Chiral iminium salts as catalysts for asymmetric epoxidation

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CHIRAL IMINIIUM SALTS AS CATALYSTS FOR ASYMMETRIC EPOXIDATION

By

Mohamud M. Farah

A Doctoral Thesis

Submitted in partial fulfilment of the requirements for the award of

Doctor of Philosophy

at Loughborough-University

Department of Chemistry

July 2007
ABSTRACT

CHIRAL IMINIIUM SALTS AS CATALYSTS FOR ASYMMETRIC EPOXIDATION

MOHAMUD M. FARAH

Key Words: Epoxidation, Alkene, Asymmetric synthesis, Iminium salt, Oxaziridinium salt, Oxone, Organocatalysis.

This thesis deals with the catalytic asymmetric epoxidation of alkenes mediated by chiral iminium salt catalysts. The first chapter contains a review of some of the most effective catalytic asymmetric methods for preparing chiral epoxides from alkenes. Merits and drawbacks of these methods are also highlighted where appropriate.

The second chapter describes our efforts to design and synthesize chiral iminium salts as catalysts for asymmetric epoxidation of alkenes using Oxone as the stoichiometric oxidant. The first part of this chapter describes the initial attempts to prepare a range of dihydroisoquinolinium salts, and led to the successful synthesis of one catalyst, which afforded up to 46% ee in the epoxidation of 1-phenyl-3,4-dihydronaphthalene.

The second part of chapter two deals with the synthesis of chiral binaphthalene-derived iminium salts. A range of these catalysts, with chiral appendages attached at the exocyclic carbon-nitrogen, were prepared and tested in epoxidation, affording asymmetric induction of up to 80% ee. Following this, several binaphthalene-derived catalysts with achiral substituents were also prepared. These catalysts afforded up to 83% ee in the epoxidation of 1-phenyl-3,4-dihydronaphthalene.

The third part of chapter two reports the synthesis of biphenyl-derived catalysts. Catalysts with 3,3'-substituents on the biphenyl unit, and L-acetonamine as the chiral appendage, failed to exhibit improved asymmetric induction over the analogous catalyst lacking substituents at the biphenyl unit. Modification of the exocyclic chiral appendage from L-acetonamine to other enantiopure “privileged” ligands was attempted in order to investigate the effect these ligands would have on enantioselectivity. These catalysts were also found to be less enantioselective and reactive than a catalyst containing L-acetonamine as the chiral appendage.

The fourth part of chapter two describes the synthesis and use of binaphthalene-derived amines as epoxidation catalysts, affording ees of up to 81% with 1-phenylcyclohexene oxide.

The third chapter contains the full experimental data for the compounds mentioned in the preceding chapter.

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

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Acknowledged for their technical assistance are: Dr Mark Edgar for the NMR service, Mr Alister Daley for elemental analysis and technical support, Mr John Kershaw and the EPSRC for the mass spectroscopy service.

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I would like to thank my family and especially my wife Idil for their continuous support, patience and love.

This work has enjoyed the financial support of Loughborough University and NPIL Pharma through a CASE award studentship.
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<td>Ac</td>
<td>acetyl</td>
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<tr>
<td>AcCl</td>
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<td>[α]D</td>
<td>specific optical rotation at the sodium D line</td>
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<td>AIBN</td>
<td>2,2'-azobisisobutyronitrile</td>
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<td>aq.</td>
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<td>BINAP</td>
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<td>BINOL</td>
<td>1,1'-bi(2-naphthol)</td>
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<tr>
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<td>tert-butoxycarbonyl</td>
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</tr>
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<td>cat.</td>
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<tr>
<td>δ</td>
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<tr>
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<tr>
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<td>dec.</td>
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<tr>
<td>Deoxofluor</td>
<td>bis(2-methoxyethyl)aminosulfur trifluoride</td>
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DET diethyl tartrate
DIPEA diisopropylethylamine
DIPT diisopropyl tartrate
dr diastereomeric ratio
DMAP 4-dimethylaminopyridine
DMDO dimethyldioxirane
DMF N,N-dimethylformamide
DMM dimethoxymethane
DMP 2,2-dimethoxypropane
DMSO-d$_6$ dimethyl sulfoxide (deuterated)
DPEN 1,2-diphenylethylene diamine
DPPP bis(diphenylphosphino)propane
EDTA ethylenediamine tetraacetic acid
ee enantiomeric excess
eq. equivalent(s)
Et ethyl
Et$_3$N triethylamine
EtOAc ethyl acetate
EtOH ethanol
g gram(s)
GC gas chromatography
h hour(s)
hfc (heptafluoropropylhydroxymethylene) camphorato
HPLC high performance liquid chromatography
IBX 1-hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide
IPC isopinocampheylamine
IR infra red
$J$ coupling constant
LDA lithium diisopropylamide
m molar
$m$-$CPBA$ $m$-chloroperbenzoic acid
Me methyl
MeMgBr methyl magnesium bromide
MeOH methanol
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<tr>
<td>mmol</td>
<td>millimole(s)</td>
</tr>
<tr>
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<td>millilitre(s)</td>
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<td>m.p.</td>
<td>melting point</td>
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<td>mass spectrometry</td>
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<tr>
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<td>molecular sieves</td>
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<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NDMBA</td>
<td>1,3-dimethylbarbituric acid</td>
</tr>
<tr>
<td>NMO</td>
<td>N-methylmorpholine-N-oxide</td>
</tr>
<tr>
<td>NMR</td>
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<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
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<tr>
<td>Oxone</td>
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<td>PDC</td>
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</tr>
<tr>
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</tr>
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</tr>
<tr>
<td>pTSA</td>
<td>toluene-p-sulfonic acid</td>
</tr>
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</tr>
<tr>
<td>i-PrOH</td>
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<tr>
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<td>Ph3P</td>
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</tr>
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<td>quat.</td>
<td>quaternary</td>
</tr>
<tr>
<td>R</td>
<td>alkyl</td>
</tr>
<tr>
<td>re</td>
<td>rectus, stereochemical descriptor</td>
</tr>
<tr>
<td>r.t.</td>
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<tr>
<td>SAE</td>
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</tr>
<tr>
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<td>salicylideneaminato ligand</td>
</tr>
<tr>
<td>SET</td>
<td>single electron transfer</td>
</tr>
<tr>
<td>si</td>
<td>sinus, stereochemical descriptor</td>
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<tr>
<td>SM</td>
<td>starting material</td>
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<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyldiphenylsilyl</td>
</tr>
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<td>Full Form</td>
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<tr>
<td>--------------</td>
<td>-----------</td>
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<tr>
<td>TBHP</td>
<td>tetrabutylhydrogen peroxide</td>
</tr>
<tr>
<td>TEMPO</td>
<td>2,2,6,6-tetramethyl-piperidine-(N)-oxyl free radical</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonate</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>(N,N,N',N')-tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMSCl</td>
<td>trimethylsilyl chloride</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetra-(n)-propylammonium perruthenate</td>
</tr>
<tr>
<td>TPPP</td>
<td>tetraphenylphosphonium monoperoxy sulfate</td>
</tr>
<tr>
<td>Ts</td>
<td>p-tolylsulfonyl</td>
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<tr>
<td>U.V</td>
<td>ultraviolet</td>
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<tr>
<td>VANOL</td>
<td>2,2'-binaphthol</td>
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<td>3,3'-biphenanthrol</td>
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Chapter One:
Introduction
1.0 Introduction.

Epoxides are saturated three-membered oxygen-containing heterocycles, which play a pivotal role as targets and versatile intermediates in organic synthesis. Like other three-membered rings such as aziridines and cyclopropanes, epoxides are highly strained compounds. Due to this inherent ring-strain, epoxides undergo facile ring opening reactions in the presence of nucleophiles to yield bifunctional compounds. The proclivity of epoxides to undergo highly regio- and stereoselective ring-cleavage reactions with various nucleophiles, coupled with the presence of the epoxide ring moiety in many biologically active natural products, renders them of great value in organic synthesis.¹ A number of representative biologically active natural compounds containing the epoxide ring, such as epothilone A and B, have shown potent anti-tumour activities, generating interest towards their total synthesis.²

![Structure of Epitholone A and B natural products.](image_url)

The gypsy moth insect is a serious pest in hardwood forests and orchards, as the larvae of these insects completely destroy trees. The female gypsy moths produce traces of a sex pheromone called (+)-disparlure to attract the male gypsy moths. The enantiomer of the sex pheromone is inactive in attracting male even in high concentrations.¹ Sex pheremones are widely used as active lures for males, and thus reduce the growth and copulation of these destructive insects.
As exemplified by the sex pheromone (+)-disparlure, individual enantiomers may display different interactions with biological systems; hence, there is an increasing need for the development of enantioselective synthetic methods. Another example of different biological activities of enantiomers is illustrated with the drug Dopa, used to treat Parkinson's disease. (S)-Dopa has the desired effect of restoring nerve function, while (R)-Dopa is not only ineffective but also toxic, necessitating the marketing of the drug as a single enantiomer. Due to the inactivity or adverse side effects displayed by racemic chiral drugs, governments have imposed stringent rules and regulations in marketing racemic drugs. In 2002, 36% of the worldwide pharma market consisted of chiral drugs amounting to >$140 billion.

There are various methods for the synthesis of enantiopure compounds; including resolution of racemic mixtures and direct asymmetric synthesis. Asymmetric synthesis can be achieved either by utilizing chiral auxiliaries, chiral reagents or chiral catalysts. Asymmetric catalysis is perhaps the most attractive and powerful method of synthesising enantiomerically enriched chiral compounds. The award of the 2001 Nobel Prize to Sharpless, Noyori and Knowles has acknowledged the significance of this field and its potential industrial applicability.

The realisation of these factors (i.e the biological activity of epoxide-containing compounds), coupled with the synthetic versatility of the epoxide ring has stimulated
research in developing facile asymmetric and enantioselective syntheses of epoxides and their eventual transformation to other synthetic intermediates.

1.1 Catalytic Asymmetric Epoxidation of Alkenes.

There are a number of methods available for the asymmetric epoxidation of alkenes. The following section discusses the most effective of these. Merits and drawbacks of the synthetic methods are also highlighted where appropriate.

1.1.1 Sharpless Asymmetric Epoxidation.

In 1980, Katsuki and Sharpless reported the first highly enantioselective metal-catalysed asymmetric epoxidation of allylic alcohols. The most effective epoxidation system was achieved by utilizing a titanium (IV) alkoxide, along with an enantiomerically pure diethyl tartrate (DET) as a ligand and t-butyl hydroperoxide (TBHP) as an oxidant, in a non-polar solvent such as dichloromethane. The Sharpless epoxidation system is highly effective in imparting high asymmetric induction with a wide range of allylic alcohols (> 90% ee).

A useful mnemonic has been devised to account for the stereochemistry displayed by the epoxide products. As illustrated in scheme 1, oxygen delivery by the active catalyst depends on the chirality of diethyl tartrate employed. All Sharpless epoxidations of allylic alcohols obey this model.

Scheme 1 Sharpless mnemonic.
Predicting the stereochemical outcome of the Sharpless epoxidation of chiral allylic alcohols is much more complicated. The stereochemistry of epoxidation of racemic secondary allylic alcohols containing only one asymmetric centre can, however, be predicted with reasonable confidence. As these alcohols consist of two enantiomers, when subjected to the epoxidation procedure, one enantiomer is expected to react faster than the other, depending on the tartrate used. This kinetic resolution has successfully been exploited by Sharpless and co-workers (Scheme 2).8

The initially reported procedure used a stoichiometric amount of the titanium reagent in achieving high enantioselectivity and reactivity for the vast majority of allylic alcohol substrates. In 1986, however, the epoxidation procedure was rendered catalytic (by using 5-10 mol% of the catalyst) with the addition of activated molecular sieves to the reaction mixture.9 The improved efficacy of the epoxidation process was thought to be caused by the removal of adventitious water which previously reduced the catalyst activity. Subsequent use of the catalytic procedure gave satisfactory conversions (>95%) and enantioselectivities (90-95% ee) over a wide range of substrates.10
Besides the advantages of economy of the reagent in the catalytic procedure over the stoichiometric version, isolation and in situ transformation of highly reactive and water-soluble epoxy alcohols such as glycidol to more stable and isolable derivative such as 3-nitrobenzenesulfonate in high yields, renders the catalytic process highly desirable. The in situ derivatization of glycidol in the catalytic procedure is favoured due to the low amount of chelated tartrate diester and isopropyl alcohol present in the reaction mixture compared to the stoichiometric reaction. It is advisable to use an excess of the tartrate ester in both the catalytic and stoichiometric procedures to achieve efficient enantioselective epoxidation.

The industrial applicability of the catalytic procedure is illustrated by the efficient and optimised multi-tonne industrial production of both enantiomers of glycidol by ARCO (Scheme 3).

A detailed mechanistic study of the Sharpless asymmetric epoxidation has revealed that, in solution, a rapid reversible ligand exchange between titanium and tartrate occurs with the release of alcohol. The equilibrium is shifted to the right due to the higher binding constant of the tartrates compared to the monodentate alcohols.

Due to the ability of Ti(OR)_4 to act as a catalyst and thus perform background epoxidation, which diminishes the enantioselectivity, efficient enantioselective epoxidation is only achieved by constantly pushing the equilibrium towards the titanium-tartrate complex. This explains why it is of paramount importance to use an excess (10-20 mol%) of the tartrate ester. Epoxidation occurs only after the two remaining alkoxide ligands are replaced by the allylic alcohol and i-butyl
hydroperoxide oxidant to give the Ti(tartrate)(TBHP)(allylic alcohol). Based on X-ray structures of a closely related titanium-dibenzyltetramide complex,\textsuperscript{14} Sharpless has proposed the active titanium-tartrate complex to be dimeric (Figure 4).

\[\text{Figure 4} \text{ Sharpless proposed transition state model for the loaded catalyst.}\]

Due to the versatility of epoxy alcohols as synthetic intermediates, the popularity of the Sharpless asymmetric epoxidation procedure as a viable and reliable method for the synthesis of valuable synthetic intermediates is evident from the vast numbers of reports in the literature. The scope of this method is illustrated below by the synthesis of an intermediate in the synthesis of the biologically active natural product (\textemdash\textperiodcentered)swainsonine (Scheme 5).\textsuperscript{15}

\[\text{Scheme 5 Utilization of Sharpless asymmetric towards the synthesis of natural product Swainsonine.}\]

One major limitation of the Sharpless asymmetric epoxidation method is the requirement for the pendent allylic hydroxyl group in order to achieve enantioselective epoxidation. Thus, this method is unselective in the epoxidation of unfunctionalized alkenes, and alkenes containing functional groups other than a hydroxyl group. This inherent limitation necessitated the development of other asymmetric epoxidation methods capable of achieving high enantioselectivities.
1.1.2 Salen-Catalysed Epoxidation.

Among many useful metal-mediated asymmetric catalysts, a chiral salen-mediated system has been shown to be the most effective. The first example of achiral metallo-salen catalysed epoxidation of alkenes was reported by Kochi et al. who found chromium-salen complexes and manganese-salen complexes to be effective catalysts for the epoxidation of unfunctionalized alkenes in the presence of iodosylbenzene as primary oxidant. Manganese(III) salen complexes have been shown to be superior than the corresponding chromium-derived catalysts. Kochi et al. has postulated the oxomanganese (V) cation to be the active species responsible for oxygen transfer to the alkene.

1.1.2.1 Jacobsen and Katsuki Salen Complexes.

The studies performed by Kochi and co-workers laid the foundation for the development of chiral metallo-salen complexes as efficient catalysts for the asymmetric epoxidation of alkenes. Subsequently, Jacobsen et al. and Katsuki et al. independently reported a class of optically active salen-manganese (III) complexes as highly enantioselective epoxidation catalysts. The complexes consist of chiral Schiff bases derived from the condensation of enantiomerically pure 1,2-diamines and substituted salicylaldehydes chelated to manganese metal ions.

The original catalyst developed by Jacobsen was found to be generally effective in the epoxidation of cis-aryl alkenes, showing enantioselectivities of up to 93% ee. Further modification of the salen ligand by placing substituents that provide steric and electronic effects led to a highly effective catalyst. Catalyst (1) displayed excellent enantioselectivities in the epoxidation of conjugated cis-aryl alkenes (89%-98% ee). However, the catalysts developed by Jacobsen portrayed poor selectivity in the epoxidation of trans-alkenes.
The more effective catalysts developed by Katsuki differ from those developed by Jacobsen in that they either incorporate chiral bulky groups or axial chirality at the 3,3' positions. Among all the catalysts synthesized and probed by Katsuki, catalyst (2) emerged as the most enantioselective, yielding >99% ee in the epoxidation of cis-aryl alkenes (Scheme 7).
A variety of terminal oxidants has been utilized in the salen-manganese catalysed epoxidation of alkenes. These oxidants include commercial bleach (NaOCl), iodosylbenzene, urea-hydrogen peroxide, dimethyldioxirane and molecular oxygen.

On the basis of molecular modelling, a side-on perpendicular approach of the olefin to the metal-oxo bond of a high valent intermediate has been invoked to account for the enantioselectivity displayed in the epoxidation of cis-olefins by chiral salen complexes. The control of the olefin’s approach is achieved mainly by introducing appropriately bulky substituents on to the salen ligand, which enforces the substrate to approach the metal-oxo bond away from the substituents.

The oxidizing species in the catalytic epoxidation reaction is postulated to be due to the manganese-oxo bond of the putative Mn (V) intermediate, which is believed to replace the Cl ligand in the Mn(III) complex.

One inherent disadvantage associated with (salen)manganese (III) mediated epoxidation is the lack of stereospecificity in the reaction. This is especially apparent in the epoxidation of aryl-substituted acyclic cis-alkenes. Epoxidation of these substrates leads to the formation of a stereoisomeric mixture of epoxides. The lack of stereospecificity has been postulated to be caused by a stepwise radical mechanism, in which bond rotation of the radical intermediate causes the scrambling of the cis-geometry to yield the trans-epoxide (Scheme 8).

![Scheme 8 Stepwise mechanism for oxo-transfer proposed by Jacobsen.](image-url)
Jacobsen has taken advantage of this lack of stereospecificity in (salen)manganese (III) mediated epoxidation to reverse the cis:trans ratio in favour of the trans-epoxides from cis-alkene substrates. The enhancement of the trans-epoxide formation was achieved by the addition of a range of quaternary cinchona alkaloid-derived salts to the reaction mixture. The enantioselectivity of the corresponding trans-epoxides ranged from 81%-90% ee. Another major drawback of the Jacobsen/Katsuki salen catalysts is the requirement of cis-aryl alkenes substrates for achieving high ees.

In addition to the epoxidation of alkenes, metallo-salen complexes have been used extensively and successfully in organic synthesis. Applications include the asymmetric synthesis of α-hydroxyketones, selective C-H bond oxidation in five and six-membered cyclic ethers, aziridination of alkenes, and asymmetric ring-opening of meso-epoxides.

The success of the (salen)manganese (III) catalyst (1) developed by Jacobsen has led to its widespread use to achieve the asymmetric epoxidation of biologically active intermediates. The industrial application of (salen)manganese (III) epoxidation is illustrated by the industrial synthesis of cis-aminoinanol, a key intermediate in the synthesis of the HIV protease inhibitor Crivixan (Indinavir). The chemists at Merck required a large-scale synthesis of enantiopure Indinavir due to the required dosing of 1 kg per patient per year. The key intermediate was achieved by the enantioselective epoxidation of the readily available indene to 1S,2R-indene oxide in the presence of (S,S)-salen manganese catalyst (1), 4-(3-phenylpropyl) pyridine N-oxide (P3NO), and NaOCl as the stoichiometric oxidant (Scheme 9). The P3NO was used to promote oxo-transfer, and leads to an increase in catalytic activity and stability.
Despite the effectiveness of metal-mediated asymmetric catalysts in achieving high ees for the epoxidation of alkenes and other asymmetric synthetic transformations, some disadvantages such as substrate specificity, stereocontrol issues, catalysts loading and turnover persist. Most transition metals are also expensive and toxic, thus making them unfavourable for use on industrial scale.

Due to these inherent disadvantages combined with stringent environmental regulations (concerning handling and disposals of toxic materials) imposed by governments, new and important catalytic methods based on metal-free organic molecules have emerged as a powerful alternative or complement to metal- and biocatalysis. This emerging field has been termed 'organocatalysis', describing the acceleration of chemical reactions through the addition of a substoichiometric quantity of an organic compound. From a practical point of view, organocatalysts have the advantages of being inexpensive and often air and water stable, hence reactions can be performed under aerobic and wet conditions.

Most organocatalysts can be broadly classified as Lewis bases, Lewis acids, Brønsted bases and Brønsted acids, even though bifunctional catalysts containing both Lewis base and Brønsted acid functionalities are increasingly being designed.

The majority of organocatalysts are heteroatom-based Lewis bases (N-, O-, P-, and S) that proceed through different mechanisms to convert substrates into activated nucleophiles or electrophiles. The most versatile Lewis base organocatalysed reactions are based on chiral amines as catalysts. The majority of chiral amine
catalysed reactions proceed through the formation of iminium or enamine species as the reactive intermediates (Scheme 10).

\[
\begin{align*}
\text{Iminium catalysis} & \quad \begin{array}{c}
\text{R}_1 \text{R}_2 \\
\text{H}_2O \quad \text{Nu}
\end{array} \\
\text{Enamine catalysis} & \quad \begin{array}{c}
\text{R}_1 \text{R}_2 \\
\text{H}_2O \quad \text{Ei}
\end{array}
\end{align*}
\]

Scheme 10 The reactive intermediates in amine catalysed reactions.

Thus, L-proline (a natural amino acid) has proven effective in catalysing diverse asymmetric reactions, such as the aldol,\(^{46}\) Mannich\(^{47}\) and nitro-Michael reactions,\(^{48}\) with high enantioselectivities (Scheme 11).

\[
\text{Catalyst (10 mol\%)} \quad \begin{array}{c}
\text{DMF, 4 °C} \\
82\% \text{ yield} \quad >99\% \text{ ee, 24:1 dr}
\end{array}
\]

Scheme 11 L-proline catalysed intermolecular enantioselective aldol reaction.

Chiral imidazolidinone catalysts developed by MacMillan and co-workers are another example of versatile organocatalysts which have found widespread synthetic application in the enantioselective transformation of \(\alpha,\beta\)-unsaturated aldehydes. Exceptionally high enantioselectivity has been achieved in the enantioselective imidazolidinone-catalysed Diels-Alder reaction (up to 93\% ee)\(^{49}\) and the 1,4-
alkylation of α,β-unsaturated aldehydes using electron-rich nucleophiles (up to 99% ee) (Scheme 12).50,51

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{+} & \quad \text{NMe}_2 \\
\text{C} & \quad \text{H} & \quad \text{Catalyst (10 mol%)} & \quad \text{CHCl}_3, -10 ^\circ \text{C} & \quad \text{Me}_2\text{N} \\
\end{align*}
\]

86% yield 96% ee

Scheme 12 Enantioselective 1,4-alkylation of electron rich dimethylaniline to α,β-unsaturated aldehyde in the presence of chiral imidazolidinone catalyst.

The use of organocatalysts in the field of asymmetric epoxidation has undergone an explosive growth over the last few years. Good to excellent enantioselectivities have been achieved in the asymmetric epoxidation of alkenes utilizing chiral amines, chiral iminium salts, and chiral dioxiranes as organocatalysts. The following section reviews the use of these organocatalysts types in the enantioselective epoxidation of alkenes.

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

In 1980, Julià reported the enantioselective epoxidation of α,β-unsaturated ketones, giving ees of up to 97%.52 This was achieved by using a triphasic system consisting of poly-L-alanine, toluene and aqueous alkaline hydrogen peroxide as the oxidizing agent (Scheme 13). Despite the high enantioselectivities achieved, the Julià epoxidation methodology suffers a narrow substrate scope and long reaction times of up to twenty-four hours required for epoxidation to occur.

\[
\begin{align*}
\text{Ph} & \quad \text{CO} & \quad \text{O} \\
\text{Ph} & \quad \text{O} & \quad \text{HCl} \\
\text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{Ph} & \quad \text{HN} & \quad \text{Me} \\
\end{align*}
\]

Scheme 13 The Julià catalytic asymmetric epoxidation of chalcone.
Roberts has reported an improved biphasic reaction system, which reduced the reaction time to thirty minutes. These improved reaction conditions involve the use of urea-hydrogen peroxide as the oxidant, DBU as the base, and immobilized poly-(L)-leucine as the catalyst. Both the oxidant and the base are soluble in THF, which is the organic solvent used. Roberts system gave epoxides with up to 95% ee and also increased the substrate scope to include the epoxidation of several substrates with enolisable enones.

The asymmetric epoxidation of \(\alpha,\beta\)-unsaturated ketones has also been achieved using a range of other chiral catalysts. Asymmetric phase transfer catalysis (PTC), pioneered by Wynberg has been used to mediate the highly enantioselective epoxidation of trans-\(\alpha,\beta\)-unsaturated ketones. Using the quinine-derived quaternary ammonium salt (3) as the chiral phase transfer catalyst and alkaline hydrogen peroxide as the stoichiometric oxidant, Wynberg was able to achieve up to 55% ee of chalcone oxide. Major improvements in the enantioselective epoxidation of enone substrates have been obtained by different research groups. For example, Lygo has reported the use of 1 mol% of catalyst (4) and 2 equivalents of sodium hypochlorite solution as the oxidant, to give epoxides with high enantioselectivities (71-90% ee). Catalysts (5) reported by Arai, and the \(C_2\)-symmetric catalyst (6) reported by Maruoka, have also afforded up to 97% ee of chalcone oxide (Scheme 14).

![Scheme 14 Examples of phase transfer catalysts used in the asymmetric epoxidation of chalcone and its derivatives.](image-url)
1.1.4 Dioxirane-based system for asymmetric epoxidation.

1.1.4.1 Historical perspective.

Dioxiranes are a powerful class of oxidants, which have found widespread use in the oxidation of a variety of functional groups such as alkenes to produce epoxides. On the basis of experimental observations that ketones catalysed the decomposition of Oxone (Potassium peroxymonosulfate), Montgomery, was the first to speculate on the existence of dioxiranes as intermediates. Subsequently, unambiguous and incontrovertible evidence of dioxiranes as intermediates was shown by kinetic and $^{18}$O labelling experiments followed by the physical isolation of dimethyldioxirane and methyl(trifluoromethyl)dioxirane. Most dioxiranes are conveniently generated in situ from ketones and Oxone in either biphasic (CH$_2$Cl$_2$/H$_2$O) or monophasic (CH$_3$CN/H$_2$O) conditions at neutral pH (7-8) (Scheme 15).

![Scheme 15: Catalytic diagram for the formation of dioxiranes from ketones and Oxone.](image)

As illustrated in scheme 15, the ketone is regenerated when epoxidation of the alkenes is accomplished. This raises the possibility of performing the reaction catalytically and asymmetrically, when chiral ketones are used in epoxidation of alkenes.

The first asymmetric epoxidation of alkenes using chiral ketone catalyst was described by Curci et al. in 1984, and afforded chiral epoxides of up to 12.5% enantiomeric excess (ee). The same researchers and others designed several other chiral ketones incorporating fluorine substituents. Only low ees of up to 20% were, however, achieved (Figure 5).
The most exciting development of chiral dioxirane catalysed epoxidation was reported in 1996 by Yang, who reasoned that $C_2$-symmetric ketones could be effective potential asymmetric epoxidation catalysts. Subsequently, the chiral binaphthalene-derived 11-membered-ring ketone (7) was designed and employed in the epoxidation of several alkenes. Moderate to high enantioselectivities were obtained for trans-disubstituted and trisubstituted alkenes, the best substrate being trans-4,4'-diphenylstilbene, giving ees of up to 87% (Scheme 16).

X-ray analysis of chiral ketone (7) revealed that positions H-3 and H-3' of the binaphthalene unit are closest in proximity to the dioxirane ring, indicating that they may provide steric control during oxygen transfer process. With this assumption, analogues of the parent ketone catalyst with different groups at these positions were
synthesized and used in epoxidation.\textsuperscript{70,71,72} Increased ees of up to 95\% were achieved when catalyst (8) and $\text{trans-4,4'}$-di-\textit{tert}-butylstilbene were employed (Scheme 17).

![Scheme 17](image)

Scheme 17 Second-generation catalyst developed by Yang.

Chiral ketone (7) has been used in the highly enantioselective and large scale epoxidation of methyl $p$-methoxycinnamate (MPC), a key intermediate towards the synthesis of the drug Diltiazem hydrochloride used in the treatment of hypertension and angina pectoris.\textsuperscript{73} The chiral epoxide was initially obtained in 78\% ee which was improved to $>99\%$ ee upon recrystallization (Scheme 18).

![Scheme 18](image)

Scheme 18 Asymmetric epoxidation of MPC by ketone catalyst (7).
1.1.4.3 Shi's Chiral-fructose derived catalysts.

A great contribution in the field of chiral dioxirane mediated epoxidation was made by Shi, who discovered that chiral fructose derived ketone catalyst (9) and Oxone could be employed in mediating highly enantioselective epoxidations of trans- and trisubstituted alkenes (up to 95% ee). However, the main drawback to the epoxidation procedure was the extensive decomposition of the catalyst, presumably due to a competing Baeyer-Villiger reaction under the reaction conditions applied (pH 7-8). This necessitated the use of sub-stoichiometric amounts of the catalyst to achieve efficient conversion of the alkenes (Scheme 19).

![Scheme 19 Epoxidation of trans-stilbene mediated by chiral fructose derived catalyst.](image)

Reasoning that the competing Baeyer-Villiger reaction could be suppressed by performing the epoxidation at a higher pH, trans-β-methylstyrene was subjected to epoxidation using 20 mol% ketone catalyst (9), Oxone and K₂CO₃ (to achieve a pH of >10). This modification led not only to enhanced conversion and enantioselectivity of the test substrate, but also reduced the amount of Oxone used from (5 eq. to 1.5 eq.). Subsequent studies utilizing the developed procedure (higher pH) and acetone as a catalyst concluded that suppression of the Baeyer-Villiger reaction and increased nucleophilicity of Oxone towards the ketone catalyst are the driving force for the increased efficacy of the fructose-derived catalyst.
The effectiveness and generality of the developed methodology was also shown to be compatible with labile functional groups. Thus, catalyst (9) was used to achieve high enantioselectivity in the epoxidation of 2,2-disubstituted vinylsilanes (up to 94% ee),\textsuperscript{78} hydroxyalkenes such as allylic and homoallylic alcohols (up to 98% ee),\textsuperscript{79} trans-enynes (up to 97% ee),\textsuperscript{80,81} enol silyl ethers and esters (up to 91% ee).\textsuperscript{82} Further synthetic utility of catalyst (9) was demonstrated in the regio- and chemoselective epoxidation of conjugated dienes\textsuperscript{83} and kinetic resolution of racemic 1,3-disubstituted cyclohexenes.\textsuperscript{84}

The methodology developed by Shi and co-workers relied on Oxone as an oxidant for the \textit{in situ} generation of the dioxirane intermediate (scheme 15). A study was thus initiated by Shi and Shu exploring the use of hydrogen peroxide as an oxidant and chiral ketone (9) as catalyst.\textsuperscript{85,86,87} Good to excellent yields (75%-84%) and ees (92%-95%) were achieved in the epoxidation of various \textit{trans}-olefins when the reaction was performed at pH 11.0. An equally important discovery was the necessity of using a nitrile containing solvent/co-solvent such as acetonitrile (CH\textsubscript{3}CN), as without it negligible epoxidation occurred. Shi and Shu postulated that the active oxidant involved in the formation of dioxirane is peroxyimidic acid formed between acetonitrile and hydrogen peroxide (Scheme 21).\textsuperscript{88}
Scheme 21 Epoxidation using hydrogen peroxide as an oxidant via the postulated peroxyimidic acid intermediate.

As seen above, catalyst (9) has been effectively utilized in the epoxidation of trans- and trisubstituted alkenes. However, it performed poorly in the enantioselective epoxidation of cis-alkenes and terminal alkenes.76

Analogues of the original catalyst were synthesized in order to gain some mechanistic insight. Among other catalysts synthesized, (-)-quinic acid-derived catalyst (10) was found to be less enantioselective for the epoxidation of trans-and trisubstituted alkenes than original catalyst (9), but superior and more reactive in the enantioselective epoxidation of cis- and terminal alkenes and certain electron-deficient alkenes (Scheme 22).89

Scheme 22 Enantioselective epoxidation of enone by (-)-quinic-acid derived catalyst (10).

The persistent problem of epoxidizing electron-deficient alkenes was solved by the design of a highly reactive catalyst, containing an electron-withdrawing acetate group. Catalyst (11) was found to be highly enantioselective in the epoxidation of trans- and trisubstituted α,β-unsaturated esters (82%-98% ee) (Scheme 23).90
Two extreme transition state geometries (spiro and planar) are employed to predict the stereochemical outcome in the epoxidation of alkenes with dioxiranes. The epoxidation of trans- and trisubstituted alkenes have been shown to be consistent with the spiro transition state, although the planar transition state is thought to be the main competing transition state. On the basis of this theoretical transition state analysis, Shi and co-workers designed a range of nitrogen-containing analogues of the original catalyst (9). The best catalyst (12), containing an N-Boc protected oxazolidinone ring was shown to be very effective in mediating the enantioselective epoxidation of cis-alkenes (83%-94% ee) and terminal alkenes (71%-85% ee) (Scheme 24).\textsuperscript{93,94}

The success of the oxazolidinone-containing catalyst (12), especially for conjugated cis-alkenes, has been suggested to stem from favoured electronic interaction between the $\pi$ system of the alkene and the oxazolidinone group of the ketone catalyst.\textsuperscript{93,94}
Studies probing the electronic effect on enantioselectivity by changing the N-Boc group to N-aryl-substituted groups have further enhanced the concept of electronic effects. A recent publication by Shi reported a highly potent carbocyclic analogue of catalyst (12) derived from (-)-quinic acid (Figure 6). Catalyst (13) was found to be highly enantioselective in the epoxidation of styrenes (89%-93% ee). The authors postulated that the enhanced enantioselectivity observed with the carbocyclic catalyst has a stereoelectronic origin, as substituting the pyranose oxygen in catalyst (12) with a carbon atom raises the energy of the non-bonding orbital of the dioxirane. Despite the high ees provided by catalyst (13), its lengthy synthesis renders it unattractive for use as a catalyst.

![Figure 6 Highly effective (-)-quinic-acid derived catalyst (13).](image)

Shi reported the N-aryl substituted oxazolidinone-containing catalysts (14) and (15), which are easily prepared in large quantities from D-glucose, and are as effective as catalyst (13). Catalysts (14) and (15) have been used in mediating the enantioselective epoxidation of styrenes (80%-92% ee), cis-alkenes (81%-98% ee), conjugated cis-dienes (76-94% ee), and conjugated cis-enynes (80%-97% ee).

![Scheme 25 N-aryl-substituted catalysts (14) and (15): Enantioselective epoxidation of cis-enynes.](image)
The scope of Shi's chiral dioxirane-mediated epoxidation is illustrated in its use in the cis-epoxidation of a key intermediate towards the total synthesis of (+)-aurilol (Scheme 26).  

\[ \text{OSEM} \quad \text{Oxone, CH}_3\text{CN/DMM/H}_2\text{O} \quad \text{OSEM} \]

\[ 83\% \text{ yield} \quad \text{dr} > 15:1 \]

\[ \text{OSEM} \]

\[ \text{Oxone, CH}_3\text{CN/DMM/H}_2\text{O} \]

\[ \text{OSEM} \]

\[ 83\% \text{ yield} \quad \text{dr} > 15:1 \]

\[ \text{(+)-Aurilol} \]

Scheme 26 Shi's fructose-derived mediated epoxidation of key intermediate towards the synthesis of (+)-aurilol.

1.14 Denmark's Chiral Dioxiranes.

A detailed and systematic investigation of the parameters involved in the in situ generation of dioxiranes under biphasic conditions was performed in 1995 by Denmark et al. These studies identified that efficient catalytic epoxidation of alkenes can be mediated by 1-oxo-piperidinium triflate (16). The success of this catalyst was thought to stem from the presence of the ammonium group, which played the dual role of activating the carbonyl group (by inductively withdrawing electrons) and acting as a phase transfer catalyst. Subsequent studies using a range of chiral oxo-ammonium salts (17) and (18) resulted in poor reactivity and disappointing enantioselectivities (34%-58% ee) (Figure 7).
A range of aromatic oxo-bis(ammonium) salts were also developed with the aim of increasing the electrophilicity of the ketone and reducing the competing Baeyer-Villiger reaction. However, these catalysts proved to be impotent in mediating asymmetric epoxidation of alkenes. In contrast, the corresponding chiral aliphatic oxo bis(ammonium) salts 19-21 were found to be highly reactive in the epoxidation of trans-2-methylstyrene, although poor enantioselectivity of up to 40% ee was achieved at best (Figure 8).

As electron-withdrawing groups had been shown to be beneficial for catalytic activity, Denmark and co-workers initiated a study utilizing a range of α-fluorine substituted 4-tert-butylcyclohexanones as catalysts in epoxidation. These studies revealed equatorial substituted fluorinecyclohexanones to be more effective catalyst than the axial-substituted analogues. Subsequently, a chiral α-fluoro-substituted tropanone-derived catalyst was employed in the epoxidation of trans-stilbene, giving the corresponding chiral epoxide in high yield (79%) and moderate enantioselectivity (58% ee).

Denmark also developed a chiral difluoro C₂-symmetric ketone (22), which proved to be highly enantioselective for the epoxidation trans-alkenes (88%-94% ee) (Scheme 27).
1.1.5 Oxaziridinium salts as oxygen transfer intermediates.

1.1.5.1 Pioneering studies by Lusinchi.

Another widely used type of electrophilic oxygen transfer intermediates beside dioxiranes, is the oxaziridinium salts as first described by Lusinchi et al. In these studies, Lusinchi and co-workers observed that unstable oxaziridinium salts could be prepared by peracid oxidation of the steroidal imine followed by quaternization using methylfluorosulfonate (Scheme 28). This new species was unstable, decomposing easily to an iminium salt, which could be directly prepared from the imine.
The scope of oxaziridinium salts as oxygen transfer agents was demonstrated by Lusinchi by isolating the dihydroisoquinoline-derived oxaziridinium salt and by its subsequent use in the epoxidation of alkenes\textsuperscript{108,109}

The \textit{in situ} generation of oxaziridinium salts from a catalytic amount of an iminium salt and Oxone was first reported by Lusinchi \textit{et al.}\textsuperscript{110}. The discovery of the catalytic system led to the prospect of performing the asymmetric epoxidation of alkenes using chiral imines. Subsequently, Lusinchi \textit{et al.} reported the first enantiomerically pure oxaziridinium salt derived from (1S,2R)-(+)-norephedrine (Scheme 29).\textsuperscript{111}

![Scheme 29 Enantiopure oxaziridinium salt derived from (1S,2R)-(+)-norephedrine.]

Epoxidation of a range of unfunctionalized alkenes utilizing either stoichiometric chiral oxaziridinium salt (24) or a catalytic amount (5 mol\%) of the iminium salt (23) in the presence of Oxone gave low to moderate enantioselectivities (5\%-42\% ee) in the corresponding product epoxides (Scheme 29).\textsuperscript{112}
Two factors have been identified to be deleterious for the iminium salt catalytic system. These include the direct hydrolysis of the acyclic iminium salt catalysts by the reaction medium, and the loss of active oxygen from the intermediate oxaziridinium salt. The later process occurs by the irreversible base catalysed isomerization of oxaziridinium salt containing α-protons to the nitrogen atom. This isomerization in turn vitiates the whole catalytic process. With the aim of ameliorating the catalytic activity by suppressing the base catalysed isomerization, Bohé and Kammoun reported an improved achiral 3,3-disubstituted -dihydroisoquinolium catalyst (25).113 This catalyst displayed enhanced reactivity compared to the unsubstituted dihydroisoquinolium catalyst (26) (Scheme 31).
Recently Bohé reported another highly reactive 3,3-disubstituted dihydroisoquinolium iminium catalyst bearing a nitro-group on the aromatic ring. This catalyst (5 mol%) achieved complete conversion of trans-stilbene in 1.5 hours, compared to the standard system, which required up to 16 hours. However, no chiral versions of these catalysts have been reported to date.

The scope of the oxaziridinium salt as oxygen transfer agent has been widened to include oxidation of sulfides to sulfoxides, and imines to oxaziridines.

1.1.5.2 Aggarwal’s C₂-symmetric iminium salt.

The success of the C₂-symmetric binaphthyl backbone in designing asymmetric catalysts is evident from their ubiquitous use as ligands in the field of asymmetric synthesis. Aggarwal and Wang successfully employed a chiral binaphthalene-derived iminium salt (27) in the epoxidation of a variety of alkenes in high yields (60%-80%) and moderate enantioselectivity (8%-71% ee) (Scheme 32).
1.1.5.3 Armstrong's iminium salts.

In their endeavours towards the synthesis and the use of iminium salts as mediators of enantioselective epoxidation of alkenes Armstrong pioneered in the use of acyclic iminium salts as catalyst. Initially, Armstrong prepared a range of simple achiral exocyclic iminium salts by condensing commercially available N-trimethylsilylpyrrolidine and substituted aromatic aldehydes in the presence of trimethylsilyl triflate (Scheme 33).

The iminium salt catalysts were utilized in the epoxidation of trans-stilbene as a test substrate and Oxone as the oxidant. Among the catalysts tested, those containing electron-withdrawing substituents ortho in the aromatic portion were found to be better catalysts. Among this group of catalysts, the ortho-CF₃ substituted catalyst (28) displayed the best reactivity and was subsequently used in the epoxidation of variety of alkenes with good to excellent yields (Scheme 33).
Attempts by Armstrong to develop chiral variants of these iminium salts proceeded uneventfully, with most catalysts being either very impure or impossible to synthesize.\textsuperscript{121} Of the few chiral iminium salts prepared, catalyst (29) derived from chiral pyrolidine and ortho-chlorobenzaldehyde portrayed the best reactivity and enantioselectivity, giving at best 22\% ee in the epoxidation of 1-phenylcyclohexene (Scheme 35). The impotency of the chiral iminium catalysts prepared is thought to stem from their ease of hydrolysis and/or the low reactivity of the oxaziridinium salt.\textsuperscript{121}

Armstrong et al. also pioneered the intramolecular regioselective epoxidation of non-conjugated dienes via their oxaziridinium salts.\textsuperscript{122} This was achieved by the oxidation of the imine moiety with Oxone to form the corresponding oxaziridine, which upon quaternization with MeOTf led to the formation of the epoxy-aldehyde after the imine hydrolysis (Scheme 36).
Armstrong widened the scope of this methodology by developing an asymmetric intramolecular epoxidation version.\textsuperscript{123} This was achieved by the oxidation of an enantiomerically pure imine with Oxone to form two separable diastereomeric oxaziridines (4:1 ratio). Subsequent N-quatemization of each diastereoisomer with MeOTf led to highly enantiopure epoxy-aldehydes (Scheme 37).

The controlling factor in the high stereoselectivity achieved is thought to stem from the oxaziridine stereochemistry rather than the chirality of the amine. The authors suggest that in order for the intramolecular epoxidation to be of a real practical value,
the diastereoselectivity of the oxaziridine formation has to be augmented by the appropriate use of a chiral amine.

1.1.5.4 Komatsu’s exocyclic iminiums salts.

Komatsu \textit{et al.} embarked upon designing a range of ketiminium salts for use in the asymmetric epoxidation of alkenes.\textsuperscript{124} Initially, achiral iminium salts were synthesized by the condensation of cyclic amines with cyclic ketones under Dean-Stark conditions. Among the catalysts synthesized, the ketiminium salt derived from pyrrolidine and cyclohexanone portrayed the best catalytic activity. Subsequent synthesis of a chiral analogue prepared from L-prolinol and cyclohexanone was used in the asymmetric epoxidation of cinnamyl alcohol in 70\% yield and 39\% ee (Scheme 38).

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme38.png}
\end{center}

\textbf{Scheme 38} Chiral ketiminium salt developed by Komatsu.

1.1.5.5 Yang’s exocyclic iminiums salts.

To obviate the need for isolation and purification of the acyclic iminium salts, some of which are moisture sensitive and difficult to purify, Yang developed a facile \textit{in situ} generation methodology for iminium salt catalysts for olefin epoxidation.\textsuperscript{125} This was achieved by mixing the alkene and the appropriate amines with aldehydes in the presence of Oxone under slightly acidic conditions. After screening a range of amines and aldehydes, chiral amine (30) and aldehyde (31) provided the best balance between reactivity and enantioselectivity (up to 59\% ee) with \textit{trans}-\textalpha-methylstilbene as a
substrate. The limitation of the developed methodology was the high catalyst loading (up to 50 mol%) required for the effective epoxidation of alkenes (Scheme 39).

Scheme 39 In situ formation of iminium salts developed by Yang.
1.1.5.6 Page's chiral iminium salts

The strategy employed by Page relies on designing chiral iminium salts that contain asymmetric centres in the exocyclic nitrogen substituent, based upon the reasoning that such designs would bring the enantiocontrolling asymmetric centres closer to the site of oxygen transfer, and hence potentially increase enantioselectivity.

1.1.5.6.1 Catalyst structure

Along this line, a range of dihydroisoquinolinium iminium salts were easily prepared by condensation of enantiomerically pure primary amines with 2-(2-bromoethyl)benzaldehyde (33), which is in turn readily prepared from isochroman (32). Treatment of isochroman (32) with bromine in carbon tetrachloride under reflux for 1 hour followed by exposure to concentrated hydrobromic acid provides aldehyde (33) in moderate (65%) yield. Subsequent condensation with a range of chiral primary amines furnished the dihydroisoquinolinium bromide salts (Scheme 40). Due to the oily nature of these salts, difficulties were encountered in purifying some of these salts using conventional methods, and this necessitated a change of counter ion. Pure crystalline iminium salts (30-80%) were obtained by using sodium tetraphenylborate as the counter ion. This synthetic sequence does not require any chromatographic purification, and is therefore ideal for scale-up.

![Scheme 40 Dihydroisoquinolinium salts preparation from 2-(2-bromoethyl)benzaldehyde (33)](image-url)
The primary amines 34-43, depicted in Figure 9, were initially converted to their corresponding iminium salts. These iminium salts (0.5-10 mol%) were subsequently used in the epoxidation of 1-phenylcyclohexene, using Oxone (2 equivalents) as oxidant, acetonitrile/water (1:2 or 1:1) as solvent, and sodium carbonate (4 equivalents) as base.

Among this group of catalysts, the N-isopinocampheyl-derived catalyst (44) provided the best balance in reactivity and enantioselectivity, and was subsequently used in the asymmetric epoxidation of other alkene substrates, giving up to 40% ee, for the epoxidation of 1-phenylcyclohexene (Scheme 41).

![Figure 9 Primary amines used to form corresponding isoquinolinium iminium salts.](image)

![Scheme 41 Early catalyst developed by Page.](image)
The mechanism for oxaziridinium salt formation is thought to proceed through an initial reversible nucleophilic attack of the persulfate oxidant on the electrophilic iminium carbon atom. This attack leads to two diastereoisomeric intermediates, arising from the attack of the oxidant at the si or re face of the iminium salt. This step is followed by the irreversible expulsion of sulfate to give diastereoisomeric oxaziridinium species, a reaction which is thought to be the rate determining step under the conditions used by Page. Diastereofacial oxygen transfer to either of the pro-chiral faces of the alkene may in principle occur with different degrees of enantiocontrol (Scheme 42).  

\[ \text{Scheme 42 Catalytic system for the generation of oxaziridinium as oxygen transfer agent.} \]

\[ \text{1.1.5.6.2 Reaction Parameters} \]

With the N-isopinocampheyl-derived catalyst (44) in hand, it was subsequently used as a model catalyst for investigating the reaction parameters necessary to achieve highly enantioselective epoxidation of alkenes.  

1.1.5.6.2.1 Effect of counter-ion.

Besides the original tetraphenylborate salt, other counter-ion derivatives of catalyst (44), such as the corresponding perchlorate, hexafluorophosphate, tetrafluoroborate and periodate salts, were prepared and used in the epoxidation of 1-
phenylcyclohexene. The epoxidations were executed under the standard aqueous conditions (acetonitrile/water, 1:1) with 5 mol% catalyst, sodium carbonate (four equivalents), and Oxone (two equivalents) at 0 °C. Almost identical enantioselectivities were obtained using the tetraphenylborate salt (40% ee) and the periodate salt (35% ee), while the hexafluorophosphate and perchlorate salts gave lower enantioselectivities of 28% ee and 20% ee respectively. All the catalysts, however, provided major epoxide product of identical configuration (R,R), and reaction completion time scale of ca. 45 minutes.

1.1.5.6.2.2 Effect of the solvent system.

As introduced above, the standard epoxidation solvent is acetonitrile/water (1:1 or 1:2). Page discovered that an increase in water to acetonitrile ratio is accompanied by an increase in the rate of reaction, presumably due to increased Oxone solubility, and thus increased nucleophilicity of the persulfate ion. For example, with 0.5 mol% catalyst (44), the yield of 1-phenylcyclohexene oxide was 30% after 1 hour at 0 °C when 1:1 ratio of the two solvents was used, but the yield was essentially quantitative at 2:1 (water:acetonitrile). 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. This effect is more pronounced when small amounts of catalysts are used.

Page also investigated potential correlation of reaction rates and extent of asymmetric induction with the polarity of the co-solvent. The co-solvents used in the epoxidation reactions differed significantly in dielectric constant (ε, indicated by the values in brackets), such as dichloromethane (8.9), trifluoroethanol (26.7) and formamide (111). Epoxidation of 1-phenylcyclohexene was performed using a solvent ratio of 1:1 and the tetraphenylborate and perchlorate salts of catalyst (44). In trifluoroethanol, the perchlorate salt mediated complete epoxidation of 1-phenylcyclohexene within 30 minutes and 26% ee, while in dichloromethane 50% conversion to epoxide was obtained after 3 hours with 33% ee. The tetraphenylborate salt mediated the same reaction in trifluoroethanol within the same time scale (30 minutes) and with the same ee as the perchlorate salt (26% ee). However, in dichloromethane, no reaction was
observed after 3 hours, presumably due to the poor miscibility of the two solvents, which limits the availability of the inorganic oxidant in the organic phase. Both the perchlorate and tetraphenylborate salts failed to mediate the epoxidation in formamide. Page postulates that the lack of reactivity might arise from the iminium species being well stabilized/solvated in this solvent, with the added possibility of an irreversible attack by the formamide.

1.1.5.6.2.3 Effect of temperature

The effect of temperature on epoxidation is limited partly by the stability and solubility of Oxone. When epoxidation of 1-phenylcyclohexene was performed at -10 °C, using catalyst 5 mol% (44), under the standard 1:1 acetonitrile-water system, low conversion to epoxide was observed. This lack of reactivity is presumably due to the limited solubility of Oxone and sodium carbonate at these temperatures. However, complete epoxidation and identical enantioselectivity (35% ee compared to 40% ee at 0 °C) was achieved at this temperature, when 1:3 acetonitrile-water solvent was used. When the epoxidation was performed at room temperature, only mediocre conversion to epoxide was observed, presumably due to the auto-decomposition of Oxone at higher temperature.

1.1.5.6.2.4 Effect of catalyst loading.

The effect of catalyst loading on epoxidation is summarized in Figure 10. An exponential increase in enantioselectivity with catalyst loading was observed. However, this trend reaches a maximum with 2 mol% catalyst loading, beyond which no increase in enantioselectivity is observed. At very low catalyst loadings substantial reduction in enantioselectivity was observed.
1.1.5.6.3 Development of iminium salt systems within the Page research group.

After these preliminary optimization studies, Page focused on the development of catalysts capable of mediating highly enantioselective epoxidation of alkenes. To this end, a range of dihydroisoquinolinium salts containing alcohol, ether and acetal functionalities were initially prepared, and utilized in the asymmetric epoxidation of alkenes.\(^\text{128}\) The polar units contained in these catalysts, it was hoped, would aid in controlling the selectivity of attack of the iminium unit by persulfate and/or orient and direct the approaching alkene substrate to one face of the oxaziridinium species.

1.1.5.6.3.1 Catalysts from chiral 1,2-diamino alcohol precursors

Initially, a range of dihydroisoquinolinium salts \(45-48\), derived from amino alcohols containing primary alcohols, were prepared, and used in the epoxidation of 1-phenylcyclohexene (Figure 11).\(^\text{128}\)
These catalysts were, however, less reactive than catalyst (44), and also gave near-racemic 1-phenylcyclohexene oxide. The lack of reactivity of these catalysts is thought to stem from their existence in an equilibrium between the ring-opened iminium salt (active) and the ring-closed oxazolidine (inactive) forms under the alkaline reaction conditions used (Scheme 43).

Scheme 43 Presumed equilibrium that leads to reduced catalytic activity.

Page also prepared iminium salts 49-51 containing secondary hydroxyl groups (Figure 12). These catalysts gave improved enantioselectivities compared to catalysts 45-48. For example, catalysts (49) and (50) provided 1-phenylcyclohexene oxide with 30% ee and 24% ee respectively.
However, these catalysts were generally less reactive than 45-48, requiring a higher catalyst loading (5 mol% compared to 2 mol%) to achieve complete epoxidation of 1-phenylcyclohexene.

1.1.5.6.3.2 Catalysts from amino-ether precursors

A range of amino ether-derived dihydroisoquinolinium salts 52-54 was prepared and used in the epoxidation of 1-phenylcyclohexene (Figure 13).128

![Figure 13 Iminium salts derived from secondary amino-ethers.](image)

These catalysts proved to be much more active than the amino-alcohol catalyst derivatives, but also gave poor enantioselectivities. For example, catalysts (52) and (53) gave 1-phenylcyclohexene oxide with 7% and 5% ee respectively.

1.1.5.6.3.3 Acetal-derived iminium salts Catalysts.

From this category, a highly reactive catalyst (55) derived from an amino acetal was synthesized and employed in the epoxidation of alkenes (Scheme 44).128 This catalyst was found to be generally more enantioselective than the corresponding N-isopinocampheyl-derived catalyst (44). The success of this catalyst is thought to stem in part from the high conformational rigidity of the six-membered acetal ring.
Catalyst (5 mol%)  
Oxone (2 eq.)  
Na₂CO₃ (4 eq.)  
CH₃CN/H₂O (1:1)  

54% yield  
59% ee

Scheme 44 Epoxidation of alkenes mediated by an amino acetal-derived iminium catalyst.

A feature of this catalyst is the cis relationship between the dihydroisoquinolinium unit and the phenyl group. This suggests that either the phenyl or the dihydroisoquinolinium must be axial if the dioxane ring retains a chair conformation, as in (56) and (57) (Scheme 45).

Conformer (57) is presumed to be the thermodynamically favoured one due to minimized 1,3-diaxial interactions. Both ¹H and ¹³C NMR evidence supports the chair conformation existence of the 1,3-dioxane ring. On the basis of single-crystal X-ray analysis, Page postulated that conformer (57) might also be favored due to a possible interaction between the oxygen lone pairs and the electron depleted carbon atom of the iminium salt.

The preferential existence of conformer (57) might explain the success of this catalyst in providing high enantioselectivities. In this conformer, the phenyl group might hinder the attack of the oxidant at that side of the iminium bond, rendering the other
face of the iminium salt more accessible. This in turn leads to the formation of two
diastereoisomeric oxaziridinium (major and minor), and enantiocontrol would then
result solely from the process of oxygen transfer to the substrate (Scheme 46).

Scheme 46 The two likely diastereoisomeric oxaziridinium species.

Page has also reported a more reactive catalyst in which the dihydroisoquinolium
moiety has been replaced with a biphenyl structure fused to a seven-membered
azepinium salt. Complete epoxidation of alkenes with catalyst (58) proceeded within
10 minutes, making it the most reactive catalyst to date. The enantioselectivity
achieved with this catalyst ranged from 10%-60% ee (Figure 14).

Figure 14 Page's highly reactive azepinium iminium catalyst.

As described above, C₂-symmetric binaphthalene-derived iminium salts have
successfully been utilized by Aggarwal to achieve a reported 71% ee in the
epoxidation of 1-phenylcyclohexene. Page developed a range of azepinium salt
catalysts containing the binaphthalene backbone and exocyclic N-isopinocampheyl or
N-aminoacetal groups. In this group, catalyst (59) proved to be the most reactive and
enantioselective, giving up to 95% ee. Catalyst loading studies on epoxidation of 1-
phenylcyclohexene with catalyst (59) revealed that decreasing the amount of catalyst
did not lead to loss of enantioselectivity. Thus, a loading as low as 0.1 mol% catalyst could be utilized to achieve complete epoxidation of 1-phenylcyclohexene and in 88% ee compared to 91% ee when 5 mol % of the catalyst was used (Scheme 47).

As indicated above, Oxone is used as a stoichiometric oxidant during iminium salts mediated epoxidation of alkenes. This in turn necessitates the use of water as co-solvent due to the poor solubility of Oxone in organic solvents. The use of water in turn limits the minimum temperature range in which the reaction can be performed to -10 °C. As low temperature generally favours enhanced enantioselectivities, the minimum temperature restriction imposes a barrier to enhancing the enantioselectivity of epoxidation reactions mediated by iminium salts. To circumvent this problem, Page embarked on finding a suitable organic soluble oxidant capable of being used in the epoxidation of alkenes without performing background epoxidation itself.

After testing a range of oxidants, Page reported the first ever non-aqueous epoxidation system mediated by iminium salt catalysts by using tetraphenylphosphonium monoperoxybisulfate (TPPP) as a terminal oxidant instead of Oxone.\(^\text{131}\) TPPP has previously been reported by Di Furia, who used it for oxygen transfer to manganese porphyrins.\(^\text{132}\) TPPP is prepared by cation exchange between Oxone and tetraphenylphosphonium chloride. In contrast to the aqueous system, where the presence of base is essential for epoxidation, no base was required using this oxidant. Furthermore, addition of amine bases was found to be deleterious for the epoxidation
reactions. The optimum conditions were found when the reaction was performed at 
−40 °C using acetonitrile as a solvent and two equivalents of TPPP as stoichiometric 
oxidant. Accordingly, a number of catalysts were employed in the epoxidation of 
alkene substrates under these optimum conditions. Biphenyl azepinium salt catalyst 
(58) proved to be superior both in reactivity (100% conversion in 3 minutes) and 
enantioselectivity (67% ee) when 1-phenylcyclohexene was employed as test 
substrate.

Page also reported a novel dihydroisoquinolium-derived catalyst (60) that expressed 
high enantioselectivity in the epoxidation of cyclic cis-alkenes under non-aqueous 
conditions with chloroform as a solvent. Typically, good to high yields (52%-89%) 
and enantioselectivities (61%-97% ee) were obtained. This catalyst was used to 
achieve excellent enantioselectivity in the epoxidation of 6-cyano-2,2-dimethyl-
benzopyran. The corresponding epoxide, a useful biologically active compound and 
intermediate was subjected to ring-cleavage reaction to access levromakalim, a 
biologically active antihypertensive agent (Scheme 48).

\[ \text{Scheme 48 Epoxidation of 2,2-dimethylbenzopyran by iminium catalyst (60): synthesis of levromakalim.} \]

1.1.6 Amine catalysed epoxidation of alkenes.

As introduced above, iminium salt catalysed epoxidation of alkenes has proven adept 
in achieving high enantioselectivities with some alkenes. However, some of these
iminium salts suffer from difficult preparation, decomposition and a narrow substrate scope for high enantioselectivity. A recent chiral amine-mediated asymmetric epoxidation system is emerging as a promising alternative to the chiral iminium salt mediated epoxidation system due to easy access to the amine catalysts.

1.1.6.1 Pioneering studies by Aggarwal.

An intriguing discovery by Aggarwal and co-workers that simple amines catalysed the epoxidation of alkenes in the presence of Oxone has aroused interest in the academic community due to the abundance of commercially available simple amines.135

A range of amines were tested in the epoxidation of test substrate 1-phenylcyclohexene, with the secondary amine pyrrolidine, emerging as the best catalyst. A major limitation to the epoxidation methodology was the substantial amount of diol side product produced under the reaction conditions. Eventually, the addition of pyridine was found to inhibit the epoxide hydrolysis. Subsequent use of pyridine and a chiral derivative [(S)-2-(diphenylmethyl)pyrrolidine 61] as the catalyst with a range alkenes, produced the corresponding epoxides in good yields, and moderate enantioselectivities (32-38% ee) (Scheme 49).

\[
\begin{align*}
\text{Catalyst (5 mol\%)} & \quad \text{Oxone (2 eq.)} \\
\text{NaHCO}_3 (10 \text{ eq.}) & \quad \text{Pyridine (0.5 eq.)} \\
\text{MeCN:H}_2\text{O (95:5), r.t.} & \quad 32-38\% \text{ ee}
\end{align*}
\]

Scheme 49 Epoxidation of 1-phenylcyclohexene mediated by chiral amine (61).

The fact that asymmetric induction was observed led Aggarwal to conclude that the amine catalyst is intimately involved in the oxygen transfer process rather than acting merely as a phase transfer catalyst.
Initially, an amine radical cation mechanism was proposed based on the results of similar selectivity to competition experiments using Bauld’s aminium-catalysed \((\text{Ar}_3\text{N}^+\text{SbCl}_6)\) reactions, which have been shown to proceed through radical cation intermediates.\(^{136}\) However, subsequent studies revealed lack of reproducibility in the competition reaction and in achieving constant enantiomeric excess in the test reaction using catalyst (61), 1-phenylecyclohexene and Oxone.\(^{137}\) This prompted Aggarwal and co-workers to address these issues and find a credible mechanism for the amine catalysed epoxidation.

The reproducibility problem was solved by utilizing the hydrochloride salt of catalyst (61), whereby consistently higher enantioselectivities (up to 66% ee) and shorter reaction times were achieved.\(^{138}\) Attempts to probe the mechanism of the reaction led the authors to exclude the possibility of the reaction being catalysed by the oxidation products of the amine catalyst. Control experiments revealed that the amine was indeed oxidized when the reaction was performed at room temperature. The authors also found the presence of the amine to be crucial for the epoxidation process to occur, as no epoxidation occurred in the absence of the amine or when possible oxidation products (nitron, hydroxyl amine) were utilized.

After exhaustive investigation of the reaction mechanism, the authors discovered the formation of an active oxidizing species complex from amine (61) and Oxone at low temperature (Scheme 50).\(^{138}\)

![Scheme 50 Isolation of the active oxidant.](Image)

Isolation and eventual use of complex (62) in the epoxidation of a range of alkenes gave identical enantioselectivities to the hydrochloride salt of catalyst (61). This observation unambiguously confirmed complex (62) to be the active oxidizing agent. These observations and Hammett correlation studies, which showed complex (62) to
be an electrophilic oxidant, led the authors to propose a new catalytic cycle for the epoxidation process (Scheme 51).

Previously, the ability of the amine to act as a phase transfer catalyst was discounted due to the inability of quaternary amines to promote the epoxidation of alkenes.\textsuperscript{135} However, the authors postulate that the protonated ammonium salts acts both as a phase transfer catalyst and Oxone activator through hydrogen bonding, generating a more electrophilic species.\textsuperscript{138} The hydrogen bonding between the ammonium salt and Oxone can occur in three different orientations and thus lower the enantioselectivity (Scheme 52).

Scheme 51 The proposed catalytic cycle of amine catalysed epoxidation.

Scheme 52 Possible interaction modes between ammonium salt complex and peroxymonosulfate.
1.1.6.2 Chiral amine catalysts developed by Yang.

In 2001, while developing a methodology towards the *in situ* generation of iminium salt catalysts for olefin epoxidation, Yang observed that a range of chiral amines effected the epoxidation of alkenes in the presence of Oxone.\(^{125}\) Subsequently a range of amines were screened for catalytic activity in the epoxidation of *trans*-stilbene as a test substrate and Oxone as the oxidant.\(^{139}\)

Like Aggarwal,\(^ {137,138}\) Yang and co-workers found cyclic secondary amines to be better catalysts than acyclic primary and secondary amines. Furthermore, the screening results indicated a cyclic secondary amine incorporating a \(\beta\)-hydroxyl substituent to be beneficial for catalytic activity in the epoxidation of alkenes. Thus, after screening a variety of pyrrolidine analogues for catalytic activity, Yang showed that amine (63), incorporating a bulky C\(\text{Ph}_2\)OH substituent, gave moderate conversion (58\%) and enantioselectivity (33\% ee) for *trans*-stilbene.

