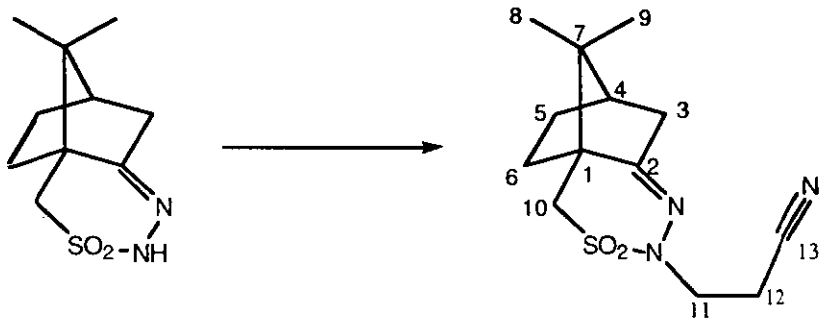
(–)-(2S,4S,5R)-3,5-dimethyl-2,4-diphenyl-oxazolidine:[67,69] An equimolar solution of benzaldehyde (3.21 g, 0.03 mol) and (1*R*,2*S*)-ephedrine (5.00 g, 0.03 mol) in 320 mL of toluene was refluxed under Dean-Stark conditions for 3 hours. Removal of the solvent in vacuuo resulted a nearly colourless oil to which light petroleum is added (65 mL), brought to boil and left to attain ambient temperature overnight. The product precipitates as colourless crystalls and collected by filtration; 6.75 g, 89% yield; m.p. 71 °C, (lit. m.p. 68 °C).[67] $[\alpha]^{20}_D$ –55.02 c=1.29, ($CHCl_3$), (lit. $[\alpha]^{20}_D$ –50.50 c=1.50, (benzene)[67]); ν_{max} /cm^{-1} (neat) 1079, 1058; δ_H ($CDCl_3$), (400 MHz), 0.81 (3 H, d, *J* 6.42 Hz, CH_3, C6), 2.21 (3 H, s, CH_3, C7), 2.96-3.02 (1 H, m, CH at C4), 4.71 (1 H, s, CH at C2), 5.17 (1 H, d, *J* 8.25 Hz, CH at C5), 7.28-7.69 (10 H, m, arom.); δ_C (100 MHz), 15.86 (CH_3, C6), 36.55 (CH, C4), 64.82 (CH_3, C7), 83.28 (CH, C5), 99.67 (CH, C2), 128.73 (CH arom.), 128.81 (2xCH arom.), 128.89 (2xCH arom.), 129.04 (2xCH arom.), 129.11 (2xCH arom.), 129.52 (CH arom.), 139.01 (C arom. quat.), 140.68 (C arom. quat.); *m/z* 253; exact mass calcd for $C_{17}H_{19}NO$ 253.1466 and for MH^+ 254.1545; found for MH^+ 254.1545. Found C, 79.20; H, 7.62; N, 5.45; $C_{17}H_{19}NO$ requires: C, 80.60; H, 7.56; N, 5.53%.

(–)-(1*S*,8*S*)-11,11-Dimethyl-3λ^6-thia-4,5-diaza-tricyclo[6.2.1.0^{1,6}]undec-5-ene-3,3-dione:



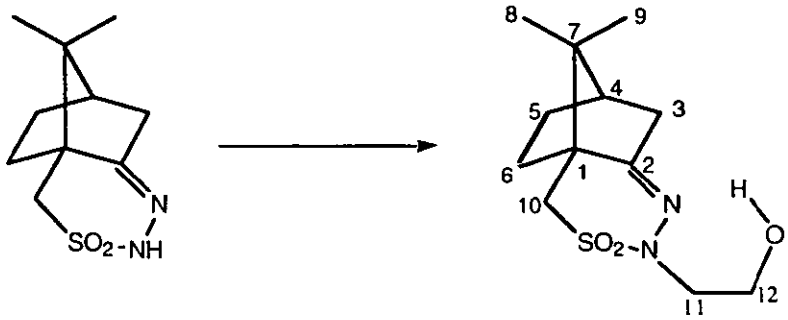
(–)-(1S,4S)-Camphor-10-sulfonylhydraz-2-one:[70,203] (+)-Camphor sulfonyl chloride (20 g, 79.76 mmol) was dissolved in dry dichloromethane (200 mL) and added dropwise over a period of 6 hours via a dropping funnel, to an ice cooled, vigorously stirred solution of hydrazine monohydrate (32 g, 0.64 mol) in dichloromethane/water (1:1, 200 mL). The reaction mixture was then transferred to a 1 L separating funnel and the layers were separated. The organic phase was washed with water (2X100 mL) and without further drying, the solvent was removed. Toluene (250 mL), was added to the residue and the solution was refluxed under Dean-Stark conditions until no water condensed. With the same apparatus the solution was concentrated to approximately one third of the original volume and allowed to attain ambient temperature slowly. The product precipitates out as colourless crystalls. In the case where crystallisation from toluene failed the sovent was removed completely in *vaccuo* and the residue is recrystallised from ethanol, (12.7 g) 70% yield, m.p. 177-179 °C (lit. m.p. 186-188 °C)[70]. $[\alpha]^{20}_D$ –12.10 c=2.20, ($CHCl_3$); ν_{max} /cm^{-1} (nujol) 3253, 1659, 1376, 1318, 1259; δ_H ($CDCl_3$), (250 MHz), 0.93 (3 H, s, CH_3 at C8), 1.01 (3 H, s, CH_3 at C9), 1.36-1.50 (1 H, m, *exo* at C5), 1.70-2.12 (4 H, m, *endo* at C5 and C6, *exo* at C6 and bridgehead H at C4), 2.34-2.47 (1 H, m, *exo* at C3), 2.51-2.64 (1 H, m, *endo* at C3), 3.16 (1 H, dd, *J* 13.18, 1.64 Hz, upfield portion of an *AB* system, CH*H*-SO_2 at C10), 3.16 (1 H, d, *J* 15.20 Hz, downfield portion of an *AB* system, C*H*HSO_2 at C10), 7.44 (1 H, br. s, NH); δ_C (100 MHz), 18.43 (CH_3, C8), 20.36 (CH_3, C9), 25.44 (CH_2, C5), 31.66 (CH_2, C6), 36.58 (CH_2, C3), 44.85 (CH, C4), 48.66 (CH_2, C10), 49.67 (C quat., C7), 56.47 (C quat., C1), 165.58 (C quat., C=N, C2); data consistent with previous report.[203] *m/z* 228; exact mass calcd for $C_{10}H_{16}N_2O_2S$ 228.0932 found 230.0932. Found C, 52.80; H, 7.11; N, 12.40; $C_{10}H_{16}N_2O_2S$ requires: C, 52.61; H, 7.06; N, 12.27%.

(+)-(1S,8S)-2-(11,11-Dimethyl-3,3-dioxo-3λ⁶-thia-4,5-diaza-tricyclo[6.2.1.0¹,⁶]undec-5-en-4-yl)propanenitrile:



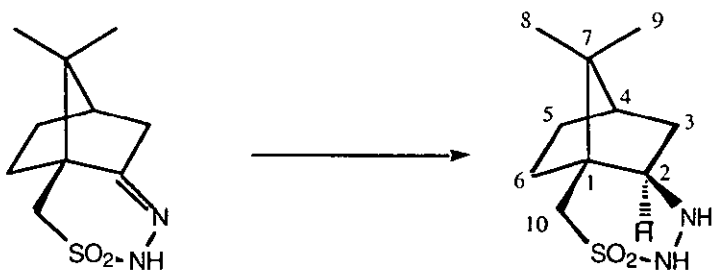
(+)-(1S,4S)-Camphor-10-sulfonylhydraz-2-one-N-(2-ethyl cyanide): To a solution of TBAF trihydrate, (0.67 g, 2.15 mmol), in dry DMF (30 mL), camphor sulfonyl hydrazone, (1.00 g, 4.3 mmol), is added, followed by acrylonitrile (0.28 g, 4.30 mmol). The solution is left to stand at ambient temperature over molecular sieves, under nitrogen, for 4 hours with occusional swirling of the flask. Water (30 mL) is added to the solution and extracted with diethyl ether (4x15 mL). The combined ethereal layers were dried over magnesium sulfate and the solvent evaporated in *vaccuo*. The colourless oil that resulted was dissolved in the minimum amount of ethyl acetate required and the product was precipitated by addition of light petroleum as a white solid; 0.77 g, 64% yield, m.p. 152-153 °C. $[\alpha]^{20}_{D}$ +45.17 c=1.20, ($CHCl_3$); ν_{max} /cm^{-1} (nujol) 2245, 1666, 1376, 1322, 1265; δ_H ($CDCl_3$), (300 MHz), 0.93 (3 H, s, CH_3 at C8), 1.02 (3 H, s, CH_3 at C9), 1.37-1.49 (1 H, m, *exo* at C5), 1.72-2.15 (4 H, m, *endo* at C5 and C6, *exo* at C6 and bridgehead H at C4), 2.30-2.46 (1 H, m, *exo* at C3), 2.51-2.66 (1 H, m, *endo* at C3), 2.72-2.83 (2 H, m, CH_2, C11), 3.23 (2 H, dd, *J* 24.48, 13.48 Hz, *AB* system, CH_2SO_2, C10), 3.66-3.95 (2 H, m, CH_2, C12); δ_C (100 MHz), 18.87 (CH_2, C5), 19.71 (CH_3, C8), 21.60 (CH_3, C9), 28.67 (CH_2, C6), 32.92 (CH_2, C3), 37.90 (CH_2, C11), 44.97 (CH_2, C10), 45.99 (CH, C4), 50.43 (CH_2, C12), 50.95 (C quat., C7), 57.96 (C quat., C1), 119.01 (C quat., C13), 166.90 (C quat., C=N–N, C2);*m/z* 281; exact mass calcd for $C_{13}H_{19}N_3O_2S$ 281.1197 found 281.1192. Found C, 55.39; H, 6.83; N, 14.93; $C_{13}H_{19}N_3O_2S$ requires: C, 55.49; H, 6.81; N, 14.93%.

(+)-(1*S*,8*S*)-4-(2-Hyroxyethyl)-11,11-dimethyl-3λ^6-thia-4,5-diazatricyclo[6.2.1.0^{1,6}]undec-5-ene-3,3-dione:



(+)-(1S,4S)-Camphor-10-sulfonylhydraz-2-one-N-(ethyl alcohol): Prepared according to the same procedure used for the N-ethanonitrile derivative, with ethylene oxide, (1.20 equivalents), as the electrophile; 28-30% yield (unoptimised), m.p. 115-117 °C. $[\alpha]^{20}_D$ +28.05 c=1.00, ($CHCl_3$); ν_{max} /cm^{-1} (nujol) 3363, 1646, 1376, 1333, 1267; δ_H ($CDCl_3$), (300 MHz), 0.94 (3 H, s, CH_3 at C8), 1.01 (3 H, s, CH_3 at C9), 1.37-1.50 (1 H, m, *exo* at C5), 1.73-2.14 (4 H, m, 4 H, m, *endo* at C5 and C6, *exo* at C6 and bridgehead H at C4), 2.33-2.48 (1 H, m, *exo* at C3), 2.51-2.65 (1 H, m, *endo* at C3), 2.71 (1 H, br. s, OH), 3.24 (2 H, dd, *J* 27.50 13.20 Hz, *AB* system, CH_2SO_2, C10), 3.83-4.00 (4 H, m, 2xCH_2 at C11 and C12); δ_C (400 MHz), 19.48 (CH_3, C8), 20.36 (CH_3, C9), 27.42 (CH_2, C5), 31.52 (CH_2, C6), 36.94 (CH_2, C3), 44.86 (CH, C4), 48.58 (CH_2, C11), 49.67 (CH_2, C10), 50.23 (C quat., C7), 56.43 (C quat., C1), 61.64 (CH_2, C12), 164.73 (C quat., C=N, C2);*m/z* 272; exact mass calcd for $C_{12}H_{20}N_2O_3S$ 272.1194 found 281.1190. Found C, 52.71; H, 7.44; N, 10.29; $C_{12}H_{20}N_2O_3S$ requires: C, 52.92; H, 7.40; N, 10.29%.

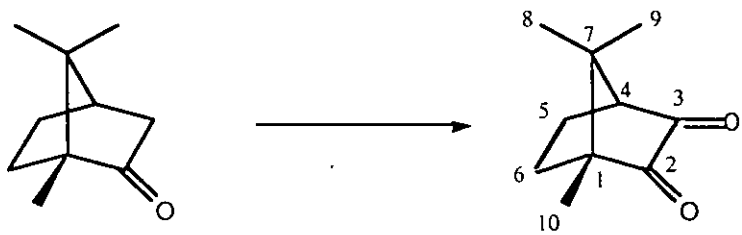
(–)-(1*S*,6*R*,8*S*)-11,11-dimethyl-3λ^6-thia-4,5-diazatricyclo[6.2.1.0^{1,6}]undecane-3,3-dione:



(–)-(1S,2R,4S)-Camphor-10-sulfonylhydraz-2-ine: To an ice cooled solution of camphor-10-sulfonyl hydrazone (2.28 g, 10 mmol) and pyridine-borane (3 mL, 10 mmol) in

ethanol/dioxane (50 mL, 1:1) was added 20% ethanolic HCl (50 mL). After stirring for 1 hour the solvents were evaporated in vacuuo and 10% sodium carbonate was added to the residue. Extraction with chloroform, drying over sodium sulfate and removal of the solvent, resulted in a pale yellow oil which was dissolved in a small amount of dichloromethane (20 mL). The product is precipitated by slow addition of hexane and recrystallised from dichloromethane/hexane; (1.74 g) 75% yield, m.p. 212 °C. $[\alpha]^{20}_D$ –93.12 c=2.17, ($CHCl_3$); ν_{max} /cm^{-1} (nujol) 3347, 3371, 3156, 3240, 1376, 1333, 1267; δ_H ($CDCl_3$), (250 MHz), 0.94 (3 H, s, CH_3 at C8), 1.18-1.28 (2 H, m, *exo* at C5 and C6), 1.38 (3 H, s, CH_3 at C9), 1.55-1.83 (5 H, m, *endo* at C3, C5 and C6, *exo* at C3 and bridgehead H at C4), 3.08 (1 H, t, *J* 5.03 Hz, *endo* at C3), 3.27 (2 H, dd, *J* 94.39, 14.51 Hz, *AB* system, CH_2SO_2, C10), 5.52 (2 H, br. s, 2xNH); δ_C (100 MHz), 20.09 (CH_3, C8), 20.78 (CH_3, C9), 25.70 (CH_2, C5), 33.67 (CH_2, C6), 37.31 (CH_2, C3), 45.28 (CH, C4), 46.36 (C quat., C7), 49.37 (C quat., C1), 49.79 (CH_2, C10), 62.91 (CH, C2);*m/z* 230; exact mass calcd for $C_{10}H_{18}N_2O_2S$ 230.1089 found 230.1089. Found C, 52.18; H, 7.93; N, 12.24; $C_{10}H_{18}N_2O_2S$ requires: C, 52.15; H, 7.88; N, 12.16%.

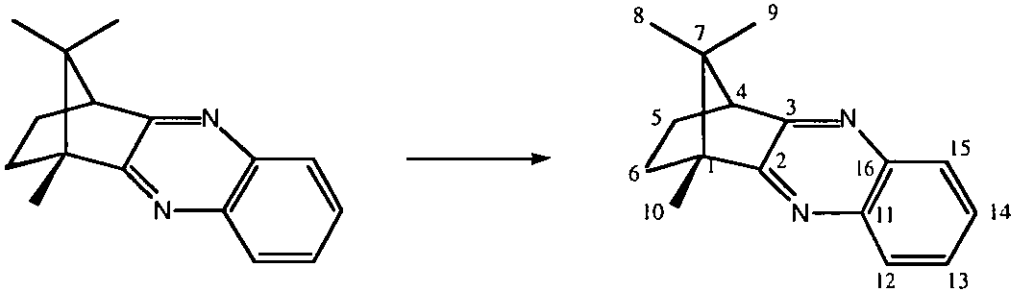
(+)-(1*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptane-2,3-dione:



(+)-(1S,4S)-Camphorquinone:[211,212] A suspension of camphor, (4.65 g, 0.030 mol), and selenium dioxide, (7.95 g, 0.070 mol), in acetic anhydride, (5 mL), was heated under reflux for 6 hours, allowed to cool and filtered. Acetic acid (2 mL) was added and the solution was neutralised with 20% sodium hydroxide; this causes the precipitation of a yellow solid. The suspension is extracted with diethyl ether and dried over sodium sulfate. Evaporation of the solvent under reduced pressure furnished the quinone which was recrystallised from hexane or hexane/ether; 4.4 g, 85% yield, m.p. 198 °C (lit. m.p. 199 °C).[211] $[\alpha]^{20}_D$ +100.05 c=2.00, (C_7H_8), (lit. $[\alpha]^{27}_D$ +105.00 c=1.96, (C_6H_6)[211]); ν_{max} /cm^{-1} (nujol) 1745; δ_H ($CDCl_3$), (400 MHz), 0.94 (3 H, s, CH_3 at C8), 1.07 (3 H, s, CH_3 at C9), 1.11 (3 H, s, CH_3 at C10), 1.62-1.68 (2 H, m, *exo* at C5 and C6), 1.90-1.96 (1 H, m, *endo* at C5), 2.21-2.14 (1 H, m, *endo* at C6), 2.64 (1 H, d, *J* 5.34 Hz, bridgehead H at C4); δ_C (100 MHz), 9.50 (CH_3, C8), 17.79 (CH_3, C9), 21.48 (CH_3, C10), 22.65 (CH_2, C5), 30.31 (CH_2, C6), 42.97 (C quat., C7), 58.35 (CH, C4), 59.03 (C quat., C1),

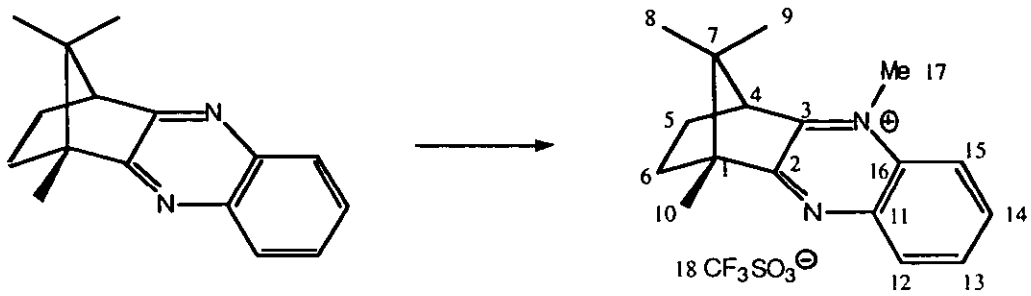
203.23 (C quat., C=O, C3), 205.21 (C quat., C=O, C2);*m/z* 166; exact mass calcd for $C_{10}H_{14}O_2$ 166.09937 found 166.09940. Found C, 72.66; H, 8.53; $C_{10}H_{14}O_2$ requires: C, 72.26; H, 8.49%.

(+)-(1*R*,12*S*)-1,15,15-trimethyl-3,10-diazatetracyclo[10.2.1.$0^{2,11}$.$0^{4,9}$]pentadeca-2,4(9),5,7,10-pentaene:



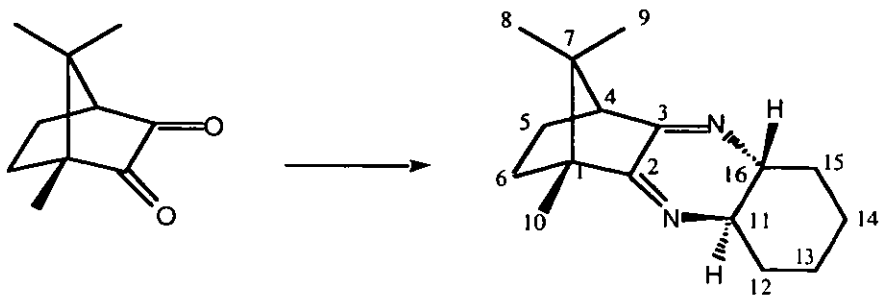
(+)-(1R,4S)-Camphorquinoxal-2,3-ine:[79-81,215] An equimolar solution of camphorquinone, (2.00 g, 0.012 mol), and 1,2-diamino-benzene, (1.30 g, 0.012 mol), in dry dichloromethane (100 mL) was allowed to stand overnight over molecular sieves. After filtration and removal of the solvent under reduced pressure, the yellow residue was (re)crystallised from hexane (seeding may be required), to furnish 2.20 g of the aromatic diimine, (quinoxaline), 77% yield, m.p. 74 °C, (lit. m.p. 74 °C).[80] $[\alpha]^{20}_D$ +27.01 c=1.15, ($CHCl_3$), (lit. $[\alpha]^{27}_D$ +29.03 c=2.00, ($CHCl_3$)[215]); ν_{max} /cm^{-1} (nujol) 1742; δ_H ($CDCl_3$), (400 MHz), 0.61 (3 H, s, CH_3 at C8), 1.09 (3 H, s, CH_3 at C9), 1.42 (3 H, s, CH_3 at C10), 1.39-1.43 (2 H, m, *exo* at C5 and C6), 2.01-2.05 (1 H, m, *endo* at C5), 2.24-2.30 (1 H, m, *endo* at C6), 3.04 (1 H, d, *J* 4.40 Hz, bridgehead H at C4), 7.59-7.63 (2 H, m, arom.), 7.96-7.98 (1 H, m, arom.), 8.01-8.04 (1 H, m, arom.); δ_C (100 MHz), 8.60 (CH_3, C8), 17.94 (CH_3, C9), 18.85 (CH_3, C10), 23.21 (CH_2, C5), 30.44 (CH_2, C6), 51.88 (CH, C4), 52.35 (C quat., C7), 52.74 (C quat., C1) [126.57 (CH arom.), 126.60 (CH arom.), 127.24 (CH arom.), 127.39 (CH arom.), C12-C15], 139.91 (C arom. quat., C11), 140.12 (C arom. quat., C16), 162.27 (C quat., C=N, C3), 164.03 (C quat., C=N, C2); *m/z* 238; exact mass calcd for $C_{16}H_{18}N_2$ 238.14699 found 238.14700. Found C, 80.70; H, 7.63; N, 11.81; $C_{16}H_{18}N_2$ requires: C, 80.63; H, 7.61; N, 11.75%.

(+)-(1*S*,12*R*)-3,12,15,15-tetramethyl-10-aza-3-azoniatetracyclo[10.2.1.$0^{2,11}$.$0^{4,9}$] pentadeca-2,4(9),5,7,10-pentaene trifluoromethanesulfonate:



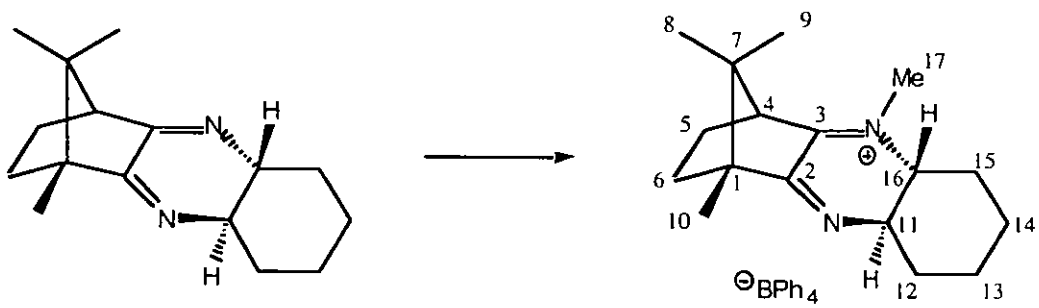
(+)-(1R,4S)-anti-N-methyl-Camphorquinoxal-2,3-inium trifluoromethanesulfonate: Prepared as described previously for the quartenisation of oxazolines and formamidines in 87% yield, white solid, m.p. 194 °C (dec.). $[\alpha]^{20}_{D}$ +77.04 c=1.05, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1522, 1264, 1156, 1035; δ_H (CD_3CN), (250 MHz), 0.73 (3 H, s, CH_3, C8), 1.22 (3 H, s, CH_3, C9), 1.50 (3 H, s, CH_3, C10), 1.53-1.60 (1 H, m, *exo* at C5), 1.68-1.79 (1 H, m, *exo* at C6), 2.14-2.25 (1 H, m, *endo* at C5), 2.50-2.62 (1 H, m, *endo* at C6), 3.95 (1 H, d, *J* 4.78 Hz, bridgehead H at C4), 4.74 (3 H, s, N–CH_3, C17), 8.04-8.12 (2 H, m, CH at C13 and C14), 8.35 (1 H, dd, *J* 8.48, 1.59 Hz, CH at C12), 8.43 (1 H, dd, *J* 8.6, 1.10 Hz, CH at C15); δ_C (400 MHz), 10.31 (CH_3, C8), 18.38 (CH_3, C9), 20.88 (CH_3, C10), 24.00 (CH_2, C6), 31.28 (CH_2, C5), 41.30 (CH, C4), 52.72 (CH_3, C17), 55.69 (C quat., C7), 56.73 (C quat., C1), 119.37 (CH arom., C12), 130.40 (C arom. quat., C11), 131.18 (CH arom., C14), 132.50 (CH arom., C15), 133.63 (CH arom., C13), 143.38 (C arom. quat., C16), 160.72 (C quat., C=N, C2), 168.47 (C quat., C=N–CH_3, C3), 178.85 (C quat. CF_3, C18); *m/z* (cation) 252; exact mass calcd for cation $C_{17}H_{21}N_2$ 253.17046 found 253.17050. Found C, 53.60; H, 5.14; N, 6.71; $C_{18}H_{21}F_3N_2O_3S$ requires: C, 53.72; H, 5.26; N, 6.96%.

(–)-(1*R*,4*R*,9R,12*S*)-15,15-trimethyl-3,10-diazatetracyclo-[10.2.1.0^{2,11}.0^{4,9}]pentadeca-2,10-diene:



(–)-(1R,4S,12R,17R)-Camphordecahydroquinoxal-2,3-ine: Prepared as the phenazine derivative in 68% yield (yellow oil). $[\alpha]^{20}_D$ –35.07 c=1.12, ($CHCl_3$); ν_{max} /cm^{-1} (neat) 1648, 1449, 1233, 1050; δ_H ($CDCl_3$), (400 MHz), 0.66 (3 H, s, CH_3, C8), 0.86 (3 H, s, CH_3, C9), 0.94 (3 H, s, CH_3, C10), 1.21-1.37 (6 H, m, *exo* at C5 and 5 H from tetramethylene group), 1.68-1.89 (4 H, m, *exo* at C6 and 3 H from tetramethylene group), 2.15-2.20 (2 H, m, *endo* at C5 and C6), 2.23-2.25 (1 H, t, *J* 3.86 Hz, bridgehead H at C4), 2.58-2.63 (2 H, m, 2xN–CH, C11 and C16); δ_C (400 MHz), 11.15 (CH_3, C8), 19.10 (CH_3, C9), 22.11 (CH_3, C10), [24.57 (CH_2), 27.44 (CH_2), 27.52 (CH_2), 35.22 (CH_2), 35.39 (CH_2), 35.59 (CH_2), C5-C6 and C12-C15], 44.78 (C quat., C7), 54.08 (C quat., C1), 54.42 (CH, C4) 60.55 (CH, N–CH, C11), 63.48 (CH, N–CH, C16). *m/z* 244; exact mass calcd for $C_{16}H_{24}N_2$ 244.19400 found 244.19380.

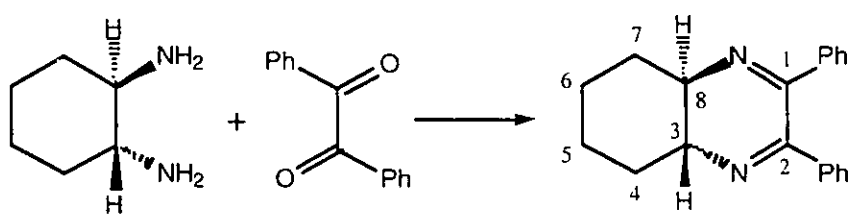
(–)-(1*S*,4*R*,9*R*,12*R*)-3,12,15,15-tetramethyl-10-aza-3-azoniatetracyclo[10.2.1.0 ^{2,11}.0 ^{4,9}]pentadeca-2,10-diene tetraphenylborate:



(–)-(1R,4S,12R,17R)-anti-N-methyl-Camphorquinonehexahydroquinoxal-2,3-inum tetraphenylborate: As the quartenised phenazine derivative, this salt was also synthesised with methyl triflate according to the same method developed for oxazolinium salts. Anion exchange was effected by dissolving the crude product in a

solution of of sodium tetraphenyl borate, (1 equivalent), in acetonitrile. Removal of the solvent furnished the desired salt which was thoroughly washed with ethanol/water, (2:1), then with diethyl ether, and collected by vacuum filtration; 89% yield, m.p. 191-193 °C (dec.). $[\alpha]^{20}_D$ –28.52 c=1.15, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1646, 1264, 1578; δ_H (CD_3CN), (250 MHz), 0.85 (3 H, s, CH_3, C8), 1.08 (3 H, s, CH_3, C9), 1.12 (3 H, s, CH_3, C10), 1.38-1.72 (6 H, m, *exo* at C5 and 5 H from tetramethylene group), 1.81-2.16 (4 H, m, *exo* at C6 and 3 H from tetramethylene group), 2.27-2.48 (2 H, m, *endo* at C5 and C6), 3.16 (1 H, d, *J* 4.75 Hz, bridgehead H at C4), 3.36 (3 H, s, CH_3, C17), 3.44-3.47 (2 H, m, 2xN–CH, C11 and C16), 6.86 (4 H, t, *J* 7.01 Hz, arom., *para* in BPh_4 group), 7.01 (8 H, t, *J* 7.27 Hz, arom., *ortho* in BPh_4 group), 7.27-7.32 (8 H, m, arom., *meta* in BPh_4 group); δ_C (400 MHz), 8.76 (CH_3, C8), 15.98 (CH_3, C9), 20.08 (CH_3, C10), [21.12 (CH_2), 24.01 (CH_2), 24.23 (CH_2), 26.41 (CH_2), 32.38 (CH_2), 32.74 (CH_2), C5-C6 and C12-C15], 38.65 (CH, C4), 48.76 (C quat., C1), 51.41 (CH, N–CH, C11), 53.09 (C quat., C7), 60.60 (CH, C16), 62.29 (CH_3, C17), 121.48 (8xCH arom., CH *ortho* in BPh_4 group), 125.31 (4xCH arom., CH *para* in BPh_4 group), 135.41 (8xCH arom., CH *meta* in BPh_4 group), 163.51 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 167.22 (C quat., C=N, C11), 173.43 (C quat., C=N–CH_3, C16). *m/z* (cation) 259; exact mass calcd for cation $C_{17}H_{27}N_2$ 259.21740 found 259.21770. Found C, 85.06; H, 8.22; N, 4.44; $C_{41}H_{47}BN$ requires: C, 85.06; H, 8.19; N, 4.84%.

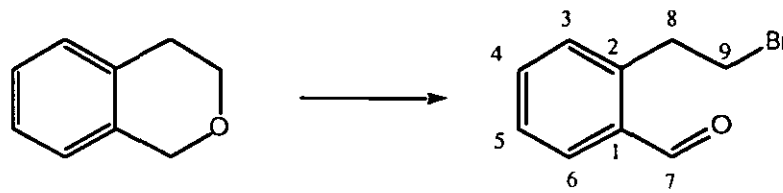
(–)-(5*R*,10*R*)-2,3-Diphenyl-5,6,7,8,9,10-hexahydroquinoxaline:



(–)-(5R,10R)-Diaminocyclohexane-benzil diimine: Prepared according to the general procedure descibed earlier for the synthesis of imines; bright yellow solid, 84% yield, m.p. 183-185 °C. $[\alpha]^{20}_D$ –180.17 c=1.13, ($CHCl_3$); ν_{max} /cm^{-1} (nujol) 1609, 1573, 1551; δ_H ($CDCl_3$), (400 MHz), [1.39-1.44 (2 H, m), 1.62-1.65 (2 H, m), 1.87-1.90 (2 H, m), 2.50 (2 H, d, *J* 11.65 Hz), 4xCH_2 at C4-C7], 2.79-2.88 (2 H, m, 2xCH, at C3 and C8), 7.18-7.26 (6 H, m, arom.), 7.37-7.39 (4 H, m, arom.); δ_C (100 MHz), 25.85 (2xCH_2, C5 and C6), 33.92 (2xCH_2, C4 and C7), 59.93 (2xCH, C3 and C8), 128.12 (4xCH arom., 4x*meta*), 128.74 (4xCH arom., 4x*ortho*), 129.88 (2xCH arom., 2x*para*), 138.20

(2xC arom. quat., 2x*ipso*), 160.07 (2xC quat., C=N, C1 and C2). *m/z* 288; exact mass calcd for $C_{20}H_{20}N_2$ 288.16264 found 288.16282. Found C, 83.12; H, 6.95; N, 9.50; $C_{20}H_{20}N_2$ requires: C, 83.29; H, 6.99; N, 9.72%.

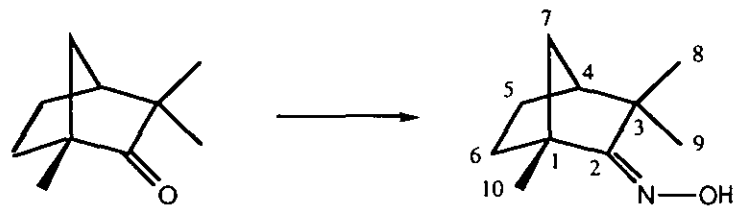
2-(2-Bromoethyl)-benzene-1-carbaldehyde:



2-(2-bromoethyl)-benzaldehyde:[86] To an ice cooled solution of isochroman (50 g, 0.37 mol), in carbon tetrachloride (200 mL), in a 500 mL flask fitted with a reflux condenser, molecular bromine (60 g, 0.37 mol), is added slowly down the condenser over a period of 5 minutes with stirring. After the vigorous reaction subsides, (*ca* 5 minutes), the cooling bath is removed and the dark brown solution is refluxed until the reaction mixture becomes pale yellow, and liberation of the white HBr smoke ceases, (indicative of complete consumption of bromine; *ca* 1 hour). The solution is the allowed to attain ambient temperature and the solvent is removed under reduced pressure. To the yellow oil obtained, (1-bromo-isochroman), 75 mL of 48% hydrobromic acid (aqueous) is added and the reaction mixture is refluxed, (dark green-blue). After approximatelly 10 -15 minutes the solution is allowed to cool and extracted with diethyl ether (4x50 mL). (Care: The solution must be at room temperature or below prior to extraction with ether; first ether extract may be the lower layer as it is very concentrated with organic material). The organic extracts are washed with water (2x30 mL), then with dilute sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure furnished 67.5 g (65% yield) of the crude 2-(2-bromoethyl) benzaldehyde as an orange oil approximatelly 85-90% pure. Analytically pure samples may be obtained by distillation under reduced pressure, *ca* 150 °C 0.5 mbar; chromatography is not recommended. The crude material which does not decompose when stored in a flask in the presence of light and air, was used for subsequent reactions unless stated othrwise. ν_{max} /cm^{-1} (neat) 2742, 1697, 1600, 1575, 1260, 1193, 755; δ_H (400 MHz), ($CDCl_3$), 3.54-3.63 (4 H, m, 2xCH_2 at C8 and C9), 7.33 (1 H, d, *J* 7.96 Hz, arom, CH at C3), 7.48 (1 H, t, *J* 7.50 Hz, arom., CH at C5), 7.54 (1 H, t, *J* 7.94 Hz, arom., CH at C4), 7.80 (1 H, d, *J* 7.56 Hz,.arom., CH at C6), 10.14 (1 H, s, CHO, at C7); δ_C (62.50 MHz), 33.17 (CH_2, C8), 36.70 (CH_2, C9), 128.10 (CH arom., C5), 132.51 (CH arom.,

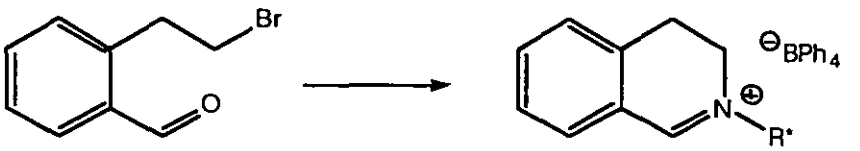
C3), 134.14 (CH arom., C4) 134.33 (C arom. quat., C2), 134.88 (CH arom., C6), 140.95 (C arom. quat., C1), 193.33 (CH, HC=O, C7). *m/z* 211; exact mass calcd for C_9H_9BrO 211.98373 found 211.98370.

(–)-(1*R*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]hept-2-one oxime:



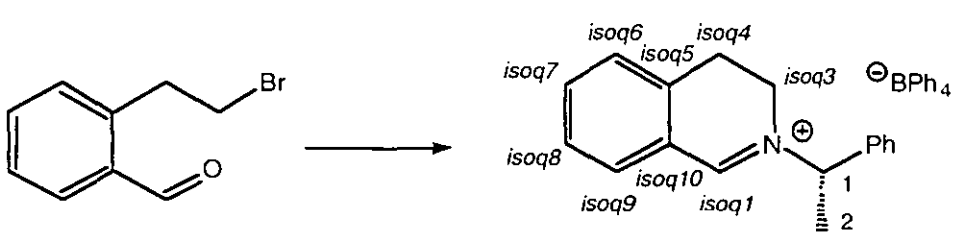
(–)-(1R,4S)-Fenchone oxime:[213,214] Hydroxylamine hydrochloride, (5.00 g, 72.00 mmol), was added to a solution of pyridine, (4 mL, 3.91 g, 49.46 mmol), in 50 mL of absolute ethanol, and the mixture was warmed untill most of the salt is dissolved. (1*R*)-(–)-Fenchone, (5.00 g, 32.80 mmol), was added and the reaction mixture is refluxed for 6 hours, then allowed to attain ambient temperature. The cool reaction mixture was stripped of most of the solvent, and 50 mL of ice cold water are added to the residue. This caused the precipitation of fenchone oxime as white crystals which were filtered, dried under sunction filtration. Recrystallisation from ethanol afforded 4.66 g of highly pure, crystalline fenchone oxime as colourless needles, 84% yield, m.p. 166-168 °C, (lit. m.p. 162-164 °C).[214] $[\alpha]^{20}_D$ –53.29 c=3.13, ($CHCl_3$), (lit. $[\alpha]^{20}_D$ –41.19 (EtOH)[214]); ν_{max} /cm^{-1} (nujol) 3282, 3149, 1682, 926; δ_H (250 MHz), ($CDCl_3$), 1.21 (3 H, s, CH_3 at C8), 1.30 (3 H, s, CH_3 at C9), 1.32 (3 H, s, CH_3 at C10), 1.34-1.36 (1 H, m), [1.45-1.57 (3 H m), 1.69-1.83 (3 H, m), 3xCH_2 at C5, C6 and C7], 9.17 (1 H, br. s, NOH); δ_C (62.50 MHz), 17.03 (CH_3, C9), 22.04 (CH_3, C8), 22.82 (CH_3, C10), 25.16 (CH_2, C5), 34.06 (CH_2, C6), 43.15 (CH_2, C7), 44.05 (C quat., C3), 48.49 (CH, C4), 50.00 (C quat., C1), 172.17 (C quat., C=NOH, C2). *m/z* 167; exact mass calcd for $C_{10}H_{17}NO$ 167.13101 found 167.13120. Found C, 72.16; H, 10.38; N, 8.15; $C_{10}H_{17}NO$ requires: C, 71.80; H, 10.25; N, 8.38%.

