RECENT ADVANCES IN IMINIUM SALT CATALYSED ASYMMETRIC EPOXIDATION

By

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ABSTRACT

RECENT ADVANCES IN IMINIUM SALT CATALYSED ASYMMETRIC EPOXIDATION

DAVID DAY

Key Terms: Epoxidation, Olefin, Iminium-salt, Kinetic resolution, Chromene, Dihydroquinoline, Tetrahydroquinoline

The research in this thesis depicts some of the most current developments in the area of asymmetric epoxidation of alkenes using chiral iminium salt catalysts. The first chapter reviews past and present developments in; catalytic asymmetric epoxidation, and covers the application of this reaction towards the kinetic resolution of racemic olefins.

Chapter two is separated into two key areas; (i) asymmetric epoxidation as a tool in the kinetic resolution of racemic chromene substrates, and (ii) investigations into the asymmetric epoxidation of new *N*-protected dihydroquinoline substrates. In the first part of chapter two, the first examples of kinetic resolution in epoxidation reactions using iminium salt catalysts are reported, providing up to 98% ee in the epoxidation of racemic *cis*-chromenes.

The second part of chapter two details the first known examples of asymmetric epoxidation upon nitrogen-protected dihydroquinoline substrates, affording enantioselectivities as high as 73% ee.

In both parts of chapter two, non-aqueous epoxidation conditions were employed using Page's dihydroisoquinolinium iminium salt catalyst. The later part of chapter two introduces a biphenylazepinium iminium salt catalyst used under aqueous epoxidation conditions.

Chapter three includes experimental data for all the compounds mentioned in chapter two, with chapter four containing HPLC traces to show determination of enantiomeric excess of epoxides, and enantioenriched alkene traces.

ACKNOWLEDGEMENTS

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Finally, I'd like to dedicate this thesis to my family; Rosemary, Edward, Martin & Emily for all their patience, love and support they have given me during this time of study.

ABBREVIATIONS

Å	Ångström
Ac	acetyl
$[\alpha]_D$	specific optical rotation at the sodium D line
aq.	aqueous
Ar	aryl
arom.	aromatic
B:	base
Bu	butyl
BOC	*tert*-butyoxycarbonyl
b.p.	boiling point
n-Bu	normal butyl
t-Bu	tertiary butyl
Bz	benzoyl
°C	degrees Celcius
cm^{-1}	wavenumber
conv.	conversion
CSA	10-camphorsulfonic acid
δ	chemical shift
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DET	diethyl tartrate
DHPN	dihydrophenylnaphthalene
DHQ	dihydroquinoline
DIPT	diisopropyl tartrate
d.r.	diastereomeric ratio
DMAP	4-dimethylaminopyridine

DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMP	dimethyoxypropane
E^+	electrophile
ee	enantiomeric excess
eq.	equivalent(s)
Et	ethyl
g	gram(s)
h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
IPA	*iso*-propyl alcohol
IR	infra red
J	coupling constant
M	molar
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MHz	megaHertz
min	minutes(s)
mmol	millimole(s)
mL	millilitre(s)
m.p.	melting point
MS	molecular sieves
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Nuc	nucleophile

Oxone®	potassium monoperoxysulfate ($2KHSO_5 . KHSO_4 . K_2SO_4$)
Pd/C	Palladium on carbon (10% Pd)
Ph	phenyl
ppm	parts per million
*p*TSA	*para*-toluenesulfonic acid
i-Pr	*iso*-propyl
i-PrOH	*iso*-propanol
n-Pr	normal propyl
R	alkyl
r.t.	room temperature
salen	salicylideneaminato ligand
SM	starting material
TBHP	tetrabutylhydrogen peroxide
TEA	triethylamine
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THQ	tetrahydroquinoline
TLC	thin layer chromatography
TPPP	tetraphenylphosphonium monoperoxysulfate
Ts	*para*-toluenesulfonyl

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CHAPTER ONE: INTRODUCTION

1.0 Introduction: Epoxides

Epoxides, or oxiranes, are 3-membered ring systems containing an oxygen atom and two atoms of carbon (Figure 1).

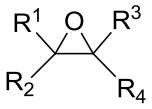
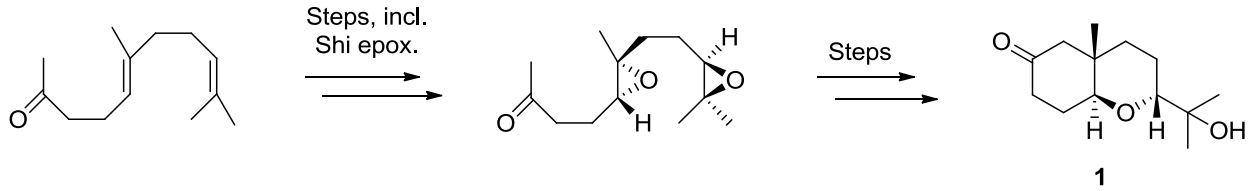


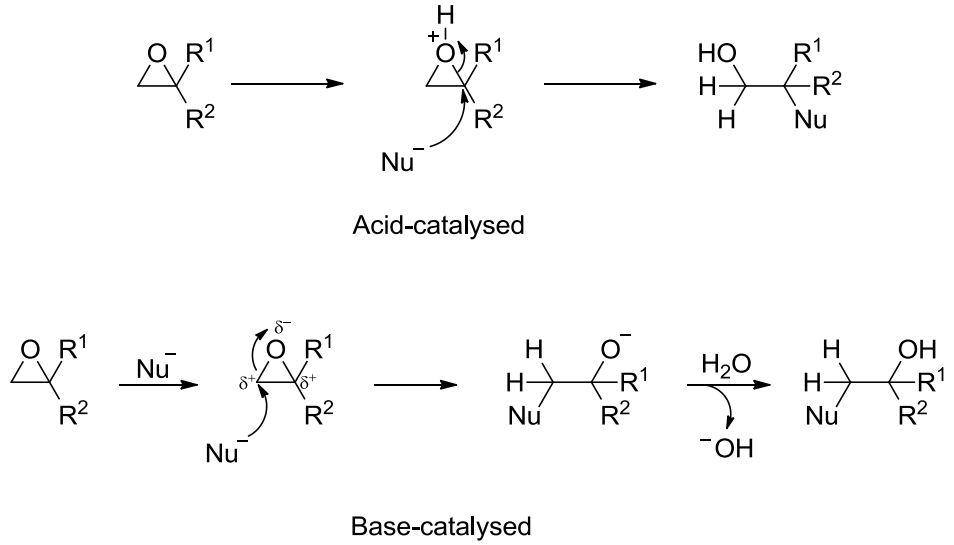
Figure 1. The epoxide moiety

Epoxides have been utilised as key synthetic tools in the synthesis of some complex organic compounds and natural products.[1] Hardcastle's total synthesis of Durgamone **1** is one of many interesting examples in the literature that utilises an epoxide moiety as the key synthetic intermediate (Scheme 1). Hardcastle employed Shi's epoxidation methodology to generate the epoxide intermediate, which was then able to undergo an intramolecular polyepoxide cyclisation process, affording the target molecule in good yield.[2]



Scheme 1. Hardcastle's synthesis of Durgamone **1**

Epoxides are more stable than some other three-membered ring systems, such as bromonium ions, but they have three internal bond angles of ~60°, creating a large amount of ring strain. Nucleophilic attack on the epoxide releases this ring strain, allowing the preferential tetrahedral angle of 109.5° to be restored. The example below illustrates how nucleophilic addition to an epoxide can occur under acid- and base-catalysed reactions (Scheme 2).



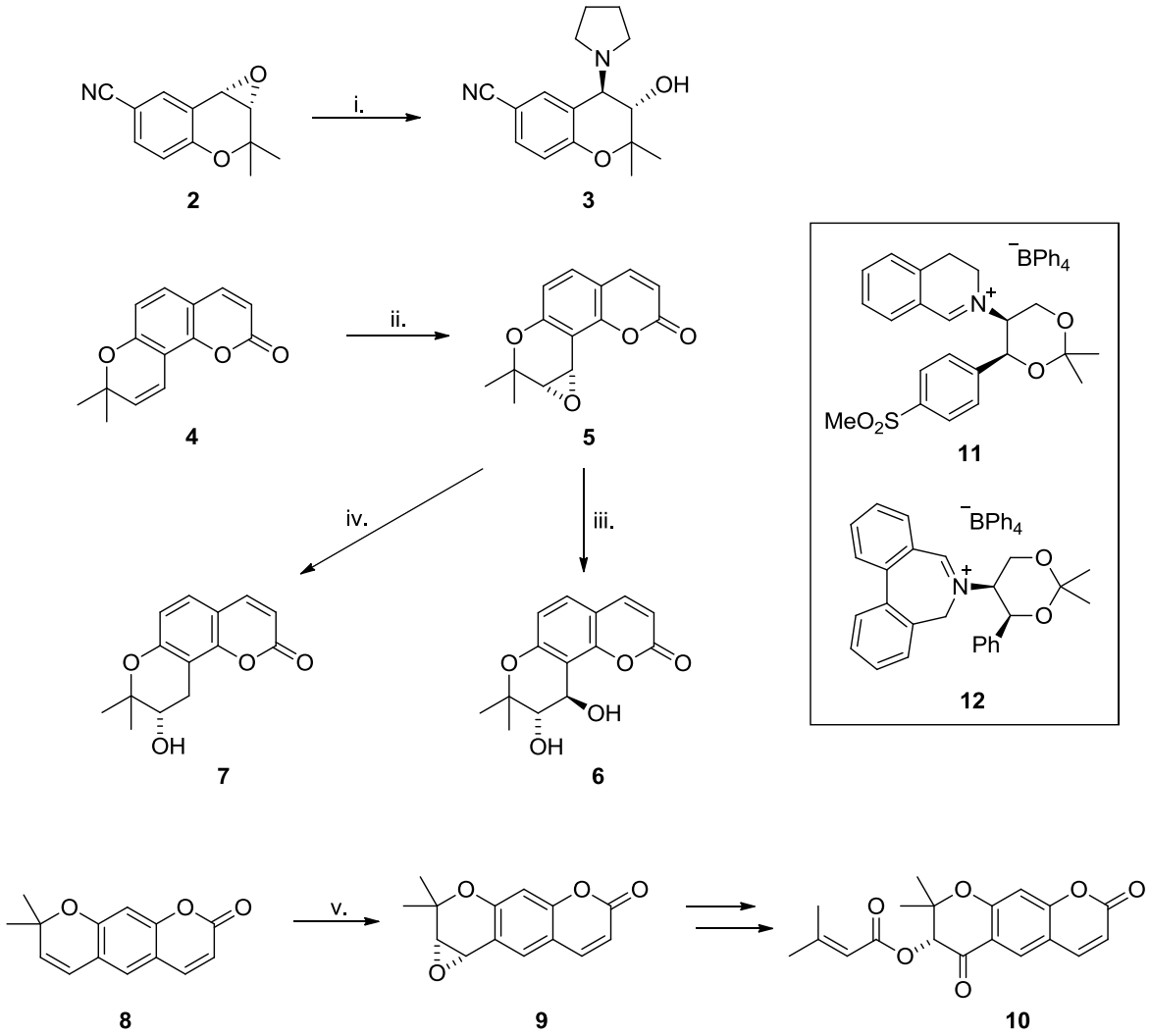
Scheme 2. Nucleophilic addition to an epoxide