A systematic modification of amine (63) led to a highly reactive and enantioselective fluoro catalyst (64) which, when utilized in the epoxidation of 1-phenylcyclohexene at room temperature, gave excellent conversion (100\%) and moderate enantioselectivity (50\% ee). The enantioselectivity was increased to 61\% ee when the reaction was performed at \(-20^\circ\text{C}\), with complete inhibition of diol formation (Scheme 53).

![Scheme 53 Amine catalysed epoxidation developed by Yang.](image)

The authors also investigated the mechanism of the amine catalysed epoxidation, whereby a range of experimental results confirmed the dual role of the amine as a
phase transfer catalyst and Oxone activator, as suggested by Aggarwal. Yang postulates that catalyst (64) is protonated \textit{in situ} to the corresponding ammonium salt due to the fact that an induction period of up to ten minutes was required for the epoxidation of 1-phenylcyclohexene to occur. The ee of the epoxide product was constant (50% ee) over the course of the reaction (60 minutes), indicating the involvement of the same chiral intermediate. The electrophilic nature of the active oxidizing species was postulated, due to the observation that higher conversions to epoxides were obtained for electron-rich substrate (60% conversion) than electron deficient substrate (21% conversion).^{139}

1.1.6.3 Chiral amines developed by Jørgensen.

As described above, exceptionally high enantioselectivity has been achieved in the diverse enantioselective transformation of \(\alpha,\beta\)-unsaturated aldehydes by chiral amines through the formation of iminium and enamine species as the reactive intermediates.\(^{46,47,48,49}\) However, the direct asymmetric epoxidation of \(\alpha,\beta\)-unsaturated aldehydes has been a challenge to achieve. Jørgensen reported the first asymmetric organocatalytic epoxidation of \(\alpha,\beta\)-unsaturated aldehydes using a range of peroxides as the oxidant.\(^{140}\) After screening a variety of chiral amines as effective mediators for the epoxidation of cinnamic aldehyde, chiral pyrrolidine derivative (65) and hydrogen peroxide emerged as an excellent catalyst and oxidant, achieving up to 96% ee of the corresponding epoxides (Scheme 54).

\[
\begin{align*}
\text{Ph} & \quad \text{H} \\
\text{C} & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{Catalyst (10 mol\%)} & \quad \text{H}_2\text{O}_2 & \quad \text{r.t.}, 4 \text{~h} & \quad \text{Ph} \quad \text{O} \\
\text{H} & \quad \text{C} & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{94.6 dr.} & \quad 96\% \text{ ee} \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 54 Chiral amine catalysed epoxidation of }\alpha,\beta\text{-unsaturated aldehydes developed by Jørgensen.}
\end{align*}
\]

Subsequent epoxidation of a series of substituted \(\alpha,\beta\)-unsaturated aldehydes using catalyst (65) and hydrogen peroxide as oxidant produced the corresponding epoxides
in high yields (60-90%), diastereoselectivities, and enantioselectivities (96-98% ee). The synthetic utility of the enantioselective methodology was subsequently portrayed in the synthesis of the sex pheromone from an acaric mite (Scheme 55).

\[
\begin{align*}
\text{Catalyst 65 (10 mol\%)} & \quad \text{H}_2\text{O}_2, \text{CH}_2\text{Cl}_2, \text{r.t., 4 h} \\
\text{73\% yield} & \quad \text{85\% ee}
\end{align*}
\]

Scheme 55 Synthesis of the sex pheromone from an acaric mite.

A mechanistic scenario involving an iminium species arising from nucleophilic addition of the chiral amine on to the aldehyde, followed by a stereoselective nucleophilic attack by peroxide on the β-carbon atom leading to the formation of chiral enamine intermediate, has been proposed. A nucleophilic attack by the enamine intermediate on to the peroxygen atom followed by hydrolysis of the iminium intermediate results in the formation of the epoxy-aldehydes (Scheme 56).

Scheme 56 Mechanistic proposal for the organocatalytic epoxidation of α,β-unsaturated aldehydes with peroxides.

A modification of this asymmetric methodology involving performing the epoxidation reaction in an aqueous medium has recently been reported.\textsuperscript{141} High
diastereoselectivities and enantioselectivities (up to 96% ee) were obtained when the reaction was performed in an ethanol-water solution, catalyst (65) and hydrogen peroxide as the oxidant.

Cordova has also screened a range of chiral amines in the enantioselective epoxidation of α,β-unsaturated aldehydes in the presence of hydrogen peroxide or sodium percarbonate as nucleophilic oxidants, yielding epoxy-aldehydes in moderate diastereoselectivities and enantioselectivities (66-98% ee) depending on the chiral amine utilized.\textsuperscript{142}
1.2 Chapter One References.

55


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Chapter Two:

Results and Discussion
2.0 Results and Discussion.

As described above, Page’s group endeavour is directed towards the development of highly enantioselective iminium salt catalysts for use in the asymmetric epoxidation of alkenes. Some of the catalysts developed by the Page group have shown to be highly enantioselective, giving up to 97% ee of the corresponding epoxides. The work described in this thesis is an extension of this work, and reports the attempts by the author towards the synthesis of new analogues of our most promising catalysts. This, we hoped, would contribute to the understanding of the factors, both steric and electronic, necessary in designing catalysts capable of achieving high enantioselectivities, over a wide range of substrates. The initial aim of the project was the synthesis of catalyst (1), an analogue of catalyst (2), which induced up to 97% ee for some substrates (Figure 1).

![Figure 1 Initial target iminium salt catalyst.](image-url)
2.1 Catalysts Based On Dihydroisoquinolinium Salts.

2.1.1 Synthesis of 4,4-dimethyl-substituted dihydroisoquinolinium salt.

We envisaged that the required catalyst (1) could be obtained through cyclocondensation of bromoaldehyde unit with primary amine (3). This primary amine could in turn be synthesized from commercially available aminodiol (4) after a range of synthetic manipulations (Scheme 1). The choice of preparing this catalyst was based on the assumption that the two methyl groups in the C4 position of the 1,3-dioxane ring might provide steric hindrance, and thus force the pro-chiral alkenes to approach from one face during the oxygen transfer step, hence increasing the enantioselectivity.

With this in mind, we proceeded towards the catalyst synthesis starting from optically pure commercially available (1S,2S)-(+)-2-amino-1-(4-methylsulfanyl-phenyl)-propane-1,3-diol [(+)-thiomicamine] (4). We believed that the optical integrity would be preserved throughout the synthesis of the catalyst.

The first synthetic step involved the protection of (+)-thiomicamine (4) as the corresponding N-Cbz protected-(+)-thiomicamine (5). The protection was achieved by reacting optically active (+)-thiomicamine (4) with benzyl chloroformate and an aqueous solution of sodium hydrogen carbonate at room temperature over three hours to give compound (5) in 90% yield. This was followed by the regioselective protection of the primary hydroxyl group in compound (5) to give the corresponding TBDPS-protected alcohol (6) in 92% yield (Scheme 2).
Cyclization of compound (6) using 2,2-dimethoxypropane (2,2-DMP) in acetone in the presence of a catalytic amount of p-toluene-sulfonic acid (pTSA) gave the oxazolidine ring (7) in an excellent 88% yield. The $^1$H-NMR spectrum of oxazolidine (7) showed two sets of signals for the ring methyl protons and complex multiplets for the ring protons due to the locked conformation. However, a clean averaged spectrum was obtained when the NMR spectrum was recorded at 100 °C. Interestingly, when the sample was cooled to room temperature, the original complex spectrum was restored, indicating slow interconversion between the conformers. This phenomenon has previously been observed for the oxazolidine ring system. Thus, all oxazolidine ring containing compounds prepared were subsequently heated in order to record simplified NMR spectra.

$m$-CPBA oxidation of the sulfide moiety in compound (7) to the sulfone was achieved in 88% yield. In this reaction, 4 equivalents of $m$-CPBA were required to achieve complete oxidation to the sulfone. Using less than four equivalents of the oxidant either gave the sulfoxide or a mixture of sulfoxide and sulfone. The sulfoxide and sulfone were easily distinguished from $^1$H-NMR analysis as the methyl signal in the sulfoxide is at δ 2.6 ppm compared to δ 3.0 ppm in the sulfone (Scheme 3).
Scheme 3 Reagents and Conditions: i: 2,2-DMP (10 eq.), acetone, pTSA (0.1 eq.), r.t., 12 h, 73%; ii: m-CPBA (5 eq.), DCM, 0 °C, 3 h, 88%.

With compound (8) in hand, deprotection of the silyl protecting group with tetrabutylammonium fluoride (TBAF) in THF proceeded to furnish alcohol (9) in 74% yield (Scheme 4). We also observed formation of minor compound (10) arising, presumably, from an intramolecular nucleophilic attack of the alcohol oxygen atom at the electrophilic carbonyl carbon (Scheme 4).

Scheme 4 Reagents and Conditions: i: TBAF (1.2 eq.), THF, 0 °C-r.t., 6 h, 74%.

The next step in the catalyst synthesis was the oxidation of the primary alcohol in compound (9) to the corresponding aldehyde (Scheme 5). There is a plethora of synthetic oxidation methods of alcohols to give aldehydes available in the literature. Due to the optical purity of our compound, a mild, neutral oxidation method was paramount to achieve the transformation of alcohol (9) to aldehyde (11) because of the potential for epimerization in the product at the asymmetric centre next to the new aldehyde. The reaction was attempted under different conditions as shown below (Table 1).
Scheme 5 Oxidation of alcohol (9) to the corresponding aldehyde (11).

Table 1 Oxidation methods attempted on alcohol (9).

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<tr>
<th>Entry</th>
<th>Reagents and reaction conditions</th>
<th>Yield of 11 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TEMPO, NaOCl, NaBr, 0 °C-r.t., 2 h, toluene:EtOAc:H₂O</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>IBX, DMSO, 0 °C-r.t., 48 h</td>
<td>10-44</td>
</tr>
<tr>
<td>3</td>
<td>IBX, EtOAc, reflux, 12 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>TPAP, NMO, DCM, 4Å ms, r.t., 16 h</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>DMSO, (COCl)₂, Et₃N, -78 °C-r.t., 3 h</td>
<td>74</td>
</tr>
</tbody>
</table>

Oxo-ammonium promoted oxidation of alcohols to aldehydes and ketones has been reported in the literature.² The most common method involves using a catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO) with a variety of oxidants such as N-chloro-succinimide³ and sodium or calcium hypochlorite.⁴ Thus, oxidation of compound (9) was attempted in the presence of a catalytic amount of TEMPO, a buffered NaOCl solution and a stoichiometric amount of NaBr in a biphasic mixture of toluene:ethyl acetate:water (1:1:1). However, no reaction occurred, with only starting material being observed after two hours (Table 1, entry 1). Attempts to initiate the reaction by continuously adding a catalytic amount of TEMPO and NaOCl failed to give any result. With the failure of the TEMPO-mediated oxidation, other suitable methods had to be tried.

The use of hypervalent iodine reagents in organic synthesis has enjoyed increasing popularity due to their easy availability, mildness and stability.⁵ Reagents such as 1-hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide (IBX) and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin Periodinane), have extensively been utilized...
in oxidation of alcohols to the corresponding carbonyl compounds. Of the two iodinanes, IBX, a precursor of Dess-Martin Periodinane, had until recently, rarely been used in mediating oxidation reactions due to its insolubility in most organic solvents, thus making Dess-Martin Periodinane a reagent of choice in performing oxidation of alcohols.6,7 However, the discovery that IBX in DMSO effectively oxidized primary alcohols to aldehydes or ketones has markedly increased the popularity of this reagent.8,9,10

When alcohol (9) was treated with 2.2 equivalents of IBX in DMSO and the reaction mixture allowed to reach completion (forty-eight hours), the aldehyde was furnished in varying 10-44% yield with complete consumption of the starting material (Table I, entry 2). The capricious nature of the reaction was presumed to stem from the decomposition of the aldehyde product under the reaction conditions used. A recent report by Finney and More described a high yielding protocol for IBX-mediated oxidation of primary alcohols using ethyl acetate as a solvent.11 However, when compound (9) was heated under reflux with IBX and ethyl acetate as a solvent for up to two hours, no reaction occurred. Leaving the reaction to reflux overnight led to extensive decomposition of the starting material (Table I, entry 3).

Attempts to oxidize alcohol (9) using catalytic tetra-n-propylammonium perruthenate (TPAP), with N-methylmorpholine-N-oxide (NMO) as stoichiometric oxidant in the presence of activated molecular sieves failed to furnish the aldehyde (11), and only starting material was recovered (Table I, entry 4).12,13 Use of a stoichiometric amount of TPAP did not have any effect on the reaction, giving back the starting material. However, when alcohol (9) was submitted to standard Swern oxidation using DMSO, oxalyl chloride and triethylamine as a base, the corresponding aldehyde was obtained in 74% yield (Table 1, entry 5).14 Careful control of the reaction temperature was found to be critical in obtaining the aldehyde. Thus, if the internal temperature in the reaction exceeded -60 °C, no aldehyde was formed.

With aldehyde (11) in hand, attempts were made to convert it to the corresponding methyl ester directly. The classical formation of methyl esters from aldehydes involves a two-step procedure involving the oxidation of aldehydes to carboxylic acids followed by the esterification of the acid under acidic or basic conditions to give the
corresponding esters. However, there is a literature precedent for the direct conversion of aldehydes into their alkyl ester derivatives (Scheme 6, Table 2).

![Scheme 6 Direct conversion of aldehyde (11) to methyl ester (12).]

**Table 2 Reaction conditions for the oxidation of aldehyde (11) to methyl ester (12).**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and reaction conditions</th>
<th>Yield of 12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaHCO₃, Br₂, MeOH, H₂O, r.t., 16h</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>Oxone, MeOH, r.t., 72 h</td>
<td>25</td>
</tr>
</tbody>
</table>

Unfortunately, when aldehyde (11) was submitted to react with molecular bromine in the presence of sodium hydrogen carbonate as a base and methanol as a solvent, no product was isolated. Increased equivalents of bromine and longer reaction times failed to mediate the reaction, with only starting material being observed. However, when aldehyde (11) was treated with Oxone in methanol according to the procedure developed by Borhan et al., the corresponding ester (12) was obtained in 25% yield alongside other unidentifiable byproducts arising, presumably, from the decomposition of the starting material under the acidic conditions (Table 2, entry 2).

Due to the low yield of this reaction, another approach involving the direct oxidation of primary alcohol (9) to the carboxylic acid was pursued (Scheme 7). When compound (9) was treated with catalytic chromium trioxide (CrO₃) in the presence of periodic acid as the stoichiometric oxidant and aqueous acetonitrile as the solvent, the corresponding carboxylic acid (13) was produced in 10-47% yield (Table 3, entry 1). Besides a small amount of starting material, other byproducts which could not be identified were
observed. Attempts to optimize the reaction by performing the reaction at low
temperatures (0 °C) failed to improve the yield of the acid.

We envisaged that the direct oxidation using potassium permanganate (KMnO₄) may
be worth trying, as KMnO₄ has extensively been employed in oxidizing alcohols and
aldehydes to the corresponding carboxylic acids over a wide pH range. However,
when compound (9) was subjected to KMnO₄ oxidation in tert-butanol, either no
reaction materialized or decomposition of the starting material was observed,
depending on the reaction conditions employed (Table 3, entry 2). For example, when
the oxidation was performed with an excess of KMnO₄ (10 eq.) at neutral pH, only
starting material was observed after leaving the reaction for up to seventy-two hours.
However, when the reaction was performed at pH 4 by using an appropriate buffer,
extensive decomposition of the starting material was observed after forty-eight hours.
Interestingly, when the reaction was performed at a higher pH (10), by adding
potassium carbonate to the reaction mixture, only the starting material was recovered.

Table 3 Reaction conditions attempted on the direct oxidation of alcohol (9) to carboxylic acid (13).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and reaction conditions</th>
<th>Yield of 13 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CrO₃, H₂IO₆, 0 °C-r.t., 16 h</td>
<td>10-47</td>
</tr>
<tr>
<td>2</td>
<td>KMnO₄, H₂O, t-BuOH at pH 7, pH 4 and pH 10</td>
<td>SM or decomposition</td>
</tr>
<tr>
<td>3</td>
<td>PDC, DMF, r.t., 48 h-72 h</td>
<td>40-62</td>
</tr>
<tr>
<td>4</td>
<td>CrO₃, H₂SO₄, acetone, 0 °C-r.t., 16 h</td>
<td>77</td>
</tr>
</tbody>
</table>

Scheme 7 Direct oxidation of alcohol (9) to carboxylic acid (13) under varying conditions.
Since its discovery by Corey and Schmidt, pyridinium dichromate (PDC) has proven robust in oxidizing primary alcohols to carboxylic acids or aldehydes, depending on the reaction solvent utilized. PDC in DMF as solvent oxidizes primary alcohols to the corresponding acids, while in dichloromethane, the corresponding aldehyde is obtained regardless of the substrate. Additives such as pyridinium trifluoroacetate and acetic acid have been found to accelerate the oxidation of alcohols to the corresponding carbonyl derivatives. Treating alcohol (9) with PDC (6 eq.) in DMF at room temperature over forty-eight to seventy-two hours gave carboxylic acid (13) in a moderate 40-62% yield (Table 3, entry 3). The varying yield was caused by the laborious work-up conditions leading to loss of some of the compound, which rendered this method unattractive, especially in larger scale reactions. Fortunately, remarkably clean carboxylic acid (13) was obtained in high yield (77%) when alcohol (9) was treated with an excess of Jones' reagent (Table 3, entry 4). The Jones' oxidation was also found to be amenable to large-scale synthesis, giving carboxylic acid (13) in multi-gram quantity.

The next synthetic step undertaken involved esterification of the carboxylic acid to the corresponding methyl ester (12). As indicated above, esterification can be achieved under basic or acidic conditions. The treatment of carboxylic acids using diazomethane is probably the most efficient route to the corresponding methyl esters. However, the toxicity and explosive nature of diazomethane overshadows the advantages of using this reagent. We therefore opted to perform the esterification under basic reaction conditions due to the lability of the oxazolidine ring under acidic conditions. Esterification of compound (13) was performed as shown below (Scheme 8, Table 4).

Scheme 8 Esterification of compound (13).
Table 4 Esterification of compound (13) under various conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Methylating reagent</th>
<th>Yield of 12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cs₂CO₃</td>
<td>DCM</td>
<td>Me₂SO₄</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>KOH</td>
<td>DMF</td>
<td>Mel</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>NaH</td>
<td>DMSO</td>
<td>Mel</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>K₂CO₃</td>
<td>DMF</td>
<td>Mel</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>*Cat. HCl</td>
<td>2,2-DMP</td>
<td>2,2-DMP</td>
<td>SM</td>
</tr>
<tr>
<td>6</td>
<td>K₂CO₃</td>
<td>acetone</td>
<td>Me₂SO₄</td>
<td>88</td>
</tr>
</tbody>
</table>

When Cs₂CO₃ was utilized as a base in the presence of dimethyl sulfate (Me₂SO₄) in dichloromethane at room temperature, no reaction was observed for up to forty-eight hours (Table 4, entry 1). Interestingly, changing the base from KOH to K₂CO₃ when using methyl iodide and DMF as solvent had an effect in the yield of ester (12) obtained (Table 4, entry 2 vs. entry 4). Attempts to improve the yield of ester (12) by using NaH as a base in the presence of MeI and DMSO failed (Table 4, entry 3). Under these conditions compound (13) failed to undergo full conversion presumably, due to the slightly wet DMSO used in the reaction.

Surprisingly, when compound (13) was treated with catalytic amount of hydrochloric acid (HCl) in the presence of 2,2-DMP as methylating agent for forty-eight hours no reaction was observed; we had expected to observe the hydrolysis of the oxazolidine ring under the acidic conditions (Table 4, entry 5).²⁴ The optimum conditions for esterification were achieved by heating compound (13) under reflux in the presence of K₂CO₃ and Me₂SO₄ in anhydrous acetone for up to four hours (Table 4, entry 6).²⁵ The advantages of this method are the simple work-up procedure involved and the ease of scaling up the reaction to multi-gram scale.

The next step in the synthesis involved the conversion of the methyl ester (12) to the corresponding tertiary alcohol (14) (Scheme 9).
Scheme 9 Reagents and Conditions: \( \text{i: MeMgBr (6 eq.), THF,} \ 0^\circ \text{C, 16 h, 40\%} \).

When compound (12) was subjected to methylmagnesium chloride (6 eq.) addition in THF at \( 0^\circ \text{C} \) over sixteen hours, the corresponding tertiary alcohol (14) was furnished in 40\% yield. Interestingly, when the reaction was performed at \(-78^\circ \text{C}\) or \(-40^\circ \text{C}\) no reaction was observed over two hours. Warming the reaction to room temperature surprisingly failed to give the product, with only starting material and other byproducts being observed after sixteen hours. Efforts to increase the yield of alcohol (14) by changing the nucleophile to methyl lithium were unsuccessful. When compound (12) was treated with methyl lithium at \(-78^\circ \text{C}\), no reaction materialized, with only starting material being observed. However, when the addition was performed at \( 0^\circ \text{C}, \) degradation of the starting material was observed. Attempts to improve the reaction by reducing the number of equivalents of methyl lithium used at \( 0^\circ \text{C} \) failed to give the desired product.

The next step involved the removal of the isopropylidene group in compound (14). This was successfully accomplished by treating compound (14) with a catalytic amount of methanolic \( p\text{TsA} \) at ambient temperature over sixteen hours, furnishing compound (15) in 65\% yield after recrystallization (Scheme 10). Due to the acceptable purity of compound (15), the crude material could be used in the next step without purification.
An X-ray crystal structure of compound (15), obtained following crystallization by slow vapour-diffusion of chloroform and hexanes, is depicted in figure 2.

We envisaged that the synthesis of compound (15) could be accomplished by a shorter route from compound (13). The strategy involved attempts to achieve a tandem esterification and hydrolysis of the oxazolidine unit under the acidic reaction conditions followed by Grignard addition. When compound (13) was heated under reflux with an excess of acetyl chloride in methanol over forty-eight hours, the corresponding acyclic ester (16) was formed in 64% yield (Scheme 11).
Unfortunately, treatment of compound (16) with excess Grignard reagent (MeMgBr) at room temperature over sixteen hours failed to give compound (15), with only starting material being recovered (Scheme 12).

The failure to form compound (15) from (16) might be due to the generation of the magnesium salt of (16) arising, presumably, from an initial deprotonation of the hydroxyl proton by the MeMgBr. We envisaged that trapping the anion with a labile electrophile/protecting group might simplify MeMgBr addition to the ester moiety. Subsequent modification of the reaction by using trimethylsilyl chloride (Me$_3$SiCl) as an in situ protecting group together with MeMgBr furnished the desired product (15), albeit in low yield (27%). A range of other unidentified byproducts were also generated in this reaction (Scheme 13).
All attempts to improve the yield of compound (15) by reducing the reaction temperature successively to $-10^\circ\text{C}$, $-40^\circ\text{C}$ and $-78^\circ\text{C}$ led exclusively to the recovery of the starting material, implicating a lack of reactivity of the Grignard reagent at these temperatures.

With the failure to improve the yield of compound (15) from (16), we decided to abandon this strategy in favour of our earlier synthetic route (See Scheme 10). The next step in the synthesis was to convert compound (15) to the corresponding 1,3-dioxane (17). However, all attempts to access compound (17) under various reaction conditions proved fruitless (Scheme 14, Table 5).
Table 5 Reaction conditions for the attempted acetonide formation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid/Base</th>
<th>Solvent</th>
<th>Reagent</th>
<th>Yield of 17 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pTSA</td>
<td>Acetone (r.t./reflux)</td>
<td>2,2-DMP</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>pTSA</td>
<td>Acetone (r.t./reflux)</td>
<td>2-methoxypropene</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>CSA</td>
<td>Acetone (r.t./reflux)</td>
<td>2-methoxypropene</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>CSA</td>
<td>DMF (r.t./80°C)</td>
<td>2,2-DMP</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>CSA</td>
<td>THF(r.t./reflux)</td>
<td>2-methoxypropene</td>
<td>SM</td>
</tr>
<tr>
<td>6</td>
<td>BF₃(OEt)₂</td>
<td>DCM(r.t./reflux)</td>
<td>2-methoxypropene</td>
<td>SM</td>
</tr>
<tr>
<td>7</td>
<td>pTSA</td>
<td>Toluene (Dean Stark)</td>
<td>2,2-DMP</td>
<td>Decomposition</td>
</tr>
<tr>
<td>8</td>
<td>2,6-lutidine</td>
<td>Acetone, −78 °C</td>
<td>TMSOTf, 2,2-DMP</td>
<td>SM</td>
</tr>
</tbody>
</table>

The standard conditions used to prepare acetonides from diols involve a catalytic amount of an acid (usually pTSA or CSA) and acetone at room temperature. However, when diol (15) was treated with catalytic pTSA or CSA in the presence of 2,2-DMP or 2-methoxypropene in acetone at room temperature for up to forty-eight hours, no reaction was observed, as analysed by TLC (Table 5, entry 1-3). Heating under reflux the reaction mixture under these conditions resulted either in the decomposition or recovery of the starting material.

The X-ray crystal structure of compound (15) revealed that each molecule forms one intramolecular and four intermolecular hydrogen bonds (two as donor, two as acceptor). Suspecting the hydrogen bonds to be the problem, the effect of solvents capable of disrupting the hydrogen bond(s) present in the molecule was investigated. When DMF was used as a solvent in the presence of 2,2-DMP at room temperature the starting material was recovered. Increasing the reaction temperature to 80 °C for three days did not lead to any product with only starting material being recovered (Table 5, entry 4). No acetonide was formed by utilizing THF as solvent either at room temperature or reflux in the presence of CSA and 2-methoxypropene (Table 5, entry 5).

Decomposition was observed when (15) was heated under reflux with catalytic pTSA, and 2,2-DMP in toluene using a Dean-Stark apparatus overnight. Attempts to utilize the
Noyori acetalization methodology by exposing compound (15) to an excess of TMSOTf (2.2 eq.), 2,2-DMP and 2,6-lutidine as a base, failed to mediate the construction of the 1,3-dioxane ring.\textsuperscript{29}

The failure to form the acetonide is thought to stem from unfavourable 1,3-diaxial interactions between the methyl groups, if the dioxane ring retains a chair conformation (Figure 3).

![Figure 3 1,3-diaxial interaction in the dioxane ring presumably disfavours its formation.](image)

We envisaged that synthesizing the corresponding methylene acetal (18) might be successful, due to minimized 1,3-diaxial interactions. Compound (15) was thus submitted to different reaction conditions in pursuit of forming dioxane (18) (Scheme 15, Table 6).

![Scheme 15 Formation of methylene acetal (18).](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid/Base</th>
<th>Solvent</th>
<th>Reagent</th>
<th>Yield of (18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOH</td>
<td>DMSO</td>
<td>CH$_2$Br$_2$</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>CSA</td>
<td>Toluene</td>
<td>Para-Formaldehyde</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>
As summarized in Table 6, the synthesis of compound (18) was far from straightforward. Reacting compound (15) with dibromomethane in DMSO in the presence of finely powdered potassium hydroxide over sixteen hours failed to give (18) (Table 6, entry 1). Acid catalysed acetalization by using a catalytic amount of CSA and \textit{para}-formaldehyde in toluene under Dean-Stark conditions for sixteen hours led to the decomposition of the starting material (Table 6, entry 2). Treating compound (15) with CSA in neat dimethoxymethane failed to give the desired product, while exposure to TMSOTf, DMM and 2,6-lutidine in acetone at 0°C, resulted in the decomposition of the starting material (Table 6, entry 3 and 4). When diol (15) in DMM was stirred with a catalytic amount of \textit{pTSA} and LiBr at room temperature for up to six days, only the starting material was recovered. However, when a stoichiometric amount of \textit{pTSA} (1 eq.) and LiBr (1 eq.) was utilized, the corresponding methylene acetal (18) was obtained in 86% yield (Table 6, entry 5). This method was found to be very effective, giving exceptionally pure (18), and thus not requiring chromatographic purification.

Having successfully synthesized the methylene acetal (18), the next task was the removal of the Cbz group to afford the primary amine (19). However, cleavage of the Cbz group proved to be extremely challenging (Scheme 16, Table 7).
Table 7 Hydrogenation conditions tried for the cleavage of Cbz-group.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and reaction conditions</th>
<th>Yield of 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂ (1 atm.), Pd/C, EtOH, r.t., 5 days</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>H₂ (40 psi.), Pd/C, EtOH, r.t., 4 days</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>H₂ (1 atm.), Pd(OH)₂/C, EtOH, r.t., 5 days</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>Ammonium formate, Pd/C, EtOH</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>LiBH₄, TMSCl, THF, r.t., 48 h</td>
<td>SM</td>
</tr>
<tr>
<td>6</td>
<td>Hydrazine hydrate, reflux, 12 h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>7</td>
<td>NaOBU₁, THF/H₂O, reflux, 16 h</td>
<td>SM</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OH)₂/C, i-PrOH, HCOONH₄, microwave, 5 minutes</td>
<td>90%</td>
</tr>
</tbody>
</table>

The standard conditions for the removal of the Cbz group is through hydrogenolysis using palladium on carbon. However, treating compound (18) with Pd/C under a hydrogen atmosphere (1 atm.) over five days failed to afford compound (19). Performing the hydrogenation under high pressure (40 psi) for up to four days also failed, with recovery of the starting material (Table 7, entry 2). Changing the catalyst from Pd/C to Pearlman’s catalyst did not alter the outcome (Table 7, entry 3). The starting material was also recovered when the reaction was performed under transfer hydrogenation conditions in the presence of ammonium formate as hydrogen donor at room temperature over forty-eight hours (Table 7, entry 4). Further attempts to cleave the Cbz group in the presence of LiBH₄ and TMSCl in THF for up to forty-eight hours led exclusively to recovery of starting material.³² Cleavage under basic reaction conditions utilizing sodium tert-butoxide in the presence of THF and water also failed (Table 7, entry 7). These reaction conditions have successfully been utilized in the deprotection of the tert-butyloxycarbonyl (Boc) group. While conventional transfer hydrogenation conditions failed to give results, an efficient (90%) and rapid cleavage of the Cbz group was finally achieved by microwave-assisted transfer hydrogenation with Pd(OH)₂/C in i-PrOH as the solvent and HCOONH₄ as hydrogen donor (Table 7, entry 8).³³

With amine (19) in hand, we proceeded with the synthesis of the 2-(2-bromoethyl)benzaldehyde (21). Treatment of isochroman (20) with bromine in carbon tetrachloride under reflux for one hour, followed by exposure to concentrated
hydrobromic acid for ten minutes provided compound (21) in a 65% yield. Subsequent condensation of aldehyde (21) with enantiopure primary amine (19) gave the catalyst (22) in 60% yield after counter-ion exchange (Scheme 17).

![Scheme 17](image)

Scheme 17 Reagents and Conditions: i: a) Br₂, CCl₄, reflux, 1 h. b) HBr (conc.), reflux, 10 min.; ii: a) amine 19 (1 eq.), EtOH, 0 °C-r.t., 12 h. b) NaBPh₄ (1.1 eq.), MeCN, r.t., 5 min., 60%.

An interesting feature of this catalyst was the observation of two sets of signals in both the $^1$H-NMR and $^{13}$C-NMR spectra. The ratio of the two iminium proton signals at ca. 8.98 ppm. and 9.65 ppm. respectively was 1:1.6, arising presumably from restricted rotation around the C-N bond. However, VT-NMR (20-120 °C) of the sample failed to coalesce the sets of signals, presumably due to a high energy barrier to rotation. A partial racemization of the precursor amine (19) during the transfer hydrogenation step is also a possibility.

These results suggest that we have an atropisomeric mixture of catalyst (22) arising exclusively from the restricted rotation around N(sp²)-C(sp³, tertiary) bond. This phenomenon has also been observed by others.³⁴,³⁵

2.1.2 Synthesis of parent dihydriodoisoquinolinium salt.

With the successful synthesis of catalyst (22), we proceeded with the synthesis of the parent catalyst (2) for comparative epoxidation studies. Catalyst (2) has previously been used in the asymmetric epoxidation of alkenes, giving the corresponding epoxides with up to 97% ee under non-aqueous conditions.³⁶
The starting point of the synthesis involved again protection of (+)-thiomamine (4) to the corresponding N-Cbz protected-(+)-thiomamine (5). Subsequent oxidation of the sulfur moiety in (5) to the sulfone was accomplished using Oxone in ethanol, giving compound (23) in a 90% yield. Cyclization of (23) with 2,2-dimethoxypropane, acetone and catalytic toluene-p-sulfonic acid (pTSA) gave the acetonide (24) in an excellent 80% yield. Cleavage of the Cbz group proceeded smoothly in the presence of Pd/C under a hydrogen atmosphere to give the primary amine (25) in 89% yield (Scheme 18).

Subsequent condensation of primary amine (25) with 2-(2-bromoethyl)benzaldehyde (21) gave the desired catalyst in good yield (Scheme 19).
2.1.3 Catalytic asymmetric epoxidation.

A range of epoxidation reactions was then carried out under aqueous conditions using the new iminium salt catalyst (22) (5 mol%), Oxone (2 equivalents), Na$_2$CO$_3$ (4 equivalents) in CH$_3$CN:H$_2$O (1:1) at 0 °C. A comparison of the results obtained with the original catalyst (2)$^{37}$ is displayed in Table 8.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Catalyst 22</th>
<th>Catalyst 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>In all cases: ee (%)$^b$; Conv. (%)$^c$; Configuration$^d$</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>phenyl</td>
<td>34, 100 (−)-1S,2S</td>
<td>39, 100 (−)-1S,2S</td>
</tr>
<tr>
<td>2</td>
<td>naphthalene</td>
<td>46, 72$^e$ (−)-1R,2S</td>
<td>47, 100 (−)-1S,2R</td>
</tr>
<tr>
<td>3</td>
<td>anthracene</td>
<td>34, 75$^e$ (−)-1S,2R</td>
<td>45, 100 (−)-1S,2R</td>
</tr>
<tr>
<td>4</td>
<td>3-phenoxy-2-methyl</td>
<td>27, 50 (−)-1S,2R</td>
<td>32, 50 (−)-1S,2R</td>
</tr>
</tbody>
</table>

$^a$ Epoxidation conditions: Iminium salt 22 (5 mol %); 2 (5 mol%), Oxone (2 eq.), Na$_2$CO$_3$ (4 eq.), MeCN:H$_2$O (1:1), 0 °C, 2 h. $^b$ Enantiomeric excess determined by $^1$H-NMR with Eu(hfc)$_3$ (0.1 mol eq.) as chiral shift reagent or by Chiral HPLC on a chiralcel OD Column or by Chiral GC. $^c$ Conversion evaluated from the $^1$H-NMR by integration of alkene versus epoxides peak. $^d$ The absolute configuration of the major enantiomer was determined by comparison to those reported in literature. $^e$ Isolated yield.

As illustrated in Table 8, both catalyst (22) and catalyst (2) induced almost identical enantioselectivities (within experimental error) for the most substrates. It is unclear as to why 1,2-dihydronaphthalene proved to be a poorer substrate with catalyst (22) (34% ee) compared to catalyst (2) (45% ee).
A possible explanation for the poor performance of catalyst (22) in expressing higher enantioselectivities is the existence of the catalyst as a diastereoisomeric mixture. This might in principle lead to four diastereoisomeric oxaziridinium salts arising from the attack of the oxidant at the re or si faces of the diastereoisomeric iminium species. This in turn, vitiates the ability of the catalyst to achieve higher enantiocontrol during the oxygen transfer step to the pro-chiral alkenes.

2.1.4 Attempted synthesis of 6-methyl substituted dihydroisoquinolinium salt.

We envisaged that another primary amine could be produced from aldehyde (11) by Grignard addition followed by subsequent manipulation. This strategy would in practice allow the synthesis of a range of primary amines, which could be used to access different catalysts.

Our initial studies utilized MeMgBr as the Grignard reagent. Thus, MeMgBr addition to aldehyde (11) at −78 °C over twelve hours proceeded in non-stereoselective manner, yielding 56% of a 1:1 mixture of diastereoisomers as analysed from the crude \(^1\)H NMR spectrum. Separation of the diastereoisomers gave 33% of one isomer (Scheme 21). This reaction was also found to give capricious yields under identical conditions.
The lack of stereoselectivity in the above reaction when using MeMgBr has also been observed in the closely related Cbz- or Boc-protected Garner’s aldehyde. Subjecting oxazolidine (26) to ring-cleavage conditions using methanolic pTSA overnight gave the corresponding diol (27) in 61% yield. However, attempts to form the acetonide from 2,2-DMP and catalytic pTSA in acetone were unsuccessful (Scheme 22).

Due to the failure to form acetonide (28), coupled with the capricious yield and poor diastereoselectivity in the MeMgBr addition step, this route was abandoned.

2.1.5 Attempted synthesis of 6-isopropyl substituted catalysts.

The failure to achieving good diastereoselectivity in the addition reaction coupled with literature precedent showing lack of selectivity when Cbz group is utilized as a protecting group prompted us to pursue other target catalysts incorporating an
isopropyl group. We hoped that the bulky isopropyl group would provide a high steric effect, and thus allow the iminium salt catalysts to induce high enantioselectivities in the epoxidation of alkenes. We initially attempted the synthesis of the two catalysts depicted in figure 4.

![Figure 4 Potential iminium salt catalysts.](image)

Our synthetic route utilized commercially available optically active aminodiols (31) and (32), which upon exposure to Boc-anhydride in dichloromethane overnight led to Boc-protected (33) and (34) quantitatively. Regioselective protection of the primary hydroxyl group to the corresponding TBDPS-protected (35) and (36) proceeded in high yields (Scheme 23).

![Scheme 23 Reagents and Conditions](image)

Subsequent cyclization of (35) and (36) with 2,2-dimethoxypropane, acetone and catalytic toluene-p-sulfonic acid (pTSA) as the acid source provided the oxazolidine ring (37) and (38) in high yields. While desilylation of (37) with TBAF proceeded in high yields, desilylation of (38) was found to be problematic, giving low to moderate yields (30-60%). However, consistently high yields (79-85%) were obtained by performing the reaction at 0 °C and in high dilution (by using syringe pump in the...
addition of TBAF), and over shorter reaction times (typically three hours). Parikh-Doering oxidation of primary alcohols (39) and (40) to the corresponding aldehydes (41) and (42) proceeded in good yields (Scheme 24). This oxidation procedure has the advantages of being performed at ambient temperature and not requiring chromatographic purification of the aldehydes, making it ideal for large scale synthesis.

![Chemical Structure](image)

**Scheme 24 Reagents and Conditions:**

1. 2,2-DMP (10 eq.), acetone, pTSA (0.1 eq.), r.t., 12 h; 2. TBAF (1.1 eq.), THF, r.t., 12 h for 37, or 0 °C, 3 h for 38; 3. SO₂-Pyridine (3 eq.), Et₃N (3 eq.), DMSO, r.t., 12 h.

As discussed above, we aimed to introduce an isopropyl group for its steric effect. Treating aldehyde (42) with isopropylmagnesium chloride (3 eq.) at -78 °C was ineffective, leading to a mixture of starting material and unknown degradation products. Reducing the amount of the Grignard used to 1.1 eq. failed to give the desired product (Scheme 25).

![Chemical Structure](image)

**Scheme 25 Reagents and Conditions:** i: t-PrMgCl (3 eq.), THF, -78 °C, 3 h.

The failure of the Grignard addition is thought to stem from the presence of the electrophilic nitro group. Indeed, Grignard and organo-lithium reagents are known to react with electrophilic functional groups such as cyano, nitro, halo and trialkylstannyl. These complications can be avoided by using either organo-titanium...
or organo-zirconium reagents which have been shown to react selectively with carbonyl compounds in the presence of nitro and cyano groups.\(^4^2\) However, these options have yet to be attempted.

Conversely, when aldehyde (41) was treated with isopropylmagnesium chloride (3 eq.) overnight at \(-78^\circ\text{C}\) to room temperature, an inseparable mixture of the desired alcohol (43) alongside starting material and reduction product (39) was obtained in a 1:1:1 ratio (Scheme 26).

![Scheme 26 Reagents and Conditions: i: i-PrMgCl (3 eq.), THF, \(-78^\circ\text{C}\)-r.t., 3 h.][1]

The difficulties in obtaining a facile addition of isopropylmagnesium chloride to aldehydes (41) and (42) forced us to abandon the synthesis of catalysts (29) and (30).

### 2.1.6 Conclusion.

In conclusion, we have successfully developed a robust and reliable synthetic route towards the synthesis of iminium catalyst (22) in twelve synthetic steps from commercially available enantiopure (+)-thiomamine (4). Catalyst (22) existed as an atropisomeric mixture due to the restricted rotation around the \(\text{N}(\text{sp}^2)-\text{C}(\text{sp}^3, \text{tertiary})\) bond. Catalyst (22) has also almost identical reactivity and enantioselectivity profile to that of catalyst (2) towards the epoxidation of alkenes under aqueous conditions. The lack of improved chiral induction by catalyst (22) is presumably due to its existence as an atropisomeric mixture. We have also attempted, and failed, to synthesize catalysts (29) and (30), incorporating an isopropyl group at the C6 position of the 1,3-dioxane ring due to the difficulties encountered in the addition of isopropylmagnesium chloride to aldehydes (41) and (42).
2.2 Catalysts Based on a Binaphthalene Structure.

2.2.1 *N*-Chiral substituted binaphthalene catalysts.

As discussed above, Page has reported the binaphthalene-derived catalyst (44), which proved to be highly enantioselective and reactive, giving ee's of up to 95\%.

![Figure 5: The most enantioselective azepinium salt catalyst previously developed.](image)

As a logical continuation of this work, we aimed to probe the electronic effects of substituents on enantioselectivity. We thus aimed to synthesize several new binaphthalene-azepinium salt analogues of (44) incorporating electron-withdrawing and electron-donating substituents at the *para*-position of the aromatic ring (Figure 6).

![Figure 6: Potential Catalysts to be prepared.](image)

2.2.1.1 Catalyst syntheses.

These catalysts were easily prepared by cyclocondensation of enantiopure primary amines with the corresponding chiral binaphthalene-derived bromoaldehyde, which
was prepared in turn from enantiomerically pure commercially available R- or S-(1,1')-binaphthalene-2,2'-diol (BINOL). When R-BINOL (49\textsubscript{R}) was treated with trifluoromethanesulfonic anhydride in the presence of DMAP as a catalyst and 2,6-lutidine as a base in dichloromethane for sixteen hours, the corresponding triflate-protected product (50\textsubscript{R}) was produced in nearly quantitative yield. This was followed by a Kumada coupling reaction of (50\textsubscript{R}) with methylmagnesium bromide in the presence of bis(diphenylphosphino)propane nickel(II) chloride [NiCl\textsubscript{2}(dppp)\textsubscript{2}] as catalyst, to give the corresponding bis-methylene product (51\textsubscript{R}) in 90% yield (Scheme 27).

\[ \text{Scheme 27 Reagents and Conditions: i: } \text{Tf}_2\text{O} \text{ (3 eq.), DMAP (0.4 eq.), 2,6-lutidine (3 eq.), DCM, } -30^\circ\text{C-r.t., 16 h, 99%}; \text{ ii: } \text{MeMgBr (4 eq.), NiCl}_2\text{(dppp)}\text{ (0.07 eq.), Et}_2\text{O, } -78^\circ\text{C-r.t., 16 h, 90%}. \]

Synthesis of the bis-bromomethyl binaphthalene (52\textsubscript{R}) was achieved by refluxing (51\textsubscript{R}) with N-bromosuccinimide (NBS) in the presence of azo-bis-isobutyronitrile (AIBN) as a radical initiator in cyclohexane for three hours. Due to the many byproducts in the reaction, the product (52\textsubscript{R}) was directly precipitated from the reaction mixture, as colourless crystals in 54% yield (Scheme 28).

\[ \text{Scheme 28 Reagents and Conditions: i: } \text{NBS (2.2 eq.), AIBN (0.1 eq.), cyclohexane, reflux, 3 h, 54%}. \]
With compound \((52_R)\) in hand, the next step involved the formation of oxepine \((53_R)\). The oxepine has previously been formed in our group by heating \((52_R)\) under reflux in saturated aqueous sodium carbonate and 1,4-dioxane for twenty-four hours. When \((52_R)\) was submitted to identical conditions for thirty-six hours, the corresponding oxepine \((53_R)\) was obtained in 81% yield. Subsequent heating of oxepine \((53_R)\) with molecular bromine for one hour afforded the corresponding bromoaldehyde \((54_R)\) in a variable 33-65% yield (Scheme 29).

![Scheme 29 Reagents and Conditions: i: Na₂CO₃ (sat. aq.)/1,4-dioxane (1:1), reflux, 40 h, 81%; ii: Br₂ (1.1 eq.), reflux, cyclohexane, 1 h, 33-65%.

A major side-product in the ring-opening reaction of oxepine \((53_R)\) was the dibromo compound \((52_R)\). The opposite S-enantiomer \((54_S)\) was also produced from the same synthetic sequence in low yields, with \((52_S)\) being a major side-product again. Attempts to inhibit the formation of \((52_R)\) by reducing the reaction time, changing the solvent from cyclohexane to CCl₄, and reducing the temperature, failed to improve the yields. Besides the low yields, the separation of compound \((54_R)\) from \((52_R)\) required laborious and careful column chromatography, rendering this step unattractive for large scale synthesis.

With the successful synthesis of bromoaldehyde \((54_R)\), we embarked upon the synthesis of the amino compounds required for the catalyst syntheses. The first amine targeted was one which incorporated an electron-donating methoxy group at the para-position of the aromatic ring.

The synthetic procedure started from commercially available L-tyrosine methyl ester \((55)\), which upon Boc-protection and methylation using potassium hydroxide and iodomethane afforded \((57)\) in excellent yield (Scheme 30).
Following the work of Ohfune, benzylic oxidation of (57) was achieved in the presence of potassium persulfate ($K_2S_2O_8$) and a catalytic amount of copper sulfate to form the corresponding oxazolidinone (58) with high diastereoselectivity (98% $R$ at C3) but poor yield (Scheme 31).45

The authors postulate that the high diastereoselectivity stems from a difference of stability between two possible benzylic cation intermediates (A) and (B). Conformer (A) suffers from steric interaction between the ester group and the ortho hydrogen atom. Intramolecular trapping of the cation of intermediate (B) by the carbonyl oxygen coupled with ready generation of the tert-butyl cation is thought to be the driving force of the reaction.

The authors also postulate the tert-butyl cation to be more stable than corresponding benzylic cation. This is supported by the author’s observations that poor yields of oxazolidinones were obtained from compounds containing Cbz-protecting groups.
Despite the high diastereoselectivity of the reaction, poor yields of (58) (30% at best) were achieved, which was not in accord with the reported 54% yield. A major side-product consistently generated from the reaction was 4-methoxybenzaldehyde (65-70%) arising presumably from over-oxidation of (58). Attempts to optimize the reaction by decreasing the reaction time and temperature led to a mixture of starting material, product (58) and 4-methoxy-benzaldehyde. Increasing the reaction times on the contrary, led to an increase in side-product formation.

Subsequent reduction of ester (58) with sodium borohydride afforded alcohol (59) in an excellent 90% yield. This was followed by the hydrolysis of (59) in refluxing 1M sodium hydroxide for thirty minutes, affording aminodiol (60) in excellent yield (Scheme 32).

\[
\begin{aligned}
58 & \xrightarrow{\text{NaBH}_4 (2.2 \text{ eq.}), \text{EtOH, } 0 \degree \text{C-r.t., } 45 \text{ min}, \text{90\\%}} 59 \\
59 & \xrightarrow{1 \text{ M NaOH, reflux, } 30 \text{ min}, \text{88\\%}} 60
\end{aligned}
\]

Scheme 32 Reagents and Conditions: i: NaBH₄ (2.2 eq.), EtOH, 0 °C-r.t., 45 min, 90%; ii: 1M NaOH, reflux, 30 min, 88%.

The next step involved the formate protection of amine (60) followed by acetonide formation. However, attempted cyclization of diol (61) with 2,2-dimethoxypropane, acetone and catalytic pTSA afforded an inseparable mixture of the desired six-membered dioxane (62) alongside five-membered oxazolidine (63) in a 1:1.5 ratio (Scheme 33).

\[
\begin{aligned}
61 & \xrightarrow{2,2\text{-DMP (10 eq.), pTSA (0.1 eq.), acetone.}} 62 + 63
\end{aligned}
\]

Scheme 33 Reagents and Conditions: i: 2,2-DMP (10 eq.), pTSA (0.1 eq.), acetone.
Attempted cyclization in the presence of catalytic boron trifluoride-diethyletherate led to the decomposition of the starting material. Eventually, an effective formation of dioxane (62) was achieved in the presence of catalytic scandium triflate. Subsequent deprotection of the formate group using hydrazine hydrate gave the desired primary amine (64) in high yield (Scheme 34).

![Scheme 34](image)

**Scheme 34 Reagents and Conditions:**

- i: 2,2-DMP (10 eq.), Sc(OTf)$_3$ (0.1 eq.), acetone, r.t., 12 h, 91%;
- ii: NH$_2$NH$_2$·H$_2$O, H$_2$O, reflux, 3 h, 95%.

Although the desired primary amine (64) was successfully prepared, this synthetic route suffered from the low yield of the benzylic oxidation step in the formation of (58) (Scheme 31). As described above, this step afforded a maximum of 30% yield, making it unattractive. Upon close scrutiny of Ohfune’s work, the authors’ reported high yield (76%) in the oxidation step was achieved, when acetate-protected (65) was used as a substrate (Figure 7).

![Figure 7](image)

**Figure 7** Good benzylic oxidation substrate.

Hence, compound (57) was reduced with sodium borohydride in ethanol, affording alcohol (66) (40%) alongside trans-esterification product (67) (33%) (Scheme 35).
A superior yield of alcohol (66) was achieved using lithium borohydride in methanol. Subsequent protection of the free alcohol to give acetate-protected (65) proceeded in a quantitative yield (Scheme 36).

Benzylic oxidation of acetate (65) under the reaction conditions described above disappointingly afforded 35-40% yield of (68), contrary to the reported 76% yield. As observed above, a substantial amount of 4-methoxybenzaldehyde was generated, and all efforts to further optimize the reaction were unsuccessful. Treatment of (68) with refluxing 1M NaOH led to the aminodiol (60) in 85% yield (Scheme 37). Primary amine (64) was then accessed using the same synthetic procedure outlined above (Scheme 34).

Scheme 35 Reagents and Conditions: i: NaBH₄ (2.2 eq.), EtOH, 0 °C-r.t., 3 h.

Scheme 36 Reagents and Conditions: i: LiBH₄ (4 eq.), Et₂O, MeOH, 0 °C-r.t., 12 h, 98%; ii: Acetic anhydride (1.2 eq.), DMAP (0.1 eq.), DIPEA (1.2 eq.), r.t., 16 h, 100%.

Scheme 37 Reagents and Conditions: i: K₂S₂O₄ (2 eq.), CuSO₄ (0.2 eq.), MeCN:H₂O (1:1), 70 °C, 2.5 h, 40%; ii: 1M NaOH, reflux, 30 min., 85%.
We also wished to prepare primary amines incorporating an electron-donating amino group, and an electron-withdrawing nitro group at the para-position of the aromatic ring. Thus, protection of aminodiols (31) and (32) with a formate group and subsequent cyclization with 2,2-DMP, acetone and catalytic HBr or pTSA as the acid source, afforded six-membered dioxane (69) and (70) in excellent yield. Treatment of (69) and (70) with hydrazine hydrate for three hours afforded (71) and diamine (73) in excellent yields, while treatment of (69) with hydrazine hydrate for forty-five minutes gave nitro-containing primary amine (73) in 50-60% yields, as extended exposure to the reaction conditions also reduced the nitro-functionality to amine (Scheme 38).

Scheme 38 Reagents and Conditions: i: MeOCHO (1.1 eq.), NaOMe (0.1 eq.), MeOH, r.t., 12 h; ii: 2,2-DMP (10 eq.), pTSA (0.1 eq.) or HBr (0.1 eq.) for (69), acetone, r.t., 12 h, 94%; iii: NH₂NH₂, H₂O, reflux.

With the successful syntheses of amines (25), (64), (71), (72) and (73), each incorporating groups with different electronic effects at the para-position of the aromatic ring, we proceeded with the catalyst syntheses. The catalysts were prepared in good to moderate yields by cyclocondensation of bromoaldehydes (54ᵣ) or (54ₛ) with the primary amines, followed by cation exchange (Scheme 39, Table 9).

Scheme 39 Reagents and Conditions: i: R*-NH₂ (1 eq.), EtOH, 40 °C, 12 h; ii: NaB₄ (1.1 eq.), MeCN, r.t., 5 min.
Table 9 Yields of iminium salt catalysts from cyclocondensation of chiral primary amines with bromoaldehydes (54).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bromo-aldehyde</th>
<th>Amine</th>
<th>Catalyst Number</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>$54_R$</td>
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<td>65</td>
</tr>
<tr>
<td>2</td>
<td>$54_R$</td>
<td><img src="image" alt="Amine 72" /></td>
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<td>69</td>
</tr>
<tr>
<td>3</td>
<td>$54_R$</td>
<td><img src="image" alt="Amine 73" /></td>
<td>47</td>
<td>68</td>
</tr>
<tr>
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<td>$54_S$</td>
<td><img src="image" alt="Amine 64" /></td>
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<td>57</td>
</tr>
<tr>
<td>5</td>
<td>$54_R$</td>
<td><img src="image" alt="Amine 71" /></td>
<td>44</td>
<td>66</td>
</tr>
</tbody>
</table>

2.2.1.2 Catalytic asymmetric epoxidation.

With the new catalysts in hand, a range of epoxidations were carried out. A comparison of the results with those obtained using the previously developed catalyst (44) is shown in Table 10.
Table 10 Catalytic asymmetric epoxidation of alkenes with catalysts 44-48.*

<table>
<thead>
<tr>
<th>Alkene</th>
<th>Catalyst</th>
<th>Conversion b</th>
<th>Yield (%) c</th>
<th>ee (%) d</th>
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<td>66</td>
<td>74</td>
<td>(-)-1S,2S</td>
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<td></td>
<td>47</td>
<td>100</td>
<td>69</td>
<td>79</td>
<td>(-)-1S,2S</td>
</tr>
<tr>
<td></td>
<td>48 f</td>
<td>100</td>
<td>71</td>
<td>80</td>
<td>(+)-1R,2R</td>
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<tr>
<td></td>
<td>44 g</td>
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<td>91</td>
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<td>18</td>
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<td>46 h</td>
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<td>58</td>
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</table>

* Epoxidation conditions: Iminium salt (5 mol %), Oxone (2 eq.), Na₂CO₃ (4 eq.), MeCN:H₂O (1:1), 0 °C, 2 h. b Conversion evaluated from the ¹H-NMR by integration of alkene versus epoxides peak. c Isolated yield. d 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 or by Chiral GC. The absolute configuration of the major enantiomer was determined by comparison to those reported in literature. Epoxidation conditions: iminium salt (5 mol %), Oxone (2 eq.), NaHCO₃ (5 eq.), MeCN:H₂O (10:1), 0 °C, 2 h. 20 min. reaction time. 3 h reaction time. 4 h reaction time. 35 min. reaction time. 45 min. reaction time.

Clearly, catalysts 45-47 are less reactive and enantioselective than the original catalyst (44). For example, catalyst (44) provided 1-phenycyclohexene oxide with 91% ee in under twenty minutes when 5 mol% of the iminium salt was employed, whereas catalysts 45, 46 and 47 required longer reaction times, and were less selective (76%, 74% and 79% ee, respectively). The same trend is seen for all the other substrates tested. For example, 1-phenyl-3,4-dihydronaphthalene was epoxidized in 95% ee using catalyst 44, compared to catalysts 45 (68% ee), 46 (69% ee) and 47 (59% ee). However, catalyst (48), containing an electron-donating methoxy group, induces enantioselectivities similar to or higher than catalyst (44) for most substrates, an exception being when 1-phenylcyclohexene (48: 80% ee vs. 44: 91% ee), and 1-phenyl-3,4-dihydronaphthalene (48: 81% ee vs. 44: 95% ee) are used as substrates.

A common feature of catalysts 45-48 was their lack of reactivity under our reaction conditions (Oxone, Na₂CO₃, CH₃CN:H₂O 1:1), when using less electron-rich and bulky alkenes. For example, when catalysts 45-48 were utilized in the epoxidation of triphenylethylene and trans-stilbene as substrates, less than 10% conversions to their corresponding epoxides were observed in two hours. Prolonged reaction times of up to six hours did not improve the conversions.

A possible explanation for the poor reactivity is decomposition of the catalyst and/or Oxone under the reaction conditions. To test this concept, a 5 mol% solution of catalyst (45) in acetonitrile was added to a mixture of Oxone and sodium carbonate in water at 0 °C, and the mixture was stirred for one hour before the addition of 1-phenylcyclohexene. Subsequent stirring of the reaction mixture for a further two hours did not lead to any epoxide, as analysed by ¹H-NMR spectroscopy. This result unambiguously proves the termination of the catalytic cycle under the reaction conditions. We have previously observed 100% conversion when the catalyst and the alkene substrate were sequentially added to the reaction mixture (see Table 10).
To examine if the catalyst survives under this reaction conditions, the same sequence was repeated, but without the addition of the alkene substrate. After three hours of stirring, the crude material was analysed by $^1$H-NMR spectroscopy. The iminium signal of the catalyst was present in the $^1$H-NMR spectrum, confirming that the catalyst is stable under our reaction conditions. We concluded that the termination of the catalytic cycle is probably due to the decomposition of Oxone. Indeed Oxone is known to decompose at higher pH.  

We observed an increase in conversions to epoxides when we utilized the reaction conditions developed by Yang (10:1 acetonitrile:water, 5 equiv. NaHCO$_3$, 2 equiv. Oxone).  

For example, epoxidation of trans-stilbene using these conditions and catalysts 45-48 proceeded quantitatively (100%) in two hours, compared to 10% conversion when using our reaction conditions over six hours.

2.2.2 $N$-Achiral substituted binaphthalene catalysts.

As indicated above in the introduction (Chapter 1, section 1.1.5.2), some years ago, Aggarwal described a binaphthalene-fused azepinium salt catalyst, bearing an achiral methyl group as the nitrogen substituent, which was reported to give up to 71% ee in the epoxidation of 1-phenylcyclohexene. Other achiral nitrogen substituents in this system were claimed in the patent literature, together with reported ees for the epoxidation of 1-phenylcyclohexene mediated by the methyl-, ethyl-, and benzyl-substituted catalysts. We conjectured that the enantioselectivity of these azepinium salt catalysts might be enhanced if a sterically bulkier group were added at the nitrogen atom.

2.2.2.1 Improved Catalyst Synthesis.

The difficulty in consistently achieving high yields of (54$_R$) coupled with the laborious purification involved, prompted us to explore a more robust synthetic route towards the azepinium salt catalysts. Ideally, the synthetic route would be high yielding and chromatography-free.
As shown above (Scheme 40), we envisaged that the iminium catalysts could easily be prepared from *bis*-bromomethyl binaphthalene ($52_R$) by double displacement of bromide from ($52_R$) with primary amines, followed by oxidation to the iminium species and cation exchange. We also envisaged that the whole synthetic sequence could be carried out chromatography-free due to the crystalline nature of the desired catalysts.

To prove our concept, we attempted a gram-scale synthesis of catalyst (44). This catalyst has previously been synthesized using bromoaldehyde ($54_R$) (Scheme 39). Dibromide ($52_R$) was treated with L-acetonamine (71)$^{52}$ to form crude amine (74), which, upon heating under reflux with NBS in dichloromethane for two hours followed by cation exchange, gave catalyst (44) in 70% yield over three steps (Scheme 41).

This chromatography-free synthetic sequence was subsequently applied to the attempted syntheses of several *N*-achiral substituted binaphthyl azepinium salts (Scheme 42). The initial double displacement of dibromide ($52_R$) with a range of amines proceeded smoothly to afford the corresponding azepines in excellent yields (Table 11, entry 1-5). However, attempts to form an azepine from 2,4,6-tribromoaniline
failed, presumably due to the bulkiness of the amine, coupled with the reduced nucleophilicity of the conjugated amine (Table 11, entry 6).

Scheme 42 Reagents and conditions: i: Amine (1.1 eq), K₂CO₃ (3 eq.), CH₃CN, reflux, 16 h.

Table 11 Preparation of azepine from dibromide (52ₐ).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Azepine Number</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂N</td>
<td>75</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>H₂N-Ph</td>
<td>76</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>NH₂</td>
<td>77</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>H₂N</td>
<td>78</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>H₂N</td>
<td>79</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>Br-Br</td>
<td>SM</td>
<td></td>
</tr>
</tbody>
</table>
Azepines 75-79 were next submitted to oxidation conditions using NBS followed by cation exchange with sodium tetraphenylborate (Scheme 43, Table 12).

![Scheme 43](image)

Scheme 43 Reagents and conditions: i: NBS (1.2 eq.), AIBN (0.05 eq.), CH₂Cl₂, reflux, 2 h; ii: NaBPh₄ (1.1 eq.), EtOH, CH₃CN, r.t., 5 min.

Table 12 Preparation of iminium salt catalysts from oxidation of azepines 75-79.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Azepine Number</th>
<th>Catalyst Number</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>76</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>80</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>78</td>
<td>81</td>
<td>59</td>
</tr>
<tr>
<td>5</td>
<td>79</td>
<td>82</td>
<td>71</td>
</tr>
</tbody>
</table>

As illustrated in Table 12, good yields of the iminium salt catalysts were obtained using the new synthesis (Table 12, entry 3-5). An exception being the attempted oxidation of azepines (75) and (76), which failed to give the corresponding iminium salts (Table 12, entry 1-2). We only observed the decomposition of the azepines under the reaction conditions, resulting presumably, from radical chain reactions. Changing the reaction
conditions by treating azepines (75) and (76) with iodine and sodium acetate, led to the ammonium salt (83), resulting from the elimination of the tert-butyl and trityl groups (Scheme 44).

\[
\begin{align*}
\text{75 } \text{R}= \text{tert-butyl} \\
\text{76 } \text{R}= \text{trityl} \\
\text{83}
\end{align*}
\]

Scheme 44 Reagents and conditions: i: I₂ (3.5 eq.), NaOAc (3.5 eq.), EtOH, reflux, 2 h; ii: NaBPh₄ (1.1 eq.), EtOH, CH₃CN, r.t., 5 min.

We consequently prepared iminium salts (84) and (85) in good yields, by cyclocondensation of bromoaldehyde (54) with tert-butylamine and 2,6-dimethylaniline respectively, followed by cation exchange with sodium tetraphenylborate (Scheme 45).

\[
\begin{align*}
\text{54}_R \\
\text{84 } \text{R}= \text{tert-butyl, 60\%} \\
\text{85 } \text{R}= \text{2,6-dimethylaniline, 79\%}
\end{align*}
\]

Scheme 45 Reagents and Conditions: i: Amine (1.1 eq.), EtOH, 40 °C, 12 h.; ii: NaBPh₄ (1.1 eq.), CH₃CN, r.t., 5 min.

2.2.2.2 Catalytic asymmetric epoxidation.

With catalysts (80), (81), (82), (84) and (85) in hand, three alkene substrates were tested, initially with catalysts (84) and (85), derived from tert-butylamine and 2,6-xylidene respectively, under our standard aqueous conditions, using a 1:1 ratio of acetonitrile to water as solvent in the presence of Na₂CO₃ (Table 13).
Table 13 Asymmetric epoxidation of alkenes with catalysts 80-82 and 84-85.