General procedure for the synthesis of dihydroisoquinolinium salts from 2-(2-bromoethyl)-benzaldehyde and primary amines, (simple or functionalised):



A solution of the amine in ethanol, (10 mL per g of amine, 1 equivalent), is added dropwise via a stoppered, pressure equalising, dropping funnel, to an ice cooled, one-neck flask, containing 2-(2-bromoethyl)-benzaldehyde, (1.60 equivalents, 1.10 if distilled previously). After the addition is complete the dropping funnel was removed and replaced by a stopper to contain the hydrogen bromide generated temporarily in the reaction. The reaction mixture was stirred overnight while attaining ambient temperature. Sodium tetraphenylborate, (or any other anion exchanging salt, 1.10 equivalents), in the minimum amount of acetonitrile, is added in one portion in the reaction mixture and after 5 minutes of stirring, the organic solvents are rotary evaporated. Ethanol is added to the residue, followed by water. The resulting solid is collected by filtation and washed with additional ethanol followed by diethyl ether. If no solid materialises after the addition of water the suspension is allowed to settle and the ethanol/water phase is decanted off. The gummy residue which may be obtained, is macerated in hot ethanol or methanol. The organic salt may then precipitate but in some rare cases it does so upon slow cooling of the hot alcoholic solution. If solubility problems arise, small amounts of acetonitrile may be added during this process.

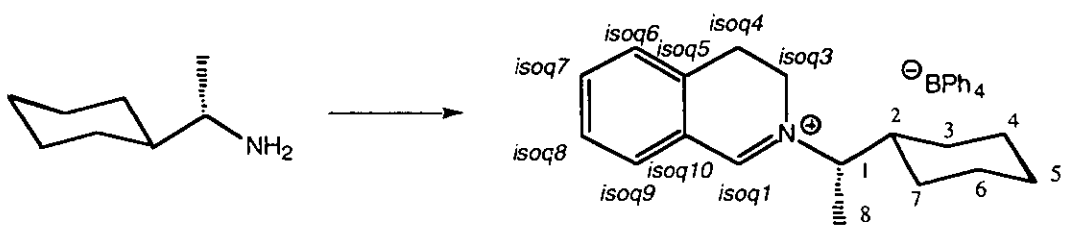
(–)-2-[(1*S*)-1-phenylethyl]-3,4-dihydroisoquinolinium tetraphenylborate:



Prepared according to the general procedure in 42% yield, pale yellow solid, m.p. 168-169 °C. $[\alpha]^{20}_{D}$ –9.42 c=1.57, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1647, 1605, 1572; δ_H (400MHz), (CD_3CN), 1.82 (3 H, d, *J* 6.90 Hz, CH_3 at C2), 2.99 (2 H, t, *J* 7.63 Hz, CH_2 at*isoq*-4), 3.65-3.71 (2 H, m, CH_2 at*isoq*-3), 5.24 (1 H, q, *J* 6.81 Hz, CH at C1), 6.82 (4 H,

t, *J* 7.22 Hz, arom., *para* in BPh_4 group), 6.97 (8 H, t, *J* 7.43 Hz, arom., *ortho* in BPh_4 group), 7.25-7.29 (8 H, m, arom., *meta* in BPh_4 group), 7.37 (1 H, d, *J* 7.62 Hz, arom, *isoq-6*), 7.45 (5 H, m, arom, Ph group), 7.54 (1 H, t, *J* 7.61 Hz, arom, *isoq-7*), 7.75 (1 H, t, *J* 7.59 Hz, arom, *isoq-8*), 7.83 (1 H, d, *J* 7.59 Hz, arom, *isoq-9*), 8.97 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), 17.61 (CH_3, C2), 24.57 (CH_2, *isoq-4*), 46.96 (CH_2, *isoq-3*), 68.86 (CH, C1), 121.53 (8xCH arom., CH *ortho* in BPh_4 group), 124.34 (C arom. quat., *isoq-5*), 125.30 (4xCH arom., CH *para* in BPh_4 group), 127.22 (2xCH arom., *ortho* in Ph group) 127.96 (CH arom., *para* in Ph group), 128.10 (CH arom., *isoq-6*), 129.05 (2xCH arom. *meta* in Ph group), 129.29 (CH arom., *isoq-8*), 130.83 (C arom. quat. *ipso* in Ph group), 133.77 (CH arom., *isoq-7*), 135.37 (8xCH arom., CH *meta* in BPh_4 group), 136.73 (C arom. quat., *isoq-10*), 138.01 (CH arom., *isoq-9*), 163.51 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 164.57 (CH, HC=N, *isoq-1*); *m/z* (cation) 236; exact mass calcd for cation $C_{17}H_{18}N$ 236.14392 found 236.14190. Found C, 86.98; H, 7.90; N, 2.36; $C_{43}H_{38}BN{\cdot}0.8\ H_2O$ requires: C, 86.86; H, 7.66; N, 2.36%.

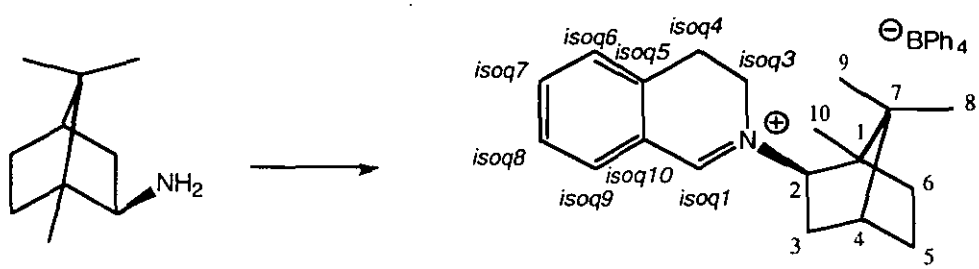
(+)-(–)-2-[(1*S*)-1-cyclohexylethyl]-3,4-dihydroisoquinolinium tetraphenylborate:



Prepared according to the general procedure in 58% yield, white solid, m.p. 178-180 °C. $[\alpha]^{20}_D$ +22.53 c=1.26, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1641, 1603, 1573; δ_H (400MHz), (CD_3CN), 1.00-1.04 (1 H, m, from cyclohexyl group), 1.18-1.27 (3 H, m, from cyclohexyl group), 1.44 (3 H, d, *J* 2.71 Hz CH_3, at C8), 1.60-1.79 (6 H, m, from cyclohexyl group), 1.92-1.94 (1 H, m, from cyclohexyl group), 3.16 (2 H, t, *J* 7.88 Hz, CH_2 at*isoq-4*), 3.83-3.87 (3 H, m, CH at C1, and CH_2 at *isoq-3*), 6.83 (4 H, t, *J* 7.20 Hz, arom., *para* in BPh_4 group), 6.98 (8 H, t, *J* 7.42 Hz, arom., *ortho* in BPh_4 group), 7.25-7.29 (8 H, m, arom., *meta* in BPh_4 group), 7.44 (1 H, d, *J* 7.62 Hz, arom., *isoq-6*), 7.51 (1 H, t, *J* 7.64 Hz, arom., *isoq-7*), 7.74-7.79 (2 H, m, arom., *isoq-8* and *isoq-9*), 8.67 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz) 14.71 (CH_3, C8), [24.41 (CH_2), 24.96 (CH_2), 25.17 (CH_2), 25.24 (CH_2), 27.89 (CH_2), 5xCH_2, C3-C7] 29.33 (CH_2, *isoq-4*), 39.55 (CH, C2), 45.24 (CH_2, *isoq-3*), 72.60 (CH, C1), 121.48 (8xCH arom., CH *ortho* in BPh_4 group), 124.21 (C arom. quat., *isoq-5*), 125.33 (4xCH arom., CH *para* in BPh_4 group), 128.00 (CH arom., *isoq-6*) 128.12 (CH arom., *isoq-8*), 133.48 (CH arom., *isoq-7*), 135.44 (8xCH

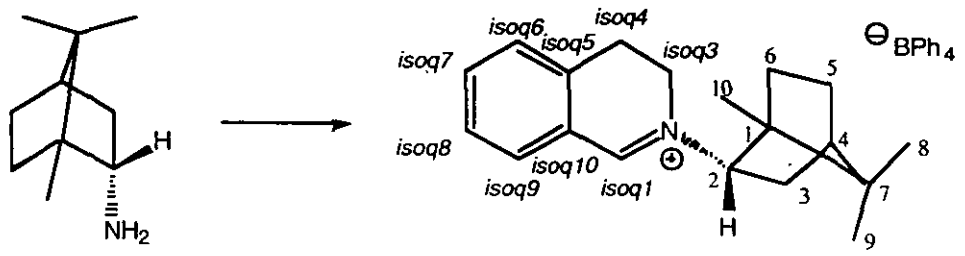
arom., CH *meta* in BPh_4 group), 136.96 (C arom. quat., *isoq-10*), 137.93 (CH arom., *isoq-9*), 163.53 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 165.15 (CH, HC=N, *isoq-1*); *m/z* (cation) 242; exact mass calcd for cation $C_{17}H_{24}N$ 242.190086 found 242.19090. Found C, 86.78; H, 7,81; N, 2.28; $C_{41}H_{44}BN \cdot 0.3\ H_2O$ requires: C, 86.76; H, 7.86; N, 2.46%.

(+)-2-[(1*R*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-3,4-dihydroisoquinolinium tetraphenylborate:



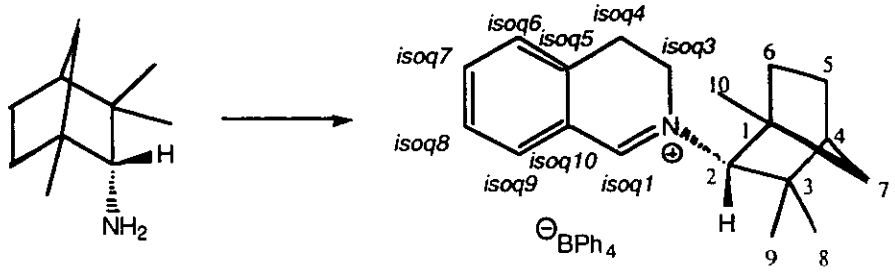
(+)-(R)-N-(2-exo-bornyl)-dihydroisoquinolinium tetraphenylborate: Prepared according to the general procedure in 17% yield, white solid, m.p. 196-197 °C. $[\alpha]^{20}_D$ +6.88 c=1.22, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1649, 1601, 1572; δ_H (CD_3CN), (400 MHz), 0.84 (3 H, s, CH_3, C8), 0.89 (3 H, s, 3 H, s, CH_3, C9), 1.12 (3 H, s, CH_3, C10), [1.25-1.31 (1 H, m), 1.36-1.40 (1 H, m), 1.67-1.72 (1 H, m), 1.85-1.91 (2 H, m), *endo* and *exo* at C5, C6 and *endo* at C3], 1.97 (1 H, t, *J* 4.34 Hz, bridgehead H at C4), 2.39-2.48 (1 H, m, *exo* at C3), 3.06-3.14 (2 H, m, CH_2 at *isoq-4*), 3.81-3.87 (1 H, m, CH, *endo* at C2), 3.89-3.95 (2 H, m, CH_2 at *isoq-3*), 6.82 (4 H, t, *J* 7.17 Hz, arom., *para* in BPh_4 group), 6.98 (8 H, t, *J* 7.44 Hz, arom., *ortho* in BPh_4 group), 7.25-7.29 (8 H, m, arom., *meta* in BPh_4 group), 7.41 (1 H, d, *J* 7.56 Hz, arom., *isoq-6*), 7.50 (1 H, t, *J* 7.60 Hz, arom., *isoq-8*), 7.75 (1 H, t, *J* 7.62 Hz, arom., *isoq-7*), 7.81 (1 H, d, *J* 7.59 Hz, arom., *isoq-9*), 8.81 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), 11.92 (CH_3, C8), 19.09 (CH_3, C9), 19.92 (CH_3, C10), 24.52 (CH_2, C5), 25.84 (CH_2, C6), 33.19 (CH_2, C3), 36.95 (CH_2, *isoq-4*), 44.39 (CH, C4), 47.99 (C quat., C7), 50.92 (C quat., C1), 52.00 (CH_2, *isoq-3*), 77.91 (CH, C2), 121.44 (8xCH arom., CH *ortho* in BPh_4 group), 124.64 (C arom. quat., *isoq-5*), 125.31 (4xCH arom., CH *para* in BPh_4 group), 127.89 (CH arom., *isoq-6*), 128.07 (CH arom., *isoq-8*), 133.71 (CH arom., *isoq-7*), 135.38 (8xCH arom., CH *meta* in BPh_4 group), 135.45 (C arom. quat., *isoq-10*), 137.91 (CH arom., *isoq-9*), 163.57 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 164.20 (CH, HC=N, *isoq-1*); *m/z* (cation) 268; exact mass calcd for cation $C_{19}H_{26}N$ 268.20651 found 268.20690. Found C, 87.38; H, 7.80; N, 2.39 $C_{43}H_{46}BN \cdot 0.2\ H_2O$ requires: C, 87.32; H, 7.84; N, 2.36%.

(–)-2-[(1*R*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-3,4-dihydroisoquinolinium tetraphenylborate:



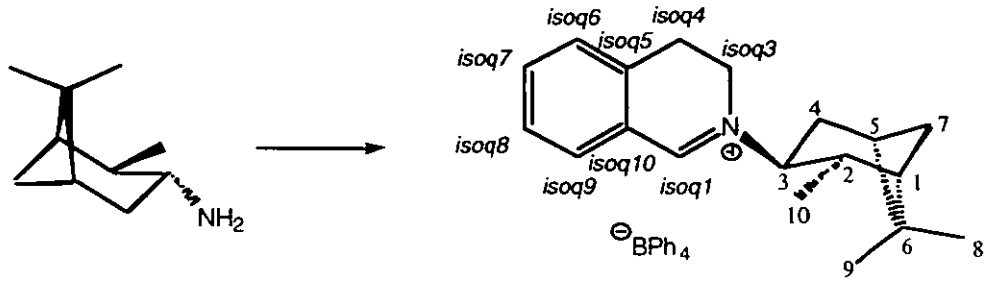
(–)-(S)-N-(2-endo-bornyl)-dihydroisoquinolinium tetraphenylborate: Prepared according to the general procedure in 26% yield, white solid, m.p. 198-200 °C. $[\alpha]^{20}_{D}$ -33.20 c=1.53, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1645, 1600, 1575; δ_H (CD_3CN), (400 MHz), 0.96 (3 H, s, CH_3, C8), 0.98 (3 H, s, CCH_3, C9), 1.00 (3 H, s, CH_3, C10), [1.22-1.28 (1 H, m), 1.47-1.51 (2 H, m), 1.65-1.70 (1 H, m), 1.85-1.91 (2 H, m), 2.29-2.36 (1 H, m), *endo* and *exo* at C3, C5, C6 and bridgehead H at C4], 3.11 (2 H, t, *J* 7.84 Hz, CH_2, at *isoq-4*), 3.81-3.88 (2 H, m, CH_2 at *isoq-3*), 4.24-4.27 (1 H, m, *exo* at C2), 6.82 (4 H, t, *J* 7.24 Hz, arom., *para* in BPh_4 group), 6.97 (8 H, t, *J* 7.66 Hz, arom., *ortho* in BPh_4 group), 7.25-7.28 (8 H, m, arom., *meta* in BPh_4 group), 7.44 (1 H, d, *J* 7.60 Hz, arom., *isoq-6*), 7.51 (1 H, t, *J* 7.63 Hz, arom., *isoq-8*), 7.75 (1 H, t, *J* 7.59 Hz, arom., *isoq-9*), 7.85 (1 H, d, *J* 7.68 Hz, arom., *isoq-9*), 8.67 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), 13.03 (CH_3, C8), 17.35 (CH_3, C9), 18.63 (CH_3, C10), 24.59 (CH_2, C5), 26.32 (CH_2, C6), 26.63 (CH_2, *isoq-4*), 31.24 (CH_2, C3), 43.85 (CH, C4), 50.11 (C quat., C7), 51.54 (C quat., C1), 51.63 (CH_2, *isoq-3*), 76.34 (CH, C2), 121.44 (8xCH arom., CH *ortho* in BPh_4 group), 124.63 (C arom. quat., *isoq-5*), 125.31 (4xCH arom., CH *para* in BPh_4 group), 127.90 (CH arom., *isoq-6*), 128.05 (CH arom., *isoq-8*), 133.71 (CH arom., *isoq-7*), 135.38 (8xCH arom., CH *meta* in BPh_4 group), 137.19 (C arom. quat., *isoq-10*), 137.87 (CH arom., *isoq-9*), 163.49 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 164.71 (CH, HC=N, *isoq-1*); *m/z* (cation) 268; exact mass calcd for cation $C_{19}H_{26}N$ 268.20651 found 268.20660. Found C, 87.04; H, 7.80; N, 2.21; $C_{43}H_{46}BN \cdot 0.2\ H_2O$ requires: C, 87.32; H, 7.84; N, 2.36%.

(+)-2-[(1*R*,2*R*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]-3,4-dihydroisoquinolinium tetraphenylborate:



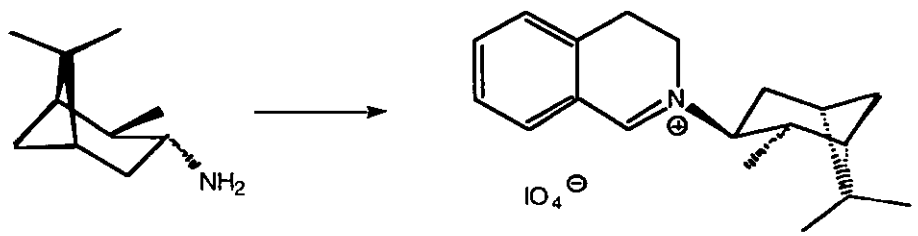
(+)-(R)-N-(2-endo-fenchyl)-dihydroisoquinolinium tetraphenylborate: Prepared from (+)-fenchylamine,[216] according to the general procedure in 61% yield, white solid, m.p. 153-155 °C. $[\alpha]^{20}_D$ +12.53 c=1.50, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1649, 1605, 1577; δ_H (CD_3CN), (400 MHz), 1.04 (3 H, s, CH_3 at C8), 1.29 (6 H, s, 2xCH_3 at C9 and C10), 1.40-1.93 (7 H, m, *endo* and *exo* at C5, C6, C7 and bridgehead H at C4), 3.15 (2 H, t, *J* 8.07 Hz, CH_2, at *isoq-4*), 3.89-3.92 (2 H, m, CH_2 at *isoq-3*), 3.65 (1 H, s, *exo* at C2), 6.83 (4 H, t, *J* 7.15 Hz, arom., *para* in BPh_4 group), 6.98 (8 H, t, *J* 7.45 Hz, arom., *ortho* in BPh_4 group), 7.25-7.29 (8 H, m, arom., *meta* in BPh_4 group) 7.43 (1 H, d, *J* 7.56 Hz, arom., *isoq-6*), 7.52 (1 H, t, *J* 7.62 Hz, arom., *isoq-8*), 7.76 (1 H, t, *J* 7.62 Hz, arom., *isoq-7*), 7.91 (1 H, d, *J* 7.57 Hz, arom., *isoq-9*), 8.75 (1 H, s, HC=N, *isoq-1*); δ_C (62.50 MHz), 18.48 (CH_3, C8), 20.30 (CH_3, C9), 24.34 (CH_2, C5), 24.94 (CH_2, C6), 25.52 (CH_2, C7), 30.74 (CH_3, C10), 40.56 (C quat., C1), 44.25 (CH_2, *isoq-4*), 48.07 (CH, C4), 49.29 (C quat., C3), 51.25 (CH_2, *isoq-3*), 83.48 (CH, C2), 121.50 (8xCH arom., CH *ortho* in BPh_4 group), 124.36 (C arom. quat., *isoq-5*), 126.43 (4xCH arom., CH *para* in BPh_4 group), 127.93 (CH arom., *isoq-6*) 128.10 (CH arom., *isoq-8*), 134.03 (CH arom., *isoq-7*), 135.87 (8xCH arom., CH *meta* in BPh_4 group), 137.09 (C arom. quat., *isoq-10*), 137.98 (CH arom., *isoq-9*), 163.50 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 164.94 (CH, HC=N, *isoq-1*); *m/z* (cation) 268; exact mass calcd for cation $C_{19}H_{26}N$ 268.20651 found 268.20650. Found C, 87.13; H, 7.95; N, 2.21; $C_{43}H_{46}BN{\cdot}0.2\ H_2O$ requires: C, 87.32; H, 7.84; N, 2.36%.

(–)-2-[(1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-2-yl]-3,4-dihydroisoquinolinium tetraphenylborate:



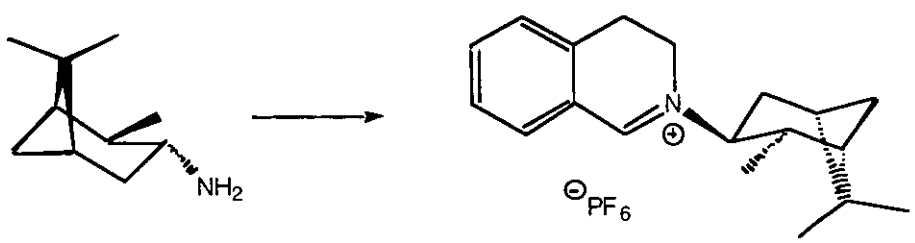
(–)-(1R,2R,3R,5S)-N-(3-isopinocampheyl)-dihydroisoquinolinium tetraphenylborate: Prepared according to the general procedure in 70% yield, white solid, m.p. 238-240 °C. $[\alpha]^{20}_{D}$ -24.70 c=1.36, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1639, 1600, 1574, 735, 710; δ_H (CD_3CN), (400 MHz), 1.12 (3 H, s, CH_3 at C8), 1.18 (3 H, d, *J* 7.02 Hz, CH_3 at C10), 1.33 (3 H, s, CH_3 at C8), [1.95-2.00 (3 H, m), 2.12-2.15 (2 H, m), 2.42-2.60 (2 H, m), CH_2 of C7 and C4, CH of C2 and bridgehead H at C1 and C5], 3.24 (2 H, t, *J* 7.60 Hz, CH_2 at *isoq-4*), 4.08 (2 H, t, *J* 7.65 Hz, CH_2 at *isoq-3*), 4.54 (1 H, m, CH at, C3), 6.86 (4 H, t, *J* 7.20 Hz, arom., *para* in BPh_4 group), 7.01 (8 H, t, *J* 7.43 Hz, arom., *ortho* in BPh_4 group), 7.28-7.32 (8 H, m, arom., *meta* in BPh_4 group) 7.49 (1 H, d, *J* 7.50 Hz, arom., *isoq-6*), 7.56 (1 H, t, *J* 7.58 Hz, arom., *isoq-8*), 7.80-7.84 (2 H, m, arom., *isoq-7* and*isoq-9*), 9.09 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), 18.71 (CH_3, C8), 22.15 (CH_3, C9), 25.00 (CH_2, C7), 26.95 (CH_3, C10), 31.38 (CH_2, C4), 33.07 (CH_2, *isoq-4*), 38.72 (C quat., C6), 39.66 (CH, C5), 40.76 (CH, C2), 44.62 (CH_2, *isoq-3*), 46.73 (CH, C1), 89.18 (CH, C3), 121.46 (8xCH arom., CH *ortho* in BPh_4 group), 124.71 (C arom. quat., *isoq-5*), 125.32 (4xCH arom., CH *para* in BPh_4 group), 127.93 (CH arom., *isoq-6*), 128.12 (CH arom., *isoq-8*), 133.42 (CH arom., *isoq-7*), 135.49 (8xCH arom., CH *meta* in BPh_4 group), 136.96 (C arom. quat., *isoq-10*), 137.89 (CH arom., *isoq-9*), 163.55 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 166.44 (CH, HC=N, *isoq-1*); *m/z* (cation) 268; exact mass calcd for cation $C_{19}H_{26}N$ 268.20651 found 268.20590. Found C, 84.92; H, 7.66; N, 2.94; $C_{43}H_{46}BN{\cdot}1.2\ H_2O$ requires: C, 84.69; H, 7.94; N, 2.29%.

(–)-2-[(1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-2-yl]-3,4-dihydroisoquinolinium periodate:



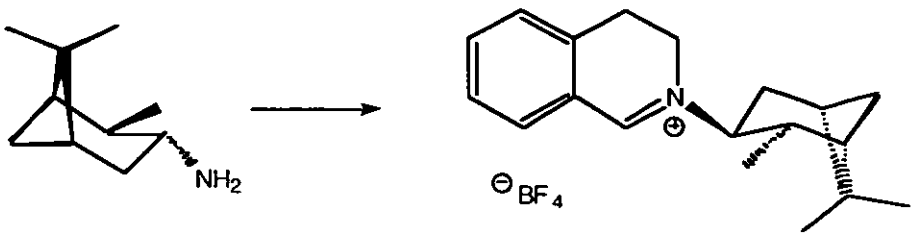
(–)-(1R,2R,3R,5S)-N-(3-isopinocampheyl)-dihydroisoquinolinium periodate: Prepared according to the general procedure in 67% yield, yellow solid, m.p. 159-161 °C (dec.). $[\alpha]^{20}_D$ –14.51 c=3.50, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1648, 1608, 1576, 844; δ_H, δ_C (CD_3CN), (400 and 100 MHz respectively), identical with tetraphenylborate derivative within 0.06 ppm, (except from the tetraphenylborate signals); *m/z* (cation) 268; exact mass calcd for cation $C_{19}H_{26}N$ 268.20651 found 268.20600.

(–)-2-[(1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-2-yl]-3,4-dihydroisoquinolinium hexafluorophosphate:



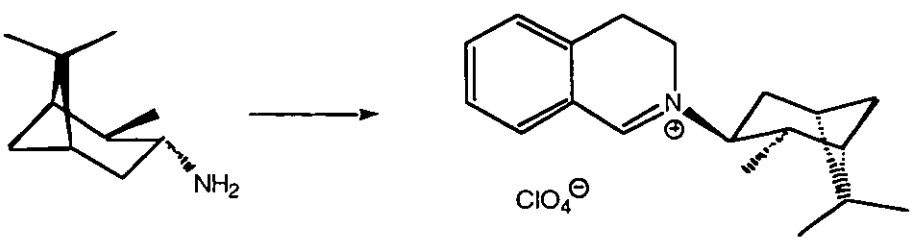
(–)-(1R,2R,3R,5S)-N-(3-isopinocampheyl)-dihydroisoquinolinium hexafluorophosphate: Prepared according to the general procedure in 58% yield, white solid, m.p. 239-241 °C. $[\alpha]^{20}_D$ –34.78 c=2.3, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1646, 1608, 1576, 877, 834; δ_H, δ_C (CD_3CN), (400 and 100 MHz respectively), identical with tetraphenylborate derivative within 0.09 ppm, (except from the tetraphenylborate signals); *m/z* (cation) 268; exact mass calcd for cation $C_{19}H_{26}N$ 268.20651 found 268.20610.

(–)-2-[(1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-2-yl]-3,4-dihydroisoquinolinium tetrafluoroborate:



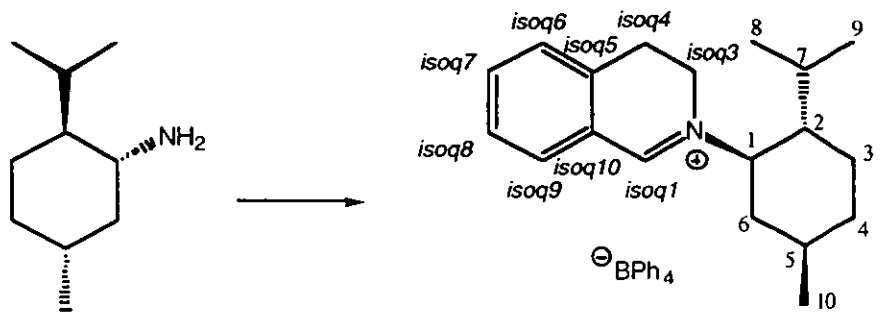
(–)-(1R,2R,3R,5S)-N-(3-isopinocampheyl)-dihydroisoquinolinium tetrafluoroborate: Prepared according to the general procedure in 52% yield, white solid, m.p. 186-188 °C. $[\alpha]^{20}_D$ –33.60 c=2.5, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1645, 1606, 1577, 1062, 933, 776, 767; δ_H, δ_C (CD_3CN), (400 and 100 MHz respectively), identical with tetraphenylborate derivative within 0.07 ppm, (except from the tetraphenylborate signals); *m/z* (cation) 268; exact mass calcd for cation $C_{19}H_{26}N$ 268.20651 found 268.20600.

(–)-2-[(1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-2-yl]-3,4-dihydroisoquinolinium perchlorate:



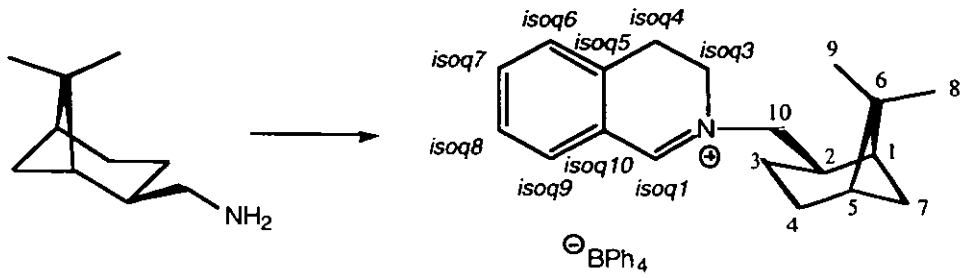
(–)-(1R,2R,3R,5S)-N-(3-isopinocampheyl)-dihydroisoquinolinium perchlorate: Prepared according to the general procedure in 63% yield, white solid. $[\alpha]^{20}_D$ –36.00 c=2.4, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1645, 1606, 1576, 1086, 1051, 768, 623; δ_H, δ_C (CD_3CN), (400 and 100 MHz respectively), identical with tetraphenylborate derivative within 0.05 ppm, (except from the tetraphenylborate signals); *m/z* (cation) 268; exact mass calcd for cation $C_{19}H_{26}N$ 268.20651 found 268.20590. Melting point and combustion analysis were not carried out, because perchlorate salts are prone to detonation, especially when dry. For this reason, this salt was kept slightly wet with water. The perchlorate salt was stored in the dark in this state, and no decomposition or detonation was experienced.

(–)-2-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl]-3,4-dihydroisoquinolinium tetraphenylborate:



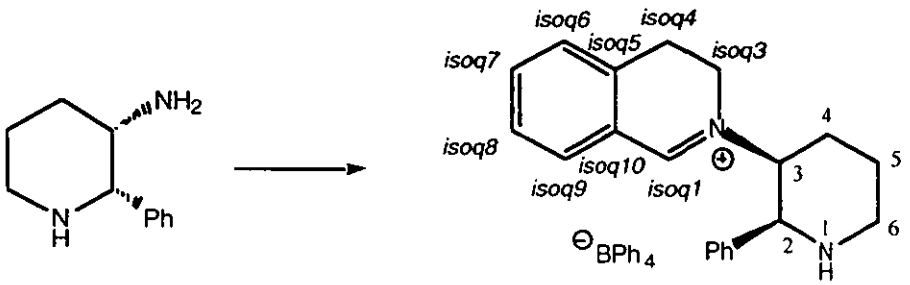
(–)-(1R,2S,5R)-N-(1-menthyl)-dihydroisoquinolinium tetraphenylborate: Prepared according to the general procedure in 38% yield, pale yellow solid, m.p. 166-168 °C. $[\alpha]^{20}_D$ –28.10 c=1.71, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1643, 1605, 1576; δ_H (CD_3CN), (400 MHz), 0.79 (3 H, d, *J* 6.90 Hz, CH_3 at C8), 0.94 (3 H, d, *J* 6.81 Hz, CH_3 at C9), 0.96 (3 H, d, *J* 6.51 Hz, CH_3 at C10), 1.21-1.25 (1 H, m), 1.45-1.49 (1 H, m), 1.51-1.68 (2 H, m), 1.70-1.82 (3 H, m), 1.84-2.00 (2 H, m), 3.13 (2 H, t, *J* 7.94 Hz, CH_2 at *isoq-4*), 3.83-3.89 (3 H, m, CH at C1 and CH_2 at *isoq-3*), 6.81 (4 H, t, *J* 7.14 Hz, arom., *para* in BPh_4 group), 6.98 (8 H, t, *J* 7.41 Hz, arom., *ortho* in BPh_4 group), 7.25-7.28 (8 H, m, arom., *meta* in BPh_4 group) 7.42 (1 H, d, *J* 7.13 Hz, arom., *isoq-6*), 7.50 (1 H, t, *J* 7.27 Hz, arom., *isoq-8*), 7.74-7.77 (2 H, m, arom., *isoq-7* and*isoq-9*), 8.74 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), 14.30 (CH_3, C10), 19.87 (CH_3, C8), 20.81 (CH_3, C9), 22.33 (CH_2, C4), 24.56 (2xCH_2, C3 and C6), 26.01 (CH, C5), 31.23 (2xCH, C2 and C7), 32.93 (2xCH_2, *isoq-4* and *isoq-3*), 72.97 (CH, C1), 121.47 (8xCH arom., CH *ortho* in BPh_4 group), 124.47 (C arom. quat., *isoq-5*), 125.31 (4xCH arom., CH *para* in BPh_4 group), 127.99 (CH arom., *isoq-6*), 128.13 (CH arom., *isoq-8*), 133.50 (CH arom., *isoq-7*), 135.44 (8 H, m, arom., CH *meta* in BPh_4 group), 137.09 (C arom. quat., *isoq-10*), 138.06 (CH arom., *isoq-9*), 163.53 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 165.76 (CH, HC=N, *isoq-1*); *m/z* (cation) 270; exact mass calcd for cation $C_{19}H_{28}N$ 270.22216 found 270.22220. Found C, 87.05; H, 8.25; N, 1.94; $C_{43}H_{48}BN{\cdot}0.2\ H_2O$ requires: C, 86.97; H, 8.15; N, 2.35%.

(–)-2-{[(1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]-methyl}-3,4-dihydroisoquinolinium tetraphenylborate:



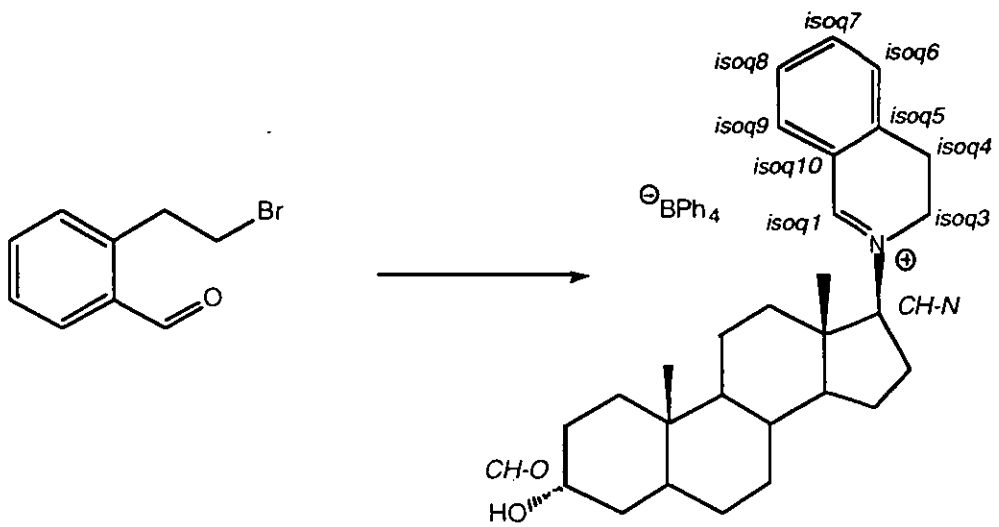
(–)-(1S,2R,5S)-N-(1-myrtanyl)-dihydroisoquinolinium tetraphenylborate: Prepared according to the general procedure in 75% yield, pale green solid, m.p. 173-174 °C. $[\alpha]^{20}_D$ –10.66 c=1.80, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1651, 1604, 1574; δ_H (CD_3CN), (400 MHz), 1.13 (3 H, s, CH_3 at C8), 1.28 (3 H, s, CH_3 at C9), 1.57-1.58 (1 H, m), 1.94-2.05 (6 H, m), 2.47-2.49 (1 H, m), 2.65-2.67 (1 H, m), 3.13 (2 H, t, *J* 7.89 Hz, CH_2 at *isoq-4*), 3.83-3.86 (4 H, m, CH_2 at C10 and CH_2 at *isoq-3*), 6.87 (4 H, t, *J* 7.16 Hz, arom., *para* in BPh_4 group), 7.02 (8 H, t, *J* 7.39 Hz, arom., *ortho* in BPh_4 group), 7.29-7.33 (8 H, m, arom., *meta* in BPh_4 group) 7.46 (1 H, d, *J* 7.27 Hz, arom., *isoq-6*), 7.54 (1 H, t, *J* 7.33 Hz, arom., *isoq-8*), 7.77-7.80 (2 H, m, arom., *isoq-7* and *isoq-9*), 8.68 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), 18.23 (CH_2, C7), 22.05 (CH_3, C8), 24.31 (CH_2, C4), 24.95 (CH_2, C3), 26.60 (CH_3, C9), 32.25 (CH_2, *isoq-4*), 37.70 (CH, C5), 37.91 (C quat., C6), 40.59 (CH, C1), 42.89 (CH, C2), 47.97 (CH_2, *isoq-3*), 65.62 (CH_2, C10), 121.46 (8xCH arom., CH *ortho* in BPh_4 group), 124.14 (C arom. quat., *isoq-5*), 125.32 (4xCH arom., CH *para* in BPh_4 group), 128.03 (CH arom., *isoq-6*), 128.05 (CH arom., *isoq-8*), 133.30 (CH arom., *isoq-7*), 135.76 (8xCH arom., CH *meta* in BPh_4 group), 136.49 (C arom. quat., *isoq-10*), 137.90 (CH arom., *isoq-9*), 163.54 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 165.77 (CH, HC=N, *isoq-1*); *m/z* (cation) 268; exact mass calcd for cation $C_{19}H_{26}N$ 268.20651 found 268.20650. Found C, 87.07; H, 7.88; N, 2.01; $C_{43}H_{46}BN{\cdot}0.3\ H_2O$ requires: C, 87.00; H, 7.85; N, 2.36%.

(+)-2-[(2*S*,3*S*)-2-phenylhexahydropyridin-3-yl]-3,4-dihydroisoquinolinium tetraphenylborate:



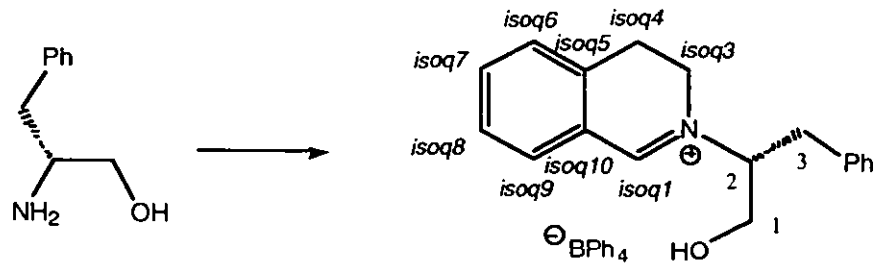
(+)-(2S,3S)-N-3-(2-phenyl-piperidinyl)-dihydroisoquinolinium tetraphenylborate: Prepared according to the general procedure in 40% yield, yellow solid, m.p. 172-174 °C (dec.). $[\alpha]^{20}_D$ +141.62 c=1.11, (CH_3CN); ν_{max} /cm^{-1} (nujol) 3320, 1634, 1603, 1576; δ_H (CD_3CN), (400 MHz), 1.91-1.98 (1 H, m), 2.24-2.33 (4 H, m), 2.47 (1 H, br. s), 2.66-2.70 (1 H, m), 2.88-2.97 (2 H, m), 3.24 (1 H, m), 3.39 (1 H, m), 4.10 (1 H, m), 4.22 (1 H, m), 4.37 (1 H, m), 5.47 (1 H, br. s, NH), 6.88 (4 H, t, *J* 7.01 Hz, arom., *para* in BPh_4 group), 7.02 (8 H, t, *J* 7.20 Hz, arom., *ortho* in BPh_4 group), 7.26-7.36 (12 H, m, arom., 8 H *para* in BPh_4 group and 4 H in Ph group) 7.40-7.42 (2 H, m, arom., 1 H in Ph group and *isoq-6*), 7.49 (1 H, t, *J* 7.24 Hz, arom., *isoq-8*), 7.72-7.79 (2 H, m, arom., *isoq-7* and *isoq-9*), 9.86 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), 18.62 (CH_2, C5), 24.40 (CH_2, C4), 27.29 (CH_2, *isoq-4*), 45.71 (CH_2, C6), 51.28 (CH_2, *isoq-3*), 61.52 (CH, C2), 68.09 (CH, C3), 121.51 (8xCH arom., CH *ortho* in BPh_4 group), 124.02 (C arom. quat., *isoq-5*), 125.36 (4xCH arom., CH *para* in BPh_4 group), 125.75 (2xCH arom., *ortho* in Ph group), 127.72 (CH arom., *para* in Ph group), 127.96 (CH arom., *isoq-6*), 128.07 (CH arom., *isoq-8*), 128.67 (2xCH arom., *meta* in Ph group), 133.65 (CH arom., *isoq-7*), 135.50 (8xCH arom., CH *meta* in BPh_4 group), 136.24 (C arom. quat., *ipso* in Ph group), 137.78 (CH arom., *isoq-9*), 139.07 (C arom. quat., *isoq-10*), 163.52 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 167.40 (CH, HC=N, *isoq-1*); *m/z* (cation) 291; exact mass calcd for cation $C_{20}H_{23}N_2$ 291.18611 found 291.18850. Found C, 85.00; H, 6.97; N, 4.48; $C_{44}H_{43}BN_2 \cdot 0.2\ H_2O$ requires: C, 85.20; H, 7.10; N, 4.51%.

