The Development and Application of Organocatalytic Asymmetric Epoxidation

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DECLARATION

This thesis is submitted to the University of East Anglia for the Degree of Doctor of Philosophy and has not been previously submitted at this or any university for assessment or for any other degree. Except where stated, and reference and acknowledgment is given, this work is original and has been carried out by the author alone.

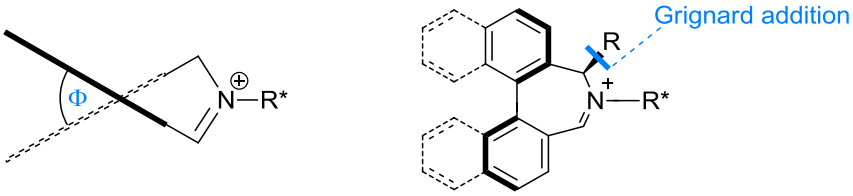
CHRISTOPHER J. BARTLETT

ABSTRACT

THE DEVELOPMENT AND APPLICATION OF ORGANOCATALYTIC ASYMMETRIC EPOXIDATION

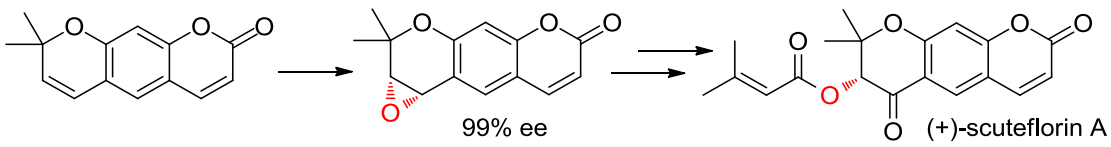
CHRISTOPHER J. BARTLETT

Epoxides are widely encountered within organic and biological chemistry, being present in many secondary metabolites and pharmaceuticals. In addition, the unique functionality of the epoxide has been exploited to facilitate the synthesis of many organic molecules. A particularly attractive way to stereoselectively epoxidise a substrate is to employ an organocatalytic system. Our group has been actively pursuing research in this area for over a decade and we have developed several catalytic systems capable of excellent stereocontrol in the epoxidation of alkene substrates. In considering possible refinements to catalyst structure, we targeted two development paths: i) variation of the dihedral angle Φ within the *atropos* azepinium systems - shown by Lacour to strongly influence the levels of stereoinduction,[1] and ii) introduction of a substituent α- to the iminium nitrogen, which we envisaged would also influence the stereochemical outcome of any process occurring at the catalytically active centre.



The application of the combined optimisations to existing catalyst frameworks allowed us to create a second generation of catalyst that was capable of furnishing epoxides in *ee*s of up to 97% for tri-substituted unfunctionalised alkenes. We observed a tangible improvement upon the previous generation, and, in explanation, we offer an in-depth discussion on the influence of α-substitution on the ratio of sp^2N-sp^3C rotamers, and the importance of that ratio on the improved enantiocontrol. As part of an extended research program within our group, we also report the emergence of atropisomerism of the traditionally *tropos* sp^2C-sp^2C axis contained within biphenyl systems, presumably caused by efficient stereochemical relays mediated by the α-substituent.

Lastly, we were able to successfully apply our methodology in the enantioselective total synthesis of (+)-scuteflorin A.[2,3] The key epoxidation step proceeded in 99% ee and 99% yield, as part of a 7-step sequence that was completed with a 14.3% overall yield.



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3. C. J. Bartlett, D. Day, Y. Chan, S. M. Allin, M. J. McKenzie, A. M. Z. Slawin, P. C. B. Page, *J. Org. Chem.*, **2012**, *77*, 772.

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It seems to have become quite fashionable in recent years to give a nickname to those we worked with during our studies in these acknowledgements. That being the case, in the instances where individuals did not previously have a nickname, or, if it wasn't in canon, I have exercised creative freedom. Some of them are quite long, and perhaps impractical, but I would like to think most of them will eventually catch-on. So, for their help and advice, for their questionable taste in music, for their obsessive-compulsive behaviour, for their at-times blatant lack of common sense or safety in the lab and ultimately for them being who they are – I have to thank:

- Celine *''Put me on the bench as far away from my husband as possible''* Roy
- Claude *''Has anyone heard from my wife?''* Roy
- Louise *''No, Claude, for the last time – I don't know where Celine is''* Appleby
- Franklin *''Dun be a bacondread me bredrin. Yous gotta put a leash on ur gurl. One love. Jah rule''* Frimpong
- Timmy *''Yes Phil, Bubble Spinner is a productive use of my time. No? Well, at least I'm in the lab. At least I'm not trawling around campus looking for my wife.''* Mace
- Yohan *''Surely you can't get much more purchase out of this, Chris?''* Chan
- Ian *''Pipe down Yohan, of course he can – he's a comedic, as well as a chemical genius. Unlike* Thomas *''OK, if m-CPBA *doesn't* first break down to give a single, highly-reactive atom of oxygen during epoxidation, you tell me a more plausible mechanism''* Dann'' Strutt
- Miklos *''I really want to ask her to marry me, but I'm worried she'd spend the whole of our wedded life avoiding me. I've seen that happen before''* De Kiss
- Wei-Wei *''I really wish he would ask me to marry him''* Wang
- Tara *''I really wish he would hurry up and ask her to marry him, she's doing my primal diet-eating head in with all that sobbing''* Dixon
- Chris *''My natural product has so much potent pharmacological activity, I feel guilty that I haven't made it yet''* Pearce
- Dave *''No. I'm not alright. I had night-terrors about LEANDRO again''* Day
- Ketan *''Resident Silverback''* Panchal
- Doyle *''Would you please put some clothes on and stop bowling round the house screeching and beating your chest. Ilhwan said he's coming round in a few minutes to fix the oven, the garage door, the shower and the central heating, or break them all trying. Also something about an election?''* Cassar

To my friends: my friends, all of whom I couldn't possibly mention, who've helped make these years I have spent in Norwich the best I've had – I want to say thank you. Particularly those in the last few months of my PhD who shared their time and were forgiving or even joined in when drinks were being thrown, house parties crashed and sinks abused.

For their unwavering belief and love, I wish to thank my parents, my brother and sister and my great-uncle and late great-auntie. Being in the privileged position to be able to start studying towards a PhD was only possible because of them, because they've supported and encouraged me in whatever it is I have ever wanted to do. That said, but for a girl, I wouldn't have finished this thesis. A girl who inspired me and who had as big an influence on my life as anyone I've ever met. A girl who, even if I fail the viva, made these three years worth it – because I got more out of my time in Norwich, just by having known her, than I ever could have imagined.

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ABBREVIATIONS

2,2-DMP	2,2-dimethylpropane diol
Å	Angstrom
Ac	acetyl
ADP	allyldiethyl phosphate
Ar	aromatic
atm/bar	1 atmosphere = 10^5 Pa (pressure)
$[\alpha]_D$	specific optical rotation at the sodium D Line
AIBN	azobis(isobutyronitrile)
aq.	aqueous
BINOL	1,1'-bi(2-naphthol)
Bn	benzyl
^{n}Bu	normal butyl
^{t}Bu	tertiary butyl
conc.	concentrated
COSY	correlation spectroscopy
°C	degrees Celsius
cat.	catalyst (catalytic amount)
c	concentration
CHP	cumene hydroperoxide
Cbz	benzyloxycarbonyl
CD	circular dichroism
CH_2Cl_2	dichloromethane
cm^{-1}	wavenumber
conv.	conversion
CSA	camphorsulfonic acid
δ	chemical shift
de	diastereoisomeric excess
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEIPS	diethylisopropylsilyl
DET	diethyltartrate
DIBAL	diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	*N,N*-dimethylformamide
DMP	2,2-dimethoxypropane
DMPU	*N*,*N*-dimethylpropylene urea
DMSO	dimethylsulfoxide
DMSO-d_6	dimethylsulfoxide (deuteriated)

dppp	1,3-bis(diphenylphosphino)propane
dr	diastereoisomeric ratio
E_A	activation energy
ee	enantiomeric excess
EI	electron impact
Et	ethyl
EtOH	ethanol
[(+)-Eu(hfc)$_3$]	europium (III) tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]
equiv.	equivalents
er	enantiomeric ratio
ES	electrospray
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
h	hour
HMPT	hexamethylphosphorus triamide
Hünig's base	diisopropylethyl amine
g	gram(s)
HPLC	High Performance Liquid Chromatography
Hz	Hertz
IBX	2-iodoxybenzoic acid
IR	infrared spectroscopy
J	coupling contant
LC-MS	Liquid Chromatography – Mass Spectrometry
LDA	lithium diisopropylamide
LG	leaving group
M	molar
***m*-**	*meta*
***m*-CPBA**	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mmol	millimole(s)
MMPP	magnesium monoperoxypthalate
min.	minutes
mL	millilitre(s)
m.p.	melting point
m/z	mass to charge ratio
NBS	*N*-bromosuccinamide

nm	nanometers
NMR	Nuclear Magnetic Resonance spectroscopy
n.O.e.	nuclear Overhauser effect
Nu	nucleophile
o-	*ortho*
p-	*para*
Pd/C	palladium on carbon
Ph	phenyl
PhIO	iodosylbenzene
PMB	*para*-methoxybenzyl
^{i}Pr	isopropyl
ppm	parts per million
psi	pound per square inch
quat.	quaternary carbon
R	undefined group
RT	room temperature
salen	salicylideneaminato ligand
sat.	saturated
S_N2	nucleophilic substitution (bimolecular)
S_N1	nucleophilic substitution (unimolecular)
TFA	trifluoroacetic acid
TfO	trifluoromethanosulfonate
THF	tetrahydrofuran
Tig	tigloyl
TLC	Thin Layer Chromatography
TPPP	tetraphenylphosphonium monoperoxy sulfate
UV	ultra violet
VT	variable temperature
w/v	weight per volume
w/w	weight per weight

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CHAPTER ONE

CHAPTER TWO

CHAPTER THREE

1.0 Introduction

1.1 Chirality

Chirality exists in molecules which do not possess a plane of symmetry; such molecules cannot be superimposed on their mirror images and possess a different configuration in 3D space in every conformation. Molecules that are mirror images of each other are termed enantiomers and have identical physical properties, e.g.; m.p., reactivity, NMR spectra and molecular weight, etc, except that each enantiomer rotates the plane of plane polarized light by an equal magnitude but in the opposite direction with respect to the other.[1]

Jean-Baptiste Biot discovered in 1815 that some natural isolates (natural products) rotated the plane of plane polarized light.[2] The reason, unknown to Biot at the time, is that many natural products exist as only one of the two possible enantiomers.

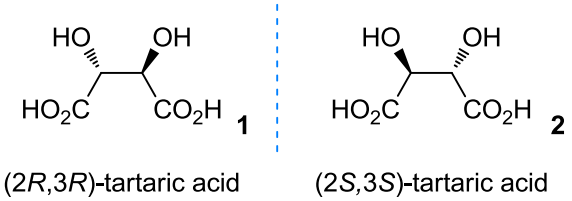


Figure 1.1: *The two enantiomers of tartaric acid.**

Naturally occurring tartaric acid **1** was shown to be optically active by Biot (Figure 1.1). However, synthetic tartaric acid made at the time by chemists was not. Of course, the synthetic acid was a 1:1, or racemic, mixture of **1** and **2** causing the net rotation of light to be zero.[3] This observation was rationalized when in 1849 by Louis Pasteur, who noticed that crystallization of the sodium ammonium salt of tartaric acid yielded two asymmetric crystals that were mirror images of each other (Figure 1.2). The two forms of the crystal were manually separated by Pasteur, and both were found to be optically active. Importantly, he correctly proposed this was due to the structure of tartaric acid being somehow asymmetric.[4]

**Tartaric acid can also exist as its meso-(R,S) isomer; it possesses two chiral centres, but also a plane of symmetry within its structure. It is, therefore, not optically active.*

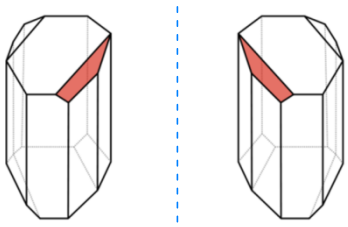


***Figure 1.1**: Illustration of the two asymmetric crystals of the tartaric acid salts.*

Jacobus Henricus van't Hoff was the first person to suggest that the tetrahedral arrangement of four different groups around a carbon atom could result in an asymmetric product and hence account for Pasteur's observations. The theory put forward in his 1874 paper and subsequently in his book ''*La chimie dans l'espace*'' was at first ridiculed by many scientists, most famously by Kolbe who in an open letter wrote:[5]

> *"A Dr. J. H. van 't Hoff of the Veterinary School at Utrecht has no liking, apparently, for exact chemical investigation. He has considered it more comfortable to mount Pegasus (apparently borrowed from the Veterinary School) and to proclaim in his 'La chimie dans l'espace' how the atoms appear to him to be arranged in space, when he is on the chemical Mt. Parnassus which he has reached by bold flight''*

J. H. van't Hoff's theory was eventually accepted by the scientific community and he went on to become one of the greatest chemists of his generation contributing hugely to the fields of organic and physical chemistry. In 1901 van't Hoff was awarded the first Nobel Prize in chemistry.

1.1.2 Chirality and Life

All life on earth is chiral - the human body for example uses only the L-amino acids and D-hexoses (Figure 1.3). The D and L notation used here corresponds to the enantiomer of glyceraldehyde, which is isolated upon chemical degradation of molecules like **3** and **4** and stands for *dextrorotatory* and *laevorotatory*.[1]

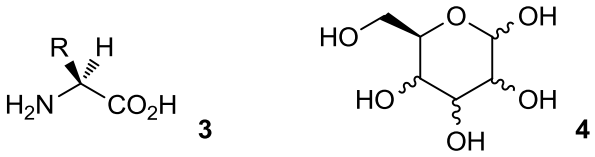


Figure 1.2: *Generic structure of the L-amino acids and D-hexoses.*

As indicated above, enantiomers in isolation have the same physical properties and reactivity. In a chiral system such as the body, however, enantiomers behave differently and can have drastically different effects.[6] The most infamous example of this disparity was observed with the use of the drug (±)-thalidomide to treat morning sickness in pregnant women (Figure 1.4).

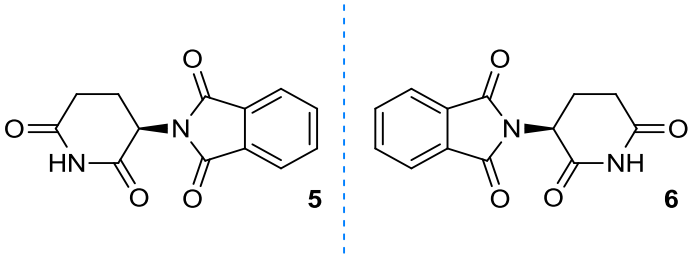


Figure 1.3: *The two enantiomers of thalidomide.*

Thalidomide was first available as a racemic mixture in 1957, and shortly after its release there was a large increase of miscarriages and many instances where babies with malformed limbs and other defects were born from mothers who were taking thalidomide.[7] A substantial research effort was directed at investigating the side-effects of the drug and it was determined that while (*R*)-thalidomide **5** did alleviate morning sickness and was non-toxic, (*S*)-thalidomide **6** was a powerful teratogen and caused severe birth defects in the developing foetus.[8] Administration of enantiomerically pure (*R*)-thalidomide was not an option in this instance as the drug was racemized *in vivo*.[9] Many lessons were learned from

this terrible incident, leading to stricter regulation on drug development to ensure a recurrence was not possible.[10]

As a result, many new drugs have to be produced as a single enantiomer, and, today, enantioselective synthetic strategies are a vital tool to achieve this. However, several decades ago there were few enantioselective techniques, and no doubt industry's need for such methodology drove its development. Consider a new drug that has only three stereocentres - it could exist as 2^3 stereoisomers. If the reactions to make these stereocentres are not selective, then over the synthesis 87.5% of the drug material is lost before the chemical yield of each step is taken into account. This would result in heavy financial strain for the pharmaceutical company, making it less probable that the drug will be financially viable. Evidently, if a drug needs to be made as one stereoisomer then the synthesis has to be stereoselective.

1.2 Epoxides

The epoxide, or oxirane, is a strained three-membered cyclic ether composed of two carbon atoms and a bridging oxygen (Figure 1.5). The internal bond angles of the epoxide are typically 60°, which is a large deviation from the preferred sp^3 hybridized bond angle of 109°, and this disparity loads the ring with substantial Baeyer strain.[11]

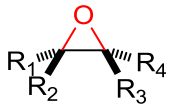
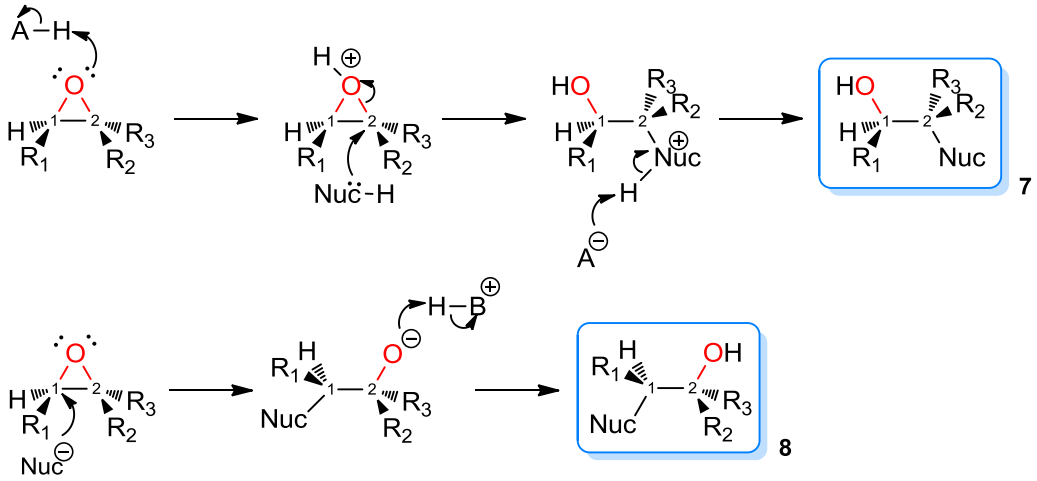


Figure 1.4: *The epoxide.*

Due to the Baeyer strain present in the ring and the δ+ charge induced on the two carbon atoms by the electronegative oxygen, epoxides are reactive electrophiles. Either electrophilic carbon can be targeted with range of nucleophiles, the most common including: oxygen,[12] nitrogen,[13] carbon[14] and sulfur[15] species. This reactivity allows easy access to many 1,2-functionalized

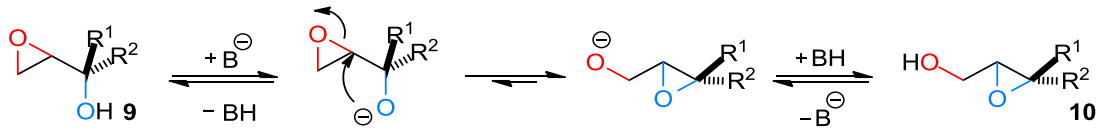
products such as **7** and **8**. An example of how either carbon can be targeted by acid or base catalysis is outlined below (Scheme 1.1).[11]



Scheme 1.1: *Acid- (or also Lewis acid) and base-catalysed ring opening of an epoxide. The nucleophile attacks the most substituted carbon in the acid catalysed reaction to give* ***7****, while the least substituted carbon is attacked in the corresponding base catalysed reaction to give* ***8****. As with all S_N2 reactions, inversion is observed at the electrophilic centre.*

Chemical groups that act to reduce the symmetry of the epoxide can differentiate the reactivity between the electrophilic carbon sites. Properties such as the steric size of attached R groups will achieve this, and functional groups close to the epoxide that affect electron density on the carbon atoms can influence regioselectivity also.

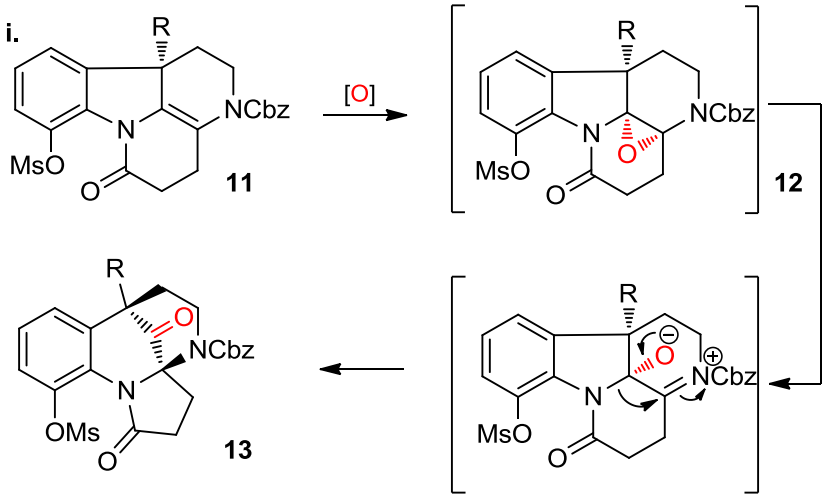
As well as the standard S_N2 type reactions, epoxides are also known to undergo several synthetically powerful rearrangements. It is possible to generate great complexity from a relatively simple epoxide-bearing skeleton, and some interesting examples are outlined below. Perhaps the most well known example is the Payne rearrangement, which describes the epoxide migration of 2,3-epoxyalcohols such as **9** in the presence of a strong base (Scheme 1.2).[16] The arrangement in this example exists as an equilibrium in which the most substituted epoxide **10** is favoured, although electron-withdrawing groups (EWG) destabilize the epoxide moiety.[17]



Scheme 1.2: *The Payne rearrangement.*

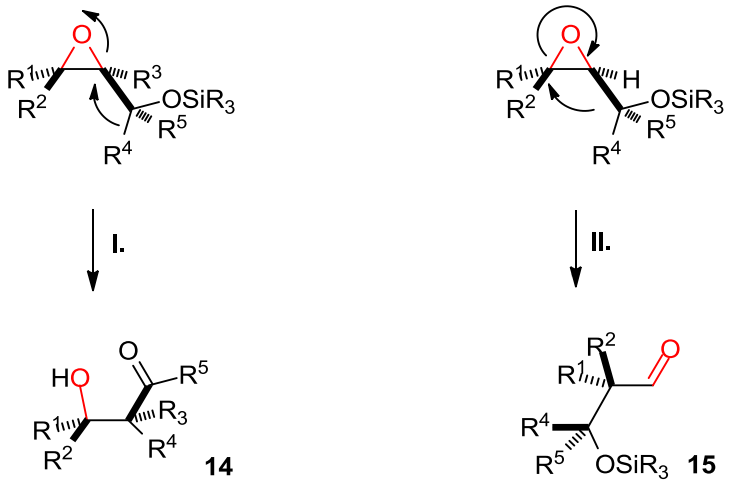
The related homo-Payne rearrangement of 3,4-epoxy alcohols is also well documented. The resulting oxetane is much more stable than the original epoxide and dominates the product constitution.[18]

An elegant rearrangement of a *trans*-diamine epoxide species **12** was utilized in Fukuyama's synthesis of haplophytine (Scheme 1.3).[19] The alkene in **11** was oxidized to the epoxide which spontaneously rearranged to furnish ketone **13**.



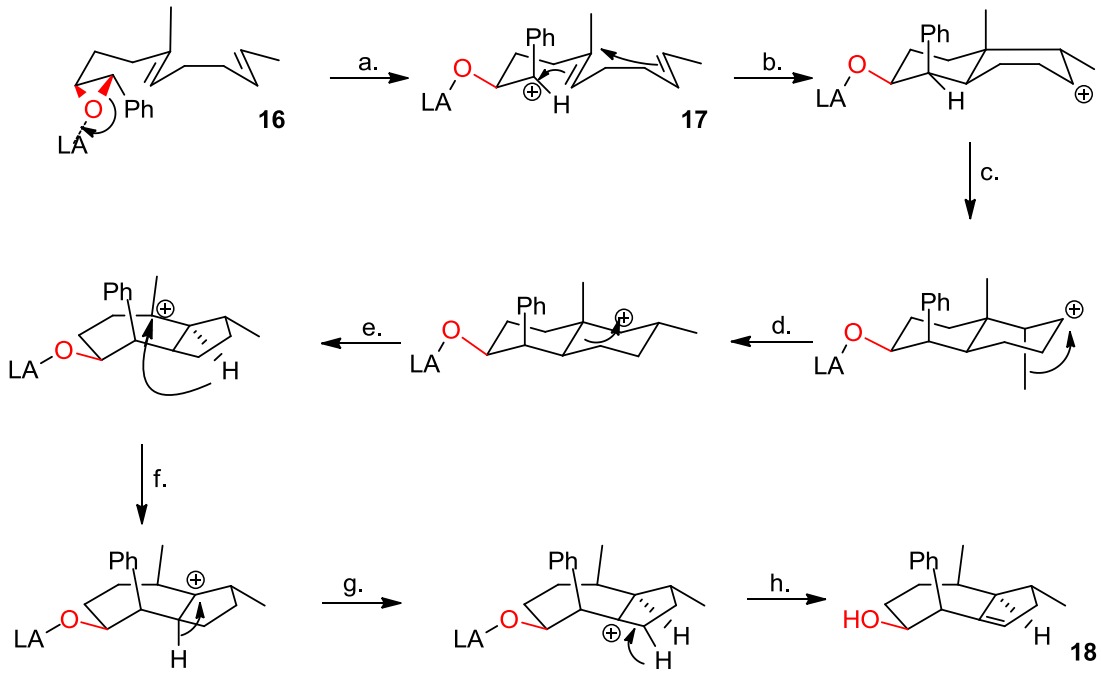
Scheme 1.3: *The use of an epoxide in Fukuyama's synthesis of haplohytine*.[19]

Many epoxide rearrangements are initiated by Lewis acids; by coordinating to the epoxide, Lewis acids activate the epoxide motif to nucleophilic attack or spontaneous ring opening.[20] Yamamoto has reported the exploitation of the well known Lewis acid-catalysed rearrangements to synthesise chiral β-hydroxy ketones **14** and β-siloxy aldehydes **15**, which are important intermediates in some natural product syntheses.[21] Route **I** has been effected by use of titanium tetrachloride,[22] while route **II** required the use of bulky aluminium species to facilitate a controlled and reliable reaction (Scheme 1.4).[23]



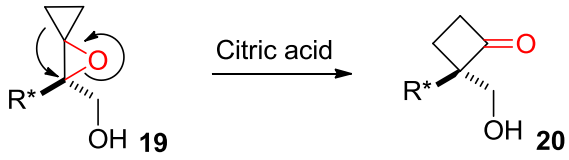
Scheme 1.4: *Yamomoto's early titanium mediated rearrangement and the more recent aluminium mediated rearrangement of 2,3-epoxysilols.*

Corey reported in 1997, while investigating potential syntheses of steroidal skeletons, a 'complex and unpredictable' rearrangement that was initiated by a Lewis acid-catalysed ring-opening of epoxide **16** to form benzylic cation **17**, which subsequently underwent a two-step cyclization followed by numerous bond and group migrations to form the bicyclic skeleton of **18** (Scheme 1.5).[24]



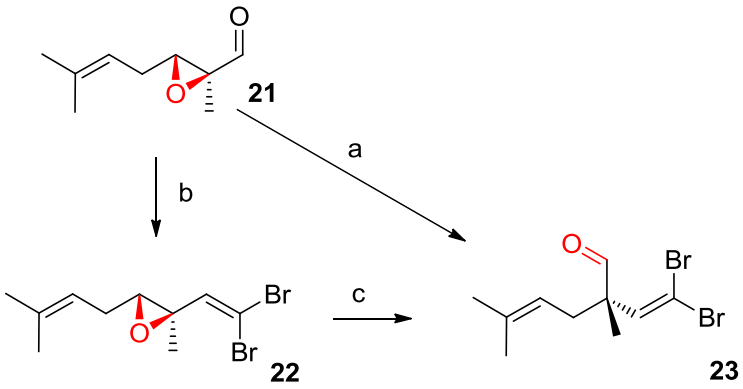
Scheme 1.5: *The cascade rearrangement reported by Corey initiated by epoxide ring-opening. a) Cation formation and bond rotation; b) two-step cyclization; c) boat to chair flip; d) methyl shift; e) fusion bond shift; f, g) hydride shift; h) elimination.*

Fukumoto took advantage of an epoxide rearrangement to synthesise chiral cyclobutanones **20**,[25] which are also key intermediates for the synthesis of natural products (Scheme 1.6).[26] The chiral epoxy-cyclopropanes **19** were prepared by the Sharpless asymmetric epoxidation (discussed below) from an allylic alcohol precursor which was then treated with citric acid in a one-pot reaction to furnish a cyclobutanone species.



Scheme 1.6: *Fukumoto's synthesis of chiral cyclobutanones.*

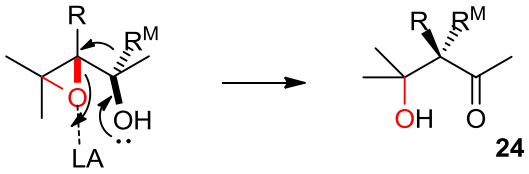
Jung has reported the utilization of a Lewis acid-accelerated epoxide rearrangement to enable the synthesis of aldehydes with an α-chiral quaternary centre.[27] This rearrangement was discovered when attempting a Corey-Fuchs homologation of 2,3-epoxy aldehyde **21**.[28] Instead of the desired allylic epoxide **22**, the main component of the isolated material was the allylic aldehyde **23** (Scheme 1.7). Jung proposed that $ZnBr_2$, formed as a by product of a successful homologation, was a potent enough Lewis acid to facilitate the rearrangement.



Scheme 1.7: *Jung's Lewis acid-catalysed rearrangement. a) Zn, Ph_3P, CBr_4, 60%; b) HMPT, CBr_4, CH_2Cl_2, 99%; c) $BF_3{\cdot}Et_2O$, 89%.*

The rearrangement was more controllable in a two step sequence with the use of the Lewis acid BF_3 on the allylic epoxide. This rearrangement has been successfully used by Jung to synthesise biologically relevant molecules.[27]

Suzuki and Tsuchihashi have demonstrated the use of the epoxy alcohol rearrangement to prepare aldol-type 1,3-disubstituted products featuring enantiopure quaternary carbon centres as in **24**.[29] This rearrangement is again Lewis acid-mediated, and the general scheme is shown below (Scheme 1.8).



Scheme 1.8: *The epoxy alcohol-aldol rearrangement used to construct chiral quaternary carbon centres.*

As well as being synthetically useful, epoxides themselves are widely encountered within organic and biological chemistry, being present in many secondary metabolites and pharmaceuticals (Figure 1.6).[30]

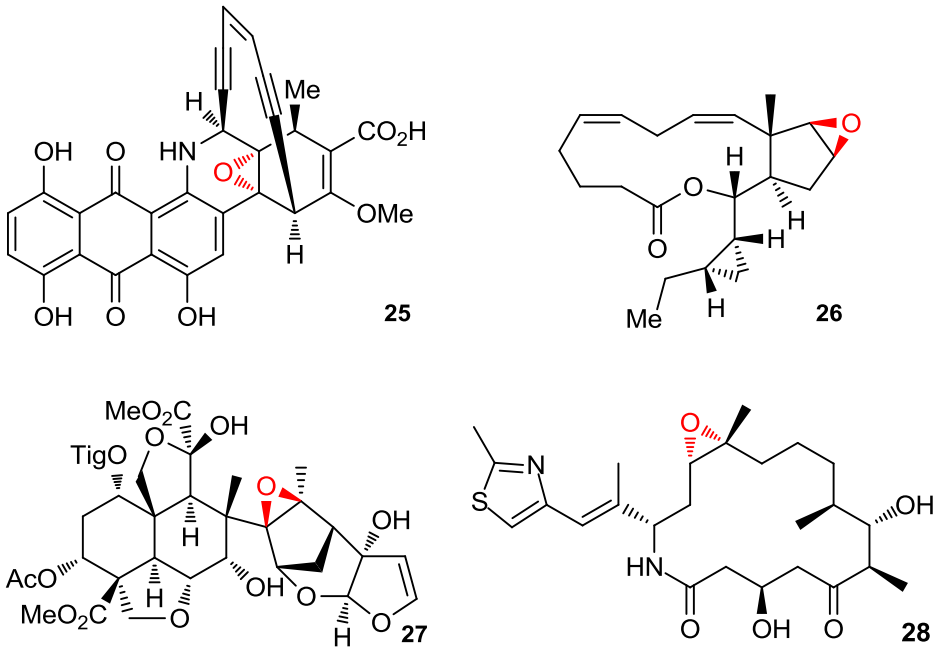
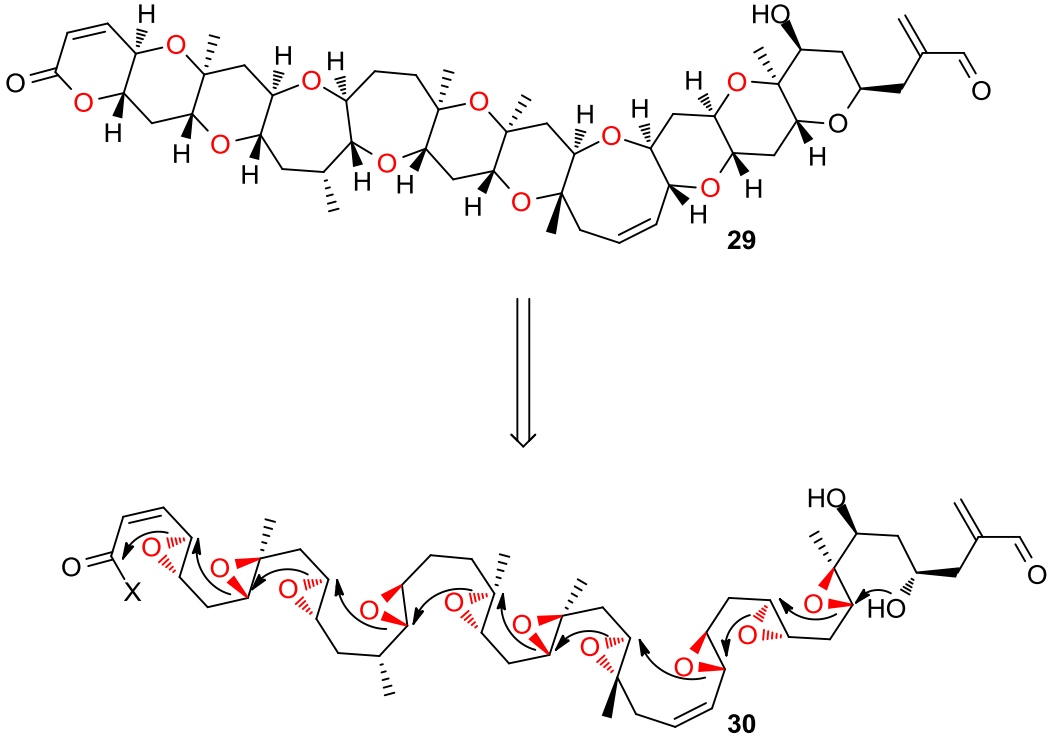


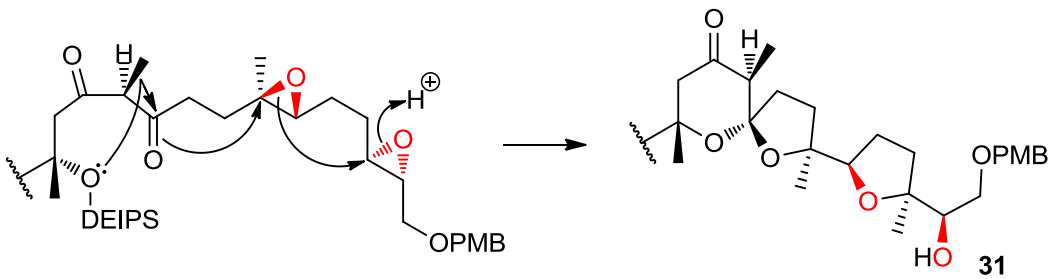
Figure 1.6: *Natural products containing an epoxide functional group: dynemicin* ***25***[31]*; hybridalactone* ***26***[32]*; azadirachtin* ***27***[33]*; and the pharmaceutical Ixempra* ***28***[34] *which is used in the treatment of metastatic breast cancers.*

The epoxide is believed to be used in nature in the synthesis of secondary metabolites, as highlighted in the proposed biomimetic sequence involved in the synthesis of brevitoxin-B **29**.[35] In this example, nucleophilic ring-opening of an epoxide in **30** by a free hydroxyl results in a reactive nucleophilic oxy-anion, which then ring-opens a second epoxide within the same molecule and so on – propagating a cascade sequence. These cascade, or domino, reactions are thought to resemble closely how some natural products are constructed in living systems (Scheme 1.9).[36]



Scheme 1.9: *A biomimetic cascade step in the synthesis of brevitoxin-B.*

In addition, the unique functionality of epoxides coupled with the many methods of introducing the moiety into a substrate, has resulted in the routine exploitation epoxides by chemists to facilitate the efficient synthesis of many complex organic molecules. For example, Paterson's synthesis of etheromycin made excellent use of an epoxide cascade strategy to efficiently construct a polycyclic ether skeleton **31** (Scheme 1.10).[37]



Scheme 1.10: *A biomimetic cascade step in Paterson's synthesis of etheromycin.*

It is clear that the epoxide is an extremely powerful and important functional group for the synthetic organic chemist, as such, it is one that used

routinely in the laboratory synthesis of natural products and pharmaceutics. If one can exert stereocontrol over the insertion of an epoxide into a compound then resolution steps will be avoided and one would not have to dispose of unwanted stereoisomers (Figure 1.7).

Figure 1.7: *Enantiomeric and diastereoisomeric epoxides.*

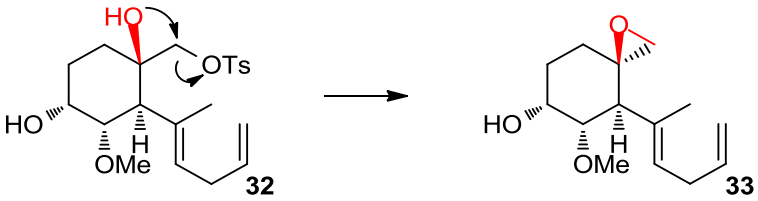
As such, over the past few decades there has been a drive to develop stereoselective processes for the introduction of epoxides into alkene substrates. There are two main classes of methodology; the first is metal-based catalysis and the second is the relatively new field of organocatalysis. Both methodologies are explored in detail below preceded by a brief overview of other epoxidation techniques.

1.3 Epoxidation Methodologies

Epoxides can be synthesised using many different and varied methodologies, and, as mentioned above, this wide range of techniques available to the synthetic chemist helps make the epoxides a particularly useful functional group.

1.3.1 Williamson Ether Synthesis

One of the simplest reactions used to form an epoxide is a type of Williamson ether synthesis. Mechanistically, a nucleophilic oxygen attacks a carbon at the β-position bearing a good leaving group such as a tosylate **32**.[38] This 3-*exo*-tet cyclization typically furnishes the epoxide in good yields. This procedure was used by Kim to install the epoxide in **33** late on in a synthesis of (–)-fumagillol in 88% yield (Scheme 1.11).[39]



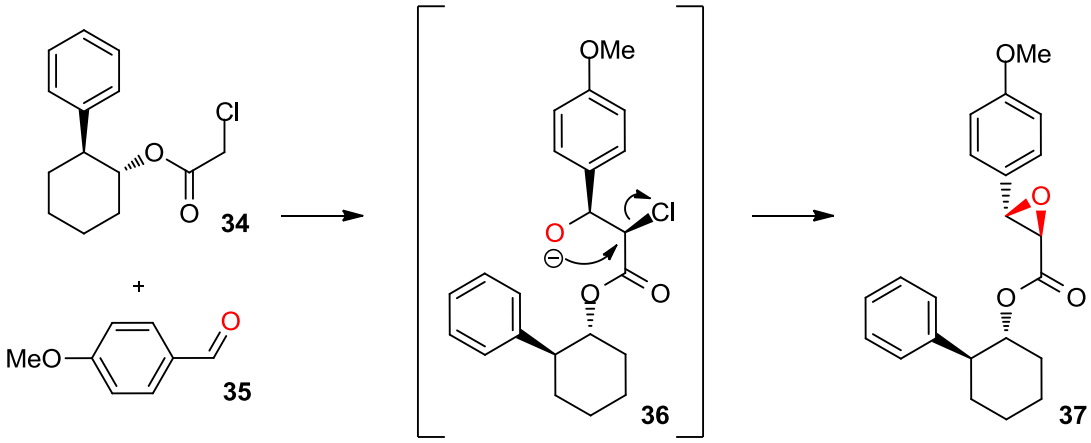
Scheme 1.11: *Williamson ether synthesis as a key step in Kim's synthesis of (–)-fumagillol.*

1.3.2 Darzens Condensation

The Darzens condensation is commonly used to synthesise α,β-epoxy esters; traditionally α-halo esters and ketones or aldehydes were used as the coupling partners.[40] However, many variations of this reaction have recently been investigated, and one can now use α-halo sulfones,[41] ketones,[42] nitriles[43] and amides,[43,44] for example, to effect a similar reaction.

This reaction is illustrated in Schwartz's synthesis of the calcium channel blocker dilatazem **37** (Scheme 1.12).[45] This proceeds similarly to the aldol reaction initially – the α-halo ester **34** is deprotonated to form an enolate, which then reacts through the C-terminus with aldehyde **35** forming a halohydrin

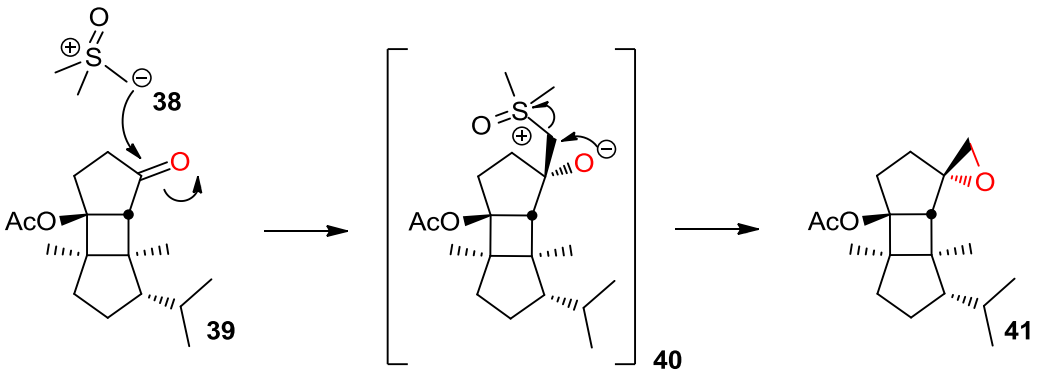
intermediate **36**. The oxy-anion of the halohydrin rapidly attacks the electrophilic carbon centre, furnishing the α,β-epoxy ester in good yield.



Scheme 1.12: *The application of the Darzens condensation in Schwartz's dilatazem synthesis.*

1.3.3 Corey-Chaykovsky Epoxidation

Johnson first described in 1961 the unexpected formation of an epoxide when he attempted a Wittig reaction between 9-dimethylsulfonium fluorenylide and a benzaldehyde.[46] But in what became known as the Corey-Chaykovsky epoxidation, sulfonium or sulfoxonium ylides are employed to transfer, in the simplest case, a methylene unit to ketones or aldehydes.[47] Ylides such as **38** are typically prepared *in situ* from either sulfoxonium or sulfonium salts. Mechanistically, a nucleophilic ylide attacks a carbonyl species **39** to form a betaine intermediate **40**, which collapses to the epoxide **41**.[48] Wickberg used the Corey-Chaykovsky epoxidation in his very short syntheses of both (+)-aphanamol I and II (Scheme 1.13).[49]



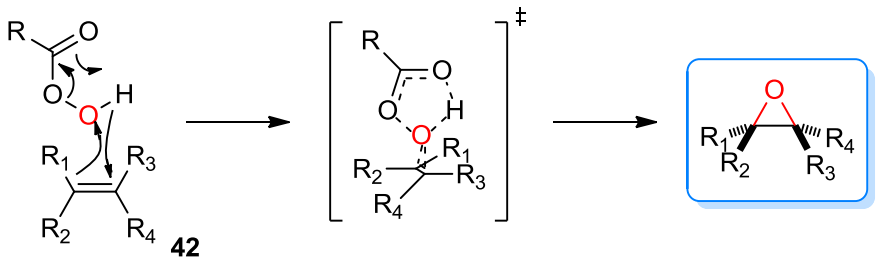
Scheme 1.13: *Use of the Corey-Chaykovsky epoxidation in Wickberg's synthesis of (+)-aphanamol I and II.*

1.4 Non-Stereoselective Epoxidation of Alkenes and Enones

The most commonly seen class of epoxidation reaction involves the transfer of an oxygen to a C=C bond. As well as the reactions below, many other oxidants may be used, including: peroxoselenic acid, peroxycarboximidic acids, O_2 + hv, magnesium monoperoxypthalate and alkyl hydroperoxides in conjunction with transition metals.[50,51]

1.4.1 Prilezhaev Epoxidation

The ability of peracids to oxidize isolated carbon-carbon double bonds was first discovered in 1909 by Prilezhaev.[52] The reaction is completely stereospecific, meaning the substrate will always carry its double bond *E*- or *Z*- geometry through to the final product. The reaction is believed to proceed through a concerted 'butterfly' transition state, which explains the observed stereospecificity.[53] The reaction can be envisaged to begin with a nucleophilic interaction of the alkene's π-orbital with the σ* orbital of the peracid's O-O bond, but it is a concerted process (Scheme 1.14).



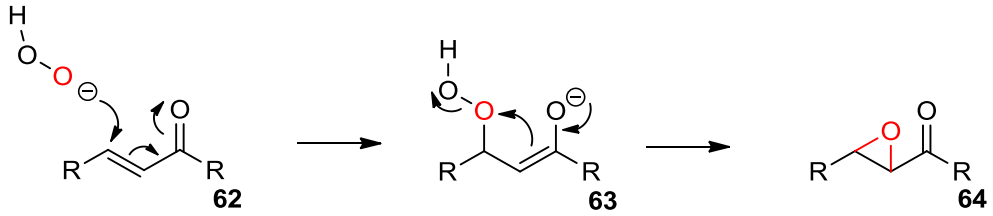
Scheme 1.14: *The concerted 'butterfly' transition state believed to operate in the Prilezhaev oxidation.*

The oxidant can attack either the top or bottom face of the planar olefin **42**, resulting in a racemic mixture if the substrate contains no chiral centres. However, if the substrate is optically active then selectivity for one face will be observed as the two transition states will be diastereoisomeric, thus their activation energies and therefore their rates of formation will be different. This facial selectivity is particularly pronounced if there is a group such as a hydroxyl close to the alkene that can coordinate to the peracid and direct it to one face.[54]

The Prilezhaev reaction is also chemoselective. The epoxidation proceeds faster with increasing electron density on the alkene. Because aliphatic groups are mildly electron-donating, a trisubstituted alkene will be epoxidized in preference of a styrene in the same molecule, for example. The reactivity is lessened when the alkene is substituted by electron-withdrawing groups. Some electron-poor olefins can be oxidized using this system, but the limit is found at α,β-unsaturated ketones, which are unreactive.[51]

1.4.2 Weitz-Scheffer Epoxidation

The electron-deficient nature of the α,β-unsaturated ketone moiety **43** does lend itself to nucleophilic attack by an alkaline hydrogen peroxide system. This methodology, developed in 1921 by Weitz and Scheffer, provides a route to α,β-epoxyketones **44** (Scheme 1.15).[55]

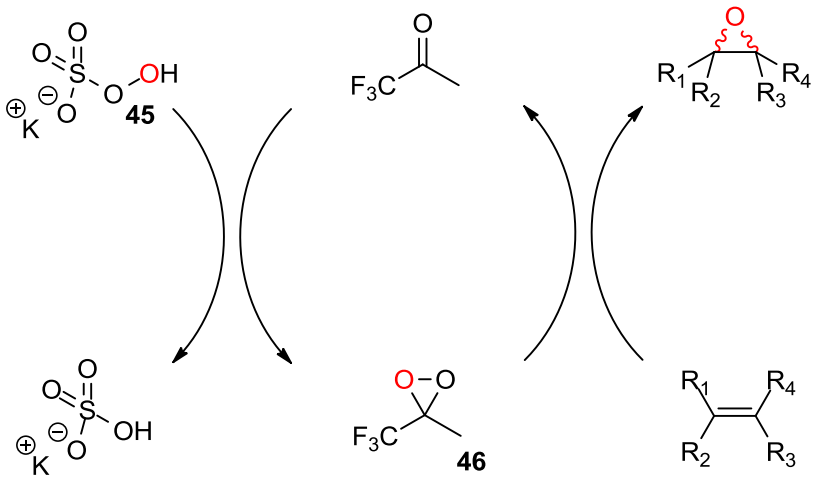


Scheme 1.15: *Weitz-Scheffer epoxidation of electron deficient alkene substrates.*

1.4.3 Dioxirane-Mediated Epoxidation

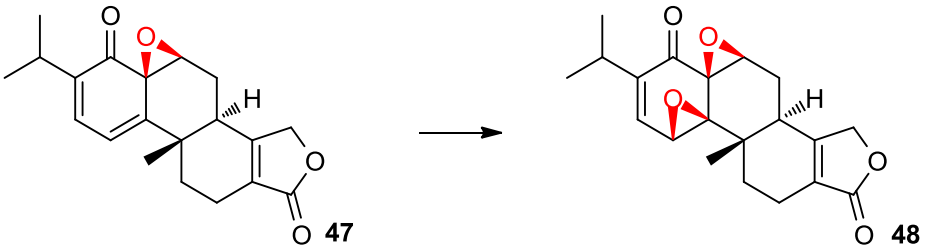
Dioxiranes are a very important class of oxidants. Their existence had been postulated since the early 1900s,[56] however, it was not until 1977 that substantial evidence was obtained in a microwave spectroscopy study that conclusively supported their existence.[57] A few years later, chemists were able to readily synthesise dioxiranes, and, with that development, their use in synthetic chemistry began to accelerate.[58,59]

For simple achiral systems, dioxiranes are typically synthesised by oxidation of simple ketones such as acetone. The ketones can be oxidized by the triple salt Oxone® ($2KHSO_5.KHSO_4.K_2SO_4$) **45**, and the resulting dioxiranes can then be isolated by distillation of the reaction mixture.[59] A more practical method, which was developed by Curci and Edwards in 1984,[60] is to form the dioxirane **46** *in situ*, which gives the opportunity to create a system catalytic in the ketone (Scheme 1.16). Chiral ketones are one of the most investigated classes of organocatalyst for asymmetric epoxidation, and while, perhaps, a catalytic system is not important if one is using acetone, it was a crucial development that later made the use of chiral ketones practical. This catalytic procedure involved the use of a biphasic CH_2Cl_2/H_2O solvent system, Oxone®, and a phase-transfer catalyst to allow the solvation of the water-soluble oxidant in the organic phase. Organic molecules that behave as phase-transfer agents are an important class of organocatalysts, and phase transfer catalysis will be discussed in more detail later.



Scheme 1.16: *Dioxirane-mediated catalytic cycle to oxidize alkenes.*

Dioxiranes have been put to good use in natural product synthesis. In 2000, Yang was able to produce methyl(trifluoromethyl)dioxirane **46** *in situ* to epoxidize a precursor of (–)-triptolide in 70% yield and, owing to the stereochemistry already present in the precursor **47**, **48** was isolated as a single diastereoisomer (Scheme 1.17). Notably, Yang used a homogenous MeCN/H_2O system to achieve good reactivity. The modification greatly improved on the previous biphasic system, developed by Curci and Edwards, which relied on phase-transfer agents to facilitate the formation of the dioxirane.[61]



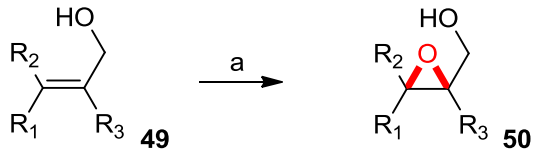
Scheme 1.17: *Oxidative step in Yang's synthesis of (–)-triptolide.*

1.5 Metal-Mediated Stereoselective Olefin Epoxidation Methodology

1.5.1 Sharpless Asymmetric Epoxidation

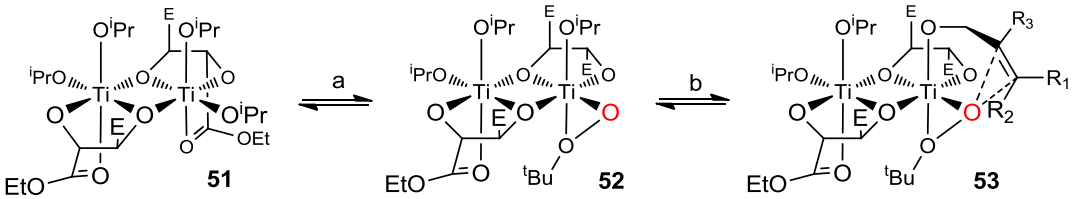
The Sharpless epoxidation is a method to transform allylic alcohols into their respective epoxyalcohols, using the transition metal titanium (Scheme 1.18).[62] It is considered one of the most important methodologies developed within organic chemistry in the past 30 years, and consequently, Sharpless shared the Nobel Prize in 2001 for his work on this and other asymmetric transformations.[63,64]

The Sharpless catalytic system is capable of imparting great stereocontrol to a range of substrates that contain the necessary allylic alcohol moiety **49**. The reaction usually furnishes the epoxide product **50** in a high yield and very high enantiomeric excess (>95 %).[65] The authors found that a relatively simple mixture of $Ti^{(IV)}(O^iPr)_4$, ^{t}BuOOH as the stoichiometric oxidant, together with a chiral diethyltartrate ligand (DET) is all that was needed to achieve high conversion and enantioselectivity.



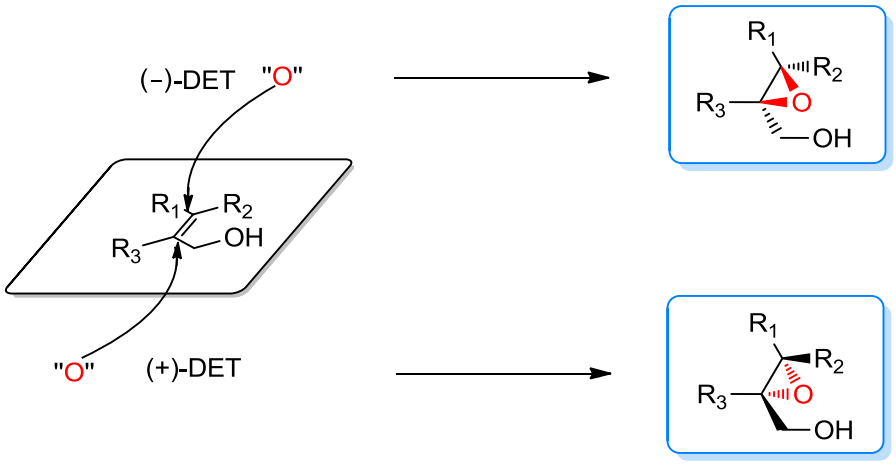
Scheme 1.18: *a) $Ti(O^iPr)_4$, (+) or (–)-DET, ^{t}BuOOH, 3-5 Å molecular sieve, CH_2Cl_2, –20 °C.*

The complex that is believed to be the active catalyst is somewhat more complicated (Scheme 1.19).[66] When carrying out this reaction, the $Ti^{(IV)}$ complex and the desired DET are added together first, typically in CH_2Cl_2 at –20 °C, to form complex **51**. The oxidant ^{t}BuOOH is then added to the solution, which undergoes ligand exchange with **51,** displacing one of the DET's carbonyl groups as well as an $^iPrO^-$ ligand, the solution is allowed to stir for 20-30 min to mature, allowing the formation of active complex **52**. Lastly, the allylic-alcohol substrate is introduced; this is believed to displace an axial $^iPrO^-$ ligand to form the transitional complex **53**.



Scheme 1.19: *a) ^{t}BuOOH, b) allylic alcohol substrate. (+)-DET is shown in this example.*

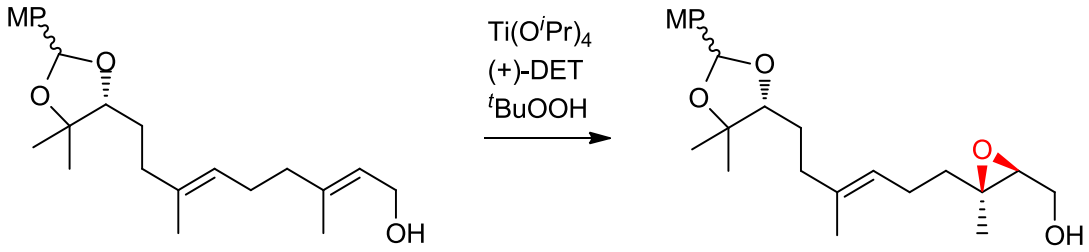
Either enantiomer of the desired epoxyalcohol can be synthesised by changing the enantiomer of DET used and, importantly, both isomers are available cheaply (Scheme 1.20). L-(+)-DET, the more commonly found form of tartrate, is extracted from grapes. The 'non-natural' form of D-(–)-DET is rare, and is more expensive.



Scheme 1.20: *The mnemonic for predicting the major product depending on the enantiomer of tartrate used.*

Molecular sieve is required to remove water from the system, as water is detrimental to the activity of the complex. Without molecular sieve, one equivalent of the active Ti complex is required. However, with them, only 5-10% of the complex is required; rendering the process catalytic.[67]

The Sharpless epoxidation is capable of extremely high *ees* (>99%), and, as such, many natural product syntheses have made use of this powerful methodology to date. Morimoto used the Sharpless epoxidation to introduce key stereochemistry and functionality in the first asymmetric total synthesis of the marine triterpene polyether (+)-intricatetraol (Scheme 1.21).[68]



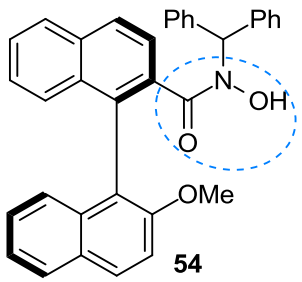
Scheme 1.21: *The Sharpless epoxidation as a key step in Morimoto's total synthesis of (+)-intricatetraol.*

The epoxidation proceeded in almost quantitative yield with complete stereocontrol. Using this powerful methodology, Morimoto was able to install the first of two epoxides which are then set-up to undergo an intricate cascade reaction, forming several of the key structural moieties present in (+)-intricatetraol.

1.5.2 Yamamoto

Over the past decade, Yamamoto has reported several powerful metal-based catalytic systems for the epoxidation of allylic alcohols.[69] These systems are designed similarly to Sharpless', and as a consequence the substrate scope is also limited to alkenes bearing a pendent alcohol group.

The transition metal centre in Yamamoto's initial systems was vanadium, introduced as V$^{(v)}$O(O^{i}Pr)$_3$, and monohydroxamic acid ligands **54** and **55** were employed as the source of stereochemical information (Figure 1.8).[69]



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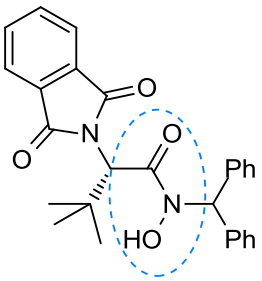
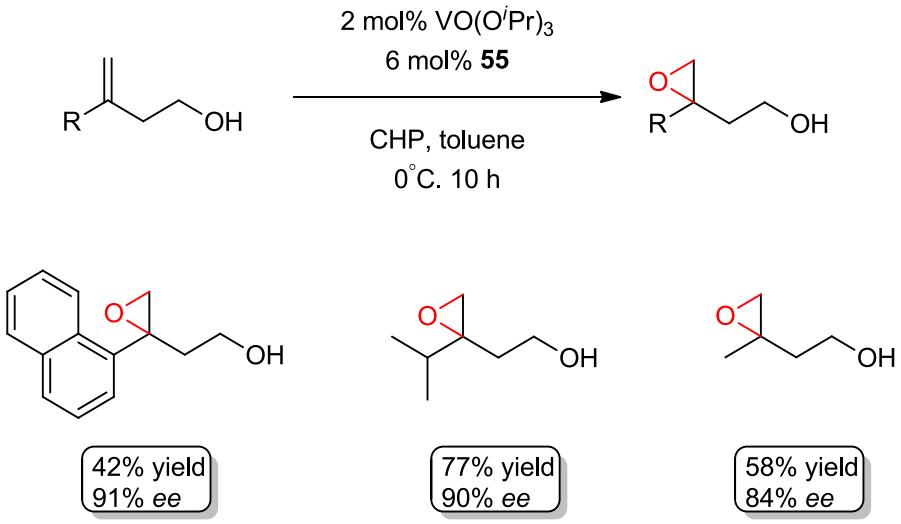


55

Figure 1.8: *Monohydroxamic ligands designed by Yamamoto.*

Early results were promising, attaining some good *ees* particularly for homoallylic alcohols (Scheme 1.22). Furthermore, the vanadium-based systems do not require the use of molecular sieve, as the water-induced attenuation of catalytic activity was not observed.



Scheme 1.22: *Epoxidation of homoallylic alcohols with Yamamoto's vanadium catalytic system.*

In his drive to further improve the facial selectivity of the vanadium-based system, Yamamoto increased the steric bulk of the ligand; however, he reported reaching the limit of reactivity before achieving the *ees* he desired.[70] Having seemingly reached a dead end, Yamamoto has recently detailed the exploration of the ability of other metals to epoxidize homoallylic and bis(homoallylic) alcohols (Figure 1.9). Several group 4 and 5 metals such as titanium, zirconium, hafnium and niobium were trialled. It was found that hafnium and zirconium, in conjunction with a bis(hydroxamic acid), provided the best results in terms of both reactivity and enantioselectivity.[70]

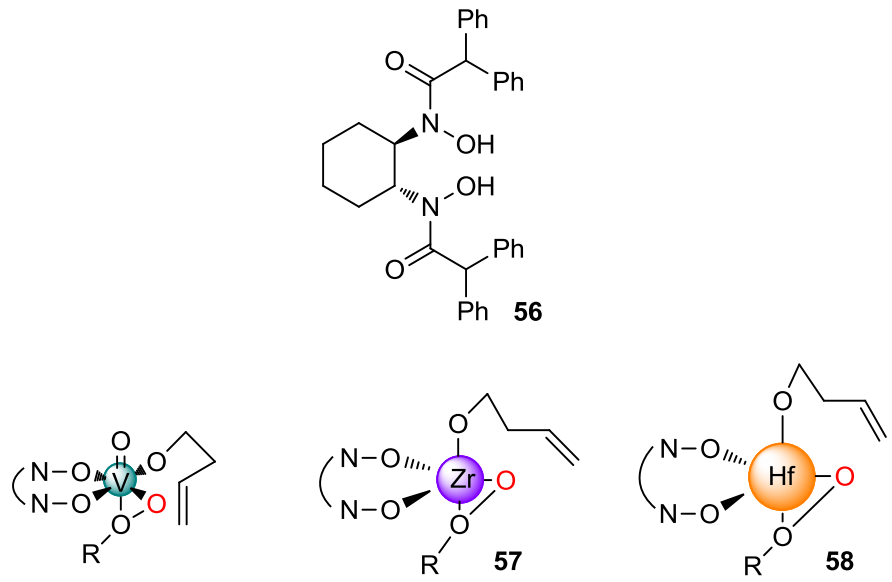
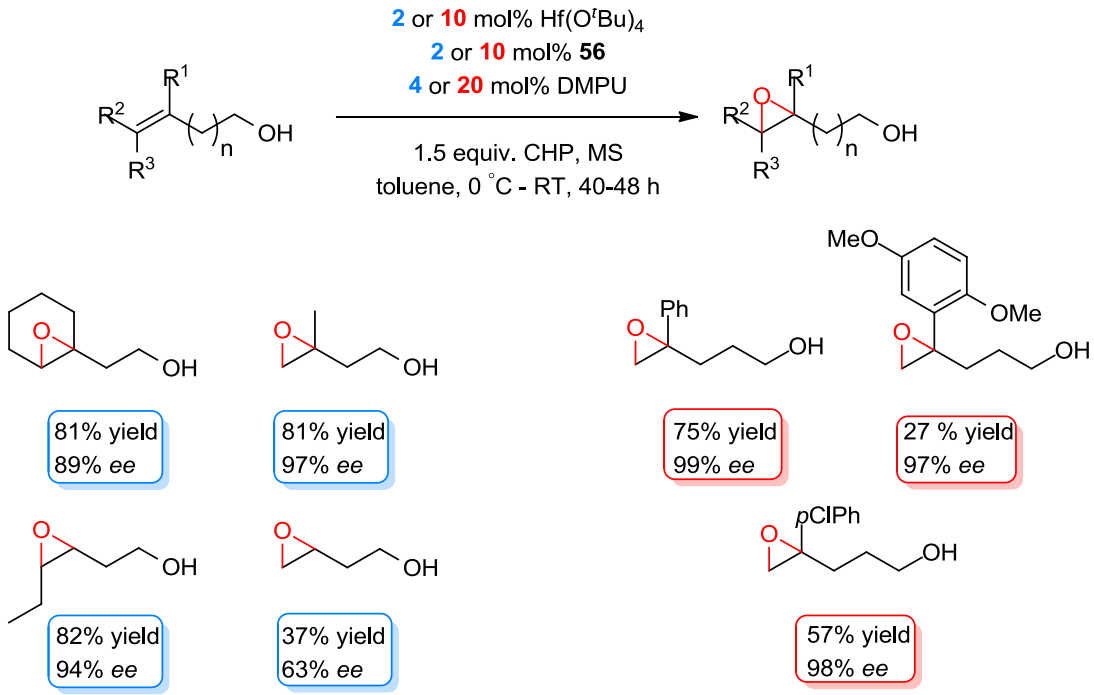


Figure 1.9**:** *Illustration of several transition metal intermediates, showing a bound homoallylic alcohol. Yamamoto the larger size of the metal centres of the later group 4 elements would alleviate some of the reactivity problems experienced with the relatively crowded vanadium analogue.*

During the optimization of the reaction parameters, it was observed that the hafnium system benefited from the addition of 4 Å molecular sieve to remove any contaminating water, while the analogous zirconium system did not. Yamamoto also discovered that the sub-stoichiometric addition of DMPU, a polar aprotic solvent, caused a large increase in yield. He noted that this was likely due for two reasons: a) the vacant coordination sites present on the zirconium and hafnium metal centres in **57** and **58** respectively could facilitate a slow oligomerisation of the catalyst species, potentially leading to a drop in activity. He suggested that DMPU occupies these sites, thus stabilizing the monomeric form; b) DMPU may accelerate the completion of the catalytic cycle by allowing the facile release of the coordinated product from the metal centre.

After optimization, it was apparent that the hafnium-based system was far superior to the analogous zirconium-based system. Yamamoto achieved some impressive *ees* for the isolated β- and γ-hydroxy epoxides, although yields were only moderate to good (Scheme 1.23). The bis(homoallylic) alcohols still present

themselves as difficult substrates, requiring a 5-fold increase in catalytic loading to approach the yields achieved for the homoallylic alcohols.[70]



Scheme 1.23: *Yamamoto's reported results for homoallylic alcohols (blue) and bis(homoallylic) alcohols (red).*

1.5.3. Jacobsen-Katsuki

In 1990, a stereoselective modification of a procedure to oxidize olefins originally developed by Kochi[71] was reported by Jacobsen and Katsuki.[72,73] This is another example of a transition metal-mediated epoxidation. In this instance, the metal species is manganese$^{(III)}$. Surrounding the metal centre is a tetradentate 'salen'$^{2-}$ ligand, and either a chlorate anion in Jacobsen's catalysts **59**, or an acetate anion in Katsuki's analogous catalysts **60** (Figure 1.10)**.** Unlike the Sharpless and Yamamoto epoxidations above, this method does not require the substrate to contain a hydroxyl group for high enantioselectivities to be attained. The advantage is that these systems are effective for a less specific range of substrates, but the compromise is that the enantioselectivity must be controlled through purely steric interactions with no coordinating functionality present.

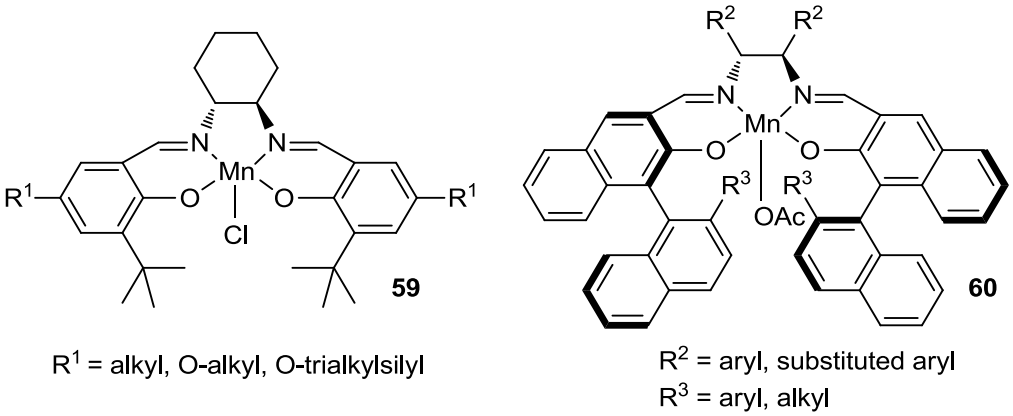
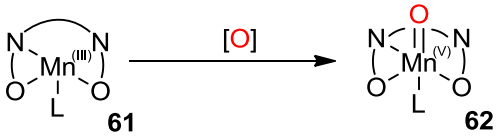


Figure 1.10: *Jacobsen's and Katsuki's general catalyst structure,* ***59*** *and* ***60*** *respectively.*

The above catalysts, although similar, demonstrate differing preference over substrate geometry; i.e. **59** and **60** each impart their greatest stereocontrol over different alkene classes. Jacobsen's catalysts **59** demonstrated enhanced enantioselectivity when *Z*-alkenes were used as substrates, while Katsuki's catalysts **60** were more selective with *E*-alkene substrates; though both require the alkene bond to be in conjugation with an aryl moiety for high *ees*. Both can be used at very low catalyst loadings; it is not uncommon for 1 mol% loadings to be used, and *ees* in the isolated epoxides can be >99%.[74]

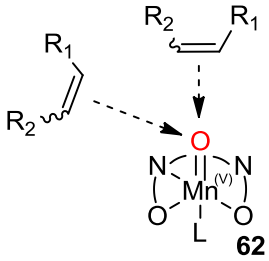
The transition metal centre is compatible with a variety of stoichiometric oxidants: NaOCl, H_2O_2 or *m*-CPBA are effective, although other less common species such as iodosobenzene (PhIO) and magnesium monoperoxypthalate (MMPP) can also be used (Scheme 1.24).[75] It is widely accepted that the active form of the catalyst is a $Mn^{(V)}$ **62** species produced upon oxidation of the $Mn^{(III)}$ complex **61**.[76]



Scheme 1.24: *The suspected catalytically active species. L = Cl, OAc.*

There are two rationales for the observed enantioselectivity in the epoxidation process, the difference between them being the approach of the

substrate to the active catalyst. Jacobsen has proposed a 'top-on' approach to the axial oxygen, whereas Katsuki has suggested a 'side-on' approach (Figure 1.11).[77]



62

Figure 1.11: *The two discussed approaches from Katsuki and Jacobsen.*

The mechanism has not yet been fully elucidated,[78] and there exist three different mechanistic explanations for how the reaction propagates (Figure 1.12).[79] The first pathway **I** is concerted, much like the oxidation with *m*-CPBA, the reaction is predicted to be stereospecific as again there is no opportunity for bonds to rotate. The second pathway **II** is also stereospecific, although unlike the first an intermediate exists – a metalla-oxetane species, which then collapses to give the epoxide with the same stereochemistry as the substrate. The third **III**, however, is the only one that can explain the observed loss of stereospecifity when some conjugated alkenes, are used. It is the only one of the three pathways that propagates along a radical pathway. The radical intermediate, produced through either a single electron transfer from the catalyst or a homolytic splitting of the Mn-C bond of the metalla-oxetane species, is stabilized in conjugated alkenes and so allows time for the stereochemistry to switch.[80]

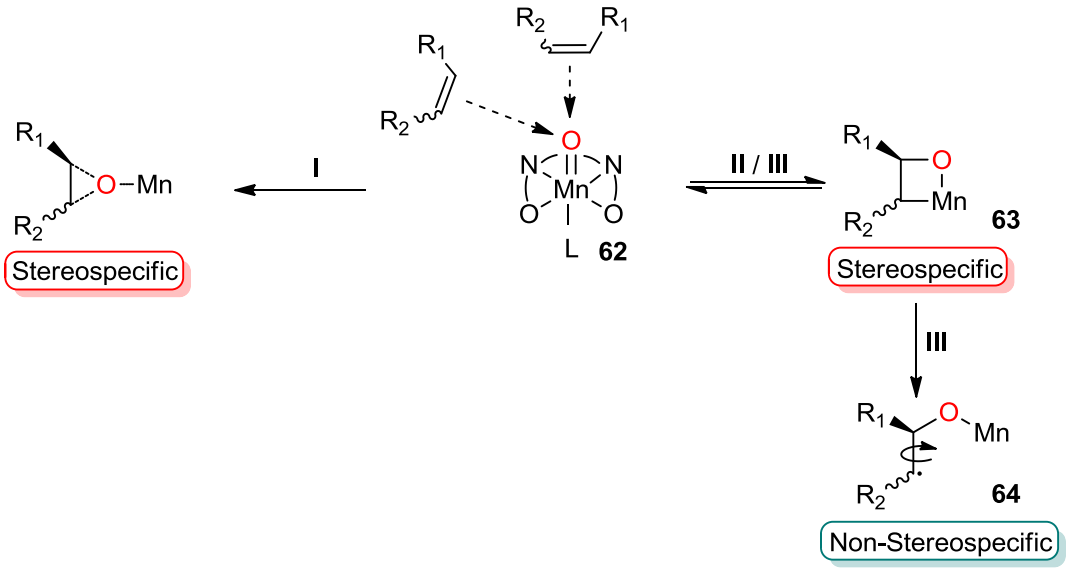


Figure 1.12: *Summary of proposed pathways.*

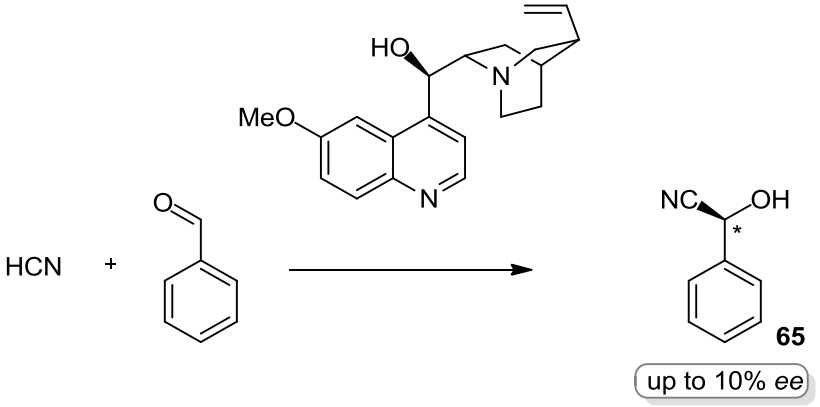
While the radical pathway is the only one that accounts for the observed loss of stereospecificity in conjugated systems, it is entirely possible that more than one of the pathways operate.

The Jacobsen-Katsuki and Sharpless-type transition metal-catalysed asymmetric epoxidation systems are among the most widely employed epoxidation protocols in organic synthesis. Many other transition metal based systems have been reported, including cobalt, ruthenium, samarium, gadolinium and ytterbium in conjunction with chiral ligands such as porphyrins and BINOL,[81] but an in depth discussion on this field is beyond the scope of this review.

1.6 Organocatalysis

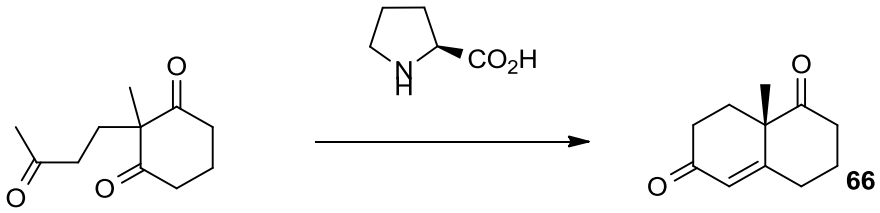
Organocatalysis is an important concept in chemistry that, over the past decade, has began to mature despite a slow beginning.[82] By the middle of the 20th century, there were only a handful of manuscripts published on the area, and, at the time, they were only seen as intriguing individual reactions, with next to no research following up on the early promise.

The first reported 'asymmetric organocatalytic' reaction was published almost 100 years ago by Fiske and Bredig – they observed that the addition of HCN to benzaldehyde was catalysed by quinine, and that the resulting cyanohydrin **65** was optically active (Scheme 1.25).[83]



Scheme 1.25: *The formation of optically active cyanohydrins like* ***65*** *by Fiske and Bredig using quinine.*

Hajos and Parrish, and Wiechert, Sauer and Eder, independently discovered in the early 1970s that the asymmetric intramolecular aldol reaction could be catalysed by chiral amines such as L-proline – a natural amino acid.[84,85] The Wieland-Miescher ketone **66**, an important intermediate in many terpene syntheses, was synthesised with a 74% *ee* by Hajos and Parrish while working at Hoffmann LaRoche, illustrating the utility of this methodology (Scheme 1.26).[85]



Scheme 1.26: *The L-proline catalysed Hajos-Parrish aldol reaction – formation of the Wieland-Miescher ketone.*

During the same period, metal-based catalysis was enjoying its golden era, ever more powerful reactions were being discovered, and the rate of development was rapid. The importance of the methodologies developed at that time cannot be over-stated; the Nobel Prize committee saw fit to award the prize in 2001 to Sharpless, Noyori and Knowles, and most recently to Heck, Suzuki and Negishi in 2010 for their work on transition-metal catalysis.

The breadth of reactivity and structural properties across different metal-centres, coupled with the ability of coordinating ligands to harness and tune the behaviour of a metal centre have ensured that transition-metal catalysis is applied to many processes. These processes can then be optimized by altering the metal's ligands – a characteristic that is very important for industrial uses. But metal-catalysis also has several disadvantages: the metals are often toxic, which potentially leads to pollution; product contamination; and the need for waste management. Also, some of the transition-metals used are exotic and are therefore expensive.[82] Considering these disadvantages, several groups in the late 90's became curious as to whether small organic molecules could achieve the same transformations.[86] In theory, these systems would have many advantages over the metal-based counterparts; namely, they would be cheaper and cleaner. Though non-chiral processes have also been addressed, only the asymmetric processes will be discussed below. The successful asymmetric work carried out by the groups of MacMillan, Barbas III, List, Lusinchi, Denmark, Corey, Page and Jørgensen, to name a few, inspired many others and created a surge in research (Figure 1.13).[87] Of course, 'organocatalysis' has been around for many years depending on one's

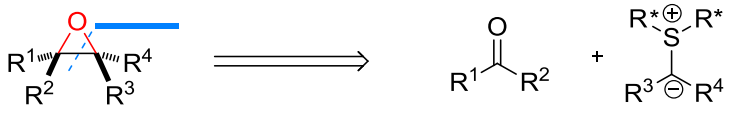
definition, but the graph below gives an indication of the growth of interest in the area.

Figure 1.13: *Graph indicating the growth in the number of papers published per year on the subject of 'organocatalysis'.*[86]

Today, organocatalysis, together with enzyme and metal-based catalysis, forms an integral part of the techniques available to the modern synthetic chemist.[88,89] For example, cinchona alkaloid-mediated catalysis, first described by Fiske and Bredig, is almost a whole field unto itself with a plethora of procedures, such as the Baylis-Hillman reaction, Michael addition and Diels-Alder reaction – all of which are accelerated and rendered enantioselective with their use.[90] The rest of the chapter concerns the development of organocatalytic epoxidation methodology.

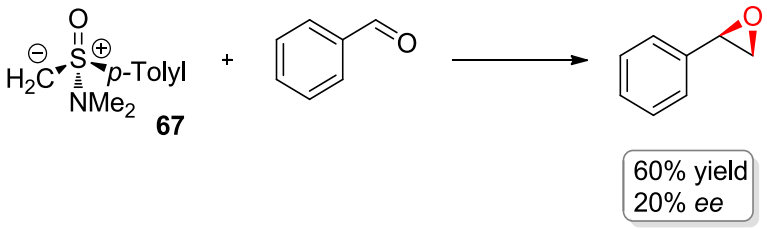
1.6.1 Asymmetric Epoxidation of Aldehydes by Sulfonium Ylides

The synthesis of chiral epoxides by the reaction of chiral sulfonium ylides with carbonyl moieties is fundamentally different from the other asymmetric organocatalytic procedures in which an unsaturated bond is oxidized. Here, the reaction between a carbonyl group and a nucleophilic carbon atom furnishes the epoxide (Scheme 1.27). While other carbon nucleophiles such as carbenes may be used,[91] the most commonly used species are sulfonium ylides.[87]



Scheme 1.27:. *Retrosynthetic disconnection of the epoxide.*

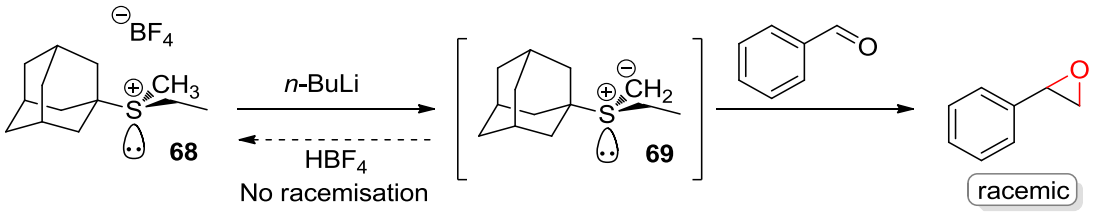
Johnson was the first to demonstrate that the asymmetric synthesis of epoxides from sulfonium ylide species and carbonyl groups was possible (Scheme 1.28). He reported that the enantiopure aminosulfoxonium ylide **67**, when used stoichiometrically, yielded the enantiomerically-enriched styrene oxide in a 20% *ee*.[92]



Scheme 1.28: *Johnson's enantioenriched synthesis of styrene oxide employing an aminosulfoxonium ylide.*

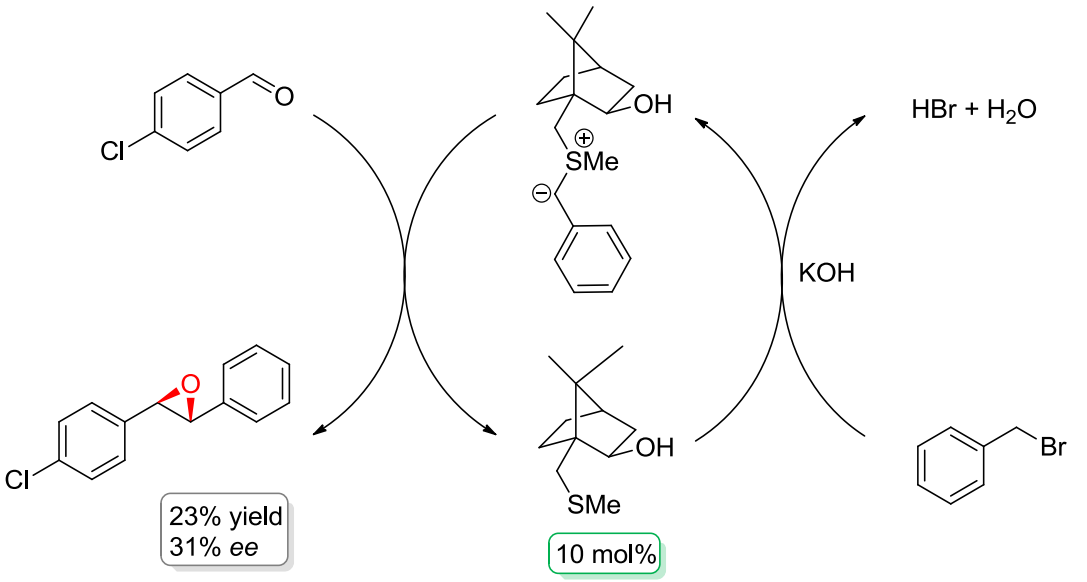
Following Johnson's preliminary research, Trost also investigated the utility of chiral sulfonium ylides for asymmetric epoxidation. The enantiopure adamantane sulfonium salt **68** was prepared and isolated; the sulfonium ylide **69** was subsequently formed *in situ* by deprotonation with ^{n}BuLi. The nucleophilic ylide generated then transferred its methylene group to benzaldehyde derivatives.[93] Curiously, the resulting styrene oxides displayed no optical activity. The

racemization of sulfonium species by inversion is known,[94] but this possibility was ultimately ruled out by Trost and **69** was demonstrated to be configurationally stable (Scheme 1.29).[93] However, it turned out that had Trost investigated the reaction of the sulfonium benzylides, he would likely had observed reasonable enantiocontrol.[91]



Scheme 1.29: *Attempts by Trost to enantioselectively transfer a methylene group to benzaldehydes were unsuccessful.*

Furukawa, however, did investigate sulfonium benzylides.[95] The ylides were formed *in situ* from sulfides derived from (+)-camphorsulfonic acid and benzyl bromides in the presence of powdered KOH. Using the procedure illustrated below, the authors were able to observe some catalytic turnover, although it was minimal (Scheme 1.30).



Scheme 1.30: *Furukawa's catalytic cycle. MeCN, KOH, RT.*

Dai's employment of closely related sulfides derived from (+)-camphor offered an improvement, and highlighted the importance of a hydroxyl group vicinal to the active centre (Figure 1.14). The *exo-trans*-sulfide **70** was prepared as well as the *endo-cis*-sulfide **71** and the *exo-cis*-sulfides **72** and **73**.[96]

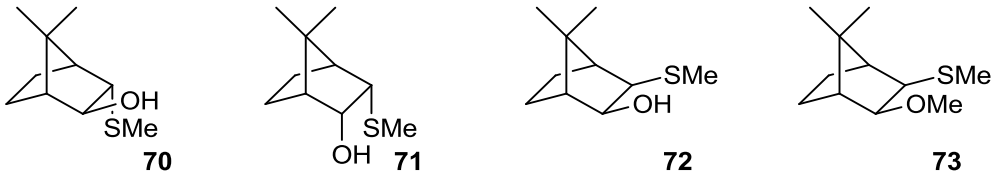
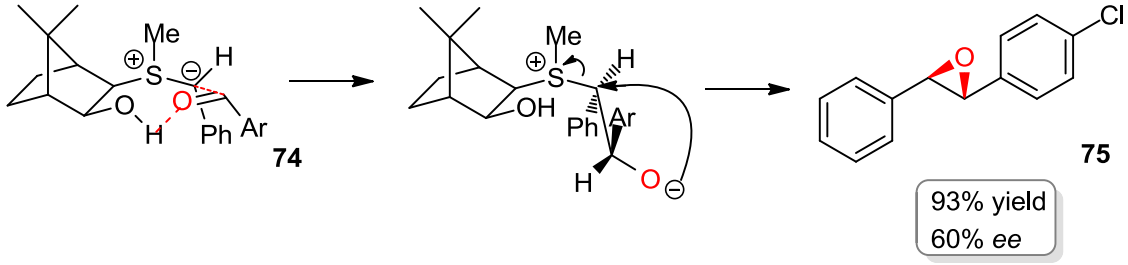


Figure 1.14: *(+)-Camphor derived sulfides prepared for this study. The hydroxyl group was found to have an accelerating and directing influence over the reaction pathway.*

It was found that if the hydroxyl was methylated as in **73**, reactivity and enantioselectivity were heavily compromized. Thus, Dai proposed that the hydroxyl group was needed to form a hydrogen bond with the ketone substrate. It was believed that such an interaction stabilized the reactive conformation, which exposed the *re*-face of the ketone to nucleophilic attack from the ylide; π-stacking was also suggested to favour the conformation **74** (Scheme 1.31).[96] Dai also reported that the products were isolated as single diastereoisomers – only the *trans*-epoxides such as **75** were observed.



Scheme 1.31: *Transition state is stabilized by co-operative H-bonding and π-stacking between the ylide and ketone substrate. In this example,* ***72*** *was used at a 20 mol% catalyst loading.*

Although Dai isolated single diastereoisomers of the epoxides, it was an exception for this transformation; the general complication of this methodology is the potential for the formation of diastereoisomeric ylide intermediates. This was

addressed by Durst with the synthesis and use of C_2-symmetric sulfides; the benzylide can only be formed as one diastereoisomer, and thus the complication was addressed (Figure 1.15).[97]

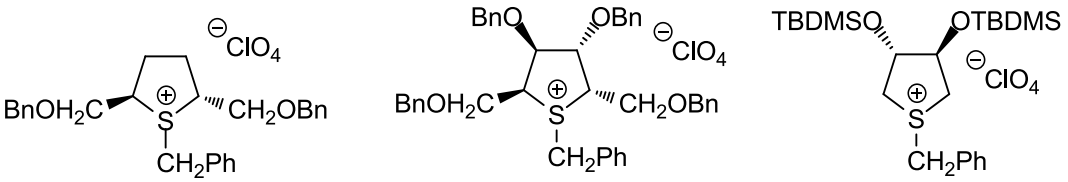


Figure 1.15: *Durst's C_2 symmetric ylides for asymmetric epoxide formation; ees of up to 83% were attained for the synthesis of 4-nitrostilbene when employing the above salts.*

In 2001, Metzner reported some exceptional results from the implementation of C_2 symmetric chiral sulfides **76** and **77** in his catalytic epoxidation procedure. Structurally and synthetically, they were the simplest sulfide catalysts to date (Figure 1.16).[98]

Figure 1.16: *Metzner's simple C_2 symmetric sulfides.*

Metzner also explored the substrate scope, and expanded it to include: furan, thiophene and naphthyl aldehydes as the electrophile. However, for this system, benzylides were still the only class of carbon nucleophiles that exhibited enantioselectivity – the analogous methylides only furnished the epoxides in a negligible *ee*. Initially, it was not uncommon for reactions to take up to one month, but through careful analysis of the reaction pathway, Metzner and co-workers identified two slow rate-determining steps: formation of the sulfonium salt and nucleophilic attack of the aldehyde to form the betaine intermediate. Since the second is the step in which enantioselectivity is determined, the authors reasoned that the first could be accelerated without any loss in epoxide *ee*.[99] To achieve the desired rate acceleration, iodide salts were used to effect a Finkelstein-type reaction of the benzyl bromide; the resulting benzyl iodide reacted much faster

with the sulfide.[98] The concentration of the aldehyde was also important: too low (0.25M) led to long reaction times whereas an elevated concentration (1M) caused the yield to drop off substantially, probably due to the competing Cannizzaro side reaction. With the optimized conditions, only 10 mol% of the catalysts were needed to obtain the epoxides in good yield, and in excellent *ee* and *de*, but reaction times were still up to several days in duration (Figure 1.17).[98]

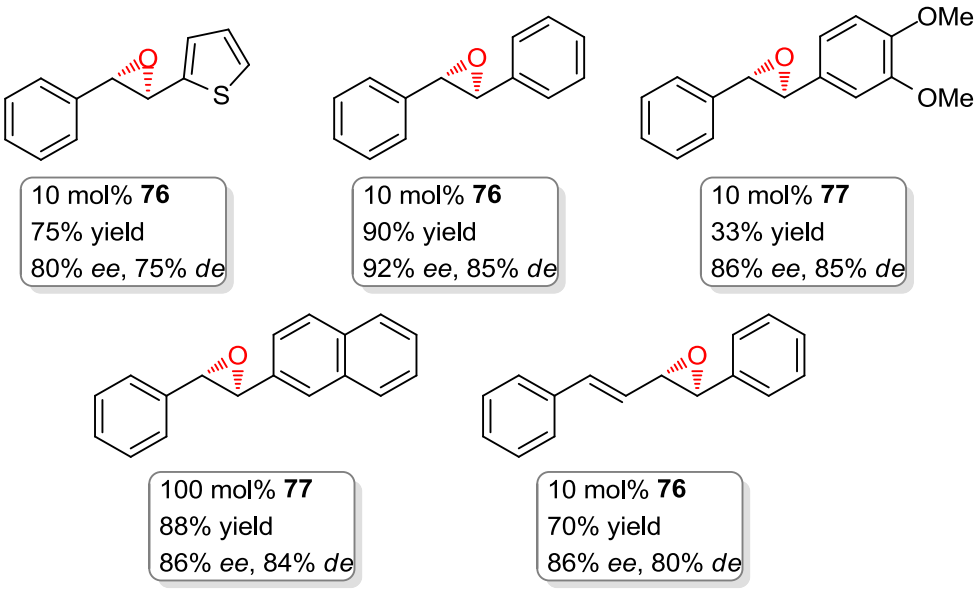
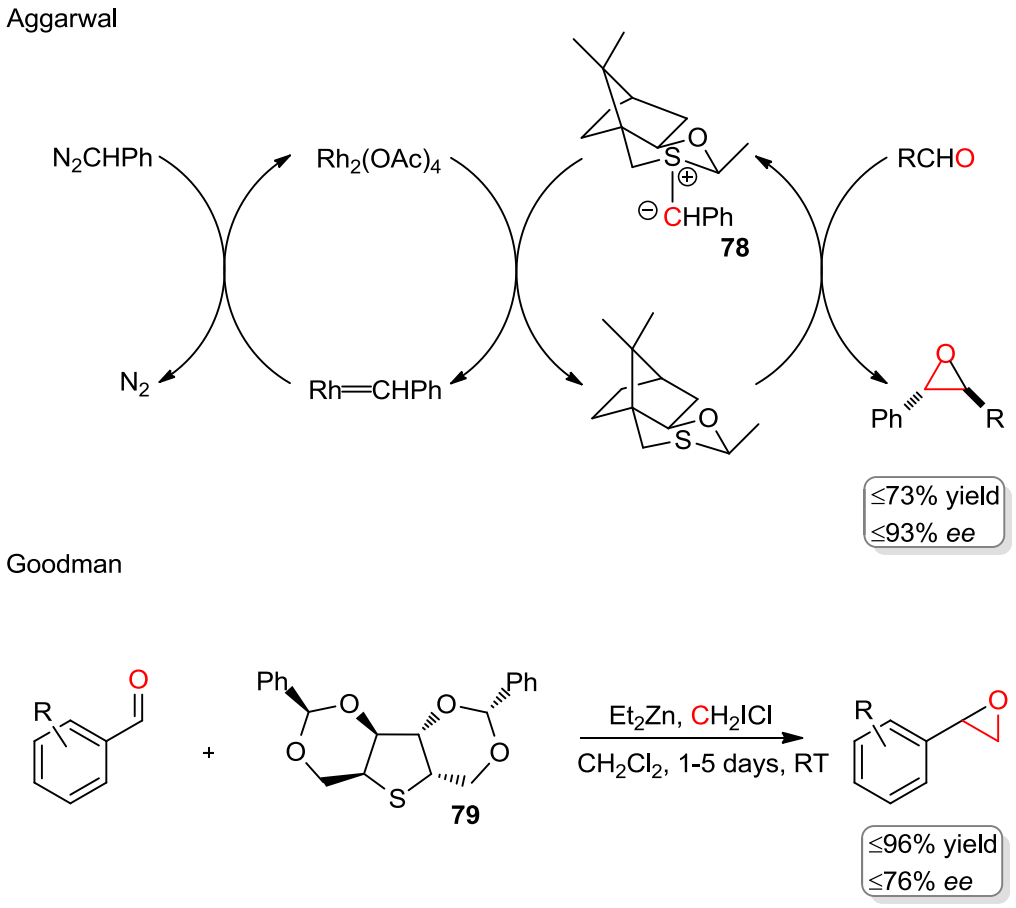


Figure 1.17: *Epoxides prepared by Metzner. NaOH, $^{t}BuOH/H_2O$, $^{n}Bu_4NI$ or NaI, 4-6 days, RT.*

Other notable contributions to this area of research have come from the groups of Aggarwal and Goodman (Scheme 1.32).. Aggarwal developed a one-pot asymmetric catalytic process in which the sulfonium ylides were generated *in situ* by the reaction of a chiral sulfide **78** with phenyldiazomethane in the presence of $Rh_2(OAc)_4$.[100] The epoxides were isolated in good yield, in up to 93% *ee* and 96% *de*. Goodman has succeeded in designing a procedure capable of methylene transfer in good *ees* of up to 70%. Although the chiral sulfide **79**, which was derived from D-mannitol, had to be used stoichiometrically, it was easily recovered.[101] No attempt is made here to go into detail about either of these studies as it is beyond the scope of this review.

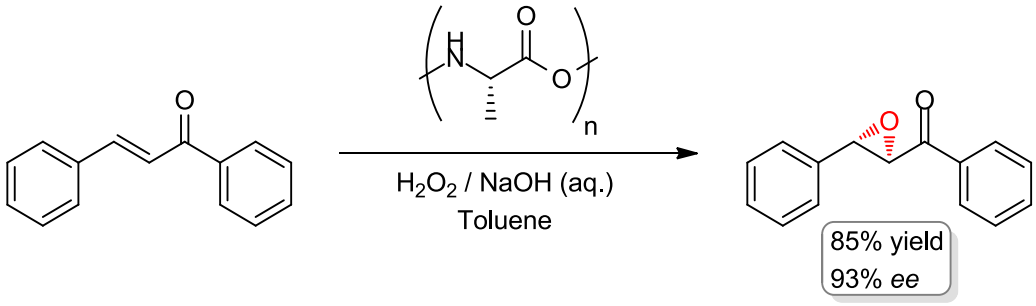


Scheme 1.32: *Chiral sulfide-mediated epoxidation by Aggarwal and Goodman.*

1.6.2 Organocatalytic Enone Epoxidation

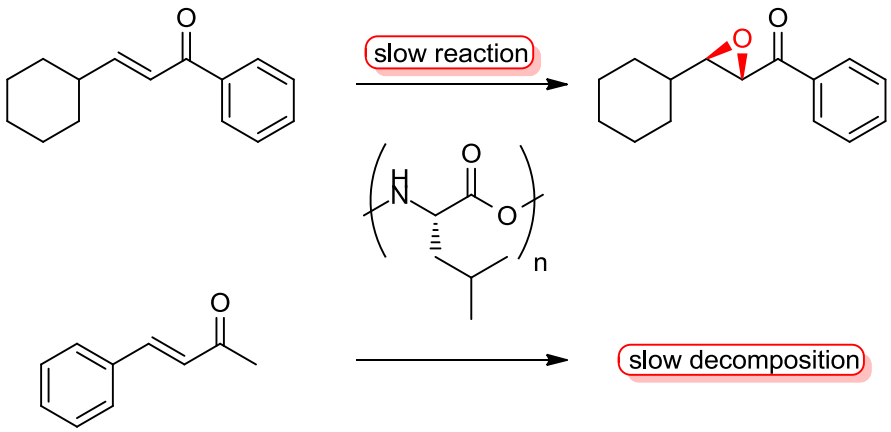
1.6.2.1 Juliá-Colonna

One of the first organocatalytic epoxidations of enones was reported by Juliá in 1980.[102] Juliá employed poly-L-alanine to epoxidize enone containing substrates, such as chalcone, with excellent enantiocontrol under heterogeneous triphasic conditions with H_2O_2 as the oxidant (Scheme 1.33).



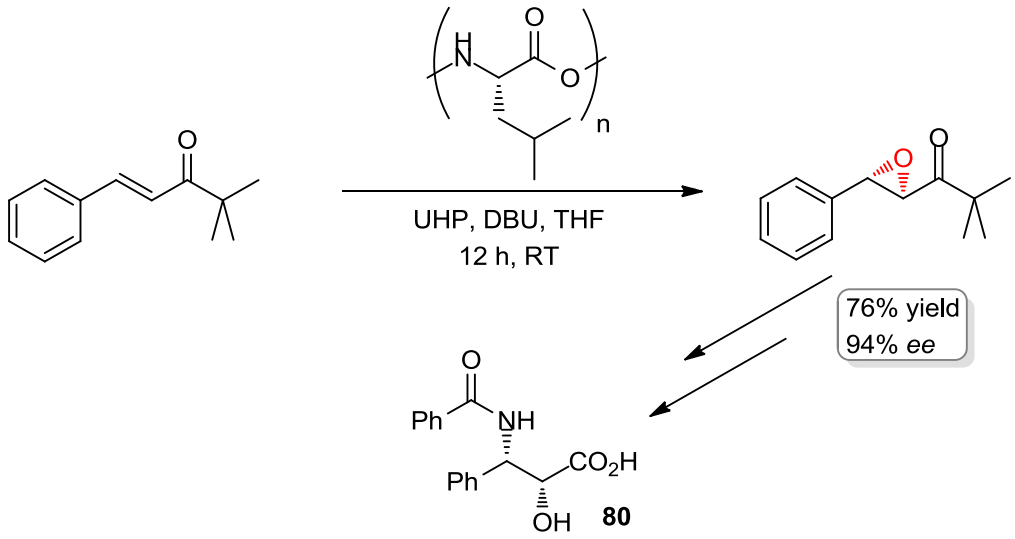
Scheme 1.33: *Epoxidation of chalcone by Juliá using poly-L-alanine*

While the insolubility of the poly-peptide was advantageous in that it allowed the recovery and subsequent re-use of the catalyst, the triphasic nature of the initial reaction conditions unfortunately led to long reaction times of up to several days.[103] Further, the strong basicity of the aqueous phase used not only degraded the peptide in some instances, but also limited the possible substrate scope; as it did not allow enolizable enones to be successfully oxidized (Scheme 1.34).[104]



Scheme 1.34: *Poor reactivity was observed with the poly-L-leucine catalyst due to its insolubility.*

Despite its drawbacks, but probably due to the perceived potential, the Juliá-Colonna procedure attracted considerable interest. Roberts first outlined his optimized biphasic non-aqueous conditions for the Juliá-Colonna epoxidation in 1997.[105] His modified conditions use urea-hydrogen peroxide as the oxidant, the strong organic base – DBU, and poly-L-leucine as the catalyst. The problems imposed by the triphasic conditions were remedied with the use of the new biphasic conditions; reaction times were reduced dramatically, and enolizable substrates were no longer problematic.[106] Roberts demonstrated the use of his modified conditions in his synthesis of the drug dilatazem, and also in his synthesis of the side chain of Taxol® **80** (Scheme 1.35).[105]



Scheme 1.35: *The use of the Juliá-Colonna epoxidation in the synthesis of the side chain of Taxol®.*

Through systematic studies, including the use of NMR and IR spectroscopy, it has been determined that the N-terminus of the poly-peptide catalysts is the probable active site.[107,108] Crucially, for the catalyst to be active, it must adopt a helical conformation. Berkessel recently proposed a mechanistic model to explain the stereocontrol observed in the Juliá-Colonna epoxidation.[108] Berkessel synthesised the oligomers of L-leucine from n = 1 → 20 and attached those oligomers to solid phase supports. Each of the supported oligomers was then used as a catalyst for the epoxidation of chalcone to study its activity. It was discovered that only five residues was needed for full stereoinduction, but the activity of the oligomer increases with n. Berkessel concluded that the stereoinduction is achieved by hydrogen bonding of non-intra-helical N–H groups of the oligomer to both the oxidant and substrate (Figure 1.18).

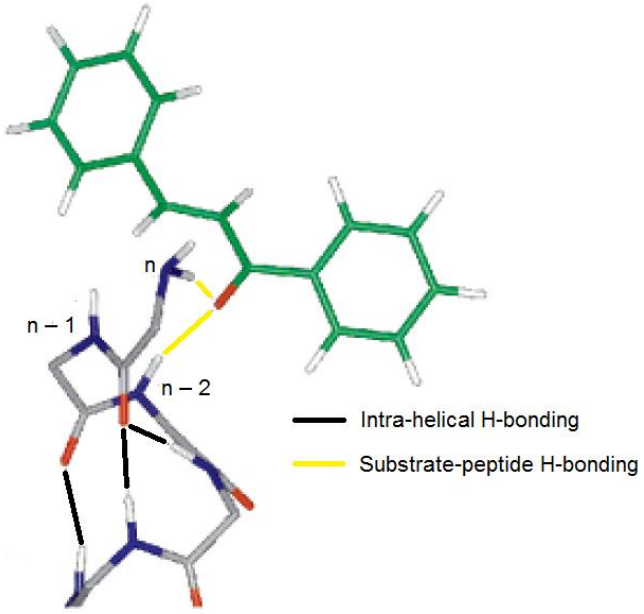
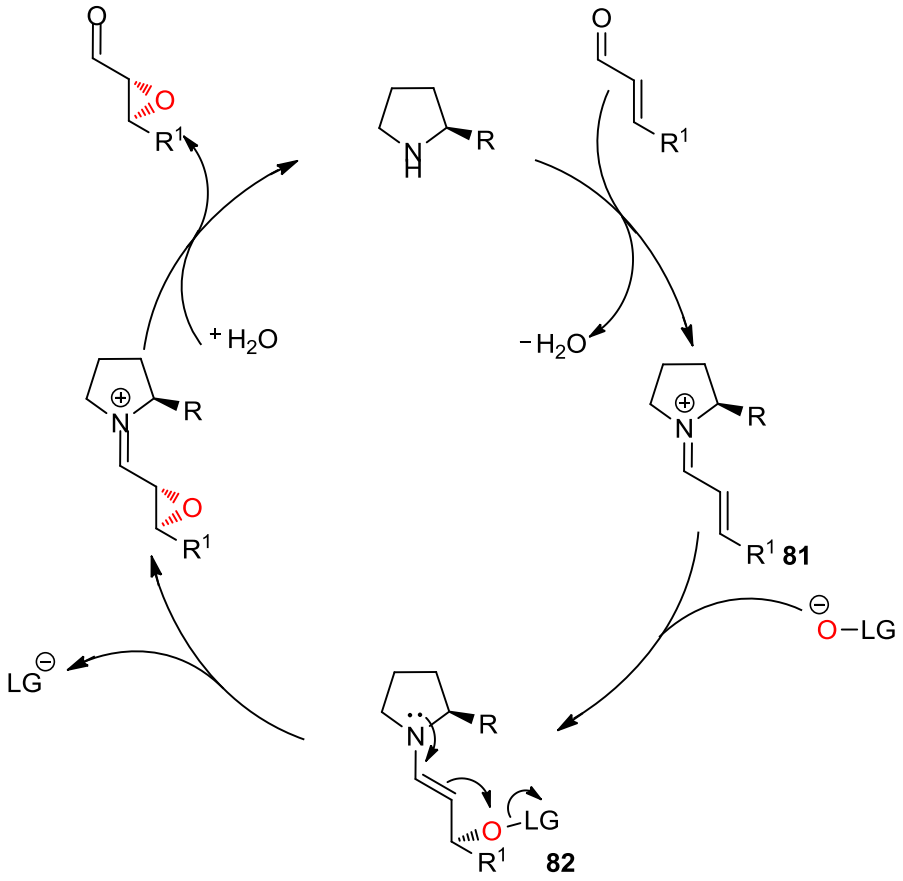


Figure 1.18: *Berkessel's proposed model of the H-bonding between the substrate and peptide responsible for the stereoinduction (yellow). It is believed by Berkessel that the peroxide H-bonds to the N–H at the (n – 1) position and is thus directed to one face of the chalcone substrate. The intra-helical H-bonding responsible for maintaining the helical structure is also shown (black).*[108]

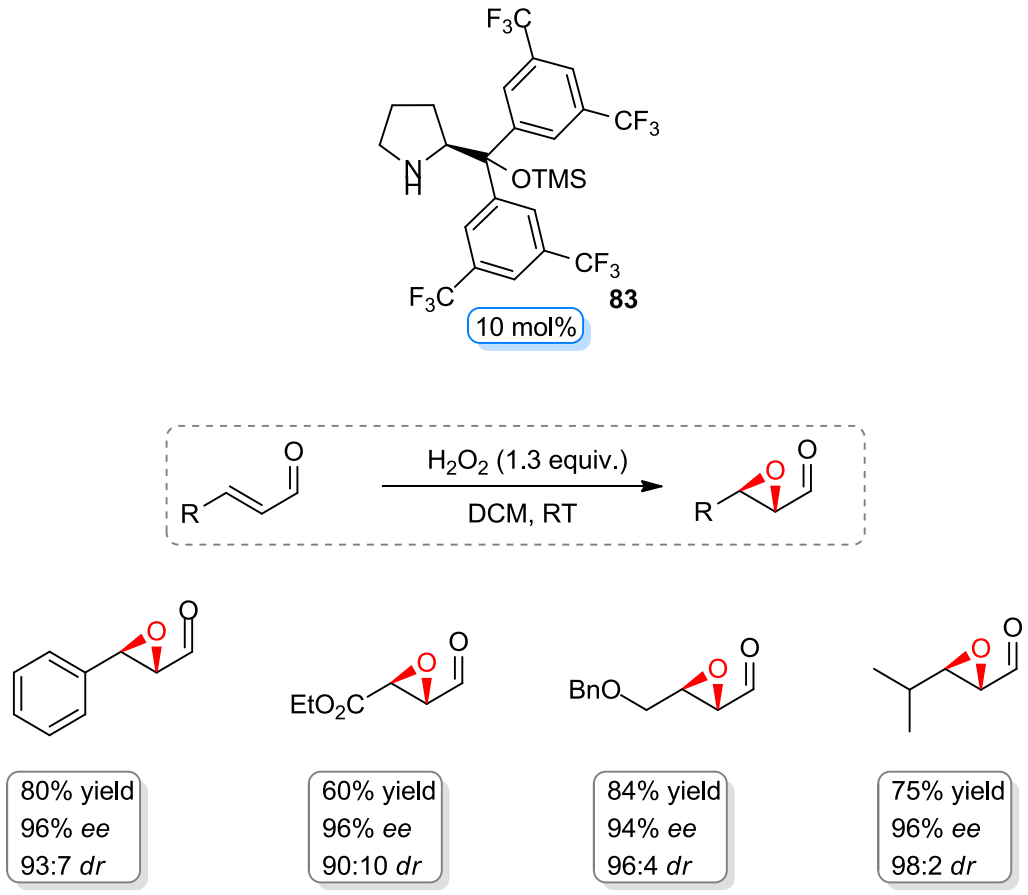
1.6.2.2. Epoxidation of α,β-unsaturated Carbonyls by Iminium Activation

During the past decade, several groups have described their efforts to create efficient techniques to epoxidize α,β-unsaturated carbonyls by temporarily condensing primary or secondary amines to the carbonyl moiety.[88] The resulting electron deficient iminium salt **81** activates the double bond to nucleophilic attack, and the covalently bonded catalyst is able to direct nucleophilic oxidants such as H_2O_2 with excellent facial selectivity, leading to high *ees* in the isolated epoxides (Scheme 1.36).[109,110]



Scheme 1.36: *General catalytic cycle of the epoxidation of enones by iminium activiation.*

Jørgensen and co-workers reported the synthesis and use of the L-proline-derived catalyst **83** in 2005, and presented an investigation into its efficacy as an enantioselective organocatalyst for epoxidation (Scheme 1.37).[109]



Scheme 1.37: *Highly enantioselective epoxidation of enones with Jørgensen's L-proline-derived amine catalyst.*

Initially, the screening of a series of conditions, covering a range of different oxidants and solvents, was performed to determine the optimum conditions for the use of **83**. Jørgensen observed that conditions that employed aprotic solvents and peroxides provided the best results in terms of *ee,* yield and diastereomeric ratio (*dr*). When protic solvents were employed the *dr* was adversely affected. This was probably due, as suggested by Jørgensen, to the stabilization of intermediate **82** in the catalytic cycle; this stabilization increases the lifespan of **82** and creates an increased potential for bond rotation.