Under acid-catalysed conditions, nucleophilic attack occurs at the most substituted carbon atom of the unsymmetrical epoxide. When R^1 and R^2 are alkyl substituents, they stabilize the positive charge on the carbon at the tertiary end of the protonated epoxide. Under base-catalysed conditions, the epoxide oxygen is a poor leaving group and attack occurs at the least substituted carbon atom of the unsymmetrical epoxide by a strong nucleophile. The epoxide ring opening reactions are stereospecific; a *cis*-epoxide undergoes nucleophilic attack with inversion giving the *trans*-product (Scheme 3).

Scheme 3. Nucleophilic attack from underneath the upward facing *cis*-epoxide

Epoxide ring-opening methodology has been applied to the synthesis of many natural products and drug molecules, in order to generate the correct stereochemistry in the desired target molecule. This approach was utilised by Page in the total synthesis of anti-hypertensive agent levcromakalim (**3**) in 2005,[3] natural products *trans*-khellactone (**6**) and lomatin (**7**) in 2009,[4] and most recently (+)-scuteflorin A (**10**) in 2012.[5] The enantioenriched epoxide intermediates generated from chiral iminium-salt mediated catalytic epoxidation processes were subjected to

ring-opening procedures, affording the desired compounds in high enantiomeric excesses in each case (Scheme 4).



Scheme 4. *Reagents and conditions*: (i) pyrrolidin-2-one, NaH, DMSO, r.t., 4 h, 52%; (ii) TPPP (2 eq.), iminium salt **11** (10 mol%), $CHCl_3$, -30°C, 24 h, 65%; (iii) 1M H_2SO_4/CH_3COCH_3 (1:2 ratio), r.t., 1 h, 95%; (iv) $NaBH_3CN$ (1 eq.), $BF_3.OEt_2$, THF, 0 °C, 30 min, 92%; (v) TPPP, iminium salt **12** (5 mol%), $CHCl_3$, -30°C, 30 h, 97%.

1.1 Natural Product Epoxides

The epoxide functional group can be found within numerous natural products, many of which exert specific biological activities. The pressure on pharmaceutical companies to supply an ever growing demand for more potent pharmaceuticals to be used in curing or treatment of illnesses has never been greater, with many drug molecules still being based upon natural product structures. This can be illustrated with the anti-cancer drug Ixempra® **13**, a semi-synthetic lactam derivative, which is based upon the bacterial natural product epothilone B **14** (Figure 2).[6]

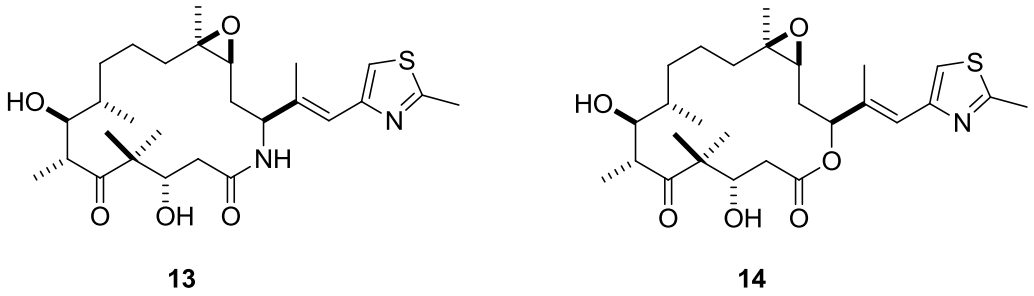
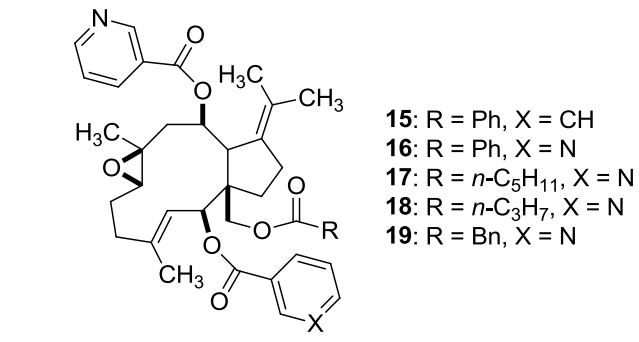


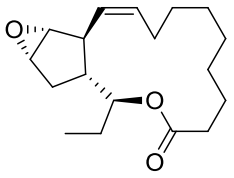
Figure 2. Advanced breast cancer drug Ixempra® and natural product Epothilone B

New natural products containing this core epoxide motif are being discovered frequently from sources including bacteria, plants (**15**-**19**), and marine fungi (**20**-**21**) (Figure 3).

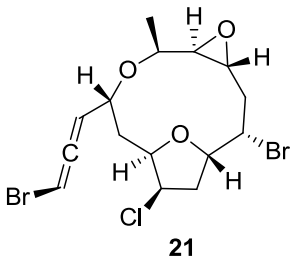


15: R = Ph, X = CH
16: R = Ph, X = N
17: R = *n*-C_5H_{11}, X = N
18: R = *n*-C_3H_7, X = N
19: R = Bn, X = N

Isolated from *Nigella Sativa* (black cumin)
Potent lipid metabolism-promoting activity



20
Isolated from various brown algae
Chemical defence against herbivores



21

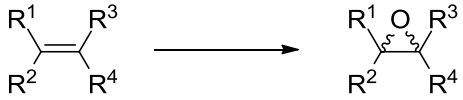
Isolated from *Laurencia Marilzae* (red algae)
Potential biological activity

Figure 3. Nigellamines **15**-**19**,[7] Ecklonialatone B **20**,[8] and 12-Epoxyobtusallene **21.**[9]

1.2 Epoxidation Reactions

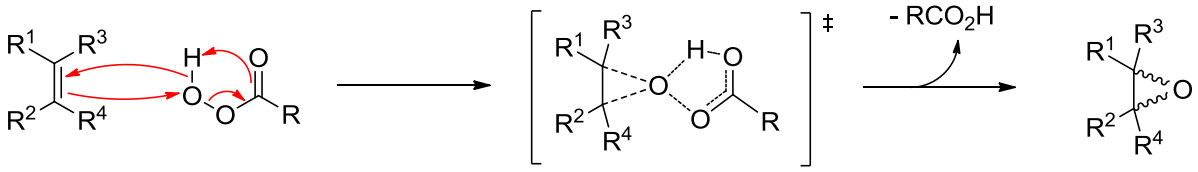
1.2.1 Prileschajew Reaction

The first non-selective epoxidation reactions using peroxycarboxylic acids were first discovered in 1909 by Prileschajew. Isolated double bonds within simple and complex molecules can be oxidized, forming oxiranes, as racemic mixtures (Scheme 5).[10]



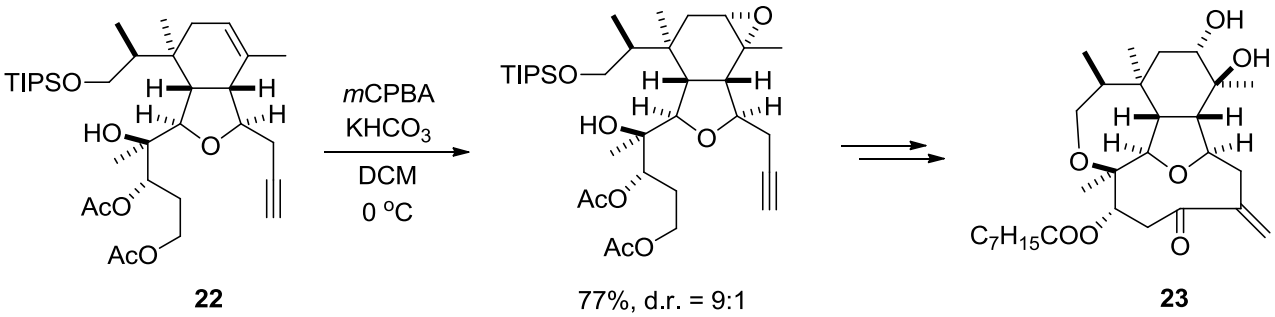
Scheme 5. *Reagents and conditions*: peroxycarboxylic acid (1 eq.), $CHCl_3/CH_2Cl_2/C_6H_6/(CH_3)_2CO$, 0 – 30 °C

The mechanism for the stereospecific Prileschajew epoxidation involves *syn* addition of electrophilic oxygen to the nucleophilic alkene double bond in a concerted process (Scheme 6). In 1950, Bartlett proposed the epoxidation of alkenes with peracids proceeded *via* a concerted butterfly mechanism,[11] in which synchronous formation of the two C-O bonds is observed. Bach[12] and Yamabe[13] reported their individual theoretical studies on the epoxidation of ethylene with performic acid, and they showed the reaction proceeds *via* a spiro transition state (however, their individual models vary only by how synchronous the two C-O bond formations occur). The peroxycarboxylic acid is consumed within the reaction, and the carboxylic acid by-product is usually quenched by the addition of a weak base ($NaHCO_3/KHCO_3/Na_2HPO_4$).[14]