(–)-2-[(3R,10S,13S,14R,17S)-3-hydroxy-10,13-dimethylperhydrocyclopenta[*a*]phenanthren-17yl]-3,4-dihydroisoquinolinium tetraphenylborate:



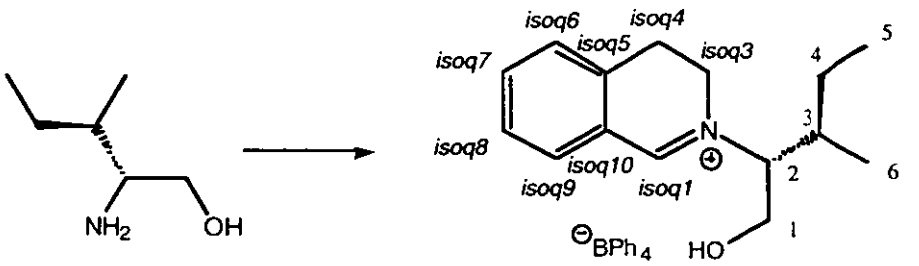
(–)-Steroidal derivative: Prepared according to the general procedure in 11% yield, white solid, m.p. 125-127 °C. $[\alpha]^{20}_D$ –1.2 c=1.33, (CH_3CN); ν_{max} /cm^{-1} (nujol) 3420, 1644, 1605, 1578; δ_H (CD_3CN), (400 MHz), [0.74 (3 H, s, CH_3), 0.79 (3 H, s, CH_3), 1.11-1.93 (22 H, m), 2.44 (1 H, m), from steroid group]3.13 (2 H, m, CH_2 at *isoq-4*), 3.87-3.92 (4 H, m, CH–O, CH–N and CH_2 at *isoq-3*), 6.82 (4 H, t, *J* 7.17 Hz, arom., *para* in BPh_4 group), 6.98 (8 H, t, *J* 7.42 Hz, arom., *ortho* in BPh_4 group), 7.25-7.29 (8 H, m, arom., *meta* in BPh_4 group) 7.47 (1 H, d, *J* 7.32 Hz, arom., *isoq-6*), 7.51 (1 H, t, *J* 7.35 Hz, arom., *isoq-8*), 7.76-7.79 (2 H, m, arom., *isoq-7* and *isoq-9*), 8.78 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), 10.92 (CH_3), 11.24 (CH_3), 20.07 (CH_2), 22.75 (CH_2), 24.13 (CH_2), 24.87 (CH_2), 28.10 (CH_2), 28.55 (CH_2), 32.02 (CH_2), 32.64 (CH_2), 35.37 (CH), 35.59 (C quat.), 35.84 (CH_2), 36.68 (CH_2, *isoq-4*), 38.82 (CH), 46.15 (C quat.), 51.34 (CH_2, *isoq-3*), 52.88 (CH), 53.92 (CH), 65.27 (CH, CH–N), 79.72 (CH, CH–O), 121.68 (8xCH arom., CH *ortho* in BPh_4 group), 124.68 (C arom. quat., *isoq-5*), 125.46 (4xCH arom., CH *para* in BPh_4 group), 128.18 (CH arom., *isoq-6*), 128.34 (CH arom., *isoq-8*), 133.82 (CH arom., *isoq-7*), 135.64 (8xCH arom., CH *meta* in BPh_4 group), 137.37 (C arom. quat., *isoq-10*), 138.10 (CH arom., *isoq-9*), 163.48 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 164.43 (CH, HC=N, *isoq-1*); *m/z* (cation) 406; exact mass calcd for cation $C_{28}H_{40}NO$ 406.31097 found 406.31100. Found C, 84.90; H, 8.22; N, 1.47; $C_{43}H_{46}BN{\cdot}0.5\ H_2O$ requires: C, 84.91; H,8.30; N, 1.90%.

(+)-(2*R*)-2-(3,4-dihydroisoquinolinium-2-yl)-3-phenylpropan-1-ol:



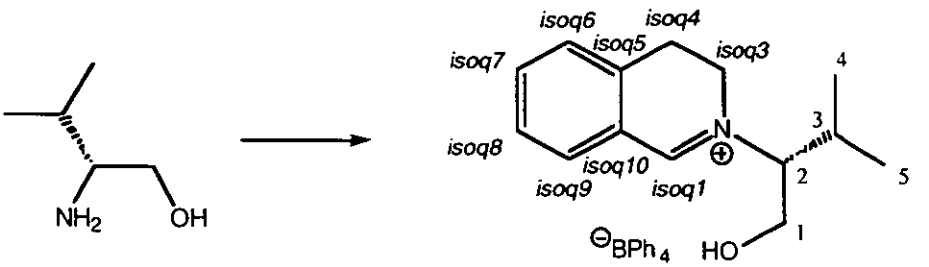
(+)-(R)-Phenyl alaninol derivative: Prepared according to the general procedure in 59% yield, white solid, m.p. 129-131 °C. $[\alpha]^{20}_D$ +84.00 c=1.20, (CH_3CN); ν_{max} /cm^{-1} (nujol) 3514, 1641, 1603, 1576; δ_H (CD_3CN), (400 MHz), 3.08-3.28 (4 H, m, CH_2 at C3 and CH_2 at *isoq-4*), 3.63 (1 H, t, *J* 4.77 Hz, downfield portion of an *ABX* system, CH*H*OH, at C1), 3.86-3.98 (4 H, m, C*H*HOH, at C1, OH and CH_2 at *isoq-3*), 4.34-4.35 (1 H, m, CH at C2), 6.89 (4 H, t, *J* 7.02 Hz, arom., *para* in BPh_4 group), 7.04 (8 H, t, *J* 7.33 Hz, arom., *ortho* in BPh_4 group), 7.33-7.45 (14 H, m, , arom., 8 H *meta* in BPh_4 group, 5 H in Ph group and *isoq-6*), 7.52 (1 H, t, *J* 7.51 Hz, arom., *isoq-8*), 7.72 (1 H, d, *J* 7.55 Hz, arom., *isoq-7*), 7.80 (1 H, t, *J* 7.49 Hz, arom., *isoq-9*), 8.68 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), 24.26 (CH_2, *isoq-4*), 33.75 (CH_2, C3), 46.28 (CH_2, *isoq-3*), 59.64 (CH_2, C1), 73.98 (CH, C2), 121.47 (8xCH arom., CH *ortho* in BPh_4 group), 123.91 (C arom. quat., *isoq-5*), 125.30 (4xCH arom., CH *para* in BPh_4 group), 127.10 (CH arom., *para* in Ph group) 128.08 (CH arom., *isoq-6*), 128.57 (CH arom., *isoq-8*), 128.70 (2xCH arom., *ortho* in Ph group), 128.76 (2xCH arom., *meta* in Ph group), 133.49 (CH arom., *isoq-7*), 135.19 (C arom. quat., *ipso* in Ph group), 135.40 (8xCH arom., CH *meta* in BPh_4 group), 136.91 (C arom. quat., *isoq-10*), 138.20 (CH arom., *isoq-9*), 163.51 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 166.29 (CH, HC=N, *isoq-1*); *m/z* (cation) 266; exact mass calcd for cation $C_{18}H_{20}NO$ 266.15448 found 266.15450. Found C, 85.40; H, 6.87; N, 2.24; $C_{42}H_{40}BNO{\cdot}0.3\ H_2O$ requires: C, 85.20; H, 6.86; N, 2.36%.

(–)-(2*R*,3*R*)-2-(3,4-dihydroisoquinolinium-2-yl)-3-methylpentan-1-ol:



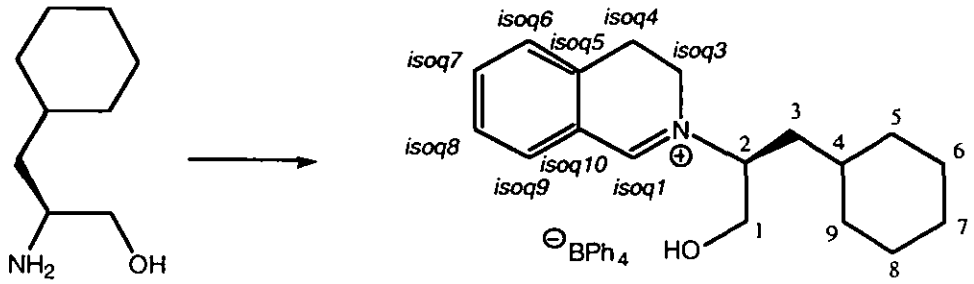
(–)-(2R,3R)-Isoleucinol derivative: Prepared according to the general procedure in 55% yield, white solid, m.p. 172 °C. $[\alpha]^{20}_{D}$ –7.85 c=1.63, (CH_3CN); ν_{max} /cm^{-1} (nujol) 3557, 1649, 1600, 1570; δ_H (CD_3CN), (400 MHz), 0.89 (3 H, t, *J* 7.42 Hz, CH_3 at C5), 0.97 (3 H d, *J* 6.64 Hz, CH_3 at C6), [1.10-1.16 (1 H, m), 1.32-1.40 (1 H, m), 1.88 (1 H, m), CH_2 at C4 and CH at C2], 3.08 (2 H, t, *J* 8.19 Hz, CH_2 at *isoq-4*), 3.67 (1 H, t, *J* 5.19 Hz, downfield portion of *ABX* system C*H*HO at C1), 3.75-3.89 (5 H, m, CH*H*O at C1, OH, CH at C2 and CH_2 at *isoq-3*), 6.83 (4 H, t, *J* 7.21 Hz, arom., *para* in BPh_4 group), 6.98 (8 H, t, *J* 7.40 Hz, arom., *ortho* in BPh_4 group), 7.27-7.31 (8 H, m, arom., *meta* in BPh_4 group) 7.36 (1 H, d, *J* 7.52 Hz, arom., *isoq-6*), 7.49 (1 H, t, *J* 7.48 Hz, arom., *isoq-8*), 7.69-7.74 (2 H, m, arom., *isoq-7* and *isoq-9*), 8.73 (1 H, s, HC=N, *isoq-1*); δ_C (62.50 MHz), 9.51 (CH_3, C5), 13.79 (CH_3, C6), 24.41 (CH_2, C4), 25.12 (CH_2, *isoq-4*), 33.66 (CH, C3), 46.31 (CH_2,*isoq-3*), 58.57 (CH_2, C1), 74.60 (CH, C2), 121.51 (8xCH arom., CH *ortho* in BPh_4 group), 124.38 (C arom. quat., *isoq-5*), 125.26 (4xCH arom., CH *para* in BPh_4 group), 128.03 (CH arom., *isoq-6*), 128.10 (CH arom., *isoq-8*), 133.65 (CH arom., *isoq-7*), 135.44 (8xCH arom., CH *meta* in BPh_4 group), 137.16 (C arom. quat., *isoq-10*), 138.03 (CH arom., *isoq-9*), 163.50 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 166.42 (CH, HC=N, *isoq-1*); *m/z* (cation) 232; exact mass calcd for cation $C_{15}H_{22}NO$ 232.17030 found 232.17010. Found C, 81.56; H, 7.51; N, 2.59; $C_{39}H_{42}BNO{\cdot}1.2\ H_2O$ requires: C, 81.79; H, 7.76; N, 2.44%.

(–)-(2*R*)-2-(3,4-dihydroisoquinolinium-2-yl)-3-methylbutan-1-ol:



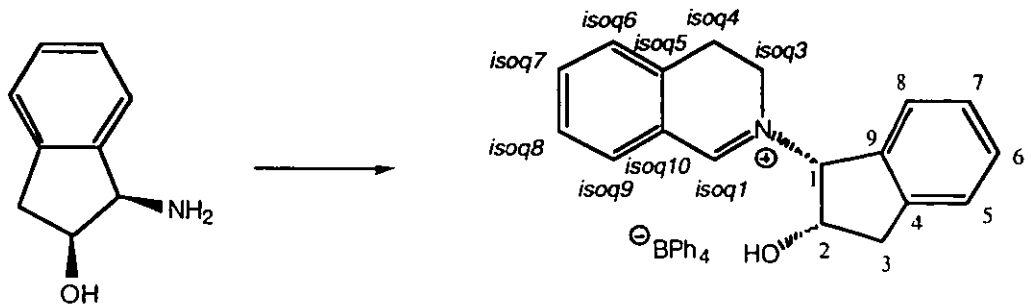
(–)-(R)-valinol derivative: Prepared according to the general procedure in 53% yield, white solid, m.p. 167-169 °C. $[\alpha]^{20}_{D}$ –12.87 c=1.46, (CH_3CN); ν_{max} /cm^{-1} (nujol) 3559, 1650, 1603, 1573; δ_H (CD_3CN), (400 MHz), 0.95 (3 H, d, *J* 6.60 Hz, CH_3 at C5), 1.04 (3 H d, *J* 6.56 Hz, CH_3 at C4), 2.18 (1 H, m, CH at C3), 3.16 (2 H, t, *J* 8.32 Hz, CH_2 at *isoq-4*), 3.35 (1 H, t, *J* 5.22 Hz, downfield portion of an *ABX* system C*H*HO at C1), [3.64-3.67 (1 H, m), 3.76-3.83 (1 H, m), 3.88-3.94 (3 H, m), CH*H*O at C1, OH, CH at C2 and CH_2 at *isoq*-3], 6.83 (4 H, t, *J* 7.20 Hz, arom., *para* in BPh_4 group), 6.98 (8 H, t, *J* 7.40 Hz, arom., *ortho* in BPh_4 group), 7.26-7.30 (8 H, m, arom., *meta* in BPh_4 group) 7.36 (1 H, d, *J* 7.51 Hz, arom., *isoq-6*), 7.49 (1 H, t, *J* 7.50 Hz, arom., *isoq-8*), 7.73-7.78 (2 H, m, arom., *isoq-7* and *isoq-9*), 8.69 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), 17.90 (CH_3, C5), 18.72 (CH_3, C4), 24.34 (CH_2, *isoq-4*), 26.65 (CH, C3), 46.09 (CH_2, *isoq-3*), 58.65 (CH_2, C1), 79.22 (CH, C2), 121.45 (8xCH arom., CH *ortho* in BPh_4 group), 124.11 (C arom. quat., *isoq-5*), 125.31 (4xCH arom., CH *para* in BPh_4 group), 128.02 (CH arom., *isoq-6*), 128.12 (CH arom., *isoq-8*), 133.61 (CH arom., *isoq-7*), 135.44 (8xCH arom., CH *meta* in BPh_4 group), 137.10 (C arom. quat., *isoq-10*), 138.07 (CH arom., *isoq-9*), 163.52 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 166.39 (CH, HC=N, *isoq-1*); *m/z* (cation) 218; exact mass calcd for cation $C_{14}H_{20}NO$ 218.15448 found 218.15450. Found C, 84.28; H, 7.44; N, 2.53; $C_{38}H_{40}BNO{\cdot}0.2\ H_2O$ requires: C, 84.26; H, 7.46; N, 2.58%.

(–)-(2*S*)-3-cyclohexyl-2-(3,4-dihydroisoquinolinium-2-yl)propan-1-ol:



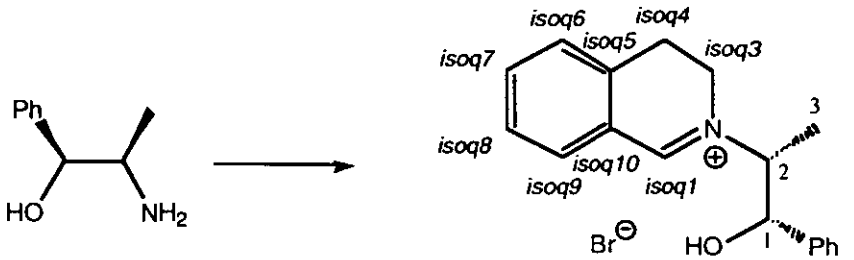
(–)-(S)-2-amino-3-cyclohexyl-propanol derivative: Prepared according to the general procedure in 64% yield, white solid, m.p. 154 °C. $[\alpha]^{20}_D$ –22.42 c=1.32, (CH_3CN); ν_{max} /cm^{-1} (nujol) 3538, 1644, 1600, 1571; δ_H (400 MHz), (CD_3CN), [1.01-1.06 (2 H, m), 1.25-1.33 (4 H, m), 1.65-1.80 (7 H, m), 13xH, C3-C9], 3.16 (2 H, t, *J* 7.94 Hz, CH_2 at *isoq-4*), 3.51 (1 H, t, *J* 5.50 Hz, downfield portion of an *ABX* system C*H*HO at C1), 3.72-3.80 (2 H, m, CH*H*O at C1 and OH), 3.89 (2 H, t, *J* 7.90 Hz, CH_2 at *isoq-3*), 4.15 (1 H, m, CH at C2), 6.90 (4 H, t, *J* 7.21 Hz, arom., *para* in BPh_4 group), 7.05 (8 H, t, *J* 7.44 Hz, arom., *ortho* in BPh_4 group), 7.33-7.37 (8 H, m, arom., *meta* in BPh_4 group), 7.42 (1 H, d, *J* 7.61 Hz, arom., *isoq-6*), 7.47 (1 H, t, *J* 7.62 Hz, arom., *isoq-8*), 7.78-7.81 (2 H, m, arom., *isoq-7* and *isoq-9*), 8.77 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz) [24.25 (CH_2), 25.10 (CH_2), 25.19 (CH_2), 25.48 (CH_2), 31.98 (CH_2), C5-C9] 32.41 (CH_2, C3), 33.07(CH, C4), 34.32 (CH_2,*isoq-4*), 45.41 (CH_2, *isoq-3*, 60.29 (CH_2, C1), 70.45 (CH, C2), 121.28 (8xCH arom., CH *ortho* in BPh_4 group), 124.06 (C arom. quat., *isoq-5*), 125.33 (4xCH arom., CH *para* in BPh_4 group), 127.83 (CH arom., *isoq-6*) 127.92 (CH arom., *isoq-8*), 133.33 (CH arom., *isoq-7*), 135.24 (8xCH arom., CH *meta* in BPh_4 group), 136.87 (C arom. quat., *isoq-10*), 137.80 (CH arom., *isoq-9*), 163.51 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 165.92 (CH, HC=N, *isoq-1*); *m/z* (cation) 272; exact mass calcd for cation $C_{18}H_{26}NO$ 272.20143 found 272.20140. Found C, 84.20; H, 7.73; N, 2.07; $C_{42}H_{46}BNO{\cdot}0.5\ H_2O$ requires: C, 83.90; H, 7.82; N, 2.33%.

(+)-(1*R*,2*S*)-2-(2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-3,4-dihydroisoquinolinium tetraphenylborate:



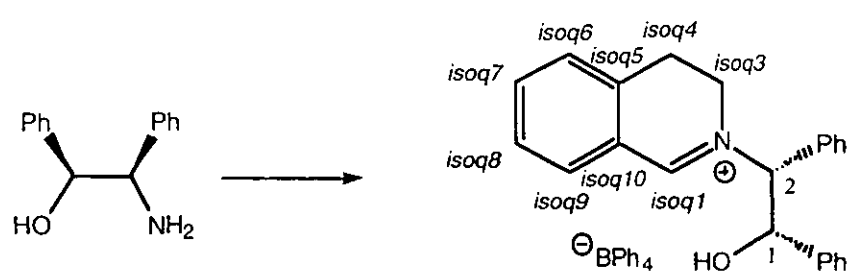
(+)-(1R,2S)-1-Aminoindan-2-ol derivative: Prepared according to the general procedure, 34% yield, white solid, m.p. 161-162 °C. $[\alpha]^{20}_D$ +58.4 c=1.63, (CH_3CN); ν_{max} /cm^{-1} (nujol) 3512, 1635, 1603, 1571; δ_H (CD_3CN), (400 MHz), 2.97 (1 H, dd, *J* 8.40, 4.56 Hz, downfield portion of an *ABX* system, CH*H*CH–O at C3), 3.04-3.13 (2 H, m, CH_2 at *isoq-4*), 3.27 (1 H, dd, *J* 8.34, 6.4 Hz, upfield portion of an *ABX* system, C*H*HCH–O, C3), 3.73-3.80 (2 H, m, CH_2 at *isoq-3*), 4.06-4.07 (1 H, d, *J* 5.36 Hz, OH), 4.78-4.82 (1 H, m, CH at C2), 5.36 (1 H, d, *J* 6.12 Hz, CH at C1), 6.82 (4 H, t, *J* 7.04 Hz, arom., *para* in BPh_4 group), 6.97 (8 H, t, *J* 7.22 Hz, arom., *ortho* in BPh_4 group), 7.28-7.34 (8 H, m, arom., *meta* in BPh_4 group), 7.36-7.43 (6 H, m, arom., 4xCH at C5-8, *isoq-6* and *isoq-8*), 7.63-7.72 (2 H, m, arom., *isoq-7* and *isoq-9*), 8.46 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), 24.32 (CH_2, *isoq-4*), 38.96 (CH_2, C3), 49.05 (CH_2, *isoq-3*), 71.13 (CH, C1), 75.97 (CH, C2), 121.48 (8xCH arom., CH *ortho* in BPh_4 group), 124.23 (C arom. quat., *isoq-5*), 125.26 (CH arom., C5), 125.33 (4xCH arom., CH *para* in BPh_4 group), 125.58 (CH arom., C7), 125.80 (CH arom., C8) 127.59 (CH arom., C6), 128.02 (CH arom., *isoq-6*), 130.21 (CH arom., *isoq-8*), 133.55 (C arom. quat., C4), 133.69 (CH arom., *isoq-7*), 135.40 (8xCH arom., CH *meta* in BPh_4 group), 137.19 (C arom. quat., *isoq-10*), 137.99 (CH arom., *isoq-9*), 142.38 (C arom. quat., C9), 163.50 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 165.86 (CH, HC=N, *isoq-1*); *m/z* (cation) 264; exact mass calcd for cation $C_{18}H_{18}NO$ 264.13883 found 264.13880. Found C, 84.22; H, 6.33; N, 2.31; $C_{42}H_{38}BNO{\cdot}1.2\ H_2O$ requires: C, 83.27; H, 6.67; N, 2.31%.

(+)-[(1*S*,2*R*)-2-(3,4-dihydroisoquinolinium-2-yl]-1-phenylpropanol bromide:



(+)-(1S,2R)-N-2-(1-phenylpropanol)-dihydroisoquinolinium bromide: Prepared according to the general procedure in 57% yield, white solid, m.p. 227-229 °C. $[\alpha]^{20}_{D}$ +35.5 c=1.26, (CH_3OH); ν_{max} /cm^{-1} (nujol) 3557, 1649, 1600, 1570; δ_H (CD_3OD), (400 MHz), 1.51 (3 H, d, *J* 6.82 Hz, CH_3 at C3), 3.28 (2 H, t, *J* 7.93 Hz, CH_2 at *isoq-4*), 4.21-4.30 (2 H, m, CH_2 at *isoq-3*), 4.49-4.55 (1 H, m, CH at C2), 5.21 (1 H, dd, *J* 4.63 Hz, CH at C1), [7.32-7.36 (1 H, m, arom.), 7.40-7.43 (2 H, m, arom.), 7.51-7.56 (4 H, m, arom.), 5xCH from Ph group, *isoq-6* and *isoq-8*], 7.83 (1 H, t, *J* 7.62 Hz, arom., *isoq-7*), 7.89 (1 H, d, *J* 7.64 Hz, arom., *isoq-9*), 9.10 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), 12.97 (CH_3, C3), 26.54 (CH_2, *isoq-4*), 50.31 (CH_2, *isoq-3*), 73.01 (CH, C2), 74.48 (CH, C1), 126.39 (C arom. quat., *isoq-5*), 127.73 (2xCH arom., CH *ortho* in Ph group), 129.60 (CH arom., CH *para* in Ph group), 129.68 (CH arom., *isoq-6*), 129.80 (CH arom., *isoq-8*), 129.92 (2xCH arom., CH *meta* in Ph group) 135.40 (CH arom., *isoq-7*), 138.82 (C arom. quat., *ipso* in Ph group), 139.57 (CH arom., *isoq-9*), 141.9 (C arom. quat., *isoq-10*), 167.78 (HC=N); *m/z* (cation) 266; exact mass calcd for cation $C_{18}H_{20}NO$ 266.15448 found 266.15450. Found C, 61.93; H, 5.81; N, 3.75; $C_{18}H_{20}BrNO{\cdot}0.2\ H_2O$ requires: C, 61.80; H, 5.83; N, 4.00%.

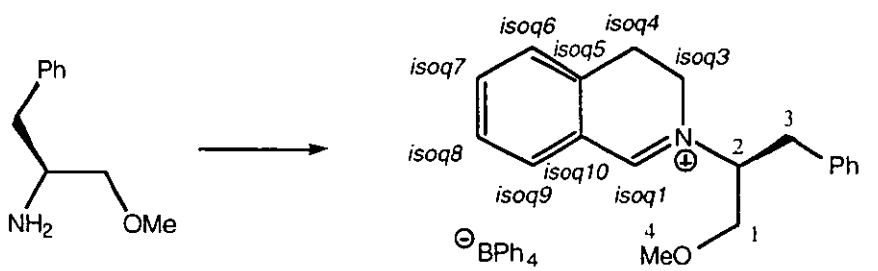
(+)-[(1*S*,2*R*)-2-(3,4-dihydroisoquinolinium-2-yl]-1,2-diphenylethanol tetraphenylborate:



(+)-(1S,2R)-N-2-(1,2-diphenylethanol)-dihydroisoquinolinium tetraphenylborate: Prepared according to the general procedure in 38% yield, pale yellow solid, m.p.

156-158 °C. $[\alpha]^{20}_D$ +38.10 c=1.48, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1634, 1600, 1565; δ_H (CD_3CN), (400 MHz), 2.97 (2 H, t, *J* 7.13 Hz, CH_2, at *isoq-4*), 3.70-3.90 (2 H, m, CH_2 at, *isoq-3*), 4.33 (1 H, d, *J* 4.42 Hz, OH), 5.24 (1 H, d, *J* 4.64 Hz, CH at C2), 5.67 (1 H, d, *J* 4.64 Hz, CH at C1), 6.82 (4 H, t, *J* 7.04 Hz, arom., *para* in BPh_4 group), 6.97 (8 H, t, *J* 7.33 Hz, arom., *ortho* in BPh_4 group), 7.28-7.31 (14 H, m, arom., 8 H *para* in BPh_4 group and 6 H from Ph groups), 7.34-7.48 (6 H, m, arom., 4 H from Ph groups, *isoq-6* and *isoq-8*), 7.72-7.75 (2 H, m, arom., *isoq-7* and *isoq-9*), 9.07 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), 24.54 (CH_2, *isoq-4*), 48.51 (CH_2, *isoq-3*), 71.45 (CH, C2), 77.03 (CH, C1), 121.45 (8xCH arom., CH *ortho* in BPh_4 group), 125.26 (C arom. quat., *isoq-5*), 125.30 (4xCH arom., CH *para* in BPh_4 group), 126.21 (2xCH arom., *ortho* in one of the Ph groups), 128.00 (CH arom., *para* in one of the Ph groups), 128.07 (CH arom., *isoq-6*), 128.12 (CH arom., *isoq-8*), 128.18 (2xCH arom., *meta* in one of the Ph groups), 128.39 (2xCH arom., *ortho* in one of the Ph groups), 129.44 (CH arom., *para* in one of the Ph groups), 129.90 (2xCH arom., *meta* in one of the Ph groups), 130.25 (C arom. quat., *ipso* in one of the Ph groups), 134.04 (CH arom., *isoq-7*) 135.39 (8xCH arom., CH *meta* in BPh_4 group), 136.66 (C arom. quat., *isoq-10*), 138.33 (CH arom., *isoq-9*), 139.37 (C arom. quat., *ipso* in one of the Ph groups), 163.51 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 166.20 (CH, HC=N, *isoq-1*); *m/z* (cation) 328; exact mass calcd for cation $C_{23}H_{22}NO$ 328.17030 found 328.17010. Found C, 86.20; H, 6.53; N, 1.84; $C_{47}H_{42}BNO{\cdot}0.3\ H_2O$ requires: C, 86.36; H, 6.52; N, 2.14%.

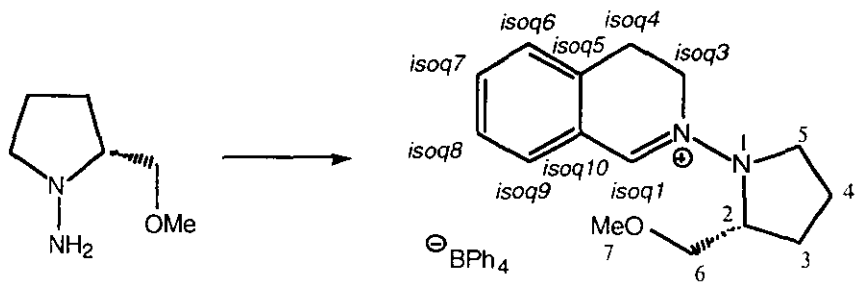
(–)-2-[(1*S*)-2-(methyloxy)-1-(phenylmethyl)ethyl]-3,4-dihydroisoquinolinium tetraphenylborate:



(–)-(S)-Phenyl alaninol methyl ether derivative: Prepared according to the general procedure in 62% yield, yellow solid, m.p. 163-164 °C. $[\alpha]^{20}_D$ –71.80 c=2.29, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1636, 1602, 1569, 1124; δ_H (CD_3CN), (400 MHz), 3.06 (2 H, t, *J* 7.89 Hz, CH_2 at *isoq-4*), 3.09-3.24 (2 H m, CH_2 at C3), 3.38 (3 H, s, CH_3 at C4), 3.71-3.73 (2 H, m, CH_2 at *isoq-3*), 3.85-3.93 (2 H, m, CH_2 at C1), 4.43-4.45 (1 H, m, CH at C2), 6.89 (4 H, t, *J* 7.13 Hz, arom., *para* in BPh_4 group), 7.04 (8 H, t, *J* 7.44 Hz, arom., *ortho* in

BPh_4 group), 7.33-7.37 (14 H, m, arom., 8 H *para* in BPh_4 group, 5 H in Ph group and *isoq-6*), 7.42 (1 H, t, *J* 7.60 Hz, arom., *isoq-8*), 7.66 (1 H, d, *J* 7.59 Hz, arom., *isoq-9*), 7.78 (1 H, t, *J* 7.64 Hz, arom., *isoq-7*), 8.61 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), 24.28 (CH_2,*isoq-4*), 33.98 (CH_2, C3), 46.08 (CH_2, *isoq-3*), 58.20 (CH_3, C4), 69.46 (CH_2, C1), 71.88 (CH, C2), 121.49 (8xCH arom., CH *ortho* in BPh_4 group), 123.84 (C arom. quat., *isoq-5*), 125.32 (4xCH arom., CH *para* in BPh_4 group), 127.19 (CH arom., *para* in Ph group) 128.08 (CH arom., *isoq-6*), 128.73 (CH arom., *isoq-8*), 128.73 (2xCH arom., *ortho* in Ph group), 128.81 (2xCH arom., *meta* in Ph group), 133.59 (CH arom., *isoq-7*), 134.97 (C arom. quat., *ipso* in Ph group), 135.44 (8xCH arom., CH *meta* in BPh_4 group), 136.94 (C arom. quat., *isoq-10*), 138.31 (CH arom., *isoq-9*), 163.50 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 166.38 (CH, HC=N, *isoq-1*); *m/z* (cation) 280; exact mass calcd for cation $C_{19}H_{22}NO$ 280.17030 found 280.17010. Found C, 85.14; H, 7.01; N; 2.17 $C_{43}H_{42}BNO{\cdot}0.3\ H_2O$ requires: C, 85.28; H, 7.04; N, 2.31%.

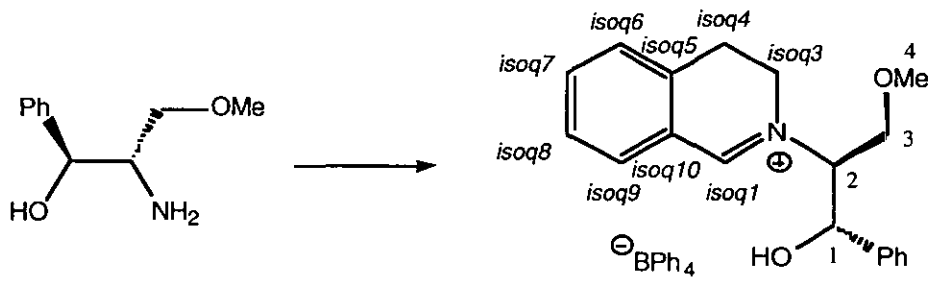
(–)-2-{(2*R*)-2-[(methyloxy)methyl]tetrahydro-1*H*-pyrrol-1yl}-3,4-dihydroisoquinolinium tetraphenylborate:



(–)-RAMP derivative: Prepared according to the general procedure in 59% yield, greenish yellow solid, m.p. 147-148 °C. $[\alpha]^{20}_D$ –41.84 c=1.30, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1653, 1603, 1576, 1099; δ_H (CD_3CN), (400 MHz), [1.55-1.59 (1 H, m), 1.89-1.94 (2 H m), 2.02-2.10 (1 H, m) 2xCH_2 at C3 and C4], 3.16 (3 H, s, CH_3 at C7), 3.13-3.22 (3 H, m, C*H*H at C5 and CH_2 at *isoq-4*), 3.35-3.38 (1 H, m, C*H*H at C5), 3.42 (2 H, d, *J* 5.58 Hz, CH_2 at C6), 3.81-3.98 (2 H, m, *isoq-3*), 4.11-4.14 (1 H, m, CH at C2), 6.83 (4 H, t, *J* 7.17 Hz, arom., *para* in BPh_4 group), 6.98 (8 H, t, *J* 7.44 Hz, arom., *ortho* in BPh_4 group), 7.27-7.30 (8 H, m, arom., *meta* in BPh_4 group), 7.34 (1 H, d, *J* 7.52 Hz, arom., *isoq-6*), 7.46 (1 H, t, *J* 7.49 Hz, arom., *isoq-8*), 7.67-7.69 (2 H, m, arom., *isoq-7* and *isoq-9*), 8.66 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), [20.38 (CH_2), 24.90 (CH_2), C3 and C4], 25.42 (CH_2, *isoq-4*), 47.42 (CH_2, *isoq-3*), 51.30 (CH_2, C5), 57.99 (CH, C2), 60.75 (CH_3, C7), 74.05 (CH_2, C6), 121.46 (8xCH arom., CH *ortho* in BPh_4 group), 124.12 (C arom. quat., *isoq-5*), 125.32 (4xCH arom., CH *para* in BPh_4 group), 127.87 (CH arom., *isoq-*

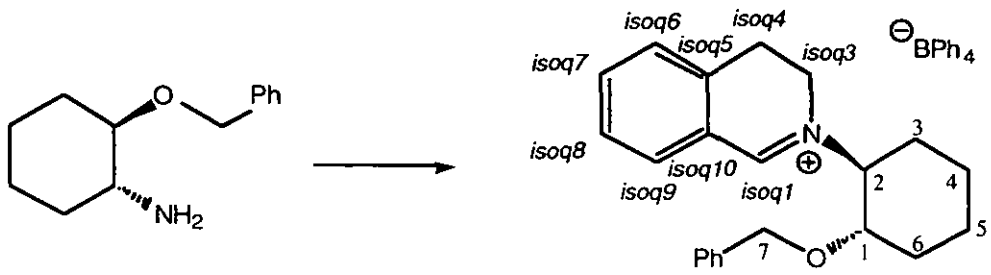
6), 128.01 (CH arom., *isoq-8*), 132.40 (CH arom., *isoq-7*), 135.39 (8xCH arom., CH *meta* in BPh_4 group), 135.60 (C arom. quat., *isoq-10*), 136.77 (CH arom., *isoq-9*), 163.51 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 158.08 (CH, HC=N, *isoq-1*); *m/z* (cation) 245; exact mass calcd for cation $C_{15}H_{21}N_2O$ 245.16540 found 245.16520. Found C, 80.11; H, 7.14; N, 4.57; $C_{39}H_{41}BN_2O{\cdot}1.1\ H_2O$ requires: C, 80.08; H, 7.39; N, 4.79%.

(+)-(1*S*,2*S*)-2-(3,4-dihydroisoquinolinium-2-yl]-3-(methyloxy)-1-phenylpropanol tetraphenylborate:



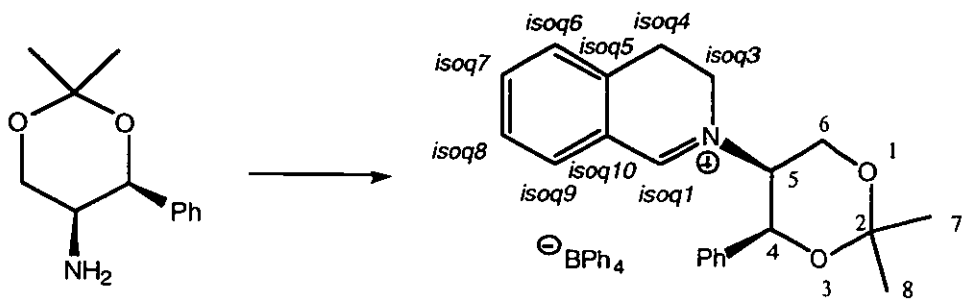
(+)-(1S,2S)-N-2-(3-methoxy-1-phenylpropanol)-dihydroisoquinolinium tetraphenylborate: Prepared according to the general procedure in 27% yield, white solid, m.p. 158-160 °C. $[\alpha]^{20}_D$ +42.70 c=2.50, (CH_3CN); ν_{max} /cm^{-1} (nujol) 3519, 1643, 1604, 1573, 1122; δ_H (CD_3CN), (250 MHz), 3.05-3.12 (2 H, m, CH_2 at *isoq-4*), 3.27 (3 H, s, CH_3 at C4), 3.57-3.73 (2 H, m, CH_2 at C3), 3.81-4.17 (2 H, m, CH_2 at *isoq-3*), 4.27 (1 H, d, *J* 4.25 Hz, OH), 4.23-4.36 (1 H, m, CH at C2), 5.11-5.15 (1 H, dd, *J* 7.15, 4.43 Hz, CH at C1), 6.83 (4 H, t, *J* 7.03 Hz, arom., *para* in BPh_4 group), 6.98 (8 H, t, *J* 7.15 Hz, arom., *ortho* in BPh_4 group), 7.23-7.35 (8 H, m, arom., *meta* in BPh_4 group), 7.35-7.47 (6 H, m, arom., 5 H from Ph group and *isoq-6*) 7.51 (1 H, t,*J* 7.50 Hz, arom., *isoq-8*), 7.75-7.82 (2 H, m, arom., *isoq-7* and *isoq-9*), 8.74 (1 H, s, HC=N, *isoq-1*); δ_C (62.50 MHz), 24.35 (CH_2, *isoq-4*), 47.65 (CH_2, *isoq-3*), 58.18 (CH_3, C4), 68.29 (CH_2, C3), 70.06 (CH, C2), 80.00 (CH, C1), 121.44 (8xCH arom., CH *ortho* in BPh_4 group), 125.19 (C arom. quat., *isoq-5*), 125.28 (4xCH arom., CH *para* in BPh_4 group), 126.05 (2xCH arom., *ortho* in Ph group), 128.08 (CH arom., *para* in Ph group), 128.16 (CH arom., *isoq-6*), 128.41 (CH arom., *isoq-8*), 128.53 (2xCH arom., *meta* in Ph group), 133.70 (CH arom., *isoq-7*), 135.39 (8xCH arom., CH *meta* in BPh_4 group), 137.57 (C arom. quat., *ipso* in Ph group), 138.28 (CH arom., *isoq-9*), 138.83 (C arom. quat., *isoq-10*), 163.52 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 167.11 (CH, HC=N, *isoq-1*); *m/z* (cation) 296; exact mass calcd for cation $C_{19}H_{22}NO_2$ 296.16504 found 296.16400. Found C, 82.70; H, 6.86; N, 1.98; $C_{43}H_{42}BNO_2{\cdot}0.5\ H_2O$ requires: C, 82.60; H, 6.88; N, 2.24%.