MacMillan and Lee reported their efforts to create an improved and completely diastereoselective modification of Jørgensen's work in 2006.[111] MacMillan had already synthesised a range of chiral imidazolidinone catalysts that were developed for the related stereoselective 1,4-addition of other nucleophiles,

and it was envisaged they would enjoy similar success with epoxidation.[112] MacMillan reasoned that by using a nucleophilic source of oxygen that was coupled to an excellent leaving group, the resulting fast ring-closure of intermediate **82** would improve enantioselectivity and diastereoselectivity by preventing unwanted bond rotation. MacMillan found that hypervalent λ^3-iodanes, such as iodosobenzene, exhibited the desired behaviour (Figure 1.19). Iodosobenzene, upon reaction with the electron deficient substrate, unveils the phenyliodonio moiety. Incredibly, the phenyliodonio moiety has a leaving group ability of roughly six orders of magnitude greater than that of the triflate group.[113] The excellent leaving group-ability of the phenyliodonio moiety facilitates the desired rapid ring-closure of intermediate **82**.

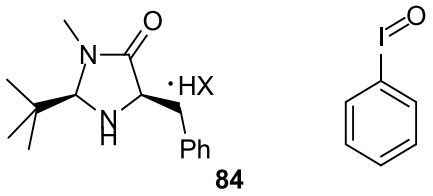
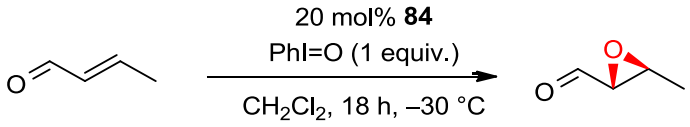


Figure 1.19: *The structure of MacMillan's imidazolidinone catalyst and iodosobenzene.*

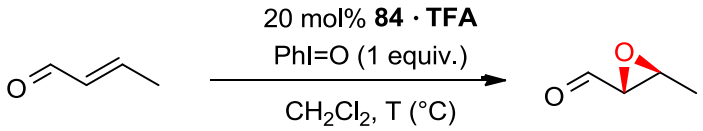
Having identified a suitable oxidant and catalyst, and using crotonaldehyde as a test substrate, MacMillan sought to investigate other variables, such as the solvent, the acid co-catalyst and temperature. Similarly to Jørgensen, MacMillan found that the use of CH_2Cl_2 and $CHCl_3$ offer the best results with regards to epoxide *ee,* but only led to moderate yields. Notably, employing wet DMF (10% H_2O) as the reaction solvent elicited the best conversion at 87%, but the *ee* was the lowest reported at 25%. An investigation into the acid co-catalyst revealed both the isolated epoxide *ees* and yield to be strongly dependent on the pKa of the acid (Table 1.1). MacMillan suspected this particular trend was due to the increased equilibrium concentration of the substrate-catalyst complex, similar to **81**, with stronger acids – this increased the observed epoxide *ees* because it ensured the catalytic pathway could 'out-compete' the racemic non-catalysed pathway.[111]



Entry	HX	pK_a	Conv. (%)	*ee* (%)
1	TfOH	–14	74	87
2	$HClO_4$	–10	68	88
3	*p*-TSA	–2.6	50	76
4	TFA	–0.3	42	72
5	DCA	1.3	27	72
6	CNA	2.5	27	69

Table 1.1: *Effect of the pK_a of the acid co-catalyst.*

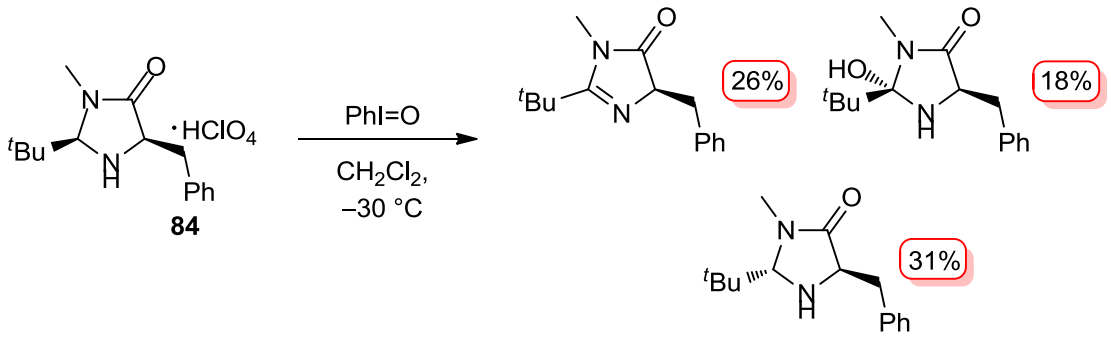
Lowering the temperature had the expected effect of increasing the epoxide *ees* in accordance with the Boltzmann distribution. It also, somewhat unexpectedly, increased the conversion and reactivity dramatically. MacMillan discovered through NMR studies that if the reaction was run at temperatures exceeding about –40 °C, the rate of decomposition of the catalyst and substrate through competing oxidative pathways became significant, and was detrimental to the efficiency of the reaction (Table 1.2).[111]



Entry	T (°C)	Time (h)	Conv. (%)	*ee* (%)
1	–20	18	49	83
2	–30	20	74	87
3	–40	15	98	89
4	–50	15	100	93

Table 1.2: *Effect of temperature.*

The substrate scope of the reaction was also investigated; it was observed that the epoxide *ees* rapidly fell off with the increasing stability of an intermediate iminium species similar to **81**. It is the addition to this species which is believed to be the rate determining step of the process. MacMillian theorized that if this species becomes less reactive, the competing and degrading nucleophilic attack of the catalyst by hypervalent λ^3-iodanes correspondingly becomes more favoured (Scheme 1.38). Thus over time, the efficiency of the process is lessened.



Scheme 1.38: *Mode of catalyst degradation.*

In an attempt to negate the degradation of the imidazolidinone **84**, *p*-Me iodosobenzene was trialled for its increased nucleophilicity, as it was believed it would react with iminium species much faster. However, it turned out that the rate of degradation was actually much higher; yields of only ≈20% of the α,β-epoxy aldehyde products were achieved. This, in comparison with the > 90% yields achieved when employing iodosobenzene as the oxidant. Macmillan discovered that this was due to the increased solubility and over-availability of the *p*-Me iodosobenzene oxidant. The oxidant was introduced as its polymeric form but *p*-Me iodosobenzene was readily solvated as the monomer, whereas iodosobenzene was not. The presence of a large concentration of the oxidant increased the rate of catalyst decomposition.[111] MacMillan focused on alternative sources of iodosobenzene that could be employed to release the reactive monomer at a much reduced rate – conceptually functioning as an 'internal syringe pump'. He discovered that [(nosylimino)iodo]benzene hydrolysed *in situ* in the presence of 1 M acetic acid, releasing iodobenzene at a rate that maintained a low but productive

concentration in the reaction mixture, and crucially, did not result in the degradation of the catalyst (Figure 1.20).

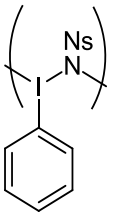
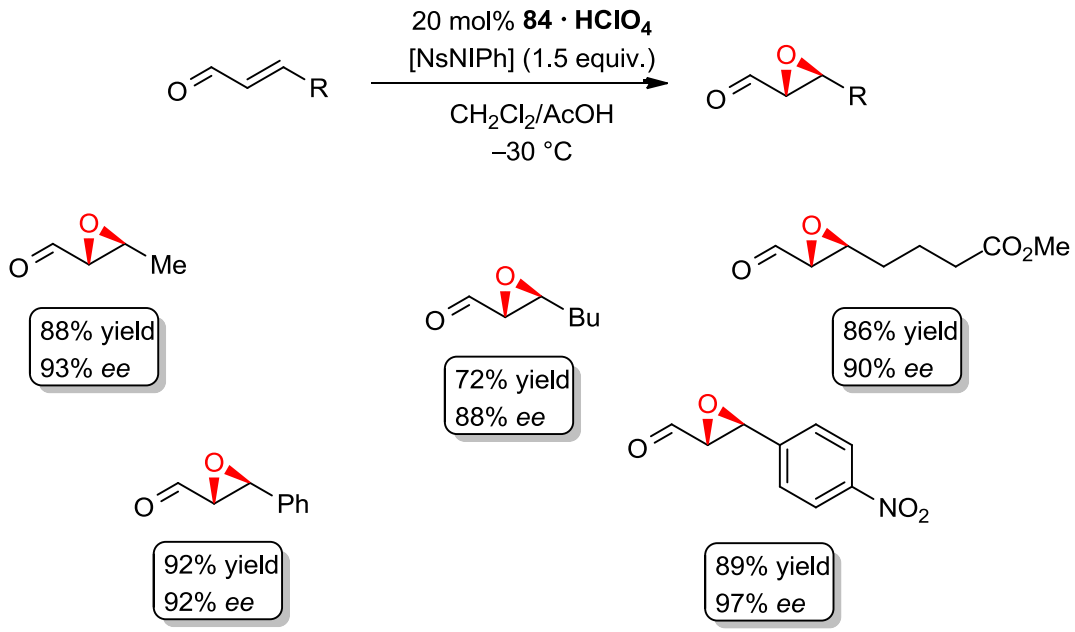


Figure 1.20: *The [(nosylimino)iodo]benzene polymer used to achieve the ''internal syringe pump'' effect.*

The employment of [(nosylimino)iodo]benzene resulted in a large improvement in the isolated epoxide *ees* for the substrates which formed more stable, less electrophilic iminium intermediates. With this development, MacMillan was able to oxidize a broad range of α,β-unsaturated aldehydes with excellent stereocontrol and in excellent yield (Scheme 1.39).[111]



Scheme 1.39: *Substrate scope with MacMillan's oxazolidinone* ***84*** *employing [(nosylimino)iodo]benzene as the oxidant.*

Recently, List has reported the use of bifunctional diamines **86**-**88** to facilitate the highly stereoselective epoxidation of cyclic α,β-unsaturated ketones.

The work is an elegant variation on the previously developed iminium-activated epoxidation. List's methodology also requires the formation of a conjugated iminium species, from the condensation of a primary amine with the α,β-unsaturated carbonyl group. The catalysts employed feature a tertiary amine that can form hydrogen bonds with H_2O_2 and actively guide the oxidant preferentially to one face of the now-activated double bond (Figure 1.21).[114]

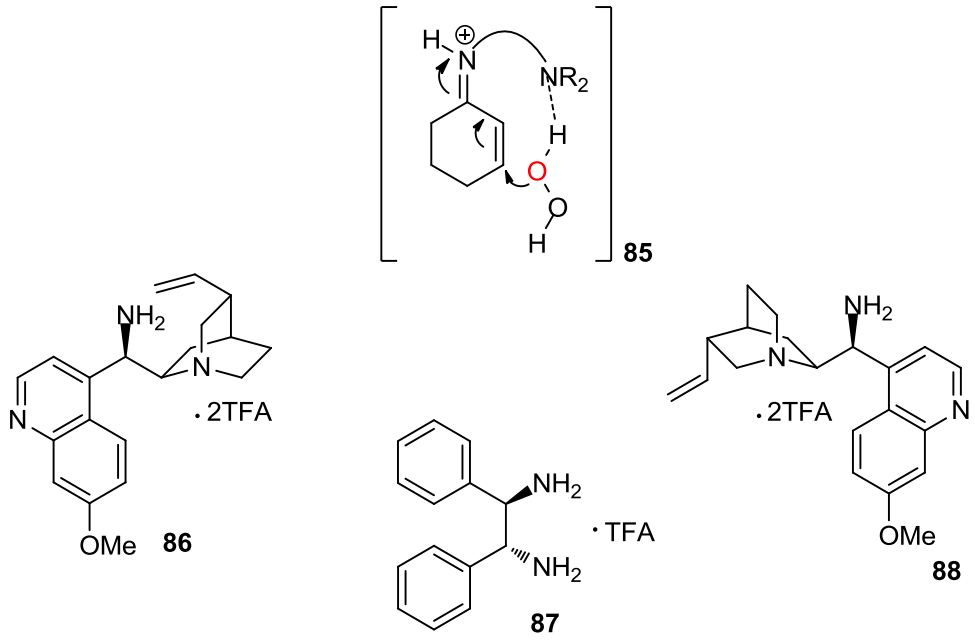
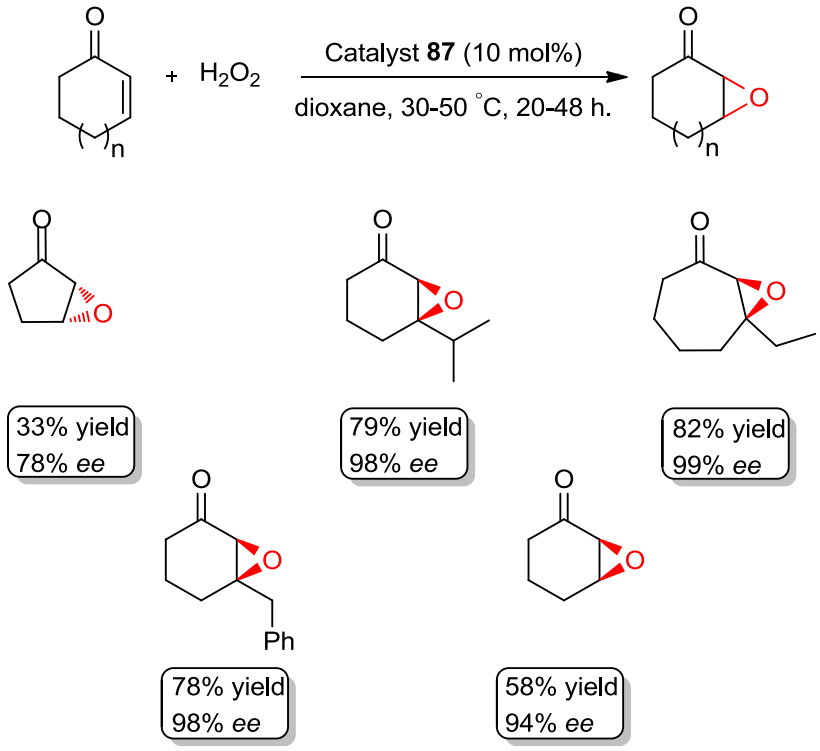


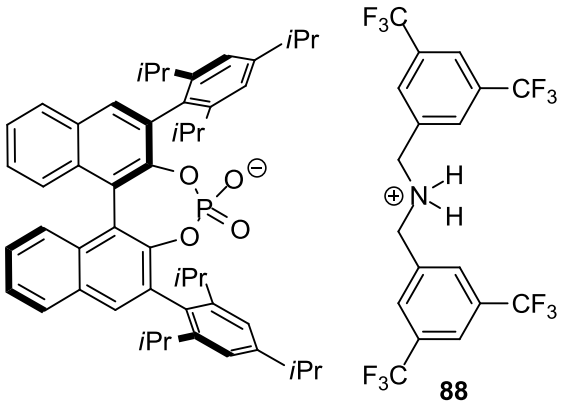
Figure 1.21: *Bifunctional catalysts used by List and their mode of action.*

Using this novel methodology, List was able to isolate epoxides in good yields and demonstrate excellent facial control over the attack of the oxidant. List observed the greatest levels of stereoinduction with β-substituted substrates, particularly for the cyclohexenone and cycloheptenone families (Scheme 1.40). Substrates that featured any α-substitution were not active under the reaction conditions.



Scheme 1.40: *Results of a substrate screen carried out by List employing his most stereoselective catalyst.*

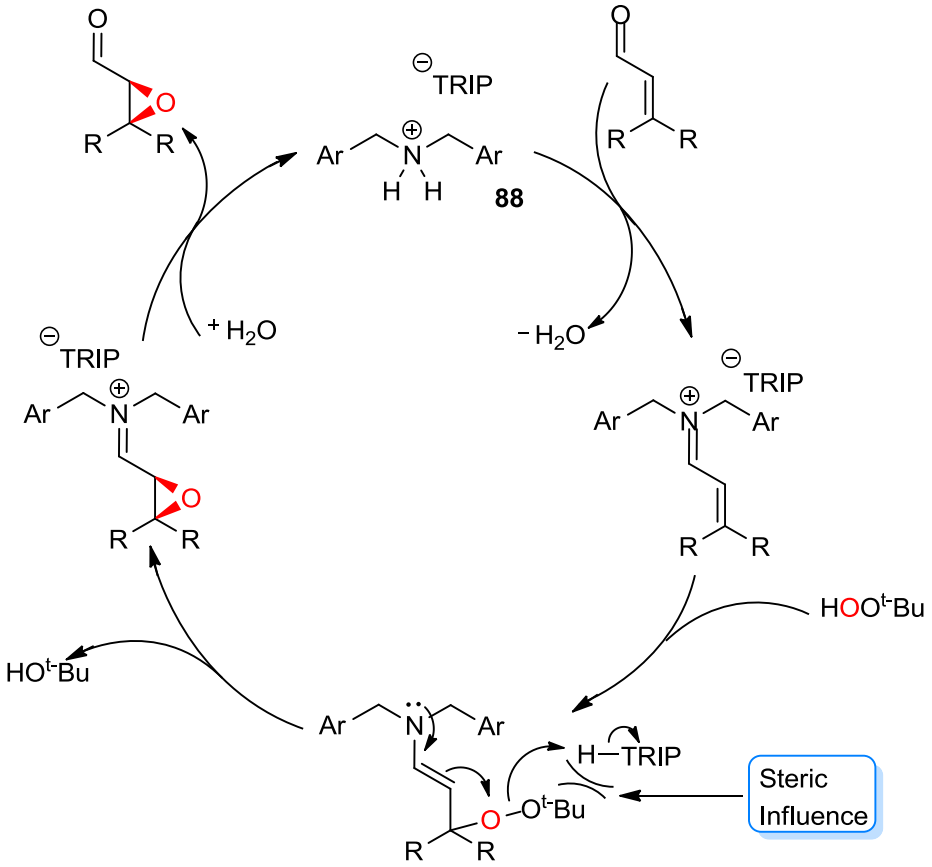
List has recently explored a procedure for asymmetric epoxidation employing an achiral ammonium salt paired with a chiral counter-anion, which he terms 'asymmetric counter-ion-directed catalysis' (ACDC) (Figure 1.22). In a recent report, he detailed his efforts in utilizing the anion 3,3'-bis(2,4,6-triisopropyl-phenyl)-1,1'-binaphthyl-2,2'-diyl phosphate (TRIP) **88**$^-$ coupled with dibenzyl ammonium salt **88**$^+$ to effect the highly stereoselective epoxidation of β,β-substituted α,β-unsaturated enals – a class of substrate that had only been oxidized with moderate to good enantiocontrol until this work.



88

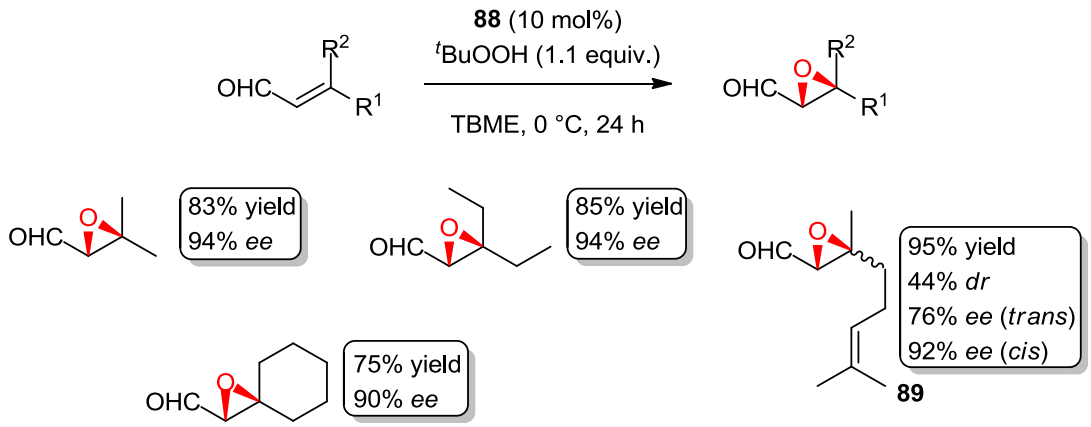
Figure 1.22: *The most enantioselective ion-pair designed by List.*

Furthermore, ion-pair **88** is also capable of oxidizing enals that are symmetrically substituted at the β-position. Because the initial addition at the β-position of the iminium moiety would not create a chiral centre, List proposes that the chiral anion must therefore be inducing the chirality by influencing the ring closing step (Scheme 1.41).



Scheme 1.41: *Proposed mode of action of List's ion-pair catalyst and origin of the stereocontrol.*

ACDC has proven to be a powerful technique to access enantioenriched β,β-substituted α,β-unsaturated enals (Scheme 1.42). Its success in oxidizing this difficult class of substrate stems from its novel mode of action.[115]



Scheme 1.42: *Various β,β-substituted α,β-epoxy ketones synthesised by List, including the sex pheromone of the acarid mite* ***89****.*

1.6.2.3 Phase Transfer Catalysis

'Phase transfer catalysis' is a term that was first coined by Starks in 1971 to explain the role lipophilic salts played in facilitating a reaction between two reagents in different immiscible solvents; today, phase transfer catalysis is an extremely important and useful tool for the synthetic organic chemist (Figure 1.23).[116] There are now many types of organocatalytic reactions that phase transfer catalysts (PTCs) have been successfully applied to, such as alkylation, Michael addition, the Horner-Wadsworth-Emmons reaction and, of course, epoxidation.[117] Quaternary ammonium salts (QUATs) are the biggest class of PTC as they are stable, easy to synthesise, and chiral diversity is easy to achieve – these features are crucial for their use in asymmetric organocatalysis.

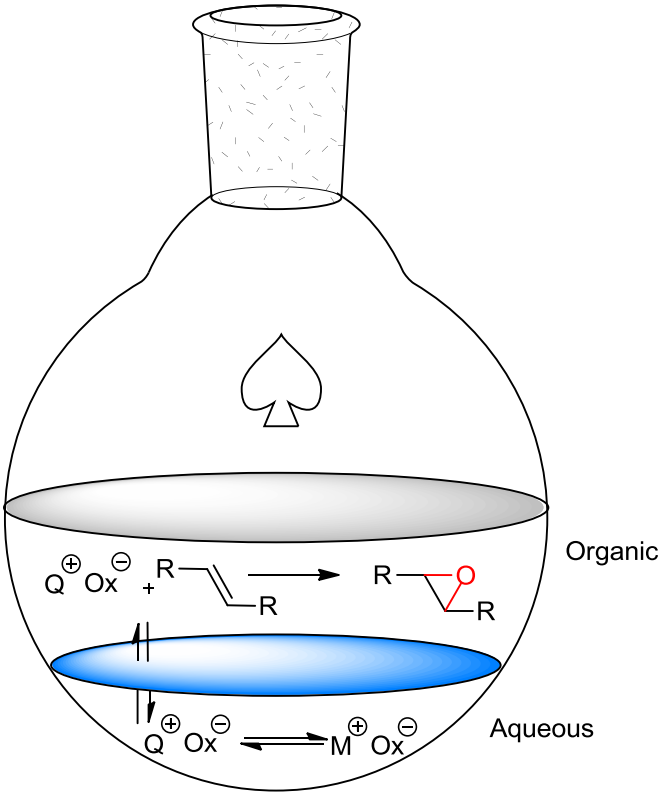


Figure 1.23: *A generalised oxidative phase transfer reaction. The hydrophilic oxidant can only transfer into the organic phase to perform a reaction once it has ion exchanged with the PTC to form a lipophilic ion pair.*

Wynberg was the first to develop a catalytic procedure to oxidize enones by employing cinchona alkaloid-derived QUATs **90** and **91**, and he achieved *ees* of up to 54% in the isolated epoxides with their use (Figure 1.24). [118,119]

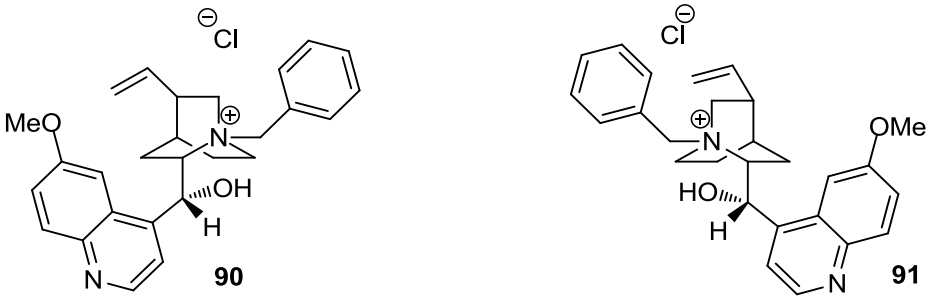
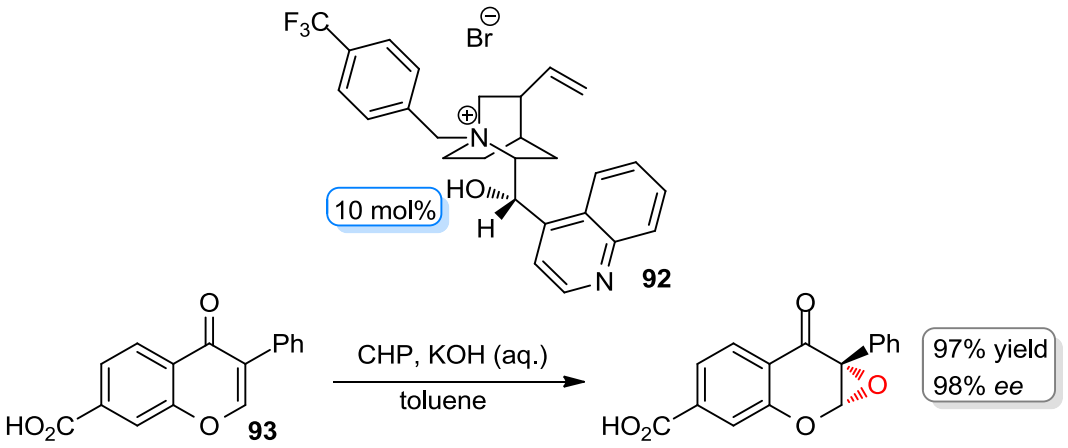


Figure 1.24: *Quinine and quinidine derived quaternary ammonium salts developed by Wynberg.*

The groups of Oda,[120] Onda[121] and Adam,[122] amongst others, followed up on this pioneering research with their own PTCs, which were also derived from cinchona alkaloids (Scheme 1.43). Impressive epoxide *ees* were achieved by these groups, particularly for the chromone derivatives **93**.



Scheme 1.43: *An example of a PTC synthesised by Adam and its use in the epoxidation of an isoflavone.*[122]

Lygo[123] and Corey[124] independently created (9-anthracenyl)methyl-containing cinchonidine-derived quaternary ammonium salts **94** and **95**, and both observed excellent *ees* for a range of enone substrates (Figure 1.25).

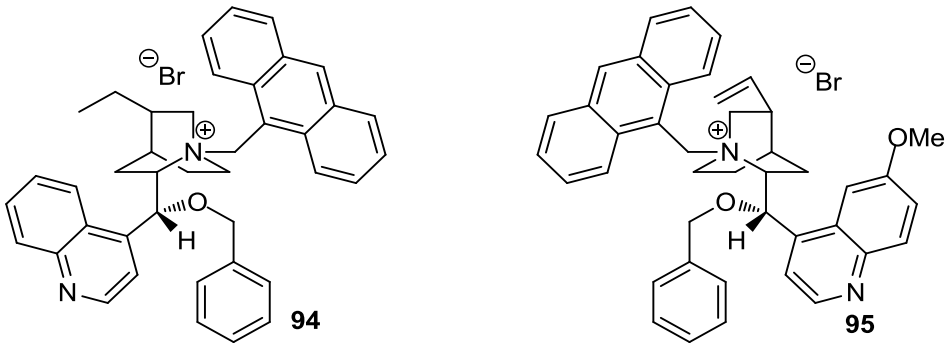
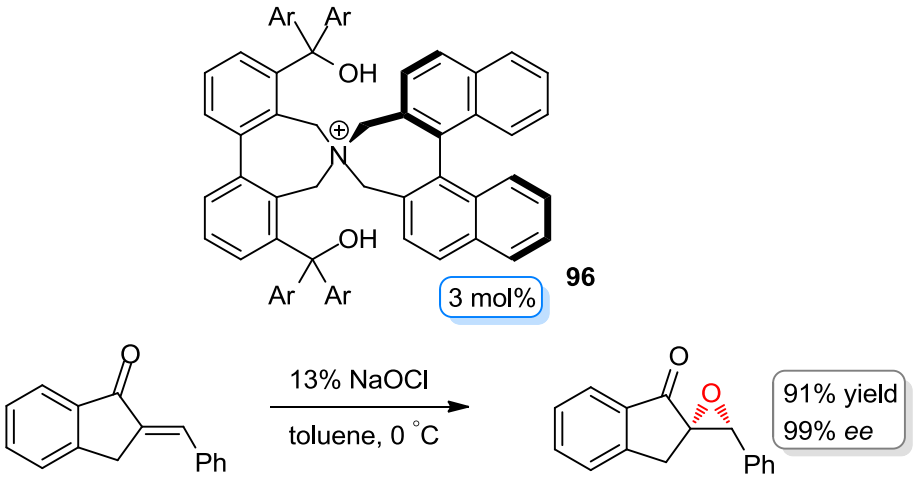


Figure 1.25: *Catalysts developed by Lygo and Corey.*

Maruoka has described the synthesis and use of binaphthalene-derived ammonium salts such as **96**, and reported high levels of enantiocontrol for the epoxidation of enone substrates with their use (Scheme 1.44).[125]



Scheme 1.44: *The spiro ammonium catalyst synthesised by Maruoka.*

Bakó created a family of monoaza-[15]-crown-5 ethers derived from cheap and readily available D-monosaccharides such as D-mannose **97** and D-galactose **98**. Using ^{t}BuOOH as the oxidant and a chiral crown ether, he reported *ees* in the isolated epoxides of up to 94% (Figure 1.26).[126]

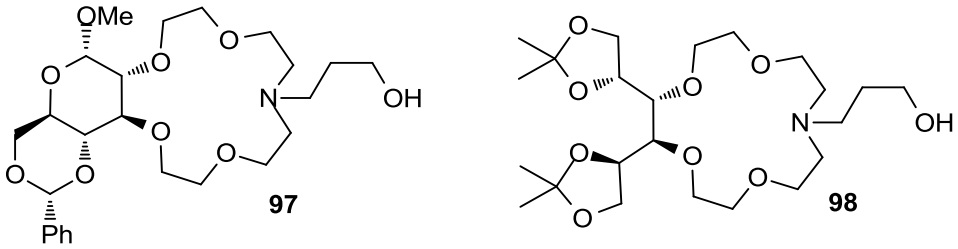


Figure 1.26: *Aza-crown ethers prepared by Bakó* ***97*** *and* ***98****, derived from* D*-mannose and* D*-galactose respectively.*

A family of C_2-symmetric salts containing the guanidinium motif were designed by Murphy and co-workers from (*S*)-malic acid, such as **99**. Guanidinium salt **99** was used for the epoxidation of chalcone derivatives, and Murphy reported achieving *ees* in excess of 90% (Figure 1.27). Impressively, **99** has also found utility in asymmetric alkylation.[127]

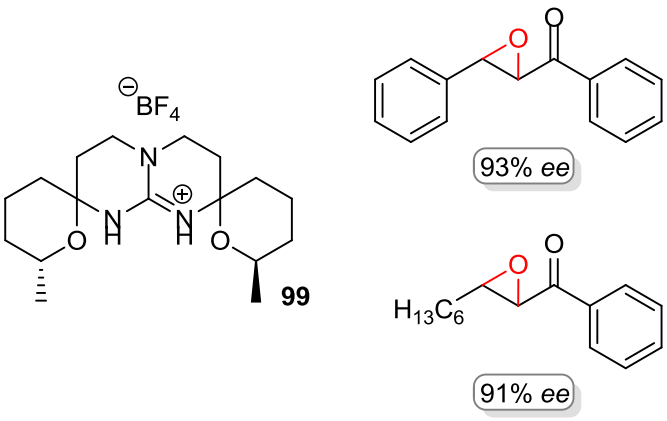
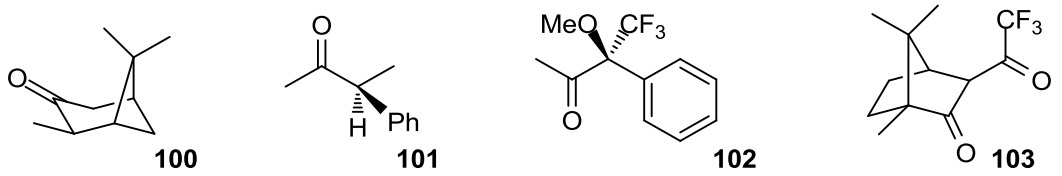


Figure 1.27: *Guanidinium salt PTC prepared by Murphy.*

1.6.3. Chiral Dioxirane-Mediated Epoxidation

A logical development of Curci's initial work with the dioxirane/ketone cyclewas to explore the possibility of asymmetric epoxidation by using chiral ketone catalysts.[58,60] Curci first investigated (+)-isopinocamphone **100** and (*S*)-(+)-3-phenylbutan-2-one **101** as potential asymmetric organocatalysts (Figure 1.28).[128] Unfortunately, these two ketones demonstrated poor enantiocontrol for unfunctionalised alkenes; the epoxides were isolated in *ees* of up to 12%. Furthermore, high catalyst loadings of 20-300 mol% had to be employed. Curci also published the use of two other chiral ketones **102** and **103** as catalysts for asymmetric epoxidation; both were poor at transferring their chiral information to the substrate, and *ees* of up to only 20% were measured in the isolated epoxides.[129]



100 **101** **102** **103**

Figure 1.28: *The chiral ketone catalysts developed by Curci between 1984 and 1995.*

Even though Curci's investigation did not provide the high *ees* that metal-based systems at the time were capable of, it was a proof of concept that helped inspire further research into the use of chiral ketones as organocatalysts by other groups.

1.6.3.1 C_2 Symmetric Ketones

In 1996, Yang was one of the first to try to improve upon the results achieved by Curci. He approached the problem by considering why Curci's catalysts were poor at asymmetric induction. She reasoned that the dioxirane, formed on oxidation of the ketone, possesses two oxygen atoms – each capable of being transferred to an alkene substrate. In theory, as the chiral environment around each oxygen atom was different in Curci's previous species, the transfer of one of

the dioxirane's oxygens could result in differing levels of stereoinduction, or even opposing stereoinduction, with respect to the other oxygen.[130]

Yang considered two solutions to the problem: 1) to block the approach of the alkene to one of the oxygens; 2) to design C_2 symmetry into the catalyst structure which necessarily implies both approaches of the alkene would be identical (Figure 1.29).

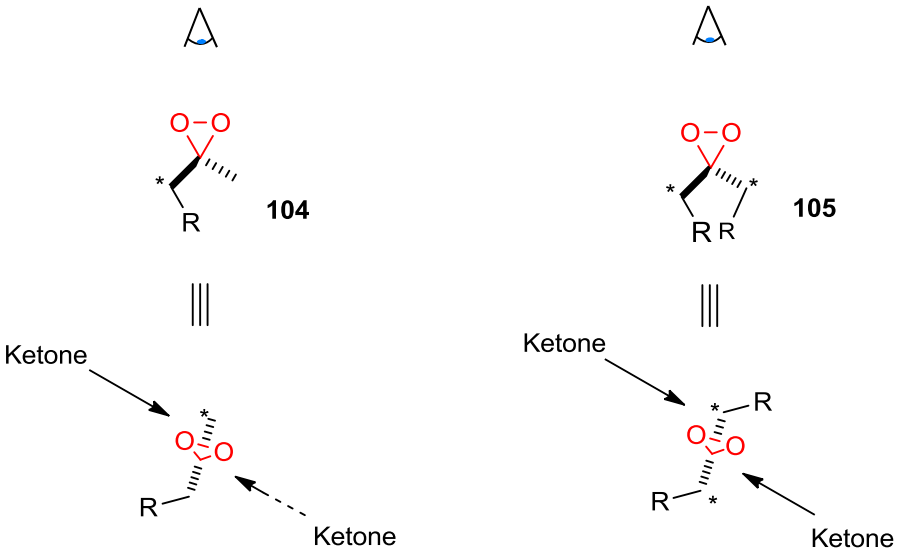
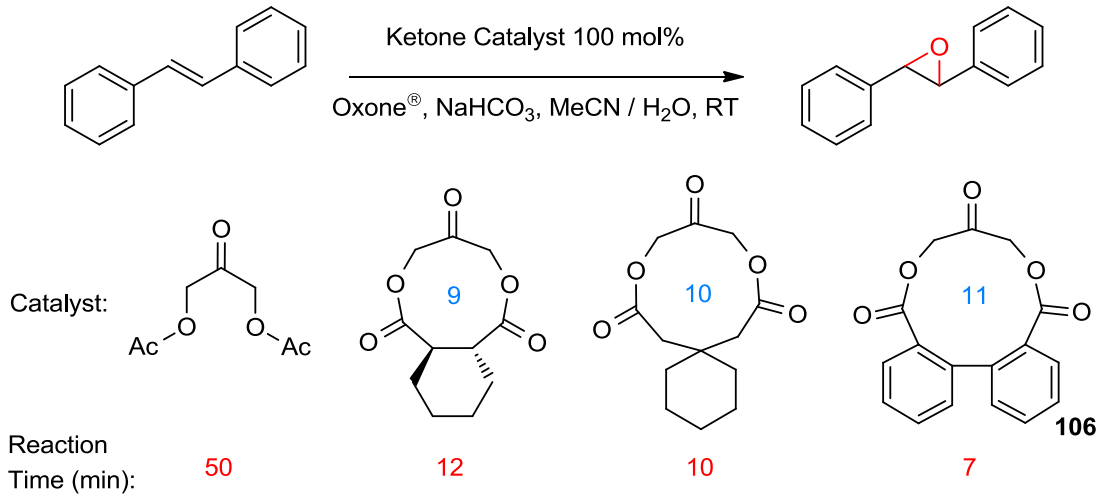


Figure 1.29: *Potential paths of attack on a non-C_2 symmetric dioxirane* ***104****, and on a C_2 symmetric dioxirane* ***105****.*[35]

Yang initially compared simple ketones to investigate which structural and chemical properties led to good reactivity. She discovered that electron-withdrawing groups close to the ketone increased its reactivity, while introducing substituents in the α-position was detrimental to reaction rate.[131]

The influence of the size of the ring bearing the ketone was also investigated and it was determined that an 11-membered ring **106** offered the best reactivity – oxidizing *trans*-stilbene to 100% conversion in only 7 min, which was over four times faster than 1,1,1-trifluroacetone (Scheme 1.45).



Scheme 1.45: *Yang's investigation into the size of the ketone bearing ring.*

To introduce chirality into the 11-membered ring system, Yang used the chiral and C_2 symmetric binaphthalene motif **107**. Yang found that she was able to induce *ees* in the isolated epoxides of up to 87% when employing **107** at a loading of only 10 mol% – a marked improvement over Curci's previous ketone catalysts (Figure 1.30).[130]

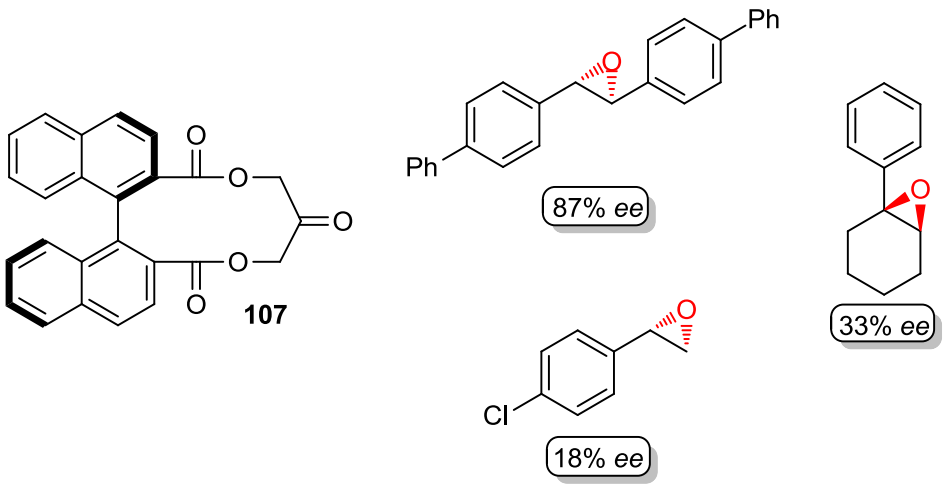
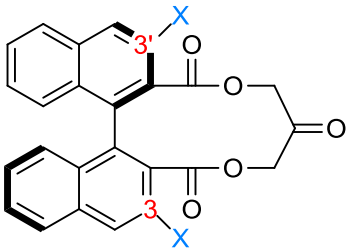


Figure 1.30: *Some of Yang's promising results with his first C_2 symmetric binaphthalene derived catalyst.*

From X-ray analysis of **107**, Yang suspected that H-3 and H-3' atoms act as the steric sensors, making them important for the transferral of the chiral

information of the catalyst to the alkene substrate. By increasing the size of the group at the 3 and 3' positions Yang believed she could further improve the facial selectivity of her catalyst.[132]

Yang introduced a range of groups at the 3 and 3' positions, and she found that as the size of the group increased, the epoxide *ees* only increased up to a point; after which, any further increase in the steric bulk led to diminished stereocontrol (Table 1.3). In a model study, which employed *trans*-stilbene as the test substrate, chloro groups were found to have the optimal steric influence. The chloro-substituted catalyst **108** oxidized *trans*-stilbene with good enantiocontrol (76% ee), which, in comparison to **107** (44% *ee*), was a marked improvement.



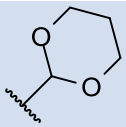
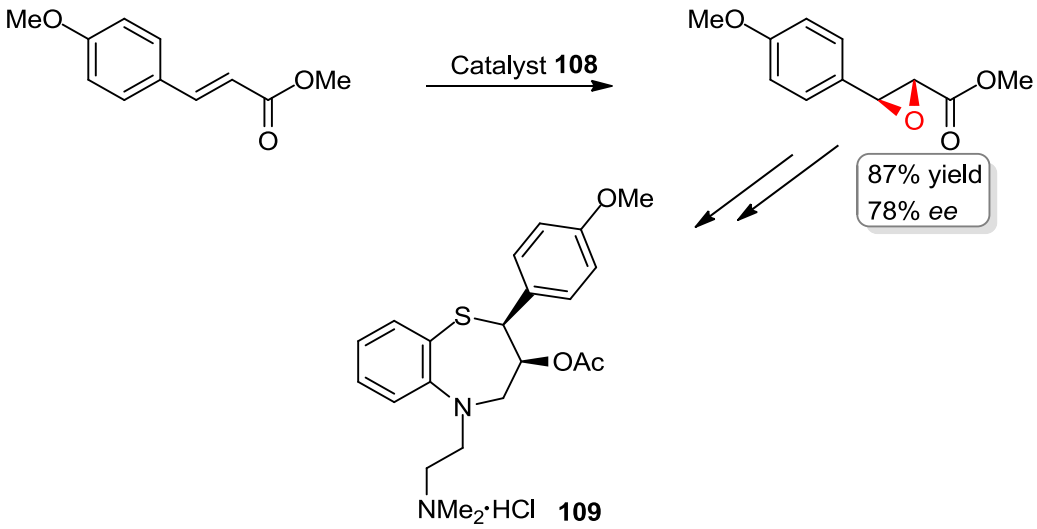
X =	*ee* (%)	X =	*ee* (%)
H	44	Me	56
Cl	76	CH_2OCH_3	66
Br	75		71
I	32	$SiMe_3$	44

Table 1.3: *Effect of the size of the steric sensor at the 3 and 3' positions on the ee of trans-stilbene oxide.*

Yang's epoxidation methodology is used industrially to synthesise Diltiazem hydrochloride by the Tenabe Seikayu company. Using the chloro-substituted catalyst, they oxidize methyl *p*-methoxycinnamate, which is isolated initially in an 87% yield with an *ee* of 78%. The epoxide is then recrystallized to obtain it in an enantiopure form (Figure 1.46).[133]



Scheme 1.46: *Tenabe Seikayu's synthesis of Diltiazem hydrochloride.*

Song[134] and Adam[135] also investigated the synthesis and use of C_2-symmetric ketones **110** and **111**, and **112** and **113** respectively. However, these catalysts were not as reactive, nor able to induce *ees* as high as Yang's binaphthalene ketones (Figure 1.31).

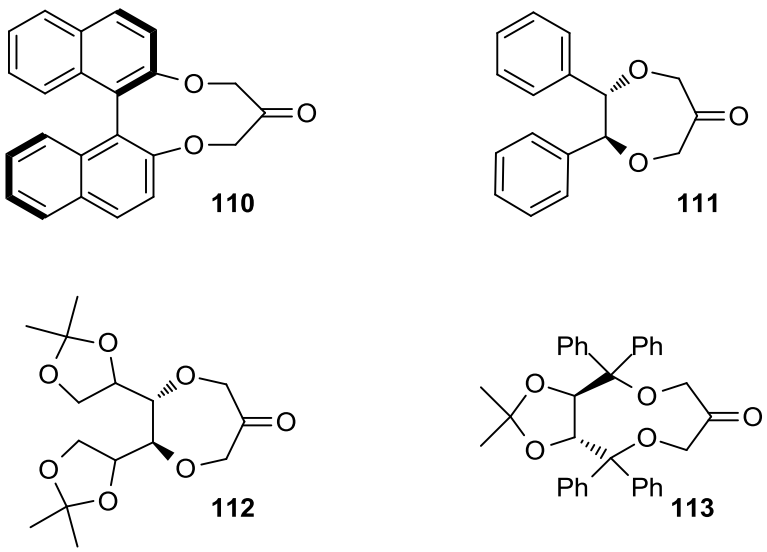
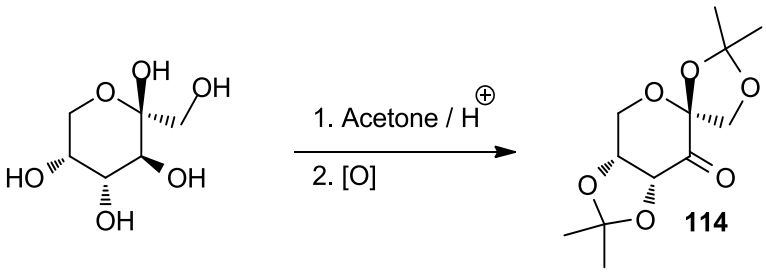


Figure 1.31: *C_2-symmetric catalysts developed by Song and Adam.*

1.6.3.2. Shi's Ketones Derived from Monosaccharides

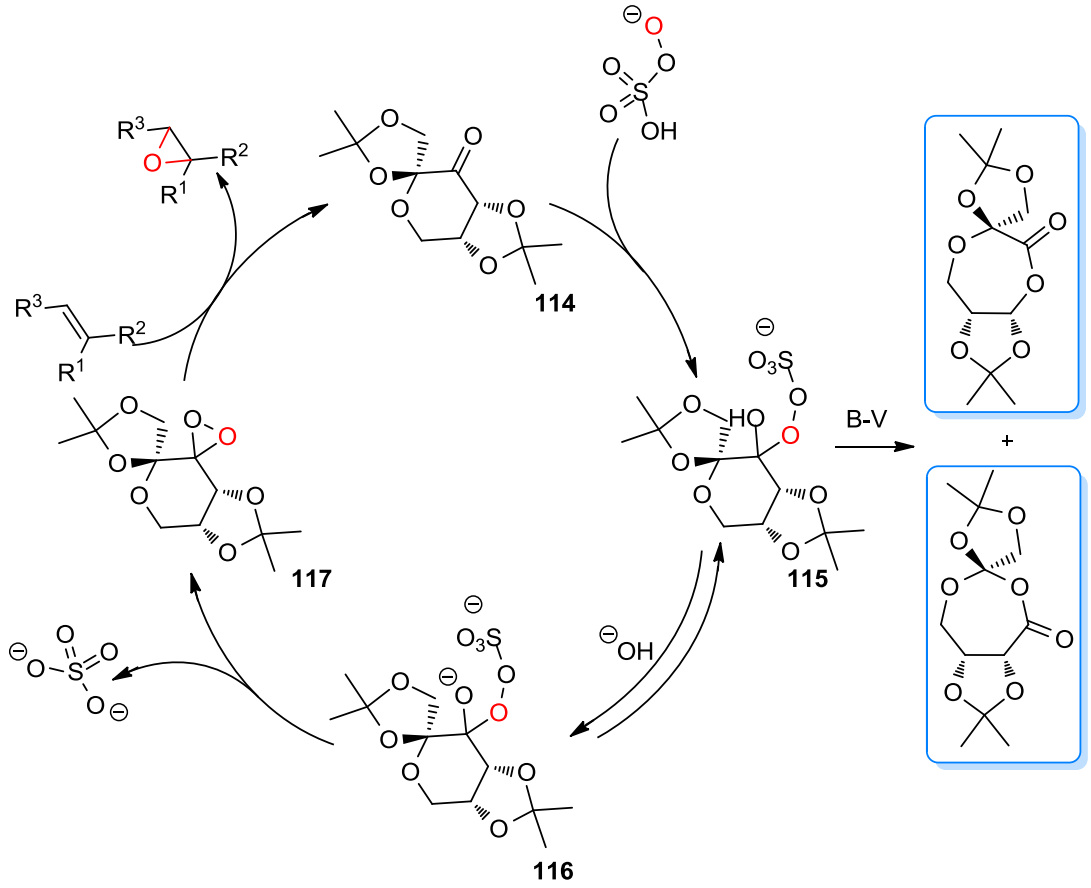
In 1996, Shi published his first paper on his research directed at developing sugar-derived ketones for asymmetric epoxidation. Over the past decade it has become one of the most powerful and versatile methodologies for organocatalytic asymmetric epoxidation.[136] Shi initially set out a few guidelines for his catalyst development: 1) The element that transfers chiral information should be located in proximity to the reacting dioxirane to maximise the stereoinduction; 2) A fused ring should be present α to the carbonyl group to minimise epimerization at this position; 3) The approach of the substrate to the dioxirane should be controlled by blocking one face, or, by a C_2 or pseudo C_2 symmetric element; 4) Electron-withdrawing functionality should be present to activate the catalytic centre.[137]

Shi's first published attempt at a catalyst was the D-fructose-derived catalyst **114** (Scheme 1.47). As well as satisfying the four guidelines above, it also fulfils another equally important criterion – low cost and ease of synthesis. It is accessible in only two high-yielding and straightforward steps. This attribute is key to any catalyst being used by other groups and industry.



Scheme 1.47: *Synthesis of Shi's D-fructose derived ketone.*

Initially, however, it was required to use **114** in excess to achieve complete conversion of the alkene to its respective epoxide.[136] Shi undertook a short investigation to understand why an excess of this 'catalyst' was required. Careful analysis of the reaction cycle suggested that **114** is decomposed under the reaction conditions through a Baeyer-Villiger pathway (Scheme 1.48).[138]



Scheme 1.48: *Catalytic cycle of the Shi asymmetric epoxidation showing the Baeyer-Villiger decomposition pathway.*

This understanding of the catalytic cycle provided insight into how to suppress the decomposition pathway. These epoxidation reactions, mediated by ketones such as **114**, were initially performed at pH 7-8. This pH was believed by Shi to favour the existence of the intermediate **115**, and it is this intermediate which is susceptible to the Baeyer-Villiger decomposition. Increasing the pH to around 10 favours the Criegee intermediate **116**, which collapses rapidly to the catalytically active dioxirane **117**. Therefore, performing the reaction at higher pH heavily favours the formation of the dioxirane over the esters. The improved efficiency of the catalytic cycle allows a sub-stoichiometric amount of ketone **114** to be used and also a 30% reduction of the amount of Oxone® required.[137]

With a truly catalytic system, Shi studied the substrate scope of the catalyst and found that **114** was extremely versatile with regards to the substrates it could

efficiently oxidize in high yield and *ee*. Many functional groups were tolerated and the observed enantiocontrol was excellent for *trans* di-substituted and tri-substituted alkenes.[138] Later studies demonstrated that hydroxyl-alkenes,[139] enol esters,[140] 2,2-disubstituted vinylsilanes,[141] enynes[142] and dienes[143] were also suitable substrates. Contrastingly, **114** provided poor *ee*s for the enantioselective epoxidation of *cis*-alkenes or terminal alkenes (Figure 1.32).

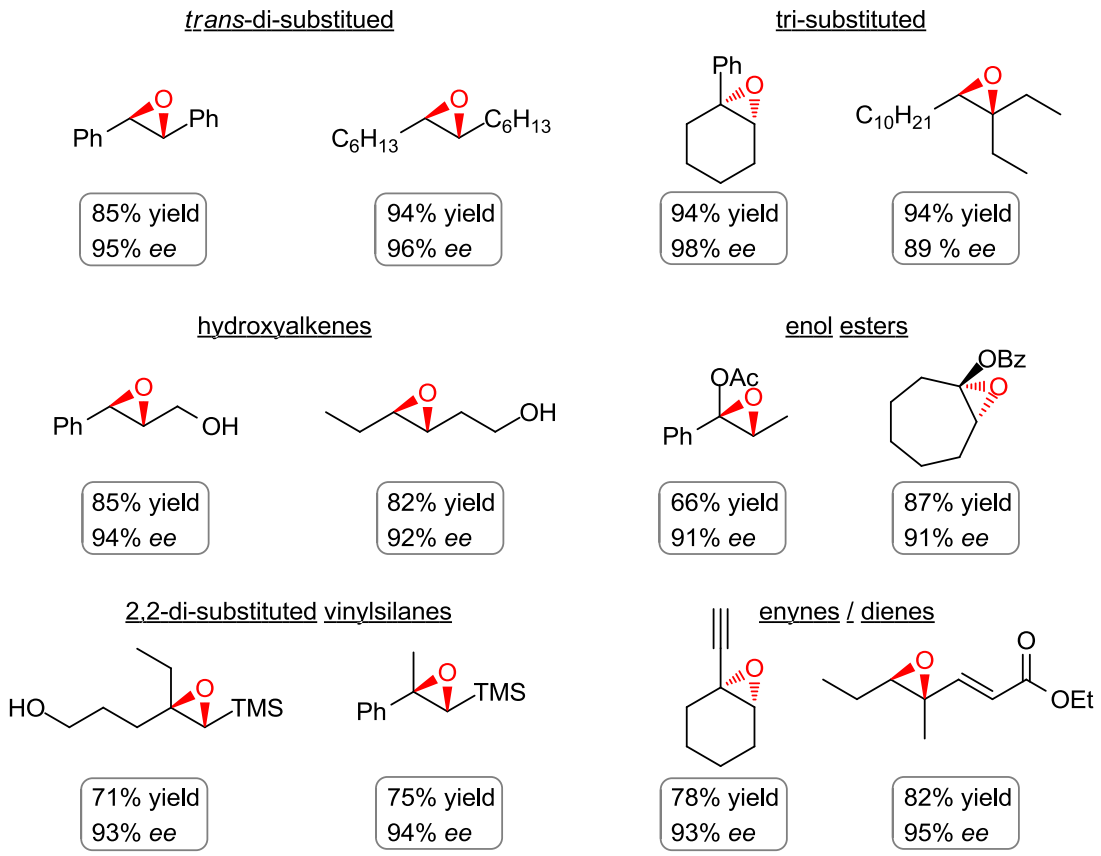
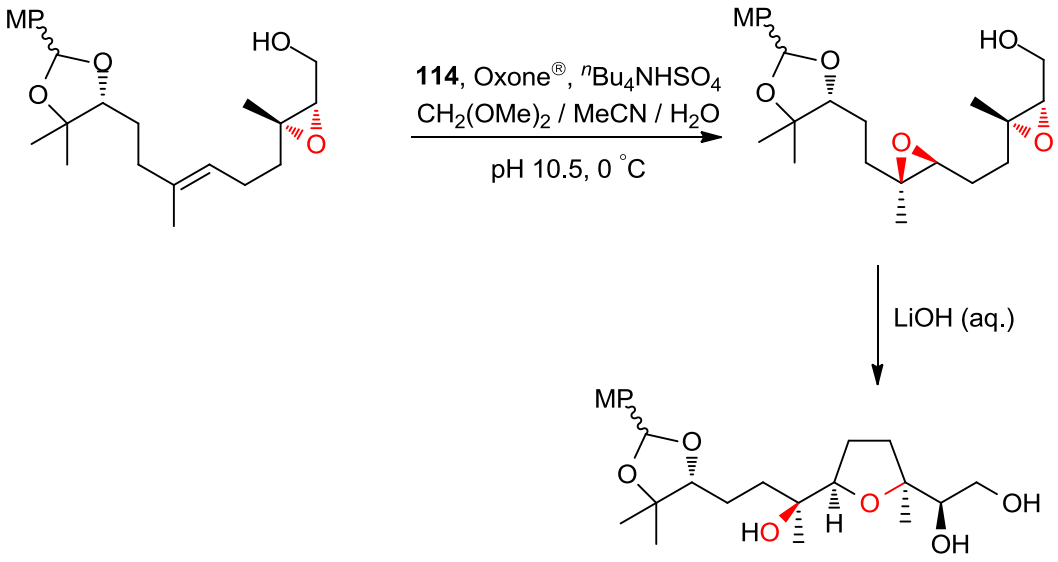


Figure 1.32: *Yields and ees for several classes of alkenes with catalyst* ***114****.*

Clearly, ketone **114** is an excellent catalyst in terms of stereoinduction, cost, the ease of its preparation and extent of its reactivity. It is not surprising then, that **114** has found widespread use outside of Shi's own lab. Several natural product syntheses have utilized Shi's methodology to access key intermediates.[36]

Morimoto used Shi's ketone to install the second epoxide, in a 6:1 *dr* and 87% yield, into a key intermediate in his synthesis of (+)-intracatetraol (Scheme 1.49). The first epoxide was introduced into the molecule using the Sharpless

epoxidation, and installation of the second preceded the base-induced rearrangement which formed some of the important structural features present in (+)-intracatetraol.[68]



Scheme 1.49: *Installation of the second epoxide into a synthetic precursor to (+)-intracatetraol.*

With the aim of making the methodology applicable to many other substrates, Shi investigated other co-oxidants. The most successful stoichiometric oxidant of those screened was H_2O_2. Oxone® has good selectivity for the catalyst, causing little to no background epoxidation; however, its active oxygen content is extremely low, and requires a large mass to be used.[144] In contrast, H_2O_2 has a high oxygen content and is far more atom economical. Shi was able to develop milder and cleaner reaction conditions, and decrease catalyst loading with its use. It was found that to successfully use H_2O_2 as the stoichiometric oxidant use of a nitrile containing solvent, such as MeCN or EtCN was essential. Shi suggests that H_2O_2 is activated by the nitrile functionality, forming a peroxyimidic acid, such as **118** in the case of MeCN, *in situ* which then oxidizes the ketone (Figure 1.33).[145]

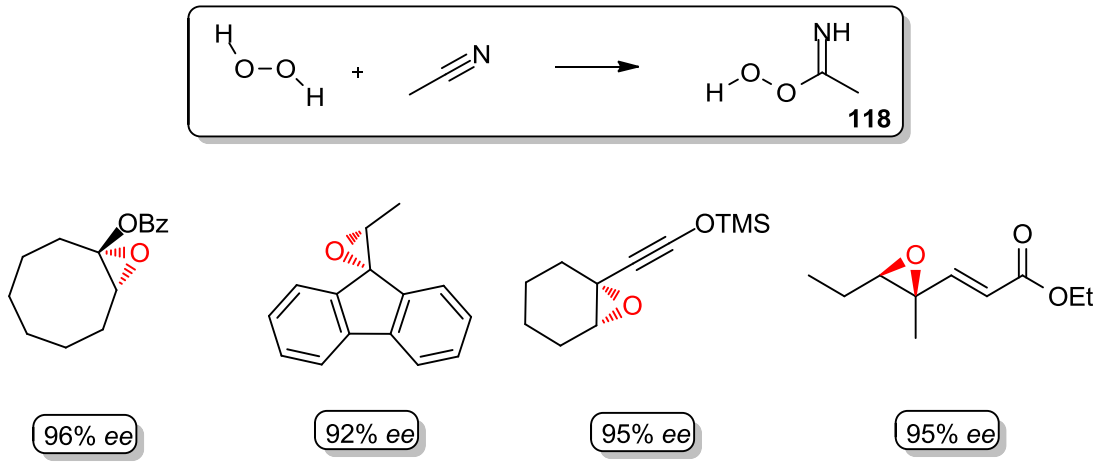


Figure 1.33: *Formation of the peroxyimidic acid* ***118****, the active co-oxidant in Shi's* H_2O_2 *system. Epoxide ees achieved using 0.1-0.3 equiv.* ***114****.*

In order to intelligently design future catalysts, it was important to understand the interaction between the substrate and catalyst in the transition state (TS). Baumstark and co-workers published experimental and computational results to suggest that a spiro TS is favoured for dioxirane-mediated epoxidation of alkenes over the planar TS.[146] Through analysis of the stereochemistry of the isolated epoxides and modelling, Shi rationalized that the epoxidations involving catalyst **114** do preferentially proceed *via* a spiro transition state (Figure 1.34).[141] It is suspected that the preference for the spiro TS is due to the existence of stabilizing interactions between the non-bonding orbitals on the oxygen atom and the empty π* orbital of the alkene. The same stabilizing orbital overlap is not geometrically possible for the planar TS, thus the spiro TS is lower in energy, and favoured over the planar TS.[147]

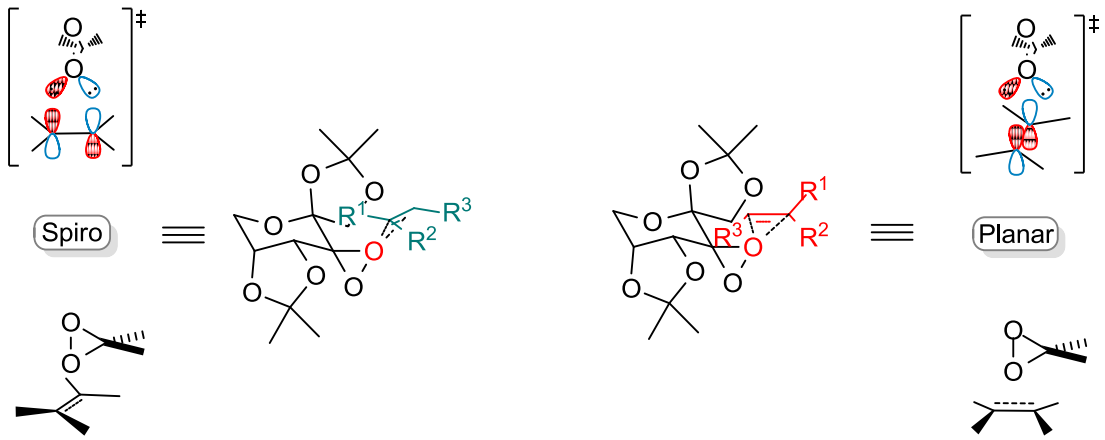


Figure 1.34: *The most favoured conformation of both the spiro and planar transition states.*

While analysis of the transition states illustrates why ketone **114** furnishes *trans* and tri-substituted epoxides in good *ee*, the study of the TS also suggests why *cis*- and terminal alkenes are poor substrates. In both of the spiro transition states, both groups on the alkene face away from the steric bulk of the catalyst, hence the catalyst cannot differentiate between the two faces of the alkene to a reasonable degree, which results in low *ees* (Figure 1.35).[148]

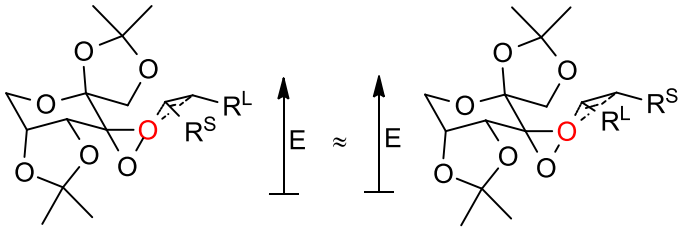


Figure 1.35: *Competing transition states for terminal (R^S=H)* and *cis*-alkenes.

With an understanding of why *cis* and terminal alkenes were very poor substrates, Shi was able to design and synthesise the oxazolidinone-containing alkene **119**. Interestingly, this new species may not differentiate between the two spiro TSs by steric interactions, instead, Shi suggests that the oxazolidinone interacts favourably with R groups that contain π density, and that this interaction is essential for high *ees* (Figure 1.36). [148]

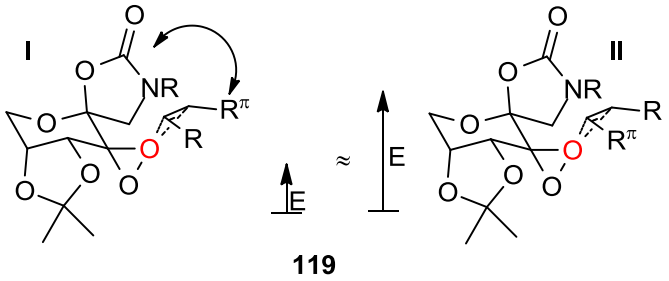


Figure 1.36: *Competing spiro transition states for the oxazolidinone catalyst.*

This interaction manifests itself with transition states analogous to **I** being favoured over **II**. It is through this mechanism that **119** imparts greater *ees* for *cis* and terminal alkenes than catalyst **114** (Figure 1.37). The new mode of facial selectivity does, however, lessen the difference in energy between the transition states for both *trans* and tri-substitued alkenes, which resulted in low *ees* for these classes of substrate when catalyst **119** was employed.

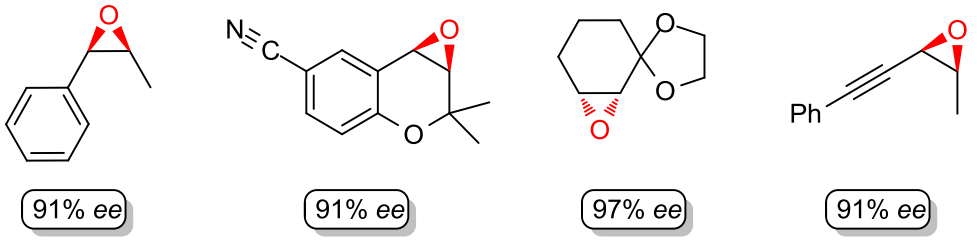


Figure 1.37: *Isolated epoxide ees when employing catalyst* ***119****.*

Shi has developed several chiral ketones capable of high stereoselectivities across most classes of alkene substrates. A disadvantage to Shi's systems is the requirement for relatively high catalyst loadings in some instances, due to the instability of the ketone to Baeyer-Villiger oxidation despite the optimized conditions.[137]

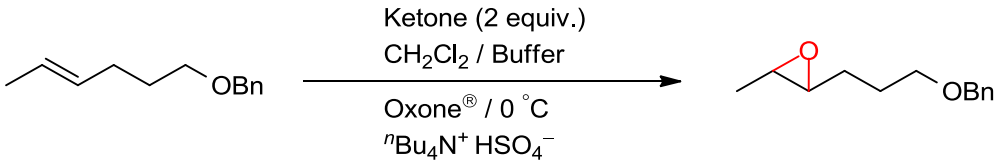
1.6.3.3 Denmark's Oxoammonium Salts and Ketones.

Denmark has made considerable contributions to the field of organocatalysis, and he has focused considerable research into asymmetric epoxidation. He has reported the synthesis and utilization of several organocatalysts which fall into two main classes; oxoammonium salts[149] and α-fluorinated ketones[150].

Denmark's initial research was directed at a systematic study of aqueous/organic biphasic reaction parameters that are used in the dioxirane-mediated epoxidations. Denmark hoped the information would provide an insight in how to design an efficient catalytic system. He explored the effects of temperature, pH and the addition rate of Oxone®.[150,151]

Temperature variation was rather limited, to 0-20 °C, since the aqueous phase freezes if the temperature is any lower, and, at higher temperatures, the rate of the decomposition of Oxone® becomes significant. Likewise, it was found that the optimal pH was also limited to a small range of 7.5-8. At low pH, Denmark observed that decomposition of the ketone catalyst, through a Baeyer-Villiger pathway, was rapid.[150] It was the decomposition of Oxone® that determined the upper limit of pH. Furthermore, epoxides can be ring opened by both acid and base catalysed pathways, further highlighting the importance of the need for pH control. It was found to be advantageous to add Oxone® slowly over a period of time to limit its decomposition. Oxone® decomposes by a bimolecular mechanism, thus, if the concentration of Oxone® in solution was kept low, the rate of decomposition was attenuated.[151]

The study of basic ketones demonstrated that efficiency significantly decreased with increasing linear chain length and that efficiency is strongly linked to ring size, agreeing with Yang's investigation (Table 1.4).



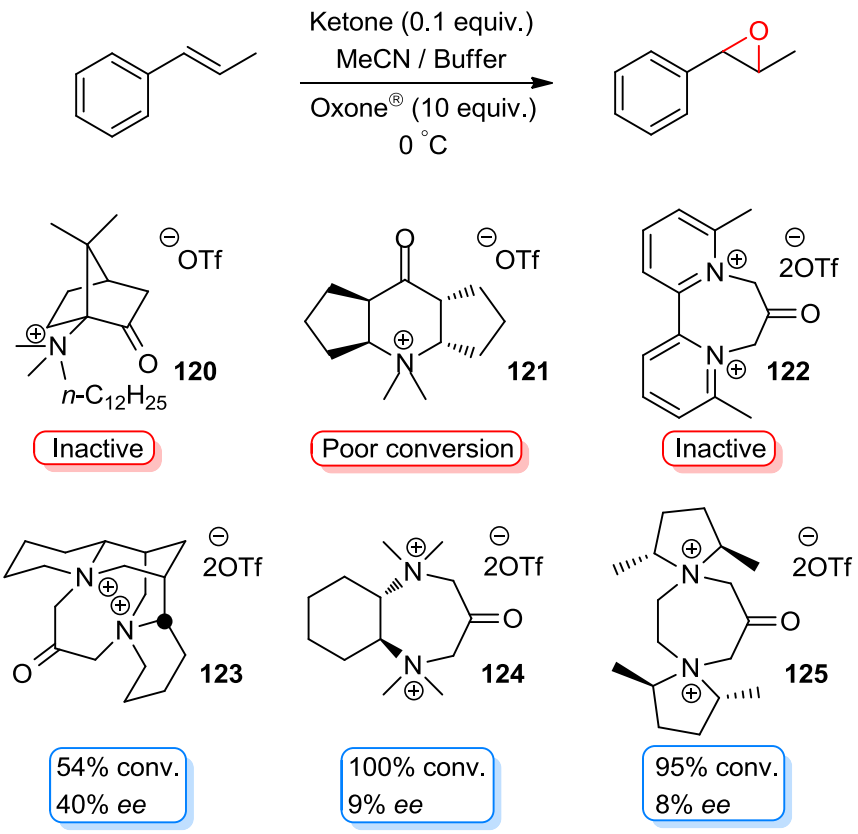
Entry	Ketone	Alkene / Epoxide ratio
1	acetone	13 / 87
2	2-butanone	60 / 40
3	3-pentanone	95 / 5
4	cyclobutanone	98 / 2
5	cyclopentanone	97 / 3
6	cyclohexanone	33 / 67
7	1,1-dimethyl-4-oxopiperidinium nitrate	98 / 2

Table 1.4: *Screening of ketone structure using Denmark's optimized conditions.*

Curiously, 1,1-dimethyl-4-oxopiperidinium nitrate did not show the activity expected (Entry 7). Denmark believed that this was due to it being strongly solvated in the aqueous layer, and therefore not available in the organic layer to epoxidize the alkene. By altering the *N*-alkyl chain length and counter-ion, Denmark was able to tune the solubility profile of the oxopiperidinium salts, such that it was readily solvated by CH_2Cl_2 and create a catalyst that was more efficient than acetone.[151]

Once the most efficient catalyst structure had been determined, chiral variants of it were investigated to try to also to exert enantiocontrol in the epoxidation process. The chiral keto-ammonium salts **120** and **121**, however, were very poor catalysts in terms of conversion. Denmark suggested that the poor reactivity may be due to congestion at the α-position.[151] In an attempt to increase the reactivity of the chiral catalysts, Denmark investigated the aromatic bis(immonium) ketone **122** (Scheme 1.50). It was hoped that the removal of the α-functionality, and having two immonium moieties in the catalyst, would help improve the reactivity. Unfortunately the aromatic bis(immonium) catalyst **122** was completely unreactive. This lack of turnover was suspected to be due to the oxidative instability of the aromatic immonium moiety, i.e. the catalyst was

destroyed by some oxidative degradation pathway faster than it could epoxidize the substrate.[151]



Scheme 1.50: *Comparison of mono and bis(ammonium) ketones and bis(immonium) ketones.*[151]

To solve the problem of oxidative instability, Denmark synthesised a range of aliphatic bis(ammonium) ketones **123**-**125**. These were much more reactive than their keto-ammonium salt counterparts; reactions typically ran to completion in under 6 h. The bis(ammonium) moiety was also very resilient to the Baeyer-Villager degradation pathway.[152]

Previous studies of α-fluoro ketones by Curci had shown them to be superior than their unsubstituted analogues for dioxirane-mediated epoxidation.[153] As such, they became an attractive target for Denmark, and he first synthesised a range of α-fluorinated 4-^{t}Bu-cyclohexanones to probe the effect of the fluoro substitution in order to gain an insight in how to design an effective catalyst (Figure 1.38).[154]

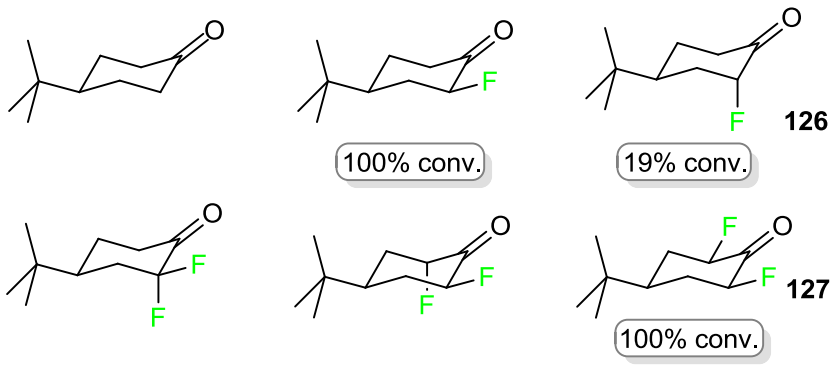
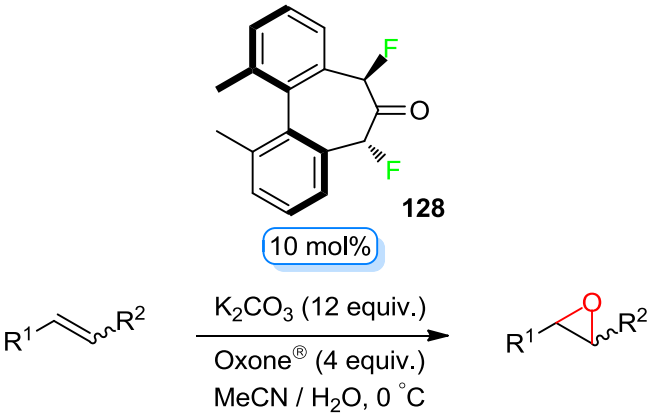


Figure 1.38: The *range of α-fluorinated 4-^{t}Bu-cyclohexanones synthesised to investigate the stereo-electronic effect of fluorine.*

Denmark found that the orientation of the fluoro substituent was critical for the activity of the catalyst, i.e. it had to be equatorial to observe the increase in reactivity for the mono-substituted cyclohexanones. Moreover, when the fluoro substituent was axial, as in **126**, the catalyst was extremely susceptible to Baeyer-Villager decomposition. Placing the second fluoro substituent axially, in either the geminal or *trans*-2,6 position relative to the first, decreased reactivity. Ketone **127**, with the *cis*-2,6 configuration of the fluorine atoms, was the most active of this series.[154]

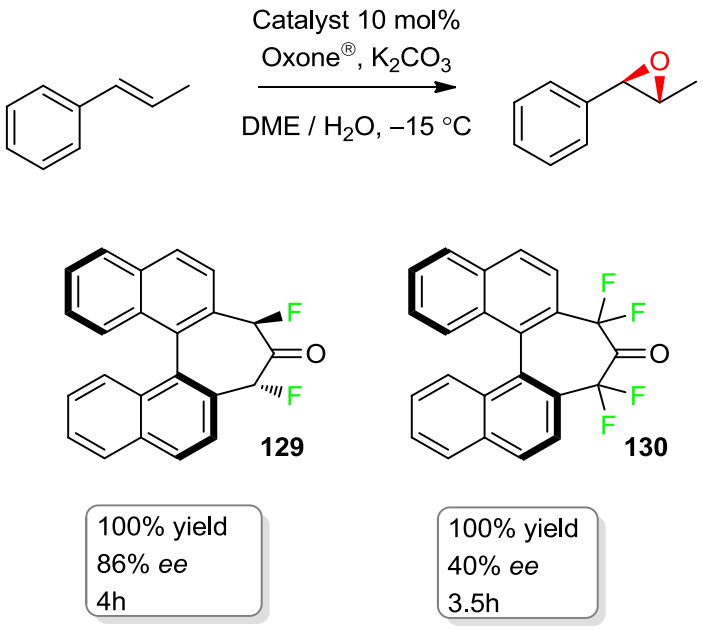
The insight gained from the investigation into the effects of the pattern of α-fluoro substitution led to the design and synthesis of **128**, which proved to be Denmark's most successful catalyst (Table 1.5). Under modified monophasic conditions, a 94% *ee* was obtained for *trans*-stilbene, and good stereoselectivity was observed across a range of other *trans*-di-substituted alkenes.[154]



Entry	Alkene	Time (h)	Yield (%)	*ee* (%)
1	(*E*)-2-methylstyrene	10	80	88
2	*trans*-stilbene	72	46	94
3	(*E*)-cinnamyl alcohol	7	93	89
5	1-phenylcyclohexene	4	78	59
6	4-chlorostyrene	30	55	43

Table 1.5: *Asymmetric epoxidation of a range of alkenes with* ***128****.*

A closely related system, based on the C_2-symmetric binaphthyl moiety, was developed by Behar.[155] Several fluorinated ketones were synthesised and screened for their reactivity and enantioselectivity against the model alkene substrate *trans*-β-styrene. In concurrence with Denmark's own investigations, the *trans*-pseudo-equatorial fluorine substitution pattern of **129** exhibited the best reactivity and enantioselectivity in the epoxidation process, furnishing *trans*-β-styrene oxide in an 86% *ee* (Scheme 1.51). Other substitution patterns, similar to those reported by Denmark, reportedly performed well, with *ees* also around 80%. However, when all four α-positions were fluorinated, the resulting catalyst demonstrated poor reactivity and enantiocontrol. Catalyst **130** existed almost exclusively as the hydrate; Behar speculated that the rate of formation of the reactive dioxirane would therefore be reduced, so explaining the decrease in reactivity and enantioselectivity.

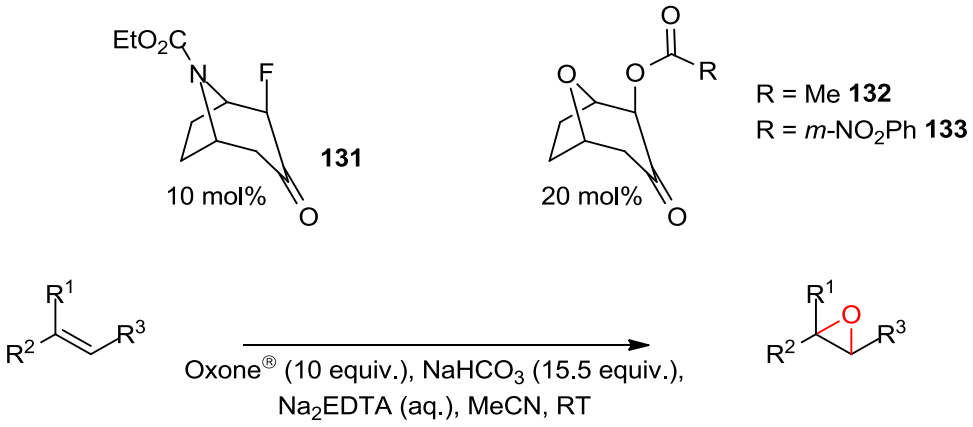


Scheme 1.51: *Asymmetric epoxidation of trans-β-methyl styrene with ketones developed by Behar.*

These novel ketones were more reactive than Denmark's 6,6'-dimethylbiphenyl analogues, but the enantioselectivity observed was, in fact, slightly lower.

1.6.3.4 Armstrong's Ketones

Armstrong has been at the forefront of research on organocatalytic epoxidation, having contributed intellectually to the development of both iminium-salt and ketone-mediated catalytic procedures. The utility of oxabicyclo[3.2.1]octanones and tropinone derivatives for the asymmetric epoxidation of alkenes was investigated by Armstrong and co-workers (Table 1.6).[156] The initial motivation for studying these conformationally rigid catalysts was to address the susceptibility of Shi's catalysts, in particular, to undergo oxidative decomposition, with the aim to reduce catalyst loadings.[157]



Entry	Ketone	Alkene	Conv. (%)	*ee* (%)
1	**131**	*trans*-stilbene	100	76
2	**131**	styrene	100	29
3	**132**	*trans*-stilbene	85	93*
4	**132**	styrene	100	48*
5	**133**	*trans*-stilbene	46	81*
6	**133**	styrene	100	40*

Table 1.6: *Example catalyst structures of the original bicycles employed by Armstrong for asymmetric epoxidation.* ee(max) = 100 x (product ee / ketone ee).*[156]

Early results were promising and highlighted the stability of the bicyclic structural motif; in some instances, it was only necessary to use a 10 mol% loading. Moreover, it was possible to isolate **131** from the reaction mixture for re-use. This stability inspired Sartori, in collaboration with Armstrong, to incorporate **131** onto a solid support, creating a heterogeneous catalytic system (Figure 1.39).[158] Binding **131** onto a mesoporous silica support created a re-useable solid-phase catalyst designated MCM-41-FT that provided the same levels of stereocontrol, and comparable reactivity to, the homogeneous catalyst. Other solid supports were trialled, including amorphous silica and Merrifield resins, but these solutions did not offer satisfactory results.

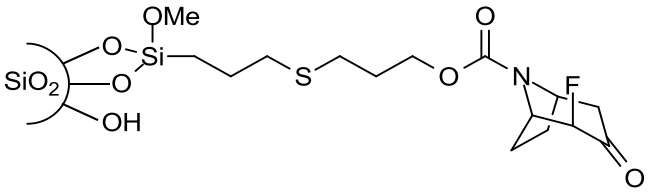


Figure 1.39: *Structural schematic of the silica-bound ketone* ***131****, designated MCM-41-FT.*

Armstrong has also investigated bicyclic ketones featuring a second electron-withdrawing substituent at the α-position (Figure 1.40).[159]

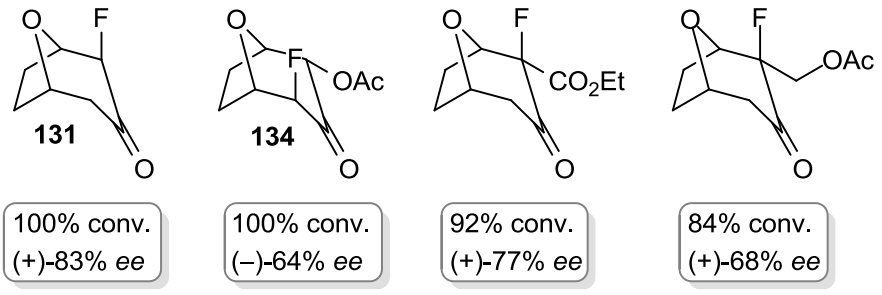


Figure 1.40: *Di-substituted oxabicyclic ketones prepared by Armstrong. Results shown are reported as the ee(max) for the epoxidation of trans-stilbene. Using 20 mol% catalyst.*

Disappointingly, each of these oxabicyclic ketones demonstrated lower enantiocontrol in the epoxidation process than the tropinone **131**. In particular, ketone **134** displayed a marked drop in enantioselectivity for the epoxidation of *trans*-stilbene. Armstrong proposed that this large drop could have been due to the manifestation of an asymmetric spiro-TS. Previous computational studies indicated that an equatorial electron-withdrawing fluorine substituent caused the shortening of the forming C–O bond closest to the fluorine.[160] Armstrong surmised that if the equatorial, and also electron-withdrawing, acetoxy group in **134** caused the same bond asymmetry then the alkene would be shifted away from the stereochemically controlling axial fluorine substituent - leading to, and explaining the decreased enantiocontrol.[159]

Armstrong and co-workers have also investigated two other structural classes of enantiopure ketone catalysts for asymmetric epoxidation, namely:

tetrahydropyran-4-ones **135** and spirocyclic N-carbethoxy-azabicyclo[3.2.1]octanones **136** (Figure 1.41).[161]

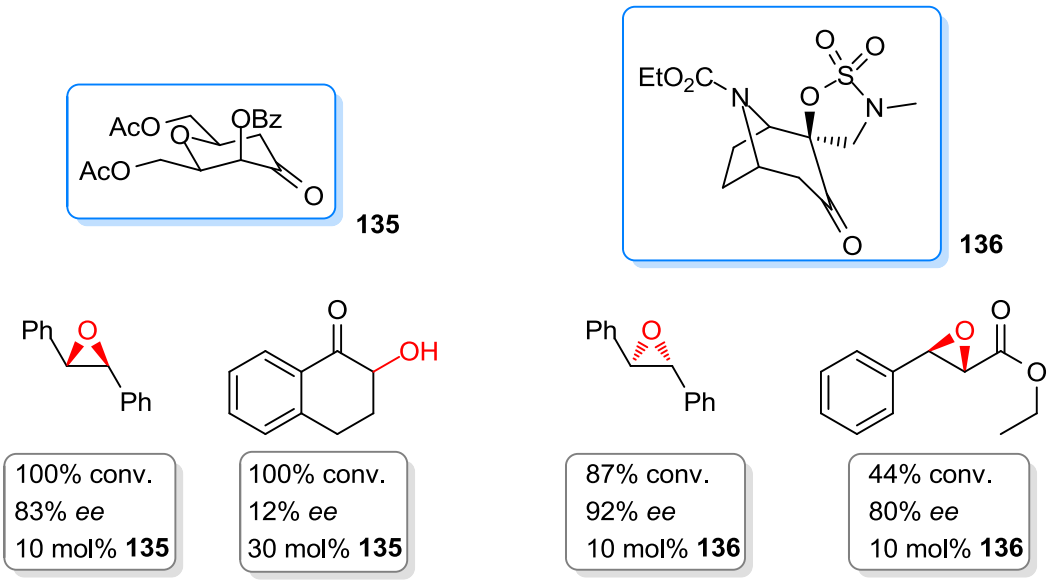


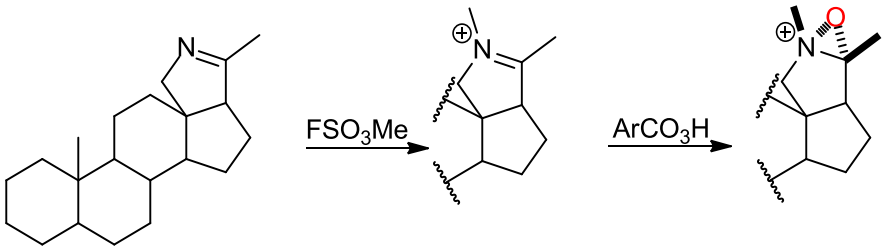
Figure 1.41: *Different structural classes of ketones synthesised by Armstrong, and a sample of the results from their employment in asymmetric epoxidation. The epoxysilylether was subjected to acidic work-up, to isolate the α-hydroxyketone. Oxone® (5 equiv.), catalyst (10-30 mol%), $NaHCO_3$ (15.5 equiv), Na_2EDTA (aq.), MeCN.*

Armstrong has been able to design several classes of ketones for dioxirane-mediated epoxidation and has succeeded in achieving his original goals of creating oxidatively stable catalysts that allow catalyst loadings as low as 10 mol% to be used, which compares favourably to Shi's hexose derived catalysts at about 30 mol%. Armstrong has proposed to investigate analogues to **136** to further improve enantiocontrol in the epoxidation process.[161]

1.6.4 Iminium Salt Mediated Epoxidation

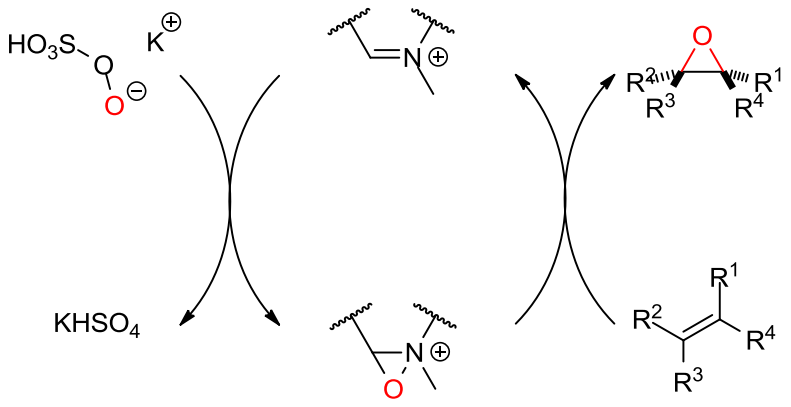
1.6.4.1 Lusinchi and Bohé's Initial Studies

In the year preceding the confirmation of dioxiranes as reactive oxidative intermediates, Lusinchi reported the preparation of an oxaziridinium species from a steroidal iminium salt (Scheme 1.52).[162] Lusinchi later demonstrated that oxaziridinium species can oxidize several functional groups: amines, sulfides, imines and alkenes.[163]



Scheme 1.52: *Synthesis of the first oxaziridinium salt.*

Crucially, Lusinchi and co-workers were subsequently able to develop a catalytic system based on an iminium/oxaziridinium cycle, employing Oxone® as the stoichiometric oxidant. A sub-stoichiometric catalyst loading makes the introduction of chirality into the catalyst a feasible option, and thus creates an organocatalytic asymmetric cycle (Scheme 1.53). The discovery of the catalytic cycle also implied that it would be possible to use the iminium salt as the pre-catalyst and oxidize it *in situ*, avoiding extra synthetic steps.



Scheme 1.53: *The iminium/oxaziridinium oxidative catalytic cycle.*

Lusinchi and Bohé later reported the synthesis of the first optically active oxaziridinium salt in 1993, which was derived from (1*R*,2*R*)-(+)-norephedrine. Importantly, they were also able to determine the structure of the oxaziridinium salt by X-ray crystallography (Figure 1.42).[164]

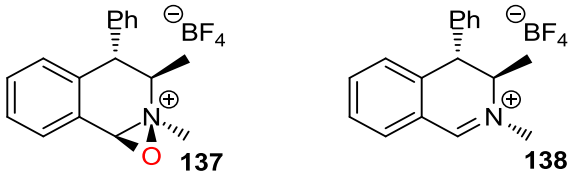
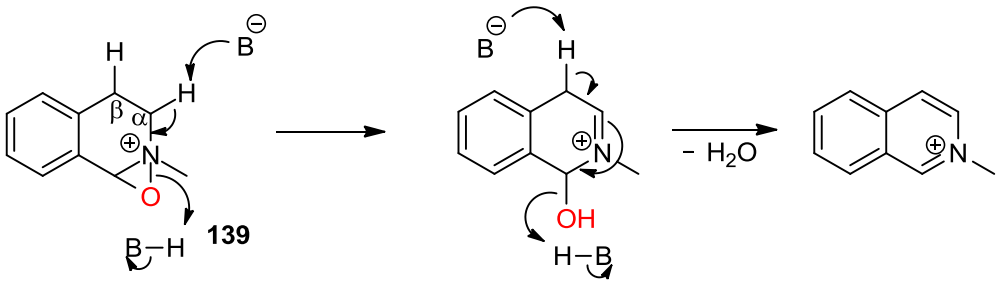


Figure 1.42: *The chiral oxaziridinium salt synthesised by Lusinchi from* (1*R*,2*R*)-(+)-norephedrine **137** and the related iminium salt **138**.

Both the oxaziridinium salt and the iminium salt were tested in the epoxidation of a range of alkenes; using **137** stoichiometrically yielded the *trans*-stilbene oxide in a 42% *ee,* whereas, employing **138** at a 5 mol% loading furnished the epoxide in a 35% *ee*. This disparity was suggested to result from the oxaziridinium species being formed as a diastereoisomeric mixture *in situ*.[165]

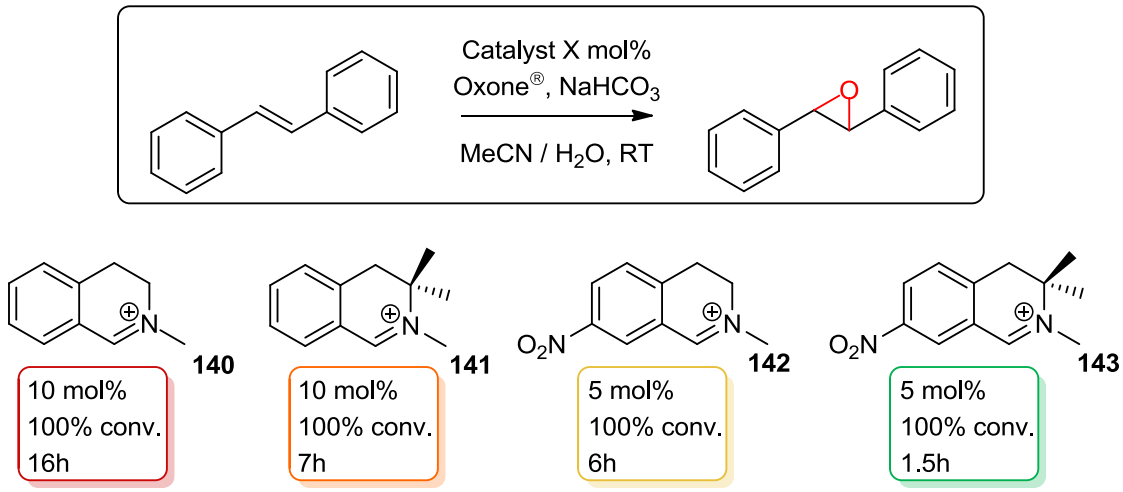
A decomposition pathway exists for the oxaziridinium species derived from the parent 3,4-dihydroisoquinolinium salts developed by Lusinchi (Scheme 1.54).[166] It was proposed by Bohé that if the irreversible, base-induced rearrangement and subsequent dehydration of oxaziridinium salts, such as **137** and particularly those derived from 3,4-dihydroisoquinolinium species like **139** that contain protons α-

and β- to the iminium nitrogen, could be blocked, then a more efficient catalytic entity would result.[167]



Scheme 1.54: *The base-catalysed decomposition of an oxaziridinium species containing α- and β- protons.*

Bohé prepared the achiral 3,3-dimethyl-dihydroisoquinolinium salt **141** and employed the new catalyst to epoxidize a range of alkenes (Scheme 1.55). By replacing both protons at the α-position, the base induced isomerization side reaction was prevented, and, accordingly, Bohé observed an improvement in the reactivity and stability of **141** under epoxidation conditions over **140**. The reactivity of the 3,3-disubstituted catalyst was augmented by incorporating an electron-withdrawing nitro group at the 7-position of the dihydroisoquinolinium moiety, as in **142** and **143**. The combined effects of blocking the decomposition pathway and the reducing the electron density on the electrophilic iminium motif as in **143**, cut the reaction time down dramatically.[167]

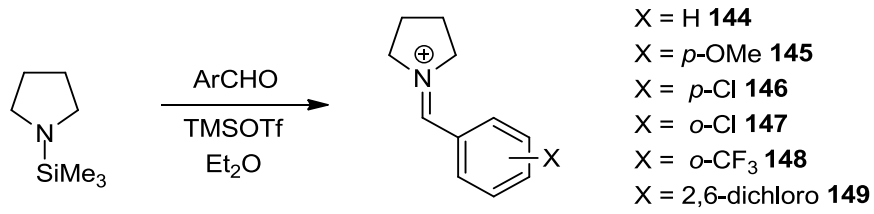


Scheme 1.55: *By incorporating an electron-withdrawing nitro group and blocking the base-induced decomposition pathway; Bohé was able to substantially increase the reactivity of the iminium species. The results shown for each catalyst are for the epoxidation of trans-stilbene.*

1.6.4.2 Armstrong's Exocyclic Iminium Salts and Intramolecular Epoxidation

In 1998, Armstrong reported the synthesis and use of a range of exocyclic iminium salt organocatalysts.[168] The synthesis of the exocyclic iminium salt variants was inspired by the potential for the formation of a combinatorial library through the condensation of chiral amines with carbonyl compounds. It was hoped such an approach would expedite the creation of a diverse library and enable the rapid discovery of an efficient catalyst, capable of transferring its stereochemical information effectively to the alkene substrate.

During his preliminary investigation Armstrong synthesised a range of benzylidinepyrrolidinium triflate salts to explore various substitution patterns on benzene (Scheme 1.56). After testing several different condensation methodologies, Armstrong found that coupling an *N*-silyl protected pyrrolidine to benzaldehydes with TMSOTf in ether generated the desired exocyclic iminium salts. In some instances, however, the catalysts were contaminated with pyrrolidinium triflate.[168]



Scheme 1.56: *Benzylidinepyrrolidinium triflate salts synthesised by Armstrong and co-workers.*

The instability of the exocyclic iminium salts to hydrolysis was a primary concern. It was conceivable that the resulting carbonyl species would be oxidized to the dioxiranes *in situ* and this could have caused unwanted background epoxidation; potentially lowering the enantioselectivity in the epoxidation process. Fortunately, in control reactions no background epoxidation was observed, but it was evident the exocyclic iminium salts were hydrolysing under the reaction conditions, particularly the electron-rich species.

It was found that the iminium salts bearing an electron-withdrawing group at the *ortho* position were superior catalysts (Table 1.7). This was postulated to be for two reasons: 1) the increased rate of attack of the iminium salt by the nucleophilic peroxide component of Oxone® or the faster electrophilic epoxidation of the alkene; 2) the *ortho* group disfavoured planarity between the iminium bond and aromatic ring, rendering it less stabilized and more reactive.

Entry	Iminium	mol%	Conv. (%)
1	**144**	100	25
2	**145**	100	0
3	**146**	100	63
4	**147**	100	100
5	**147**	25	100
6	**146**	10	24
7	**147**	10	82
8	**148**	10	100
9	**149**	10	28
10	**147**	5	52
11	**148**	5	52

Table 1.7: *Initial screening of the benzylidenepyrrolidinium salts.*

Armstrong investigated structural variance in the iminium moiety to establish which features were beneficial, to aid the design of improved chiral iminium salts. He synthesised catalysts analogous to **144** by employing morpholine, piperidine and diethylamine. However, all of these iminium species underwent rapid hydrolysis and were ineffective as catalysts. Noting that there had been no literature reports of acyclic catalysts prepared from ketone derivatives, Armstrong and co-workers investigated generating acyclic catalysts by coupling pyrrolidine to several ketone motifs.

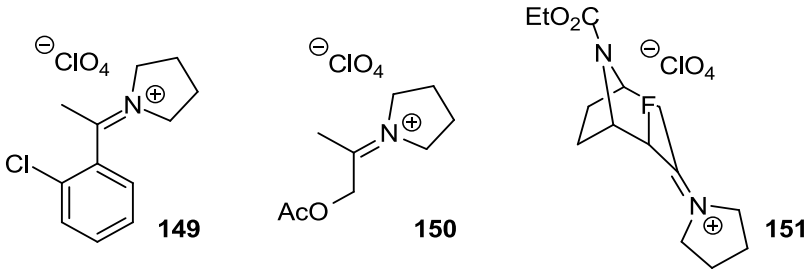


Figure 1.43: *Iminium salts generated from ketones.*

The methyl analogue of **147**, **149**, was prepared and was shown to be less active, converting only 44% of the alkene to the epoxide at 100 mol% catalyst loading. Likewise, **150** was not as active as many of the benzylidenepyridinium salts,

though Armstrong noted that the presence of an electron-withdrawing acetoxy group at the α-position did have a positive effect. This observation led to the idea of using an existing ketone **131**, developed for dioxirane mediated epoxidation. Unfortunately, the synthesis of iminium salt **151** was problematic and all attempts to isolate it were unsuccessful (Figure 1.43).

Armstrong investigated two strategies to incorporate chirality into pyrrolidinium salt catalysts; to employ either chiral aldehydes or chiral pyrrolidines (Figure 1.44). Again, for both strategies, he encountered significant problems trying to isolate the pyrrolidinium salts cleanly, if at all. The best *ee* was only 22%, achieved when employing crude **152** to epoxidize 1-phenylcyclohexene at 100 mol% loading. Clearly, these exocyclic iminium salts were not viable as enantioselective organocatalysts, and no further effort was directed towards their development.[168]

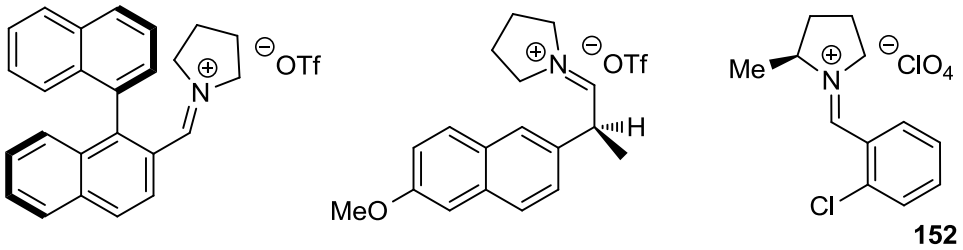
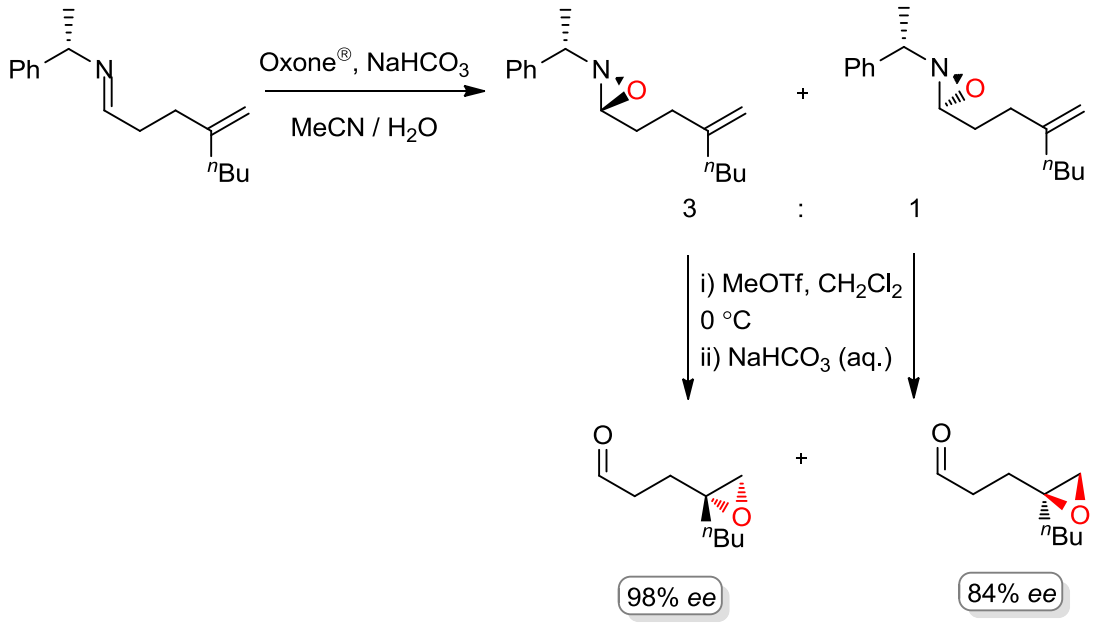


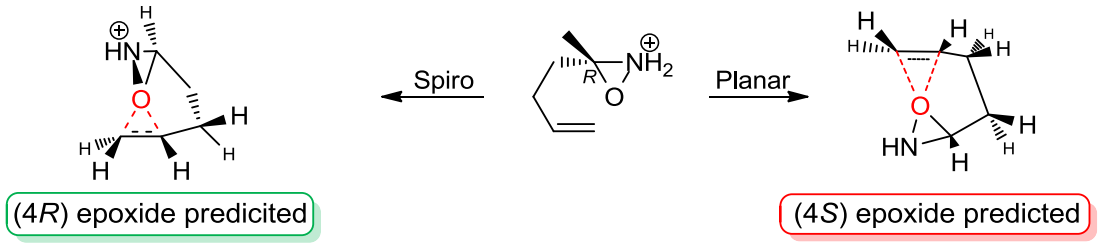
Figure 1.44: *Chiral pyrrolidinium catalysts synthesised by Armstrong.*

In 1999, Armstrong reported an extremely interesting intramolecular oxidation (Scheme 1.57). Oxidation of a chiral imine with Oxone®, synthesised by coupling an enantiopure amine to an unsaturated aldehyde, yielded a separable pair of diastereoisomeric oxaziridines. Methylation of the oxaziridine to generate the oxaziridinium salt, led to the concomitant transfer of the electrophilic oxygen to the pendent alkene. A basic work-up cleaved the imine and furnished the epoxy-aldehyde, usually in excellent *ee*.[169]



Scheme 1.57: *Preparation of the oxaziridine diastereoisomers in a 3:1 ratio. Oxidation of the oxaziridine motif and subsequent hydrolysis of the chiral auxiliary resulted in isolation of the epoxy aldehyde in excellent ee.*

This cunning procedure also provided much needed insight into the transition state of the epoxidation process (Scheme 1.58). Computational analysis of the epoxidation of a model substrate demonstrated that the epoxidation process prefers to proceed *via* the spiro TS in favour of the planar TS, analogously to the dioxirane systems. This hypothesis was consistent for all examples, with the major epoxide enantiomer observed suggesting the spiro TS.