<table>
<thead>
<tr>
<th>Alkene</th>
<th>Catalyst</th>
<th>Conversion to epoxide</th>
<th>Conversion to diol</th>
<th>Yield of epoxide (%)</th>
<th>ee (%)</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>84 e</td>
<td>78</td>
<td>—</td>
<td>54</td>
<td>84</td>
<td>(-)-1S,2S</td>
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<tr>
<td></td>
<td>85 e</td>
<td>40</td>
<td>—</td>
<td>30</td>
<td>40</td>
<td>(-)-1S,2S</td>
</tr>
<tr>
<td></td>
<td>84 f</td>
<td>83</td>
<td>17</td>
<td>67</td>
<td>72</td>
<td>(-)-1S,2S</td>
</tr>
<tr>
<td></td>
<td>81 f</td>
<td>84</td>
<td>16</td>
<td>62</td>
<td>71</td>
<td>(-)-1S,2S</td>
</tr>
<tr>
<td></td>
<td>82 f</td>
<td>89</td>
<td>11</td>
<td>73</td>
<td>82</td>
<td>(-)-1S,2S</td>
</tr>
<tr>
<td>PhMe</td>
<td>84 e</td>
<td>5</td>
<td>—</td>
<td>&lt;5</td>
<td>-</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>85 e</td>
<td>10</td>
<td>—</td>
<td>&lt;5</td>
<td>-</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>84 f</td>
<td>38</td>
<td>—</td>
<td>25</td>
<td>67</td>
<td>(-)-1S,2S</td>
</tr>
<tr>
<td></td>
<td>85 f</td>
<td>70</td>
<td>—</td>
<td>47</td>
<td>16</td>
<td>(-)-1S,2S</td>
</tr>
<tr>
<td></td>
<td>80 f</td>
<td>90</td>
<td>—</td>
<td>69</td>
<td>51</td>
<td>(-)-1S,2S</td>
</tr>
<tr>
<td></td>
<td>81 f</td>
<td>90</td>
<td>—</td>
<td>65</td>
<td>48</td>
<td>(-)-1S,2S</td>
</tr>
<tr>
<td></td>
<td>82 f</td>
<td>100</td>
<td>—</td>
<td>64</td>
<td>64</td>
<td>(-)-1S,2S</td>
</tr>
<tr>
<td>PhPh</td>
<td>84 e</td>
<td>4</td>
<td>—</td>
<td>&lt;5</td>
<td>-</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>85 e</td>
<td>5</td>
<td>—</td>
<td>&lt;5</td>
<td>-</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>80 f</td>
<td>90</td>
<td>—</td>
<td>74</td>
<td>25</td>
<td>(+)-S</td>
</tr>
<tr>
<td></td>
<td>81 f</td>
<td>67</td>
<td>—</td>
<td>52</td>
<td>22</td>
<td>(+)-S</td>
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<tr>
<td></td>
<td>82 f</td>
<td>90</td>
<td>—</td>
<td>71</td>
<td>28</td>
<td>(+)-S</td>
</tr>
</tbody>
</table>

a Conversions were evaluated from the \(^1\)H-NMR spectra by integration of alkene/diol/epoxide signals. 
Isolated yield. 
b Enantiomeric excesses were determined by \(^1\)H-NMR spectroscopy with Eu(hfc)\(_3\) (10 mol\%) as chiral shift reagent, or by chiral HPLC on a Chiralcel OD column, or by chiral GC on a Chiraldex B-DM column. d The absolute configurations of the major enantiomers were determined by comparison with literature values. e Epoxidation conditions: Iminium salt (5 mol\%), Oxone (2 eq.), Na\(_2\)CO\(_3\) (4 eq.), MeCN:H\(_2\)O (1:1), 0 °C, 2 h. f Epoxidation conditions: Iminium salt (5 mol\%), Oxone (2 eq.), NaHCO\(_3\) (5 eq.), MeCN:H\(_2\)O (10:1), 0 °C, 2 h.

As illustrated in Table 13, both catalyst (84) and (85) were relatively unreactive, leading for example to maximum conversions of 78% and 40% respectively when 1-phenylcyclohexene was used as a substrate (Table 13). Prolonged reaction times of up to six hours did not improve the conversions. The poor reactivity of these catalysts is
highlighted by the epoxidation of trans-\(\alpha\)-methylstilbene and triphenylethylene, where extremely poor conversions to epoxides were observed. Catalyst (84), however, afforded an excellent 84% ee in the epoxidation of 1-phenyle cyclohexene, so proving to be much more enantioselective than (85) (40% ee).

Interestingly, once again when the reaction conditions were amended to those of Yang to use a 10:1 ratio of acetonitrile to water as solvent and slightly more acidic conditions (use of NaHCO\(_3\) as base rather than Na\(_2\)CO\(_3\)), an increase in conversion was observed when using catalysts (84) and (85) and trans-\(\alpha\)-methylstilbene as a substrate. These conditions, however, tend to produce diol products in some cases, presumably through in situ hydrolysis of the epoxides, an effect which is exacerbated by use of an increased proportion of water. Despite the high enantioselectivity provided by catalyst (84), we abandoned its further use due to its poor reactivity, which perhaps results from high steric bulk at the nitrogen substituent.

We next screened catalysts 80-82, with a range of structural features in the nitrogen substituents but with less bulk than (84) proximal to the azepinium ring, under the same reaction conditions (Table 13). Catalysts (80) and (82) provide roughly identical reactivity. Catalyst (82) imparts higher enantioselectivities for most substrates than does catalyst (80), and is similar in enantioselectivity to (84) while providing much greater reactivity, and thus provides the best balance of selectivity and reactivity, presumably resulting in part from the size and shape of the isopropyl nitrogen substituent. For example, 1-phenyle cyclohexene and trans-\(\alpha\)-methyl stilbene are epoxidized with 82% and 64% ee respectively using catalyst (82), compared to 72% and 51% ee with catalyst (80). Catalyst (81) was less enantioselective than (80) and (82), affording similar enantioselectivities (up to 71% ee) to the catalyst developed by Aggarwal.\(^5^0\)

The observed increase in conversion under Yang's reaction conditions may arise from the increase in substrate solubility with added organic solvent. The slightly acidic conditions might also be responsible for the increased conversion, as Oxone is known to decompose at higher pH.\(^4^7\) To investigate which of these two factors was responsible for the observed increase in conversion, we tested the epoxidation of trans-\(\alpha\)-methylstilbene using catalyst (82) under four sets of reaction conditions (Table 14).
Asymmetric epoxidation of trans-α-methylstilbene under different conditions using catalyst (82). *

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oxone (2 eq.), Na₂CO₃ (4 eq.), MeCN:H₂O (1:1)</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>Oxone (2 eq.), NaHCO₃ (5 eq.), MeCN:H₂O (1:1)</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>Oxone (2 eq.), NaHCO₃ (5 eq.), MeCN:H₂O (10:1)</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>Oxone (2 eq.), Na₂CO₃ (4 eq.), MeCN:H₂O (10:1)</td>
<td>21</td>
</tr>
</tbody>
</table>

* Reaction time: 2 h. *Conversion evaluated from the ¹H-NMR by integration of alkene versus epoxides peak.

As illustrated in Table 14, the highest conversion was obtained using Yang’s reaction conditions (Table 14, entry 3). The use of NaHCO₃ and 1:1 ratio of acetonitrile to water also afforded complete conversion to epoxide (Table 14, entry 2). Interestingly, the use of our reaction conditions (entry 1), and the use of a 10:1 ratio of acetonitrile to water with Na₂CO₃ as base (entry 4), provided identical conversions. These results support our hypothesis that the increased conversion stems from the decreased auto-decomposition of Oxone under the slightly acidic conditions.

We prepared a range of cycloalkenes incorporating groups with different electronic effects at the para-position of the aromatic ring. Cyclohexanone (86) was treated with freshly prepared 4-methoxyphenylmagnesium bromide and 4-methylsulfone-phenylmagnesium bromide in tetrahydrofuran to afford tertiary alcohols (87) and (88) in excellent yields. Treatment of cycloheptanone (91) with phenylmagnesium bromide also afforded excellent yield of alcohol (92). Subsequent treatment of these alcohols with excess trifluoroacetic acid (TFA) in chloroform gave the corresponding alkenes (89), (90) and (93) in excellent yield (Scheme 46).
A number of alkenes including these were subjected to epoxidation mediated by catalyst (82) (Table 15).

**Table 15 Asymmetric epoxidation of alkenes with catalyst (82).**

<table>
<thead>
<tr>
<th>Alkene</th>
<th>Conversion to epoxide (%)</th>
<th>Conversion to diol (%)</th>
<th>Yield of epoxide (%)</th>
<th>ee (%)</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>89</td>
<td>11</td>
<td>73</td>
<td>82</td>
<td>(-)-1S,2S</td>
</tr>
<tr>
<td>Ph=Me=Ph</td>
<td>100</td>
<td>—</td>
<td>85</td>
<td>64</td>
<td>(-)-1S,2S</td>
</tr>
<tr>
<td>Ph=Ph=Ph</td>
<td>90</td>
<td>—</td>
<td>71</td>
<td>28</td>
<td>(+)-S</td>
</tr>
<tr>
<td>Ph</td>
<td>100</td>
<td>—</td>
<td>75</td>
<td>22</td>
<td>(-)-S,S</td>
</tr>
<tr>
<td>Ph</td>
<td>—</td>
<td>91</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ph</td>
<td>90</td>
<td>—</td>
<td>68</td>
<td>83</td>
<td>(+)-1R,2S</td>
</tr>
<tr>
<td>Ph</td>
<td>94</td>
<td>83</td>
<td>27</td>
<td>(+)-1R,2S</td>
<td></td>
</tr>
<tr>
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<td>OMe</td>
<td>Ph</td>
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<tr>
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<td>-----</td>
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<td>90</td>
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</tr>
<tr>
<td>93</td>
<td>80</td>
<td>20</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* Epoxidation conditions: iminium salt (5 mol%), Oxone (2 eq.), NaHCO₃ (5 eq.), MeCN:Η₂O (10:1), 0 °C, 2 h, unless otherwise indicated. b Conversions were evaluated from the ¹H-NMR spectra by integration of alkene/diol/epoxide signals. c Isolated yield. d Enantiomeric excesses were determined by ¹H-NMR spectroscopy with Eu(hfc)₃ (10 mol%) as chiral shift reagent, or by chiral HPLC on a Chiralcel OD column, or by chiral GC on a Chiraldex B-DM column. e The absolute configurations of the major enantiomers were determined by comparison with literature values except where indicated. f Epoxidation conditions: iminium salt (5 mol %), Oxone (2 eq.), Na₂CO₃ (4 eq.), MeCN:Η₂O (1:1), 0 °C, 2 h. g Reaction under Yang's conditions (footnote a) is capricious. h The absolute configurations of the major enantiomers were assigned by analogy with other examples on the basis of substrate and catalyst structure, and spectroscopic evidence.

Catalyst (82) proved to be the most effective catalyst of this series, achieving >90% conversion for all substrates and moderate to good enantioselectivities (21-83% ee). Catalyst (82) was also utilized in the epoxidation of cycloalkenes (89), (90) and (93), incorporating groups with different electronic effects at the para-position of the aromatic ring (Table 15). Once again, we observed excellent conversions to epoxides and moderate enantioselectivities. Interestingly, all the cycloalkenes gave poorer enantioselectivities than 1-phenylcyclohexene and 1-phenyl-3,4-dihydronaphthalene. It
is also unclear why alkenes containing a para-substituted electron-withdrawing (SO₂Me) group and alkenes containing an electron-donating (OMe) group both gave lower enantioselectivities than the parent 1-phenylecyclohexene.

Due to the slightly more acidic nature of the reaction mixture, hydrolysis of some of the epoxides to the corresponding diols occurs in some instances, particularly for 1-phenyl-3,4-dihydronaphthalene and para-methoxy-1-phenylecyclohexene substrates, where complete conversion to the corresponding diols is observed in two hours. When 1-phenylecyclohexene was used as a substrate, we observed between 11-20% conversion to the diol. This hydrolysis of the epoxide products was obviated by use of our more basic epoxidation conditions (Oxone, Na₂CO₃, MeCN:HO (1:1)).

Recent studies by Lacour have shown both biphenyl and binaphthyl-derived tertiary azepines and their corresponding iminium salts to be effective epoxidation catalysts in the presence of Oxone and sodium bicarbonate, leading to epoxides of almost identical enantioselectivities and configurations. The amines were observed to perform best in terms of both enantioselectivity and conversion when monophasic 10:1 acetonitrile:water reaction conditions were used, while the iminium salts in some cases gave better results in biphasic 3:2 dichloromethane:water conditions in the presence of 18-crown-6 (18-C-6), which presumably acts as a phase transfer catalyst.

We have therefore tested tertiary azepine (79) (5 mol%) as a catalyst in the epoxidation of trans-α-methylstilbene under various reaction conditions (Scheme 47, Table 16).

![Scheme 47 Epoxidation of trans-α-methylstilbene using amine (79) as a catalyst.](image-url)
### Table 16 Asymmetric epoxidation of 1-trans-α-methylstilbene using amine catalyst (79).)*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Conv.(%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oxone (2 eq.), NaHCO₃ (5 eq.), MeCN:H₂O (10:1), 0 °C</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>Oxone (2 eq.), NaHCO₃ (5 eq.), 18-C-6 (2.5 mol%), MeCN:H₂O (10:1), 0 °C</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>Oxone (1.1 eq.), NaHCO₃ (4 eq.), 18-C-6 (2.5 mol%), CH₂Cl₂: H₂O (3:2), 0 °C</td>
<td>=5</td>
</tr>
</tbody>
</table>

* Reaction time: 2 h. b Conversion evaluated from the ¹H-NMR by integration of alkene versus epoxides peak.

Interestingly, little epoxidation (9%) of the substrate was achieved over two hours under the 10:1 acetonitrile:water conditions of Yang, using NaHCO₃ as base. Addition of catalytic 18-crown-6 did not improve conversion (<5%) over the same reaction time; this procedure does not appear to have been previously tested. The biphasic 3:2 dichloromethane:water conditions developed by Lacour were also unsuccessful (<5% conversion) in this case. For comparison, the corresponding iminium salt catalyst (82) gave 100% conversion under the 10:1 acetonitrile:water conditions at 0 °C over two hours (Table 15).

**2.2.3 Conclusion.**

In order to probe the electronic effect of substituents on enantioselectivity, we have prepared a range of binaphthalene-derived azepinium salts catalysts 45-48, with chiral appendages at the nitrogen atom, and incorporating either electron-withdrawing or electron-donating substituents at the para-position of the aromatic ring. However, these catalysts were less reactive and enantioselective than the parent catalyst (44), affording ees of up to 80% compared to 95% ee with catalyst (44) in the epoxidation of 1-phenyl-3,4-dihydrornaphthalene.

We have also prepared a range of novel chiral binaphthalene-derived catalysts achiral at the nitrogen atom, and utilized them in the asymmetric epoxidation of unfunctionalized alkenes. The N-isopropyl substituted catalyst (82) proved to be the
most reactive and enantioselective, affording up to 83% ee, and is superior in enantioselection to the N-methyl analogue reported by Aggarwal for a range of alkene substrates. Appropriate choice of reaction conditions allows for the successful epoxidation of relatively unreactive substrates, and for the isolation of sensitive epoxides without hydrolysis. Catalyst (82) is also more reactive than the corresponding tertiary azepine (79).

2.3 Catalysts Based on a Biphenyl Structure.

Page has reported a series of more reactive catalysts in which the dihydroisoquinolinium moiety has been replaced by a biphenyl structure fused to a seven-membered azepinium salt (Figure 8).\textsuperscript{55,56} Epoxidations using these catalysts proceeded very much faster than with their dihydroisoquinolinium counterparts, and the enantioselectivities ranged from 10-63% ee. Catalyst (94) emerged as the most reactive; it mediated the complete epoxidation of alkenes within ten minutes, and provided 60% ee with 1-phenylcyclohexene. The methoxy-substituted catalyst (95) emerged as the most enantioselective in this series, giving enantiomeric excesses between 26 and 63% ee.\textsuperscript{56}

![Figure 8 Biphenyl-azepinium salts catalysts reported by Page.](image-url)
2.3.1 Novel 3,3’-disubstituted biphenyl-azepinium salt catalysts.

The biphenyl catalysts described above suffer from poor generality in terms of inducing high enantioselectivities over a wide range of substrates. A potential explanation for the poor enantioselectivities often obtained is the existence of these catalysts as rapidly interconverting atropisomeric mixtures (Ra and Sa), resulting from the rotation of the aryl-aryl bond.\(^{57}\) Recently, there have been tremendous efforts in the development and use of atropisomERICally stable biphenyl ligands in asymmetric catalysis.\(^{58}\) The ability to isolate atropisomers, and preserve the enantiomeric integrity of the chiral biphenyl, rests on slowing the aryl-aryl bond rotation. This is usually obtained by having at least three ortho-substituents adjacent to the aryl-aryl bond.\(^{59}\)

Recently, Lygo has synthesized a library of chiral quaternary ammonium salt catalysts for use in the asymmetric phase transfer alkylation of glycine imine.\(^{60}\) These catalysts were conveniently prepared by bis-alkylation of a conformationally dynamic biphenyl unit with a range of chiral amines. Catalyst (96) emerged as the most effective phase transfer catalyst, in terms of reactivity (requiring 1 mol% catalyst loading), and enantioselectivities (89-97% ee) (Scheme 48). Interestingly, comparison studies utilizing chiral ammonium salt catalysts, derived from an unsubstituted biphenyl unit, gave low ees (2-6%), highlighting the importance of substituting the biphenyl unit to achieve high asymmetric induction.

![Scheme 48](image)

Scheme 48 Highly enantioselective phase transfer catalyst developed by Lygo.
We envisaged that the asymmetric induction available from our biphenyl-azepinium salt catalysts might be enhanced if we combined Lygo's biaryl unit with our 1,3-dioxane chiral appendage, to access, for example, catalyst (97) depicted in figure 9. We also envisaged that the powerful electron-withdrawing bis(trifluoromethyl)-phenyl group might lead to increased reactivity, as both the iminium salt and the corresponding oxaziridinium species should be highly electrophilic.

![Figure 9 Substituted biaryl-azepinium target catalyst.](image)

With this target in mind, we embarked upon the synthesis of the target catalyst, starting with the synthesis of the biphenyl unit. Treatment of commercially available phenol (98) using NBS in CCl₄ at room temperature over three hours gave the ortho-brominated product (99) and the para-brominated product (100) in 55% and 33% yield respectively, alongside 10% starting material (Scheme 49). Increased reaction times barely increased the amount of para-brominated product (100) obtained.

![Scheme 49 Reagents and Conditions: i: NBS (1.0 eq.), CCl₄, r.t., 3 h.](image)
Copper-catalysed oxidative couplings are often used to obtain both symmetrical and unsymmetrical biaryl compounds.\textsuperscript{61} This method, using stoichiometric amounts of a copper(II)-diamine complex, has been used extensively in the preparation of racemic and enantio-enriched binaphthols from the corresponding 2-naphthols.\textsuperscript{62} Several research groups have also developed catalytic copper-catalysed oxidative coupling procedures, rendering this method attractive for use in organic synthesis.\textsuperscript{63,64} These catalytic processes are based on the reoxidation of Cu(I) to Cu(II) using oxidants such as silver chloride\textsuperscript{63} or molecular oxygen.\textsuperscript{64}

Using the catalytic procedure developed by Nakajima, the ortho-brominated phenol (99) was treated with a catalytic amount of Cu(OH)Cl•TMEDA complex, which is readily prepared from a mixture of CuCl, TMEDA and molecular oxygen in aqueous methanol over two hours. The aerobic oxidative coupling reaction using this complex in dichloromethane or methanol at room temperature proceeded to furnish the desired biphenyl unit (101) in 54\% yield alongside 5-7\% of isomer (102) (Scheme 50).

\begin{equation}
\text{Scheme 50 Reagents and Conditions: } \text{i: Cu(OH)}\text{Cl•TMEDA (0.1 eq.), air, MeOH/CH}_2\text{Cl}_2, \text{r.t., 16 h.}
\end{equation}

The NMR spectra of biphenyl (101) and (102) were very similar, and unambiguous structural determination of (101) was obtained by X-ray crystallography. The crystal structure of (101) was obtained following a recrystallization by slow vapour-diffusion of chloroform and hexanes, and is depicted in figure 10.
Methylation of (101) using MeI and KOH in DMF overnight gave the bis-methylated product (103) in excellent yield. Suzuki-Miyaura coupling of (103) with 3,5-bis-(trifluoromethyl)-phenylboronic acid and Pd(PPh₃)₄ in DMF at 90 °C for sixteen hours furnished the 3,3-disubstituted product (104) in 73% yield. Subsequent radical benzylic bromination using NBS and AIBN as a radical initiator in refluxing CCl₄ over 1.5 hours, afforded the desired product (105) in excellent 92% yield (Scheme 51).

The next step in the synthesis involved the double displacement of bromide from (105) with L-acetonamine (71) to form the corresponding azepine. Thus, azepine (106) was obtained in excellent 91% yield by heating a solution of (105), L-acetonamine (71) and
K₂CO₃ in acetonitrile under reflux overnight. Subsequent oxidation of (106) using NBS and AIBN in refluxing CCl₄ followed by cation exchange provided the desired catalyst (97) in good overall yield over the two steps (Scheme 52). It is worth noting that when the same oxidation procedure was attempted using dichloromethane as a solvent, no iminium salt was formed.

Scheme 52 Reagents and Conditions: i: L-acetonamine (71) (1.1 eq.), K₂CO₃ (3 eq.), CH₃CN, reflux, 16 h, 91%; ii: NBS (1.2 eq.), AIBN (0.05 eq.), CCl₄, 3 h; iii: NaBPh₄ (1.1 eq.), EtOH, CH₃CN, r.t., 5 min., 85%.

Due to the presence of a chiral appendage in (97), it was of interest to us to ascertain whether the catalyst was diastereoisomerically pure or consisted of a mixture of rapidly interconverting diastereoisomers (Ra) and (Sa). We therefore performed ¹H-NMR analysis of salt (97) at temperatures between −40 °C and 20 °C while monitoring the iminium proton signal (Figure 11).

Figure 11 VT-NMR of iminium signal of catalyst (97).
At these temperatures, we observed only two signals: a major and a minor signal for the iminium proton, indicating the existence of a diastereoisomeric (Ra) and (Sa) mixture. The ratio of the two iminium proton signals was 1:10.2 at 20 °C, increasing to a ratio of 1:32 at −40 °C. This clearly shows the dominance of one diastereoisomer in the mixture. However, we are unable to determine or predict, if the configurational chirality of the predominant atropisomer in the biphenyl unit is (Ra) or (Sa).

With catalyst (97) in hand, we tested it towards the epoxidation of three different substrates, using the reaction conditions developed by Yang (Oxone, NaHCO₃, CH₃CN:H₂O 1:1). A comparison of the results with those obtained using the original biphenyl catalyst (94) is shown in Table 17.

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Catalyst 94</th>
<th>Catalyst 97</th>
</tr>
</thead>
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<td>22, 63</td>
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<td></td>
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<td>(−)-1S,2S e</td>
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<td>(−)-1S,2S e</td>
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<td>59, 90</td>
<td>8, 7</td>
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<td></td>
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<td>(−)-1S,2S e</td>
<td>(−)-1S,2S e</td>
</tr>
</tbody>
</table>

a Epoxidation conditions: Iminium salt (5 mol %), Oxone (2 eq.), NaHCO₃ (5 eq.), MeCN:H₂O (10:1), 0 °C, 5 h. b Enantiomeric excesses were determined by chiral HPLC on a Chiralcel OD column, or by chiral GC on a ChiralDEX B-DM column. c Conversions were evaluated from the ¹H-NMR spectra by integration of alkene and epoxide signals. d The absolute configurations of the major enantiomers were determined by comparison with literature values except where indicated. e Epoxidation conditions: Iminium salt (5 mol %), Oxone (2 eq.), Na₂CO₃ (4 eq.), MeCN:H₂O (1:1), 0 °C, 2 h.
As illustrated in Table 17, catalyst (97) performed poorly in terms of both reactivity and enantioselectivity. Epoxidations using this catalyst gave at best 63% conversion in five hours, when using 1-phenylcyclohexene as the substrate. Disappointingly, the ees obtained using this catalyst were also extremely poor, inducing at best 14% ee with trans-stilbene. For comparison, the original catalyst (94) is far superior in reactivity, giving complete epoxidation of 1-phenylcyclohexene within ten minutes, and 60% ee for the corresponding epoxide.

The poor reactivity portrayed by catalyst (97) might be due to the steric congestion at the biphenyl unit, or to the difficulty in generating the active oxaziridinium species. As indicated above, we expected the iminium salt (97) to be highly electrophilic due to the powerful electron-withdrawing character of the 3,5-bis(trifluoromethyl)-phenyl group, hence leading to ready nucleophilic attack of the oxidant on the iminium carbon atom. However, the rate-determining expulsion of the sulfate, to generate the oxaziridinium ion, might be unfavourable due to the diminished nucleophilicity of the nitrogen atom, caused by the electron-withdrawing effects of the 3,5-bis(trifluoromethyl)-phenyl group. The poor enantioselectivities induced by (97) might also arise from the steric bulk of the biphenyl unit. This catalyst was remarkably stable under the reaction conditions as 1H-NMR analysis of the crude epoxidation mixture revealed only the epoxide, alkene and the catalyst signals.

With the aim of improving the reactivity and enantioselectivity, we envisaged the synthesis of iminium salt (107) lacking the tert-butyl groups and the methoxy groups at the biphenyl unit, but with the same 3,3-substituent and chiral appendage as the previously developed iminium salt (97). We also envisaged that the mode of access towards this catalyst would be through the main intermediate (110), which could in turn be synthesized from commercially available diphenic acid (108) (Scheme 53).
We prepared the corresponding isopropyl ester and diethylamide of diphenic acid for use in ortho-metallation strategy. This was achieved by treating diphenic acid (108) with thionyl chloride to form the corresponding acid chloride, which was subsequently treated with an excess of i-PrOH and pyridine to form ester (109a) quantitatively. Amide (109b) was also prepared in an excellent yield from the corresponding acid chloride and diethylamine (Scheme 54).

Our strategy towards bis-brominated compound (110) relied on ortho-metallation followed by addition of bromine as the electrophile. Unfortunately, we were unable to prepare (110) using this strategy (Scheme 55).
Scheme 55 Attempted ortho-metallation followed by trapping with bromine failed to give the desired product.

We initially attempted ortho-magnesiation of ester (109a) using a solution of (TMP)₂Mg generated from MgBr₂ and LiTMP at 0 °C for two hours. Subsequent reaction of the generated anion with molecular bromine (8 eq.) at −78 °C, and allowing the reaction to reach room temperature over twelve hours resulted in the recovery of the starting material. Maruoka has recently reported the synthesis of (110a) using the same strategy by generating the anion at room temperature over three hours. Attempted ortho-lithiation using sec-BuLi at −78 °C, in the presence or absence of TMEDA, led to the decomposition of the starting material. Amides are well known to have an excellent ortho-directing effect, and have been widely used in ortho-lithiation strategy. However, repeated efforts to ortho-lithiate amide (109b) using sec-BuLi and TMEDA as an additive, failed to give the desired product with the complete recovery of the starting material.

Failure to prepare compounds (110) changed our retrosynthetic analysis towards the known key intermediate (112), which after a range of synthetic manipulations should lead to the desired iminium salt catalyst (Scheme 56). This strategy required the assembly of the biphenyl unit from commercially available aniline (111).

Scheme 56 New retrosynthetic analysis employing biphenyl (112).
Diazotization of aniline (111) and subsequent Sandmeyer reaction of the diazonium salt with potassium iodide provided compound (113) in 85% yield. Since its discovery in 1901, Ullmann coupling, which involves coupling of two molecules of aryl halides in the presence of activated copper powder, has extensively been utilized in the synthesis of racemic and chiral biphenyls. The ortho-substituents on the aromatic ring influence the reaction outcome, with substituents such as nitro and ester groups favouring the reaction, while substituents such as amino and hydroxyl groups, and bulky substituents, inhibit the reaction.

Ullmann coupling of (113) using a stoichiometric amount of activated copper in DMF at 190 °C furnished 53% of the desired biphenyl (114) alongside 13% of the starting material, and 33% of compound (115), resulting from the reductive dehalogenation of (113) (Scheme 57). The use of activated copper was found to be crucial for the success of the Ullmann coupling, as the reaction failed when commercially available copper powder was used directly.

Treatment of biphenyl (114) with refluxing hydrazine hydrate for eight hours led to diamino-substituted biphenyl (116) in excellent yield. Subsequent diazotization at 0 °C and iodination using potassium iodide at 50 °C overnight gave the desired biphenyl (112) in 82% yield. Suzuki-Miyaura cross coupling of (112) with 3,5-bis-(trifluoromethyl)-phenylboronic acid in the presence of Pd(PPh₃)₄ and K₂CO₃ in DMF at 90 °C for sixteen hours furnished the coupling product (117) in 73% yield alongside 5-10% homo-coupling product (118) (Scheme 58).
Benzyllic bromination of (117) using NBS in CCl₄ heated under reflux with AIBN as the radical initiator afforded the desired compound (119) in 85% yield. Dibromide (119) was subsequently treated with L-acetonamine (71) and K₂CO₃ in boiling acetonitrile to form azepine (120) in 90% yield. The desired catalyst (107) was obtained over two steps from azepine (120) in 67% yield (Scheme 59).

We next employed both azepine (120) and the iminium salt (107) in the catalytic asymmetric epoxidation of alkene substrates, and the results obtained are depicted in Table 18.
Table 18 Catalytic asymmetric epoxidation of alkenes using amine and iminium catalysts.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>120</th>
<th>107</th>
</tr>
</thead>
<tbody>
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<td>Entry</td>
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</tr>
<tr>
<td>1</td>
<td>Ph</td>
<td>47, 100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-)-1S,2S</td>
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<tr>
<td>2</td>
<td>Ph$\cdots$Ph</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ph$\cdots$Ph</td>
<td>13, 82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(+)-S</td>
</tr>
<tr>
<td>4</td>
<td>Ph$\cdots$Ph</td>
<td>7, 62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-)-1S,2S</td>
</tr>
</tbody>
</table>

$^a$ Epoxidation conditions: Iminium salt (5 mol %), Oxone (2 eq.), NaHCO$_3$ (5 eq.), MeCN:H$_2$O (10:1), 0 °C, 3 h. $^b$ Enantiomeric excesses were determined by chiral HPLC on a Chiralcel OD column, or by chiral GC on a Chiraldex B-DM column. $^c$ Conversions were evaluated from the $^1$H-NMR spectra by integration of alkene versus epoxide signals. $^d$ The absolute configurations of the major enantiomers were determined by comparison with literature values except where indicated.

Both amine (120) and iminium salt (107) gave epoxides with identical enantioselectivities and configurations, suggesting perhaps the involvement of the same chiral intermediate when using these two different catalysts. These observations are in accord with Lacour's studies$^{54}$ which reported the same effects when amines and iminium salt catalysts were utilized in the asymmetric epoxidation of alkenes.

Interestingly, while the ees of both catalysts were identical, amine (120) was more reactive in catalysing the epoxidation of alkenes. For example, amine (120) mediated the conversion of triphenylethylene and trans-stilbene to their corresponding epoxides in 82% and 62% respectively in three hours, compared to 22% and 30% conversions mediated by the iminium salt (107) also in three hours. It is not clear as to why amine (120) is more reactive than iminium (107).
Iminium salt (107) is, however, more reactive than catalyst (97), giving, for example, 100% conversion in the epoxidation of 1-phenylcyclohexene in three hours, compared to 63% conversion with iminium salt (97) in five hours. Catalyst (107) also induces higher enantioselectivities than catalyst (97). For example, 1-phenylcyclohexene and trans-α-methylstilbene was epoxidized in 44% ee and 26% ee respectively using catalyst (107) (Table 18, entry 1-2), while catalyst (97) provided 1-phenylcyclohexene oxide with 22% ee and racemic trans-α-methylstilbene oxide (Table 17, entry 1-2). However, iminium salt (97) epoxidized trans-stilbene in 14% ee, compared to 6% ee induced by (107). Both iminium salts (97) and (107) are however, less reactive and enantioselective than previously developed catalyst (94).

2.3.2 Privileged ligand-derived biphenyl catalysts.

The design of chiral iminium salt catalysts in our group has often relied on the use of L-acetonamine (71) and its derivatives as chiral appendages, which are effective presumably due to the electronic and steric roles played by the 1,3-dioxane ring and the phenyl group. Studies performed in the group have confirmed that the aromatic C4 substituent in the 1,3-dioxane is vital to obtain high enantioselectivities. Other chiral appendages used for the synthesis of biphenyl-derived iminium salt catalysts, for example N-(−)-isopinocampheylamine (IPC), gave lower enantioselectivities than their six-membered counterparts.

In the past decade, optically active trans-1,2-diaminocyclohexane (DACH) has been extensively used as a chiral ligand and as a chiral appendage in catalysts for use in diverse asymmetric reactions. For example, DACH has been used in the synthesis of highly efficient Jacobsen salen ligands used in the asymmetric epoxidation of alkenes, chiral thio-ureas used as hydrogen-bonding catalysts, and Trost’s ligands used in the palladium catalysed allylic alkylations.

Therefore, we envisaged that a catalyst incorporating DACH or its derivatives might be a potent chiral inducer with the potential to enhance enantioselectivities induced by iminium salt catalysts. With this in mind, we aimed to prepare iminium salt catalyst (121), depicted in Figure 12.
We initially embarked on the synthesis of the amino compound. Enantiopure (1S,2S)-DACH (122) was obtained from the resolution of racemic trans-DACH (122) with D-tartaric acid and subsequent liberation of the monotartrate salt (123) using aqueous sodium hydroxide (Scheme 60).

Using the procedure developed by Gawronski and Kaik,\textsuperscript{76} monophthaloylation of (1S,2S)-(122) was achieved in excellent yield by heating a solution of (1S,2S)-(122), phthalic anhydride and pTSA in xylenes under reflux for one hour. The resulting salt was liberated using saturated sodium hydrogen carbonate overnight to give compound (124). Eschweiler-Clark methylation of (124) using para-formaldehyde and formic acid as the hydrogen donor afforded the bis-methylated product (125) in 85% yield. Subsequent deprotection of the phthaloyl protecting group using hydrazine monohydrate gave the desired compound (126) in 50-60% yield (Scheme 61).
The biphenyl portion was conveniently prepared from commercially available 2,2-
biphenyl dimethanol (127), which, after treatment with aqueous hydrobromic acid at
100 °C for 40 minutes, gave the oxepine (128). Subsequent treatment of (128) with
molecular bromine in refluxing carbon tetrachloride for one hour led to carboxaldehyde
(129) in 60% yield. Cyclocondensation of amine (126) with bromoaldehyde (129)
followed by cation exchange furnished the ammonium salt (130) in 70% yield, instead
of the expected iminium salt (121) (Scheme 62). We assume that the formation of
iminium salt (121) is followed by an intramolecular reversible conjugate addition of the
nitrogen lone pair at the iminium carbon atom, leading to the formation of the
thermodynamically more stable product (130).

Ammonium salt (130) was subsequently tested in the epoxidation of 1-
phenylcyclohexene. However, this quaternary ammonium salt failed to mediate any
epoxidation of the alkene substrate, even when catalyst loadings of 10 mol% were used.

We also prepared iminium salt (131), by cyclocondensation of commercially available
(2S)-N-ethyl-2-methylamine-pyrrolidine with bromoaldehyde (129) in 58% yield. We
subsequently used catalyst (131) in the attempted epoxidation of 1-phenylcyclohexene
and trans-a-methylstilbene. However, this catalyst produced near quantitative 1-phenylcyclohexene oxide with a poor 8% ee, and failed to mediate the epoxidation of trans-a-methylstilbene (Scheme 63). Attempts to characterize this iminium salt by NMR failed. Both the $^1$H-NMR and $^{13}$C-NMR analysis at room temperature, low temperature (0 °C to −40 °C) and high temperature (20 °C to 100 °C) revealed complex spectra. Although broad, the $^1$H-NMR spectrum showed the presence of the iminium signal at ca. 9 ppm.

![Scheme 63]

**Scheme 63 Reagents and Conditions:** i: Iminium salt (5 mol%), Oxone (2 eq.), NaHCO₃ (5 eq.), CH₃CN:H₂O (10:1), 0 °C, 2 h.

We also prepared bis-iminium catalysts (132) and (133), from condensation of (1S,2S)-(122), and commercially available (1S,2S)-(−)-1,2-diphenylethylenediamine (DPEN) with bromoaldehyde (129). We hoped these two catalysts would prove to be highly reactive due to the potential formation of bis-oxaziridinium salts species (Scheme 64). Iminium salt (133) was of low purity and repeated efforts to purify it by recrystallization from boiling ethanol failed to improve the purity level.

![Scheme 64]

**Scheme 64 Reagents and Conditions:** i: amine (0.5 eq.), EtOH, r.t., 48 h; ii: NaBP₄ (1.1 eq.), EtOH, CH₃CN, r.t., 5 min.

We subsequently utilized these catalysts in the epoxidation of the substrates shown below (Table 19).
Table 19 Asymmetric epoxidation of alkenes using \textit{bis-iminium} salts (132) and (133).\footnote{Epoxidation conditions: Iminium salt (5 mol \%), Oxone (2 eq.), NaHCO\textsubscript{3} (5 eq.), MeCN:H\textsubscript{2}O (10:1), 0 °C, 2 h. Enantiomeric excesses were determined by chiral HPLC on a Chiralcel OD column, or by chiral GC on a ChiralDEX B-D column. Conversions were evaluated from the \textsuperscript{1}H-NMR spectra by integration of alkene versus epoxide signals. The absolute configurations of the major enantiomers were determined by comparison with literature values except where indicated. Epoxidation conditions: iminium salt (5 mol \%), Oxone (2 eq.), Na\textsubscript{2}CO\textsubscript{3} (4 eq.), MeCN:H\textsubscript{2}O (I:1), 0 °C, 4 h. f 5 h.}

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Both catalysts (132) and (133) were more reactive than their 3,3'-disubstituted counterparts, giving full epoxide conversions for most substrates. Interestingly, catalyst (132) was more reactive than (133). It completely epoxidized \textit{trans-\textalpha-}methylstilbene and \textit{trans-}stilbene in two hours, while catalyst (133) required prolonged reaction times of up to five hours to achieve 100\% conversion of \textit{trans-\textalpha-}methylstilbene, and gave a moderate 55\% epoxide conversion with \textit{trans-}stilbene in five hours. Both catalysts also induced almost identical enantioselectivities for most substrates, except with 1,2-dihydronaphthalene with catalyst (132) giving relatively higher enantioselectivity than (133) (55\% vs. 18\% ee). The difference in enantioselectivities for this substrate might result from a destabilization of the transition state arising from \pi-stacking between the aromatic groups of catalyst (133) and the alkene substrate.
2.2.3 Conclusion.

In conclusion, we have successfully prepared two novel biphenyl catalysts (97) and (107), with 3,3'-substituents on the biphenyl unit, and identical chiral appendages as catalyst (94). However, these catalysts were less reactive and enantioselective than catalyst (94), suggesting perhaps that substitution on the biphenyl unit might be deleterious for catalytic activity and enantioselectivity. More detailed studies which involves changing the chiral appendages as well as the 3,3'-substituents on the biphenyl unit, is highly recommended before making a definitive conclusion.

Attempts to prepare iminium salt (121), derived from DACH, gave the ammonium salt (130) arising presumably from an intramolecular conjugate addition of the nitrogen atom on the iminium unit. Unsurprisingly, (130) failed to mediate any epoxidation of alkenes. Iminium salt (131), prepared from a proline-derivative, proved to be unreactive for most substrates, and afforded a poor 8% ee with 1-phenylcyclohexene. The bis-iminium salts (132) and (133) were more reactive than (130) and (131) and gave enantioselectivities of up to 55% ee with 1,2-dihydronaphthalene. All of these iminium salt catalysts are, however, less enantioselective and reactive than the parent catalyst (94), indicating a chiral appendage from L-acetonamine is vital for obtaining high enantioselectivities.
2.4 Amine catalysed epoxidation.

As described above, the chiral amine-mediated epoxidation pioneered by Aggarwal and Yang has provided moderate enantioselectivities of up to 61% ee. These pioneering studies showed secondary amines to be better catalysts than the corresponding primary and tertiary amines, and chiral pyrrolidine or pyrrolidine analogues to be effective mediators for the enantioselective epoxidation of alkene substrates. Surprisingly, no studies using chiral binaphthalene-derived secondary amines have been reported to date.

2.4.1 Binaphthalene-derived amine catalysts.

With this in mind, we envisaged that the known chiral BINOL-derived dihydroazepinium hydrochloride salt (135) might prove to be an effective epoxidation catalyst due to its conformational rigidity. Dihydroazepine and its analogues have indeed been widely used as chiral auxiliaries for diverse asymmetric syntheses reactions. These include: Hawkin’s asymmetric stereoselective carbon-nitrogen bond formation, Cram’s asymmetric addition of organolithium reagents to aldehydes, and in chiral phase transfer catalysis.

Our synthetic point started from (52R), which upon treatment with allylamine as ammonia surrogate and triethylamine as a base led to allyl dihydroazepine (134) in good yield. Subsequent N-deallylation of (134) using Pd(OAc)$_2$, Ph$_3$P and 1,3-dimethylbarbituric acid (NDMBA) in dichloromethane, followed by treatment with concentrated hydrochloric acid furnished the dihydroazepine hydrochloride (135) in excellent yield (Scheme 65).
Scheme 65 Reagents and conditions: i: Allylamine (1.7 eq.), Et₃N (3 eq.), THF, 55 °C, 3 h., 68%; ii: Pd(OAc)₂ (2 mol%), Ph₃P (0.1 eq.), NDMBA (1.5 eq.), DCM, 35 °C, 6 h.; iii: HCl (1.1 eq.), 90%.

Ammonium salt (135) (5 mol%) was subsequently used in the epoxidation of 1-phenylcyclohexene in the presence of Oxone (2 eq.), NaHCO₃ (5 eq.) in MeCN:H₂O (10:1). Disappointingly, (135) was found to be relatively unreactive and a poor chiral inducer, giving only 28% conversion to the epoxide with 7% ee after two hours. Increasing the catalyst loading to 10 mol% failed to increase the rate of conversion.

The poor reactivity of (135) might stem from the lack of heteroatom (e.g. O- and F-) groups capable of stabilizing (either inductively or through hydrogen bonding) the active oxidizing species (See chapter 1, section 1.1.6.2).

Scheme 66 Reagents and conditions: i: Amine (1.1 eq.), K₂CO₃ (3 eq.), CH₃CN, reflux, 16 h.

In order to investigate this structural motif further, we subsequently prepared a range of chiral binaphthalene-derived amino alcohols 136-140 from dibromide (52ₐ) (Scheme 66). With amines 136-140 in hand, we tested them (10 mol%) in the epoxidation of trans-α-methylstibene as a test substrate (Table 20).
### Table 20 Asymmetric epoxidation of \textit{trans}-\textit{a}-methylstilbene using amine catalysts 136-140.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Amine Catalyst</th>
<th>Conversion (%\textsuperscript{b})</th>
<th>ee (%)\textsuperscript{c}</th>
<th>Configuration\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>136</td>
<td>$&lt;5$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>137</td>
<td>$&lt;5$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>138</td>
<td>88</td>
<td>45</td>
<td>(-)-1\textit{S},2\textit{S}</td>
</tr>
<tr>
<td>139</td>
<td>$&lt;5$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>140</td>
<td>16</td>
<td>40</td>
<td>(-)-1\textit{S},2\textit{S}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Epoxidation conditions: iminium salt (10 mol\%), Oxone (2 eq.), NaHCO\textsubscript{3} (5 eq.), MeCN:H\textsubscript{2}O (10:1), 0 °C, 5 h, unless otherwise indicated. \textsuperscript{b}Conversions were evaluated from the \textsuperscript{1}H-NMR spectra by integration of alkene/epoxide signals. \textsuperscript{c}Isolated yield. \textsuperscript{d}Enantiomeric excesses were determined by by chiral HPLC on a Chiralcel OD column. \textsuperscript{e}The absolute configurations of the major enantiomers were determined by comparison with literature values except where indicated.

Interestingly, all but amines (138) and (140) failed to show any catalytic activity. Catalyst (138) proved to be the most reactive and enantioselective in this series, giving 88% conversion and 45% ee. \textsuperscript{1}H-NMR analysis of the crude mixture revealed that the amines decomposed under the reaction conditions. We were puzzled by the difference in reactivity of these relatively similar amines and embarked on investigating potential decomposition products of these amines which inhibited their catalytic activities.

We were interested to discover that amine (140) decomposed to give the diastereoisomerically pure oxazolidine product (141) when submitted to the epoxidation reaction conditions (Oxone (2 eq.), NaHCO\textsubscript{3} (5 eq.), CH\textsubscript{3}CN:H\textsubscript{2}O (10:1). The same oxazolidine (141) is also partially formed when a chloroform solution of
amine (140) is left to stand at room temperature overnight (Scheme 67). The stereochemistry of (141) was established by NOE.

Scheme 67 Reagents and conditions: i: Oxone (2 eq.), NaHCO₃ (5 eq.), CH₃CN:H₂O (10:1), 0 °C, 5 h.

Oxazolidine formation was also observed when using amines (138) and (139) but not amines (136) and (137). At this stage, we rationalize that the formation of the oxazolidine product (141) arises from an iminium salt formed under the reaction conditions. We postulate that, under our reaction conditions, amine (140) is oxidized to the corresponding N-oxide (142). Subsequent protonation and loss of water leads to the iminium salt (143). This iminium salt is presumably in equilibrium with the oxazolidine (141) under the alkaline reaction conditions (Scheme 68), and the oxaziridinium species is probably the mediators of epoxidation.

Scheme 68 Potential pathway for the formation of oxazolidine product.

A potential explanation for the difference in reactivity portrayed by the amines 138-140 towards the epoxidation of alkenes is the competition between the oxidation of iminium salt (143) to oxaziridinium species, and oxazolidine formation.

With amine (138) being the most reactive in this series, a number of other alkenes were subjected to epoxidation mediated by catalyst (138) (Table 21).
As illustrated in Table 21, catalyst (138) acts as an effective catalyst for the enantioselective epoxidation of a range of substrates. While the conversions to epoxides are moderate to good (44-100%), enantioselectivities of up to 81% were obtained with 1-phenylcyclohexene oxide. This amine catalyst, while being less reactive, is comparable in enantioselection to our previously reported N-isopropyl substituted catalyst (82) which afforded up to 83% ee. Interestingly, amine (138)
epoxidized 1,2-dihydronaphthalene with higher ee (47%) than all other reported binaphthalene-derived amines and iminium salts to date.

An interesting observation during the course of the epoxidation was that the reaction changed from colourless to intense yellow, which may indicate the formation of the corresponding iminium salt, which is itself generally a yellow solid when isolated. After the completion of the epoxidation, the yellow residue was triturated in diethyl ether, and the sample analysed by $^1$H-NMR spectroscopy and MS. We observed the iminium signal at ca. 10 ppm., while the MS analysis revealed almost 100% molecular ion at 380.2021, corresponding to the iminium cation. Theses observations are in agreement with our postulation that iminium salts are generated in situ from the amines, and are the active catalysts mediating the epoxidation of alkenes.

With the aim of improving the reactivity of our amines and inhibiting the oxazolidine formation, we next prepared fluorine-containing compounds (144) and (145) in one step from amines (138) and (140). The substitution of electron-withdrawing groups such fluorine atom, β- to the nitrogen atom has been found to be beneficial for catalytic activity of amines. Diethylaminosulfur trifluoride (DAST) is widely used to mediate the direct conversion of alcohols into fluorides in high yields. Treatment of amines (138) and (140) in dichloromethane with DAST at room temperature for five hours afforded fluorinated products (144) and (145) respectively, albeit in low yields (28-30%) alongside other unidentified by-products. Improved yields were obtained when bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor) was used as the fluorinating reagent (Scheme 69).

![Scheme 69](image)

<table>
<thead>
<tr>
<th>138</th>
<th>R= CH(CH$_3$)$_2$</th>
<th>140</th>
<th>R= tert-Butyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>144</td>
<td>R= CH(CH$_3$)$_2$, 66%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>145</td>
<td>R= tert-Butyl, 60%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Scheme 69 Reagents and conditions: i. Deoxofluor (1.05 eq.), CH$_2$Cl$_2$, 0 °C-r.t., 24 h.
We subsequently tested amines (144) and (145) (10 mol%) in the epoxidation of trans-α-methylstiblene under Yang’s reaction conditions. Surprisingly, no conversion to epoxide was observed using these amines after five hours. Changing the reaction conditions to the biphasic 3:2 dichloromethane:water conditions in the presence of 18-crown-6 (18-C-6), developed by Lacour also failed.

Recently, Lacour reported a range of enantiopure (diastereoisomeric) doubly bridged biphenyl azepines and azepinium salts as catalysts for the asymmetric epoxidation of alkenes, affording ees of up to 85% ee. Lacour observed that some amines were effective catalysts while others showed no catalytic activity at all, and subsequently identified a decomposition pathway involving Cope elimination, which presumably inhibited the catalytic activities of the amines. The catalytic activity of the amine could be restored by the addition of NBS (5 mol%) to the amine prior to that of the substrates and other reagents. In our hands, addition of catalytic amounts of NBS (10 mol%) to amines (144) and (145) in dichloromethane (1 mL) for 10 minutes prior to the addition of water (0.5 mL), the substrate, 18-C-6, Oxone and NaHCO₃ failed to give any epoxide after five hours reaction time.

2.4.2 Conclusion.

In conclusion, we have prepared a range of binaphthalene-derived azepines containing alcohol functionality, and used them in the asymmetric epoxidation of alkenes. In this series, amine (138) portrayed the best reactivity and enantioselectivity profile, giving ees of up to 81%. We have also identified a pathway involving formation of oxazolidine, which presumably derails the catalytic activity of these amines. We have obtained limited ¹H-NMR and MS evidence, which points to the potential involvement of iminium salt catalysis in the epoxidation reactions when using amine (138).
2.5 General Conclusion.

The aim of this research project centred on the development of chiral iminium salt catalysts capable of inducing high enantioselectivities in the epoxidation of alkenes. Thus, the first phase of the project involved the synthesis of chiral iminium salts, followed by their eventual use as catalysts using Oxone as the oxidant.

Catalyst (22), an analogue of catalyst (2), was prepared as an atropisomeric mixture in twelve steps from enantiopure (+)-thiomicamine (4). This catalyst, however, provided identical ees to catalyst (2), giving up to 46% ee in the epoxidation of 1-phenyl-3,4-dihyronaphthalene.

![Chemical structure of catalyst (22)](image)

We have also prepared a range of binaphthalene-derived iminium salts, and utilized them in the asymmetric epoxidation of unfunctionalized alkenes. Catalyst (48) and (82) emerged as the most enantioselective in this series, giving ees of up to 80% and 83% respectively in the epoxidation of 1-phenyl-3,4-dihyronaphthalene.

![Chemical structures of catalysts (48) and (82)](image)
A range of biphenyl based catalysts, such as (97) and (107), were also prepared, and used in the epoxidation of alkenes. However, all of these catalysts failed to induce higher enantioselectivities than our original biphenyl catalyst (94). These catalysts were also less reactive than (94).

We have attempted to use a range of binaphthalene-derived amines as epoxidation catalysts. In this series, amine catalyst (138) emerged as the most reactive and enantioselective, giving 100% conversion and 81% ee in the epoxidation of 1-phenylcyclohexene.
2.6 Future Work.

A modification of the 3,3'-substituents in catalyst (107) is highly recommended. These substitutions will aid in gaining an insight into the influence of the steric and electronic effects which would be beneficial or detrimental for catalytic activity and enantioselectivity.

Catalysts derived from vaulted biaryl ligands such as 3,3'-biphenanthrol (VAPOL) and 2,2'-binaphthol (VANOL), have been used to obtain high enantioselectivities in diverse asymmetric reactions. These catalysts have been shown to induce substantially higher enantioselectivities over those catalysts derived from BINOL. The following VAPOL-derived iminium salts could easily be prepared from (R)-VAPOL following the same synthetic sequence used to synthesize binaphthalene-derived catalysts. Subsequent use in the asymmetric epoxidation of alkenes should hopefully lead to enhanced enantioselectivities over their BINOL-derived counterparts discussed in this thesis.

Finally, we need to gain an insight into the possible transition states models that our catalysts adopt. Therefore, it is of paramount importance to carry out computational and molecular modelling studies, to aid us in explaining the results we have achieved
with our catalysts. This would hopefully lead us to design more effective catalysts capable of inducing higher enantioselectivities than our current range.
2.7 Chapter Two References.


23 For a review, see Pizey, J. S.; *Synthetic Reagents*, vol. 2; Wiley: New York, 1974, 65.


52 L-acetonamine is (+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane.
68 Ullmann, F.; Bielecki, J. Ber. 1901, 34, 2174.
73 For a review see a) Jacobsen, E. N.; Taylor, M. S. Angew. Chem. Int. Ed. 2006, 45, 1520.


Chapter Three:
Experimental
3.0 Experimental details.

3.1 General experimental procedures.

Thin layer chromatography was performed on aluminum backed plates coated in 0.25 mm Merck Kiesel 60 F254 silica gel. The plates were either visualized by U.V radiation at a wavelength of 254 nm, or by dipping the plate in ethanolic solution of phosphomolybdic acid (acidified with concentrated sulfuric acid), followed by heating the plate with a hair dryer. Flash column chromatography was performed using Merck Kiesel silica gel 60 (70-230 mesh).

$^1$H-NMR and $^{13}$C-NMR spectra were recorded on a Bruker AC spectrometer operating 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.

The following references have been used in the description of the NMR spectra: $\delta=$ chemical shift (in ppm), $J=$ coupling constant (in Hz), $s=$ singlet, $bs=$ broad singlet, $dd=$ double doublet, $dt=$ double triplet, $d=$ doublet, $m=$ multiplet

All infrared spectra were obtained using a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer. Solid samples were run as nujol mulls or as thin films of their solution in DCM on sodium chloride plates. Liquid samples were run neat.

The mass spectra were recorded using a Jeol-SX102 instrument utilizing electron impact (EI), fast atom bombardment (FAB), and by the EPSRC national mass spectrometry service at the University of Wales, Swansea, utilizing electonspray (ES) and MALDI-TOF.

Melting points were recorded using an Electrothermal-IA 9100 melting point instrument and are uncorrected.
Optical rotation values were measured with an optical Activity-polAAr 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.

Microanalysis were performed on a Perkin Elmer Elemental analyzer 2400 CHN.

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

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

The proton nuclear magnetic resonance spectra were recorded in deuterated chloroform on a Bruker DPX 400 MHz spectrometer operating at 400.13, in the presence of europium (III) tris [3-(hepta-fluoropropylhydroxymethylene)-(+)-camphorate], \([+]-\text{Eu(hfc)}_3\), 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.

The chiral column used for the determination of enantiomeric excesses (ee.), of non-racemic mixtures by chiral GC-FID was Chiradex B-DM on a CE instruments GC 8000 series spectrometer, with flame ionisation detector and a Chrome-card integrator. The solvent used to gain measurements (hexane) was 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. (13C 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.](image1)

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.](image2)
3.3 Individual experimental procedures

(1S,2S)-N-(Benzyloxy carbonyl)-2-amino-1-(4-methylthiophenyl)-1,3-propanediol (5):

(1S,2S)-(+) -2-Amino-1-(4-methylthiophenyl)-1,3-propanediol (4) (5.00 g, 23.44 mmol) was added to a stirring solution of sodium hydrogen carbonate (3.6 g, 35.16 mmol) in water (60 mL). The mixture was then allowed to stir for 5 minutes before benzyl chloroformate (3.70 mL, 25.79 mmol) was added dropwise to the mixture. The reaction mixture was left to stir for 3 hours until complete disappearance of the starting material was observed by TLC. The reaction mixture was then filtered and the resulting white crude product successively washed with diethyl ether and hexane to give the title compound as a white solid (7.32 g, 90%); m.p. 138-139 °C; [α]$_{D}^{20}$ +39.6 (c 1.00, MeOH); $ν_{max}$(film)/cm$^{-1}$ 3430 (OH), 2949, 1710 (NC=O), 1605, 1539, 1347, 1246, 1160, 1057, 757; $^1$H-NMR (400 MHz, DMSO-d$_6$): $δ$ 2.45 (3 H, s, SCH$_3$), 3.25-3.28 (1 H, m, CHHOH, H3), 3.47-3.53 (1 H, m, CH/N, H2), 3.62-3.67 (1 H, m, CHHOH, H3$'$), 4.74-4.85 (2 H, m, CHOH, H1 and CH$_2$OH), 4.95 (2 H, d, $J$= 12.4 Hz, N-Cbz CH$_2$), 5.34 (1 H, s, CHOH), 6.70 (1 H, d, $J$= 9.2 Hz, NH), 7.17-7.34 (9 H, m, 9 x CH arom., Ph gp.); $^{13}$C-NMR (100 MHz, DMSO-d$_6$): $δ$ 14.89 (CH$_3$, SCh$_3$), 58.44 (CH, CHN, C2), 60.70 (CH$_2$, CH$_2$OH, C3), 64.87 (N-Cbz CH$_2$), 69.82 (CH, CHOH, C1), 125.48 (2 x CH arom., C7, C8), 126.81 (2 x CH arom., C5, C6), 127.21 (2 x CH arom., ortho in Ph gp.), 127.52 (CH arom., para in Ph gp.), 128.20 (2 x CH arom., meta in Ph gp.), 135.94 (C quat. arom., ipso to SCh$_3$, C9), 137.31 (C quat. arom., ipso to CHOH, C4), 140.29 (C quat. arom., ipso in Ph gp.), 155.92 (C quat., N-Cbz C=O); $m/z$ (FAB) 348.1262; C$_{18}$H$_{21}$NO$_4$S [M+H]$^+$ requires 348.1270.
(1S,2S)-N-(Benzyloxy carbonyl)-2-amino-3-(tert-butyldiphenylsilyloxy)-1-hydroxy-1-(4-methylthiophenyl)-propane (6):

Imidazole (0.85 g, 12.43 mmol) was added to a solution of compound (5) (3.60 g, 10.36 mmol) in dichloromethane (60 mL). The resulting cloudy mixture was left to stir for 5 minutes before 4-dimethylaminopyridine (0.13 g, 1.04 mmol) and tert-butyldiphenylsilyl chloride (2.92 mL, 11.40 mmol) were added to the stirring mixture. The mixture was then left to stirrer for 16 h. The solvent was removed under reduced pressure to give white crude solid. Column chromatography of the crude product using ethyl acetate/light petrol (1:7:1:1) afforded the title compound as a colourless oil (5.58 g, 92%); [α]_D^20 +49.0 (c 1.15, CHCl₃); ν_max(film)/cm⁻¹ 3434 (OH), 2939, 2355, 1704 (NC=O), 1508; ^1H-NMR (400 MHz, CDCl₃): δ 1.02 (9 H, s, C(CH₃)₃), 2.40 (3 H, s, SCH₃), 3.18 (1 H, d, J= 2.7 Hz, CHOH), 3.71-3.74 (2 H, m, N-CHCH₂OSiPh₂t-Bu, H₃), 3.81-3.84 (1 H, m, NCH, H₂), 4.94 (2 H, s, N-Cbz CH₂), 4.98 (1 H, dd, J= 3.2 Hz, N-CHCH-OH, H1), 5.32 (1 H, d, J= 8.9 Hz, NH), 7.10-7.40 (15 H, m, 15 × CH arom., Ph gp.), 7.54-7.56 (4 H, m, 4 × CH arom., Ph gp.); ^13C-NMR (100 MHz, CDCl₃): δ 15.87 (C quat., C(CH₃)₃), 19.23 (CH₃, S(CH₃)), 26.96 (3 × CH₃, C(CH₃)₃), 57.17 (CH, CHN, C2), 65.06 (CH₂, N-CHCH₂OSiPh₂t-Bu, C3), 66.80 (N-Cbz CH₂), 73.55 (CH, N-CHCH-OH, C1), 126.52 (2 × CH arom.), 126.56 (2 × CH arom.), 127.94 (6 × CH arom.), 128.13 (CH arom.), 128.54 (2 × CH arom.), 130.08 (2 × CH arom.), 136.41 (C quat., arom.), 137.73 (C quat., arom.), 137.85 (C quat., arom.), 156.51 (C quat., N-Cbz C=O); m/z (FAB) 586.2437; C₃₄H₃₉NO₄Si [M+H]^+ requires 586.2447.
pTSA (0.48 g, 2.50 mmol) was added to a solution of compound (6) (14.69 g, 25.08 mmol) in acetone (100 mL). The reaction mixture was stirred for 5 minutes before 2,2-dimethoxypropane (30.00 mL, 250.80 mmol) was added dropwise to the mixture. The mixture was then stirred for 16 h. The solvent was removed under reduced pressure, and the resulting yellow oil crude product was redissolved in ethyl acetate, washed with saturated sodium hydrogen carbonate (2 x 30 mL) and brine (2 x 30 mL). The combined organic extracts were dried (Na2SO4) and the solvent removed in vacuo to give a yellow oil (13.79 g, 88%); [α]20° +9.6 (c 1.00, CHCl3); νmax(film)/cm⁻¹ 3068, 2955, 2930, 1704 (C=O), 1601, 1588, 1495, 1470, 1407, 1350, 1259, 1212, 1113, 1091, 964, 820, 740, 701; ¹H-NMR (400 MHz, DMSO-d6, 100 °C): δ 1.01 (9 H, s, C(CH3)3), 1.57 (3 H, s, CH3, H6), 1.60 (3 H, s, CH3, H7), 2.49 (3 H, s, SCH3), 3.74 (1 H, dd, J= 10.2 Hz, 2.4 Hz, H8), 3.85-3.91 (1 H, m, CHN, H4), 4.12 (1 H, dd, J= 10.2 Hz, 5.8 Hz, H8'), 5.04 (2 H, d, J= 12.4 Hz, N-Cbz CH2), 5.19 (1 H, d, J= 6.4 Hz, ArCH, H5), 7.22-7.31 (9 H, m, 9 x CH arom., Ph gp.), 7.35-7.46 (6 H, m, 6 x CH arom., Ph gp.), 7.57-7.65 (4 H, m, 4 x CH arom., Ph gp.); ¹³C-NMR (100 MHz, DMSO-d6, 100 °C): δ 14.68 (C quat., C(CH3)3), 18.23 (CH3, S CH3), 25.61 (CH3, C6), 26.18 (3 x CH3, C(CH3)3), 26.52 (CH3, C7), 62.00 (CH2OSiPh2t-Bu, C8), 63.92 (CHN, C4), 65.69 (N-Cbz CH2), 77.58 (CH, C5), 94.05 (C quat., C2), 125.83 (2 x CH arom.), 126.74 (4 x CH arom.), 127.12 (2 x CH arom.), 127.16 (2 x CH arom.), 127.71 (2 x CH arom.), 129.04 (2 x CH arom.), 129.19 (CH arom.), 132.44 (2 x C quat., arom.), 134.54 (4 x CH arom.), 135.65 (C quat., arom.), 135.90 (C quat., arom.), 137.77 (C quat., arom.), 151.22 (C quat., N-Cbz C=O); m/z (EI) 625.2675; C37H43NO4SSi (M⁺) requires 625.2682.
(4S,5S)-N-(Benzyloxy carbonyl)-4-[(tert-butyl diphenyl silyloxy)methyl]-5-(4-(methanesulfonyl) phenyl)-2,2-dimethyl-1,3-oxazolidine (8):

Oxazolidine (7) (1.77 g, 2.76 mmol) was dissolved in dichloromethane (40 mL) and the solution cooled to 0 °C. m-CPBA (2.86 g, 16.55 mmol) in dichloromethane (5 mL) was added dropwise to the solution over 5 minutes. The reaction was then left to stir for 3 h after which saturated sodium hydrogen carbonate (10 mL) was added slowly. The mixture was then transferred into a separatory funnel, and washed with more saturated aqueous sodium hydrogen carbonate (2 x 30 mL) and brine (2 x 30 mL) and dried (Na₂SO₄). The solvents were removed in vacuo to give a colourless oil (1.60 g, 88%); [α]D²⁰ +10.8 (c 1.00, CHCl₃); νmax(film)/cm⁻¹ 2928, 2856, 2360, 1701 (C=O), 1471, 1406, 1349, 1315, 1257, 1213, 1151, 1112, 1090, 954, 765, 702; ¹H-NMR (400 MHz, DMSO-d₆, 100 °C): δ 1.00 (9 H, s, C(CH₃)₃), 1.59 (3 H, s, CH₃, H6), 1.63 (3 H, s, CH₃, H7), 3.16 (3 H, s, SO₂CH₃), 3.84 (1 H, dd, J= 10.2 Hz, 2.5 Hz, H8), 3.85-3.91 (1 H, m, CHN, H4), 4.10 (1 H, dd, J= 10.2 Hz, 5.2 Hz, H8'), 5.04 (2 H, d, J= 12.4 Hz, N-Cbz CH₂), 5.33 (1 H, d, J= 6.4 Hz, H5), 7.25-7.30 (4 H, m, 4 x CH arom., Ph gp.), 7.39-7.53 (7 H, m, 7 x CH arom., Ph gp.), 7.60-7.66 (6 H, m, 6 x CH arom., Ph gp.), 7.91 (2 H, d, J= 8.0 Hz, 2 x CH arom., H12, H13); ¹³C-NMR (100 MHz, DMSO-d₆, 100 °C): δ 19.33 (C quat., C(CH₃)₃), 26.79 (CH₃, C6 or C7), 27.67 (CH₃, C6 or C7), 27.31 (C(CH₃)₃), 44.31 (CH₃, SO₂CH₃), 62.36 (CH₂OSiPh₂-t-Bu, C8), 65.08 (CHN, C4), 66.93 (N-Cbz CH₂), 78.58 (CH, C5), 95.71 (C quat., C2), 127.61 (2 x CH arom.), 128.24 (4 x CH arom.), 128.32 (2 x CH arom.), 128.36 (2 x CH arom.), 128.86 (2 x CH arom.), 130.40 (2 x CH arom.), 130.44 (2 x CH arom.), 133.45 (2 x C quat., arom.), 135.68 (4 x CH arom.), 136.90 (C quat., arom.), 141.66 (C quat., arom.), 145.74 (C quat., arom.), 152.27 (C quat., N-Cbz C=O); m/z (EI) 657.2570; C₃₇H₄₉NO₆SSi (M⁺) requires 657.2580.
(4S,5S)-N-(Benzyloxycarbonyl)-4-hydroxymethyl-5-(4-(methanesulfonyl)phenyl)-2,2-dimethyl-1,3-oxazolidine (9):

A solution of sulfone-oxazolidine (8) (1.08 g, 1.73 mmol) in THF (15 mL) was cooled to 0 °C before tetra-butylammonium fluoride (1.0 M, 2.08 mL) was added dropwise to the mixture. The reaction mixture was then left to stir for 6 h after which complete disappearance of the starting material was observed by TLC. The reaction mixture was concentrated in vacuo and the resulting yellow oil subjected to column chromatography using ethyl acetate/light petrol (1:1) as eluent to afford the title compound as a colourless oil (0.54 g, 74%); [α]20D +3.5 (c 1.48, MeOH); νmax(film)/cm⁻¹ 3494 (OH), 1701 (C=O), 1600, 1410, 1350, 1310, 1254, 1213, 1149, 1089, 1065, 957, 767, 699; ¹H-NMR (400 MHz, DMSO-d₆, 100 °C): δ 1.52 (3 H, s, CH₃, H6), 1.61 (3 H, s, CH₃, H7), 3.15 (3 H, s, SO₂CH₃), 3.68-3.71 (1 H, m, CHHOH, H8), 3.77-3.82 (1 H, m, CHHOH, H8'), 3.87-3.90 (1 H, m, CHN, H4), 5.09 (2 H, s, N-Cbz CH₂), 5.26 (1 H, d, J= 5.6 Hz, ArCH, H5), 7.22-7.39 (5 H, m, 5 x CH arom., Ph gp.), 7.69 (2 H, d, J= 8.4 Hz, 2 × CH arom., H10, H11), 7.92 (2 H, d, J= 8.4 Hz, 2 × CH arom., H12, H13); ¹³C-NMR (100 MHz, DMSO-d₆, 100 °C): δ 25.72 (CH₃, C6 or C7), 26.66 (CH₃, C6 or C7), 43.22 (CH₃, SO₂CH₃), 59.13 (CH₂, NCHCH₂OH, C8), 64.66 (CHN, C4), 65.74 (N-Cbz CH₂), 77.38 (CH, C5), 94.38 (C quat., C2), 126.37 (2 × CH arom., C12, C13), 126.83 (2 × CH arom., C10, C11), 127.11 (2 × CH arom., ortho in Ph gp.), 127.25 (CH arom., para in Ph gp.), 127.78 (2 × CH arom., meta in Ph gp.), 136.07 (C quat. arom., ipso to SO₂CH₃, C14), 140.28 (C quat. ipso in Ph gp.), 145.68 (C quat. arom., ipso, C9), 151.21 (C quat., N-Cbz C=O); m/z (FAB) 420.1481; C₂₁H₂₅NO₆S [M+H]⁺ requires 420.1481.
By-product (10):

A by-product obtained in the desilylation of oxazolidine (8), using tetra-
butylammonium fluoride as described above; v_{max}(film)/cm^{-1} 3608, 2988, 1758
(NC=O), 1386, 1309, 1245, 1150, 1051, 957, 831, 767; ^1H-NMR (400 MHz, CDCl3):
1.59 (3 H, s, CH3, H6), 1.97 (3 H, s, CH3, H7), 2.99 (3 H, s, SO2CH3), 3.98-4.04 (1 H,
m, NCH-CH2O, H4), 4.27 (1 H, dd, J= 9.5 Hz, 3.7 Hz, NCHCHH-O, H8), 4.34 (1 H,
dd, J= 9.5 Hz, 8.2 Hz, NCHCHH-O, H8'), 4.71 (1 H, d, J= 8.6 Hz, ArCH, H5), 7.51
(2 H, d, J= 12.0 Hz, 2 x CH arom., H11, H12), 7.91 (2 H, d, J= 12.0 Hz, 2 x CH
arom., H13, H14); ^13C-NMR (100 MHz, CDCl3): δ 20.68 (CH3, C6 or C7), 29.46
(CH3, C6 or C7), 44.49 (CH3, SO2CH3), 63.08 (CH2, NCHCH2-OC=O, C8), 65.61
(CH, CHN, C4), 81.07 (CH, ArCH, C5), 95.98 (C quat., C2), 127.11 (2 x CH arom.,
C13, C14), 128.11 (2 x CH arom., C11, C12), 141.02 (C quat. arom., ipso to SO2CH3,
C15), 142.79 (C quat. arom., ipso, C10), 156.46 (C quat., N-C=O-O); m/z (EI) 311.0834; C_{14}H_{17}NO_{5}S (M^+) requires 311.0828.