(+)-2-{(1*S*,2*S*)-2-[(Phenylmethyl)oxy]cyclohexyl}-3,4-dihydroisoquinolinium tetraphenylborate:



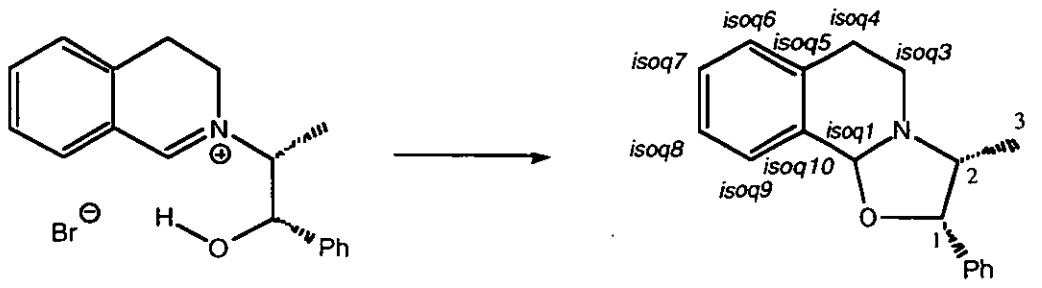
(+)-(1S,2S)-2-(Benzyloxy)-cyclohexylamine derivative: Prepared according to the general procedure in 82% yield, white solid, m.p. 166-168 °C. $[\alpha]^{20}_D$ +37.38 c=2.10, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1643, 1601, 1573, 1069; δ_H (CD_3CN), (400 MHz), [1.29-1.36 (3 H, m), 1.65-2.14 (4 H, m), 2.42-2.45 (1 H, m), 2.80-2.85 (1 H, m), 2.95-3.00 (1 H, m), 4xCH_2 at C3-C6 and CH_2 at *isoq-4*), 3.52-3.61 (2 H, m, CH_2 at *isoq-3*), 3.73-3.82 (2 H, m, 2xCH at C1 and C2), 4.47 (2 H, dd *J* 118.18, 11.86 Hz, *AB* system, CH_2 at C7), 6.82 (4 H, t, *J* 7.16 Hz, arom., *para* in BPh_4 group), 6.98 (8 H, t, *J* 7.40 Hz, arom., *ortho* in BPh_4 group), 7.12-7.16 (5 H, m, arom., Ph group), 7.26-7.29 (8 H, m, arom., *meta* in BPh_4 group), 7.34 (1 H, d, *J* 7.34 Hz, arom., *isoq-6*), 7.47 (1 H, t, *J* 7.42 Hz, arom., *isoq-8*), 7.61 (1 H, d, *J* 7.39 Hz, arom., *isoq-9*), 7.76 (1 H, t, *J* 7.56 Hz, arom., *isoq-7*), 8.50 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), [22.76 (CH_2), 23.44 (CH_2), 24.22 (CH_2), 27.97 (CH_2), C3-C6] 29.81 (CH_2, *isoq-4*), 45.76 (CH_2, *isoq-3*), 69.47 (CH_2, C7), 74.20 (CH, C2), 75.70 (CH, C1), 121.46 (8xCH arom., CH *ortho* in BPh_4 group), 123.99 (C arom. quat., *isoq-5*), 125.24 (4xCH arom., CH *para* in BPh_4 group), 127.43 (CH arom., *para* in Ph group)), 127.65 (CH arom., *isoq-6*), 127.94 (CH arom., *isoq-8*), 127.98 (2xCH arom., *ortho* in Ph group), 128.04 (2xCH arom., *meta* in Ph group), 133.45 (CH arom., *isoq-7*), 135.37 (8xCH arom., CH *meta* in BPh_4 group), 136.82 (C arom. quat., *ipso* in Ph group), 137.64 (C arom. quat., *isoq-10*), 137.96 (CH arom., *isoq-9*), 163.50 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 165.80 (CH, HC=N, *isoq-1*); *m/z* (cation) 320; exact mass calcd for cation $C_{22}H_{26}NO$ 320.20143 found 320.20140. Found C, 85.61; H, 7.12; N, 1.76; $C_{46}H_{46}BNO_2 \cdot 0.3\ H_2O$ requires: C, 85.56; H, 7.22; N, 2.16%.

(+)-2-[(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-3,4-dihydroisoquinolinium tetraphenylborate:



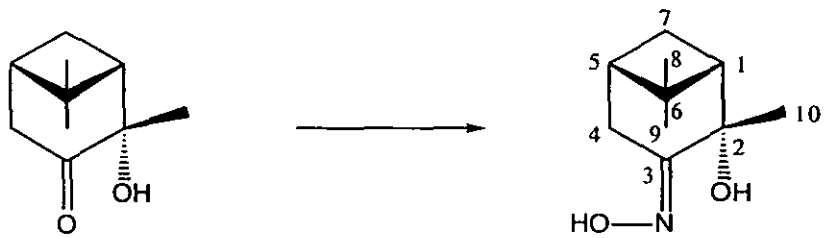
(+)-(4S,5S)-N-5-(2,2-dimethyl-4-phenyl-1,3-dioxane)-dihydroisoquinolinium tetraphenylborate: Prepared according to the general procedure in 75% yield, recrystallised from acetone, yellow solid, m.p. 169-170 °C. $[\alpha]^{20}_{D}$ +38.60 c=2.70, (CH_3CN); ν_{max} /cm^{-1} (nujol) 1637, 1603, 1571, 1480, 1266, 1202, 1166, 1108, 1073; δ_H (CD_3CN), (250 MHz), 1.65 (3 H, s, CH_3 at C7, eq.), 1.94 (3 H, s, CH_3 at C8, ax.), [2.39-2.48 (1 H, m), 2.70-2.82 (1 H, m), CH_2 at *isoq-4*], [3.25-3.40 (1 H, m), 3.81-3.97 (1 H, m), CH_2 at *isoq-3*], 4.06 (1 H, m, CH at C5), 4.30 (1 H, d, *J* 13.72 Hz, upfield portion of an *ABX* system, CH*H*–O1 at C6, eq.), 4.58 (1 H, dd, *J* 13.72 3.05 Hz, downfield portion of an *ABX* system, C*H*H–O1 at C6, ax.), 5.70 (1 H, d, *J* 2.75 Hz, CH at C4), 6.81 (4 H, t, *J* 7.15 Hz, arom., *para* in BPh_4 group), 6.99 (8 H, t, *J* 7.32 Hz, arom., *ortho* in BPh_4 group), 7.22-7.35 (8 H, m, *meta* in BPh_4 group), 7.35-7.40 (6 H, m, 5 H from phenyl group and *isoq-6*), 7.46 (1 H, t, *J* 7.33 Hz, arom., *isoq-8*), 7.65-7.74 (2 H, m, arom., *isoq-7* and *isoq-9*), 8.92 (1 H, s, HC=N, *isoq-1*); δ_C (62.50 MHz), 17.98 (CH_3, C7), 24.06 (CH_2, *isoq-4*), 28.68 (CH_3, C8), 51.55 (CH_2, *isoq-3*), 61.44 (CH_2, C6), 65.46 (CH, C5), 70.72 (CH, C4), 104.88 (C quat., C2), 121.85 (8xCH arom., CH *ortho* in BPh_4 group), 124.29 (C arom. quat., *isoq-5*), 125.44 (2xCH arom., *meta* in Ph group), 125.72 (2xCH arom., *ortho* in Ph group), 128.14 (CH arom., *isoq-6*), 128.46 (CH arom., *isoq-8*), 128.62 (CH arom., *para* in Ph group), 128.04 (4xCH arom., CH *para* in BPh_4 group), 134.39 (CH arom., *isoq-7*), 135.79 (8xCH arom., CH *meta* in BPh_4 group), 136.97 (C arom. quat., *ipso* in Ph group), 137.68 (C arom. quat., *isoq-10*), 138.72 (CH arom., *isoq-9*), 163.51 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 167.48 (CH, HC=N, *isoq-1*); *m/z* (cation) 322; exact mass calcd for cation $C_{21}H_{24}NO_2$ 322.18069 found 322.18090.

(2*R*,3*S*)-3-methyl-2-phenyl-2,3,6,10b-tetrahydro-5*H*-[1,3]oxazolo[2,3-*a*]isquinoline:



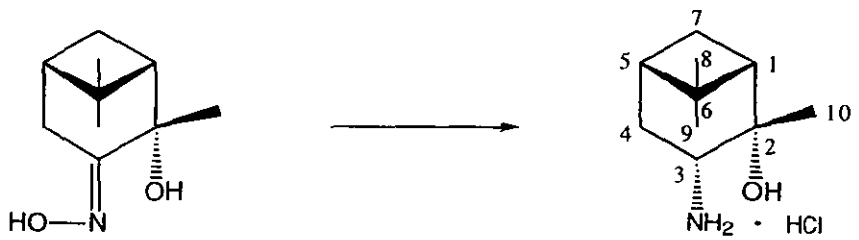
Norephedrine derived bicyclo-oxazolidine: To a solution of the norephedrine derived dihydroisoquinolinium bromide, (5.00 g, 14.44 mmol), in 70 mL of dry dichloromethane, 20 mL of a 40% aqueous solution of sodium bicarbonate is added and the reaction mixture was stirred at room temperature for one hour. Seraration of the organic phase, followed by drying over sodium sulphate and evaporation of the solvent, furnished 3.74 g, of the bicyclo-oxazolidine as a pale yellow oil, as a mixture of inseperable diastereoisomers in 4.8:1 ratio, 97% combined yield. ν_{max} /cm^{-1} (neat) 1604, 1495, 1453, 1395, 1302, 1088, 1065, 1025, 933, 915, 780, 746, 700; δ_H ($CDCl_3$), (400 MHz), main signals for the major diastereoisomer: 0.83 (3 H, d, *J* 7.13 Hz, CH_3), 3.70 (1 H, quintet, *J* 6,76 Hz, CH at C2), 5.33 (1 H, d, *J* 6.32 Hz, CH at C1), 5.83 (1 H, s, O–CH–N, *isoq-1*); main signals for the minor diastereoisomer: 0.92 (3 H, d, *J* 6.96 Hz), 5.11 (1 H, d, *J* 8.40 Hz), 5.82 (1 H, s); other signals are observed at: 2.79-3.11 (m), 3.77-3.79 (m), 7.17-7.52 (m, arom). δ_C (100 MHz), signals for the major diastereoisomer: 16.42 (CH_3, C3), 29.29 (CH_2, *isoq-4*), 46.82 (CH_2, *isoq-3*), 65.70 (CH, C2), 78.31 (CH, C1), 89.25 (CH, O–CH–N, *isoq-1*), 126.42 (CH arom., *isoq-6*), 126.55 (2xCH arom., *meta* in Ph group), 126.85 (CH arom., *isoq-8*), 127.32 (CH arom., *isoq-7*), 128.50 (2xCH arom., *ortho* in Ph group), 128.53 (CH arom., *para* in Ph group), 129.32 (CH arom., *isoq-9*), 133.24 (C arom. quat., *isoq-5*), 135.26 (C arom. quat., *ipso* in Ph group), 140.57 (C arom. quat., *isoq-10*); *m/z* 265; exact mass calcd for $C_{18}H_{20}NO$ 265.14670 found 265.14631. Found C, 81.21; H, 7.21; N, 5.10; $C_{18}H_{19}NO$ requires: C, 81,48; H, 7.22; N, 5.28%.

(+)-(1*S*,2*S*,5*S*)-2-Hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-one oxime:



(+)-(1S,2S,5S)-2-Hydroxy-pinan-3-one oxime:[128] To a solution of (–)-(1*S*,2*S*,5*S*)-2-hydroxypinan-3-one, (5.90 g, 35 mmol), in 40 mL of ethanol, was added 50% aqueous hydroxylamine solution, (15 g, 227 mmol), and the reaction was refluxed for 24 hours. The reaction mixture was then allowed to cool and the organic solvent was removed by rotary evaporation. The resulting residue was redissolved in 25 mL of 2M aqueous NaOH and washed with hexane (2x10 mL). The aqueous layer was cooled and then acidified with dropwise addition of concentrated hydrochloric acid until the pH was between 1-3, and extracted with ethyl acetate, (3x25 mL). The organic extracts were washed with water, then brine, and dried over $MgSO_4$. Evaporation of the solvent furnished 5.12 g of the crude oxime which was recrystallised from ethyl acetate/hexane to give 4.41 g of pure 2-hydroxypinan-3-one oxime, m.p. 119-121 °C, (lit. m.p. 117-118 °C).[128] $[\alpha]^{20}_D$ +22.22 c= 2.25, ($CHCl_3$), (lit. $[\alpha]^{22}_D$ +18.90 c= 3.00, ($CHCl_3$)[128]); ν_{max} /cm^{-1} (nujol) 3260, 1644, 1157, 1084, 1002, 976, 894; δ_H ($CDCl_3$), (250 MHz), 0.85 (3 H, s, CH_3 at C8), 1.29 (3 H, s, CH_3 at C9), 1.55 (3 H, s, CH_3 at C10), 1.60 (1 H, d, *J* 10.63 Hz, CH bridgehead at C1), 1.99 (2 H, d, *J* 5.98 Hz, CH_2 bridgehead at C7), 2.26-2.34 (1 H, m, CH bridgehead at C5), 2.72 (2 H, dd, *J* 24.11, 18.63 Hz, *AB* system, CH_2 at C4); δ_C (62.50 MHz), 22.38 (CH_3, C8), 27.21 (CH_3, C9), 27.94 (CH_2, C7), 28.07 (CH_3, C10), 29.97 (CH_2, C4), 37.50 (CH, C5), 38.70 (C quat., C6), 51.50 (CH, C1), 74.86 (C quat., C2), 163.28 (C quat., C=N, C3); *m/z* 183; exact mass calcd for $C_{10}H_{17}NO_2$ 183.12592 found 183.12570. Found C, 65.23; H, 9.32; N, 7.62; $C_{10}H_{17}NO_2$ requires: C, 65.53; H, 9.36; N, 7.65%.

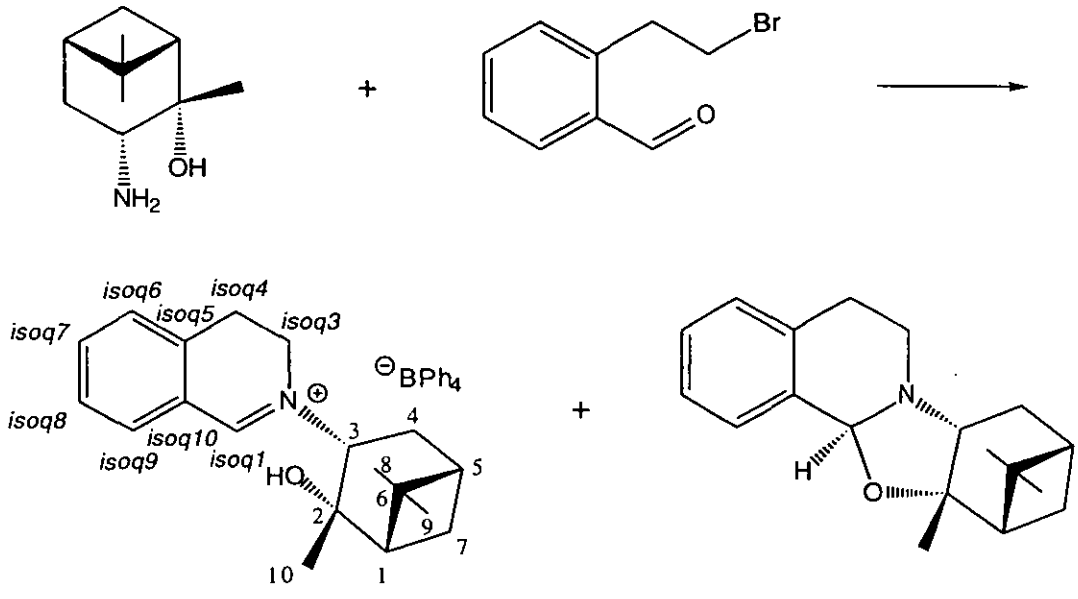
(+)-(1*S*,2*S*,3*R*,5*S*)-3-Amino-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol hydrochloride:



(+)-(1S,2S,3R,5S)-3-Amino-2-hydroxy-pinane hydrochloride:[128] 2-hydroxypinan-3-one oxime, (3.66 g, 20 mmol), was placed in a two neck flask equiped with a condenser, nitrogen bubbler and rubber septum. The flask was cooled to 0 °C by means of an ice bath and 60 mL of a 1M solution of lithium aluminium hydride in diethyl ether (60 mmol, 3 equivalents), was added dropwise via a syringe. When the addition was complete, the ice bath was removed and replaced by an oil bath. The reaction mixture was gently refluxed overnight. The reaction mixture was cooled to 0 °C, and ethyl acetate was added dropwise in order to destroy the excess of reducing agent, followed by 15 mL of 1M solution of cold sodium hydroxide and 15 mL of water. The slurry was extracted with ether, (5x30) and the organic extracts were rotary evaporated. The residue was acidified with 2M hydrochloric acid until the pH was between 1-3, and washed with hexane (2x10 mL). The aqueous layer was then made strongly alkaline, (pH 10), by addition of 5M aqueous sodium hydroxide solution, and extracted thoroughly with dichloromethane. The organic extracts were dried over sodium sulfate and evaporated under reduced pressure to furnish the crude amino alcohol which was recrystallised from ethyl acetate/light petroleum. In order to obtain an analytically pure sample, it was however necessary to convert this to the hydrochloride salt by addition of hydrogen chloride etherate. The organic salt precitatated instantly and it was also recrystallised from ethyl acetate/light petroleum to provide 2.46 g of the 3-amino-2-hydroxypinane hydrochloride, 61% yield, m.p. 223-225 °C, (free amine lit. m.p. 45-46.5 °C).[128] $[\alpha]^{20}_{D}$ +4.52 c= 1.77, (DMSO), (free amine lit. $[\alpha]^{22}_{D}$ −14.30 c= 1.77, ($CHCl_3$)[128]);ν_{max} /cm^{-1} (nujol) 3360, 1600, 1475, 1115, 1092; δ_H ($CDCl_3$), (250 MHz), 0.94 (3 H, s, CH_3 at C8), 1.27 (3 H, s, CH_3 at C9), 1.51 (3 H, s, CH_3 at C10), 1.66 (1 H, d, *J* 10.72 Hz, CH bridgehead at C1), 1.97-2.04 (3 H, m, CH_2 bridgehead at C7, and C*H*H at C4), 2.26-2.34 (1 H, m, CH bridgehead at C5), 2.48 (1 H, m, CH*H* at C4), 3.07 (1 H, m, CH at C3), 3.92 (1 H, br. s, OH), 8.07 (3 H, br. s, NH_3^+); δ_C (62.50 MHz), 23.79 (CH_3, C8), 27.51 (CH_3, C9), 27.74 (CH_2, C7), 29.27 (CH_3, C10), 32.76 (CH_2, C4), 38.47 (C quat., C6), 39.94 (CH, C5), 50.85 (CH, C1), 54.21 (CH, C3), 73.29 (C quat., C2); *m/z* (free amine) 169; exact

mass calcd for the free amine $C_{10}H_{19}NO$ 169.14666 found 169.14660. Found C, 58.18; H, 9.90; N, 6.79; $C_{10}H_{20}ClNO$ requires: C, 58.38; H, 9.80; N, 6.81%.

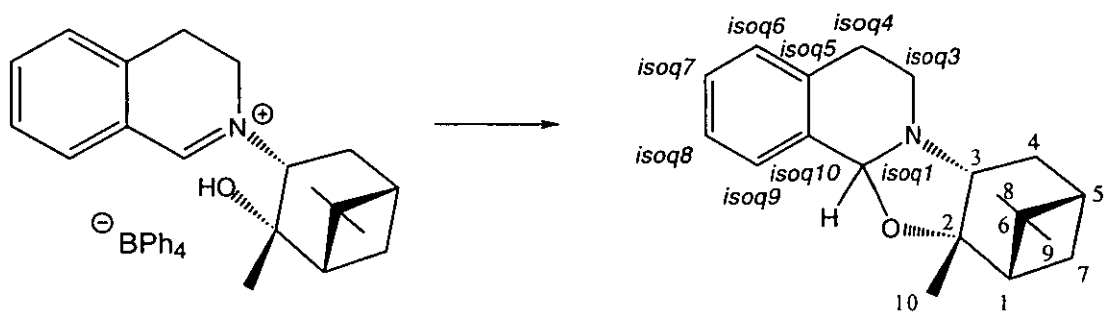
(–)-2-[(1*S*,2*S*,3*R*,5*S*)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]-3,4-dihydroisoquinolinium tetraphenylborate:



(–)-(1S,2S,3R,5S)-N-3-(2-hydroxyisopinocampheyl)-dihydroisoquinolinium tetraphenylborate: A solution of 3-amino-2-hydroxy pinane, (2.00 g, 11.80 mmol), in 30 mL of ethanol, was added dropwise via a stoppered, pressure equalising, dropping funnel, to an ice cooled, one-neck flask, containing distilled 2-(2-bromoethyl)-benzaldehyde, (2.60 g, 12.00 mmol). After the addition was complete the dropping funnel was removed and replaced by a stopper. The reaction mixture was stirred overnight while attaining ambient temperature. Sodium tetraphenylborate, (4.40 g, 12.84 mmol), in 30 mL of acetonitrile, is added in the reaction mixture and after 5 minutes of stirring, the organic solvents were rotary evaporated. Ethanol is added to the residue, followed by water. The resulting white solid was collected by filtation and washed with additional ethanol followed by diethyl ether, 1.24 g. This solid was shown by NMR to be an equilibrium mixture of the expected dihydroisoquinolinium salt and one of the corresponding diastereoisomeric oxazolidines in 3:1 ratio in favour of salt. The ratio was established by comparison of the integrals corresponding to the iminium proton, δ 8.79 ppm, and the oxazolidine proton, δ 6.27 ppm. This equilibrium could not be shifted to the side of the iminium salt by addition of trifluoacetic or concentrated hydrobromic

acid. ν_{max} /cm^{-1} (nujol) 3510, 1642, 1606, 1574, 737, 706, 611; δ_H ($CDCl_3$), (250 MHz), characteristic signals for the iminium salt: 1.04 (3 H, s, CH_3 at C8), 1.32 (3 H, s, CH_3 at C9), 1.38 (3 H, s, CH_3 at C10), 1.57 (1 H, d, *J* 8.85 Hz, CH bridgehead at C1), 3.14 (1 H, t, *J* 5.50 Hz, CH_2 at *isoq-4*), 3.76-3.91 (1 H, m, CH bridgehead at C5), 4.19 (1 H, t, *J* 5.80 Hz, CH*H*N *isoq-3*), 4.24 (1 H, t, *J* 5.48 Hz, C*H*HN *isoq-3*), 4.54 (1 H, dd, *J* 10.19, 7.16 Hz, CH at C3), 6.84 (4 H, t, *J* 7.03 Hz, arom., *para* in BPh_4 group), 6.98 (8 H, t, *J* 7.48 Hz, arom., *ortho* in BPh_4 group), 7.25-7.31 (9 H, m, arom., 8 H *meta* in BPh_4 group and*isoq-6*), 7.44 (2 H, m, arom., *isoq-8* and*isoq-9*), 7.52 (1 H, t, *J* 7.36 Hz, arom., *isoq-7*), 8.79 (1 H, s, HC=N, *isoq-1*); other signals are observed at: 2.00-2.24 (m), 2.32-2.75 (m), 3.00-3.60 (m); δ_C (62.50 MHz), 22.52 (CH_3, C8), 24.72 (CH_2, *isoq-4*), 26.90 (CH_3, C9), 26.95 (CH_2, C7), 28.44 (CH_3, C10), 30.54 (CH_2, C4), 39.34 (C quat., C6), 39.79 (CH, C5), 49.74 (CH_2, *isoq-3*), 53.86 (CH, C1), 70.87 (CH, C3), 75.12 (C quat., C2), 121.55 (8xCH arom., CH *ortho* in BPh_4 group), 124.98 (C arom. quat., *isoq-5*), 125.34 (4xCH arom., CH *para* in BPh_4 group), 125.42 (CH arom., *isoq-6*), 128.06 (CH arom., *isoq-8*), 133.57 (CH arom., *isoq-7*), 135.50 (8xCH arom., CH *meta* in BPh_4 group), 138.64 (C arom. quat., *isoq-10*), 138.96 (CH arom., *isoq-9*), 163.51 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 167.60 (CH, HC=N, *isoq-1*). *m/z* (cation) 282; exact mass calcd for cation $C_{19}H_{26}NO$ 282.18578 found 282.18535.

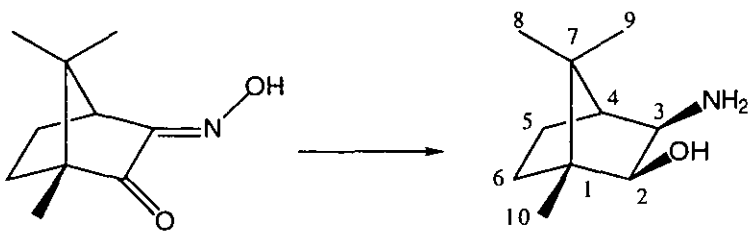
(1*S*,2*S*,14*R*,16*S*)-2,17,17-trimethyl-3-oxa-13-azapentacyclo[14.1.1.0^{2,14}.0^{4,13}.0^{5,10}]-octadeca-5(10),6,8-triene:



(1S,2S,3R,5S)-3-Amino-2-hydroxy pinane derived bicyclo-oxazolidine: The equilibrium mixture, (0.61 g, 1.00 mmol), of the 3-amino-2-hydroxy pinane derived dihydroisoquinolinium tetraphenylborate and the corresponding oxazolidine, was dissolved in dry dichloromethane and stirred over 3.00 g of sodium carbonate overnight. Filtration and removal of the solvent furnished a mixture of diastereoisomeric oxazolidines in 3.2:1 ratio, as an pale yellow oil, 0.18 g, 62% combined yield. These were inseperable by column chromatography. ν_{max} /cm^{-1}

(neat) 1494, 1455, 1315, 1201, 1114, 1086, 1062, 1037, 1016, 969, 930, 869, 745; δ_H ($CDCl_3$), (250 MHz), characteristic signals for the major diastereoisomer: 0.88 (3 H, s, CH_3 at C8), 1.21 (3 H, s, CH_3 at C9), 1.23 (3 H, s, CH_3 at C10), 1.58 (1 H, d, *J* 10.49 Hz, CH bridgehead at C1), 2.12 (1 H, t, *J* 5.82 Hz, C*H*H, *isoq-4*), 2.38-2.60 (2 H, m, CH_2 bridgehead at C7), 2.70-2.82 (2 H, m), 2.94-3.05 (1 H, m), 3.14-3.18 (1 H, m), 3.35 (1 H, dd, *J* 10.12, 4.47 Hz, CH at C3), 5.68 (1 H, s, *isoq-1*), 7.05-7.16 (3 H, m, arom., *isoq-6,7,8*), 7.36 (1 H, dd, *J* 5.32, 3.62 Hz, *isoq-9*); characteristic signals for the minor diastereoisomer: 0.82 (3 H, s, CH_3 at C8), 1.20 (3 H, s, CH_3 at C9), 1.38 (3 H, s, CH_3 at C10), 4.71 (1 H, s, *isoq-1*); other signals are observed at: 1.60-2.06 (m), 2.20-2.24 (m); δ_C (62.50 MHz), major diastereoisomer: 23.99 (CH_3, C8), 26.92 (CH_2, *isoq-4*), 27.26 (CH_3, C9), 28.70 (CH_2, C7), 30.28 (CH_3, C10), 34.96 (CH_2, C3), 39.42 (C quat., C6), 40.19 (CH, C5), 46.85 (CH_2, *isoq-3*), 54.00 (CH, C1), 65.03 (CH, C3), 84.22 (C quat., C2), 89.68 (CH, *isoq-1*), 126.31 (CH arom., *isoq-6*), 127.68 (CH arom., *isoq-8*), 128.01 (CH arom., *isoq-7*), 128.62 (CH arom., *isoq-9*), 134.77 (C arom. quat., *isoq-5*), 136.10 (C arom. quat., *isoq-10*); minor diastereoisomer: 23.69 (CH_3, C8), 26.79 (CH_3, C9), 27.00 (CH_2, *isoq-4*), 27.45 (CH_3, C10), 29.42 (CH_2, C7), 30.54 (CH_2, C4), 37.70 (C quat., C6), 40.02 (CH, C5), 44.43 (CH_2, *isoq-3*)), 50.79 (CH, C1), 61.96 (CH, C3), 85.80 (C quat., C2), 88.75 (CH, *isoq-1*), 123.84 (CH arom., *isoq-6*), 125.57 (CH arom., *isoq-8*), 127.03 (CH arom., *isoq-7*), 128.25 (CH arom., *isoq-9*), 134.68 (C arom. quat., *isoq-5*), 135.99 (C arom. quat., *isoq-10*).

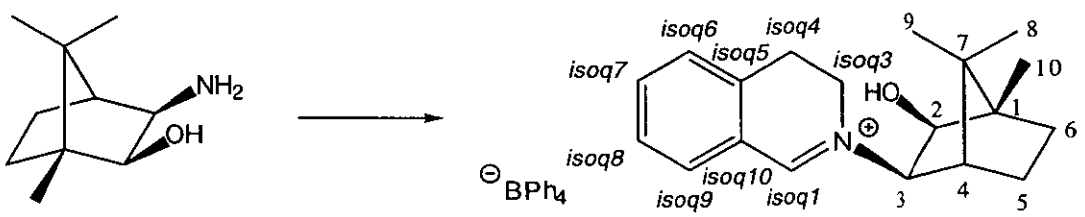
(+)-(1*R*,2*S*,3*R*,5*S*)-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol:



(+)-(1R,2S,3R,5S)-Cis-exo-3-amino-borne-2-ol:[131,217] 2.17 g (12 mmol), of *anti*-(1*R*)-(+)-camphor quinone monooxime was placed in a two neck flask equiped with a condenser, nitrogen bubbler and rubber septum. The flask was cooled to 0 °C by means of an ice bath and 36 mL of a 1M solution of lithium aluminium hydride in diethyl ether (36 mmol, 3 equivalents), was added dropwise via a syringe. When the addition was complete, the ice bath was removed and replaced by an oil bath. The reaction mixture was gently refluxed overnight. The reaction mixture was cooled to 0 °C, and ethyl acetate was added dropwise in order to destroy the excess of

reducing agent, followed by 20 mL of 1M solution of cold sodium hydroxide. The resulted slurry was extracted thoroughly with diethyl ether (4x50 mL), and the ether extracts were dried over sodium sulfate. Evaporation of the solvent and recrystallisation of the residue from hexane furnished 1.24 g of*cis-exo*-3-amino-borneol, 61% yield, m.p. 204-206 °C, (lit. m.p. 197-200 °C).[131,217] $[\alpha]^{20}_D$ +7.88 c= 2.74, (DMSO), (lit. $[\alpha]^{20}_D$ –1.30 c= 1.43, (MeOH)[217]); ν_{max} /cm^{-1} (nujol) 3384, 3293, 3149, 1094, 1061; δ_H ($CDCl_3$), (250 MHz), 0.75 (3 H, s, CH_3, at C8), 0.91 (3 H, s, CH_3, at C9), 1.02 (3 H, s, CH_3 at C10), 1.33-1.45 (2 H, m, *exo* at C5 and C6), 1.51 (1 H, d, *J* 4.58 Hz, bridgehead H at C4), 1.60-1.74 (2 H, m, *endo* at C5 and C6), 2.58 (3 H, br. s, OH and NH_2), 3.00 (1 H, d, *J* 7.32 Hz, CH *endo* at C3), 3.35 (1 H, d, *J* 7.62 Hz, CH *endo* at C2); δ_C (62.50 MHz), 11.33 (CH_3, C8), 21.13 (CH_3, C9), 21.86 (CH_3, C10), 26.78 (CH_2, C5), 33.05 (CH_2, C6), 46.53 (C quat., C7), 53.30 (CH, C4), 54.26 (C quat., C1), 57.32 (CH, C3), 78.90 (CH, C2).

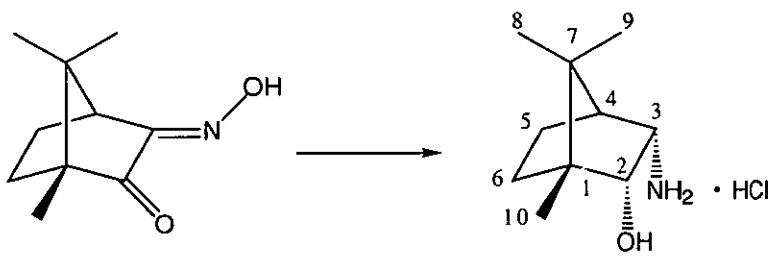
(+)-2-[(1*R*,2*S*,3*R*,5*S*)-2-hydroxy-1,6,6-trimethylbicyclo[2.2.1]hept-3-yl]-3,4-dihydroisoquinolinium tetraphenylborate:



(+)-(1R,2S,3R,5S)-N-3-exo-(exo-borne-2-ol)-dihydroisoquinolinium tetraphenylborate: Prepared according to the general procedure in 47% yield, m.p. 179-180 °C. $[\alpha]^{20}_D$ +28.81 c= 1.18, (DMSO); ν_{max} /cm^{-1} (nujol) 3522, 1651, 1604, 1577, 1510, 1064, 1031, 754, 735, 706, 612; δ_H (DMSO-d_6), (250 MHz), 0.60 (3 H, s, CH_3 at C8), 0.83 (3 H, s, CH_3 at C9), 0.95 (3 H, s, CH_3 at C10), 1.25-1.77 (2 H, m, *exo* at C5 and C6), 2.22 (1 H, d, *J* 4.50 Hz, *endo* at C5), 2.53 (1 H, d, *J* 4.45 Hz, *endo* at C6), 2.92-3.14 (2 H, m, CH_2 at *isoq-4*), 3.72-3.84 (2 H, m, CH_2 at *isoq-3*), 3.91 (1 H, d, *J* 7.72 Hz, bridgehead H at C4), 4.15 (1 H, d, *J* 8.55 Hz, CH–N, *endo* at C3), 5.09 (1 H, d, *J* 8.58 Hz, CH–O, *endo* at C2), 6.61 (4 H, t, *J* 7.08 Hz, arom., *para* in BPh_4 group), 6.76 (8 H, t, *J* 7.19 Hz, arom., *ortho* in BPh_4 group), 6.98-7.25 (8 H, m, arom., *meta* in BPh_4 group), 7.26 (1 H, d, *J* 7.53 Hz, arom., *isoq-6*), 7.62 (1 H, t, *J* 7.56 Hz, arom., *isoq-8*), 7.70 (1 H, t, *J* 7.58 Hz, arom., *isoq-7*), 7.85 (1 H, d, *J* 7.33 Hz, arom., *isoq-9*), 9.05 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), 10.38 (CH_3, C8), 11.68 (CH_3, C9), 21.08 (CH_3, C10), 23.86 (CH_2, *isoq-4*), 25.44 (CH_2, C5), 41.97 (CH, C4), 42.19 (CH_2, C6), 47.35 (C quat., C7), 49.55 (C quat., C1), 51.82

(CH_2, *isoq-3*), 68.24 (CH, C3), 78.75 (CH, C2), 121.70 (8xCH arom., CH *ortho* in BPh_4 group), 124.41 (C arom. quat., *isoq-5*), 125.49 (4xCH arom., CH *para* in BPh_4 group), 128.19 (CH arom., *isoq-6*), 128.30 (CH arom., *isoq-8*), 133.71 (CH arom., *isoq-7*), 135.72 (8xCH arom., CH *meta* in BPh_4 group), 137.06 (C arom. quat., *isoq-10*), 137.85 (CH arom., *isoq-9*), 163.51 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 163.72 (CH, HC=N, *isoq-1*). *m/z* (cation) 284; exact mass calcd for cation $C_{19}H_{26}NO$ 284.20143 found 284.20097. Found C, 85.50; H, 7.56; N, 2.20; $C_{43}H_{46}BNO{\cdot}0.3\ H_2O$ requires: C, 85.52; H, 7.68; N, 2.32%.

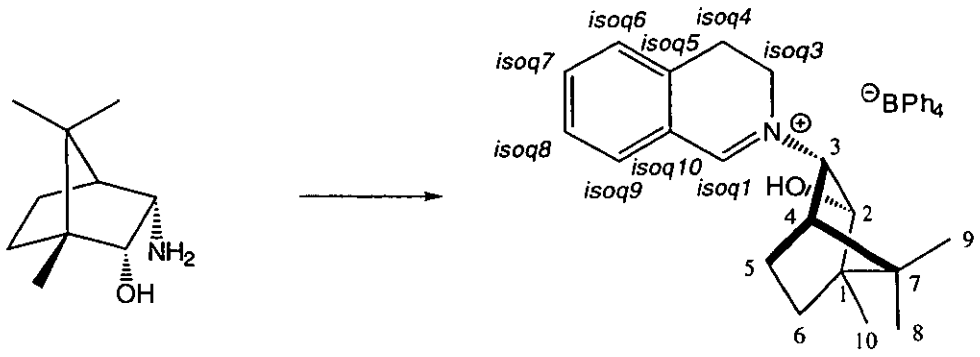
(+)-(1*R*,2*R*,3*S*,5*S*)-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol:



(+)-(1R,2R,3S,5S)-Cis-endo-3-amino-borne-2-ol:[219,220] A solution of *anti*-(1*R*)-(+)-camphor quinone monooxime (1.82 g, 10 mmol), was dissolved in 40 mL of a 1M solution of hydrogen chloride in diethyl ether, followed by 250 mg of 10 % palladium on activated carbon. The suspension was placed in a Parr hydrogenator. Hydrogen atmosphere was established, and the reaction mixture was hydrogenated (60 lb/sq. in.), with mechanical shaking overnight. During the reaction the amino alcohol hydrochloride precipitated out of the reaction mixture. 50 mL of ethanol were added and the suspension was brought to boil to dissolve the hydrochoride salt and filtered. The solvents are evaporated and 10% of aqueous sodium carbonate solution was added to the residue untill pH 10. Thorough extraction with dichloromethane, drying over sodium sulfate and evaporation of the solvent, gives a yellow oil which slowly solidifies. The product, *cis-endo*-3-amino-borneol is recrystallised from hexane, 0.88 g, 52% yield. It was however found, that the hydrochloride salt is more suitable for long term storage. This was prepared by action of ethereal hydrogen chloride, (instant precipitation) on the solid isolated. The following characterisation refers to the hydrochloride salt; m.p. 218-220 °C, (lit. m.p. 226-228 °C).[219] $[\alpha]^{20}_D$ +125.30 c= 1.89, (DMSO), (lit. $[\alpha]^{20}_D$ +24.50 c= 0.5, (EtOH)[220]); ν_{max} /cm^{-1} (nujol) 3164, 3057, 1606, 1504, 1050, 1002, 931, 894, 731; δ_H ($CDCl_3$), (400 MHz), 0.89 (3 H, s, CH_3 at C8), 0.93 (3 H, s, CH_3 at C9), 1.01 (3 H, s, CH_3 at C10), [1.33-1.36 (1 H, m) 1.62-1.78 (4 H, m), 2xCH_2 *exo* and *endo* at C5, C6 and bridgehead

H at C4], 2.14 (1 H, d, *J* 4.34 Hz, CH at *exo* at C3), 3.48 (1 H, d, *J* 4.84 Hz, CH *exo* at C2); δ_C (100 MHz), 9.88 (CH_3, C8), 18.93 (CH_2, C6), 19.43 (CH_3, C9), 20.14 (CH_3, C10), 32.55 (CH_2, C5), 44.37 (C quat., C7), 49.60 (CH, C4), 58.86 (C quat., C1), 59.05 (CH, C3), 77.41 (CH, C2).