Scheme 1.58: *Depiction of the possible spiro and planar transition states. Isolation of the 4R epoxide as the major enantiomer suggests that the epoxidation of alkene bonds by oxaziridinium salts favours the spiro TS.*

Computer studies, later performed by Houk, provided further evidence in support of the proposal that the reaction proceeds *via* the spiro TS.[170]

1.6.4.3 Komatsu's Exocyclic Iminium Salts

A short study into the synthesis and use of novel exocyclic iminium salts for asymmetric epoxidation was reported by Komatsu and co-workers in 2000. Initially, simple ring skeletons were screened for their effectiveness as epoxidation mediators (Figure 1.45).[171]

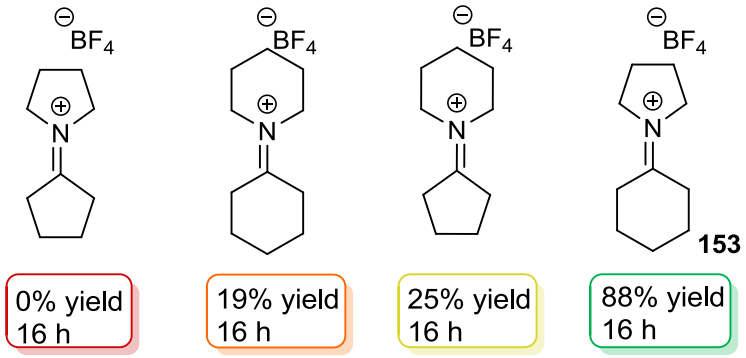


Figure 1.45: *Achiral, exocyclic iminium salts. Oxone® (1 equiv.), $NaHCO_3$ (4 equiv.), H_2O / MeCN, 10 mol% iminium salt, RT.*

Fortunately, unlike Armstrong's examples, these exocyclic iminium salts were synthesised easily by condensing cyclic amines with cyclic ketones under Dean-Stark conditions, in the presence of HBF_4. The most proficient catalyst skeleton proved to be **153**. Subsequently, a chiral variant **154** was synthesised from L-prolinol and screened and demonstrated to have reasonable catalytic efficiency. Unfortunately, with regard to the *ees* observed in the isolated epoxides, Komatsu and co-workers were left wanting (Figure 1.46).

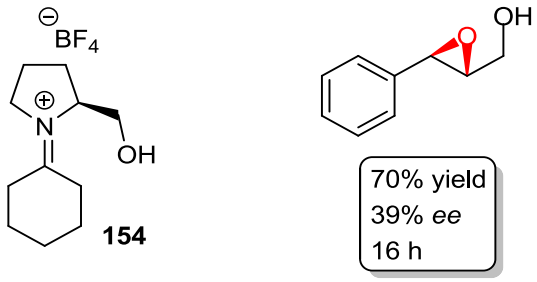


Figure 1.46: *Enantioselective epoxidation of cinnamyl alcohol. Oxone® (1 equiv.), $NaHCO_3$ (4 equiv.), H_2O / MeCN,* ***154*** *10 mol%, RT.*

1.6.4.4 Aggarwal's Studies

In 1996, Aggarwal reported the preparation of a binaphthyl-based iminium salt **155**, with which he was able to epoxidize 1-phenylcyclohexene with a 71% *ee* while employing only a 5 mol% catalyst loading (Figure 1.47).[172]

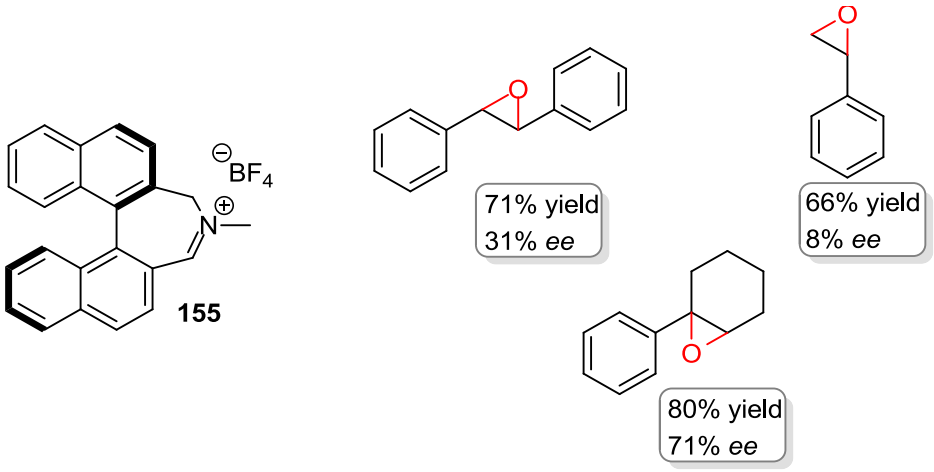
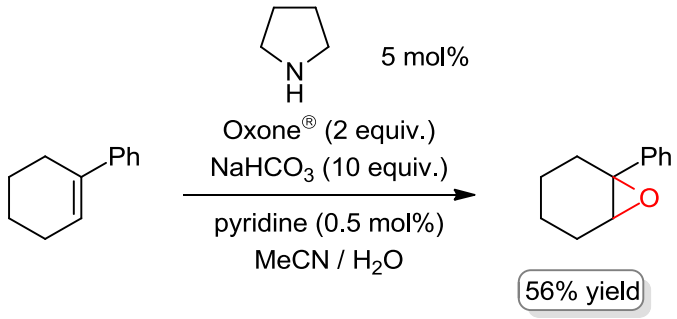


Figure 1.47: *Aggarwal's chiral binaphthyl catalyst and the epoxide ees achieved.*

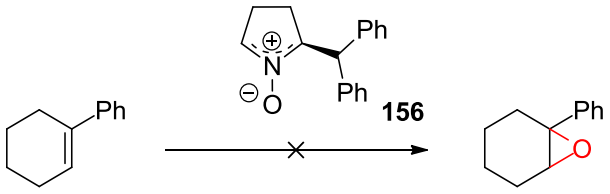
The idea of generating the iminium salt by condensing carbonyls with amines *in situ* was independently investigated by both Yang and Aggarwal.[173] While both groups found it was possible in certain instances, thus negating some synthetic investment in the catalyst, the most interesting result came from routine control experiments. It was observed by Aggarwal that the pyrrolidine fragment alone was capable of catalyzing the epoxidation (Figure 1.59).[174]



Scheme 1.59:. *Conditions under which Aggarwal and co-workers observed epoxidation using amines such as pyrrolidine. Pyridine is used to prevent the hydrolysis of the epoxide to the diol.*

To understand this process further, Aggarwal planned and executed a series of experiments to elucidate the role of the amine in the catalytic cycle. There is literature precedent for the oxidation of alkenes to occur *via* a radical cationic amine species.[175] Initial results obtained by the group seemed to suggest that this was plausible, however, these results were irreproducible and later discounted.[176]

It was theorized that an oxidized species of the amine - such as a nitrone - generated *in situ*, could catalyze the epoxidation. While the nitrone was found to be produced in the reaction mixture at RT, it was later proved not to be capable of oxidizing the alkene substrate (Scheme 1.60). Furthermore, when the reaction was performed at –10 °C, the amine could be recovered in good yield and the nitrone **156** was not observed.



Scheme 1.60: *A control experiment ascertained that the nitrone species **156** could not epoxidize the alkene under the reaction conditions.*

One important experiment utilized the HCl salt **157** as the catalytic entity. Aggarwal and co-workers found this salt was far more active than the neutral amine itself. This observation led the group to prepare ammonium salts **158** and **159**

(Figure 1.48). Contrastingly, a substantial drop in reactivity and enantioselectivity was observed when employing the tri-substituted salt **158**, and the quaternary ammonium salt **159** was exceptionally poor, behaving almost identically to the quaternary ammonium salt **160**. The authors note that these results suggested that the ammonium salt **157** was somehow activating Oxone® for nucleophilic attack, and that this behaviour was in addition to phase-transfer catalysis.[176]

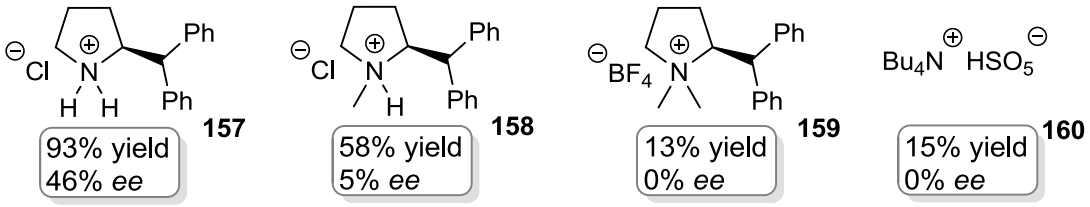


Figure 1.48: *The series of ammonium salts synthesised by Aggarwal that suggested salt **157** was somehow activating Oxone®.*

Aggarwal proposed that the catalytic behaviour of ammonium salt **157** in the presence of Oxone® could be explained by the existence of an electrophilically activating hydrogen bonding mode between **157** and the monoperoxysulfate component of Oxone® (Figure 1.49). To support this theory, salt **161** was synthesised and used to epoxidize a range of test substrates directly. It was found to produce identical results to when the HCl salt **157** was employed catalytically with Oxone®.

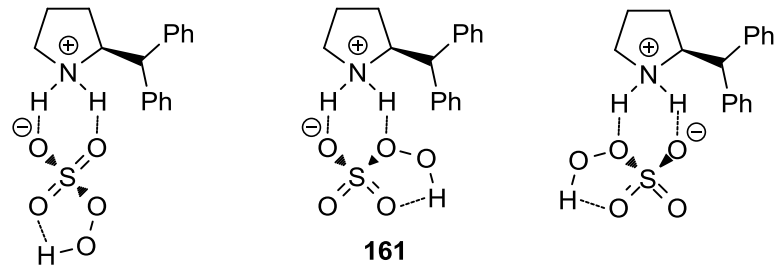


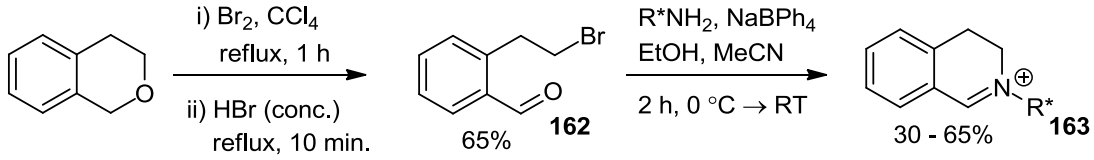
Figure 1.49: *Different bonding modes proposed by Aggarwal that explain why Oxone® was electrophilically activated.*

Potentially, there are several analogous bonding modes, differing in the orientation of the monoperoxysulfate anion. The existence of several of these

species was believed to have a negative effect on enantioselectivity, since each orientation would be expected to exert varying enantiocontrol.

1.6.4.5. Page's Studies

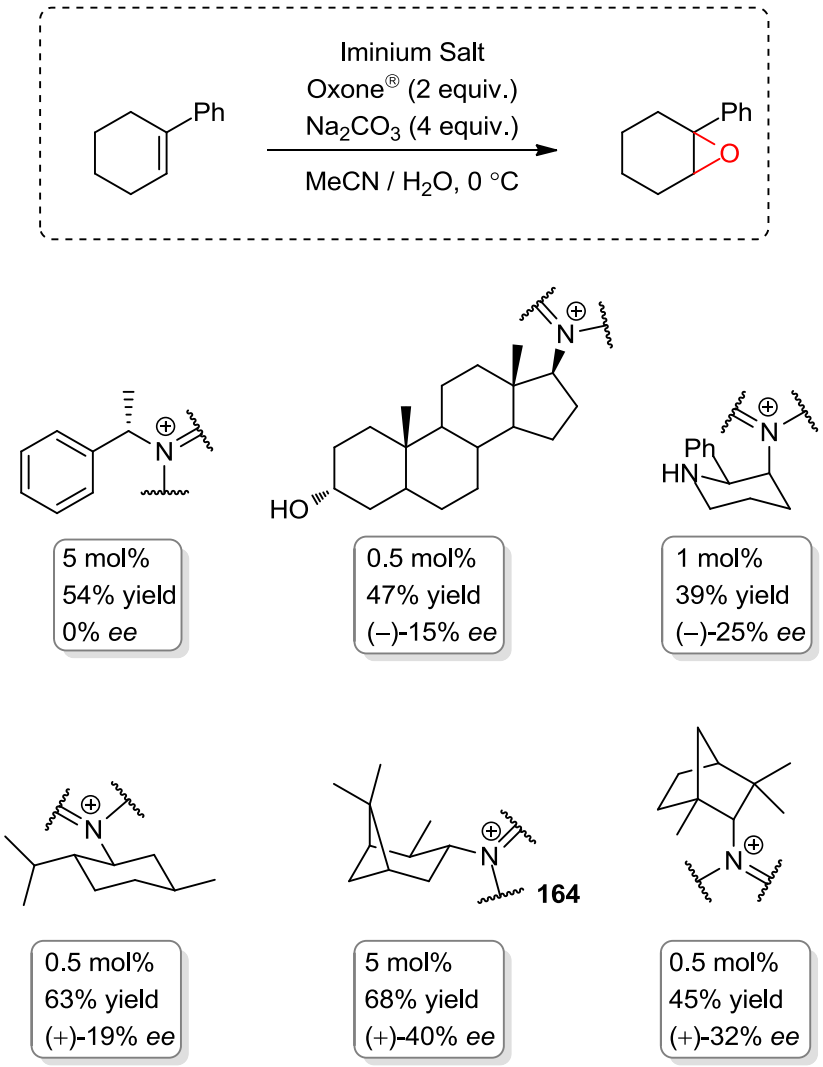
Page first reported his efforts towards designing iminium salts for organocatalytic asymmetric epoxidation in 1998; and since then, he has made significant contributions to this important area of research.[177] There were two main ideas that formed the concept for his catalyst design: the first was that chirality should be present as close as possible to the site of oxygen transfer as possible to enable the efficient relay of stereochemical information; secondly, it was important for the synthetic route to allow the incorporation of primary amines from the vast chiral pool to enable the rapid creation of a library of iminium salts (Scheme 1.61). Because of the demonstrated superiority of cyclic iminium salts over the acyclic analogues, the first structural class investigated was based on the cyclic dihydroisoquinolinium motif **163**.



Scheme 1.61: *Rapid synthesis of chiral dihydroisoquinolinium $^{-}BPh_4$ salts.*

The syntheses of the dihydroisoquinolinium salts were clean and rapid, requiring no column chromatography at any stage. The isolated yield of the salts were heavily dependent on the steric size of the amine; i.e. the larger amines produced lower yields probably due to their increased preference to act as bases, facilitating the decomposition of the bromaldehyde **162**. Impressively, the synthesis of the iminium-tetraphenylborate ($^{-}BPh_4$) salts from scratch through to isolation of the epoxide could be completed in as little as 6 h. Furthermore, in epoxidation catalysis only 0.5 mol% of iminium salt was required to achieve full conversion in 1

h in some instances – outperforming those previously synthesised by all other groups (Scheme 1.62).[177]

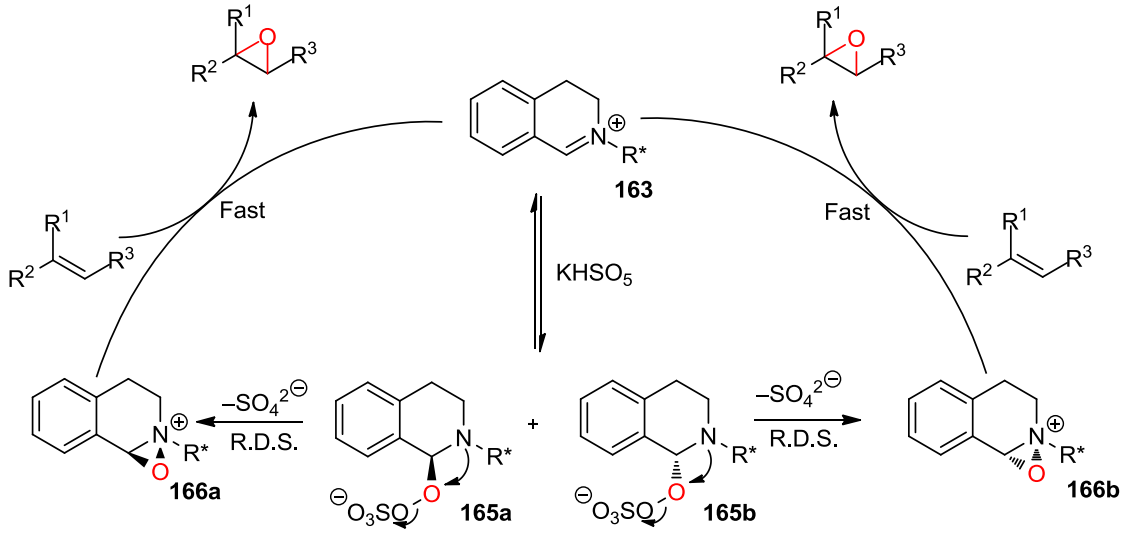


Scheme 1.62: *Screening of dihydroisoquinolinium salts for the epoxidation of 1-phenylcyclohexene.*

After screening the catalysts against a model, substrate 1-phenyl cyclohexene, catalyst **164** was singled out and used to epoxidize several other substrates. The best result was achieved when employing **164** at 10 mol% loading for the epoxidation of *trans*-stilbene in 73% *ee*.

In order better to understand the epoxidation system, and perhaps to establish leads into possible optimization and development pathway, an exploratory study of the reaction parameters was undertaken.[178] Some basic

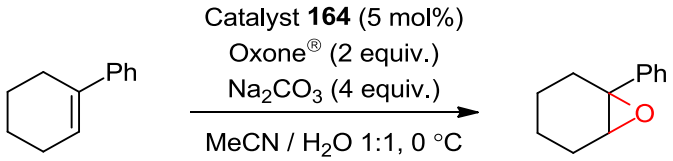
mechanistic insight was provided by the investigation, and the proposed catalytic cycle is presented below (Scheme 1.63).[179]



Scheme 1.63: *Proposed catalytic cycle involving the nucleophilic attack of the iminium moiety by Oxone® and subsequent expulsion of sulfate to form the reactive oxaziridinium species. There is the complication of the potential formation of a diastereoisomeric oxaziridinium pair, which would be expected to lower epoxide ees.*

The iminium salt **163** can be attacked reversibly by persulfate from either its *si* or *re* face; theoretically forming diastereoisomeric adducts **165 a** or **b**. Irreversible ring closure and expulsion of sulfate is believed to be the rate determining step and forms a diastereoisomeric pair of oxaziridinium species, which were expected to impart differing, if not opposing, levels of enantioselectivity. Transfer of the oxygen from the oxaziridinium species to the substrate regenerates the iminium salt, and is believed to be fast and non-rate determining.

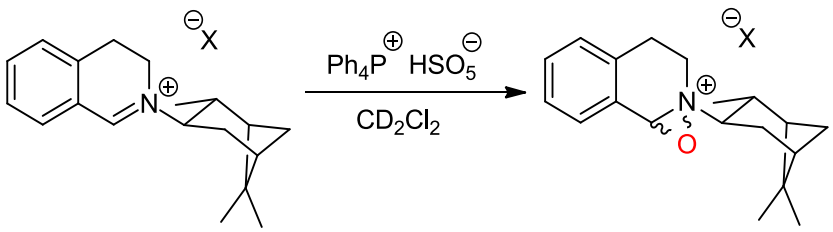
Effect of Counter-Ion: Several anion pairings of *N*-isopinocampheyl catalyst **164** were prepared and assessed for their relative reactivity and enantiocontrol for the epoxidation of 1-phenylcyclohexene (Table 1.8).



Entry	Counter-Ion	*ee* (%)	Conv. (%)
1	$^{-}BPh_4$	(+)-40	100
2	$^{-}BF_4$	(+)-28	100
3	$^{-}PF_6$	(+)-28	100
4	$^{-}IO_4$	(+)-35	100
5	$^{-}ClO_4$	(+)-20	100

Table 1.8: *Effect of the counter-ion on epoxide ee. All reactions ran to completion in ≤45 min, and all epoxide configurations were (R,R).*

Having established that perchlorate and periodate were not oxidizing catalyst **164**, or the alkene, the results suggested that the catalytic species existed as ion pairs in solution and that the anion had a significant influence on *ee* in this system. It was suggested that the anion amplifies the intrinsic enantioselectivity of the iminium salt by further differentiating the activation energies for the diastereoisomeric transition states. It has been shown that the diastereoselectivity in the transfer of oxygen to the iminium species is partly controlled by the counter-ion (Table 1.9).



Entry	Counter-Ion	*dr*	*ee (%)*
1	$^{-}BPh_4$	27 : 73	33
2	$^{-}BF_4$	34 : 66	32
3	$^{-}PF_6$	31 : 69	31
4	$^{-}ClO_4$	42 : 58	22

Table 1.9: *Determination of the oxaziridinium diastereoisomeric ratio by NMR spectroscopy.*

The same experiment also suggested that the subsequent transfer of oxygen to the substrate was sensitive to the counter-ion because the relationship between the diastereoisomeric ratio and the *ee* was not linear. For example, the $^{-}BF_4$ species had a ratio of 34:66 and an *ee* of 32% whereas the $^{-}PF_6$ species possessed a greater diastereoenrichment of 31:69 yet it gave a marginally lower *ee* of 31%. So it is probable that the counter-ion does influence the relative energies of the diastereoisomeric transition states of both oxygen transfer steps.[180]

Effect of Solvent System: Several solvents were chosen, such that a range of dielectric constants were covered, (ε): CH_2Cl_2 (8.9), trifluoroethanol (26.7), MeCN (37.5), water (78.4), DMF (109.0), formamide (111.0), (Table 1.10).

Entry	Organic Solvent	Counter-Ion	Time (h)	Conv. (%)	*ee* (%)
1	CH_2Cl_2	$^-ClO_4$	3	50	33
2	CF_3CH_2OH	$^-ClO_4$	0.5	100	26
3	MeCN	$^-ClO_4$	0.5	100	20
4	H_2NCHO	$^-ClO_4$	3	0	-
5	CH_2Cl_2	$^-BPh_4$	3	0	-
6	CF_3CH_2OH	$^-BPh_4$	0.5	100	26
7	MeCN	$^-BPh_4$	0.5	100	40
8	H_2NCHO	$^-BPh_4$	3	0	-

Table 1.10: *Comparison between organic co-solvents used with water 1:1.*

Interestingly, no reaction occurred with formamide and it was suggested this was either due to irreversible attack of the iminium salt by formamide, or that the iminium salts are just too well solvated and therefore rendered unreactive. In contrast, the epoxidation does proceed in DMF (65% in 4 h) and its dielectric constant is equally high.

Employing trifluoroethane as co-solvent provided an interesting result. When the iminium salts paired with the periodate anion were screened, the epoxide *ees* and reactivity were the same - suggesting that the generation of the trifluroroethoxide anion pair occurs and displaces the original anion.

The solvent with the lowest dielectric constant, CH_2Cl_2, provided the poorest reactivity – believed to be due to the poor availability of Oxone® in the organic phase. Although, more recently, Lacour has enjoyed much success employing CH_2Cl_2 along with the phase-transfer catalyst 18-crown-6 ,which acts to increase the concentration of the oxidant in the presence of the catalyst.[181]

The best organic co-solvent used, in terms of both enantioselectivity and reactivity, was MeCN. The ratio of MeCN to water was investigated, and it was found that increasing the proportion of water significantly increased the rate of reaction without affecting epoxide *ees*, this was particularly true for low catalyst loadings of 0.5 mol%. Higher catalyst loadings of 5 mol% outweighed the

accelerating effect of water - using any H_2O / MeCN ratio from 1:9 to 9:1 led to full conversion in ≤20 min. The fact that the rate increase is observed alongside unchanged epoxide *ees* when increasing the ratio of water in the solvent system supports that the formation of adduct **165** is indeed the rate determining step It was proposed that the rate increase is due to increased Oxone® solubility and the increased solvation of the leaving sulfate group.

Effect of Temperature: Page and co-workers investigated the effect of temperature on the system's behaviour. It was a limited study as the characteristics of Oxone® only allowed for a narrow range of temperatures to be surveyed. The solubility of Oxone® at temperatures below 0 °C, when employing a 1:1 MeCN / H_2O solvent system, drops off dramatically - its availability is therefore decreased and the reaction effectively stops. It is mentioned above that the rate of reaction increased significantly when a greater ratio of water in the solvent system was employed, and a 1:3 MeCN / H_2O solvent system offset the decreased solubility and allowed the temperature to be decreased to –10 °C, although this made little difference to the *ee* of the isolated epoxide.

Decomposition of Oxone® was rapid under the alkaline epoxidation conditions at much above RT and negligible conversion was observed at >25 °C. Across the functional temperature range studied the *ees* of the isolated epoxides remained consistent.

Effect of Catalyst Loading: The trend in *ee* caused by the variation of catalyst loading suggested that it was an important parameter. Since it had been established that no background epoxidation occurs in the absence of an iminium salt catalyst, the pattern of *ees* supported the proposal that it was the breakdown of the ion-pairs at low concentration that caused the sharp drop-off (Figure 1.50).

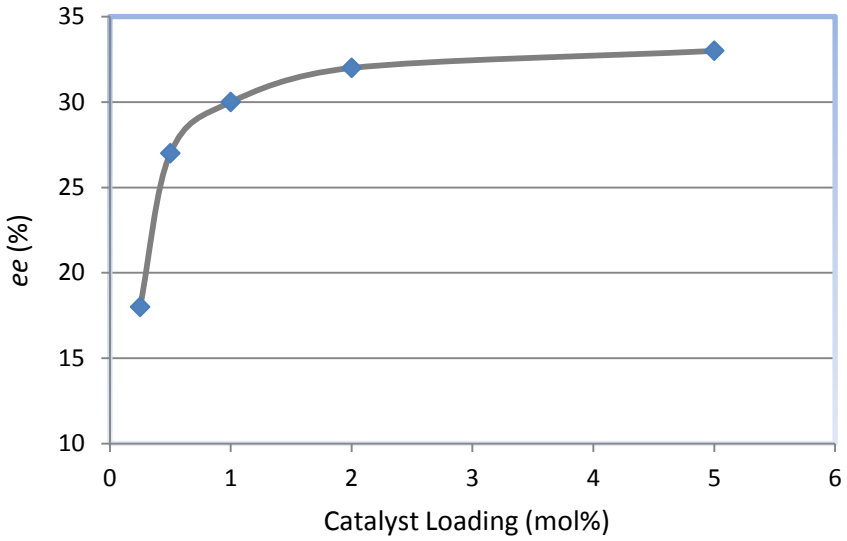


Figure 1.50: *Graph indicating the dependence of catalyst loading on the isolated ee of 1-phenylcyclohexene oxide.*

As mentioned above, the counter-ion was believed to play an important role in maintaining the integrity of the transferral of stereochemical information from the catalyst to the substrate. Thus, if the ion-pair is dissociated in solution, the enantioselectivity of the process decreases.

By studying reaction parameters Page was able better to understand the iminium salt-mediated epoxidation system. Page noted that because the step in which enantioselectivity is imparted is non-rate determining, there was great potential to increase the enantioselectivity of the system without affecting the rate deleteriously.[178] Also, a rather obvious problem for iminium salt catalysts was the formation of the diastereoisomeric oxaziridinium species. In order better to control the diastereoselectivity of oxaziridinium formation, Page believed it would be possible to direct the stoichiometric oxidant to one face of the iminium bond by incorporating polar, co-ordinating functionality into the pendent chiral amine (Figure 1.51). To this end, a small family of catalysts derived from 1,2-aminoalcohols were prepared and screened.[179]

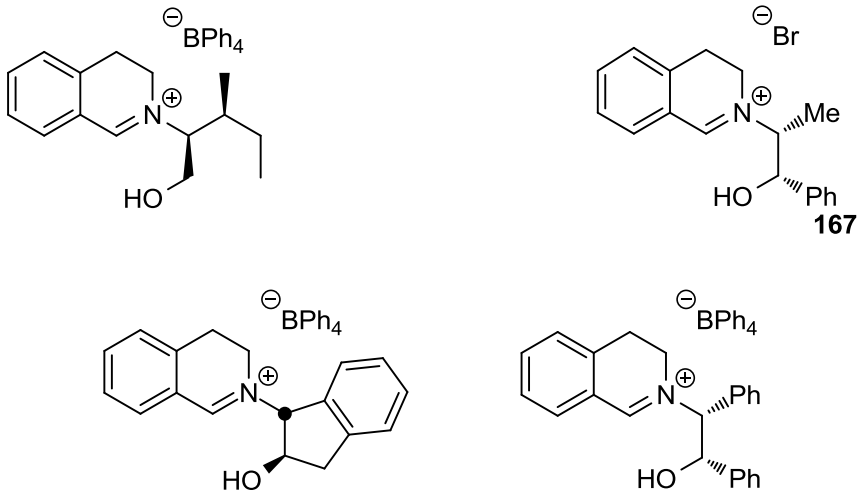
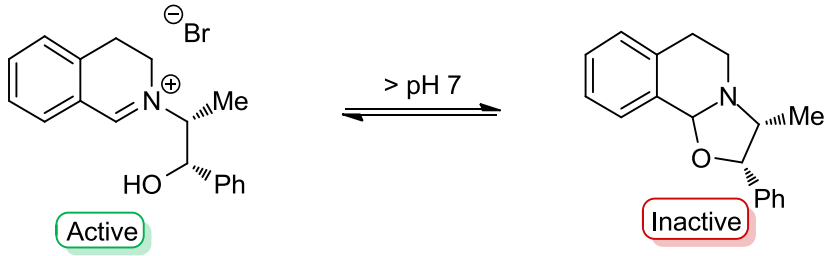


Figure 1.51: *Dihydroisoquinolinium catalysts prepared from chiral 1,2-aminoalcohols by Page.*

It was immediately evident that these new catalysts were less active than previous iterations. It is believed that this behaviour was due to the equilibrium between the ring-open (active) and ring-closed (inactive) forms in the slightly basic epoxidation conditions (Scheme 1.64).



Scheme 1.64: *Equilibrium between the active and inactive forms of the iminium salt* ***167*** *believed to operate under the alkaline reaction conditions.*

Catalysts bearing a primary hydroxyl group all imparted almost zero enantioselectivity on test alkene substrates. In contrast, those bearing a chiral secondary hydroxyl group did impart some enantioselectivity (12-33% *ee*), although they were even less active than the primary hydroxyl derivatives, requiring up to five times the catalyst loading to achieve the same conversion.

To address this deactivating equilibrium process, Page prepared a range of ether derivatives, maintaining the coordinating ability of the oxygen, but, crucially,

rendering it much less nucleophilic (Figure 1.52). Unfortunately, the epoxide *ees* attained when using the catalysts were only in single figures, although they did demonstrate greater reactivity than the hydroxyl-bearing catalysts.[179]

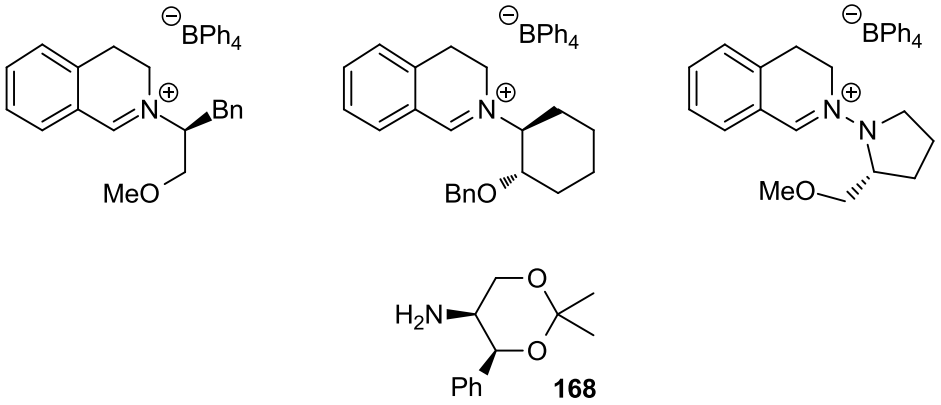


Figure 1.52: *Ether-containing catalysts prepared by Page, and (S,S)-acetonamine* ***168****.*

While experimenting with the ether-containing chiral amines, Page and co-workers investigated (*S*,*S*)-acetonamine **168**, which was prepared from ketalization of (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol. The synthesis of **169** was high yielding and it proved to be a far superior catalyst to **164**. In fact, amine **168** and derivatives thereof, are now used exclusively in Page's most recent and successful catalyst designs.

Having identified a chiral amine that possessed significant potential, Page and co-workers sought to investigate other 'backbone' moieties to use in conjunction with **168** in the hope improving enantioselectivity and reactivity.[182] A series of catalysts featuring the azepinium ring system, the type first employed by Aggarwal for asymmetric epoxidation, were prepared from 2,2'-bis(hydroxymethyl)biphenyl in a similar manner to the dihydroisoquinolinium species and tested under Page's standard epoxidation conditions (Figure 1.53).

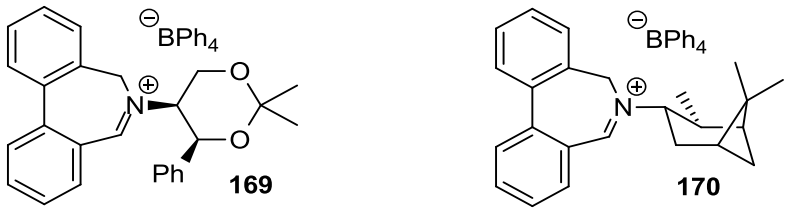


Figure 1.53: *Biphenyl-azepinium catalysts prepared by Page and co-workers.*

It was immediately apparent that these new *tropos* azepinium catalysts were very reactive; in some instances full conversion was observed within 3 min when using a 5 mol% loading. Catalyst **169** was particularly active and it also demonstrated good enantiocontrol in the epoxidation process (Figure 1.54).

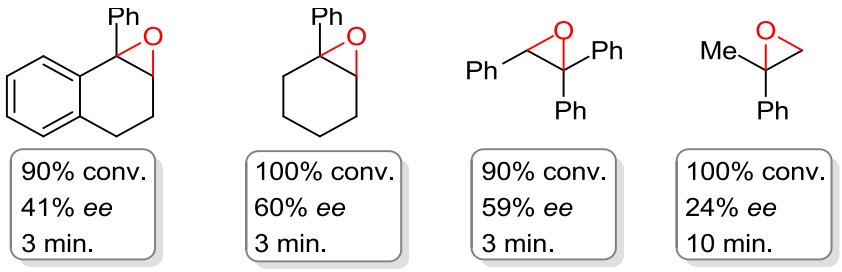


Figure 1.54: *A sample of epoxidation results using a new azepinium salt catalyst. Catalyst* ***169*** *(5 mol%), Oxone® (2 equiv.),* Na_2CO_3 *(4 equiv.), MeCN /* H_2O *(1:1), 0 °C.*

Having established that the (*S*,*S*)-acetonamine-containing azepinium motif was very reactive, and with the aim of improving the observed epoxide *ees*, Page incorporated the *atropos* binaphthylene backbone to introduce another source of chiral information to the catalyst structure in the hope that it would reinforce that already possessed by **168** (Figure 1.55).[183]

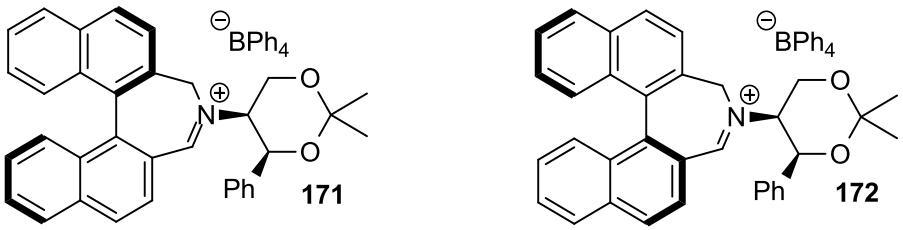


Figure 1.55: *The so-called 'matched'* ***171*** *and 'mismatched'* ***172*** *BINOL-derived catalysts.*

Both diastereoisomers were synthesised, and, through screening, it was apparent that they possess startlingly different reactivity (Figure 1.56). The (R_a)-binaphthylene azepinium **171** demonstrated excellent enantiocontrol in the epoxidation process and was very reactive indeed; whereas (S_a)-binaphthylene-azepinium **172** was an inefficient catalyst, resulting in poor conversion (<5%) under the reaction conditions in most cases. Evidently, the constituent chiral amine and backbone of the 'matched' azepinium were acting synergistically, resulting in a catalyst that was the most enantioselective iminium salt catalyst to date (up to 95% ee). Of course, the opposite was true of the 'mismatched' diastereoisomers where the chiral elements combined to be destructive to catalytic behaviour.

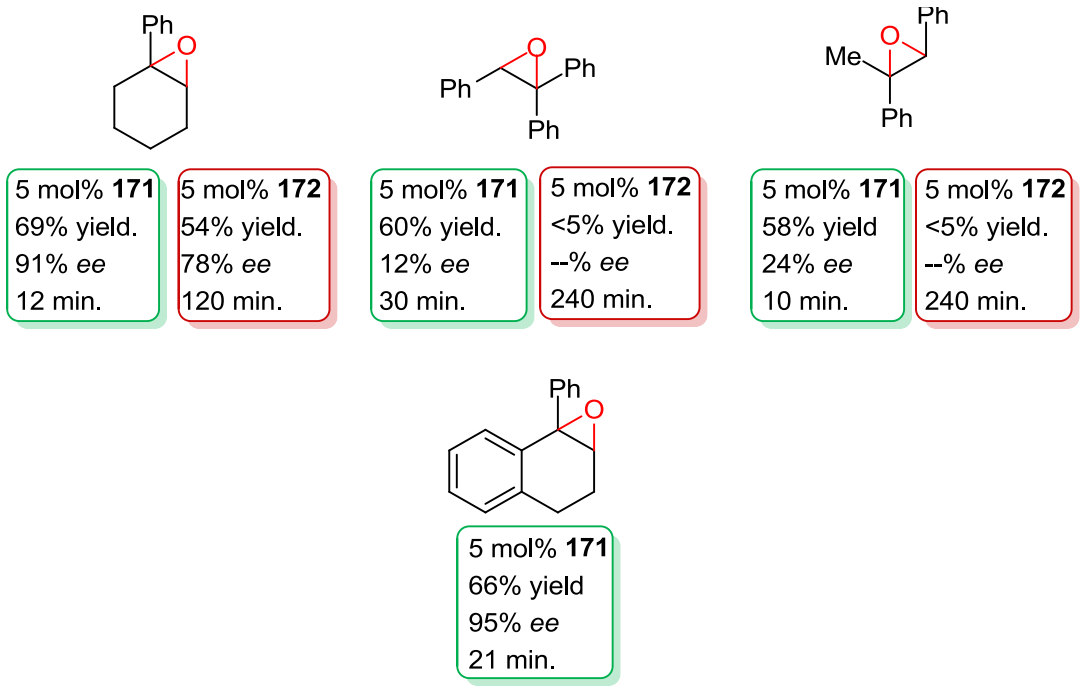


Figure 1.56: *Substrate screen with 'matched' catalyst **171** (green), and 'mismatched' catalyst **172** (red). Oxone® (2 equiv.), Na_2CO_3 (4 equiv.), MeCN / H_2O (1:1), 0 °C.*

Remarkably, catalyst **171** was still potent at 0.1 mol%, with the epoxidation of 1-phenylcyclohexene running to full conversion in 88% *ee* after only 6 h. On average, therefore, the catalyst is performing 1000 turnovers, which for an organocatalyst was unprecedented.[183]

Following the success of catalysts containing **168**, a whole series of amines varying in their stereochemistry and functionality were synthesised to determine why it was a successful pendent amine and also to try to improve upon it. The amines were condensed with bromaldehyde **162** to generate their respective catalysts (Figure 1.57).[184]

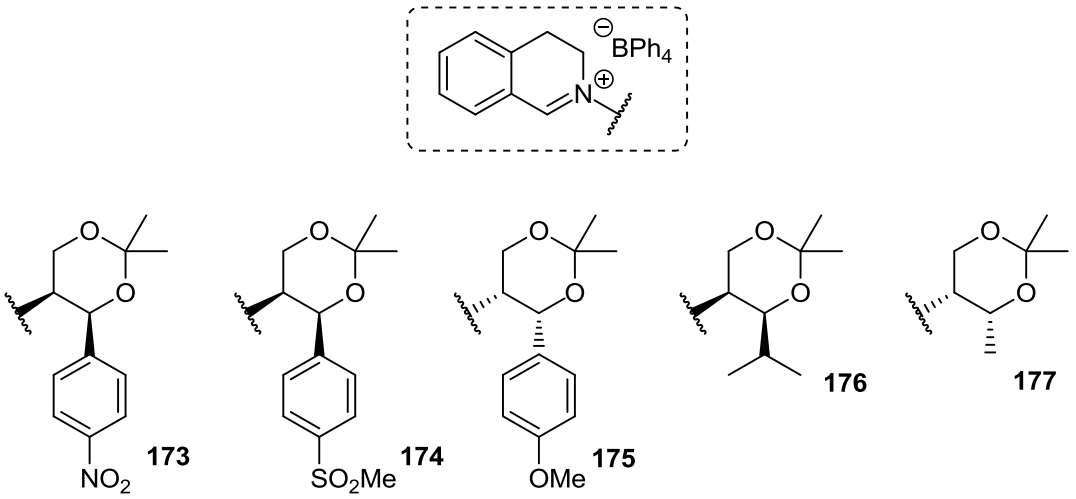


Figure 1.57: *An example of other chiral dihydroisoquinolinium salts investigated by Page to gain an insight into the importance of certain structural features.*

The isolated $^{-}BPh_4$ dihydroisoquinolinium salts were employed in the epoxidation of tri- and di-substituted alkenes under Page's standard MeCN/H_2O conditions. The *para*-substituted aryl catalysts **173** and **174** demonstrated slightly reduced asymmetric induction in comparison with **169**, but the electron-rich *para*-methoxy substituted catalyst **175** elicited superior enantiocontrol than **169** in some instances, but it was not as reactive. Interestingly, catalysts **176** and **177**, although reactive, imparted almost no enantioselectivity (<5%) (Table 1.11).

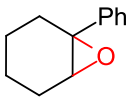
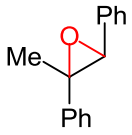
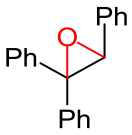
	Catalyst					
Alkene	**169**	**173**	**174**	**175**	**176**	**177**
	100% conv. 60% *ee* (–)-(1*S*,2*S*)	48% conv. 38% *ee* (–)-(1*S*,2*S*)	47% conv. 56% *ee* (–)-(1*S*,2*S*)	63% conv. 50% *ee* (+)-(1*R*,2*R*)	<5% *ee*	<5% *ee*
	95% conv. 37% *ee* (–)-(1*S*,2*S*)	30% conv. 17% *ee* (–)-(1*S*,2*S*)	100 conv. 21% *ee* (–)-(1*S*,2*S*)	61% conv. 50% *ee* (+)-(1*S*,2*S*)	No Result	No Result
	90% conv. 59% *ee* (+)-*S*	22% conv. 11% *ee* (+)-*S*	55% conv. 10% *ee* (+)-*S*	63% conv. 26% *ee* (–)-*R*	No Result	No Result

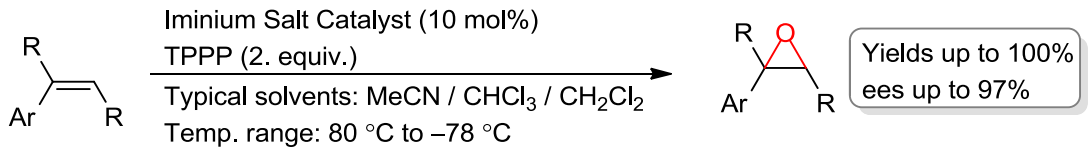
Table 1.11: *Screening of new acetonamine-type catalysts. Iminium salt (10 mol%), Oxone® (2 equiv.), Na_2CO_3 (4 equiv.), MeCN / H_2O (1:1), 2 h, 0 °C.*

Analysis of the results suggested that the presence of an aromatic group on the acetonamine derivatives was crucial to obtaining significant enantioselectivity in the epoxidation process.

Water is required in the above systems to solubilize Oxone®, and without water the reaction does not proceed.[185] A major disadvantage of the aqueous conditions described thus far, is that there is a strict lower limit to the temperatures that can be used owing to the freezing point of water. Lowering the temperature is advantageous, because according to the Boltzmann distribution, which describes the energies of molecules in a bulk substance, epoxide *ees* should improve with cooling; i.e., colder temperatures led to greater differentiation between the diastereoisomeric transition states. Thus, the development of the non-aqueous conditions required the employment of an oxidant that was readily solvated by organic solvents; ensuring its availability to participate in the catalytic cycle.

Page investigated many stoichiometric oxidants for use under the new non-aqueous conditions; some caused achiral background epoxidation (peracids, persulfates) while the rate of reaction was impractically low for others (perselenates, iodosobenzene diacetate, perborates). The best candidate turned out to be a modified Oxone® species – tetraphenylphosphonium

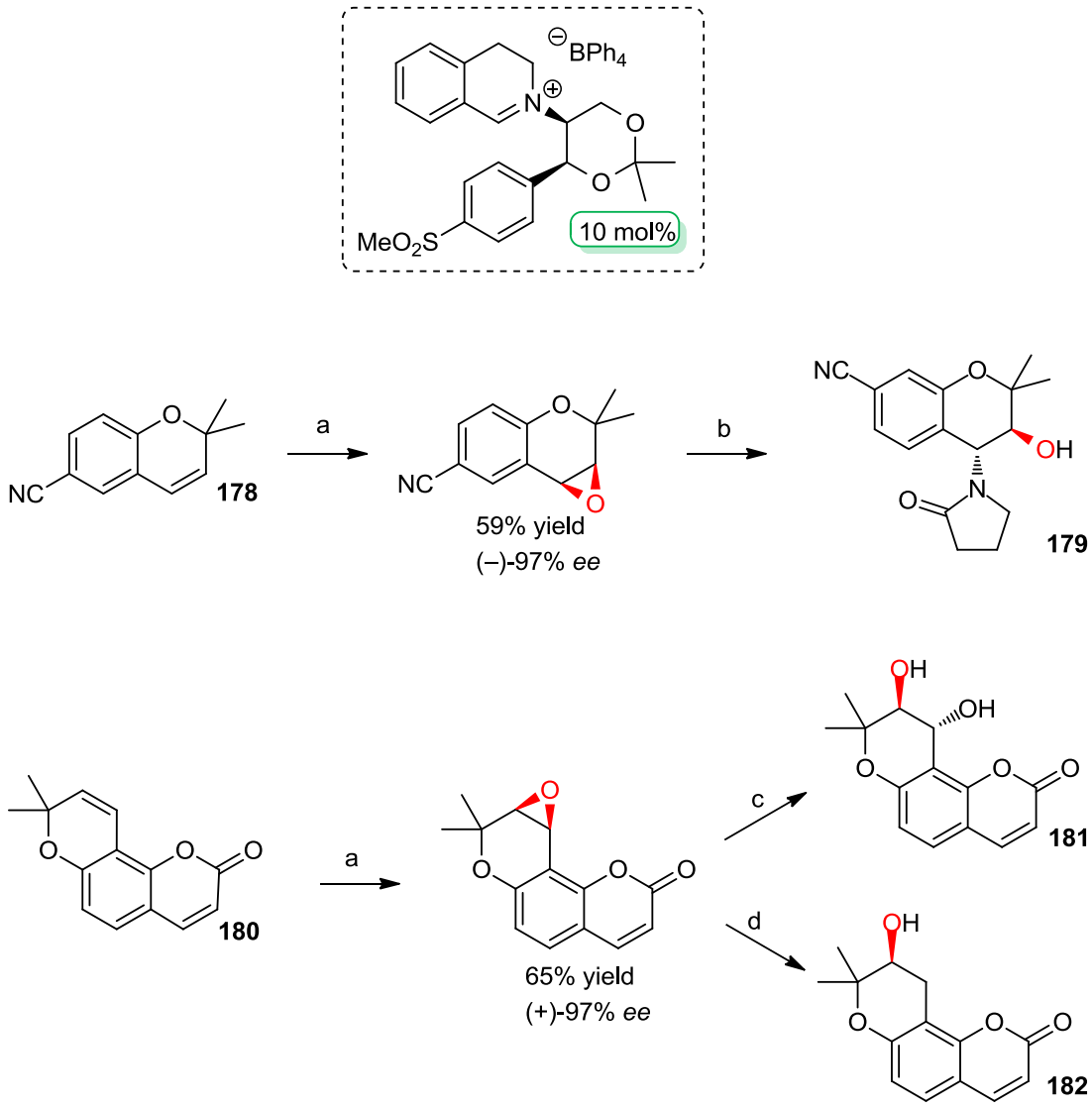
monoperoxysulfate (TPPP), first reported by Di Furia for oxidation of manganese porphyrin species.[186] It exhibited excellent reactivity while causing no background epoxidation, andits employment led to the creation of an extremely efficient epoxidation system (Scheme 1.65).



Scheme 1.65: *Non-aqueous conditions developed by Page.*

Performing the epoxidations at much cooler temperatures was made practical by using the non-aqueous conditions. Another advantage of the non-aqueous system was its simplicity; no form of base is needed and the work-up only required the dilution of the reaction mixture with Et_2O to precipitate excess TPPP and its by-products, followed by a filtration. Also, if the reaction had run to completion, the epoxide was the only product and it could be isolated in excellent purity.[187]

It was discovered that, under the non-aqueous conditions, catalyst **174** displayed excellent enantioselectivity for *cis*-disubstituted alkenes.[13] Page was able to utilize this catalyst for the highly enantioselective total synthesis of several natural products, all featuring asymmetric epoxidation mediated by **174** as the key step: (–)-cromakalim **179**,[13] (+)-(3*S*,4*R*)-*trans*-khellactone **181,**[188] and (–)-(3*S*)-lomatin **182** [188] (Scheme 1.66).



Scheme 1.66: *Total syntheses of (–)-cromakalim, (+)-(3S,4R)-trans-khellactone and (–)-(3S)-lomatin. a) Alkene (1 equiv.),* ***174*** *(10 mol%), TPPP (2 equiv.), $CHCl_3$, –40 °C - (6-cyano-2,2-dimethylbenzopyran* ***178****) or –30 °C - (seselin* ***180****). b) Pyrrolidin-2-one, NaH, DMSO, RT, 52%. c) 1M H_2SO_4 (aq.), acetone, RT, 95%. d) $NaBH_3CN$ (1 equiv.), $BF_3{\cdot}OEt_2$, THF, 0 °C, 92%.*

Recently, Page has also explored other variants of the aqueous systems, principally trialling other stoichiometric oxidants.[189] Hydrogen peroxide was investigated as it is one of the most environmentally friendly oxidants; it has a high active oxygen content and its reduced product is water. Sodium hypochlorite has also been employed under the aqueous conditions, but the results were much

poorer than when employing Oxone®, and catalyst degradation was an important factor in contributing to this.[190] Page has described an interesting oxidant system in which the stoichiometric oxidant was generated *in situ* electrochemically. The results were comparable to those achieved when employing Oxone®, and the technique is under further development.[191]

1.6.4.6 Lacour's Studies

Preceeding their contributions to the field of iminium salt-mediated organocatalysis, Lacour and co-workers reported the preparation and resolution of the chiral anion tris(tetrachlorobenzenediolato)phosphate (V) or 'TRISPHAT' **183** (Figure 1.58).[192] It had been successfully used as an NMR chiral shift reagent, as well as a resolving agent for organometallic species and cationic organic salts.[193] A TRISPHAT ion-pair is highly lipophilic, easily solvated by organic solvents and does not partition itself in an aqueous layer.[194]

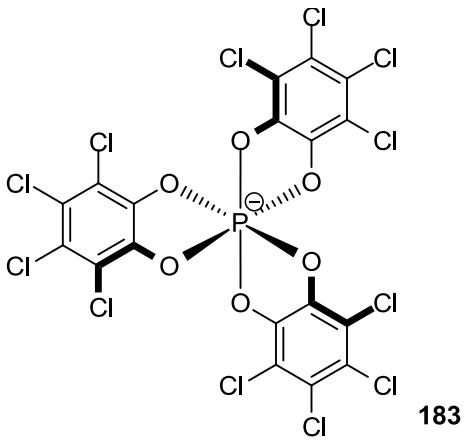


Figure 1.58: The *Δ-TRISPHAT anion designed by Lacour.*

Following the evidence for a charged transition state for the oxygen transfer, Lacour envisaged that if one could engineer the epoxidation to occur only in the organic phase, the charged diastereoisomeric transition states would be less stabilized, which would hopefully facilitate improved differentiation between the two conformations of the transition states, and led to greater enantioenrichment of

the resulting epoxides.[181] To investigate this idea, Lacour and co-workers prepared a range of iminium salts paired with enantiopure TRISPHAT. Taking the efficient iminium salt **169**, described above, both diastereoisomers of the TRISPHAT ion pairs were synthesised and isolated **184**. A non-chiral iminium salt was also prepared **185** as a standard to determine if the chiral anion caused any stereoinduction (Figure 1.59).[181]

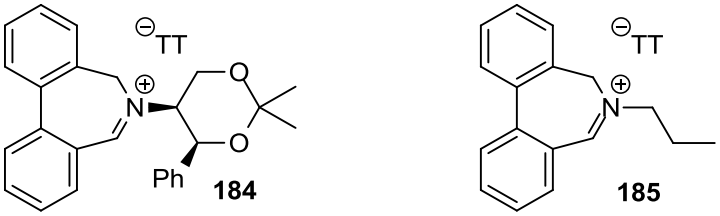
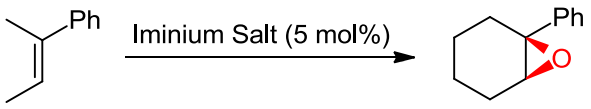


Figure 1.59: *Example ion-pairs prepared by Lacour. TT = TRISPHAT. Both the Δ and Λ enantiomers were used separately to generate diastereoisomeric ion-pairs.*

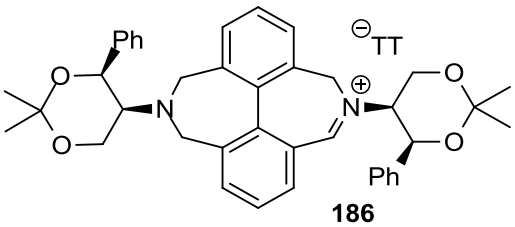
A comparison was made with Page's $^{-}BPh_4$ species under the polar MeCN / H_2O conditions. Interestingly, a near identical result was attained – Lacour stated this was probably due to the ion-pairs being fully disassociated in the polar medium, (Table 1.12).[195] Under the new biphasic conditions, however, a meaningful jump in epoxide *ee* was observed. It was evident that the chirality of the anion had no stereochemical influence on the epoxidation process as both diastereoisomeric ion pairs gave identical epoxide *ees* and also the achiral iminium salt that was paired with Δ-TRISPHAT imparted no stereoinduction. For the biphasic conditions, PTC 18-crown-6 was required to transfer the monoperoxysulfate component of Oxone® into the organic layer to allow the oxidation of the iminium salt.



Entry	Iminium	Anion	Solvent System	Conv. (%)	*ee* (%)
1	184	$-BPh_4$	MeCN / H_2O 1:1, 0 °C	100	(–)-60
2	184	ΛTT–	MeCN / H_2O 1:1, 0 °C	100	(–)-61
3	184	ΔTT–	CH_2Cl_2 / H_2O 3:2, 18-crown-6, 0 °C	100	(–)-69
4	184	ΛTT–	CH_2Cl_2 / H_2O 3:2, 18-crown-6, 0 °C	100	(–)-69
5	185	ΔTT–	CH_2Cl_2 / H_2O 3:2, 18-crown-6, 0 °C	100	0

Table 1.12: *Screening of the new the biphasic conditions and TRISPHAT counter-ion through the epoxidation of 1-phenylcyclohexene.*

Lacour has made significant advances in catalyst design in recent years and this began with the synthesis of doubly-bridged biphenyl species, such as **186** (Figure 1.60).[196]



186

Figure 1.60: *A doubly-bridged biphenyl iminium salt.*

The DBB iminium salts led to an appreciation of the influence of the two dihedral angles within the aromatic backbones on the enantioselectivity of the epoxidation process. It has been reported that the dihedral angle is an important parameter in enantioselective catalytic transformations and Lacour took this into consideration for catalyst development (Figure 1.61).

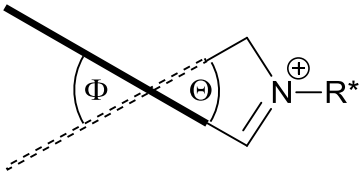
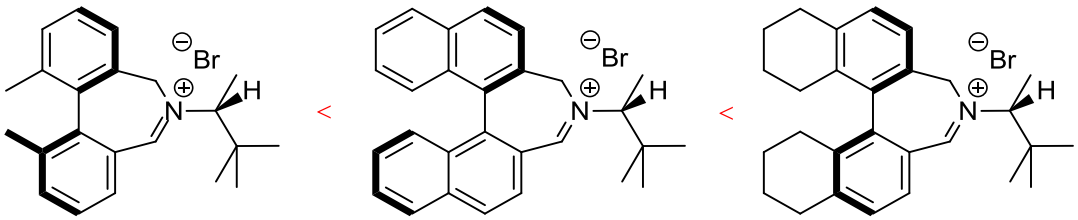


Figure 1.61 *Illustration of the internal and external dihedral angles – θ and Φ respectively.*

To probe this effect, three backbone moieties were selected that covered a range of dihedral angles: the 6,6'-dimethylbiphenyl, binaphthyl, and 5,5',6,6',7,7',8,8'-octahydrobinaphthyl (Figure 1.62).[197] Lacour has incorporated several different chiral amines in his catalyst designs. In this study, designs containing 3,3-dimethyl-2-butylamine were the most proficient, and a comparison of the three iminium salts **187**-**189** which probes the effect of the dihedral angles is offered below (Table 1.13). The iminium salts in this study were prepared *in situ*; the precursor azepines were stirred for ≈5 min prior to their use and were the bromide salts.



Θ ≈ 52.2°
Φ ≈ 57.5°

Θ ≈ 51.6°
Φ ≈ 61.0°

Θ ≈ 55.1°
Φ ≈ 67.0°

Figure 1.62: *6,6'-dimethylbipheny* ***187****, binaphthyl* ***188****, and 5,5',6,6',7,7',8,8'-octahydrobinaphthyl* ***189*** *derived iminium salts featuring (R)-3,3'dimethyl-2-butylamine. The dihedral angles shown are from a related iminium salt series featuring (S)-1-phenyl-1-propylamine and are offered to provide a sense of scale.*

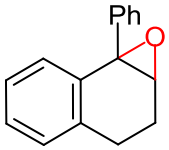
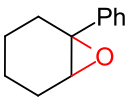
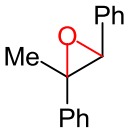
Alkene	187	188	189
	(+)-57% *ee*	< (+)-85% *ee*	< (+)-92% *ee*
	(–)-67% *ee*	< (–)-75% *ee*	< (–)-83% *ee*
	(–)-44% *ee*	< (–)-54% *ee*	< (–)-67% *ee*

Table 1.13: *Substrate screen. Iminium salt (5 mol%), Oxone® (1 equiv.), $NaHCO_3$ (4 equiv.), 18-crown-6 (2.5 mol%), CH_2Cl_2 / H_2O (3:2), 0 °C*

Clearly, increasing the dihedral angle has the effect of increasing the isolated epoxide *ees* over this range. The external dihedral angle Φ offers the best correlation with epoxide *ee*. A slight increase in *ee* was observed on employing the pre-isolated $^{-}BPh_4$ salts, concurring with Page's results during his investigation of the effect of the counter-ion.

Lacour and co-workers recently reported an interesting consequence of using the $^{-}BPh_4$ counter-ion – increasing the catalyst loading decreased the isolated epoxide *ees*. In searching for an explanation of this behaviour, large amounts of 1,1'-biphenyl were observed in reaction mixture. It was proposed that 1,1'-biphenyl arose from the oxidative breakdown of the counter-ion; indeed, stirring $NaBPh_4$ with Oxone® led to the production of 1,1'-biphenyl.[198]

The counter-ion was switched for an oxidatively-stable $^{-}SbF_6$ anion AND the resulting catalyst has since been used at low loadings (2.5 mol%) to oxidize two classes of substrates: tri-substituted unfunctionalized alkenes and tri-substituted allylic alcohols (Figure 1.63).[199]

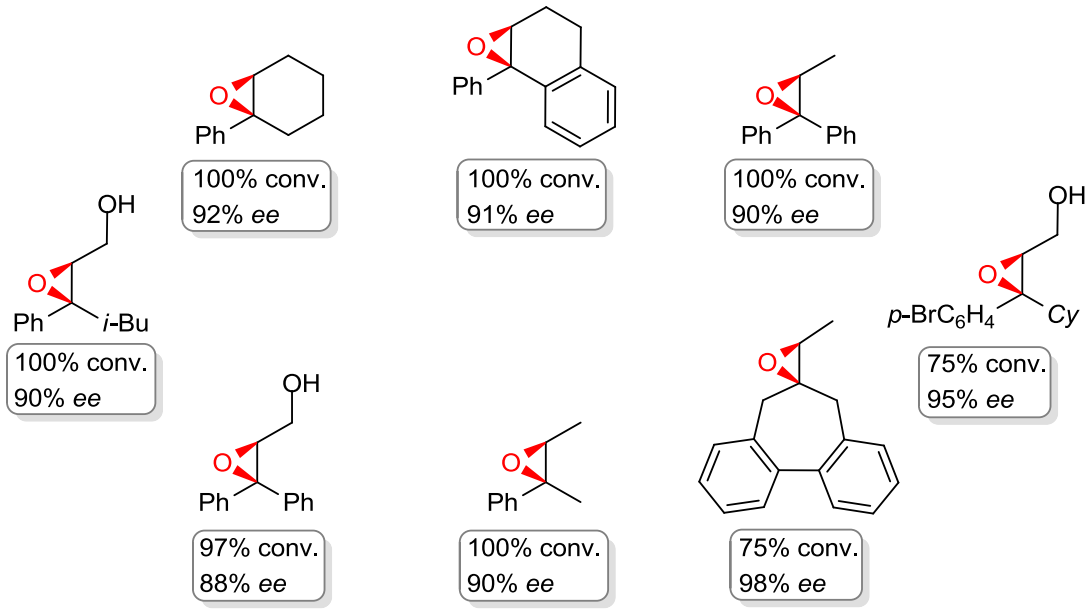


Figure 1.63: *Substrate screen. Iminium salt* ***189*** *$^{-}SbF_6$ (2.5 mol%), Oxone® (1.1 equiv.), $NaHCO_3$ (4 equiv.), 18-crown-6 (2.5 mol%), CH_2Cl_2 / H_2O (3:2), 0 °C*

The extensive range of substrates screened by Lacour and co-workers has allowed them to propose a mnemonic for predicting the major enantiomer of the epoxidation process (Figure 1.64).

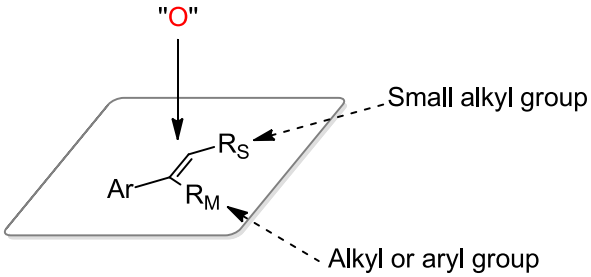


Figure 1.64: *Predictive mnemonic for* ***189*** *$^{-}SbF_6$ proposed by Lacour.*

1.7. Conclusion

In the preceding pages, a brief overview of chirality which emphasises the importance of enantioselective synthesis and a concise overview of the structure, behaviour and reactivity of epoxides has been offered. It is hoped that the versatility and utility of epoxides in modern day organic chemistry has been conveyed. Much attention has been paid to the preparation of chiral epoxides, in particular to methods which involve organocatalytic oxygen transfer to an alkene as it is this field on which the work presented herein is focused.

1.8. References for Chapter 1

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2.0 Results and Discussion

2.1 Previous Work and Outline of Initial Direction

Recent research within the Page group, some of which is discussed above, has been focused towards developing iminium salt-mediated organocatalytic systems for the asymmetric epoxidation of alkenes. The work described herein builds upon the discoveries and the developments reported previously by us, and also by others.

Lacour has shown in a recent study that the enantiocontrol imparted by azepinium salt catalysts over the epoxidation of alkenes is heavily influenced by the dihedral angle Φ.[1] We considered that incorporation of a substituent at the prochiral carbon α- to the nitrogen would allow us greater influence over any process occurring at the catalytically-active iminium functionality. We hoped to design new and improved iminium salts through the investigation of these two development paths (Figure 2.1). Initial work was towards the preparation and study of a family of iminium salts based on the 6,6'-dimethylbiphenyl backbone motif to perform a preliminary study.

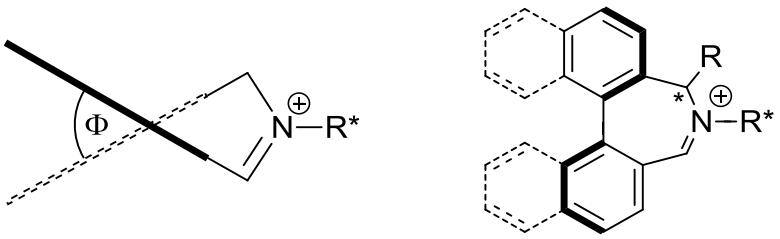
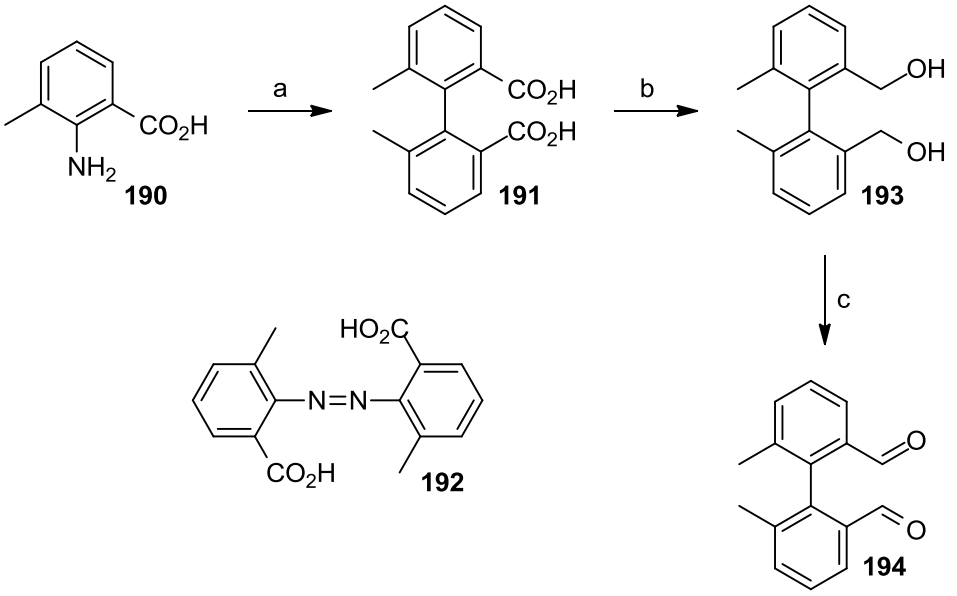


Figure 2.1: *The two routes investigated herein to attempt the optimization of catalyst function: i) effect of the dihedral angle within the backbone structure;[1] ii) effect of substitution α- to the iminium nitrogen.*

2.2 Catalysts based on the 6,6'-Dimethylbiphenyl-Azepinium Motif

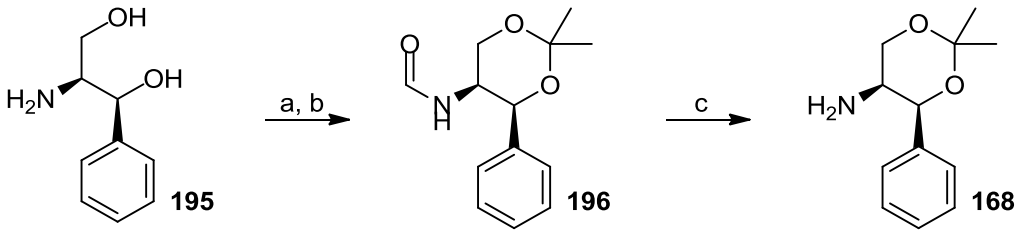
Synthesis of the backbone motif followed a procedure used and reported by Denmark,[2] and began with the copper-mediated coupling of 2-amino-3-methyl benzoic acid **190** (Scheme 2.1) The diazonium salt of **190** was first prepared by its exposure to solution of nitrous acid; the solution of the intermediate diazonium salt was then transferred into a vessel containing a reducing copper-containing solution. The yield of the racemic bis(benzoic acid) **191** was very sensitive to the rate at which the two are mixed: i.e. if the addition was too slow, the azo-containing compound **192** was isolated as the major product; to achieve **191** in good yields, the concentration of the diazonium salt in the reducing solution needed to be kept high as possible while maintaining the temperature below 5 °C, and the best yield achieved for the coupling reaction was 58%. The bis(hydroxymethyl) **193** was isolated in an essentially quantitative yield by the treatment of **191** with $LiAlH_4$., subsequently, the bis(benzaldehyde) **194** required for the coupling of the amine was prepared in good yield by exposure to PCC.



Scheme 2.1: *a) HCl, $NaNO_2$; then Cu_2SO_4, $(NH_4OH)_2$.H_2SO_4, NH_4OH, 5 °C, 58%; b) $LiAlH_4$ (3 equiv.), Et_2O, RT, 96%; c) PCC (3 equiv.), CH_2Cl_2, RT, 87%.*

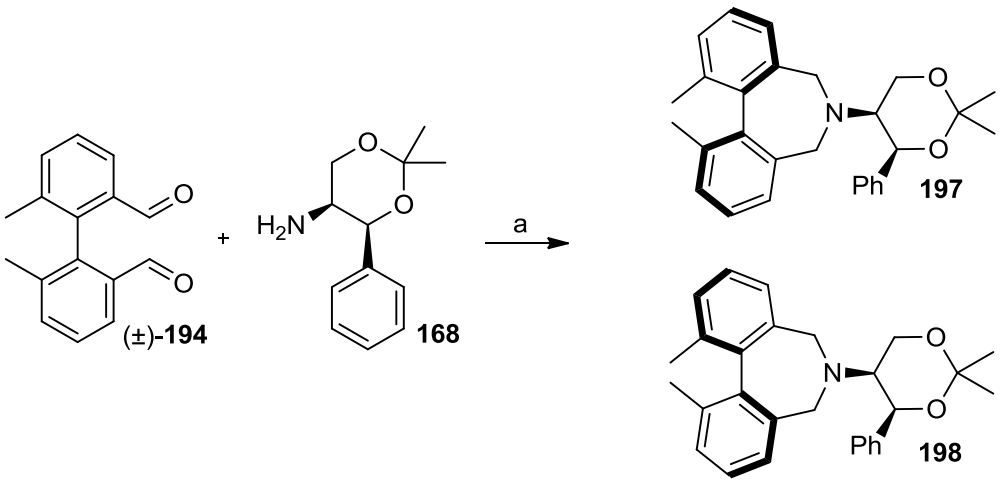
(*S*,*S*)-Acetonamine **168** has been demonstrated by us to be one of the most effective chiral amine motifs for iminium salt-mediated asymmetric epoxidation.[3]

Catalysts derived from **168** are generally the most reactive and also display the highest levels of enantiocontrol. On paper at least, **168** could conceivably be synthesized in one step by the ketalization of the 1,3-diol present in (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol **195**; of course the more-nucleophilic primary amine functionality does not permit such a synthesis, and the amine must first be protected as its formamide prior to ketalization in a one-pot procedure to give **196** (Scheme 2.2). Deprotection of the amine finishes the preparation of **168** in a 69% overall yield over 3 steps.[3]



Scheme 2.2: *Synthesis of (S,S)-acetonamine **168**: a) Methyl formate (1.2 equiv.), MeOH, NaOMe (0.1 equiv.), RT; b) toluene, CSA (0.1 equiv.), 2,2-DMP (5 equiv.), 94% over two steps; c) hydrazine, reflux, 3 h, 73%.*

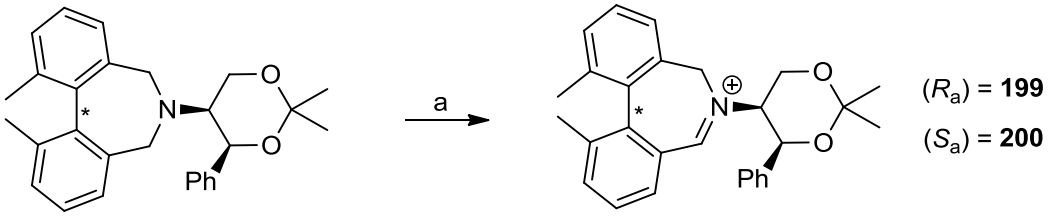
The coupling of **168** to **194** to prepare the 7-membered-ring azepine construct was achieved by a reductive amination procedure,[1] creating a pair of diastereoisomers **197** and **198**, owing to the employment of (±)-**194**. Fortunately, we were able to separate the diastereoisomers by flash column chromatography (Scheme 2.3).



Scheme 2.3: *Synthesis of the (R_a) and (S_a)-6,6'-dimethylbiphenyl azepine: a) $NaBH_3CN$ (2.2 equiv.), MeOH, AcOH, RT, 24 h, **197**-49%, **198**-26%.*

To determine the absolute stereochemistry of the two azepines, the spectral data and optical rotation of each were compared with an authentic sample of **198**, itself prepared from (*S*)-**191** which was isolated by resolution with quinine prior to the manipulation of its oxidation state.[2]

The oxidation of **197** and **198** up to their respective iminium salt species **199** and **200** was readily achieved on exposure to NBS and subsequent ion-exchange with $NaBPh_4$ (Scheme 2.4).



Scheme 2.4: *Synthesis of the (R_a) and (S_a)-6,6'-dimethylbiphenyl azepinium salts: a) NBS (1.1 equiv.), CH_2Cl_2, 0 °C → reflux, 2; then $NaBPh_4$ (1.1 equiv.), EtOH / MeCN, 61% (**199**), 83% (**200**).*

A model study was conducted with catalyst **199** and 1-phenyl-3,4-dihydronaphthylene as substrate under a range of previously reported conditions, to establish under which these new catalysts performed best (Table 2.1).

Entry	Conditions	Time	Conv. (%)	ee (%)	Config.
1	MeCN / H_2O 10:1, Oxone®, $NaHCO_3$, 0 °C	30 min.	99	89	(+)-(1*R*,2*S*)
2	MeCN / H_2O 1:1, Oxone®, $NaHCO_3$, 0 °C	20 min.	98	81	(+)-(1*R*,2*S*)
3	CH_2Cl_2 3:2, Oxone®, $NaHCO_3$, 0 °C	2 h	80	47	(+)-(1*R*,2*S*)
4	$CHCl_3$, TPPP, –30 °C	72 h	47	4	(–)-(1*S*,2*R*)
5	MeCN, TPPP, –30 °C	2 h	99	77	(+)-(1*R*,2*S*)

Table 2.1: *Evaluation of the epoxidation conditions with catalyst **199** against* 1-phenyl-3,4-dihydronaphthylene.

The aqueous MeCN systems out-performed the other systems in terms of both reactivity and enantioselectivity (Entries **1** and **2**). Clearly, the ratio of water in the

system had a significant effect; a higher ratio of water in the solvent system augmented the reactivity, no doubt in part due to increased solubility and availability of Oxone® - which is involved in the proposed rate determining step. It is also reasonable to suggest that the water stabilizes the charged transition state involved in the formation of the oxaziridinium in the rate determining step - lowering the E_A, which would have the effect of increasing the reaction rate. Moreover, an increased water ratio would be expected to stabilize both charged diastereoisomeric transition states involved in the enantioselective transfer of oxygen to the alkene, which in this instance has manifested itself as a decrease in the enantioselectivity of the process. We decided to employ the conditions which offered the highest levels of enantiocontrol to assess the new catalysts against a range of unfunctionalized alkene substrates (Table 2.2).

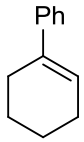
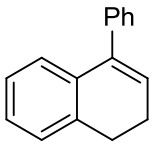
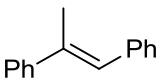
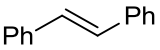
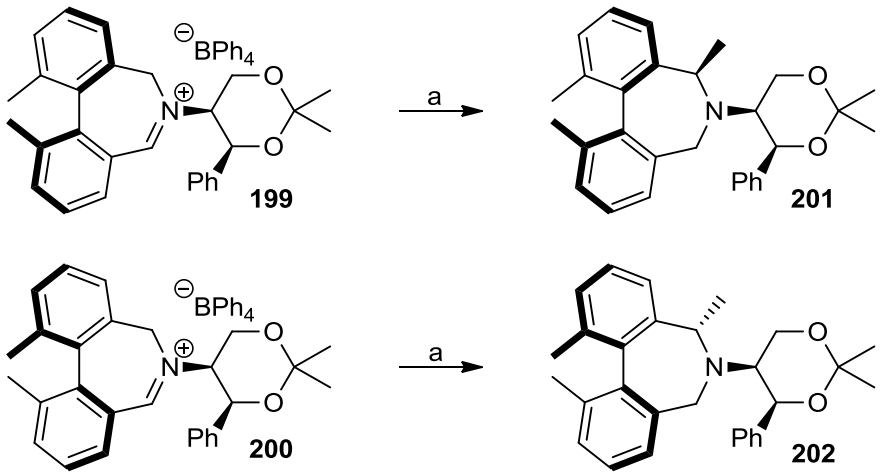
Substrate	Catalyst	
	199	**200**
	0.8 h, 99, 87, (–)-(1*S*,2*S*)	1.8 h, 99, 82, (+)-(1R,2R)
	0.5 h, 99, 89, (+)-(1*R*,2*S*)	2 h, 99, 82, (–)-(1*S*,2*R*)
	3 h, 99, 67, (–)-(1*S*,2*S*)	6 h, 99, 60, (+)-(1*R*,2*R*)
	4.3 h, 99, 15, (–)-(1*S*,2*S*)	6 h, 99, 8, (+)-(1*R*,2*R*)

Table 2.2. *Epoxidation of unfunctionalized alkenes: In each case (time, conversion (%), ee%, config.). Conditions; Alkene (1 equiv., 0.4 mmol), Oxone® (2 equiv.), $NaHCO_3$ (5 equiv.), catalyst (5 mol%), MeCN / H_2O 10:1. Run to completion.*

It was the pairing of the R_a backbone with the (*S,S*)-acetonamine that produced the most reactive and enantioselective catalyst **199** – the so-called 'matched' catalyst. It was expected, due to the smaller dihedral angle within the chiral backbone, that

199 would be less able to differentiate between the enantiotopic faces of the alkene than the analogous binaphthyl-azepinium salt **171** described above in Chapter 1, and indeed, this was the case. Further, in comparing the results obtained with the 6,6'-dimethylbiphenyl azepinium to the binaphthyl-azepinium, it was noted that the configuration of the major epoxides isolated were identical in all instances. This concurred with Lacour's suggestion that it is the backbone that controls the absolute stereochemistry, while the amine and its relationship with the backbone (synergistic or otherwise) has a lesser effect.[1]

We next wanted to investigate the influence that a substituent at the methylene unit adjacent to the iminium nitrogen had on the epoxidation process; we envisaged that we should be able to introduce such a substituent to the 6,6'-dimethylbiphenyl-azepinium salts by the nucleophilic attack of a Grignard reagent at the C terminus of the iminium bond. We were uncertain with regards to the potential stereochemical outcome of such a reaction but, when the addition was performed at –78 °C with MeMgCl in THF, we observed the formation of the azepines **201** and **202** as single diastereoisomers (Scheme 2.5).

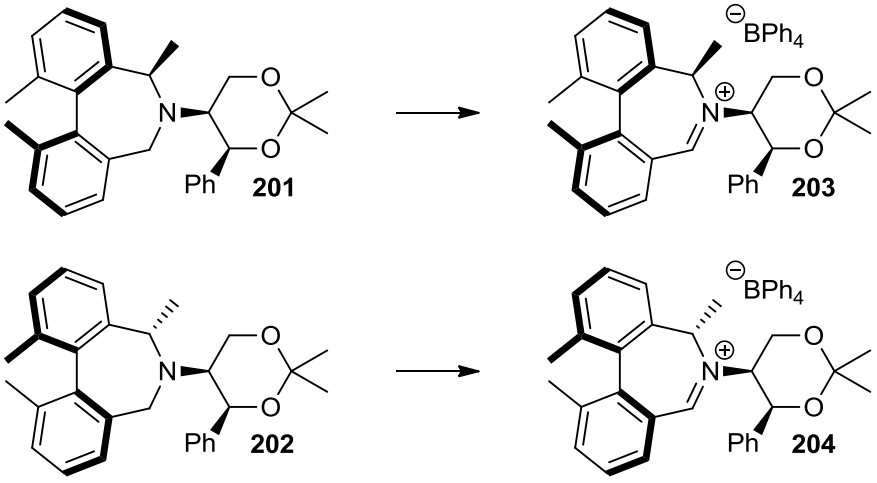


Scheme 2.5: *Diastereoselective introduction of a methyl substituent by Grignard addition: a) MeMgCl (10 equiv.), THF,* –78 °C → RT, 94% (**201**), 99% (**202**).

For both azepines, the methyl resonance was shifted far up-field of where we expected, δ_H = 0.21 ppm (**201**), 0.14 ppm (**202**). From the analysis of a model, and analysis of similar systems by Wallace,[4] it is clear that if the methyl substituent is

pseudo-axial, it is held in close proximity to the face of the aromatic ring opposite it on the azepine ring. This arrangement subjects the methyl substituent to a ring-current during the acquisition of the NMR, lowering the local magnetic field B_0, thus causing the apparent up-field shift in the methyl substituent's resonance. Crucially, exposure to a ring-current is not possible if the methyl substituent exists in the *pseudo*-equatorial configuration. Thus, the absolute configuration of the methyl substituent was inferred from the ^{1}H and ^{13}C NMR spectra - addition to **199** resulted in the *R* configuration at the α-position while addition to **200** resulted in the *S* configuration at the α-position. The fact that the absolute configuration of the methyl-bearing carbon changes with the backbone suggests that it is the backbone that controls the facial selectivity of the Grignard addition - not the chiral amine.

Oxidation of the novel 6,6'-dimethylbiphenyl-methylazepines **201** and **202** with NBS to their respective methylazepinium salts, **203** and **204**, was surprisingly low yielding, although both were formed as single regio- and diastereoisomers (Scheme 2.6).



Scheme 2.6: *Synthesis of the novel* 6,6'-dimethylbiphenyl methylazepinium salts: *a) NBS (1.1 equiv.), CH_2Cl_2, 0 °C → reflux, 2 h, 30% (**203**), 32% (**204**).*

The reason for the low yield was that the reaction did not go to full completion with 1.1 equivalents of NBS, and because crystallization to obtain **203** and **204** could only be performed once; subsequent crystallizations were contaminated by products which at the time were unidentified and never isolated. We have since obtained MS

evidence to suggest the presence of brominated salts, such as **205**. The presence of **205** explained why the conversion of the azepine was incomplete - NBS was being consumed in the by-reaction (Figure 2.2).

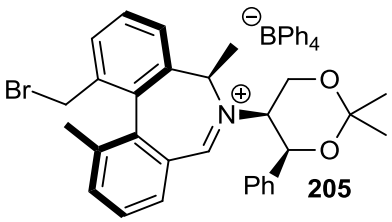


Figure 2.2: *Proposed representative structure of the brominated impurities.*

The iminium bond could potentially have formed as one of two regioisomers – depending on whether the new iminium bond formed from the least substituted carbon α- to nitrogen **207** or from the most substituted carbon **208**. Interestingly, we only observed and isolated the former from the reaction mixture, which to a crude approximation, we would have expected to be the least thermodynamically favoured of the two as it is the least substituted. This result implied, and originally led us to believe, that the regioselectivity of the oxidation process was therefore kinetically controlled and not due to an equilibrium. The oxidation is believed to proceed through the initial bromination of the nitrogen **206**. From the resulting positively charged intermediate, the iminium bond is then formed by abstraction of a proton and concomitant expulsion of bromide in an E_2 mechanism. The E_2 mechanism requires the *anti*-periplanar relationship of the H to the Br to provide the necessary orbital overlap. Thus, as the methyl group occupies a *pseudo*-axial position, the proton on that same carbon is *pseudo*-equatorial (H_{eq}) and is not in the correct alignment with the bromine to eliminate. The only proton that can attain the necessary *anti*-periplanar alignment is therefore the *pseudo*-axial proton (H_{ax}), and so it is from the least substituted carbon that the iminium bond is formed **207** (Figure 2.3).

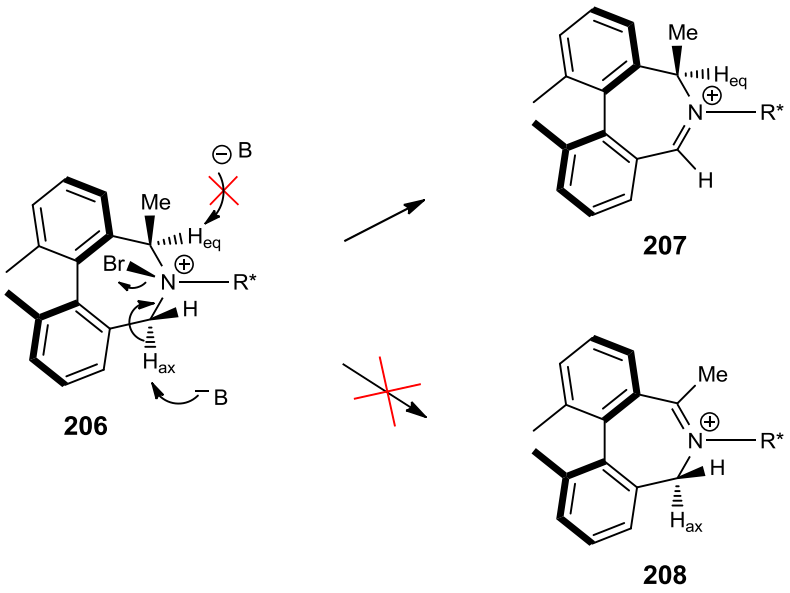


Figure 2.3: *The kinetically favoured abstraction of the pseudo-axial H is believed to be the sole reason for the exclusive formation of the regioisomer* ***207****.*

For these 6,6'-dimethylbiphenyl methylazepinium systems, this kinetic model concisely explained the regioselectivity we observed.

Methyl-substituted catalysts **203** and **204** were screened under the same conditions as their parent catalysts, against the unfunctionalized alkenes displayed below (Table 2.3).

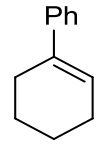
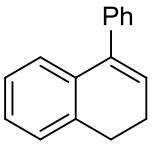
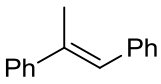
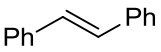
Substrate	Catalyst	
	203	**204**
	1 h, 99, 92, (–)-(1*S*,2*S*)	3 h, 99, 82, (+)-(1*R*,2*R*)
	1 h, 99, 85, (+)-(1*R*,2*S*)	6 h, 77, 78, (–)-(1*S*,2*R*)
	3 h, 99, 73, (–)-(1*S*,2*S*)	6 h, 99, 48, (+)-(1*R*,2*R*)
	6 h, 99, 39, (–)-(1*S*,2*S*)	6 h, 99, 10, (+)-(1*R*,2*R*)

Table 2.3 *Epoxidation of unfunctionalized alkenes: In each case (time, conversion (%), ee%, config.). Conditions; Alkene (1 equiv., 0.4 mmol), Oxone® (2 equiv.), $NaHCO_3$ (5 equiv.), catalyst (5 mol%), MeCN / H_2O 10:1. Run to completion.*

It was clear that this new generation of methylated azepinium salt was less reactive than the previous (Fig 1.52). We tentatively considered this may have been due to a slight increase in the electron-density on the methylazepinium ring caused by the weakly electron donating methyl substituent, but the effect appeared too large; the reaction times increased by up to a factor of 2 in some instances.

Interestingly, incorporation of the methyl substituent to give **203** had a positive effect on the enantioselectivity in comparison with **199**, while its incorporation into the 'mismatched' catalyst **200** created a less enantioselective azepinium salt **204**. We were unable to explain the influence that the methyl substituent had over the epoxidation process at this point, but buoyed by the jump in enantioselectivity **204** exhibited, we decided to initiate a more thorough study and prepare a larger family of binaphthyl-azepinium salts to ascertain whether this effect was more general, and importantly – to develop a theoretical model to explain our observations.

2.3 Regioselective Iminium Bond Formation and Stereochemical Relays

The biphenyl backbone contained in catalysts **169** and **170**, does not possess stable atropisomers, as the absence of sterically demanding substituents at the 6 and 6' positions allow the rapid rotation about the sp^2C-sp^2C bond at room temperature (Figure 2.4).

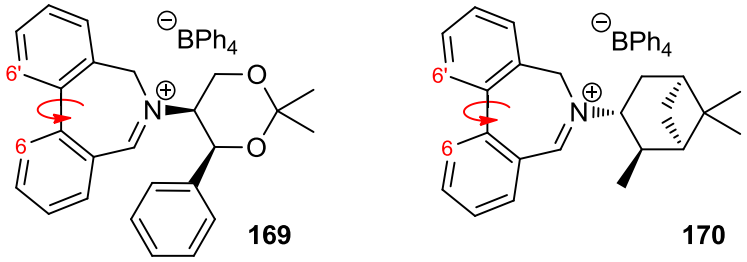
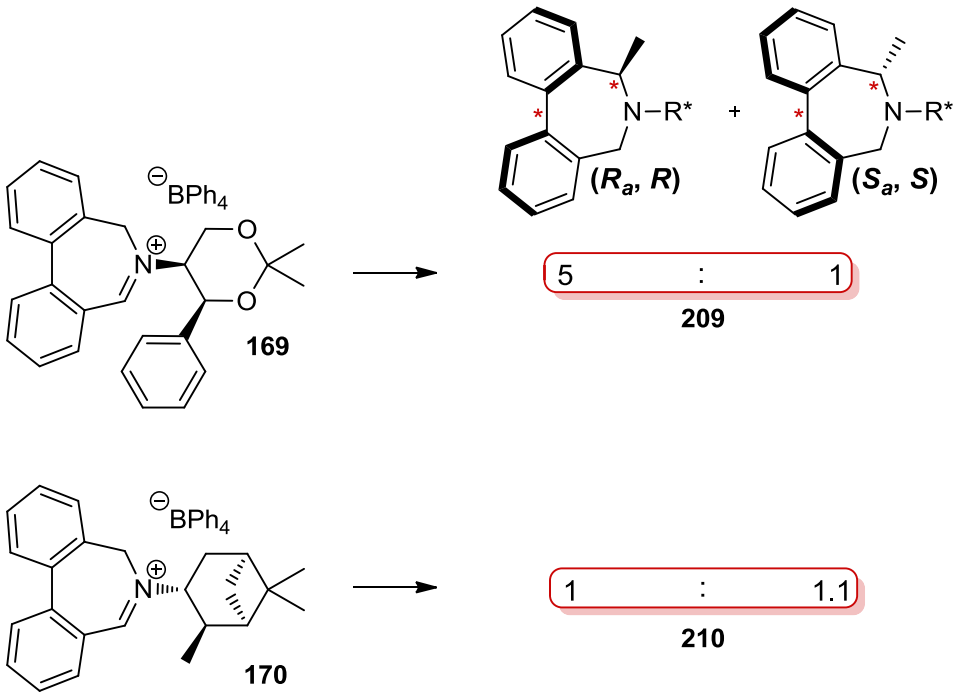


Figure 2.4: *Rotation about the biphenyl axis is rapid at RT.*

So, the isolation of a mixture of two isomers from the Grignard addition for each was not unexpected, but the exact nature of the isomers was surprising and also provided further evidence for our hypothesis that it is the backbone that ultimately controls the stereochemistry of the Grignard reagent addition (Scheme 2.7). The backbone could have this influence directly, i.e. it could physically hinder the Burgi-Dunitz approach of the Grignard reagent required to achieve a reaction with the iminium bond. Or, it could be that it is the conformation of the azepinium ring itself - determined by the conformation of the backbone - that results in the facial selectivity. Axial attack on six membered iminium systems is favoured due to the reduction of 1,3-diaxial interactions.[5] The resultant *pseudo*-axial configuration of the methyl substituent in our azepinium systems, could just be a result of the accepted kinetic rules for fixed-conformation ring attack.



Scheme 2.7: *Grignard addition to* ***169*** *and* ***170*** *produced a mixture of two atropisomers.*

The methyl substituent in both isomers of **209** and **210** (**(*R*a, *R*)** and **(*S*a, *S*)**) displayed the characteristic up-field shift in their respective NMR spectra indicating the methyl group was axial in both, which implied that the two isomers had to therefore be atropisomers. That is to say - the methyl group, once inserted, significantly increases the barrier to rotation of the biaryl sp^2C-sp^2C bond, creating an atropisomeric centre at room temperature. The backbone's configuration is much more stable to inversion because the sp^2C-sp^2C bond rotation movement required to do so, in the presence of a bulky pendent amine,[4] causes the methyl to clash with the H atom at the 3' position, giving the inversion a high energy barrier (Figure 2.5)

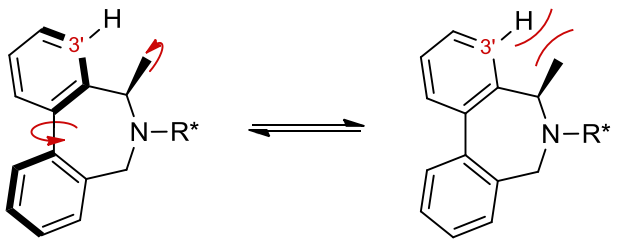


Figure 2.5: *Illustration of the high-energy bond rotation movement required for inversion at the atropisomeric centre.*

To understand the origin of the atropisomeric ratio observed for the Grignard addition to **169** and **170**, we probed the catalysts by conducting NOESY experiments at –80 °C – the same temperature at which the Grignard addition is performed. We observed the existence of distinct sp^2C-sp^2C rotamers in **169** and **170** at that temperature; interestingly, the ratio of the rotamers corresponded very closely to the atropisomeric ratio observed in the biphenyl methylazepines **209** and **210**.

For **169**, sp^3C-sp^2N roatamers were also observed at –80 °C. This resulted in a total of 4 iminium peaks in the NMR spectra. Comparison to the NOESY data of the closely related binaphthyl analogue **171**, described below, and correlation data obtained from the NOESY spectra of **170** allowed us to confidently assign which peak corresponded to which conformation, and therefore deduce the sp^2C-sp^2C ratio. Only two iminium peaks were present in the spectra of **170 at** –80 °C, both of which were the *syn* rotamer, therefore the two conformations were deduced to be sp^2C-sp^2C roatamers (Figure 2.6).

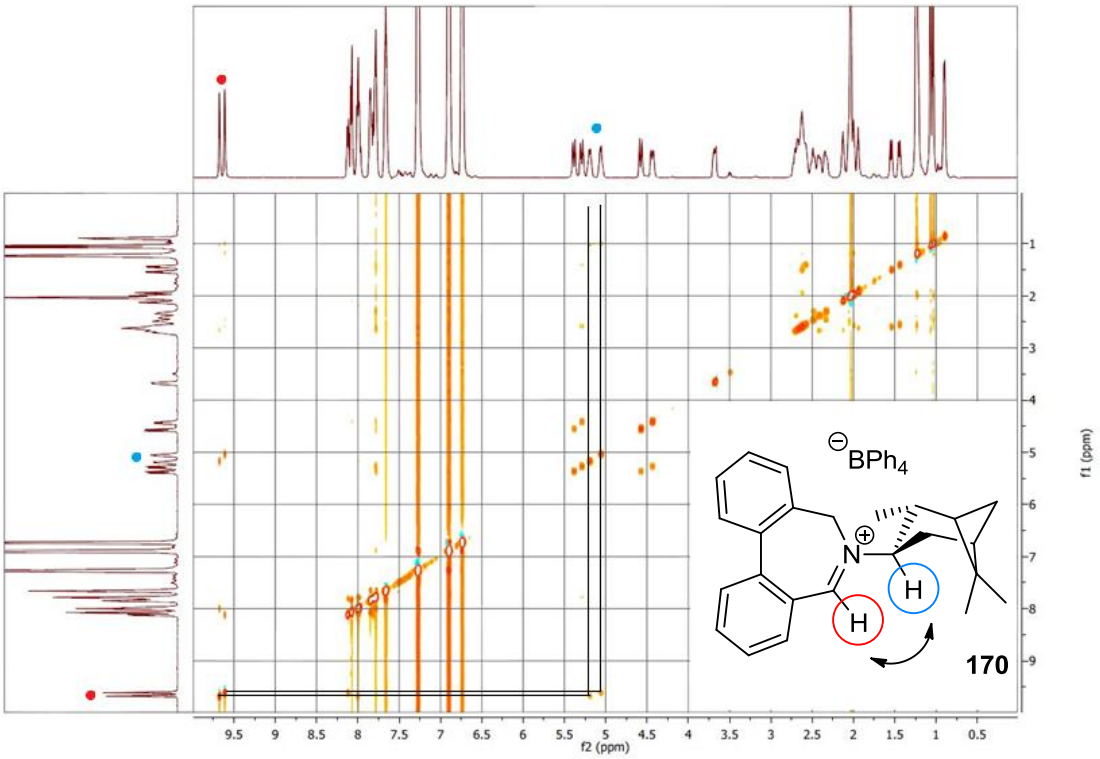
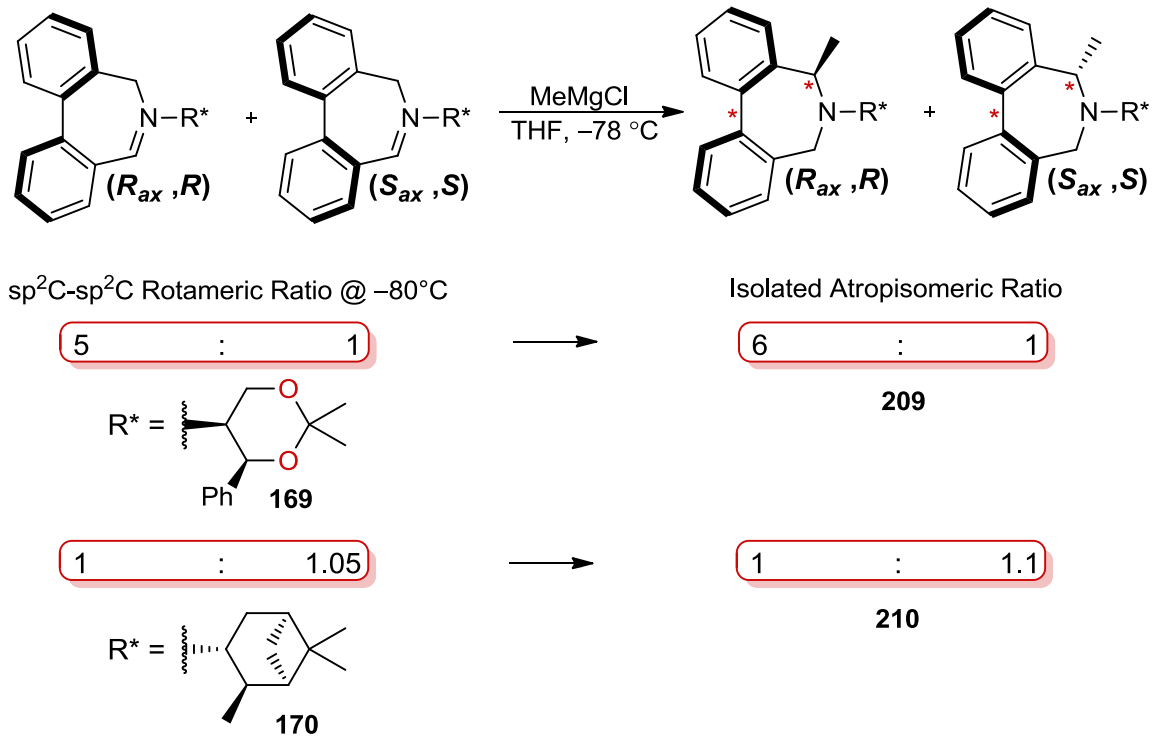


Figure 2.6: *NOESY spectra of* ***170*** *at the* sp^2C-sp^2C at –80 °C, showing that both iminium signals (red) show correlations with the proton on the chiral amine (blue).

Since the methyl substituent is axial in all cases and since the observed rotameric ratio is approximately equal to isolated atropisomeric ratio, it follows that the backbone somehow ultimately controls the insertion to be axial, and that the insertion stabilises the rotamer (Scheme 2.8).



Scheme 2.8: *Relation of the* sp^2C-sp^2C *ratio of rotamers observed at* –80 °C by nOe to the isolated atropisomeric ratio.

Of course, it is the chirality of the pendent amine which determines the extent to which the two possible *pseudo*-diastereoisomeric rotamers are occupied at low temperature. So, in effect, we have observed a stereochemical relay of point → axial → point chirality. The isopinocampheyl-derived group in **170** was not as capable of transferring its stereochemical information as **168**, perhaps due to its less bulky substituent at the position indicated by the circle (Figure 2.7).

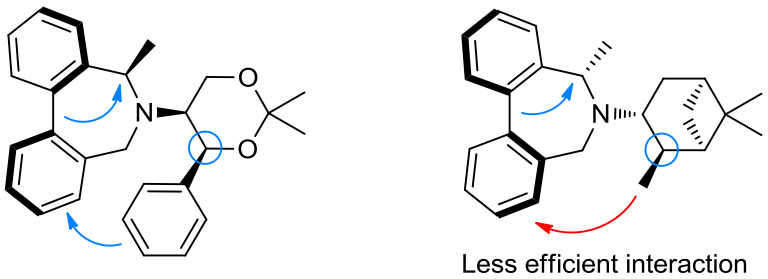


Figure 2.7: *Transfer of* point → axial → point chirality.

2.4 Catalysts based on the Binaphthyl-Azepinium Motif

The atropisomeric binaphthyl motif is one of the most widely exploited sources of chiral information today, finding utility in organocatalysis, metal mediated catalysis, resolving agents and chromatographic stationary phases.[6] We,[7] and others,[1,8] have described the preparation of azepinium salt catalysts based on the binaphthyl motif previously and reported some of the highest enantioselectivities for the epoxidation of unfunctionalized tri-substituted alkenes with their use, some of which are highlighted above in Chapter 1. Given the already high levels of stereocontrol exhibited by these species, we were keen to investigate the potential gains we could achieve by modification at the α-position. Following on from the work performed on the 6,6'-dimethyl biphenyl-azepinium catalysts, we planned to probe the effect of other substituents, as well as other pendent amines, to better understand the underlying mechanism by which the introduced substituent exerts its influence on the epoxidation process (Figure 2.8).

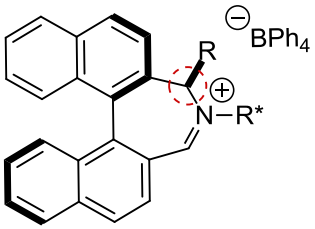
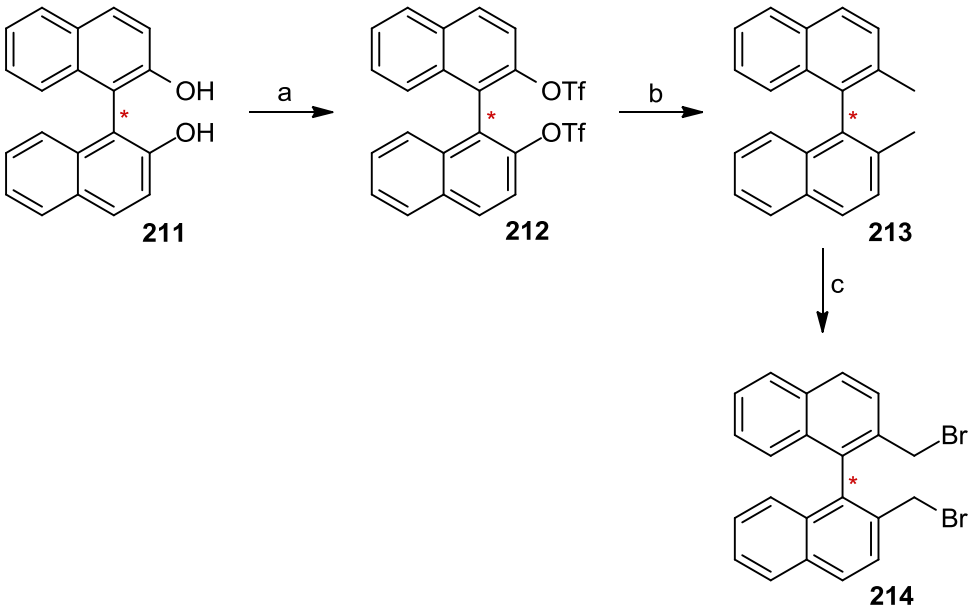


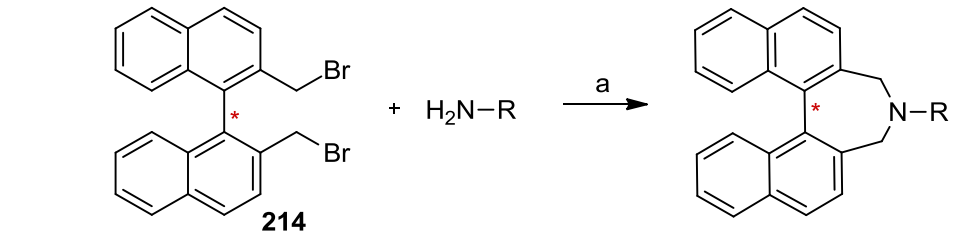
Figure 2.8: *Schematic of the general structure of the binaphthyl-azepinium salts, highlighting the site of our modification.*

The synthesis of the unsubstituted binaphthyl-azepinium catalysts is rapid, requires no column chromatography, and begins from (*R*)-(+)- and (*S*)-(–)-BINOL **211**. Triflation of the phenolic hydroxyl groups was achieved with triflic anhydride **212**, which appropriately functionalized the 2 / 2' positions for the subsequent Kumada coupling used to install the required carbons of **213**.[7] The activated benzylic positions were then brominated by the action of NBS and AIBN to furnish bis(bromomethyl) **214**, needed for the coupling of the amine (Scheme 2.11).

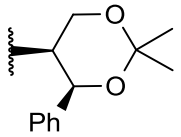


Scheme 2.11: *Synthesis of (R) and (S)*-2,2'-bis(bromomethyl)-binaphthylenyl: a)Tf_2O (3 equiv.), DMAP (0.4 equiv.), 2,6-lutidine (3 equiv.), CH_2Cl_2, 16 h, –30 °C → RT, 99%; b) MeMgBr (4 equiv.), Ni(II)Cl dppe, Et_2O, 16 h, –30 °C → RT, 88%; c) NBS (2.2 equiv.), AIBN (5 mol%), cyclohexane, reflux, 3 h, 58%.

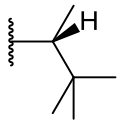
For this extended study, we employed (*R*) and (*S*)-3,3-dimethyl-2-butylamine **215** and the non-chiral isopropylamine **216**, alongside **168** to prepare the initial azepines (Scheme 2.12). The coupling was readily achieved by refluxing a 1:1 mixture of **214** and the desired amine in MeCN overnight in the presence of K_2CO_3 to furnish the azepines **217**-**221** in excellent yield and purity.



