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New systems for catalytic asymmetric epoxidation

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NEW SYSTEMS FOR CATALYTIC ASYMMETRIC EPOXIDATION

By

© Phillip Parker MChem, AMRSC.

A Doctoral Thesis

Submitted in partial fulfilment of the requirements for the award of

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Department of Chemistry

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Supervised by

Professor Philip C. Bulman Page B.Sc., Ph.D., D.I.C., FRSC

ABSTRACT

New systems for catalytic asymmetric epoxidation

Phillip Parker

Key Words: Epoxidation, Alkene, Asymmetric Synthesis, Iminium salt, Oxaziridinium salt, Oxone, Hydrogen Peroxide, Sodium Hypochlorite, Oxidation, Organocatalysis, Catalysis

This thesis describes the catalytic asymmetric epoxidation of olefins mediated by chiral iminum salts. The first chapter introduces some of the most novel and effective catalytic asymmetric methods for preparing chiral oxiranes.

The second chapter is divided into three sections. The first section of chapter two is dedicated to our efforts to develop new aqueous oxidative conditions using both hydrogen peroxide and sodium hypochlorite as efficient, green oxidants that remove the temperature boundaries observed with the use of Oxone® as the stoichiometric oxidant. A wider range of available temperatures was examined allowing optimization of both oxidative systems. Ethereal hydrogen peroxide was observed to mediate asymmetric epoxidation within an acetonitrile monophasic co-solvent system giving enantioselectivities of up to 56%. When sodium hypochlorite was used in a biphasic solvent system in conjunction with dichloromethane; it was observed to mediate oxidation of the substrate alkenes in up to 71% ee.

The second and third sections of chapter two are dedicated to our efforts to synthesize chiral iminium salts as catalysts for asymmetric epoxidation based on a biphenyl azepinium salt catalyst structure.

From previous work within the Page group, the asymmetric synthesis and subsequent defined stereochemistry of a chiral carbon atom α to the iminium nitrogen atom was shown to have significant effect on the enantiocontrol of epoxidation using the iminium salt catalyst. Work was completed on biphenyl azepinium salt catalysts, inserting an alkyl or aryl Grignard reagent into the iminium bond using a pre-defined dioxane unit as a chiral auxiliary. Oxidation of the subsequent azepine gave a single diastereoisomerically pure azepinium salt. The methyl analogue of this sub-family of azepinium catalysts has been shown to give up to 81% *ee* for epoxidation of 1-phenylcyclohexene, furthermore, the binaphthalene azepinium salt with an additional methyl group was also synthesized and was shown to give up to 93% for epoxidation of 1-phenylcyclohexene.

Continuation of the substitution α to the nitrogen atom gave rise to an interesting tetracyclic (biphenyl) azepinum salt catalyst. Construction of an asymmetric oxazolidine ring unit encapsulating the azepinium nitrogen and one of the methylene carbon atoms was achieved. In doing so two chiral centres α to the nitrogen atom were generated. The azepinium chiral carbon atom was populated by an addition methyl group with variation in the substitution on the oxazolidine chiral carbon atom. The benzyl analogue of this sub-family of tetracyclic azepinium catalysts has shown to give up to 79% *ee* for epoxidation 1-phenylcyclohexene.

The third chapter is the experimental section and is dedicated to the methods of synthesis and characterization of the compounds mentioned in the previous chapter.

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

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And finally I should like to thank my amazing wife Rachel for her patience and love; without her support I can honestly say I would not be the person I am today, I would not be in a position to submit my thesis as I do now. Thank you for giving me a beautiful son, Reece, you are my rock on which I depend, I love you.

ABBREVIATIONS

Å	Angström
Ac	acetyl
AcCl	acetyl chloride
AIBN	2,2’-azobis(isobutyronitrile)
aq.	aqueous
Ar	aromatic
BINAP	binaphthalene
BINOL	1,1’bi(2-napthol)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
n-butyl	normal butyl
t-butyl	*tert*-butyl
°C	degrees celsius
c	concentration
cm^{-1}	wavenumber
conc.	concentrated
conv.	conversion
CSA	10-camphorsulphonic acid
δ	chemical shift
d	*dextrorotatory* (optical rotation)
D	*dextro* (Fischer projection)
DCM	methylene chloride
DET	diethyl tartrate
DIPEA	diethylpropylamine
DIPT	diisopropyl tartrate
DMP	2,2-dimethoxypropane
DPPF	1,1'-bis(diphenylphosphino)ferrocene
DPPP	bis(diphenylphosphino)propane
dr	diastereoisomeric ratio
ee	enantiomeric excess
equiv.	equivalent(s)
Et	ethyl

Et_3N	triethylamine
g	gram(s)
GC-FID	gas chromatography, flame ionisation detector
h	hour(s)
hfc	(heptafluoropropylhydroxymethylene)camphorato
J	coupling constant
l	*laevorotatory* (optical rotation)
L	*laevo* (Fischer projection)
LCMS	liquid chromatography mass spectroscopy
m-CPBA	*m*-chloroperbenzoic acid
Me	methyl
MHz	mega hertz
min	minute(s)
mmol	milli-moles
mL	milli-litres
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
NBS	*N*-bromosuccinamide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Oxone®	potassium monoperoxysulphate ($KHSO_4 \cdot K2SO4 \cdot 2KHSO_5$)
Pd(DPPF)	paladium (1,1'-bis(diphenylphosphino)ferrocene)
Ph	phenyl
Pg	protecting group
ppm	parts per million
PTC	phase-transfer catalyst
^{i}Pr	isopropyl
*p*TSA	toluene- *para*-sulphonic acid
quat.	quaternary
R	alkyl
re	*rectus*, stereochemical descriptor
RDS	rate determining step
R_f	retention factor
rt	room temperature

si	*sinister*, stereochemical descriptor
SM	starting material
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butylhydroperoxide
TBME	*tert*-butylmethyl ether
Tf	trifluoromethansulphonyl
TEA	Triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
TPPP	tetraphenylphosphonium monoperoxysulfate
Tr	trityl (triphenylmethyl)
Ts	toluenesulfonyl
U.V.	ultraviolet

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Chapter One:

Introduction

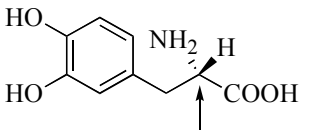
1 Introduction

"The universe is dissymmetrical; for if the whole of the bodies which compose the solar system were placed before a glass moving with their individual movements, the image in the glass could not be superimposed on reality…….. Life is dominated by dissymmetrical actions. I can foresee that all living species are primordially, on their structure, in their external generates functions of cosmic dissymmetry."

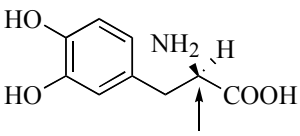
– Louis Pasteur, 1848[1]

1.1 Asymmetric synthesis

Louis Pasteur identified that all living organisms, as well as the molecules they house, can be 'dissymmetrical'. Dissymmetry, or asymmetry is the lack of equivalence between two objects, this is the case for carbon atoms containing four in–equivalent groups. The central carbon atom is deemed chiral and chirality is one of the most fundamental concepts in chemistry.



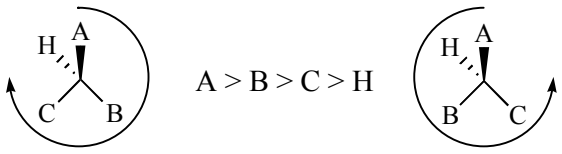
1, L-DOPA



2, D-DOPA

Chiral comes from the Greek word '*cheir'* which in English translates as 'hand'. A pair of hands are mirror images of one another, they cannot be superimposed. Chiral molecules also behave in this way. Molecule **1** can be reflected in a mirror and observed as a molecule identical to **2**. Both **1** and **2** have identical physical and chemical identities, melting point, boiling point and molecular weight etc, all except their conformation in space. This means that **1** cannot be superimposed on **2**. Molecules exhibiting this characteristic such as **1** and **2** are named enantiomers, the central carbon atom in each molecule is deemed chiral.

The general nomenclature for two enantiomers at a chiral carbon atom is the *R* and *S* notation. *R* is the notation for *rectus*, Latin for right and *S* is the notation for *sinister*, Latin for left. Figures **3** and **4** are an example of *R* and *S* enantiomers. The notation of each chiral carbon is denoted *via* the Cahn–Ingold–Prelog rules; the atom with the lowest atomic number attached to the central carbon is held furthest from the eye through the central carbon atom, the three remaining atoms are ranked A, B and C by the value of its atomic number (high to low). The *R* enantiomer, **3**, has the configuration that rotates clockwise through the three largest atoms, whereas the *S* enantiomer, **4**, rotates through the same atoms in an anti–clockwise direction.[2]



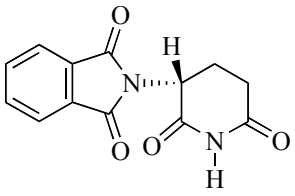
3, R–enantiomer ***4, S–enantiomer***

In the human body, enantiomers may work as independent chemical entities to one another as they can be absorbed, activated and degraded in different ways and at different rates. Cell membranes and enzymes in the human body contain protein receptors made of chiral amino acids.[1] The chiral receptors operate using a "lock and key" mechanism, in which the receptors are able to distinguish between individual enantiomers and they preferentially interact with the enantiomer that has the desired chirality, fitting together as a "lock and key". This allows the receptor to initialise a chemical process, a bodily function or initiate therapeutic effects. If the chiral receptor were to interact with the opposite enantiomer no response may occur, but ultimately a detrimental response may also occur. Therefore the preferred enantiomer can show increased activity over its enantiomer, whether it be higher levels of therapeutic effectiveness or oppositely higher levels of toxicity.[1]

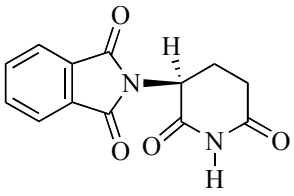
Two examples of chiral drug recognition are *L*-DOPA and *R*–thalidomide. Emil Fischer devised the *D* and *L* nomenclature when attempting to identify unknown enantiomers of common amino acids and sugars. He portrayed glyceraldehyde in its Fischer projection and gave each enantiomer a notation: the (+)-enantiomer was labelled *D* for *dextro* and

the (–)-enantiomer was labelled *L* for *laevo.* In 1951 it was proven that the *D* enantiomer actually had the *R* absolute configuration, and consequently *L* was *S*.[1]

L-DOPA, **1**, is used in the treatment of Parkinson's disease. *L*-DOPA is administered into the body as a 'pro-drug' as dopamine itself cannot cross the blood brain barrier.[3] When *L*-DOPA is taken into brain cells it is automatically converted to dopamine by enzyme catalysed *in–vivo* decarboxylation. The enzyme used is *L*-DOPA decarboxylase; this is a chiral enzyme and enantiomer specific; it will not convert *D*-DOPA, **2**, into dopamine. Therefore the administration of DOPA must be exclusively in the *L* form, as the *D* form will not be converted into the required drug dopamine, and a build up of *D*-DOPA can become toxic inside the human body.



5, R–Thalidomide



6, S–Thalidomide

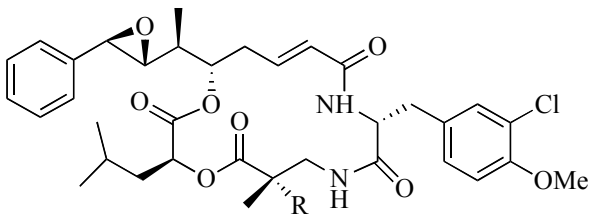
The second and far more serious example is in the case of *R* and *S*–thalidomide, **5** and **6**. Thalidomide was discovered in the 1950's as a powerful sedative and anti–nausea drug that could have great potential in early pregnancy sickness. Unbeknown at the time, one enantiomer was a powerful teratogen, which causes extremely harmful effects on a growing foetus.[4] A *racemic* mixture, a 50% mixture of both enantiomers, was given to the pregnant mothers, and upon the birth of their babies, teratogenic effects were observed affecting the growth of the new born baby's limbs. After extensive testing it was found that *R*–thalidomide was the active and therapeutic drug that showed no teratogenic effects even in high concentrations, whereas *S*–thalidomide was shown to be the teratogen and had little sedative and anti–nausea effect.

As observed from these two examples, when designing drugs and utilising natural products, stereo-discrimination is essential to produce enantiomerically pure compounds

that can be used for human and animal consumption. Due to the inactivity or adverse effects shown by racemic drugs, stringent rules have been imposed over monitoring, regulation and testing. In 2002, 36% of the worldwide pharmacy market consisted of chiral drugs, amounting to >$140 billion.[5]

1.2 Epoxides

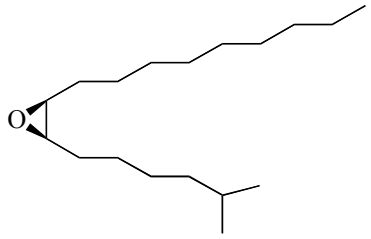
Epoxides are a sub–class of ethers in that they contain the C–O–C unit, but they are configured in a three membered heterocyclic ring system.[6] Due to the epoxides heterocyclic structure, which is analogous to cyclopropane and aziridines, it is highly strained, with bond angles at approximately sixty degrees. Therefore epoxides undergo facile ring opening with even the weakest of nucleophiles to generate compounds with stereo- and regio- selective functionality, with the driving force behind the ring opening being the relief of the epoxides highly strained cyclic system.[7] Asymmetric epoxidation is an example of asymmetric catalysis that is being developed by multinational research groups.[8,9,10,11] The development of enantioselective catalysts enable the generation of one 'major' epoxide enantiomer. This, in turn, will enable the highly enantioselective construction of many natural products that contain an epoxide unit.



7, cryptophycin 1: R = H

8, cryptophycin 52: R = Me

Cryptophycin 1 and 52 (**7** & **8**) are two examples of natural products containing an epoxide functionality that exhibits cytotoxic activity against malignant tumours in the human body.[12]



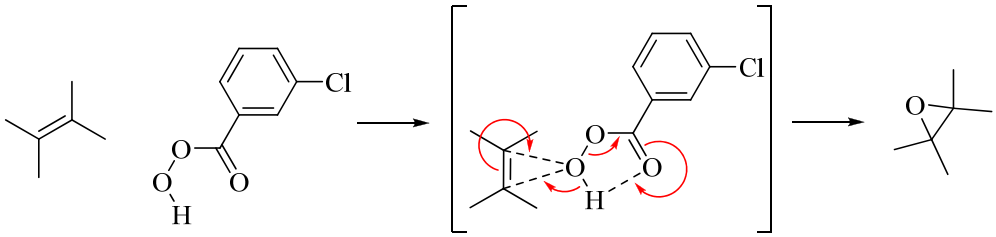
9, (+)-disparlure

The gypsy moth is native to parts of the UK and temperate Europe, but accidental introduction to the US in 1879 caused widespread damage and destruction. The female gypsy moth is incapable of flight; she releases a sex pheromone containing an epoxide functionality, (+)-disparlure (**9**), when ready for mating.[13] The male moth will become attracted to this pheromone, find the female and copulate. The (–)-disparlure enantiomer was found to be totally inactive and shows no activity even at high concentrations. Therefore the active (+)-enantiomer can be used to falsely attract the male gypsy moth in order that numbers can be regulated.

Many natural products contain the epoxide functionality as a single enantiomer, which may be essential for biological activity. The synthesis of chiral epoxides in natural products or as versatile intermediates has shown great potential for economic viability and for future scientific research, especially when incorporated into asymmetric catalytic cycles where the amount of catalyst used remains low and the output of the chiral epoxide is large compared with the quantity of catalyst used.[14]

1.3 Achiral epoxidation of alkenes

The generation of achiral epoxides is often accomplished by the oxidation of alkenes using organic peracids, first discovered in 1909 by Prileshaev.[15] Hydrogen peroxide is the general oxidant used to generate a peracid, the most useful peracids perhaps being peracetic and perbenzoic acids, and substituted derivatives such as *m*–chloroperbenzoic acid (*m*–CPBA) the mechanism of oxygen transfer is shown in Scheme 1.



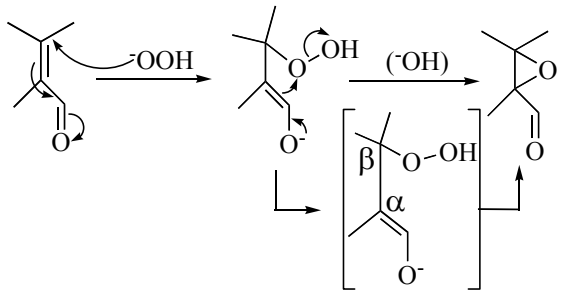
Scheme 1

Originally the transition state model of this reaction was though to be planar (**10**),[16,17,18,19,20] but further research has calculated that the transition state must be a lower energy spiro transition state conformation (**11**), this transition state model is also known as the 'butterfly mechanism' first published by Barlett in 1950. Both transition state models proceed through a concerted mechanism, and therefore the epoxidation is stereospecific.



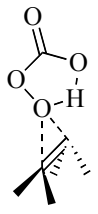
10, Planar TS model ***11, Spiro TS model***

Alkenes with α-situated electron withdrawing groups such as enones can be directly oxidised by a solution of hydrogen peroxide. Weitz and Scheffer first described the use of an alkaline solution of hydrogen peroxide;[15] the alkaline solution deprotonates the hydrogen peroxide, the nucleophilic hydroperoxy anion can then reversibly attack the enones conjugated alkene (Scheme 2).[15] The system can then ring close through nucleophilic attack of the carbon anion at the more electrophilic peroxy–oxygen atom, displacing a hydroxide molecule and generating the epoxide. Due to the long life expectancy of the carbanion, the α,β carbon–carbon sigma bond can rotate during the stepwise mechanism and therefore the reaction is not stereospecific.



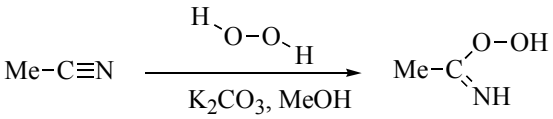
Scheme 2

A second method, used by Richardson and Yao, is achieved by using a bicarbonate-activated peroxide (BAP) at neutral pH.[21] The generation of the electrophilic peracid requires the presence of a carbonate atom, generally sodium hydrogen carbonate or ammonium hydrogen carbonate in a water–based solution. Hydrogen peroxide undergoes nucleophilic attack on the most electrophilic peroxy–oxygen by HCO_3^- anions, generating peracidic HCO_4^- anions in solution. The HCO_4^- percarbonate generates the racemic epoxide through a mechanistic pathway similar to the *m*–CPBA peracidic mechanism observed in Scheme 1, *via* transition state 12.



12, transition states for percarbonate epoxidation

Payne, has developed another method of hydrogen peroxide mediated epoxidation.[22,23] In this system hydrogen peroxide is used in conjunction with a nitrile functionality to generate epoxides in good yield. In the presence of base, hydroperoxy anions nucleophilically attack the nitrile carbon to generate a peroxyimidic acid intermediate (Scheme 3). The peroxyimidic acid is then thought to generate the racemic epoxide through a similar concerted mechanism to that occurring in peracidic epoxidation (Scheme 1). There is however no direct evidence that this mechanism is correct.



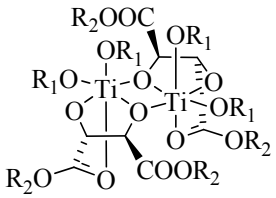
Scheme 3

1.4 Metal-catalysed asymmetric epoxidation of alkenes

Due to the growing interest in asymmetric epoxidation, many international research groups have developed a range of oxidation catalysts and systems. Several of the most innovative and efficient approaches are reviewed here, with a discussion of their advantages and disadvantages in modern asymmetric catalysis.

1.4.1 The Sharpless catalytic asymmetric epoxidation of allylic alcohols

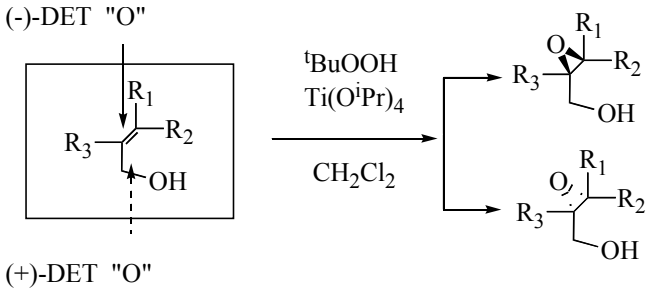
The Sharpless epoxidation of allylic alcohols was discovered in 1980 by Sharpless and Katsuki.[24] First, using vanadium and molybdenum metal centred catalysts,[25] Sharpless found that an allylic alcohol could be substituted for an alkoxide ligand that was already chelated to the metal catalyst. In later work using titanium, the oxidant, *t*-butyl peroxide also displaces an alkoxide ligand, thus generating a titanium complex with both a *t*-butyl peroxide and an allylic alcohol co-ordinated to the central titanium atom. Due to the proximity of the two chelated ligands, the weakly nucleophilic alkene forced nucleophilic attack on to the peroxide generating the epoxide. After further modification, Sharpless discovered the most advanced and efficient catalyst, which was a titanium tetra–isopropoxide-diethyl tartrate (DET) catalyst (**13**).



R_1 = Et, R_2 = ^{i}Pr

13, Sharpless titanium(VI) complex.

The advantages of this methodology were that the procedure is both catalytic and enantioselective.[26] As observed in **13**, the chiral Ti(VI) complex exists as a dimer with a C2 plane of symmetry. The predictibility of the stereochemical induction in the epoxide product (Scheme 4) is the main reason that the Sharpless epoxidation has become so important and is so widely used today.

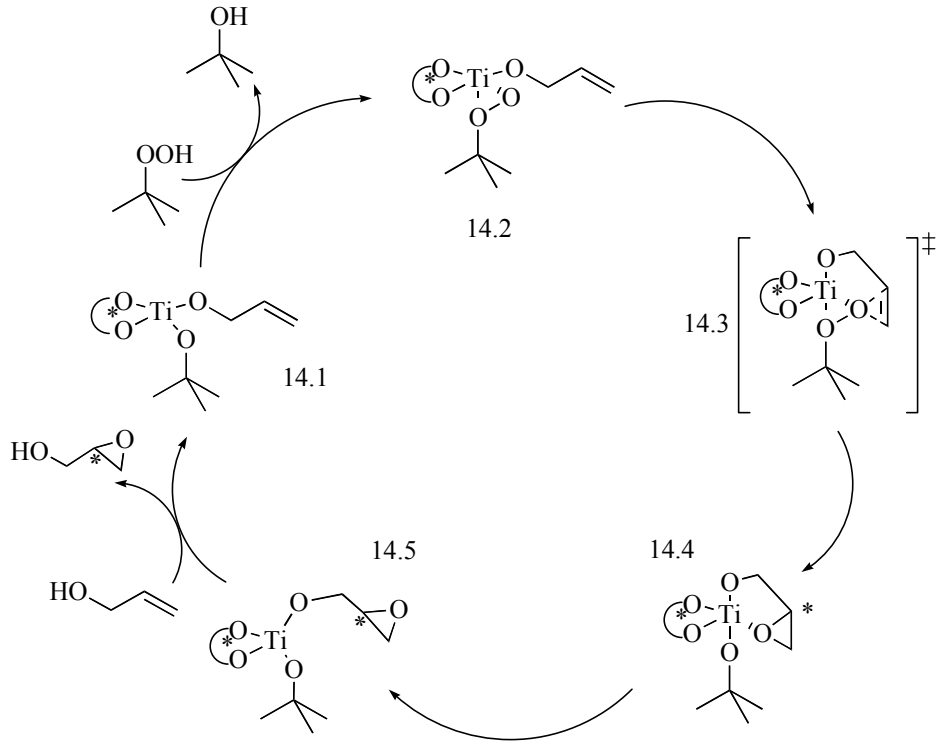


Scheme 4

The Sharpless epoxidation has become one of the most important discoveries over the last thirty years, and in 2001 Barry K. Sharpless was presented with the Nobel Prize for Chemistry in acknowledgement of this research.[2]

The dimeric complex is insensitive to other functionality and therefore the process is totally specific to the allylic alcohol moiety, even over other alkenes that may be present.[27] With the selection of the appropriate enantiomer of the catalyst and the correct geometry of the allylic alcohol, generation of the required epoxide enantiomer can be observed in over 90% *ee* (Scheme 4).

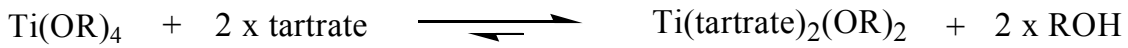
Sharpless epoxidation requires an allylic alcohol, an oxidant; ^{t}butyl peroxide (TBHP), and the pre–catalyst; Ti(VI) isopropoxide-diethyl tartrate (DET) (Scheme 5). *In–situ* the allylic alcohol becomes chelated to the chiral Ti(VI) metal centre ((Figure 14.1). The most electrophilic TBHP oxygen atom is then nucleophilically attacked by the Ti(VI) chelated *t*–butyl ester thus, generating the Ti(IV) peroxide ((Figure 14.2).



Scheme 5

(Figure 14.1 – 14.5)

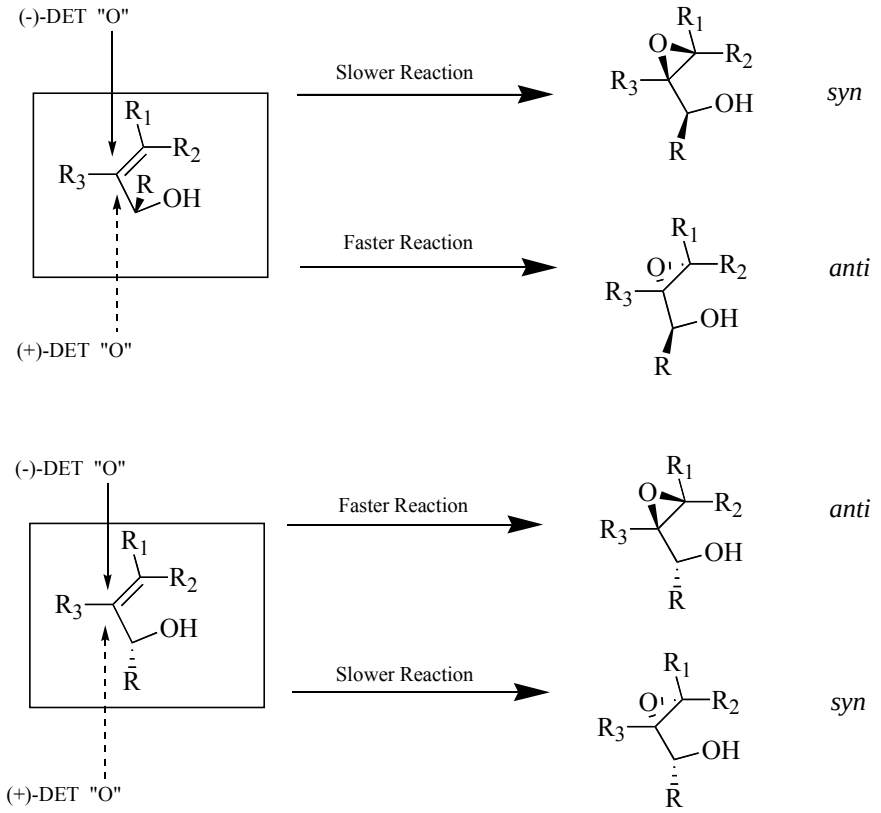
The Ti(IV) is in a bidentate arrangement to both the alkyl alkoxide and the TBHP anion.[28] Due to the close proximity of the two ligands the activated TBHP is then attacked by the weakly nucleophilic alkene at the most electrophilic oxygen ((Figure 14.3). This generates the epoxide preferentially on one of the two enantiotopic faces of the alkene ((Figure 14.4). The Ti(VI) is regenerated by the release of the epoxide, now co–ordinated to the epoxy alkoxide and *t*–butoxide ((Figure 14.5). The catalytic cycle replaces the epoxy alkoxide with another allylic alcohol ((Figure 14.1), and the *t*–butoxide with another *t*–butyl peroxide group ((Figure 14.2). The recycling of the Ti(IV) catalyst has been proven through mechanistic studies (Scheme 6).



Scheme 6

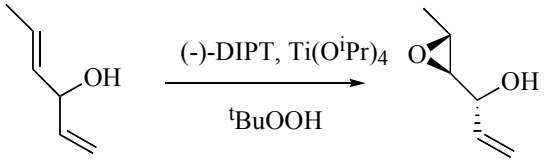
It was observed that if the alkoxide ligands are replaced by DET–allylic alcohol ligands (Scheme 6),[29] the equilibrium lies to the right, towards the DET ester chelated complex. Once the allylic alcohol reacts with the activated THBP, the recycled Ti(IV) releases the epoxy alkoxide and re–chelates to another allylic alcohol.

In previous work Sharpless observed that vanadium and titanium complexes generate intrinsically 1,2–*anti* products when the allylic alcohol contains functionality at carbon one. Kinetic resolution will occur when using a *racemic* C1 functionalised allylic alcohol, as one enantiomer will react quicker than its opposite enantiomer.[28] Therefore, the Ti(IV) complex will generate the *anti*–enantiomer faster than the *syn*-derivative. The slower reacting alkene enantiomer therefore becomes enantiomerically enriched (Scheme 7).



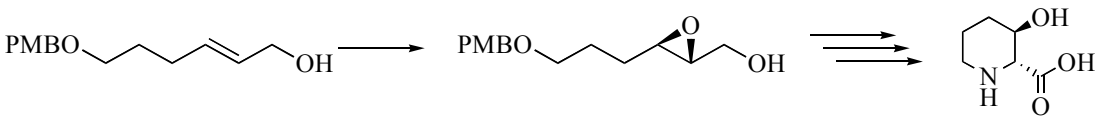
Scheme 7

Taking a molecule containing two double bonds that could potentially undergo Sharpless epoxidation, the more nucleophilic of the two reacts more readily (Scheme 8).[30] Again one enantiomer of the epoxide is generated faster than the other, so this enantiomer is observed in the final mixture as the major product, giving a yield of 35% (out of a possible 50%) and with an enantiomeric excess of greater than 95% *ee*. The unreacted allylic alcohol is therefore also enantiomerically enriched.



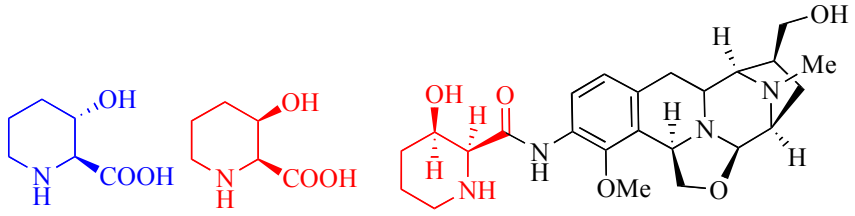
Scheme 8

The Sharpless asymmetric epoxidation is a widely used and efficient method for the production of versatile epoxide intermediates, building blocks and the generation of natural products used in organic chemistry.

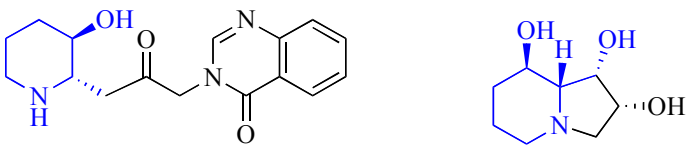


Scheme 9

For example, the Sharpless methodology has been used to produce one enantiomer of 3–hydroxypipecolic acid (Scheme 9).[31] The *trans*–isomer, **15** generates part of the structure of febrifugine (**18**), a potent antimalarial agent, and also of (–)- swainsonine (**19**), which has shown potent and specific α-*D*–mannosidase inhibitory activity. The *cis*–isomer, **16** is a precursor of tetrazomine (**17)** an anti–tumor antibiotic.



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

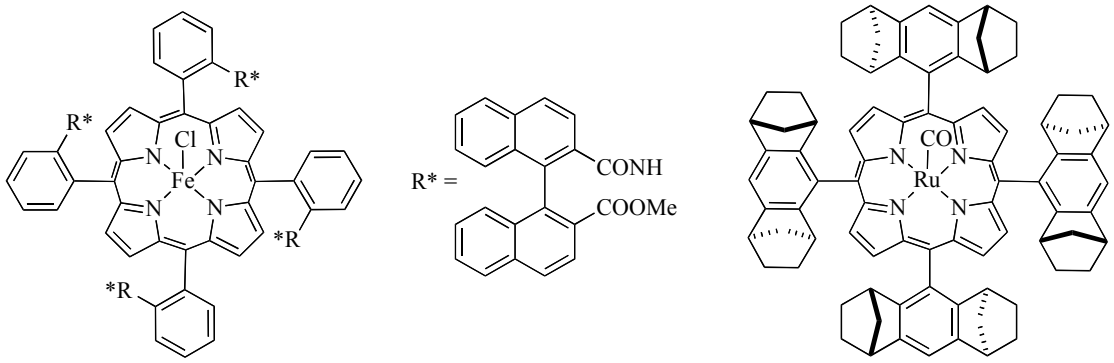


18 ***19***

One major limitation of the Sharpless asymmetric epoxidation method is the requirement for the allylic hydroxyl group in order to achieve enantioselective epoxidation. Therefore this method is ineffective in the epoxidation of unfunctionalised alkenes. This limitation has spurred the development of other asymmetric epoxidation methods capable of achieving high enantioselectivity for unfunctionalised alkenes.

1.4.2 Metalloporphyrins as catalysts for asymmetric epoxidation.

In 1983 Groves and Myers first discovered that planar Fe(III) porphyrin complexes are models for the oxidising enzyme cytochrome P450 monooxygenase.[32,33] Groves and Myers first developed a Fe(III) porphyrin complex catalyst (**20**) with the ability to oxidise unfunctionalised alkenes.



20, Fe(III) porphyrin complex catalyst ***21***

Many combinations of metal centres and diverse chiral ligands have been screened to try and increase both reactivity and enantiomeric excess. Recently chiral metal porphyrins have been developed that have given moderate to good *ee;* Berkessel's carbonyl ruthenium(II) metalloporphyrin,[34] with a novel D4 symmetric ligand (**21**),[35,36] Naruta's iron complex,[37] with either binaphthalene or a bitetralin–linked porphyrin, and Collman's iron α,α,β,β–tetrakis(aminophenyl)porphyrin with attached binaphthyl moieties.[38]

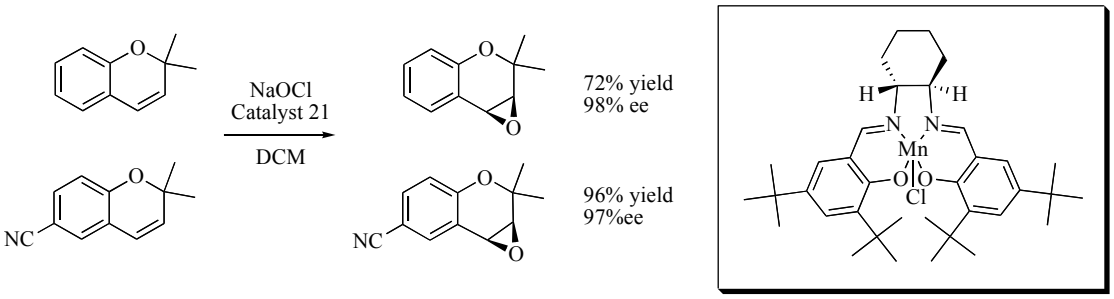
Unfortunately this methodology is substrate-specific, requiring styrene based alkenes producing the corresponding styrene oxides with up to 89% *ee*. The greatest problem with this epoxidation methodology is the low yielding multistep approach to synthesise the large and complex chiral catalysts.[39]

1.4.3 Chiral Salen complexes for asymmetric epoxidation.

In 1985, Kochi first devised and reported a manganese(III) Salen complex capable of catalytic epoxidation of unfunctionalised alkenes.[40,41] Both porphyrins and Salen complexes are initially based on the oxidising enzyme cytochrome P450 mono–oxygenase; it is the oxomanganese(V) cation that is thought to be the active oxidising agent. The major difference between these two types of chiral catalyst is that the oxidised metal porphyrins are planar, whereas Katsuki has shown that the oxidised Salen complexes are based on tetrahedral carbons in close proximity to the metal centre, which give the Salen complexes a folded structure.[42] This amplifies the asymmetric induction imposed by the chiral catalyst on the generation of the epoxide.

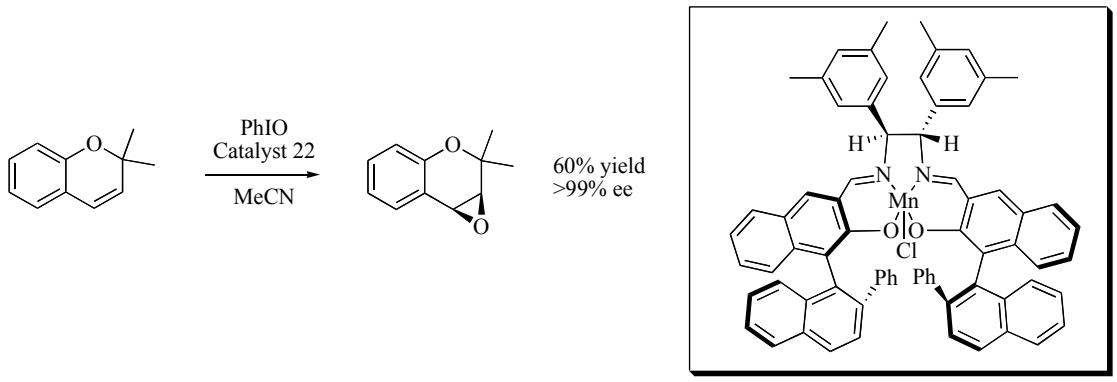
1.4.4 Jacobsen and Katsuki's chiral Salen complexes.

Jacobsen has developed a multitude of catalysts based on the manganese(III) Salen complexes of chiral Schiff bases. The ligands are derived from chiral 1,2-diamines and substituted salicylaldehydes. Oxidising agents such as periodates and sodium hypochlorite have been utilised to oxidise the Salen pre–catalyst to the oxomanganese(V) active catalyst. Jacobsen's catalysts have been observed to be particularly effective in the oxidation of *cis*-aryl substituted olefins, for example, catalyst **22** has been shown to produce high *ee*, up to 98% for certain dimethylchromene derivatives (Scheme 10).[43,44,45,46,47] However, Jacobsen's catalysts generate poor selectivity when used in conjunction with *trans*-aryl and aliphatic alkenes.



Scheme 10 ***22, Jacobsen's catalyst***

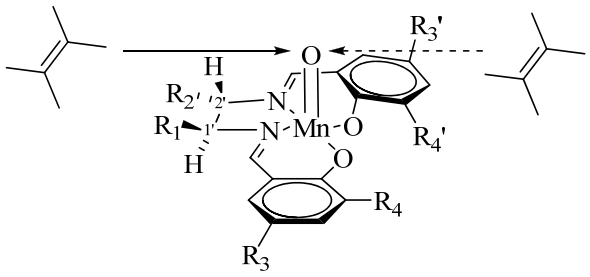
Katsuki has also reported chiral Mn(III) catalysts, developing catalyst **23**. This method uses chiral residues attached at an aromatic carbon *ortho* to a phenolic group.



Scheme 11 ***23, Katsuki's catalyst***

Katsuki's catalyst contains the standard asymmetric centres at the 1' and 2' positions, but Katsuki's catalyst, **23**, differs from Jacobsen's as it also contains axial chirality in the form of enantiomerically pure binaphthyl groups incorporated in to 3,3' positions.[48,49,50,51,52,53] Katsuki's system exhibits similar enantioselectivities to the Jacobsen catalyst for *cis*–aryl alkenes, greater than 99% *ee* for certain dimethylchromene derivatives (Scheme 11). However greater enantioselectivities are observed when oxidising *trans*–alkenes.[54]

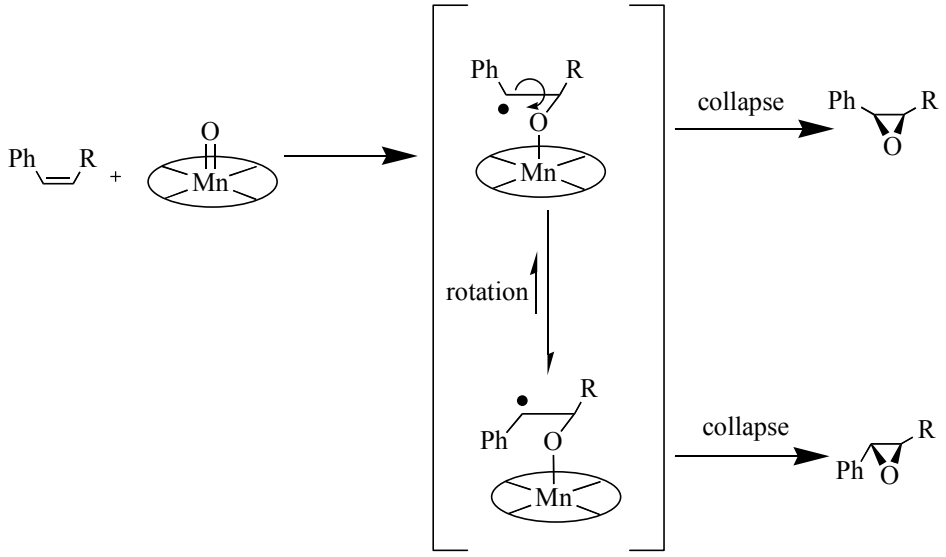
The enantioselectivity in epoxidation is believed to be induced by a chiral Salen catalyst through a side on approach of the alkene to the oxomanganese(V) intermediate. It is known that asymmetric centres at carbon 1' and 2' induces higher enantioselectivity in epoxidation of *cis*–aryl alkenes.



24, Preferential alkene approach to the chiral Salen complex

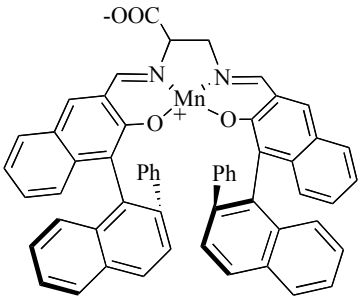
The 3,3' axial symmetry (R_4/ R_4' groups) directs the orientation of the approach of the substrate alkene towards the oxo–Mn(V) bond (solid arrow, figure **24**). The 3,3' functionality inhibits approach from the more sterically hindered face (dashed arrow). Therefore, these interactions enforce enantiofacial selection of the oxygen transfer and explain the raised enantioselectivity of the Katsuki Salen complex, especially for *trans*-alkenes.

One major disadvantage with Salen Mn(III) epoxidation is the lack of retention of the alkene configuration in the epoxidation of some substrates. This is especially the case when attempting to oxidise aryl–substituted acyclic *cis*–alkenes. Epoxidation of these acyclic alkenes does not occur with retention of configuration.



Scheme 12

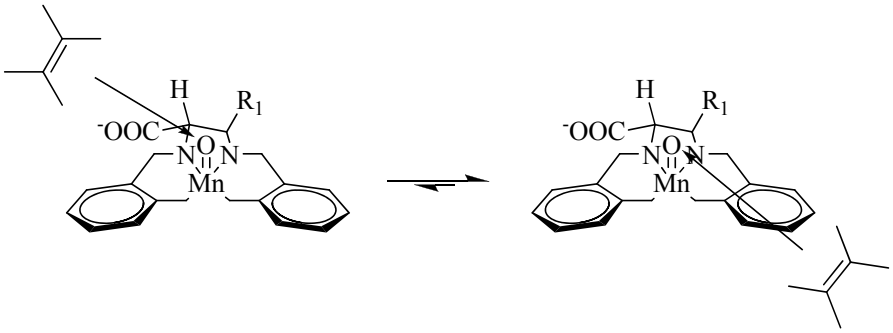
The cause of this (Scheme 12) is postulated to be a step–wise radical mechanism in which bond rotation of the radical intermediate causes the scrambling of the *cis*–geometry to yield the *trans*–epoxide. This problem was 'modified' by the addition of quaternary cinchona alkaloid-derived salts to the reaction mixture, to give *trans*–epoxides in up to 90% *ee.*



25, Conformationally reversed Salen complex

More recently, Katsuki has developed a conformationally reversed Salen complex (**25**), with an attached carboxylate group on the ethylenediamine moiety.[55]

In a standard Salen complex, due to the tetrahedral geometry of carbon 1, which would hold the asymmetric functionality, this group is forced pseudoequatorial (Scheme 13), making the Salen complex adopt a folded rather than planar conformation confining the olefin to only approach from over the 1', 2' positions. It is this conformation that controls the asymmetric induction of the epoxidation in all Salen complexes.



Scheme 13, Pseudoequatorial and pseudoaxial conformations of Mn-Salen complexes

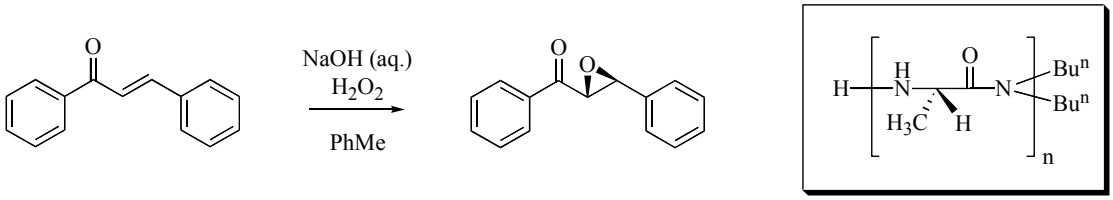
In the conformationally reversed Salen complex, the catalysts conformation forces the carboxylate group, at carbon 1', pseudoaxial (Scheme 13). Due to the exchange from pseudoequatorial to pseudoaxial conformation, the carboxylate group can then stabilise the oxo–Mn(V) active catalyst. This change in conformation now confines olefin approach from over the 3 and 3' positions, thus inducing the opposite enantiocontrol. For example, dimethylchromene derivatives are oxidised with up to >99% *ee*.

The Jacobsen/Katsuki Salen-mediated asymmetric epoxidation has proven to be one of the most successful methods for epoxidation of *cis*–aryl alkenes with high enantiomeric excess. Unfortunately Salen catalysed reactions suffer from two fundamental problems. Firstly a loss of stereospecificity through a radical intermediate is observed. Secondly, and most importantly, Salen complexes are only successful in the oxidation of aryl alkenes, meaning that Salen complex methodology is of limited use.

1.5 Metal-free catalytic asymmetric epoxidation.

1.5.1 Julia–Colonna epoxidation of α,β–unsaturated ketones.

In 1980 Julia and Colonna demonstrated that high enantioselectivities, up to 97%, could be achieved in epoxidation of an α,β–unsaturated ketone such as chalcone (Scheme 14).[56,57] Julia developed a triphasic oxidative system containing poly–L–alanine, toluene, and aqueous alkaline hydrogen peroxide as the oxidant. Unfortunately the Julia methodology suffers from extended reaction times of up to 24 hours and low substrate scope.

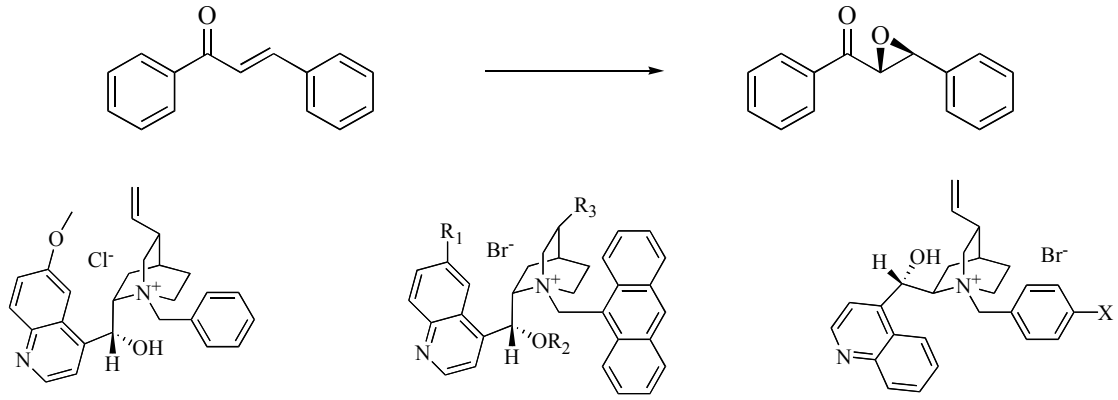


Scheme 14 ***97% ee***

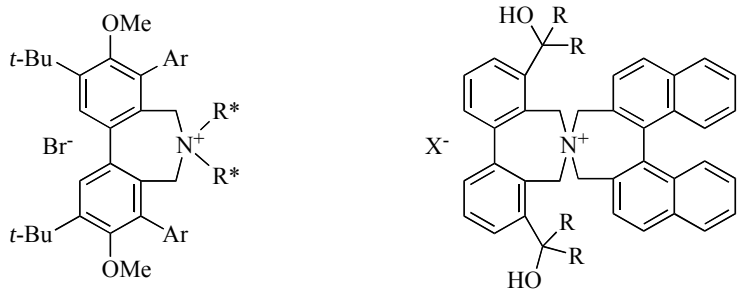
Roberts has further investigated the Julia–Colonna epoxidation. Roberts has produced an

improved biphasic system that reduces reaction times to approximately thirty minutes,[58,59] increasing the enone substrate range to include some unreactive, α-substituted and *cis* substituted aryl, heteroaryl and alkenyl enones, but most importantly maintaining the enantioselectivity (97% *ee* for chalcone). Under the new biphasic conditions the reaction is performed in a non–aqueous solvent, such as THF, using a water–free source of hydrogen peroxide; the readily available urea–hydrogen peroxide popularised by Heaney was the oxidant of choice.[60] DBU is used as a non–nucleophilic base.[61]

In 1976 Wynberg introduced the idea of phase transfer catalysis (PTC) for epoxidation, an alternative method to facilitate the production of an epoxide from an α,β–unsaturated ketone with high enantiocontrol. Wynberg used a quinine-derived quaternary ammonium salt (**26**) as the chiral phase transfer catalyst in the presence of alkaline hydrogen peroxide and a stoichiometric oxidant, giving up to 55% enantiocontrol when using chalcone as the test substrate.[62,63,64,65,66,67]



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



29 ***30***

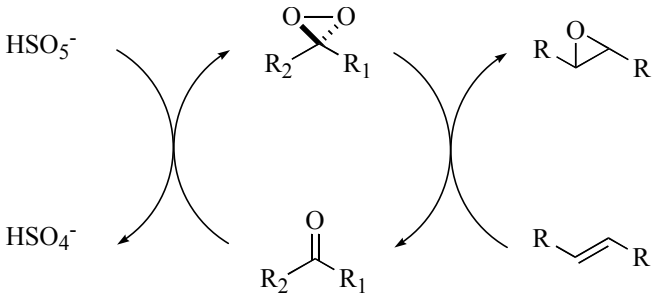
Scheme 15

Further work by other research groups has proven that the quinine-derived quaternary ammonium salts, such as **26** –**28**, generate high *ee* when investigating enantioselective α,β–unsaturated ketone epoxidation. Lygo has generated modifications of catalyst **27** giving enantioselectivities of 71 – 90%,[68,69,70] and Arai has identified catalyst **28**; by exchanging the halogen group on the benzyl functionality up to 92% enantiocontrol has been achieved.[71,72] Lygo and Maruoka have also produced C2–symmetric catalysts **29** and **30**, containing BINAP and a biphenyl azepinium ring functionalities, both giving up to 97% enantioselectivity.[73,74,75]

1.5.2 Dioxirane mediated asymmetric epoxidation.

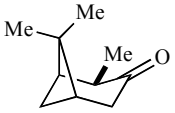
1.5.2.1 General overview

Dioxirane–mediated asymmetric epoxidation has emerged as one of the most effective methods for producing enantiomerically enriched epoxides over the past twenty years. The general method for production of a dioxirane is by the use of a ketone and a stoichiometric oxidant, generally Oxone®, in either a monophasic (CH_3CN/H_2O) or a biphasic (CH_2Cl_2/H_2O) system at neutral pH (7–8) (Scheme 16). The composition of Oxone® is $2KHSO_5.KHSO_4.K_2SO_4$, the active component being potassium monopersulfate ($KHSO_5$, potassium peroxomonosulfate). The use of Oxone® has increased rapidly due to good stability, simple handling, the non-toxic nature, the versatility of the reagent and the low cost.

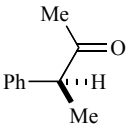


Scheme 16, dioxirane mediated epoxidation

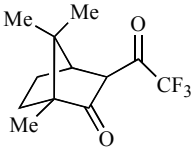
In the early 1980's, research groups lead by Curci and Marples both described the generation of stoichiometric dioxiraines from chiral ketones (**31** – **35**).[76,77,78] They were used as pre–catalysts for dioxirane-mediated asymmetric epoxidation of alkenes, affording their respective epoxides in up to 20% *ee.*



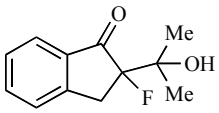
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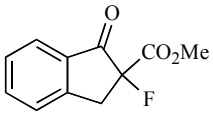
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33



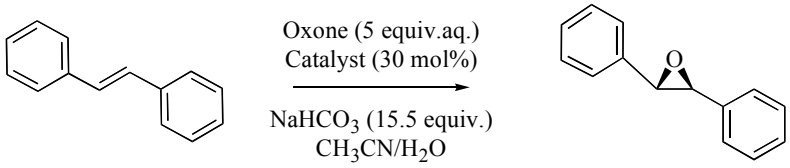
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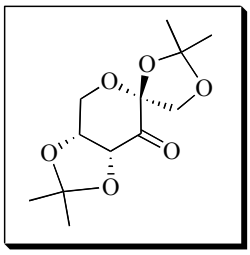
35

1.5.2.2 Shi's chiral–fructose derived ketone catalysts.

In 1990 Shi designed a fructose-based ketone catalyst, **36**, that displayed remarkably desirable features for asymmetric epoxidation, affording up to 95% *ee* in the epoxidation of *trans*–stilbene (Scheme 17).



Scheme 17

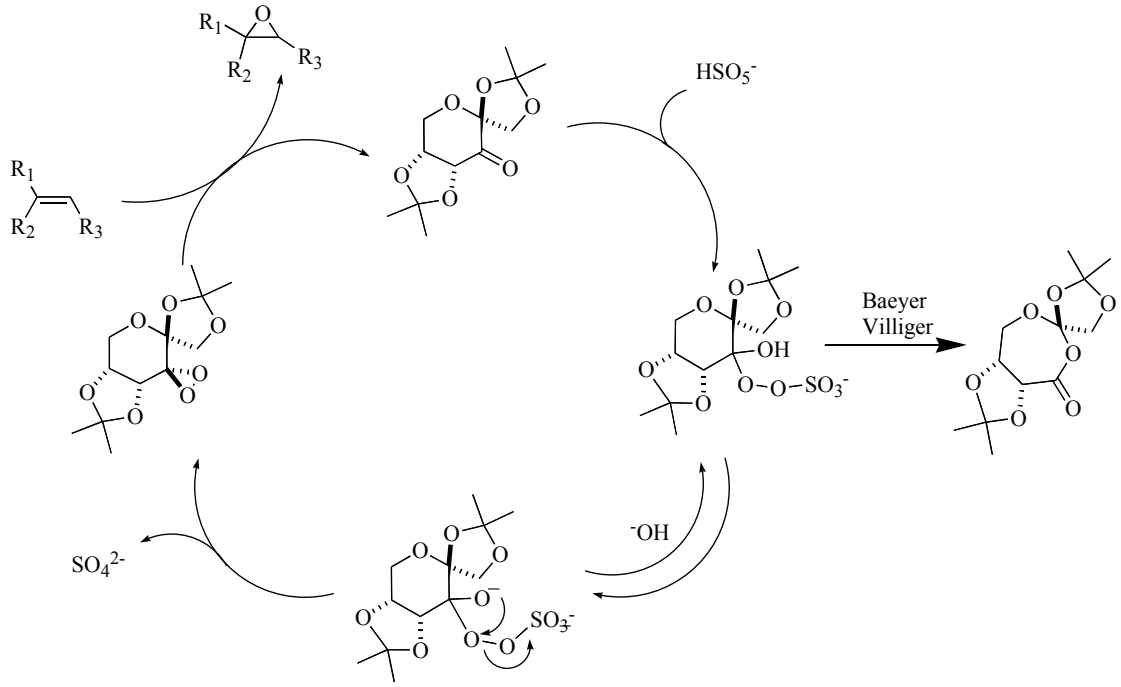


Catalyst 36, 95% ee

The fructose ketone catalyst (**36**), is oxidised to the dioxirane with a stoichiometric oxidant such as Oxone® (Scheme 18).[79]

The electrophilic dioxirane undergoes nucleophilic attack from the alkene, which generates the epoxide. *Trans*– and *tri*-substituted alkenes give from 80% to 95% *ee.* The desriable features of the fructose catalyst are the close spacing of the stereogenic centre(s) and the reacting centre(s), resulting in efficient chemical communication

between the dioxirane and the substrate. The fused rings on the α–carbons reduce epimerisation of the stereogenic centres. Electron-withdrawing groups may be added to the ketone to activate the carbonyl functionality. [80,81]



Scheme 18, Shi's catalytic dioxarine epoxidation

Unfortunately, Shi's catalyst undergoes decomposition through Baeyer–Villiger oxidation,[82,83] and so the amount of catalyst is typically 30 mol% (Scheme 18). This problem was eased by raising the pH of the reaction from neutral, pH 7/8, to alkaline, > pH 10 with the addition of potassium carbonate. The resulting epoxides were gained with increased *ee* ranging from 91% to 97% and are stable under basic conditions (Scheme 17).

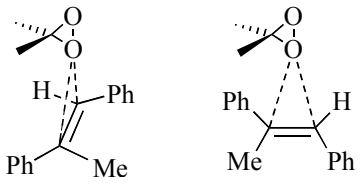
Another result of the raised pH was that the nucleophilicity of the Oxone® was also increased. Not only does this help supress the Baeyer–Villiger side reaction therefore increasing the yields of selected epoxides to 95%, but increased the rate of reaction therefore reducing the amount of catalyst required to 20 mmol%.

The synthetic utility of this methodology[84,85] was widely explored by the asymmetric epoxidation of various hydroxyalkenes (90–94% ee), enol ethers and enol esters (80–

91% ee), enynes (90–97% ee), vinylsilanes (84–94% ee), *cis*–alkenes (84–97% ee), terminal alkenes (30–94% ee), and mono–epoxidation of conjugated dienes (90–97% ee). The epoxidation of conjugated dienes has also been shown to be highly enantioselective. Kinetic resolution of racemic 1,3-disubstituted cyclohexenes and racemic allylic substituted cyclic olefins has also been completed.[86,87]

1.5.2.2.1 Transition States for ketone catalysts

There are two possible transition state models (transition state–models) to describe how the alkene interacts with the dioxirane, the spiro and planar transition state models (Scheme 19).[10,16, 87, 88]

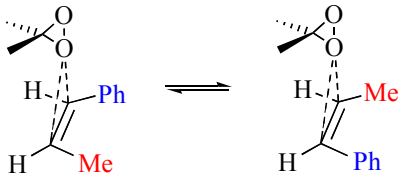


Scheme 19, Spiro and Planar transition state models

A transition state model is invaluable for predicting the stereochemical outcome of the epoxidation reaction. The large, bulky functional groups on both the alkene and the dioxirane directly determine the angle and orientation of the approach of the substrate to the catalyst, therefore determining the regio- and stereochemistry of the epoxide produced. Scheme 19 shows the two major transition state models for Shi's fructose catalyst, spiro and planar. The alkene approaches the dioxirane, placing the bulky R groups away from the dioxiranes ketal moeities, therefore reducing repulsive steric and electronic interactions.

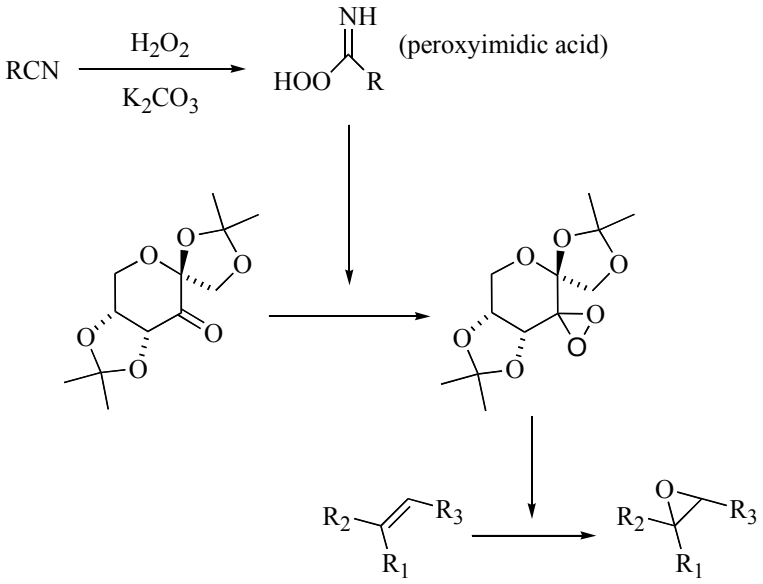
The spiro transision state model is favoured over the planar model, due to the overlap and therefore stabilising interaction between the reacting lone pair of the oxygen and the the π^* orbital of the alkene (stereoelectronic origin). The oxygen lone pair and the π^* orbital do not overlap in the planar transision state model, so there is less stabilisation.

Shi showed that the asymmetric epoxidation of *trans* and *tri*-substituted alkenes was efficiently completed with the fructose-derived ketone catalyst. The stereochemistry was predictable using a simple model. Unfortunately *cis* and terminal alkenes were a problem as the largest group(s) on the alkene could point away from the dioxirane, resulting in poor selectivity as the alkene could flip 180 degrees (Scheme 20).



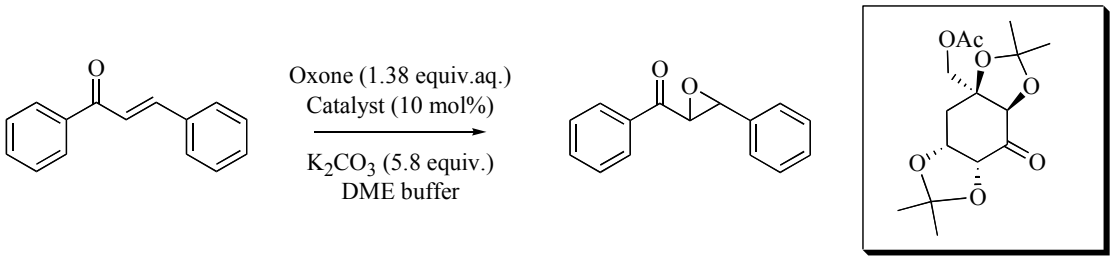
Scheme 20

Shi has also reported alkaline hydrogen peroxide-mediated asymmetric epoxidation in the presence of nitriles.[89] The peroxyimidic acid reported by Payne is postulated to be the active oxidant in the dioxirane generation of the fructose catalyst (Scheme 21).[22,23] High yields and enantioselectivities under these reaction conditions with up to 95% *ee* for 1–phenylcyclohexene oxide have been reported.



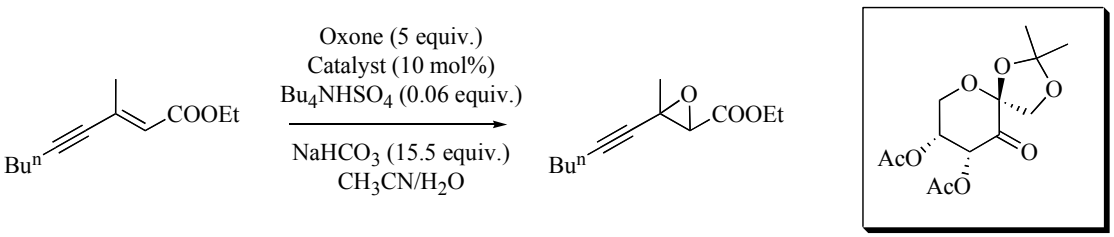
Scheme 21, hydrogen peroxide-mediated dioxirane epoxidation

Unfortunately the original fructose catalyst is ineffective for electron-deficient and α,β–unsaturated alkenes due to the decomposition through the Baeyer–Villiger reaction. Shi designed two further catalysts. From wide screening, Shi observed that (–)-quinic acid-derived catalyst **37** showed increased enantiocontrol, up to 94% *ee,* and increased rates of reaction, up to 80%, over the original fructose catalyst (**36**).[90]



Scheme 22 ***Catalyst 37, 94% ee***

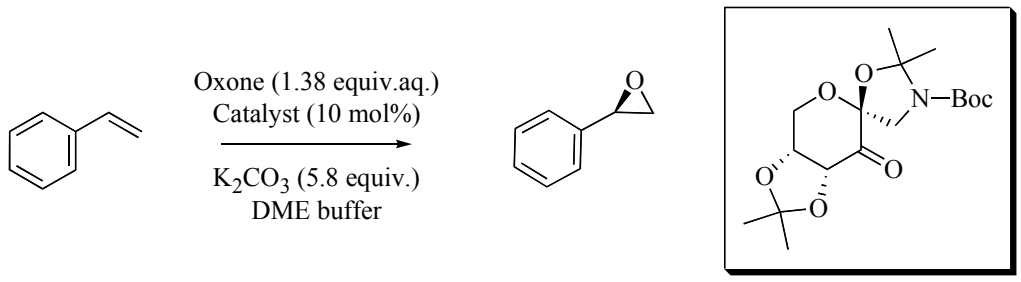
With the success resulting from this additional acetate group, Shi then adapted the original fructose catalyst, exchanging the lower 2,3- ketals for two acetate moieties, generating catalyst **38**.[84] The electron withdrawing ability of the acetate groups again inhibited the Baeyer–Villiger reaction. The enantiocontrol was increased for *trans* and *tri*-substituted alkenes as well as for α,β–unsaturated alkenes (82 – 98% *ee*). The rate of reaction was also greatly increased.[91]



Scheme 23 ***Catalyst 38, > 95% ee***

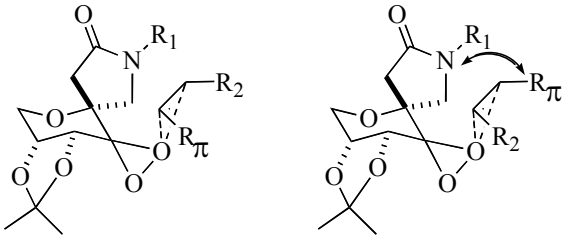
Shi designed a nitrogen analogue of the fructose catalyst,[82,85] the rationale being that the nitrogen substitution could impart enantiocontrol in the epoxidation of *cis* and terminal alkenes. The nitrogen functionality was added to the fructose ketone by the Amadori rearrangement,[82,85,929394] and the highest enantiocontrol was observed when a *N*–Boc

group was incorporated in the catalyst (**39**). The enantioselectivity for *trans* alkenes was observed to be lower when using **39**,[82,85] but for *cis* and terminal alkenes the nitrogen analogue gave up to 94% and 85% *ee* respectively (Scheme 24). An additional feature of the nitrogen analogue is that it retards the Baeyer–Villiger reaction to a higher degree than the original fructose catalyst (**36**).



Scheme 24 ***Catalyst 39, 91% ee***

Shi has suggested that there may be an attraction between the Rπ functionality of the approaching alkene and the oxazolidinone of the ketone catalyst (**41**).[16,95] As a result of this, alkene groups containing Rπ functionality (**41**) may be significantly differentiated from those without (**40**), leading to increased enantioselectivity. Shi further demonstrated that catalysts containing *N*-aryl substitution (R_1) strengthen the attractive interaction through conjugative electron withdrawal from the oxazolidinone functionality. It is postulated that the approaching alkene containing π functionality and the electron poor oxazolidinone undergo an electronic field effect i.e. a through-space electrostatic interaction.[96,97,98] The exact nature of this attractive interaction between the Rπ functionality and the oxazolidinone is not clear at present.[16,99]



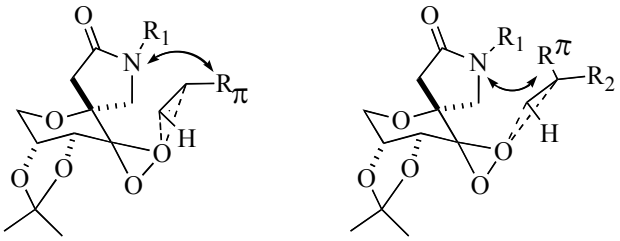
R_1 = aryl or alkyl. R_2 = alkyl. Rπ = aryl or conjugated system.

40 ***41***

Spiro ***Spiro (favoured)***

Structural evidence of most effective catalysts revealed that the nitrogen substituent (R_2) points firmly away from the dioxirane, therefore proving that it (R_2) could not influence the alkene sterically, only electronic factors may be important.[17]

The same rationale was applied to terminal and geminal alkenes.[17,82,85] The ketone catalysts oxazolidinone functionality may differentiate, using an electronic field interaction, between the approaching alkenes functional groups; those in which contain Rπ functionality (**42** & **43**) and those in which the Rπ functionality is absent. This differentiation imparts increased enantiocontrol onto the selected alkene.

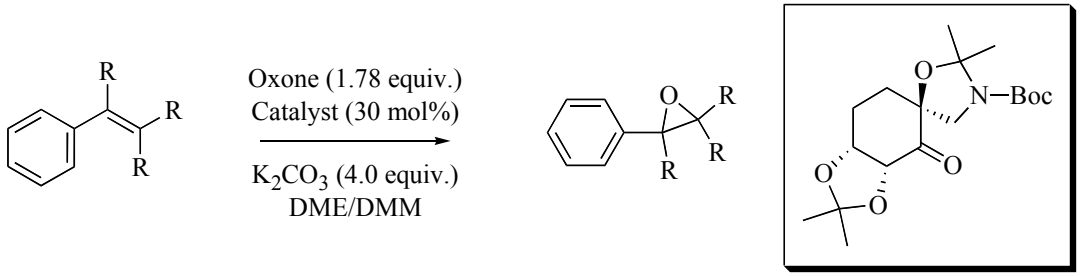


R_1 = aryl or alkyl. R_2 = alkyl. Rπ = aryl or conjugated system.

42 ***43***

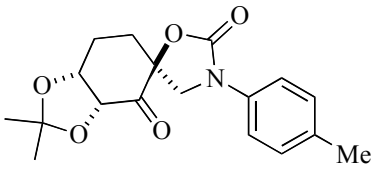
Due to the need for π character the Catalyst **39** performs poorly with non-aryl alkenes.

Shi has reported a skeletal alteration of the pyranose catalyst **39** by generating a catalyst with carbocyclic skeleton, catalyst **44**, which has been shown to give enantioselectivities of 89 – 93%, unfortunately the difficult and lengthy synthesis of **44** paired with the requirement of an aryl alkene makes it an unattractive tool for catalysis.

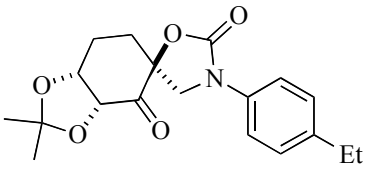


Scheme 25 ***Catalyst 44, 89 – 93% ee***

Most recently Shi has formed more efficient derivatives of pyranose catalyst **39**. Catalysts **45** and **46** are prepared from *D*–glucose and have been used to impart enantiocontrol over styrene (80 – 92% *ee*), *cis* alkenes (81 – 98% *ee*), conjugated *cis*-dienes (76 – 94% *ee*) and conjugated *cis*–enynes (80 – 97% *ee*).



45

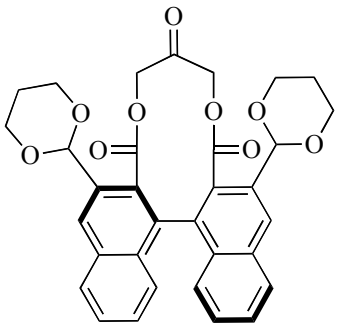


46

Other research groups such as Shing, Adam and Zhao have all generated sugar based dioxirane catalysts. [100,101,102] These oxidations are believed to proceed through similar transition states to Shi's fructose catalyst, however they have not provided epoxides with high enantioselectivity.

1.5.2.3 **Dan Yang:** C2 **symmetric dioxirane catalysts**

Yang's most efficient C2 catalyst (**47**) has been developed from 1,1'–binaphthyl–2,2' dicarboxylic acid.[103] In these C2 symmetric molecules the binaphthalene units are used as the chiral control element keeping the C2 symmetric ketone rigid. The catalyst also contains two large ketal groups at positions 3 and 3'. These groups have two responsibilities, first to help facilitate activation of the carbonyl functionality, through electron withdrawal, enabling the formation of the dioxirane catalyst.[104,105] Secondly, and most importantly, they act as steric control elements. The ketals are the closest functionalities in space to the dioxirane when oxygen transfer occurs, and they help to direct the approach of the alkene.

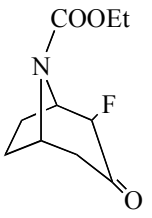


47, Yang's* C2 *symmetrical ketone Catalyst

High enantioselectivities were obtained for *trans*-disubstituted and *tri*-substituted alkenes, the best substrate being *trans*-4,4'-diphenylstilbene, giving 95% *ee.*

1.5.2.4 Armstrong's α–functionalised dioxiraine

In 1998 Armstrong reported the electronic activation of a catalyst capable of asymmetric alkene epoxidation. Armstrong focused on α–functionalised ketones. As previous research within the group had shown that α–Amido ketones were unsuccessful as the carbon atom alpha to both the amine and ketone becomes highly electropositive due to extensive electron withdrawal. The α-carbon is therefore prone to Baeyer–Villiger decomposition. β–Amido ketones are not prone to the Baeyer–Villiger reaction and thus favoured as dioxiraine catalysts. Armstrong was able to generate well-defined chiral catalysts based on tropinone derivatives (**48**).[106]



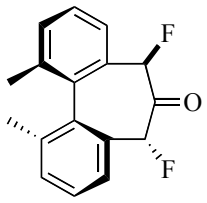
48, Armstrong's tropinone catalyst

Fluorine, a very strong electron-withdrawing group, was placed α to the ketone, in order to activate the ketone by withdrawal of electron density. The equatorial fluoro compounds were the most reactive as well as being the most stable to the Baeyer–Villiger reaction.[107,108] These α–fluoroketone catalysts oxidised *tri*-substituted aryl alkenes with up to 83% ee

The enantioselectivity of the epoxide generation has been explained by transition state–models.[109] The α–fluorine has a dipole interaction with the approaching alkene, and this directs the alkene to one enantiotopic face, generating a enantioselective epoxidation.

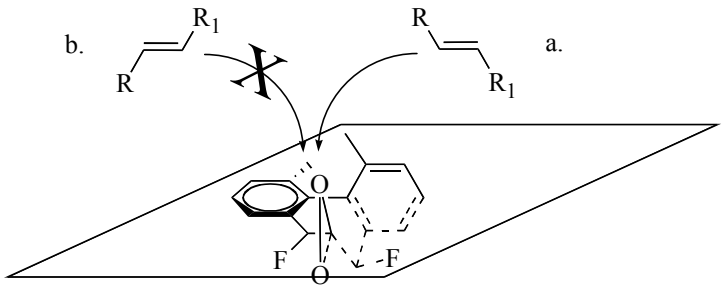
1.5.2.5 Denmark's α–functionalised chiral dioxiranes

Denmark has devised, among other chiral ketone catalysts, a *bis*-fluoro dioxiraine catalyst with the ability to catalyse asymmetric epoxidation.[110,111,112] Denmark has shown that good to excellent enantioselectivities for *trans*–alkenes can be achieved when using catalyst **49**. However, catalyst loadings are high (30 mol%).



49, Denmark's α–fluoro chiral ketone

Denmark postulated a spiro transition state model for this biaryl chiral dioxirane. Due to the catalysts C2 symmetry, the activated dioxirane oxygen atoms become homotopic,[112] the alkene may then approach the biaryl skeleton through either route a, or route b (Scheme 26).



***Scheme 26, Denmarks spiro transition state model.*[112]**

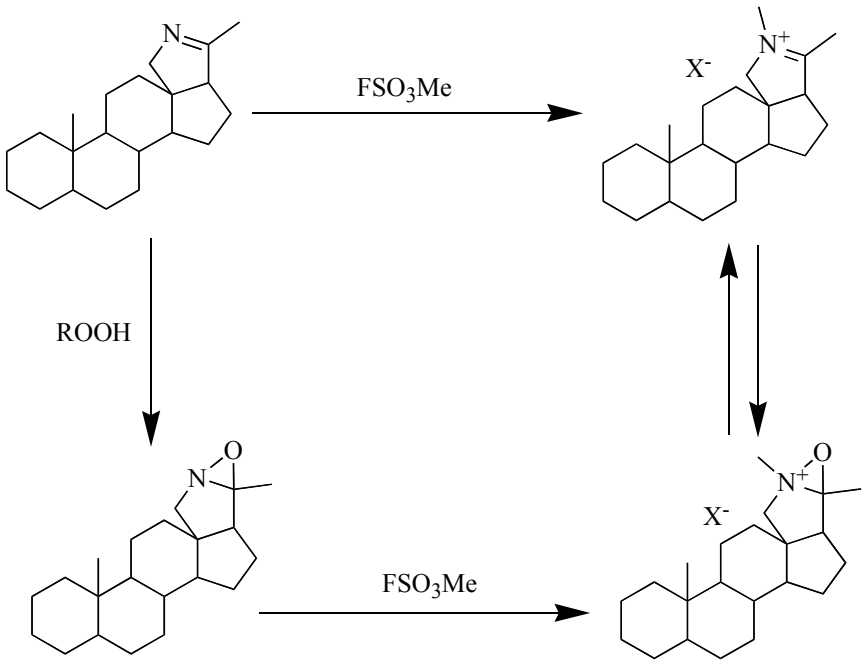
The approach through route b is disfavoured due to the proximity of the methyl substituents. Route a does not suffer from this steric interaction and therefore becomes the favoured spiro transition state. Denmark has also postulated that catalyst **49** may impart higher levels of enantiocontrol over alkenes with aryl functionality, this may be due to an electronic, π-π stacking interaction between the catalyst, and the alkenes aryl substituents.

1.5.3 Iminium/oxaziridinium salt mediated asymmetric epoxidation

1.5.3.1 Initial observations by Lusinchi

In 1976 Lusinchi first reported the use of oxaziridinium salts in asymmetric epoxidation. He observed that an unstable oxaziridinium salt could be prepared by peracid oxidation of an achiral steroidal imine with Oxone®, followed by quaternisation using methyl fluorosulfonate (Scheme 27).[113,114,115]

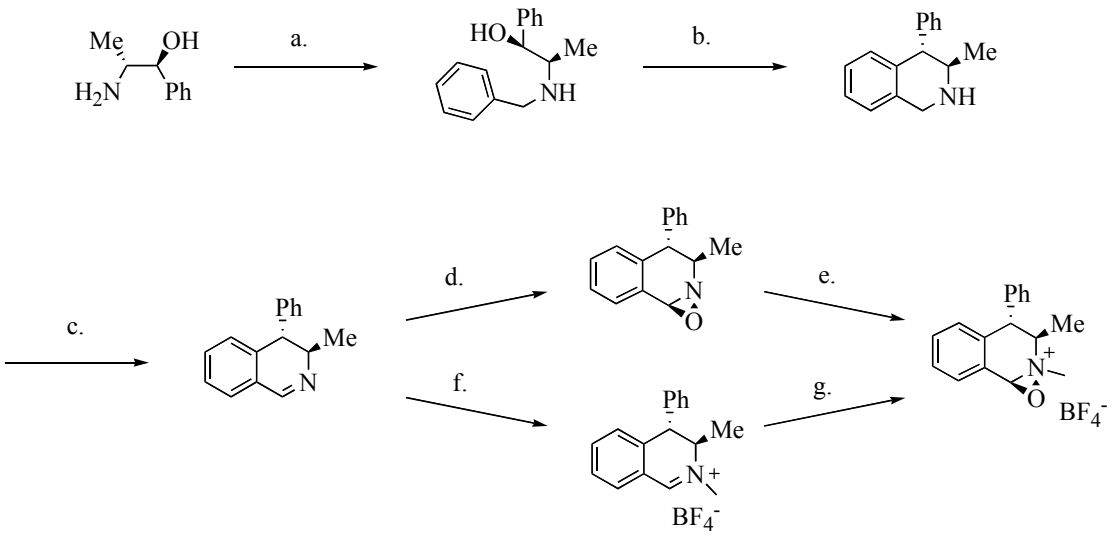
The oxaziridinium salt so generated contains a highly electrophilic oxygen atom. Lusinchi postulated that this highly strained heterocycle could then transfer the oxygen to an alkene.[116]



Scheme 27

Lusinchi proved his postulate by deriving an oxaziridinium salt from dihydroisoquinoline.[116,117,118,119] The imine was oxidised to the oxaziridine with a peracid and then quaternised with methyl fluorosulfonate. This oxaziridinium salt transferred the electrophilic oxygen to several simple nucleophilic alkenes in good yield**.**

Following this breakthrough, Lusinchi prepared the first enantiomerically pure oxaziridinium salt. This was achieved by quaternisation of an oxaziridine, derived from (1*S*,2*R*)-(+)-norephedrine, producing the oxaziridinium salt, **50** (Scheme 28).[120]



50

Reaganets and conditions; (a) PhCHO, $NaBH_4$. (b) CF_3COOH, H_2SO_4. (c) NaOCl, NaOMe. (d) MCPBA, MeOH. (e) $Me_3O^+BF_4^-$. (f) $Me_3O^+BF_4^-$, MeOH. (g) $NaHCO_3$, p-nitrobenzoic acid

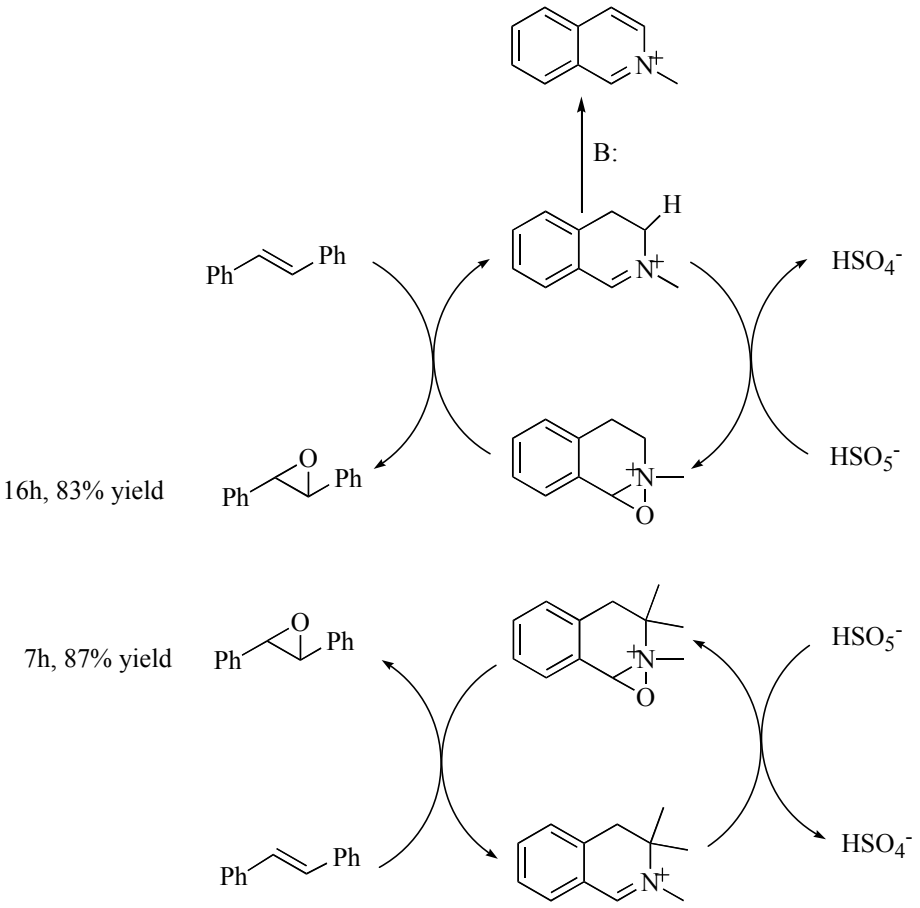
Scheme 28

Lusinchi used this enantiomerically pure oxaziridinium salt (**50**) in stoichiometric amounts to oxidise simple alkenes to their corresponding epoxides, for example *trans*–stilbene gave up to 33% *ee*. Lusinchi reported that a side product of the reaction was the iminium salt. He described that upon oxygen transfer from the oxaziridinium salt to the substrate alkene, the iminium salt catalyst was generated. If an oxidant is then added to this iminium ion, the oxaziridinium ion is regenerated and, capable of oxygen transfer to the alkene..