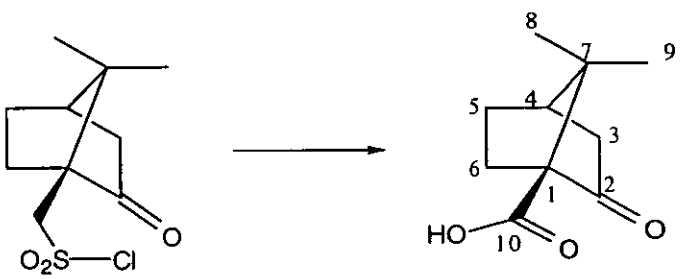
(+)-2-[(1*R*,2*R*,3*S*,5*S*)-2-Hydroxy-1,6,6-trimethylbicyclo[2.2.1]hept-3-yl]-3,4-dihydroisoquinolinium tetraphenylborate:



(+)-(1R,2R,3S,5S)-N-3-Endo-(endo-borne-2-ol)-dihydroisoquinolinium tetraphenylborate: Prepared according to the general procedure in 45% yield, m.p. 186-188 °C (dec.). $[\alpha]^{20}_D$ +110.45 c= 1.55, (DMSO), ν_{max} /cm^{-1} (nujol) 3440, 1639, 1602, 1572, 1227, 1031, 734, 709, 610; δ_H (CD_3CN), (400 MHz), 0.99 (3 H, s, CH_3 at C8), 1.01 (3 H, s, CH_3 at C9), 1.10 (3 H, s, CH_3 at C10), 1.26 (1 H, t, *J* 7.89 Hz, *exo* at C6), 1.54 (1 H, t, *J* 7.92 Hz, *exo* at C5), 1.90-1.94 (2 H, m, *endo* at C5 and C6), 2.69-2.71 (1 H, m, bridgehead H at C4), 3.10-3.22 (3 H, m, CH *endo* at C3 and CH_2 at *isoq-4*), 3.85 (2 H, t, *J* 8.02 Hz, CH_2 at *isoq-3*), 4.65 (1 H, d, *J* 4.40 Hz, CH *endo* at C2), 6.83 (4 H, t, *J* 7.20 Hz, arom., *para* in BPh_4 group), 6.98 (8 H, t, *J* 7.40 Hz, arom., *ortho* in BPh_4 group), 7.24-7.30 (8 H, m, arom., *meta* in BPh_4 group), 7.42 (1 H, d, *J* 7.60 Hz, *isoq-6*), 7.52 (1 H, t, *J* 7.56 Hz, *isoq-8*), 7.80 (1 H, t, *J* 7.60 Hz, *isoq-7*), 7.86 (1 H, d, *J* 7.68 Hz, *isoq-9*), 8.63 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), 0.61 (CH_3, C8), 10.00 (CH_3, C9), 19.61 (CH_3, C10), 20.39 (CH, C4), 20.61 (CH_2, C5), 26.01 (CH_2, *isoq-4*), 30.87 (CH_2, C6), 45.60 (C quat., C7), 48.39 (CH, C3), 50.49 (CH_2, *isoq-3*), 61.24 (C quat., C1), 74.24 (CH, C2), 123.26 (8xCH arom., CH *ortho* in BPh_4 group), 126.00 (C arom. quat., *isoq-5*), 127.05 (4xCH arom., CH *para* in BPh_4 group), 129.91 (CH arom., *isoq-6*), 129.95 (CH arom., *isoq-8*), 136.22 (CH arom., *isoq-7*), 137.18 (8xCH arom., CH *meta* in BPh_4 group), 138.77 (C arom. quat., *isoq-10*), 140.22 (CH arom., *isoq-9*, 163.51 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 167.63 (CH, HC=N, *isoq-1*). *m/z* (cation) 284; exact mass calcd for (cation–2H) $C_{19}H_{24}NO$ 282.18580 found 282.18633. Found C, 84.71; H, 7.44; N, 2.15;

$C_{43}H_{46}BNO{\cdot}0.3\ H_2O$ requires: C, 84.76; H, 7.65; N, 1.97%.

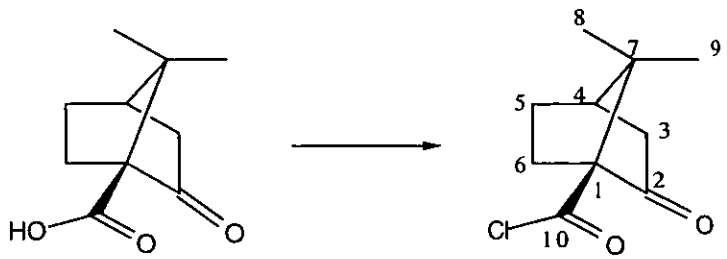
(+)-(1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-carboxylic acid:



(+)-(1S,4R)-Ketopinic acid:[222-224] A solution of anhydrous sodium carbonate, (50 g, 0.48 mol), in 450 mL of water in a 2 L beaker, is heated to approximatelly 80 °C with sufficient stirring. To the hot solution is added potassium permanganate, (25 g, 0.32 mol), as a solution in 300 mL of hot water, followed by (+)-(1*S*)-camphor-10-sulfonyl chloride, (25 g, 0.10 mol). After an interval of 15 minutes, a second portion of potassium permanganate, (25 g in 300 mL of hot water), is added, followed by second 25 g portion of camphorsulfonyl chloride and heating is continued for an additional hour. The excess permanganate is destroyed by the addition of an acidified, (conc. H_2SO_4), saturated sodium sulfite solution, (20 mL), and the reaction mixture is allowed to cool. Subsequently it was made strongly acidic (pH 1), by cautious addition of 20% sulfuric acid, (foaming occurs), and reheated to 80 °C. The precipitated manganese dioxide, (black residue), is dissolved slowly upon addition of sodium sulfite powder, (approximatelly 25 g). The resulting solution, (white inorganic solids usually precipitate at this stage), was allowed to attain ambient temperature and extracted with diethyl ether (4x120 mL), and the organic extracts were dried over sodium sulfate. Removal of of the solvent by rotary evaporation afforded 16 g of (1*S*)-ketopinic acid as a white solid, which was recrystallised from hot water, 46% yield, m.p. 235-237 °C, (lit. m.p. 230-238 °C).[222] $[\alpha]^{20}_D$ +57.28 c=1.00, ($CHCl_3$), (lit. $[\alpha]^{20}_D$ +26.40 c=0.65, (MeOH)[224]); δ_H ($CDCl_3$), (400 MHz), 1.15 (3 H, s, CH_3 at C8), 1.16 (3 H, s, CH_3 at C9), [1.42-1.48 (1 H, m), 1.77-1.84 (1 H, m), *exo* at C5 and C6], 2.01 (1 H, d, *J* 18.59 Hz, bridgehead H at C4), 2.04-2.16 (2 H, m, *endo* at C5 and C6), 2.34-2.46 (1 H, m, *exo* at C3), 2.55-2.63 (1 H, m, *endo* at C3), 9.89 (1 H, br. s, CO_2H); δ_C (100 MHz), 20.23 (CH_3, C8), 21.33 (CH_3, C9), 26.99 (CH_2, C5), 27.17 (CH_2, C6), 44.11 (CH_2, C3), 44.55 (CH, C4), 50.14 (C quat., C7), 67.69 (C quat., C1), 175.55 (C quat., CO_2H, C10), 213.06 (C quat., C=O, C2). *m/z* 182; exact mass calcd for $C_{10}H_{14}O_3$ 182.09429 found 182.09405. Found C, 65.79; H, 7.65; $C_{10}H_{14}O_3$ requires: C,

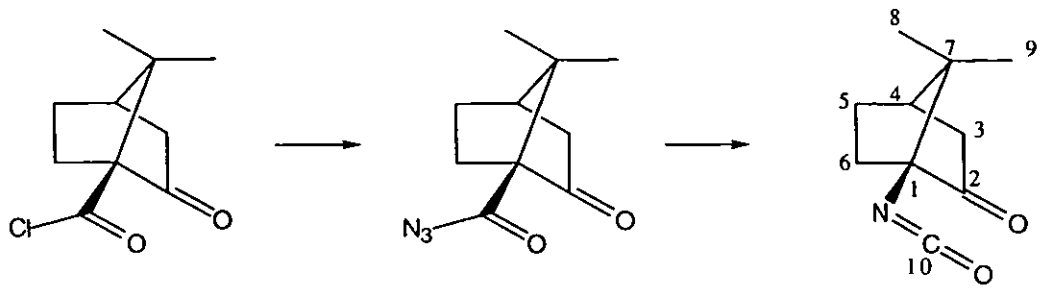
65.90; H, 7.75%.

(+)-(1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-carbonyl chloride:



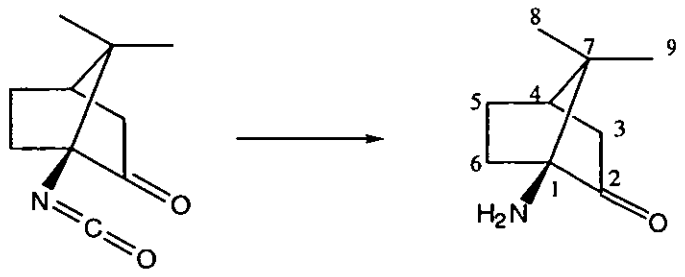
(+)-(1S,4R)-Ketopinic acid chloride:[225-227] Ketopinic acid, (10 g, 55 mmol), was dissolved in 20 mL of thionyl choride. The flask was fitted with a bubbler to allow vent for the gaseous products and was allowed to stirr overnight at ambient temperature. The excess of thionyl chloride was removed by rotary evaporation. The residue obtained was dissolved in 70 mL of diethyl ether and washed once with 35 mL of cold, dilute sodium bicarbonate solution, and water, (3x50 mL). The ethereal layer was dried over $MgSO_4$, and after evaporation of the solvent furnished a white flaky solid, which was recrystallised from hexane to afford 7.38 g of crystaline ketopinic acid chloride, (darkens upon storage), 67% yield, m.p. 118-120 °C, (lit. m.p. 112 °C).[226] $[\alpha]^{20}_D$ +52.20 c= 1.18, ($CHCl_3$), ((–)-enantiomer, lit. $[\alpha]^{20}_D$ +41.00 c= 1.90, ($CHCl_3$)[226]); ν_{max} /cm^{-1} (CH_2Cl_2 film) 1746, 1700, 1267, 1048, 892, 795, 766, 737, 704; δ_H ($CDCl_3$), (400 MHz), 1.19 (3 H, s, CH_3 at C8), 1.21 (3 H, s, CH_3 at C9), [1.50-1.54 (1 H, m), 2.00-2.20 (4 H, m), *exo* and *endo* at C5,6 and bridgehead H at C4], 2.48-2.63 (2 H, m, *exo* and *endo* at C3); δ_H (100 MHz), 20.03 (CH_3, C8), 20.45 (CH_3, C9), 26.71 (CH_2, C5), 28.83 (CH_2, C6), 44.23 (CH_2, C3), 44.64 (CH, C4), 50.81 (C quat., C7), 76.36 (C quat., C1), 172.39 (C quat., Cl–C=O, C10), 208.05 (C quat., C=O, C2).

(–)-(1*S*,4*R*)-1-isocyanato-7,7-dimethylbicyclo[2.2.1]heptan-2-one:



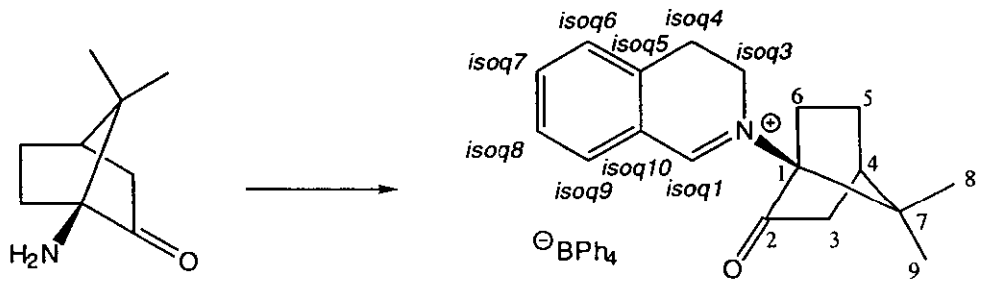
(–)-(1S,4R)-Amino-apocamphor isocyanate:[228-231] A solution of the crude acid chloride, (4.10 g, 20 mmol), was dissolved in 25 mL of THF and the solution was cooled to –25 °C. A solution of sodium azide, (3.00 g, 46 mmol), in water, 30 mL, was added in one portion and the resulting reaction mixture was stirred at that temperature for 45 minutes. It was then allowed to attain ambient temperature and stirred further for 30 minutes. The reaction mixture was then poored into ice/water, and extracted with toluene, (3x30 mL). Without drying the organic extracts, the solvents were removed under reduced pressure and a white solid was obtained. The NMR spectrum of this solid indicates the presence of two camphor derivatives, identified as the corresponding acyl azide and the expected isocyanate in 3:1 ratio, in favour of the azide. The mixture of solids is redissolved in toluene and heated at reflux for one hour. Evaporation of toluene furnished 2.85 g of pure aminoapocamphor icocyanate, 80% yield, m.p. 109 °C, (lit. m.p. 107-108 °C).[228] $[\alpha]^{20}_D$ –26.17 c=1.62, ($CHCl_3$), (lit. $[\alpha]^{20}_D$ –41.00 c=5.00, (Et_2O)[228]); ν_{max} /cm^{-1} (nujol) 2241, 1753, 1026; δ_H ($CDCl_3$), (400 MHz), 0.91 (3 H, s, CH_3 at C8), 1.07 (3 H, s, CH_3 at C9), [1.52-1.57 (1 H, m), 1.68-1.73 (1 H, m), *exo* at C5 and C6], 2.01-2.18 (4 H, m, *endo* at C5 and C6, bridgehead H at C4, and *exo* at C3), 2.45-2.51 (1 H, m, *endo* at C3); δ_C (100 MHz), 18.98 (CH_3, C8), 19.24 (CH_3, C9), 27.08 (CH_2, C5), 28.72 (CH_2, C6), 40.40 (CH, C4), 41.85 (CH_2, C3), 47.57 (C quat., C7), 76.39 (C quat., C1), 128.82 (C quat., N=C=O, C10), 211.96 (C quat., C=O, C2). *m/z* 179; exact mass calcd for $C_{10}H_{13}NO_2$ 179.09462 found 179.09480. Found C, 67.13; H, 7.36; N, 7.70; $C_{10}H_{13}NO_2$ requires: C, 67.00; H, 7.32; N, 7.82%.

(+)-(1*S*,4*R*)-1-Amino-7,7-dimethylbicyclo[2.2.1]heptan-2-one:



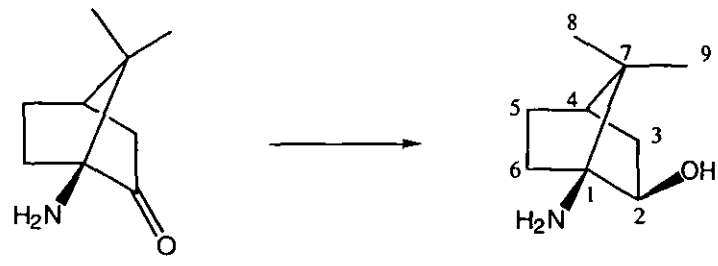
(+)-(1S,4R)-Amino-apocamphor:[229,230] To a solution of amino apocamphor isocyanate, (5.00 g, 28 mmol), in 50 mL of toluene, 20 mL of 10M hydrochloric acid are added, and the reaction mixture was refluxed for 3 hours. The reaction mixture is then allowed to cool, and the solvents are evaporated under reduced pressure. 20% aqueous Na_2CO_3 solution is added to the residue until pH 10, followed by extraction with dichloromethane, (4x20 mL). The organic extracts were dried over sodium sulphate and stripped of solvent under reduced pressure, to furnish a brown oil which solidifies slowly on standing. The crude product is recrystallised from hexane to provide aminoapocamphor, (2.02 g), in 47% yield. Amino apocamphor can also be obtained from ketopinic acid chloride without isolation of intermediates according to the reactions described above. This is accomplished by admission of concentrated hydrochloric acid in the toluene solution of the isocyanate, without significant loss in yield, m.p. 195 °C, (lit. m.p. 194 °C).[230] $[\alpha]^{20}_D$ +92.62 c= 1.31, ($CHCl_3$), (lit. $[\alpha]^{17.5}_D$ +107.50 c= 2.05, (EtOH)[230]); ν_{max} /cm^{-1} (nujol) 3471, 3388, 3318, 1745, 1605, 1451, 1416, 1387, 1054, 736; δ_H ($CDCl_3$), (400 MHz), 0.84 (3 H, s, CH_3 at C8), 1.04 (3 H, s, CH_3 at C9), 1.40 (2 H, br. s, NH_2), [1.38-1.45 (1 H, m), 1.50-1.56 (1 H, m), *endo* at C5 and C6], 1.72-1.82 (1 H, m, *exo* at C6), 1.97 (1 H, d, *J* 18.41 Hz, bridgehead H at C4), 2.00-2.12 (2 H, m, *endo* at C6 and *exo* at C3), 2.35-2.43 (1 H, m, *endo* at C3); δ_C (100 MHz), 17.39 (CH_3, C8), 17.62 (CH_3, C9), 25.62 (CH_2, C5), 28.64 (CH_2, C6), 39.60 (CH, C4), 40.99 (CH_2, C3), 45.33 (C quat., C7), 70.75 (C quat., C1), 217.01 (C quat., C=O, C2). *m/z* 153; exact mass calcd for $C_9H_{15}NO$ 153.11536 found 153.11522.

(+)-2-[(1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]-3,4-dihydroisoquinolinium tetraphenylborate:



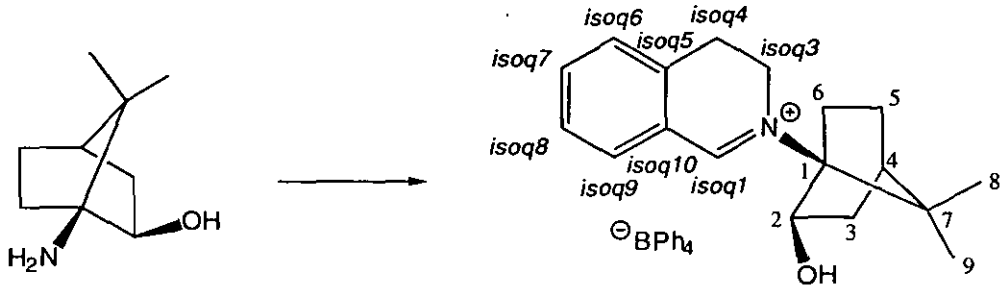
(+)-(1S,4R)-N-1-(apocamphor)-dihydroisoquinolinium tetraphenylborate: Prepared according to the general procedure in 31% yield, m.p. 205-207 °C. $[\alpha]^{20}_{D}$ +42.14 c= 1.12, (DMSO) δ_H (CD_3CN), (400 MHz), 1.25 (3 H, s, CH_3 at C8), 1.26 (3 H, s, CH_3 at C9), [1.67-1.71 (1 H, m), 1.96-2.04 (2 H, m), 2.26-1.35 (2 H, m), *endo* and *exo* at C5,6 and bridgehead H at C4], 2.64-2.89 (2 H, m, *endo* and *exo* at C3), 3.20-3.27 (2 H, m, CH_2 at *isoq-4*), 3.91-3.99 (2 H, m, CH_2 at *isoq-3*), 6.88 (4 H, t, *J* 7.10 Hz, arom., *para* in BPh_4 group), 7.03 (8 H, t, *J* 7.37 Hz, arom., *ortho* in BPh_4 group), 7.29-7.35 (8 H, m, arom., *meta* in BPh_4 group), 7.50 (1 H, d, *J* 7.47 Hz, arom., *isoq-6*), 7.58 (1 H, t, *J* 7.46 Hz, arom., *isoq-8*), 7.85 (1 H, t, *J* 7.55 Hz, arom., *isoq-7*), 7.93 (1 H, d, *J* 7.59 Hz, arom., *isoq-9*), 8.74 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), 17.93 (CH_3, C8), 20.11 (CH_3, C9), 24.57 (CH_2, C5), 24.83 (CH_2, C6), 25.47 (CH_2, *isoq-4*), 41.69 (CH_2, C3), 42.41 (CH, C4), 48.58 (CH_2, *isoq-3*), 49.62 (C quat., C7), 86.39 (C quat., C1), 121.45 (8xCH arom., CH *ortho* in BPh_4 group), 124.72 (C arom. quat., *isoq-5*), 125.29 (4xCH arom., CH *para* in BPh_4 group), 127.94 (CH arom., *isoq-6*), 128.22 (CH arom., *isoq-8*), 134.32 (CH arom., *isoq-7*), 135.41 (8xCH arom., CH *meta* in BPh_4 group), 137.43 (C arom. quat., *isoq-10*), 138.69 (CH arom., *isoq-9*), 163.50 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 168.00 (CH, HC=N, *isoq-1*), 206.85 (C quat., C=O, C2); *m/z* (cation) 260; exact mass calcd for cation $C_{18}H_{22}NO$ 268.17013 found 268.17010. Found C, 84.93; H, 7.08; N, 2.21; $C_{42}H_{42}BNO{\cdot}0.3\ H_2O$ requires: C, 85.03; H, 7.18; N, 2.36%.

(+)-(1*S*,2*R*,4*R*)-1-amino-7,7-dimethylbicyclo[2.2.1]heptan-2-ol:



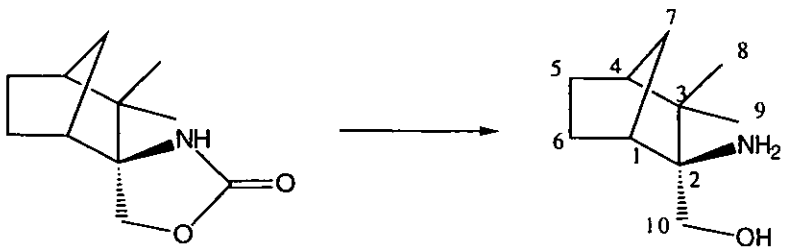
(+)-(1S,2R,4R)-1-Amino-(exo)-apocamphol:[232,233] To an ice cooled solution of amino apocamphor, (1.00 g, 6.53 mmol), in 25 mL of methanol, sodium borohydride, (0.50 g, 13.50 mmol, 2.07 equivalents), is added portionwise over 15 minutes. The solution is allowed to stirr overnight while attaining ambient temperature. The reaction was quenched by the addition of 5 mL of 2M hydrochloric acid and the volatiles were evaporated under reduced pressure. Saturated potassium carbonate solution was added to the resulted residue until pH 10, diluted with water, and the aqueous phase was extracted with dichloromethane, (3x20 mL). The organic extracts were dried over sodium sulphate and rotary evaporated to furnish a amino apocamphor, (0.93 g), in 92% yield. The NMR spectrum of the crude product shows the two diastereoisomeric amino alcohols are present in 10.8:1 ratio in favour of the *exo* alcohol. Recrystallisation of the crude product from hexane provides 0.71 g of pure *exo*-amino apocamphol, 70% yield, m.p. 218-220 °C, (lit. m.p. 220-221 °C).[232] $[\alpha]^{20}_{D}$ +18.78 c= 1.47, ($CHCl_3$), (lit. $[\alpha]^{22}_{D}$ –16.20 c= 9.00, (CH_2Cl_2)[232]); ν_{max} /cm^{-1} (nujol) 3511, 3488, 3358, 1076, 1054; δ_H ($CDCl_3$), (400 MHz), 0.84 (3 H, s, CH_3 at C8), 1.01 (3 H, s, CH_3 at C8), [1.13-1.16 (2 H, m), 1.51-1.57 (1 H, m), 1.72-1.80 (4 H, m), *endo* and *exo* at C3,5,6 and bridgehead H at C4], 2.40 (3 H, br, s, NH_2 and OH), 3.71 (1 H, t, *J* 5.92 Hz, *endo* at C3); δ_C (100 MHz), 18.80 (CH_3, C8), 19.27 (CH_3, C9), 26.21 (CH_2, C5), 32.08 (CH_2, C6), 38.53 (CH_2, C3), 42.02 (CH, C4), 45.15 (C quat., C7), 64.31 (C quat., C1), 77.03 (CH, C2). *m/z* 155; exact mass calcd for $C_9H_{17}NO$ 155.13101 found 155.13090.

(+)-2-[(1*S*,2*R*,4*R*)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-yl]-3,4-dihydroisoquinolinium tetraphenylborate:



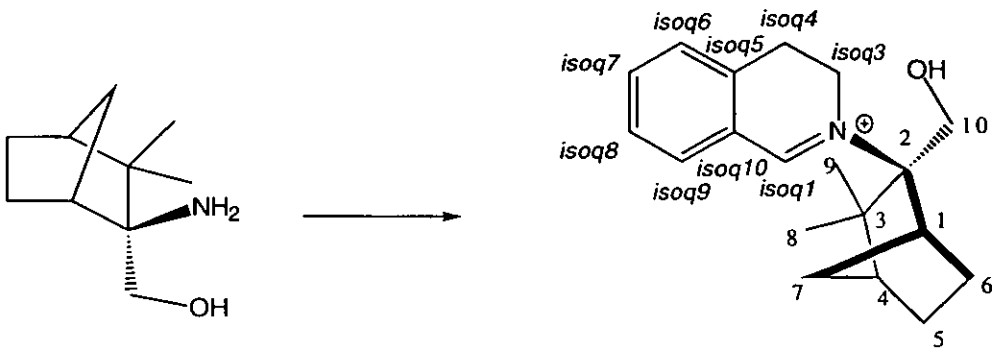
(+)-(1S,2R,4R)-N-1-[(exo)-apocamphol]-dihydroisoquinolinium tetraphenylborate: Prepared according to the general procedure in 37% yield, m.p. 184 °C. $[\alpha]^{20}_{D}$ +24.42 c= 1.13, (DMSO), ν_{max} /cm^{-1} (nujol) 3515, 1635, 1604, 1574, 732, 716, 703; δ_H (CD_3CN), (400 MHz), 1.20 (3 H, s, CH_3 at C8), 1.25-1.37 (2 H, m, *exo* at C5 and C6), 1.55 (3 H, s, CH_3 at C9), 1.80-2.25 (5 H, m, *endo* and *exo* at C3, *endo* at C5 and C6 and bridgehead H at C4), 3.19 (2 H, t, *J* 7.76 Hz, CH_2 at *isoq-4*), 3.82-4.20 (3 H, m, CH*endo* at C3 and CH_2 at *isoq-3*), 6.83 (4 H, t, *J* 7.16 Hz, arom., *para* in BPh_4 group), 6.98 (8 H, t, *J* 7.41 Hz, arom., *ortho* in BPh_4 group), 7.25-7.29 (8 H, m, arom., *meta* in BPh_4 group), 7.45 (1 H, d, *J* 7.51 Hz, arom., *isoq-6*), 7.53 (1 H, t, *J* 7.59 Hz, arom., *isoq-8*), 7.78 (1 H, t, *J* 7.56 Hz, arom., *isoq-7*), 7.91 (1 H, d, *J* 7.59 Hz, arom., *isoq-9*), 8.64 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz), 19.20 (CH_3, C8), 20.80 (CH_3, C9), 24.46 (CH_2, C5), 24.55 (CH_2, *isoq-4*), 29.78 (CH_2, C6), 39.29 (CH_2, C6), 45.84 (CH, C4), 47.34 (CH_2, *isoq-3*), 47.69 (C quat., C7), 74.68 (CH, C2), 80.47 (C quat., C1), 121.45 (8xCH arom., CH *ortho* in BPh_4 group), 124.66 (C arom. quat., *isoq-5*), 125.28 (4xCH arom., CH *para* in BPh_4 group), 127.76 (CH arom., *isoq-6*), 128.12 (CH arom., *isoq-8*), 133.85 (CH arom., *isoq-7*), 135.42 (8xCH arom., CH *meta* in BPh_4 group), 136.83 (C arom. quat., *isoq-10*), 137.93 (CH arom., *isoq-9*), 163.51 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 165.39 (CH, HC=N, *isoq-1*); *m/z* (cation) 262; exact mass calcd for cation $C_{18}H_{24}NO$ 270.18578 found 270.18580. Found C, 85.66; H, 7.43; N, 2.11 $C_{42}H_{44}BNO$ requires: C, 85.52; H, 7.52; N, 2.38%.

(–)-(1*S*,2*R*,4*R*)-2-Amino-3,3-dimethylbicyclo[2.2.1]hept-2-yl)methanol:



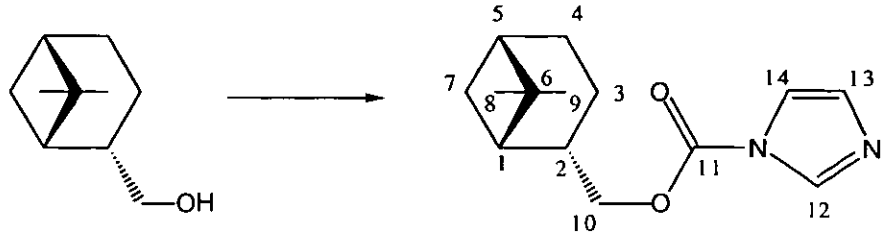
(–)-(1S,2R,4R)-2-Amino-[(endo)-camphanol]:[135] To a solution of the amino camphanol derived spiro-oxazolidinone,[135,138] (2.00 g, 10.24 mmol), in 20 mL of ethanol, 10 mL of 2M potassium hydroxide were added, and the solution was refluxed for 8 hours and then allowed to stirr overnight while attaining ambient temperature. The volatiles were removed by rotary evaporation, and the aqueous residue was acidified to pH 1 with 2M HCl. The aqueous phase was washed with hexane, (2x10 mL), and was subsequently made alkaline, pH 10, by addition of 2M KOH solution. Extraction with dichloromethane, (3x25 mL), drying over sodium sulphate , and evaporation of the organic extracts, furnished the crude amino alcohol. Recrystallisation from hexane/ethyl acetate, (9:1), provided 0.83 g of pure *exo*-2-amino-[(*endo*)-camphanol] as a white powder, 64% yield. m.p. 221 °C. $[\alpha]^{20}_{D}$ –0.96 c= 1.25, ($CHCl_3$); ν_{max} /cm^{-1} (nujol) 3419, 3362, 3298, 1577, 1096, 1049, 976, 933; δ_H ($CDCl_3$), (250 MHz), 0.91 (3 H, s, CH_3 at C9), 0.98 (3 H, s, CH_3 at C8), 1.14 (1 H, d, *J* 10.30 Hz, bridgehead H at C4), [1.29-1.61 (5 H, m), 1.74-1.97 (2 H, m), *endo* and *exo* at C5 and C6, CH_2 at C7 and bridgehead H at C1], 2.13 (1 H, br. s, OH), 2.25 (2 H, br. s, NH_2), 3.48 (2 H, dd, *J* 62.90, 10.80 Hz, *AB* system, CH_2 at C10); δ_C (62.50 MHz), 21.10 (CH_3, C9), 23.15 (CH_2, C5), 23.37 (CH_2, C6), 26.40 (CH_3, C8), 34.51 (CH_2, C7), 42.55 (C quat., C2), 48.02 (CH, C4), 50.28 (CH, C1), 62.84 (C quat., C3), 63.94 (CH_2, C10). *m/z* 169; exact mass calcd for $C_{10}H_{19}NO$ 169.14665 found 179.14668.

(+)-(1*R*,2*S*,4*S*)-2-(3,4-dihydro-isoquinolinium-2-yl)-3,3-dimethylbicyclo[2.2.1]hept-2-yl]methanol tetraphenylborate



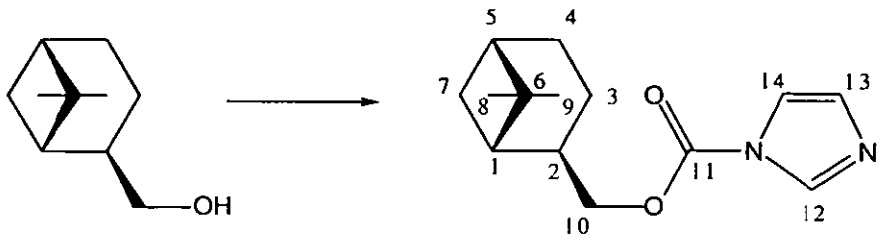
(+)-(1R,2S,4S)-N-2-[(endo)-camphanol]-dihydroisoquinolinium tetraphenylborate: Prepared according to the general procedure with distilled 2-(2-bromoethyl)-benzaldehyde in 17% yield. m.p. 161-163 °C (dec.). $[\alpha]^{20}_{D}$ +3.70 c= 1.08, (DMSO); ν_{max} /cm^{-1} (nujol) 3522, 1638, 1606, 1577, 734, 702, 612; δ_H (CD_3CN), (250 MHz), 1.10 (3 H, s, CH_3 at C9), 1.14 (3 H, s, CH_3 at C8), 1.37-1.94 (6 H, m, *endo* and *exo* at C5,6, C*H*H at C7 and bridgehead H at C4), 2.90-3.34 (4 H, m, CH_2 at *isoq-4*, CH*H* at C7 and bridgehead H at C1), 3.87-4.15 (4 H, m, CH_2 at *isoq-3* and CH_2 at, C10), 6.83 (4 H, t, *J* 7.15 Hz arom., *para* in BPh_4 group), 6.99 (8 H, t, *J* 7.31 Hz arom., *ortho* in BPh_4 group), 7.20-7.33 (8 H, m arom., *meta* in BPh_4 group), 7.45 (1 H, d, *J* 7.62 Hz, arom., *isoq-6*), 7.53 (1 H, t, *J* 7.62 Hz, arom., *isoq-8*), 7.78 (1 H, t, *J* 7.62 Hz, arom., *isoq-7*), 7.92 (1 H, d, *J* 7.92 Hz, arom., *isoq-9*), 8.96 (1 H, s, HC=N, *isoq-1*); δ_C (62.50 MHz), 19.15 (2xCH_3, C8,9), 21.68 (CH_2, C5), 24.20 (CH_2, C6), 25.01 (CH_2, *isoq-4*), 26.49 (CH, C4), 33.61 (CH_2, C7), 44.78 (CH, C1), 48.85 (CH_2, *isoq-3*), 51.93 (C quat., C3), 58.39 (C quat., C2), 63.19 (CH_2, C10), 121.53 (8xCH arom., CH *ortho* in BPh_4 group), 124.90 (C arom. quat., *isoq-5*), 125.41 (4xCH arom., CH *para* in BPh_4 group), 127.89 (CH arom., *isoq-6*), 128.15 (CH arom., *isoq-8*), 134.10 (CH arom., *isoq-7*), 135.49 (8xCH arom., CH *meta* in BPh_4 group), 137.24 (C arom. quat., *isoq-10*), 137.95 (CH arom., *isoq-9*), (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 164.95 (CH, HC=N, *isoq-1*); *m/z* (cation) 284; exact mass calcd for cation $C_{19}H_{26}NO$ 284.20143 found 284.20069. Found C, 85.67; H, 7.73; N, 2.53; $C_{43}H_{46}BNO{\cdot}0.3\ H_2O$ requires: C, 85.52; H, 7.68; N, 2.32%.

(–)-(1*S*,2*S*,5*S*)-(6,6-dimethylbicyclo[3.1.1]hept-2-yl)methyl-1*H*-imidazole-1-carboxylate:



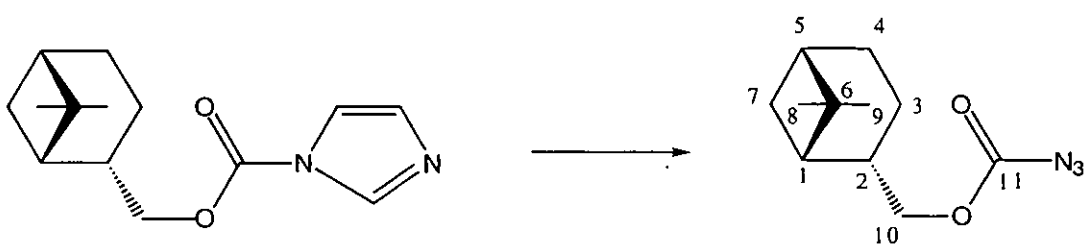
(–)-(1S,2S,5S)-(trans)-myrtanol-imidazole carbamate: To a solution of (–)-*trans*-myrtanol, (10 g, 64.80 mmol), and N-ethyldiisopropylamine, (10 g, 77.37 mmol, 1.19 equivalents), in 250 mL of dry dichloromethane, N,N'-carbonyl diimidazole, (15 g, 92.50 mmol, 1.42 equivalents), was added in the solid form in one portion. Nitrogen atmosphere was established and the reaction mixture, (initially a suspension), was stirred for 2 hours at ambient temperature. The reaction mixture was transferred in a separating funnel and was washed twice with 100 mL of saturated aqueous ammonium chloride, and finally with 100 mL of water. The organic phase was then dried over sodium sulphate and rotary evaporated to provide 16 g of a colourless oil which solidifies very slowly, (1-2 days), on standing, 99% yield. m.p. 63-65 °C. $[\alpha]^{20}_{D}$ –21.80 c=1.67, ($CHCl_3$); ν_{max} /cm^{-1} (neat) 3125, 1753, 1528, 1402, 1300, 1252, 1181, 1102, 1005, 864, 767; δ_H ($CDCl_3$), (250 MHz), 0.88 (3 H, s, CH_3 at C8), 1.24 (3 H, s, CH_3 at C9), [1.32-1.42 (2 H, m), 1.69-1.94 (5 H, m), 2.09-2.15 (1 H, m), CH_2 at C3,4,7 and 2xbridgehead H at C1,5], 2.44-2.56 (1 H, m, CH at C2), 4.22 (1 H, dd, *J* 4.27, 0.98 Hz, downfield portion of an*ABX* system, CH*H*O at C10), 4.22 (1 H, dd, *J* 13.47, 0.98 Hz, upfield portion of an*ABX* system, C*H*HO at C10), 7.06 (1 H, s, arom., CH at C13), 7.42 (1 H, s, arom., CH at C14), 8.13 (1 H, s, arom., CH at C12); δ_C (62.50 MHz), 17.80 (CH_2, C4), 20.00 (CH_3, C8), 23.30 (CH_2, C3), 23.68 (CH_2, C7), 26.44 (CH_3, C9), 34.15 (CH, C5), 39.13 (C quat., C6), 40.55 (CH, C1), 42.08 (CH, C2), 71.51 (CH_2, C10), 116.98 (CH, arom., C13), 130.42 (CH, arom., C14), 136.95 (CH, arom., C12), 148.65 (C quat., C=O, C11); *m/z* 249, 248, 136; exact mass calcd for $C_{14}H_{20}N_2O_2$ 248.15295 found 248.15270. Found C, 67.81; H, 8.21; N, 10.96; $C_{14}H_{20}N_2O_2$ requires: C, 67.70; H, 8.12; N, 11.29%.