(4R,5S)-N-(Benzyloxycarbonyl)-4-formyl-5-(4-(methanesulfonyl)phenyl)-2,2-
dimethyl-1,3-oxazolidine (11):
A solution of dry DMSO (0.23 mL, 3.22 mmol) in dry dichloromethane (5 mL) was added dropwise to a solution of oxalyl chloride (0.11 mL, 1.31 mmol) in dry dichloromethane (5 mL) over 5 minutes at −78 °C under nitrogen gas atmosphere. The solution was left to stir at this temperature for 30 minutes before a solution of alcohol (9) (0.50 g, 1.19 mmol) in dry dichloromethane (5 mL) was added dropwise at −78 °C over 5 minutes. The mixture was then left to stir at this temperature for another 30 minutes before triethylamine (0.83 mL, 5.60 mmol) was added dropwise to the mixture over 10 minutes. After further 20 minutes at −78 °C, the reaction mixture was allowed to reach ambient temperature over 2 h. Water was added to the reaction mixture and the organic phase separated. The combined organic extracts were washed with brine (2 × 20 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure, and the resulting crude yellow oil was subjected to flash column chromatography using ethyl acetate/light petrol (2:1) as eluent to afford the product as a yellow oil (0.37 g, 74%); [α]²⁰D −20.0 (c 0.46, MeOH); νmax(film)/cm⁻¹ 2989, 2925, 1708, 1600, 1534, 1427, 1369, 1255, 1163, 1090, 1070, 874, 737; ¹H-NMR (250 MHz, DMSO-d₆, 100 °C): 1.68 (3 H, s, CH₃, H6), 1.70 (3 H, s, CH₃, H7), 3.17 (3 H, s, SO₂CH₃), 4.33 (1 H, dd, J= 7.5 Hz, 3.3 Hz, CHN, H4), 5.15 (2 H, s, N-Cbz CH₂), 5.36 (1 H, d, J= 7.5 Hz, ArCH, H5), 7.29-7.44 (5 H, m, 5 × CH arom., Ph gp.), 7.68 (2 H, d, J= 8.3 Hz, 2 × CH arom., H10, H11), 7.96 (2 H, d, J= 8.3 Hz, 2 × CH arom., H12, H13), 9.63 (1 H, d, J= 3.3 Hz, HC=O, H8); ¹³C-NMR (100 MHz, DMSO-d₆, 100 °C): δ 26.03 (CH₃, C6 or C7), 26.97 (CH₃, C6 or C7), 40.97 (CH₃, SO₂CH₃), 67.53 (N-Cbz CH₂), 70.97 (CHN, C4), 75.39 (CH, C5), 96.12 (C quat., C2), 127.67 (2 × CH arom., C12, C13), 128.04 (2 × CH arom., C10, C11), 128.23 (2 × CH arom., ortho in Ph gp.), 128.54 (CH arom., para in Ph gp.), 128.92 (2 × CH arom., meta in Ph gp.), 136.61 (C quat. arom., ipso to SO₂CH₃, C14), 142.02 (C quat. ipso in Ph gp.), 143.48 (C quat. arom., ipso, C9), 152.26 (Cquat., N-Cbz C=O), 197.90 (C quat., HC=O, C8); m/z (FAB) 418.1320; C₂₁H₂₃N₀₆S [M+H]⁺ requires 418.1329.
(4R,5S)-N-(Benzyloxycarbonyl)-5-(4-(methanesulfonyl)phenyl)-2,2-dimethyl-oxazolidine 4-carboxylic acid (13):

Jones’ reagent (1 M) was prepared from chromium trioxide (1.0 g) dissolved in water (2 mL) and concentrated sulfuric acid (8 mL).

Jones’ reagent (1.0 M, 2.99 mL, 2.5 eq.) was added dropwise to a solution of alcohol (9) (0.5 g, 1.19 mmol) in acetone (15 mL) at 0 °C. The resulting yellowish reaction mixture was left to stir for 16 h. Isopropyl alcohol (30 mL) and celite (1 g) were added to the mixture. The precipitate was filtered off and the filtrate was adjusted to pH 9 with saturated aqueous sodium hydrogen carbonate, and then concentrated in vacuo. The aqueous phase was washed with ethyl acetate (2 × 20 mL), and acidified to pH 2 with 1 M HCl. The aqueous phase was extracted with ethyl acetate (2 × 30 mL) and the combined organic extract washed with brine (2 × 20 mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure to yield the product as a colourless oil (0.40 g, 77%); [α]²⁰_d =−33.9 (c 1.04, MeOH); ν_max (film)/cm⁻¹ 3488 (OH), 1699 (NC=O), 1411, 1352, 1311, 1150, 1091, 1067, 960, 833, 769; ¹H-NMR (250 MHz, DMSO-d₆, 100 °C): 1.65 (3 H, s, CH₃, H6 or H7), 1.67 (3 H, s, CH₃, H6 or H7), 3.15 (3 H, s, SO₂CH₃), 4.11 (1 H, d, J= 6.7 Hz, CHN, H4), 4.99 (1 H, d, J= 13.0 Hz N-Cbz CHH), 5.09 (1 H, d, J= 13.0 Hz, N-Cbz CHH), 5.20 (1 H, d, J= 6.7 Hz, ArCH, H5), 7.23-7.49 (5 H, m, 5 × CH arom., Ph gp.), 7.97 (2 H, d, J= 8.4 Hz, 2 × CH arom., H11, H12), 7.97 (2 H, d, J= 8.4 Hz, 2 × CH arom., H13, H14); ¹³C-NMR (100 MHz, DMSO-d₆, 100 °C): 25.19 (CH₃, C6 or C7), 27.26 (CH₃, C6 or C7), 41.00 (CH₃, SO₂CH₃), 66.43 (CHN, C4), 67.08 (N-Cbz CH₂), 79.09 (CH, C5), 96.25 (C quat., C2), 127.65 (2 × CH arom., C12, C13), 128.00 (2 × CH arom., C10, C11), 128.06 (2 × CH arom., ortho in Ph gp.), 128.32 (CH arom., para in Ph gp),
128.84 (2 × CH arom., meta in Ph gp.), 136.91 (C quat. arom., ipso to SO₂CH₃, C14), 141.97 (C quat. ipso in Ph gp.), 144.53 (C quat. arom., ipso, C9), 152.06 (C quat., N-Cbz C=O), 171.09 (C quat., CO₂H, C8); m/z (FAB) 434.1266; C₂₁H₂₃N⁰₇S [M+H]⁺ requires 434.1274.

(4R,SS)-N-(Benzyloxycarbonyl)-5-(4-(methanesulfonyl)phenyl)-2,2-dimethyl-4-methylxoycarbonyl-1,3-oxazolidine (12):

K₂CO₃ (0.51 g, 3.69 mmol) and dimethyl sulfate (0.18 mL, 1.85 mmol) were added to a solution of carboxylic acid (13) (0.40 g, 0.92 mmol) in dry acetone (50 mL). The reaction mixture was then heated under reflux for 4 h after which complete consumption of the starting material was confirmed by TLC. After cooling the reaction mixture to room temperature, the acetone was removed under reduced pressure, and the resulting residue was dissolved in water. The aqueous phase was extracted with ethyl acetate (2 × 30 mL) and the combined organic extract washed with brine (2 × 30 mL) and dried (Na₂SO₄). The solvent was removed in vacuo to yield a colourless crude oil. Column chromatography of the crude product using ethyl acetate/light petrol (1:2) afforded the title compound as a colourless oil (0.35 g, 85%); [α]²⁰D -49.3 (c 1.73, MeOH); vₘₐₓ(film)/cm⁻¹ 2987, 2951, 1750 (C=O), 1713 (NC=O), 1602, 1407, 1348, 1313, 1247, 1215, 1151, 1090, 1066, 1017, 960, 833, 767, 699; ¹H-NMR (250 MHz, DMSO-d₆, 100 °C): 1.73 (3 H, s, CH₃, H6 or H7), 1.77 (3 H, s, CH₃, H6 or H7), 3.24 (3 H, s, SO₂CH₃), 3.69 (3 H, s, CO₂CH₃), 4.11 (1 H, d J= 7.5 Hz, CHN, H4), 5.12 (1 H, d, J= 12.4 Hz N-Cbz CH₂), 5.19 (1 H, d, J= 12.4 Hz, N-Cbz CH₂), 5.33 (1 H, d, J= 7.5 Hz, ArCH, H5), 7.39-7.41 (5 H, m, 5 × CH arom., Ph gp.), 7.73 (2 H, d, J= 8.1 Hz, 2 × CH arom., H11, H12), 8.02 (2 H, d, J= 8.1 Hz, 2 × CH arom., H13, H14); ¹³C-NMR (100 MHz, DMSO-d₆, 100 °C): 8 25.16 (CH₃, C6 or C7),
27.14 (CH₃, C6 or C7), 44.25 (CH₃, SO₂CH₃), 52.84 (CH₃, CO₂CH₃), 66.30 (CH₅N, C4), 67.26 (N-Cbz CH₂), 78.80 (CH, C5), 96.37 (C quat., C2), 127.70 (2 × CH arom., C13, C14), 128.30 (2 × CH arom., C11, C12), 128.23 (2 × CH arom., ortho in Ph gp.), 128.49 (CH arom., para in Ph gp), 128.88 (2 × CH arom., meta in Ph gp), 136.73 (C quat. arom., ipso to SO₂CH₃, C15), 142.11 (C quat. ipso in Ph gp.), 143.95 (C quat. arom., ipso, C10), 151.86 (C quat. N-Cbz C=O), 170.24 (C quat., CO₂CH₃, C8); m/z (FAB) 448.1425; C₂₂H₂₅N₀₇S [M+H]+ requires 448.1430.

(4R,5S)-N-(Benzyloxycarbonyl)-4-[(2-hydroxy)propyl]-5-(4-(methanesulfonyl)phenyl)-2,2-dimethyl-1,3-oxazolidine (14):

Ester (12) (0.37 g, 0.82 mmol) was dissolved in dry THF (30 mL) in a dried round-bottomed flask under a nitrogen atmosphere. The mixture was cooled to 0 °C before MeMgBr (1.63 mL, 4.89 mmol) was added dropwise over 10 minutes. The resulting yellowish mixture was left to stir at room temperature for 16 h. The mixture was quenched with saturated ammonium chloride (20 mL), and extracted with ethyl acetate (2 × 30 mL). The combined organic extract was washed with brine (2 × 30 mL), dried (Na₂SO₄) and the solvent removed in vacuo to give crude yellow oil. Column chromatography of the crude product using ethyl acetate/light petrol (1:2-1:1) as eluent afforded the title compound as a colourless oil (0.15 g, 40%); [α]²⁰D −4.0 (c 1.21, CHCl₃); νmax(film)/cm⁻¹ 3504 (OH), 2981, 2936, 1701 (C=O), 1402, 1347, 1311, 1211, 1150, 1068, 958, 767; ¹H-NMR (400 MHz, DMSO-d₆, 100 °C): δ 1.19 (3 H, s, CH₃, H6 or H7), 1.24 (3 H, s, CH₃, H8 or H9), 1.42 (3 H, s, CH₃, H8 or H9), 1.65 (3 H, s, CH₃, H6 or H7), 3.17 (3 H, s, SO₂CH₂), 4.39 (1 H, d, J= 2.4 Hz, CHN, H4), 4.57 (1 H, m, OH), 5.07 (1 H, d, J= 12.4 Hz N-Cbz CH₂), 5.18 (1 H, d, J= 12.4 Hz, N-Cbz CH₂), 5.42 (1 H, d, J= 2.4 Hz, ArCH, H5), 7.29-7.37 (5 H, m, 5 × CH arom., Ph gp.), 7.72 (2 H, d, J= 8.0 Hz, 2 × CH arom., H12, H13), 7.92 (2 H, d, J= 8.0 Hz, 2 × CH
arom., H14, H15). $^{13}$C-NMR (100 MHz, DMSO-d$_6$, 100 °C): δ 26.59 (CH$_3$, C6 or C7), 27.91 (CH$_3$, C6 or C7), 32.03 (2 x CH$_3$, C9, C10), 44.23 (CH$_3$, SO$_2$CH$_3$), 67.14 (N-Cbz CH$_2$), 70.99 (CHN, C4), 72.31 (C quat., C8), 77.89 (CH, C5), 97.00 (C quat., C2), 127.31 (2 × CH arom., C14, C15), 127.77 (2 × CH arom., C12, C13), 128.37 (2 × CH arom., ortho in Ph gp.), 128.39 (CH arom., para in Ph gp), 128.79 (2 × CH arom., meta in Ph gp.), 136.84 (C quat. arom., ipso to SO$_2$CH$_3$, C16), 140.99 (C quat. ipso in Ph gp.), 148.77 (C quat. arom., ipso, C11), 154.23 (C quat., N-Cbz C=O); m/z (FAB) 448.1788; C$_{23}$H$_{29}$N$_{6}$S$_{2}$ [M+H]$^+$ requires 448.1794.

$(1S,2R)$-N-(Benzyloxy carbonyl)-2-amino-1-(4-(methanesulfonyl)phenyl)-3-methyl-1,3-butanediol (15):

Compound (14) (0.15 g, 0.33 mmol) was dissolved in methanol (15 mL). After 5 minutes of stirring pTSA (0.02 g, 0.07 mmol) was added, and the mixture left to stir for further 16 h. Saturated sodium carbonate (15 mL) was added to the mixture, and the resulting milky solution was concentrated in vacuo to remove methanol. The aqueous phase was extracted with ethyl acetate (2 × 30 mL) and the combined organic extracts were washed with brine (2 × 30 mL) and dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure to yield a dark-orange oil. Recrystallisation of the crude oil from chloroform/hexane afforded colourless crystals (0.09 g, 65%); m.p.132-133 °C; [α]$_{20}^D$ +80.7 (c 1.08, CHCl$_3$); ν$_{max}$(film)/cm$^{-1}$ 3420 (OH), 2975, 2924, 1700 (C=O), 1598, 1517, 1454, 1405, 1305, 1217, 1147, 1088, 1050, 956, 752, 698;

$^1$H-NMR (400 MHz, CDCl$_3$): δ 1.17 (3 H, s, CH$_3$, H4 or H5), 1.46 (3 H, s, CH$_3$, H4 or H5), 2.87 (3 H, s, SO$_2$CH$_3$), 3.58 (1 H, dd, J= 10.0 Hz, 1.6 Hz, NCH, H2), 4.17 (1 H, s, OH), 4.75 (1 H, d, J= 12.4 Hz N-Cbz CH$_2$), 4.83 (1 H, d, J= 12.4 Hz, N-Cbz CH$_2$), 5.33 (1 H, s, CH-OH, H1), 5.58 (1 H, d, J= 10.0 Hz, NH), 7.07-7.26 (5 H, m, 5 × CH
arom., Ph gp.), 7.40 (2 H, d, J= 7.6 Hz, 2 × CH arom., H7, H8), 7.65 (2 H, d, J= 7.6 Hz, 2 × CH arom., H9, H10); 13C-NMR (100 MHz, CDCl3): δ 27.91 (CH3, C4 or C5), 28.05 (CH3, C4 or C5), 44.58 (CH3, SO2CH3), 61.26 (CHN, C2), 66.62 (N-Cbz CH2), 72.19 (CH, N-CHCH-OH, C1), 75.17 (C quat., C(CH3)2-OH, C3), 126.90 (2 × CH arom., C9, C10), 127.21 (2 × CH arom., C7, C8), 127.67 (2 × CH arom., ortho in Ph gp.), 128.22 (CH arom., para in Ph gp), 128.56 (2 × CH arom., meta in Ph gp.), 136.39 (C quat. arom., ipso to SO2CH3, C11), 139.19 (C quat. ipso in Ph gp.), 147.60 (C quat. arom., ipso, C6), 156.41 (C quat., N-Cbz C=O); m/z (ESI) 425.1741; C20H25N06S [M+NH4]+ requires 425.1741.

(2R,3S)-2-Benzoylcarbamoylenamino-3-hydroxy-3-(4-methanesulfonyl-phenyl)-propionic acid methyl ester (16):

Acetyl chloride (0.16 mL, 2.30 mmol) was added dropwise to methanol (30 mL) at 0 °C. After 5 minutes at 0 °C, carboxylic acid (13) (0.1 g, 0.23 mmol) in methanol (5 mL) was added dropwise to the stirring mixture. After a further 10 minutes reaction at 0 °C, the reaction was heated under reflux for 48 h. The methanol was then removed under reduced pressure. The residue was redissolved in ethyl acetate (20 mL) and washed with brine (2 × 30 mL) and dried (Na2SO4). The solvent was removed in vacuo to yield a colourless oil (0.06 g, 64 %); [α]D 20 +51.9 (c 0.94, CHCl3); νmax(film)/cm⁻¹ 3356 (OH), 2935, 1721 (C=O), 1698 (NC=O), 1519, 1455, 1435, 1403, 1302, 1214, 1148, 1059, 1016, 958, 915; 1H-NMR (400 MHz, CDCl3): δ 2.88 (3 H, s, SO2CH3), 3.71 (3 H, s, CO2CH3), 3.77 (1 H, d, J= 4.1 Hz, CH-OH), 4.49 (1 H, dd, J= 9.6 Hz, 2.3 Hz, NCH, H2), 4.88 (2 H, s N-Cbz CH2), 5.32 (1 H, s, CH-OH, H3), 5.69 (1 H, d, J= 9.5 Hz, NH), 7.13-7.27 (5 H, m, 5 × CH arom., Ph gp.), 7.43 (2 H, d, J= 8.3 Hz, 2 × CH arom., H7, H8), 7.66 (2 H, d, J= 8.3 Hz, 2 × CH arom., H9, H10); 13C-NMR (100 MHz, CDCl3): δ 44.24 (CH3, SO2CH3), 52.92 (CH3, CO2CH3),
59.60 (CH, CHN, C2), 67.07 (N-Cbz CH₂), 72.64 (CH, ArCH-OH, C3), 127.06 (2 × CH arom., C9, C10), 127.25 (2 × CH arom., C7, C8), 127.82 (2 × CH arom., ortho in Ph gp.), 128.27 (CH arom., para in Ph gp.), 128.54 (2 × CH arom., meta in Ph gp.), 136.02 (C quat. arom., ipso to SO₂CH₃, C11), 139.54 (C quat. ipso in Ph gp.), 146.52 (C quat. arom., ipso, C6), 156.35 (C quat., N-Cbz C=O), 170.67 (C quat., CO₂CH₃, C1); m/z (ESI) 425.1378; C₁₉H₂₁N₀₇S [M+NH₄]⁺ requires 425.1377.

(5R,6S)-N-(Benzyloxycarbonyl)-5-amino-6-(4-(methanesulfonyl)phenyl)-4,4-dimethyl-1,3-dioxane (18):

Compound (15) (0.05 g, 0.12 mmol) was dissolved in dimethoxymethane (3 mL). Lithium bromide (0.03 g, 0.37 mmol) and pTSA (0.07 g, 0.37 mmol) were added to the stirring mixture. The reaction mixture was then left to stir for 16 h after which complete consumption of the starting material was observed by TLC. The mixture was diluted with dichloromethane (20 mL) and filtered through a pad of celite to remove the lithium bromide. The organic phase was washed with saturated sodium hydrogen carbonate (2 × 20 mL), brine (2 × 20 mL) and dried (Na₂SO₄). The solvent was removed in vacuo to yield the title compound as a colourless oil (0.04 g, 86%); [α]²⁰D +46.6 (c 1.03, CHCl₃); νmax(film)/cm⁻¹: 3345 (NH), 2986, 2926, 1714, 1514, 1302, 1215, 1175, 1085, 1015, 958, 754; ¹H-NMR (400 MHz, acetone-d₆): δ 1.10 (3 H, s, CH₃, H7 or H8), 1.49 (3 H, s, CH₃, H7 or H8), 2.92 (3 H, s, SO₂CH₃), 3.74 (1 H, dd, J= 10.4 Hz, 1.7 Hz, CHN, H5), 4.69 (1 H, d, J= 12.9 Hz N-Cbz CH₂), 4.77 (1 H, d, J= 12.9 Hz, N-Cbz CH₂), 4.86 (1 H, d, J= 6.8 Hz, OCHHO, H2), 5.12 (1 H, d, J= 6.8 Hz, OCHHO, H2'), 5.33 (1 H, s, Ar-CH, H6), 6.09 (1 H, d, J= 10.4 Hz, NH), 6.98-7.21 (5 H, m, 5 × CH arom., Ph gp.), 7.54 (2 H, d, J= 8.0 Hz, 2 × CH arom., H10, H11), 7.75 (2 H, d, J= 8.0 Hz, 2 × CH arom., H12, H13); ¹³C-NMR (100 MHz,
CDCl₃): δ 21.57 (CH₃, C7 or C8), 27.34 (CH₃, C7 or C8), 44.40 (CH₂, SO₂CH₃), 56.63 (CH, NCH, C5), 66.26 (N-Cbz CH₂), 75.60 (C quat., C4), 75.92 (Ar-CH, C6), 88.74 (CH₂, C2), 126.64 (2 × CH arom., C10, C11), 127.66 (2 × CH arom., C12, C13), 127.92 (2 × CH arom., ortho in Ph gp.), 128.43 (CH arom., para in Ph gp), 129.19 (2 × CH arom., meta in Ph gp.), 138.37 (C quat. arom., ipso to SO₂CH₃, C14), 141.06 (C quat. ipso in Ph gp.), 146.30 (C quat. arom., C9), 157.08 (C quat., N-Cbz C=O); m/z (ESI) 437.1748; C₂₁H₂₅N₀₆S [M+N⁺]⁺ requires 437.1741.

(5R,6S)-5-amino-6-(4-(methanesulfonyl)phenyl)-4,4-dimethyl-1,3-dioxane (19):

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\begin{align*}
\text{Compound (18):} & & \text{(0.05 g, 0.12 mmol) and isopropanol (5 mL) was irradiated with} \\
& & \text{microwave energy (300 W) for 1 minute. Ammonium formate (0.03 g, 0.48 mmol)} \\
& & \text{and palladium hydroxide on carbon Pd(OH)₂/C (10% w/w, 0.005 g) were then added} \\
& & \text{to the solution. The mixture was then irradiated with microwave energy for 1 minute} \\
& & \text{followed by 1 minute rest until complete disappearance of the starting material was} \\
& & \text{observed (5 cycles). The mixture was then diluted with methanol (30 mL) and filtered} \\
& & \text{through a pad of celite, and the solvents removed under reduced pressure to afford} \\
& & \text{colourless crystals of the formate salt. The solid was dissolved in ethylacetate and} \\
& & \text{washed with saturated sodium hydrogen carbonate (2 × 30 mL), dried (MgSO₄) and} \\
& & \text{the solvent removed in vacuo to afford the product as colourless oil (0.03 g, 90%);} \\
& & \text{[α]D}^20 +45.2 (c 1.00, CHCl₃); \nu_{max}(film)/cm⁻¹; 3386 (NH₂), 2980, 2925, 1599, 1371, \\
& & 1297, 1214, 1174, 1146, 1083, 1033, 958, 777; ^1H-NMR (400 MHz, CDCl₃): δ 1.29 (3 \\
& & H, s, CH₃, H7 or H8), 1.51 (3 H, s, CH₃, H7 or H8), 2.76 (1 H, d, J= 1.4 Hz, NH₂CH₃, \\
& & H5), 3.00 (3 H, s, SO₂CH₃), 5.00 (1 H, d, J= 6.7 Hz, OCHH-O, H2), 5.09 (1 H, d, J= \\
& & 6.7 Hz, OCHH-O, H2'), 5.16 (1 H, s, Ar-CH, H6'), 7.47 (2 H, d, J= 8.5 Hz, 2 × CH \\
& & arom., H10, H11), 7.90 (2 H, d, J= 8.5 Hz, 2 × CH arom., H12, H13); ^13C-NMR (100 \\
& & MHz, CDCl₃): δ 21.66 (CH₃, C7 or C8), 27.35 (CH₃, C7 or C8), 44.53 (CH₃, \\
& & \text{160})
\end{align*}
\]
SO₂CH₃), 55.79 (CH, NCH, C5), 74.72 (C quat, C4), 75.62 (CH, Ar-CH, C6), 88.16 (CH₂, C2), 126.44 (2 × CH arom., C10, C11), 127.74 (2 × CH arom., C12, C13), 139.78 (C quat. arom., ipso to SO₂CH₃, C14), 146.17 (C quat. arom., ipso C9); m/z (El) 285.1039; C₁₃H₁₉NO₄S (M⁺) requires 285.1035.

**(1S,2S)-N-(Benzyloxycarbonyl)-2-amino-1-(4-(methanesulfonyl)phenyl)-1,3-propanediol (23):**

Oxone (1.06 g, 1.72 mmol) was added to a stirred solution of (5) (0.30 g, 0.86 mmol) in ethanol (50 mL) and water (10 mL) and the reaction was left to stir for 24 h. The solution was then concentrated in vacuo. The resulting residue was taken up in water (50 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were washed with brine (2 × 30 mL) and dried (Na₂SO₄). The solvent was removed in vacuo to afford a colourless solid. Recrystallization from methanol/diethyl ether afforded the product as colourless crystals (0.29 g, 90%); m.p. 120-122 °C; [α]₂⁰°D +50.8 (c 0.63, MeOH); ¹H-NMR (400 MHz, DMSO-d₆): δ 3.18 (3 H, s, SO₂CH₃), 3.28-3.34 (1 H, m, N-CHH-OH, H3), 3.51-3.57 (1 H, m, N-CHHOH, H3'), 3.70-3.75 (1 H, m, CH₂, CH₂OH, C3), 4.81-4.96 (3 H, m, CHOH, H1 and N-Cbz CH₂), 5.62 (1 H, d, J= 4.3 Hz, CHOH), 6.83 (1 H, d, J= 9.3 Hz, NH), 7.19-7.36 (5 H, m, 5 × CH arom., Ph gp.), 7.57 (2 H, d, J= 8.4 Hz, 2 × CH arom., H7, H8), 7.85 (2 H, d, J= 8.4 Hz, 2 × CH arom., H5, H6); ¹³C-NMR (100 MHz, DMSO-d₆): δ 43.58 (CH₃, SO₂CH₃), 58.24 (CH, CHN, C2), 60.59 (CH₂, CH₂OH, C3), 64.88 (N-Cbz CH₂), 69.74 (CH, CHOH, C1), 126.79 (2 × CH arom., C7, C8), 127.46 (2 × CH arom., C5, C6), 127.58 (2 × CH arom., ortho in Ph gp.), 127.93 (CH arom., para in Ph gp.), 128.62 (2 × CH arom., meta in Ph gp.), 137.25 (C quat. arom., ipso to SO₂CH₃, C9), 139.02 (C quat. arom., ipso to CHOH, C4), 149.68 (C quat. ipso in Ph gp.), 155.91 (C quat., N-Cbz C=O); m/z (FAB) 380.1175; C₁₅H₂₁NO₆S [M+H]+ requires 380.1168.
(4S,5S)-N-(Benzyloxycarbonyl)-5-amino-2,2-dimethyl-4-(4-(methanesulfonyl)phenyl)-1,3-dioxane (24):

Compound (23) (1.00 g, 2.64 mmol) was dissolved in acetone (20 mL), and pTSA (0.05 g, 0.26 mmol) was added to the mixture. The reaction mixture was left to stir for 5 minutes before 2,2-dimethoxypropane (3.24 mL, 26.36 mmol) was added dropwise to the mixture. The mixture was then left to stir for 16 h. The solvent was removed under reduced pressure and the resulting yellow oil crude product was redissolved in ethyl acetate (30 mL), washed with saturated sodium hydrogen carbonate (2 × 30 mL) and brine (2 × 30 mL). The combined organic extracts were dried (Na2SO4) and the solvent removed in vacuo to yield colourless oil. Recrystallization from chloroform/hexane afforded the product as a colourless powder (0.88 g, 80%); m.p. 103-106 °C; [α]20D +70.4 (c 0.96, CHCl3); νmax(film)/cm⁻¹ 3357 (NH), 2991, 2941, 1714, 1509, 1454, 1405, 1382, 1312, 1271, 1236, 1149, 1089, 950, 848, 758; 1H-NMR (400 MHz, CDCl3): δ 1.56 (3 H, s, CH3, H7 or H8), 1.60 (3 H, s, CH3, H7 or H8), 3.02 (3 H, s, S02CH3), 3.93 (1 H, dd, J=12.2 Hz, 1.8 Hz, NCHCHH-O, H6), 4.00-4.04 (1 H, m, NCH, H5), 4.32 (1 H, dd, J=12.2 Hz, 1.8 Hz, NCHCHH-O, H6'), 4.90 (1 H, d, J= 12.3 Hz, N-Cbz CHH), 5.49 (1 H, d, J= 9.8 Hz, NH), 7.20-7.38 (5 H, m, 5 × CH arom., Ph gp.), 7.57 (2 H, d, J= 8.4 Hz, 2 × CH arom., H10, H11), 7.92 (2 H, d, J= 8.4 Hz, 2 × CH arom., H12, H13); 13C-NMR (100 MHz, CDCl3): δ 15.30 (CH3, C7 or C8), 29.62 (CH3, C7 or C8), 44.54 (CH3, SO2CH3), 48.55 (CH, NCH, C5), 64.82 (CH2, C6), 66.79 (N-Cbz CH2), 72.10 (Ar-CH, C4), 99.91 (C quat., C2), 126.79 (2 × CH arom., C10, C11), 127.27 (2 × CH arom., C12, C13), 127.94 (2 × CH arom., ortho in Ph gp.), 128.31 (CH arom., para in Ph gp), 128.59 (2 × CH arom., meta in Ph gp.), 136.10 (C quat. arom., ipso to SO2CH3, C14), 139.56 (C quat. ipso in Ph gp.), 144.66 (C quat.
arom., C9), 155.72 (C quat., N-Cbz C=O); m/z (ESI) 437.1738; C$_{21}$H$_{23}$NO$_6$S [$M+NH_4]^+$ requires 437.1741.

(4S,5S)-5-Amino-2,2-dimethyl-4-(4-(methanesulfonyl)phenyl)-1,3-dioxane (25):

Compound (24) (0.40 g, 0.95 mmol) was dissolved in ethanol (20 mL) and placed in a three-necked round-bottomed flask charged with palladium on carbon (10% w/w, 0.04 g) under an atmosphere of hydrogen (balloon). The reaction was left to stir for 24 h after which complete consumption of the starting material was observed. The mixture was filtered through a pad of celite and the solvent removed under reduced pressure to give a yellow solid. The solid was dissolved in diethyl ether (40 mL), and the solvent evaporated in vacuo to afforded a colourless powder (0.24 g, 86%); m.p. 120-122 °C; [α]$^D_{20} +50.0$ ($c$ 1.00, CHCl$_3$); $\nu$$_{\text{max}}$(film)/cm$^{-1}$ 3372 (NH$_2$), 2991, 1601, 1380, 1197, 1078; $^1$H-NMR (400 MHz, CDC$_3$): $\delta$ 1.49 (6 H, s, 2 × CH$_3$, H7, H8), 2.77-2.78 (1 H, m, NCH, H5), 2.99 (3 H, s, SO$_2$CH$_3$, H16), 3.81 (1 H, dd, $\text{J}$= 11.8 Hz, 1.8 Hz, NCH$_2$CH$_2$-O, H6$'$), 5.11 (1 H, d, $\text{J}$= 1.0 Hz, Ar-CH, H4), 7.48 (2 H, d, $\text{J}$= 9.9 Hz, 2 × CH arom., H10, H11), 7.88 (2 H, d, $\text{J}$= 9.9 Hz, 2 × CH arom., H12, H13); $^{13}$C-NMR (100 MHz, CDC$_3$): $\delta$ 18.59 (CH$_3$, C7 or C8), 29.68 (CH$_3$, C7 or C8), 44.57 (CH$_3$, SO$_2$CH$_3$, C16), 49.41 (CH, NCH, C5), 66.36 (CH$_2$, C6), 73.46 (Ar-CH, C4), 99.50 (C quat., C2), 126.80 (2 × CH arom., C10, C11), 127.51 (2 × CH arom., C12, C13), 139.46 (C quat. arom., C14), 146.17 (C quat. arom., C9); m/z (EI) 285.1031; C$_{13}$H$_{19}$NO$_4$S (M$^+$) requires 285.1035.
(4S,5S)-N-(Benzyloxycarbonyl)-4-(1-hydroxyethyl)-5-(4-(methanesulfonyl)-phenyl)-2,2-dimethyl-1,3-oxazolidine (26):

Aldehyde (11) (0.20 g, 0.48 mmol) was dissolved in dry THF (10 mL) in a dried round-bottomed flask under a nitrogen atmosphere. The mixture was cooled to -78 °C before MeMgBr (0.50 mL, 1.80 mmol) was added dropwise over 10 minutes. The reaction mixture was allowed to reach room temperature over 16 h. The mixture was quenched with saturated ammonium chloride (10 mL), and extracted with ethyl acetate (2 x 30 mL). The combined organic extract was washed with brine (2 x 30 mL), dried (Na₂SO₄) and the solvent removed in vacuo to give crude yellow oil consisting of 1:1 diastereoisomers (0.31 g). Column chromatography of the crude product using ethyl acetate/light petrol (1:2-1:1) as eluent afforded one diastereoisomer as a colourless oil (0.07 g, 34%); [α]²⁰D −8.3 (c 1.00, CHCl₃); v max (film)/cm⁻¹ 3439 (OH), 2926, 1696 (C=O), 1409, 1308, 1149, 1089; ¹H-NMR (400 MHz, DMSO-d₆, 100 °C): δ 1.04 (3 H, d, J= 8.0 Hz, CH₃, H9), 1.57 (3 H, s, CH₃, H6 or H7), 1.60 (3 H, s, CH₃, H6 or H7), 3.17 (3 H, s, SO₂CH₃), 4.03 (1 H, t, J= 4.4 Hz, CHN, H4), 4.17 (1 H, dd, J= 8.0 Hz, 4.4 Hz, CHOH, H8), 5.14 (2 H, s, N-Cbz CH₂), 5.43 (1 H, d, J= 4.4 Hz, ArCH, H5), 7.27-7.44 (5 H, m, 5 x CH arom., Ph gp.), 7.70 (2 H, d, J= 8.4 Hz, 2 x CH arom., H11, H12), 7.96 (2 H, d, J= 8.4 Hz, 2 x CH arom., H13, H14), 13C-NMR (100 MHz, DMSO-d₆, 100 °C): δ 20.73 (CH₃, C9), 27.32 (CH₃, C6 or C7), 28.32 (CH₃, C6 or C7), 44.22 (CH₃, SO₂CH₃), 65.94 (CHOH, C8), 66.84 (CH₂, N-Cbz CH₂), 69.23 (CHN, C4), 77.13 (CH, C5), 95.68 (C quat., C2), 126.63 (CH arom., para in Ph gp), 127.45 (2 x CH arom., C13, C14), 128.21 (2 x CH arom., C11, C12), 128.30 (2 x CH arom., ortho in Ph gp.), 128.81 (2 x CH arom., meta in Ph gp.), 137.05 (C quat. arom., ipso to SO₂CH₃, C15), 141.31 (C quat. ipso in Ph gp.), 147.70 (C quat. arom., ipso, C10), 152.58 (C quat., N-Cbz C=O); m/z (FAB) 434.1633; C₂₂H₂₇NO₆S [M+H]⁺ requires 434.1637.
To an ice cooled solution of isochroman (20) (8.00 g, 59.62 mmol), 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 (ca. 1.5 h). The solution was allowed to reach 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 heated under reflux for 15 minutes. The reaction mixture was allowed to cool and extracted with diethyl ether (4 × 50 mL). The combined organic extracts were washed with water (2 × 30 mL), saturated sodium hydrogen carbonate (2 × 30 mL), and dried (Na₂SO₄). Evaporation of the solvent under reduced pressure furnished the crude 2-(2-bromoethyl) benzaldehyde as an orange oil, approximately 85-95% pure (8.30 g, 65%); νmax(neat)/cm⁻¹ 2742, 1697, 1600, 1575, 1260, 1193, 755; ¹H-NMR (400 MHz,CDCl₃): δ 3.54-3.63 (4H, m, Ph(CH₂)₂Br), 7.33 (1H, d, J= 7.9 Hz, CH arom., ortho to bromoethyl group), 7.48 (1H, t, J= 7.5 Hz, CH arom., para to bromoethyl group), 7.54 (1H, t, J= 7.9 Hz, CH arom., para to formyl group), 7.80 (1H, d, J= 7.5 Hz, CH arom., ortho to formyl group), 10.14 (1H, s, CHO); ¹³C-NMR (100 MHz,CDCl₃): δ 33.17 (CH₂, PhCH₂), 36.70 (CH₂, CH₂Br), 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).
General procedure for the synthesis of dihydroisoquinolinium salts from 2-(2-bromoethyl) benzaldehyde and primary amines:

A solution of the amine (1 equivalent) in ethanol (10 mL per gram of amine), was added dropwise to an ice cooled solution of 2-(2-bromoethyl) benzaldehyde (1.60 equivalents) in ethanol (10 mL per gram of amine). The reaction mixture was stirred overnight while attaining ambient temperature. Sodium tetraphenylborate (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 few drops of 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. 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.

(+)-N-(SR,6S)-S-(6-(4-Methanesulfonyl)phenyl)-4,4-dimethyl-1,3-dioxanyl)-3,4-dihydro-isoquinolinium tetraphenylborate (22):
Prepared according to the general procedure from amine (19) (0.19 g, 0.69 mmol). The product was isolated as an inseperable atropisomeric mixture. Yellow powder (0.29 g, 60%); m.p. 218-220 °C (dec.); [α]D +79.2 (c 1.00, CH3CN); Found: C, 76.46; H, 6.41; N, 1.89. C46H45BN04S requires C, 76.76; H, 6.44; N, 1.95%.; νmax(film)/cm⁻¹ 3053, 1631, 1603, 1570, 1477, 1425, 1314, 1145, 1087, 1012; ¹H-NMR (400 MHz, DMSO-d6): δ 1.29 (3 H, s, CH3, H7major), 1.40 (3 H, s, CH3, H7 minor), 1.71 (3 H, s, CH3, H8major), 1.73 (3 H, s, CH3, H8 minor), 1.99-2.08 (1 H, m, Ar-CHH, isoq-4 major), 2.66-2.74 (1 H, m, Ar-CHH, isoq-4 minor), 3.03-3.28 (8 H, m, 2 x CH3, 2 x SO2CH3, H16major and minor, 1 H, Ar-CHH, isoq-4' minor and 1 H, CHHN, isoq-3 major), 3.93-4.00 (1 H, m, CHHN, isoq-3 minor), 4.03-4.11 (1 H, d, J= 2.4 Hz, NCH, H5major), 4.76 (1 H, d, J= 2.8 Hz, NCH, H5 minor), 5.28 (1 H, d, J= 6.8 Hz, OCHH-O, H2major), 5.33 (1 H, d, J= 6.8 Hz, OCHH-O, H2 minor), 5.37 (1 H, d, J= 6.4 Hz, OCHH-O, H2' major), 5.40 (1 H, d, J= 7.2 Hz, OCHH-O, H2' minor), 5.99-6.01 (2 H, m, ArCH, H6major and minor), 6.80 (8 H, t, J= 7.2 Hz, 8 x CH arom., para in BPh4 gp.), 6.93 (16 H, t, J= 7.2 Hz, 16 x CH arom., ortho in BPh4 gp.), 7.18-7.21 (16 x CH arom., meta in BPh4 gp.), 7.55-7.62 (2 H, m, 2 x CH arom., isoq-6major and isoq-6 minor), 7.67 (2 H, d, J= 8.4 Hz, 2 x CH arom., C10, C11major), 7.73-7.81 (4 H, m, 4 x CH arom., isoq-7major and minor, C10, C11 minor), 7.93 (4 H, t, J= 8.4 Hz, 4 x CH arom., C12, C13major and minor), 8.25 (1 H, d, J= 8.4 Hz, CH arom., isoq-9 major), 8.97 (1 H, s, HC=N, isoq-1 minor), 9.64 (1 H, s, HC=N, isoq-1 major); ¹³C-NMR (100 MHz, DMSO-d6): δ 21.49 (CH3, C7 major), 22.66 (CH3, C7 minor), 23.55 (Ar-CH2, isoq-4 major), 24.18 (Ar-CH2, isoq-4 minor), 25.90 (CH3, C8 major), 26.64 (CH3, C8 minor), 43.31 (SO2CH3, C16 major), 43.35 (SO2CH3, C16 minor), 48.14 (CH2N, isoq-3 minor), 54.24 (CH2N, isoq-3 major), 71.24 (NCH, C5 major), 72.14 (NCH, C5 minor), 72.78 (ArCH, C6 major), 73.02 (ArCH, C6 minor), 73.34 (C quat., C4 major), 73.64 (C quat., C4 minor), 87.72 (CH2, C2 minor), 87.81 (CH2, C2 major), 121.41 (8 x CH arom., para in BPh4 gp.), 123.63 (C quat., arom., isoq-10 minor), 124.30 (C quat., arom., isoq-10 major), 125.18 (16 x CH arom., ortho in BPh4 gp.), 125.78 (2 x CH arom., C12, C13 minor), 126.07 (2 x CH arom., C12, C13 major), 127.26 (2 x CH arom., C10, C11 minor), 127.38 (2 x CH arom., C10, C11 major), 128.14 (CH arom., isoq-8 minor), 128.17 (CH arom., isoq-8 major), 128.20 (CH arom., isoq-6 minor), 128.33 (CH arom., isoq-6 major), 133.75 (CH arom., isoq-9 minor), 135.29 (CH arom., isoq-9 major), 135.46 (16 x CH arom., meta in BPh4 gp.), 136.70 (C quat., arom.,
(+)-N-(4S,5S)-5-(4-(4-Methanesulfonyl)phenyl)-2,2-dimethyl-1,3-dioxany1)-3,4-
dihydro-isoquinolinium tetraphenylborate (2):²

Prepared according to the general procedure from amine (25) (0.25 g, 0.88 mmol).

The product was isolated as a yellow powder (0.46 g, 73%); m.p. 199-200 °C (dec.); [Lit.² m.p. 199-201 °C (dec.)); [α]²⁰ D +125.0 (c 1.00, acetone); [Lit.² [α]²⁰ D +126.7 (c 1.20, acetone)); νmax(film)/cm⁻¹ 1636, 1603, 1572, 1478, 1383, 1314, 1266, 1202, 1150, 1076, 1032, 956; ¹H-NMR (400 MHz, acetone-d₆): δ 1.69 (3H, s, CH₃, H7), 1.72 (3H, s, CH₃, H8), [2.60-2.69 (1 H, m), 2.85-2.96 (1 H, m), Ar-CH₂, isaq-4], 3.00 (3H, s, SO₂CH₃, H16), [3.65-3.72 (1 H, m), 4.12-4.20 (1 H, m), CH₂N, isaq-3], 4.49 (1 H, d, J= 13.6 Hz, N-CHCH₂-O, H6), 5.79 (1 H, m, NCH, H5), 4.77 (1 H, dd, J= 13.6, 2.8 Hz, N-CHCH₂-O, H6), 6.05 (1 H, d, J= 2.8 Hz, Ar-CH, H4), 6.80 (4 H, t, J= 7.2 Hz, 4 × CH arom., para in BPh₄ gp.), 7.33 (8 H, m, 8 × CH meta in BPh₄ gp.), 7.49 (1 H, t, J= 7.6 Hz, CH arom., isaq-8), 7.73-7.83 (3 H, m, 3 × CH arom., isaq-6,7,9), 7.82 (2 H, d, J= 8.2 Hz, 2 × CH arom., H10, H11), 7.95 (2 H, d, J= 8.2 Hz, 2 × CH arom., H12, H13); 9.28 (1 H, s, HC= N, isaq-1); ¹³C-NMR (100 MHz; acetone-d₆): δ 18.83 (CH₃, C7), 25.40 (Ar-CH₂, isaq-4), 29.45 (CH₃, C8), 44.26 (SO₂CH₃, C16), 52.33 (CH₂N, isaq-3), 62.87 (CH₃, C6), 66.10 (NCH, C5), 71.54 (Ar-CH, C4), 101.69 (C quat., C2), 122.31 (8 × CH arom., ortho in BPh₄ gp.), 125.33 (C quat., arom., isaq-10), 126.09 (2 × CH arom., C12, C13), 127.56 (2 × CH arom., C11, C12), 128.84 (CH arom., isaq-
6), 129.27 (CH arom., isoq-8), 129.35 (4 x CH arom., para in BPI4 gp.), 135.41 (CH arom., isoq-7), 137.00 (8 x CH arom., meta in BPI4 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= 49.1 Hz, C-B, ipso in BPI4 gp.), 168.99 (HC=N, isoq-1); m/z (ESI) 400.1586; C_{22}H_{26}N_{0}4S (cation) requires 400.1583.

(1S,2S)-N-(tert-Butyloxycarbonyl)-2-amino-1-phenyl-1,3-propanediol (33):

(1S,2S)-( -)-2-Amino-1-phenyl-1,3-propanediol (31) (4.00 g, 23.96 mmol) was dissolved in methanol (30 mL), and the solution cooled to 0 °C in an ice bath. A solution of Boc-anhydride (5.75 g, 26.35 mmol) in methanol (30 mL) was added dropwise over 10 minutes to the cooled mixture. The reaction mixture was heated under reflux for 2 h after which TLC analysis showed complete disappearance of the starting material. The solvents were removed under reduced pressure, and the resulting residue was redissolved in dichloromethane (30 mL) and the mixture transferred to a separatory funnel. The mixture was then washed with water (2 x 20 mL), brine (2 x 20 mL), dried (Na_{2}SO_{4}) and the solvent removed under reduced pressure to yield a yellow oil (5.66 g, 90%); [α]_{D}^{20} +58.4 (c 1.00, CHCl_{3}); ν_{max}(film)/cm⁻¹ 3437 (OH), 2958, 2929, 2856, 1691 (NC=O), 1495, 1427, 1391, 1366, 1169, 1112, 822, 739, 700; ^1H-NMR (400 MHz, CDCl_{3}): δ 1.26 (9 H, s, CH₃), 3.30 (1 H, s, CH₂OH), 3.36-3.72 (3 H, m, CH₂OH, H3 and CHN, H2), 3.83 (1 H, s, CHOH), 4.88 (1 H, t, J= 3.4 Hz, CHOH, H1), 5.23 (1 H, d, J= 6.0 Hz, NH), 7.18-7.28 (5 H, m, 5 x CH arom., Ph gp.); ^13C-NMR (100 MHz, CDCl_{3}): δ 28.27 (3 x CH₃, C(CH₃)₃), 57.07 (CH, CHN, C2), 63.53 (CH₂, CH₂OH, C3), 73.88 (CH, ArCHOH, C1), 79.90 (C quat., C(CH₃)₃), 126.09 (2 x CH arom., C5, C6), 127.66 (CH arom., C9), 128.36 (2 x CH arom., C7, C8), 141.27 (C quat. arom., ipso to CHOH, C4), 156.61 (C quat., N-Boc C=O); m/z (FAB) 268.1555; C_{14}H_{21}NO_{4} [M+H]^+ requires 268.1549.
(1S,2S)-N-(tert-Butyloxycarbonyl)-2-amino-1-(4-nitrophenyl)-1,3-propanediol (34):\(^3\)

![Chemical Structure](image)

(1S,2S)-(+)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol (32) (5.00 g, 23.56 mmol) was dissolved in methanol:dichloromethane (1:2, 80 mL) and the solution cooled to 0 °C before the dropwise addition of Boc-anhydride (5.65 g, 25.92 mmol) in dichloromethane (30 mL). The reaction was then left to stir for 48 h at room temperature. The solvents were removed under reduced pressure and the resulting residue redissolved in isopropanol (50 mL) and water (60 mL) and the mixture transferred to a separatory funnel. The mixture was then washed with hexane (2 × 60 mL) and the hexane phase discarded. Dichloromethane (80 mL) was added to the aqueous mixture and extracted twice. The dichloromethane phase was separated and dried with MgSO\(_4\) for 2 hours with stirring. The solution was then filtered and the solvent removed under reduced pressure to yield a white solid (7.30 g, 99%); m.p. 112-113 °C; [Lit.\(^3\) 113-114 °C]; \([\alpha]^{20}_D\) +79.3 (c 0.57, CHCl\(_3\)); [Lit.\(^3\) \([\alpha]^{20}_D\) -22.0 (c 1.00,MeOH); \(v_{\text{max}}\) (film)/cm\(^{-1}\) 3390 (OH), 2979, 1694 (NC=O), 1605, 1519, 1347, 1249, 1165, 1059, 857, 757; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.21 (9 H, s, qCH\(_3\)), 3.73-3.75 (3 H, m, CH\(_2\)OH, H3 and CHN, H2), 4.43 (1 H, s, CH\(_2\)OH), 5.08 (1 H, s, ArCHOH, H1), 5.24 (1 H, d, \(J = 8.3\) Hz, NH), 7.47 (2 H, d, \(J = 8.6\) Hz, 2 × CH arom., H5, H6), 8.09 (2 H, d, \(J = 8.6\) Hz, 2 × CH arom., H7, H8); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 28.14 (3 × CH\(_3\), C(CH\(_3\))), 56.75 (CH, CHN, C2), 63.16 (CH\(_2\), CH\(_2\)OH, C3), 72.50 (CH, ArCHOH, C1), 80.33 (C quat., C(CH\(_3\))), 123.40 (2 × CH arom., C7, C8), 126.94 (2 × CH arom., C5, C6), 147.21 (C quat. arom., ipso to CHOH, C4), 149.15 (C quat. arom., ipso to NO\(_2\) gp., C9), 156.37 (C quat., N-Boc C=O); m/z (FAB) 313.1396; C\(_{14}\)H\(_{20}\)N\(_2\)O\(_6\) [M+H]\(^+\) requires 313.1400.
General procedure for the synthesis of tert-butyldiphenylsilyloxy-protected compounds from \(N\)-Boc-aminodiols:

The \(N\)-Boc-aminodiol (1.0 equivalent) was dissolved in dichloromethane (40 mL per gram of \(N\)-Boc-aminodiol) and imidazole (1.2 equivalents) was added to the mixture. The resulting mixture was left to stir for 5 minutes before 4-dimethylaminopyridine (0.1 equivalents) was added. This was followed by the dropwise addition of tert-butyldiphenylsilyl chloride (1.1 equivalents). The mixture was then left to stir for 16 h, and the solvents removed under reduced pressure to yield a crude yellow oil. The mixture was washed with water (2 \(\times\) 30 mL per gram of \(N\)-Boc-aminodiol) and brine (2 \(\times\) 30 mL per gram of \(N\)-Boc-aminodiol). The organic phase was separated, dried (\(Na_2SO_4\)) and the solvent removed under reduced pressure.

\((1S,2S)-N-(\text{tert-Butyloxycarbonyl})-2\text{-amino-3-(\text{tert-butyldiphenylsilyloxy})-1-hydroxy-1-phenyl-propane} (35):

Prepared according to the general procedure from \((1S,2S)-N-(\text{tert-Butyloxycarbonyl})-2\text{-amino-1-phenyl-1,3-propanediol} (33) (5.66 \, g, \, 21.29 \, mmol). Column chromatography of the crude product using ethyl acetate/light petrol (1:6) as the eluent afforded the product as a colourless solid (9.69 g, 90%); m.p. 106-108 °C; \([\alpha]^{20}_D\)
+32.9 (c 1.12, CHCl₃); \( \nu_{\text{max}} \text{(film)/cm}^{-1} \) 3434 (OH), 3060, 2936, 2863, 1696 (NC=O), 1499, 1371, 1246, 1168, 1109, 912, 819, 735, 702, 609; \(^1\)H-NMR (400 MHz, CDCl₃): \( \delta \) 1.01 (9 H, s, SiC(CH₃)₃), 1.27 (9 H, s, NCO₂C(CH₃)₃), 3.42 (1 H, bs, CHOH), 3.63 (1 H, dd, \( J=10.0, \) 3.2 Hz, CH/OSiPh₂t-Bu, H3), 3.69 (1 H, dd, \( J=10.0, \) 3.2 Hz, CHHOSiPh₂t-Bu, H3'), 3.75-3.77 (1 H, m, CHN, H2), 4.93 (1 H, t, \( J=3.2 \text{ Hz,} \) CHOH, H1), 5.08 (1 H, d, \( J=8.4 \text{ Hz,} \) NH), 7.12-7.36 (11 H, m, 11 × CH arom.), 7.54-7.63 (4 H, m, 4 × CH arom.); \(^{13}\)C-NMR (100 MHz, CDCl₃): \( \delta \) 19.30 (C quat., SiC(CH₃)₃), 26.98 (3 × CH₃, SiC(CH₃)₃), 28.37 (3 × CH₃, NCO₂C(CH₃)₃), 57.03 (CH, CHN, C2), 65.00 (CH₂, CH₂OSiPh₂t-Bu, C3), 74.27 (CH, CHOH, C1), 79.61 (C quat., NCO₂C(CH₃)₃), 126.26 (CH arom.), 127.61 (CH arom.), 127.68 (CH arom.), 127.93 (2 × CH arom.), 127.94 (2 × CH arom.), 128.32 (2 × CH arom.), 130.03 (2 × CH arom.), 132.76 (2 × C quat., arom., ipso to Silica gp.), 135.60 (2 × CH arom.), 135.63 (2 × CH arom.), 141.29 (C quat., arom., ipso to CHOH, C4), 156.32 (C quat., N-Boc C=O); \( m/z \) (FAB) 506.2728; \( C_{36}H_{39}NO_{4}Si \) [M+H]⁺ requires 506.2727.

\((1S,2S)-N-(\text{tert-Butyloxycarbonyl})-2\text{-amino-3-}(\text{tert-butylidiphenylsilyloxy})-1\text{-hydroxy-1-}(4\text{-nitrophenyl})\text{-propane (36):} \)

\[ \text{O}_2\text{N} \]
\[ \text{H} \]
\[ \text{N} \]
\[ \text{O} \]
\[ \text{O} \]
\[ \text{H} \]
\[ \text{O} \]
\[ \text{H} \]
\[ 34 \]

\[ \text{O}_2\text{N} \]
\[ \text{H} \]
\[ \text{N} \]
\[ \text{O} \]
\[ \text{O} \]
\[ \text{H} \]
\[ \text{O} \]
\[ \text{Si} \]
\[ \text{H} \]
\[ \text{B} \]
\[ 36 \]

Prepared according to the general procedure from \((1S,2S)-N-(\text{tert-Butyloxycarbonyl})-2\text{-amino-1-}(4\text{-nitrophenyl})\text{-3-propanediol (34) (0.82 g, 2.70 mmol). Column chromatography of the crude yellow oil using ethyl acetate/light petrol (1:5) as the eluent afforded the title compound as a colourless oil (1.23 g, 85%); [\( \alpha \] ]\(^{20}_D \) +19.5 (c 0.78, CHCl₃); \( \nu_{\text{max}} \text{(film)/cm}^{-1} \) 3428 (OH), 2929, 1684 (NC=O), 1605, 1521, 1427, 1391, 1346, 1167, 1113, 823, 739, 702; \(^1\)H-NMR (400 MHz, CDCl₃): \( \delta \) 1.04 (9 H, s, SiC(CH₃)₃), 1.25 (9 H, s, NCO₂C(CH₃)₃), 3.71 (1 H, d, \( J=2.4 \text{ Hz,} \) ArCHOH), 3.75-3.76 (3 H, m, NCHCH₂OSiPh₂t-Bu, H3 and CHN, H2), 5.08 (1 H, t, \( J=2.4 \text{ Hz,} \) ArCHOH, H1), 7.31-7.44 (8 H, m, 4 × CH arom., meta in Ph gp., 2 × CH arom., para
in Ph gp. and 2 × CH arom., H5, H6), 7.57 (4 H, dd, J= 7.9 Hz, 1.3 Hz, 4 × CH arom., ortho in Ph gp.), 8.08 (2 H, d, J= 8.7 Hz, 2 × CH arom., H7, H8); 13C-NMR (100 MHz, CDCl3): δ 19.23 (C quat., SiC(CH3)3), 26.94 (3 × CH3, SiC(CH3)3), 28.22 (3 × CH3, NCO2C(CH3)3), 56.46 (CH, CHN, C2), 65.38 (CH2, NCHCH2OSiPh2–Bu, C3), 73.85 (CH, ArCHOH, C1), 80.03 (C quat., NCO2C(CH3)3), 123.43 (2 × CH arom., C7, C8), 126.98 (2 × CH arom., C5, C6), 128.04 (4 × CH arom., meta in Ph gp.), 130.23 (2 × CH arom., para in Ph gp.), 132.31 (2 × C quat., arom., ipso to Silica gp.), 135.54 (2 × CH arom., ortho in Ph gp.) 135.57 (2 × CH arom., ortho in Ph gp.), 147.30 (C quat., arom., ipso to CHOH, C4), 148.70 (C quat., arom., ipso to NO2 gp., C9), 156.02 (C quat., N-Boc C=O); m/z (FAB) 551.2579; C30H38N2O6Si [M+H]+ requires 551.2577.