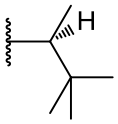
R =



168



(*R*)-215



(*S*)-215

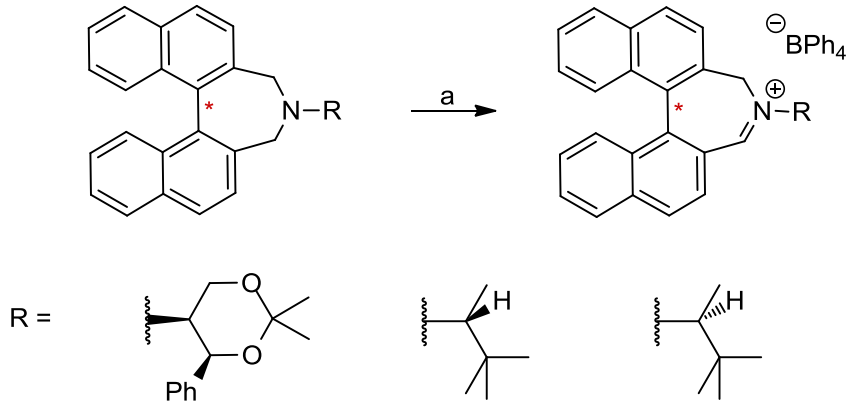
216

(*R*)-214	**217** (99%)	**218** (99%)	**219** (99%)	**220** (98%)
(*S*)-214	**221** (93%)			

Scheme 2.12: *Synthesis of binaphthyl azepines: a) RNH_2 (1 equiv.),* ***214*** *(1 equiv.), K_2CO_3 (3 equiv.), MeCN, reflux, 16 h.*

The chiral amines **215** were chosen because they have been shown by Lacour to be excellent mediators of enantiocontrol when partnered with the binaphthyl- motif. The diastereoisomeric pair **218** and **219** also demonstrated 'matched' and 'mismatched' behaviour that we wanted to assess further, particularly because for this pair, one diastereoisomer is more reactive, while the other is more enantioselective. That relationship contrasts with that between **171** and **172**, where **171** is both more reactive and more enantioselective.[1] The non-chiral amine **216** was selected as a 'control'.[9] We hoped the catalysts synthesized from its use would allow us to determine if the influence of the α-substituent manifested itself through an interaction with the pendent amine.

The formation of the tetraphenylborate binaphthyl-azepinium salts prepared below was effected by exposure to NBS and subsequent ion-exchange in varying yield (Scheme 2.13).



(R_a)	**171** (63%)	**222** (74%)	**223** (87%)	**224** (55%)
(S_a)	**172** (46%)			

Scheme 2.13: *Synthesis of binaphthyl azepinium catalysts: a) NBS (1.1 equiv.), CH_2Cl_2, reflux, 1 h; then $NaBPh_4$ (1.1 equiv.), EtOH / MeCN.*

With the five catalysts in hand, a preliminary substrate screen was performed. Catalysts **171**, **172** and **224** were assessed under standard MeCN / H_2O conditions. There was a much greater 'matched' and 'mismatched' disparity between **171** and **172** than there was for the 6,6'-dimethylbiphenyl-azepinium analogues **199** and **200**. Presumably, the larger Φ angle contained within the binaphthyl backbone was the cause – exacerbating the conflicting chiral information contained within **172** while reinforcing the cooperant chiral information in **171.** It was also interesting to observe that **171** was more reactive than **224** despite it containing a far bulkier amine (Table 2.4). Catalysts **222** and **223** were used under Lacour's CH_2Cl_2 / H_2O conditions.[10] It was clear the difference between the two diastereoisomers was small, but nevertheless **222** demonstrated slightly more stereocontrol, while **223** was more reactive (Table 2.5).

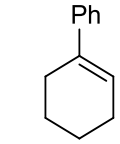
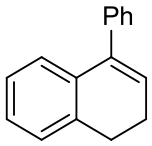
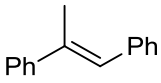
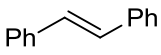
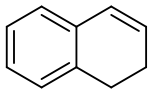
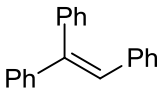
Substrate	171	172	224
	0.2 h, 99, 91, (–)-(1*S*,2*S*)	1.5 h, 99, 79, (+)-(1*R*,2*R*)	0.5 h, 99, 75, (–)-(1*S*,2*S*)
	0.3 h, 99, 94, (+)-(1*R*,2*S*)	2.2 h, 80, 57, (–)-(1*S*,2*R*)	0.7 h, 99, 91, (+)-(1*R*,2*S*)
	0.3 h, 99, 49, (–)-(1*S*,2*S*)	4.6 h, 40, 49, (+)-(1*R*,2*R*)	2.5 h, 99, 53, (–)-(1*S*,2*S*)
	0.3 h, 99, 15, (–)-(1*S*,2*S*)	4.6 h, 28, 11, (+)-(1*R*,2*R*)	--
	0.6 h, 99, 18, (+)-(1*R*,2*S*)	1.5 h, 99, 21, (–)-(1*S*,2*R*)	--
	13 h, 81, 16, (+)-(*S*)	13 h, 7, 3, (–)-(*R*)	--

Table 2.4: *Epoxidation of unfunctionalized alkenes: In each case: (time, conversion (%), ee%, config.). Conditions; Alkene (1 equiv., 0.4 mmol), Oxone® (2 equiv.), $NaHCO_3$ (5 equiv.), catalyst (5 mol%), MeCN / H_2O 1:1, 0 °C.*

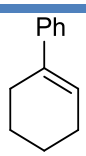
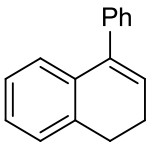
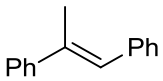
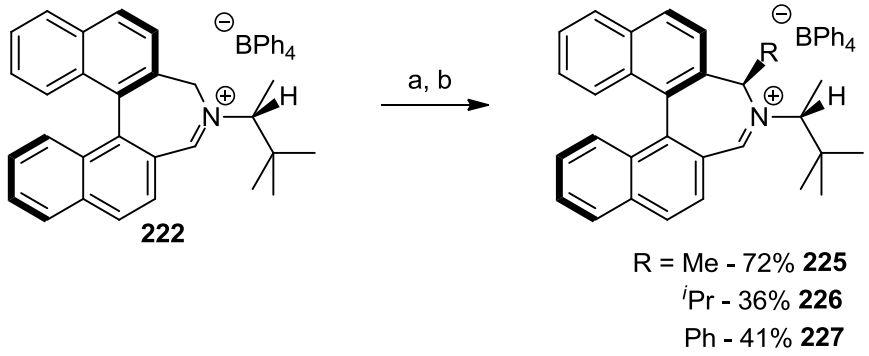
Substrate	222	223
	99, 75, (–)-(1*S*,2*S*)	99, 74, (–)-(1*S*,2*S*)
	80, 85, (+)-(1*R*,2*S*)	99, 83, (+)-(1*R*,2*S*)
	18, 52, (–)-(1*S*,2*S*)	56, 44, (–)-(1*S*,2*S*)

Table 2.5: *Epoxidation of unfunctionalized alkenes: In each case (conversion (%), ee%, config.). Conditions; Alkene (1 equiv., 0.3 mmol), Oxone® (1 equiv.), $NaHCO_3$ (4 equiv.), 18-crown-6 (2.5 mol%), catalyst (5 mol%), CH_2Cl_2 / H_2O 3:2, 0 °C, 2 h.*

After the preliminary screen of the non-substituted binaphthyl azepinium catalysts, we next investigated the incorporation of substituents into **222**, to create a small range of α-substituted binaphthyl azepinium salts (Scheme 2.14).



Scheme 2.14: *Preparation of several α-substituted binaphthyl-azepinium salts: a) RMgBr (10 equiv.), THF, –78 °C → RT, 16 h; b) NBS (1.1 equiv.), CH_2Cl_2, RT, 10 min; then $NaBPh_4$ (1.1 equiv.), EtOH / MeCN.*

Again, an up-field shift was witnessed of the methyl substituent in the NMR spectra for **225**, and also of the ^{i}Pr group in **226**, which provided strong evidence that these substituents were *pseudo*-axially orientated; it was difficult to assess such a marked shift for the Ph group in **227**, but we suspect, by analogy to all other results, it too was *pseudo*-axial.

The catalysts were assessed under the biphasic CH_2Cl_2 / H_2O conditions for the epoxidation of 1-phenyl-3,4-dihydronaphthylene – a substrate that the azepinium catalysts were typically able to epoxidize with excellent enantiocontrol. Catalyst **225** was an improvement upon **222** in terms of enantiocontrol. Unfortunately, however, the reactivity was substantially compromised, if still practical (Table 2.6). We were pleased to observe that the incorporation of a methyl group improved upon the enantiocontrol demonstrated by **222**, particularly because this showed that the modification was effective for other chiral amines as well as other backbone motifs. However, from this small study, and from other results previously obtained within the group,[11] it was apparent that a methyl group was the only candidate which achieved the desired augmentation of the catalyst's enantiocontrol. Bulkier substituents were extremely deleterious to both reactivity and enantioselectivity.

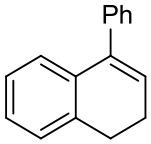
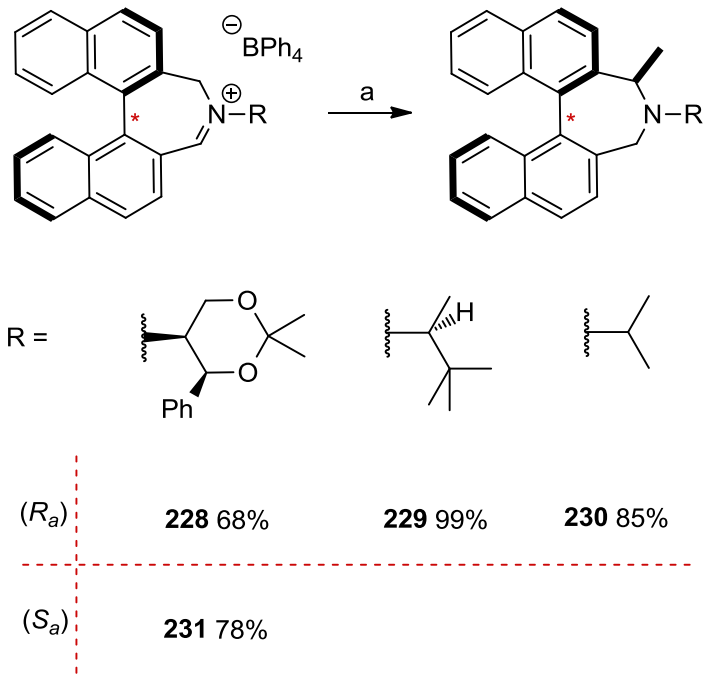
Substrate	225	226	227
	2 h, 40, 87, (+)-(1*R*,2*S*)	5 h, 12,45, (+)-(1*R*,2*S*)	16 h, 4,-, -

Table 2.6: *Epoxidation of unfunctionalized alkenes: In each case (conversion (%), ee%, config.). Conditions; Alkene (1 equiv., 0.3 mmol), Oxone® (1 equiv.), $NaHCO_3$ (4 equiv.), 18-crown-6 (2.5 mol%), catalyst (5 mol%), CH_2Cl_2 / H_2O 3:2, 0 °C, 2 h.*

Having satisfied ourselves that a methyl substituent was likely to be the optimal alkyl substituent to incorporate at the α-position, we applied the modification to a range of binaphthyl-azepinium salts (Scheme 2.15).



Scheme 2.15: *Synthesis of the binaphthyl-methyl azepines: a) MeMgBr (10 equiv.), THF, –78 °C → RT, 16 h.*

All NMR spectra of the binaphthyl-methyl azepines prepared above displayed the same up-field shift of the methyl substituent, and the spectrum of **228** is shown below (Figure 2.9). We also obtained a crystal X-ray structure of **228**, which confirmed the *pseudo*-axial configuration of the methyl substituent and is also shown below (Figure 2.10).

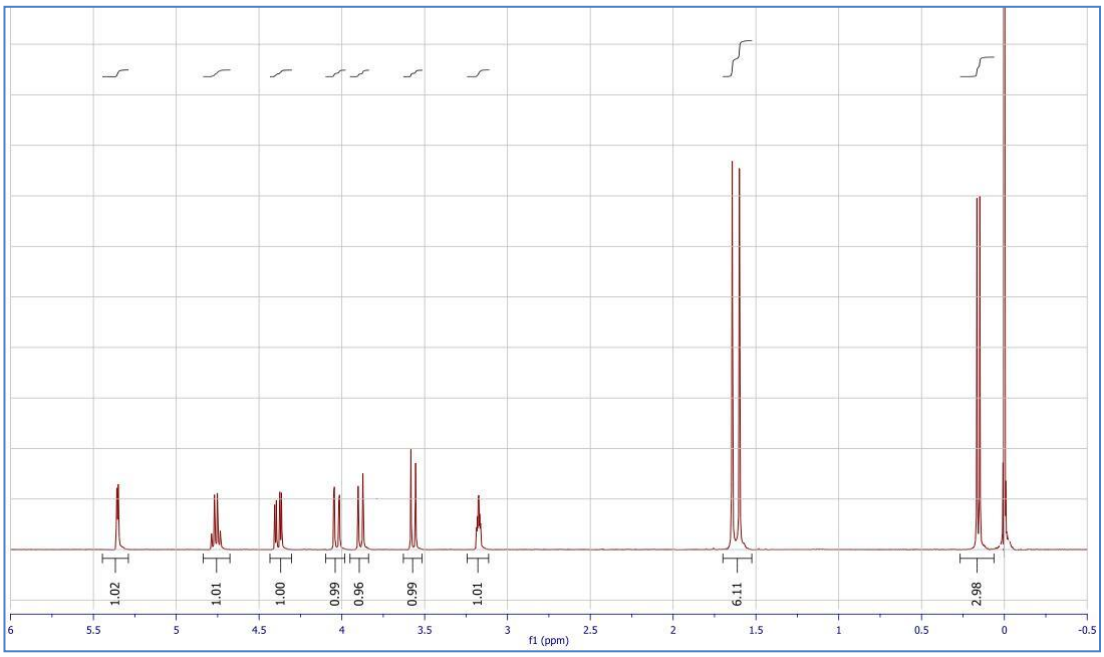


Figure 2.9: *Large up-field shift of the methyl group in* ***228****,* δ_H *= 0.12 ppm.*

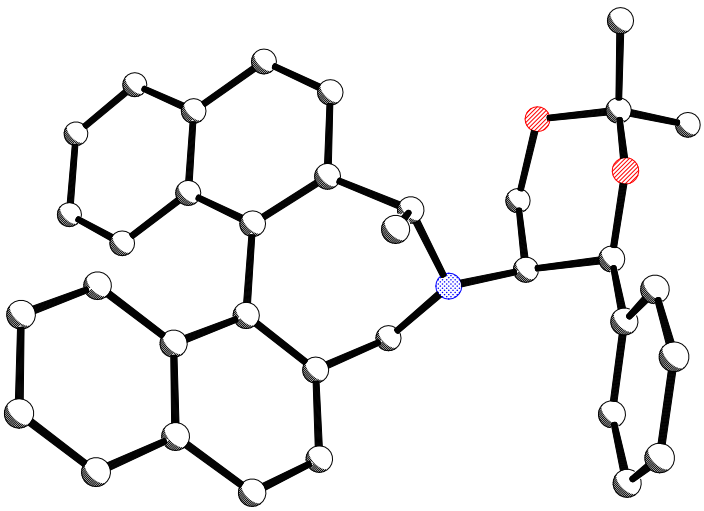
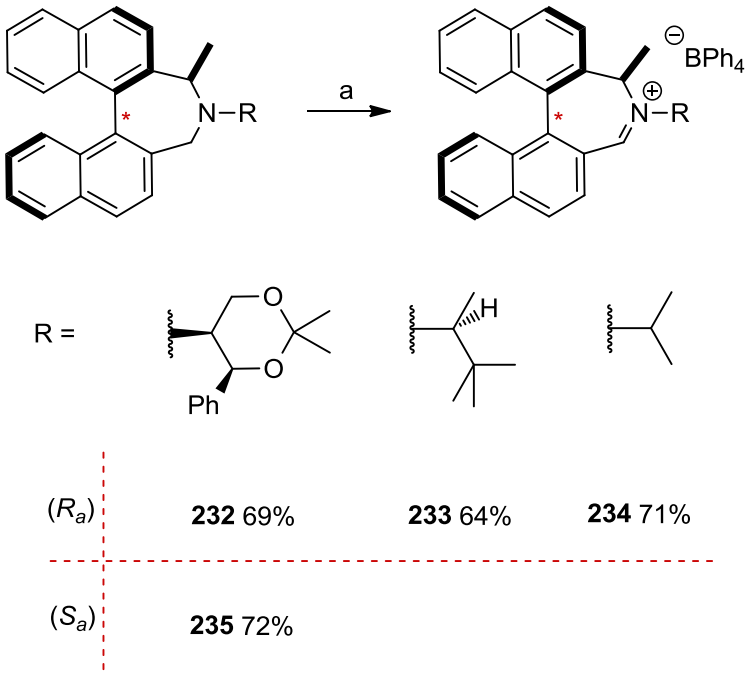


Figure 2.10: *Crystal X-ray structure of* ***228****, clearly showing the configuration of the methyl substituent.*

Oxidation of the binaphthyl-methylazepines and isolation of the binaphthyl-methylazepinium $^{-}BPh_4$ salts were achieved in the usual way. As expected, the least-substituted iminium bond regioisomers were obtained, with complete retention of stereochemistry at the α-position in all instances (Scheme 2.16).



Scheme 2.16: *Synthesis of* binaphthyl-methyl azepinium $^{-}BPh_4$ salts: a) NBS (1.1 equiv.), CH_2Cl_2, RT, 10 min; *then $NaBPh_4$ (1.1 equiv.), EtOH / MeCN.*

The new generation of catalysts was then tested against a range of substrates to test their efficacy as enantioselective organocatalysts. The results are outlined below (Tables 2.7 and 2.8).

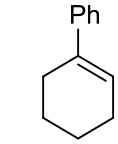
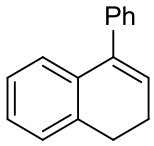
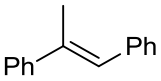
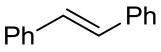
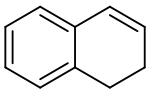
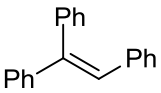
Substrate	232	235	234
	0.3 h, 99, 94, (–)-(1*S*,2*S*)	2 h, 99, 44, (+)-(1*R*,2*R*)	0.5 h, 99, 79, (–)-(1*S*,2*S*)
	0.5 h, 99, 94, (+)-(1*R*,2*S*)	4 h, 93, 63, (–)-(1*S*,2*R*)	0.6 h, 99, 85, (+)-(1*R*,2*S*)
	0.6 h, 99, 64, (–)-(1*S*,2*S*)	4 h, 26, 30, (+)-(1*R*,2*R*)	2.5 h, 99, 55, (–)-(1*S*,2*S*)
	1.2 h, 99, 36, (–)-(1*S*,2*S*)	4 h, 14, 7, (+)-(1*R*,2*R*)	--
	0.6 h, 99, 15, (+)-(1*R*,2*S*)	2 h, 99, 26, (–)-(1*S*,2*R*)	--
	13 h, 38, 28, (+)-(1*S*,2*S*)	13 h, 6, 1, (–)-(1*R*,2*R*)	--

Table 2.7: *Epoxidation of unfunctionalized alkenes: In each case (time, conversion (%), ee (%), config.). Conditions; Alkene (1 equiv., 0.4 mmol), Oxone® (2 equiv.), $NaHCO_3$ (5 equiv.), catalyst (5 mol%), MeCN / H_2O 1:1, 0 °C.*

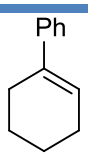
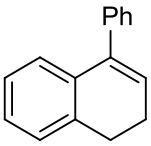
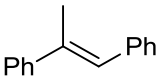
Substrate	225	233
	88, 92, (–)-(1*S*,2*S*)	99, 88, (–)-(1*S*,2*S*)
	40, 87, (+)-(1*R*,2*S*)	99, 90, (+)-(1*R*,2*S*)
	17, 55, (–)-(1*S*,2*S*)	40, 50, (–)-(1*S*,2*S*)

Table 2.8: *Epoxidation of unfunctionalized alkenes: In each case (conversion (%), ee%, config.). Conditions; Alkene (1 equiv., 0.3 mmol), Oxone® (1 equiv.), $NaHCO_3$ (4 equiv.), 18-crown-6 (2.5 mol%), catalyst (5 mol%), CH_2Cl_2 / H_2O 3:2, 0 °C, 2 h.*

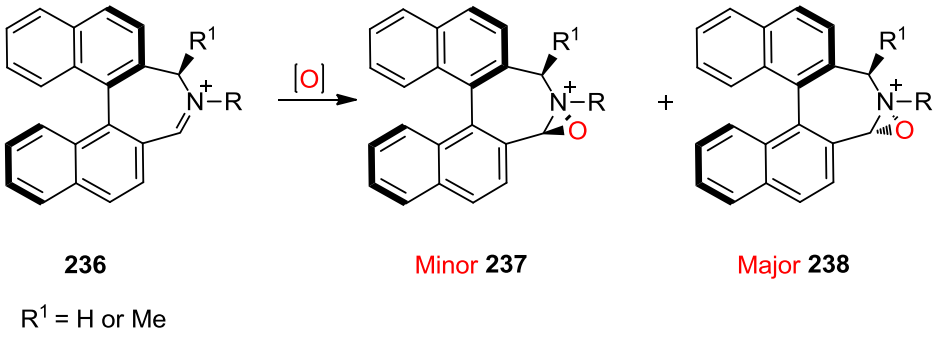
Again, incorporation of the methyl substituent into the catalyst structure had a profound effect on the levels of enantiocontrol imparted by the catalysts, with the exception the ^{i}Pr-based **224** and **234**. However, the reactivity of the ''second generation'' binaphthyl-methylazepinium salts was generally lower than the ''first generation''. Now that we had a larger body of results, which backed up those we obtained from the 6,6'-dimethyl biphenyl system, we wanted to understand how the methyl substituent's presence influences the both the enantioselectivity and rate of the epoxidation process.

2.5 The Influence of sp^2N-sp^3C Rotamers on Enantioselectivity

We considered several models to explain our observations, and in order to strengthen the argument for that which we ultimately proposed, it was important to accumulate evidence to rule out other reasonable mechanisms.

I. The possibility of the formation of the oxidatively active oxaziridinium salts as a mixture of diastereoisomers from oxidation of the planar pro-chiral pre-catalytic iminium species is well documented.[12] As is mentioned above in Chapter 1, when discussing a diastereoisomeric mixture of oxaziridinium salts during the catalytic cycle mediated by the dihydroisoquinolinium salts, each diastereoisomer would be expected to impart differing - if not opposing - levels of enantiocontrol. Our first consideration was that the oxidation of the iminium motif **236** would have been less favoured from the face on which methyl group was present because of the extra steric bulk (Scheme 2.17). Regardless, assuming the minor diastereoisomer **237** did form, it was also a possibility that the methyl group instead blocked the substrate's approach. Thus, the oxidation of the substrate by the minor oxaziridinium diastereoisomer would become much slower. In any case, Houk has shown with a model system (R = Me, R^1 = H)[13] that the intermediate of the oxidation of **236** by Oxone® leading to the formation of the minor diastereoisomer **237**, was "8.1 kcalmol^{-1} higher in energy than the intermediate leading to the major

diastereoisomer **238**'', noting that the difference was due to steric repulsion between the monoperoxysulfate and the arene H at the 3 position.



Scheme 2.17: *Formation of oxaziridinium epimers.*

II. We considered the possibility that the added methyl substituent was able to influence the dihedral angle Φ; we conceived that in an attempt to reduce the unfavourable steric interaction between the methyl substituent and the H atom at the 3' position of the backbone in the modified catalyst **249** might be encouraged to adopt a wider angle than its parent catalyst **250** (Figure 2.11).

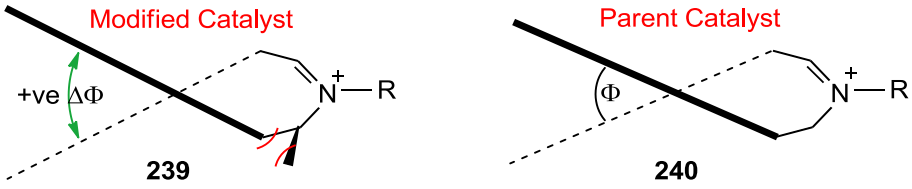
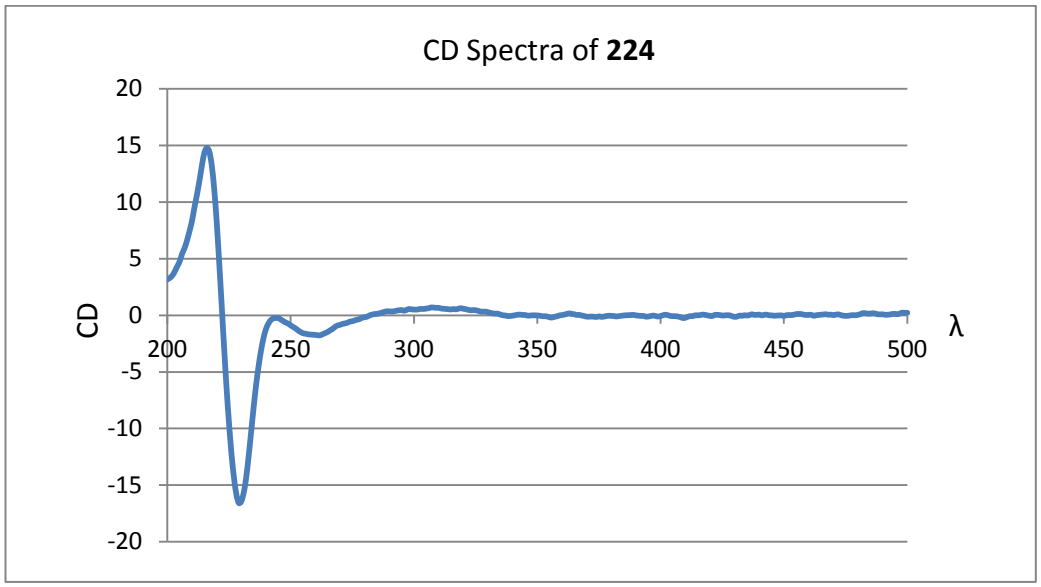


Figure 2.11: *An increase in the dihedral angle Φ was postulated to result from the presence of the α-substituent, and perhaps affect enantioselectivity.*

We were able to rule this model out through the comparison of the CD spectra between generations. It has been shown by Sandstrom that the λ_{MAX} absorbance value of aromatic axially-chiral species is dependent on the dihedral angle.[14] The λ_{MAX} values were almost identical for the species measured, suggesting that the dihedral angle is the same for both generations, and that a change in the dihedral angle was not responsible for our observations (Figure 2.12).



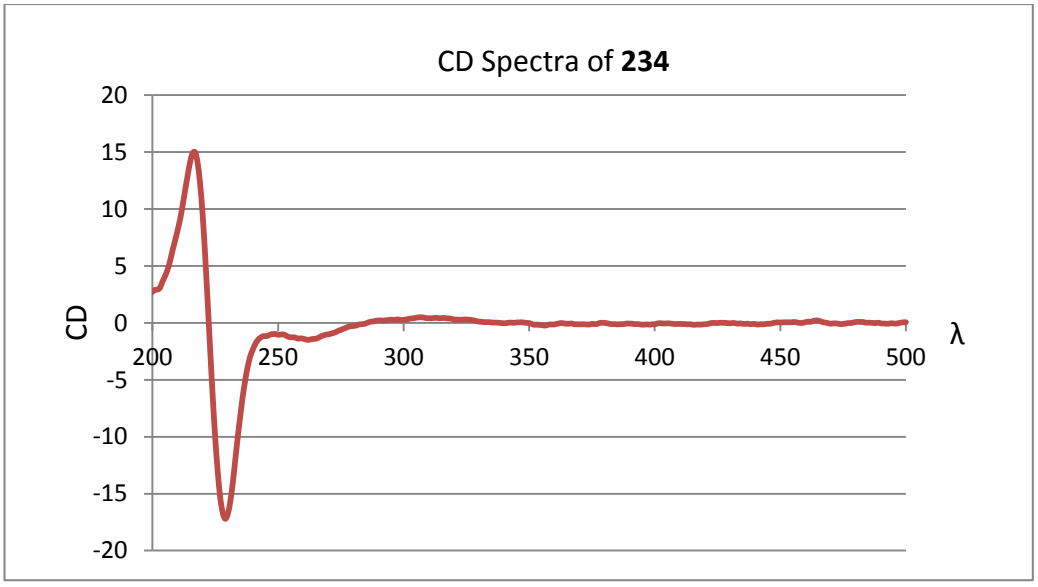


Figure 2.12: *The CD spectra of* ***224*** *and* ***234****.Both had* λ_{MAX} *values in their UV spectra of 218 nm.*

The two theories detailed above in I and II attempt to explain the effect the methyl group has by its interaction with the backbone and ring system, i.e. they do not take into account the pendent amine and are independent of it. So, we would expect that if one of the above models were accurate, the same jump in the isolated epoxide *ees* would have been observed for **234**, and that was not the case. This indicated to us that the methyl group's influence is acting through an interaction with the pendent amine group.

III. It seemed reasonable to us that the methyl group could increase the energy for rotation around the sp^2N-sp^3C bond through steric interaction with the bulkier pendent amines. We conceived that this would have created a more rigid, well-defined catalytic entity which would have been more efficient at transferring its stereochemical information to the substrate (Figure 2.13).

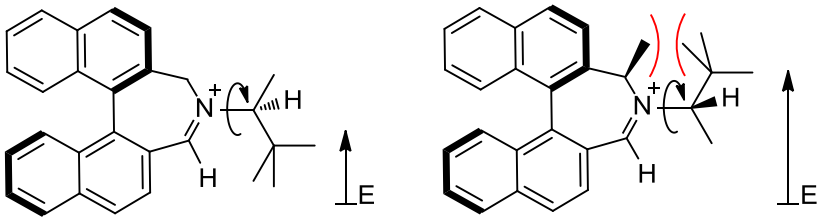


Figure 2.13: *The presence of the methyl group could conceivably have increased the energy barrier for sp^2N-sp^3C bond rotation.*

However, the energy for rotation remained unchanged – VT NMR experiments estimated the energy barrier for rotation of both generations of catalyst to be ≈11-12 kcal mol^{-1} by inputting the coalescence temperature and the separation (Hz) of the two resulting signals into the mathematical relationship: $\Delta G^{+}=RT_c[22.96+\ln(T/\Delta\upsilon)]$ (Figure 2.14). Of course, this is not surprising when one considers that the sp^2N-sp^3C bond rotation pathway is degenerate. That is to say, the amine has two different paths to rotate between any two positions (clockwise or anti-clockwise); one direction will bring the bulky pendent amine into close proximity with the methyl substituent and the other direction will avoid the unfavourable interaction. So even though the energy is raised for one of the given rotation pathways, the other is unchanged. The lowest energy pathway will be used, and therefore we observe no change in the energy barrier for rotation about the sp^2N-sp^3C bond.

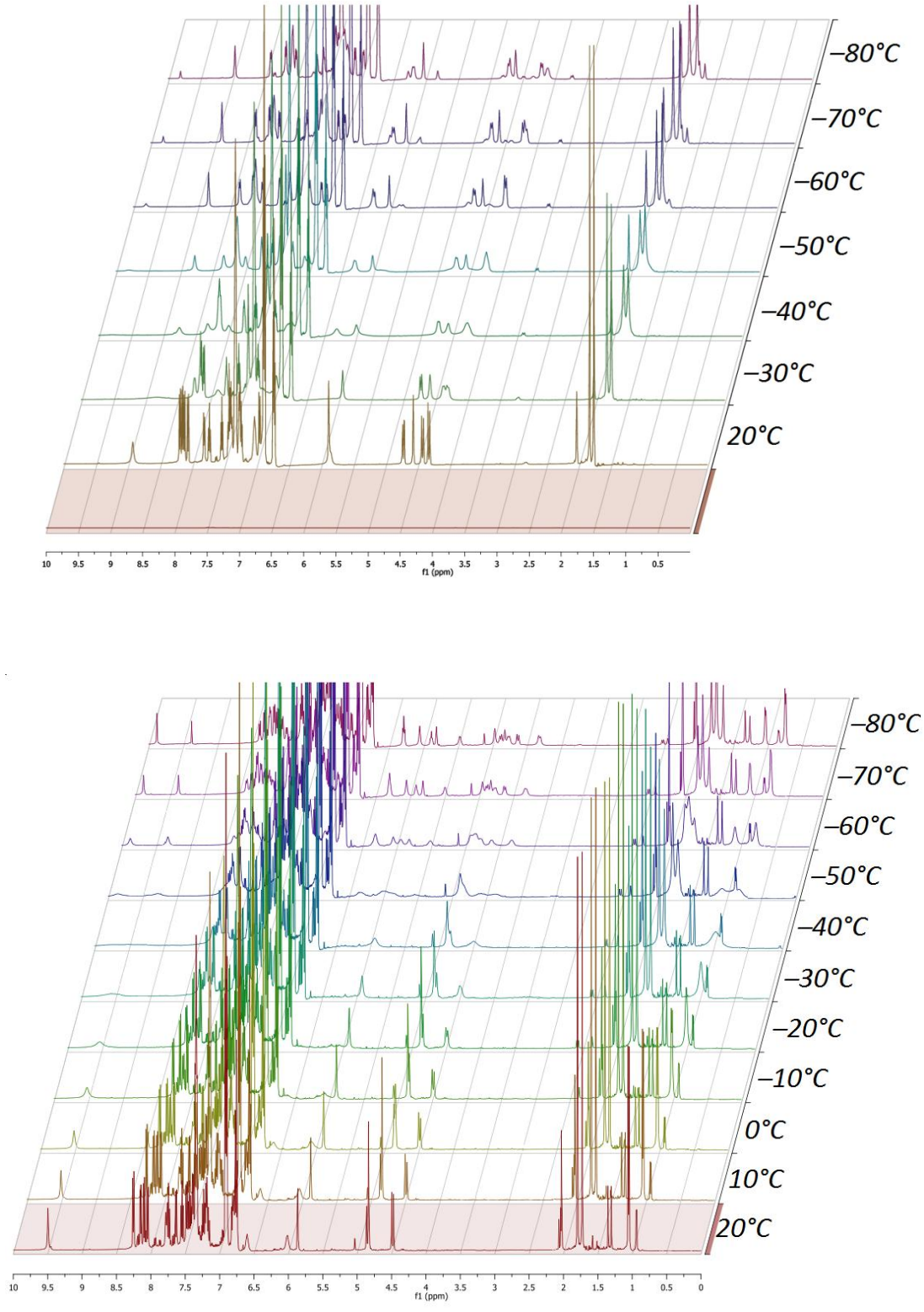
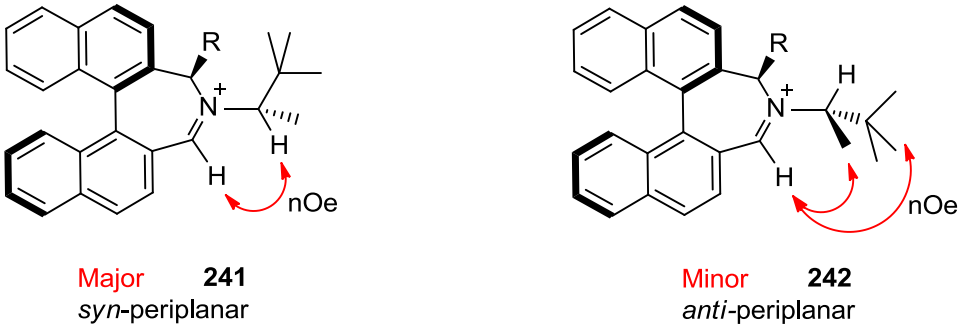


Figure 2.14: *Collated VT NMR data recorded for* ***171*** *and* ***232*** *respectively.*

IV. The addition of the methyl group did, however, affect the ratio of sp^2N-sp^3C rotamers (Figure 2.15).[15] From NOESY experiments performed at –80 °C (Figure 2.15), it was evident these systems heavily, if not entirely, favoured the *syn*-periplanar rotamer **241** where R = H. Where R = Me, the proportion of the *anti*-periplanar rotamer increased significantly **242** (Table 2.9).



Major **241**
syn-periplanar

Minor **242**
anti-periplanar

Figure 2.15: *Illustration of the syn- and anti-periplanar rotamers.*

From the illustrations it is clear that in the *syn*-periplanar rotamer, the stereochemical information is held away from the 'active site' of the catalyst, while the same stereochemical information is positioned much closer to the active site in the *anti*-periplanar rotamer, facilitating its more efficient transfer to the substrate. The reactivity difference between the two generations can be explained by this model too, and Lacour has suggested that the *anti*-periplanar rotamer is less reactive. Indeed, the extra steric crowding near the active site would be expected to increase the energy barrier for transfer of the electrophilic oxygen to the alkene substrate. While the rotamers do not exist discretely at the temperature these salts are employed at (0 °C), the ratio does represent the time-averaged conformation of the catalyst, and provides an indication of the steric influence the pendent amine has.

	Syn-periplanar	*Anti*-periplanar
171	88	12
232 (Me)	60	40
172	72	28
235 (Me)	61	39
223	100	0
233 (Me)	80	20
224	100	0
234 (Me)	100	0

Table 2.9: *Comparison between the* sp^2N-sp^3C rotameric *ratio of the two generations of catalyst. Determined by NOESY @ –80 °C.*

This model also explains why little difference in enantioselectivity was observed between the two isopropylamine-derived catalysts **224** and **234**. In this case, there was no difference between the rotameric ratio, with both entirely favouring the *syn*-periplanar rotamer.

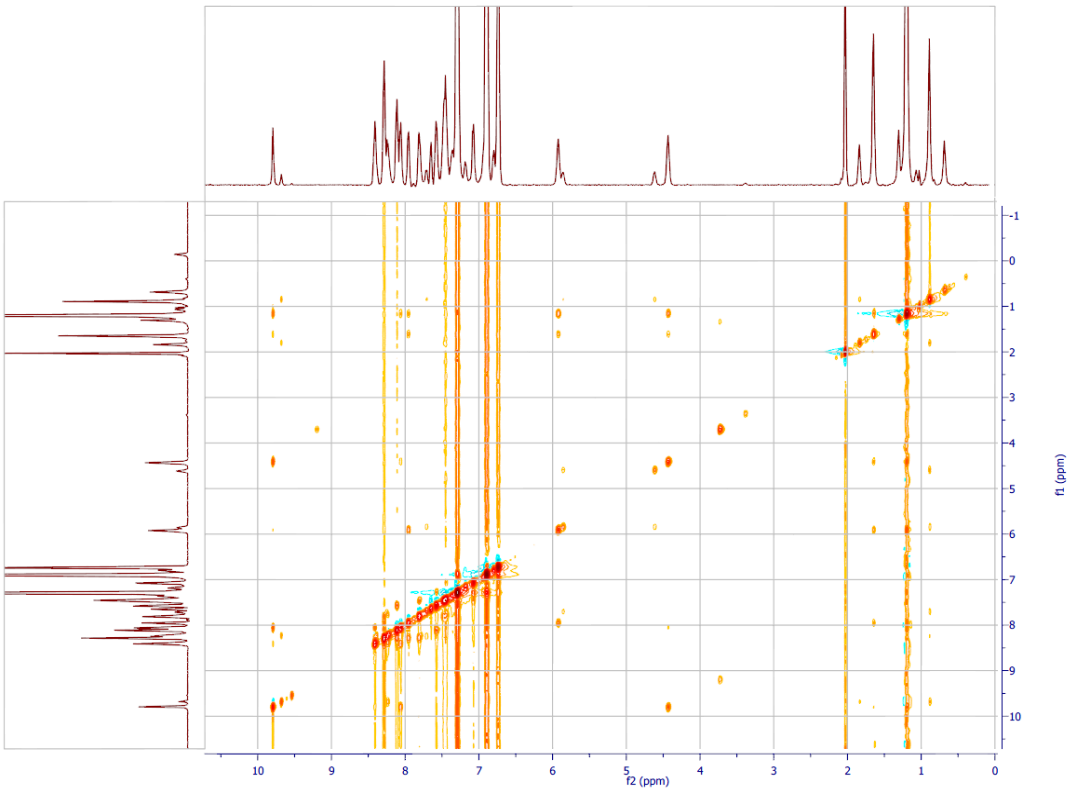


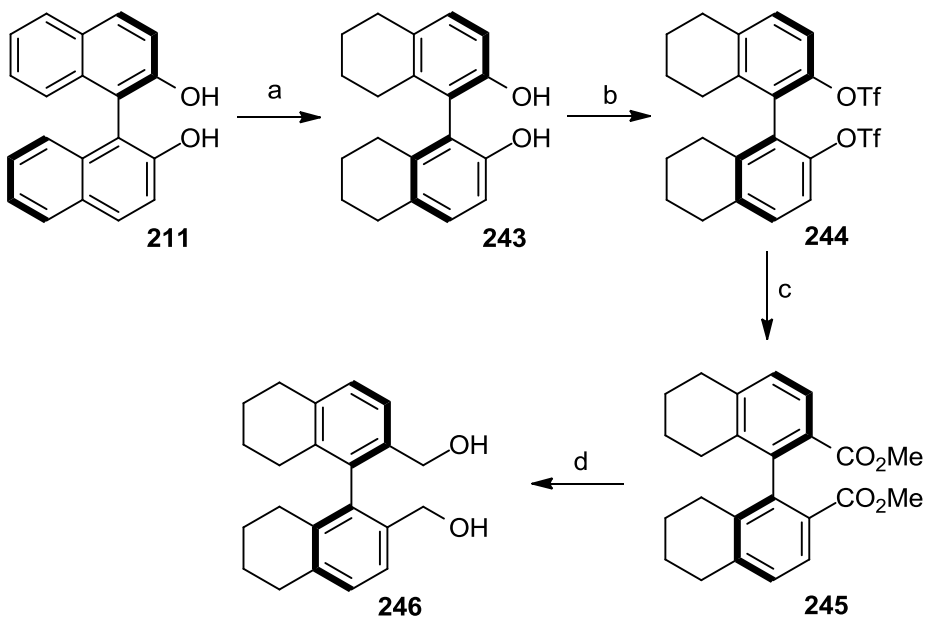
Figure 2.16: *Sample NOESY spectra* ***233****.*

There is one caveat - we have already suggested that the formation of the oxaziridinium salt is completely diastereoselective for the first generation, and so we believe the oxygen transfer to the alkene must be the step in which the pendent amine influences the stereoselectivity. The rotameric ratios would be expected to be different for the oxaziridinium species, and we have not directly measured those values. However, we suspect that the substitution would increase the proportion of the *anti*-periplanar rotamer for the oxaziridinium species too, and this model thus remains valid.

2.6 Catalysts Based on the 5,5',6,6',7,7',8,8'-Octahydrobinaphthyl Azepinium Motif

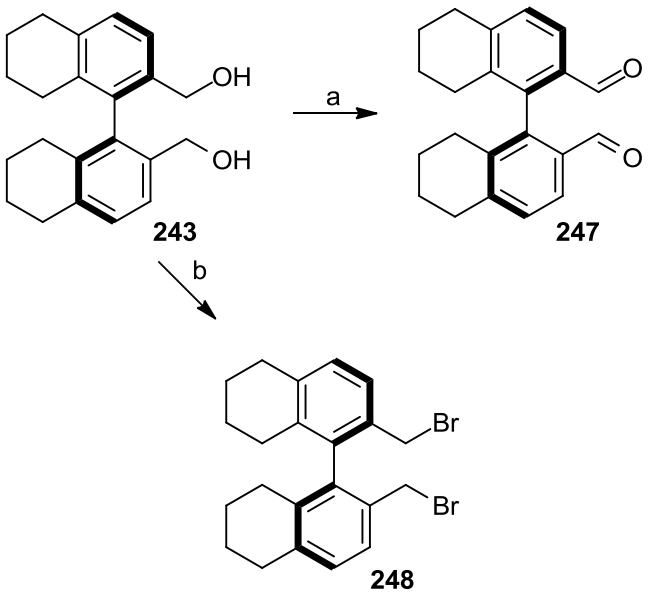
The octahydrobinaphthyl-azepinium backbone motif has been demonstrated by Lacour to contain a larger dihedral angle Φ than the analogous binaphthyl species, when part of an azepinium system.[1] We aimed to create a range of catalysts based on this motif and to incorporate the α-methyl substitution into their structure. We hoped that by marrying the larger dihedral angle with the now-understood modification at the α-position, we could create the most enantioselective iminium catalyst for the epoxidation of tri-substituted alkenes to date.

The synthesis began with the reduction of (R_a)-**211** to octahydro-BINOL **243** using Pd/C with H_2 at a pressure of 3.5 bar.[16] From **243** it was conceivable that we could follow the same route used in the manipulation of the binaphthyl- motif to obtain the desired bis(bromomethyl) octahydrobinaphthyl- species **248**. It has been reported in the literature that this route is unsuccessful – the required benzylic oxidation with NBS was problematic and a complex mixture of brominated products was isolated.[17] The route taken by others and used by us avoided any process which required benzylic C-H functionalization (Scheme 2.18).[1,18] The bis(triflate) **244** was obtained quantitatively from the treatment of **243** with Tf_2O; this functionality allowed the subsequent transformation of **244** to the (bis)methyl ester **245** by a palladium-mediated carbonylation. The reduction of the ester functionality to the diol **246** was achieved with $LiAlH_4$. From **246** two routes were investigated to prepare the desired azepines.



Scheme 2.18: *Synthesis of the bis-alcohol: a) Pd/C, H_2 (3.5 bar), AcOH, 80 ℃,10 d., 45%; b) Tf_2O (3 equiv.), DMAP (0.4 equiv.), 2,6-lutidine (3 equiv.), –30 ℃ → RT, 16 h, 99%; c) $Pd(OAc)_2$ (0.15 equiv.), dppp (0.15 equiv.), MeOH (50 equiv.), DMSO, Hunig's Base, CO (2 bar), 80 ℃, 48 h. 85%; d) $LiAlH_4$ (2 equiv.), Et_2O, 99%.*

Lacour had effected the coupling of the octahydrobinaphthyl- motif to the amine species through its bis(benzaldehyde) **247**, although in our experience it is much simpler, cleaner and higher yielding to achieve the ring formation through (bis)bromomethyl species **248** (Scheme 2.19).

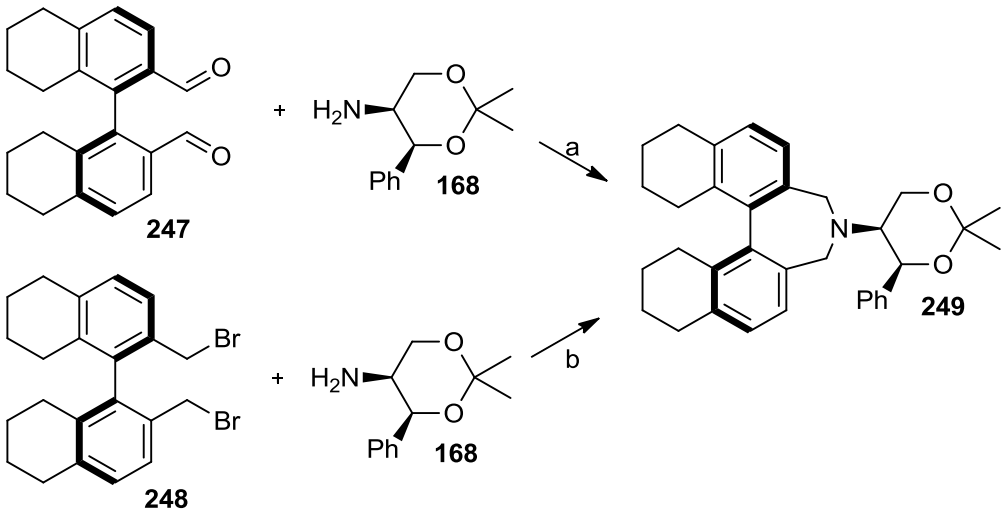


Scheme 2.19: *a) PCC (1 equiv.), CH_2Cl_2, RT, 2 h, 99%; b) PBr_3 (3 equiv.), pyridine (0.1 equiv.), toluene, 60 °C, 3 h, 90%.*

Oxidation of **243** with PCC was simple and furnished **247** in an excellent yield.[1] The synthesis of **248** was more troublesome, however, and three routes were investigated: the first was an acidic displacement of the hydroxyl and required HBr (48% aq.), the reaction did proceed in a good yield, but it appeared that complete racemization had occurred, and we later discovered that a report published by Rawal observed the same result;[17] secondly, we tried to apply the Appel reaction to **243**, this procedure also worked well, but the removal of the triphenylphosphine oxide by-product was time-consuming and difficult; finally, our third route utilized PBr_3, and we were pleased that the isolated product did not require any further purification after work-up, **248** was isolated cleanly in a 90% yield.

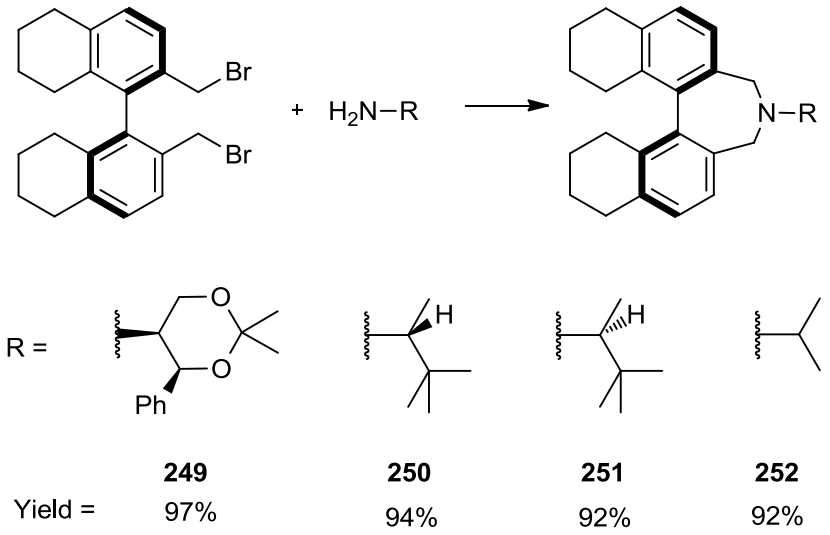
The formation of the azepine ring system with **168** was successful for both of the differently functionalized backbone motifs. The reductive amination procedure did run to full conversion, but the product **259** was impure and required purification by column chromatography; some of the product was lost on the column despite the eluent being buffered with TEA and the yield was compromised as a result, echoing our experiences with the 6,6'-dimethylbiphenyl-azepine species. Contrastingly, the

quantitative isolation of **249** in excellent purity was achieved using exactly the same reaction parameters used for the synthesis of the binaphthyl-azepines (Scheme 2.20).



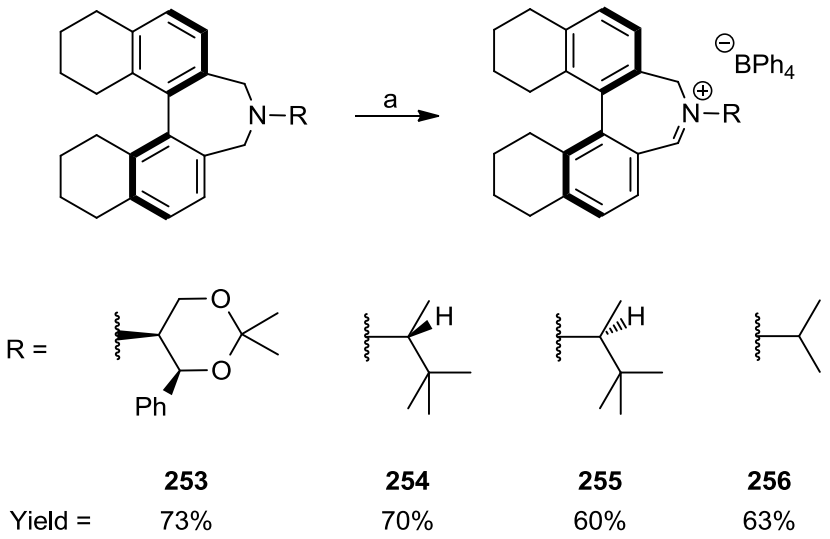
Scheme 2.20: *Comparison of the two methods to synthesize the azepine: a) $NaCNBH_3$ (2.2 equiv.), AcOH, RT, 24 h, 67%; b)* ***168*** *(1 equiv.),* ***248*** *(1 equiv.), K_2CO_3 (3. equiv.), MeCN, reflux, 16 h, 97%.*

We synthesized four octahydrobinaphthyl-azepines following route b), and their preparation is summarized below (Scheme 2.21).



Scheme 2.21: *The family of octahydrobinaphthyl-azepines prepared.*

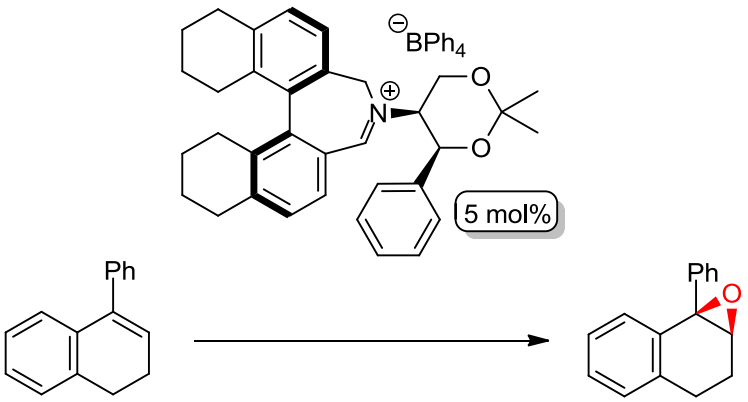
The octahydrobinaphthyl- azepinium salts were prepared by oxidation with NBS, and isolated as their $^{-}BPh_4$ salts following ion exchange, summarized below (Scheme 2.22).



	253	**254**	**255**	**256**
Yield =	73%	70%	60%	63%

Scheme 2.22: *The family of octahydrobinaphthyl-azepiniums prepared: a) NBS (1.1 equiv.), CH_2Cl_2, RT, 30 min; then $NaBPh_4$ (1.1 equiv.), EtOH / MeCN.*

We first assessed **253** for the epoxidation of 1-phenyl-3,4-dihydronaphthylene under a range of aqueous conditions, to determine under which it performed best (Table 2.10). We have recently reported the employment of H_2O_2 or NaOCl as the stoichiometric oxidant; it is desirable to be able to use such oxidants because they are extremely cheap and offer excellent atom efficiency. Oxone® by comparison is relatively expensive and atom inefficient. Unfortunately, we observed only catalyst degradation with **253**, and no catalytic turnover for both the peroxide and hypochlorite systems. Surprisingly, under the two Oxone® systems, **253** demonstrated poorer enantioselectivity than its analogous binaphthyl-azepinium salt **171** when the same 1:1 solvent system was used (Entry 2). We had expected **253** to be slightly superior due to the greater dihedral angle within its backbone.[1] The enantioselectivity was improved when employing the 10:1 solvent system, but still did not match that of **171**.



Entry	Conditions	Time (h)	Conv. (%)	ee (%)
1	Oxone® (2 equiv.), $NaHCO_3$ (5 equiv.), MeCN / H_2O 10:1, 0 °C	0.7	99	93, (+)-(1*R*,2*S*)
2	Oxone® (2 equiv.), $NaHCO_3$ (5 equiv.), MeCN / H_2O 1:1, 0 °C	1.3	99	86, (+)-(1*R*,2*S*)
3	H_2O_2 (6 equiv., 50% aq.), $NaHCO_3$ (0.2 equiv.), MeCN, 0 °C	4	0	-
4	NaOCl (3 equiv., 16% aq.), K_2CO_3 (0.25 equiv.), MeCN, 0 °C	4	0	-

Table 2.10: *Assessment of* ***253*** *for the epoxidation of 1-phenyl-3,4-dihydronaphthylene under a range of aqueous conditions.*

The substrate range was expanded for the two Oxone® condition sets, to include two other tri-substituted alkenes; it was clear that the 10:1 system's superiority was general (Table 2.11).

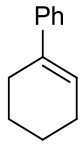
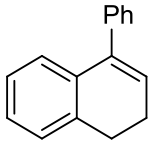
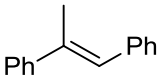
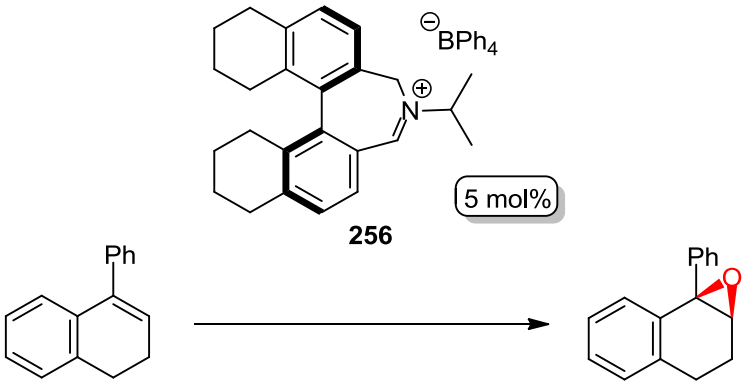
	MeCN / H_2O	
Substrate	**10:1**	**1:1**
	0.6 h, 99, 90, (–)-(1*S*,2*S*)	1 h, 99, 80, (–)-(1*S*,2*S*)
	0.7 h, 99, 93, (+)-(1*R*,2*S*)	1.3 h, 99, 86, (+)-(1*R*,2*S*)
	1 h, 99, 60, (–)-(1*S*,2*S*)	2 h, 99, 63, (–)-(1*S*,2*S*)

Table 2.11: *Extended substrate screen for* **253***, conditions as per Table 2.10: In each case (time, conversion (%), ee (%), config.)*

An assessment of **256** under various epoxidation conditions, including several non-aqueous systems, was also undertaken. It was evident that **256** was much less reactive under the non-aqueous conditions, while the *ee* of the isolated epoxide was similar for all the conditions, although we highlight the (+)-96% *ee* achieved under the non-aqueous MeCN system (Table 2.12).



Entry	Conditions	Time (h)	Conv. (%)	ee (%)
1	Oxone® (2 equiv.), $NaHCO_3$ (5 equiv.), MeCN / H_2O 10:1, 0 °C	1.3	99	90, (+)-(1*R*,2*S*)
2	Oxone® (1 equiv.), $NaHCO_3$ (4 equiv.), 18-crown-6 (2.5 mol%), CH_2Cl_2 / H_2O 3:2, 0 °C, 2 h.	2	99	91, (+)-(1*R*,2*S*)
3	CH_2Cl_2, TPPP (2 equiv.), –20 °C	48	68	90, (+)-(1*R*,2*S*)
4	$CHCl_3$, TPPP (2 equiv.), –20 °C	48	29	86, (+)-(1*R*,2*S*)
5	MeCN, TPPP (2 equiv.), –20 °C	48	88*	96, (+)-(1*R*,2*S*)

Table 2.12: *Assessment of **256** for the epoxidation of 1-phenyl-3,4-dihydronaphthylene under several solvent systems. *16% of which had ring-opened to the diol.*

Two other tri-substituted alkenes were oxidized with the conditions above (from Entries **1** and **2**). The *ees* of the isolated epoxides were similar between the two sets of conditions, but **256** was more reactive under the MeCN-containing conditions (Table 2.13), due, most likely, to the more polar nature of the MeCN solvent system. One could make a case for **256** demonstrating improved stereocontrol over **224**, as indeed it was expected to, but that would be based on the result of the epoxidation of 1-phenylcyclohexene.

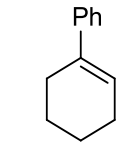
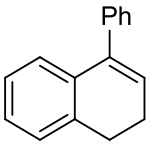
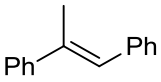
	Solvent System	
Substrate	**MeCN / H_2O**	**CH_2Cl_2 / H_2O**
	1 h, 99, 90, (–)-(1*S*,2*S*)	2 h, 99, 92, (–)-(1*S*,2*S*)
	1.3 h, 99, 90, (+)-(1*R*,2*S*)	2 h, 75, 91, (+)-(1*R*,2*S*)
	3.5 h, 99, 66, (–)-(1*S*,2*S*)	2 h, < 3, -

Table 2.13: *Extended substrate screen for* ***256****, conditions as per Table 2.12. In each case (time, conversion (%), ee (%), config.)*

The two catalysts derived from 3,3-dimethyl-2-butylamine, previously prepared by Lacour as the $^{-}SbF_6$ ion-pair, were tested under Lacour's conditions (Table 2.14). The anion made little difference in this instance, as our results with the $^{-}BPh_4$ species were almost identical to those reported by Lacour for the $^{-}SbF_6$ species.[13]

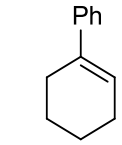
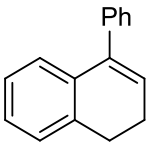
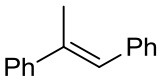
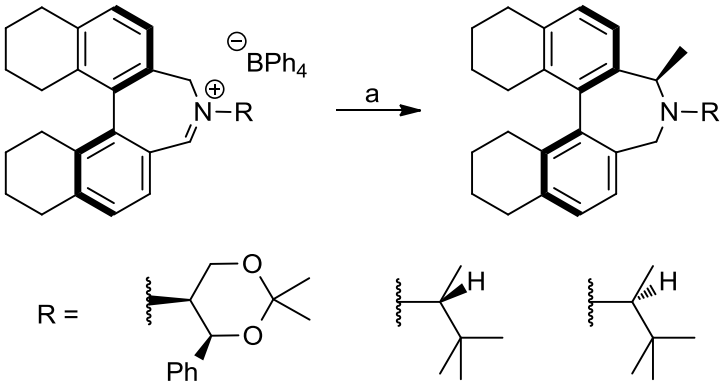
	Catalyst	
Substrate	**254**	**255**
	99, 92, (–)-(1*S*,2*S*)	99, 89, (–)-(1*S*,2*S*)
	89, 93, (+)-(1*R*,2*S*)	99, 87, (+)-(1*R*,2*S*)
	< 4, -	43, 61, (–)-(1*S*,2*S*)

Table 2.14: *Substrate screen for* ***254*** *and* ***255****: Catalyst (5 mol%),* Oxone® (1 equiv.), $NaHCO_3$ (4 equiv.), 18-crown-6 (2.5 mol%), CH_2Cl_2 / H_2O 3:2, 0 °C, 2 h. *In each case: (conversion (%), ee (%), config.).*

Both catalysts **254** and **255** were superior to their respective binaphthyl-azepinium salts with regards to the stereocontrol they demonstrated over the epoxidation process. The epoxidation of *trans*-α-methylstilbene by **254** appears anomalous as its

reactivity is typically similar to the other tri-substituted alkenes, but the same result was achieved several times, and also for **256** under Lacour's conditions. Lacour chose the CH_2Cl_2 / H_2O conditions because he believed the TS would not be stabilized to the same extent in a solvent with a low ε and so would lead to higher epoxide ees. It is perhaps the case, in these instances, that this solvent system exacerbates a so-far unknown unfavourable interaction in any potential TS with the *trans*-α-methylstilbene. It would be expected that an ion-pair solvated by a solvent which possesses a low ε would be held more compactly. Likewise, so would any charged TS, thus any potential unfavourable interaction would be exacerbated.

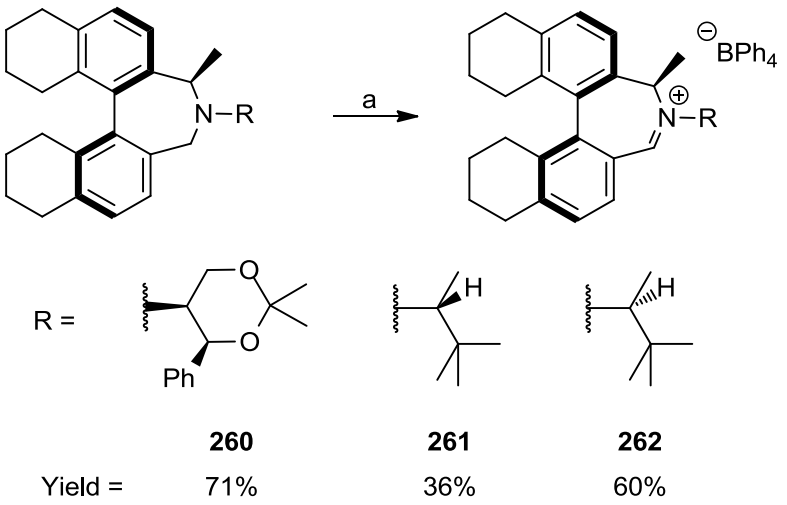
The investigation of the octahydrobinaphthyl motif continued with the introduction of the methyl group to the C-terminus of the iminium bond, generating the three methylazepines shown below (Scheme 2.23). We did not invest any further resources into the modification of **256**, since we did not expect to elicit any improvement in enantiocontrol by the incorporation of the methyl group at the α-position from our results with the analogous binaphthylazepinium salts.



	257	**258**	**259**
Yield =	79%	68%	68%

Scheme 2.23: *Synthesis of the octahydrobinaphthyl-methylazepines: a) MeMgBr (10 equiv.), THF, –78 °C → RT, 16 h.*

The insertion was achieved with MeMgBr and was entirely diastereoselective in all three instances when performed at –78 °C (Scheme 2.24). The assignment of the *pseudo*-axial configuration of the methyl substituent was again possible due to its observed up-field shift in the NMR spectra of the methylazepines.[4]



Scheme 2.24: *Synthesis of the octahydrobinaphthyl-methylazepinium salts: a) NBS (1.1 equiv.), CH_2Cl_2, RT, 15 min.*

The formation of the iminium salts proceeded well; they were again each isolated as the expected regioisomer with the configuration of the methyl substituent maintained in all instances. However, the work-up of **261** was, problematic, the crude salt was macerated in hot EtOH and the resulting powdery solid which formed on cooling was filtered off and washed with Et_2O. These salts usually show no solubility in Et_2O, so it was somewhat unexpected when the solid congealed and formed a viscous yellow oil. The oil was dissolved in CH_2Cl_2 and filtered into a flask, removal of the solvent *in vacuo* eventually provided **261** as a stiff foam in good purity, albeit in low yield. The same occurred for **262**, but the work-up was planned and executed with the expectation that it would show the same behaviour when washed with Et_2O, so no complications arose.

The three octahydrobinaphthyl-methylazepinium salts were tested for their reactivity and stereoselectivity in the epoxidation of a battery of alkene substrates. We were extremely pleased with the stereocontrol exhibited by **260** - we achieved the highest *ees* for the epoxidation of 1-phenylcyclohexene and 1-phenyl-3,4-dihydronaphthylene that have been reported to date for an iminium salt organocatalyst (Table 2.15).

The reactivity of **260** did drop off somewhat in comparison to **253**, but the drop was far larger for the substrates which contained the *trans*-stilbene motif, similar to the

reactivity pattern observed for **254** and **255**. Presumably, in this instance, the more pronounced existence of the *anti*-rotamer caused the manifestation of a strong steric interaction with one of the phenyl substituents present on those substrates (Table 2.15).

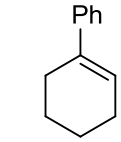
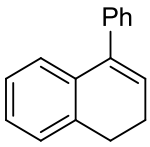
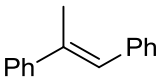
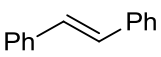
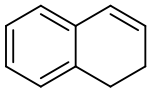
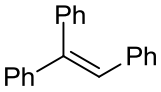
Substrate	260
	1.5 h, 99, 96, (–)-(1*S*,2*S*)
	3 h, 87, 97, (+)-(1*R*,2*S*)
	18 h, 80, 69, (–)-(1*S*,2*S*)
	18 h, 15, 34, (–)-(1*S*,2*S*)
	0.8 h, 99, 0, (+)-(1*R*,2*S*)
	18 h, < 4, -

Table 2.15: *Substrate screen for* ***260****: Oxone® (2 equiv.), $NaHCO_3$ (5 equiv.), MeCN / H_2O 1:1, 0 °C. In each case: (time, conversion (%), ee (%), config.)*

Lacour has previously proposed a mnemonic to predict the facial selectivity that occurs with these catalysts with R_a chirality, explaining the observed enantioselectivity by splitting the interactions into four quadrants.[15] A pendent phenyl group on the alkene has been shown to be crucial to observe high enantioselectivity for these systems, suggesting the existence and necessity of a π-stacking interaction, an interaction which exists in the lower left quadrant **1** as drawn below (Figure 2.17).

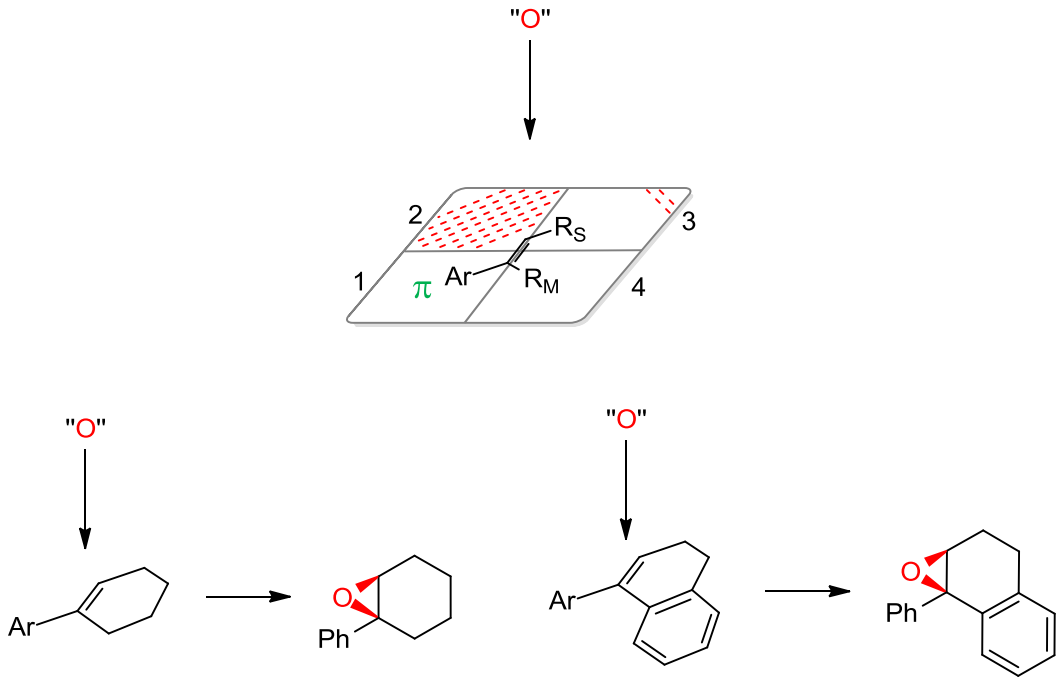


Figure 2.17: *Mnemonic proposed by Lacour, displaying the four quadrants and the key interactions in each. The quadrants have been arbitrarily numbered.*

It has been suggested that quadrant **2** is sterically encumbered from the stereochemical outcome of the epoxidations of (*E*) and (*Z*)-1-methyl-1-phenyl-1-propene, and any substituent other than a proton is subject to a unfavourable steric interaction. Quadrant **3** has been suggested to exert some steric interaction; small R groups are accommodated in quadrant **3** and substrates which satisfy that requirement can led to high ees. This mnemonic suggests why the tri-substituted *trans*-α-methylstilbene is not oxidized with the same enantiocontrol as other tri-substituted alkenes such as 1-phenyl-3,4-dihydronaphthylene and 1-phenylcyclohexene – the relatively large phenyl group would sit in quadrant **3** and be subject to some unfavourable steric interactions, so causing an increase in the energy of the favoured TS, leading to the lower enantiocontrol observed. We suggest that the poor reactivity of the alkenes containing the *trans*-stilbene motif for **260** in this instance is because of an increased steric encumbrance in quadrant **3** (Figure 2.18). Witnessing an improvement in the enantioselectivity for *trans*-α-methylstilbene despite the large increase in steric hindrance suggested to us that the TS from which the minor epoxide is formed was affected by the extra steric encumbrance to an even greater extent.

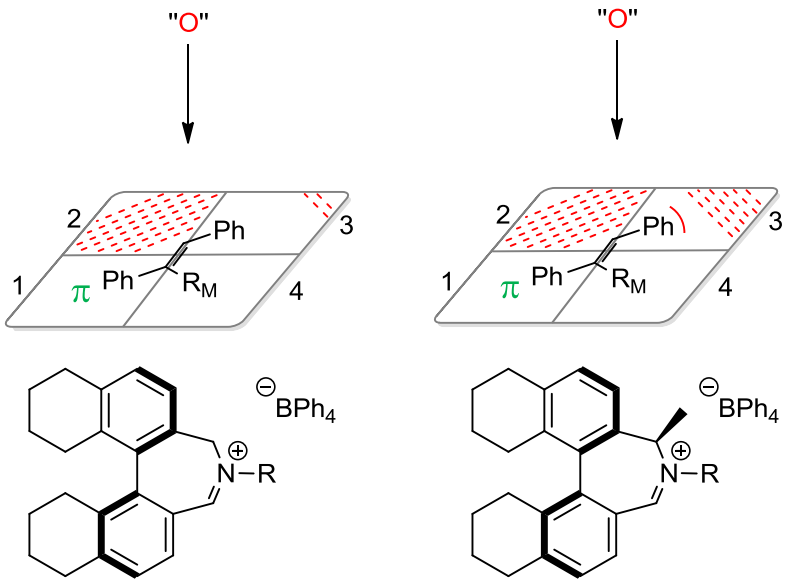


Figure 2.18: *Mnemonic to suggest why the substrates that contain the trans-stilbene motif suffered a large drop in their reactivity with* ***260****.*

Obviously, the factors that determine the stereochemical outcome of these epoxidations mediated by these iminium salts requires a more detailed analysis. The nuances of a 3-D chiral pocket will be lost in translation to a 2-D mnemonic, and to fully understand these observations, to take a full and balanced account of the many factors that contribute to reactivity and enantioselectivity, a detailed computer modelling study is required.

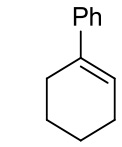
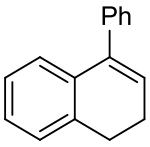
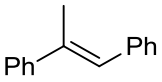
	Catalyst	
Substrate	**261**	**262**
	13 h, 53, 85, (–)-(1*S*,2*S*)	2 h, 99, 90, (–)-(1*S*,2*S*)
	13 h, 44, 90, (+)-(1*R*,2*S*)	2 h, 99, 95, (+)-(1*R*,2*S*)
	13 h, 0, -	2 h, 33, 62, (–)-(1*S*,2*S*)

Table 2.16: *Substrate screen for **261** and **262**: Catalyst (5 mol%), Oxone® (1 equiv.), $NaHCO_3$ (4 equiv.), 18-crown-6 (2.5 mol%), CH_2Cl_2 / H_2O 3:2, 0 °C, 2 h. In each case: (time, conversion (%), ee (%), config.)*

The results from the epoxidations using the catalysts derived from 3,3-dimethyl-2-butylamine were also interesting and offered further insight into the action of the methyl substituent, and by extrapolation, the action of the ^{i}Pr- and Ph- substituents in **226** and **227**. So, for **262** we observe an increase in *ees* of the isolated epoxides and that is what we had expected. Also, the exacerbated reduction in reactivity toward *trans*-α-methylstilbene does concur with our observations with **260**. For **261**, however, we not only see a reduction in the reactivity towards all substrates, but also a reduction in the imparted enantioselectivity. The only other time we had witnessed a drop in epoxide ees, on incorporation of a substituent at the α-position for a 'matched' azepinium system, was when we incorporated ^{i}Pr- and Ph-substituents into **222**. Lacour has shown, and we know firsthand from our own measurements, that the (R_a)-(*R*)-3,3-dimethyl-2-butylamine species favour the *anti*-periplanar rotamer more than the (R_a)-(*S*)-3,3-dimethyl-2-butylamine species *vide supra*. We were not able to measure the rotameric situation for **226** or **227**, but it is no leap of logic to suggest that the bulkier substituents caused an even greater increase in the existence of the *anti*-periplanar rotamer than did the methyl group. This led us to conclude that the relationship between the occupancy of the two rotamers and the enantioselectivity of the resulting catalyst is not linear. That is to

say, that beyond a certain point, an increase in the existence of the *anti*-periplanar rotamer may cause enantioselectivity to decrease (Figure 2.19).

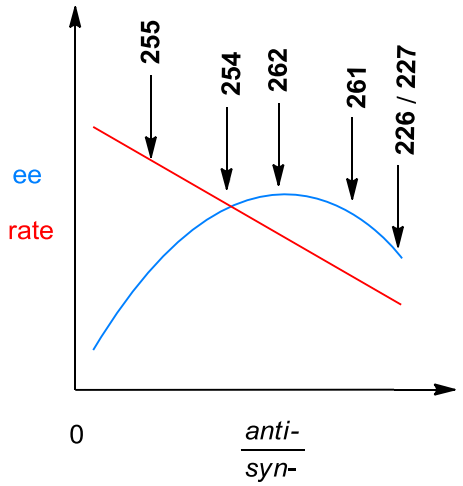


Figure 2.19: *Graph to illustrate how the ratio of the rotamers appear to influence both rate and ee. (Arbitrary units).*

This can be crudely rationalized by considering an increasing steric bulk in sector **3**; to the point at which even a small R group (R_S) becomes subject to unfavourable steric interactions (Figure 2.20). That, for such tri-substituted substrates, leads to a decrease in both reactivity and enantioselectivity.

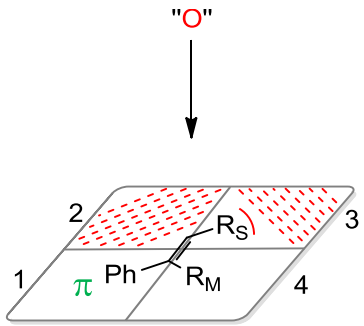
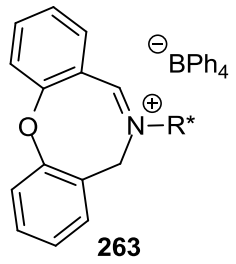


Figure 2.20: *Mnemonic to illustrate an increased unfavourable steric interaction in quadrant **3** present in catalysts **226, 227** and **261**.*

2.7 Investigation Into the Utility of 1,5-Oxazocines as Organocatalysts for the Asymmetric Epoxidation of Alkenes

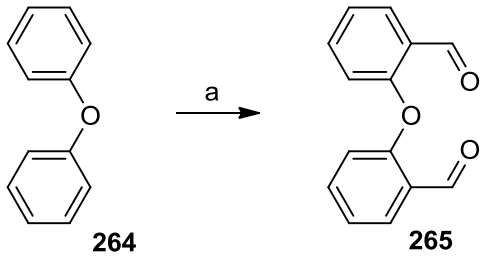
With the different families of iminium salt catalyst we have designed to date, we can epoxidize *cis*-di-substituted and tri-substituted alkenes that contain aromatic functionality with excellent enantiocontrol. To investigate whether we might be able to create a range of catalysts that might demonstrate excellent enantioselectivity for other structural classes of alkenes, we began a preliminary study into the synthesis and use of a new family of iminium salt catalysts based on a *tropos* 8-membered 1,5-oxazocinium ring system **263** (Figure 2.21).



263

Figure 2.21: *General target structure for the new iminium salt species.*

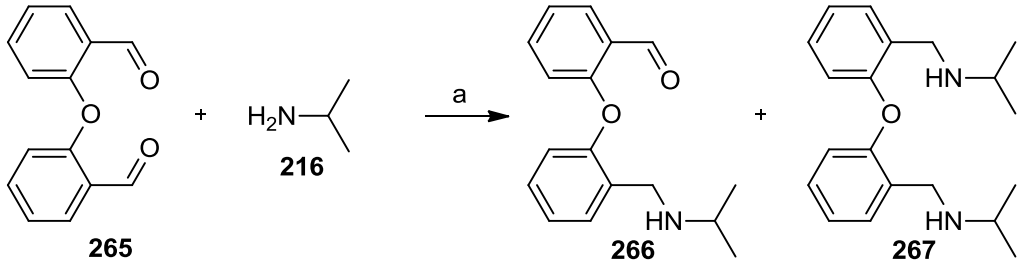
We initially planned to form the 1,5-oxazocine ring system using a reductive amination procedure. The required *bis*(benzaldehyde) **265** was prepared in one step by a di-*ortho*-formylation of diphenyl ether **264**, which was achieved by an *ortho*-lithiation procedure employing ^{n}BuLi. The resulting dianion was quenched with DMF, and **265** was isolated in a 48% yield (Scheme 2.25).



264 **265**

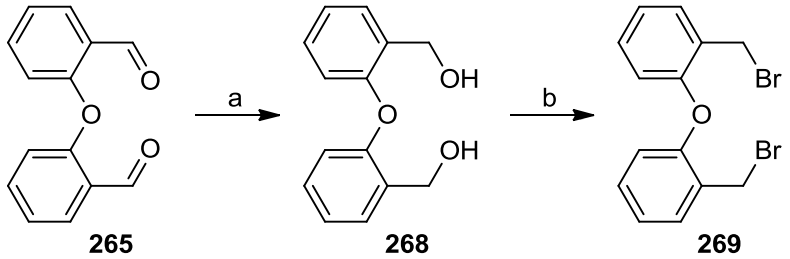
Scheme 2.25: *Synthesis of (bis)aldehyde* ***265****: a)* ^{n}*BuLi (3 equiv.),* −78°C → RT, 16 h, then DMF (3 equiv.), 48%.

The reductive amination was attempted using the conditions which had been successful for the formation of the azepine ring systems; in this instance, however, no ring closure with **265** was observed. The NMR spectrum of the crude mixture showed what appeared to be a mixture of 3 compounds: un-reacted **265**, mono-addition **266** of the amine and di-addition **267**. Repeating the reaction at high dilution (1 mM) and slow addition of the amine (6 h) still did not result in the formation of the desired cyclised product (Scheme 2.26).



Scheme 2.26: *Attempted synthesis of a 1,5-oxazocine: a) $NaCNBH_3$ (2.2 equiv.), AcOH, RT, 1 mM, 10 h.*

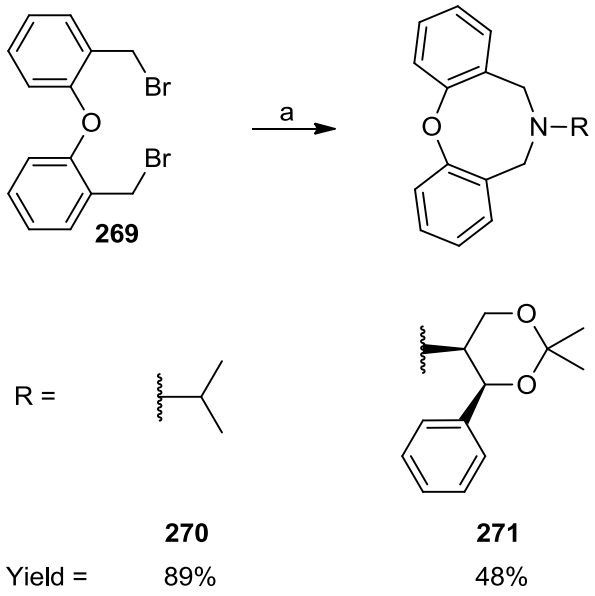
We considered that the required 8-exo-trig cyclisation might be unfavourable; to circumvent the problem, we envisaged that an 8-exo-tet cyclisation might be more facile. We therefore prepared the (bis)bromomethyl compound **269**, *via* diol **268** Scheme 2.27).



Scheme 2.27: *Synthesis of bis-bromomethylene **269**: a) $LiAlH_4$, Et_2O, 0 °C, 98%; b) HBr (48%), reflux, 4 h., 85%.*

Much to our delight, the coupling of **269** and **216** to form the oxazocine **270** ring was successful when employing the same simple procedure used for the binaphthyl- and octahydrobinaphthyl- species, and we used the procedure to create chiral oxazocine **271** from **168**. The amines were added over 6 h to a refluxing

solution of **269** in MeCN, as a precaution to ensure ring closure was achieved. The yield of the cyclisation with the bulkier **168** was somewhat lower than for the smaller **216**, though much of the disparity was due to the requirement for further purification of **271** (Scheme 2.28).

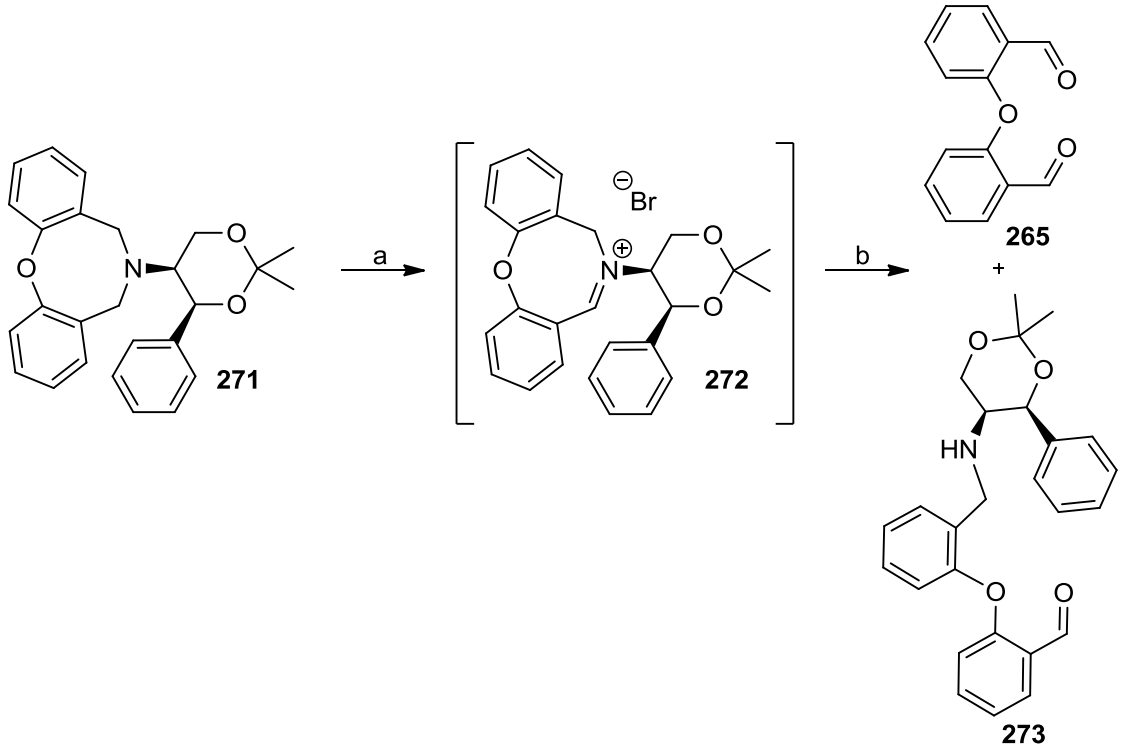


Scheme 2.28: *Synthesis of the oxazocines: a) K_2CO_3 (3 equiv.), MeCN, reflux, 16 h.*

We expected these species would not be conformationally well-defined, and indeed, the interchange between several conformations of the acetonamine-containing oxazocine was slow on the NMR timescale at RT.

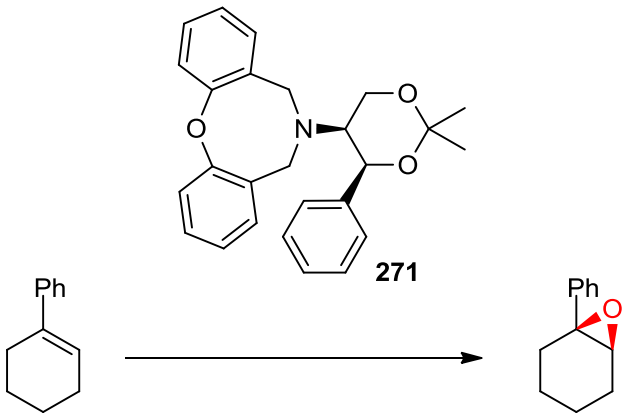
We intended to synthesize the respective oxazocinium salts of the species prepared above to test their efficacy as organocatalysts for the epoxidation of alkenes. Much to our surprise, all attempts to isolate the salts failed - we observed decomposition of the SM in all instances. On addition of NBS to a stirring solution of the oxepines, the colour rapidly changed to an intense yellow, perhaps indicating that the iminium salt **272** did form. However, the colour rapidly dissipated during aqueous work-up. This observation led us to suspect that the oxazocinium was being hydrolysed. To investigate our suspicion, we performed the oxidation of **271** in an NMR tube in CD_2Cl_2; indeed, we observed the rapid colour change and emergence of a signal at 9.21 ppm – characteristic of the N=C<u>H</u> proton. To test its susceptibility to hydrolysis, we then introduced a few drops of D_2O and mixed the biphasic

mixture by ultrasound at RT for several minutes. After that time, a second NMR spectrum was recorded; the iminium signal had disappeared while two signals at 10.51 and 9.98 ppm appeared – one of which corresponded to the bis(benzaldehyde), and the other, presumably, corresponded to the partially hydrolysed product **273** (Scheme 2.29).



Scheme 2.29: *Decomposition of the oxazocine: a) NBS (1.1 equiv.), CD_2Cl_2, RT, 5 min., then b) D_2O, ultrasound, 5 min, RT.*

It has been shown that the synthetic precursors to azepinium salts also catalyse the epoxidation reaction, so in spite of the failure to synthesize the oxazocinium salts, we screened the oxazocines under several sets of conditions to ascertain whether or not this class of compound were capable of catalysing the epoxidation of alkenes (Table 2.17).



Entry	Conditions	Time (h)	Conv. (%)	ee (%)
1	Oxone® (2 equiv.), $NaHCO_3$ (5 equiv.), MeCN / H_2O 10:1, 0 °C	5	0	-
2	Oxone® (2 equiv.), $NaHCO_3$ (5 equiv.), MeCN / H_2O 1:1, 0 °C	5	50	35
3	Oxone® (2 equiv.), $NaHCO_3$ (4 equiv.), 18-crown-6, CH_2Cl_2 / H_2O 3:2, 0 °C	8	0	-
4	$CHCl_3$, TPPP (2 equiv.), –20 °C	8	0	-
5	$CHCl_3$, TPPP (2 equiv.), 0 °C	8	0	-
6	MeCN, TPPP (2 equiv.), 0 °C	8	0	-
7	CH_2Cl_2, TPPP (2 equiv.), 0 °C	8	0	-

Table 2.17: *Assessment of oxazocine* ***271*** *in the epoxidation of 1-phenylcyclohexene under a range of conditions.*

When binaphthyl-azepines were used in the recent study by Lacour and Page, they noted that the azepines performed best in the most polar conditions with remarkable similarity - in terms of reactivity and enantioselectivity - to their respective iminium salt counterparts. The similarity did seem to indicate that the iminium salt was formed *in situ*, and the reaction then proceeded along the established pathway. Our results with the oxazocines did echo these results somewhat, i.e. we observed the best conversion with the most polar conditions, but differed in that we did not observe conversion under any other conditions. In this instance however, given that we have shown the oxazocinium species to be readily hydrolysed, the fact that the oxidation only proceeded under the conditions with the highest ratio of water was perplexing and counterintuitive. We concluded then, that these systems did not mediate the epoxidation through the iminium / oxaziridinium mechanism.

Aggarwal demonstrated, as described above in Chapter 1, that under similar conditions, secondary amines were capable of mediating the epoxidation of alkenes.[19] The amines were believed to exist as their respective ammonium salts *in situ*, and were able to coordinate to Oxone® and augment its reactivity in doing so. A process similar to that Aggarwal described did fit our data; it was conceivable that the oxazocinium species was formed *in situ* and then rapidly hydrolysed to **273** and / or **168**, either of which could theoretically hydrogen bond as its ammonium salt to Oxone®, thus activating it to nucleophilic attack (Figure 2.22).

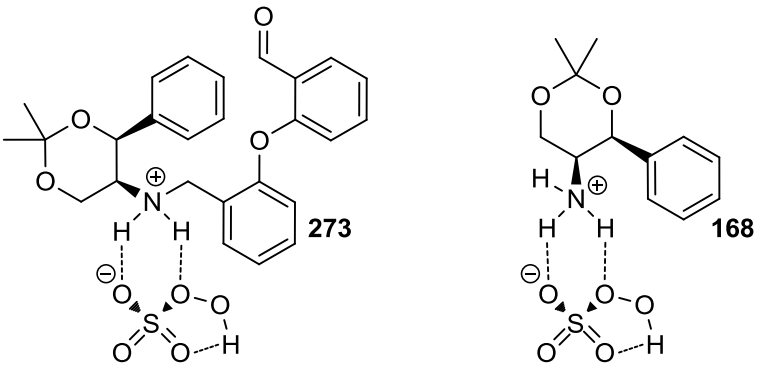


Figure 2.22: *Possible activation of Oxone® to nucleophilic attack by H-bonding interactions between 2° and 1° ammonium salts.*

That there was significant stereoinduction for the epoxidation of 1-phenylcyclohexene more or less ruled out the idea that a dioxirane, formed by oxidation of the benzaldehyde on **273**, was responsible for the epoxidation. The resultant dioxirane would probably be too far removed from the chiral information to impart a 35% ee. Further, a dioxirane-mediated epoxidation is unlikely to be feasible from a simple benzaldehyde.

To investigate, an epoxidation of 1-phenylcyclohexene was attempted under the MeCN / H_2O 1:1 conditions with **168** (5 mol%). After 4 h, the reaction was stopped and the conversion was assessed by NMR to be 32%, which was remarkably close to the conversion achieved with the oxazocine **271**. This provided strong evidence in support of a mode of action similar to that proposed by Aggarwal.

It was clear that the oxazocines were a dead end, and while we were pleased to understand why they made poor catalysts, we did not take our investigation into the utility of 1,5-oxazocines as organocatalysts any further.

2.8 Application of the Page Asymmetric Epoxidation in the Synthesis of (+)-Scuteflorin A

The *scutellaria* genus, more commonly known as skullcaps, has been used in herbal remedies for many hundreds of years. To date, around 300 individual compounds have been isolated from the *scutellaria* and many of these have been shown to have pharmacological activities, including anti-bacterial; anti-angiogenesis; anti-viral; anti-convulsant and anti-cancer activities.[20] *Scutellaria lateriflora L.*, or the American skullcap, has demonstrated particular utility as a therapy for anxiety in a recent study of healthy subjects.[21] During an investigation to elucidate the origin of the therapeutic activity of the American skullcap, Khan reported the isolation and characterization of two new dihydropyranocoumarins – scuteflorins A **274** and B **275** (Figure 2.23).[22]

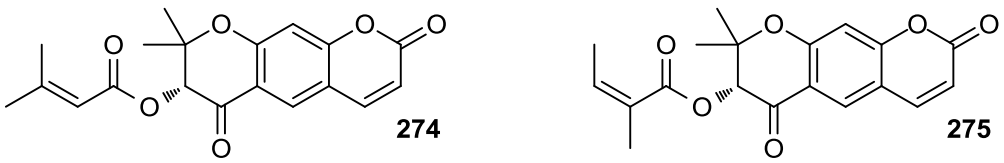


Figure 2.23: *The recently isolated novel dihydropyranocoumarins.*

We have previously reported the highly enantioselective epoxidation of the *cis*-alkene seselin **180** as the key step in the synthesis of (–)-(3'*S*)-lomatin **182** and (+)-(3'*S*,4'*R*)-*trans*-khellactone **181**, using our non-aqueous epoxidation conditions.[23] To our knowledge, only the racemic synthesis of **274** has so far been accomplished.[24] We envisaged that the synthesis of the scuteflorins could be effected by a similar epoxidation of xanthyletin **276** to install the stereocentre and functionality required for further manipulation. Owing to the similarity of the alkene motif in **180** and **276**, we believed that we would be able to form the epoxide with excellent enantiocontrol (Figure 2.24).

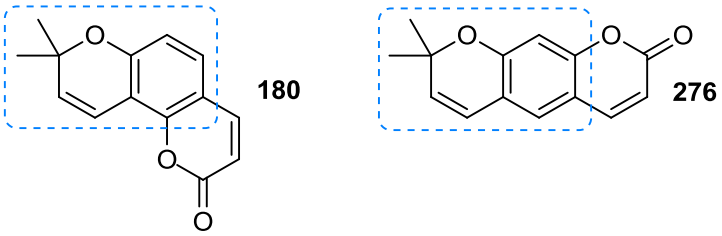


Figure 2.24: *The cis-di-substituted alkenes seselin* ***180*** *and xanthyletin* ***276****.*

A disconnection which summarizes our retrosynthetic analysis to **276** is shown below (Figure 2.25).

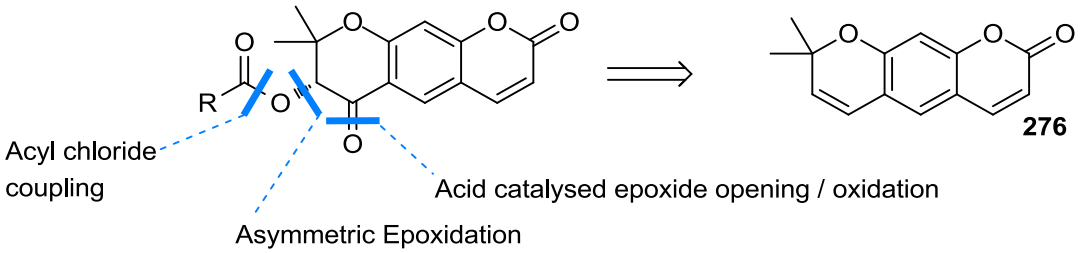
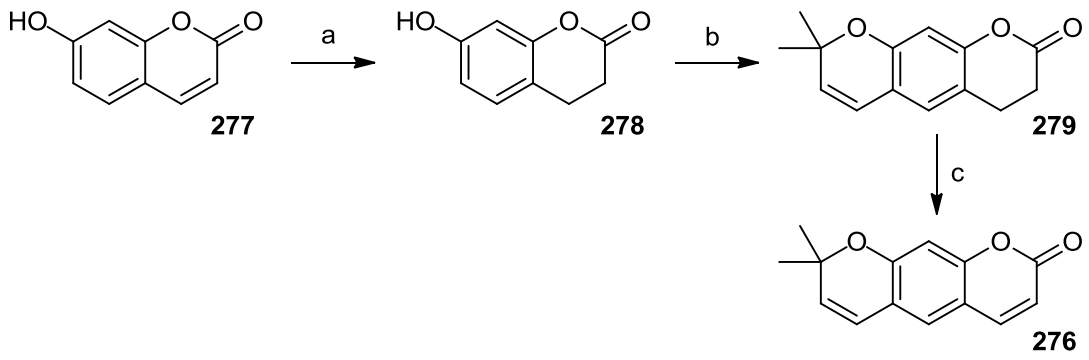


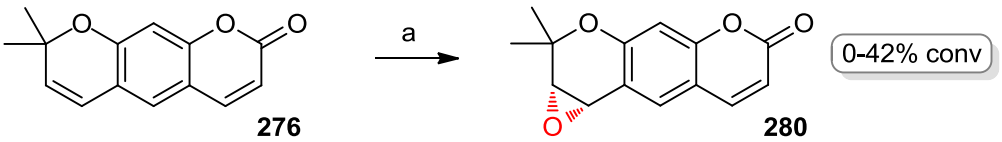
Figure 2.25: *Retrosynthetic summary.*

The synthesis of **276** was straightforward, and originally followed the route starting from 7-hydroxycoumarin **277** outlined by Jun (Scheme 2.30).[25] The hydrogenation of **277** proceeded as expected, and, after the complete consumption of the coumarin was observed by TLC, a solvent change was performed followed by an aqueous work-up. Subsequent filtration though celite then carbon black yielded chroman **278** in an essentially quantitative yield. The phenylboronic acid-catalysed cyclisation of 3-methyl-2-butenal with **278** was achieved applying Jun's optimized conditions in a yield of 51%. This *ortho*- directing cyclisation on a phenol with an enal species was first outlined by Nagata in 1976, who proposed that the cyclisation proceeds through a [3,3]-sigmatropic rearrangement.[26]



Scheme 2.30: *Synthesis of xanthyletin: a) Pd/C, AcOH, H_2, 30 °C, 16 h, 99%; b) 3-methyl-2-butenal, $PhB(OH)_2$, toluene / AcOH, reflux, 40 h, 51%; c) DDQ, toluene, reflux, 10 h, 52%.*

The re-introduction of the enone moiety with DDQ proceeded well with full conversion, and the isolated yield was high on a small scale (>90%). There were complications with the work-up when the reaction was scaled-up and those complications did compromise the isolated yields (52%). The purification of the crude deep red oil was attempted by flash column chromatography. Unfortunately, **276** isolated from this procedure was not pure and held a distinct red colour. Despite successive purification attempts and crystallizations, an unidentified residual impurity from the dehydrogenation step could not be removed - in some cases, a solution made from seemingly pure, colourless, crystalline xanthyletin turned red on addition of TPPP. The subsequent epoxidation under our non-aqueous conditions was frustratingly and uncharacteristically irreproducible - the conversion would typically range from 0% to 42% (Scheme 2.31).



Scheme 2.31: *Epoxidation of xanthyletin prepared by Jun's route: a) TPPP, $CHCl_3$, –30 °C, iminium salt **174** (10 mol%).*

In an attempt to solve the issue, the possibility of using DDQ catalytically to achieve the dehydrogenation was investigated as well as several other methods including: a Pd mediated protocol described by Shvo;[27] Nicolaou's IBX methodology[28] and also a selenoxide elimination procedure. Presented below are the results from the attempts to synthesize xanthyletin (Table 2.18).

Entry	Conditions	Conv.	Yield
1	DDQ (5 mol%), NMO, CH_2Cl_2 / MeCN, reflux 20 h	0%	
2	IBX, DMSO, fluorobenzene, 72 h, 70 - 80 °C	33%	
3	$Pd(OAc)_2$, ADP, $NaHCO_3$, THF, reflux, 40 h	0%	
4	LDA, PhSeCl, THF, –78 °C then H_2O_2, THF, 0 °C, 1 h		4%

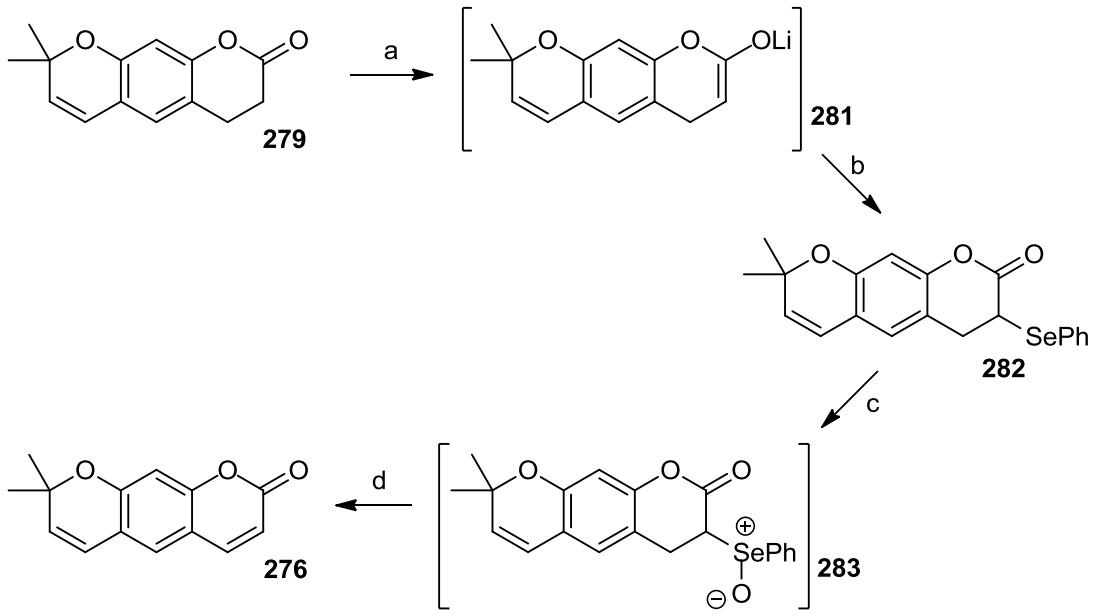
Table 2.18: *Attempted oxidations of* ***276****.*

Disappointingly, the experiment with a catalytic loading of DDQ was completely unsuccessful, most likely because it was ill-conceived.[29] Perhaps a more thorough investigation of potential stoichiometric re-oxidants and other parameters could have elicited a successful protocol, but this route was not pursued any further.

The oxidation with IBX, developed by Nicolaou, was initially promising and significant conversion was observed; however, we were unable to optimise the procedure significantly and acknowledged that a 33% yield was not acceptable.

The formation of an enone from an α,β-unsaturated ketone with a palladium species is well known. The procedure chosen for the attempted oxidation employed $Pd(OAc)_2$ and required a stoichiometric quantity of allyl diethyl phosphate (ADP) – which plays a critical role in the catalytic cycle. Unfortunately, in our hands, the procedure was unsuccessful.

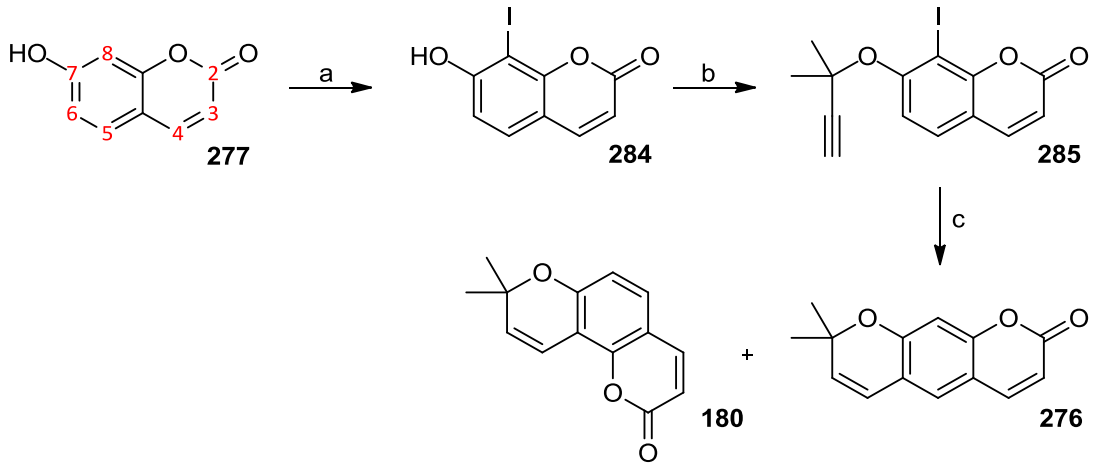
The selenoxide pathway was more taxing and less economical than the DDQ or IBX mediated procedures, but, if we were able to achieve a high yield, it would certainly have made a viable route. Formation of the selenyl species **282** *via* the intermediate lithium enolate **281** was straightforward, and **282** isolated in an acceptable yield.



Scheme 2.32: *Formation of xanthyletin by a selenoxide elimination: a) LDA, –78 °C, THF; b) PhSeCl, THF, –78 °C to RT, 48%; c) 30% H_2O_2, THF, 0 °C, 7%.*

Many methods for the oxidation of selenide compounds are known, though the presence of an electron-rich double bond did rule out the use of O_3, because the facile ozonolysis would be impossible to control. The chance for the epoxidation of the double bond, and also the potential Bayer-Villiger oxidation of the ester, ruled out the use of peracids. Aqueous hydrogen peroxide (30% w/v) presented the most promise, and we decided to attempt a protocol involving its use. The reaction was performed at 0 °C - a temperature at which the elimination is known to occur.[30] Indeed, the formation of **276** appeared to be complete by TLC, so we were then surprised to observe the presence of **282** by TLC after the work-up. A four-fold excess of peroxide was used and so the reaction was quenched with sat. aq. Na_2SO_3 preceding extraction. It is conceivable, we believe, that some of the selenoxide **283** had not undergone elimination and was reduced back to the selenide by the thiosulfate. Frustratingly, only a 7% yield of xanthyletin and 10% of **279** were obtained after flash column chromatography. The exhaustion of starting materials and time constraints caused us to cease our efforts with this method (Scheme 2.32).