Lusinchi developed this approach with the addition of a catalytic amount (20 mol%) of the norephedrine iminium salt (**50**). He observed that *trans*–stilbene was again generated with 33% *ee*.

Lusinchi has shown that oxaziridinium salts are wide-spectrum oxygen transfer reagents. They are capable of transferring oxygen to other nucleophilic substrates such as; sulfides, to generate sulphoxides;[121] amines, to generate nitrones; and imines, to generate oxaziridines.[122]

Bohé, a student of Lusinchi, has since shown that dihydroisoquinolinium salt catalysts can under go loss of active oxygen from the oxaziridinium salt.[123] This occurs with irreversible base catalysed isomerisation of the oxaziridinium salt containing protons α to the nitrogen atom. This isomerisation causes a breakdown in the catalytic cycle.

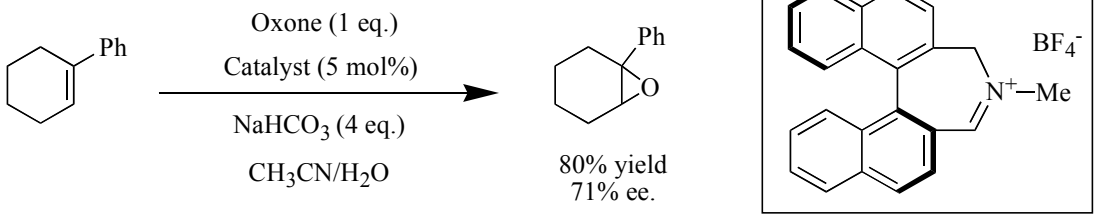


Scheme 29

Bohé has therefore developed a more stable achiral 3,3-disubstituted dihydroisoquinolinium catalyst (Scheme 29). This catalyst has displayed increased stability in comparison to the unsubstituted dihydroisoquinolinium catalyst, as it cannot undergo base catalysed isomerisation, due to there being no α–protons adjacent to the nitrogen atom.[123,124]

1.5.3.2 A C2–symmetric binaphthalene based iminium salt.

Aggarwal and Wang have reported an iminium salt catalyst that is based on a C2 symmetric binaphthalene functionality.[125,126,127] Catalyst 51 is thought to undergo oxidation with Oxone® to produce preferentially one diastereoisomer of the active oxaziridinium catalyst. This helps to induce enantiocontrol in the epoxidation by the exclusion of the competing oxygen transfer transition states on the more hindered face of the oxaziridinium salt.[128]

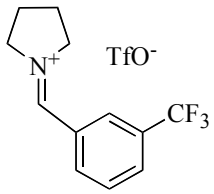


Scheme 30 ***Catalyst 51, 42% ee***

This binaphthyl-based iminium catalyst afforded 1–phenylcyclohexene oxide inducing 71% *ee*. All other alkenes tested gave lower *ee.*

1.5.3.3 Acyclic/exocyclic iminium salt catalysed asymmetric epoxidation

Armstrong has produced a range of acyclic iminium salt catalysts that transfer oxygen from the oxaziridinium unit to the nucleophilic alkene. These exocyclic iminium salts (**52**) were produced by the condensation of trimethylsilylpyrrolidine with aromatic aldehydes in the presence of trimethylsilyl triflate.[129]

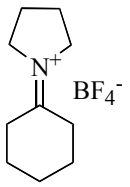


52, exocyclic iminium salts

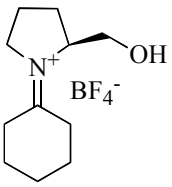
Armstrong observed that only aromatic iminium salt derivatives with a substituted electron–withdrawing group such as a chlorine or trifluoromethyl group would catalyse the reaction. Catalyst **52** afforded 100% conversion of *trans*–stilbene to the corresponding epoxide.[130]

Armstrong attempted to derive a range of exocyclic iminium salt catalysts comprising of binaphthyl units, methoxy substituted naphthyl groups, and chiral pyrrolidines. The only positive results were gained with the pyrrolidine catalysts, but these catalysts gave low enantioselectivities.

Komatsu has produced a set of aliphatic ketiminium salts bearing an exocyclic iminium unit. They are easily prepared by the condensation of cyclic amines with cyclic ketones in the presence of HBF_4.[131]



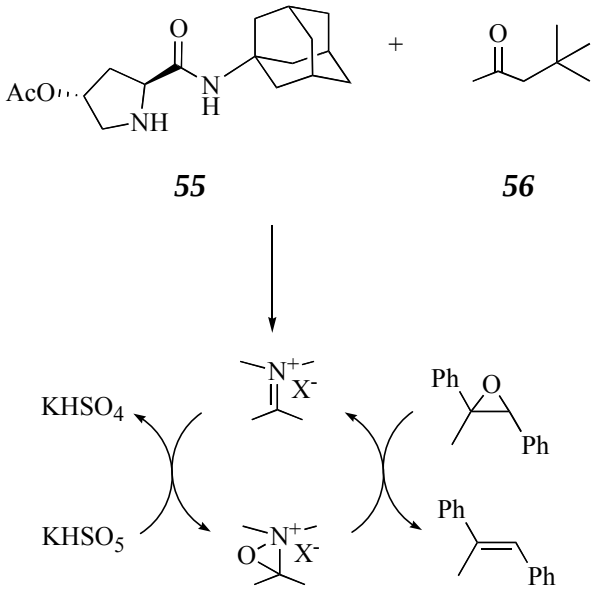
53



54

It was found that **53** gave the best conversion to the epoxide. A chiral version of this ketiminium salt, **54,** was produced, which gave 39% *ee* and 70% conversion when using cinnamyl alcohol as the substrate.

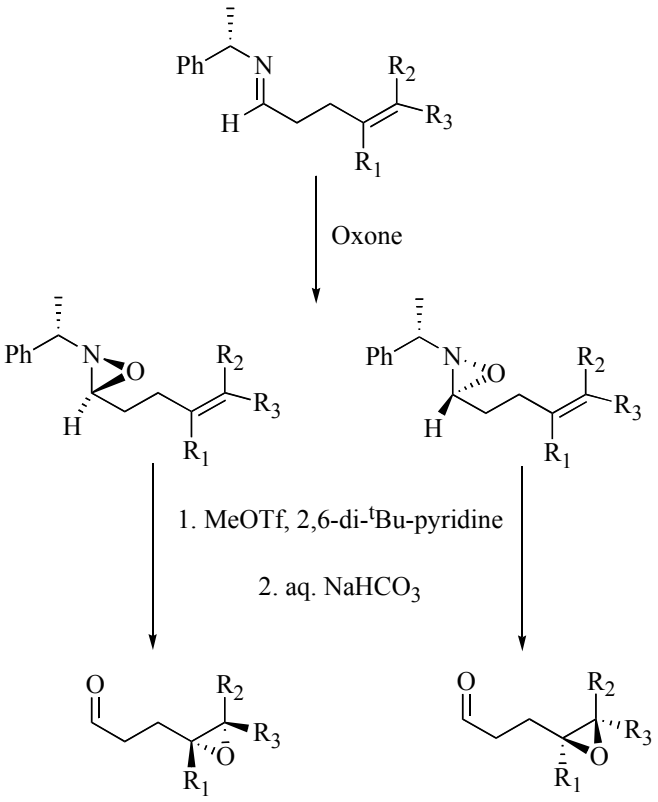
More recently, Yang discovered that the condensation of an amine (**55**) with a suitable ketone (**56**) under acidic conditions generated the iminium salt *in situ*; this iminium salt then efficiently catalysed the epoxidation of *trans*–α–methylstilbene, imparting 59% *ee* (Scheme 31). Further research showed that some amines could individually mediate the epoxidation of alkenes by oxygen transfer *via* a peracid intermediate.[132]



Scheme 31, in situ generation of the iminium salt

1.5.3.4 Intramolecular epoxidation of unsaturated oxaziridines

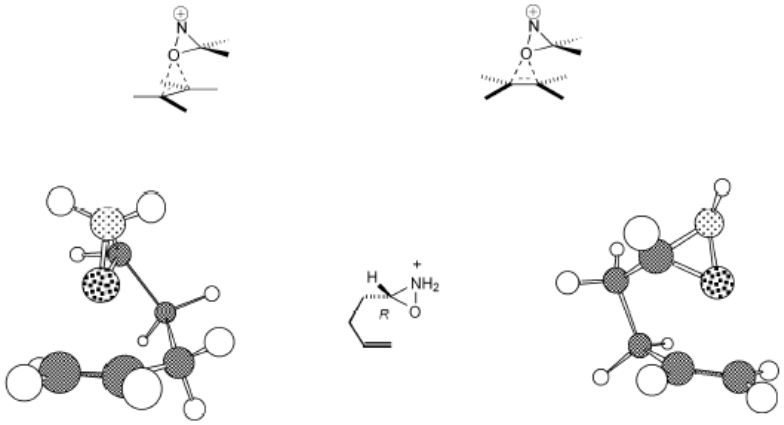
Armstrong has also reported his findings on an enantioselective intramolecular asymmetric epoxidation.[133] An imine was generated from the condensation of a primary amine and an unsaturated aldehyde. The imine was converted to the oxaziridine salt as a pair of separable diastereoisomers (Scheme 32).



Scheme 32

Both oxaziridines were converted in to oxaziridinium salts by methylation of the nitrogen with methyl trifluoromethanesulfonate. In the presence of these oxaziridinium salts, the attached alkene underwent intramolecular asymmetric epoxidation with 84 – 98% *ee* depending on the identity of R_1, R_2 and R_3.

Armstrong has suggested that the high stereoselectivity occurs through each of the two diastereoisomeric oxaziridinium salts progressing through one of two different transition states.[134,135] The planar transition state model (**58**) generates the opposite stereochemistry to that of the parent oxaziridine. For example, the planar transition state of the (2*R*, 3*R*) gives the pro–*S* conformation. The spiro transition state model (**57**), however, retains the stereochemistry from the oxaziridine used; the (2*R*, 3*R*) oxaziridine gives the pro–*R* conformation.



57 ***58***

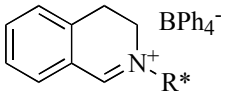
Spiro model, (4R) epoxide predicted ***Planar model, (4S) epoxide predicted***

Experiment shows that both diastereoisomers of the oxaziridinium species give results consistent with the spiro transition state model (**57**). Unfortunately there is a loss of selectivity when the chain length exceeds three atoms between the aldehyde and alkene.

1.5.3.5 Page's chiral iminium salt catalysts

1.5.3.5.1 Dihydroisoquinolinium salt catalysts

Initially based around the findings of Lusinchi and Bohé the Page group produced their own dihydroisoquinolinium salt catalysts with important variations. They introduced a chiral exocyclic nitrogen substituent through cyclo-condensations of primary amines with 2–(2–bromoethyl)-benzaldehyde and subsequent counter ion exchange with tetraphenylborate to generate the crystalline iminium salts (**59**). The rationale was that the close proximity of the exocyclic asymmetric centre to the site of oxygen transfer would increase the enantiocontrol induced in the epoxidation of alkenes.[136]



59, Page's isoquinolinium salt catalyst

A range of primary amines were cyclo-condensed with the bromoaldehyde and tested for their enantioselectivity in the epoxidation of simple alkenes.

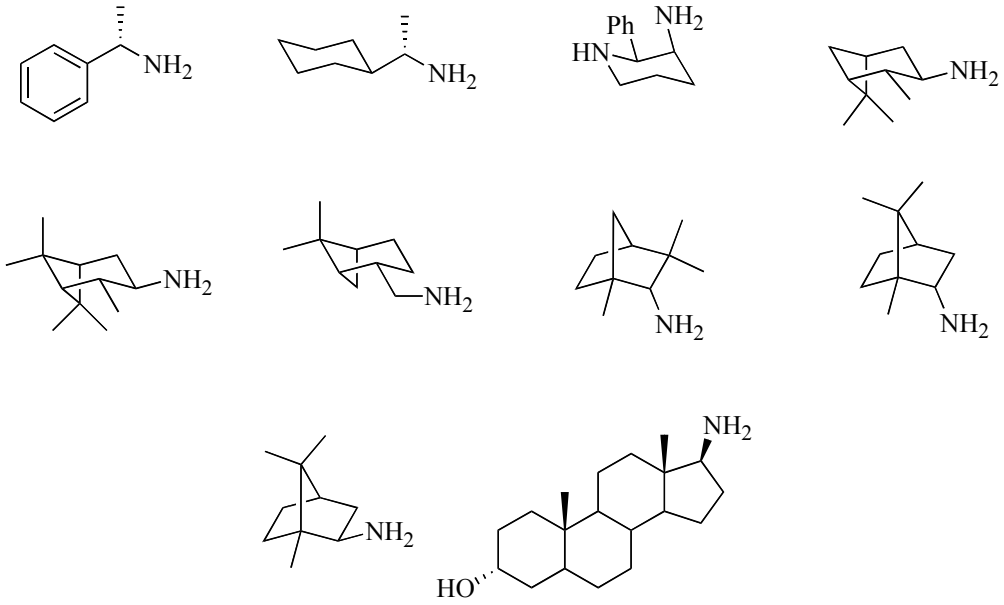
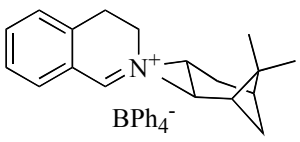


Figure 60

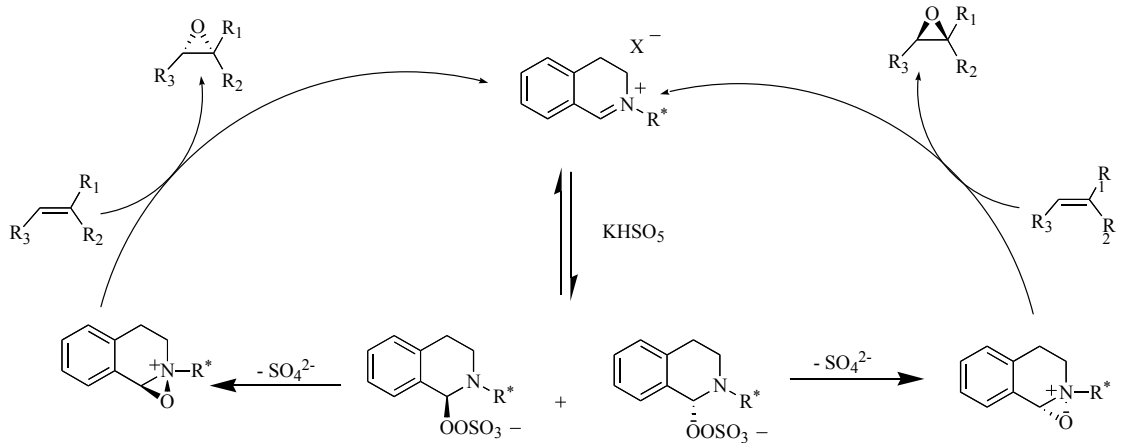
The general method of epoxidation used Oxone® (2 equiv.) as the stoichiometric oxidant in MeCN/H_2O (1:1), Na_2CO_3 (4 equiv.) as base and the iminium salt catalyst (10 mol%). Initial observations showed that one catalyst gave higher enantioselectivity than all others; this was the *N*–isopinocampheyl derivative (**61**) that gave 40% enantioselectivity at 0 ºC for the epoxidation of 1–phenylcyclohexene .



61, N–isopinocampheyl iminum salt catalyst

The mechanism of oxidation is hypothesised to occur through nucleophilic attack of the persulphate oxidant ($KHSO_5$) on the electrophilic iminium carbon atom, forming a pair of persulphate diastereoisomers as the nucleophile can attack at either the *Re* or *Si* face of the iminium bond.[137]

It is currently suspected that the rate-determining step is the subsequent nitrogen lone pair attack on to the most electrophilic oxygen, displacing a sulphate-leaving group to give the two corresponding diastereoisomeric oxaziridinium salts. The oxygen transfer by these diastereoisomeric oxaziridinium salts onto the prochiral faces of the alkene substrate may occur with varying degrees of enantiocontrol through a spiro transition state model (Scheme 33).[138]



Scheme 33

1.5.3.5.2 Reaction parameters

A review of the reaction parameters was completed in order to optimise the reaction conditions with respect to the enantioselectivity of the oxidation process. The isopinocampheylamine derivative was chosen as the model catalyst for the optimisation of the parameters that were thought to influence the enantioselectivity of the process.[139]

In addition to the original tetraphenylborate anion, the corresponding bromide, tetrafluoroborate, hexafluorophosphate, perchlorate and periodate salts were also prepared. All of the salts were tested in the asymmetric catalytic epoxidation of 1–phenylcyclohexene . The periodate and bromide salts produced enantioselectivies (35%

and 40% respectively) comparable to those obtained with the tetraphenylborate catalyst (40% *ee*), while the fluoride containing counter–ions afforded lower *ee* (28%), as did the perchlorate salt (20% *ee*). All of the salts produced the same enantiomer of the epoxide product (*R*,*R*) as the major component, and all of the reactions were complete within the same time scale, ~ 45 minutes.

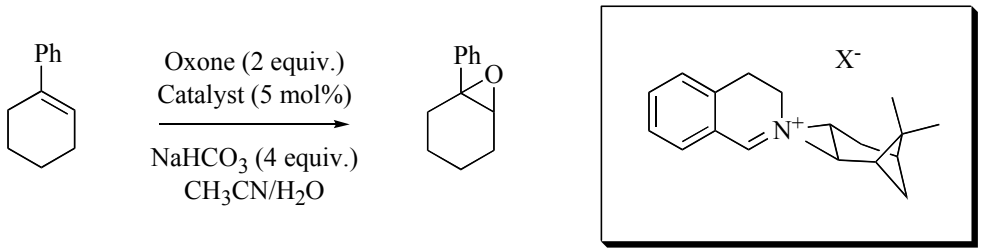
As previously indicated, the standard oxidation solvent used was acetonitrile/water (1:1 or 2:1). Initial observations suggested that increasing the water concentration in acetonitrile also increased the rate of oxidation. Presumably a result of increasing Oxone® solubilisation with increasing water concentration, such that the rate of nucleophilic attack by persulphate on the iminium species is increased, leading to a concentration effect coupled with better solvation of the departing sulfate ion. Yang has more recently published evidence that in the presence of a bicarbonate salt the rate of reaction can be increased, if the amount of water is reduced to 10% in acetonitrile.[105]

Reducing the amount of Oxone® and base by a factor of two (*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 may result from competitive decomposition of Oxone® under the basic conditions, and hence, in a faster reaction, more of the unstable oxidant is consumed in the desired oxygen transfer process. The effect is more pronounced when small amounts of catalysts are used. It was also observed that there was no significant change in enantiocontrol when the reaction temperature was varied from –10 °C to 30 °C for varying co-solvent ratios.

Increasing the water content of the reaction solvent system gives a considerable rate change without change in enantioselectivity. This suggests that the rate-determining step does not involve oxygen transfer to the substrate, *i.e.* that the subsequent enantioselective oxygen transfer to alkene is not the rate-determining step under these conditions (Scheme 33).

Also investigated was the potential correlation of reaction rates and extent of asymmetric induction with the polarity of the co–solvent, The co–solvents used were selected so that they differed significantly in dielectric constant (indicated by the values in brackets):

dichloromethane (8.9), trifluoroethanol (26.7), acetonitrile (37.5), water (78.4), formamide (111).



Catalyst 61

Scheme 34

The epoxidation of 1–phenylcyclohexene with the isopinocampheyl catalyst (**61**) was performed in a 1:1 ratio of co–solvents. In order also to examine the counter–ion effect (Scheme 34), the catalyst was tested both as its perchlorate and tetraphenylborate salts (20 and 40% *ee* respectively, in acetonitrile). The perchlorate and tetraphenylborate salts mediate the quantitative epoxidation of 1–phenylcyclohexene in trifluoroethanol within 30 minutes and 26% *ee.* There was no reaction in formamide for either salt, suggesting that the iminium species are too well stabilised, and the possibility of an irreversible reaction with formamide is also possible. In dichloromethane, enantioselectivity mediated by the perchlorate salt increased to 33% but only 50% conversion after three hours whereas the tetraphenylborate gave no oxygen transfer. The difference in reactivity for the counter–ions in dichloromethane/water reflects the poor miscibility of the two solvents, which must severely limit the availability of the inorganic oxidant in the organic phase.

For the isopinocampheyl tetraphenylborate salt, catalyst loading with respect to enantiocontrol is shown in Figure 62. Using a fixed concentration of 1–phenylcyclohexene as substrate, the graph shows that the enantioselectivity remains within experimental error as the catalyst loading decreases from 5 mol% to 1 mol%. Lower catalyst loading, down to 0.1 mol%, results with complete conversion of the substrate alkene to the desired epoxide but with a reduction in the enantioselectivity. Later work has shown that other catalysts appear to suffer less in this regard.

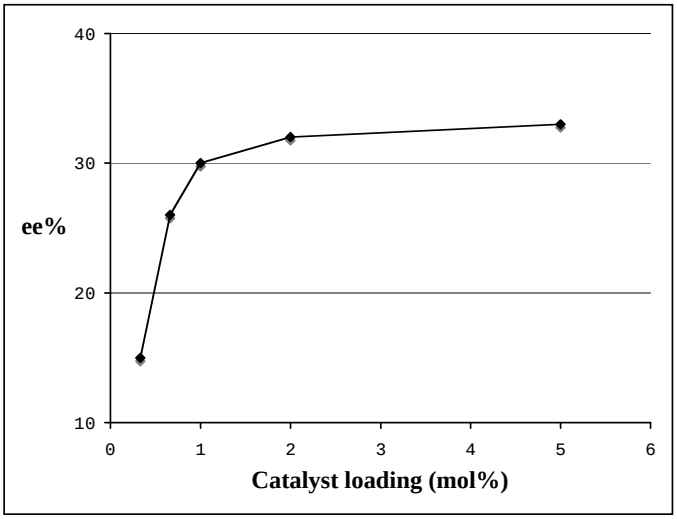
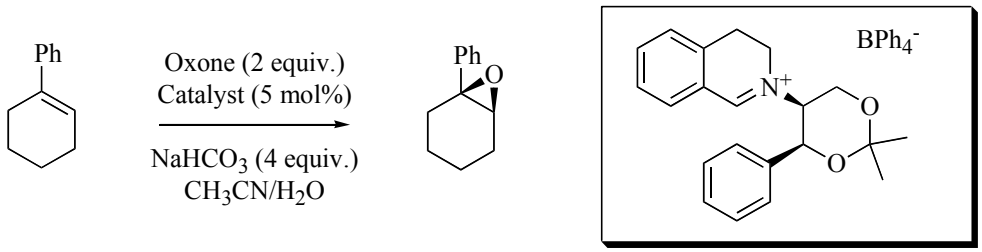


Figure 62

1.5.3.5.3 Development of iminium salt catalysts

Page hypothesised that the presence of a primary or secondary hydroxyl group may improve enantioselectivity. Therefore a range of iminium salt catalysts was prepared from chiral amino alcohols, but unfortunately both poor reactivity and enantioselectivity were observed.[139]

Page then introduced a substituted dioxane functionality, using (1*S*, 2*S*)-2–amino–1–phenylpropane–1,3-diol, which was protected as the acetonide. This gave a dioxane unit with a primary amine that would undergo cyclo-condensation with the bromoaldehyde. This *N*–aminodioxane-functionalised iminium salt catalyst (**63**) was employed in the epoxidation of alkenes, and it induced similar enantiocontrol to the *N*–isopinocampheyl derivative, for example giving 40% *ee* at 0 ºC when oxidising 1–phenylcyclohexene (Scheme 35).

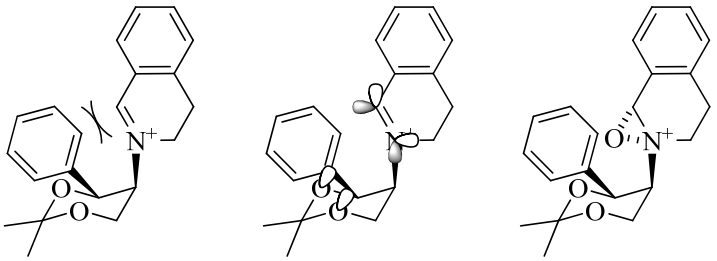


Catalyst 63, 40% ee

Scheme 35

1.5.3.5.4 Electronic control of dioxane sub–units

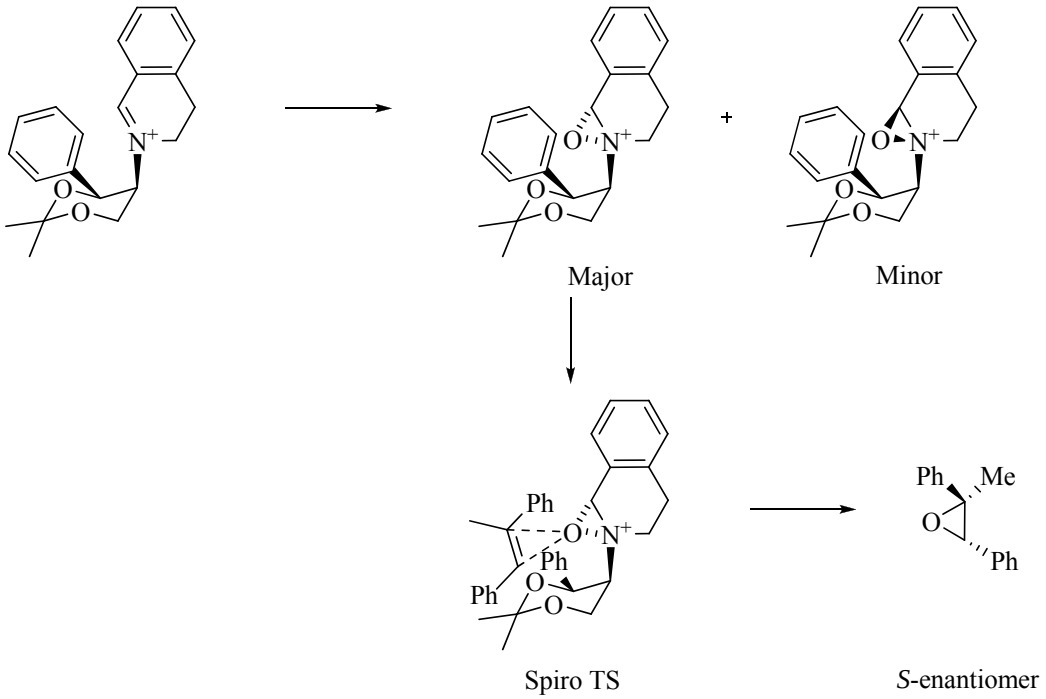
The success of this *N*–aminodioxane catalyst is thought to stem from the high conformational rigidity of the six–membered dioxane ring and also the *syn* relationship between the nitrogen heterocycle and the phenyl moiety. NMR spectroscopy and single crystal X-ray analysis suggest that the dioxane ring retains its chair conformation by placing the nitrogen heterocycle axial and the equally large phenyl ring equatorial (**64**). This thermodynamically favourable conformation reduces the 1,3-diaxial interactions and allows electronic interactions between the oxygen lone pairs and the electron poor carbon iminium atom (**65**). [138]



64 ***65*** ***66***

Therefore the thermodynamic conformation leading to the equatorial positioning of the phenyl ring may then help inhibit approach toward one face of the iminium unit by either the Oxone® oxidant or the approaching olefin. One diastereoisomeric oxaziridinium salt may therefore be favoured (**66**) over the other and in turn generating epoxides with increased *ee*.

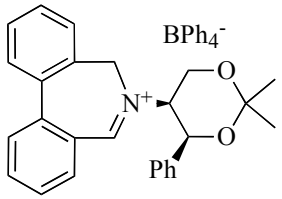
Of the two generalised transition state models, the spiro transition state is the accepted model with in iminium salt catalysed asymmetric epoxidation. Due to the postulated conformer **64**, the presence of the phenyl group may hinder the attack of the oxidant at the *si* face therefore generating the minor oxaziridinium diastereoisomer (Scheme 36). The oxidant attack at the *re* face is therefore favoured, thus generating the major oxaziridinium diastereoisomer, which through a spiro transition state undergoes oxygen transfer to the alkene yielding the epoxide with high enantiocontrol.



Scheme 36

1.5.3.5.5 Biphenyl azepinium salts

The Page group have also exchanged the dihydroisoquinolinium backbone (**63**) for a biphenyl structure fused into an azepinium salt (**67**) in the hope of increased enantioselectivity. [11]

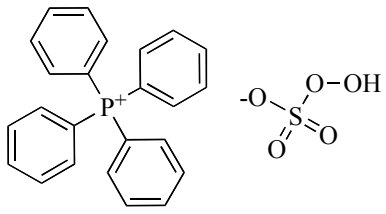


67, azepinium salt catalyst

Preparation of this catalyst proceeded through ring closure of 2,2'–biphenyldimethanol with HBr to give the dibenzooxepine. Treatment with bromine generated the bromoaldehyde, which can then be condensed with the primary aminodioxane. Addition of $NaBPh_4$ gave the desired iminium salt catalyst (**67**). This azepinium salt catalyst generated 60% *ee* and 100% conversion for 1-phenylcyclohexene in under 10 minutes (5 mol%), showing that the biphenyl substructure increased both enantioselectivity and rate of reaction over previous catalysts (40% *ee* for both catalyst **61**and Catalyst **63**).

It was observed that the Oxone® system would only work if the solvent system in use contained a high percentage of water. Oxone® has the highest solubility in water over any organic solvent. Due to the quantity of Oxone® used (2 mmol) it will only dissolve in a considerable volume of water (~ 4.25ml), this is equal to the amount of the co–solvent (MeCN) required, making the ratio of solvents 1:1. This has a limiting effect on the range of temperatures at which the reaction can be carried out. The highest reaction temperature is defined by Oxone® itself as it starts to decompose at approximately 30 °C.[140] The lowest temperature is defined by the solvent system; the use of a 1:1 (MeCN:H_2O) co–solvent system allows the temperature to be reduced to –8 °C before the aqueous phase freezes. An opportunity to enhance the enantioselectivity of the process could be provided if the reaction could be completed at lower temperatures.

Therefore the Page group investigated other oxidants with the idea of designing a non–aqueous epoxidation system. They found that tetraphenylphosphonium monoperoxysulfate (TPPP, **68**) gave the highest enantioselectivity of all oxidants tested. Most importantly, it is completely soluble in organic media, gave no background epoxidation and at –40 ºC gave good enantioselectivity in the epoxidation of 1–phenylcyclohexene , attaining 67% ee[141]

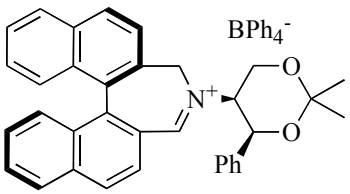


68, TPPP

A temperature study was undertaken, as lower temperature could now be attained without freezing of the reaction medium. First it was found that MeCN gave higher *ee* than methylene chloride when used as the reaction solvent. Secondly, and most importantly, as the temperature of the reaction decreases the enantioselectivity of the reaction increases.

1.5.3.5.6 Binaphthalene azepinium salts

Aggarwal has produced a binaphthalene–fused azepinium salt catalyst (**68**) that is achiral at the nitrogen substituent; this iminium salt catalyst affords 71% *ee* for 1–phenylcyclohexene and 45% *ee* for α–methylstilbene.[128] The Page group postulated they could create a range of *N*–chiral catalysts that would induce higher levels of enantiocontrol by simply exchanging the biphenyl group for a binaphthalene unit, as in **69**.

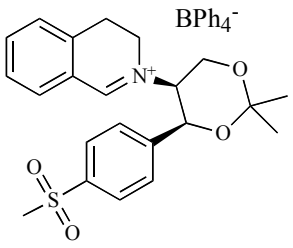


69, binaphthalene azepinium salt

The bromomethyl carbaldehyde was prepared from commercial (*R*) or (*S*) BINOL. To this, the aminodioxane was added, cyclo-condensing to generate the iminium salt (**69**).[142]

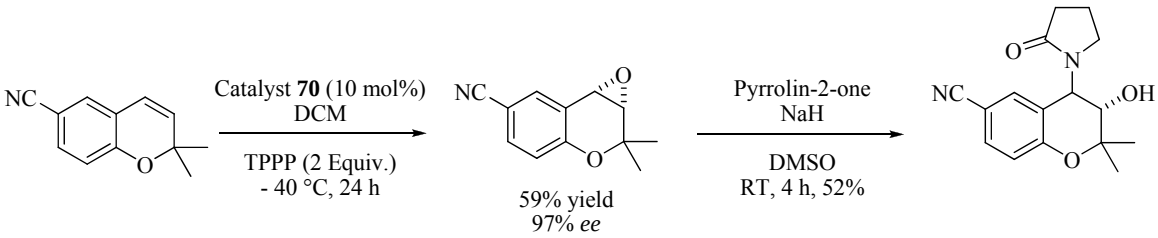
Catalyst **69** generated 91% *ee* for 1–phenylcyclohexene oxide, 95% *ee* for 1–phenyldihydronapthylene oxide, and 29% *ee* for 4-vinylbiphenyl oxide, which is the highest reported *ee* for the epoxidation of a terminal alkene using an iminium salt catalyst.

The Page group have recently reported a novel sulphone functionalised isoquinolinium derived catalyst (**70**) that has given high enantiocontrol in the epoxidation of cyclic *cis*–alkenes under non–aqueous conditions using chloroform as a solvent.[143]



70, sulphone functionalised isoquinolinium catalyst

High yields of up to 86% and up to 97% *ee* were obtained. Catalyst **70** has been used to obtain excellent enantiocontrol in the epoxidation of 6–cyano–2,2-dimethylbenzopyran. The resulting epoxide is a useful intermediate, which when subjected to ring opening gives access to levcromakalim, a biologically active antihypertensive agent (Scheme 37).[143]

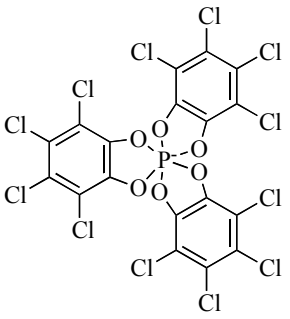


Scheme 37

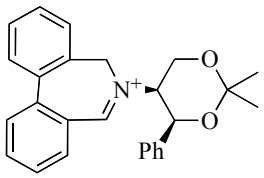
Azepinium binaphthalene iminium salt catalysts have generated some of the highest enantioselectivities for iminium salt catalysed epoxidation. Even with decreased catalyst loading; a 0.1 mol% loading of catalyst **67** gives 88% *ee* for 1–phenylcyclohexene .

1.5.3.6 Lacour's trisphat counterion chiral iminium salt catalysts

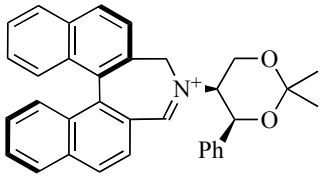
Lacour's research utilised the same iminium ion developed by Page; his derivation was to use a TRISPHAT [tris(tetrachlorobenzenediolato)phosphate(v)] counter-ion to pair with the active iminium species.[144] The TRISPHAT anion and subsequent catalyst pairings are lipophilic and have preference for the less polar organic layer. The pairing of the enantiomerically pure TRISPHAT anion with a biphenyl catalyst leads to the formation of diastereoisomeric intramolecular and/or intermolecular interactions, which shifts the conformational equilibrium towards one preferred, (*R*a) or (*S*a), diastereoisomer of the active catalyst's biaryl backbone. With one diastereoisomer preferred the observed enantiocontrol might increase. The binaphthyl based catalysts, with their fixed axial chirality, would not benefit from such pairing. [145]



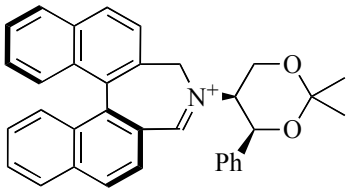
71



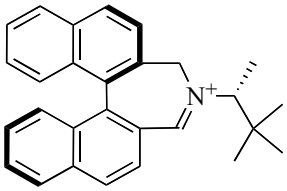
72



73



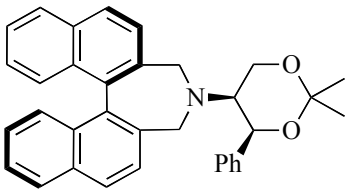
74



75

The TRISPHAT anion **71** was paired with biphenyl catalyst **72**, matched (S_a,*S*) binaphthyl catalyst **73**, mis–matched (R_a,*S*) binaphthyl catalyst **74** and mis-matched (S_a,*R*) catalyst **75**. Catalyst **72** induced up to 54% and 68% *ee* when using 1–phenylcyclohexane and 1,2-dihydronaphthylene respectively as the alkene substrates. Matched catalyst **73** induced 81% and 83% *ee,* whilst its atropisomer, mis–matched **74**,

induced 79% and 78% *ee* over the same alkene substrates. Catalyst **75** offers the highest enantiocontrol for a TRISPHAT counter ion iminium salt catalyst giving 86% and 87% *ee*.[146] It was observed that the TRISPHAT counter-ion decreases the enantiocontrol induced by the selected iminium salt catalysts.[147]



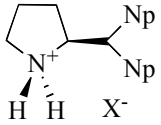
76

In a small number of cases, amine **76** displayed similar enantioselectivity to its iminium salt catalyst derivative **73.** Amine **76** imparted 80% *ee* for 1,2-dihydronaphthylene oxide and 49% *ee* for methyl *trans* stilbene oxide.

1.5.4 Amine catalysed Epoxidation

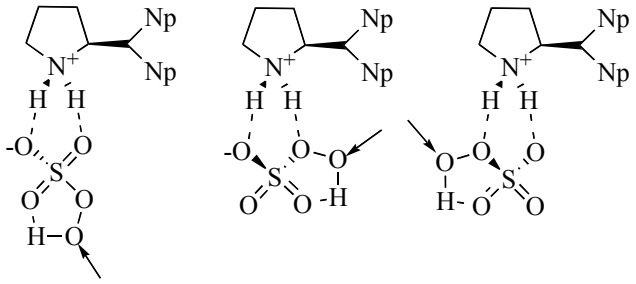
1.5.4.1 Initial observations by Aggarwal

Aggarwal has also examined amine–catalysed epoxidation; his initial observations, based on control epoxidations, showed that a chosen secondary amine hydrogen chloride salt, with added bicarbonate salt and Oxone®, could mediate the alkene epoxidation alone. Condensation with a selected ketone, as previously shown, to produce the iminium salt catalyst was not required. This observation resulted in the trial of a multitude of secondary amines for activity.[148]



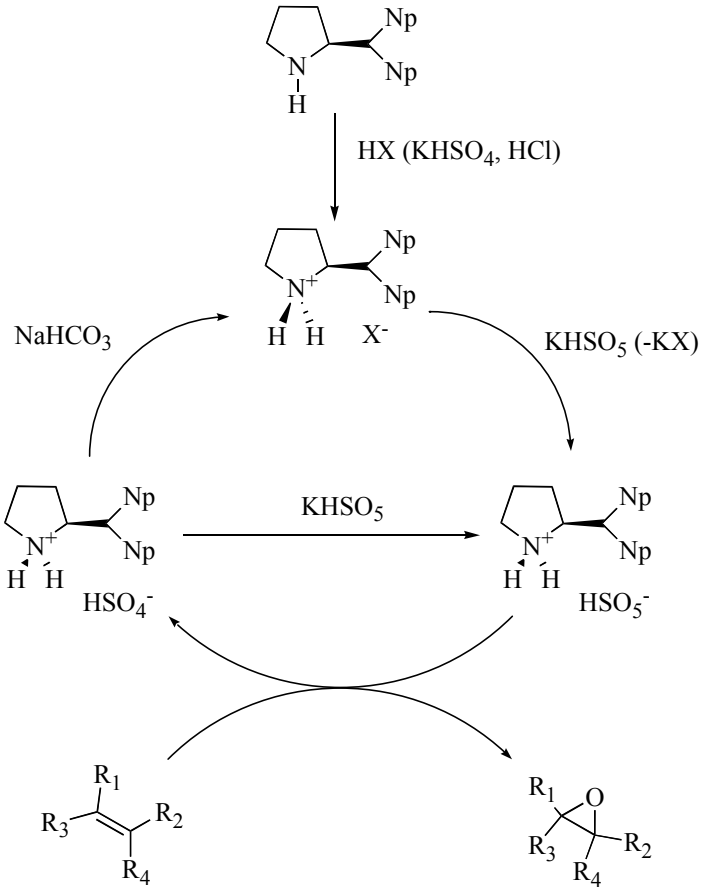
77, dinaphthyl–methyl pyrrolidine

Aggarwal produced an amine hydrogen chloride salt catalyst based on the most reactive and enantioselective secondary amine; this was a chiral dinaphthyl–methyl pyrrolidinium salt (**77**). [149] Using their optimised conditions, **77** mediated epoxidation, inducing up to 66% *ee*.



78, persulphate stabilised complex

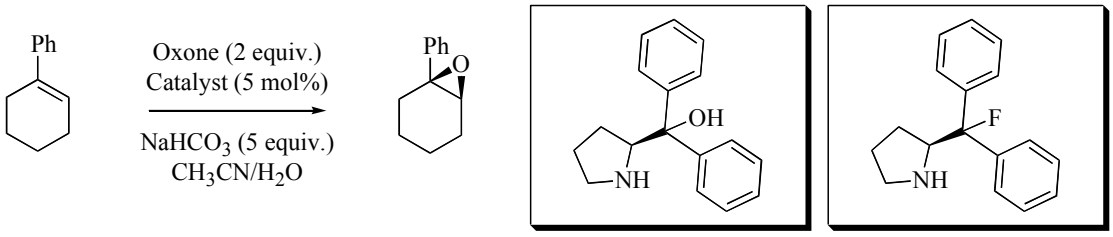
Mechanistic studies of the oxidation process were completed. It was observed that on the addition of Oxone® to the chiral amine, the active oxidant, persulphonic acid, becomes hydrogen bonded to the amine salt, this may occur in three differing orientations (Figure 78).[150] A reduction in enantioselectivity may be envisaged due to the presence of these three competing transition states. The alkene then approaches the amine–peracid complex, and oxygen transfer occurs (Scheme 38).



Scheme 38

1.5.4.2 Developments by Yang

Whilst developing the *in situ* generation of iminium salt catalysts for asymmetric epoxidation, Yang also observed that control experiments involving just an amine facilitated the production of an epoxide from the alkene substrate.[132] Following these observations Yang examined a variety of amines to determine their activity in asymmetric epoxidation. Yang found that cyclic secondary amines gave the highest levels of enantiocontrol, especially cyclic secondary amines containing a β–hydroxyl group. Yang optimised the process further by screening a range of pyrrolidine analogues for increased levels of enantiocontrol in the epoxidation of *trans*–stilbene. It was observed that amine **79** induced a fair level of enantiocontrol, giving up to 33% *ee* and 58% conversion.



Scheme 39 ***79*** ***80***

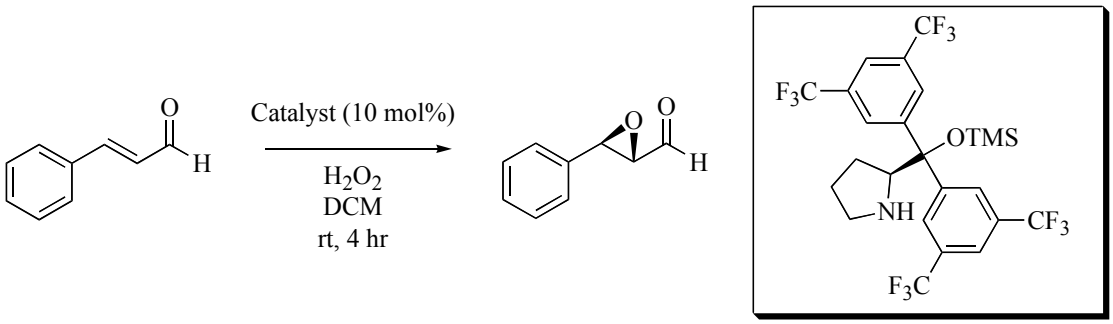
33% ee ***rt = 50% ee***

– 20 °C = 60% ee

Further work showed that conversion of the hydroxyl group in to the corresponding fluoro group gave catalyst (**80**) with increased reactivity, which was observed to give enantiocontrol of up to 50% with 100% conversion with 1–phenylcyclohexene (Scheme 39). The enantiocontrol was increased further with the reduction of the temperature to –20 °C, giving up to 60% *ee.* Yang also completed mechanistic studies similar to those of Aggarwal and agreed that the mechanism does progress through a pyrrolidinium complex.[151]

1.5.4.3 Jørgensen's oxidation of α,β–unsaturated ketones.

Jørgensen produced his first organo–catalytic asymmetric epoxidation of α,β–unsaturated ketones using various peroxides as the stoichiometric oxidant.[152] A number of chiral amines were examined as facilitators for the asymmetric epoxidation of cinnamic aldehyde. It was once more observed that a chiral pyrrolidine derivative, amine **80**, in conjunction with hydrogen peroxide afforded good *ee*, up to 96% *ee* in the product epoxide (Scheme 39).



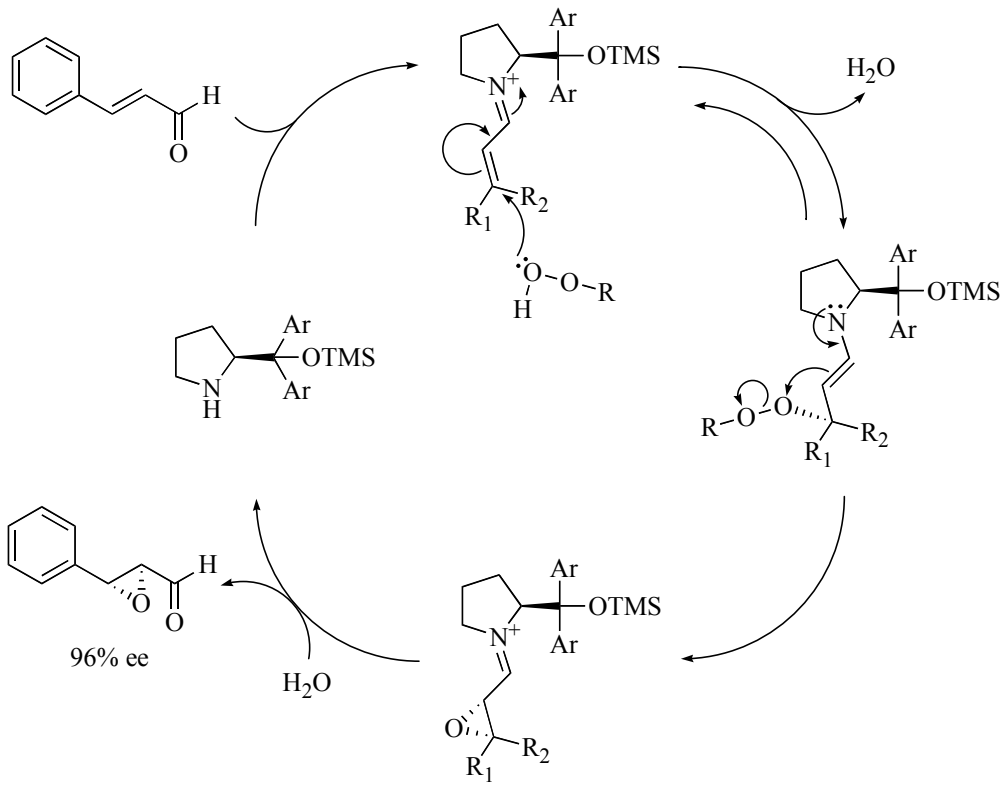
Catalyst 81, 96% ee

Scheme 40

Further investigations utilising amine **80** and hydrogen peroxide gave epoxides with high enantiomeric control (96 – 98%) and yield (60 – 90%). Jørgensen also published their mechanistic rationale for this procedure.

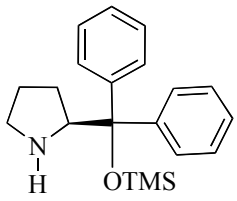
The mechanism is postulated as involving initial nucleophilic attack by the amine on the aldehyde to generate the iminium intermediate. Nucleophilic attack of the peroxide on the β–carbon generates the chiral enamine intermediate. Nucleophile attack by the enamine at the most electrophilic per–oxygen then gives the epoxy–iminium adduct. Hydrolysis of the iminium functionality generates the desired epoxy–aldehyde and the amine catalyst (Scheme 41).

The solvent of choice is usually dichloromethane, but recently Jørgensen has published a modification in which the reaction can be completed in an aqueous medium (ethanol/water) using amine **80** and hydrogen peroxide as a stoichiometric oxidant, generating up to 96% *ee*.[153]

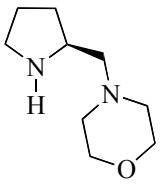


Scheme 41

Cordova has also investigated related catalytic systems using catalysts **82** and **83** similar result have been published using sodium percarbonate and hydrogen peroxide as stoichiometric oxidants, generating up to 98% *ee*.[154]



82



83

1.6 Chapter one references

1 Lin, G. Q.; Li, Y. M.; Chan, A. S. C. *In Principles and Applications of Asymmetric Synthesis.* Wiley Interscience. **2001**, *3*.

2 http://nobelprize.org/*Chemistry*/educational/poster/2001/index.html

3 Clayden, Greeves, Worren & Wothers, *Organic Chemistry,* Oxford University Press. **2001**, 1220.

4 Blaschke, G.; Kraft, H. P.; Markgraf, H. *Chem. Ber.* **1980**, *113*, 2318.

5 Rouhi, M. *Chem. Eng. News* **2002**, *80*, 43.

6 http://www.*Chem.*ucalgary.ca/courses/351/carey/ch16/ch16–4.html

7 Pawwa, A.; Murphree, S. S. *Arkivoc* **2006**, part iii, 6.

8 Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974

9 Zhang, W.; Leobach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801.

10 Tu, Y.; Wang, Z.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806.

11 Page, P. C. B.; Rassias, G. A.; Barros, D.; Ardakani, A.; Bethell, D.; Merifield, E. *Synlett* **2002**, 580.

12 Hoard, D. W.; Moher, E. D.; Martinelli, M. J.; Norman, B. H. *Org. Lett.* **2002**, *4*, 1813.

13 Besse, P.; Veschambre, H.; *Tetrahedron* ***19*94**, *50*, 8885.

14 Trost, B. M. *Proc. Nat. Acad. Sci.* **2004**, *101,* 5348.

15 Bartok, M.; Lang, K. L. *Small Ring Heterocycles* (Ed. Hassner, A.), Wiley Interscience, Vol. 42, Part 3, **1985**.

16 Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.

17 Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5795

18 Bartlett, P. D. *Rec. Chem. Prog.* **1950**, *11*, 47.

19 Bartlett, P. D. *Rec. Chem. Prog.* **1957**, *18*, 111.

20 Shi, H.; Zhang, Z.; Wang, Y. *J. Mole. Catal. A: Chemical* **2005**, *238,* 13.

21 Yao, H.; Richardson, D. E. *J. Am. Chem. Soc.* **2000**, *122*, 3220.

22 Payne, G. B.; Denning, P. H.; Williams, P. H. *J. Org. Chem.* **1961,** 26*,* 659.

23 Payne, G. B. *Tetrahedron* ***19*62,** *18,* 763.

24 Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

25 Michaelson, R. C.; Palermo, R. E.; Sharpless, K. B. *J. Am. Chem. Soc*. **1977**, *99*, **1990**.

26 Lin, G. Q.; Li, Y. M.; Chan, A. S. C. *In Principles and Applications of Asymmetric Synthesis,* Wiley Interscience, **2001**, 195 – 202.

27 Woodward, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113.

28 Martin, V. S.; Woodwar, S. S.; Katsuki, T.; Yamada, Y.; Keda, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

29 Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 106.

30 Procter, G. *Asymmetric Synthesis*, Oxford University Press **1996.**

31 Kumar, P.; Bodas, S, M. *J. Org. Chem.* **2005**, *70*, 360.

32 Groves, J. T.; Nemo, T. E.; Myers, R. S. *J. Am. Chem. Soc.* **1979**, *101*, 1032

33 Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791

34 Berkessel, A.; Frauenkron, M. *J Chem. Soc. Perkin Trans. 1,* **1997**, 2265.

35 Halterman, R. L.; Jan, S. –T. *J. Org. Chem.* **1991**, *56,* 5253.

36 Halterman, R. L.; Jan, S. –T.; Nimmons, H. L.; Standlee, D. J.; Kahn, M. A. *J. Org. Chem.* **1991**, *56,* 5253.

37 Naruta, Y.; Tani, F.; Maruyama, K. *Tetrahedron Lett.* **1992**, *33*, 6362.

38 Collman, J. P.; Wang, Z.; Strausmanis, A.; Qualquejeu, M. *J. Am. Chem. Soc.* **1999**, *121*, 460.

39 a) Collman, J. P.; Lee, V. J.; Kellen–Yuen, C. J.; Zhang, X.; Ibers, J. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1995**, *117,* 692; b) Naruta, Y.; Ishihara, N.; Tani, F.; Maruyama, K. *Bull. Chem. Soc. Jpn.* **1993**, *66,* 158.

40 Samsel, E. G.; Srinivasan, K.; Kochi, J. K. *J. Am. Chem. Soc.* **1985**, *107***,** 7606.

41 Srinivasan K.; Michaud, P.; Kochi, J. K.; *J. Am. Chem. Soc.* **1986**, *108***,** 2309.

42 Ito, Y. N; Katsuki, T. *Tetrahedron Lett.* **1998**, *39*, 4325.

43 Zhang, W. Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112***,** 2801.

44 Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296.

45 Zhang, W.; Jacobsen, E. N.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063.

46 Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333.

47 Cavallo, L.; Jacobsen, H. *Inorg. Chem.* **2004**, *43*, 2175.

48 Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345

49 Irie, R.; Noda, K.; Ito, Y.; Katsuki, T. *Tetrahedron Lett.* **1990**, *32*, 1058.

50 Hosoya, N.; Irie, R.; Ito, Y.; Katsuki, T. *Synlett* **1991**, 691

51 Hatayama, A.; Hosoya, N.; Ito, Y.; Katsuki, T. *Synlett* **1992**, 407.

52 Hosoya, N.; Irie, R.; Katsuki, T. *Synlett* **1993**, 261.

53 Hosoya, N.; Hatayama, A.; Yanai, K.; Fujii, H.; Irie, R.; Katsuki, T. *Synlett* **1993**, 641.

54 Lin, G. Q.; Li, Y. M.; Chan, A. S. C. *In Principles and Applications of Asymmetric Synthesis,* Wiley Interscience, **2001**, 237 – 243.

55 Ito, Y.; Katsuki, T. *Tetrahedron Lett.* **1998**, *39*, 4325.

56 Julia, S.; Masana, J.; Vega, J. C. *Agnew. Chem. Int. Ed. Engl.* **1980**, ***19***, 929.

57 Julia, S.; Masana, J.; Alvarez, A. Colonna, S.; Molinari. H.; Banfi, S. *Tetrahedron* ***19*****83**, *39*, 1635.

58 Bently, P.A.; Bergeron, S.; Cappi, M. W.; Hibbs, D. E.; Hursthouse, M. B.; Nugent, T. C.; Pulido, R.; Roberts, S. M.; Wu, L. E. *Chem. Commun.* **1997**, 739.

59 Geller, T.; Gerlach, A.; Kruger, C. M.; Militzer, H.–C. *J. Mol. Catal. A: Chemical 251,* **2006**, 71.

60 Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett* **1990**, 533.

61 Porter, J. M.; Roberts, S. M.; Skidmore, J. *Biol. Med. Chem.* **1999**, *7*, 2145.

62 Helder. R.; Hummelen, J. C.; Laane, R. W. P. M.; Wiering, J. S.; Wynbery, H. *Tetrahedron Lett.* **1976**, *21*, 1831.

63 Wynberg, H.; Gerijdanus, B. J. *J. Chem. Soc. Chem. Commun.* **1978**, 427.

64 Hummelen, J. C.; Wynberg, H. *Tetrahedron Lett.* **1978**, *12*, 1089.

65 Marsman, B.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2312.

66 Marsman, B.; Wynberg, H. *J. Org. Chem.* **1980**, *45*, 158.

67 Pluim, H.; Wynberg, H. *J. Org. Chem.* **1980**, *45*, 2498.

68 Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1998**, *39*, 1599.

69 Lygo, B.; Wainwright, P. G. *Tetrahedron* **1999**, *55*, 6289.

70 Lygo, B.; To, D. C. M. *Tetrahedron Lett,* **2001**, *42*, 1343.

71 Arai, S.; Tsuge, H.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 7563.

72 Arai, S.; Tsuge, H.; Oku, M.; Miura, M.; Shioiri, T. *Tetrahedron 2***002**, *58*, 1623.

73 Lygo, B.; Allbutt, B.; James, S. R. *Tetrahedron Lett.* **2003**, *44*, 5629.

74 Lygo, B.; Allbutt, B. *Synlett* **2004**, 326.

75 Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 6844.

76 Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc. Chem. Commun.* **1984**, 155.

77 Curci, R.; D'Accolti, L.; Fiorentino, M.; Rosa, A. *Tetrahedron Lett.* **1995**, *36*, 2437.

78 Brown, D. S.; Marples, B. A.; Smith, P; Walton, L. *Tetrahedron* **1995**, *51*, 3587

79 Yong, T.; Wang, Z. X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 8475.

80 Wang, Z. X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 6443.

81 Wang, Z. X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 6443.

82 Tian, H.; She, X.; Shi, Y. *Org. Lett.* **2001**, *3*, 715.

83 Frohn, M.; Shi, Y. *Synthesis.,* **2000**, *14*, 1979.

84 Wu, X. Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792.

85 Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435.

86 Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5.

87 Frohn, M.; Zhou, X.; Zhou, J. R.; Tang, Y.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 7718.

88 Lorenz, J. C.; Frohn, M.; Zhou, X.; Zhang, J. R.; Tang, Y.; Burke, C.; Shi, Y. *J. Org. Chem.* **2004**, *69*.

89 Shu, L.; Shi, Y. *Tetrahedron* **2001**, *57*, 5213.

90 Wang, Z. X.; Shi, Z. X.; Shi, Y. *J. Org. Chem.* **1997**, 62, 8622

91 Wu, X. Y.; Shi, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792.

92 Maillard, L. C. *C R Acad. Sci. Ser. 2*, **1912**, *154*, 66.

93 Ledl, F.; Schleicher, E. *Angew. Chem*. **1990**, *102*, 597

94 Kuhn, R.; Weygand, F. *Ber*., **1937**, *70*, 769.

95 Shu, L.; Wang, P.; Gan, Y.; Shi, Y. *Org. Lett.,* **2003**, *5*, 293.

96 Yang, D.; Yip, Y-C.; Chen, J.; Cheung, K-K. *J. Am. Chem. Soc.* **1998**, *120*, 7659.

97 Bowden, K.; Grubbs, E. J. *J. Chem. Soc. Rev.* **1996**, *171*.

98 Hennion, M-C.; Coquart, V.; Guenu, S.; Sella, C. *J. Chromatogr.,* **1995**, *712*, 287.

99 Shu, L.; Wang, P.; Gan, Y.; Shi, Y. *Org. Lett.,* **2003**, *5*, 293.

100 Shing, T. K. M.; Leung, G. Y. C. *Tetrahedron* **2002**, *58*, 7545.

101 Adam, W.; Fell, R. T.; Chantu, S, M, R.; Zhao, C. G. *Tetrahedron: Asymmetry* **1998**, *9*, 397.

102 Adam, W.; Chantu, S, M, R.; Zhao, C. G. *Tetrahedron: Asymmetry* **1999**, *10*, 2749.

103 Yang, D.; Yip, M. C.; Tang, M. M.; Wong, M. K.; Cheung, K. K. *J. Org. Chem.* **1998**, *63*, 9888.

104 Yang, D.; Jiao, G. S.; Yip, Y. C.; Lai, T. H.; Wong, M. K. *J. Org. Chem.* **2001**, *66*, 46**19**.

105 Yang, D. *Acc. Chem. Res.,* **2004**, *37*, 497.

106 Armstrong, A.; Hayter, B. R. *Chem. Comm.,* **1998**, 621.

107 Armstrong, A.; Hayter, B. R.; Moss, W. O.; Reeves, J. R.; Wailes, J. S. *Tetrahedron: Asymmetry* **2000**, *11*, 2057.

108 Armstrong, A.; Moss, W. O.; Reeves, J. R. *Tetrahedron: Asymmetry* **2001**, *12*, 2779.

109 Armstrong, A.; Washington, I.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 6297.

110 Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391.

111 Denmark, S. E.; Wu, Z. *J. Org. Chem.* **1997**, *62*, 8288.

112 Denmark, S. E.; Matsuhashi, H. *J. Org. Chem.* **2002**, *67*, 3479.

113 Milliet, P.; Picot, A.; Lusinchi, X. *Tetrahedron Lett.* **1976**, 1573.

114 Milliet, P.; Picot, A.; Lusinchi, X. *Tetrahedron Lett.* **1976**, 1577.

115 Milliet, P.; Picot, A.; Lusinchi, X. *Tetrahedron* **1981**, *24*, 4201.

116 Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1987**, *28*, 6061.

117 Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1988**, *29,* 3941.

118 Lusinchi, X.; Hanquet, G. *Tetrahedron* **1997**, *53*, 13727.

119 Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1993**, *34,* 7271.

120 Bohé, L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 141.

121 Bohé, L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 155.

122 Hanquet, G.; Lusinchi, X. *Tetrahedron* **1994**, *50*, 12185.

123 Bohé, L.; Kammoun, M. *Tetrahedron Lett.* **2002**, *43*, 803.

124 Bohé, L.; Kammoun, M. *Tetrahedron Lett.* **2004**, *45*, 747.

125 Miyahita, A; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.

126 Kitamura, M.; Tsukamoto, M.; Bessho, Y.; Yoshimura, M.; Kobs, U.; Widhalm, M.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6649.

127 Knowles, W. S.; Noyori, R. *Acc. Chem. Res.* **2007**, *40*, 1238.

128 Aggarwal, V. K.; Wang, M. F. *Chem. Comm.* **1996**, 191.

129 Armstrong, A.; Ahmed, G.; Garnett, I.; Goacolou, K.; Wailes, J. S. *Tetrahedron* **1999**, *55*, 2341.

130 Armstrong, A.; Ahmed, G.; Garnett, I.; Goacolou, K. *Synlett* **1997**, 1075.

131 Minakata, S.; Takemiya, A.; Nakamure.; Ryu, I.; Komatsu, M. *Synlett* **2000**, 1810.

132 Wong, M. K.; Ho, L. M.; Zheng, Y. S.; Ho, C. Y.; Yang, D. *Org. Lett.* **2001**, *3*, 2587.

133 Armstrong, A.; Draffan, A. G. *Synlett* **1998**, 646.

134 Armstrong, A.; Draffan, A. G. *Tetrahedron Lett.* **1999**, *40*, 4453.

135 Armstrong, A.; Draffan, A. G. *J. Chem. Soc. Perkin Trans. 1,* **2001**, 2861.

136 Page, P. C. B.; Rassias, G. A.; Bethell, D.; Schilling, M. B. *J. Org. Chem.* **1998**, *63*, 2774.

137 Page, P. C. B.; Rassias, G. A.; Barros, D.; Bethell, D.; Schilling, M. B. *J. Chem. Soc. Perkin Trans. 1,* **2000**, 3325.

138 Page, P. C. B.; Rassias, G. A.; Barros, D.; Adel, A.; Buckley, B.; Bethell, D.; Smith, T. A. D.; Slawin, A. M. Z. *J. Org. Chem.* **2001**, *66*, 6926.

139 Buckley, B. R. PhD Thesis submitted to Loughborough University. **2003**.

140 http://www.dupont.com/oxone/techinfo/

141 Page, P. C. B.; Barros, D.; Buckley, B. R.; Ardakani, A.; Marples, B. A. *J. Org. Chem.* **2004**, *69*, 3595.

142 Page, P. C. B.; Buckley, B. R.; Blacker, A. J. *Org. Lett.* **2004**, *6*, 1543.

143 Page, P. C. B.; Buckley, B. R.; Heaney, H.; Blacker, A. J. *Org. Lett.* **2005***, 7*, 375.

144 Vachon, J.; Perollier, C.; Monchaud, D.; Marsol, C.; Ditrich, K.; Lacour, J. *J. Org. Chem.* **2005**, *70*, 5903.

145 Lacour, J.; Monchaud, D.; Marsol, C. *Tetrahedron Lett.* **2002**, *43*, 8257.

146 Vachon, J.; Lauper, C.; Ditrich, K.; Lacour, J. *Tetrahedron: Asymmetry* **2006,** *17*, 2334.

147 Goncalves, M. H.; Martinez, A.; Grass, S.; Page, P. C. B.; Lacour, J. *Tetrahedron Lett.* **2006**, *47*, 5297.

148 Adamo, M. F.; Aggarwal, V. K.; Sage, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 8317

149 Aggarwal, V. K.; Lopin, C.; Sandrinelli, F. *J. Am. Chem. Soc.* **2003**, *125*, 7596.

150 Armstrong, A. *A. Angew. Chem. Int. Ed.,* **2004**, *43*, 1460.

151 Ho, C. Y.; Chen, Y. C.; Wong, M. K.; Yang, D. *J. Org. Chem.* **2005**, *70*, 898.

152 Marigo, M.; Franzen, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964.

153 Zhuang, W.; Marigo, M.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 3883.

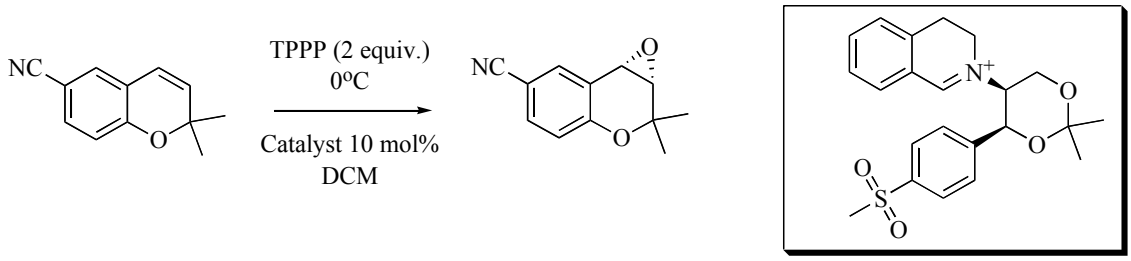
154 Sunden, H.; Ibrahim, I.; Cordova, A. *Tetrahedron Lett.* **2006**, *47*, 99.

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2 Results and discussion.

The Page group's epoxidation research has centred on the development of two core ideas. Firstly the development of highly enantioselective iminium salt organocatalysts for use in the asymmetric epoxidation of alkenes. To date several catalysts have given greater than 90% enantiocontrol, the most enantioselective catalyst, **1**, has given up to 97% *ee* in the epoxidation of 6-cyano-2,2-dimethylbenzopyran (Scheme 1).

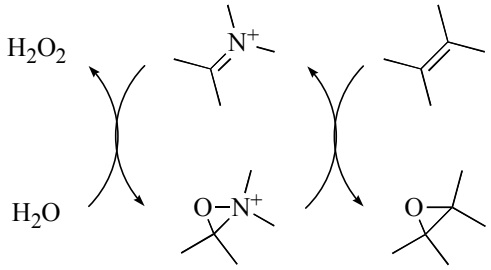


Catalyst 1, 97% ee

Scheme 1

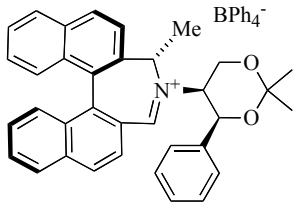
The second field of study is in the development of novel oxidative systems for use with our enantioselective catalysts. To date the TPPP oxidative system has given the highest enantioselectivity of all oxidants screened, up to 97% *ee* (Scheme 1).

The work described in this thesis is an extension of the work previously completed and is novel within the Page group. The first two sections of this chapter describe the efforts made by the author to develop new aqueous oxidative systems using hydrogen peroxide and sodium hypochlorite as stoichiometric oxidants. This would enable the constraints of other universal oxidants such as Oxone® to be lifted and potentially increased enantiocontrol to be achieved. It also would give us insight into the factors which organocatalysed oxidative systems facilitate oxygen transfer (Scheme 2).

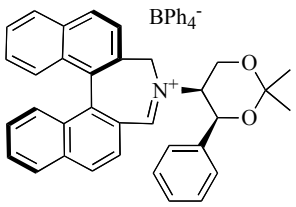


Scheme 2

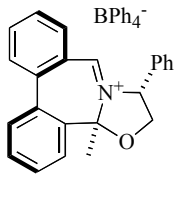
The third and fourth sections of this chapter describe the efforts made towards the synthesis of catalyst **2**, a sub-structure of catalyst **3**, inducing up to 95% *ee* on our test substrate 1-phenylcyclohexene, and catalyst **4**, a novel catalyst based on the biphenyl backbone seen in catalyst **5**, the most effective biphenyl iminium salt, which induces up to 60% *ee* with our test substrate. We anticipated that further research into catalyst design would enable us to determine how steric and electronic factors influence enantiocontrol, both intra- and inter-molecularly, with respect to the organocatalyst and in achieving high enantioselectivity.



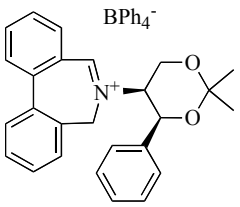
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3



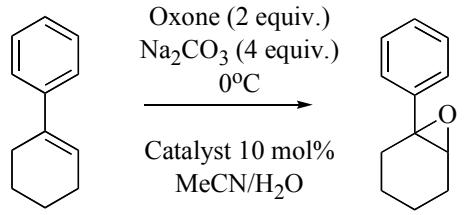
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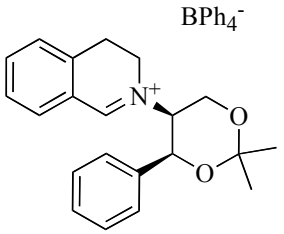
The standard iminium salt epoxidation conditions employ the triple salt Oxone® ($2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$) as a stoichiometric oxidant, sodium carbonate, and acetonitrile:water as the solvent mixture (Scheme 3). The presence of water was essential for Oxone® solubility, and the base was essential for the epoxidation reaction to proceed. The major limitation to this system was the restricted range of temperatures at which the epoxidation can be performed (0 °C to room temperature). The upper limit was determined by the stability of Oxone®, which decomposes relatively quickly in the basic medium at room temperature.[1] The lower limit was determined by the use of the aqueous medium: the

typical ratios of acetonitrile to water solvent used as solvent lie between 1:1 and 10:1, and the medium, at a ratio of 1:1, freezes at around – 8 °C. A large quantity of inorganic by-product was also generated from the decomposition of the oxidant. [1]

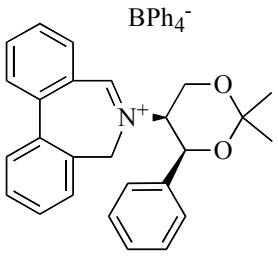


Scheme 3

Iminium salt catalysts **6** and **7** mediate the epoxidation of 1-phenylcyclohexene in 41% and 59% *ee* when using Oxone® as the oxidant. We have recently prepared and utilised the tetraphenylphosphonium salt (TPPP) of monoperoxysulfate as a stoichiometric oxidant that was soluble in organic solvents. Enantiocontrol increases in these cases when using TPPP, in a solution of dichloromethane below 0 °C, to 43% and 67% *ee* respectively.



6

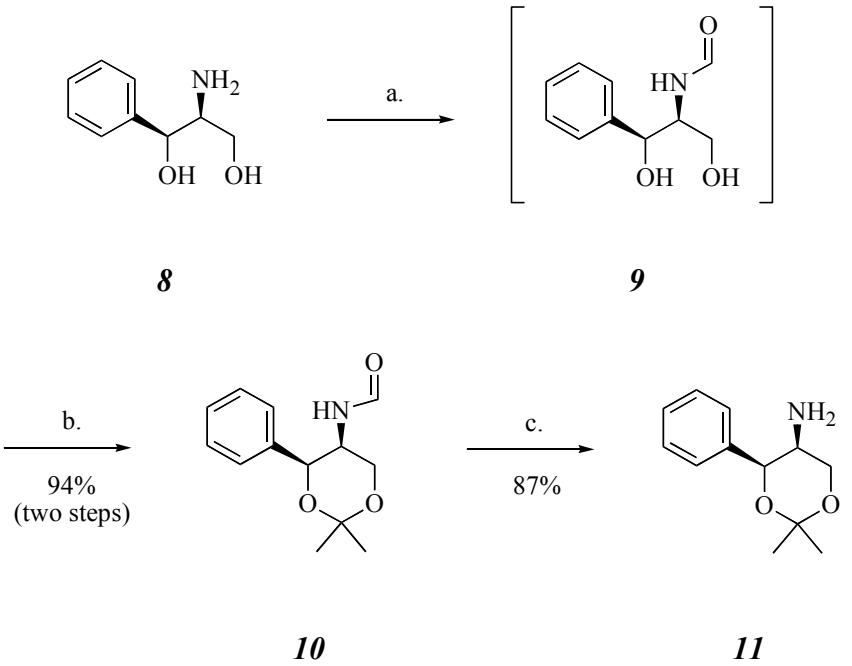


7

2.1 Optimisation of new systems for catalytic asymmetric epoxidation.

2.1.1 Formulation of the iminium salt catalysts

The synthesis of iminium salt catalysts **6** and **7** is shown below (Schemes 4, 5 and 6). The first step was the construction of aminodioxane unit. Commercially available (*S*)-(–)-2-Amino-3-phenyl-1-propandiol **8** was *N*-protected with methyl formate to give **9** which was not isolated, subsequent diol protection with dimethoxypropane gave the 6-membered acetal unit **10**. Finally, N-deprotection using hydrazine hydrate gave the aminodioxane unit **11** in 87% yield over three steps.

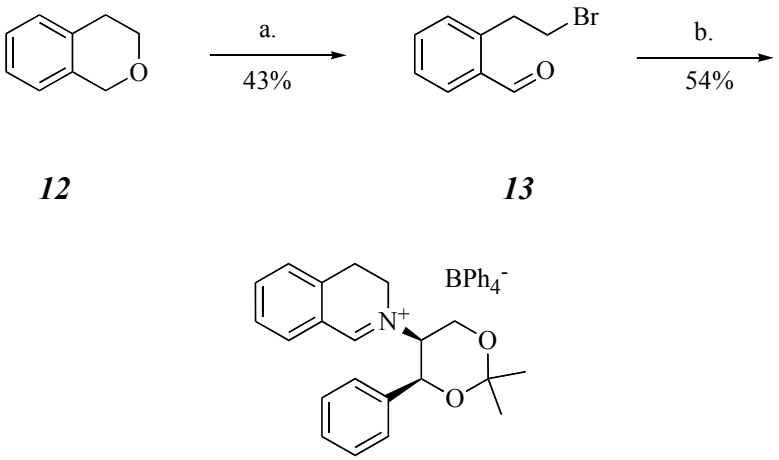


8 ***9*** ***10*** ***11***

Reagents and conditions; (a) MeOH, NaOMe, MeOCHO, rt, 2 hrs. (b) Acetone, 2,2-dimethoxypropane, HBr, rt, 4 hrs. (c) hydrazine hydrate, Δ, 4 hrs.

Scheme 4

The synthesis of catalyst **6** was initiated by the ring cleavage of *iso*chroman **12** with bromine to generate the bromoaldehyde **13**. On cylco-condensation with the amino dioxane **11** and anion exchange with sodium tetraphenylborate, the desired iminium salt catalyst was generated in 54% yield over two steps.



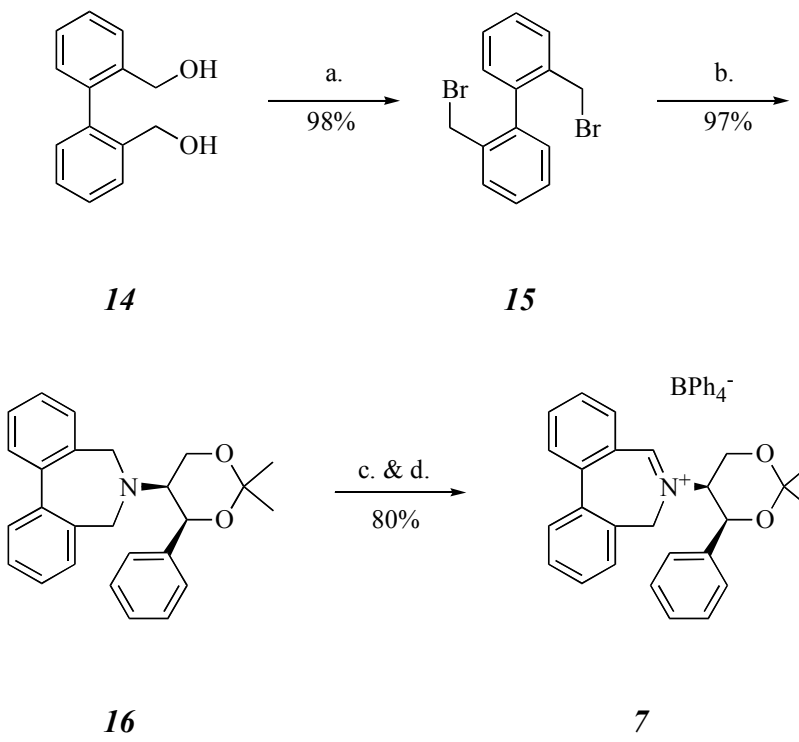
12 ***13***

6

Reagents and conditions; (a) 11, CCl_4, Br_2, HBr, Δ, 2 hrs.
(b) EtOH, $NaBPh_4$, MeCN, 0 °C → rt, 17 hrs.

Scheme 5

Catalyst **7** was produced using bis(hydroxymethyl)biphenyl **14** as the starting material. Exposure to aqueous hydrogen bromide generated the dibrominated intermediate **15**. The condensation of the aminodioxane **11** gave the tertiary amine **16**, which was oxidised to the iminium salt with *N*-bromosuccinamide. Subsequent anion exchange gave iminium salt catalyst **7** in 82% yield over three steps.



14 ***15***

16 ***7***

Reagents and conditions; (a) HBr, Δ, 2 hrs. (b) 11, THF, TEA, Δ, 16 hrs. (c) NBS, $CHCl_2$, Δ, 10 mins. (d) $NaBPh_4$, EtOH, rt, 20 mins.

