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New systems for catalytic asymmetric epoxidation

by Benjamin R. Buckley

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ABSTRACT

NEW SYSTEMS FOR CATALYTIC ASYMMETRIC EPOXIDATION

BENJAMIN R. BUCKLEY

This thesis describes the catalytic asymmetric epoxidation of olefins mediated by oxaziridinium salts. The introduction highlights some of the most successful methods for preparing chiral oxiranes and hints at the synthetic utility of this versatile molecule.

The second chapter is dedicated to our efforts to synthesize chiral iminium salts as catalysts for asymmetric epoxidation. The first part of this chapter describes previous Page group findings and leads on to the current author's efforts in this area. Initial results from modified amino acids, cyclo-condensed to form dihydroisoquinolinium salts, showed that an aromatic unit at C4 of our catalysts was vital for asymmetric induction. Following this, several catalysts substituted at the 4-position of the aromatic functionality were tested, and found to be effective mediators for asymmetric epoxidation. Triphenylethylene was epoxidized with up to 71 % ee when using oxone as the stoichiometric oxidant.

Modification of the "backbone" of the catalyst was also tested to see what effect replacing the dihydroisoquinolinium moiety would have. Initially this was replaced by a biphenyl structure fused to form a seven-membered azepinium salt. These catalysts were found to be more reactive than their dihydroisoquinolinium counter-parts, but the selectivity pattern was somewhat different, with up to 63 % ee for 1-phenylcyclohexene oxide when using oxone as the stoichiometric oxidant. Further modification, incorporating a binaphthyl unit as the "backbone", resulted in up to 95 % ee in the epoxidation of 1-phenyl-3,4-dihydronaphthylene.

Development of a new stoichiometric oxidant, tetraphenylphosphonium monoperoxysulfate, which is soluble in many organic solvents, has allowed epoxidation reactions to be carried out at sub-zero temperatures. This has resulted in the highest reported ee for oxaziridinium salt mediated epoxidation (97 % ee) and the highly enantioselective synthesis of the anti-hypertensive agent levromakalim. 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 characterization of the compounds mentioned in the previous chapter.

X-ray reports regarding the crystallographic representation of the structures presented in chapter two are provided in appendix A. Appendix B contains the analytical spectra for the determination of enantiomeric excess of the epoxides.

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However, without the spark of interest in the chemical sciences developed by my friendship with Gavin Jack and a merit chemistry set, as well as my chemistry teachers at school and later Dr Ken Williamson at MMU, I would of, no doubt, become a professional footballer!

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To My Parents and Grandparents

ABBREVIATIONS

Å	Ångström
Ac	acetyl
$[\alpha]_D$	specific optical rotation at the sodium D line
AIBN	2,2'-azobis-(2-methylpropionitrile)
aq.	aqueous
Ar	aryl
arom.	aromatic
BINAP	binaphthalene
BINOL	1,1'-bi(2-naphthol)
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
bp	boiling point
ⁿ Bu	normal butyl
^t Bu	<i>tert</i> -butyl
°C	degrees Celsius
c	concentration
cat.	catalyst (catalytic amount)
cm ⁻¹	wavenumber
conc.	concentrated
conv.	conversion
CSA	camphorsulfonic acid
Cbz	benzyloxycarbonyl
δ	chemical shift
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
de	diastereomeric excess
DIBAL	diisobutylaluminium hydride
DIOX	1,3-dioxane
DMDO	dimethyldioxirane
DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide

DMM	dimethoxymethane
DMP	2,2-dimethoxypropane
DMSO-d ₆	dimethyl sulphoxide (deuteriated)
Δ	reflux
EDCI	1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride
EDTA	ethylenediamine tetraacetic acid
ee	enantiomeric excess
eq	equivalent
Et	ethyl
EtOH	ethanol
h	hour(s)
hfc	(heptafluoropropylhydroxymethylene)camphorato
HPLC	high performance liquid chromatography
IPC	isopinocampheylamine
g	gram(s)
IR	infra red
<i>J</i>	coupling constant
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
m	molar
<i>m</i> -CPBA	<i>m</i> -chloroperbenzoic acid
Me	methyl
MeOH	methanol
MHz	megahertz
min	minute(s)
mmol	millimole(s)
ml	millilitre(s)
m.p.	melting point
MS	molecular sieves
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NMM	<i>N</i> -methyl morpholine
NMR	nuclear magnetic resonance
Nu	nucleophile

NOE	nuclear Overhauser effect
Tf	trifluoromethanesulfonate
Oxone	potassium monoperoxysulphate
PDC	pyridinium dichromate
Pd/C	palladium on charcoal
Ph	phenyl
ppm	parts per million
PPTS	pyridinium toluene- <i>p</i> -sulfonate
PTC	phase-transfer catalyst
PTSA	toluene- <i>p</i> -sulfonic acid
ⁱ Pr	isopropyl
psi	pounds per square inch
quat.	quaternary
R	alkyl
rt	room temperature
salen	salicylideneaminato ligand
SET	single electron transfer
s.m.	starting material
S _N 1	nucleophilic substitution (unimolecular)
S _N 2	nucleophilic substitution (bimolecular)
TBAB	tetrabutylammonium bromide
TBACl	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBHP	tetrabutylhydrogen peroxide
TEMPO	2,2,6,6-tetramethyl-piperidine- <i>N</i> -oxyl free radical
TFA	trifluoroacetic acid
TFAP	2,2,2-trifluoroacetophenone
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
TPPP	tetraphenylphosphonium monoperoxysulphate
Ts	<i>p</i> -tolylsulfonyl
Z	benzyloxycarbonyl

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Chapter One

Introduction

1.0 Introduction

1.1 Epoxides, general considerations.

Epoxides, or oxiranes as they are otherwise known, are reactive heterocycles and are unlike most other cyclic ethers, which are generally used as unreactive organic solvents. The reason for their reactivity can be attributed to the ring strain associated with their structure, where the bond angles are close to 60° rather than the *ca.* 109° that is expected for tetrahedral carbon or oxygen atoms. Thus, ring opening of the epoxide functionality is the driving force behind many reactions. Epoxides readily undergo reactions in which the three membered ring is opened by nucleophiles, and this can take place under neutral, basic or acidic conditions, giving the corresponding alcohols (Scheme 1).



Scheme 1: Ring opening of the epoxide functionality.

This high degree of reactivity has established the epoxide moiety as an important molecule not only in organic synthesis but also in biological systems. Epoxides are found in a large variety of natural products and as key intermediates in the synthesis of several biologically active compounds.

1.2 Epoxides found in natural products.

A growing class of naturally occurring antitumor agents are the epothilones. "Epothilones have occupied centre stage on the scenes of total synthesis, chemical biology and medicine for the last five years, no doubt because of their intriguing mode of action and unusually high potency against tumour cells".¹ The epoxide functionality is very important for biological activity within these systems, and the deoxy derivatives were less efficient against lymphoblastic leukaemic cells than the

epoxide-containing epothilone B (Figure 1). Epothilone B was found to be more effective than taxol, vinblastine and etoposide, thus making epothilone B one of the most active anti-cancer drugs to date. Novartis have found epothilone B to be a viable drug candidate and it is currently in phase II clinical trials, having been successfully evaluated in phase I clinical trials.¹

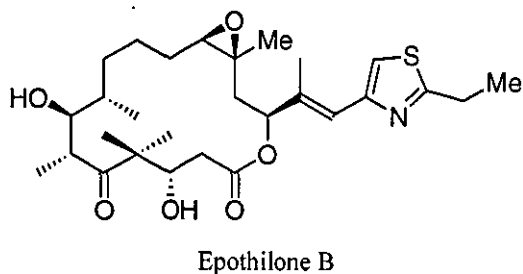


Figure 1: One of the most active anti-cancer drugs to date.

Another series of compounds with potent biological activity are the leukotrienes (Figure 2). Of these, Leukotriene C is the compound known as the slow reacting substance responsible for anaphylactic shock, the body's response to a foreign substance that provokes a severe allergic reaction, as in the case of asthma or insect stings.²

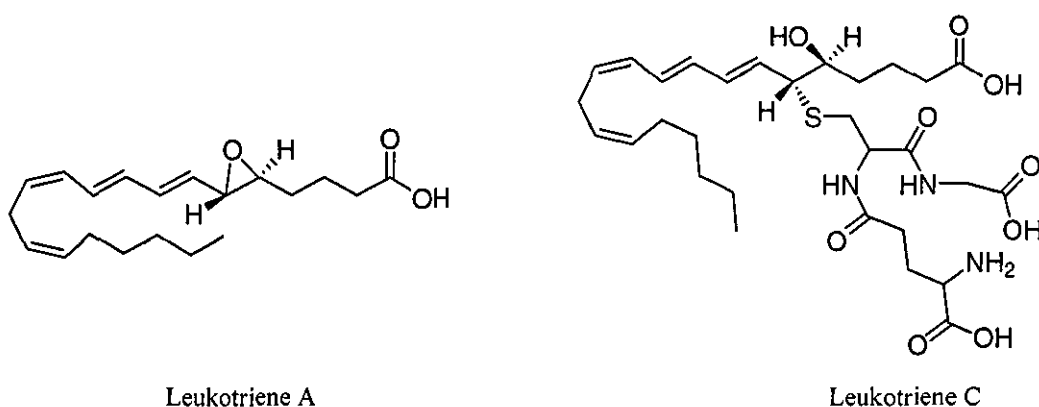


Figure 2: Two of the biologically active leukotrienes.

Leukotriene A is the biogenetic precursor of the Leukotriene C, and the transformation of A to C involves addition of glutathione (a peptide) to the oxirane.

The gypsy moth, *Lymantria dispar*, is a devastating pest of hardwood forests and fruit orchards because the larvae damage trees severely by eating their leaves. Female gypsy moths do not fly, so they must attract males by secretion of their volatile pheromones if mating is to take place. At present, sex pheromones are used as lures in traps that allow control of such pests.

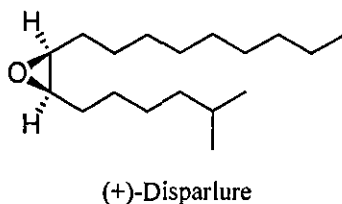


Figure 3: The sex pheromone of the gypsy moth.

The sex pheromone for the gypsy moth is a chiral oxirane (Figure 3). The dextrorotatory compound, known as disparlure, is a potent attractant to male gypsy moths while the other enantiomer, the laevorotatory compound, has no activity. This is just one example of biological systems that recognise the members of a pair of enantiomers as different compounds and as a consequence, different responses are observed.

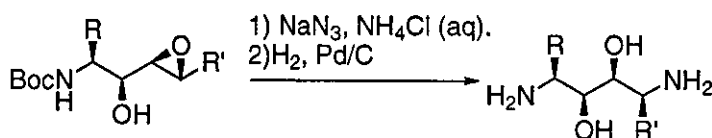
The synthesis of enantiopure compounds is achieved through a number of methods: resolution, separation of diastereomers, chromatographic separation of enantiomers, or asymmetric synthesis. The latter may be achieved by chiral auxiliary methods or chiral reagents. More importantly, catalytic asymmetric synthesis is the most elegant and challenging approach. This has not gone unnoticed in the pharmaceutical and agrochemical industries which have invested time and money to advance technology in this area.

1.3 Epoxides as versatile synthetic intermediates.

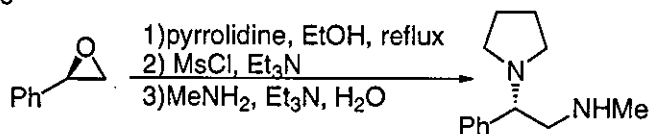
The usefulness of epoxides as key intermediates in organic synthesis is well documented. There are plethoras of elegant synthesis using this moiety and some of these will touched upon later. Of the many synthetically useful examples chiral

epoxides have been successfully used to give enantiomerically enriched 1,2-aminoalcohols,³ by attack of the epoxide with either ammonia or sodium azide; 1,2-diamines,⁴ by ring opening with a secondary amine and subsequent aziridinium formation followed by attack of a primary amine; and aziridines,⁵ through reaction of the epoxide with sodium azide followed by treatment with triphenylphosphine (Scheme 2).

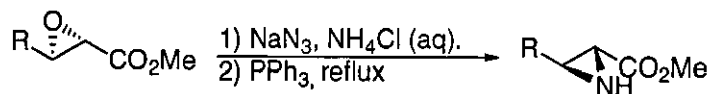
1,2-amino alcohols



1,2-diamines



Aziridination

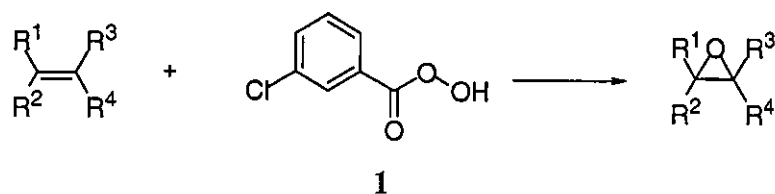


Scheme 2: Some useful manipulations of the epoxide functionality.

1.4 Achiral synthesis of epoxides.

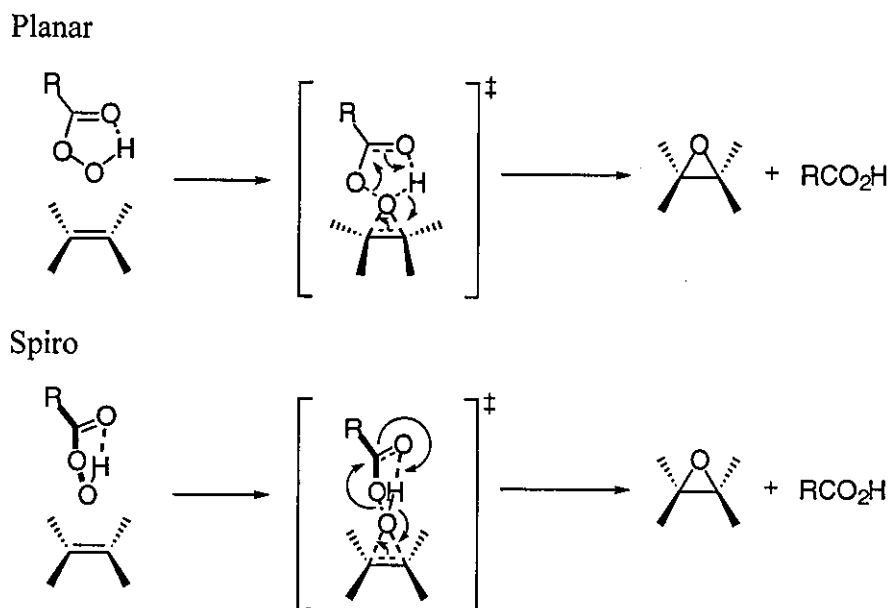
The most widely used method for the production of epoxides is through the oxidation of alkenes using organic peracids and was first discovered in 1909 by Prileschaev.⁶ The oxidants required for this type of reaction are generally made from hydrogen peroxide. These are usually perbenzoic acid, its substituted derivatives or, mainly used in industry, aliphatic peracids.

Of the percarboxylic acids, commercially available *m*-chloroperbenzoic acid (*m*-CPBA) (**1**) is the most favoured and inert solvents such as dichloromethane, chloroform and benzene are commonly used in the reaction media (Scheme 3).



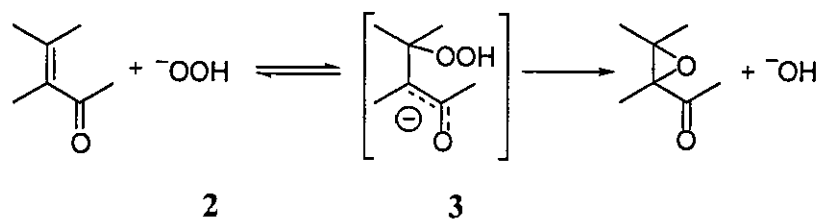
Scheme 3: Epoxidation of alkenes mediated by *m*-CPBA.

Peracid oxidation is an electrophilic process in which the driving force of the reaction is provided by the electron donating nature of the alkene double bond and the electron accepting nature of the peracid group. The transition state of this type of reaction was originally believed to be planar or “butterfly”.⁷ However, recent calculations favour the spiro transition state (Scheme 4).⁸ The transfer of oxygen is concerted and hence the reactions are stereospecific.



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

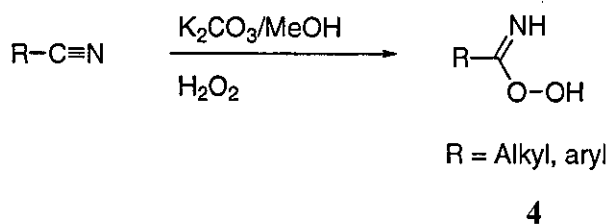
Hydrogen peroxide is important in the production of oxidizing agents but enones can be directly oxidized by this compound. Weitz and Scheffer described the first method,⁶ where the oxidation is performed with an alkaline source of hydrogen peroxide. A reversible attack by the nucleophilic hydroperoxy anion (2), in a conjugated enone system, followed by ring closure and hydroxide elimination from the intermediate enolate anion (3), affords the epoxide (Scheme 5).



Scheme 5: Hydrogen peroxide mediated epoxidation.

Good yields are generally observed for this type of reaction; however, it is non-stereospecific, due to the extended life time of the intermediate enolate anion, which has time to rotate around the alpha and beta carbon-carbon bond. Oxides of transition metals are often used as catalysts with hydrogen peroxide to afford the epoxides of electron poor alkenes.

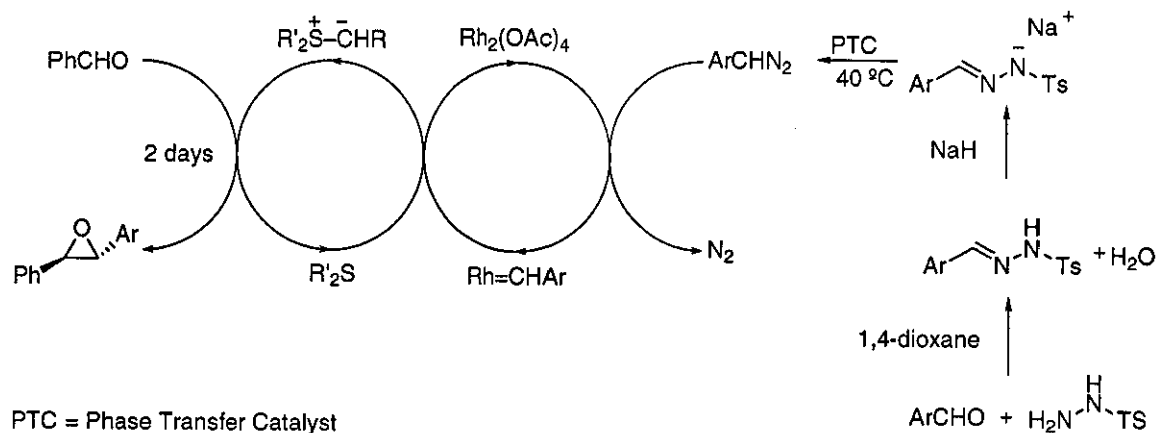
Payne has also reported that alkenes present in an alkaline solution of hydrogen peroxide can be epoxidized. The presence of a nitrile is required and alkenes are epoxidized in good to excellent yields.^{9,10} It is thought that the reaction proceeds through a peroxyimidic acid (4), which is the addition adduct resulting from nucleophilic attack of hydroperoxide on the nitrile carbon atom, but this intermediate has never been isolated (Scheme 6). In the absence of substrate, the hydroperoxyimine (or peroxyimidic acid) disproportionates to give the corresponding primary amide and molecular oxygen, and this process constitutes the Radziszewski reaction.⁹ 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 and therefore retention of alkene geometry is observed.



Scheme 6: Formation of Peroxyimidic acid, the reactive intermediate in the Payne epoxidation of alkenes.

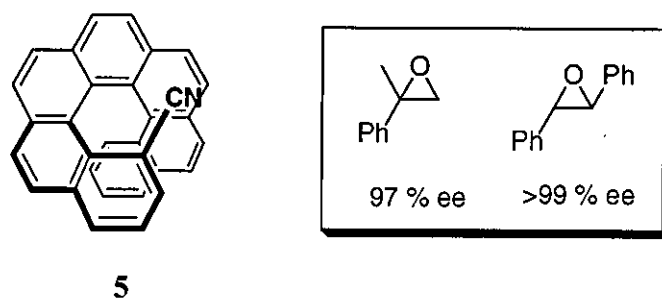
1.5 Catalytic Asymmetric Epoxidation methods.

Approaches to chiral epoxides from carbonyl compounds are known and these reactions are usually mediated by chiral sulfur ylides and good to excellent ees have been observed (Scheme 7).^{11,12,13,14} However, epoxidation of alkenes remains the usual mode of access.



Scheme 7: The sulfur ylide approach towards enantiomerically enriched epoxides from carbonyl compounds.

Non-racemic chiral peracids are also of limited value for asymmetric epoxidation.¹⁵ A asymmetric version of the related Payne procedure, mediated by a nitrile and hydrogen peroxide, has provided high ees.¹⁶ 2-Cyanoheptahelicene (**5**) was reported to epoxidise *trans*-stilbene and α -methylstyrene under Payne conditions, with high enantiocontrol. The use of helicenes in asymmetric epoxidation, however, has not been elaborated, presumably due to the difficulty of synthesis of helicenes in enantiomerically pure form (Scheme 8).¹⁷



Scheme 8: 2-Cyanoheptahelicene as a chiral mediator in the classical Payne epoxidation.

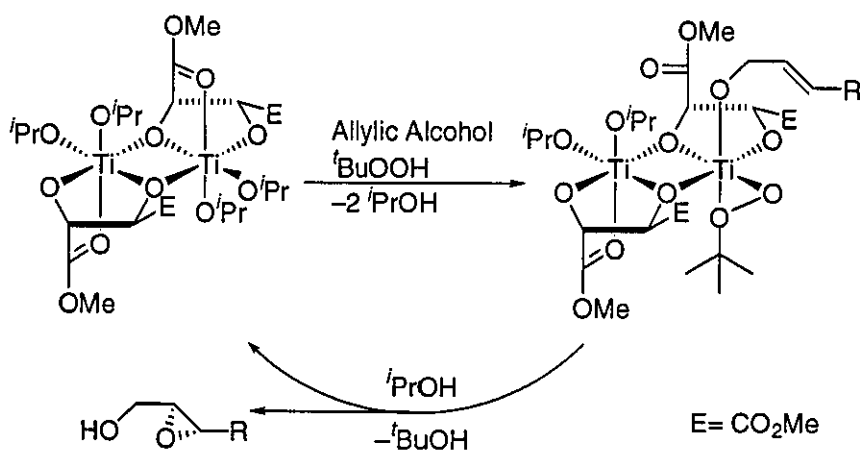
1.5.1 The Sharpless catalytic asymmetric epoxidation of allylic alcohols.

There is a large variety of systems that have been used as mediators in asymmetric epoxidation. Processes catalysed by transition metal complexes have proven to be synthetically useful, for example the Sharpless epoxidation process developed in the early 1980's. Transition metal mediated epoxidation has received much attention over the past 20 years and in this section the major accomplishments are covered, but no attempt is made to describe all of the reported approaches.

Sharpless and Katsuki first reported the highly enantioselective epoxidation of allylic alcohols in 1980.¹⁸ This process was mediated by a titanium (IV) alkoxide, a chiral tartrate ester and tertiary-butylhydroperoxide (TBHP) as the oxidant. Generally this process produced 2,3-epoxyalcohols in good yield and with enantiomeric excesses of greater than 90 % ee.

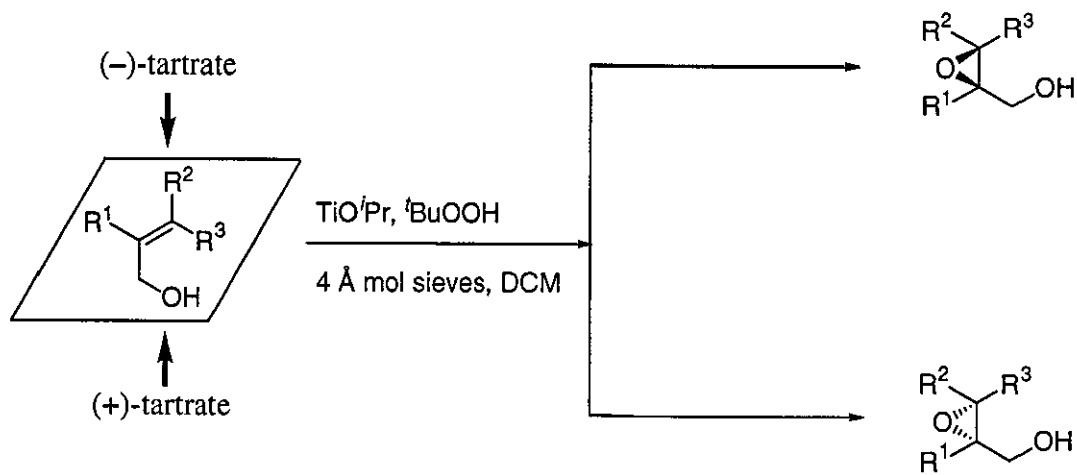
This process is now widely used in asymmetric synthesis and has established itself as one of the most important discoveries in organic chemistry in the past 25 years. This was acknowledged by the award to K. B. Sharpless of the Nobel Prize for chemistry in 2001.

The success of this method depends on the presence of the hydroxyl group of the allylic alcohol which coordinates to the metal and binds the molecule to the chiral complex (Scheme 9). 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 9: The Sharpless epoxidation procedure.

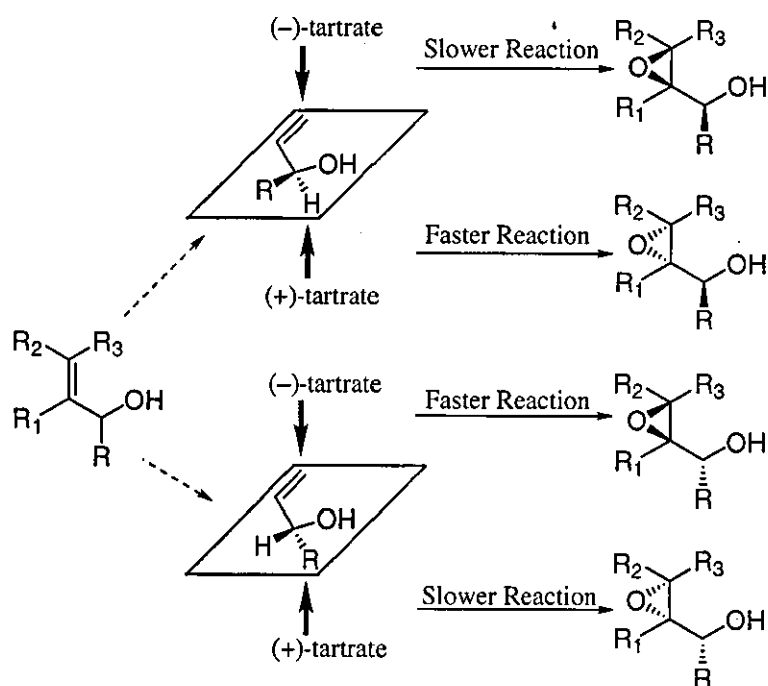
One of the most important features of this procedure is the ability to predict the absolute configuration of the epoxide produced by using a simple model (Scheme 10).¹⁹



Scheme 10: The Sharpless prediction model.

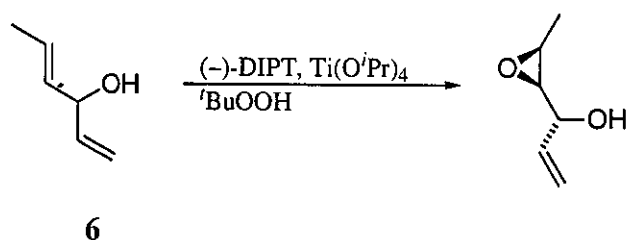
The effectiveness of this epoxidation process is indicated by the large number of differently substituted allylic alcohols which can be oxidized with high enantioselectivity. In fact nearly all types of prochiral primary allylic alcohols are epoxidized with high enantiomeric excess.

The Sharpless epoxidation of allylic alcohols which contain a substituent at C1 can also be predicted even though this is complicated by the fact that these compounds have an additional stereogenic centre (Scheme 11). Of the four possible diastereoisomers shown in Scheme, the two *syn*- isomers are disfavoured through hinderance of the approach of the tartrate by the R group, producing the corresponding *anti*-epoxides as the major products.



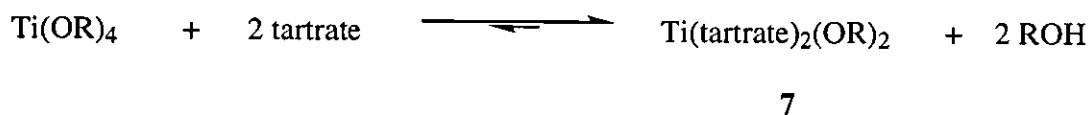
Scheme 11: Prediction of enantioselectivity for substrates containing additional chiral centres.

This method has been harnessed for kinetic resolution.¹⁹ High yields and enantioselectivities have been observed, and there are many examples in the literature. One example is shown in Scheme 12: compound (6) contains two double bonds that have the potential to undergo Sharpless epoxidation; the more nucleophilic of the two reacts more readily. One of the two enantiomers of (6) reacts faster than the other, and only one epoxide is formed, giving a yield of 35 % (out of a possible 50 %) and an enantiomeric excess of greater than 95 % ee. The unreacted alcohol is also enantiomerically enriched.



Scheme 12: kinetic resolution mediated by the Sharpless asymmetric epoxidation method.

Mechanistic studies of the Sharpless epoxidation have revealed the key step in the reaction. In solution, titanium(IV) alkoxides undergo rapid ligand exchange with other alcohols.^{19,20,21} Upon reaction with the tartrate ester, the equilibrium lies on the side of the chelate (7) (Scheme 13).



Scheme 13: Titanium(IV) alkoxides undergo rapid ligand exchange with alcohols.

Epoxidation will only occur when the catalyst ligands (alkoxides RO^-) have been completely replaced with *tert*-butyl hydroperoxide and the allylic alcohol. After epoxidation takes place the titanium complex releases the product and "re-loads" itself for the next allylic alcohol. The active species is thought to be dimeric and is shown in Figure 4.²²

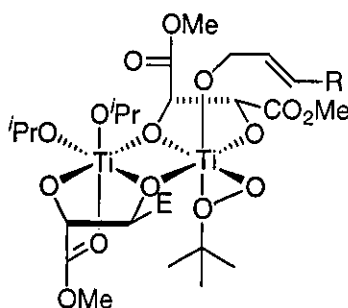
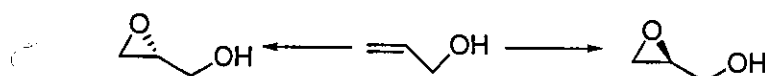
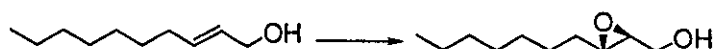


Figure 4: The dimeric active species believed to be involved in the asymmetric epoxidation process.

The Sharpless asymmetric epoxidation is limited in that the substrate must possess a group which can coordinate with the catalyst, a hydroxyl group and therefore the procedure is limited to allylic alcohols. Despite this, the catalytic procedure has prompted much interest from industrial companies and has been scaled up by ARCO for the production of both enantiomers of glycidol (Scheme 14) on at least a 600 g/mol scale.²³ This process has also been operated by Upjohn to give enantiomerically pure (3-heptyl-oxiranyl)-methanol (Scheme 15).²³

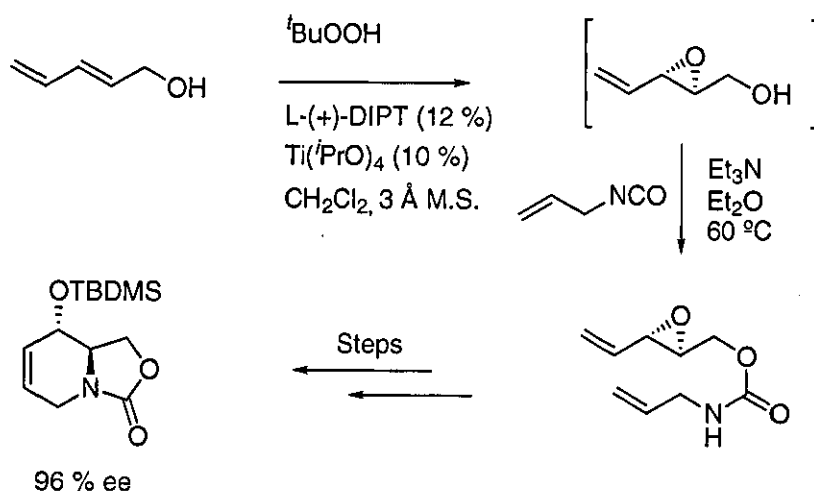


Scheme 14: ARCO's scaled up synthesis of glycidol using the Sharpless asymmetric epoxidation.



Scheme 15: Upjohn's synthesis of (3-heptyl-oxiranyl)-methanol using the Sharpless method.

The Sharpless asymmetric epoxidation has also been used to produce key intermediates in the syntheses of various natural and biologically active compounds. Percias and Riera have recently used this method to access an intermediate in glycosidase inhibitor synthesis (Scheme 16).²⁴



Scheme 16: Percias and Riera's synthesis of a key intermediate of glycosidase inhibitors utilising the Sharpless asymmetric epoxidation.

1.5.2 Metalloporphyrins as catalysts for asymmetric epoxidation.

The Sharpless procedure is effective for the asymmetric epoxidation of allylic alcohols; however, obtaining high enantioselectivities in the epoxidation of alkenes bearing no functionality remains a challenging problem. It is difficult to obtain high enantioselectivity in the asymmetric epoxidation of unfunctionalized 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 due to the large range of substrates available.

Interest in transition metal porphyrin complexes for asymmetric epoxidation arose from Groves discovery that Fe(III) porphyrin complexes are models for cytochrome P-450 monooxygenase.²⁵ In 1983 Groves and Meyers described the first example of catalytic asymmetric epoxidation of simple olefins mediated by chiral porphyrin complexes (Figure 5).²⁶ Hence cytochrome P450 analogues based upon porphyrin-transition metal complexes have been used in an attempt to mimic the biosynthetic pathway of epoxide formation.²⁷ Many chiral complexes based on cyclic polyamines/polyimines have been synthesized,²⁸ but enantioselectivities are low, and the reaction is limited in scope, styrenes usually being the best substrates.^{29,30}

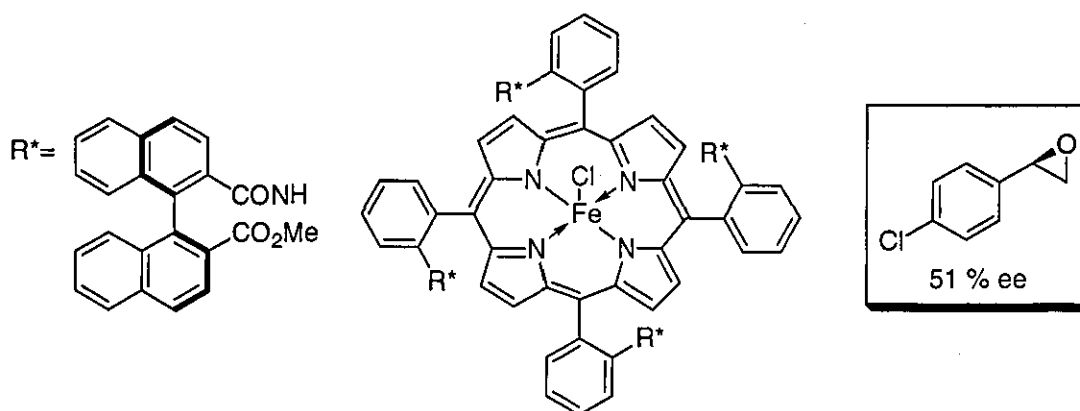


Figure 5: Groves chiral porphyrin giving 51 % ee for *p*-chlorostyrene oxide.

Many groups have been involved in the synthesis of metalloporphyrins, and these systems have encompassed a wide variety of ligands and metal centres [iron(III), manganese(III) and ruthenium(III)]. One of the most successful systems, developed

by Berkessel, employs a carbonyl ruthenium (II) metalloporphyrin and a novel D₄ symmetric ligand developed by Halterman (Figure 6),^{31,32} dihydronaphthylene oxide was epoxidized in 77 % ee. Greater enantiomeric excesses have been achieved by other groups, but the metalloporphyrin catalysts used are relatively inaccessible.^{30,33}

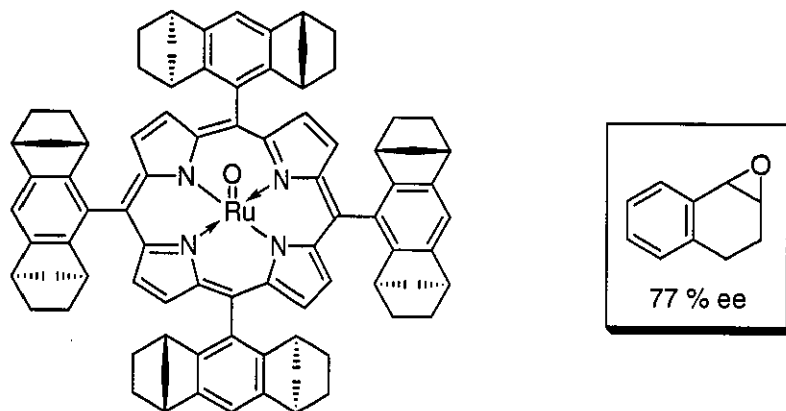


Figure 6: Berkessel's carbonyl ruthenium (II) metalloporphyrin.

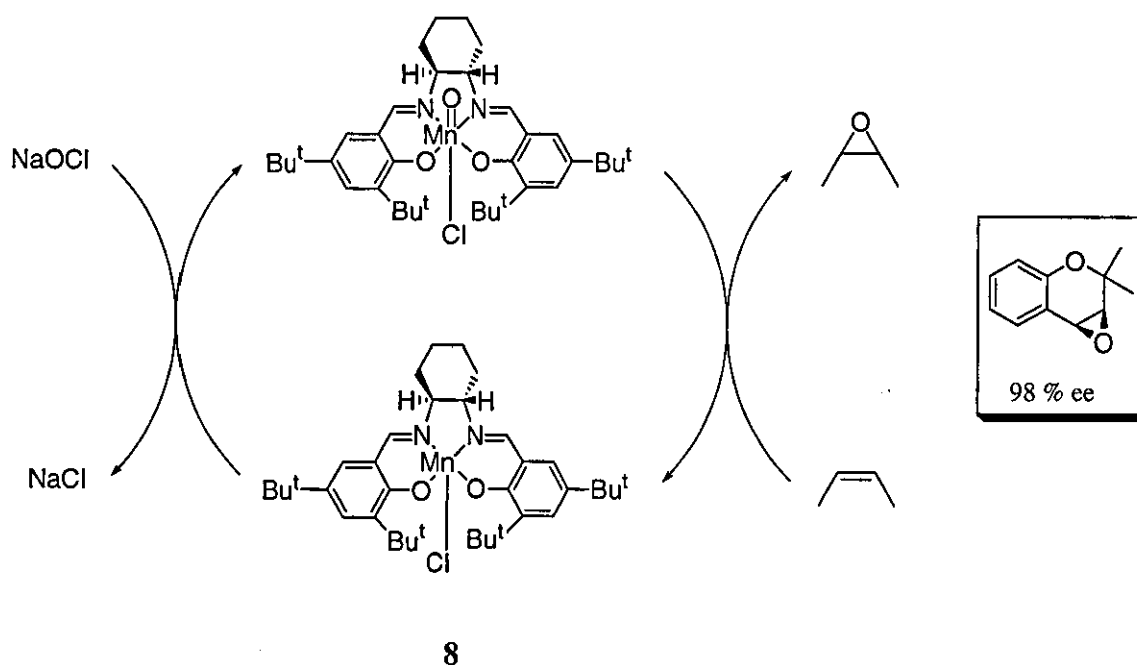
The usually poor yielding multi-step synthesis of these types of catalyst unfortunately limits this approach to chiral epoxides. However, recent development of the related salen systems which are easily accessed and exhibit excellent ees are an attractive alternative.

1.5.3 Chiral Salen Complexes for asymmetric epoxidation.

Achiral salen complexes were first shown to catalyse the epoxidation of unfunctionalized alkenes by Kochi in 1986.^{34,35} In contrast to the related metalloporphyrins, salen complexes are not completely planar, and are able to contain asymmetric centres at the tetrahedral carbon atoms near the metal/reaction site. This is the key feature for the origin of the improved asymmetric induction observed in the catalytic epoxidation mediated by salen complexes.³⁶

1.5.3.1 The Jacobsen Epoxidation.

Jacobsen has produced a variety of catalysts using Manganese(III) salen complexes of chiral Schiff bases;^{19,23,37,38,39} these permit the epoxidation of a range of alkyl- and aryl- substituted olefins. The ligands are generally derived from chiral 1,2-diamines and substituted salicylaldehydes. Epoxidations are usually carried out with 1-10 mol % of the chiral manganese(III) salen complex and 1 or 2 equivalents of a stoichiometric oxidant. A variety of oxidizing agents have successfully been employed including dioxiranes,⁴⁰ periodates,⁴¹ peracids,⁴² hydrogen peroxide,⁴³ Oxone,⁴⁴ and molecular oxygen.⁴⁵ However, the usual method employs sodium hypochlorite (bleach).^{46,47}



Scheme 17: Jacobsen's most effective chiral salen complex for asymmetric epoxidation.

After the synthesis of many salen catalysts, Jacobsen discovered several factors which govern the level of enantioselectivity induced, and that asymmetric induction was highly dependent on the electronic properties of the chiral ligand.⁴⁶ The bulky tertiary butyl and electron donating groups were therefore introduced into the catalyst structure, and the catalyst (**8**) was produced giving excellent enantiomeric excesses ranging from 85 to 98 % ee for *cis*-disubstituted alkenes. This has proved to be Jacobsen's most successful catalyst to date (Scheme 17).⁴⁸

1.5.3.2 Katsuki's Salen Complex.

Katsuki has also independently reported chiral manganese(III) catalysts for asymmetric epoxidation, and these focus on a chiral residue attached at the aromatic carbon *ortho* to the phenolic group.⁴⁹ These are also good catalysts for asymmetric epoxidation; they differ from Jacobsen's catalysts in that the best systems contain axial chirality at the 5,5' positions as well as asymmetric centres (Figure 7).⁵⁰ This axial chirality is achieved by incorporation of enantiomerically pure binaphthyl groups in the catalyst's substructure. In comparison to the Jacobsen catalyst the Katsuki system exhibits similar enantioselectivities for *cis*-alkenes but greater enantioselectivities for *trans*-alkenes.

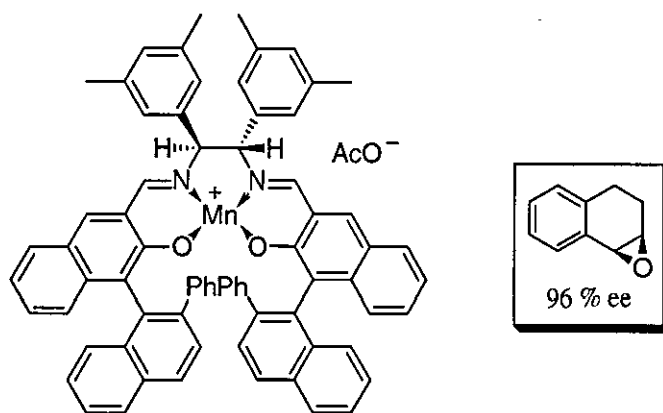
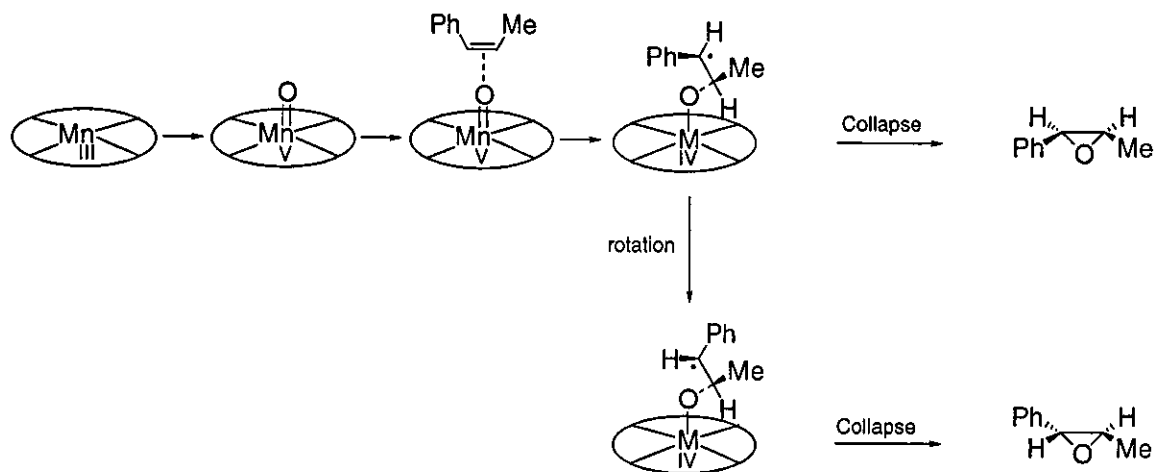


Figure 7: Katsuki's binaphthylene based Salen complex for catalytic asymmetric epoxidation.

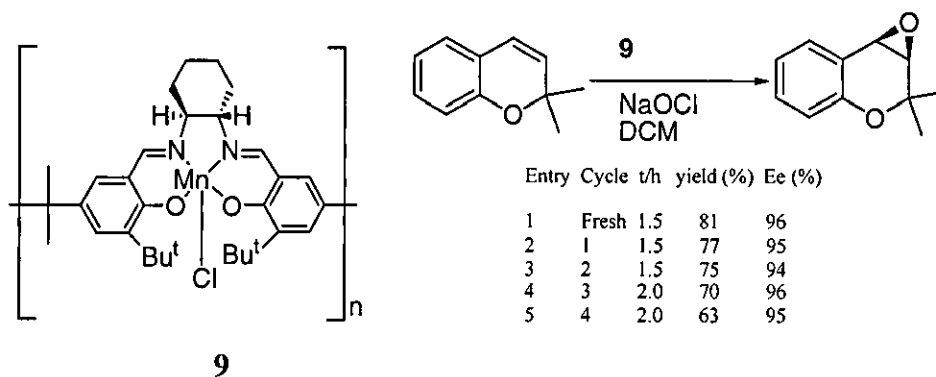
A major problem associated with the salen-mediated epoxidation method is the scrambling of olefin geometry in the epoxides of acyclic *cis*-disubstituted alkenes. This is believed to be due to the formation of radical intermediates at the metal centre. Jacobsen's proposed mechanism is highlighted in Scheme 18.⁵¹ The extent of degradation is rather dependent on the substitution pattern of the olefin, but in general no loss of geometry is observed for *cis*-dialkyl alkene substrates, and so the mechanism is believed to be concerted. Conjugated *cis*-alkenes are thought to proceed stepwise through a electron transfer process, which gives rise to radicals and hence scrambling of the double bond geometry. Mono-epoxidation of conjugated double bonds, whether *cis-cis*, *trans-trans* or *cis-trans* related all give mixtures of geometrical products. A method for increasing the *cis-trans* ratio of epoxidation products by

addition of a cinchona alkaloid has been developed by Jacobsen.⁵² However, the additive only has a limited effect on some substrates.



Scheme 18: Jacobsen's proposed mechanism for salen mediated epoxidation and possible cause of scrambling of olefin geometry.

Salen-Mn(III) complexes also undergo decomposition under the reaction conditions and cannot be recovered and re-used.⁵³ Many groups have directed their research to modifications of typical salen-Mn(III) complexes, such as polymer-supported systems.⁵⁴ These modified catalysts have been found to separate well, but this has generally compromised the catalytic activity of the complex, and ees have rarely reached that of the original salen-Mn(III) complex. Recent independent work reported by Seebach⁵⁵ and Zheng has shown some advances in this area.⁵³ Zheng has shown that a poly-salen-Mn(III) complex (**9**), which can be regarded as a polymer of Jacobsen's original salen-Mn(III) catalyst, gives consistently high ees even after being recycled up to 4 times (Scheme 19).



Scheme 19: Zheng's polymeric salen-Mn(III) complex.

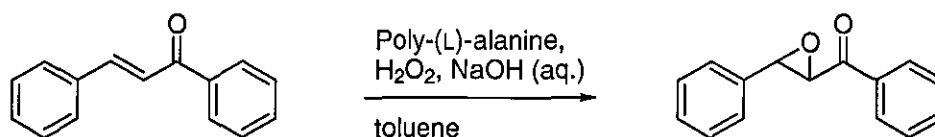
Salen catalysts have also been used for kinetic resolution of racemic alkenes,⁵⁶ allenes,⁵⁷ and racemic terminal epoxides.⁵⁸ Asymmetric epoxidation of an alkene intermediate in the synthesis of leukotriene methyl ester, an important inhibitor of phosphodiesterases, has also been achieved using this methodology.⁵⁹

The salen mediated asymmetric epoxidation has proven to be one of the most successful methods for producing unfunctionalized aryl epoxides of high enantiomeric purity. However, loss of stereospecificity, problems with catalyst turnover, and a preference for *cis*-substituted substrates renders this approach of limited value.

Over the past couple of decades there have been major advances in catalytic methods based on metal-free organic molecules. There are many advantages in using this type of system; for example the reactions can usually be performed under an aerobic atmosphere with wet solvents, and the catalysts are generally inexpensive and air-stable.⁶⁰

1.5.4 The Julià epoxidation of α,β -unsaturated ketones.

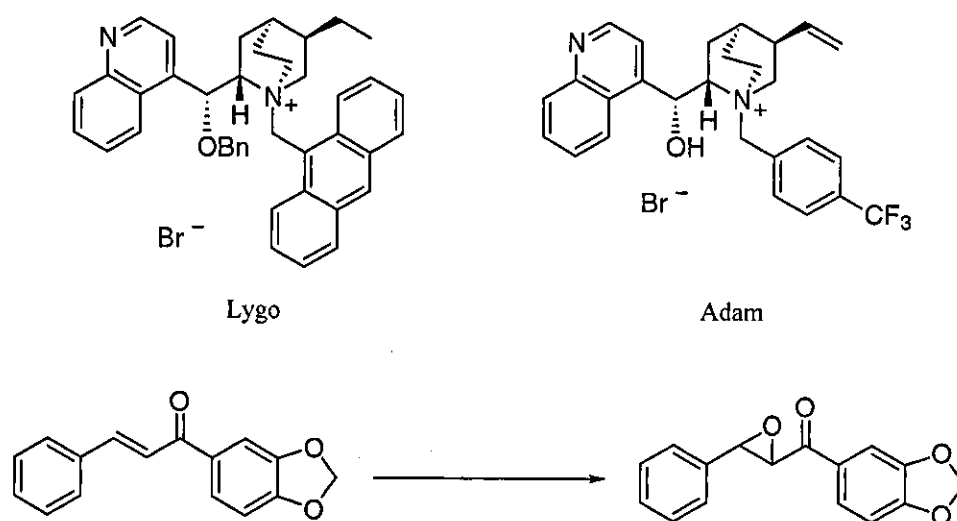
Synthetic polypeptides were found, by Julià, to epoxidize α,β -unsaturated ketones with high enantioselectivity.⁶¹ The Julià process can be easily performed at 0 °C, and using a triphasic system comprising of toluene, water and polyalanine in the presence of alkaline hydrogen peroxide, chalcone oxide was produced in 97 % ee (Scheme 20). The Julià process has become the method of choice for the epoxidation of *trans*-1,3-diarylenones. However, this methodology is extremely substrate-specific, and enones with enolisable α -protons are usually poor substrates.



Scheme 20: The Julià catalytic asymmetric epoxidation of chalcone.

Roberts has shown that the asymmetric epoxidation of chalcone can be catalysed by polyamino acid derivatives under non-aqueous conditions.⁶² This improved reaction involves the use of a urea-hydrogen peroxide complex in THF, in the presence of an organic base (DBU) and immobilized poly-(L)-leucine. Under these conditions, the reaction of chalcone derivatives and related substrates provided the corresponding epoxides in 70-99% yield and 83-95% ee within 30 minutes. Several substrates with enolisable enones have also been epoxidized successfully.⁶³

The asymmetric epoxidation of the chalcone type of substrate has also been accomplished using other types of chiral catalysts.⁶⁴ Wynberg was the first to use chiral ammonium salts, and obtained chalcone oxide with 55% ee using alkaline hydrogen peroxide as the stoichiometric oxidant and a quinine-derived quaternary ammonium salt as the chiral phase transfer catalyst.⁶⁵ More recently, Lygo re-examined the effect of the structure of the chinchona derived ammonium salt on the enantioselectivity of the process (Figure 8).⁶⁶ Optimization led to superior catalysts for the asymmetric epoxidation of 1,3-diarylenones and some substrates with aliphatic substituents. The enantioselectivities for the substrates tested ranged between 69 and 89% ee. Further modification by Adam has produced ees of up to 98%.⁶⁷

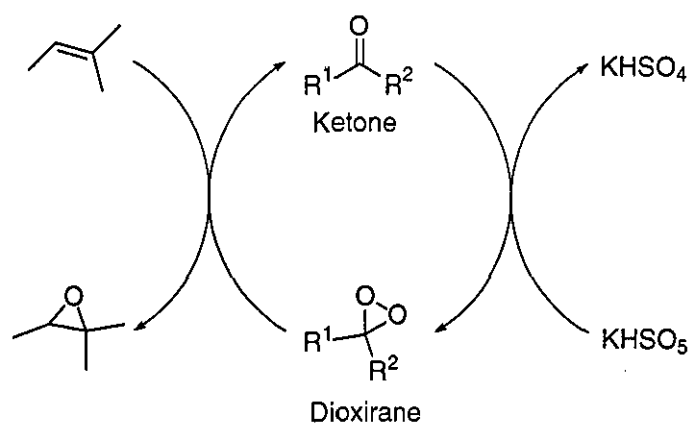


Reagents and Conditions: Lygo's PTC (10 mol%), 11% aq. NaOCl (2 eq.), toluene, 48 h, 25 C.

Figure 8: Lygo's and Adam's chinchona-derived quaternary ammonium salts for catalytic asymmetric epoxidation.

1.5.5 Dioxirane-based systems for asymmetric epoxidation.

Dioxirane-based systems for asymmetric epoxidation have received much attention over the past decade, and they have emerged as one of the most effective methods for producing enantiomerically enriched oxiranes. Their reactivity stems from the ring strain associated with the three membered ring and the relatively weak O-O bond. They are readily attacked even by poor nucleophiles such as olefins. The general method to produce a dioxirane is through the use of a ketone and a stoichiometric oxidant (usually Oxone) in either acetonitrile or dimethoxymethane (Scheme 21).



Scheme 21: Generation of dioxiranes using Oxone as stoichiometric oxidant in the epoxidation of alkenes.

Initially several research groups (Curci and Marples) studied chiral ketones as catalysts for asymmetric epoxidation, but until recently enantioselectivities with these systems were only up to *ca.* 20 % ee (Figure 9).^{68,69,70}

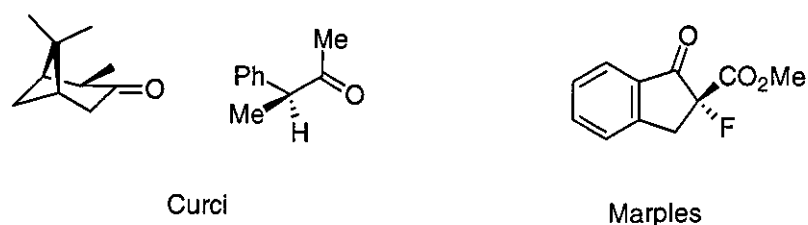
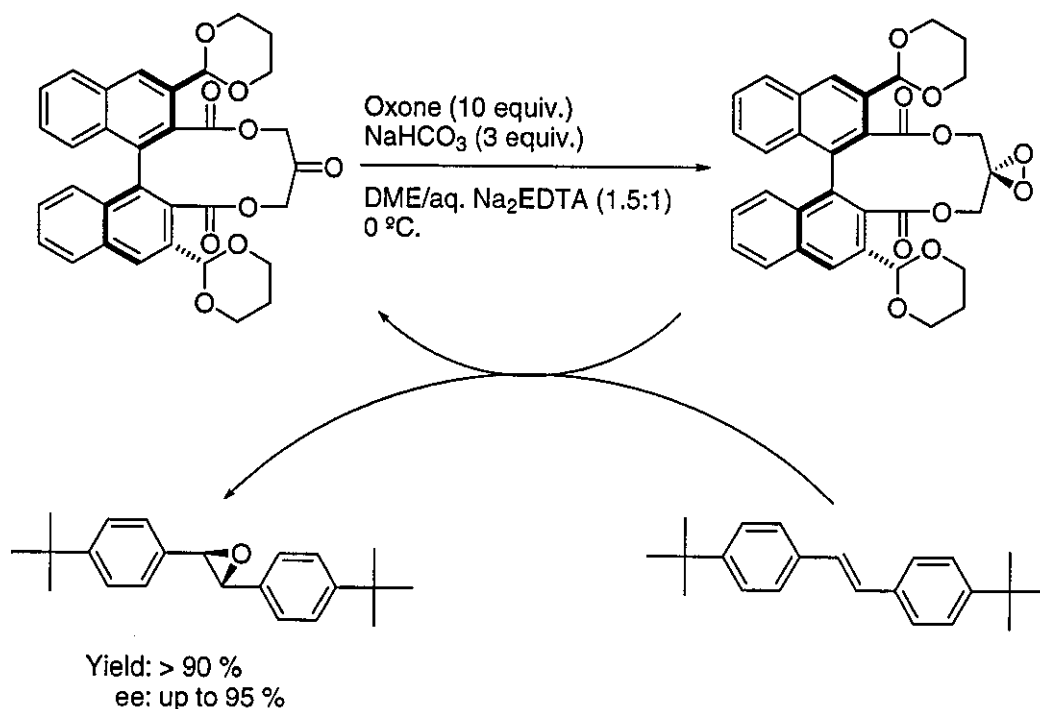


Figure 9: Initial chiral ketones screened by Curci and Marples for dioxirane-based asymmetric epoxidation.

1.5.5.1 Highly enantioselective systems developed by Yang.

In 1996 Yang first reported the asymmetric epoxidation of olefins mediated by a C₂ symmetric dioxirane generated from the corresponding ketone.⁷¹



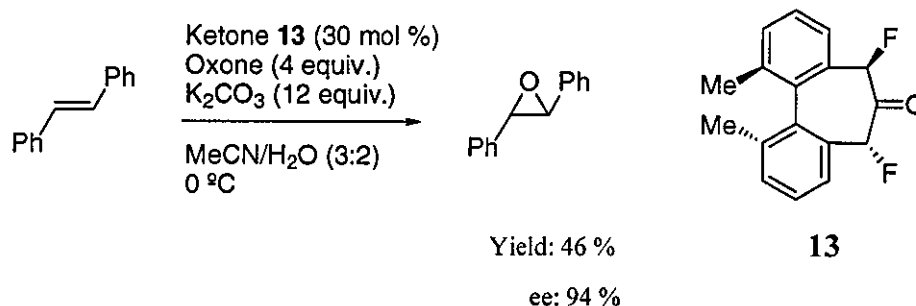
Scheme 22: Yang's chiral ketone derived dioxirane based on BINAP.

The chiral ketone was derived from BINAP, and exhibited enantioselectivities typically between 5 and 50 % ee under stoichiometric conditions, and 87 % ee in the epoxidation of *trans*-4,4'-diphenylstilbene. With modification of the original C₂ symmetric ketone and development of the reaction to run catalytically, Yang was able to increase the enantioselectivity of the process.^{72,73} With very hindered alkenes, such as *trans*-4,4'-ditert-butylstilbene, enantioselectivities of up to 95 % ee were achieved (Scheme 22).

1.5.5.2 Denmark's dioxiranes for asymmetric epoxidation.

After establishing oxo ammonium salts (Figure 10) as useful mediators in the catalytic epoxidation of several alkenes,^{74,75} Denmark developed two chiral systems which

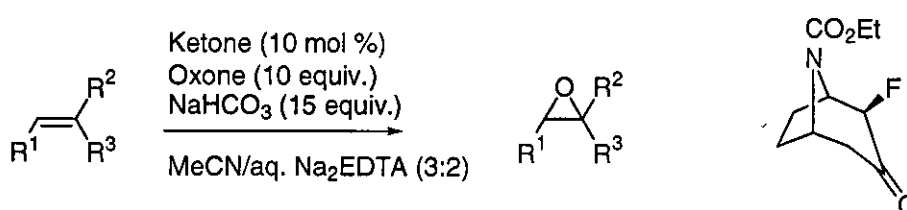
excellent enantioselectivities can be achieved with catalyst **(13)** for *trans*-olefins (Scheme 23). However, catalyst loadings are high (30 mol %).⁷⁷



Scheme 23: Denmark's most successful system containing a fluoro ketone.

1.5.5.3 Armstrong's α -fluoroketone as a precursor in dioxirane mediated epoxidation.

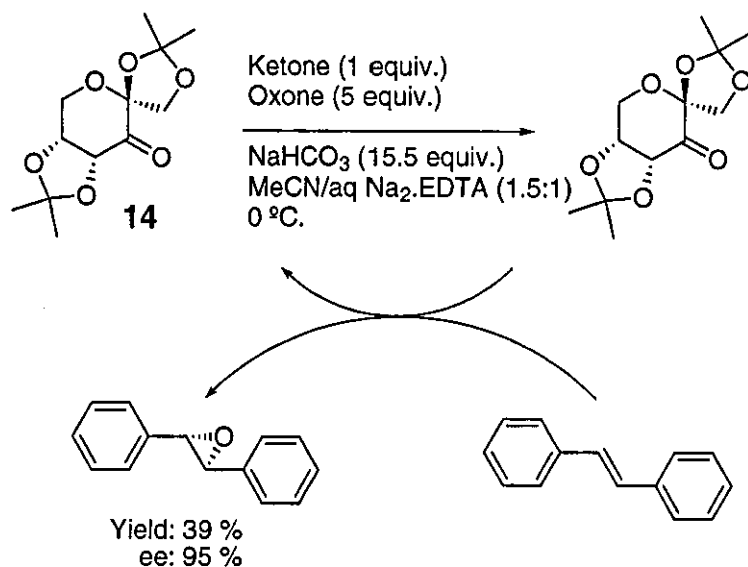
Several other attempts at producing highly enantioselective dioxirane-based catalysts for asymmetric epoxidation have been reported;^{78,79} of these Armstrong's tropinone-derived α -fluoroketone was found to be a good mediator (Scheme 24).⁸⁰ The ketone exhibited enantioselectivities in the range of 64-83 % ee for various substrates. Armstrong argued that the α -fluoro group exerts a stabilizing and directing effect by interacting with the olefinic proton in the substrate during the transition state of oxygen transfer.



1.5.5.4 Shi's highly enantioselective dioxirane epoxidation mediated by a fructose-derived dioxirane.

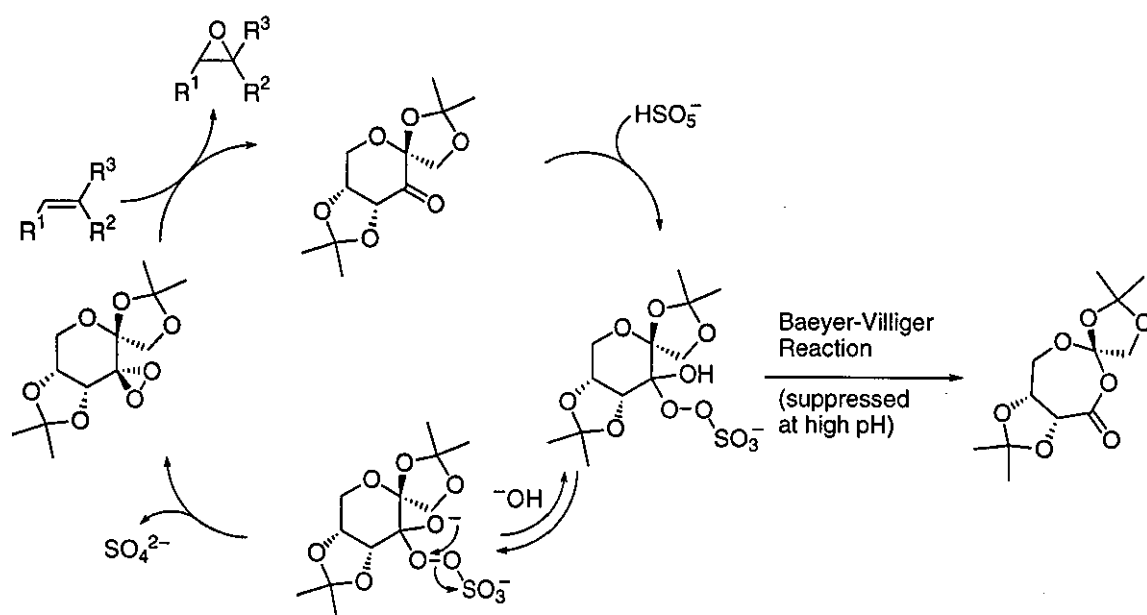
A breakthrough in dioxirane-mediated epoxidation was achieved by Shi in the late 1990's. He reported excellent ees for a wide variety of substrates using the fructose-

derived ketone (**14**).⁸¹ This catalyst is easily prepared in two steps, and typical enantioselectivities range from 80 to 95 % ee. However, the chiral ketone decomposes under the reaction conditions (pH 7-8), presumably through Baeyer-Villiger oxidation, and initially a large excess of the mediator had to be used (3 equivalents, with respect to the substrate) (Scheme 25).



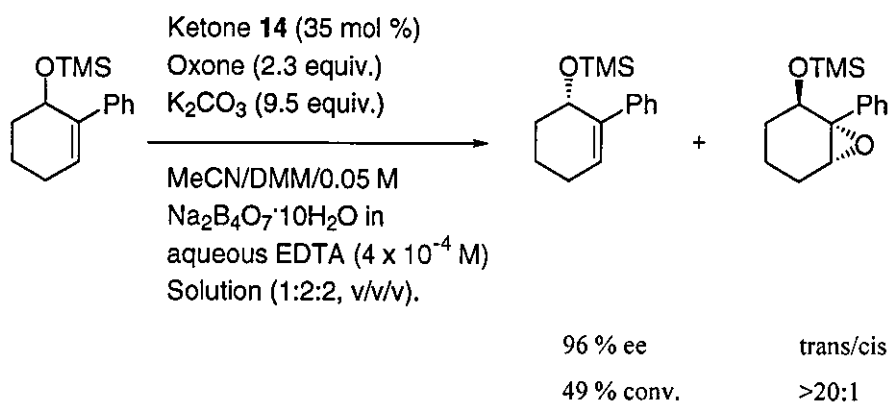
Scheme 25: Shi's fructose derived ketone for asymmetric epoxidation.

After experimentation it was found that Baeyer-Villiger oxidation could be suppressed and the amount of catalyst could be reduced to 20 mol % if the reaction was carried out between pH 10 and 11 (Scheme 26).^{82,83} Yields were increased (65-95 %) and the catalytic system resulted in slightly higher ees (91-97 % ee). The synthetic utility of this system has been widely explored with the successful asymmetric epoxidation of various hydroxyalkenes (90-94 % ee),⁸⁴ enol ethers and enol esters (80-91 % ee),⁸⁵ enynes (90-97 % ee),⁸⁶ vinylsilanes (84-94 % ee),⁸⁷ cis-alkenes (84-97 % ee),^{88,89} terminal alkenes (30-94 % ee),⁹⁰ and mono-epoxidation of conjugated dienes (90-97 % ee).⁹¹



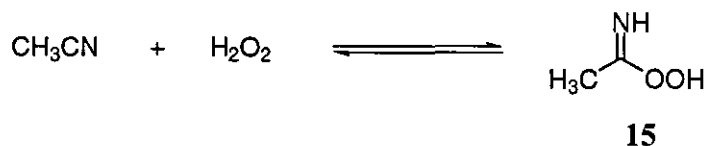
Scheme 26: Shi's proposed mechanism of dioxirane mediated epoxidation.

Shi has even expanded this work to the kinetic resolution of racemic cyclic olefins.⁹² Successful resolution of cyclic olefins with the chiral centre at the allylic position has been achieved (Scheme 27).



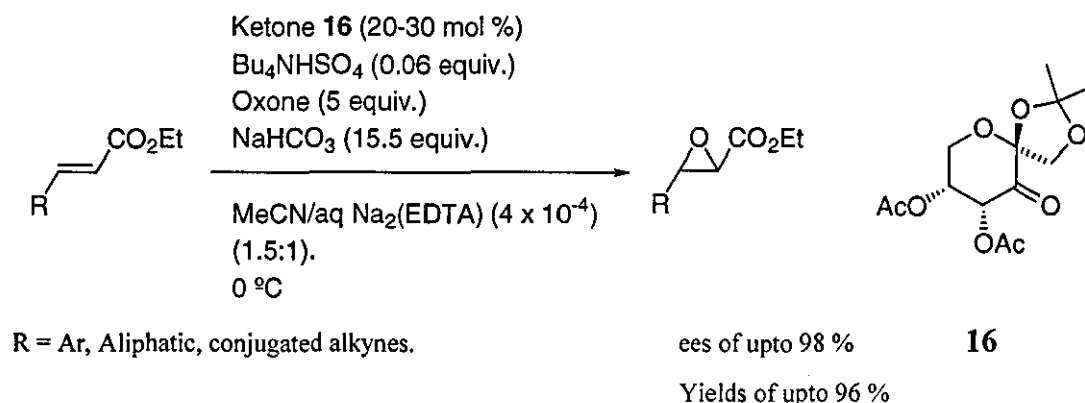
Scheme 27: Shi's Kinetic resolution of cyclic olefins.

Shi has also recently reported asymmetric epoxidation mediated by alkaline hydrogen peroxide.^{93,94} High yields and ees were obtained under these reaction conditions with up to 95 % ee for 1-phenylcyclohexene oxide using the original fructose derived catalyst (**14**). Peroxyimidic acid (**15**) is postulated to be the active oxidant (Scheme 28).



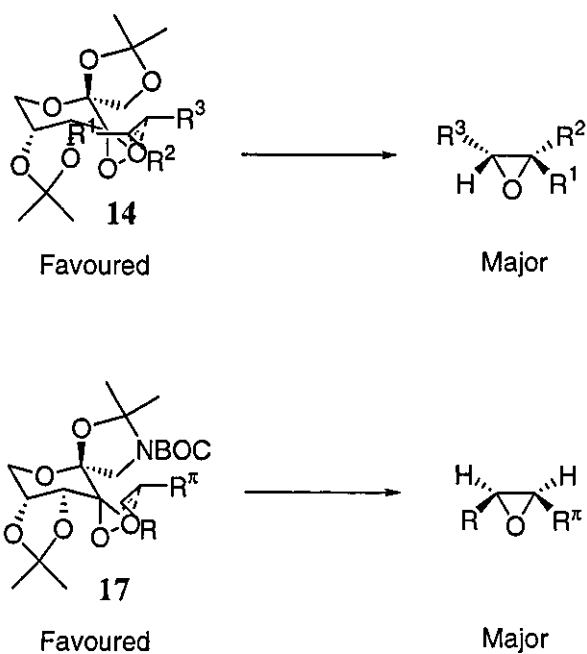
Scheme 28: Postulated formation of peroxyimidic acid in the asymmetric epoxidation reaction using hydrogen peroxide as primary oxidant.

In his most recent publication, highly efficient asymmetric epoxidation of α,β -unsaturated esters has been achieved using a modified fructose catalyst.⁹⁵ It was found that the original catalyst (**14**) was not effective toward α,β -unsaturated esters due to its decomposition under the reaction conditions by Baeyer-Villiger oxidation. Replacement of the fused ketal in (**14**) with more electron withdrawing groups (acetates) produced a active and highly enantioselective catalyst (**16**, Scheme 29).