Scheme 6. Mechanistic view of the Prileschajew reaction

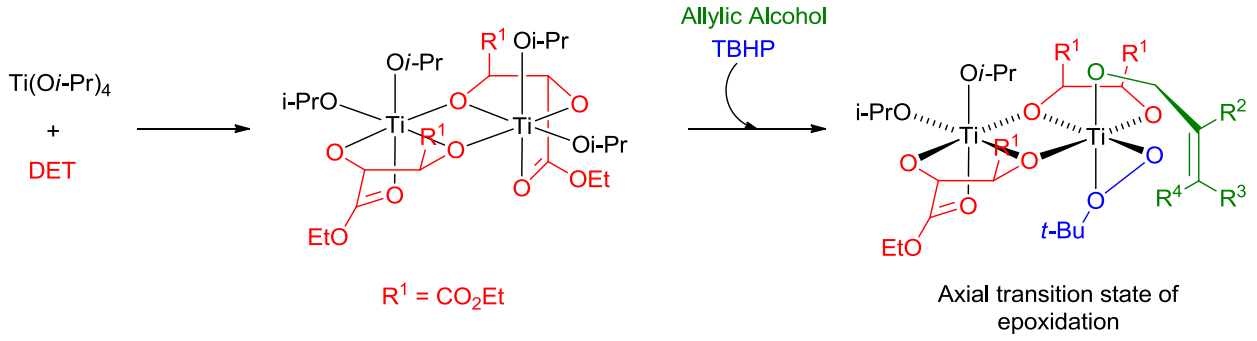
The application of the Prileschajew reaction has been essential to many natural product syntheses. In 2003, Overman applied the Prileschajew reaction as a key step in the synthesis of Briarellin F **23**. The epoxidation of alkene **22** proceeded in good yield and diastereoselectivity, in which oxygen transfer is favoured from the underside of alkene **22** (Scheme 7).[15]



Scheme 7. Overman's synthesis of Briarellin F **23**

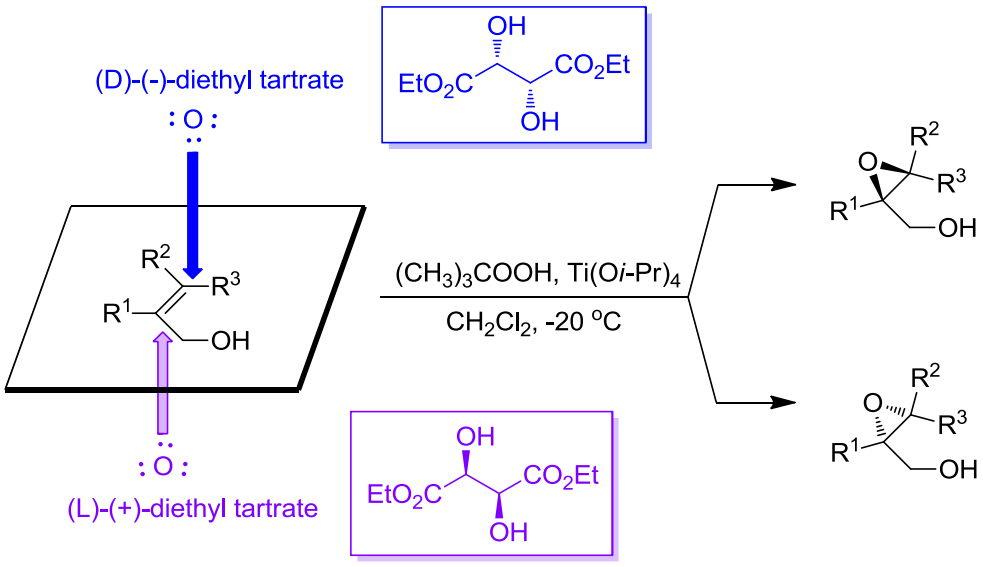
1.2.2 Sharpless Asymmetric Epoxidation

The first advancements in highly enantioselective asymmetric epoxidation involved the use of metal-based catalysts. The epoxidation of allylic alcohols by Sharpless and Katsuki reported the first high enantioselectivities with metal based catalysts.[16] The proposed mechanism for the Sharpless asymmetric epoxidation can be broken down into key steps (Scheme 8). Firstly, titanium(IV) tetra*iso*propoxide undergoes ligand exchange with a chiral diethyl tartrate, forming an active dimeric structure. The allylic alcohol substrate and the nucleophilic oxidant *tert*-butylhydroperoxide (TBHP) undergo ligand exchange with isopropoxide ligands. Both the allylic alcohol and TBHP are now coordinated axially on the titanium metal centre, allowing enantioselective epoxidation of the alkene.[16,17] Sharpless was later awarded the Nobel prize for chemistry in 2001 for his groundbreaking discoveries in asymmetric catalysis.



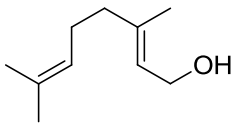
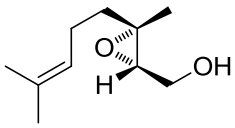
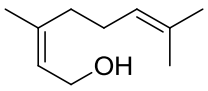
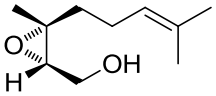
Scheme 8. Sharpless chemoselective asymmetric epoxidation

Depending on whether the natural L-(+)- or unnatural D-(–)-tartrate is used, it is possible to obtain either enantiomer of the epoxide product. All Sharpless epoxidation reactions follow a mnemonic model (Scheme 9).



Scheme 9. Sharpless's epoxidation of allylic alcohols.

Sharpless reported a range of different allylic alcohol substrates which could be epoxidized using this metal-based asymmetric epoxidation methodology (using the natural L-(+)-diethyl tartrate), affording yields of 70 – 87%, and enantiomeric excesses greater than 90% (Table 1).

Allylic Alcohol Substrate	Epoxyalcohol Product	% Yield (% ee)
		77 (95)
		79 (94)

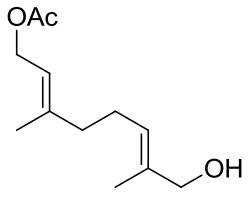
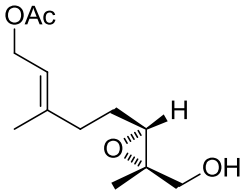
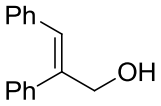
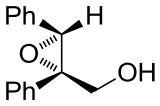
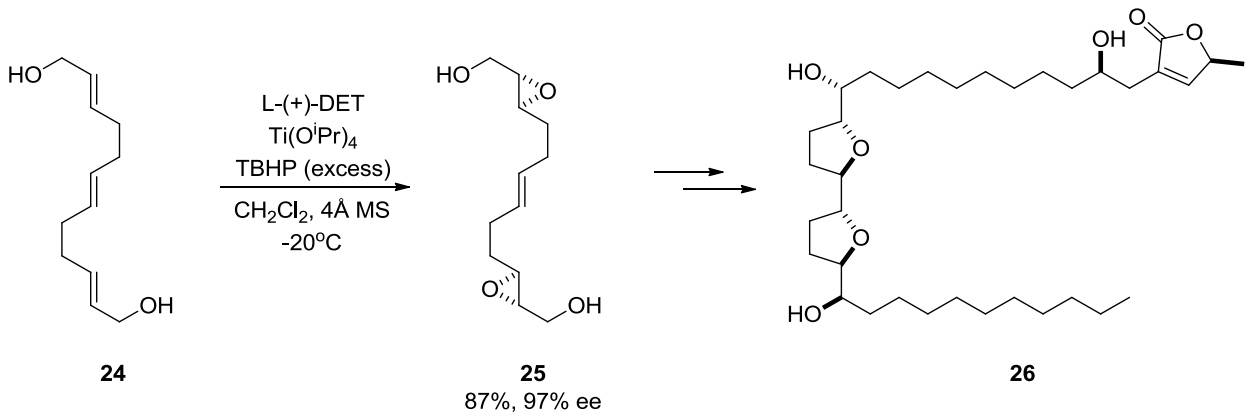
		70 (>95)
		87 (>95)

Table 1. Asymmetric epoxidation of various allylic alcohols

However, the Sharpless asymmetric epoxidation has its drawbacks; the use of potentially toxic transition metals is undesirable in organic reactions, and, more importantly, the methodology is limited to substrates that contain an allylic alcohol moiety. Furthermore, Sharpless noticed that trace amounts of water in the system poisoned the titanium-based catalyst, resulting in incomplete conversions (60% max.), longer reaction times and reduced enantioselectivities (39 – 80% ee).[18] This problem could, however, be overcome by the addition of 3Å or 4Å molecular sieves to the reaction, which in turn allowed the reduction of the titanium(IV) *iso*propoxide catalyst loading to a more economic 5 – 10 mol%.