(–)-(1*S*,2*R*,5*S*)-(6,6-dimethylbicyclo[3.1.1]hept-2-yl)methyl-1*H*-imidazole-1-carboxylate:



(–)-(1S,2R,5S)-(cis)-myrtanol-imidazole carbamate: Prepared according to the procedure employed for the *trans* analogue, 99% yield, m.p. 33-35 °C. $[\alpha]^{20}_D$ –6.17 c=1.02, ($CHCl_3$); ν_{max} /cm^{-1} (neat) 3126, 3108, 1760, 1472, 1405, 1378, 1319, 1290, 1240, 1183, 1094, 1060, 1005, 762, 651; δ_H ($CDCl_3$), (250 MHz), 0.98 (1 H, d, *J* 9.76 Hz, bridgehead H at C1), 1.04 (3 H, s, CH_3 at C8), 1.21 (3 H, s, CH_3 at C9), [1.51-1.60 (1 H, m), 1.89-2.03 (5 H, m), 2.39-2.43 (1 H, m), CH_2 at C3,4,7 and bridgehead H at C5] 2.53-2.57 (1 H, m, CH at C2), 4.35 (1 H, dd, *J* 10.40, 7.72 Hz, downfield portion of an*ABX* system, CH*H*O at C10), 4.35 (1 H, dd, *J* 23.67, 10.42 Hz, upfield portion of an*ABX* system, C*H*HO at C10), 7.06 (1 H, s, arom., CH at C13), 7.42 (1 H, s, arom., CH at C14), 8.12 (1 H, s, arom., CH at C12); δ_C ($CDCl_3$), (62.50 MHz), 18.11 (CH_2, C4), 23.02 (CH_3, C8), 25.50 (CH_2, C3), 27.60 (CH_3, C9), 32.62 (CH_2, C7), 38.37 (C quat.), 39.89 (CH, C5), 40.96 (CH, C2), 42.57 (CH, C1), 72.14 (CH_2, C10), 116.91 (CH, arom., C13), 130.41 (CH, arom., C14), 136.89 (CH, arom., C12), 148.55 (C quat., C=O, C11); *m/z* 249, 248, 136; exact mass calcd for $C_{14}H_{20}N_2O_2$ 248.15295 found 248.15270. Found C, 67.56; H, 7.94; N, 11.47; $C_{14}H_{20}N_2O_2$ requires: C, 67.72; H, 8.12; N, 11.47%.

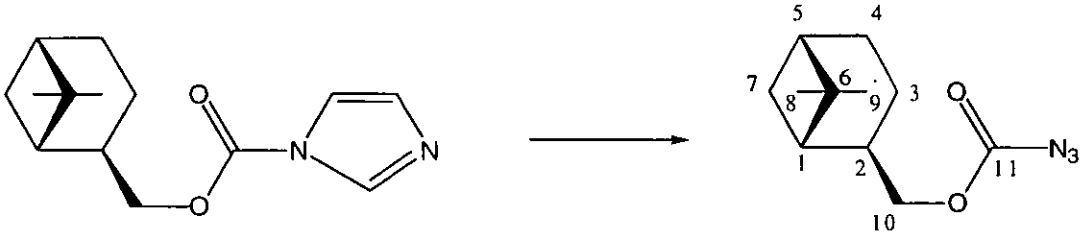
(–)-[({[(1*S*,2*S*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]methyl}oxy)carbonyl]azide:



(–)-(1S,2S,5S)-(trans)-myrtanol azidoformate: It is imperative that this reaction is carried out in a well ventilated fumehood. To a solution of (*trans*) myrtanol imidazole carbamate, (10 g, 40.32 mmol) in 150 mL of dichloromethane, a solution of sodium azide, (9.75 g, 150 mmol, 3.72 equivalents), in 100 mL of water is added, followed by

50 mL of acetic acid. Immediately after the addition of the acid, a nitrogen bubbler was fitted on the flask, in order to restrict the liberation of toxic gaseous products, (hydrazoic acid). The reaction mixture was allowed to stirr overnight at ambient temperature. The solution was then transferred in aseparatory funnel and the organic layer was separated, washed twice with 150 mL of water, once with dilute sodium bicarbonate solution and dried over sodium sulphate. The combined aqueous extracts including the original one, were neutralised with sodium hydroxide solution and discarded. The organic phase was stripped of the solvent and furnished 8.36 g of the desired azidoformate as a colourless oil, 99% yield. $[\alpha]^{20}_D$ –24.60 c= 3.87, ($CHCl_3$); ν_{max} /cm^{-1} (nujol) 2155, 1690, 1474, 1421, 1268, 1234, 1218, 1141, 908, 731; δ_H ($CDCl_3$), (250 MHz), 0.58 (3 H, s, CH_3 at C8), 0.97 (3 H, s, CH_3 at C9), [0.99-1.08 (2 H, m), 1.36-1.52 (1 H, m), 1.55-1.64 (4 H, m), 1.78-1.84 (1 H, m), CH_2 at C3,4,7 and 2xbridgehead H at C1,5], 2.10 (1 H, quintet, *J* 7.88 Hz, CH at C2), 3.75 (1 H, dd, *J* 7.81, 1.57 Hz, downfield portion of an*ABX* system, CH*H*O at C10), 3.75 (1 H, dd, *J* 15.01, 1.57 Hz, upfield portion of an*ABX* system, C*H*HO at C10); δ_C (62.50 MHz), 17.72 (CH_2, C4), 19.99 (CH_3, C8), 23.21 (CH_2, C3), 23.74 (CH_2, C7), 26.43 (CH_3, C8), 34.07 (CH, C5), 39.06 (C quat.), 40.61 (CH, C1), 41.95 (CH, C2), 71.82 (CH_2, C10), 157.78 (C quat., C=O, C11); *m/z* 196, 195, 152, 136; exact mass calcd for cation $-N_2$ $C_{11}H_{17}N_3O_2$ $-N_2$ 195.12592 found 195.12540.

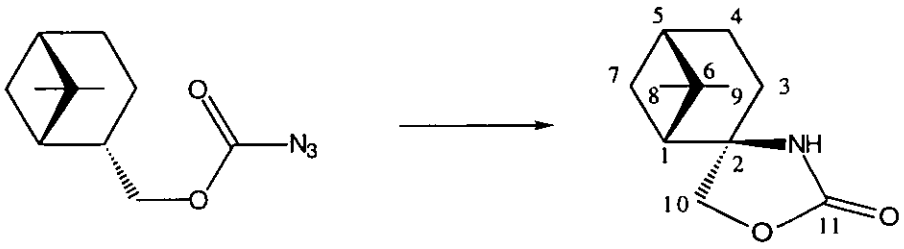
(–)-[({[(1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]methyl}oxy)carbonyl]azide:



(–)-(1S,2R,5S)-(cis)-myrtanol azidoformate: Prepared according to the procedure employed for the *trans* analogue; colourless oil, 99% yield. $[\alpha]^{20}_D$ –6.05 c=1.19, ($CHCl_3$); ν_{max} /cm^{-1} (neat) 2988, 2944, 2909, 2883, 2136, 1757, 1731, 1470, 1229, 745; δ_H ($CDCl_3$), (250 MHz), 0.94 (1 H, d, *J* 9.78 Hz, bridgehead H at C1), 1.00 (3 H, s, CH_3 at C8), [1.20 (3 H, s, CH_3 at C9), [1.43-1.51 (1 H, m), 1.86-1.99 (5 H, m), 2.35-2.44 (2 H, m), CH_2 at C3,4,7, bridgehead H at C5 and CH at C2], 4.15 (1 H, dd, *J* 21.06, 10.45, Hz, downfield portion of an*ABX* system, CH*H*O at C10), 4.15 (1 H, dd, *J* 10.43, 5.30, Hz, upfield portion of an*ABX* system, C*H*HO at C10); δ_C (62.50 MHz), 18.12 (CH_2, C4), 22.99 (CH_3, C8), 25.57 (CH_2, C3), 27.61 (CH_3, C9), 32.65 (CH_2, C7), 38.36 (C

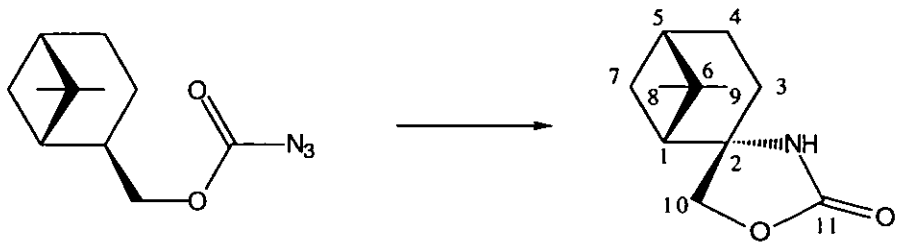
quat., C6), 39.90 (CH, C5), 41.04 (CH, C1), 42.57 (CH, C2), 72.61 (CH_2, C10), 157.25 (C quat., C=O, C11); *m/z* 223, 196, 195, 135, 121; exact mass calcd for $C_{11}H_{17}N_3O_2$ 223.13207 found 223.13170.

(–)-(1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]-10-oxa-2-azaspiro[2.10]undecan-11-one:



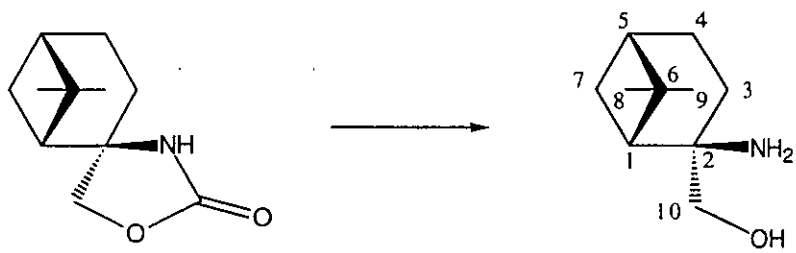
(–)-(1S,2R,5S)-2-Amino-(trans)-myrtanol-spiro-oxazolidinone: In a 1L flask equiped with reflux condenser and nitrogen bubbler, a solution of the azidoformate, (3.33 g. 15.00 mmol), in 350 mL of 1,1,2,2-tetrachloroethane, was heated to 140 °C. At this temperature gas evolution is manifested and the reaction mixture was kept at the same temperature for one and a half hours. It was then allowed to attain ambient temperature and the organic solvent is removed by distillation under reduced pressure, *ca* 40 °C at 5 mbar. It is advisable not to exceed 45 °C during the evaporation of the solvent as it may lead to decreased yield. The dark brown/orange oily residue obtained, is columned on silica gel with light petroleum/ethyl acetate, (65:35) as the eluent. The spiro-oxazolidinone, which can be recrystallised from light petroleum/ethyl acetate, (9:1), is obtained as a white crystalline solid (1.00 g, 34% yield), m.p. 135-137 °C. $[\alpha]^{20}_D$ –46.21 c= 1.61, ($CHCl_3$); ν_{max} /cm^{-1} (nujol) 3275, 1745, 1297, 1249, 1026; δ_H ($CDCl_3$), (250 MHz), 1.00 (1 H, d, *J* 10.59 Hz, bridgehead H at C1), 1.04 (3 H, s, CH_3 at C8), 1.24 (3 H, s, CH_3 at C9), 1.77-2.16 (6 H, m), 2.25-2.30 (1 H, m), CH_2 at C3,4,7 and bridgehead H at C5], 4.13 (2 H, *J* 29.38, 8.36 Hz, *AB* system, CH_2 at C10), 6.15 (1 H, br. s, NH); δ_C (62.50 MHz), 22.60 (CH_3, C8), 23.81 (CH_2, C4), 26.45 (CH_2, C7), 26.50 (CH_3, C9), 29.61 (CH_2, C3), 37.87 (C quat., C6), 39.46 (CH, C5), 50.98 (CH, C1), 62.04 (C quat., C2), 78.92 (CH_2, C10), 158.92 (C quat., C=O, C11); *m/z* 196, 195, 167, 152, 140; exact mass calcd for $C_{11}H_{17}NO_2$ 195.12592 found 195.12624. Found C, 67.65; H, 8.90; N, 7.09; $C_{11}H_{17}NO_2$ requires: C, 67.66; H, 8.78; N, 7.17%.

(+)-(1*S*,2*S*,5*S*)-6,6-dimethylbicyclo[3.1.1]-10-oxa-2-azaspiro[2.10]undecan-11-one:



(+)-(1S,2S,5S)-2-Amino-(cis)-myrtanol-spiro-oxazolidinone: Prepared according to the procedure employed for the *trans* analogue in 50% yield, m.p. 150 °C. $[\alpha]^{20}_D$ +11.05 c=1.05, ($CHCl_3$); ν_{max} /cm^{-1} (nujol) 3204, 3112, 1758, 1053; δ_H ($CDCl_3$), (250 MHz), 0.86 (3 H, s, CH_3 at C8), 1.23 (1 H, d, *J* 10.62 Hz, bridgehead H at C1), 1.24 (3 H, s, CH_3 at C9), [1.83-2.15 (6 H, m), 2.28-2.33 (1 H, m), CH_2 at C3,4,7 and bridgehead H at C5], 4.22 (2 H, *J* 9.83, 8.71 Hz, *AB* system, CH_2 at C10), 6.50 (1 H, br. s, NH); δ_C (62.50 MHz), 22.71 (CH_3, C8), 23.58 (CH_2, C4), 26.39 (CH_2, C7), 26.58 (CH_3, C9), 30.82 (CH_2, C3), 38.22 (C quat., C6), 39.61 (CH, C5), 51.86 (CH, C1), 62.50 (C quat., C2), 78.32 (CH_2, C10), 159.00 (C quat., C=O, C11); *m/z* 196, 195, 167, 152, 140; exact mass calcd for CATION $C_{11}H_{17}NO_2$ 195.12592 found 195.12620. Found C, 67.66; H, 8.56; N, 7.14; $C_{11}H_{17}NO_2$ requires: C, 67.66; H, 8.78; N, 7.17%.

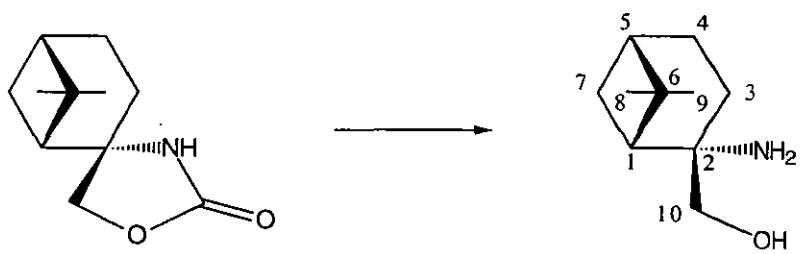
(–)-(1*S*,2*S*,5*S*)-2-Amino-(6,6-dimethylbicyclo[3.1.1]hept-2-yl)methanol:



(–)-(1S,2R,5S)-2-Amino-[(trans)-myrtanol]: To a solution of the spiro-oxazolidinone, (2.00 g, 10.24 mmol), in 20 mL of ethanol, 10 mL of 2M potassium hydroxide were added, and the solution was refluxed for 8 hours and then allowed to stirr overnight while attaining ambient temperature. The volatiles were removed by rotary evaporation, and the aqueous residue was acidified to pH 1 with 2M HCl. The aqueous phase was washed with hexane, (2x10 mL), and was subsequently made alkaline, pH 10, by addition of 2M KOH solution. Extraction with dichloromethane, (3x25 mL), drying over sodium sulphate , and evaporation of the organic extracts,

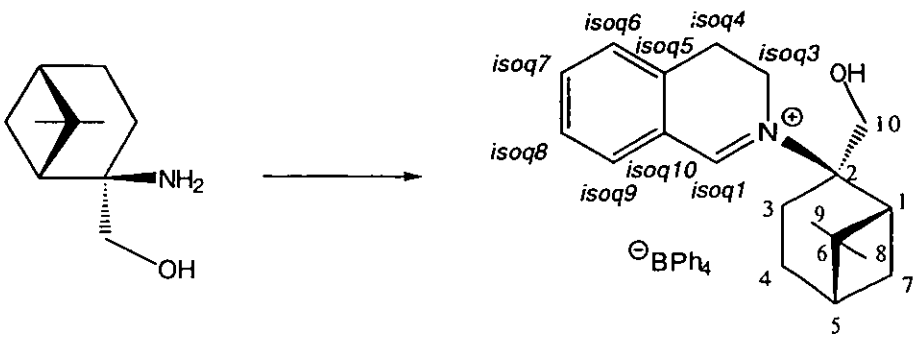
furnished the crude aminoalcohol. Recrystallisation from hexane/ethyl acetate, (9:1), provided pure 2-amino-[(*trans*)-myrtanol] as a white crystalline solid (0.83 g, 48% yield), m.p. 122-124 °C. $[\alpha]^{20}_D$ –5.11 c= 1.41, ($CHCl_3$); ν_{max} /cm^{-1} (nujol) 3389, 3157, 1060; δ_H ($CDCl_3$), (250 MHz), 1.06 (1 H, d, *J* 10.46 Hz, bridgehead H at C1), 1.09 (3 H, s, CH_3 at C8), 1.22 (3 H, s, CH_3 at C9), [1.40-1.53 (1 H, m), 1.64-1.75 (2 H, m), 1.87-1.91 (2 H, m), 2.12-2.22 (2 H, m), CH_2 at C3,4,7 and bridgehead H at C5], 2.35 (3 H, br. s, NH_2, OH) 3.26 (2 H, *J* 35.16, 10.42 Hz, *AB* system, CH_2 at C10); δ_C (62.50 MHz), 23.71 (CH_3, C8), 24.51 (CH_2, C4), 27.64 (CH_3, C9), 27.84 (CH_2, C7), 28.42 (CH_2, C3), 38.27 (C quat., C6), 40.63 (CH, C5), 49.35 (CH, C1), 57.45 (C quat., C2), 69.67 (CH_2, C10); *m/z* 170, 153, 138; exact mass calcd for $C_{10}H_{19}NO$ 169.14666 found 169.14630. Found C, 70.86; H, 11.53; N, 8.31; $C_{11}H_{19}NO$ requires: C, 70.86; H, 11.32; N, 8.28%.

(–)-(1*S*,2*R*,5*S*)-2-Amino-6,6-dimethylbicyclo[3.1.1]hept-2-yl)methanol:



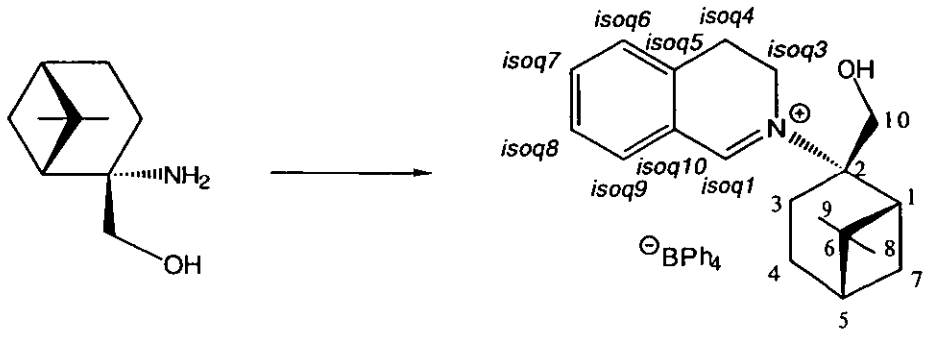
(–)-(1S,2S,5S)-2-Amino-[(cis)-myrtanol]: Prepared according to the procedure employed for the *trans* analogue in 52% yield, m.p. 50-51 °C. $[\alpha]^{20}_D$ –18.87 c= 1.06, ($CHCl_3$); ν_{max} /cm^{-1} (nujol) 3389, 3157, 1060; δ_H ($CDCl_3$), (250 MHz), 0.97 (3 H, s, CH_3 at C8), 1.24 (3 H, s, CH_3 at C9), 1.27 (1 H, d, *J* 10.23 Hz, bridgehead H at C1), [1.82-1.94 (6 H, m), 2.20-2.29 (1 H, m), CH_2 at C3,4,7 and bridgehead H at C5], 4.40 (2 H, dd, *J* 33.65, 10.42 Hz, *AB* system, CH_2 at C10); δ_C (62.50 MHz), 23.73 (CH_3, C8), 24.98 (CH_2, C4), 27.69 (CH_3, C9), 27.87 (CH_2, C7), 27.92 (CH_2, C3), 41.21 (CH, C5), 44.00 (C quat., C6), 50.71 (CH, C1), 57.44 (C quat., C2), 70.01 (CH_2, C10); *m/z* 170, 153, 138; exact mass calcd for $C_{10}H_{19}NO$ 169.14666 found 169.14620. Found C, 70.69; H, 11.38; N, 8.23; $C_{11}H_{19}NO$ requires: C, 70.86; H, 11.32; N, 8.28%.

(+)-(1*R*,2*R*,5*S*)-2-(3,4-dihydro-isoquinolinium-2-yl)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]methanol tetraphenylborate



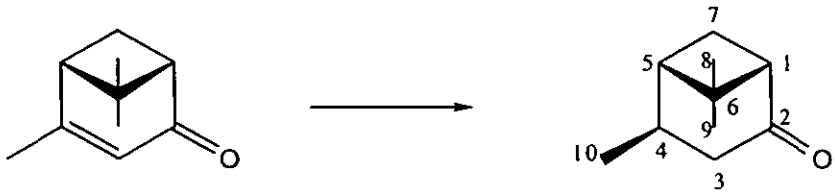
(+)-(1R,2R,5S)-N-2-[(trans)-myrtanol]-dihydroisoquinolinium tetraphenylborate:
Prepared according to the general procedure in 22% yield, white solid, m.p. 125-127 °C (dec.). $[\alpha]^{20}_D$ +8.83 c=1.63, (DMSO); ν_{max} /cm^{-1} (nujol) 3529, 1644, 1600, 1573; δ_H (CD_3CN), (250 MHz), 0.80 (3 H, s, CH_3 at C8), 1.37 (1 H, d, *J* 11.27 Hz, bridgehead H at C1), 1.42 (3 H, s, CH_3 at C9), [1.70-2.07 (4 H, m), 2.22-2.38 (1 H, m), 2.44-2.61 (1 H, m), 2.86-2.94 (1 H, m), CH_2 at C3,4,7 and bridgehead H at C5], 3.16 (2 H, t, *J* 7.32 Hz, CH_2 at *isoq-4*), 3.47-3.75 (3 H, m, CH_2 at *isoq-3* and OH), 3.93-4.04 (2 H, m, CH_2 at C10), 6.83 (4 H, t, *J* 7.02 Hz, arom., *para* in BPh_4 group), 6.98 (8 H, t, *J* 7.31 Hz, arom., *ortho* in BPh_4 group), 7.21-7.34 (8 H, m, arom., *meta* in BPh_4 group), 7.45 (1 H, d, *J* 7.32 Hz, arom., *isoq-6*), 7.53 (1 H, t, *J* 7.47 Hz, arom., *isoq-8*), 7.79 (1 H, t, *J* 7.62 Hz, arom., *isoq-7*), 7.91 (1 H, d, *J* 7.62 Hz, arom., *isoq-9*), 8.59 (1 H, s, HC=N, *isoq-1*); δ_C (62.50 MHz), 20.43 (CH_2, C4), 21.49 (CH_3, C8), 23.17 (CH_2, C7), 25.01 (CH_2, *isoq-4*), 25.44 (CH_3, C9), 26.48 (CH_2, C3), 39.80 (CH, C5), 41.61 (C quat., C6), 42.66 (CH, C1), 45.42 (CH_2, *isoq-3*), 57.51 (C quat., C2), 63.94 (CH_2, C10), 121.48 (8xCH arom., CH *ortho* in BPh_4 group), 123.81 (C arom. quat., *isoq-5*), 125.28 (4xCH arom., CH *para* in BPh_4 group), 127.90 (CH arom., *isoq-6*), 128.25 (CH arom., *isoq-8*), 133.71 (CH arom., *isoq-7*), 135.42 (8xCH arom., CH *meta* in BPh_4 group), 138.02 (C arom. quat., *isoq-10*), 139.25 (CH arom., *isoq-9*), 163.50 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 164.77 (CH, HC=N, *isoq-1*); *m/z* (cation) 284; exact mass calcd for cation $C_{19}H_{26}NO$ 284.20143 found 284.20060. Found C, 83.68; H, 7.59; N, 2.17; $C_{43}H_{46}NO{\cdot}0.6$ H_2O requires: C, 83.87; H, 7.67; N, 2.27%.

(–)-(1*R*,2*S*,5*S*)-2-(3,4-dihydro-isoquinolinium-2-yl)-6,6-dimethylbicyclo[3.1.1]hept-2-yl]methanol tetraphenylborate



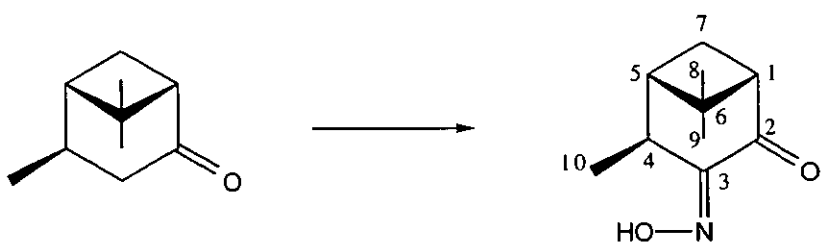
(–)-(1R,2S,5S)-N-2-[(cis)-myrtanol)]-dihydroisoquinolinium tetraphenylborate:
Prepared according to the general procedure, 33% yield, m.p. 136-138 °C (dec.). $[\alpha]^{20}_D$ –10.69 c=1.01, (CH_3CN); ν_{max} /cm^{-1} (nujol) 3509, 1641, 1605, 1573, 742, 709; δ_H (CD_3CN), (250 MHz), 0.83-0.88 (1 H, m), 1.03 (1 H, d, *J* 10.68 Hz, bridgehead H at C1), 1.09 (3 H, s, CH_3 at C8), 1.38 (3 H, s, CH_3 at C9), 1.85-2.05 (4 H, m), [2.50-2.56 (1 H, m), 2.61-2.76 (1 H, m), CH_2 at C3], 3.10-3.18 (2 H, m, CH_2 at *isoq*-4), 3.56-3.76 (2 H, m, CH_2 at *isoq*-3), 3.77-3.95 (3 H, m, CH_2 at C10 and OH), 6.83 (4 H, t, *J* 7.16 Hz, arom., *para* in BPh_4 group), 6.98 (8 H, t, *J* 7.32 Hz, arom., *ortho* in BPh_4 group), 7.19-7.31 (8 H, m, arom., *meta* in BPh_4 group), 7.44 (1 H, d, *J* 7.62 Hz, arom., *isoq-6*), 7.52 (1 H, t, *J* 7.62 Hz, arom., *isoq-8*), 7.77 (1 H, t, *J* 7.62 Hz, arom., *isoq-7*), 7.91 (1 H, d, *J* 7.62 Hz, arom., *isoq-9*), 8.46 (1 H, s, HC=N, *isoq-1*); δ_C (62.50 MHz), 21.57 (CH_2, C4), 22.25 (CH_3, C8), 24.21 (CH_2, C7), 25.07 (CH_2, *isoq*-4), 26.81 (CH_3, C9), 27.06 (CH_2, C3), 39.54 (CH, C5), 40.00 (C quat., C6), 43.48 (CH, C1), 45.33 (CH_2, *isoq-3*), 54.00 (C quat., C2), 64.10 (CH_2, C10), 121.50 (8xCH arom., CH *ortho* in BPh_4 group), 123.30 (C arom. quat., *isoq-5*), 125.32 (4xCH arom., CH *para* in BPh_4 group), 127.77 (CH arom., *isoq-6*), 128.17 (CH arom., *isoq-8*), 134.80 (CH arom., *isoq-7*), 135.48 (8xCH arom., CH *meta* in BPh_4 group), 137.13 (C arom. quat., *isoq-10*), 137.78 (CH arom., *isoq-9*), 163.50 (4xC arom. quat., q, *J* 196.40 Hz, C–B *ipso* in BPh_4 group), 165.57 (CH, HC=N, *isoq-1*); *m/z* (cation) 284; exact mass calcd for cation $C_{19}H_{26}BNO$ 284.20143 found 284.20060.

(–)-(1*S*,4*R*,5*S*)-4,6,6-trimethylbicyclo[3.1.1]heptan-2-one:



(–)-(1S,4R,5S)-Verbanone:[151,154] To a solution of commercially available verbenone, (1.22 g, 8.12 mmol, ~50% ee), in ethanol 150 mg of 10 % palladium on activated carbon was added and the suspension was placed in a Parr hydrogenator. Hydrogen atmosphere was established, and the reaction mixture was hydrogenated (60 lb/sq. in.), with mechanical shaking until consumption of hydrogen was complete as monitored by the manometer on the apparatus. The suspension was filtered through celite and washed with dry dichloromethane. Evaporation of the organic solvents afforded 1.04 g of pure verbanone as a colourless oil, 84% yield. $[\alpha]^{20}_{D}$ –26.40 c= 1.00, ($CHCl_3$), (verbanone of 90% ee lit. $[\alpha]^{20}_{D}$ –56.50 c= 1.00, ($CHCl_3$)[151]); ν_{max} /cm^{-1} (neat) 1711, 1471, 1305, 1250, 1200, 736; δ_H ($CDCl_3$) (250 MHz), 1.01 (3 H, s, CH_3 at C8), 1.17 (3 H, d, *J* 7.37 Hz, CH_3 at C10), 1.34 (3 H, s, CH_3 at C9), 1.40 (1 H, d, *J* 9.91 Hz, bridgehead H at C5), 2.11-2.20 (2 H, m, CH_2, C7), 2.23-2.44 (1 H, m, CH at C4), 2.53-2.62 (2 H, m, CH_2 at C3), 2.84-2.92 (1 H, m, bridgehead H at C1); δ_C (62.50 MHz), 20.97 (CH_3, C8), 24.51 (CH_3, C9), 26.89 (CH_3, C10), 28.34 (CH_2, C7), 30.96 (CH, C5), 40.16 (C quat., C6), 41.29 (CH_2, C3), 47.23 (CH, C4), 57.86 (CH, C1), 214.54 (C quat., C=O, C2). *m/z* 152; exact mass calcd for $C_{10}H_{16}O$ 152.12011 found 152.12000.

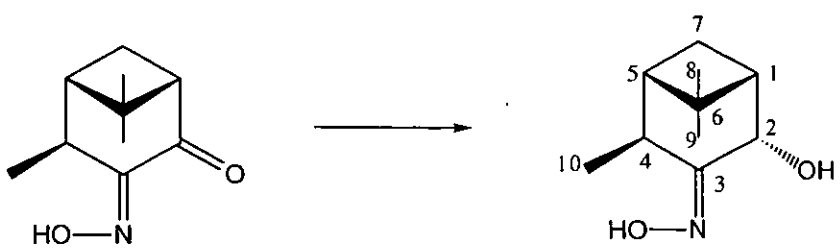
(+)-(1*S*,4*R*,5*S*)-3-hydroxyimino-4,6,6-trimethylbicyclo[3.1.1]heptan-2-one:



(+)-(1S,4R,5S)-3-hydroxyimino-verbanone:[161,234] To an ice-cold solution of verbanone, (5.00 g, 32.84 mmol), in 150 mL of dry ethanol, tert-butyl nitrite, (technical grade 90%, 4.20 g, 36.65 mmol, 1.11 equivalents), is added dropwise via a syringe over 5 minutes. 37 mL of 1M solution of hydrogen chloride in diethyl ether, (37 mmol, 1.12

equivalents), was then added slowly with the aid of a syringe pump over one hour. The solution quickly turns pale blue indicative of the presence of nitroso species. After the addition is complete, the reaction mixture is left to stirr overnight while attaining ambient temperature. The solvents are rotary evaporated and dilute sodium hydroxide solution is added to the residue until pH 10. The aqueous phase is extracted twice with light petroleum and the organic extracts are discarded. The aqueous solution is then made acidic, (pH 3), by the addition of 2M hydrochloric acid, and extracted with dichloromethane. The organic extracts were dried over sodium sulphate and stripped of solvent in the rotary evaporator to afford the diketone-monoxime as the sole product, (NMR), as a brown oil, 97%. The crude product is sufficiently pure to be reacted further but analytically pure samples may be obtained by addition diethyl ether. A small amount, (*ca* 30% of theoretical yield), of a white solid precipitated from this solution, after it was left to stand for several days at ambient temperature. The characterisation that follows was conducted on the crystalline product which should also be of ~50% ee, m.p. 163-165 °C (dec.), (lit. m.p. 171-172 °C).[234] $[\alpha]^{20}_D$ +13.44 c= 1.25, ($CHCl_3$); ν_{max} /cm^{-1} (nujol) 3207, 1722, 1693, 1622, 1389, 990, 946, 933, 842, 826; δ_H ($CDCl_3$), (250 MHz), 1.05 (3 H, s, CH_3 at C8), 1.40 (3 H, s, CH_3 at C9), 1.45 (3 H, d, *J* 11.57 Hz, CH_3 at C10), 1.47 (1 H, d, *J* 10.44 Hz, bridgehead H at C5), [2.17-2.23 (1 H, m), 2.63-2.74 (2 H, m), CH_2 at C7 and CH at C4], 3.17-3.27 (1 H, m, bridgehead H at C1); δ_C (62.50 MHz), 15.90 (CH_3, C8), 23.88 (CH_3, C9), 27.24 (CH_3, C10), 28.20 (CH_2, C7), 36.29 (CH, C5), 42.17 (C quat., C6), 45.60 (CH, C4), 56.23 (CH, C1), 155.49 (C quat., C=N, C3), 199.22 (C quat., C=O, C2). *m/z* 181; exact mass calcd for $C_{10}H_{15}NO_2$ 181.11028 found 181.11010

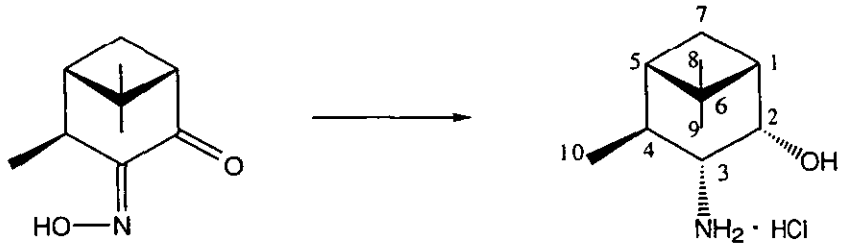
(+)-(1*S*,2*S*,4*S*,5*S*)-2-hydroxy-4,6,6-trimethylbicyclo[3.1.1]heptan-2-one oxime:



(+)-(1S,2S,4S,5S)-3-hydroxyimino-verbanol: To an ice cold solution of 3-hydroximino-verbanone, (1.18 g, 7 mmol), in 25 mL of methanol, sodium borohydride, (0.50 g, 13.50 mmol, 1.93 equivalents), is added portionwise over 15 minutes. The solution is allowed to stirr overnight while attaining ambient temperature. The reaction was quenched by the addition of 5 mL of 2M hydrochloric acid and the volatiles were

evaporated under reduced pressure. Saturated potassium carbonate solution was added to the resulted residue until pH 10, diluted with water, and the aqueous phase was extracted with dichloromethane, (3x20 mL). The organic extracts were dried over sodium sulphate and rotary evaporated to furnish exclusively the *endo*-hydroxy-oxime, (0.92 g), in 72% yield, m.p. 140-142 °C. $[\alpha]^{20}_{D}$ +11.60 c= 1.31, ($CHCl_3$); ν_{max} /cm^{-1} (nujol) 3242, 3245, 1640, 1093, 1056, 1022, 976, 934, 892; δ_H ($CDCl_3$), (250 MHz), 0.77 (1 H, d, *J* 10.80 Hz, bridgehead H at C5), 1.16 (3 H, s, CH_3 at C8), 1.29 (3 H, s, CH_3 at C9), 1.45 (3 H, d, *J* 7.14 Hz, CH_3 at C10), [1.86-1.92 (1 H, m), 2.19-2.26 (1 H, m), 2.33-2.40 (1 H, m), CH_2 at C7 and bridgehead H at C1], 2.97-3.06 (1 H, m, CH at C4), 4.88 (1 H, d, *J* 3.03 Hz, CH at C2), 6.27 (2 H, br. s, C–OH, N–OH); δ_C (62.50 MHz), 17.54 (CH_3, C8), 24.13 (CH_3, C9), 27.87 (CH_3, C10), 29.28 (CH_2, C7, 38.28 (C quat., C6), 38.77 (CH, C5), 44.79 (CH, C1), 46.37 (CH, C4), 73.10 (CH, C2), 164.11 (C quat., C=N, C3). *m/z* 183; exact mass calcd for $C_{10}H_{17}NO_2$ 183.12592 found 183.12596. Found C, 65.78; H, 9.51; N, 7.32; $C_{10}H_{17}NO_2$ requires: C, 65.53; H, 9.36; N, 7.65%.

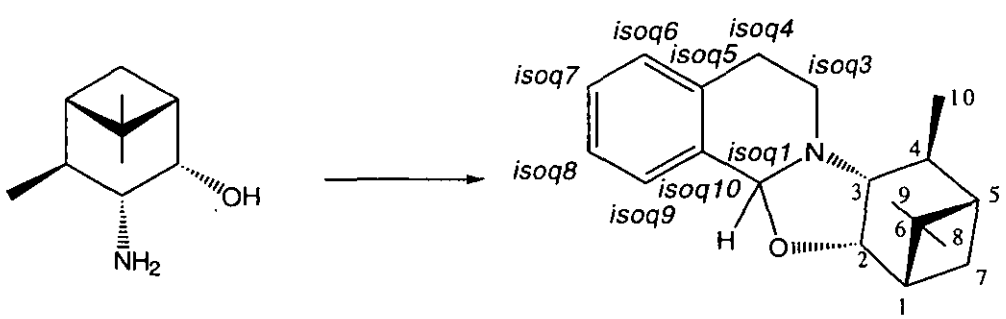
(+)-(1*S*,2*S*,3*R*,4*S*,5*S*)-3-amino-4,6,6-trimethylbicyclo[3.1.1]heptan-2-ol:



(+)-(1S,2S,3R,4S,5S)-Cis-3-amino-verbanol hydrochloride:[161] 3-Hydroxyimino-verbanone, (2.17 g, 12 mmol), was placed in a two neck flask equiped with a condenser, nitrogen bubbler and rubber septum. The flask was cooled to 0 °C by means of an ice bath and 36 mL of a 1M solution of lithium aluminium hydride in diethyl ether (36 mmol, 3 equivalents), was added dropwise via a syringe. When the addition was complete, the ice bath was removed and replaced by an oil bath. The reaction mixture was gently refluxed overnight. The reaction mixture was cooled to 0 °C, and ethyl acetate was added dropwise in order to destroy the excess of the reducing agent, followed by 20 mL of 1M solution of cold sodium hydroxide. The resulted slurry was stirred for 30 minutes, extracted thoroughly with diethyl ether (4x50 mL), and the organic extracts were dried over sodium sulphate. Evaporation of the solvent and recrystallisation of the residue from hexane furnished the crude *cis-endo*-3-amino-verban-2-ol as an oil, (1.24 g 61% yield). Although the crude

product is sufficiently pure to be reacted further, in order to obtain analytically pure samples, it was converted to the hydrochloride salt by addition of 10 mL of 1M solution of anhydrous hydrogen chloride in diethyl ether. The resulting solution was diluted with light petroleum and left to stand overnight. The hydrochloride salt of amino verbanol was obtained as a white solid, (25 % yield), where the subsequent characterisation refers to, m.p. 276-277 °C (dec.), (free amine lit. m.p. 111 °C).[161] $[\alpha]^{20}_{D}$ –21.65 c= 1.94, (DMSO); ν_{max} /cm^{-1} (nujol) 3289, 3115, 3111, 1616, 1505, 1055 δ_H (DMSO-d_6), (250 MHz), 1.08 (3 H, d, *J* 9.75 Hz, CH_3 at C10), 1.10 (3 H, s, CH_3 at C8), 1.13 (3 H, s, CH_3 at C9), 1.15 (1 H, d, *J* 10.78 Hz, bridgehead H at C5), [1.83-1.87 (1 H, m), 2.04-2.16 (2 H, m), 2.50-2.65 (1 H, m), CH_2 at C7, CH at C4 and bridgehead H at C1], 3.82-3.93 (1 H, m, CH at C3), 4.39 (1 H, dd, *J* 8.46, 4.51 Hz, CH at C2), 5.42 (1 H, br. s, OH), 8.00, (3 H, br. s, NH_3^+); δ_C (62.50 MHz), 19.73 (CH_3, C8), 30.80 (CH_3, C9), 31.27 (CH_2, C7), 33.87 (CH_3, C10), 40.28 (CH, C5), 42.63 (C quat., C6), 50.90 (CH, C1), 51.21 (CH, C4), 52.63 (CH, C3), 74.54 (CH, C2). *m/z* (free amine) 169; exact mass calcd for the free amine $C_{10}H_{19}NO$ 169.14670 found 169.14684. Found C, 58.48; H, 9.84; N, 6.73; $C_{10}H_{20}ClNO$ requires: C, 58.50; H, 9.83; N, 6.83%.