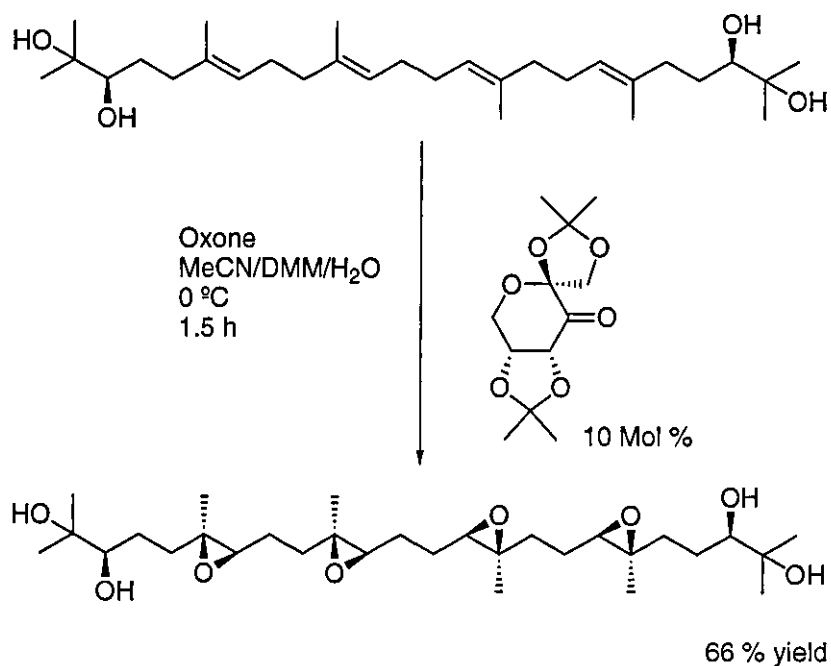
Scheme 29: Shi's new fructose derived catalyst for α,β -unsaturated esters.

The success of Shi's catalyst is believed to stem from a well ordered transition state, and results favour the spiro transition state (Scheme 30). The favoured transition state for *trans* or trisubstituted olefins is shown mediated by catalyst (**14**) and the favoured transition state for *cis* disubstituted olefins is shown, mediated by the BOC protected catalyst (**17**).



Scheme 30: Shi's proposed transition states for dioxirane mediated epoxidation.

A recent application in the synthesis of (-)-glabrescol, by Corey, illustrates the scope of dioxirane-mediated asymmetric epoxidation (Scheme 31).⁹⁶

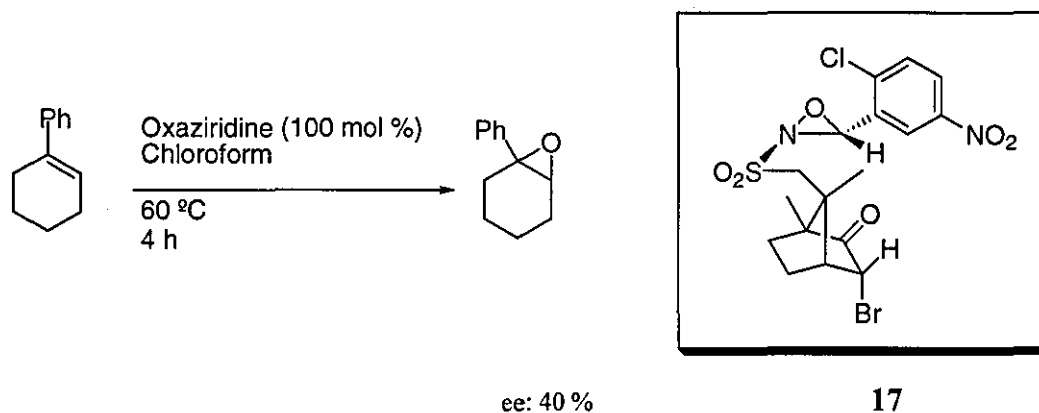


Scheme 31: Corey's Synthesis of (-)-glabrescol using Shi's fructose derived ketone.

1.5.6 Oxaziridines.

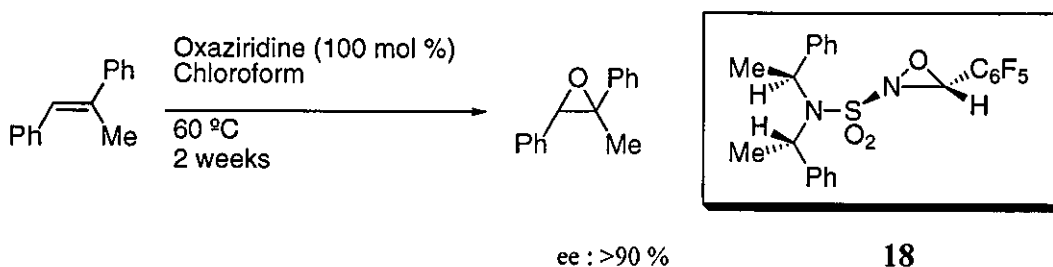
Oxaziridines, the nitrogen analogues of dioxiranes, also act as oxygen transfer agents. Major accomplishments in this area have been pioneered by Davis. It was shown that oxaziridines can epoxidize simple alkenes, but the reaction is significantly slower (3-12 hours at 60 °C) than for dioxiranes.⁹⁷ Oxaziridines are generally accessed by oxidation of the corresponding imines, which are produced upon oxygen transfer to substrates.^{98,99} This is a stoichiometric method, and at present no catalytic procedure for the epoxidation reaction mediated by oxaziridines has been described. However, this method appears attractive for sensitive substrates because epoxidations can take place under neutral conditions with no additional reagents. The oxygen transfer occurs with retention of configuration of the original olefin geometry and is therefore believed to be a concerted process.

Davis has described many examples of asymmetric epoxidation mediated by oxaziridines. The first chiral oxaziridine reported was derived from bromocamphor, but the observed enantioselectivities were low, the best being 40 % ee for 1-phenylcyclohexene oxide (Scheme 32).¹⁰⁰



Scheme 32: Davis's first chiral oxaziridine for asymmetric epoxidation.

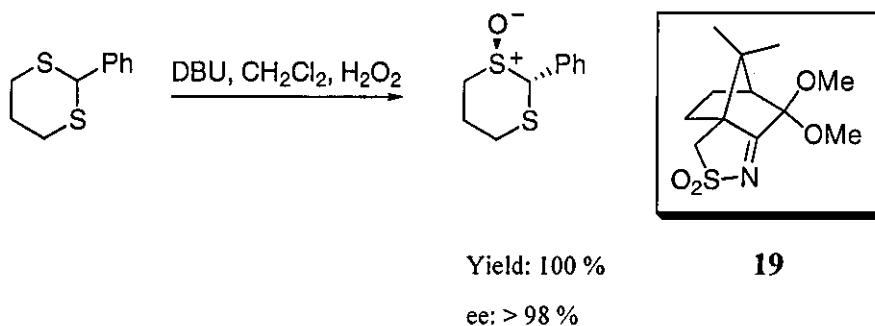
Increased enantioselectivities were observed when oxaziridine (**18**) was employed, and ees of greater than 90 % for *trans*- α -methylstilbene oxide were observed. However, reaction times were extremely long (2 weeks at 60 °C) (Scheme 33).¹⁰¹



Scheme 33: Davis's highly enantioselective oxaziridine for asymmetric epoxidation.

A large proportion of Davis's work has been involved in the elucidation of the transition state employed in the transfer of the oxygen from the oxaziridine to the olefin substrate. Davis favoured the planar transition state and was at the time supported by theoretical calculations; however, more recent calculations favour the spiro transition state.⁸ Davis has also described the asymmetric oxidation of enolate anions by chiral oxaziridines, which led to α -hydroxyketones with enantioselectivities of up to 95 % ee.^{102,103} Silyl enol ethers have also been reported to give epoxides when treated with oxaziridines, but the instability of these compounds is too great to allow isolation.^{104,105,106} To date, only Davis has reported successful isolation of α -silyloxy epoxides.¹⁰⁷

Davis has also successfully transferred the oxygen moiety from oxaziridines to sulfides¹⁰⁸ to form chiral sulfoxides, with ees of up to 78 %.¹⁰⁹ This procedure has been successfully modified into a catalytic system by Page and Bethell.^{110,111} The most successful system is derived from a camphor sulfonyl imine (**19**), giving enantiomerically enriched sulfides with ees of greater than 98 % (Scheme 34).¹¹¹ More recently, 3-substituted-1,2-benzisothiazole-1,1-dioxides have been employed.^{112,113}



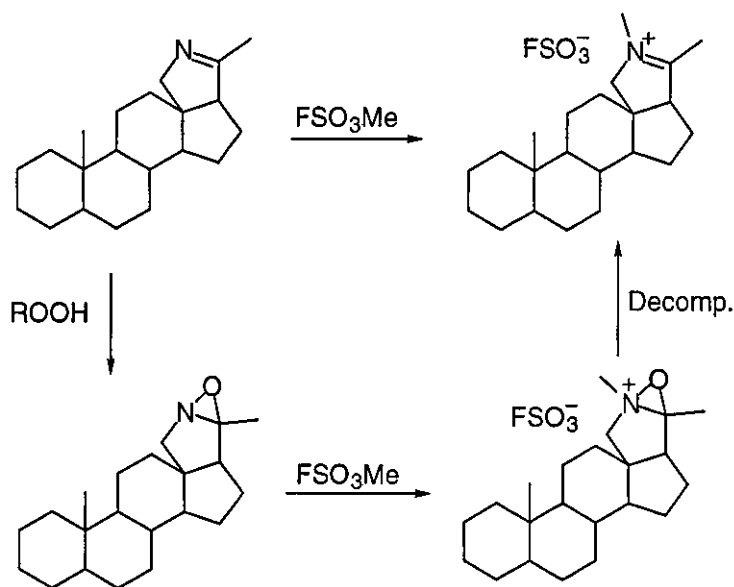
Scheme 34: Page and Bethell's sulfonyl imine (**19**) giving ees of up to 98 %.

1.5.7 Oxaziridinium/iminium salt systems for asymmetric epoxidation.

Oxaziridinium salts are the quarternized analogues of oxaziridines, and as a result of being more electrophilic, transfer oxygen efficiently to nucleophilic substrates.

1.5.7.1 Initial studies, by Lusinchi.

The first oxaziridinium salt, described by Lusinchi in 1976,^{114,115,116} was based on a steroidal pyrrolinic skeleton. Through peracid oxidation of the steroidal imine and quaternization using methylfluorosulfonate it was shown that an oxaziridinium species can be formed (Scheme 35). This new species was rather unstable, and upon decomposition reverted to an iminium salt, which could be directly prepared from the imine. However, it was not until some eleven years later that the potential of this type of system to transfer oxygen was realised.^{117,118}

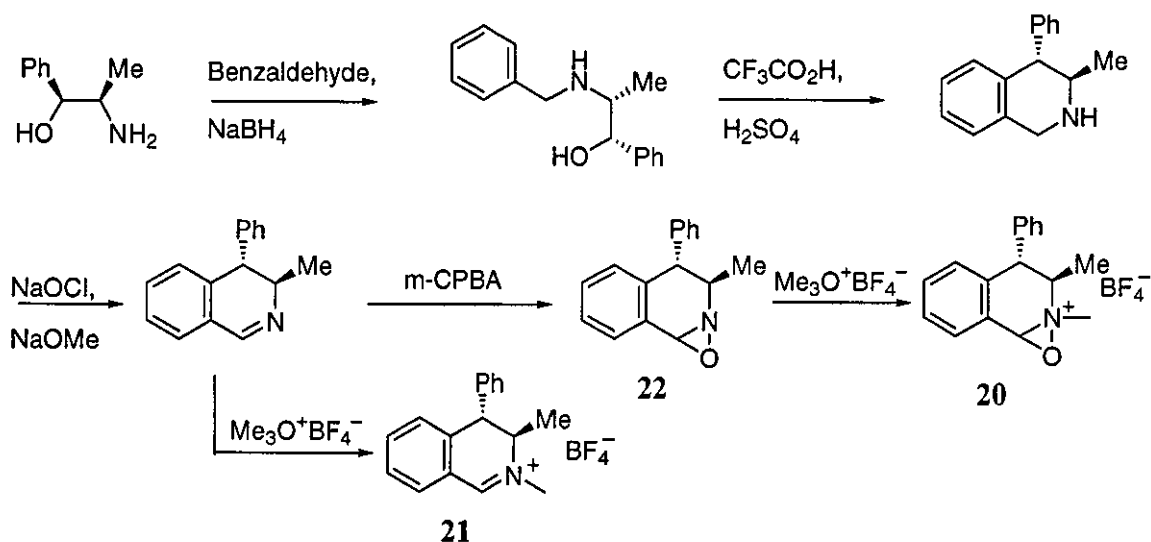


Scheme 35: The first example of an oxaziridinium salt developed by Lusinchi.

Using an oxaziridinium salt derived from dihydroisoquinoline, Lusinchi was able to transfer the oxygen to several simple alkenes in good yield (Scheme 36).^{118,119} Following this work, the first enantiomerically pure oxaziridinium salt was prepared.¹²⁰ Quaternization of a chiral oxaziridine, derived from (1*S*,2*R*)-(+)-norephedrine, produced the oxaziridinium salt (**20**) (Scheme 37).



Scheme 36: Oxygen transfer to alkenes mediated by a oxaziridinium salt derived from tetrahydroisoquinoline.

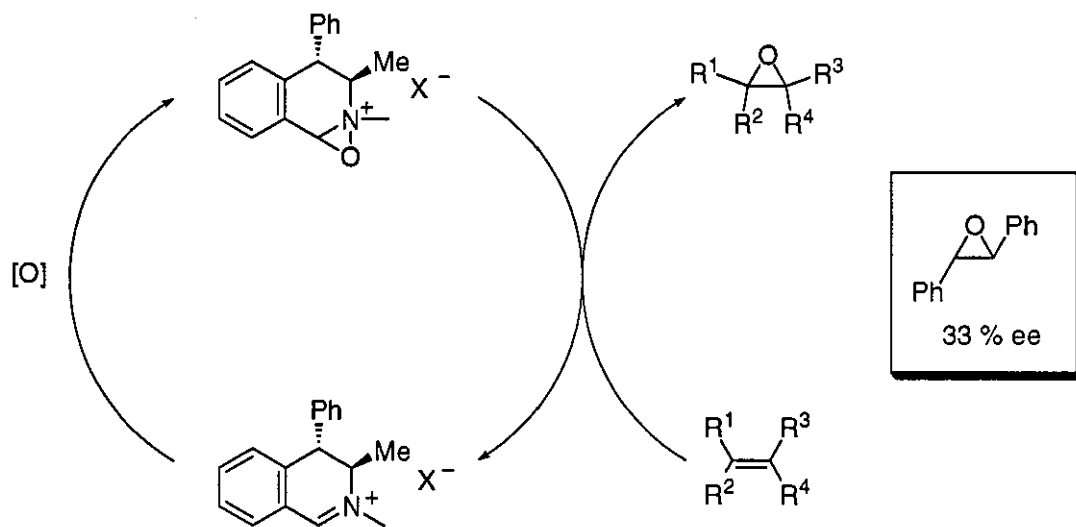


Scheme 37: The first enantiomerically pure oxaziridinium salt derived from (1S,2R)-(+)-norephidrine.

This oxaziridinium salt was also able to transfer oxygen to olefins, and induced moderate enantiocontrol, epoxidizing *trans*-stilbene with 33% ee. With the side product of the reaction being an iminium salt, there was potential to develop this chemistry catalytically. If this iminium salt could be re-oxidized to the oxaziridinium *in situ*, catalytic transfer of oxygen to alkenes could be achieved (Scheme 38).

Lusinchi was able to develop this catalytic system using Oxone, similar to that developed for dioxiranes; however, less pH control is required as there is no competitive Baeyer-Villiger oxidation. The enantiomerically pure iminium salt (**21**) is thus able to epoxidize *trans*-stilbene catalytically (20 mol %) with the same degree of selectivity as the stoichiometric oxaziridinium salt (33 % ee). Lusinchi has also shown that oxaziridinium salts are capable of transferring oxygen to other

nucleophilic substrates such as sulfides to form sulfoxides,¹²¹ amines to form nitrones, and imines to form oxaziridines.¹²²



Scheme 38: Catalytic cycle for epoxidations mediated by oxaziridinium salts.

Lusinchi's group has reported the only X-ray determination of an oxaziridinium salt.^{120,123} Its geometry is similar to that of the parent oxaziridine, and the N-O bond length of 1.468 Å in the oxaziridinium salt is shortened compared with the mean bond length of 1.508 Å observed for oxaziridines. It is also interesting to note that the oxaziridine ring is perpendicular to the isoquinoline ring (Figure 12).

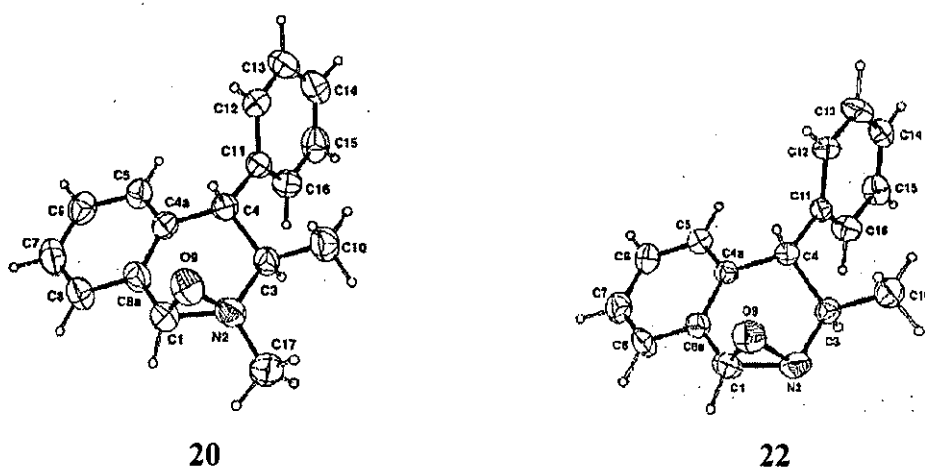


Figure 12: X-ray crystal structures of oxaziridinium species 21 and oxaziridine 22.

1.5.7.2 Aggarwal and Wang's binaphthylene based iminium salt.

Since Lusinchi's early work, several groups have identified an interest in oxaziridinium/iminium salt chemistry. Aggarwal and Wang produced a cyclic binaphthalene-derived iminium salt, which was shown to be effective in the epoxidation of 1-phenylcyclohexene giving 71 % ee.¹²⁴ However, this catalyst appeared somewhat substrate dependent, the best ee for other olefins tested being only 45 % (Figure 13).

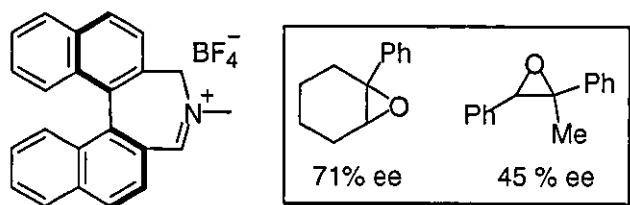
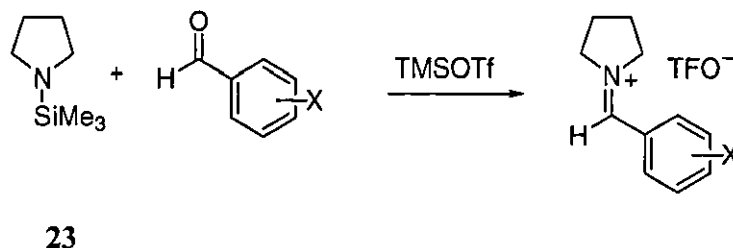


Figure 13: Aggarwal's Binaphthylene based iminium salt catalyst.

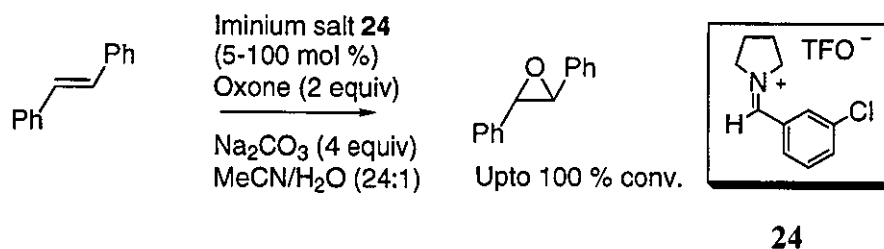
1.5.7.2 Armstrong's acyclic iminium salts.

Armstrong has shown that even acyclic iminium salts can mediate epoxidation by Oxone;¹²⁵ however, enantiomeric excesses are low.¹²⁶ By condensing *N*-trimethylsilylpyrrolidine (**23**) with a range of aromatic aldehydes in the presence of trimethylsilyltriflate, Armstrong was able to produce a range of substituted exocyclic iminium salts (Scheme 39).



Scheme 39: Armstrong's synthesis of exocyclic iminium salts.

It was found that only those compounds with electron withdrawing groups present on the aromatic ring were active mediators. Catalytic reactions were carried out with the *ortho*-Cl (**24**) derivative, giving good conversion to epoxide (Scheme 40).



Scheme 40: Epoxidation of *trans*-stilbene with Armstrong's catalyst (**24**).

Despite many attempts at producing chiral variants of this catalyst system, Armstrong was unable to gain significant ees, catalyst (**25**) giving only 22 % ee for 1-phenylcyclohexene (Figure 14).

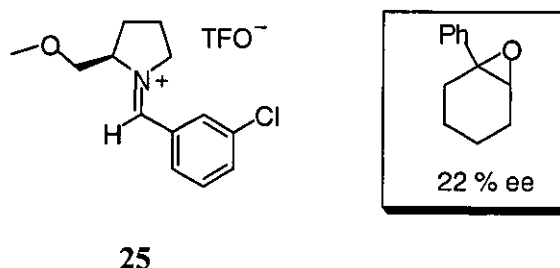
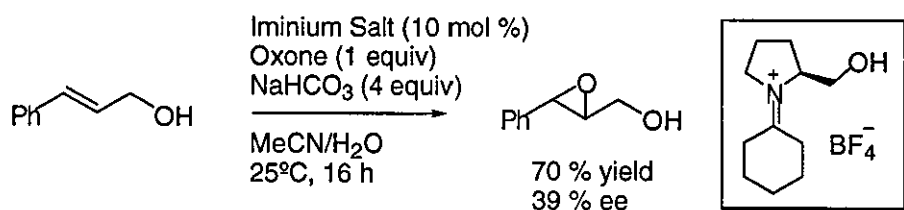


Figure 14: Armstrong's most successful chiral iminium salt catalyst.

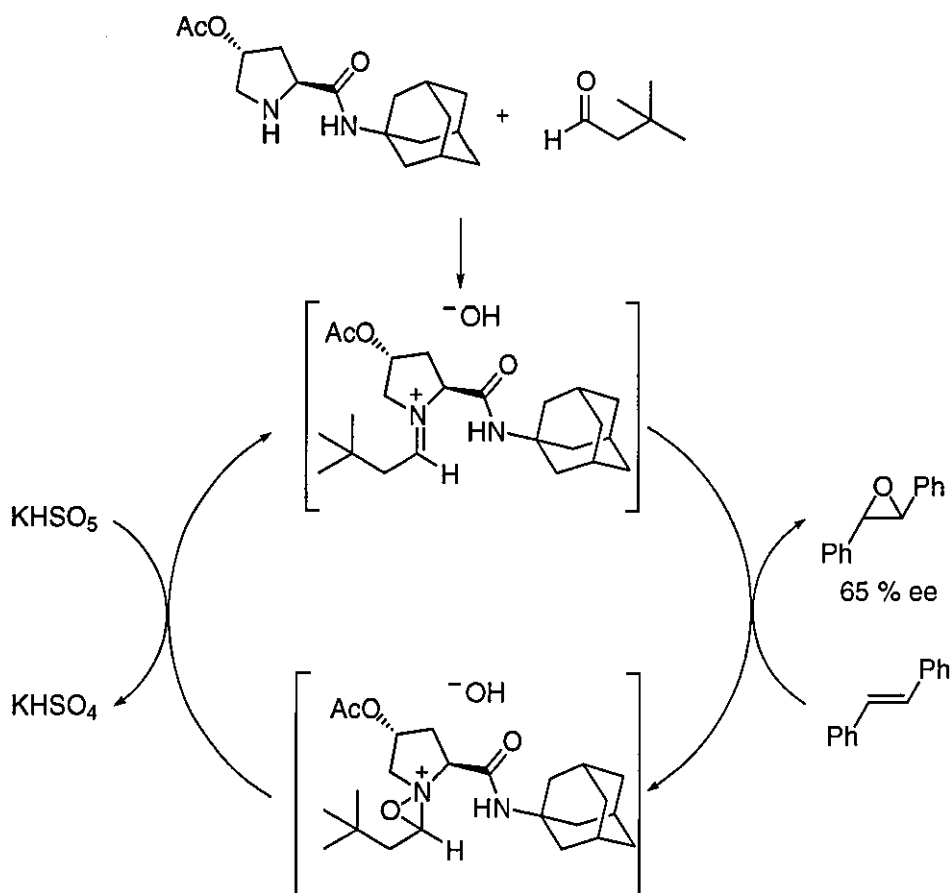
1.5.7.3 Komatsu and Wong's exocyclic iminium salts.

Recently, two other groups have shown that exocyclic iminium salts can be useful mediators in asymmetric epoxidation. Komatsu has developed a system based on ketiminium salts,¹²⁷ through the condensation of aliphatic cyclic amines and ketones. A chiral variant was also produced, derived from prolinol and cyclohexanone, which gave 70 % yield and 39 % ee for cinnamyl alcohol (Scheme 41).



Scheme 41: Komatsu's ketiminium salt mediated epoxidation.

Moderate ees have been achieved by Yang using another exocyclic iminium salt system.¹²⁸ However, these salts are not isolated and are generated *in situ*, thus obviating the difficulties inherent in the preparation and isolation of unstable iminium salts.



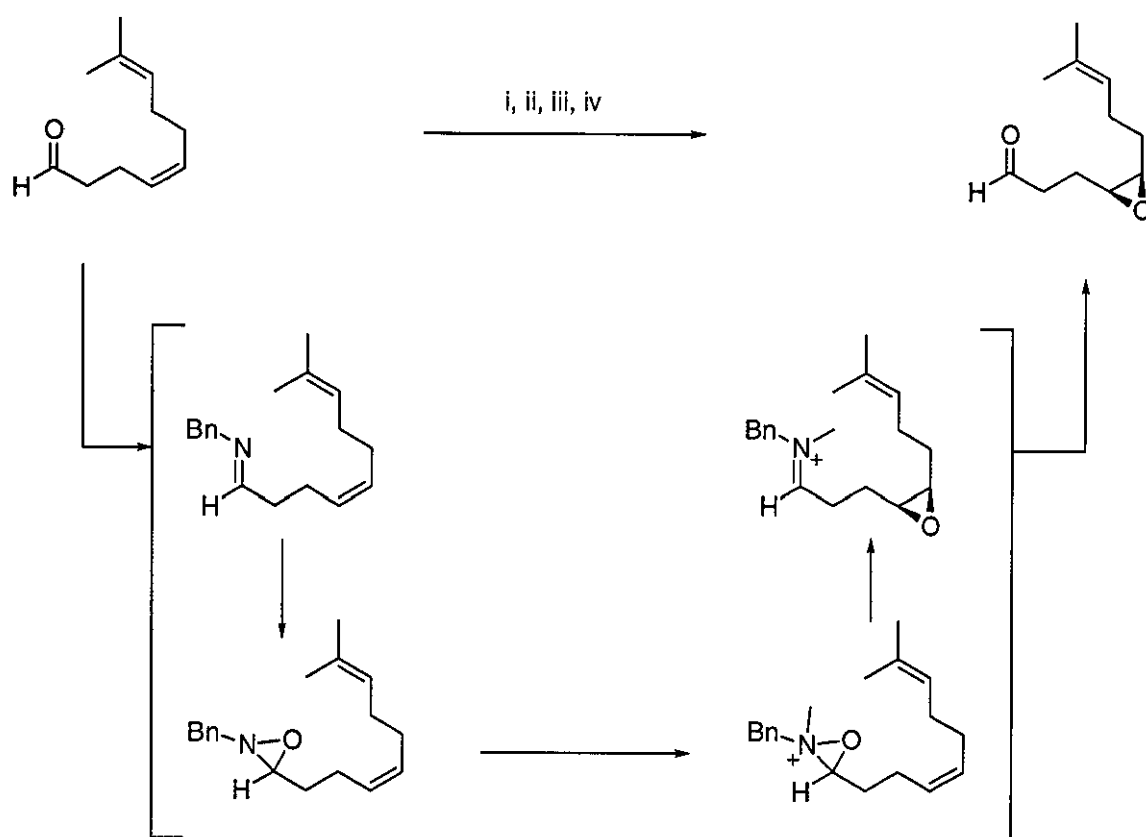
Scheme 42: Wong's *in situ* based iminium salt epoxidation system.

A major drawback to this type of system is the catalyst loadings; for an efficient rate of reaction up to 50 mol % of iminium salt is generally required. Nevertheless, ees of

up to 65 % have been achieved. A range of amines and aldehydes were screened, and a novel proline based amine and a branched hexanal were found to be the best precursors (Scheme 42).

1.5.7.4 Armstrong's intramolecular epoxidation.

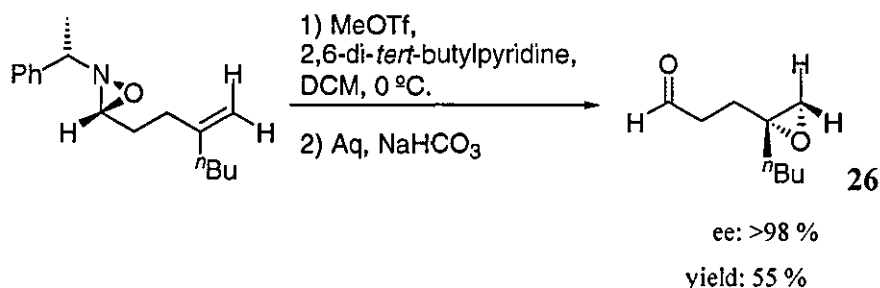
Armstrong has also published an *in situ* epoxidation, mediated by an intramolecular oxaziridinium salt, which gave good regio selectivity (Scheme 43).¹²⁹



Reagents and Conditions: i: BnNH₂, 4Å mol. sieves, DCM; ii: Oxone, NaHCO₃, MeCN/H₂O; iii: MeOTf, DCM; iv: NaHCO₃ (aq.).

Scheme 43: Armstrong's intramolecular epoxidation.

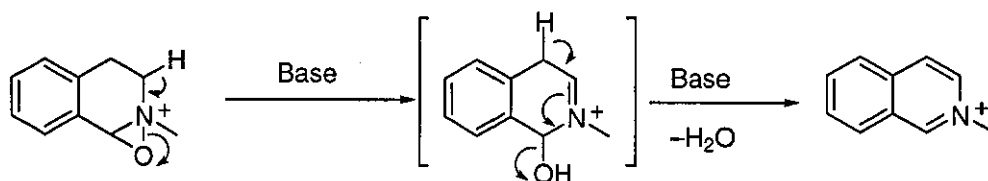
With modification of this procedure, using an oxaziridine, Armstrong was able to demonstrate the synthetic utility of this method by introducing a chiral amine to afford enantiomerically enriched products, and greater than 98 % ee was obtained for (**26**), which is a terminal epoxide (Scheme 44).¹³⁰ However, a loss of selectivity was observed when chain lengths between the aldehyde and alkene exceeded 3 atoms.



Scheme 44: Armstrong's chiral version of the intramolecular epoxidation reaction.

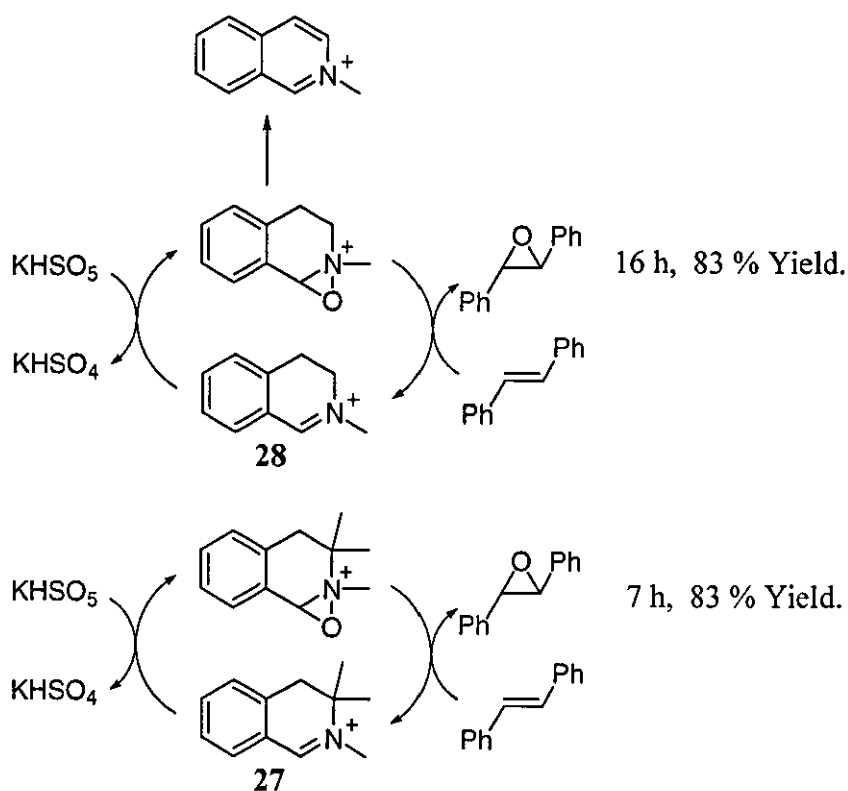
1.5.7.5 Bohé's improved achiral catalyst.

More recently Bohé, a former co-worker with Lusinchi, has reported an improved achiral catalyst which prevents some common side reactions observed in iminium salt-mediated epoxidation.¹³¹ Two factors are known to reduce the catalytic efficiency of the epoxidation process; hydrolysis of the iminium salt directly by the reaction medium generally only affects the acyclic systems. However, loss of active oxygen from the intermediate oxaziridinium species, through a reaction which does not regenerate the iminium can occur to all systems containing protons α to the nitrogen atom. This is an irreversible base-catalysed isomerization (Scheme 45).



Scheme 45: Bohé's proposed irreversible base-catalysed isomerization.

A dramatic increase in catalyst efficiency is observed when the 3,3-disubstituted-dihydroisoquinolinium salt (**27**) is used in place of catalyst (**28**), thus eliminating the base catalysed isomerization (Scheme 46).



Scheme 46: Bohé's improved achiral catalyst for catalytic epoxidation.

1.6 Conclusions.

A wide variety of methods for producing enantiomerically enriched epoxides has been presented in this chapter and these can be roughly split into two categories: transition metal catalysts and organo-catalysts. Many of these systems are able to produce oxiranes with high enantioselectivities, but one problem still remains: the formation of a general catalyst that works at low catalyst loadings, produces excellent enantioselectivities and yields has yet to be invented. One exception to this may be the fructose-derived dioxirane catalysts developed by Shi, although high catalyst loadings are still employed (i.e. the catalyst quickly decomposes) and ees for terminal epoxides are still only moderate to good (*ca* 80 % ee).

Of the areas covered in this short review, epoxidation mediated by iminium salts or their oxaziridinium counter-parts has emerged as one of the most attractive. However,

the current major drawback in this area is the low to moderate enantioselectivities observed.

The discussion which follows describes the efforts of the present author toward the goal of low catalyst loading and high enantioselectivity, demonstrating new catalytic systems for asymmetric epoxidation.

1.7 Chapter One References.

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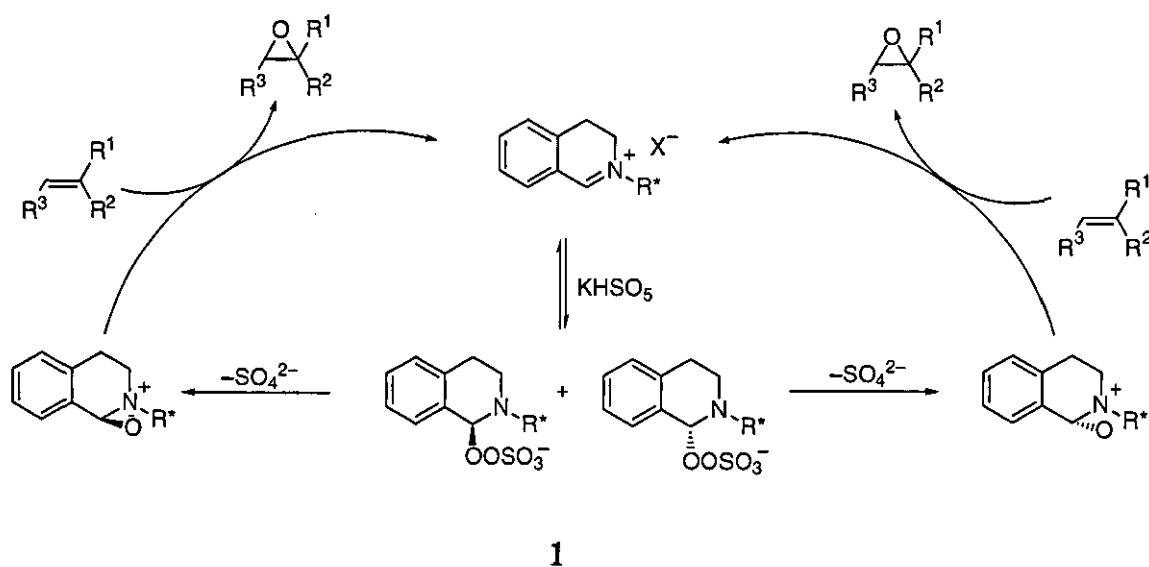
Chapter Two

Results and Discussion

2.0 Results and Discussion

2.1 Previous Page group findings.

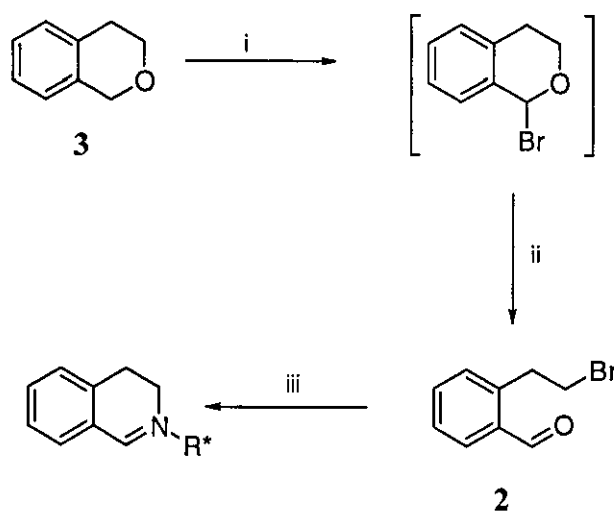
In the search for a new and highly enantioselective system for iminium salt mediated catalytic asymmetric epoxidation, several parameters and catalyst substructures were examined. The method of oxidation, using Oxone, was established after some experimentation and a possible catalytic cycle for an oxaziridinium ion as the oxidative intermediate is depicted in Scheme 1.^{1,2,3} The first stage is the formation of an initial adduct (1), uncharged at nitrogen, formed by (probably reversible) nucleophilic attack of the oxidant on the iminium salt. This is followed by irreversible expulsion of sulfate to give the oxaziridinium ion, which is believed to be the rate-determining step under the reaction conditions. Oxygen may then be transferred to a substrate in a subsequent step, the rate of which would not be expected to have any great solvent dependence. An interesting but complicating feature of these processes is that it is not one but two diastereoisomeric oxaziridinium salts which may be formed, by attack of oxidant at the *si* or *re* face of the iminium species. Each may deliver the oxygen atom to either of the prochiral faces of the alkene substrate with a different degree of enantiocontrol, and they may be in competition for the alkene substrate.



Scheme 1: Catalytic cycle for the oxaziridinium ion as an oxidative intermediate in the epoxidation reaction.

2.1.1 Catalyst Structure

An ideal method for testing a wide variety of substructures was developed through the condensation of enantiomerically pure chiral primary amines with 2-(2-bromoethyl)benzaldehyde (**2**) as shown in Scheme 2.



Reagents and conditions: i: Br₂, CCl₄, 1 h; ii: HBr (conc), Δ, 10 min; iii: a) R*NH₂, EtOH, 0 °C-r.t., 12 h, b) NaBPh₄, MeCN, 5 min.

Scheme 2: The 2-(2-bromoethyl)benzaldehyde method for forming dihydroisoquinolinium salts.

The iminium salts prepared by this method have the advantage that they are extremely easy to prepare on any scale and that the structural variation available is large, because the chirality is resident in the amine component. Treatment of isochroman (**3**) with bromine in carbon tetrachloride under reflux for 1 hour followed by exposure to concentrated hydrobromic acid provides 2-(2-bromoethyl)benzaldehyde (**2**) in 65 % yield.⁴ Primary amines condense smoothly with this material to furnish the corresponding dihydroisoquinolinium bromides. These organic salts are generally oils, and the inherent difficulties in purification by conventional methods, necessitated a change in counterion. Addition of sodium tetraphenylborate, at the end of the reaction, in the minimum amount of acetonitrile induces rapid formation of the corresponding tetraphenylborate salts as crystalline solids. Overall yields of catalyst are generally between 30 and 80 %, limited in part as a consequence of a side reaction, elimination of hydrogen bromide from the bromoethyl moiety of the precursor. No chromatography is necessary at any point in this sequence.

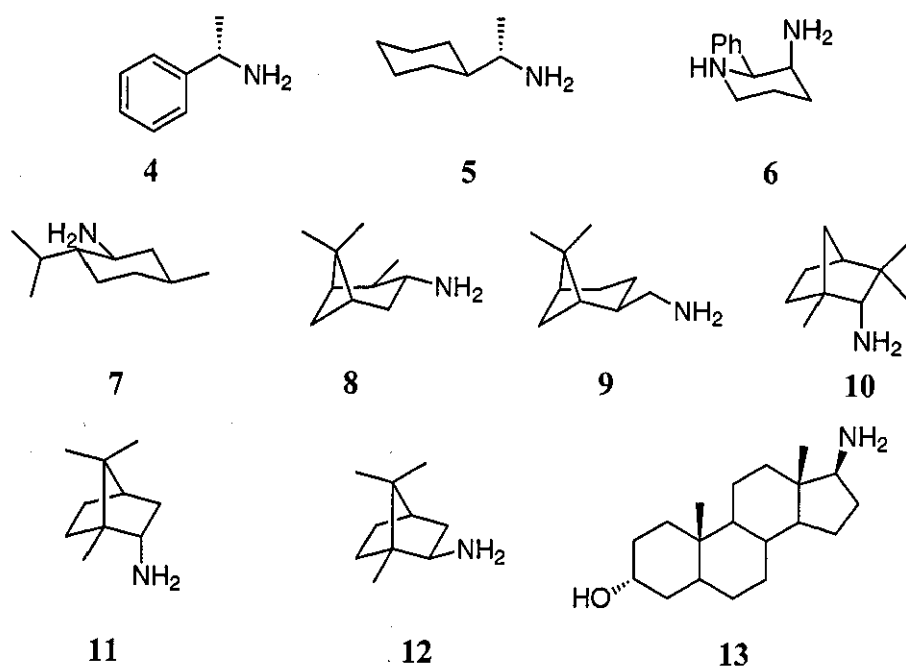


Figure 1: Initial primary amines condensed with 2-(2-bromoethyl)benzaldehyde (**2**) to form iminium salts.

Very hindered amines give inferior yields of iminium salt, typically 25-30 %, presumably due to an increased tendency to act as bases rather than nucleophiles, as evidenced by the increased levels of 2-vinylbenzaldehyde and derived imine.

A range of structurally different chiral primary amines was converted to their corresponding iminium tetraphenylborate salts (Figure 1) and tested in the asymmetric epoxidation of the standard test substrate 1-phenylcyclohexene, using oxone (4 equivalents) as the stoichiometric oxidant, sodium carbonate (8 equivalents) as base, in acetonitrile/water (2:1) at 0 °C (Table 1).

With the first two entries in Table 1, using the structurally simplest amines, no asymmetric induction was observed, and it became clear that a conformationally more defined and rigid system was required to impart reasonable enantioselectivities. Both the camphor and menthyl based systems gave low ees, although these are two of the more common systems upon which chiral auxiliaries have been based. The fenchyl derivative is the most selective under these reaction conditions. However, the *N*-(isopinylcamphyl) dihydroisoquinolinium salt, which is considerably less sterically

hindered than the fenchyl, is almost as selective, giving a better yield and increased rate of reaction.

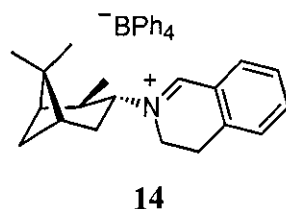
Table 1: Epoxidation of 1-phenylcyclohexene with dihydroisoquinolinium tetraphenylborate salts derived from chiral primary amines.^a

Entry	Amine Precursor	Catalyst load (mol %)	Yield (%)	ee (%)	Configuration
1	4	5.0	54	0	–
2	5	5.0	70	0	–
3	6	1.0	39	25	(–)-(1 <i>S</i> ,2 <i>S</i>)
4	7	0.5	63	19	(+)-(1 <i>R</i> ,2 <i>R</i>)
5	8	0.5	68	27	(+)-(1 <i>R</i> ,2 <i>R</i>)
6	9	0.5	66	12	(–)-(1 <i>S</i> ,2 <i>S</i>)
7	10	0.5	45	32	(+)-(1 <i>R</i> ,2 <i>R</i>)
8	11	0.5	60	18	(+)-(1 <i>R</i> ,2 <i>R</i>)
9	12	0.5	58	8	(+)-(1 <i>R</i> ,2 <i>R</i>)
10	13	0.5	47	14	(–)-(1 <i>S</i> ,2 <i>S</i>)

^aConditions: 4 equiv. Oxone; 8 equiv. Na₂CO₃; 0 °C; H₂O/MeCN 1:2; reactions monitored by TLC.

2.1.2 The Reaction Parameters.

Having found a catalyst which exhibited a good reaction profile in terms of ees and rates, an examination of some of the reaction parameters was carried out in order to optimize the reaction conditions with respect to the enantioselectivity of the oxygen transfer process. The *N*-(isopinylcampeyl) dihydroisoquinolinium salt (**14**) was chosen as the model catalyst for optimization studies.



2.1.2.1 Effect of counter-ion.

In addition to the original tetraphenylborate, the corresponding tetrafluoroborate, hexafluorophosphate, perchlorate and periodate salts were prepared. All of these were tested in the asymmetric catalytic epoxidation of 1-phenylcyclohexene. A catalyst loading of 5 mol % was used in a 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 gave a similar ee (35 %) to that of the tetraphenylborate species (40 % ee), while the fluoride-containing counterions afforded lower ees (28 %). The perchlorate salt furnished inferior enantioselectivities (20 % ee). All of the salts however invariably produced the same major enantiomer of the epoxide product (*R,R*), and all of the reactions were complete in a similar time scale (*ca.* 45 minutes).

2.1.2.2 Effect of the solvent system.

The standard conditions employed within the Page group describe the solvent system as a 1:1 mixture of acetonitrile and water, using two equivalents of Oxone and four equivalents of sodium carbonate at 0 °C. An increase in water to acetonitrile ratio is accompanied by an increase in the reaction rate. For example, the yield of 1-phenylcyclohexene oxide after 1 hour using catalyst (**14**) was 30 % at 0 °C when a 1:1 ratio of the two solvents was used, but the yield was essentially quantitative using a 2:1 (water/acetonitrile) ratio. Reducing the amount of Oxone and base by a factor of 2 (*i.e.* using one equivalent of Oxone and two equivalents of sodium carbonate), resulted in incomplete conversion after one hour in the improved (2:1) solvent system. It was found that higher catalyst loadings accelerate the rate of reaction to an extent that outweighs the effect of water content.

An investigation into the co-solvent employed was also carried out. The solvents were selected so that they differed significantly in dielectric constant (ϵ , indicated by the values in brackets); dichloromethane (8.9), trifluoroethanol (26.7), acetonitrile (37.5), water (78.4) and formamide (111). The epoxidation of 1-phenylcyclohexene with catalyst (**14**) was tested using these co-solvents with water in a 1:1 ratio. Epoxidation

did not occur in dichloromethane; this is perhaps due to the poor miscibility of the two solvents, thus limiting the availability of the inorganic oxidant in the organic phase. No reaction was also observed in formamide. This could be due to the iminium species being too well stabilised/solvated and the possibility of an irreversible attack by the formamide cannot be dismissed. However, in trifluoroethanol the reaction had a similar profile to that in acetonitrile; both reactions were complete in 30 minutes, but the ee was somewhat lower (26 % ee in trifluoroethanol and 40 % ee in acetonitrile).

2.1.2.3 Effect of temperature.

This parameter is severely limited by the stability and solubility of Oxone. When the reaction was carried out at $-10\text{ }^{\circ}\text{C}$ it was sluggish because the solubility of the inorganic oxidant and base in water was dramatically reduced. When an increased volume of water was employed, (3:1 ratio with acetonitrile), oxidation of 1-phenylcyclohexene mediated by catalyst (**14**) (5 mol %) resulted, within 45 minutes, in complete consumption of the starting material, and afforded the corresponding epoxide in slightly improved yield. The enantioselectivity was slightly reduced (35 %) from that of the reaction carried out at $0\text{ }^{\circ}\text{C}$ (40 %).

When the oxidation was carried out at ambient temperature, negligible conversion to epoxide was observed; this is believed to be due to the instability of oxone at this temperature.⁵

2.1.2.4 Effect of catalyst loading.

This was expected to have a large effect on the enantioselectivity of the process; However, the effect was negligible; decreased loadings resulted in longer reaction times, but the enantioselectivity of the system remained fairly consistent, reaching a maximum at 2 mol % (Figure 2). Enantioselectivities below this loading decreased from 33 % ee at 2 mol % loading, to 18 % ee at 0.3 mol % catalyst loading.

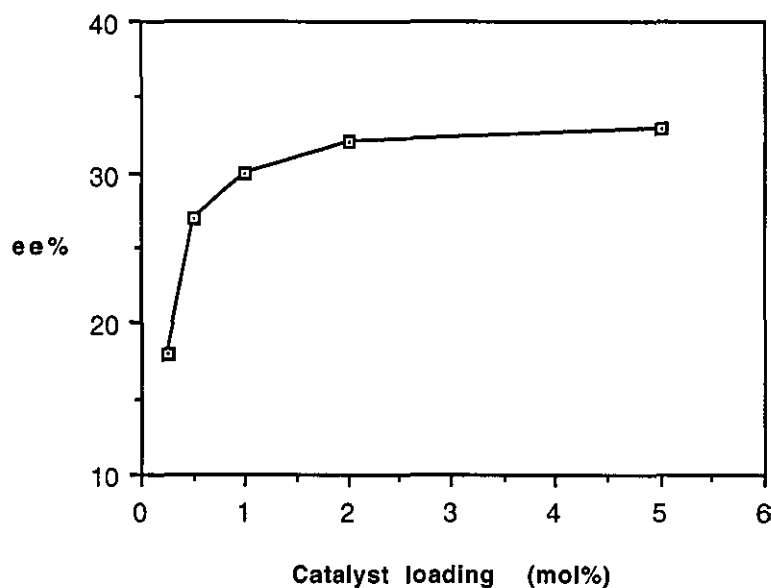


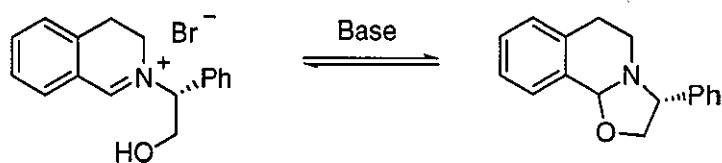
Figure 2: Graph of catalyst loading study

2.1.3 Initial Findings

After this early work in setting up the optimum reaction conditions, a further, more detailed, study of catalyst structure was instigated. A range of dihydroisoquinolinium salts containing alcohol, ether and acetal functionalities was tested for possible catalysts.⁶

2.1.3.1 Alcohol containing iminium salts.

It was hoped that this series of catalysts might offer increased ees due to the ability of hydroxyl functionality, to direct the approach of the impending alkene towards the site of epoxidation. However, epoxidation reactions using this type of functionality resulted in a sluggish reactivity and low enantioselectivity. This inhibited reactivity is thought to stem from the existence of an equilibrium between the ring open iminium salt (active) and the ring closed oxazolidine (inactive) forms of the catalysts under the slightly alkaline reaction conditions (Scheme 3). In fact it is known that dihydroisoquinolinium salts can undergo base-induced ring closure to form the corresponding oxazolidines with high diastereoselectivity and yields.⁷



Scheme 3: Base induced ring closure of hydroxy dihydroisoquinolinium salts to oxazolidines.

2.1.3.2 Catalysts from aminoether precursors.

Several aminoether-based dihydroisoquinolinium salts were produced, and they proved to be much more active than the related derivatives of the parent amino alcohols, but again poor enantioselectivity was observed in the epoxidation of 1-phenylcyclohexene (Figure 3). This suggested that the size of the ether substituent in such catalysts is not particularly important for asymmetric induction during oxygen transfer to the alkene.

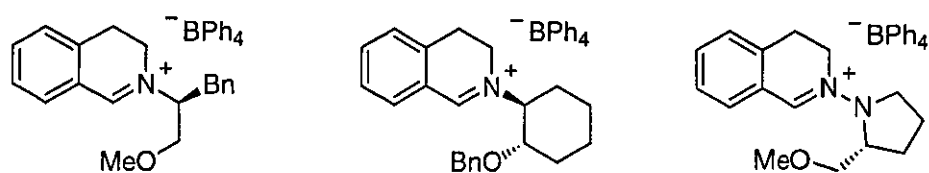
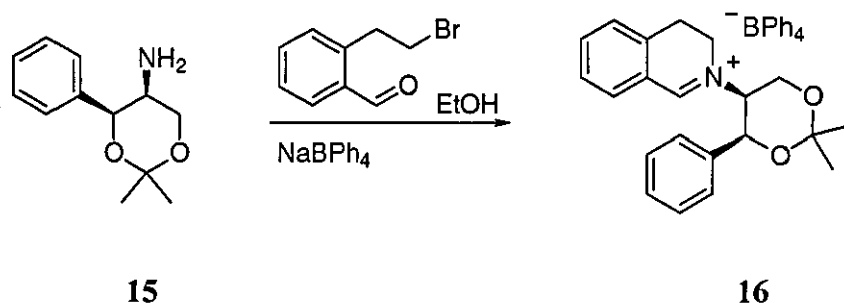


Figure 3: Some of the amino ether based catalysts tested in the epoxidation of 1-phenylcyclohexene.

2.1.3.3 A catalyst from an aminoacetal precursor.

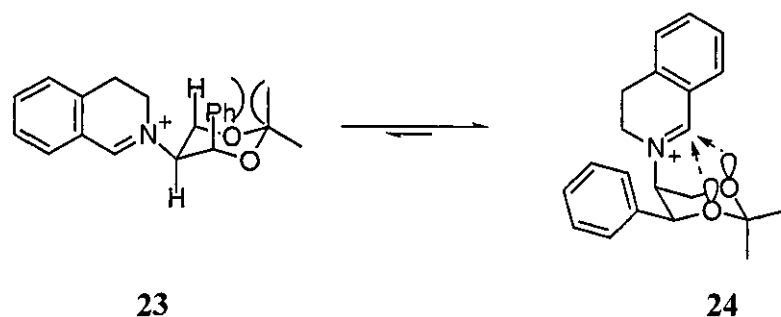
(1*S*,2*S*)-5-Amino-2,2-dimethyl-4-phenyl-1,3-dioxane (**15**) reacted smoothly with 2-(2-bromoethyl)benzaldehyde (**2**) under the usual conditions to furnish the corresponding dihydroisoquinolinium tetraphenylborate salt in greater than 75 % yield (**16**) (Scheme 4).



Scheme 4: The amino acetal catalyst derived from (1*S*,2*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane.

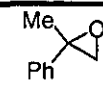
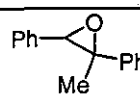
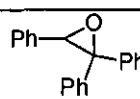
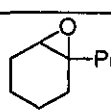
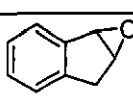
This iminium salt was tested in the catalytic asymmetric epoxidation of several alkenes at 0 °C, and a comparison of the results with those obtained using catalyst (14) is presented in Table 2. These results indicated that catalyst (16) in general induces much higher enantioselectivity in asymmetric epoxidation than others that were screened, providing in some cases dramatic improvements in ee over catalyst (14).

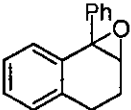
A feature of catalyst (16) is the *syn* relationship between the nitrogen heterocycle and the phenyl group. This implies that either the phenyl or the dihydroisoquinolinium group must be axial if the dioxane retains a chair conformation, as in (23) or (24) (Scheme 5).



Scheme 5: For a chair conformation one of the substituents must be axial.

Table 2: Catalytic asymmetric epoxidation using catalysts (14) and (16).^a

Catalyst	14			16		
	Yield (%)	ee (%)	Config.	Yield (%)	ee (%)	Config.
17 	68	8	(+)-(R)	64	20	(+)-(R)
18 	72	15	(+)-(1R,2R)	52	52	(-)-(1S,2S)
19 	43	5	(+)-(S)	54	59	(+)-(S)
20 	68	40	(+)-(1R,2R)	55	41	(-)-(1S,2S)
21 	34	3	(+)-(1S,2R)	52	17	(+)-(1S,2R)

22		73	20	(-)-(1 <i>S</i> ,2 <i>R</i>)	64	49	(-)-(1 <i>S</i> ,2 <i>R</i>)
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^a Conditions: Oxone (2 equiv), sodium carbonate (4 equiv), water/acetonitrile (1:1), 0 °C, 5 mol % catalyst.

Despite the similar size of the two substituents, ¹H NMR spectroscopy suggests the presence of only one conformer at ambient temperature; first, all the proton signals are sharp and the coupling constants corresponding to each of the protons of the 1,3-dioxane ring are consistent with a chair conformation, in accord with previous reports of substituted 2,2-dimethyl-1,3-dioxane rings.⁸ Secondly, in the ¹³C NMR spectrum, the geminal methyl groups appear at 17.98 and 28.68 ppm (axial and equatorial respectively); this is also consistent with a chair conformation.⁹ Conformer (**24**) would be expected to be the thermodynamically favored one as a result of reduced 1,3-diaxial interactions.

It is tempting to propose a stabilizing interaction between the electron cloud associated with the oxygen atom lone pairs and the electron-depleted carbon atom of the iminium unit, as shown in (**24**). One could envisage a bonding interaction between the p orbital on the carbon atom of the iminium unit and the in-phase combination of the axial lone pair sp³ orbitals on the two oxygen atoms.

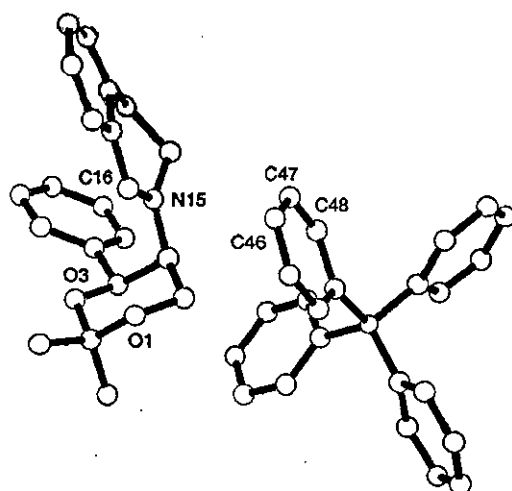


Figure 4: X-ray crystal structure of catalyst (**16**).

This suggestion is supported by single-crystal X-ray analysis (Figure 4). It is interesting that the X-ray analysis does not indicate a twist-boat conformation. The relative success of the dioxane-derived catalyst may stem partly from the high conformational rigidity, perhaps a result of the stereoelectronic effects discussed above. The strong preference of similar systems, such as those shown in Figure 5, to exist in such a conformation has been documented both experimentally and theoretically by Wilson.¹⁰

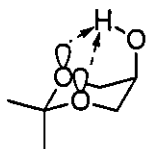
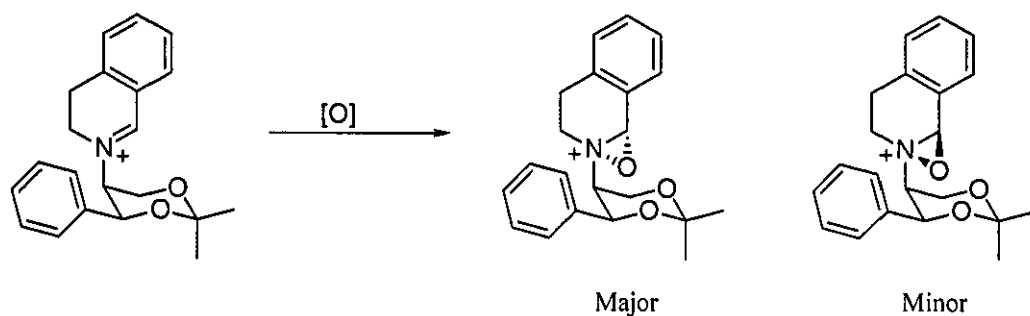


Figure 5: Wilson's work describing conformationally stabilizing electrostatic interactions.

In conformer (**24**), the phenyl substituent may hinder the attack of the oxidant at that side of the iminium bond, rendering the opposite side more accessible. This arrangement is thus likely to produce a preponderance of one of the two possible diastereoisomeric oxaziridinium intermediates (Scheme 6), and enantiocontrol would then result solely from the process of oxygen transfer to the substrate.



Scheme 6: The two possible diastereoisomers produced in oxaziridinium formation.

This high conformational rigidity is absent from the dihydroisoquinolinium salt (**14**) derived from (–)-isopinocampheylamine (Figure 6). Consequently, in that case, rotation around the bond between the nitrogen atom and the chiral unit may result in both diastereotopic faces of the iminium moiety becoming susceptible to attack by the oxidant, and the two diastereoisomeric oxaziridinium salts so formed may be very different in their potential for asymmetric induction in the epoxidation process.

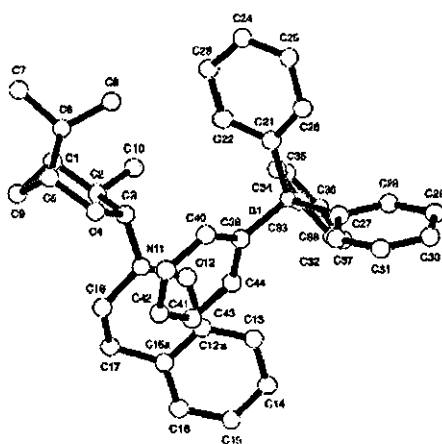


Figure 6: X-ray crystal structure of catalyst (14).

Two transition states have been proposed for the epoxidation of alkenes by dioxiranes and oxaziridines, the spiro and the planar (Figure 7). 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. In the planar transition state, the two components approach one another in such a way that these axes are parallel to one another, and they and the oxygen atom are in the same plane.

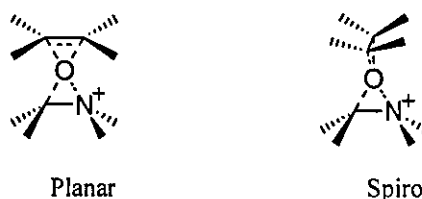


Figure 7: Geometrical approaches between the substrate and the reactive intermediate.

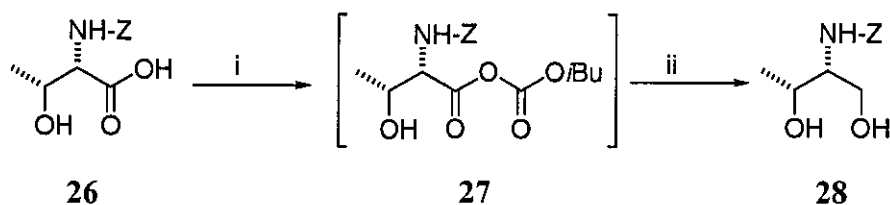
The spiro transition state is now generally accepted as the mechanism in operation during both dioxirane and oxaziridine mediated epoxidation. This work is also supported by theoretical and computational studies.¹¹

2.2 New Catalysts Based on Dihydroisoquinolinium Salts.

2.2.1 Iminium salts derived from amino acids.

The previous work, in section 2.1, concerning asymmetric epoxidation with iminium salt derived catalysts, pointed to a system containing a 1,3-dioxane unit (**16**), as this particular catalyst when tested gave the best results, i.e. when compared to the other systems tested, generally the enantiomeric excesses were higher. These results led to the idea that by altering the nature of the substituents located around the 1,3-dioxane unit of this catalyst we might be able to increase its effectiveness as a reagent for asymmetric epoxidation and investigate the properties which enable a high generality for differing substrates.

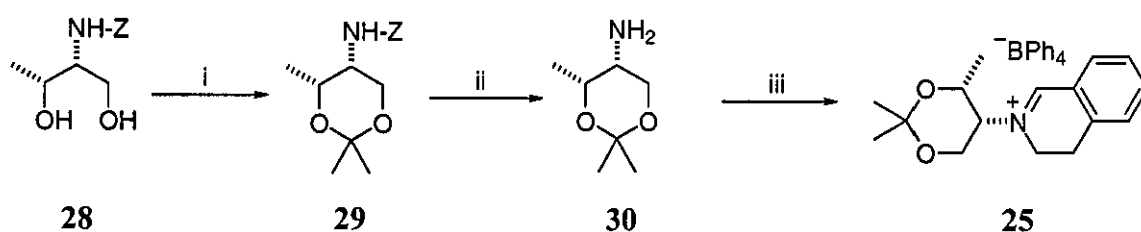
The first catalyst synthesized (**25**), bearing a methyl group at C4, was derived from *N*-Cbz protected (L)-threonine (**26**) in four synthetic steps. It was thought that this catalyst may help in elucidating the effect of large substituents at C4 of the 1,3-dioxane ring. Formation of the mixed anhydride (**27**), from (**26**) and subsequent reduction *in situ*, afforded the desired *N*-Cbz protected diol (**28**) in 70 % yield (Scheme 7).



Reagents and Conditions: i: NMM, *t*Bu-O-CO-Cl, DME, -15°C , 1 min; ii: NaBH_4 , H_2O , -15°C , 1 min, 70 %.

Scheme 7: Formation of **28** from *N*-CBZ protected (L)-threonine **26**.

Cyclization of (**28**) with 2,2-dimethoxypropane, acetone and *p*-toluenesulfonic acid produced the acetonide (**29**) in good yield (85 %), and subsequent removal of the *N*-Cbz group, with Pd/C under H_2 , afforded the primary amine required for cyclocondensation with the catalyst precursor 2-(2-bromoethyl)benzaldehyde (**2**) (Scheme 8), which gave the iminium salt (**25**) in 66 % yield.

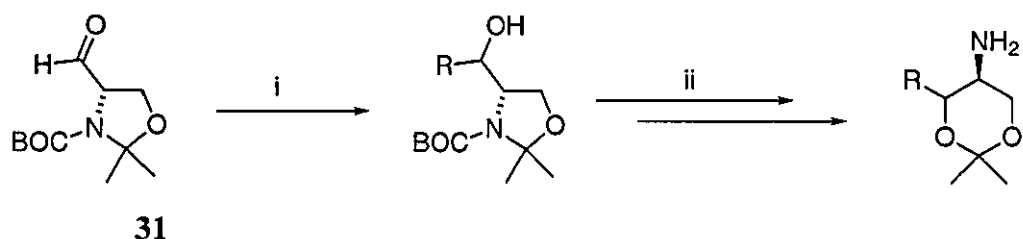


Reagents and Conditions: i: 2,2-DMP, acetone, *p*-TsOH, r.t., 8 h, 85 %; ii: Pd/C, H₂, ethanol, r.t., 8 h, 90 %; iii: 2, NaBPh₄, ethanol, r.t., 24 h, 66 %.

Scheme 8: Formation of catalyst **25** amino diol **28**.

This was a quick and convenient method for producing this type of catalyst and in theory large quantities of catalyst could be easily accessed. However this method does not allow for large catalyst diversity.

We envisaged that a range of primary amines could be produced from intermediate (**31**), Garner's aldehyde,¹² through a previously reported Grignard addition,¹³ and subsequent manipulations would then in theory allow significant catalyst diversity (Scheme 9).

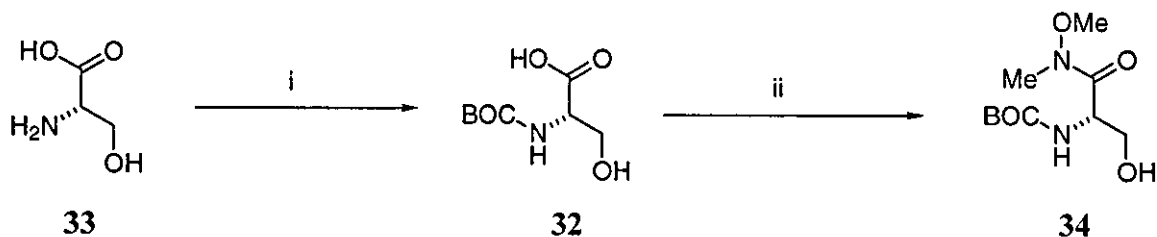


Reagents and Conditions: i: RMgX, ii: Steps.

Scheme 9: Grignard addition to Garner's aldehyde (**31**) as a possible route towards C4 substituted 5-amino-1,3-dioxanes.

Since Garner's first reported synthesis of aldehyde (**31**),¹² there has been considerable interest in this synthetic unit and improved syntheses have been reported.¹⁴ Of these, Taylor's synthetic strategy appears the most attractive,¹⁵ producing the aldehyde in 88 % overall yield from (D)-serine in four steps. This method also avoids several problematic and hazardous steps present in the other methods of synthesis, such as DIBAL-H reduction (inconsistent yields),¹⁶ Swern oxidation,¹⁶ and the use of diazomethane and iodomethane.¹²

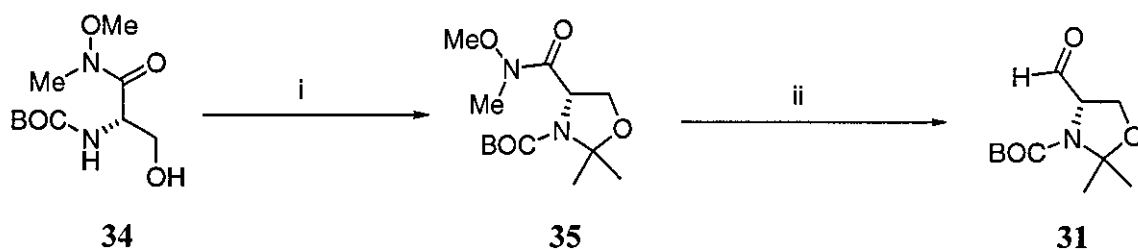
Garner's aldehyde was therefore synthesized using Taylor's method with comparable yields. Boc-(L)-serine (**32**) was produced quantitatively, from (L)-serine (**33**), using Boc anhydride and an aqueous solution of sodium hydroxide / 1,4-dioxane at 0 °C over 48 h. Formation of the Weinreb amide (**34**) was also high yielding; using *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride as the coupling agent and *N,O*-dimethylhydroxylamine with *N*-methylmorpholine as base, the product was isolated in 89 % yield (Scheme 10).



Reagents and Conditions: i: (Boc)₂O, NaOH (aq.), 1,4-dioxane, 0 °C-r.t., 48 h, 100 %.; ii: MeNH(OMe).HCl, EDCI, NMM, DCM, -15 °C, 1.5 h, 89 %.

Scheme 10: Synthesis of the Weinreb amide **34** from (L)-serine **33**.

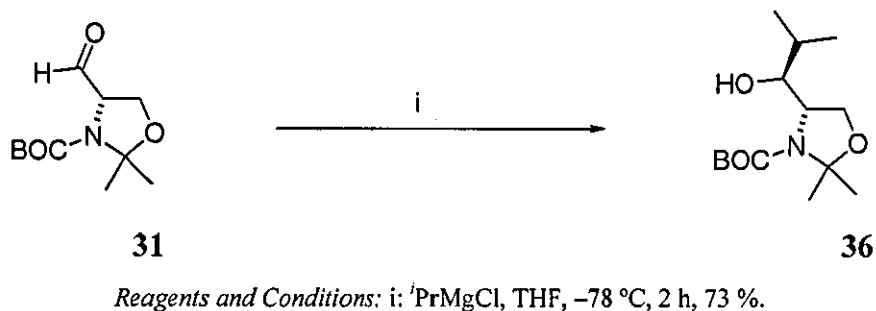
Subsequent cyclization of (**34**) with 2,2-dimethoxypropane in acetone and boron trifluoride-diethyletherate as the acid source provided the precursor (**35**) to Garner's aldehyde in high yield. Lithium aluminium hydride reduction of the Weinreb amide furnished the desired aldehyde (**31**) in good yield and it was found to be *ca.* 95 % pure by ¹H-NMR spectroscopy. This sequence has the added benefit of not requiring chromatography at any stage (Scheme 11).