The key step in a total synthesis of (+)-parviflorin **26** was achieved using the Sharpless asymmetric epoxidation of the *bis*-allylic alcohol **24**, using the natural L-(+)-diethyl tartrate, to give the enantiopure *bis*-epoxide in 87% yield (99% ee). The epoxide in turn undergoes a Sharpless asymmetric dihydroxylation to afford the *bis*-tetrahydrofuran backbone of the natural product (Scheme 10).[19]

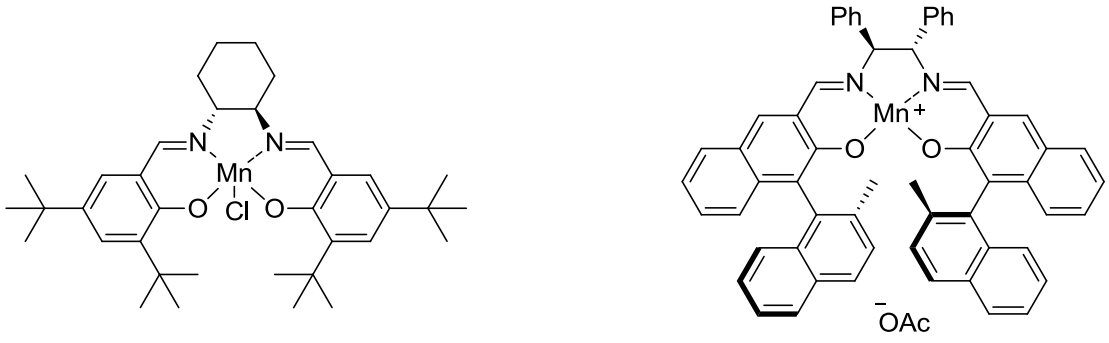


24 **25** 87%, 97% ee **26**

Scheme 10. Hoye's total synthesis of (+)-Parviflorin **26** utilising the Sharpless epoxidation

1.2.3 Jacobsen-Katsuki Epoxidation

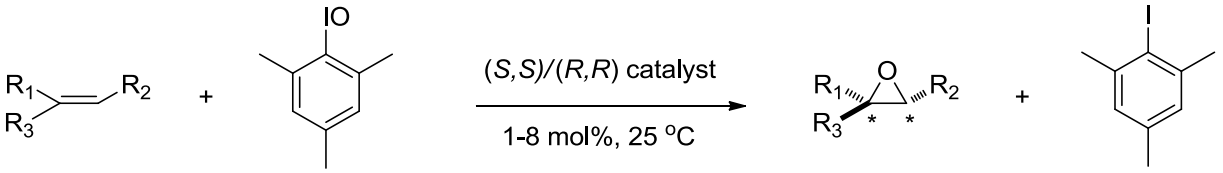
The Jacobsen-Katsuki epoxidation of alkenes involves a manganese-salen based catalyst (Figure 4). Depending on the temperature required for the reaction, a range of oxidants (iodosylbenzene, sodium hypochlorite, Oxone™, hydrogen peroxide) can be used to oxidize the manganese(III) metal centre to manganese(V). The synthesis of salen-based catalysts is generally simple, and can be fine-tuned by choosing the appropriate diamine and salicylaldehyde precursors.

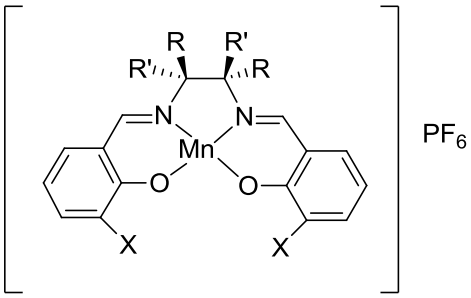


27 **28**

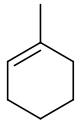
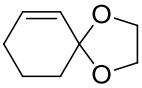
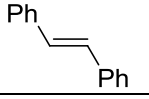
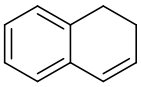
Figure 4. Examples of Jacobsen's **27** and Katsuki's **28** manganese-salen catalysts

Jacobsen initially showed that his manganese-salen catalysts could oxidize a range of alkyl and aryl substituted olefins in good to high enantioselectivities (Table 2).[20]





29-(*S*,*S*): R = Ph, R' = H, X = H
30-(*R*,*R*): R = H, R' = Ph, X = ^{t}Bu

Olefin	Catalyst	% Yield	% ee	Configuration
	**30**-(*R*,*R*)	50	59	(–)-1*R*,2*S*
	**30**-(*R*,*R*)	52	93	(–)[a]
	**29**-(*S*,*S*)	63	33	(–)-*S*,*S*
	**30**-(*R*,*R*)	72	78	(+)-1*R*,2*S*

[a] Absolute configuration not ascertained. Solvents used vary depending upon which catalyst used; (*R*,*R*) = CH_2Cl_2, (*S*,*S*) = CH_3CN.

Table 2. The first examples of high enantioselectivities observed using a manganese-salen catalyst

Further probing of the ligands surrounding the manganese metal centre yielded catalyst (**27**) (Figure 4), showing further increases in enantioselectivity. Jacobsen tested other oxidants, including commercial bleach, and found that epoxidation reactions at 4 °C yielded enantioselectivities above 90% ee for selected olefins (Table 3).[21]

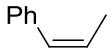
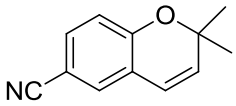
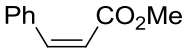
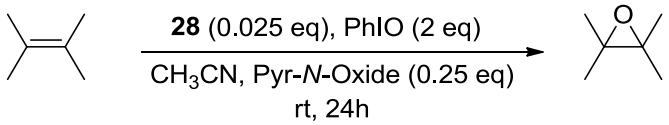
Olefin	Epoxide yield / %	% ee
	84	92
	96	97
	65	89

Table 3. Asymmetric epoxidation of representative olefins using catalyst (**27**)

Katsuki reported some excellent enantioselectivities for the catalytic asymmetric epoxidation of *cis*-olefins with his salen-manganese(III) complex (Figure 4, catalyst **28**). Their best conditions involved the use of iodosylbenzene as the terminal oxidant in the presence of an additive, such as pyridine *N*-oxide, with enantiomeric excesses as high as 91% (Table 4).[22]



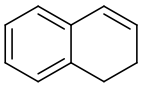
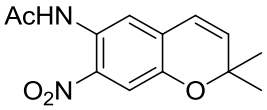
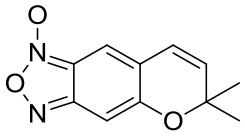
Cis-olefin substrate	Time, (h)	% Yield	% ee
	24	77	86
	24	99	89
	24	52	91

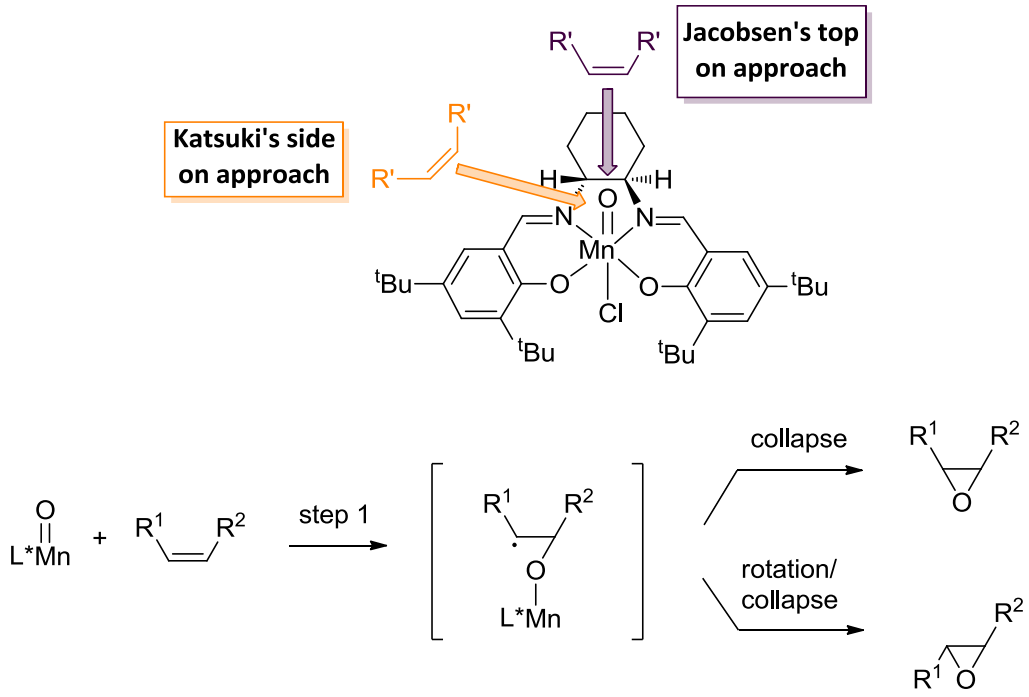
Table 4. Katsuki's asymmetric epoxidation of various *cis*-olefins

Both Jacobsen and Katsuki have proposed their own mechanisms to explain how the oxygen transfer to the olefin occurs, but both mechanisms are consistent in assuming the intermediate is the manganese(V) species.[23] The different mechanisms proposed by Jacobsen and Katsuki account for the enantioselectivity observed. Lineker has also discussed the mechanistic aspects of the manganese-salen catalysed epoxidation.[24]

For the manganese salen catalyst drawn below (Scheme 11), Jacobsen's theory involves the approach of the olefin from a 'top-on' approach, where the olefin approaches from the direction of the diimine bridge, with the smallest substituent on the olefin aligned with the axial hydrogen of the chiral center. Jacobsen reported the high enantioselectivity observed in the epoxidation of *cis*-β-methylstyrene was due to the less hindered diimine bridge (in comparison to diimine bridge in catalyst **28**-(*R*,*R*), table 2), favouring attack from above, and any side-on olefin approaches were nullified by the introduction of large ^{t}Bu groups.[17] Jacobsen's theory was supported by testing upon further *cis*-olefins, affording ee's above 90% (Table 3).

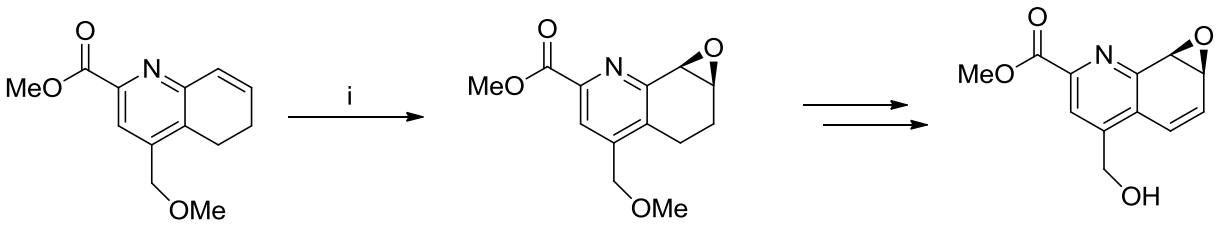
In contrast, Katsuki has suggested a 'side-on' approach of the olefin to the manganese-oxo bond due to favourable π-π interactions.[25]

The lack of stereospecificity observed in the manganese-catalysed epoxidations has led to controversy in the mechanism of oxygen transfer to the double bond. A radical mechanism suggests that the *trans*-epoxide can be formed by a single electron transfer mechanism, due to C-C bond rotation around the intermediate species (Scheme 11).[26]



Scheme 11. The proposed mechanisms of enantioselective epoxidation utilising manganese-salen based catalysts.