(+)-(1S,2S,14R,15S,16S)-15,17,17-trimethyl-3-oxa-13-azapentacyclo[14.1.1.0^{2,14}.0^{4,13}.0^{5,10}]octadeca-5(10),6,8-triene:

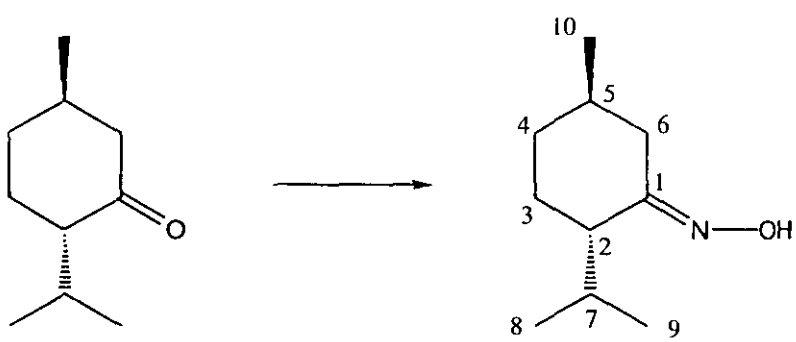


(1S,2S,3R,4S,5S)-3-Amino-verbanol derived bicyclo-oxazolidine:

A solution of 3-amino-verban-2-ol, (0.5 g, 2.95 mmol), in 10 mL of ethanol, was added dropwise via a stoppered, pressure equalising, dropping funnel, to an ice cooled, one-neck flask, containing distilled 2-(2-bromoethyl)-benzaldehyde, (0.65 g, 3.00 mmol). After the addition was complete the dropping funnel was removed and replaced by a stopper. The reaction mixture was stirred overnight while attaining ambient temperature. Sodium tetraphenylborate, (1.10 g, 3.21 mmol), in 10 mL of acetonitrile, is added in the reaction mixture and after 5 minutes of stirring, the organic solvents were rotary evaporated. Ethanol is added to the residue, followed

by water. The resulting solid was collected by filtation and washed with additional ethanol followed by diethyl ether, 0.19 g. This solid was shown by NMR to be an equilibrium mixture of the expected dihydroisoquinolinium salt and the corresponding oxazolidine in 1:3.5 ratio in favour of the latter. The ratio was established by comparison of the integrals corresponding to the iminium proton, δ 8.99 ppm, and the oxazolidine proton, δ 6.46 ppm. This equilibrium could not be shifted to the side of the iminium salt by addition of trifluoacetic acid and due to the complexity of the spectrum the crude mixture was dissolved in dry dichloromethane and stirred over 1.50 g of sodium carbonate for 10 hours. Filtration and removal of the solvent furnished a mixture of diastereoisomeric oxazolidines in 2.3:1 ratio, as an orange oil, 47 mg, 19% combined yield. These were inseperable by column chromatography. ν_{max} /cm^{-1} (nujol) 1733, 1717, 1699, 1684, 1646, 1456, 1376, 1285, 1156, 1120, 1074. δ_H ($CDCl_3$), (250 MHz), characteristic signals for the major diastereoisomer: 1.20 (3 H, s, CH_3 at C8), 1.24 (3 H, d, *J* 10.79, 3.59 Hz, CH_3 at C10), 1.32 (3 H, s, CH_3 at C9), 3.55 (2 H, t, *J* 9.23 Hz, CH_2 at *isoq-3*), 4.37 (1 H, dd, *J* 9.08, 3.59 Hz, CH at C2), 5.79 (1 H, s, N–CH–O, *isoq-1*), 7.05-7.24 (3 H, m, arom., *isoq-6,7,8*), 7.34-7.38 (1 H, m, arom., *isoq-9*); characteristic signals for the minor diastereoisomer: 4.23-4.25 (1 H, m, CH at C2), 5.67 (1 H, s, N–CH–O, *isoq-1*); other signals are observed at: 0.7-1.29 (m), 1.80-2.50 (m), 3.10-3.37 (m); δ_H (62.50 MHz), signals of major diastereoisomer: 10.61 (CH_3, C8), 16.61 (CH_2, C7), 18.39 (CH_3, C9), 23.90 (CH_3, C10), 24.00 (CH_2, *isoq-4*), 34.06 (CH, C5), 38.85 (C quat., C6), 40.00 (CH, C4), 40.46 (CH_2, *isoq-3*) 45.87 (CH, C1), 47.49 (CH, C3), 76.87 (CH, C2), 84.13 (CH, *isoq-1*), 121.60 (CH arom., *isoq-6*), 121.68 (CH arom., *isoq-8*), 122.37 (CH arom., *isoq-7*), 129.68 (C arom. quat., *isoq-5*), 131.24 (CH arom., *isoq-9*), 133.20 (C arom. quat., *isoq-10*). *m/z* 283; exact mass calcd for $C_{19}H_{25}NO$ 283.19361 found 283.19281.

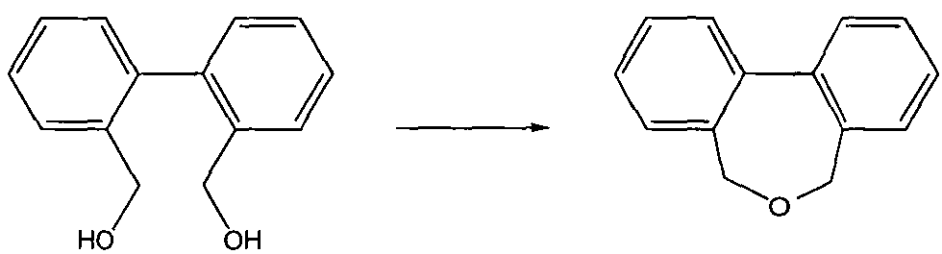
(–)-(2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexan-1-one oxime:



(–)-(2S,5R)-Menthone oxime:[209,235,251] To a solution of (–)-menthone, (10.00 g, 64.83

mmol), in 150 mL of ethanol, 20 mL of a 50% aqueous hydroxylamine solution, (10 g, 0.30 mol), is added, and the solution was refluxed for 24 hours. It was then allowed to cool and stand at ambient temperature for further 24 hours. The organic volatiles were removed by rotary evaporation and the resulting oily residue was diluted with 100 mL of water and extracted with diethyl ether, (3x50 mL). The organic extracts were dried over sodium sulphate and evaporated to afford the pure oxime as a colourless oil which solidifies upon drying under vacuum, (9.32 g 85% yield), m.p. 58-60 °C, (lit. m.p. 58-59 °C).[251] $[\alpha]^{20}_D$ –16.00 c= 2.1, ($CHCl_3$), (lit. $[\alpha]^{23}_D$ –40.30 c= 0.95, (EtOH)[235]); ν_{max} /cm^{-1} (nujol) 3286, 1666, 1255, 931, 891, 847, 754, 664; δ_H ($CDCl_3$), (400 MHz), 0.91 (3 H, d, *J* 6.71, Hz, CH_3 at C8), 0.93 (3 H, d, *J* 6.74, Hz, CH_3 at C9), 0.98 (3 H, d, *J* 6.34, Hz, CH_3 at C10), [1.10-1.28 (1 H, m), 1.32-1.45 (1 H, m), 1.64-1.94 (5 H, m), CH_2 at C3,4,6 and CH at C5], 1.91 (1 H, octet, *J* 6.55, Hz, CH at C7), 3.00-3.10 (1 H, m, CH at C2), 9.53 (1 H, br. s, N–OH); δ_C (62.50 MHz), 20.71 (CH_3, C8), 21.73 (CH_3, C9), 22.05 (CH_3, C10), 26.65 (CH, C5), 27.10 (CH_2, C3), 32.19 (CH_2, C4), 32.66 (CH), 33.07 (CH_2, C6), 49.06 (CH, C2), 161.60 (C quart, C=NOH, C1). *m/z* 169; exact mass calcd for $C_{10}H_{19}NO$ 169.14665 found 169.14668. Found C, 70.85; H, 11.51; N, 8.15; $C_{10}H_{19}NO$ requires: C, 70.94; H, 11.32; N, 8.28%.

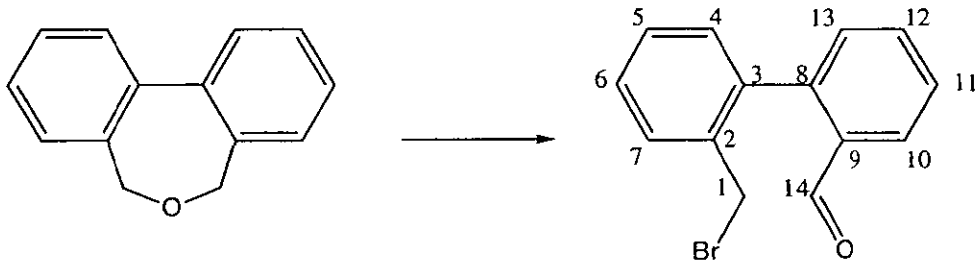
5,7-dihydrodibenzo[*c,e*]oxepine:



Dibenzoxepane:[190] A suspension of 2.2'-biphenyl dimethanol, (4.22 g, 19.53 mmol), in 160 mL of concentrated hydrobromic acid, (48% in water), was heated to 80 °C for one hour. After that time interval the reaction mixture becomes clear solution and is allowed to cool to ambient temperature. The aqueous phase is extracted with diethyl ether, (3x50 mL), and the organic extracts are washed with 50 mL of saturated sodium carbonate solution and then dried over sodium sulphate. Evaporation of the solvent furnished a white solid which was recrystallised from light petroleum to provide 3.43 g of the cyclic ether, as a white solid, 88% yield, m.p. 71 °C, (lit. m.p. 72-73 °C)[190]. ν_{max} /cm^{-1} (nujol) 1567, 1197, 1073,1042, 904, 892, 753, 602; δ_H ($CDCl_3$), (400 MHz), 4.42 (4 H, s, 2xCH_2O), 7.45-7.50 (4 H, m, arom.), 7.53-

7.58 (2 H, m, arom.), 7.60-7.63 (2 H, m, arom.); δ_C (100 MHz), 68.01 (2xCH_2, 2xCH_2O), 127.93 (2xCH arom.), 128.72 (2xCH arom.), 129.39 (2xCH arom.), 130.16 (2xCH arom.), 135.55 (2xC arom. quat., biphenyl link), 141.64 (2xC arom. quat., *ipso*). *m/z* 196; exact mass calcd for $C_{14}H_{12}O$ 196.08881 found 196.08865. Found C, 85.57; H, 6.10; $C_{14}H_{12}O$ requires: C, 85.68; H, 6.17%.

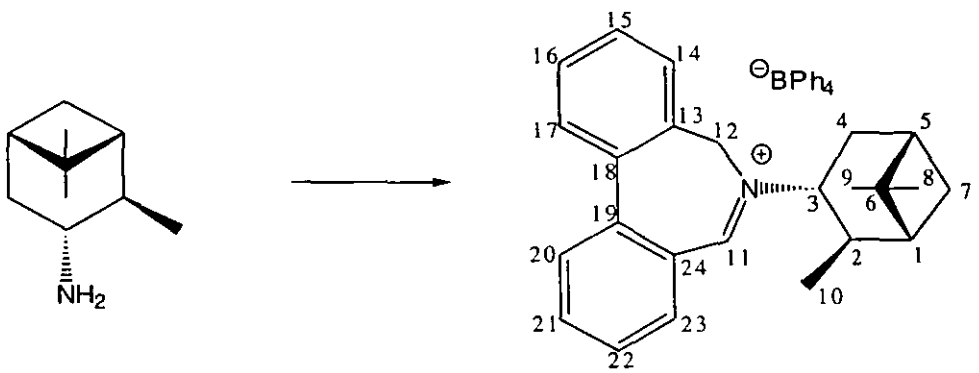
2-[2-(bromomethyl)phenyl]benzene carbaldehyde:



(2-Bromomethyl-2'-carboxaldehyde)-biphenyl:[190] To an ice cooled solution of dibenzoxepane (3.50 g, 17.67 mmol), in carbon tetrachloride (50 mL), in a 100 mL flask fitted with a reflux condenser, molecular bromine (2.85 g, 17.81 mmol, 1 equivalent), is added slowly down the condenser over a period of 5 minutes with stirring. After the vigorous reaction subsides, (*ca* 5 minutes), the cooling bath is removed and the dark brown solution is refluxed until the reaction mixture becomes pale yellow, (indicative of complete consumption of bromine), *ca* 1 hour. The solution is then allowed to attain ambient temperature and the solvent is removed under reduced pressure. To the residue obtained, 15 mL of 48% hydrobromic acid (aqueous) is added and the reaction mixture is warmed to 40 °C 10 -15 minutes with stirring. The solution is then allowed to cool and extracted with diethyl ether (4x20 mL). The organic extracts are washed with water (2x20 mL), then with dilute sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure furnished the crude (2-bromomethyl-2'-carboxaldehyde)-biphenyl. Recrystallisation from light petroleum provided 2.86 of pure product which was stored in a dry dessicator but darkening of the compound could not be prevented, 59% yield, m.p. 56-58 °C. ν_{max} /cm^{-1} (nujol) 1694,1594, 1255, 1221, 1197, 761; δ_H ($CDCl_3$), (400 MHz), 4.21 (2 H, dd, *J* 40.00, 10.12 Hz, *AB* system, CH_2 at C1), 7.12 (1 H, dd, *J* 7.83, 1.22 Hz, CH arom at C5), 7.28-7.36 (3 H, m, arom., CH at C7 and 2xCH at C11 and C13), 7.46 (2 H, dd, *J* 7.82, 0.77 Hz, 2xCH arom. at C4 and C6), 7.56 (1 H, dd, *J* 7.78, 1.43 Hz, CH arom. at C10), 7.98 (1 H, dd, *J* 7.86, 1.26 Hz, CH arom. at C12), 9.65 (1 H, s, HC=O at C14); δ_C (100 MHz),

33.83 (CH_2, C1), 129.96 (CH arom., C5), 130.88 (CH arom., C7), 131.02 (CH arom., C4), 131.40 (CH arom., C6), 133.00 (CH arom., C11), 133.05 (CH arom., C13), 133.39 (CH arom., C10), 135.95 (CH arom., C12), 136.41 (C arom. quat., C2), 138.28 (C arom. quat., C8), 140.16 (C arom. quat., C8), 145.63 (C arom. quat., C9), 194.08 (C quat., HC=O, C14). *m/z* (^{81}Br isotope) 275; exact mass calcd for ^{81}Br isotope $C_{14}H_{11}BrO$ 275.99740 found 275.99766.

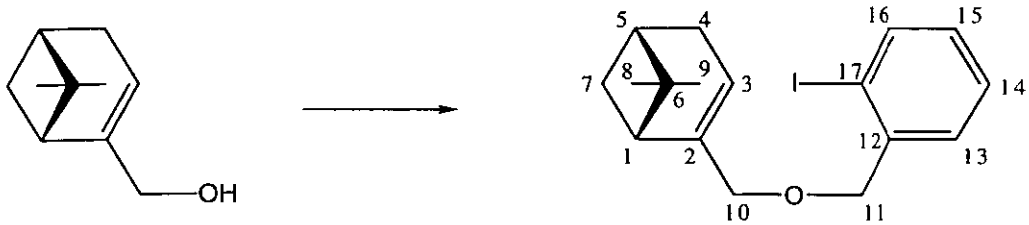
(–)-6-[(1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]-5*H*-dibenzo[*c*,*e*]azepinium tetraphenylborate:



(–)-(1R,2R,3R,5S)-N-(3-isopinocampheyl)-dibenzoazepinium tetraphenylborate: Prepared according to the general procedure in 42% yield, m.p. 212 °C (dec.). $[\alpha]^{20}_D$ –19.50 c= 2.31, (DMSO); ν_{max} /cm^{-1} (nujol) 1630, 1599, 1580, 1557,1209, 756, 705, 612; δ_H (DMSO-d_6, 80 °C), (400 MHz), 1.02 (3 H, d, *J* 11.28 Hz, CH_3 at C10), 1.14 (3 H, s, CH_3 at C8), 1.35 (3 H, s, CH_3 at C9), 1.48 (1 H, d, *J* 16.84, Hz, bridgehead H at C1), 2.02 (1 H, td, *J* 9.26, 2.58 Hz, C*H*H at C7), 2.10-2.31 (2 H, m, CH*H* at C7 and bridgehead H at C5), 2.55-2.74 (3 H, m, CH at C2 and CH_2 at C4), 4.84-5.12 (3 H, m, CH_2 at C12 and CH at C3), 6.80 (4 H, t, *J* 11.38 Hz, arom., *para* in BPh_4 group), 6.93 (4 H, t, *J* 11.84 Hz, arom., *ortho* in BPh_4 group), 7.20-7.29 (8 H, m, arom., *meta* in BPh_4 group), [7.61-7.92 (6 H, m, arom.), 8.02 (1 H, td, *J* 11.64, 2.24 Hz), 8.07-8.16 (1 H, m), biphenyl group], 9.69 (1 H, s, HC=N at C11); δ_C (DMSO-d_6, 80 °C), (100 MHz), 19.92 (CH_3, C8), 23.76 (CH_3, C9), 28.97 (CH_3, C10), 33.69 (CH_2, C7), 34.80 (CH_2, C12), 40.00 (C quat., C6), 41.12 (CH, C5), 42.15 (CH, C2), 48.36 (CH, C1), 53.99 (CH_2, C4), 74.28 (CH, C3), 122.23 (8xCH arom., CH *ortho* in BPh_4 group), 125.96 (4xCH arom., CH *para* in BPh_4 group), 127.77 (C arom. quat., C13), 129.41 (CH arom., C15), 129.65 (CH arom., C17), 129.94 (CH arom., C14), 130.31 (CH arom., C16), 130.69 (CH arom., C22), 131.08 (CH arom., C20), 131.12 (CH arom., C23), 135.41 (C arom. quat., C18), 135.74 (CH arom., C21), 136.55 (8xCH arom., CH *meta* in BPh_4 group), 137.93 (C arom. quat., C19), 141.90 (C arom. quat., C24), 164.50 (4xC arom. quat., q, *J* 196.40 Hz, C–B

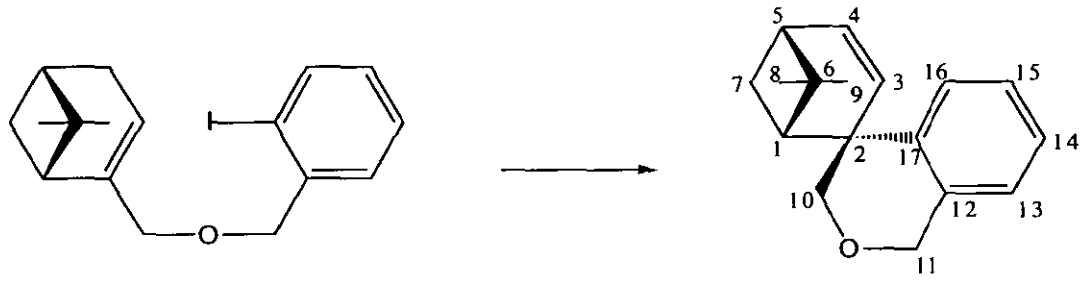
ipso in BPh_4 group), 171.15 (CH, HC=N, C11). *m/z* (cation) 330; exact mass calcd for cation $C_{24}H_{28}N$ 330.22216 found 330.22281.

(–)-(1*R*,5*S*)-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl-[(2-iodophenyl)methyl] ether:



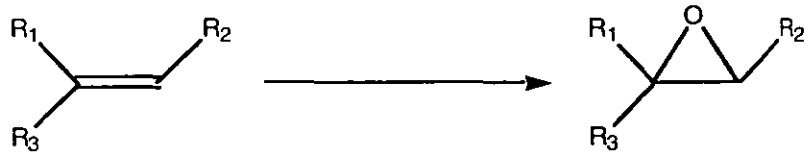
(–)-(1R,5S)-Myrtenol-(2-iodobenzyl)-ether: To a suspension of sodium hydride, (3.40 g of a 60% suspension in mineral oil contains 2.04 g, 85 mmol), in 300 mL of dry THF, in a two neck flask equiped with a condenser, nitrogen bubbler and rubber septum, (–)-(1*R*,5*S*)- myrtenol, (10.00 g, 65.68 mmol), is added via a syringe and the reaction mixture was refluxed for one hour. 2-Iodobenzyl bromide, (19.30 g, 65.00 mmol), was then added in one portion, as a solution in dry THF, (70 mL), and the reaction mixture was refluxed gently overnight. The organic solvent was removed in *vacuuo* and to the residue was added light petroleum, (250 mL), and saturated ammonium chloride solution, (100 mL). The organic phase was separated, washed twice with water, dried over magnesium sulphate and after evaporation of the solvents, afforded a pale yellow oil which was chromatographed on silica gel with light petroleum/ethyl acetate, (95:5), as the eluent, and furnished 15.48 g of the 2-iodobenzyl ether as a colourless oil, 70% yield. $[\alpha]^{20}_D$ –11.03 c= 2.03, ($CHCl_3$); ν_{max} /cm^{-1} (neat), 1565, 1463, 1436, 1364, 1381, 1204, 1129, 1091, 1091, 1012, 747, δ_H ($CDCl_3$), (250 MHz), 0.88 (3 H, s, CH_3 at C8), 1.23 (1 H, d, *J* 8.53 Hz, bridgehead H at C1), 1.31 (3 H, s, CH_3 at C9), 2.12-2.47 (5 H, m, 2xCH_2 at C4 and 7 and bridgehead H at C5), 3.98 (2 H, dd, *J* 3.07, 1.52 Hz, *AB* system, CH_2 at C10), 4.45 (2 H, s, CH_2 at C11), 5.56-5.59 (1 H, m, C3), 6.97 (1 H, td, *J* 7.61, 1.67 Hz, arom., C15), 7.35 (1 H, td, *J* 7.42, 0.95 Hz, arom., C14), 7.35 (1 H, dd, *J* 7.56, 1.49 Hz, arom., C13), 7.81 (1 H, dd, *J* 7.76, 0.97 Hz, arom., C16); δ_C (62.50 MHz), 21.16 (CH_3, C8), 26.25 (CH_3, C9), 31.32 (CH_2, C7), 31.62 (CH_2, C4), 38.02 (C quat., C6), 40.91 (CH, C5), 43.39 (CH, C1), 73.55 (CH_2, C10), 77.44 (CH_2, C11), 97.47 (C quart., C2), 120.56 (CH, C3), 128.09 (CH arom., C15), 128.50 (CH arom., C14), 128.86 (CH arom., C13), 138.95 (CH arom., C16), 140.92 (C arom. quat., C12) 145.20 (C arom. quat., C17).

(+)-3,3-[(1*R*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2,2-yl]spiroisochroman:



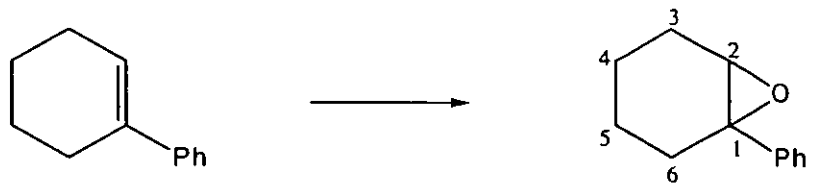
(+)-(1R,2R,5S)-3,3-[2,2-Myrtanyl]spiroisochroman: To a suspension of palladium (II) acetate, (0.50 g, 2.23 mmol), in dry acetonitrile, in a two neck flask equiped with a condenser, nitrogen bubbler and rubber septum, triphenyl phosphine is added, (2.35 g, 9.00 mmol), in one portion and almost immediately a bright yellow solid precipitates out of the solution. A solution of myrtenol-(2-iodobenzyl) ether, (3.00 g, 8.15 mmol), and triethylamine, (3.30 g, 32.60 mmol), in dry THF, is added via a syringe and the reaction mixture is refluxed for 24 hours. The solvents are removed in vacuuo, the resulting residue is macerated with light petroleum, and the suspension obtained is stirred for 30 minutes before filtered through celite. The organic extracts are then washed with saturated ammonium chloride solution and dried over sodium sulphate. Evaporation of the solvents afforded a yellow oil which was chromatographed on silica gel with light petroleum/ethyl acetate, (95:5), as the eluent, and furnished 1.23 g of the spiro-isochroman as a colourless oil, 63% yield. This product proved to be extremely air sensitive, (decomposed within hours in contact with air at ambient temperature), and hence was stored under nitrogen. $[\alpha]^{20}_{D}$ +145.40 c= 2.44, ($CHCl_3$); ν_{max} /cm^{-1} (neat) 1620, 1487, 1448, 1376, 1248, 1209, 1118, 1087, 941, 759, 727, 699; δ_H ($CDCl_3$), (250 MHz), 1.19 (3 H, s, CH_3 at C8), 1.26 (1 H, d, *J* 11.70 Hz, bridgehead H at C1), 1.38 (3 H, s, CH_3 at C9), 2.11-2.30 (3 H, m, CH_2 at C7 and bridgehead H at C5), 3.54 (2 H, dd, *J* 213.63, 11.07 Hz, *AB* system, CH_2 at C10), 4.88 (2 H, d, *J* 10.96 Hz, CH_2 at C11), 5.38 (1 H, m, CH at C4), 6.48 (1 H, dd, *J* 8.84, 6.38 Hz, CH at C3), 6.97 (1 H, m, arom., C16), 7.15-7.21 (2 H, m, arom., 2xCH at C14 and C15), 7.32 (1 H, m, arom., C13); δ_C (62.50 MHz), 24.41 (CH_3, C8), 27.65 (CH_3, C9), 27.68 (CH_2, C7), 42.48 (CH, C5), 43.80 (C quat., C6), 48.49 (CH, C1), 67.55 (CH_2, C10), 68.50 (CH_2, C11), 74.72 (C quat., C spiro, C2), 124.04 (CH olefinic, C4), 125.32 (CH olefinic, C3), 125.48 (CH arom., C16), 126.35 (CH arom., C14), 129.00 (C arom. quat., C17) 129.18 (CH arom., C15), 134.31 (C arom. quat., C12), 138.79 (CH arom., C13). *m/z* 240; exact mass calcd for $C_{17}H_{20}O$ 240.15141 found 240.15151.

General procedure for the catalytic asymmetric epoxidation of simple alkenes mediated by iminium salts:



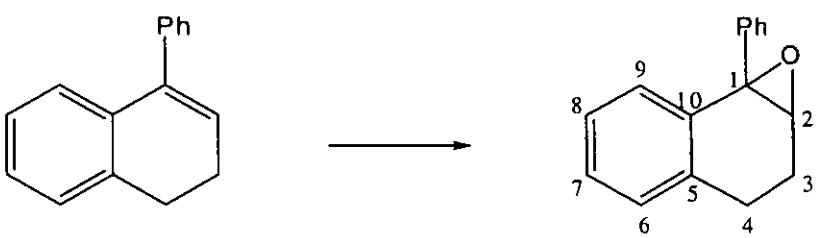
To an ice cooled solution of sodium carbonate, (4 equivalents), in water, (12 mL per 1.50 g of sodium carbonate), Oxone™ (2 equivalents), is added with vigorous stirring and the resulting foaming suspension is left to stir for 5 minutes so that most of the initial effervescence subsides. The iminium salt, (5-10 mol% with respect to the substrate), is then added as a solution in acetonitrile, (7 mL per 100 mg of catalyst), followed by the alkene substrate, (1 equivalent, 100 mol%), also as a solution in acetonitrile of the same volume as the solution of the catalyst. The substrates which are solids, are added directly in the reaction mixture as such. The suspension is stirred at the same temperature until the substrate is completely consumed by TLC or after overnight stirring for the slowest reactions. Finally, the reaction mixture is diluted with water until most of the inorganics dissolve and extracted 4 times with diethyl ether. The organic extracts are washed once with water, then with brine, and dried over sodium sulphate. Filtration and evaporation of the solvents furnishes a yellow or light brown residue which is macerated with light petroleum and filtered. The organic solution is then stripped of solvent to provide the crude epoxides which are *ca* 90% pure by NMR for completed or nearly completed reactions. Analytically pure epoxides can be obtained by chromatography on a short column of silica gel, eluting initially with light petroleum to remove non polar impurities and/or parent alkene, followed by light petroleum/ethyl acetate (95:5) to afford the epoxides. These are easily identified on silica by the quick manifestation of a deep blue stain upon exposure to an ethanolic solution of phosphomolybdic acid acidified with concentrated sulfuric acid. It must be noted that several epoxides are very volatile and when solutions of these compounds are rotary evaporated, it is best that the water bath does not exceed 30 °C. Epoxides are very sensitive compounds and storage for prolonged periods of time, (days), is best to be done under nitrogen.

1a-Phenylperhydro-1-benzoxirene:



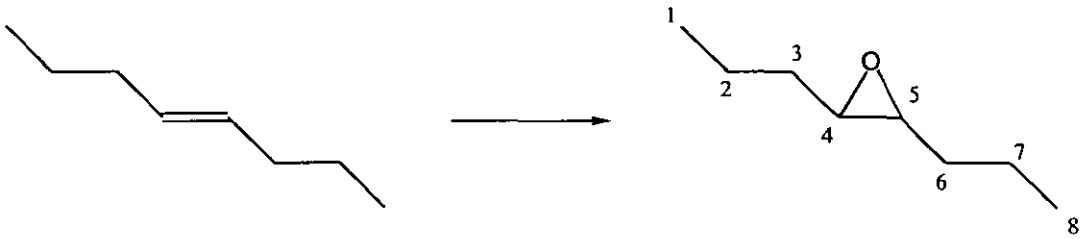
1-Phenylcyclohex-1-ene oxide:[236-238] Colourless oil, 68% yield; a sample of 32% ee exhibited $[\alpha]^{20}_D$ +17.97 c=2.47, ($CHCl_3$). ν_{max} /cm^{-1} (neat) 3084, 1602, 1495, 1446, 1359, 1249, 1173, 1132, 1079, 1030, 993, 974; δ_H ($CDCl_3$), (250 MHz), [1.22-1.35 (1 H, m), 1.53-1.64 (3 H m), 1.99-2.06 (2 H, m) 2.16-2.18 (1 H, m), 2.26-2.32 (1 H, m), 4xCH_2 at C3-C6], 3.10 (1 H, t, *J* 2.04 Hz, CH at C2), 7.28-7.44 (5 H, m, arom., Ph group); δ_C (62.50 MHz), [19.78 (CH_2), 20.09 (CH_2), 24.69 (CH_2), 28.15 (CH_2), C3-C6], 60.13 (C quat., C1), 61.84 (CH, C2) 125.26 (2xCH arom., 2xCH *ortho* in Ph group), 127.12 (CH arom., CH *para* in Ph group), 128.20 (2xCH arom., 2xCH *meta* in Ph group), 142.80 (C arom. quat., *ipso* in Ph group).

7b-Phenyl-1a,2,3,7b-tetrahydronaphtho[1,2-*b*]oxirene:



1-Phenyl-3,4-dihydronaphthalene oxide:[236,239] Pale yellow solid, 72% yield, m.p. 104-106 °C, (lit. m.p. 94-97 °C).[239] A sample of 63% ee exhibited $[\alpha]^{20}_D$ +16.21 c=1.48, ($CHCl_3$). ν_{max} /cm^{-1} (nujol) 1602, 1486, 1307, 1155, 1074, 1042, 953; δ_H ($CDCl_3$), (250 MHz), 2.10 (1 H, td, *J* 13.69, 5.76 Hz, CH*H* at C3), 2.49-2.60 (1 H, m, C*H*H atC4), 2.77 (1 H, dd, *J* 15.53, 5.63 Hz, C*H*H at C3), 2.98-3.06 (1 H, m, CH*H* at C4), 3.71 (1 H, d, *J* 3.08 Hz, CH at C2), [7.11-7.31 (4 H, m, arom.), 7.45-7.61 (5 H, m, arom.), 9xCH at C6-C9 and Ph group]; δ_C (62.50 MHz), 22.14 (CH_2, C4), 25.43 (CH_2, C3), 60.89 (C quat., C1), 62.98 (CH, C2) [125.95 (CH arom.), 127.68 (CH arom.), 127.87 (2xCH arom.), 128.07 (CH arom.), 128.18 (2xCH arom.), 128.58 (CH arom.), 129.82 (CH arom.), 134.99 (C arom. quat.), 137.45 (C arom. quat.), 138.82 (C arom. quat.), C5-C10 and aromatic carbon atoms at Ph group].

(*E*)-2,3-Dipropyloxirane:

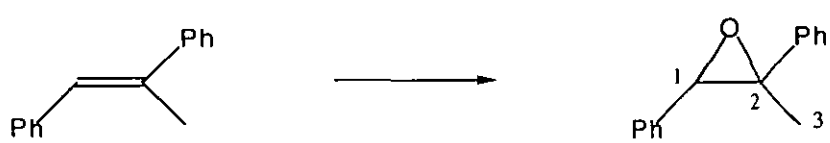


trans-4-Octene oxide:[240,241] Colourless oil, 38% yield; ν_{max} /cm^{-1} (neat) 1465, 1380, 911; δ_H ($CDCl_3$), (400 MHz), 0.94-1.00 (6 H, m, 2xCH_3 at C1 and C8), 1.45-1.53 (8 H m, 4xCH_2 at C2-3 and C6-7), 2.64-2.68 (2 H, m, 2xCH at C4 and C5); δ_C (100 MHz), 14.33 (2xCH_3, C1 and C8), 19.73 (2xCH_2, C2 and C7), 34.56 (2xCH_2, C3 and C6), 59.05 (2xCH, C4 and C5).

(*E*)-2,3-Diphenyloxirane:

trans-stilbene oxide:[236,242,243] White solid, 76% yield, m.p. 66-67 °C, (lit. m.p. 61-63 °C).[242] ν_{max} /cm^{-1} (nujol) 1601, 1492, 1284, 1176, 1157, 1094, 1072, 1025; δ_H ($CDCl_3$), (400 MHz), 3.84 (2 H, s, 2xPhCH–O), 7.28-7.37 (10 H m, arom., from 2 Ph groups); δ_C (100 MHz), 63.28 (2xCH, 2xPhCH–O), 125.98 (4xCH arom., 4xCH *ortho* in the 2 Ph groups), 128.62 (2xCH arom., 2xCH *para* in the 2 Ph groups), 129.31 (4xCH arom., 4xCH *meta* in the 2 Ph groups), 137.60 (2xC arom. quat., 2xC *ipso* in the 2 Ph groups).

2-Methyl-(*E*)-2,3-diphenyloxirane:



trans-(α-Methyl)-stilbene oxide:[121] colourless oil, 55% yield; a sample of 17% ee exhibited $[\alpha]^{20}_D$ +9.86 c=3.00, ($CHCl_3$); ν_{max} /cm^{-1} (neat) 3061, 1602, 1495, 1449, 1381, 1279, 1157, 1118, 1065, 1027, 980; δ_H ($CDCl_3$) (400 MHz), 1.46 (3 H, s, CH_3, C3), 3.96 (1 H, s, CH at C1), 7.30-7.46 (10 H, m, arom., from 2 Ph groups); δ_C (100 MHz), 17.14

(CH_3, C3), 63.48 (C quat. C2), 67.52 (CH, C1), [125.57 (2xCH arom.), 126.92 (2xCH arom.), 127.70 (CH arom.), 127.93 (CH arom.), 128.60 (2xCH arom.), 129.21 (2xCH arom.), 136.36 (C arom. quat.), 142.75 (C arom. quat.) , from 2 Ph groups].

6,6a-Dihydro-1a*H*-indeno[1,2-*b*]oxirene:

Indene oxide:[244,245,246] Colourless oil, 52% yield; a sample of 17% ee exhibited $[\alpha]^{20}_D$ +5.76 c=1.18, ($CHCl_3$); ν_{max} /cm^{-1} (neat) 3027, 2917, 1482, 1464, 1390, 1372, 1232, 1183, 1142, 829, 758, 745, 723; δ_H ($CDCl_3$) (200 MHz), 2.97 (1 H, dd, *J* 18.14, 2.74 Hz, upfield portion of an *ABX* system, C*H*H at C3 *syn* to H at C2), 3.21 (1 H, d, *J* 17.58 Hz, downfield portion of an *ABX* system, CH*H* at C3 *anti* to H at C2), 4.13 (1 H, t, *J* 3.03 Hz, CH at C2), 4.26 (1 H, dd, *J* 2.76, 1.10 Hz, CH at C1), [7.14-7.29 (3 H, m), 7.49 (1 H, dd, *J* 6.59, 1.65 Hz) 4xCH at C5-C8]; δ_C (100 MHz), 34.62 (CH_2, C3), 57.64 (CH, C2), 59.09 (CH, C1), 125.22 (CH arom., C7), 126.12 (CH arom., C6), 126.28 (CH arom., C5), 128.59 (CH arom., C8), 140.99 (C arom. quat., C4), 143.64 (C arom. quat., C9).

2,2,3-Triphenyloxirane:

Triphenyl ethylene oxide:[237,247] Colourless oil which slowly solidified, m.p. 66-67 °C, (lit. m.p. 75 °C). A sample of 58% ee exhibited $[\alpha]^{20}_D$ +16.29 c=1.35, ($CHCl_3$). ν_{max} /cm^{-1} (neat) 3062, 3030, 2957, 2925, 2856, 1605, 1596, 1499, 1471, 1448, 1262, 1221, 741, 698, 621; δ_H ($CDCl_3$) (250 MHz), 4.40 (1 H, m, CHPh), 7.10-7.47 (15 H, m, from 3 Ph groups); δ_C (62.50 MHz), 68.03 (CH, CHPh), [68.34 (C quat., CPh_2), 126.33 (2xCH arom.), 126.75 (2xCH arom.), 127.50 (2xCH arom.), 127.55 (2xCH arom.), 127.64 (CH arom.), 127.70 (2xCH arom.), 127.78 (2xCH arom.), 127.83 (CH arom.), 127.95 (CH arom.), 128.20 (2xCH arom.), 128.62 (2xCH arom.), 135.42 (CH arom. quat.), 135.88 (CH arom. quat.), 141.12 (CH arom. quat.) aromatic carbon atoms from 3 Ph groups].

(*E*)-2-Methyl-3-phenyloxirane:

trans-β-Methylstyrene oxide:[244,248,252] Colourless oil, ν_{max} /cm^{-1} (neat) 2987, 1604, 1496, 1461, 1424, 1376, 1020, 953, 860, 766, 743, 698, 611; δ_H ($CDCl_3$) (250 MHz), 1.44 (3 H, d, *J* 5.06 Hz, CH_3 at C3), 3.02 (1 H, m, CH at C2), 1.44 (3 H, d, *J* 2.02 Hz, CH at C1), 7.23-7.33 (5 H, m, arom., Ph group); δ_C (62.50 MHz), 17.82 (CH_3, C3), 58.94 (CH, C2), 59.45 (CH, C1), 125.48 (2xCH arom., 2xCH *ortho* in Ph group), 127.95 (CH arom., CH *para* in Ph group), 128.36 (2xCH arom., 2xCH *meta* in Ph group), 138.05 (C arom. quat., *ipso* in Ph group).