The unsuccessful attempts to isolate significant quantities of xanthyletin of suitable purity through the route outlined by Jun and variants thereof, led us to seek alternatives. The most promising in the literature was an apparently robust synthesis again beginning from **277**.[31] The procedure first requires the iodination of **277** at the 8 position **284** followed by the attachment of 3-methyl-butyne at the phenolic hydroxyl **285**, which was then cyclised at high temperature. Coumarin **277** participates in electrophilic aromatic substitution principally through the 8 position, a propensity which was demonstrated in North's synthesis of **180** from **277**.[32] So, the iodination was required to alter this preference, and causes the cyclisation to occur preferentially at the otherwise less favoured 6 position. NMR analysis of our crude cyclisation reaction mixture showed that **276** and **180** were both produced and in a ratio of ≈4:1. The iodine is concomitantly removed in the cyclisation process, perhaps explaining the formation of **180**. This second route allowed us access to pure **276** on a gram scale in an overall yield of 30% (Scheme 2.33).



Scheme 2.33: *The second route used for the synthesis of xanthyletin: a) I_2, KI, NH_4OH, RT, 4 h, 65%; b)* 3-chloro-3-methyl-butyne, K_2CO_3, CuI, Cu, acetone, reflux, 3 h, 99%; c) *N,N-dimethylaniline, 250 °C, µW,* ***276*** *45%,* ***180*** *12%.*

We wanted to assess the three main structural classes of catalyst developed by our group, for the epoxidation of **276**, namely: biphenyl-azepinium;[33] dihydroisoquinolinium[10,34] and octahydrobinaphthyl-azepinium salts (Figure 2.26). Catalysts **169** and **286** were prepared according to well-used procedures within our

group that are outlined in Chapter 3, while a sample of catalyst **174** was available to use from previous studies and was not synthesized during this work.

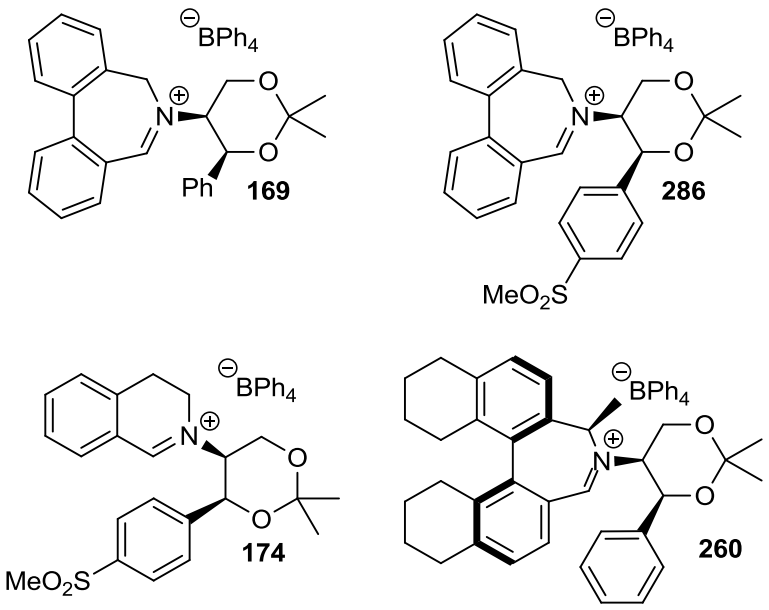


Figure 2.26: *The four catalysts assessed in the epoxidation of xanthyletin, covering the three main structural classes of catalyst used within our group.*

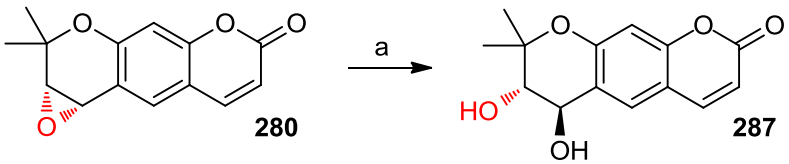
We screened the catalysts for the epoxidation of both **276** and **180**. We were not surprised to observe that the **260** was poor for both alkenes; the backbones featuring atropisomerism only show good selectivity and reactivity for electron rich tri-substituted alkenes. However, we were slightly disappointed that catalyst **174**, used previously for the enantioselective epoxidation of **180**, gave only a 94% *ee* for the epoxidation of **276** as we suspected it would be the best catalyst for this motif. Somewhat surprisingly, and much to our delight, the biphenyl catalyst **169** was actually superior in terms of reactivity and enantioselectivity. Full conversion and an *ee* of 99% was achieved in <30 h. Because the sulfone group was present in **174**, and because it had shown the best selectivity under non-aqueous conditions previously, we wanted to know whether we could improve upon the reactivity **169** displayed, and thus prepared **286**. Unfortunately it performed worse for unknown reasons, but the reactivity of **169** was more than acceptable, and accordingly we employed **169** in the epoxidation of **276**.

Entry	Catalyst	Substrate	Conditions	Conv. (%)	ee (%)	Enantiomer
1	**169**	**276**	TPPP (2 equiv.), $CHCl_3$, –30 °C, <30 h	99	99	(–)
2	**287**	**276**	TPPP (2 equiv.), $CHCl_3$, –30 °C, <30 h	80	98	(–)
3	**174***	**276**	TPPP (2 equiv.), $CHCl_3$, –30 °C, 39 h	82	94	(–)
4	**270**	**276**	Oxone® (2 equiv.), $NaHCO_3$, MeCN / H2O, 0 °C,	2	-	-
5	**169**	**180**	TPPP (2 equiv.), $CHCl_3$, –30 °C, 18 h	90	98	(+)
6	**287**	**180**	TPPP (2 equiv.), $CHCl_3$, –30 °C, 39 h	40	93	(+)
7	**174***	**180**	TPPP (2 equiv.), $CHCl_3$, –30 °C, 39 h	98	96	(+)
8	**270**	**180**	Oxone® (2 equiv.), $NaHCO_3$, MeCN / H2O, 0 °C,	3	-	

Table 2.19: *Attempted epoxidations, run at 5 mol% loading. *10mol% loading.*

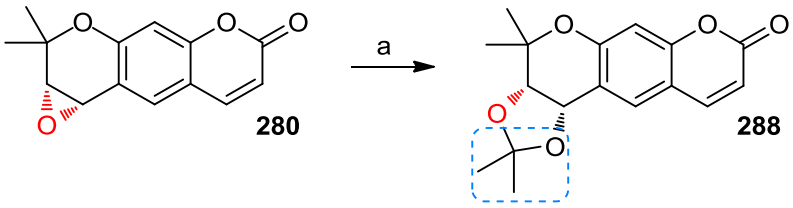
On smaller scales (<50 mg of **276**), (+)-**280** was isolated quantitatively in very good purity negating the need for column chromatography; the work-up required the addition of Et_2O to precipitate any TPPP and its reduced by-products, followed by filtration through celite and the removal of solvents. However, when the epoxidation was performed on a larger scale (0.8 g) the epoxide was not obtained with the same purity (incomplete conversion) and purification by column chromatography was required. Despite buffering the eluent with TEA at 2%, a substantial amount of the epoxide was unrecovered, which dropped the isolated yield to 69%.

The next step followed an acid-catalysed epoxide ring-opening procedure used by our group previously in the synthesis of **181**. The epoxide (–)-**280** was stirred in a mixture of acetone and 1M H_2SO_4, and this was expected to furnish (+)-*trans*-decursinol **287** quantitatively in good purity (Scheme 2.34).



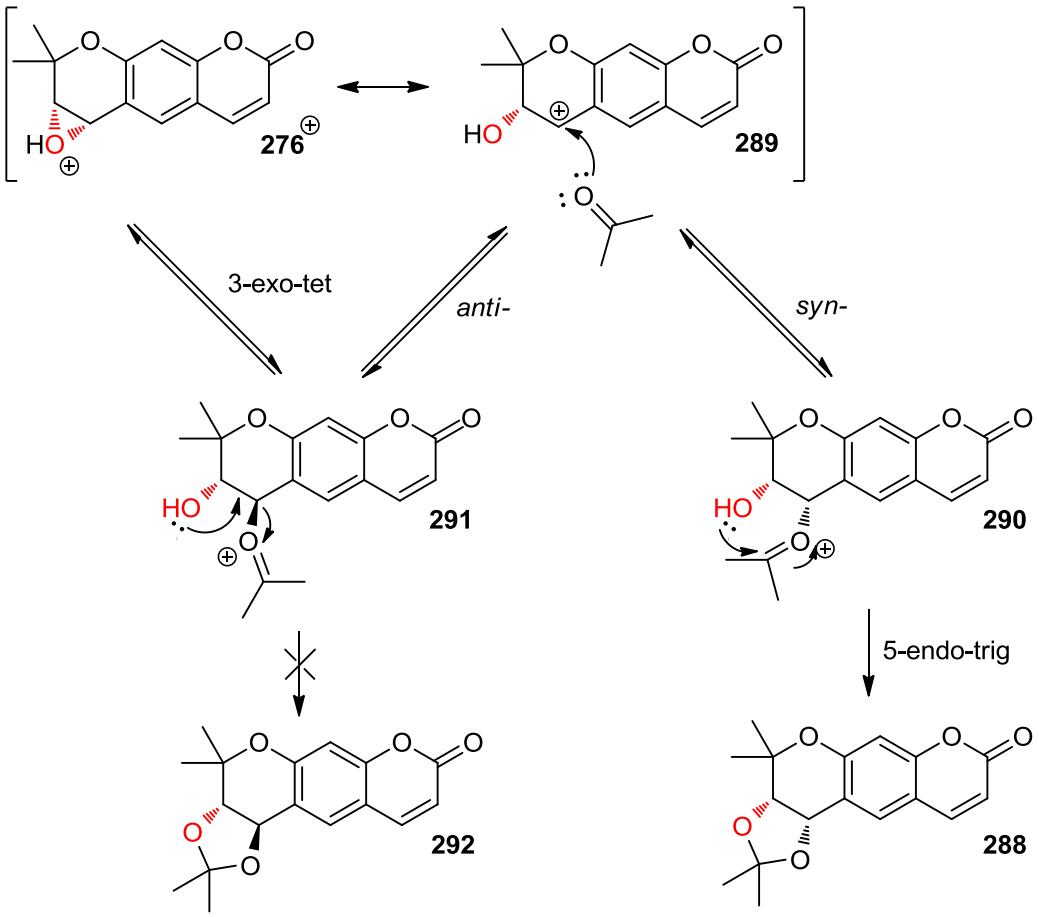
Scheme 2.34: *Acid catalysed ring opening of the epoxide: a) acetone / 1M H_2SO_4 (2:1), RT, 10 min., 60%.*

Interestingly, a significant by-product **288** was observed (8%), which we were unable to conclusively identify by NMR spectroscopy, though it seemed clear there were two extra methyl groups present. Results from high resolution mass spectrometry suggested the addition of a C_3H_6O fragment, and we concluded it was due, somehow, to the incorporation of acetone, which the NMR data also supported, but we were still unsure of the connectivity. Fortunately, we were able to obtain a single crystal for X-ray analysis, which gave us the structure. The structure seemed to suggest that acetone had participated in a variant of the Ritter reaction with the epoxide (Scheme 2.35).[35]



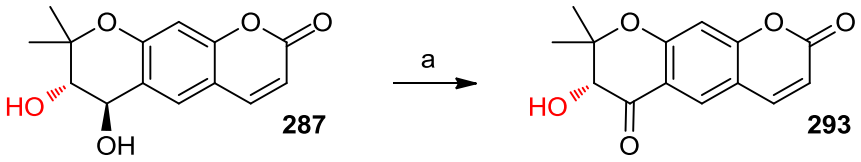
Scheme 2.35: *Acetone Ritter-type product from xanthyletin oxide: a) H_2SO_4, acetone, RT, 10 min, 8%.*

The stability of the benzylic cation **289** and the *cis*- configuration of the acetal in **288** imply that acetone first interacts with the empty p orbital with a lone pair on its oxygen to give **290**. Hydrogen bonding could explain the observed configuration, but also, if one considers the scenario in which acetone approaches the p orbital *anti*- to the hydroxyl **291**, - the required 5-endo-trig cyclisation is prevented and **292** was not observed because the reactive centres are held apart. Furthermore, the reverse 3-exo-tet reaction to expel acetone from the *anti*- configuration would presumably be be rapid (Scheme 2.36).



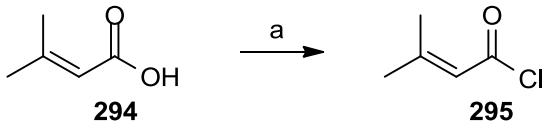
Scheme 2.36: *Ritter-type reaction pathway.*

The oxidation of the benzylic hydroxyl of (+)-*trans*-decursinol was first attempted with MnO_2, since it is mild and was expected to leave the more hindered non-benzylic hydroxyl completely untouched. At RT, in CH_2Cl_2 no conversion to the α-hydroxy ketone **293** was observed with 10 equiv. of MnO_2. When searching the literature for a method to augment the reactivity, we discovered that MnO_2 readily cleaves *cis*-, and even *trans*- 1,2-diols.[36] In light of this, we immediately abandoned using MnO_2. Due to its excellent reactivity, and the mild conditions required, we next employed Dess-Martin periodinane to effect the oxidation of the benzylic hydroxyl. Pleasingly, it appeared that only one major product was formed and, this was confirmed by NMR spectoscopy. The crude reaction mixture was purified by flash column chromatography and **293** was isolated in excellent yield (Scheme 2.37).



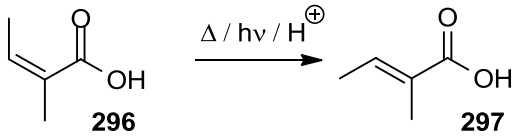
Scheme 2.37: *Selective oxidation of the benzylic hydroxyl with DMP; a) DMP (1 equiv.), $CHCl_3$, RT, 95%.*

As described above, the side chain fragments of the scuteflorins were to be introduced as their acyl chlorides – 3,3-dimethylacryloyl chloride **295** for **274** and angeloyl chloride **299** for **275**. The preparation of **295** was achieved by reacting 3,3-dimethylacrylic acid **294** with a slight excess of oxalyl chloride in CH_2Cl_2 at RT (Scheme 2.38). Solvents were removed 1 h after the effervescence ceased. To ensure excess oxalyl chloride was removed, $CHCl_3$ was added and removed *in vacuo* to constant weight three times. The acyl chloride **294** was isolated as a pungent pale-yellow oil and stored under an inert atmosphere to prevent re-formation of the acid **295**.



Scheme 2.38: *Synthesis of acryloyl chloride; a) Oxalyl chloride (1.1 equiv.), CH_2Cl_2, RT, 99%.*

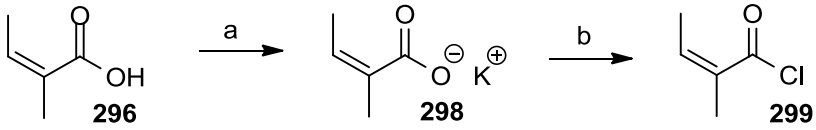
The same method could not be used for the angeloyl side chain as angelic acid **296** is, reportedly, extremely sensitive to acid, light, heat and moisture; which cause it to isomerize to tiglic acid **297** (Scheme 2.39).



Scheme 2.39: *Isomerization of angeloyl chloride*

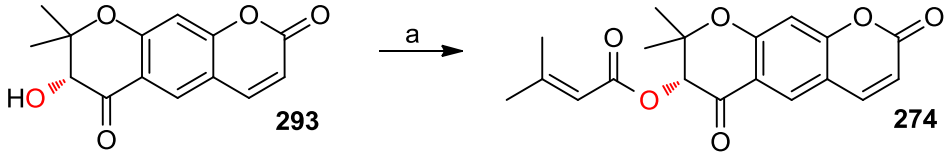
Direct exposure to oxalyl chloride causes it to isomerize due to the HCl produced as a by-product over the course of the reaction.[37] This problem was circumvented by first isolating the potassium salt **298**, and then treating that with oxalyl chloride. In our hands, the angeloyl chloride **299** was not produced cleanly, and purification by

preparative TLC was required to obtain a pure sample for the coupling, which, of course, significantly compromised the yield (Scheme 2.40).



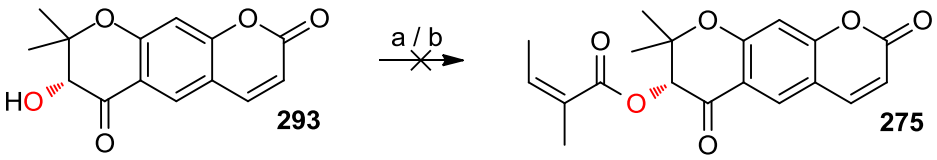
Scheme 2.40: *Preparation of angeloyl chloride: a) KOH (1 equiv.), EtOH, 10 min.; b) Oxalyl chloride (1.1 equiv.), Et_2O, 0 °C, 9 % over two steps.*

The attachment of the acryloyl side chain was straightforward, and **274** was isolated in good yield following purification. The optical rotation for the synthetic material matched that reported by Khan for the authentic sample (Scheme 2.41).



Scheme 2.41: *Coupling of the acryloyl side chain: a)* ***295*** *(5 equiv.), $NaHCO_3$ (1.1 equiv.), THF, RT, 5 h, 88%.*

The same reaction was attempted for the attachment of angeloyl side chain, but, unfortunately, after 24 h, there was no formation of **275** and both components were still intact. Couplings of this sort can usually be accelerated by the addition of catalytic amounts of DMAP or pyridine, which activate the acyl chloride, but, due to the capricious nature of the angeloyl species, isomerization to tigloyl has been observed with their use.[35] We did try the addition of DMF (1 equiv.), but no reaction was seen under these conditions after 10 h, and again, the two coupling partners were still intact (Scheme 2.42).

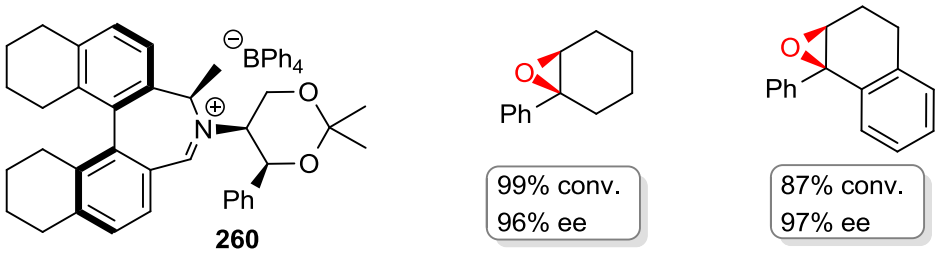


Scheme 2.42: *Attempted coupling of the angeloyl side chain: a)* ***299*** *(5 equiv.), THF, RT, 24 h, 0%; b)* ***299*** *(5 equiv.), DMF (1 equiv.), THF, RT, 10 h, 0%.*

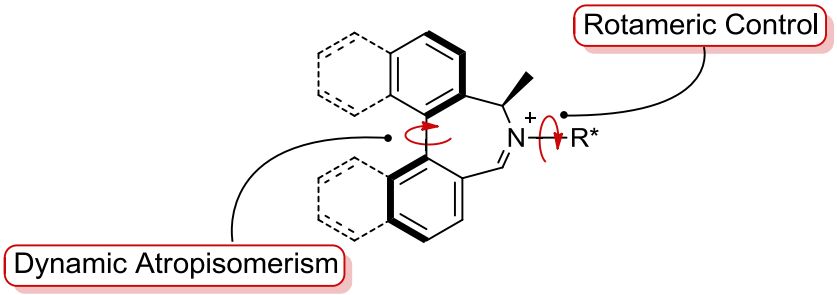
It was frustrating and confusing not to observe any conversion at all, particularly when the coupling with **295** was so facile. We certainly did not exhaust the known methods to achieve the coupling, and work to this end is continuing within our group.

2.9 Conclusions and Future Work

At the beginning of this work, we challenged ourselves to create a more enantioselective iminium-salt catalyst for organocatalytic epoxidation. We believe we achieved that goal with the development of catalyst **260**, which arose from the combination of two modifications: a larger Φ angle, and α-substitution. Iminium-salt **260** demonstrated the best facial selectivity across a range of tri-substituted alkene substrates bearing an aryl group that we had seen to date, *ees* of up to 97% being achieved with its use.



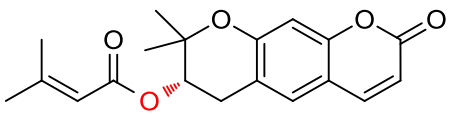
The most interesting and important aspect of this project however, and those closely linked to it within the group, came from the investigation into how substitution at the α-position influenced enantioselectivity in the epoxidation process.



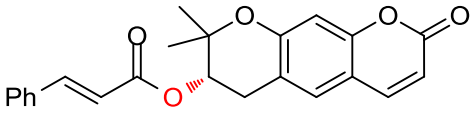
This investigation gave us great insight to the structures and behaviour of these iminium salts, both in isolation and during the epoxidation process. This understanding will allow the directed design of future iminium-salt catalysts. That aspect of the work was important because, while the development of catalyst **260** was an interesting intellectual exercise, in all likelihood, it will never be employed by any other academic group or in industry. This is because a large synthetic investment is required for its synthesis (11 steps in total) – an investment which

perhaps outweighs its proficient enantiocontrol. Taking into account its synthesis and its high mass of 826 Da, any process it could be used for would suffer from poor atom economy.[38] Furthermore, these azepinium catalysts suffer from narrow substrate scope. Thus, any future work directed at developing catalysts which are capable of epoxidizing these and other substrate classes will require a paradigm shift in catalyst structure and synthetic strategy in particular.

That said, work within the group has highlighted the particular utility of biphenyl catalyst **169** for the enantioselective epoxidation of *cis*-alkene substrates, especially chromenes. We employed **169** to install the required stereochemistry and epoxide functionality necessary for the subsequent manipulation to achieve the first enantioselective total synthesis of (+)-scuteflorin A. Our enantioselective epoxidation of xanthyletin also offers a route to the asymmetric synthesis of decursin,[39] which inhibits the estrogen-stimulated and estrogen-independent growth and survival of breast cancer cells, and related analogues, such as dihydropyranocoumarin D2, which has been shown to be a microphthalmia-associated transcription factor (MITF) degrading agent, acting by inhibiting the synthesis of melanin at the transcription level.[40]



decursin



dihydropyranocoumarin D2

These syntheses should be achievable by the reductive ring opening of **280**, followed by acyl chloride coupling of the side chains.

2.10 References for Chapter Two

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3.0 Experimental

3.1 General Experimental

3.1.1 Physical Characterisation and Spectroscopic Techniques

^{1}H- and ^{13}C-NMR spectra were recorded in Fourier Transform mode either on a Varian Unity Plus 400 or a Varian Gemini 300 spectrometer operating at nominal ^{1}H NMR frequencies of 400 MHz and 300 MHz respectively using the specified deuteriated solvent. All spectra were processed using MestRe-C Nova software. The chemical shifts for both ^{1}H- and ^{13}C-spectra were recorded in ppm and were referenced to the residual solvent peak or TMS peak. Multiplicities in the NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, sept. = septet, m = multiplet, br = broad singlet; coupling constants (*J*) are reported in Hz. Low resolution mass spectra were recorded using a Shimadzu LCMS 2010EV instrument operated under electrospray ionization in positive (ES+) or negative (ES–) modes. Accurate Mass spectra were recorded by the EPSRC national mass spectrometry service at the University of Wales, using electron-impact (EI), fast atom bombardment (FAB) or electrospray (ES) techniques. Melting points were recorded using open capillary tubes on a Büchi B-545 melting point instrument; melting points quoted as a range were observed manually while those quoted as a specific value were recorded by the instrument and correspond to the temperature at which the sample reached 40% translucency in accordance with the British Pharmacopeia. Infrared spectra were recorded as neat samples using a Perkin-Elmer Spectrum BX FT-IR Spectrophotometer, or as thin films on NaCl plates using a Perkin-Elmer Paragon 2000 FT-IR spectrophotometer. All IR data were analysed using Spectrum v5.0.1 software. Optical rotation measurements were obtained using a Bellingham and Stanley ADP-440 polarimeter operating at the sodium (D) line emission of 589 nm at a nominal 20 °C.

3.1.2 Enantiomeric Excess Determination

Enantiomeric excesses were determined either by Chiral HPLC or ^{1}H-NMR spectroscopy. Chiral HPLC traces were run on a Chiracel OD column eluting with HPLC grade Hexane/IPA. The ^{1}H-NMR spectra were run on a Varian Gemini 300 spectrometer operating at a nominal 300 MHz in the presence of [(+)-Eu(hfc)$_3$] as the chiral shift reagent and TMS as the internal standard.

3.1.3 Chromatographic Techniques

Flash chromatography was carried out using glass columns packed with Davisil 45-60 μm silica-gel. Thin layer chromatography was carried out on Merck aluminium-backed plates coated with 0.2 mm Kieselgel 60 GF_{254}. After elution, the TLC plates were visualized under UV light followed by staining with phosphomolybdic acid (10% solution in EtOH) or vanillin and developed by heating.

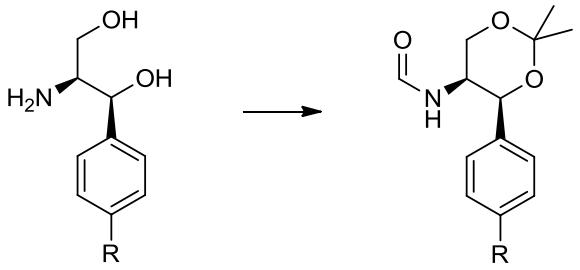
3.1.4 Reagent, Solvent and Apparatus Preparation

Commercially available reagents were used as supplied, without any further purification, and stored according to the manufacturer's recommendations, unless stated otherwise. DMF, specified as dry, was bought as such. DMSO, toluene, Hünig's base and CH_2Cl_2 were distilled over CaH_2. Et_2O and THF were dried using the Na / benzoquinone ketyl radical system prior to distillation, and MeOH was dried over activated Mg ribbon prior to distillation. Water and light petroleum (b.p. 40-60 °C) were distilled prior to use. For procedures where the exclusion of water was necessary, apparatus was dried using a flame gun while the vessel was flushed with a stream of Ar or N_2.

3.2 Individual Experimental Procedures

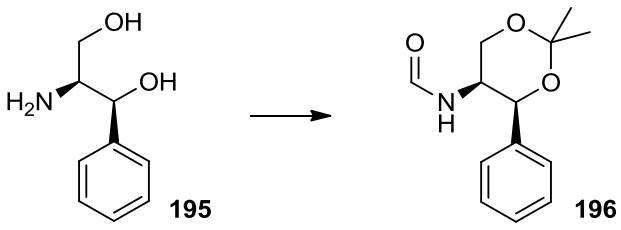
3.2.1 Experimental Procedures Related to the Synthesis of Chiral Amines

General procedure for the formation of the formate protected 5-amino-1,2-dixoanes from commercially available amino diols



Methyl formate (1.2 equiv.) and sodium methoxide (0.1 equiv.) were added to a solution of the aminodiol (1 equiv.) in dry MeOH (10 mL per g of aminodiol). The reaction was stirred until full conversion was observed by TLC analysis. At which point the solvents were removed under reduced pressure. Toluene (30 mL per g of aminodiol) was added to a flask containing the crude oily residue and heated under reflux. Any MeOH remaining in the oil was collected in the attached Dean-Stark apparatus. The mixture was allowed to cool to 50 °C and CSA (0.1 equiv.) and 2,2-DMP (5 equiv.) were added. The reaction mixture was again heated to reflux and the MeOH that evolved was collected in the Dean-Stark apparatus as the reaction proceeded. When the collection of MeOH in the Dean-Stark apparatus had ceased, the reaction was allowed to cool and the solvents removed under reduced pressure. The crude oil was re-dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ (2 x 15 mL per g of aminodiol) followed by brine (2 x 15 mL per g of aminodiol). The organic fraction was dried over $MgSO_4$ then filtered, solvents were then again removed under reduced pressure to yield the 5-amino-1,2-dioxanes in good purity.

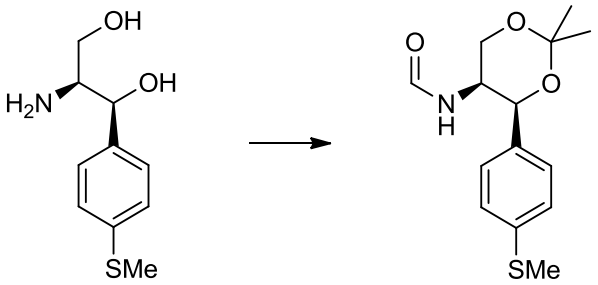
(5*S*,6*S*)-*N*-Formyl-5-amino-6-phenyl-2,2-dimethyl-1,3-dioxane[1,2] (196)



195 **196**

Prepared according to the general procedure from **195** (5.00 g, 29.9 mmol). The known product **196** was isolated as a yellow oil (6.64 g, 94%): ν_{max}(neat)/cm^{-1} 2991, 1668, 1507, 1380, 1199, 1087, 845, 701; δ_H (400 MHz; $CDCl_3$) 1.48 (3H, s, C$\underline{Me}_2$), 1.52 (3H, s, C$\underline{Me}_2$), 3.79 (1H, dd, *J* = 10.5 Hz, 1.5 Hz, NCH-C$\underline{H}_2$-O, upfield portion of ABX system), 4.17 (1H, d, *J* = 10.5 Hz, NCH-C$\underline{H}_2$-O, downfield portion of ABX system), 4.21 (1H, d, *J* = 1.6 Hz, -NC$\underline{H}$-), 5.15 (1H, s, NCH-C$\underline{H}$Ar-O), 6.48 (1H, br, -N$\underline{H}$-), 7.14-7.27 (5H, m, 5 x C$\underline{H}$ *arom*.), 7.89 (1H, s, NC$\underline{H}$O); δ_C (75 MHz; $CDCl_3$) 18.3 (1C, C$\underline{Me}_2$), 29.5 (1C, C$\underline{Me}_2$), 44.9 (1C, -N$\underline{C}$H), 64.5 (1C, NCH-$\underline{C}H_2$-O), 71.5 (1C, NCH-$\underline{C}$HAr-O), 100.0 (1C, $\underline{C}Me_2$, *C quat*.), 123.5 (2C, 2 x $\underline{C}$H *arom.*), 126.5 (2C, 2 x $\underline{C}$H *arom*.), 145.5 (1C, $\underline{C}$ *quat. arom*), 147.5 (1C, *quat. arom.*), 160.3 (1C, s, N$\underline{C}$HO).

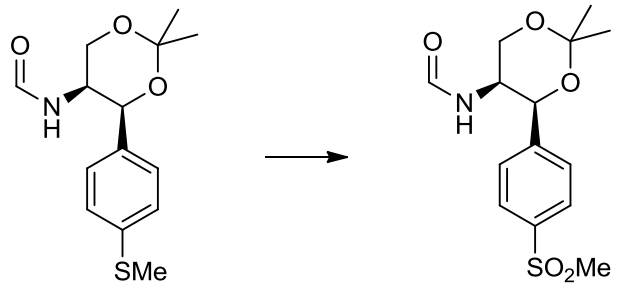
(5*S*,6*S*)-*N*-Formyl-5-amino-6-(4-methylthiophenylether)-2,2-dimethyl-1,3-dioxane[3]



Prepared according to the general procedure from (*S*)-thiomicamine (5.00 g, 23.4 mmol.). The crude compound was isolated as an orange oil which was purified by column chromatography eluting with 2:1 EtOAc / EtOH. The known compound was isolated as a colourless oil (3.10 g, 47%): $[\alpha]^{20}_D$ +1.5 (c = 1.05, $CHCl_3$), *lit.* $[\alpha]^{20}_D$ +1.6 (c = 1.00, $CHCl_3$); ν_{max}(neat)/ cm^{-1} 3311, 2985, 2360, 1666, 1494, 1381, 1198, 1085,

946; δ_H (300 MHz; $CDCl_3$) 1.58 (3H, s, C<u>Me</u>$_2$), 1.62 (3H, s, C<u>Me</u>$_2$), 2.50 (3H, s, -S<u>Me</u>), 3.92 (1H, dd, *J* = 7.5 Hz, 1.5 Hz, NCH-C<u>H</u>$_2$-O, upfield portion of ABX system), 4.30 (1H, dd, *J* = 7.5 Hz, 1.5 Hz, NCH-C<u>H</u>$_2$-O, downfield portion of ABX system), 4.35 (1H, m, -NC<u>H</u>-), 5.22 (1H, s, NCH-C<u>H</u>Ar-O), 6.18 (1H, d, *J* = 5.8 Hz, -N<u>H</u>-) 7.28 (4H, s, 4 x C<u>H</u> *arom*.), 8.04 (1H, s, NC<u>H</u>O).

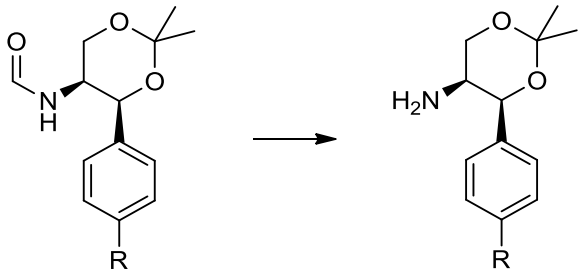
(5*S*,6*S*)-*N*-Formyl-amino-6-(4-methylsulfonylphenyl)-2,2-dimethyl-1,3-dioxane[3]



(5*S*,6*S*)-*N*-Formyl-5-amino-6-(4-methylthiophenylether)-2,2-dimethyl-1,3-dioxane (2.50 g, 8.88 mmol) was dissolved in $CHCl_3$ (80 mL) and the solution was allowed to cool to 0 °C. *m*-CPBA (3.37 g, 19.5 mmol) was dissolved in CH_2Cl_2 (40 mL) and dried over $MgSO_4$ before being filtered into the allowed to cool solution of the sulfide. The reaction was allowed to reach ambient temperature, and stirred overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (100 mL); the resulting biphasic mixture was transferred to a separating funnel. The organic layer was separated and washed with 1M NaOH (200 mL) and then dried over $MgSO_4$, followed by the addition of carbon black. Solvents were then removed under reduced pressure to yield the known title compound as a colourless foam in good purity (2.47 g, 88%): $[\alpha]^{20}_D$ +11.4 (c = 0.98, $CHCl_3$), *lit.* $[\alpha]^{20}_D$ +11.3 (c = 1.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3053, 2994, 1676, 1516, 1383, 1301, 1341, 1202, 1149, 1087, 947; δ_H (300 MHz; $CDCl_3$) 1.54 (3H, s, C<u>Me</u>$_2$), 1.56 (3H, s, C<u>Me</u>$_2$), 3.00 (3H, s, -SO_2<u>Me</u>), 3.82 (1H, dd, *J* = 12.0 Hz, 1.8 Hz, NCH-C<u>H</u>$_2$-O, upfield portion of ABX system), 4.28 (1H, dd, *J* = 12.0 Hz, 1.8 Hz, NCH-C<u>H</u>$_2$-O, downfield portion of ABX system), 4.38 (1H, dd, *J* = 10.0 Hz, 1.6 Hz -NC<u>H</u>-), 5.24 (1H, s, NCH-C<u>H</u>Ar-O), 6.38

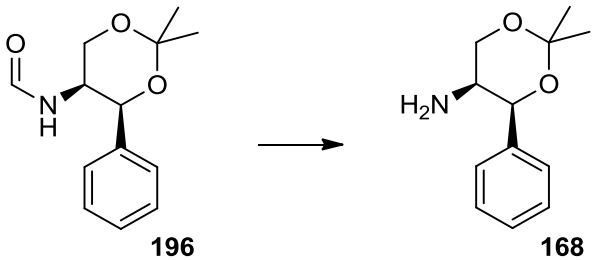
(1H, d, *J* = 9.8 Hz, NH), 7.52 (2H, d, *J* = 8.1 Hz, 2 x CH *arom*.), 7.86 (2H, d, *J* = 8.0 Hz, 2 x CH *arom*.), 7.90 (1H, s, NCHO).

General procedure for the deprotection of formamides with hydrazine hydrate



The formate-protected acetonide was dissolved in 50% aq. hydrazine hydrate (20 mL per g of the dioxane) and the solution heated under reflux for up to 3 h. The solution was allowed to cool to room temperature and extracted with EtOAc (3 x 30 mL per g of the dioxane). The organic layers were combined and washed with water (2 x 30 mL per g of the dioxane) followed by brine (2 x 20 mL per g OF the dioxane). The organic layer was dried over $MgSO_4$, and the solvents were then removed under reduced pressure to furnish the unprotected amines in excellent purity.

(5*S*,6*S*)-5-Amino-6-phenyl-2,2-dimethyl-1,3-dioxane[2] (168)

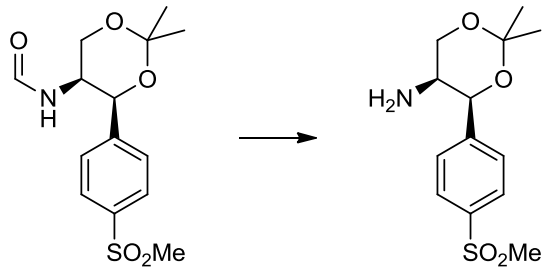


196 **168**

Prepared according to the general procedure from **196** (6.60 g, 28.0 mmol). The known title compound **168** was isolated as a pale yellow oil (4.21 g, 73%): $[\alpha]^{20}_D$ +61.5 (c = 0.98, $CHCl_3$), *lit.* $[\alpha]^{20}_D$ +61.5 (c = 0.99, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2991, 2940, 2868, 1673, 1586, 1498, 1450, 1378, 1270, 1239, 1196, 1159, 1130, 1086, 1051, 1030, 998, 942, 863, 844, 792; δ_H (300 MHz; $CDCl_3$) 1.54 (3H, s, CMe_2), 1.55 (3H, s,

C<u>Me</u>$_2$), 2.76 (1H, dd, *J* = 2.0 Hz, 4.1 Hz, -NC<u>H</u>-), 3.90 (1H, dd, *J* = 2.0 Hz, 12.1 Hz, NCH-C<u>H</u>$_2$-O, upfield portion of ABX system), 4.30 (1H, dd, *J* = 1.9 Hz, 12.2 Hz, NCH-C<u>H</u>$_2$-O, downfield portion of ABX system), 5.11 (1H, s, NCH-C<u>H</u>Ar-O), 7.25-7.41 (5H, m, 5 x C<u>H</u> *arom.*); δ_C (75 MHz; $CDCl_3$) 18.6 (1C, C<u>Me</u>$_2$), 29.7 (1C, C<u>Me</u>$_2$), 49.57 (1C, -N<u>C</u>H-), 65.9 (1C, NCH-<u>C</u>H$_2$-O), 73.7 (1C, NCH-<u>C</u>HAr-O), 95.0 (1C, <u>C</u>Me$_2$, *C. quat*.), 125.7 (2C, 2 x <u>C</u>H *arom.*), 127.4 (1C, <u>C</u>H *arom*.) 128.4 (2C, 2 x <u>C</u>H *arom*.) 139.8 (1C, C *quat. arom.*); *m/z* (HNES) 208.1331 - $C_{12}H_{17}NO_2$ $[M+H]^+$ requires 208.1332.

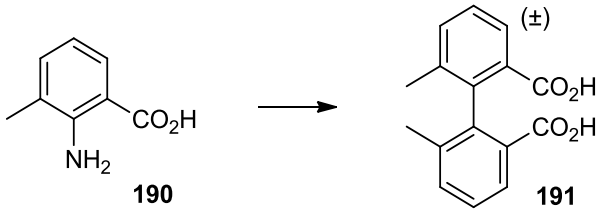
(5*S*,6*S*)- 5-Amino-6-(4-methylsulfonylphenyl)-2,2-dimethyl-1,3-dioxane[3]



Prepared according to the general procedure from (5*S*,6*S*)-*N*-formyl-5-amino-6-(4-methylsulfonylphenyl)-2,2-dimethyl-1,3-dioxane (2.40 g, 7.65 mmol). The known title compound was isolated as a clear pale yellow oil (2.05 g, 94%): $[\alpha]^{20}_D$ +48.5 (c = 1.08, $CHCl_3$), *lit.* $[\alpha]^{20}_D$ +47.5 (c = 0.99, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3371, 2990, 1602, 1380, 1197, 1076, 948; δ_H (300 MHz; $CDCl_3$) 1.48 (2H, br, -N<u>H</u>$_2$) 1.55 (6H, s, 2 x C<u>Me</u>$_2$), 2.86 (1H, s, -NC<u>H</u>-) 3.06 (3H, s, -SO$_2$<u>Me</u>), 3.91 (1H, dd, *J* = 11.6 Hz, 2.1 Hz, upfield portion of ABX system, NCH-C<u>H</u>$_2$-O), 4.35 (1H, dd, *J* = 11.7 Hz, 2.3 Hz, downfield portion of ABX system, NCH-C<u>H</u>$_2$-O), 5.19 (1H, s, NCH-C<u>H</u>Ar-O), 7.57 (2H, d, *J* = 8.0 Hz, 2 x C<u>H</u> *arom*.), 7.98 (2H, d, *J* = 8.0 Hz, 2 x C<u>H</u> *arom*.); δ_C (75 MHz; $CDCl_3$) 18.8 (1C, C<u>Me</u>$_2$), 29.9 (1C, C<u>Me</u>$_2$), 44.8 (1C, SO$_2$<u>Me</u>), 49.6 (1C, -N<u>C</u>H-), 66.5 (1C, NCH-<u>C</u>H$_2$-O), 73.6 (1C, NCH-<u>C</u>HAr-O) , 99.7 (1C, <u>C</u>Me$_2$, *C. quat*.), 127.0 (2C, 2 x <u>C</u>H *arom*.), 127.7 (2C, 2 x <u>C</u>H *arom*.), 139.6 (1C, <u>C</u> *quat. arom.*), 146.3 (1C, <u>C</u> *quat. arom.*).

3.2.2 Experimental Procedures Related to the 6,6'-Dimethylbiphenyl Systems

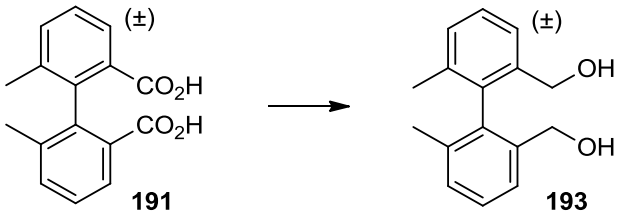
6,6'-Dimethylbiphenyl-2,2'-bis(carboxylic acid)[4] (191)



$NaNO_2$ (7.8 g, 0.11 mol) was added in one portion to an ice cold solution of **190** (17.0 g, 0.11 mol) in 2.45 M NaOH (60 mL). The mixture was then stirred at 0 °C until it became homogeneous. To this solution, a 4 M aqueous solution of HCl (240 mL) that had been pre-cooled to 0 °C, was added at a rate such that the temperature remained below 5 °C. The resulting orange solution of the diazonium salt was stirred at 0 °C for 20 min. $Cu_2SO_4 \bullet 5H_2O$ (24.0 g, 96 mmol) and water (75 mL) were added to a flask and the resulting solution was left to cool in a large ice-bath. When the solution had reached 5 °C, 30% w/v NH_4OH solution (47.5 mL) was added in one portion. A freshly prepared solution of NH_2OH, prepared from treatment of $(NH_2OH) \bullet H_2SO_4$ (8.8 g, 53.5 mmol) with a 3 M ice-cold aqueous solution of NaOH (38 mL, 0.11 mol), was added to the resulting deep-blue solution. The deep blue solution was stirred for 20 min. to cool to 0 °C. The diazonium salt prepared above was added to the copper solution in three equal portions of 50 mL via a syringe with the needle below the liquid surface. The temperature was maintained below 7 °C throughout the procedure. After the addition was complete, the resulting orange/red solution was heated under reflux for 30 min. The vessel was removed from the heat and allowed to cool. After the red solution had attained ambient temperature, conc. HCl (37.5 mL) was added slowly and the mixture was allowed to stand overnight to provide for the complete precipitation of the product. The yellow/brown precipitate was removed by filtration using a Büchner funnel, washed with water and air-dried. The crude material was stirred in boiling EtOH (200 mL); any remaining bright yellow solid was removed by filtration, leaving a clear brown filtrate. Crystallization of the known bis(carboxylic acid) **191**

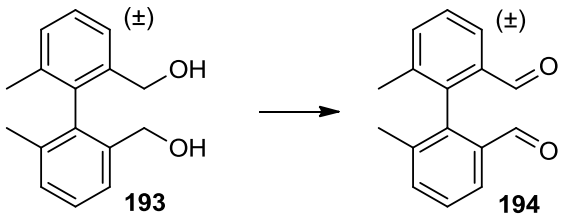
was induced by the addition of water to the filtrate to yield light brown crystals (8.4 g, 55%): m.p. 225.6-230.1 °C (dec.); ν_{max}(neat)/cm^{-1} 2982, 2907, 2667, 2579, 1680, 1583, 1436, 1377, 1316, 1159, 962, 799, 768, 722; δ_H (400 MHz; DMSO) 1.85 (6H, s, 2 x Ar-Me), 7.35 (2H, t, *J* = 8.0 Hz, 2 x C<u>H</u> *arom*.), 7.48 (2H, d, *J* = 8.0 Hz, 2 x C<u>H</u> *arom*.), 7.75 (2H, d, *J* = 8.0 Hz, 2 x C<u>H</u> *arom*.), 12.27 (2H, br, -CO_2<u>H</u>).

6,6'-Dimethyl-2,2'-bis(hydroxymethyl)biphenyl[4] (193)



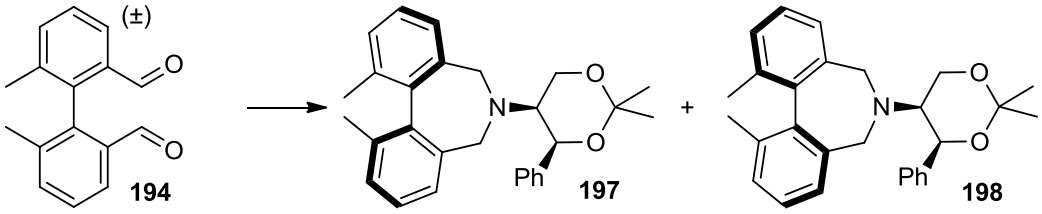
191 (2.20 g, 8.2 mmol) was dissolved in Et_2O (30 mL) under a nitrogen atmosphere. The resulting pale yellow solution was then allowed to cool to 0 °C, and $LiAlH_4$ (0.93 g, 24.5 mmol) was added slowly at a rate that just maintained the effervescence. The resulting suspension was heated under reflux for 1 h, after which time the reaction mixture was removed from the heat and allowed to cool to RT. Solid Na_2SO_4 (6.0 g) was added to the suspension, which was then allowed to cool in an ice-bath and stirred for 5 min. Water (10 mL) was added dropwise to quench the excess $LiAlH_4$. The mixture was then stirred for 30 min., filtered through a layered pad of Celite and Na_2SO_4, and the colourless filtrate was then concentrated under reduced pressure to yield known **193** as a colourless crystalline solid (1.91 g, 96%): ν_{max}(neat)/cm^{-1} 3254, 3064, 3017, 2935, 2880, 1679, 1592, 1458, 1378, 1239, 1211, 1163, 1028, 994, 902, 783, 760, 623; δ_H (400 MHz; DMSO) 1.85 (6H, s, 2 x Ar-<u>Me</u>), 3.99 (4H, s, 2 x -C<u>H</u>$_2$OH), 5.03 (2H, s, 2 x -CH$_2$O<u>H</u>), 7.24 (2H, s, *J* = 8.0 Hz, 2 x C<u>H</u> *arom*.), 7.32 (2H, t, *J* = 8.1 Hz, 2 x C<u>H</u> *arom*.), 7.45 (2H, d, *J* = 8.0 Hz, 2 x C<u>H</u> *arom*.); m/z (HNES) 265.1200 - $C_{16}H_{18}O_2$ $[M+Na]^+$ requires 265.1199.

6,6'-Dimethyl-1,1'-biphenyl-2,2'-bis(carboxaldehyde)[4] (194)



PCC (1.33 g, 62.0 mmol) was added in one portion to a solution of **193** (0.50 g, 20.7 mmol) in CH_2Cl_2 (20 mL), producing a dark-orange solution. The solution was stirred vigorously for 3 h at RT. Et_2O (20 mL) and a spatula of Celite was added to the resulting black mixture, which was stirred for a further 30 min. The reaction mixture was filtered through a layered pad of Celite and silica gel. Solvents were removed under reduced pressure to yield the known **194** as a colourless crystalline solid (0.43 g, 87%): m.p. 108.7 °C; δ_H (400 MHz; DMSO) 1.92 (6H, s, 2 x Ar-Me), 7.62 (2H, t, *J* = 8.0 Hz, 2 x CH *arom.*), 7.74 (2H, d, *J* = 8.0 Hz, 2 x CH *arom.*), 7.88 (2H, d, *J* = 8.0 Hz, 2 x CH *arom.*), 9.48 (2H, s, 2 x -CHO) m/z (HNES) 256.1333 - $C_{16}H_{14}O_2$ $[M+NH_4]^+$ cation requires 256.1332.

(+)-(*R*)-6-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-1,11-dimethyl-6,7-dihydro-5*H*-dibenzo[*c,e*]azepine (197) and **(+)-(*S*)-6-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-1,11-dimethyl-6,7-dihydro-5*H*-dibenzo[*c,e*]azepine (198)**



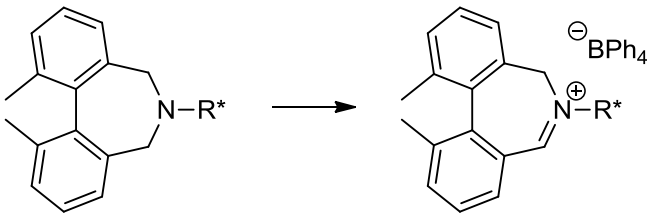
168 (2.70 g, 12.9 mmol) was added to a solution of **194** (2.81 g, 11.8 mmol) in MeOH (160 mL). After being stirred for 5 min., $NaBH_3CN$ (1.62 g, 25.8 mmol) and glacial acetic acid (1 mL) were added. The solution was stirred for 24 h at RT. The reaction was quenched by the addition of a 1 M aqueous solution of NaOH (20 mL). Et_2O (100 mL) was added and the resulting biphasic mixture was transferred to a separating funnel where the organic layer was collected. The aqueous layer was further extracted with Et_2O (2 x 30 mL). The organic fractions were combined, washed with brine, and dried over Na_2SO_4. The solvents were removed under reduced pressure to yield a crude oil that was then subjected flash column chromatography to purify and separate the diastereomers, eluting with light petroleum / EtOAc (10:1), buffered with 2% TEA.

First eluting amine **197** was obtained as a colourless crystalline solid (1.18 g, 49%): $[\alpha]_D$ +54.9 (c = 0.97, $CDCl_3$); ν_{max}(neat)/cm^{-1} 2990, 2934, 2860, 1452, 1378, 1308, 1263, 1236, 1200, 1172, 1150, 1075, 1027 953, 852, 787, 749, 727, 698; δ_H (400 MHz; $CDCl_3$) 1.58 (3H, s, C$\underline{Me}_2$), 1.64 (3H, s, C$\underline{Me}_2$), 2.11 (6H, s, Ar-$\underline{Me}$), 2.65 (1H, d, *J* = 1.9 Hz, -NC$\underline{H}$-), 3.16 (2H, d, *J* = 12.1 Hz, 2 x ArC$\underline{H}_2$N, upfield portion of AB system), 3.67 (2H, d, *J* = 12.1 Hz, 2 x ArC$\underline{H}_2$N, downfield portion of AB system), 4.12-4.21 (2H, m, 2 x NCH-C$\underline{H}_2$-O), 5.10 (1H, d, *J* = 3.1 Hz, NCH-C$\underline{H}$Ar-O), 6.98-7.02 (2H, m, 2 x C$\underline{H}$ *arom*.), 7.14-7.18 (4H, m, 4 x C$\underline{H}$ *arom*.), 7.24-7.36 (5H, m, 5 x C$\underline{H}$ *arom*.); δ_C (100 MHz; $CDCl_3$) 19.3 (1C, C$\underline{Me}_2$), 20.0 (2C, 2 x Ar-$\underline{Me}$), 29.9 (1C, C$\underline{Me}_2$), 53.2 (2C, 2 x Ar$\underline{C}H_2$N), 60.1 (1C, -N$\underline{C}$H-), 61.9 (1C, NCH-$\underline{C}H_2$-O), 75.3 (1C, NCH-$\underline{C}$HAr-O), 99.3 (1C, $\underline{C}Me_2$, C *quat.*), 126.4 (2C, 2 x $\underline{C}$H *arom.*), 126.7 (2C, 2 x $\underline{C}$H *arom.*), 126.9 (1C, $\underline{C}$H

arom.), 127.5 (2C, 2 x CH *arom.*), 127.8 (2C, 2 x CH *arom.*), 129.0 (2C, 2 x CH *arom.*), 135.4 (2C, 2 x C *quat. arom.*), 136.7 (2C, 2 x C *quat. arom.*), 138.6 (1C, C *quat. arom.*), 140.5 (1C, C *quat. arom.*), C *quat. arom.* not observed; *m/z* 414.2431 - $C_{28}H_{32}NO_2$ $(M+H)^+$ requires 414.2428.

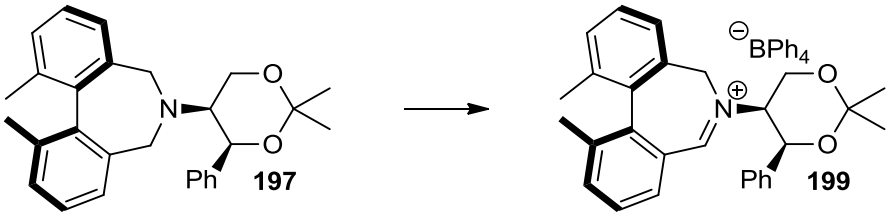
The second eluting amine **198** was obtained as a colourless foam, (0.62 g, 26%): $[\alpha]_D$ +121.0 (c = 1.07, $CDCl_3$); ν_{MAX}(neat)/cm^{-1} 2990, 2939, 2859, 1497, 1452, 1378, 1332, 1263, 1236, 1198, 1168, 1140, 1076 1024, 1001, 952, 853, 787, 750, 722, 697, 665; δ_H (400 MHz; $CDCl_3$) 1.46 (3H, s, CMe_2), 1.49 (3H, s, CMe_2), 2.12 (6H, s, Ar-Me), 3.01 (1H, br, -NCH-), 3.31 (2H, d, *J* = 12.5 Hz, 2 x ArCH_2N, upfield portion of AB system), 3.46 (2H, d, *J* = 12.4 Hz, 2 x ArCH_2N, downfield portion of AB system), 3.92 (1H, d, *J* = 12.4 Hz, NCH-CH_2-O, upfield portion of ABX system), 4.13 (1H, d, *J* = 12.4 Hz, NCH-CH_2-O, downfield portion of ABX system), 5.13 (1H, d, *J* = 3.0 Hz, NCH-CHAr-O), 6.80-7.02 (2H, m, 2 x CH *arom*.), 7.16-7.27 (4H, m, 4 x CH *arom*.), 7.33 (2H, t, *J* = 7.6 Hz, 2 x CH *arom.*), 7.45 (2H, d, *J* = 7.6 Hz, 2 x CH *arom.*); *m/z* 414.2425 - $C_{28}H_{32}NO_2$ $(M+H)^+$ requires 414.2428.

General procedure for the synthesis of 6,6'-dimethylbiphenyl iminium salts



NBS (1.1 equiv.) was added to a flask containing a solution of the azepine substrate (1 equiv.) in CH_2Cl_2 in a flask equipped with a stirrer bar and allowed to cool in an ice-bath. The resulting yellow solution was removed from the ice-bath and allowed to attain ambient temperature. The reaction mixture was then heated under reflux for 2 h. After the vessel had been removed from the heat and allowed to cool, a solvent switch to EtOH was performed. $NaBPh_4$ (1.1 equiv.) dissolved in the minimum amount of MeCN was added to the ethanolic solution. The resulting precipitate was isolated by filtration and washed with cold EtOH then Et_2O.

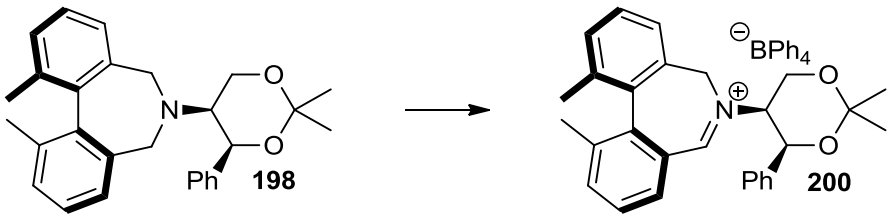
(–)-(R_a)-6-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-1,11-dimethyl-5*H*-dibenzo[*c,e*]azepin-6-ium tetraphenylborate (199)



Prepared according to the general procedure from **197** (1.10 g, 2.66 mmol). Title compound **199** was isolated as a fine yellow powder (1.18 g, 61%): $[\alpha]^{20}_D$ –190.5 (c = 1.01, MeCN); ν_{max}(neat)/cm^{-1} 3055, 3002, 2161, 2041, 1976, 1629, 1580, 1478, 1450, 1426, 1382, 1350, 1263, 1238, 1202, 1164, 1107, 1031, 955, 847, 790, 730, 664, 611; δ_H (400 MHz; DMSO) 1.70 (3H, s, C<u>Me</u>$_2$), 1.71 (3H, s, C<u>Me</u>$_2$), 1.94 (3H, s, Ar-<u>Me</u>), 2.18 (3H, s, Ar-<u>Me</u>), 3.96 (1H, d, *J* = 12.7 Hz, ArC<u>H</u>$_2$N, upfield portion of AB system), 4.17 (1H, d, *J* = 13.7 Hz, NCH-C<u>H</u>$_2$-O, upfield portion of ABX system), 4.53 (1H, s, -NC<u>H</u>-), 4.62 (1H, dd, *J* = 13.7 Hz, 2.9 Hz, NCH-C<u>H</u>$_2$-O, downfield portion of

ABX system), 5.55 (1H, br, ArC<u>H</u>$_2$N, downfield portion of AB system), 5.82 (1H, d, *J* = 2.5 Hz, NCH-C<u>H</u>Ar-O), 6.79 (4H, t, *J* = 7.1 Hz, 4 x C<u>H</u> *arom.*, *para*- $^{-}$BPh$_4$), 6.92 (8H, t, *J* = 7.3 Hz, 8 x C<u>H</u> *arom., meta*- $^{-}$BPh$_4$), 7.10-7.29 (14H, m, 6 x C<u>H</u> *arom.* / 8 x C<u>H</u> *arom., ortho*- $^{-}$BPh$_4$), 7.36 (1H, d, *J* = 7.9 Hz, C<u>H</u> *arom.*), 7.41-7.48 (2H, m, 2 x C<u>H</u> *arom*.), 7.53 (1H, t, *J* = 7.8 Hz, C<u>H</u> *arom.*), 7.71 (1H, d, *J* = 7.6 Hz, C<u>H</u> *arom.*), 8.92 (1H, s, -N=C<u>H</u>-); δ_C (100 MHz; DMSO-d6) 19.3 (1C, C<u>Me</u>$_2$), 20.2 (2C, 2 x Ar-<u>Me</u>), 29.9 (1C, C<u>Me</u>$_2$), 56.2 (1C, N-<u>C</u>H$_2$-Ar), 61.2 (1C, NCH-<u>C</u>H$_2$-O), 66.5 (1C, -N<u>C</u>H-), 71.3 (1C, NCH-<u>C</u>HAr-O), 100.8 (1C, <u>C</u>Me$_2$, C *quat.*), 122.2 (4C, s, 4 x <u>C</u>H *arom*., *para*- $^{-}$BPh$_4$), 125.5 (2C, 2 x C<u>H</u> *arom*.), 125.8 (1C, <u>C</u>H *arom*.), 125.9 (8C, 8 x <u>C</u>H *arom*., *meta*- $^{-}$BPh$_4$), 128.4 (1C, <u>C</u> *quat. arom.*), 128.4 (2C, 2 x <u>C</u> *quat. arom.*), 128.4 (1C, <u>C</u>H *arom*.), 129.1 (2C, 2 x <u>C</u>H *arom*.), 129.7 (1C, <u>C</u>H *arom*.), 132.2 (1C, <u>C</u>H *arom*.), 136.2 (8C, 8 x <u>C</u>H *arom*., *ortho*- $^{-}$BPh$_4$), 137.1 (1C, <u>C</u>H *arom*.), 138.3 (1C, <u>C</u> *quat. arom.*), 139.0 (1C, <u>C</u> *quat. arom.*), 139.9 (1C, <u>C</u> *quat. arom.*), 164.0 (4C, q, *J* = 49 Hz, 4 x <u>C</u> *quat*. *arom*., *ipso*- $^{-}$BPh$_4$), <u>C</u> *quat. arom.* and -N=<u>C</u>H- not observed; *m/z* 412.2273 - $C_{28}H_{30}NO_2$ $[M–BPh_4]^+$ requires 412.2271.

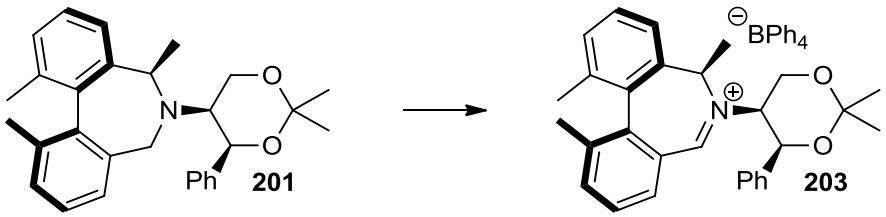
(+)-(S_a)-6-((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-1,11-dimethyl-5*H*-dibenzo[*c,e*] azepinium tetraphenylborate (200)



Prepared according to the general procedure from **198** (0.56 g, 1.35 mmol) The title compound **200** was isolated as a yellow solid (0.83 g, 83%): $[\alpha]^{20}_D$ +329.8 (c = 0.98, MeCN); ν_{max}(neat)/cm^{-1} 3059, 2989, 2161, 1977, 1623, 1578, 1559, 1427, 1381, 1359, 1308, 1263, 1239, 1168, 1122, 1086, 1069, 1031, 1000, 969, 43, 783, 728, 664, 608; δ_H (400 MHz; DMSO-d6) 1.72 (3H, s, C<u>Me</u>$_2$), 1.75 (3H, s, C<u>Me</u>$_2$), 2.03 (3H, s, Ar-<u>Me</u>), 2.23 (3H, s, Ar-<u>Me</u>), 3.83 (1H, d, *J* = 13.2 Hz, ArC<u>H</u>$_2$N, upfield portion of AB system), 4.19 (1H, d, *J* = 13.7 Hz, ArC<u>H</u>$_2$N, downfield portion of AB system),

4.70 (1H, dd, *J* = 13.8 Hz, 3.9 Hz, NCH-C<u>H</u>$_2$-O, upfield portion of ABX system), 4.83 (1H, s, -NC<u>H</u>-), 4.97 (1H, d, *J* = 13.5 Hz, NCH-C<u>H</u>$_2$-O, downfield portion of ABX system), 5.85 (1H, d, *J* = 2.9 Hz, NCH-C<u>H</u>Ar-O), 6.84 (4H, t, *J* = 7.2 Hz, 4 x C<u>H</u> *arom.*, *para*- $^{-}$BPh$_4$), 6.98 (8H, t, *J* = 7.4 Hz, 8 x C<u>H</u> *arom., meta*- $^{-}$BPh$_4$), 7.10-7.19 (5H, m, 5 x C<u>H</u> *arom.*), 7.21-7.29 (8H, m, 8 x C<u>H</u> *arom., ortho*- $^{-}$BPh$_4$), 7.42 (1H, d, *J* = 8.0 Hz, C<u>H</u> *arom.*), 7.49 (1H, t, *J* = 7.5 Hz, C<u>H</u> *arom.*), 7.55 (1H, d, *J* = 8.0 Hz, C<u>H</u> *arom.*), 7.64 (1H, t, *J* = 7.7 Hz, C<u>H</u> *arom.*), 7.71-7.76 (2H, m, 2 x C<u>H</u> *arom*.), 9.17 (1H, s, -N=C<u>H</u>-); *m/z* 412.2268 - $C_{28}H_{30}NO_2$ $[M–BPh_4]^+$ requires 412.2271.

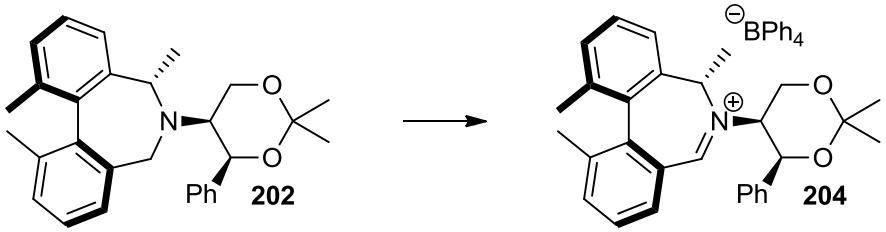
(–)-(5*R*, 11b*R*$_a$)-6-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-1,5,11-trimethyl-5*H*-dibenzo[*c,e*]azepin-6-ium tetraphenylborate (203)



Prepared according to the general procedure from **201** (0.34 g, 0.81 mmol). The title compound **203** was isolated as a yellow powder, (0.18 g, 30%): $[\alpha]^{20}_D$ –167.2 (c = 1.00, MeCN); ν_{MAX}(neat)/cm^{-1} 3053, 2986, 1632, 1579, 1559, 1540, 1478, 1425, 1379, 1298, 1262, 1239, 1201, 1165, 1107, 1085, 1045, 1032; δ_H (400 MHz; DMSO) 0.78 (3H, br, N-CH<u>Me</u>-Ar), 1.68 (3H, s, C<u>Me</u>$_2$), 1.70 (3H, s, C<u>Me</u>$_2$), 1.90 (3H, s, Ar-<u>Me</u>), 2.16 (3H, s, Ar-<u>Me</u>), 4.26 (1H, d, *J* = 13.2 Hz, NCH-C<u>H</u>$_2$-O, upfield portion of ABX system), 4.63-4.68 (2H, m, NCH-C<u>H</u>$_2$-O, downfield portion of ABX system / -NC<u>H</u>-), 5.76 (1H, br, N-C<u>H</u>Me-Ar), 5.82 (1H, s, NCH-C<u>H</u>Ar-O), 6.79 (4H, t, *J* = 7.2 Hz, 4 x C<u>H</u> *arom.*, *para*- $^{-}$BPh$_4$), 6.92 (8H, t, *J* = 7.4 Hz, 8 x C<u>H</u> *arom., meta*- $^{-}$BPh$_4$), 7.10-7.25 (14H, m, 6 x C<u>H</u> *arom.* / 8 x C<u>H</u> *arom*. *ortho*- $^{-}$BPh$_4$), 7.32-7.40 (2H, m, 2 x C<u>H</u> *arom*.), 7.59 (1H, br, 2 x C<u>H</u> *arom.*), 7.71-7.74 (1H, m, C<u>H</u> *arom.*), 9.20 (1H, s, -N=C<u>H</u>-); δ_C (100 MHz; DMSO) 14.9 (1C, N-CH<u>Me</u>-Ar), 19.3 (1C, C<u>Me</u>$_2$), 19.9 (1C, Ar-<u>Me</u>), 20.0 (1C, Ar-<u>Me</u>), 29.9 (1C, C<u>Me</u>$_2$), 62.0 (1C, NCH-<u>C</u>H$_2$-O), 65.9 (1C, N-<u>C</u>HMe-Ar), 67.4 (1C, -N<u>C</u>H-), 70.8 (1C, NCH-<u>C</u>HAr-O), 101.0 (1C, <u>C</u>Me$_2$, <u>C</u> *quat.*), 122.2 (4C,

s, 4 x CH *arom*., *para*- $^{-}BPh_4$), 125.2 (2C, 2 x CH *arom*.), 125.9 (1C, CH *arom*.), 126.5 (8C, s, 8 x CH *arom*., *meta*- $^{-}BPh_4$), 127.5 (1C, C *arom*.), 128.3 (1C, C *arom*.), 128.7 (1C, CH *arom*.), 128.8 (2C, 2 x CH *arom*.), 129.7 (1C, C *arom*.), 131.1 (1C, CH *arom*.), 132.0 (1C, CH *arom*.), 132.1 (1C, C *arom*.), 136.2 (8C, 8 x CH *arom*., *ortho*- $^{-}BPh_4$), 136.4 (1C, C *arom*.), 137.7 (1C, CH *arom*.), 138.8 (1C, C *arom*.), 139.2 (1C, C *arom*.), 140.2 (1C, C *arom*.), 164.0 (4C, q, *J* = 49 Hz, 4 x C *quat*. *arom*., *ipso*- $^{-}BPh_4$), -N=CH- not observed; *m/z* 428.2435 - $C_{29}H_{32}NO_2$ $[M–BPh_4]^+$ requires 428.2428.

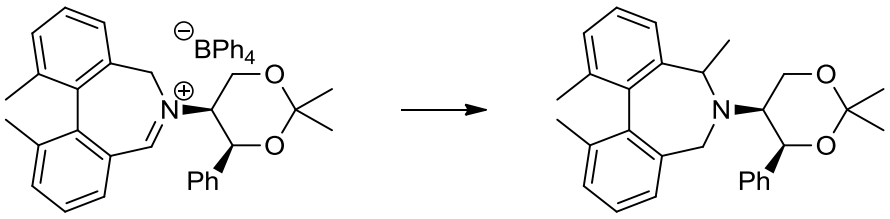
(+)-(5*S*, 11b*S*$_a$)-6-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-1,5,11-trimethyl-5*H*-dibenzo[*c,e*]azepin-6-ium tetraphenylborate (204)



Prepared according to the general procedure from **202** (0.25 g, 0.58 mmol). The title compound **204** was isolated as a pale yellow powder (0.14 g, 32%): $[\alpha]^{20}_D$ +310.0 (c = 1.00, MeCN); ν_{max}(neat)/cm^{-1} 3055, 2999, 1625, 1580, 1562, 1478, 1452, 1427, 1383, 1306, 1262, 1202, 1166, 1112, 1085, 1032, 952, 844, 789, 748, 734, 666, 611; δ_H (400 MHz; DMSO) 0.65 (3H, d, *J* = 7.2 Hz, N-CHMe-Ar), 1.67 (6H, s, 2 x CMe_2), 1.96 (3H, s, Ar-Me), 2.13 (3H, s, Ar-Me), 4.15 (1H, d, *J* = 14.3 Hz, NCH-CH_2-O, upfield portion of ABX system), 4.65-4.69 (2H, m, -NCH- / NCH-CH_2-O, downfield portion of ABX system), 5.76 (1H, q, *J* = 7.3 Hz, N-CHMe-Ar), 5.85 (1H, s, NCH-CHAr-O), 6.79 (4H, t, *J* = 7.2 Hz, 4 x CH *arom.*, *para*- $^{-}BPh_4$), 6.92 (8H, t, *J* = 7.4 Hz, 8 x CH *arom., meta*- $^{-}BPh_4$), 7.04-7.22 (13H, m, 5 x CH *arom.* / 8 x CH *arom*., *ortho*- $^{-}BPh_4$), 7.38 (1H, *J* = 7.4 Hz, CH *arom.*), 7.42-7.52 (2H, m, 2 x CH *arom.*), 7.59 (1H, t, *J* = 7.7 Hz, CH *arom.*), 7.72 (2H, t, *J* = 7.7 Hz, CH *arom.*), 8.98 (1H, s, -N=CH-); δ_C (100 MHz; DMSO) 14.4 (1C, N-CHMe-Ar), 19.3 (1C, CMe_2), 19.9 (1C, Ar-Me), 20.0 (1C, Ar-Me), 30.0 (1C, CMe_2), 61.6 (1C, NCH-CH_2-O), 68.1 (1C, N-CHMe-Ar), 68.4 (1C, -NCH-), 71.8 (1C, NCH-CHAr-O), 101.0 (1C, CMe_2, C *quat.*), 122.2 (4C, s, 4 x CH

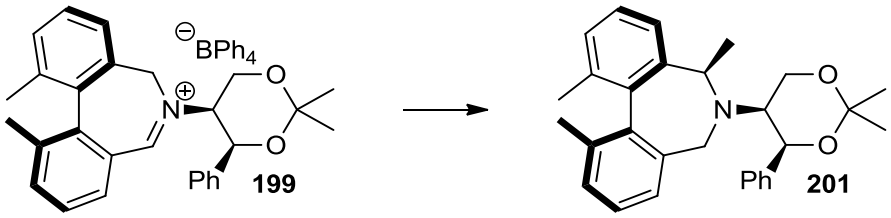
arom., *para*- $^{-}BPh_4$), 125.9 (2C, 2 x CH *arom*.), 126.0 (8C, s, 8 x CH *arom*., *meta*- $^{-}BPh_4$), 127.65 (1C, C *arom.*), 127.70 (1C, C *arom.*), 128.4 (1C, C *arom.*), 128.6 (1C, C *arom.*), 128.9 (2C, 2 x CH *arom.*), 129.5 (1C, C *arom.*), 132.1 (1C, C *arom.*), 132.3 (1C, C *arom.*), 132.5 (1C, C *arom.*), 136.17 (8C, 8 x CH *arom*., *ortho*- $^{-}BPh_4$), 136.18 (1C, C *arom.*), 136.5 (1C, C *arom.*), 137.9 (1C, C *arom.*), 139.0 (1C, C *arom.*), 139.3 (1C, C *arom.*), 140.1 (1C, C *arom.*), 141.1 (1C, C *arom.*), 164.0 (4C, q, *J* = 49 Hz, 4 x C *quat*. *arom*., *ipso*- $^{-}BPh_4$), 170.7 (-N=CH-); *m/z* 426.2424 - $C_{29}H_{32}NO_2$ $[M–BPh_4]^+$ requires 426.2428.

General Procedure for the Grignard Addition to Iminium Salts



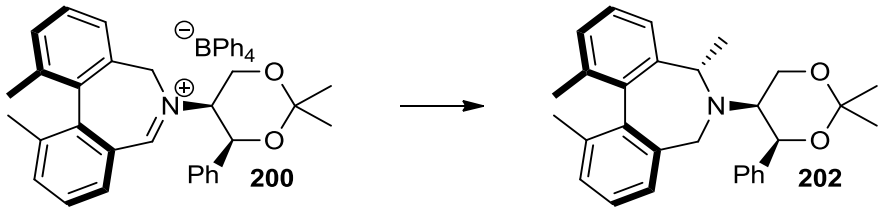
The desired iminium salt (1 equiv.) and Et_2O (50 mL per g of iminium salt) was added to a flame dried round-bottomed flask under an atmosphere of N_2. The solution was then allowed to cool to –78 °C in a Dewar of dry ice/acetone. 3 M MeMgCl in THF (10 equiv.) was added drop wise over 10 min. After 1 h, the flask was removed from the Dewar and allowed to attain ambient temperature overnight. The reaction was then quenched with saturated aqueous NH_4Cl solution (5 mL per g of iminium salt) and CH_2Cl_2 (30 mL per g of iminium salt) was then added to dilute the mixture. The resulting biphasic mixture was transferred to a separating funnel and brine (100 mL) was added. The organic layer was collected and the remaining aqueous layer was washed with CH_2Cl_2 (2 x 50 mL per g of iminium salt). The combined organics were washed with water (2 x 100 mL per g of iminium salt) and brine (2 x 100 mL per g of iminium salt). The organic fraction was dried over $MgSO_4$, evaporated to dryness under reduced pressure to yield the desired methyl-azepines.

(5*R*, 11bR_a)-6-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-1,5,11-trimethyl-6,7-dihydro-5*H*-dibenzo[*c,e*]azepine (201)



Prepared according to the general procedure from **199** (0.60 g, 1.45 mmol). The title compound **201** was isolated as a colourless foam (0.34 g, 94%): ν_{max}(neat)/cm^{-1} 3059, 2991, 2921, 2859, 1593, 1497, 1452, 1378, 1342, 1265, 1239, 1201, 1156, 1079, 1029, 955, 910, 885, 853, 787, 744, 700; δ_H (400 MHz; $CDCl_3$) 0.21 (3H, d, *J* = 7.2 Hz, N-CHMe-Ar), 1.56 (3H, s, CMe_2), 1.63 (3H, s, CMe_2), 2.07 (3H, s, Ar-Me), 2.13 (3H, s, Ar-Me), 2.91 (1H, dd, *J* = 6.0 Hz, 3.9 Hz, -NCH-), 3.35 (1H, d, *J* = 11.4 Hz, $ArCH_2N$, upfield portion of AB system), 3.52 (1H, d, *J* = 11.4 Hz, $ArCH_2N$, downfield portion of AB system), 4.08 (1H, dd, *J* = 12.3 Hz, 2.1 Hz, upfield portion of ABX system, NCH-CH_2-O), 4.22 (1H, dd, *J* = 12.0 Hz, 4.0 Hz, downfield portion of ABX system, NCH-CH_2-O), 4.33 (1H, q, *J* = 7.0 Hz, N-CHMe-Ar), 5.15 (1H, d, *J* = 3.5 Hz, NCH-CHAr-O), 6.81 (1H, t, *J* = 4.4 Hz, CH *arom.*), 6.86 (1H, dd, *J* = 6.7 Hz, 2.0 Hz, CH *arom.*), 7.09-7.15 (4H, m, 4 x CH *arom.*), 7.20-7.38 (5H, m, 5 x CH *arom.*); δ_C (100 MHz; $CDCl_3$) 19.2 (1C, CMe_2), 19.3 (1C, Ar-Me), 19.4 (1C, Ar-Me), 21.0 (1C, N-CHMe-Ar), 29.1 (1C, CMe_2), 54.0 (1C, $ArCH_2N$), 59.7 (1C, N-CHMe-Ar), 60.0 (1C, -NCH-), 63.2 (1C, NCH-CH_2-O), 74.2 (1C, NCH-CHAr-O), 99.3 (1C, CMe_2, C *quat.*), 126.0 (1C, CH *arom.*), 126.4 (2C, 2 x CH *arom.*), 126.6 (1C, CH *arom.*), 126.8 (1C, CH *arom.*), 127.4 (2C, 2 x CH *arom.*), 127.6 (2C, 2 x CH *arom.*), 128.5 (1C, CH *arom.*), 128.7 (1C, CH *arom.*), 135.9 (2C, 2 x C *quat. arom.*), 136.9 (1C, C *quat. arom.*), 138.9 (1C, C *quat. arom.*), 139.2 (1C, C *quat. arom.*), 140.3 (1C, C *quat. arom.*), 141.3 (1C, C *quat. arom.*); *m/z* (HNES) 428.2582 - $C_{29}H_{33}NO_2$ $[M+H]^+$ requires 428.2584.

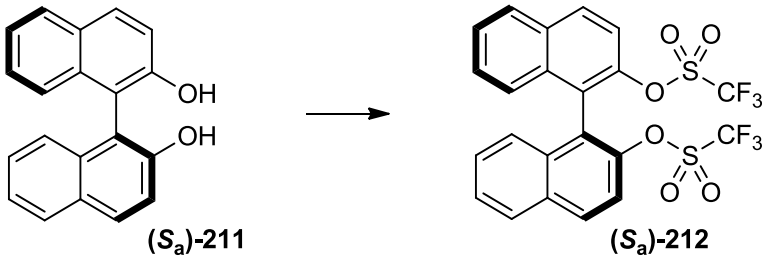
(5*S*, 11bS_a)-6-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-1,5,11-trimethyl-6,7-dihydro-5*H*-dibenzo[*c,e*]azepine (202)



Prepared according to the general procedure from **200**, (0.40 g, 0.97 mmol). The title compound **202** was isolated as a colourless foam, (0.23 g, 99%): $\nu_{max(}$neat)/cm^{-1} 3059, 2991, 2921, 2859, 1593, 1497, 1452, 1378, 1342, 1265, 1239, 1201, 1156, 1079, 1029, 955, 910, 885, 853, 787, 744, 700; δ_H (400 MHz; $CDCl_3$) 0.14 (3H, d, *J* = 7.2 Hz, N-CHMe-Ar), 1.47 (3H, s, CMe$_2$), 1.50 (3H, s, CMe$_2$), 2.05 (3H, s, Ar-Me), 2.14 (3H, s, Ar-Me), 3.02 (1H, dd, *J* = 6.5 Hz, 4.1 Hz, -NCH-), 3.31 (1H, d, *J* = 11.3 Hz, ArCH$_2$N, upfield portion of AB system), 3.63 (1H, q, *J* = 7.1 Hz, N-CHMe-Ar), 3.90 (1H, d, *J* = 11.3 Hz, ArCH$_2$N, downfield portion of AB system), 4.01 (1H, dd, *J* = 12.3 Hz, 2.4 Hz, NCH-CH$_2$-O, upfield portion of ABX system), 4.15 (1H, dd, *J* = 12.3 Hz, 4.0 Hz, NCH-CH$_2$-O, downfield portion of ABX system), 5.20 (1H, d, *J* = 4.2 Hz, NCH-CHAr-O), 6.65-6.71 (1H, m, CH *arom*.), 6.95 (1H, dd, *J* = 6.6 Hz, 2.1 Hz, CH *arom*.), 7.02-7.07 (2H, m 2 x CH *arom*.), 7.15-7.24 (3H, m, 3 x CH *arom*.), 7.32 (2H, t, *J* = 7.7 Hz, 2 x CH *arom*.), 7.46 (2H, t, *J* = 7.1 Hz, 2 x CH *arom*.); *m/z* (HNES) 428.2579 - $C_{29}H_{33}NO_2$ $[M+H]^+$ requires 428.2584.

3.2.3 Experimental Procedures Related to the Binaphthyl- Systems

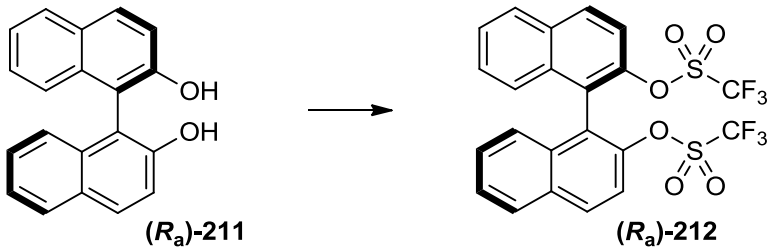
(+)-(S_a)-[1,1']-Binaphthalene-2,2'-diol-*bis*-trifluoromethanesulfonate[5] ((S_a)-212)



(S_a)-211 (S_a)-212

(S_a)-211 (5.0 g, 17.5 mmol) was added to a flame dried flask and dissolved in CH_2Cl_2 (100 mL) under and atmosphere of N_2. The vessel was placed in a Dewar and allowed to cool to −30 °C with stirring. After the solution had reached the correct temperature, DMAP (0.85 g, 7.0 mmol), 2,6-lutidine (5.3 mL, 3 equiv., 45.0 mmol) and Tf_2O (7.6 mL, 3 equiv., 45 mmol) were added to the solution. The resulting brown solution was removed from the Dewar and allowed to reach ambient temperature with stirring overnight. Silica gel was added to the dark brown solution and stirred for 20 min. Solvents were removed under reduced pressure to load the silica gel with the reaction mixture. The loaded silica gel was transferred to a sintered glass funnel containing a pad of silica gel, and washed with hexane until the product had eluted. The solvents were removed under reduced pressure to yield the known **(S_a)-212** as a colourless crystalline solid (9.5 g, 99%): m.p. 76.3-78.2 °C; $[\alpha]^{20}_D$ +150.3 (c = 1.03, $CHCl_3$), , *lit.* $[\alpha]^{20}_D$ +154.2 (c = 1.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1624, 1584, 1509, 1471, 1407, 1325, 1208, 1173, 1133, 1065, 960, 938, 867, 856, 826, 811, 773, 750, 701, 675, 615; δ_H (300 MHz; $CDCl_3$) 7.26 (2H, d, *J* = 8.5 Hz, 2 x C<u>H</u> *arom.*), 7.41 (2H, d, *J* = 7.2 Hz, 2 x C<u>H</u> *arom.*), 7.59 (2H, d, *J* = 7.7 Hz, 2 x C<u>H</u> *arom.*), 7.63 (2H, d, *J* = 9.1 Hz, 2 x C<u>H</u> *arom.*), 8.02 (2H, d, *J* = 8.2 Hz, 2 x C<u>H</u> *arom.*), 8.14 (2H, d, *J* = 9.2 Hz, 2 x C<u>H</u> *arom.*).

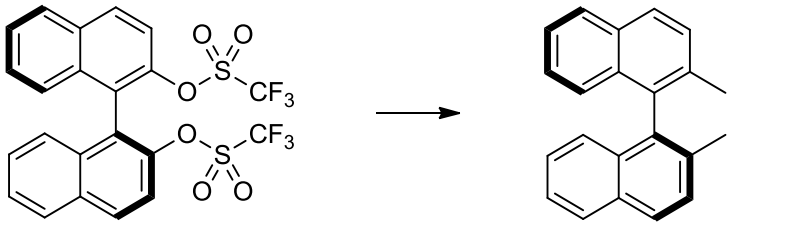
(–)-(R_a)-[1,1']-Binaphthalene-2,2'-diol-*bis*-trifluoromethanesulfonate[5] ((R_a)-212)



(R_a)-211 (R_a)-212

Prepared in an identical manner to **(S_a)-212** above, from **(R_a)-211** (0.97 g, 3.39 mmol). The known **(R_a)-212** was Isolated as a colourless crystalline solid (1.85 g, 99 %): m.p. 76.5-78.2 °C; $[\alpha]^{20}_{D}$ –150.9 (c = 1.01, $CHCl_3$). All other data closely matched that of **(S_a)-212**.

(+)-(S_a)-Dimethyl-[1,1']-binaphthalene[5] ((S_a)-213)

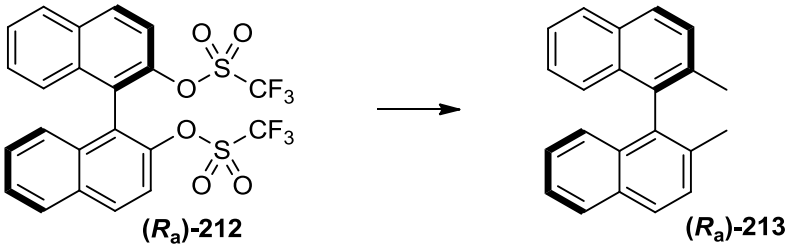


(S_a)-212 (S_a)-213

(S_a)-212 (9.0 g, 16.4 mmol) and 1,3-bis(diphenylphosphino)propane nickel (II) chloride (1.3 g, 2.45 mmol) were placed in a flame dried flask equipped with a stirrer bar, under an atmosphere of N_2. Et_2O (60 mL) was added to the vessel to dissolve the reaction components. The vessel was then allowed to cool to −30 °C prior to the the slow addition of 3 M MeMgBr in Et_2O (21.8 mL, 65.6 mmol). After 15 min., the vessel was removed from the Dewar and left to reach ambient temperature, with stirring, overnight. The reaction mixture was diluted with Et_2O (60 mL) prior to the addition of Celite. The suspension was then stirred for 30 min. before it was filtered through a sintered glass funnel containing a pad of Celite. The filtrate was transferred to a separating funnel and washed consecutively with 2 M aqueous HCl (30 mL), water (100 mL) and brine (100 mL). Removal of the solvent under reduced pressure yielded the known **(S_a)-213** as a colourless powder (4.12 g,

88%): m.p. 72.5-73.9 °C; $[\alpha]^{20}_{D}$ +41.1 (c = 0.99, $CHCl_3$), *lit.* $[\alpha]^{20}_{D}$ +42.0 (c = 1.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3045, 2918, 2857, 1618, 1594, 1509, 1421, 13779, 1352, 1261, 1221, 1158, 1143 1028, 958, 947, 898, 864, 810, 775, 743, 720, 656; δ_H (300 MHz; $CDCl_3$) 2.03 (6H, s, 2 x Ar-Me), 7.04 (2H, d, *J* = 8.0 Hz, 2 x CH *arom.*), 7.19 (2H, m, 2 x CH *arom.*), 7.39 (2H, m, 2 x CH *arom*.), 7.50 (2H, d, *J* = 8.4 Hz, 2 x CH *arom*.), 7.86 (2H, d, *J* = 4.6 Hz, 2 x CH *arom*.), 7.89 (2H, d, *J* = 4.5 Hz, 2 x CH *arom.*); δ_C (75 MHz; $CDCl_3$); 20.1 (2C, 2 x Ar-Me), 124.9 (2C, 2 x CH-*arom.*), 125.7 (2C, 2 x CH-*arom.*), 126.1 (2C, 2 x CH-*arom.*), 127.3 (2C, 2 x CH-*arom.*), 127.8 (2C, 2 x CH-*arom.*), 128.8 (2C, 2 x CH-*arom.*), 132.2 (2C, 2 x C *quat. arom.*), 132.8 (2C, 2 x C *quat. arom.*), 134.3 (2C, 2 x C *quat. arom.*), 135.2 (2C, 2 x C *quat. arom.*).

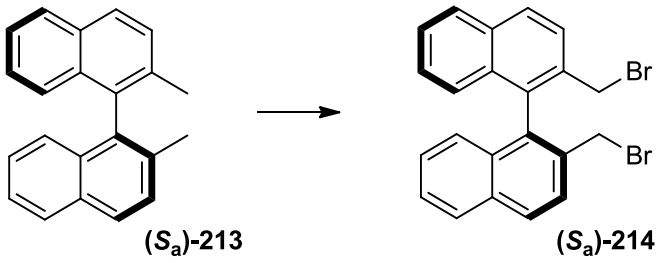
(–)-(R_a)-Dimethyl-[1,1']-binaphthalene[5] ((R_a)-213)



(R_a)-212 → (R_a)-213

Prepared in an identical manner to **(S_a)-213** (0.58 g, 1.05 mmol). The known title compound **(R_a)-213** was isolated as a colourless powder (0.23 g, 80%): m.p. 72.1-73.9 °C; $[\alpha]^{20}_{D}$ –40.9 (c = 1.19, $CHCl_3$). All other data closely matched that of **(S_a)-213.**

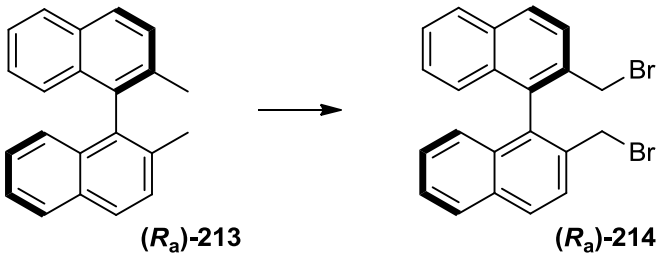
(–)-(S_a)-*Bis*-bromomethyl-[1,1']-binaphthylenyl[5] ((S_a)-214)



(S_a)-213 (S_a)-214

(S_a)-213 (3.5 g, 12.4 mmol) was dissolved in cyclohexane (24.5 mL). N-bromosuccinimide (4.85 g, 27.3 mmol) and AIBN (0.21 g, 1.24 mmol) were added and the reaction mixture was heated under reflux. The reaction was removed from the heat when the consumption of the starting material had been observed by TLC analysis. After the vessel was removed from the heat and allowed to cool to ambient temperature, water (52.5 mL) and EtOAc (7.75 mL) were added to dissolve by-products and excess NBS. The biphasic suspension was stirred for 1 h to allow the complete precipitation of **(S_a)-214**. The solid was isolated by filtration, washed with cold cyclohexane and then dried to yield the known **(S_a)-214** as a colourless powder (3.17 g, 58%): m.p. 184.3-187.2 °C; $[\alpha]^{20}_D$ –162.2 (c = 1.09, $CHCl_3$), *lit.* $[\alpha]^{20}_D$ -–161.5 (c = 1.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3049, 2925, 1772, 1722, 1507, 1433, 1361, 1329, 1211, 1025, 969, 928, 820, 752, 722, 686, 626; δ_H (400 MHz; $CDCl_3$) 4.25 (4H, s, 2 x -CH_2Br), 7.07 (2H, dq, *J* = 0.8 Hz, 8.5 Hz, 2 x CH *arom.*), 7.27 (2H, m, 2 x CH *arom.*), 7.49 (2H, m, 2 x CH *arom*.), 7.74 (2H, d, *J* = 8.6 Hz, 2 x CH *arom*.), 7.92 (2H, d, *J* = 8.2 Hz, 2 x CH *arom*.), 8.02 (2H, d, *J* = 8.5 Hz, 2 x CH *arom.*).

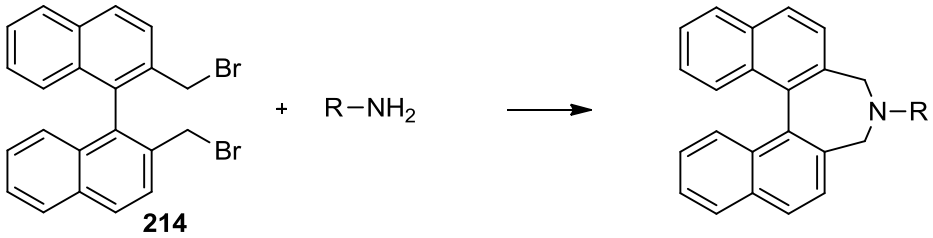
(+)-(R_a)-*Bis*-bromomethyl-[1,1']-binaphthylenyl[5] ((R_a)-214)



(R_a)-213 **(R_a)-214**

Prepared in an identical manner to **(S_a)-214** from **(R_a)-213** (3.5 g, 12.4mmol). The known title compound **(R_a)-214** was isolated as a colourless powder (3.02 g, 55%): m.p. 182.9-184.8 °C; $[\alpha]^{20}_D$ +162.2 (c = 1.07, $CHCl_3$). All other data closely matched that of **(S_a)-214**.

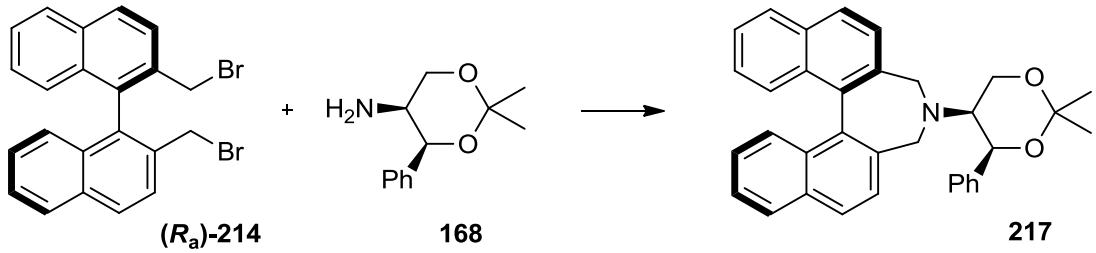
General procedure for the synthesis of binaphthalene-derived azepines



214

The primary amine (1 equiv.) was added to a solution of **(R_a)-** or **(S_a)-214** (1 equiv.) and K_2CO_3 (3 equiv.) in dry MeCN (10 mL per g of **214**) at RT. The reaction mixture was heated under reflux overnight under an atmosphere of N_2. Solvents were removed under reduced pressure and the resulting residue was dissolved in CH_2Cl_2 (40 mL per g of **214**) and filtered into a separating funnel to remove excess K_2CO_3.The organic layer was washed with water (2 x 30 mL per g of **214**) and brine (1 x 30 mL per g of **214**). The organic phase was collected, dried over $MgSO_4$ and evaporated to dryness under reduced pressure to furnish the desired azepines in excellent purity.

(–)-(R_a)-4-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine[6] (217)

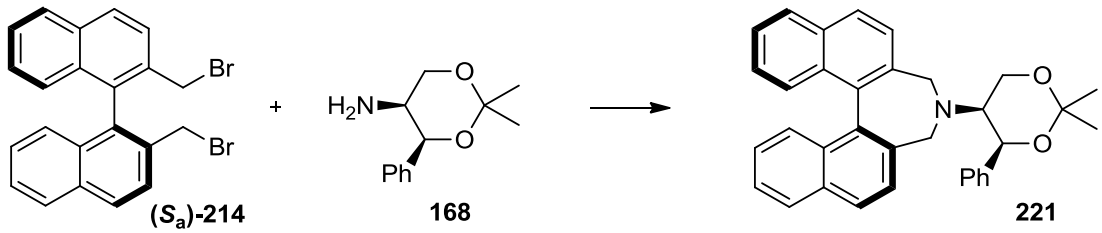


(R_a)-214 **168** **217**

Prepared according to the general procedure from **(R_a)-214** (0.48 g, 1.12 mmol) and **168** (0.23 g, 1.12 mmol). The known **217** was isolated as a colourless foam (0.51 g, 99 %): $[\alpha]^{20}_D$ –342.8 (c = 1.06, $CHCl_3$), *lit.* $[\alpha]^{20}_D$ -–360.8 (c = 1.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2989, 1710, 1507, 1450, 1380, 1237, 1197, 1146, 1079, 1060, 1018, 953, 851, 818, 770, 750, 697; δ_H (300 MHz; $CDCl_3$) 1.62 (3H, s, C<u>Me</u>$_2$), 1.71 (3H, s,

C<u>Me</u>$_2$), 2.72 (1H, td, *J* = 1.4 Hz, 3.5 Hz, -NC<u>H</u>-), 3.35 (2H, d, *J* = 12.2 Hz, 2 x ArC<u>H</u>$_2$N, upfield portion of an AB system), 3.92 (2H, d, *J* = 12.2 Hz, 2 x ArC<u>H</u>$_2$N, downfield portion of an AB system), 4.11 (1H, dd, *J* = 12.6 Hz, 1.5 Hz, NCH-C<u>H</u>$_2$-O, upfield portion of an ABX system), 4.24 (1H, dd, *J* = 12.6 Hz, 3.6 Hz, NCH-C<u>H</u>$_2$-O, downfield portion of an ABX system), 5.18 (1H, d, *J* = 3.3 Hz, NCH-C<u>H</u>Ar-O), 7.18-7.45 (13H, m, 13 x C<u>H</u> *arom.*), 7.85 (2H, d, *J* = 8.3 Hz, 2 x C<u>H</u> *arom.*), 7.89 (2H, d, *J* = 8.1 Hz, 2 x C<u>H</u> *arom.*).

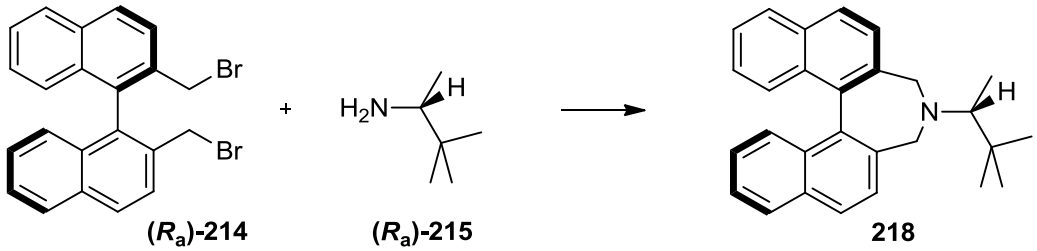
(*S*$_a$)-4-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine[6] (221)



(*S*$_a$)-214 168 221

Prepared according to the general procedure from **(*S*$_a$)-214** (0.48 g, 1.12 mmol) and **168** (0.23 g, 1.12 mmol). The known **221** was isolated as a colourless foam (0.49 g, 93 %): ν_{max}(neat)/cm^{-1} 3049, 2989, 2857, 1708, 1594, 1507, 1449, 1378, 1237, 1195, 1136, 1078, 1061, 1027, 1014, 953, 851, 838, 817, 770, 751, 736, 697; δ_H (300 MHz; $CDCl_3$) 1.46 (3H, s, C<u>Me</u>$_2$), 1.51 (3H, s, C<u>Me</u>$_2$), 2.72 (1H, dd, *J* = 3.8 Hz, 6.0 Hz, -NC<u>H</u>-), 3.50 (2H, d, *J* = 12.5 Hz, 2 x ArC<u>H</u>$_2$N, upfield portion of AB system), 3.70 (2H, d, *J* = 12.5 Hz, 2 x ArC<u>H</u>$_2$N, downfield portion of AB system), 3.96 (1H, dd, *J* = 12.6 Hz, 2.1 Hz, NCH-C<u>H</u>$_2$-O, upfield portion of ABX system), 4.20 (1H, dd, *J* = 12.6 Hz, 3.7 Hz, NCH-C<u>H</u>$_2$-O, downfield portion of ABX system), 5.19 (1H, d, *J* = 3.7 Hz, NCH-C<u>H</u>Ar-O), 7.20-7.27 (3H, m, 3 x C<u>H</u> *arom.*), 7.34-7.42 (8H, m, 8 x C<u>H</u> *arom.*), 7.50-7.56 (2H, m, 2 x C<u>H</u> *arom.*), 7.82-7.90 (4H, m, 4 x C<u>H</u> *arom.*); *m/z* (HNES) 486.2420 - $C_{34}H_{31}NO_2$ $[M+H]^+$ requires 486.2428.

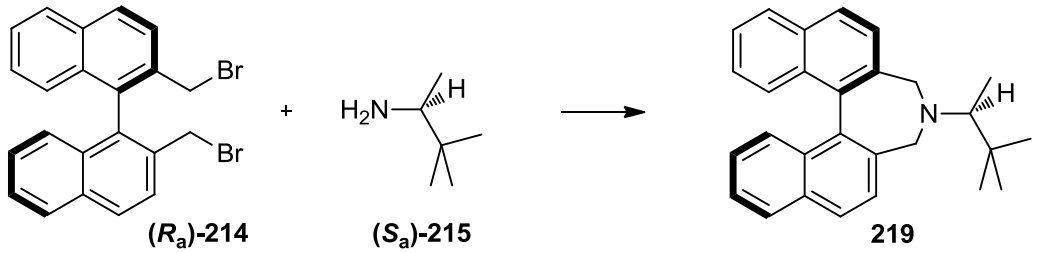
(–)-(R_a)-4-((*R*)-3,3-Dimethylbutan-2-yl)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine[7] (218)



(R_a)-214 (R_a)-215 218

Prepared according to the general procedure from **(R_a)-214** (1.50 g, 3.39 mmol) and **(*R*)-215** (0.34 g, 3.39 mmol). The known **218** was isolated as a colourless foam (1.20 g, 99%): $[\alpha]^{20}_D$ –256.5 (c = 1.77, $CDCl_3$), *lit.* $[\alpha]^{20}_D$ -–254.8 (c = 1.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2957, 1709, 1508, 1459, 1377, 1357, 1243, 1195, 1162, 1144, 1109, 1028, 865, 821, 731; δ_H (400 MHz; $CDCl_3$) 0.82 (3H, d, *J* = 7.2 Hz, N-CHMe^{t}Bu), 0.96 (9H, s, N-CHMe^{t}Bu), 2.80 (1H, q, *J* = 7.2 Hz, N-CHMe^{t}Bu), 3.51 (2H, d, *J* = 12.1 Hz, 2 x ArCH_2N, upfield portion of AB system), 3.55 (2H, d, *J* = 12.1 Hz, 2 x ArCH_2N, downfield portion of AB system), 7.25 (2H, ddd, *J* = 1.3 Hz, 6.8 Hz, 8.3 Hz, 2 x CH *arom.*), 7.42 (2H, ddd, *J* = 1.2 Hz, 6.8 Hz, 8.1 Hz, 2 x CH *arom.*), 7.48 (2H, d, *J* = 8.5 Hz, 2 x CH *arom.*), 7.53 (2H, d, *J* = 8.3 Hz, 2 x CH *arom.*), 7.93 (4H, d, *J* = 8.2 Hz, 4 x CH *arom.*).

(–)-(R_a)-4-((*S*)-3,3-Dimethylbutan-2-yl)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine[7] (219)

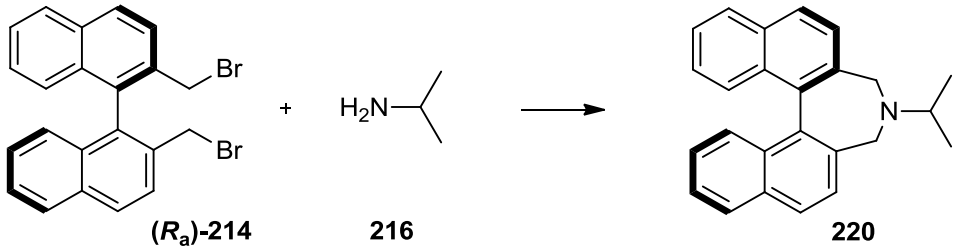


(R_a)-214 (S_a)-215 219

Prepared according to the general procedure from **(R_a)-214** (0.34 g) and **(*S*)-215** (1.50 g). The known **219** was isolated as a colourless foam (1.18 g, 99%): $[\alpha]^{20}_D$ –301.4 (c = 1.98, $CHCl_3$), *lit.* $[\alpha]^{20}_D$ –285.3 (c = 1.00, $CHCl_3$); ν_{MAX}(neat)/cm^{-1} 3409,

2967, 1711, 1595, 1508, 1465, 1352, 1144, 1113, 1050, 864, 815, 783, 749; δ_H (400 MHz; $CDCl_3$) 0.96 (9H, s, N-CHMe^{t}Bu), 1.10 (3H, d, *J* = 7.2 Hz, N-CHMe^{t}Bu), 2.48 (1H, q, *J* = 6.9 Hz, N-CHMe^{t}Bu), 3.50 (2H, d, *J* = 12.2 Hz, 2 x ArCH_2N, upfield portion of AB system), 3.71 (2H, d, *J* = 12.2 Hz, 2 x ArCH_2N, downfield portion of AB system), 7.23 (2H, ddd, *J* = 1.3 Hz, 6.8 Hz, 8.3 Hz, 2 x CH *arom.*), 7.35-7.46 (4H, m, 4 x CH *arom.*), 7.56 (2H, d, *J* = 8.3 Hz, 2 x CH *arom)*, 7.91 (2H, dd, *J* = 2.6 Hz, 8.0 Hz, 2 x CH *arom.*).

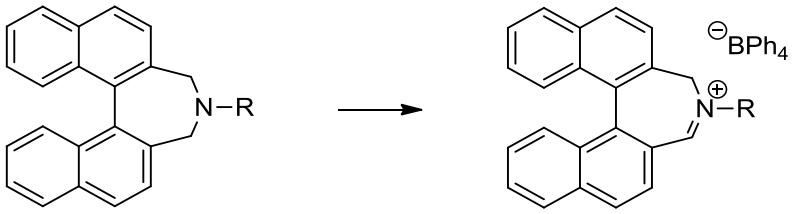
(–)-(R_a)-4-Isopropyl-2,7-dihydrodinaphtho[2,1-c;1',2'-e]azepine[8] (220)



(R_a)-214 **216** **220**

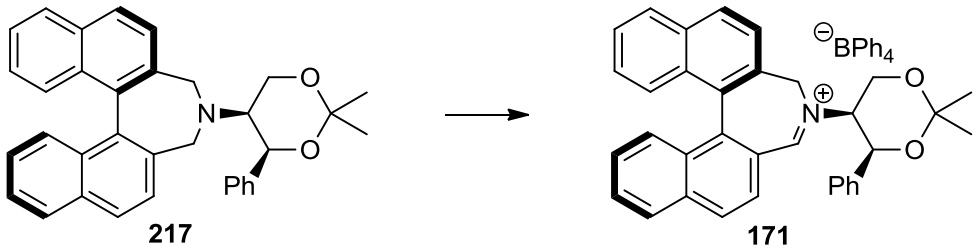
Prepared according to the general procedure from **(R_a)-214** (1.20 g, 2.73 mmol) and **226** (0.16 g, 2.73 mmol). The known **220** was isolated as a colourless powder, (0.91 g, 98%): m.p. 158.5-160.2°C; $[\alpha]^{20}_D$ –473.6 (c = 0.47, $CHCl_3$), *lit.* $[\alpha]^{20}_D$ –474.2 (c = 1.08, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3043, 2966, 2923, 2802, 1709, 1591, 1506, 1459, 1388, 1373, 1349, 1261, 1239, 1160, 1112, 1086, 1065, 1028, 957, 945, 869, 852, 840, 819, 806, 772, 755, 732, 693, 667, 624; δ_H (300 MHz; $CDCl_3$) 1.14 (3H, d, *J* = 6.4 Hz, NCHMe$_2$), 1.28 (3H, d, *J* = 6.3 Hz, NCHMe$_2$), 2.77 (1H, sept., *J* = 6.4 Hz, NCHMe$_2$), 3.26 (2H, d, *J* = 12.4 Hz, ArCH_2N, upfield portion of AB system), 3.93 (2H, d, *J* = 12.4 Hz, ArCH_2N, downfield portion of AB system), 7.26 (2H, m, 2 x CH *arom*.), 7.45 (4H, m, 4 x CH *arom*.), 7.60 (2H, d, *J* = 8.3 Hz, 2 x CH *arom*.), 7.95 (4H, d, *J* = 8.0 Hz, 4 x CH *arom*.); δ_C (75 MHz; $CDCl_3$) 21.1 (1C, NCHMe$_2$), 22.0 (1C, NCHMe$_2$), 52.2 (2C, 2 x ArCH_2N), 52.9 (1C, NCHMe$_2$), 125.4 (2C, 2 x CH *arom*.), 125.7 (2C, 2 x CH *arom*.), 127.5 (2C, 2 x CH *arom*.), 128.0 (2C, 2 x CH *arom*.), 128.3 (2C, 2 x CH *arom*.), 128.4 (2C, 2 x CH *arom*.), 131.4 (2C, 2 x C *quat. arom*.), 133.1 (2C, 2 x C *quat. arom*.), 134.2 (2C, 2 x C *quat. arom*.), 135.1 (2C, 2 x C *quat. arom*.).