Jacobsen found that epoxidation reactions using his manganese-salen based catalysts can be affected by chiral quaternary ammonium salts, which cause a dramatic reversal in epoxidation diastereoselectivity, favouring the *trans*-epoxide products in high d.r. (>96:4) and high enantioselectivity (>80 %) (Scheme 11).[27] The Jacobsen-Katsuki epoxidation has recently been utilized in the synthesis of the tetrasubstituted dihydroquinoline portion of Siomycin D_1 **33** (related to peptide antibiotics) by Hashimoto. Epoxidation of the double bond at the C7-C8 position gave epoxide **32** in 43% yield and 91% ee (Scheme 12).[28]

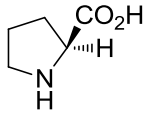
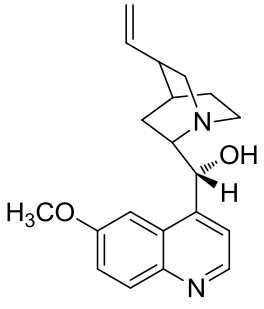


31 **32** **33**

Scheme 12. *Reagents and conditions*: (i) 4-phenylpyridine-*N*-oxide (50 mol%), NaOCl, CH_2Cl_2, **28** (5 mol%), r.t., 2.5 h, 43%, 91% ee.

1.3 Organocatalysis

Entering the 21st century, the demand for organic chemists to develop new methodologies and strategies to make syntheses of drug molecules and natural products more cost-efficient and most importantly, environmentally-friendly, has never been greater. With rapid progress being made in 'green chemistry', a reduction in the use of toxic metals becomes ever more desirable. The discovery of metal-free catalysts that are easily synthesized, that give high levels of conversion at low catalyst loadings, and provides high enantioselectivities would be an ideal alternative. Such catalysts have been coined 'organocatalysts', with many being derived from simple, cheap, low molecular weight starting materials, obtained from the pool of chiral compounds. There are many examples of these organocatalysts in the literature, but a few of the most successful are highlighted below, all affording enantiomeric excesses of >90% (Table 5). The organocatalysts themselves could be taken from the chiral pool directly, for example proline and quinine, and others are formed after short syntheses from chiral building blocks.

Precursor to organocatalyst / Organocatalyst	**Discovered By/Year...**	**Reaction / Function**
 *L*-proline	Hajos and Parrish,[29] Eder, Sauer and Wiechert.[30]	Catalyses Aldol type reactions, *via* iminium ion or enamine pathways
 Quinine	Wynberg *et al.*[31] / Bolm *et al.*[32]	Chiral base catalysed Michael additions, 2 + 2 cycloadditions/ Alkaloid-mediated opening of prochiral cyclic anhydrides

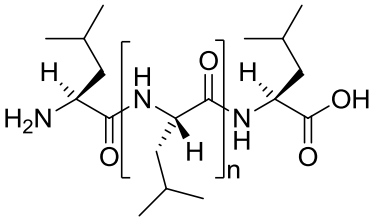
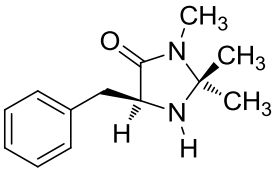
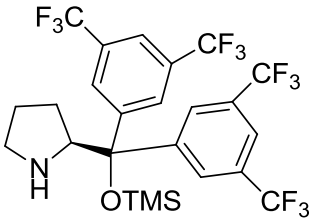
 n = 5, 7, 10 or 30 Oligo-*L*-Leu amino acid	Juliá, Colonna *et al.*[33]	Epoxidation of chalcones
 Oxazolidinone	MacMillan *et al.*[34]	Secondary amine catalysed Diels-Alder reaction
 Chiral pyrrolidine	Jørgensen *et al.*[35]	Asymmetric Organocatalytic Epoxidation of α,*β*-Unsaturated Aldehydes

Table 5. Organocatalysts used to affect asymmetry in different organic reactions

The popularity of organocatalysts is evident; a recent search in the literature showed that in 2011 alone, over 584 reviews, journals and publications contained the terminology 'organocatalyst'.[36] Over the past few decades, there has been a significant increase in publications in this ever developing area of organic chemistry, as represented in the chart below (Figure 5).

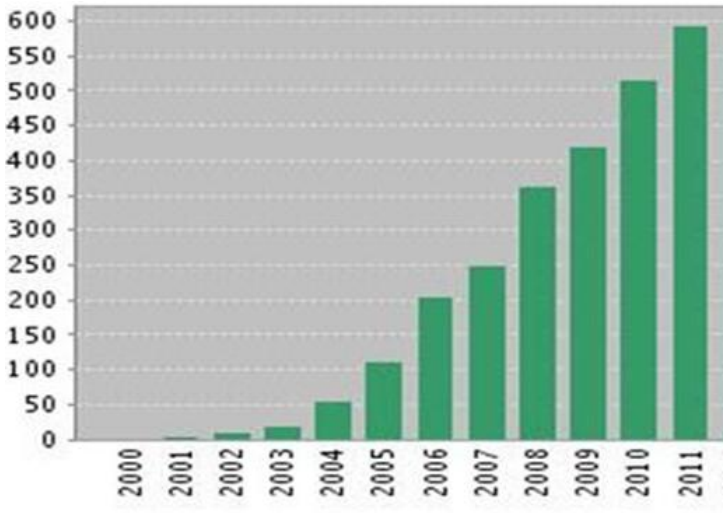


Figure 5. Publications containing the term 'organocatalyst' from 2000 onwards [36]

1.4 Non-Metal Catalysed Epoxidations

Most recently, a new generation of metal-free epoxidation catalysts have been developed and offer some key advantages. Organocatalysts used in epoxidation reactions show a lack of sensitivity to moisture and oxygen allowing the use of water as a solvent in reactions, and have low toxicity due to the absence of transition metals (e.g Ti, Mn, Co).

Chiral dioxiranes, oxaziridines, amines and oxaziridinium salts are all examples of organocatalysts that have been recently reported to effect the asymmetric epoxidation of both electron rich and deficient olefins, and their corresponding successes are discussed in depth below.

1.4.1 Ketone Catalysed Epoxidations

When suitable ketones are used in the presence of an oxidant (e.g. Oxone™), dioxirane species are formed *in situ*, which are potent oxygen transfer agents.[37] Some of the most powerful dioxirane reagents can be prepared from cheap ketones, such as acetone. The most common dioxiranes used in epoxidation reactions are dimethyldioxirane **34** and methyl(trifluoromethyl)dioxirane **35** (Figure 6).

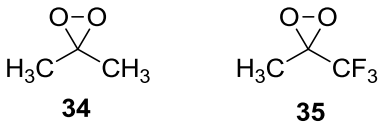
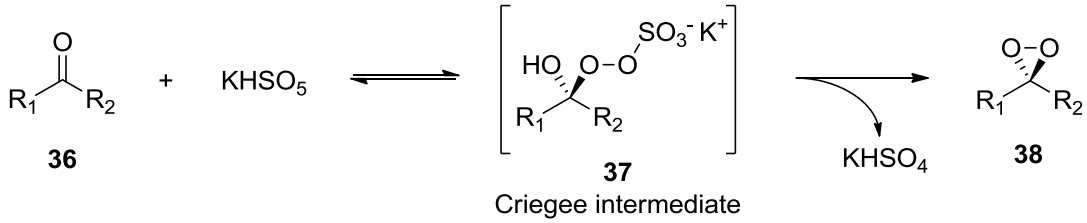


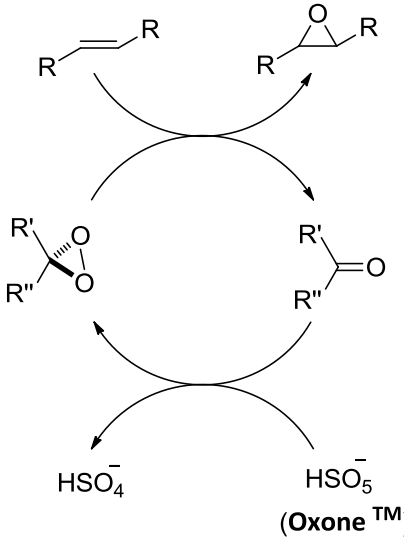
Figure 6. dimethyldioxirane **34** and methyl(trifluoromethyl)dioxirane **35**

Isolation of the dioxiranes shown above is generally achieved by distillation of the crude reaction mixture between the ketone and Oxone™. Dioxirane formation starts by nucleophilic attack of a peroxomonosulfate anion on the carbon atom of ketone **36** affording Criegee intermediate **37**. This intermediate breaks down to form dioxirane **38** driven by the loss of potassium hydrogen sulfate (Scheme 13).



Scheme 13. Formation of dioxirane from ketone

The catalytic cycle shown below indicates the transfer of electrophilic oxygen to an alkene, resulting in the formation of an epoxide product, and the recycling process involving the ketone catalyst (Scheme 14).



Scheme 14. Catalytic cycle for ketone-catalysed epoxidation with Oxone™

In the instance of the ketone being chiral, oxygen transfer to a prochiral alkene will occur with chirality induced into the epoxide product, thus making the catalytic cycle asymmetric. Dioxiranes are useful synthetic tools. They are usually employed under mild conditions, and they can be used for the epoxidation of electron-rich and electron-deficient alkenes. Another key advantage of dioxiranes is their stereoselectivity.