**General procedure for the synthesis of N-Boc-2,2-dimethyl-derived oxazolidines:**

![Chemical structure](image)

The N-Boc-tert-butylidiphenylsilyloxy-protected compound (1.0 equivalent) was dissolved in acetone (50 mL per gram of sily-protected compound) and pTSA (0.1 equivalents) and 2,2-dimethoxypropane (10.0 equivalents) were added at room temperature. The mixture was then left to stir for 16 h and the solvents removed under reduced pressure. The residue was redissolved in ethyl acetate (10 mL per gram of sily-protected compound), washed with saturated sodium hydrogen carbonate (2 × 20 mL per gram of sily-protected compound) and brine (2 × 20 mL per gram of sily-protected compound). The combined organic extracts were dried (Na2SO4) and the solvent removed in vacuo.
(4S,5S)-N-(tert-Butyloxycarbonyl)-4-[(tert-butylidiphenylsilayloxy)methyl]-2,2-
dimethyl-5-phenyl-1,3-oxazolidine (37):

Prepared according to the general procedure from compound (35) (4.90 g, 9.70
mmol). Column chromatography of the crude product using ethyl acetate/light petrol
(1:20) afforded the product as a colourless oil (4.07 g, 89%); [a]$_D^{20}$ +13.8 (c 0.93,
CHCl$_3$); $\nu_{\text{max}}$(film)/cm$^{-1}$ 2964, 2931, 1697, 1470, 1392, 1375, 1259, 1174, 1111, 702;
$\text{^1H-NMR}$ (400 MHz, DMSO-d$_6$, 100 °C): $\delta$ 1.07 (9 H, s, SiC(CH$_3$)$_3$), 1.39 (9 H, s,
NCO$_2$C(CH$_3$)$_3$)major rotamer), 1.49 (9 H, s, NCO$_2$C(CH$_3$)$_3$)minor rotamer), 1.56 (3 H, s, CH$_3$,
H6 or H7major rotamer); 1.60 (6 H, s, CH$_3$, H6 or H7major and minor rotamer), 1.63 (3 H, s, CH$_3$,
H6 or H7minor rotamer), 3.65 (1 H, dd, $J$= 11.2 Hz, 3.2 Hz, NCHCHHO, H8major rotamer),
3.77-3.84 (4 H, m, H8minor rotamers, NCHCHHO, H8major rotamer, CHN,
H4major and minor rotamers), 4.16 (1 H, dd, $J$= 11.2 Hz, 3.2 Hz, NCHCHHO, H8minor rotamer),
5.12 (1 H, d, $J$= 6.2 Hz, CHO, H5major rotamer) 5.22 (1 H, d, $J$= 6.2 Hz, CHO, H5minor
rotamer), 7.30-7.49 (16 H, m, 16 x CH arom.major and minor rotamers), 7.63-7.67 (4 H, m, 4 x
CH arom.major and minor rotamers); $\text{^{13C-NMR}$ (100 MHz, DMSO-d$_6$, 100 °C): $\delta$ 19.30 (C
quat., SiC(CH$_3$)$_3$), 26.75 (CH$_3$, C6 or C7major rotamer), 26.86 (CH$_3$, C6 or C7minor rotamer),
27.23 (3 x CH$_3$, SiC(CH$_3$)$_3$), 27.76 (CH$_3$, C6 or C7major rotamer), 27.82 (CH$_3$, C6 or
C7minor rotamer), 28.52 (3 x CH$_3$, NCO$_2$C(CH$_3$)$_3$minor rotamer), 28.62 (3 x CH$_3$,
NCO$_2$C(CH$_3$)$_3$major rotamer), 60.23 (CH$_2$, NCHCH$_2$O, C8major rotamer), 61.80 (CH$_2$,
NCHCH$_2$O, C8minor rotamer), 65.15 (CH, CHN, C4minor rotamer), 65.77 (CH, CHN, C4major
rotamer), 78.60 (CH, CHO, C5minor rotamer), 78.66 (CH, ArCH, C5major rotamer), 79.81 (C
quat., NCO$_2$C(CH$_3$)$_3$major rotamer), 79.93 (C quat., NCO$_2$C(CH$_3$)$_3$minor rotamer), 94.53 (C
quat., C$_2$major rotamer), 94.73 (C quat., C$_2$minor rotamer), 126.98 (CH arom.), 127.18 (CH
arom.), 128.14 (CH arom.), 128.16 (CH arom.), 128.46 (CH arom.), 128.65 (CH
arom.), 128.76 (CH arom.), 130.22 (CH arom.), 130.25 (CH arom.), 133.49 (C quat.,
arom.), 133.55 (C quat., arom.), 135.62 (CH arom.), 135.64 (CH arom.), 140.05 (C quat., arom.), 141.11 (C quat., arom.), 151.66 (C quat., C=O_major rotamer), 151.83 (C quat., C=O_minor rotamer); m/z (FAB) 546.3049; C_{33}H_{43}NO_{3}Si [M+H]^+ requires 546.3040.

\[(4S,5S)-N-(\text{tert-Butyloxycarbonyl})-4-[(\text{tert-butyldiphenylsilayloxy)methyl}]2,2\text{-dimethyl-5-(4-nitrophenyl)-1,3-oxazolidine (38):}\]

\[
\begin{align*}
\text{36} & \quad \text{38}
\end{align*}
\]

Prepared according to the general procedure from compound (36) (1.13 g, 2.09 mmol). Column chromatography of the crude product using ethyl acetate/light petrol (1:6) afforded the product as a yellow oil (0.96 g, 79%); \([\alpha]^{20}_D +4.7\ (c\ 0.69,\ \text{CHCl}_3);\)

\[
\nu_{\text{max}}(\text{film})/\text{cm}^{-1} 2931, 1697 (\text{NC}=\text{O}), 1605, 1523, 1471, 1427, 1392, 1346, 1174, 1112, 851, 702; \]

\[
\nu_{\text{max}}(\text{film})/\text{cm}^{-1} 2931, 1697 (\text{NC}=\text{O}), 1605, 1523, 1471, 1427, 1392, 1346, 1174, 1112, 851, 702; \]

\[
1^H\text{-NMR (400 MHz, DMSO-d}_6, 100\ ^\circ\text{C}): } \delta\ 1.06 (9\ H, s, \text{SiC(CH}_3)_3), 1.38 (9\ H, s, \text{NCO}_2\text{C(CH}_3)_3), 1.60 (3\ H, s, \text{CH}_3, \text{H6 or H7}), 1.64 (3\ H, s, \text{CH}_3, \text{H6 or H7}), 3.85-3.88 (1\ H, m, \text{NCHCHHOSiPh}_2\text{t-Bu, H8}), 3.90-3.93 (1\ H, m, \text{NCH, H4}), 4.14 (1\ H, \text{dd, } J= 10.0\ Hz, 5.6\ Hz, \text{NCHCHHOSiPh}_2\text{t-Bu, H8'}), 5.32 (1\ H, d, J= 6.4\ Hz, \text{ArCH, H5}), 7.40-7.49 (6\ H, m, 4 \times \text{CH arom., meta in Ph gp.}, \text{and } 2 \times \text{CH arom., para in Ph gp.}), 7.60-7.65 (6\ H, m, 4 \times \text{CH arom., ortho in Ph gp.}, \text{and } 2 \times \text{CH arom., H10, H11}), 8.16 (2\ H, d, J= 8.8\ Hz, 2 \times \text{CH arom., H12, H13}); \]

\[
1^C\text{-NMR (100 MHz, DMSO): } \delta\ 19.28 (C\ quat., \text{SiC(CH}_3)_3), 26.82 (\text{CH}_3, \text{C6 or C7}), 27.25 (3 \times \text{CH}_3, \text{SiC(CH}_3)_3), 27.74 (\text{CH}_3, \text{C6 or C7}), 28.47 (3 \times \text{CH}_3, \text{NCO}_2\text{C(CH}_3)_3), 62.34 (\text{CH}_2, \text{NCHCH}_2\text{OSiPh}_2\text{t-Bu, C8}), 65.01 (\text{CH, CHN, C4}), 78.05 (\text{CH, ArCH, C5}), 80.23 (C\ quat., \text{NCO}_2\text{C(CH}_3)_3), 95.37 (C\ quat., C2), 123.84 (2 \times \text{CH arom., C13, C14}), 128.17 (2 \times \text{CH arom., meta in Ph gp.}), 128.22 (2 \times \text{CH arom., meta in Ph gp.}), 128.37 (2 \times \text{CH arom., C10, C11}), 130.28 (\text{CH arom., para in Ph gp.}), 130.31 (\text{CH arom., para in Ph gp.}), 133.37 (C\ quat., arom., ipso to Silica gp.), 133.45 (C\ quat., arom., ipso to}
Silica gp.), 135.61 (2 × CH arom., ortho in Ph gp.), 135.62 (2 × CH arom., ortho in Ph gp.), 147.60 (C quat., arom., ipso C9), 148.91 (C quat., arom., ipso to NO2 gp., C14), 155.55 (C quat., N-Boc C=O); m/z (FAB) 591.2881; C33H42N2O6Si [M+H]+ requires 591.2890.

(4S,5S)-N-(tert-Butyloxycarbonyl)-4-hydroxymethyl-2,2-dimethyl-5-phenyl-1,3-oxazolidine (39):

Tetra-butylammonium fluoride (1.0 M, 10.60 mL) was added dropwise over 5 minutes to a solution of compound (37) (5.25 g, 9.64 mmol) in THF. The reaction mixture was then left to stir at room temperature overnight. The reaction mixture was concentrated in vacuo and the resulting yellow oil diluted with ethyl acetate (30 mL), washed with water (2 × 30 mL), brine (2 × 30 mL), dried (MgSO4) and the solvents removed in vacuo. Column chromatography using ethyl acetate/light petrol (1:10-1:5) as an eluent afforded the product as a yellow oil (2.45 g, 84%); [α]20 D +37.2 (c 1.58, CHCl3); νmax(film)/cm−1 3433 (OH), 2977, 2932, 1683 (NC=O), 1460, 1395, 1253, 1169, 1065, 969, 856, 760, 700; 1H-NMR (400 MHz, CDCl3): δ 1.44 (9 H, s, NCO₂C(CH₃)₃), 1.51 (3 H, s, CH₃, H6 or H7), 1.62 (3 H, s, CH₃, H6 or H7), 3.60-3.74 (3 H, m, NCH, H4 and NCHCH₂OH, H8), 4.45 (1 H, bs, NCHCH₂OH), 4.80 (1 H, bs, CHO, H5), 7.24-7.35 (5 H, m, 5 × CH arom.); 13C-NMR (100 MHz, CDCl3): δ 26.03 (CH₃, C6 or C7), 27.72 (CH₃, C6 or C7), 28.42 (3 × CH₃, NCO₂C(CH₃)₃), 63.46 (CH₂, NCHCH₂OH, C8), 67.66 (CH, CHN, C4), 78.39 (CH, CHO, C5), 81.46 (C quat., NCO₂C(CH₃)₃), 94.73 (C quat., C2), 127.35 (2 × CH arom., C10, C11), 128.70 (2 × CH arom., C12, C13), 128.87 (CH arom., C14), 137.23 (C quat., arom., C9), 154.22 (C quat., N-Boc C=O); m/z (FAB) 308.1869; C₁₇H₂₅NO₄ [M+H]+ requires 308.1862.
A solution of compound (38) (5.27 g, 9.06 mmol) in THF (100 mL) was cooled to 0 °C before tetra-butylammonium fluoride (1.0 M, 9.97 mL) in THF (30 mL) was added dropwise over 30 minutes using a syringe pump. The reaction mixture was then left to stir at 0 °C for 3 h. The reaction mixture was concentrated in vacuo and the resulting yellow oil diluted with ethyl acetate (50 mL), washed with water (2 × 30 mL), brine (2 × 30 mL), dried (MgSO₄) and the solvents removed in vacuo. Column chromatography using ethyl acetate/light petrol (1:4) as an eluent afforded the product as a yellow oil (2.58 g, 81%); [α]²⁰D +18.1 (c 1.06, CHCl₃); νₚₑₚₑ(film)/cm⁻¹ 3439 (OH), 2978, 2934, 1691 (NC=O), 1605, 1523, 1454, 1367, 1347, 1255, 1170, 1067, 852; ¹H-NMR (400 MHz, DMSO-d₆, 100 °C): δ 1.28 (9 H, s, NCO-C(CH₃)₃), 1.57 (3 H, s, CH₃, H6), 1.62 (3 H, s, CH₃, H7), 3.75-3.81 (3 H, m, NCH, H4 and NCHCH₂OH, H8), 4.75 (1 H, d, J= 5.6 Hz, ArCH, H5), 7.72 (2 H, d, J= 8.8 Hz, 2 × CH arom., H10, H11), 8.21 (2 H, d, J= 8.8 Hz, 2 × CH arom., H12, H13); ¹³C-NMR (100 MHz, DMSO): δ 26.92 (CH₃, C6 or C7), 27.85 (CH₃, C6 or C7), 28.59 (3 × CH₃, NCO₂C(CH₃)₃), 60.55 (CH₂, NCHCH₂OH, C8), 65.68 (CH, CHN, C4), 78.18 (CH, ArCH, C5), 80.09 (C quat., NCO₂C(CH₃)₃), 95.14 (C quat., C2), 123.78 (2 × CH arom., C12, C13), 128.13 (2 × CH arom., C10, C11), 148.01 (C quat., arom., ipso, C9), 148.78 (C quat., arom., ipso to NO₂ gp., C14), 151.65 (C quat., N-Boc C=O); m/z (FAB) 353.1718; C₁₇H₂₄N₂O₆ [M+H]⁺ requires 353.1713.
General procedure for the synthesis of N-Boc-2,2-dimethyl-derived oxazolidine aldehydes:

The alcohol-oxazolidine (1.0 equivalent) was dissolved in anhydrous dimethyl-sulfoxide (1 mL per gram of alcohol) and triethylamine (3.0 equivalents) was added dropwise to the mixture at room temperature. A solution of sulfurtrioxide pyridine complex (3.0 equivalents) in anhydrous dimethyl-sulfoxide (1 mL per gram of alcohol) was then added to the mixture. The reaction mixture was then left to stir at room temperature for 16 h. The reaction was quenched with ice-cooled water (10 mL per gram of alcohol) and extracted with ethylacetate (3 x 30 mL per gram of alcohol). The combined organic extracts were washed with water (5 x 30 mL per gram of alcohol), brine (6 x 30 mL per gram of alcohol), dried (MgSO₄) and the solvents removed under reduced pressure.

(4R,5S)-N-(tert-Butyloxy carbonyl)-4-formyl-2,2-dimethyl-5-phenyl-1,3-oxazolidine (41):

Prepared according to the general procedure from compound (39) (0.50 g, 1.63 mmol). Column chromatography of the crude product using ethyl acetate/light petrol (1:5) afforded the product as a colourless oil (0.33 g, 66%); [α]₂₀° +16.3 (c 1.50, CHCl₃); ν_max(film)/cm⁻¹ 2978, 2932, 1710, 1456, 1372, 1259, 1160, 1094, 949, 880,
756; $^1$H-NMR (400 MHz, DMSO-$d_6$, 100 °C): $\delta$ 1.39 (9 H, s, NCO$_2$C(CH$_3$)$_3$), 1.63 (3 H, s, CH$_3$, H6), 1.71 (3 H, s, CH$_3$, H7), 4.01 (1 H, dd, $J$= 8.4 Hz, 3.6 Hz, CHN, H4), 4.90 (1 H, d, $J$= 8.4 Hz, ArCH, H5), 7.25-7.33 (5 H, m, 5 x CH arom.), 9.45 (1 H, d, $J$= 3.6 Hz, HC=O, H8); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ 25.23 (CH$_3$, C6 or C7), 26.15 (CH$_3$, C6 or C7), 28.18 (3 x CH$_3$, NCO$_2$C(CH$_3$)$_3$), 71.30 (CHN, C4), 76.05 (ArCH, C5), 81.67 (C quat., NCO$_2$C(CH$_3$)$_3$), 95.62 (C quat., C2), 126.52 (CH arom., C14), 128.79 (2 x CH arom., C10, C11), 128.94 (2 x CH arom., C12, C13), 136.41 (C quat., arom., ipso, C9), 150.86 (C quat., N-Boc C=O), 197.03 (C quat., HC=O, C8); All attempts to get accurate mass failed.

$(4R,5S)$-$N$-(tert-Butyloxycarbonyl)-4-formyl-2,2-dimethyl-5-(4-nitrophenyl)-1,3-oxazolidine (42):

Prepared according to the general procedure from compound (40) (2.55 g, 7.23 mmol). Column chromatography of the crude product using ethyl acetate/light petrol (1:6) afforded the product as a colourless oil (1.78 g, 70%); [$\alpha$]$^{20}$D +24.0 (c 1.00, CHCl$_3$); $\nu_{\text{max}}$(film)/cm$^{-1}$ 2979, 2932, 1712 (HC=O), 1605 (NC=O), 1524, 1457, 1371, 1260, 1160, 1090, 1070, 854, 734; $^1$H-NMR (400 MHz, DMSO-$d_6$, 100 °C): $\delta$ 1.43 (9 H, s, NCO$_2$C(CH$_3$)$_3$), 1.61 (3 H, s, CH$_3$, H6), 1.65 (3 H, s, CH$_3$, H7), 4.15 (1 H, dd, $J$= 8.0 Hz, 3.4 Hz, CHN, H4), 5.32 (1 H, d, $J$= 8.0 Hz, ArCH, H5), 7.67 (2 H, d, $J$= 8.8 Hz, 2 x CH arom., H10, H11), 8.21 (2 H, d, $J$= 8.8 Hz, 2 x CH arom., H12, H13), 9.57 (1 H, d, $J$= 3.4 Hz, HC=O, H8); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ 26.05 (CH$_3$, C6 or C7), 26.90 (CH$_3$, C6 or C7), 28.38 (3 x CH$_3$, NCO$_2$C(CH$_3$)$_3$), 70.99 (CHN, C4), 74.85 (ArCH, C5), 81.55 (C quat., NCO$_2$C(CH$_3$)$_3$), 95.67 (C quat., C2), 123.96 (2 x CH arom., C12, C13), 128.40 (2 x CH arom., C10, C11), 145.17 (C quat., arom., ipso,
(R)-[1,1']Binaphthalene-2,2'-diol bis-trifluoromethanesulfonate (50a):

(R)-[1,1']Binaphthalene-2,2'-diol (3.00 g, 10.50 mmol) was dissolved in dichloromethane (60 mL) and the solution cooled to −30 °C and stirred at this temperature for 5 minutes before addition of 4-dimethylaminopyridine (0.51 g, 4.20 mmol), 2,6-lutidine (3.70 mL, 31.40 mmol) and triflic anhydride (5.30 mL, 31.40 mmol). The resulting dark-brown reaction mixture was allowed reach ambient temperature and stirred overnight. Silica gel was added to the solution and the solvent removed in vacuo. The product mixture, adsorbed onto silica gel, was transferred to a sintered glass funnel, and the material washed with hexane until the product had eluted. The solvent was removed in vacuo to give a colourless solid, which was crystallized from hexane to afford the product as colourless crystals (5.72 g, 99%); m.p. 76-78 °C [Lit.4 m.p. 82-85 °C]; [α]20D −147.7 (c 1.01, CHCl3) [Lit.4 [α]20D −146.0 (c 1.00, CHCl3); 1H-NMR (400 MHz, CDCl3): δ 7.17-7.19 (2 H, m, 2 × CH arom., binap-3,-3'), 7.32-7.36 (2 H, m, 2 × CH arom., binap-7,-7'), 7.49-7.56 (4 H, m, 4 × CH arom., binap-8,-8'-9,9'), 7.94 (2 H, d, J= 8.2 Hz, 2 × CH arom., binap-4,-4'), 8.07 (2 H, d, J= 9.0 Hz, 2 × CH arom., binap-6,-6'); 13C-NMR (100 MHz, CDCl3): δ 116.53 (2 × C quat., q, J= 79.5 Hz, 2 × CF3), 119.34 (2 × CH arom., binap-8,-8'), 123.45 (2 × C quat., arom., binap-1,-1'), 126.76 (2 × CH arom., binap-3,-3'), 127.33 (2 × CH arom., binap-7,-7'), 127.99 (2 × CH arom., binap-9,-9'), 128.361 (2 × CH arom., binap-4,-4'), 132.01 (2 × CH arom., binap-6,-6'), 132.34 (2 × C quat., arom., binap-5,-5'), 133.13 (2 × C quat., arom., binap-10,-10'), 145.38 (2 × C quat., arom., binap-2,-2'); m/z (ESI) 568.0316; C_{22}H_{12}F_{6}O_{6}S_{2} [M+NH4]^{+} requires 568.0318.
(S)-[1,1']binaphthalene-2,2'-diol bis-trifluoromethanesulfonate (50S):

Prepared in an identical manner to the (R)-enantiomer (50R) above, from (R)-[1,1']Binaphthalene-2,2'-diol (3.00 g, 10.50 mmol). Colourless crystals (5.72 g, 99%); having almost identical spectroscopic data to (50R): m.p. 75-77 °C; [α]_D^20 +145.0 (c 1.00, CHCl3).

(R)-2,2'-Dimethyl-[1,1']binaphthalene (51R):^5

(R)-[1,1']binaphthalene-2,2'-diol bis-trifluoromethanesulfonate (50R) (13.70 g, 24.87 mmol) and 1,3-bis(diphenylphosphino)propane nickel (II)chloride (1.17 g, 1.79 mmol) were dissolved in anhydrous diethyl ether (100 mL). The reaction was cooled to −30 °C, and methylmagnesium bromide (3 M in Et₂O, 33.16 mL, 99.48 mmol) added dropwise over 30 minutes. The reaction was allowed to reach room temperature and left stirred for 16 h. The resulting dark/green reaction mixture was diluted with diethyl ether (100 mL) and filtered through a pad of celite. The filtrate was washed with 35% aqueous hydrochloric acid (20 mL), water (100 mL) and brine (100 mL). Removal of the solvent under reduced pressure gave reddish crude oil, which was purified by column chromatography, eluting with ethyl acetate/hexane (1:4) to give colourless powder. Crystallization from methanol afforded the product as colourless crystals (6.32 g, 90%); m.p. 74-78 °C; [Lit. ^5 m.p. 67-71 °C]; [α]_D^20 -40.0 (c 1.12,
CHCl$_3$) [Lit.$^5$ $[\alpha]^{20}_D$ $-35.6 \ (c \ 1.00, \ CHCl_3)$]; v$_{\text{max}}$(film)/cm$^{-1}$ 3053, 2246, 1594, 1506, 1422, 1379, 1351; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 2.09 (6 H, s, 2 $\times$ Ar-CH$_3$), 7.10 (2 H, dd, $J$= 8.5 Hz, 0.96 Hz, 2 $\times$ CH arom., binap-3,-3'), 7.23-7.28 (2 H, m, 2 $\times$ CH arom., binap-7,-7'), 7.42-7.46 (2 H, m, 2 $\times$ CH arom., binap-4,-4'), 7.92-7.95 (4 H, m, 4 $\times$ CH arom., binap-9,-9' and binap-6,-6'); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 20.08 (2 $\times$ Cl-h, 2 $\times$ Ar-CH$_3$), 124.93 (2 $\times$ CH arom., binap-7,-7'), 125.68 (2 $\times$ CH arom., binap-8,-8'), 126.12 (2 $\times$ CH arom., binap-4,-4'), 127.29 (2 $\times$ CH arom., binap-9,-9'), 127.80 (2 $\times$ CH arom., binap-6,-6'), 128.77 (2 $\times$ CH arom., binap-3,-3'), 132.24 (2 $\times$ C quat., arom., binap-5,-5'), 137.32 (2 $\times$ C quat., arom., binap-10,-10'), 134.32 (2 $\times$ C quat., arom., binap-2,-2'), 135.16 (2 $\times$ C quat., arom., binap-1,-1'); $m/z$ (EI) 282.1400; C$_{22}$H$_{18}$ (M$^+$) requires 282.1403.

(S)-2,2'-Dimethyl-[1,1']binaphthylene (51$_s$):

\[ \text{Prepared in an identical manner to the (R)-enantiomer (51}_R\) above from (R)-[1,1']binaphthylene-2,2'-diol bis-trifluoromethanesulfonate (50$_s$) (13.70 g, 24.87 mmol). Colourless crystals (6.32 g, 90%); having almost identical spectroscopic data to (51$_R$): m.p. 72-74 °C; $[\alpha]^{20}_D$ +38.0 (c 1.00, CHCl$_3$).\]
(R)-2,2'-Bis-bromomethyl-[1,1']binaphthalenyl (52R):\(^6\)

(R)-2,2'-Dimethyl-[1,1']binaphthalene (51R) (2.00 g, 7.08 mmol) was dissolved in cyclohexane (14 mL), and N-bromosuccinimide (2.77 g, 15.58 mmol) and azo-bis-isobutyronitrile (0.12 g, 0.71 mmol) were added with stirring. The mixture was then heated to reflux for 3 h, after which time complete disappearance of the starting material was observed by TLC. After cooling to room temperature, ethyl acetate (5 mL) and water (30 mL) were added to the reaction mixture to dissolve byproducts and excess NBS. The resulting suspension was stirred for 1 h, after which time precipitation has ceased. The mixture was filtered to afford the product as colourless solid (1.54 g, 50%); m.p. 180-183 °C [Lit.\(^6\) m.p. 171-174 °C]; [\(\alpha\)]\(^{20}\)\(_D\) +186.4 (c 1.00, benzene) [Lit.\(^6\) [\(\alpha\)]\(^{20}\)\(_D\) +148.0 (c 1.70, benzene)]; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3049, 2360, 1506, 1432, 1211, 818, 759; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 4.17 (4 H, s, 2 \(\times\) Ar-CH\(_2\)), 7.00 (2 H, d, \(J=8.6\) Hz 2 \(\times\) CH arom., binap-3,-3'), 7.17-7.19 (2 H, m, 2 \(\times\) CH arom., binap-7,-7'), 7.39-7.41 (2 H, m, 2 \(\times\) CH arom., binap-8,-8'), 7.67 (2 H, d, \(J=8.6\) Hz, 2 \(\times\) CH arom., binap-4,-4'), 7.85 (2 H, d, \(J=8.2\) Hz, 2 \(\times\) CH arom., binap-9,-9'), 7.94 (2 H, d, \(J=8.6\) Hz, 2 \(\times\) CH arom., binap-6,-6'); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 31.63 (2 \(\times\) Ar-CH\(_2\)), 126.87 (2 \(\times\) CH arom., binap-7,-7'), 126.88 (2 \(\times\) CH arom., binap-8,-8'), 127.08 (2 \(\times\) CH arom., binap-4,-4'), 127.77 (2 \(\times\) CH arom., binap-9,-9'), 128.18 (2 \(\times\) CH arom., binap-6,-6'), 129.89 (2 \(\times\) CH arom., binap-3,-3'), 132.52 (2 \(\times\) C quat., arom., binap-5,-5'), 133.28 (2 \(\times\) C quat., arom., binap-10,-10'), 134.12 (2 \(\times\) C quat., arom., binap-2,-2'), 134.22 (2 \(\times\) C quat., arom., binap-1,-1'); m/z (El) 437.9612; C\(_{22}\)H\(_{16}\)Br\(_2\) (M\(^+\)) requires 437.9613.
(S)-2,2'-Bis-bromomethyl-[1,1']binaphthalenyl (52_s):

\[ \text{Prepared in an identical manner to the (R)-enantiomer (52_R) above, from (S)-2,2'-dimethyl-[1,1']binaphthalene (18_s) (2.00 g, 7.08 mmol). Colourless crystals (6.32 g, 90%); having almost identical spectroscopic data to (52_R): m.p. 180-182 °C; [Lit.}^{5} \text{ m.p. 181-182 °C]; } [\alpha]^{20}_{D} -158.0 (c 1.00, benzene); [Lit.}^{5} \text{ [\alpha]}^{20}_{D} -157.3 (c 1.00, benzene)].

(R)-2,7-Dihydrodinaphtho[2,1-c;1',2'-e]oxepine (53_R):

\[ \text{(R)-2,2'-Bis-bromomethyl-[1,1']binaphthalene (52_R) (1.16 g, 2.65 mmol) was suspended in a mixture of saturated aqueous sodium carbonate (40 mL) and 1,4-dioxane (40 mL). The mixture was heated under reflux for 36 h, allowed to cool to room temperature, and extracted with diethyl ether (2 \times 40 mL). The combined organic extracts were washed with brine (2 \times 30 mL) and dried (Na}_2\text{SO}_4), the solution filtered to remove the drying agent, and the solvent removed in vacuo to give a yellow oil. The crude product was purified by flash column chromatography using ethyl acetate/light petrol (0:100-5:95) as eluent to afford the product as a colourless solid (0.30 g, 81%); m.p. 184-186 °C; [Lit.}^{7} \text{ m.p. 188-189 °C]; } [\alpha]^{20}_{D} -551.2 (c 1.00, CHCl}_3); v_{\text{max}}(\text{film})/\text{cm}^{-1} 3049, 2959, 2923, 1594, 1507, 1463, 1367, 1237, 1195, 1057.} \]
909, 828; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 4.12 (2 H, d, \(J=11.3\) Hz, Ar-CH\(_2\)O), 4.56 (2 H, d, \(J=11.3\) Hz, Ar-CH\(_2\)O), 7.19-7.25 (2 H, m, 2 \(\times\) CH arom., binap-3,-3'), 7.41-7.47 (4 H, m, 4 \(\times\) CH arom., binap-7,-7', binap-8,-8'); \(^13\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 67.46 (2 \(\times\) Cl-h, 2 \(\times\) Ar-CH\(_2\)), 125.95 (2 \(\times\) CH arom., binap-7,-7'), 125.98 (2 \(\times\) CH arom., binap-8,-8'), 127.39 (2 \(\times\) CH arom., binap-4,-4'), 127.62 (2 \(\times\) CH arom., binap-9,-9'), 128.39 (2 \(\times\) CH arom., binap-6,-6'), 129.19 (2 \(\times\) CH arom., binap-3,-3'), 131.16 (2 \(\times\) C quat., arom., binap-5,-5'), 133.56 (2 \(\times\) C quat., arom., binap-10,-10'), 133.64 (2 \(\times\) C quat., arom., binap-2,-2'), 135.48 (2 \(\times\) C quat., arom., binap-1,-1'); m/z (ESI) 314.1542; C\(_{22}\)H\(_{16}\)O [M+NH\(_3\)]\(^+\) requires 314.1539.

(S)-2,7-Dihyrodinaphtho[2,1-c;1',2'-e]oxepine (53\(\_S\)):

\[
\begin{array}{c}
\text{Br} \\
\text{Br} \\
52_S \\
\end{array}
\quad \rightarrow \quad
\begin{array}{c}
\text{O} \\
\text{53}_S \\
\end{array}
\]

Prepared in an identical manner to the (R)-enantiomer (53\(\_R\)) above, from (S)-2,2'-bis-bromomethyl-[1,1']binaphthalenyl (52\(\_S\)) (1.16 g, 2.65 mmol). Colourless crystals (0.30 g, 81%); having almost identical spectroscopic data to (53\(\_R\)): m.p. 184-186 °C; \([\alpha]^{20}_D\) +568.2 (c 1.00, CHCl\(_3\)).

(R)-2'-Bromomethyl-[1,1']binaphthalene-2-carboxaldehyde (54\(\_R\))^8

\[
\begin{array}{c}
\text{O} \\
\text{53}_R \\
\end{array}
\quad \rightarrow \quad
\begin{array}{c}
\text{Br} \\
\text{54}_R \\
\end{array}
\]
(R)-2,7-Dihydrodinaphtho[2,1-c;1',2'-e]oxepine (53R) (0.50 g, 1.69 mmol) was dissolved in cyclohexane, and the solution cooled to 0 °C. Bromine (0.31 g, 1.86 mmol) was added dropwise with stirring over 10 minutes. After stirring for a further 5 more minutes at this temperature, the reddish reaction mixture was heated to reflux for 1 h, until it became pale yellow. The solvent was removed in vacuo, and the resulting yellow residue redissolved in diethyl ether (30 mL), and washed with saturated aqueous sodium carbonate (2 x 30 mL) and brine (2 x 30 mL). The combined organic extracts were dried (Na2SO4), and the solvent removed in vacuo to give a yellow oil. The crude product was purified by flash column chromatography using ethyl acetate/light petrol (0:100) as eluent, to afford the product as a colourless solid (0.43 g, 68%); m.p. 150-152 °C; [Lit.8] m.p. 151-153 °C; [α]20D +144.0 (c 1.00, CHCl3); [Lit.8] [α]20D +144.7 (c 1.02, CHCl3); νmax(film)/cm⁻¹ 3057, 2845, 2357, 1688, 1616, 1593, 1509, 1429, 1324, 1240, 1027, 909, 870, 821, 750, 730; ¹H-NMR (400 MHz, CDCl3): δ 4.01 (1 H, d, J= 10.1 Hz, Ar-CH₂Br), 4.26 (1 H, d, J= 10.1 Hz, Ar­CH₂Br), 6.95 (1 H, dd, J= 8.5 Hz, 0.8 Hz, CH arom., binap-7'), 7.16-7.29 (3 H, m, 3 × CH arom., binap-3,-8'-4'), 7.43 (1 H, m, CH arom., binap-7), 7.55 (1 H, m, CH arom., binap-8), 7.65 (1 H, d, J= 8.6 Hz, CH arom., binap-4), 7.87 (1 H, d, J= 8.4 Hz, CH arom., binap-6), 7.93 (1 H, d, J= 8.4 Hz, CH arom., binap-6'), 7.98 (1 H, d, J= 8.5 Hz, CH arom., binap-9), 8.02 (1 H, d, J= 8.5 Hz, CH arom., binap-9'), 8.14 (1 H, d, J= 8.6 Hz, CH arom., binap-3'), 9.49 (1 H, d, J= 0.9 Hz, CHO); ¹³C-NMR (100 MHz, CDCl3): δ 31.93 (CH₂, Ar-CH₂), 122.39 (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 × 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 quat., arom., binap-5'), 132.42 (Cquat., arom., binap-10'), 132.53 (C quat., arom., binap-2), 132.97 (Cquat., arom., binap-5), 134.87 (C quat., arom., binap-2'), 134.63 (Cquat., arom., binap-1'), 136.29 (Cquat., arom., binap-10), 141.59 (Cquat., arom., binap-1), 191.84 (CHO); m/z (ESI) 392.0643; C22H15BrO [M+NH₄]⁺ requires 392.0645.
(S)-2'-Bromomethyl-[1,1'binaphthalene-2-carboxaldehyde (54S):

\[
\begin{align*}
\text{\[53_s\]} & \quad \rightarrow \quad \text{\[54_s\]} \\
& \quad \quad \quad \quad \quad \text{(54S)}
\end{align*}
\]

Prepared in an identical manner to the (R)-enantiomer (54R) above, from (S)-2,7-
Dihydrodinaphtho[2,1-c;1',2'-e]oxepine (53s) (0.50 g, 1.69 mmol). Colourless crystals
(0.22 g, 34%); having almost identical spectroscopic data to (54R): m.p. 153-154 °C;
\[\alpha\]_{D}^{20} -143.0 (c 1.00, CHCl_3).

(2S)-N-(tert-Butyloxycarbonyl)-2-amino-3-(4-hydroxyphenyl)-methyl-propionic
acid (56):

\[
\begin{align*}
\text{\[55\]} & \quad \rightarrow \quad \text{\[56\]} \\
& \quad \quad \quad \quad \quad \text{(56)}
\end{align*}
\]

To a cooled 0 °C solution of L-tyrosine-methyl ester hydrochloride salt (55) (8.00 g,
34.53 mmol) in dichloromethane (100 mL) was added triethylamine (9.63 mL, 69.06
mmol). The mixture was then stirred for 30 minutes at this temperature before a
solution of t-butyloxycarbonyl anhydride (8.29 g, 37.98 mmol) in dichloromethane
(10 mL) was added dropwise. The mixture was then left to stir at room temperature
for 16 h. The reaction mixture was then transferred to a separatory funnel and washed
with 1M citric acid (2 \times 30 mL), brine (2 \times 30 mL) and the organic phase dried
(Na_2SO_4). The solvent was then removed under reduced pressure to give colourless
oil. Crystallisation achieved from dichloromethane to give colourless crystals (10.10
g, 99%); m.p. 102-103 °C; [Lit.\] m.p. 100-104 °C]; \[\alpha\]_{D}^{20} +52.8 (c 1.00, CHCl_3);
\[\alpha\]_{D}^{20} +51.0 (c 1.00, CHCl_3)]; \nu_{max}(film)/\text{cm}^{-1} 3364 (OH), 2977, 1689 (C=O),
1614, 1515, 1444, 1366, 1225, 1166, 1058; ^1H-NMR (400 MHz, CDCl_3): 8 1.43 (9 H,
s, NCO_2C(CH_3)_3), 2.98-3.04 (2 H, m, Ar-CH_2, H3); 3.70 (3 H, s, CO_2CH_3), 4.54 (1 H,
q, J= 8.2 Hz, CHN, H2), 5.13 (1 H, d, J= 8.4 Hz, NH), 6.75 (2 H, d, J= 8.3 Hz, 2 × CH arom., H7, H8), 6.96 (2 H, d, J= 8.3 Hz, 2 × CH arom., H5, H6); 13C-NMR (100 MHz, CDCl3): δ 28.31 (3 × CH3, NCO2C(CH3)3), 37.47 (CH2, ArCH2, C3), 52.37 (CH3, CO2CH3), 54.40 (CH, CHN, C2), 80.43 (C quat., NCO2C(CH3)3), 115.58 (2 × CH arom., C7, C8), 127.06 (C quat., arom., ipso to C3 in Ar gp., C4), 130.31 (2 × CH arom., C5, C6), 155.47 (C quat., N-Boc C=O), 155.53 (C quat., arom., ipso to OH in Ar gp., C9), 172.82 (C quat., C=O, CO2CH3); mlz (FAB) 296.1496; C15H21NO5 [M+H]⁺ requires 296.1498.

(2S)-N-(tert-Butyloxy carbonyl)-2-amino-3-(4-methoxyphenyl)-methyl-propionic acid (57):

(2S)-N-(tert-Butyloxy carbonyl)-2-amino-3-(4-hydroxyphenyl)-methyl-propionic acid (56) (9.90 g, 33.72 mmol) was dissolved in N,N-dimethylformamide (70 mL) and grounded potassium hydroxide (2.31 g, 40.46 mmol) was added followed by the dropwise addition of iodomethane (2.52 mL, 40.46 mmol) to the mixture at 0 °C. The reaction was then left to stir at room temperature for 16 h. The reaction mixture was then diluted with ethyl acetate (100 mL) and washed with water (6 × 50 mL), brine (6 × 50 mL) and dried (Na2SO4). The solvent was removed under reduced pressure to yield a colourless oil (9.38 g, 90%); \( \nu_{\text{max}} \) (film)/cm⁻¹ 3367, 2976, 1746 (C=O), 1715 (NC=O), 1612, 1514, 1441, 1366, 1249, 1167, 1034; 1H-NMR (400 MHz, CDCl3): δ 1.34 (9 H, s, NCO2C(CH3)3), 2.92-2.97 (2 H, m, Ar-CH2, H3), 3.63 (3 H, s, CO2CH3), 3.70 (3 H, s, ArOCH3), 4.46 (1 H, q, J= 8.2 Hz, CHN, H2), 4.95 (1 H, d, J= 8.2 Hz, NH), 6.75 (2 H, d, J= 8.7 Hz, 2 × CH arom., H7, H8), 6.96 (2 H, d, J= 8.7 Hz, 2 × CH arom., H5, H6); 13C-NMR (100 MHz, CDCl3): δ 28.29 (3 × CH3, NCO2C(CH3)3), 37.41 (CH2, ArCH2, C3), 52.18 (CH3, CO2CH3), 54.40 (CH, CHN, C2), 55.19 (CH3, ArOCH3), 79.83 (C quat., NCO2C(CH3)3), 113.94 (2 × CH arom., C7, C8), 127.83 (C quat., arom., ipso to C3 in Ar gp., C4), 130.31 (2 × CH arom., C5, C6), 155.12 (C
quat., N-Boc C=O), 158.62 (C quat., arom., ipso to OCH₃ in Ar gp., C9), 172.45 (C quat., C=O, CO₂CH₃); m/z (FAB) 310.1651; C₁₈H₂₃NO₅ [M+H]⁺ requires 310.1655.

(4S,5R)-Methyl-5-(4-methoxyphenyl)-1,3-oxazolidin-2-one-4-carboxylate (58):¹⁰

![Chemical structure of compound 58](image)

Compound (57) (5.00 g, 16.26 mmol) was dissolved in acetonitrile (200 mL). A solution of potassium persulfate (8.79 g, 32.51 mmol) in water (150 mL) and copper (II) sulfate (0.80 g, 3.21 mmol) in water (50 mL) were added to the mixture. The reaction mixture was then heated to 70 °C for 3 h under nitrogen atmosphere. The solution was then allowed to cool to room temperature before being extracted with ethyl acetate (3 × 70 mL), dried (Na₂SO₄) and the solvent removed under reduced pressure to give a yellow oil. Column chromatography with ethyl acetate/petroleum ether (1:1) afforded a colourless solid (1.03 g, 25%); m.p. 92-94 °C; [Lit.¹¹ 94-96 °C]; [α]D²⁰ +85.2 (c 1.00, CHCl₃); [Lit.¹¹ [α]D²⁰ +83.5 (c 1.15, CHCl₃); νmax(film)/cm⁻¹ 3314, 2954, 2841, 1762 (C=O), 1612, 1514, 1441, 1381, 1246, 1119, 1024, 921, 833, 735; ¹H-NMR (400 MHz, CDCl₃): δ 3.74 (3 H, s, CO₂CH₃), 3.76 (3 H, s, ArOCH₃), 4.24 (1 H, dd, J= 5.2 Hz, 0.6 Hz, CHN, H4), 5.50 (1 H, d, J= 5.2 Hz, ArCH, H5), 6.75 (1 H, s, NH), 6.85 (2 H, d, J= 8.6 Hz, 2 × CH arom., H9, H10), 7.27 (2 H, d, J= 8.6 Hz, 2 × CH arom., H7, H8); ¹³C-NMR (100 MHz, CDCl₃): δ 53.18 (CH₃, CO₂CH₃), 55.38 (CH₃, ArOCH₃), 61.46 (CH, CHN, C4), 79.53 (CH, ArCH, C5), 114.36 (2 × CH arom., C9, C10), 127.14 (2 × CH arom., C7, C8), 129.93 (C quat., arom., ipso to C5 in Ar gp., C6), 158.56 (C quat., NC=O, C2), 160.25 (C quat., arom., ipso to OCH₃ in Ar gp., C11), 170.28 (C quat., C=O, CO₂CH₃); m/z (El) 251.0799; C₁₂H₁₃NO₅ (M⁺) requires 251.0794.
(4R,5R)-4-Hydroxymethyl-5-(4-methoxyphenyl)-1,3-oxazolidin-2-one (59):\textsuperscript{11}

![Chemical Structure](image)

Compound (58) (1.14 g, 4.55 mmol) was dissolved in ethanol (30 mL) and cooled to 0 °C. A solution of sodium borohydride (0.38 g, 10.01 mmol) in ethanol (5 mL) was added dropwise to the mixture. After the addition was complete the ice bath was removed and the reaction stirred at room temperature for 55 minutes. The reaction was cooled down to 0 °C and concentrated hydrochloric acid (2 mL) was added, followed by water (20 mL). The ethanol was removed under reduced pressure and the remaining aqueous solution extracted with ethyl acetate (3 x 40 mL). The combined organic extracts was washed with brine (2 x 30 mL), dried (Na$_2$SO$_4$) and the solvents removed under reduced pressure to yield the \textit{title compound} as colourless powder (0.95 g, 94\%); m.p. 138-140 °C; [Lit.\textsuperscript{11} m.p. 140-142 °C]; [α]$^20_D$ +74.6 (c 1.01, acetone); [Lit.\textsuperscript{11} [α]$^20_D$ +74.8 (c 1.08, acetone)]; νmax (nujol)/cm$^{-1}$ 3239, 1725, 1614, 1514, 1459, 1376, 1251, 1174, 1062, 1016, 828; $^1$H-NMR (400 MHz, acetone-d$_6$): δ 3.78 (3 H, m, CHN, H$_4$ and CH$_2$OH, H$_6$), 3.86 (3 H, s, ArOCH$_3$), 5.35 (1 H, d, J= 5.3 Hz, ArCH, H$_5$), 7.01 (2 H, d, J= 8.6 Hz, 2 × CH arom., H$_{10}$, H$_{11}$), 7.41 (2 H, d, J= 8.6 Hz, 2 × CH arom., H$_{8}$, H$_{9}$); $^{13}$C-NMR (100 MHz, acetone-d$_6$): δ 56.03 (CH, CHN, C$_4$), 63.05 (CH$_3$, ArOCH$_3$), 64.24 (CH$_2$, C$_6$), 80.39 (CH, ArCH, C$_5$), 115.36 (2 × CH arom., C$_{10}$, C$_{11}$), 128.67 (2 × CH arom., C$_8$, C$_9$), 133.24 (C quat., arom., ipso to C$_5$ in Ar gp., C$_7$), 159.61 (C quat., NC=O, C$_2$), 161.28 (C quat., arom., ipso to OCH$_3$ in Ar gp., C$_{12}$); m/z (El) 223.0843; C$_{11}$H$_{13}$NO$_4$ (M$^+$) requires 223.0845.
(1R,2R)-(−)-2-Amino-1-(4-methoxyphenyl)-1,3-propanediol (60):\(^{11}\)

![Chemical structure of compound 59 and 60]

A mixture of compound (59) (0.66 g, 2.95 mmol) and 1M sodium hydroxide (30 mL) were heated under reflux for 45 minutes. The reaction mixture was allowed to cool to room temperature and extracted with ethyl acetate (9 × 40 mL). The combined organic extracts were dried (MgSO\(_4\)) and the solvents removed under reduced pressure to afford a colourless solid which was recrystallised from methanol/diethyl ether (0.51 g, 88%); m.p. 129-131 °C; [Lit.\(^{11}\) m.p. 132-134 °C]; \(\alpha\)^20\(_D\) = −33.6 (c 1.00, 2 M aq. HCl); [Lit.\(^{11}\) \(\alpha\)^20\(_D\) = −28.3 (c 1.06, 2 M aq. HCl)]; \(\nu_{\text{max}}\) (nujol)/cm\(^{-1}\) 3339, 1619, 1584, 1517, 1459, 1377, 1253, 1064, 873; \(^1\)H-NMR (400 MHz, CD\(_3\)OD): \(\delta\) 2.91 (1 H, m, CH\_N, H2), 3.30 (1 H, dd, \(J\) = 10.8 Hz, 4.2 Hz, N\_\_CH\_O-H, H3), 3.43 (1 H, dd, \(J\) = 10.8 Hz, 4.2 Hz, N\_\_CH\_O-H, H3'), 3.80 (3 H, s, ArOCH\(_3\)), 4.50 (1 H, d, \(J\) = 7.2 Hz, ArCH, H1), 6.93 (2 H, d, \(J\) = 8.7 Hz, 2 × CH arom., H7, H8), 7.29 (2 H, d, \(J\) = 8.7 Hz, 2 × CH arom., H5, H6); \(^{13}\)C-NMR (100 MHz, acetone-d\(_6\)): \(\delta\) 55.71 (CH\(_3\), ArOCH\(_3\)), 59.93 (CH, CH\_N, C2), 63.96 (CH\(_2\), C3), 75.38 (CH, ArCH, C1), 114.77 (2 × CH arom., C7, C8), 128.84 (2 × CH arom., C5, C6), 135.93 (Cquat., arom., ipso to C1 in Ar gp., C4), 160.70 (Cquat., arom., ipso to OCH\(_3\) in Ar gp., C9); \(m/z\) (FAB) 98.1127; C\(_{10}\)H\(_{12}\)NO\(_3\) [M+H] requires 198.1130.
(2S)-N-(tert-Butyloxy carbonyl)-2-amino-1-hydroxy-3-(4-methoxyphenyl)-propane (66):

Compound (57) (5.20 g, 16.91 mmol) was placed in a dried three-necked round-bottomed flask equipped with a reflux condenser and under nitrogen atmosphere. Dry diethyl ether (100 mL) was added to the flask and the resulting solution cooled to 0 °C using an ice bath. Lithium borohydride (1.47 g, 67.62) was added to the cooled reaction mixture portionwise over 15 minutes. Methanol (40 mL) was then added dropwise, and the reaction mixture left to stir at room temperature overnight. The reaction mixture was diluted with ethyl acetate (100 mL) followed by the dropwise addition of saturated ammonium chloride. The organic phase was separated and washed with water (2 x 20 mL), brine (2 x 20 mL), dried (Na2SO4) and the solvent removed under reduced pressure to afford the product as a colourless oil (4.75 g, 99.8%); [α]D20 -9.7 (c 1.16, CHCl3); νmax(film)/cm⁻¹ 3380 (OH), 2970, 1691 (NC=O), 1613, 1511, 1367, 1248, 1168, 1041, 912; ¹H-NMR (400 MHz, CDCl3): δ 1.33 (9 H, s, NCO2C(CH3)3), 2.69 (2 H, d, J= 6.9 Hz, Ar-CH2, H3), 3.44 (1 H, dd, J= 10.9 Hz, 5.0 Hz, NCH-CHH-OH, H1), 3.54 (1 H, dd, J= 10.9 Hz, 4.0 Hz, NCH-CHH-OH, H1'), 3.69 (3 H, s, ArOCH3), 3.74 (1 H, d, J= 4.0 Hz, CHN, H2), 4.88 (1 H, d, J= 6.2 Hz, NH), 6.75 (2 H, d, J= 8.6 Hz, 2 x CH arom., H7, H8), 7.05 (2 H, d, J= 8.6 Hz, 2 x CH arom., H5, H6); ¹³C-NMR (100 MHz, CDCl3): δ 28.36 (3 x CH3, NCO2C(CH3)3), 36.46 (CH2, ArCH2, C3), 53.75 (CH, CHN, C2), 55.22 (CH3, ArOCH3), 63.90 (CH2, CH2OH, C1), 79.60 (C quat., NCO2C(CH3)3), 113.90 (2 x CH arom., C7, C8), 129.89 (C quat., arom., ipso to C3 in Ar gp., C4), 130.29 (2 x CH arom., C5, C6), 156.27 (C quat., N-Boc C=O), 158.19 (C quat., arom., ipso to OCH3 in Ar gp., C9); m/z (FAB) 282.1710; C15H23NO4 [M+H]+ requires 282.1705.
(2S)-N-(tert-Butyloxycarbonyl)-1-Acetoxy-2-amino-3-(4-methoxyphenyl)-propane (65):

Compound (66) (4.80 g, 17.06 mmol) was dissolved in dichloromethane (50 mL) and cooled to 0 °C before acetic anhydride (1.94 mL, 20.60 mmol), N,N-diisopropylamine (3.60 mL, 20.60 mmol) and DMAP (0.21 g, 1.72 mmol) were added to the reaction flask. The reaction mixture was then left to stir at room temperature for 16 h before the reaction was quenched with 1% HCl (40 mL). The reaction mixture was transferred to a separatory funnel and the organic phase separated. The organic layer was washed with 1% HCl (2 × 40 mL) and brine (2 × 40 mL). The organic layer was dried (Na₂SO₄) and the solvent removed under reduced pressure to yield the product as a red oil (5.20 g, 94.3%); [α]²⁰ D −8.8 (c 1.00, CHCl₃); ν max(film)/cm⁻¹ 3360 (NH), 2973, 1706 (C=O), 1612, 1511, 1456, 1368, 1242, 1169, 1040, 916, 821, 735; ¹H-NMR (400 MHz, CDCl₃): δ 1.34 (9 H, s, NCO₂C(CH₃)₃), 2.00 (3 H, s, CH₂-OCOCH), 2.63-2.74 (2 H, m, Ar-CH₂, H3), 3.69 (3 H, s, ArOCH), 3.92-3.96 (3 H, m, CHN, H2 and NCHCH₂O, H1), 4.58 (1 H, d, J= 6.8 Hz, NH), 6.75 (2 H, d, J= 8.6 Hz, 2 × CH arom., H7, H8), 7.02 (2 H, d, J= 8.6 Hz, 2 × CH arom., H5, H6); ¹³C-NMR (100 MHz, CDCl₃): δ 20.85 (CH), 28.33 (3 × CH₃, NCO₂C(CH₃)₃), 36.96 (CH₂, ArCH₂, C3), 50.70 (CH, CHN, C2), 55.21 (CH₃, ArOCH₃), 65.04 (CH₂, NCHCH₂-O, C1), 79.48 (C quat., NCO₂C(CH₃)₃), 113.96 (2 × CH arom., C7, C8), 129.17 (C quat., arom., ipso to C3 in Ar gp., C4), 130.22 (2 × CH arom., C5, C6), 155.29 (C quat., N-Boc C=O), 158.33 (C quat., arom., ipso to OCH₃ in Ar gp., C9), 170.94 (C quat., C=O); m/z (EI) 323.1738; C₁₇H₂₅NO₅ (M⁺) requires 323.1733.
Compound (65) (3.53 g, 10.92 mmol) was dissolved in acetonitrile (80 mL). A solution of potassium persulfate (5.89 g, 21.83 mmol) in water (70 mL) and copper (II) sulfate (0.35 g, 2.16 mmol) in water (10 mL) were added. The reaction mixture was then heated to 70 °C for 2.5 h under nitrogen atmosphere. The solution was then allowed to cool to room temperature before being extracted with ethyl acetate (3 × 70 mL), dried (Na₂SO₄) and the solvent removed under reduced pressure to yield a crude yellow oil. Column chromatography with ethyl acetate/petroleum ether (1:1) afforded a colourless solid (1.09 g, 38%); m.p. 99-100 °C; [α]²⁰º +55.8 (c 1.29, CHCl₃); νmax(film)/cm⁻¹ 3328 (NH), 2958, 2839, 1745 (C=O), 1612, 1515, 1376, 1248, 1179, 1037, 917, 833, 732; ¹H-NMR (400 MHz, CDCl₃): δ 2.00 (3 H, s, O-CO-CH₃, H₉), 3.72 (3 H, s, ArOCH₃), 3.89-3.94 (1 H, m, CHN, H₄), 4.07 (1 H, dd, J= 11.5 Hz, 5.8 Hz, NCH-CH₂-O, H₆), 4.19 (1 H, dd, J= 11.5 Hz, 4.6 Hz, NCH-CH₂-O, H₆'), 5.13 (1 H, d, J= 6.2 Hz, ArCH, H₅), 6.83 (2 H, d, J= 8.7 Hz, 2 × CH arom., H₁₁, H₁₂), 6.95 (1 H, s, NH), 7.21 (2 H, d, J= 8.7 Hz, 2 × CH arom., H₁₁, H₁₂); ¹³C-NMR (100 MHz, CDCl₃): δ 19.65 (CH₃, O-CO-CH₃, C₉), 54.33 (CH₃, ArOCH₃), 58.12 (CH, CHN, C₄), 63.38 (CH₂, NCH-CH₂-O, C₆), 79.00 (CH, ArCH, C₅), 113.32 (2 × CH arom., C₁₁, C₁₂), 126.49 (2 × CH arom., C₁₁, C₁₂), 128.69 (C quat., arom., C₁₀), 158.19 (C quat., NC=O, C₂), 159.21 (C quat., arom., ipso to OCH₃ in Ar gp., C₁₄), 169.76 (C quat., C=O, C₈); m/z (FAB) 266.1033; C₁₃H₁₅NO₅ [M+H]⁺ requires 266.1029.
(4R,5R)-N-Formyl-5-amino-4-(4-methoxyphenyl)-2,2-dimethyl-1,3-dioxane (62):

\[
\begin{align*}
&\text{(1R,2R)-(--)2-Amino-1-(4-methoxyphenyl)-1,3-propanediol (60) (0.63 g, 3.20 mmol)} \\
&\text{was dissolved in methanol (20 mL) and methyl formate (0.22 mL, 3.52 mmol) was} \\
&\text{added followed by a solution of sodium methoxide (0.02 mL). The reaction was left to} \\
&\text{stir overnight and the solvent removed under reduced pressure. The crude product was} \\
&\text{then dissolved in acetone (30 mL) before the addition of 2,2-dimethoxypropane (5} \\
&\text{mL, 31 mmol) and scandium triflate (0.16 g, 0.31 mmol). The reaction was left to stir} \\
&\text{overnight and the solvents removed under reduced pressure. The resulting residue was} \\
&\text{redissolved in ethyl acetate and the organic phase washed with saturated sodium} \\
&\text{hydrogen carbonate (2 × 30 mL), brine (2 × 30 mL), dried (Na}_2\text{SO}_4) \text{and the solvents} \\
&\text{removed under reduced pressure to yield a crude yellow oil. Column chromatography} \\
&\text{with ethyl acetate/petroleum ether (1:2) afforded the product as a colourless oil (0.75} \\
&\text{g, 91%); } [\alpha]^{20}_D \text{-7.3 (c 1.15, CHCl}_3) \text{; [Lit.}^{11} [\alpha]^{20}_D \text{-2.7 (c 1.20, CHCl}_3) \text{; } \\
&\nu_{\text{max}}(\text{film})/\text{cm}^{-1} \text{3302 (NH), 2988, 2871, 2243, 1673, 1512, 1378, 1247, 1196, 1083,} \\
&1036, 935, 836, 733, 628; [\text{H-NMR (400 MHz, CDCl}_3): } 8 1.54 (3 \text{ H, s, CH}_3, \text{H7 or} \\
&\text{H8), 1.58 (3 \text{ H, s, CH}_3, \text{H7 or H8), 3.78 (3 \text{ H, s, ArOCH}_3), 3.87 (1 \text{ H, dd, J=10.3 Hz,} \\
&\text{1.8 Hz, NCHCHH-O, H6), 4.23-4.27 (2 \text{ H, m, NCH, H5 and NCHCHH-O, H6''), 5.16} \\
&\text{(1 \text{ H, s, Ar-CH}, H4), 6.39 (1 \text{ H, d, J= 9.1 Hz, NH}), 6.87 (2 \text{ H, d, J= 8.7 Hz, 2 × CH} \\
&\text{arom., H12, H13), 7.23 (2 \text{ H, d, J= 8.7 Hz, 2 × CH} \text{ arom., H10, H11), 7.97 (1 \text{ H, s,} \\
&\text{NCHO}), 13\text{C-NMR (100 MHz, CDCl}_3): } 8 18.57 (\text{CH}_3, \text{C7 or C8), 29.71 (\text{CH}_3, \text{C7} \\
&\text{or C8), 45.52 (\text{CH, NCH, C5), 55.23 (CH}_3, \text{ArOCH}_3), 64.58 (\text{CH}_2, \text{C6}), 71.39 (\text{Ar-CH,} \\
&\text{C4), 99.68 (C quat., C2), 113.68 (2 × CH arom., C12, C13), 126.49 (2 × CH arom.,} \\
&\text{C10, C11), 130.17 (C quat., arom., C9), 158.96 (C quat., arom., C14), 160.66 (NCHO,} \\
&\text{C15); m/z (EI) 265.1318; C}_{14}\text{H}_{19}\text{NO}_4 (M^+) \text{requires 265.1314.} \right]
\]
Compound (62) (0.49 g, 1.84 mmol) was dissolved in aqueous hydrazine hydrate (85%) (15 mL) and the solution heated under reflux for 3 h. The solution was allowed to cool to room temperature and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts was washed with water (2 × 30 mL), brine (2 × 30 mL), dried (Na₂SO₄) and the solvents removed under reduced pressure to give the product as a colourless oil (0.41 g, 95%); [α]²⁰D −39.6 (c 1.00, CHCl₃); [Lit.][α]²⁰D −28.9 (c 1.08, CHCl₃); νmax (film)/cm⁻¹ 3372 (NH), 2987, 2937, 1609, 1512, 1458, 1375, 1246, 1192, 1046, 944, 860, 802; ¹H-NMR (400 MHz, CDCl₃): δ 1.46 (3 H, s, CH₃, H7 or H8), 1.48 (3 H, s, CH₃, H7 or H8), 2.63 (1 H, dd, J=3.8 Hz, 1.8 Hz, NCH, H5), 3.74 (3 H, s, ArOCH₃), 3.83 (1 H, dd, J=11.7 Hz, 1.8 Hz, NCHCHH-O, H6), 4.22 (1 H, dd, J=11.7 Hz, 2.3 Hz, NCHCHH-O, H6'), 4.99 (1 H, d, J=1.6 Hz, Ar-CH, H4), 6.85 (2 H, d, J= 8.9 Hz, 2 × CH arom., H12, H13), 7.18 (2 H, d, J= 8.9 Hz, 2 × CH arom., H10, H11); ¹³C-NMR (100 MHz, CDCl₃): δ 18.63 (CH₃, C7 or C8), 29.80 (CH₃, C7 or C8), 49.78 (CH, NCH, C5), 55.32 (CH₃, ArOCH₃), 66.02 (CH₂, C6), 73.49 (Ar-CH, C4), 99.18 (C quat., C2), 113.87 (2 × CH arom., C10, C11), 126.87 (2 × CH arom., C12, C13), 131.67 (C quat., arom., C9), 158.90 (C quat., arom., C14); m/z (FAB) 238.1448; C₁₃H₁₉NO₃ [M+H]⁺ requires 238.1443.
General procedure for the formation of the formate protected 5-amino-1,3-dioxanes from commercially available amino diols:

The aminodiol (1.0 equivalent) was dissolved in methanol (10 mL per gram of aminodiol) and methyl formate (1.1 equivalents) was added with sodium methoxide (0.1 equivalent). 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 (0.1 equivalent) in acetone (50 mL per gram of aminodiol) and 2,2-dimethoxypropane (10.0 equivalents). 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 saturated aqueous sodium hydrogen carbonate (2 x 20 mL per gram of aminodiol) and brine (2 x 20 mL per gram of aminodiol). The organics are dried (MgSO₄) and solvents removed under reduced pressure.

\[
(4S,5S)-N\text{-Formyl-5-Amino-4-phenyl-2,2-dimethyl-1,3-dioxane (69)}:^{12}
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Prepared according to the general procedure from (1S,2S)-(+)2-amino-1-phenyl-1,3-propanediol (31) (5.00 g, 29.90 mmol). The product was isolated as a colourless oil (6.61 g, 94%); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3295, 2990, 1668, 1505, 1381, 1200, 1089, 844, 700; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.49 (3 H, s, \(CH_3\), H7 or H8), 1.53 (3 H, s, \(CH_3\), H7 or H8), 3.80 (1 H, dd, \(J=\) 10.4 Hz, 1.6 Hz, NCHCHH-O, H6), 4.19 (1 H, dd, \(J=\) 10.4 Hz, 1.6 Hz, NCHCHH-O, H6'), 4.23 (1 H, s, NCH, H5), 5.14 (1 H, s, ArCH, H4), 7.16-
7.28 (5 H, m, 5 × CH arom., Ph gp.), 7.89 (1 H, s, NCHO); $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 17.51 (CH$_3$, C7 or C8), 28.67 (CH$_3$, C7 or C8), 44.41 (CH, NCH, C5), 63.56 (CH$_2$, C6), 70.61 (Ar-CH, C4), 98.86 (C quat., C2), 124.23 (2 × CH arom., C10, C11), 126.65 (CH arom., C14), 127.28 (2 × CH arom., C12, C13), 136.99 (C quat., arom., C9), 159.50 (NCHO, C15).

(4S,5S)-N-Formyl-5-Amino-4-(4-nitrophenyl)-2,2-dimethyl-1,3-dioxane (70):$^{11}$

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\[\text{32} \rightarrow \text{70}\]
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Prepared according to the general procedure from (1S,2S)-(+)2-amino-1-(4-nitrophenyl)-1,3-propandiol (32) (3.00 g, 14.14 mmol). The product was isolated as a colourless oil (3.72 g, 94%); [α]$^{20}$D +7.0 (c 1.43, CHCl$_3$); [Lit.$^{11}$ [α]$^{20}$D +3.5 (c 1.02, CHCl$_3$)]; $\nu$$_{\text{max}}$(film)/cm$^{-1}$ 2992, 1684, 1601, 1521, 1382, 1346, 1270, 1199, 1086, 856, 735; $^1$H-NMR (400 MHz, CDCl$_3$): δ 1.48 (3 H, s, CH$_3$, H7 or H8), 1.54 (3 H, s, CH$_3$, H7 or H8), 3.77 (1 H, dd, J = 12.2 Hz, 1.8 Hz, NCHCHH-O, H6), 4.26 (1 H, dd, J = 12.2 Hz, 1.8 Hz, NCHCHH-O, H6'), 4.35 (1 H, dd, J = 9.8 Hz, 1.8 Hz, NCH, H5), 5.22 (1 H, d, J = 1.8 Hz, ArCH, H4), 6.36 (1 H, d, J = 9.8 Hz, NH), 7.44 (2 H, d, J = 8.9 Hz, 2 × CH arom., H12, H13), 7.86 (1 H, s, NCHO), 8.12 (2 H, d, J = 8.9 Hz, 2 × CH arom., H10, H11); $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 18.49 (CH$_3$, C7 or C8), 29.58 (CH$_3$, C7 or C8), 45.07 (CH, NCH, C5), 66.28 (CH$_2$, C6), 71.58 (Ar-CH, C4), 100.06 (C quat., C2), 123.74 (2 × CH arom., C12, C13), 126.76 (2 × CH arom., C10,11), 145.51 (C quat., arom., C9), 147.52 (C quat., arom., C14), 163.01 (NCHO, C15). m/z (ESI) 298.1399; C$_{13}$H$_{18}$N$_2$O$_5$ [M+NH$_4^+$] requires 298.1397.
General procedure for the deprotection of formamides with hydrazine hydrates:

The formate protected acetonide was dissolved in aqueous hydrazine hydrate (85%) (20 mL per gram of acetonide) and the solution heated under reflux for 3 h. The solution was allowed to reach ambient temperature and extracted with ethyl acetate (3 x 30 mL per gram of acetonide). The organic layers were washed with water (2 x 30 mL per gram of acetonide), brine (2 x 30 mL per gram of acetonide) and dried (Na₂SO₄) and the solvents removed under reduced pressure.