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



NBS (1.1 equiv.) was added to a solution of the azepine substrate (1 equiv.) in CH_2Cl_2 (30 mL per g of azepine). The resulting yellow solution was stirred for 1 h, when the solvent was switched to EtOH (20 mL per g of azepine). $NaBPh_4$ (1.1 equiv.), which had previously been dissolved in the minimum amount of MeCN, was added to the ethanolic solution. Solvents were removed under reduced pressure to yield an intensely yellow foam. EtOH (20 mL per g of azepine) was added and heated until the solid had dissolved (a few drops of MeCN was sometimes required to completely solvate some of the iminium salts). The solution was then allowed to cool to RT and the precipitate was isolated by filtration. The precipitate was washed with cold EtOH followed by Et_2O and hexane. The fine yellow crystalline solids were left to dry under reduced pressure in an oven at 60 °C overnight.

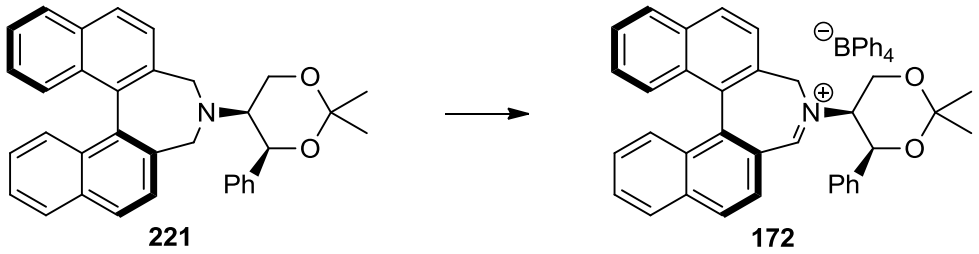
(–)-(R_a)-4-((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate[5] (171)



217 **171**

Prepared according to the general procedure from **217** (0.41 g, 0.84 mmol). The known **171** was isolated as a bright yellow powder (0.43 g, 63%): m.p. 153.8-163.9 °C (dec.); $[\alpha]^{20}_D$ –357.7 (c = 0.99, acetone), *lit.* $[\alpha]^{20}_D$ –357.8 (c = 1.00, acetone); ν_{max}(neat)/cm^{-1} 3056, 2997, 1612, 1580, 1548, 1463, 1426, 1381, 1266, 1237, 1200, 1165, 1112, 1084, 1031, 961, 850, 818, 750, 730, 701, 668, 624; δ_H (400 MHz; acetone-d_6) 1.80 (3H, s, C$\underline{Me}_2$), 1.85 (3H, s, C$\underline{Me}_2$), 4.41 (1H, d, *J* = 13.9 Hz, ArC$\underline{H}_2$N, upfield portion of AB system), 4.51 (1H, d, *J* = 13.8 Hz, NCH-C$\underline{H}_2$-O, upfield portion of an ABX system), 4.71 (1H, t, *J*=3 Hz, -NC$\underline{H}$-), 4.81 (1H, dd, *J* = 13.8 Hz, 3.0 Hz, NCH-C$\underline{H}_2$-O, downfield portion of ABX system), 5.94 (1H, s, ArC$\underline{H}_2$N, downfield portion of AB system), 5.96 (1H, d, *J* = 3.0 Hz, NCH-C$\underline{H}$Ar-O), 6.75 (4H, t, *J* = 7.3 Hz, 4 x C$\underline{H}$ *arom.*, *para*- $^{-}$BPh$_4$), 6.92 (8H, t, *J* = 7.4 Hz, 8 x C$\underline{H}$ *arom., meta*- $^{-}$BPh$_4$), 6.85-7.00 (1H, m, C$\underline{H}$ a*rom.*), 6.95 (1H, d, *J* = 8.6 Hz, C$\underline{H}$ *arom*.), 7.05 (2H, m, 2 x C$\underline{H}$ *arom.*), 7.27 (1H, ddd, *J* = 8.6 Hz, 6.9 Hz, 1.3 Hz, C$\underline{H}$ *arom.*), 7.28-7.38 (10H, m, 2 x C$\underline{H}$ *arom.* / 8 x C$\underline{H}$ *arom*. *ortho*- $^{-}$BPh$_4$), 7.40-7.51 (3H, m, 3 x C$\underline{H}$ *arom.*), 7.57 (1H, ddd, *J* = 8.0 Hz, 6.8 Hz, 1.2 Hz, C$\underline{H}$ *arom*.), 7.78 (1H, m, C$\underline{H}$ *arom.*), 7.86 (1H, d, *J* = 8.4 Hz, C$\underline{H}$ *arom.*), 8.10 (1H, d, *J* = 8.2 Hz, C$\underline{H}$ *arom*.), 8.17 (1H, d, *J* = 8.3 Hz, C$\underline{H}$ *arom.*), 8.21 (1H, d, *J* = 8.6 Hz, C$\underline{H}$ *arom.*), 8.22 (1H, d, *J* = 8.3 Hz, C$\underline{H}$ *arom*.), 9.09 (1H, s, -N=C$\underline{H}$-).

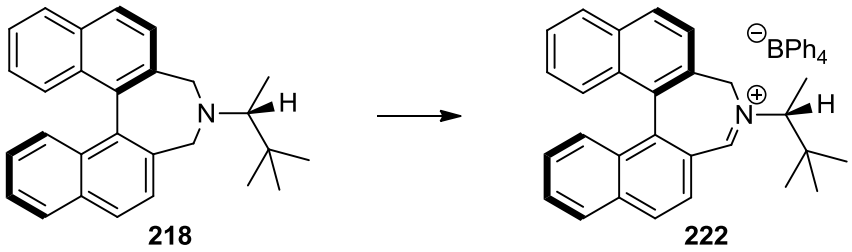
(+)-(S_a)-4-((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate[5] (172)



221 **172**

Prepared according to the general procedure from **221** (0.48 g, 0.99 mmol). The known **172** was isolated as a yellow powder (0.42 g, 46%): m.p. 217.3-224.9 °C (dec.); $[\alpha]^{20}_D$ +533.3 (c = 0.99, acetone), *lit.* $[\alpha]^{20}_D$ –534.2 (c = 1.00, acetone); ν_{max}(neat)/cm^{-1} 3054, 2998, 1637, 1613, 1580, 1548, 1461, 1426, 1383, 1337, 1263, 1201, 1160, 1110, 1059, 1031, 966, 838, 817, 733, 704; δ_H (400 MHz; acetone-d_6) 1.75 (3H, s, C$\underline{Me}_2$), 1.79 (3H, s, C$\underline{Me}_2$), 4.20 (1H, d, *J* = 13.6 Hz, ArC$\underline{H}_2$N, upfield portion of AB system), 4.33 (1H, d, *J* = 13.9 Hz, 1 x NCH-C$\underline{H}_2$-O, upfield portion of ABX system), 4.84 (1H, dd, *J* = 3.0 Hz, 13.9 Hz, NCH-C$\underline{H}_2$-O, downfield portion of ABX system), 5.06 (1H, t, *J* = 2.6 Hz, -NC$\underline{H}$-), 5.08 (1H, d, *J* = 13.5 Hz, ArC$\underline{H}_2$N, downfield portion of AB system), 6.02 (1H, d, *J* = 2.7 Hz, NCH-C$\underline{H}$Ar-O), 6.77 (4H, t, *J* = 7.2 Hz, 4 x C$\underline{H}$ *arom.*, *para*- $^-BPh_4$), 6.92 (8H, t, *J* = 7.4 Hz, 8 x C$\underline{H}$ *arom., meta*- $^-BPh_4$), 6.95-7.10 (4H, m, 4 x C$\underline{H}$ a*rom.*), 7.25 (2H, d, *J* = 6.8 Hz, 2 x C$\underline{H}$ *arom*.), 7.30 (1H, m, C$\underline{H}$ *arom.*), 7.32-7.35 (8H, m, 8 x C$\underline{H}$ *arom*., *ortho*- $^-BPh_4$), 7.40-7.47 (2H, m, 2 x C$\underline{H}$ *arom*.), 7.59 (1H, t, *J* = 7.5 Hz, C$\underline{H}$ *arom.*), 7.79 (1H, ddd, *J* = 8.2 Hz, 5.8 Hz, 2.4 Hz, C$\underline{H}$ *arom.*), 7.90 (1H, d, *J* = 8.5 Hz, C$\underline{H}$ *arom.*), 8.04 (1H, d, *J* = 8.5 Hz, C$\underline{H}$ *arom.*), 8.12 (1H, d, *J* = 8.2 Hz, C$\underline{H}$ *arom*.), 8.21 (1H, d, *J* = 8.3 Hz, C$\underline{H}$ *arom.*), 8.28 (1H, d, *J* = 8.5 Hz, C$\underline{H}$ *arom*.), 8.34 (1H, d, *J* = 8.6 Hz, C$\underline{H}$ *arom.*), 9.67 (1H, s, -N=C$\underline{H}$-).

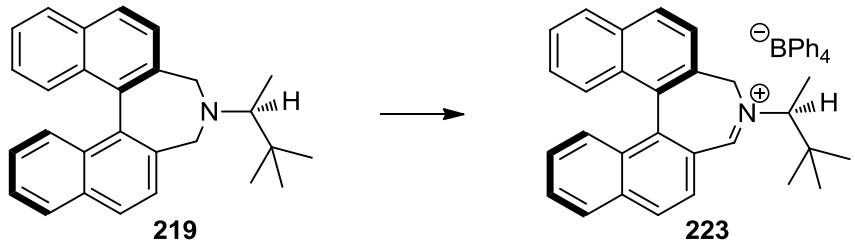
(–)-(R_a)-4-((*R*)-3,3-Dimethylbutan-2-yl)-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate (222)



218 222

Prepared according to the general procedure from **218** (0.82 g, 2.16 mmol). **222** was isolated as a bright yellow powder (1.11 g, 74 %): m.p. 197.8-204.2 °C (dec.); $[\alpha]^{20}_{D}$ –468.1 (c = 1.01, acetone); ν_{max}(neat)/cm^{-1} 3055, 2982, 1740, 1614, 1580, 1548, 1470, 1425, 1370, 1325, 1228, 1135, 1080, 1033, 957, 840, 816, 745, 733, 702, 671, 623; δ_H (400 MHz; acetone-d_6) 1.21 (9H, s, N-CHMe^{t}Bu), 1.54 (3H, d, *J* = 7.0 Hz, N-CHMe^{t}Bu), 4.77 (1H, q, *J* = 7.1 Hz, N-CHMe^{t}Bu), 5.08 (1H, d, *J* = 13.3 Hz, ArCH$_2$N, upfield portion of AB system), 5.47 (1H, d, *J* = 13.3 Hz, ArCH$_2$N, downfield portion of AB system), 6.76 (4H, t, *J* = 7.17 Hz, 4 x CH *arom.*, *para*- $^-$BPh$_4$), 6.92 (8H, t, *J* = 7.4Hz, 8 x CH *arom., ortho*- $^-$BPh$_4$), 7.11 (1H, d, *J* = 8.7 Hz, CH *arom.*), 7.32-7.35 (8H, m, 8 x CH *arom.*, *meta*- $^-$BPh$_4$), 7.48 (1H, m, CH *arom.*), 7.56 (1H, d, *J* = 8.5 Hz, CH *arom.*), 7.58 (1H, ddd, *J* = 8.1 Hz, 6.8 Hz, 1.1 Hz, CH *arom.*), 7.81 (1H, ddd, *J* = 8.1 Hz, 6.7 Hz, 1.3 Hz, CH *arom.*), 8.02 (1H, t, *J* = 8.2 Hz, CH *arom.*), 8.12 (1H, d, *J* = 8.5 Hz, CH *arom.*), 8.23 (1H, d, *J* = 7.8 Hz, CH *arom.*), 8.28 (1H, d, *J* = 8.5 Hz, CH *arom.*), 8.35 (1H, d, *J* = 8.7 Hz, CH *arom.*), 9.62 (1H, s, -N=CH-).

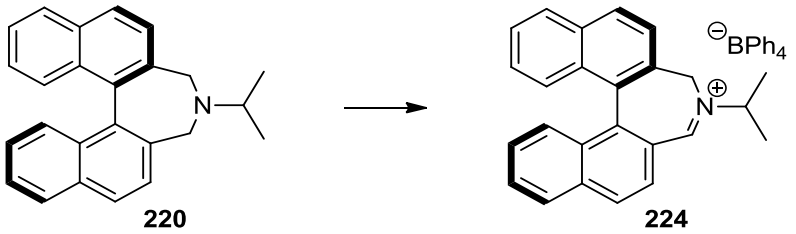
(–)-(R_a)-4-((*S*)-3,3-Dimethylbutan-2-yl)-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate (223)



219 **223**

Prepared according to the general procedure from **219** (0.92 g, 2.53 mmol). **223** was isolated as a bright yellow powder (1.53 g, 87%): m.p. 217.8-223.4 °C (dec.); $[\alpha]^{20}_D$ –390.0 (c = 1.07, acetone); ν_{max}(neat)/cm^{-1} 3055, 2981, 1738, 1613, 1590, 1478, 1428, 1374, 1328, 1253, 1226, 1122, 1098, 1032, 960, 841, 817, 750, 734, 664, 610; δ_H (400 MHz; acetone-d_6) 1.23 (9H, s, N-CHMe^{t}Bu), 1.77 (3H, d, *J* = 7.0 Hz, N-CHMe^{t}Bu), 4.47 (1H, q, *J* = 6.7 Hz, N-CHMe^{t}Bu), 4.90 (1H, d, *J* = 13.6 Hz, ArCH$_2$N, upfield portion of AB system), 5.43 (1H, d, *J* = 13.7 Hz, ArCH$_2$N, downfield portion of AB system), 6.75 (4H, t, *J* = 7.2 Hz, 4 x CH *arom.*, *para*- $^-$BPh$_4$), 6.89 (8H, t, *J* = 7.4 Hz, 8 x CH *arom., meta*- $^-$BPh$_4$), 7.09 (1H, d, *J* = 8.7 Hz, CH *arom.*), 7.28-7.37 (9H, m, 8 x CH *arom*. *ortho*- $^-$BPh$_4$ / CH *arom.*), 7.48 (1H, m, CH *arom.*), 7.53 (1H, t, *J* = 8.6 Hz, CH *arom.*), 7.58 (1H, ddd, *J* = 8.1 Hz, 6.8 Hz, 1.1 Hz, CH *arom.*), 7.81 (1H, ddd, *J* = 8.2 Hz, 6.6 Hz, 1.4 Hz, CH *arom.*), 7.98 (1H, d, *J* = 8.5 Hz, CH *arom.*), 8.03 (1H, d, *J* = 8.6 Hz, CH *arom.*), 8.10 (1H, d, *J* = 8.2 Hz, CH *arom.*), 8.25 (2H, t, *J* = 8.8 Hz, 2 x CH *arom.*), 8.34 (1H, d, *J* = 8.7 Hz, CH *arom.*), 9.51 (1H, s, -N=CH-).

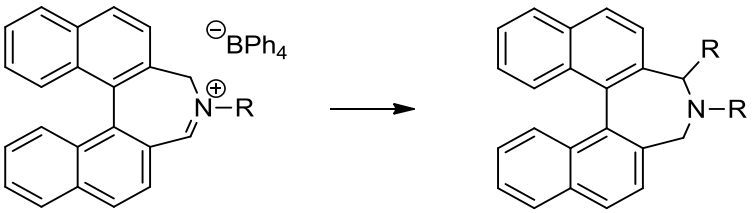
(–)-(R_a)-4-Isopropyl-*3H*-dinaphtho-[2,1-c;1',2'-e]azepin-4-ium tetraphenylborate[8] (224)



220 224

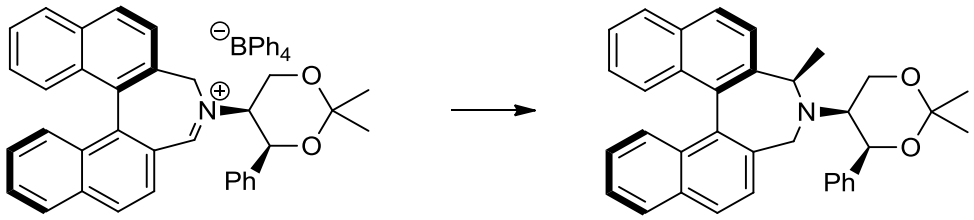
Prepared according to the general procedure from **220** (0.80 g, 2.37 mmol). The known **224** was isolated as a fine yellow powder (0.85 g, 55%): m.p. 174.0 °C (dec); $[\alpha]^{20}_D$ –485.8 (c = 1.12, acetone), *lit.* $[\alpha]^{20}_D$ –481.4 (c = 1.01, acetone); ν_{max}(neat)/cm^{-1} 3052, 2981, 1633, 1578, 1551, 1459, 1426, 1375, 1354, 1253, 1128, 1031, 841, 820, 749, 738, 731, 699, 669, 624, 611; δ_H (300 MHz; $CDCl_3$) 1.58 (3H, d, *J* = 6.6 Hz, NCH$\underline{Me}_2$), 1.61 (3H, d, *J* = 6.6 Hz, NCH$\underline{Me}_2$), 4.67 (1H, dd, *J* = 1.9 Hz, 13.5 Hz, ArC$\underline{H}_2$N, upfield portion of AB system), 4.68 (1H, sept., *J* = 6.7 Hz, NC$\underline{H}$Me$_2$), 5.40 (1H, dd, *J* = 1.2 Hz, 13.7 Hz, ArC$\underline{H}_2$N, downfield portion of AB system), 6.66 (4H, t, *J* = 7.1 Hz, 4 x C$\underline{H}$ *arom*., *para*- $^-$BPh$_4$), 6.82 (8H, t, *J* = 7.4 Hz, 8 x C$\underline{H}$ *arom*., *meta*- $^-$BPh$_4$), 7.01 (1H, dd, *J* = 0.8 Hz, 8.7 Hz, C$\underline{H}$ *arom*.), 7.25 (9H, m, C$\underline{H}$ *arom*., 8 x C$\underline{H}$ *arom*., *ortho*- $^-$BPh$_4$), 7.41 (2H, m, 2 x C$\underline{H}$ *arom*.), 7.51 (1H, ddd, *J* = 1.1 Hz, 6.8 Hz, 8.1 Hz, C$\underline{H}$ *arom*.), 7.73 (1H, ddd, *J* = 1.8 Hz, 6.2 Hz, 8.2 Hz, C$\underline{H}$ *arom*.), 7.93 (2H, t, *J* = 8.5 Hz, 2 x C$\underline{H}$ *arom*.), 8.03 (1H, d, *J* = 8.0 Hz, C$\underline{H}$ *arom*.), 8.15 (1H, d, *J* = 8.3 Hz, C$\underline{H}$ *arom*.), 8.20 (1H, d, *J* = 8.4 Hz, C$\underline{H}$ *arom*.), 8.26 (1H, d, *J* = 8.6 Hz, C$\underline{H}$ *arom*.), 9.31 (1H, s, -N=C$\underline{H}$-); δ_C (75 MHz; $CDCl_3$) 20.8 (1C, NCH$\underline{Me}_2$), 21.1 (1C, NCH$\underline{Me}_2$), 54.0, 66.8, 122.4, (4C, 4 x $\underline{C}$H *arom*., *para*- $^-$BPh$_4$), 126.2 (8C, 8 x $\underline{C}$H *arom*., *meta*- $^-$BPh$_4$), 126.8 (1C, $\underline{C}$H *arom*.), 127.9 (1C, $\underline{C}$H *arom*.), 127.95 (1C, $\underline{C}$H *arom*.), 127.99 (1C, $\underline{C}$ *quat. arom.*), 128.2 (1C, $\underline{C}$H *arom*.), 128.3 (1C, $\underline{C}$H *arom*.), 128.7 (1C, $\underline{C}$H *arom*.), 129.7 (1C, $\underline{C}$H *arom*.), 129.8 (1C, $\underline{C}$H *arom*.), 130.3 (1C, $\underline{C}$H *arom*.), 130.4 (1C, $\underline{C}$H *arom*.), 131.2 (1C, $\underline{C}$H *arom*.), 132.3 (1C, $\underline{C}$H *arom*.), 132.6 (1C, $\underline{C}$ *quat. arom.*), 133.0 (1C, $\underline{C}$ *quat. arom.*), 134.9 (1C, $\underline{C}$ *quat. arom.*), 136.4 (1C, $\underline{C}$ *quat. arom.*), 137.19 (1C, $\underline{C}$ *quat. arom.*), 137.21 (8C, 8 x $\underline{C}$H *arom*. *ortho*- $^-$BPh$_4$) 137.6 (1C, $\underline{C}$ *quat. arom.*), 142.4 (1C, $\underline{C}$ *quat. arom.*), 165.2 (4C, q, *J* = 49.4 Hz, 4 x $\underline{C}$H *arom*. *ipso*- $^-$BPh$_4$ gp), 169.5 (1C, -N=$\underline{C}$H-).

General Procedure for the Grignard Addition to Binpahthyl-iminium Salts



A flame dried round-bottomed flask under an atmosphere of N_2 was charged with the desired iminium salt (1 equiv.) and THF (50 mL per g of iminium salt). The resulting bright-yellow solution was then allowed to cool to –78 °C in a Dewar containing dry ice / acetone slurry. While maintaining the nitrogen atmosphere and temperature, the desired Grignard reagent (10 equiv.) was added dropwise down the inside of the flask. After a period of 1 h, the flask was removed from the Dewar and allowed to attain ambient temperature overnight. The reaction was then quenched with saturated aqueous NH_4Cl solution (5 mL per g of iminium salt) and the reaction mixture was concentrated to a viscous slurry under reduced pressure. The slurry was diluted with EtOAc and filtered into a separating funnel removing any undissolved solid. The organic layer was collected and washed sequentially with water (2 x 60 mL per g of iminium salt) and brine (50 mL per g of iminium salt). The organic layer was dried over $MgSO_4$. Solvents removed under reduced pressure after filtration to yield the desired azepine. The crude azepines were purified using flash column chromatography, typically eluting with light petroleum / EtOAc (5:1), buffered with 2% TEA.

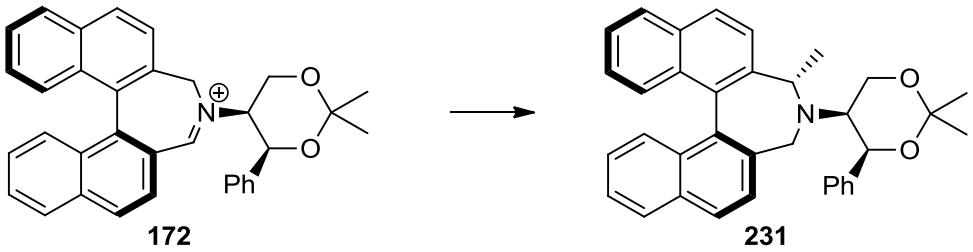
(–)-(3*R*,11c*R*$_a$)-4-((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-3-methyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (228)



171 **228**

Prepared according to the general procedure from **171** (1.20 g, 1.49 mmol). **228** was isolated as a colourless solid (0.51 g, 68%): m.p. 200.4 °C (dec.); $[\alpha]^{20}_D$ –152.35 (c = 0.68, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3044, 2987, 2857, 1496, 1448, 1378, 1196, 1144, 1101, 1078, 1016, 952, 907, 850, 818, 767, 749, 727, 697; δ_H (400 MHz; $CDCl_3$) 0.12 (3H, d, *J* = 6.9 Hz, N-CHMe-Ar), 1.50 (3H, s, CMe_2), 1.59 (3H, s, CMe_2), 2.87 (1H, s, -NCH-), 3.52 (1H, d, *J* = 11.5 Hz, $ArCH_2N$, upfield portion of AB system), 3.72 (1H, d, *J* = 11.4 Hz, $ArCH_2N$, downfield portion of AB system), 3.97 (1H, d, *J* = 12.4 Hz, NCH-CH_2-O, upfield portion of ABX system), 4.19 (1H, dd, *J* = 12.4 Hz, 3.6 Hz, NCH-CH_2-O, downfield portion of ABX system), 4.44 (1H, q, *J* = 6.8 Hz, N-CHMe-Ar), 5.12 (1H, s, NCH-CHAr-O), 7.06-7.33 (13H, m, 13 x CH *arom*.), 7.72-7.80 (4H, m, 4 x CH *arom*.); δ_C (75 MHz; $CDCl_3$) 19.2 (1C, CMe_2), 21.1 (1C, N-CHMe-Ar), 29.3 (1C, CMe_2), 54.1 (1C, $ArCH_2N$), 59.9 (1C, s, -NCH-, C5), 60.1 (1C, N-CHMe-Ar), 63.9 (1C, NCH-CH_2-O), 72.3 (1C, NCH-CHAr-O), 99.4 (1C, s, CMe_2, C *quat.*), 125.1 (1C, CH *arom*.), 125.1 (1C, CH *arom*.), 125.4 (1C, CH *arom*.), 125.6 (1C, CH *arom*.), 126.3 (2C, 2 x CH *arom*.), 126.7 (1C, CH *arom*.), 127.4 (1C, CH *arom*.), 127.5 (1C, CH *arom*.), 127.6 (1C, CH *arom*.), 127.8 (2C, 2 x CH *arom*.), 128.0 (1C, CH *arom*.), 128.2 (1C, CH *arom*.), 128.4 (2C, 2 x CH *arom*.), 128.6 (1C, CH *arom*.), 128. 9 (1C, CH *arom*.), 131.9 (1C, C *quat. arom*.), 132.0 (1C, C *quat. arom*.), 132.3 (1C, C *quat. arom*.), 132.6 (1C, C *quat. arom*.), 133.0 (1C, C *quat. arom*.), 135.0 (1C, C *quat. arom*.), 136.5 (1C, C *quat. arom*.), 140.0 (1C, C *quat. arom*.), 140.3 (1C, C *quat. arom*.); *m/z* (HNES) 500.2576 - $C_{35}H_{33}NO_2$ $[M+H]^+$ requires 500.2584.

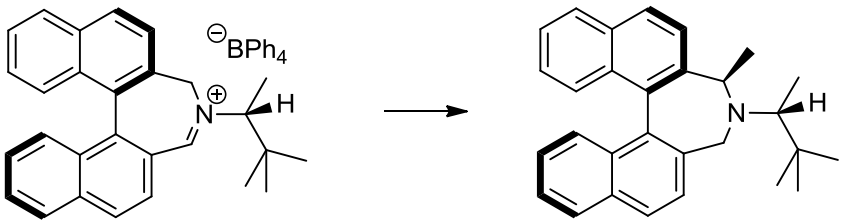
(+)-(3*S*,11c*S*$_a$)-4-((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-3-methyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (231)



172 **231**

Prepared according to the general procedure from **172** (0.39 g, 0.49 mmol). **231** was isolated as a colourless foam (0.21 g, 78%): $[\alpha]^{20}_D$ +227.1 (c = 0.93, acetone); ν_{max}(neat)/cm^{-1} 2991, 2920, 1714, 1596, 1498, 1449, 1378, 1221, 1197, 1079, 1014, 854, 819, 768, 752, 698; δ_H (400 MHz; acetone-d$_6$) 0.15 (3H, d, *J* = 7.1 Hz, N-CHMe-Ar), 1.38 (3H, s, CMe$_2$), 1.51 (3H, s, CMe$_2$), 3.28 (1H, m, -NCH-), 3.55 (1H, d, *J* = 11.4 Hz, ArCH$_2$N, upfield portion of AB system), 4.00-4.19 (2H, m, NCH-CH$_2$-O, upfield portion of ABX system / N-CHMe-Ar), 4.26 (1H, d, *J* = 11.4 Hz, ArCH$_2$N, downfield portion of AB system), 4.37 (1H, dd, 1H, d, *J* = 3.5 Hz, 12.4 Hz, NCH-CH$_2$-O, downfield portion of ABX system), 5.38 (1H, d, *J* = 4.0 Hz, NCH-CHAr-O), 7.09 (1H, d, *J* = 8.3 Hz, CH *arom.*), 7.17-7.29 (4H, m, 4 x CH *arom.*), 7.33-7.41 (4H, m, 4 x CH *arom.*), 7.45 (1H, ddt, *J* = 1.1 Hz, 6.7 Hz, 8.7 Hz, CH *arom.*), 7.57-7.61 (3H, m, 3 x CH *arom.*), 7.78 (1H, d, *J* = 8.3 Hz, CH *arom.*), 7.90 (1H, d, *J* = 8.3 Hz, CH *arom.*), 8.00 (1H, d, *J* = 8.2 Hz, CH *arom.*), 8.04 (1H, d, *J* = 8.3 Hz, CH *arom*.); δ_C (75 MHz; acetone-d$_6$) 19.3 (1C, CMe$_2$), 22.8 (1C, N-CHMe-Ar.), 28.8 (1C, CMe$_2$), 52.1 (1C, ArCH$_2$N), 62.9 (1C, -NCH-), 63.9 (1C, NCH-CH$_2$-O), 66.8 (1C, N-CHMe-Ar.), 74.3 (1C, NCH-CHAr-O), 99.6 (1C, CMe$_2$, C *quat.*), 126.0 (1C, CH *arom*.), 126.4 (1C, CH *arom*.), 126.5 (1C, CH *arom*.), 126.6 (1C, CH *arom*.), 126.9 (2C, 2 x CH *arom*.), 127.2 (1C, CH *arom*.), 127.8 (1C, CH *arom*.), 128.0 (1C, CH *arom*.), 128.3 (2C, 2 x CH *arom*.), 129.1 (1C, CH *arom*.), 129.2 (1C, CH *arom*.), 129.3 (2C, 2 x CH *arom*.), 129.9 (2C, 2 x CH *arom*.), 132.7 (1C, C *quat. arom*.), 133.0 (1C, C *quat. arom*.), 133.8 (1C, C *quat. arom*.), 133.9 (1C, C *quat. arom*.), 134.0 (1C, C *quat. arom*.), 135.7 (1C, C *quat. arom*.), 137.5 (1C, C *quat. arom*.), 140.8 (1C, C *quat. arom*.), 141.7 (1C, C *quat. arom*.); *m/z* (HNES) 500.2577 - $C_{35}H_{33}NO_2$ $[M+H]^+$ requires 500.2584.

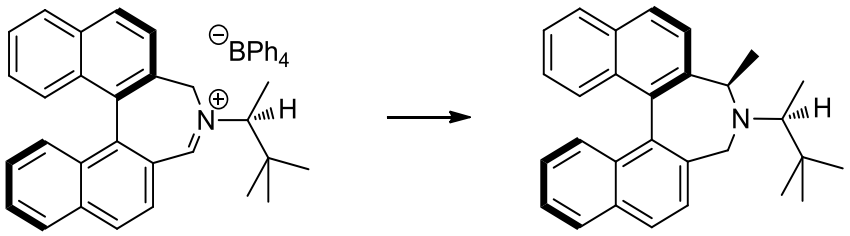
(3*R*,11cR_a)-4-((*R*)-3,3-Dimethylbutan-2-yl)-3-methyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine



222

Prepared according to the general procedure from **222** (0.50 g, 0.72 mmol). The title compound was isolated as a colourless foam (0.29 g, 99%): $[\alpha]^{21}_{D}$ –291.3 (c = 1.03, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3046, 2953, 2912, 2860, 1739, 1505, 1469, 1455, 1377, 1364, 1325, 1313, 1248, 1218, 1199, 1166, 1147, 1110, 1071, 997, 815; (400 MHz; acetone-d6) 0.51 (3H, d, *J* = 7.1 Hz, N-CHMe-Ar), 0.98 (1H, d, *J* = 7.1 Hz, N-CHMe^{t}Bu), 1.04 (9H, s, N-CHMe^{t}Bu), 2.73 (1H, q, *J* = 6.9 Hz, N-CHMe^{t}Bu), 3.29 (1H, d, *J* = 10.8 Hz, ArCH_2N, upfield portion of AB system), 3.70 (1H, d, *J* = 10.8 Hz, ArCH_2N, downfield portion of AB system), 4.11 (1H, q, *J* = 7.0 Hz, N-CHMe-Ar), 7.25-7.32 (2H, m, 2 x CH *arom.*), 7.35 (1H, d, *J* = 8.4 Hz, CH *arom*.), 7.41-7.51 (3H, m, 3 x CH *arom.*), 7.59 (1H, d, *J* = 8.3 Hz, CH *arom.*), 7.64 (1H, d, *J* = 8.3 Hz, CH *arom.*), 7.98-8.08 (4H, m, 4 x CH *arom.*); δ_C (100 MHz; acetone-d6) 10.5 (1C, N-CHMe^{t}Bu), 22.5 (1C, N-CHMe-Ar), 27.7 (3C, N-CHMe^{t}Bu), 35.8 (1C, N-CHMe^{t}Bu, C *quat.*), 49.4 (1C, ArCH_2N), 70.1 (1C, N-CHMe-Ar), 73.0 (1C, N-CHMe^{t}Bu), 125.4 (1C, CH *arom.*), 125.5 (1C, CH *arom.*), 125.8 (1C, CH *arom.*), 125.9 (1C, CH *arom.*), 127.0 (1C, CH *arom.*), 127.1 (1C, CH *arom.*), 127.9 (1C, CH *arom.*), 128.4 (1C, CH *arom.*), 128.6 (1C, CH *arom.*), 128.9 (1C, CH *arom.*), 129.0 (1C, CH *arom.*), 129.2 (1C, CH *arom.*), 132.0 (1C, C *quat. arom.*), 132.1 (1C, C *quat. arom.*), 132.3 (1C, C *quat. arom.*), 133.1 (1C, C *quat. arom.*), 133.2 (1C, C *quat. arom.*), 135.3 (1C, C *quat. arom.*), 136.8 (1C, C *quat. arom.*), 140.3 (1C, C *quat. arom.*); *m/z* (HNES) 324.2531 - $C_{29}H_{32}N$ $[M+H]^+$ requires 394.2529.

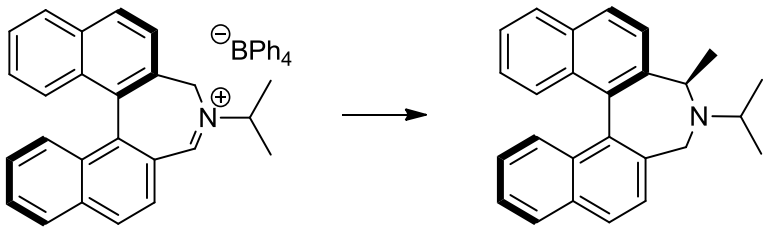
(3*R*,11cR_a)-4-((*S*)-3,3-dimethylbutan-2-yl)-3-methyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (229)



223 **229**

Prepared according to the general procedure from **222** (0.50 g, 0.72 mmol). **229** was isolated in good purity as a yellow foam (0.29 g, 99%): $[\alpha]^{20}_D$ –185.6 (c = 0.97, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2950, 2920, 1688, 1505, 1458, 1431, 1388, 1364, 1321, 1245, 1226, 1217, 1206, 1173, 1158, 1137, 1080, 1006, 863, 817; (400 MHz; acetone-d6) 0.52 (3H, d, *J* = 7.1 Hz, N-CHMe-Ar), 1.00 (9H, s, N-CHMe^{t}Bu), 1.10 (1H, d, *J* = 7.0 Hz, N-CHMe^{t}Bu) 2.63 (1H, q, *J* = 7.0 Hz, N-CHMe^{t}Bu), 3.65 (1H, d, *J* = 10.9 Hz, ArCH_2N, upfield portion of AB system), 3.68 (1H, d, *J* = 11.0 Hz, ArCH_2N, downfield portion of AB system), 4.26 (1H, q, *J* = 7.1 Hz, N-CHMe-Ar), 7.25-7.31 (3H, m, 3 x CH *arom.*), 7.40 (1H, d, *J* = 8.6 Hz, CH *arom*.), 7.44-7.51 (2H, m, 2 x CH *arom.*), 7.57 (1H, d, *J* = 8.4 Hz, CH *arom*.), 7.67 (1H, d, *J* = 8.3 Hz, CH *arom*.), 7.99-8.05 (4H, m, 4 x CH *arom.*); δ_C (100 MHz; acetone-d6) 11.6 (1C, N-CHMe^{t}Bu), 22.6 (1C, N-CHMe-Ar), 27.1 (3C, N-CHMe^{t}Bu), 36.8 (1C, N-CHMe^{t}Bu, C *quat.*), 57.5 (1C, ArCH_2N), 59.9 (1C, N-CHMe-Ar), 69.7 (1C, N-CHMe^{t}Bu), 126.3 (1C, CH *arom.*), 126.4 (1C, CH *arom.*), 126.6 (1C, CH *arom.*), 126.7 (1C, CH *arom.*), 127.9 (1C, CH *arom.*), 128.0 (1C, CH *arom.*), 129.2 (1C, CH *arom.*), 129.3 (1C, CH *arom.*), 129.5 (1C, CH *arom.*), 129.6 (1C, CH *arom.*), 129.9 (1C, CH *arom.*), 130.5 (1C, CH *arom.*), 132.9 (1C, C *quat. arom.*), 133.0 (1C, C *quat. arom.*), 133.8 (1C, C *quat. arom.*), 134.0 (1C, C *quat. arom.*), 134.2 (1C, C *quat. arom.*), 136.1 (1C, C *quat. arom.*), 137.2 (1C, C *quat. arom.*), 140.8 (1C, C *quat. arom.*); *m/z* (HNES) 324.2530 - $C_{29}H_{32}N$ $(M+H)^+$ requires 394.2529.

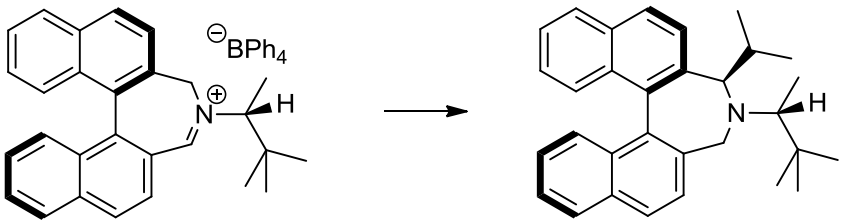
(–)-(3*R*,11c*R*$_a$)-4-Isopropyl-3-methyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (230)



224 **230**

Prepared according to the general procedure from **224** (0.70 g, 1.07 mmol). **230** was isolated as a colourless foam (0.32 g, 85%): $[\alpha]^{20}_D$ –375.3 (c = 1.02, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3044, 2958, 2802, 1594, 1505, 1458, 1363, 1317, 1243, 1164, 1101, 1057, 979, 948, 862, 810, 767, 749, 699, 674, 628; δ_H (300 MHz; $CDCl_3$) 0.50 (3H, d, *J* = 7.2 Hz, N-CHMe-Ar), 1.05 (3H, d, *J* = 6.5 Hz, NCHMe$_2$), 1.13 (3H, d, *J* = 6.7 Hz, NCHMe$_2$), 3.12 (1H, sept., *J* = 6.6 Hz, NCHMe$_2$), 3.44 (1H, d, *J* = 10.5 Hz, ArCH$_2$N, upfield portion of AB system), 3.64 (1H, d, *J* = 10.5 Hz, ArCH$_2$N, downfield portion of AB system), 4.23 (1H, q, *J* = 7.2, N-CHMe-Ar), 7.26 (3H, m, 3 x CH *arom*.), 7.38 (1H, dd, *J* = 0.9 Hz, 8.6 Hz, CH *arom*.), 7.46 (2H, m, 2 x CH *arom*.), 7.61 (1H, d, *J* = 8.4 Hz, CH *arom*.), 7.66 (1H, d, *J* = 8.3 Hz, CH *arom*.), 8.01 (4H, m, 4 x CH *arom*.); δ_C (75 MHz; $CDCl_3$) 18.9 (1C, N-CHMe-Ar), 21.2 (1C, NCHMe$_2$), 24.5 (1C, NCHMe$_2$), 53.1 (1C, NCHMe$_2$), 57.0 (1C, ArCH$_2$N), 60.0 (1C, ArCHMe), 126.3 (1C, CH *arom*.), 126.4 (1C, CH *arom*.), 126.6 (1C, CH *arom*.), 126.7 (1C, CH *arom*.), 128.0 (1C, CH *arom*.), 129.0 (1C, CH *arom*.), 129.2 (1C, CH *arom*.), 129.3 (1C, CH *arom*.), 129.4 (1C, CH *arom*.), 129.7 (1C, CH *arom*.), 129.7 (1C, CH *arom*.), 130.4 (1C, CH *arom*.), 132.9 (1C, C *quat*. *arom*.), 133.0 (1C, C *quat*. *arom*.), 133.87 (1C, C *quat*. *arom*.), 133.93 (1C, C *quat*. *arom*.), 134.1 (1C, C *quat*. *arom*.), 135.9 (1C, C *quat*. *arom*.), 137.2 (1C, C *quat*. *arom*.), 141.0 (1C, C *quat*. *arom*.); *m/z* (HNES) 352.2064 - $C_{26}H_{26}N$ $[M+H]^+$ requires 352.2060.

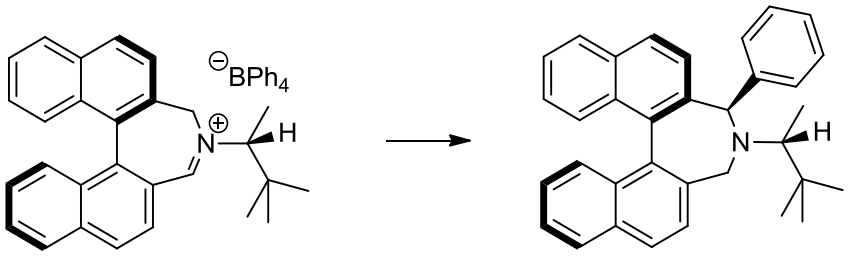
(–)-(3*R*,11c*R*$_a$)-4-((*R*)-3,3-Dimethylbutan-2-yl)-3-isopropyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine



222

Prepared according to the general procedure from **222** (0.55 g, 0.80 mmol) and 3 M solution of ^{i}PrMgCl in Et_2O (4.00 mL, 7.96 mmol). The crude product isolated as a yellow foam (0.32 g, 95%). A sample was purified by preparative TLC, eluting with light petroleum / EtOAc (5:1), which yielded a colourless residue for spectral analysis: $[\alpha]^{20}_{D}$ −225.0 (c = 0.88, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3051, 2955, 2864, 1507, 1462, 1428, 1366, 1319, 1227, 1138, 1086, 996, 952, 865, 814, 803, 744; δ_H (300 MHz; $CDCl_3$) 0.18 (3H, d, *J* = 6.4 Hz, Ar-CH(CH$\underline{Me_2}$)-N), 0.30 (1H, m, Ar-CH(C$\underline{H}$Me$_2$)-N), 0.78 (3H, d, *J* = 6.3 Hz, Ar-CH(CH$\underline{Me_2}$)-N), 0.91 (1H, d, *J* = 6.8, N-CH$\underline{Me}^{t}$Bu), 1.09 (9H, s, N-CHMe$^{t}\underline{Bu}$), 2.62 (1H, q, *J* = 6.8 Hz, N-C$\underline{H}$Me^{t}Bu), 3.23 (1H, d, *J* = 10.2 Hz, Ar-C$\underline{H}$(CHMe$_2$)-N), 3.32 (1H, d, *J* = 10.5 Hz, ArC$\underline{H_2}$N, upfield portion of AB system), 3.67 (1H, d, *J* = 10.4 Hz, ArC$\underline{H_2}$N, downfield portion of AB system), 7.16-7.22 (2H, 2 x C$\underline{H}$ *arom.*), 7.33 (1H, *J* = 7.4 Hz, C$\underline{H}$ *arom.*), 7.35-7.47 (4H, m, 4 x C$\underline{H}$ *arom.*), 7.56 (1H, d, *J* = 7.1 Hz, C$\underline{H}$ *arom.*), 7.86-7.93 (4H, m, 4 x C$\underline{H}$ *arom.*); δ_C (75 MHz; $CDCl_3$) 9.6, 21.1, 21.3, (1C, Ar-CH(CH$\underline{Me_2}$)-N), 29.2 (3C, N-CHMe$^{t}\underline{Bu}$), 33.6, 36.1, 48.2 (1C, Ar$\underline{C}$H$_2$N), 72.60, 81.12, 125.1 (1C, $\underline{C}$H *arom.*), 125.2 (1C, $\underline{C}$H *arom.*), 125.50 (1C, $\underline{C}$H *arom.*), 125.52 (1C, $\underline{C}$H *arom.*), 127.3 (1C, $\underline{C}$H *arom.*), 127.5 (1C, $\underline{C}$H *arom.*), 127.9 (1C, $\underline{C}$H *arom.*), 128.00 (1C, $\underline{C}$H *arom.*), 128.02 (1C, $\underline{C}$H *arom.*), 128.3 (1C, $\underline{C}$H *arom.*), 128.5 (1C, $\underline{C}$H *arom.*), 131.1 (1C, $\underline{C}$H *arom.*), 131.6 (1C, $\underline{C}$ *quat. arom.*), 131.8 (1C, $\underline{C}$ *quat. arom.*), 132.55 (1C, $\underline{C}$ *quat. arom.*), 132.57 (1C, $\underline{C}$ *quat. arom.*), 132.9 (1C, $\underline{C}$ *quat. arom.*), 135.4 (1C, $\underline{C}$ *quat. arom.*), 136.1 (1C, $\underline{C}$ *quat. arom.*), 139.2 (1C, $\underline{C}$ *quat. arom.*); *m/z* (HNES) 422.2836 - $C_{31}H_{35}N$ $[M+H]^+$ requires 422.2842.

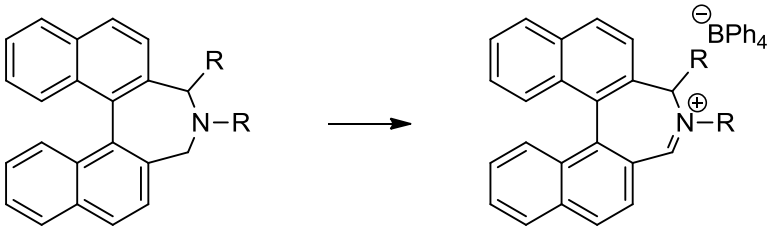
(3*R*,11cR_a)-4-((*R*)-3,3-Dimethylbutan-2-yl)-3-phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine



222

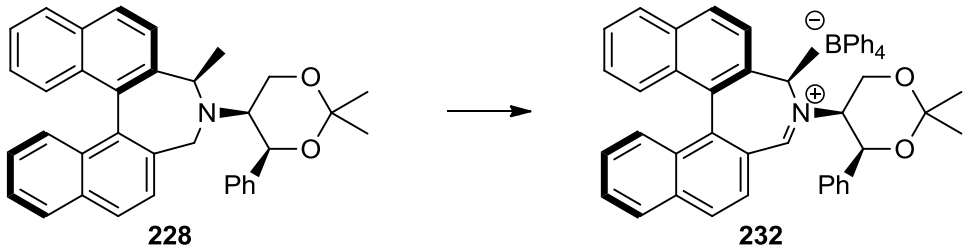
Prepared according to the general procedure from **222** (0.56 g, 0.81 mmol) and 3 M solution of PhMgCl in Et_2O (4.02 mL, 8.1 mmol). The crude product was isolated as yellow foam (0.30 g, 82%). Purification was attempted by preparative TLC, after various crystallization attemps failed. An unidentified impurity could not be removed. δ_H (300 MHz; $CDCl_3$) 1.03 (3H, d, *J* = 7.2 Hz, N-CHMe^{t}Bu), 1.11 (9H, s, N-CHMe^{t}Bu), 2.86 (1H, q, *J* = 7.2 Hz, N-CHMe^{t}Bu), 3.43 (1H, d, *J* = 10.5 Hz, ArCH_2N, upfield portion of AB system), 3.78 (1H, d, *J* = 10.5 Hz, ArCH_2N, downfield portion of AB system), 5.16 (1H, s, N-CHPh-Ar), 6.33 (1H, t, *J* = 7.5 Hz, CH *arom*.), 6.45 (2H, t, *J* = 7.5 Hz, 2 x CH *arom*.), 6.81 (1H, d, *J* = 8.2 Hz, CH *arom*.), 6.87-6.95 (2H, m, 2 x CH *arom*.), 7.16-7.24 (2H, m, 2 x CH *arom*.), 7.28-7.53 (6H, m, 6 x CH *arom*.), 7.59 (2H, m, 2 x CH *arom*.), 7.66 (1H, d, *J* = 8.3 Hz, CH *arom*.), 7.72 (1H, d, *J* = 8.3 Hz, CH *arom*.), 7.96 (1H, d, *J* = 8.1 Hz, CH *arom*.), 8.03 (1H, d, *J* = 8.2 Hz, CH *arom*.); *m/z* (HNES) 456.2677 - $C_{34}H_{34}N$ $[M+H]^+$ requires 456.2686

General Procedure for the Synthesis of Substituted Binaphthyl Azepiniums



NBS (1.1 equiv.) was added in one portion to a solution of the azepine substrate (1 equiv.) in CH_2Cl_2 (30 mL per g of azepine) in a flask equipped with a stirrer bar. The resulting yellow solution was stirred for 10 min. The reaction was transferred to a separating funnel and the organic layer was washed with water (2 x 60 mL per g of azepine) and brine (30 mL per g of azepine), then dried over $MgSO_4$. A solvent switch to EtOH was then performed. $NaBPh_4$ (1.1 equiv.) in the minimum amount of MeCN was added to the ethanolic solution, resulting in the formation of a precipitate. Solvents were removed under reduced pressure to yield a almost solid residue. EtOH (40 mL per g of azepine) was added to the residue and heated until it had dissolved; a few drops of MeCN were added in the instances where the residue was not completely solvated. The solution was allowed to cool to ambient temperature and the precipitate was filtered off. The precipitate was washed with cold EtOH followed by hexane and Et_2O. The fine powders were left to dry under reduced pressure in an oven at 60 °C overnight.

(–)-(3*R*,11c*R*$_a$)-4-((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-3-methyl-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate (232)

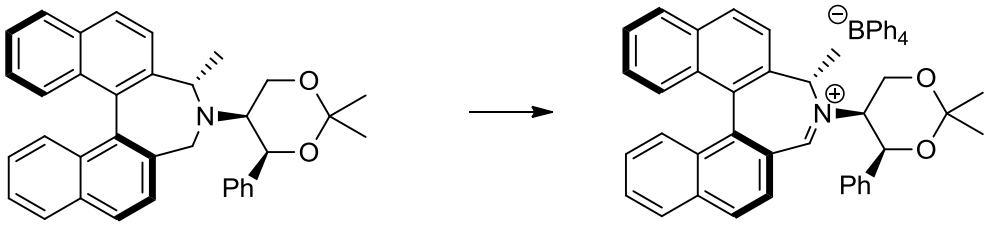


228 **232**

Prepared according to the general procedure from **228** (0.48 g, 0.96 mmol), **232** was isolated as orange-yellow powder (0.54 g, 69 %): m.p. 126.5-128.4 °C (dec.); $[\alpha]^{20}_D$ –302.48 (c = 1.05, acetone); ν_{max}(neat)/cm^{-1} 3055, 2983, 2358, 2335, 1633, 1612, 1580, 1551, 1464, 1426, 1380, 1262, 1238, 1201, 1164, 1111, 1031, 958, 857, 816, 749, 733, 702, 668, 631, 611; δ_H (300 MHz; MeCN-d_3) 1.00 (3H, d, *J* = 7.1 Hz, N-CHMe-Ar), 1.69 (3H, s, CMe$_2$), 1.76 (3H, s, CMe$_2$), 4.35 (1H, dd, *J* = 1.1 Hz, 13.8 Hz, NCH-CH$_2$-O, upfield portion of ABX system), 4.44 (1H, td, *J* = 1.0 Hz, 3.0 Hz, -N-CH-), 4.73 (1H, dd, *J* = 3.0 Hz, 13.8 Hz, NCH-CH$_2$-O, downfield portion of ABX system), 5.61 (1H, q, *J* = 6.9 Hz, N-CHMe-Ar), 5.67 (1H, d, *J* = 2.9 Hz, NCH-CHAr-O), 6.47 (1H, t, *J* = 7.5 Hz, CH *arom.*), 6.67 (2H, t, *J* = 7.8 Hz, CH *arom.*), 6.81-6.89 (5H, m, CH *arom.* / 4 x CH *arom., para*- $^-$BPh$_4$), 6.95-7.06 (10H, m, 2 x CH *arom.* / 8 x CH *arom*., *meta*- $^-$BPh$_4$), 7.16-7.24 (1H, m, CH *arom*.), 7.25-7.37 (11H, m, 3 x CH *arom*. / 8 x CH *arom*. *ortho* in $^-$BPh$_4$), 7.55 (1H, ddd, *J* = 1.1 Hz, 6.8 Hz, 8.1 Hz, CH *arom*.), 7.73 (2H, ddd, *J* = 1.7 Hz, 4.9 Hz, 7.9 Hz, 2 x CH *arom*.), 8.01 (1H, d, *J* = 8.2 Hz, CH *arom*.), 8.02 (1H, d, *J* = 8.3 Hz, CH *arom*.), 8.12 (1H, d, *J* = 8.3 Hz, CH *arom*.), 8.21 (1H, d, *J* = 8.5 Hz, CH *arom*.), 9.31 (1H, s, -N=CH-); δ_C (75 MHz; MeCN-d_3) 13.8 (1C, s, N-CHMe-Ar), 18.0 (1C, CMe$_2$), 28.9 (1C, CMe$_2$) 62.0 (1C, NCH-CH$_2$-O), 68.4 (1C, -NCH-), 69.7 (1C, N-CHMe-Ar) 71.2 (1C, NCH-CHAr-O), 101.2 (1C, CMe$_2$, C *quat.*), 122.0 (4C, 4 x CH *arom*., *para*- $^-$BPh$_4$), 124.8 (2C, 2 x CH *arom*.), 124.9 (1C, C *quat. arom.*), 125.8-125.9 (8C, 8 x CH *arom*., *meta*- $^-$BPh$_4$), 126.2 (1C, CH *arom*.), 126.4 (1C, CH *arom*.), 127.1 (2C, 2 x CH *arom*.), 127.2 (1C, CH *arom*.), 127.9 (1C, CH *arom*.), 128.1 (1C, CH *arom*.), 128.5 (2C, 2 x CH *arom*.), 128.7 (1C, CH *arom*.), 129.0 (1C, CH *arom*.), 129.49 (1C, CH *arom*.), 129.50 (1C, CH *arom*.), 131.0 (1C, CH *arom*.), 131.9 (1C, C *quat*. *arom*.), 132.0 (1C, CH *arom*.), 133.0 (1C, C *quat*. *arom*.), 134.0 (1C, C *quat*. *arom*.),

135.8 (1C, C *quat*. *arom*.), 135.9 (1C, C *quat*. *arom*.), 136.0 (8C, 8 x CH *arom*., *ortho*-$^{-}BPh_4$), 138.9 (1C, C *quat*. *arom*.), 142.1 (1C, C *quat*. *arom*.), 164.2 (4C, q, *J* = 49.0 Hz, 4 x C *quat*. *arom*., *ipso*- $^{-}BPh_4$), 169.2 (1C, -N=CH-), C *quat*. *arom*. not observed; *m/z* (HNES) 498.2415 - $C_{35}H_{32}NO_2$ $[M–BPh_4]^+$ requires 498.2428.

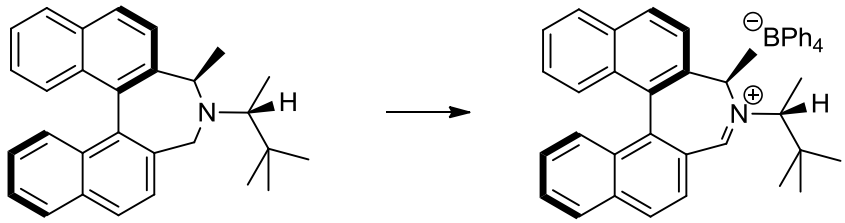
(+)-(3*S*,11c*S*$_a$)-4-((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-3-methyl-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate (235)



Prepared according to the general procedure from **231** (0.17 g, 0.34 mmol). **235** was isolated as bright yellow powder (0.20 g, 72%): m.p. 203.1 - 204.5 °C (dec.); $[\alpha]^{20}_D$ +421.4 (c = 0.99, acetone); ν_{max}(neat)/cm^{-1} 3054, 2986, 1631, 1611, 1586, 1554, 1464, 1426, 1379, 1240, 1198, 1120, 1086, 1048, 1030, 952, 834, 821, 753, 733, 701, 672; δ_H (400 MHz; acetone-d_6) 0.75 (1H, d, *J* = 7.1 Hz, N-CHMe-Ar), 1.73 (3H, s, CMe$_2$), 1.74 (3H, s, CMe$_2$), 4.29 (1H, d, *J* = 13.9 Hz, NCH-CH$_2$-O, upfield portion of ABX system), 4.88 (1H, dd, *J* = 2.9 Hz, 13.9 Hz, NCH-CH$_2$-O, downfield portion of ABX system), 5.01 (1H, t, *J* = 2.7 Hz, -NCH-), 6.02 (1H, d, *J* = 2.9 Hz, NCH-CHAr-O), 6.05 (1H, q, *J* = 7.1 Hz, N-CHMe-Ar), 6.78 (4H, t, *J* = 7.2 Hz, 4 x CH *arom.*, *para*- $^{-}BPh_4$), 6.93-7.04 (12H, 8 x CH *arom., ortho*- $^{-}BPh_4$ / 4 x CH *arom*.), 7.24-7.46 (13H, m, 8 x CH *arom*. *meta*- $^{-}BPh_4$ / 5 x CH *arom*.), 7.59 (1H, t, *J* = 7.2 Hz, CH *arom.*), 7.75-7.81 (2H, m, CH *arom.*), 7.95 (1H, d, *J* = 8.6 Hz, CH *arom.*), 8.12 (1H, d, *J* = 8.2 Hz, CH *arom.*), 8.17 (1H, d, *J* = 8.2 Hz, CH *arom.*), 8.28 (1H, d, *J* = 8.6 Hz, CH *arom.*), 8.29 (1H, d, *J* = 8.3 Hz, CH *arom.*), 9.47 (1H, s, N=CH); δ_C (75 MHz; acetone-d_6) 12.4 (1C, N-CHMe-Ar), 17.9 (1C, CMe$_2$), 28.6 (1C, CMe$_2$), 61.8 (1C, NCH-CH$_2$-O), 68.8 (1C, NCH-CHAr-O), 69.2 (1C, -NCH-), 71.8 (1C, N-CHMe-Ar), 101.1 (1C, CMe$_2$, C *quat.*), 121.6 (4C, 4 x CH *arom*., *para*- $^{-}BPh_4$), 125.3 (8C, 8 x CH *arom*., *meta*- $^{-}BPh_4$), 125.5

(2C, 2 x CH *arom*.), 126.6 (1C, CH *arom*.), 127.1 (1C, CH *arom*.), 127.2 (1C, CH *arom*.), 127.25 (1C, CH *arom*.), 127.29 (1C, CH *arom*.), 128.2 (1C, CH *arom*.), 128.3 (1C, CH *arom*.), 128.7 (1C, CH *arom*.), 128.8 (2C, 2 x CH *arom*.), 129.0 (1C, CH *arom*.), 129.3 (1C, CH *arom*.), 129.5 (1C, C *quat*. *arom*.), 129.6 (1C, CH *arom*.), 131.0 (1C, CH *arom*.), 131.7 (1C, CH *arom*.), 131.8 (1C, C *quat*. *arom*.), 132.9 (1C, C *quat*. *arom*.), 134.0 (1C, C *quat*. *arom*.), 135.9 (1C, C *quat*. *arom*.), 139.6 (1C, C *quat*. *arom*.), 141.8 (1C, C *quat*. *arom*.), 164.3 (4C, q, *J* = 49.0 Hz, 4 x CH *arom*., *ipso*- $^{-}BPh_4$), 176.2 (1C, -N=CH-), 2 x C *quat*. *arom*. not observed; *m/z* (HNESP) 498.2413 - $C_{35}H_{32}NO_2$ $[M-BPh_4]^+$ requires 498.2428.

(–)-(3*R*,11c*R*$_a$)-4-((*R*)-3,3-Dimethylbutan-2-yl)-3-methyl-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate (225)

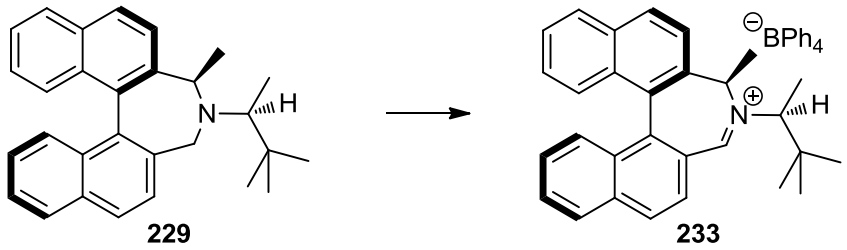


225

Prepared according to the general procedure from (3*R,* 11c*R*)-4-((*R*)-3,3-dimethylbutan-2-yl)-3-methyl-4,5-dihydro-*3H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (0.25 g, 0.64 mmol). The title compound **225** was isolated as a fine yellow powder (0.33 g, 72%): m.p. 108.3 °C (dec.); $[\alpha]^{20}_D$ –324.00 (c = 1.00, acetone); ν_{max}(neat)/cm^{-1} 3054, 2981, 1610, 1585, 1557, 1464, 1425, 1373, 1120, 1089, 1032, 817, 731, 702, 666, 611; δ_H (400 MHz; acetone-d_6) 0.97 (9H, s, N-CHMe^{t}Bu), 1.29 (3H, d, *J* = 7.1 Hz, NCHMeAr), 1.80 (3H, br, N-CHMe^{t}Bu), 4.59 (1H, q, *J* = 6.9 Hz, N-CHMe^{t}Bu), 5.88 (1H, q, *J* = 7.1 Hz, NCHMeAr), 6.74 (4H, t, *J* = 7.1 Hz, 4 x CH arom., *para*- $^{-}BPh_4$), 6.89 (8H, t, *J* = 7.4 Hz, CH arom., *ortho*- $^{-}BPh_4$), 7.06 (1H, d, *J* = 8.6 Hz, CH arom.), 7.25-7.35 (11H, m, 3 x CH arom. / 8 x CH arom., *meta*- $^{-}BPh_4$), 7.42 (1H, m, CH arom.), 7.56 (1H, ddd, *J* = 1.1 Hz, 6.8 Hz, 8.1 Hz, CH arom.), 7.77 (1H, ddd, *J* = 1.2 Hz, 6.8 Hz, 8.1 Hz, CH arom.), 7.82 (1H, d, *J* = 8.5 Hz, CH arom.), 8.04 (1H, d, *J* = 8.6 Hz, CH arom.), 8.07 (1H, d, *J* = 8.2 Hz, CH arom.), 8.19 (1H, d, *J* = 8.3 Hz, CH arom.), 8.26 (1H, d, *J* =

8.4 Hz, CH arom.), 8.33 (1H, d, *J* = 8.5 Hz, CH arom.), 9.67 (1H, s, -N=CH-); δ_C (75 MHz; acetone-d_6); 12.2 (1C, N-CHMe^{t}Bu), 14.7 (1C, N-CHMe-Ar), 26.5 (3C, N-CHMe^{t}Bu), 35.8 (1C, N-CHMe^{t}Bu, C *quat.*), 62.1 (1C, N-CHMe-Ar), 81.8 (1C, N-CHMe^{t}Bu), 122.3 (4C, 4 x CH *arom*., *para*- $^-$BPh$_4$), 126.1 (8C, 8 x CH *arom*., *meta*- $^-$BPh$_4$), 126.6 (1C, *arom*.), 128.05 (1C, CH *arom*.), 128.13 (1C, CH *arom*.), 128.2 (1C, CH *arom*.), 128.3 (1C, C *arom*.), 128.9 (1C, CH *arom*.), 129.5 (1C, CH *arom*.), 129.8 (1C, CH *arom*.), 130.1 (1C, CH *arom*.), 130.4 (1C, CH *arom*.), 131.0 (1C, C *arom*.), 131.7 (1C, CH *arom*.), 132.1 (1C, C *quat. arom.*), 132.8 (1C, C *quat. arom.*), 133.3 (1C, C *quat. arom.*), 134.6 (1C, C *quat. arom.*), 136.9 (1C, C *quat. arom.*), 137.2 (8C, 8 x CH *arom*., *ortho*- $^-$BPh$_4$), 140.7 (1C, C *arom*.), 142.7 (1C, C *quat. arom.*), 165.3 (4C, q, *J* = 49.0 Hz, 4 x C *quat*. *arom*., *ipso*- $^-$BPh$_4$) 171.7 (1C, -N=CH-), C *arom*. not observed; *m/z* (HNESP) 392.2370 - $C_{29}H_{30}N$ $[M–BPh_4]^+$ requires 392.2373.

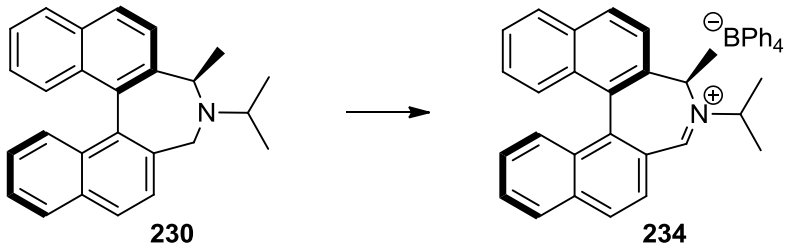
(–)-(3*R*,11c*R*$_a$)-4-((*S*)-3,3-Dimethylbutan-2-yl)-3-methyl-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate (233)



229 233

Prepared according to the general procedure from **229** (0.27 g, 0.69 mmol). **233** was isolated as a fine orange-yellow powder (0.31 g, 64%): m.p. 131.2 °C (dec.); $[\alpha]^{20}_D$ –259.56 (c = 0.90, acetone); ν_{max}(neat)/cm^{-1} 3056, 2986, 1612, 1587, 1552, 1478, 1426, 1381, 1261, 1119, 1088, 1032, 960, 817, 732, 702, 670, 632, 611; δ_H (400 MHz; acetone-D_6) 1.18 (9H, br, N-CHMe^{t}Bu), 1.33 (3H, d, *J* = 6.9 Hz, N-CHMe-Ar), 1.74 (3H, br, N-CHMe^{t}Bu), 4.55 (1H, br, N-CHMe^{t}Bu), 5.89 (1H, q, *J* = 7.0 Hz, N-CHMe-Ar), 6.73 (4H, t, *J* = 7.2 Hz, 4 x CH arom., *para*- $^-$BPh$_4$), 6.88 (8H, t, *J* = 7.4 Hz, CH arom., *meta*- $^-$BPh$_4$), 7.07 (1H, d, *J* = 8.6 Hz, CH arom.), 7.29 (9H, m, CH arom. / 8 x CH arom., *ortho*- $^-$BPh$_4$), 7.45 (2H, m, 2 x CH arom.), 7.55 (1H, ddd, *J* = 1.1 Hz, 6.8 Hz, 8.0 Hz, CH arom.), 7.79 (1H, m, CH arom.), 7.85 (1H, br, CH arom.), 8.06 (1H, d, *J* = 8.2 Hz, CH arom.), 8.10 (1H, br, CH arom.), 8.21 (1H, d, *J* = 8.3 Hz, CH arom.), 8.22 (1H, d, *J* = 8.5 Hz, CH arom.), 8.34 (1H, d, *J* = 8.6 Hz, CH arom.), 9.52 (1H, br, -N=CH-); δ_C (75 MHz; MeCN-d_3) 13.6 (1C, 1 N-CHMe-Ar), 26.1 (3C, N-CHMe^{t}Bu), 35.8 (1C, N-CHMe^{t}Bu, C *quat.*), 80.6 (1C, N-CHMe^{t}Bu), 121.5 (4C, 4 x CH *arom*., *para*- $^-$BPh$_4$), 125.3 (8C, 8 x CH *arom*., *meta*- $^-$BPh$_4$), 125.7 (1C, C *arom.*), 127.2 (1C, CH arom.), 127.3 (2C, 2 x CH arom.), 128.2 (1C, CH arom.), 128.7 (1C, CH arom.), 129.0 (1C, CH arom.), 129.3 (1C, CH arom.), 129.8 (1C, CH arom.), 129.8 (1C, C *quat*. *arom*.), 130.8 (1C, CH arom.), 131.5 (1C, CH arom.), 132.0 (1C, C *quat*. *arom*.), 132.7 (1C, C *quat*. *arom*.), 133.9 (1C, C *quat*. *arom*.), 135.9 (1C, C *quat*. *arom*.), 136.4 (8C, 8 x CH *arom*., *ortho*- $^-$BPh$_4$), 141.6 (1C, C *quat*. *arom*.), 164.3 (4C, q, *J* = 49.0 Hz, 4 x CH *arom*., *ipso*- $^-$BPh$_4$), N-CHMe^{t}Bu, NCHMeAr, 3 x C *arom.* and -N=CH- not observed; *m/z* (HNESP) 392.2372 - $C_{29}H_{30}N$ [M–BPh$_4$]$^+$ requires 392.2373.

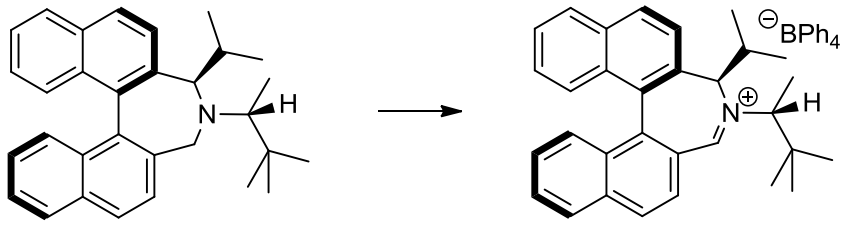
(–)-(3*R*,11c*R*$_a$)-4-isopropyl-3-methyl-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate (234)



230 **234**

Prepared according to the general procedure from **230** (0.32 g, 0.92 mmol). The title compound **234** was isolated as a bright yellow powder (0.43 g, 71%): m.p. 209.0-218.3 °C (dec.); $[\alpha]^{20}_D$ –358.38 (c = 0.99, acetone); ν_{max} (neat)/cm^{-1} 2053, 1652, 1591, 1578, 1552, 1474, 1461, 1524, 1376, 1359, 1262, 1211, 1134, 1109, 1045, 1030, 969, 867, 823, 796, 746, 735, 702; δ_H (300 MHz; DMSO) 1.05 (3H, d, *J* = 7.1 Hz, N-CHMe-Ar), 1.44 (3H, d, *J* = 6.5 Hz, NCHMe$_2$), 1.57 (3H, d, *J* = 6.5 Hz, NCHMe$_2$), 4.57 (1H, sept., *J* = 6.5 Hz, NCHMe$_2$), 5.90 (1H, q, *J* = 7.1 Hz, N-CHMe-Ar), 6.76 (4H, t, *J* = 7.2 Hz, 4 x CH *arom., para*- $^-$BPh$_4$), 6.90 (8H, t, *J* = 7.3 Hz, 8 x CH *arom., meta*- $^-$BPh$_4$), 6.97 (1H, d, *J* = 8.5 Hz, CH *arom.*), 7.17 (8H, m, 8 x CH *arom., ortho*- $^-$BPh$_4$), 7.26 (1H, ddd, *J* = 1.3 Hz, 6.8 Hz, 8.2 Hz, CH *arom.*), 7.34 (1H, d, *J* = 8.6 Hz, CH *arom.*), 7.45 (1H, ddd, *J* = 1.2 Hz, 6.8 Hz, 8.0 Hz, CH *arom.*), 7.53 (1H, ddd, *J* = 1.0 Hz, 6.8 Hz, 8.0 Hz, CH *arom.*), 7.76 (1H, ddd, *J* = 1.0 Hz, 6.8 Hz, 8.0 Hz, CH *arom.*), 7.90 (1H, d, *J* = 8.5 Hz, CH *arom.*), 8.07 (2H, m, 2 x CH *arom.*), 8.23 (2H, t, *J* = 8.6 Hz, 2 x CH *arom.*), 8.36 (1H, d, *J* = 8.6 Hz, CH *arom.*), 9.52 (1H, s, -N=CH-); δ_C (75 MHz; DMSO) 14.3, 19.4, 20.0, 60.2, 66.7, 121.7 (4C, 4 x CH *arom*., *para*- $^-$BPh$_4$), 125.5 (8C, 8 x CH *arom*., *meta*- $^-$BPh$_4$), 125.8 (1C, CH *arom*.), 126.6 (1C, CH *arom*.), 126.7 (1C, CH *arom*.), 126.9 (1C, CH *arom*.), 127.0 (1C, CH *arom*.), 127.1 (1C, CH *arom*.), 128.0 (1C, CH *arom*.), 128.7 (1C, CH *arom*.), 129.0 (1C, CH *arom*.), 129.25 (1C, CH *arom*.), 129.34 (1C, CH *arom*.), 130.3 (1C, CH *arom*.), 131.3 (1C, CH *arom*.), 131.4 (1C, CH *arom*.), 132.0 (1C, CH *arom*.), 133.3 (1C, CH *arom*.), 134.7 (1C, CH *arom*.), 135.0 (1C, CH *arom*.), 135.8 (8C, 4 x CH *arom*., *ortho*- $^-$BPh$_4$), 140.2 (1C, C *arom*.), 140.4 (1C, C *arom*.), 163.6 (4C, q, *J* = 49.0 Hz, 4 x C *quat. arom*., *ipso*- $^-$BPh$_4$), 167.6 (1C, -N=CH-); *m/z* (HNESP) 350.1904 - $C_{26}H_{25}N$ [M–BPh$_4$]$^+$ requires 350.1903.

(–)-(3*R*,11c*R*$_a$)-4-((*R*)-3,3-Dimethylbutan-2-yl)-3-isopropyl-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate (226)

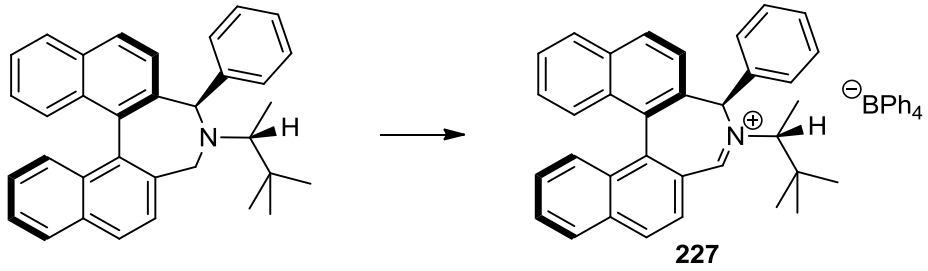


226

Prepared according to the general procedure from (–)-(3*R*,11c*R*$_a$)-4-((*R*)-3,3-dimethylbutan-2-yl)-3-isopropyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (0.32 g, 0.69 mmol) and NBS (0.14 g, 0.76 mmol). Title compound **226** was isolated as a dark yellow powder (0.20 g, 38%): m.p. 113.6 °C (dec.); $[\alpha]^{20}_D$ –373.5 (1.04, acetone); ν_{max}(neat)/cm^{-1} 3049, 2969, 1587, 1549, 1465, 1426, 1372, 1120, 1086, 1032, 842, 815, 732, 666, 621, 612; δ_H (400 MHz; $CDCl_3$) 0.85 (12H, m, N-CH(CH$\underline{Me}_2$)-Ar / N-CHMe^t$\underline{Bu}$), 0.92 (3H, d, *J* = 6.8 Hz, N-CH$\underline{Me}$^{t}Bu), 1.85 (3H, d, *J* = 6.9 Hz, N-CH(CH$\underline{Me}_2$)-Ar), 4.63 (1H, q, *J* = 7.0 Hz, N-C$\underline{H}$Me^{t}Bu), 5.34 (1H, d, *J* = 10.7 Hz, N-C$\underline{H}$(CHMe$_2$)-Ar), 6.77 (4H, t, *J* = 7.3 Hz, 4 x C$\underline{H}$ *arom.*, *para*- $^-$BPh$_4$), 6.92 (8H, t, *J* = 7.4 Hz, 8 x C$\underline{H}$ *arom., meta*- $^-$BPh$_4$), 7.13 (1H, d, *J* = 8.7 Hz, C$\underline{H}$ *arom.*), 7.31-7.43 (10H, m, 2 x C$\underline{H}$ *arom.* / 8 x C$\underline{H}$ *arom., ortho*- $^-$BPh$_4$), 7.44 (1H, ddd, *J* = 8.1 Hz, 6.8 Hz, 1.1 Hz, C$\underline{H}$ *arom.*), 7.60 (1H, ddd, *J* = 8.1 Hz, 6.8 Hz, 1.1 Hz, C$\underline{H}$ *arom.*), 7.80 (1H, ddd, *J* = 8.1 Hz, 6.7 Hz, 1.2 Hz, C$\underline{H}$ *arom.*), 7.95 (1H, d, *J* = 8.5 Hz, C$\underline{H}$ *arom.*), 8.12 (1H, d, *J* = 8.4 Hz, C$\underline{H}$ *arom.*), 8.13 (1H, d, *J* = 8.4 Hz, C$\underline{H}$ *arom.*), 8.22 (1H, d, *J* = 8.6 Hz, C$\underline{H}$ *arom.*), 8.33 (1H, d, *J* = 8.4 Hz, C$\underline{H}$ *arom.*), 8.34 (1H, d, *J* = 8.5 Hz, C$\underline{H}$ *arom.*), 9.79 (1H, s, -N=C$\underline{H}$-); δ_C (75 MHz; $CDCl_3$) 13.4, 19.5, 19.9, 25.8, 26.5 (3C, N-CHMe^t$\underline{Bu}$), 35.9, 72.9, 81.8, 121.5 (4C, 4 x $\underline{C}$H *arom*., *para*- $^-$BPh$_4$), 125.3 (8C, 8 x $\underline{C}$H *arom*., *meta*- $^-$BPh$_4$), 125.4 (1C, $\underline{C}$ *quat. arom.*), 126.7 (1C, $\underline{C}$H *arom.*), 127.4 (1C, $\underline{C}$H *arom.*), 127.5 (2C, 2 x $\underline{C}$H *arom.*), 128.2 (1C, $\underline{C}$H *arom.*), 128.7 (1C, $\underline{C}$H *arom.*), 129.1 (1C, $\underline{C}$H *arom.*), 129.2 (1C, $\underline{C}$H *arom.*), 129.3 (1C, $\underline{C}$H *arom.*), 129.7 (1C, $\underline{C}$ *quat. arom.*), 129.9 (1C, $\underline{C}$H *arom.*), 130.9 (1C, $\underline{C}$H *arom.*), 131.0 (1C, $\underline{C}$H *arom.*), 131.8 (1C, $\underline{C}$ *quat. arom.*), 133.1 (1C, $\underline{C}$ *quat. arom.*), 133.7 (1C, $\underline{C}$ *quat. arom.*), 136.2 (1C, $\underline{C}$ *quat. arom.*), 136.4 (8C, 8 x $\underline{C}$H *arom*., *ortho*- $^-$BPh$_4$), 140.2 (1C, $\underline{C}$ *quat. arom.*), 141.9 (1C,

C *quat. arom.*), 163.8 (4C, q, *J* = 49.0 Hz, 4 x C *quat*. *arom*., *ipso*- $^{-}BPh_4$), 170.9 (1C, -N=CH-); *m/z* (HNES) 420.2684 - $C_{31}H_{34}N$ $(M+H)^+$ requires 420.2686.

(3*R*,11c*R*$_a$)-4-((*R*)-3,3-Dimethylbutan-2-yl)-3-phenyl-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate (227)



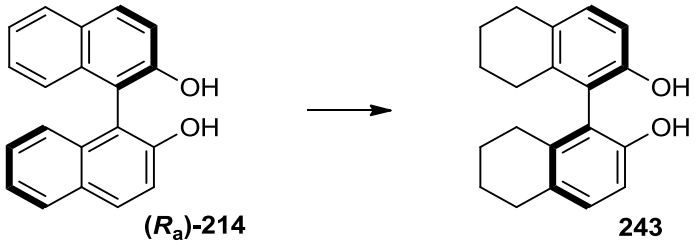
227

Prepared according to the general procedure from crude (3*R*,11c*R*$_a$)-4-((*R*)-3,3-dimethylbutan-2-yl)-3-phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (0.25 g, 0.55 mmol) and NBS (0.11 g, 0.61 mmol). The title compound **227** was isolated as a yellow powder (0.21 g, 48%): m.p. 113.6°C (dec.) ν_{max}(neat)/cm^{-1} 3056, 2966, 1945, 1686, 1594, 1552, 1494, 1448, 1427, 1372, 1259, 1151, 1120, 1094, 1030, 1001, 869, 816, 797, 731; δ_H (400 MHz; acetone-d6) 1.04 (9H, s, N-CHMe^{t}Bu), 1.89 (3H, d, *J* = 6.8 Hz, N-CHMe^{t}Bu), 5.07 (1H, q, *J* = 6.8 Hz, N-CHMe^{t}Bu), 6.78 (6H, m, 2 x CH *arom*. / 4 x CH *arom.*, *para*- $^{-}BPh_4$), 6.93 (8H, t, *J* = 7.4 Hz, 8 x CH *arom., meta*- $^{-}BPh_4$), 6.98-7.04 (3H, m, 3 x CH *arom*.), 7.07 (1H, s, CH *arom*.), 7.12 (1H, d, *J* = 8.6 Hz, CH *arom*.), 7.22-7.28 (2H, m, 2 x CH *arom*.), 7.34-7.39 (8H, m, 8 x CH *arom., ortho*- $^{-}BPh_4$), 7.57-7.67 (2H, m, 2 x CH *arom*.), 7.92 (1H, d, *J* = 8.2 Hz, CH *arom*.), 8.06 (2H, s, 2 x CH *arom*.), 8.17 (1H, d, *J* = 8.2 Hz, CH *arom*.), 8.28 (1H, d, *J* = 8.5 Hz, CH *arom*.), 8.42 (1H, d, *J* = 8.5 Hz, CH *arom*.), 10.24 (1H, s, -N=CH-); δ_C (75 MHz; acetone-d6) 26.1, 26.6, 36.0, 80.7, 121.6 (4C, 4 x CH *arom*., *para*- $^{-}BPh_4$), 125.3 (8C, 8 x CH *arom*., *meta*- $^{-}BPh_4$), 125.6 (2C, 2 x CH *arom*.), 126.4 (1C, CH *arom*.), 127.0 (1C, CH *arom*.), 127.3 (1C, CH *arom*.), 127.4 (1C, CH *arom*.), 127.46 (1C, CH *arom*.), 127.49 (1C, CH *arom*.), 127.6 (1C, CH *arom*.), 128.0 (2C, 2 x CH *arom*.), 128.3 (1C, C *quat. arom.*), 128.5 (1C, CH *arom*.), 128.8 (2C, 2 x CH *arom*.), 129.0 (1C, CH *arom*.), 129.1 (1C, CH *arom*.), 129.4 (1C, CH *arom*.), 129.5 (1C, C *quat. arom.*), 130.5 (1C, C *quat. arom.*), 131.0 (1C, C *quat. arom.*), 131.1 (1C, C *quat. arom.*), 133.2 (1C, C *quat.*

arom.), 133.4 (1C, C *quat. arom.*), 134.0 (1C, C *quat. arom.*), 135.4 (1C, C *quat. arom.*), 136.4 (8C, 8 x CH *arom*., *ortho*- $^{-}BPh_4$), 164.3 (4C, q, *J* = 49.0 Hz, 4 x C *quat*. *arom*., *ipso*- $^{-}BPh_4$), 172.45 (1C, -N=CH-); *m/z* (HNES) 454.2524 - $C_{34}H_{32}N$ $(M+H)^+$ requires 454.2529.

3.2.4 Experimental Procedures Related to the Octahydrobinaphthyl- Systems

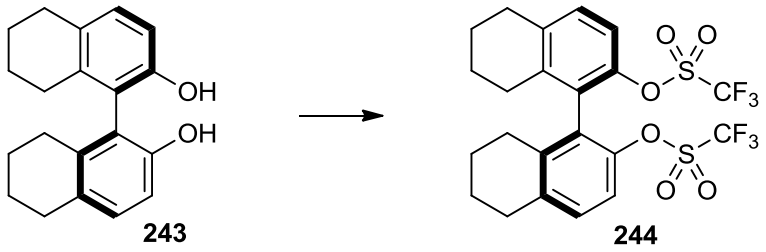
(–)-(R_a)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl-2,2'-diol[9] (243)



(R_a)-214 243

(R_a)-214 (3.00 g, 11.5 mmol) was divided equally between 3 test tubes each containing Pd/C 10% w/w (0.20 g). Glacial acetic acid (4.0 mL) was added to each of the test tubes and mixed. The tubes were then placed in hydrogenation apparatus, and were charged and evacuated with H_2 two times. The pressure was then increased to 50 atm while the reactions stirred at ambient temperature. The reactions were monitored over 10 days and full conversion was not achieved. The vials were removed from the apparatus and filtered through celite with $CHCl_3$. The organic filtrate was washed with saturated aqueous $NaHCO_3$ (1 x 50 mL), water (2 x 50 mL) and brine (1 x 50 mL). The organic layer was dried over $MgSO_4$ and solvents were then removed under reduced pressure to yield a colourless solid. Column chromatography was performed, eluting with light petroleum ether / EtOAc (4:1) to yield known **243** as a colourless solid which was crystallised from hexane to give fine colourless needles (1.63 g, 52%): $[\alpha]^{20}_D$ –42.6 (c = 1.06, $CHCl_3$), *lit.* $[\alpha]^{20}_D$ –42.5 (c = 1.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3475, 3381, 2929, 2856, 1587, 1472, 1333, 1287, 1248, 1195, 1152, 936, 828, 812, 726; δ_H (300 MHz; $CDCl_3$) 1.63-1.78 (8H, m, 8 x -C$\underline{H}_2$-), 2.16 (2H, dt, *J* = 17.0 Hz, 6.0 Hz, 2 x -C$\underline{H}_2$-), 2.29 (2H, dt, *J* = 17.0 Hz, 6.1 Hz, 2 x -C$\underline{H}_2$-), 2.75 (4H, t, *J* = 6.2 Hz, 4 x -C$\underline{H}_2$-), 4.56 (2H, br, 2 x Ar-O$\underline{H}$), 6.83 (2H, d, *J* = 8.4 Hz, 2 x C$\underline{H}$ *arom.*), 7.07 (2H, d, *J* = 8.3 Hz, 2 x C$\underline{H}$ *arom.*); δ_C (75 MHz; $CDCl_3$) 22.8 (2C, 2 x -$\underline{C}H_2$-), 22.9 (2C, 2 x -$\underline{C}H_2$-), 27.0 (2C, 2 x -$\underline{C}H_2$-), 29.1 (2C, 2 x -$\underline{C}H_2$-), 113.0 (2C, 2 x $\underline{C}$H *arom.*), 118.8 (2C, 2 x $\underline{C}$ *quat. arom.*), 130.2 (2C, 2 x $\underline{C}$ *quat. arom.*), 131.1 (2C, 2 x $\underline{C}$H *arom.*), 137.2 (2C, 2 x $\underline{C}$ *quat. arom.*), 151.5 (2C, 2 x $\underline{C}$ *quat. arom.*).

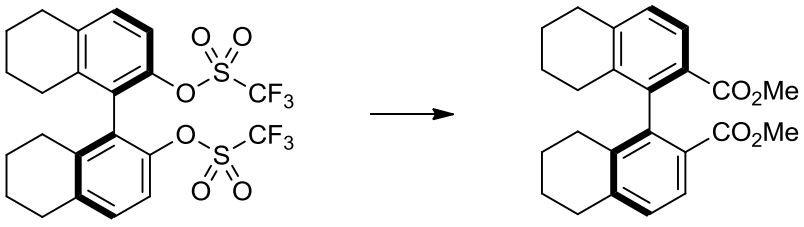
(–)-(R_a)-2,2'-Trifluoromethanesulfonyloxy-5,5'6,6'7,7',8,8'-octahydro-1,1'-binaphthyl[10] (244)



243 **244**

243 (10.0 g, 34 mmol) was dissolved in CH_2Cl_2 (250 mL) in a flame-dried flask under an atmosphere of N_2. The vessel was placed in a Dewar to cool to –30 °C. After the solution had allowed to cool, DMAP (1.66 g, 13.6 mmol), 2,6-lutidine (11.9 mL, 102 mmol) and Tf_2O (17.2 mL, 102 mmol) were added to the solution and stirred for 10 min. The solution was then removed from the Dewar and stirred at RT overnight. Silica gel was added to the dark brown solution and stirred for 20 min., after which time solvents were removed under reduced pressure. The loaded silica gel was transferred to a sintered glass funnel containing a layer of silica gel topped with filter paper and washed with hexane until the product had eluted. The solvent was removed under reduced pressure to yield known **244** as a colourless crystalline solid (28.01 g, 99%): m.p. 120.0 °C; $[\alpha]^{20}_D$ –259.6 (c = 1.03, $CHCl_3$), *lit.* $[\alpha]^{20}_D$ –260.3 (c = 1.00, $CHCl_3$); ν_{max}(neat)/cm^{-1}; 2947, 2870, 2836, 1476, 1464, 1451, 1410, 1249, 1202, 1182, 1138, 1048, 926, 872, 926, 872, 853, 834, 806, 763, 699, 644; δ_H (300 MHz; $CDCl_3$) 1.75 (8H, m, 8 x -C<u>H</u>$_2$-), 2.28 (2H, dt, *J* = 6.0 Hz, 17.4 Hz, 2 x -CH_2-), 2.43 (2H, dt, *J* = 6.0, 17.7 Hz, 2 x -CH_2-), 2.86 (4H, t, *J* = 6.0 Hz, 4 x -C<u>H</u>$_2$-), 7.16 (2H, d, *J* = 8.6 Hz, 2 x C<u>H</u> *arom*.), 7.23 (2H, d, *J* = 8.6 Hz, 2 x CH *arom*.); δ_C (75 MHz; $CDCl_3$) 22.2 (2C, 2 x -<u>C</u>H_2-), 22.3 (2C, 2 x -<u>C</u>H_2-), 27.4 (2C, 2 x -<u>C</u>H_2-), 29.3 (2C, 2 x -<u>C</u>H_2-), 118.1 (2C, 2 x <u>C</u>H *arom*.), 118.2 (2C, q, *J* = 1274 Hz, 2 x -<u>C</u>F_3), 127.1 (2C, 2 x <u>C</u> *quat. arom.*), 130.9 (2C, 2 x <u>C</u>H *arom.*), 138.3 (2C, 2 x <u>C</u> *quat. arom.*), 139.3 (2C, 2 x <u>C</u> *quat. arom.*), 144.8 (2C, 2 x <u>C</u> *quat. arom.*).

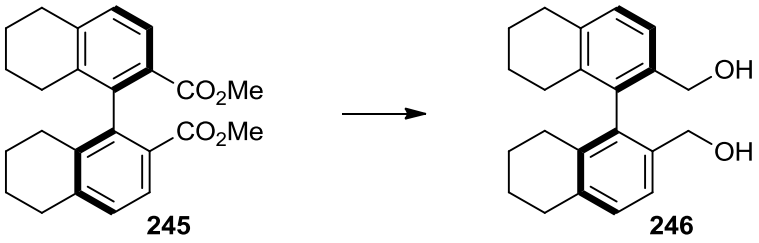
(–)-(R_a)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl-2,2'-bis(carboxylate)[10] (245)



244 **245**

To a thick-walled glass vessel under an atmosphere of Ar containing **244** (1.50 g, 17.9 mmol), $Pd(OAc)_2$ (0.61 g, 4.7 mmol) and dppp (1.11 g, 4.70 mmol) were added: DMSO (90 mL), MeOH (36.0 mL, 1.56 mol) and Hünig's base (13.4 mL, 137 mmol). The vessel was sealed with a gas-manifold and pressurised with CO (g) at 2 bar followed by evacuation of the atmosphere until the orange solution just begins to boil and that cycle was repeated five times. During the cycles, the solution turned to opaque black. The vessel was heated to 80 °C and maintained at at a pressure of 2.4 atm. of CO for 48 h. The reaction mixture was then transferred to a round-bottomed flask and solvents were removed under reduced pressure to yield an oily residue. This crude residue was purified by column chromatography eluting with light petroleum / EtOAc (5:1). The known title compound **245** was obtained as a colourless crystalline solid (5.9 g, 88%): m.p. = 99.0-105.1 °C; $[\alpha]^{20}_D$ –2.1 (c = 0.96, $CHCl_3$), *lit.* $[\alpha]^{20}_D$ –1.9 (c = 1.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2926, 2853, 1718, 1588, 1430, 1400, 1289, 1251, 1186, 1164, 1124, 1066, 1050, 878, 861, 832, 771, 749; δ_H (300 MHz; $CDCl_3$) 1.69 (8H, m, 8 x -C$\underline{H}_2$-), 1.99 (2H, dt, *J* = 5.9 Hz, 17.0 Hz, 2 x -C$\underline{H}_2$-), 2.18 (2H, dt, *J* = 6.4 Hz, 17.2 Hz, 2 x -C$\underline{H}_2$-), 2.86 (4H, m, 4 x -C$\underline{H}_2$-), 3.57 (6H, s, 2 x Ar-$CO_2\underline{Me}$), 7.13 (2H, d, *J* = 8.1 Hz, 2 x C$\underline{H}$ *arom.*), 7.76 (2H, d, *J* = 8.1 Hz, 2 x C$\underline{H}$ *arom.*); δ_C (75 MHz; $CDCl_3$) 22.4 (2C, 2 x -$\underline{C}H_2$-), 23.0 (2C, 2 x -$\underline{C}H_2$-), 27.2 (2C, 2 x -$\underline{C}H_2$-), 30.2 (2C, 2 x -$\underline{C}H_2$-), 51.5 (2C, 2 x Ar-$CO_2\underline{Me}$), 126.6 (2C, $\underline{C}$ *quat. arom.*), 127.1 (2C, 2 x $\underline{C}$H *arom.*), 128.0 (2C, 2 x $\underline{C}$H *arom.*), 135.4 (2C, $\underline{C}$ *quat. arom.*), 141.7 (2C, 2 x $\underline{C}$ *quat. arom.*), 141.9 (2C, 2 x $\underline{C}$ *quat. arom.*), 167.6 (2C, 2 x Ar-$\underline{C}O_2$Me).

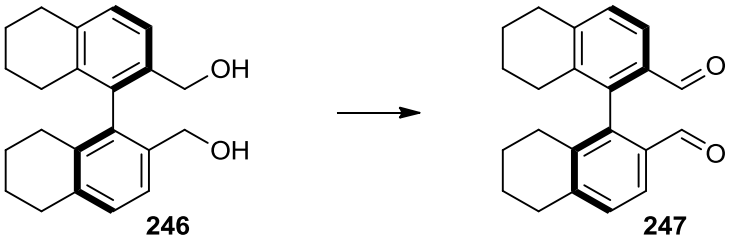
(–)-(R_a)-5,5',6,6',7,7',8,8'-Octahydro-1,1'-binaphthyl-2,2'-dimethanol[11] (246)



245 **246**

$LiAlH_4$ (0.30 g, 7.94 mmol) was suspended in Et_2O (50 mL). The suspension was then placed under N_2 and allowed to cool to 0 °C. **245** (1.50 g, 3.97 mmol) was added slowly, which caused a slight effervescence. After the effervescence had ceased, the reaction mixture was heated under reflux for a further 30 min. The solution was then removed from the heat and placed in an ice bath. Na_2SO_4 (1.50 g) and Celite were added in one portion and stirred for 10 min. followed by the dropwise addition of water (2.0 mL). After 30 min. of stirring, the reaction was filtered through a pad of celite and Na_2SO_4, washing though with Et_2O. The solvents were removed under reduced pressure to yield the known title compound **246** as a colourless foam in quantitative yield (1.24 g, 99%): $[\alpha]^{20}_D$ –39.1 (c = 0.96, MeOH), *lit.* $[\alpha]^{20}_D$ –39.0 (c = 1.01, MeOH); ν_{MAX}(neat)/cm^{-1} 3257, 2923, 2853, 1594, 1433, 1231, 1061, 1005, 899, 815, 740; δ_H (300 MHz; $CDCl_3$) 1.69 (8H, m, 8 x -C$\underline{H}_2$-), 2.02 (4H, m, 4 x -C$\underline{H}_2$-), 2.82 (4H, t, *J* = 8.8 Hz, 4 x -C$\underline{H}_2$-), 2.92 (2H, s, 2 x Ar-$CH_2O\underline{H}$), 4.02 (2H, d, *J* = 12.0 Hz, 2 x Ar-C$\underline{H}_2$OH), 4.21 (2H, d *J* = 12.0 Hz, 2 x Ar-C$\underline{H}_2$OH), 7.11 (2H, d, *J* = 8.8 Hz, 2 x C$\underline{H}$ *arom.*), 7.24 (2H, d, *J* = 8.8 Hz, 2 x C$\underline{H}$ *arom.*); δ_C (75 MHz; $CDCl_3$) 22.7 (2C, 2 x -$\underline{C}H_2$-), 23.2 (2C, 2 x -$\underline{C}H_2$-), 27.6 (2C, 2 x -$\underline{C}H_2$-), 29.8 (2C, 2 x -$\underline{C}H_2$-), 62.9 (2C, 2 x Ar-$\underline{C}H_2$OH), 127.2 (2C, 2 x $\underline{C}$H *arom.*), 128.9 (2C, 2 x $\underline{C}$H *arom.*), 134.8 (2C, 2 x $\underline{C}$ *quat. arom.*), 135.7 (2C, 2 x $\underline{C}$ *quat. arom.*), 137.6 (2C, 2 x $\underline{C}$ *quat. arom.*), 138.3 (2C, 2 x $\underline{C}$ *quat. arom.*).

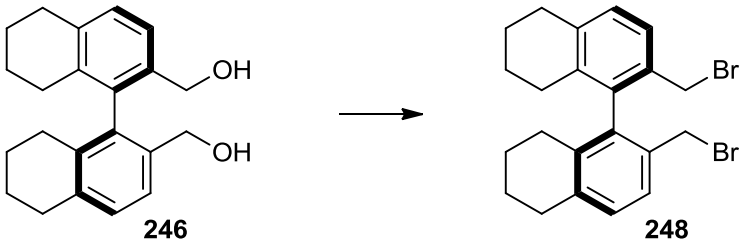
(+)-(R_a)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl-2,2'-bis(carbaldehyde)[11] 247



246 **247**

To a solution of **246** (0.11 g, 0.34 mmol) in CH_2Cl_2 (20 mL) was added PCC (0.22 g, 1.02 mmol) in one portion. The resulting dark orange solution was stirred for 2 h, after which time celite was added followed by the addition of Et_2O (20 mL). The mixture was stirred for an additional 30 min. and then filtered through a layered pad of silica and Celite. The desired compound was eluted with Et_2O. Solvents were then removed to furnish the known title compound **247** as colourless crystals (0.11 g, 99 %): m.p. 129.4-131.2 °C; $[\alpha]^{20}_D$ +110.4 (c = 0.83, $CHCl_3$), *lit.* $[\alpha]^{20}_D$ +108.5 (c = 1.00, $CHCl_3$); $\nu_{max(}$neat)/cm^{-1} 2931, 2851, 2747, 1688, 1672, 1582, 1441, 1383, 1315, 1292, 1268, 1246, 1230, 1162, 1125, 996, 968, 943, 913, 897, 836, 811, 760; δ_H (300 MHz; $CDCl_3$) 1.73 (8H, m, 8 x -C<u>H</u>$_2$-), 2.15 (4H, m, 4 x -C<u>H</u>$_2$-), 2.91 (4H, t, *J* = 6.1 Hz, 4 x -C<u>H</u>$_2$-), 7.29 (2H, d, *J* = 8.1 Hz, 2 x C<u>H</u> *arom.*), 7.82 (2H, d, *J* = 8.1 Hz, 2 x C<u>H</u> *arom.*), 9.51 (2H, s, 2 x Ar-C<u>H</u>O); δ_C (75 MHz; $CDCl_3$) 22.2 (2C, 2 x -<u>C</u>H$_2$-), 22.7 (2C, 2 x -<u>C</u>H$_2$-), 27.4 (2C, 2 x -<u>C</u>H$_2$-), 30.4 (2C, 2 x -<u>C</u>H$_2$-), 125.1 (2C, 2 x <u>C</u>H *arom*.), 129.8 (2C, 2 x <u>C</u>H *arom*.), 132.4 (2C, 2 x <u>C</u> *quat. arom*.), 136.2 (2C, 2 x <u>C</u> *quat. arom*.), 140.7 (2C, 2 x <u>C</u> *quat. arom*.), 145.2 (2C, 2 x <u>C</u> *quat. arom*.), 191.5 (2H, 2 x Ar-<u>C</u>HO).

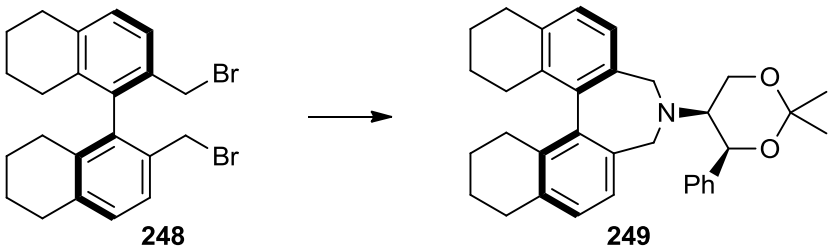
(R_a)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl-2,2'-bis(bromomethyl)[11] (248)



246 **248**

246 (2.03 g, 6.3 mmol) was dissolved in toluene (60 mL) and pyridine (0.05 mL, 0.7 mmol) in a flask under an atmosphere of N_2. Tribromophosphine (1.78 mL, 18.9 mmol) was added dropwise to the solution. After the addition was complete, the reaction was heated at 60 °C for 3 h. The reaction was quenched by the slow addition of water (50 mL), the resulting biphasic mixture was transferred to a separating funnel and the organic layer was isolated and washed with $NaHCO_3$ (20 mL, saturated aqueous). The organic layers were dried over $MgSO_4$ and decoloured with a spatula of carbon black. Solvents were then removed under reduced pressure to yield **248** as a colourless powder (2.79 g, 99%): $[\alpha]^{20}_D$ 0.0 (c = 2.05, $CHCl_3$), *lit.* $[\alpha]^{20}_D$ +36.5 (c = 1.00, CH_2Cl_2); ν_{max}(neat)/cm^{-1} 2920, 2851, 1592, 1457, 1376, 1235, 1204, 928, 862, 831, 814, 759, 723, 623; δ_H (300 MHz; $CDCl_3$) 1.71 (8H, m, 8 x -C$\underline{H}_2$-), 2.07 (2H, dt, *J* = 6.4 Hz, 17.6 Hz, 2 x -C$\underline{H}_2$-), 2.34 (2H, dt, *J* = 5.5 Hz, 17.0 Hz, 2 x -C$\underline{H}_2$-), 2.83 (4H, t, *J* = 5.9 Hz, 4 x -C$\underline{H}_2$-), 4.10 (2H, d, *J* = 9.9 Hz, 2 x Ar-C$\underline{H}_2$Br), 4.15 (2H, d, *J* = 10.0 Hz, 2 x Ar-C$\underline{H}_2$Br), 7.14 (2H, d, *J* = 7.9 Hz, 2 x C$\underline{H}$ *arom.*), 7.33 (2H, d, *J* = 7.9 Hz, 2 x C$\underline{H}$ *arom.*); δ_C (75 MHz; $CDCl_3$) 22.6 (2C, 2 x -$\underline{C}H_2$-), 22.9 (2C, 2 x -$\underline{C}H_2$-), 27.5 (2C, 2 x -$\underline{C}H_2$-), 29.9 (2C, 2 x -$\underline{C}H_2$-), 32.9 (2C, 2 x Ar-$\underline{C}H_2$Br), 128.1 (2C, 2 x $\underline{C}$H *arom.*), 129.6 (2C, 2 x $\underline{C}$H *arom.*), 132.3 (2C, 2 x $\underline{C}$ *quat. arom.*), 135.6 (2C, 2 x $\underline{C}$ *quat. arom.*), 137.9 (2C, 2 x $\underline{C}$ *quat. arom.*), 138.6 (2C, 2 x $\underline{C}$ *quat. arom.*).

(–)-(R_a)-4-((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-4,5,8,9,10,11,12,13,14,15-decahydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (249)

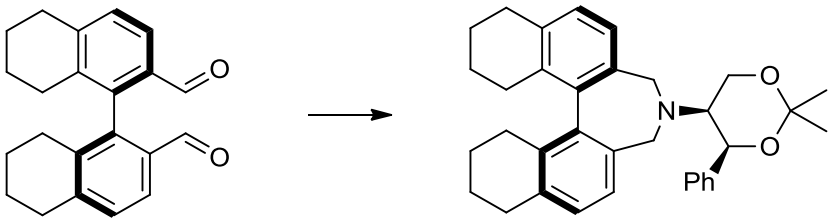


248 **249**

Method 1

To a solution of **248** (0.17 g, 0.38 mmol) in MeCN (10 mL) in oven dried flask under an atmosphere of N_2, was added K_2CO_3 (0.15 g, 1.11 mmol) and **168** (79 mg, 0.38 mmol) pre-dissolved in MeCN (2 mL). The reaction was stirred at RT for 1 h before being heated under reflux overnight. The flask was then removed from the heat and allowed to cool, after which time CH_2Cl_2 (30 mL) and water (30 mL) were added. The organic layer was separated and the aqueous layer was washed further with CH_2Cl_2 (2 x 20 mL). The organic layers were combined and dried over $MgSO_4$, solvents were then removed under reduced pressure to yield **249** in excellent purity as colourless crystals (0.18 g, 97%): $[\alpha]^{20}_D$ –27.7 (c = 0.72, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2928, 2832, 1451, 1377, 1291, 1267, 1237, 1194, 1172, 1147, 1074, 1053, 1017, 939, 898, 852, 829, 810, 753, 723, 700, 654, 640, 628; δ_H (300 MHz; $CDCl_3$) 1.46-1.57 (2H, m, 2 x -C$\underline{H}_2$-), 1.57 (3H, s, C$\underline{Me}_2$), 1.62 (3H, s, C$\underline{Me}_2$), 1.67-1.82 (6H, m, 6 x -CH_2-), 2.13 (2H, dt, *J* = 5.9 Hz, 11.5 Hz, 2 x -CH_2-), 2.58-2.65 (3H, m, 2 x -C$\underline{H}_2$- / -NC$\underline{H}$-), 2.75-2.86 (4H, m, 4 x -CH_2-), 3.09 (2H, d, *J* = 12.1 Hz, 2 x ArC$\underline{H}_2$N, upfield portion of AB system), 3.57 (2H, d, *J* = 12.2 Hz, 2 x ArC$\underline{H}_2$N, downfield portion of AB system), 4.17 (2H, m, NCH-C$\underline{H}_2$-O), 5.07 (1H, d, *J* = 3.1 Hz, NCH-C$\underline{H}$Ar-O), 6.89 (2H, d, *J* = 7.6 Hz, 2 x C$\underline{H}$ *arom.*), 6.98 (2H, d, *J* = 7.6 Hz, 2 x C$\underline{H}$ *arom.*), 7.30 (5H, m, 5 x CH *arom.*); δ_C (75 MHz; $CDCl_3$) 19.1 (2C, C$\underline{Me}_2$), 22.7 (2C, 2 x -$\underline{C}H_2$-), 22.9 (2C, 2 x -$\underline{C}H_2$-), 27.6 (2C, 2 x -$\underline{C}H_2$-), 29.4 (2C, 2 x -$\underline{C}H_2$-), 29.6 (2C, C$\underline{Me}_2$), 52.7 (2C, 2 x Ar$\underline{C}H_2$N), 59.8 (1C, NCH-$\underline{C}H_2$-O), 61.8 (1C, -N$\underline{C}$H-), 75.0 (1C, NCH-$\underline{C}$HAr-O), 99.1 (1C, $\underline{C}Me_2$, C *quat.*), 126.0 (2C, 2 x $\underline{C}$H *arom.*), 126.7 (2C, 2 x $\underline{C}$H *arom.*), 127.6 (2C, 2 x $\underline{C}$H *arom.*), 128.2 (2C, 2 x $\underline{C}$H *arom.*), 133.6 (2C, 2 x $\underline{C}$ *quat. arom.*), 135.0 (2C, 2 x $\underline{C}$ *quat. arom.*), 136.0 (2C, 2 x

C *quat. arom.*), 138.2 (2C, 2 x C *quat. arom.*), 140.4 (1C, C *quat. arom.*), CH *arom*. not observed; *m/z* (HNES) 494.3039 - $C_{34}H_{40}NO_2$ $[M+H]^+$ requires 494.3039.