1.4.2 Curci's Ketones: The First Examples of Ketone Based Asymmetric Epoxidation

Comprehensive studies by Curci,[38] Adam[39] and Baumstark[40] attempted to elucidate the oxygen transfer mechanism from dioxirane species to alkene substrates. Epoxidation of acyclic alkenes with dimethyldioxirane was found to yield the *cis*-epoxides from *cis*-alkenes at a much faster rate than the *trans*-epoxide from *trans*-alkenes.[39,40] Baumstark originally proposed a *spiro* arrangement in the transition state to be favoured;[40] however, calculations by Bach, and more recently calculations by Houk, have shown that the energy difference between the two extreme geometries turned out to be quite small (Figure 7).[41]

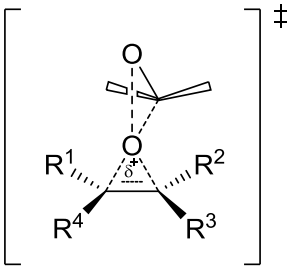
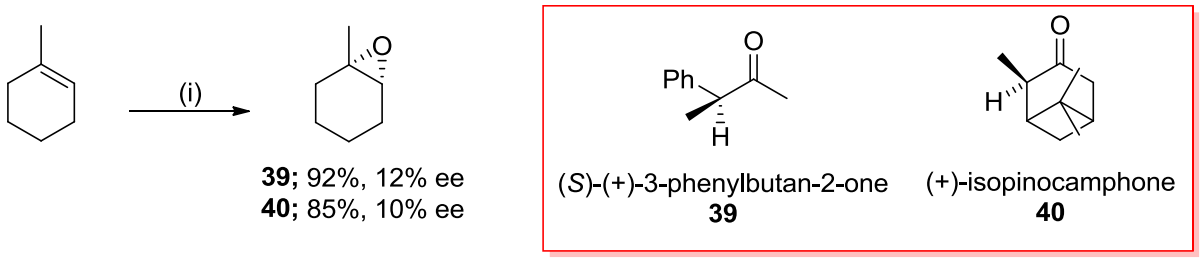


Figure 7. '*Spiro*' transition state

Curci showed that ketone-mediated epoxidations could be applied asymmetrically. His reported initial enantioselectivities were low (10 – 12% ee), when chiral ketones (*S*)-(+)-3-phenylbutan-2-one **39** and (+)-isopinocamphone **40** were used in the epoxidation of 1-methylcyclohexene (Scheme 15).[42]



Scheme 15. *Reagents and conditions*: (i) Ketone (0.2 – 0.5 eq.), Oxone (2.5 eq.), CH_2Cl_2-H_2O, pH 7-8 (Bu_4N^+ HSO_4^-), 5°C, 8 – 24 h.

The chiral ketones used by Curci have only one stereogenic centre adjacent to the carbonyl group. With good yields being generated using the ketone-based epoxidation, an explanation for the low enantioselectivites observed was proposed. It is thought that the olefin has access to both faces of the non-C_2-symmetric dioxirane, which would result in differing stereoselectivities, and potentially opposing stereoselectivity, during the transfer of oxygen to the olefin (Figure 8).[43]

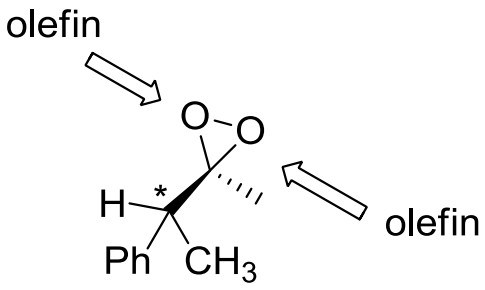


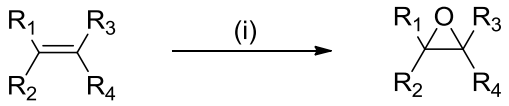
Figure 8. Curci's asymmetric epoxidation utilising non-C_2-symmetric dioxiranes

The pioneering work reported by Curci, however, set the foundations for further advancements in asymmetric epoxidation reactions using chiral ketones.

1.4.3 Yang's Ketone-Based Epoxidations

Yang's first development in the field of ketone-catalysed epoxidations was the introduction of a new biphasic solvent system: acetonitrile-water (Scheme 16). These new biphasic epoxidation conditions improved upon the previous dichloromethane-water biphasic conditions employed by Curci, which were known to induce much lower reaction rates.

Methyl(trifluoromethyl)dioxirane **35** was already known to be 1000 times more reactive than DMDO, so in choosing dioxirane **35** coupled with the new solvent system, both electron-deficient olefins and electron-rich olefins were successfully oxidized in excellent yields (Table 6).[44]



Scheme 16. *Reagents and conditions*: (i) Methyl(trifluoromethyl)dioxirane **35**, Oxone, $NaHCO_3$, CH_3CN-H_2O, 0 °C, pH 7 – 7.5, <2 h.

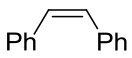
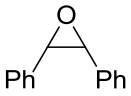
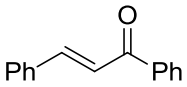
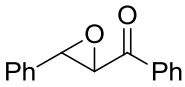
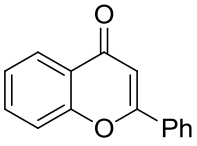
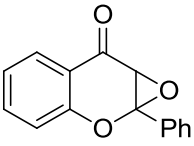
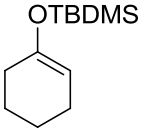
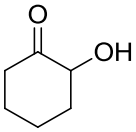
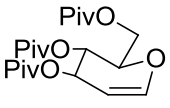
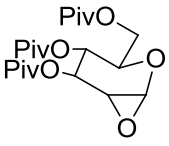
Olefin	Time	Epoxide	% Yield
	15 min		96
	30 min		99
	1.3 h		99
	1.25 h		99
	30 min		97
	15 min		84

Table 6. Epoxidation of olefins using methyl(trifluoromethyl)dioxirane **35** generated *in situ*

Yang identified two key approaches to improve upon the poor enantioselectivities observed in the case of Curci's non-C_2-symmetric dioxiranes. By blocking one face of the dioxirane, it would allow oxygen transfer to take place at the other face exclusively. Alternatively, Yang

proposed designing a ketone-based catalyst that has C_2-symmetry, which would give rise to the same enantioselectivity irrespective of which face the olefin approaches. Both faces of the dioxirane in this instance have the same chiral environment for oxygen transfer (Figure 9).

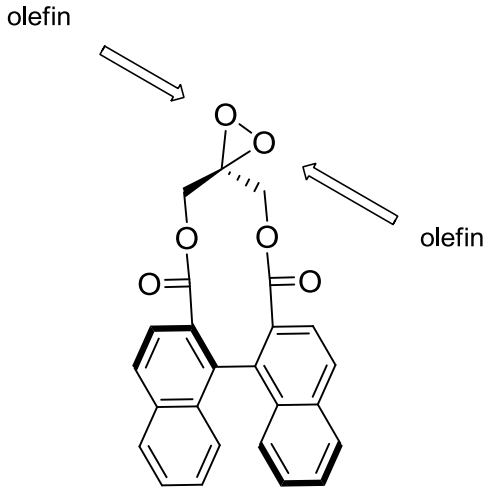
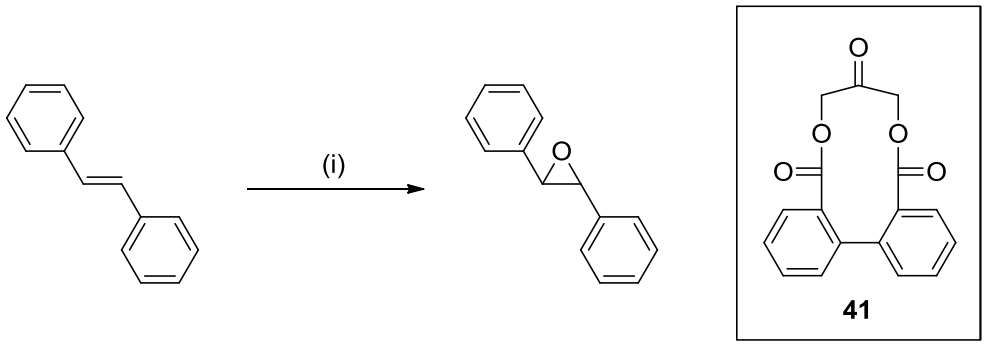


Figure 9. Asymmetric epoxidation by C_2 symmetric dioxiranes.

In 1998, Yang and co-workers investigated the catalytic activities of various cyclic ketones in the epoxidation of *trans*-stilbene. Their best result came from a biphenyl-derived 11-membered-ring ketone catalyst **41**. *Trans*-stilbene oxide was obtained in 99% yield in 7 minutes, with 93% catalyst recovery (Scheme 17).[45]



Scheme 17. *Reagents and conditions*: (i) Ketone **41** (1 mol%), Oxone, $NaHCO_3$, CH_3CN-H_2O, pH 7 – 7.5, r.t., 5 min.

Epoxides that are acid labile could be easily isolated when sodium bicarbonate was used to regulate the pH of the reaction at around 7 – 7.5. A range of olefins were then tested using this

biphenyl-derived 11-membered-ring ketone catalyst under these conditions, resulting in high yields ranging from 75 – 96% (Table 7).[45]

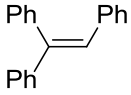
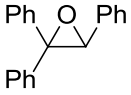
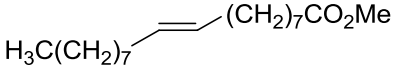
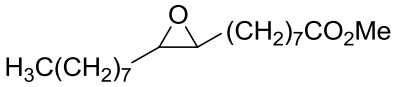
Alkene	Time (min)	Product	% Yield
	160		91
	60		75
	330		96

Table 7. *Reagents and conditions*: Ketone **41** (5 mol%), Alkene (0.2 mmol), Oxone™ (0.4 mmol), $NaHCO_3$ (1.24 mmol), $MeCN/H_2O$ (1.5:1)

Encouraged by these results, Yang replaced the biphenyl segment on their 11-membered ring ketone catalyst **41** with a chiral binaphthalene unit, to generate a chiral ketone catalyst that has C_2-symmetry. Chiral ketone **42** catalysed the asymmetric epoxidation of *trans*-4,4'-diphenylstilbene in 87% ee (Figure 10).[46]

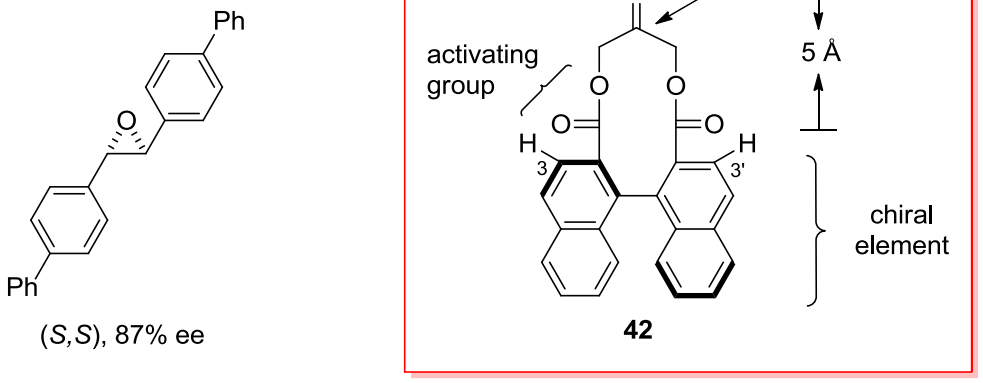
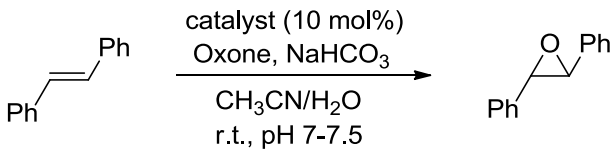