Reagents and Conditions: i: 2,2-DMP, acetone, BF₃.Et₂O, r.t., 1.5 h, 89 %.; ii: LiAlH₄, THF, 0 °C, 30 min, 96 %.

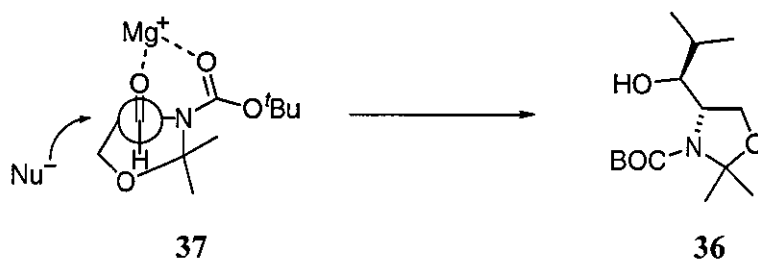
Scheme 11: The synthesis of Garner's aldehyde **31** using Taylor's method.

With Garner's aldehyde in hand we were able to attempt a catalyst synthesis. A catalyst containing no aromatic substitution at C4 of the 1,3-dioxane was required. It was hoped that this type of catalyst would indicate whether a steric or electronic effect helped to induce chirality in epoxidations carried out with catalyst (**16**). Therefore efforts were concentrated on producing a 5-amino-1,3-dioxane substituted with an isopropyl group at C4 (**36**) in place of the phenyl group present in the original catalyst (**16**). A report by Joullié has shown that isopropylmagnesium chloride adds to the Garner's aldehyde in a highly stereoselective manner.¹³ However, their reported selectivity (6:1 in favour of the *syn* product) disagrees with another group's work where their reported selectivity is higher (14:1 in favour of the *syn* product).¹⁷ In our hands this reaction is very efficient and a yield of 73 % was observed with only the *syn* product being detectable by ¹H NMR spectroscopy (only one set of doublets being observed for the methylene protons associated with the isopropyl group) (Scheme 12).



Scheme 12: Addition of *iso*-propylmagnesium chloride to Garner's aldehyde **31**.

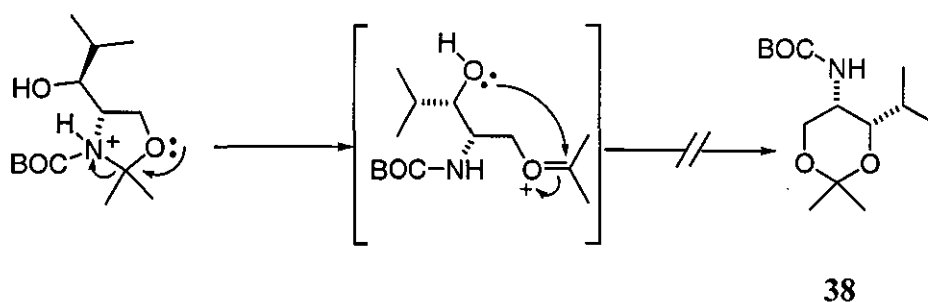
The origin of selectivity is thought to stem from a chelated intermediate as shown in Scheme 13. The chelated Cram model (**37**) explains the isolation of the *syn* isomer (**36**) as the major product.



Scheme 13: Postulated Cram chelate intermediate in the synthesis of **36**.

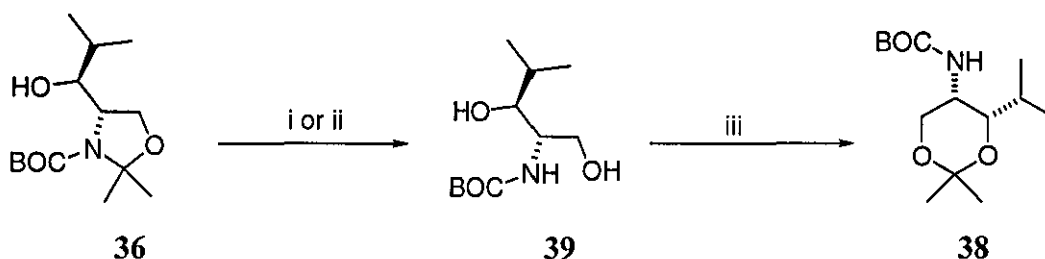
The next step in the synthesis was to convert the Grignard addition product (**36**) into the corresponding 1,3-dioxane (**38**). We believed that this process could be achieved

in one step, by an intramolecular cyclization. Use of camphor sulfonic acid, 2,2-dimethoxypropane and acetone, protonation of the nitrogen group and subsequent attack by the free oxygen of the hydroxy group should yield the desired product (Scheme 14). However, this attempt failed yielding only unreacted starting material. At elevated temperatures we believed that the 1,3-dioxane would be produced because we had expected it to be the thermodynamic product, but again only unreacted starting material was recovered. Other reagents were tried, such as trifluoroacetic acid in dichloromethane, which is reported to induce such transformations,¹⁸ but destroyed the starting material. The required product was not produced using this methodology.



Scheme 14: Proposed mechanism for the conversion of **36** to **38**.

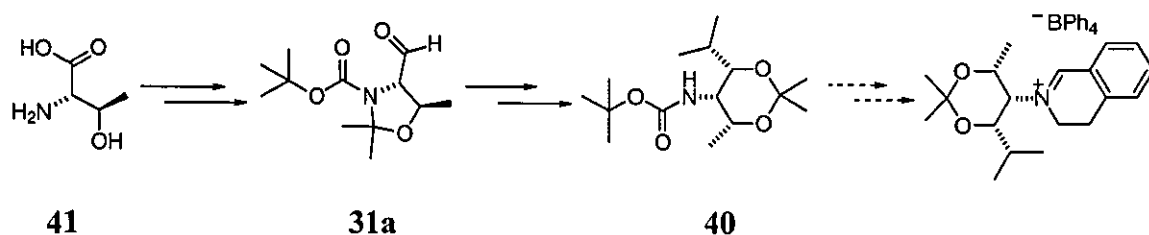
We therefore adopted an intermolecular approach by stirring the Grignard addition product (**36**) with Amberlyst-15 resin in methanol to give the 1,3 diol (**39**) in approximately 55 % yield. This was improved by using *p*-toluenesulfonic acid in methanol to give a yield of 80 %. The diol produced was then stirred in acetone and 2,2-dimethoxypropane with a catalytic amount of *p*-toluenesulfonic acid, to afford the desired 1,3-dioxane (**38**) in 82 % yield (Scheme 15).



Reagents and Conditions: i: Amberlyst 15, MeOH, r.t., 12 h, r.t., 55 %; ii: *p*-TsOH, MeOH, r.t., 12 h, 80 %; iii: 2,2-DMP, acetone, *p*-TsOH, r.t., 82 %.

Scheme 15: An intermolecular approach to 1,3-dioxane **38**.

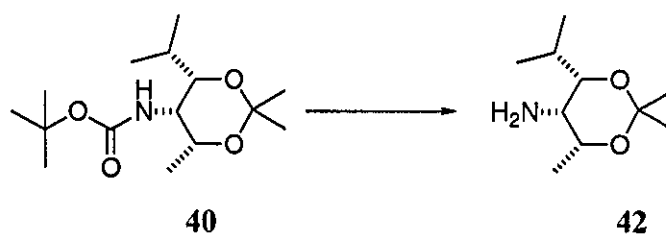
During the synthesis of this intermediate the analogous compound (**40**) derived from (L)-threonine (**41**) was synthesized using the same methodology. This compound would add a methyl group at C6 in the catalyst structure, which could in theory help control the approach of the incoming substrate during the epoxidation (Scheme 16).



Scheme 16: An analogous catalyst derived from (L)-threonine

The next step in the synthesis was to produce the primary amines for condensation with 2-(2-bromoethyl)benzaldehyde (**2**). However, this proved somewhat problematic. There are a plethora of reports describing Boc deprotection and the standard method is the use of trifluoroacetic acid in dichloromethane.¹⁹ This procedure is not applicable to our substrates due to the presence of the acid-labile acetonide group. Indeed reactions using this particular method only resulted in decomposition of the starting material, even when reactions were conducted at low temperature (in the range $-78 - 0$ °C).

A mild method of deprotection was therefore required. Work by Subhas Bose²⁰ on Lewis acid removal of the *N-tert*-butoxycarbonyl protecting group had shown that in a variety of compounds, whether acid or base sensitive, the *N*-Boc group could be removed effectively using aluminium chloride in dichloromethane. Following the original conditions described, one equivalent of aluminium chloride, 0 °C- r.t., the threonine derived 1,3-dioxane (**40**) was submitted to the reaction. After 24 h formation of product (**42**) had occurred, but some starting material still remained. Leaving the reaction mixture for a further 24 hours gave no change in the TLC, and work up showed that the compound had been deprotected, but in a low yield, 24 %, with 30 % of unreacted starting material being recovered (Scheme 17).

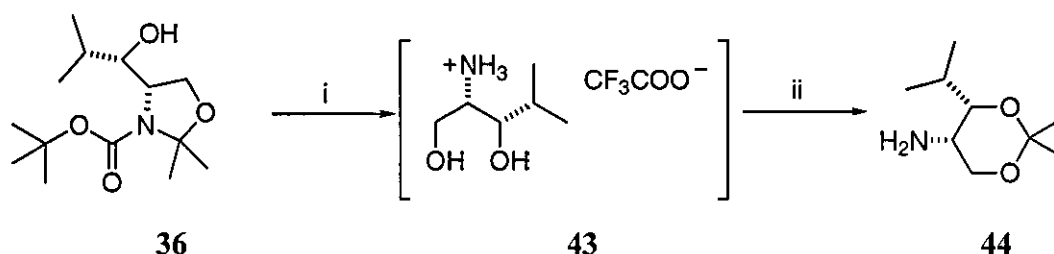


Reagents and Conditions: AlCl_3 , DCM, r.t., 48 h, 24 %.

Scheme 17: Attempted deprotection of **41** using Bose's method, with AlCl_3 .

In an effort to increase the yield the solutions were cooled to $-78\text{ }^\circ\text{C}$ before addition of the aluminium chloride. The reaction was monitored by TLC and after 8 hours at this temperature formation of product had not occurred. The solution was allowed to reach room temperature overnight; however, this method failed to increase the yield significantly, giving only 30 % of product (**42**) and 25 % of recovered starting material. Perhaps elevating the temperature here would have driven the reaction to completion; further work in this area is required to optimize this method for the synthesis of 5-amino-1,3-dioxanes.

It therefore appeared that a more successful and reliable method of *N*-Boc deprotection was required. By moving a couple of steps back in the catalyst synthesis to the Grignard addition product (**36**), we could perform a global deprotection of both the acetonide and the Boc group simultaneously with trifluoroacetic acid in dichloromethane (Scheme 18). Exposing the substrate (**36**) to TFA in dichloromethane at $0\text{ }^\circ\text{C}$, after three hours yielded the crude deprotected diol as the trifluoroacetic acid salt (**43**). The free amine proved difficult to isolate and so the crude product was used directly to form the 1,3-dioxane (**44**).

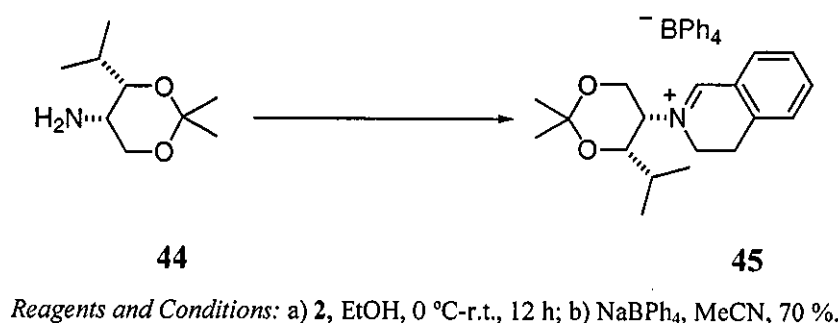


Reagents and Conditions: i: TFA, DCM, $-78\text{ }^\circ\text{C}$ -r.t., 3 h; ii: 2,2-DMP, acetone, *p*-TsOH, r.t., 8 h, 70 %.

Scheme 18: Boc deprotection and subsequent cyclization to form the desired primary amine **44**.

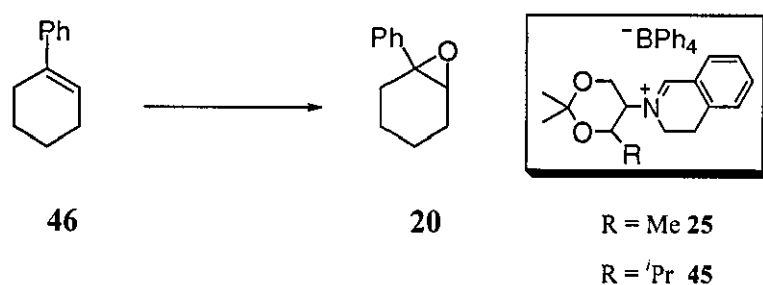
There is literature precedent for this type of reaction, hydrobromide salts usually being the preferred substrates.^{21,22} Treatment of the trifluoroacetic acid salt (**43**) with 2,2-dimethoxypropane in acetone and *p*-toluene sulfonic acid gave only one product, the desired 5-amino-1,3-dioxane (**44**) in 70 % yield (Scheme 18). However, this method did not always give reproducible results and similar attempts using the threonine analogue proved unsuccessful.

The primary amine (**44**) was then cyclocondensed with 2-(2-bromoethyl)benzaldehyde (**2**) to form the corresponding iminium salt (**45**) in 70 % yield (Scheme 19).



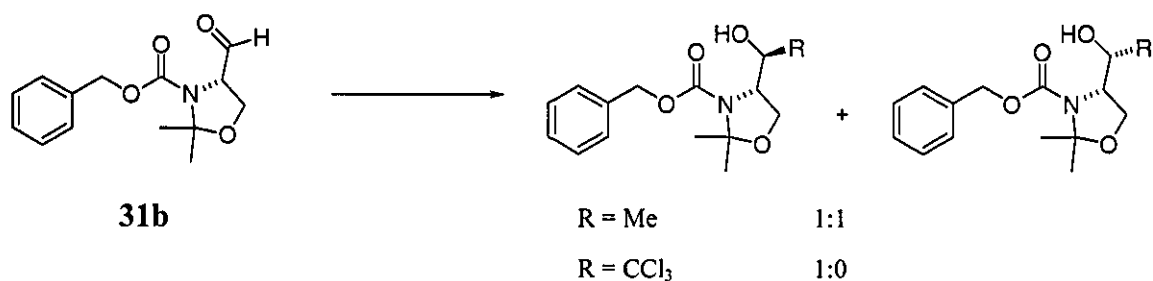
Scheme 19: Formation of the isopropyl substituted iminium salt **45**.

Catalyst (**25**) and (**45**) were used for the standard epoxidation of 1-phenylcyclohexene (**46**) described in section 2.1 (Scheme 20). The catalysts were quite reactive and gave complete conversion to epoxide within one hour when 10 mol % of catalyst was employed. Disappointingly, both catalysts produced near-racemic 1-phenylcyclohexene oxide (**20**).



Scheme 20: Catalytic asymmetric epoxidation of 1-phenyl cyclohexene **46** using catalysts **25** and **45**.

Due to the inherent problems of Boc deprotection, this approach to 5-amino-1,3-dioxanes was abandoned. However, it should be noted here that an analogous synthesis using the Cbz protecting group in preference to the Boc group was attempted and good yield of the corresponding Garner aldehyde equivalent (**31b**) was achieved. But isopropylmagnesium chloride addition did not prove as selective and a complex mixture of products was observed. This is in accord with other findings in this area;²³ Beaulieu has reported that addition of methylmagnesium bromide to the Garner aldehyde equivalent (**31b**), at $-78\text{ }^{\circ}\text{C}$, led to a 1:1 mixture of diastereoisomers (Scheme 21). Selectivity is only observed when the sterically demanding trichloromethane anion is employed as the nucleophile.

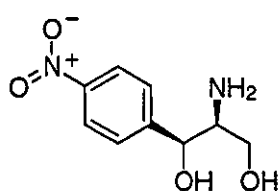


Reagents and Conditions: Where R = Me: MeMgBr, THF, $-78\text{ }^{\circ}\text{C}$; Where R = CCl₃: Cl₃CCOOTMS, K₂CO₃, 18-crown-6. Neat, $90\text{ }^{\circ}\text{C}$.

Scheme 21: Beaulieu's observed selectivity for addition of nucleophiles to compound **31c**.

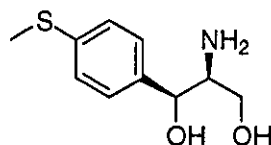
2.2.2 Iminium salts derived from amino diols.

The results described in the previous section suggest that an aromatic C4 substituent present in the 1,3-dioxane is vital for catalyst enantioselectivity. We therefore began the synthesis of a variety of catalysts containing different substitution patterns in the aromatic ring at C4. Fortunately we found that two amino diols, (1*S*,2*S*)-(+)-2-amino-1-(*p*-nitrophenyl)-1,3-propanediol (**47**) and (1*S*, 2*S*)-(+)-2-amino-1-(*p*-methylthiophenyl)-1,3-propanediol [(+)-thiomicamine] (**48**), are commercially available.



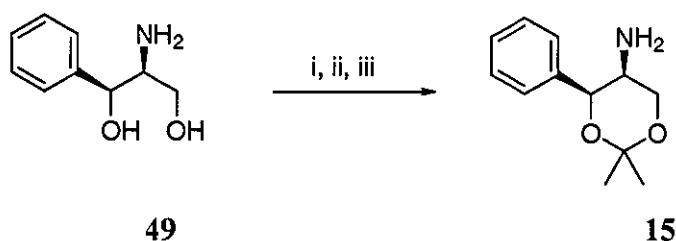
47

48



48

By using an analogous procedure to that described by Nordin and Thomas for the conversion of (1*S*,2*S*)-(+)-2-amino-1-(phenyl)-1,3-propanediol (**49**) to the 5-amino-1,3-dioxane (**15**) (Scheme 22), we were able to produce two primary amines for condensation to form the corresponding iminium salts.²²

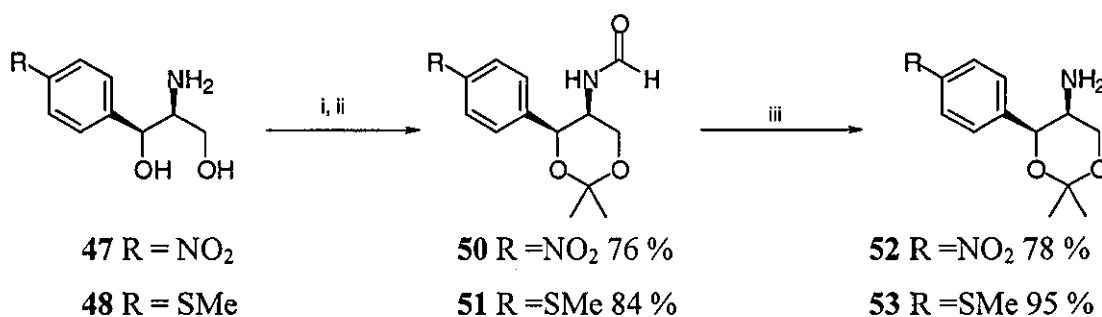


49

15

Reagents and Conditions: i: MeOCHO, MeOH, r.t.; ii: 2,2-DMP, acetone, CSA, r.t.; iii: H₂NNH₂·H₂O, Δ, 79 % from **49**.

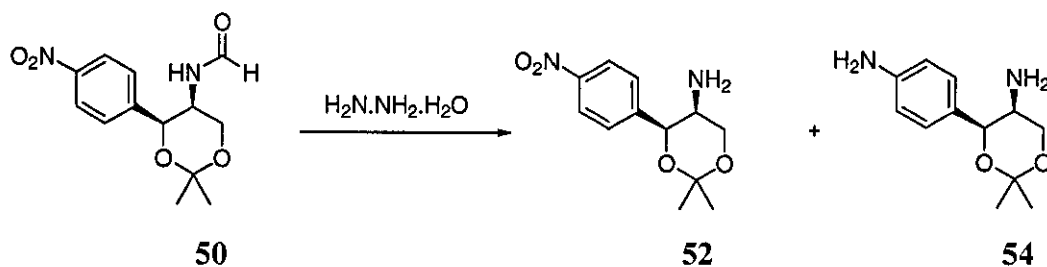
Scheme 22: Nordin and Thomas's approach to the 5-amino-1,3-dioxane **15**.



Reagents and Conditions: i: MeOCHO, MeOH, r.t.; ii: 2,2-DMP, acetone, CSA, r.t.; iii: H₂NNH₂·H₂O, Δ.

Scheme 23: Formation of 5-amino-1,3-dioxanes, **52** and **53**, from amino diols.

Treatment of the aminodiols (**47**) and (**48**) with methyl formate in methanol furnished the formate protected diols, subsequent cyclization with 2,2-dimethoxypropane, acetone and (+/-)-10-camphor sulfonic acid (CSA) afforded the 5-amido-1,3-dioxanes (**50**) and (**51**), and simple deprotection with hydrazine hydrate under reflux afforded the desired primary amines (**52**) and (**53**) (Scheme 23). This method is convenient and high yielding. Conversion of the nitro compound (**50**) to the free amine (**52**) required some modification, as prolonged exposure to hydrazine hydrate also reduced the nitro functionality to the amine (**54**). Optimum conditions were therefore established: a 78 % yield of the desired compound could be achieved if the reaction mixture was only refluxed for 1 h. Poor conversions to (**52**) are observed if the reactions are carried out at ambient temperature (Scheme 24, Table 3).

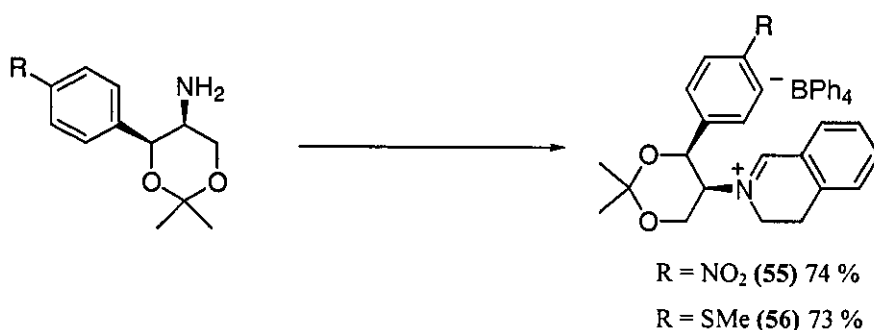


Scheme 24: Deprotection of formamide **50** resulted in a mixture of two products **52** and **54**.

Table 3: Effect of reaction time on the formation of **52**.

Entry	Reaction Time (h)	Yield of 52 (%)	Yield of 54 (%)
1	2.5	5	89
2	1.5	40	53
3	1.0	78	8

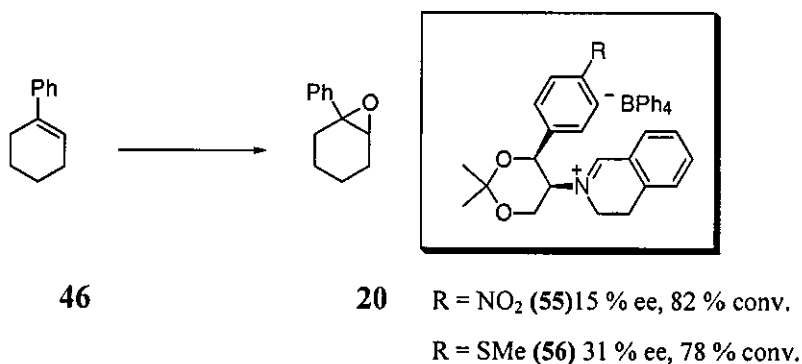
With the amines in hand, two further catalysts, (**55**) and (**56**), were produced in good yield, each with groups offering a different electronic effect in the aromatic group at C4 (Scheme 25). Again a standard epoxidation of 1-phenylcyclohexene (**46**) with 10 mol % of catalyst was performed (Scheme 26).



Reagents and Conditions: a) **2**, EtOH, 0 °C-r.t., 12 h; b) NaBPh₄, MeCN.

Scheme 25: Iminium salt formation using 5-amino-1,3-dioxanes **52** and **53**.

These catalysts were found to be slightly less reactive than catalyst (**16**) and even after 2 hours did not afford complete conversions to epoxide. The ee of the epoxide formed for catalyst (**55**) was quite low (15 % ee) compared to the ee obtained with catalyst (**16**) (40 % ee). Catalyst (**56**) showed slightly less conversion to epoxide; the ee was somewhat better than catalyst (**55**) (31 % ee), but not as good as that obtained with the original catalyst (**16**).



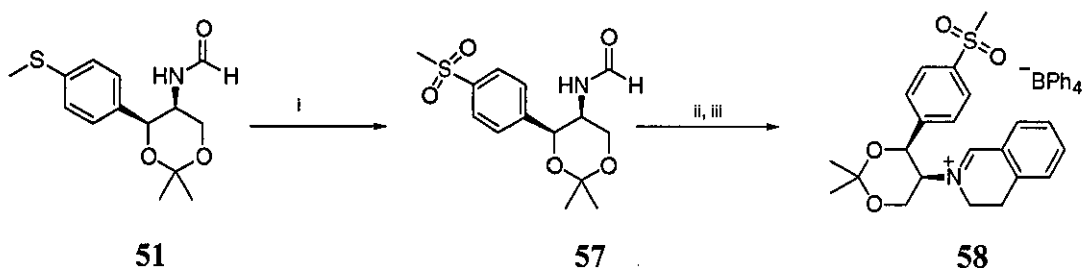
Reagents and Conditions: Iminium Salt (10 mol %), Oxone (2 eq.), Na₂CO₃ (4 eq.), MeCN/H₂O (1:1), 0 °C, 2 h.

Scheme 26: Epoxidation of 1-phenylcyclohexene (**46**) using catalysts **55** and **56**.

We found that the thiomethyl catalyst (**56**) is susceptible to oxidation during the epoxidation reaction. It is well known that oxone can be used to oxidize sulfides to sulfoxides or sulfones.²⁴ Analysis of the catalyst by ¹H NMR spectroscopy after being subjected to the reaction conditions showed the proton signal for the thiomethyl group to have shifted from δ 2.42 to δ 3.0. Comparison with authentic material, prepared by

isolation of catalyst (**58**) after exposure to the epoxidation conditions, confirmed that the catalyst had been oxidized to the sulfone. Interestingly no sulfoxide was observed.

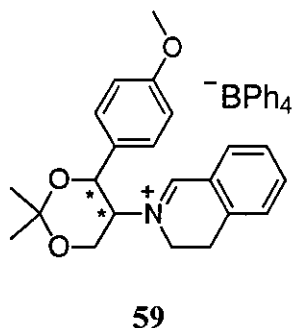
Due to the modification of this catalyst under the reaction conditions two further catalysts were synthesized. These cannot be altered by the reaction conditions; the first was a simple modification of catalyst (**56**). Using the previously described intermediate (**51**) *m*-CPBA oxidation of the sulfide to the sulfone (**57**) was achieved in 85 % yield. Then, using the conditions described earlier, the formate (**57**) was deprotected with hydrazine hydrate, and cyclocondensed to form the corresponding iminium salt (**58**), again in good yield (Scheme 27).



Reagents and Conditions: i: *m*-CPBA (2.2 eq.), DCM/CHCl₃, 0 °C, 4 h, 85 %; ii: H₂NNH₂·H₂O, Δ, 95 %; iii: a) **2**, EtOH, 0 °C-r.t., 12 h; b) NaBPh₄, MeCN, 73 %.

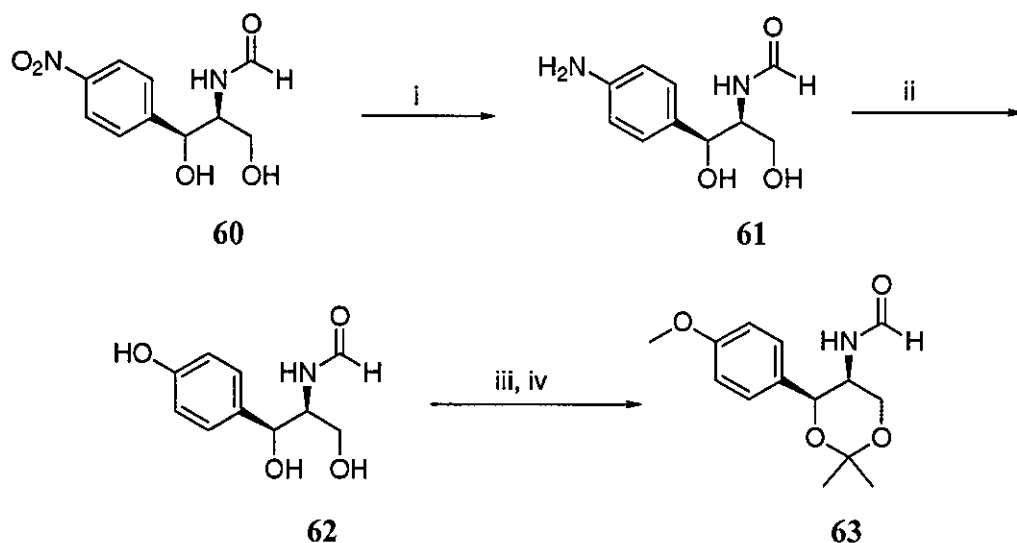
Scheme 27: *m*-CPBA oxidation of sulfide **51** and subsequent iminium salt formation.

The second target was to produce a catalyst bearing an electron donating group in the *para*-position of the aromatic ring at C4 (**59**). Initial attempts, however, proved fruitless.



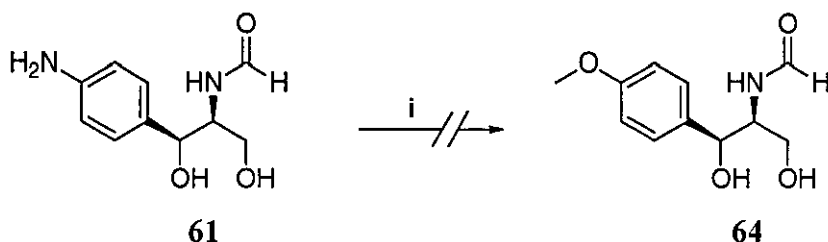
Our original strategy utilized a diazotization reaction (Scheme 28). Hydrogenation of the previously prepared *N*-{(1*S*,2*S*)-[2-hydroxy-1-hydroxymethyl-2-(4-nitro-phenyl)-ethyl]}-formamide (**60**) to the corresponding amino compound (**61**) proved highly successful (99 % yield). However, the subsequent diazotization reaction was

extremely poor, giving at best 15 % yield, even though the reaction had previously been reported to give yields of up to 35%.²⁵ Further manipulation of product (61) afforded the 4-hydroxyphenyl-1,3-dioxane (62). Methylation, after some experimentation, was achieved with caesium carbonate and dimethyl sulfate, producing the 4-methoxyformate (63), but separation from by products brought through from the initial diazotization reaction proved difficult. Before this approach was abandoned, an interesting reaction, where direct conversion from an amine group to a methoxy group is possible, reported by Quin and Macdiarmid, using *iso*-amyl nitrite in methanol, was attempted (Scheme 29).²⁶ Unfortunately, when using our substrate, this led to a complex mixture of products, including loss of the formate protecting group.



Reagents and Conditions: i: H₂/Pd, ethanol, r.t. 24 h, 99 %; ii: a) NaNO₂, H₂SO₄, b) pH 6, Δ, 15 %; iii, 2,2-DMP, acetone, CSA, r.t., 4 h, 72 %; iv: Cs₂CO₃, Me₂SO₄, CH₂Cl₂, 48 h, 72 %.

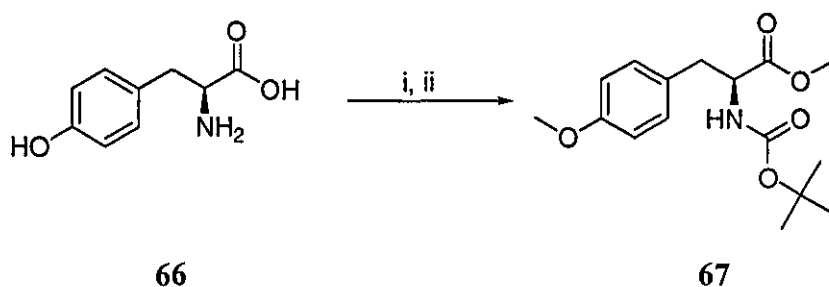
Scheme 28: Initial synthesis of the *p*-methoxy formate.



Reagents and Conditions: i: a) H₂SO₄, MeOH, (CH₃)₂CHCH₂CH₂ONO, 0 °C, 3 h; b) Δ, 1 h.

Scheme 29: Attempted synthesis of 64 using Quin and Macdiarmid's method.

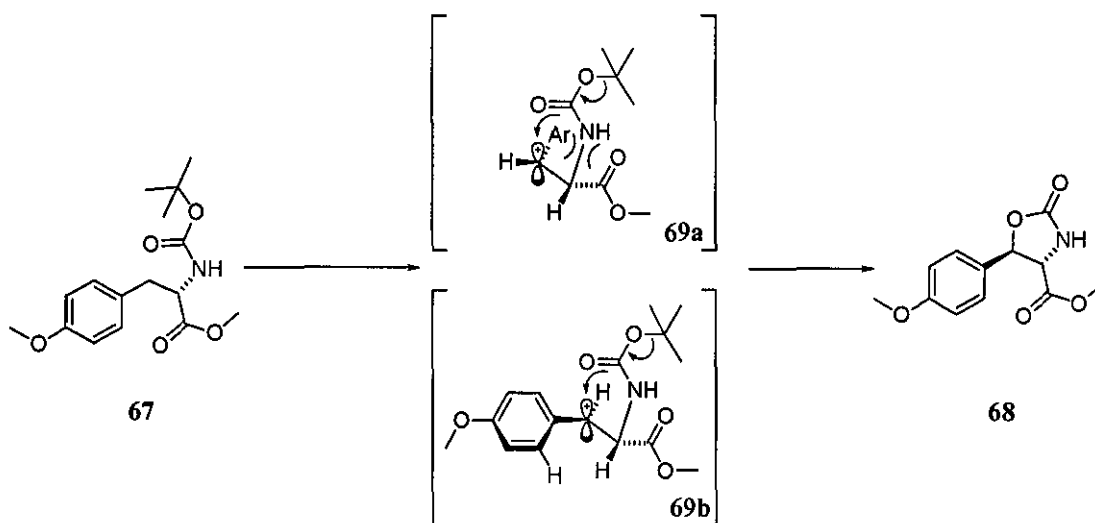
Methoxyaryl catalyst (**65**) was eventually produced from commercially available (L)-tyrosine (**66**) (Scheme 30). Boc protection and methylation of the acid and phenol with potassium hydroxide and iodomethane afforded (**67**) the required precursor to (**68**).



Reagents and Conditions: i: (Boc)₂O, NaOH (aq.), 1,4-dioxane, 0 °C-r.t., 48 h, 73 %; ii: MeI (2.2 eq.), KOH (2.2 eq.), DMF, 0 °C-r.t. 3.5 h, 74 %.

Scheme 30: Formation of Boc protected, dimethylated (L)-tyrosine.

Following the work of Ohfuné,²⁷ the benzylic position of (**67**) was oxidized with potassium persulfate (K₂S₂O₈) and copper sulfate (cat.) to form the oxazolidinone (**68**) in a highly diastereoselective manner (diastereomeric ratio ≥ 98 % *R* at C3) (Scheme 31).



Reagents and Conditions: K₂S₂O₈, CuSO₄, H₂O/MeCN (1:1), 70 °C, 3h, 52 %.

Scheme 31: Ohfuné's cyclic carbamate formation.

The authors suggest that this high selectivity in cyclic carbamate formation arises because the reaction proceeds via the more stable benzyl cation intermediate (**69b**). The conformer (**69a**) is more strained than (**69b**) by steric interaction between the ester group and the *ortho* hydrogen. Intramolecular trapping of this cation by a carboxyl oxygen and subsequent release of the *tert*-butyl cation, which is believed to be more stable than the benzylic cation of (**69**), is thought to be a driving force for the reaction. This was supported by Ohfuné's observation that only poor yields were obtained from compounds containing other amino protecting groups, such as the Cbz group. Confirmation of the stereoselectivity was achieved from the X-ray crystal structure of compound (**68**), as shown in Figure 8.

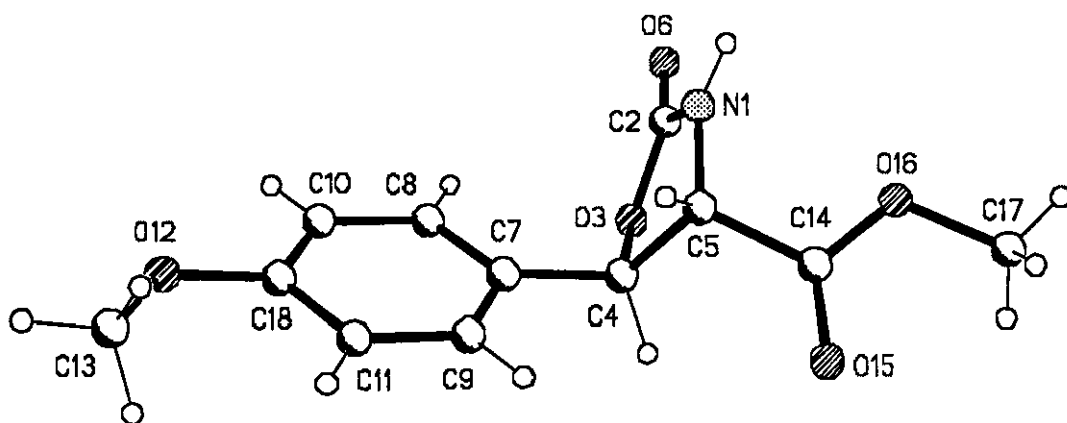
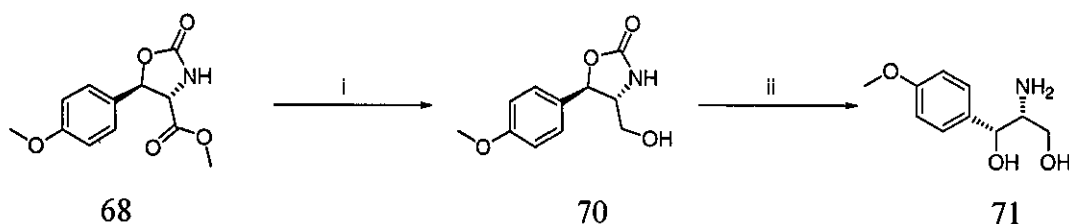


Figure 8: X-ray crystal structure of compound (**68**).

Although this reaction is highly stereoselective, some problems were encountered during the synthesis. Yields tended to vary on scale up of the reaction. Initially the reaction on 4 mmol of substrate afforded 50 % of desired product (a good yield according to the literature yield of 55 %), but on increasing the quantities up to 26 mmol a drop in yield to 40 % was observed. Optimum conditions were found when carrying the reaction out on a 16 mmol scale - a 52 % yield of product was obtained. Attempts to drive the reaction to completion proved fruitless. Generally increased reaction times and temperatures decreased the overall yield due to generation of higher levels of the side product 4-methoxy-benzaldehyde (a product of over-oxidation).²⁸ Milder reaction conditions resulted in no product formation.

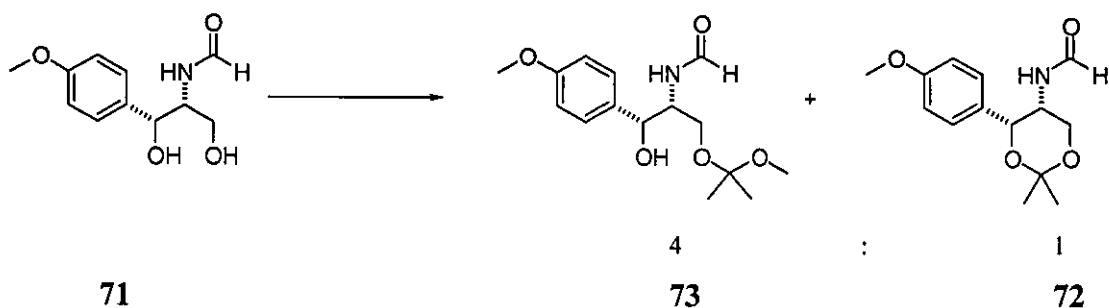
The carbamate (**68**) was then reduced to (**70**); this was initially achieved with lithium aluminium hydride, but sodium borohydride provided a superior yield (91 % compared to 77 %), probably due to the ease of work-up associated with the sodium borohydride reactions. Hydrolysis in refluxing 1M sodium hydroxide yielded the *syn*-(1*R*,2*R*)-amino diol (**71**) in 20 minutes (Scheme 32). Interestingly when the reaction was carried out at room temperature no product was observed for up to 48 h.



Reagents and Conditions: i: NaBH₄, EtOH, 0 °C-r.t. 45 min, 91 %, ii: 1M NaOH, Δ, 20 min, 93 %.

Scheme 32: Formation of the *p*-methoxy diol **69**.

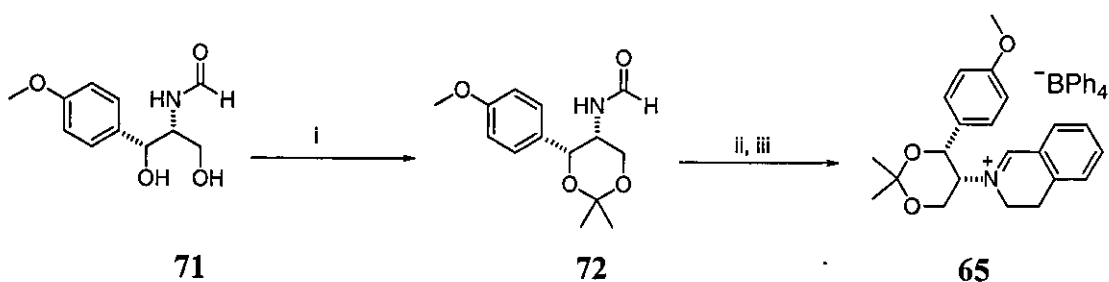
The aminodiol was then subjected to the synthetic procedure outlined in Scheme 23. However, attempted cyclization of the formate protected diol (**71**) to give the 1,3-dioxane (**72**) did not proceed smoothly with camphor sulfonic acid (Scheme 33). Instead, the uncyclized product (**73**) was formed as the major product in a 4:1 ratio with (**72**).



Reagents and Conditions: 2,2-DMP, acetone, CSA, r.t., 12 h.

Scheme 33: Attempted formation of dioxane **72** using CSA.

Increased equivalents of CSA, elevated temperatures and longer reaction times failed to increase the ratio of (72) and (73). This problem was also noted on formation of the formate dioxane of the original amine (15); there the problem was rectified by using a catalytic amount of HBr as the acid source.²² However, under these conditions we only observed degradation of the starting material (71). Eventually, we discovered that the addition of catalytic boron trifluoride-diethyletherate to the reaction gave the desired 6-membered dioxane (72) exclusively in good yield. Subsequent deprotection and condensation with 2-(2-bromoethyl)benzaldehyde yielded the catalyst (65) (Scheme 34).

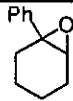
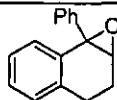
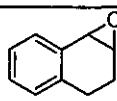
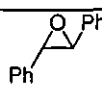
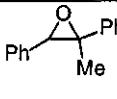
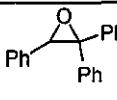


Reagents and Conditions: i: 2,2-DMP, acetone, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, r.t. 45 min, 81 %; ii: $\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$, Δ , 2.5 h, 95 %; iii: a) 2-(2-bromoethyl)benzaldehyde, EtOH, 0 °C-r.t., 12 h b) NaBPh_4 , MeCN, r.t., 5 min., 71 %.

Scheme 34: Formation of the p-methoxy catalyst 65.

With these further two catalysts in hand, a range of substrates were tested in the asymmetric epoxidation reaction (Table 4).

Table 4: Catalytic asymmetric epoxidation of unfunctionalized alkenes using Oxone and iminium salts **16**, **55**, **56**, **58** and **65**^a

Catalyst	16	55	56	58	65 ^f
R =	(H)	(NO ₂)	(SMe)	(SO ₂ Me)	(OMe)
Epoxide	In all cases: ee (%) ^b / Conversion (%) ^c / Configuration ^d				
20 	41 / 55 ^e / (-)-1 <i>S2S</i>	15 / 82 / (-)-1 <i>S2S</i>	31 / 78 / (-)-1 <i>S2S</i>	39 / 100 / (-)-1 <i>S2S</i>	45 / 54 ^e / (+)-1 <i>R2R</i>
22 	49 / 64 ^e / (-)-1 <i>S2R</i>	42 / 100 / (-)-1 <i>S2R</i>	49 / 100 / (-)-1 <i>S2R</i>	47 / 100 / (-)-1 <i>S2R</i>	63 / 62 ^e / (+)-1 <i>R2S</i>
74 	40 / 92 / (-)-1 <i>S2R</i>	41 / 52 / (-)-1 <i>S2R</i>	35 / 82 / (-)-1 <i>S2R</i>	45 / 61 / (-)-1 <i>S2R</i>	46 / 83 / (+)-1 <i>R2S</i>
75 	15 / 56 ^e / (-)- <i>S,S</i>	0 / 100 / -	0 / 85 / -	0 / 100 / -	35 / 54 ^e / (+)- <i>R,R</i>
18 	52 / 52 ^e / (-)-1 <i>S2R</i>	35 / 100 / (-)-1 <i>S2R</i>	42 / 85 / (-)-1 <i>S2R</i>	32 / 100 / (-)-1 <i>S2R</i>	60 / 55 ^e / (+)-1 <i>R2S</i>
19 	59 / 54 ^e / (+)-(<i>S</i>)	33 / 100 / (+)-(<i>S</i>)	51 / 67 / (+)-(<i>S</i>)	50 / 100 / (+)-(<i>S</i>)	71 / 60 ^e / (-)-(<i>R</i>)

^a Epoxidation conditions: Iminium salt (10 mol %), Oxone (2 eq), Na₂CO₃ (4 eq), MeCN:H₂O (1:1), 0°C, 2 h. ^b Enantiomeric excess determined by ¹H-NMR with Eu(hfc)₃ (0.1 mol eq) as chiral shift reagent or by Chiral HPLC on a Chiralcel OD column. ^c Conversion evaluated from the ¹H-NMR by integration alkene versus epoxide. ^d The absolute configuration of the major enantiomer was determined by comparison to those reported in the literature. ^e Isolated yield. ^f Catalyst configuration (4*R*,5*R*).

We found that the thiomethyl catalyst (**56**) gave the poorest epoxide conversions; we believe this to be due to the reason presented above (the susceptibility of the thiomethyl group to undergo oxidation during the epoxidation reaction).

Iminium salt (**55**), containing the strongly electron-withdrawing 4-nitro group, generally gave lower conversions than did catalysts (**16**), (**58**), and (**73**), all of which gave similar conversions to epoxide. By far the most active catalysts were (**16**) and (**73**), both of which completely epoxidized 1-phenylcyclohexene (**46**) in under 3 minutes.

In terms of enantioselectivity the 4-nitroiminium salt (**55**) gave the worst results,

giving at best 41% ee for 1,2-dihydronaphthalene (entry 3). Both sulfur-based catalysts (**55**) and (**56**) gave similar ees (probably due to the oxidation of (**55**) to (**56**) under the reaction conditions). One interesting point to note is that catalysts with an electron-withdrawing group at the 4-position (**55**, **56** and **58**) are unable to epoxidize *trans*-stilbene enantioselectively (entry 4).

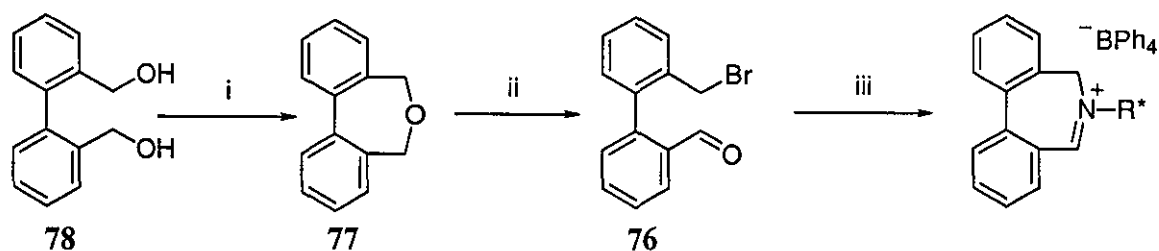
Undoubtedly the best catalyst was the 4-methoxyiminium salt (**65**). It imparted the highest enantioselectivity we have observed, giving triphenylethylene oxide with 71% ee in 60% yield in only 30 minutes (entry 6). In general, the ees for each of the alkenes tested have been improved by this catalyst over others we have tested, and even *trans*-stilbene oxide (**75**) is formed with 35% ee.

2.3 Catalysts Based on Dibenzo[*c,e*]azepinium salts.

In our ongoing efforts to develop new and more selective catalysts based on iminium salts a new family of catalyst was produced, in which the dihydroisoquinolinium moiety has been replaced by a biphenyl structure fused to a seven-membered azepinium salt.²⁹ A similar system was developed some years ago by Aggarwal but with axial chirality, achiral at the nitrogen;³⁰ the system reported some good results, although the enantioselectivity of the catalyst was dependent upon the substitution pattern of the alkene.

2.3.1 Introduction. Previous findings using dibenzo[*c,e*]azepinium salts.³¹

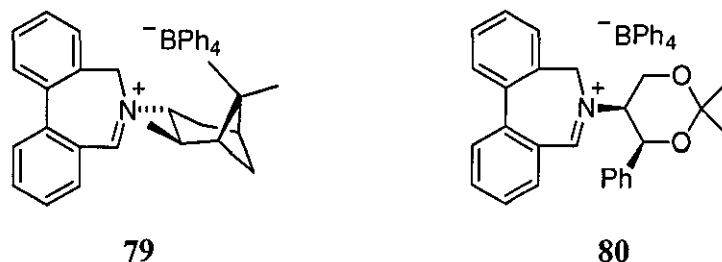
The preparation of this new family of catalyst was achieved by starting from an enantiomerically pure primary amine and 2-[2-(bromomethyl)phenyl]benzaldehyde (**76**) (Scheme 35). 2-[2-(bromomethyl)phenyl]benzaldehyde was prepared from the corresponding dibenzoxepine (**77**), by treatment with molecular bromine in refluxing carbon tetrachloride for 1 h, following a similar procedure already proven in the dihydroisoquinolinium salt series. The catalysts are synthesized in three steps starting from commercially available 2,2'-biphenyl dimethanol (**78**).



Reagents and Conditions: i: HBr (24 %, in water), 100 °C, 40 min, 85 %; ii: Br₂, CCl₄, Δ, 1 h, 59 %; iii: a) R*NH₂, EtOH, 0 °C-r.t., 12 h, b) NaBPh₄, MeCN, 5 min.



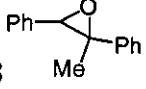
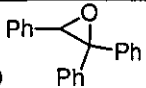
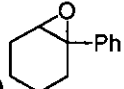
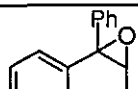
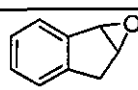
Scheme 35: Formation of the dibenzo[*c,e*]azepinium salts.

Initially two new iminium salt catalysts were prepared following this procedure: catalyst (**79**), derived from the (–)-IPC amine (**8**), in 60 % yield, and the 1,3-dioxane catalyst (**80**), derived from amine (**15**), in 68 % yield. These two amine precursors were selected as they are the parent compounds of our earlier most effective dihydroisoquinolinium catalysts (**14** and **16** respectively).



A range of epoxidations were carried out using these new iminium salts and a comparison of the results obtained with the original dihydroisoquinolinium catalysts (**14**) and (**16**) is displayed in Table 5. It is clear that both of the new seven membered catalysts are more reactive in the epoxidation reaction than the six-membered equivalents. Catalyst (**79**) gives in general poorer ees than the catalyst (**80**) but in some cases provides superior ees to that of its six membered counter-part (**14**). For example, 1-phenyl-3,4-dihydronaphthylene oxide (**22**) is formed with 20 % ee when catalyst (**14**) is employed, but when catalyst (**79**) is used an ee of 38 % is observed. Catalyst (**80**) provides ees of up to 60 %, although with a somewhat different pattern of selectivity from catalyst (**16**), for example giving an improved 60 % ee for 1-phenylcyclohexene oxide (**20**) (catalyst **16** gives 41 % ee), but an identical 59 % ee for triphenylethylene oxide. It is also worth noting that all the reactions with catalyst (**80**) are complete within 10 minutes or less at 0 °C, making it one of our most reactive iminium salt catalysts discovered to date.

Table 5: Catalytic asymmetric epoxidation mediated by the new dibenzo[*c,e*]azepinium salts (**79** and **80**); a comparison to the corresponding dihydroisoquinolinium salts (**14** and **16**).^a

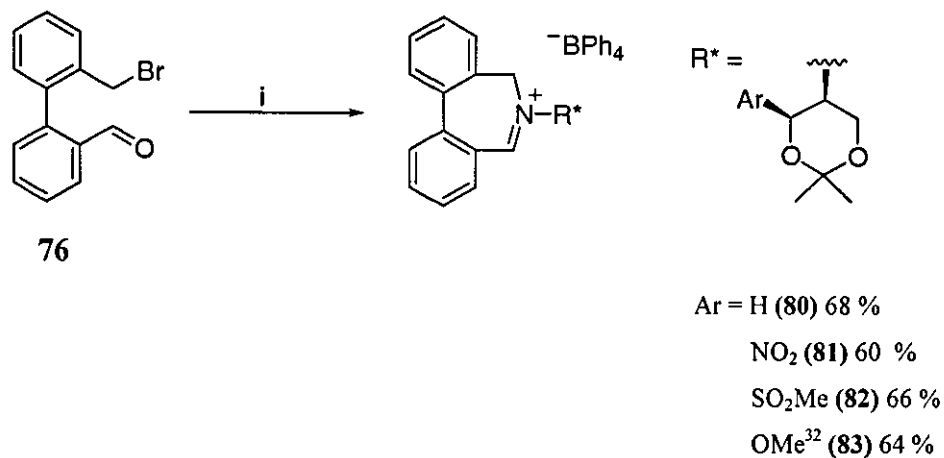
Epoxide	Catalyst			
	14	79	16	80
	In each case: ee (%) ^b ; Conv. (%) ^c , major enantiomer ^d			
	8, 68 ^e (+)- <i>R</i>	3, 90 (+)- <i>R</i>	20, 64 ^e (+)- <i>R</i>	24, 100 (+)- <i>R</i>
	–	0, 95 –	15, 56 ^e (–)- <i>S,S</i>	15, 90 (–)- <i>S,S</i>
	15, 72 ^e (+)-1 <i>R</i> ,2 <i>R</i>	14, 93 (+)-1 <i>R</i> ,2 <i>R</i>	52, 52 ^e (–)-1 <i>S</i> ,2 <i>S</i>	37, 95 (–)-1 <i>S</i> ,2 <i>S</i>
	5, 43 ^e (+)- <i>S</i>	17, 100 (+)- <i>S</i>	59, 54 ^e (+)- <i>S</i>	59, 90 (+)- <i>S</i>
	40, 68 ^e (+)-1 <i>R</i> ,2 <i>R</i>	29, 100 (+)-1 <i>R</i> ,2 <i>R</i>	41, 55 ^e (–)-1 <i>S</i> ,2 <i>S</i>	60, 100 (–)-1 <i>S</i> ,2 <i>S</i>
	20, 73 ^e (–)-1 <i>S</i> ,2 <i>R</i>	38, 95 (–)-1 <i>S</i> ,2 <i>R</i>	49, 64 ^e (–)-1 <i>S</i> ,2 <i>R</i>	41, 90 (–)-1 <i>S</i> ,2 <i>R</i>
	3, 34 ^e (+)-1 <i>S</i> ,2 <i>R</i>	8, 95 (+)-1 <i>S</i> ,2 <i>R</i>	17, 52 ^e (+)-1 <i>S</i> ,2 <i>R</i>	10, 100 (+)-1 <i>S</i> ,2 <i>R</i>

^a Epoxidation conditions: Iminium salt (5 mol %), Oxone (2 eq), Na₂CO₃ (4 eq), MeCN:H₂O (1:1), 0°C, 2 h. ^b Enantiomeric excess determined by ¹H-NMR with Eu(hfc)₃ (0.1 mol eq) as chiral shift reagent or by Chiral HPLC on a Chiracel OD column. ^c Conversion evaluated from the ¹H-NMR by integration alkene versus epoxide. ^d The absolute configuration of the major enantiomer was determined by comparison to those reported in the literature. ^e Isolated yield. ^f Catalyst configuration (4*R*,5*R*).

2.3.2 New dibenzo[*c,e*]azepinium salt catalysts.

Following the success of the dibenzo[*c,e*]azepinium catalysts (**79** and **80**) and the substituted catalysts (**55**), (**56**), (**58**), and (**65**) reported in section 2.2, cyclocondensation of the more effective amines in the dihydroisoquinolinium series, with the bromo-aldehyde (**76**) to produce the corresponding azepinium salts was achieved. Again, the new catalysts (**81**), (**82**), and (**83**) were prepared in good yields (Scheme 36). These catalysts were tested in the asymmetric epoxidation of three substrates

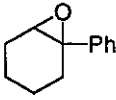
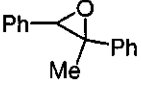
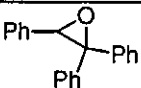
(Table 6). These new catalysts in general provided poorer ees than their dihydroisoquinolinium counterparts. However, catalyst (**83**) epoxidized 1-phenylcyclohexene with 63 % ee (compared to 45 % ee for catalyst **16**). Disappointingly, for reasons which at this moment are unclear, triphenylethylene proved to be a poor substrate with catalysts (**81**) (11 % ee), (**82**) (10 % ee), and (**83**) (26 % ee), but we have previously reported 59 % ee when catalyst (**80**) is employed.



Reagents and Conditions: a) R^*NH_2 , EtOH, 0 °C-r.t., 12 h, b) NaBPh_4 , MeCN, 5 min.

Scheme 36: Synthesis of the substituted dibenzo[*c,e*]azepinium salts.

Table 6: Catalytic asymmetric epoxidation of unfunctionalized alkenes using dibenzo[*c,e*]azepinium salts **80**, **81**, **82**, and **83**.^a

Alkene R =	Catalyst			
	80 H	81 NO ₂	82 SO ₂ Me	83 OMe ^b
	In each case: ee (%) ^c / Conv. (%) ^d / Configuration ^e			
20 	60 / 100 / (-)-1 <i>S</i> ,2 <i>S</i>	38 / 48 / (-)-1 <i>S</i> ,2 <i>S</i>	47 / 56 / (-)-1 <i>S</i> ,2 <i>S</i>	63 / 50 ^f / (+)-1 <i>R</i> ,2 <i>R</i>
18 	37 / 95 / (-)-1 <i>S</i> ,2 <i>S</i>	17 / 30 / (-)-1 <i>S</i> ,2 <i>S</i>	21 / 100 / (-)-1 <i>S</i> ,2 <i>S</i>	50 / 61 ^f / (+)-1 <i>R</i> ,2 <i>R</i>
19 	59 / 90 / (+)- <i>S</i>	11 / 22 / (+)- <i>S</i>	10 / 55 / (+)- <i>S</i>	26 / 63 ^f / (-)- <i>R</i>

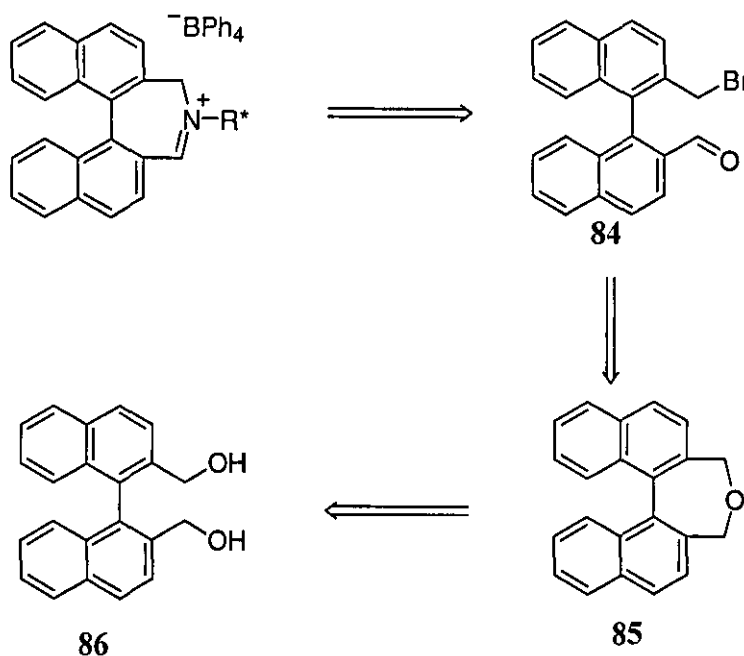
^a Epoxidation conditions: Iminium salt (5 mol %), Oxone (2 eq), Na₂CO₃ (4 eq), MeCN:H₂O (1:1), 0°C, 2 h. ^b Catalyst configuration (4*R*,5*R*). ^c Enantiomeric excess determined by ¹H-NMR with (+)-Eu(hfc)₃ (0.1 mol eq) as chiral shift reagent. ^d Conversion evaluated from the ¹H-NMR by integration alkene versus epoxide. ^e The absolute configuration of the major enantiomer was determined by comparison to those reported in the literature. ^f Isolated yield.

2.4 Catalysts Based on a Binaphthalene Structure.

Due to the encouraging findings described in the previous section we felt that a logical continuation of this work would be in the synthesis of the axially chiral binaphthalene analogues. As mentioned previously, Aggarwal has described an iminium salt based upon a binaphthalene unit; however, this catalyst is unsubstituted at the nitrogen atom. We believed that addition of a chiral group on the nitrogen could lead to greater substrate control and hence higher enantioselectivity. One of the inherent problems associated with the addition of other chiral centres in this type of molecule is the advent of matched and mis-matched pairs of diastereoisomers, something which had to be considered during the catalyst synthesis. We predicted that if the binaphthalene component was of the *R*-configuration and the 1,3-dioxane component is of the 4*S*,5*S* configuration, then this would be a matched pair, as Aggarwal's *S*-iminium salt (Chapter 1, Figure 13) produced, in general, the oppositely configured epoxides to those obtained with either catalysts (**16**) or (**80**).

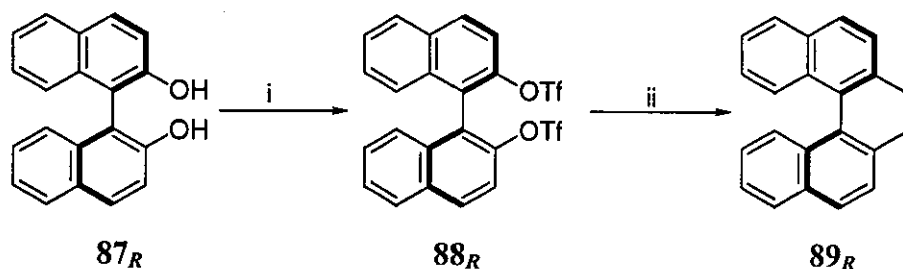
2.4.1 Catalyst Synthesis.

We envisaged that the mode of access to these catalysts would be through the familiar bromoaldehyde unit (**84**) (Scheme 37). This in turn could be synthesized from the oxepine (**85**) by ring opening with bromine; again, synthesis of the oxepine (**85**) could be accomplished by cyclization of the bis-methanol compound (**86**), as previously proven in the dibenzo[*c,e*]azepinium salt synthesis (section 2.3.1). This material (**86**) is not commercially available, but several syntheses of compound (**86**), in enantiomerically pure form, have been reported.^{33,34,35} These generally involve a resolution at some point during the synthesis, but to avoid this, the synthesis can be achieved from commercially available enantiomerically pure *R* (**87_R) or *S* (**87_S) BINOL. Formation of the desired bis-methanol compound (**86**) has been described by Mazaleyrat from a bis-methyl binaphthalene, which in turn can be synthesized from BINOL (**87**).³⁴****



Scheme 37: Retrosynthetic analysis of the desired iminium salt.

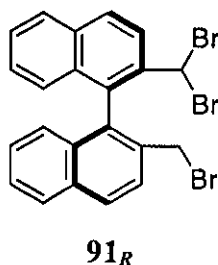
The initial reaction required in the synthesis was the formation of the bis-triflate protected binaphthalene (**88_R**). Using *R*-BINOL (**87_R) in dichloromethane with trifluoromethanesulfonic anhydride, DMAP, and 2,6-lutidine, the product was produced in near-quantitative yield after 4 hours (Scheme 38).³⁶ Subsequent cross-coupling with methylmagnesium bromide and the nickel catalyst [NiCl₂(dppp)₂] afforded the bis-methylene compound (**89_R**), again in excellent yield (90 %).³⁷**



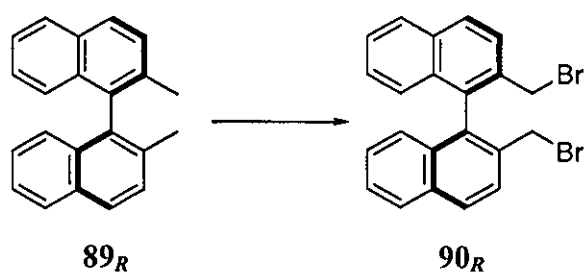
Reagents and Conditions: i: TF_2O , DMAP (cat.), 2,6-lutidine, DCM, $-30\text{ }^\circ\text{C}$ -r.t., 99 %; ii: MeMgBr , $\text{NiCl}_2(\text{dppp})_2$, Et_2O , 12 h, 90 %.

Scheme 38: Formation of the bis-methylene compound **89_R**.

Synthesis of the desired bis-bromomethyl binaphthalene (**90_R**) has also been reported in the literature. The route reported involved the use of NBS in refluxing carbon tetrachloride using benzoyl peroxide as the initiator,³⁴ and afforded the product in 64 % yield (Scheme 39, Table 7). However, this process was occasionally unreliable, and what we believe to be the tribromo compound (**91_R**) was sometimes formed as the major product, as indicated by the presence of a proton signal at 6.22 ppm (singlet, H adjacent to the two bromine atoms) and a double doublet at 4.24 ppm ($\text{CH}_2\text{-Br}$) in the $^1\text{H-NMR}$ spectrum. This side product has also been described, under these reaction conditions by RajanBabu.³⁸



Slight modification of this procedure, however, had a dramatic effect upon the yield of the reaction. Replacing the initiator with AIBN, removing the heat, and stirring at room temperature for 5 h under visible light (150 W) afforded the desired compound (**90_R**) in up to 88 % yield. Further modification, by removing the carbon tetrachloride and replacing with cyclohexane, surprisingly, did not alter the rate or yield of the reaction.



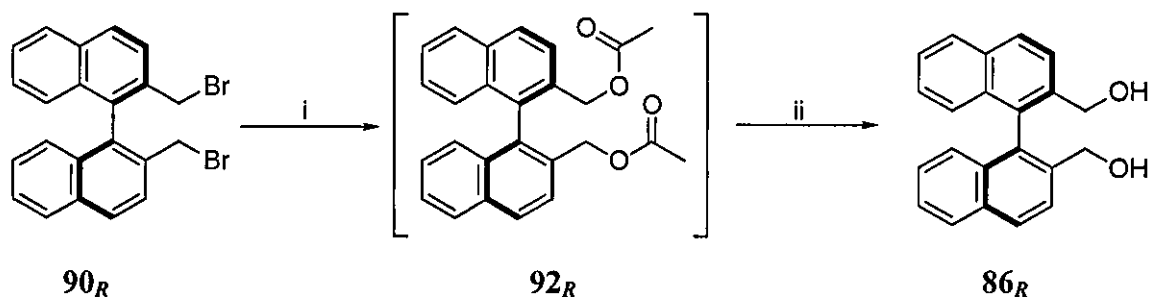
Reagents and Conditions: NBS (2 eq.), Solvent, Δ or light.

Scheme 39: Bromination of the bis-methylene 89_R with NBS.

Table 7: The effect of several reaction parameters on the formation of 90_R

Entry	Solvent	Initiator	Δ or Light	Time (h)	Yield (%)
1	CCl_4	Benzoyl Peroxide	Δ	24	64
2	CCl_4	AIBN	Light (r.t.)	5	88
3	Cyclohexane	AIBN	Light (r.t.)	5	88

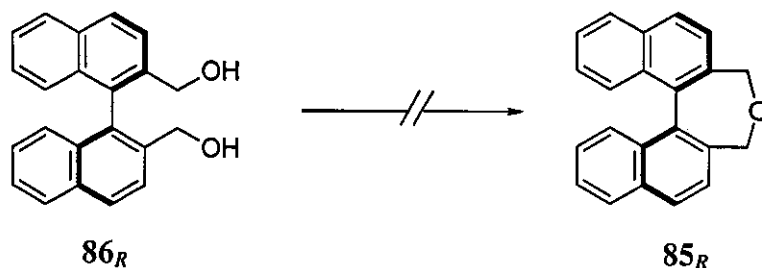
Conversion of the bis-bromomethyl binaphthalene (90_R) species to the bis-methanol binaphthalene (86_R) required the formation of the intermediate ester (92_R) with potassium acetate and a catalytic amount of tetrabutylammonium bromide in DMF (Scheme 40). Subsequent hydrolysis with aqueous potassium hydroxide (1 M) afforded the bis-methanol binaphthalene (86_R) as colourless plates in 88 % overall yield.



Reagents and Conditions: i: KCO_2CH_3 , Bu_4NBr (cat.), DMF, 80°C , 20 h; ii: KOH (aq. 50%):1,4-dioxane (1:1), Δ , 24 h, 88 %.

Scheme 40: Formation of the bis-methanol compound 86_R

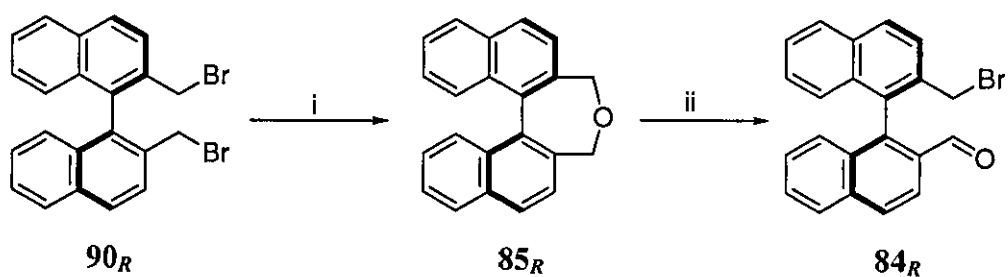
However, attempted cyclization to form the desired oxepine (**85_R**) under the conditions developed for the corresponding biphenyl derivative (**77**) [HBr (aq. 24 %), 100 °C, 1 h] did not work (Scheme 41). Increasing the concentration of the HBr or the reaction time also had no effect, and complete recovery of the starting material was observed in each case.



Reagents and Conditions: HBr (aq. 24 %), 100 °C, 1 h.