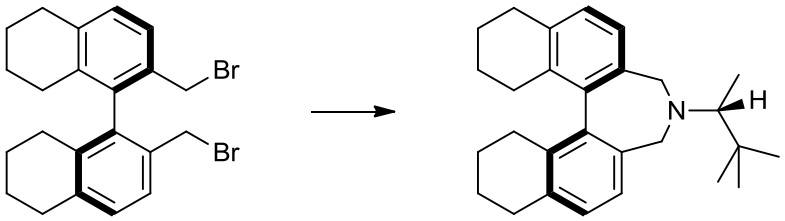


247 **249**

Method 2[12]

To an oven dried flask under an atmosphere of N_2, containing a suspension of **247** (0.11 g, 0.35 mmol) in MeOH (4 mL), was added **168** (79 mg, 1.1 equiv., 0.38 mmol) as a solution in MeOH (1 mL) followed by $NaCNBH_3$ (44 mg, 2 equiv., 0.70 mmol) and glacial acetic acid (0.2 mL). The reaction was stirred for 24 h at ambient temperature, then quenched with a 1 M aq. solution of NaOH (25 mL). The title compound was extracted from the aqueous layer with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$. Solvents were removed under reduced pressure to yield a faint yellow foam that was purified by column chromatography eluting with light petroleum ether / EtOAc (5:1), **249** was isolated as colourless crystals (116 mg, 67 %): $[\alpha]^{20}_D$ –28.2 (c = 0.89, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2928, 2832, 1451, 1377, 1291, 1267, 1237, 1194, 1172, 1147, 1074, 1053, 1017, 939, 898, 852, 829, 810, 753, 723, 700, 654, 640, 628; δ_H (300 MHz; $CDCl_3$) 1.46-1.57 (2H, m, 2 x -C<u>H</u>$_2$-), 1.57 (3H, s, C<u>Me</u>$_2$), 1.62 (3H, s, C<u>Me</u>$_2$), 1.67-1.82 (6H, m, 6 x -CH_2-), 2.13 (2H, dt, *J* = 5.9 Hz, 11.5 Hz, 2 x -CH_2-), 2.58-2.65 (3H, m, 2 x -C<u>H</u>$_2$- / -NC<u>H</u>-), 2.75-2.86 (4H, m, 4 x -CH_2-), 3.09 (2H, d, *J* = 12.1 Hz, 2 x ArC<u>H</u>$_2$N, upfield portion of AB system), 3.57 (2H, d, *J* = 12.2 Hz, 2 x ArC<u>H</u>$_2$N, downfield portion of AB system), 4.17 (2H, m, NCH-C<u>H</u>$_2$-O), 5.07 (1H, d, *J* = 3.1 Hz, NCH-C<u>H</u>Ar-O), 6.89 (2H, d, *J* = 7.6 Hz, 2 x C<u>H</u> *arom*.), 6.98 (2H, d, *J* = 7.6 Hz, 2 x C<u>H</u> *arom*.), 7.30 (5H, m, 5 x CH *arom.*)

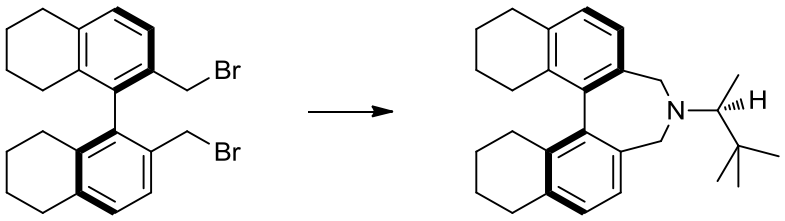
(–)-(R_a)-4-((*R*)-3,3-Dimethylbutan-2-yl)-4,5,8,9,10,11,12,13,14,15-decahydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine[12] (250)



248 **250**

Prepared according to the general procedure described in method 1 from **(*R*)-215** (0.40 mL, 2.98 mmol) and **248** (1.00 g, 2.23 mmol). The known title compound **250** was isolated as a colourless crystalline solid in good purity (0.80 g, 94%): m.p. 151.6-158.5 °C (dec.); $[\alpha]^{20}_D$ –78.8 (c = 1.03, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2928, 2863, 1454, 1356, 1109, 1065, 922, 816, 735, 628, 620, 614; δ_H (400 MHz; $CDCl_3$) 0.80 (3H, d, *J* = 7.2 Hz, N-CHMe^{t}Bu), 0.91 (9H, s, N-CHMe^{t}Bu), 1.50-1.59 (2H, m, 2 x -CH_2-), 1.74-1.86 (6H, m, 6 x -CH_2-), 2.24 (2H, dt, *J* =10.6 Hz, 6.1 Hz, 2 x -CH_2-), 2.64-2.75 (3H, m, 2 x -CH_2- / N-CHMe^{t}Bu), 2.75-2.85 (4H, m, 4 x -CH_2-), 3.28 (4H, 2 x ArCH_2N), 7.05 (4H, m, 4 x C*H arom.*); δ_C (75 MHz; $CDCl_3$) 11.4, 22.7, 22.8, 27.0, 27.7, 29.4, 37.0, 55.2, 69.1, 125.4, 128.2, 134.3, 135.2, 136.1, 138.1; *m/z* (HNES) 388.2991 - $C_{28}H_{38}N$ $[M+H]^+$ requires 388.2999.

(–)-(R_a)-4-((*S*)-3,3-Dimethylbutan-2-yl)-4,5,8,9,10,11,12,13,14,15-decahydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine[12] (251)

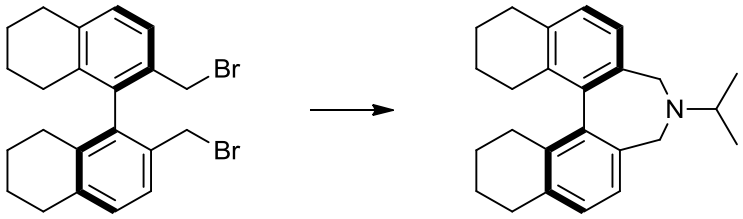


248 **251**

Prepared according to the general procedure described in method 1 from **(*S*)-215** (0.30 mL, 2.23 mmol) and **248** (1.00 g, 2.23 mmol). The known title compound **251** was isolated as a colourless foam in good purity (0.79 g, 92%): $[\alpha]^{20}_D$ –64.1 (c =

0.98, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2932, 2858, 1436, 1348, 1113, 1070, 907, 830, 810, 732, 632, 614; δ_H (400 MHz; $CDCl_3$) 0.89 (9H, s, N-CHMe^{t}Bu), 1.03 (3H, d, *J* = 7.1 Hz, N-CHMe^{t}Bu), 1.50-1.60 (2H, m, 2 x -CH_2-), 1.73-1.84 (6H, m, 6 x -CH_2-), 2.19 (2H, dt, *J* = 10.3 Hz, 6.1 Hz, 2 x -CH_2-), 2.39 (1H, q, *J* = 7.1 Hz, N-CHMe^{t}Bu), 2.68 (3H, ddd, *J* = 16.2 Hz, 7.9 Hz, 4.5 Hz, 2 x -CH_2-), 2.76-2.87 (4H, m, 4 x -CH_2-), 3.29 (2H, d, *J* = 12.2 Hz, 2 x ArCH_2N, upfield portion of AB system), 3.44 (2H, d, *J* = 12.3 Hz, 2 x ArCH_2N, downfield portion of AB system), 7.07 (4H, m, 4 x CH *arom.*); δ_C (75 MHz; $CDCl_3$) 11.5, 22.7, 22.9, 26.8, 27.6, 29.4, 36.8, 53.6, 67.8, 126.6 (2C, s, CH *arom*.), 128.2 (2C, s, CH *arom*.), 134.1 (2C, s, C *quat. arom*.), 135.1 (2C, s, C *quat. arom*.), 135.9 (2C, s, C *quat. arom*.), 138.2 (2C, s, C *quat. arom*.); *m/z* (HNES) 388.2991 - $C_{28}H_{38}N$ $[M+H]^+$ requires 388.2999.

(–)-(R_a)-4-Isopropyl-4,5,8,9,10,11,12,13,14,15-decahydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (252)

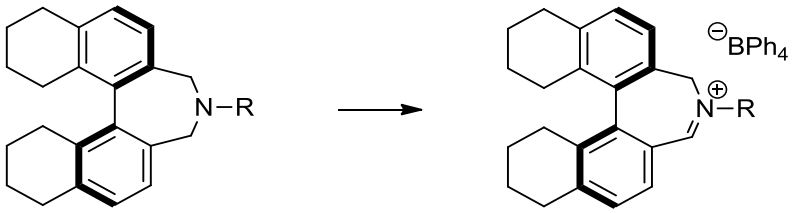


248 **252**

Prepared according to the general procedure described in method 1 from **216** (0.30 mL, 2.23 mmol) and **248** (1.00 g, 2.23 mmol). The title compound **252** was isolated as a colourless foam in good purity (0.79 g, 92%): $[\alpha]^{20}_D$ –136.70 (c = 1.03, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2927, 2858, 1449, 1378, 1325, 1212, 1162, 1125, 1064, 1024, 908, 869, 829, 811, 731, 638; δ_H (400 MHz; $CDCl_3$) 1.08 (3H, d, *J* = 6.4 Hz, NCHMe$_2$), 1.21 (3H, d, *J* = 6.4 Hz, NCHMe$_2$), 1.51-1.61 (2H, m, 2 x -CH_2-), 1.74-1.85 (6H, m, 6 x -CH_2-), 2.23 (2H, dt, *J* = 10.5 Hz, 6.0 Hz, 2 x -CH_2-), 2.53 (1H, sept., *J* = 6.5 Hz, NCHMe$_2$), 2.66-2.72 (2H, m, 2 x -CH_2-), 2.84 (4H, *J* = 11.0 Hz, 6.5 Hz, 4 x -CH_2-), 2.92 (2H, d, *J* = 12.4 Hz, 2 x ArCH_2N, upfield portion of AB system), 3.65 (2H, d, *J* = 12.4 Hz, 2 x ArCH_2N, downfield portion of AB system), 7.04 (2H, d, *J* = 7.7 Hz, 2 x CH *arom.*), 7.08 (2H, d, *J* = 7.7 Hz, 2 x CH *arom.*); δ_C (75 MHz; $CDCl_3$) 21.2 (1C, NCHMe$_2$), 22.0 (1C,

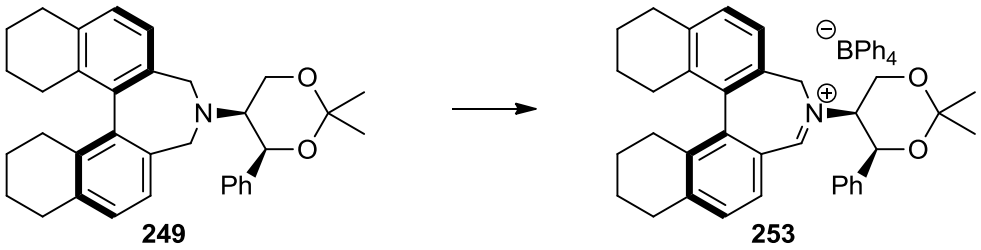
NCH$\underline{Me}_2$), 22.7 (2C, 2 x -$\underline{C}H_2$-), 22.8 (2C, 2 x -$\underline{C}H_2$-), 27.6 (2C, 2 x -$\underline{C}H_2$-), 29.4 (2C, 2 x -$\underline{C}H_2$-), 51.8 (2C, 2 x Ar$\underline{C}H_2$N), 51.8 (1C, N$\underline{C}$HMe_2), 126.3 (2C, 2 x $\underline{C}$H *arom*.), 128.0 (2C, 2 x $\underline{C}$H *arom*.), 132.4 (2C, 2 x $\underline{C}$ *quat. arom*.), 135.5 (2C, 2 x $\underline{C}$ *quat. arom*.), 136.7 (2C, 2 x $\underline{C}$ *quat. arom*.), 138.3 (2C, 2 x $\underline{C}$ *quat. arom*.); *m/z* (HNES) 346.2533 $(M+H)^+$ - $C_{25}H_{31}N$ $(M+H)^+$ requires 346.2529.

Synthesis of Octahydro-binaphthyl derived iminium salts



To a solution of the azepine substrate (1 equiv.) in CH_2Cl_2 (30 mL per g of azepine) in a flask equipped with a stirrer bar, was added NBS (1.1 equiv.). The resulting bright yellow solution was stirred for 30 min. at RT, after which time the solvent was switched for EtOH. To the ethanolic solution was added $NaBPh_4$ (1.1 equiv.) in the minimum amount of MeCN, which caused the iminium salt to precipitate. The solvent was switched to CH_2Cl_2 and transferred to a separating funnel. The organic layer was washed with water (2 x 60 mL per g of azepine) and brine (30 mL per g of azepine) and transferred straight in to a round bottomed flask. The crude product isolated after the removal of solvents, was recrystallized from hot EtOH. The crystalline product was filtered off and washed with cold EtOH followed by Et_2O and hexane. The isolated iminium salts were left to dry under reduced pressure in an oven at 60 °C overnight.

(–)-(R_a)-4-((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-8,9,10,11,12,13,14,15-octahydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate (253)

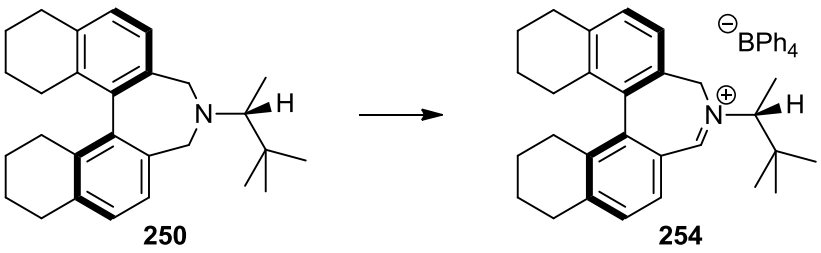


249 **253**

Prepared according to the general procedure from **249** (1.47 g, 2.98 mmol) and NBS (0.58 g, 3.28 mmol). Ion exchange was performed with $NaBPh_4$ (1.12 g, 3.28 mmol). Title compound **253** was isolated as a fine, pale-yellow crystalline solid (1.51 g, 63%): m.p. 195.2-199.3 °C; $[\alpha]^{20}_D$ –331.9 (c = 1.01, acetone); ν_{max}(neat)/cm^{-1} 3053, 2982, 2936, 2864, 1615, 1577, 1479, 1450, 1424, 1380, 1304, 1263, 1235, 1198, 1107, 1083, 1010, 954, 941, 904, 835, 763, 746, 731, 701, 660, 623, 609; δ_H (400 MHz; acetone-d6, 50 °C) 1.35-1.41 (1H, m, -C$\underline{H}_2$-), 1.45-1.56 (1H, m, -C$\underline{H}_2$-), 1.67 (3H, s, C$\underline{Me}_2$), 1.70 (3H, s, C$\underline{Me}_2$), 1.67-1.85 (6H, m, 6 x -CH_2-), 2.01-2.06 (1H, m, -C$\underline{H}_2$-), 2.24 (1H, *J* = 7.5 Hz, -C$\underline{H}_2$-), 2.53-2.62 (1H, m, -C$\underline{H}_2$-), 2.70-3.01 (5H, m, 5 x -C$\underline{H}_2$-), 4.12 (1H, d, *J* = 13.2 Hz, ArC$\underline{H}_2$N, upfield portion of AB system), 4.21 (2H, d, *J* = 13.7 Hz, NCH-C$\underline{H}_2$-O, upfield portion of ABX system), 4.41 (1H, t, *J* = 2.6 Hz, -NC$\underline{H}$-), 4.63 (1H, dd, *J* = 13.7 Hz, 3.0 Hz, NCH-C$\underline{H}_2$-O, downfield portion of ABX system), 5.18 (1H, d, *J* = 13.7 Hz, ArC$\underline{H}_2$N, downfield portion of AB system), 5.74 (1H, d, *J* = 3.0 Hz, NCH-C$\underline{H}$Ar-O), 6.75 (4H, t, *J* = 7.2 Hz, 4 x C$\underline{H}$ *arom.*, *para*- $^-BPh_4$), 6.89 (8H, t, *J* = 7.4 Hz, 8 x C$\underline{H}$ *arom., ortho*- $^-BPh_4$), 7.06-7.21 (6H, m, 6 x C$\underline{H}$ *arom.*), 7.23-7.40 (11H, m, 8 x C$\underline{H}$ *arom*. *meta*- $^-BPh_4$ / 3 x C$\underline{H}$ *arom.*), 8.73 (1H, s, -N=C$\underline{H}$-); δ_C (75 MHz; acetone-d6) 18.0 (1C, -$\underline{C}H_2$-), 21.6 (1C, -$\underline{C}H_2$-), 21.9 (1C, -$\underline{C}H_2$-), 22.0 (1C, -$\underline{C}H_2$-), 22.1 (1C, -$\underline{C}H_2$-), 27.4 (1C, -$\underline{C}H_2$-), 27.5 (1C, -$\underline{C}H_2$-), 28.9 (1C, C$\underline{Me}_2$), 29.2 (1C, C$\underline{Me}_2$), 29.8 (1C, -$\underline{C}H_2$-), 57.6 (1C, Ar$\underline{C}H_2$N), 60.1 (1C, NCH-$\underline{C}$HAr-O), 66.0 (1C, -N$\underline{C}$H-), 71.3 (1C, NCH-$\underline{C}$HAr-O), 100.8 (1C, $\underline{C}Me_2$, C *quat.*), 121.6 (4C, s, 4 x $\underline{C}$H *arom*., *para*- $^-BPh_4$), 124.9 (1C, $\underline{C}$H *arom.*), 125.0 (2C, 2 x $\underline{C}$H *arom.*), 125.3 (8C, 8 x $\underline{C}$H *arom.*, *meta*- $^-BPh_4$), 125.8 (1C, $\underline{C}$ *quat. arom.*), 128.1 (1C, $\underline{C}$H *arom.*), 128.8 (2C, 2 x $\underline{C}$H *arom.*), 129.1 (1C, $\underline{C}$H *arom.*), 129.4 (1C, $\underline{C}$ *quat. arom.*), 130.4 (1C, $\underline{C}$H *arom.*), 133.5 (1C, $\underline{C}$ *quat. arom.*), 134.5 (1C, $\underline{C}$ *quat. arom.*), 136.3 (1C, $\underline{C}$ *quat. arom.*), 136.3 (8C, 8 x $\underline{C}$H

arom., *ortho*- $^{-}BPh_4$), 137.7 (1C, C *quat. arom.*), 139.1 (1C, C *quat. arom.*), 139.9 (1C, C *quat. arom.*), 140.9 (1C, C *quat. arom.*), 145.0 (1C, C *quat. arom.*), 164.3 (4C, q, *J* = 49 Hz, 4 x C *quat*. *arom*., *ipso*- $^{-}BPh_4$), 169.7 (1C, -N=CH-); *m/z* (HNES) 492.2895 - $C_{34}H_{38}NO_2$ $[M–BPh_4]^+$ requires 492.2897.

(–)-(R_a)-4-((*R*)-3,3-Dimethylbutan-2-yl)-8,9,10,11,12,13,14,15-octahydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium (254)

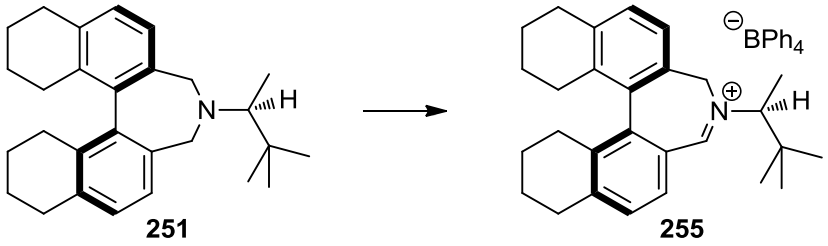


250 **254**

Prepared according to the general procedure from **250** (0.79 g, 2.03 mmol) and NBS (0.40 g, 2.23 mmol). Ion exchange was performed with $NaBPh_4$ (0.77 g, 2.23 mmol). Title compound **254** was isolated as pale yellow crystalline solid (0.99 g, 70%): m.p. 126.3 °C (dec.); $[\alpha]^{20}_D$ –478.8 (c = 1.03, acetone); ν_{max}(neat)/cm^{-1} 2942, 1622, 1574, 1478, 1429, 1370, 1320, 1149, 1085, 1030, 973, 836, 812, 732, 704, 662; δ_H (400 MHz; acetone-d6) 1.08 (9H, s, N-CHMe^{t}Bu), 1.32-1.42 (1H, m, -CH_2-), 1.39 (3H, d, *J* = 6.9 Hz, N-CHMe^{t}Bu), 1.50-1.61 (1H, m, -CH_2-), 1.63-2.01 (7H, m, 7 x -CH_2-), 2.35 (1H, dt, *J* = 16.4 Hz, 5.5 Hz, -CH_2-), 2.63-3.12 (6H, m, 6 x -CH_2-), 4.48 (1H, sept., *J* = 7.1 Hz, N-CHMe^{t}Bu), 4.61 (1H, d, *J* = 13.1 Hz, ArCH_2N, upfield portion of AB system), 4.98 (1H, d, *J* = 13.2 Hz, ArCH_2N, downfield portion of AB system), 6.73 (4H, t, *J* = 7.2 Hz, 4 x CH *arom.*, *para*- $^{-}BPh_4$), 6.88 (8H, t, *J* = 7.4 Hz, 8 x CH *arom., ortho*- $^{-}BPh_4$), 7.26 (1H, d, *J* = 7.9 Hz, CH *arom.*), 7.28-7.35 (8H, m, 8 x CH *arom., meta*- $^{-}BPh_4$), 7.45 (1H, d, *J* = 8.0 Hz, CH *arom.*), 7.48 (1H, d, *J* = 8.0 Hz, CH *arom.*), 7.73 (2H, *J* = 8.0 Hz, 2 x CH *arom.*), 9.14 (1H, s, -N=CH-); δ_C (75 MHz; $CDCl_3$) 15.80 (1C, N-CHMe^{t}Bu), 21.7 (1C, -CH_2-), 21.97 (1C, -CH_2-), 22.01 (1C, -CH_2-), 22.2 (1C, -CH_2-), 25.9 (3C, N-CHMe^{t}Bu), 27.5 (1C, -CH_2-), 27.6 (1C, -CH_2-), 29.1 (1C, -CH_2-), 29.8 (1C, -CH_2-), 36.0 (1C, N-CHMe^{t}Bu, C *quat.*), 60.3 (1C, ArCH_2N), 76.5 (1C, N-CHMe^{t}Bu), 121.5 (4C, 4 x CH *arom*., *para*- $^{-}BPh_4$), 125.27 (8C, 8 x CH *arom*., *meta*- $^{-}BPh_4$), 125.32 (1C, CH

arom.), 127.0 (1C, C *quat. arom.*), 129.2 (1C, CH *arom*.), 129.6 (1C, CH *arom*.), 130.2 (1C, CH *arom*.), 134.0 (1C, C *quat. arom.*), 135.3 (1C, C *quat. arom.*), 136.4 (8C, 8 x CH *arom*., *ortho*- $^{-}BPh_4$), 138.1 (1C, C *quat. arom.*), 139.3 (1C, C *quat. arom.*), 140.2 (1C, C *quat. arom.*), 141.0 (1C, C *quat. arom.*), 146.7 (1C, C *quat. arom.*), 163.3 (4C, q, *J* = 49 Hz, 4 x C *quat*. *arom*., *ipso*- $^{-}BPh_4$), 168.7 (1C, -N=CH-); *m/z* (HNES) 386.2845 - $C_{28}H_{36}N$ $[M–BPh_4]^+$ requires 386.2842.

(–)-(R_a)-4-((*S*)-3,3-Dimethylbutan-2-yl)-8,9,10,11,12,13,14,15-octahydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium (255)

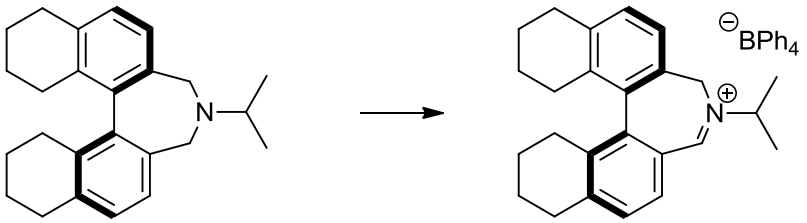


251 **255**

Prepared according to the general procedure from **251** (0.75 g, 1.92 mmol) and NBS (0.38 g, 2.14 mmol). Ion exchange was performed with $NaBPh_4$ (0.72 g, 2.14 mmol). Title compound **255** was isolated as cream powder (0.81 g, 60 %): m.p. 111.5-115.7 °C (dec.); $[\alpha]^{20}_D$ –344.08 (c = 1.03, acetone); ν_{max}(neat)/cm^{-1} 3056, 2935, 2863, 1718, 1621, 1578, 1478, 1426, 1382, 1309, 1244, 1221, 1122, 1099, 1032, 972, 848, 810, 732, 702, 611; δ_H (400 MHz; acetone-d6) 1.10 (9H, s, N-CHMe^{t}Bu), 1.38-1.50 (1H, m, -CH$_2$-), 1.51-1.63 (1H, m, -CH$_2$-) 1.61 (3H, d, *J* = 6.9 Hz, N-CHMe^{t}Bu), 1.64-1.92 (6H, m, 6 x -CH$_2$-), 1.95-2.03 (1H, -CH$_2$-), 2.36 (1H, dt, *J* = 10.6 Hz, 3.7 Hz, -CH$_2$-), 2.65-3.12 (6H, m, 6 x -CH$_2$-), 4.23 (1H, sept., *J* = 6.9 Hz, N-CHMe^{t}Bu), 4.43 (1H, d, *J* = 13.8 Hz, ArCH$_2$N, upfield portion of AB system), 4.98 (1H, d, *J* = 13.7 Hz, ArCH$_2$N, downfield portion of AB system), 6.76 (4H, t, *J* = 7.2 Hz, 4 x CH *arom.*, *para*- $^{-}BPh_4$), 6.89 (8H, t, *J* = 7.4 Hz, 8 x CH *arom., ortho*- $^{-}BPh_4$), 7.28 (1H, d, *J* = 7.8 Hz, CH *arom.*), 7.29-7.37 (8H, m, 8 x CH *arom., meta*- $^{-}BPh_4$), 7.45 (1H, d, *J* = 8.3 Hz, CH *arom.*), 7.48 (1H, d, *J* = 8.2 Hz, CH *arom.*), 7.64 (1H, *J* = 7.9 Hz, CH *arom.*), 9.03 (1H, s, -N=CH-); δ_C (75 MHz; $CDCl_3$) 13.2 (1C, N-CHMe^{t}Bu), 21.7 (1C, -

$\underline{C}H_2$-), 22.0 (2C, 2 x -$\underline{C}H_2$-), 22.2 (1C, -$\underline{C}H_2$-), 26.2 (3C, N-CHMe^t$\underline{Bu}$), 27.57 (1C, -$\underline{C}H_2$-), 27.59 (1C, -$\underline{C}H_2$-), 29.1 (1C, -$\underline{C}H_2$-), 29.8 (1C, -$\underline{C}H_2$-), 35.9 (1C, N-CHMe^t$\underline{Bu}$, C *quat.*), 53.5 (1C, Ar$\underline{C}H_2$N), 77.9 (1C, N-$\underline{C}$HMe^{t}Bu), 121.6 (4C, 4 x $\underline{C}$H *arom.*, *para*- $^-$BPh$_4$), 125.3 (8C, 8 x $\underline{C}$H *arom.*, *meta*- $^-$BPh$_4$), 126.1 (1C, $\underline{C}$H *arom.*), 126.5 (1C, $\underline{C}$ *quat. arom.*), 129.3 (1C, $\underline{C}$H *arom.*), 129.6 (1C, $\underline{C}$H *arom.*), 130.1 (1C, $\underline{C}$H *arom.*), 134.7 (1C, $\underline{C}$ *quat. arom.*), 135.5 (1C, $\underline{C}$ *quat. arom.*), 136.4 (8C, 8 x $\underline{C}$H *arom.*, *ortho*- $^-$BPh$_4$), 137.7 (1C, $\underline{C}$ *quat. arom.*), 139.4 (1C, $\underline{C}$ *quat. arom.*), 139.9 (1C, $\underline{C}$ *quat. arom.*), 140.9 (1C, $\underline{C}$ *quat. arom.*), 146.6 (1C, $\underline{C}$ *quat. arom.*), 164.3 (4C, q, *J* = 49 Hz, 4 x $\underline{C}$ *quat*. *arom.*, *ipso*- $^-$BPh$_4$), 170.2 (1C, -N=$\underline{C}$H-); *m/z* (HNES) 386.2839 - $C_{28}H_{36}N$ $[M–BPh_4]^+$ requires 386.2842.

(–)-(R_a)-4-Isopropyl-8,9,10,11,12,13,14,15-octahydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate (256)

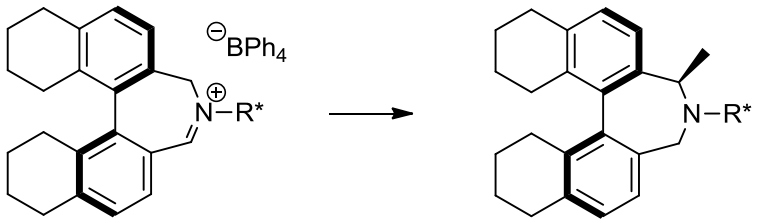


252 **256**

Prepared according to the general procedure from **252** (1.47 g, 2.98 mmol) and NBS (0.58 g, 3.28 mmol). Ion exchange was performed with $NaBPh_4$ (1.12 g, 3.28 mmol). Title compound **256** was isolated as pale yellow fine crystalline solid (1.51 g, 63%): m.p. 167.4 °C; $[\alpha]^{20}_D$ –443.1 (c = 1.04, acetone); ν_{max}(neat)/cm^{-1} 3054, 2929, 1628, 1577, 1426, 1306, 1311, 1030, 968, 843, 733, 703, 611; δ_H (400 MHz; acetone-d6) 1.31-1.42 (1H, m, -C$\underline{H}_2$-), 1.50-1.62 (1H, m, -C$\underline{H}_2$-), 1.51 (3H, d, *J* = 6.5 Hz, NCH$\underline{Me}_2$), 1.56 (3H, d, *J* = 6.7 Hz, NCH$\underline{Me}_2$), 1.67-1.90 (6H, m, 6 x -C$\underline{H}_2$-), 1.91-2.05 (1H, m, -C$\underline{H}_2$-), 2.30-2.41 (1H, m, -C$\underline{H}_2$-), 2.67-3.08 (6H, m, 6 x -C$\underline{H}_2$-), 4.29 (1H, d, *J* = 13.4 Hz, ArC$\underline{H}_2$N, upfield portion of AB system), 4.49 (1H, sept., *J* = 6.6 Hz, NC$\underline{H}$Me$_2$), 5.02 (1H, d, *J* = 13.6 Hz, ArC$\underline{H}_2$N, downfield portion of AB system), 6.72 (4H, t, *J* = 7.2 Hz, 4 x C$\underline{H}$ *arom.*, *para*- $^-$BPh$_4$), 6.87 (8H, t, *J* = 7.4 Hz, 8 x C$\underline{H}$ *arom., ortho*- $^-$BPh$_4$), 7.25 (1H, d, *J* = 7.8 Hz, C$\underline{H}$ *arom.*), 7.28-7.39 (8H, m, 8 x C$\underline{H}$ *arom., meta*- $^-$BPh$_4$), 7.44 (1H,

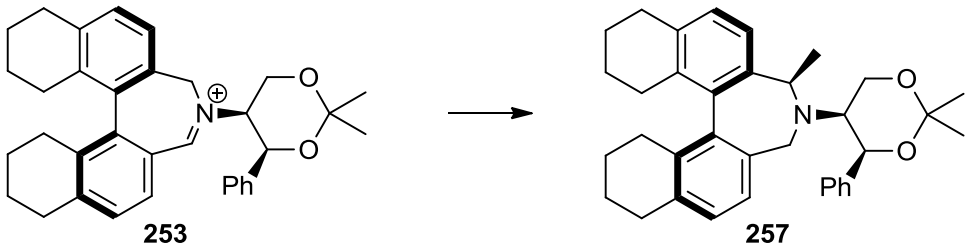
d, *J* = 8.4 Hz, C<u>H</u> *arom.*), 7.48 (1H, d, *J* = 8.4 Hz, C<u>H</u> *arom.*), 7.73 (1H, d, *J* = 8.0 Hz, C<u>H</u> *arom.*), 8.93 (1H, s, -N=C<u>H</u>-); δ_C (75 MHz; $CDCl_3$) 19.98 (1C, -<u>C</u>H_2-), 20.03 (1C, -<u>C</u>H_2-), 21.6 (1C, -<u>C</u>H_2-), 22.0 (2C, 2 x NCH<u>Me</u>$_2$), 22.24 (1C, -<u>C</u>H_2-), 27.54 (1C, -<u>C</u>H_2-), 27.58 (1C, -<u>C</u>H_2-), 29.1 (1C, -<u>C</u>H_2-), 29.8 (1C, -<u>C</u>H_2-), 52.9 (1C, Ar<u>C</u>H_2N), 64.5 (1C, N-<u>C</u>HMe_2), 121.5 (4C, 4 x <u>C</u>H *arom*., *para*- $^{-}BPh_4$), 125.3 (8C, 8 x <u>C</u>H *arom*., *meta*- $^{-}BPh_4$), 125.6 (1C, <u>C</u>H *arom*.), 126.7 (1C, <u>C</u> *quat. arom*.), 129.1 (1C, <u>C</u>H *arom*.), 129.7 (1C, <u>C</u>H *arom*.), 130.2 (1C, <u>C</u>H *arom*.), 134.4 (1C, <u>C</u> *quat. arom*.), 135.7 (1C, <u>C</u> *quat. arom*.), 136.3 (8C, 8 x <u>C</u>H *arom*., *ortho*- $^{-}BPh_4$), 137.7 (1C, <u>C</u> *quat. arom*.), 139.2 (1C, <u>C</u> *quat. arom*.), 139.8 (1C, <u>C</u> *quat. arom*.), 141.0 (1C, <u>C</u> *quat. arom*.), 146.4 (1C, <u>C</u> *quat. arom*.), 164.4 (4C, q, *J* = 49 Hz, 4 x <u>C</u> *quat*. *arom*., *ipso*- $^{-}BPh_4$), 167.1 (1C, -N=<u>C</u>H-); *m/z* (HNES) 344.2378 - $C_{25}H_{30}N$ $[M–BPh_4]^+$ requires 344.2373.

General Procedure for the Grignard Addition to Octahydro-binpahthyl Iminium Salts



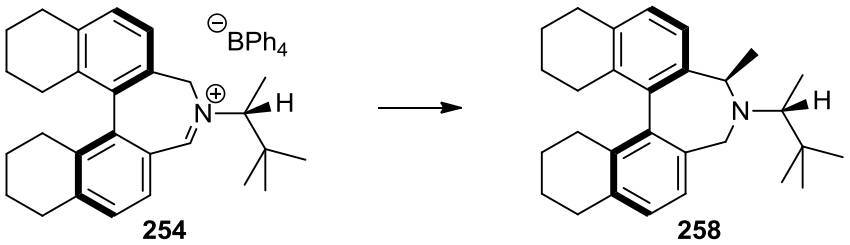
A flame dried round-bottomed flask under nitrogen atmosphere was charged with the desired iminium salt (1 equiv.) and THF (50 mL per g of iminium salt), the yellow solution was then allowed to cool to –78 °C in a Dewar containing dry ice / acetone. While maintaining the N_2 atmosphere and temperature, 3 M MeMgBr in Et_2O (10 equiv.) was added drop-wise down the inside of the flask. After complete addition, the reaction was allowed to slowly attain ambient temperature overnight. Excess Grignard was then quenched with saturated aqueous NH_4Cl solution (5 mL per g of iminium salt) and the organic solvents were then removed under reduced pressure. The aqueous emulsion was diluted with EtOAc to dissolve the organic component, and filtered into a separating funnel to remove any undissolved solid. The organic layer was separated and washed with water (2 x 60 mL per g of iminium salt) and brine (40 mL per g of iminium salt). The organic layer was then dried over $MgSO_4$, and solvents were then removed under reduced pressure to yield the desired azepine. The crude azepines were purified by column chromatography, typically eluting with light petroleum / EtOAc and buffered with 2% TEA.

(–)-(3*R*,11c*R*$_a$)-4-((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-3-methyl-4,5,8,9,10,11,12,13,14,15-decahydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (257)



Prepared according to the general procedure from **253** (1.28 g, 1.57 mmol) and 3 M MeMgBr (5.26 mL, 15.7 mmol). The crude mixture was purified by column chromatography eluting with light petroleum / EtOAc (5:1), buffered with 2% TEA. The title compound **257** was isolated as a colourless oil (0.63 g, 79%): $[\alpha]^{20}_D$ –8.4 (c = 2.04, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 0.18 (3H, d, *J* = 7.1 Hz, N-CHMe-Ar), 1.42-1.63 (2H, m, 2 x -CH_2-), 1.55 (3H, s, CMe$_2$), 1.63 (3H, s, CMe$_2$), 1.68-1.81 (6H, m, 6 x -CH_2-), 2.09-2.19 (2H, m, 2 x -CH_2-), 2.54-2.69 (2H, m, 2 x -CH_2-), 2.77-2.82 (4H, m, 4 x -CH_2-), 2.91 (1H, td, *J* = 4.2 Hz, 2.5 Hz, -NCH-), 3.31 (1H, d, *J* = 11.2 Hz, ArCH_2N, upfield portion of AB system), 3.35 (1H, d, *J* = 11.2 Hz, ArCH_2N, downfield portion of AB system), 4.09 (1H, dd, *J* = 12.3 Hz, 2.4 Hz, NCH-CH_2-O, upfield portion of ABX system), 4.21 (1H, dd, *J* = 12.3 Hz, 4.3 Hz, NCH-CH_2-O, downfield portion of ABX system), 4.34 (1H, q, *J* = 7.0 Hz, N-CHMe-Ar), 5.13 (1H, d, *J* = 3.5 Hz, NCH-CHAr-O), 6.81 (1H, d, *J* = 7.6 Hz, CH *arom.*), 6.81 (1H, d, *J* = 7.7 Hz, CH *arom.*), 6.94 (1H, d, *J* = 7.6 Hz, CH *arom.*), 6.97 (1H, d, *J* = 7.7 Hz, CH *arom.*), 7.22-7.38 (1H, m, 5 x CH *arom.*); δ_C (75 MHz; $CDCl_3$) 19.4 (1C, CMe$_2$), 21.0 (1C, N-CHMe-Ar), 22.7 (1C, -CH_2-), 22.8 (2C, 2 x -CH_2-), 22.9 (1C, -CH_2-), 27.3 (2C, 2 x -CH_2-), 29.0 (1C, -CH_2-), 29.3 (1C, CMe$_2$), 29.4 (1C, -CH_2-), 54.3 (1C, N-CH_2-Ar), 59.0 (1C, N-CHMe-Ar), 60.1 (1C, -NCH-), 62.9 (1C, NCH-CH_2-O), 74.1 (1C, NCH-CHAr-O), 99.3 (1C, CMe$_2$, C *quat.*), 125.9 (1C, CH *arom.*), 126.4 (2C, 2 x CH *arom.*), 126.5 (1C, CH *arom.*), 126.6 (1C, CH *arom.*), 127.6 (2C, 2 x CH *arom.*), 128.1 (1C, CH *arom.*), 128.2 (1C, CH *arom.*), 135.2 (1C, C *quat. arom.*), 135.5 (1C, C *quat. arom.*), 135.6 (1C, C *quat. arom.*), 135.7 (1C, C *quat. arom.*), 136.1 (1C, C *quat. arom.*), 136.6 (1C, C *quat. arom.*), 138.4 (1C, C *quat. arom.*), 138.8 (1C, C *quat. arom.*), 140.3 (1C, C *quat. arom.*); *m/z* (HNES) 508.3204 - $C_{34}H_{40}NO_2$ $[M+H]^+$ requires 508.3210

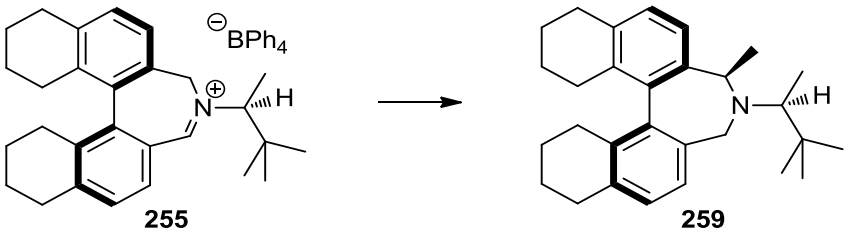
(–)-(3*R*,11c*R*$_a$)-4-((*R*)-3,3-Dimethylbutan-2-yl)-3-methyl-4,5,8,9,10,11,12,13,14,15-decahydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (258)



254 **258**

Prepared according to the general procedure from **254** (0.80 g, 1.13 mmol) and 3 M MeMgBr in Et_2O (3.77 mL, 11.3 mmol). The crude mixture was purified by column chromatography eluting with light petroleum / EtOAc (17.5:1), buffered with 2% TEA. The title compound **258** was isolated as a colourless foam (0.31 g, 68%): $[\alpha]^{20}_D$ –60.0 (c = 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2933, 2862, 1448, 1363, 1316, 1248, 1151, 1105, 1068, 998, 923, 828, 812, 783, 754; δ_H (400 MHz; $CDCl_3$) 0.51 (3H, d, *J* = 7.2 Hz, N-CHMe-Ar), 0.92 (3H, d, *J* = 7.0 Hz, N-CHMe^{t}Bu), 0.96 (9H, s, N-CHMe^{t}Bu), 1.45-1.60 (2H, m, 2 x -CH_2-), 1.72-1.83 (6H, m, 6 x -CH_2-), 2.23 (2H, dt, *J* = 16.9 Hz, 5.8 Hz, 2 x -CH_2-), 2.48 (1H, q, *J* = 7.1 Hz, N-CHMe^{t}Bu), 2.62-2.77 (2H, m, 2 x -CH_2-), 2.78-2.90 (4H, m, 4 x -CH_2-), 3.01 (1H, d, *J* = 10.7 Hz, ArCH_2N, upfield portion of AB system), 3.33 (1H, d, *J* = 10.7 Hz, ArCH_2N, downfield portion of AB system), 3.65 (1H, q, *J* = 7.2 Hz, N-CHMe-Ar), 6.92 (1H, d, *J* = 7.6 Hz, CH *arom.*), 7.02 (1H, d, *J* = 7.7 Hz, CH *arom.*), 7.05 (1H, d, *J* = 7.8 Hz, CH *arom.*), 7.08 (1H, d, *J* = 7.8 Hz, CH *arom.*); δ_C (75 MHz; $CDCl_3$) 11.1 (1C, N-CHMe^{t}Bu), 22.9 (1C, -CH_2-), 22.97 (1C, N-CHMe-Ar), 23.04 (1C, -CH_2-), 23.2 (1C, -CH_2-), 27.6 (1C, -CH_2-), 27.7 (1C, -CH_2-), 28.3 (3C, N-CHMe^{t}Bu), 29.0 (1C, -CH_2-), 29.4 (1C, -CH_2-), 36.3 (1C, -CH_2-), 49.3 (1C, ArCH_2N), 70.7 (1C, N-CHMe-Ar), 73.4 (1C, N-CHMe^{t}Bu), 126.2 (1C, CH *arom.*), 126.9 (1C, CH *arom.*), 128.5 (1C, CH *arom.*), 128.6 (1C, CH *arom.*), 136.0 (1C, C *quat. arom.*), 136.1 (1C, C *quat. arom.*), 136.17 (1C, C *quat. arom.*), 136.22 (1C, C *quat. arom.*), 136.27 (1C, C *quat. arom.*), 136.29 (1C, C *quat. arom.*), 139.0 (1C, C *quat. arom.*), 139.2 (1C, C *quat. arom.*), N-CHMe^{t}Bu, C *quat*. not observed; *m/z* (HNES) 402.3149 - $C_{29}H_{40}N$ $[M+H]^+$ requires 402.3155.

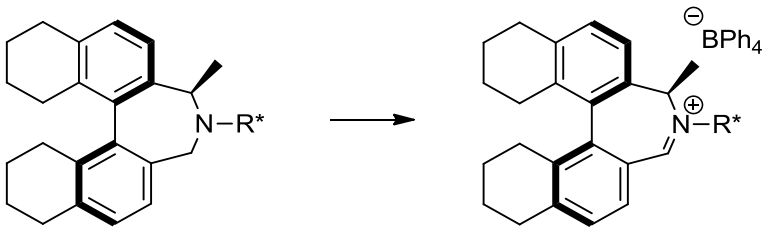
(–)-(3*R*,11c*R*$_a$)-4-((*S*)-3,3-Dimethylbutan-2-yl)-3-methyl-4,5,8,9,10,11,12,13,14,15-decahydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepine (259)



255 **259**

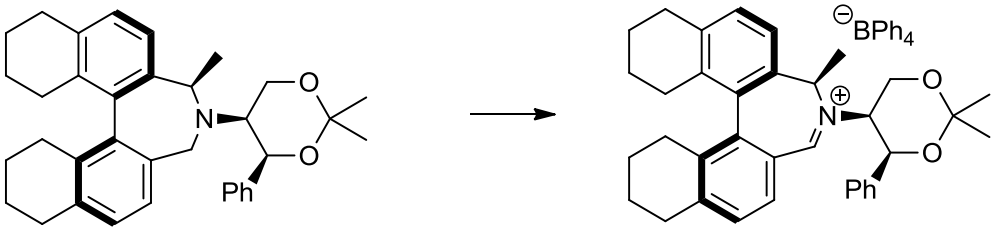
Prepared according to the general procedure from **255** (0.60 g, 0.85 mmol) and 3 M MeMgBr in Et_2O (2.83 mL, 8.5 mmol). The crude mixture was purified by column chromatography eluting with light petroleum / EtOAc (30:1), buffered with 2% TEA. The title compound **259** was isolated as a colourless foam (0.23g, 68%): $[\alpha]^{20}_D$ −346.0 (c = 0.98, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2931, 2861, 1437, 1388, 1359, 1249, 1172, 1121, 1079, 1000, 926, 829, 812, 784, 752; δ_H (400 MHz; $CDCl_3$) 0.50 (3H, d, *J* = 7.1 Hz, N-CHMe-Ar), 0.91 (9H, s, N-CHMe^{t}Bu), 0.99 (3H, d, *J* = 7.0 Hz, N-CHMe^{t}Bu), 1.44-1.66 (2H, m, 2 x -CH_2-), 1.71-1.84 (6H, m, 6 x -CH_2-), 2.15-2.35 (2H, m, 2 x -CH_2-), 2.46 (1H, q, *J* = 6.9 Hz, N-CHMe^{t}Bu), 2.58-2.77 (2H, m, 2 x -CH_2-), 2.77-2.90 (4H, m, 4 x -CH_2-), 3.29 (1H, d, *J* = 11.1 Hz, ArCH_2N, upfield portion of AB system), 3.41 (1H, d, *J* = 11.0 Hz, ArCH_2N, downfield portion of AB system), 3.87 (1H, q, *J* = 6.9 Hz, N-CHMe-Ar), 6.91 (1H, d, *J* = 7.7 Hz, CH *arom.*), 7.02 (1H, d, *J* = 7.8 Hz, CH *arom.*), 7.05 (1H, d, *J* = 7.5 Hz, CH *arom.*), 7.09 (1H, d, *J* = 7.5 Hz, CH *arom.*); δ_C (75 MHz; $CDCl_3$) 11.0 (1C, N-CHMe^{t}Bu), 21.7, 22.7, 22.8, 23.0, 27.1 (3C, N-CHMe^{t}Bu), 27.3, 27.4, 29.3, 36.2, 56.1, 59.0, 68.4 (1C, N-CHMe^{t}Bu), 126.4 (1C, CH *arom.*), 127.3 (1C, CH *arom.*), 128.1 (1C, CH *arom.*), 128.3 (1C, CH *arom.*), 135.5 (1C, C *quat. arom.*), 135.5 (1C, C *quat. arom.*), 135.7 (1C, C *quat. arom.*), 135.9 (1C, C *quat. arom.*), 136.3 (1C, C *quat. arom.*), 136.8 (1C, C *quat. arom.*), 138.83 (1C, C *quat. arom.*), 138.87 (1C, C *quat. arom.*); *m/z* (HNES) 402.3154 - $C_{29}H_{40}N$ $[M+H]^+$ requires 402.3155.

General Procedure for the Synthesis of Methyl Substituted Octahydro-binaphthyl Azepinium Salts



NBS (1.1 equiv.) was added to a solution of the azepine substrate (1 equiv.) in CH_2Cl_2 (20 mL per g of azepine) in a flask equipped with a stirrer bar. The resulting bright yellow solution was stirred for 15 min. at RT, after which time the solvents were removed under reduced pressure. The resulting crude yellow foam was dissolved in EtOH. To the ethanolic solution was added $NaBPh_4$ (1.1 equiv.) in the minimum amount of MeCN which caused the iminium salt to precipitate out. Solvents were then switched to CH_2Cl_2, and the organic solution was washed with water (2 x 45 mL per g of azepine) and brine (30 mL per g of azepine), then transferred into a round bottomed flask and evaporated to dryness under reduced pressure. The resulting foam was then recrystallized from EtOH. The crystalline product was filtered off and washed with EtOH and hexane. The isolated iminium salts were left to dry under reduced pressure in an oven at 60 °C overnight.

(–)-(3*R*,11c*R*$_a$)-4-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-3-methyl-8,9,10,11,12,13,14,15-octahydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium tetraphenylborate (260)

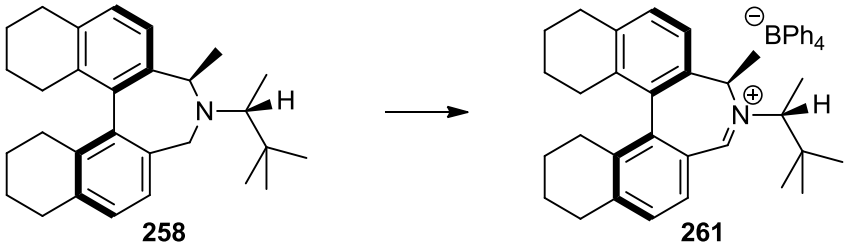


257 **260**

Prepared according to the general procedure from **257** (0.62 g, 1.22 mmol) and NBS (0.24 g, 1.34 mmol). Ion exchange was performed using $NaBPh_4$ (0.46 g, 1.34 mmol). The title compound **260** was isolated as pale yellow crystals (0.71 g, 71%): m.p. 121.6 °C; $[\alpha]^{20}_D$ –232.8 (c = 1.00, acetone); ν_{max}(neat)/cm^{-1} 3055, 2986, 2936, 2864, 1623, 1575, 1479, 1449, 1426, 1381, 1308, 1265, 1236, 1201, 1165, 1107, 1080, 1031, 1000, 956, 910, 835, 731; δ_H (400 MHz; acetone-d6) 1.05 (3H, d, *J* = 7.1 Hz, N-CHMe-Ar), 1.35-1.58 (2H, m, 2 x -CH$_2$-), 1.66-1.90 (6H, m, 6 x -CH$_2$-), 1.69 (3H, s, CMe$_2$), 1.74 (3H, s, CMe$_2$), 2.25 (1H, dt, *J* = 10.4 Hz, 5.7 Hz, -CH$_2$-), 2.47-2.60 (1H, m, -CH$_2$-), 2.72-2.88 (4H, m, -CH$_2$-), 2.98 (2H, dd, *J* = 11.7 Hz, 6.5 Hz, 2 x -CH$_2$-), 4.39 (1H, dd, *J* = 0.8 Hz, 13.6 Hz, NCH-CH$_2$-O, upfield portion of ABX system), 4.74 (1H, t, *J* = 2.5 Hz, -NCH-), 4.81 (1H, dd, *J* = 13.7 Hz, 2.9 Hz, NCH-CH$_2$-O, downfield portion of ABX system), 5.49 (1H, q, *J* = 6.5 Hz, N-CHMe-Ar), 5.83 (1H, d, *J* = 2.8 Hz, NCH-CHAr-O), 6.78 (4H, t, *J* = 7.1 Hz, 4 x CH *arom.*, *para*- $^-$BPh$_4$), 6.92 (8H, t, *J* = 7.4 Hz, 8 x CH *arom., ortho*- $^-$BPh$_4$), 7.02-7.23 (7H, m, 7 x CH *arom*.), 7.28-7.37 (8H, m, 8 x CH *arom., meta*- $^-$BPh$_4$), 7.44 (1H, d, *J* = 8.0 Hz, CH *arom.*), 7.60 (1H, d, *J* = 8.0 Hz, CH *arom.*), 9.25 (1H, s, -N=CH-); δ_C (100 MHz; acetone-d6) 14.9 (1C, N-CHMe-Ar), 18.1 (1C, CMe$_2$), 21.6 (1C, CMe$_2$), 22.1 (1C, -CH$_2$-), 22.2 (1C, -CH$_2$-), 22.4 (1C, -CH$_2$-), 27.3 (1C, -CH$_2$-), 27.6 (1C, -CH$_2$-), 29.1 (1C, -CH$_2$-), 29.3 (1C, -CH$_2$-), 30.0 (1C, -CH$_2$-), 61.9 (1C, NCH-CH$_2$-O), 67.5 (1C, -NCH-), 69.8 (1C, N-CHMe-Ar), 71.1 (1C, NCH-CHAr-O), 101.0 (1C, CMe$_2$, C *quat.*), 121.6 (4C, 4 x CH *arom*., *para*- $^-$BPh$_4$), 124.8 (1C, C *quat*. *arom*.), 124.9 (2C, 2 x CH *arom*.), 125.3 (8C, 8 x CH *arom*., *meta*- $^-$BPh$_4$), 125.8 (1C, CH *arom*.), 128.0 (1C, CH *arom*.), 128.6 (2C, 2 x CH *arom*.), 129.2 (1C, CH *arom*.), 130.2 (1C, CH *arom*.), 130.5 (1C, CH *arom*.), 131.3 (1C, C *quat*. *arom*.), 136.0 (1C, C

quat. *arom*.), 136.4 (8C, 8 x CH *arom*., *ortho*- $^{-}BPh_4$), 138.1 (1C, C *quat*. *arom*.), 139.5 (1C, C *quat*. *arom*.), 139.7 (1C, C *quat*. *arom*.), 141.2 (1C, C *quat*. *arom*.), 147.7 (1C, C *quat*. *arom*.), 164.3 (4C, q, *J* = 49.0 Hz, 4 x C *quat*. *arom*., *ipso*- $^{-}BPh_4$), 168.6 (1C, -N=CH-); *m/z* (HNES) 506.3054 - $C_{35}H_{40}NO_2$ $[M–BPh_4]^+$ requires 506.3043

(–)-(3*R*,11c*R*$_a$)-4-((*R*)-3,3-dimethylbutan-2-yl)-3-methyl-8,9,10,11,12,13,14,15-octahydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium (261)

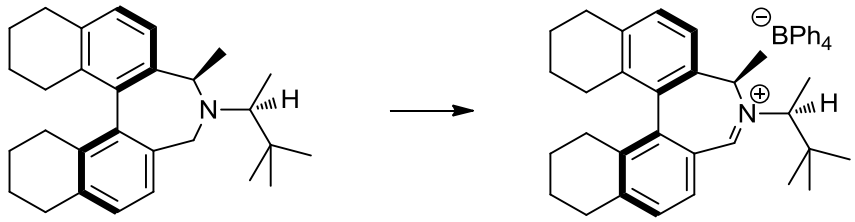


258 261

Prepared according to the general procedure from **258** (0.30 g, 0.75 mmol) and NBS (0.15 g, 0.82 mmol). Ion exchange was performed using $NaBPh_4$ (0.28 g, 0.82 mmol). The product isolated according to the general procedure above was not of satisfactory purity, accordingly the yellow powder was washed with Et_2O, which caused the solid to coalesce. The residual thick yellow oil was dissolved in CH_2Cl_2 and the solvents were then removed under reduced pressure to yield **261** as a yellow foam in good purity (0.19 g, 36%): $[\alpha]^{20}_D$ –346.9 (c = 0.98 acetone); ν_{max}(neat)/cm^{-1} 3056, 2938, 1621, 1575, 1478, 1448, 1427, 1385, 1370, 1310, 1248, 1180, 1121, 1102, 1032, 970, 896, 833, 732, 702, 610; δ_H (400 MHz; acetone-d6) 0.98 (9H, s, N-CHMe^{t}Bu), 1.24 (3H, d, *J* = 7.1 Hz, N-CHMe-Ar), 1.38-1.52 (1H, m, -CH$_2$-), 1.53-1.63 (1H, m, -CH$_2$-), 1.65-2.00 (9H, m, 6 x -CH$_2$- / N-CHMe^{t}Bu), 2.12-2.19 (1H, m, -CH$_2$-), 2.35 (1H, dt, *J* = 15.8 Hz, 4.7 Hz, -CH$_2$-), 2.68-2.99 (4H, m, 4 x -CH$_2$-), 3.00-3.12 (2H, m, 2 x -CH$_2$-), 4.44 (1H, q, *J* = 6.9 Hz, N-CHMe^{t}Bu), 5.47 (1H, q, *J* = 7.0 Hz, N-CHMe-Ar), 6.79 (4H, t, *J* = 7.2 Hz, 4 x CH *arom.*, *para*- $^{-}BPh_4$), 6.94 (8H, t, *J* = 7.4 Hz, 8 x CH *arom., ortho*- $^{-}BPh_4$), 7.31 (1H, d, *J* = 7.8 Hz, CH *arom.*), 7.33-7.45 (9H, m, 8 x CH *arom., meta*- $^{-}BPh_4$ / CH *arom*.), 7.50 (1H, d, *J* = 8.0 Hz, CH *arom.*), 7.77 (1H, d, *J* = 8.0 Hz, CH *arom.*), 9.36 (1H, s, -N=CH-); δ_C (75 MHz; $CDCl_3$) 15.5 (1C, Me), 21.5 (1C, -CH$_2$-), 21.95 (1C, -CH$_2$-), 22.00 (1C, -CH$_2$-), 22.3 (1C, -CH$_2$-), 26.4 (3C,

N-CHMe^{t}Bu), 27.3 (1C, -CH$_2$-), 27.4 (1C, -CH$_2$-), 29.9 (1C, -CH$_2$-), 35.4 (1C, N-CHMe^{t}Bu, C *quat.*), 80.7 (1C, N-CHMe^{t}Bu), 121.5 (4C, 4 x CH *arom.*, *para*- $^{-}$BPh$_4$), 125.3 (8C, 8 x CH *arom.*, *meta*- $^{-}$BPh$_4$), 125.6 (1C, C *arom.*), 127.0 (1C, CH *arom.*), 129.3 (1C, CH *arom.*), 129.8 (1C, CH *arom.*), 131.2 (1C, C *arom.*), 132.6 (1C, C *arom.*), 136.4 (8C, 8 x CH *arom.*, *ortho*- $^{-}$BPh$_4$), 138.8 (1C, C *quat. arom.*), 139.8 (1C, C *quat. arom.*), 139.9 (1C, C *quat. arom.*), 141.3 (1C, C *quat. arom.*), 148.0 (1C, C *quat. arom.*), 164.3 (4C, q, *J* = 49 Hz, 4 x C *quat. arom.*, *ipso*- $^{-}$BPh$_4$), 169.8 (1C, -N=CH-); -CH$_2$- / Me / C *arom.* not observed; *m/z* (HNES) 400.2993 - $C_{29}H_{38}N$ [M–BPh$_4$]$^{+}$ requires 400.2999

(–)-(3*R*,11c*R*$_a$)-4-((*S*)-3,3-dimethylbutan-2-yl)-3-methyl-8,9,10,11,12,13,14,15-octahydro-3*H*-dinaphtho[2,1-*c*:1',2'-*e*]azepin-4-ium (262)



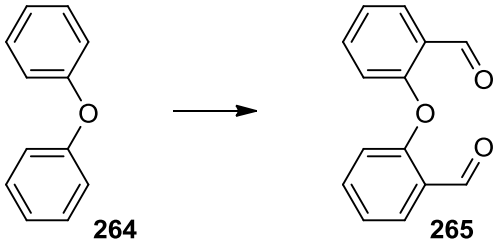
259 **262**

Prepared according to the general procedure from **259** (0.21 g, 0.52 mmol) and NBS (0.10 g, 0.58 mmol). Ion exchange was performed using NaBPh$_4$ (0.20 g, 0.858 mmol). The initially isolated product was not of satisfactory purity, accordingly the yellow powder was washed with Et$_2$O causing the solid to coalesce. The residual thick yellow oil was dissolved in CH$_2$Cl$_2$ and the solvents were then removed under reduced pressure to yield **262** as a yellow foam in good purity (0.23 g, 60%): $[\alpha]^{20}_{D}$ −279.6 (c = 0.94, acetone); ν_{max}(neat)/cm^{-1} 3049, 2937, 1624, 1572, 1477, 1425, 1308, 1117, 1031, 894, 842, 731, 704, 644, 631, 611; δ_H (400 MHz; acetone-d6) 1.11 (9H, br, N-CHMe^{t}Bu), 1.28 (3H, d, *J* = 7.1 Hz, N-CHMe-Ar), 1.32-1.56 (1H, m, -CH$_2$-), 1.57-1.74 (4H, m, -CH$_2$- / N-CHMe^{t}Bu), 1.77-2.04 (6H, m, 6 x -CH$_2$-), 2.08-2.15 (1H, m, -CH$_2$-), 2.41 (1H, dt, *J* = 16.6 Hz, 5.6 Hz, -CH$_2$-), 2.20-2.66 (4H, m, 4 x -CH$_2$-), 3.07 (2H, q, *J* = 6.1, 2 x -CH$_2$-), 4.36 (1H, br, N-CHMe^{t}Bu), 5.47 (1H, q, *J* = 7.0 Hz, N-

CHMe-Ar), 6.82 (4H, t, *J* = 7.2 Hz, 4 x CH *arom.*, *para*- $^{-}BPh_4$), 6.95 (8H, t, *J* = 7.4 Hz, 8 x CH *arom., ortho*- $^{-}BPh_4$), 6.76 (1H, d, *J* = 8.0 Hz, CH *arom.*), 7.31-7.44 (9H, m, 8 x CH *arom., meta*- $^{-}BPh_4$ / CH *arom*.), 7.52 (1H, d, *J* = 7.9 Hz, CH *arom.*), 7.81 (1H, br, CH *arom.*), 9.10 (1H, s, -N=CH-); δ_C (75 MHz; $CDCl_3$) 14.3 (1C, Me), 21.5 (1C, -CH_2-), 21.98 (1C, -CH_2-), 22.01 (1C, -CH_2-), 22.3 (1C, -CH_2-), 26.1 (3C, N-CHMe^{t}Bu), 27.3 (1C, -CH_2-), 27.5 (1C, -CH_2-), 29.0 (1C, -CH_2-), 29.8 (1C, -CH_2-), 35.6 (1C, N-CHMe^{t}Bu, C *quat.*), 79.9 (1C, N-CHMe^{t}Bu), 121.5 (4C, 4 x CH *arom*., *para*- $^{-}BPh_4$), 125.3 (8C, 8 x CH *arom*., *meta*- $^{-}BPh_4$), 125.6 (1C, C *arom.*), 129.3 (1C, CH *arom*.), 130.1 (1C, CH *arom*.), 132.5 (1C, C *auat. arom.*), 136.3 (8C, 8 x CH *arom*., *ortho*- $^{-}BPh_4$), 138.4 (1C, C *auat. arom.*), 139.8 (1C, C *auat. arom.*), 139.9 (1C, C *auat. arom.*), 141.2 (1C, C *auat. arom.*), 164.3 (4C, q, *J* = 49.0 Hz, 4 x C *quat*. *arom*., *ipso*- $^{-}BPh_4$); Me / ArCHMeN / 4 x C *arom.* / -N=CH- not observed; *m/z* (HNES) 400.2993 - $C_{29}H_{38}N$ $[M–BPh_4]^+$ requires 400.2999

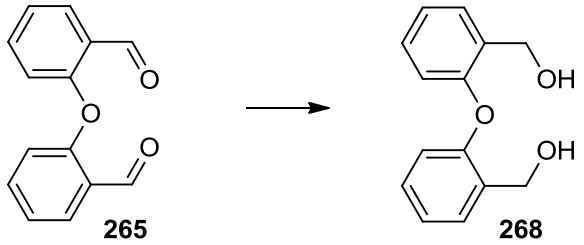
3.2.5 Experimental Procedures Related to the 1,5-Oxazocine Systems

2,2'-Oxydibenzaldehyde (265)



THF (80 mL) was added to a flame dried flask under N_2, containing **264** (7.32 g, 42.3 mmol) and a magnetic stirrer flea. This solution was allowed to cool to −78 °C with a Dewar flask containing cardice and acetone. ^{n}BuLi 2.5 M in hexanes (35.26 mL, 127 mmol) was added to the allowed to cool solution slowly over 5 min. After 1 h, the Dewar was removed and the reaction was left to attain RT with stirring overnight, during which time, the solution had turned bright yellow. DMF (6.80 mL, 127 mmol) was added to the reaction slowly, which caused the solution to lose its yellow hue. The solvents were then switched for CH_2Cl_2 (50 mL), washed with water (3 x 50 mL) and then brine (1 x 50 mL) and dried over $MgSO_4$. Solvents were removed under reduced pressure to give a colourless foam. The crude foam was subjected to column chromatography, eluting with light petroleum / EtOAc (3:1). The title compound **265** was isolated as colourless crystals (4.60 g, 48%): m.p. 89.9-92.1 °C; ν_{max}(neat)/cm^{-1} 2858, 1678, 1642, 1595, 1574, 1470, 1452, 1391, 1270, 1222, 1204, 1186, 1159, 1151, 1097, 878, 827, 754, 630, 613; δ_H (400 MHz; $CDCl_3$) 6.96 (2H, d, *J* = 8.3 Hz, 2 x C<u>H</u> *arom.*), 7.31 (2H, t, *J* = 7.0 Hz, 2 x C<u>H</u> *arom.*), 7.60 (2H, t, *J* = 8.3 Hz, 2 x C<u>H</u> a*rom.*), 8.00 (2H, d, *J* = 7.7 Hz, 2 x C<u>H</u> *arom.*), 10.51 (2H, s, 2 x Ar-C<u>H</u>O); δ_C (100 MHz; $CDCl_3$) 119.3 (2C, 2 x <u>C</u>H *arom*.), 124.8 (2C, 2 x <u>C</u>H *arom*.), 127.4 (2C, 2 x <u>C</u> *quat. arom.*), 129.4 (2C, 2 x <u>C</u>H *arom.*), 136.3 (2C, 2 x <u>C</u>H *arom*.), 159.1 (2C, 2 x <u>C</u> *quat. arom.*), 188.8 (2C, 2 x Ar-<u>C</u>HO); *m/z* (HNES) 227.0703 - $C_{14}H_{10}O_3$ $[M+H]^+$ requires 227.0703.

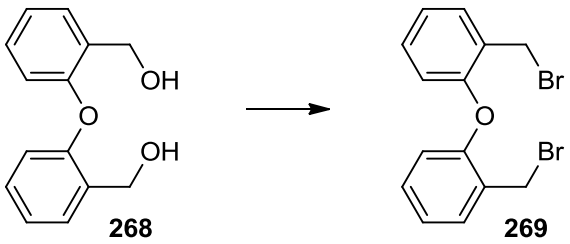
2,2'-Oxybis(2,1-phenylene)dimethanol (268)



265 **268**

To a flame dried round-bottomed flask under N_2, containing **265** (3.40 g, 15.0 mmol), was added Et_2O (100 mL). The colourless solution was then allowed to cool to 0 °C. $LiAlH_4$ (1.17 g, 30.0 mmol) was then added slowly, to a slight effervescence. The resulting suspension was stirred at RT for 1h. The suspension was then re-allowed to cool in an ice bath and Na_2SO_4 (4 g) was added to the suspension, which was then stirred for 5 min., after which time water (4.6 mL) was added dropwise to quench excess hydrides. The mixture was then allowed to stir for 30 min. The quenched mixture was then filtered through a layered pad of Celite and Na_2SO_4. The filtrate was concentrated under reduced pressure to yield **268** as a colourless crystalline solid (3.42 g, 99%): m.p. 97.3-100.0 °C; ν_{max}(neat)/cm^{-1} 3253, 2886, 1579, 1479, 1445, 1371, 1334, 1301, 1225, 1099, 995, 934, 879, 811, 755, 715; δ_H (400 MHz; $CDCl_3$) 3.39 (2H, t, *J* = 5.6 Hz, 2 x Ar-CH_2O<u>H</u>), 4.62 (4H, d, *J* = 5.6 Hz, 2 x Ar-C<u>H</u>$_2$OH), 6.81 (2H, dd, *J* = 8.0 Hz, 0.8 Hz, C<u>H</u> *arom.*), 7.09 (2H, dt, *J* = 1.2 Hz, 7.6 Hz, C<u>H</u> *arom.*), 7.24 (2H, td, *J* = 8.0 Hz, 1.8 Hz, C<u>H</u> a*rom.*), 7.35 (2H, dd, *J* = 1.6 Hz, 7.6 Hz, C<u>H</u> *arom.*); δ_C (100 MHz; $CDCl_3$) 62.0 (2C, Ar-<u>C</u>H_2OH), 118.2 (2C, 2 x <u>C</u>H *arom*.), 124.0 (2C, 2 x <u>C</u>H *arom*.), 129.9 (2C, 2 x <u>C</u>H *arom*.), 131.3 (2C, 2 x <u>C</u>H *arom*.), 132.5 (2C, 2 x <u>C</u> *quat. arom.*), 155.2 (2C, 2 x <u>C</u> *quat. arom.*); *m/z* (HNES) 253.0837 - $C_{14}H_{14}O_3$ $[M+Na]^+$ requires 253.0835.

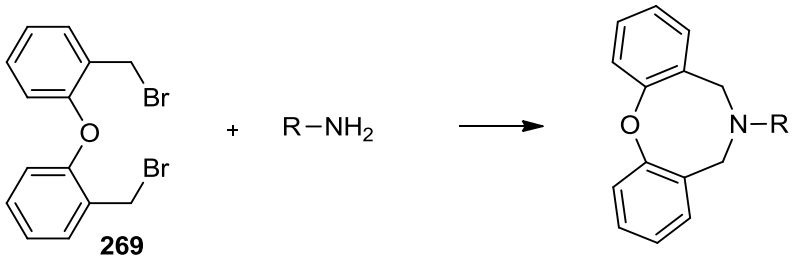
2,2'-Oxybis((bromomethyl)benzene) (269)



268 **269**

To a flask containing **268** (2.50 g, 10.8 mmol) and a stirrer bar was added 48% HBr (aq., 100 mL). The solution was heated under reflux for 4 h, after which time the reaction was allowed to cool to RT, transferred to a separating funnel, and extracted with Et_2O (3 x 100 mL), washed with water (2 x 50 mL) and then brine (1 x 50 mL). The organic layer was dried over $MgSO_4$, and filtered into a flask containing silica, solvents were then removed under reduced pressure. The resulting loaded silica gel was placed into a sintered funnel containing a layer of silica gel. The silica was washed through with Et_2O, until the product had eluted, solvents were removed to yield **269** a colourless solid (3.34 g, 85%): m.p. 82.1-83.4 °C; ν_{max}(neat)/cm^{-1} 3059, 2981, 2925, 2852, 1918, 1579, 1486, 1449, 1430, 1239, 1220, 1184, 1086, 1039, 899, 853, 793, 738; δ_H (400 MHz; $CDCl_3$) 4.65 (4H, s, 2 x Ar-C$\underline{H_2}$Br), 6.84 (2H, d, *J* = 8.1 Hz, 2 x C$\underline{H}$ *arom*.), 7.12 (2H, t, *J* = 7.5 Hz, 2 x C$\underline{H}$ *arom*.), 7.24-7.30 (2H, m, 2 x C$\underline{H}$ *arom*.), 7.47 (2H, dd, *J* = 7.5 Hz, 1.5 Hz, 2 x C$\underline{H}$ *arom*.); δ_C (100 MHz; $CDCl_3$) 28.1 (2C, 2 x Ar-$\underline{C}H_2$Br), 118.7 (2C, 2 x $\underline{C}$H *arom*.), 124.7 (2C, 2 x $\underline{C}$H *arom*.), 129.1 (2C, 2 x $\underline{C}$ *quat. arom.*), 130.5 (2C, 2 x $\underline{C}$H *arom.*), 131.6 (2C, 2 x $\underline{C}$H *arom*.), 155.1 (2C, 2 x $\underline{C}$ *quat. arom.*); *m/z* (HNES) 373.9572 - $C_{14}H_{12}Br_2O$ $[M+NH_4]^+$ requires 373.9573.

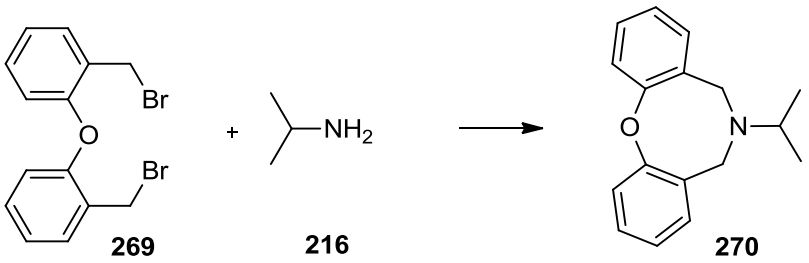
General procedure for the synthesis of 1,5-oxazocines



269

The primary amine (1 equiv.), dissolved in dry MeCN (20 mL per g of amine), was added to a suspension of **269** (1 equiv.) and K_2CO_3 (3 equiv.) in MeCN (100 mL per g of amine) at RT over a period of 6 h. The reaction mixture was heated under reflux overnight. Solvents were then switched for CH_2Cl_2 (40 mL per g of amine) and filtered into a separating funnel to remove excess K_2CO_3. The organic phase was washed with water (2 x 30 mL per g of amine) and brine (1 x 30 mL per g of amine). The organic phase was collected, dried over $MgSO_4$ and evaporated to dryness under reduced pressure to yield the desired 1,5-oxazocines.

6-isopropyl-6,7-dihydro-5H-dibenzo[b,g][1,5]oxazocine (270)

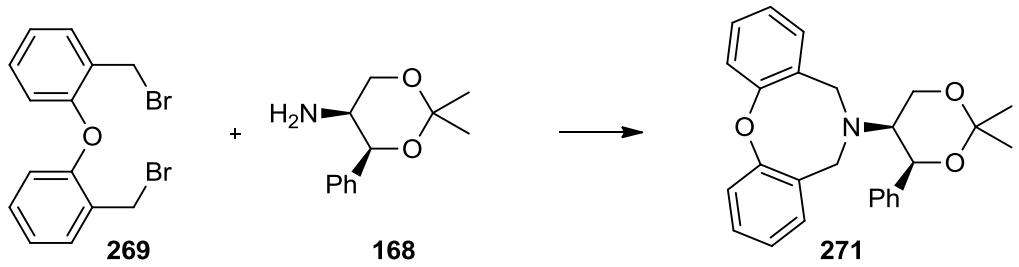


269 **216** **270**

Prepared according to the general procedure from **269** (0.40 g, 0.11 mmol) and **216** (0.13 g, 0.22 mmol). The title compound **270** was isolated in good purity as a colourless solid (0.25 g, 89%): m.p. 83.5 °C; ν_{max}(neat)/cm^{-1} 3021, 2997, 2962, 2921, 2867, 1601, 1578, 1478, 1447, 1377, 1347, 1330, 1260, 1213, 1173, 1104, 1084, 1048, 1037, 950, 930, 892, 877, 794, 774, 758, 714; δ_H (400 MHz; $CDCl_3$) 1.10 (6H, br., NCH$\underline{Me_2}$), 2.67 (1H, sept., *J* = 6.0 Hz, NC$\underline{H}Me_2$), 3.84 (4H, br, 2 x Ar$C\underline{H_2}$N), 7.04 (2H, d, *J* = 8.0 Hz, 2 x C$\underline{H}$ *arom*.), 7.14-7.50 (2H, br, 2 x C$\underline{H}$ *arom*.) 7.15 (2H, d, *J* = 7.2

Hz, 2 x CH *arom*.), 7.23 (2H, m, 2 x CH *arom*.); *m/z* (HNES) 254.1542 - $C_{17}H_{20}NO$ $[M+H]^+$ requires 254.1539. No signals seen in the 13C spectra taken at ambient temperature.

(+)-6-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-6,7-dihydro-5H-dibenzo[*b,g*][1,5]oxazocine (271)

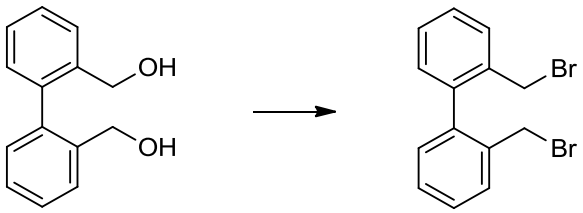


269 **168** **271**

Prepared according to the general procedure from **269** (0.68 g, 1.93 mmol) and **168** (0.40 g, 1.93 mmol). The crude product was columned with light petroleum / EtOAc (5:1) to yield the title compound **271** as colourless foam (0.37 g, 48%); $[\alpha]^{20}_D$ +108.4 (c = 0.85, EtOH); ν_{max}(neat)/cm^{-1} 3070, 2991 2904, 2882, 1601, 1578, 1479, 1449, 1421, 1380, 1360, 1311, 1265, 1197, 1022, 969, 880, 835; δ_H (400 MHz; DMSO, 85 °C) 1.42 (3H, s, CMe$_2$), 1.45 (3H, s, CMe$_2$), 3.01 (1H, s, -NCH-, underneath the residual water peak), 3.39 (1H, d, *J* = 12.4 Hz, NCH-CH$_2$-O, upfield portion of ABX system), 3.55 (2H, d, *J* = 13.8 Hz, 2 x ArCH$_2$N, upfield portion of AB system), 3.90 (1H, dd, *J* = 12.2 Hz, 4.2 Hz, NCH-CH$_2$-O, downfield portion of ABX system), 4.01 (2H, d, *J* = 14.3 Hz, 2 x ArCH$_2$N downfield portion of AB system), 5.15 (1H, d, *J* = 2.9 Hz, NCH-CHAr-O), 6.97 (4H, d, *J* = 3.9 Hz, 4 x CH *arom.*), 7.19 (5H, m, 5 x CH *arom.*), 7.36 (2H, t, *J* = 7.6 Hz, 2 x CH *arom.*), 7.43 (2H, d, *J* = 7.2 Hz, 2 x CH *arom.*); δ_C (100 MHz; DMSO, 85 °C) 18.5 (1C, CMe$_2$), 19.1 (1C, CMe$_2$), 53.7 (2C, 2 x ArCH$_2$N), 57.8 (1C, -NCH-), 61.8 (1C, NCH-CH$_2$-O), 73.9 (1C, NCH-CHAr-O), 98.2 (1C, CMe$_2$, C quat.), 121.0, (1C, CH *arom.*), 123.7 (1C, CH *arom.*), 125.8 (1C, CH *arom.*), 126.1 (1C, CH *arom.*), 127.0 (1C, CH *arom.*), 128.2 (1C, CH arom.), 130.2 (1C, CH *arom*.), no C *quat. arom.* signals observed; *m/z* (HNES) 402.2064 - $C_{26}H_{27}NO_3$ $[M+H]^+$ requires 402.2064

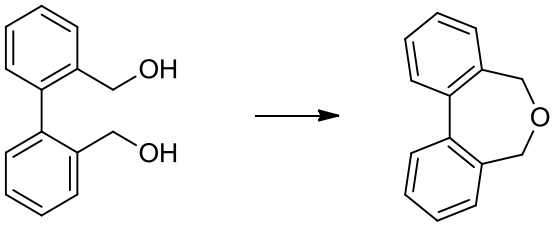
3.2.6 Experimental Procedures Related to the Biphenyl- Systems

2,2'-Bis(bromomethyl)-1,1'-biphenyl[13]



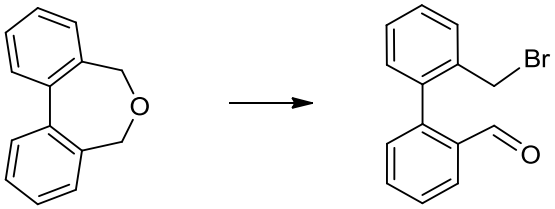
2,2-biphenyl dimethanol (2.0 g, 9.33 mmol) was dissolved in 48% aq. HBr (50 mL), and heated under reflux for 2h. The reaction was allowed to cool and the acid solution was transferred to a separating funnel and extracted with CH_2Cl_2 (2 x 60 mL). The organic layers were combined and washed with saturated aqueous $NaHCO_3$ (2 x 50 mL) followed by brine (50 mL). The organic fraction was dried over $MgSO_4$, and a spatula of carbon black was added to remove any residual impurities. Solvents were removed after filtration to yield the title compound as a colourless crystalline solid (2.95 g, 93%); m.p. 91.3 °C; ν_{max}(neat)/cm^{-1} 2993, 1736, 1652, 1598, 1567, 1474, 1451, 1435, 1370, 1270, 1217, 1197, 1156, 1136, 1085, 1048, 1006, 989, 956, 809, 755; δ_H (300 MHz; $CDCl_3$) 4.20 (2H, d, *J* = 10.1 Hz, 2 x -C<u>H</u>$_2$Br, upfield portion of AB system), 4.36 (2H, d, *J* = 10.0 Hz, 2 x -C<u>H</u>$_2$Br, downfield portion of AB system), 7.28 (2H, m, 2 x C<u>H</u> *arom*), 7.40 (4H, m, 4 x C<u>H</u> *arom*), 7.56 (2H, dd, *J* = 7.4 Hz, 1.5 Hz, 2 x C<u>H</u> *arom.*); δ_C (75 MHz; $CDCl_3$) 27.7 (2C, 2 x -<u>C</u>H$_2$Br), 124.3 (2C, 2 x <u>C</u>H *arom.*), 124.6 (2C, 2 x <u>C</u>H *arom.*), 126.1 (2C, 2 x <u>C</u>H *arom.*), 126.7 (2C, 2 x <u>C</u>H *arom.*), 131.9 (2C, 2 x <u>C</u> *quat. arom.*), 135.4 (2C, 2 x <u>C</u> *quat. arom.*).

5,7-Dihydro[c,e]oxepine[14]



A suspension of 2,2-biphenyl dimethanol (4.20 g, 19.5 mmol) in HBr (60 mL, 24% aq.) was heated under reflux for 45 min. The slightly green solution was removed from the heat and allowed to cool, transferred to a separating funnel and extracted with CH_2Cl_2 (2 x 40 mL). The organic layers were combined and washed with $NaHCO_3$ solution (40 mL, saturated aqueous) and then dried over $MgSO_4$ and decoloured with carbon black (1 spatula). Solvents were removed under reduced pressure to furnish the known title compound as a colourless solid (3.04 g, 80%): m.p. 72.0 °C; ν_{max}(neat)/cm^{-1} 2852, 1651, 1556, 1447, 1377, 1199, 1071, 1046, 997, 902, 893, 753, 668; δ_H (300 MHz; $CDCl_3$) 4.20 (4H, s, 2 x Ar-C<u>H</u>$_2$O-), 7.22-7.47 (8H, m, 8 x C<u>H</u> *arom.*); δ_C (75 MHz; $CDCl_3$) 67.8 (2C, 2 x Ar-<u>C</u>H$_2$O-), 127.6 (2C, 2 x <u>C</u>H *arom.*), 128.5 (2C, 2 x <u>C</u>H *arom.*), 129.0 (2C, 2 x <u>C</u>H *arom.*), 129.9 (2C, 2 x <u>C</u>H *arom.*), 135.2 (2C, 2 x <u>C</u> *quat. arom.*), 141.4 (2C, 2 x <u>C</u> *quat. arom.*).

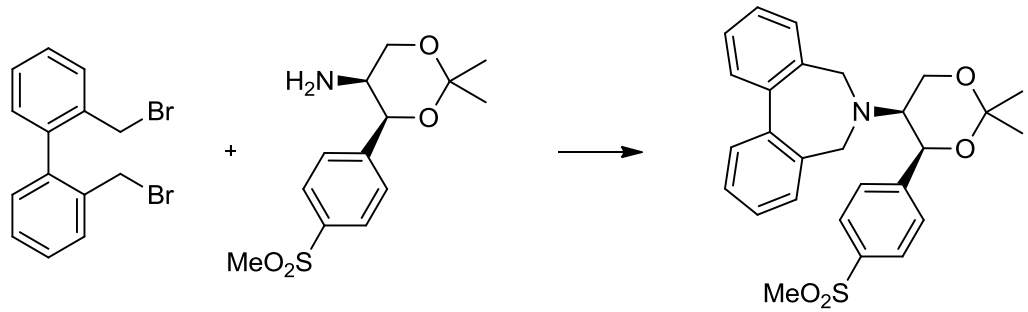
2-Bromomethyl-2'-formyl-1,1'-biphenyl[14]



5,7-Dihydro[c,e]oxepine (3.00 g, 15.3 mmol) was dissolved in CCl_4 (30 mL) in a flask equipped with a reflux condenser. The solution was first allowed to cool in an ice bath prior to the dropwise addition of Br_2 (0.86 mL, 6.6 mmol). After stirring for 5 min, the vessel was heated under reflux for 2 h. After which time, the solvents were removed and the residue was dissolved with Et_2O (50 mL). The organic phase

was washed with Na_2CO_3 solution saturated aqueous (2 x 30 mL) and brine (30 mL) and dried over $MgSO_4$ and decoloured with carbon black. The crude product was recrystallized from EtOAc / light petroleum to yield the known title compound as a colourless crystalline solid (2.45 g, 58%): m.p. 56.8 °C; ν_{max}(neat)/cm^{-1} 3188, 1667, 1589, 1391, 1248, 1198, 774, 722, 630; δ_H (400 MHz; $CDCl_3$) 4.25 (2H, d, *J* = 10.4 Hz, 2 x Ar-C<u>H</u>$_2$Br, upfield portion of AB system), 4.35 (2H, d, *J* = 10.4 Hz, Ar-C<u>H</u>$_2$Br, downfield portion of AB system), 7.22 (1H, dd, *J* = 7.5 Hz, 1.2 Hz, C<u>H</u> *arom*.), 7.38 (1H, ddd, *J* = 7.4 Hz, 7.3 Hz, 1.3 Hz, C<u>H</u> *arom*.), 7.39-7.48 (2H, m, 2 x C<u>H</u> *arom*.), 7.49-7.54 (2H, m, 2 x C<u>H</u> *arom*.), 7.68 (1H, ddd, *J* = 7.4 Hz, 7.4 Hz, 1.3 Hz, C<u>H</u> *arom*.), 8.08 (1H, ddd, *J* = 7.7 Hz, 1.4 Hz, 0.6 Hz, C<u>H</u> *arom*.), 9.75 (1H, d, *J* = 0.7 Hz, Ar-C<u>H</u>O); δ_C (100 MHz; $CDCl_3$) 31.5 (2C, 2 x Ar-<u>C</u>H$_2$Br), 127.6 (1C, <u>C</u>H *arom.*), 128.4 (1C, <u>C</u>H *arom.*), 128.6 (1C, <u>C</u>H *arom.*), 129.0 (1C, <u>C</u>H *arom.*), 130.67 (1C, <u>C</u>H *arom.*), 130.71 (1C, <u>C</u>H *arom.*), 131.1 (1C, <u>C</u>H *arom.*), 133.6 (1C, <u>C</u>H *arom.*), 134.8 (2C, 2 x <u>C</u> *quat. arom.*), 143.3 (2C, 2 x <u>C</u> *quat. arom.*).

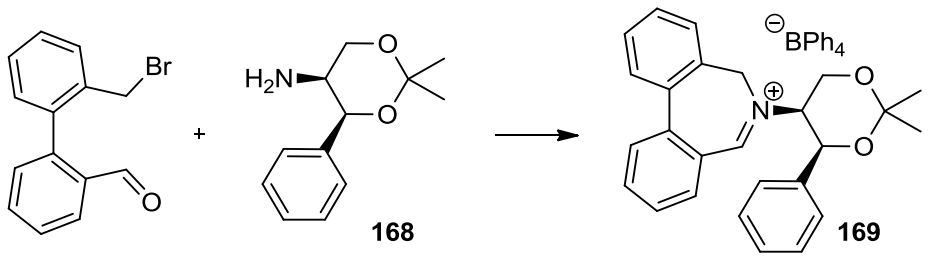
(+)-6-[(4*S*,5*S*)-2,2-Dimethyl-4-(4-(methylsulfonyl)phenyl)-1,3-dioxan-5-yl]6,7-dihydro-5*H*-dibezo[c,e]azepine



The (4*S*,5*S*)-5-amino-6-(4-methylsulfone)-2,2-dimethyl-1,3-dioxane (0.88 g, 3.08 mmol) was added to a nitrogen purged stirred solution of 2,2'-bis(bromomethyl)-1,1'-biphenyl (1.04 g, 3.08 mmol) and $CsCO_3$ (2.0 g, 5.68 mmol) in MeCN (30 mL) at RT. The reaction mixture was heated at reflux overnight under an atmosphere of N_2. Solvents were switched to CH_2Cl_2 (30 mL) and the resulting suspension was filtered into a separating funnel to remove excess $CsCO_3$.The mixture was washed

with water (2 x 30 mL) and brine (1 x 30 mL). The organic phase was separated, dried over $MgSO_4$ and solvents were then removed under reduced pressure to give the title compound as a yellow foam in excellent purity (0.86 g, 60%): $[\alpha]^{20}_D$ +124.6 (c = 1.22, $CHCl_3$), *lit.* $[\alpha]^{20}_D$ +123.5 (c = 1.15, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3060, 2991, 1735, 1670, 1602, 1480, 1449, 1376, 1309, 1298, 1267, 1238, 1200, 1171, 1143, 1108, 1078, 1011, 951, 912, 851; δ_H (400 MHz; $CDCl_3$) 1.58 (3H, s, C<u>Me</u>$_2$), 1.60 (3H, s, C<u>Me</u>$_2$), 3.04 (1H, s, -NC<u>H</u>-), 3.05 (3H, s, -SO_2<u>Me</u>), 3.45 (2H, d, *J* = 12.6 Hz, 2 x Ar$C\underline{H}_2$N, upfield portion of AB system), 3.68 (2H, d, *J* = 12.6 Hz, 2 x Ar$C\underline{H}_2$N, downfield portion of AB system), 4.24 (2H, m, NCH-$C\underline{H}_2$-O), 5.31 (1H, s, NCH-C<u>H</u>Ar-O), 7.19 (2H, d, 2 x C<u>H</u> *arom.*), 7.25-7.45 (6H, m, 6 x C<u>H</u> *arom.*), 7.66 (2H, d, *J* = 8.4 Hz, 2 x C<u>H</u> *arom.*), 7.93 (2H, d, *J* = 8.4 Hz, 2 x C<u>H</u> *arom.*); δ_C (100 MHz; $CDCl_3$) 19.3 (1C, s, C<u>Me</u>$_2$), 29.6 (1C, s, C<u>Me</u>$_2$), 44.9 (1C, s, -SO_2<u>Me</u>), 54.2 (2C, s, 2 x Ar<u>C</u>H_2N), 60.6 (1C, -N<u>C</u>H-), 61.8 (1C, s, NCH-<u>C</u>H_2-O), 74.4 (1C, s, NCH-<u>C</u>HAr-O), 99.5 (1C, <u>C</u>Me_2, C *quat.*), 126.9 (2C, 2 x <u>C</u>H *arom.*), 127.3 (2C, 2 x <u>C</u>H *arom.*), 127.6 (2C, 2 x <u>C</u>H *arom.*), 127.9 (2C, 2 x <u>C</u>H *arom.*), 128.1 (2C, 2 x <u>C</u>H *arom.*), 129.4 (2C, 2 x <u>C</u>H *arom.*), 136.4 (2C, 2 x <u>C</u> *quat. arom.*), 138.8 (2C, 2 x <u>C</u> *quat. arom.*), 141.0 (2C, 2 x <u>C</u> *quat. arom.*), 127.2 (2C, 2 x <u>C</u> *quat. arom.*); *m/z* (HNES) 462.1721 - $C_{27}H_{28}O_4N_1S_1$ $[M–2H]^+$ requires 462.1734.

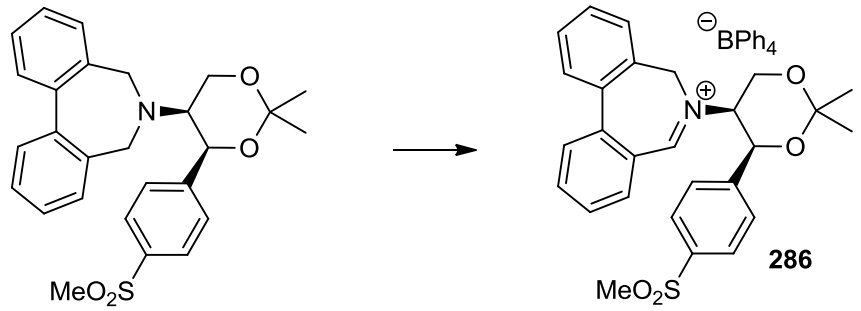
(–)-6-[(4S,5S)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl]-5*H*-dibezo[c,e]azepinium tetraphenylborate[14] (169)



A solution of **168** (0.86 g, 4.18 mmol) dissolved in EtOH (10 mL), was added to an ice-allowed to cool solution of 2-[2-(bromomethyl)-phenyl]benzene carbaldehyde (1.28 g, 4.60 mmol) in EtOH (20 mL). The solution was allowed to attain ambient temperature overnight. $NaBPh_4$ (1.57 g, 4.60 mmol) was dissolved in the minimum

amount of MeCN and added in one portion to the reaction, which caused the formation of a precipitate. Solvents were removed under reduced pressure and the remaining residue was macerated in hot EtOH and allowed to cool to ambient temperature. The crystalline product was filtered off and washed with cold EtOH followed by Et_2O. The iminium salt was left to dry in an oven under reduced pressure at 60 °C overnight for 4 h (1.83 g, 63%): m.p. 186.3-188.1 °C (dec.); $[\alpha]^{20}_D$ –44.4 (c = 1.25, MeCN), *lit.* $[\alpha]^{20}_D$ –42.5 (c = 1.00, MeCN); ν_{max}(neat)/cm^{-1} 3050, 2967, 1630, 1479, 1447, 1382, 1341, 1264, 1205, 1113, 733, 705; δ_H (400 MHz; DMSO, 80 °C) 1.65 (3H, s, C$\underline{Me}_2$), 1.72 (3H, s, C$\underline{Me}_2$), 4.29 (1H, d, *J* = 13.5 Hz, NCH-C$\underline{H}_2$-O, upfield portion of ABX system), 4.52 (1H, d, *J* = 11.5 Hz, ArC$\underline{H}_2$N, upfield portion of AB system), 4.65-4.72 (2H, m, -NC$\underline{H}$- / NCH-C$\underline{H}_2$-O, downfield portion of ABX system), 5.18 (1H, d, *J* = 12.1 Hz, ArC$\underline{H}_2$N, downfield portion of AB system), 5.83 (1H, d, *J* = 2.1 Hz, NCH-C$\underline{H}$Ar-O), 6.77 (4H, t, *J* = 7.2 Hz, 4 x C$\underline{H}$ *arom., para*- $^-$BPh$_4$), 6.88 (8H, t, *J* = 7.2 Hz, 8 x C$\underline{H}$ *arom., meta*- $^-$BPh$_4$), 7.09-7.22 (13H, m, 5 x C$\underline{H}$ *arom*. / 8 x C$\underline{H}$ *arom*. *ortho*- $^-$BPh$_4$), 7.57-7.68 (6H, m, 6 x C$\underline{H}$ *arom.*), 7.90-7.95 (2H, m, 2 x C$\underline{H}$ *arom*.), 9.05 (1H, s, -N=C$\underline{H}$-); δ_C (100 MHz; DMSO 80 °C) 18.2 (1C, C$\underline{Me}_2$), 28.7 (1C, C$\underline{Me}_2$), 54.1 (1C, Ar$\underline{C}H_2$N), 60.8 (1C, NCH-$\underline{C}H_2$-O), 66.1 (1C, s, -N$\underline{C}$H-), 70.6 (1C, NCH-$\underline{C}$HAr-O), 99.9 (1C, *quat.,* $\underline{C}$Me$_2$), 120.8 (4C, 4 x $\underline{C}$H *arom*., *para*- $^-$BPh$_4$), 124.46 (8C, 8 x $\underline{C}$H *arom*., *meta*- $^-$BPh$_4$), 124.47 (2C, 2 x $\underline{C}$H *arom.*), 124.55 (1C, $\underline{C}$H *arom.*), 124.57 (2C, 2 x $\underline{C}$H *arom.*), 125.4 (2C, 2 x $\underline{C}$ *quat. arom.*), 127.4 (1C, $\underline{C}$H *arom.*), 127.9 (1C, $\underline{C}$H *arom.*), 128.0 (1C, $\underline{C}$H *arom.*), 128.4 (1C, $\underline{C}$H *arom.*), 129.3 (1C, $\underline{C}$H *arom.*), 129.6 (1C, $\underline{C}$H *arom.*), 129.6 (1C, $\underline{C}$H *arom.*), 132.9 (2C, 2 x $\underline{C}$ *quat. arom*.), 133.8 (1C, $\underline{C}$H *arom.*), 135.1 (8C, 8 x $\underline{C}$H *arom*., *ortho*- $^-$BPh$_4$), 136.1 (2C, 2 x $\underline{C}$ *quat. arom.*), 140.5 (2C, 2 x $\underline{C}$ *quat. arom.*), 163.3 (4C, q, *J* = 49.0 Hz, 4 x $\underline{C}$ *quat*. *arom*., *ipso*- $^-$BPh$_4$), 170.4 (1C, -N=$\underline{C}$H-).

(–)-6-[(4*S*,5*S*)-2,2-Dimethyl-4-(4-(methylsulfonyl)phenyl)-1,3-dioxan-5-yl]-5*H*-dibezo[c,e]azepin-6-ium tetraphenylborate (286)

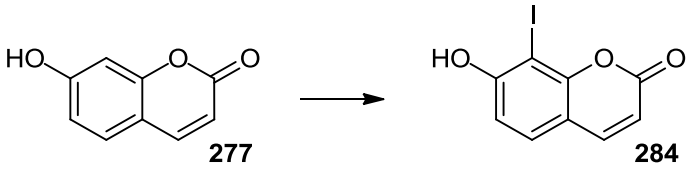


To a solution of (+)-6-[(4*S*,5*S*)-2,2-dimethyl-4-(4-(methylsulfonyl)phenyl)-1,3-dioxan-5-yl]6,7-dihydro-5*H*-dibezo[c,e]azepine (0.82 g, 1.76 mmol) in CH_2Cl_2 (20 mL) in a flask equipped with a stirrer bar, was added NBS (0.35 g, 1.94 mmol). The resulting bright yellow solution was stirred for 15 min. at RT, after which time the solvent was switched for EtOH. To this solution was added $NaBPh_4$ (0.66 g, 1.94 mmol) pre-dissolved in the minimum amount of MeCN. The solvent was then switched for CH_2Cl_2 and transferred to a separating funnel. The organic layer was washed with water (2 x 45 mL) and brine (30 mL) and transferred straight in to a round bottomed flask and solvents were removed. The resulting foam was then recrystallized from EtOH. The crystalline product was filtered off and washed with cold EtOH followed by hexane, and dried under reduced pressure in an oven at 60 °C overnight (0.82 g, 60%): m.p. 153.6-156.8 °C (dec.); $[\alpha]^{20}_{D}$ –52.7 (c = 1.07, acetone); ν_{max}(neat)/cm^{-1} 3054, 2995, 1639, 1600, 1580, 1554, 1480, 1454, 1427, 1404, 1382, 1351, 1304, 1237, 1199, 1147, 1128, 1109, 1086, 1054, 1030, 973, 948, 871, 841, 827, 782, 767, 704; δ_H (400 MHz; acetone-d6, 50 °C) 1.80 (3H, s, C$\underline{Me}_2$), 1.83 (3H, s, C$\underline{Me}_2$), 2.98 (3H, s, -$SO_2\underline{Me}$), 4.48 (1H, br, Ar$C\underline{H}_2$N, upfield portion of AB system), 4.50 (1H, d, *J* = 13.2 Hz, NCH-$C\underline{H}_2$-O, upfield portion of ABX system), 4.87 (1H, dd, *J* = 13.8 Hz, 2.9 Hz, NCH-$C\underline{H}_2$-O, downfield portion of ABX system), 4.91 (1H, br, -NCH-), 5.61 (1H, br, Ar$C\underline{H}_2$N, upfield portion of AB system), 6.09 (1H, d, *J* = 2.1 Hz, NCH-C$\underline{H}$Ar-O), 6.77 (4H, tt, *J* = 7.3 Hz, 1.4 Hz, 4 x C$\underline{H}$ *arom., para-* $^{-}BPh_4$), 6.92 (8H, t, *J* = 7.4 Hz, 8 x C$\underline{H}$ *arom., meta-* $^{-}BPh_4$), 7.32-7.39 (8H, m, 8 x C$\underline{H}$ *arom. ortho-* $^{-}BPh_4$), 7.60-7.64 (5H, m, 5 x C$\underline{H}$ *arom.*), 7.72-7.77 (5H, m, 5 x C$\underline{H}$ *arom.*),

7.94-7.80 (2H, m, 2 x CH *arom.*), 9.24 (1H, s, -N=CH-); δ_C (100 MHz; acetone-d6, 50 °C) Only the counter-ion's ^{13}C signals were observed.

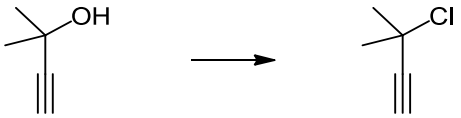
3.2.7 Experimental Procedures for the Total Synthesis of Scuteflorins A and B

8-Iodo-7-hydroxy-2*H*-benzopyran-2-one[15] (284)



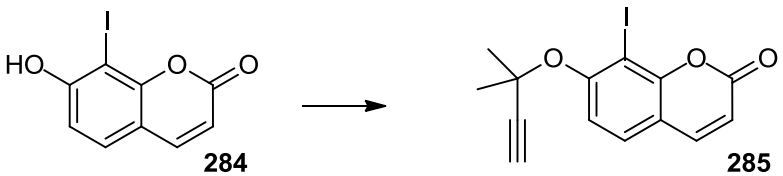
7-hydroxycoumarin **277** (1.00 g, 6.2 mmol) was dissolved in 20% NH_4OH solution (40 mL). In a separate flask, KI (4.91 g, 29.6 mmol) and I_2 (1.88 g, 7.5 mmol) were dissolved in water (67 mL). The resulting triiodide solution was transferred dropwise *via* cannula to the stirring alkaline solution of 7-hydroxycoumarin at RT, during which time the reaction was observed to change from pale yellow to orange. After the complete consumption of 7-hydroxycoumarin was observed by TLC (≈ 4 h), the ammonia was removed under reduced pressure at RT until the solution was pH 7-8. The aqueous solution was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 60 mL), the combined organic extracts were dried over $MgSO_4$ and evaporated to dryness under reduced pressure to yield a brown solid. The crude solid was recrystallized from hot EtOAc to yield the known title compound **284** as light brown crystals (0.75 g, 65%): m.p. 215.8 °C; ν_{max}(neat)/cm^{-1} 3334, 1769, 1603, 1547, 1498, 1406, 1311, 1234, 1168, 1144, 1106, 1031, 928, 840, 738; δ_H (300 MHz; $CDCl_3$) 6.19 (1H, d, *J* = 9.5 Hz, -CH=C<u>H</u>-CO_2-), 6.95 (1H, d, *J* = 8.5 Hz, C<u>H</u> *arom*.), 7.52 (1H, d, *J* = 8.5 Hz, C<u>H</u> arom.), 7.83 (1H, d, *J* = 9.5 Hz, -C<u>H</u>=CH-CO_2-), 10.00 (1H, br, -O<u>H</u>); δ_C (75 MHz; acetone-d6) 111.8 (1C, -<u>C</u>H), 112.7 (1C, -<u>C</u>H), 129.7 (1C, -<u>C</u>H), 144.0 (1C, -<u>C</u>H=CH–CO_2-), no quaternary carbons were observed.

3-Chloro-3-methylbut-1-yne[16]



To a flask charged with $CaCl_2$ (23.0 g, 209 mmol), CuCl (20.0 g, 204 mmol) and Cu powder (0.4 g, 6.67 mmol), was added ice-cold conc. HCl (250 mL). The dark green solution was placed under an atmosphere of Ar and stirred at 0 °C for 5 min. While maintaining the reaction at 0 - 5 °C, 2-methyl-3-butyn-2-ol (65.0 mL, 667 mmol) was added slowly to the acidic solution. After complete addition of the alcohol, the reaction was stirred at 0 °C for 1 h. The biphasic reaction mixture was transferred to a separating funnel and the aqueous layer was removed. The remaining organic layer was then washed with cold HCl (3 x 150 mL), cold water (2 x 150 mL) and saturated aqueous $NaHCO_3$ (150 mL). The remaining cloudy organic fraction was dried over $MgSO_4$ and filtered to yield the known title compound as a clear colourless liquid (40.1 g, 59%): ν_{max}(neat)/cm^{-1} 3300, 2988, 1368, 1227, 1119, 787, 652, 595; δ_H (400 MHz; $CDCl_3$) 1.81 (6H, s, 2 x Me), 2.59 (1H, s, -C≡C-H); δ_c (100 MHz; $CDCl_3$) 34.70 (2C, 2 x Me), 57.42 (1C, -$CClMe_2$, C *quat.*), 72.08 (1C, -C≡C-H), 86.78 (1C, -C≡C-H, C *quat.*).