Scheme 6

2.1.2 The utilisation of hydrogen peroxide as a stoichiometric oxidant.

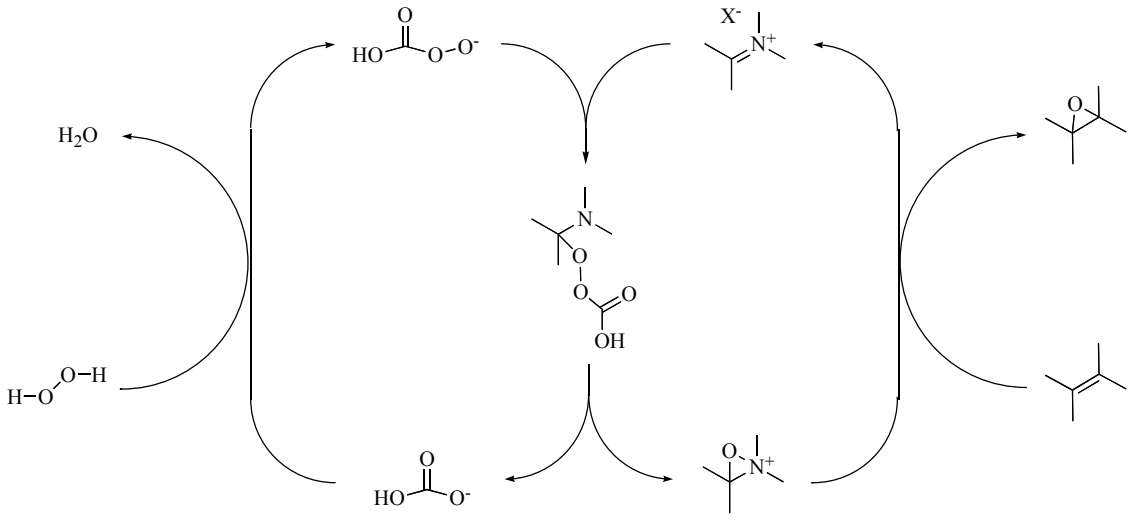
We were keen to investigate other potential oxidants in order to widen the range of usable reaction conditions, but most oxidants either do not drive the catalysed reaction or generate considerable achiral product through background oxidation of the alkene substrates. Hydrogen peroxide is perhaps the second most environmentally friendly oxidant available after oxygen, in terms of by-products, and its use as a stoichiometric oxidant would allow an inexpensive and 'green' process to be developed.[2] Hydrogen peroxide is a standard reagent used to oxidise electron-deficient alkenes, such as enones and conjugated esters, to their corresponding epoxides in the presence of base and polyleucine catalyst (known as the Julia olefination).[3]

In order to develop a hydrogen peroxide-driven system using oxaziridinium salts as catalyst, several problems had to be addressed. Unlike Oxone®, hydrogen peroxide does not induce epoxidation in the absence of base. A co–catalyst that could be oxidised to a species that is capable of oxygen transfer to an iminium salt was therefore required. In the solid state, sodium percarbonate has been shown by X-ray crystallographic analysis to consist of a layered solid corresponding to $Na_2CO_4 \bullet 1.5\ H_2O$.[4] Richardson and Yao have since reported that, upon addition of hydrogen peroxide to sodium hydrogen carbonate, an equilibrium between sodium hydrogen carbonate and the corresponding percarbonate was established (Equation 1).[5]

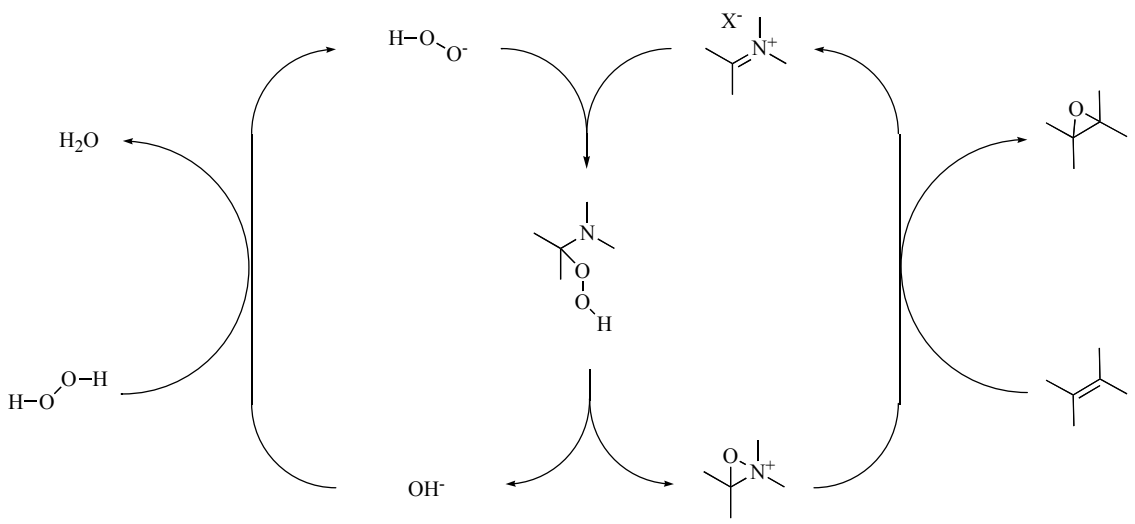
$$H_2O_2 + HCO_3^- \rightleftharpoons HCO_4^- + H_2O$$

Equation 1

We reasoned that the percarbonate could, in principle, oxidise an iminium salt to the corresponding oxaziridinium salt,[6] expelling carbonate as the leaving group. Upon trialling this we were pleased to find that commercial sodium percarbonate does indeed drive the reaction when present in large excess. The oxaziridinium salt could then directly oxidise the alkene substrate to the corresponding epoxide. The essential features of this proposed double catalytic cycle are illustrated in Scheme 7.



Scheme 7, Pathway A



Scheme 8, Pathway B

We were pleased to find that initial experiments utilising hydrogen peroxide (50%, 6 equiv.) and sodium hydrogen carbonate (0.2 equiv.) in an acetonitrile:water (9:1) solvent system using catalyst **6** (10 mol%) induced asymmetric epoxidation of 1-phenylcyclohexene with up to 22% *ee* at 20 °C.

2.1.2.1 Effects of the base on the reaction

Previous work in investigating the ability of hydrogen peroxide to oxidise an iminium salt to the oxaziridinium salt in the presence of an alkene showed no evidence of epoxidation in the absence of base. In this context, we have tested several bases as possible promoters (Table 1). Our initial reactions were completed at both 0 °C and 20 °C, using 0.2 equivalents of a range of mediators, including potassium hydrogen phosphate, potassium hydrogen sulphate, and sodium and potassium sulphates, in addition to those indicated in the table. From our previous work using Oxone® as the stoichiometric oxidant,[7] we found that a 9:1 ratio in the acetonitrile:water solvent system gave optimum conversion and *ee*, and that catalyst **7** provided superior enantioselectivities to catalyst **6**. We therefore used this solvent ratio and catalyst **7** in our investigation.

Table 1; Asymmetric Epoxidation of 1–Phenylcyclohexene mediated with Hydrogen peroxide by Catalyst 7

Entry[a]	Base	Equiv.	Temp./ °C	Conv./ %[b]	ee/ %[b]
1	Li_2CO_3	0.2	0	29	19
2	LiOH	0.2	0	100	28
3	$NaHCO_3$	0.01	0	< 5	< 5
4	$NaHCO_3$	0.1	0	22	35
5	$NaHCO_3$	0.2	0	63	33
6	$NaHCO_3$	0.2	20	100	29
7	$NaHCO_3$	1	0	34	35
8	$NaHCO_3$	1	20	100	31
9	$NaHCO_3$	2	0	35	35
10	$NaHCO_3$	2	20	100	32
11	Na_2CO_3	0.2	0	52	36
12	Na_2CO_3	0.2	20	100	27
13	Na_2CO_3	1	0	47	34
14	Na_2CO_3	2	0	42	36
15	NaOH	0.2	0	100	28
16	$KHCO_3$	0.2	0	19	35
17	$KHCO_3$	0.2	20	57	32
18	K_2CO_3	0.2	0	26	39
19	K_2CO_3	0.2	20	96	34
20	KOH	0.2	0	58	34
21	Rb_2CO_3	0.2	0	29	35
22	Rb_2CO_3	0.2	20	75	31
23	Cs_2CO_3	0.2	0	41	36
24	Cs_2CO_3	0.2	20	89	30
25	NH_4HCO_3	0.2	0	7	40

[a] epoxidation conditions: Iminium salt catalyst **7** (10 mol%), hydrogen peroxide (50%, 6 equiv.). Base, Acetonitrile:H_2O (9:1), 24 hours. [b] Conversions and enantiomeric excesses were determined from the chiral GC–FID spectra by comparison of the alkene/epoxide and epoxide/epoxide peak areas respectively; the major enantiomer generated was the (1*S*,2*S*) epoxide.

Background epoxidation utilising 0.2 equivalents of base, at 0 °C over 24 hours, in the absence of any catalyst, was not observed for sodium, potassium, or lithium carbonates, but was observed at a low level when using caesium or rubidium carbonates (<5%), and ammonium bicarbonate (approx 2%). At room temperature, over 24 hours, the extent of the background epoxidation varied with the cation used: sodium (<5%), potassium (11%), rubidium (15%), caesium (15%) carbonates, and ammonium bicarbonate (20%). These results suggest that decreasing ion association increases background reaction; large organic cations, and the iminium salt when present, could enhance background epoxidation by this purely physical means, because their size makes interionic distance too large for electrostatic association.

Table 1 shows that the potassium salts at 0 °C provide the highest enantioselectivity for reasonable conversions, giving 34% *ee* (KOH), 35% *ee* ($KHCO_3$), and 39% *ee* (K_2CO_3). Rubidium and caesium carbonate also gave good enantiocontrol, but show the highest level of background epoxidation at 0 °C, although this was still low at <5%. The sodium salts show decreased enantiocontrol compared with their analogous potassium salts.

It appears that the enantioselectivity achieved was largely independent of the type of mediator (HCO_3^-, CO_3^{2-} or OH^-) used to promote the reaction. As we have previously established, in the absence of base no epoxidation occurs, and indeed even experiments containing very small amounts of base (0.01 equiv.) showed no epoxidation (entry 3). When the amount of base was increased to 0.1 equivalents, the desired epoxidation reaction furnished 1-phenylcyclohexene oxide with enantioselectivities of 35% *ee* for $NaHCO_3$, 33% *ee* for Na_2CO_3 and 28% *ee* for NaOH. We also observed that for any base added at a level greater than 0.1 equivalents (up to 2 equivalents), the *ee* remained approximately constant.

For the carbonate bases we next tested the effect of the accompanying counter-ion, but little variation in the product *ee* was observed (36% *ee* for Cs_2CO_3, 35% *ee* for Ru_2CO_3, 39% *ee* for K_2CO_3, 31% *ee* for Na_2CO_3). Interestingly, similar levels of enantioselectivity were observed with rubidium and caesium carbonates despite increased background epoxidation in the absence of catalyst. Presumably the presence of an iminium salt catalyst offers a lower energy pathway, leading to asymmetric epoxidation.

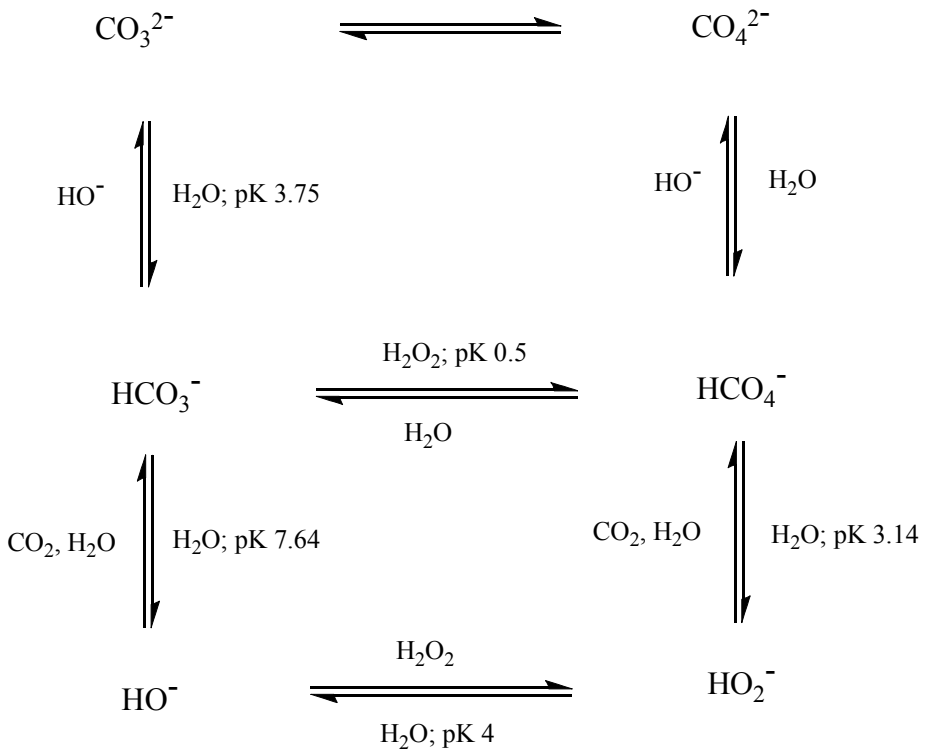
In interpreting the observations it must be borne in mind that several equilibria determine the availability of the key species responsible for generating the oxaziridinium cations. The interrelation of these is shown in Scheme 9, in which are indicated pK-values for some of the individual processes in water that can be deduced from literature values for the pK_a-values of water, hydrogen peroxide and carbonic acid, together with that for the equilibrium in Equation 1.

For a solution of bicarbonate and hydrogen peroxide, formally 1 M in each at a pH such that we do not need to consider the presence of carbonate or percarbonate dianions (a fixed pH in the range 10-11), the ratio of $[HCO_3^-]$ to $[HCO_4^-]$ is ca. 3:1, i.e. approx. 0.75M H-carbonate to 0.25M H-percarbonate. Each of these species is in equilibrium with $[CO_2^-]$ ions and, $[OH^-]$ ions or $[HOO^-]$ ions to a small degree, the effective equilibrium constant in the case of $[HCO_3^-]$ being 2.3×10^{-8}, and that in the case of $[HCO_4^-]$ 7.2×10^{-4}. The $[HO^-] + [HOO^-]$ concentrations will therefore be given by the square root of $Kc = 1.3 \times 10^{-4}$ for $[HO^-]$ and 1.35×10^{-2} for $[HOO^-]$. At the autogenerated pH of the solution (ca. 10) any surplus H_2O_2 will contribute to the concentration of $[HOO^-]$ and this could be as much as the concentration generated by dissociation of $[HCO_4^-]$. Hence the ratio of $[HCO_4^-]/[HOO^-]$ is of the order of 10 – 20. [8] The ratio may perhaps be manipulated by buffering the pH.

Under the reaction conditions the situation will be substantially different because in 90% aqueous MeCN the water activity is much lower than in pure water and this will increase the ratio $[HCO_4^-]/[HOO^-]$.[5] Also remember that only the proton transfer processes are effectively instantaneous; additions to and dissociations from CO_2 are relatively slow (half-lives of the order of minutes to hours, depending on solvent) compared with the proton transfers.

Bearing in mind that the hydrogen percarbonate anion can exist in two prototropic forms, $HOO\text{-}CO\text{-}O^-$ and $HO\text{-}CO\text{-}OO^-$ only the less stable of which (the latter) is expected to be an effective oxidising agent for the iminium cation, and that hydroperoxide anion may be intrinsically more reactive, the balance of reaction between pathways A and B in Scheme 9 may be substantially less than 20. Percarbonate and hydroperoxide anions can be expected to convert chiral iminium salts to the oxaziridinium species with different facial

selectivities, giving different diastereoisomeric excesses. Since each diastereoisomeric oxaziridinium cation will have its own overall reactivity and enantioselectivity in transferring an oxygen atom to the alkene, the enantioselection observed in the epoxide produced in iminium ion-catalysed oxidation was expected to be dependent on the choice of oxidant. Different enantioselectivities are thus to be anticipated from iminium ion mediated oxygen transfer using as oxidant Oxone®, hydrogen peroxide in the presence of a carbonate base, and hydrogen peroxide using a strong base capable only of deprotonating it.



Scheme 9

The active oxidant in Oxone® is $KHSO_5$, and so $KHSO_4$ was tested to determine if the hydrogen peroxide oxidant could oxidise the potassium salt to the active persulfate *in situ*, in the hope that this system might give similar enantioselectivity to the Oxone® epoxidation system. When Na_2SO_4, K_2SO_4 and $KHSO_4$ were used in test reactions poor levels of conversion to the respective epoxides (<15%) were observed.

2.1.2.2 Effect of temperature on the reaction

We next investigated the effect of temperature on the enantioselectivity in epoxidation reactions carried out between –10 and 30 °C (Table 2). A small increase in enantioselectivity was observed as the temperature was reduced. As the temperature decreased the rate also decreased, requiring one week for the reaction to reach completion at 0 °C, whereas full conversion to the epoxide at 20 °C was observed in less than 24 hours. At 30 °C, the reaction was complete after 2.5 hours. Catalyst **7** showed increased levels of enantioselectivity over catalyst **6**, but **6** generally gave better conversion to the epoxide at lower temperatures.

Table 2; Effect of Temperature on the Asymmetric Epoxidation of 1–Phenylcyclohexene Mediated by Catalysts 6 and 7 [a]

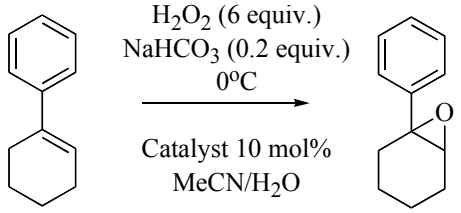
Entry	Catalyst	Temp./ °C	Time/ h	Conv./ %[b]	ee/ %[b]
1	**7**	–10	24	19	35
2	**7**	–5	24	21	38
3	**6**	0	24	62	15
4	**6**	0	7 days	100	13
5	**7**	0	24	48	36
6	**7**	0	7 days	100	34
7	**7**	10	24	66	32
8	**6**	20	23	100	18
9	**7**	20	22	100	29
10	**7**	30	2.5	100	32

[a] Epoxidation conditions: Iminium salt catalyst (10 mol%), hydrogen peroxide (50%, 6 equiv.). $NaHCO_3$ (0.2 equiv.), Acetonitrile:H_2O (9:1), 24 hours. [b] Conversions and enantiomeric excesses were determined from the chiral GC–FID spectra by comparison of the alkene/epoxide and epoxide/epoxide peak areas respectively. The major enantiomer generated was the (1*S*,2*S*) epoxide as deduced by both GC-FID and optical rotation against enantiopure standards.

2.1.2.3 Effects of solvents on the reaction

2.1.2.3.1 Effects of the ratio of co-solvents used

Our first reactions were carried out using an acetonitrile:water (9:1) solvent system. We have investigated the effect of the proportion of water on the enantioselectivity of the epoxidation process (Scheme 10).



Scheme 10

Reactions were carried out using six molar equivalents of hydrogen peroxide from a 50% aqueous solution; the results are shown in Table 3. In each case the volumes of water and hydrogen peroxide in the reagent were taken into account when determining the proportion of water present in the total solvent volume. A 0% water solvent system was achieved by the use of ethereal hydrogen peroxide.

Table 3; Asymmetric Epoxidation of 1–Phenylcyclohexene Mediated by Catalyst 7 with varying concentrations of acetonitrile and water solvent system

Entry	H_2O/ %	Temp/ °C	Time/ h	Conv./ % [b]	ee/ % [b]
1 [d]	0 [c]	–5	7 days	100	56
2	0 [c]	0	24	39	42
3	0 [c]	20	24	100	45
5 [d]	13	–5	7 days	100	46
6	13	0	24	59	42
4	13	20	24	100	39
7	20	0	24	78	35
8	20	20	24	100	32
9	24	0	24	77	35
10	24	20	24	100	28
11	35	0	24	71	34
12	35	20	24	100	26
13	50	0	24	46	30
14	50	20	24	100	23
15	61	0	24	27	30
16	61	20	24	100	23

[a] Epoxidation conditions: Iminium salt catalyst **7** (10 mol%), hydrogen peroxide (50%, 6 equiv.). $NaHCO_3$ (0.2 equiv.), Acetonitrile:H_2O, 0 ºC, 24 hours. [b] Conversions and enantiomeric excesses were determined from the chiral GC–FID spectra by comparison of the alkene/epoxide and epoxide/epoxide peak areas respectively. The major enantiomer generated was the (1*S*,2*S*) epoxide as deduced by both GC-FID and optical rotation against enantiopure standards. [c] Ethereal hydrogen peroxide used; reaction volume contained 13% Et_2O. [d] K_2CO_3 used as base.

The table clearly shows that increasing the proportion of water present decreases the observed *ee* under these conditions. This was in sharp contrast to our aqueous Oxone® system, in which *ee* was unaffected by the proportion of water, but in which the rate of reaction increases sharply as the proportion of water was increased.[7b] Although many hours or even days may be required for these reactions to reach completion, the enantioselectivity of the epoxide product remained constant throughout this time. Maximum enantioselectivity was obtained under the anhydrous reaction conditions (56% *ee*); this was comparable to the Oxone®-mediated system (60% *ee*), when using 1-

phenylcyclohexene as the substrate and iminium salt **7** as catalyst.[9] This effect of water content with respect to enantioselectivity may perhaps be interpreted in terms of water influencing the stereochemical course of the reaction by affecting the diastereofacial selectivity of addition of the peroxy anion to the iminium carbon atom (Scheme 8, Pathway B), for example by diastereofacially selective co-ordination of water molecules to the electron-deficient iminium units. Changing the solvent will, of course alter the equilibria shown in Scheme 9, perhaps slowing down the percarbonate generation relative to the fast proton transfers; thus hydroperoxide may become relatively more important than percarbonate, and this also might reduce enantioselectivity. Further, anions generally are less active in aqueous solvents than in dipolar aprotic ones, and this might slow down the addition of percarbonate or hydroperoxide to the iminium ion.

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2.1.2.3.2 Effects of change of organic co-solvent

A range of reactions with different co-solvents was carried out using catalyst **7**, hydrogen peroxide, and potassium carbonate, at – 5 °C to prevent background epoxidation (Table 4)

Table 4; Asymmetric Epoxidation of 1–Phenylcyclohexene Mediated by Catalyst 7 in Various Solvent Systems [a]

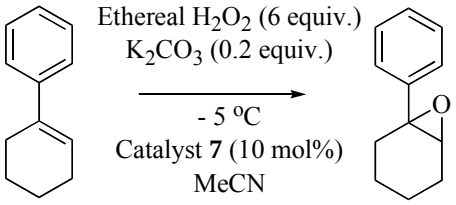
Entry	Co-solvent	Conv./% [b]	ee/% [c]
1	Cyclohexane	26	32
2	Hexane	0	0
3	Toluene	0	0
4	Ether	27	27
5	Chloroform	0	0
6	Ethyl acetate	0	0
7	THF	53	30
8	Dichloromethane	0	0
9	Methyl isobutyl ketone	69	26
10	Acetone	5	53
11	Ethanol	12	0
12	Methanol	13	42
13	Acetonitrile	19	35

[a] Epoxidation conditions: Iminium salt catalyst **7** (10 mol%), hydrogen peroxide (50%, 6 equiv., K_2CO_3 (0.2 equiv.), solvent (1 ml), – 5 ºC, 24 hours. [b] Conversions were evaluated from the chiral GC–FID spectra by comparison of the alkene and epoxide peak areas. [c] Enantiomeric excesses were determined by chiral GC–FID spectra by comparison of the two epoxide peak areas. The major enantiomer generated was the (1*S*,2*S*) epoxide as deduced by both GC-FID and optical rotation against enantiopure standards.

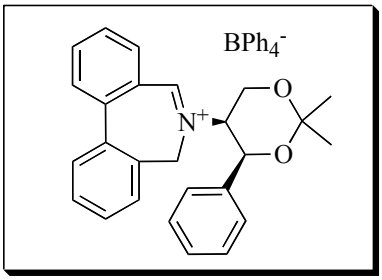
It appears that solvents that provide good base solubility and also provide a homogenous reaction mixture increase the enantioselectivity of the epoxidation, for example acetone (53% *ee*), methanol (44% *ee*), and acetonitrile (37% *ee*).

2.1.2.4 Conclusion

We have successfully demonstrated the use of hydrogen peroxide as the stoichiometric oxidant in iminium salt-catalysed asymmetric epoxidation, providing a cheaper and greener alternative to Oxone®. The reaction was promoted by a catalytic amount of inorganic mediators such as carbonate, hydrogen carbonate and hydroxide. The enantioselectivity of the reaction was largely independent of the amount of base and catalyst, and the nature of cation associated with the base. In contrast, water content and temperature appear to have the greatest impact on the enantioselectivity and rate. We believe that this process operates through a double catalytic cycle (Scheme 2).



Scheme 11



Catalyst 7, 56% ee

Optimisation of the oxidative system enabled asymmetric epoxidation of 1–phenylcyclohexene with 56% *ee* utilising catalyst **7** and ethereal hydrogen peroxide in the absence of water at – 5 °C (Scheme 11). Further work on alternative oxidants and catalysts towards more enantioselective systems is in progress.

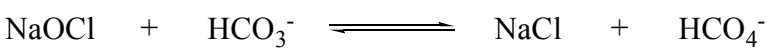
2.1.3 The utilisation of sodium hypochlorite as an organic oxidant.[9]

During our work with hydrogen peroxide, we observed that carbonate salts co-catalysed the epoxidation effectively, with no background epoxidation being observed when reactions were carried out at temperatures of up to 5 °C. We suggested that a double catalytic cycle may operate in these processes, with percarbonate providing an intermediate oxidising stage.[5] We conjectured that sodium hypochlorite might provide an alternative stoichiometric oxidant for our iminium salt-catalysed systems by generating a percarbonate oxidant *in-situ* in the presence of a carbonate salt.

Sodium hypochlorite is inexpensive, relatively safe, and has high oxygen content. In the form of commercial bleach it can oxidize electron-deficient alkenes, such as enones and conjugated esters, to their corresponding epoxides with the addition of catalytic base,[3a] but does not generally directly oxidize electron-rich alkenes to their corresponding epoxides.[10] Bleach has been used as an oxidant in asymmetric epoxidation using a range of catalysts including chiral salen complexes,[11] manganese porphyrin complexes,[12] and quaternary ammonium salts.[13] There is also precedent for the use of other hypochlorite oxidants such as potassium hypochlorite for oxygen transfer,[22b,14,15] for example oxidations of alcohols to ketones,[16] aldehydes to acid chlorides,[17] ketones to carboxylic acids,[18] sulfides to sulfoxides,[19] phosphines and phosphites to phosphine oxides and phosphates.[20] Donohoe has reported the use of potassium hypochlorite as an oxidant for catalytic asymmetric aminohydroxylation,[21] and Corey has reported asymmetric epoxidation catalysed by dihydrocinchonidinium salts using potassium hypochlorite as oxidant.[22b]

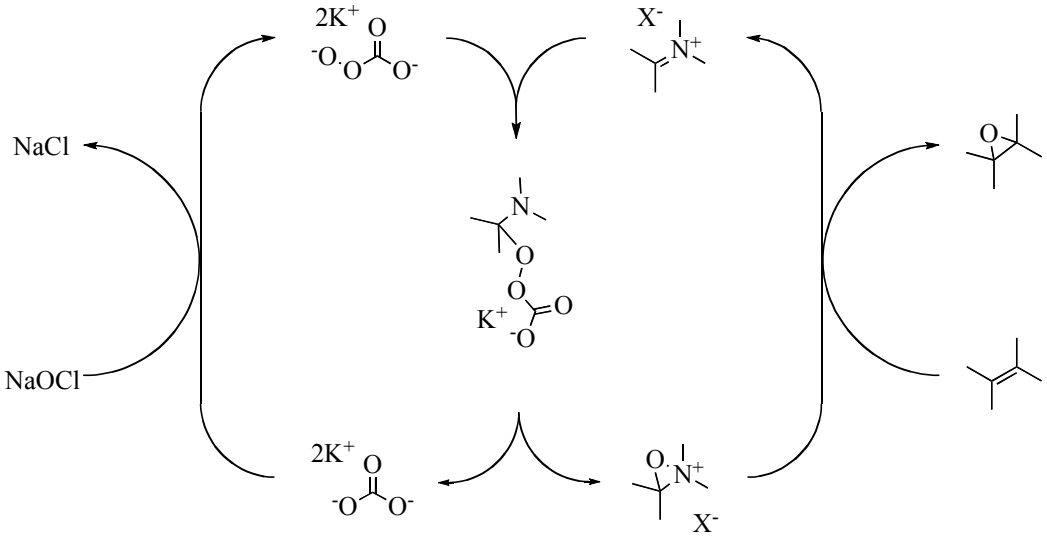
Sodium hypochlorite itself does not directly oxidise simple alkenes under our reaction conditions: blank reactions in the presence of potassium carbonate, but in the absence of an iminium salt catalyst, show no conversion to the epoxide over 24 hours. Under the same conditions and in the presence of the iminium salt, epoxidation was observed.

It was therefore postulated that sodium hypochlorite could generate the percarbonate *in-situ* (Equation 2),[3b,5] which in turn could oxidise the iminium salt to the oxaziridinium salt thus generating a species capable of oxygen transfer to the alkene substrate.

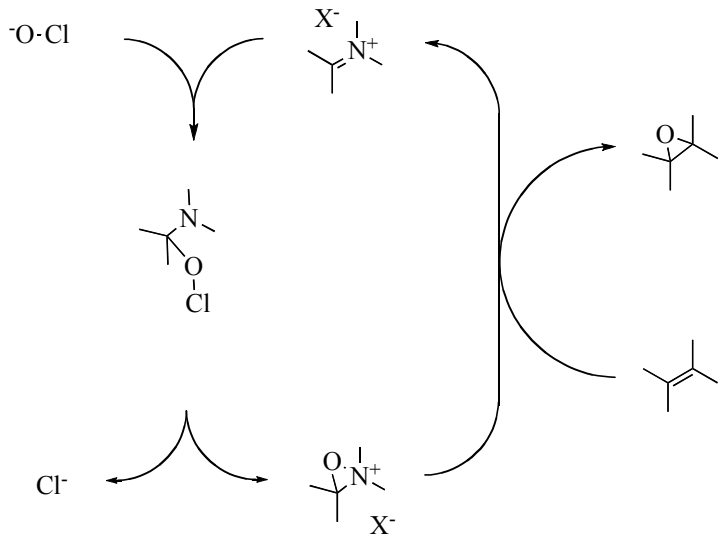


Equation 2

Two possible catalytic cycles are illustrated in Scheme 12, Pathway A and Scheme 13, Pathway B for the proposed process. Hypochlorite may generate percarbonate, which then acts as the oxygen transfer agent, followed by oxaziridinium ion formation (Scheme 12, Pathway A); such a double catalytic cycle involving a second mediator does not appear to have been previously proposed for other processes involving hypochlorite. Alternatively, hypochlorite may add directly to the iminium unit (Scheme 13, Pathway B). Both pathways involve expulsion of a leaving group to generate the oxaziridinium intermediates, potentially as a pair of diastereoisomers, each of which may induce asymmetric oxygen transfer to a substrate. These diastereoisomers would be expected to display different enantioselectivities in any such reaction; the observed *ee* in each case may therefore be an aggregate of the two.

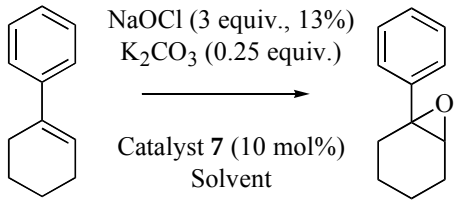


Scheme 12, Pathway A



Scheme 13, Pathway B

Initial experiments carried out at room temperature using sodium hypochlorite solution (13%, 3 equiv.) as stoichiometric oxidant, potassium carbonate (0.25 equiv.) as mediator, and iminium salt catalyst **7** (10 mol%) in an acetonitrile medium induced asymmetric epoxidation of 1-phenylcyclohexene with up to 50% *ee* (Scheme 14). We were encouraged by this observation to investigate the parameters affecting this potentially attractive reaction system.



Scheme 14

The effect of inorganic mediator on asymmetric epoxidation

Mixtures containing iminium salt **7** and sodium hypochlorite in the presence of an alkene substrate but in the absence of an inorganic mediator showed no conversion to the corresponding epoxides. Therefore sodium hypochlorite, like hydrogen peroxide under similar conditions, is unable to drive the epoxidation process, and thus presumably does not oxidize iminium salts to oxaziridinium salts, in the absence of inorganic mediator. We

therefore investigated the effects on the reactions of several added mediators in reactions carried out over 24 hours (Table 5).

Table 5; Asymmetric Epoxidation of 1–Phenylcyclohexene using Different Mediators [a]

Entry	Base	Conv./%[b]	ee/%[c]
1	-	2	0
2	K_2CO_3	50	68
3	K_2CO_3 [d]	53	66
4	K_2CO_3 [e]	71	69
5	K_2CO_3 [f]	32	66
6	KOH	13	67
7	K_2HPO_4	27	63
8	$NaHCO_3$	92	60
9	KF	14	< 5
10	TBAF	89	16

[a] Epoxidation conditions: iminium salt **7** (10 mol%), sodium hypochlorite (13%, 6 equiv.), mediator (0.25 equiv.), dichloromethane (1 ml) 0 ºC, 24 h. [b] Conversions were evaluated by GC analysis based upon alkene and epoxide content. [c] Enantiomeric excesses were determined by chiral GC analysis; the major enantiomer was the (1*S*,2*S*)-epoxide. [d] Epoxidation conditions: iminium salt **7** (10 mol%), sodium hypochlorite (13%, 6 equiv.), mediator (0.40 equiv.), dichloromethane (1 ml) 0 ºC, 24 h. [e] Epoxidation conditions: iminium salt (10 mol%), sodium hypochlorite (13%, 6 equiv.), mediator (1.00 equiv.), dichloromethane (1 ml) 0 ºC, 24 h. [f] Epoxidation conditions: iminium salt (10 mol%), sodium hypochlorite (13%, 6 equiv.), mediator (0.25 equiv.), no solvent, 0 ºC, 24 h.

Rewardingly, the reactions proceeded smoothly when a mediator was included, and the enantioselectivity observed was largely independent of the type of mediator (hydrogen carbonate, carbonate or hydroxide) used to promote the reaction. Experiments containing a very low proportion of mediator (0.01 equiv.) showed minimal conversion to the epoxide. When the proportion of mediator was increased to 0.25 equivalents, the reaction furnished 1-phenylcyclohexene oxide with 68% *ee* with K_2CO_3, 60% *ee* with $NaHCO_3$, and 67% *ee* with KOH. For any mediator, the *ee* remained constant when the mediator was added in greater proportion than 0.1 equivalents. We concluded that, in those cases using carbonates as bases, percarbonate may be generated, and this may mediate the generation of an oxaziridinium ion. The large variation in conversions and to a lesser extent on the

enantioselectivity, due to the change of mediator may reflect that the conversion mirrors rate of reaction. The rate of reaction is dependent on the ease of generation of the oxaziridinium species, and this would be affected by factors such as the multiphase structure, ion association, identity of the peroxy nucleophile generated; while by contrast the *ee* should be less variable, unless there is a large variation in the direction of attack on the iminium salt using different inorganic mediators.

The effects of solvent and temperature

As potassium carbonate appeared to offer the best *ee*s, together with margins for improvement in both conversions and *ee*s, we chose this mediator for further studies. Several solvents were investigated, with reactions carried out at room temperature and 0 °C using catalyst **7** (Table 6).

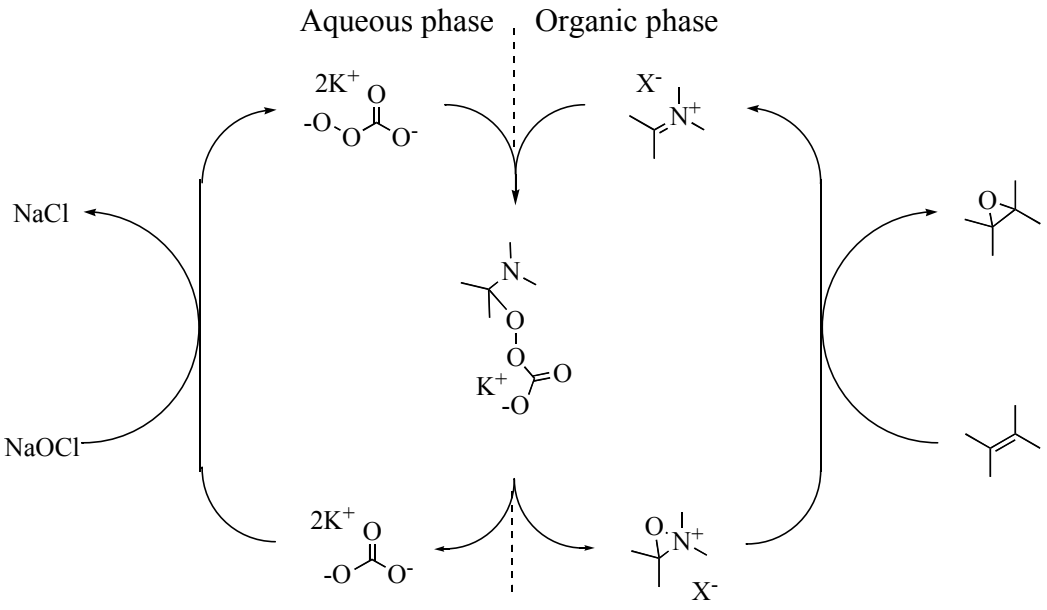
Table 6; Asymmetric Epoxidation of 1–Phenylcyclohexene Mediated by Catalyst 7 with varying solvents. [a]

Entry	Solvent	Temp./°C	Catalyst	Time/h	Conv./%[a]	ee/%[a]
1	acetonitrile	rt	_	24	100	< 5
2	dichloromethane	rt	_	24	0	-
3	chloroform	0	_	24	0	-
4	acetonitrile	rt	**7**	2	100	50
5	dichloromethane	rt	**7**	2	100	60
6	acetonitrile	0	**7**	4	100	56
7	dichloromethane	0	**7**	24	50	68
8	chloroform	0	**7**	24	47	48

Iminium salt Catalyst **7** (10 mol%), sodium hypochlorite (13%, 3 equiv.), K_2CO_3 (0.25 equiv.), solvent (1ml), alkene substrate (1 equiv.). [a] Conversions and enantiomeric excesses were determined by chiral GC analysis; the major enantiomer was the (1*S*,2*S*)-epoxide.

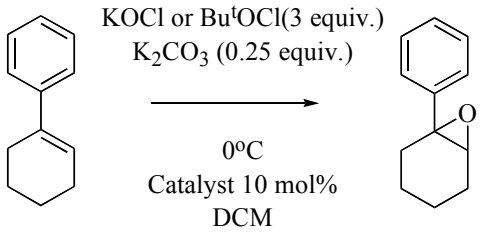
The results presented in table 2 show that acetonitrile facilitates complete conversion to the epoxide in less than 24 hours in the absence of the iminium salt catalyst, perhaps as a result of peroxyimidic acid formation. No such background epoxidation was seen over the same period when using dichloromethane or chloroform as the reaction solvent. Interestingly, in the presence of catalyst **7**, the epoxide was obtained in 50% *ee* at rt and 56% *ee* at 0 °C in acetonitrile solvent, despite the ready background pathway, the presence of the iminium salt catalyst presumably offering a lower energy pathway for reaction, leading to asymmetric epoxidation. When using dichloromethane as the reaction solvent, iminium salt catalyst **7** induces epoxidation with 60% *ee* at rt and 68% *ee* at 0 °C. Oxygen transfer, for example from percarbonate, to the iminium ion may take place at the solvent-solvent interface (Scheme 15). Alternatively, the iminium salts may act as phase transfer agents, the oxidation to oxaziridinium species then taking place in the aqueous phase before return of the oxaziridinium ion to the organic phase. Assuming that hypochlorite will be largely contained in the aqueous phase, the oxaziridinium species would then become the dominant oxidant in the organic phase.

It seems likely that the decreased enantiocontrol in the acetonitrile reaction was due to background epoxidation, rather than a genuine solvent effect. Use of chloroform, however, clearly results in poorer induced enantioselectivity, although chloroform does not promote background epoxidation. We have previously observed excellent enantiocontrol when using chloroform as the solvent under non-aqueous conditions, with TPPP as stoichiometric oxidant.[8,9]



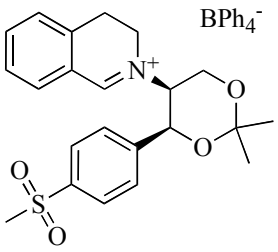
Scheme 15

Stronger hypochlorite oxidants such as potassium hypochlorite and *t*-butyl hypochlorite have also shown precedent for oxygen transfer,[14,22] Therefore both oxidants were tested for their capacity as an oxidant within our current conditions (Scheme 16). Unfortunately *t*-butyl hypochlorite proved too strong an oxidant as full conversion to the epoxide was observed without inducing enantioselectivity.



Scheme 16

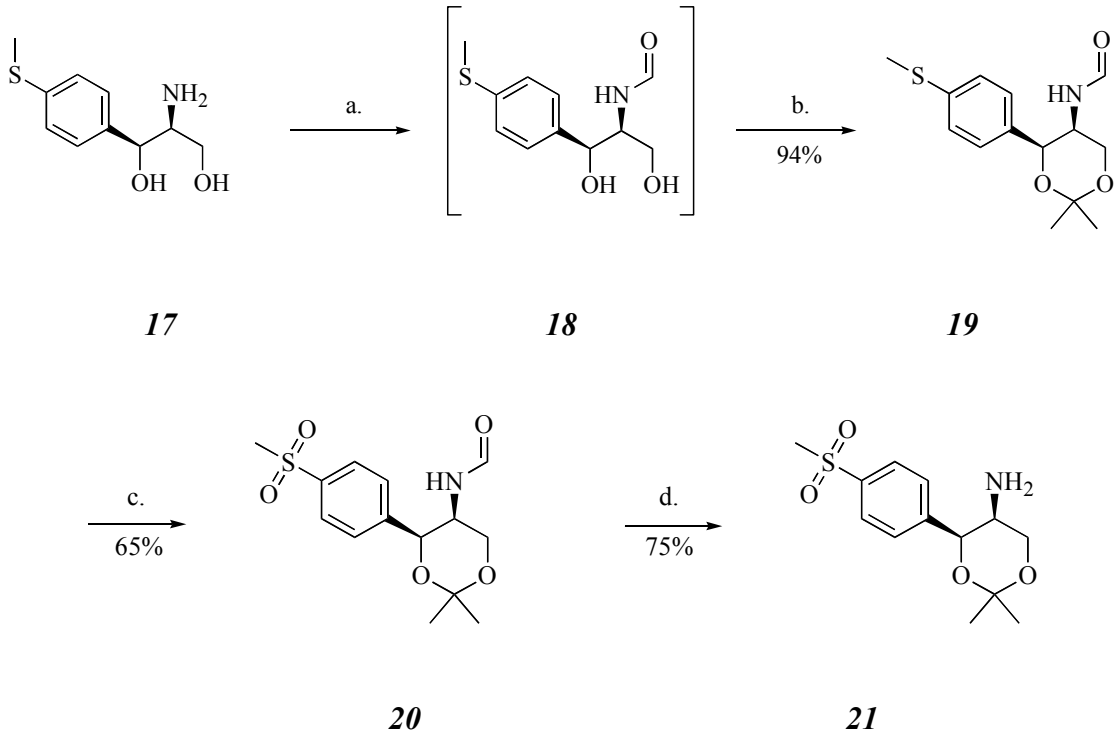
In previous work it was observed that when attempting to oxidise *cis*-substituted alkenes, the utilisation of iminium salt catalyst **1**, a sulphone derivative of catalyst **6**, gave high levels of enantiocontrol. More interestingly, when using chloroform as a solvent, catalyst **1** generated the opposite enantiomer of the desired epoxide. When epoxidation was attempted in any other solvent the enantiocontrol decreased and the stereochemistry of the epoxide product reverted back to that of which the parent catalyst **6** yielded.



Catalyst 1

With the new sodium hypochlorite system giving good enantiocontrol when used in conjunction with chloroform and iminium salt catalyst **7** (up to 47%), it was proposed that the use of iminium salt **1** when used under these same sodium hypochlorite conditions would give encouraging results.

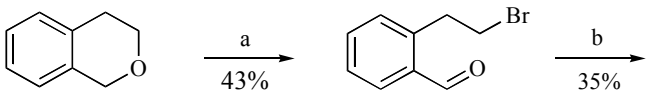
Thiomicamine, **17** was formate protected at the nitrogen (**18**, Scheme 17), allowing subsequent *p*-TSA catalysed diol protection, **19** with 2,2-dimethoxypropane. The thiol was oxidised to the sulphone, **20** with *m*-CPBA. The formate protecting group was removed using hydrazine hydrate generating sulphone aminodioxane **21** in 26% over four steps.



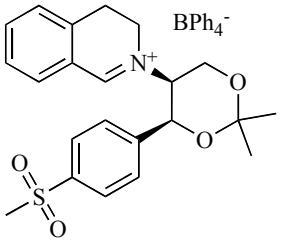
Reagents and conditions; (a) MeOH, NaOMe, Methyl formate, rt, 2 hrs. (b) Acetone, 2,2-DMP, p-TSA, rt, 4 hrs. (c) m-CPBA, DCM, rt, 16 hrs. (d) N_2H_4, Δ, 4hrs.

Scheme 17

*Iso*chroman was ring opened with bromine to generate the phenyl bromo aldehyde **23** (Scheme 18). The sulphone aminodioxane **21** was then condensed with bromoaldehyde **23** to yield iminium salt **1** in 34%.



22 ***23***



1

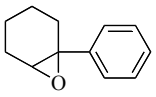
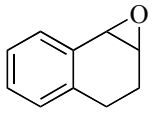
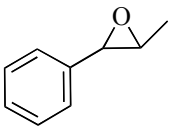
Reagents and conditions; (a) CCl_4, Br_2, HBr, rt, 2 hrs.
(b) 21, EtOH, $NaBPh_4$, MeCN, 0 °C → rt, 17 hrs.

Scheme 18

Catalyst **1**, **6** and **7** were then tested with in the new oxidative system to observe their effectiveness on a range of test substrates (Table 7).

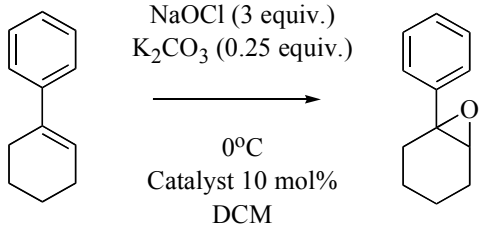
It was observed that using iminium salt catalyst **7** in dichloromethane gave the best reaction profile when using sodium hypochlorite as the oxidant giving up to 68 % conversion, and up to 71 % *ee* for 2,3-dihydronaphthylene. Decreased enantioselectivities were observed when using either acetonitrile or chloroform as the solvent. Reversal of enantiocontrol was not observed for any substrate used when employing salt catalyst **1** and chloroform as the solvent.

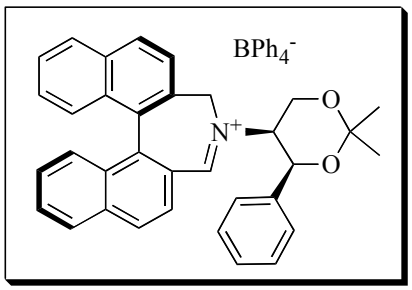
Table 7; Asymmetric Epoxidation of Unfunctionalised Alkenes Mediated by Catalysts 6, 1 and 7.[a]

Epoxide	Catalyst	Solvent	Conversion/% [c]	ee/% [c]	Major enantiomer [d]
	**6**	MeCN	49	17	(–)-1*S*,2*S*
	6	CH_2Cl_2	10	49	(–)-1*S*,2*S*
	1	MeCN	100	28	(–)-1*S*,2*S*
	1	CH_2Cl_2	50	17	(–)-1*S*,2*S*
	1	$CHCl_3$	60	19	(–)-1*S*,2*S*
	7	MeCN	100	55	(–)-1*S*,2*S*
	7	CH_2Cl_2	50	68	(–)-1*S*,2*S*
	7	$CHCl_3$	47	48	(–)-1*S*,2*S*
	**6**	MeCN	9	21	(–)-1*S*,2*R*
	6	CH_2Cl_2	23	33	(–)-1*S*,2*R*
	1	$CHCl_3$	13	46	(–)-1*S*,2*R*
	7	MeCN	24	66	(–)-1*S*,2*R*
	7	CH_2Cl_2	68	71	(–)-1*S*,2*R*
	**6**	MeCN	34	8	(–)-1*S*,2*S*
	6	CH_2Cl_2	42	9	(+)-1*R*,2*R*
	1	$CHCl_3$	44	8	(+)-1*R*,2*R*
	7	MeCN	20	14	(–)-1*S*,2*S*
	7	CH_2Cl_2	98	13	(–)-1*S*,2*S*

[a] epoxidation conditions: Iminium salt catalyst (10 mol%), Sodium hypochlorite (13%, 6 equiv.). K_2CO_3 (0.25 equiv.), Solvent (1 ml) 0ºC, 24 hours. [b] Enantiomeric excesses were determined by chiral GC–FID spectra by comparison of the two epoxide peak areas. [c] Conversions were evaluated from the chiral GC–FID spectra by comparison of the alkene and epoxide peak areas. [d] Absolute configurations of the major enantiomers were determined by comparison of both optical rotation and GC-FID with those reported in the literature.

With the new sodium hypochlorite oxidative system inducing up to 71% *ee*, the next step was to assess catalyst **3** with in this system (Scheme 2), which induces up to 95% *ee* under the original Oxone® conditions.





Scheme 19 ***3***

When catalyst **3** was used under the sodium hypochlorite conditions, little conversion to the epoxide was observed. This was due to the decomposition of the binaphthalene based catalyst under the reaction conditions over the prolonged 24 hour reaction time.

2.1.3.1 Conclusion.

The addition of the K_2CO_3 elevates the pH of the reaction to $\geq$ 11.0. This rise in pH facilitates the generation of hypochlorite anions in the reaction mixture. The hypochlorite anion then follows one of the two hypothesised pathways (Scheme 12, Pathway A and Scheme 13, Pathway B) via either an aminohypochlorite adduct or an aminopercarbonate adduct. Both pathways collapse to generate the oxaziridinium intermediate as a pair of diastereoisomers with the expulsion of an appropriate leaving group. These diastereoisomers almost certainly operate through different transition states during the oxygen transfer to the substrate and with different kinetics therefore inducing different enantioselectivities. The observed *ee* in each case was an average of the two processes.

Commercial sodium hypochlorite has shown to be a useful stoichiometric oxidant in iminium salt-catalysed asymmetric epoxidation. Addition of sodium hypochlorite to a carbonate salt forms an extremely reactive species capable of oxidising iminium salts to their corresponding oxaziridinium salt. Optimization of the oxidative system has enabled asymmetric epoxidation with good enantiocontrol of up to 71%, in the epoxidation of 2,3-dihydronapthylene when using iminium salt **7**. The overall process enjoys simplicity and environment friendliness that may be of benefit to both industrial and academic laboratories.

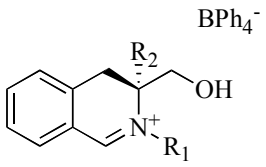
2.2 New novel catalysts for catalytic asymmetric epoxidation.

Over the last ten years Page has developed a range of iminium salt catalysts incorporating a chiral substituent at the iminium nitrogen atom. The presence of chirality α to the iminium nitrogen has been shown to induce increased enantiocontrol in epoxidation reactions compared to catalysts that contain an *N*-achiral substituent.

We hypothesised that more complex chiral groupings α to the iminium nitrogen and at other strategic locations may further increase the enantioselectivity induced in asymmetric epoxidation.

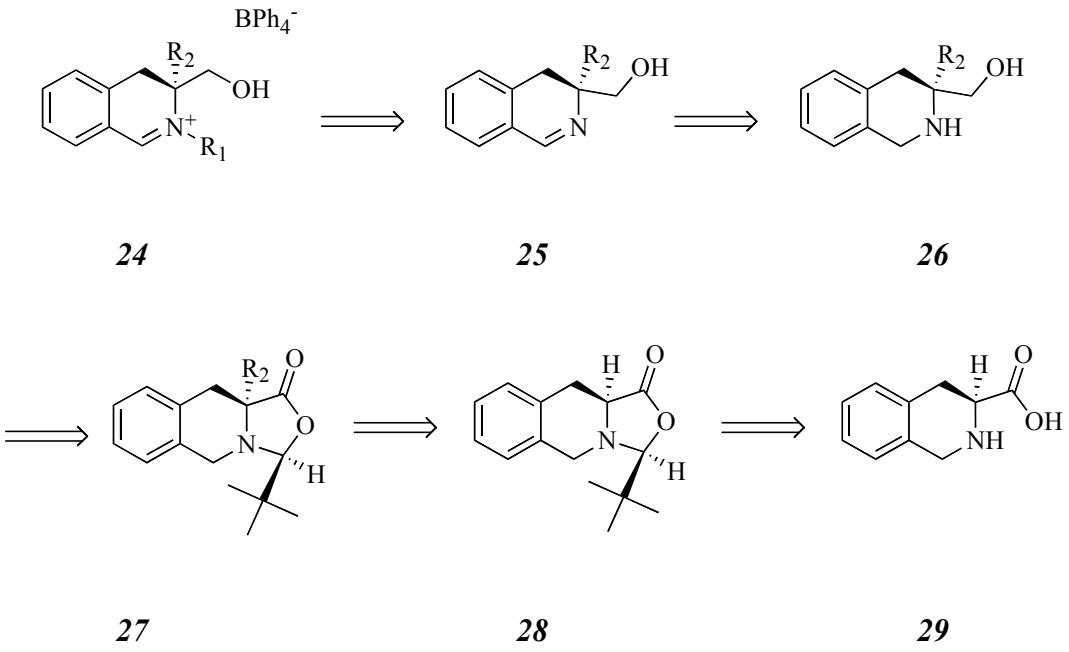
2.2.1 Dihydroisoquinolinium salt catalysts with α nitrogen chirality.

Work within the group was aimed towards the generation of dihydroisoquinolinium salt catalysts with chiral functionality incorporated into the dihydroisoquinolinium ring and also α to the iminium nitrogen atom. Iminium salt **24** is one such target.



24

With iminium salt **24** identified, a retro-synthetic outline was postulated (Scheme 20).



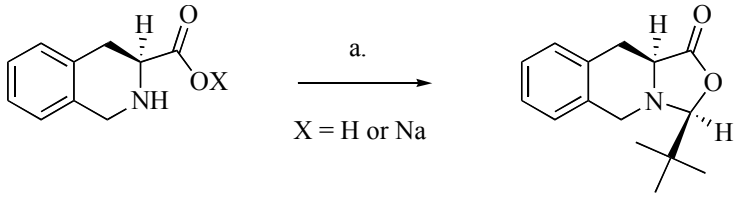
24 ***25*** ***26***

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

Scheme 20

The desired iminium salt **24** would be generated by quarternisation of **25** with a suitable alkyl group. Oxidation of amine **26** with NBS would generate imine **25**, the former (**26**) would be generated by the acid deprotection and reduction of **27**. Using Seebach methodology, base deprotonation of **28** α to the carbonyl group and trapping with the introduction of 'RX' would generate the substituted tricycle **27** maintaining the chirality present in **29**. [23] And finally the first hypothesised synthetic step would be the cyclisation of enantiomerically pure tetrahydroisoquinoline **29** with pivaldehyde so generating the *t*-butyl acetal **28**.

Using 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**29**) as the starting material, attempts to cyclise the amino and carboxylic acid functionalities with pivaldehyde under Dean and Stark conditions were unsuccessful (Scheme 21). A range of reaction conditions using both the acid and its sodium salt, were attempted in an effort to cyclise the starting material; unfortunately these conditions were all unsuccessful (Table 8). Further attempts to prepare this family of catalysts was therefore abandoned



Reagents and conditions; (a) Pivaldehyde (for conditions see Table 8).

Scheme 21

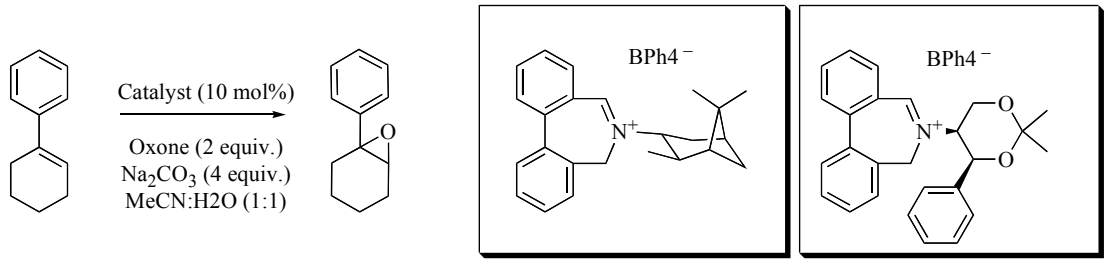
Table 8; Methods for the cyclisation of

1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid.

Entry	Starting material	Solvent	Acid / Lewis Acid	Temp./ °C	Time/ h	Product
1	Sodium salt	Pentane	-	36	48	SM
2	Sodium salt	Toluene	-	110	48	SM
3	Acid	Pentane	-	36	48	SM
4	Acid	Toluene	-	110	48	SM
5	Sodium salt	Pentane	PTSA	36	48	SM
6	Sodium salt	Toluene	PTSA	110	48	SM
7	Acid	Pentane	PTSA	36	48	SM
8	Acid	Toluene	PTSA	110	48	SM
9	Sodium Salt	Acetonitrile	BF_3.OEt	rt	48	SM
10	Sodium Salt	Acetonitrile	BF_3.OEt	82	48	SM
11	Sodium Salt	Pentane	BF_3.OEt	36	48	SM
12	Acid	Acetonitrile	BF_3.OEt	rt	48	SM
13	Acid	Acetonitrile	BF_3.OEt	82	48	SM
14	Acid	Pentane	BF_3.OEt	36	48	SM
15	Acid	Pentane	TFA	36	48	SM
16	Acid	Toluene	TFA	110	48	SM

2.2.2 Iminium salt catalysts based on a biphenyl azepinium backbone

Page has reported that iminium salt catalysts based on a biphenyl skeleton fused with an azepinium salt induce good enantioselectivity and excellent reactivity in terms of conversion of an alkene to the corresponding epoxide (Scheme 22).



30 ***7***

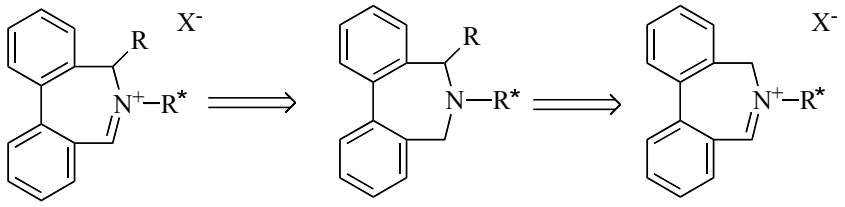
29% ee ***60% ee***

100% conv. ***100% conv.***

Scheme 22

It was evident that iminium salt catalysts containing an *N*-chiral appendage gave increased enantiocontrol over chiral catalysts containing an achiral *N*-substituent. The approach of the oxidant or the alkene substrate to the iminium or the oxaziridinium salt (respectively) is presumably directed electronically or sterically by this α-chirality, therefore increasing enantiocontrol.

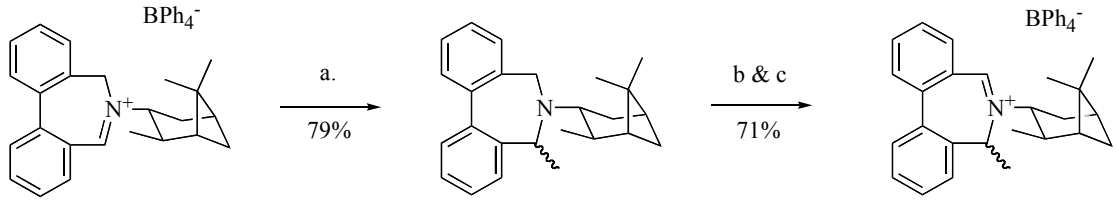
The biphenyl azepinium catalysts contain a methylene group α to the nitrogen. It was postulated that the biphenyl azepinium iminium bond (**5**) could undergo Grignard addition to generate the corresponding amine **32**, this amine could then be re-oxidised to the iminium salt **31**, using NBS (Scheme 23). This would give a second chiral centre α to the iminium nitrogen, which we hoped would induce increased enantioselectivity by electronic and/or steric interaction with the approaching oxidant or alkene substrate.



31 ***32*** ***5***

Scheme 23

Using *N*-isopinocampheyl iminium salt **30** as a model substrate, methyl magnesium bromide was added to the iminium bond. The addition proceeded smoothly generating an inseparable pair of diastereoisomers **33**, determined by ^{1}H NMR spectroscopy as a 1:1 diastereoisomeric ratio. Reaction of the diasteoisomeric mixture with NBS generated the bromide iminium salt, which underwent ion exchange to generate the tetraphenyl borate iminium salt **34** as a 1:1 mixture of inseparable diastereoisomers. Only oxidation at the methylene carbon atom α to the nitrogen atom was observed, no oxidation is observed at the new chiral carbon centre α to the nitrogen.



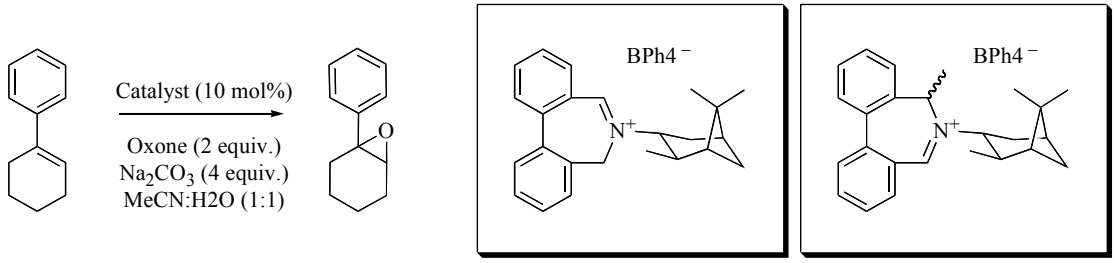
30 ***33*** ***34***

Reagents and conditions; (a) MeMgBr, THF, –78 °C → rt, 2 hrs. (b) NBS, DCM, rt, 10 mins. (c) EtOH, $NaBPh_4$, rt, 2 hrs .

Scheme 24

This second-generation iminium salt catalyst **34** was tested for its ability to induce enantiocontrol in asymmetric epoxidation of 1-phenylcyclohexene (Scheme 25). Catalyst **34** imparts 61% *ee* in 1 hour, with 100% conversion to the epoxide. In comparison to the parent catalyst **30**, which imparts 29% *ee* with 100% conversion in less than 30 minutes,

showing that the α-substituted iminium salt catalyst **34** induces considerably increased levels of enantioselectivity over 30.



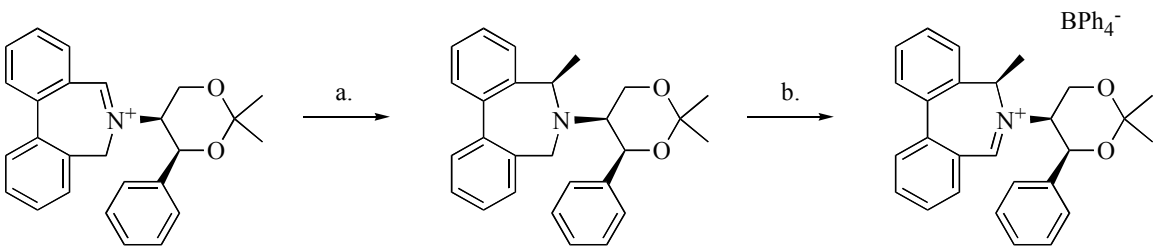
35 ***7***

29% ee ***61% ee***

100% conv. ***100% conv.***

Scheme 25

From this encouraging result we focused our attention on the substitution of *N*-dioxane iminium salt catalyst **7**, as this has proven to impart higher levels of enantiocontrol than the isopinocampheyl catalyst **30**. Several Grignard reagents (MeMgBr, ^{i}PrMgBr, PhMgBr & BnMgBr) were added to the iminium bond generating the respective amines **36** – **39** (Scheme 26). NBS oxidation converted the amines into their bromide iminium salts in good yields (**40** – **43**).



7

36 R = Me (91%)
37 R = ^{i}Pr (62%)
38 R = Ph (47%)
39 R = Bn (60%)

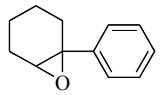
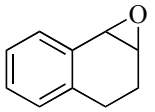
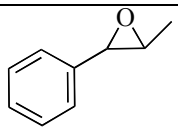
40 R = Me (63%)
41 R = ^{i}Pr(83%)
42 R = Ph (91%)
43 R = Bn (83%)

Reagents and conditions; (a) RMgBr, THF, –78 °C to rt, 2 hrs.
(b) NBS, DCM, Δ, 10 – 25 mins.

Scheme 26

From the V.T. ^{13}C NMR data, we calculated that the addition of all Grignard reagents to catalyst **7** gave one single diastereoisomer in each case. Epoxidation of our test substrate 1-phenylcyclohexene was completed using these new iminium salt catalysts; the catalysts displaying the highest enantiocontrol were then used to catalyse oxidation of two other representative alkenes (Table 9).

Table 9; Asymmetric Epoxidation of Unfunctionalised Alkenes Mediated by Catalyst 7, and catalysts 40 – 43.[a]

Epoxide	Catalyst	Conversion/% [c]	ee/% [c]	Major enantiomer [d]
	**7**	100	61	(–)-1*S*,2*S*
	40	100	81	(–)-1*S*,2*S*
	41	100	72	(–)-1*S*,2*S*
	42	100	71	(–)-1*S*,2*S*
	43	72	75	(–)-1*S*,2*S*
	**7**	100	32	(–)-1*S*,2*R*
	40	100	56	(–)-1*S*,2*R*
	43	56	25	(–)-1*S*,2*R*
	**7**	90[e]	41[f]	(–)-1*S*,2*S*
	40	100[e]	75[f]	(+)-1*R*,2*R*

[a] epoxidation conditions: Iminium salt catalyst (10 mol%), Oxone® (2 equiv.). Na_2CO_3 (4 equiv.), Solvent (1:1 Acetonitrile/H_2O) 0ºC. [b] Enantiomeric excesses were determined by chiral GC–FID spectra by comparison of the two epoxide peak areas. [c] Conversions were evaluated from the chiral GC–FID spectra by comparison of the alkene and epoxide peak areas. [d] Absolute configurations of the major enantiomers were determined by comparison of both optical rotation and GC-FID with those reported in the literature. [e] Enantiomeric excesses were determined by chiral HPLC spectra by comparison of the two epoxide peak areas. [f] Conversions were evaluated from the ^{1}H NMR spectra by comparison of the alkene and epoxide peak integrations.

The parent catalyst **7** induces up to 61% *ee* in the epoxidation of 1-phenylcyclohexene. Increased enantiocontrol was observed for all of the second generation catalysts, with catalyst **40**, containing an added methyl group, inducing the highest enantiocontrol, giving up to 81% *ee* and 100% conversion in one hour.

Catalyst **40** shows increased levels of enantiocontrol over its analogues (**41 - 43**). From the crystal structure (Figure **44**), it is evident that there are possibly two factors which contribute to high enantioselectivity. The additional axial methyl substituent C(29) α to the iminium nitrogen N(1) probably impedes the approach of the oxidant from the *si* face due to the steric hindrance. The methyl group may inhibit approach to the *si* face of the

iminium bond without hindering the bond rotation of the aminodioxane unit around the, N(1)-C(5). As high enantiocontrol is then directly related to the approach of the alkene towards the 'free' *re* face, any interference with the aminodioxane rotation could directly hinder the *re* face.

Substitution of larger alkyl and aryl substituent's at C(28) may cause higher levels of interference with this aminodioxane rotation, causing enantiocontrol to be reduced as observed in catalysts **41** - **43** presumably by preventing the adoption of the optimal approach control. The introduction of a methyl group appears to be the optimal substitution, balancing *si* face hindrance with controlled approach of the alkene.

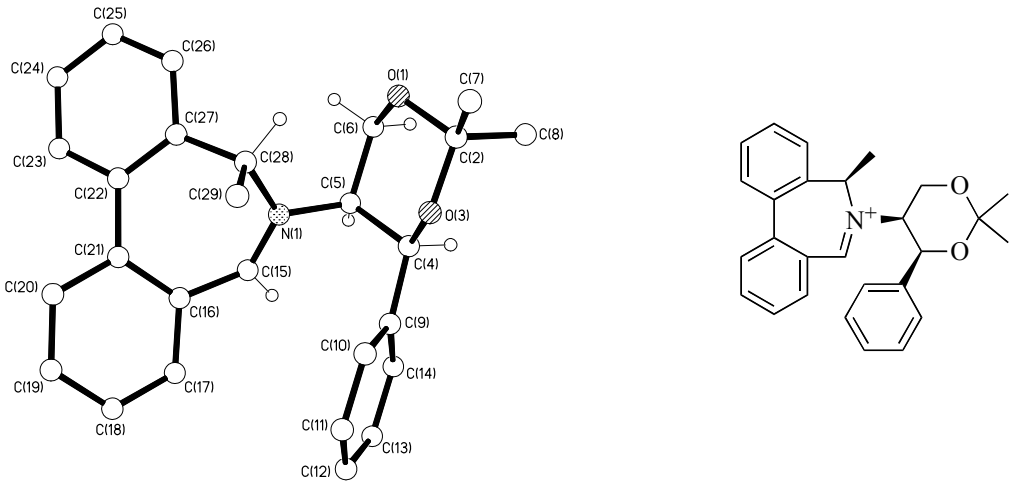
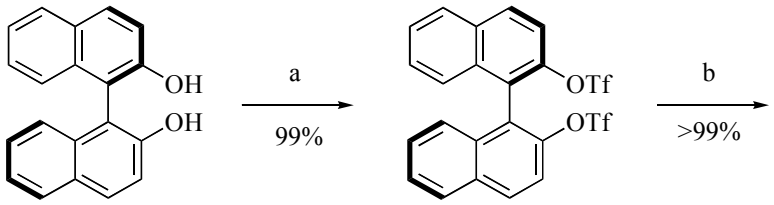


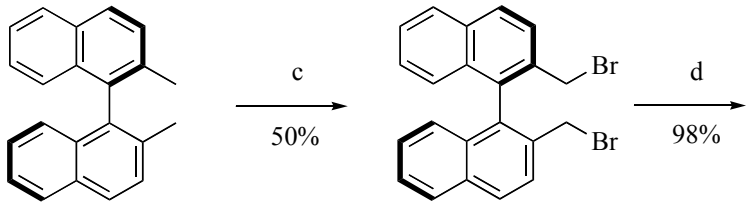
Figure 44, X-ray crystal structure of catalyst 40

The next logical step was to use this methodology to insert a methyl group in to the iminium bond of binaphthyl based iminium salt catalyst **3** (Scheme 27).

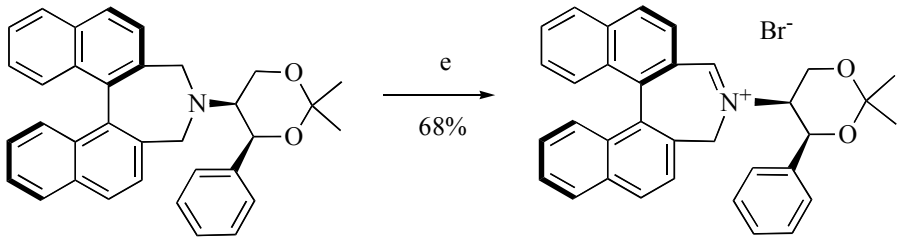
R-Binol (**45**, Scheme 27) was converted to the triflate, **46**. This underwent Kumada coupling with methyl magnesium bromide to yield the *bis*methyl-binaphthyl compound **47**. NBS bromination initiated by AIBN generated the dibromobinaphthylene, **48**, which was smoothly condensed with aminodioxane **11** to generate the cyclic amine, **49**. NBS oxidation of this amine gave the iminium bromide salt **50**.



45 ***46***



47 ***48***

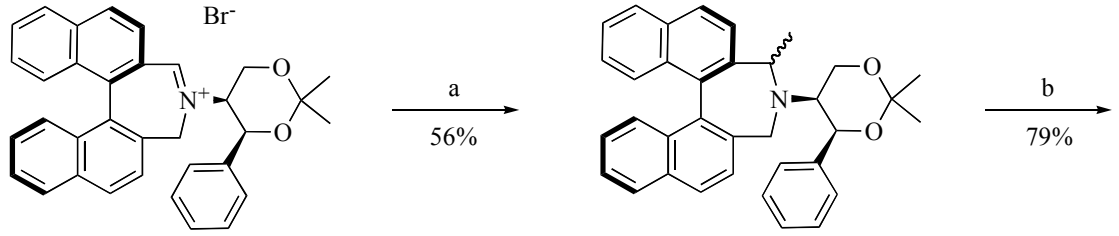


49 ***50***

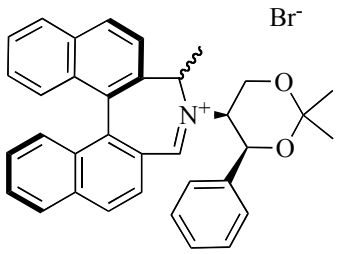
Reagents and conditions; (a) Triflic anhydride, 2,6-lutidine, DMAP, DCM, –30 °C → rt, 4 hrs. (b) MeMgBr, $Ni(Cl)_2(PPh_2)_2$, Et_2O. (c) NBS, CCl_4, AIBN, hv, rt, 5 hrs. (d) 11, THF, TEA, Δ → rt, 5 mins. (e) NBS, DCM, rt, 20 mins.

Scheme 27

The binaphthyl azepinium bromide salt **50** was treated with methyl magnesium bromide, generating the tertiary amine **51** as a pair of diastereoisomers in a 3:2 ratio, determined by ^{13}C NMR spectroscopy data.



50 ***51***



52

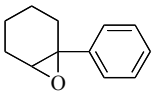
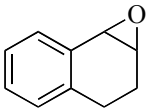
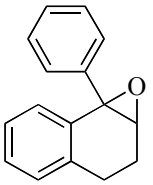
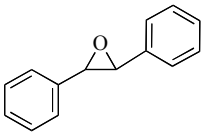
Reagents and conditions; (a) MeMgBr, THF, –78 °C to rt, 2 hrs.
(b) NBS, DCM, Δ, 15 mins.

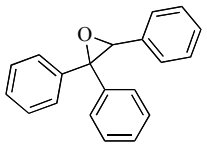
Scheme 28

Amine **51** was subjected to NBS oxidation generating the desired azepinium bromide salt **52** in good yield as a pair of inseparable diastereoisomers.

Catalyst **52** was then compared to its parent, catalyst **3**, as were catalysts **34** and **40** to test for their ability to induce enantioselectivity in the epoxidation of several alkene substrates (Table 10).

Table 10; Asymmetric Epoxidation of various alkenes with the original parent catalysts and also the second generation catalysts.[a]

Epoxide	Catalyst	Conversion/% [d,e]	ee/% [b,c]	Major enantiomer [f]
	**30**	100	17	(+)1*R*,2*R*
	34	100	61	(+)1*R*,2*R*
	7	100	60	(–)1*S*,2*S*
	40	100	81	(–)1*S*,2*S*
	3	100	91	(–)1*S*,2*S*
	52	100	93	(–)1*S*,2*S*
	**30**	100	10	(–)1*R*,2*S*
	34	100	28	(–)1*R*,2*S*
	7	100	32	(+)1*S*,2*R*
	40	100	56	(+)1*S*,2*R*
	3	100	17	(+)1*S*,2*R*
	52	100	24	(+)1*S*,2*R*
	**30**	95	38	(+)1*S*,2*R*
	34	23	68	(+)1*S*,2*R*
	7	90	41	(–)1*R*,2*S*
	40	100	75	(–)1*R*,2*S*
	3	100	95	(–)1*R*,2*S*
	52	90	96	(–)1*R*,2*S*
	**30**	95	0	-
	34	95	6	(+)1*R*,2*R*
	7	90	15	(–)1*S*,2*S*
	40	100	21	(–)1*S*,2*S*
	3	100	12	(–)1*S*,2*S*
	52	81	12	(–)1*S*,2*S*

	**30**	100	38	(+)1*R*
	34	100	38	(+)1*R*
	7	90	24	(–)1*S*
	40	100	21	(–)1*S*
	3	98	20	(–)1*S*
	52	81	25	(–)1*S*

[a] epoxidation conditions: Iminium salt catalyst (2.5 mol%), Oxone® (2 equiv.). Na_2CO_3 (4 equiv.), Solvent (1:1, Acetonitrile:H_2O 5 ml) 0ºC, 17 mins – 6 hrs. [b] Enantiomeric excesses were determined by chiral GC–FID spectra by comparison of the two epoxide peak areas. [c] Conversions were evaluated from the chiral GC–FID spectra by comparison of the alkene and epoxide peak areas. [d] Enantiomeric excess determined by Chiral HPLC on a Chiracel OH-D column. [e] Conversion evaluated from the ^{1}H-NMR by integration alkene versus epoxide. [f] Absolute configurations of the major enantiomers were determined by comparison of both optical rotation and GC-FID with those reported in the literature.

From Table 10 it can be seen that the second generation of iminium salt catalysts induce, in most cases, higher enantiocontrol than the parent catalyst. The addition of a methyl substituent as for catalyst **40**, **3**, and **34**, gives increased enantiocontrol, presumably due to the additional methyl group sterically and/or electronically controlling the approach of either the oxidant and the alkene substrate. This is remarkable in the case of **52** as the catalyst is used as a pair of diastereoisomers. One possible explanation is that one diastereoisomers is far more reactive than the other.

2.2.2.1 Conclusion

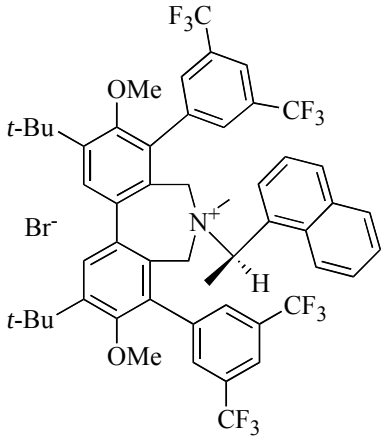
On reflection, we have observed that the introduction of a chiral carbon atom α to the iminium nitrogen significantly increases the enantiocontrol of azepinium salt catalysts towards epoxidation of unfunctionalised alkenes.

The introduction of an aryl or alkyl substituent may increase the steric hindrance around one of the two prochiral faces available, therefore increasing the preference for formation of one diastereoisomeric oxaziridinium intermediate, and may also help to control the subsequent approach of the alkene substrate.

2.2.3 Iminium salt catalysts based on a 7,5-fused bicyclic lactam substructure.

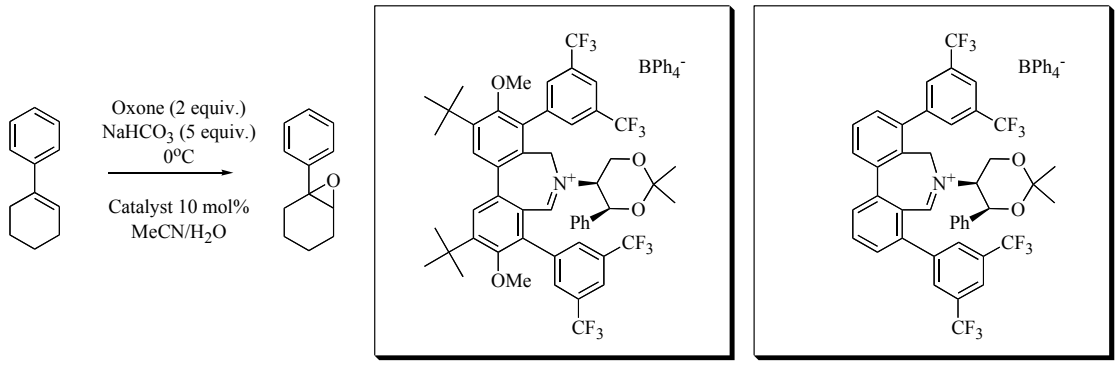
It has been shown that variations to our original biphenyl azepinium salt catalyst substructure have enabled increased levels of enantiocontrol in epoxidation of selected alkenes.

Furthermore, work investigating the impact of a second chiral carbon atom α to the iminium nitrogen shows increased enantiocontrol over alkene substrates. We therefore postulate that other iminium salt catalyst sub-structures based on the original biphenyl motif but containing multiple chiral carbons α to the iminium nitrogen could generate high levels of enantioselectivity.



53

A fundamental problem concerning biphenyl structures is their ability to rotate around the aryl/aryl bond forming two interconverting atropoisomers denoted *R*a and *S*a by Cahn-Ingold-Prelog rules. Recent work has concerned atropo-enantioselective reactions generating a single atropoisomer. Work reported by Lygo on asymmetric phase transfer alkylation,[24,25] generated catalyst **53** by insertion of six bulky substituent's on the azepinium biphenyl skeleton. This slows the biphenyl aryl/aryl rotation and establishes one thermodynamically favourable atropoisomer. Our group, using catalyst **53** as the template, incorporated amino dioxane **11** in to the biphenyl skeleton, so generating iminium salt catalysts **54** and **55.**[26] Under the standard Oxone® conditions 22% and 44% *ee* (respectfully) was generated with our test substrate 1-phenylcyclohexene (Scheme 29).