(4S,5S)-5-Amino-4-phenyl-2,2-dimethyl-1,3-dioxane (71): 12

Prepared according to the general procedure from acetonide (69) (6.58 g, 28.1 mmol). The product was isolated as a yellow oil (5.39 g, 87% yield). [α]20D +45.5 (c 2.33, ethanol); νmax (film)/cm⁻¹ 3365 (NH), 2990, 1663, 1498, 1379, 1271, 1239, 1198, 1159, 1130, 1087, 1052, 945, 845, 740, 701; ¹H-NMR (400 MHz, CDCl₃): δ 1.44 (6 H, s, 2 x CH₃), 2.64 (1 H, dd, J= 4.0 Hz, 2.0 Hz, NCH, H5), 3.79 (1 H, dd, J= 12.0 Hz, 2.0 Hz, NCHCHH-O, H6), 4.18 (1 H, dd, J= 12.0 Hz, 2.0 Hz, NCHCHH-O, H6'), 4.98 (1 H, s, PhCH, H4), 7.16-7.29 (5 H, m, 5 x CH arom., Ph gp.); ¹³C-NMR (100 MHz, CDCl₃): δ 18.57 (CH₃, C7 or C8), 29.74 (CH₃, C7 or C8), 49.57 (CH, NCH, C5), 56.92 (CH₂, C6), 73.66 (Ar-CH, C4), 94.98 (C quat., C2), 125.66 (2 x CH arom., C10, C11), 127.38 (CH arom., C14), 128.39 (2 x CH arom., C12, C13), 139.77 (C quat., arom., C9).
Prepared according to the general procedure from acetonide (70) (1.00 g, 3.57 mmol) except the reaction was heated under reflux for 1 hour. Column chromatography using ethyl acetate as an eluent gave a yellow oil (0.54 g, 60%); [α]$_D^{20}$ +91.6 (c 0.83, CHCl$_3$); [Lit.$^{11}$ [α]$_D^{20}$ +66.2 (c 1.13, CHCl$_3$)]; $\nu_{\text{max}}$(film)/cm$^{-1}$ 3373 (NH), 2991, 2939, 1600, 1518, 1380, 1347, 1271, 1239, 1198, 1158, 1078, 946, 856; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 1.49 (6 H, s, 2 x CH$_3$, H7 H8), 2.79 (1 H, dd, $J$= 3.9 Hz, 2.0 Hz, NCH, H5), 3.81 (1 H, dd, $J$= 12.3 Hz, 1.8 Hz, NCHCHH-O, H6), 4.26 (1 H, dd, $J$= 12.3 Hz, 2.2 Hz, NCHCHH-O, H6'), 5.12 (1 H, d, $J$= 1.6 Hz, Ar-CH, H4), 7.44 (2 H, d, $J$= 10.5 Hz, 2 x CH arom., H12, H13), 8.16 (2 H, d, $J$= 10.5 Hz, 2 x CH arom., H10, H11); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 18.57 (CH$_3$, C7 or C8), 29.66 (CH$_3$, C7 or C8), 49.40 (CH, NCH, C5), 66.33 (CH$_2$, C6), 73.40 (Ar-CH, C4), 99.53 (C quat., C2), 123.60 (2 x CH arom., C10, C11), 126.37 (2 x CH arom., C12, C13), 147.22 (C quat., arom., C9), 147.34 (C quat., arom., C14); $m/z$ (FAB) 253.1186; C$_{12}$H$_{16}$N$_2$O$_4$ [M+H]$^+$ requires 253.1183.

Prepared according to the general procedure from acetonide (70) (2.0 g, 7.14 mmol). The product was obtained as a yellow oil (1.55 g, 98%); [α]$_D^{20}$ +62.0 (c 1.13, CHCl$_3$); $\nu_{\text{max}}$(film)/cm$^{-1}$ 3361 (NH), 2990, 2939, 1614, 1518, 1380, 1272, 1239, 1198, 1157,
1127, 1050, 948, 849, 813; $^1$H-NMR (400 MHz, CDCl$_3$): δ 1.45 (3 H, s, CH$_3$, H7 or H8), 1.46 (3 H, s, CH$_3$, H7 or H8), 2.61 (1 H, dd, J = 2.3 Hz, 1.8 Hz, NCH, H5), 2.67 (4 H, s, 4 × NH), 3.82 (1 H, dd, J = 12.8 Hz, 2.3 Hz, NCHCHH-O, H6), 4.19 (1 H, dd, J = 12.8 Hz, 2.3 Hz, NCHCHH-O, H6'), 4.93 (1 H, d, J = 1.8 Hz, Ar-CH, H4), 6.64 (2 H, d, J = 8.5 Hz, 2 × CH arom., H12, H13), 7.03 (2 H, d, J = 8.5 Hz, 2 × CH arom., H10, H11); $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 18.61 (CH$_3$, C7 or C8), 29.80 (CH$_3$, C7 or C8), 49.69 (CH, NCH, C5), 65.73 (CH$_2$, C6), 73.52 (Ar-CH, C4), 99.15 (C quat., C2), 115.10 (2 × CH arom., C12, C13), 126.74 (2 × CH arom., C10, C11), 129.31 (C quat., arom., C9), 145.75 (C quat., arom., C14); m/z (FAB) 223.1445; C$_{12}$H$_{18}$N$_2$O$_4$ [M+H]$^+$ requires 223.1447.

**General procedure for the synthesis of binaphthalene-derived iminium salt catalysts.**

**Method 1:** From (R) or (S)-2'-Bromomethyl-[1,1']binaphthalene-2-carboxaldehyde and primary amines.

A solution of the amine (1 equivalent) in ethanol (10 mL per gram of amine) was added dropwise to a solution of (R) or (S)-2'-bromomethyl-[1,1']binaphthalenyl-2-carboxaldehyde ($S_4$) or ($S_8$) (1.10 equivalent wrt amine) in ethanol (10 mL per gram of carboxaldehyde) at 40 °C. The reaction mixture was stirred at 40 °C overnight. The yellowish mixture was left to cool to room temperature before addition of sodium tetraphenylborate (1.10 equivalents) in the minimum amount of acetonitrile in one portion. The reaction mixture was stirred for further 5 minutes, and the solvents were removed under reduced pressure. The yellow residue was dissolved in dichloromethane (40 mL per gram of amine), and washed with water (2 × 30 mL per gram of amine), brine (2 × 30 mL per gram of amine), the organic phase dried (Na$_2$SO$_4$) and the solvents removed in vacuo. The yellow solid was recrystallized from ethanol, washed with cold ethanol followed by hexanes, and dried at 90 °C.
(R)-N-[(4S,5S)-5-(4-(4-Methanesulfonyl)phenyl)-2,2-dimethyl-1,3-dioxanyl]-7H-dinaphtho[2,1-c;1',2'-e]azepinium tetraphenylborate (45):

Prepared according to the general procedure, method 1, from amine (25) (0.54 g, 1.89 mmol). The product was isolated as yellow powder (1.08 g, 65%); m.p. 159-163 °C (dec.); \([\alpha]^{20}_D -283.7\) (c 0.86, acetone); Found: C, 78.89; H, 5.78; N, 1.50. C_{59}H_{52}BN_{10}O_{10} requires C, 78.74; H, 6.04; N, 1.56%; \(v_{\text{max}}\) (film)/cm\(^{-1}\) 3050, 2953, 1617, 1532, 1512, 1461, 1376, 1301, 1248, 1203, 1098, 1030, 963, 818, 735; \(^1\)H-NMR (400 MHz, acetone-\(d_6\)): \(\delta\) 1.70 (3 H, s, CH\(_3\), H7 or H8), 1.76 (3 H, s, CH\(_3\), H7 or H8), 2.85 (3 H, s, SO\(_2\)CH\(_3\)), 4.30 (1 H, d, J = 13.8 Hz, NCHCH\(_2\)O, H6), 4.82 (1 H, d, J = 8.6 Hz, CH arom., ortho in BPh\(_4\) gp.), 7.12-7.21 (9 H, m, 5 × CH arom., \(para\) in BPh\(_4\) gp.), 7.43 (1 H, ddd, J = 8.0 Hz, 6.8 Hz, 1.2 Hz, \(binap\)), 7.61-7.69 (5 H, m, 5 × CH arom., \(binap\) and H10, H11, H12, H13), 7.82 (1 H, d, J = 8.5 Hz, \(binap\)), 7.97 (1 H, d, J = 8.3 Hz, \(binap\)), 8.05 (1 H, d, J = 8.4 Hz, \(binap\)), 8.08 (1 H, d, J = 8.6 Hz, \(binap\)), 8.14 (1 H, d, J = 8.6 Hz, \(binap\)), 9.06 (1 H, s, HC=\(N\)); \(^{13}\)C-NMR (100 MHz, acetone-\(d_6\)): \(\delta\) 18.21 (CH\(_3\), C7 or C8), 29.06 (CH\(_3\), C7 or C8), 43.42 (CH\(_3\), SO\(_2\)CH\(_3\)), 56.37 (CH\(_2\), ArCH\(_2\)N), 61.05 (CH\(_2\), NCHCH\(_2\)O, C6), 66.92 (CH, NCH, C5), 71.53 (CH, ArCH, C4), 101.11 (C quat., C2), 121.54 (4 × CH arom., \(para\) in BPh\(_4\) gp.), 125.03 (CH arom., \(binap\)), 125.11 (CH arom., \(binap\)), 125.21 (CH arom., \(binap\)), 125.26 (8 × CH arom., ortho in BPh\(_4\) gp.), 126.0 (C quat., arom.), 126.51 (2 × CH arom., C12, C13), 126.82 (CH arom., \(binap\)), 127.05 (CH arom., \(binap\)), 127.31 (CH arom., \(binap\)), 127.91 (2 × CH arom., C10, C11), 128.81 (CH arom., \(binap\)), 202
128.94 (CH arom., binap), 129.37 (CH arom., binap), 129.55 (CH arom., binap), 130.62 (CH arom., binap), 131.21 (C quat., arom.), 131.37 (C quat., arom.), 131.71 (CH arom., binap), 131.73 (C quat., arom.), 131.75 (CH arom., binap), 131.77 (C quat., arom.), 133.88 (C quat., arom.), 135.47 (C quat., arom.), 135.79 (C quat., arom.), 136.17 (8 x CH arom., meta in BP14 gp.), 141.36 (C quat., arom.), 141.80 (C quat., arom.), 142.16 (C quat., arom.), 164.03 (4 x C quat., arom., q, J= 49.1 Hz, 4 x CoB ipso in BP14 gp.), 170.58 (HC=N); mlz (ESI) 562.2044; C₃₅H₃₂N₀₄S (cation) requires 562.2047.

(R)-N-[(4S,SS)-S-(4-(4-Nitrophenyl)-2,2-dimethyl-1,3-dioxanyl)-1-7H-dinaphtho[2,1-c;1',2'-e]azepinium tetraphenylborate (46):

Prepared according to the general procedure, method 1, from amine (72) (0.40 g, 1.59 mmol). The product was isolated as a yellow powder (0.93 g, 69%); m.p. 144-146 °C (dec.); [α]D²⁰ =-360.0 (c 1.00, acetone); Found: C, 78.21; H, 5.55; N, 3.17. C₅₈H₄₅BN₂O₄·2H₂O requires C, 78.73; H, 6.04; N, 3.17%; ν max (film)/cm⁻¹ 3052, 2950, 1608, 1523, 1461, 1427, 1382, 1348, 1265, 1237, 1201, 1108, 1031, 851, 819, 735, 705; ¹H-NMR (400 MHz, acetonitrile-d3): δ 1.72 (3 H, s, CH₃, H7 or H8), 1.82 (3 H, s, CH₃, H7 or H8), 4.36 (1 H, d, J= 13.6 Hz, NCHCHHO, H6), 4.42 (1 H, d, J= 13.3 Hz, ArCHHN), 4.72 (1 H, dd, J= 13.6 Hz, 2.6 Hz, NCHCHHO, H6'), 5.15 (1 H, bs, ArCHHN), 5.79 (1 H, d, J= 2.6 Hz, ArCH, H4), 6.60-6.64 (5 H, m, CH arom., binap and 4 x CH arom., para in BPh₄ gp.), 7.01 (8 H, t, J= 7.3 Hz, 8 x CH arom., ortho in BPh₄ gp.), 7.18 (1 H, ddd, J= 8.5 Hz, 6.8 Hz, 1.3 Hz, CH arom., binap), 7.25-7.37 (12 H, m, 4 x CH arom., and 8 x CH arom., meta in BPh₄ gp.), 7.45-7.58 (4 H, m, 4 x CH arom.), 7.72-7.800 (2 H, m, 2 x CH arom.), 7.95 (1 H, d, J= 8.1 Hz, binap), 8.07 (1 H, d, J= 8.4 Hz, binap), 8.15 (1 H, d, J= 8.8 Hz, binap), 8.23 (1 H, d, J= 8.6 Hz, binap), 9.32 (1 H, s, HC=N); ¹³C-NMR (100 MHz, acetonitrile-d3): δ 17.63 (CH₃, C7 or C8), 28.42 (CH₃, C7 or C8), 58.89 (CH₂,
ArCH(N), 60.78 (CH, NCHCH₂O, C6), 65.30 (CH, NCH, C5), 70.35 (CH, ArCH, C4), 100.99 (C quat., C2), 121.46 (4 × CH arom., para in BPh₄ gp.), 122.96 (2 × CH arom., C12, C13), 124.64 (CH arom., binap), 125.28 (8 × CH arom., ortho in BPh₄ gp.), 125.58 (C quat., arom.), 125.68 (2 × CH arom., C10, C11), 126.16 (CH arom., binap), 126.70 (CH arom., binap), 128.09 (CH arom., binap), 129.18 (CH arom., binap), 130.02 (C quat., arom.), 130.26 (CH arom., binap), 130.97 (C quat., arom.), 131.26 (CH arom., binap), 131.59 (C quat., arom.), 133.14 (C quat., arom.), 134.10 (C quat., arom.), 134.45 (CH arom., binap), 135.08 (C quat., arom.), 135.42 (8 × CH arom., meta in BPh₄ gp.), 141.51 (C quat., arom.), 142.46 (C quat., arom.), 146.37 (C quat., arom.), 163.47 (4 × C quat., arom., q, J= 49.1 Hz, 4 × C-B ipso in BPh₄ gp.), 168.86 (HC= N).

(5S)-N-[(4R,5R)-5-(4-(4-Methoxyphenyl)-2,2-dimethyl-1,3-dioxany1)-7H-dinaphtho[2,1-c;1',2'-e]azepinium tetraphenylborate (48):

Prepared according to the general procedure, method I, from (4R,5R)-S-amino-4-(4-methoxyphenyl)-2,2-dimethyl-I,3-dioxane (64) (0.30 g, 1.26 mmol). The product was isolated as yellow powder (0.60 g, 51%); m.p. 199-200 °C (dec.); [a]D +353.5 (c 0.86, acetone); Found: C, 84.59; H, 6.28; N, 1.80. C₉₉H₅₂BNO₃ requires C, 84.98; H, 6.29; N, 1.68%; ʋmax(film)/cm⁻¹ 3053, 2969, 1611, 1548, 1512, 1463, 1379, 1305, 1255, 1201, 1110, 1031, 961, 817, 737, 707, 612; ¹H-NMR (400 MHz, acetone-d₆): δ 1.79 (3 H, s, CH₃, H7 or H8), 1.84 (3 H, s, CH₃, H7 or H8), 3.57 (3 H, s, ArOCH₃), 4.41 (1 H, d, J= 13.5 Hz, NCH-CHH-O, H6), 4.54 (1 H, d, J= 13.2 Hz, ArCHH-N), 4.64 (1 H, t, J= 3.1 Hz, NCH, H5), 4.79 (1 H, dd, J= 13.5 Hz, 3.1 Hz, NCH-CHH-O, H6'), 5.87-5.88 (2 H, m, ArCH, H4 and ArCHH-N), 6.57 (2 H, d, J= 8.7 Hz, 2 × CH arom., H12, H13), 6.74-6.79 (4 H, m, 4 × CH arom., para in BPh₄ gp.), 6.92 (8 H, t,
$J = 7.2$ Hz, $8 \times CH$ arom., ortho in BPh$_4$ gp.), $7.00$ (1 H, d, $J = 8.7$ Hz, CH arom., binap), $7.19$ (2 H, d, $J = 8.7$ Hz, $2 \times CH$ arom., H10, H11), $7.27-7.31$ (1 H, m, CH arom., binap), $7.33-7.37$ (8 H, m, $8 \times CH$ arom., meta in BPh$_4$ gp.), $7.43-7.49$ (2 H, m, $2 \times CH$ arom., binap), $7.53-7.61$ (2 H, m, $2 \times CH$ arom., binap), $7.77-7.83$ (2 H, m, $2 \times CH$ arom., binap), $8.11$ (1 H, dd, $J = 8.2$ Hz, 0.6 Hz, CH arom., binap), $8.20$ (1 H, dd, $J = 8.4$ Hz, 0.8 Hz, CH arom., binap), $8.23$ (1 H, d, $J = 8.6$ Hz, CH arom., binap), $8.26$ (1 H, d, $J = 8.6$ Hz, CH arom., binap), $9.09$ (1 H, s, HC=N); $^{13}$C-NMR (100 MHz, acetone-d$_6$): 8 18.94 (CH$_3$, C7 or C8), 29.89 (CH$_3$, C7 or C8), 55.51 (CH$_3$, ArOCH$_3$), 58.16 (CH$_2$, ArCH$_2$N), 61.86 (CH$_2$, NCH-CH$_2$-O, C6), 68.25 (CH, NCH, C5), 72.36 (CH, ArCH, C4), 101.62 (C quat., C2), 114.81 (2 $\times$ CH arom., C12, C13), 122.34 (4 $\times$ CH arom., para in BPh$_4$ gp.), 126.07 (8 $\times$ CH arom., ortho in BPh$_4$ gp.), 126.31 (2 $\times$ CH arom., C10, C11), 127.06 (C quat., arom., binap-2), 127.23 (2 $\times$ CH arom., binap), 127.68 (CH arom., binap), 127.75 (CH arom., binap), 128.05 (CH arom., binap), 128.68 (CH arom., binap), 128.87 (C quat., arom., C9), 129.65 (CH arom., binap), 129.70 (CH arom., binap), 130.19 (CH arom., binap), 130.29 (CH arom., binap), 131.35 (CH arom., binap), 131.76 (C quat., arom., binap-10), 132.24 (C quat., arom., binap-5'), 132.54 (CH arom., binap), 132.82 (C quat., arom., binap-10'), 134.78 (C quat., arom., binap-5), 136.27 (C quat., arom., binap-2'), 136.47 (C quat., arom., binap-1'), 137.05 (8 $\times$ CH arom., meta in BPh$_4$ gp.), 142.49 (C quat., arom., binap-1'), 160.36 (C quat., arom., C14), 164.93 (4 $\times$ C quat., arom., q, $J = 49.1$ Hz, 4 $\times$ C-B ipso in BPh$_4$ gp.), 170.74 (HC=N); m/z (ESI) 541.2386; C$_{35}$H$_{32}$N$_{03}$ (cation) requires 541.2382.

(R)-N-tert-Butyl-7H-dinaphtho[2,1-c;1',2'-e]azepinium tetraphenylborate (84):$^{13}$

Prepared according to the general procedure, method 1, from tert-butylamine (0.11 g, 1.44 mmol). The product was isolated as yellow powder (0.57 g, 60%); m.p. 215-218
°C (dec.); [α]$_{D}^{20}$ = -589.2 (c 0.78, acetone); Found: C, 88.10; H, 6.48; N, 2.14. C$_{50}$H$_{44}$BN·0.5H$_{2}$O requires C, 88.48; H, 6.68; N, 2.06%; $v_{\text{max}}$(film)/cm$^{-1}$ 3053, 2982, 1627, 1593, 1472, 1429, 1374, 1362, 1253, 1224, 1177, 1030, 818, 752, 735; $^{1}$H-NMR (400 MHz, acetone-d$_{6}$): $\delta$ 1.86 (9 H, s, C(CH$_{3}$)$_{3}$), 4.70 (1 H, dd, J = 13.9 Hz, 1.4 Hz, Ar-CHHN), 5.79 (1 H, dd, J = 13.9 Hz, 1.4 Hz, Ar-CHHN), 6.75-6.79 (4 H, m, 4 × CH arom., para in BPh$_{4}$ gp.), 6.92 (8 H, t, J = 7.3 Hz, 8 × CH arom., ortho in BPh$_{4}$ gp.), 7.11 (1 H, d, J = 8.8 Hz, CH arom., binap-3'), 7.29-7.37 (9 H, m, 8 × CH arom., meta in BPh$_{4}$ gp. and binap-7'), 7.48-7.52 (2 H, m, 2 × CH arom., binap-8,8'), 7.59-7.62 (1 H, m, CH arom., binap-3), 7.79-7.83 (1 H, m, CH arom., binap-7), 8.05 (1 H, d, J = 8.8 Hz, CH arom., binap-4'), 8.11 (1 H, d, J = 8.3 Hz, CH arom., binap-4), 8.20 (1 H, d, J = 8.6 Hz, CH arom., binap-9'), 8.23 (1 H, dd, J = 8.8 Hz, 0.5 Hz, CH arom., binap-6') 8.27 (1 H, d, J = 8.5 Hz, CH arom., binap-6), 8.35 (1 H, d, J = 8.7 Hz, CH arom., binap-9), 9.66 (1 H, t, J = 1.4 Hz, HC=N); $^{13}$C-NMR (100 MHz, acetone-d$_{6}$): $\delta$ 27.88 (3 × CH$_{3}$, C(CH$_{3}$)$_{3}$), 53.47 (CH$_{2}$, Ar-CH$_{2}$N), 71.22 (C quat., C(CH$_{3}$)$_{3}$), 122.52 (4 × CH arom., para in BPh$_{4}$ gp.), 126.02 (8 × CH arom., ortho in BPh$_{4}$ gp.), 127.00 (CH arom., binap-7'), 127.47 (CH arom., binap-8'), 127.82 (CH arom., binap-8), 127.98 (CH arom., binap-7), 128.04 (CH arom., binap-3), 128.17 (C quat., binap-2), 128.45 (CH arom., binap-4'), 129.55 (CH arom., binap-4), 129.62 (CH arom., binap-9'), 129.96 (CH arom., binap-6'), 130.15 (CH arom., binap-6), 130.98 (CH arom., binap-9), 131.83 (CH arom., binap-3'), 132.30 (C quat., arom., binap-10), 132.75 (C quat., arom., binap-5'), 132.81 (C quat., arom., binap-10'), 134.70 (C quat., arom., binap-5), 136.16 (C quat., arom., binap-2'), 137.05 (8 × CH arom., meta in BPh$_{4}$ gp.), 137.37 (C quat., arom., binap-1'), 141.87 (C quat., arom., binap-1), 164.95 (4 × C quat., arom., q, J = 49.1 Hz, 4 × C-B ipso in BPh$_{4}$ gp.), 167.08 (HC=N); m/z (FAB) 350.1909; C$_{26}$H$_{24}$N (cation) requires 350.1909.
Prepared according to the general procedure, method 1, from 2,6-dimethylaniline (0.10 g, 0.85 mmol), but heated under reflux for 16 h. The product was isolated as yellow powder (0.53 g, 79%), m.p. 211-214 °C (dec.); [α]20° D −725.0 (c 0.96, acetone); Found: C, 89.68; H, 6.03; N, 1.85. C54H44BN·0.3H2O requires C, 89.69; H, 6.21; N, 1.94%; νmax (film)/cm⁻¹ 3052, 1608, 1583, 1544, 1505, 1426, 1416, 1378, 1265, 1168, 1032, 817; ¹H-NMR (400 MHz, DMSO-d6): δ 1.33 (3 H, s, ArCH), 2.43 (3 H, s, ArCH), 5.42 (2 H, s, Ar-CH₂N), 6.77-6.81 (4 H, m, 4 × CH arom., para in BPh₄ gp.), 6.93 (8 H, t, J= 7.4 Hz, 8 × CH arom., ortho in BPh₄ gp.), 7.09 (1 H, d, J= 8.6 Hz, CH arom., binap-3'), 7.17-7.25 (9 H, m, 8 × CH arom., meta in BPh₄ gp. and binap-7'), 7.35 (1 H, ddd, J= 8.5 Hz, 6.9 Hz, 1.3 Hz, CH arom., binap-7), 7.45-7.47 (2 H, m, 2 × CH arom., binap-8,8'), 7.52-7.54 (2 H, m, CH arom., binap-3,4'), 7.56 (1 H, ddd, J= 8.0 Hz, 6.8 Hz, 1.0 Hz, CH arom., binap-4), 7.82 (1 H, d, J= 8.4 Hz, CH arom., H4 in Ar gp.), 7.86 (1 H, ddd, J= 8.1 Hz, 5.9 Hz, 2.0 Hz, CH arom., binap-9'), 8.14 (1 H, d, J= 8.1 Hz, CH arom., binap-6'), 8.21 (1 H, d, J= 8.7 Hz, CH arom., binap-6), 8.29 (2 H, d, J= 8.6 Hz, 2 × CH arom., H3 and H5 in Ar gp.), 8.47 (1 H, d, J= 8.7 Hz, CH arom., binap-9), 9.80 (1 H, s, HC= N); ¹³C-NMR (100 MHz, DMSO-d₆): δ 16.48 (CH₃, C7 or C8), 17.70 (CH₂, C7 or C8), 59.94 (CH₂, Ar-CH₂N), 121.50 (4 × CH arom., para in BPh₄ gp.), 125.29 (8 × CH arom., ortho in BPh₄ gp.), 126.08 (CH arom., binap-7'), 126.65 (CH arom., binap-8'), 126.90 (CH arom., binap-7), 126.96 (CH arom., C4 in Ar gp.), 127.07 (C quat., arom., binap-2), 127.38 (CH arom., binap-8), 127.89 (CH arom., binap-3), 128.74 (CH arom., binap-4'), 128.83 (CH arom., binap-4), 128.96 (CH arom., binap-9'), 129.28 (CH arom., C3 in Ar gp.), 129.36 (CH arom., binap-6'), 129.50 (CH arom., binap-6), 130.64 (CH arom., binap-9), 130.70 (CH arom., binap-3'), 130.73 (C quat., arom., C1 in Ar gp.),
131.23 (C quat., arom., binap-10), 131.36 (C quat., arom., binap-10'), 131.44 (CH arom., C5 in Ar gp.), 132.08 (C quat., arom., binap-10'), 133.01 (C quat., arom., binap-5), 133.33 (C quat., arom., binap-2'), 135.20 (C quat., arom., binap-1') 135.50 (8 × CH arom., meta in BPh₄ gp.), 136.22 (C quat., arom., binap-1), 141.51 (C quat., arom., C6 in Ar gp.), 143.01 (C quat., arom., C2 in Ar gp.), 163.33 (4 × C quat., arom., q, J = 49.1 Hz, 4 × C-B ipso in BPh₄ gp.), 173.10 (HC=N); m/z (FAB) 398.1911; C₃₀H₂₄N (cation) requires 398.1909.

**General procedure for the synthesis of binaphthalene-derived azepines from (R)-2,2'-bis(bromomethyl)-[1,1']binaphthalene (52₆) and primary amines.**

![Diagram](image_url)

The primary amine (1.1 equivalent) was added to a nitrogen purged stirred solution of (R)-2,2'-bis(bromomethyl)-[1,1']binaphthalene (52₆) (1.0 equivalent) and potassium carbonate (3 equivalents) in acetonitrile (10 mL per gram of dibromide) at room temperature. The reaction mixture was heated under reflux overnight or until starting material disappearance was observed by TLC. The mixture was diluted with dichloromethane (40 mL per g dibromide) and washed with water (2 × 30 mL per gram of dibromide) and brine (2 × 30 mL per gram of dibromide). The organic phase was separated, dried (Na₂SO₄) and the solvent removed in vacuo to give the desired products in good purity.
(R)-N-[(4S,5S)-5-(4-phenyl-2,2-dimethyl-1,3-dioxanyl)]-2,7-dihydronaphtho[2,1-c;1',2'-e]azepine (74):

Prepared according to the general procedure from L-acetonamine (71) (0.39 g, 1.74 mmol). The product was isolated as a colourless foam (0.75 g, 98%); \([\alpha]_{D}^{20} -339\) (c 1.00, CHCl₃); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3058, 2990, 1687, 1594, 1450, 1380, 1232, 1199, 1098, 909, 819, 731; \(^1\)H-NMR (400 MHz, CDCl₃): \(\delta\) 1.55 (3 H, s, CH₃, H7 or H8), 1.64 (3 H, s, CH₃, H7 or H8), 2.65 (1 H, ddd, \(J = 3.4\) Hz, 3.4 Hz, 1.3 Hz, NCH, H5), 3.28 (2 H, d, \(J = 12.0\) Hz, ArCH₂N), 3.85 (2 H, d, \(J = 12.0\) Hz, ArCH₂N), 4.05 (1 H, dd, \(J = 12.5\) Hz, 1.3 Hz, NCHCHHO, H6), 4.16 (1 H; dd, \(J = 12.5\) Hz, 3.4 Hz, NCHCHHO, H6\(^\prime\)), 5.10 (1 H, d, \(J = 3.4\) Hz, ArCH, H4), 7.10-7.24 (5 H, m, 5 × CH arom.), 7.27-7.39 (8 H, m, 8 × CH arom.), 7.78 (2 H, d, \(J = 8.2\) Hz, 2 × CH arom.), 7.84 (2 H, d, \(J = 8.5\) Hz, 2 × CH arom.), \(^{13}\)C-NMR (100 MHz, CDCl₃): \(\delta\) 19.07 (CH₃, C7 or C8), 29.83 (CH₃, C7 or C8), 53.15 (2 × CH₂, ArCH₂N), 59.82 (CH, NCH, C5), 61.88 (CH₂, NCHCH₂O, C6), 75.07 (CH, ArCH, C4), 99.29 (Cquat., C2), 125.01 (2 × CH arom.), 125.42 (2 × CH arom.), 126.43 (2 × CH arom.), 126.76 (CH arom., C14), 127.53 (2 × CH arom.), 127.61 (2 × CH arom.), 127.82 (2 × CH arom.), 128.10 (2 × CH arom.), 128.39 (2 × CH arom.), 131.22 (2 × Cquat., arom., binap), 132.81 (2 × Cquat., arom., binap), 134.64 (2 × Cquat., arom., binap), 134.83 (2 × Cquat., arom., binap), 141.29 (Cquat., arom., C9); \(m/z\) (FAB) 486.2431; C₃₄H₃₁NO₂ [M+H]⁺ requires 486.2433.
(R)-N-tert-Butyl-2,7-dihydrodinaphtho[2,1-c;1',2'-e]azepine (75):

Prepared according to the general procedure from tert-butylamine (0.05 g, 0.72 mmol). The product was isolated as a colourless foam (0.24 g, 95%); $[\alpha]^{20}_D -357$ (c 1.30, CHCl$_3$); $\nu_{\text{max}}$/film/cm$^{-1}$ 3048, 2926, 2852, 1450, 1360, 1106, 908, 816, 737; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 1.20 (9 H, s, C(CH$_3$)$_3$), 3.27 (2 H, d, $J$= 12.4 Hz, ArCH$_2$-N), 3.96 (2 H, d, $J$= 12.4 Hz, ArCH$_2$-N), 7.12-7.16 (2 H, m, 2 $\times$ CH arom., binap-3,3'), 7.32-7.35 (4 H, m, 4 $\times$ CH arom., binap-7,7'-8,8'), 7.52 (2 H, d, $J$= 8.3 Hz, 2 $\times$ CH arom., binap-4,4'), 7.83 (4 H, d, $J$= 8.2 Hz, 2 $\times$ CH arom., binap-6,6' and binap-9,9'); $^{13}$C-NMR (100 MHz, CDCl$_3$): 28.59 (3 $\times$ CH$_3$, C(CH$_3$)$_3$), 49.08 (2 $\times$ CH$_2$, 2 $\times$ Ar-CH$_2$N), 55.62 (C quat., C(CH$_3$)$_3$), 125.29 (2 $\times$ CH arom., binap-7,7'), 125.56 (2 $\times$ CH arom., binap-8,8'), 127.58 (2 $\times$ CH arom., binap-4,4'), 128.25 (2 $\times$ CH arom., binap-9,9'), 128.42 (2 $\times$ CH arom., binap-6,6'), 128.50 (2 $\times$ CH arom., binap-3,3'), 131.27 (2 $\times$ C quat., arom., binap-5,5'), 132.98 (2 $\times$ C quat., arom., binap-10,10'), 135.07 (2 $\times$ C quat., arom., binap-2,2'), 135.23 (2 $\times$ C quat., arom., binap-1,1'); m/z (EI) 351.1985; C$_{26}$H$_{25}$N (M$^+$) requires 351.1987.
(R)-N-Trityl-2,7-dihyrdodinaphtho[2,1-c;1',2'-c]azepine (76):

Prepared according to the general procedure from tritylamine (0.19 g, 0.72 mmol). The product was isolated as a colourless foam (0.24 g, 95%); [α]$_{D}$ -357 (c 1.30, CHCl$_3$); $\nu_{\text{max (film)}}$ (cm$^{-1}$) 3046, 2928, 2850, 1678, 1643, 1458, 1465, 1361, 1058, 957, 803, 757; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 3.34 (2 H, d, $J$= 12.5 Hz, ArCH$_2$-N), 4.07 (2 H, d, $J$= 12.5 Hz, ArCH$_2$-N), 7.00-7.18 (13 H, m, 9 × CH arom., Ph gp. and 4 × CH arom., binap), 7.23-7.32 (4 H, m, 4 × CH arom., binap), 7.46 (6 H, d, $J$= 7.4 Hz, 6 × CH arom., Ph gp.), 7.59 (2 H, d, $J$= 8.6 Hz, 2 × CH arom., binap), 7.72 (2 H, d, $J$= 8.1 Hz, 2 × CH arom., binap); $^{13}$C-NMR (100 MHz, CDCl$_3$): 50.75 (2 × CH$_2$, 2 × Ar-CH$_2$N), 78.12 (C quat., C(Ph)$_3$), 125.24 (2 × CH arom., binap), 125.44 (2 × CH arom., binap), 126.14 (3 × CH arom., para in Ph gp.), 127.61 (2 × CH arom., binap), 127.81 (6 × CH arom., ortho in Ph gp.), 128.03 (2 × CH arom., binap), 128.13 (2 × CH arom., binap), 128.23 (2 × CH arom., binap), 129.78 (6 × CH arom., meta in Ph gp.), 131.16 (2 × C quat., arom., binap), 132.74 (2 × C quat., arom., binap), 134.69 (2 × C quat., arom., binap), 134.95 (2 × C quat., arom., ipso in Ph gp.); m/z (EI) 537.2452; C$_{41}$H$_{31}$N (M$^+$) requires 537.2456.
(R)-N-Cyclohexyl-2,7-dihydropinaphtho[2,1-c;1',2'-e]azepine (77):

Prepared according to the general procedure from cyclohexylamine (0.17 g, 1.75 mmol). The product was isolated as a colourless foam (0.59 g, 99%); [α]_D^20 -278 (c 1.34, CHCl₃); ν_max(film)/cm⁻¹: 3048, 2926, 2851, 1507, 1449, 1362, 135, 1115, 917, 817, 751, 732; ¹H-NMR (400 MHz, CDCl₃): δ 1.05-1.31 (5 H, m, cyclohexyl protons), 1.54 (1 H, d, J= 7.6 Hz, cyclohexyl proton), 1.66-1.76 (2 H, m, cyclohexyl protons), 1.84 (1 H, d, J= 12.0 Hz, cyclohexyl proton), 2.11 (1 H, d, J= 12.0 Hz, cyclohexyl proton), 2.26-2.33 (1 H, m, NCH, H1), 3.18 (2 H, d, J= 12.4 Hz, ArCH₂-N), 3.84 (2 H, d, J= 12.3 Hz, ArCH₂-N), 7.10-7.18 (2 H, m, 2 × CH arom., binap-3,3'), 7.29-7.43 (4 H, m, 4 × CH arom., binap-7,7'-8,8'), 7.49 (2 H, d, J= 8.3 Hz, 2 × CH arom., binap-4,4'), 7.84 (4 H, d, J= 8.2 Hz, 2 × CH arom., binap-6,6' and binap-9,9'); ¹³C-NMR (100 MHz, CDCl₃): 25.79 (CH₂, cyclohexyl carbon), 25.83 (CH₂, cyclohexyl carbon), 26.21 (CH₂, cyclohexyl carbon), 31.29 (CH₂, cyclohexyl carbon), 31.77 (CH₂, cyclohexyl carbon), 51.98 (2 × CH₂, 2 × Ar-CH₂N), 61.72 (CH, NCH₂, C1), 125.33 (2 × CH arom., binap-7,7'), 125.68 (2 × CH arom., binap-8,8'), 127.52 (2 × CH arom., binap-4,4'), 128.00 (2 × CH arom., binap-9,9'), 128.29 (2 × CH arom., binap-6,6'), 128.36 (2 × CH arom., binap-3,3'), 131.34 (2 × C quat., arom., binap-5,5'), 133.04 (2 × C quat., arom., binap-10,10'), 134.54 (2 × C quat., arom., binap-2,2'), 135.06 (2 × C quat., arom., binap-1,1'); m/z (EI) 377.2138; C₂₈H₂₇N (M⁺) requires 377.2144.
(R)-N-Butyl-2,7-dihydronaphtho[2,1-c;1',2'-c]azepine (78):

Prepared according to the general procedure from butylamine (0.13 g, 1.75 mmol) except the reaction was heated under reflux for 5 hour. The product was isolated as a colourless oil (0.54 g, 97%); $[\alpha]^{20}_D -212.8$ (c 0.69, CHCl$_3$); $v_{\text{max}}$(film)/cm$^{-1}$ 3049, 2949, 2805, 1678, 1506, 1457, 1365, 1258, 1099, 817, 748; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 0.88 (3 H, t, $J$= 7.3 Hz, CH$_3$H$_3$, H4), 1.26-1.33 (2 H, m, CH$_2$, H3), 1.48-1.59 (2 H, m, CH$_2$, H2), 2.31 (1 H, ddd, $J$= 15.6, 10.0, 5.5 Hz, NCHH-CH$_2$, H1), 2.50 (1 H, ddd, $J$= 15.6, 10.0, 5.5 Hz, NCHH-CH$_2$, H1'), 3.10 (2 H, d, $J$= 12.3 Hz, ArCH$_2$-N), 3.64 (2 H, d, $J$= 12.3 Hz, ArCH$_2$-N), 7.16-7.20 (2 H, m, 2 $\times$ CH arom., binap-3,3'), 7.35-7.41 (4 H, m, 4 $\times$ CH arom., binap-7,7'-8,8'), 7.48 (2 H, d, $J$= 8.3 Hz, 2 $\times$ CH arom., binap-4,4'), 7.86 (4 H, d, $J$= 8.1 Hz, 2 $\times$ CH arom., binap-6,6' and binap-9,9'); $^{13}$C-NMR (100 MHz, CDCl$_3$): 14.16 (CH$_3$, C4), 20.86 (CH$_2$, C3), 30.39 (CH$_2$, C2), 55.27 (CH, NCH$_2$, C1), 55.44 (2 $\times$ CH$_2$, 2 $\times$ Ar-CH$_2$N), 125.39 (2 $\times$ CH arom., binap-7,7'), 125.73 (2 $\times$ CH arom., binap-8,8'), 127.48 (2 $\times$ CH arom., binap-4,4'), 127.87 (2 $\times$ CH arom., binap-9,9'), 128.26 (2 $\times$ CH arom., binap-6,6'), 128.31 (2 $\times$ CH arom., binap-3,3'), 131.40 (2 $\times$ C quat., arom., binap-5,5'), 133.14 (2 $\times$ C quat., arom., binap-10,10'), 133.64 (2 $\times$ C quat., arom., binap-2,2'), 135.01 (2 $\times$ C quat., arom., binap-1,1'); m/z (FAB) 352.2065; C$_{26}$H$_{25}$N [M+H]$^+$ requires 352.2065.
Prepared according to the general procedure, from isopropylamine (0.24 g, 4.09 mmol). Purification by passing through a short pad of silica using ethylacetate/petroleum ether (1:1) as eluent afforded the product as colourless solid (1.03 g, 97%). Analytically pure sample was obtained by trituration in acetone (1-2 mL) for 5 minutes and collecting the colourless crystals by filtration; m.p. 158-159 °C; [α]_{D}^{20} = -491.8 (c 0.98, acetone); ν_{max}(film)/cm⁻¹ 3048, 2965, 2806, 1507, 1460, 1376, 1122, 1032, 908, 816, 748; ¹H-NMR (400 MHz, CDCl₃); δ 10.05 (3 H, d, J= 6.4 Hz, CH₃, H2 or H3), 1.19 (3 H, d, J= 6.3 Hz, CH₃, H2 or H3), 2.64-2.71 (1 H, septet, NCH(CH₃)₂), 3.17 (2 H, d, J= 12.4 Hz, ArCH₂-N), 3.82 (2 H, d, J= 12.4 Hz, ArCH₂-N), 7.15-7.19 (2 H, m, 2 x CH arom., binap-3,3'), 7.34-7.40 (4 H, m, 4 x CH arom., binap-7,7'-8,8'), 7.50 (2 H, d, J= 8.2 Hz, 2 x CH arom., binap-4,4'), 7.85 (4 H, d, J= 8.2 Hz, 2 x CH arom., binap-6,6' and binap-9,9'); ¹³C-NMR (100 MHz, CDCl₃); δ 21.33 (CH₃, C2 or C3), 21.94 (CH₃, C2 or C3), 52.32 (CH, CH(CH₃)₂, C1), 52.89 (2 x CH₂, 2 x Ar-CH₂N), 125.36 (2 x CH arom., binap-7,7'), 125.69 (2 x CH arom., binap-8,8'), 127.51 (2 x CH arom., binap-4,4'), 127.97 (2 x CH arom., binap-3,3'), 128.29 (2 x CH arom., binap-9,9'), 128.34 (2 x CH arom., binap-9,9'), 131.34 (2 x C quat., arom., binap-5,5'), 133.08 (2 x C quat., arom., binap-10,10'), 133.34 (2 x C quat., arom., binap-2,2'), 135.03 (2 x C quat., arom., binap-1,1'); m/z (EI) 337.1826; C₂₃H₂₃N (M⁺) requires 337.1831.
General procedure for the synthesis of binapthalene-derived iminium salt catalysts.

Method 2: From (R)-azepines

\[ \text{N-Bromosuccinimide (1.2 equivalents) and azo-bis-iso-butyronitrile (0.05 equivalents) were added to a solution of the azepine in dichloromethane (5 mL per gram of azepine), and the mixture heated under reflux for 2 h, after which the reaction mixture was allowed to cool to room temperature. The solvent was removed in vacuo, and the residue redissolved in ethanol. A solution of sodium tetraphenylborate (1.1 equivalents) in minimum amount of acetonitrile was added in one portion. The resulting mixture was stirred for further 5 minutes, after which the solvents were removed in vacuo. The yellow residue was dissolved in dichloromethane (40 mL per gram of azepine) and washed with water (2 × 30 mL per gram of azepine), brine (2 × 30 mL per gram of azepine), the organic phase dried (Na$_2$SO$_4$) and the solvents removed in vacuo. The yellow solid was recrystallized from ethanol, washed with cold ethanol followed by hexanes, and dried at 90°C.} \]

\[(R)-N-[\{(4S,5S)-5-(4-phenyl-2,2-dimethyl-1,3-dioxanyl)\}-7H-dinaphtho[2,1-c;1',2'-e]azepinium tetraphenylborate (44):^8\]

Prepared according to the general procedure, method 2, from azepine (74) (0.75 g, 1.54 mmol). The product was isolated as yellow powder (0.86 g, 70%); m.p. 111-112
°C (dec.); [Lit. 8 m.p. 111-113 °C (dec.)]; [α]D 20 −341.0 (c 1.00, acetone); [Lit. 8 [α]D 20 −98.5 (c 1.04, acetone)]; νmax (film)/cm−1 3053, 2984, 1628, 1610, 1593, 1548, 1478, 1450, 1382, 1266, 1203, 1110, 846, 817, 735, 704; 1H-NMR (400 MHz, acetone-δ6): δ 1.67 (3 H, s, CH₃, H7 or H8); 1.72 (3 H, s, CH₃, H7 or H8), 4.31 (1 H, d, J= 13.6 Hz, Ar-CHHN), 4.42 (1 H, d, J= 13.2 Hz, N-CHCHH-O, H6), 4.70 (2 H, m, N-CHCHH-O, H6' and NCH, H5), 5.85 (2 H, m, Ar-CH, H4 and Ar-CHHN), 6.62 (4 H, t, J= 7.2 Hz, 4 × CH arom., para in BPh₄ gp.), 6.77 (9 H, t, J= 7.6 Hz, 8 × CH arom., ortho in BPh₄ gp. and CH arom., binap), 6.83 (1 H, d, J= 8.8 Hz, CH arom., binap), 6.92 (2 H, t, J= 7.2 Hz, 2 × CH arom., binap), 7.12 (1 H, t, J= 8.4 Hz, CH arom., H14), 7.18-7.22 (10 H, m, 8 × CH arom., meta in BPh₄ gp. and 2 × CH arom., binap), 7.32 (2 H, d, J= 8.1 Hz, 2 × CH arom., H10, H11), 7.37 (1 H, d, J= 8.8 Hz, CH arom., binap), 7.43 (1 H, t, J= 7.2 Hz, CH arom., binap), 7.67 (1 H, dd, J= 11.0 Hz, 5.6 Hz, CH arom., binap), 7.74 (1 H, d, J= 8.4 Hz, CH arom., binap), 7.96 (1 H, d, J= 8.0 Hz, CH arom., binap), 8.04 (1 H, d, J= 8.0 Hz, CH arom., binap), 8.10 (2 H, d, J= 8.1 Hz, 2 × CH arom., H12, H13), 9.03 (1 H, s, HC=N); 13C-NMR (100 MHz, acetone-δ6): δ 18.92 (CH₃, C7 or C8), 29.69 (CH₃, C7 or C8), 57.00 (Ar-CH₂N), 61.89 (CH₂, C6), 68.17 (NCH, C5), 72.62 (Ar-CH, C4), 101.72 (C quat., C2), 120.51 (C quat., arom., binap), 122.26 (4 × CH arom., para in BPh₄ gp.), 124.33 (CH arom., C14) 126.02 (8 × CH arom., ortho in BPh₄ gp.), 126.18 (C quat., arom., binap), 126.91 (C quat., arom., binap), 127.74 (CH arom., binap), 128.00 (CH arom., binap), 128.17 (2 × CH arom., C10, C11), 128.67 (2 × CH arom., C12, C13), 128.84 (2 × CH arom., binap), 129.51 (2 × CH arom., binap), 129.62 (CH arom., binap), 129.71 (CH arom., binap), 130.21 (CH arom., binap), 130.28 (CH arom., binap), 131.34 (CH arom., binap), 132.22 (C quat., arom., binap), 132.56 (C quat., arom., binap), 132.92 (CH arom., binap), 134.89 (C quat., arom., binap), 136.26 (C quat., arom., binap), 136.56 (C quat., arom., binap), 137.14 (8 × CH arom., meta in BPh₄ gp.) 142.44 (C quat., arom., C9), 164.72 (4 × C quat., q, J= 49.0 Hz, arom., C-B ipso in BPh₄ gp.), 171.23 (HC=N); m/z (ESI) 484.2282; C₃₄H₃₆NO₂ (cation) requires 484.2277.
(R)-N-Cyclohexyl-7H-dinaphtho[2,1-c;1',2'-e]azepinium tetraphenylborate (80).\textsuperscript{13}

Prepared according to the general procedure, method 2, from azepine (77) (0.60 g, 1.58 mmol). The product was isolated as yellow powder (0.79 g, 72%); m.p. 241-243 °C (dec.); [a] \textsuperscript{20}D -261.7 (c 1.00, CH\textsubscript{3}CN); Found: C, 88.85; H, 6.63; N, 2.15. C\textsubscript{32}H\textsubscript{46}BN\textsubscript{0.5}H\textsubscript{2}O requires C, 88.62; H, 6.72; N, 1.99%; v\textsubscript{max}(film)/cm\textsuperscript{-1} 3053, 2937, 2858, 1633, 1613, 1580, 1551, 1478, 1363, 1265, 1150, 818, 734, 706, 610; \textsuperscript{1}H-NMR (400 MHz, DMSO-d\textsubscript{6}): δ 1.23-1.41 (3 H, m, cyclohexyl protons), 1.66-2.01 (7 H, m, 7 x CH cyclohexyl), 4.21-4.29 (1 H, m, NCH, HI), 4.53 (1 H, d, J= 14.0 Hz, ArCHH-N), 5.44 (1 H, d, J= 14.0 Hz, ArCHH-N), 6.78 (4 H, t, J= 7.2 Hz, 4 x CH arom., para in BPi\textsubscript{4} gp.), 6.92 (8 H, t, J= 7.2 Hz, 8 x CH arom., ortho in BPi\textsubscript{4} gp.), 6.99 (1 H, d, J= 8.4 Hz, CH arom., binap-3'), 7.17-7.20 (8 H, m, 8 x CH arom., meta in BPi\textsubscript{4} gp.), 7.28 (1 H, ddd, J= 8.8, 6.8, 1.2 Hz, CH arom., binap-7'), 7.41-7.48 (2 H, m, 2 x CH arom., binap-8,8'), 7.54 (1 H, dd, J= 8.0 Hz, 0.8 Hz, CH arom., binap-7), 7.77 (1 H, ddd, J= 8.4 Hz, 6.4 Hz, 1.2 Hz, CH arom., binap-3), 8.00 (1 H, d, J= 8.4 Hz, CH arom., binap-4'), 8.08 (2 H, d, J= 8.8 Hz, 2 x CH arom., binap-4,9'), 8.23 (1 H, d, J= 8.4 Hz, CH arom., binap-6'), 8.26 (1 H, d, J= 8.4 Hz, CH arom., binap-9), 9.47 (1 H, s, HC=N); \textsuperscript{13}C-NMR (100 MHz, DMSO-d\textsubscript{6}): δ 24.14 (2 x CH\textsubscript{2}, C4, C5), 24.46 (CH\textsubscript{2}, C6), 24.51(CH\textsubscript{2}, C2 or C3), 30.23 (CH\textsubscript{2}, C2 or C3), 53.20 (CH\textsubscript{2}, Ar-CH\textsubscript{2}N), 71.69 (CH, NCH, C1), 121.50 (4 x CH arom., para in BPi\textsubscript{4} gp.), 125.28 (8 x CH arom., ortho in BPi\textsubscript{4} gp.), 125.96 (CH arom., binap-7'), 126.36 (CH arom., binap-8'), 126.67 (CH arom., binap-8), 126.72 (CH arom., binap-7), 126.93 (C quat., arom., binap-2), 126.98 (CH arom., binap-3), 127.52 (CH arom., binap-4'), 128.62 (CH arom., binap-4), 128.65 (CH arom., binap-9'), 128.84 (CH arom., binap-6'), 128.97 (CH arom., binap-6), 129.87 (CH arom., binap-9), 130.83 (CH arom., binap-3'), 130.88 (C quat., arom., binap-10), 130.91 (C quat., arom., binap-5'), 131.27 (C quat., arom., binap-10'), 133.19 (C quat., arom., binap-
(R)-N-Butyl-7H-dinaphtho[2,1-c;1',2'-e]azepinium tetraphenyldiborate (81): 13

Prepared according to the general procedure, method 2, from azepine (78) (0.56 g, 1.58 mmol). The product was isolated as yellow powder (0.62 g, 59%); m.p. 220-222 °C (dec.); [α]D20 -537.1 (c 1.05, CH3CN); Found: C, 88.88; H, 6.61; N, 2.17. C49H42BN·0.4H2O requires C, 88.72; H, 6.67; N, 2.07%; 1H-NMR (400 MHz, DMSO-d6): δ 0.85 (3 H, t, J= 7.6 Hz, -CH2CH3, H4), 1.04-1.24 (2 H, m, -CH2, H3), 1.89-1.94 (2 H, m, CH2, H2), 4.14-4.23 (2 H, m, NCH2, H1), 4.68 (1 H, d, J= 13.6 Hz, ArCHH-N), 5.30 (1 H, d, J= 13.6 Hz, ArCHH-N), 6.79 (4 H, t, J= 7.2 Hz, 8 x CH arom., para in BPh4 gp.), 6.92 (8 H, t, J= 7.2 Hz, 8 x CH arom., ortho in BPh4 gp.), 7.00 (1 H, d, J= 8.8 Hz, CH arom., binap-3'), 7.17-7.21 (8 H, m, 8 x CH arom., meta in BPh4 gp.), 7.30 (1 H, ddd, J= 8.4, 6.8, 1.6 Hz, CH arom., binap-7'), 7.43-7.51 (2 H, m, 2 x CH arom., binap-8,8'), 7.56 (1 H, ddd, J= 8.0, 6.8, 1.2 Hz, CH arom., binap-7), 7.79 (1 H, ddd, J= 8.0 Hz, 6.8 Hz, 1.2 Hz, CH arom., binap-3), 8.00 (1 H, d, J= 8.4 Hz, CH arom., binap-4'), 8.05 (1 H, d, J= 8.8 Hz, CH arom., binap-4), 8.11 (1 H, d, J= 8.0 Hz, CH arom., binap-9'), 8.25 (1 H, d, J= 8.0 Hz, CH arom., binap-6'), 8.29 (1 H, d, J= 8.4 Hz, CH arom., binap-6), 8.38 (1 H, d, J= 8.4 Hz, CH arom., binap-9), 9.56 (1 H, s, HC=N); 13C-NMR (100 MHz, DMSO-d6): δ 13.23 (CH3, C4), 18.68 (CH2, C3), 29.19 (CH2, C2), 55.75 (CH2, Ar-CH2N), 61.68 (CH, NCH2, C1), 121.49 (4 x CH arom., para in BPh4 gp.), 125.28 (8 x CH arom., ortho in BPh4 gp.), 125.87 (CH arom., binap-7'), 126.09 (CH arom., binap-8'), 126.68 (2 x CH arom., binap-7,8), 126.94 (C quat., arom., binap-2), 127.05 (CH arom., binap-3), 127.59 (CH arom.,
binap-4'), 128.65 (CH arom., binap-4), 128.67 (CH arom., binap-9'), 128.90 (C quat., arom., binap-10), 130.59 (C quat., arom., binap-9'), 131.27 (C quat., arom., binap-10), 132.25 (C quat., arom., binap-5), 134.61 (C quat., arom., binap-2'), 135.50 (8 × CH arom., meta in BP!4 gp.), 136.48 (C quat., arom., binap-1), 140.21 (C quat., arom., binap-1), 163.33 (4 × C quat., arom., q, J= 49.1 Hz, 4 × C-B ipso in BP!4 gp.), 168.63 (HC=N); m/z (FAB) 350.1909; C_{26}H_{24}N(cation) requires 350.1909.

(R)-N-Isopropyl-7H-dinaphtho[2,1-c;1',2'-e]azepinium tetraphenylborate (82): Prepared according to the general procedure, method 2, from azepine (79) (0.50 g, 1.48 mmol). The product isolated as yellow powder (0.69 g, 71%); m.p. 159-162 °C (dec.); [α]_{D}^{20} = -440.0 (c 0.65, acetone); Found: C, 87.59; H, 6.38; N, 2.23. C_{49}H_{42}BN·1.0H_{2}O requires C, 87.36; H, 6.58; N, 2.08%; ν_{max}(film)/cm^{-1} 3050, 2994, 1947, 1637, 1585, 1552, 1472, 1427, 1374, 1263, 1133, 1031, 959, 845, 818, 738, 707; ¹H-NMR (400 MHz, acetone-d₆): δ 1.53 (3 H, d, J= 6.6 Hz, CH₃, H₂ or H3), 1.56 (3 H, d J= 6.6 Hz, CH₃, H2 or H3), 4.59-4.67 (2 H, m, NCH(CH₃)₂, H1 and ArCHH-N), 5.37 (1 H, d, J= 13.7 Hz, ArCHH-N), 6.57-6.63 (4 H, m, 4 × CH arom., para in BPh₄ gp.), 6.77 (8 H, t, J= 7.3 Hz, 8 × CH arom., ortho in BPh₄ gp.), 6.94 (1 H, d, J= 8.6 Hz, CH arom., binap-3'), 7.16-7.26 (9 H, m, 8 × CH arom., meta in BPh₄ gp. and binap-7'), 7.29-7.40 (2 H, m, 2 × CH arom., binap-8,8'), 7.45 (1 H, ddd, J= 7.0 Hz, 6.8 Hz, 1.0 Hz, CH arom., binap-3), 7.67 (1 H, dd, J= 6.4 Hz, 3.3 Hz, 1.6 Hz, CH arom., binap-7), 7.87 (1 H, d, J= 8.6 Hz, CH arom., binap-4'), 7.91 (1 H, d, J= 8.6 Hz, CH arom., binap-4), 7.97 (1 H, d, J= 8.2 Hz, CH arom., binap-9'), 8.09 (1 H, d, J= 8.3 Hz, CH arom., binap-6'), 8.14 (1 H, d, J= 8.5 Hz, CH arom., binap-6), 8.20 (1 H, d, J= 8.7 Hz, CH arom., binap-9), 9.31 (1 H, s, HC=N); ¹³C-NMR (100 MHz,
acetone-d$_6$): δ 20.88 (CH$_3$, C2 or C3), 21.09 (CH$_3$, C2 or C3), 53.88 (CH$_2$, Ar-CH$_2$N), 66.71 (CH, CH(CH$_3$)$_2$, C1), 122.31 (4 × CH arom., para in BPh$_4$ gp.), 126.09 (8 × CH arom., ortho in BPh$_4$ gp.), 126.69 (CH arom., binap-7'), 127.02 (CH arom., binap-8'), 127.80 (CH arom., binap-8), 128.05 (CH arom., binap-7), 128.53 (CH arom., binap-3), 129.59 (CH arom., binap-4'), 129.67 (CH arom., binap-4), 130.16 (CH arom., binap-9'), 130.20 (CH arom., binap-6'), 130.74 (CH arom., binap-6), 131.06 (CH arom., binap-9), 132.12 (C quat., arom., binap-2), 131.83 (CH arom., binap-3'), 132.43 (C quat., arom., binap-10), 132.44 (C quat., arom., binap-5'), 132.81 (C quat., arom., binap-10'), 134.73 (C quat., arom., binap-5), 135.25 (C quat., arom., binap-2'), 136.18 (C quat., arom., binap-1'), 137.04 (8 × CH arom., meta in BPh$_4$ gp.), 137.37 (C quat., arom., binap-1), 164.95 (4 × C quat., arom., q, J = 49.1 Hz, 4 × C-B ipso in BPh$_4$ gp.), 168.22 (HC=N); m/z (FAB) 336.1755; C$_{25}$H$_{22}$N(cation) requires 336.1752.

(R)-2,7-dinaphtho[2,1-c;1',2'-e]azepinium tetraphenylborate (83):

Iodine (1.41 g, 5.56 mmol) and sodium acetate (0.45 g, 5.56 mmol) were added to a solution of compound (76) (0.86 g, 1.59 mmol) in absolute ethanol (5 mL) at room temperature. The mixture was subsequently heated under reflux for 2 h, after which the reaction mixture was allowed to reach room temperature, and the solvent removed in vacuo. The residue was redissolved in dichloromethane (30 mL) and washed with saturated solution of sodium thiosulfate (2 × 10 mL), brine (2 × 20 mL), dried (Na$_2$SO$_4$) and the solvent removed in vacuo. The residue was redissolved in absolute ethanol (5 mL) and a solution of sodium tetraphenylborate (0.59 g, 1.75 mmol) in minimum amount of acetonitrile was added in one portion and the mixture was stirred for 5 minutes. The resulting yellow solid was collected by filtration, and washed with ethanol to give the ammonium salt as a yellow solid (0.63 g, 65%); $\nu_{max}$(film)/cm$^{-1}$ 3412, 2928, 2744, 2588, 1670, 1582, 1503, 1449, 1367, 1268, 1213, 837, 748; $^1$H-NMR (400 MHz, DMSO-d$_6$): δ 3.89 (2 H, d, J = 13.5 Hz, ArCH$_2$-N), 4.40 (2 H, d, J =
13.2 Hz, ArCH$_2$-N), 6.79 (4 H, t, $J= 7.2$ Hz, 4 x CH arom., para in BPh$_4$ gp.), 6.92 (4 H, t, $J= 7.2$ Hz, 2 x CH arom., binap-9,9'), 7.46 (2 H, ddd, $J= 8.2$ Hz, 7.5 Hz, 1.2 Hz, 2 x CH arom., binap-7,7'), 7.69 (2 H, dd, $J= 8.2$ Hz, 7.5 Hz, 0.9 Hz, 2 x CH arom., binap-8,8'), 8.23 (2 H, d, $J= 8.4$ Hz, 2 x CH arom., binap-3,3'), 8.27 (2 H, d, $J= 7.5$ Hz, 2 x CH arom., binap-6,6'), 8.46 (2 H, d, $J= 8.4$ Hz, 2 x CH arom., binap-4,4'); $^{13}$C-NMR (100 MHz, DMSO-d$_6$): $\delta$ 59.79 (2 x CH$_2$, 2 x ArCH$_2$-N), 121.48 (4 x CH arom., para in BPh$_4$ gp.), 125.28 (8 x CH arom., ortho in BPh$_4$ gp.), 126.62 (2 x C quat., arom., binap-5,5'), 126.99 (2 x CH arom., binap-9,9'), 127.17 (2 x CH arom., binap-7,7'), 127.45 (2 x CH arom., binap-8,8'), 128.76 (4 x CH arom., binap-3,3'-binap-6,6'), 130.33 (2 x CH arom., binap-4,4'), 130.88 (2 x C quat., arom., binap-10,10'), 134.07 (2 x C quat., arom., binap-2,2'), 135.51 (8 x CH arom., meta in BPh$_4$ gp.), 136.00 (2 x C quat., arom., binap-1,1'); m/z (FAB) 295.1359; C$_{22}$H$_{18}$N [M–H]$^+$ requires 295.1361.

2-Bromo-6-tert-butyl-3-methyl-phenol (99):

\[
\begin{align*}
\text{OH} & \\
\text{Me} & \\
\text{98} & \\
\text{Br} & \\
\text{99}
\end{align*}
\]

$N$-Bromosuccinimide (5.42 g, 30.44 mmol) was added portionwise over five minutes to a solution of 2-tert-butyl-5-methyl-phenol (98) (5.00 g, 30.44 mmol) in carbon tetrachloride (121.80 mL, c 0.25 M). The reaction mixture was then left to stir for 3 h after which the solvents were removed under reduced pressure. The residue was dissolved in dichloromethane (40 mL) and the organic phase washed with water (2 x 30 mL), brine (2 x 30 mL), dried (Na$_2$SO$_4$) and the solvents removed in vacuo. Column chromatography using petrol as an eluent gave the product as a colourless oil (4.07 g, 55%); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3495, 3075, 2956, 2914, 2871, 1662, 1486, 1444, 1401, 1363, 1320, 1271, 1192, 1142, 1032, 957, 842, 806, 746, 684; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 1.38 (9 H, s, ArC(CH$_3$)$_3$), 2.35 (3 H, s, ArCH$_3$), 5.91 (1 H, s, OH), 6.73 (1 H, dd, $J= 8.0$ Hz, 0.8 Hz, CH arom., H4), 7.09 (1 H, d, $J= 8.0$ Hz, CH arom., H5); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 23.06 (CH$_3$, ArCH$_3$), 29.45 (3 x CH$_3$, ArC(CH$_3$)$_3$),
35.07 (C quat., ArC(CH₃)₃), 115.33 (C quat., arom., C2), 121.56 (CH arom., C4), 125.47 (CH arom., C5), 134.61 (C quat., arom., C6), 135.95 (C quat., arom., C3), 150.39 (C quat., arom., C1); m/z (FAB) 242.0311; C₁₁H₁₅BrO [M+H]⁺ requires 242.0306.