8-Iodo-7-((2-methylbut-3-yn-2-yl)oxy)-2*H*-chromen-2-one[17] **(285)**

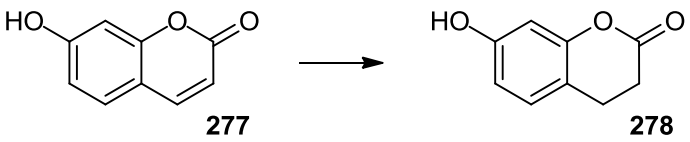


284 **285**

8-iodo-7-hydroxy-2H-1-benzopyran-2-one **284** (0.78 g, 2.70 mmol), K_2CO_3 (1.12 g, 8.11 mmol), KI (1.12 g, 6.76 mmol) and CuI (15 mg, 0.079 mmol) were added to a flame dried flask equipped with a reflux condenser under an inert atmosphere of Ar. Dried acetone (30 mL) was added *via* cannula through the bung on top of the condenser. The suspension was stirred for 5 min. prior to the addition of 3-chloro-

3-methyl-1-butyne (0.47 mL, 4.06 mmol). The reaction mixture was heated under reflux for 3 h over which time the reaction turned bright yellow. The reaction was allowed to cool and a solvent switch to EtOAc (40 mL) was performed. The organic solution was washed with water (40 mL), and the aqueous phase was extracted further with EtOAc (2 x 40 mL), the combined organic extracts were washed with brine (50 mL) and dried over $MgSO_4$. The solvent was boiled off until crystals began to form and the crystallising solution was allowed to cool to RT before being placed in the freezer. The colourless crystals of the known title compound were collected by filtration (0.95 g, 99%): m.p. 185.6 °C; δ_H (300 MHz; $CDCl_3$) 1.77 (6H, s, 2 x Me), 2.68 (1H, s, -C≡C-H), 6.27 (1H, d, *J* = 9.5 Hz, -CH=CH-CO_2-), 7.38 (1H, d, *J* = 8.6 Hz, CH *arom*.), 7.56 (1H, d, *J* = 8.6 Hz, CH arom.), 7.59 (1H, d, *J* = 9.5 Hz, -CH=CH-CO_2-); δ_C (75 MHz; $CDCl_3$) 29.5 (2C, 2 x Me), 74.6 (1C, CMe_2, C *quat*.), 75.1 (1C, -C≡C-H), 81.2 (1C, C-I), 85.0 (1C, -C≡C-H), 114.48 (1C, -CH), 114.54 (1C, -CH), 128.1 (1C, -CH), 143.1 (1C, -CH=CH–CO_2-), 155.1 (1C, C *quat.*), 159.3 (1C, C *quat.*), 160.5 (1C, C *quat.*).

7-Hydroxychroman-2-one[18] (278)

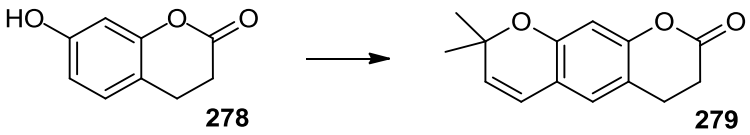


277 **278**

277 (5.00 g, 30.7 mmol) and Pd/C (0.50 g, 10% wt/wt), were suspended in AcOH (150 mL). The flask was sealed with a bung and flushed with H_2 and subsequently maintained under an atmosphere of H_2 for 20 h. The solvent was switched for EtOAc (120 mL), and the organic solution was then washed with 50% saturated aqueous, $NaHCO_3$ (60 mL) and water (2 x 60 mL) to remove any residual AcOH. The organic layer was dried over $MgSO_4$ and filtered through celite to remove the Pd/C. Solvents were removed under reduced pressure to furnish the known title compound **278** as a colourless powder (5.01 g, 99%): m.p. 133.8 °C; ν_{max}(neat)/cm^{-1} 3291, 1725, 1630, 1603, 1512, 1463, 1350, 1285, 1251, 1153, 1110, 976, 902, 841,

815, 768; δ_H (300 MHz; $CDCl_3$) 2.73 (2H, m, 2 x -C<u>H</u>$_2$-), 2.92 (2H, m, 2 x -C<u>H</u>$_2$-), 6.48 (1H, d, *J* = 2.4 Hz, C<u>H</u> *arom.*), 6.60 (1H, dd, *J* = 8.2 Hz, 2.4 Hz, C<u>H</u> *arom.*), 7.07 (1H, d, *J* = 8.2 Hz, C<u>H</u> *arom.*), 8.58 (1H, br, -O<u>H</u>); δ_C (75 MHz; $CDCl_3$) 22.6 (1C, -<u>C</u>H$_2$-), 29.1 (1C, -<u>C</u>H$_2$-), 103.6 (1C, <u>C</u>H *arom.*), 111.3 (1C, <u>C</u>H *arom.*), 114.1 (1C, <u>C</u> *quat. arom.*), 128.9 (1C, <u>C</u>H *arom.*), 153.1 (1C, <u>C</u> *quat. arom.*), 157.5 (1C, <u>C</u> *quat. arom.*), 168.1 (1C, <u>C</u> *quat.*).

8,8-Dimethyl-3,4-dihydropyrano[3,2-*g*]chromen-2(8*H*)-one[19] (279)

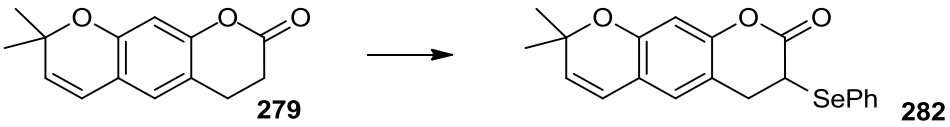


278 279

Chroman **278** (0.50 g, 3.05 mmol) and $PhB(OH)_2$ (0.74 g, 6.10 mmol) were placed in a flame dried flask, under N_2, equipped with a condenser to which toluene (45 mL) and AcOH (14 mL) were added. The mixture was stirred until the solids had completely dissolved. 3-methyl-2-butenal (0.43 mL, 4.57 mmol) was added in one portion and the clear colourless solution was wrapped in foil and heated under reflux until the starting material was judged to have been consumed by TLC analysis (≈24 h). The solvents were switched for Et_2O (50 mL) and water (50 mL). The ethereal layer was separated and washed with 50% saturated aqueous $NaHCO_3$ (2 x 30 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$ and evaporated to dryness under reduced pressure to yield an orange oil. The oil was purified by column chromatography, eluting with light petroleum / EtOAc (9:1) to furnish **279** as a colourless powder (0.41 g, 51%): ν_{max}(neat)/cm^{-1} 3006, 2989, 2948, 2907, 1764, 1635, 1620, 1579, 1489, 1446, 1425, 1385, 1373, 1362, 1334, 1303, 1282, 1258, 1230, 1218, 1174, 1143, 1117, 1026, 987, 949, 932, 919, 860, 789, 761, 741, 709, 702; δ_H (300 MHz; $CDCl_3$) 1.39 (6H, s, 2 x <u>Me</u>), 2.71 (2H, m, 2 x -C<u>H</u>$_2$-), 2.86 (2H, m, 2 x -CH_2-), 5.55 (1H, d, *J* = 9.8 Hz, -CH=C<u>H</u>-CMe_2O-), 6.22 (1H, d, *J* = 9.8 Hz, -C<u>H</u>=CH-CMe_2O-), 6.47 (1H, s, C<u>H</u> *arom.*), 6.74 (1H, s, C<u>H</u> *arom.*); δ_C (75 MHz; $CDCl_3$) 23.2 (1C, -<u>C</u>H$_2$-), 28.1 (2C, 2 x <u>Me</u>), 29.7 (1C, -<u>C</u>H$_2$-), 76.8 (1C, <u>C</u>Me_2, C *quat*.), 105.5 (1C, <u>C</u>H *arom.*), 114.6 (1C, <u>C</u> *quat. arom.*), 118.1 (1C, <u>C</u> *quat. arom.*), 121.5 (1C, -

C̲H=CH-CMe$_2$O-), 125.3 (1C, C̲H *arom.*), 130.5 (1C, -CH=C̲H-CMe$_2$O-), 152.3 (1C, C̲ *quat. arom.*), 153.1 (1C, C̲ *quat. arom.*), 168.8 (1C, C̲=O, C *quat.*).

8,8-Dimethyl-3-(phenylselanyl)-3,4-dihydropyrano[3,2-*g*]chromen-2(8*H*)-one (282)



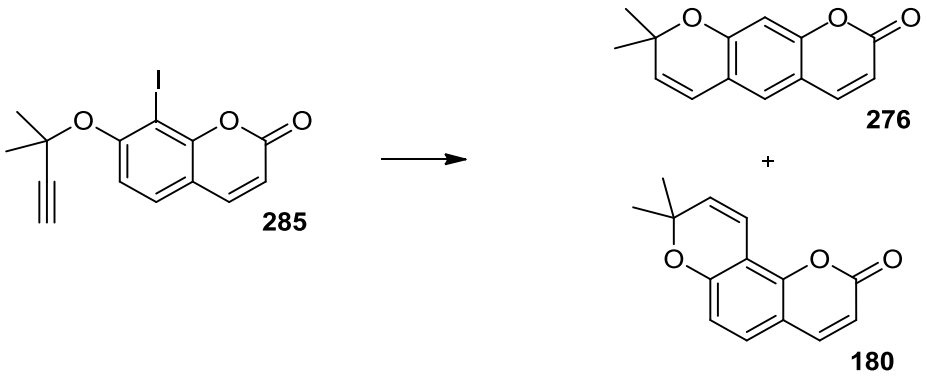
279 **282**

A solution of ^{n}BuLi (1.63 mL, 1.6 M in hexanes, 2.61 mmol) in THF (5 mL) was allowed to cool to –78 °C in a round bottomed flask under Ar. Diisopropylamine (0.34 mL, 2.39 mmol) was added to the allowed to cool solution and stirred for 5 min. to allow the formation of LDA. In a separate flask, also under Ar, **279** (0.50 g, 2.17 mmol) was dissolved in THF (15 mL) and allowed to cool to –78 °C. The solution of LDA was transferred dropwise *via* cannula to the flask containing the dihydroxanthyletin and the vessel was stirred for a further 10 min. Phenylselenyl chloride (0.46 g, 2.39 mmol) was dissolved in THF (6 mL) and syringed into the yellow solution of the lithium enolate over a period of 2 min. The resulting light-orange solution was left to attain ambient temperature over a period of 1 h, then, saturated aqueous NH_4Cl (10 mL) was added to the flask to quench the reaction. The resulting biphasic mixture was transferred to a separating funnel. The organic phase was collected and the aqueous phase was washed with Et_2O (2 x 10 mL). The organic layers were combined and washed with brine (20 mL) and dried over $MgSO_4$. Solvents were then removed under reduced pressure to yield a dark-yellow tar which was purified by column chromatography, eluting with light petroleum / EtOAc (8:1). The title compound **282** was isolated as a light-yellow oil (0.40 g, 48%). ν_{max}(neat)/cm^{-1} 3051, 2973, 2930, 1748, 1639, 1621, 1581, 1485, 1438, 1364, 1369, 1362, 1332, 1312, 1284, 1261, 1243, 1221, 1162, 1106, 1045, 952, 904, 738; δ_H (300 MHz; $CDCl_3$) 1.41 (3H, s, M̲e), 1.45 (3H, s, M̲e), 3.04 (1H, dd, *J* = 16.7 Hz, 3.2 Hz, -C̲H$_2$-), 3.43 (1H, dd, *J* = 16.5 Hz, 5.0 Hz, -C̲H$_2$-), 4.12 (1H, m, -C̲HSePh), 5.59 (1H, d, *J* = 9.8 Hz, -CH=C̲H-CMe$_2$O-), 6.25 (1H, d, *J* = 9.9 Hz, -C̲H=CH-CMe$_2$O-), 6.47 (1H, s, C̲H

arom.), 6.72 (1H, s, CH *arom.*), 7.25 (3H, m, 3 x CH *arom.*), 7.59 (2H, m, 2 x CH *arom.*); δ_C (75 MHz; $CDCl_3$) 27.8 (1C, Me), 28.1 (1C, Me), 30.6 (1C, -CH_2-), 37.9 (1C, -CHSePh), 105.0 (1C, CH *arom.*), 111.9 (1C, C *quat. arom.*), 118.0 (1C, C *quat. arom.*), 121.3 (1C, -CH=CH-CMe_2O-), 125.6 (1C, CH *arom.*), 127.3 (1C, C *quat. arom.*), 129.0, (1C, CH *arom.*), 129.4 (2C, 2 x CH *arom.*), 130.6 (1C, -CH=CH-CMe_2O-), 135.6 (2C, 2 x CH *arom.*), 151.8 (1C, C *quat. arom.*), 153.5 (1C, C *quat. arom.*), 167.2 (1C, C=O, C *quat.*), CMe_2, C *quat*. – was not observed; *m/z* (HNESP) 398.0823 - $C_{20}H_{22}O_3SeN$ $[M+NH_4]^+$ requires 398.0819 .

Xanthyletin (276) / Seselin (180)

Route A

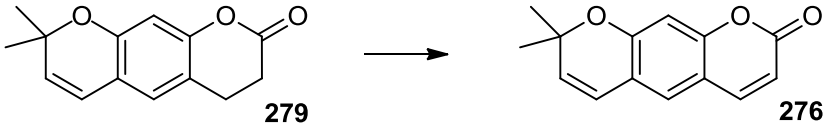


The alkyne **285** (0.30 g, 0.84 mmol) was placed in a microwave vessel and *N*,*N*-dimethylaniline (4 mL) was added The flask was sealed and flushed with Ar and gently warmed until the alkyne had completely dissolved. The reaction mixture was heated to 200 °C by μW irradiation for 10 min., turning dark blue. The mixture was resubmitted to a total of 90 min. at 240 °C, after which time the reaction had turned dark red and judged to have run to completion by TLC. The *N*,*N*-dimethylaniline was removed under reduced pressure, the crude residue was purified by column chromatography eluting with light petroleum / EtOAc (8.5:1.5) to yield xanthyletin **276** (0.095 g, 45%) and seselin **180** (0.027g, 12.5%) as colourless solids.

180:[20] m.p. 119.6 °C; ν_{max}(neat)/cm^{-1} 2976, 2361, 1734, 1597, 1485, 1152; δ_H (300 MHz; $CDCl_3$) 1.45 (6H, s, 2 x Me), 5.72 (1H, d, *J* = 10.0 Hz, -CH=CH-CMe_2O-), 6.21

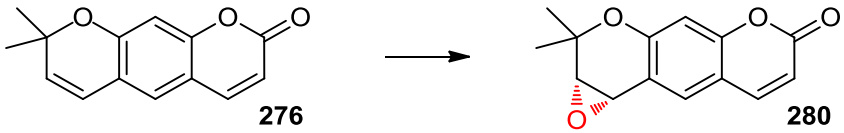
(1H, d, *J* = 9.5 Hz, CH=C<u>H</u>-CO_2-), 6.70 (1H, d, *J* = 10.0 Hz, -C<u>H</u>=CH-CMe_2O-), 6.86 (1H, d, *J* = 8.0 Hz, C<u>H</u> *arom.*), 7.03 (1H, s, C<u>H</u> *arom.*), 7.56 (1H, d, *J* = 9.5 Hz, –C<u>H</u>=CH-CO_2–).

Route B[18]



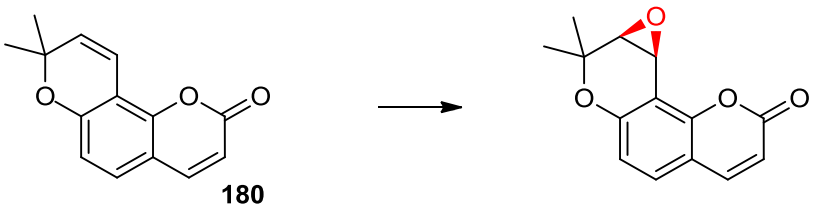
DDQ (2.50 g, 11.0 mmol) was added in one portion to a solution of chroman **279** (2.40 g, 10.5 mmol) in toluene (200 mL). The reaction was heated under reflux for 14 h after which time DDQ (0.24 g, 1.05 mmol) was added every two hours until the reaction was judged to have run to completion by TLC, (0.96 g in total). Solvents were removed under reduced pressure and the residue was re-dissolved in EtOAc (300 mL). Any residual solid was filtered off on transferral to the separating funnel. The organic solution was washed with water (4 x 300 mL) followed by 50% saturated aqueous $NaHCO_3$ (2 x 200 mL) and brine (200 mL). The organic layer was dried over $MgSO_4$ and evaporated to dryness under reduced pressure. The crude orange oil was purified by column chromatography, eluting with light petroleum / EtOAc (4:1) to yield an orange solid (1.32 g). This orange solid was then sequentially re-crystallised three times from CH_2Cl_2 / light petroleum, and twice from hot EtOH to yield **276** as colourless crystals (1.23 g, 52%): m.p. 130.2 °C; ν_{max}(neat)/cm^{-1} 3275, 2983, 1731, 1596, 1535, 1479, 1451, 1429, 1397, 1389, 1371, 1289, 1232, 1186, 1169, 1132, 1098, 1050, 974, 952, 924, 897, 828, 810, 785, 752, 731, 703; δ_H (300 MHz; $CDCl_3$) 1.44 (6H, s, 2 x <u>Me</u>), 5.67 (1H, d, *J* = 10.0 Hz, -CH=C<u>H</u>-CMe_2O-), 6.19 (1H, d, *J* = 9.5 Hz, -CH=C<u>H</u>-CO_2), 6.32 (1H, d, *J* = 10.0 Hz, -C<u>H</u>=CH-CMe_2O-), 6.69 (1H, s, C<u>H</u> *arom.*), 7.03 (1H, s, C<u>H</u> *arom.*), 7.56 (1H, d, *J* = 9.5 Hz, -C<u>H</u>=CH-CO_2-); δ_C (75 MHz; $CDCl_3$) 28.2 (2C, 2 x <u>Me</u>), 77.7 (1C, <u>C</u>Me_2, C *quat*.) 104.1 (1C, <u>C</u>H *arom.*), 112.7 (1C, <u>C</u> *quat. arom.*), 113.0 (1C, <u>C</u>H), 118.5 (1C, <u>C</u> *quat. arom.*), 121.1 (1C, <u>C</u>H), 124.8 (1C, <u>C</u>H *arom.*), 131.3 (1C, <u>C</u>H) 143.4 (1C, -<u>C</u>H=CH-CO_2-), 155.5 (1C, <u>C</u> *quat.*), 156.9 (1C, <u>C</u> *quat.*), 161.3 (1C, <u>C</u> *quat.*).

(+)-Xanthyletin oxide[21] (280)



Xanthyletin **276** (24 mg, 0.11 mmol) was dissolved in $CHCl_3$ (2.5 mL) and allowed to cool to –30 °C. TPPP (96 mg, 0.22 mmol) was added in one portion followed by catalyst **169** (3.7 mg, 0.0053 mmol). The reaction was stirred vigorously at –30 °C until the xanthyletin had been consumed (≈ 20 h) at which time Et_2O (20 mL), pre-allowed to cool to the reaction temperature, was added to precipitate the TPPP and by-products. The suspension was then filtered through celite and solvents were then removed under reduced pressure. The epoxide **280** was isolated in good purity and no further purification was required (26 mg, 97%): m.p. 157.6°C; $[\alpha]^{18}_D$ +280.1 (c = 1.23, $CHCl_3$), *lit.* $[\alpha]^{20}_D$ +281.3 (c = 1.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2984, 2961, 2928, 1730, 1627, 1562, 1496, 1459, 1435, 1390, 1367, 1348, 1333, 1282, 1271, 1235, 1207, 1189, 1144, 1103, 1035, 1001, 981, 948, 915, 894, 852, 834, 819, 755, 717; δ_H (300 MHz; $CDCl_3$) 1.29 (3H, s, Me) 1.59 (3H, s, Me), 3.53 (1H, d, *J* = 4.4 Hz, -CHO-), 3.96 (1H, d, *J* = 4.4 Hz, -CHO-), 6.26 (1H, d, *J* = 9.5 Hz, -CH=CH-CO_2-), 6.75 (1H, s, CH *arom.*), 7.45 (1H, d, *J* = 9.5 Hz, -CH=CH-CO_2), 7.62 (1H, s, CH *arom.*); δ_C (75 MHz; $CDCl_3$) 22.9 (1C, Me), 25.3 (1C, Me), 50.1 (1C, -CHO-), 61.9 (1C, -CHO-), 74.6 (1C, CMe_2, C *quat*.), 106.1 (1C, CH *arom.*), 113.01 (1C, C *quat. arom.*), 113.9 (1C, -CH=CH-CO_2-), 117.3 (1C, C *quat. arom.*), 128.9 (1C, CH *arom.*), 142.9 (1C, -CH=CH-CO_2-), 156.2 (1C, C *quat.*), 160.9 (1C, C *quat.*), C *quat*. not observed. HPLC conditions - hexane/2-propanol (90:10), oven temp 20 °C, column Chiracel OD-H 01 250 × 4.6 mm, 5 μm particle size, flow rate 1 mL/min, 254 nm: : t_r – 34.89 min (+), 37.00 min (–).

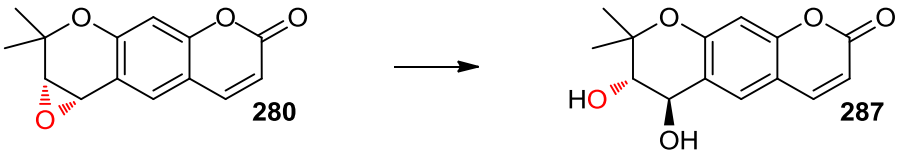
(+)-Seselin oxide[20]



180

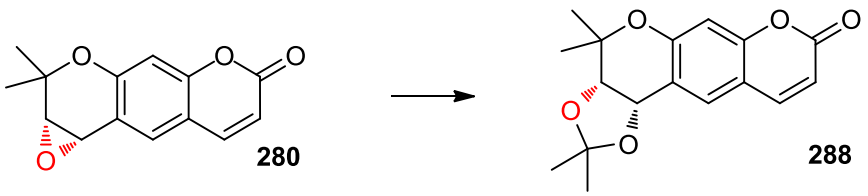
Seselin **180** (20 mg, 0.088 mmol) was dissolved in $CHCl_3$ (2.0 mL) and allowed to cool to –30 °C. TPPP (80 mg, 0.18 mmol) was added in one portion followed by catalyst **169** (3.0 mg, 0.0044 mmol). The reaction was stirred at –30 °C for 39 h at which time Et_2O (20 mL), pre-allowed to cool to the reaction temperature, was added to precipitate the TPPP and by-products. The suspension was then filtered through celite and the solvents were then removed under reduced pressure. The known epoxide was isolated as a colourless solid after preparative TLC eluting with light petroleum / EtOAc (4:1) (8.8 mg, 41%): m.p. 147.8 °C (dec.); $[\alpha]^{20}_D$ +7.3 (c = 0.98, $CDCl_3$), *lit.* $[\alpha]^{20}_D$ +7.5 (c = 1.02, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3422, 3057, 2983, 2918, 1694, 1289, 1263, 1074, 1063, 1024, 976, 862, 762, 743; δ_H (300 MHz; $CDCl_3$) 1.16 (3H, s, Me), 1.43 (3H, s, Me), 3.58 (1H, d, *J* = 9.02 Hz, -CHO-), 3.87 (1H, br, –CHO–), 4.17 (1H, br, –CHOH–), 4.52 (1H, d, *J* = 8.6 Hz, –CHOH–), 6.05 (1H, d, *J* = 9.5 Hz, –CH=CH-CO_2–), 6.53 (1H, s, CH *arom.*), 7.46 (1H, d, *J* = 9.5 Hz, –CH=CH-CO_2–), 7.47 (1H, s, CH *arom.*); δ_C (75 MHz; acetone-d6) 19.0 (1C, CH_3), 26.2 (1C, CH_3), 68.2 (1C, -CHOH-), 75.2 (1C, -CHOH-), 80.19 (1C, CMe_2, C *quat*.) 103.2 (1C, CH *arom.*), 112.9 (1C, –CH=CH–CO_2–), 123.0 (1C, C *quat. arom.*), 128.5 (1C, CH *arom.*), 143.9 (1C, –CH=CH–CO_2–), 155.1 (1C, C *quat.*), 156.2 (1C, C *quat.*), 160.3 (1C, C *quat.*), C *quat*. not observed. HPLC conditions - hexane/2-propanol (90:10), oven temp 20 °C, column Chiracel OD-H 01 250 × 4.6 mm, 5 μm particle size, flow rate 1 mL/min, 254 nm.

(+)-*Trans*-decursinol[21] (287)



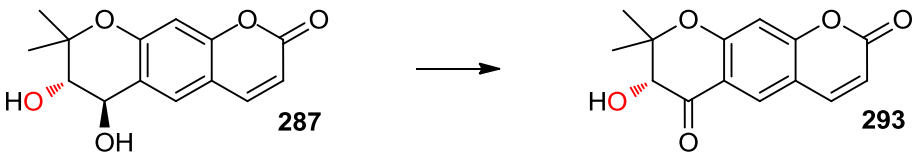
Xanthyletin oxide **280** (0.20 g, 8.92 mmol) was dissolved in acetone (10 mL) and 1 M aq. solution of HCl (5 mL) was added in one portion. The reaction was stirred until it was judged by TLC that the starting material had been completely consumed, (≈5 min). The solution was diluted with CH_2Cl_2 (30 mL) and water (30 mL), the organic layer was collected and the aqueous was extracted further with CH_2Cl_2 (2 x 30mL). The combined organic extracts were washed with brine (50 mL), and dried over $MgSO_4$. The solvents were removed under reduced pressure to leave a colourless oily residue which was purified by column chromatography eluting with 1:1 light petroleum / EtOAc to yield the title compound **287** as a colourless foam (140 mg, 60%): m.p. 147.8 °C (dec.); $[\alpha]^{20}_D$ +146.1 (c = 0.33, MeOH), *lit.* $[\alpha]^{20}_D$ –148.2 (c = 1.00, MeOH); ν_{max}(neat)/cm^{-1} 3422, 3057, 2983, 2918, 1694, 1289, 1263, 1074, 1063, 1024, 976, 862, 762, 743; δ_H (300 MHz; $CDCl_3$) 1.16 (3H, s, Me) 1.43 (3H, s, Me), 3.58 (1H, d, *J* = 9.0 Hz, -CHOH-), 3.87 (1H, br, -CHOH-), 4.17 (1H, br, -CHOH-), 4.52 (1H, d, *J* = 8.6 Hz, -CHOH-), 6.05 (1H, d, *J* = 9.5 Hz, -CH=CH-CO_2-), 6.53 (1H, s, CH *arom.*), 7.46 (1H, d, *J* = 9.5 Hz, -CH=CH-CO_2-), 7.47 (1H, s, CH *arom.*); δ_C (75 MHz; acetone-d6) 19.0 (1C, Me), 26.2 (1C, Me), 68.2 (1C, -CHOH-), 75.2 (1C, -CHOH-), 80.2 (1C, CMe_2, C *quat.*), 103.2 (1C, CH *arom.*), 112.9 (1C, -CH=CH-CO_2-), 123.0 (1C, C *quat. arom.*), 128.5 (1C, CH *arom.*), 143.9 (1C, -CH=CH-CO_2-), 155.1 (1C, C *quat.*), 156.2 (1C, C *quat.*), 160.3 (1C, C *quat.*), C *quat*. not observed; *m/z* (ASAP) 263.0911 - $C_{14}H_{14}O_5$ $[M+H]^+$ requires 263.0914.

(3a*S*, 11b*S*)-2,2,4,4-tetramethyl-3a,4-dihydro-[1,3]dioxolo[4,5-*c*]pyrano[3,2-*g*]chromen-8(11b*H*)-one (288)



This Ritter-type product **288** was isolated as a colourless solid during purification of the acid-catalysed ring-opening reaction above (19 mg, 8%): ν_{max}(neat)/cm^{-1} 2984, 2931, 1725, 1622, 1564, 1494, 1461, 1391, 1371, 1334, 1298, 1263, 1221, 1161, 1134, 1081, 1022, 967, 946, 922, 899, 865, 850, 821, 785, 751, 731; δ_H (300 MHz; $CDCl_3$) 1.16 (3H, s, Me), 1.25 (3H, s, Me), 1.42 (3H, s, Me), 1.52 (3H, s, Me), 3.71 (1H, d, *J* = 2.4 Hz, -OH), 4.45 (1H, d, *J* = 6.0 Hz, -CHO-), 5.16 (1H, d, *J* = 6.0 Hz, -CHO-), 6.25 (1H, d, *J* = 9.5 Hz, -CH=CH-CO_2-), 6.78 (1H, s, CH *arom.*), 7.48 (1H, s, CH *arom.*), 7.62 (1H, d, *J* = 9.3 Hz, -CH=CH-CO_2-); *m/z* (ASAP) HNESP 303.1226 - $C_{14}H_{12}O_5$ $[M+H]^+$ requires 303.1227

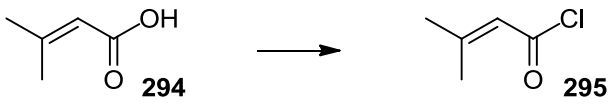
(+)-(*R*)-7-Hydroxy-8,8-dimethyl-7,8-dihydropyrano[3,2-*g*]chromene-2,6-dione (293)



(+)-*Trans*-decursinol **287** (0.055 g, 0.21 mmol) was dissolved in $CHCl_3$ (4 mL) in a round-bottomed flask equipped with a stirrer bar. DMP (0.89 g, 0.21 mmol) was added in two equal portions and the reaction was stirred for an hour between additions. After the reaction was judged to have run to completion by TLC, the reaction was transferred to a separating funnel and washed with 50% saturated aqueous $NaHCO_3$ (15 mL). The aqueous phase was extracted with $CHCl_3$ (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$ and evaporated to

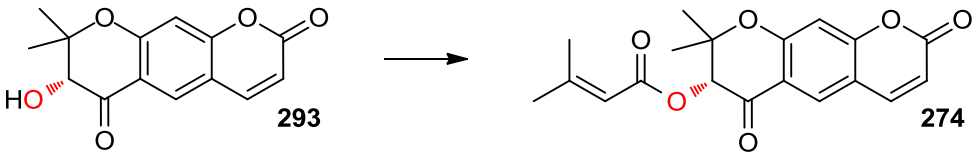
dryness under reduced pressure. The crude yellow oil was purified by column chromatography, eluting with light petroleum / EtOAc (8:5). The title compound **293** was isolated as a colourless oil (0.52 g, 95%): $[\alpha]^{20}_{D}$ +31.37 (c = 0.51, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3289, 3062, 2984, 1736, 1698, 1610, 1560, 1483, 1445, 1389, 1372, 1336, 1284, 1201, 1140, 1101, 1018, 978, 905, 843, 826, 801, 764, 740, 657; δ_H (300 MHz; $CDCl_3$) 1.25 (3H, s, Me) 1.68 (3H, s, Me), 3.71 (1H, d, *J* = 2.4 Hz, -OH), 4.45 (1H, d, *J* = 2.3 Hz, -CHOH-), 6.33 (1H, d, *J* = 9.3 Hz, -CH=CH-CO_2-), 6.85 (1H, s, CH *arom.*), 7.67 (1H, d, *J* = 9.6 Hz, -CH=CH-CO_2-), 7.99 (1H, s, CH *arom.*); δ_C (75 MHz; $CDCl_3$) 17.6 (1C, Me), 26.6 (1C, Me), 76.9 (1C, -CHOH-), 84.7 (1C, CMe_2, C *quat*.) 105.9 (1C, CH *arom.*), 113.7 (1C, C *quat. arom.*), 115.0 (1C, -CH=CH-CO_2-), 116.2 (1C, C *quat. arom.*), 127.4 (1C, CH *arom.*), 143.0 (1C, -CH=CH-CO_2-), 159.7 (1C, C *quat.*), 159.8 (1C, C *quat.*), 162.2 (1C, C *quat.*), 193.0 (1C, C=O, C *quat.*); *m/z* (ASAP) 261.0759 $[M+H]^+$ - $C_{14}H_{12}O_5$ $[M+H]^+$ requires 261.0757.

3,3-Dimethyl-acryloyl chloride[22] (295)



To a flame-dried flask under an atmosphere of Ar, containing a solution of 3,3-dimethyl-acrylic acid **294** (3.0 g, 30 mmol) in CH_2Cl_2 (25 mL), oxalyl chloride (2.83 mL, 3.3 mmol) was added dropwise over a period of 5 min. The reaction was stirred at RT for 1 h after the evolution of gas had ceased. Solvents were then removed under reduced pressure without the use of a heated water bath. The excess oxalyl chloride was removed by three cycles of redissolving the product in $CHCl_3$ and subsequent concentration under reduced pressure. The known title compound **295** was isolated as an odorous pale yellow oil (3.57 g, 99 %): ν_{max}(neat)/cm^{-1} 2254, 1753, 1617, 1444, 1377, 1205, 1091, 1011, 904, 831, 764, 723, 650; δ_H (400 MHz; $CHCl_3$); 1.92 (3H, s, Me), 2.11 (3H, s, Me), 5.71 (1H, s, Me_2C=CH-); δ_C (75 MHz; $CHCl_3$) 21.5 (1C, Me), 27.2 (1C, Me), 122.6 (1H, s, Me_2C=CH-), 163.7 (1C, C quat.), 164.3 (1C, C quat.).

(+)-Scuteflorin A[23] (274)



The α-hydroxy ketone **293** (0.041 g, 0.15 mmol) and $NaHCO_3$ (0.014 g, 0.17 mmol) were placed in a oven-dried flask, equipped with a stirrer bar under an atmosphere of Ar. THF (2.0 mL) was added and the suspension was stirred for 2 min. preceding the addition of 3,3-dimethyl acryloyl chloride (0.087 mL, 0.75 mmol). The reaction was stirred for 4 h when the complete consumption of **293** had been observed by TLC. The reaction mixture was then filtered and concentrated under reduced pressure, the crude oil was purified by column chromatography, eluting with petroleum ether / EtOAc (3.5:1). (+)-Scuteflorin A was isolated as a colourless solid (0.045 g, 88%): $[\alpha]^{22}_D$ +27.0 (c 0.38, MeOH), *lit.* $[\alpha]^{20}_D$ +27.0 (c = 1.00, MeOH): ν_{max}(neat)/cm^{-1} 2985, 2906, 1749, 1728, 1699, 1647, 1626, 1611, 1562, 1486, 1443, 1389, 1354, 1342, 1287, 1260, 1221, 1201, 1168, 1128, 1095, 1084, 1070, 1029, 913, 840, 823, 752, 740, 701, 655, 620, 600; δ_H (400 MHz; CD_3OD); 1.35 (3H, s, -OC$\underline{Me}_2$-), 1.53 (3H, s, -OC$\underline{Me}_2$-), 1.96 (3H, s, $\underline{Me}_2$C=), 2.18 (3H, s, $\underline{Me}_2$C=), 5.69 (1H, s, -C$\underline{H}$-), 5.82 (1H, s, Me_2C=C$\underline{H}$-), 6.31 (1H, d, *J* = 9.6 Hz, -CH=C$\underline{H}$-CO_2-), 6.89 (1H, s, C$\underline{H}$ *arom.*,) 7.91 (1H, d, *J* = 9.4 Hz, -C$\underline{H}$=CH-CO_2-), 8.06 (1H, s, C$\underline{H}$ *arom.*); δ_C (75 MHz; CD_3OD) 20.0 (1C, -OC$\underline{Me}_2$-), 20.7 (1C, -OC$\underline{Me}_2$-), 26.4 (1C, $\underline{Me}_2$C=), 27.7 (1C, $\underline{Me}_2$C=), 77.3 (1C, -$\underline{C}$HO-), 84.16 (1C, -O$\underline{C}Me_2$-), 106.6 (1C, $\underline{C}$H *arom.*), 115.76 (1C, Me_2C=$\underline{C}$H-), 115.80 (1C, -CH=$\underline{C}$H-CO_2-), 118.9 (1C, C *quat. arom.*), 129.3 (1C, $\underline{C}$H *arom.*), 145.4 (1C, –$\underline{C}$H=CH–CO_2–), 161.2 (1C, –CH=CH–$\underline{C}O_2$–), 161.7 (1C, $Me_2\underline{C}$=), 161.8 (1C, C *quat. arom.*), 163.1 (1C, C *quat. arom.*), 166.5 (1C, Me_2CH=CH-$\underline{C}O_2$-), 189.3 (1C, $\underline{C}$=O, C *quat.*), C *quat. arom.* not observed; *m/z* (HNESP) 343.1180 - $C_{19}H_{19}O_6$ $[M+H]^+$ requires 343.1176.

3.2.6 Procedures regarding the epoxidation of alkenes

General procedure for the formation of racemic epoxides

The desired alkene was dissolved in CH_2Cl_2 (10 mL per g of alkene) and allowed to cool to 0 °C. A solution of *m*-CPBA (2 equiv.) in CH_2Cl_2 (10 mL per g of alkene), dried over $MgSO_4$, was filtered into the solution of alkene. The reaction was allowed to achieve ambient temperature and stirred until complete conversion of the alkene was observed by TLC. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (10 mL per g of alkene) and the mixture transferred to a separating funnel. The organic layer was collected and washed with 1M NaOH (10 mL per g of alkene) and dried over $MgSO_4$. Solvents were removed under reduced pressure. Analytically pure samples of the epoxides were obtained by means of flash column chromatography, typically eluting with light petroleum / EtOAc (99:1), buffered with 2% TEA.

General procedure for catalytic asymmetric epoxidation of alkenes with Oxone® mediated by iminium salts under aqueous conditions

Method A

Oxone® (2 equiv.) and $NaHCO_3$ (5 equiv) were added to a solution of the catalyst (5 mol%) in MeCN (1 mL) and water (0.1 mL) at 0 °C. After 5 min. of stirring, the alkene (1 equiv., 3 mmol) dissolved in MeCN (1 mL), was added. The mixture was stirred at 0 °C until either complete conversion of the alkene was observed by TLC or 6 h had past. The reaction mixture was then diluted with Et_2O (10 mL) and the resulting suspension filtered through a mixed pad of Na_2SO_3 and $MgSO_4$. Solvents were removed under reduced pressure and analytically pure samples of the epoxide were obtained by means of flash column chromatography or preparative TLC, typically eluting with light petroleum / EtOAc (99:1), containing 2% TEA. The major enantiomer was determined by $[\alpha]^{20}D$ measurements and comparison to the literature, enantioselectivities were determined by either chiral HPLC, or by the use of the a resolving agent in ^1H NMR.

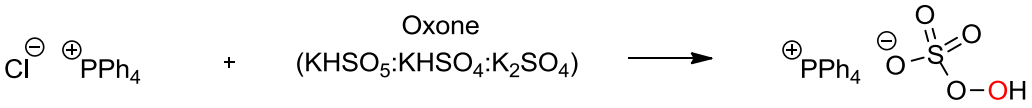
Method B

Water (1 ml), MeCN (1 mL) and $NaHCO_3$ (100 mg, 1.2 mmol) were added to a test-tube immersed in an ice-bath at 0 °C, followed, after 1 min, by Oxone® (370 mg, 0.6 mmol). After the effervescence had subsided, the catalyst (5 mol%) was added followed, after 1 min, by the alkene (0.3 mmol). The mixture was stirred at 0 °C until either complete conversion of the alkene was observed by TLC or 6 h had past. The reaction mixture was then diluted with Et_2O (10 mL per 0.10 g of substrate), the resulting suspension was filtered through a mixed pad of Na_2SO_3 and $MgSO_4$. Solvents were then removed under reduced pressure and analytically pure samples of the epoxide were obtained by either flash column chromatography or preparative TLC, eluting with light petroleum / EtOAc (99:1), containing 2% TEA. The major enantiomer was determined by $[\alpha]^{20}D$ measurements and comparison with the literature, enantioselectivities were determined by either chiral HPLC, or by the use of the a resolving agent in ^1H NMR.

Method C

Water (0.8 mL) and $NaHCO_3$ (67 mg, 0.80 mmol) were added to a test-tube immersed in an ice-bath at 0 °C, equipped with a magnetic stirring bar. Oxone® (132.0 mg, 0.21 mmol) was added and the solution stirred until the effervescence had ceased. The alkene (0.20 mmol) was dissolved in in CH_2Cl_2 (0.5 mL) and added to the aqueous solution. The catalyst (5 mol%) and 18-crown-6 (1 mg, 2.5 mol%) were dissolved in CH_2Cl_2 (0.7 mL) and allowed to cool to 0 °C, and added to the stirring biphasic mixture. The reaction mixture was then vigorously stirred, typically for 2 h at that temperature. To isolate the epoxides, CH_2Cl_2 (10mL) and water (10mL), both previously cooled to around 0 °C, were added. The organic layer was collected and dried over $MgSO_4$. Solvents were removed under reduced pressure and analytically pure samples of the epoxide were obtained by either column chromatography or preparative TLC, eluting with light petroleum / EtOAc (99:1), containing 2% TEA. The major enantiomer was determined by $[\alpha]^{20}D$ measurements, enantioselectivities were determined by either chiral HPLC, or by the use of the a resolving agent in ^1H NMR.

Tetraphenylphosphonium monoperoxysulfate[24]



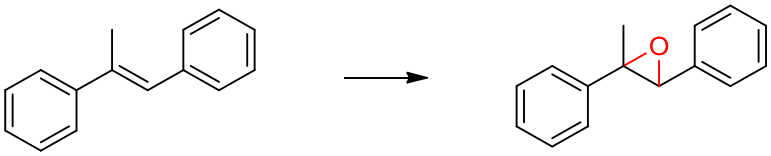
Tetraphenylphosphonium chloride (15.0 g, 40 mmol) was dissolved in CH_2Cl_2 (200 mL) and allowed to cool to 10 °C in a round bottomed flask equipped with a stirrer bar. Oxone® (15.0 g, 48 mmol), previously dissolved in deionised water (300 mL) and allowed to cool to 10 °C, was added over a period of 5 min. The resulting biphasic mixture was stirred vigorously for 1 h. The organic layer was separated and solvents were removed under reduced pressure at RT. The crude colourless solid was transferred to a sintered glass funnel and washed with deionised water (3 x 80 mL). The solid was re-dissolved in CH_2Cl_2 (150 mL) and dried over $MgSO_4$, hexane was added to this solution until a solid precipitate just started to form, the flask was then placed in the freezer overnight. The resulting colourless crystalline solid was filtered and measured to be 94% pure in peroxide, (12.87 g, 71%): ν_{max}(neat)/cm^{-1} 3210, 3060, 1586, 1484, 1435, 1262, 1226, 1162, 1106, 1058, 1041, 996, 721; δ_H (400 MHz; $CDCl_3$) 7.58-7.69 (8H, 8 x C<u>H</u> *arom.*), 7.71-7.80 (8H, 8 x C<u>H</u> *arom.*), 7.82-7.86 (4H, 4 x C<u>H</u> *arom.*), 9.18 (1H, s, -O<u>H</u>). The oxygen content was measured by comparing the integrals of the aromatic signals with with hydroxyl portion.

General procedure for catalytic asymmetric epoxidation of alkenes with TPPP mediated by iminium salts under non-aqueous conditions

The alkene (1 equiv.) and the desired solvent was added to a flask. The solution was allowed to cool down to the required temperature and TPPP was added in one portion and stirred for 2 min. The catalyst was then added as a solid in small portions over 1 min. The reaction was stirred until complete consumption of the starting alkene had been observed, or, until it was judged that no further conversion was occurring by TLC. Et_2O, allowed to cool to 0 °C was added to prepcipitate out TPPP and its reduced by-products. The suspension was filtered

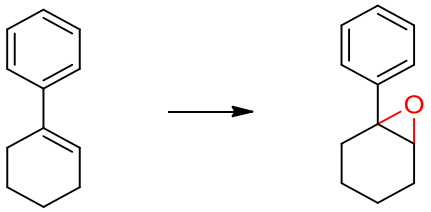
through a thin pad of celite and silica to yield the desired epoxide. If column chromatography was required, it was performed typically eluting with light petroleum / EtOAc (99:1), containing 2% TEA. The major enantiomer was determined by $[\alpha]^{20}D$ measurements and comparison to the literature, enantioselectivities were determined by either chiral HPLC, or by the use of the a resolving agent in ^{1}H NMR.

2-Methyl-(*E*)-2,3-diphenyloxirane[25]



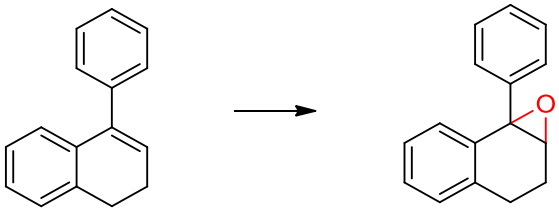
Isolated as a colourless crystalline solid: ν_{max}(neat)/cm^{-1} 3061, 1601, 1495, 1449, 1370, 1278, 1156, 1117, 1065, 1026, 980; δ_H (300 MHz; $CDCl_3$) 1.46 (3H, s, Me), 3.95 (1H, s, =CHAr), 7.30-7.45 (10H, m, CH *arom.*). HPLC conditions - hexane/2-propanol (80:20), oven temp 20 °C, column Chiracel OD-H 01 250 × 4.6 mm, 5 μm particle size, flow rate 1 mL/min, 254 nm: t_r - 4.00 min (–)-(1*S*,2*S*), 6.92 min (+)-(1*R*,2*R*).

1-Phenyl-7-oxa-bicyclo[4.1.0]heptane[25]



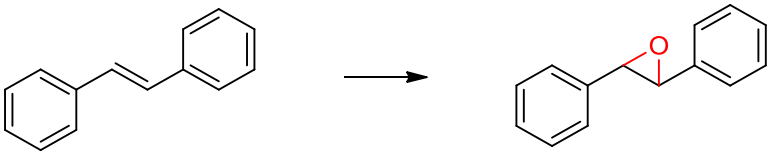
Isolated as a colourless oil: ν_{max}(neat)/cm^{-1} 3083, 1602, 1495, 1445, 1359, 1248, 1174, 1133, 1078, 1030, 993, 974; δ_H (300 MHz; $CDCl_3$) 1.20-1.33 (1H, m, -CH$_2$-), 1.51-1.62 (3H, m, 3 x -CH$_2$-), 1.97-2.05 (2H, m, 2 x -CH$_2$-), 2.16-2.18 (1H, m, -CH$_2$-), 2.24-2.31 (1H, m, -CH$_2$-), 3.10 (1H, t, *J* = 2.0 Hz, -CHO-), 7.26-7.41 (5H, m, 5 x CH *arom.*).

7b-Phenyl-1a,2,3,7b-tetrahydro-1oxa-cyclopropa[*a*]naphthalene[25]



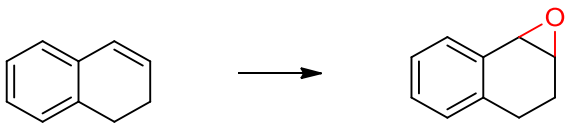
Isolated as a colourless crystalline solid: ν_{max}(neat)/cm^{-1} 3087, 1601, 1493, 1284, 1176, 1158, 1094, 1072, 1028; δ_H (300 MHz; $CDCl_3$) 2.10 (1H, td, *J* = 15.5 Hz, 5.6 Hz, -C$\underline{H}_2$-) 2.48-2.59 (1H, m, -C$\underline{H}_2$-), 2.76 (1H, dd, *J* = 15.5 Hz, 5.5 Hz, -C$\underline{H}_2$-) 2.96-3.07 (1H, m, -C$\underline{H}_2$-), 3.70 (1H, d, *J* = 3.0 Hz, -C$\underline{H}$O-), 7.09-3.29 (4H, m, C$\underline{H}$ *arom.*), 7.45-7.60 (5H, m, C$\underline{H}$ *arom.*). HPLC conditions - hexane/2-propanol (90:10), oven temp 20 °C, column Chiracel OD-H 01 250 × 4.6 mm, 5 μm particle size, flow rate 1 mL/min, 254 nm: t_r - 4.51 min (–)-(1*S*,2*R*), 5.94 min (+)-(1*R*,2*S*).

(E)-2,3-diphenyloxirane[25]



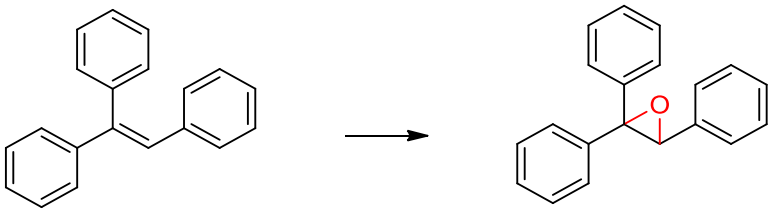
Isolated as a colourless crystalline solid: ν_{max}(neat)/cm^{-1} 3081, 1776, 1602, 1485, 1336, 1155, 1074, 1042, 953; δ_H (400 MHz; $CDCl_3$) 3.87 (2H, s, 2 x -C$\underline{H}$O-), 7.29-7.39 (10H, m, 10 x C$\underline{H}$ *arom.*); δ_C (75 MHz; $CDCl_3$) 63.3 (2C, 2 x -$\underline{C}$HO-), 126.0 (4C, 4 x $\underline{C}$H *arom.*), 128.6 (2C, 2 x $\underline{C}$H *arom.*), 129.3 (4C, 4 x $\underline{C}$H *arom.*), 137.6 (2C, 2 x $\underline{C}$ *quat. arom.*). HPLC conditions - hexane/2-propanol (80:20), oven temp 20 °C, column Chiracel OD-H 01 250 × 4.6 mm, 5 μm particle size, flow rate 1 mL/min, 254 nm: t_r - 4.98 min (–)-(1*S*,2*S*), 6.54 min (+)-(1*R*,2*R*).

1a,2,3,7b-Tetrahydro-1-oxa-cyclopropa[*a*]naphthalene[26]



Isolated as a colourless oil: ν_{max}(neat)/cm^{-1} 3058, 3028, 2931, 2850, 1602, 1492, 1314, 1129, 1088, 1031, 965; δ_H (400 MHz; $CDCl_3$) 1.65-1.84 (1H, m, -C<u>H</u>$_2$-), 2.33-2.42 (1H, m, -C<u>H</u>$_2$-), 2.52 (1H, dd, *J* = 15.5 Hz, 5.5 Hz, -C<u>H</u>$_2$-), 2.67-2.85 (1H, m, -C<u>H</u>$_2$-), 3.71-3.80 (1H, m, -C<u>H</u>O-), 3.81-3.89 (1H, m, -C<u>H</u>O-), 7.05 (1H, d, *J* = 7.2 Hz, C<u>H</u> *arom.*), 7.18-7.35 (2H, m, 2 x C<u>H</u> *arom.*), 7.40 (1H, d, *J* = 7.1 Hz, C<u>H</u> *arom.*).

2,2,3-Triphenyloxirane[26]

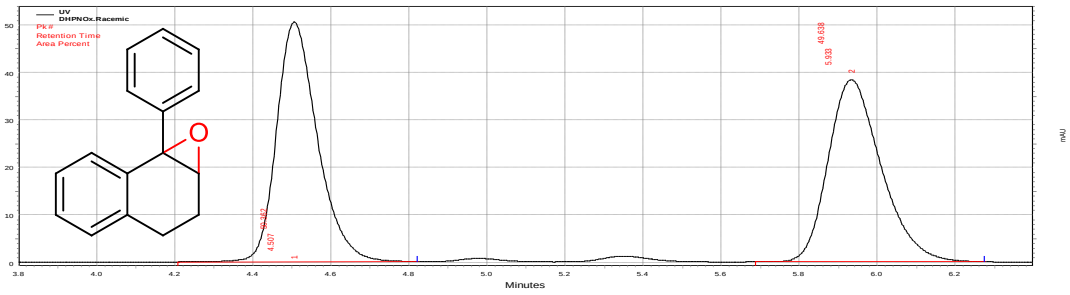


Isolated as a colourless crystalline solid: ν_{max}(neat)/cm^{-1} 3061, 3031, 2956, 2924, 2857, 1604, 1595, 1498, 1471, 1448, 1262, 1220, 741, 699; δ_H (400 MHz; $CDCl_3$) 4.42 (1H, s, -C<u>H</u>O-), 7.13- 5.50 (15H, m, 15 x C<u>H</u> *arom.*). HPLC conditions - hexane/2-propanol (90:10), oven temp 20 °C, column Chiracel OD-H 01 250 × 4.6 mm, 5 μm particle size, flow rate 1 mL/min, 254 nm: t_r – 4.26 min (+)-(*S*), 7.47 min (–)-(*R*).

3.3 Supporting Chiral Separation Data

Area % report of racemic 1-phenyl-3,4-dihydronaphthalene oxide

Data File: C:\EZChrom Elite\Enterprise\Projects\Chris\DHPNOx.Racemic.dat
Method: C:\EZChrom Elite\Enterprise\Projects\yohan\Method\90.10 30min.met



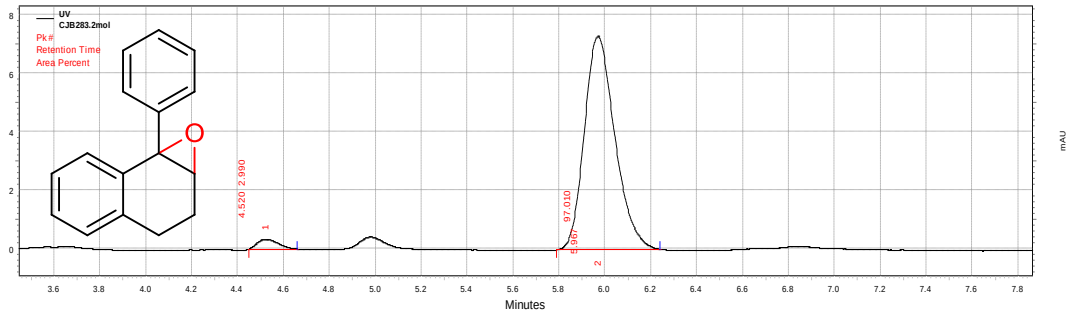
UV Results

Retention Time	Area	Area %	Height	Height %
4.507	1467968	50.36	201731	56.82
5.933	1446888	49.64	153330	43.18

Totals	2914856	100.00	355061	100.00

Area % Report of enantioenriched 1-phenyl-3,4-dihydronaphthalene oxide

Data File: C:\EZChrom Elite\Enterprise\Projects\Chris\CJB281.dat
Method: C:\EZChrom Elite\Enterprise\Projects\yohan\Method\lactoneacidBn.met



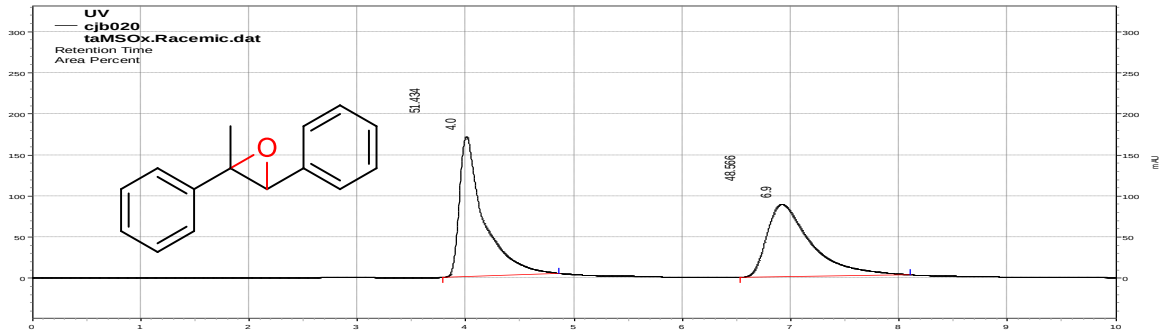
UV Results

Retention Time	Area	Area %	Height	Height %
4.520	8323	2.99	1336	4.37
5.967	270063	97.01	29254	95.63

Totals	278386	100.00	30590	100.00

Area % Report of racemic *trans*-α-methylstilbene oxide

Data File: C:\EZChrom Elite\Enterprise\Projects\Chris\taMSOx.Racemic.dat
Method: C:\EZChrom Elite\Enterprise\Projects\yohan\Method\Trans-Stilbene2.met



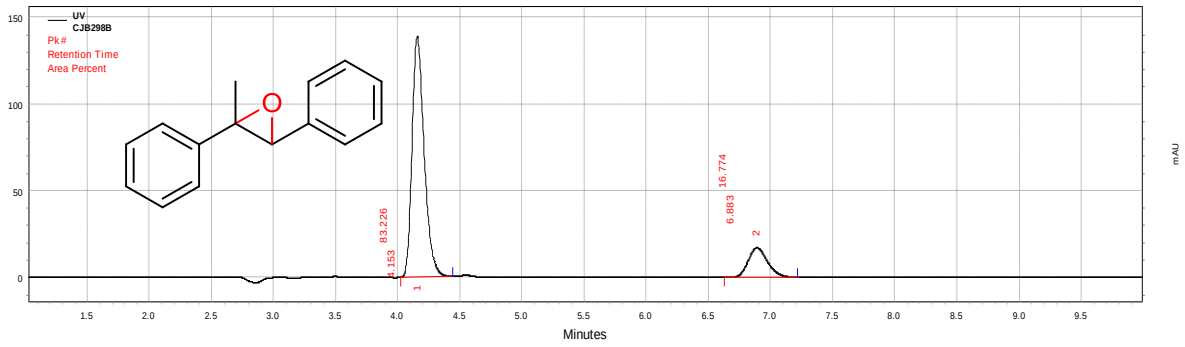
UV Results

Retention Time	Area	Area %	Height	Height %
4.007	10514211	51.43	680756	65.88
6.917	9928030	48.57	352506	34.12

Totals	20442241	100.00	1033262	100.00

Area % Report of enantioenriched *trans*-α-methylstilbene oxide

Data File: C:\EZChrom Elite\Enterprise\Projects\Chris\CJB298B.dat
Method: C:\EZChrom Elite\Enterprise\Projects\yohan\Method\lactoneacidBn.met



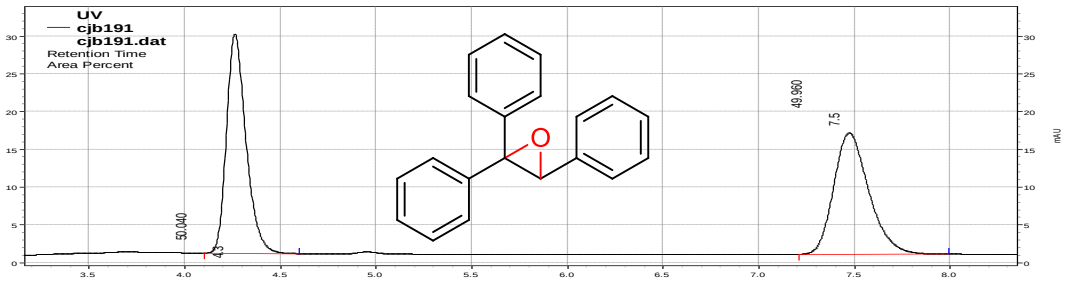
UV Results

Retention Time	Area	Area %	Height	Height %
4.153	3766399	83.23	555041	88.93
6.883	759085	16.77	69085	11.07

Totals	4525484	100.00	624126	100.00

Area % report of racemic triphenylethylene oxide

Data File: C:\EZChrom Elite\Enterprise\Projects\Chris\TPEOx.racemic.dat
Method: C:\EZChrom Elite\Enterprise\Projects\yohan\Method\90.10 30min.met



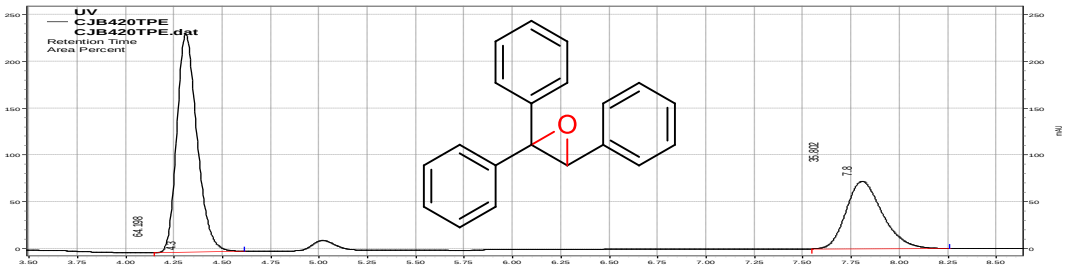
UV Results

Retention Time	Area	Area %	Height	Height %
4.260	822126	50.04	115909	64.36
7.470	820825	49.96	64180	35.64

Totals				
	1642951	100.00	180089	100.00

Area % report of enantioenriched triphenylethylene oxide

Data File: C:\EZChrom Elite\Enterprise\Projects\Chris\CJB420TPE.dat
Method: C:\EZChrom Elite\Enterprise\Projects\yohan\Method\90.10 30min.met



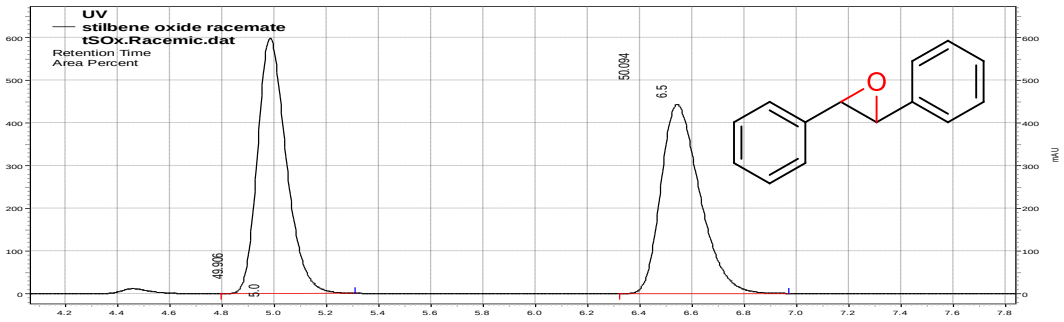
UV Results

Retention Time	Area	Area %	Height	Height %
4.310	6759060	64.20	933684	76.40
7.803	3769479	35.80	288474	23.60

Totals				
	10528539	100.00	1222158	100.00

Area % Report of racemic *trans*-stilbene oxide

Data File: C:\EZChrom Elite\Enterprise\Projects\Chris\tSOx.Racemic.dat
Method: C:\EZChrom Elite\Enterprise\Projects\yohan\Method\Trans-Stilbene2.met



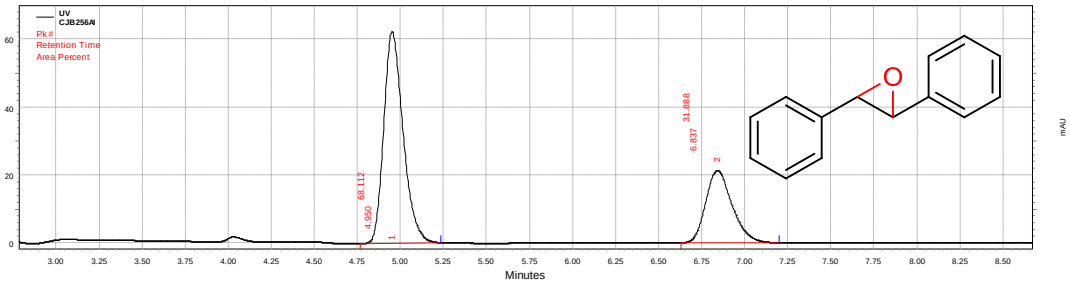
UV Results

Retention Time	Area	Area %	Height	Height %
4.983	18312411	49.91	2394160	57.45
6.543	18381757	50.09	1773413	42.55

Totals				
	36694168	100.00	4167573	100.00

Area % Report of enantioenriched *trans*-stilbene oxide

Data File: C:\EZChrom Elite\Enterprise\Projects\Chris\CJB256A.dat
Method: C:\EZChrom Elite\Enterprise\Projects\yohan\Method\lactoneacidBn.met



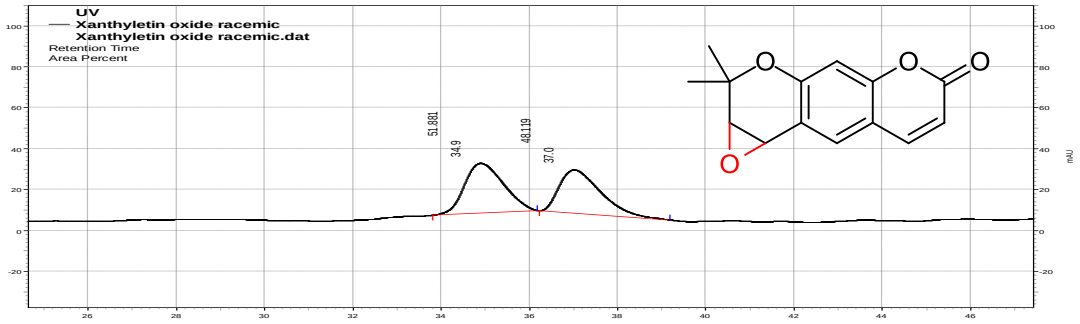
UV Results

Retention Time	Area	Area %	Height	Height %
4.950	1946063	68.11	249137	74.51
6.837	911091	31.89	85225	25.49

Totals				
	2857154	100.00	334362	100.00

Area % Report of (±)-Xanthlyetin Oxide

Data File: C:\EZChrom Elite\Enterprise\Projects\Chris\Xanthoxideracemic.dat
Method: C:\EZChrom Elite\Enterprise\Projects\ben\Method\90.10.1h.met



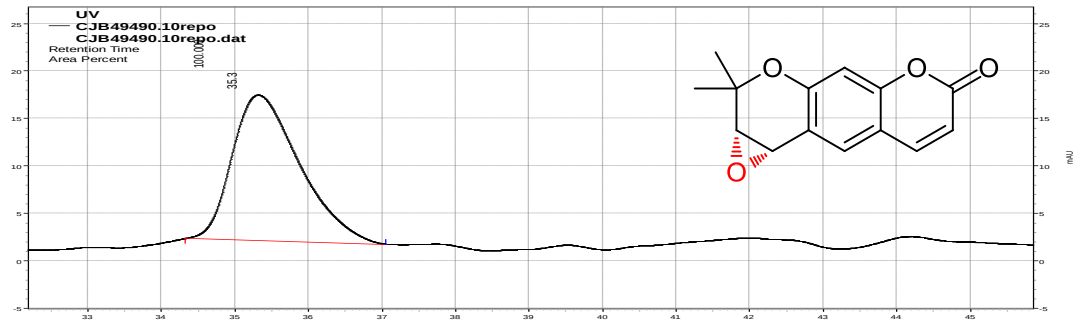
UV Results

Retention Time	Area	Area %	Height	Height %
34.890	5984246	51.88	97467	53.54
37.003	5550421	48.12	84580	46.46

Totals				
	11534667	100.00	182047	100.00

Area % Report of (+)-Xanthlyetin Oxide

Data File: C:\EZChrom Elite\Enterprise\Projects\Chris\CJB49490.10repo.dat
Method: C:\EZChrom Elite\Enterprise\Projects\ben\Method\90.10.1h.met

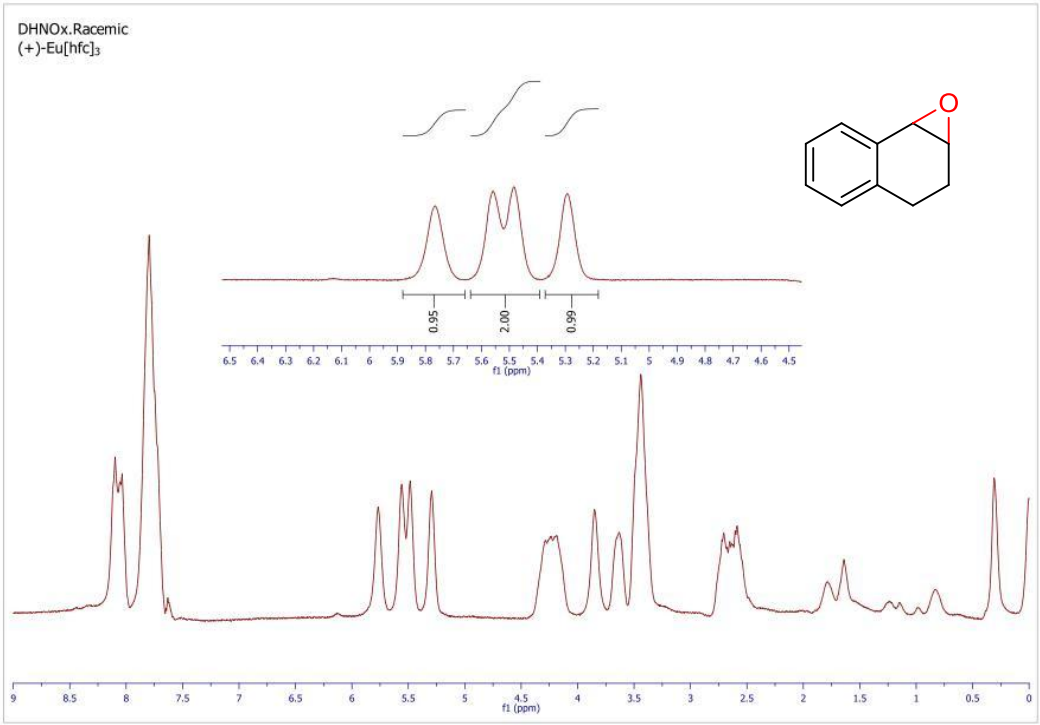


UV Results

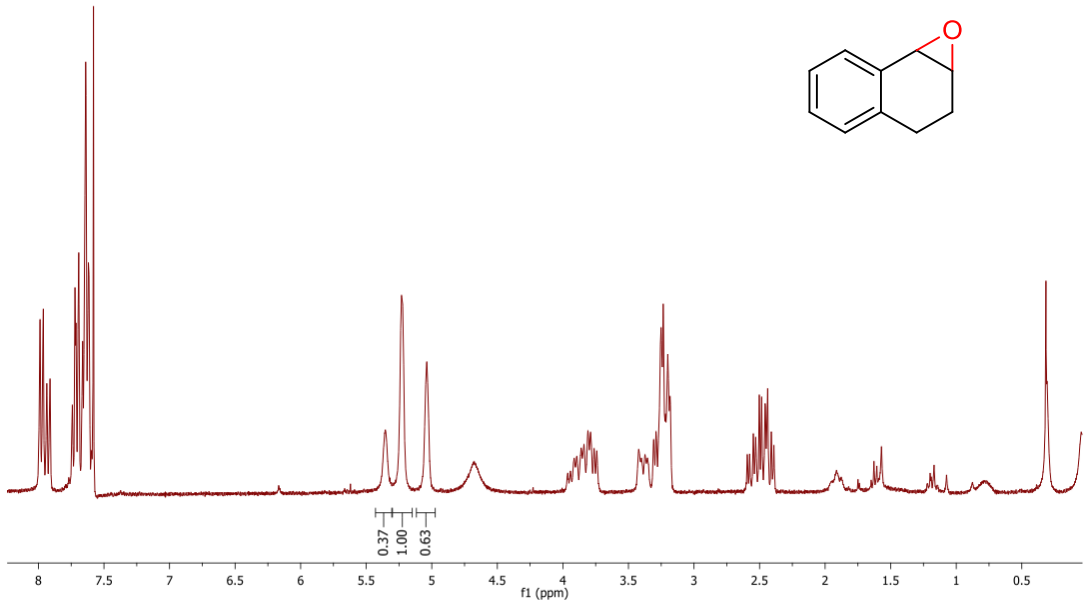
Retention Time	Area	Area %	Height	Height %
35.313	3913986	100.00	61307	100.00

Totals				
	3913986	100.00	61307	100.00

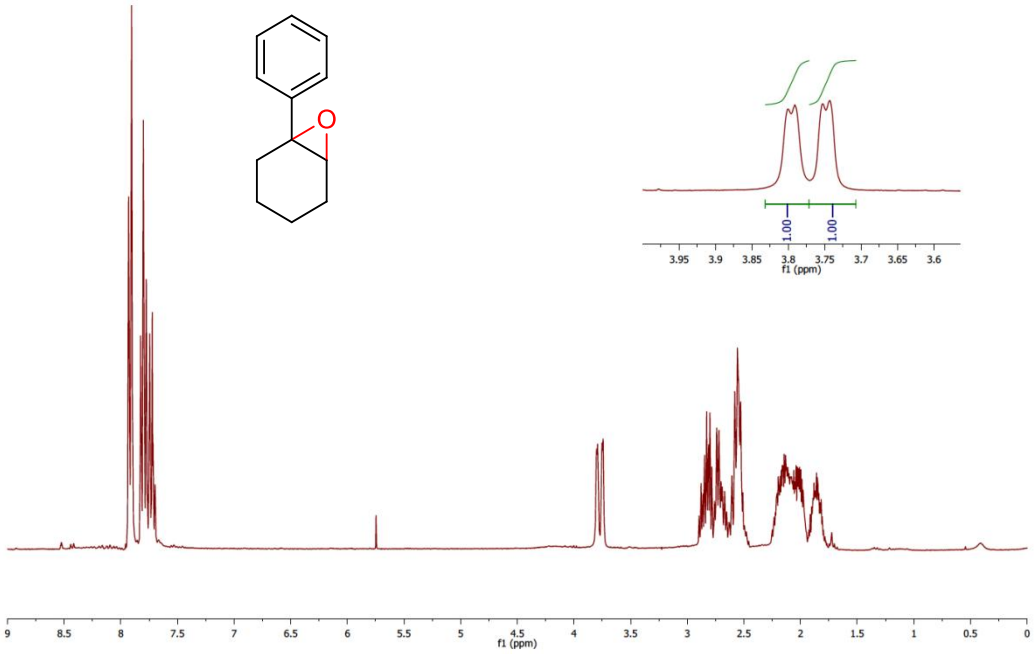
NMR spectrum of racemic 1,2-dihydonaphthalene oxide



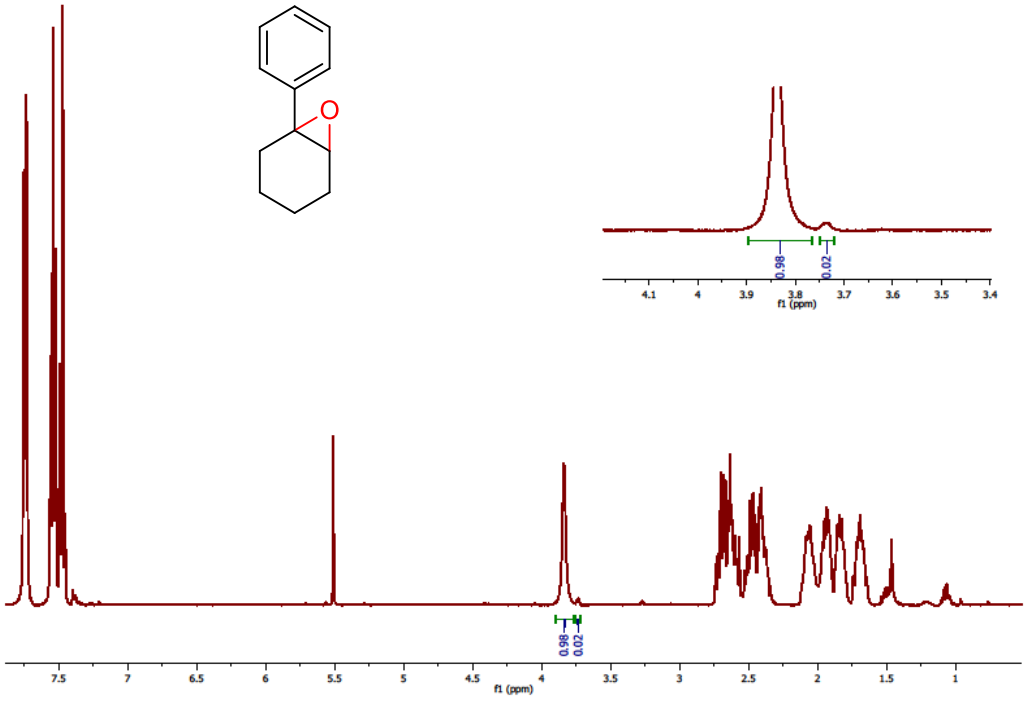
NMR spectrum of enantioenriched 1,2-dihydronaphthalene oxide



NMR of racemic 1-phenyl-3,4-cyclohexene oxide

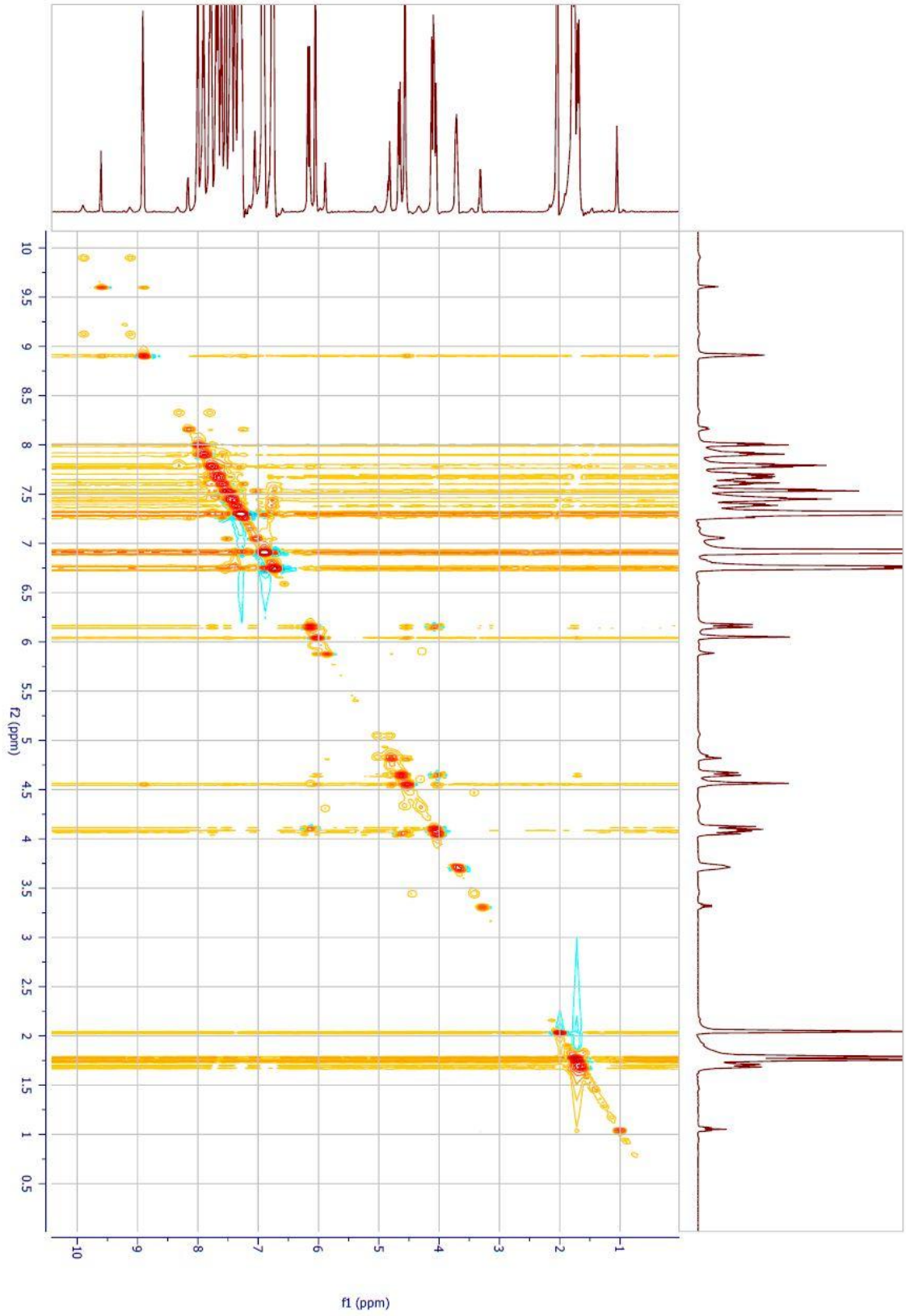


NMR sample of enantioenriched 1-phenylcyclohexene oxide

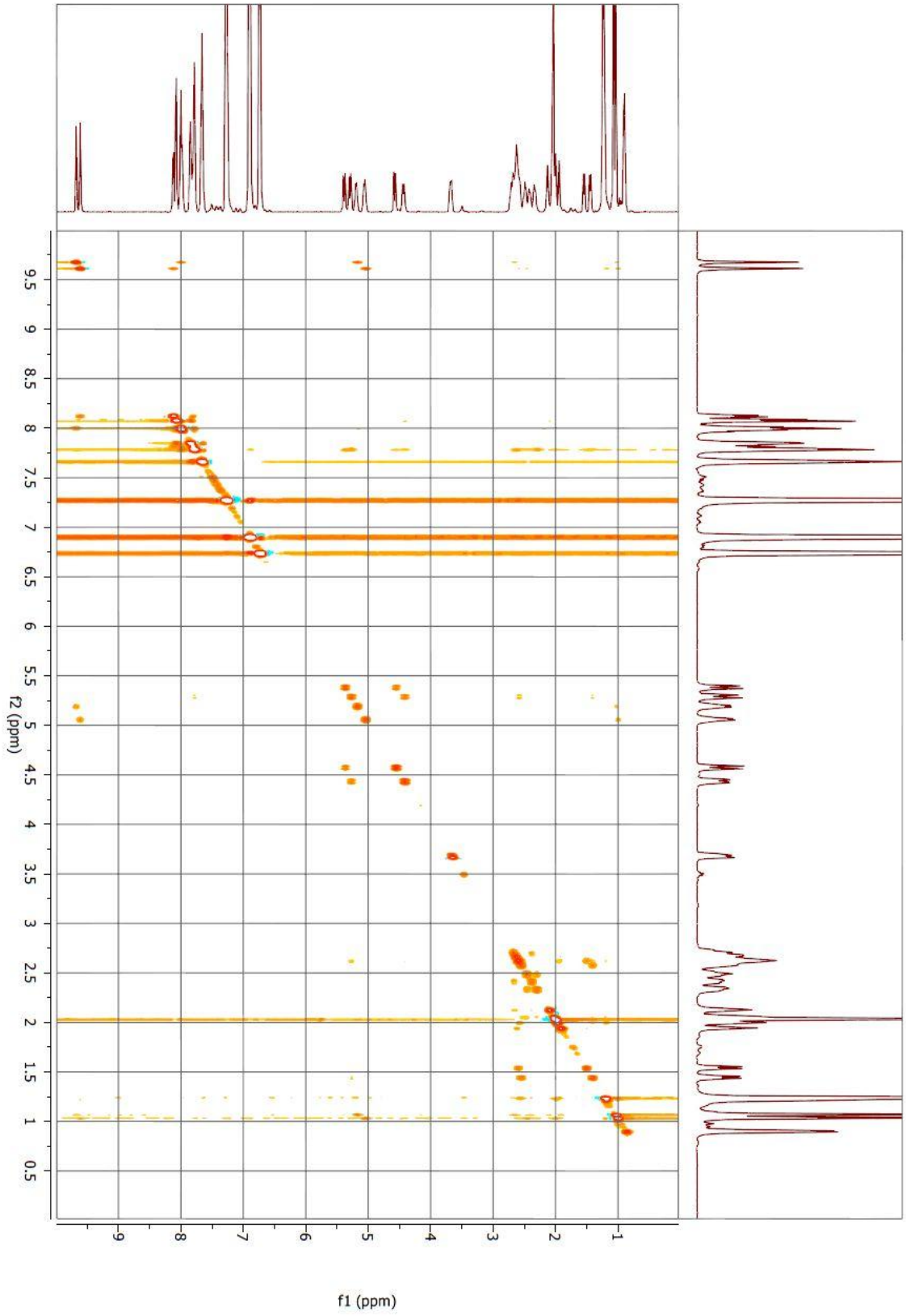


3.4 Supplementary NMR Data

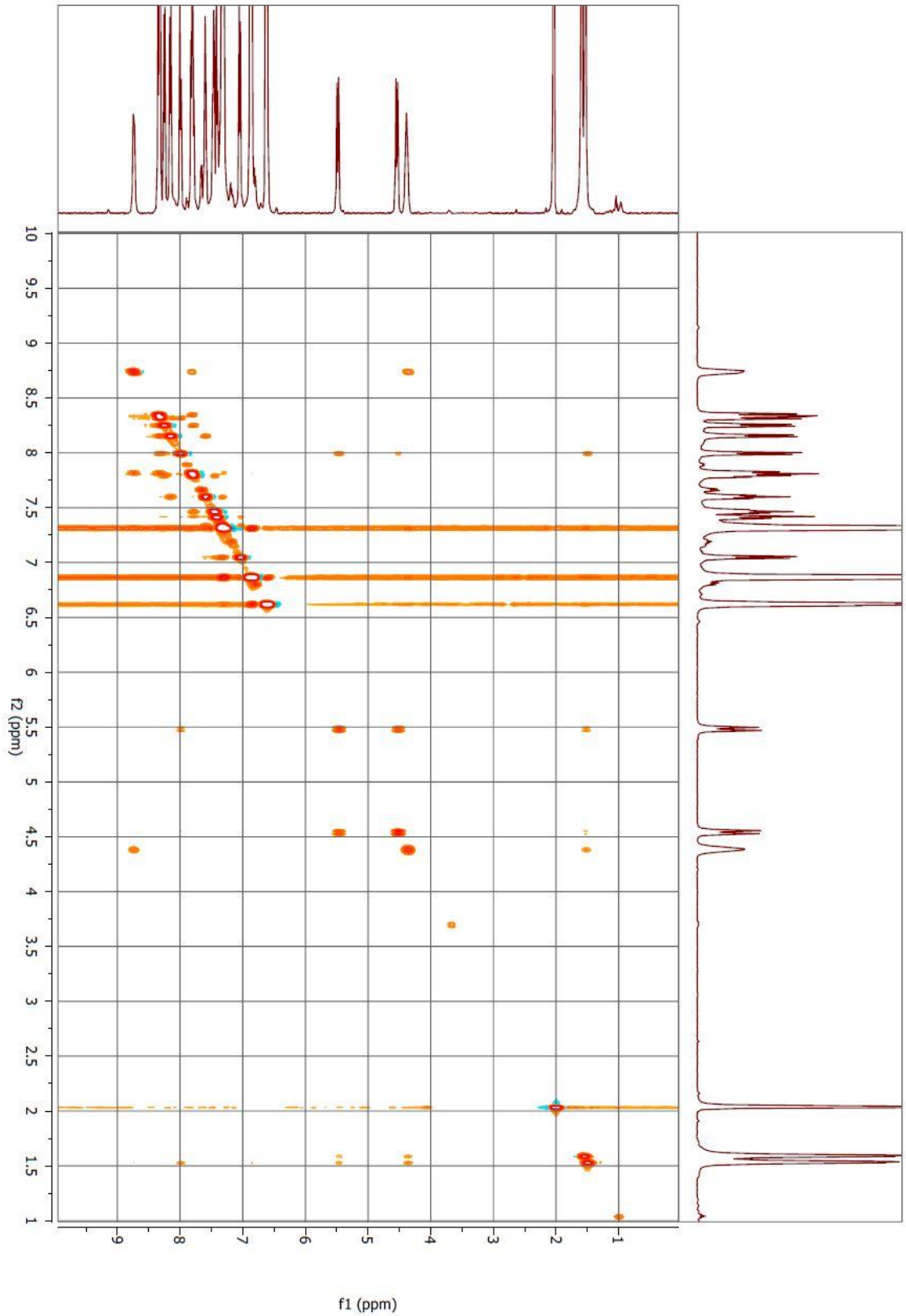
NOESY NMR Spectra for **169** @ -80C



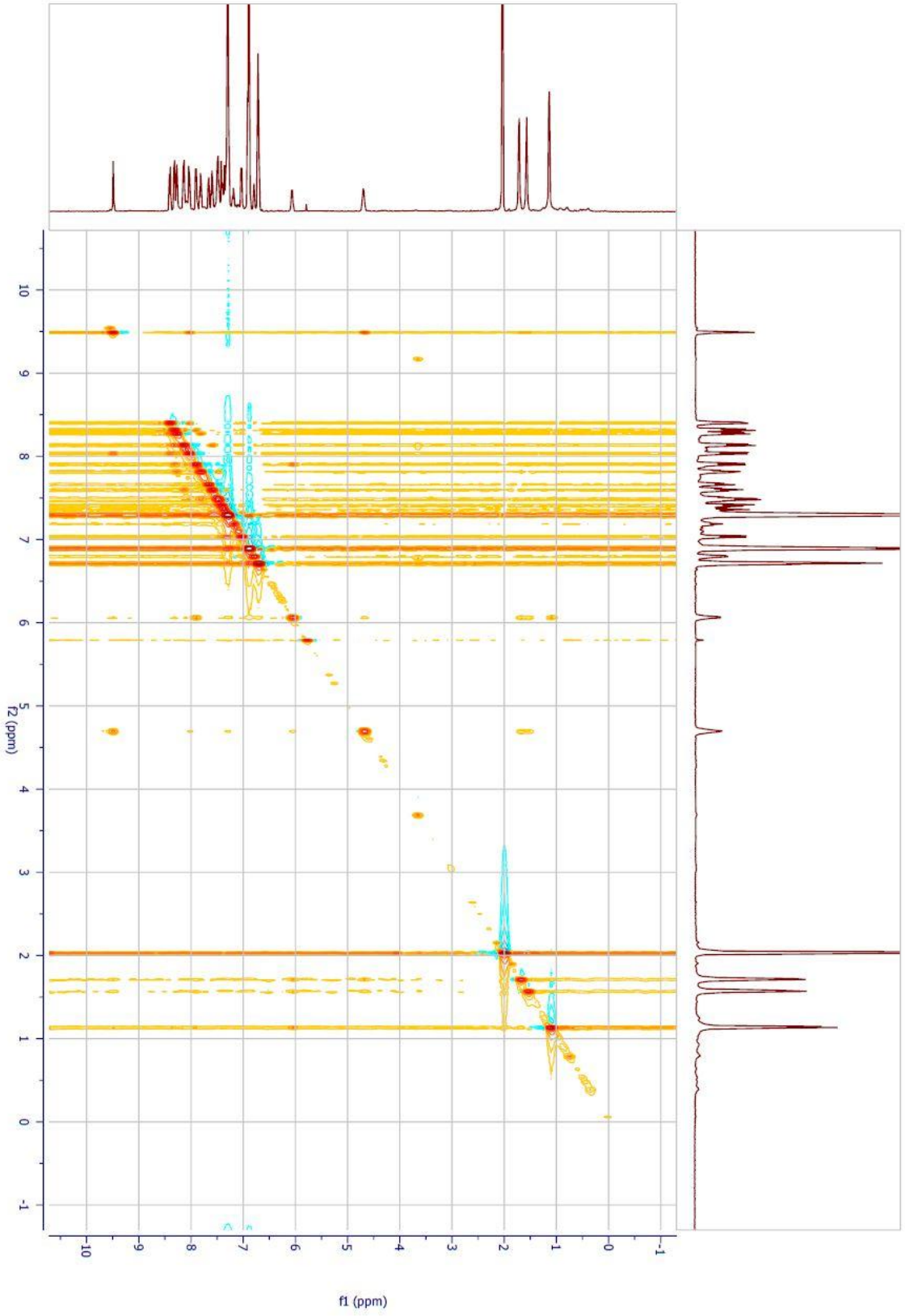
NOESY NMR Spectra for **170** @ -80C



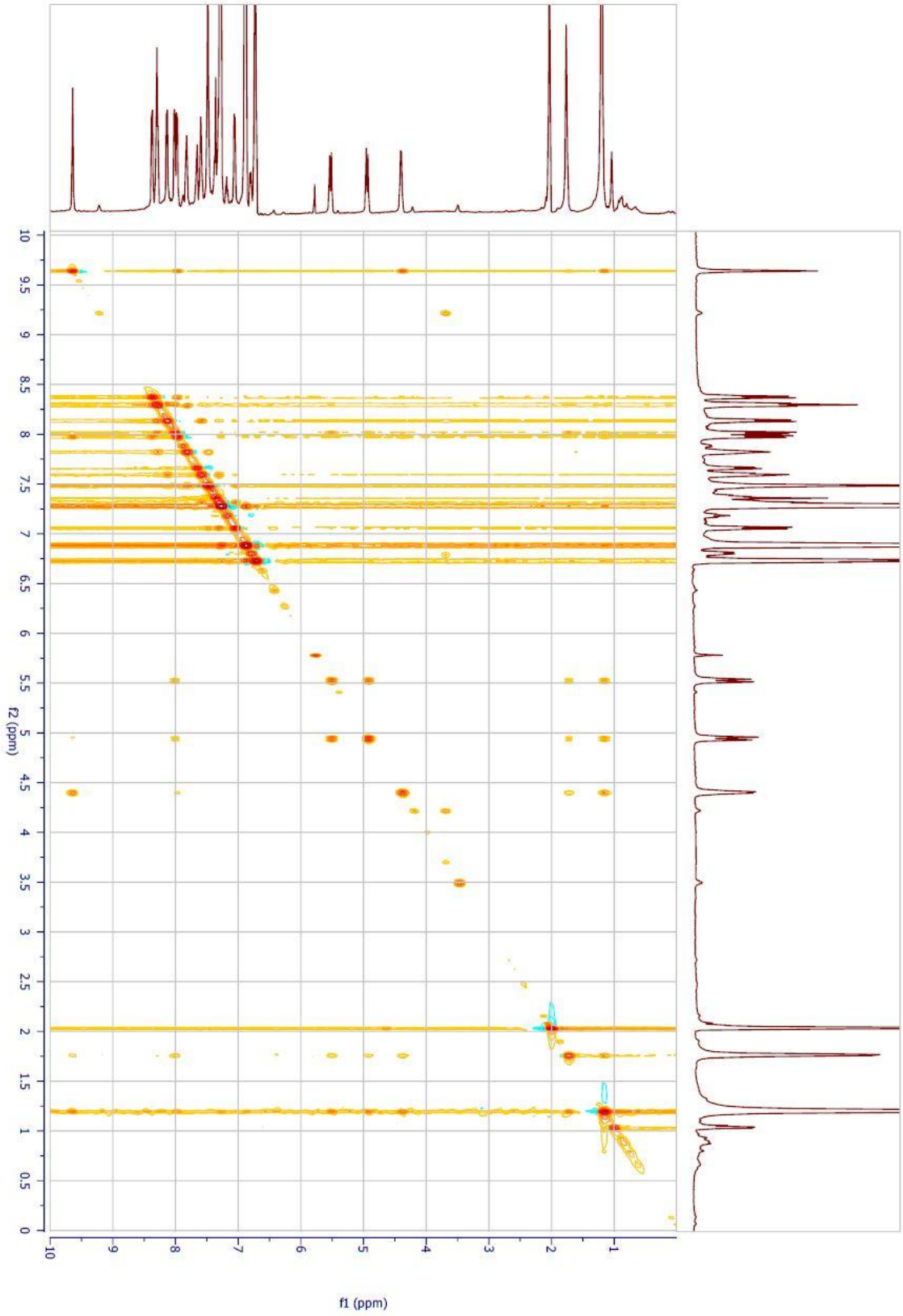
NOESY NMR Spectra for **224** @ -80C



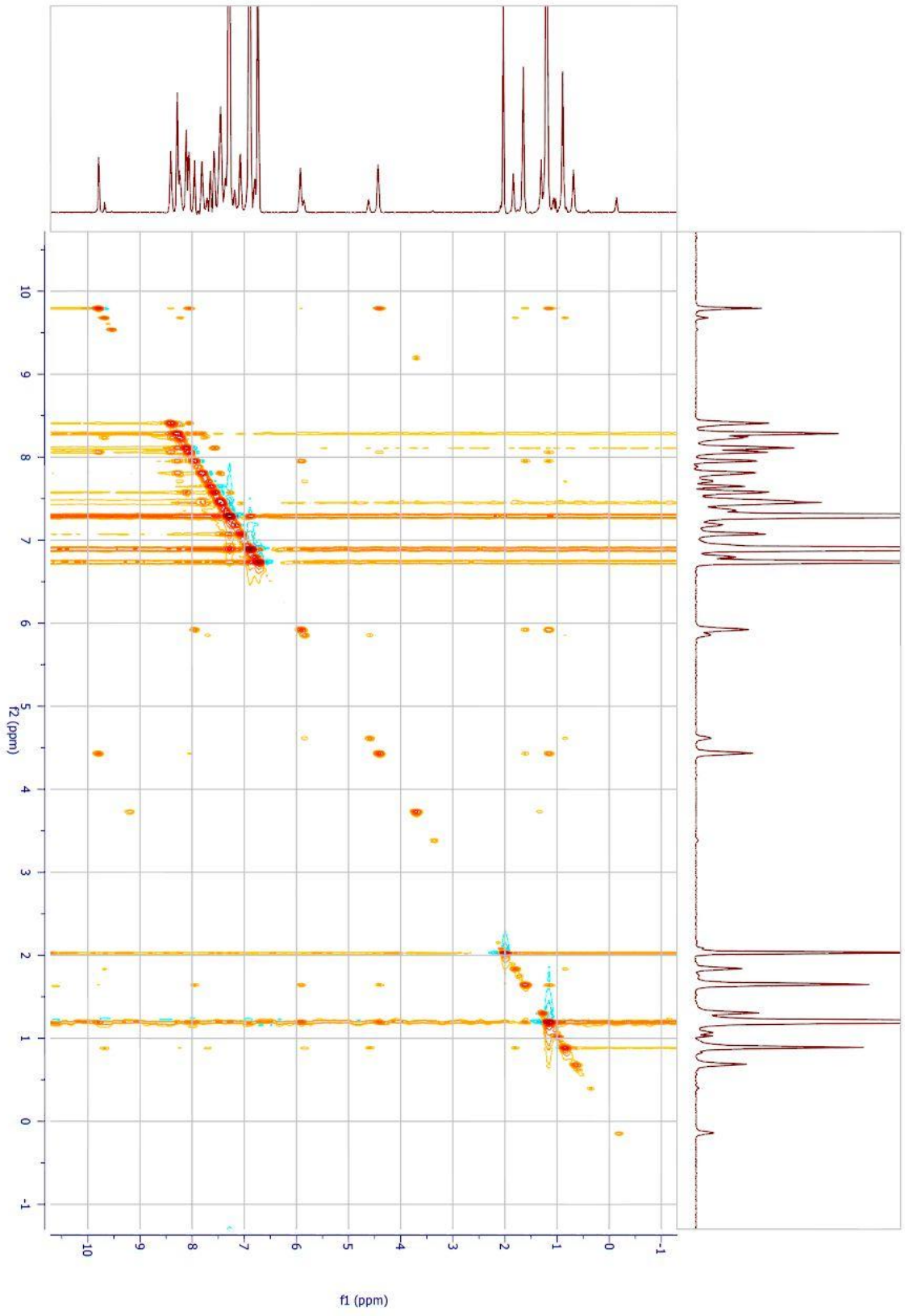
NOESY NMR Spectra for **234** @ -80C



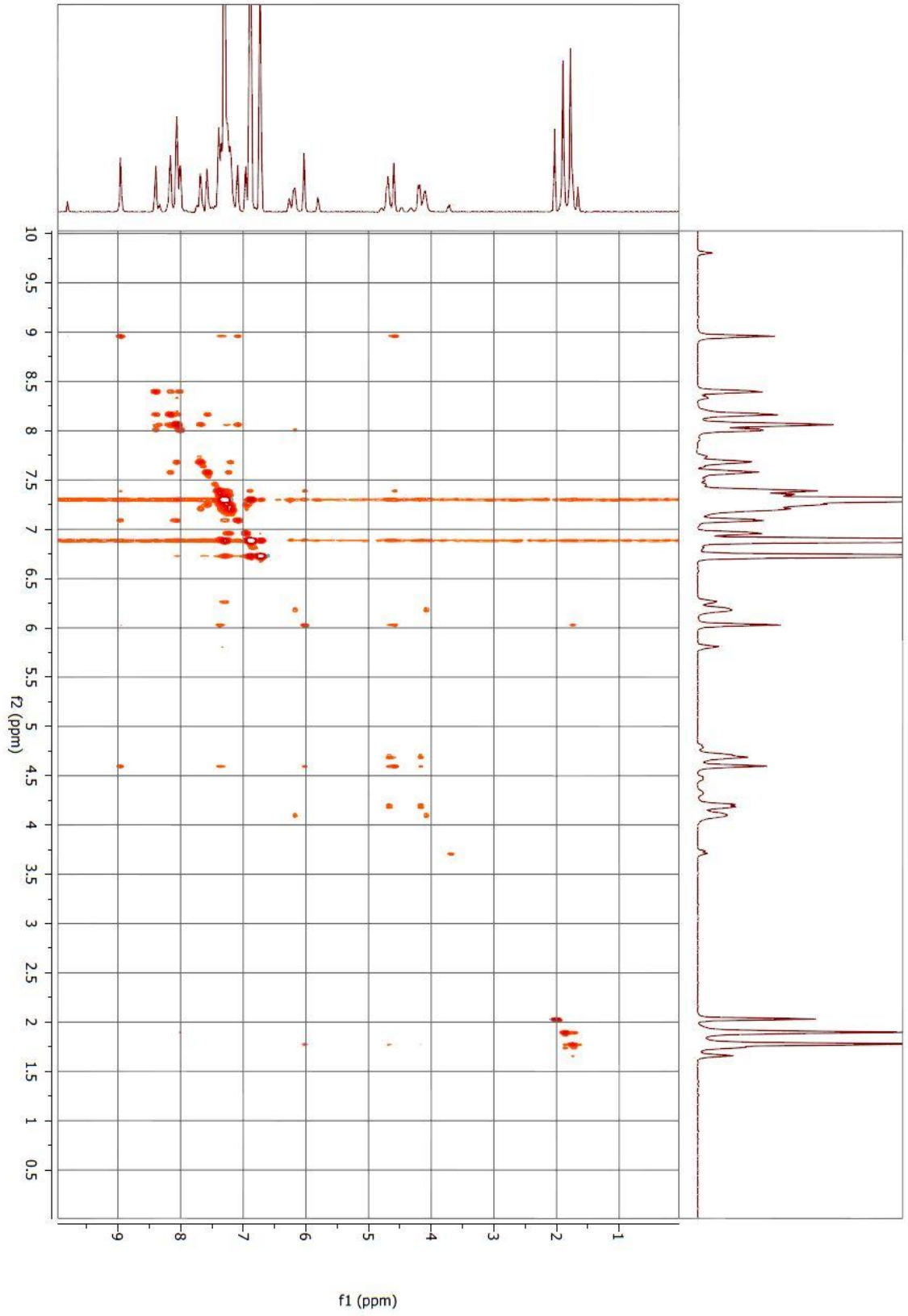
NOESY NMR Spectra for **222** @ -80C



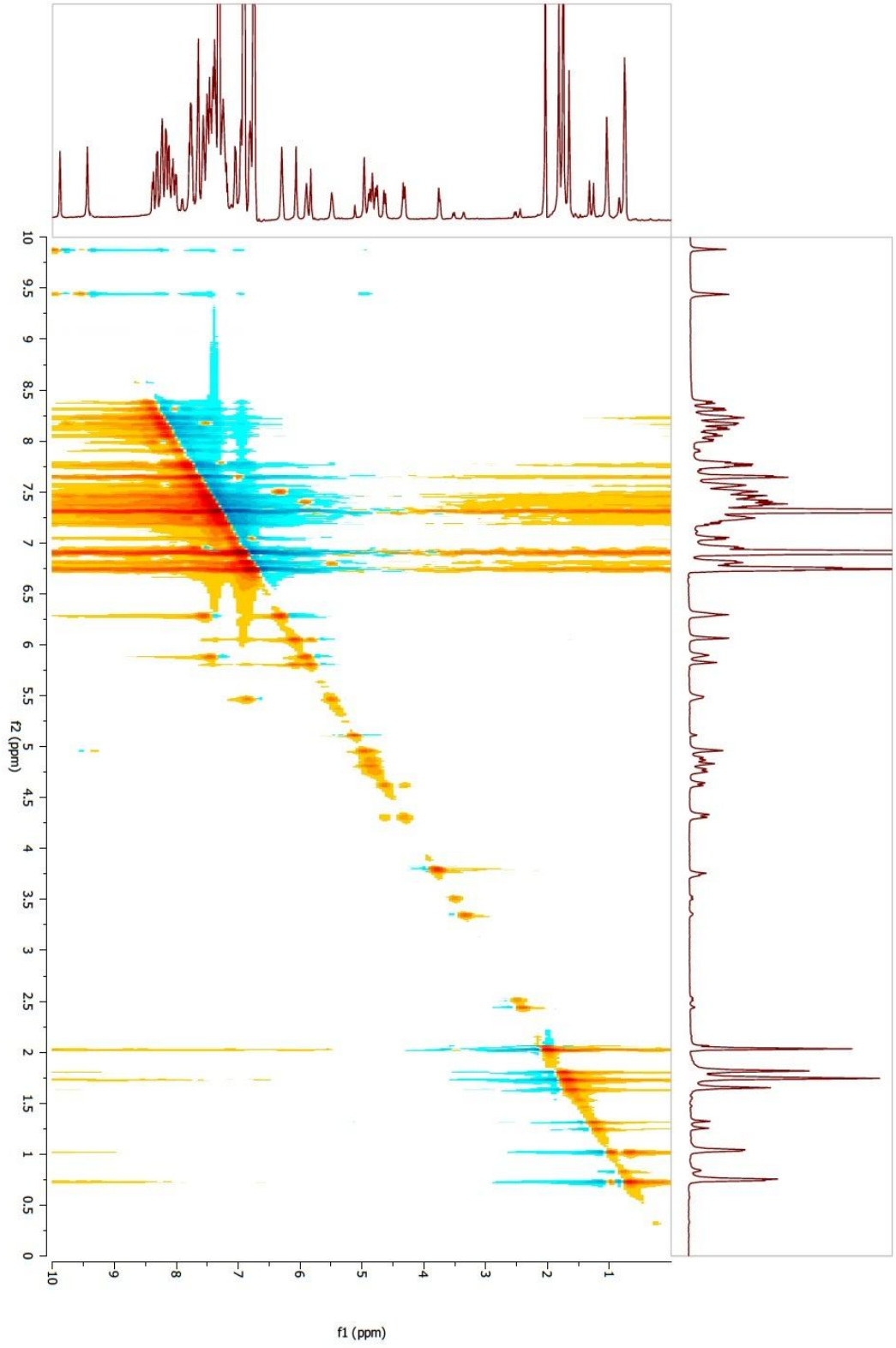
NOESY NMR Spectra for **225** @ -80C



NOESY NMR Spectra for **171** @ -80C



NOESY NMR Spectra **232** @-80C



3.5 X-Ray Data Reports

Crystal Data and Structure Refinement for 228

Identification code	page12	
Empirical formula	C35 H33 N O2	
Formula weight	499.62	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 11.198(3) Å	α= 90°.
	b = 12.171(3) Å	β= 90°.
	c = 19.804(5) Å	γ = 90°.
Volume	2699.0(11) $Å^3$	
Z	4	
Density (calculated)	1.230 Mg/m^3	
Absorption coefficient	0.075 mm^{-1}	
F(000)	1064	
Crystal size	0.2000 x 0.2000 x 0.2000 mm^3	
Theta range for data collection	1.96 to 25.33°.	
Index ranges	-13<=h<=13, -11<=k<=14, -22<=l<=23	
Reflections collected	17103	
Independent reflections	4914 [R(int) = 0.0687]	
Completeness to theta = 25.00°	99.8 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.7911	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4914 / 0 / 343	
Goodness-of-fit on F^2	0.978	
Final R indices [I>2sigma(I)]	R1 = 0.0526, wR2 = 0.1188	
R indices (all data)	R1 = 0.0669, wR2 = 0.1277	
Absolute structure parameter	0.7(17)	
Largest diff. peak and hole	0.243 and -0.226 $e.Å^{-3}$	

Crystal Data and Structure Refinement for 278

Identification code	page20	
Empirical formula	C17 H18 O5	
Formula weight	302.31	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 23.18(3) Å	α= 90°.
	b = 5.353(6) Å	β= 90.93(3)°.
	c = 12.036(13) Å	γ = 90°.
Volume	1493(3) $Å^3$	
Z	4	
Density (calculated)	1.345 Mg/m^3	
Absorption coefficient	0.099 mm^{-1}	
F(000)	640	
Crystal size	0.20 x 0.08 x 0.08 mm^3	
Theta range for data collection	2.42 to 25.35°.	
Index ranges	-26<=h<=26, -6<=k<=5, -14<=l<=12	
Reflections collected	4642	
Independent reflections	2175 [R(int) = 0.2869]	
Completeness to theta = 25.00°	98.0 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.000 and 0.9031	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2175 / 1 / 200	
Goodness-of-fit on F^2	1.187	
Final R indices [I>2sigma(I)]	R1 = 0.1817, wR2 = 0.4014	
R indices (all data)	R1 = 0.2189, wR2 = 0.4379	
Absolute structure parameter	3(5)	
Extinction coefficient	0.031(10)	
Largest diff. peak and hole	0.600 and -0.427 $e.Å^{-3}$	

3.5 References for Chapter Three

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