54
22% ee
63% conv.

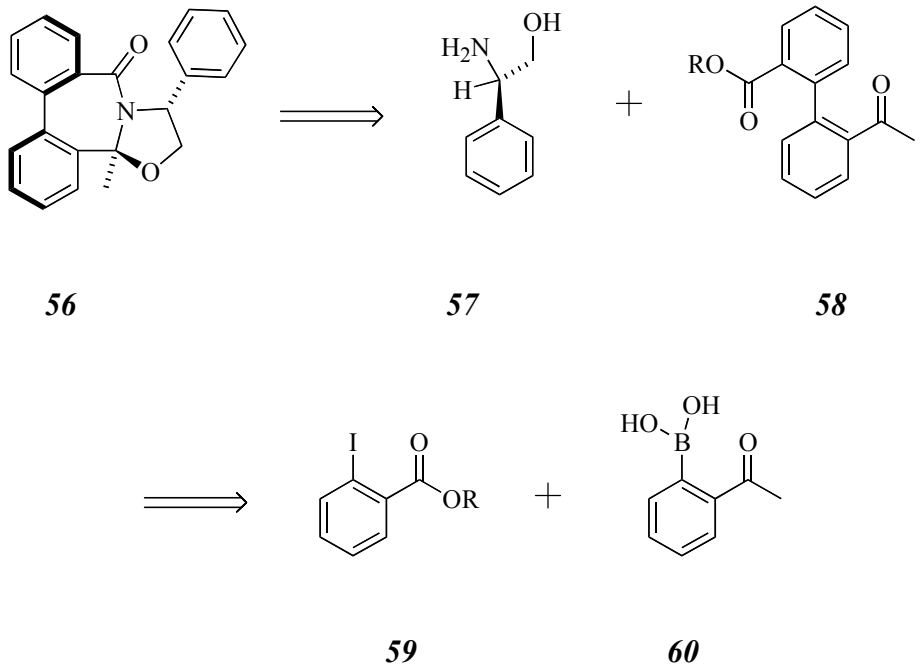
55
44% ee
100% conv.

Scheme 29

It was observed by V.T. ^{1}H NMR spectroscopy that an atropoisomeric mixture of iminium salt catalyst **55** was present, at 20 °C this was 1:10.2 increasing to a ratio of 1:32 at -40 °C, therefore displaying the preference for one atropoisomer, the identity of which is unknown at present.

From this work it was envisaged that if the biphenyl skeleton could be generated atropo-enantioselectively with out the presence of the bulky substituents, the presence of a single atropoisomer could be sufficiently investigated.

It was reported by Levacher,[27] that Meyers' bicyclic lactam methodology was widely used in the stereoselective construction of five- and six- membered ring nitrogen heterocycles.[28] These lactams provide a number of highly functionalised chiral building blocks that may be used further, in a wide range of stereoselective transformations, resulting in a chiral axis of the biaryl motif in greater than 95% de (Scheme 30). The desired lactam was generated from an amino alcohol condensation with the acetyl bicyclic ester. This acetyl bicyclic ester was further disconnected using Suzuki methodology to give acetyl phenyl boronic acid and 2-iodobenzoic ester.

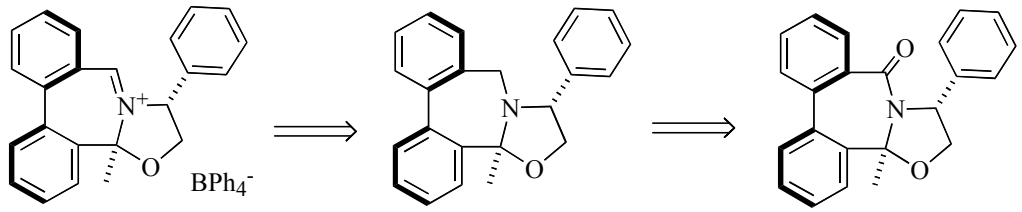


56 ***57*** ***58***

59 ***60***

Scheme 30

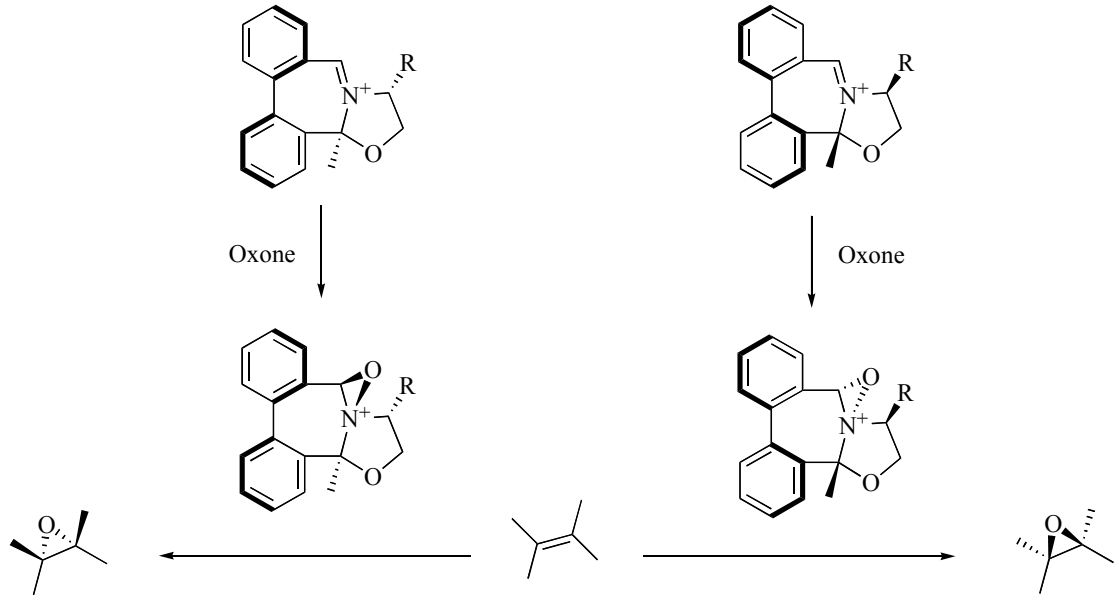
We hypothesised this 7,5-fused bicyclic lactam substructure **56** could be used to generate iminium salt catalyst **61** (Scheme 31), by the reduction of amide **56** to amine **62** and subsequent NBS induced iminium salt formation would give the desired iminium salt catalyst **61.**



61 ***62*** ***56***

Scheme 31

This methodology would allow almost any amino alcohol to be condensed within the biphenyl backbone. As demonstrated by Levacher, the condensation of (*R*)-phenyl glycinol gives excellent diastereoisomeric and atropoisomeric control.

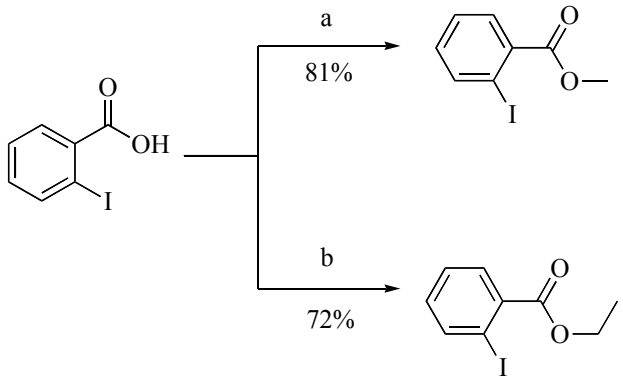


Scheme 32

Furthermore either, enantiomer of the selected amino alcohol could be condensed within the biphenyl backbone so generating either enantiomer of the iminium salt catalyst (Scheme 32). Oxidation of the enantiopure iminium salt would generate, preferentially, one diastereoisomer of the oxaziridinium salt intermediate. This diastereoisomer of the

oxaziridinium salt in turn would then, preferentially, generate one enantiomer of the epoxide.

The synthesis of the desired bicyclic lactam was initiated using 2-iodo-benzoic acid (**63**) as our starting material; this was converted to the methyl ester, **64** with acetyl chloride in methanol (Scheme 33). The ethyl ester **65** was prepared by using thionyl chloride followed by potassium carbonate in ethanol (Scheme 33).

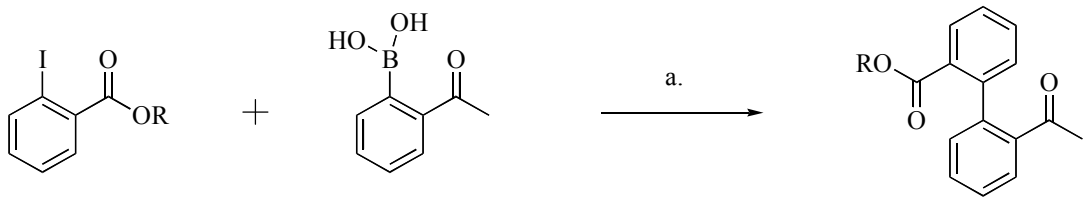


63 ***64 (Me)***
65 (Et)

Reagents and conditions; (a) Acetyl chloride, MeOH, Δ, 12 hrs. (b) Thionyl chloride, Δ, 2 hrs. K_2CO_3, absolute EtOH, Δ, 12 hrs.

Scheme 33

The esters (**64** & **65**) underwent coupling with 2-acetylphenylboronic acid (**60**) using Suzuki methodology to yield the desired methyl and ethyl esters, 66 (Me) & 67 (Et).



64 (Me) ***60*** ***66 (Me, 64%)***

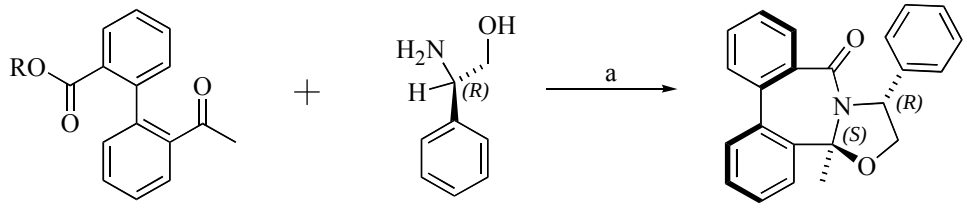
65 (Et) ***67 (Et, 76%)***

Reagents and conditions; (a) Toluene, EtOH, 5% aq. K_2CO_3, $Pd(PPh_3)_4$, Δ, 48 hrs.

Scheme 34

The Suzuki conditions used by Levacher were a toluene:ethanol:water solvent system (10:1:1), potassium carbonate as the base (3 equiv.) and a palladium catalyst, specifically $Pd(PPh_3)_4$ (10 mol%), but we have observed similar yields when employing Pd(DPPF). The reaction was heated under reflux over 48 h to give the biphenyl compounds in 64% (R = Me) and 76% (R = Et) yields.

The 2'-acetyl-biphenyl-2-carboxylic acid esters 66 (Me) & 67 (Et), underwent amino alcohol condensation with *R*-phenyl glycinol to generate the 7,5-fused bicyclic lactams with 95% de (R = Me) and 98% de (R = Et) as determined by ^{13}C NMR spectroscopy (Scheme 35).



66 (Me) ***57*** ***56 (Me, 57%)***

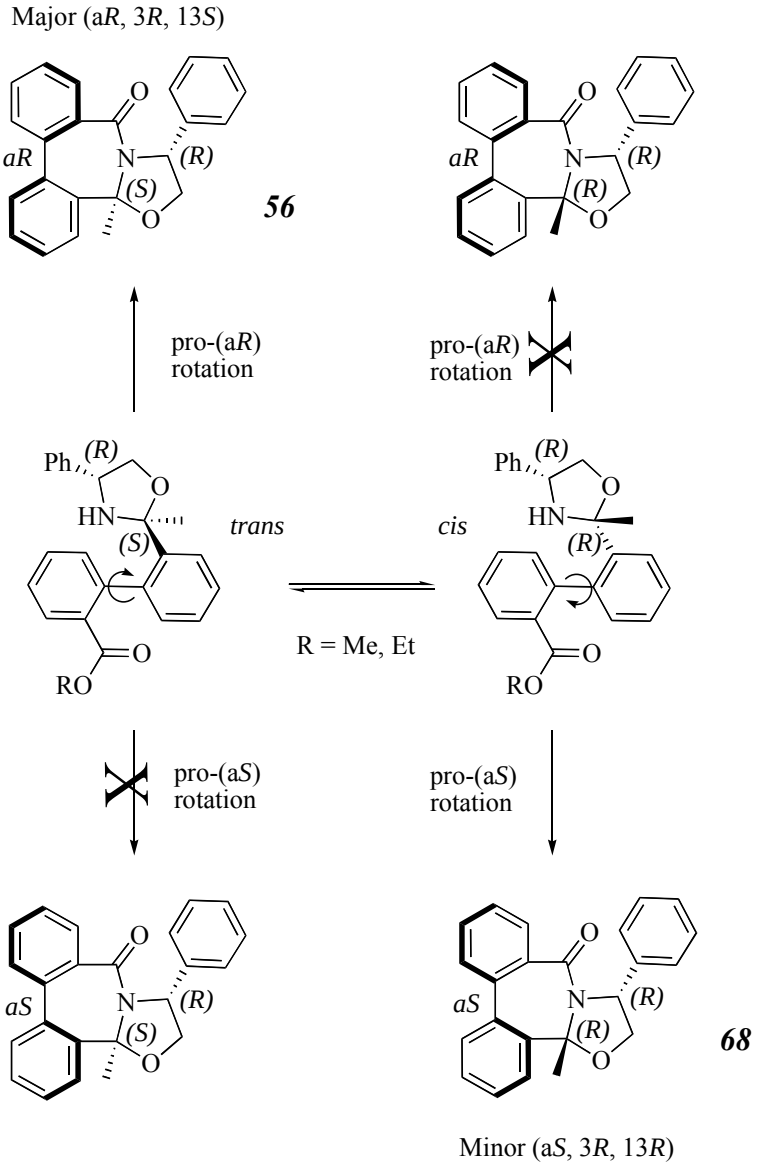
67 (Et) ***(Et, 45%)***

Reagents and conditions; Toluene, Δ, (Me) 18 hr, (Et) 138 hr.

Scheme 35

The condensation generates the lactam as a pair of diastereoisomers with the major diastereoisomer **56** (a*R*,3*R*,13*S* based on CIP rules) generated in 86% yield displaying both functional groups of the oxazolidine moiety in a *trans* relationship (Scheme 36). Levacher describes this diastereoselectivity through ^{1}H and ^{13}C NMR spectroscopy. Our reported NMR spectroscopy data is in agreement with Levacher's reported quotation.[27]

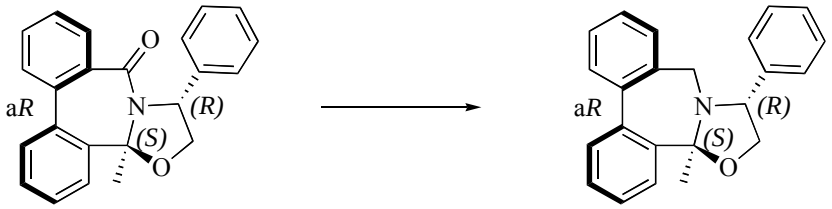
Levacher postulates that the *trans*-oxazolidine intermediate forms the lactam through a "pro-(a*R*) rotation" about the biaryl axis, giving rise to the exclusive formation of bicyclic lactam (a*R*,3*R*,13*S*) **56**. Conformational restrictions in the 5,7-fused bicyclic lactam prevents the lactamisation of the *trans*-oxazolidine intermediate from taking place through a "pro-(a*S*) rotation" about the biaryl axis.[27]



Scheme 36

In contrast, the only way for the *cis*-oxazolidine intermediate to further react with the carboxylic acid or ester is to initiate a "pro-(a*S*) rotation" about the biaryl axis to produce the (a*S*,3*R*,13*R*) minor isomer **56**. The absolute configuration of the chiral axis present in the biaryl unit was therefore controlled by that of the N,O-acetal centre in the oxazolidine intermediate.

With the desired single diastereoisomer of the 7,5-fused bicyclic lactam in hand, we endeavored to reduce the amide to the tertiary amine (Scheme 37, Table 11).[29]



56 ***62***

Scheme 37

Table 11; Methods for the reduction of amide 56

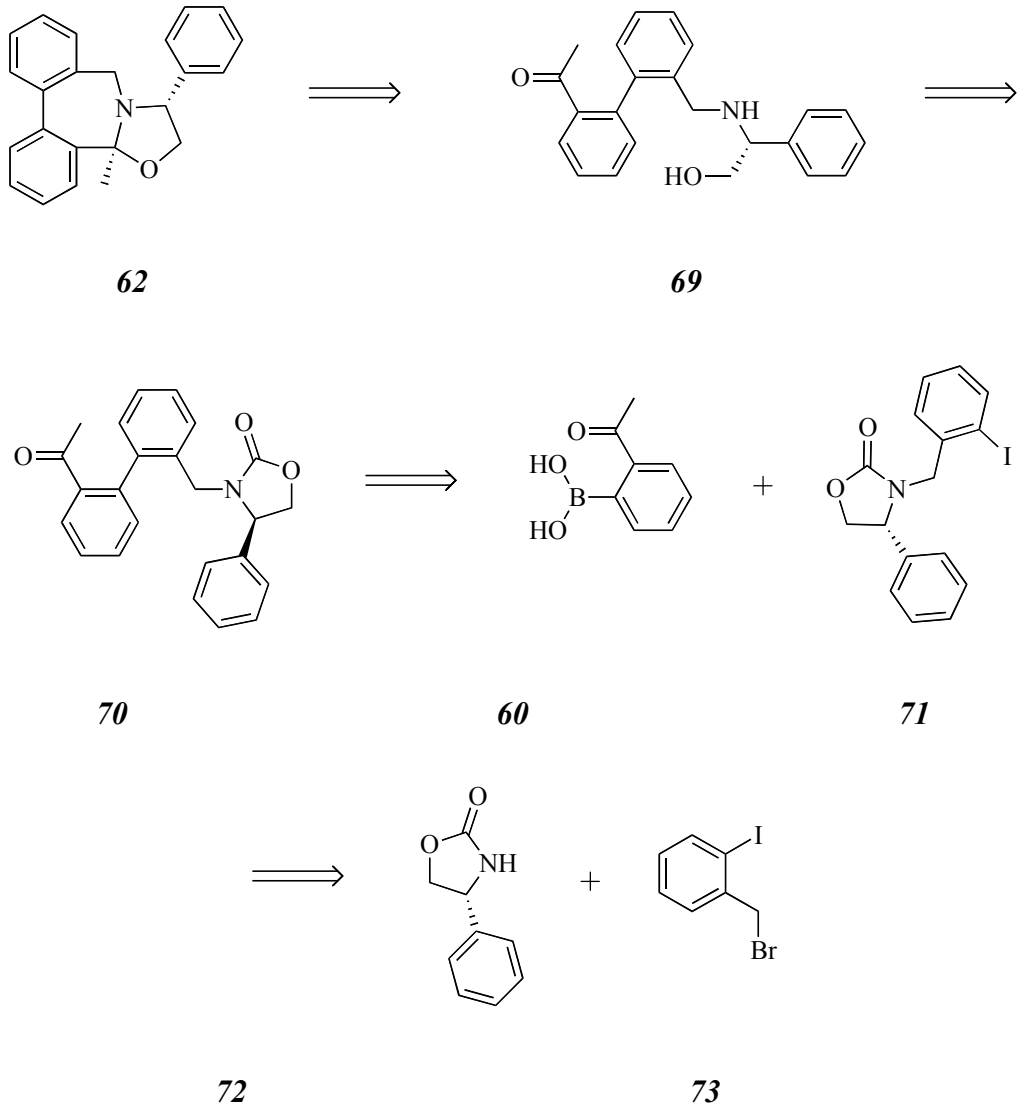
Entry	Solvent	Reductant	Temp./ °C	Time/ h	Product
1	THF	$BH_3.S(CH_3)_2$	0 → Δ	2	decomposition
2	THF	BH_3.THF	0 → Δ	2	decomposition
3	THF	LAH	-78 → 0	2	decomposition
4	THF	$NaBH_4$	-78 → 0	2	decomposition

Unfortunately the reduction of the amide did not occur using the reductive methodology shown. After aqueous work-up crude, ^{1}H NMR spectroscopy showed no presence of the desired methylene protons, but more importantly the oxazolidine methyl group disappears, indicating decomposition of the starting material.

2.2.4 An alternative synthesis of 7,5-fused bicyclic azepinium salt catalysts.

Using Lavacher's biphenyl lactam work as a synthetic guideline it was decided that an alternate route would be attempted in the absence of an amide group, hence removing the problematic reductive step.

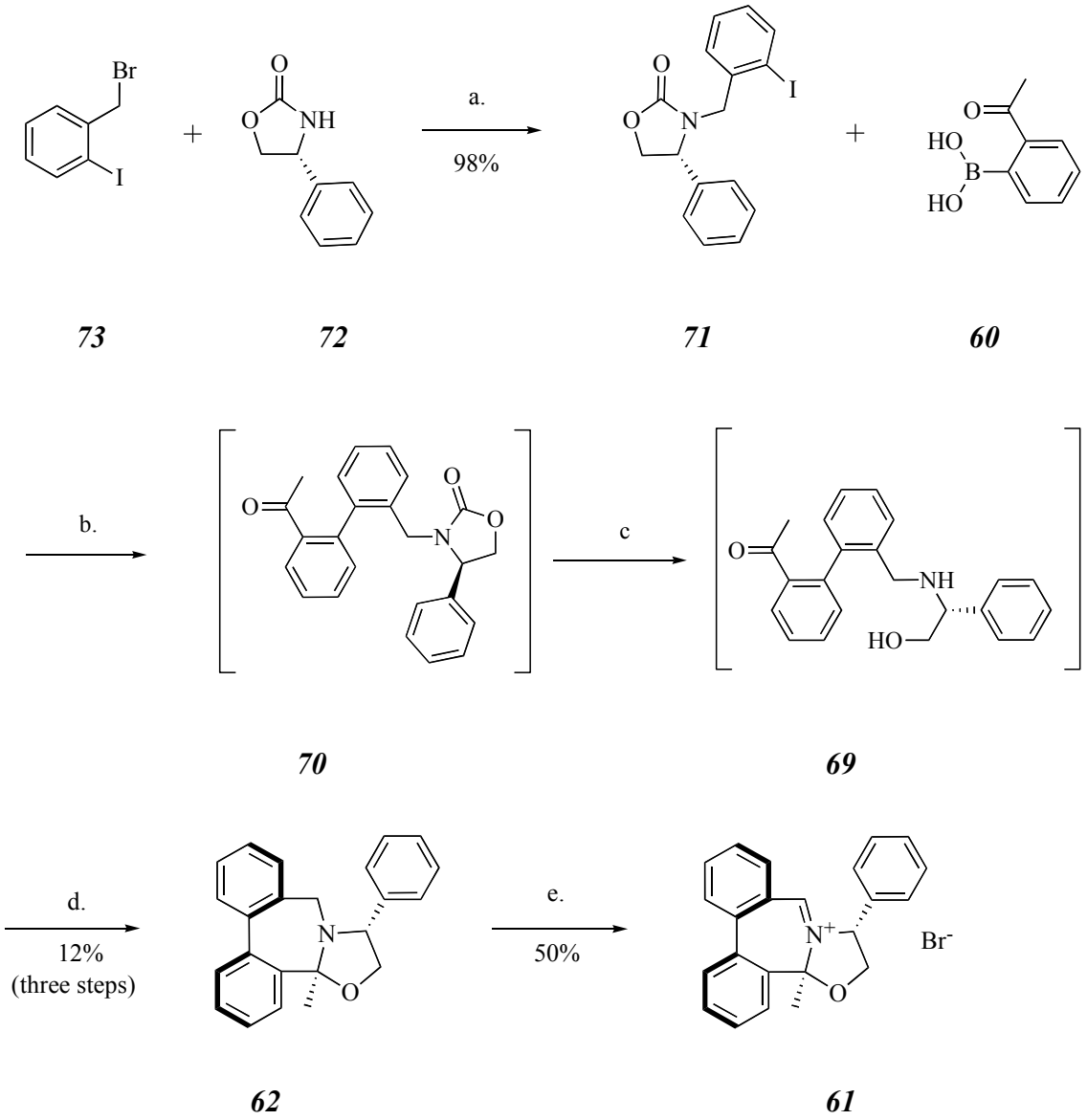
We postulated that the tetracyclic amine **62** could be retrosynthetically disconnected to the biphenyl amino alcohol **69** (Scheme 38); this amino alcohol would be generated from oxazolidinone **70**, which in turn would be prepared using Suzuki methodology from boronic acid **60** and oxazolidinone **71** Reductive amination of substituted oxazolidinone **72** with 2-iodobenzylbromide **73** would be used to initiate the synthesis.



62 ***69*** ***70*** ***60*** ***71*** ***72*** ***73***

Scheme 38

Our first synthetic step was the alkylation of (*R*)-phenyl oxazolidinone **72** with 2-iodobenzylbromide in 95% yield (Scheme 39).



73 ***72*** ***71*** ***60***

70 ***69***

62 ***61***

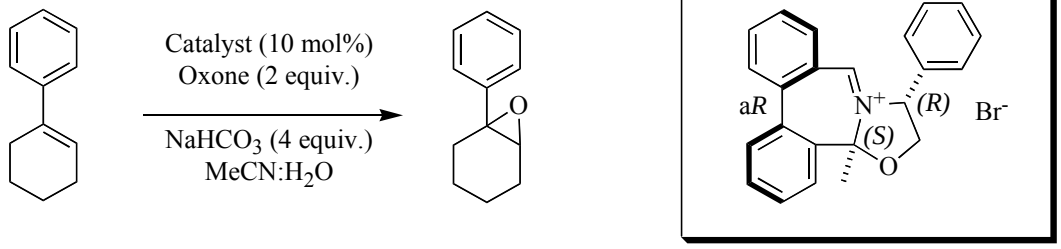
Reagents and conditions; a. NaHMDS, KO^{t}Bu, rt → 50℃, 2 hrs. (b) PhMe:H_2O:EtOH, $Pd(PPh_3)_4$, aq. K_2CO_3, Δ, 24hrs. (c) aq. NaOH, DCM, Δ, 16 hrs. (d) HCl, TBME, Δ, 30 mins. (e) NBS, DCM, 0℃ → rt, 20 mins.

Scheme 39

The *N*-benzyl oxazolidinone **71** was coupled with acetyl phenyl boronic acid using Suzuki methodology described in the previous synthesis. The yield of this step was extremely poor when utilising $Pd(PPh_3)_4$ or Pd(DPPF) as the palladium catalyst within

several solvent systems (DMF, Tol:H_2O:EtOH, NMP, 1,4-dioxane) and base (K_2CO_3, KF, KOAc) combinations. With a difficult purification process also involved we therefore decided that the crude material would be taken on into the next synthetic step. Hydrolysis of the oxazolidinone was completed within aqueous sodium hydroxide in dichloromethane; the organic phase was immediately treated with *p*TSA in methanol to generate the desired tetracyclic amine **62** in 10% yield over three steps. Finally the iminium bromide salt **61** was generated using NBS in chloroform.

We immediately tested iminium salt **61** for its catalytic ability (Scheme 40), using 1-phenylcyclohexene as our test substrate under our standard Oxone® oxidative conditions. Catalyst **61** gave 100% conversion within thirty minutes imparting a modest 55% *ee* for 1-phenylcyclohexene oxide.



Catalyst 61

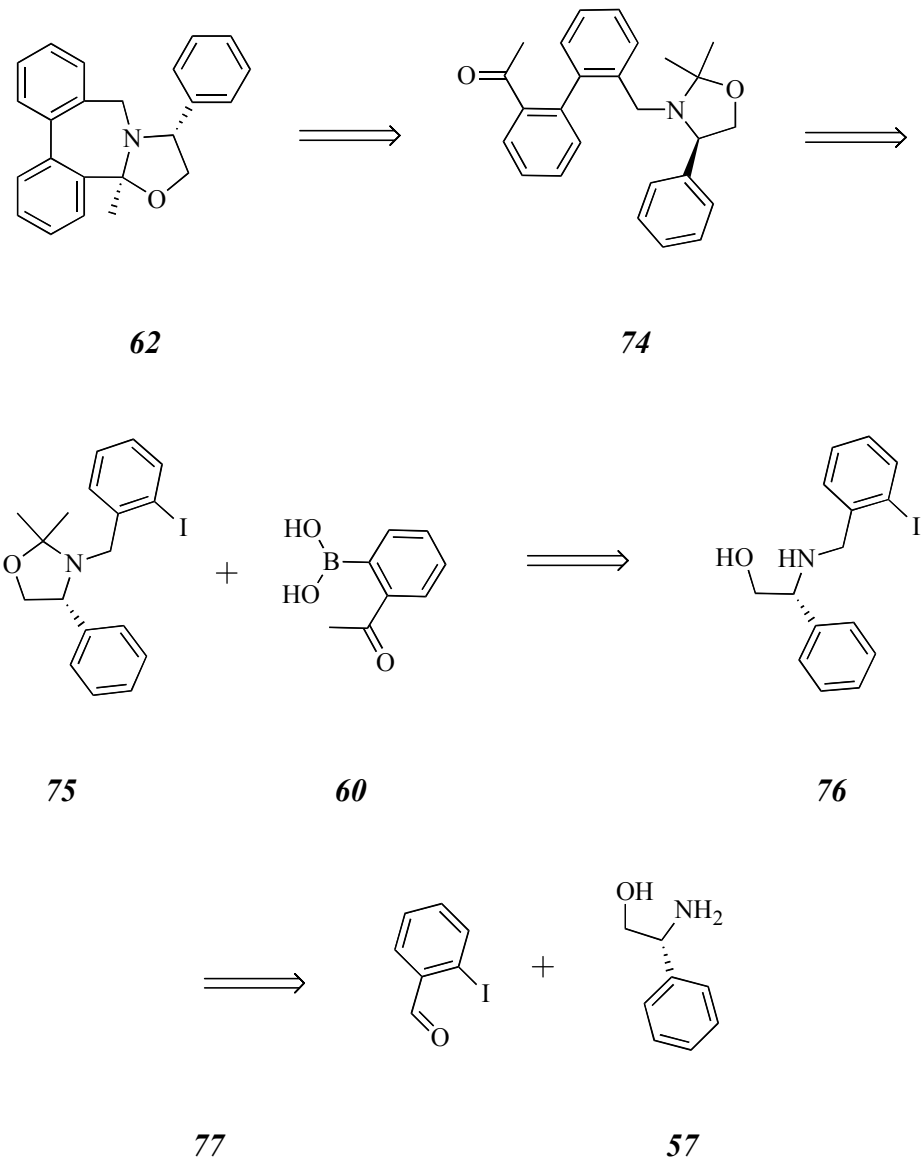
55% ee

100% conv.

Scheme 40

From this result we had established a new group of iminium salt catalysts that was active for the catalytic asymmetric epoxidation of alkenes. Unfortunately the overall yield in this synthetic route tied with the problematic purification of many of the intermediates led us to seek another synthetic route.

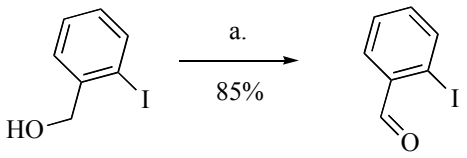
We attributed the low yield of the second synthetic route to the presence of the oxazolidinone functionality. Both Suzuki methodology and oxazolidinone deprotection were thought to be sensitive procedures. The desired starting material and/or product are thought to degrade under one or both reaction conditions. We therefore decided to focus our attention on a synthetic intermediate that did not contain this problematic oxazolidinone.



Scheme 41

Scheme 41 shows our postulated retrosynthesis. The tetracyclic amine **62** would again be derived from a biphenyl backbone, but in this route the amino alcohol would be protected as the dimethyl acetal, **74**. Disconnection with Suzuki methodology as before suggests the protected amino alcohol **75** as the precursor; this would be taken back through the iodobenzyl amino alcohol **76** and back to the starting materials, which we anticipated to be 2-iodobenzaldehyde (**77**) and phenyl glycinol (**57**).

It was decided that 2-Iodobenzaldehyde **77** would be generated within the laboratory, as it was not cost effective to purchase directly. Oxidation of 2-iodobenzyl alcohol **78** occurred with 85% yield (Scheme 42).



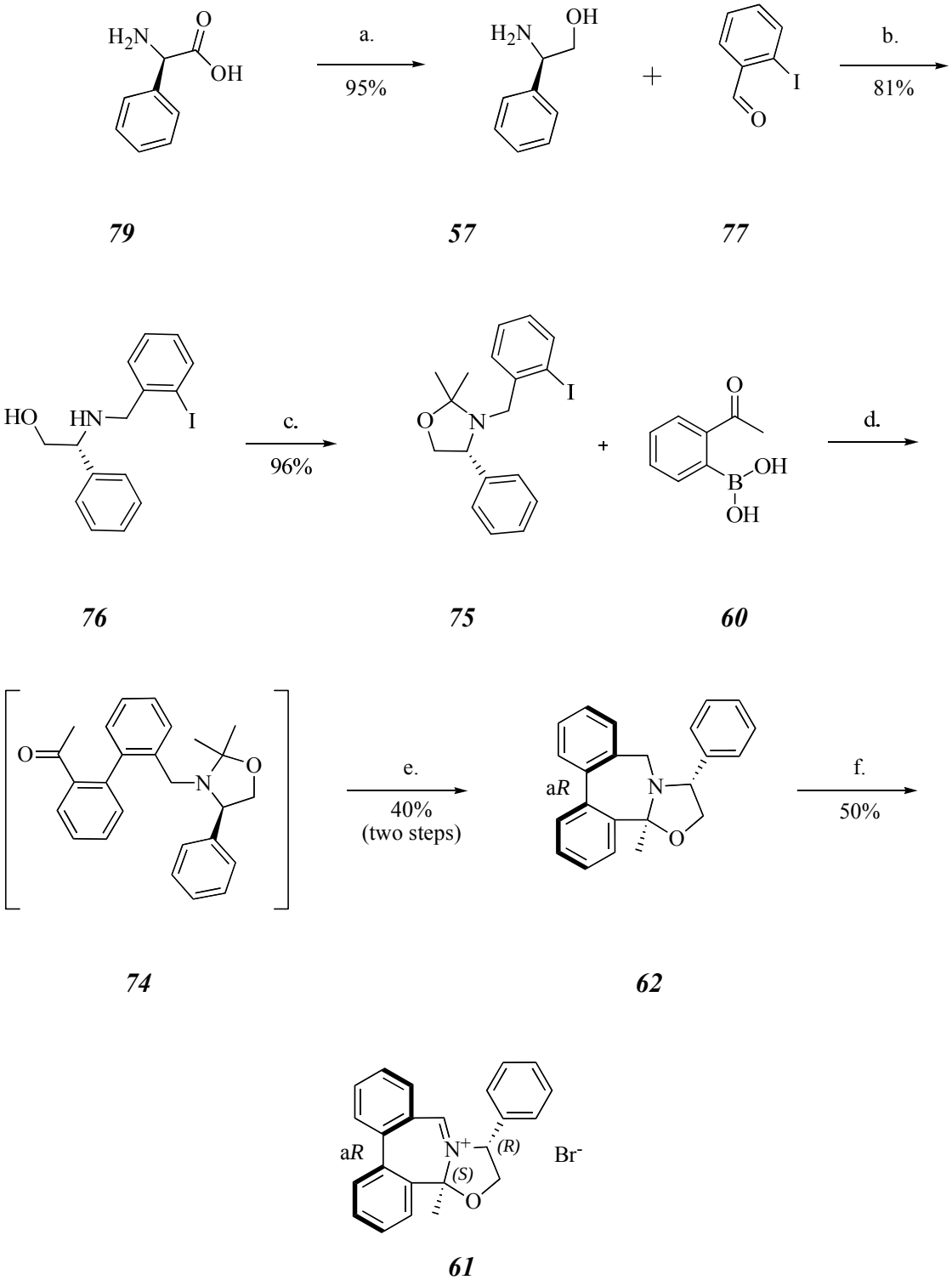
78 ***77***

Reagents and conditions; a. $CHCl_3$, MnO_2, Δ, 2 hrs.

Scheme 42

Lithium aluminium hydride was used to reduce (*R*)-Phenyl glycine **79**, thus generating (*R*)-phenyl glycinol **57** retaining its enantiopurity as assigned by optical rotation (Scheme 43). Reductive amination of 2-iodobenzaldehyde with (*R*)-phenyl glycinol gave the *N*-benzyl amino alcohol **76** in 80% yield. Protection of the amino alcohol functionality with dimethoxypropane yielded the oxazolidine **75** in 91% yield.

The oxazolidine **75** was coupled with acetyl phenyl boronic acid **60** under what now were our 'standard' Suzuki conditions of a toluene:ethanol:water (10:1:1) solvent system, potassium carbonate base and catalysed by $Pd(PPh_3)_4$. Purification using column chromatography to isolate oxazolidine **74**, gave two compounds by TLC. On closer inspection the acidic silica was deprotecting the dimethyl acetal, causing the molecule to ring close, generating the desired tetracyclic, 6,6,7,5 ring core **62**. The reaction mixture was therefore treated with silica gel in chloroform over a 16-hour period. The reaction material was purified, giving the tertiary amine as a single diastereoisomer, the structure of which was absolutely defined by single X-ray analysis (Figure **80**); this was smoothly converted to iminium salt **61** in 80% yield.



79 ***57*** ***77***

76 ***75*** ***60***

74 ***62***

61

Reagents and conditions; (a) LAH, TMS-Cl, THF, –78 ℃ → rt, 2 hrs. (b) MeOH, $NaBH_3CN$, 0 ℃ → rt, 16 hrs. (c) DMP, PhMe, pTSA, Δ, 4 hrs. (d) PhMe:H_2O:EtOH, $Pd(PPh_3)_4$, aq. K_2CO_3, Δ, 24 hrs. (e) Silica gel, $CHCl_3$, rt, 30 mins. (f) NBS, $CHCl_3$, rt, 15 mins.

Scheme 43

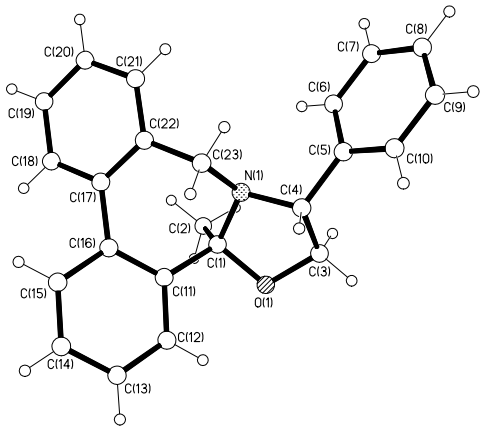
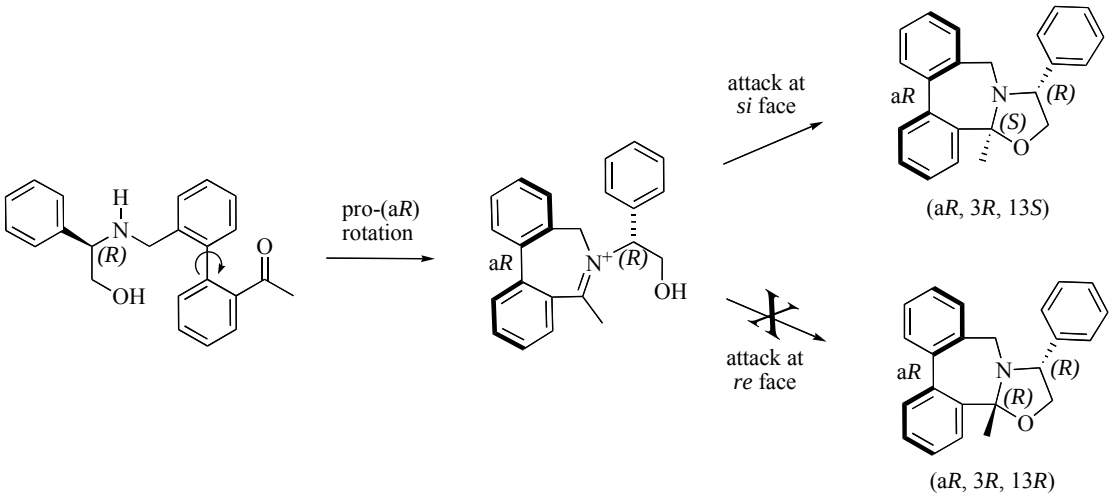


Figure 80 An X-ray crystal of (R)-phenyl 6,6,7,5 tetracyclic tertiary amine

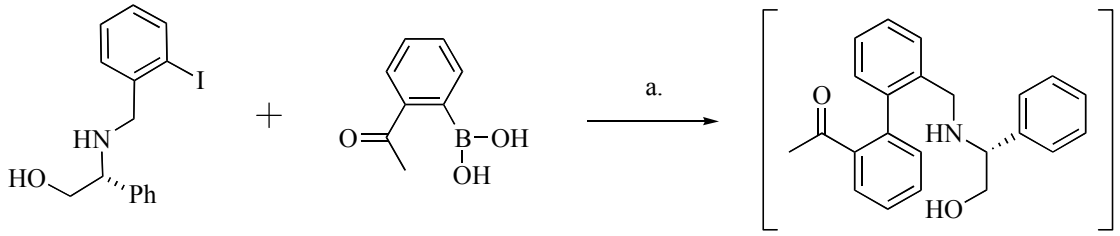
It was observed from **Figure 80** that cyclisation of the amino alcohol functionality occurs placing the methyl and phenyl functionalities in a *cis*-relationship. Scheme 44 shows the mechanism of intramolecular cyclisation.



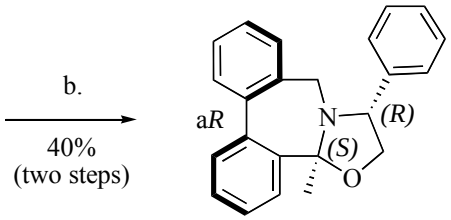
Scheme 44

On oxidation of the tertiary amines only one iminium proton is observed in the ^{1}H NMR spectrum, therefore either, only one single atropoisomer is produced from the cyclisation step or, there is a rapid interconversion during the NMR time scale between the two possible atropoisomers favouring the more thermodynamically stable conformation when in the deuterated solvent. We also observe 95% diastereoselectivity in regard to the oxazolidine cyclisation.

Amino alcohol **76** was also tested for its activity under Suzuki methodology. What was expected was inactivation of the phosphorus catalyst leading to, at best, our unused starting material and no di-functionalised biphenyl backbone. To our delight, however, we achieved a one pot Suzuki coupling and intramolecular cyclisation generating the tetrcyclic, 6,6,7,5 ring core (**62**) as one diastereoisomer in 40% yield in one step.



76 ***60*** ***81***



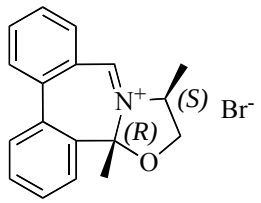
62

Reagents and conditions; (a) PhMe:H_2O:EtOH, $Pd(PPh_3)_4$, aq.K_2CO_3, Δ, 24 hrs. (b) Silica gel, $CHCl_3$, rt, 30mins.

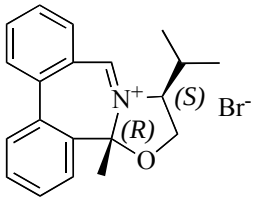
Scheme 45

From this route we were able to remove the protection and deprotection steps of the synthetic route, thus generating a new robust synthetic route with fewer steps, in which the phenyl substituted bromide azepinium iminium salt was generated in 24% yield over four steps.

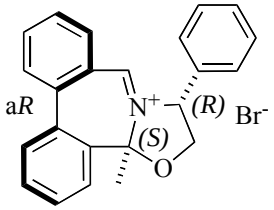
Several analogues were then synthesised using (*S*)-alanine, (*S*)-valine, (*R*)- & (*S*)-phenylalanine and (1*S*,2*R*)-2-amino-1-phenyl-1-propanol (*D*-(+)-norephedrine). Catalysts **82, 83, 84, 85** and **86** were isolated as single diastereoisomers with the yields of the key steps in Table 12 and the overall yields indicated in parentheses.



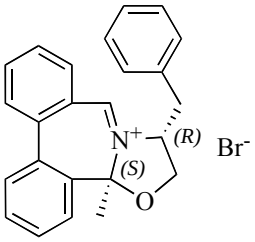
82 (2%)



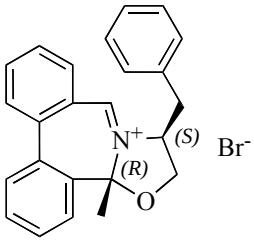
83 (6%)



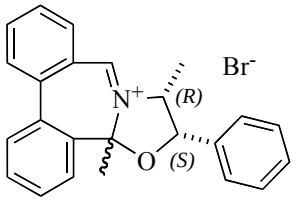
61 (16%)



84 (44%)



85 (19%)



86 (15%)

Table 12; The isolated yields of the key intermediates in generating six tetracyclic iminium salt catalysts.

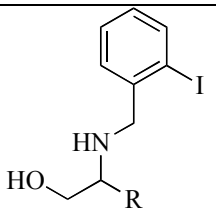
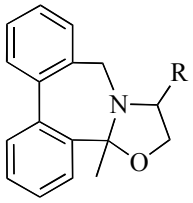
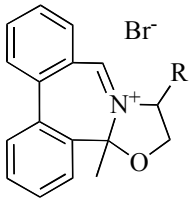
			
R = (*S*)-Me	14% (**87**)	22% (**88**)	74% (**82**)
R = (*S*)-^{i}Pr	16% (**89**)	47% (**90**)	81% (**83**)
R = (*R*)-Ph	81% (**76**)	40% (**62**)	50% (**61**)
R = (*R*)-Bn	90% (**91**)	60% (**92**)	82% (**84**)
R = (*S*)-Bn	86% (**93**)	30% (**94**)	75% (**85**)
R = (*R*)-Me R_1 = (*S*)-Ph	67% (**95**)	30% (**96**)	75% (**86**)

Figure **97** shows the structure of the 6,6,7,5 tetracyclic tertiary amine of (*S*)-phenyl alinol (30% (94) the amine precursor for iminium salt catalyst **85**. The methyl group and the benzyl group form a *cis* relationship. One single atropoisomer is again observed.

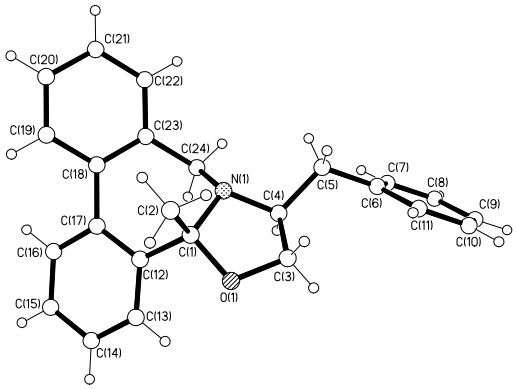
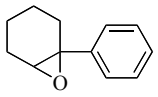
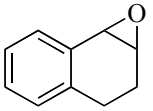
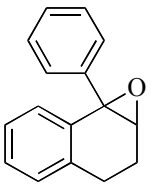
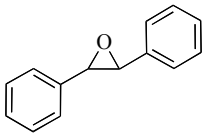
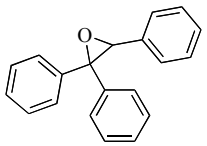


Figure 97 An X-ray crystal of S-benzyl 6,6,7,5 tetracyclic tertiary amine 30% (94

Catalysts **61** and **82** – **86** were tested in epoxidation reactions under our standard Oxone® conditions.

Table 13; Asymmetric Epoxidation of a range of alkenes by Catalysts 82 – 86[a]

Epoxide	Catalyst	Conversion/% [c, d]	ee/% [b, c]	Major enantiomer [f]
	**7**	100	60	(–)-1*S*,2*S*
	82	100	30	(–)-1*S*,2*S*
	83	100	30	(–)-1*S*,2*S*
	61	100	55	(+)1*R*,2*R*
	84	100	64	(+)1*R*,2*R*
	85	100	64	(–)-1*S*,2*S*
	86	100	30	(–)-1*S*,2*S*
	**7**	100	32	(+)1*S*,2*R*
	61	100	76	(–)1*R*,2*S*
	84	100	46	(–)1*R*,2*S*
	85	100	47	(+)1*S*,2*R*
	**7**	34	41	(–)1*R*,2*S*
	61	20	64	(+)1*S*,2*R*
	84	47	52	(+)1*S*,2*R*
	85	39	55	(–)1*R*,2*S*
	**7**	90	15	(–)1*S*,2*S*
	61	100	22	(+)1*R*,2*R*
	84	98	18	(+)1*R*,2*R*
	85	95	13	(–)1*S*,2*S*
	**7**	90	24	(–)1*S*
	61	100	30	(+1*R*
	84	100	23	(+)1*R*
	85	100	19	(–)1*S*

[a] epoxidation conditions: Iminium salt catalyst (5 mol%), Oxone® (2 equiv.). Na_2CO_3 (4 equiv.), Solvent (1:1, Acetonitrile:H_2O 5 ml) 0ºC, 1 hr – 6 hrs. [b] Enantiomeric excesses were determined by chiral GC–FID spectra by comparison of the two epoxide peak areas. [c] Conversions were evaluated from the chiral GC–FID spectra by comparison of the alkene and epoxide peak areas. [d] Enantiomeric excess determined by Chiral HPLC on a Chiracel OH-D column. [e] Conversions were evaluated from the ^{1}H-NMR spectra by integration of alkene and epoxide signals. [f] Absolute configurations of the major enantiomers were determined by comparison of both optical rotation and GC-FID.

From Table 13 it is evident that catalysts **61** (55%), **84** (64%) and **85** (64%) perform better when oxidising, 1-phenylcyclohexene, in terms of enantiocontrol, than catalysts **82, 83** and **86** (all give 30% *ee*). The enantioselectivities imparted to the test substrate are comparable to the original azepinium catalyst **7**, which itself gives up to 60% *ee*. When other alkene substrates were tested in conjunction with these three catalysts, the enantiocontrol observed by each catalytic iminium salt was different, depending on the alkene substrate used. As a general rule the tetracyclic azepinium catalysts give similar or increased levels of enantioselectivity compared with catalyst **7**. The best results are observed when oxidising a *cis* alkene such as dihydronaphthalene where catalysts **61** (76%), **84** (46%) and **85** (46%) outperform the original catalyst **7** (32%) considerably.

2.2.4.1 Conclusion

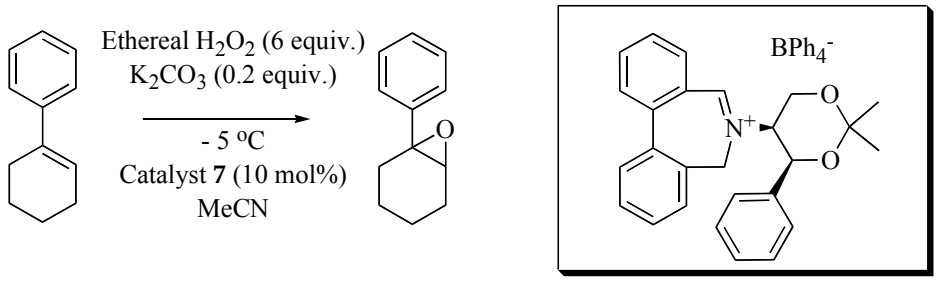
To conclude, we have successfully developed a new sub-structure of iminium salt catalyst containing a 6,6,7,5-ring tetracyclic core. The synthesis of these compounds has been streamlined and now the formulation of these novel iminium salts can be completed within four steps in good yields. We have postulated that the cyclisation occurs through one favoured atropoisomer giving rise to a favoured diastereoisomer in all the iminium salt catalysts generated. Catalysts **61**, **84** and **85** generally perform better than or equal to catalyst **7**.

2.3 Conclusion and Future work.

2.3.1 Conclusions

The aim of this thesis was the development of two novel ideas in the progression of catalytic asymmetric epoxidation. The first was the development of new oxidative systems for the use in asymmetric synthesis to induce higher levels of enantioselectivity for the epoxidation of unfunctionalised alkenes. The second was to develop chiral iminium salt catalysts with the ability to induce high levels of enantiocontrol in epoxidation of selected alkene substrates.

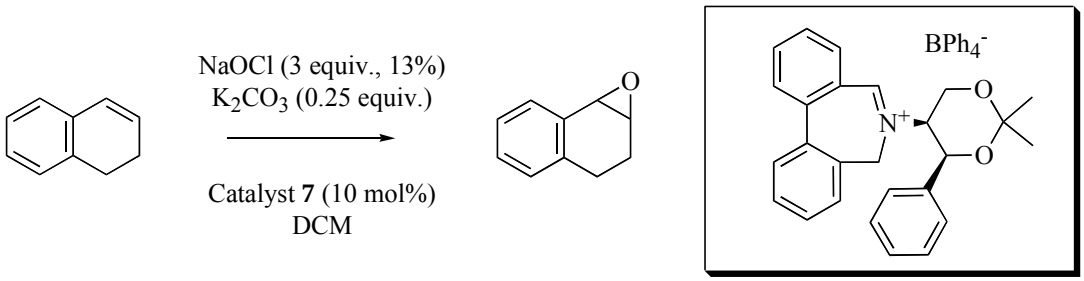
The new hydrogen peroxide-mediated epoxidation methodology offers modest enantiocontrol, up to 56% *ee* with the 7-membered azepine catalyst **7** that was capable of enantiocontrol up to 70% when using TPPP as the stoichiometric oxidant (Scheme 46). The major problem with the H_2O_2 system was the low levels of conversion to the desired epoxide.



Catalyst 7, 56% ee

Scheme 46

The new sodium hypochlorite methodology offers much higher enantiocontrol and conversion when used in conjunction with the same azepinium catalyst over the H_2O_2 procedure, affording up to 71% *ee* (Scheme 47), similar to the enantioselectivities observed using TPPP as the oxidant. Comparison of the NaOCl system with Oxone® mediated epoxidation shows that the conversions are somewhat reduced.



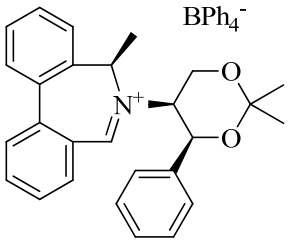
Catalyst 7, 71% ee

Scheme 47

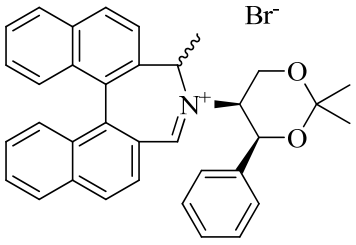
Neither of these methods have ever previously been reported for oxidation of an iminium salt system. Optimisation has shown that lower reaction temperatures (– 5 °C), anhydrous conditions, specific solvents and exchange of the sodium bicarbonate salt for potassium carbonate best facilitates asymmetric epoxidation when added in sub-stoichiometric amounts (0.25 equiv.), therefore acting as a co-catalyst in these systems.

Unfortunately due to the unstable nature of the binaphthalene based iminium salt catalyst in organic solvents, little conversion and *ee* was gained from these catalysts.

We have also developed two new sub-structures of biphenyl azepinium salt catalysts. The asymmetric introduction of a methyl substituent has been completed using an aminodioxane unit as a chiral element. In almost all cases, increased enantioselectivity was achieved by catalyst **40** compared with the parent catalyst **7** when used in conjunction with our standard Oxone® conditions.



40

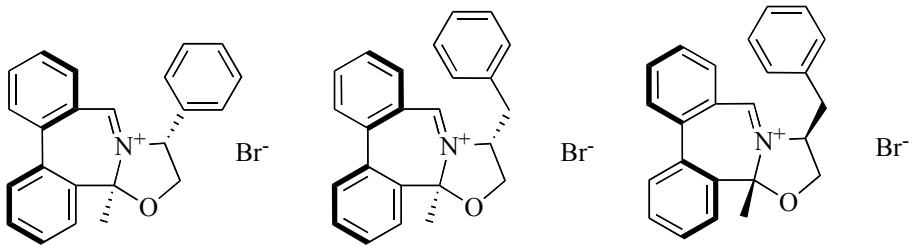


52

Binaphthyl catalyst **52** was generated as a pair of diastereoisomers. When catalyst **52** was

used the mixture of diastereoisomeric salts gave up to 93% *ee*, marginally higher enantiocontrol in the epoxidation of 1-phenylcyclohexene over the parent catalyst **4** (91% *ee*).

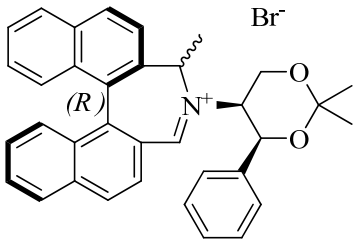
The 6,6,7,5-ring tetracyclic azepinium salt catalysts show promise as a new form of iminium salt catalyst. Thus far the phenyl (**61**) and benzyl (**84** & **85**) substituted catalysts have given the best reaction profiles, giving increased enantioselectivity over the original azepinium catalyst **7**. Further work is on going in this field.



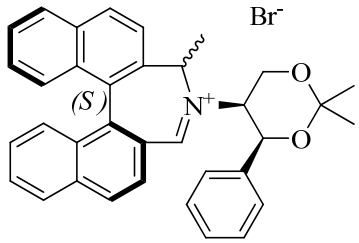
61 ***84*** ***85***

2.3.2 Future Work

Thus far only binaphthyl iminium salt **52** has been generated with Grignard addition to the 'mis-matched' diastereoisomer of the binaphthyl iminium salt. A pair of diastereoisomers was generated as the conflicting asymmetry of the binaphthyl and dioxane moieties both direct the Grignard addition. If the Grignard addition were introduced to the matched diastereoisomer iminium salt, catalyst **98** could be generated. Asymmetric addition may be observed due to the matching asymmetry of the two functionalities, therefore possibly generating one diastereoisomer. In turn increased enantiocontrol in subsequent epoxidations may also be observed.

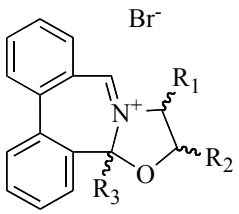


52



98

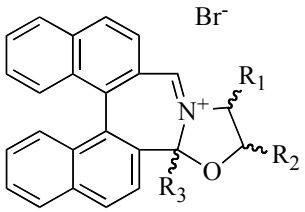
Optimisation of the 6,6,7,5 tetracyclic azepinium salt catalysts is suggested. This can be completed by investigation into the presence of multiple chiral groups α to both the iminium nitrogen and the oxygen atoms (R_1 and R_2, **99**).



99

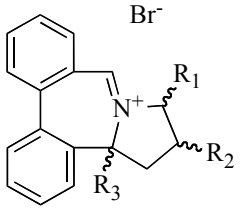
A progression of this is the variance of the substitution on the chiral carbon on the azepinium ring (R_3, **99**). This range of optimisations would identify the most effective iminium salt in this sub-structure of catalyst.

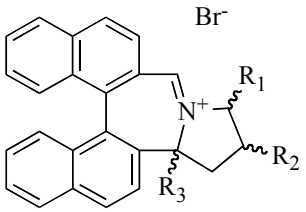
Modification of the 6,6,7,5-ring tetracyclic azepinium salt catalysts to include a binaphthyl axis in place of the biphenyl axis is recommended. Increased enantiocontrol has been imparted by catalysts that contain this binaphthyl skeleton.



100

Again full variance on all 'R' groups would complete optimisation, identifying the most effective iminium salt in this sub-structure of iminium salt catalyst





101 ***102***

Construction of a 6,6,7,5-ring tetracyclic azepinium salt catalysts without the oxazolidine ring such as **101** and **102**, would present an interesting comparison to the 6,6,7,5-ring tetracyclic azepinium salt catalyst that have already been synthesised.

Finally we need to investigate the mechanism by which our catalysts work. The use of computational and molecular modelling is possibly the best way to progress in aiding our research into explaining how our catalysts work. This approach may lead us to design more effective iminium salt catalysts capable of selecting one enantiotopic face in favour of the other, thus inducing higher enantiocontrol than our current catalysts.

2.4 Chapter two references

1 http://www.dupont.com/Oxone®/techinfo/

2 ten Brink, G-J.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105.

3 a. Bartok, M.; Lang, K. L. *Small Ring Heterocycles,* (ed. Hassner, A.), Wiley Interscience, Vol. 42, Part 3, **1985**; b. Da, C-S.; Wei, J.; Dong, S-L.; Xin, Z-Q.; Liu, D-X.; Xu, Z-Q.; Wang, R. *Synth. Commun.* **2003**, *33*, 2787.

4 Adams, J. M.; Pritchard, R. G. *Acta Cryst*. **1977**, *B33*, 3650.

5 a. Richardson, D. E.; Yao, H.; Frank, K. M.; Bennett, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 1729; b. Richardson, D. E.; Yao, H. *J. Am. Chem. Soc.* **2000**, *122*, 3220.

6 McKillop, A.; Sanderson, W. R. Tetrahedron Report 373, *Tetrahedron* **1995**, *51*, 6145.

7 Gonclaves, M-H.; Martinez, A.; Grass, S.; Page, P. C. B.; Lacour, J. *Tetrahedron Lett.* **2006**, *47*, 5297.

8 Page, P. C. B.; Parker, P.; Rassias, G. A.; Buckley, B. R.; Bethell, D. *Adv. Synth. Catal.* **2008**, *350*, 1867.

9 Page, P. C. B.; Parker, P.; Rassias, G. A.; Buckley, B. R.; Bethell, D. *Adv. Synth. Catal.* **2008**, *350*, 1867.

10 Sato, K.; Aoki, M.; Ogawa, M.; Hashimoto, T.; Noyori, R. *J. Org. Chem*. **1996**, *61*, 8310.

11 a. Michaelson, R. C.; Palermo, R. E.; Sharpless, K. B. *J. Am. Chem. Soc*. **1977**, *99*, 1990; b. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974; c. Jacobsen, E. N.; Zhang, W. *J. Org. Chem.* **1991**, *56*, 2296; d. Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063; e. Hughes, D. L.; Smith, G. B.; Lui, J.; Dezeny, G. C.; Senanayake, C. H.; Larson, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2222; f. Angelinio, M. D.; Laibinis, P. E. *Macromolecules* **1998**, *31*, 7581; g. Ito, Y.; Katsuki, T. *Tetrahedron Lett.* **1998**, *39*, 4325; h. Kureshy, R. I.; Kahn, N-U. H.; Abdi, S. H. R.; Singh, S.; Ahmed, I.; Jasra, R. V. *J. Mol. Catal. A* **2004**, *218*, 141.

12 a. Groves, J. T.; Nemo, T. E.; Myers, R. S. *J. Am. Chem. Soc.* **1979**, *101*, 1032; b. Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791; c. Meunier, B.; Guilmet, E.; Carvalho, M-E. D.; Poilblanc, R. *J. Am. Chem. Soc.* **1984**, *106*, 6668; d. Berkessel, A.; Frauenkron, M. *J Chem. Soc. Perkin Trans. 1,* **1997**, 2265; e. Halterman, R. L.; Jan, S. -T. *J. Org. Chem.* **1991**, *56,* 5253; f. Naruta, Y.; Tani, F.; Maruyama, K. *Tetrahedron Lett*. **1992**, 33, 6362; g. Collman, J. P.; Wang, Z.; Strausmanis, A.; Qualquejeu, M. *J. Am. Chem. Soc*. **1999**, 121, 460; h. Collman, J. P.; Lee, V. J.; Kellen-Yuen, C. J.; Zhang, X.; Ibers, J. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1995**, *117,* 692; i. Naruta, Y.; Ishihara, N.; Tani, F.; Maruyama, K. *Bull. Chem. Soc. Jpn.* **1993**, *66,* 158; j. Meunier, B.; Martinez, A.; Hemmert, C.; Loup, C.; Barré, G. *J. Org. Chem.* **2006**, *71*, 1449.

13 a. Lygo, B.; Wainwright, P. G. *Tetrhedron Lett.* **1998**, *39*, 1599; b. Corey, E. J.; Zhang, F-Y. *Org. Lett.* **1999**, *1*, 1287; c. Lygo, B.; Wainwright, P. G. *Tetrahedron* **1999**, *55*, 6289; d. Lygo, B.; To, D. C. M. *Tetrahedron Lett.* **2001**, *42*, 1343; e. Murphy, P. J.; Allingham, M. T.; Howard-Jones, A.; Thomas, D. A.; Caulkett, P. W. R. *Tetrahedron Lett.* **2003**, *44*, 8677; f. Maruoka, K.; Ooi, T.; Ohara, D.; Tamura, M. *J. Am. Chem. Soc.* **2004**, *126*, 6844.

14 Mintz, M. J.; Walling, C. *Org. Synth. Coll. Vol. V.* **1973**, 184.

15 a. Newman, M. S.; Holmes, H. L. *Org. Synth. Coll. Vol. II,* **1943**, 428; b. Enders, D.; Fey, P.; Kipphardt, H. *Org. Synth. Coll. Vol. VIII,* **1993**, 26.

16 Stevens, R. V.; Caeta, F. C. A. *J. Am. Chem. Soc.* **1977**, *99*, 6105.

17 Bergmann, F.; Weizmann, M.; Dimant, E.; Patai, J.; Szmuskowicz, J. *J. Am. Chem. Soc.* **1948**, *70*, 1612.

18 Schiessler, R. W.; Eldred, N. R. *J. Am. Chem. Soc.* **1941**, *66*, 836.

19 Johnson, C. R.; McCants, D. Jr. *J. Am. Chem. Soc*. **1965**, *87*, 1109.

20 Denney, D. B.; DiLeone, R. R. *J. Am. Chem. Soc.* **1962**, *84*, 4737.

21 a. Donohoe, T. J.; Johnson, P. D.; Cowley, A.; Keenan, M. *J. Am. Chem. Soc.* 2002, *124*, 12934; b. Donohoe, T. J.; Johnson, P. D.; Pye, R. J.; Keenan, M. *Org. Lett.* 2004, *6*, 2583.

22 Duncan, B. L. *J. Chem. Eng. Data.* **1994**, *39*, 863.

23 Fitz, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277.

24 Lygo, B.; Allbutt, B.; James, S. R. *Tetrahedron Lett.* **2003**, *44*, 5629.

25 Lygo, B.; Allbutt, B. *Synlett* **2004**, 326.

26 Farah, M. M. PhD Thesis submitted to Loughborough University. **2007**.

27 Penhoat, M.; Levacher, V.; Dupas, G. *J. Org. Chem.* **2003**, *68*, 9517.

28 a) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1. b) Amat, M.; Canto, M.; Llor, N.; Ponzo, V.; Perez, M.; Bosch, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 335. c) Amat, M.; Canto, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 5343. d) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919. e) Ennis, M. D.; Hoffman R. L.; Ghazal, N. B.; Old, D. W.; Mooney, P. A. *J. Org. Chem.* **1996**, *61*, 5813. f) Allin, S. M.; James, S. L.; Elsegood, M. R. J.; Martin, W. P. *J. Org. Chem.* **2002**, *67*, 9464.

29 Houpis, J. N.; Molina, A.; Reamer, R. A.; Joseph, J. E.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1993**, *34*, 2593.

Chapter Three:

Experimental

3 Experimental

3.1 General experimental

Infrared spectra were acquired 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.

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

Mass spectra were recorded using a Jeol-SX102 instrument utilising electron impact (E.I.) and fast atom bombardment (F.A.B.). Analysis by GCMS utilised a Fisons GC 8000 series (AS 800), using a 15 m *x* 0.25 mm DB-5 column and an electron impact low-resolution mass spectrometer.

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

Optical rotation values were measured with an Optical Activity-polAAar 2001 instrument, operating at λ=589 nm, corresponding to the sodium D line at the temperatures indicated. The solvents used for these measurements were of spectrophotometric grade. The solutions for these measurements were prepared in volumetric flasks for maximum accuracy of the volume of solvent used.

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

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

Reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere unless otherwise stated, using glassware dried for 16 h at 150 ºC. Reaction solvents were obtained commercially dry, except for the following light petroleum (b.p. 40-60 ºC) was distilled from calcium chloride prior to use. Ethyl acetate was distilled over calcium sulphate or chloride. Dichloromethane was distilled over calcium hydride. Tetrahydrofuran was distilled under a nitrogen atmosphere from the sodium/benzophenone ketyl radical.

Enantiomeric excesses were determined by either chiral shift proton Nuclear Magnetic Resonance, Chiral Gas Chromatography Flame Ionisation (GC-FID), or by Chiral High Performance Liquid Chromatography, (Chiral HPLC).

The chiral shift proton nuclear magnetic resonance spectra were recorded in deuteriated chloroform on a Bruker DPX 400, operating at 400.13 MHz, in the presence of europium (III) tris [3-(hepta-floropropylhydroxymethylene)-(+)-camphorate], [(+)-Eu(hfc)$_3$], as the chiral shift reagent and tetramethylsilane as the internal standard.

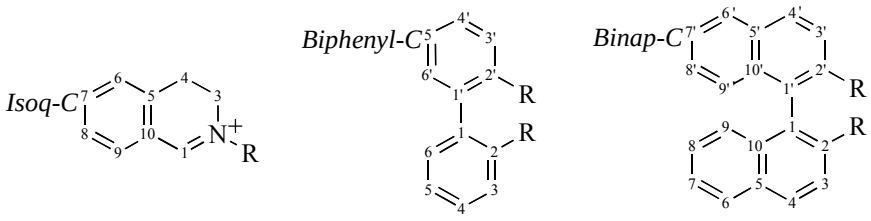
The chiral column used for the determination of enantiomeric excesses (ee) of non-racemic mixtures by chiral HPLC was Chiracel OD on a TSP Thermo-Separating-Products Spectra Series P200 instrument, with a TSP Spectra Series UV100 ultra-violet absorption detector set at 254 nm and a Chromojet integrator.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

3.2 Numbering systems.

The assignments of the proton and carbon-13 resonances have been made according to several numbering systems (Scheme 1). Some of these systems used are standard chemical nomenclature while others were introduced arbitrarily by a previous author.[1] In the latter case, the introduced system was based on the structural resemblance of the compounds to others in the literature.

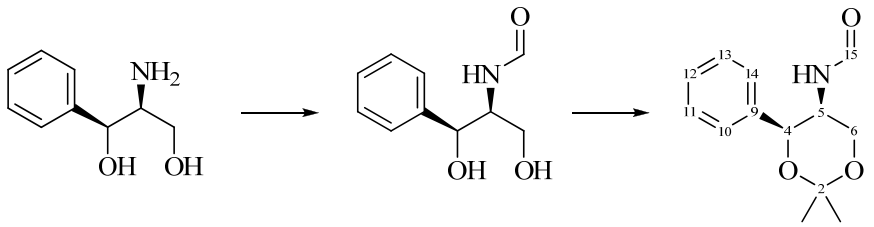
Aromatic systems are numbered according to standard protocols. Aromatic carbon atoms bearing a substituent are always quaternary, quat.Ar-C. All aromatic carbon atoms which are attached to a hydrogen atom are termed Ar-CH (^{13}C spectra) or Ar-CH (^{1}H spectra). The dihydroisoquinolinium nucleus is numbered according to a standard system but the carbon atoms of this moiety are termed *isoq.* The *biphenyl* system is also numbered and carbon atoms of this moiety are termed *biphenyl*. The binapthylene nucleus is numbered with the carbon atoms termed *binap*.



Scheme 1 Numbering systems employed in the experimental procedures.

3.3 Individual experimental proceedures

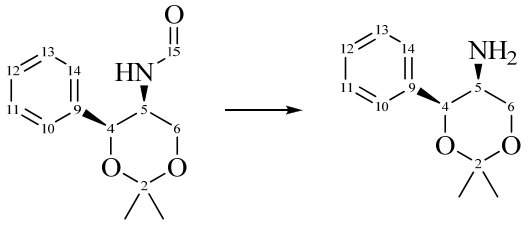
(3*S*,4*S*)-*N*-(2,2-Dimethyl-4-phenyl-(1,3)dioxan-5-yl)-formamide.[2]



8 ***9*** ***10***

(1*S*,2*S*)-2-Aminophenyl-1,3-propanediol (**8**) (5.00 g, 29.9 mmol) was dissolved in methanol (50.0 mL), methyl formate (2.00 g, 32.9 mmol) was added followed by an aqueous solution of sodium methoxide (25% *w/v*, 2.03 mL, 3.00 mmol). The reaction was monitored by TLC until complete consumption of the starting material was observed (typically 2 h). The resulting solution was evaporated under reduced pressure to afford the formyl-protected amine (**9**) as a yellow oil. The oil was dissolved in acetone (250 mL), and 2,2-dimethoxypropane (31.1 g, 3.00 mol) and aqueous hydrogen bromide (48%, 0.34 mL, 3.00 mmol) were added. The reaction was monitored by TLC until consumption of the intermediate compound was observed (typically 1.5 h). The solvents were removed under reduced pressure to give the crude formyl-protected acetonide (**10**) as a colourless oil (6.58 g, 29.1 mmol, 97%). ν_{max}(film) /cm^{-1} 3325 (N-H), 2990, 1663 (C=O), 1499, 1382, 1200, 1087, 844, 733, 700. δ_H (400 MHz; $CDCl_3$) 1.49 (3 H, s, C^{8}H$_3$), 1.53 (3 H, s, C^{7}H$_3$), 3.35 (1 H, s, NC^{5}H), 3.81 (1 H, m, OC^{6}HH upfield portion of the ABX system), 4.23 (1 H, m, OC^{6}HH downfield portion of the ABX system), 5.16 (1 H, s, PhC^{4}H), 6.48 (1 H, broad s, NH), 7.27 (5 H, m, 5 *x* Ar-C$^{10\text{-}14}$H), 7.88 (1 H, s, NC^{15}(O)H). δ_C (100 MHz; $CDCl_3$) 17.5 (C^{7}H$_3$), 28.7 (C^{8}H$_3$), 44.4 (NC^{5}H), 63.6 (OC^{6}H$_2$), 70.6 (PhC^{4}H), 98.9 (quat.C^2), 124.2 (2 *x ortho* Ar-C$^{10\&14}$H), 126.6 (*para* Ar-C^{12}H), 127.3 (2 *x meta* Ar-C$^{11\&13}$H), 137.0 (Ar- quat.^{i}C^{2}H), 159.5 (C^{15}=O)

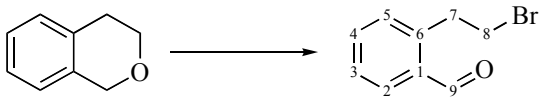
(3*S*,4*S*)-5-Amino-2,2-Dimethyl-6-phenyl-(1,3)dioxane. [2]



10 ***11***

Formamide **10** (6.58 g, 28.1 mmol) was suspended in an 85% saturated aqueous solution of hydrazine hydrate (100 mL) and the mixture heated under reflux for 4 h. The reaction mixture was extracted with toluene and ethyl acetate (1:1, 75 mL), and the combined organic layers were washed with water (3 *x* 75 mL) and dried over $MgSO_4$. The solvents were removed under reduced pressure to give the desired amine as a yellow oil (**11**) (5.39 g, 87% yield). $[\alpha]^{20}_D$ +45.5 ° (*c* 2.33, EtOH). ν_{max}(film) /cm^{-1} 3365 (N-H), 2990, 1379, 1239, 1159, 1052, 945, 845, 740, 701. δ_H (400 MHz; $CDCl_3$) 1.44 (6 H, s, 2 *x* $C^{7\&8}\underline{H}_3$), 2.64 (1 H, q, *J* 1.8 Hz, $NC^5\underline{H}$), 3.78 (1 H, dd, *J* 1.7 & 11.7 Hz, $OC^6\underline{H}H$), 4.18 (1 H, dd, *J* 2.3 & 11.7 Hz, $OC^6H\underline{H}$), 4.99 (1 H, s, $PhC^4\underline{H}$), 7.23 (5 H, m, 5 *x* Ar-$C^{10\text{-}14}\underline{H}$). δ_C (100 MHz; $CDCl_3$) 18.6 ($\underline{C}^8H_3$), 29.7 ($\underline{C}^7H_3$), 49.6 ($N\underline{C}^5H$), 65.9 ($O\underline{C}^6H_2$), 73.7 ($Ph\underline{C}^4H$), 99.1 (quat.$\underline{C}^2$), 125.9 (2 *x ortho* Ar-$\underline{C}^{10\&14}H$), 127.4 (*para* Ar-$\underline{C}^{12}H$), 128.4 (2 *x meta* Ar-$\underline{C}^{11\&13}H$), 139.8 (Ar- quat.$\underline{C}^9$).

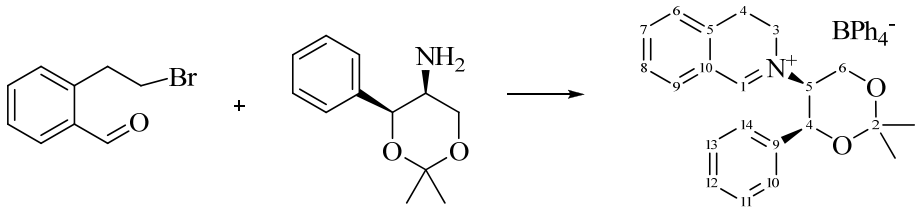
2-(2-Bromoethyl)benzaldehyde. [3]



12 ***13***

Bromine (3.24 mL, 63.1 mmol) was added slowly to an ice-cooled solution of isochroman (**12**) (7.70 g, 57.4 mmol) in carbon tetrachloride (10 mL) over a period of 10 min with stirring. After the exothermic reaction subsided, the cooling bath was removed and the dark brown solution heated under reflux until the reaction mixture became pale yellow and liberation of HBr fumes ceased (typically 1.5 h). The solution was allowed to attain ambient temperature temperature and the solvent removed under reduced pressure. A 48% saturated aqueous solution of hydrobromic acid (50 mL) was added to the yellow oil obtained (1-bromoisochroman), and the reaction mixture heated under reflux. After 15 min the solution was allowed to cool and extracted with diethyl ether (4 *x* 50 mL). The combined organic extracts were washed with water (2 *x* 30 mL) and saturated aqueous sodium bicarbonate, and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure furnished crude 2-(2-bromo-ethyl)benzaldehyde (**13**) as an orange oil; about 85 – 90% pure (5.30 g, 43%). Analytically pure samples could be obtained by distillation under reduced pressure; chromatography is not recommended. Both the crude and the distilled compound can be used in the synthesis of dihydroisoquinolinium salts. Found: C, 50.95; H, 4.20%; C_9H_9BrO requires C, 50.73; H, 4.26 %. ν_{max}/cm^{-1} (neat) 2742, 1697 (C=O), 1600, 1575, 1260, 1193, 755. δ_H (400 MHz; $CDCl_3$), 3.50 (4 H, m, $Ph(C^{7\&8}H_2)_2Br$), 7.24 (1 H, td, *J* 6.96 & 0.5 Hz, Ar-H), 7.39 (1 H, dt, *J* 8.8 & 1.3 Hz, Ar-CH), 7.47 (1 H, dt, *J* 9.1 & 1.6 Hz, Ar-CH), 7.73 (1 H, dd, *J* 1.6 & 7.6 Hz, Ar-CH) 10.05 (1 H, s, C^8HO). δ_C (100 MHz; $CDCl_3$), 32.8 (PhC^7H_2), 36.3 (BrC^8H_2), 127.7 (Ar-CH), 132.2 (Ar-CH), 133.7 (Ar-CH), 134.6 (Ar-CH), 140.6 (2xquat.Ar-$^iC^{1\&6}$), 193.0 (C^8HO).