Scheme 41: Attempted formation of the oxepine **85_R**

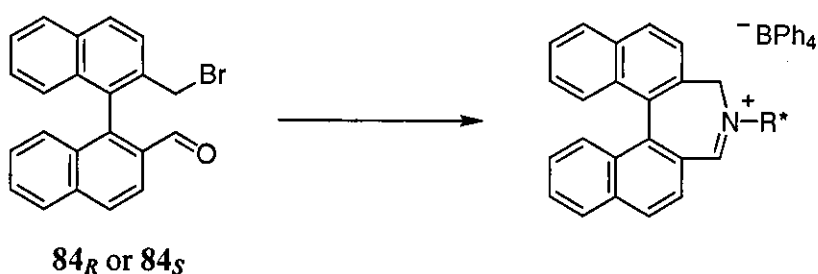
Fortunately, upon closer inspection of the Mazaleyrat paper, a brief comment on “cyclic ether” formation indicates that the bis-bromomethyl binaphthalene (**90_R**) can be directly converted to the oxepine by refluxing in 1,4-dioxane/saturated sodium carbonate solution (Scheme 42).³⁴ Indeed cyclization, under these conditions, did occur and the oxepine (**85_R**) was produced in 65 % yield after 24 h. When the reaction mixture was heated for 36 h, yields could be increased to 76 %. Ring opening of the oxepine (**85_R**) under the standard conditions employed previously using bromine in refluxing carbon tetrachloride afforded the bromoaldehyde (**84_R**) in 68 % yield. Repeating the synthetic sequence with the *S*-enantiomer of BINOL (**87_S**) produced the corresponding bromoaldehyde (**84_S**) in comparable yields. HPLC analysis of the bromo- aldehydes indicated them to have greater than 99 % ee.



Reagents and Conditions: i: Na_2CO_3 (sat. aq.)/1,4-dioxane (1:1), Δ , 36 h, 76 %; ii Br_2 , CCl_4 , Δ , 1 h, 65 %.

Scheme 42: Formation of the catalyst precursor 84_R

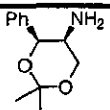
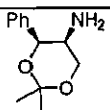
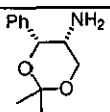


With both enantiomers of the bromoaldehyde (84) available several new iminium salts were synthesized and tested in the asymmetric epoxidation reaction (Scheme 43, Table 8). Similar yields to those obtained with the other bromoaldehydes were observed for iminium salt formation.



Reagents and Conditions: a) $\text{NH}_2\text{-R}^*$, EtOH, r.t. 12 h; b) NaBPh_4 , MeCN, r.t. 5 min.

Scheme 43: Iminium salt formation using bromo-aldehydes 84_R or 84_S with a range of primary amines.

Table 8: Yields of iminium salt formation using bromo-aldehydes **84_R** or **84_S** with a range of primary amines.

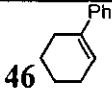
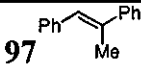
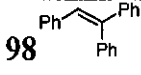
Entry	Bromo-aldehyde	Amine	Compound No.	Yield (%)
1	84_R		93	66
2	84_S		94	63
3	84_S		<i>ent-93</i>	64
4	84_R		95	71
5	84_S		96	73

2.4.2 Catalytic asymmetric epoxidation.

With these new catalysts in hand we were able to test their effectiveness in a variety of epoxidation reactions. Initially we screened the catalysts with our usual test substrates, 1-phenylcyclohexene (**46**), α -methylstilbene (**97**), and triphenylethylene (**98**) (Table 9). Catalyst (**93**) showed the best reaction profile, being far more reactive than the other catalysts. Catalyst (**93**) formed 1-phenylcyclohexene oxide (**20**) with 91 % ee in under 20 minutes when 5 mol % of the iminium salt was employed, whereas the other catalysts (apart from *ent-93*) were not as selective and the reaction times were low when compared to catalyst (**93**). It appears that the isopinocampheyl moiety offers little enantiocontrol, leading to epoxides with only moderate ees. The poor reactivity of catalysts (**94-96**) is highlighted by the attempted epoxidation of α -methylstilbene (**97**), and triphenylethylene (**98**), where no epoxides were formed after 4 hours when employing 5 mol % of catalyst. Catalyst (**93**) however afforded complete conversion to the corresponding epoxides in a much shorter time and yields

of *ca* 60 %, although the ees were somewhat disappointing (49 % and 12 % ee respectively).

Table 9: Epoxidation of several unfunctionalized alkenes with catalysts **93-96**.^a


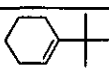
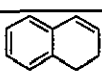
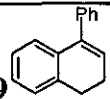
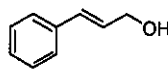
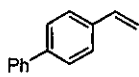
Alkene	Catalyst	Time (h)	Yield (%) ^b	ee (%) ^c	Configuration ^d
 46	93	0.20	69	91	(-) <i>1S,2S</i>
	<i>ent</i> - 93	0.20	66	88	(+) <i>1R,2R</i>
	94	2.0	54	78	(+) <i>1R,2R</i>
	95	2.0	40	53	(-) <i>1S,2S</i>
	96	2.0	44	58	(+) <i>1R,2R</i>
 97	93	0.40	58	49	(-) <i>1S,2S</i>
	94	4.0	0	—	—
	95	4.0	0	—	—
	96	4.0	0	—	—
 98	93	0.50	60	12	(+)- <i>S</i>
	94	4.0	0	—	—
	95	4.0	0	—	—
	96	4.0	0	—	—

^a Conditions: Iminium salt (5 mol %), Oxone (2 equiv.), Na₂CO₃ (4 equiv.), MeCN/H₂O (1:1), 0 °C.

^b Isolated yield. ^c Enantiomeric excess determined by ¹H-NMR with (+)-Eu(hfc)₃ (0.1 mol eq) as chiral shift reagent. ^d The absolute configuration of the major enantiomer was determined by comparison to those reported in the literature.

Catalyst (**93**) was subsequently used to epoxidize several other olefins. Again the reactivity of the catalyst (5 mol %) was good, but a wide range of ees were observed (Table 10). 1-Phenyl-3,4-dihydronaphthylene (**99**) was epoxidized with high enantioselectivity (95 % ee and 66 % yield after 35 minutes). *para*-Phenyl styrene (**100**) was also epoxidized using catalyst (**93**) and gave the highest reported ee (29 %) for any terminal epoxide using iminium salt catalysis.

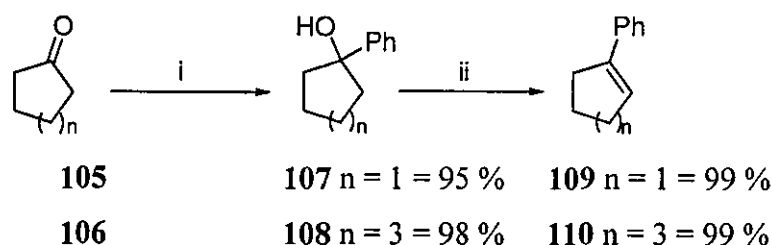
Table 10: Epoxidation of various alkenes with catalyst **93**.^a

Alkene	Time (h)	Yield (%) ^b	ee (%) ^c	Configuration ^d
101 	0.45	58	20	(-)- <i>S,S</i>
102 	0.25	63	25	(-)- <i>1S,2S</i>
103 	0.30	60	17	(-)- <i>1S,2R</i>
99 	0.35	66	95	(-)- <i>1S,2R</i>
104 	2.0	67	38	(-)- <i>2S,3S</i>
100 	1.0	70	29	(+)- <i>S</i>

^a Conditions: Iminium salt **93** (5 mol %), Oxone (2 equiv.), Na₂CO₃ (4 equiv.), MeCN/H₂O (1:1), 0 °C.

^b Isolated yield. ^c Enantiomeric excess determined by ¹H-NMR with (+)-Eu(hfc)₃ (0.1 mol eq) as chiral shift reagent or by chiral HPLC using a Chiracel OD column. ^d The absolute configuration of the major enantiomer was determined by comparison to those reported in the literature.

Having established the most successful epoxidation substrates for catalyst (**93**), several cycloalkenes with various ring sizes were prepared (Scheme 44). Both cyclopentanone (**105**) and cycloheptanone (**106**) were treated with phenylmagnesium bromide in tetrahydrofuran to afford the alcohols (**107**) and (**108**) in excellent yields (95 and 98 % respectively); subsequent treatment with a five-fold excess of TFA in chloroform, as described by de Costa,³⁹ provided 1-phenylcyclopentene (**109**) and 1-phenylcycloheptene (**110**), again in very good yields (99 %).



Reagents and Conditions: i: PhMgBr, THF, r.t., 2 h; ii: TFA, CHCl₃, 5 min.

Scheme 44: Formation of cyclo-alkenes **109** and **110**.

These new substrates were tested in the asymmetric epoxidation reaction. Reactions were carried out using just 1 mol % of catalyst (**93**) (Table 11). Again good conversions to epoxides were achieved, and, interestingly, the five- (**109**) and seven- (**110**) membered ring cycloalkenes were less reactive than 1-phenylcyclohexene (**46**). The reactions took almost five times as long to approach completion, and enantioselectivities were poorer than those observed for 1-phenylcyclohexene: 1-phenylcyclopentene oxide was formed in 55 % ee and 1-phenylcycloheptene oxide in 76 % ee.

Table 11: Effect of ring size on the epoxidation of several cyclo-alkenes with catalyst **93**.^a

Alkene	Time (h)	Yield (%) ^b	ee (%) ^c	Configuration ^d
109	5.0	52	55	(-)-1 <i>S</i> ,2 <i>S</i>
46	1.1	64	91	(-)-1 <i>S</i> ,2 <i>S</i>
110	5.0	57	76	(-)-1 <i>S</i> ,2 <i>S</i>

^a Conditions: iminium salt **93** (1 mol %), Oxone (2 equiv.), Na₂CO₃ (4 equiv.), MeCN/H₂O (1:1), 0 °C.

^b Isolated yield. ^c Enantiomeric excess determined by ¹H-NMR with (+)-Eu(hfc)₃ (0.1 mol eq) as chiral shift reagent. ^d The absolute configuration of the major enantiomer was determined by comparison to those reported in the literature.

Using catalyst (**93**) we also conducted a catalyst loading study using our test substrate 1-phenylcyclohexene (**46**), with catalyst loadings ranging from 0.1 to 5 mol % (Table

12). We were delighted and extremely surprised to observe high levels of asymmetric induction with low catalyst loadings. We have previously reported that it is possible to use just 0.5 mol % of catalyst, but we usually observe a loss in selectivity. In this case, however, catalyst loadings are so low that effective epoxidation of 1.0 g of 1-phenylcyclohexene (**46**), with 78 % yield and 88 % ee, can be achieved using just 5 mg (0.1 mol %) of catalyst (**93**).

Table 12: Catalyst loading study on the epoxidation of 1-phenylcyclohexene **46** with catalyst **93**.^a

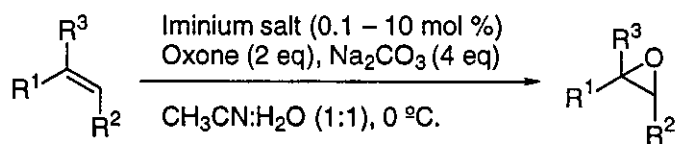
Entry	Cat. (mol %)	Time (h)	Yield (%) ^b	ee (%) ^c	Configuration ^d
1	5.0	0.2	69	91	(-)-1 <i>S</i> ,2 <i>S</i>
2	1.0	1.1	64	91	(-)-1 <i>S</i> ,2 <i>S</i>
3	0.5	2.0	65	91	(-)-1 <i>S</i> ,2 <i>S</i>
4	0.1	6.0	68	88	(-)-1 <i>S</i> ,2 <i>S</i>

^a Conditions: iminium salt **93**, Oxone (2 equiv.), Na₂CO₃ (4 equiv.), MeCN/H₂O (1:1), 0 °C. ^b Isolated yield. ^c Enantiomeric excess determined by ¹H-NMR with (+)-Eu(hfc)₃ (0.1 mol eq) as chiral shift reagent. ^d The absolute configuration of the major enantiomer was determined by comparison to those reported in the literature.

2.5 Catalytic Asymmetric Anhydrous Epoxidation, Mediated by Tetraphenylphosphonium mono-peroxysulfate and Iminium salts.

2.5.1 Introduction. Reasons for employing a new stoichiometric oxidant.

The standard conditions employed in epoxidation reactions catalysed by iminium salts involve the use of oxone as stoichiometric oxidant, a base (2 molar equivalents of Na₂CO₃ per equivalent of oxone) and water / acetonitrile as solvent mixture (Scheme 45): the presence of water is essential for oxone solubility. Under the reaction conditions, there are separate aqueous and organic phases; it is possible that the catalyst acts as a phase transfer agent in these reactions.



Scheme 45: The standard conditions applied for catalytic asymmetric epoxidation mediated by oxone and iminium salts.

The principal limitation to this system is the restricted range of temperatures in which the epoxidation can be performed (0 °C to room temperature). The upper limit is determined by the oxone, which decomposes relatively quickly in the basic medium at room temperature.⁵ The lower limit is determined by the use of the aqueous medium; the normal ratio of the water and acetonitrile solvents used is 1:1, and this mixture freezes at around -8 °C.

One potential opportunity to enhance the enantioselectivity of the process would be provided if the reaction could be carried out at a lower temperatures. This would require the development of non-aqueous reaction conditions, and because of the solubility profile of oxone, which has no significant solubility in any organic solvent, this in turn dictates a need for a new stoichiometric oxidant, soluble in organic solvents at low temperatures. Crucially, this oxidant must not oxidize alkenes under the reaction conditions in the absence of the catalyst (background oxidation).

2.5.2 Selection of tetraphenyl phosphonium mono-peroxysulfate.

Several oxidants were tested in an epoxidation reaction in the presence of iminium salt catalysts to determine which offers the best profile in the absence of water.⁴⁰ These reactions were carried out at 0 °C with 1-phenylcyclohexene (**46**) as substrate and (**14**) and/or (**16**) as catalysts (5-20 mol %), in dichloromethane as solvent. Most of the systems examined showed either high levels of background epoxidation (alkaline hydrogen peroxide, peracids, persulfates) or very low rates of reaction even in the presence of 20 mol % of the catalysts (perselenates, percarbonates, perborates and iodosobenzene diacetate). Tetra-*N*-butylammonium oxone, reported by Trost,⁴¹ was also unsuccessful as oxidant.

From all of those tested, tetraphenylphosphonium mono-peroxysulfate (TPPP), reported by Di Furia in 1994 for oxygen transfer to manganese porphyrins,⁴² showed the best profile. A modification of oxone, TPPP is prepared by cation exchange (K^+ to Ph_4P^+) between oxone and tetraphenyl phosphonium chloride (Scheme 46). Further crystallization of the triple salt from CH_2Cl_2 and hexane afforded the desired compound as a colourless solid in 75 % yield, which iodometric titration reveals to have *ca* 85% of the theoretically available oxygen. This composition was also confirmed by 1H -NMR spectroscopy (CD_2Cl_2), by integration of the aromatic hydrogen of the tetraphenyl moiety and the peroxyacidic proton (8.5 ppm).



Scheme 46: Formation of tetraphenylphosphonium mono-peroxysulfate from oxone.

For epoxidation to proceed, the presence of base is essential under the aqueous conditions when using oxone as oxidant. We were pleased to discover that, in contrast, the addition of one equivalent of any of a range of bases (KF, TBAF, CsF, pyridine, 2,6-lutidine, DBN, DBU, DABCO, LiH, NaH) to the test reaction in dichloromethane at 0 °C, with TPPP as oxidant, did not improve the reaction; indeed, the amine bases suppressed epoxidation altogether.

Formation of epoxide was not observed upon treatment of 1-phenylcyclohexene (**46**) with TPPP in dichloromethane solution at 0 °C in the absence of catalyst. Indeed, such background epoxidation only becomes competitive with the catalyzed reaction when the temperature reaches *ca.* 40 °C.

The optimum conditions for the asymmetric epoxidation reaction were developed. Due to the exothermic nature of the reaction, a solution of TPPP in the reaction medium is cooled to the desired temperature; the catalysts and substrate are also separately dissolved in the reaction solvent and cooled to the desired temperature. The solution of catalyst is added dropwise to the solution of oxidant, to minimize the increase in reaction temperature, which is allowed to stabilize before dropwise

addition of the substrate. The alkene is added last to help maintain the epoxidation process at a constant temperature. The reaction is stopped by high dilution with diethyl ether, in which both the catalyst and oxidant display a low solubility profile.

We have also found that when the catalyst reacts with TPPP an anionic interchange between the two salts occurs. The tetraphenyl borate (BPh_4^-) is displaced from the iminium salt by the monoperoxysulfate anion (HSO_5^-), and the corresponding tetraphenylphosphonium tetraphenylborate is formed. This is rather insoluble in dichloromethane and can be isolated and characterized by filtration from the reaction.

2.5.3 Asymmetric epoxidations using TPPP.

2.5.3.1 Temperature studies.

Several reactions with our test substrate 1-phenylcyclohexene (**46**) were performed using catalyst (**80**) and our dihydroisoquinolinium catalyst (**16**) under these new conditions. Runs were conducted using 10 mol % of catalyst over a range of temperatures; the results obtained are displayed in Table 13 (it is important to note here that the corresponding catalysts derived from the (-)-IPC amine (**8**) (**14** and **79**) gave poor conversions and ees under these conditions. For example, catalyst (**79**) (10 mol %) afforded only 60 % conversion to 1-phenylcyclohexene oxide (**20**) and 13 % ee after two hours at $-40\text{ }^\circ\text{C}$). As a comparison the reported aqueous/acetonitrile results are included.^{6,29}

We observed that in each case the highest enantiomeric excess is obtained at the lowest temperature (entries 1 to 5 and 10 to 14 for catalyst (**80**), and 6 to 9 and, 15 to 18 for catalyst (**16**)). The increase in ee is coupled with a decrease in epoxide conversion at lower temperatures. A comparison of the two catalysts show that the biphenyl catalyst (**80**) is much more reactive (as it is under the oxone conditions) at lower temperatures and far more selective regardless of solvent.

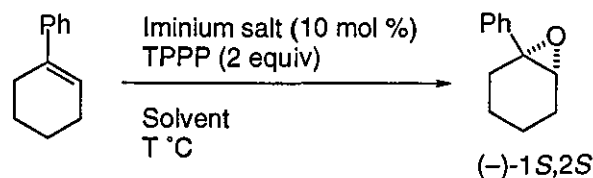
The best selectivities are obtained when a mixture of solvents is employed (entries 10-18). A 1:1 ratio of dichloromethane/acetonitrile allows the reaction mixture to be

homogeneous at $-78\text{ }^{\circ}\text{C}$ (acetonitrile alone freezes at $-45\text{ }^{\circ}\text{C}$) and catalyst (**80**) has produced one of the best ee values obtained in any epoxidation reaction mediated by iminium salts previously described by us or others (70 % ee, entry 10). Even when the catalyst loading is reduced to 2 mol % (entry 11) we are able to gain 25 % conversion (a better result than catalyst (**16**) with 10 mol % at $-78\text{ }^{\circ}\text{C}$), and the ee remains consistent (70 %).

With the co-solvent system the biphenyl catalyst (**80**) outperforms the dihydroisoquinolinium catalyst (**16**), which is still rather unreactive at $-78\text{ }^{\circ}\text{C}$ (entry 15). The levels of enantioselectivity observed for catalyst (**16**) under the new anhydrous conditions do not exceed those obtained using the oxone, acetonitrile/water conditions, but in contrast it appears that the new experimental conditions enhance selectivity in the case of the biphenyl catalyst (**80**). Hence this catalyst was selected to screen a range of unfunctionalized alkenes (Table 14).

These olefins were not as reactive towards catalyst (**80**) as the previously tested substrate 1-phenylcyclohexene (**46**), therefore the majority of reactions were carried out at $-40\text{ }^{\circ}\text{C}$. Again, the dichloromethane/acetonitrile conditions produce the better results in terms of both enantiomeric excess and epoxide conversion, over the dichloromethane conditions. Triphenylethylene (**98**) was extremely unreactive when compared to all the other alkenes tested (entries 3, 4, 10 and 11). The best ee obtained was for 1-phenyl-3,4-dihydronaphthalene (**99**) at $-40\text{ }^{\circ}\text{C}$ in dichloromethane/acetonitrile which in three hours gave 100 % conversion and 65 % ee. This is even more remarkable when one considers that 1-phenyl-3,4-dihydronaphthalene (**99**) also gave the poorest result in dichloromethane (7 % ee).

Table 13: Catalytic asymmetric epoxidation of 1-phenylcyclohexene (**46**) using TPPP and catalysts (**16**) and (**80**).^a

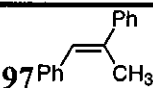
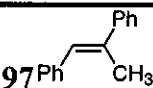
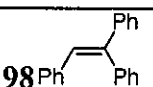
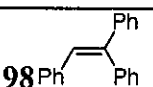
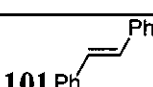
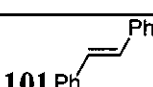
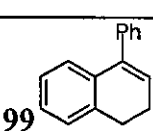
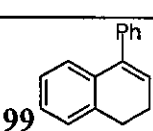


Entry	Solvent	Catalyst	T °C	t (min)	Conv. (%) ^b	ee (%) ^c
1	DCM	80	-78	120	52	50
2	DCM	80	-60	120	50	36
3	DCM	80	-40	90	100	28
4	DCM	80	0	10	100	26
5	DCM	80	40	<5	100	23
6	DCM	16	-78	480	15	23
7	DCM	16	-40	120	70	37
8	DCM	16	0	10	100	16
9	DCM	16	40	25	75	0
10	DCM / MeCN	80	-78	240	80	70
11	DCM / MeCN	80	-78	480	25	70 ^d
12	DCM / MeCN	80	-40	30	100	53
13	DCM / MeCN	80	0	<5	100	51
14	DCM / MeCN	80	40	<5	100	43
15	DCM / MeCN	16	-78	480	35	45
16	DCM / MeCN	16	-40	120	83	46
17	DCM / MeCN	16	0	10	100	34
18	DCM / MeCN	16	40	10	100	25
19	MeCN / H ₂ O ^e	80	0	5	100	60
20	MeCN / H ₂ O ^e	16	0	10	55 ^f	41

^a Conditions: Iminium salt (10 mol %), TPPP (2 equiv.), Solvent, T °C. ^b Conversion evaluated from the ¹H-NMR by integration alkene versus epoxide. ^c Enantiomeric excess determined by ¹H-NMR with (+)-Eu(hfc)₃ (0.1 mol eq) as chiral shift reagent. ^d 2 mol % catalyst. ^e Conditions: Oxone (2 equiv), sodium carbonate (4 equiv), water/acetonitrile (1:1), 0 °C. ^f Isolated yield.

Overall, the differences in enantiomeric excess between the two solvent systems was not as vast as those observed in reactions with 1-phenylcyclohexene (**46**). However the conversions to epoxide differed significantly; all the experiments recorded in dichloromethane required longer reaction times and in some cases still did not reach the level of conversion observed using the dichloromethane/acetonitrile system.

Table 14: Catalytic asymmetric epoxidation of several alkenes mediated by catalyst (**80**).^a

Entry	Alkene	Solvent	T °C	t (h)	Conv. (%) ^b	ee (%) ^c	Epoxide Config. ^d
1		DCM	-78	8	5	20	(-)-1 <i>S</i> ,2 <i>S</i>
2	97 	DCM/MeCN	-78	2	15	44	(-)-1 <i>S</i> ,2 <i>S</i>
3		DCM	-40	6	100	50	(-)-1 <i>S</i> ,2 <i>S</i>
4		DCM/MeCN	-40	2	86	50	(-)-1 <i>S</i> ,2 <i>S</i>
5		DCM	-78	8	0	-	-
6	98 	DCM/MeCN	-78	8	0	-	-
7		DCM	-40	2	7	47	(+)- <i>S</i>
8		DCM/MeCN	-40	1	30	29	(+)- <i>S</i>
9		DCM	-40	4	100	39	(-)-1 <i>S</i> ,2 <i>S</i>
10	101 	DCM/MeCN	-40	2	100	33	(-)-1 <i>S</i> ,2 <i>S</i>
11		DCM	-40	4	100	7	(-)-1 <i>S</i> ,2 <i>R</i>
12	99 	DCM/MeCN	-40	3	100	65	(-)-1 <i>S</i> ,2 <i>R</i>

^a Conditions: Iminium salt (10 mol %), TPPP (2 equiv.), Solvent, T °C. ^b Conversion evaluated from the ¹H-NMR by integration alkene versus epoxide. ^c Enantiomeric excess determined by ¹H-NMR with (+)-Eu(hfc)₃ (0.1 mol eq) as chiral shift reagent or by Chiral HPLC, on a Chiracel OD column. ^d The configuration of the major enantiomer was determined by correlation to the known epoxides.

A temperature study was also carried out using dichloromethane as solvent and two molar equivalents of TPPP over a range of temperatures with the substituted dihydroisoquinolinium catalysts (**55**), (**56**), (**58**), and (**65**), described above in section 2.2. The results obtained are collected in Table 15. As it can be seen from the table,

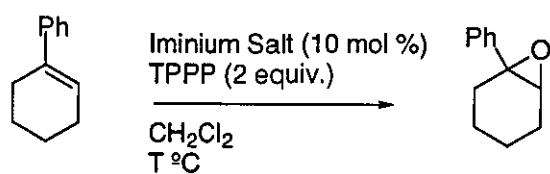
again we observe that as the temperature of reaction decreases, the enantioselectivity increases significantly. Unfortunately at the same time the conversion decreases, probably due to a decrease in reaction rates with the temperature.

The highest ee (50 %) was obtained when the reaction was carried out at $-78\text{ }^{\circ}\text{C}$ (entry 18). Under these conditions (using 10 mol % of catalyst), the conversion to epoxide is rather low (15 %). Surprisingly, the *p*-methoxyaryl catalyst (**65**) is not as selective as it is under the aqueous conditions, the best ee being only 29 % (45 % ee in the original aqueous conditions).

We were also surprised to find that when the R group at C4 of the catalyst is electron-withdrawing we observe a change in the configuration of the epoxide formed.

The thiomethyl catalyst (**56**) gives the (+)-1*R*,2*R* enantiomer of 1-phenylcyclohexene between temperatures of $0\text{ }^{\circ}\text{C}$ and $-50\text{ }^{\circ}\text{C}$ (Table 15, entries 3, 8, 12), but at $-78\text{ }^{\circ}\text{C}$ the (-)-1*S*,2*S* enantiomer is formed (Table 15, entry 18). This we believe is due to the sulfide being oxidized at temperatures above $-78\text{ }^{\circ}\text{C}$ to the sulfone, therefore altering the electronic nature of the catalyst. Catalyst (**65**), which also has an electron-donating group at C4 (OMe), cannot be altered by the epoxidation conditions, and regardless of temperature produces the same enantiomer of epoxide. This perhaps indicates that at $-78\text{ }^{\circ}\text{C}$ it is the un-oxidized sulfide group which is present as the active catalyst.

X-ray structure analysis may offer one explanation as to why we observe the change in enantiomer of epoxide formed (Figure 9). A comparison of catalyst (**16**) and the sulfone catalyst (**58**) shows that in the case of (**16**) the iminium carbon sits above O(1) and the *re*-face is blocked by the phenyl ring. In the case of the sulfone catalyst (**58**) the iminium carbon faces away from the dioxane ring and so the *re*-face is now open to attack from the oxidant, therefore producing the oppositely configured oxaziridinium. However, this may only be true in the solid state and cannot directly indicate what occurs in solution phase.

Table 15: Catalytic asymmetric epoxidation of 1-phenylcyclohexene using TPPP in CH₂Cl₂.^a

Entry	Temp (°C)	Catalyst	Conv. (%) ^b	ee (%) ^c	Configuration ^d
1	0	16 R = H	100	16	(-)-1 <i>S</i> ,2 <i>S</i>
2		55 R = NO ₂	100	25	(+)-1 <i>R</i> ,2 <i>R</i>
3		56 R = SMe	72	16	(+)-1 <i>R</i> ,2 <i>R</i>
4		58 R = SO ₂ Me	100	33	(+)-1 <i>R</i> ,2 <i>R</i>
5		65 ^e R = OMe	–	–	–
6	–30	16	–	–	–
7		55	100	28	(+)-1 <i>R</i> ,2 <i>R</i>
8		56	92	33	(+)-1 <i>R</i> ,2 <i>R</i>
9		58	100	36	(+)-1 <i>R</i> ,2 <i>R</i>
10		65 ^e	76	25	(+)-1 <i>R</i> ,2 <i>R</i>
11	–45	16	70	37 ^f	(-)-1 <i>S</i> ,2 <i>S</i>
12		55	54	30	(+)-1 <i>R</i> ,2 <i>R</i>
13		56	67	33	(+)-1 <i>R</i> ,2 <i>R</i>
14		58	96	42	(+)-1 <i>R</i> ,2 <i>R</i>
15		65 ^e	–	–	–
16	–78	16	15	23 ^g	(-)-1 <i>S</i> ,2 <i>S</i>
17		55	no rxn	–	–
18		56	15	50 ^g	(-)-1 <i>S</i> ,2 <i>S</i>
19		58	no rxn	–	–
20		65 ^e	13	29 ^g	(+)-1 <i>R</i> ,2 <i>R</i>

^a Conditions: Iminium salt (10 mol %), TPPP (2 eq), DCM, T °C, 4.0 h. ^b Conversion evaluated from the ¹H-NMR spectrum by integration of alkene versus epoxide. ^c Enantiomeric excess determined by ¹H-NMR with (+)-Eu(hfc)₃ (0.1 mol eq) as chiral shift reagent. ^d The absolute configuration of the major enantiomer was determined by comparison to those reported in the literature. ^e Catalyst configuration (4*R*,5*R*). ^f Reaction carried out at –40 °C. ^g Reaction time 8 h.

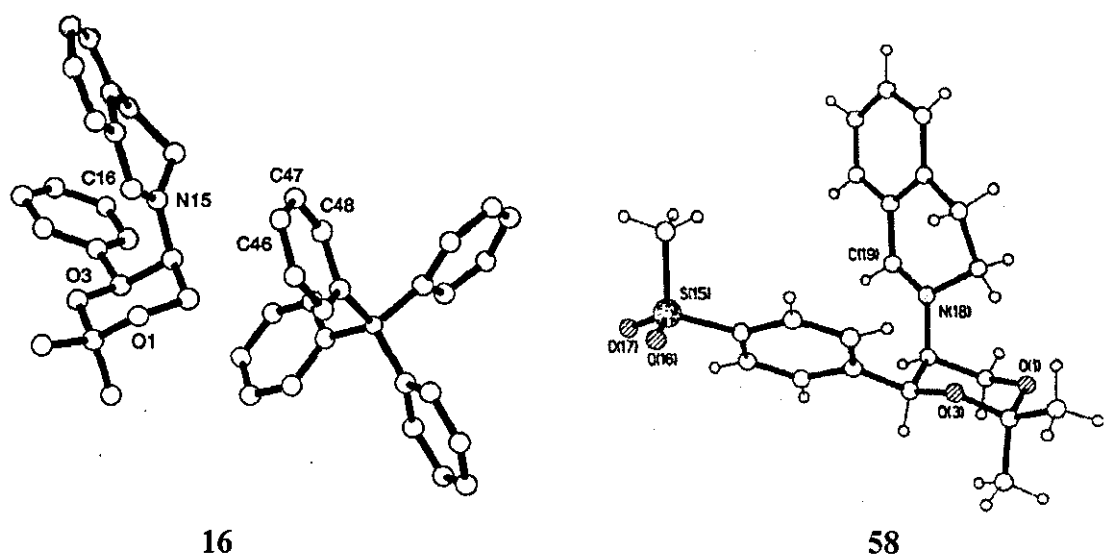


Figure 9: X-ray crystal structures of catalysts **16** and **58**.

To prove that the active catalyst at temperatures above $-78\text{ }^{\circ}\text{C}$ was the oxidized sulfone a standard epoxidation reaction was performed in deuteriated dichloromethane and subjected to ^1H NMR spectroscopic analysis. We noticed that the chemical shift for the thiomethyl group shifted from δ 2.42 to 3.03, indicating that the sulfide had been oxidized to the sulfone (by comparison to authentic catalyst **58**). This was an extremely rapid and exothermic process, and the sulfoxide intermediate was not observed. Further to this the pattern of the AA'BB' aromatic system was consistent with that of a sulfone, the chemical shifts being around δ 8.00.

2.5.3.2 The effect of reaction solvent.

To determine if the electronic effect could enhance enantiomeric excess, in the epoxidation reaction several other solvents were screened, using our three most effective dihydroisoquinolinium salt catalysts (**16**), (**58**) and (**65**) (Table 16). TPPP was found to be insoluble in carbon tetrachloride, ethyl acetate and dimethoxyethane. In dimethylformamide the TPPP dissolved but no reaction occurred when employing catalyst (**16**). However, TPPP was soluble in 1,2-dichloroethane, and epoxidation reactions performed in this solvent gave almost identical results to those obtained with dichloromethane for catalysts (**58**) and (**65**) (Table 16, entries 3). Catalyst (**16**) was far less reactive in this medium (compared to the corresponding reaction in

dichloromethane, 70 % conversion to 29 % after 4 h) and gave a lower ee (24 % compared to 37 %). When the reactions were repeated in chloroform (Table 16, entries 4) we observed a dramatic decrease in ee for catalyst (65), catalyst (16) giving similar results to those obtained in dichloromethane (33 % ee). Catalyst (58) in chloroform, however, gave the best ee for 1-phenylcyclohexene oxide (20) that we have observed with this set of iminium salt catalysts. Interestingly, in acetonitrile the change in major epoxide enantiomer formed did not occur with catalyst (58), and at $-30\text{ }^{\circ}\text{C}$ we observe a similar degree of selectivity to that of the reaction carried out in chloroform (48 % ee, (+)-(1*R*2*R*) enantiomer) producing in acetonitrile, (-)-(1*S*2*S*)-phenylcyclohexene oxide with 45 % ee.

Table 16: Asymmetric epoxidation of 1-phenylcyclohexene using various solvents.^a

Entry	Solvent	Catalyst		
		(16) R = H	(58) R = SO ₂ Me	(65) R = OMe ^b
In all cases: ee (%) ^c / Conv. (%) ^d / time (h) / Config. ^e				
1	CH ₃ CN	43 ^f , 42, 1.0 h, (-)-1 <i>S</i> ,2 <i>S</i>	45, 89, 2.5 h, (-)-1 <i>S</i> ,2 <i>S</i>	44, 30, 0.2 h, (+)-1 <i>R</i> ,2 <i>R</i>
2	CH ₂ Cl ₂	37 ^f , 70, 4 h, (-)-1 <i>S</i> ,2 <i>S</i>	36, 100, 4 h, (+)-1 <i>R</i> ,2 <i>R</i>	25, 76, 4 h, (+)-1 <i>R</i> ,2 <i>R</i>
3	C ₂ H ₄ Cl ₂	24, 29, 24 h, (-)-1 <i>S</i> ,2 <i>S</i>	32, 97, 4 h, (+)-1 <i>R</i> ,2 <i>R</i>	17, 87, 24 h, (+)-1 <i>R</i> ,2 <i>R</i>
4	CHCl ₃	33, 52, 24 h, (-)-1 <i>S</i> ,2 <i>S</i>	48, 100, 12 h, (+)-1 <i>R</i> ,2 <i>R</i>	11, 73, 24 h, (+)-1 <i>R</i> ,2 <i>R</i>

^a Epoxidation conditions: Iminium salt (10 mol %), TPPP (2 eq), solvent, $-30\text{ }^{\circ}\text{C}$ T $^{\circ}\text{C}$. ^b Catalyst configuration (4*R*,5*R*). ^c Enantiomeric excess determined by ¹H-NMR with (+)-Eu(hfc)₃ (0.1 mol eq) as chiral shift reagent. ^d Conversion evaluated from the ¹H-NMR by integration alkene versus epoxide. ^e The absolute configuration of the major enantiomer was determined by comparison to those reported in the literature. ^f Reaction carried out at $-40\text{ }^{\circ}\text{C}$.

The substituted dibenzo[*c,e*]azepinium salts (**80**), (**81**), (**82**), and (**83**) were also tested, using the optimum conditions established from Table 4, at a temperature of $-40\text{ }^{\circ}\text{C}$ (Table 17). Under these conditions, acetonitrile appears to be the solvent of choice, with the *p*-methoxyaryl catalyst (**83**) producing 1-phenylcyclohexene oxide (**20**) in 73 % ee. However, catalyst (**82**) was not as effective as the corresponding dihydroisoquinolinium salt (**58**), in either of the solvents. Interestingly no asymmetric induction was observed in chloroform, previously our most effective reaction solvent. Epoxidation of other substrates using catalyst (**80**) in acetonitrile has been previously reported by other members of the Page group,⁴³ and generally the ees are disappointing, with triphenylethylene (**98**) and 1-phenylcyclohexene (**46**) being the best substrates (60 and 67 % ee respectively).

Table 17: Catalytic asymmetric epoxidation of 1-phenylcyclohexene using the dibenzo[*c,e*]azepinium salts and TPPP.^a

Catalyst	Solvent	Conversion (%) ^b	Ee (%) ^c	Configuration ^d
80	CH ₃ CN ⁴³	100	67	(-)-(1 <i>S</i> ,2 <i>S</i>)
R = H	CHCl ₃	84	19	(-)-(1 <i>S</i> ,2 <i>S</i>)
81	CH ₃ CN	100	38	(-)-(1 <i>S</i> ,2 <i>S</i>)
R = NO ₂	CHCl ₃	no rxn	-	-
(82)	CH ₃ CN	100	40	(-)-(1 <i>S</i> ,2 <i>S</i>)
R = SO ₂ Me	CHCl ₃	75	0	-
(83)	CH ₃ CN	100	73	(+)-(1 <i>R</i> ,2 <i>R</i>)
R = OMe ^e	CHCl ₃	57	5	(+)-(1 <i>R</i> ,2 <i>R</i>)

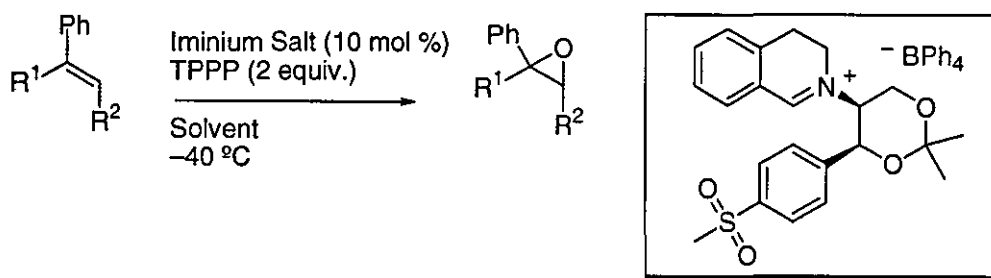
^a Epoxidation conditions: Iminium salt (10 mol %), TPPP (2 eq), solvent, $-40\text{ }^{\circ}\text{C}$ T $^{\circ}\text{C}$. ^b Conversion evaluated from the ¹H-NMR by integration alkene versus epoxide, numbers in brackets represent isolated yield. ^c Enantiomeric excess determined by ¹H-NMR with (+)-Eu(hfc)₃ (0.1 mol eq) as chiral shift reagent. ^d The absolute configuration of the major enantiomer was determined by comparison to those reported in the literature. ^e Catalyst configuration (4*R*,5*R*).

As previously found under the aqueous oxone conditions, the enantioselectivity of the dibenzo[*c,e*]azepinium salt catalysts is quite substrate dependent. The corresponding dihydroisoquinolinium salts; however, show less substrate dependency and, further to the interesting phenomena observed with these catalysts, we wanted to see whether

the change in major enantiomer formed is observed in the epoxidation of alkenes other than 1-phenylcyclohexene (**46**). Using the most selective dihydroisoquinolinium catalyst (**58**) from the above study, in acetonitrile and chloroform we were able to epoxidize several unfunctionalized alkenes (Table 18). Reactions were carried out at a temperature of $-40\text{ }^{\circ}\text{C}$, with 10 mol % of the catalyst.

Again, we observed the switch in major enantiomer on changing the reaction solvent, and the catalyst appeared less-substrate dependent than the corresponding dibenzo[*c,e*]azepinium salts.

Table 18: Catalytic asymmetric epoxidation of various alkenes using TPPP and catalyst **58**.^a



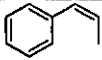
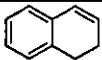
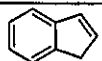

Solvent	CH ₃ CN			CHCl ₃			
	Alkene	Yield (%) ^b	ee (%) ^c	Conf. ^d	Yield (%) ^b	ee (%) ^c	Conf. ^d
	46	73	45	(-)-1 <i>S</i> ,2 <i>S</i>	77	48	(+)-1 <i>R</i> ,2 <i>R</i>
	101	13 ^e	30	(-)- <i>S,S</i>	31	67	(+)- <i>R,R</i>
	97	42	48	(-)-1 <i>S</i> ,2 <i>R</i>	35	2	(+)-1 <i>R</i> ,2 <i>S</i>
	98	25	27	(+)- <i>S</i>	11 ^e	63	(-)- <i>R</i>
	99	56	38	(-)-1 <i>S</i> ,2 <i>R</i>	98	59	(+)-1 <i>R</i> ,2 <i>S</i>

^a Epoxidation conditions: Iminium salt (10 mol %), TPPP (2 eq), Solvent, $-40\text{ }^{\circ}\text{C}$, 24 h. ^b Isolated yield. ^c Enantiomeric excess determined by ¹H-NMR with (+)-Eu(hfc)₃ (0.1 mol eq) as chiral shift reagent or by Chiral HPLC on a Chiralcel OD column. ^d The absolute configuration of the major enantiomer was determined by comparison to those reported in the literature. ^e Conversion evaluated from the ¹H-NMR by integration alkene versus epoxide.

However, enantioselectivities were dramatically increased in chloroform (apart from the anomalous reaction with α -methyl-stilbene **97**), when compared to those achieved in acetonitrile. We found that *trans*-stilbene (**101**), usually a poor substrate with our catalysts, is epoxidized with 67 % ee in chloroform, whereas the corresponding reaction, performed in acetonitrile only affords *trans*-stilbene oxide (**75**) with 30 % ee.

Further to this work, a range of unfunctionalized *cis*-alkenes was subjected to the reaction conditions (Table 19). Interestingly, we found that no change in configuration of epoxide occurred with this type of substrate. However, the general trend of increased enantiomeric excess in chloroform over acetonitrile was still present. 1,2-Dihydronaphthylene (**103**) was epoxidized with 82 % ee in 89 % yield when chloroform was employed as the reaction solvent. Good ees for the epoxidation of *cis*- β -methylstyrene (**111**) and indene (**112**) were also observed (70 % ee and 61 % ee respectively). Asymmetric epoxidation of the non-aryl substrate (**113**) did not occur with any selectivity, giving rise to racemic product.

Table 19: Catalytic asymmetric epoxidation of various *Cis*-alkenes using TPPP and catalyst **58**.^a

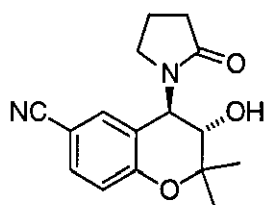
	Solvent	MeCN				CHCl ₃			
	Alkene	T (h)	Yield (%) ^b	ee (%) ^c	Conf. ^d	T (h)	Yield (%) ^b	ee (%) ^c	Conf. ^d
111		24	71	53	(+)-1 <i>S</i> ,2 <i>R</i>	24	85	70	(+)-1 <i>S</i> ,2 <i>R</i>
103		16	80	56	(-)-1 <i>S</i> ,2 <i>R</i>	17	89	82	(-)-1 <i>S</i> ,2 <i>R</i>
112		–	–	–	–	24	83	61	(+)-1 <i>S</i> ,2 <i>R</i>
113		–	–	–	–	24	100 ^e	0	–

^a Epoxidation conditions: Iminium salt (10 mol %), TPPP (2 eq), Solvent, –40 °C. ^b Isolated yield. ^c

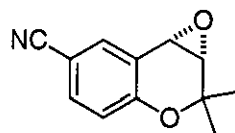
Enantiomeric excess determined by ¹H-NMR with (+)-Eu(hfc)₃ (0.1 mol eq) as chiral shift reagent. ^d

The absolute configuration of the major enantiomer was determined by comparison to those reported in the literature. ^e Conversion evaluated from the ¹H-NMR by integration alkene versus epoxide.

The asymmetric epoxidation of *cis*-alkenes is particularly important when one considers the importance of some of the biologically active compounds that ring-opening of the oxirane moiety can give. Cromakalim (**114**),⁴⁴ a anti-hypertensive agent, is just one of the compounds available from ring opening of the epoxide functionality, and was traditionally synthesized in enantiomerically pure form by resolution,⁴⁵ until Jacobsen's chiral salen complexes became available.⁴⁶ It has been found that the main biological activity resides in the leavorotatory enantiomer (levcromakalim), while the dextrorotatory compound exhibits no significant activity.⁴⁵ The powerful cyano electron withdrawing group at C6 of the benzopyran system was found to be essential for good blood pressure-lowering activity.⁴⁵ Several other research groups have reported the enantiopure synthesis of levcromakalims precursor (**115**).⁴⁷ However, Shi's fructose-derived ketone catalyst produces the inactive dextrorotatory enantiomer.⁴⁸

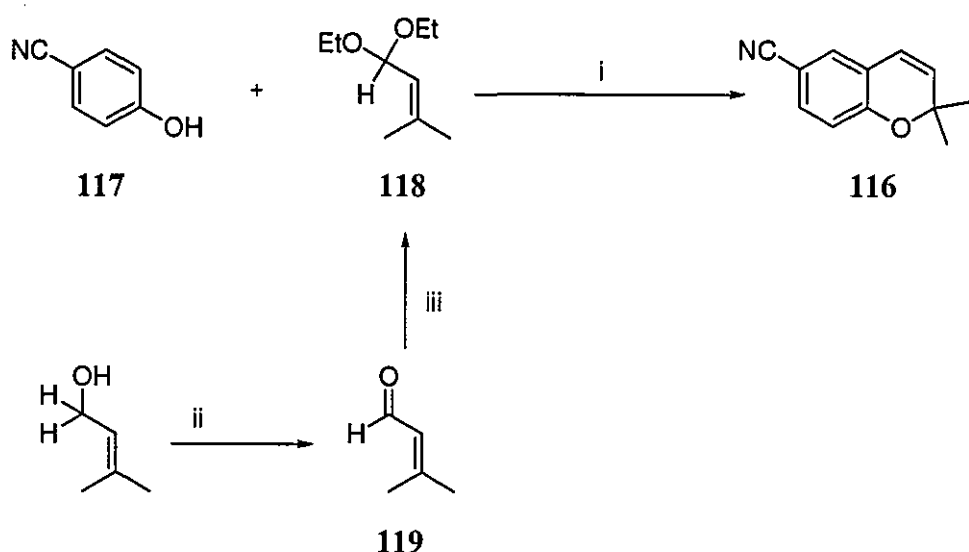


114



115

Oxidized benzopyrans are also postulated to be the bioactivated intermediates responsible for the cytotoxic activity of the precocenes (benzopyrans) in insects and in mammalian tissues.⁴⁶ Cyano-benzopyran (**116**) was prepared using North's method,⁴⁹ in one step from 4-cyanophenol (**117**) and 1,1-diethoxy-3-methyl-2-butene (**118**), which in turn was synthesized from 3-methyl-2-butanal (**119**) (Scheme 47).⁵⁰ Epoxidations of (**116**) using catalyst (**58**) in both acetonitrile and chloroform produced the desired (-)-3*S*,4*S* enantiomer of (**115**) in good to excellent enantiomeric excesses (Table 20). In acetonitrile the epoxide was formed with 80 % ee, and 63 % yield, but, in chloroform the epoxide was formed with 97 % ee in 59 % yield.



Reagents and Conditions: i: 3-picoline (0.25 equiv.), *p*-xylene, 110-120 °C, 24 h, 63 %; ii: PDC:DCM, r.t. 6 h, 82 %; iii: CH(OEt)₃, KHSO₄, EtOH, 0 °C-r.t., 2 h, 74 %.

Scheme 47: Formation of the benzopyran **116** using North's method.

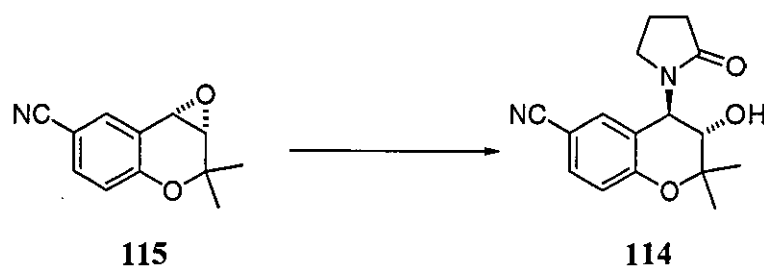
Table 20: Highly enantioselective epoxidation of benzopyran **116** using catalyst **58** and TPPP.^a

Alkene	CH ₃ CN				CHCl ₃			
	Time (h)	Yield (%) ^b	ee (%) ^c	Conf. ^d	Time (h)	Yield (%) ^b	ee (%) ^c	Conf. ^d
 116	24	63	80	(-)-3 <i>S</i> ,4 <i>S</i>	24	59	97	(-)-3 <i>S</i> ,4 <i>S</i>

^a Epoxidation conditions: Iminium salt (10 mol %), TPPP (2 eq), Solvent, -40 °C. ^b Isolated yield. ^c

Enantiomeric excess determined by Chiral HPLC on a Chiracel OD column. ^d The absolute configuration of the major enantiomer was determined by comparison to those reported in the literature.

Treatment of compound (**115**) with pyrrolidone and sodium hydride afforded levcromakalim (**114**) in 52 yield (Scheme 48).



Reagents and Conditions: i. Pyrrolidin-2-one, NaH, DMSO, r.t. 6 h, 52 %.

Scheme 48: Ring opening of the epoxide to form the anti-hypertensive agent Levchromakalim.

Efficient asymmetric epoxidation of terminal alkenes remains a challenging problem. A range of unfunctionalized terminal olefins were screened under our optimum conditions.

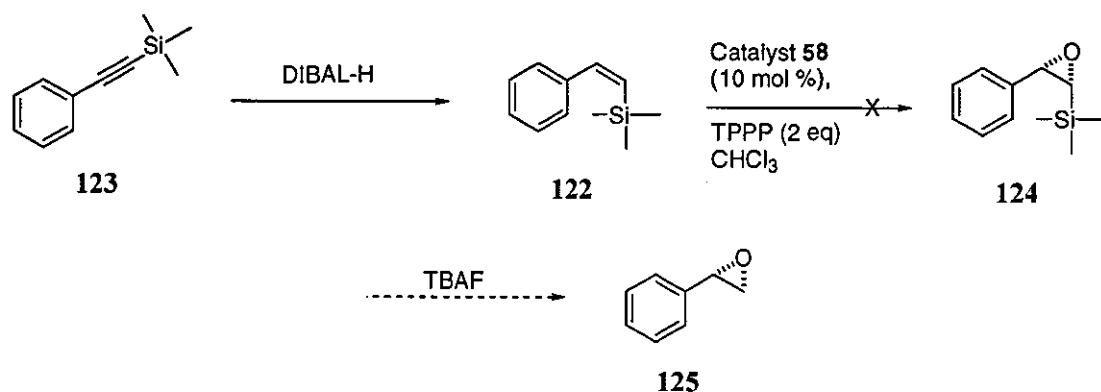
Table 21: Epoxidation of terminal alkenes using catalyst **58** under non-aqueous TPPP conditions.^a

Alkene	Solvent	Time (h)	Yield (%) ^b	ee (%)	Configuration ^c
120	CHCl ₃	24	73	18 ^d	(+)- <i>S</i>
121	CHCl ₃	24	0	–	–
100	CHCl ₃	24	58	13 ^e	(+)- <i>S</i>

^a Epoxidation conditions: Iminium salt (10 mol %), TPPP (2 eq), Solvent, –40 °C. ^b Isolated yield. ^c The absolute configuration of the major enantiomer was determined by comparison to those reported in the literature. ^d Enantiomeric excess determined by ¹H-NMR with (+)-Eu(hfc)₃ (0.1 mol eq) as chiral shift reagent. ^e Enantiomeric excess determined by Chiral HPLC on a Chiracel OD column.

Disappointingly, enantiomeric excesses were low. However, Shi has recently reported the highly enantioselective oxidation of a range of 2,2-disubstituted vinylsilanes, which on treatment with TBAF afford terminal epoxides with high ee.⁵¹ Due to the ability of catalyst (**58**) to afford good to excellent ees for *cis*-alkenes, epoxidation of the *cis*-vinyl silane (**122**) was attempted (Scheme 49). Reduction of the commercially available corresponding alkyne (**123**) was achieved using DIBAL in 90 % yield.⁵²

Subsequent epoxidation at $-40\text{ }^{\circ}\text{C}$ in chloroform using catalyst (**58**) and TPPP did not afford the desired epoxide (**124**); in fact no reaction had occurred after 24 hours. Even when carrying the reaction out at elevated temperatures ($0\text{ }^{\circ}\text{C}$ – reflux at *ca.* $80\text{ }^{\circ}\text{C}$) no reaction occurred.

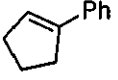
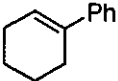
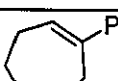
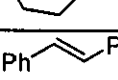
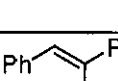
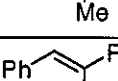


Scheme 49: Attempted formation of styrene oxide **125** from the vinyl silane **122**.

2.5.4 Epoxidations using the binaphthalene catalyst (**93**).

Following the success of binaphthalene catalyst (**93**) under the aqueous oxone conditions, described in section 2.4, we decided to test the catalyst with TPPP as the stoichiometric oxidant (Table 22). Several substrates were epoxidized, using acetonitrile as solvent at $-40\text{ }^{\circ}\text{C}$, and we observed a similar level of selectivity to those reactions carried out under the aqueous oxone conditions. The ee for α -methylstilbene oxide (**18**) is slightly increased under these conditions (61 % ee compared to 49 % ee under the oxone system).

Table 22: Epoxidation of several unfunctionalized alkenes using catalyst **93** and TPPP.^a

Alkene	Time (h)	Yield (%) ^b	ee (%) ^c	Conf. ^d
109 	14	77	39	(-)-1 <i>S</i> ,2 <i>S</i>
46 	7 (18) ^e	81 (67) ^e	89 (82) ^e	(-)-1 <i>S</i> ,2 <i>S</i>
110 	14	74	77	(-)-1 <i>S</i> ,2 <i>S</i>
101 	24	45	11	(-)- <i>S,S</i>
97 	24	66	61	(-)-1 <i>S</i> ,2 <i>S</i>
98 	24	26	0	-

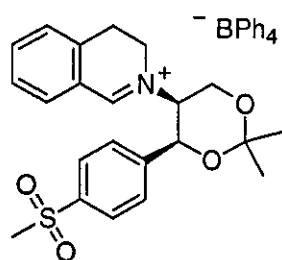
^a Epoxidation conditions: Iminium salt **93** (10 mol %), TPPP (2 eq), MeCN, -40 °C. ^b Isolated yield. ^c Enantiomeric excess determined by ¹H-NMR with (+)-Eu(hfc)₃ (0.1 mol eq) as chiral shift reagent. ^d The absolute configuration of the major enantiomer was determined by comparison to those reported in the literature. ^e Numbers in brackets refer to the corresponding reaction carried out in chloroform.

The reaction remained highly enantioselective when using chloroform as the reaction solvent. 1-Phenylcyclohexene is epoxidized with 89 % ee in acetonitrile and 82 % ee with chloroform. This is in contrast to the corresponding dihydroisoquinolinium (**16**) and dibenzo[*c,e*]azepinium salts (**80**), which give poorer enantioselectivities in chloroform. Catalyst (**16**) gives 1-phenylcyclohexene oxide (**20**) in 43 % ee in acetonitrile and 33 % ee in chloroform, and catalyst (**80**) gives 1-phenylcyclohexene oxide (**20**) with 67 % ee in acetonitrile and only 19 % ee in chloroform.

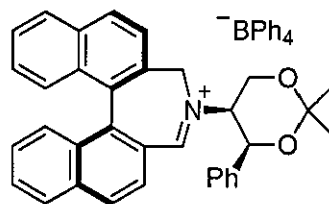
2.6 Conclusion

Through this research project we have developed a number of new iminium salt catalysts based around a 1,3-dioxane unit. These have incorporated different aryl groups in the C4 position, and we have shown that catalysts bearing biphenyl and binaphthalene backbones can also be effective mediators in the asymmetric epoxidation of unfunctionalized alkenes.

Of the systems tested, two catalysts have been developed which have provided epoxides with excellent enantioselectivity. The binaphthalene derived catalyst (**93**) gave up to 95 % ee and catalyst loadings as low as 0.1 mol %.

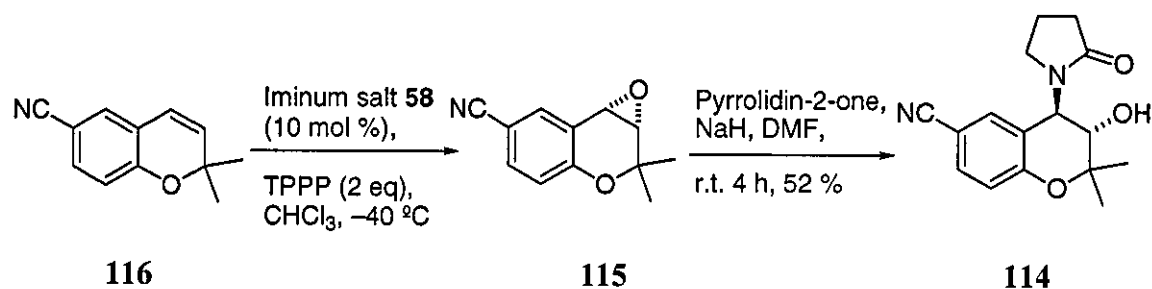


58



93

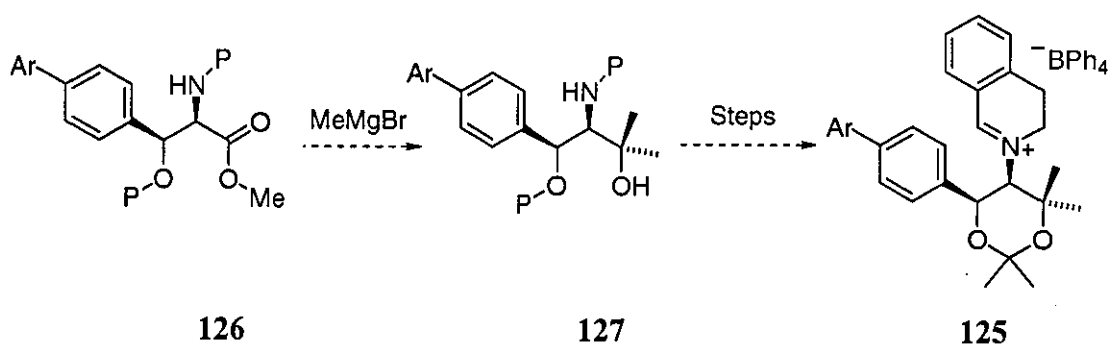
The development of the anhydrous TPPP conditions has allowed us to perform reactions at low temperature, and this has resulted in the highest ever reported ee for iminium salt mediated epoxidation. Catalyst (**58**) provided levromakalims precursor (**115**) in up to 97 % ee, and the enantiopure synthesis of the anti-hypertensive agent levromakalim (**114**) was achieved.



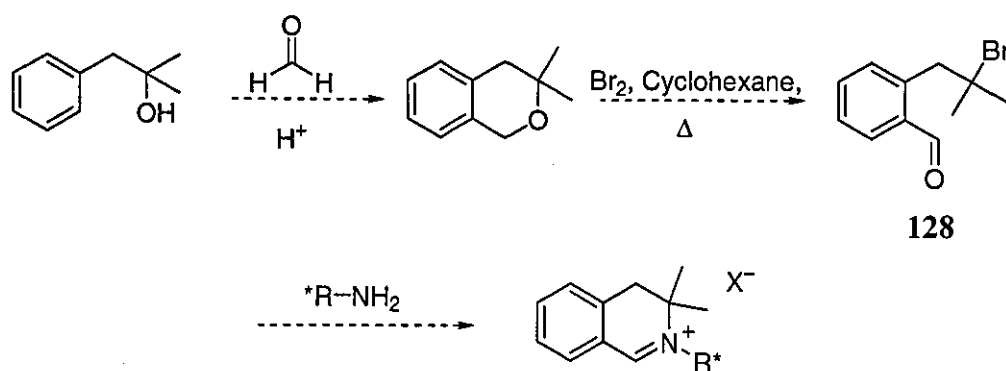
With the development of iminium salt catalysts that give high enantioselectivity, we hope that iminium salt mediated asymmetric epoxidation can now be considered as a viable method for the formation of enantiomerically enriched epoxides.

2.7 Future Work

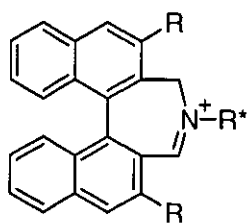
One could envisage a wide range of new catalyst structures which may give rise to higher enantioselectivity in the asymmetric epoxidation of alkenes. Those depicted in the following schemes are thought to be the most promising. Catalysts of the type (125) are thought to benefit from added control of the incoming substrate by having methyl groups in the C6 position of the 1,3-dioxane ring. This type of catalyst could be synthesized in a similar manner to those reported in section 2.2, with addition of methylmagnesium bromide to the ester (126) to give compound (127).



A similar system could also be developed with the bromoaldehyde (128), with similarities to Bohé's achiral catalyst described in chapter one.



Modifications to the binaphthalene system could also be achieved by addition of groups to the 3,3'-positions (129), as in Yang's dioxirane catalyst (chapter one).



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Further catalyst developments should preferably be made after computational studies have been carried out with our current range of catalysts. This may help in the elucidation of a transition state model which can account for the range of enantioselectivities we have observed, not only in the new anhydrous TPPP conditions but also under the original Oxone, water/acetonitrile system.

Greater understanding of the transition state for the transfer of oxygen from the catalyst to the substrate could therefore lead to the synthesis of new catalysts which are less substrate dependent than the current range of catalysts described in this thesis.

2.9 Chapter Two References

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Chapter Three

Experimental

3.0 Experimental

3.1 General experimental

All infrared spectra were obtained using a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer; thin film spectra were acquired using sodium chloride plates.

All ^1H and ^{13}C NMR spectra were measured at 250.13 and 62.86 MHz using a Bruker AC 250 MHz spectrometer or at 400.13 and 100.62 MHz using a Bruker DPX 400 MHz spectrometer. The solvent used for NMR spectroscopy was CDCl_3 (unless stated otherwise) using TMS (tetramethylsilane) as the internal reference. Chemical shifts are given in parts per million (ppm) and J values are given in Hertz (Hz).

The mass spectra were recorded using a Jeol-SX102 instrument utilising electron impact (E.I.), fast atom bombardment (F.A.B.) and by the EPSRC national mass spectrometry service at the University of Wales, Swansea, utilising electrospray (ES.). Analysis by GCMS utilised a Fisons GC 8000 series (AS 800), using a 15 m x 0.25 mm DB-5 column and an electron impact low resolution mass spectrometer.

Melting points were recorded using an Electrothermal-IA 9100 melting point instrument and are uncorrected.

Optical rotation values were measured with an Optical Activity-polAAar 2001 instrument, operating at $\lambda=589$ 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 solvent used.

Microanalyses were performed on a Perkin Elmer Elemental Analyser 2400 CHN.

All chromatographic manipulations used silica gel as the adsorbent. Reactions were monitored using thin layer chromatography (TLC) on aluminium backed plates with Merck Kiesel 60 F254 silica gel. TLC visualised by UV radiation at a wavelength of 254 nm, or stained by exposure to an ethanolic solution of phosphomolybdic acid

(acidified with concentrated sulphuric acid), followed by charring where appropriate. Purification by column chromatography used Merck Kiesel 60 H silica adsorbent.

The reactions requiring anhydrous conditions were carried out using glassware dried overnight at 150 °C, under a nitrogen atmosphere unless otherwise stated. Reaction solvents were obtained commercially dry, except light petroleum (b.p. 40-60 °C) which was distilled from calcium chloride prior to use. Ethyl acetate was distilled over calcium sulphate or chloride. Dichloromethane was distilled over calcium hydride. Tetrahydrofuran (THF), was distilled under a nitrogen atmosphere from the sodium/benzophenone ketyl radical or from lithium aluminium hydride.

All *N*-protected amino acids were either purchased commercially or produced from known literature procedures.^{1,2}

Enantiomeric excesses were determined by either proton nuclear magnetic resonance (¹H-NMR), or by Chiral High Performance Liquid Chromatography, (Chiral HPLC).

The proton nuclear magnetic resonance spectra were recorded in deuterated chloroform on a Bruker AC 250, operating at 250.13 MHz, in the presence of europium (III) tris [3-(hepta-fluoropropylhydroxymethylene)-(+)-camphorate], [(+)-Eu(hfc)₃], as the chiral shift reagent and tetramethylsilane as the internal standard.

The chiral column used for the determination of enantiomeric excesses (ee), of non-racemic mixtures by chiral HPLC, was Chiracel OD on a TSP Thermo-Separating-Products Spectra Series P200 instrument, with TSP Spectra Series UV100 ultra-violet absorption detector set at 254 nm and a Chromojet integrator. Both solvents used to gain measurements (hexane and isopropanol), were of HPLC grade.

3.2 Numbering systems.

The assignments of the proton and carbon-13 resonances have been made according to numbering systems (Figure 1). Some of these systems used are standard chemical nomenclature while others were introduced arbitrarily by the present author. In the

latter case, the introduced system was based on the structural resemblance of the compounds with others that possessed a formal system.

Aromatic systems are numbered according to the standard protocol. Aromatic carbon atoms bearing a substituent are always quaternary (C quat., arom.). All aromatic carbon atoms which are attached to a hydrogen atom are termed C arom. (^{13}C spectra) or CH arom. (^1H spectra). The dihydroisoquinolinium nucleus is numbered according to a standard system but the carbon atoms of this moiety are termed *isoq*. Except for those in the dimethylene part which are designated Ar-CH₂ and CH₂N in the assignment. The biphenyl system is also numbered and carbon atoms of this moiety are termed *biphenyl*. The binaphthylene nucleus is numbered, with the carbon atoms termed *binap*.

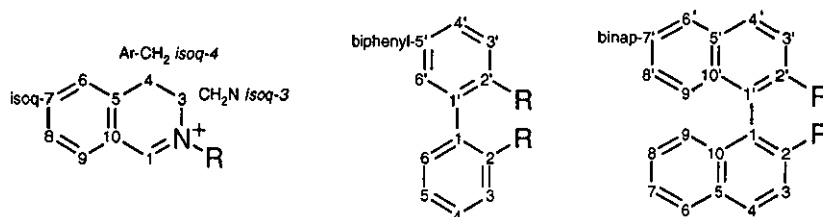


Figure 1: Numbering systems employed in the experimental procedures.

N-protected amino acid derivatives are numbered with the carboxylic acid carbon first as in the example given in Figure 2. The protecting group will be referred to by its abbreviation. The 1,3-dioxane nucleus is numbered according to the standard protocol as are the 5-membered oxazolidines, with substituents off the ring being numbered in order.

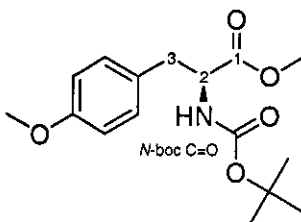
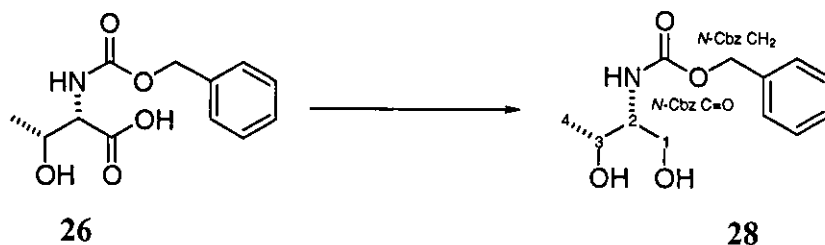


Figure 2: Numbering system employed for amino acid derivatives.

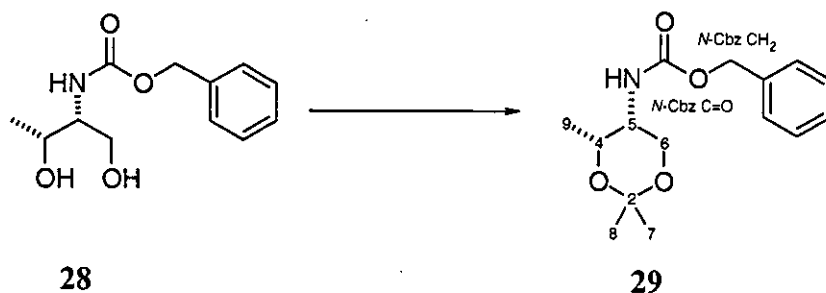
3.3 Individual experimental procedures and characterisation

(1*R*,2*R*)-[2-Hydroxy-1-hydroxymethyl-propyl]-carbamic acid benzyl ester (28):



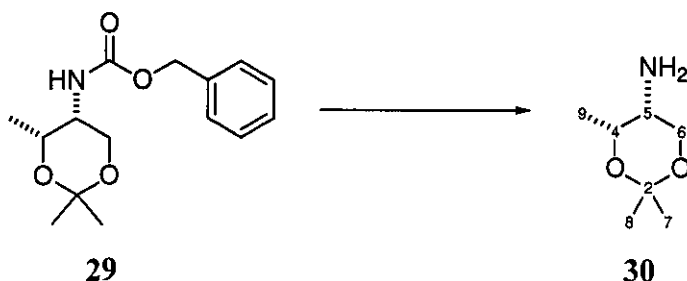
To a cooled ($-15\text{ }^{\circ}\text{C}$) solution of (2*S*,3*R*)-2-benzyloxycarbonylamino-3-hydroxybutyric acid (**26**) (5.00 g, 19.8 mmol) in 1,2-dimethoxyethane (20 ml) were successively added *N*-methyl morpholine (2.20 ml, 19.8 mmol) and isobutyl chloroformate (2.50 ml, 19.8 mmol). After 1 min the white precipitate was removed by filtration, washed with 1,2-dimethoxyethane (2 x 5 ml) and the filtrate placed in a flask and cooled in a ice/salt bath. A solution of NaBH_4 (1.13 g, 29.6 mmol) in H_2O (50 ml) was added in one portion producing a strong evolution of gas. After the evolution subsided H_2O (250 ml) was added. The reaction mixture was then extracted with ethyl acetate (3 x 75 ml). The organic layers washed with brine (2 x 50 ml), dried (MgSO_4) and solvents removed under reduced pressure to give a colourless oil (3.30 g, 70%), $[\alpha]_{\text{D}} -15.0$ (c 1.12, CHCl_3); ν_{max} (film) $/\text{cm}^{-1}$ 3334, 2971, 2360, 1698, 1522, 1456, 1251, 1069; δ_{H} (250 MHz; CDCl_3) 1.20 (3 H, d, J 6.4 Hz, CH_3 , C4), 2.74 (2 H, bs, 2 x OH), 3.57 (1 H, m, CH, C3), 3.81 (2 H, bs, CH_2 , C1), 4.12 (1 H, m, NCH, C2), 5.11 (2 H, s, *N*-Cbz CH_2), 5.54 (1 H d, J 8.6 Hz, NH), 7.35 (5 H, m, 5 x CH arom., Ph gp.); δ_{C} (100 MHz; CDCl_3) 20.22 (CH_3 , C4), 56.33 (NCH, C2), 64.38 (CH_2 , *N*-Cbz CH_2), 66.98 (CH_2 , C1), 128.19 (CH arom., *para* in Ph gp.), 128.19 (2 x CH arom., *ortho* in Ph gp.), 128.55 (2 x CH arom., *meta* in Ph gp.), 136.31 (C quat. arom., *ipso* in Ph gp.), 157.18 (C quat. *N*-Cbz C=O); m/z 239.1152; $\text{C}_{12}\text{H}_{17}\text{NO}_4$ (M^+) requires 239.1158.