**4-Bromo-2-tert-butyl-5-methyl-phenol (100)**

A by-product obtained in the bromination of 2-tert-butyl-5-methyl-phenol (98), using N-bromosuccinimide as described above; Isolated as a colourless oil (2.34 g, 33%); νmax(film)/cm⁻¹ 3490 (OH), 3074, 2953, 2914, 2871, 1660, 1490, 1444, 1401, 1360, 1320, 1278, 1190, 1142, 1032, 957, 847, 806, 740, 684; ¹H-NMR (400 MHz, CDCl₃): δ 1.28 (9 H, s, ArC(CH₃)₃), 2.18 (3 H, s, ArCH₃), 4.81 (1 H, s, OH), 6.45 (1 H, s, CH arom., H6), 7.27 (1 H, s, CH arom., H3); ¹³C-NMR (100 MHz, CDCl₃): δ 21.06 (CH₃, ArCH₃), 28.37 (3 × CH₃, ArC(CH₃)₃), 33.27 (C quat., ArC(CH₃)₃), 114.21 (C quat., arom., C4), 117.77 (CH arom., C6), 129.64 (CH arom., C3), 134.79 (C quat., arom., C2), 135.05 (C quat., arom., C5), 152.17 (C quat., arom., C1); m/z (FAB) 242.0302; C₁₁H₁₅BrO [M+H]⁺ requires 242.0306.

**3,3' -Dibromo-5,5'-di-tert-butyl-4,4'-dihydroxy-2,2'-dimethyl-1,1'-biphenyl (101):**
Copper(I) chloride CuCl (0.07 g, 0.75 mmol) was added to a solution of \(N,N,N',N'\)-tetramethyl-ethane-1,2-diamine TMEDA (0.13 mL, 0.82 mmol) in dichloromethane (10 mL) and the mixture sonicated under oxygen atmosphere to afford a green solution. A solution of 2-bromo-6-\textit{tert}-butyl-3-methyl-phenol (99) (1.81 g, 7.46 mmol) in dichloromethane (10 mL) was added and the mixture left to stir for 16 h under oxygen gas. The solvents were removed under reduced pressure and the crude residue subjected to column chromatography using petrol as an eluent to give the product as a colourless solid (0.98 g, 54%); m.p. 202-203 °C; \(\nu_{\text{max}}\text{(film)}/\text{cm}^{-1}\) 3492 (OH), 2956, 1595, 1465, 1384, 1310, 1255, 1184, 1028, 906, 734, 675; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.40 (18 H, s, 2 \(\times\) ArC(CH\(_3\))\(_3\)), 2.35 (6 H, s, 2 \(\times\) ArCH\(_3\)), 5.96 (2 H, s, 2 \(\times\) ArOH), 6.96 (2 H, s, 2 \(\times\) CH arom., \textit{biphenyl}-6,6\(\text{'}\)); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 20.90 (2 \(\times\) CH\(_3\), 2 \(\times\) ArCH\(_3\)), 29.52 (6 \(\times\) CH\(_3\), 2 \(\times\) ArC(CH\(_3\))\(_3\)), 35.17 (2 \(\times\) C quat., 2 \(\times\) ArC(CH\(_3\))\(_3\)), 115.98 (2 \(\times\) C quat., arom., \textit{biphenyl}-3,3\(\text{'}\)), 127.57 (2 \(\times\) CH arom., \textit{biphenyl}-6,6\(\text{'}\)), 133.98 (4 \(\times\) C quat., arom., \textit{biphenyl}-1,1\(\text{'}\)-5,5\(\text{'}\)), 134.14 (2 \(\times\) C quat., arom., \textit{biphenyl}-2,2\(\text{'}\)), 149.44 (2 \(\times\) C quat., arom., \textit{biphenyl}-4,4\(\text{'}\)); \(m/z\) (El) 482.0461; \(C_{22}H_{28}Br_2O_2\) (M\(^+\)) requires 482.0456.

\textbf{4,4\text{'}-Dibromo-2,2\text{'}-di-\textit{tert}-butyl-3,3\text{'}-dihydroxy-5,5\text{'}-dimethyl-1,1\text{'}-biphenyl (102):}

![Diagram](attachment:image.png)

A by-product obtained in the oxidative coupling of 2-bromo-6-\textit{tert}-butyl-3-methyl-phenol (99), using CuCl and TMEDA as described above; Isolated as a colourless powder; \(\nu_{\text{max}}\text{(film)}/\text{cm}^{-1}\) 3492 (OH), 2955, 1459, 1385, 1265, 1184, 1029; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.37 (18 H, s, 2 \(\times\) ArC(CH\(_3\))\(_3\)), 2.53 (6 H, s, 2 \(\times\) ArCH\(_3\)), 5.92 (2 H, s, 2 \(\times\) ArOH), 7.39 (2 H, s, 2 \(\times\) CH arom., \textit{biphenyl}-2,2\(\text{'}\)); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 24.02 (2 \(\times\) CH\(_3\), 2 \(\times\) ArCH\(_3\)), 29.19 (6 \(\times\) CH\(_3\), 2 \(\times\) ArC(CH\(_3\))\(_3\)), 35.25 (2 \(\times\) C quat., 2 \(\times\) ArC(CH\(_3\))\(_3\)), 114.58 (2 \(\times\) C quat., arom., \textit{biphenyl}-4,4\(\text{'}\)), 115.53 (2 \(\times\) C quat.,

\[\text{Br}\]
arom., biphenyl-2,2'), 129.69 (2 × CH arom., biphenyl-6,6'), 134.72 (2 × C quat., arom., biphenyl-1,1'), 136.23 (2 × C quat., arom., biphenyl-5,5'), 149.83 (2 × C quat., arom., biphenyl-3,3'); m/z (EI) 482.0448; C_{22}H_{28}Br_2O_2 (M)^+ requires 482.0456.

3,3'-Dibromo-5,5'-di-tert-butyl-4,4'-dimethoxy-2,2'-dimethyl-1,1'-biphenyl (103):

![Chemical Structure](image1)

A solution of compound (101) (0.37 g, 0.76 mmol) in N,N-dimethylformamide (10 mL) was treated with grounded potassium hydroxide (0.11 g, 1.91 mmol) followed by the dropwise addition of iodomethane (0.12 mL, 1.91 mmol) at 0 °C. The reaction was then left to stir at room temperature for 16 h. The reaction mixture was then diluted with ethyl acetate (40 mL) and washed with water (6 × 50 mL), brine (6 × 50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield a colourless solid (0.38 g, 98%); m.p. 123-125 °C; ν_{\text{max}}(\text{film})/\text{cm}^{-1} 2956, 1459, 1359, 1258, 1223, 1044, 1003, 976, 908, 847, 734; ^{1}H-NMR (400 MHz, CDCl_3): δ 1.39 (18 H, s, 2 × ArC(CH_3)_3), 2.10 (6 H, s, 2 × ArCH_3), 3.97 (6 H, s, 2 × ArOCH_3), 7.00 (2 H, s, 2 × CH arom., biphenyl-6,6'); ^{13}C-NMR (100 MHz, CDCl_3): δ 20.99 (2 × CH_3, 2 × ArCH_3), 30.97 (6 × CH_3, 2 × ArC(CH_3)_3), 35.27 (2 × C quat., 2 × ArC(CH_3)_3), 61.48 (2 × OCH_3, 2 × ArOCH_3), 122.03 (2 × C quat., arom., biphenyl-3,3'), 127.50 (2 × CH arom., biphenyl-6,6'), 135.76 (2 × C quat., arom., biphenyl-1,1'), 137.70 (2 × C quat., arom., biphenyl-5,5'), 141.57 (2 × C quat., arom., biphenyl-2,2'), 155.80 (2 × C quat., arom., biphenyl-4,4'); m/z (FAB) 510.0776; C_{24}H_{32}Br_2O_2 [M+H]^+ requires 510.0769.
3,3'-Bis-(3,5-(trifluoromethyl)phenyl)-5,5'-di-tert-butyl-4,4'-dimethoxy-2,2'-dimethyl-1,1'-biphenyl (104):

A solution of compound (103) (0.33 g, 0.65 mmol) in dry N,N-dimethylformamide (8 mL) was degassed with nitrogen gas for 15 minutes before the addition of Pd(PPh)$_4$ (0.075 g, 0.065 mmol), 3,5-bis-(trifluoromethyl)-phenylboronic acid (0.42 g, 1.62 mmol) and potassium carbonate (0.67 g, 4.86 mmol). The mixture was degassed for a further 10 minutes and backfilled with nitrogen gas. The reaction mixture was subsequently heated to 90 °C overnight. The mixture was then poured into saturated ammonium chloride (30 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed with water (4 x 30 mL), brine (4 x 30 mL), dried (Na$_2$SO$_4$) and the solvent removed under reduced pressure. The resulting crude product was purified by column chromatography using petrol as an eluent to give the product as colourless foam (0.36 g, 73%); $\nu_{\text{max}}$(film)/cm$^{-1}$ 2960, 2868, 1618, 1466, 1425, 1392, 1354, 1323, 1278, 1238, 1179, 1135, 1084, 1051, 903, 847, 739, 684; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 1.43 (18 H, s, 2 x ArC(CH$_3$)$_3$), 1.79 (6 H, s, 2 x ArCH$_3$), 3.17 (6 H, s, 2 x ArOCH$_3$), 7.20 (2 H, s, 2 x CH arom., biphenyl-6,6'), 7.88 (2 H, s, 2 x CH arom., biphenyl-6,6'), 7.91 (4 H, dd, $J$= 4.4 Hz, 0.4 Hz, 4 x CH arom., H8, H8'-H9, H9'); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 18.10 (2 x CH$_3$), 31.04 (6 x CH$_3$, 2 x ArC(CH$_3$)$_3$), 35.05 (2 x C quat., 2 x ArC(CH$_3$)$_3$), 60.62 (2 x OCH$_3$, 2 x ArOCH$_3$), 120.82 (2 x CH arom., septet, $J$= 3.7 Hz, C12, C12'), 123.44 (4 x C quat., q, $J$= 271.0 Hz, 4 x CF$_3$), 129.11 (2 x CH arom., biphenyl-6,6'), 131.07 (4 x CH arom., C8, C8'-C9, C9'), 131.57 (4 x C quat., arom., q, $J$= 33.0 Hz, C10, C10'-C11, C11'), 133.08 (2 x C quat., arom., biphenyl-3,3'), 133.23 (2 x C quat., arom., biphenyl-1,1'), 137.54 (2 x C quat., arom., biphenyl-5,5'), 140.46 (2 x C quat., arom.,
biphenyl-2,2'), 141.04 (2 × C quat., arom., C7, C7'), 156.31 (2 × C quat., arom., biphenyl-4,4'); m/z (MALDI-TOF) 778.3; C₄₀H₈₁F₁₂O₂ [M]^+ requires 778.2680.

2,2'-Bis-bromomethyl-3,3'-bis-(3,5-(trifluoromethyl)phenyl)-5,5'-di-tert-butyl-4,4'-dimethoxy-1,1'-biphenyl (105):

3,3'-Bis-(3,5-(trifluoromethyl)phenyl)-5,5'-di-tert-butyl-4,4'-dimethoxy-2,2'-dimethyl-1,1'-biphenyl (104) (0.27 g, 0.34 mmol) was dissolved in carbon tetrachloride (5 mL). N-Bromosuccinimide (0.14 g, 0.75 mmol) and azo-bis-isobutyronitrile (0.006 g, 0.035 mmol) were added with stirring at room temperature. The mixture was then heated under reflux for 2 h after which complete disappearance of the starting material was observed by TLC. Upon cooling of the reaction to room temperature, the solvents were removed under reduced pressure and the residue redissolved in dichloromethane (30 mL). The organic layer was washed with water (2 × 20 mL), brine (2 × 20 mL), dried (Na₂SO₄) and the solvent removed under reduced pressure. Flash column chromatography of the crude material using ethyl acetate/petroleum ether (1:15) as eluent afforded the product as a colourless powder (0.29 g, 92%); m.p. 208-209 °C; ν_max (film)/cm⁻¹ 2960, 1462, 1394, 1358, 1278, 1244, 1178, 1137, 1083, 1047, 906, 847, 735; ¹H-NMR (400 MHz, CDCl₃): δ 1.37 (18 H, s, 2 × ArC(CH₃h), 3.14 (6 H, s, 2 × ArOCH₃), 3.82 (2 H, d, J = 10.2 Hz, ArCH₂Br), 3.88 (2 H, d, J = 10.2 Hz, ArCH₂Br), 7.33 (2 H, s, 2 × CH arom., biphenyl-6,6'), 7.90 (4 H, d, J = 8.0 Hz, 4 × CH arom., H12, H12'and H8, H8' or H9, H9'), 8.08 (2 H, s, 2 × CH arom., H8, H8 or H9, H9'); ¹³C-NMR (100 MHz, CDCl₃): δ 29.25 (2 × CH₃, 2 × ArCH₂Br₂), 29.71 (6 × CH₃, 2 × ArC(CH₃h), 34.38 (2 × C quat., 2 × ArC(CH₃h), 59.91 (2 × OCH₃, 2 ×
ArOCH₃), 120.64 (2 × CH arom., septet, J= 3.7 Hz, C12, C12'), 122.25 (2 × C quat., q, J= 271.4 Hz, 2 × CF₃), 122.28 (2 × C quat., q, J= 271.4 Hz, 2 × CF₃), 129.24 (2 × CH arom., biphenyl-6,6'), 129.70 (2 × CH arom., C8, C8' or C9, C9'), 130.05 (2 × CH arom., C8, C8' or C9, C9'), 130.84 (2 × C quat., arom., q, J= 33.3 Hz, C10, C10' or C11, C11'), 130.93 (2 × C quat., arom., q, J= 33.3 Hz, C10, C10' or C11, C11'), 131.70 (2 × C quat., arom., biphenyl-3,3'), 133.04 (2 × C quat., arom., biphenyl-1,1'), 134.79 (2 × C quat., arom., biphenyl-5,5'), 137.87 (2 × C quat., arom., biphenyl-2,2'), 142.86 (2 × C quat., arom., C7, C7'), 156.38 (2 × C quat., arom., biphenyl-4,4'); m/z (FAB) 934.0871; C₄₀H₃₇Br₂F₁₂O₂ [M+H]+ requires 934.0890.

N-(4S,5S)-5-(2,2-dimethyl-4-phenyl-1,3-dioxanyl)-3,3'-bis-(3,5-(trifluoromethyl)phenyl)-5,5'-di-tert-butyl-4,4'-dimethoxy-2,7-dihydridibenzo[c,e]azepine (106):

L-acetonamine (71) (0.06 g, 0.30 mmol) was added to a nitrogen purged stirred solution of dibromide (105) (0.25 g, 0.27 mmol) and potassium carbonate (0.11 g, 0.80 mmol) in dry acetonitrile (4 mL) at room temperature. The reaction mixture was heated under reflux overnight. The solvent was removed under reduced pressure and the resulting residue was diluted with dichloromethane (40 mL), washed with water (2 × 30 mL), brine (2 × 30 mL), dried (Na₂SO₄) and the solvents removed under reduced pressure to give the product as an orange foam (0.24 g, 91%); [α]D₃⁰ +8.6 (c 0.93, CHCl₃); νmax(film)/cm⁻¹ 2961, 2869, 1465, 1362, 1234, 1278, 1326, 1187, 1082, 1041, 904, 847, 736, 684; ¹H-NMR (400 MHz, CDCl₃): δ 0.93 (3 H, s, CH₃, H19 or H20), 1.21 (3 H, s, CH₃, H19 or H20), 1.37 (18 H, s, 2 × ArC(CH₃)₃), 1.91 (1 H, d, J= 2.8 Hz, NCH, H17), 2.99 (6 H, s, 2 × ArOCH₃), 3.18 (4 H, d, J= 12.4 Hz, 2 × ArCH₂N),
3.66 (2 H, d, J= 2.4 Hz, NCHCH₂O, H18), 4.36 (1 H, d, J= 2.4 Hz, ArCH, H16), 6.58 (2 H, dd, J= 7.2 Hz, 3.6 Hz, 2 × CH arom., H22, H23), 7.00-7.02 (3 H, m, 2 × CH arom., H24, H25 and H26), 7.33 (2 H, s, 2 × CH arom., biphenyl-6,6'), 7.60 (2 H, s, 2 × CH arom., H8, H8 or H9, H9'), 7.86 (2 H, s, 2 × CH arom., H8, H8 or H9, H9'), 7.90 (2 H, s, 2 × CH arom., H12, H12'); ¹³C-NMR (100 MHz, CDCl₃): δ 17.67 (CH₃, C19 or C20), 27.89 (CH₃, C19 or C20), 29.93 (6 × CH₃, 2 × ArCH(CH₃)₂), 34.15 (2 × C quat., 2 × ArCH(CH₃)₂), 48.66 (2 × CH₂, 2 × ArCH₂N), 57.85 (CH, NCH, C17), 59.68 (2 × OCH₃, 2 × ArOCH₃), 60.31 (CH₂, C18), 73.36 (CH, ArCH, C16), 97.56 (C quat., C14), 120.09 (2 × CH arom., septet, J= 3.7 Hz, C12, C12'), 122.24 (2 × C quat., q, J= 271.3 Hz, 2 × CF₃), 122.39 (2 × C quat., q, J= 271.3 Hz, 2 × CF₃), 124.69 (2 × CH arom., C22, C23), 125.61 (CH arom., C26), 126.44 (2 × CH arom., C24, C25), 126.65 (2 × CH arom., biphenyl-6,6'), 130.32 (2 × CH arom., C8, C8'or C9, C9'), 130.34 (4 × C quat., arom., q, J= 33.3 Hz, C10, C10'-C11, C11'), 130.48 (2 × CH arom., C8, C8'or C9, C9'), 131.42 (2 × Cquat., arom., biphenyl-3,3'), 131.84 (2 × Cquat., arom., biphenyl-1,1'), 136.23 (2 × Cquat., arom., biphenyl-2,2'), 138.05 (2 × Cquat., arom., biphenyl-5,5'), 139.19 (2 × Cquat., arom., C7, C7'), 141.39 (Cquat., arom., C21), 155.89 (2 × Cquat., arom., biphenyl-4,4').

**(4S,5S)-4,8-Bis-(3,5-bis-trifluoromethyl-phenyl)-2,10-di-tert-butyl-6-(2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3,9-dimethoxy-5H-dibenzo[c,e]azepinium tetraphenyborate (97):**

![Diagram of the molecule](image)

Azepine (106) (0.23 g, 0.23 mmol) was dissolved in carbon tetrachloride (3 mL). N-Bromosuccinimide (0.05 g, 0.28 mmol) and azo-bis-isobutyronitrile (0.002 g, 0.012...
mmol) were added with stirring at room temperature. The mixture was then heated under reflux for 3 h. Upon cooling of the reaction to room temperature, the solvents were removed under reduced pressure and the residue redissolved in ethanol. A solution of sodium tetraphenylborate (0.087 g, 0.26 mmol) in minimum amount of acetonitrile was added in one portion. The resulting mixture was stirred for further 5 minutes, after which few drops of water were added. The resulting yellow solid was collected by filtration and washed with hexane (0.26 g, 85%); m.p. 140-142 °C (dec.); $[\alpha]^{20}_D$ -70.8 (c 0.52, CH$_3$OH); Found: C, 67.41; H, 5.20; N, 1.20.

C$_{76}$H$_{70}$BF$_{12}$NO$_{2}$·3H$_2$O requires C, 67.41; H, 5.66; N, 1.03%; $v_{\text{max}}$(film)/cm$^{-1}$ 3055, 2965, 1626, 1579, 1357, 1278, 1241, 1183, 1140, 1081, 1045, 904, 847; $^{1}$H-NMR (400 MHz, acetonitrile-d$_3$): $\delta$ 0.43 (3 H, s, CH$_3$), 1.28 (3 H, s, CH$_3$ or H$_2$O), 1.42 (9 H, s, ArC(CH$_3$)$_3$), 1.47 (9 H, s, ArC(CH$_3$)$_3$), 2.88 (3 H, s, ArOCH), 3.06 (3 H, s, ArOCH), 3.30 (1 H, t, $J$= 2.4, NCH, H$_2$O), 4.03 (1 H, d, $J$= 13.4 Hz, NCHCHHO, H$_2$O), 4.25 (1 H, dd, $J$= 13.4 Hz, 2.4 Hz, NCHCHHO, H$_2$O), 4.49 (1 H, d, $J$= 12.4 Hz, ArCHHN), 4.53 (1 H, d, $J$= 12.4 Hz, ArCHHN), 5.14 (1 H, d, $J$= 7.2 Hz, ArCHHN), 6.65 (2 H, d, $J$= 7.3 Hz, 2 × CH arom., H$_2$2, H$_2$3), 6.75 (4 H, t, $J$= 7.2 Hz, 4 × CH arom., para in BP$_1$4 gp.), 6.91 (10 H, t, $J$= 7.4 Hz, 8 × CH arom., ortho in BP$_1$4 gp., and 2 × CH arom., H$_2$4, H$_2$5), 6.97-6.99 (1 H, m, CH arom.), 7.18-7.20 (8 H, m, 8 × CH arom., meta in BP$_1$4 gp.), 7.59 (1 H, bs, CH arom.), 7.67 (1 H, bs, CH arom.), 7.77 (1 H, bs, CH arom.), 7.81 (1 H, bs, CH arom.), 7.99 (1 H, bs, CH arom.), 8.14 (1 H, bs, CH arom.), 8.23 (1 H, bs, CH arom.), 8.88 (1 H, s, HC= N); $^{13}$C-NMR (100 MHz, acetonitrile-d$_3$, −40 °C): $\delta$ 17.04 (O,b, CI9 or C20), 27.07 (CH$_3$, C19 or C20), 29.28 (3 × CH$_3$, ArC(CH$_3$)$_3$), 29.77 (3 × CH$_3$, ArC(CH$_3$)$_3$), 34.83 (C quat., ArC(CH$_3$)$_3$), 35.97 (C quat., ArC(CH$_3$)$_3$), 57.16 (CH$_2$, ArCH$_2$N), 60.43 (CH$_3$, ArOCH$_3$), 60.58 (CH$_3$, ArOCH$_3$), 62.42 (CH$_2$, C18), 65.66 (CH, CHN, C17), 70.79 (CH, ArCH, C16), 100.02 (C quat., C14), 121.43 (4 × CH arom., para in BP$_1$4 gp.), 122.24 (CH arom.), 123.60 (CH arom.), 124.49 (CH arom.), 124.85 (C quat.), 125.05 (2 × CH arom., C22, C23), 125.27 (8 × CH arom., ortho in BP$_1$4 gp.), 126.61 (C quat.), 127.95 (2 × CH arom., C24, C25), 128.57 (C quat.), 128.68 (CH arom.), 129.00 (CH arom.), 129.74 (CH arom.), 130.39 (C quat.), 131.09 (CH arom.), 131.30 (C quat.), 131.43 (C quat.), 131.50 (CH arom.), 132.19 (C quat., q, $J$= 33.4 Hz), 133.32 (CH arom.), 135.24 (C quat.), 135.43 (8 × CH arom., meta in BP$_1$4 gp.), 135.60 (C quat.), 136.02 (C quat.), 136.49 (C quat.), 136.89 (C quat.), 144.89 (C quat.), 152.73 (C quat.), 157.15 (C quat.), 158.70 (C quat.), 163.49 (4 × C quat.,...
A solution of diphenic acid (108) (5.00 g, 20.64 mmol) in thionyl chloride (20 mL) was heated under reflux for 4 h under nitrogen atmosphere. The excess thionyl chloride was removed under reduced pressure, and the resulting yellow residue was dissolved in propan-2-ol (30 mL). Pyridine (5.0 mL, 61.92 mmol) was dropwise added to the mixture at 0 °C. The mixture was subsequently heated under reflux for 3 h. The solvent was removed under reduced pressure and the resulting yellow solid redissolved in ethyl acetate (30 mL). The organic phase was washed with water (2 × 30 mL), brine (2 × 30 mL), dried (Na$_2$SO$_4$) and the solvent removed under reduced pressure to afford the product as a yellow powder (6.67 g, 99%); $\nu_{\text{max}}$(film)/cm$^{-1}$ 3061, 2979, 1710 (C=O), 1598, 1445, 1374, 1347, 1288, 1257, 1179, 1132, 1106, 1047, 918, 761; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 0.91 (6 H, d, $J= 6.3$ Hz, 2 × CH$_3$), 1.00 (6 H, d, $J= 6.3$ Hz, 2 × CH$_3$), 4.94 (2 H, septet, $J= 6.3$ Hz, 2 × CH(CH$_3$)$_2$), 7.20 (2 H, ddd, $J= 7.8$ Hz, 1.5 Hz, 0.6 Hz, 2 × CH arom., biphenyl-6,6'), 7.43 (2 H, ddd, $J= 7.8$ Hz, 7.8 Hz, 1.5 Hz, 2 × CH arom., biphenyl-4,4'), 7.50 (2 H, ddd, $J= 7.8$ Hz, 7.8 Hz, 1.5 Hz, 2 × CH arom., biphenyl-5,5'), 8.03 (2 H, ddd, $J= 7.8$ Hz, 1.5 Hz, 0.6 Hz, 2 × CH arom., biphenyl-3,3'); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 21.28 (2 × CH$_3$), 21.33 (2 × CH$_3$), 67.95 (2 × CH, 2 × C(CH$_3$)$_2$), 126.98 (2 × CH arom., biphenyl-4,4'), 129.91 (2 × CH arom., biphenyl-3,3'), 130.12 (2 × CH arom., biphenyl-6,6'), 130.36 (2 × C quat., arom., biphenyl-2,2'), 131.14 (2 × CH arom., biphenyl-5,5'), 142.69 (2 × C quat., arom., biphenyl-1,1'), 167.07 (2 × C quat., 2 × C=O).
Biphenyl-2,2'-dicarboxylic acid bis-diethylamide (109b):

A solution of diphenic acid (108) (3.00 g, 12.39 mmol) in thionyl chloride (15 mL) was heated under reflux for 4 h under nitrogen atmosphere. The excess thionyl chloride was removed under reduced pressure, and diethylamine (12.0 mL, 120.39 mmol) followed by triethylamine (5.0 mL, 37.16 mmol) were added dropwise at 0 °C. The mixture was subsequently heated under reflux for 2 h. The solvent was removed under reduced pressure, and the resulting yellow solid redissolved in ethyl acetate (30 mL). The organic phase was washed with water (2 × 30 mL), brine (2 × 30 mL), dried (Na₂SO₄) and the solvent removed under reduced pressure to afford the product as an orange powder (4.2 g, 96%); $\nu_{\text{max}}$(film)/cm$^{-1}$: 3534, 3461, 2970, 2930, 1626 (NC=O), 1597, 1439, 1378, 1296; $^1$H-NMR (400 MHz, DMSO-d$_6$, 100 °C): δ 0.94 (12 H, t, $J$= 7.2 Hz, 4 × CH$_3$), 3.35 (8 H, bs, 4 × CH$_2$), 7.24-7.38 (8 H, 8 × CH arom., biphenyl); $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 12.04 (2 × CH$_3$), 13.71 (2 × CH$_3$), 38.27 (2 × CH$_2$, 2 × NCH$_2$CH$_3$), 42.65 (2 × CH$_2$, 2 × NCH$_2$CH$_3$), 126.70 (2 × CH arom., biphenyl), 127.52 (2 × CH arom., biphenyl), 128.32 (2 × CH arom., biphenyl), 129.94 (2 × CH arom., biphenyl), 136.45 (2 × C quat., arom., biphenyl), 136.99 (2 × C quat., arom., biphenyl), 170.37 (2 × C quat., 2 × NC=O).
2-Methyl-3-nitro-iodobenzene (113):

A solution of concentrated sulfuric acid (8 mL) was added to a solution of 2-methyl-3-nitroaniline (111) (5.00 g, 32.86 mmol) in water (50 mL). The mixture was cooled to 0 °C, and a solution of sodium nitrite (2.49 g, 36.15 mmol) in water (5 mL) was added dropwise. The mixture was stirred for 1 h, and a solution of potassium iodide (8.18 g, 49.29 mmol) in water (20 mL) was added dropwise. The reaction was stirred for 1 h and then extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed with saturated aqueous sodium thiosulfate (Na₂S₂O₃), dried (Na₂SO₄) and the solvents removed under reduced pressure to yield a crude oil. The crude mixture was purified by flash column chromatography using ethyl acetate/petroleum ether (1:10) to afford the product as a yellow solid (7.43 g, 85 %); m.p. 36-37 °C; ν_{max}(film)/cm⁻¹ 3082, 1591, 1519, 1443, 1348, 1273, 1204, 1087, 1001, 860, 794, 735, 696; ¹H-NMR (400 MHz, CDCl₃): δ 2.52 (3 H, s, CH₃), 6.96 (1 H, t, J= 8.0 Hz, CH arom., H5), 7.64 (1 H, dd, J= 8.0 Hz, 1.2 Hz, CH arom., H6), 7.80 (1 H, dd, J= 8.0 Hz, 1.2 Hz, CH arom., H4); ¹³C-NMR (100 MHz, CDCl₃): δ 25.02 (CH₃, ArCH₃), 103.55 (C quat., arom., C1), 123.94 (CH arom., C4), 127.98 (CH arom., C5), 135.03 (C quat., arom., C2), 143.14 (CH arom., C6), 150.41 (C quat., arom., C3); m/z (EI) 262.9439; C₇H₆NO₂I (M⁺) requires 262.9443.


2,2'-Dimethyl-3,3'-dinitro-1,1'-biphenyl (114);

 Activation of copper powder:  

Copper powder (2.00 g) was stirred with 2% iodine (w/w wrt copper) in acetone (100 mL) for 10 minutes. The powder was filtered and stirred to slurry with 1:1 solution of concentrated hydrochloric acid in acetone (200 mL). The copper iodide dissolves and the copper powder remaining is filtered and washed with acetone (200 mL). The activated copper is then dried in a vacuum dessicator and used immediately.

2-Methyl-3-nitro-iodobenzene (113) (1.00 g, 3.80 mmol) and activated copper (1.21 g, 19.01 mmol) were dissolved in dry N,N-dimethylformamide (8 mL) and the mixture heated to 190 °C for 24 h. After cooling to ambient temperature, the mixture was diluted with dichloromethane (100 mL), washed with 4% aqueous ammonia (5 × 100 mL), water (4 × 50 mL), brine (3 × 50 mL), dried (Na₂SO₄) and the solvent removed under reduced pressure to yield a dark crude oil. Column chromatography of the crude material using ethyl acetate/petroleum ether (1:10) gave the product as a yellow solid (0.27 g, 53%); m.p. 120-121 °C; νmax(film)/cm⁻¹ 3086, 1604, 1524, 1458, 1350, 1279, 1219, 1106, 995, 859, 807, 736, 718, 674; ¹H-NMR (400 MHz, CDCl₃): δ 2.13 (6 H, s, 2 × CH₃), 7.29 (2 H, dd, J= 7.6 Hz, 1.4 Hz, 2 × CH arom., biphenyl-5,5'), 7.36 (2 H, ddd, J= 8.0 Hz, 7.6 Hz, 0.5 Hz, 2 × CH arom., biphenyl-6,6'), 7.83 (2 H, dd, J= 8.0 Hz, 1.4 Hz, 2 × CH arom., biphenyl-4,4'); ¹³C-NMR (100 MHz, CDCl₃): δ 15.37 (2 × CH₃, 2 × ArCH₃), 123.06 (2 × CH arom., biphenyl-4,4'), 125.71 (2 × CH arom., biphenyl-5,5'), 129.77 (2 × C quat., arom., biphenyl-2,2'), 132.58 (2 × CH arom., biphenyl-6,6'), 141.32 (2 × C quat., arom., biphenyl-1,1'), 149.90 (2 × C quat., arom., biphenyl-3,3'); m/z (EI) 272.0793; C₁₄H₁₂N₂O₄(M⁺) requires 272.0797.
2-nitrotoluene (115):

![Chemical structure](image)

2-Methyl-3-nitro-iodobenzene (113) (1.00 g, 3.80 mmol) and activated copper (1.21 g, 19.01 mmol) were dissolved in dry N,N-dimethylformamide (8 mL) and the mixture heated to 190 °C for 24 h. After cooling to ambient temperature, the mixture was diluted with dichloromethane (100 mL), washed with 4% aqueous ammonia (5 × 100 mL), water (4 × 50 mL), brine (3 × 50 mL), dried (Na₂SO₄) and the solvent removed under reduced pressure to yield a dark crude oil. Column chromatography of the crude material using ethyl acetate/petroleum ether (1:10) gave the product as a colourless oil (0.17 g, 33%); v_max(film)/cm⁻¹ 3056, 1602, 1520, 1443, 1356, 1281, 1195, 1115, 998, 735; ¹H-NMR (400 MHz, CDCl₃): δ 2.51 (3 H, s, CH₃, ArCH₃), 7.23-7.27 (2 H, m, 2 × CH arom., H₆, H₄), 7.41 (1 H, ddd, J= 7.5 Hz, 7.5 Hz, 1.4 Hz, CH arom., H₅), 7.87 (1 H, dd, J= 8.6 Hz, 1.4 Hz, CH arom., H₃); ¹³C-NMR (100 MHz, CDCl₃): δ 19.36 (CH₃, ArCH₃), 123.58 (CH arom., C3), 125.84 (CH arom., C4), 131.72 (CH arom., C6), 131.98 (CH arom., C5), 132.50 (C quat., arom., C1), 148.20 (C quat., arom., C1).

3,3'-Diamino-2,2'-dimethyl-1,1'-biphenyl (116):

![Chemical structure](image)

2,2'-Dimethyl-3,3'-dinitro-biphenyl (114) (0.25 g, 0.92 mmol) was dissolved in aqueous hydrazine hydrate (85%) (20 mL) and the solution heated to reflux for 16 h. The solution was allowed to cool to ambient temperature and extracted with ethyl acetate (4 × 30 mL). The organic layers were washed with water (2 × 30 mL), brine (2 × 30 mL) and dried (Na₂SO₄) and the solvents removed under reduced pressure to
afford the product as an orange powder (0.17 g, 86%); m.p. 162-164 °C; 
\( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 3463 (NH), 3364 (NH), 1615, 1579, 1455, 793; \( ^1\text{H-NMR} \) (400 MHz, 
CDCl\( _3 \)): \( \delta \) 1.79 (6 H, s, 2 \( \times \) CH\( _3 \)), 3.51 (4 H, s, 2 \( \times \) ArNH\( _2 \)), 6.51 (2 H, dd, \( J = 7.7 \text{ Hz}, 1.0 \text{ Hz}, 2 \times \text{CH arom.}, \text{biphenyl-4,4' \( ) \), 6.61 (2 H, dd, \( J = 7.7 \text{ Hz}, 1.0 \text{ Hz}, 2 \times \text{CH arom.}, \text{biphenyl-6,6' \( ) \), 6.96 (2 H, t, \( J = 7.7 \text{ Hz}, 2 \times \text{CH arom.}, \text{biphenyl-5,5' \( ) \), \text{Cl}_{14}H_{16}N_{2} \text{ (M) \text{ requires 212.1314.}}

\[3,3'\text{-Diodo-2,2'-dimethyl-1,1'-biphenyl (112):}^{17}\]

Concentrated sulfuric acid (5 mL) was added to a suspension of 2,2'-dimethyl-
biphenyl-3,3'-diamine (116) (0.17 g, 0.79 mmol) in water (15 mL). The mixture was 
cooled to 0 °C before the addition of sodium nitrite (0.12 g, 1.74 mmol) in water (3 
ml). The resulting solution was stirred for 50 minutes at 0 °C before the dropwise 
addition of potassium iodide (0.79 g, 4.74 mmol) in water (3 mL). The reaction 
mixture was then heated at 50 °C overnight. The dark-brown mixture was cooled and 
extracted with dichloromethane (3 \( \times \) 40 mL). The combined organic extracts were 
was washed with saturated sodium thiosulfate (2 \( \times \) 50 mL), water (2 \( \times \) 50 mL), brine (2 \( \times \) 50 mL), dried (Na\( _2 \)SO\( _4 \)) and the solvent removed under reduced pressure. The residue 
was filtered through a short pad of silica using petrol as eluent to give the product as 
brown solid (0.28 g, 81%); m.p. 103-105 °C; \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 3053, 2961, 2918, 1550, 
1427, 1378, 1260, 1180, 1073, 1022, 988, 781, 718, 653; \( ^1\text{H-NMR} \) (400 MHz, 
CDCl\( _3 \)): \( \delta \) 2.08 (6 H, s, 2 \( \times \) CH\( _3 \)), 6.82 (2 H, t, \( J = 7.8 \text{ Hz}, 2 \times \text{CH arom.}, \text{biphenyl-5,5' \( ) \), 6.96 (2 H, dd, \( J = 7.8 \text{ Hz}, 1.0 \text{ Hz}, 2 \times \text{CH arom.}, \text{biphenyl-6,6' \( ) \), 7.76 (2 H, dd,
\[ J = 7.8 \text{ Hz}, 1.0 \text{ Hz}, 2 \times CH \text{ arom., biphenyl-4,4'}; \]

\[ ^{13}\text{C-NMR (100 MHz, CDCl}_3): \delta \]

- 24.92 \( (2 \times CH_3, 2 \times ArCH_3) \)
- 101.52 \( (2 \times C \text{quat., arom., biphenyl-3,3'}) \)
- 126.21 \( (2 \times CH \text{ arom., biphenyl-6,6'}) \)
- 128.26 \( (2 \times CH \text{ arom., biphenyl-5,5'}) \)
- 137.59 \( (2 \times CH \text{ arom., biphenyl-4,4'}) \)
- 137.80 \( (2 \times C \text{quat., arom., biphenyl-1,1'}) \)
- 141.48 \( (2 \times C \text{quat., arom., biphenyl-2,2'}) \)

\[ m/z \text{ (EI) 433.9032; C}_{14}H_{12}I_2 (M^+) \text{ requires 433.9028.} \]

3,3'-Bis-(3,5-(trifluoromethyl)phenyl)-2,2'-dimethyl-1,1'-biphenyl (117):

![Diagram](image)

A solution of 3,3'-diiodo-2,2'-dimethyl-1,1'-biphenyl (112) \((0.72 \text{ g, 1.65 mmol})\) in dry \(N,N\)-dimethylformamide \((8 \text{ mL})\) was degassed for 15 minutes before the addition of \(\text{Pd(PPh}_3)_4\) \((0.19 \text{ g, 0.17 mmol})\), 3,5-bis(trifluoromethyl)-phenylboronic acid \((1.71 \text{ g, 6.61 mmol})\) and potassium carbonate \((0.91 \text{ g, 6.61 mmol})\). The mixture was degassed for a further 10 minutes and backfilled with nitrogen gas. The reaction mixture was subsequently heated to 90 °C overnight. The mixture was then poured into saturated ammonium chloride \((30 \text{ mL})\) and extracted with diethyl ether \((3 \times 30 \text{ mL})\). The combined organic extracts were washed with water \((4 \times 30 \text{ mL})\), brine \((4 \times 30 \text{ mL})\), dried \((\text{Na}_2\text{SO}_4)\) and the solvent removed under reduced pressure. The resulting dark crude oil was purified by column chromatography using petrol as an eluent to give the product as a colourless solid \((0.73 \text{ g, 73%})\); m.p. 143-145 °C; \(v_{\text{max}}(\text{film})/\text{cm}^{-1} 3057, 1617, 1578, 1454, 1379, 1280, 1176, 1134, 1051, 899, 846, 799; {^1}\text{H-NMR (400 MHz, CDCl}_3): \delta \]

- 1.90 \( (6 \text{ H, s, } 2 \times CH_3) \)
- 7.16 \( (2 \text{ H, d, } J = 7.3 \text{ Hz, } 2 \times CH \text{ arom., biphenyl-4,4'}) \)
- 7.17 \( (2 \text{ H, dd, } J = 7.3 \text{ Hz, } 1.0 \text{ Hz, } 2 \times CH \text{ arom., biphenyl-6,6'}) \)
- 7.28 \( (2 \text{ H, t, } J = 7.3 \text{ Hz, } 2 \times CH \text{ arom., biphenyl-5,5'}) \)
- 7.76 \( (4 \text{ H, s, } 4 \times CH \text{ arom., H8, H8', H9, H9'}) \)
- 7.81 \( (2 \text{ H, s, } 2 \times CH \text{ arom., H12, H12'}) \); \(^{13}\text{C-NMR (100 MHz, CDCl}_3): \delta \)

- 17.83 \( (2 \times CH_3, 2 \times ArCH_3) \)
- 120.91 \( (2 \times CH \text{ arom., septet, } J = 3.8 \text{ Hz, C12, C12'}) \)
- 123.38 \( (4 \times C \text{ arom., biphenyl-6,6'}) \)
quat., q, J = 271.2 Hz, 4 × CF₃), 126.01 (2 × CH arom., biphenyl-5,5'), 129.01 (2 × CH arom., biphenyl-4,4'), 129.54 (4 × CH arom., C8, C8'-C9, C9'), 129.84 (2 × CH arom., biphenyl-6,6'), 131.57 (4 × C quat., q, J = 33.0 Hz, C10, C10'-C11, C11'), 133.09 (2 × C quat., arom., biphenyl-2,2'), 139.68 (2 × C quat., arom., C7, C7'), 142.68 (2 × C quat., arom., biphenyl-3,3'), 144.21 (2 × C quat., arom., biphenyl-1,1'); m/z (EI) 606.1218; C₃₀H₁₈F₁₂(M⁺) requires 606.1217.

2,2'-Bis-bromomethyl-3,3'-bis-(3,5-(trifluoromethyl)phenyl)-1,1'-biphenyl (119):

3,3'-bis-(3,5-trifluoromethylphenyl)-2,2'-dimethyl-1,1'-biphenyl (117) (0.23 g, 0.38 mmol) was dissolved in carbon tetrachloride (5 mL). N-Bromosuccinimide (0.15 g, 0.84 mmol) and azo-bis-isobutyronitrile (0.006 g, 0.038 mmol) were added with stirring at room temperature. The mixture was then heated under reflux for 3 h after which complete disappearance of the starting material was observed by TLC. Upon cooling of the reaction to room temperature, the solvents were removed under reduced pressure and the residue redissolved in dichloromethane (30 mL). The organic layer was washed with water (2 × 20 mL), brine (2 × 20 mL), dried (Na₂SO₄) and the solvents removed under reduced pressure. Flash column chromatography of the crude material using ethyl acetate/petroleum ether (1:10) as eluent afforded the product as a colourless powder (0.25 g, 85%); m.p. 203-205 °C; νₘₙₓ(film)/cm⁻¹ 2359, 2340, 1378, 1277, 1175, 1132, 1106, 1047, 901; ¹H-NMR (400 MHz, CDCl₃): δ 4.00 (2 H, d, J = 10.4 Hz, ArCH₂), 4.09 (2 H, d, J = 10.4 Hz, ArCH₂), 7.27 (2 H, dd, J = 7.6 Hz, 1.5 Hz, 2 × CH arom., biphenyl-4,4'), 7.39 (2 H, dd, J = 7.6 Hz, 1.5 Hz, 2 × CH arom., biphenyl-6,6'), 7.46 (2 H, t, J = 7.6 Hz, 2 × CH arom., biphenyl-5,5'), 7.89 (2 H, d, J = 0.6 Hz, 2 × CH arom., H12, H12'), 7.95 (4 H, s, 4 × CH arom., H8, H8', H9, H9');
$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 28.64 (2 $\times$ CH$_2$, 2 $\times$ ArCH$_2$Br$_2$), 120.76 (2 $\times$ CH arom., septet, $J$=3.8 Hz, C12, C12'), 122.21 (4 $\times$ C quat., q, $J$= 271.2 Hz, 4 $\times$ CF$_3$), 127.56 (2 $\times$ CH arom., biphenyl-5,5'), 128.36 (4 $\times$ CH arom., C8, C8'-C9, C9'), 129.56 (2 $\times$ CH arom., biphenyl-4,4'), 129.80 (2 $\times$ CH arom., biphenyl-6,6'), 130.64 (4 $\times$ C quat., q, $J$= 33.0 Hz, C10, C10'-C11, C11'), 132.21 (2 $\times$ C quat., arom., biphenyl-2,2'), 139.62 (2 $\times$ C quat., arom., C7, C7'), 139.67 (2 $\times$ C quat., arom., biphenyl-3,3'), 141.17 (2 $\times$ C quat., arom., biphenyl-1,1'); m/z (EI) 761.9429; C$_{30}$H$_{16}$Br$_2$F$_{12}$ requires 761.9433.

(4S,5S)-4,8-Bis-(3,5-bis-trifluoromethyl-phenyl)-6-(2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-6,7-dihydro-5H-dibenzo[c,e]azepine (120):

L-acetonamine (71) (0.17 g, 0.83 mmol) was added to a nitrogen-purged stirred solution of 2,2'-bis-bromomethyl-3,3'-bis-(3,5-trifluoromethylphenyl)-1,1'-biphenyl (119) (0.58 g, 0.75 mmol) and potassium carbonate (0.31 g, 2.26 mmol) in dry acetonitrile (10 mL) at room temperature. The reaction mixture was heated under reflux overnight. The solvent was removed under reduced pressure, and the resulting residue was diluted with dichloromethane (40 mL), washed with water (2 $\times$ 30 mL), brine (2 $\times$ 30 mL), dried (Na$_2$SO$_4$) and the solvents removed under reduced pressure. Column chromatography of the crude oily product using ethyl acetate/petroleum ether (1:10) gave the product as a colourless foam (0.55 g, 90%); $\alpha_D^{20}$ +46.8 (c 0.83, CHCl$_3$); $\nu_{max}$(film)/cm$^{-1}$ 2961, 1452, 1379, 1278, 1174, 1136; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 0.94 (3 H, s, CH$_3$, H19), 1.23 (3 H, s, CH$_3$, H20), 2.15 (1 H, d, $J$= 2.9 Hz, NCH, H17), 3.24 (2 H, d, $J$= 13.0 Hz, ArCH$_2$N), 3.40 (2 H, bs, ArCH$_2$N), 3.70 (2 H,
d, J= 2.9 Hz, NCHCH\textsubscript{2}O, H18), 4.44 (1 H, d, J= 2.9 Hz, ArCH, H16), 6.63 (2 H, dd, J= 7.8 Hz, 1.6 Hz, 2 × CH arom., H22, H23), 6.96-7.04 (3 H, m, 2 × CH arom., H24, H25 and H26), 7.17 (2 H, dd, J= 7.6 Hz, 1.6 Hz, 2 × CH arom., \textit{biphenyl}-4,4'), 7.38 (2 H, t, J= 7.6 Hz, 2 × CH arom., \textit{biphenyl}-5,5'), 7.43 (2 H, dd, J= 7.6 Hz, 1.6 Hz, 2 × CH arom., \textit{biphenyl}-6,6'), 7.70 (4 H, bs, 4 × CH arom., H8, H8', H9, H9'), 7.89 (2 H, s, 2 × CH arom., H12, H12'); \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}): δ 17.72 (CH\textsubscript{3}, C19), 27.79 (CH\textsubscript{3}, C20), 48.45 (2 × CH\textsubscript{2}, 2 × ArCH\textsubscript{2}N), 58.11 (CH, NCH, C17), 60.21 (CH\textsubscript{2}, C18), 73.36 (CH, ArCH, C16), 97.61 (C quat., C14), 120.15 (2 × CH arom., septet, J= 3.8 Hz, C12, C12'), 122.27 (4 × C quat., q, J= 271.4 Hz, 4 × CF\textsubscript{3}), 124.82 (2 × CH arom., C22, C23), 125.72 (CH arom., C26), 126.43 (2 × CH arom., C24, C25), 126.49 (2 × CH arom., \textit{biphenyl}-5,5'), 127.59 (2 × CH arom., \textit{biphenyl}-6,6'), 128.76 (4 × CH arom., C8, C8'-C9, C9'), 129.01 (2 × CH arom., \textit{biphenyl}-4,4'), 130.39 (4 × C quat., J= 33.0 Hz, 4 × CCF\textsubscript{3}, C10, C10'-C11, C11'), 131.92 (2 × Cquat., arom., \textit{biphenyl}-2,2'), 137.69 (2 × Cquat., arom., C7, C7'), 137.86 (2 × Cquat., arom., \textit{biphenyl}-3,3'), 141.25 (2 × Cquat., arom., \textit{biphenyl}-1,1'), 142.74 (Cquat., arom., C21); m/z (EI) 809.2176; C\textsubscript{42}H\textsubscript{31}F\textsubscript{12}N\textsubscript{2}O\textsubscript{2} (M') requires 809.2163.

\[(4S,5S)-4,8\text{-bis-(3,5-bis-trifluoromethyl-phenyl)-6-(2,2-dimethyl-4-phenyl-1,3)dioxan-5-yl}-5H\text{-dibenzo[c,e]azepinium tetraphenylborate (107):}\]

Azepine (120) (0.48 g, 0.60 mmol) was dissolved in carbon tetrachloride (3 mL). N-Bromosuccinimide (0.13 g, 0.72 mmol) and azo-bis-isobutyronitrile (0.005 g, 0.012 mmol) were added with stirring at room temperature. The mixture was heated under
reflux for 3 h. Upon cooling of the reaction to room temperature, the solvents were removed under reduced pressure and the residue redissolved in ethanol. A solution of sodium tetraphenylborate (0.23 g, 0.66 mmol) in a minimum amount of acetonitrile was added in one portion. The resulting mixture was stirred for a further 5 minutes, after which a few drops of water were added. The resulting yellow solid was collected by filtration and washed with ethanol followed by diethyl ether, and dried at 90 °C (0.46 g, 67%); m.p. 221-222 °C (dec.); [α] D 20 = -144.1 (c 1.00, CH3CN); Found: C, 67.96; H, 4.38; N, 1.21. C66H50BF12NO2·2H2O requires C, 68.11; H, 4.68; N, 1.20%; v max(film)/cm⁻¹ 3054, 1632, 1579, 1450, 1377, 1278, 1183, 1139, 902; ¹H-NMR (400 MHz, acetonitrile-d₆, -40 °C): δ 0.56 (3 H, s, CH₃, H19 or H20), 1.41 (3 H, s, CH₃, H19 or H20), 3.57 (1 H, d, J= 2.0 Hz, NCH, H17), 4.26 (1 H, d, J= 13.2 Hz, NCHCHHO, H18), 4.47 (1 H, d, J= 13.2 Hz, NCHCHHO, H18'), 4.78 (1 H, d, J= 13.0 Hz, ArCHH), 4.86 (1 H, d, J= 13.0 Hz, ArCHH), 5.39 (1 H, d, J= 2.0 Hz, ArCHH, H16), 6.74 (2 H, d, J= 6.4 Hz, 2 × CH arom.), 6.85 (4 H, t, J= 7.2 Hz, 4 × CH arom., para in BPh₄ gp.), 6.91-6.97 (3 H, m, 3 × CH arom.), 7.02 (8 H, t, J= 7.6 Hz, 8 × CH arom., ortho in BPh₄ gp.), 7.28-7.35 (9 H, m, CH arom., and 8 × CH arom., meta in BPh₄ gp.), 7.48 (1 H, t, J= 8.0 Hz, CH arom.), 7.64 (1 H, d, J= 7.6 Hz, CH arom.), 7.83-7.85 (2 H, m, 2 × CH arom.), 8.00-8.06 (3 H, m, 3 × CH arom.), 8.10 (1 H, s, CH arom.), 8.29 (2 H, s, CH arom.), 8.36 (1 H, s, CH arom.), 9.09 (1 H, s, HC=N); ¹³C-NMR (100 MHz, DMSO-d₆): δ 18.00 (CH₃, C19 or C20), 27.16 (CH₃, C19 or C20), 57.39 (2 × CH₂, 2 × ArCH₂N), 62.83 (CH₃, C18), 66.61 (CH, NCH, C17), 70.67 (CH, ArCH, C16), 99.62 (C quat., C14), 121.48 (4 × CH arom., para in BPh₄ gp.), 121.89 (CH arom., septet, C12 or C12'), 123.25 (CH arom., septet, C12 or C12'), 125.02 (CH arom.), 125.07 (C quat., arom.), 125.27 (8 × CH arom., ortho in BPh₄ gp.), 128.00 (CH arom.), 128.33 (CH arom.), 129.62 (CH arom.), 130.70 (CH arom.), 130.88 (CH arom.), 131.14 (CH arom.), 131.48 (C quat., arom.), 131.80 (CH arom.), 135.04 (CH arom.), 135.51 (8 × CH arom., meta in BPh₄ gp.), 135.75 (C quat., arom.), 135.86 (C quat., arom.), 136.56 (C quat., arom.), 136.78 (C quat., arom.), 139.71 (C quat., arom.), 140.70 (C quat., arom.), 141.04 (C quat., arom.), 143.29 (C quat., arom.), 163.33 (C quat., arom., J= 49.1 Hz, 4 × C-B ipso in BPh₄ gp.), 167.72 (HC=N); m/z (ESI) 808.2078; C₄₂H₃₆F₁₂NO₂(cation) requires 808.2079.
Resolution of trans-1,2-diaminocyclohexane (122).^{18}

A 250 mL beaker equipped with a large magnetic stirrer bar was charged with D-(-)-tartaric acid (8.56 g, 57.03 mmol) and distilled water (25 mL). The mixture was stirred at room temperature until complete dissolution was achieved, at which point a mixture of racemic trans-1,2-diaminocyclohexane (14.00 mL, 114.14 mmol) was added at a rate such that the reaction mixture reached 60 °C. Glacial acetic acid (6 mL) was added to the resulting mixture at such a rate that the reaction temperature reached 65 °C. The resulting heterogeneous white slurry was vigorously stirred as it was cooled to room temperature over 2 hours. The reaction mixture was then cooled to 5 °C in an ice bath for over 2 hours and the precipitate was collected by vacuum filtration. The wet white cake was washed with ice cooled water (6 mL) and rinsed with ice cooled methanol (5 x 6 mL). The white crude product was then recrystallized from water (1:10 w/v) by heating to 90 °C and cooling it to 5 °C overnight. The product was then dried under pressure (40 °C) to yield the desired compound (S,S)-1,2-diammoniumcyclohexane mono tartrate salt (123) as a white crystalline solid (10.63 g, 40%); m.p. 170-173 °C; [Lit.\textsuperscript{19} 280-284 °C]; [\alpha]\textsubscript{D}\textsuperscript{20} = -12.4 (c 4.00, H\textsubscript{2}O); [Lit.\textsuperscript{19} [\alpha]\textsubscript{D} = -12.4 (c 4.00, H\textsubscript{2}O)];

The salt was liberated by washing with 4 M NaOH (20 mL) and extraction into dichloromethane (3 x 30 mL). The combined organic extracts was dried (Na\textsubscript{2}SO\textsubscript{4}) and the solvent removed in vacuo to afford (1S,2S)-1,2-diammoniumcyclohexane as colourless crystals.
A solution of (1S,2S)-diaminocyclohexane (122) (2.04 g, 17.90 mmol) in xylenes was added pTSA (3.40 g, 17.90 mmol) and phthalic anhydride (2.65 g, 17.90 mmol) at room temperature. The reaction mixture was then heated under reflux with vigorous stirring until homogeneous solution was obtained and the product begun to crystalize (2 h). After cooling the mixture to room temperature, the colourless solid product was collected by filtration, washed with xylenes, hexanes and dried under vacuum (6.79 g, 95%); m.p. 250-251 °C; [Lit.20 249-252 °C]; [α]20D +18.2 (c 1.00, CHCl3); [Lit.20 [α]20D −15.8 (c 1.0, CHCl3)]; νmax(film)/cm⁻¹ 3384, 3027, 2930, 2885, 1770, 1703, 1495, 1389, 1219, 809, 680; ¹H-NMR (400 MHz, CDCl₃): δ 1.22 (2 H, m, CH₂, cyclohexyl protons), 1.43-1.51 (1 H, m, cyclohexyl proton), 1.67-1.70 (3 H, m, cyclohexyl protons), 2.34 (3 H, s, ArCH₃), 3.92 (1 H, m, CHN, H1), 4.18 (1 H, dt, J=11.7 Hz, 3.9 Hz, CHN, H2), 7.00 (2 H, d, J= 8.0 Hz, 2 × CH arom., Ar gp.), 7.31 (2 H, d, J= 8.1 Hz, 2 × CH arom., Ar gp.), 7.42 (2 H, dd, J= 7.4 Hz, 4.4 Hz, 2 × CH arom., H14, H15), 7.42 (2 H, dd, J= 7.4 Hz, 3.0 Hz, 2 × CH arom., H12, H13); ¹³C-NMR (100 MHz, CDCl₃): δ 21.34 (CH₃, ArCH₃), 23.66 (CH₂, C4), 24.47 (CH₂, C5), 28.97 (CH₂, C3), 30.01 (CH₂, C6), 50.71 (CH, C2), 52.40 (CH, C1), 122.90 (2 × CH arom.), 125.90 (2 × CH arom., C12, C13), 128.65 (2 × CH arom.), 131.96 (2 × C quat., arom., C10, C11), 133.32 (2 × CH arom., C14, C15), 139.92 (C quat., arom., ipso to SO₂N in Ar gp.), 141.02 (C quat., arom., ipso to CH₃ in Ar gp.), 168.53 (2 × C quat., 2 × C=O).

A solution of the salt (6.70 g, 16.80 mmol) in dichloromethane (30 mL) was stirred overnight with saturated sodium hydrogen carbonate solution (10 mL). The organic phase was separated, dried (Na₂SO₄) and the solvent removed in vacuo to give the product as a colourless solid (3.65 g, 89%); m.p. 126-127 °C; [Lit.20 123-125 °C];
\[ \alpha \] \textsuperscript{D} +78.5 \text{ (c 1.00, CHCl\textsubscript{3}); [Lit.\textsuperscript{20} \alpha \] \textsuperscript{D} -79.3 \text{ (c 1.00, CHCl\textsubscript{3});} \]\n
\[ \nu_{\text{max(film)}}/\text{cm}^{-1} \text{ \textsuperscript{1}} \text{H-NMR (400 MHz, CDCl\textsubscript{3}): } \delta 1.08-1.41 \text{ (5 H, m, cyclohexyl protons), 1.66-1.77 (3 H, m, cyclohexyl protons), 1.94-2.00 (1 H, m, cyclohexyl proton), 2.06-2.18 (1 H, m, cyclohexyl protons), 3.34 (1 H, dt, } J = 11.1 \text{ Hz, 4.1 Hz, CHN, H1), 3.72 (1 H, dt, } J = 10.5 \text{ Hz, 3.9 Hz, CHN, H2), 7.63 (2 H, dd, } J = 5.4 \text{ Hz, 3.2 Hz, 2 } \times \text{ CH arom., H14, H15), 7.75 (2 H, dd, } J = 5.5 \text{ Hz, 3.2 Hz, 2 } \times \text{ CH arom., H12, H13); } \]

\[ \nu_{\text{max(film)}}/\text{cm}^{-1} \text{ \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}): } \delta 25.10 \text{ (CH}, 2\text{C), 25.65} \text{ (CH}, 2\text{C), 29.31} \text{ (CH}, 2\text{C), 36.66} \text{ (CH}, 2\text{C), 50.84} \text{ (CH}, 2\text{C), 58.52} \text{ (CH, C1), 123.14} \text{ (2 } \times \text{ CH arom., C12, C13), 131.89} \text{ (2 } \times \text{ C quat., arom., C10, C11), 133.87} \text{ (2 } \times \text{ CH arom., C14, C15), 168.79} \text{ (2 } \times \text{ C quat., 2 } \times \text{ C=O, C8, C9); } m/z \text{ (El) 244.1208; } C_{14}H_{16}N_{2}O_{2} \text{ (M)}^{+} \text{ requires 244.1212.} \]

\[ (1S,25)-N,N'-Dimethyl-N'-Phthaloyl-1,2-diaminocyclohexane (125): \textsuperscript{20} \]

A mixture of (1S,2S)-N-Phthaloyl-1,2-diaminocyclohexane (124) (2.28 g, 9.32 mmol), 90% formic acid (5 mL) and 37% formaldehyde solution (1.60 mL, 20.50 mmol) was heated under reflux overnight. The solvents were removed in vacuo and the resulting residue was dissolved in dichloromethane (40 mL). The organic phase was washed with saturated aqueous sodium hydrogen carbonate (2 \times 30 mL), dried (Na\textsubscript{2}SO\textsubscript{4}) and the solvent removed in vacuo to give yellow powder (2.18 g, 86%); m.p. 123-124 °C; [Lit.\textsuperscript{20} 123-125 °C]; \[ \alpha \] \textsuperscript{D} +31.5 \text{ (c 1.00, CHCl\textsubscript{3}); [Lit.\textsuperscript{20} \alpha \] \textsuperscript{D} -32.5 \text{ (c 1.00, CHCl\textsubscript{3});} \]

\[ \nu_{\text{max(film)}}/\text{cm}^{-1} \text{ 2926, 2358, 1759, 1701, 1500, 1385, 1136, 1077, 715; } \text{\textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): } \delta 1.10-1.27 \text{ (3 H, m, cyclohexyl protons), 1.71-1.78 (3 H, m, cyclohexyl proton), 1.84-1.89 (1 H, m, cyclohexyl protons), 2.08 (6 H, s, 2 } \times \text{ CH}, \text{N(CH}_{3}\text{)}_{2}\text{), 2.10-2.15 (1 H, m, cyclohexylprotons), 3.24 (1 H, dt, } J = 11.2 \text{ Hz, 3.2 Hz, CHN, H1), 4.04 (1 H, dt, } J = 11.2 \text{ Hz, 4.0 Hz, CHN, H2), 7.61 (2 H, dd, } J = 5.2 \text{ Hz, 2.8 Hz, 2 } \times \text{ CH arom., H14, H15), 7.73 (2 H, dd, } J = 5.2 \text{ Hz, 3.2 Hz, 2 } \times \text{ CH arom., H12, H13); } \]

\[ \nu_{\text{max(film)}}/\text{cm}^{-1} \text{ \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}): } \delta 21.69 \text{ (CH}, 2\text{C), 24.09} \text{ (CH}, 2\text{C), 24.74} \text{ (CH}_2, \text{C);} \]
A solution of (1S,2S)-N,N-Dimethyl-N'-Phthaloyl-1,2-diaminocyclohexane (125) (0.64 g, 2.35 mmol) in ethanol (5 mL) was added hydrazine hydrate (0.29 mL, 2.20 mmol) at room temperature. The reaction mixture was then heated under reflux until complete disappearance of the starting material was observed (typically 1 h). After cooling the reaction mixture to room temperature, diethyl ether (30 mL) was added to the mixture and the resulting precipitate filtered. The filtrate was then evaporated to dryness to give the product as pale-yellow oil (0.20 g, 60%); \([\alpha]_{D}^{20} +32.0 \ (c \ 1.00, \ CHCl_3)\); \([\alpha]_{D}^{20} -36.0 \ (c \ 1.00, \ CHCl_3)\); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3360, 2926, 2778, 1574, 1450, 1376, 1338, 1268, 1167, 1098, 1057, 1035, 942, 871, 819; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta 0.91-1.08 \ (4 \ H, \ m, \ cyclohexyl \ protons), 1.51-1.65 \ (3 \ H, \ m, \ cyclohexyl \ proton), 1.79-1.83 \ (1 \ H, \ m, \ cyclohexyl \ protons), 1.89 \ (1 \ H, \ dt, \ J= 10.0 \ Hz, \ 3.2 \ Hz, \ CHN, H2), 2.09 \ (6 \ H, \ s, \ 2 \times \ CH_3, \ N(\text{CH}_3)_2), 2.33 \ (2 \ H, \ bs, \ NH_2), 2.43 \ (1 \ H, \ dt, \ J= 10.4 \ Hz, 4.4 \ Hz, \ CHNH_2, H1); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta 20.36 \ (\text{CH}_2, \ C5), 24.84 \ (\text{CH}_2, \ C4), 25.34 \ (\text{CH}_2, \ C3), 34.74 \ (\text{CH}_2, \ C6), 39.93 \ (2 \times \ CH_3, \ N(\text{CH}_3)_2), 51.11 \ (\text{CH}, \ C1), 69.45 \ (\text{CH}, \ C2).
5,7-Dihydro-dibenzo[c,e]oxepine (128): 22

A suspension of 2,2'-biphenyl dimethanol (127), (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 × 50 mL). The organic layers are then washed with brine (50 mL), saturated aqueous sodium hydrogen carbonate (50 mL), dried (Na₂SO₄) and the solvent removed under reduced pressure to afford the product as a colourless solid (3.25 g, 85%); m.p. 69-71 °C; νₘₐₓ(film)/cm⁻¹ 2852, 1652, 1558, 1447, 1376, 1198, 1072, 1046, 997, 903, 891, 753, 668; ¹H-NMR (400 MHz, CDCl₃):  δ 4.21 (4 H, s, 2 × CH₂OH), 7.23-7.48 (8 H, m, 8 × CH arom.); ¹³C-NMR (100 MHz, CDCl₃):  δ 67.84 (2 × Ar-Gl₂O), 127.61 (2 × CH arom., biphenyl), 128.52 (2 × CH arom., biphenyl), 129.01 (2 × CH arom., biphenyl), 129.93 (2 × CH arom., biphenyl), 135.20 (2 × C quat., arom., biphenyl), 141.43 (2 × C quat., arom., biphenyl); m/z (EI) 196.0884; C₁₄H₁₂O (M⁺) requires 196.0888.