(3*S*,4*S*)-(2,2-Dimethyl-4-phenyl-(1,3)-dioxan-5-yl)-3,4-dihydroisoquinolinium tetraphenyl borate. [4, 5]

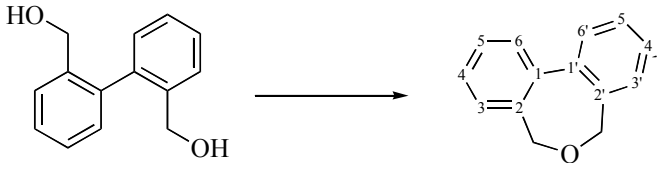


13 ***11*** ***6***

A solution of amine **11** (2.70 g, 13.1 mmol) in ethanol (30.0 mL) was added dropwise to 2-(2-bromoethyl)benzaldehyde (**13**) (3.34 g, 15.7 mmol) at 0 °C. The reaction mixture was stirred for 16 h while reaching ambient temperature. A solution of sodium tetraphenylborate (4.91 g, 14.4 mmol) in the minimum amount of acetonitrile (approximately 5 mL) was added in 1 portion to the reaction mixture. After stirring for 5 min the organic solvents were removed under reduced pressure. Ethanol (10 mL) was added to the reaction mixture, followed by water (10 mL) and diethyl ether (10 mL). Washing with cold ethanol (10 mL), then cold diethyl ether (2 *x* 10 mL) and subsequent filtration yielded the desired yellow crystalline catalyst (**6**) (4.48 g, 54%). Lit.[4] mp 169-170 ºC, mp 168-170 ºC. ν_{max}(film) /cm^{-1} 2921, 2357, 1558, 1456, 1377, 742, 707, 667, 624, 606. $[\alpha]^{20}_{D}$ +40.2 ° (*c* 1.10, CH_3CN). δ_H (400 MHz; d_6Acetone), 1.69 (3 H, s, $C^8\underline{H}_3$), 1.75 (3 H, s, $C^7\underline{H}_3$), 2.69 (1 H, m, *isoq*-$C^4\underline{H}$), 2.95 (1 H, m, *isoq*-$C^4\underline{H}$), 3.62 (2 H, m, *isoq*-$NC^3\underline{H}_2$), 4.24 (1 H, m, $NC^5\underline{H}$), 4.58 (1 H, m, $OC^6\underline{H}H$, upfield portion of ABX system), 4.83 (1 H, q, *J* 3.2 Hz, $OC^6\underline{H}H$, downfield portion of ABX system), 5.64 (1 H, s, $OC^4\underline{H}Ph$), 6.79 (4 H, t, *J* 7.3 Hz, 4 *x* Ar-C<u>H</u> *para* in BPh_4^-), 6.94 (8 H, t, *J* 7.5 Hz, 8 *x* Ar-C<u>H</u> *ortho* in BPh_4^-), 7.42 (8 H, m, 8 *x* Ar-C<u>H</u> *meta* in BPh_4^-), 7.55 (6 H, m, 5 *x* phenyl Ar-C<u>H</u> & 1 H, *isoq*-$C^6\underline{H}$), 7.55 (1 H, t, *J* 7.5 Hz, *isoq*-$C^7\underline{H}$), 7.82 (1 H, m, *isoq*-$C^8\underline{H}$), 7.89 (1 H, d, *J* 7.7 Hz, *isoq*-$C^9\underline{H}$), 9.32 (1 H, s, N=$C^1\underline{H}$). δ_C (100 MHz; d_6Acetone), 18.81 ($\underline{C}^7H_3$), 25.4 (*isoq*-$\underline{C}^4H_2$), 31.2 ($\underline{C}^8H_3$), 52.5 (*isoq*-$N\underline{C}^3H_2$), 62.8 ($O\underline{C}^6H_2$), 66.7 ($N\underline{C}H$), 71.7 ($O\underline{C}^4HPh$), 101.4 (quat.$\underline{C}^2(CH_3)_2$), 122.3 (8 *x* Ar-<u>C</u>H, *ortho* in BPh_4^-), 125.5

(*isoq*-quat.C[10]), 126.0 (2 *x* Ar-C[11&13]H, *meta* in phenyl ring), 129.2 (*isoq*-C[6]H), 129.38 (*isoq*-C[8]H), 129.4 (1 *x* Ar-C[12]H, *para* in phenyl ring), 129.9 (4 *x* Ar-CH, *para* in BPh_4^-), 135.3 (*isoq*-C[7]H), 137.0 (8 *x* Ar-CH, *meta* in BPh_4^-), 137.6 (quat.C[9], ipso in phenyl ring), 137.9 (*isoq*-quat.C[5]), 164.2, 165.2, 165.4, 165.7 (4 *x* quat.C, ipso in BPh_4^-), 168.6 (N=C[1]H). *m/z* 321.8652 ; $C_{29}H_{33}NO_2$ requires 322.1822.

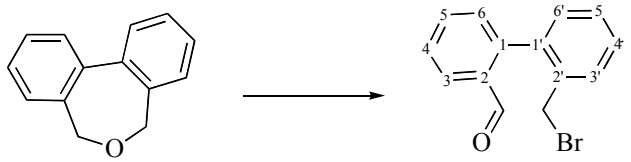
5,7-Dihydrodibenzo-(*c*,*e*)-oxepine. [6]



14 ***98***

A suspension of 2,2'-biphenyl dimethanol (**14**) (5.46 g, 25.5 mmol) in a 24% hydrobromic acid solution (100 mL) was heated to 100 °C for 40 min. The solution was allowed to cool, after which the saturated aqueous phase was extracted with diethyl ether (3 *x* 50 mL). The organic fractions were washed with saturated aqueous saturated $NaHCO_3$ (2 *x* 50 mL), and saturated brine (2 *x* 50 mL) and dried over magnesium sulphate. The solvent was removed under reduced pressure to yield colourless crystals of the desired oxepine (**98**) (4.85 g, 24.7 mmol, 97%.). mp 69 – 71 ºC (dec); Lit.[6] mp 69 – 71 °C. ν_{max}(film) /cm^{-1} 1556, 1446, 1196, 1072, 1041, 903, 891, 753, 667, 620. δ_H (400 MHz; $CDCl_3$), 4.27 (4 H, s, 2 *x* OCH$_2$), 7.32 (2 H, dt, *J* 1.2 & 7.6 Hz, *biphenyl*-C[6&6']H), 7.34 (2 H, dt, *J* 1.2 & 5.6 Hz, *biphenyl*-C[5&5']H), 7.41 (2 H, dt, *J* 7.6 & 2.0 Hz, *biphenyl*-C[3&3']H), 7.47 (2 H, d, *J* 7.6 Hz, *biphenyl*-C[4&4']H). δ_C (100 MHz; $CDCl_3$), 67.8 (2 *x* OCH$_2$), 127.6 (2 *x* *biphenyl*-C[4&4']H), 128.4 (2 *x* *biphenyl*-C[6&6']H), 129.0 (2 *x* *biphenyl*-C[3&3']H), 129.8 (2 *x* *biphenyl*-C[5&5']H), 135.2 (2 *x* quat. *biphenyl*-C[1&1']), 141.3 (2 *x* quat. *biphenyl*-C[2&2']).

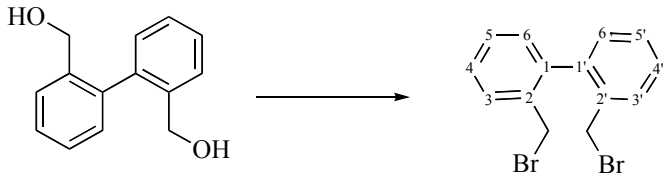
2-(2-(Bromomethyl)phenyl)benzene carbaldehyde. [6]



98 ***99***

To an ice cooled solution of oxepine **98** (9.17 g, 46.7 mmol) a solution of bromine (2.64 mL, 51.4 mmol) in cyclohexane (60 mL) was added dropwise over 5 min; the reaction turned to a deep red colour. The cooling bath was removed and the reaction mixture heated under reflux until the liberation of HBr ceased (typically 2 h) and the reaction mixture turned pale yellow. The solvent was removed under reduced pressure, dissolved in diethyl ether (150 mL), washed with saturated aqueous $NaHCO_3$ (2 *x* 60 mL), and saturated brine (2 *x* 60 mL), and dried over magnesium sulphate. The solvent was removed under reduced pressure to yield an orange oil which was recrystallized in ethyl acetate/hexane to give colourless crystals of **99**. (4.22 g, 15 mmol, 33%). mp 57 – 58 °C; Lit.[6] mp 57 – 58 °C. ν_{max}(film) /cm^{-1} 3189, 1667 (C=O), 1393, 1148, 774, 739, 721, 631. δ_H (400 MHz; $CDCl_3$), 4.33 (2 H, q, *J* 10.0 Hz, CH_2Br), 7.24 (1 H, dd, *J* 1.2 & 7.6 Hz, *biphenyl*-CH), 7.40 (1 H, td, *J* 1.6 & 7.6 Hz, *biphenyl*-CH), 7.44 (1 H, ddd, *J* 1.2 & 7.6 Hz, *biphenyl*-CH), 7.47 (1 H, td, *J* 1.6 & 7.6 Hz, *biphenyl*-$C^{3'}H$), 7.59 (2 H, m, *biphenyl*-$C^{3\&4}H$), 7.69 (1 H, td, *J* 1.6 & 3.6 Hz, *biphenyl*-CH), 8.09 (1 H, ddd, *J* 1.6 & 8.0 Hz, *biphenyl*-CH), 9.76 (1 H, s, CHO). δ_C (100 MHz; $CDCl_3$), 31.40 (CH_2Br), 127.6 (*biphenyl*-C^1H), 128.4 (*biphenyl*-$C^{2'}H$), 128.6 (*biphenyl*-C^3H), 129.1 (*biphenyl*-$C^{3'}H$), 130.7 (*biphenyl*-C^4H), 130.7 (*biphenyl*-$C^{4'}H$), 131.1 (*biphenyl*-$C^{1'}H$), 133.6 (*biphenyl*-C^2H), 134.1 (quat. *biphenyl*-C), 136.0 (quat. *biphenyl*-C), 137.9 (quat. *biphenyl*-C), 139.4 (quat. *biphenyl*-C), 143.3 (CHO).

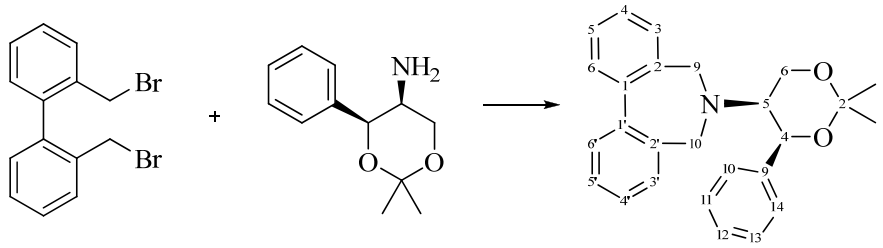
2,2'-*bis*-Bromomethyl-biphenyl.



14 ***15***

Biphenyl dimethanol (**14**) (10.0 g, 46.7 mmol) was added to an aqueous hydrobromic acid solution (48%, 100 mL) and the mixture heated under reflux until complete consumption of the starting material was observed was observed by TLC (typically 2 h). The reaction was allowed to cool to ambient temperature and diethyl ether (100ml) added. The organic layer was washed with saturated brine (3 *x* 30 mL), saturated aqueous $NaHCO_3$ (3 *x* 30 mL), and water (3 *x* 30 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the desired product (**15**) as colourless crystals (15.9 g, 45.7 mmol, 98%). Found: C, 49.63; H, 3.51%. $C_{14}H_{12}Br_2$ requires: C, 49.45; H, 3.56%. ν_{max}(film) /cm^{-1} 2359, 2340, 1652, 1474, 1436, 1220, 1091, 808, 760, 668. δ_H (400 MHz; $CHCl_3$), 4.94 (4 H, q, *J* 11.5 Hz, 2 *x* C<u>H</u>HBr), 7.37 – 7.38 (2 H, *J* 2.2 & 2.7 Hz, 2 *x biphenyl*-C<u>H</u>), 7.45 (2 H, *J* 0.7 & 7.8 Hz, 2 *x biphenyl*-C<u>H</u>), 7.54 – 7.59 (2 H, m, 2 *x biphenyl*-C<u>H</u>), 7.91 (2 H, *J* 7.8 Hz, 2 *x biphenyl*-C<u>H</u>). δ_C (100 MHz; $CHCl_3$), 69.2 (2 *x* <u>C</u>H_2Br), 128.5 (*biphenyl*-<u>C</u>H), 128.61 (*biphenyl*-<u>C</u>H), 128.62 (*biphenyl*-<u>C</u>H), 128.71 (*biphenyl*-<u>C</u>H), 128.73 (*biphenyl*-<u>C</u>H), 130.2 (*biphenyl*-<u>C</u>H), 130.7 (*biphenyl*-quat.<u>C</u>), 132.0 (*biphenyl*-<u>C</u>H), 132.6 (*biphenyl*-<u>C</u>H), 134.9 (*biphenyl*-quat.<u>C</u>), 137.3 (*biphenyl*-quat.<u>C</u>), 139.0 (*biphenyl*-quat.<u>C</u>).

(–)-2-((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-(1,3)-dioxan-5-yl)-6,7-dihydro-5*H*-dibenzo-(*c*,*e*)-azepine



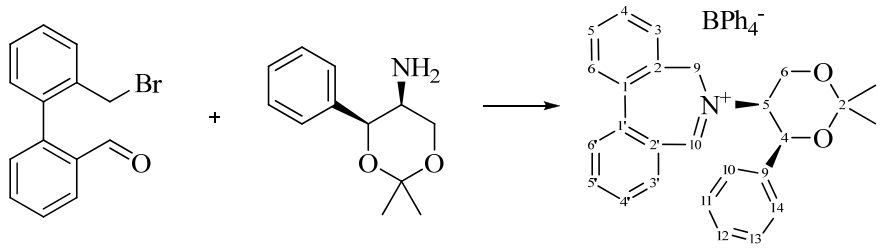
15 ***11*** ***16***

2,2'-*bis*-Bromomethylbiphenyl **15** (15.6 g, 46.0 mmol) and TEA (5.04 g, 50.0 mmol) were added to a nitrogen-purged stirred solution of amine **11** (10.4 g, 50.0 mmol) in anhydrous THF (200 mL) at ambient temperature. The reaction mixture was heated under reflux for 16 h. The solvent was removed under reduced pressure and the resulting residue dissolved in ethyl acetate (150 mL). The combined organic layers were washed with water (3 *x* 30 mL), and saturated brine (3 *x* 30 mL), and dried over $MgSO_4$. The solvents were removed under reduced pressure. Column chromatography of the crude oil using ethyl acetate/petroleum ether (1:20) gave the product (**16**) as a yellow foam (17.2 g, 44.5 mmol, 97%). ν_{max}(film) /cm^{-1} 3390, 2989, 2359, 1651, 1452, 1378, 1198, 1079, 752, 698. $(\alpha]^{20}_{D}$ +71.4 ° (*c* 1.11, $CHCl_3$). δ_H (400 MHz; $CHCl_3$), 1.50 (6 H, s, 2 *x* $C^{7/8}\underline{H}_3$), 2.88 (1 H, q, *J* 2.8 Hz, $NC^5\underline{H}$), 3.41 (2 H, d, *J* 12.8 Hz, $NC^{9/10}\underline{H}H$, downfield portion of ABX system), 3,59 (2 H, d, *J* 12.8 Hz, $NC^6H\underline{H}$, upfield portion of ABX system), 4.17 (2 H, d, *J* 2.8 Hz, $OC^6\underline{H}H$), 5.12 (1 H, d, *J* 3.2 Hz, $OC^4\underline{H}$Ph), 7.14 (2 H, dd, *J* 0.8 & 7.2 Hz, 2 *x biphenyl*-C<u>H</u>), 7.17 – 7.24 (3 H, m, 3 *x biphenyl*-C<u>H</u>), 7.28 (4 H, dt, *J* 1.2 & 7.2 Hz, 4 *x biphenyl*-C<u>H</u>), 7.34 (2 H, dd, *J* 7.2 & 1.6 Hz, 2 *x biphenyl*-C<u>H</u>), 7.38 – 7.40 (2 H, m, Ar-C<u>H</u>, *ortho* in phenyl). δ_C (100 MHz; $CHCl_3$), 18.1 ($\underline{C}^7H_3$), 28.4 ($\underline{C}^8H_3$), 53.0 (2 *x* $N\underline{C}^{9/10}H_2$), 59.8 ($N\underline{C}^5H$), 61.1 ($O\underline{C}^6HH$), 73.7 ($\underline{C}^4H$Ph), 98.0 (quat-$\underline{C}^2$), 125.2 (2 *x* Ar-<u>C</u>H, *ortho* in phenyl), 125.8 (Ar-<u>C</u>H, *para* in phenyl), 126.3 (2 *x biphenyl*-<u>C</u>H), 126.4 (2 *x* Ar-<u>C</u>H), 126.7 (2 *x* Ar-<u>C</u>H), 126.8 (2 *x biphenyl*-<u>C</u>H), 128.3 (2 *x*

biphenyl-CH), 135.6 (2 *x biphenyl*-quat.C), 139.1 (quat.C, *ipso* in phenyl), 139.9 (2 *x biphenyl*-quat.C). *m/z*; observed 386.28184. $C_{26}H_{27}NO_2$ requires 385.20418.

6-(2,2-Dimethyl-4-phenyl-(1,3)dioxan-5-yl)-5 H-dibenzo-(*c,e*)- azepinium.[6]

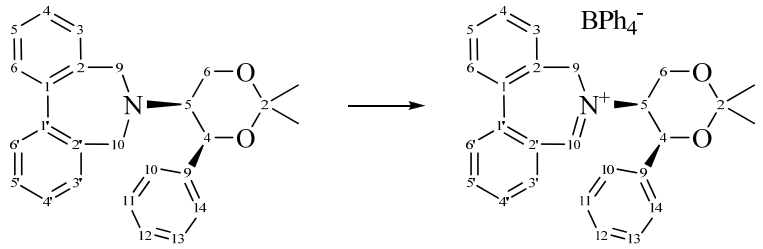
Method A



99 ***11*** ***7***

To an ice cooled solution of carbaldehyde **99** (3.30 g, 12.0 mmol) in ethanol (35 mL), a solution of amine **11** (2.05 g, 7.00 mmol) in ethanol (20 mL) was added and left to heat to ambient temperature for 16 h. Sodium tetraphenylborate (3.76 g, 12.0 mmol) was dissolved in the minimal amount of acetonitrile (approximately 5 mL). This was then added to the reaction mixture and after 5 min gave a yellow precipitate. Ethanol and water were added to the reaction mixture. The mixture was then filtered, washed with cold ethyl acetate (3 *x* 10 mL), cold water (1 *x* 10 mL) and diethyl ether (3 *x* 10 mL) yielding the desired azepinium tetraphenyl borate salt (**7**) as a yellow powder.

Method B

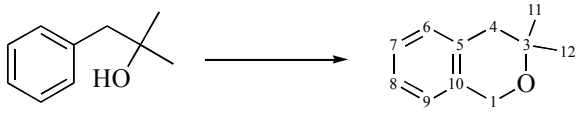


16 ***7***

n-Bromosuccinimide (2.53 g, 14.2 mmol) was added to a stirred solution of azepine **16** (5.00 g, 13.0 mmol) in chloroform (50 mL) at ambient temperature. The reaction was monitored by TLC and once complete consumption of the azepine was observed, typically 15 mins, the solvent was removed under reduced pressure to yield the iminium bromide salt intermediate. The salt was dissolved in ethanol (25 mL) and sodium tetraphenylborate (4.86 g, 14.2 mmol) was added in a minimal volume of MeCN. The reaction was allowed to stir at ambient temperature for 20 min. The solvents were removed under reduced pressure and dissolved in chloroform (25 mL). The combined organic layers were washed with water (3 *x* 10 mL), and saturated brine (3 *x* 10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the resultant residue was recrystallized from ethanol to yield iminium salt catalyst (**7**) as a bright yellow powder. (5.60 g, 8.00 mmol, 80%). m.p. 187-189 ºC (dec.); Lit.[6] m.p. 187-188 ºC. $[\alpha]^{20}_{D}$ −44.3 ° (*c* 1.05, CH_3CN). ν_{max}(film) /cm^{-1} 3051, 1630, 1479, 1382, 1201, 966, 843, 733, 704, 610. δ_H (400 MHz; DMSO), 1.72 (3 H, s, $C^8\underline{H}_3$), 1.75 (3 H, s, $C^7\underline{H}_3$), 4.33 (1 H, d, *J* 13.2 Hz, $OC^6\underline{H}H$, upfield portion of *AB*X system), 4.47 (1 H, d, *J* 12.1 Hz, $NC^9\underline{H}H$), 4.70 (1 H, d, *J* 3.2 Hz, $OC^6H\underline{H}$, downfield portion of *AB*X system), 4.73 (1 H, t, *J* 4.1 Hz, $NC^5\underline{H}$), 5.14 (1 H, broad peak, $NC^9H\underline{H}$), 5.64 (1 H, s, $OC^4\underline{H}Ph$), 6.77 (4 H, t, *J* 7.2 Hz, 4 *x* Ar-C<u>H</u> *para* in BPh_4^-), 6.9 (8 H, t, *J* 7.3 Hz, 8 *x* Ar-C<u>H</u> *ortho* in BPh_4^-), 7.23 (8 H, m, 8 *x* Ar-C<u>H</u> *meta* in BPh_4^-), 7.59 (6 H, m, 4 *x biphenyl*-C<u>H</u> & 2 *x* Ar-

$C^{11\&13}\underline{H}$ *meta* in phenyl ring), 7.70 (4 H, m, 4 *x biphenyl*-C<u>H</u>), 7.94 (2 H, m, $2C^{10\&14}\underline{H}$ *ortho* in phenyl ring), 9.03 (1 H, s, N=$C^{10}\underline{H}$). δ_C (100 MHz; DMSO), 18.2 ($\underline{C}^7H_3$), 28.7 ($\underline{C}^8H_3$), 55.5 (N$\underline{C}^9H_2$), 60.82 (O$\underline{C}^6H_2$), 66.1 (N$\underline{C}^5$H), 70.5 ($\underline{C}^4$HPh), 99.9 (quat.$\underline{C}^2$), 120.8 (8 *x* Ar-<u>C</u>H *ortho* in BPh_4^-), 124.5 (4 *x* Ar-<u>C</u>H *para* in BPh_4^-), 124.5 (2 *x* Ar-$\underline{C}^{11\&13}$H *meta* in phenyl), 124.5 (2 *x* Ar-$\underline{C}^{10\&14}$H *ortho* in phenyl), 124.5 (Ar-$C^{12}\underline{H}$ *para* in phenyl), 125.3 (*biphenyl*-quat.$\underline{C}^5$), 127.4 (*biphenyl*-quat.$\underline{C}^{2'}$), 127.8 (*biphenyl*-$\underline{C}^{4'}$H), 128.0 (*biphenyl*-$\underline{C}^{6'}$H), 128.4 (*biphenyl*-$\underline{C}^{3'}$H), 128.5 (*biphenyl*-$\underline{C}^{5'}$H), 129.3 (*biphenyl*-$\underline{C}^4$H), 129.6 (*biphenyl*-$\underline{C}^6$H), 129.6 (*biphenyl*-$\underline{C}^3$H), 132.9 (*biphenyl*-$\underline{C}^{2'}$H), 133.8 (*biphenyl*-$\underline{C}^2$H), 135.1 (8 *x* Ar-<u>C</u>H *meta* in BPh_4^-), 136.1 (*biphenyl*-quat.$\underline{C}^{1'}$), 140.5 (*biphenyl*-quat.$\underline{C}^2$), 162.4, 162.8, 162.3, 163.8 (4 *x* quat.$\underline{C}^4$ *ipso* in BPh_4^-), 170.3 (N=$\underline{C}^{10}$H).

3,3-Dimethyl-isochroman.

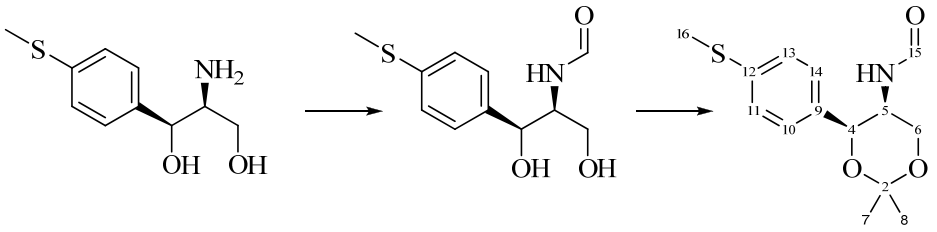


100 ***101***

Trifluoroacetic acid (10.0 mL, 1ml/g) and paraformaldehyde (2.42 g, 79.9 mmol) were added to a cooled solution of 2,2-dimethyl-1-phenyl-propan-2-ol (**100**) (10.0 g, 66.6 mmol). The reaction was monitored by TLC until consumption of the starting material was observed (typically 1 h). The reaction mixture was washed with NaOH (1 M, 2 *x* 60 mL), saturated brine (2 *x* 60 mL) and dried over magnesium sulphate to yield up to 85% pure product. The washed product was distilled (typically 170 °C @ 2 mbar) to give pure 3,3-dimethyl-isochroman as a colourless oil (**101**) (8.90 g, 55.5 mmol, 83%). ν_{max}(film) /cm^{-1} 3461, 2971, 2360, 1776, 1453, 1367, 1212, 1181, 1081, 881, 746. δ_H (400 MHz;

$CDCl_3$), 1.20 (6 H, s, 2 *x* $C^{11\&12}\underline{H}_3$, s), 2.62 (2 H, s, $C^4\underline{H}_2$), 4.71 (2 H, s, $OC^1\underline{H}_2$), 6.91 (1 H, q, *J* 3.8 Hz, Ar-C<u>H</u>), 6.98 (1 H, q, *J* 3.6 Hz, Ar-<u>H</u>), 7.04 − 7.08 (2 H, Ar-<u>H</u>, m). δ_C (100 MHz; $CDCl_3$), 26.5 (2 *x* $\underline{C}^{11\&12}H_3$), 39.7 ($Ph\underline{C}^4H_2$), 63.1 ($O\underline{C}^1H_2$), 70.7 (quat.$\underline{C}^3(CH_3)_2$), 123.9 (Ar-<u>C</u>H), 125.8 (Ar-<u>C</u>H), 126.5 (Ar-<u>C</u>H), 129.2 (Ar-<u>C</u>H), 133.0 (quat.Ar-<u>C</u>), 133.9 (quat.Ar-<u>C</u>).

N-((4S,5S)-2,2-Dimethyl-4-(4-(methylsulfanyl)-phenyl)-1,3-dioxan-5-yl)formamide.[7]

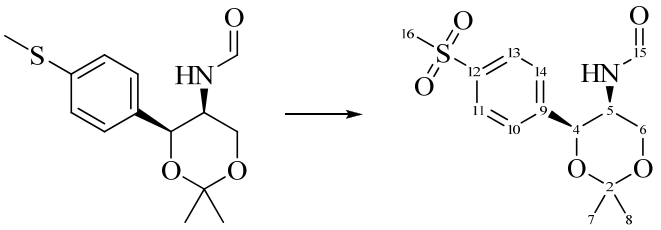


17 ***18*** ***19***

Thiomicamine (**17**) (10.0 g, 46.9 mmol.) was dissolved in methanol (100 mL), and methyl formate (3.20 mL, 51.4 mmol) added followed by a methanoic aqueous solution of sodium methoxide (25% *w/v*, 1.08 mL, 4.70 mmol). The reaction was monitored by TLC until complete consumption of the starting material was observed (typically 2 h). The resulting solution was evaporated under reduced pressure to afford the formyl-protected amine **18** as a yellow oil. The oil was dissolved in acetone (500 mL), 2,2-dimethoxypropane (57.6 mL, 0.469 mol) and *p*-TSA (0.89 g, 4.70 mmol) were added. The reaction was monitored by TLC until consumption of the intermediate product was observed (typically 1.5 h). The solvents were removed under reduced pressure and the residue re-dissolved in ethyl acetate (100 mL), which underwent saturated aqueous work up with saturated aqueous $NaHCO_3$ (3 *x* 60 mL). The organics were dried over $MgSO_4$ and solvents removed under reduced pressure affording acetonide **19** (13.2 g, 46.9 mmol,

> 99%). Lit. $[\alpha]_D$ +1.3 ° (*c* 1.27, $CHCl_3$), $[\alpha]^{20}_D$ +43.3 ° (*c* 1.06, $CHCl_3$). ν_{max}(film) /cm^{-1} 3321, 2989, 2362, 1671, 1497, 1380, 1199, 1074, 942. δ_H (400 MHz; $CDCl_3$) 1.54 (3 H, s, $C^8\underline{H}_3$), 1.57 (3 H, s, $C^7\underline{H}_3$), 2.45 (3 H, s, $SC^{16}\underline{H}_3$), 3.85 (1 H, dd, *J* 1.6 & 12.0 Hz, upfield portion of an *AB*X system, $OC^6H\underline{H}$), 4.23 (1 H, d, *J* 9.6 Hz, downfield portion of an *AB*X system, $OC^6\underline{H}H$), 4.28 (1 H, m, $NC^5\underline{H}$), 6.39 (1 H, s, $OC^4\underline{H}$Ph), 7.21 (4 H, m, 4 *x* Ar-C<u>H</u>), 7.95 (1 H, s, $NC^{15}\underline{H}O$); δ_C (100 MHz; $CDCl_3$) 14.2 ($S\underline{C}^{16}H_3$), 18.5 ($\underline{C}^7H_3$), 29.7 ($\underline{C}^8H_3$), 45.3 ($N\underline{C}^5H$), 64.6 ($O\underline{C}^6H_2$), 71.4 ($O\underline{C}^4$HPh), 99.7 (quat.$\underline{C}^2$), 125.8 (2 *x* Ar-<u>C</u>H), 126.5 (2 *x* Ar-<u>C</u>H), 135.0 (quat.Ar-<u>C</u>), 137.7 (quat.Ar-<u>C</u>), 160.6 ($N\underline{C}^{15}HO$).

_N_-((4_S_,5_S_)-2,2-Dimethyl-4-(4-(methylsulfonyl)-phenyl)-1,3-dioxan-5-yl) formamide.[7]

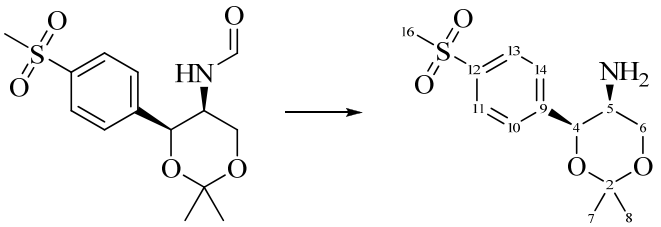


19 ***20***

Formamide **19** (13.2 g, 46.9 mmol) was dissolved in dichloromethane (250 mL) and cooled to 0 ºC. A solution of *m*-CPBA (17.8 g, 0.10 mol) in chloroform (50 mL) was added dropwise over 10 min. The reaction was then left to stir for 2 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 *x* 75 mL), saturated brine (3 *x* 75 mL) and dried over $MgSO_4$. The solvents were removed under reduced pressure to yield a colourless oil (**20**) (9.55 g, 30.5 mmol 65%). Lit. $[\alpha]_D$ +11.6 ° (*c* 1.21, $CHCl_3$), $[\alpha]^{20}_D$ +70.1 ° (*c* 1.12, $CHCl_3$). ν_{max}(film) /cm^{-1} 3371, 2984, 1609, 1400, 1191, 1070, 945. δ_H (400 MHz; $CDCl_3$) 1.48 (3 H, s, $C^8\underline{H}_3$), 1.51 (3 H, s, $C^7\underline{H}_3$), 2.96 (3 H, s, $SC^{15}\underline{H}_3$), 3.75 (1 H, dd, *J* 1.6 & 12.0 Hz, upfield portion of an *AB*X system, $OC^6H\underline{H}$),

4.23, (1 H, dd, *J* 1.6 & 12.0 Hz, downfield portion of an *AB*X system, OC^{6}H$\underline{H}$), 4.31 (1 H, dd, *J 2.0* & 9.6 Hz, NC^{5}$\underline{H}$), 6.62 (1 H, d, *J* 10.0 Hz, OC^{4}$\underline{H}$Ph), 7.47 (2 H, d, *J* 8.4 Hz, 2 *x* Ar-C$^{10\&14}$H), 7.85 (2 H, dd, *J* 2.0 & 6.8 Hz, 2 *x* Ar-C$^{11\&13}$H), 7.82 (1 H, d, *J* 1.2 Hz, NC^{15}$\underline{H}$O); δ_C (100 MHz; $CDCl_3$) 18.5 ($\underline{C}^{7}H_3$), 29.5 ($\underline{C}^{8}H_3$), 44.4 (S$\underline{C}^{16}H_3$) 45.1 (N$\underline{C}^{5}$H), 64.5 (O$\underline{C}^{6}H_2$), 71.5 (O$\underline{C}^{4}$HPh), 99.9 (quat.$\underline{C}^{2}$), 126.6 (2 *x* Ar-$\underline{C}^{10\&14}$H), 127.1 (2 *x* Ar-$\underline{C}^{11\&13}$H), 139.5 (quat.Ar-$\underline{C}^{14}$), 144.6 (quat.Ar-$\underline{C}^{9}$), 160.6 (N$\underline{C}^{15}$HO).

(4*S*,5*S*)-2,2-Dimethyl-4-(4-(methylsulfonyl)-phenyl)-1,3-dioxan-5-amine.[7]

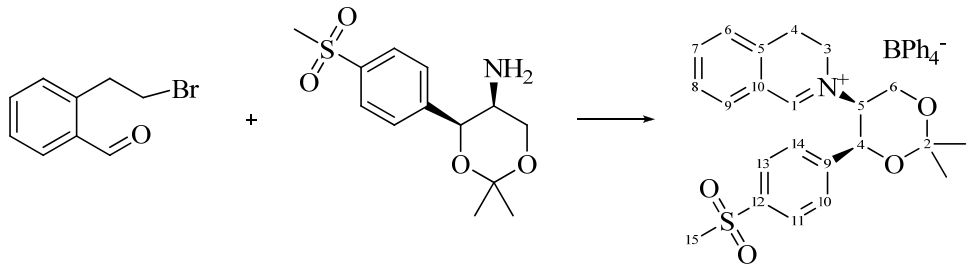


20 ***21***

Formamide **20** (4.65 g, 14.5 mmol) was suspended in saturated aqueous hydrazine hydrate (85%) (200 mL), the suspension was heated under reflux for 2.5 h. The solution was allowed to cool to ambient temperature and extracted with ethyl acetate. The combined organic layers were washed with water (2 *x* 150 mL), dried over $MgSO_4$ and solvents removed under reduced pressure to yield colourless crystals (**21**) (3.50 g, 12.4 mmol, 75%). Lit. mp. 120 – 122 ºC, mp. 121 – 123 ºC ν_{max}(film) /cm^{-1} 3369, 2995, 1607, 1372, 1197, 1077, 945. $[\alpha]^{20}_{D}$ +50.0 ° (*c* 1.00, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 1.49 (6 H, s, 2 *x* C$^{7\&8}\underline{H}_3$), 2.78 (1 H, dd, *J* 1.6 & 3.6 Hz, NC^{5}$\underline{H}$), 2.99 (3 H, s, SC$^{15}\underline{H}_3$), 3.81 (1 H, dd, *J* 6.0 & 16.0 Hz, upfield portion of an *AB*X system, OC^{6}H$\underline{H}$), 4.25 (1 H, dd, *J* 2.0 & 11.6 Hz, downfield portion of an *AB*X system, OC^{6}$\underline{H}$H), 5.11 (1 H, d, *J* 0.8 Hz, OC^{4}$\underline{H}$Ph), 7.48 (2 H, m, 2 *x* Ar-C$^{10\&14}$H), 7.95 (2 H, m, 2 *x* Ar-C$^{11\&13}$H); δ_C (100 MHz; $CDCl_3$) 18.6 ($\underline{C}^{7}H_3$), 29.7 ($\underline{C}^{8}H_3$), 44.6 (S$\underline{C}^{15}H_3$), 49.4 (N$\underline{C}^{5}$H), 66.4 (O$\underline{C}^{6}H_2$), 73.5

(O<u>C</u>^{4}HPh), 99.5 (quat.<u>C</u>^{2}), 126.8 (2 *x* Ar-<u>C</u>$^{10\&14}$H), 127.5 (2 *x* Ar-<u>C</u>$^{11\&13}$H), 139.5 (quat.<u>C</u>^{14}), 146.2 (quat.<u>C</u>^{9}).

(+)-((4*S*,5*S*)-2,2-Dimethyl-4-(4-(methylsulfonyl)-phenyl)-1,3-dioxan-5-yl)-3,4-dihydroisoquinolinium tetraphenylborate.[7]

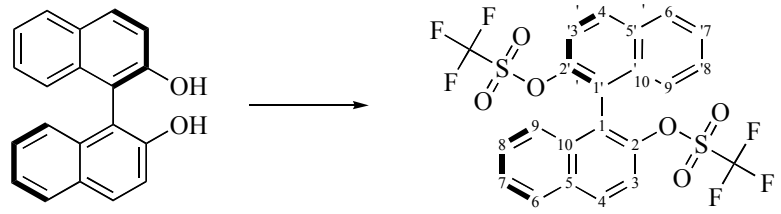


13 ***21*** ***1***

A solution of amine **21** (3.53 g, 12.4 mmol) in ethanol (70 mL) was added dropwise to 2-(2-bromoethyl)benzaldehyde (**13**) (3.17 g, 14.9 mmol) at 0 °C. The reaction mixture was stirred for 16 h while reaching ambient temperature. Sodium tetraphenylborate (5.10 g, 14.9 mmol) in the minimum amount of acetonitrile (approximately 5 mL) was added in 1 portion to the reaction mixture, and after stirring for 5 min the organic solvents were removed under reduced pressure. Ethanol was added to the reaction mixture followed by water followed by diethyl ether. Washing and filtration with ethanol and diethyl ether yielded the desired tetraphenyl borate salt, **1**, as a yellow powder (0.35 g, 0.50 mmol, 35%). Lit. mp 218 – 220 °C; mp 218 – 220 °C. ν_{max}(film) /cm^{-1} 3269, 2924, 1643, 1603, 1361, 1314, 1149, 1089, 759, 702. $[\alpha]^{20}_{D}$ +126.4 ° (*c* 0.97, acetone). δ_H (400 MHz; acetone-d_6), 1.51 (3 H, s, C<u>H</u>$_3$), 1.54 (3 H, s, C<u>H</u>$_3$), 2.49 (2 H, m, *isoq*-C^{4}H$_2$), 2.93 (3 H, s, SO$_2$C^{15}<u>H</u>$_3$), 3.26 (1 H, m, *isoq*-NC^{3}<u>H</u>H), 3.36 (1 H, m, *isoq*-NC^{3}H<u>H</u>), 3.73 (1 H, d, *J* 14.4 Hz, upfield portion of an *AB*X system, OC^{6}H<u>H</u>), 3.80 (1 H, m, NC^{5}<u>H</u>), 4.12 (1 H, d,

J 13.6 Hz, downfield portion of an *AB*X system, OC^{6}HH), 5.30 (1 H, m, OC^{4}HPh), 6.85 (4 H, t, *J* 7.2 Hz, 4 *x* Ar-CH, *para* in BPh_4), 7.00 (8 H, t, *J 8.8* Hz, 8 *x* Ar-CH, *ortho* in BPh_4), 7.11 (1 H, d, *J* 2.4 Hz, *isoq*-C^{8}H), 7.20 (3 H, m, 3 *x isoq*-C^{6,7,9}H), 7.37 (8 H, m, 8 *x* Ar-CH, *meta* in BPh_4), 7.63 (1 H, dd, *J* 2.4 & 8.8 Hz, Ar-C^{10}H), 7.72 (1 H, ddd, *J 1.2,* 8.2 & 17.2 Hz, Ar-C^{11}H), 7.83 (2 H, d, *J* 8.4 Hz, Ar-C$^{12\&13}$H), 8.51 (1 H, s, *isoq*-HC^{1}=N); δ_C (100 MHz; acetone-d_6), 18.8 (C$^{7}H_3$), 25.4 (*isoq*-C$^{4}H_2$), 29.5 (C$^{8}H_3$), 44.3 (SO_2C$^{15}H_3$,), 52.3 (*isoq*-C$^{3}H_2$N), 62.9 (OC$^{6}H_2$), 66.1 (NC^{5}H), 71.5 (OC^{4}HPh), 101.7 (quat.C$^{2}(CH_3)_2$), 122.3 (8 *x* Ar-CH, *ortho* in BPh_4), 125.3 (*isoq*-quat.C^{10}), 126.1 (2 *x* Ar-C$^{11\&13}$H, *meta* to ^{i}C^{9} in phenyl ring), 127.6 (2 *x* Ar-C$^{10\&14}$H, *ortho* to ^{i}C^{9} in phenyl ring), 128.8 (*isoq*-C^{6}H), 129.3 (*isoq*-C^{8}H), 129.4 (4 *x* Ar-CH, *para* in BPh_4), 135.4 (*isoq*-C^{7}H), 137.0 (8 *x* Ar-CH, *meta* in BPh_4), 137.0 (*isoq*-C^{9}H), 137.9 (quat.Ar-CSO_2Me), 142.4 (*isoq*-quat.C^{5}), 143.2 (quat.Ar-C, *ipso* in phenyl ring), 165.0 (4 *x* quat.Ar-C, *ipso* in BPh_4), 169.0 (*isoq*-HC^{1}=N).

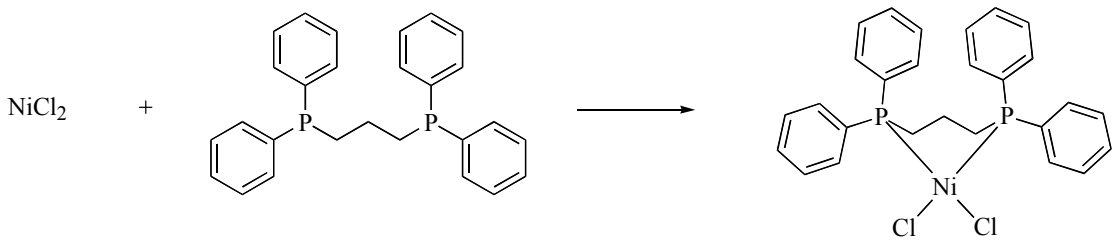
(*R*)-Trifluoro-methanesulfonic acid 2'-trifluoromethanesulfonyloxy (1,1')binaphthalenyl-2-yl ester.[8]



45 ***46***

(*R*)-[1,1']Binaphthalenyl-2,2'-diol (**45**) (3.40 g, 11.8 mmol) was dissolved in dichloromethane (40.0 mL) and cooled to − 30 ºC. To this was added 4-dimethylaminopyridine (0.58 g, 4.72 mmol), 2,6-lutidine (3.80 mL, 35.5 mmol) and triflic anhydride (5.97 mL, 35.5 mmol). The solution was allowed to warm to ambient temperature and stirred for 4 h. Silica gel was added to the solution and the solvent evaporated under reduced pressure. The compound, adsorbed on silica, was transferred to a fritted glass funnel and washed with ethyl acetate/light petroleum until the title compound had eluted. Solvents were removed under reduced pressure to yield a crude colourless solid, which was recrystallized from hexane to give colourless crystals (**46**) (5.39 g, 9.23 mmol, 99%). Lit.[9] mp 82 – 85 °C, mp 76 – 78 °C. ν_{max}(film) /cm^{-1} 1419, 1215, 1139 (S-O), 1065 (S=O), 1030 (S=O), 962, 940, 830. $[\alpha]^{20}_{D}$ −140 ° (*c* 1.06, $CHCl_3$). [δ_H (400 MHz; $CDCl_3$) 7.17 (1 H, q, *J* 0.8 Hz, *Binap*-C^{3}H), 7.19 (1 H, q, *J* 0.8 Hz, *Binap*-C$^{3'}$H), 7.33 (2 H, m, *Binap*-C$^{2\&2'}$H). 7.51 (2 H, m, *Binap*-C$^{8\&8'}$H), 7.54 (2 H, d, *J* 9.2 Hz, *Binap*-C$^{9\&9'}$H), 7.93 (2 H, dt, *J* 0.4 & 8.4 Hz, *Binap*-C$^{4\&4'}$H), 8.07 (2 H, d, *J* 8.8 Hz, *Binap*-C$^{6\&6'}$H). δ_C (100 MHz; $CDCl_3$) 119.3 (2 *x* CF_3), 119.7 (2 *x Binap*-C$^{3\&3'}$), 123.5 (2 *x Binap*-quat.C$^{1\&1'}$), 126.8 (2 *x Binap*-C$^{7\&7'}$), 127.3 (2 *x Binap*-C$^{9\&9'}$), 128.0 (2 *x Binap*-C$^{8\&8'}$), 128.4 (2 *x Binap*-C$^{6\&6'}$), 132.0 (2 *x Binap*-C$^{4\&4'}$), 132.3 (2 *x Binap*-quat.C$^{5\&5'}$), 133.1 (2 *x Binap*-quat.C$^{10\&10'}$), 145.4 (2 *x Binap*-quat.C$^{2\&2'}$).

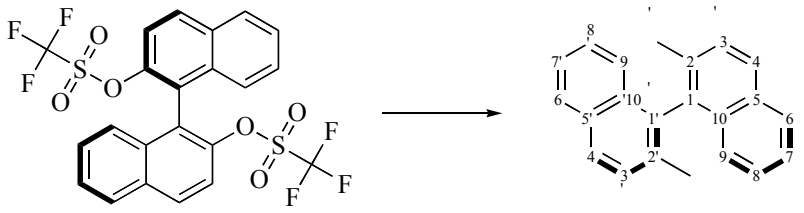
1,3-bis(diphenylphosphino)propane nickel(II)chloride.[10]



102 ***103*** ***104***

$NiCl_2.H_2O$ (**102**) (6.43 g, 27.1 mmol) and 1,3-bis(diphenylphosphino)propane (**103**) (12.3 g, 29.8 mmol) were dissolved in DCM/MeOH (1:1, 150 mL) and refluxed for 1.5 h. The solution was allowed to cool to ambient temperature and the solvents were removed under reduced pressure. The remaining oil was dissolved in DCM and passed through a pad of silica and celite removing diamagnetic nickel chloride. The solvent was reduced (typically 15 mL) and cooled to −19 °C to yield bright red crystals of the desired nickel complex (**104**) (12.9 g, 24.0 mmol, 88%). ν_{max}(film) /cm^{-1} 2925, 2358, 2339, 1650, 1485, 1435, 1099, 787, 741, 731, 690, 668.[11] $C_{27}H_{26}P_2Cl_2Ni$ requires (M^+) 540.02403. C_{27} $H_{26}P_2ClNi$ requires (M^+ − Cl^- ion) 505.05518. Observed mass 505.05605.[11] [75% of Cl^{35} 34.968853. 68% of Ni^{58} 57.935346. 26% of Ni^{60} 59.938786].

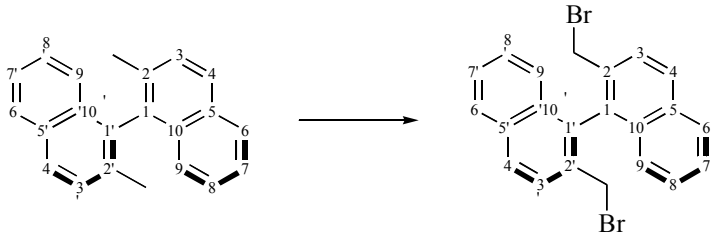
(*R*)-2,2'-Dimethyl-(1,1')binaphthalenyl.[10]



46 ***47***

(*R*)- [1,1']binaphthalene-2,2'-diol *bis*-trifluoromethanesulfonate (**46**) (5.39 g, 9.23 mmol) and 1,3-bis(diphenylphosphino)propane nickel chloride (**102**) (0.35 g, 0.65 mmol) were dissolved in anhydrous diethyl ether (50 mL). The reaction was cooled to −8 ºC and methylmagnesium bromide (3 M in Et_2O, 12.3 mL, 36.9 mmol) was added dropwise over 30 min. The reaction was stirred at ambient temperature for 16 h. The dark green/brown solution was dissolved with diethyl ether (100 mL) and filtered though celite in order to remove the nickel catalyst). The filtrate was washed with 0.5 M hydrochloric acid (2 *x* 50 mL) and saturated brine (50 mL). Removal of solvent under reduced pressure yielded a red/orange crude oil, which was purified by column chromatography eluting with hexane to give a yellow oil. Crystallization from methanol afforded the product as colourless crystals (**47**) (2.61 g, 9.19 mmol, > 99%). ν_{max}(film) /cm^{-1} 3049, 2918, 2853, 2359, 1506, 1221, 810, 742. Lit. mp 74 – 78 °C mp 74 – 78 °C. $[\alpha]^{20}_D$ −45 ° (*c* 1.01, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 1.96 (6 H, s, 2 *x* C$\underline{H}_3$), 6.97 (2 H, d, *J* 0.9 Hz, *Binap*-C$^{3\&3'}\underline{H}$), 7.13 (2 H, m, *Binap*-C$^{7\&7'}\underline{H}$), 7.32 (2 H, m, *Binap*-C$^{8\&8'}\underline{H}$), 7.43 (2 H, d, *J* 8.4 Hz, *Binap*-C$^{4\&4'}\underline{H}$), 7.81 (4 H, t, *J* 6.8 Hz, *Binap*-C$^{9\&9'/6\&6'}\underline{H}$). δ_C (100 MHz; $CDCl_3$) 20.1 (2 *x* $\underline{C}H_3$), 124.9 (2 *x Binap*-$\underline{C}^{7\&7'}$H), 125.7 (2 *x Binap*-$\underline{C}^{8\&8'}$H), 126.1 (2 *x Binap*-$\underline{C}^{4\&4'}$H), 127.4 (2 *x Binap*-$\underline{C}^{9\&9'}$H), 127.9 (2 *x Binap*-$\underline{C}^{6\&6'}$H), 128.8 (2 *x Binap*-$\underline{C}^{3\&3'}$H), 132.2 (2 *x Binap*-quat.$\underline{C}^{5\&5'}$H), 132.8 (2 *x Binap*-quat.$\underline{C}^{10\&10'}$H), 134.3 (2 *x Binap*-quat.$\underline{C}^{2\&2'}$H), 135.1 (2 *x Binap*-quat.$\underline{C}^{1\&1'}$H).

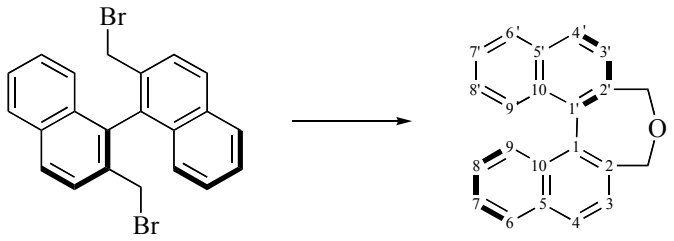
(*R*)-2,2'-Dibromomethyl-(1,1')binaphthalenyl.[11]



47 ***48***

(*R*)-2,2'-Dimethyl-[1,1']binaphthalenyl (**47**) (2.60 g, 9.15 mmol), *N*-bromosuccinimide (3.25 g, 18.3 mmol) and AIBN (10 mol%, 0.15 g, 1.10 mmol) were dissolved in carbon tetrachloride (35 mL). The solution was irradiated with visible light (150 Watt Philips tungsten bulb) for 5 h. The reaction mixture was filtered through a fritted glass funnel and a scoop of silica added. The solvent was removed under reduced pressure to give the reaction mixture adsorbed onto silica, which was immediately purified eluting with light petroleum/ethyl acetate (97:3) to afford a colourless solid. Recrystallized from chloroform/hexane to give colourless crystals (**48**) (4.04 g, 9.14 mmol, > 99%). Lit. mp 180 – 183 °C, mp 180 – 183 °C. ν_{max}(film) /cm^{-1} 3049, 2360, 2239, 1504, 1460, 1439, 1367, 1227, 1183. $[\alpha]^{20}_{D}$ −166 ° (*c* 1.09, benzene). δ_H (400 MHz; $CDCl_3$) 4.29 (4 H, s, 2 *x* C$\underline{H}_2$Br), 7.11 (2 H, dq, *J* 0.4 & 1.6 Hz, *Binap*-C$^{3\&3'}\underline{H}$), 7.30 (2 H, dt, *J* 6.8 & 1.6 Hz, *Binap*-C$^{7\&7'}\underline{H}$), 7.52 (2 H, dt, *J* 6.8 & 1.6 Hz, *Binap*-C$^{8\&8'}\underline{H}$), 7.78 (2 H, d, *J* 8.4 Hz, *Binap*-C$^{4\&4'}\underline{H}$), 7.96 (2 H, d, *J* 8.4 Hz, *Binap*-C$^{9\&9'}\underline{H}$), 8.06 (2 H, d, *J* 8.4 Hz, *Binap*-C$^{6\&6'}\underline{H}$). δ_C (100 MHz; $CDCl_3$) 32.8 (2 *x* $\underline{C}H_3$Br), 126.9 (4 *x* *Binap*-$\underline{C}^{7\&7'/8\&8'}$H), 127.8 (2 *x* *Binap*-$\underline{C}^{4\&4'}$H), 1 28.1 (4 *x* *Binap*-$\underline{C}^{6\&6'/9\&9'}$H), 129.4 (2 *x* *Binap*-$\underline{C}^{3\&3'}$H), 132.5 (2 *x* *Binap*-quat.$\underline{C}^{5\&5'}$H), 133.3 (2 *x* *Binap*-quat.$\underline{C}^{10\&10'}$H), 134.1 (2 *x* *Binap*-quat.$\underline{C}^{2\&2'}$H), 134.2 (2 *x* *Binap*-quat.$\underline{C}^{1\&1'}$H).

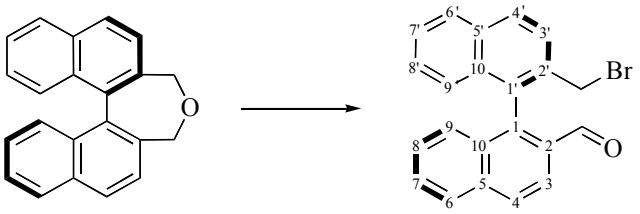
(*R*)-3,5-Dihydro-4-oxa-cyclohepta(2,1-a;3,4-a')dinaphthalene.[12]



48 ***105***

(*R*)-2,2'-Bis-bromomethyl-[1,1']binaphthalenyl (**48**) (4.04 g, 9.14 mmol) was suspended in a mixture of saturated saturated aqueous Na_2CO_3 solution and 1,4-dioxane (1:1, 450 mL). The solution was heated under reflux for 3 days. Upon cooling the mixture was extracted with diethyl ether (5 *x* 50 mL), washed with saturated brine (5 *x* 50 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded a yellow oil which upon TLC visualised using UV light showed the desired product as bright blue spot. Column chromatography eluting with ethyl acetate/light petroleum (0:100-10:90) gave a colourless solid (**105**), recrystallized from chloroform/hexane, (2.47 g, 8.32 mmol, 91%). Lit. mp 184 – 186 °C, mp 184 – 186 °C. ν_{max}(film) /cm^{-1} 2997, 2938, 2358, 2238, 1462, 1382, 1184, 1150, 819, 751, 668. $[\alpha]^{20}_D$ −553 ° (*c* 1.03, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 4.12 (2 H, d, *J* 11.6 Hz, upfield portion of *AB*X system, C<u>H</u>HO), 4.56 (2 H, d, *J* 11.2 Hz, downfield portion of *AB*X system, CH<u>H</u>O), 7.22 (2 H, ddd, *J* 1.2, 6.8 & 8.4 Hz, *Binap*-C$^{3\&3'}$<u>H</u>), 7.43 (4 H, m, *Binap*-C$^{7\&7'/8\&8'}$<u>H</u>), 7.55 (2 H, d, *J* 8.4 Hz, *Binap*-C$^{4\&4'}$<u>H</u>), 7.90 (2 H, d, *J* 8.4 Hz, *Binap*-C$^{9\&9'}$<u>H</u>), 7.93 (2 H, d, *J* 8.4 Hz, *Binap*-C$^{6\&6'}$<u>H</u>). δ_C (100 MHz; $CDCl_3$) 67.45 (2 *x* <u>C</u>H_2O), 125.9 (2 *x* *Binap*-<u>C</u>$^{7\&7'}$H), 126.0 (2 *x* *Binap*-<u>C</u>$^{8\&8'}$H), 127.4 (2 *x* *Binap*-<u>C</u>$^{4\&4'}$H), 127.6 (2 *x* *Binap*-<u>C</u>$^{9\&9'}$H), 128.4 (2 *x* *Binap*-<u>C</u>$^{6\&6'}$H), 129.2 (2 *x* *Binap*-<u>C</u>$^{3\&3'}$H), 131.2 (2 *x* *Binap*- quat.<u>C</u>$^{5\&5'}$), 133.6 (2 *x* *Binap*-quat.<u>C</u>$^{10\&10'}$), 133.6 (2 *x* *Binap*-quat.<u>C</u>$^{2\&2'}$), 135.5 (2 *x* *Binap*-quat.<u>C</u>$^{1\&1'}$).

(*R*)-2'-Bromomethyl-(1,1')binaphthalenyl-2-carbaldehyde.[8]

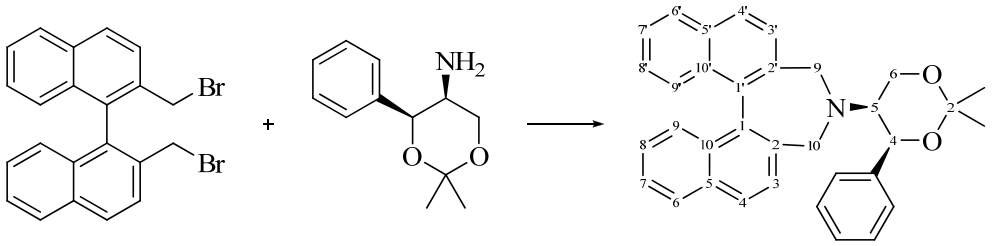


105 ***106***

Molecular bromine (1.09 g, 6.82 mmol) in a solution of carbon tetrachloride (5 mL) was added to an ice-cooled solution of (*R*)-3,5-dihydro-4-oxa-cyclohepta[2,1-a;3,4-a']dinaphthalene (**105**) (2.48 g, 8.32 mmol) also in carbon tetrachloride (50 mL) over a period of 5 min. After a further 5 min the ice bath was removed and the reaction mixture was heated under reflux until it became pale yellow (typically 1 h). The solvent was removed under reduced pressure and the residue obtained was dissolved in diethyl ether. The organic solvents were washed with saturated aqueous $NaHCO_3$ (3 *x* 40 mL), saturated brine (3 *x* 25 mL), dried over $MgSO_4$ and solvents were removed under reduced pressure to yield an orange oil. Crystallization from ethyl acetate afforded the product as colourless crystals (**106**) (1.94 g, 5.15 mmol 62%); Lit. mp 150 – 152 °C, mp 150 – 152 °C. ν_{max}(film) /cm^{-1} δ_H 3055, 2840, 1688 (C=O), 1223, 1209, 1027, 820, 751. $[\alpha]^{20}_D$ +142 ° (*c* 0.97, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 4.01 (1 H, d, *J* 10.0 Hz, upfield portion of *AB*X system, CHHBr), 4.06 (1 H, d, *J* 10.4 Hz, downfield portion of *AB*X system, CHHBr), 6.95 (1 H, d, *J* 8.4 Hz, *Binap*-C$^{7'}$H), 7.16 (1 H, d, *J* 8.4 Hz, *Binap*-C$^{4'}$H), 7.22 (1 H, ddd, *J* 1.2, 6.8 & 8.4 Hz, *Binap*-C$^{9'}$H), 7.27 (1 H, ddd, *J* 1.2, 6.8 & 8.4 Hz, *Binap*-C$^{6'}$H), 7.43 (1 H, ddd, *J* 1.2, 6.8 & 8.4 Hz, *Binap*-C$^{8'}$H), 7.55 (1 H, ddd, *J* 1.2, 6.8 & 8.4 Hz, *Binap*-C$^{3'}$H), 7.65 (1 H, d, *J* 8.8 Hz, *Binap*-C^{8}H), 7.87 (1 H, d, *J* 8.4 Hz, *Binap*-C^{4}H), 7.93 (1 H, d, *J* 8.4 Hz, *Binap*-C^{6}H), 7.98 (1 H, d, *J* 8.4 Hz, *Binap*-C^{9}H), 8.02 (1 H, d, *J* 8.8 Hz, *Binap*-C^{7}H), 8.14 (1 H, d, *J* 8.8 Hz, *Binap*-C^{3}H), 9.49 (1 H, d, *J* 0.8 Hz, CHO). δ_C (100 MHz; $CDCl_3$) 32.0 (CH_2Br), 122.4 (*Binap*-C^{3}H), 126.6 (*Binap*-C$^{7'}$H), 127.0 (*Binap*-C$^{8'}$H), 127.0 (*Binap*-C$^{4'}$H), 127.4 (3 *x* *Binap*-C$^{8/6'/9'}$H), 128.2

(*Binap*-C^{4}H), 128.5 (Binap-C^{6}H), 129.2 (*Binap*-C$^{3'}$H), 129.4 (*Binap*-C^{7}H), 129.9 (*Binap*-C^{9}H), 132.4 (*Binap*-quat.C$^{5'}$), 132.4 (*Binap*-quat.C$^{10'}$), 132.5 (*Binap*-quat.C^{2}), 133.0 (*Binap*-quat.C^{5}), 133.6 (*Binap*-quat.C$^{2'}$), 134.6 (*Binap*-quat.C$^{1'}$), 136.3 (*Binap*-quat.C^{10}), 141.6 (*Binap*-quat.C^{1}), 191.9 (CHO).

4-(2,2-Dimethyl-4-phenyl-(1,3)dioxan-5-yl)-4,5-dihydro-3*H*-4-aza-cyclohepta(2,1-*a*;3,4-*a*')dinaphthalene. [13]



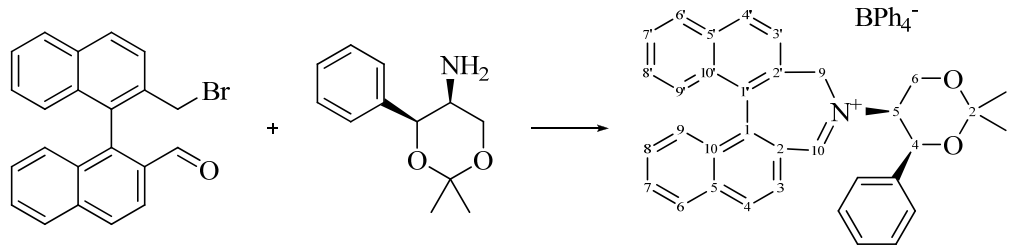
48 ***11*** ***49***

To an ice cooled solution of (*R*)-2,2'-bis-bromomethyl-[1,1']binaphthalenyl (**48**) (0.79 g, 1.80 mmol) in tetrahydrofuran (10 mL), a solution of acetonide (**11**) (0.41 g, 2.50 mmol) and triethylamine (0.20 g, 2.00 mmol) in tetrahydrofuran (10 mL) was added and allowed to warm to ambient temperature over 16 h. The reaction mixture was extracted from water (3 *x* 50 mL) and saturated brine (3 *x* 50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to leave a yellow/brown foam, which was purified by column chromatography using a light petrol/ethyl acetate eluent (97:3) to yield the amine as a colourless foam (**49**) (0.86 g, 1.77 mmol, 98%). ν_{max}(film) /cm^{-1} 3051, 1683, 1506, 1451, 1378, 1263, 1198, 1079, 819, 737, 698. Lit. $[\alpha]^{20}_{D}$ −339 ° (*c* 1.00, $CHCl_3$), $[\alpha]^{20}_{D}$ −345 ° (*c* 1.10, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 1.48 (3 H, s, C^{7}H$_3$), 1.59 (3 H, s, C^{8}H$_3$), 2.55 (1 H, s, NC^{5}H), 3.24 (2 H, d, *J* 12.4 Hz, upfield portions of

ABX systems 2 *x* NC$^{9/10}$HH), 3.80 (2 H, d, *J* 12.4 Hz, downfield portions of ABX systems 2 *x* NC$^{9/10}$HH), 3.97 (1 H, d, *J* 12.4 Hz, upfield portion of ABX system, OC^{6}HH), 4.07 (1 H, dd, *J* 3.2 & 12.4 Hz, downfield portion of ABX system, OC^{6}HH), 5.03 (1 H, d, *J* 3.2 Hz, OC^{4}HPh), 7.03 – 7.07 (2 H, m, 2 *x* Ar-CH), 7.11 – 7.19 (3 H, m, 3 *x* Ar-CH), 7.22 – 7.27 (6 H, m, 6 *x* Ar-CH), 7.31 (2 H, d, *J* 8.0 Hz, 2 *x* Ar-CH), 7.69 – 7.74 (4 H, m, *4 x* Ar-CH). δ_C (100 MHz; $CDCl_3$) 17.9 (C^{7}H$_3$), 28.8 (C^{8}H$_3$), 52.3 (2 *x* NC$^{9/10}$H$_2$), 58.7 (NC^{5}H), 60.7 (OC^{6}H$_2$), 73.9 (C^{4}HPh), 98.2 (quat.C^{2}(CH$_3$)$_2$), 124.0 (2 *x* Ar-CH), 124.3 (2 *x* Ar-CH), 125.3 (2 *x* Ar-CH), 125.7 (Ar-CH, *para* in Ph group), 126.3 (2 *x* Ar-CH), 126.5 (2 *x* Ar-CH), 126.7 (2 *x* Ar-CH), 127.0 (2 *x* Ar-CH), 127.3 (2 *x* Ar-CH), 130.1 (2 *x* *Binap*-quat.C), 131.7 (2 *x* *Binap*-quat.C), 133.5 (2 *x* *Binap*-quat.C), 133.7 (2 *x* *Binap*-quat.C), 139.2 (quat.Ar-C). *m/z* 486.2431; $C_{34}H_{31}NO_2[M+H]^+$ requires 486.2433.

(*R*)-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-3 H-4-azapinium-cyclohepta (2,1-a;3,4-a')dinaphthalene tetraphenylborate.[8]

Method A

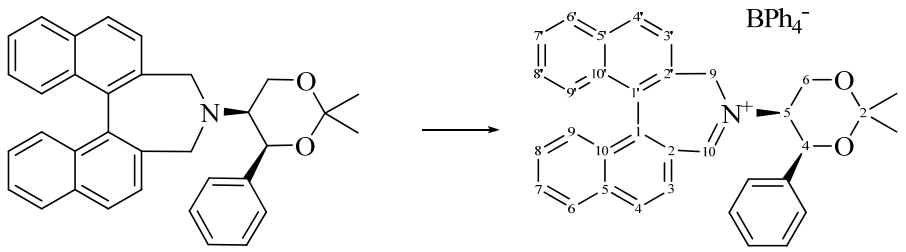


106 ***11*** ***3***

To an ice cooled solution of (*R*)-2'-Bromomethyl-[1,1']binaphthalenyl-2-carbaldehyde (**106**) (0.72 g, 1.91 mmol) in ethanol (8 mL), a solution of amine **11** (0.38 g, 1.84 mmol)

in ethanol (5 mL) was added and allowed to warm to ambient temperature over 16 h. Sodium tetraphenylborate (0.69 g, 1.91 mmol) was dissolved in the minimal amount of acetonitrile (approximately 5 mL). This solution was subsequently added to the reaction mixture and, after approximately 5 min, gave a yellow precipitate. Ethanol, followed by water, was then added to the reaction mixture. The mixture was then filtered, washed with cold ethanol, cold water and diethyl ether giving the desired yellow crystals (**3**) (1.01 g, 1.25 mmol, 68%).

Method B

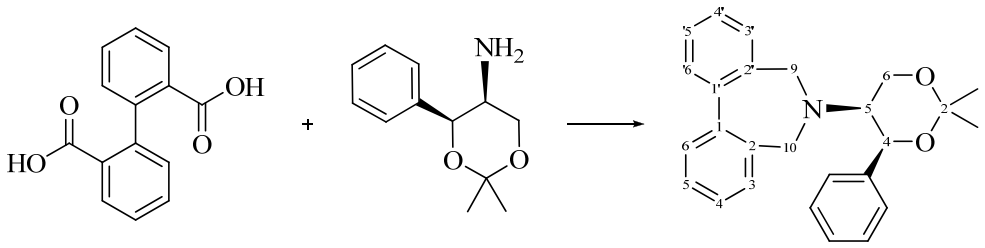


49 ***3***

N-Bromosuccinimide (0.35 g, 1.95 mmol) was added to a solution of amine **49** (0.87 g, 1.77 mmol) in $CHCl_3$ (10 mL). The reaction was stirred under reflux for 5 min. The solution was cooled to ambient temperature and extracted from water (3 *x* 50 mL), saturated brine (3 *x* 50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, the resulting yellow foam was dissolved in ethanol and cooled to 0 °C. Sodium tetraphenylborate (0.86 g, 2.5 mmol) was dissolved in the minimal amount of acetonitrile (approximately 5 mL), this solution was subsequently added to the reaction mixture and allowed to warm to ambient temperature to give a yellow precipitate. Ethanol followed by water was added to the reaction mixture. The mixture was then filtered, washed with cold ethanol, cold water and diethyl ether giving the desired yellow crystals (**3**) (0.68 g , 1.2 mmol, 68%). ν_{max}(film) /cm^{-1} 3053, 2995, 2358, 1610, 1382, 1110, 751, 733, 704. Lit. mp 111 – 113 °C, m.p. 111 – 113 °C. $[\alpha]^{20}_D$ – 341 ° (*c* 1.07,

$CHCl_3$). δ_H (400 MHz; $CDCl_3$) 1.67 (3 H, s, $C^8\underline{H}_3$), 1.72 (3 H, s, $C^7\underline{H}_3$), 4.32 (1 H, d, *J* 13.6 Hz, upfield portion of *AB*X system, *biphenyl*-$C^9\underline{H}$HN), 4.46 (1 H, d, *J* 13.2 Hz, $OC^6\underline{H}H$), 4.655 (1 H, s, upfield portion of *AB*X system, $OC^6H\underline{H}$), 4.72 (1 H, dt, *J* 14 Hz, $NC^5\underline{H}$), 5.85 (2 H, m, $C^4\underline{H}$Ph), 6.83 (1 H, d, *J* 8.8 Hz, Ar-$C^{14}\underline{H}$ *para* in Ph group), 6.91 (2 H, t, *J 8.8 Hz,* Ar-$C^{13\&15}\underline{H}$ *meta* in Ph group), 6.62 (4 H, t, *J* 7.2 Hz, Ar-C<u>H</u> *para* in BPh_4^-), 6.77 (8 H, t, *J* 7.6 Hz, Ar-C<u>H</u> *ortho* in BPh_4^-), 7.14 (2 H, t, *J* 8.4 Hz, Ar-$C^{12\&16}\underline{H}$ *ortho* in Ph group), 7.20 (10 H, m, 8 *x* Ar-C<u>H</u> *meta* in BPh_4^- & 2 *x* *Binap*-C<u>H</u>), 7.32 (2 H, d, *J* 3.6 Hz, *Binap*-C<u>H</u>), 7.37 (1 H, d, *J* 8.8 Hz, *Binap*-C<u>H</u>), 7.44 (1 H, t, *J* 7.2 Hz, *Binap*-C<u>H</u>), 7.67 (1 H, m, *Binap*-C<u>H</u>), 7.74 (1 H, d, *J* 8.4 Hz, *Binap*-C<u>H</u>), 7.96 (1 H, d, *J* 8.0 Hz, *Binap*-C<u>H</u>), 8.04 (1 H, d, *J* 8.0 Hz, *Binap*-C<u>H</u>), 8.09 (2 H, d, *J* 8.4 Hz, *Binap*-C<u>H</u>), 9.03 (1 H, s, N=$C^{10}\underline{H}$). δ_C (100 MHz; $CDCl_3$) 18.9 ($\underline{C}^7H_3$), 29.0 ($\underline{C}^8H_3$), 57.0 (NC^9H_2Ph), 61.9 ($O\underline{C}^6H_2$), 68.2 ($N\underline{C}^5$H), 72.6 ($O\underline{C}^4$HPh), 101.7 (quat.$\underline{C}^2$), 116.0 (*Binap*-quat.$\underline{C}^2$), 122.3 (4 *x* Ar-$\underline{C}^{14}$H, *para* in BPh_4^-), 126.0 (8 *x* Ar-<u>C</u>H, *ortho* in BPh_4^-), 126.2 (*Binap*-quat.$\underline{C}^{10}$), 126.9 (*Binap*-quat.$\underline{C}^{5'}$), 127.8 (2 *x* *Binap*-$\underline{C}^{7'\&8'}$H), 128.0 (2 *x* Ar-$\underline{C}^{12\&16}$H, *ortho* in Ph group), 128.2 (Ar-<u>C</u>H, *para* in Ph group), 128.7 (2 *x* Ar-$\underline{C}^{13\&15}$H, *meta* in Ph group), 129.5 (2 *x* *Binap*-$\underline{C}^{7\&8}$H), 129.6 (*Binap*-$\underline{C}^3$H), 129.7 (*Binap*-$\underline{C}^{4'}$H), 129.7 (2 *x* *Binap*-$\underline{C}^{6\&9}$H), 130.2 (*Binap*-$\underline{C}^4$H), 130.2 (*Binap*-quat.$\underline{C}^{9'}$), 130.3 (*Binap*-$\underline{C}^{6'}$H), 131.6 (*Binap*-$\underline{C}^{3'}$H), 132.2 (*Binap*-quat.$\underline{C}^{10'}$), 132.9 (*Binap*-quat.$\underline{C}^5$), 136.3 (*Binap*-quat.$\underline{C}^{2'}$), 136.6 (*Binap*-quat.$\underline{C}^{1'}$), 137.2 (*Binap*-quat.$\underline{C}^1$), 137.1 (8 *x* Ar-<u>C</u>H, *meta* in BPh_4^-), 142.4 (quat.Ar-$\underline{C}^{11}$, *ipso* in Ph group), 164.2, 164.7, 165.2, 165.8 (4 *x* quat.<u>C</u> *ipso* in BPh_4^-, *J* 152 Hz), 171.4 (N=$\underline{C}^{10}$H).

6-(2,2-Dimethyl-4-phenyl-(1,3)dioxan-5-yl)-dibenzo-(*c*,*e*)-azepine-5,7-dione.



107 ***11*** ***108***

Diphenic acid (**107**) (0.50 g, 2.10 mmol) was added to a solution of the acetonide (**11**) (0.43 g, 2.10 mmol) in chloroform (10 mL). The solution was heated under reflux for 3 h. The solution was then allowed to cool down to ambient temperature and the solvent was removed under reduced pressure. The crude reaction mixture was dissolved in a saturated aqueous solution of $NaSO_4$ (5 mL) in acetic anhydride (50 mL) and was heated under reflux for 30 min, hot water was then added. The solution was allowed to cool down to ambient temperature, the crude compound was then extracted with DCM (3 *x* 20 mL), the combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting dark yellow powder was re-crystallized from methanol to yield the desired imide as a yellow powder (**108**) (0.71 g, 1.70 mmol, 81%). ν_{max}(film) /cm^{-1} 3059, 2994, 1700 (C =O), 1520, 1451, 1418, 1382, 1273, 1240, 1200, 1120, 1044, 955, 842, 755, 701. $[\alpha]^{20}_{D}$ +182 ° (*c* 1.00, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 1.06 (3 H, s, C^{8}H$_3$), 1.35 (3 H, s, C^{7}H$_3$), 2.73 (1 H, s, NC^{5}H), 3.85 (2 H, q, *J* 12.4 Hz, OC^{6}H$_2$), 4.90 (1 H, s, OC^{4}HPh), 7.11 (2 H, t, *J* 7.2 Hz, Ar-CH), 7.18 – 7.15 (6 H, m, Ar-CH), 7.22 – 7.36 (5 H, m, Ar-CH). δ_C (100 MHz; $CDCl_3$) 17.24 (C^{7}H$_3$), 28.06 (C^{8}H$_3$), 48.08 (NC^{5}H), 60.84 (OC^{6}H$_2$), 70.15 (OC^{4}HPh), 99.06 (quat.C^2), 125.3 (2 *x* Ar-CH), 125.7 (2 *x* Ar-CH), 127.7 (Ar-C^{12}H *para* in phenyl group), 128.0 (2 *x* Ar-CH), 128.03 (2 *x* Ar-CH), 129.3 (2 *x* Ar-CH), 130.1 (2 *x* Ar-CH), 133.6 (2 *x Biphenyl*-quat.C), 134.9 (quat.C^9, *ipso* on phenyl ring), 140.7 (2 *x Biphenyl*-quat.C), 172.3 (2 *x* C=O).

General procedure for the addition of Grignard reagents to biphenyl azepinium salts.

The desired azepinium salt (1 equiv) was dissolved in anhydrous THF (30 mL per g) under nitrogen and cooled to −78 °C. The desired Grignard reagent (3 equiv) was added dropwise over 5 min to the cold solution. The reaction was then allowed to warm to ambient temperature and stirred for 2 h. The reaction was then cooled to 0 °C and quenched with Rochelle's salt. The reaction was allowed to warm to ambient temperature where it was extracted with water, saturated brine and dried over $MgSO_4$. The solution was filtered and silica was added, the solvent was removed under reduced pressure. The crude reaction mixture was purified *via* column chromatography using 1:99 (ethyl acetate/petrol) to yield the desired amine.

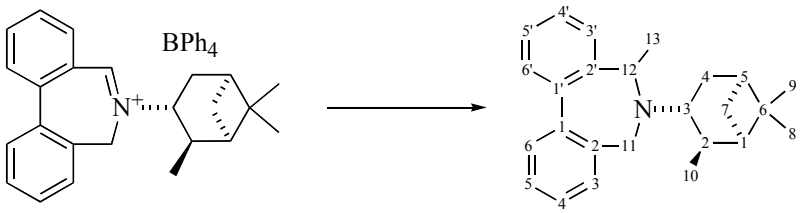
General procedure for the synthesis of biphenyl azepinium bromide salts from heterocyclic amines and *N*-bromosuccinimide.

To a solution of the desired amine (1 equiv) in DCM (15 mL g of amine) was added *N*-bromosuccinimide (1.1 equiv) in DCM (15 mL per g of NBS) and the reaction mixture was refluxed for 2 h. The reaction was cooled to ambient temperature when it was then extracted with water, saturated brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield the crude bromide iminium salt. Recrystalisation from diethyl ether gave the purified biphenyl azepinium bromide salt

.General procedure for the synthesis of biphenyl azepinium tetraphenylborate salts from biphenyl azepinium bromide salts.

To a ice cooled solution of the desired biphenyl azepinium salt (1 equiv) in DCM was added sodium tetraphenylborate (1.2 equiv) dissolved in the minimal amount of acetonitrile (approximately 5 mL). The reaction mixture was stirred whilst attaining ambient temperature over 10 min forming a yellow precipitate. The precipitate was filtered, washed with cold ethanol, cold water and diethyl ether to yield the desired yellow crystals.

5-Methyl-6-(2,6,6-trimethyl-bicyclo(3.1.1)hept-3-yl)-6,7-dihydro-5H-dibenzo-(*c*,*e*)-azepine.

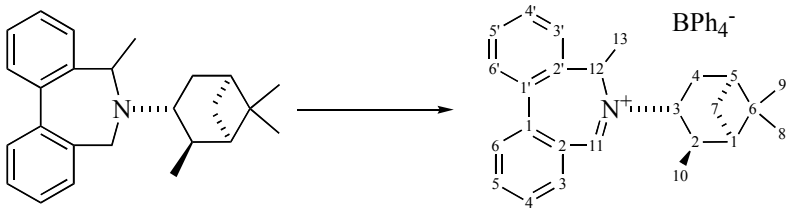


30 ***33***

Prepared according to the general procedure from (+)-6-[(1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]-5*H*-dibenzo[*c*,*e*]azepinium tetraphenylborate (**30**) (0.50 g, 0.77 mmol) and methyl magnesium bromide (0.28 mL, 0.85 mmol). The purified amine was isolated as a colourless oil, as a pair of diastereoisomers (**33**) (0.16 g, 0.61 mmol, 79%). ν_{max}(film) /cm^{-1} 3057, 3054, 2923, 2359, 2339, 1627, 1596, 1558, 1472, 1448, 1424, 1387, 1261, 1091, 1031, 799, 734, 703, 667. $[\alpha]^{20}_{D}$ +81.3 ° (*c* 0.30,

$CHCl_3$). δ_H (400 MHz; DMSO 90 °C) 0.74 (3 H, d, *J* 11.6 Hz, minor $C^{13}\underline{H}_3$), 0.78 (3 H, d, *J* 11.6 Hz, major $C^{13}\underline{H}_3$), 0.95 (3 H, s, major $C^{9}\underline{H}_3$), 0.96 (3 H, s, minor $C^{9}\underline{H}_3$), 1.00 (1 H, d, *J* 10.0 Hz, upfield portion of ABX system, minor $C^{11}\underline{H}H$), 1.06 (7 H, dd, *J* 6.8 & 9.2 Hz, major and minor $C^{10}\underline{H}_3$ and upfield portion of ABX system, major $C^{11}\underline{H}H$), 1.31 (3 H, s, minor $C^{8}\underline{H}_3$), 1.41 (3 H, s, major $C^{8}\underline{H}_3$), 1.72 – 1.86 (6 H, m, major & minor $C^{1}\underline{H}$ and major & minor $C^{7}\underline{H}\underline{H}$), 2.00 – 2.15 (4 H, m, major & minor $C^{2}\underline{H}$ and major & minor $C^{5}\underline{H}$), 2.21 – 2.34 (2 H, m, downfield portion of ABX system, major & minor $C^{11}H\underline{H}$), 3.29 – 3.41 (2 H, m, major & minor $C^{3}\underline{H}$), 3.42 (1 H, d, *J* 11.2 Hz, minor $C^{4}\underline{H}H$), 3.51 (1 H, s, major $C^{4}H\underline{H}$), 3.52 (1 H, s, minor $C^{4}H\underline{H}$), 3.59 (1 H, d, *J* 11.2 Hz, major $C^{4}\underline{H}H$), 4.00 (1 H, q, *J* 6.8 Hz, minor $C^{12}\underline{H}$), 4.14 (1 H, q, *J* 7.2 Hz, major $C^{12}\underline{H}$), 7.19 – 7.32 (12 H, m, major and minor *Biphenyl*-C$\underline{H}$), 7.34 – 7.40 (4 H, m, major and minor *Biphenyl*-C$\underline{H}$). δ_C (100 MHz; DMSO 90 °C) 20.2 (major $\underline{C}^{10}H_3$), 21.4 (minor $\underline{C}^{10}H_3$), 22.2 (minor $\underline{C}^{9}H_3$), 22.4 (major $\underline{C}^{9}H_3$), 23.4 (major & minor $\underline{C}^{13}H_3$), 27.0 (major $\underline{C}^{8}H_3$), 27.2 (minor $\underline{C}^{8}H_3$), 28.6 (major $\underline{C}^{7}H_2$), 29.7 (minor $\underline{C}^{7}H_2$), 32.0 (major $\underline{C}^{11}H_2$), 32.8 (minor $\underline{C}^{11}H_2$), 38.2 (major quat.$\underline{C}^{6}$), 38.4 (major quat.$\underline{C}^{6}$), 39.8 (major $\underline{C}^{2}H$), 40.2 (minor $\underline{C}^{2}H$), 40.7 (minor $\underline{C}^{5}H$), 40.8 (major $\underline{C}^{5}H$), 47.0 (major $\underline{C}^{1}H$), 47.3 (minor $\underline{C}^{1}H$), 49.8 (major & minor $\underline{C}^{4}H_2$), 56.8 (major $\underline{C}^{12}H$), 61.2 (minor $\underline{C}^{12}H$), 63.7 (minor $\underline{C}^{3}H$), 65.0 (major $\underline{C}^{3}H$), 125.8 (minor *Biphenyl*-$\underline{C}^{a}H$), 126.0 (major *Biphenyl*-$\underline{C}^{a}H$), 126.1 (major *Biphenyl*-$\underline{C}^{b}H$), 126.2 (minor *Biphenyl*-$\underline{C}^{b}H$), 126.61 (major *Biphenyl*-$\underline{C}^{c}H$), 126.64 (minor *Biphenyl*-$\underline{C}^{c}H$), 126.80 (major *Biphenyl*-$\underline{C}^{d}H$), 126.82 (minor *Biphenyl*-$\underline{C}^{d}H$), 126.9 (major and minor *Biphenyl*-$\underline{C}^{e}H$), 127.6 (minor *Biphenyl*-$\underline{C}^{f}H$), 127.7 (major *Biphenyl*-$\underline{C}^{f}H$), 128.46 (major *Biphenyl*-$\underline{C}^{g}H$), 128.51 (minor *Biphenyl*-$\underline{C}^{g}H$), 128.6 (major and minor *Biphenyl*-$\underline{C}^{H}H$), 136.5 (major and minor *Biphenyl*-quat.$\underline{C}^{i}$), 138.1 (major *Biphenyl*-quat.$\underline{C}^{j}$), 138.3 (minor *Biphenyl*-quat.$\underline{C}^{j}$), 139.86 (major *Biphenyl*-quat.$\underline{C}^{k}$), 139.92 (minor *Biphenyl*-quat.$\underline{C}^{k}$), 140.65 (major *Biphenyl*-quat.$\underline{C}^{l}$), 140.75 (minor *Biphenyl*-quat.$\underline{C}^{l}$). *m/z*; $C_{25}H_{31}N$ requires 345.5203.