(1*R*,2*R*)-(2,2,4-Trimethyl-[1,3]dioxan-5-yl)-carbamic acid benzyl ester (29):



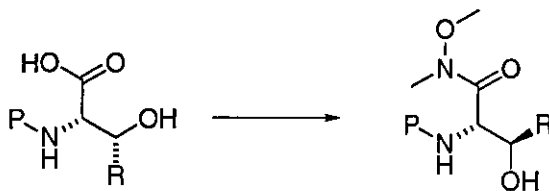
[(1*R*,2*R*)-2-Hydroxy-1-hydroxymethyl-propyl]-carbamic acid benzyl ester (**28**) (0.20 g, 0.87 mmol), was dissolved in acetone (20.0 ml) and 2,2-dimethoxypropane (1.10 ml, 8.70 mmol). A catalytic amount of *p*-toluene sulphonic acid (10 mol%, 0.016 g, 0.09 mmol) was added and the reaction left to stir overnight at room temperature. The solvent was evaporated under reduced pressure. The residue which remained was dissolved in ethyl acetate, washed with sodium hydrogen carbonate (50%)(2 x 20 ml) and brine (2 x 20 ml). The organic layers were combined, dried (Mg₂SO₄) and solvent removed under reduced pressure to yield a colourless oil (0.24 g, 85%), [α]_D -8.2 (*c* 1.04, CHCl₃); Found: C, 64.27; H, 7.46; 4.61. C₁₅H₂₁NO₄ requires C, 64.50; H, 7.58; N, 5.01.; ν_{\max} (film) /cm⁻¹ 2360, 1716, 1505, 1455, 1381; δ_{H} (400 MHz; CDCl₃) 1.60 (3 H, d, *J* 6.3 Hz, CH₃, C9), 1.40 (3 H, s, CH₃, C7), 1.48 (3 H, s, CH₃, C8), 3.53 (1 H, dq, *J* 9.8, 1.9 Hz, NCH, C5), 3.78 (1 H, dd, *J* 12.0, 1.8 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C6), 4.09 (1 H, dd, *J* 12.0, 2.0 Hz, downfield portion of an *ABX* system, N-CHCHH-O, C6), 4.15 (1 H, ddd, *J* 6.3, 1.9, CH, C4), 5.16 (2 H, s, *N*-Cbz CH₂), 5.58 (1 H, d, *J* 9.8 Hz, NH), 7.37 (5 H, m, 5 x CH arom., Ph gp.); δ_{C} (100 MHz; CDCl₃) 18.17 (CH₃, C9), 18.95 (CH₃, C7), 30.06 (CH₃, C8), 49.98 (NCH, C5), 65.34 (*N*-Cbz CH₂), 67.24 (CH₂, C6), 67.39 (CH, C4), 99.41 (C quat., C2), 127.32 (CH arom., *para* in Ph gp.), 128.53 (2 x CH arom., *ortho* in Ph gp.), 128.87 (2 x CH arom. *meta* in Ph gp.), 136.86 (C quat. arom. *ipso* in Ph gp.), 156.82 (C quat., *N*-Cbz C=O); *m/z* 279.1471; C₁₅H₂₁NO₄ (M⁺) requires 279.1471.

(1*R*,2*R*)-2,2,4-Trimethyl-[1,3]dioxan-5-yl-amine (30):



(1*R*,2*R*)-(2,2,4-Trimethyl-[1,3]dioxan-5-yl)-carbamic acid benzyl ester (**30**) (1.30 g, 4.7 mmol) was dissolved in ethanol and placed in a three necked round bottom flask charged with palladium (10% on carbon) (0.10 g) under an atmosphere of hydrogen (ballon). The reaction was stirred at room temperature for 12 h. The solution was filtered through a pad of celite and the ethanol removed under reduced pressure to yield a colourless oil (0.61 g, 90%), $[\alpha]_D -26.7$ (c 1.05, CHCl_3); δ_H (250 MHz; CDCl_3) 1.16 (3 H, d, J 6.4 Hz, CH_3 , C9), 1.41 (3 H, s, CH_3 , C7), 1.46 (3 H, s, CH_3 , C8), 1.60 (2 H, bs, NH_2), 2.42 (1 H, q, J 4.0, 2.0 Hz, NCH , C5), 3.72 (1 H, dd, J 11.8, 2.0 Hz, upfield portion of an ABX system, N-CHCHH-O , C6), 4.11 (1H, dd, J 11.8, 2.0 Hz, downfield portion of an ABX system, N-CHCHH-O , C6), 4.09 (1 H, m, CH , C4); δ_C (100 MHz; CDCl_3) 18.34 (CH_3 , C7), 19.02 (CH_3 , C9), 30.11 (CH_3 , C8), 49.23 (NCH , C5), 67.38 (CH_2 , C6), 68.01 (CH , C4), 99.11 (C quat. , C2).

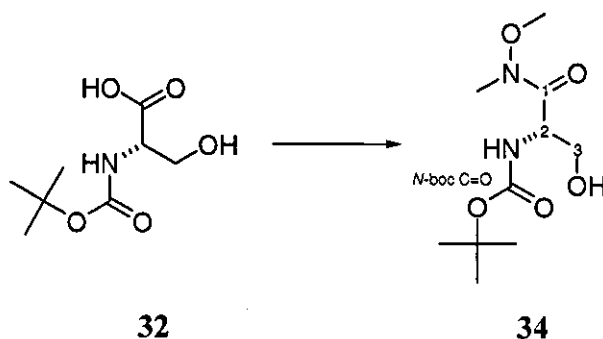
General procedure for the formation of Weinreb amides from amino acid derivatives:



The amino acid derivative (1.0 equiv.) was dissolved in dichloromethane (20 ml/g) and cooled to -15 °C, followed by addition of *N,O*-dimethylhydroxylamine hydrochloride (1.02 equiv.) and *N*-methylmorpholine (1.02 equiv.). *N*-(3-

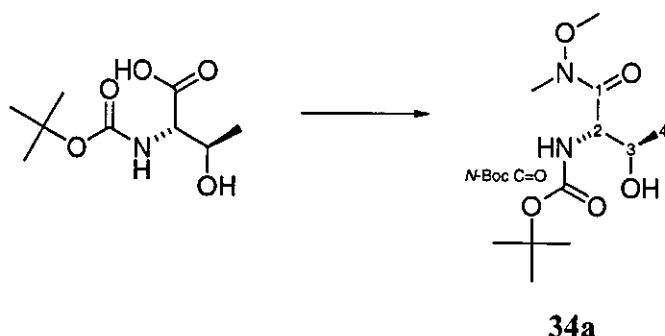
dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (1.02 equiv.) was then added portionwise as a solid over 30 min. The reaction was stirred for 1 h at $-15\text{ }^{\circ}\text{C}$ and ice cold aq. hydrochloric acid (1 M) (3 ml/g) was added. The aqueous layer was extracted with dichloromethane (10 ml/g) and the combined organic layers washed with sat. aq. sodium hydrogen carbonate solution (3 ml/g). The organic layer was dried (MgSO_4), filtered and the solvent removed under reduced pressure.

(*S*)-[2-Hydroxy-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid *tert*-butyl ester (34):



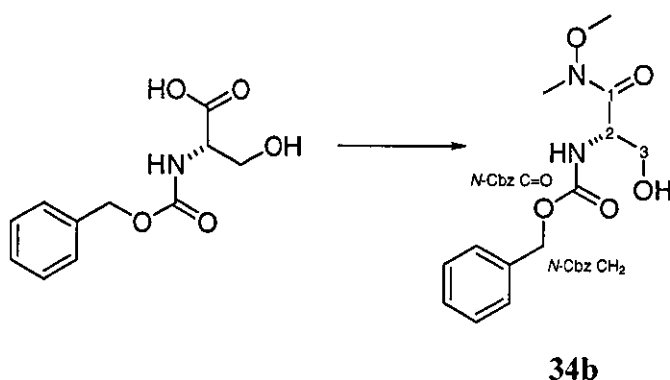
Prepared according to the general procedure from *N*-Boc-L-serine (**32**) (5.00 g, 24.4 mmol). Colourless solid (5.4 g, 89%); m.p. $116\text{-}117\text{ }^{\circ}\text{C}$ (lit.³ mp $118\text{-}119\text{ }^{\circ}\text{C}$); $[\alpha]_{\text{D}}^{20} +3.8$ (c 1.04, CHCl_3) [Lit.³ $[\alpha]_{\text{D}} -1.4$ (c 2.6, CHCl_3 for D-enantiomer)]; Found: C, 48.55; H, 8.12; N, 11.24. $\text{C}_{10}\text{H}_{20}\text{N}_2\text{O}_5$ requires C, 48.36; H, 8.12; N, 11.29.; $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3467, 1702, 1646, 1458, 1377, 1180; δ_{H} (250 MHz; CDCl_3) 1.45 (9 H, s, $(\text{CH}_3)_3\text{C}$), 3.23 (3 H, s, NCH_3), 3.77 (3 H, s, OCH_3), 3.82 (2 H, d, J 2.0 Hz, CH_2OH , C3), 4.72-4.86 (1 H, m, NCH , C2), 5.65 (1 H, s, NH); δ_{C} (100 MHz; CDCl_3) 28.4 (3 x CH_3 , $(\text{CH}_3)_3\text{C}$), 32.2 (NCH_3), 52.6 (NCH , C2), 61.7 (OCH_3 C14), 63.4 (CH_2OH , C3), 80.0 (C quat., $(\text{CH}_3)_3\text{C}$), 155.8 (C quat., *N*-Boc $\text{C}=\text{O}$), 171.1 (C quat., $\text{C}=\text{O}$, C1); m/z 249.1451; $\text{C}_{10}\text{H}_{20}\text{N}_2\text{O}_5$ (M^+H) requires 249.1451.

(2*R*,3*S*)-[2-Hydroxy-1-(methoxy-methyl-carbamoyl)-propyl]-carbamic acid *tert*-butyl ester (34a):



Prepared according to the general procedure from *N*-Boc-L-threonine (5.00 g, 22.4 mmol). Colourless solid (5.70 g, 93%), m.p. 66-67 °C; $[\alpha]_{\text{D}}^{20} -11.6$ (c 1.07, CHCl_3); [lit.⁴ $[\alpha]_{\text{D}}^{20} -9.8$ (c 1.40, CHCl_3)]; $\nu_{\text{max}}(\text{film}) / \text{cm}^{-1}$ 3391, 1704, 1647, 1463, 1377, 1184; δ_{H} (250 MHz; CDCl_3) 1.22 (3 H, d J 6.35, CH_3 , C4), 1.45 (9 H, s, $(\text{CH}_3)_3\text{C}$), 2.90 (3 H, s, NCH_3), 3.24 (3 H, s, OCH_3), 4.08 (1 H, ddd, J 2.1, 6.4 Hz, CH , C2), 4.65 (1 H, d, J 7.6 Hz, CH , C3), 5.44 (1 H, d, J 9.1 Hz NH); δ_{C} (100 MHz; CDCl_3) 19.3 (CH_3 , C4), 28.3 ($(\text{CH}_3)_3\text{C}$), 31.2 (NCH_3), 54.1 (CH , C2), 61.7 (OCH_3), 67.7 (CH , C3), 79.8 (C quat., $(\text{CH}_3)_3\text{C}$), 156.1 (C quat., *N*-Boc C=O), 172.2 (C quat., C=O, C1); m/z 263.1607; $\text{C}_{11}\text{H}_{22}\text{N}_2\text{O}_5$ (M^+H) requires 263.1602.

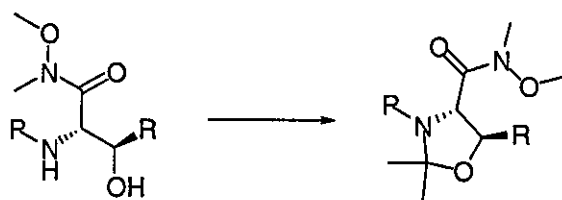
(*S*)-[2-Hydroxy-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid benzyl ester (34b):



Prepared according to the general procedure from *N*-Cbz-L-serine (5.00 g, 22.4 mmol). Pale yellow oil (5.60 g, 89%); $[\alpha]_{\text{D}}^{20} +5.4$ (c 1.04, CHCl_3); $\nu_{\text{max}}(\text{film}) / \text{cm}^{-1}$ 3398, 1715, 1652, 1456, 1377, 1178; δ_{H} (250 MHz; CDCl_3) 3.22 (3 H, s, NCH_3), 3.77 (3 H, s, OCH_3), 3.84 (2 H, d, J 4.4 Hz, CH_2OH , C3), 4.80-4.90 (1 H, m, NCH_2 ,

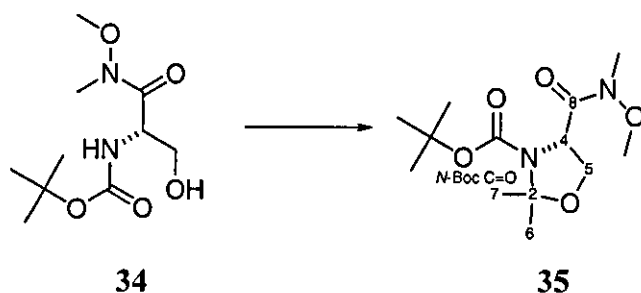
C2), 5.16 (2 H, s, CH₂, *N*-Cbz CH₂), 5.96 (1 H, d, *J* 8.2 Hz, NH), 7.32 (5 H, 5 x CH arom., Ph gp.); δ_C (100 MHz; CDCl₃) 32.15 (NCH₃), 52.90 (CH, C2), 61.60 (OCH₃), 63.43 (CH₂OH, C3), 67.08 (CH₂, *N*-Cbz CH₂), 128.08 (2 x CH arom., *ortho* in Ph gp.), 128.18 (2 x CH arom., *meta* in Ph gp.), 128.53 (CH arom., *para* in Ph gp.), 136.22 (C quat. arom., *ipso* in Ph gp.), 156.42 (C quat., *N*-Cbz C=O), 170.62 (C quat., C=O, C1); *m/z* 283.0937; C₁₃H₁₈N₂O₅ (M⁺H) requires 283.0939.

General procedure for the formation of 2,2-dimethyl oxazolanes:



The Weinreb amide (1.0 equiv.) was dissolved in acetone (15 ml/g), 2,2-dimethoxypropane (5 ml/g) and boron trifluoride diethyl etherate (Cat.) was added dropwise until there was a permanent change in colour (colourless to dark yellow). The reaction was stirred for up to 90 min at room temperature and triethylamine (0.1 ml/g) was added to quench the reaction. The solvent was evaporated under reduced pressure.

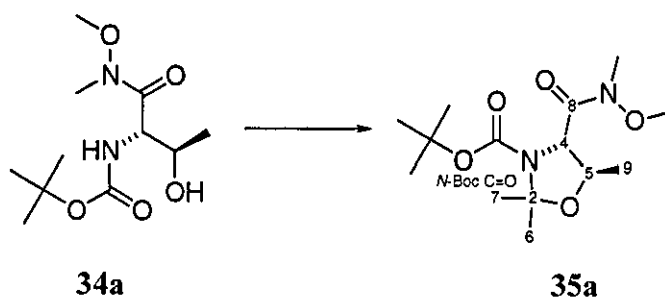
(4*S*)-4-(Methoxy-methyl-carbamoyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (35):



Prepared according to the general procedure from (*S*)-[2-Hydroxy-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid *tert*-butyl ester (34) (5.00 g, 20.2 mmol). Pale yellow solid, recrystallized from light petroleum to give colourless crystals (5.20

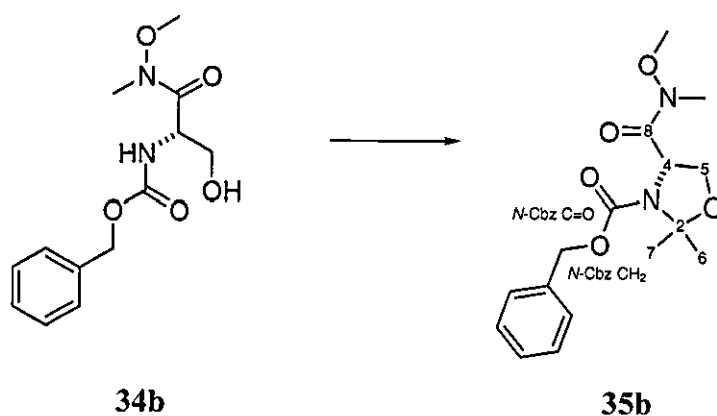
g, 89%); mp 66-67 °C (Lit.³ 65-67 °C); $[\alpha]_D^{20}$ -36.5 (*c* 1.11, CHCl₃); [lit.¹ $[\alpha]_D$ +37.1 for D-enantiomer]; ν_{\max} (film) /cm⁻¹ 1716, 1680, 1458, 1175; δ_H (400 MHz; DMSO-d₆, 80 °C) 1.40 (9 H, s, (CH₃)₃C), 1.49 (3 H, s, CH₃, C6), 1.58 (3 H, s, CH₃, C7), 3.14 (3 H, s, NCH₃), 3.70 (3 H, s, OCH₃), 3.82 (1 H, dd, *J* 3.6, 8.8 Hz, upfield portion of an ABX system, N-CHCHH-O, C5), 4.20 (1 H, dd, *J* 8.8, 7.2 Hz, downfield portion of an ABX system, N-CHCHH-O, C5), 4.77 (1 H, dd, *J* 3.6, 7.2 Hz, NCH, C4); δ_C (62.50 MHz; DMSO-d₆, 80 °C) 24.45 (2 x CH₃, C6,7), 27.59 ((CH₃)₃C), 32.07 (NCH₃), 56.79 (CH, C4), 60.56 (OCH₃), 65.27 (CH₂, C5), 78.82 (C quat., C2), 93.50 (C quat., (CH₃)₃C), 150.53 (C quat., *N*-Boc C=O), 170.20 (C quat., C8); *m/z* 288.1686; C₁₃H₂₄N₂O₅ (M⁺) requires 288.1685.

(4*S*,5*R*)-4-(Methoxy-methyl-carbamoyl)-2,2,5-trimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (35a):



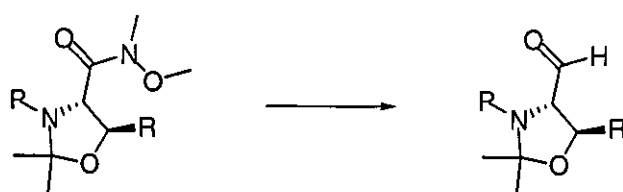
Prepared according to the general procedure from (2*R*,3*S*)-[2-Hydroxy-1-(methoxy-methyl-carbamoyl)-propyl]-carbamic acid *tert*-butyl ester (34a) (5.00 g, 19.2 mmol). Colourless oil, (5.20 g, 91%); $[\alpha]_D^{20}$ -8.8 (*c* 1.36, CHCl₃); [lit.⁴ $[\alpha]_D^{20}$ -9.8 (*c* 1.40, CHCl₃)]; ν_{\max} (film) /cm⁻¹ 1706, 1681, 1452, 1174; δ_H (250 MHz; DMSO-d₆, 80 °C) 1.39 (3 H, d, *J* 6.1 Hz, CH₃, C9), 1.45 (9 H, s, (CH₃)₃C), 1.59 (3 H, s, CH₃, C6), 1.62 (3 H, s, CH₃, C7), 3.21 (3 H, s, NCH₃), 3.78 (3 H, s, OCH₃), 4.12 (1 H, quint, *J* 6.1, 12.4 Hz, CH, C5), 4.45 (1 H, d, *J* 6.1 Hz, CH, C4); δ_C (62.50 MHz; DMSO-d₆, 80 °C) 19.20 (CH₃, C9), 24.30 (CH₃, C6), 26.99 (CH₃, C7), 27.62 ((CH₃)₃C), 32.07 (NCH₃), 60.38 (NCH, C4), 62.77 (OCH₃), 73.75 (CH, C5), 78.96 (C quat., C2), 93.65 (C quat., (CH₃)₃C), 150.47 (C quat., *N*-Boc C=O), 169.73 (C quat., C8); *m/z* 302.1836; C₁₄H₂₆N₂O₅ (M⁺) requires 302.1842.

(4*S*)-4-(Methoxy-methyl-carbamoyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid benzyl ester (35b):



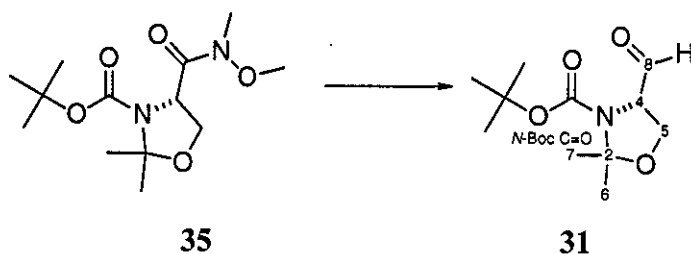
Prepared according to the general procedure from (*S*)-[2-Hydroxy-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid benzyl ester (**34b**) (5.00 g, 17.7 mmol); Colourless oil, (5.13 g, 90%); $[\alpha]_D^{20} -5.0$ (*c* 1.36, CHCl₃); [lit.⁵ $[\alpha]_D^{20} -5.0$ (*c* 0.60, CHCl₃)]; ν_{\max} (film) /cm⁻¹ 1713, 1680, 1463, 1175; δ_H (400 MHz; DMSO-d₆, 100 °C) 1.53 (3 H, s, CH₃, C6), 1.63 (3 H, s, CH₃, C7), 3.11 (3 H, s, NCH₃), 3.62 (3 H, s, OCH₃), 3.89 (1 H, dd, *J* 9.2, 3.6 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C5), 4.25 (1 H, dd, *J* 9.2, 7.4 Hz, downfield portion of an *ABX* system, N-CHCHH-O, C5), 4.88 (1 H, dd, *J* 7.4, 3.6 Hz, NCH, C4), 5.07 (2 H, s, CH₂, *N*-Cbz CH₂), 7.35 (5 H, 5 x CH arom., Ph gp.); δ_C (100 MHz; DMSO-d₆, 80 °C) 21.40 (CH₃, C6), 25.58 (CH₃, C7) 33.28 (NCH₃), 58.01 (NCH, C4), 61.82 (OCH₃), 66.82 (CH₂, C5), 67.02 (CH₂, *N*-Cbz CH₂), 95.22 (C quat., C2), 128.29 (2 x CH arom., *ortho* in Ph gp.), 128.57 (2 x CH arom., *meta* in Ph gp.), 129.08 (CH arom., *para* in Ph gp.), 137.48 (C quat., arom., *ipso* in Ph gp.), 152.34 (C quat., *N*-Cbz C=O), 171.05 (C quat., C=O, C8); *m/z* 323.1605; C₁₆H₂₂N₂O₅ (M⁺H) requires 323.1607.

General procedure for the formation of Garner's aldehyde and analogous compounds:



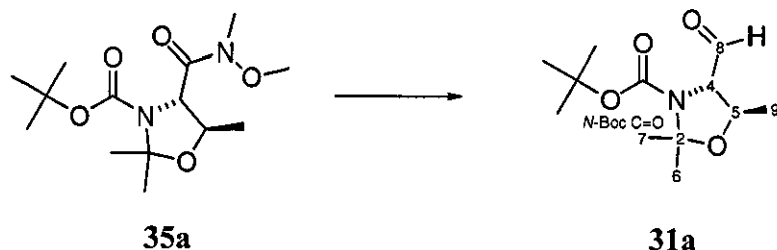
The weinreb protected oxazolidine (1.0 equiv.) was dissolved in anhydrous tetrahydrofuran (15 ml/g) and cooled to 0 °C. LiAlH₄ in tetrahydrofuran (1.0 M) (5.19 ml, 5.2 mmol) was added dropwise and the mixture was stirred for 30 min. The reaction was cooled further to -15 °C and sat. aq. potassium hydrogen sulfate (10 ml/g) was added carefully, the solution was diluted with diethyl ether (30 ml/g) and stirred vigorously for 30 min. The organic layer was separated, dried (Na₂SO₄), filtered and the solvent evaporated under reduced pressure.

(S)-4-Formyl-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (31):



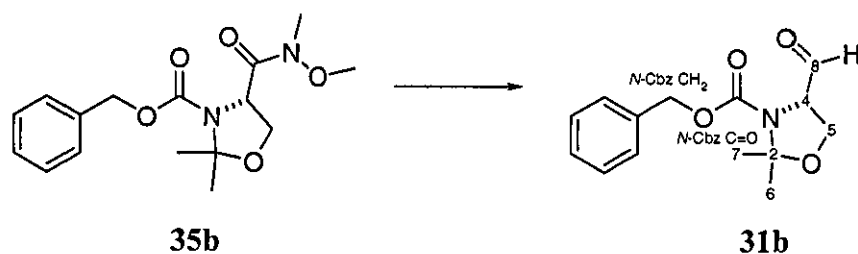
Prepared according to the general procedure from (*S*)-4-(Methoxy-methyl-carbamoyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (**35**) (3.00 g, 10.4 mmol). Pale yellow oil (2.3 g, 96%); $[\alpha]_D^{20}$ -84.8 (*c* 1.04, CHCl₃); [lit.⁶ $[\alpha]_D$ -91.7 (*c* 1.34, CHCl₃)]; ν_{\max} (film) /cm⁻¹ 3453, 2980, 2936, 1739, 1708, 1478, 1392, 1172; δ_H (400 MHz; DMSO-d₆, 80 °C) 1.38 (9 H, s, (CH₃)₃C), 1.43 (3 H, s, CH₃, C6), 1.49 (3 H, s, CH₃, C7), 3.98 (1 H, dd, *J* 9.2, 3.6 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C5), 4.04 (1 H, dd, *J* 9.2, 7.2 Hz, downfield portion of an *ABX* system, N-CHCHH-O, C5), 4.29 (1 H, ddd, *J* 9.2, 7.2, 3.6, 2.0 Hz, NCH, C4), 9.48 (1 H, d, 2.0 Hz, HC=O, C8); δ_C (100 MHz; DMSO-d₆, 80 °C) 25.05 (CH₃, C6), 26.62 (CH₃, C7), 28.81 ((CH₃)₃C), 63.89 (CH₂, C5), 65.36 (CH, C4), 80.96 (C quat., C2), 94.88 (C quat., (CH₃)₃C), 165.11 (C quat., N-Boc C=O), 199.87 (HC=O, C8); *m/z* 230.1396; C₁₁H₁₉NO₄ (M⁺H) requires 230.1392.

(4*S*,5*R*)-4-Formyl-2,2,5-trimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (31a):



Prepared according to the general procedure from (4*S*,5*R*)-4-(Methoxy-methyl-carbamoyl)-2,2,5-trimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (**35a**) (5.50 g, 19.0 mmol). Pale yellow oil (3.90 g, 90%); $[\alpha]_D^{20}$ -61.0 (c 1.05, CHCl_3); [lit.⁶ $[\alpha]_D$ -65.8 (c 1.66 CHCl_3)]; ν_{max} (film) $/\text{cm}^{-1}$ 3584, 2980, 2937, 1740, 1713, 1456, 1368, 1170; δ_{H} (400 MHz; DMSO-d_6 , 80 °C) 1.20 (3 H, d, J 6.0 Hz, CH_3 , C9), 1.35 (9 H, s, $(\text{CH}_3)_3\text{C}$), 1.46 (3 H, s, CH_3 , C6), 1.48 (3 H, s, CH_3 , C7), 3.68 (1 H, quint, J 8.0, 3.6 Hz, CH C5), 4.09 (1 H, m, NCH , C4), 9.36 (1 H, d, J 4.0 Hz, HC=O , C8); δ_{C} (100 MHz; DMSO-d_6 , 80 °C) 17.40 (CH_3 , C9), 24.77 (CH_3 , C6), 26.14 (CH_3 , C7), 27.36 ($(\text{CH}_3)_3\text{C}$), 69.37 (CH , C5), 70.21 (NCH , C4), 79.94 (C quat., $(\text{CH}_3)_3\text{C}$), 93.53 (C quat., C2), 151.00 (C quat., N-Boc C=O), 197.37 (HC=O , C8); m/z 243.1472; $\text{C}_{12}\text{H}_{21}\text{NO}_4$ (M^+) requires 243.1471.

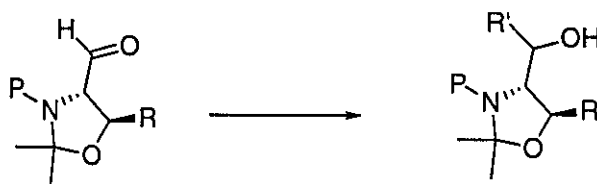
(*S*)-4-Formyl-2,2-dimethyl-oxazolidine-3-carboxylic acid benzyl ester (31b):



Prepared according to the general procedure from (*S*)-4-(Methoxy-methyl-carbamoyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid benzyl ester (**35b**) (1.80 g, 6.8 mmol). Pale yellow oil (1.60 g, 90%); $[\alpha]_D^{20}$ -77.5 (c 1.00, CHCl_3); [lit.⁵ $[\alpha]_D$ -80.1 (c 1.02, CHCl_3)]; ν_{max} (film) $/\text{cm}^{-1}$ 3461, 3032, 2981, 2933, 1740, 1702, 1498, 1410, 1379, 1160; δ_{H} (400 MHz; DMSO-d_6 , 80 °C) 1.43 (3 H, s, CH_3 , C6), 1.57 (3 H, s,

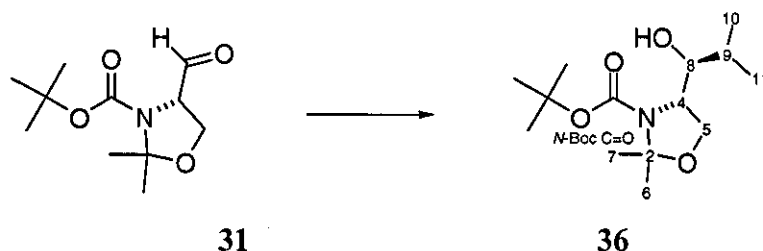
CH_3 , C7), 3.59 (1 H, dd, J 8.0, 8.0 Hz, upfield portion of an ABX system, N-CHCHH-O, C5), 3.72 (1 H, dd, J 8.0, 4.0 Hz, downfield portion of an ABX system, N-CHCHH-O, C5), 3.97 (1 H, m, NCH, C4), 5.01 (2 H, s, N -Cbz CH_2), 7.14 (5 H, m, 5 x CH arom., Ph gp.), 9.32 (1 H, s, $HC=O$, C8).

General procedure for the addition of Grignard reagents to Garners aldehyde and substituted derivatives:



To a precooled solution of the aldehyde (1.0 equiv.) in tetrahydrofuran (50 ml/g) at -78 °C under a stream of N_2 was added, dropwise a solution of the Grignard in tetrahydrofuran (3.3 equiv.), over 30 min. The resulting dark yellow solution was stirred for an additional 2 h at -78 °C and then warmed to 0 °C. The reaction mixture was diluted with diethyl ether (50 ml/g) and quenched with sat. ammonium chloride solution (10 ml/g). The organic layers were washed with brine, dried (Na_2SO_4), filtered and solvent removed under reduced pressure.

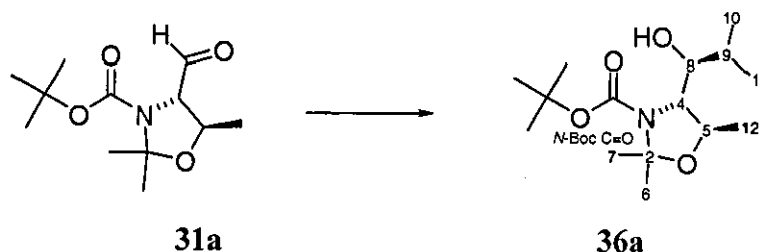
(*S*)-4-[(1*S*)-1-Hydroxy-2-methyl-propyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (36):



Prepared according to the general procedure from (4*S*)-4-formyl-2,2-dimethyl-oxazolidin-3-carboxylic acid *tert*-butyl ester (**31**) (1.20 g, 5.2 mmol) with a 2M solution of isopropylmagnesium chloride (8.60 ml, 17.2 mmol). Crude yellow solid, column chromatography eluting with ethyl acetate/light petroleum (1:8) and

recrystallization (ethyl acetate/light petroleum) produced colourless crystals (1.2 g, 73%); m.p. 77-79 °C (lit⁷ m.p. 78-80 °C); $[\alpha]_D^{20} -52.2$ (c 1.06, CHCl_3) [lit⁴ $[\alpha]_D -54.3$ (c 1.00, CHCl_3)]; Found: C, 61.92; H, 9.93; N, 4.96%. $\text{C}_{14}\text{H}_{27}\text{NO}_4$ requires C, 61.51; H, 9.96; N, 5.12%; ν_{max} (film) $/\text{cm}^{-1}$ 3582, 3396, 1702, 1670, 1459, 1377, 1366, 1174; δ_{H} (250 MHz; CDCl_3) 0.90 (3 H, d, J 6.7, CH_3 , C10), 0.98 (3 H, d, J 6.8, CH_3 , C11), 1.44 (9 H, s, $(\text{CH}_3)_3\text{C}$), 1.51 (3 H, s, CH_3 , C6) 1.60 (3 H, s, CH_3 , C7), 1.63-1.70 (1 H, m, $\text{CH}(\text{CH}_3)_2$, C9), 3.45-3.49 (1 H, m, CH , C4), 3.70-3.96 (1 H, m, CH_2 , C5), 3.98-4.10 (1 H, m, CH , C8); δ_{C} (100 MHz; CDCl_3) 14.29 (CH_3 , C10), 20.42 (CH_3 , C11), 24.39 ($\text{CH}(\text{CH}_3)_2$, C9), 27.25 (CH_3 , C6), 28.39 ($(\text{CH}_3)_3\text{C}$), 31.02 (CH_3 , C7), 60.59 (NCH, C4), 65.29 (CH_2 , C5), 78.48 (CH , C8), 81.39 (C quat., $(\text{CH}_3)_3\text{C}$), 94.11 (C quat., C2), 155.7 (C quat., $N\text{-Boc C=O}$); m/z 273.1944; $\text{C}_{14}\text{H}_{27}\text{NO}_4$ (M^+) requires 273.1940.

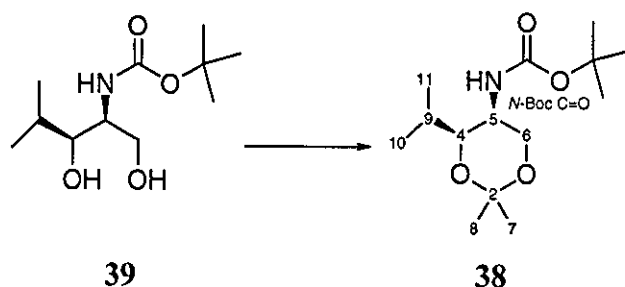
(4*S*,5*R*)-4-[(1*S*)-1-Hydroxy-2-methyl-propyl]-2,2,5-trimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (36a):



Prepared according to the general procedure from (4*S*,5*R*)-4-formyl-2,2,5-trimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (**31a**) (4.50 g, 18.4 mmol) with a 2M solution of isopropylmagnesium chloride (30.43 ml, 60.85 mmol) to give a crude yellow oil. Column chromatography with ethyl acetate/light Petroleum (1:9) and recrystallization (ethyl acetate/light Petroleum) afforded colourless crystals (1.5 g, 70%); $[\alpha]_D^{20} -39.3$ (c 1.13, acetone); Found: C, 62.21; H, 10.08; N, 4.98%. $\text{C}_{11}\text{H}_{23}\text{N}_2\text{O}_5$ requires C, 62.89; H, 9.86; N, 4.89%; ν_{max} (film) $/\text{cm}^{-1}$ 3476, 2975, 1700, 1663, 1459, 1396, 1255, 1174; δ_{H} (250 MHz; CDCl_3) 0.92 (3 H, d, J 6.7, CH_3 , C10), 1.02 (3 H, d, J 6.9, CH_3 , C11), 1.32 (3 H, d, J 6.45 CH_3 , C12) 1.50 (9 H, s, $(\text{CH}_3)_3\text{C}$), 1.53 (3 H, s, CH_3 , C6) 1.64 (3 H, s, CH_3 , C7), 1.54-1.65 (1 H, m, $\text{CH}(\text{CH}_3)_2$, C9), 3.47 (1 H, m, NCH, C4), 3.85 (1 H, m, CH , C8), 4.00 (1 H, dq, J 2.55 and 6.83 CH , C5); δ_{C} (100 MHz; CDCl_3) 14.4 (CH_3 , C10), 17.8 (CH_3 , C11), 20.5 (CH_3 , C12), 21.2

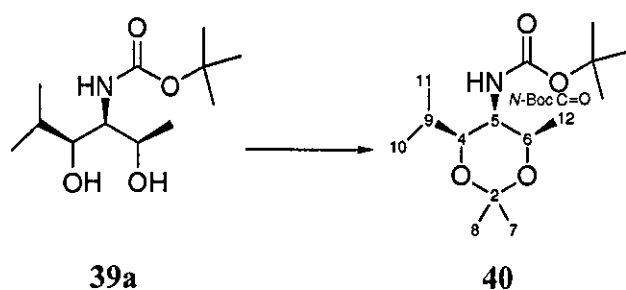
(CH(CH₃)₂, C9), 28.3 (CH₃, C6), 28.4 ((CH₃)₃C), 31.1 (CH₃, C7), 66.2 (NCH, C4), 74.4 (CH, C8), 79.1 (C quat., (CH₃)₃C), 81.4 (C quat., C2) and 197.51 (C quat., *N*-Boc C=O); *m/z* 287.2095; C₁₅H₂₉NO₄ (M⁺) requires 287.2096.

(4*S*,5*S*)-1,1-dimethylethyl *N*-[2,2-dimethyl-4-(1-methylethyl)-1,3-dioxan-5-yl]carbamate (38):



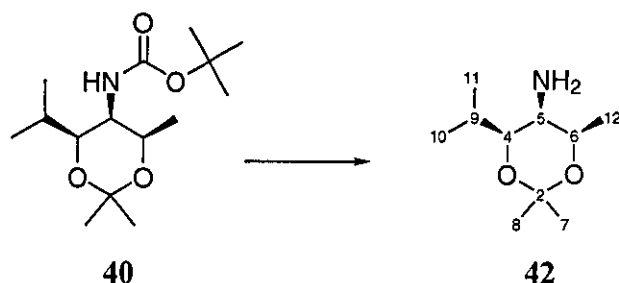
A solution of ((1*S*,2*S*)-2-Hydroxy-1-hydroxymethyl-3-methylbutyl)-carbamic acid *tert*-butyl ester (**39**) (1.40 g, 6.0 mmol), *p*-toluene sulphonic acid (0.11g, 0.6 mmol), 2,2-dimethoxypropane (7.37 ml, 60.0 mmol), in acetone (85 ml) was stirred at room temperature for 24 h. The resulting solution was concentrated under reduced pressure, diluted with ethyl acetate and washed with sodium hydrogen carbonate (50%) (2 x 25 ml) The organic layers were washed with brine, dried (MgSO₄) and concentrated to yield a colourless oil. Column chromatography was performed eluting with ethyl acetate/light petroleum (1:12) to give a colourless solid (1.35 g, 82%); mp 58-59 °C; [α]²⁰_D +5.7, (*c* 1.40, CHCl₃); *v*_{max} (film) /cm⁻¹ 3583, 3450, 2980, 2874, 2252, 1705, 1503, 1367, 1243, 1166; δ_H (250 MHz; CDCl₃) 0.87 (3 H, d, *J* 6.6 Hz CH₃, C10), 0.92 (3 H, d, *J* 6.5 Hz, CH₃, C11), 1.41 (3 H, s, CH₃, C7), 1.43 (3 H, s, CH₃, C8), 1.44 (9 H, s, (CH₃)₃C), 1.60-1.69 (1 H, m, CH(CH₃)₂, C9), 3.27 (1 H, dd, *J* 9.5, 1.6 Hz CH, C5), 3.50 (1H, m, CH, C4), 3.62 (1 H, dd, *J* 12.0, 1.9 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C6), 3.86 (1 H, dd, 12.0, 1.9 Hz, downfield portion of an *ABX* system, N-CHCHH-O, C6), 5.18 (1 H, d, *J* 9.8 Hz, NH); *m/z* 273.1906; C₁₄H₂₇NO₄ (M⁺) requires 273.1940.

(2*R*,3*S*,4*S*)-1,1-dimethylethyl-*N*-[2,2,4-trimethyl-6-(1-methylethyl)-1,3-dioxan-5-yl]carbamate (40):



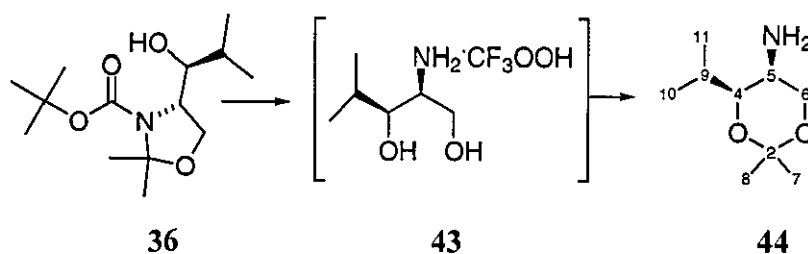
A solution of (1*S*,2*S*,3*R*)-[2-Hydroxy-1-(hydroxy-ethyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester (2.50 g, 10.1 mmol), *p*-toluene sulphonic acid (0.19 g, 1.0 mmol), 2,2-dimethoxypropane (12.43 ml, 101.2 mmol), in acetone (150 ml) was stirred at room temperature for 24 h. The resulting solution was concentrated under reduced pressure, diluted with ethyl acetate and washed with sodium hydrogen carbonate (50%) (2 x 25 ml). The organic layers were washed with brine, dried (MgSO₄) and concentrated to yield a colourless oil. Column chromatography was performed eluting with ethyl acetate/light petroleum (1:12) to give a colourless solid (2.27 g, 78%); $[\alpha]_D^{20} +7.4$, (*c* 1.12, CHCl₃); ν_{\max} (film) /cm⁻¹ 3443, 3053, 2982, 2306, 1710, 1501, 1367, 1265, 1171, 739, 705; δ_H (250 MHz; CDCl₃) 0.87 (3 H, d, *J* 6.7 Hz, CH₃, C10), 0.93 (3 H, d, *J* 6.6 Hz, CH₃, C11), 1.13 (3 H, d, *J* 6.3 Hz, CH₃, C12), 1.40 (3 H, s, CH₃, C7), 1.43 (3H, s, CH₃, C8), 1.44 (9 H, s, (CH₃)₃C), 1.67-1.76 (1 H, m, CH(CH₃)₂, C9), 3.35 (1 H, dd, *J* 9.5, 1.6 Hz, CH, C5), 3.50 (1 H, dt, *J* 10.4, 1.7 Hz, CH, C4), 4.00 (1 H, dq, *J* 6.2, 1.5 Hz, CH, C6), 4.97 (1 H, d, *J* 10.3 Hz, NH); δ_C (100 MHz; CDCl₃) 17.40 (CH₃, C12), 19.12 (CH₃, C10), 19.20 (CH₃, C11), 28.34 ((CH₃)₃C), 28.92 (CH₃, C7), 29.87 (CH₃, C8), 48.74 (NCH, C5), 49.97 (CH(CH₃)₂, C9), 68.8 (CH, C6), 78.32 (CH, C4), 79.02 (C quat., (CH₃)₃C), 99.13 (C quat., C2), 156.1 (C quat., *N*-Boc C=O); *m/z* 287.2093; C₁₅H₂₉NO₄ (M⁺) requires 287.2096.

(4*R*,5*R*,6*S*)-2,2,4-trimethyl-6-(1-methylethyl)-1,3-dioxan-5-amine (42):



(2*R*,3*S*,4*S*)-1,1-dimethylethyl-*N*-[2,2,4-trimethyl-6-(1-methylethyl)-1,3-dioxan-5-yl]carbamate (**40**) (0.170 g, 0.59 mmol) was dissolved in dichloromethane and cooled to 0°C, under a N₂ atmosphere. Aluminium chloride (0.079 g, 0.59 mmol) was added portionwise over 5 min. The solution was then left to stir for 48 h. The mixture was then neutralized with sat. sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic phase was then dried (MgSO₄), filtered and concentrated to give a crude slightly orange oil. Column chromatography, eluting with ethyl acetate/light petroleum (1:6) produced a colourless oil (0.027 g, 25%); ν_{\max} (film) /cm⁻¹ 3592, 2968, 2364, 2301, 1680, 1476, 1259, 1142; $[\alpha]_{\text{D}}^{20} +40.1^\circ$, (*c* 1.21, CHCl₃); δ_{H} (250 MHz; CDCl₃) 0.86 (3 H, d, *J* 6.7 Hz, CH₃, C12), 0.95 (3 H, d, *J* 6.5 Hz, CH₃, C10), (3 H, d, *J* 6.3 Hz, CH₃, C11), 1.39 (3 H, s, CH₃, C7), 1.40 (3 H, s, CH₃, C8), 1.77-1.89 (1 H, m, CH(CH₃)₂, C9), 2.42 (1 H, t, *J* 1.6 Hz, NCH, C5), 3.25 (1 H, dd, *J* 9.7, 1.4 Hz, CH, C4), 3.94 (1 H, dq, *J* 6.2, 1.6 Hz, CH, C6).

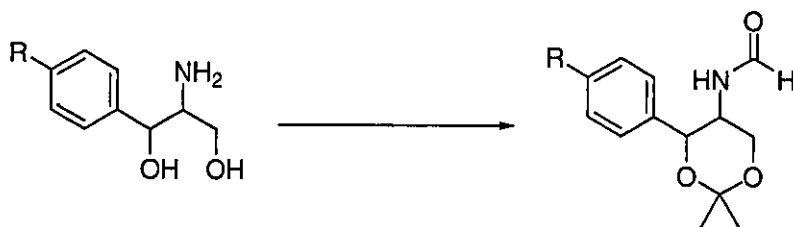
(4*S*,5*S*)-2,2-dimethyl-4-(1-methylethyl)-1,3-dioxan-5-amine (44):



(*S*)-4-[(1*S*)-1-Hydroxy-2-methyl-propyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (**36**) (0.10 g, 0.37 mmol) was dissolved in dichloromethane (1 ml) and cooled to 0 °C, at which point neat trifluoroacetic acid (0.50 ml, 6.50 mmol) was added dropwise. The reaction mixture was left to stir for 1.5 hours in ice and then warmed to room temperature for a further 1.5 hours, at which point the TLC showed the formation of product upon the baseline at expense of starting material. No attempt at neutralizing this compound was made. Solvents were removed under reduced pressure and the product was submitted directly into the cyclisation step. The compound was dissolved in acetone (25 ml) and 2,2-dimethoxypropane (0.45 ml, 3.70 mmol) with a catalytic amount of *p*-toluene sulphonic acid. The reaction mixture was left to stir overnight at room temperature. The solvents were removed under reduced pressure and the dark oil redissolved in dichloromethane and washed with sat. aq. sodium hydrogen

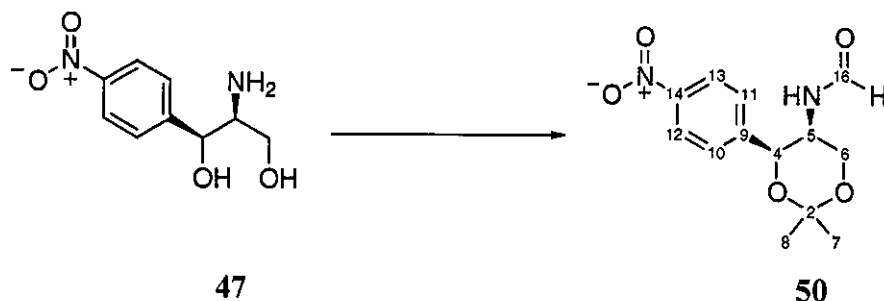
carbonate, dried (MgSO_4) and solvent removed under reduced pressure to yield a pale yellow oil (0.045 g, 70%); ν_{max} (film) $/\text{cm}^{-1}$ 3583, 2966, 2361, 2306, 1675, 1471, 1265, 1138; $[\alpha]_{\text{D}}^{20} +32.2$, (c 1.02, CHCl_3); δ_{H} (250 MHz; CDCl_3) 0.86 (3H, d, J 6.7 Hz, CH_3 , C10), 0.95 (3 H, d, J 6.5 Hz, CH_3 , C11), 1.41 (3 H, s, CH_3 , C7), 1.42 (3 H, s, CH_3 , C8), 1.69-1.87 (1 H, m, $\text{CH}(\text{CH}_3)_2$, C9), 2.05-2.25 (2 H, bs, NH_2), 2.65 (1 H, q, J 3.8, 2.0 Hz, NCH , C5), 3.32 (1 H, dd, J 9.6, 1.6 Hz, upfield portion of an ABX system, N-CHCHH-O , C6), 3.72 (1 H, dd, J 11.9, 2.0 Hz, , downfield portion of an ABX system, N-CHCHH-O , C6), 4.06 (1 H, dd, J 11.8, 2.1 Hz, CH , C4); δ_{C} (100 MHz; CDCl_3) 19.01 (CH_3 , C10), 19.09 (CH_3 , C11), 27.63 (CH_3 , C7), 28.07 (CH_3 , C8), 32.48 ($\text{CH}(\text{CH}_3)_2$, C9), 63.12 (NCH , C5), 64.33 (CH_2 , C6), 84.05 (CH , C4), 94.57 (C quat., C2).

General procedure for the formation of the formate protected 5-amino-1,3-dioxanes from commercially available amino diols:



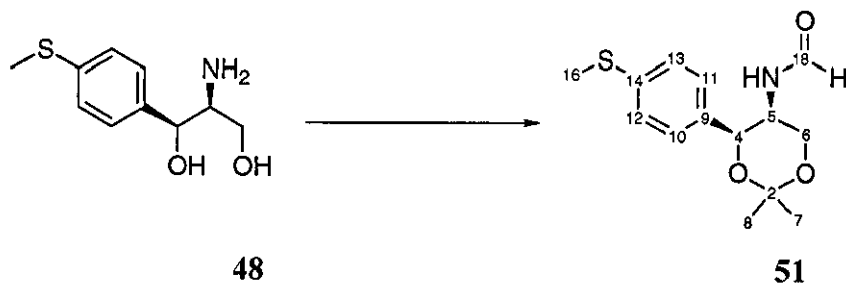
The amino diol (1.0 equiv.) was dissolved in methanol (10 ml/g) and methyl formate (1.1 equiv.) was added with sodium methoxide (10 mol%). The reaction was left to stir for 3.5 h and the solvent removed under reduced pressure. The crude yellow oil was dissolved with CSA (10 mol%) in acetone (50 ml/g) and 2,2-dimethoxypropane (10.0 equiv.). The reaction was left to stir for up to 4 h and monitored by TLC. Solvents are removed under reduced pressure and the residue re-dissolved in ethyl acetate, which was washed with sat. aq. sodium hydrogen carbonate. The organics are dried (MgSO_4) and solvents removed under reduced pressure.

N-[(4*S*,5*S*)-2,2-Dimethyl-4-[4-nitro-phenyl]-1,3-dioxan-5-yl]formamide (50):



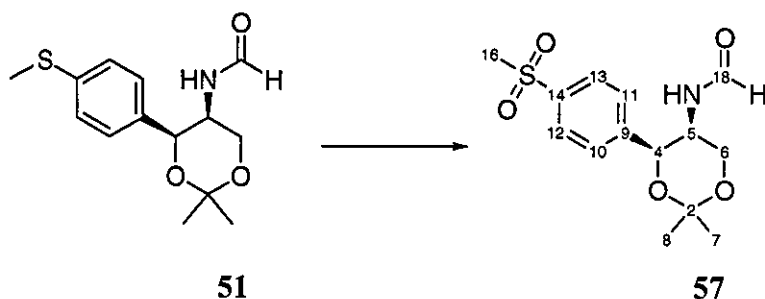
Prepared according to the general procedure from (1*S*,2*S*)-(+)-2-amino-1-(4-nitrophenyl)-1,3-propanediol (**47**) (1.00 g, 4.71 mmol). Colourless oil (1.12 g, 85%); $[\alpha]_D +3.5$ (*c* 1.02, CHCl₃); $\nu_{\max}(\text{film}) / \text{cm}^{-1}$ 1674, 1520, 1346, 856; δ_H (250 MHz; CDCl₃) 1.55 (3 H, s, CH₃, C7), 1.59 (3 H, s, CH₃, C8), 3.83 (1 H, dd, *J* 12.1, 1.7 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C6), 4.24 (1 H, dd, *J* 12.1, 1.8 Hz, downfield portion of an *ABX* system, N-CHCHH-O, C6), 4.40 (1 H, m, NCH, C5), 5.26 (1 H, d, *J* 1.0 Hz, Ar-CH, C4), 7.50 (2 H, d, *J* 8.9 Hz, 2 x CH arom., C10,11), 7.91 (1 H, s, NCHO, C16), 8.15 (2H, d, *J* 8.9 Hz, 2 x CH arom., C12,13); δ_C (62.5 MHz; CDCl₃) 18.81 (CH₃, C7), 29.29 (CH₃, C8), 45.38 (NCH, C5), 64.86 (CH₂, C6), 71.91 (Ar-CH, C4), 100.70 (C quat., C2), 123.72 (2 x CH arom., C12,13), 126.79 (2 x CH arom., C10,11), 145.80 (C quat., arom., C9), 147.80 (C quat., arom., C14), 160.62 (NCHO, C16). *m/z* 298.1399; C₁₃H₁₆N₂O₅ (M⁺NH₄) requires 298.1403.

N-[(4*S*,5*S*)-2,2-Dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-yl]formamide (51):



Prepared according to the general procedure from (1*S*,2*S*)-(+)-2-amino-1-(4-methylthiophenyl)-1,3-propanediol (**48**) (5.00 g, 23.4 mmol). Colourless oil (5.50 g, 84%); $[\alpha]_D +1.3$ (*c* 1.27, CHCl₃); $\nu_{\max}(\text{film}) / \text{cm}^{-1}$ 3315, 2988, 2362, 1667, 1494, 1380, 1197, 1084, 947; δ_H (250 MHz; CDCl₃) 1.54 (3 H, s, CH₃, C7), 1.58 (3 H, s, CH₃, C8), 2.45 (3 H, s, SCH₃, C16), 3.87 (1 H, dd, *J* 7.5, 1.0 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C6), 4.24 (1 H, dd, *J* 7.5, 1.0 Hz, downfield portion of an *ABX* system, N-CHCHH-O, C6), 4.28 (1 H, m, NCH, C5), 5.16 (1 H, d, *J* 1.3 Hz, Ar-CH, C4), 6.27 (1 H, d, *J* 5.8 Hz, NH), 7.20 (4 H, s, 4 x CH arom.), 7.97 (1 H, s, NCHO, C18); δ_C (100 MHz; CDCl₃) 15.80 (SCH₃, C16), 18.54 (CH₃, C7), 29.69 (CH₃, C8), 45.34 (NCH, C5), 64.59 (CH₂, C6), 71.41 (Ar-CH, C4), 99.72 (C quat., C2), 125.80 (2 x CH arom., C10,11), 126.61 (2 x CH arom., C12,13), 134.97 (C quat., arom., C14), 137.79 (C quat., arom., C9), 160.51 (NCHO, C18); *m/z* 281.1081; C₁₄H₁₉NO₃S (M⁺) requires 281.1085.

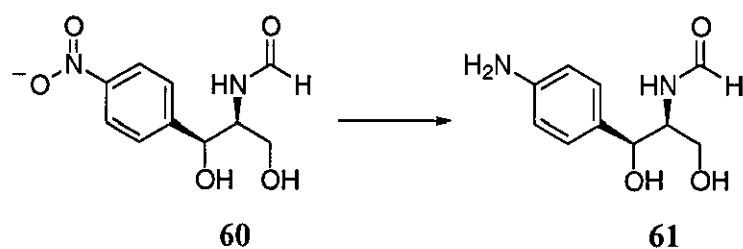
***N*-[(4*S*,5*S*)-2,2-Dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-yl]formamide (**57**):**



N-[(4*S*,5*S*)-2,2-Dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-yl]formamide (**51**) (4.0 g, 14.2 mmol) was dissolved in dichloromethane (100 ml) and cooled to 0 °C. To this solution was added *m*-CPBA (2.2 eq, 7.03 g, 31.0 mmol) as a solution in chloroform (20 ml), dropwise over 10 min. The reaction was then left to stir for 2 h. The reaction mixture was transferred to a separating funnel and washed with sat. aq. sodium hydrogen carbonate (2 x 40 ml), brine (2 x 40 ml) and dried (MgSO₄). Solvents were removed under reduced pressure to yield a colourless oil. Crystallized from chloroform/diethyl ether, colourless crystals (3.80 g, 85%); m.p. 146-147 °C; $[\alpha]_D -11.6$ (*c* 1.21, CHCl₃); $\nu_{\max}(\text{film}) / \text{cm}^{-1}$ 3054, 2993, 1675, 1516, 1382, 1300, 1239, 1202, 1149, 1086, 948; Found C, 52.68; H, 6.12; N, 4.33. C₁₄H₁₉NO₅S requires

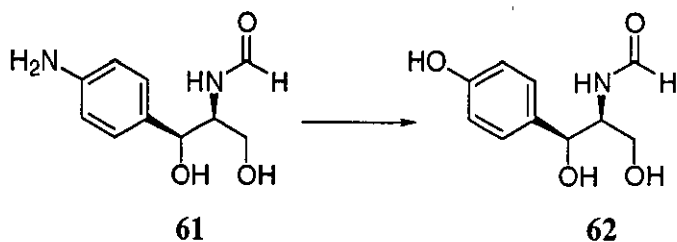
C, 53.66; H, 6.11; N, 4.47.; δ_H (400 MHz; $CDCl_3$) 1.54 (3 H, s, CH_3 , C7), 1.57 (3 H, s, CH_3 , C8), 3.01 (3 H, s, SCH_3 , C16), 3.82 (1 H, dd, J 12.0, 2.0 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C6), 4.33 (1 H, dd, J 12.0, 1.6 Hz, downfield portion of an *ABX* system, N-CHCHH-O, C6), 4.37 (1 H, dd, J 10.0, 1.6 Hz, NCH, C5), 5.25 (1 H, s, Ar-CH, C4), 6.51 (1 H, d, J 9.2 Hz, NH), 7.52 (2 H, d, J 8.0 Hz, 2 x CH arom., C10,11), 7.85 (2 H, d, J 8.0 Hz, 2 x CH arom., C12,13), 7.89 (1H, s, NCHO, C18); δ_C (100 MHz; $CDCl_3$) 18.91 (CH_3 , C7), 29.94 (CH_3 , C8), 44.83 (SCH_3 , C16) 45.43 (NCH, C5), 64.93 (CH_2 , C6), 71.91 (Ar-CH, C4), 100.38 (C quat., C2), 126.96 (2 x CH arom., C13,13), 127.49 (2 x CH arom., C11,12), 140.00 (C quat., arom., C14), 144.95 (C quat., arom., C9), 160.86 (NCHO, C18); m/z 314.1058; $C_{14}H_{19}NO_5S$ (M^+H) requires 314.1062.

***N*-[(1*S*,2*S*)-[2-(4-Amino-phenyl)-2-hydroxy-1-hydroxymethyl-ethyl]]-formamide (61):**



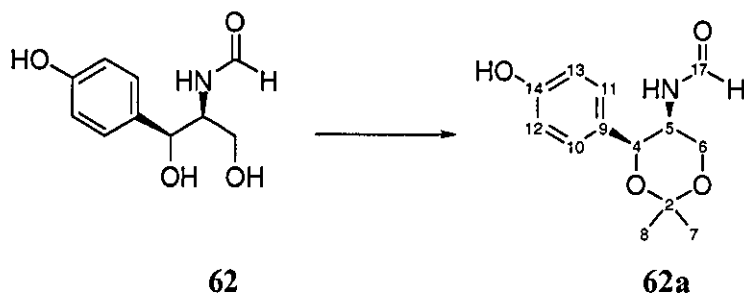
N-[(1*S*,2*S*)-[2-Hydroxy-1-hydroxymethyl-2-(4-nitro-phenyl)-ethyl]]-formamide (**60**) (10.0 g, 41.7 mmol) was dissolved in ethanol (100 ml) and placed in a three necked round bottom flask charged with palladium (10% on carbon) (1.00 g) under an atmosphere of hydrogen (ballon). The reaction was stirred at room temperature for 24 h. At which point the tlc showed complete consumption of starting material to a new more polar product. The reaction mixture was filtered through celite (to remove Pd/C) and the ethanol was removed to yield a yellow solid. (8.70 g, 99%).

***N*-[(1*S*,2*S*)-[2-Hydroxy-1-hydroxymethyl-2-(4-hydroxy-phenyl)-ethyl]]-formamide (62):**



N-{(1*S*,2*S*)-[2-(4-Amino-phenyl)-2-hydroxy-1-hydroxymethyl-ethyl]}-formamide (**61**) (10.0 g, 47.6 mmol) was dissolved in sulfuric acid (5%, aq., 50 ml) and cooled to 0 °C. Sodium nitrite (1.2 eq., 3.94 g, 57.2 mmol) was added portionwise so as not to allow the temperature to exceed 5 °C (*ca* 10 min). After the addition was complete the reaction was stirred for a further 20 min at 0 °C. Urea was then added to quench any excess sodium nitrite, the pH was altered to ~6 by the addition of sodium hydrogen carbonate. The mixture was then warmed to 80 °C for 30 min. After the heating period was over the solution was allowed to cool and the aqueous evaporated under reduced pressure by the addition of toluene. The residue obtained was then taken up in methanol and passed through a bed of celite (to remove inorganics and residual H₂O). The methanol was then removed under reduced pressure and the residue flash chromatographed using ethyl acetate as eluent. (1.5 g, 15%).

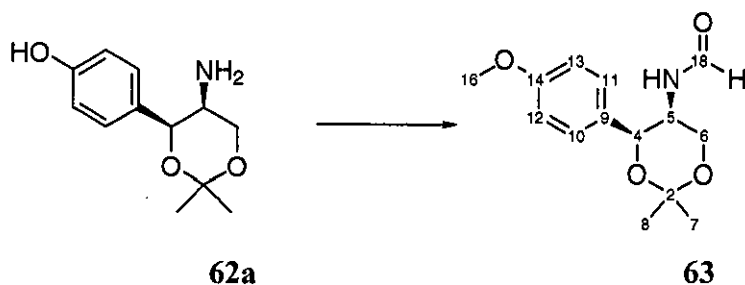
***N*-[(4*S*,5*S*)-2,2-Dimethyl-4-[4-hydroxy-phenyl]-1,3-dioxan-5-yl]formamide (62a):**



(1*S*,2*S*)-(+)-2-amino-1-(4-hydroxyphenyl)-1,3-propanediol (**62**) (2.00 g, 9.5 mmol) was dissolved in acetone (50 ml), 2,2-dimethoxypropane (25 ml) and a catalytic amount of camfor sulfonic acid was added. The reaction was stirred for 4 h and solvents removed

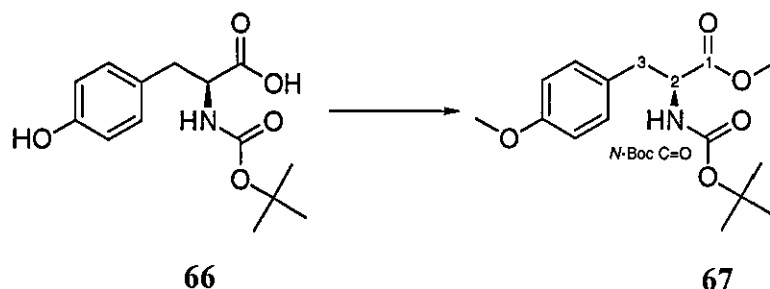
under reduced pressure. The residue obtained was re-dissolved in ethyl acetate and washed successively with sat. sodium hydrogen sulfate, brine and dried (MgSO_4). Solvents were removed under reduced pressure to afford a yellow oil. Column chromatography performed eluting with ethyl acetate/light petroleum (3:2), pale yellow oil (1.75 g, 72%); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3410, 1659, 1519, 1381; δ_{H} (250 MHz; CDCl_3) 1.54 (3 H, s, CH_3 , C7), 1.59 (3 H, s, CH_3 , C8), 3.85 (1 H, m, upfield portion of an *ABX* system, N-CHCHH-O, C6), 4.31 (2 H, m, downfield portion of an *ABX* system, N-CHCHH-O, C6 & NCH, C5), 5.16 (1 H, s, Ar-CH, C4), 6.46 (1 H, d, J 9.25 Hz, NH), 6.71 (2 H, d, J 8.80 Hz, 2 x CH arom., C12, 13), 7.14 (2 H, d, J 8.80 Hz, 2 x CH arom., C11,12), 7.96 (1H, s, NCHO, C17).

***N*-{(4*S*,5*S*)-2,2-Dimethyl-4-[4-(methoxy)-phenyl]-1,3-dioxan-5-yl}formamide (65):**



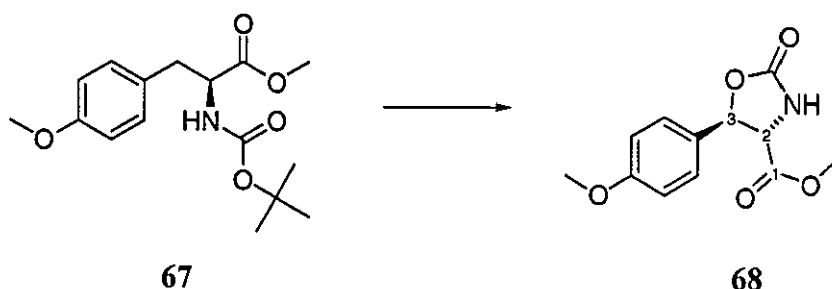
N-{(4*S*,5*S*)-2,2-Dimethyl-4-[4-hydroxy-phenyl]-1,3-dioxan-5-yl}formamide (**62a**) (0.24 g, 1.0 mmol), was dissolved in dichloromethane (40 ml) and placed under a nitrogen atmosphere. To this was added cesium carbonate (0.62 g, 1.91 mmol) and dimethyl sulfate (0.18 ml, 1.91 mmol), the reaction was left to stir for 48 h. A colour change was observed; pale yellow after addition of cesium carbonate to colourless solution at completion of reaction. The organic solution was transferred to a separating funnel, washed with water (2 x 25 ml), brine (2 x 20 ml) and dried (MgSO_4). Solvents were removed under reduced pressure to yield a colourless oil which was purified by column chromatography, eluting with ethyl acetate/light petroleum (1:1). Colourless oil (0.19 g, 72%); Having almost identical spectroscopic data to compound (**72**): $[\alpha]_{\text{D}}^{20} +2.1$ (c 1.11, CHCl_3).

(2*S*)-tert-Butoxycarbonylamino-3-(4-methoxy-phenyl)-propionic acid methyl ester (67):



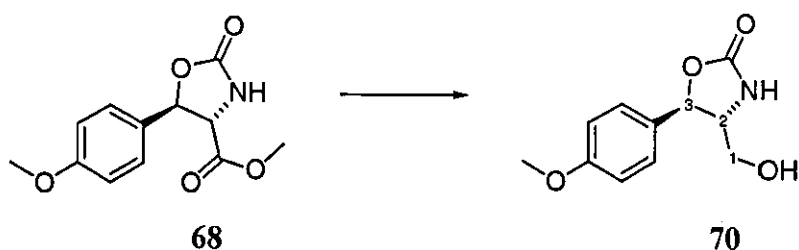
A solution of (2*S*)-tert-Butoxycarbonylamino-3-(4-hydroxy-phenyl)-propionic acid (**66**) (8.00 g, 28.5 mmol) in dimethylformamide (80 ml) was treated with ground potassium hydroxide (1.72 g, 31.3 mmol) and iodomethane (1.95 ml, 31.3 mmol) (in 20 ml dimethylformamide) was added dropwise over 5 min at 0 °C. The reaction was stirred at room temperature for 30 min and, after this time period, additional ground potassium hydroxide (1.72 g, 31.3 mmol) and iodomethane (1.95 ml, 31.3 mmol) (in 20 ml dimethylformamide) were added at 0 °C. The reaction was then left to stir for 3 h. The solution was poured onto ice (150 ml) and extracted with ethyl acetate (3 x 75 ml). The organic layers were washed with water (3 x 50 ml), brine (2 x 50 ml) and dried (MgSO₄). The solvent was removed under reduced pressure to yield a colourless oil. Crystallization was achieved from ethyl acetate/light petroleum, to give colourless crystals (6.5 g, 74%); m.p. 52-53 °C; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2976, 1746, 1716, 1612, 1515, 1391, 1366, 1248, 1175, 1058, 1034; δ_{H} (250 MHz; CDCl₃) 1.42 (9 H, s, ((CH₃)₃C), 3.02 (2 H, m, CH₂, C3), 3.71 (3 H, s, OCH₃), 3.78 (3 H, s, Ar-OCH₃), 4.53 (1 H, q, *J* 5.7 Hz, NCH, C2), 5.00 (1 H, d, *J* 6.7 Hz, NH), 6.82 (2 H, d, *J* 8.7 Hz, 2 x CH arom., *meta* in Ar gp.), 7.03 (2 H, d, *J* 8.7 Hz, 2 x CH arom., *ortho* in Ar gp.); δ_{C} (100 MHz; CDCl₃) 28.34 ((CH₃)₃C), 37.61 (CH₂, C3), 52.09 (OCH₃), 54.69 (NCH), 55.25 (Ar-OCH₃), 79.89 (C quat., (CH₃)₃C), 114.10 (2 x CH arom., *meta* in Ar gp.), 128.10 (C quat., arom., *ipso* to C3 in Ar gp.), 130.31 (2 x CH arom., *ortho* in Ar gp.), 155.12 (C quat., *N*-Boc C=O), 158.81 (C quat., arom., *ipso* to OCH₃ in Ar gp.), 172.43 (C quat., C=O); *m/z* 309; C₁₆H₂₃NO₅ requires 309.15762.

Methyl (4*S*,5*R*)-5-[4-(methoxy)phenyl]-2-oxo-1,3-oxazolane-4-carboxylate (68):



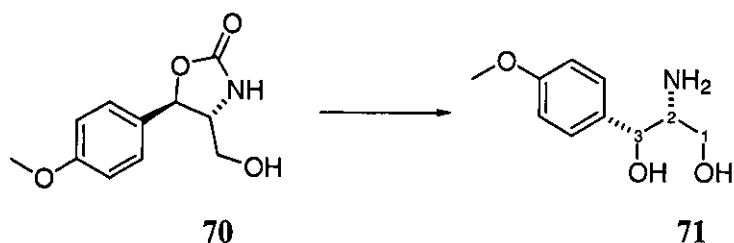
(2*S*)-*tert*-Butoxycarbonylamino-3-(4-methoxy-phenyl)-propionic acid methyl ester (**67**) (5.0 g, 16.2 mmol) was dissolved in CH₃CN (200 ml). To this was added K₂S₂O₈ (8.75 g, 32.4 mmol) as a solution in water (210 ml) and CuSO₄ (0.52 g, 3.2 mmol) also as a solution in water (50 ml). The reaction mixture was then heated to 70 °C, under a blanket of N₂, for 3 h. The solution was allowed to cool and extracted with ethyl acetate (3 x 150 ml), dried (MgSO₄), concentrated under reduced pressure to yield a crude dark yellow oil. Column chromatography eluting with ethyl acetate/light petroleum (1:10-1:1) afforded a colourless solid, which was recrystallized from ethyl acetate/light petroleum to afford colourless crystals (2.10g, 52%); m.p. 94-96 °C; [α]_D²⁰ +83.5 (*c* 1.15, CHCl₃); ν_{max}(film) /cm⁻¹ 3316, 2956, 2362, 2337, 1762, 1613, 1515, 1382, 1250, 1224, 1026, 834, 763; δ_H (400 MHz; CDCl₃) 3.81 (3 H, s, OCH₃), 3.83 (3 H, s, Ar-OCH₃), 4.31 (1 H, d, *J* 5.20, CHN, C2), 5.56 (1 H, d, *J* 5.20, Ar-CH, C3), 6.81 (1 H, s, NH), 6.93 (2 H, d, *J* 4.80 Hz, 2 x CH arom., *ortho* in Ar gp.), 7.33 (2H, d, 4.80 Hz, 2 x CH arom., *meta* in Ar gp.), δ_C (100 MHz; CDCl₃), 53.50 (Ar-OCH₃), 55.74 (CH₃, OCH₃), 61.83 (CHN, C2), 79.91 (Ar-CH, C3), 114.76 (2 x CH arom., *ortho* in Ar gp.), 127.51 (2 x CH arom., *meta* in Ar gp.), 130.34 (C quat., arom., *ipso* to C3 in Ar gp.), 158.65 (C quat., arom., *ipso* to OCH₃ in Ar gp.), 160.65 (C quat., NC=O), 170.66 (C quat., C=O); *m/z* 251.0794; C₁₂H₁₃NO₅ (M⁺) requires 251.0794.