2-Methyl-2-phenyloxirane:

α-Methylstyrene oxide:[249,250] Colourless oil, 64% yield; a sample of 20% ee exhibited $[\alpha]^{20}_D$ +1.43 c=2.70, ($CHCl_3$).ν_{max} /cm^{-1} (neat) 3034, 2958, 2929, 2872, 1604, 1496, 1447, 1381, 1343, 1061, 1027, 860, 759, 699; δ_H ($CDCl_3$) (250 MHz), 0.86 (3 H, d, *J* 6.55 Hz, CH_3 at C3), 2.79 (1 H, dd, *J* 5.43, 0.75 Hz, C*H*H at C1*cis* to Ph group), 2.96 (1 H, d, *J* 5.41 Hz, CH*H* at C1*trans* to Ph group), 7.24-7.38 (5 H, m, arom., Ph group); δ_C (62.50 MHz), 21.74 (CH_3, C3), 56.66 (C quat., C2), 56.93 (CH_2, C1), 125.23 (2xCH arom., 2xCH *ortho* in Ph group), 127.37 (CH arom., CH *para* in Ph group), 128.25 (2xCH arom., 2xCH *meta* in Ph group), 129.00 (C arom. quat., *ipso* in Ph group).

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APPENDIX 1

X-RAY REPORTS

X-ray reports.

The crystallographic data for the structures presented in the text are given in this section. The first crystallographic analysis was carried out at the University of Liverpool by J. Barckley, while the others were carried out at Loughborough University by Dr. A. M. Z. Slawin.

Crystal data for *trans*-[pyrrolidine-N'-(4-chlorophenyl)]formamidinium tetrafluoroborate (Scheme 14, p. 134). $C_{11}H_{14}ClN_2BF_4$, triclinic, a = 8.771 (3)Å, b = 9.792 (4)Å, c = 8.734 (2)Å, V = 662.2 (4)Å, space group P1, Z = 2, d = 1.487 g/cm^3, μ(MoKα) = 3.21 cm^{-1}. Reflections were measured on a Rigaku AFC6S diffractometer.The structure was solved by direct methods. Crystal and electronic stability was observed and therefore no decay correction was applied. R = 0.015.

Crystal data for (–)-(4*S*,5*R*)-4-methyl-5-phenyl-2-(4-nitrophenyl)-oxazoline (Scheme 25, p. 145). $C_{16}H_{14}N_2O_3$, orthorhombic, a = 7.127 (2)Å, b = 28.587 (3)Å, c = 6.748 (4)Å, V = 1387.8 (8)Å, space group $P2_12_12_1$, Z = 4, d = 1.35 g/cm^3, μ(CuKα) = 7.4 cm^{-1}, F_{000} = 592. Reflections were measured on a Rigaku AFC7S diffractometer. The structure was solved by direct methods and expanded using Fourier techniques. Linear correction was applied to account for a 7.4% decrease in the standards R=0.038 and R_W = 0.043.

Crystal data for (–)-(1*S*,2*R*,4*S*)-camphor-10-sulfonylhydraz-2-ine (Scheme 35, p. 156). $C_{10}H_{18}N_2O_2S$, orthorhombic, a = 7.636 (2)Å, b = 7.6357 Å, c = 18.995 (2)Å, V = 1107.5 (6)Å, space group $P2_12_12_1$, Z = 4, d = 1.38 g/cm^3, μ(CuKα) = 24.7 cm^{-1}, F_{000} = 496. Reflections were measured on a Rigaku AFC7S diffractometer. The structure was solved by direct methods and expanded using Fourier techniques. Linear correction was applied to account for a 0.9% decrease in the standards. R=0.042 and R_W = 0.045.

Crystal data for (–)-(1*R*,2*R*,3*R*,5*S*)-N-(3-isopinocampheyl)-dihydroisoquinolinium tetraphenylborate (Scheme 46, p. 167). $C_{43}H_{46}BN$, orthorhombic, a = 16.807 (5)Å, b = 19.921 (3)Å, c = 10.161 (2)Å, V = 3402 (1)Å, space group $P2_12_12_1$, Z = 4, d = 1.15 g/cm^3, μ(CuKα) = 4.8 cm^{-1}, F_{000} = 1264. Reflections were measured on a Rigaku AFC7S diffractometer. The structure was solved by direct methods and expanded using Fourier techniques. Linear correction was applied to account for a 1.6% decrease in the standards. R=0.038 and R_W = 0.035.

Crystal data for (+)-(4*S*,5*S*)-N-5-(2,2-dimethyl-4-phenyl-1,3-dioxane)-dihydroisoquinolinium tetraphenylborate (Figure 3, p. 188). $C_{45}H_{44}BNO_2$, monoclinic, a = 9.37 (1)Å, b = 22.104 (8)Å, c = 9.457 (5)Å, V = 1957 (3)Å, space group $P2_1$, Z = 2, d = 1.19 g/cm^3, μ(CuKα) = 5.6 cm^{-1}, F_{000} = 748. Reflections were measured on a Rigaku AFC7S diffractometer. The structure was solved by direct methods and expanded using Fourier techniques. Linear correction was applied to account for a 3.4% decrease in the standards. R=0.059 and R_W = 0.045.

Crystal data for (–)-(1*S*,4*R*)-aminoapocamphor isocyanate (Scheme 69, p. 204). $C_{10}H_{13}NO_2$, orthorhombic, a = 11.332 (3)Å, b = 11.337 (3)Å, c = 7.333 (3)Å, V = 942.1 (4)Å, space group $P2_12_12_1$, Z = 4, d = 1.26 g/cm^3, μ(CuKα) = 6.8 cm^{-1}, F_{000} = 384. Reflections were measured on a Rigaku AFC7S diffractometer. The structure was solved by direct methods and expanded using Fourier techniques. Linear correction was applied to account for a 14% decrease in the standards. R=0.043 and R_W = 0.033.

Crystal data for (–)-(1*S*,2*R*,5*S*)-2-amino-(*trans*)-myrtanol-spiro-oxazolidinone (Scheme 77, p. 213). $C_{11}H_{17}NO_2$, orthorhombic, a = 11.426 (2)Å, b = 22.128 (2)Å, c = 8.379 (2)Å, V = 2118.5 (6)Å, space group $P2_12_12_1$, Z = 8, d = 1.22 g/cm^3, μ(CuKα) = 6.4 cm^{-1}, F_{000} = 848. Reflections were measured on a Rigaku AFC7S diffractometer. The structure was solved by direct methods and expanded using Fourier techniques. Linear correction was applied to account for a 1% decrease in the standards. R=0.045 and R_W = 0.040.

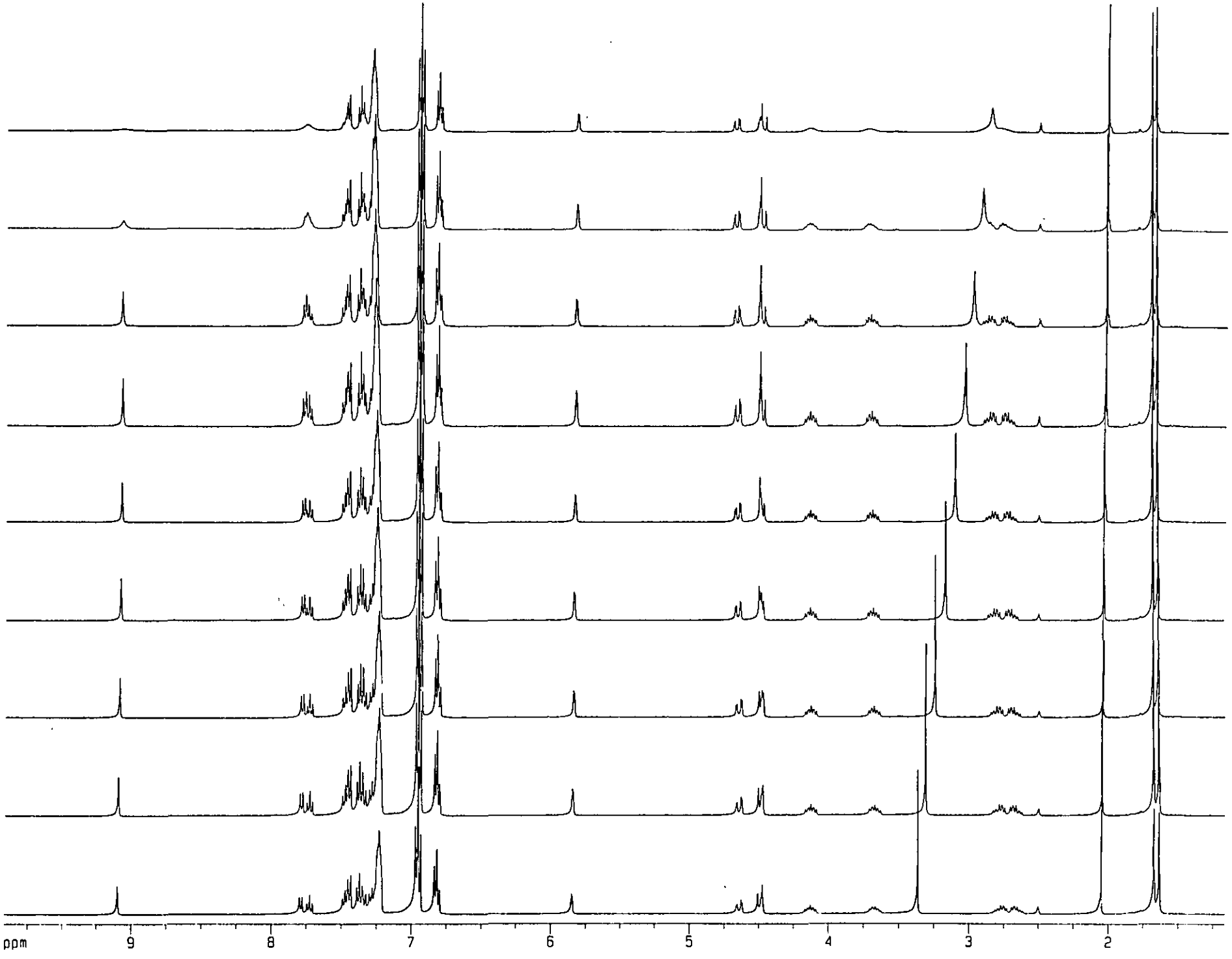
Crystal data for (–)-(1*S*,2*R*,5*S*)-2-amino-[(*trans*)-myrtanol] (Scheme 78, p. 214). $C_{10}H_{19}NO$, orthorhombic, a = 8.409 (5)Å, b = 18.914 (4)Å, c = 6.180 (5)Å, V = 982.8 (4)Å, space group $P2_12_12_1$, Z = 4, d = 1.14 g/cm^3, μ(CuKα) = 6.8 cm^{-1}, F_{000} = 376. Reflections were measured on a Rigaku AFC7S diffractometer. The structure was solved by direct methods and expanded using Fourier techniques. Linear correction was applied to account for a 35.2% decrease in the standards. R=0.050 and R_W = 0.053.

APPENDIX 2

NMR DATA

NMR data.

The additional NMR data that are provided in this section refer to (+)-(4*S*,5*S*)-N-5-(2,2-dimethyl-4-phenyl-1,3-dioxane)-dihydroisoquinolinium tetraphenylborate and supplement the characterisation data given in the experimental section.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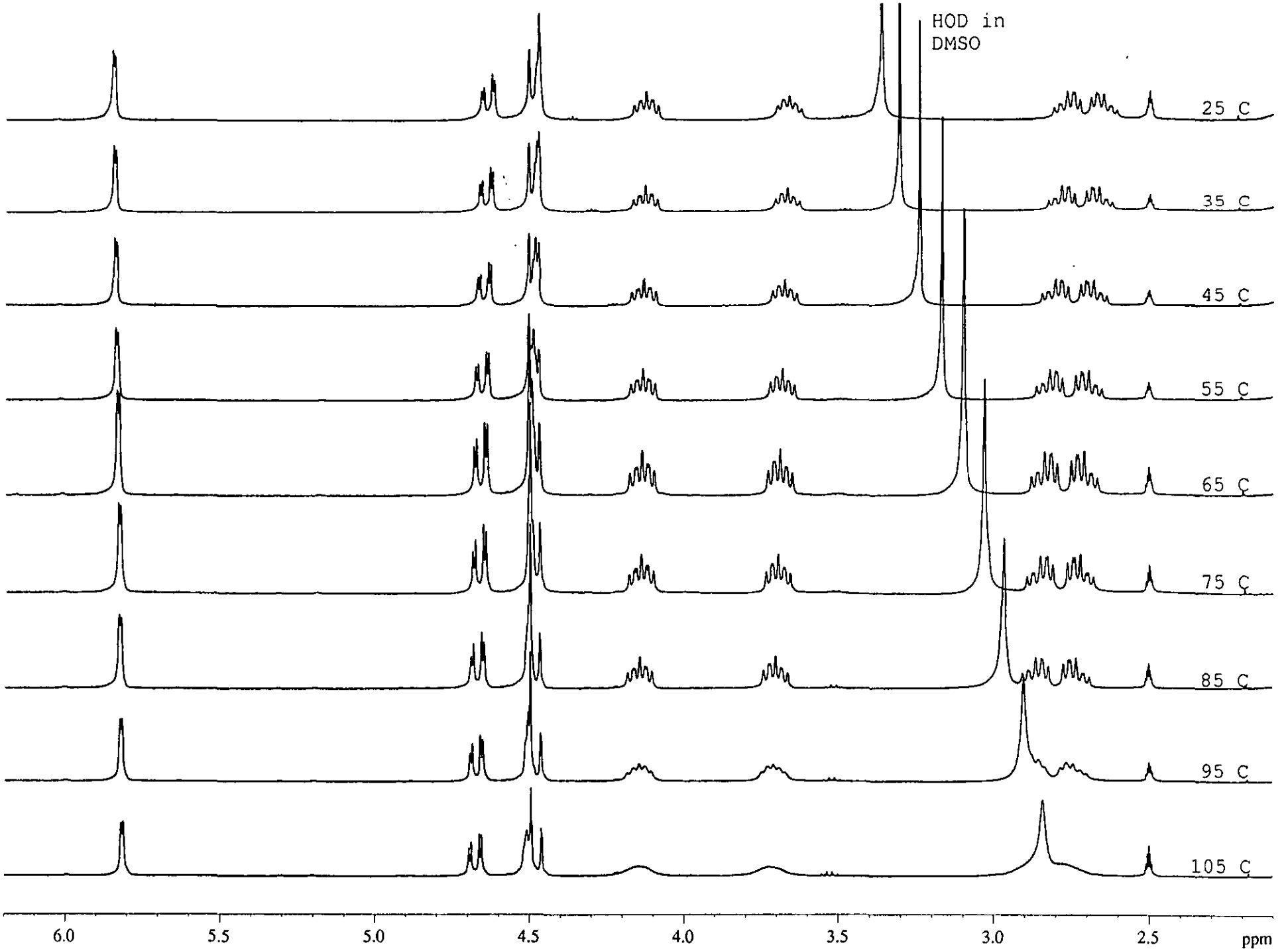
8
7
6
5
4
3
2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DMSO
25 C
35 C
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55 C
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4.0
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3.0
2.5
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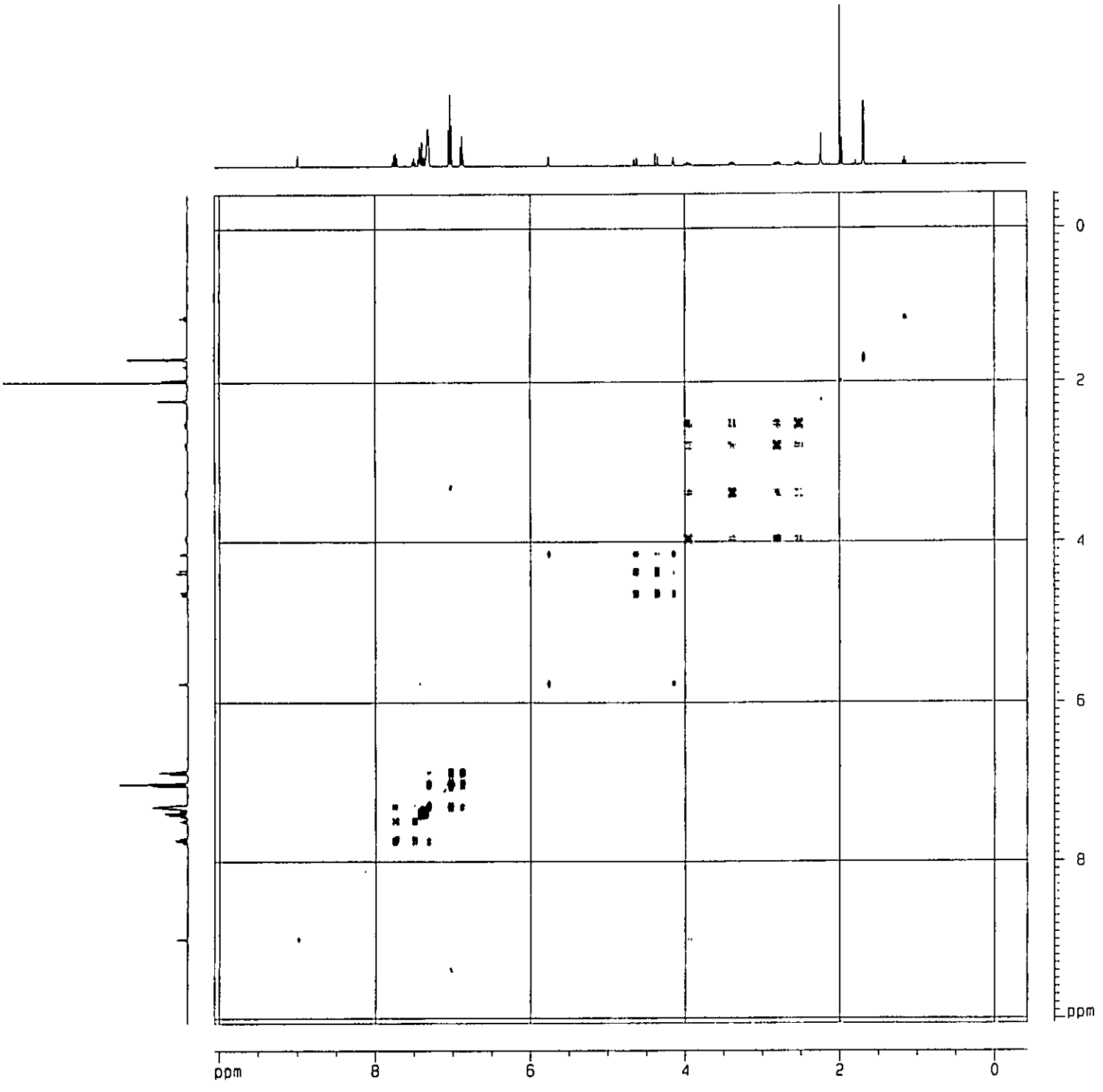

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PROCNO	1

F2 - Acquisition Parameters

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PULPROG	cosydfto
TD	2048
SOLVENT	D2O
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DS	16
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FIDRES	2.048160 Hz
AQ	0.2441716 sec
RG	322.5
DW	119.200 usec
DE	7.50 usec
TE	300.0 K
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d13	0.00000300 sec
D1	3.00000000 sec
P1	10.25 usec
SFO1	400.1319291 MHz
NUC1	1H
PL1	-6.00 dB
IN0	0.00011920 sec

F1 - Acquisition parameters

ND0	2
TD	1013
SFO1	400.1319 MHz
FIDRES	4.140800 Hz
SW	10.483 ppm

F2 - Processing parameters

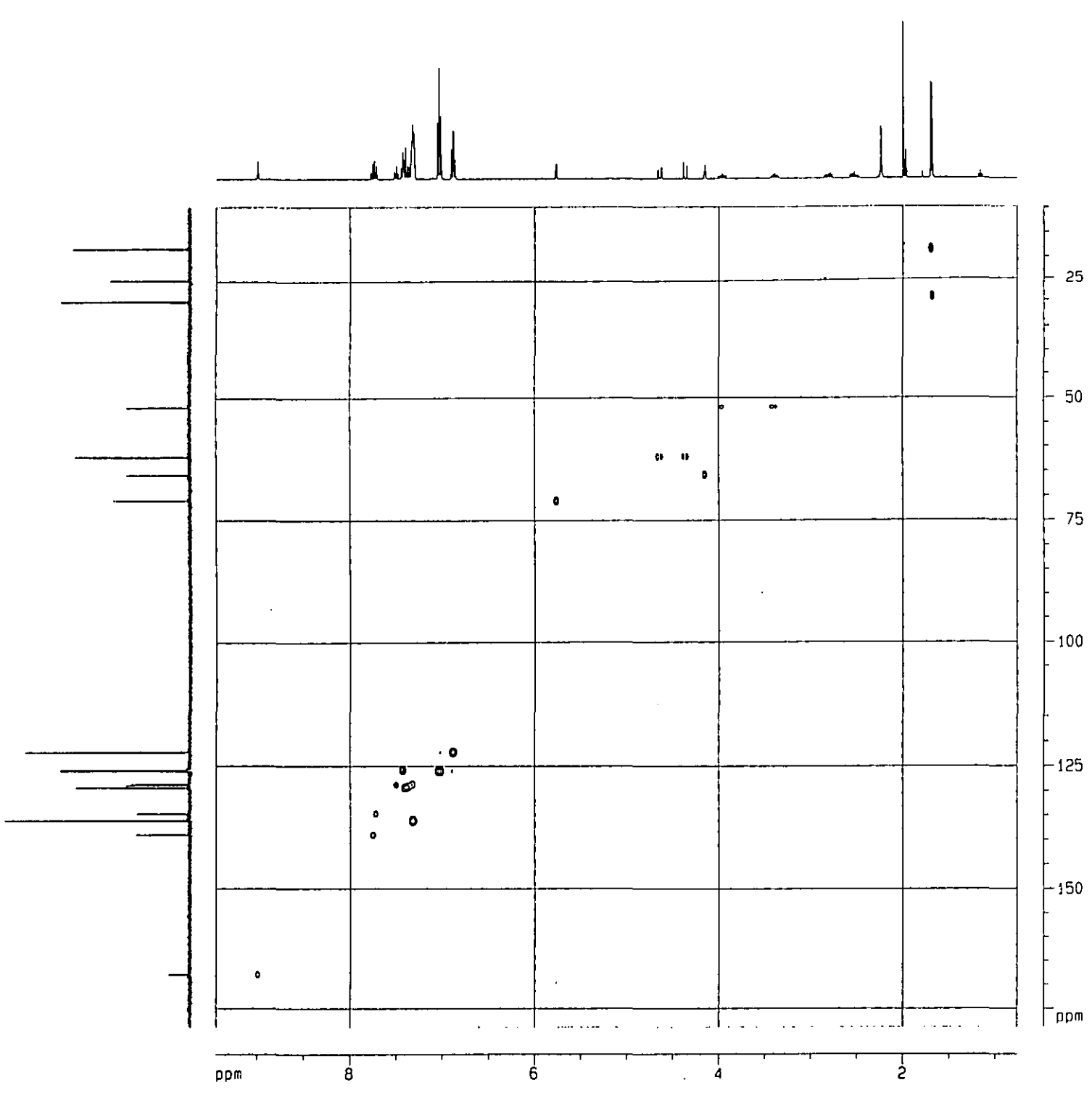
SI	2048
SF	400.1300000 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	2048
MC2	TPPI
SF	400.1300000 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	10.063 ppm
F2LO	4026.44 Hz
F2PHI	-0.420 ppm
F2HI	-168.19 Hz
F1PLO	10.063 ppm
F1LO	4026.44 Hz
F1PHI	-0.420 ppm
F1HI	-168.19 Hz
F2PPMCM	0.69888 ppm/cm
F2HZCM	279.64206 Hz/cm
F1PPMCM	0.69888 ppm/cm
F1HZCM	279.64206 Hz/cm



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PROCNO	1

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SOLVENT	DMSO
NS	8
DS	16
SWH	3472.222 Hz
FIDRES	3.390842 Hz
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RG	181
DW	144.000 usec
DE	7.50 usec
TE	300.0 K
P1	10.25 usec
p2	20.50 usec
P3	5.50 usec
p4	11.00 usec
d0	0.00000300 sec
CNST2	145.0000000
d2	0.00344828 sec
D1	1.50000000 sec
SFO1	400.1320415 MHz
NUC1	1H
PL1	-6.00 dB
PL2	-6.00 dB
SFO2	100.6222226 MHz
NUC2	13C
D7	0.70840061 sec
PL12	12.00 dB
CPDPRG2	garp
PCPD2	85.00 usec
INO	0.00001470 sec

F1 - Acquisition parameters

NDO	4
TD	256
SFO1	100.6222 MHz
FIDRES	66.432023 Hz
SW	169.015 ppm

F2 - Processing parameters

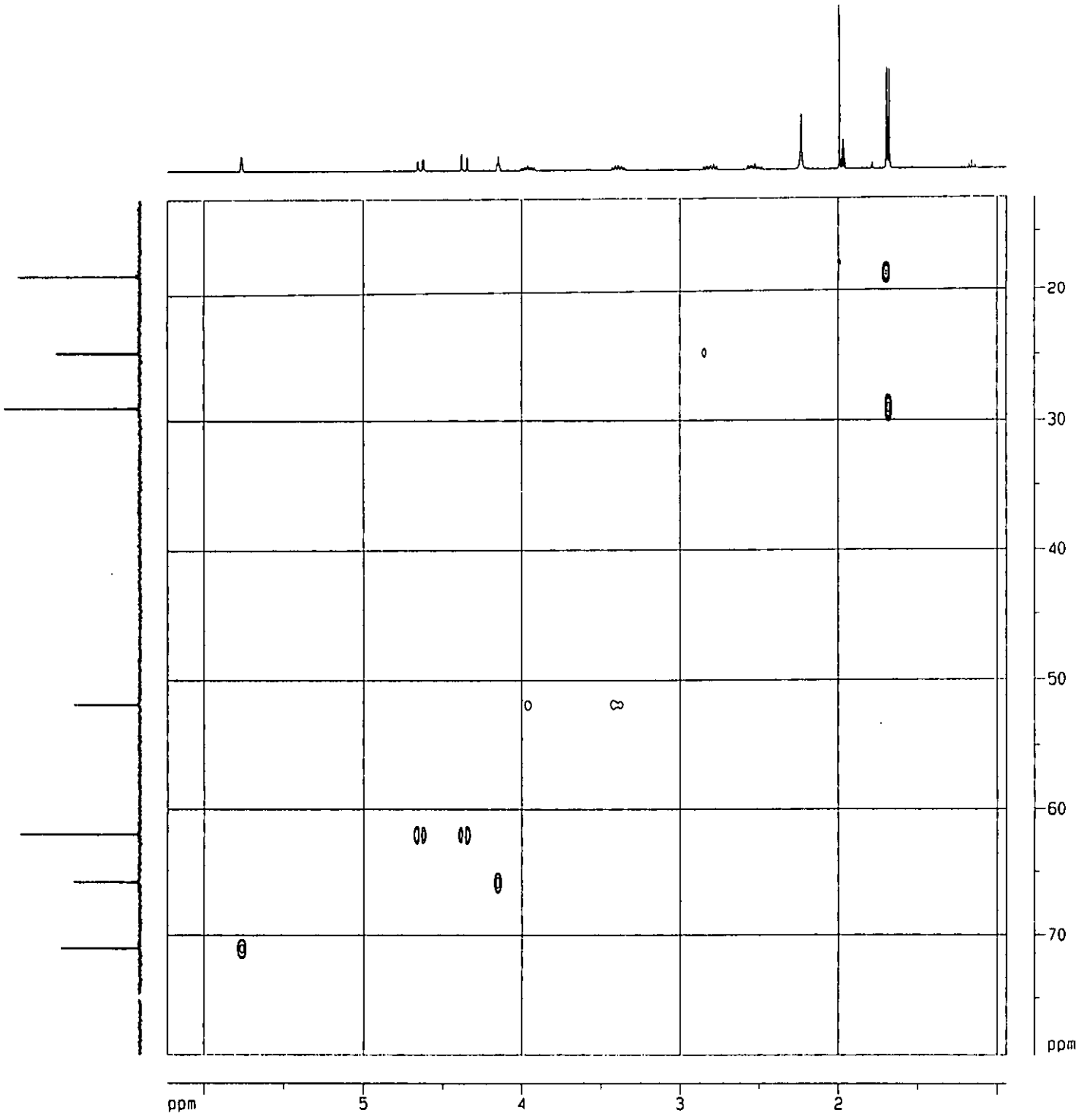
SI	2048
SF	400.1300000 MHz
WDW	USINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	2048
MC2	TPPI
SF	100.6127290 MHz
WDW	SINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	9.441 ppm
F2LO	3777.57 Hz
F2PHI	0.763 ppm
F2HI	305.35 Hz
F1PLO	178.874 ppm
F1LO	17996.96 Hz
F1PHI	9.841 ppm
F1HI	990.16 Hz
F2PPMCM	0.57852 ppm/cm
F2HZCM	231.48149 Hz/cm
F1PPMCM	11.26882 ppm/cm



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DS	16
SWH	3472.222 Hz
FIDRES	3.390842 Hz
AQ	0.1475060 sec
RG	181
DW	144.000 usec
DE	7.50 usec
TE	300.0 K
P1	10.25 usec
p2	20.50 usec
P3	5.50 usec
p4	11.00 usec
d0	0.00000300 sec
CNST2	145.0000000
d2	0.00344828 sec
D1	1.50000000 sec
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NUC1	1H
PL1	-6 00 dB
PL2	-6.00 dB
SFO2	100.6222226 MHz
NUC2	13C
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PL12	12.00 dB
CPDPRG2	garp
PCPD2	85 00 usec
INO	0 0000147D sec

F1 - Acquisition parameters

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TD	256
SFO1	100 6222 MHz
FIDRES	66 432023 Hz
SW	169.016 ppm

F2 - Processing parameters

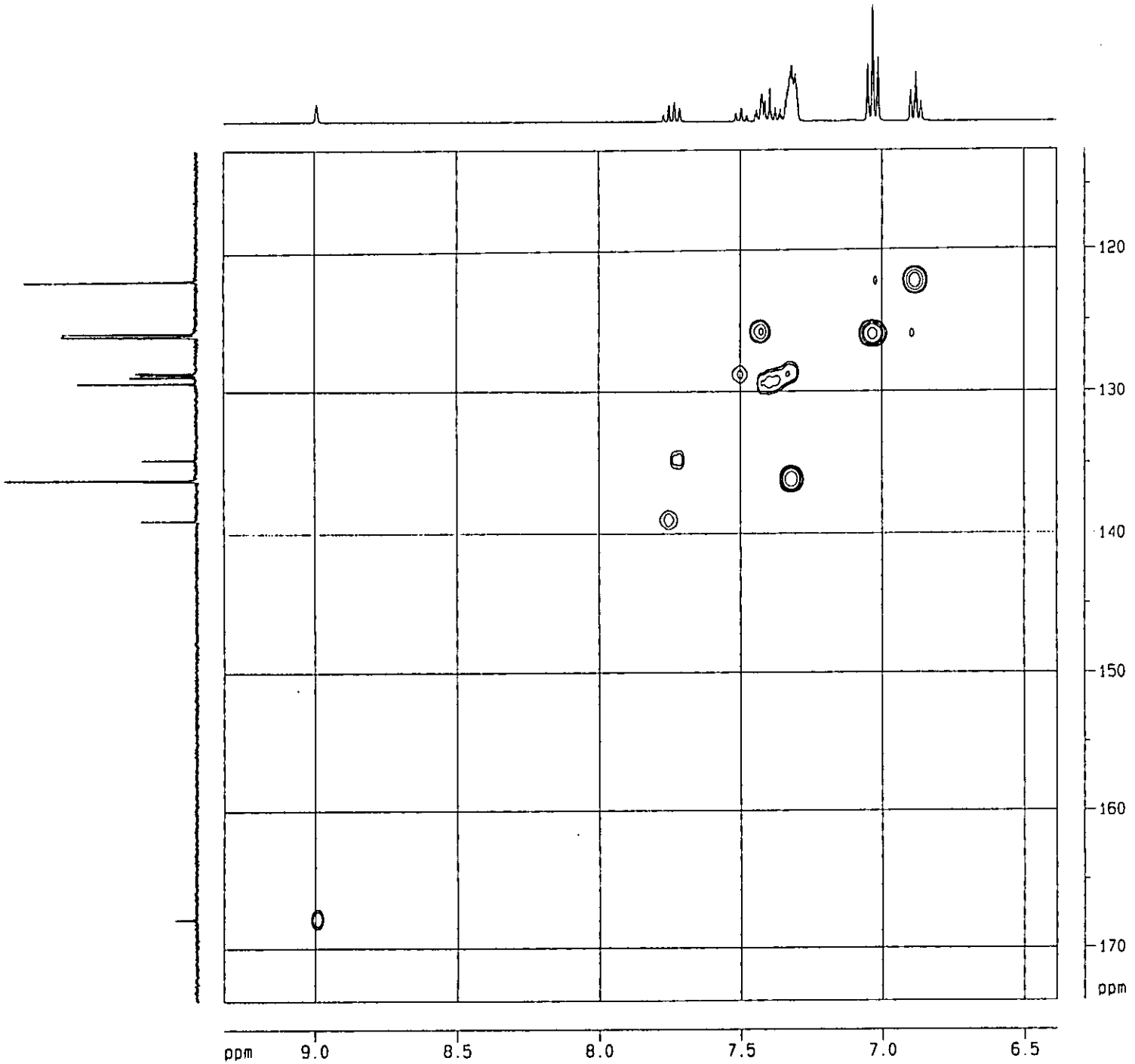
SI	2048
SF	400 1300000 MHz
WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	2048
MC2	IPPI
SF	100.6127290 MHz
WDW	SINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PL0	6.229 ppm
F2L0	2492.44 Hz
F2PHI	0.941 ppm
F2HI	376.56 Hz
F1PL0	79.501 ppm
F1L0	7998.82 Hz
F1PHI	12.400 ppm
F1HI	1247.58 Hz
F2PPMCM	0.35253 ppm/cm
F2HZCM	141.05902 Hz/cm
F1PPMCM	4.47341 ppm/cm
F1HZCM	498.08243 Hz/cm



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PROCNO	1

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TE	300.0 K
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p2	20.50 usec
P3	5 50 usec
p4	11.00 usec
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PL2	-6 00 dB
SFO2	100.6222226 MHz
NUC2	13C
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PL12	12.00 dB
CPDPRG2	garp
PCPD2	85.00 usec
INO	0 00001470 sec

F1 - Acquisition parameters

MDD	4
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SFO1	100.6222 MHz
FIDRES	66.432823 Hz
SW	169.016 ppm

F2 - Processing parameters

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WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	2048
MC2	TPPI
SF	100.6127290 MHz
WDW	SINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	9.318 ppm
F2LO	3728.40 Hz
F2PHI	6.386 ppm
F2HI	2555.17 Hz
F1PLO	173.839 ppm
F1LO	17490.41 Hz
F1PHI	112.515 ppm
F1HI	11320.46 Hz
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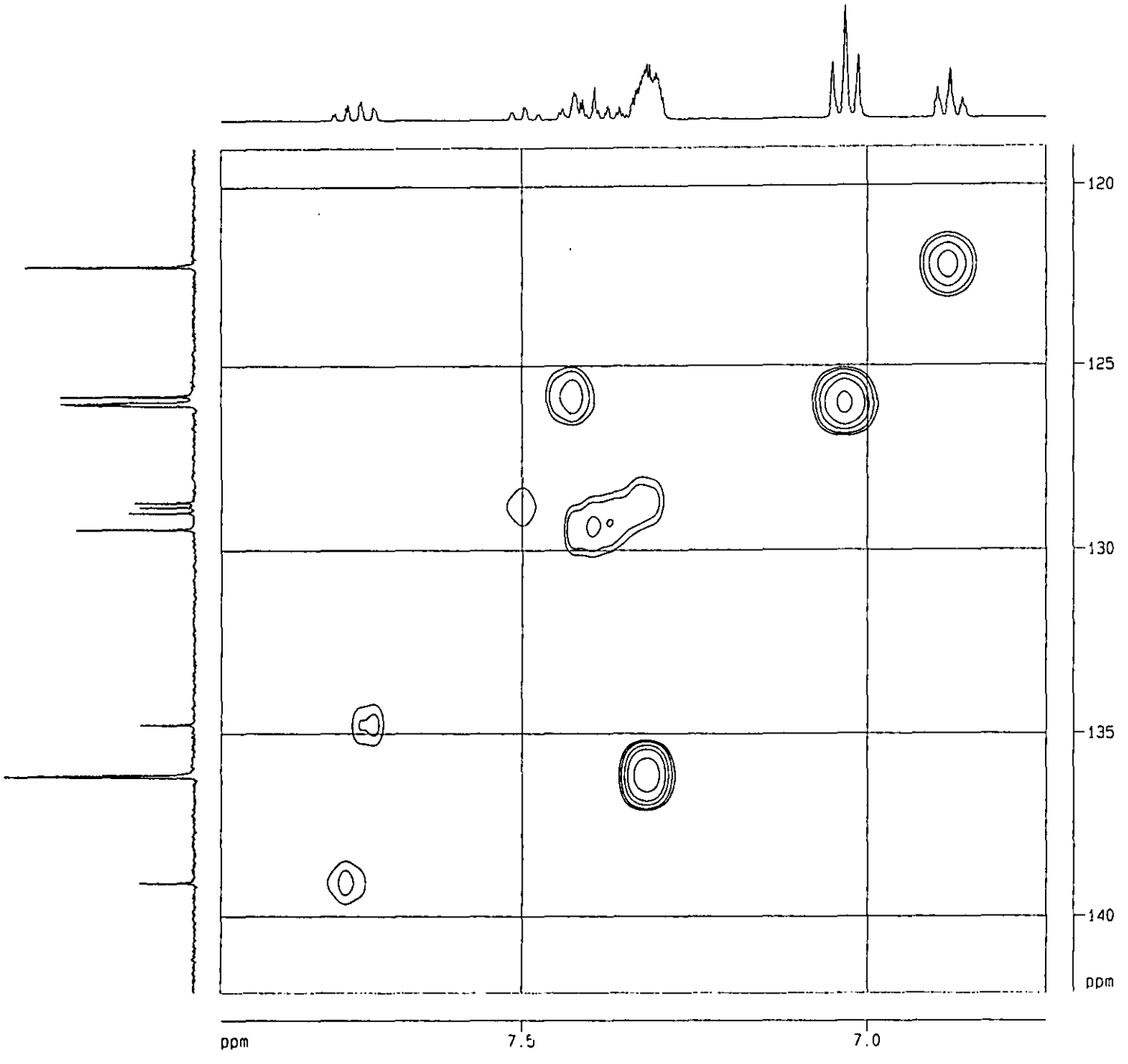
F2HZCM	78.21542 Hz/cm
F1PPMCM	4.08825 ppm/cm
F1HZCM	411.32993 Hz/cm



Current Data Parameters

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PROCNO	1

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SOLVENT	DMSO
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DS	16
SWH	3472.222 Hz
FIDRES	3.390842 Hz
AQ	0.1475060 sec
RG	181
DW	144.000 usec
DE	7.50 usec
TE	300.0 K
P1	10.25 usec
p2	20.50 usec
P3	5.50 usec
p4	11.00 usec
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CNST2	145.0000000
d2	0.00344828 sec
D1	1.50000000 sec
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NUC1	1H
PL1	-6.00 dB
PL2	-6.00 dB
SFO2	100.6222226 MHz
NUC2	13C
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PL12	12.00 dB
CPDPRG2	garp
PCPD2	85.00 usec
IN0	0.00001470 sec

F1 - Acquisition parameters

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SFO1	100.6222 MHz
FIDRES	66.432823 Hz
SW	169.016 ppm

F2 - Processing parameters

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WDW	QSINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	2048
MC2	TPPI
SF	100.6127290 MHz
WDW	SINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	7.932 ppm
F2LO	3174.00 Hz
F2PHI	6.742 ppm
F2HI	2697.59 Hz
F1PLO	142.145 ppm
F1LO	14301.64 Hz
F1PHI	118.953 ppm
F1HI	11968.18 Hz
F2PPMCM	0.07936 ppm/cm
F2HZCM	31.76088 Hz/cm
F1PPMCM	1.54616 ppm/cm