5-Methyl-6-(2,6,6-trimethyl-bicyclo(3.1.1)hept-3-yl)-5*H*-dibenzo-(*c*,*e*)-azepinium tetraphenylborate.

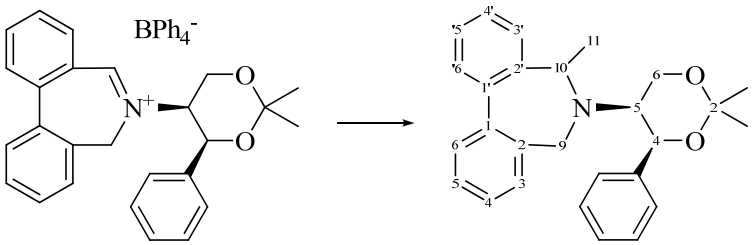


33 ***34***

Prepared according to the general procedure from the desired methylated amine (**33**) (0.16 g, 0.61 mmol) and *N*-bromosuccinimide (0.11 g, 0.61 mmol) to yield the desired yellow crystaline tetraphenylborate azepinium salt as a pair of diastereoisomers (**34**) (0.29 g, 0.43 mmol, 71%). mp 220 – 222 °C (dec.)ν_{max}(film) /cm^{-1} 3397, 3055, 2995, 2924, 2360, 2339, 1628, 1597, 1479, 1448, 1426, 1387, 1262, 1218, 1155, 1119, 1031, 757, 736, 703, 667. $[\alpha]^{20}_{D}$ +56.3 ° (*c* 0.98, $CHCl_3$). δ_H (400 MHz; DMSO 90 °C) 0.89 (3 H, d, *J* 6.8 Hz, minor NCHC^{13}H$_3$), 1.10 (1 H, d, *J* 7.2 Hz, minor C^{1}H), 1.15 (6H, s, major & minor C^{8}H$_3$), 1.21 (3 H, d, *J* 6.8 Hz, major NCHC^{13}H$_3$), 1.26 (3 H, d, *J* 6.8 Hz, major C^{10}H$_3$), 1.30 (3 H, d, *J* 6.8 Hz, minor C^{10}H$_3$), 1.35 (6H, s, major & minor C^{9}H$_3$), 1.512 (2 H, m, major C^{1}H & minor C^{7}HH), 1.98 − 2.01 (1 H, m, minor C^{5}H), 2.05 − 2.08 (2 H, m, major C^{7}HH & minor C^{4}HH), 2.12 − 2.13 (2 H, m, major C^{7}HH & minor C^{7}HH), 2.16 − 2.20 (1 H, m, major C^{5}H), 2.29 – 2.34 (1 H, m, major C^{4}HH) 2.55 − 2.71 (4 H, m, major & minor C^{2}H and minor & minor C^{4}HH), 5.01 − 5.08 (2 H, m, minor major NC^{12}HMe & minor C^{3}H), 5.68 − 5.73 (2 H, m, minor NC^{12}HMe & major C^{3}H), 6.79 (6 H, t, *J* 7.2 Hz, Ar-CH, *para* in BPh_4^-), 6.92 (12 H, t, 7.4 Hz, Ar-CH, *ortho* in BPh_4^-), 7.20 − 7.26 (12 H, broad s, Ar-CH, *meta* in BPh_4^-), 7.65 − 7.67 (4 H, m, *Biphenyl*-CH), 7.80 – 7.84 (1 H, m, *Biphenyl*-CH), 7.86 (1 H, m, *Biphenyl*-CH), 8.01 (1 H, m, *Biphenyl*-CH), 8.11 – 8.14 (2 H, m, *Biphenyl*-CH), 8.18 – 8.20 (1 H, m, *Biphenyl*-CH), 9.77 (1 H, s, major N=C^{11}H), 9.79 (1 H, s, minor N=C^{11}H). δ_C (100 MHz; DMSO 90 °C) 16.0 (minor NCHC^{13}H$_3$), 16.1 (major NCHC^{13}H$_3$), 18.0 (minor C^{8}H$_3$), 18.6 (major C^{8}H$_3$), 21.3 (minor C^{9}H$_3$), 22.2

(major $\underline{C}^{9}H_3$), 27.6 (major $\underline{C}^{10}H_3$), 27.9 (minor $\underline{C}^{10}H_3$), 33.0 ($\underline{C}^{7}H_2$), 33.5 (minor N$\underline{C}^{12}$HMe), 33.6 (major N$\underline{C}^{12}$HMe), 47.06 (minor $\underline{C}^{1}$H) 47.08 (major $\underline{C}^{1}$H), 74.1 (minor $\underline{C}^{3}$H), 74.8 (major $\underline{C}^{3}$H), 120.7 (16 *x* Ar-CH, *ortho* in BPh_4^-), 124.4 (8 *x* Ar-CH, *para* in BPh_4^-), 128.02 (minor *Biphenyl*-quat.$\underline{C}^{2}$), 128.04 (major *Biphenyl*-quat.$\underline{C}^{2}$), 128.3 (minor *Biphenyl*-$\underline{C}^{4}$H), 128.6 (major *Biphenyl*-$\underline{C}^{4}$H), 128.80 (*Biphenyl*-$\underline{C}^{6}$H), 128.83 (minor *Biphenyl*-$\underline{C}^{3}$H), 128.9 (major *Biphenyl*-$\underline{C}^{3}$H), 129.52 (minor *Biphenyl*-$\underline{C}^{5}$H), 129.54 (major *Biphenyl*-$\underline{C}^{5}$H), 130.01 (minor *Biphenyl*-$\underline{C}^{4'}$H), 130.03 (major *Biphenyl*-$\underline{C}^{4'}$H), 130.05 (minor *Biphenyl*-$\underline{C}^{6'}$H), 130.07 (major *Biphenyl*-$\underline{C}^{6'}$H), 134.3 (major & minor *Biphenyl*-quat.$\underline{C}^{1}$), 134.69 (minor *Biphenyl*-quat.$\underline{C}^{5'}$), 134.71 (major *Biphenyl*-quat.$\underline{C}^{5'}$), 135.1 (16 *x* Ar-CH, *meta* in BPh_4^-), 135.6 (minor *Biphenyl*-quat.$\underline{C}^{1'}$), 135.7 (major *Biphenyl*-quat.$\underline{C}^{1'}$), 164.5 (8 *x* C quat., arom., *J* 196.40 Hz, C-B *ipso* in BPh_4 ring), 171.2 (H$\underline{C}$=N). *m/z*; $C_{25}H_{30}N^+$ (cation) requires 344.2373.

6-(2,2-Dimethyl-4-phenyl-(1,3)dioxan-5-yl)-5-methyl-6,7-dihydro-5*H*-dibenzo-(*c*, *e*)-azepine.



7 ***36***

Method A

Prepared according to the general procedure from 6-(2,2-Dimethyl-4-phenyl-

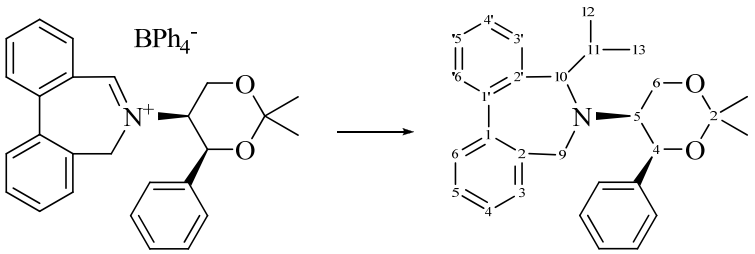
[1,3]dioxan-5-yl)-5*H*-dibenzo[*c*,*e*]azepinium (**7**) (0.35 g, 0.76 mmol) and methyl magnesium chloride (2.3 mL, 0.77 mmol) to yield the desired methylated amine as a colourless oil (**36**) (0.28 g, 0.69 mmol, 91%).

Method B

Prepared according to the general procedure from 6-(2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-5*H*-dibenzo[*c*,*e*]azepinium (**7**) (0.35 g, 0.76 mmol) and methyl magnesium bromide (2.3 mL, 0.77 mmol) to yield the desired methylated amine as a colourless oil (**36**) (0.24 g, 0.60 mmol, 79%).

ν_{max}(film) /cm^{-1} 3413, 3062, 3025, 2987, 2927, 2859, 2775, 2358, 1956, 1604, 1479, 1449, 1377, 1263, 1238, 1196, 1147, 1084, 956, 940, 852, 803, 755, 736, 695. $[\alpha]^{20}_{D}$ +30.3 ° (*c* 0.30, $CHCl_3$). δ_H (400 MHz; $CDCl_3$ 55 °C) 0.68 (3 H, d, *J* 7.0 Hz, C^{11}H$_3$), 1.64 (3 H, s, C^{7}H$_3$), 1.69 (3 H, s, C^{8}H$_3$), 3.19 (1 H, q, *J* 4.1 Hz, NC^{5}H), 3.79 (2 H, s, NC^{9}HH), 4.20 (1 H, dd, *J* 2.4 & 12.4 Hz, OC^{6}HH), 4.32 (2 H, dd, *J* 4.8 & 12.3 Hz, OC^{6}HH & OC^{10}HCH$_3$), 5.31 (1 H, s, C^{4}HPh), 7.18 – 7.14 (2 H, m, *Biphenyl*-CH), 7.36 – 7.29 (3 H, m, *Biphenyl*-CH), 7.45 – 7.37 (5 H, m, *Biphenyl*-CH), 7.49 (1 H, dd, *J* 1.4 & 7.6 Hz, *Biphenyl*-CH), 7.53 (2 H, d, *J* 7.3 Hz, *Biphenyl*-CH). δ_C (100 MHz; $CDCl_3$ 55 °C) 19.6 (C^{7}H$_3$), 21.2 (C^{11}H$_3$), 29.1 (C^{8}H$_3$), 53.7 (NC^{9}HH), 58.6 (NC^{5}H), 58.8 (C^{10}HCH$_3$), 63.2 (OC^{6}HH), 74.4 (C^{4}HPh), 99.4 (quat.C^{2}(CH$_3$)$_2$), 126.3 (2 *x Biphenyl*-CH), 126.6 (*Biphenyl*-CH), 127.0 (*Biphenyl*-CH), 127.1 (*Biphenyl*-CH), 127.4 (*Biphenyl*-CH), 127.6 (*Biphenyl*-CH), 127.7 (2 *x Biphenyl*-CH), 127.8 (*Biphenyl*-CH), 128.4 (*Biphenyl*-CH), 128.5 (*Biphenyl*-CH), 128.9 (*Biphenyl*-CH), 138.1 (quat.*Biphenyl*-C), 139.5 (quat.*Biphenyl*-C), 140.4 (quat.*Biphenyl*-C), 141.3 (quat.*Biphenyl*-C), 141.4 (quat.*Biphenyl*-C). *m/z* 398.21268 [- 1.7 ppm]; $C_{27}H_{29}N$ requires 399.2198.

6-(2,2-Dimethyl-4-phenyl-(1,3)dioxan-5-yl)-5-isopropyl-6,7-dihydro-5*H*-dibenzo-(*c*, *e*)-azepine.

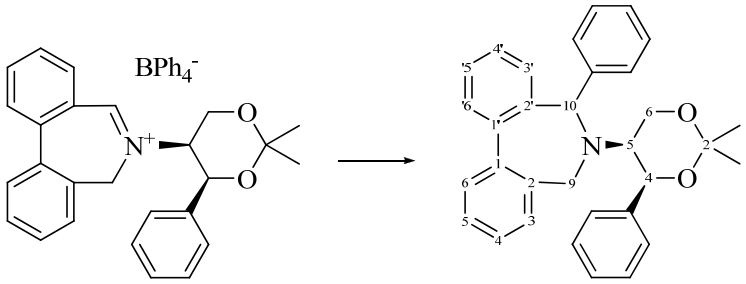


7 ***37***

Prepared according to the general procedure from 6-(2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-5*H*-dibenzo[*c*,*e*]azepinium (**7**) (0.35 g, 0.76 mmol) and isopropyl magnesium chloride (2.30 mL, 0.77 mmol) to yield the desired alkylated amine as a colourless oil (**37**) (0.20 g, 0.47 mmol, 62%). ν_{max}(film) /cm^{-1} 3359, 3060, 2957, 2920, 2855, 2358, 2336, 1726, 1711, 1692, 1661, 1608, 1551, 1535, 1514, 1449, 1378, 1260, 1197, 1080, 850, 800, 754, 697. $[\alpha]^{20}_{D}$ +98.3 ° (*c* 0.96, $CHCl_3$). δ_H (400 MHz; $CDCl_3$ 55 °C) 0.12 (3 h, d, *J* 6.0 Hz, C^{12}H$_3$), 0.74 (1 H, m, C^{11}H(CH$_3$)$_2$), 0.82 (3 H, d, *J* 6.0 Hz, C^{13}H$_3$), 1.61 (3 H, s, C^{7}H$_3$), 1.68 (3 H, s, C^{8}H$_3$), 3.05 (1 H, m, NC^{5}H), 3.37 (1 H, d, *J* 10.0 Hz, C^{10}HPr^{i}), 3.66 (1 H, d, *J* 11.6 Hz, NC^{9}HH), 4.28 (1 H, d, *J* 12.0 Hz, NC^{9}HH), 4.42 (1 H, d, *J* 12.0 Hz, OC^{6}HH) 4.49 (1 H, dd, *J* 4.0 & 12.4 Hz, OC^{6}HH), 5.26 (1 H, d, *J* 2.8 Hz, C^{4}HPh), 6.32 (1 H, d, *J* 7.6 Hz, Ar-CH, *ortho* in phenyl gp), 7.10 – 7.07 (1 H, m, Ar-CH, *para* in phenyl gp), 7.23 (1 H, d, *J* 7.2 Hz, Ar-CH, *ortho* in phenyl gp), 7.27 – 7.36 (8 H, m, *Biphenyl*-CH), 7.47 – 7.46 (2 H, m, 2 *x* Ar-CH, *meta* in phenyl gp). δ_C (100 MHz; $CDCl_3$ 55 °C) 18.4 (C^{8}H$_3$), 19.5 (C^{13}H$_3$), 20.2 (C^{12}H$_3$), 28.0 (C^{7}H$_3$), 33.5 (C^{11}H(CH$_3$)$_2$), 51.9 (NC^{9}H$_2$), 62.4 (NC^{5}H), 65.5 (OC^{6}H$_2$), 74.4 (C^{4}HPh), 75.7 (C^{10}HPr^{i}), 98.5 (quat.C^{2}), 125.4 (*Biphenyl*-CH), 125.6 (*Biphenyl*-CH), 125.7 (*Biphenyl*-CH Ar-CH), 125.9 (*Biphenyl*-CH), 126.0 (*Biphenyl*-CH), 126.3 (2 *x* Ar-CH in phenyl gp), 126.5 (Ar-CH, *para* in phenyl gp), 126.8 (2 *x* Ar-CH in phenyl gp), 127.2 (*Biphenyl*-CH), 127.6 (*Biphenyl*-CH), 130.3 (*Biphenyl*-CH), 137.1 (quat.Ar-C), 137.3 (quat.Ar-C), 138.1

(quat.Ar-C), 139.4 (quat.Ar-C), 140. 5 (quat.Ar-C). *m/z* 426.2439 [- 1.5 ppm]; $C_{29}H_{33}NO_2$ requires 427.5781.

6-(2,2-Dimethyl-4-phenyl-(1,3)dioxan-5-yl)-5-phenyl-6,7-dihydro-5*H*-dibenzo-(*c*, *e*)-azepine.



7 ***38***

Method A

Prepared according to the general procedure from 6-(2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-5*H*-dibenzo[*c*,*e*]azepinium (**7**) (0.50 g, 1.10 mmol) and phenyl magnesium bromide (1.10 mL, 3.30 mmol) to yield the desired alkylated amine as a colourless oil (**38**) (0.24 g, 0.52 mmol, 47%).

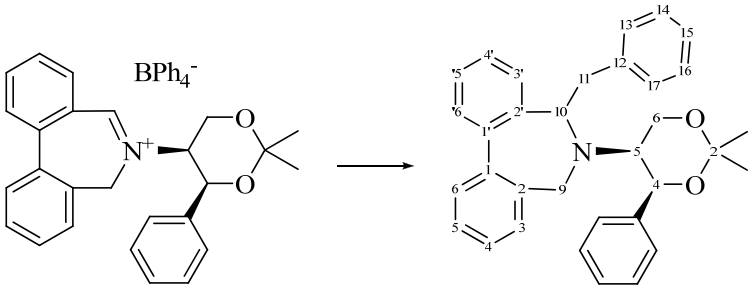
Method B

Prepared according to the general procedure from 6-(2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-5*H*-dibenzo[*c*,*e*]azepinium (**7**) (0.50 g, 1.10 mmol) and phenyl

magnesium chloride (1.10 mL, 3.30 mmol) to yield the desired alkylated amine as a colourless oil (**30**) (0.20g, 0.43 mmol, 40%).

ν_{max}(film) /cm^{-1} 3343, 2987, 2988, 2854, 2366, 1656, 1638, 1598, 1479, 1444, 1371, 1343, 1322, 1265, 1240, 1197, 1176, 1150, 1136, 1801, 1064, 1026, 1008, 955, 921, 876, 852, 780, 763, 733, 697, 657, 610. $[\alpha]^{20}_{D}$ ° (*c*, $CHCl_3$). δ_H (400 MHz; $CDCl_3$ 55 °C) 1.50 (3 H, s, $C^7\underline{H}_3$), 1.57 (3 H, s, $C^8\underline{H}_3$), 2.99 (1 H, q, *J* 2.8 Hz, $NC^5\underline{H}$), 3.73 (1 H, d, *J* 11.6 Hz, $OC^6\underline{H}H$), 3.99 (1 H, d, *J* 12.0 Hz, $OC^6H\underline{H}$), 4.25 (2 H, d. *J* 2.4 Hz, $NC^9\underline{H}_2$), 5.20 (1 H, d, *J* 3.6 Hz, $OC^4\underline{H}$Ph), 5.42 (1 H, s, $NC^{10}\underline{H}$Ph), 6.21 (2 H, d, *J* 7.6 Hz, 2 *x* Ar-CH, *ortho* in phenyl 'A'), 6.55 (2 H, dt, *J* 6.4 & 1.6 Hz, 2 *x* Ar-CH, *meta* in phenyl 'A'), 6.62 (1 H, t, *J* 7.2 Hz, Ar-CH, *para* in phenyl 'A'), 6.80 (1 H, dt, *J* 1.6 & 7.6 Hz, *Biphenyl* 'A'-C<u>H</u>), 6.92 (1 H, dt, *J* 7.6 & 1.6 Hz, *Biphenyl* 'A'-C<u>H</u>), 7.02 (1 H, dt, *J* 7.6 & 1.6 Hz, *Biphenyl* 'A'-C<u>H</u>), 7.07 (1 H, dd, *J* 1.4 &7.8 Hz, *Biphenyl* 'A'-C<u>H</u>), 7.14 – 7.29 (9 H, m , 4 *x Biphenyl* 'B'-C<u>H</u> & 5 *x* phenyl 'B'-C<u>H</u>). δ_C (100 MHz; $CDCl_3$ 55 °C) 18.0 ($\underline{C}^7H_3$), 28.6 ($\underline{C}^8H_3$), 53.2 ($OC^6\underline{H}_2$), 28.9 ($NC^5\underline{H}$), 62.4 ($NC^9\underline{H}_2$), 66.9 ($NC^{10}\underline{H}$Ph), 73.5 ($OC^4\underline{H}$Ph), 98.4 (quat.$\underline{C}^2$), 123.4 (Ar-CH, *para* in phenyl 'A'), 125.0 (2 *x* Ar-<u>C</u>H), 125.3 (2 *x* Ar-CH, *meta* in phenyl 'A'), 125.4 (2 *x* Ar-CH, *ortho* in phenyl 'A'), 125.7 (2 *x* Ar-<u>C</u>H), 126.0 (*Biphenyl*-<u>C</u>H), 126.2 (*Biphenyl*-<u>C</u>H), 126.27 (*Biphenyl*-<u>C</u>H), 126.29 (Ar-<u>C</u>H), 126.31 (Ar-<u>C</u>H), 127.1 (Ar-<u>C</u>H), 127.5 (*Biphenyl*-<u>C</u>H), 128.0 (Ar-<u>C</u>H), 129.8 (Ar-<u>C</u>H), 136.6 (quat.Ar-<u>C</u>), 138.6 (quat.Ar-<u>C</u>), 139.2 (quat.Ar-<u>C</u>), 139.7 (2 *x* quat.Ar-<u>C</u>), 144.3(quat.Ar-<u>C</u>). *m/z* 461.2355 [- 1.2 ppm]; $C_{32}H_{31}NO_2$ requires 460.2272.

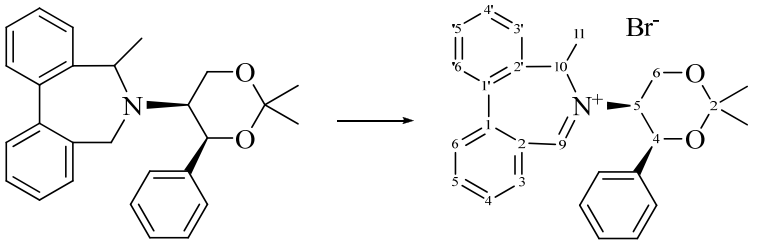
6-(2,2-Dimethyl-4-phenyl-(1,3)dioxan-5-yl)-5-phenyl-6,7-dihydro-5*H*-dibenzo-(*c*, *e*)-azepine.



7 ***31***

Prepared according to the general procedure from 6-(2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-5*H*-dibenzo[*c*,*e*]azepinium (**7**) (0.35 g, 0.76 mmol) and benzyl magnesium chloride (0.77 mL, 2.3 mmol) to yield the desired alkylated amine as a colourless oil (**31**) (0.21 g, 0.45 mmol, 60%). ν_{max}(film) /cm^{-1} 3414, 3060, 3024, 2989, 2935, 2856, 2359, 2339, 1602, 1495, 1481, 1450, 1379, 1348, 1309, 1263, 1237, 1198, 1177, 1147, 1080, 1029, 952, 852, 800, 778, 755, 736, 698, 668. $[\alpha]^{20}_{D}$ −11.8 ° (*c* 1.02, $CHCl_3$). δ_H (400 MHz; $CDCl_3$ 55 °C) 1.63 (3 H, s, C^{7}H$_3$), 1.72 (3 H, s, C^{8}H$_3$), 1.89 – 1.83 (1 H, m, C^{11}HH), 2.20 (1 H, dd, *J* 5.6 & 12.8 Hz, C^{11}HH), 3.00 (1 H, s, NC^{5}H), 3.78 (1 H, d, *J* 11.2 Hz, NC^{9}HH), 3.94 (1 H, d, *J* 11.2 Hz, NC^{9}HH), 4.17 (1 H, d, *J* 12.4 Hz, OC^{6}HH), 4.24 (1 H, dd, *J* 4.4 & 12.4 Hz, OC^{6}HH), 4.53 (1 H, dd, *J* 6.0 & 9.6 Hz, OC^{10}HBn), 5.28 (1 H, d, *J* 3.2 Hz, OC^{4}HPh), 6.63 (1 H, d, *J* 7.2 Hz, Ar-CH), 6.68 (2 H, d, *J* 7.6 Hz, Ar- CH), 7.01 – 7.09 (4 H, m, Ar- CH), 7.26 – 7.34 (3 H, m, Ar- CH), 7.35 – 7.40 (3 H, m, Ar- CH), 7.43 – 7.47 (2 H, m, Ar- CH), 7.52 – 7.54 (3 H, m, Ar- CH). δ_C (100 MHz; $CDCl_3$ 55 °C) 19.4 (C^{7}H$_3$), 29.4 (C^{8}H$_3$), 43.0 (C^{11}H$_2$), 54.2 (NC^{9}H$_2$), 60.9 (NCH), 63.8 (OC^{6}H$_2$), 68.3 (C^{10}HBn), 74.3 (OC^{4}HPh), 99.5 (quat.C^2), 125.3 (Ar-CH), 126.2 (2 *x* Ar-CH), 126.8 (Ar-CH), 127.1 (Ar-CH), 127.1 (Ar-CH), 127.4 (Ar-CH), 127.6 (2 *x* Ar-CH), 127.8 (Ar-CH), 127.9 (Ar-CH), 128.0 (2 *x* Ar-CH), 128.2 (Ar-CH), 129.18 (2 *x* Ar-CH), 129.21 (Ar-CH), 130.9 (Ar-CH), 137.9 (quat.C), 138.8 (quat.C), 139.0 (quat.C), 140.4 (2 *x* quat.C), 141.6 (quat.C). *m/z* 474.2426 [- 1.6 ppm]; $C_{33}H_{33}NO_2$ requires 475.2511.

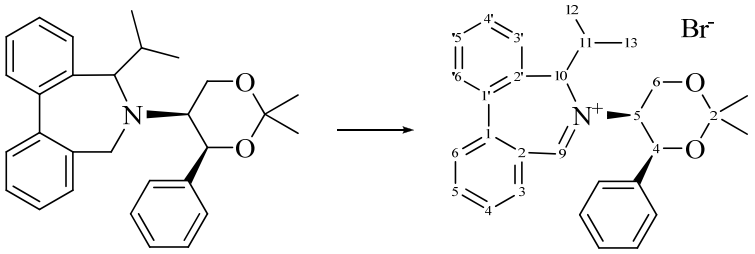
6-(2,2-Dimethyl-4-phenyl-(1,3)dioxan-5-yl)-5-methyl-5*H*-dibenzo-(*c*,*e*)-azepinium ; bromide.



36 ***40***

Prepared according to the general procedure from 6-(2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-5-methyl-6,7-dihydro-5*H*-dibenzo[*c, e*]azepine (**36**) (0.35 g, 0.89 mmol) and *N*-bromosuccinimide (0.17 g, 0.98 mmol) to yield the desired bromide azepinium salt as a yellow powder (**40**) (0.27g, 0.56 mmol, 63%). ν_{max}(film) /cm^{-1} 3364, 2987, 2359, 1709, 1640, 1595, 1558, 1486, 1449, 1384, 1265, 1202, 1080, 958, 835, 764, 729, 701. $[\alpha]^{20}_{D}$ −62.9 ° (*c* 0.96, $CHCl_3$). δ_H (400 MHz; DMSO 90 °C) 0.96 (3 H, d, *J* 7.1 Hz, $C^{11}\underline{H}_3$), 1.74 (3 H, s, $C^{7}\underline{H}_3$), 1.75 (3 H, s, $C^{8}\underline{H}_3$), 4.43 (1 H, d, *J* 13.7 Hz, $OC^{6}\underline{H}H$), 4.79 (1 H, dd, *J* 2.8 & 13.7 Hz, $OC^{6}H\underline{H}$), 5.16 (1 H, s, $NC^{5}\underline{H}$), 5.87 – 5.92 (2 H, m, $OC^{4}\underline{H}Ph$ & $NC^{10}\underline{H}CH_3$), 7.51 – 7.14 (3 H, m, *Biphenyl*-$C^{a'/a''/a'''}H$), 7.31 – 7.34 (3 H, m, *Biphenyl*-$C^{b/c/d}H$), 7.49 (2 H, m, *Biphenyl*-$C^{e/f}H$), 7.69 (1 H, dd, *J* 1.7 & 7.2 Hz, *Biphenyl*-$C^{g}H$), 7.75 (1 H, dt, *J* 1.2 & 7.6 Hz, *Biphenyl*-$C^{H}H$), 7.85 (1 H, d, *J* 7.8 Hz, *Biphenyl*-$C^{I}H$), 7.96 (1 H, dt, *J* 1.2 & 7.6 Hz, *Biphenyl*-$C^{J}H$), 8.02 (1 H, d, *J* 7.9 Hz, *Biphenyl*-$C^{K}H$), 9.49 (1 H, s, $N{=}C^{9}\underline{H}$) . δ_C (100 MHz; DMSO 90 °C) 15.7 ($\underline{C}^{11}H_3$), 19.3 ($\underline{C}^{7}H_3$), 29.8 ($\underline{C}^{8}H_3$), 62.8 ($O\underline{C}^{6}H_2$), 66.5 ($N\underline{C}^{10}HCH_3$), 67.7 ($N\underline{C}^{5}H$), 70.8 ($O\underline{C}^{4}HPh$), 101.0 (quat.$\underline{C}^{2}$), 125.4 (*Biphenyl*-$C^{d}H$), 125.8 (quat.C), 128.3 (*Biphenyl*-$C^{c}H$), 128.7 (*Biphenyl*-$C^{a'/a''/a'''}H$), 129.2 (*Biphenyl*-$C^{H}H$), 129.5 (*Biphenyl*-$C^{b}H$), 130.0 (*Biphenyl*-$C^{k}H$), 130.3 (*Biphenyl*-$C^{f}H$), 130.7 (*Biphenyl*-$C^{g}H$), 130.9 (*Biphenyl*-$C^{e}H$), 134.5 (quat.C), 135.5 (*Biphenyl*-$C^{I}H$), 136.4 (quat.C), 136.9 (*Biphenyl*-$C^{J}H$), 138.0 (quat.C), 141.4 (quat.C), 170.6 ($N{=}\underline{C}^{9}H$). *m/z* 398.21153 [- 1.2 ppm]; $C_{27}H_{28}NO_2^+$ requires 398.21200.

6-(2,2-Dimethyl-4-phenyl-(1,3)-dioxan-5-yl)-5-isopropyl-5*H*-dibenzo-(*c,e*)-azepinium; bromide.

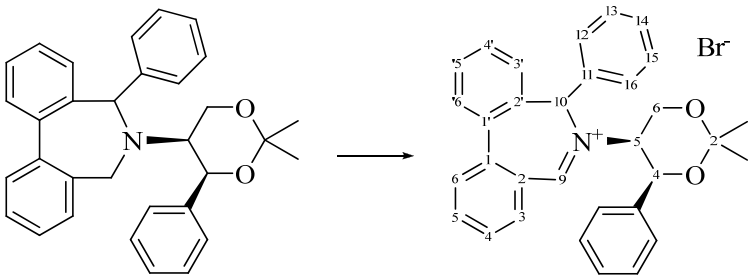


29 ***33***

Prepared according to the general procedure from 6-(2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-5-isopropyl-6,7-dihydro-5*H*-dibenzo[*c, e*]azepine (**29**) (0.18 g, 0.43 mmol) and *N*-bromosuccinimide (0.08 g, 0.47 mmol) to yield the desired bromide azepinium salt as a yellow powder (**33**) (0.18g, 0.36 mmol, 83%). ν_{max}(film) /cm^{-1} 3385, 2964, 2926, 2359, 2339, 1714, 1636, 1557, 1455, 1385, 1201, 1079, 960, 841, 763, 752, 700, 667. $[\alpha]^{20}_{D}$ −8.1 ° (*c* 0.64, $CHCl_3$). δ_H (400 MHz; DMSO 90 °C) 0.46 (3 H, d, *J* 6.4 Hz, C^{12}H$_3$), 0.91 (3 H, d, *J* 6.4 Hz, C^{13}H$_3$), 1.47 – 1.59 (1 H, m, C^{11}H(CH$_3$)$_2$), 1.70 (6 H, s, C^{7}H$_3$ & C^{8}H$_3$), 4.63 (1 H, d, *J* 13.6 Hz, OC^{6}HH), 4.82 (1 H, dd, *J* 2.0 & 13.2 Hz, OC^{6}HH), 5.07 (1 H, d, *J* 10.4 Hz, C^{10}HPr^{i}), 5.14 (1 H, s, NC^{5}H), 5.83 (1 H, s, OC^{4}HPh), 6.79 (2 H, t, *J* 7.6 Hz, Ar-C$^{16/18}$H, *meta* in phenyl ring), 6.88 (1 H, t, *J* 7.2 Hz, Ar-C^{17}H, *para* in phenyl ring), 6.97 (2 H, d, *J* 7.2 Hz, Ar-C$^{15/19}$H, *ortho* in phenyl ring), 7.05 (1 H, d, *J* 7.2 Hz, *Biphenyl* 'A'-C^{d}H), 7.40 (1 H, dt, *J* 1.2 & 7.6 Hz, *Biphenyl* 'A'-C^{e}H), 7.48 (1 H, dt, *J* 1.2 & 7.6 Hz, *Biphenyl* 'A'-C^{f}H), 7.58 (1 H, d, *J* 6.8 Hz, *Biphenyl* 'A'-C^{g}H), 7.75 – 7.81 (1 H, m, *Biphenyl* 'B'-C^{H}H), 7.97 (2 H, d, *J* 4.0 Hz, *Biphenyl* 'B'-C$^{i/j}$H), 8.11 – 8.13 (1 H, d, *J* 7.6 Hz, *Biphenyl* 'B'-C^{k}H), 9.63 (1 H, s, N=C^{9}H). δ_C (100 MHz; DMSO 90 °C) 19.4 (C^{7}H$_3$), 19.6 (C^{12}H$_3$), 20.0 (C^{13}H$_3$), 26.8 (C^{11}H(CH$_3$)$_2$), 29.5 (C^{8}H$_3$), 62.2 (C^{6}H$_2$), 68.5 (NC^{5}H), 71.4 (OC^{4}HPh), 80.4 (C^{10}HPr^{i}), 101.3 (quat.C^{2}), 125.1 (2 *x* Ar-C$^{15/19}$H, ortho in phenyl ring), 125.6 (quat.C), 128.30 (Ar-C^{17}H, *para* in phenyl ring), 128.33 (2 *x* Ar-C$^{16/18}$H, *meta* in phenyl ring), 129.2 (*Biphenyl* 'A'-CH), 129.88 (*Biphenyl*

'A'-CH), 129.93 (*Biphenyl* 'A'-CH), 130.5 (*Biphenyl* 'B'-CH), 130.8 (*Biphenyl* 'A'-CH), 131.0 (*Biphenyl* 'B '-CH), 133.7 (quat.C), 135.7 (quat.C), 135.9 (quat.C), 136.2 (*Biphenyl* 'B'-CH), 137.2 (*Biphenyl* 'B'-CH), 141.7 (quat.C), 169.6 (N=C^{9}H). *m/z* 426.24378 [+ 1.1 ppm]; $C_{29}H_{32}NO_2^+$ requires 426.24330.

6-(2,2-Dimethyl-4-phenyl-(1,3)dioxan-5-yl)-5-phenyl-5*H*-dibenzo(*c,e*)azepinium ; bromide.

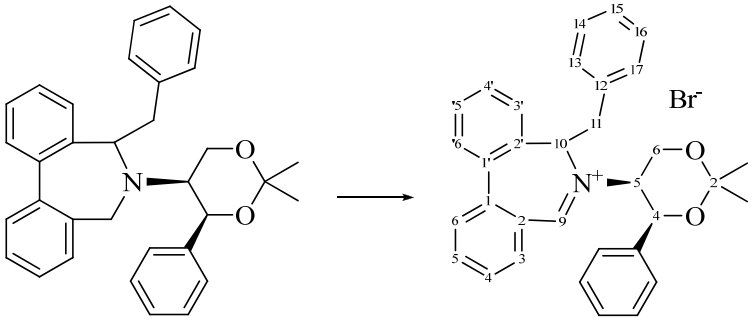


38 ***42***

Prepared according to the general procedure from 6-(2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-5-phenyl-6,7-dihydro-5*H*-dibenzo[*c, e*]azepine (**38**) (0.07 g, 0.15 mmol) and *N*-bromosuccinimide (0.03 g, 0.17 mmol) to yield the desired bromide azepinium salt as a yellow powder (**42**) (0.07 g, 0.14 mmol, 91%). ν_{max}(film) /cm^{-1} 3024, 2921, 2360, 1628, 1599, 1448, 1260, 1086, 1027, 800, 756, 698. $[\alpha]^{20}_{D}$ −21.2 ° (*c* 0.98, $CHCl_3$). δ_H (400 MHz; DMSO 90 °C) 1.79 (3 H, s, C^{7}H$_3$), 1.81 (3 H, s, C^{8}H$_3$), 3.56 (1 H, s, NC^{10}HPh), 4.64 (1 H, d, *J* 13.6 Hz, OC^{6}HH), 4.93 (1 H, dd, *J* 2.4 & 14.0 Hz, OC^{6}HH), 5.56 (1 H, s, NC^{5}H), 5.97 (1 H, d, *J* 2.0 Hz, OC^{4}HPh), 6.53 (2 H, m, Ar-CH), 6.92 (3 H, m, Ar-CH), 6.99 (3 H, m, Ar-CH), 7.16 (2 H, d, *J* 7.2 Hz, Ar-CH), 7.46 – 7.50 (1 H, m, Ar-CH), 7.51 – 7.55 (1 H, m, Ar-CH), 7.67 – 7.62 (2 H, m, Ar-CH), 7.64 – 7.69 (3 H, m, Ar-CH), 7.79 (1 H, d, *J* 7.2 Hz, Ar-CH), 7.88 (1 H, d, *J* 7.6 Hz, Ar-CH), 9.73 (1 H,

N=C^{9}H). δ_C (100 MHz; DMSO 90 °C) 19.4 (C^{7}H$_3$), 29.8 (C^{8}H$_3$), 30.0 (OC^{6}H$_2$), 30.8 (NC^{5}H), 61.9 (NC^{9}H$_2$), 67.6 (NC^{10}HPh), 70.5 (OC^{4}HPh), 101.6 (quat.C^{2}), 125.0 (Ar-CH), 125.8 (Ar-CH), 126.8 (Ar-CH), 127.0 (Ar-CH), 126.0 (Ar-CH), 126.2 (Ar-CH), 126.3 (Ar-CH), 128.3 (Ar-CH), 128.5 (Ar-CH), 129.5 (Ar-CH), 130.7 (Ar-CH), 130.9 (Ar-CH), 135.0 (Ar-CH), 135.8 (quat.Ar-C), 136.6 (quat.Ar-C), 140.3 (quat.Ar-C), 141.3 (quat.Ar-C), 141.5 (quat.Ar-C), 171.2 (N=C^{9}H). (. *m/z* 460.22711 [- 1.2 ppm]; $C_{32}H_{30}NO_2^+$ requires 460.22765.

5-Benzyl-6-(2,2-dimethyl-4-phenyl-(1,3)dioxan-5-yl)-5*H*-dibenzo(*c*,*e*)azepinium ; bromide.

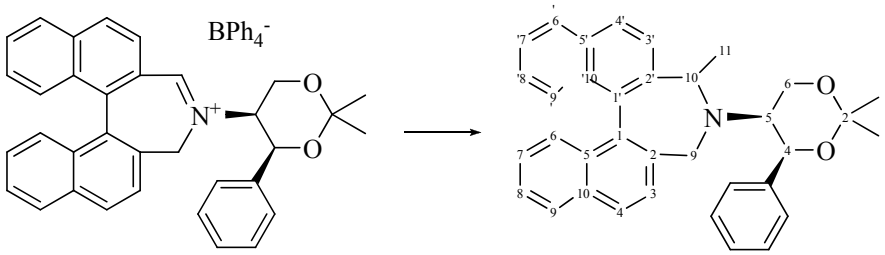


39 ***43***

Prepared according to the general procedure from 6-(2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-5-phenyl-6,7-dihydro-5*H*-dibenzo[*c, e*]azepine (**39**) (0.10 g, 0.21 mmol) and *N*-bromosuccinimide (0.04 g, 0.23 mmol) to yield the desired bromide azepinium salt as a yellow powder (**43**) (0.10 g, 0.17 mmol, 83%). ν_{max}(film) /cm^{-1} 3372, 2960, 2359, 1708, 1639, 1448, 1383, 1260, 1201, 1083, 1027, 799, 751, 700. $[\alpha]^{20}_D$ −18.5 ° (*c* 1.06, $CHCl_3$). δ_H (400 MHz; DMSO 90 °C) 1.67 (3 H, s, C^{7}H$_3$), 1.68 (3 H, s, C^{8}H$_3$), 2.56 (2 H, d, *J* 8.8 Hz, C^{11}H$_2$Ph), 3.55 (1 H, d, *J* 13.6 Hz, OC^{6}HH), 4.52 (1 H, dd,

J 3.2 & 13.6 Hz, OC^{6}HH), 5.01 (1 H, s, NC^{5}H), 5.76 – 5.81 (2 H, m, OC^{4}HPh & NC^{10}HBn), 6.86 – 6.88 (2 H, m, Ar-C$^{a'/a''}$H), 6.96 (1 H, m, Ar-C^{b}H), 6.97 – 7.04 (3 H, m, Ar-C $^{c'/c''/c'''}$H), (5 H, m, Ar-C$^{d'/d''/e'/e''/e'''}$H), 7.34 (1 H, dt, *J* 0.8 & 7.4 Hz, Ar-C^{f}H), 7.48 (1 H, dt, *J* 1.2 & 7.4 Hz, Ar-C^{g}H), 7.68 (1 H, d, *J* 7.2 Hz, Ar-C^{H}H), 7.86 (1 H, dt, *J* 1.4 & 7.4 Hz, Ar-C^{i}H), 8.05 – 8.12 (3 H, m, Ar-C$^{j/k/l}$H), 9.61 (1 H, s, N=CH). δ_C (100 MHz; DMSO 90 °C) 19.2 (C^{7}H$_3$), 29.6 (C^{8}H$_3$), 34.1 (OC^{6}H$_2$), 65.2 (C^{11}H$_2$Ph), 68.6 (NC^{5}H), 71.2 (OC^{4}HPh), 74.2 NC^{10}HBn), 101.2 (quat.C^{2}), 125.4 (Ar-C$^{e'/e''/e'''}$H), 126.0 (quat.C), 127.8 (Ar-C$^{c'/c''/c'''}$H), 128.4 (Ar-C$^{a'/a''}$H), 128.7 (Ar-C^{i}H), 129.0 (Ar-C$^{d'/d''}$H), 129.4 (Ar-C^{l}H), 130.2 (Ar-C^{g}H), 130.5 (Ar-C^{H}H), 130.6 (Ar-C^{f}H), 130.7 (Ar-C^{b}H), 134.6 (quat.C), 130.6 (quat.C), 135.7 (quat.C), 136.1 (quat.C), 136.2 (quat.C), 137.5 (Ar-C^{k}H), 141.9 (quat.C), 170.6 (N=C^{9}H). *m/z* 474.24268 [- 1.3 ppm]; $C_{33}H_{32}NO_2^+$ requires 474.24330.

4-(2,2-Dimethyl-4-phenyl-(1,3)dioxan-5-yl)-3-methyl-4,5-dihydro-3*H*-4-aza-cyclohepta(2,1-*a*;3,4-*a*')dinaphthalene

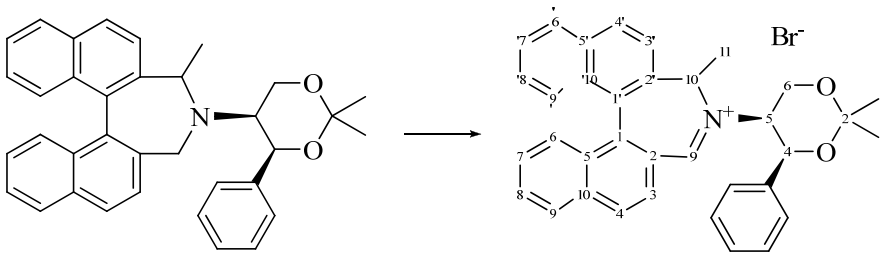


3 ***51***

Prepared according to the general procedure from azepinium (**3**) (0.69 g, 1.20 mmol) and methyl magnesium bromide (1.20 mL, 3.60 mmol) to yield the desired methylated amine (**51**) as a colourless powder (0.34 g, 0.67 mmol, 56%). ν_{max}(film) /cm^{-1} 2921, 2359, 1379, 1260, 1198, 1100, 1082, 1028, 819, 699. $[\alpha]^{20}_D$ −96.4 ° (*c* 0.71, $CHCl_3$). δ_H (400

MHz; $CDCl_3$) 0.12 (3 H, d *J* 7.2 Hz, $C^{11}\underline{H}_3$), 1.51 (3 H, s, $C^7\underline{H}_3$), 1.60 (3 H, s, $C^8\underline{H}_3$), 2.90 (1 H, sextet, *J* 2.0 & 4.0 Hz, $NC^5\underline{H}$), 3.54 (1 H, d, *J* 11.6 Hz, upfield portion of ABX system, $NC^9\underline{H}H$), 3.74 (1 H, d, *J* 11.2 Hz, downfield portion of ABX system, $NC^9H\underline{H}$), 4.01 (1 H, dd, *J* 1.6 & 12.4 Hz, upfield portion of ABX system, $OC^6\underline{H}H$), 4.23 (1 H, dd, *J* 2.8 & 15.2 Hz, downfield portion of ABX system, $OC^6H\underline{H}$), 4.45 (1 H, q, *J* 7.2 Hz, $NC^{10}\underline{H}Me$), 5.13 (1 H, d. 3.2 Hz, $OC^4\underline{H}Ph$), 7.07 – 7.14 (3 H, m, 3 *x* Ar-C<u>H</u>), 7.19 – 7.25 (5 H, m, 5 *x* Ar-C<u>H</u>), 7.28 – 7.34 (5 H, m, 5 *x* Ar-C<u>H</u>), 7.73 – 7.82 (4 H, m, 4 *x* Ar-C<u>H</u>). δ_C (100 MHz; $CHCl_3$) 18.3 ($\underline{C}^7H_3$), 20.2 ($\underline{C}^{11}H_3$), 28.4 ($\underline{C}^8H_3$), 53.2 ($N\underline{C}^9H_2$), 58.8 ($N\underline{C}^{10}HMe$), 59.1 ($N\underline{C}^5H$), 62.9 ($O\underline{C}^6H_2$), 73.3 ($O\underline{C}^4HPh$), 98.4 (quat.$\underline{C}^2$), 124.00 (Ar-<u>C</u>H), 124.03 (Ar-<u>C</u>H), 124.2 (Ar-<u>C</u>H), 124.5 (Ar-<u>C</u>H), 125.2 (2 *x* Ar-<u>C</u>H), 125.6 (Ar-<u>C</u>H), 126.3 (Ar-<u>C</u>H), 126.4 (Ar-<u>C</u>H), 126.5 (Ar-<u>C</u>H), 126.7 (2 *x* Ar-<u>C</u>H), 126.8 (Ar-<u>C</u>H), 127.1 (Ar-<u>C</u>H), 127.3 (Ar-<u>C</u>H), 127.5 (Ar-<u>C</u>H), 127.8 (Ar-<u>C</u>H), 130.8 (quat.Ar-<u>C</u>), 130.9 (quat.Ar-<u>C</u>), 131.5 (quat.Ar-<u>C</u>), 131.7 (quat.Ar-<u>C</u>), 131.9 (quat.Ar-<u>C</u>), 133.9 (quat.Ar-<u>C</u>), 135.3 (quat.Ar-<u>C</u>), 138.8 (quat.Ar-<u>C</u>), 139.1 (quat.Ar-<u>C</u>). $C_{35}H_{33}NO_2$ requires 499.2511.

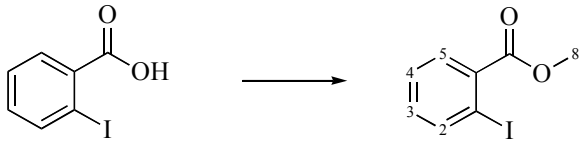
4-(2,2-Dimethyl-4-phenyl-(1,3)dioxan-5-yl)-3-methyl-3*H*-4-azonia-cyclohepta(2,1-*a*;3,4-*a*')dinaphthalene; Bromide salt.



51 ***52***

Prepared according to the general procedure from amine **51** (0.34 g, 0.66 mmol) and NBS (0.24 g, 1.33 mmol) to yield the desired binapthalene azepinium salt catalyst **52** As a dark yellow powder (0.30 g, 0.52 mmol, 79%). ν_{max}(film) /cm^{-1} 3392, 2359, 1695, 1377, 1190, 1112, 820, 753, 667. $[\alpha]^{20}_{D}$ −96.4 ° (*c* 0.71, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 1.05 (3 H. d, *J* 7.2 Hz, NCH($C^{11}\underline{H}_3$)), 1.70 (6 H, s, 2 *x* $C^{7\&8}\underline{H}_3$), 4.34 (1 H. d, *J* 14.0 Hz, upfield portion of ABX system, $OC^{6}\underline{H}H$), 4.97 (1 H. dd, *J* 2.4 & 14.0 Hz, downfield portion of ABX system, $OC^{6}H\underline{H}$), 5.41 (1 H, s (broad), $NC^{5}\underline{H}$), 5.72 (1 H. d, *J* 2.0 Hz, $OC^{4}\underline{H}$Ph), 5.98 – 6.08 (1 H, m, $NC^{10}\underline{H}(CH_3)$, 6.74 (1 H, d, *J* 9.2 Hz, Ar-C<u>H</u>), 7.05 – 7.16 (3 H. m, 3 *x* Ar-C<u>H</u>), 7.24 – 7.36 (3 H. m, 3 *x* Ar-C<u>H</u>), 7.37 – 7.50 (3 H, m, 3 *x* Ar-C<u>H</u>), 7.54 – 7.67 (3 H. m, 3 *x* Ar-C<u>H</u>), 7.86 (1 H. d, *J* 8.0 Hz, Ar-C<u>H</u>), 7.94 (2 H. dd, *J* 8.4 & 10.8 Hz, 2 *x* Ar-C<u>H</u>), 8.05 (1 H. d, *J* 8.4 Hz, Ar-C<u>H</u>), 9.54 (1 H, s, N=C<u>H</u>). δ_C (100 MHz; $CHCl_3$) 18.7 ($\underline{C}^{11}H_3$), 29.8 ($\underline{C}^{7\text{ or }8}H_3$), 31.0 ($\underline{C}^{7\text{ or }8}H_3$), 62.5 ($O\underline{C}^{6}H_2$), 67.1 (<u>C</u>H), 67.9 (<u>C</u>H), 71.2 (<u>C</u>H), 101.0 (quat.Ar-$\underline{C}^{2}$H), 124.5 (Ar-<u>C</u>H), 124.6 (Ar-<u>C</u>H), 125.5 (Ar-<u>C</u>H), 126.8 (Ar-<u>C</u>H),127.4 (Ar-<u>C</u>H),128.01 (Ar-<u>C</u>H), 128.06 (Ar-<u>C</u>H), 128.2 (Ar-<u>C</u>H), 128.3 (Ar-<u>C</u>H), 128.5 (Ar-<u>C</u>H), 129.3 (Ar-<u>C</u>H), 129.7 (Ar-<u>C</u>H), 130.8 (Ar-<u>C</u>H), 132.2 (Ar-<u>C</u>H), 134.7 (quat.Ar-<u>C</u>), 135.4 (quat.Ar-<u>C</u>), 136.9 (quat.Ar-<u>C</u>), 137.1 (quat.Ar-<u>C</u>), 137.6 (quat.Ar-<u>C</u>), 139.4 (quat.Ar-<u>C</u>), 141.2 (quat.Ar-<u>C</u>), 142.6 (quat.Ar-<u>C</u>), 169.2 (quat.Ar-<u>C</u>), 177.4 (N=<u>C</u>H). *m/z* 498.24435 [+ 1.9 ppm]; $C_{35}H_{32}NO_2Br$ requires 498.24331.

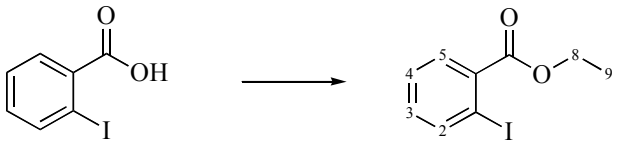
2-iodo-benzoic acid methyl ester. [14]



63 ***64***

Acetyl chloride (0.31 mL, 4.40 mmol) was added to a solution of 2-iodobenzoic acid (**63**) (1.00 g, 4.00 mmol) in methanol (50 mL). The reaction mixture was heated under reflux for 16 h. The reaction was allowed to cool to ambient temperature. The crude product was extracted from saturated aqueous hydrochloric acid (2 *x* 50 mL, 1 M), and saturated brine (2 *x* 50 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield the desired product (**64**) as a yellow oil (0.84 g, 3.20 mmol, 81%). ν_{max}(film) /cm^{-1} 1726, 1284, 1254, 1130, 1107, 1014, 743. δ_H (400 MHz; $CDCl_3$) 3.85 (3 H, s, $OC^8\underline{H}_3$), 7.06 (1 H, dt, *J* 8.0 & 2.0 Hz, Ar-$C^5\underline{H}$ *ortho* to ester group), 7.31 (1 H, dt, *J* 1.2 & 7.6 Hz, Ar-$C^2\underline{H}$ *meta* to ester group, *ortho* to iodo group), 7.72 (1 H, dd, *J* 1.6 & 8.0 Hz, Ar-$C^3\underline{H}$ *para* to ester group), 7.90 (1 H, dd, *J* 1.2 & 8.0 Hz, Ar-$C^4\underline{H}$ *meta* to ester group, *para* to iodo group). δ_C (100 MHz; $CDCl_3$) 14.6 ($O\underline{C}^8H_3$), 94.3 (quat.C^1 *ipso* to iodo group), 128.2 (Ar-$\underline{C}$H), 131.2 (Ar-$\underline{C}$H), 132.8 (Ar-$\underline{C}$H), 135.8 (quat.C^6 *ipso* to ether), 141.6 (Ar-$\underline{C}$H), 167.0 (quat.C=O).

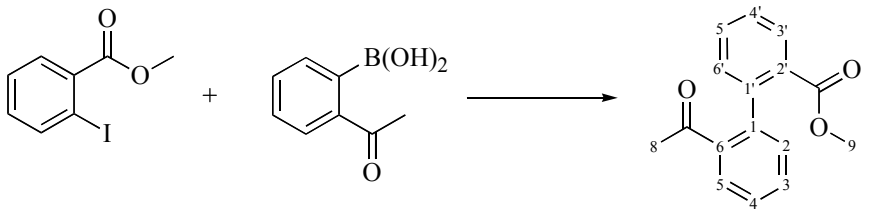
2-iodo-benzoic acid ethyl ester. [14]



63 ***65***

A solution of 2-iodobenzoic acid (**63**) (1.00 g, 4.00 mmol) in thionyl chloride (10 mL, 142 mmol) was heated under reflux for 2 h. The reaction was allowed to cool to ambient temperature and the solvent removed under reduced pressure. The crude intermediate was dissolved in absolute ethanol (14 mL) and heated under reflux for 12 h. The reaction was allowed to cool to ambient temperature. The solvent was removed under reduced pressure and the residue dissolved in 5% saturated aqueous potassium carbonate solution. The organic phase was extracted into DCM and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield the desired ester as a yellow oil (**65**). ν_{max}(film) /cm^{-1} 1724, 1285, 1255, 1133, 1102, 1015, 741. δ_H (400 MHz; $CDCl_3$) 1.33 (3 H, dt, *J* 6.8 & 2.4 Hz, $OCH_2C^9\underline{H}_3$), 4.32 (2 H, dq, *J* 7.2 & 2.8 Hz, $OC^8\underline{H}_2CH_3$), 7.05 (1 H, t, *J* 7.2 Hz, Ar-$C^5\underline{H}$ *ortho* to ester group), 7.31 (1 H, t, *J* 7.6 Hz, Ar-$C^2\underline{H}$ *meta* to ester, *ortho* to iodo group), 7.70 (1 H, d, *J* 7.6 Hz, Ar-$C^3\underline{H}$ *para* to ester), 7.89 (1 H, d, *J* 8.0 Hz, Ar-$C^4\underline{H}$ *meta* to ester, *para* to iodo group). δ_C (100 MHz; $CDCl_3$) 14.3 ($\underline{C}^9H_3$), 61.7 ($O\underline{C}^8H_2$), 94.0 (quat.$\underline{C}^1$ *ipso* to iodo), 127.9 (Ar-$\underline{C}$H), 130.8 (Ar-$\underline{C}$H), 132.5 (Ar-$\underline{C}$H), 135.4 (quat.C^6 *ipso* to ether), 141.2 (Ar-$\underline{C}$H), 166.6 (quat.$\underline{C}$=O).

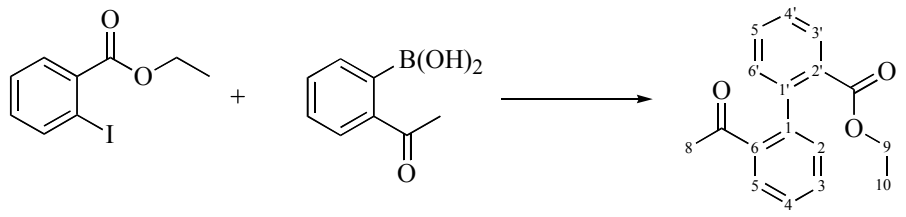
2'-Formyl-biphenyl-2-carboxylic acid methyl ester. [14]



64 ***60*** ***66***

Acetyl phenyl boronic acid (**50**) (0.53 g, 3.20 mmol) and saturated aqueous potassium carbonate (1.32 g, 9.40 mmol) were added to a solution of 2-iodo-benzoic acid methyl ester (**64**) (0.93 g, 3.40 mmol) in toluene (50 mL), ethanol (5 mL) and water (6 mL). The reaction mixture was degassed with a nitrogen flow over 30 min. After adding $Pd(PPh_3)_4$ (185 mg, 0.16 mmol) the reaction mixture was degassed under a nitrogen flow over 15 min. The mixture was stirred under reflux and a nitrogen atmosphere for 24 h and allowed to cool to ambient temperature. The reaction mixture was then filtered through a plug of celite and the organic solvents were removed under reduced pressure and the crude reaction mixture was dissolved in diethyl ether (50 mL). The combined organic layers were washed with water (2 *x* 40 mL) and dried over $MgSO_4$. The solvents were removed under reduced pressure, and the crude compound was purified by flash chromatography (ethyl acetate/petrol 15% − 100%) to afford the desired biaryl compound as a yellow oil (**66**) (0.66 g, 2.6 mmol, 76%). ν_{max}(film) /cm^{-1} 2949, 1725, 1688, 1289, 1254, 1127, 1091, 761. δ_H (400 MHz; $CDCl_3$) 2.08 (3 H, d, *J* 0.8 Hz, OC^{9}H$_3$), 3.53 (3 H, d, *J* 0.4 Hz, COC^{8}H$_3$), 7.06 (1 H, ddd, *J* 0.4, 0.8 & 7.2 Hz, Ar-CH), 7.10 (1 H, ddd, *J* 0.4, 0.8 & 7.6 Hz, Ar-CH), 7.293 − 7.432 (4 H, m, Ar-CH), 7.62 (1 H, ddd, *J* 0.4, 0.8 & 7.6 Hz, Ar-CH), 7.88 (1 H, ddd, *J* 0.4, 0.8 & 7.6 Hz, Ar-CH). δ_C (100 MHz; $CDCl_3$) 29.4 (OC^{9}H$_3$), 52.0 (COC^{8}H$_3$), 127.4 (Ar-CH), 127.6 (Ar-CH), 128.2 (Ar-CH), 129.6 (quat.Ar-C), 130.2 (Ar-CH), 130.8 (Ar-CH), 130.9 (Ar-CH), 131.7 (Ar-CH), 138.7 (Ar-CH), 138.7 (quat.Ar-C), 140.9 (quat.Ar-C), 142.8 (quat.Ar-C), 167.5 (quat.Ar-C), 201.7 (quat.Ar-C).

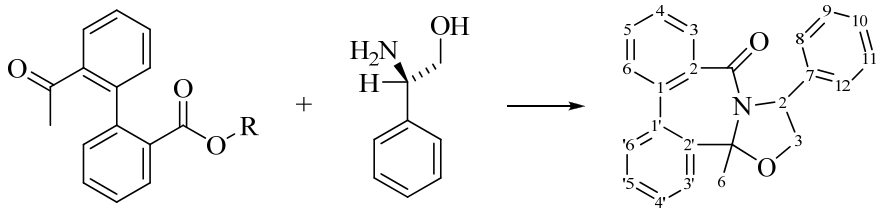
2'-Formyl-biphenyl-2-carboxylic acid ethyl ester. [14]



65 ***60*** ***67***

Acetyl phenyl boronic acid (**60**) (0.56 g, 3.4 mmol) and saturated aqueous potassium carbonate (1.4 g, 10 mmol) were added to a solution of 2-iodo-benzoic acid ethyl ester (**65**) (0.93 g, 3.4 mmol) in toluene (50 mL), ethanol (5 mL) and water (6 mL). The reaction mixture was degassed with a nitrogen flow over 30 min. After adding $Pd(PPh_3)_4$ (196 mg, 0.17 mmol) the reaction mixture was degassed under a nitrogen flow over 15 min. The mixture was stirred under reflux and a nitrogen atmosphere for 48 h and allowed to cool to ambient temperature. The reaction mixture was filtered through a plug of celite and the organic solvents were removed under reduced pressure. The crude reaction mixture was then dissolved in diethyl ether (50 mL) and the combined organic layers were washed with water (2 *x* 40 mL) and dried over $MgSO_4$. The solvents were removed under reduced pressure, and the crude compound was purified by flash chromatography (ethyl acetate:petrol 15% − 100%) to afford the desired biaryl compound as a yellow oil (**67**) (0.66 g, 2.6 mmol, 76%). ν_{max}(film) /cm^{-1} 2980, 1718, 1688, 1287, 1251, 1129, 1089, 760. δ_H (400 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 7.0 Hz, $OCH_2C^{10}\underline{H}_3$), 2.04 (3 H, s, $COC^8\underline{H}_3$), 3.95 (2 H, dq, *J* 2.4 & 7.2 Hz),$OC^9\underline{H}_2CH_3$), 7.05 (1 H, ddd, *J* 0.8, 2.0 & 6.8 Hz, Ar-C<u>H</u>), 7.08 (1 H, ddd, *J* 0.4, 1.2 & 7.2 Hz, Ar-C<u>H</u>), 7.28 − 7.41 (4 H, m, Ar-C<u>H</u>), 7.60 (1 H, dd, *J* 1.6 & 7.2 Hz, (Ar-C<u>H</u>), 7.88 (1 H, dd, *J* 1.6 & 7.6 Hz, Ar-C<u>H</u>). δ_C (100 MHz; $CDCl_3$) 12.7 ($OCH_2\underline{C}^{10}H_3$), 28.4 ($\underline{C}O\underline{C}^8H_3$), 59.7 ($O\underline{C}^9H_2CH_3$), 126.3 (Ar-<u>C</u>H), 126.5 (Ar-<u>C</u>H), 127.1 (Ar-<u>C</u>H), 129.0 (Ar-<u>C</u>H), 129.1 (quat.Ar-C), 129.2 (Ar-<u>C</u>H), 129.6 (Ar-<u>C</u>H), 129.7 (Ar-<u>C</u>H), 130.4 (Ar-<u>C</u>H), 137.7 (quat.Ar-<u>C</u>), 140.0 (quat.Ar-<u>C</u>), 141.3 (quat.Ar-<u>C</u>), 166.1 ($\underline{C}OCH_3$), 200.7 (<u>C</u>OOEt).

(a*R*,3*R*,13b*S*)-13b-Methyl-3-phenyl-2,3-dihydro-13b*H*-dibenz-(*c*,*e*)- oxazolo(3,2-a) azepine-5-1. [14]

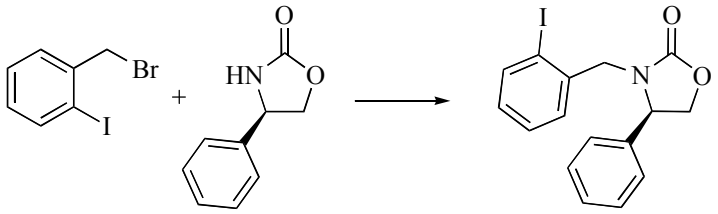


66 (R = Me) ***57*** ***56***

67 (R = Et)

2'-Formyl-biphenyl-2-carboxylic acid methyl ester (**66**) (0.66 g, 2.60 mmol) [or 2'-formyl-biphenyl-2-carboxylic acid ethyl ester (**67**) (0.70 g, 2.60 mmol)] and *R*-phenylglycinol (**57**) (0.37 g, 2.60 mmol) were dissolved in toluene (13 mL) in a Dean-Stark apparatus. The mixture was stirred at reflux for 16 h. The reaction was allowed to cool to ambient temperature and solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (ethyl acetate/petrol 10 − 25%) to provide the desired lactam (**56)** as a colourless oil, as a pair of diastereoisomers (0.39 g, 1.16 mmol, 57%). ν_{max}(film) /cm^{-1} 3061, 2986, 2935, 2877, 1634, 1449, 1396, 1239, 1038, 743, 697. $[\alpha]^{20}_{D}$ +108 ° (*c* 1.00, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 1.45 (3 H. s, C^{6}H$_3$), 4.18 (1 H, dd, *J* 1.2 & 8.8 Hz, upfield portion of *AB*X system, OC^{3}HH), 4.32 (1 H, q, *J* 6.0 Hz, downfield portion of *AB*X system, OC^{3}HH), 5.36 (1 H, d, *J* 6.0 Hz, NC^{2}HPh), 7.22 (1 H, *J* 1.2, 6.4 & 14.8 Hz. Ar-CH), 7.28 − 7.51 (10 H, m, Ar-CH), 7.58 − 7.60 (1 H, m, Ar-CH), 7.80 (1 H, d, 1.2 & 7.6 Hz, Ar-CH). δ_C (100 MHz; $CDCl_3$) 25.7 (C^{6}H$_3$), 61.8 (NC^{2}HPh), 71.0 (OC^{3}H$_2$), 93.9 (quat.C^{5}OCH$_3$), 122.3 (Ar-CH), 126.9 (2 *x* Ar-CH), 127.6 (Ar-CH), 128.1 (Ar-CH), 128.3 (Ar-CH), 128.6 (2 *x* Ar-CH), 128.8 (Ar-CH), 128.9 (Ar-CH), 130.4 (Ar-CH),130.8 (Ar-CH), 131.3 (Ar-CH), 133.4 (quat.C), 135.9 (quat.C), 137.2 (quat.C), 141.0 (quat.C), 142.0 (quat.C), 165.6 (quat.C^{13}O).

3-(2-iodo-benzyl)-4-phenyl-oxazolidin-2-one.



73 ***72*** ***71***

Method A

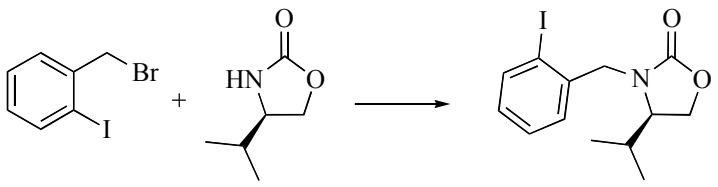
To a solution of *R*-(-)-4-phenyl-2-oxazolidinone (**72**) (0.20 g, 1.23 mmol) in THF (2 mL) at ambient temperature under a nitrogen atmosphere was added NaHMDS (2M in THF, 0.68 mL, 1.35 mmol) in one portion. After 30 min a solution of 2-iodobenzylbromide (**73**) (0.40 g, 1.35 mmol) in THF (2 mL) was added, the reaction mixture was heated to 50 °C and monitored by HPLC for completion. The reaction was allowed to cool to ambient temperature at which point saturated potassium carbonate and TBME were added. The organic fraction was separated and dried over magnesium sulphate. The solvent was removed under reduced pressure to yield the desired alkylated oxazolidinone as a low melting solid (**71**) (0.46 g, 1.21 mmol, 98%).

Method B

To a solution of *R*-(-)-4-phenyl-2-oxazolidinone (**72**) (0.54 g, 3.36 mmol) in THF (5 mL) at ambient temperature under a nitrogen atmosphere was added potassium butoxide (12% in THF, 3.27 g, 29.1 mmol) in one portion. After 30 min a solution of 2-iodobenzylbromide (**73**) (0.80 g, 3.37 mmol) in THF (5 mL) was added, the reaction

mixture was heated to 50 °C and monitored by HPLC for completion. The reaction was allowed to cool to ambient temperature at which point saturated potassium carbonate and TBME were added. The organic fraction was dried over magnesium sulphate and the solvent was removed under reduced pressure to yield the desired alkylated oxazolidinone as a low melting solid (**71**) (1.13 g, 2.99 mmol, 89%). ν_{max}(film) /cm^{-1} 2960, 1749, 1428, 1240, 1081, 1012, 751, 668. $[\alpha]^{20}_{D}$ −56.0 ° (*c* 0.65, $CHCl_3$), δ_H (400 MHz; $CDCl_3$) 4.00 (1 H, d, *J* 16.0 Hz, NCHH), 4.18 (1 H, dd. *J* 8.0 & 12.0 Hz, NCHPh), 4.57 (1 H, dd, *J* 4.0 & 12.0 Hz, OCHH), 4.63 (1 H, t, *J* 8.0 Hz, OCHH), 4.79 (1 H, d, *J* 16.0 Hz, OCHH), 6.97 (1 H, t, *J* 8.0 Ar-CH), 7.15 – 7.19 (3 H, m, 3 *x* Ar-CH), 7.26 – 7.30 (1 H, m, Ar-CH), 7.34 – 7.41 (3 H, m, 3 *x* Ar-CH), 7.79 (1 H, d, *J* 8.0 Hz, Ar-CH). δ_C (100 MHz; $CHCl_3$) 51.1 (OCH_2), 59.7 (NCHPh), 70.5 (NCH_2), 99.3 (quat.Ar-C, *ipso* in iodopenyl ring), 114.4 (Ar-CH), 126.6 (Ar-CH), 127.6 (Ar-CH), 129.0 (Ar-CH), 129.6 (Ar-CH), 129.8 (Ar-CH), 130.1 (Ar-CH), 130.4 (Ar-CH), 138.2 (quat.Ar-CI), 138.3 (quat.Ar-C, *ipso* in phenyl ring) 140.3 (Ar-CH), 158.8 (C=O). *m/z* 380.21; $C_{16}H_{14}NO_2I$ requires 379.0069

3-(2-iodo-benzyl)-4-isopropyl-oxazolidin-2-one.

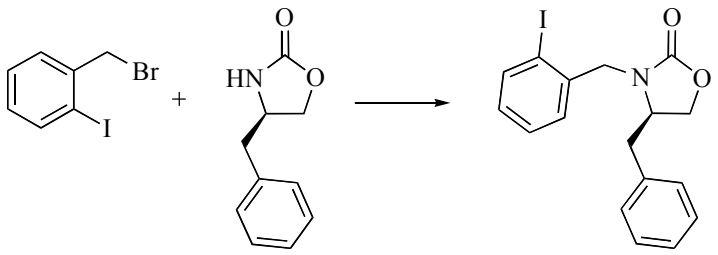


73 ***109*** ***110***

To a solution of *R*-(-)-4-isopropyl-2-oxazolidinone (**109**) (4.8 g, 37.2 mmol) in THF (80 mL) at ambient temperature under a nitrogen atmosphere was added potassium

butoxide (12% solution in THF, 50.0 g, 448 mmol) in one portion. After 30 min a solution of 2-iodobenzylbromide (**73**) (13.27 g, 44.8 mmol) in THF (20 mL) was added and monitored by HPLC for completion. On consumption of the starting material saturated potassium carbonate and TBME were added. The organic fraction was dried over magnesium sulphate and the solvent was removed under reduced pressure to yield the desired alkylated oxazolidinone as a foam (**110**) (12.3 g, 35.7 mmol, 96%). ν_{max}(film) /cm^{-1} 2960, 1749, 1428, 1240, 1081, 1012, 751, 668. $[\alpha]^{20}_{D}$ −19.4 ° (*c* 1.09, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 0.84 (3 H, d, *J* 8.0 Hz, C$\underline{H}_3$), 0.89 (3 H, d, *J* 8.0 Hz, C$\underline{H}_3$), 2.13 (1 H, dectet (m), 4.0 Hz, C$\underline{H}(CH_3)_2$), 3.59 (1 H, ddd, *J* 4.0 & 6.0 Hz, NC$\underline{H}$Pr^i), 4.13 (1 H, dd, *J* 4.0 & 8.0 Hz, OC$\underline{H}$H), 4.21 – 4.26 (2 H, m, OCH$\underline{H}$ & NC$\underline{H}$H), 4.82 (1 H, d, *J* 16 Hz, NCH$\underline{H}$), 6.98 – 7.02 (1 H, m, Ar-C$\underline{H}$), 7.35 (2 H, d, *J* 4.0 Hz, 2 *x* Ar-C$\underline{H}$), 7.85 (1 H, d, *J* 8.0 Hz, Ar-C$\underline{H}$). δ_C (100 MHz; $CHCl_3$) 14.2 (C$\underline{H}_3$), 17.7 (C$\underline{H}_3$), 27.6 (C$\underline{H}$Pr^i), 50.4 (OC$\underline{H}$H), 58.7 (C$\underline{H}$Ph), 62.9 (NC$\underline{H}$H), 98.6 (quat.Ar-C, *ipso* in iodophenyl ring), 128.7 (Ar-C$\underline{H}$), 129.3 (Ar-C$\underline{H}$), 129.6 (Ar-C$\underline{H}$), 138.3 (quat.Ar-C$\underline{I}$), 139.8 (Ar-C$\underline{H}$), 158.6 (C$\underline{=}$O). *m/z* 346.02983 [- 1.4 ppm]; $C_{13}H_{17}INO_2^+$ requires 346.03040.

3-(2-iodo-benzyl)-4-benzyl-oxazolidin-2-one.



73 ***110*** ***111***

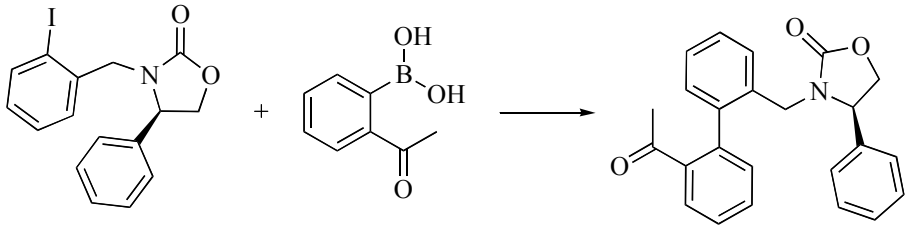
To a solution of *R*-(-)-4-benzyl-2-oxazolidinone (**110**) (5.00 g, 28.2 mmol) in THF (40 mL) at ambient temperature under a nitrogen atmosphere was added potassium butoxide (12% solution in THF, 32 mL, 256 mmol) in one portion. After 30 min a solution of 2-iodobenzylbromide (**73**) (7.61 g, 25.6 mmol) in THF (10 mL) was added and monitored by HPLC for completion. On consumption of the starting material saturated potassium carbonate and TBME were added. The organic fraction was dried over magnesium sulphate and the solvent was removed under reduced pressure to yield the desired alkylated oxazolidinone as a foam (**111**) (10.4 g, 26.6 mmol, 95%). ν_{max}(film) /cm^{-1} 1750, 1418, 1237, 1081, 1012, 743, 701, 668. $[\alpha]^{20}_{D}$ −26.8 ° (*c* 1.09, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 2.64 (1 H, dd, *J* 10.0 & 16.0 Hz, C<u>H</u>HPh), 3.17 (1 H, dd, *J* 4.0 & 12.0 Hz, CH<u>H</u>Ph), 3.82 – 3.88 (1 H, m, NC<u>H</u>Ph), 4.07 (1 H, dd, *J* 4.0 & 8.0 Hz, OC<u>H</u>H), 4.16 (1 H, t, *J* 8.0 Hz, OCH<u>H</u>), 4.44 (1 H, d, 16 Hz, NC<u>H</u>H), 4.81 (1 H, d, *J* 16.0 Hz, NCH<u>H</u>), 7.00 – 7.05 (1 H, m, Ar-C<u>H</u>), 7.08 (2 H, d, *J* 8.0 Hz, 2 *x* Ar-C<u>H</u>), 7.23 – 7.30 (3 H, m, 3 *x* Ar-C<u>H</u>), 7.37 (2 H, d, *J* 4.0 Hz, Ar-C<u>H</u>), 7.87 (1 H, d, *J* 8.0 Hz, Ar-C<u>H</u>). δ_C (100 MHz; $CHCl_3$) 38.4 (<u>C</u>HHPh), 50.9 (O<u>C</u>HH), 56.0 (NC<u>H</u>), 66.8 (N<u>C</u>HH), 98.7 (quat.Ar-<u>C</u>, *ipso* in iodophenyl ring), 127.7 (Ar-<u>C</u>H), 128.8 (Ar-<u>C</u>H), 128.9 (2 *x* Ar-<u>C</u>H), 129.1 (2 *x* Ar-<u>C</u>H), 129.5 (Ar-<u>C</u>H), 129.8 (Ar-<u>C</u>H), 135.4 (quat.Ar-<u>C</u>I), 138.5 (quat.Ar-<u>C</u> in benzyl ring), 139.8 (Ar-<u>C</u>H), 158.2 (<u>C</u>=O). *m/z* 394.03105; $C_{17}H_{17}NO_2I^+$ requires 394.03040.

General procedure for the addition of 3-(2-iodo-benzyl)-4-a*lkyl*-oxazolidin-2-ones to acetylphenyl boronic acid using Suzuki methodology.

To a solution of the desired 3-(2-iodo-benzyl)-4-alkyl-oxazolidin-2-one (1 equiv.) in toluene (10 vol.) and ethanol (15 vol.), were added boronic acid (**50**) (1 equiv.) and saturated aqueous potassium carbonate solution (2M in water, 10 vol.). The reaction mixture was degassed with a nitrogen flow over 30 min. After adding the desired palladium catalyst (5%mol), the reaction mixture was degassed with a nitrogen flow over 15 min. The mixture was stirred at under reflux and under nitrogen atmosphere whilst monitoring by HPLC, once full consumption of the starting material was observed the

reaction was allowed to cool to ambient temperature. The solution was filtered through a plug of celite and toluene was removed under reduced pressure. To the resulting saturated aqueous phase TBME was added. After phase separation, the organic layer were washed with water and dried over $MgSO_4$. The solvents were removed under reduced pressure to afford the crude Suzuki biphenyl compound.

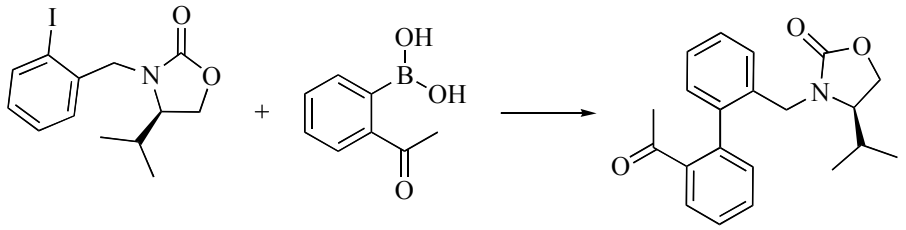
3-(2'-acetyl-biphenyl-2-ylmethyl)-4-phenyl-oxazolidin-2-one.



71 ***60*** ***70***

Prepared according to the general procedure from the 3-(2-iodo-benzyl)-4-phenyl-oxazolidin-2-one (**71**) (0.46 g, 1.21 mmol), boronic acid (**60**) (0.20 g, 1.21 mmol) and $Pd(DPPF)_4$ (70.0 mg, 0.06 mmol), to afford the crude biphenyl compound (**70**). The crude material was immediately carried forward into the next reaction.