(4*R*,5*R*)-4-(hydroxymethyl)-5-[4-(methoxy)phenyl]-1,3-oxazolan-2-one (70):



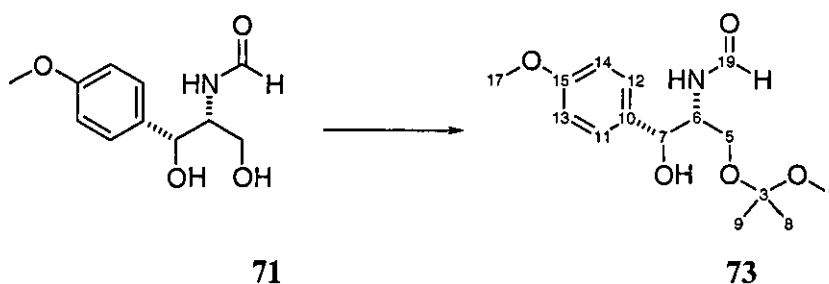
Methyl (4*S*,5*R*)-5-[4-(methoxy)phenyl]-2-oxo-1,3-oxazolan-4-carboxylate (**68**) (2.20 g, 8.8 mmol) was dissolved in ethanol (25 ml) and cooled to 0 °C. To this was added dropwise NaBH₄ (0.70 g, 19.3 mmol) as a solution in ethanol (8 ml). After the addition was complete the ice bath was removed and the reaction stirred at room temperature for 45 min. The reaction was cooled down to 0 °C and conc. HCl (1.5 ml) was added, followed by water (15 ml). The ethanol was evaporated under reduced pressure and the remaining aqueous solution extracted with ethyl acetate (3 x 50 ml). The organics were dried (MgSO₄) and solvents removed to afford a crude off white solid, which was recrystallized from ethyl acetate/light petroleum, to afford colourless crystals (1.75 g, 90%); m.p. 140-142 °C; $[\alpha]_D^{20} +74.8$ (*c* 1.08, CH₃COCH₃); $\nu_{\max}(\text{nujol})/\text{cm}^{-1}$ 3239, 1725, 1614, 1514, 1459, 1376, 1251, 1174, 1062, 1016, 828; δ_{H} (250 MHz; acetone-*d*₆) 3.78 (3 H, m, CHN, C2 & CH₂, C1), 3.86 (3 H, s, Ar-OCH₃), 5.35 (1 H, d, *J* 5.3 Hz, Ar-CH, C3), 7.01 (2 H, d, *J* 8.6 Hz, 2 x CH arom., *ortho* in Ar gp.), 7.41 (2 H, d, *J* 8.6 Hz, 2 x CH arom.); δ_{C} (100 MHz; CDCl₃) 56.03 (Ar-OCH₃), 63.05 (CHN, C2), 64.24 (CH₂, C6) 80.39 (Ar-CH, C3), 115.35 (2 x CH arom., *ortho* in Ar gp.) 128.67 (2 x CH arom., *meta* in Ar gp.), 133.24 (C quat., arom., *ipso* to C3 in Ar gp.), 159.61 (C quat., arom., *ipso* to OCH₃ in Ar gp.), 161.28 (C quat., NC=O); *m/z* 223.0842; C₁₁H₁₃NO₄ (M⁺) requires 223.0845.

(1*R*,2*R*)-(-)-2-Amino-1-(4-methoxy-phenyl)-1,3-propanediol (71):



4-Hydroxymethyl-5-(4-methoxy-phenyl)-oxazolidin-2-one (**70**) (1.65 g, 7.4 mmol) was suspended in 1M NaOH (40 ml) and heated under reflux for 30 min. The reaction was allowed to cool to room temperature and extracted with ethyl acetate (8 x 30 ml). The organics were dried (MgSO₄) and solvents removed to afford a colourless solid, recrystallized from methanol/diethyl ether (1.33 g, 91%); m.p. 132-134 °C; $[\alpha]_D^{20}$ -28.3 (*c* 1.06, 2 M aq. HCl); Found: C, 61.14; H, 7.51; N 6.96. requires C, 60.90; H, 7.67; N 7.10.; $\nu_{\max}(\text{nujol})/\text{cm}^{-1}$ 3338, 1615, 1583, 1515, 1459, 1376, 1253, 1064, 873; δ_{H} (400 MHz; CD₃OD) 2.90 (1 H, m, NCH, C2), 3.32 (1 H, dd, *J* 10.8, 4.4 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C1), 3.42 (1 H, dd, *J* 10.8, 4.4 Hz, downfield portion of an *ABX* system, N-CHCHH-O, C1), 3.80 (3 H, s, OCH₃), 4.49 (1 H, d, *J* 7.2 Hz, Ar-CH, C3), 4.90 (2 H, bs, NH₂), 6.90 (2 H, d, *J* 8.8 Hz, 2 x CH arom., *meta* in Ar gp.), 7.29 (2 H, d, *J* 8.8 Hz, 2 x CH arom., *ortho* in Ar gp.); δ_{C} (100 MHz; CD₃OD) 56.11 (OCH₃), 60.31 (CHN, C2), 64.41 (CH₂, C1), 75.78 (Ar-CH, C3), 115.17 (2 x CH arom. *meta* in Ar gp.), 129.22 (2 x CH arom. *ortho* in Ar gp.), 136.35 (C quat. arom., *ipso* to C3 in Ar gp.), 161.07 (C quat. arom., *ipso* to OCH₃ in Ar gp.); *m/z* 198.1125; C₁₀H₁₅NO₃ (M⁺H) requires 198.1130.

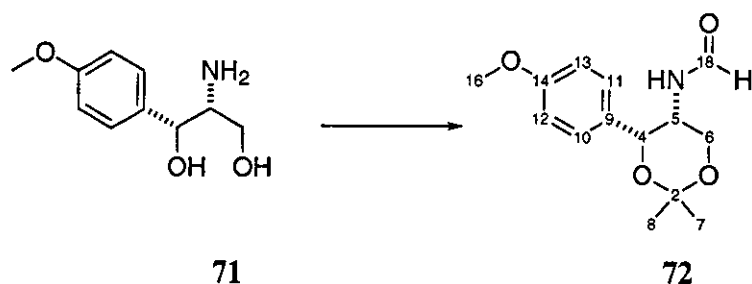
(1*R*,2*R*)-*N*-[2-Hydroxy-1-(1-methoxy-1-methyl-ethoxymethyl)-2-(4-methoxy-phenyl)-ethyl]-formamide (73**):**



N-{(1*R*,2*R*)-[2-Hydroxy-1-hydroxymethyl-2-(4-methoxy-phenyl)-ethyl]}-formamide (**71**) (0.23 g, 1.0 mmol) was dissolved in acetone (15 ml) and 2,2-dimethoxypropane (1.26 ml, 10.2 mmol). To this was added camphorsulfonic acid (0.024 g, 0.1 mmol). The reaction was stirred at room temperature for 12 h. Solvents were removed under reduced pressure and the residue diluted with ethyl acetate (30 ml). The organic layer was washed with sat. aq. sodium hydrogen carbonate (2 x 15 ml), brine (2 x 15 ml)

and dried (MgSO_4). Solvents were removed to give a pale yellow oil (0.213 g, 80%); δ_{H} (250 MHz; CDCl_3) 1.34 (6 H, s, 2 x CH_3 , C8,9), 3.19 (3 H, s, OCH_3 , C1), 3.53 (1 H, m, upfield portion of an *ABX* system, N-CHCHH-O, C6), 3.63 (1 H, m, downfield portion of an *ABX* system, N-CHCHH-O, C6), 3.78 (3 H, s, OCH_3 , C17), 4.28 (1 H, m, NCH, C6), 4.97 (1 H, d, *J* 3.70 Hz, Ar-CH, C7), 6.86 (2 H, d, *J* 8.55 Hz, 2 x CH arom., C13,14), 7.26 (2 H, d, *J* 8.55 Hz, 2 x CH arom., C11,12), 8.12 (1 H, s, NCHO).

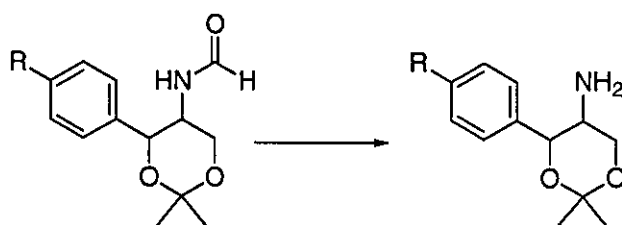
***N*-{(4*R*,5*R*)-2,2-Dimethyl-4-[4-(methoxy)-phenyl]-1,3-dioxan-5-yl}formamide (72):**



(1*R*,2*R*)-(-)-2-Amino-1-(4-methoxy-phenyl)-1,3-propanediol (**71**) (1.2 g, 6.1 mmol) was dissolved in methanol (25 ml) and methyl formate (0.45 ml, 7.3 mmol) was added with sodium methoxide (0.1 ml). The reaction was left to stir for 3.5 h and the solvent removed under reduced pressure. The crude yellow oil was then dissolved in acetone (60 ml), 2,2-dimethoxypropane (10 equiv.) and boron-trifluoride-diethyletherate was added until pale yellow colour persisted (*ca* 0.2 ml). The reaction was then left to stir for 45 min. Solvents were again removed under reduced pressure and the residue re-dissolved in ethyl acetate, which was washed with sat. aq. sodium hydrogen carbonate. The organics were dried (MgSO_4) and solvents removed to yield a pale yellow oil (1.21 g, 75%); $[\alpha]_{\text{D}} -2.7$ (*c* 1.20, CHCl_3); $\nu_{\text{max}}(\text{film}) / \text{cm}^{-1}$ 2992, 1668, 1515, 1381, 1248, 1199, 1084, 1032, 949; δ_{H} (250 MHz; CDCl_3) 1.54 (3 H, s, CH_3 , C7), 1.58 (3 H, s, CH_3 , C8), 3.78 (3 H, s, OCH_3 , C16), 3.87 (1 H, dd, *J* 12.25, 1.95 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C6), 4.26 (2 H, m, downfield portion of an *ABX* system, N-CHCHH-O, C6 & NCH, C5), 5.16 (1 H, s, Ar-CH, C4), 6.19 (1 H, d, *J* 8.55 Hz, NH), 6.85 (2 H, d, *J* 8.90 Hz, 2 x CH arom., C10,11), 7.23 (2 H, d, *J* 8.90 Hz, 2 x CH arom., C12,13), 8.00 (1 H, s, NCHO, C18); δ_{C} (100 MHz;

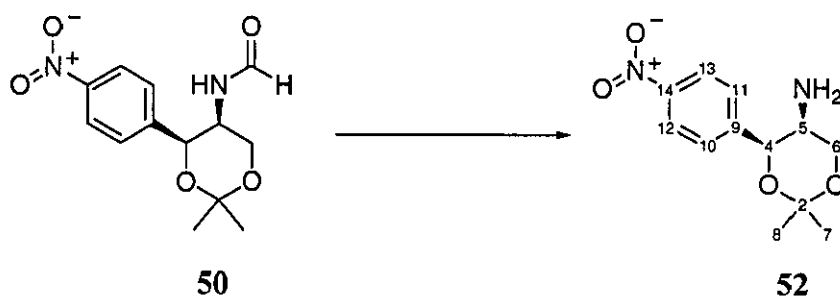
CDCl₃) 18.56 (CH₃, C7), 29.62 (CH₃, C8), 45.57 (NCH, C5), 55.25 (OCH₃, C16), 64.60 (CH₂, C6), 71.40 (Ar-CH, C4), 99.70 (C quat., C2), 113.76 (2 x CH arom., C10,11), 126.45 (2 x CH arom., C12,13), 130.14 (C quat., arom., C9), 159.04 (C quat., arom., C14), 160.51 (NCHO, C18); *m/z* 266.1390; C₁₄H₁₉NO₄ (M⁺H) requires 266.1392.

General procedure for the deprotection of formamides with hydrazine hydrate:



The formate protected acetonide was dissolved in aq. hydrazine hydrate (85%) (20 ml/g) and the solution heated under reflux for 2.5 h. The solution was allowed to cool to room temperature and extracted with ethyl acetate (3 x 20 ml/g). The organic layers were washed with water (2 x 20 ml/g), dried (MgSO₄) and solvents removed under reduced pressure.

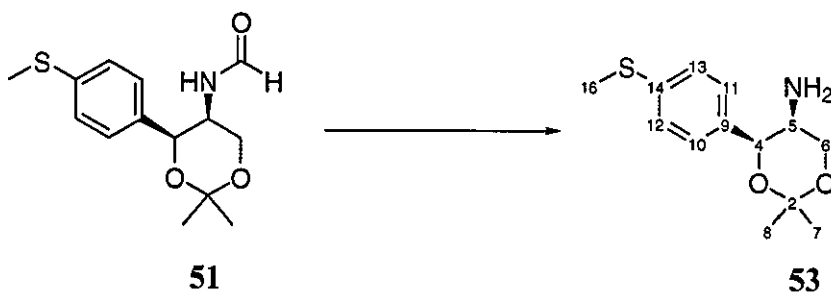
(4*S*,5*S*)-2,2-dimethyl-4-[4-nitro-phenyl]-1,3-dioxan-5-amine (52):



Prepared according to the general procedure from *N*-[(4*S*,5*S*)-2,2-Dimethyl-4-[4-nitrophenyl]-1,3-dioxan-5-yl]formamide (**50**) (4.00 g, 14.9 mmol), except reaction heated under reflux for 1 h. Chromatography performed eluting with ethylacetate. Pale yellow plates. (2.80 g, 78%); mp 117-119 °C; [α]_D²⁰ +66.2 (*c* 1.13, CHCl₃); Found: C, 57.05; H, 6.51; N, 10.77. C₁₂H₁₆N₂O₄ requires C, 57.13; H, 6.39; N, 11.10.; ν_{max} (film)

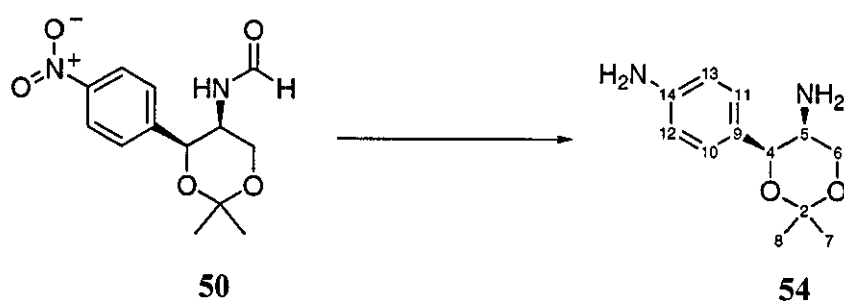
cm^{-1} 1605, 1520, 1350, 1196, 1080, 941, 856; δ_{H} (250 MHz; CDCl_3) 1.56 (6 H, s, C7,8), 2.84 (1 H, q, J 1.9 Hz, NCH, C5), 3.86 (1 H, dd, J 11.8, 1.9 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C6), 4.31 (1 H, dd, J 11.8, 2.3 Hz downfield portion of an *ABX* system, N-CHCHH-O, C6), 5.17 (1 H, d, J 0.7 Hz, Ar-CH, C4), 7.49 (2 H, d, J 7.5 Hz, 2 x CH arom., C10, 11), 8.22 (2 H, d, J 7.5 Hz, 2 x CH arom., C12,13); δ_{C} (100 MHz; CDCl_3) 18.59 (CH_3 , C7), 29.66 (CH_3 , C8), 49.42 (NCH, C5), 66.32 (CH_2 , C6), 73.42 (Ar-CH, C4), 99.57 (C quat., C2), 123.63 (2 x CH arom., C10,11), 126.66 (2 x CH arom., C12,13), 147.17 (C arom., quat., C9), 147.29 (C arom., quat., C14); m/z 253.1191; $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_4$ (M^+) requires 253.1188.

(4*S*,5*S*)-2,2-dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-amine (53):



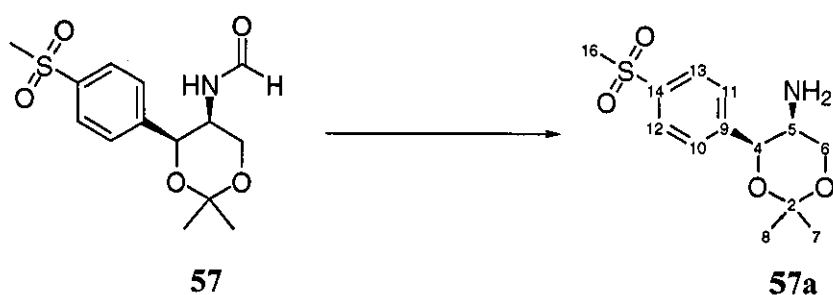
Prepared according to the general procedure from *N*-[(4*S*,5*S*)-2,2-Dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-yl]formamide (**51**) (1.50 g, 5.34 mmol). Colourless oil (1.28 g, 95%); $[\alpha]_{\text{D}}^{20} +44.7$ (c 1.20, CHCl_3); ν_{max} (film) cm^{-1} 3369, 2990, 1599, 1495, 1379, 1198, 1076, 947; δ_{H} (400 MHz; CDCl_3) 1.53 (3 H, s, CH_3 , C7), 1.54 (3 H, s, CH_3 , C8), 2.47 (3 H, s, SCH_3 , C16), 2.72 (1 H, q, 2.0 Hz, NCH, C5), 3.88 (1 H, dd, J 12.0, 2.0 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C6), 4.27 (1 H, dd, J 12.0, 2.4 Hz, downfield portion of an *ABX* system, N-CHCHH-O, C6), 5.05 (1 H, d, J 1.6 Hz, Ar-CH, C4), 7.23-7.28 (4 H, m, 4 x CH arom.); δ_{C} (100 MHz; CDCl_3) 16.01 (SCH_3 , C16), 18.61 (CH_3 , C7), 29.74 (CH_3 , C8), 49.64 (NCH, C5), 66.05 (CH_2 , C6), 73.52 (Ar-CH, C4), 99.20 (C quat., C2), 126.39 (2 x CH arom., C10,11), 126.81 (2 x CH arom., C12,13), 136.59 (C quat., arom., C9), 137.44 (C quat., arom., C14); m/z 253.1137; $\text{C}_{13}\text{H}_{19}\text{NO}_2\text{S}$ (M^+) requires 253.1137.

(4*S*,5*S*)-2,2-dimethyl-4-[4-amino-phenyl]-1,3-dioxan-5-amine (54):



Prepared according to the general procedure from *N*-[(4*S*,5*S*)-2,2-Dimethyl-4-[4-nitrophenyl]-1,3-dioxan-5-yl]formamide (**50**) (0.80 g, 2.9 mmol). Pale yellow oil, (0.65 g, 89%), δ_{H} (250 MHz; CDCl_3) 1.50 (3 H, s, CH_3 , C7), 1.52 (3 H, s, CH_3 , C8), 2.66 (1 H, q, J 1.8, NCH, C5), 3.87 (1 H, dd, J 11.7, 1.7 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C6), 4.23 (1 H, dd, J 11.7, 2.2 Hz downfield portion of an *ABX* system, N-CHCHH-O, C6), 4.98 (1 H, bs, Ar-CH, C4), 6.67 (2 H, d, J 8.4 Hz, 2 x CH arom., C10,11), 7.08 (2 H, d, J 8.4 Hz, 2 x CH arom., C12,13); δ_{C} (62.5 MHz; CDCl_3) 18.93 (CH_3 , C7), 30.11 (CH_3 , C8), 50.06 (NCH, C5), 66.10 (CH_2 , C6), 73.86 (Ar-CH, C4), 99.50 (C quat., C2), 115.40 (2 x CH arom., C10,11), 127.06 (2 x CH arom., C12,13), 129.50 (C arom., quat., C9), 146.00 (C arom., quat., C14).

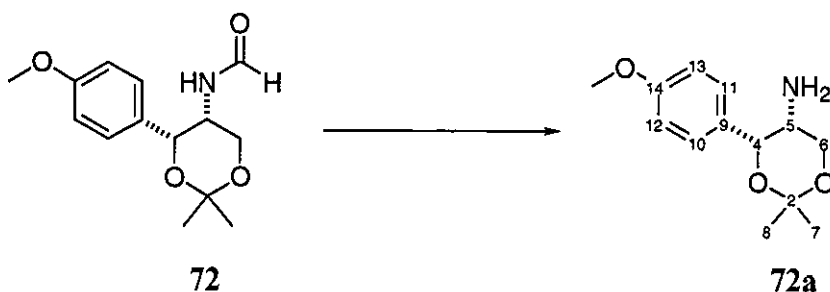
(4*S*,5*S*)-2,2-dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-amine (57a):



Prepared according to the general procedure from *N*-[(4*S*,5*S*)-2,2-Dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-yl]formamide (**57**) (1.80 g, 5.8 mmol). Product isolated as a colourless oil, crystallized from diethyl ether/ethylacetate. Colourless crystals (1.59 g, 96%); m.p. 120-122 °C; $[\alpha]_{\text{D}}^{20} +50.0$ (c 1.00, CHCl_3); Found: C 54.64, H 6.69, N 4.83, requires C 54.72, H 6.71, N 4.91; $\nu_{\text{max}}(\text{film}) / \text{cm}^{-1}$ 3372, 2991,

1601, 1380, 1198, 1077, 949; δ_{H} (400 MHz; CDCl_3) 1.56 (6 H, s, 2 x CH_3 , C7,8), 2.85 (1 H, m, NCH, C5), 3.06 (3 H, s, SCH_3), 3.88 (1 H, dd, J 11.6, 2.0 Hz, upfield portion of an ABX system, N-CHCHH-O, C6), 3.24 (1 H, dd, J 11.6, 2.4 Hz, downfield portion of an ABX system, N-CHCHH-O, C6), 5.18 (1 H, m, Ar-CH, C4), 7.55 (2 H, d, J 8.0 Hz, 2 x CH arom., C10,11), 7.95 (2 H, d, J 8.0 Hz, 2 x CH arom., C12,13); δ_{C} (100 MHz; CDCl_3) 18.97 (CH_3 , C7), 30.04 (CH_3 , C8), 44.93 (SCH_3 , C19), 49.80 (NCH, C5), 66.77 (CH_2 , C6), 73.85 (Ar-CH, C4), 99.86 (C quat., C2), 127.17 (2 x CH arom., C10,11), 127.85 (2 x CH arom., C12,13), 139.87 (C quat., arom., C14), 146.56 (C quat., arom., C9); m/z 285.1028; $\text{C}_{13}\text{H}_{19}\text{NO}_4\text{S}$ (M^+) requires 285.1035.

(4*R*,5*R*)-2,2-dimethyl-4-[4-(methoxy)-phenyl]-1,3-dioxan-5-amine (72a):



Prepared according to the general procedure from *N*-[(4*R*,5*R*)-2,2-Dimethyl-4-[4-(methoxy)-phenyl]-1,3-dioxan-5-yl]formamide (**72**) (0.70 g, 2.6 mmol). Colourless oil. (0.59 g, 95%). $[\alpha]_{\text{D}}^{20}$ -28.9 (c 1.08, CHCl_3); ν_{max} (film) $/\text{cm}^{-1}$ 3050, 2991, 2925, 1612, 1515, 1458, 1380, 1249, 1199, 1129, 1079, 948, 850; δ_{H} (250 MHz; CDCl_3) 1.53 (3 H, s, CH_3 , C7), 1.55 (3 H, s, CH_3 , C8), 2.72 (1 H, q, 2.0 Hz, NCH, C5), 3.81 (3 H, s, OCH_3 , C16), 3.89 (1 H, dd, J 13.4, 1.7 Hz, upfield portion of an ABX system, N-CHCHH-O, C6), 4.29 (1 H, dd, J 11.7, 2.3 Hz, downfield portion of an ABX system, N-CHCHH-O, C6), 5.05 (1 H, d, J 1.9 Hz, Ar-CH, C4), 6.89 (2 H, d, J 8.8 Hz, 2 x CH arom., C10,11), 7.24 (2 H, d, J 8.8 Hz, 2 x CH arom., C12,13); δ_{C} (100 MHz; CDCl_3) 19.01 (CH_3 , C7), 30.07 (CH_3 , C8), 50.16 (NCH, C5), 55.68 (OCH_3 , C16), 66.44 (CH_2 , C6), 73.90 (Ar-CH, C4), 99.54 (C quat., C2), 114.25 (2 x CH arom., C10, 11), 127.23 (2 x CH arom., C12, 13), 132.08 (C arom., quat., C9), 159.29 (C arom., quat., C14); m/z 238.1443; $\text{C}_{13}\text{H}_{19}\text{NO}_3$ (M^+H) requires 238.1443.

2-(2-Bromoethyl)-benzene-1-carbaldehyde (2):⁸



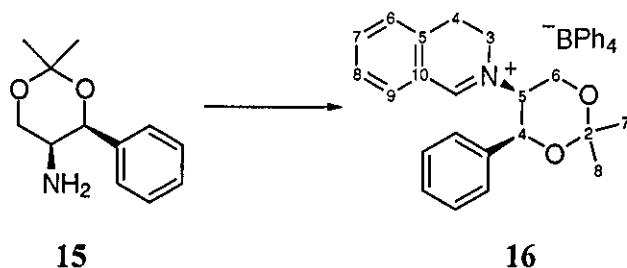
To an ice cooled solution of isochroman (**3**) (50.0 g, 0.37 mol), in carbon tetrachloride (200 ml), was added molecular bromine, slowly over 5 minutes with stirring. After the vigorous reaction subsides, the cooling bath was removed and the dark brown solution was heated under reflux until the reaction mixture becomes pale yellow, and liberation of hydrogen bromide gas ceases. The solution was allowed to attain ambient temperature and the solvent removed in vacuo. To the yellow oil obtained, (1-bromoisochroman), hydrobromic acid (75 ml, 48% aq), was added and the reaction mixture was again heated under reflux, (dark green-blue). After approximately 10-15 minutes the solution was allowed to cool and extracted with diethyl ether (4 x 50 ml). The organic extracts are washed with water (2 x 30 ml), then with dilute sodium hydrogen carbonate and dried (MgSO_4). Evaporation of the solvent under reduced pressure furnished 67.5 g (65% yield) of the crude 2-(2-bromoethyl) benzaldehyde as an orange oil, approximately 85-95% pure. Purification was achieved via vacuum distillation, *ca* 100 °C, 0.5 mbar. $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2742, 1697, 1600, 1575, 1260, 1193, 755; δ_{H} (400 MHz), 3.54-3.63 (4H, m, $\text{Ph}(\text{CH}_2)_2\text{Br}$), 7.33 (1H, d, J 7.96 Hz, CH arom., *ortho* to bromoethyl group), 7.48 (1 H, t, J 7.50 Hz, CH arom., *para* to bromoethyl group), 7.54 (1H, t, J 7.94 Hz, CH arom., *para* to formyl group), 7.80 (1H, d, J 7.56 Hz, CH arom., *ortho* to formyl group), 10.14 (1H, s, CHO); δ_{C} (62.50 MHz; CDCl_3) 33.17 (CH_2 , PhCH_2), 36.70 (CH_2 , CH_2Br), 128.10 (CH arom, *para* to bromoethyl group), 132.51 (CH arom., *ortho* to bromoethyl group), 134.14 (CH arom., *para* to formyl group), 134.33 (C quat., arom., *ipso* to bromoethyl group), 134.88 (CH arom., *ortho* to formyl group), 140.95 (C quat., arom., *ipso* to formyl group), 193.33 (CH, HC=O). m/z 211.9837; $\text{C}_9\text{H}_9\text{BrO}$ (M^+) requires 211.9837.

General procedure for the synthesis of dihydroisoquinolinium salts from 2-(2-bromoethyl) benzaldehyde and primary amines:



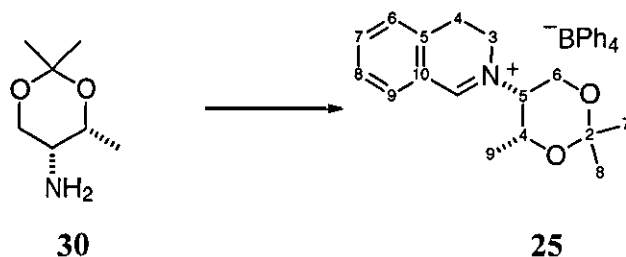
A solution of the amine in ethanol, (10 ml per g of amine, 1 equivalent), was added dropwise via a stoppered, pressure equalising, dropping funnel, to an ice cooled, one-neck flask, containing 2-(2-bromoethyl) benzaldehyde, (1.60 equivalents, 1.10 if distilled previously). After the addition was complete 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, was added in one portion to the reaction mixture and after 5 minutes of stirring, the organic solvents are removed under reduced pressure. Ethanol was added to the residue, followed by water. The resulting solid was collected by filtration and washed with additional ethanol followed by diethyl ether. If no solid materialises after the addition of the water the suspension was allowed to settle and the ethanol/water phase was decanted off. The gummy residue which may be obtained, was 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 do arise, small amounts of acetonitrile may be added during this process.

(+)-2-[(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-3,4-dihydroisoquinolinium tetraphenylborate (16):^{9,10}



Prepared according to the general procedure. Yield 75%, recrystallized from acetone/diethyl ether, yellow solid, m.p. 169-170 °C; $[\alpha]_D^{20} +38.6$ (c 2.70, CH₃CN); $\nu_{\max}/\text{cm}^{-1}$ (nujol) 1637, 1603, 1571, 1480, 1266, 1202, 1166, 1108, 1073; δ_{H} (250 MHz; CD₃CN), 1.65 (3 H, s, CH₃, C7), 1.94 (3 H, s, CH₃, C8), [2.39-2.48 (1 H, m), 2.70-2.82 (1 H, m), Ar-CH₂, *isoq-4*], [3.25-3.40 (1 H, m), 3.81-3.97 (1 H, m), CH₂N, *isoq-3*], 4.06 (1 H, m, NCH, C5), 4.30 (1 H, d, J 13.7 Hz upfield portion of an *ABX* system, N-CHCHH-O, C6), 4.58 (1 H, dd, J 13.7, 3.1 Hz, downfield portion of an *ABX* system, N-CHCHH-O, C6), 5.70 (1 H, d, J 2.8 Hz, Ph-CH, C4), 6.81 (4 H, t, J 7.2 Hz, 4 x CH arom., *para* in BPh₄ group), 7.35-7.40 (6 H, m, 5 x CH arom., Ph gp., CH arom., *isoq-6*), 7.46 (1 H, t, J 7.3 Hz, CH arom., *isoq-8*), 7.65-7.74 (2 H, m, 2 x CH arom., *isoq-7*, *isoq-9*), 8.92 (1 H, s, HC=N, *isoq-1*); δ_{C} (62.50 MHz; CD₃CN) 17.98 (CH₃, C7), 24.06 (Ar-CH₂, *isoq-4*), 28.68 (CH₃, C8), 51.55 (CH₂N, *isoq-3*), 61.44 (CH₂, C6), 65.46 (NCH, C5), 70.72 (Ph-CH, C4), 104.88 (C quat., C2), 121.85 (8 x CH arom., *ortho* in BPh₄ gp.), 124.29 (C quat., arom., *isoq-10*), 125.44 (2 x CH arom., *ortho* in Ph gp.), 125.72 (2 x CH arom., *meta* in Ph gp.), 128.14 (CH arom., *isoq-6*), 128.46 (CH arom., *isoq-8*), 128.62 (CH arom., *para* in Ph gp.), 128.04, (4 x CH arom., *para* in BPh₄ gp.), 134.39 (CH arom., *isoq-7*), 135.79 (8 x CH arom., *meta* in BPh₄ gp.), 136.97 (C quat., arom., *ipso* in Ph gp.), 137.68 (C quat., arom., *isoq-5*), 138.72 (CH arom., *isoq-9*), 163.51 (4 x C quat., arom., q, J 196.40 Hz, C-B, *ipso* in BPh₄ gp.), 167.48 (HC=N, *isoq-1*); m/z 322.1809; C₂₁H₂₄NO₂ (cation) requires 322.1807.

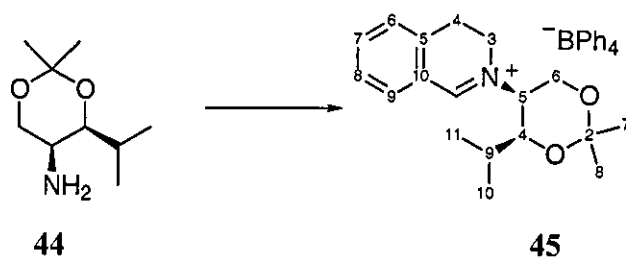
(-)-2-[(4*R*,5*R*)-2,2,4-Trimethyl-1,3-dioxan-5-yl]-3,4-dihydroisoquinolinium tetraphenylborate (25):



Prepared according to the general procedure from (1*R*,2*R*)-2,2,4-Trimethyl-[1,3]dioxan-5-yl-amine (**30**) (0.75 g, 2.96 mmol). Recrystallized from DCM/hexane, yellow plates (1.13 g, 66%); Recrystallized from acetone/ethyl acetate. Yield (0.149 g,

66%); mp 164-165 °C (dec.); $[\alpha]_D^{20}$ -22.3 (*c* 1.05, acetone); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3054, 1636, 1604, 1576, 1477, 1268, 1201, 1180; δ_{H} (400 MHz; CD_3CN), 1.26 (3 H, d, *J* 6.4 Hz, CH_3 , C9), 1.46 (3 H, s, CH_3 , C7), 1.55 (3 H, s, CH_3 , C8), 3.25 (2 H, t, *J* 8.0 Hz, Ar- CH_2 , *isoq-4*), 3.89 (1 H, t, 2.4 Hz, NCH, C5), 4.23 (1 H, dd, *J* 13.6, 0.8 Hz upfield portion of an *ABX* system, N-CHCHH-O, C6), 4.27-4.36 (2 H, m, CH_2N , *isoq-3*), 4.46 (1 H, dd, *J* 14.0, 3.2 Hz, downfield portion of an *ABX* system, N-CHCHH-O, C6), 4.63 (1 H, dq, *J* 6.4, 2.8 Hz, CH, C4), 6.83 (4 H, t, *J* 7.2 Hz, 4 x CH arom., *para* in BPh_4 gp.), 6.93 (8 H, t, *J* 7.6 Hz, 8 x CH arom., *ortho* in BPh_4 gp.), 7.22-7.33 (8 H, m, 8 x CH arom., *meta* BPh_4 group), 7.45 (1 H, d, *J* 7.6 Hz, CH arom., *isoq-6*), 7.53 (1 H, t, *J* 7.6 Hz, CH arom., *isoq-7*), 7.80 (1 H, dt, *J* 7.6, 1.2 Hz, CH arom., *isoq-8*), 7.86 (1 H, d, *J* 7.6 Hz, CH arom., *isoq-9*), 9.05 (1 H, s, HC=N, *isoq-1*); δ_{C} (100 MHz; acetone- d_6), 17.70 (CH_3 , C9), 18.68 (CH_3 , C7), 25.57 (Ar- CH_2 , *isoq-4*), 51.70 (CH_2N , *isoq-3*), 62.88 (CH_2 , C6), 66.08 (NCH, C5), 66.49 (CH, C4), 100.62 (C, quat., C2), 122.33 (4 x CH arom., *para* in BPh_4 gp.), 125.65 (C quat., arom., *isoq-10*), 126.09 (8 x CH arom., *ortho* in BPh_4 gp.), 129.31 (2 x CH arom., *isoq-8,-9*), 135.98 (CH arom., *isoq-6*), 136.98 (8 x CH arom., *meta* in BPh_4 gp.), 138.24 (C quat., arom., *isoq-5*), 139.42 (CH arom., *isoq-7*), 164.85 (4 x C quat., arom., *q*, *J* 196.0 Hz, C-B, *ipso* in BPh_4 gp.), 168.72 (HC=N, *isoq-1*); *m/z* 260.1655; $\text{C}_{16}\text{H}_{22}\text{NO}_2$ (cation) requires 260.1651.

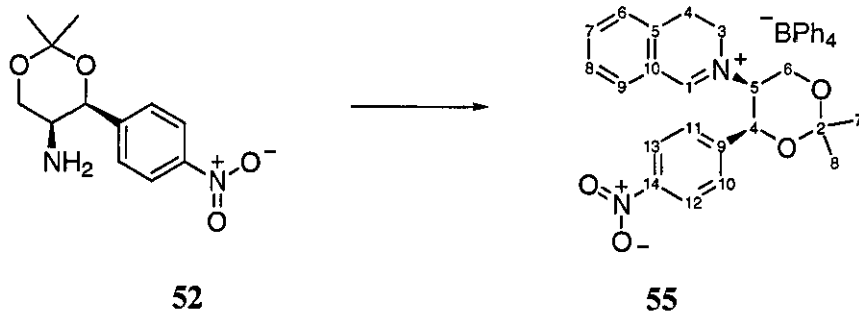
(+)-2-[(4*S*,5*S*)-2,2-dimethyl-4-(1-methylethyl)-1,3-dioxan-5-yl]-3,4-dihydroisoquinolinium tetraphenylborate (45):



Prepared according to the general procedure from (4*S*,5*S*)-2,2-dimethyl-4-(1-methylethyl)-1,3-dioxan-5-amine (**44**) (0.05 g, 0.29 mmol). Recrystallized from acetone/diethyl ether, yellow plates (0.120 g, 70%); mp 166-167 °C (dec.); $[\alpha]_D^{20}$ +31.7 (*c* 1.16, acetone); $\nu_{\max}(\text{film})/\text{cm}^{-1}$, 3055, 1637, 1604, 1574, 1479, 1265, 1202, 1152, 1088; δ_{H} (400 MHz; CD_3CN), 0.89 (3 H, d, *J* 7.8 Hz, CH_3 , C10), 0.97 (3 H, d,

J 6.4 Hz, CH_3 , C11), 1.48 (3 H, s, CH_3 , C7), 1.51 (3 H, s, CH_3 , C8) 1.69-1.75 (1 H, m, $\text{CH}(\text{CH}_3)_2$, C9), 3.14-3.22 (2 H, m, 2 x CH , C5, *isoq-4*), 3.89 (2 H, m, 2 x CH , C4, *isoq-4*), 4.06 (2 H, m, CH , C6, *isoq-3*), 4.33 (2 H, m, CH , C6, *isoq-3*), 6.84 (4 H, t, J 7.1 Hz, 4 x CH arom., *para* in BPh_4 gp.), 6.99 (8 H, t, J 7.4 Hz, CH arom., *ortho* in BPh_4 gp.), 7.23-7.29 (8 H, m, 8 x CH arom., *meta* in BPh_4 gp.), 7.44 (1 H, d, J 7.4 Hz, CH arom., *isoq-6*), 7.51 (1 H, t, J 7.6, CH arom., *isoq-7*), 7.80 (2 H, m, 2 x CH arom., *isoq-8,9*), 9.13 (1 H, s, $\text{HC}=\text{N}$, *isoq-1*); δ_{C} (100 MHz; CD_3CN) 16.96 (CH_3 , C10), 17.42 (CH_3 , C11), 17.88 (CH_3 , C7), 24.54 ($\text{Ar}-\text{CH}_2$, *isoq-4*), 28.27, (CH_3 , C8), 28.60 ($\text{CH}(\text{CH}_3)_2$, C9), 50.63 (CH_2-N , *isoq-3*), 62.04 (CH_2 , C6), 62.32 (NCH , C5), 74.81 (CH , C4), 99.88 (C quat., C2), 121.47 (8 x CH arom., *ortho* in BPh_4 gp.), 124.41 (C quat., arom., *isoq-10*) 125.31 (4 x CH arom., *para* in BPh_4 gp.), 128.59 (CH arom., *isoq-6*), 129.20 (CH arom., *isoq-7*), 134.20 (CH arom., *isoq-8*), 135.44 (8 x CH arom., *meta* in BPh_4 gp.), 137.00 (C quat., arom., *isoq-5*), 138.44 (CH arom., *isoq-9*), 163.45 (4 x C quat., arom., q, J 145.0 Hz, C-B, *ipso* in BPh_4 gp.), 167.77 ($\text{HC}=\text{N}$, *isoq-1*); m/z 288.1959; $\text{C}_{18}\text{H}_{26}\text{NO}_2$ (cation) requires 288.1964.

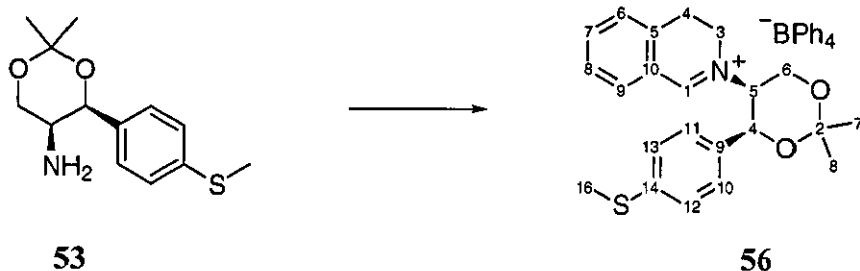
**(+)-[(4*S*,5*S*)-2,2-dimethyl-4-[4-(nitro)-phenyl]-1,3-dioxan-5-yl]-
dihydroisoquinolinium tetraphenylborate (55):**



Prepared according to the general procedure from (+)-(4*S*,5*S*)-2,2-dimethyl-4-[4-(nitro)-phenyl]-1,3-dioxan-5-amine (**52**) (0.19 g, 0.8 mmol). Recrystallized from DCM/hexane, yellow plates (0.36 g, 74%); m.p. 176-178 °C (dec.); $[\alpha]_{\text{D}}^{20} +107.7$ (c 1.30, acetone; Found C, 77.73; H, 6.23; N, 4.00; $\text{C}_{45}\text{H}_{43}\text{BN}_2\text{O}_4 \cdot 0.5\text{H}_2\text{O}$ requires: C, 77.66; H, 6.38; N, 4.03.; $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 1635, 1604, 1571, 1524, 1478, 1384, 1202, 1163, 1107, 1032; δ_{H} (400 MHz; acetone- d_6), 1.72 (3H, s, CH_3 , C7), 1.76 (3H, s, CH_3 , C8), [2.70-2.80 (1 H, m), 2.88-2.96 (1 H, m), $\text{Ar}-\text{CH}_2$, *isoq-4*], [3.65-3.74 (1 H, m),

4.19-4.23 (1 H, m), CH_2N , *isoq-3*], 4.54 (1 H, d, J 13.6 Hz, upfield portion of an *ABX* system, N-CHCHH-O , C6), 4.65 (1 H, m, NCH , C5), 4.82 (1 H, dd, J 13.6, 2.8 Hz, downfield portion of an *ABX* system, N-CHCHH-O , C6), 6.11 (1 H, d, J 2.4 Hz, Ar-CH , C4), 6.80 (4 H, t, J 6.8 Hz, 4 x CH arom., *para* in BPh_4 gp.), 6.94 (8 H, t, J 7.2 Hz, 8 x CH arom., *ortho* in BPh_4 gp.), 7.36 (8 H, m, 8 x CH arom., *meta* in BPh_4 gp.), 7.51 (1 H, t, J 7.6 Hz, CH arom., *isoq-8*), 7.59-7.88 (3 H, m, 3 x CH arom., *isoq-6,-7,-9*), 7.85 (2 H, d, J 8.4 Hz, CH arom., C10,11), 7.95 (2 H, d, J 8.8 Hz, CH arom., C12,13), 9.28 (1 H, s, HC=N , *isoq-1*); δ_{C} (100 MHz; acetone- d_6), 19.24 (CH_3 , C7), 25.88 (Ar-CH_2 , *isoq-4*), 29.95 (CH_3 , C8), 52.80 (CH_2N , *isoq-3*), 63.36 (CH_2 , C6), 66.44 (NCH , C5), 71.85 (Ar-CH , C4), 102.20 (C quat., C2), 122.71 (8 x CH arom., *ortho* in BPh_4 gp.), 125.34 (2 x CH arom., C10,11), 125.78 (C quat., *isoq-10*), 126.41 (2 x CH arom., C12,13), 128.25 (CH arom., *isoq-8*), 129.68 (CH arom., *isoq-9*), 129.77 (4 x CH arom., *para* in BPh_4 gp.), 135.90 (CH arom., *isoq-7*), 137.42 (8 x CH arom., *meta* in BPh_4 gp.), 138.44 (C quat., *isoq-5*), 140.13 (CH arom., *isoq-6*), 145.00 (C quat., C9), 149.00 (C quat., C14), 165.00 (4 x CH, quat., arom., J 196.0 Hz, C-B, *ipso* in BPh_4 gp.), 169.53 (HC=N , *isoq-1*); m/z 367.1658; $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_4$ (cation) requires 367.1658.

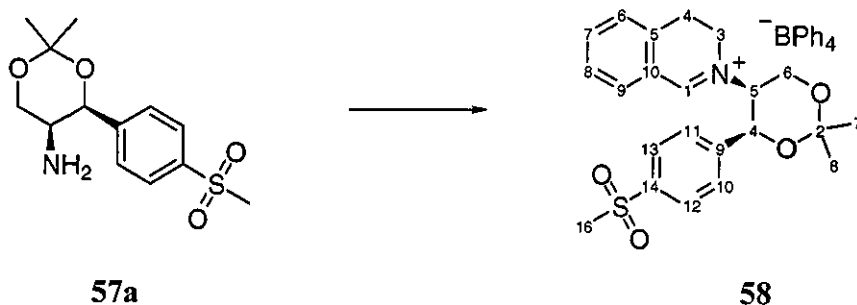
(+)-[(4*S*,5*S*)-2,2-dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-yl]-dihydroisoquinolinium tetraphenylborate (56):



Prepared according to the general procedure from (4*S*,5*S*)-2,2-dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-amine (**53**) (0.50 g, 2.0 mmol). Recrystallized from DCM/hexane, yellow plates (1.00 g, 73%); m.p. 146-148 °C (dec.); $[\alpha]_{\text{D}}^{20}$ +115.9 (c 1.41, acetone); Found: C, 79.05; H, 6.59; N, 1.93. $\text{C}_{46}\text{H}_{46}\text{BNO}_2\text{S}\cdot 0.5\text{H}_2\text{O}$ requires C, 79.27; H, 6.66; N, 2.01.; $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3053, 2996, 2360, 2341, 1634, 1603, 1571, 1478, 1265, 1201, 1162, 1108, 1075; δ_{H} (250 MHz; acetone- d_6) 1.66 (3H,

s, CH₃, C7), 1.72 (3H, s, CH₃, C8), 2.42 (3H, s, SCH₃, C16), [2.66-2.84 (1 H, m), 2.90-3.03 (1 H, m), Ar-CH₂, *isoq-4*], [3.62-3.74 (1 H, m), 4.13-4.26 (1 H, m), CH₂N, *isoq-3*], 4.53 (2 H, m, upfield portion of an *ABX* system, N-CHCHH-O, C6 & NCH, C5), 4.78 (1 H, dd, *J* 13.8, 3.1 Hz, downfield portion of an *ABX* system, N-CHCHH-O, C6), 5.91 (1 H, d, *J* 2.6 Hz, Ar-CH, C4), 6.78 (4 H, t, *J* 7.2 Hz, 4 x CH arom., *para* in BPh₄ gp.), 6.92 (8 H, t, *J* 7.40 Hz, 8 x CH arom., *ortho* in BPh₄ gp.), 7.34 (8 H, m, 8 x CH arom., *meta* in BPh₄ gp.), 7.40-7.56 (6 H, m, 6 x CH arom., 4 x CH, Ar gp., 2 x CH *isoq-8,9*), 7.76-7.87 (2 H, m, 2 x CH arom., *isoq-6,7*), 9.30 (1 H, s, HC=N, *isoq-1*); δ_C (100 MHz; acetone-d₆) 15.36 (SCH₃, C16), 18.83 (CH₃, C7), 25.37 (Ar-CH₂, *isoq-4*), 30.01 (CH₃, C8), 52.33 (CH₂N, *isoq-3*), 62.70 (CH₂, C6), 66.46 (NCH, C5), 71.53 (Ar-CH, C4), 101.39 (C quat., C2), 122.31 (8 x CH arom., *ortho* in BPh₄ gp.), 125.32 (C quat., arom., *isoq-10*), 126.05 (2 x CH arom., C12,13), 126.93 (2 x CH arom., C10,11), 127.35 (4 x CH arom., *para* in BPh₄ gp.), 129.23 (CH arom., *isoq-6*), 129.29 (CH arom., *isoq-7*), 133.92 (C quat., arom., C14), 135.21 (CH arom., *isoq-8*), 137.01 (8 x CH arom., *meta* in BPh₄ gp.), 137.82 (C quat., arom., *isoq-5*), 139.47 (CH arom., *isoq-9*), 140.45 (C quat., arom., C9), 165.00 (4 x C quat., arom., *J* 196.0 Hz, C-B, *ipso* in BPh₄ gp.), 168.49 (HC=N, *isoq-1*); *m/z* 368.1682; C₂₂H₂₆NO₂S (cation) requires 368.1684.

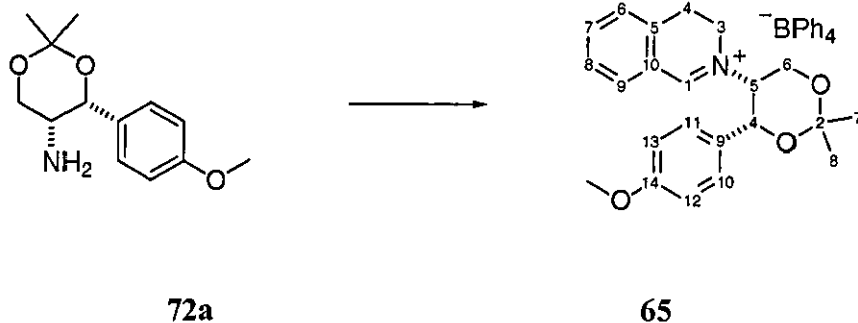
(+)-[(4*S*,5*S*)-2,2-dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-yl]-3,4-dihydroisoquinolinium tetraphenylborate (58):



Prepared according to the general procedure from (4*S*,5*S*)-2,2-dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-amine (**57a**) (0.75 g, 2.96 mmol). Recrystallized from DCM/hexane, yellow plates (1.55 g, 73%); m.p. 199-201 °C (dec.); [α]_D²⁰ +126.7 (*c* 1.20, acetone); Found: C, 75.62; H, 6.32; N, 1.84. C₄₆H₄₆BNO₄S·0.5H₂O requires C, 75.79; H, 6.50; N, 1.92.; ν_{max}(film) /cm⁻¹ 1636,

1603, 1572, 1478, 1383, 1314, 1266, 1202, 1150, 1076, 1032, 956; δ_{H} (400 MHz; acetone- d_6), 1.69 (3H, s, CH_3 , C7, eq.), 1.72 (3H, s, CH_3 , C8, ax.), [2.60-2.69 (1 H, m), 2.85-2.96 (1 H, m), Ar- CH_2 , *isoq-4*], 3.00 (3H, s, SO_2CH_3 , C16), [3.65-3.72 (1 H, m), 4.12-4.20 (1 H, m), CH_2N , *isoq-3*], 4.49 (1 H, d, J 13.6 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C6, eq.), 4.57 (1 H, m, NCH, C5), 4.77 (1 H, dd, J 13.6, 2.8 Hz downfield portion of an *ABX* system, N-CHCHH-O, C6, ax.), 6.05 (1 H, d, J 2.8 Hz, Ar-CH, C4), 6.80 (4 H, t, J 7.2 Hz, 4 x CH arom., *para* in BPh₄ gp.), 6.92 (8 H, t, J 7.2 Hz, 8 x CH arom., *ortho* in BPh₄ gp.), 7.33 (8 H, m, 8 x CH *meta* in BPh₄ gp.), 7.49 (1 H, t, J 7.6 Hz, CH arom., *isoq-8*), 7.73-7.83 (3 H, m, 3 x CH arom., *isoq-6,7,9*), 7.82 (2 H, d, J 8.2 Hz, 2 x CH arom., C10,11), 7.95 (2 H, d, J 8.2 Hz, 2 x CH arom., C12,13), 9.28 (1 H, s, HC=N, *isoq-1*); δ_{C} (100 MHz; acetone- d_6), 18.83 (CH_3 , C7), 25.40 (Ar- CH_2 , *isoq-4*), 29.45 (CH_3 , C8), 44.26 (SO_2CH_3 , C16), 52.33 (CH_2N , *isoq-3*), 62.87 (CH_2 , C6), 66.10 (NCH, C5), 71.54 (Ar-CH, C4), 101.69 (C quat., C2), 122.31 (8 x CH arom., *ortho* in BPh₄ gp.), 125.33 (C quat., arom., *isoq-10*), 126.09 (2 x CH arom., C12,13), 127.56 (2 x CH arom., C11,12), 128.84 (CH arom., *isoq-6*), 129.27 (CH arom., *isoq-8*), 129.35 (4 x CH arom., *para* in BPh₄ gp.), 135.41 (CH arom., *isoq-7*), 137.00 (8 x CH arom., *meta* in BPh₄ gp.), 137.01 (CH arom., *isoq-9*), 137.94 (C quat., arom., C14), 142.41 (C quat., arom., *isoq-5*), 143.15 (C quat., arom., C9), 165.00 (4 x C, quat., arom., J 196.0 Hz, C-B, *ipso* in BPh₄ gp.), 168.99 (HC=N, *isoq-1*); m/z 400.1586; $\text{C}_{22}\text{H}_{26}\text{NO}_4\text{S}$ (cation) requires 400.1583.

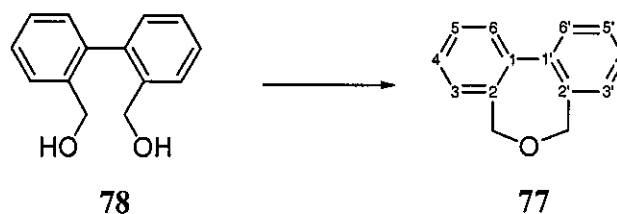
(-)-[(4*R*,5*R*)-2,2-dimethyl-4-[4-(methoxy)-phenyl]-1,3-dioxan-5-yl]-dihydroisoquinolinium tetraphenylborate (65):



Prepared according to the general procedure (-)-(4*R*,5*R*)-2,2-dimethyl-4-[4-(methoxy)-phenyl]-1,3-dioxan-5-amine (72a) (0.40 g, 1.7 mmol). Recrystallized

from DCM/hexane, yellow plates (0.83 g, 74%); m.p. 171-173 °C (dec.); $[\alpha]_D^{20}$ -108.6 (c 1.40, acetone); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1639, 1604, 1573, 1514, 1382, 1254, 1202, 1107, 1031; Found C, 77.70; H, 6.50; N, 1.88. $\text{C}_{46}\text{H}_{46}\text{BNO}_3 \cdot 0.5\text{Et}_2\text{O}$ requires C, 77.92; H, 6.54; N, 1.98.; δ_{H} (400 MHz; CDCl_3) 1.51 (3H, s, CH_3 , C7), 1.52 (3H, s, CH_3 , C8), [2.20-2.25 (1 H, m), 2.31-2.35 (1 H, m), Ar- CH_2 , *ipso*-4], [2.85-2.90 (1 H, m), 3.00-3.10 (1 H, m), CH_2N , *isoq*-3], 3.04 (1 H, m, NCH, C5), 3.56 (1 H, d, J 14.4 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C6), 3.72 (3 H, s, OCH_3 , C16), 3.90 (1 H, dd, J 14.0, 2.8 Hz, downfield portion of an *ABX* system, N-CHCHH-O, C6), 5.11 (1 H, d, J 2.4 Hz, Ar-CH, C4), 6.79 (2 H, d, J 2.0 Hz, CH arom., C10,11), 6.87 (2 H, m, CH arom., C12,13 & 4 x CH arom., *para* in BPh_4 gp.), 7.02 (8 H, t, J 7.6 Hz, 8 x CH arom., *ortho* in BPh_4 gp.), 7.23 (2 H, m, CH arom., *isoq*-8,-9) 7.24 (1 H, m, CH arom., *isoq*-6), 7.41 (8 H, m, 8 x CH arom., *meta* in BPh_4 gp.), 7.57 (1 H, m, CH arom., *isoq*-7), 8.25 (1 H, s, $\text{HC}=\text{N}$, *isoq*-1); δ_{C} (100 MHz; CDCl_3) 18.37 (CH_3 , C7), 24.64 (Ar- CH_2 , *isoq*-4), 29.44 (CH_3 , C8), 50.52 (CH_2N , *isoq*-3), 55.38 (OCH_3 , C16) 61.85 (CH_2 , C6), 64.88 (NCH, C5), 70.52 (Ar-CH, C4), 100.40 (C quat., C2), 114.40 (2 x CH arom., C12,13), 122.19 (8 x CH arom., *ortho* in BPh_4 gp.), 123.70 (C quat., arom., *isoq*-10), 125.86 (4 x CH arom., *para* in BPh_4 gp.), 127.31 (2 x CH arom., C10,11), 127.90 (C quat., arom., C9), 128.65 (CH arom., *isoq*-8), 129.50 (CH arom., *isoq*-8), 134.00 (CH arom., *isoq*-6), 134.73 (C quat., arom., *isoq*-5) 136.19 (8 x CH arom., *meta* in BPh_4 gp.), 138.82 (CH arom., *isoq*-7), 159.75 (C quat., arom., C14), 163.80 (4 x C quat., arom., J 147.00 Hz, C-B, *ipso* in BPh_4), 169.53 ($\text{HC}=\text{N}$, *isoq*-1); m/z 352.1915; $\text{C}_{22}\text{H}_{26}\text{NO}_3$ (cation) requires 352.1913.

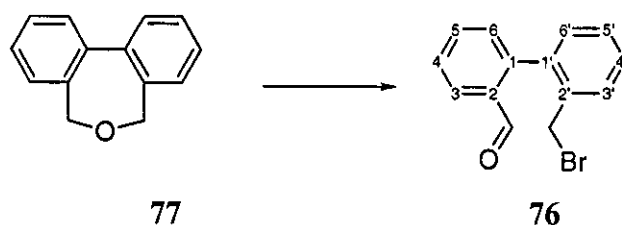
5,7-dihydrodibenzo[*c,e*]oxepine (77):



A suspension of 2,2'-biphenyl dimethanol (**78**), (4.22 g, 19.5 mmol), in hydrobromic acid (60 ml, 24% in water), was heated to 100 °C for 40 min. The cloudy solution was then allowed to cool and the aqueous phase extracted with diethyl ether (3 x 50 ml).

The organic layers are then washed with brine (50 ml), sat. aq. Sodium hydrogen carbonate and dried (MgSO_4). Solvent was removed to yield a colourless solid. Recrystallized from ethyl acetate/light petroleum to give colourless crystals, (3.25 g, 85%); m.p. 71 °C; $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 1567, 1197, 1073, 1042, 903, 891, 754, 602; δ_{H} (400 MHz; CDCl_3) 4.35 (4 H, s, 2 x CH_2O), 7.23-7.56 (8 H, m, 8 x CH arom.); δ_{C} (100 MHz; CDCl_3) 67.53 (2 x Ar- CH_2O), 127.46 (2 x CH arom., *biphenyl-4,4'*), 128.24 (2 x CH arom., *biphenyl-6,6'*), 128.91 (2 x CH arom., *biphenyl-3,3'*), 129.69 (2 x CH arom., *biphenyl-5,5'*), 135.16 (2 x C quat., arom., *biphenyl-1,1'*), 141.19 (2 x C quat., arom., *biphenyl-2,2'*); m/z 196.0887; $\text{C}_{14}\text{H}_{12}\text{O}$ (M^+) requires 196.0888.

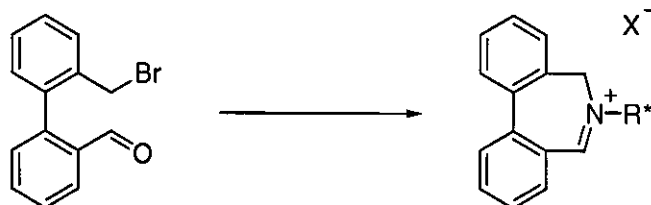
2-[2-(bromomethyl)phenyl]benzene carbaldehyde (76):⁸



To an ice cooled solution of 5,7-dihydrodibenzo[*c,e*]oxepine (**77**) (2.00 g, 10.2 mmol), in carbon tetrachloride (50 ml), in a round bottom flask equipped with a reflux condenser was added molecular bromine (1.76 g, 11.0 mmol), in carbon tetrachloride (6 ml), dropwise over 5 min (the reaction turns deep red). The cooling bath was removed and the reaction mixture irradiated with ultra violet light for 5 h (after 20 min solution turns pale yellow, indicative of complete consumption of bromine). The resultant solution was evaporated under reduced pressure, then diluted with diethyl ether, washed with sat. aq. Sodium carbonate, brine and dried (MgSO_4). Solvents were removed under reduced pressure to yield a orange oil. Crystallized from ethyl acetate/light petroleum as colourless crystal. (1.80 g, 64%); m.p. 56-58 °C; $\nu_{\text{max}}(\text{nujol})/\text{cm}^{-1}$ 1694, 1594, 1255, 1221, 1197, 761; δ_{H} (400 MHz; CDCl_3) 4.21 (2 H, dd, J 40.0, 10.1 Hz, CH_2Br), 7.12-7.98 (8 H, m, 8 x CH , arom.), 9.65 (1 H, s, $\text{HC}=\text{O}$); δ_{C} (100 MHz; CDCl_3) 33.83, (CH_2Br), 129.96 (CH , arom., *biphenyl-5*), 130.88 (CH arom., *biphenyl-3*), 131.02 (CH , arom., *biphenyl-4*), 131.40 (CH , arom., *biphenyl-6*), 133.00 (CH , arom., *biphenyl-4'*), 133.05 (CH , arom., *biphenyl-6'*), 133.39 (CH , arom., *biphenyl-3'*), 135.95 (CH , arom., *biphenyl-5'*), 136.41 (CH , quat., arom., *biphenyl-2*),

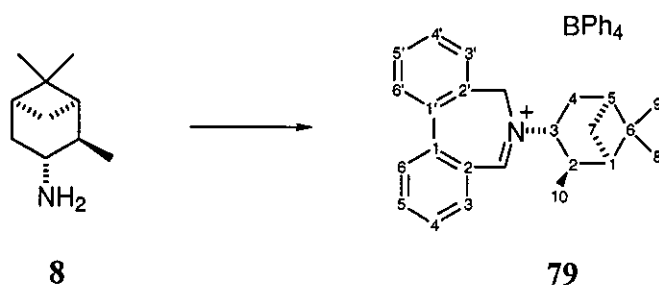
138.28 (CH, quat., arom., *biphenyl-1*), 140.16 (CH, quat., arom., *biphenyl-1'*), 145.63 (C, quat., arom., *biphenyl-2*), 194.08 (C quat., HC=O); m/z 275.9977 (^{81}Br isotope); $\text{C}_{14}\text{H}_{11}\text{BrO}$ (M^+) requires 275.9974.

General procedure for the synthesis of 5*H*-dibenzo[*c,e*]azepinium salts from 2-[2-(bromomethyl)phenyl]benzene carbaldehyde and primary amines:



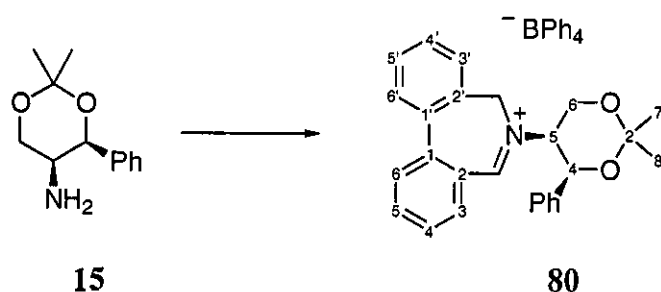
A solution of the amine in ethanol, (10 ml per g of amine, 1 equivalent), was added dropwise via a stoppered, pressure equalising, dropping funnel, to an ice cooled, one-neck flask, containing a solution of 2-[2-(bromomethyl)phenyl]benzene carbaldehyde, (1.10 equiv.) in ethanol (10 ml/g carbaldehyde). After the addition was 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, was added in one portion to the reaction mixture and after 5 minutes of stirring, the organic solvents are removed under reduced pressure. Ethanol was added to the residue, followed by water. The resulting solid was collected by filtration and washed with additional ethanol followed by diethyl ether. If no solid materialises after the addition of the 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 do arise, small amounts of acetonitrile may be added during this process.

(+)-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 (79):⁸



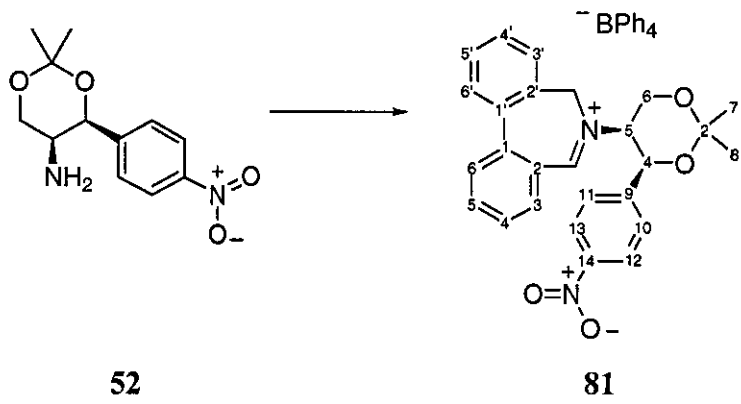
Prepared according to the general procedure from (–)-isopinocampheylamine (**8**) (3.12 g, 20.5 mmol). The product was isolated as yellow plates (8.00 g, 60%); m.p. 212 °C (dec.); $[\alpha]_D^{20} +22.4$ (*c* 1.00, CH₃CN); Found: C, 87.81; H, 7.20; N, 1.95. C₄₈H₄₈BN•0.3H₂O requires C, 87.79; H, 7.37; N, 1.95.; ν_{\max} (nujol) /cm⁻¹ 1630, 1599, 1580, 1557, 1209, 756, 705, 612; δ_H (400 MHz; DMSO-d₆, 80 °C) 1.02 (3 H, d, *J* 11.28 Hz, CHCH₃, C10), 1.14 (3 H, s, CCH₃, C8), 1.35 (3 H, s, CCH₃, C9), 1.48 (1 H, d, *J* 16.8 Hz, CH, C1), 2.02 (1 H, td, *J* 9.3, 2.6 Hz, CHH, C7), 2.10-2.31 (2 H, m, CHH, C7 and CH, C5), 2.55-2.74 (3 H, m, CH, C2 and CH₂, C4), 4.84-5.12 (3 H, m, Ar-CH₂N and CH, C3), 6.80 (4 H, t, *J* 11.4 Hz, 4 x CH arom., *para* in BPh₄ gp.), 6.93 (8 H, t, *J* 11.8 Hz, 8 x CH arom., *ortho* in BPh₄ gp.), 7.20-7.29 (8 H, m, arom., *meta* in BPh₄ gp.), 7.61-7.92 (6 H, m, 6 x CH arom., *biphenyl-3*, *biphenyl-4,4'*, *biphenyl-5,5'*, *biphenyl-6*), 8.02 (1 H, td, *J* 11.64, 2.24 Hz, CH arom., *biphenyl-6'*), 8.07-8.16 (1 H, m, CH arom., *biphenyl-3'*), 9.69 (1 H, s, HC=N); δ_C (100 MHz; DMSO-d₆, 80 °C) 19.92 (CH₃, C8), 23.76 (CH₃, C9), 28.97 (CH₃, C10), 33.69 (CH₂, C7), 34.80 (CH₂, CH₂N), 40.00 (C quat., C6), 41.12 (CH, C5), 42.15 (CH, C2), 48.36 (CH, C1), 53.99 (CH₂, C4), 74.28 (CH, C3), 122.23 (8 x CH arom., *ortho* in BPh₄ gp.), 125.96 (4 x CH arom., *para* in BPh₄ gp.), 127.77 (C quat., arom., *biphenyl-2*), 129.41 (CH arom., *biphenyl-4*), 129.65 (CH arom., *biphenyl-6*), 129.94 (CH arom., *biphenyl-3*), 130.31 (CH arom., *biphenyl-5*), 130.69 (CH arom., *biphenyl-4'*), 131.08 (CH arom., *biphenyl-6'*), 131.12 (CH arom., *biphenyl-3'*), 135.41 (C quat., arom., *biphenyl-1*), 135.74 (CH arom., *biphenyl-5'*), 136.55 (8 x CH arom., *meta* in BPh₄ gp.), 137.93 (C quat., arom., *biphenyl-1'*), 141.90 (C quat., arom., *biphenyl-2'*), 164.50 (4 x C quat., arom., *J* 196.40 Hz, C-B *ipso* in BPh₄ gp.), 171.15 (HC=N). *m/z* 330.2228; C₂₄H₂₈N (cation) requires 330.2222.

(-)-2-[(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-5*H*-dibenzo[*c,e*]azepinium tetraphenylborate (80):



Prepared according to the general procedure from (+)-(4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-amine (**15**) (3.85 g, 18.8 mmol). The product was isolated as yellow plates (9.00 g, 68%); m.p. 187-188 °C (dec.); $[\alpha]_D^{20}$ -44.0 (*c* 1.01, CH₃CN); Found C, 85.23; H, 6.52; N, 1.96. C₅₀H₄₆BNO₂ requires C, 85.34; H, 6.59; N, 1.99.; ν_{\max} (film) /cm⁻¹ 3055, 3038, 2999, 1633, 1579, 1480, 1451, 1385, 1203, 1114, 848, 735, 706; δ_H (400 MHz; DMSO-d₆, 115 °C) 1.71 (3 H, s, CH₃, C7), 1.74 (3 H, s, CH₃, C8), 4.32 (1 H, d, *J* 21.8 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C6, eq.), 4.49 (1 H, d, *J* 21.6 Hz, Ar-CHHN), [4.68-4.77 (1 H, m, NCH, C5), 4.72 (1 H, dd, *J* 5.2, 21.8 Hz, downfield portion of an *ABX* system, N-CHCHH-O, C6, eq.)], 5.15 (1 H, d, *J* 22.2 Hz, Ar-CHHN), 5.82 (1 H, d, *J* 4.1 Hz, Ar-CH, C4), 6.75 (4 H, t, *J* 11.4 Hz, arom., *para* in BPh₄ gp.), 6.88 (8 H, t, *J* 11.5 Hz, arom., *ortho* in BPh₄ gp.), 7.11-7.16 (5 H, m, Ph gp.), 7.20-7.25 (8 H, m, arom., *meta* in BPh₄ gp.), [7.55-7.63 (3 H, m, arom.), 7.64-7.69 (3 H, m, arom.), 7.92-7.94 (2 H, m, arom.), *biphenyl* gp.], 9.03 (1 H, s, HC=N); δ_C (100 MHz; DMSO-d₆, 120 °C) 18.05 (CH₃, C8), 28.41 (CH₃, C9), 55.77 (Ar-CH₂N), 60.81 (CH₂, C6), 66.12 (NCH, C5), 70.49 (Ar-CH, C4), 99.87 (C quat., C2), 120.42 (8 x CH arom., *ortho* in BPh₄ gp.), 124.10 (4 x CH arom., *para* in BPh₄ gp.), 124.16 (2 x CH arom., *meta* in Ph gp.), 124.19 (2 x CH arom., *ortho* in Ph gp.), 124.39 (CH arom., *para* in Ph gp.), 127.32 (C quat., arom., *biphenyl*-4'), 127.59 (CH arom., *biphenyl*-4'), 127.69 (CH arom., *biphenyl*-6'), 128.19 (CH arom., *biphenyl*-3'), 128.26 (CH arom., *biphenyl*-5'), 129.00 (CH arom., *biphenyl*-4), 129.31 (CH arom., *biphenyl*-6), 129.39 (CH arom., *biphenyl*-3), 132.58 (C quat., arom., *biphenyl*-1'), 133.57 (CH arom., *biphenyl*-5), 134.95 (8 x CH arom., *meta* in BPh₄ gp.), 135.23 (C quat., arom., *biphenyl*-1), 140.46 (C quat., arom., *biphenyl*-2), 163.30 (4 x C quat., arom., q, *J* 196.0 Hz, C-B *ipso* in BPh₄ gp.), 170.11 (HC=N); *m/z* 384.1968; C₂₆H₂₆NO₂ (cation) requires 384.1964.