Figure 10. Asymmetric epoxidation of *trans*-4,4'-diphenylstilbene using Yang's C_2-symmetric chiral (*R*)-binaphthalene catalyst **42**

Yang expected the H-3 and H-3' atoms of the binaphthyl group to act as steric recognition elements. The distance between the catalytic keto group and the H-3 and H-3' atoms of the binaphthyl group is around 5 Å apart. By replacing the protons with other larger atoms or groups (ketones **43-49**, Table 8) Yang hoped that increased enantioselectivities would be obtained. The reported enantioselectivities are shown below (Table 8).[46]



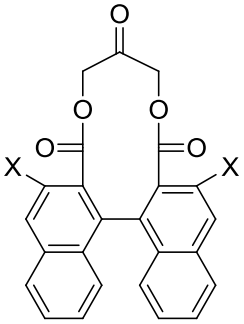
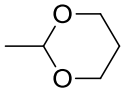
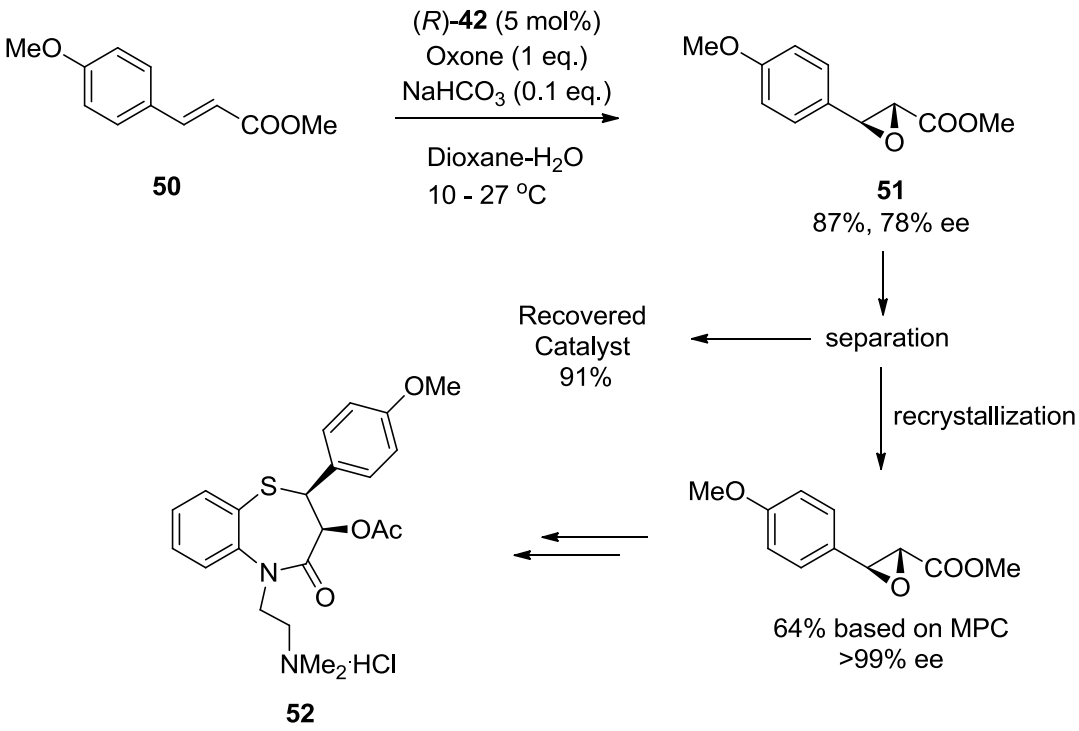
	Catalyst	X	ee (%)	Epoxide Config.
	(*R*)-**42**	*H*	47	(−)-(*S*,*S*)
	(*R*)-**43**	Cl	76	(−)-(*S*,*S*)
	(*R*)-**44**	Br	75	(−)-(*S*,*S*)
	(*R*)-**45**	I	32	(−)-(*S*,*S*)
	(*S*)-**46**	Me	56	(+)-(*R*,*R*)
	(*R*)-**47**	CH_2OCH_3	66	(−)-(*S*,*S*)
	(*R*)-**48**		71	(−)-(*S*,*S*)
	(*S*)-**49**	$SiMe_3$	44	(+)-(*R*,*R*)

Table 8. Asymmetric epoxidation of *trans*-stilbene catalysed by ketones **42-49**

Interestingly, the enantioselectivities increase with increasing size of group X, to a point, then decrease when the group is too large, i.e. when X = I, $SiMe_3$.

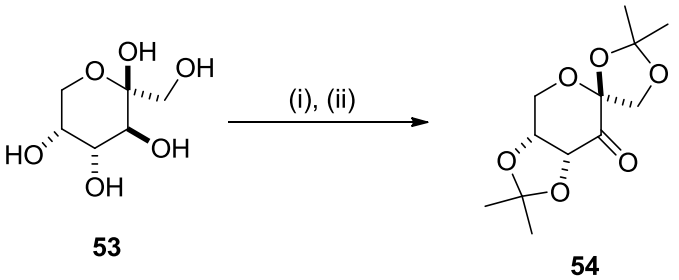
Yang's ketone catalyst (*R*)-**42** was used by the Japanese company Tanabe Seikayu to effect the epoxidation of methyl *p*-methoxycinnamate **50** (MPC), which yields an important chiral epoxide intermediate **51** (64% yield, 99% ee after recryst.) in the synthesis of the chiral drug Diltiazem hydrochloride **52** (Scheme 18).[47]



Scheme 18. Asymmetric epoxidation of MPC catalysed by (*R*)-**42**

1.4.4 Shi's Fructose Ketone Epoxidations

In 1996, Shi reported fructose-derived ketone **54** as an enantioselective epoxidation catalyst.[48] This chiral ketone catalyst can be easily synthesized from D-fructose **53** in two steps (Scheme 19).[49]



Scheme 19. *Reagents and conditions*: (i) Acetone, $HClO_4$, 0 °C, 53%; (ii) PCC, CH_2Cl_2, r.t., 93%

In 1997, Shi reported extremely high enantioselectivities for catalyst **54** when used catalytically (30 mol%) for the asymmetric epoxidation of various *trans*- and trisubstituted olefins (Table 9).[48]

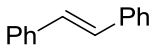
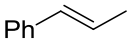
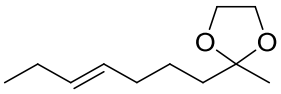
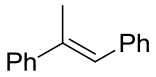
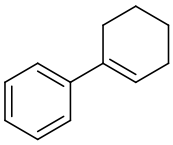
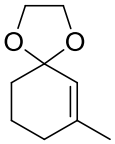
Substrate	% Yield	% ee / (config.)
	85	98 (*R*,*R*)
	94	96 (*R*,*R*)
	92	92 (*R*,*R*)
	89	96 (*R*,*R*)
	94	98 (*R*,*R*)
	41	97 (*R*,*R*)

Table 9. Shi's epoxidation examples of *trans* and trisubstituted olefins with chiral ketone **54**

Shi also showed that catalyst **54** was highly effective for the epoxidation of various 2,2-disubstituted vinylsilanes, affording ee's up to 94%.[50] Shi further showed that hydroxyalkenes,[51] conjugated dienes,[52] conjugated enynes,[53] and silyl enol ethers and esters[54] all underwent asymmetric epoxidation reactions using ketone **54** in very high enantioselectivity (>90% ee) (Table 10).

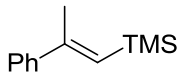
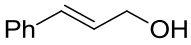
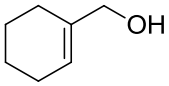
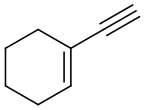
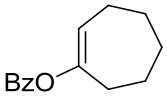
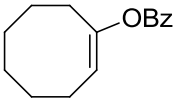
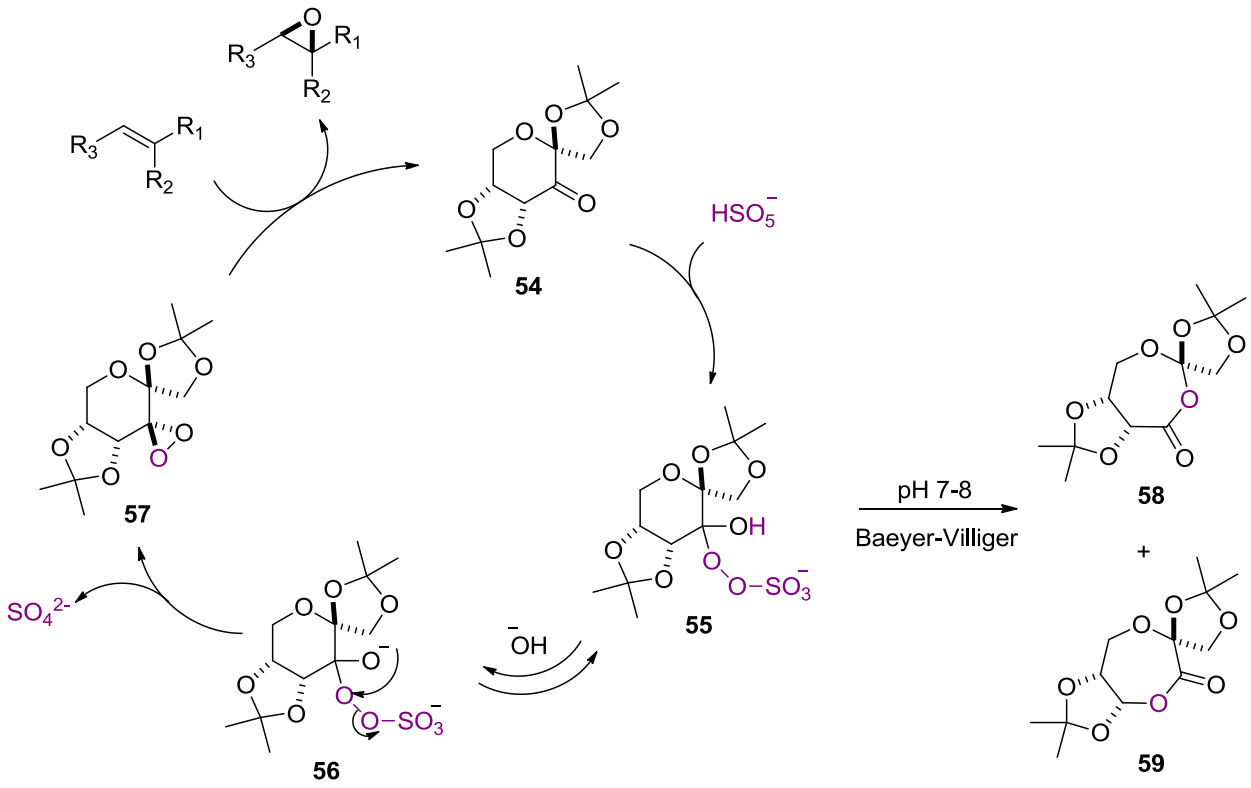
Substrate	% Yield	% ee / (config.)
	74	94 (*R*,*R*)
	85	94 (*R*,*R*)
	93	94 (*R*,*R*)
	78	93 (*R*,*R*)
	87	91 (*R*,*R*)
	82	95 (*R*,*R*)