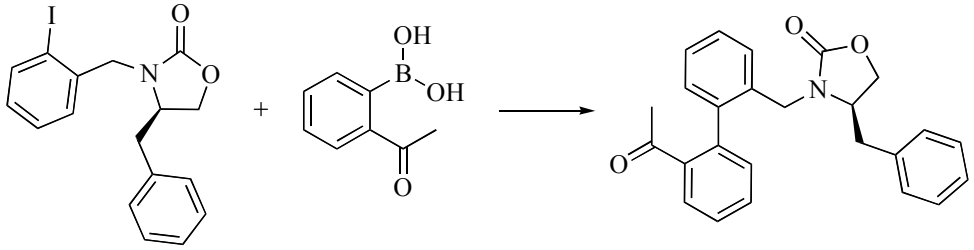
3-(2'-acetyl-biphenyl-2-ylmethyl)-4-isopropyl-oxazolidin-2-one.



110 ***60*** ***112***

Prepared according to the general procedure from the desired 3-(2-iodo-benzyl)-4-isopropyl-oxazolidin-2-one (**110**) (1.00 g, 2.90 mmol), boronic acid (**60**) (0.48 g, 2.90 mmol) and Pd(DPPF) (0.12 g, 0.15 mmol) to afford the crude biphenyl compound (**112**). The crude material was immediately carried forward into the next reaction.

3-(2'-acetyl-biphenyl-2-ylmethyl)-4-benzyl-oxazolidin-2-one.



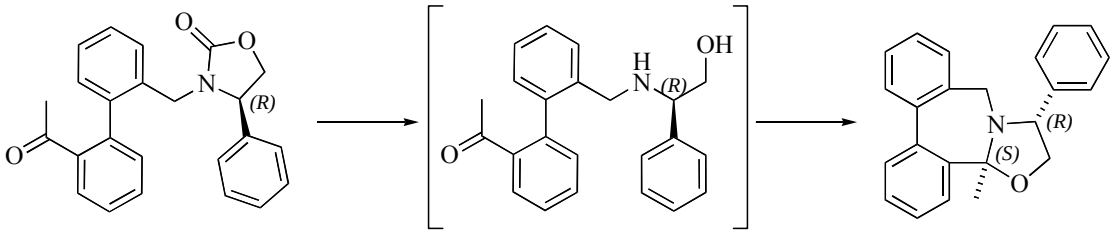
111 ***60*** ***113***

Prepared according to the general procedure from the desired 3-(2-iodo-benzyl)-4-benzyl-oxazolidin-2-one (**111**) (1.00 g, 2.90 mmol), boronic acid (**60**) (0.48 g, 2.9 mmol) and Pd(DPPF) (0.12 g, 0.15 mmol) to afford the crude biphenyl compound (**113**). The crude material was immediately carried forward into the next reaction.

General procedure for the deprotection of biphenyl oxazolidinones and the subsequent cyclisation in the generation tetracyclic compounds.

To a crude solution of the desired biphenyl oxazolidinone in ethanol (10 vol.) was added saturated aqueous NaOH (2M in water, 10 vol.). The reaction mixture was heated under reflux for 16 h then allowd to cool to ambient temperature. The organic solvent was removed under reduced pressure and the resulting residue was dissolved in TBME (10 vol.) and HCl (5M in water, 10 vol.). The reaction mixture was stirred for 30 min and the organic layer was separated, dried over magnesium sulphate and the solvent was removed under reduced pressure to yield the crude cyclised product. The desired compounds were isolated by flash chromatography on silica gel (ethyl acetate:heptane 1 – 5%).

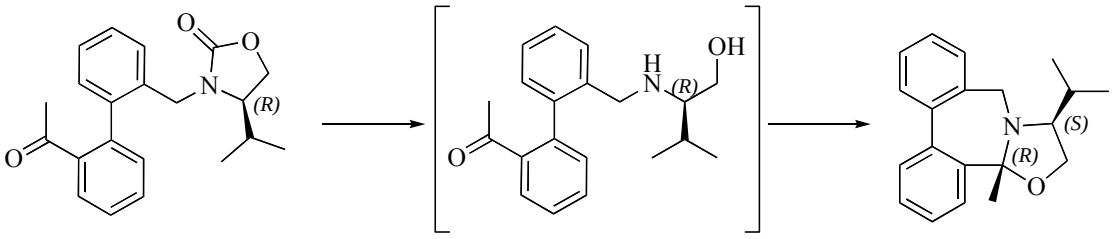
4b-Methyl-7-phenyl-6,7-dihydro-4b*H*,8*H*-5-oxa-7a-aza-dibenzo(*e*,*g*) azulene.



70 ***69*** ***62***

Prepared according to the general procedure using a crude solution of 3-(2'-acetyl-biphenyl-2-ylmethyl)-4-phenyl-o**x**azolidin-2-one (**70**) to afford the desired tetracycle as one diastereoisomer isolated as a foam (**62**) (two steps; 0.049 g, 0.15 mmol, 12%). ν_{max}(film) /cm^{-1} 2963, 1449, 1260, 1153, 1038, 897, 802, 758, 740, 701. $[\alpha]^{20}_{D}$ – 25.1 ° (*c* 1.10, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 1.01 (3 H, s, NC(C<u>H</u>$_3$)O), 2.98 (1 H, d, *J* 10.8 Hz, NC<u>H</u>H), 3.47 (1 H, d, *J* 10.8 Hz, NCH<u>H</u>), 3.75 (1 H, dd, *J* 7.6 & 9.6 Hz, OC<u>H</u>H), 3.83 (1 H, dd, *J* 6.0 & 9.6 Hz, OCH<u>H</u>), 4.26 (1 H, dd, *J* 6.4 & 7.2 Hz, NC<u>H</u>Ph), 7.12 (1 H, d, *J* 7.2 Hz, *Biphenyl*-C<u>H</u>), 7.19 – 7.24 (2 H, m, 2 *x* Ar-C<u>H</u>), 7.25 – 7.31 (3 H, m, 3 *x* Ar-C<u>H</u>), 7.33 – 7.41 (6 H, m, 4 *x Biphenyl*-C<u>H</u> & 2 *x* Ar-C<u>H</u>), 7.78 – 7.81 (1 H, m, Ar-C<u>H</u>). δ_C (100 MHz; $CHCl_3$) 29.4 (<u>C</u>H$_3$), 51.3 (O<u>C</u>H$_2$), 68.1 (<u>C</u>HPh), 71.5 (N<u>C</u>H$_2$), 96.1 (N<u>C</u>(Me)O), 124.7 (Ar-<u>C</u>H), 126.4 (Ar-<u>C</u>H), 126.60 (Ar-<u>C</u>H), 126.63 (2 *x* Ar-<u>C</u>H), 126.80 (Ar-<u>C</u>H), 126.84 (Ar-<u>C</u>H), 126.9 (Ar-<u>C</u>H), 127.3 (Ar-<u>C</u>H), 127.6 (2 *x* Ar-<u>C</u>H), 127.9 (Ar-<u>C</u>H), 128.0 (Ar-<u>C</u>H), 134.0 (quat.Ar-<u>C</u>), 135.7 (quat.Ar-<u>C</u>), 137.9 (quat.Ar-<u>C</u>), 139.2 (quat.Ar-<u>C</u>), 140.9 (quat.Ar-<u>C</u>). *m/z* 327.16263 [+ 1.0 ppm]; $C_{23}H_{21}NO$ requires 327.16231.

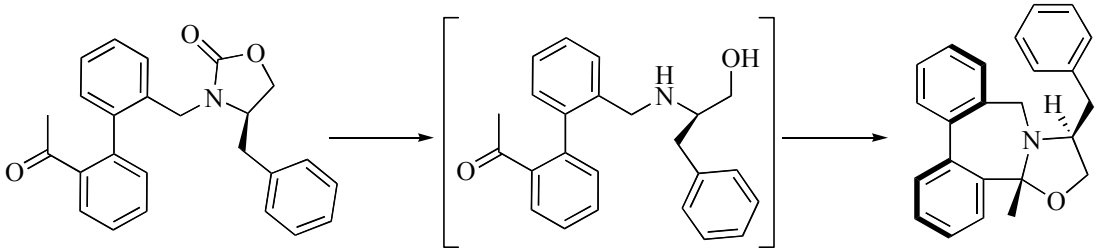
7-isopropyl-4b-methyl-6,7-dihydro-4b*H*,8*H*-5-oxa-7a-aza-dibenzo(*e*,*g*) azulene.



112 ***114*** ***90***

Prepared according to the general procedure using a crude solution of 3-(2'-acetyl-biphenyl-2-ylmethyl)-4-isopropyl-o**x**azolidin-2-one (**112**) to afford the desired tetracycle as one diastereoisomer, isolated as a foam (**90**) (two steps; 0.08 g, 0.29 mmol, 10%). ν_{max}(film) /cm^{-1} 3419, 2954, 2871, 1459, 1365, 1213, 1160, 1043, 756, 730. $[\alpha]^{20}_{D}$ – 98.8 ° (*c* 1.21, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 1.13 – 1.15 (9 H, m, 3 *x* C<u>H</u>$_3$), 2.03 (1 H, octet, *J* 6.4 & 12.8 z, C<u>H</u>$(CH_3)_2$), 2.95 (1 H, q, *J* 5.6 Hz, C<u>H</u>Pr^i), 3.39 (1 H, d, *J* 10.8 Hz, upfield portion of ABX system, NC<u>H</u>H), 3.88 (1 H, d, *J* 11.2 Hz, downfield portion of ABX system, NCH<u>H</u>), 4.01 (1 H, dd, *J* 5.6 & 8.0 Hz, OC<u>H</u>H), 4.16 (1 H, t(dd), *J* 7.6 (7.2), OCH<u>H</u>), 7.44 (1 H, m, *Biphenyl*-C<u>H</u>), 7.47 – 7.49 (1 H, m, *Biphenyl*-C<u>H</u>), 7.50 – 7.55 (3 H, m, 3 *x Biphenyl*-C<u>H</u>), 7.57 – 7.61 (2 H, m, 2 *x Biphenyl*-C<u>H</u>), 7.89 – 7.91 (1 H, m, *Biphenyl*-C<u>H</u>). δ_C (100 MHz; $CHCl_3$) 15.9 (<u>C</u>H$_3$), 18.4 (<u>C</u>H$_3$), 28.9 (<u>C</u>H$(CH_3)_2$), 29.5 (<u>C</u>H$_3$), 53.0 (N<u>C</u>H$_2$), 64.5 (O<u>C</u>H$_2$), 68.8 (<u>C</u>HPr^i), 96.9 (quat.<u>C</u>O), 123.9 (*Biphenyl*-<u>C</u>H), 126.3 (*Biphenyl*-<u>C</u>H), 126.65 (*Biphenyl*-<u>C</u>H), 126.67 (*Biphenyl*-<u>C</u>H), 126.7 (*Biphenyl*-<u>C</u>H), 126.9 (*Biphenyl*-<u>C</u>H), 127.1 (*Biphenyl*-<u>C</u>H), 127.9 (*Biphenyl*-<u>C</u>H), 134.5 (*Biphenyl*-quat.<u>C</u>), 136.1 (*Biphenyl*-quat.<u>C</u>), 139.2 (*Biphenyl*-quat.<u>C</u>), 140.8 (*Biphenyl*-quat.<u>C</u>). *m/z* $C_{20}H_{23}NO$ requires 293.17796

7-benzyl-4b-methyl-6,7-dihydro-4b*H*,8*H*-5-oxa-7a-aza-dibenzo(*e*,*g*) azulene.



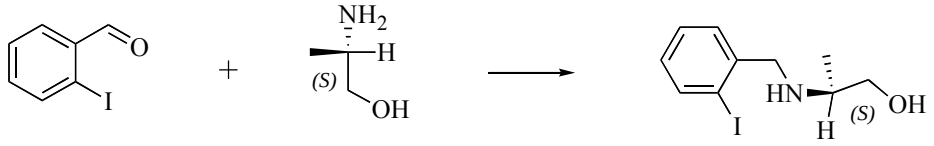
113 ***115*** ***94***

Prepared according to the general procedure using a crude solution of 3-(2'-acetyl-biphenyl-2-ylmethyl)-4-isopropyl-o**x**azolidin-2-one (**113**) to afford the desired tetracycle as one diastereoisomer, isolated as a foam (**94**) (two step; 0.08 g, 0.23 mmol, 8%). ν_{max}(film) /cm^{-1} 2926, 1493, 1452, 1365, 1215, 1158, 1069, 1043, 761, 738, 700. $[\alpha]^{20}_{D}$ −133.8 ° (*c* 1.10, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 0.93 (3 H, s, NC(C<u>H</u>$_3$)O), 2.64 (1 H, q, *J* 10.4 Hz, PhC<u>H</u>H), 3.01 – 3.10 (3 H, m, NC<u>H</u>H, PhCH<u>H</u> & NC<u>H</u>Bn), 3.68 (1 H, d, *J* 10.8 Hz, NCH<u>H</u>), 3.75 (1 H, t, *J* 7.2 Hz, OC<u>H</u>H), 3.94 (1 H, dd, *J* 6.0 & 7.6 Hz, OCH<u>H</u>). 7.13 – 7.17 (2 H, m, 2 *x* Ar-C<u>H</u>), 7.20 – 7.26 (3 H, m, 3 *x* Ar-C<u>H</u>), 7.27 – 7.33 (2 H, m, 2 *x* Ar-C<u>H</u>), 7.34 – 7.40 (4 H, m, 4 *x* Ar-C<u>H</u>), 7.56 – 7.63 (2 H, m, 2 *x* Ar-C<u>H</u>). δ_C (100 MHz; $CHCl_3$) 29.5 (<u>C</u>H$_3$), 38.5 (Ph<u>C</u>H$_2$), 52.4 (N<u>C</u>H$_2$), 65.1 (<u>C</u>HBn), 68.9 (O<u>C</u>H$_2$), 96.9 (quat.<u>C</u>(CH$_3$)), 124.3 (Ar-<u>C</u>H), 125.3 (Ar-<u>C</u>H), 126.4 (Ar-<u>C</u>H), 126.7 (Ar-<u>C</u>H), 126.83 (Ar-<u>C</u>H), 126.84 (Ar-<u>C</u>H), 127.3 (3 *x* Ar-<u>C</u>H), 127.9 (Ar-<u>C</u>H), 128.0 (Ar-<u>C</u>H), 128.1 (2 *x* Ar-<u>C</u>H), 133.8 (quat.Ar-<u>C</u>), 135.9 (*biphenyl*-quat.<u>C</u>), 137.7 (*biphenyl*-quat.<u>C</u>), 138.9 (*biphenyl*-quat.<u>C</u>), 140.9 (*biphenyl*-quat.<u>C</u>). *m/z* 342.18529 [- 1.5 ppm]; $C_{24}H_{23}NO$ requires 341.17796.

General procedure for the reductive amination using 2-iodobenzaldehyde and amino alcohols.

2-iodobenzaldehyde (1.1 equiv.) and the desired amino alcohol (1.0 equiv.) were dissolved in methanol (10 vol.) and agitated over 5 h. To the reaction mixture sodium cyanoborohydride (1.1 equiv.) was added and stirred at ambient temperature for 15 h. The reaction was quenched with ammonium chloride and the solvent was removed under reduced pressure. The remaining residue was dissolved in DCM and was separated from saturated brine and dried over magnesium sulphate. The crude oil was purified by column chromatography using a DCM/MeOH eluent (100:0 – 95:5) to yield the desired secondary amine.

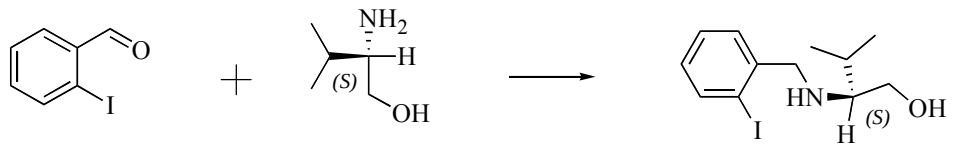
2*S*-(2-iodo-benzylamino)-propan-1-ol.



77 ***116*** ***87***

Prepared according to the general procedure using 2-iodobenzaldehyde (**77**) (6.38 g, 27.5 mmol) and 2-(*S*)-aminopropanol (**116**) (1.88 g, 25 mmol) to yield the desired secondary amine as an oil (**87**) (1.05 g, 3.60 mmol, 14%). ν_{max}(film) /cm^{-1} 3324, 2956, 1563, 1435, 1045, 1011, 750, 648. $[\alpha]^{20}_{D}$ +14.3 ° (*c* 1.09, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 1.05 (3 H, d, *J* 6.4 Hz, C<u>H</u>$_3$), 2.76 – 2.83 (1 H, m (dectet), NC<u>H</u>), 3.24 (1 H, dd, *J* 6.8 & 10.8 Hz, OC<u>H</u>H), 3.57 (1 H, dd, *J* 4.0 & 10.8 Hz, OCH<u>H</u>), 3.70 (1 H, d, *J* 13.2 Hz, NC<u>H</u>H), 3.84 (1 H, d, *J* 13.2 Hz, NCH<u>H</u>), 6.90 (1 H, dt, *J* 1.6 & 7.6 Hz, Ar-C<u>H</u>), 7.25 (1 H, dt, *J* 1.2 & 7.2 Hz, Ar-C<u>H</u>), 7.31 (1 H, dd, *J* 1.6 & 7.6 Hz, Ar-C<u>H</u>), 7.76 (1 H, dd, *J* 1.2 & 8.0 Hz, Ar-C<u>H</u>). δ_C (100 MHz; $CHCl_3$) 17.2 (<u>C</u>H$_3$), 53.9 (N<u>C</u>H), 55.5 (N<u>C</u>H$_2$), 65.4 (O<u>C</u>H$_2$), 99.9 (quat.<u>C</u>), 128.5 (Ar-<u>C</u>H), 129.1 (Ar-<u>C</u>H), 129.9 (Ar-<u>C</u>H), 139.6 (Ar-<u>C</u>H), 141.9 (quat.<u>C</u>I). *m/z* 292.02037 [+ 1.8 ppm]; $C_{10}H_{14}NO^+$ requires 292.01984.

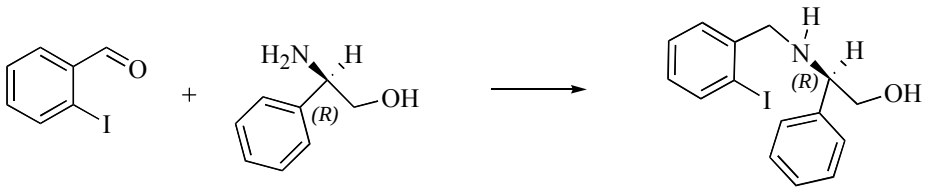
2*S*-(2-iodo-benzylamino)-3-methyl-butan-1-ol .



77 ***117*** ***89***

Prepared according to the general procedure using 2-iodobenzaldehyde (**77**) (6.38 g, 27.5 mmol) and (*S*)-valinol (**117**) (2.56 g, 25.0 mmol) to yield the desired secondary amine as an oil (**89**) (1.30 g, 4.09 mmol, 16%). ν_{max}(film) /cm^{-1} 3321, 2956, 1563, 1464, 1435, 1045, 1011, 750, 648. $[\alpha]^{20}_{D}$ +11.3 ° (*c* 1.42, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 0.85 (3 H, d, *J* 6.8 Hz, C(C$\underline{H}_3$)(CH_3)), 0.91 (3 H, d, *J* 6.8 Hz, C(CH_3)(C$\underline{H}_3$)), 1.81 (1 H, sextet, *J* 6.8 & 13.6 Hz, Pr^i-$\underline{H}$), 2.41 (1 H, dd, *J* 6.0 & 10.0 Hz, NC$\underline{H}$), 3.01 (2 H, s, O$\underline{H}$ & N$\underline{H}$), 3.36 (1 H, dd *J* 7.2 & 10.8 Hz, OC$\underline{H}$H), 3.60 (1 H, dd, *J* 4.0 & 10.8 Hz, OCH$\underline{H}$), 3.73 (1 H, d, *J* 13.2 Hz, NC$\underline{H}$H), 3.80 (1 H, d, *J* 13.2 Hz, NCH$\underline{H}$), 6.89 (1 H, dt, *J* 2.0 & 7.6 Hz, Ar-C$\underline{H}$, *para* to CCH_2), 7.24 (1 H, dt, *J* 1.2 & 7.2 Hz, Ar-C$\underline{H}$, *para* to CI), 7.29 (1 H, dd, *J* 1.2 & 7.6 Hz, Ar-C$\underline{H}$, *orho* to CCH_2), 7.75 (1 H, dd, *J* 1.2 & 8.0 Hz, Ar-C$\underline{H}$, *ortho* to CI). δ_C (100 MHz; $CHCl_3$) 18.6 ($\underline{C}H_3$), 19.7 ($\underline{C}H_3$), 28.8 ($\underline{C}H(CH_3)_2$), 55.8 (N$\underline{C}H_2$), 66.4 (O$\underline{C}H_2$), 63.9 (N$\underline{C}$HPr^i), 99.9 (quat.Ar-$\underline{C}CH_2$), 128.5 (Ar-$\underline{C}$H, *para* to quat.CCH_2), 129.1 (Ar-$\underline{C}$H, *para* to quat.CI), 130.1 (Ar-$\underline{C}$H, *ortho* to quat.CCH_2), 139.6 (Ar-$\underline{C}$H, *ortho* to quat.CI), 142.0 (quat.Ar-$\underline{C}$I). *m/z* 320.05114 [- 0.0 ppm]; $C_{12}H_{18}INO$ requires 320.05114.

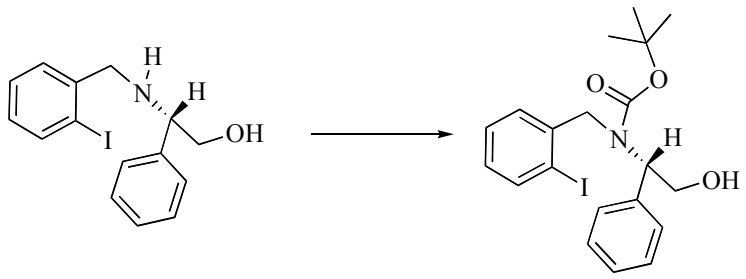
2-(2-iodo-benzylamino)-2-phenyl-ethanol.



77 ***57*** ***76***

To a solution of *R*-phenylglycinol (**57**) (1.32 g, 9.60 mmol) in MeOH (25 mL) at 0 °C under a nitrogen atmosphere was added 2-iodobenzaldehyde (**77**) (2.20 g, 9.50 mmol). The reaction was allowed to warm to ambient temperature whilst being monitored by HPLC. When complete consumption of the starting materials was observed the crude reaction mixture was cooled to 0 °C and $NaBH_4$ (0.66 g, 17.4 mmol) was added over 30 min. The reaction was then allowed to stir for 16 h at ambient temperature. The reaction mixture was then cooled to 0 °C and quenched with saturated $NaHCO_3$ (10% in water, 30 mL). The organic solvent was removed under reduced pressure and dissolved with TBME. The organic fraction underwent saturated aqueous acid/base washing to isolate the pure amino alcohol as a colourless low melting solid (**76**) (2.77 g, 7.80 mmol, 81%). $[\alpha]^{20}_D$ +2.5 ° (*c* 1.10, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 3.57 (1 H, d, *J* 8.8 & 10.4 Hz, OC<u>H</u>H), 3.65 (1 H, d, *J* 13.2 Hz, NC<u>H</u>H), 3.72 (1 H, dd, *J* 4.4 & 6.4 Hz, NC<u>H</u>Ph), 3.78 (1 H, d, *J* 13.2 Hz, NCH<u>H</u>), 3.81 (1 H, dd, *J* 4.4 & 8.4 Hz, OCH<u>H</u>), 6.94 – 6.97 (1 H, m, Ar-C<u>H</u>), 7.26 – 7.40 (7 H, m, 7 *x* Ar-C<u>H</u>), 7.80 – 7.83 (1 H, m, Ar-C<u>H</u>). δ_C (100 MHz; $CHCl_3$), 55.7 (N<u>C</u>HH), 63.8 (N<u>C</u>H), 66.9 (<u>C</u>H_2N), 99.9 (quat.Ar-<u>C</u>(CH_2N)), 127.4 (2 *x* Ar-<u>C</u>H in phenyl ring) 127.8 (Ar-<u>C</u>H), 128.3 (Ar-<u>C</u>H), 128.7 (2 *x* Ar-<u>C</u>H in phenyl ring), 129.0 (Ar-<u>C</u>H), 130.1 (Ar-<u>C</u>H), 139.6 (Ar-<u>C</u>H), 140.2 (quat.Ar-<u>C</u>), 142.1 (quat.Ar-<u>C</u>). *m/z* 354.03630 [+ 2.3 ppm]; $C_{15}H_{16}INO$ requires 353.02766.

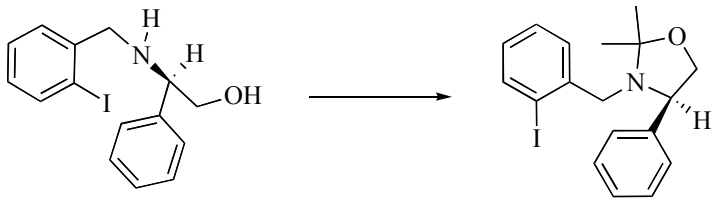
(2-Hydroxy-1-phenyl-ethyl)-(2-iodo-benzyl)-carbamic acid *tert*-butyl ester.



76 ***118***

To 2-(2-iodo-benzylamino)-2-phenyl-ethanol (**76**) (0.38 g, 1.08 mmol) in THF (5 mL), di-*tert*-butyl dicarbonate (0.71 g, 3.24 mmol) and TEA (0.15 mL, 1.1 mmol) were added under a nitrogen atmosphere. The reaction was heated under reflux for 16 h at which the reaction was allowed to cool to ambient temperature. The organic solvent was removed under reduced pressure and re-dissolved in TBME, the crude reaction mixture then underwent saturated aqueous acid/base workup in an attempt to isolate the Boc-protected amido alcohol (**118**). No reaction was observed.

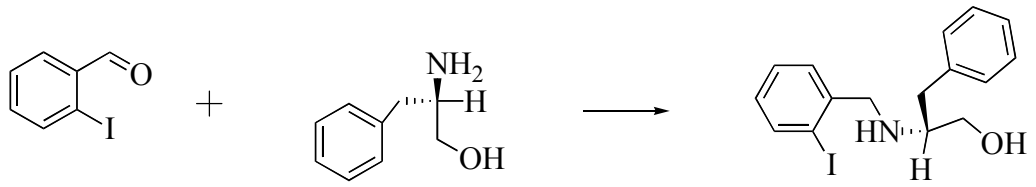
3-(2-Iodo-benzyl)-2,2-dimethyl-4-phenyl-oxazolidine.



76 ***75***

To a solution of 2-(2-iodo-benzylamino)-2-phenyl-ethanol (**76**) (650 mg, 1.84 mmol) in toluene (10 mL) was added DMP (2.25 mL, 18.4 mmol) and *p*-TSA (70.0 mg, 0.37 mmol). The reaction was heated under reflux in Dean and Stark apparatus. The reaction was monitored by TLC and the azeotropic removal of solvents. The crude reaction mixture was separated from saturated brine (3 *x* 20 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification *via* column chromatography using silica gel (washed with 4% TEA) and an ethylacetate/light petrol eluent (10%) yielded the desired acetal as a yellow low melting solid (**75**). (694 mg, 1.76 mmol, 96%). ν_{max}(film) /cm^{-1} 3420, 2972, 1455, 1362, 1255, 1187, 1054, 1011, 753, 700. $[\alpha]^{20}_{D}$ −60.2 (*c* 1.19, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 1.27 (3 H, s, $C^{a}\underline{H}_3$), 1.30 (3 H, s, $C^{b}\underline{H}_3$), 3.59 (1 H,d, *J* 14.8 Hz, NC<u>H</u>H), 3.68 (1 H, t, *J* 8.0 Hz, OC<u>H</u>H), 3.82 (1 H, d, *J* 14.8, NCH<u>H</u>), 4.01 (1 H, t, *J* 7.6 Hz, NC<u>H</u>Ph), 4.14 (1 H, t, *J* 7.2, OCH<u>H</u>), 6.68 (1 H, dt, *J* 1.6 & 7.6 Hz, *meta* in phenyl ring), 7.04 – 7.08 (2 H, m, *meta* in phenyl ring & Ar-C<u>H</u>), 7.10 – 7.14 (2 H, m, *para* in phenyl ring & Ar-C<u>H</u>), 7.27 – 7.31 (2 H, m, 2 *x* Ar-C<u>H</u>), 7.36 (1 H, dd, *J* 1.6 & 8.0 Hz, *ortho* in phenyl ring), 7.54 (1 H, dd, *J* 1.2 & 8.0 Hz, *ortho* in phenyl ring). δ_C (100 MHz; $CHCl_3$) 20.4 ($\underline{C}^{a}H_3$), 27.6 ($\underline{C}^{b}H_3$), 55.6 (N<u>C</u>H_2), 66.6 (N<u>C</u>HPh), 70.9 (O<u>C</u>H_2), 95.2 (quat.<u>C</u>$(CH_3)_2$), 98.4 (quat.<u>C</u>), 126.4 (Ar-<u>C</u>H), 126.5 (Ar-<u>C</u>H), 126.9 (2 *x* Ar-<u>C</u>H), 127.1 (2 *x* Ar-<u>C</u>H), 127.6 (Ar-<u>C</u>H),130.1 (Ar-<u>C</u>H), 137.9 (Ar-<u>C</u>H), 139.4 (quat.Ar-<u>C</u>), 140.0 (quat.Ar-<u>C</u>). *m/z* 393.05828 [+1.7 ppm]; $C_{18}H_{20}INO$ requires 393.05896

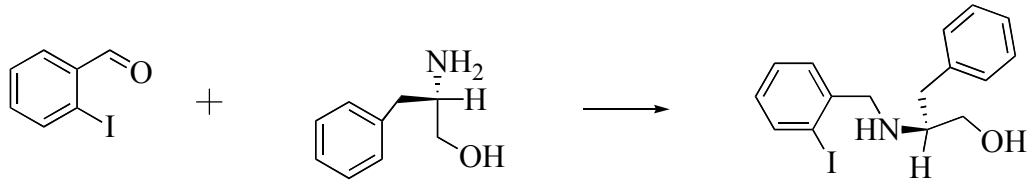
2*R*-(2-iodo-benzylamino)-3-phenyl-propan-1-ol.



77 ***119*** ***91***

Prepared according to the general procedure using 2-iodobenzaldehyde (**77**) (3.00 g, 21.5 mmol) and 2*R*-amino-3-phenyl-propan-1-ol (**119**) (2.92 g, 19.6 mmol) to yield the desired secondary amine as a viscous oil (**91**) (6.47 g, 17.6 mmol, 90%). ν_{max}(film) /cm^{-1} 3441, 2359, 1652, 1635, 1113, 743, 699, 668. $[\alpha]^{20}_{D}$ −21.4 ° (*c* 1.12, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 2.67 – 2.78 (2 H, m [octet], C<u>H</u>$_2$Ph), 2.85 – 2.91 (1 H, m, NC<u>H</u>), 3.30 (1 H, dd, *J* 5.2 & 10.8 Hz, OC<u>H</u>H), 3.62 (1 H, dd, *J* 3.6 & 10.8 Hz, OCH<u>H</u>), 3.71 (2 H, s, NC<u>H</u>H), 6.86 (1 H, dt, *J* 1.6 & 7.6 Hz, Ar-C<u>H</u>, *para* to quat.CCH_2), 7.09 – 7.07 (2 H, m, 2 *x* Ar-C<u>H</u>), 7.12 – 7.16 (2 H, m, 2 *x* Ar-C<u>H</u>), 7.18 – 7.23 (3 H, m, 3 *x* Ar-C<u>H</u>), 7.71 (1 H, dd, *J* 1.2 & 8.0 Hz, Ar-C<u>H</u>, *ortho* to CI). δ_C (100 MHz; $CHCl_3$) 38.2 (<u>C</u>H_2Ph), 55.6 (<u>C</u>H_2), 59.3 (N<u>C</u>H), 62.5 (<u>C</u>H_2), 99.9 (quat.Ar-<u>C</u>), 126.5 (Ar-<u>C</u>H), 128.4 (Ar-<u>C</u>H), 128.7 (2 *x* Ar-<u>C</u>H), 129.0 (Ar-<u>C</u>H), 129.3 (2 *x* Ar-<u>C</u>H), 129.8 (Ar-<u>C</u>H), 138.3 (quat.Ar-<u>C</u>), 139.6 (Ar-<u>C</u>H), 141.9 (quat.Ar-<u>C</u>I). *m/z* 336 (<u>C</u>$_{15}H_{15}NI^+$, minus methanol fraction); $C_{16}H_{18}NOI$ requires 367.0344

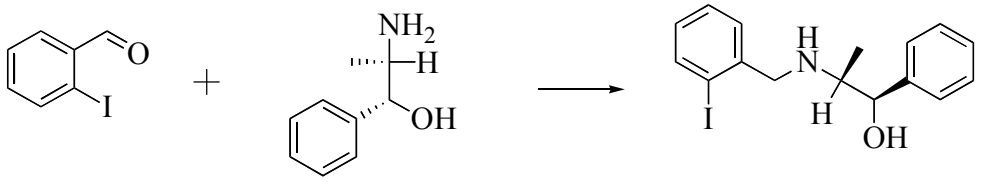
2*S*-(2-iodo-benzylamino)-3-phenyl-propan-1-ol.



77 ***120*** ***93***

Prepared according to the general procedure using 2-iodobenzaldehyde (**77**) (3.00 g, 21.5 mmol) and 2*S*-amino-3-phenyl-propan-1-ol (**120**) (2.92 g, 19.6 mmol) to yield the desired secondary amine as a viscous oil (**93**) (6.19 g, 16.9 mmol, 86%). Having almost identical spectroscopic data to (**91**). ν_{max}(film) /cm^{-1} 3450, 2358, 1645, 1112, 745, 670, 668. $[\alpha]^{20}_{D}$ +19.2 ° (*c* 1.00, $CHCl_3$).

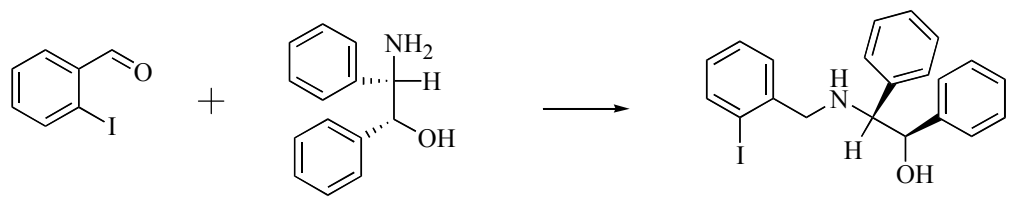
2*R*-(2-iodo-benzylamino)-1*R*-phenyl-propan-1-ol.



77 ***121*** ***95***

Prepared according to the general procedure using 2-iodobenzaldehyde (**77**) (3.00 g, 21.5 mmol) and 2-amino-1-phenyl-propan-1-ol as a viscous oil (**121**) (2.00 g, 13.2 mmol) to yield the desired secondary amine (**95**) (3.26 g, 8.90 mmol, 67%). ν_{max}(film) /cm^{-1} 3403, 3058, 2969, 2869, 1450, 1115, 1011, 741, 701. $[\alpha]^{20}_{D}$ −27.3 ° (*c* 1.10, $CHCl_3$), δ_H (400 MHz; $CDCl_3$) 0.78 (3 h , d, *J* 6.4 Hz, C<u>H</u>$_3$), 2.85 – 2.79 (1 H, m, C<u>H</u>CH$_3$), 3.71 (1 H, d, *J* 13.2 Hz, NC<u>H</u>H), 3.71 (1 H, d, *J* 13.2 Hz, NC<u>H</u>H), 4.63 (1 H, d, *J* 4.0 Hz, C<u>H</u>(Ph)OH), 6.82 – 6.86 (1 H, m, Ar-C<u>H</u>), 7.10 – 7.16 (1 H, m, Ar-C<u>H</u>), 7.17 – 7.22 (6 H, m, 6 *x* Ar-C<u>H</u>) 7.69 – 7.71 (1 H, m, Ar-C<u>H</u>). δ_C (100 MHz; $CHCl_3$) 14.7 (<u>C</u>H$_3$), 55.7 (N<u>C</u>H$_2$), 57.8 (<u>C</u>HCH$_3$), 73.5 (<u>C</u>HOH), 99.9 (quat.Ar-<u>C</u>CH$_2$), 126.3 (2 *x* Ar-<u>C</u>H), 127.2 (Ar-<u>C</u>H), 128.2 (2 *x* Ar-<u>C</u>H), 128.5 (Ar-<u>C</u>H), 129.2 (Ar-<u>C</u>H), 130.0 (Ar-<u>C</u>H), 139.7 (Ar-<u>C</u>H), 141.4 (quat.Ar-<u>C</u>, *ipso* in phenyl ring), 141.8 (quat.Ar-<u>C</u>I). *m/z* 368.05135 [+ 0.6 ppm]; $C_{16}H_{18}INO$ requires 367.04332.

2-(2-iodo-benzylamino)-1,2-diphenyl-ethanol.



77 ***122*** ***123***

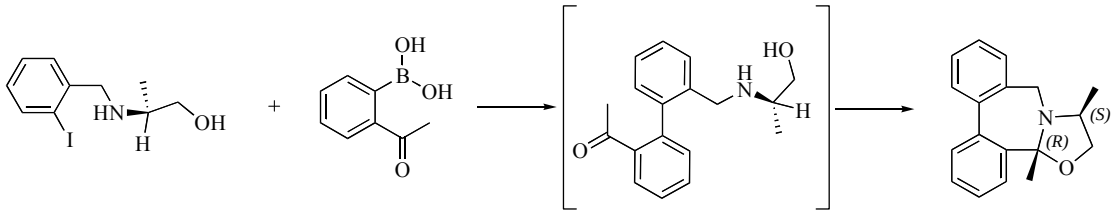
Prepared according to the general procedure using 2-iodobenzaldehyde (**77**) (3.36 g, 14.5 mmol) and 2-amino-1,2-diphenyl-ethanol (**122**) (2.82 g, 13.2 mmol) to yield the desired secondary amine as a foam (**123**) (4.10 g, 9.56 mmol, 66%). ν_{max}(film) /cm^{-1} 3060, 2965, 3006, 2965, 1450, 1416, 1092, 1047, 748, 700. $[\alpha]^{20}_{D}$ −32.1 ° (*c* 0.96, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 3.49 (1 H, d, 13.6 Hz, NC<u>H</u>H), 3.61 (1 H, d, 13.6 Hz, NCH<u>H</u>), 3.78 (1 H,

d,6.0 Hz, NCHPh), 4.71 (1 H, d, 6.4 Hz, OCHPh), 6.86 (1 H, dt, 1.6 & 7.6 Hz, Ar-CH, *para* to quat.CCH_2), 7.02 (1 H, dd, *J* 1.6 & 7.6 Hz, Ar-CH, *para* to quat.CI), 7.08 – 7.06 (1 H, m, Ar-CH), 7.15 – 7.21 (6 H, m, 6 *x* Ar-CH), 7.22 – 7.29 (4 H, m, 4 *x* Ar-CH), 7.69 (1 H, dd, *J* 1.2 & 8.0 Hz, Ar-CH, *ortho* to quat.CI). δ_C (100 MHz; $CHCl_3$) 55.5 (NCH_2), 67.9 (NCHPh), 77.1 (OCHPh), 99.8, (quat.Ar-CCH_2), 127.0 (2 *x* Ar-CH), 127.8 (Ar-CH), 127.9 (Ar-CH), 128.17 (Ar-CH), 128.24 (2 *x* Ar-CH), 128.4, (2 *x* Ar-CH), 128.5 (2 *x* Ar-CH), 129.0 (Ar-CH), 130.2 (Ar-CH), 139.1 (quat.Ar-CCHN), 139.6 (Ar-CH), 140.3 (quat.Ar-CCHO), 141.7 (quat.Ar-CI). *m/z* 430.06602 [+ 1.8 ppm]; $C_{21}H_{21}INO$ requires 430.06678.

General procedure for the addition of iodo-amino alcohols to acetylphenyl boronic acid using Suzuki methodology.

To a solution of the desired amino alcohol (1 equiv.) in toluene (10 vol.) and ethanol (1 vol.), were added boronic acid (1 equiv.) and saturated aqueous potassium carbonate solution (2M in water, 1 vol.). The reaction mixture was degassed with a nitrogen flow over 30 min. After adding the desired palladium catalyst (10%mol), the reaction mixture was then degassed over 15 min. The mixture was stirred at reflux under nitrogen atmosphere whilst monitoring by HPLC, once full consumption of the starting material was observed the reaction was allowed to cool to ambient temperature. The solution was filtered through a plug of celite and toluene was removed under reduced pressure. TBME was then added to the resulting saturated aqueous phase. After phase separation, the combined organic layers were washed with water and dried over $MgSO_4$. The solvents were removed under reduced pressure to afford the crude Suzuki biphenyl compound.

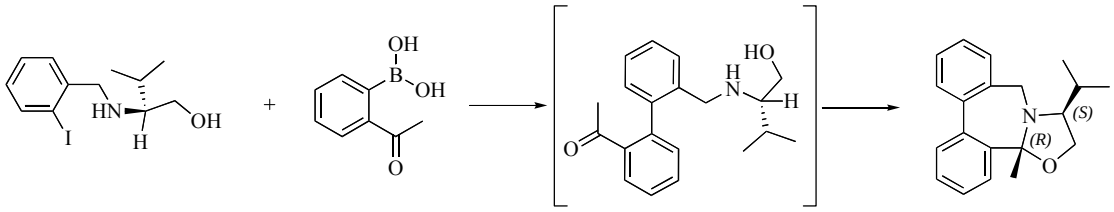
4b,7-dimethyl-6,7-dihydro-4b*H*,8*H*-5-oxa-7a-aza-dibenzo(*e*,*g*)azulene



87 ***60*** ***88***

Prepared according to the general procedure from 2-(2-iodo-benzylamino)-propan-1-ol (**87**) (1.05 g, 3.60 mmol) and acetylphenylbronic acid (**60**) (1.77 g, 10.8 mmol) to yield the desired tetracycle as a viscous oil. (**88**) (0.21 g, 0.80 mmol, 22%). ν_{max}(film) /cm^{-1} 3377, 2966, 1448, 1365, 1217, 1161, 1097, 1046, 756, 738. $[\alpha]^{20}_{D}$ −69.2 ° (*c* 0.96, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 0.90 (3 H, s, NCHC<u>H</u>$_3$), 1.13 (3 H, d, *J* 6 Hz, NC(C<u>H</u>$_3$)O), 2.76 – 2.85 (1 H, m, NC<u>H</u>CH$_3$), 2.92 (1 H, d, *J* 10.8 Hz, NC<u>H</u>H), 3.59 (1 H, dd, *J* 7.6 & 9.6 Hz, OC<u>H</u>H), 3.76 (1 H, d, *J* 11.2 Hz, NCH<u>H</u>), 4.11 (1 H, dd, *J* 6.0 & 7.2 Hz, NCH<u>H</u>), 7.24 – 7.38 (7 H, m, 7 *x Biphenyl*-C<u>H</u>), 7.68 – 7.70 (1 H, m, *Biphenyl*-C<u>H</u>). δ_C (100 MHz; $CHCl_3$) 14.7 (NCH<u>C</u>H$_3$), 29.3 (NC(<u>C</u>H$_3$)O), 51.7 (N<u>C</u>H$_2$), 58.5 (N<u>C</u>HCH$_3$), 70.5 (O<u>C</u>H$_2$), 96.3 (quat.<u>C</u>CH$_3$), 124.7 (*Biphenyl*-<u>C</u>H), 126.4 (*Biphenyl*-<u>C</u>H), 126.5 (*Biphenyl*-<u>C</u>H), 126.9 (2 *x Biphenyl*-<u>C</u>H), 127.5 (*Biphenyl*-<u>C</u>H), 127.8 (*Biphenyl*-<u>C</u>H), 128.1 (*Biphenyl*-<u>C</u>H), 133.7 (*Biphenyl*-quat.<u>C</u>), 135.7 (*Biphenyl*-quat.<u>C</u>), 139.1 (*Biphenyl*-quat.<u>C</u>), 141.2 (*Biphenyl*-quat.<u>C</u>). *m/z* $C_{18}H_{19}NO$ requires 265.14666.

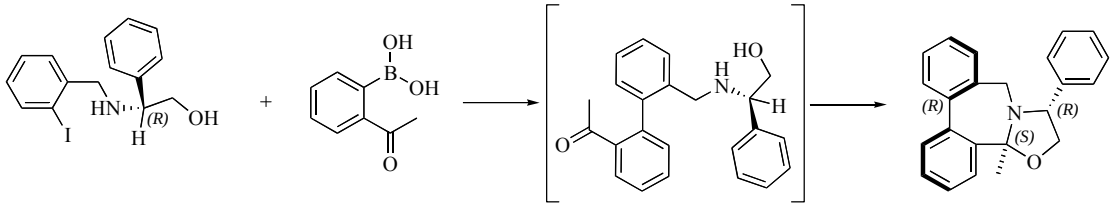
7-isopropyl-4b-methyl-6,7-dihydro-4b*H*,8*H*-5-oxa-7a-aza-dibenzo (*e*,*g*) azulene.



89 ***60*** ***90a***

Prepared according to the general procedure from 2-(2-Iodo-benzylamino)-3-methyl-butan-1-ol (**89**) (1.30 g, 4.09 mmol) and acetylphenylbronic acid (**60**) (2.01 g, 12.3 mmol) to yield the desired tetracycle as a foam. (**90a**), having almost identical spectroscopic data to (**90**). (0.54 g, 1.90 mmol, 47%). ν_{max}(film) /cm^{-1} 3419, 2954, 2871, 1459, 1365, 1213, 1160, 1043, 756, 730. $[\alpha]^{20}_{D}$ −98.8 ° (*c* 1.21, $CHCl_3$). *m/z* $C_{20}H_{23}NO$ requires 293.17796.

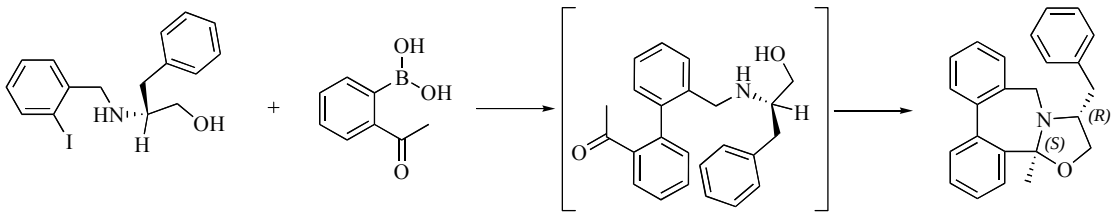
4b-Methyl-7-phenyl-6,7-dihydro-4b*H*,8*H*-5-oxa-7a-aza-dibenzo(*e*,*g*) azulene



76 ***60*** ***62a***

Prepared according to the general procedure from 2-(2-iodo-benzylamino)-2-phenyl-ethanol (**76**) (2.29 g, 6.50 mmol) and acetylphenylbronic acid (**60**) (3.20 g, 19.5 mmol) to yield the desired tetracycle as colourless foam (**62a**), having almost identical spectroscopic data to (**62**). (0.85 g, 2.60 mmol, 40%). ν_{max}(film) /cm^{-1} 2963, 1449, 1260, 1153, 1038, 897, 802, 758, 740, 701. $[\alpha]^{20}_{D}$ −22.9 ° (*c* 1.10, $CHCl_3$). *m/z* 327.16263 [+ 1.0 ppm]; $C_{23}H_{21}NO$ requires 327.16231.

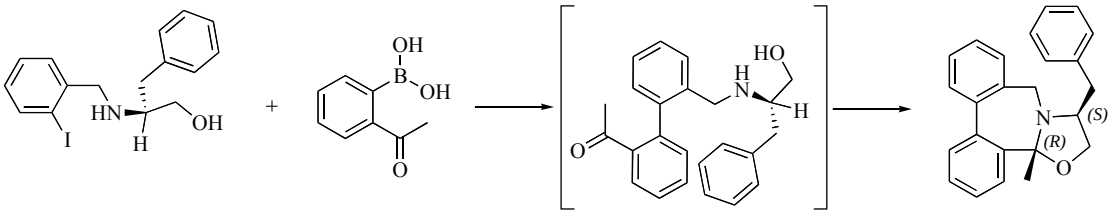
7-Benzyl-4b-methyl-6,7-dihydro-4b*H*,8*H*-5-oxa-7a-aza-dibenzo (*e*,*g*) azulene



91 ***60*** ***92***

Prepared according to the general procedure from 2-(2-Iodo-benzylamino)-3-phenyl-propan-1-ol (**100**) (1.00 g, 2.70 mmol) and acetylphenylbronic acid (**50**) (1.34 g, 8.20 mmol) to yield the desired tetracycle as colourless foam (**92**), having almost identical spectroscopic data to (**93**). (0.51 g, 1.60 mmol, 60%). ν_{max}(film) /cm^{-1} 2926, 1493, 1452, 1365, 1215, 1158, 1069, 1043, 761, 738, 700. $[\alpha]^{20}_{D}$ −130.1 ° (*c* 0.99, $CHCl_3$).

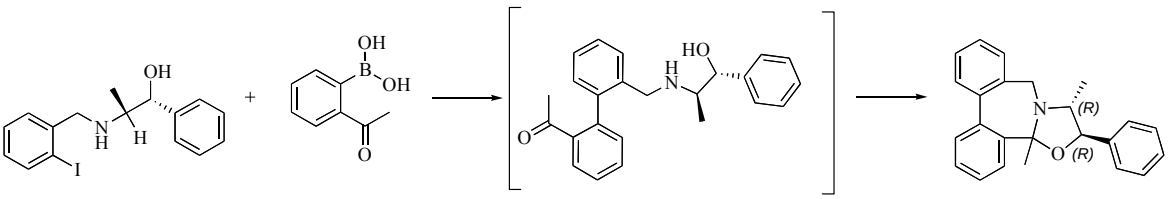
7-Benzyl-4b-methyl-6,7-dihydro-4b*H*,8*H*-5-oxa-7a-aza-dibenzo (*e*,*g*) azulene.



93 ***60*** ***94***

Prepared according to the general procedure from 2-(2-Iodo-benzylamino)-3-phenyl-propan-1-ol (**93**) (1.00 g, 2.70 mmol) and acetylphenylbronic acid (**60**) (1.34 g, 8.20 mmol) to yield the desired tetracycle as colourless foam (**94**), having almost identical spectroscopic data to (**93**). (0.27 g, 0.80 mmol, 30%). ν_{max}(film) /cm^{-1} 2927, 1602, 1452, 1365, 1215, 1156, 1070, 761, 738, 700. $[\alpha]^{20}_{D}$ +130.9 ° (*c* 1.03, $CHCl_3$).

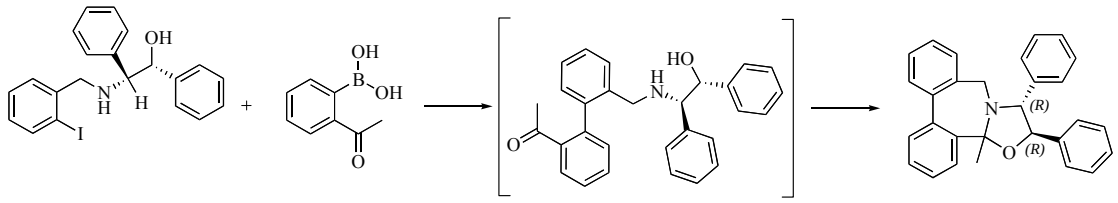
4b,7-Dimethyl-6-phenyl-6,7-dihydro-4b*H*,8*H*-5-oxa-7a-aza-dibenzo (*e*,*g*)azulene



95 ***60*** ***96***

Prepared according to the general procedure from 2-(2-iodo-benzylamino)-propan-1-ol (**95**) (0.33 g, 0.89 mmol) and acetylphenylbronic acid (**60**) (0.44 g, 2.67 mmol) to yield the desired tetracycle as colourless crystals as a mixture of two diastereoisomers as a viscous oil. (**96**) (0.11 g, 0.27 mmol, 30%).ν_{max}(film) /cm^{-1} 3055, 2927, 1723, 1600, 1488, 1437, 1286, 757, 738, 699. $[\alpha]^{20}_{D}$ −18.4 ° (*c* 1.00, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 0.74 (3 H, d, *J* 6.8 Hz, minor-CHC<u>H</u>$_3$), 0.89 – 0.93 (3 H. m, major-CHC<u>H</u>$_3$), 1.17 – 1.21 (3 H, m, minor-NCC<u>H</u>$_3$), 2.44 (3 H, s, major-NCC<u>H</u>$_3$), 3.02 (1 H, d, *J* 10.8 Hz, minor-NC<u>H</u>H), 3.10 – 3.14 (1 H, m, minor-C<u>H</u>CH$_3$), 3.81 (1 H, d, *J* 11.2 Hz, minor-NC<u>H</u>H), 4.18 –4.26 (1 H, m, major-C<u>H</u>CH$_3$), 4.65 (1 H, d, *J* 14.4 Hz, major-NC<u>H</u>H), 4.87 (1 H, d, *J* 14.0 Hz, major-NCH<u>H</u>), 5.26 (1 H, d, *J* 8.0 Hz, minor-C<u>H</u>Ph), 6.47 (1 H, s, major-C<u>H</u>Ph), 7.13 – 7.17 (1 H, m, major-Ar-C<u>H</u>), 7.21 – 7.46 (20 H, m, 9 *x* major & 11 *x* minor Ar-C<u>H</u>), 7.50 – 7.52 (1 H, m, major-Ar-C<u>H</u>), 7.56 (1 H, dd, *J* 1.2 & 7.2 Hz, major-Ar-C<u>H</u>), 7.62 – 7.64 (1 H, m, major-Ar-C<u>H</u>), 7.67 (1 H, dd, *J* 3.2 & 5.6 Hz, minor-Ar-C<u>H</u>), 7.77 – 7.79 (1 H, m, minor-Ar-C<u>H</u>). δ_C (100 MHz; $CHCl_3$) 9.91 (major C<u>C</u>H$_3$), 9.96 (major CH<u>C</u>H$_3$), 13.1 (minor C<u>C</u>H$_3$), 14.9 (minor CH<u>C</u>H$_3$), 46.5 (major N<u>C</u>H$_2$), 53.1 (minor N<u>C</u>H$_2$), 62.6 (minor <u>C</u>HCH$_3$), 67.0 (major <u>C</u>HCH$_3$), 80.5 (minor <u>C</u>HPh), 96.5 (major quat.<u>C</u>CH$_3$), 105.6 (major <u>C</u>HPh), 121.6 (minor quat.<u>C</u>CH$_3$), 124.4 (minor Ar-<u>C</u>H), 125.6 (major Ar-<u>C</u>H), 127.0 (major Ar-<u>C</u>H), 126.5 (minor Ar-<u>C</u>H), 126.56 (minor Ar-<u>C</u>H), 126.58 (major Ar-<u>C</u>H), 126.61 (major Ar-<u>C</u>H), 126.69 (minor Ar-<u>C</u>H), 126.73 (minor Ar-<u>C</u>H), 126.9 (major Ar-<u>C</u>H), 126.95 (minor Ar-<u>C</u>H), 127.0 (Ar-<u>C</u>H), 127.1 (2 *x* Ar-<u>C</u>H), 127.2 (2 *x* Ar-<u>C</u>H), 127.3 (major Ar-<u>C</u>H), 127.4 (minor Ar-<u>C</u>H), 127.6 (minor Ar-<u>C</u>H), 127.7 (minor Ar-<u>C</u>H), 127.8 (major Ar-<u>C</u>H), 127.9 (minor Ar-<u>C</u>H), 128.2 (minor Ar-<u>C</u>H), 128.9 (major Ar-<u>C</u>H), 129.2 (major Ar-<u>C</u>H), 129.8 (major Ar-<u>C</u>H), 131.1 (major quat.Ar-<u>C</u>), 131.3 (minor quat.Ar-<u>C</u>), 133.9 (minor quat.Ar-<u>C</u>), 135.0 (major quat.Ar-<u>C</u>), 136.1 (minor quat.Ar-<u>C</u>), 136.4 major (quat.Ar-<u>C</u>), 139.0 (major quat.Ar-<u>C</u>), 141.4 (minor quat.Ar-<u>C</u>), 166.6 (major quat.Ar-<u>C</u>), 169.9 (mior quat.Ar-<u>C</u>). *m/z* $C_{24}H_{23}NO$ requires 341.17796 .

4b-Methyl-6,7-diphenyl-6,7-dihydro-4b*H*,8*H*-5-oxa-7a-aza-dibenzo (*e*,*g*)azulene



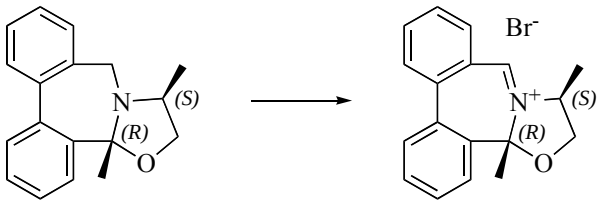
123 ***60*** ***124***

Prepared according to the general procedure from 2-(2-iodo-benzylamino)-1,2-diphenyl-ethanol (**123**) (1.62 g, 3.8 mmol) and acetylphenylbronic acid (**60**) (1.87 g, 11.5 mmol) to yield the desired tetracycle as viscous oil. (**124**) (0.30 g, 0.70 mmol, 18%).ν_{max}(film) /cm^{-1} 3747, 3055, 1599, 1505, 1456, 1262, 1182, 1027, 803, 756, 737, 699. $[\alpha]^{20}_{D}$ – 32.1 ° (*c* 0.96, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 0.01 (3 H, s, C<u>H</u>$_3$), 4.54 (1 H, d, *J* 14.0 Hz, NC<u>H</u>H), 4.75 (1 H, d, *J* 14.0 Hz, NCH<u>H</u>), 6.60 (1 H, d, *J* 1.2 Hz, NC<u>H</u>Ph), 6.97 – 7.08 (7 H, m, 6 *x* Ar-C<u>H</u> & OC<u>H</u>Ph), 7.10 – 7.46 (8 H, m, Ar-C<u>H</u>), 7.54 – 7.61 (2 H, m, Ar-C<u>H</u>), 7.69 – 7.70 (1 H, m, Ar-C<u>H</u>). δ_C (100 MHz; $CHCl_3$) 0.0 (<u>C</u>H$_3$), 46.7 (N<u>C</u>H$_2$), 96.7 (quat.<u>C</u>CH$_3$), 106.0 (N<u>C</u>HPh), 124.1 (O<u>C</u>HPh), 126.0 (Ar-<u>C</u>H), 126.3 (Ar-<u>C</u>H), 126.8 (Ar-<u>C</u>H), 126.9 (Ar-<u>C</u>H), 127.0 (Ar-<u>C</u>H), 127.1 (Ar-<u>C</u>H), 127.4 (Ar-<u>C</u>H), 127.4 (Ar-<u>C</u>H), 127.47 (Ar-<u>C</u>H), 127.52 (Ar-<u>C</u>H), 127.6 (Ar-<u>C</u>H), 127.7 (Ar-<u>C</u>H), 128.2 (Ar-<u>C</u>H), 129.17 (Ar-<u>C</u>H), 129.20 (Ar-<u>C</u>H), 130.5 (Ar-<u>C</u>H), 132.6 (Ar-<u>C</u>H), 132.8 (Ar-<u>C</u>H), 135.19 (quat.Ar-<u>C</u>), 135.24 (quat.Ar-<u>C</u>), 136.0 (quat.Ar-<u>C</u>), 136.2 (quat.Ar-<u>C</u>), 136.5 (quat.Ar-<u>C</u>), 139.1 (quat.Ar-<u>C</u>). *m/z* 384.17935 [+ 1.6 ppm]; $C_{28}H_{24}NO$ requires 384.17996.

General procedure for the oxidation of tertiary cyclic amines with *N*-bromosuccinimide.

To an ice-cooled solution of the desired tertiary cyclic amine (1 equiv.) in dichloromethane (5 vol.) was added *N*-bromosuccinimide (2 equiv.). The reaction mixture was removed from the ice bath and stirred for 20 min whilst monitoring by HPLC/TLC. Water (10 vol.) was added to the reaction mixture and the DCM layer was separated and dried over magnesium sulphate. The solvent was removed under reduced pressure to yield the desired tetracyclic iminium bromide salt.

4b,7-Dimethyl-6,7-dihydro-4b*H*-5-oxa-7a-azonia-dibenzo(*e*,*g*)azulene; bromide salt.

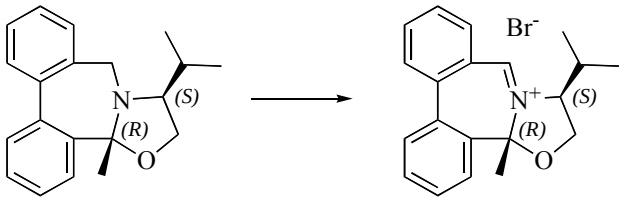


88 ***82***

Prepared following the general procedure using **88** (0.21 g, 0.80 mmol) in dichloromethane (2 mL) and *N*-bromosuccinimide (0.29 g, 1.60 mmol) to yield the tetracyclic iminium bromide salt as a pair of diastereoisomers (**82**) (0.20 g, 0.59 mmol, 74%). ν_{max}(film) /cm^{-1} 2965, 1704, 1652, 1558, 1259, 1184, 1102, 1017, 763, 615. $[\alpha]^{20}_{D}$ 107.6 ° (*c* 10.3, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 1.33 (3 H, s, minor-NCC$\underline{H}_3$), 1.45 (3 H, s, minor-NCC$\underline{H}_3$), 1.40 (3 H, d, *J* 6.4 Hz, minor-CHC$\underline{H}_3$), 1.91 (3 H, d, *J* 6.8 Hz, major-CHC$\underline{H}_3$), 3.84 (1 H, dd, *J* 0.4 & 8.4 Hz, minor-OC$\underline{H}$H), 4.00 (1 H, dd, *J* 4.4 & 8.8 Hz,

minor-OCHH), 4.30 (1 H, dd, *J* 2.4 & 9.6 Hz, major-OCHH), 4.42 (1 H, dd, *J* 5.2 & 9.2 Hz, minor-OCHH), 4.44 – 4.50 (1 H, m, minor-CHCH$_3$), 5.06 – 5.10 (1 H, m, major-CHCH$_3$), 7.33 – 7.36 (4 H, m, 4 *x* minor-Ar-CH), 7.56 (2 H, dd, *J* 1.6 & 7.2 Hz, 2 *x* major-Ar-CH), 7.59 (1 H, td, *J* 2.0 & 7.6 Hz, major-Ar-CH), 7.65 – 7.71 (6 H, m, 2 *x* major-Ar-CH & 4 *x* minor-Ar-CH), 7.88 – 7.91 (2 H, m, 2 *x* major-Ar-CH), 8.32 (1 H, d, *J* 7.6 Hz, major-Ar-CH), 9.92 (1 H, s, N=CH). δ_C (100 MHz; $CHCl_3$) 17.9 (minor NCCH$_3$), 20.0 (major NCCH$_3$), 22.5 (major OCCH$_3$), 25.4 (minor OCCH$_3$), 53.5 (minor CHMe), 63.8 (major CHMe), 68.8 (minor CHHO), 69.7 (major CHHO), 92.1 (minor quat.CMe), 98.8 (major quat.CMe), 121.2 (*Biphenyl*-CH), 122.5 (*Biphenyl*-CH), 123.7 (*Biphenyl*-quat.C), 127.0 (*Biphenyl*-CH), 127.3 (*Biphenyl*-CH) minor, 127.7 (*Biphenyl*-CH), 128.1 (*Biphenyl*-CH), 128.2 (*Biphenyl*-CH), 129.2 (*Biphenyl*-CH), 129.3 (*Biphenyl*-CH), 129.7 (*Biphenyl*-CH), 129.8 (*Biphenyl*-CH), 130.0 (*Biphenyl*-CH), 130.4 (*Biphenyl*-CH), 130.9 (*Biphenyl*-CH), 131.9 (*Biphenyl*-quat.C), 132.5 (*Biphenyl*-quat.C), 134.5 (*Biphenyl*-quat.C), 135.1 (*Biphenyl*-CH), 136.1 (*Biphenyl*-CH), 136.3 (*Biphenyl*-quat.C), 136.6 (*Biphenyl*-quat.C), 140.8 (*Biphenyl*-quat.C), 141.5 (*Biphenyl*-quat.C), 143.3 (*Biphenyl*-quat.C), 146.7 (*Biphenyl*-quat.C), 146.8 (*Biphenyl*-quat.C), 163.30 (major N=CH), 176.65 (minor N=CH). *m/z* $C_{18}H_{18}NO^+$ requires 246.13884.

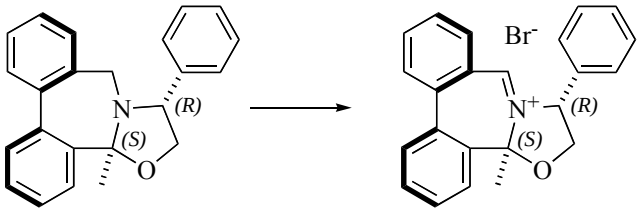
7-Isopropyl-4b-methyl-6,7-dihydro-4b*H*-5-oxa-7a-azonia-dibenzo(*e*,*g*) azulene; bromide salt.



90 ***83***

Prepared following the general procedure using **90** (0.54 g, 1.90 mmol) in dichloromethane (2 mL) and *N*-bromosuccinimide (0.68 g, 3.80 mmol) to yield the desired tetracyclic iminium bromide salt (**83**) (0.57 g, 1.50 mmol, 81%). ν_{max}(film) /cm^{-1} 3397, 2359, 1699, 1652, 1635, 1558, 1259, 1184, 1098, 744. $[\alpha]^{20}_{D}$ 125.9 ° (*c* 1.16, $CHCl_3$).δ_H (400 MHz; $CDCl_3$) 1.13 (3 H, d, *J* 6.8 Hz, CH(C<u>H</u>$_3$)(CH$_3$)), 1.21 (3 H, d, *J* 6.8 Hz, CH(CH$_3$)(C<u>H</u>$_3$)), 1.37 (3 H, s, NCC<u>H</u>$_3$), 2.58 – 2.66 (1 H, m [sextet], C<u>H</u>(CH$_3$)$_2$), 4.27 (1 H, dd, *J* 5.2 & 10.0 Hz, OC<u>H</u>H), 4.42 (1 H, d, *J* 9.6 Hz, OCH<u>H</u>), 5.00 (1 H, s (broad) NC<u>H</u>Pr^i), 7.40 – 7.44 (1 H, m, *Biphenyl*-C<u>H</u>), 7.50 – 7.59 (2 H, m, 2 *x Biphenyl*-C<u>H</u>), 7.61 – 7.66 (2 H, m, 2 *x Biphenyl*-C<u>H</u>), 7.84 – 7.89 (2 H, m, 2 *x Biphenyl*-C<u>H</u>), 8.23 (1 H, d, *J* 7.6, *Biphenyl*-C<u>H</u>) 10.61 (1 H, s, N=C<u>H</u>). δ_C (100 MHz; $CHCl_3$) 17.2 (<u>C</u>H$_3$), 18.1 (<u>C</u>H$_3$), 21.4 (quat.<u>C</u>H$_3$), 30.8 (<u>C</u>H(Me)$_2$), 66.1 (O<u>C</u>HH), 71.0 (<u>C</u>HPr^i), 98.4 (quat.<u>C</u>Me), 122.5 (*Biphenyl*-<u>C</u>H), 123.8 (*Biphenyl*-quat.<u>C</u>), 128.1 (*Biphenyl*-<u>C</u>H), 129.0 (*Biphenyl*-<u>C</u>H), 129.7 (*Biphenyl*-<u>C</u>H), 129.8 (*Biphenyl*-<u>C</u>H), 129.9 (*Biphenyl*-<u>C</u>H), 132.6 (*Biphenyl*-quat.<u>C</u>), 134.4 (*Biphenyl*-<u>C</u>H), 135.7 (*Biphenyl*-<u>C</u>H), 136.9 (*Biphenyl*-quat.<u>C</u>), 141.2 (*Biphenyl*-quat.<u>C</u>), 164.7 (N=<u>C</u>H). *m/z* 292.17045 [+ 1.1 ppm]; $C_{20}H_{22}NO^+$ Br$^-$ requires 292.17014.

4b-Methyl-7-phenyl-6,7-dihydro-4b*H*-5-oxa-7a-azonia-dibenzo(*e,g*) azulene; bromide salt.

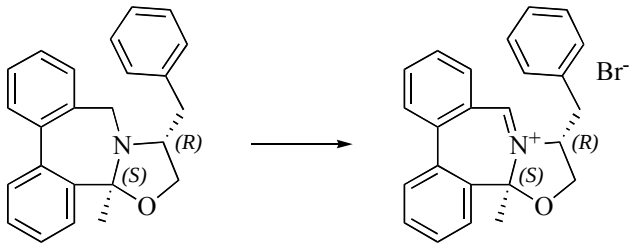


62 ***61***

Prepared following the general procedure using **62** (0.43 g, 1.32 mmol) in dichloromethane (2 mL) and *N*-bromosuccinimide (0.47 g, 2.64 mmol) to generate the desired tetracyclic iminium bromide salt (**61**) (0.27 g, 0.66 mmol, 50%). ν_{max}(film) /cm^{-1} 3394, 3055, 2359, 1713, 1639, 1436, 1181, 751, 722, 696. $[\alpha]^{20}_{D}$ – 20.0 ° (*c* 1.00, $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 1.42 (3 H, s, major-C<u>H</u>$_3$), 1.47 (3 H, s, minor-C<u>H</u>$_3$), 4.19 (1 H, dd, *J* 0.8 & 8.4 Hz, minor-C<u>H</u>HO), 4.33 (1 H, dd, *J* 6.4 & 8.8 Hz, minor-CH<u>H</u>O), 4.65 (1 H, dd. *J* 5.6 & 9.6 Hz, major-C<u>H</u>HO), 4.77 (1 H, dd. *J* 1.2 & 9.6 Hz, major-CH<u>H</u>O), 5.36 (1 H, d, *J* 6.4 Hz, minor-C<u>H</u>Ph) minor, 6.50 (1 H, d, *J* 5.2 Hz, major-C<u>H</u>Ph), 7.29 – 7.33 (1 H, m, Ar-C<u>H</u>), 7.368 – 7.475 (6 H, m, 6 *x* Ar-C<u>H</u>), 7.54 – 7.60 (3 H, m, 3 *x* Ar-C<u>H</u>), 7.61 – 7.65 (2 H, m, 2 *x* Ar-C<u>H</u>), 7.73 (1 H, dd, *J* 1.2 & 8.0 Hz, Ar-C<u>H</u>), 7.78 – 7.87 (5 H, m, 5 *x* Ar-C<u>H</u>), 7.93 – 7.91 (1 H, m, Ar-C<u>H</u>), 7.98 – 8.01 (2 H, m, 2 *x* Ar-C<u>H</u>), 10.38 (1 H, s, N=C<u>H</u>). δ_C (100 MHz; $CHCl_3$) 22.1 (CH_3), 24.6 (minor <u>C</u>H$_3$), 60.7 (minor <u>C</u>HPh), 68.0 (major <u>C</u>HPh), 69.6 (major O<u>C</u>HH), 70.0 (minor O<u>C</u>HH), 92.8 (minor quat.<u>C</u>Me), 98.7 (major quat.<u>C</u>Me), 121.2 (minor Ar-<u>C</u>H), 122.3 (major Ar-<u>C</u>H), 123.8 (major quat.Ar-<u>C</u>), 125.8 (2 *x* minor Ar-<u>C</u>H), 126.5 (minor Ar-<u>C</u>H), 127.0 (minor Ar-<u>C</u>H), 127.2 (minor Ar-<u>C</u>H), 127.3 (3 *x* Ar-<u>C</u>H, 2 *x* major & 1 *x* minor), 127.4 (2 *x* minor Ar-<u>C</u>H), 127.8 (minor Ar-<u>C</u>H), 127.88 (minor Ar-<u>C</u>H), 127.91 (major Ar-<u>C</u>H), 128.9 (2 *x* major Ar-<u>C</u>H), 129.1 (major Ar-<u>C</u>H), 129.3 (major Ar-<u>C</u>H), 129.786 (major Ar-<u>C</u>H), 129.787 (minor Ar-<u>C</u>H), 130.0 (major Ar-<u>C</u>H), 130.3 (minor Ar-<u>C</u>H), 131.0 (major Ar-<u>C</u>H), 132.3 (minor quat.Ar-<u>C</u>), 132.6 (major quat.Ar-<u>C</u>), 134.5 (major

quat.Ar-C), 134.8 (minor quat.Ar-C), 135.0 (major quat.Ar-C), 135.8 (major Ar-CH), 136.1 (minor quat.Ar-C), 136.7 (major quat.Ar-C), 139.9 (minor quat.Ar-C), 140.8 (minor quat.Ar-C), 141.8 (major quat.Ar-C), 163.6 (minor N=CH), 164.0 (major N=CH). *m/z* 326.15489 [+ 1.2 ppm]; $C_{23}H_{20}NO^{+}$ Br^{-} requires 326.15449.

7-Benzyl-4b-methyl-6,7-dihydro-4b*H*-5-oxa-7a-azonia-dibenzo(*e*,*g*) azulene; bromide salt.

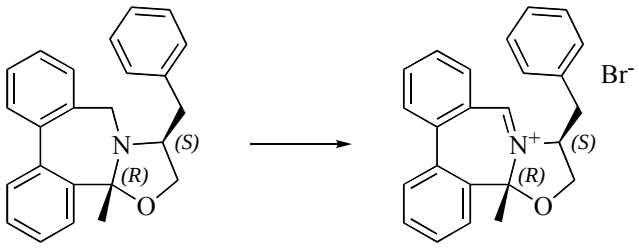


92 ***84***

Prepared following the general procedure using **92** (0.27 g, 0.80 mmol) in dichloromethane (2 mL) was added *N*-bromosuccinimide (0.29 g, 1.60 mmol) to yield the desired tetracyclic iminium bromide salt (**84**) (0.28 g, 0.66 mmol, 82%). ν_{max}(film) /cm^{-1} 3445, 2358, 1714, 1654, 1616, 1558, 1454, 1404, 1257, 1182, 1104, 744, 701, 668. $[\alpha]^{20}_{D}$ – 17.4 ° (*c* 0.99, $CHCl_3$). δ_H (400 M Hz; $CDCl_3$) 1.26 (3 H, s, minor CH_3), 1.42 (3 H, s, major CH_3), 2.77 (1 H, d, *J* 10.4 Hz, minor CHHPh), 3.34 (1 H, dd, *J* 2.8 & 12.8 Hz, major CHHPh), 3.39 – 3.49 (2 H, m, major CHHPh), 3.79 (1 H, dd, *J* 1.2 & 5.6 Hz, minor OCHH), 3.96 (1 H, d, *J* 9.2 Hz, minor OCHH), 4.32 (1 H, dd, *J* 4.4 & 9.6 Hz, major OCHH), 4.42 (1 H, d, *J* 9.6 Hz, major OCHH), 4.46 – 4.54 (1 H, m, minor NCH), 5.13 – 5.21 (1 H, m, major NCH), 7.23 – 7.25 (2 H, m, 2 *x* Ar-CH), 7.31 – 7.56 (21 H, [7.31 – 7.37 (m), 7.39 – 7.47 (m), 7.48 – 7.55 (m), 7.60 (ddt, *J* 1.2 & 7.6 Hz)] 21 *x* Ar-CH), 7.80 – 7.85 (2 H, m, 2 *x* Ar-CH), 7.92 (1 H, dd, *J* 1.2 & 7.6 Hz, Ar-CH), 8.97 (1H,

s, minor N=C<u>H</u>), 8.99 (1 H. s, major N=C<u>H</u>). δ_C (100 M Hz; $CHCl_3$) 22.3 (major <u>C</u>H_3), 24.9 (minor <u>C</u>H_3), 36.9 (minor PhC<u>H</u>$_2$), 39.0 (major PhC<u>H</u>$_2$), 59.3 (minor NC<u>H</u>), 65.7 (minor OC<u>H</u>$_2$), 67.9 (major NC<u>H</u>), 68.0 (major OC<u>H</u>$_2$), 92.5 (minor quat.<u>C</u>Me), 99.0 (major quat.<u>C</u>Me), 121.1 (minor quat.Ar-<u>C</u>), 122.3 (major quat.Ar-<u>C</u>), 123.3 (major quat.Ar-<u>C</u>), 125.6 (minor quat.Ar-<u>C</u>), 127.1 (minor quat.Ar-<u>C</u>), 127.2 (major quat.Ar-<u>C</u>), 127.3 (minor quat.Ar-<u>C</u>), 127.6 (major quat.Ar-<u>C</u>), 127.7 (minor quat.Ar-<u>C</u>), 128.0 (major quat.Ar-<u>C</u>), 128.2 (minor quat.Ar-<u>C</u>), 128.6 (major 2 *x* minor quat.Ar-<u>C</u>), 128.7 (major 2 *x* quat.Ar-<u>C</u>), 129.2 (major 2 *x* minor quat.Ar-<u>C</u>), 129.2 (major 2 *x* quat.Ar-<u>C</u>), 129.3 (minor quat.Ar-<u>C</u>), 129.7 (minor quat.Ar-<u>C</u>), 129.8 (major quat.Ar-<u>C</u>), 130.0 (major quat.Ar-<u>C</u>), 130.6 (minor quat.Ar-<u>C</u>), 130.9 (major quat.Ar-<u>C</u>), 131.7 (minor quat.Ar-<u>C</u>), 132.4 (major quat.Ar-<u>C</u>), 133.1 (major quat.Ar-<u>C</u>), 133.8 (major quat.Ar-<u>C</u>), 134.5 (minor quat.Ar-<u>C</u>), 135.9 (major quat.Ar-<u>C</u>), 136.3 (minor quat.Ar-<u>C</u>), 136.6 (major quat.Ar-<u>C</u>), 137.0 (minor quat.Ar-<u>C</u>), 140.7 (minor quat.Ar-<u>C</u>), 141.4 (major quat.Ar-<u>C</u>), 163.4 (major N=<u>C</u>H), 176.5 (minor N=<u>C</u>H). *m/z* 340.17068 [+ 1.6 ppm]; $C_{24}H_{22}NO^+$ Br^- requires 340.17014.

7-Benzyl-4b-methyl-6,7-dihydro-4b*H*-5-oxa-7a-azonia-dibenzo(*e,g*) azulene; bromide salt.

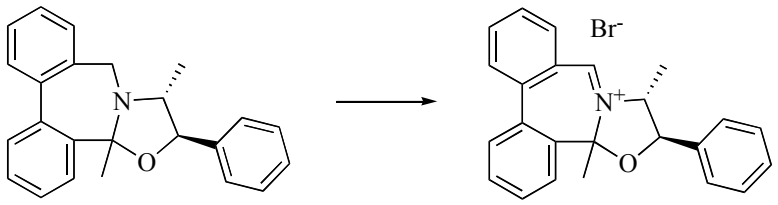


94 ***85***

Prepared following the general procedure using **94** (0.51 g, 1.60 mmol) in

dichloromethane (2 mL) was added *N*-bromosuccinimide (0.57 g, 3.20 mmol) to yield the desired tetracyclic iminium bromide salt (**85**) (0.62 g, 1.20 mmol, 75%). Having almost identical spectroscopic data to (**84**). ν_{max}(film) /cm^{-1} 3445, 2358, 1714, 1654, 1616, 1558, 1454, 1404, 1257, 1182, 1104, 744, 701, 668. $[\alpha]^{20}_{D}$ +15.0 ° (*c* 1.07, $CHCl_3$).

4b,7-Dimethyl-6-phenyl-6,7-dihydro-4b*H*-5-oxa-7a-azonia-dibenzo (*e*,*g*)azulene; bromide salt.



96 ***86***

Prepared following the general procedure using **96** (0.11 g, 0.32 mmol) in dichloromethane (2 mL) was added *N*-bromosuccinimide (0.11 g, 0.64 mmol) to yield the desired tetracyclic iminium bromide salt. (**86**) (0.10 g, 0.24 mmol, 75%). ν_{max}(film) /cm^{-1} 3380, 3053, 2360, 1724, 1641, 1597, 1259, 1172, 908, 733, 703. $[\alpha]^{20}_{D}$ 10.1 ° (*c* 1.11, $CHCl_3$). δ_H (400 M Hz; $CDCl_3$) 0.98 (3 H, d, *J* 6.8 Hz, CHC$\underline{H}_3$), 1.32 (3 H, s, NC(C$\underline{H}_3$)O), 3.80 – 3.86 (1 H, m, NC$\underline{H}$(CH$_3$)), 4.99 – 4.98 (1 H, d, *J* 4.8 Hz, C$\underline{H}$Ph), 6.66 – 6.70 (2 H, m, 2 *x* Ar-C$\underline{H}$), 6.80 (2 H, t (dd), *J* 7.2/7.6, 2 *x* Ar-C$\underline{H}$), 7.26 – 7.31 (3 H, m, 3 *x* Ar-C$\underline{H}$), 7.32 – 7.43 (2 H, m, 2 *x* Ar-C$\underline{H}$), 7.49 – 7.52 (2 H, m, 2 *x* Ar-C$\underline{H}$), 7.60 – 7.65 (1 H, m, Ar-C$\underline{H}$), 7.80 – 7.82 (1 H, m, Ar-C$\underline{H}$). δ_C (100 M Hz; $CHCl_3$) 16.9 (CH$\underline{C}$H$_3$), 22.8 (NC($\underline{C}$H$_3$)O), 66.1 (N$\underline{C}$H), 78.5 ($\underline{C}$HPh), 97.5 (quat.$\underline{C}$CH$_3$), 121.1 (Ar-$\underline{C}$H), 124.9 (Ar-$\underline{C}$H), 126.1 (Ar-$\underline{C}$H), 126.2 (Ar-$\underline{C}$H), 127.3 (Ar-$\underline{C}$H), 127.7 (Ar-$\underline{C}$H), 127.9 (Ar-$\underline{C}$H), 129.5 (Ar-$\underline{C}$H), 130.8 (Ar-$\underline{C}$H), 131.7 (Ar-$\underline{C}$H), 135.0 (Ar-$\underline{C}$H), 164.1

(N=CH) (no signal for 5 *x* quaternary aromatic carbon atoms). *m/z* 340.17025 [+ 0.3 ppm]; $C_{24}H_{22}NO^{+}$ Br^{-} requires 340.17014.