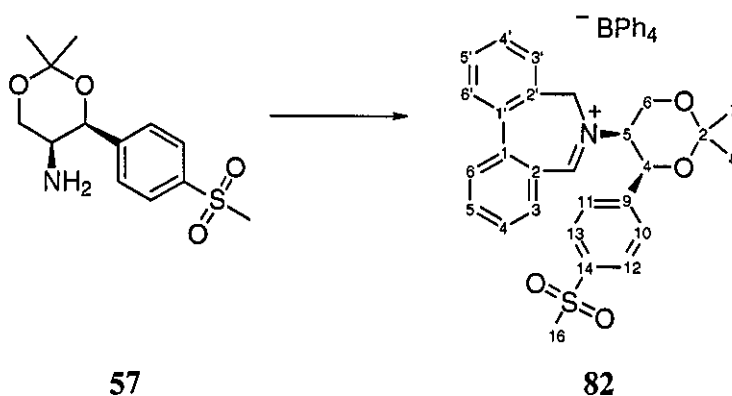
(-)-2-[(4*S*,5*S*)-2,2-Dimethyl-4-[4-(nitro)-phenyl]-1,3-dioxan-5-yl]-5*H*-dibenzo[*c,e*]azepinium tetraphenylborate (81):



Prepared according to the general procedure from (+)-(4*S*,5*S*)-2,2-Dimethyl-4-[4-(nitro)-phenyl]-1,3-dioxan-5-amine (**52**) (0.30 g, 1.19 mmol). The product was isolated as yellow plates (0.57 g, 64%); m.p. 209-210 °C (dec.); $[\alpha]_D^{20}$ -68.0 (*c* 1.17, acetone); Found: C, 85.23; H, 6.52; N, 1.96. C₅₀H₄₆BNO₂ requires C, 85.34; H, 6.59; N, 1.99.; $\nu_{\max}(\text{film}) / \text{cm}^{-1}$ 3055, 2998, 1633, 1600, 1579, 1523, 1480, 1451, 1385, 1349, 1204, 1106, 969, 852; $\delta_{\text{H}}(400 \text{ MHz; DMSO-}d_6, 100 \text{ }^\circ\text{C})$ 1.67 (3 H, s, CH₃, C7), 1.71 (3 H, s, CH₃, C8), 4.35 (1 H, d, *J* 13.2 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C6), 4.49 (1 H, d, *J* 12.8 Hz, Ar-CHHN), 4.66 (1 H, d, *J* 13.2 Hz, downfield portion of an *ABX* system, N-CHCHH-O, C6), 4.82 (1 H, s, NCH, C5), 4.99 (1 H, d, *J* 12.8 Hz, Ar-CHHN), 5.91 (1 H, s, Ar-CH, C4), 6.71 (4 H, t, *J* 6.8 Hz, 4 x CH arom., *para* in BPh₄ gp.), 6.85 (8 H, t, *J* 6.8 Hz, 8 x CH arom., *ortho* in BPh₄ gp.), 7.17 (8 H, m, 8 x CH arom., *meta* in BPh₄ gp.), 7.44 (4 H, m, 2 x CH arom., C12, 13 & 2 x CH arom., *biphenyl* gp.), 7.56-7.75 (4 H, m, 4 x CH arom., *biphenyl* gp.), 7.84 (2 H, d, *J* 8.4 Hz, 2 x CH arom., C10, 11), 7.88 (2 H, m, 2 x CH arom., *biphenyl* gp.), 9.19 (1 H, s, HC=N); $\delta_{\text{C}}(100 \text{ MHz; DMSO-}d_6, 100 \text{ }^\circ\text{C})$ 19.67 (CH₃, C7), 30.05 (CH₃, C8), 58.04 (CH₂, Ar-CH₂N), 62.65 (CH₂, C6), 67.14 (CH, NCH, C5), 71.61 (Ar-CH, C4), 101.82 (C quat., C2), 122.18 (4 x CH arom., *para* in BPh₄ gp.), 124.21 (2 x CH arom., C12,13), 125.91 (8 x CH arom., *ortho* in BPh₄ gp.), 126.91 (C quat., arom., *biphenyl*-2), 127.53 (2 x CH arom., C10,11), 129.46 (CH arom., *biphenyl*-5'), 129.86 (CH arom., *biphenyl*-4), 130.00 (CH arom., *biphenyl*-6), 130.81 (CH arom., *biphenyl*-6'), 130.89 (CH arom., *biphenyl*-4'), 134.09 (C quat., arom., *biphenyl*-2),

135.75 (CH arom., *biphenyl-3*), 136.59 (9 x CH arom., 8 CH *meta* in BPh₄ gp. & CH *biphenyl-5*), 137.10 (CH arom., *biphenyl-3'*), 137.42 (C quat., arom., *biphenyl-1*), 142.09 (C quat., arom., *biphenyl-1'*), 143.97 (C quat., arom., C9), (C quat., arom., C14), 164.60 (4 x C quat., arom., q, *J* 196.0 Hz, C-B *ipso* in BPh₄ gp.), 171.97 (HC=N); *m/z* 429.1815; C₂₆H₂₅N₂O₄ (cation) requires 429.1814.

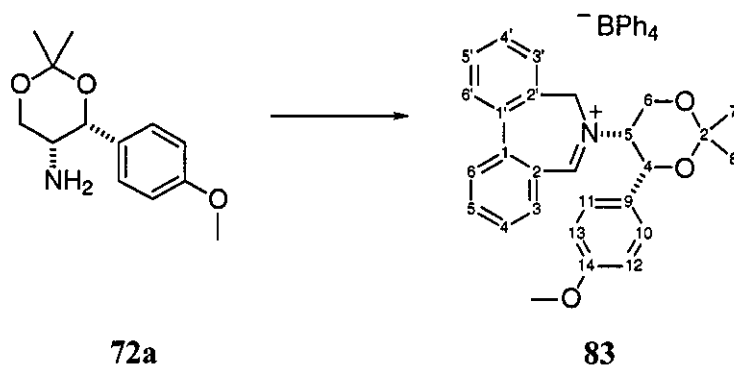
(-)-2-[(4*S*,5*S*)-2,2-Dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-yl]-5*H*-dibenzo[*c,e*]azepinium tetraphenylborate (82):



Prepared according to the general procedure from (+)-(4*S*,5*S*)-2,2-dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-amine (**57**) (0.30 g, 1.05 mmol). The product was isolated as yellow plates (0.54 g, 66%); m.p. 162-165 °C (dec.); $[\alpha]_D^{20}$ -50.3 (c 1.09, acetone); Found: C, 75.14; H, 5.89; N, 1.75. C₅₁H₄₈BNO₄S•2.0H₂O requires C, 74.87; H, 6.29; N, 1.71.; $\nu_{\max}(\text{film})$ /cm⁻¹ 3052, 2997, 1636, 1599, 1551, 1479, 1454, 1385, 1304, 1205, 1148, 1090, 947.6, 844; $\delta_{\text{H}}(400 \text{ MHz; DMSO-}d_6, 100 \text{ }^\circ\text{C})$ 1.79 (3 H, s, CH₃, C7), 2.01 (3 H, s, CH₃, C8), 3.01 (3 H, s, SCH₃, C16), 4.40 (1 H, d, *J* 13.6 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C6), 4.56 (1 H, d, *J* 13.2 Hz, Ar-CHHN), 4.66 (1 H, dd, *J* 13.6, 3.2 Hz, downfield portion of an *ABX* system, N-CHCHH-O, C6), 4.88 (1 H, bs, NCH, C5), 5.15 (1 H, d, *J* 12.8 Hz, Ar-CHHN), 5.91 (1 H, d, *J* 2.8 Hz, Ar-CH, C4), 6.79 (4 H, t, *J* 6.8 Hz, 4 x CH arom., *para* in BPh₄ gp.), 6.92 (8 H, t, *J* 7.6 Hz, 8 x CH arom., *ortho* in BPh₄ gp.), 7.17 (8 H, m, 8 x CH arom., *meta* in BPh₄ gp.), 7.52-7.58 (4 H, m, 2 x CH arom., C12,13 & 2 x CH arom., *biphenyl* gp.), 7.65-7.74 (4 H, m, 2 x CH arom., C10,11, & 2 x CH arom., *biphenyl* gp.), 7.91-7.97 (2 H, m, 2 x CH arom., *biphenyl* gp.), 9.16 (1 H, s, HC=N); $\delta_{\text{C}}(100 \text{ MHz; DMSO-}d_6, 100 \text{ }^\circ\text{C})$ 19.28 (CH₃, C7), 29.67 (CH₃, C8), 44.23 (SCH₃), 57.04

(Ar-CH₂N), 62.07 (CH₂, C6), 66.80 (NCH, C5), 71.35 (Ar-CH, C4), 101.34 (C quat., C2), 121.77 (4 x CH arom., *para* in BPh₄ gp.), 125.50 (8 x CH arom., *ortho* in BPh₄ gp.), 126.43 (C quat., arom., *biphenyl-2*), 126.79 (2 x CH arom., C12,13), 127.39 (2 x CH arom., C12,13), 128.64 (C quat., arom., C14), 129.02 (CH arom., *biphenyl-5*'), 129.48 (CH arom., *biphenyl-4*), 129.59 (CH arom., *biphenyl-6*), 130.35 (CH arom., *biphenyl-6*'), 130.61 (CH arom., *biphenyl-4*'), 130.80 (CH arom., *biphenyl-3*), 135.06 (CH arom., *biphenyl-5*), 136.19 (8 x CH arom., *meta* in BPh₄ gp.), 136.66 (CH arom., *biphenyl-3*'), 137.06 (C quat., arom., *biphenyl-2*'), 141.48 (C quat., arom., *biphenyl-1*'), 141.68 (C quat., arom., *biphenyl-1*'), 142.02 (C quat., arom., C9), 164.10 (4 x C quat., arom., q, *J* 196.0 Hz, C-B *ipso* in BPh₄ gp.), 171.63 (HC=N); *m/z* 462.1739; C₂₇H₂₈NO₄S (cation) requires 462.1739.

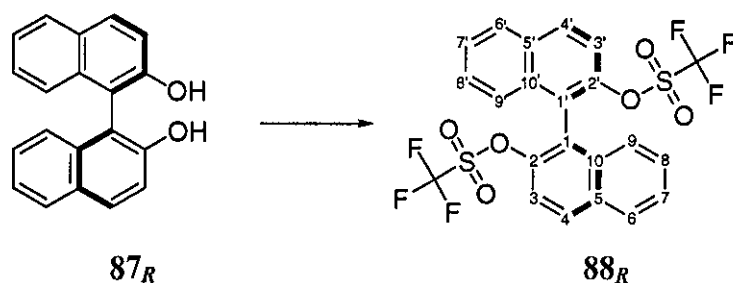
(+)-2-[(4*S*,5*S*)-2,2-Dimethyl-4-[4-(methoxy)-phenyl]-1,3-dioxan-5-yl]-5*H*-dibenzo[*c,e*]azepinium tetraphenylborate (83):



Prepared according to the general procedure from (-)-(4*R*,5*R*)-2,2-dimethyl-4-[4-(methoxy)-phenyl]-1,3-dioxan-5-amine (**72a**) (0.13 g, 0.48 mmol). The product was isolated as yellow plates (0.23 g, 64%); m.p. 207-209 °C (dec.); $[\alpha]_D^{20} +37.8$ (*c* 1.09, acetone); Found: C, 76.58; H, 6.02; N, 1.84. C₅₁H₄₈BNO₃•3.5H₂O requires C, 76.84; H, 6.52; N, 1.76.; ν_{\max} (film) /cm⁻¹ 3055, 2998, 1633, 1613, 1579, 1557, 1514, 1480, 1384, 1253, 1202, 1031, 966; δ_H (400 MHz; DMSO-d₆, 100 °C) 1.66 (3 H, s, CH₃, C7), 1.68 (3 H, s, CH₃, C8), 3.60 (3 H, s, OCH₃, C16), 4.28 (1 H, dd, *J* 14.4, 2.0 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C6), 4.43 (1 H, d, 14.0 Hz, Ar-CHHN), 4.65 (2 H, m, downfield portion of an *ABX* system, N-CHCHH-O, C6 &

CHN, C5), 5.02 (1 H, d, J 14.0 Hz, Ar-CHHN), 5.70 (1 H, d, J 2.8 Hz, Ar-CH, C4), 6.63 (2 H, d, J 8.6 Hz, 2 x CH arom., C12, 13), 6.72 (4 H, t, J 7.4 Hz, 4 x CH arom., *para* in BPh₄ gp.), 6.86 (8 H, t, J 7.4 Hz, 8 x CH arom., *ortho* in BPh₄ gp.), 7.08 (2 H, d, J 8.6 Hz, 2 x CH arom., C10, 11), 7.18 (8 H, m, 8 x CH arom., *meta* in BPh₄ gp.), 7.52 (3 H, m, 3 x CH arom., *biphenyl-3',4',5'*), 7.65 (3 H, m, 3 x CH arom., *biphenyl-3,4,5*), 7.91 (2 H, m, 2 x CH arom., *biphenyl-6,6'*), 9.00 (1 H, s, HC=N, C18); δ_c (100 MHz; DMSO-*d*₆, 100 °C) 18.28 (CH₃, C7), 28.80 (CH₃, C8), 54.79 (OCH₃, C16), 56.11 (Ar-CH₂N), 60.94 (CH₂, C6), 66.42 (NCH, C5), 70.45 (Ar-CH, C4), 100.03 (C quat., C2), 113.75 (2 x CH arom., C12, 13), 120.81 (4 x CH arom., *para* in BPh₄ gp.), 124.58 (8 x CH arom., *ortho* in BPh₄ gp.), 125.57 (C quat., arom., *biphenyl-2*), 125.92 (2 x CH arom., C10, 11), 127.47 (C quat., arom., C9), 128.02 (CH arom., *biphenyl-4*), 128.49 (CH arom., *biphenyl-5'*), 128.54 (CH arom., *biphenyl-5*), 129.37 (CH arom., *biphenyl-6'*), 129.60 (CH arom., *biphenyl-4'*) 129.67 (CH arom., *biphenyl-4*), 132.92 (C quat., arom., *biphenyl-2'*), 133.91 (CH arom., *biphenyl-3*), 135.21 (8 x CH arom., *meta* in BPh₄ gp.), 135.51 (CH arom., *biphenyl-6*), 136.15 (C quat., arom., *biphenyl-1*), 140.69 (C quat., arom., *biphenyl-1'*), 158.74 (C quat., arom., C14), 163.25 (4 x C quat., arom., q , J 196.0 Hz, C-B *ipso* in BPh₄ gp.), 170.21 (HC=N); m/z 414.2063; C₂₇H₂₈NO₃ (cation) requires 414.2069.

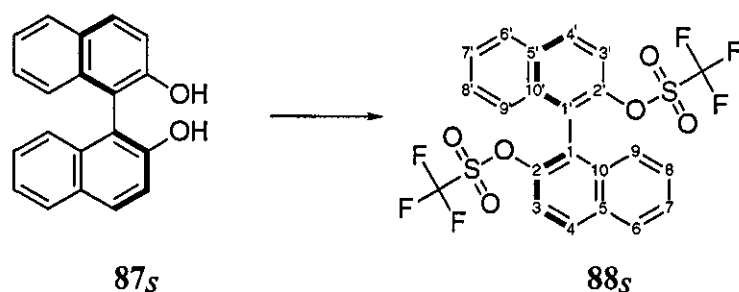
(R)-Trifluoro-methanesulfonic acid 2'-trifluoromethanesulfonyloxy [1,1']binaphthalenyl-2-yl ester (88_R):



(R)-[1,1']Binaphthalenyl-2,2'-diol (87_R) (1.70 g, 5.9 mmol) was dissolved in dichloromethane (40 ml) and cooled to -30 °C. To this was added 4-dimethylaminopyridine (0.289 g, 2.4 mmol), 2,6-lutidine (2.06 ml, 17.7 mmol) and triflic anhydride (2.98 ml, 17.7 mmol). The solution was allowed to warm to room temperature and stirred for 4 h. Silica gel was added to the solution and the solvent

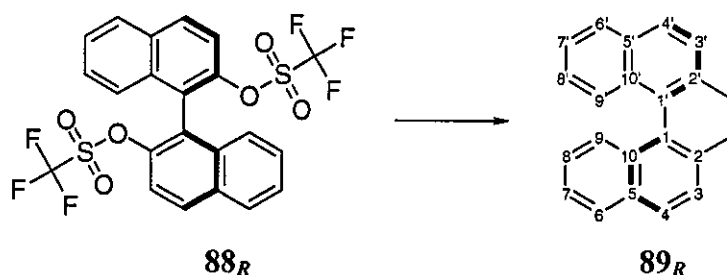
evaporated under reduced pressure. The compound adsorbed on silica was transferred to a fritted glass funnel and washed with ethyl acetate/light petroleum until the title compound had eluted. Solvents were removed under reduced pressure to yield a crude colourless solid, which was recrystallized from hexane to give colourless crystals (3.20 g, 99%), m.p. 68-70 °C; $[\alpha]_D^{20} -145.3$ (c 1.08, CHCl_3) [Lit¹¹ +142.0 (c 1.04, CHCl_3), for (*S*)-enantiomer]; $\nu_{\text{max}}(\text{film}) / \text{cm}^{-1}$ 3062, 1508, 1424, 1246, 1140, 1065, 963, 865; δ_{H} (250 MHz; CDCl_3) 7.25 (2 H, m, 2 x CH arom., *binap*-3,-3'), 7.40 (2 H, m, 2 x CH arom., *binap*-7,-7'), 7.59 (4 H, m, 4 x CH arom., *binap*-7,-7',-9,-9'), 8.00 (2 H, d, J 8.2 Hz, 2 x CH arom., *binap*-4,-4'), 8.13 (2 H, d, J 9.0 Hz, 2 x CH arom., *binap*-6,-6'); δ_{C} (100 MHz; CDCl_3) 118.12 (2 x C quat., q J 318.0 Hz, 2 x CF_3), 119.33 (2 x CH arom., *binap*-3,-3'), 123.46 (2 x C quat., arom., *binap*-1,-1'), 126.76 (2 x CH arom., *binap*-7,-7'), 127.33 (2 x CH arom., *binap*-9,-9'), 127.99 (2 x CH arom., *binap*-8,-8'), 128.36 (2 x CH arom., *binap*-6,-6'), 132.00 (2 x CH arom., *binap*-4,-4'), 132.37 (2 x C quat., arom., *binap*-5,-5'), 133.17 (2 x C quat., arom., *binap*-10,-10'), 145.41 (2 x C quat., arom., *binap*-2,-2'); m/z 549.9974; $\text{C}_{22}\text{H}_{12}\text{F}_6\text{O}_6\text{S}_2$ (M^+) requires 549.9980.

(*S*)-Trifluoro-methanesulfonic acid 2'-trifluoromethanesulfonyloxy [1,1']binaphthalenyl-2-yl ester (88_S**):**



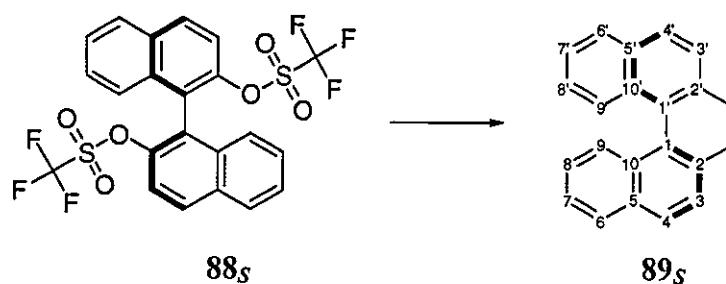
Prepared in an identical manner to the (*R*)-enantiomer (**88_R**) above, from (*S*)-[1,1']binaphthalenyl-2,2'-diol (**87_S**) (6.76 g, 24.0 mmol). Colourless crystals (13.0 g, 99%); having almost identical spectroscopic data to (**88_R**): m.p. 65-67 °C; $[\alpha]_D^{20} +140.6$ (c 1.09, CHCl_3).

(R)-2,2'-Dimethyl-[1,1']binaphthalenyl (89_R):



(R)-Trifluoro-methanesulfonic acid 2'-trifluoromethanesulfonyloxy [1,1']binaphthalenyl-2-yl ester (**88_R**) (13.0 g, 23.6 mmol) and 1,3-bis(diphenylphosphino)propane nickel(II)chloride (1.10 g, 1.7 mmol) were dissolved in anhydrous diethyl ether (100 ml). The reaction was cooled to $-10\text{ }^{\circ}\text{C}$ in a ice/salt bath and methylmagnesium bromide (3 M in Et_2O , 31.5 ml, 94.4 mmol) was added dropwise over 30 min. The reaction was allowed to attain ambient temperature and stirred over night. The dark green/brown solution was diluted with diethyl ether (150 ml) and filtered through celite (to remove the nickel catalyst). The filtrate was washed with 0.5 M hydrochloric acid (2 x 50 ml) and brine (50 ml). Removal of solvent under reduced pressure yielded a red/orange crude oil, which was purified by column chromatography eluting with hexane to give a pale yellow oil. Crystallization from methanol afforded the product as colourless crystals (6.00 g, 90%); m.p. $68\text{-}72\text{ }^{\circ}\text{C}$ (Lit¹² $67\text{-}71\text{ }^{\circ}\text{C}$); $[\alpha]_{\text{D}}^{20} -39.0$ (c 1.12, CHCl_3) [Lit¹³ $[\alpha]_{\text{D}}^{21} +37.7$ (c 1.00, CHCl_3) for (S)-enantiomer]; $\nu_{\text{max}}(\text{film}) / \text{cm}^{-1}$ 3053, 2246, 1594, 1506, 1421, 1379, 1351, 1221, 1143, 1027, 913, 865; δ_{H} (250 MHz; CDCl_3) 2.03 (6 H, s, 2 x Ar- CH_3), 7.04 (2 H, d, J 8.4 Hz, 2 x CH arom., *binap*-3,-3'), 7.19 (2 H, m, 2 x CH arom., *binap*-7,-7'), 7.35 (2 H, m, 2 x CH arom., *binap*-8,-8'), 7.37 (2 H, d, J 8.3 Hz, 2 x CH arom., *binap*-4,-4'), 7.86 (2 H, d, J 8.4 Hz, 2 x CH arom., *binap*-9,-9'), 7.88 (2 H, d, J 8.4 Hz, 2 x CH arom., *binap*-6,-6'); δ_{C} (100 MHz; CDCl_3) 20.01 (2 x Ar- CH_3), 124.87 (2 x CH arom., *binap*-7,7'), 125.62 (2 x CH arom., *binap*-8,-8'), 126.06 (2 x CH arom., *binap*-4,4'), 127.41 (2 x CH arom., *binap*-9,-9'), 127.90 (2 x CH arom., *binap*-6,-6'), 128.70 (2 x CH arom., *binap*-3,-3'), 132.20 (2 x C quat., arom., *binap*-5,-5'), 132.75 (2 x C quat., arom., *binap*-10,-10'), 134.25 (2 x C quat., arom., *binap*-2,-2'), 135.11 (2 x C quat., arom., *binap*-1,-1'); m/z 300.1747; $\text{C}_{22}\text{H}_{22}\text{N}$ (M^+NH_4) requires 300.1752.

(S)-2,2'-Dimethyl-[1,1']binaphthalenyl (89_S):



Prepared in an identical manner to the (*R*)-enantiomer (89_R) above, from (*S*)-trifluoromethanesulfonic acid 2'-trifluoromethanesulfonyloxy [1,1']binaphthalenyl-2-yl ester (88_S) (5.00 g, 9.0 mmol). Colourless crystals (2.33 g, 92%); having almost identical spectroscopic data to (89_R): m.p. 71-73 °C; $[\alpha]_D^{20} +37.0$ (*c* 1.01, CHCl₃).

(R)-2,2'-Dibromomethyl-[1,1']binaphthalenyl (90_R):

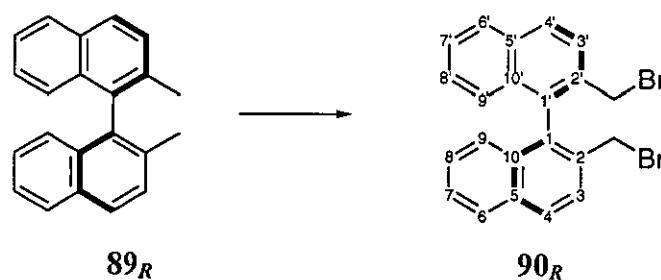


Table 7, Method 1:

(*R*)-2,2'-Dimethyl-[1,1']binaphthalenyl (89_R) (5.00 g, 17.7 mmol) was dissolved in carbon tetrachloride (70 ml) and *N*-bromosuccinamide (6.63 g, 37.2 mmol), benzoyl peroxide (0.057 g, 0.2 mmol) were added. The mixture was heated under reflux for 24 h and upon cooling the solvent was removed under reduced pressure. The red/brown residue which remained, was diluted with chloroform and washed with water and brine. The organics were dried (MgSO₄) and solvent removed under reduced pressure. Recrystallization from chloroform/hexane afforded the product as colourless crystals (3.5 g, 45%). The remaining filtrate was concentrated and subjected to column chromatography eluting with light petroleum/ethyl acetate (97:3). Giving 0.18 g of

starting material and a further 1.50 g of product (after recrystallization from chloroform/hexane), a total of 5.0 g, 64%.

Table 7, Method 2:

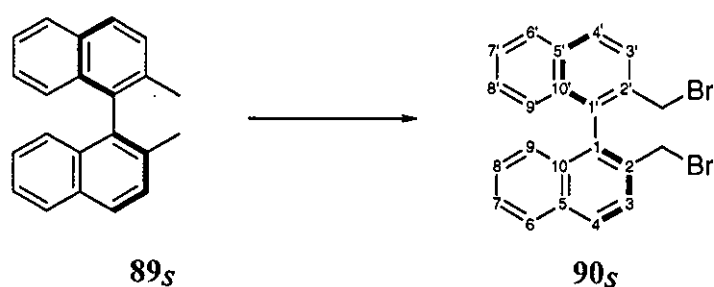
(*R*)-2,2'-Dimethyl-[1,1']binaphthalenyl (**89_R**) (3.00 g, 10.6 mmol), *N*-bromosuccinamide (3.78 g, 21.3 mmol) and AIBN (10 mol%, 0.174 g, 1.1 mmol) were stirred in carbon tetrachloride (35 ml). The solution was irradiated with visible light (150 Watt Philips tungsten bulb) for 5 h. The reaction mixture was filtered through a fritted glass funnel and a scoop of silica added. The solvent was removed under reduced pressure to give the reaction mixture adsorbed onto silica. Immediately chromatographed eluting with light petroleum/ethyl acetate (97:3) to afford a colourless solid, recrystallized from chloroform/hexane. Colourless crystals (4.10 g, 88%).

Table 7, Method 3:

Prepared as Method 2, from (*R*)-2,2'-Dimethyl-[1,1']binaphthalenyl (**89_R**) (4.00 g, 14.2 mmol), using cyclohexane as reaction solvent (60 ml). Colourless crystals (5.50 g, 88%).

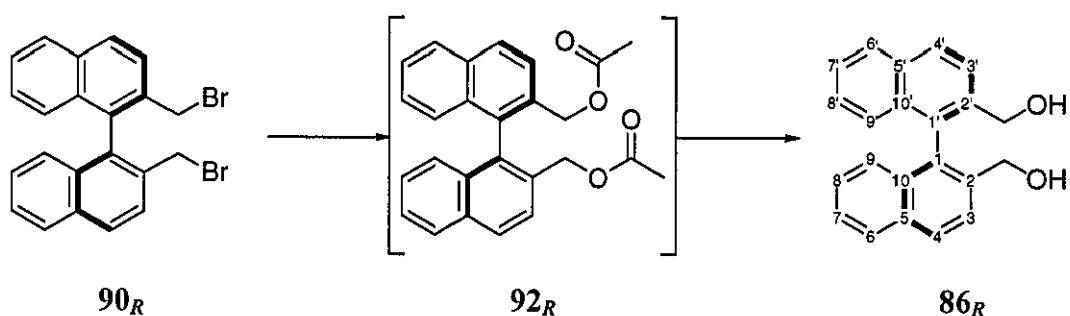
m.p. 185-187 °C; $[\alpha]_D^{20}$ -164.4 (*c* 1.04, benzene); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3049, 2360, 1506, 1431, 1210, 818, 749, 684; δ_{H} (400 MHz; CDCl₃) 4.25 (4 H, s, 2 x Ar-CH₂), 7.07 (2 H, d, *J* 8.0 Hz, 2 x CH arom., *binap*-3,-3'), 7.25 (2 H, m, 2 x CH arom., *binap*-7,-7'), 7.46 (2 H, m, 2 x CH arom., *binap*-8,-8'), 7.74 (2 H, d, *J* 8.0 Hz, 2 x CH arom., *binap*-4,-4'), 7.91 (2 H, d, *J* 8.0 Hz, 2 x CH arom., *binap*-9,-9'), 8.00 (2 H, d, *J* 8.0 Hz, 2 x CH arom., *binap*-6,-6'); δ_{C} (100 MHz; CDCl₃) 32.61 (2 x Ar-CH₂), 126.78 (2 x CH arom., *binap*-7,-7'), 126.80 (2 x CH arom., *binap*-8,-8'), 127.61 (2 x CH arom., *binap*-4,-4'), 127.74 (2 x CH arom., *binap*-9,-9'), 128.02 (2 x CH arom., *binap*-6,-6'), 129.35 (2 x CH arom., *binap*-3,-3'), 132.50 (C quat., arom., *binap*-5,-5'), 133.25 (C quat., arom., *binap*-10,-10'), 134.07 (C quat., arom., *binap*-2,-2'), 134.17 (C quat., arom., *binap*-1,-1'); *m/z* 437.9614; C₂₂H₁₆Br₂ (M⁺) requires 437.9619.

(S)-2,2'-Dibromomethyl-[1,1']binaphthalenyl (90_S):



Prepared in an identical manner to the (*R*)-enantiomer (**90_R**) above (method 1), from (*S*)-2,2'-dimethyl-[1,1']binaphthalenyl (**89_S**) (2.00 g, 7.1 mmol). Colourless crystals (1.87 g, 60%); having almost identical spectroscopic data to (**90_R**): m.p. 181-183 °C (lit¹³ 183-184 °C); $[\alpha]_D^{20} -159.0$ (*c* 1.17, benzene) [lit¹³ $[\alpha]_D^{20} -160.0$ (*c* 1.00, benzene)].

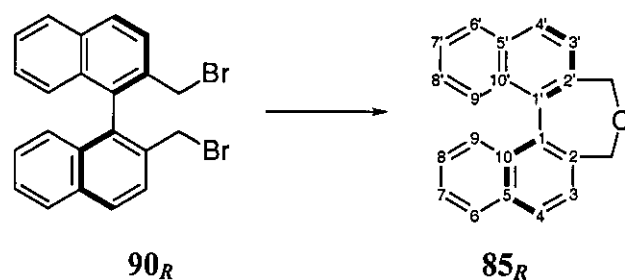
(R)-(2'-Hydroxymethyl-[1,1']binaphthalenyl-2-yl)-methanol (86_R):



A solution of (*R*)-2,2'-Dibromomethyl-[1,1']binaphthalenyl (**90_R**) (3.50 g 8.0 mmol) was dissolved in dimethylformamide (300 ml) and stirred at 80 °C with potassium acetate (3.75 g, 38.2 mmol) and tetrabutylammonium bromide (1.0 g) for 24 h. The mixture was allowed to cool, diluted with brine (150 ml) and extracted with diethyl ether (3 x 100 ml). The organics were combined and washed with brine (2 x 50 ml), dried (MgSO₄) and solvents removed under reduced pressure to yield a pale yellow/brown oil. Recrystallized from chloroform/hexane. (*R*)-Acetic acid 2'-acetoxymethyl-[1,1']binaphthalenyl-2-ylmethyl ester (3.0 g, 7.5 mmol) was hydrolysed in refluxing potassium hydroxide (50% in water)/1,4-dioxane (1:1, 100 ml) for 24 h. The solution was allowed to cool and extracted with diethyl ether (3 x

50ml). The organic layers were combined and washed with brine (2 x 50 ml) to give a crude yellow/brown oil. Crystallized from chloroform/hexane to give colourless crystals (2.10 g, 88%); m.p. 167-169 °C; $[\alpha]_D^{20} +63.2$ (*c* 1.35, acetone) [Lit¹⁰ $[\alpha]_D^{24} -67.5$ (*c* 1.00, acetone) for (*S*)- enantiomer]; $\nu_{\max}(\text{film}) / \text{cm}^{-1}$ 3384, 3057, 1648, 1507, 1428, 1216, 1013, 822; δ_{H} (250 MHz; CDCl₃) 3.26 (2 H, bs, 2 x OH), 4.08 (2 H, d, *J* 11.1 Hz, Ar-CH₂), 4.37 (2 H, d, *J* 11.1 Hz, Ar-CH₂), 7.01 (2 H, d, *J* 8.24, 2 x CH arom., *binap-3,-3'*), 7.22 (2 H, m, 2 x CH arom., *binap-7,-7'*), 1.97 (2 H, m, 2 x CH arom., *binap-8,-8'*), 7.68 (2 H, d, *J* 8.8 Hz, 2 x CH arom., *binap-4,-4'*), 7.94 (4 H, m, 4 x CH arom., *binap-6,-6'*, *binap-9,-9'*); δ_{C} (100 MHz; CDCl₃) 63.40 (2 x Ar-CH₂), 126.27 (2 x CH arom., *binap-7,-7'*), 126.54 (2 x CH arom., *binap-8,-8'*), 126.66 (2 x CH arom., *binap-4,-4'*), 127.70 (2 x CH arom., *binap-9,-9'*), 128.46 (2 x CH arom., *binap-6,-6'*), 129.02 (2 x CH arom., 3,-3'), 133.46 (2 x C quat., arom., *binap-5,5'*), 133.55 (2 x C quat., arom., *binap-10,-10'*), 134.69 (2 x C quat., arom., *binap-1,-1'*), 137.57 (2 x C quat., arom., *binap-2,-2'*); *m/z* 332.1650; C₂₂H₁₈O₂ (M⁺NH₄) requires 332.1651.

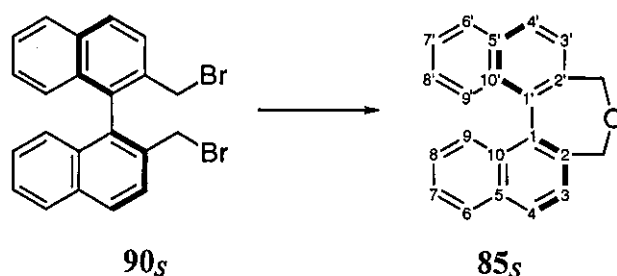
(*R*)-3,5-Dihydro-4-oxa-cyclohepta[2,1-*a*;3,4-*a'*]dinaphthalene (85_R):



(*R*)-2,2'-Dibromomethyl-[1,1']binaphthalenyl (90_R) (0.50 g, 1.1 mmol) was suspended in a mixture of sat. aq. sodium carbonate solution and 1,4-dioxane (1:1, 60 ml). The solution was heated under reflux for 12 h. Upon cooling the mixture was extracted with diethyl ether (3 x 30 ml), washed with brine (2 x 20 ml) and dried. Removal of the solvent under reduced pressure afforded a yellow oil (TLC visualised using UV shows product as bright blue spot). Column chromatography eluting with ethyl acetate/light petroleum (0:100-10:90) gave a colourless solid, recrystallized from chloroform/hexane, (0.21 g 65%); m.p. 187-188 °C (lit.¹⁴ 188-189 °C); $[\alpha]_D^{20} -551.2$ (*c* 1.12, CHCl₃); $\nu_{\max}(\text{film}) / \text{cm}^{-1}$ 3052, 2983, 2926, 1594, 1508, 1465, 1420, 1368,

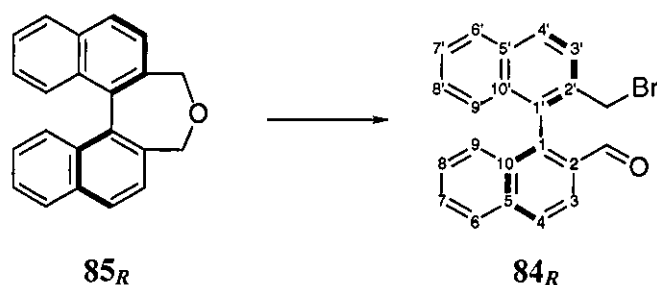
1265, 1158, 1056, 895; δ_{H} (250 MHz; CDCl_3) 4.18 (2 H, d, J 11.33 Hz, Ar- CH_2O), 4.64 (2 H, d, J 11.33 Hz, Ar- CH_2O), 7.29 (2 H, m, 2 x CH arom., *binap*-3,-3'), 7.50 (4 H, m, 4 x CH arom., *binap*-7,-7', *binap*-8,-8'), 7.61 (2 H, d, J 8.33 Hz, 2 x CH arom., *binap*-4,-4'), 7.97 (4 H, dd, J 7.99 Hz, 4 x CH arom., *binap*-6,-6', *binap*-9,-9'); δ_{C} (100 MHz; CDCl_3) 67.44 (2 x CH_2 , 2 x Ar- CH_2), 125.85 (2 x CH arom., *binap*-7,-7'), 125.94 (2 x CH arom., *binap*-8,-8'), 127.35 (2 x CH arom., *binap*-4,-4'), 127.59 (2 x CH arom., *binap*-9,-9'), 128.35 (2 x CH arom., *binap*-6,-6'), 129.15 (2 x CH arom., *binap*-3,-3'), 131.16 (2 x C quat., arom., *binap*-5,-5'), 133.55 (2 x C quat., arom., *binap*-10,-10'), 133.64 (2 x C quat., arom., *binap*-2,-2'), 135.46 (2 x C quat., arom., *binap*-1,-1'); m/z 296.1205; $\text{C}_{22}\text{H}_{16}\text{O}$ (M^+) requires 296.1201.

(*S*)-3,5-Dihydro-4-oxa-cyclohepta[2,1-*a*;3,4-*a'*]dinaphthalene (85_S**):**



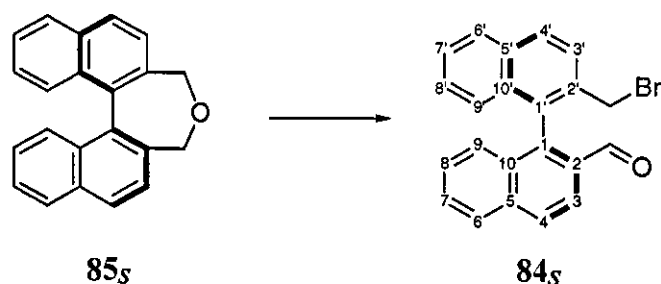
Prepared in an identical manner to the (*R*)-enantiomer (**85_R**) above, from (*S*)-2,2'-dibromomethyl-[1,1']binaphthalenyl (**90_S**) (7.00 g, 15.9 mmol). Colourless crystals (3.10 g, 66%); having almost identical spectroscopic data to (**90_R**): m.p. 186-188 °C; $[\alpha]_{\text{D}}^{20} +572.6$ (c 1.04, CHCl_3).

(*R*)-2'-Bromomethyl-[1,1']binaphthalenyl-2-carbaldehyde (84_R**):**



To an ice-cooled solution of (*R*)-3,5-dihydro-4-oxa-cyclohepta[2,1-*a*;3,4-*a'*]dinaphthalene (**85_R**) (3.0 g, 9.6 mmol) in carbon tetrachloride (50 ml), molecular bromine (1.24 g, 7.8 mmol) as a solution in carbon tetrachloride (5 ml) was added over a period of 5 min (solution turned dark red). After a further 5 min the ice bath was removed and the reaction mixture heated under reflux until it became pale yellow (*ca* 1 h). The solvent was removed under reduced pressure and the residue obtained dissolved in diethyl ether. The organic solvents were washed with sat. aq. sodium hydrogen carbonate (2 x 50 ml) and brine (2 x 30 ml). The organic solution was dried (MgSO₄) and solvents were removed under reduced pressure to yield a orange oil. Crystallization from ethyl acetate afforded the product as colourless crystals (2.33 g, 65%); m.p. 151-153 °C; [α]_D²⁰ +144.7 (*c* 1.02, CHCl₃); Found: C, 70.04; H, 3.78. C₂₂H₁₅BrO requires C, 70.41; H, 4.03.; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3058, 1688, 1594, 1430, 1324, 1212, 1027, 821, 749; δ_{H} (250 MHz; CDCl₃) 4.07 (1 H, d, *J* 10.2 Hz, Ar-CHH), 4.27 (1 H, d, *J* 10.2 Hz, Ar-CHH), 7.01 (1 H, dq, *J* 8.4, 2.0 Hz, CH arom., *binap*-7') 7.22-7.38 (3 H, m, 3 x CH arom., *binap*-3',-8',-4'), 7.50 (1 H, m, CH arom., *binap*-7), 7.63 (1 H, m, CH arom., *binap*-8), 7.72 (1 H, d, *J* 8.6 Hz, CH arom., *binap*-4), 7.93-8.12 (4 H, m, 4 x CH arom., *binap*-6,-6',-9,-9'), 8.22 (1 H, d, *J* 8.6 Hz, CH arom., *binap*-3), 9.56 (1 H, d, *J* 0.9 Hz, CHO); δ_{C} (100 MHz; CDCl₃) 31.92 (Ar-CH₂) 122.38 (CH arom., *binap*-3), 126.56 (CH arom., *binap*-7'), 126.94 (CH arom., *binap*-8'), 127.03 (CH arom., *binap*-4'), 127.39 (CH arom., *binap*-8), 127.40 (2 x CH arom., *binap*-6',-9'), 128.17 (CH arom., *binap*-4), 128.48 (CH arom., *binap*-6), 129.20 (CH arom., *binap*-3'), 129.34 (CH arom., *binap*-7), 129.85 (CH arom., *binap*-9), 132.41 (C arom., quat., *binap*-5'), 132.42 (C arom., quat., *binap*-10'), 132.53 (C arom., quat., *binap*-2), 132.97 (C arom., quat., *binap*-5), 133.56 (C arom., quat., *binap*-2'), 134.63 (C arom., quat., *binap*-1'), 136.29 (C arom., quat., *binap*-10), 141.59 (C arom., quat., *binap*-1), 191.81 (CHO); *m/z* 374.0310; C₂₂H₁₅BrO (M⁺) requires 374.0306; HPLC retention time (Chiracel OD column) 12.75 min; Hex:IPA (90:10), Flow 1.0, Atten 512, C.S. 0.5.

(*S*)-2'-Bromomethyl-[1,1']binaphthalenyl-2-carbaldehyde (84_S**):**



Prepared in an identical manner to the (*R*)-enantiomer (**84_R**) above, from (*S*)-3,5-dihydro-4-oxa-cyclohepta[2,1-*a*;3,4-*a'*]dinaphthalene (**85_S**) (2.30 g, 7.8 mmol). Colourless crystals (1.87 g, 64%); having almost identical spectroscopic data to (**84_R**): m.p. 154-155 °C; $[\alpha]_{\text{D}}^{20} -140.3$ (*c* 1.13, CHCl₃); HPLC retention time (Chiracel OD column) 11.71 min; Hex:IPA (90:10), Flow 1.0, Atten 512, C.S. 0.5.

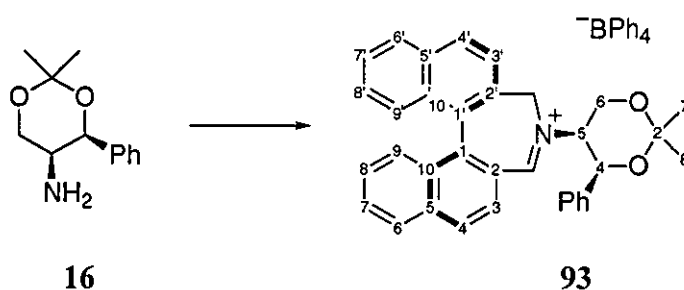
General procedure for the synthesis of 3*H*-4-azapinium-cyclohepta[2,1-*a*;3,4-*a'*]dinaphthalene salts from (*R*) or (*S*)-2'-Bromomethyl-[1,1']binaphthalenyl-2-carbaldehyde and primary amines:



A solution of the amine in ethanol, (10 ml per g of amine, 1 equivalent), was added dropwise via a stoppered, pressure equalising, dropping funnel, to a one-neck flask, containing a solution of (*R*) (**84_R**) or (*S*)-2'-Bromomethyl-[1,1']binaphthalenyl-2-carbaldehyde (**84_S**), (1.10 equiv.) in ethanol (10 ml/g carbaldehyde) warmed at 35 °C. After the addition was 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, was added in one portion to the reaction mixture and

after 5 minutes of stirring, the organic solvents are removed under reduced pressure. Ethanol was added to the residue, followed by water. The resulting solid was collected by filtration and washed with additional ethanol followed by hexane. If no solid materialises after the addition of the 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 do arise, small amounts of acetonitrile may be added during this process.

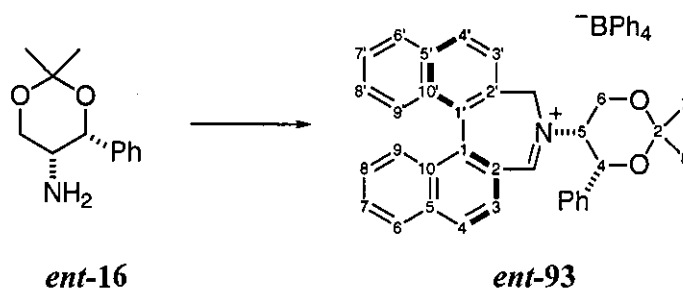
(R)-[(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-3*H*-4-azapinium-cyclohepta[2,1-*a*;3,4-*a'*]dinaphthalene tetraphenylborate (93):



Prepared according to the general procedure from (+)-(4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-amine (**16**) (0.15 g, 0.72 mmol). The product was isolated as yellow plates (0.39 g, 66%); m.p. 111-113 °C (dec.); $[\alpha]_D^{20} -98.5$ (*c* 1.04, acetone); Found: C, 84.44; H, 5.97; N, 1.71. $C_{58}H_{50}BNO_2 \cdot 1.0H_2O$ requires C, 84.73; H, 6.13; N, 1.71.; $\nu_{\max}(\text{film}) / \text{cm}^{-1}$ 3055, 2986, 1626, 1610, 1593, 1548, 1478, 1450, 1382, 1266, 1203, 1110, 846, 817, 735, 704; $\delta_H(400 \text{ MHz; acetone-}d_6)$ 1.79 (3 H, s, CH_3 , C7), 1.85 (3 H, s, CH_3 , C8), 4.43 (1 H, d, *J* 13.2 Hz, Ar-*CHHN*), 4.51 (1 H, d, *J* 13.6 Hz, upfield portion of an *ABX* system, N-*CHCHH*-O, C6), 4.86 (2 H, m, downfield portion of an *ABX* system, N-*CHCHH*-O, C6, & NCH, C5), 5.98 (2 H, m, Ar-*CH*, C4 & Ar-*CHHN*), 6.76 (4 H, t, *J* 7.2 Hz, 4 x *CH* arom., *para* in BPh_4 gp.), 6.93 (8 H, t, *J* 7.6 Hz, 8 x *CH* arom., *ortho* in BPh_4 gp.), 6.95-7.10 (5 H, m, 5 x *CH* arom., Ph gp.), 7.18-7.32 (2 H, m, 2 x *CH* arom., *binaphthyl* gp.), 7.34 (8 H, m, 8 x *CH* arom., *meta* in BPh_4 gp.), 7.45 (3 H, m, 3 x *CH* arom., *binaphthyl* gp.), 7.45-7.65 (2 H, m, 2 x *CH* arom., *binaphthyl* gp.), 7.78 (1 H, m, *CH* arom., *binaphthyl* gp.), 7.88 (1 H, d, *J* 8.4 Hz, *CH* arom., *binap-4'*), 8.10 (1 H, d, *J* 8.4 Hz, *CH* arom., *binap-4*), 8.17 (1 H, d, *J*

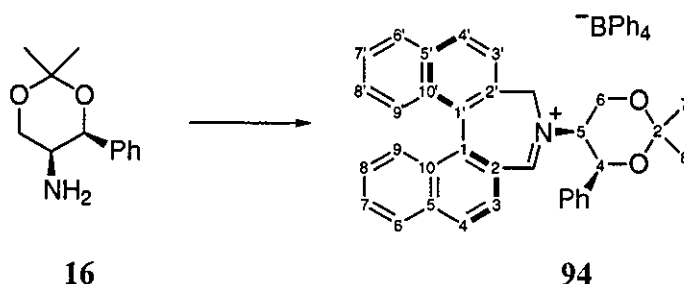
8.4 Hz, CH arom., *binap-6'*), 8.23 (1 H, dd, J 8.4, 2.4 Hz, CH arom., *binap-6*), 9.29 (1 H, s, HC=N); δ_{H} (400 MHz; acetone- d_6) 19.34 (CH₃, C7), 29.69 (CH₃, C8), 57.00 (Ar-CH₂N), 62.26 (CH₂, C6), 68.42 (NCH, C5), 72.94 (Ar-CH, C4), 102.06 (C quat., C2), 120.51 (C quat., arom., *binap-2*), 122.67 (4 x CH arom., *para* in BPh₄ gp.), 126.33 (CH arom., *para* in Ph gp.) 126.40 (8 x CH arom., *ortho* in BPh₄ gp.), 126.58 (C quat., arom., *binap-10*), 127.30 (C quat., arom., *binap-5'*), 128.11 (CH arom., *binap-7'*), 128.15 (CH arom., *binap-8'*), 128.38 (2 x CH arom., *ortho* in Ph gp.), 129.05 (2 x CH arom., *meta* in Ph gp.), 129.19 (2 x CH arom., *binap-7,8*), 129.88 (2 x CH arom., *binap-6,9*), 130.04 (CH arom., *binap-3*), 130.12 (CH arom., *binap-4'*), 130.57 (CH arom., *binap-4*), 130.65 (CH arom., *binap-9'*), 131.70 (CH arom., *binap-6'*), 132.16 (C quat., arom., *binap-10'*), 132.57 (C quat., arom., *binap-5*), 132.92 (CH arom., *binap-3'*), 133.25 (C quat., arom., *binap-2'*), 135.25 (C quat., arom., *binap-1'*), 136.61 (C quat., arom., *binap-1*), 137.43 (8 x CH arom., *meta* in BPh₄ gp.) 142.75 (C quat., arom., *ipso* in Ph gp.), 165.25 (4 x C quat., q , J 196.0 Hz, arom., C-B *ipso* in BPh₄ gp.), 171.37 (HC=N); m/z 484.2275; C₃₄H₃₀NO₂ (cation) requires 484.2277.

(S)-[(4*R*,5*R*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-3*H*-4-azapinium-cyclohepta[2,1-*a*;3,4-*a'*]dinaphthalene tetraphenylborate (*ent-93*):



Prepared according to the general procedure from (–)-(4*R*,5*R*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-amine (*ent-16*) (0.16 g, 0.77 mmol). The product was isolated as yellow plates (0.40 g, 64%), having almost identical spectroscopic data to its enantiomer (**93**): m.p. 109-112 °C (dec.); $[\alpha]_{\text{D}}^{20}$ +95.3 (c 1.01, acetone).

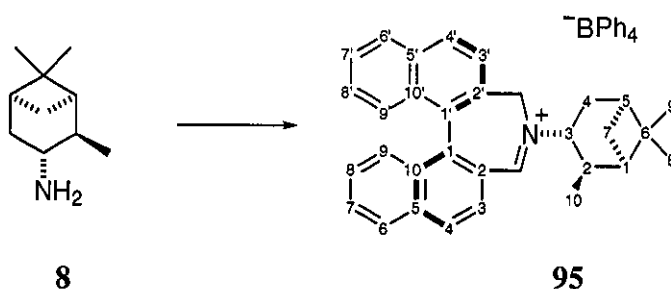
(S)-[(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-3*H*-4-azapinium-cyclohepta[2,1-*a*;3,4-*a'*]dinaphthalene tetraphenylborate (94):



Prepared according to the general procedure from (+)-(4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-amine (**16**) (0.20 g, 0.97 mmol). The product was isolated as yellow plates (0.50 g, 64%); m.p. 218 °C (dec.); $[\alpha]_D^{20} +360.4$ (*c* 1.10, acetone); Found: C, 84.33; H, 6.06; N, 1.64. $C_{58}H_{50}BNO_2 \cdot 1.0H_2O$ requires C, 84.73; H, 6.13; N, 1.71.; $\nu_{\max}(\text{film}) / \text{cm}^{-1}$ 3054, 2998, 1626, 1609, 1579, 1545, 1477, 1458, 1383, 1266, 1201, 1110, 840, 817, 733, 704; $\delta_H(250 \text{ MHz; acetone-}d_6)$ 1.72 (3 H, s, CH_3 , C7), 1.78 (3 H, s, CH_3 , C8), 4.23 (1 H, d, *J* 13.4 Hz, Ar-CHHN), 4.31 (1 H, d, *J* 13.9 Hz, upfield portion of an *ABX* system, N-CHCHH-O, C6, eq.), 4.73 (1 H, dd, *J* 13.8, 3.0 Hz, downfield portion of an *ABX* system, N-CHCHH-O, C6, ax.), 4.90 (1 H, bs, NCH, C5), 5.35 (1 H, d, *J* 13.5 Hz, Ar-CHHN), 5.86 (1 H, d, *J* 2.3 Hz, Ar-CH, C4) 6.76 (4 H, t, *J* 7.1 Hz, 4 x CH arom., *para* in BPh_4 gp.), 6.93 (8 H, t, *J* 7.1 Hz, 8 x CH arom., *ortho* in BPh_4 gp.), 6.90-6.95 (5 H, m, 5 x CH arom., Ph gp.), 7.21 (8 H, m, 8 x CH arom., *meta* in BPh_4 gp.), 7.26-7.33 (3 H, m, 3 x CH arom., *binap*-3',-7',-8), 7.44 (1 H, m, CH arom., *binap*-7), 7.58 (1 H, m, CH arom., *biphenyl*-8'), 7.77 (1 H, m, CH arom., *binap*-3), 7.93 (2 H, dd, *J* 8.6, 2.2 Hz, 2 x CH arom., *binap*-4,-4'), 8.13 (1 H, d, *J* 7.9 Hz, CH arom., *binap*-9'), 8.17 (1 H, d, *J* 8.4 Hz, CH arom., *binap*-6'), 8.29 (2 H, dd, *J* 8.6, 5.3 Hz, CH arom., *binap*-6,-9), 9.30 (1 H, s, HC=N); $\delta_H(400 \text{ MHz; acetone-}d_6)$ 19.13 (CH_3 , C7), 29.75 (CH_3 , C8), 57.29 (Ar- CH_2 N), 61.31 (CH_2 , C6), 67.00 (NCH, C5), 71.47 (Ar-CH, C4), 100.64 (C quat., C2), 115.57 (C quat., arom., *binap*-2), 121.88 (4 x CH arom., *para* in BPh_4 gp.), 125.47 (CH arom., *para* in Ph gp.) 125.66 (8 x CH arom., *ortho* in BPh_4 gp.), 126.47 (C quat., arom., *binap*-10), 126.94 (CH arom., *binap*-7'), 127.04 (CH arom., *binap*-8'), 127.31 (2 x CH arom., *ortho* in Ph gp.), 127.77 (2 x CH arom., *meta* in Ph gp.), 127.88 (2 x CH arom., *binap*-7,-8), 128.13 (2 x CH arom., *binap*-6,-9), 128.67 (C quat., arom., *binap*-5'), 128.87 (CH

arom., *binap-3*), 129.28 (CH arom., *binap-4'*), 129.49 (CH arom., *binap-4*), 130.56 (CH arom., *binap-9'*), 130.89 (CH arom., *binap-6'*), 131.09 (C quat., arom., *binap-10'*), 131.15 (C quat., arom., *binap-5*), 131.98 (C quat., arom., *binap-2'*), 133.42 (CH arom., *binap-3'*), 133.70 (C quat., arom., *binap-1'*), 134.43 (C quat., arom., *binap-1*), 141.08 (C quat., arom., *ipso* in Ph gp.), 163.75 (4 x C quat., q, J 196.0 Hz, arom., C-B *ipso* in BPh₄ gp.), 170.82 (HC=N); m/z 484.2282; C₃₄H₃₀NO₂ (cation) requires 484.2277.

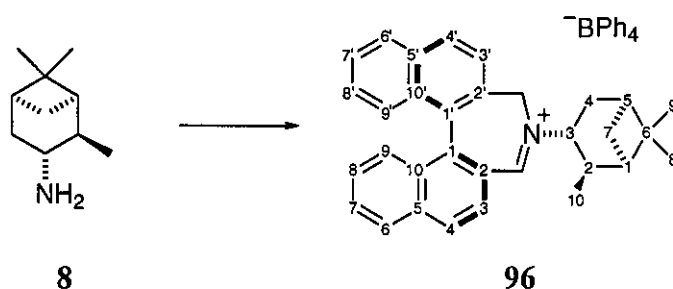
(-)-(R)-6-[(1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]-3H-4-azapinium-cyclohepta[2,1-*a*;3,4-*a'*]dinaphthalene tetraphenylborate (95):



Prepared according to the general procedure from (-)-isopinocampheylamine (8) (0.25 g, 1.6 mmol). The product was isolated as yellow plates (0.82 g, 73%), mp 219-221 °C (dec); $[\alpha]_D^{20}$ -318.8 (c 1.37, acetone); Found: C, 88.22; H, 6.81; N, 1.79%. C₄₈H₄₈BN•0.5H₂O requires C, 88.61; H, 6.91; N, 1.85%; ν_{max} (nujol)/cm⁻¹ 3055, 2997, 1629, 1612, 1588, 1551, 1155, 818, 734, 706; δ_H (400 MHz; acetone-d₆) 1.10 (3 H, s, CCH₃, C8), 1.21 (3 H, d, J 6.8 Hz, CHCH₃, C10), 1.32 (3 H, s, CCH₃, C9), 1.53 (1 H, d, J 10.4 Hz, CH, C1), 2.01-2.08 (1 H, m, CHH, C7), 2.15-2.17 (1 H, m, CHH, C7) 2.42 (1 H, m, CH, C5), 2.63-2.70 (3 H, m, CH, C2, CH₂, C4), 4.80 (1 H, dd, J 13.6, 1.2 Hz, Ar-CHH) 5.06 (1 H, q, J 7.6 Hz, CH, C3), 5.48 (1 H, d, J 14.0 Hz, Ar-CHH) 6.73 (4 H, t, J 8.0 Hz, 4 x CH arom., *para* in BPh₄ gp.), 6.88 (8 H, t, J 8.0 Hz, 8 x CH arom., *ortho* in BPh₄ gp.), 7.06 (1 H, d, J 8.4 Hz, CH arom., *binap-3'*), 7.27 (8 H, t, J 8.0 Hz, 8 x CH arom., *meta* in BPh₄ gp.), 7.45-7.49 (3 H, m, 3 x CH arom., *binap-8,8',7'*), 7.56-7.63 (1 H, m, CH arom., *binap-3*), 7.77-7.80 (1 H, m, CH arom., *binap-7*), 7.99 (1 H, d, J 8.8 Hz, CH arom., *binap-4'*), 8.03 (1 H, d, J 8.4 Hz, CH arom., *binap-4*), 8.08 (1 H, d, J 8.4 Hz, CH arom., *binap-9'*), 8.20 (1 H, d, J 8.4 Hz, CH arom., *binap-6'*), 8.26 (1 H, d, J 8.4 Hz, CH arom., *binap-6*), 8.31 (1 H, d, J 8.4

Hz, CH arom., *binap-9*), 9.62 (1 H, s, HC=N); δ_C (100 MHz; acetone- d_6) 20.32 (CH₃, C8), 23.86 (CH₃, C9), 28.78 (CH₃, C10), 34.07 (CH₂, C7), 35.22 (Ar-CH₂N), 40.64 (C quat., C6), 42.09 (CH, C5), 42.60 (CH, C2), 48.59 (CH, C1), 54.24 (CH₂, C4), 75.64 (CH, C3), 122.69 (4 x CH arom., *para* in BPh₄ gp.), 126.45 (8 x CH arom., *ortho* in BPh₄ gp.), 127.17 (CH arom., *binap-7'*), 127.56 (CH arom., *binap-8'*), 128.15 (C quat., arom., *binap-2*), 128.33 (CH arom., *binap-8*), 128.58 (CH arom., *binap-7*), 129.05 (CH arom., *binap-3*), 129.99 (CH arom., *binap-6'*), 130.07 (C quat., arom., *binap-10*), 130.14 (C quat. arom., *binap-5'*), 130.60 (CH arom., *binap-4*), 130.76 (CH arom., *binap-9'*), 131.64 (CH arom., *binap-6'*), 132.81 (CH arom., *binap-9*), 132.92 (CH arom., *binap-6*), 133.14 (CH arom., *binap-3'*), 133.26 (C quat., arom., *binap-10'*), 135.15 (C quat., arom., *binap-5*), 135.38 (C quat., arom., *binap-2'*), 136.74 (C quat., arom., *binap-1'*), 137.47 (8 x CH arom., *meta* in BPh₄ gp.), 142.81 (C quat., arom. *binap-1*), 165.35 (4 x C quat., arom., J 196.40 Hz, 4 x C-B *ipso* in BPh₄ gp.) 170.77 (HC=N); m/z 430.2540; C₃₂H₃₂N (cation) requires 430.2535.

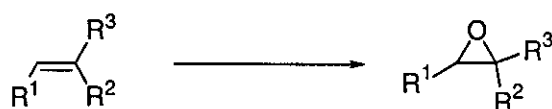
(+)-(S)-6-[(1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]-3H-4-azapinium-cyclohepta[2,1-a;3,4-a']dinaphthalene tetraphenylborate (96):



Prepared according to the general procedure from (–)-isopinocampheylamine (**8**) (0.25 g, 1.6 mmol). The product was isolated as yellow plates (0.82 g, 73%), mp 225–227 °C (dec); $[\alpha]_D^{20} +359.1$ (c 1.31, acetone); Found: C, 88.38; H, 6.86; N, 1.80%. C₄₈H₄₈BN•0.5H₂O requires C, 88.61; H, 6.91; N, 1.85%; ν_{max} (nujol)/cm⁻¹ 3053, 2996, 1627, 1610, 1580, 1549, 1206, 750, 705; δ_H (400 MHz; acetone- d_6) 0.84 (3 H, d, J 4.0 Hz, CHCH₃, C10), 1.13 (3 H, s, CCH₃, C8), 1.32 (3 H, s, CCH₃, C9), 1.51 (1 H, d, J 8.0 Hz, CH, C1), 2.04 (1 H, m, CHH, C7), 2.18 (1 H, m, CHH, C7) 2.35 (1 H, m, CH, C5), 2.67 (1 H, m, CH, C2), 2.78 (2 H, CH₂, C4), 4.80 (1 H, dd, J 13.6, 1.2 Hz, Ar-CHHN) 5.14 (1 H, q, J 7.6 Hz, CH, C3), 5.50 (1 H, d, J 14.0 Hz, Ar-CHHN)

6.74 (4 H, t, J 8.0 Hz, 4 x CH arom., *para* in BPh₄ gp.), 6.89 (8 H, t, J 8.0 Hz, 8 x CH arom., *ortho* in BPh₄ gp.), 7.06 (1 H, d, J 8.4 Hz, CH arom., *binap-3'*), 7.33 (8 H, t, J 8.0 Hz, 8 x CH arom., *meta* in BPh₄ gp.), 7.50 (3 H, m, 3 x CH arom., *binap-8,-8',-7'*), 7.75 (1 H, m, CH arom., *binap-3*), 7.77-7.80 (1 H, m, CH arom., *binap-7*), 7.94 (1 H, d, J 8.8 Hz, CH arom., *binap-4'*), 7.99 (1 H, d, J 8.4 Hz, CH arom., *binap-4*), 8.08 (1 H, d, J 8.4 Hz, CH arom., *binap-9'*), 8.20 (1 H, d, J 8.4 Hz, CH arom., *binap-6'*), 8.24 (1 H, d, J 8.4 Hz, CH arom., *binap-6*), 8.29 (1 H, d, J 8.4 Hz, CH arom., *binap-9*), 9.72 (1 H, s, HC=N); δ_C (100 MHz; acetone-*d*₆) 19.35 (CH₃, C8), 23.36 (CH₃, C9), 28.45 (CH₃, C10), 33.78 (CH₂, C7), 35.05 (Ar-CH₂N), 40.22 (C quat., C6), 41.63 (CH, C5), 42.26 (CH, C2), 48.23 (CH, C1), 54.65 (CH₂, C4), 75.38 (CH, C3), 122.23 (8 x CH arom., *ortho* in BPh₄ gp.), 125.94 (4 x CH arom., *para* in BPh₄ gp.), 125.97 (CH arom., *binap-7'*), 126.00 (CH arom., *binap-8'*), 126.01 (C quat., arom., *binap-2*), 126.03 (CH arom., *binap-8*), 126.38 (CH arom., *binap-7*), 127.87 (CH arom., *binap-3*), 127.93 (CH arom., *binap-6'*), 128.00 (C quat., arom., *binap-10*), 128.04 (C quat. arom., *binap-5'*), 128.07 (CH arom., *binap-4*), 128.57 (CH arom., *binap-9'*), 129.57 (CH arom., *binap-6'*), 129.63 (CH arom., *binap-9*), 130.21 (CH arom., *binap-6*), 130.24 (CH arom., *binap-3'*), 131.19 (C quat., arom., *binap-10'*), 132.33 (C quat., arom., *binap-5*), 137.01 (C quat., arom., *binap-2'*), 137.03 (C quat., arom., *binap-1'*), 137.04 (8 x CH arom., *meta* in BPh₄ gp.), 142.38 (C quat., arom. *binap-1*), 164.90 (4 x C quat., arom., J 196.40 Hz, 4 x C-B *ipso* in BPh₄ gp.), 171.15 (HC=N). m/z 430.2536; C₃₂H₃₂N (cation) requires 430.2535.

General procedure for catalytic asymmetric epoxidation of simple alkenes mediated by iminium salts using Oxone:



To an ice cooled solution of sodium carbonate, (4 equivalents), in water (12 ml per 1.50 g of sodium carbonate), OxoneTM (2 equivalents), was added with stirring and the resulting foaming solution was left to stir for 5-10 minutes, so that most of the initial effervescence subsides. The iminium salt, (10 mol% with respect to the substrate), was then added as a solution in acetonitrile, (6 ml per 1.50 g of sodium carbonate

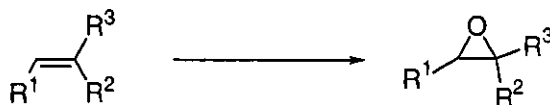
used), followed by the alkene substrate, (1 equivalent, 100 mol%), also as a solution in acetonitrile of the same volume as the solution of the catalyst. The suspension was stirred at the same temperature until the substrate was completely consumed by TLC. The reaction mixture was then diluted with ice cooled diethyl ether (20 ml per 100 mg substrate) and was immediately followed by the addition of the same volume of water. The aqueous phase was washed 4 times with diethyl ether and the organics are combined, washed with brine and dried. Filtration and evaporation of the solvents furnishes a yellow or light brown residue. Column chromatography was then performed typically using ethyl acetate : Light petroleum 1:99 to produce the pure epoxide.

Tetraphenylphosphonium monoperoxysulfate:



OxoneTM triple salt (2 KHSO₅:KHSO₄:K₂SO₄) (15.0 g, 48.8 mmol, w.r.t. KHSO₅) was dissolved in deionised water (300 ml) in a conical flask (1L) and kept under magnetic stirring at 10–15 °C (water bath). To this solution tetraphenylphosphonium chloride (15.0 g, 40.0mmol) in distilled dichloromethane (300 ml) was gradually added over 5 min. After an additional 30 min, stirring was interrupted, the organic layer was separated and solvent was removed under vacuum at room temperature. The crude white salt was then transferred to a fritted glass funnel and washed with distilled water (2 x 75 ml). The solid was dissolved in dichloromethane (180 ml), dried (MgSO₄) and hexane was added until cloudiness develops and the flask was placed in the freezer (–20 °C) overnight, producing a solid white precipitate. *Ca* 85% pure in peroxide, yield 15.4 g, 70%. δ_{H} (250 MHz; CDCl₃) 7.64 (8 H, m, 8 x CH arom.), 7.78 (8 H, m, 8 x CH arom.), 7.89 (4 H, m, 4 x CH arom., *para* to P), 8.92 (1 H, s, OH).

General procedure for catalytic asymmetric epoxidation of simple alkenes mediated by iminium salts using Tetraphenylphosphonium monoperoxysulfate:



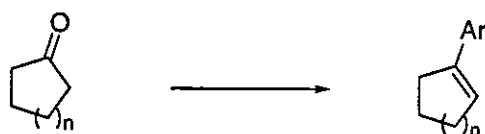
Tetraphenylphosphonium monoperoxy sulfate (2 eq with respect to the substrate) was dissolved in the desired solvent (2 ml per 0.1 g oxidant) and cooled to the required temperature. To this was added the iminium salt as a solution in the solvent (0.5 ml per 0.1 g oxidant). This iminium salt solution was cooled to the same temperature as the solution containing the oxidant and added dropwise over 15-20 min, the temperature of the reaction vessel was monitored to minimize increase in temperature during the addition. The substrate (100 mol%) was also added as a solution in the reaction solvent (0.5 ml per 0.1 g oxidant) in the same manner as the catalyst. The reaction was stirred at the same temperature until the substrate was completely consumed by TLC. Diethyl ether (pre-cooled to the reaction temperature) (20 ml per 0.1 g oxidant) was then added to precipitate the remaining oxidant. The solution was then filtered through Celite. Solvents are removed. Diethyl ether (40 ml) was then added to the brown residue obtained and the solution passed through a short pad of silica (to remove catalyst residues). Solvent was again removed to yield the pure epoxide. If the reaction did not go to completion the epoxide can be separated from the alkene through the use of column chromatography eluting with ethyl acetate/light petroleum 1:99.

General procedure for the formation of authentic racemic epoxides for ee determinations:

The alkene (1 eq.) was dissolved in DCM (10 ml/g) and cooled to 0 °C. *m*-CPBA (2 eq.) was added as a solution also in DCM (10 ml/g, pre-dried over MgSO₄). The reaction was allowed to attain ambient temperature and stirred until complete consumption of the substrate was observed by TLC. The reaction was quenched with the addition of sat. aq. NaHCO₃ (10 ml/g) and the layers separated. The organic layer was washed with sat. NaOH (1.0 M) (10 ml/g) and dried (MgSO₄). Solvents were removed under reduced pressure and analytically pure samples of the epoxides were obtained through column chromatography, typically eluting with ethyl acetate/light petroleum (1:99).

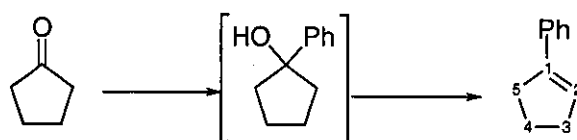
Alkene Synthesis:

General procedure for the formation of 1-aryl-cycloalkenes:



The Cyclo-ketone (1.0 equiv.) in THF (10 ml/g) was cooled to 0 °C and phenylmagnesium bromide (freshly prepared, 2.0 equiv.) was added dropwise over 10 min. The reaction was stirred for 4 h and quenched by addition of sat. aq. ammonium chloride (1 ml/g). Diethyl ether was added reaction mixture, the organics were separated and dried (MgSO_4). Solvents were removed under reduced pressure to yield a crude oil, *ca* 95% pure. The crude product was then dissolved in chloroform (7 ml/g) and cooled to 0 °C. TFA (4 equiv.) was then added in one portion and the reaction stirred for 5 min. The reaction was quenched by dropwise addition of sat. aq. Sodium hydrogen carbonate (10 ml/g). The organic layer was separated and washed with a further portion of sat. aq. Sodium hydrogen carbonate (10 ml/g), brine (10 ml/g) and dried (MgSO_4). Solvents were removed under reduced pressure to yield the desired product.

Cyclopent-1-enyl-benzene (109):

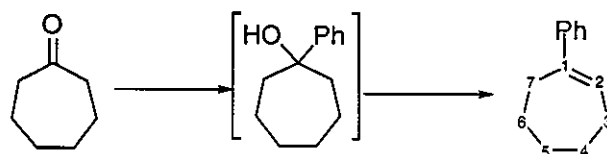


109

Prepared according to the general procedure from cyclopentanone (10.0 g, 120.0 mmol) giving 1-Phenyl-cyclopentene as a pale yellow oil (17.1 g, 99%); $\nu_{\text{max}}(\text{neat})$ / cm^{-1} 3076, 3054, 2953, 2842, 1684, 1597, 1493, 1447, 1179, 1073, 1037, 957, 752, 691; (δ_{H} (250 MHz; CDCl_3) 2.10-2.30 (2 H, m, CH_2 , C4), 2.70-2.78 (2 H, m, CH_2 , C3), 2.87-2.96 (2 H, m, CH_2 , C5), 6.36-6.40 (1 H, m, CH, C2), 7.33-7.70 (5 H, 5 x CH arom., Ph gp.); δ_{C} (62.5 MHz; CDCl_3) 23.87 (CH_2 , C4), 33.67 (CH_2 , C3), 33.88 (CH_2 , C5), 125.99 (2 x CH arom., *ortho* in Ph gp.), 126.37 (CH, C2), 127.24 (CH

arom., *para* in Ph gp.), 128.66 (2 x CH arom., *meta* in Ph gp.), 137.19 (C quat., arom., *ipso* in Ph gp.), 142.85 (C quat., C1).