2'-Bromomethyl-2-formyl-1,1'-biphenyl (129): 22

To an ice cooled solution of 5,7-dihydrodibenzo[c,e]oxepine (128) (5.00 g, 25.48 mmol), in carbon tetrachloride (50 mL), in a round bottom flask equipped with a reflux condenser was added molecular bromine (1.44 mL, 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 heated under reflux for 2 h. The solvent was evaporated under reduced pressure, and then diluted with diethyl ether (80 mL). The organic layer was washed with saturated aqueous sodium carbonate (2 x 50 mL), brine (2 x 30 mL), dried (Na₂SO₄) and the solvents removed under reduced pressure to yield a orange oil. Recrystallization from ethyl acetate/light petroleum afforded the product as colourless crystal. (4.20 g, 60%); m.p. 57-58 °C; νmax(nujol) /cm⁻¹ 3188, 1667, 1590, 1391, 1248, 1198, 774, 722, 632; ¹H-NMR (400 MHz, CDCl₃): δ 4.30 (2 H, dd, J= 40.0, 10.4 Hz, CH₂Br), 7.21 (1 H, dd, J= 7.4 Hz, 1.2 Hz, CH arom., biphenyl), 7.38 (1 H, ddd, J= 7.4 Hz, 7.4 Hz, 1.4 Hz, CH, arom., biphenyl), 7.40-7.47 (2 H, m. 2 × CH, arom., biphenyl), 7.54-7.47 (2 H, m. 2 × CH, arom., biphenyl), 7.67 (1 H, ddd, J= 7.4 Hz, 7.4 Hz, 1.4 Hz, CH, arom., biphenyl), 8.07 (1 H, ddd, J= 7.8 Hz, 1.4 Hz, 0.6 Hz, CH, arom., biphenyl), 9.73 (1 H, d, J= 0.8 Hz, HC=O); ¹³C-NMR (100 MHz, CDCl₃): δ 31.41, (CH₂Br), 127.63 (CH arom., biphenyl), 128.37 (CH arom., biphenyl), 128.55 (CH arom., biphenyl), 129.06 (CH arom., biphenyl), 130.67 (CH arom., biphenyl), 130.71 (CH arom., biphenyl), 131.05 (CH arom., biphenyl), 133.59 (CH arom., biphenyl), 134.10 (C quat., arom., biphenyl), 135.96 (C quat., arom., biphenyl), 137.83 (C quat., arom., biphenyl), 143.29 (C quat., arom., biphenyl), 191.73 (C quat., HC=O); m/z (EI) 275.9979; C₁₄H₁₁BrO (M⁺) requires 275.9974.

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

A solution of the amine (1 equivalent) in ethanol (10 mL per gram of amine), was added dropwise to an ice cooled solution of 2-[2-(bromomethyl)-phenyl]benzene carbaldehyde (1.10 equivalents) in ethanol (10 mL per gram carbaldehyde). The reaction mixture was stirred overnight while attaining ambient temperature. Sodium tetraphenylborate (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 few drops of 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.

(−)-2-[(4S,SS)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-5H-dibenzo[c,e]azepinium tetraphenylborate (94):23

Prepared according to the general procedure from L-acetonamine (71) (3.85 g, 18.8 mmol). The product was isolated as yellow powder (9.00 g, 68%); m.p. 185-187 °C; [α]²⁰°D -44.3 (c 1.00, CH₃CN); νmax(film)/cm⁻¹ 3051, 2975, 1630, 1479, 1447, 1382, 1264, 1202, 1114, 733, 704; ¹H-NMR (400 MHz, DMSO-d₆, 100 °C): δ 1.66 (3 H, s, CH₃, H7 or H8), 1.68 (3 H, s, CH₃, H7 or H8), 4.27 (1 H, d, J= 13.6 Hz, N-CHCHH-O, H6), 4.47 (1 H, d, J= 12.0 Hz, Ar-CHHN), 4.63-4.69 (2 H, m, NCH, H5 and N-CHCHH-O, H6'), 5.14 (1 H, d, J= 12.0 Hz, Ar-CHHN), 5.78 (1 H, d, J= 2.0 Hz, Ar-CH, H4), 6.72 (4 H, t, J= 7.2 Hz, 4 × CH arom., para in BPh₄ gp.), 6.84 (8 H, t, J= 7.2 Hz, arom., ortho in BPh₄ gp.), 7.06-7.20 (13 H, m, 8 H, m, 8 × CH arom., meta in BPh₄ gp. and 5 × CH arom. in Ph gp.), 7.53-7.64 (6 H, m, 6 × CH arom., biphenyl), 7.86-7.92 (2 H, m, 2 × CH arom., biphenyl), 9.03 (1 H, s, HC=NC);¹³C-NMR (100 MHz, DMSO-d₆, 100 °C): δ 18.22 (CH₃, C7 or C8), 28.73 (CH₃, C7 or C8), 54.03 (Ar-CH₂N), 60.82 (CH₂, C6), 66.10 (NCH, C5), 70.54 (Ar-CH, C4), 99.92 (C quat., C2), 120.76 (8 × CH arom., ortho in BPh₄ gp.), 124.45 (4 × CH arom., para in BPh₄
(1S,2S)-14,14-Dimethyl-9b,10,11,12,13,13a,14,14a-octahydro-9H-9a-aza-14-azonia-tribenzo[a,e,g]azulene tetraphenylborate (130):

Prepared according to the general procedure from (1S,2S)-N,N-dimethyl-1,2-diaminocyclohexane (126) (0.04 g, 0.28 mmol). The ammonium salt byproduct (130) was isolated as a yellow powder (0.13 g, 70%); m.p. 186-187 °C; [α]D +60.8 (c 1.00, CH3CN); Found: C, 85.99; H, 7.39; N, 4.34. C46H7BN2 requires C, 86.50; H, 7.42; N, 4.39%; νmax(film)/cm−1 3049, 2940, 1642, 1579, 1473, 1450, 1425, 1265, 1208, 1141, 736, 706, 612; 1H-NMR (400 MHz, acetonitrile-d3, −40 °C): δ 1.06-1.25 (4 H, m, cyclohexyl protons), 1.66-1.92 (4 H, m, cyclohexyl protons), 2.46 (6 H, s, 2 × CH3, N(CH3)2), 2.71 (1 H, bs, NCH, H1), 3.15 (1 H, t, J = 9.2 Hz, NCH, H2), 3.58 (1H, bs, ArCHHN), 3.81 (1 H, d, J = 15.2 Hz, ArCHHN), 5.57 (1 H, bs, ArCHN2), 6.74 (4 H, t, J = 7.2 Hz, 4 × CH arom., para in BPh4 gp.), 6.90 (8 H, t, J = 7.2 Hz, 8 × CH arom., ortho in BPh4 gp.), 7.17-7.20 (8 H, m, 8 × CH arom., meta in BPh4 gp.), 7.26-7.35 (2 H, m, 2 × CH arom., biphenyl), 7.38-7.54 (4 H, m, 4 × CH arom., biphenyl), 7.67-7.71 (2 H, m, 2 × CH arom., biphenyl); 13C-NMR (100 MHz, acetonitrile-d3): δ 22.06 (CH2, C3), 23.14 (CH2, C5), 23.69 (CH2, C4), 29.94 (CH2, C6), 41.48 (2 × CH3, N(CH3)2), 49.59 (CH2, ArCHN), 64.70 (CH, CHN, C1), 70.45 (CH, CHN, C2), 248
101.74 (CH, ArCHN₂), 121.68 (4 × CH arom., para in BPh₄ gp.), 125.27 (8 × CH arom., ortho in BPh₄ gp.), 126.33 (C quat., arom., biphenyl), 128.45 (CH arom., biphenyl), 128.62 (CH arom., biphenyl), 129.05 (CH arom., biphenyl), 129.30 (CH arom., biphenyl), 129.55 (CH arom., biphenyl), 131.19 (CH arom., biphenyl), 133.46 (CH arom., biphenyl), 134.22 (CH arom., biphenyl), 135.22 (C quat., arom., biphenyl), 135.37 (8 × CH arom., meta in BPh₄ gp.), 138.57 (C quat., arom., biphenyl), 141.77 (C quat., arom., biphenyl); m/z (El) 320.2257; C₂₂H₂₇N₂ (cation) requires 320.2253.

(1S,2S)-Bis-iminium salt (132):

Prepared according to the general procedure from (1S,2S)-diaminocyclohexane (122) (0.10 g, 0.88 mmol) except that 2.1 equivalents of 2-[2-(bromomethyl)phenyl]benzene carbaldehyde (129) was used. The product was isolated as yellow powder (0.51 g, 52%); m.p. 145-147 °C; [α]D²⁰ -170.2 (c 0.59, CH₃CN); νmax (film)/cm⁻¹ 3052, 2933, 1597, 1552, 1480, 1445, 1425, 1332, 1265, 1208, 761, 731, 705; ¹H-NMR (400 MHz, DMSO-d₆, 100 °C): δ 1.77 (2 H, d, J= 12.0 Hz, cyclohexyl protons), 2.01 (2 H, d, J= 8.0 Hz, cyclohexyl protons), 2.30 (2 H, d, J= 8.0 Hz, cyclohexyl protons), 2.51 (2 H, m, cyclohexyl protons), 4.71 (2 H, d, J= 12.0 Hz, ArCH₂N), 5.06 (2 H, d, J= 12.0 Hz, ArCH₂N), 5.71 (2 H, s, 2 × CHN, H₁, H₂), 6.83 (8 H, t, J= 7.2 Hz, 8 × CH arom., para in BPh₄ gp.), 6.97 (16 H, t, J= 7.2 Hz, 16 × CH arom., ortho in BPh₄ gp.), 7.17-7.26 (18 H, m, 2 × CH arom., biphenyl and 16 × CH arom., meta in BPh₄ gp.), 7.52 (4 H, bs, 4 × CH arom., biphenyl), 7.73-7.79 (4 H, m, 4 × CH arom., biphenyl), 7.87-8.06 (8 H, m, 8 × CH arom., biphenyl); ¹³C-NMR (100 MHz, DMSO-d₆, 100 °C): δ 24.03 (2 × CH₂, C₄, C₅), 32.09 (2 × CH₂, C₃, C₆), 55.00 (2 × CH₂, 2 × ArCH₂), 72.07 (2 × CH, 2 × CHN, C₁, C₂), 121.88 (8 × CH arom., para in BPh₄ gp.), 125.10 (2 × CH arom., biphenyl), 125.61 (16 × CH arom., ortho in BPh₄.
(R)-N-Allyl-2,7-dinaphtho[2,1-c;1',2'-e]azepine (134): \(^{24}\)

To a nitrogen purged stirred solution of (R)-2,2'-bis-bromomethyl-[1,1']binaphthalene (52\(_R\)) (2.00 g, 4.54 mmol) and triethylamine (1.90 mL, 13.62 mmol) in THF (10 mL) was added allylamine (0.58 mL, 7.72 mmol) at room temperature. The reaction mixture was then heated at 55 °C for 4 h after which starting material disappearance was observed by TLC. The mixture was diluted with dichloromethane (40 mL) and washed with water (2 × 30 mL), brine (2 × 30 mL). The organic phase was separated and dried (Na\(_2\)SO\(_4\)) and the solvent removed under reduced pressure. The resulting yellow residue was suspended in acetone (3 mL) and stirred for 5 minutes after which the precipitated crystals were collected by filtration and dried to yield the desired compound as colourless crystals (1.04 g, 68%); m.p. 175-177 °C [Lit.\(^{24}\) 177-178 °C]; [\(\alpha\)]\(_D\)\(^{20}\) \(-379.8\) (c 1.00, CHCl\(_3\)) [Lit.\(^{24}\) [\(\alpha\)]\(_D\)\(^{20}\) \(-396.3\) (c 0.24, CHCl\(_3\))]; \(v\)\(_{max}\) (film)/cm\(^{-1}\) 3048, 2935, 2801, 2363, 1593, 1507, 1461, 1367, 1335, 1237, 1094, 1062, 986, 816, 751, 732; \(1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 3.00-3.06 (2 \(H\), m, NCH\(_2\)CH, H\(_3\)), 3.08 (2 \(H\), d, \(J=12.4\) Hz, ArCH\(_2\)-N), 3.67 (2 \(H\), d, \(J=12.4\) Hz, ArCH\(_2\)-N), 5.14-5.23 (2 \(H\), m, CH=CH\(_2\), H\(_3\)), 5.88-5.98 (1 \(H\), m, NCHCH=CH\(_2\), H\(_2\)), 7.16-7.21 (2 \(H\), m, 2 × CH arom., binap-3,3'), 7.36-7.41 (4 \(H\), m, 4 × CH arom., binap-7,7′-8,8), 7.47 (2 \(H\), d, \(J=8.2\) Hz, 2 × CH arom., binap-4,4'), 7.87 (4 \(H\), d, \(J=8.2\) Hz, 2 × CH arom., binap-6,6′ and binap-9,9′); \(13\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 54.84 (2 × CH\(_2\), 2 × ArCH\(_2\)-N),
58.53 (CH$_2$, NCH$_2$-CH=CH$_2$, C1), 118.01 (CH$_2$, NCH$_2$-CH=CH$_2$, C3), 125.44 (2 × CH arom., *binap*-7,7'), 125.76 (2 × CH arom., *binap*-8,8'), 127.49 (2 × CH arom., *binap*-4,4'), 127.82 (2 × CH arom., *binap*-3,3'), 128.33 (4 × CH arom., *binap*-6,6' and *binap*-9,9'), 131.43 (2 × C quat., arom., *binap*-5,5'), 133.15 (2 × C quat., arom., *binap*-10,10'), 133.45 (2 × C quat., arom., *binap*-2,2'), 135.07 (2 × C quat., arom., *binap*-1,1'), 136.34 (CH, NCH$_2$-CH=CH$_2$, C2).

(R)-2,7-dinaphtho[2,1-c;1',2'-e]azepinium hydrochloride (135):

![Chemical structure of 135](image)

Under an atmosphere of nitrogen, 1,3-dimethylbarbituric acid (NDMBA, 0.23 g, 1.49 mmol), palladium (II) acetate (0.005 g, 0.02 mmol) and triphenyl phosphine (0.03 g, 0.10 mmol) were added in sequence to a solution of (R)-N-allyl-2,7-dinaphtho[2,1-c;1',2'-e]azepine (134) (0.33 g, 0.99 mmol) in dry dichloromethane (10 mL) at room temperature. The mixture was then stirred and heated at 35 °C for 6 h. The reaction mixture was then filtered through a pad of celite to remove the palladium residue. The mixture was then washed with 1 M NaOH (2 × 10 mL), water (2 × 10 mL), brine (2 × 20 mL) and dried (MgSO$_4$). 32% Hydrochloric acid (0.03 mL, 0.99 mmol) was added to the dichloromethane solution at room temperature. The stirring was continued for 5 minutes after which the solvent was removed under reduced pressure. The resulting residue was suspended in hot chloroform (5 mL) with stirring. The precipitated solid was filtered and washed with chloroform (5 mL) and dried *in vacuo* with heating (40 °C) to give the product as a colourless powder (0.29 g, 89%); m.p. 217-220 °C; [α]$_{D}^{20}$ -349.3 (c 1.08, MeOH); $v_{\text{max}}$(film)/cm$^{-1}$ 3415, 2933, 2737, 2588, 1677, 1592, 1507, 1446, 1364, 1336, 1264, 1213, 820, 749; $^1$H-NMR (400 MHz, CD$_3$OD): 8 3.71 (2 H, d, $J$= 13.2 Hz, ArCH$_2$-N), 4.39 (2 H, d, $J$= 13.2 Hz, ArCH$_2$-N), 7.29-7.35 (4 H, m, 4 × CH arom., *binap*-3,3'- *binap*-7,7'), 7.56 (2 H, ddd, $J$= 8.1 Hz, 5.8 Hz, 2.2 Hz, 2 × CH arom., *binap*-8,8'), 7.77 (2 H, d, $J$= 8.4 Hz, 2 × CH arom., *binap*-4,4'), 8.06 (2 H, d, $J$= 8.2 Hz, 2 × CH arom., *binap*-9,9'), 8.16 (2 H, d, $J$= 8.4 Hz, 2 × CH arom., *binap*-
6,6'), \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 47.11 (2 × CH\(_2\), 2 × ArCH\(_2\)-N), 127.91 (2 × CH arom., binap-7,7'), 128.12 (2 × CH arom., binap-8,8'), 128.24 (2 × CH arom., binap-4,4'), 128.29 (2 × CH arom., binap-9,9'), 129.32 (2 × C quat., arom., binap-5,5'), 129.77 (2 × CH arom., binap-6,6'), 131.15 (2 × CH arom., binap-3,3'), 132.55 (2 × C quat., arom., binap-10,10'), 135.72 (2 × C quat., arom., binap-2,2'), 136.79 (2 × C quat., arom., binap-1,1'); m/z (EI) 295.1359; C\(_{22}\)H\(_{18}\)N \([M-H]^+\) requires 295.1361.

General procedure for the synthesis of binaphthalene-derived amino-alcohols catalysts.

The primary amino alcohol (1.1 equivalent) was added to a nitrogen purged stirred solution of (R)-2,2'-bis-bromomethyl-[1,1']binaphthalene (52\(_R\)) (1.0 equivalent) and potassium carbonate (3 equivalents) in acetonitrile (10 mL per gram of dibromide) at room temperature. The reaction mixture was heated under reflux overnight or until starting material disappearance was observed by TLC. The mixture was diluted with dichloromethane (40 mL per gram of dibromide) and washed with water (2 × 30 mL per gram of dibromide) and brine (2 × 30 mL per gram of dibromide). The organic phase was separated, dried (Na\(_2\)SO\(_4\)) and the solvent removed \textit{in vacuo} to give the desired product.

\(N\)-(2(S)-(1-Hydroxy-propyl)-(R)-2,7-dinaphtho[2,1-c;1',2'-c]azepine (136):

\(52\(_R\)\)
Prepared according to the general procedure from L-alaninol (0.05 g, 0.68 mmol). The product was isolated as a colourless foam (0.24 g, 98%); [α]²⁰⁰D -356.2 (c 1.06, CHCl₃); νmax(film)/cm⁻¹ 3410 (OH), 3049, 2962, 1507, 1462, 1370, 1241, 1140, 1042, 908, 818, 732; ¹H-NMR (400 MHz, CDCl₃): δ 0.93 (3 H, d, J= 6.6 Hz, CH₃), 1.12 (1 H, t, J= 7.0 Hz, OH), 2.83-2.93 (1 H, m, NCH, H2), 3.38 (1 H, dd, J= 15.3 Hz, 2.9 Hz, CHHOH, H1), 3.40 (2 H, d, J= 12.5 Hz, ArCH₂N), 3.47 (1 H, dd, J= 15.3 Hz, 7.0 Hz, CHHOH, H1'), 3.62 (2 H, d, J= 12.5 Hz, ArCH₂N), 7.15 (2 H, ddd, J= 8.2 Hz, 8.0 Hz, 1.0 Hz, 2 × CH arom., binap-7,7'), 7.31 (2 H, d, J= 8.5 Hz, 2 × CH arom., binap-3,3'), 7.38 (2 H, ddd, J= 8.3 Hz, 8.0 Hz, 1.0 Hz, 2 × CH arom., binap-8,8'), 7.47 (2 H, d, J= 8.3 Hz, 2 × CH arom., binap-9,9'), 7.84 (2 H, d, J= 8.0 Hz, 2 × CH arom., binap-4,4'), 7.85 (2 H, d, J= 8.2 Hz, 2 × CH arom., binap-6,6'); ¹³C-NMR (100 MHz, CDCl₃): δ 12.57 (Gh, C3), 50.08 (2 × Oh, 2 × Ar-GhN), 58.80 (CH, NCH₂CH₃, C2), 62.46 (CH₂, CH₂OH, C1), 124.46 (2 × CH arom., binap-7,7'), 124.74 (2 × CH arom., binap-8,8'), 126.43 (2 × CH arom., binap-3,3'), 126.94 (2 × CH arom., binap-4,4'), 127.19 (2 × CH arom., binap-9,9'), 127.59 (2 × CH arom., binap-6,6'), 130.22 (2 × C quat., arom., binap-5,5'), 131.94 (2 × C quat., arom., binap-10,10'), 132.88 (2 × C quat., arom., binap-2,2'), 133.87 (2 × C quat., arom., binap-1,1'); m/z (El) 353.1772; C₂₅H₂₃NO (M⁺) requires 353.1780.

N-2(S)-(1-Hydroxy-phenylethyl)-(R)-2,7-dinaphtho[2,1-c;1',2'-e]azepine (137):

Prepared according to the general procedure from (S)-2-phenylglycinol (0.11 g, 0.79 mmol). The product was isolated as a colourless foam (0.32 g, 96%); [α]²⁰⁰D -388.5 (c 1.03, CHCl₃); νmax(film)/cm⁻¹ 3413 (OH), 3053, 2978, 1507, 1452, 1369, 1260, 1050, 907, 819, 752; ¹H-NMR (400 MHz, CDCl₃): δ 3.17 (2 H, d, J= 12.5 Hz, ArCH₂N), 3.67 (1 H, t, J= 5.6 Hz, NCH, H2), 3.71 (2 H, d, J= 12.5 Hz, ArCH₂N), 3.99 (2 H, J= 5.6 Hz, CH₂OH, H1), 7.14-7.27 (7 H, m, 7 × CH arom.), 7.35-7.39 (4 H, m, 4 ×
$CH$ arom.), 7.42 (2 H, d, $J=8.2$ Hz, 2 $\times CH$ arom.), 7.82 (2 H, d, $J=8.3$ Hz, 2 $\times CH$ arom.), 7.86 (2 H, d, $J=7.6$ Hz, 2 $\times CH$ arom.); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 51.81 (2 $\times CH_2$, 2 $\times Ar-CH_2N$), 62.92 (CH$_2$, CH$_2$OH, C1), 67.66 (CH, NCH, C2), 124.41 (2 $\times CH$ arom.), 124.69 (2 $\times CH$ arom.), 126.42 (2 $\times CH$ arom.), 126.66 (2 $\times CH$ arom.), 126.76 (CH arom., C8), 127.24 (2 $\times CH$ arom.), 127.35 (2 $\times CH$ arom.), 127.47 (2 $\times CH$ arom.), 127.61 (2 $\times CH$ arom.), 130.18 (2 $\times C$ quat., arom., $binap$), 132.03 (2 $\times C$ quat., arom., $binap$), 130.52 (2 $\times C$ quat., arom., $binap$), 134.05 (2 $\times C$ quat., arom., $binap$), 138.58 (C quat., arom., C3); m/z (EI) 415.1945; C$_{30}$H$_{25}$NO (M$^+$) requires 415.1936.

$N$-$2(S)-(1$-$Hydroxy$-$3$-$methylbutyl$)$-$R$)-2,7$-$dinaphtho[2,1$-$c$;$1'$$-$,2'$-$e]$-azepine (138):

![Diagram](52R_138)

Prepared according to the general procedure from $(S)$-2-amino-3-methyl-1-butanol (0.09 g, 0.91 mmol). The product was isolated as a colourless foam (0.34 g, 98%); $[\alpha]^D_0$ $-269.6$ (c 1.00, CHCl$_3$); $\nu_{\text{max}}$(film)/cm$^{-1}$: 3409 (OH), 2956, 1507, 1460, 1364, 1242, 1101, 1064, 1013, 908, 817, 752, 732; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 0.59 (3 H, d, $J=6.6$ Hz, CH$_3$, H4 or H5), 0.82 (3 H, d, $J=6.6$ Hz, CH$_3$, H4 or H5), 1.94-2.03 (1 H, m, CH(CH$_3$)$_2$, H3), 2.49 (1 H, ddd, $J=9.5$ Hz, 9.5 Hz, 5.0 Hz, NCH, H2), 3.23 (1 H, t, $J=9.5$ Hz, CHHOH, H1'), 3.58 (1 H, d, $J=9.5$ Hz, CHHOH, H1'), 3.60 (2 H, d, $J=12.2$ Hz, ArCH$_2$N), 3.68 (2 H, d, $J=12.2$ Hz, ArCH$_2$N), 7.17 (2 H, ddd, $J=8.3$ Hz, 6.8 Hz, 1.2 Hz, 2 $\times CH$ arom., $binap$-$7$, $7'$), 7.33 (2 H, d, $J=8.5$ Hz, 2 $\times CH$ arom., $binap$-$3$, $3'$), 7.38 (2 H, ddd, $J=8.3$ Hz, 6.8 Hz, 1.2 Hz, 2 $\times CH$ arom., $binap$-$8$, $8'$), 7.49 (2 H, d, $J=8.5$ Hz, 2 $\times CH$ arom., $binap$-$4$, $4'$), 7.86 (2 H, d, $J=8.3$ Hz, 2 $\times CH$ arom., $binap$-$9$, $9'$), 7.88 (2 H, d, $J=8.3$ Hz, 2 $\times CH$ arom., $binap$-$6$, $6'$); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 19.96 (CH$_3$, C4 or C5), 23.06 (CH$_3$, C4 or C5), 30.51 (CH, CH(CH$_3$)$_2$, C3), 52.17 (2 $\times CH_2$, 2 $\times Ar-CH_2N$), 60.22 (CH$_2$, CH$_2$OH, C1), 71.74 (CH, NCH, C2), 125.52 (2 $\times CH$ arom., $binap$-$7$, $7'$), 125.86 (2 $\times CH$ arom., $binap$-$8$, $8'$).
127.51 (4 × CH arom., \textit{binap}-3,3'-\textit{binap}-4,4'), 128.29 (2 × CH arom., \textit{binap}-6,6'), 129.00 (2 × CH arom., \textit{binap}-7,7'), 131.39 (2 × CH arom., \textit{binap}-5,5'), 132.97 (2 × CH arom., \textit{binap}-10,10'), 133.93 (2 × CH arom., \textit{binap}-2,2'), 134.98 (2 × CH arom., \textit{binap}-1,1'); m/z (FAB) 382.2177; C_{27}H_{27}NO [M+H]^+ requires 382.2171.

\textbf{\textit{N-2(S)-(1-Hydroxy-4-methylpentyl)-(R)-2,7-dinaphtho[2,1-c;1',2'-e]azepine}} (139):

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{139.png}
\caption{Structure of \textit{N-2(S)-(1-Hydroxy-4-methylpentyl)-(R)-2,7-dinaphtho[2,1-c;1',2'-e]azepine (139).}}
\end{figure}

Prepared according to the general procedure from (S)-2-amino-4-methyl-1-pentanol (0.11 g, 0.91 mmol). The product was isolated as a colourless foam (0.35 g, 98%); [\alpha]^{25D}_{D} = -236.2 (c 1.15, CHCl\_3); \nu_{\text{max}}(\text{film})/\text{cm}^{-1} 3403 (OH), 3050, 2952, 2865, 1594, 1461, 1360, 1143, 1102, 1032, 909, 817, 735; \textit{H}-NMR (400 MHz, CDCl\_3): \delta 0.77 (3 H, d, J= 6.0 Hz, CH\_3, H5 or H6), 0.82 (3 H, d, J= 6.0 Hz, CH\_3, H5 or H6), 1.20-1.37 (3 H, m, CH\_2CH(CH\_3)\_2, H3 and CH(CH\_3)\_2, H4), 2.93-3.00 (1 H, m, NCH, H2), 3.41 (1 H, t, J= 10.4 Hz, CH\_2OH, H1), 3.54-3.61 (3 H, m, CH\_2OH, H1' and ArCH\_2N), 3.69 (2 H, d, J= 12.8 Hz, ArCH\_2N), 7.23 (2 H, ddd, J= 8.2 Hz, 6.8 Hz, 1.2 Hz, 2 × CH arom., \textit{binap}-7,7'), 7.40 (2 H, d, J= 8.5 Hz, 2 × CH arom., \textit{binap}-3,3'), 7.38 (2 H, ddd, J= 8.1 Hz, 6.8 Hz, 1.2 Hz, 2 × CH arom., \textit{binap}-4,4'), 7.93 (2 H, d, J= 8.1 Hz, 2 × CH arom., \textit{binap}-9,9'), 7.95 (2 H, d, J= 8.2 Hz, 2 × CH arom., \textit{binap}-6,6'); \textit{C}-NMR (100 MHz, CDCl\_3): \delta 20.35 (CH\_3, C5 or C6), 22.02 (CH\_3, C5 or C6), 25.48 (CH\_3, CH(CH\_3)\_2, C4), 37.87 (CH\_2, C3), 51.21 (2 × CH\_2, 2 × Ar-CH\_2N), 61.77 (CH\_2, CH\_2OH, C1), 63.09 (CH, NCH, C2), 125.47 (2 × CH arom., \textit{binap}-7,7'), 125.75 (2 × CH arom., \textit{binap}-8,8'), 127.47 (2 × CH arom., \textit{binap}-3,3'), 127.97 (2 × CH arom., \textit{binap}-4,4'), 128.23 (2 × CH arom., \textit{binap}-9,9'), 128.68 (2 × CH arom., \textit{binap}-6,6'), 131.26 (2 × CH arom., \textit{binap}-5,5'), 132.96 (2 × CH arom., \textit{binap}-10,10'), 133.89 (2 × CH arom., \textit{binap}-2,2'), 134.84 (2 × CH arom., \textit{binap}-1,1'); m/z (FAB) 396.2334; C_{28}H_{29}NO [M+H]^+ requires 396.2327.
$N$-2($S$)-(1-Hydroxy-3,3-dimethyl-butyl)-(R)-2,7-dinaphtho[2,1-c;1',2'-e]azepine (140):

Prepared according to the general procedure from ($S$)-tert-leucinol (0.11 g, 0.91 mmol). The product was isolated as a colourless foam (0.35 g, 97%); $\left[\alpha\right]_{D}^{20} = -253.4$ (c 1.00, CHCl$_3$); $\nu_{\text{max}}$(film)/cm$^{-1}$ 3444 (OH), 3048, 2954, 1506, 1460, 1361, 1115, 1034, 994, 908, 816, 733; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 0.92 (9 H, s, C(CH$_3$)$_3$), 2.1 (1 H, dd, $J= 10.0$ Hz, 4.0 Hz, NCH, H2), 3.54-3.61 (4 H, m, CH$_2$OH, H1 and ArCH$_2$N), 3.70 (2 H, d, $J= 12.2$ Hz, ArCH$_2$N), 7.18 (2 H, ddd, $J= 8.2$ Hz, 6.8 Hz, 1.2 Hz, 2 $\times$ CH arom., binap-7,7'), 7.36 (2 H, ddd, $J= 8.3$ Hz, 6.8 Hz, 1.2 Hz, 2 $\times$ CH arom., binap-8,8'), 7.38 (2 H, d, $J= 8.4$ Hz, 2 $\times$ CH arom., binap-3,3'), 7.48 (2 H, d, $J= 8.4$ Hz, 2 $\times$ CH arom., binap-9,9'), 7.89 (2 H, d, $J= 8.2$ Hz, 2 $\times$ CH arom., binap-6,6'); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 28.34 (3 $\times$ CH$_3$, C(CH$_3$)$_3$), 36.75 (C quat., C(CH$_3$)$_3$), 54.48 (2 $\times$ CH$_2$, 2 $\times$ Ar-CH$_2$N), 59.36 (CH$_2$, CH$_2$OH, C1), 77.15 (CH, NCH, C2), 125.43 (2 $\times$ CH arom., binap-8,8'), 125.87 (2 $\times$ CH arom., binap-7,7'), 127.28 (2 $\times$ CH arom., binap-3,3'), 127.54 (2 $\times$ CH arom., binap-4,4'), 128.35 (2 $\times$ CH arom., binap-9,9'), 129.15 (2 $\times$ CH arom., binap-6,6'), 131.49 (2 $\times$ C quat., arom., binap-5,5'), 132.96 (2 $\times$ C quat., arom., binap-10,10'), 134.32 (2 $\times$ C quat., arom., binap-2,2'), 134.83 (2 $\times$ C quat., arom., binap-1,1'); m/z (FAB) 396.2321; C$_{28}$H$_{29}$NO $[M+H]^+$ requires 396.2327.
Binaphthalene-oxazolidine (141):

A byproduct of amine (140) when treated with Oxone or upon storage at room temperature in chloroform solution. The product was isolated as a colourless oil. 

$[\alpha]^2$D $-99.8$ (c 1.00, CHCl$_3$); $\nu_{\text{max}}$(film)/cm$^{-1}$ 3047, 2951, 1477, 1360, 1045, 814, 748; 

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 0.97 (9 H, s, C(CH$_3)_3$), 2.96 (1 H, t, $J$= 8.2 Hz, NCH, H2), 3.09 (1 H, t, $J$= 8.2 Hz, CHHO, H1), 3.23 (1 H, t, $J$= 8.2 Hz, CH/HO, H1'), 3.48 (1 H, d, $J$= 14.3 Hz, ArCHHN), 3.97 (1 H, d, $J$= 14.3 Hz, ArCHHN), 5.34 (1 H, s, ArCH), 7.20-7.25 (2 H, m, 2 $\times$ CH arom., binap), 7.38-7.49 (5 H, m, 5 $\times$ CH arom., binap), 7.58 (1 H, d, $J$= 8.7 Hz, 2 $\times$ CH arom., binap), 7.87 (1 H, d, $J$= 8.1 Hz, 2 $\times$ CH arom., binap), 7.91 (1 H, d, $J$= 8.2 Hz, 2 $\times$ CH arom., binap), 7.94 (1 H, d, $J$= 8.1 Hz, 2 $\times$ CH arom., binap), 7.96 (1 H, d, $J$= 8.2 Hz, 2 $\times$ CH arom., binap); 

$^1$H-NMR (100 MHz, CDCl$_3$): $\delta$ 26.23 (3 $\times$ CH$_3$, C(CH$_3)_3$), 34.49 (C quaternary, C(CH$_3)_3$), 57.27 (CH$_2$, ArCH$_2$N), 64.74 (CH$_2$, CH$_2$OH, C1), 71.43 (CH, NCH, C2), 97.96 (CH, ArCH), 125.23 (CH arom.), 125.60 (CH arom.), 125.90 (CH arom.), 126.05 (CH arom.), 126.84 (CH arom.), 127.36 (CH arom.), 127.49 (CH arom.), 127.75 (CH arom.), 128.02 (CH arom.), 128.13 (CH arom.), 128.17 (2 $\times$ CH arom.), 132.21 (C quaternary, arom.), 132.41 (C quaternary, arom.), 132.95 (C quaternary, arom.), 133.84 (C quaternary, arom.), 133.96 (C quaternary, arom.), 134.58 (C quaternary, arom.), 135.77 (C quaternary, arom.), 135.93 (C quaternary, arom.); 

$m/z$ (FAB) 394.2177; C$_{28}$H$_{27}$NO [M+H]$^+$ requires 394.2171.
General procedure for the synthesis of binaphthalene-derived amino-fluorides (1):

The binaphthalene-derived amino alcohol (1.0 equivalent) was dissolved in dry dichloromethane (10 mL per gram of starting material) and the solution cooled to 0 °C. Bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor) solution in toluene (1.05 equivalents) was added dropwise to the mixture. The yellowish reaction mixture was left to stir at room temperature for 16 h. Saturated sodium hydrogen carbonate (5 mL per gram of starting material) was added dropwise and the mixture transferred into a separatory funnel. The organic layer was washed with water (2 x 10 mL per gram starting material), brine (2 x 30 mL per gram of starting material), dried (Na₂SO₄) and the solvent removed in vacuo to give the desired crude product.

N-2(S)-(1-Fluoro-3-methylbutyl)-(R)-2,7-dinaphtho[2,1-c;1',2'-e]azepine (144):

Prepared according to the general procedure from compound (138) (0.32 g, 0.85 mmol). Column chromatography of the crude product using ethyl acetate/light petrol (1:5) afforded the product as colourless foam (0.22 g, 66%); [α]D²⁰ -364.0 (c 1.00, CHCl₃); vmax(film)/cm⁻¹ 2961, 2820, 1507, 1463, 1365, 1240, 1097, 1025, 909, 818, 734; ¹H-NMR (400 MHz, CDCl₃): δ 0.91 (6 H, dd, J= 6.8 Hz, 1.2 Hz, 2 x CH₃, H4 and H5), 1.78-1.87 (1 H, m, CH(CH₃)₂, H3), 2.43 (1 H, ddd, J= 42.0 Hz, 14.0 Hz, 1.8 Hz, CHHF, H1), 2.78 (1 H, ddd, J= 21.8 Hz, 14.0 Hz, 7.8 Hz, CHHF, H1'), 3.16 (2 H, d, J= 12.3 Hz, ArCH₂N), 3.75 (2 H, d, J= 12.3 Hz, ArCH₂N), 4.49 (1 H, ddd, J= 42.0
Hz, 5.4 Hz, 1.8 Hz, NCH, H2), 7.18 (2 H, ddd, J= 8.3 Hz, 6.9 Hz, 1.2 Hz, 2 × CH arom., binap-7,7'), 7.38 (2 H, ddd, J= 8.3 Hz, 6.8 Hz, 1.2 Hz, 2 × CH arom., binap-8,8'), 7.40 (2 H, d, J= 8.6 Hz, 2 × CH arom., binap-3,3'), 7.52 (2 H, d, J= 8.6 Hz, 2 × CH arom., binap-4,4'), 7.87 (4 H, d, J= 8.3 Hz, 4 × CH arom., binap-9,9'-binap-6,6');

13C-NMR (100 MHz, CDCl3): δ 16.89 (CH3, d, J= 6.7 Hz, C4 or C5), 18.65 (CH3, d, J= 6.7 Hz, C4 or C5), 31.73 (CH, d, J= 20.5 Hz, CH(CH3)2, C3), 55.62 (2 × CH2, d, J= 1.8 Hz, 2 × Ar-CH2N), 57.09 (CH2, d, J= 21.2 Hz, CH2F, C1), 97.86 (CH, d, J= 171.1 Hz, NCH, C2), 125.47 (2 × CH arom., binap-7,7'), 125.77 (2 × CH arom., binap-8,8'), 127.50 (2 × CH arom., binap-3,3'), 127.93 (2 × CH arom., binap-4,4'), 128.33 (2 × CH arom., binap-9,9'), 128.38 (2 × CH arom., binap-6,6'), 131.39 (2 × C quat., arom., binap-5,5'), 133.19 (2 × C quat., arom., binap-10,10'), 133.26 (2 × C quat., arom., binap-2,2'), 135.11 (2 × C quat., arom., binap-1,1'); m/z (FAB) 384.2132; C27H26NF [M+H]+ requires 384.2128.

N-2(S)-(1-Fluoro-3,3-dimethyl-butyl)-(R)-2,7-dinaphtho[2,1-c;1',2'-e]azepine (145):

Prepared according to the general procedure from compound (140) (0.16 g, 0.40 mmol). Column chromatography of the crude product using ethyl acetate/light petrol (1:5) afforded the product as colourless foam (0.10 g, 60%); [α]20D = −350.3 (c 1.00, CHCl3); νmax (film)/cm−1 3049, 2958, 1462, 1365, 1040, 909, 817, 751, 732; 1H-NMR (400 MHz, CDCl3): δ 0.97 (9 H, d, J= 1.2 Hz, 3 × CH3, C(CH3)3), 2.56 (1 H, ddd, J= 43.3 Hz, 14.1 Hz, 1.2 Hz, CHHF, H1), 2.77 (1 H, ddd, J= 22.2 Hz, 14.1 Hz, 8.1 Hz, CHHF, H1'), 3.23 (2 H, d, J= 12.3 Hz, ArCH2N), 3.86 (2 H, d, J= 12.3 Hz, ArCH2N), 4.45 (1 H, ddd, J= 43.3 Hz, 8.1 Hz, 1.2 Hz, NCHF, H2), 7.25 (2 H, ddd, J= 8.2 Hz, 7.0 Hz, 1.3 Hz, 2 × CH arom., binap-7,7'), 7.46 (2 H, ddd, J= 8.2 Hz, 7.0 Hz, 1.2 Hz, 2 × CH arom., binap-8,8'), 7.48 (2 H, d, J= 8.4 Hz, 2 × CH arom., binap-3,3'), 7.61 (2 H,
d, $J=8.4$ Hz, $2 \times CH$ arom., \textit{binap-4,4'}, 7.95 (4 H, d, $J=8.2$ Hz, $4 \times CH$ arom., \textit{binap-9,9'-binap-6,6'}), $^{13}$C-NMR (100 MHz, CDCl$_3$), $\delta$ 25.38 (3 $\times$ CH$_3$, d, $J=4.9$ Hz, C(CH$_3$_3)), 34.45 (C quat, d, $J=19.4$ Hz, C(CH$_3$_3)), 55.08 (CH$_2$, d, $J=21.5$ Hz, CH$_2$F, C1), 55.41 (2 $\times$ CH$_2$, d, $J=1.9$ Hz, $2 \times$ Ar-CH$_2$N), 100.43 (CH, d, $J=173.7$ Hz, NCH, C2), 125.42 (2 $\times$ CH arom., \textit{binap-7,7'}), 125.72 (2 $\times$ CH arom., \textit{binap-8,8'}), 127.47 (2 $\times$ CH arom., \textit{binap-3,3'}), 127.93 (2 $\times$ CH arom., \textit{binap-4,4'}), 128.30 (2 $\times$ CH arom., \textit{binap-9,9'}), 128.32 (2 $\times$ CH arom., \textit{binap-6,6'}), 131.35 (2 $\times$ C quat., arom., \textit{binap-5,5'}), 133.16 (2 $\times$ C quat., arom., \textit{binap-10,10'}), 133.18 (2 $\times$ C quat., arom., \textit{binap-2,2'}), 135.09 (2 $\times$ C quat., arom., \textit{binap-1,1'}); m/z (FAB) 398.2289; C$_{28}$H$_{28}$NF $\text{[M+H]}^+$ requires 398.2284.

**General procedure for the formation of enantiopure epoxides**

**Method A:**

Sodium carbonate (4 equivalents wrt alkene) was dissolved in water (1.7 mL) and the mixture cooled to 0 °C. Oxone (2 equivalents) was added as a solid to the cooled mixture and the resulting slurry was vigorously stirred at 0 °C for 5 minutes. To the mixture was added the catalyst (5 mol % wrt to alkene) dissolved in acetonitrile (0.85 mL), followed by a solution of the alkene (0.5 mmol) in acetonitrile (0.85 mL). The reaction mixture was stirred at 0 °C until complete conversion of the substrate was observed by TLC. Diethyl ether at 0-5 °C (20 mL) was added to the reaction mixture, followed by water at 0-5 °C (20 mL). The aqueous phase was extracted with diethyl ether (2 $\times$ 10 mL), and the combined organic extracts were washed with brine (2 $\times$ 20 mL), dried (Na$_2$SO$_4$) and the solvent removed \textit{in vacuo}. Pure epoxides were obtained by column chromatography using petroleum ether as eluent.

**Method B:**

A mixture of alkene (0.40 mmol, 1 equivalent) and catalyst (5 mol\%) was dissolved in acetonitrile (1 mL) and water (0.1 mL) and the mixture cooled to 0 °C. A mixture of Oxone (0.492 g, 0.8 mmol, 2 equivalents) and sodium hydrogen carbonate (0.168 g, 2.0 mmol, 5 equivalents) was added as a solid in one portion to the mixture with vigorous stirring. The mixture was stirred at 0 °C until complete conversion of the
alkene was observed by TLC. Diethyl ether (10 mL) was added, and the reaction mixture was filtered through a pad of mixed MgSO₄ and sodium bisulfite (NaHSO₃). The solvent was then removed in vacuo. Pure epoxides were obtained by column chromatography using petroleum ether as eluent.

**Alkene Synthesis:**

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

![Chemical structure](image)

The Cyclo-ketone (1.0 equivalent) in THF (10 mL per gram of substrate) was cooled to 0 °C and the appropriate Grignard reagent (freshly prepared, 2.0 equiv.) was added dropwise over 10 min. The reaction was stirred for 4 h and quenched by the addition of saturated aqueous ammonium chloride (1 mL per gram of substrate). Diethyl ether (4 mL per gram of substrate) was added to the reaction mixture; the organics were separated and dried (MgSO₄). Solvents were removed under reduced pressure to yield a crude oil, ca 95% pure. The crude product was then dissolved in chloroform (4 mL per gram of substrate) and cooled to 0 °C. TFA (4 equivalents) was then added in one portion and the reaction stirred for 5 minutes. The reaction was quenched by the dropwise addition of saturated aqueous sodium hydrogen carbonate (10 mL per gram of substrate). The organic layer was separated and washed with a further portion of saturated aqueous sodium hydrogen carbonate (10 mL per gram of substrate), brine (10 mL per gram of substrate) and dried (MgSO₄). Solvents were removed under reduced pressure to yield the desired product.
1-(4-(Methanesulfonyl)phenyl)cyclohexene (90):

Prepared according to the general procedure from cyclohexanone (86) (10.00 g, 101.90 mmol) giving the product as white solid (22.80 g, 95%); $\nu_{\text{max}}$(film)/cm$^{-1}$ 3035, 2928, 2879, 1718, 1596, 1410, 1348, 1237, 1130, 1089, 961, 832, 774, 688; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 1.68-1.71 (2 H, m, CH$_2$, H5), 1.81-1.84 (2 H, m, CH$_2$, H4), 2.23-2.27 (2 H, m, CH$_2$, H6), 2.28-2.44 (2 H, m, CH$_2$, H3), 3.07 (3 H, s, SO$_2$CH$_3$), 6.30 (1 H, septet, $J=1.6$ Hz, H2), 7.56 (2 H, d, $J=8.6$ Hz, 2 x CH arom., H8, H9); 7.88 (2 H, d, $J=8.6$ Hz, 2 x CH arom., H8, H9); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 21.83 (CH$_2$, C3), 22.78 (CH$_2$, C5), 26.00 (CH$_2$, C4), 27.19 (CH$_2$, C6), 44.64 (CH$_3$, SO$_2$CH$_3$), 125.65 (2 x CH arom., C10, C11), 127.37 (2 x CH arom., C8, C9), 128.60 (CH, C2), 135.35 (C quat., arom., C12), 138.01 (C quat., arom., C7), 148.15 (C quat., C1).

1-Phenyl-cycloheptene (93):

Prepared according to the general procedure from cycloheptanone (91) (10.00 g, 89.20 mmol) giving 1-Phenyl-cycloheptene as a pale yellow oil (14.90 g, 99%); $\nu_{\text{max}}$(neat)/cm$^{-1}$ 3078, 3054, 2926, 2848, 1700, 1596, 1490, 1444, 1354, 1281, 1076, 964, 853, 754, 699; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 1.45-1.51 (2 H, m, CH$_2$, H5), 1.54-1.60 (2 H, m, CH$_2$, H6), 1.73-1.79 (2 H, m, CH$_2$, H4), 2.21 (2 H, dd, $J=11.2$ Hz, 6.6 Hz, CH$_2$, H7), 2.52-2.55 (2 H, m, CH$_2$, H3), 6.02 (1 H, t, $J=6.6$ Hz, CH, H2), 7.10-7.26 (5 H, 5 x CH arom., Ph gp.); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 26.65 (CH$_2$, C7), 26.96 (CH$_2$, C4), 28.90 (CH$_2$, C6), 32.81 (CH$_2$, C5), 32.83 (CH$_2$, C3), 125.67 (2
General procedure for the formation of authentic racemic epoxides for ee determinations:

The alkene (1 equivalent) was dissolved in dichloromethane (10 mL per gram of alkene) and cooled to 0 °C. m-CPBA (2.5 equivalents) was also added as a solution in dichloromethane (10 mL per gram of alkene, pre-dried over MgSO₄) followed by NaHCO₃ (3 equivalents). The reaction was allowed to attain room temperature and stirred until starting material disappearance was observed by TLC. The reaction was then quenched with the addition of saturated sodium hydrogen carbonate (30 mL per gram alkene). The organic phase was washed with 1 M sodium hydroxide (2 × 20 mL per gram alkene) and dried (MgSO₄). The solvents were removed under reduced pressure and analytically pure samples of the epoxides were obtained through column chromatography (buffered with 2% triethylamine) using petroleum ether as the eluent.

trans-α-Methyl-stilbene oxide:

\[
\text{Ph} \quad \text{-CH=CH-Ph} \quad \xrightarrow{\text{oxidation}} \quad \text{Ph} \quad \overset{\text{O}}{\text{-CH(=O)-Ph}}
\]

Colourless oil; \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 3061, 1602, 1495, 1449, 1381, 1279, 1157, 1118, 1065, 1027, 980; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.46 (3 H, s, H3), 3.96 (1 H, s, H1), 7.30-7.46 (10 H, m, 10 × CH arom., 2 × Ph gp.); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 17.1 (CH\(_3\), C3), 63.5 (C quat., C2), 67.5 (CH, C1), [125.6, 126.9, 127.7, 127.9, 128.6, 129.2 (10 × CH arom.), 136.4, 142.8 (2 × C quat., arom.) 2 × Ph gp.].

Triphenylethylene oxide:

\[
\text{Ph} \quad \text{-CH=CH-Ph} \quad \xrightarrow{\text{oxidation}} \quad \text{Ph} \quad \overset{\text{O}}{\text{-CH(=O)-Ph}}
\]
Colourless oil which slowly solidified, m.p. 66-67 °C; [Lit. 27 75 °C]; $v_{\text{max}}$(film)/cm$^{-1}$ 3062, 3030, 2957, 2925, 2856, 1605, 1596, 1499, 1471, 1448, 1262, 1221, 741, 698; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 4.40 (1 H, m, PhCH), 7.10-7.47 (15H, m, 3 × Ph gp.);
$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 68.00 (CH, PhCH), [68.33 (C quat., Ph$_2$C), 126.36, 126.82, 127.51, 127.64, 127.78, 127.84, 128.00, 128.26, 128.65 (15 × CH arom.)].
135.42, 135.93, 141.17, (3 × C quat., arom.) 3 × Ph gp.].

1-Phenylcyclohex-1-ene oxide: 28

![Diagram of 1-Phenylcyclohex-1-ene oxide]

Colourless oil; $v_{\text{max}}$(neat)/cm$^{-1}$ 3084, 1602, 1495, 1446, 1359, 1249, 1173, 1132, 1079, 1030, 993, 974; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ [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) H3, H4, H5 & H6]], 3.10 (1 H, t, $J$ = 2.0 Hz, CH, H2), 7.28-7.44 (5 H, m, arom., Ph gp.); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ [19.83, 20.14, 24.70, 28.23 (4 × CH$_2$, C3, C4, C5, C6)], 60.15 (C quat., C1), 61.89 (CH, C2), 125.32 (2 × CH arom., ortho in Ph gp.), 127.14 (CH arom., para in Ph gp.), 128.27 (2 × CH arom., meta in Ph gp.), 142.81 (C quat., arom., ipso in Ph gp.).

1-Phenyl-3,4-dihyronaphthalene oxide: 28

![Diagram of 1-Phenyl-3,4-dihyronaphthalene oxide]

Colourless solid; m.p. 104-106 °C; [Lit. 28 94-97 °C]; $v_{\text{max}}$ (film)/cm$^{-1}$ 1602, 1486, 1307, 1155, 1074, 1042, 953; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 2.10, (1 H, td, $J$ = 13.7 Hz, 5.6 Hz, HCH, H3), 2.49-2.60 (1 H, m, HCH, H4), 2.77 (1 H, dd, $J$ = 13.7 Hz, 5.6 Hz, HCH, H3), 2.98-3.06 (1 H, m, HCH, H4), 3.71 (1 H, d, $J$ = 3.1 Hz, H2), [7.11-7.31 (4 H, m, arom.), 7.45-7.61 (5 H, m, arom.), 9 × CH at H6, 7, 8, 9 & Ph gp.]; $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 22.18 (CH$_2$, C4), 25.42 (CH$_2$, C3), 60.91 (C quat., C1), 63.07
trans-Stilbene oxide: 29

\[
\begin{align*}
\text{Ph} & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \q
1-(4-(Methanesulfonyl)phenyl)-cyclohexene oxide (1):

![Chemical structure]

Colourless oil; \(v_{\text{max}}\) (neat) cm\(^{-1}\) 2935, 1405, 1307, 1218, 1149, 1089, 961, 832, 770; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.32-1.64 (4 H, m, 2 \(\times\) CH\(_2\), H4, H5), 2.00-2.04 (2 H, m, CH\(_2\), H3), 2.12 (1 H, ddd, \(J=\) 14.7 Hz, 8.4 Hz, 5.4 Hz, CHH, H6), 2.31 (1 H, ddd, \(J=\) 14.7 Hz, 8.4 Hz, 5.4 Hz, CHH, H6'), 3.05 (4 H, s, SO\(_2\)CH\(_3\) and CHO, H2), 7.58 (2 H, d, \(J=\) 8.6 Hz, H8, H9), 7.91 (2 H, d, \(J=\) 8.6 Hz, H10, H11); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 19.50 (CH\(_2\), C5), 19.88 (CH\(_2\), C4), 24.83 (CH\(_2\), C3), 28.14 (CH\(_2\), C6), 44.42 (CH\(_3\), SO\(_2\)CH\(_3\)), 59.82 (C quat., C1), 62.22 (CH, CHO, C2), 126.40 (2 \(\times\) CH arom., C10, C11), 127.44 (2 \(\times\) CH arom., C8, C9), 139.20 (C quat., arom., C12), 148.88 (C quat., arom., C7).

1-(4-Methoxyphenyl)-cyclohexene oxide (2):

![Chemical structure]

Colourless oil; \(v_{\text{max}}\) (neat) cm\(^{-1}\) 2932, 2853, 1721, 1609, 1511, 1449, 1248, 1179, 1034, 828, 751; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.29-1.57 (4 H, m, 2 \(\times\) CH\(_2\), H4, H5), 1.96-2.00 (2 H, m, CH\(_2\), H3), 2.10 (1 H, ddd, \(J=\) 14.6 Hz, 8.6 Hz, 5.3 Hz, CHH, H6), 2.23 (1 H, ddd, \(J=\) 14.6 Hz, 8.6 Hz, 5.3 Hz, CHH, H6'), 3.06 (1 H, t, \(J=\) 2.1 Hz, CHO, H2), 3.79 (3 H, s, ArOCH\(_3\)), 6.87 (2 H, d, \(J=\) 8.8 Hz, H10, H11), 7.29 (2 H, d, \(J=\) 8.8 Hz, H8, H9); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 19.20 (CH\(_2\), C5), 20.00 (CH\(_2\), C4), 24.72 (CH\(_2\), C3), 28.66 (CH\(_2\), C6), 55.25 (CH\(_3\), ArOCH\(_3\)), 59.80 (C quat., C1), 61.78 (CH, CHO, C2), 113.61 (2 \(\times\) CH arom., C10, C11), 126.50 (2 \(\times\) CH arom., C8, C9), 134.61 (C quat., arom., C7), 158.75 (C quat., arom., C12).
3.3 Chapter Three References

4 The mp and [α]D values of 17R recorded in Aldrich catalogue are cited as authentic ones.
9 Aldrich catalogue 2006, 520.
19 Aldrich catalogue, 2006, 804.


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 (15), Dr M. R. J. Elsegood (101).

Crystal data and structure refinement for (1S,2R)-N-(Benzyloxycarbonyl)-2-amino-1-(4-(methanesulfonyl)phenyl)-3-methyl-1,3-butanediol (15):

<table>
<thead>
<tr>
<th>Identification code</th>
<th>pcbp55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C20 H25 N O6 S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>407.47</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2(1)2(1)2(1)</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 8.1932(5) Å, α = 90°, b = 9.7165(6) Å, β = 90°, c = 26.2969(16) Å, γ = 90°</td>
</tr>
<tr>
<td>Volume</td>
<td>2093.5(2) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.293 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.190 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>864</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.35 x 0.32 x 0.25 mm³</td>
</tr>
<tr>
<td>Crystal description</td>
<td>colourless trigonal prism</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>1.55 to 28.86°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-10&lt;=h&lt;=10, -12&lt;=k&lt;=12, -34&lt;=l&lt;=34</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>18081</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>4981 [R(int) = 0.0221]</td>
</tr>
<tr>
<td>Completeness to theta = 25.00°</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>
Absorption correction  Semi-empirical from equivalents
Max. and min. transmission  1.00000 and 0.909190
Refinement method  Full-matrix least-squares on F^2
Data / restraints / parameters  4981 / 0 / 262
Goodness-of-fit on F^2  1.045
Final R indices [I>2sigma(I)]  R1 = 0.0371, wR2 = 0.0929
R indices (all data)  R1 = 0.0418, wR2 = 0.0962
Absolute structure parameter  0.03(6)
Largest diff. peak and hole  0.309 and -0.229 e.Å^-3

Crystal data and structure refinement for 3,3'-Dibromo-5,5'-di-tert-butyl-4,4'-
dihydroxy-2,2'-dimethyl-1,1'-biphenyl (101):

Data collection method  Bruker SMART 1000 diffractometer
Chemical formula  C_{22}H_{28}Br_{2}O_{2}
Formula weight  484.26
Temperature  150(2) K
Radiation, wavelength  MoKα, 0.71073 Å
Crystal system, space group  triclinic, P ̅ 1
Unit cell parameters  
\[\begin{align*}
    a &= 8.4330(5) \text{ Å} \\
    b &= 11.2668(7) \text{ Å} \\
    c &= 24.0261(14) \text{ Å}
\end{align*}\]
\[\begin{align*}
    \alpha &= 92.731(2)^\circ \\
    \beta &= 98.376(2)^\circ \\
    \gamma &= 102.723(2)^\circ
\end{align*}\]
Cell volume  2195.5(2) Å^3
Z  4
Calculated density  1.465 g/cm^3
Absorption coefficient μ  3.705 mm^-1
F(000)  984
Crystal colour and size  colourless, 0.52 × 0.29 × 0.13 mm^3
Reflections for cell refinement  6199 (θ range 2.51 to 28.28°)
Data collection method  Bruker APEX 2 CCD diffractometer
θ range for data collection  1.72 to 28.84°
Index ranges
Completeness to $\theta = 27.50^\circ$ 99.5%
Intensity decay 0%
Reflections collected 23572
Independent reflections 11380 ($R_{int} = 0.0356$)
Reflections with $F^2 > 2\sigma$ 8281
Absorption correction semi-empirical from equivalents
Min. and max. transmission 0.239 and 0.619
Structure solution Patterson synthesis
Refinement method Full-matrix least-squares on $F^2$
Weighting parameters a, b 0.0433, 0.0000
Data / restraints / parameters 11380 / 0 / 489
Final R indices [$F^2 > 2\sigma$] $R_1 = 0.0372$, $wR_2 = 0.0835$
R indices (all data) $R_1 = 0.0624$, $wR_2 = 0.0924$
Goodness-of-fit on $F^2$ 0.999
Largest and mean shift/au 0.002 and 0.000
Largest diff. peak and hole 0.741 and $-0.528$ eÅ$^{-3}$
Appendix B

Determination of enantiomeric excess: Examples

Determination of enantiomeric excess of 1-phenylcyclohexene oxide by gc ChiralDEX B-DM column. Oven temperature 120 °C

Racemic material:
Determination of enantiomeric excess of 1-phenylecyclohexene oxide by gc; catalyst (84): ChiralDEX B-DM column. Oven temperature 120 °C

Determination of enantiomeric excess of 1-phenylecyclohexene oxide by gc; catalyst (82): ChiralDEX B-DM column. Oven temperature 120 °C
Determination of enantiomeric excess of methyl stilbene oxide by NMR spectroscopy

$^1$H-NMR conditions: 8-10 mg substrate; 3-5 mg (+)-Eu(hfc)$_3$

solvent: CDCl$_3$

Racemic material:

![NMR spectra of racemic material](image)

Determination of enantiomeric excess of methyl stilbene oxide by NMR; catalyst (82):

![NMR spectra with catalyst](image)
Determination of enantiomeric excess of *trans*-α-methyl stilbene oxide by hplc

HPLC conditions:
- Flow: 1.0
- CS: 0.5
- Atten: 512
- Hex:IPA 80:20

Racemic material: Retention times: \((S,S) = 7.96\); \((R,R) = 12.84\).

Determination of enantiomeric excess of *trans*-α-methyl stilbene oxide by hplc; catalyst (80):

Retention times: \((S,S) = 7.92\); \((R,R) = 12.90\).
Determination of enantiomeric excess of trans-α-methyl stilbene oxide by HPLC; catalyst (81):

Retention times: (S,S) = 7.94; (R,R) = 12.85.
Determination of enantiomeric excess of triphenylethylene oxide by NMR spectroscopy

$^1$H-NMR conditions: 8-10 mg substrate; 3-5 mg (+)-Eu(hfc)$_3$
solvent: CDCl$_3$

Racemic material:

![NMR spectrum diagram]

Determination of enantiomeric excess of triphenylethylene oxide by NMR; catalyst (82):

![NMR spectrum diagram]
Determination of enantiomeric excess of triphenylethylene oxide by HPLC; catalyst (80):

HPLC conditions:
- Flow: 1.0
- CS: 0.5
- Atten: 512
- Hex: IPA 80:20

Determination of enantiomeric excess of triphenylethylene oxide by HPLC; catalyst (81):
Determination of enantiomeric excess of *trans*-stilbene oxide by HPLC

HPLC conditions:
- Flow: 1.0
- CS: 0.5
- Atten: 512
- Hex:IPA 80:20

Racemic material: Retention times: \((S,S) = 12.46; (R,R) = 16.20\).

Determination of enantiomeric excess of *trans*-stilbene oxide by HPLC; catalyst (82):
Retention times: \((S,S) = 12.08; (R,R) = 15.71\).
Determination of enantiomeric excess for 1-phenylcycloheptene oxide by gc ChiralDEX B-DM column; Oven temperature 130 °C

Racemic material: Retention times: \((1R,2S) = 38.01; (1S,2R) = 39.52\)

Determination of enantiomeric excess for 1-phenylcycloheptene oxide by gc; catalyst (82):
Retention times: \((1R,2S) = 38.23; (1S,2R) = 39.98\)
Determination of enantiomeric excess of dihydronaphthalene oxide by gc: Chiraldex B-DM column; Oven temperature 120 °C
Racemic material:

Retention times: \((1R,2S) = 18.37\); \((1S,2R) = 20.36\).
Determination of enantiomeric excess for 1-phenyldihyronaphthalene oxide by hplc

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

Racemic material: Retention times: \((1R,2S) = 9.26; (1S,2R) = 12.24\).