General procedure for the formation of racemic epoxides for ee determinations

The alkene (1.0 equiv) was dissolved in dichloromethane (10 mL/g) and cooled to 0 ºC. *m*-CPBA (2 equiv) was added as a solution in dichloromethane (10 mL/g). The reaction was allowed to attain ambient temperature temperature and stirred until complete consumption of the substrate was observed by TLC. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (10 mL/g) and the layers separated. The organic layer was washed with saturated NaOH (1.0 M) (10 mL/g) and dried ($MgSO_4$). Solvents were removed under reduced pressure. The pure epoxide was obtained after column chromatography eluting with ethyl acetate/light petroleum (1:99).

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

Oxone (2 equiv) was added to an ice cooled solution of Na_2CO_3, (4 equiv) in water (12 mL per 1.50 g of Na_2CO_3), the resulting foaming solution was left to stir for 5-10 min. The iminium salt (10 mol%) was then added as a solution in acetonitrile, (6 mL per 1.50 g of Na_2CO_3 used), followed by the alkene substrate (1 equiv) also as a solution in acetonitrile of the same volume as the solution of the catalyst. The mixture was stirred at 0 °C until the alkene substrate was completely consumed as observed by TLC. The reaction mixture was then dissolved with ice cooled diethyl ether (20 mL per 100 mg substrate) and was immediately followed by the addition of the same volume of water. The saturated aqueous phase was washed 4 times with diethyl ether and the organics

were combined, washed with saturated brine and dried over magnesium sulphate. Filtration and evaporation of the solvents gave a yellow/brown residue. The pure epoxide was obtained after column chromatography eluting with ethyl acetate/light petroleum (1:99).

General procedure for catalytic asymmetric epoxidation of simple alkenes mediated by iminium salts using hydrogen peroxide and bicarbonate salts

The bicarbonate salt (0.2 equiv) and the iminium salt catalyst (10 mol%) were dissolved in acetonitrile (1 mL) and cooled to −5 °C. To this solution the substrate alkene (1 equiv) and hydrogen peroxide (6 equiv) were added. The reaction was monitored by TLC until complete consumption of the substrate alkene was observed or after 24 h of reaction time has elapsed. The reaction was then quenched with saturated brine and extracted with diethyl ether. The ether layer was dried over $MgSO_4$ to give the crude epoxide.

General procedure for catalytic asymmetric epoxidation of simple alkenes mediated by iminium salts using sodium hypochlorite and bicarbonate salts

The bicarbonate salt (0.25 equiv) was disolved in NaOCl (3 equiv) and cooled to 0 °C. In a separate vessel also cooled to 0 °C the iminium salt catalyst (10 mol%) and the substrate alkene (1 equiv) were dissolved in dichloromethane (1 mL). The dichloromethane solution was then added to the NaOCl solution. The reaction was monitored by TLC until complete consumption of the substrate alkene was observed or after 24 h of reaction time has elapsed. The reaction was then quenched with saturated brine and extracted with diethyl ether. The ether layer was dried over $MgSO_4$ to give the crude epoxide.

3.4 Chapter three references.

1 Buckley, B. R. PhD Thesis submitted to Loughborough University., **2007**.

2 Nordin, I. C.; Thomas, J. A. *Tetrahedron Lett*. **1984**, *25*, 5723.

3 Rieche, A.; Schmitz, A. *Chem. Ber.* **1956**, *89*, 1257.

4 Page, P. C. B.; Rassias, G. A.; Barros, D.; Adel, A.; Buckley, B.; Bethell, D.; Smith, T. A. D.; Slawin, A. M. Z. *J. Org. Chem.* **2001**, *66*, 6926.

5 Rassias, G. A. PhD Thesis submitted to Loughborough University., **1999**.

6 Page, P. C. B.; Rassias, G. A.; Barros, D.; Adel, A.; Bethell, D.; Merifield, E. *Synlett* **2002**, *4*, 580.

7 Page, P. C. B.; Buckley, B. R.; Heaney, H.; Blacker, J. A. *Org. Lett*. **2005**, *7*, 375.

8 Page, P. C. B.; Buckley, B. R.; Blacker, J. A. *Org. Lett*. **2004**, *6*, 1543.

9 The m.p. and [α]D values of **38** recorded in the Aldrich catalogue are cited as authentic.

10 Mecca, T.; Superchi, S.; Giorgio, E.; Rosini, C. *Tetrahedron Asymmetry* **2001**, *12*, 1225.

11 Harris, J. M.; McDonald, R.; Vederas. J C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2669.

12 Mislow, K.; Glas, M. A. W.; O'Brien, R. E.; Rotkin, P.; Steinberg, D. H.; Weiss, J.; Djerassi, C. *J. Am. Chem. Soc.* **1962**, *84*, 1455.

13 Farah, M. M. PhD Thesis submitted to Loughborough University., **2007**.

14 Penhoat, M. I.; Levacher, V.; Dupas, G. *J. Org. Chem.* **2003**, *68*, 9517

3.5 Appendices

3.5.2 Appendix A; X-Ray data 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 Dr M. R. J. Elsegood

Crystal data and the structure refinement for 6-(2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-5-methyl-5*H*-dibenzo [*c, e*]azepinium; bromide (**44**):

Identification code	pcbp69	
Chemical formula	$C_{53}H_{52}BCl_4NO_2$	
Formula weight	887.57	
Temperature	150(2) K	
Radiation, wavelength	Mokα, 0.71073 Å	
Crystal system, space group	monoclinic, PS_1	
Unit cell parameters	a = 11.0253(7) Å	α = 90°
	b = 18.2597(11) Å	β = 109.694(2) °
	c = 11.9748(2) Å	γ = 90°
Cell volume	2269.7(2) $Å^3$	
Z	2	
Calculated density	1.299 g/cm^3	
Absorption coefficient μ	0.304 mm^{-1}	
F(000)	932	
Crystal colour and size	colourless, 0.70 x 0.49 x 0.30 mm^3	
Reflections for cell refinement	6011 (θ range 2.23 to 30.39°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	ω rotation with narrow frames	

θ range for data collection	1.81 to 27.50°
Index ranges	h – 14 to 14, k – 23 to 23, l – 15 to 15
Completeness to θ = 26.00°	99.9%
Intensity decay	0%
Reflections collected	22134
Independent reflection	10396 (R_{int} = 0.0247)
Reflections with $F^2>2\sigma$	9587
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.816 and 0.914
Structure solution	direct methods
Refinement method	Full-matrix least squares on F^2
Weighting parameters a, b	0.1599, 1.0002
Data/restraints/parameters	10396/1/553
Final R indices [$F^2>2\sigma$]	R1 = 0.0712, wR2 = 0.2110
R indices (all data)	R1 = 0.0763, wR2 = 0.2197
Goodness-of-fit on F2	1.073
Absolute structure parameter	0.01(9), well determined
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.812 and – 1.054 e $Å^{-3}$

Crystal data and the structure refinement for 4b-Methyl-7-phenyl-6,7-dihydro-4b*H*-5-oxa-7a-azonia-dibenzo[*e*,*g*] azulene. (**80**):

Identification code	pcbp77
Chemical formula	$C_{23}H_{21}NO$
Formula weight	327.41
Temperature	150(2) K
Radiation, wavelength	Mokα, 0.71073 Å
Crystal system, space group	monoclinic, $P2_1$
Unit cell parameters	a = 8.4016(5) Å α = 90°

	b = 9.9253(6) Å	β = 97.2928(9)°
	c = 10.5431(7) Å	γ = 90°
Cell volume	872.06(9) $Å^3$	
Z	2	
Calculated density	1.247 g/cm^3	
Absorption coefficient μ	0.076 mm^{-1}	
F(000)	348	
Crystal colour and size	colourless, 0.32 × 0.29 × 0.10 mm^3	
Reflections for cell refinement	3905 (θ range 2.45 to 28.24°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	1.95 to 28.31°	
Index ranges	h –11 to 11, k –13 to 13, l –14 to 14	
Completeness to θ = 28.31°	99.7 %	
Intensity decay	0%	
Reflections collected	9089	
Independent reflections	2284 (R_{int} = 0.0255)	
Reflections with $F^2>2$□	2146	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.976 and 0.993	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0530, 0.1214	
Data / restraints / parameters	2284 / 1 / 227	
Final R indices [$F^2>2\sigma$]	R1 = 0.0342, wR2 = 0.0858	
R indices (all data)	R1 = 0.0370, wR2 = 0.0881	
Absolute structure not determined from the data. Friedel pairs merged.		
Goodness-of-fit on F^2	1.038	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.224 and –0.207 e $Å^{-3}$	

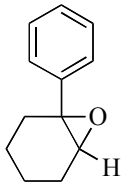
Crystal data and the structure refinement for 7-Benzyl-4b-methyl-6,7-dihydro-4b*H*,8*H*-5-oxa-7a-azonia-dibenzo [*e*,*g*] azulene. (**97**):

Identification code	pcbp80	
Chemical formula	$C_{24}H_{23}NO$	
Formula weight	341.43	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1$	
Unit cell parameters	a = 8.5648(4) Å	α = 90°
	b = 9.8551(5) Å	β = 98.4207(7)°
	c = 11.1777(5) Å	γ = 90°
Cell volume	933.30(8) $Å^3$	
Z	2	
Calculated density	1.215 g/cm^3	
Absorption coefficient μ	0.073 mm^{-1}	
F(000)	364	
Crystal colour and size	colourless, 0.52 × 0.38 × 0.36 mm^3	
Reflections for cell refinement	4517 (θ range 2.40 to 30.51°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	1.84 to 30.56°	
Index ranges	h –11 to 12, k –14 to 14, l –15 to 15	
Completeness to θ = 30.56°	99.6 %	
Intensity decay	0%	
Reflections collected	11151	
Independent reflections	3010 (R_{int} = 0.0271)	
Reflections with $F^2>2\sigma$	2761	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.963 and 0.974	
Structure solution	direct methods	

Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0760, 0.0558
Data / restraints / parameters	3010 / 1 / 236
Final R indices [F^2>2□]	R1 = 0.0420, wR2 = 0.1128
R indices (all data)	R1 = 0.0455, wR2 = 0.1158
Goodness-of-fit on F^2	1.072
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.296 and –0.222 e $Å^{-3}$

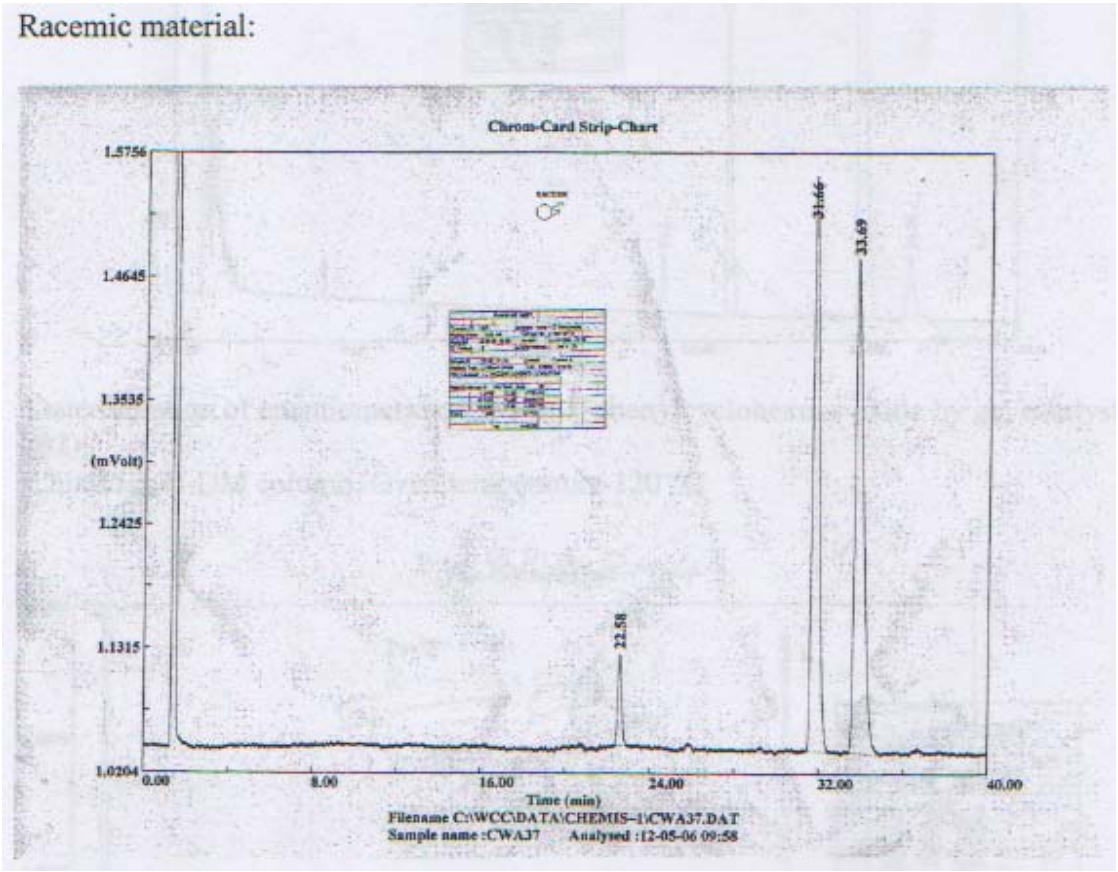
3.5.2 Appendix B; Supporting chiral separation data

Determination of enantiomeric excess for racemic 1phenylcyclohex-1-ene oxide

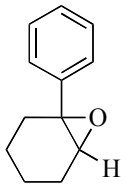


GC – flame ionisation detector using a Chiraldex B-DM column at an oven temperature of 120 °C

Racemic 1-phenylcyclohex-1-ene oxide

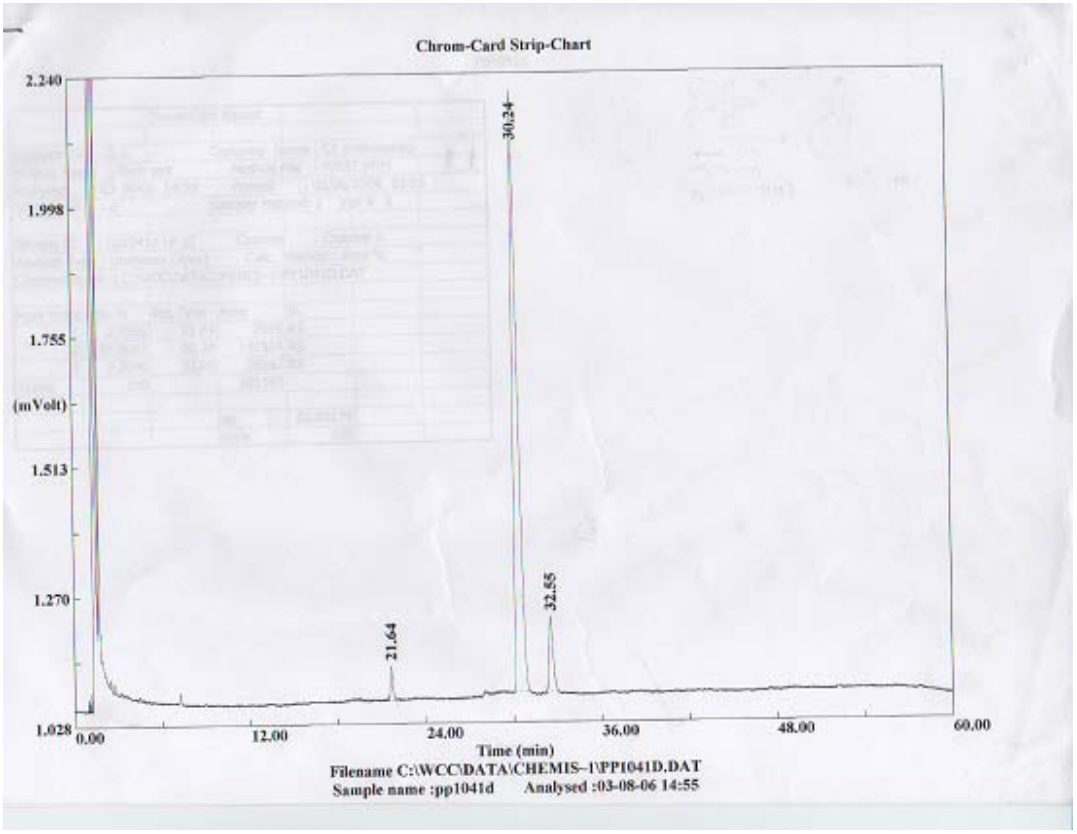


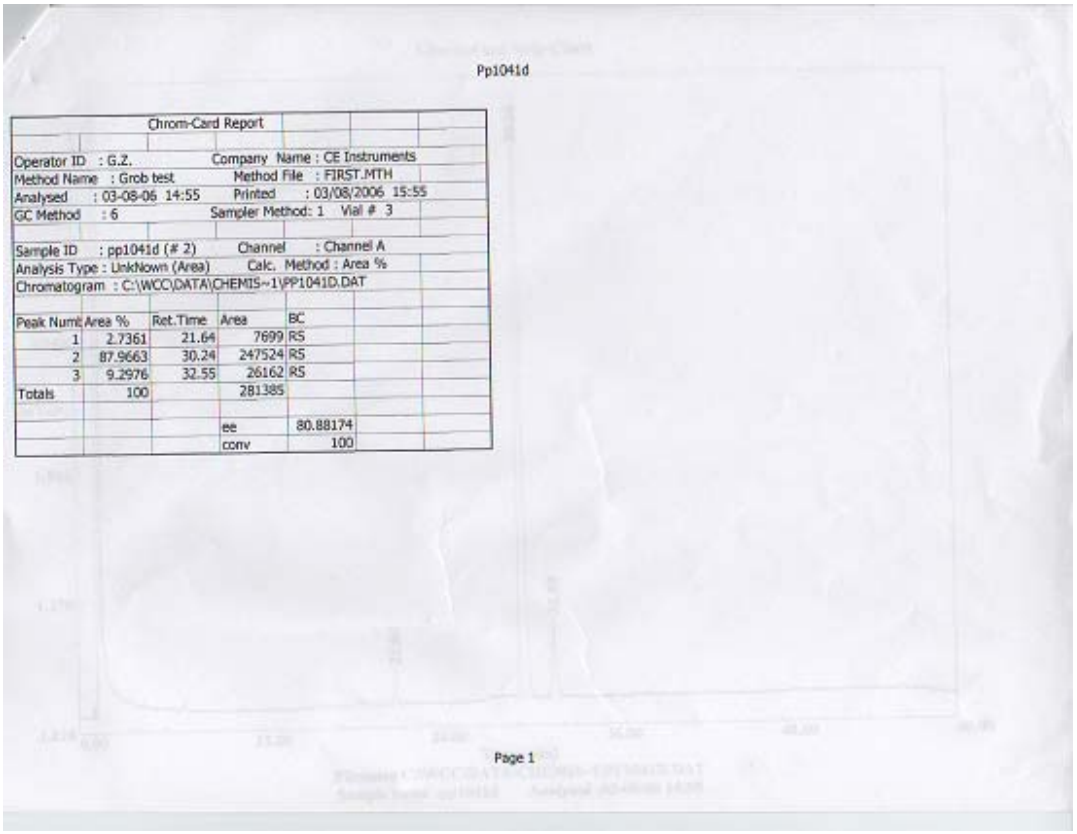
Determination of enantiomeric excess for 1phenylcyclohex-1-ene oxide when catalysed by **40**



GC – flame ionisation detector using a Chiraldex B-DM column at an oven temperature of 120 °C

1041d 1 phenylcyclohex-1-ene oxide





Pp1041d

Chrom-Card Report

Operator ID : G.Z. Company Name : CE Instruments
Method Name : Grob test Method File : FIRST.MTH
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GC Method : 6 Sampler Method: 1 Vial # 3

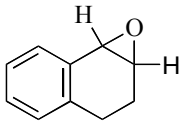
Sample ID : pp1041d (# 2) Channel : Channel A
Analysis Type : UnkNown (Area) Calc. Method : Area %
Chromatogram : C:\WCC\DATA\CHEMIS~1\PP1041D.DAT

Peak Num	Area %	Ret.Time	Area	BC
1	2.7361	21.64	7699	RS
2	87.9663	30.24	247524	RS
3	9.2976	32.55	26162	RS
Totals	100		281385	

ee	80.88174
conv	100

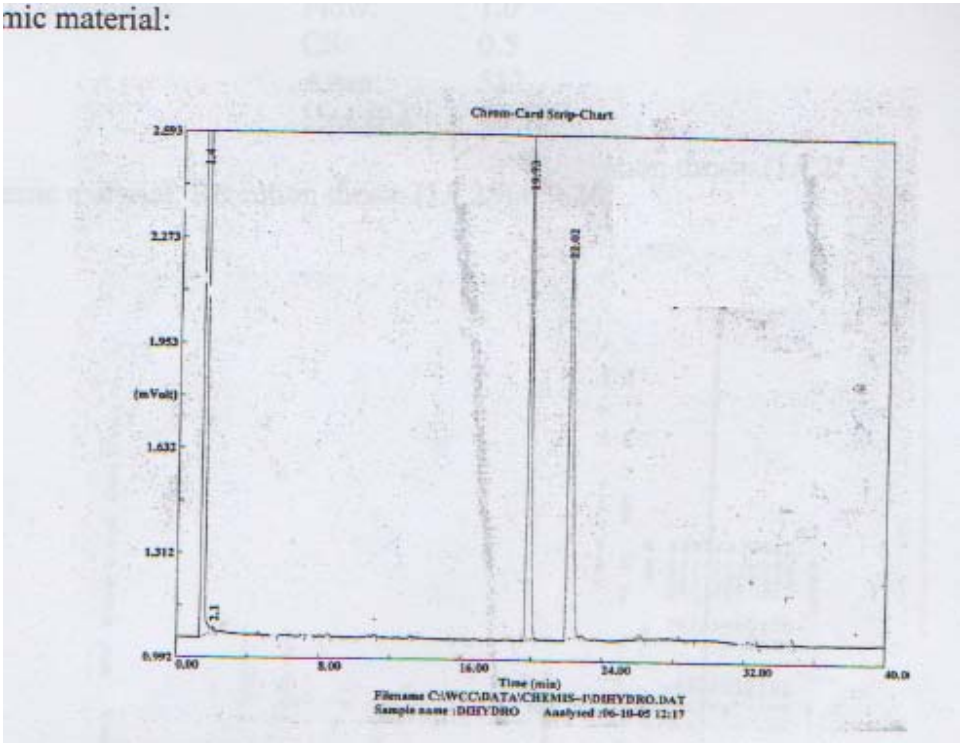
Page 1

Determination of enantiomeric excess for racemic dihydronaphthalene oxide

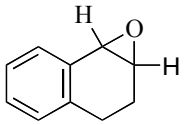


GC – flame ionisation detector using a Chiraldex B-DM column at an oven temperature of 120 °C

Racemic dihydronaphthalene oxide

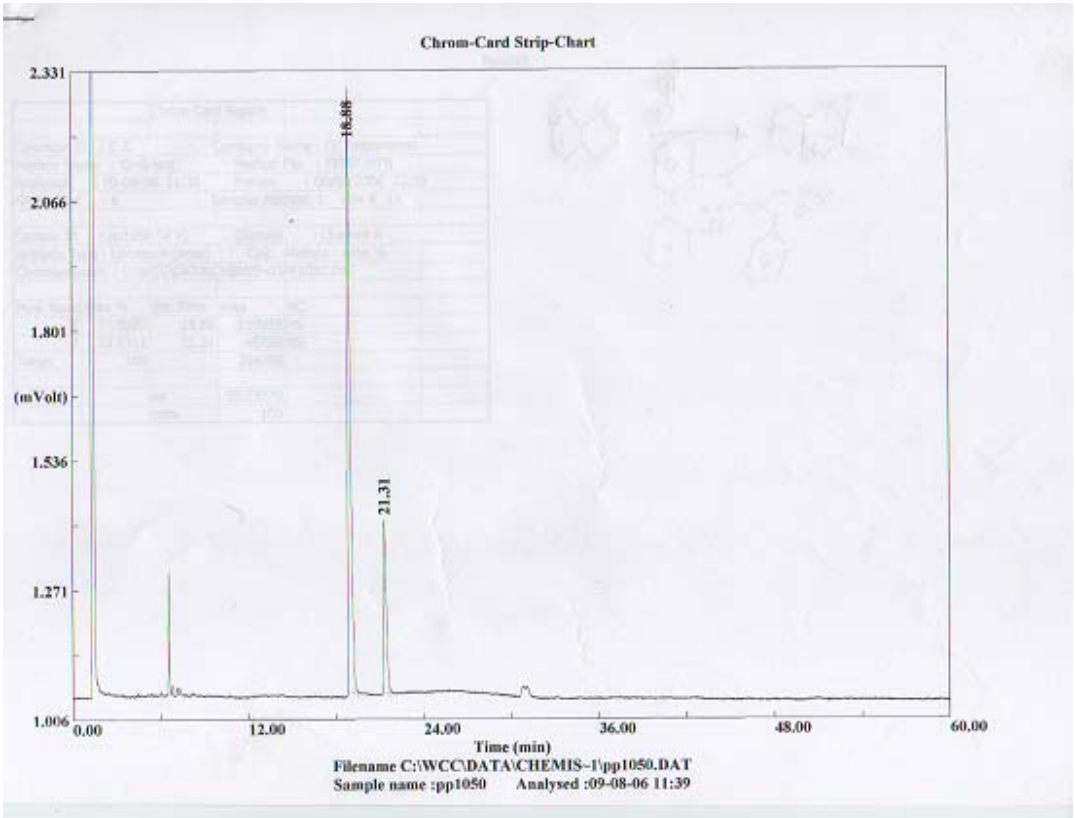


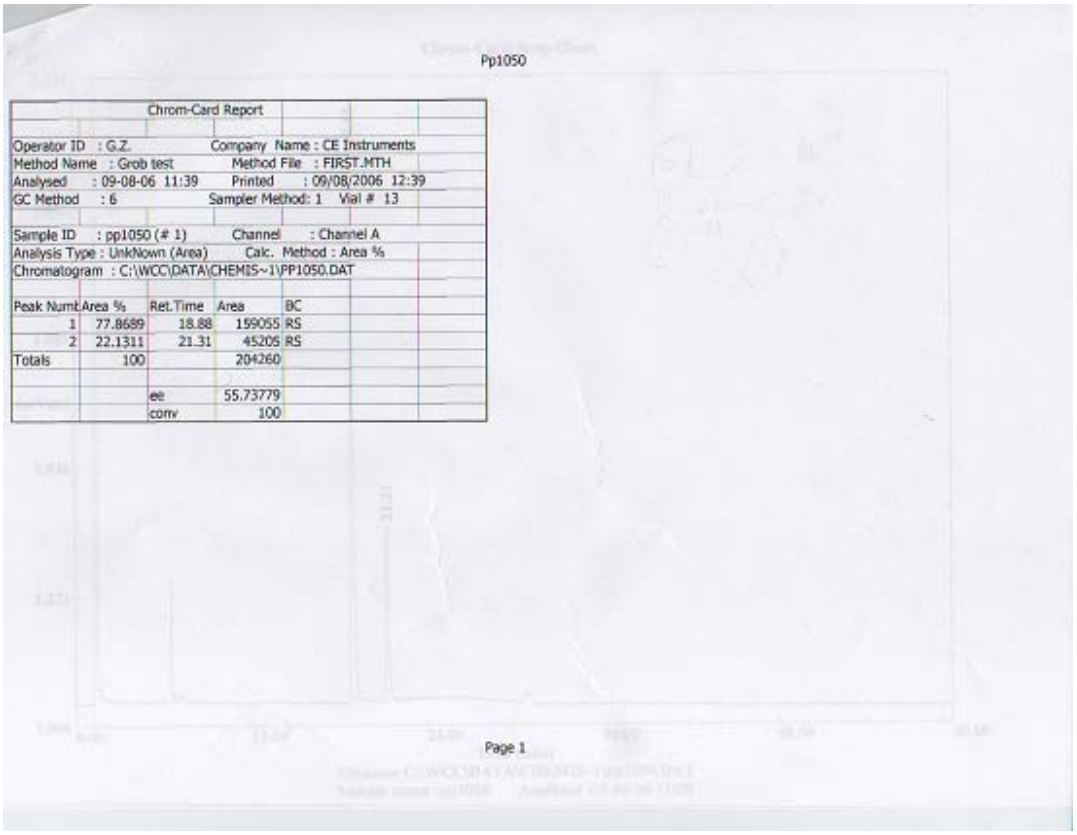
Determination of enantiomeric excess for dihydronaphthalene oxide when catalysed by **40**



GC – flame ionisation detector using a Chiraldex B-DM column at an oven temperature of 120 °C

1050 Dihydronaphthalene oxide





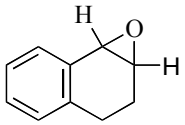
Pp1050

Chrom-Card Report

Operator ID : G.Z.			Company Name : CE Instruments	
Method Name : Grob test			Method File : FIRST.MTH	
Analysed : 09-08-06 11:39			Printed : 09/08/2006 12:39	
GC Method : 6			Sampler Method: 1 Vial # 13	
Sample ID : pp1050 (# 1)			Channel : Channel A	
Analysis Type : UnkNown (Area)			Calc. Method : Area %	
Chromatogram : C:\WCC\DATA\CHEMIS~1\PP1050.DAT				
Peak Numb	Area %	Ret.Time	Area	BC
1	77.8689	18.88	159055	RS
2	22.1311	21.31	45205	RS
Totals	100		204260	
		ee	55.73779	
		conv	100	

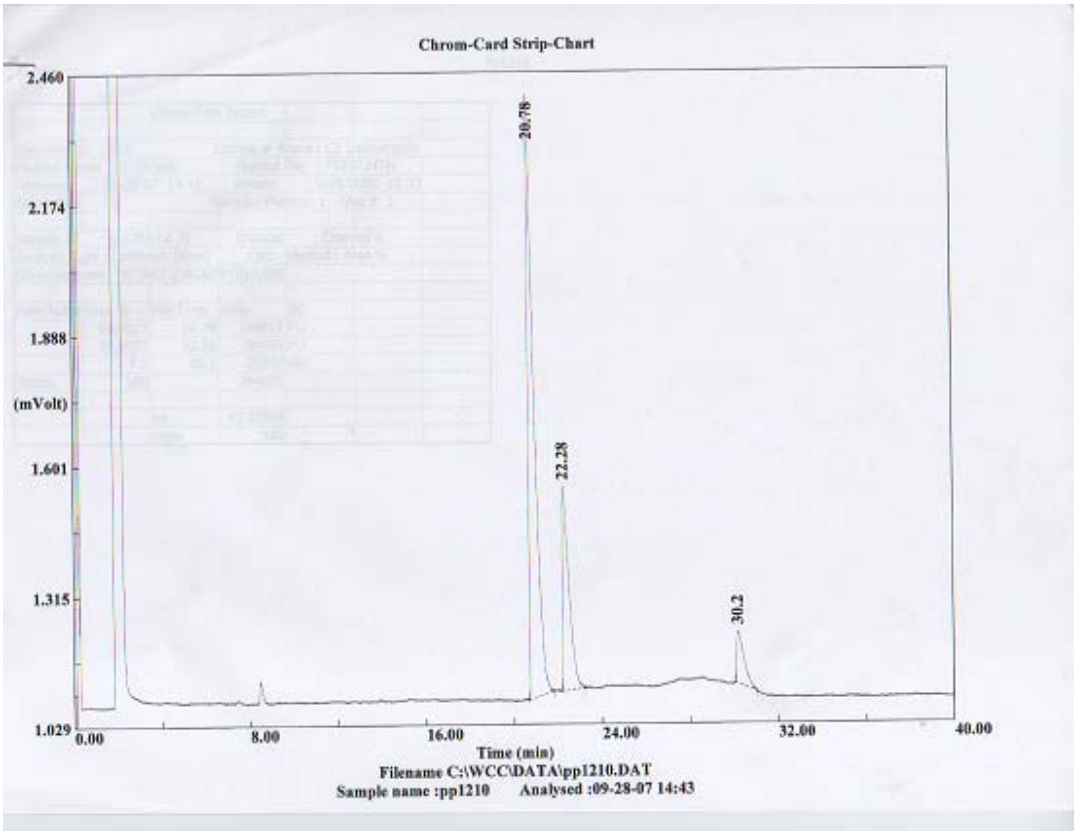
Page 1

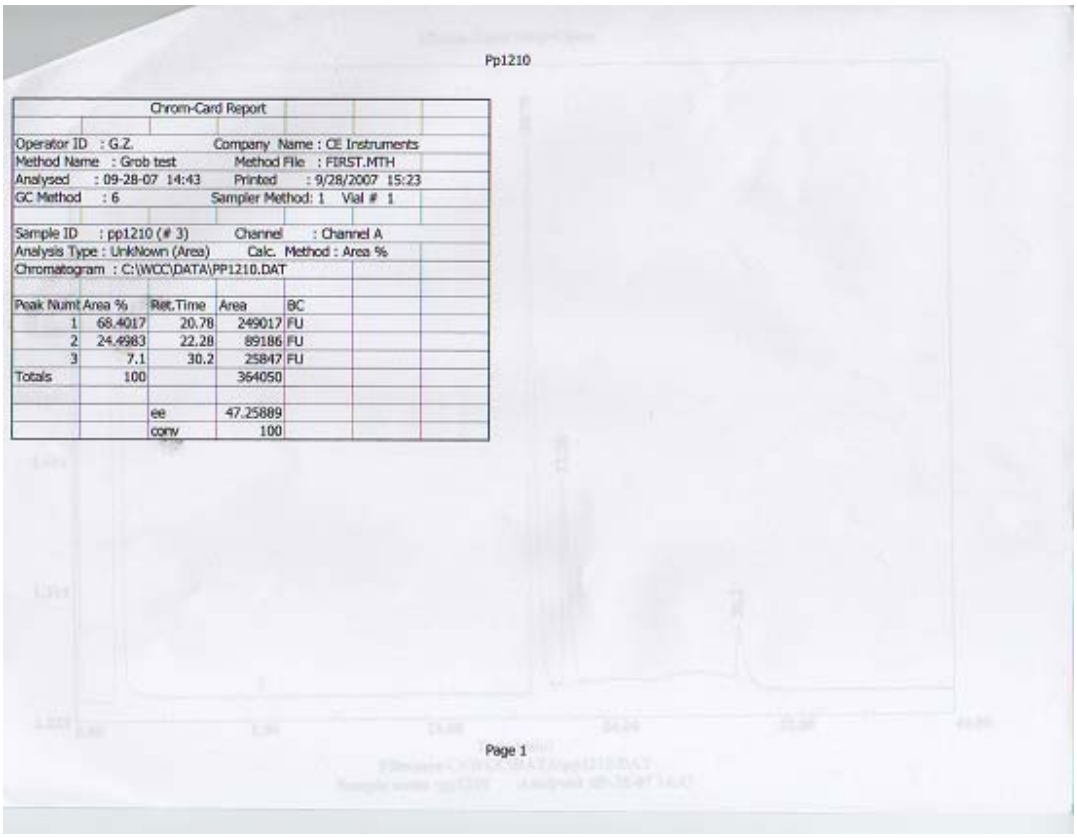
Determination of enantiomeric excess for dihydronaphthalene oxide when catalysed by **85**



GC – flame ionisation detector using a Chiraldex B-DM column at an oven temperature of 120 °C

1210 dihydronaphthalene oxide





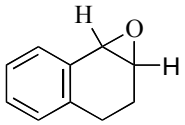
Pp1210

Chrom-Card Report

Operator ID : G.Z.			Company Name : CE Instruments		
Method Name : Grob test			Method File : FIRST.MTH		
Analysed : 09-28-07 14:43			Printed : 9/28/2007 15:23		
GC Method : 6			Sampler Method: 1 Vial # 1		
Sample ID : pp1210 (# 3)			Channel : Channel A		
Analysis Type : UnkNown (Area)			Calc. Method : Area %		
Chromatogram : C:\WCC\DATA\PP1210.DAT					
Peak Num	Area %	Ret.Time	Area	BC	
1	68.4017	20.78	249017	FU	
2	24.4983	22.28	89186	FU	
3	7.1	30.2	25847	FU	
Totals	100		364050		
		ee	47.25889		
		conv	100		

Page 1

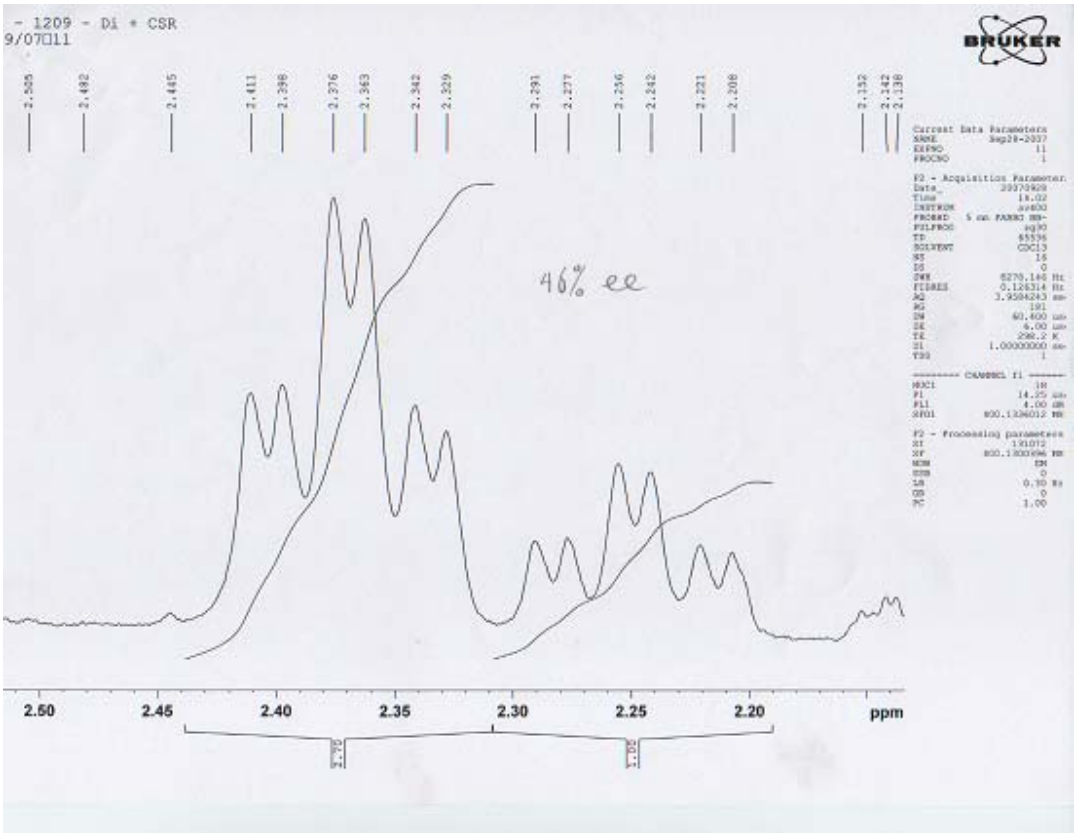
Determination of enantiomeric excess for dihydronaphthalene oxide when catalysed by **85**



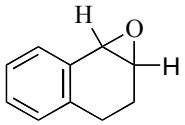
Racemic literature reference: Wong, M.-K.; Ho, L.-M.; Zheng, Y.-S.; Ho, C.-Y.; Yang, D. *Org. Lett.* 2001, *3*, 2587

^{1}H-NMR spectroscopy. 8 – 10 mg substrate; 3 – 5 mg (+)-Eu(hfc)$_3$ using $CDCl_3$ as solvent

1209 dihydronaphthalene oxide

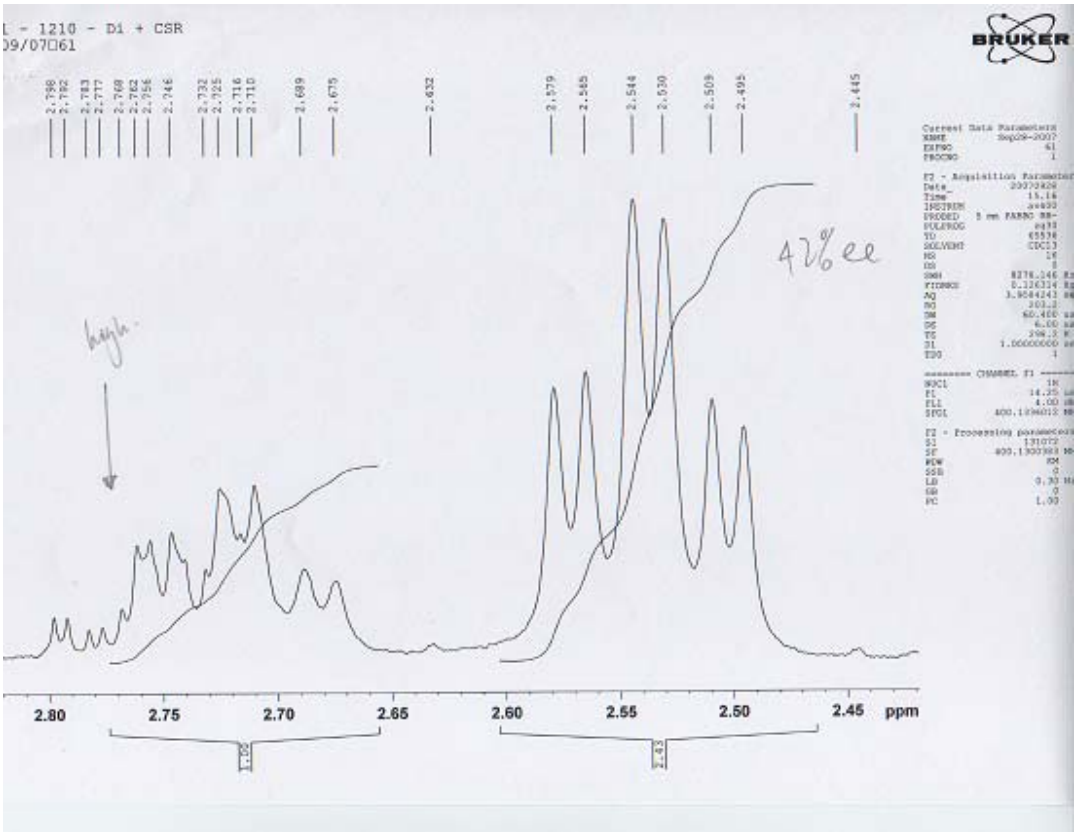


Determination of enantiomeric excess for dihydronaphthalene oxide when catalysed by **85**

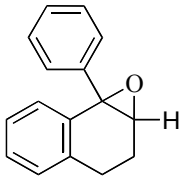


^{1}H-NMR spectroscopy. 8 – 10 mg substrate; 3 – 5 mg (+)-Eu(hfc)$_3$ using $CDCl_3$ as solvent

1210 dihydronaphthalene oxide



Determination of enantiomeric excess for racemic 1-phenyl dihydronaphthalene oxide

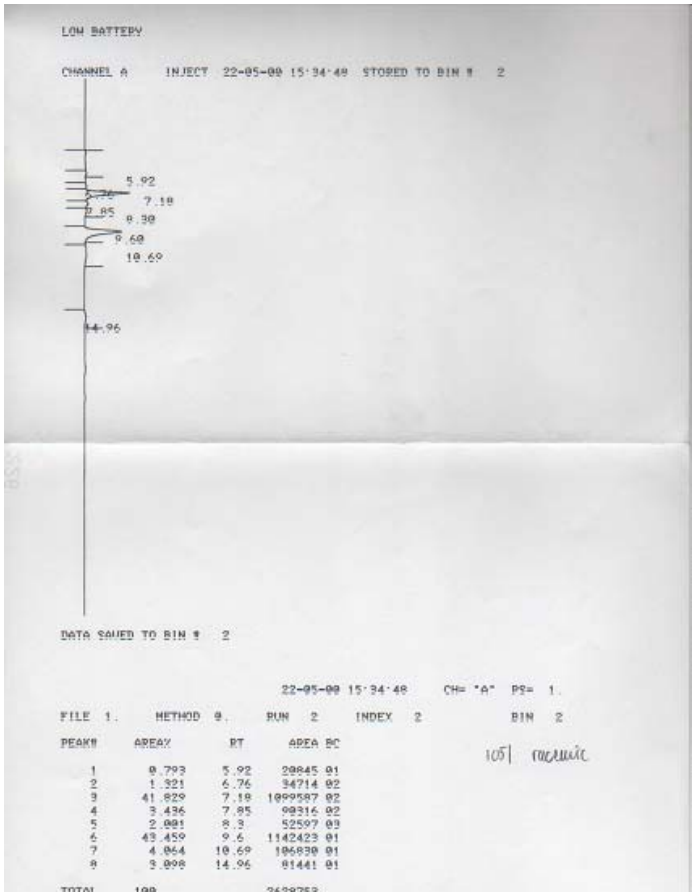


HPLC analysis; Flow 1.0, CS 0.5, Atten. 512, Hex:IPA 90:10.

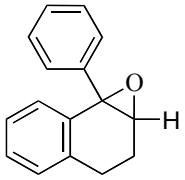
Literature reference: Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* 1997, *119*, 11224

Racemic 1-phenyldihydronaphthalene oxide

Retension times (1*R*,2*S*) = 7.18; (1*S*, 2*R*) = 9.6



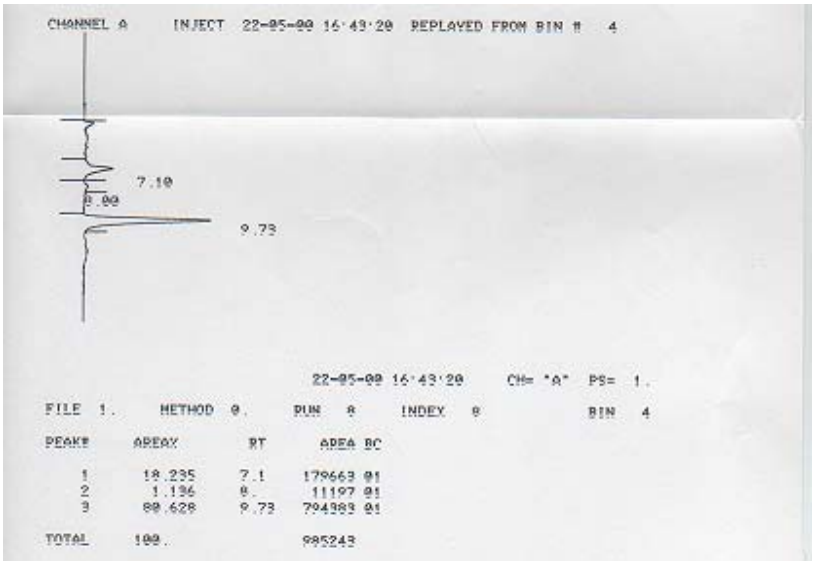
Determination of enantiomeric excess for racemic 1-phenyl dihydronaphthalene oxide when catalysed by **40**



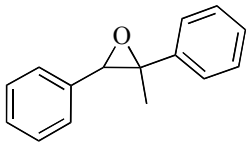
HPLC analysis; Flow 1.0, CS 0.5, Atten. 512, Hex:IPA 90:10

1051 1 phenyldihydronaphthalene oxide

Retension times (1*R*,2*S*) = 7.10; (1*S*, 2*R*) = 9.73



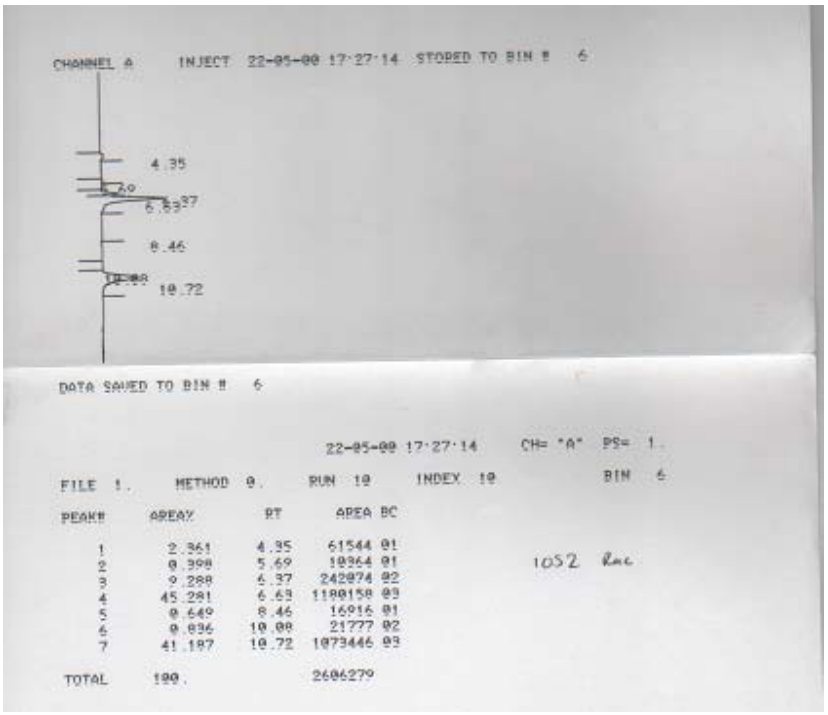
Determination of enantiomeric excess for racemic *trans* methyl stilbene oxide



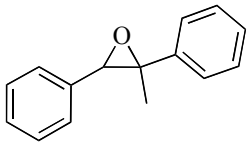
HPLC analysis; Flow 1.0, CS 0.5, Atten. 512, Hex:IPA 80:20.

Racemic *trans* methyl stilbene oxide

Retension times (*S*,*S*) = 6.63; (*R*,*R*) = 10.72



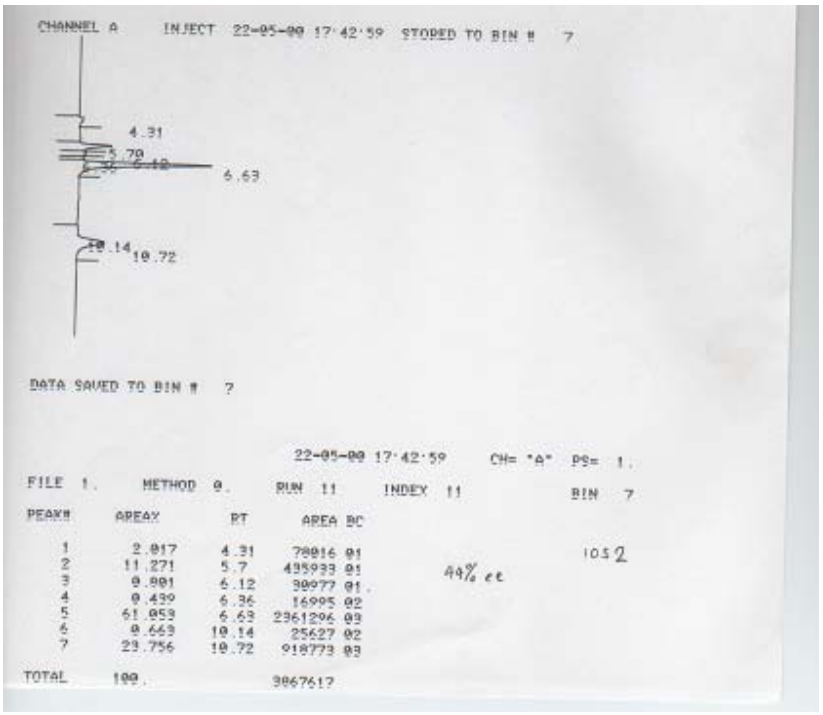
Determination of enantiomeric excess for *trans* methyl stilbene oxide when catalysed by **40**



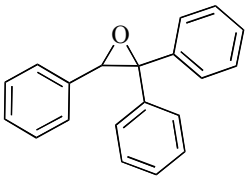
HPLC analysis; Flow 1.0, CS 0.5, Atten. 512, Hex:IPA 80:20.

1052 *trans* methyl trans stilbene oxide

Retension times (*S*,*S*) = 6.63; (*R*,*R*) = 10.72



Determination of enantiomeric excess for racemic triphenylethylene oxide

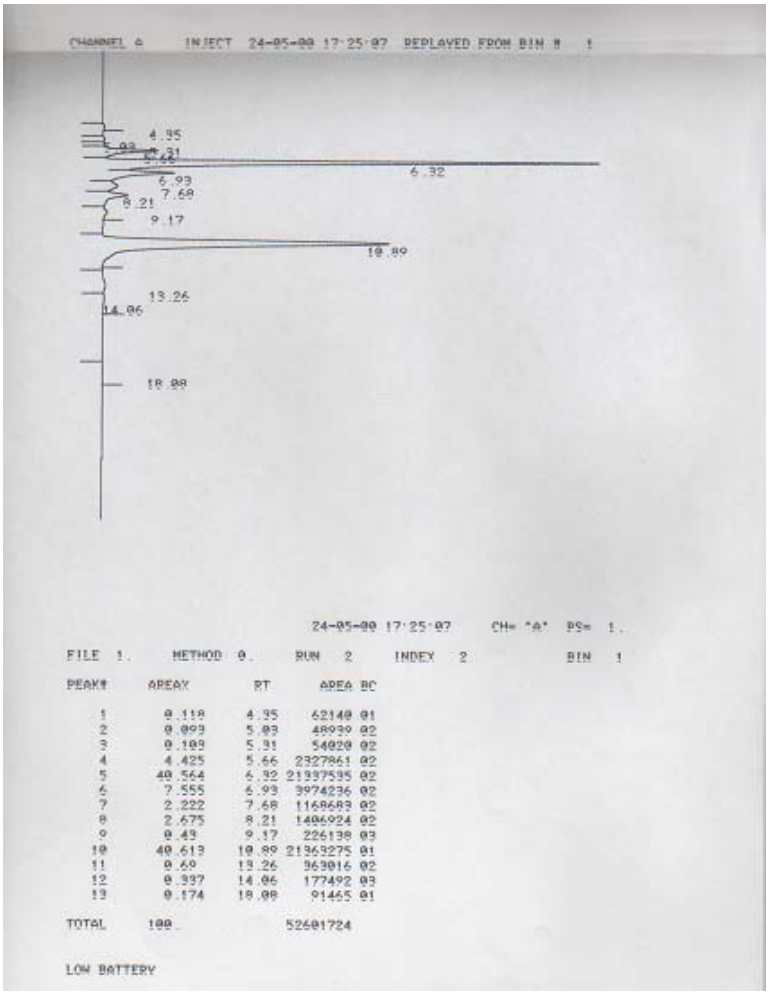


HPLC analysis; Flow 1.0, CS 0.5, Atten. 512, Hex:IPA 80:20.

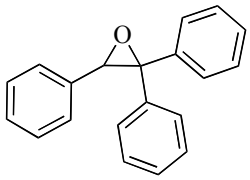
Literature reference; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* 1996,, *118*, 9806.

Racemic triphenylethylene oxide

Retension times (*S*) = 6.32; (*R*) = 10.89



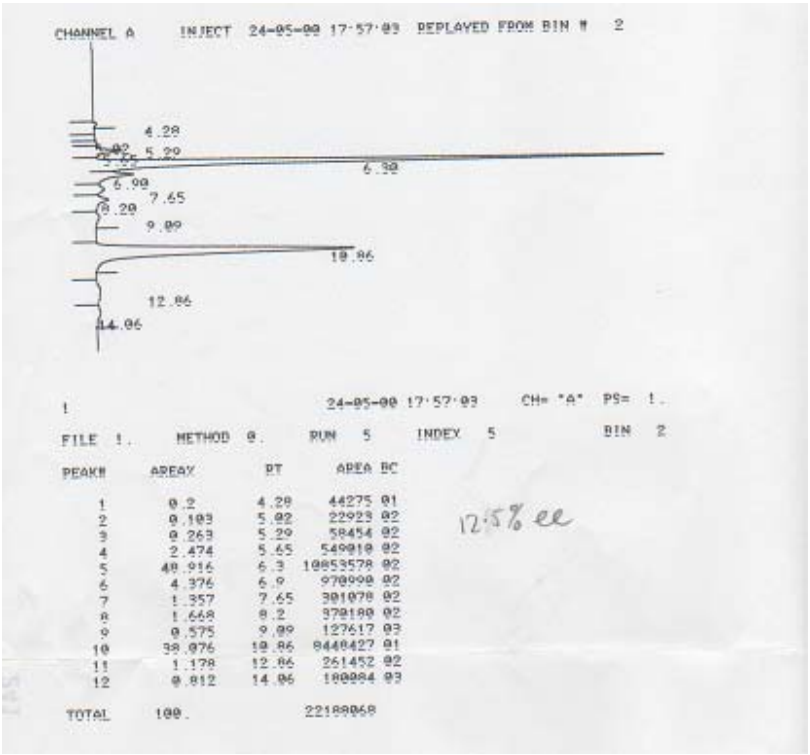
Determination of enantiomeric excess for triphenylethylene oxide when catalysed by **40**



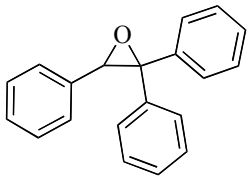
HPLC analysis; Flow 1.0, CS 0.5, Atten. 512, Hex:IPA 80:20.

1054 triphenylethylene oxide

Retension times (*S*) = 6.30; (*R*) = 10.06

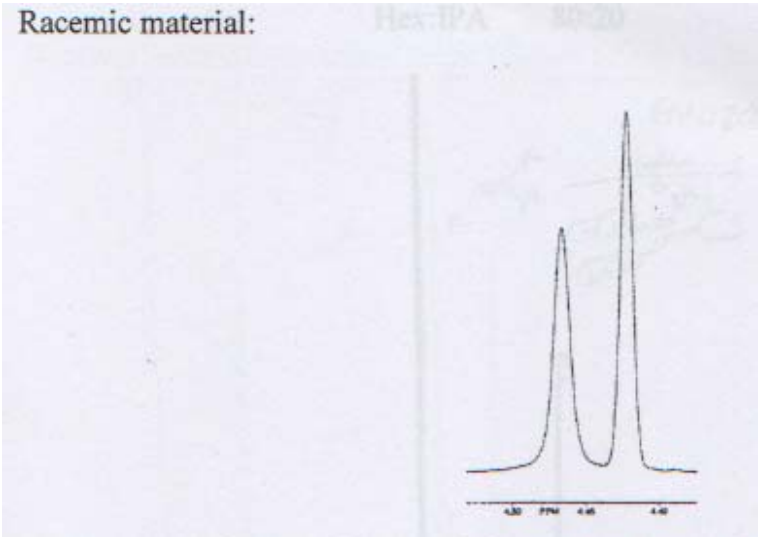


Determination of enantiomeric excess for triphenylethylene oxide

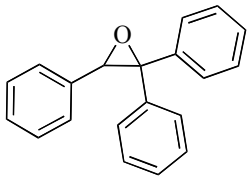


^{1}H-NMR spectroscopy. 8 – 10 mg substrate; 3 – 5 mg (+)-Eu(hfc)$_3$ using $CDCl_3$ as solvent

Racemic Triphenylethylene oxide

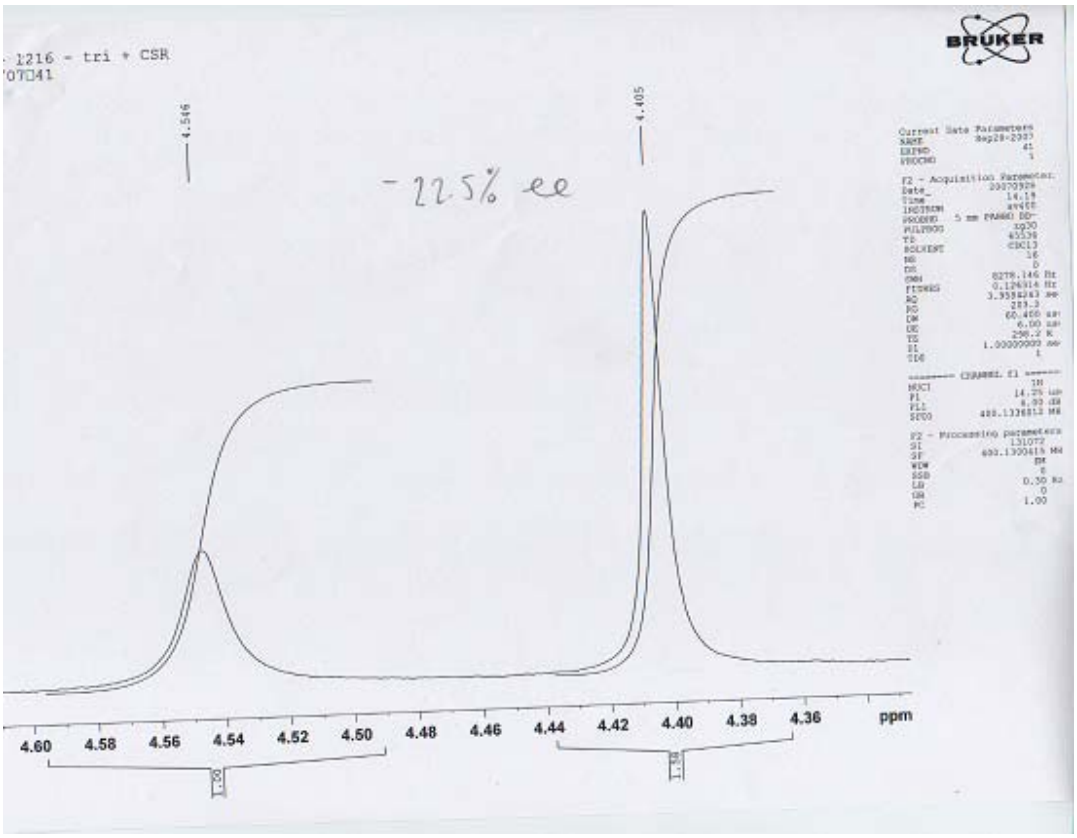


Determination of enantiomeric excess for triphenylethylene oxide when catalysed by **85**

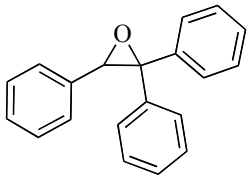


^{1}H-NMR spectroscopy. 8 – 10 mg substrate; 3 – 5 mg (+)-Eu(hfc)$_3$ using $CDCl_3$ as solvent

1216 triphenylethylene oxide

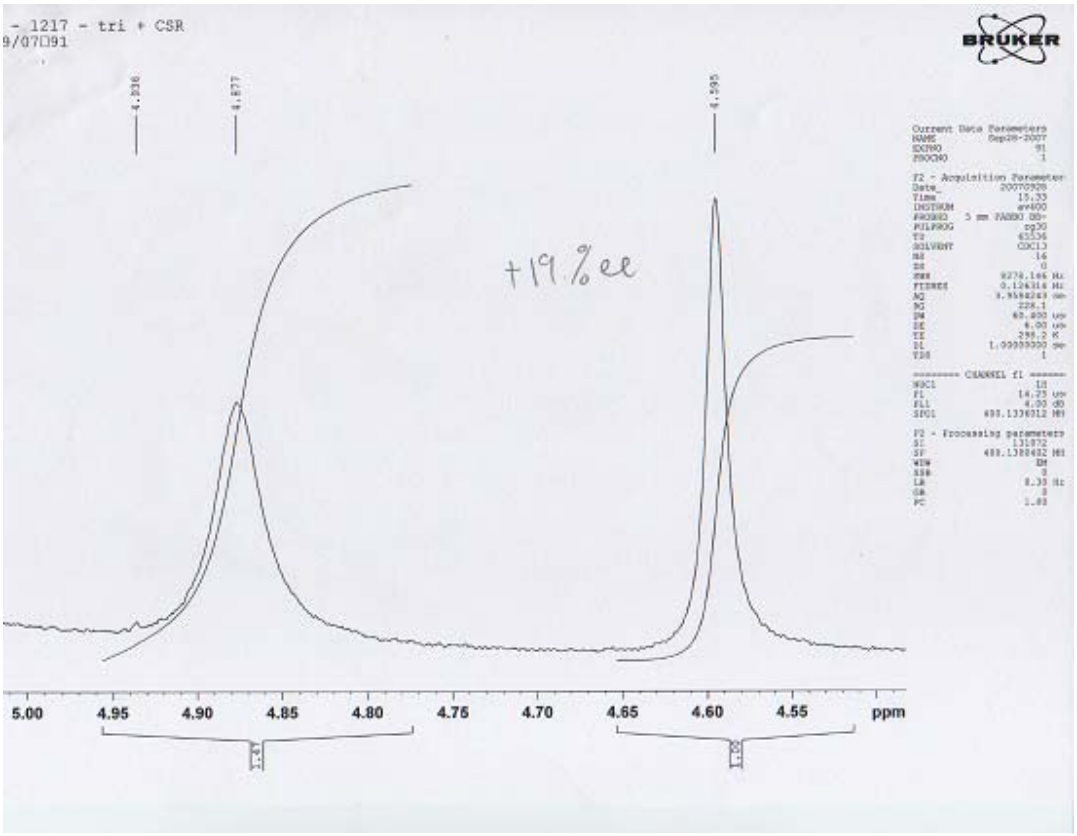


Determination of enantiomeric excess for triphenylethylene oxidem when catalysed by **85**

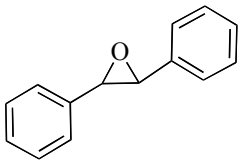


^{1}H-NMR spectroscopy. 8 – 10 mg substrate; 3 – 5 mg (+)-Eu(hfc)$_3$ using $CDCl_3$ as solvent

1217 triphenylethylene oxide



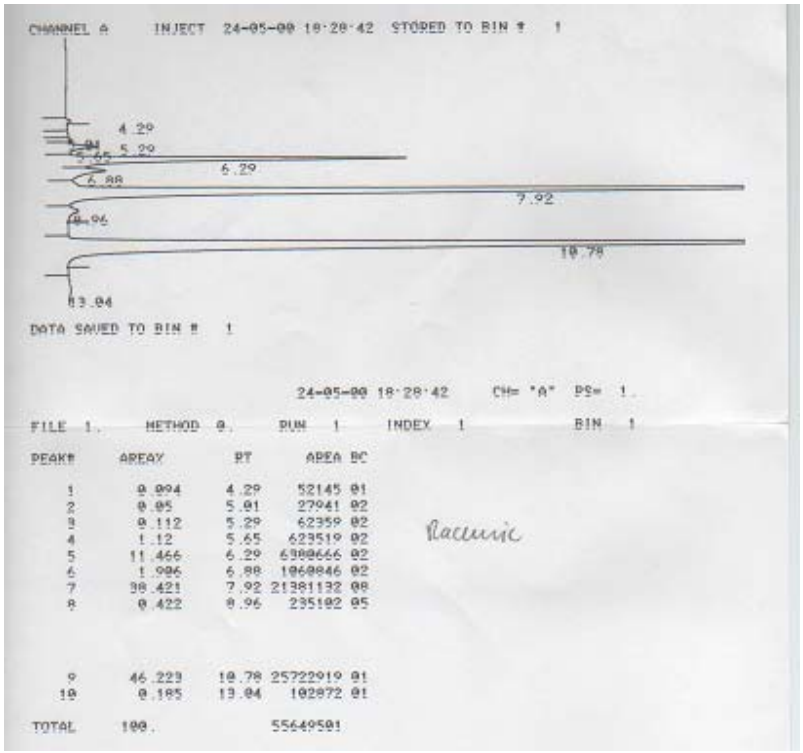
Determination of enantiomeric excess for racemic *trans* stilbene oxide



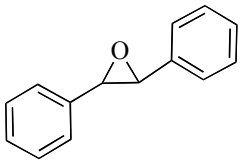
HPLC analysis; Flow 1.0, CS 0.5, Atten. 512, Hex:IPA 80:20.

Racemic *trans* stilbene oxide

Retension times (*S*,*S*) = 7.92; (*R*,*R*) = 10.78



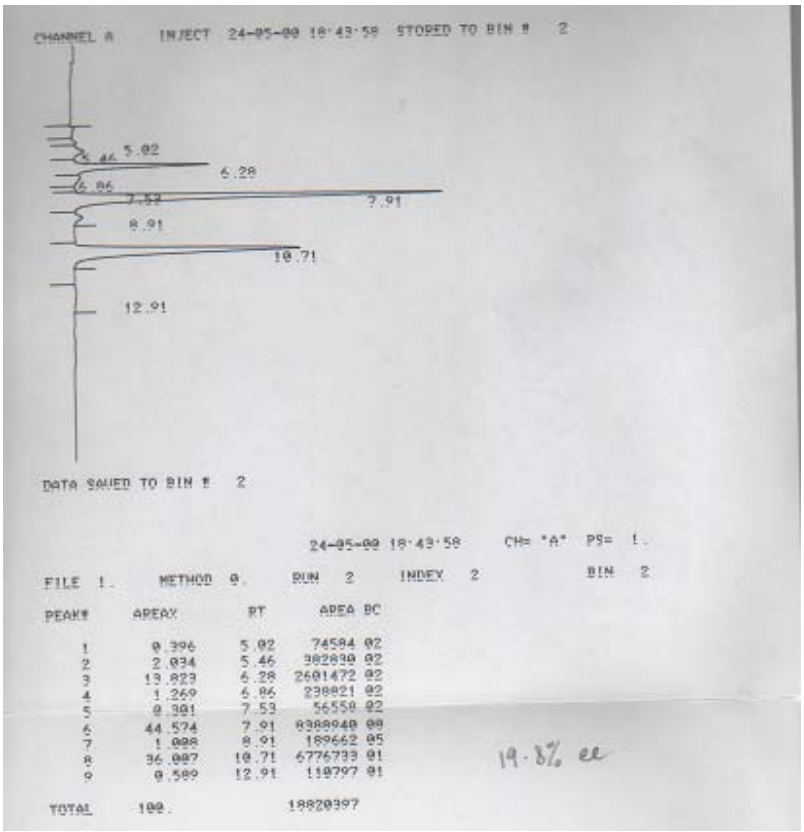
Determination of enantiomeric excess for racemic *trans* stilbene oxide when catalysed by **40**



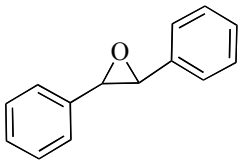
HPLC analysis; Flow 1.0, CS 0.5, Atten. 512, Hex:IPA 80:20.

1055 *trans* stilbene oxide

Retension times (*S*,*S*) = 7.91; (*R*,*R*) = 10.71

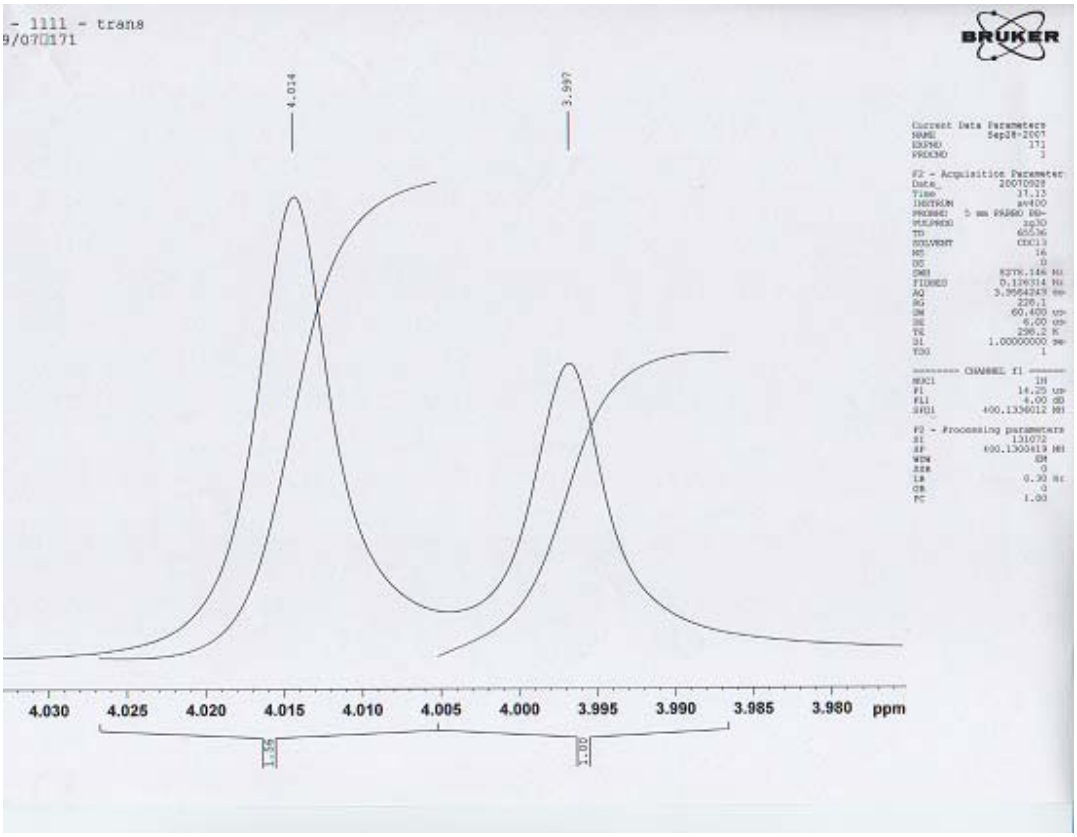


Determination of enantiomeric excess for *trans* stilbene oxide when catalysed by **61**

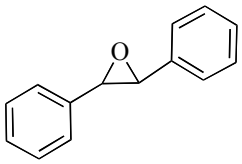


^{1}H-NMR spectroscopy. 8 – 10 mg substrate; 3 – 5 mg (+)-Eu(hfc)$_3$ using $CDCl_3$ as solvent

1111 *trans* stilbene oxide

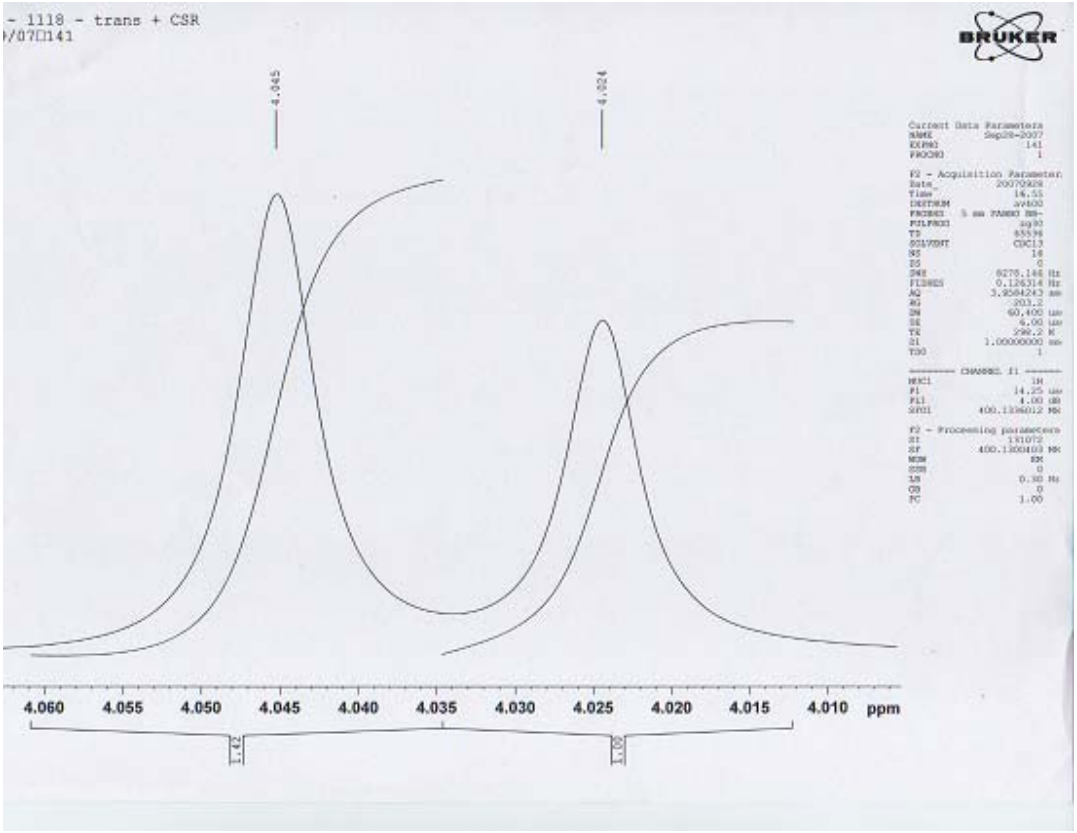


Determination of enantiomeric excess for *trans* stilbene oxide when catalysed by **43**

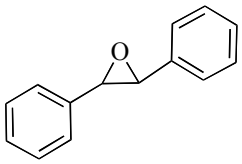


^{1}H-NMR spectroscopy. 8 – 10 mg substrate; 3 – 5 mg (+)-Eu(hfc)$_3$ using $CDCl_3$ as solvent

1118 trans stilbene oxide

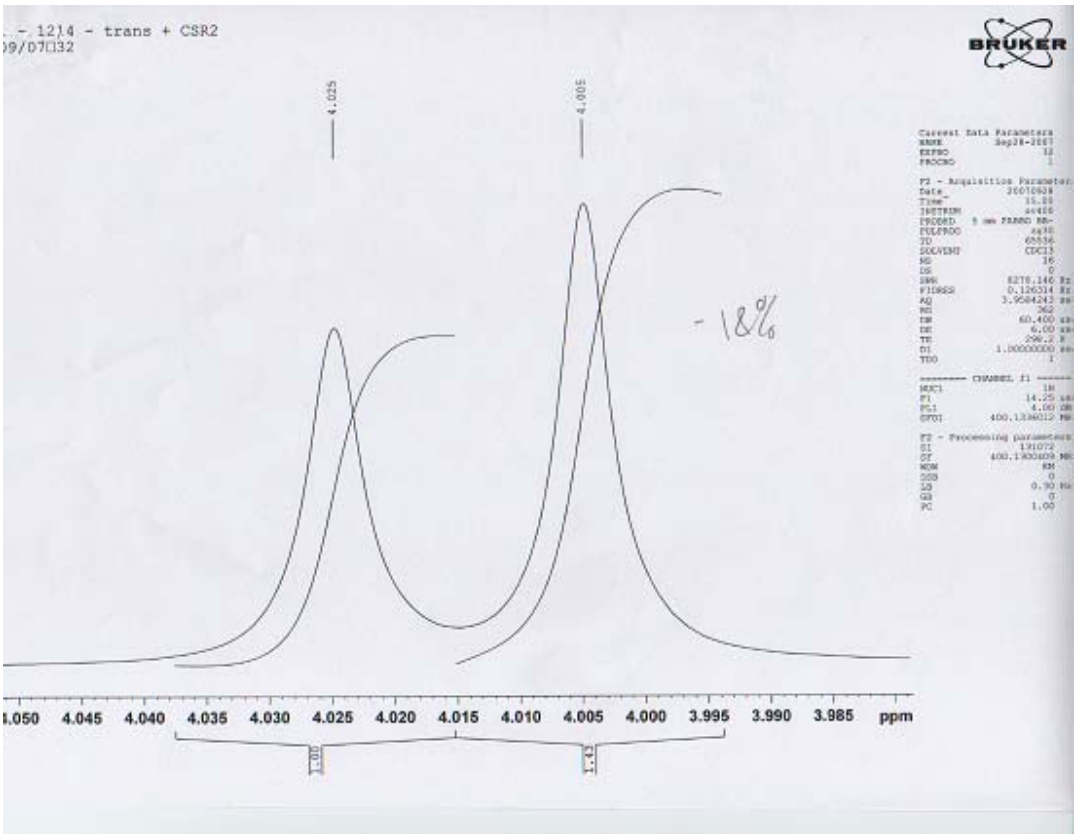


Determination of enantiomeric excess for *trans* stilbene oxide when catalysed by **85**

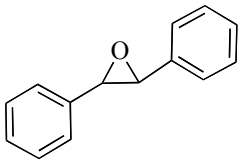


^{1}H-NMR spectroscopy. 8 – 10 mg substrate; 3 – 5 mg (+)-Eu(hfc)$_3$ using $CDCl_3$ as solvent

1214 trans stilbene oxide



Determination of enantiomeric excess for *trans* stilbene oxide (**129**) when catalysed by **84**



^{1}H-NMR spectroscopy. 8 – 10 mg substrate; 3 – 5 mg (+)-Eu(hfc)$_3$ using $CDCl_3$ as solvent

1215 trans stilbene oxide