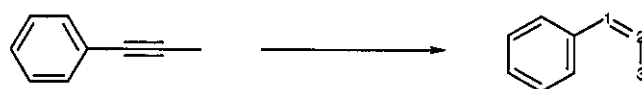
1-Phenyl-cycloheptene (110):¹⁵



110

Prepared according to the general procedure from cycloheptanone (10.0 g, 89.2 mmol) giving 1-Phenyl-cycloheptene as a pale yellow oil (14.9 g, 99%); $\nu_{\max}(\text{film}) / \text{cm}^{-1}$ 3078, 3054, 2926, 2848, 1700, 1596, 1490, 1444, 1354, 1281, 1076, 964, 853, 754, 699; (δ_{H} (400 MHz; CDCl_3) 1.68 (2 H, m, CH_2 , C5), 1.78 (2 H, m, CH_2 , C6), 1.96 (2 H, m, CH_2 , C4), 2.42 (2 H, dd, J 6.4 Hz, CH_2 , C7), 2.74 (2 H, m, CH_2 , C3), 6.22 (1 H, t, J 6.8 Hz, CH, C2), 7.30-7.74 (5 H, 5 x CH arom., Ph gp.); δ_{C} (100 MHz; CDCl_3) 27.26 (CH_2 , C7), 27.39 (CH_2 , C4), 29.30 (CH_2 , C6), 33.22 (CH_2 , C5), 33.24 (CH_2 , C3), 126.09 (2 x CH arom., *ortho* in Ph gp.), 126.67 (CH, C2), 128.54 (2 x CH arom., *meta* in Ph gp.), 130.82 (CH arom., *para* in Ph gp.), 145.41 (C quat. arom., *ipso* in Ph gp.), 145.44 (C quat., C1).

Cis-Propenyl-benzene (111):

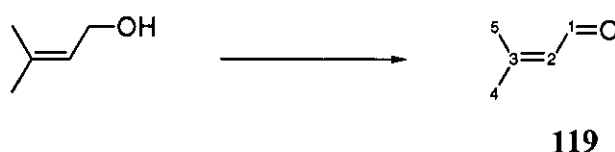


111

Lindlars catalyst (5 % Pd on Calcium Carbonate) (0.10 g), was placed in a Schlenk round bottom flask (150 ml). To this was added 1-phenyl-1-propyne (1.0 g, 8.62 mmol) as a solution in hexane (40 ml). The flask was cooled to 0 °C, evacuated and a balloon of hydrogen added. The reaction was monitored by TLC every 5 min to avoid complete hydrogenation to the alkane. After 20 min TLC showed complete consumption of starting material. The reaction mixture was filtered through a bed of celite and solvents removed under reduced pressure to afford (111) as a volatile

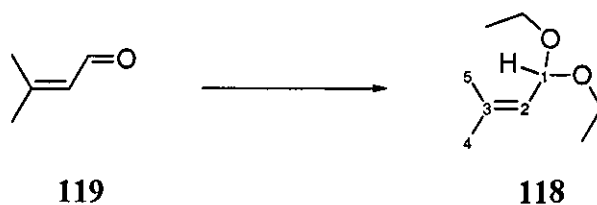
colourless oil (0.88 g, 87 %); $\nu_{\max}(\text{film}) / \text{cm}^{-1}$ 3058, 3018, 2959, 2936, 1600, 1494, 1445, 1367, 913, 766, 697; δ_{H} (250 MHz; CDCl_3) 1.84 (3 H, dd, J 7.2, 1.9 Hz, CH_3 , C3), 5.73 (1 H, dq, J 7.2 Hz, CH, C1) 6.40 (1 H, dq, J 7.2, 1.9 Hz, CH, C2), 7.80-7.28 (5 H, m, 5 x CH arom., Ph gp.); δ_{C} (62.5 MHz; CDCl_3) 15.10 (CH_3 , C3), 126.83 (CH, C2), 127.11 (CH arom., *para* in Ph gp.), 128.56 (2 x CH arom., *meta* in Ph gp.), 129.30 (2 x CH arom., *ortho* in Ph gp.), 130.40 (CH, C1), 138.07 (C quat., arom., *ipso* in Ph gp.).

3-Methyl-but-2-enal (119):



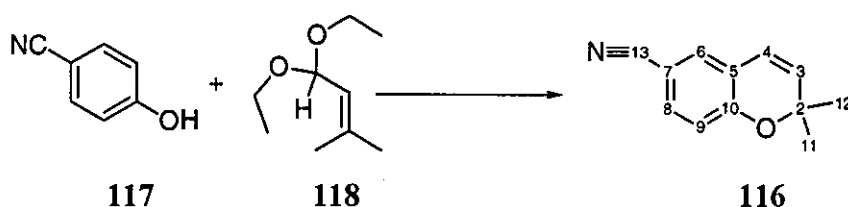
3-Methyl-but-2-en-1-ol (10.0 g, 99.0 mmol) was added to a stirred solution of DCM (140 ml) and PDC (55.6 g, 147.0 mmol). The reaction was stirred at room temperature for 5 h. Hexane (50 ml) was added and the solution filtered through a pad of celite/silica to give the product as a colourless oil, containing a substantial amount of pyridine. The oil was re-dissolved in DCM (75 ml), washed with aq. CuSO_4 solution (50 %) (2 x 50 ml) and dried (MgSO_4). Solvents were removed under reduced pressure to afford (**119**) as a colourless oil; $\nu_{\max}(\text{neat}) / \text{cm}^{-1}$ 2978, 2939, 1684, 1642, 1447, 1256, 1174, 1156; δ_{H} (250 MHz; CDCl_3) 1.99 (3 H, d, J 1.2 Hz, CH_3 , C4), 2.18 (3 H, d, J 1.2 Hz, CH_3 , C5), 5.90 (1 H, dq, J 1.3, 8.2 Hz, CH, C2), 9.95 (1 H, d, 8.2 Hz, CHO, C1); δ_{C} (100 MHz; CDCl_3) 19.27 (CH_3 , C4), 27.60 (CH_3 , C5), 128.51 (CH, C2), 160.95 (C quat., C3), 191.45 (CHO, C1).

1,1-Diethoxy-3-methyl-but-2-ene (118):



To absolute ethanol (23.9 ml, 416.5 mmol) at 4 °C were successively added: triethyl orthoformate (13.9 ml, 83.3 mmol) and 3-methyl-but-2-enal (**119**) (6.00 g, 83.3 mmol). The colourless solution was further cooled to 2 °C and potassium hydrogen sulfate (0.60 g, 4.3 mmol) was added. The solution was allowed to warm to room temperature over 45 min and stirred for a further 15 min. The insoluble material was removed by filtration and washed with ethanol (2 x 5 ml). To the combined filtrate was added potassium carbonate (1.22 g, 8.9 mmol). After stirring for 1 hour the solution was filtered and the solvents removed under reduced pressure to afford the title compound as a colourless oil, which was *ca* 95% pure by ¹H-NMR spectroscopy.

2,2-Dimethyl-2*H*-chromene-6-carbonitrile (**116**):



To a round bottom flask (100 ml), fitted with dean-stark apparatus, was added 1,1-diethoxy-3-methyl-but-2-ene (**118**) (1.79 g, 11.3 mmol), *p*-xylene (20 ml) and 4-cyanophenol (**117**) (1.00 g, 8.4 mmol). The reaction mixture was heated to 120 °C (external temp). After 24 h the reaction was allowed to cool to room temperature and the reaction mixture directly chromatographed, eluting with light petroleum/ethyl acetate (100:0-97:3) affording the title compound as colourless crystals (1.32 g, 63%); m.p. 45-47 °C (lit¹⁶ 47 °C); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3049, 2978, 2934, 2612, 2555, 2225, 1641, 1604, 1570, 1487, 1464, 1368, 1278, 1212, 1170, 961; δ_{H} (400 MHz; CDCl₃) 1.46 (6 H, s, 2 x CH₃, C11,12), 5.70 (1 H, d, *J* 10.0 Hz, CH, C3), 6.28 (1 H, d, *J* 10.0 Hz, CH, C4), 6.79 (1 H, d, *J* 8.4 Hz, CH arom., C9), 7.24 (1 H, m, CH arom., C8), 7.37 (1 H, dd, *J* 8.4, 2.0 Hz, CH, C6); δ_{C} (100 MHz; CDCl₃) 28.73 (2 x CH₃, C11,12), 78.23 (C quat., C2), 104.12 (CH quat. arom., C7), 117.56 (CH arom., C9), 119.63 (CN quat., C13) 121.01 (CH, C4), 122.08 (C quat. arom., C5), 130.47 (CH arom., C6), 132.57 (CH, C3), 133.66 (CH arom., C8), 157.13 (C quat. arom., C10); *m/z* 185.0837; C₁₂H₁₁NO (M⁺) requires 185.0841.

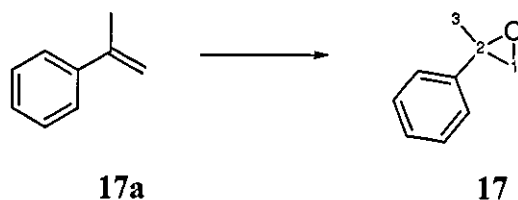
(Z)-Trimethyl-styryl-silane (122):¹⁷



To a solution of DIBAL-H (1.0 M in hexane) (20 ml, 20 mmol) in hexane (20 ml) was added 1-methylpyrrolidine (1.70 g, 20 mmol) at room temperature. After stirring for 5 min 1-phenyl-2-(trimethylsilyl)acetylene (**123**) (3.48 g, 20 mmol) was added. The solution was stirred at 70 °C for 12 h. After the reaction mixture had cooled to room temperature conc. H₂SO₄ (1 ml) was added cautiously, immediately followed by water (20 ml). The layers were separated and the aqueous layer extracted with hexane (2 x 20 ml). The combined organic layers were washed with brine and dried (MgSO₄). Solvents were removed under khrugleroh distillation to give the title compound as a volatile colourless oil (1.94 g, 55%), $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3059, 2958, 2899, 1592, 1571, 1492, 1445, 1246, 1156, 1072, 910; δ_{H} (400 MHz; CDCl₃) 0.00 (9 H, s, 3 x CH₃, Si(CH₃)₃), 5.77 (1 H, d, *J* 15.2 Hz, CH, C2), 7.17-7.27 (5 H, m, 5 x CH arom., Ph gp, C4-8), 7.31 (1 H, d, 15.2 Hz, CH, C2); δ_{C} (100 MHz; CDCl₃) 0.00 (Si(CH₃)₃), 127.13 (CH, C1), 127.71 (2 x CH arom., *ortho* in Ph gp.), 127.93 (2 x CH arom., *meta* in Ph gp.), 132.65 (CH arom., *para* in Ph gp.) 139.91 (C quat., arom., *ipso* in Ph gp.), 146.41 (CH, C2).

The Epoxides:

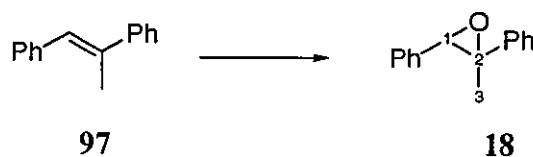
2-Methyl-2-phenyl-oxirane (17):^{7,8}



α-Methylstyrene oxide:¹⁸ Colourless oil; $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3034, 2958, 2929, 2872, 1604, 1496, 1447, 1381, 1343, 1061, 1027, 860, 759, 699; δ_{H} (250 MHz; CDCl₃) 0.86

(3 H, d, J 6.6 Hz, C3), 2.79 (1 H, dd, J 0.8 and 5.4 Hz, HCH, C1_{cis} to Ph gp.), 2.96 (1 H, d, J 5.4 Hz, HCH, C1_{trans} to Ph gp.), 7.24-7.38 (5 H, m, arom., Ph gp.); δ_c (62.5 MHz; CDCl₃) 21.7 (CH₃, C3), 56.7 (C quat., C2), 56.9 (CH₂, C1), 125.2 (2 x CH, arom., *ortho* in Ph gp.), 127.4 (CH, arom., *para* in Ph gp.), 128.3 (2 x CH, arom., *meta* in Ph gp.), 129.0 (C quat., arom., *ipso* in Ph gp.).

2-Methyl-(*E*)-2,3-diphenyloxirane (18):



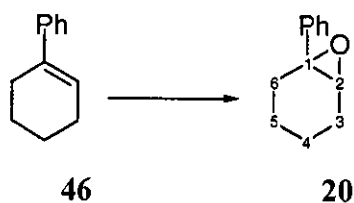
Trans-(α -Methyl)-stilbene oxide:²¹ Colourless oil; ν_{max} (neat)/cm⁻¹ 3061, 1602, 1495, 1449, 1381, 1279, 1157, 1118, 1065, 1027, 980; δ_H (400 MHz; CDCl₃) 1.46 (3 H, s, C3), 3.96 (1 H, s, C1), 7.30-7.46 (10 H, m, arom., 2 x Ph gp.); δ_c (100 MHz; CDCl₃) 17.1 (CH₃, C3), 63.5 (C quat., C2), 67.5 (CH, C1), [125.6, 126.9, 127.7, 127.9, 128.6, 129.2 (10 x CH, arom.), 136.4, 142.8 (2 x C quat., arom.) 2 x Ph gp.].

2,2,3-Triphenyloxirane (19):



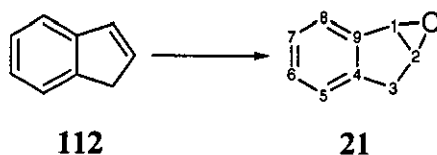
Triphenylethylene oxide:^{19,20} Colourless oil which slowly solidified, mp 66-67 °C, (lit. mp 75 °C); ν_{max} (neat)/cm⁻¹ 3062, 3030, 2957, 2925, 2856, 1605, 1596, 1499, 1471, 1448, 1262, 1221, 741, 698, 621; δ_H (250 MHz; CDCl₃) 4.40 (1 H, m, PhCH), 7.10-7.47 (15 H, m, 3 x Ph gp.); δ_c (62.5 MHz; CDCl₃) 68.0 (CH, PhCH), [68.3 (C quat., Ph₂C), 126.3, 126.8, 127.5, 127.6, 127.7, 127.8 128.0, 128.2, 128.6 (15 x CH, arom.), 135.42, 135.9, 141.1 (3 x C quat., arom.) 3 x Ph gp.].

1-Phenyl-7-oxa-bicyclo[4.1.0]heptane (20):



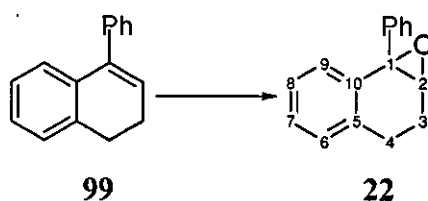
1-Phenylcyclohex-1-ene oxide:²⁰ Colourless oil; $\nu_{max}(\text{neat})/\text{cm}^{-1}$ 3084, 1602, 1495, 1446, 1359, 1249, 1173, 1132, 1079, 1030, 993, 974; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ [1.22-1.35 (1 H, m), 1.53-1.64 (3 H, m), 1.99-2.06 (2 H, m), 2.16-2.18 (1 H, m), 2.26-2.32 (1 H, m), C3, 4, 5 & 6], 3.10 (1 H, t, J 2.0 Hz, CH at C2), 7.28-7.44 (5 H, m, arom., Ph gp.); $\delta_{\text{C}}(62.5 \text{ MHz}; \text{CDCl}_3)$ [19.8, 20.1, 24.7, 28.2 (4 x CH₂, C3, 4, 5 & 6)], 60.1 (C quat., C1), 61.8 (CH, C2) 125.3 (2 x CH arom., *ortho* in Ph gp.), 127.1 (CH arom., *para* in Ph gp.), 128.2 (2 x CH arom., *meta* in Ph gp.), 142.8 (C quat., arom., *ipso* in Ph gp.).

6,6a-Dihydro-1aH-indeno[1,2-b]oxirene (21):



Indene oxide:²¹ Colourless oil; $\nu_{max}(\text{neat})/\text{cm}^{-1}$ 3027, 2917, 1482, 1464, 1390, 1372, 1232, 1183, 1142, 829, 758, 745, 723; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 2.97 (1 H, dd, J 2.7 and 18.1 Hz, HCH, C3 *syn* to C2), 3.21 (1 H, d, J 17.6 Hz, HCH, C3 *anti* to C2), 4.13 (1 H, t, J 3.0 Hz, C2), 4.26 (1 H, dd, J 1.1 and 2.8 Hz, C1), [7.14-7.29 (3 H, m), 7.49 (1 H, dd, J 1.7 and 6.6 Hz) C5, 6, 7 & 8]; $\delta_{\text{C}}(100 \text{ MHz}; \text{CDCl}_3)$ 34.6 (CH₂, C3), 57.6 (CH, C2), 59.1 (CH, C1), 125.2 (CH, arom., C6), 126.1 (CH, arom., C5), 126.3 (CH, arom., C4), 128.6 (CH, arom., C7), 141.0 (C quat., arom., C4), 143.6 (C quat., arom., C9).

7b-Phenyl-1a,2,3,7b-tetrahydro-1-oxa-cyclopropa[a]naphthalene (22):



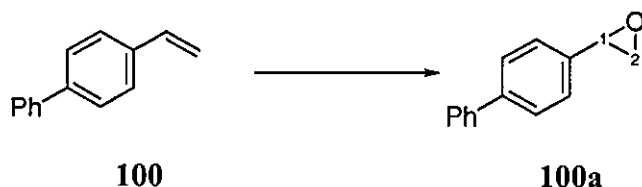
1-Phenyl-3,4-dihydronaphthalene oxide:^{20,22} Pale yellow solid; mp 104-106 °C, (lit.²² mp 94-97 °C); $\nu_{max}(\text{nujol})/\text{cm}^{-1}$ 1602, 1486, 1307, 1155, 1074, 1042, 953; $\delta_{\text{H}}(250 \text{ MHz; CDCl}_3)$ 2.10 (1 H, td, J 5.8 and 13.7 Hz, HCH, C3), 2.49-2.60 (1 H, m, HCH, C4), 2.77 (1 H, dd, J 5.6 and 15.5 Hz, HCH, C3), 2.98-3.06 (1 H, m, HCH, C4), 3.71 (1 H, d, J 3.1 Hz, C2), [7.11-7.31 (4 H, m, arom.), 7.45-7.61 (5 H, m, arom.), 9 x CH at C6, 7, 8, 9 & Ph gp.]; $\delta_{\text{C}}(62.5 \text{ MHz; CDCl}_3)$ 22.1 (CH₂, C4), 25.4 (CH₂, C3), 60.9 (C quat., C1), 63.0 (CH, C2) [126.0, 127.7, 127.9, 128.1, 128.2, 128.6, 129.8 (9 x CH, arom.), 135.0, 137.5, 138.8 (3 x C quat., arom.), C5, 6, 7, 8, 9, 10 & Ph gp.].

(*E*)-2,3-Diphenyloxirane (75):^{7,8}



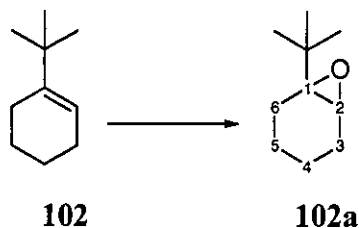
Trans-stilbene oxide:^{20,23} Colourless solid; mp 66-67 °C, (lit.²³ mp 61-63 °C). $\nu_{max}(\text{nujol})/\text{cm}^{-1}$ 1601, 1492, 1284, 1176, 1157, 1094, 1072, 1025; $\delta_{\text{H}}(400 \text{ MHz; CDCl}_3)$ 3.84 (2 H, s, 2 x PhCH-O), 7.28-7.37 (10 H m, arom., 2 x Ph gp.); $\delta_{\text{C}}(100 \text{ MHz; CDCl}_3)$ 63.3 (2 x CH, 2 x PhCH-O), 126.0 (4 x CH, arom., *ortho* in 2 x Ph gp.), 128.6 (2 x CH, arom., *para* in 2 x Ph gp.), 129.3 (4 x CH, arom., *meta* in 2 x Ph gp.), 137.6 (2 x C quat., arom., *ipso* in 2 x Ph gp.).

2-Biphenyl-4-yl-oxirane (100a):



para-Phenylstyrene oxide:²⁶ Colourless solid; mp 94-96 °C, (lit.²⁴ mp 115-117 °C). δ_{H} (400 MHz; CDCl_3) 2.85 (1 H, dd, J 2.6 and 5.5 Hz, C2), 3.91 (1 H, dd, J 2.5 and 4.0 Hz, C1), 7.30-7.68 (9 H, m, arom., 2 x Ph gp.); δ_{C} (100 MHz; CDCl_3) 51.2 (CH, C2), 52.2 (C quat., C3), 126.0, 127.1, 127.3, 127.4, 128.8 (9 x CH, arom., BiPh gp.), 136.6, 140.7, 141.2 (3 x C quat., arom., BiPh gp.).

1-*tert*-Butyl-7-oxa-bicyclo[4.1.0]heptane (102a):



1-*tert*-Butyl-cyclohex-1-ene oxide: Colourless oil; ν_{max} (nujol)/ cm^{-1} 2938, 2868, 1481, 1433, 1363, 1036, 921, 767; δ_{H} (250 MHz; CDCl_3) 0.73 (9 H, s, $\text{C}(\text{CH}_3)_3$), 0.91-1.10 (2 H, m, CH_2 , C4), 1.12-1.36 (2 H, m, CH_2 , C5), 1.46-1.61 (2 H, m, CH_2 , C6), 1.64-1.81 (2 H, CH_2 , C3), 2.91-2.93 (1 H, m, CH, C2); δ_{C} (62.5 MHz; CDCl_3) 19.69 (CH_2 , C5), 21.09 (CH_2 , C4), 24.82 (CH_2 , C6), 25.29 (CH_2 , C3), 25.53 (3 x CH_3 , $\text{C}(\text{CH}_3)_3$), 44.77 (C quat., $\text{C}(\text{CH}_3)_3$), 55.16 (CH, C2), 64.66 (C quat., C1).

1a,2,3,7b-Tetrahydro-1-oxa-cyclopropa[*a*]naphthalene (103a):



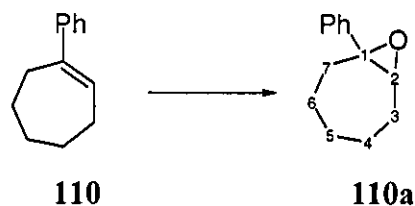
1,2-Dihydronaphthylene oxide:²⁶ Colourless oil; $\nu_{max}(\text{neat})/\text{cm}^{-1}$ 3059, 3028, 2930, 2850, 1602, 1493, 1316, 1129, 1088, 1030, 964; $\delta_{\text{H}}(400 \text{ MHz}; \text{CDCl}_3)$ 1.67 (1 H, m, HCH at C3), 2.33 (1 H, m, HCH at C3), 2.45 (1 H, dd, J 15.6, 5.6 Hz, HCH, C4), 2.67 (1 H, m, HCH, C4), 3.65 (1 H, t, J 4.0 Hz, CH, C2), 3.78 (1 H, d, J 4.4 Hz, CH, C1), 7.01 (1 H, d, J 7.2 Hz, CH arom., C6), 7.17 (2 H, m, CH arom., C7, 8), 7.33 (1 H, d, J 7.2 Hz, CH arom., C9); $\delta_{\text{C}}(100 \text{ MHz}; \text{CDCl}_3)$ 22.19 (C4), 24.78 (C3), 55.16 (C1), 55.52 (C2), 126.51 (CH arom., C6), 128.80 (CH arom., C7), 128.83 (CH arom., C8), 129.94 (CH arom., C9), 132.91 (C quat., arom., C5), 137.07 (C quat., arom., C10).

(3-Phenyl-oxiranyl)-methanol (104a):



Trans-Cinnamyl alcohol oxide:²⁵ Colourless solid; $\nu_{max}(\text{neat})/\text{cm}^{-1}$ 3322, 3266, 2863, 1664, 1494, 1449, 1091, 1007, 733; $\delta_{\text{H}}(400 \text{ MHz}; \text{CDCl}_3)$ 1.92 (1 H, s, OH), 3.22 (1 H, ddt, J 0.1, 2.0 and 3.8 Hz, HCH, C3), 3.80 (1 H, dd, J 3.8 and 12.7 Hz, HCH, C3), 3.93 (1 H, d, J 2.1 Hz, C1), 4.02-4.08 (1 H, dd, J 2.3 and 12.7 Hz, C2), 7.26-7.41 (5 H, m, arom., Ph gp.); $\delta_{\text{C}}(100 \text{ MHz}; \text{CDCl}_3)$ 55.7 (CH, C1), 61.3 (CH, C2), 62.6 (CH, C3), 125.8, 128.3, 128.5 (5 x CH, arom., Ph gp.), 136.7 (C quat., arom., *ipso* in Ph gp.).

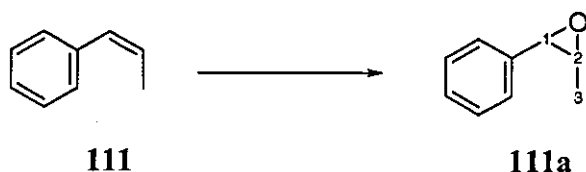
1-Phenyl-8-oxa-bicyclo[5.1.0]octane (110a):



1-Phenylcyclohept-1-ene oxide: Colourless oil; $\nu_{max}(\text{neat})/\text{cm}^{-1}$ 3084, 1602, 1494, 1445, 1358, 1255, 1166, 1128, 1088, 1030, 964, 855, 738; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 1.50-1.85 (6 H, m, 3 x CH_2 , C4, 5, 6), 1.90-2.20 (2 H, m, CH_2 , C3), 2.38-2.50 (2 H, m,

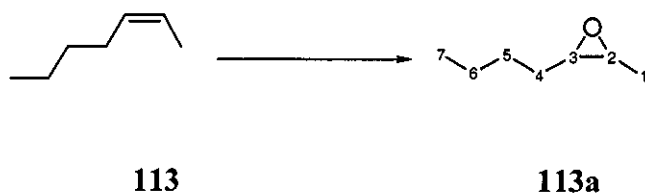
CH₂, C7), 3.04 (1 H, q, *J* 3.8 Hz, CH, C2), 7.25-7.40 (5 H, m, 5 x CH arom., Ph gp.); δ_C (62.5 MHz; CDCl₃) 24.90 (CH₂, C6), 25.47 (CH₂, C4), 29.85 (CH₂, C3), 31.69 (CH₂, C5), 33.87 (CH₂, C7), 63.38 (CH, C2), 65.78 (C quat., C1), 125.38 (2 x CH arom., *ortho* in Ph gp.), 127.25 (CH arom., *para* in Ph gp.), 128.45 (2 x CH arom., *meta* in Ph gp.), 143.97 (C quat., arom., *ipso* in Ph gp.).

(Z)-2-Methyl-3-phenyl-oxirane (111a):



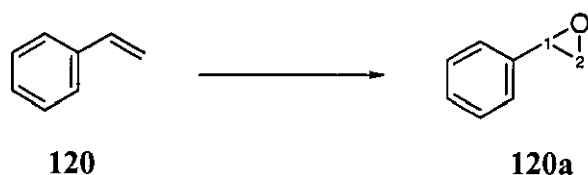
Cis-β-methylstyrene oxide:²⁶ Colourless oil; ν_{max} (neat)/cm⁻¹ 3061, 2994, 1604, 1496, 1450, 1258, 1149, 9563, 853, 742, 700, 619; δ_H (250 MHz; CDCl₃) 1.12, (3 H, d, *J* 5.4 Hz, CH₃, C3), 3.32-3.40 (1 H, m, CH, C2), 4.08 (1 H, d, *J* 4.3 Hz, CH, C1), 7.24-7.39 (5 H, m, 5 x CH arom., Ph gp.); δ_C (62.5 MHz; CDCl₃) 12.84 (CH₃, C3), 55.37 (CH, C2), 57.78 (CH, C1), 126.85 (2 x CH arom., *ortho* in Ph gp.), 127.74 (CH arom., *para* in Ph gp.), 128.26 (2 x CH arom., *meta* in Ph gp.), 135.84 (C quat., arom., *ipso* in Ph gp.).

(Z)-2-Methyl-3-butyloxirane (113a):



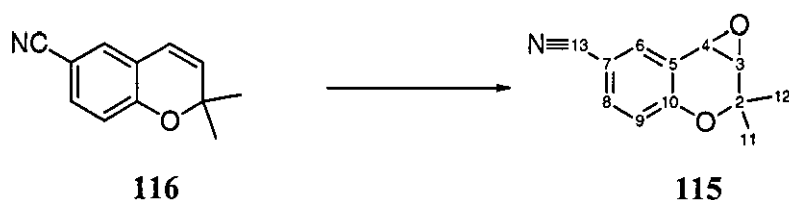
Cis-2,3-Epoxyheptene:²⁷ Colourless oil, 68% yield; ν_{max} (neat)/cm⁻¹ 2959, 2930 2874, 1390, 1259, 1218, 1151, 1114, 1032, 752; δ_H (400 MHz; CDCl₃) 0.93 (3 H, t, *J* 8.0 Hz, C7), 1.20 (3 H, d, *J* 4.0 Hz, C1), 1.32-1.50 (6 H, m, C4, 5 & 6), 2.86-2.91 (1 H, m, C3), 2.99-3.06 (1 H, m, C2); δ_C (100 MHz; CDCl₃) 12.2 (CH₃, C7), 13.0 (CH₃, C1), 21.6 (CH₂, C6), 26.2 (CH₂, C5), 27.6 (CH₂, C4), 51.6 (CH, C2), 56.1 (CH, C3).

2-Phenyl-oxirane (120a):



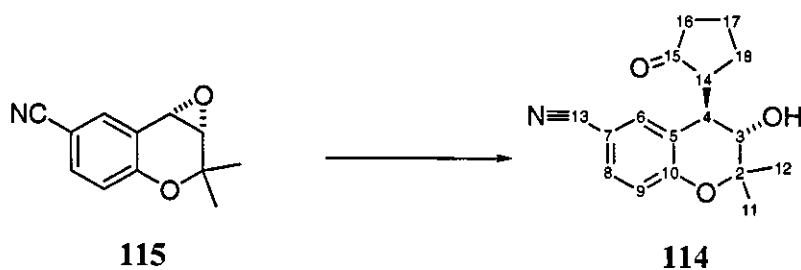
Styrene oxide.²⁶ Colourless oil; $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3037, 2987, 1606, 1496, 1476, 1451, 1387, 1252, 1201, 984, 876, 751, 698; $\delta_{\text{H}}(400 \text{ MHz}; \text{CDCl}_3)$ 2.84 (1 H, dd, J 2.8, 5.6 Hz, CHH, C3), 3.18 (1 H, dd, J 4.0 and 5.6 Hz, CHH, C2), 3.90 (1 H, dd, J 2.4, 4.0 Hz, CH, C1) 7.36 (5 H, m, 5 x CH arom., Ph gp.); $\delta_{\text{C}}(100 \text{ MHz}; \text{CDCl}_3)$ 51.65 (C2), 52.77 (C1), 125.91 (2 x CH arom., *meta* in Ph gp.), 128.61 (C quat., arom., *para* in Ph gp.), 128.71 (2 x CH arom., *ortho* in Ph gp.), 138.02 (C quat., arom., *ipso* in Ph gp.).

(-)-3*S*,4*S*-2,2-Dimethyl-1*a*,7*b*-dihydro-2*H*-1,3-dioxo-cyclopropa[*a*]naphthalene-6-carbonitrile (115):



Prepared according to the TPPP general epoxidation procedure in 59% yield, 97% ee. Colourless oil which solidified: $[\alpha]_{\text{D}}^{20} -59.5$ (c 1.09, CHCl_3), $[\text{lit}^{28} +62.7$ (c 0.71, CHCl_3) for (+)-3*R*,4*R* enantiomer]; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3089, 3038, 2979, 2934, 2226, 1615, 1579, 1490, 1346, 1279, 1157, 1107, 1046, 955; $\delta_{\text{H}}(400 \text{ MHz}; \text{CDCl}_3)$ 1.22 (3 H, s, CH_3 , C11), 1.52 (3 H, s, CH_3 , C11), 3.47 (1 H, d, J 4.4 Hz, CH, C3), 3.86 (1 H, d, J 4.4 Hz, CH, C4), 6.79 (1 H, d, J 8.4 Hz, CH arom., C9), 7.45 (1 H, dd, J 2.0, 8.4 Hz, CH arom., C8), 7.58 (1 H, d, J 2.4 Hz, CH arom., C6); $\delta_{\text{C}}(100 \text{ MHz}; \text{CDCl}_3)$ 23.41 (C11), 25.88 (C12), 50.26 (C4), 62.69 (C3), 75.07 (C quat., C2), 104.65 (C quat., arom., C7), 118.97 (C quat., C13), 119.15 (CH arom., C9), 121.51 (C quat., arom., C5), 134.21 (CH arom., C8), 134.80 (CH arom., C6), 156.87 (C quat., arom., C10); m/z 219.1132; $\text{C}_{12}\text{H}_{11}\text{NO}_2$ (M^+NH_4) requires 219.1134.

(-)-(3*S*,4*R*)-3-Hydroxy-2,2-dimethyl-4-(2-oxo-cyclopentyl)-chroman-6-carbonitrile (114):



Pyrrolidin-2-one (2.12 g, 2.49 mmol) was treated with NaH (60 %) (0.06 g, 2.49 mmol) and (-)-3*S*, 4*S*-2,2-Dimethyl-1*a*,7*b*-dihydro-2*H*-1,3-dioxo-cyclopropa[*a*]naphthalene-6-carbonitrile (**115**) (0.50 g, 2.49 mmol) in DMSO (20 ml). The reaction was left to stir and after 6 h cautiously quenched with water and extracted with ethyl acetate (3 x 50 ml). The organic layer was washed with water (2 x 30 ml), brine (30 ml) and dried (MgSO₄). Solvents were removed under reduced pressure to give a pale yellow oil. Purified by column chromatography eluting with hexane/ethyl acetate. Crystallized from ethanol, colourless crystals (0.37 g, 52%); m.p. 237-240 °C (lit²⁹ 242-244 °C); [α]_D²⁰ -53.1 (c 1.12, CHCl₃), [lit [α]_D²⁶ -52.2 (c 1.00, CHCl₃)]; ν_{max}(film)/cm⁻¹ 3229, 2975, 2222, 1650; δ_H(250 MHz; CDCl₃) 1.28 (CH₃, C11), 1.55 (CH₃, C12), 2.07-2.17 (2 H, m, CH₂, C17), 2.55-2.61 (2 H, m, CH₂, C16), 3.00-3.09 (1 H, m, CHH, C18), 3.36-3.43 (1 H, m, CHH, C18), 3.67-3.78 (2 H, m, OH & CH, C3), 5.23 (1 H, d, *J* 10.4 Hz, CH, C4), 6.88 (1 H, d, *J* 8.6 Hz, CH arom., C6), 7.24 (1 H, t, *J* 1.9 Hz, CH arom., C8), 7.45 (1 H, dd, *J* 8.5, 2.0 Hz, CH arom., C9); δ_C(62.5 MHz; CDCl₃) 18.39 (CH₂, C17), 18.73 (CH₃, C11), 26.97 (CH₃, C12), 42.38 (CH, C4), 51.95 (CH₂, C18), 69.99 (C quat., C2), 80.78 (CH, C3), 104.16, (C quat., arom., C7), 118.90 (CH arom., C9), 119.25 (C quat., CN), 121.08 (C quat., arom., C5), 131.87 (CH arom., C8), 133.27 (CH arom., C8), 157.65 (C quat., C10), 178.23 (C quat., C=O).

3.4 Chapter Three References

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Appendix A

X-Ray Reports

Appendix A

X-ray Reports

The crystallographic data for the structures presented in the text are given in this section. Crystallographic analyses were carried out at Loughborough University by Professor V. McKee (68), Dr M. R. J. Elsegood (58, 79) and Dr A. M. Z. Slawin (14, 16).

Crystal data and structure refinement for (-)-(1*R*,2*R*,3*R*,5*S*)-N-(3-isopinocampheyl)-dihydroisoquinolinium tetraphenylborate (14):

Data collection method	Rigaku AFC7S diffractometer
Empirical formula	C ₄₃ H ₄₆ BN
Formula weight	587.65
Temperature	20.0 °C
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
Unit cell dimensions	a = 16.807(5) Å b = 19.921(3) Å c = 10.161(2) Å
Volume	3402.0(1) Å ³
Z	4
Density (calculated)	1.147 g/cm ³
Absorption coefficient	4.83 cm ⁻¹
F(000)	1264.00
Crystal size	0.10 x 0.20 x 0.50 mm ³
Crystal description	Clear, block
Theta range for data collection	65.7 to 74.8°.
Reflections collected	2892
Absorption correction	Lorentz-polarization absorption
Refinement method	Direct methods (SIR92)

Data / restraints / parameters	2279 / 407 / 5.60
Goodness-of-fit on F^2	2.77
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.038$, $wR_2 = 0.035$
Largest diff. peak and hole	0.17 and $-0.16 \text{ e.}\text{\AA}^{-3}$

Crystal data and structure refinement for (+)-2-[(4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-3,4-dihydroisoquinolinium tetraphenylborate (**16**):

Data collection method	Rigaku AFC7S diffractometer	
Empirical formula	$\text{C}_{45}\text{H}_{44}\text{BNO}_2$	
Formula weight	641.47	
Temperature	20.0 °C	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	$a = 9.37(1) \text{ \AA}$	
	$b = 22.104(8) \text{ \AA}$	$\beta = 92.84(7)^\circ$
	$c = 9.457(5) \text{ \AA}$	
Volume	$1957.0(3) \text{ \AA}^3$	
Z	2	
Density (calculated)	1.188 g/cm^3	
Absorption coefficient	5.60 cm^{-1}	
$F(000)$	748.00	
Crystal size	$0.20 \times 0.20 \times 0.30 \text{ mm}^3$	
Crystal description	Pale, prism	
Theta range for data collection	60.6 to 73.9°.	
Reflections collected	3210	
Independent reflections	3010 [$R(\text{int}) = 0.134$]	
Absorption correction	Lorentz-polarization absorption	
Refinement method	Direct methods (SnB)	
Data / restraints / parameters	1914 / 479 / 4.00	
Goodness-of-fit on F^2	4.16	
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.059$, $wR_2 = 0.045$	
Largest diff. peak and hole	0.17 and $-0.15 \text{ e.}\text{\AA}^{-3}$	

Crystal data and structure refinement for (+)-{(4*S*,5*S*)-2,2-dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-yl}-3,4-dihydroisoquinolinium tetraphenylborate (**58**):

Data collection method	Bruker SMART 1000 CCD diffractometer ω rotation with narrow frames
Empirical formula	C ₄₆ H ₄₆ BNO ₄ S
Formula weight	719.71
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	tetragonal, P4 ₁
Unit cell dimensions	a = 9.9705(4) Å $\alpha = 90^\circ$. b = 9.9705(4) Å $\beta = 99.005(2)^\circ$. c = 38.749(2) Å $\gamma = 90^\circ$.
Volume	3852.0(3) Å ³
Z	4
Density (calculated)	1.241 g/cm ³
Absorption coefficient	0.129 mm ⁻¹
F(000)	1528
Crystal size	0.51 x 0.36 x 0.30 mm ³
Crystal description	Pale yellow
Theta range for data collection	2.04 to 28.74°.
Index ranges	-13 ≤ h ≤ 13, -13 ≤ k ≤ 13, -51 ≤ l ≤ 51
Reflections collected	32885
Independent reflections	9155 [R(int) = 0.0241]
Completeness to theta = 25.00°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.937 and 0.962
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	9155 / 309 / 563
Goodness-of-fit on F ²	1.049
Final R indices [I > 2σ(I)]	R1 = 0.0410, wR2 = 0.1021
R indices (all data)	R1 = 0.0459, wR2 = 0.1053
Absolute structure parameter	-0.07(6)

Largest diff. peak and hole 0.257 and -0.237 e.Å⁻³

Crystal data and structure refinement for Methyl (4*S*,5*R*)-5-[4-(methoxy)phenyl]-2-oxo-1,3-oxazolan-4-carboxylate (**68**):

Data collection method	Bruker SMART 1000 CCD diffractometer ω rotation with narrow frames
Empirical formula	C ₁₂ H ₁₃ NO ₅
Formula weight	251.23
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 7.0103(8) Å $\alpha = 90^\circ$ b = 5.5734(6) Å $\beta = 99.005(2)^\circ$ c = 15.6004(18) Å $\gamma = 90^\circ$
Volume	602.01(12) Å ³
Z	2
Density (calculated)	1.386 Mg/m ³
Absorption coefficient	0.109 mm ⁻¹
F(000)	264
Crystal size	0.41 x 0.09 x 0.08 mm ³
Crystal description	Colourless needle
Theta range for data collection	2.64 to 28.44°.
Index ranges	-8 ≤ h ≤ 9, -7 ≤ k ≤ 7, -20 ≤ l ≤ 20
Reflections collected	5035
Independent reflections	2684 [R(int) = 0.0122]
Completeness to theta = 25.00°	99.8 %
Absorption correction	Multiscan
Max. and min. transmission	1.00000 and 0.956062
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	2684 / 1 / 166
Goodness-of-fit on F ²	1.033
Final R indices [I > 2σ(I)]	R1 = 0.0315, wR2 = 0.0744
R indices (all data)	R1 = 0.0356, wR2 = 0.0766
Absolute structure parameter	0.2(8)
Largest diff. peak and hole	0.231 and -0.158 e.Å ⁻³

Crystal data and structure refinement for (+)-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 (79):

Data collection method	Bruker SMART 1000 CCD diffractometer ω rotation with narrow frames
Empirical formula	C ₄₈ H ₄₈ N
Formula weight	649.68
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
Unit cell dimensions	a = 12.8066(7) Å $\alpha = 90^\circ$ b = 15.5040(8) Å $\beta = 90^\circ$ c = 18.5443(10) Å $\gamma = 90^\circ$
Volume	3682.0(3) Å ³
Z	4
Density (calculated)	1.172 g/cm ³
Absorption coefficient	0.066 mm ⁻¹
F(000)	1392
Crystal size	0.78 x 0.61 x 0.49 mm ³
Crystal description	Colourless
Theta range for data collection	1.93 to 29.03°.
Index ranges	-16 ≤ h ≤ 17, -19 ≤ k ≤ 20, -24 ≤ l ≤ 23
Reflections collected	32341
Independent reflections	8865 [R(int) = 0.0387]
Completeness to theta = 25.00°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.950 and 0.968
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	8865 / 0 / 454
Goodness-of-fit on F ²	1.052
Final R indices [I > 2σ(I)]	R1 = 0.0363, wR2 = 0.0843
R indices (all data)	R1 = 0.0451, wR2 = 0.0908
Absolute structure parameter	-2(2)
Largest diff. peak and hole	0.218 and -0.171 e.Å ⁻³

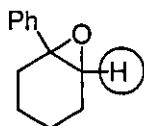
Appendix B

Epoxidation Data

Appendix B

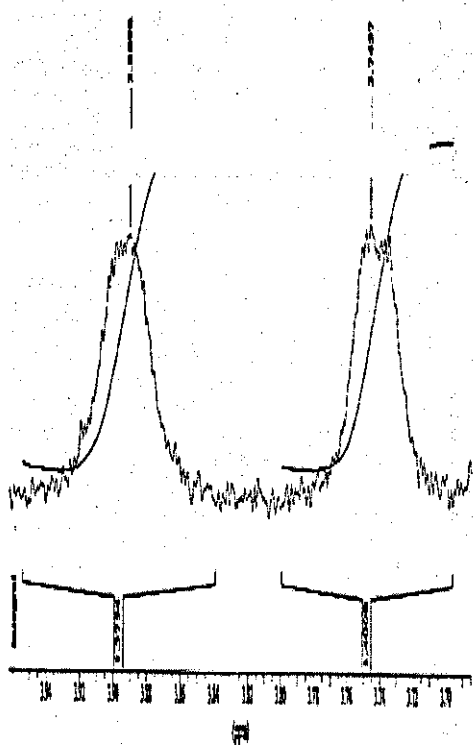
Determination of enantiomeric excess: Examples

Determination of enantiomeric excess for 1-Phenyl-7-oxa-bicyclo[4.1.0]heptane (**20**):

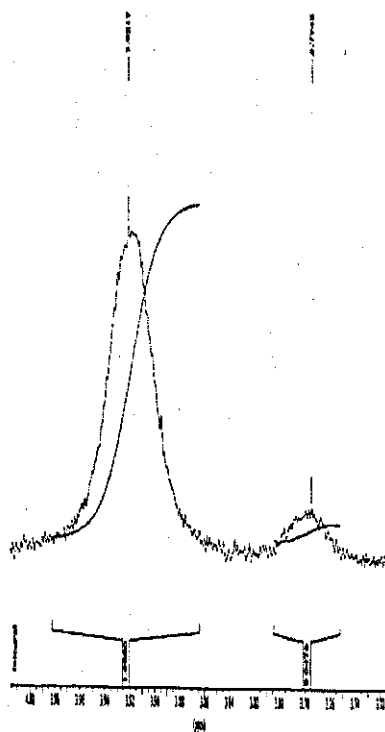


$^1\text{H-NMR}$ conditions: 8-10 mg substrate
 3-5 mg (+)-Eu(hfc)₃

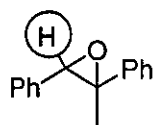
Racemic:



Enantiomerically enriched:



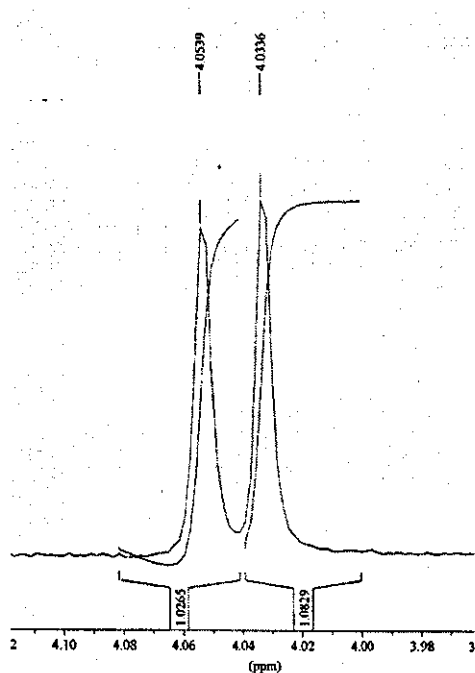
Determination of enantiomeric excess for 2-Methyl-(*E*)-2,3-diphenyloxirane (**18**):



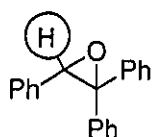
¹H-NMR conditions: 8-10 mg substrate
3-5 mg (+)-Eu(hfc)₃

Racemic:

Enantiomerically enriched:

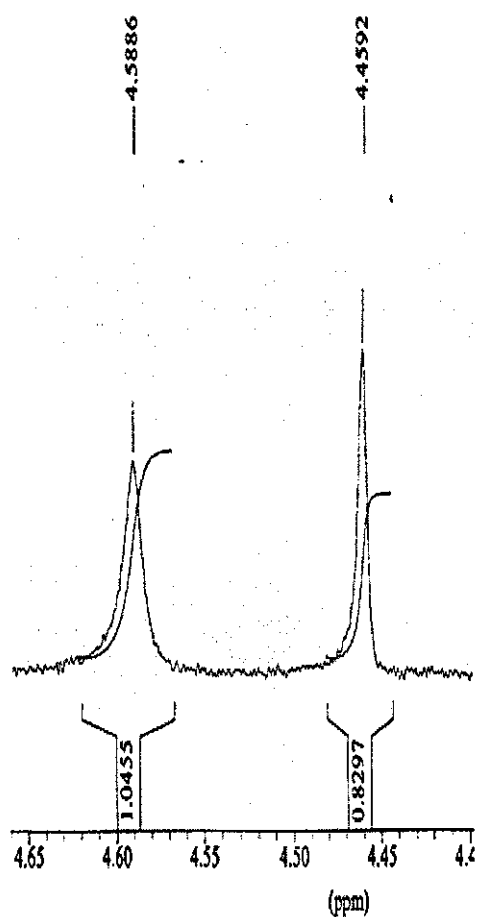


Determination of enantiomeric excess for 2,2,3-Triphenyloxirane (**19**):

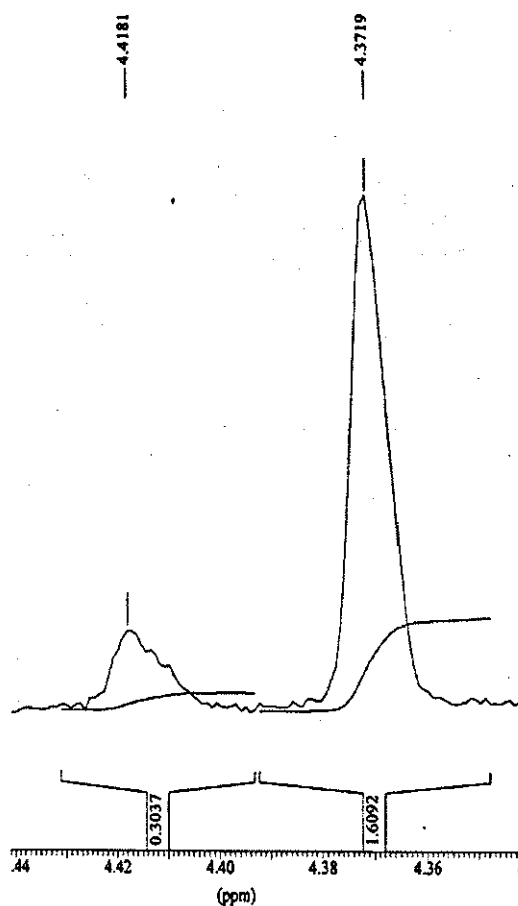


¹H-NMR conditions: 8-10 mg substrate
3-5 mg (+)-Eu(hfc)₃

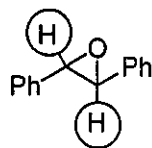
Racemic:



Enantiomerically enriched:

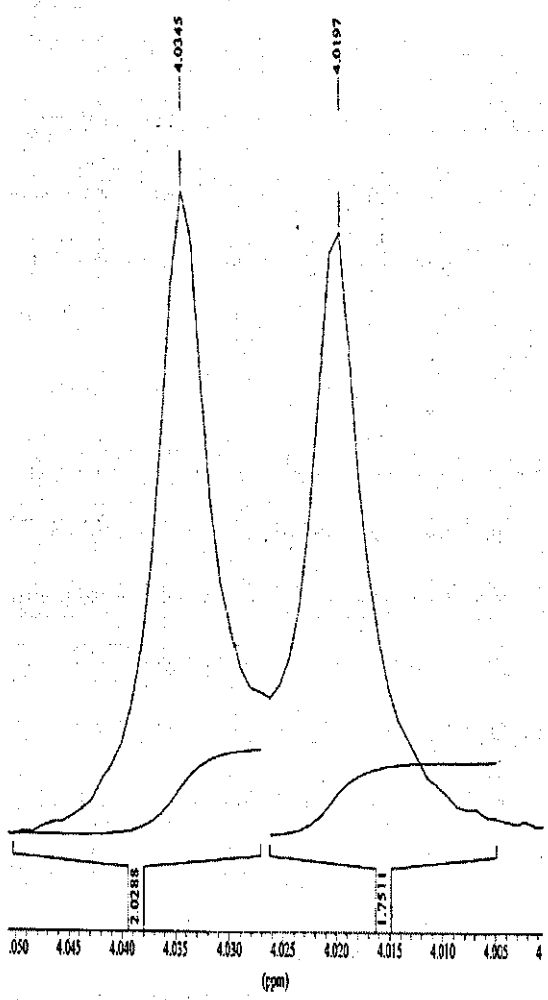


Determination of enantiomeric excess for (*E*)-2,3-Diphenyloxirane (**75**):

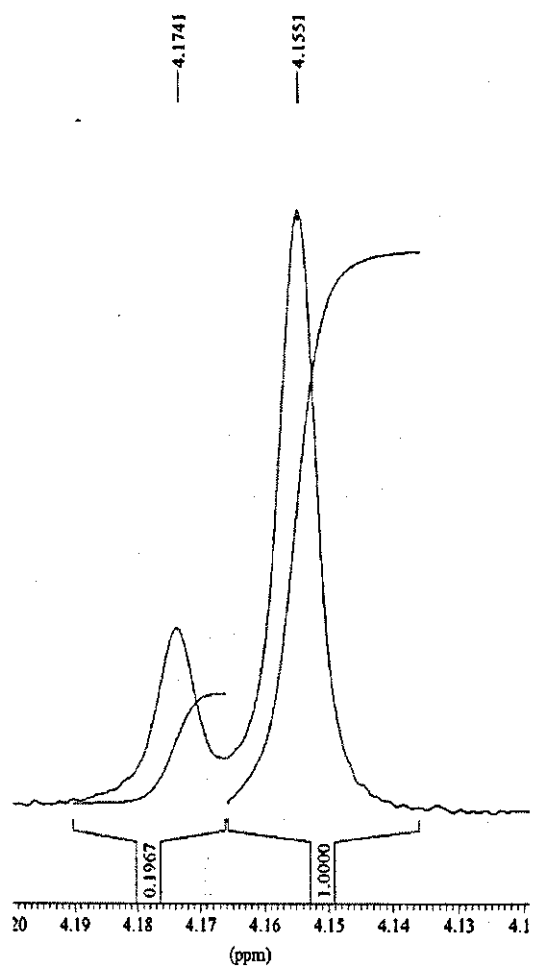


¹H-NMR conditions: 8-10 mg substrate
3-5 mg (+)-Eu(hfc)₃

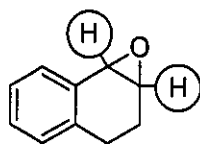
Racemic:



Enantiomerically enriched:



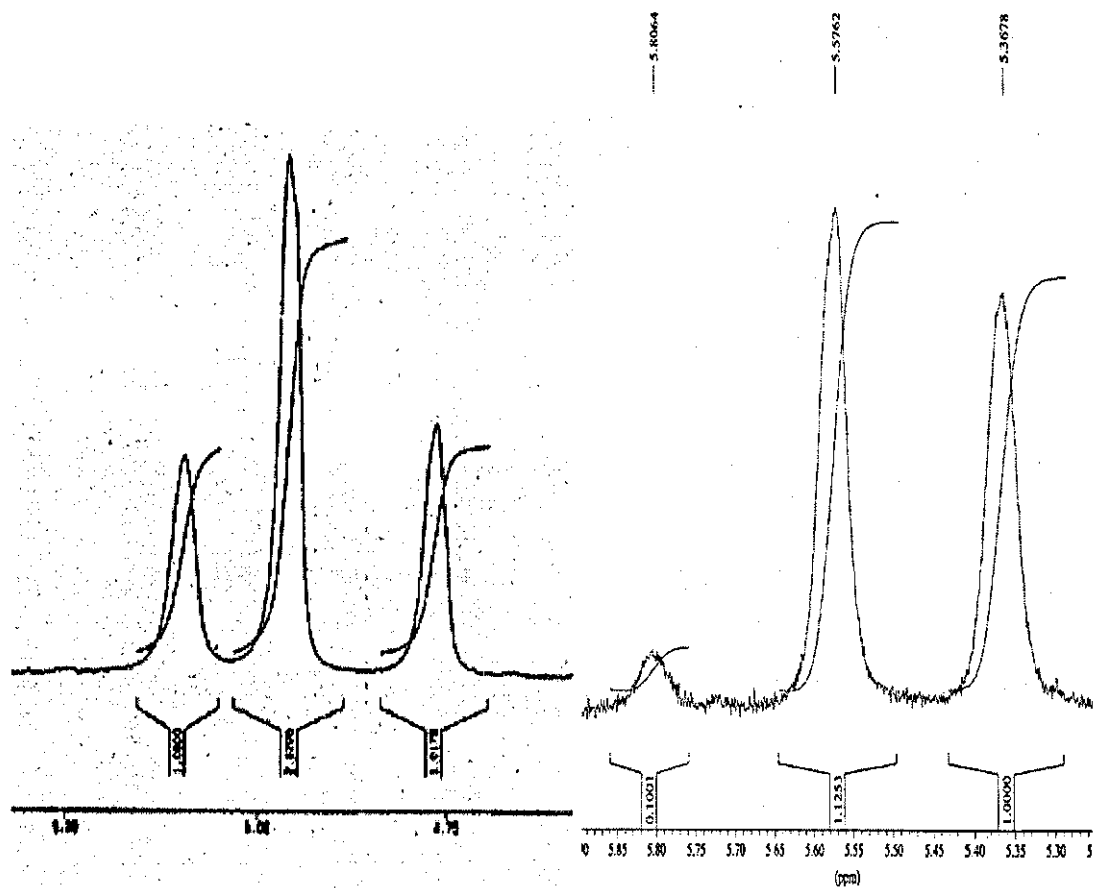
Determination of enantiomeric excess for 1a,2,3,7b-Tetrahydro-1-oxa-cyclopropa[a]naphthalene (**103a**):



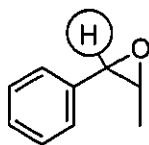
$^1\text{H-NMR}$ conditions: 8-10 mg substrate
3-5 mg (+)-Eu(hfc)₃

Racemic:

Enantiomerically enriched:

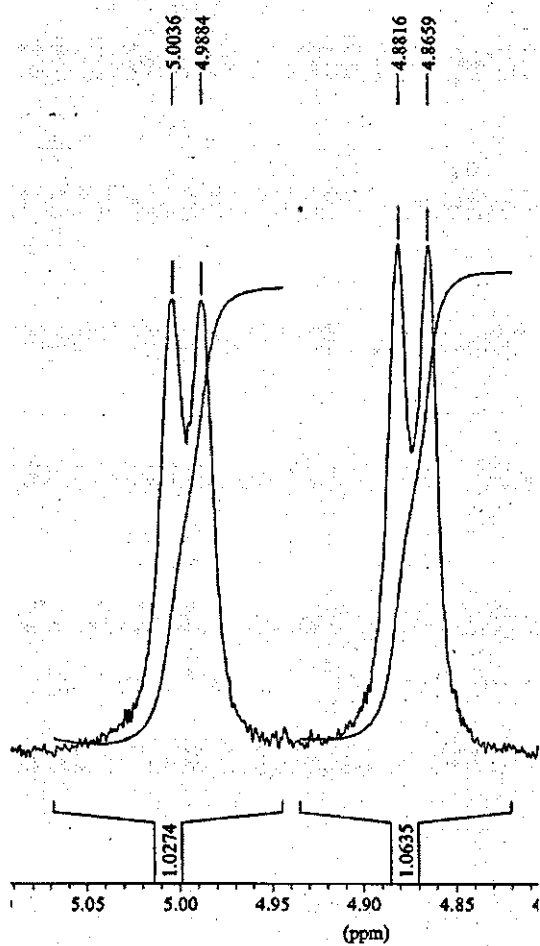


Determination of enantiomeric excess for (*Z*)-2-Methyl-3-phenyl-oxirane (**111a**):

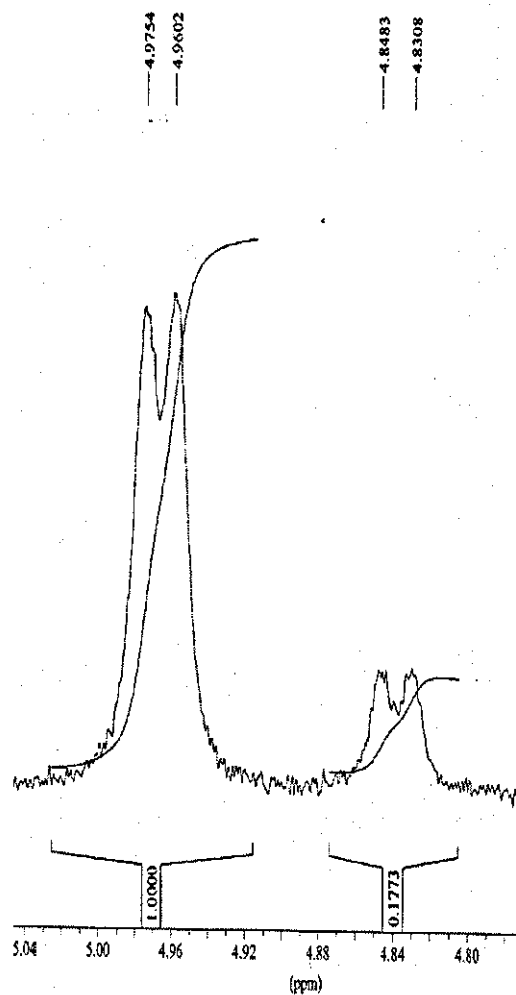


¹H-NMR conditions: 8-10 mg substrate
3-5 mg (+)-Eu(hfc)₃

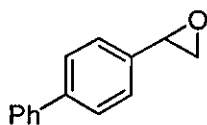
Racemic:



Enantiomerically enriched:

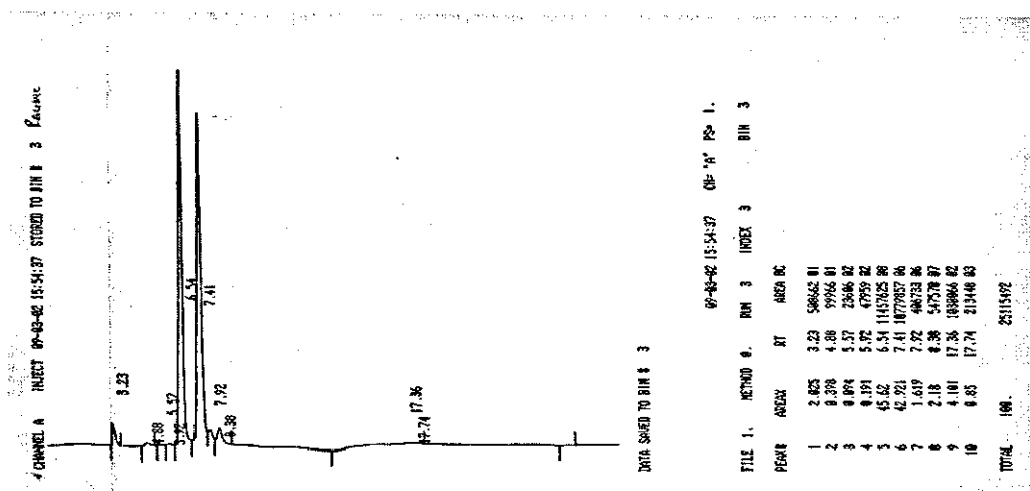


Determination of enantiomeric excess for 2-Biphenyl-4-yl-oxirane (100a):

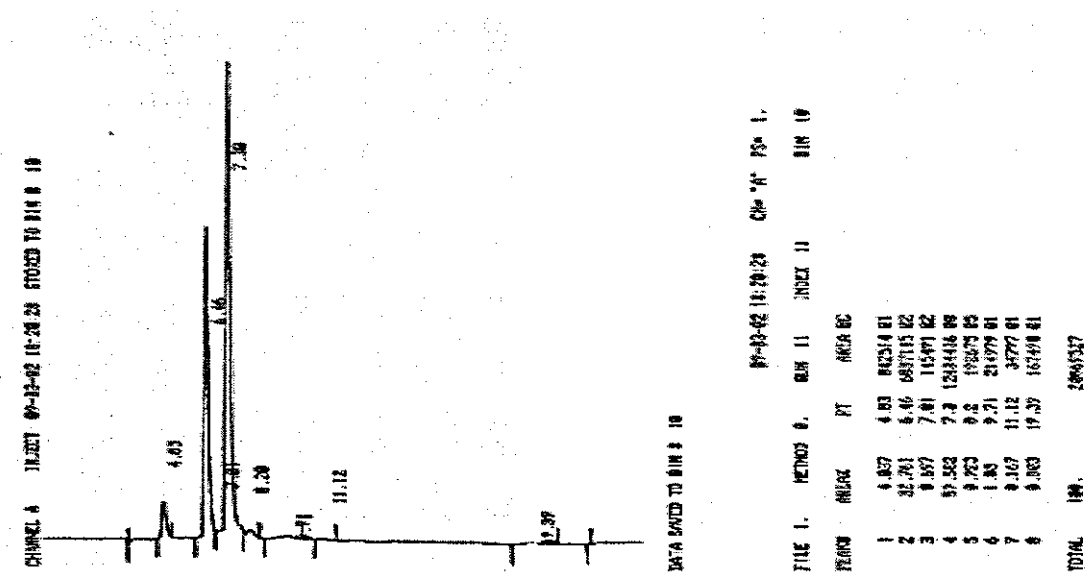


HPLC conditions: Flow : 1.5
 CS : 0.5
 Atten : 512
 Hex:IPA : 95:15

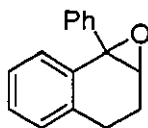
Racemic: Retention times: (R) = 6.54; (S) = 7.41.



Enantiomerically enriched: Retention times: (R) = 6.60; (S) = 7.49.

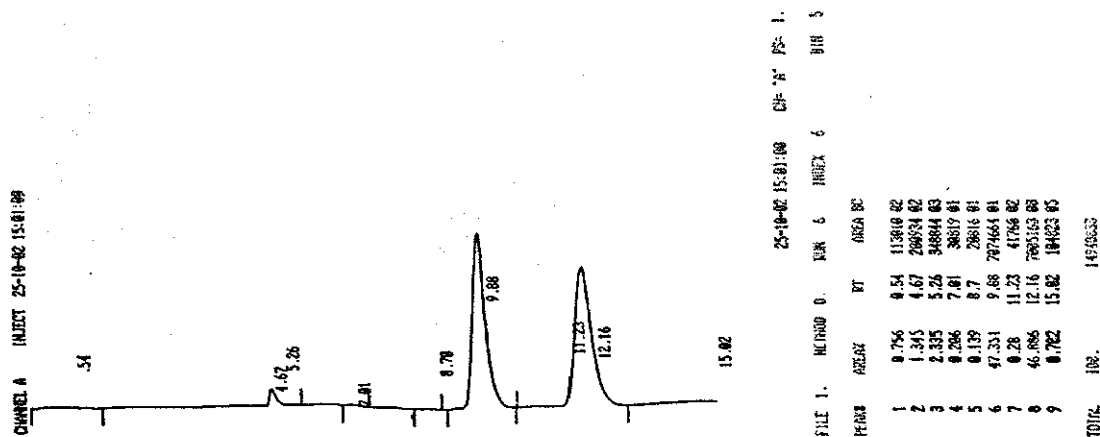


Determination of enantiomeric excess for 7b-Phenyl-1a,2,3,7b-tetrahydro-1-oxa-cyclopropa[a]naphthalene (**22**):

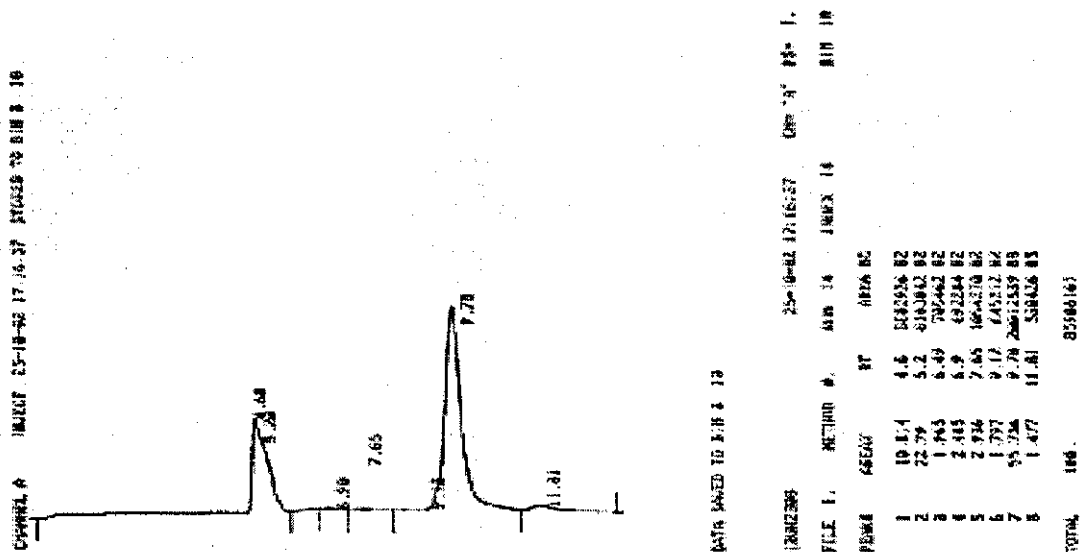


HPLC conditions: Flow : 1.0
 CS : 0.5
 Atten : 512
 Hex:IPA : 90:10

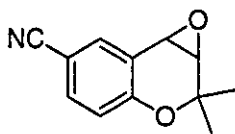
Racemic: Retention times: (1*S*,2*R*) = 9.88; (1*R*,2*S*) = 12.16.



Enantiomerically enriched: Retention times: (1*S*,2*R*) = 9.78; (1*R*,2*S*) = 11.81.



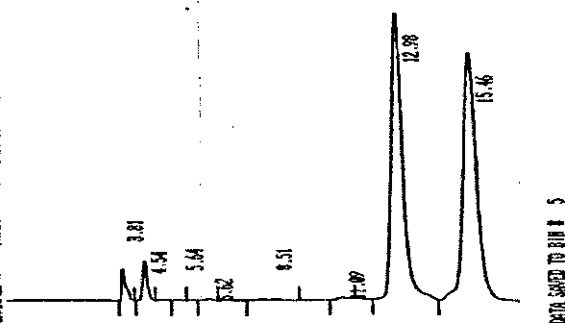
Determination of enantiomeric excess for 2,2-Dimethyl-1a,7b-dihydro-2H-1,3-dioxacyclopropa[a]naphthalene-6-carbonitrile (**115**):



HPLC conditions: Flow : 1.3
 CS : 0.5
 Atten : 512
 Hex:IPA : 90:10

Racemic: Retention times: (3*R*,4*R*) = 12.98; (3*S*,4*S*) = 15.46.

CHANNEL A INJECT 11-03-02 20:25:57 STORED TO BIN # 5



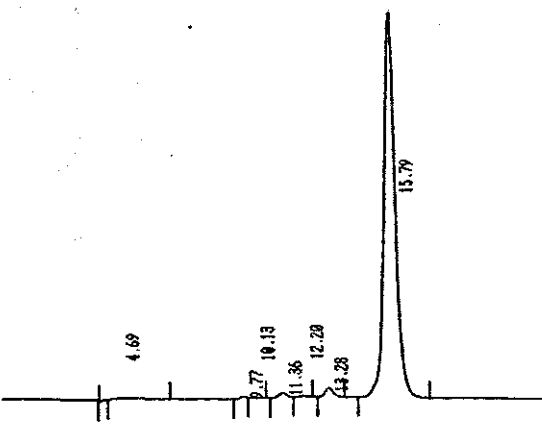
DATA SAVED TO BIN # 5

11-03-02 20:25:57 CH= W PS= 1.

FILE 1.	METHOD	RUN	INDEX	5	BIN	5
PEAK#	AREA#	RT	AREA	BC		
1	1.04	3.81	740288	#1		
2	2.579	4.54	594254	#1		
3	0.059	5.54	22515	#1		
4	0.15	6.52	57801	#1		
5	0.222	6.51	84621	#1		
6	0.229	11.89	92328	#1		
7	47.074	12.98	1765897	#8		
8	47.727	15.46	1821819	#5		
TOTAL	100.		3416133			

Enantiomerically enriched: Retention times: (3*R*,4*R*) = 13.28; (3*S*,4*S*) = 15.79.

CHANNEL A INJECT 11-03-02 20:01:26 STORED TO BIN # 4



DATA SAVED TO BIN # 4

11-03-02 20:01:26 CH= "A" PS= 1.

FILE 1.	METHOD	RUN	INDEX	4	BIN	4
PEAK#	AREA#	RT	AREA	BC		
1	0.53	4.69	123155	#1		
2	0.393	9.77	91249	#2		
3	0.25	10.13	58119	#3		
4	0.078	11.36	227649	#2		
5	0.212	12.2	49168	#3		
6	1.607	13.28	373103	#1		
7	96.83	15.79	22276463	#1		
TOTAL	100.		23218317			