Table 10. Shi's epoxidation of a broad range of olefin substrates utilizing versatile catalyst **54**

After the initial successes achieved with chiral ketone **54**, Shi observed that it would be desirable to reduce the high catalyst loadings associated with the methodology (usually 30 mol%). He studied the effect of pH on the epoxidation reaction, and found at pH 7-8 that enantiomeric excesses >90% could be achieved for *trans*- and trisubstituted olefins.[48] He believed that the high catalyst loadings were required at this pH as intermediate **55** could undergo a decomposition side reaction through a Baeyer-Villiger oxidation, to yield the corresponding lactones **58** and **59** (Scheme 20).



Scheme 20. Mechanism of oxygen transfer in Shi's asymmetric epoxidation utilising chiral ketone **54**

Shi reported the epoxidation of *trans-β*-methylstyrene with ketone **54** at pH >10, and found that the higher pH enhanced catalyst efficiency, without any loss of enantioselectivity observed during the epoxidation reaction (ee's remained high, >90%). The optimum pH for the reaction was 10.5, at which ketone **54** reacts with Oxone at a greater rate than that of the autodecomposition of Oxone at a higher pH.[55]

Hydrogen peroxide is a suitable alternative to Oxone; hydrogen peroxide possesses a high active oxygen content and its reduction product is water. Shi found that replacing Oxone, the traditional oxidant used in dioxirane formation, with a system that generates peroxyimidic acid *in situ* was capable of yielding the corresponding dioxirane from ketone **54**. Shi reported good yields and enantioselectivities for a range of olefins under these acetonitrile-hydrogen peroxide conditions (Table 11).[56]

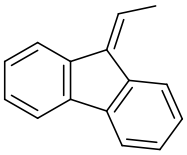
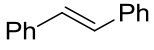
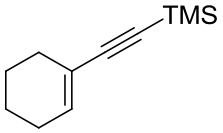
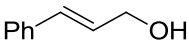
Substrate	% Yield	% ee
	77	92
	90	98
	93	95
	71	89

Table 11. Asymmetric epoxidation with ketone **54** and H_2O_2 as oxidant

As stated briefly above, Curci,[38] Adam[39] and Baumstark[40] have shown that dioxirane-mediated epoxidations of olefins occur *via* a spiro transition state, as opposed to a planar one. The spiro transition state is favoured for the epoxidation of ethylene with DMDO due to oxygen lone pair interactions with the π* orbital of the alkene (Figure 11).[40]

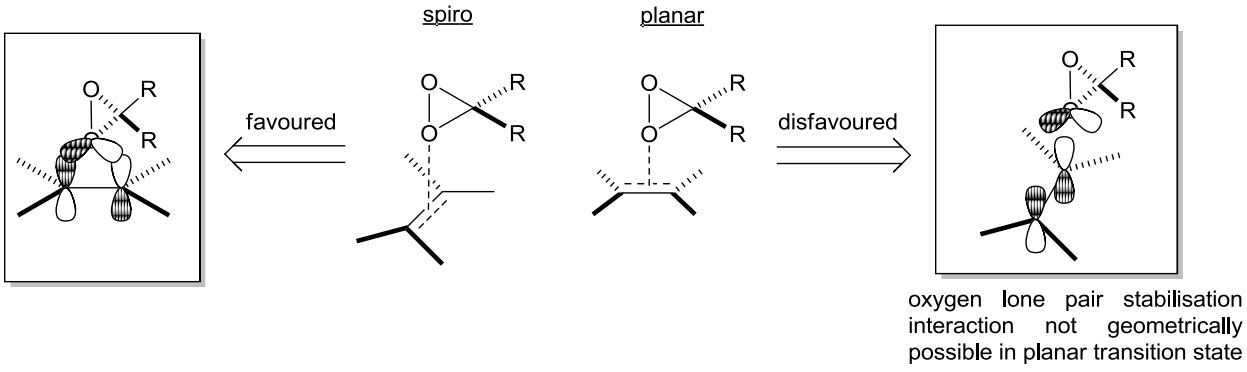


Figure 11. 'Favoured' spiro and 'Disfavoured' planar transition states

Shi reported that chiral ketone catalyst **54** can form two key sterically favoured transition states in the asymmetric epoxidation of various *trans* and trisubstituted olefins; these are the favoured spiro transition state and a competing planar transition state (Figure 12).

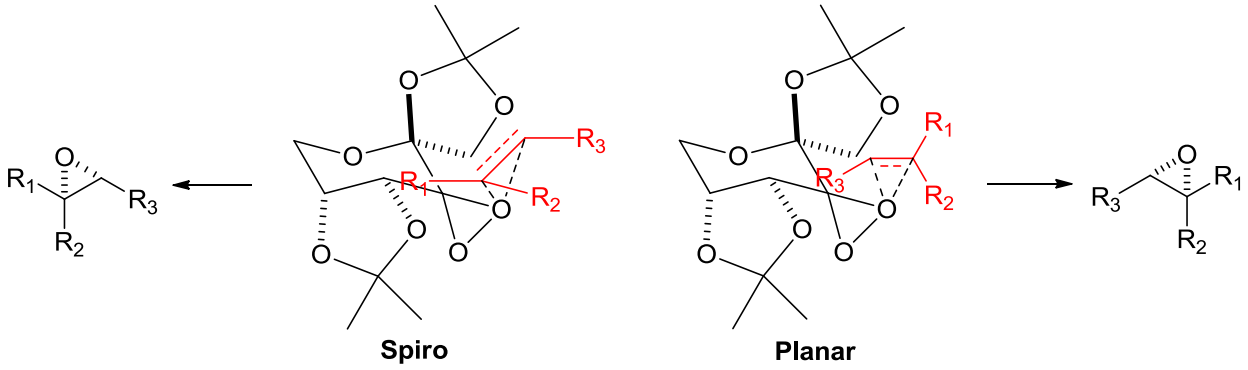


Figure 12. Possible spiro and planar transition states with catalyst **54**

As shown (Figure 12) the spiro transition state and planar transition state yield opposite configurations of the epoxide product. However, the planar transition state may become more prominent depending on the electronic and steric substituents on the olefin substrate. Spiro transition states are favoured when the olefin contains a conjugated group, such as phenyl/alkyne, or for example when R_1 is small in size, encouraging a spiro transition state, or when R_3 is large, disfavouring a planar transition state (Figure 13).

Shi furthered these studies with the kinetic resolution of racemic olefins with ketone **54**.[57] Shi later reported a number of analogues of chiral ketone catalyst **54** prepared in order to investigate the key moieties of the catalyst structure (Figure 13). Initially, he replaced the 5-membered spiro ketal in ketone **54** with a 6-membered cyclic ketal **60**,[58] varied the size of the groups attached to the ketal **61**, and replacing the oxygen of the pyranose ring **62**.[59] In each structural comparison, ketone **54** was still the superior catalyst, indicating that all moieties in catalyst **54** are beneficial to catalyst functionality.

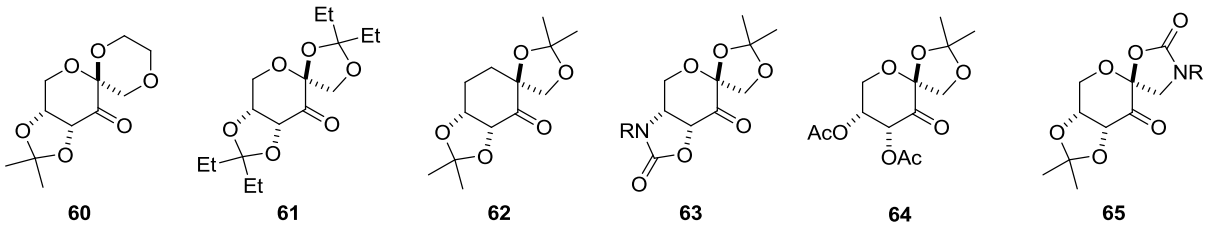


Figure 13. Shi's analogues of ketone catalyst **54**

Shi initially reported two possible lactones, **58** and **59**, could be generated in the competing Baeyer-Villiger decomposition reaction (Scheme 20). When ketone catalyst **54** was reacted with *m*CPBA, he observed lactone **59** was the major product, indicating that C_4 on ketone catalyst **54** is more prone to migrate than C_2 in the Baeyer-Villiger reaction.[60] Shi synthesized oxazolidinone catalyst **63** in order to investigate the electronic effect at C_4 in these ketone catalysts. The electron withdrawing nature of the oxazolidinone moiety in catalyst **63** allowed lower catalyst loadings (1 – 5 mol%, in comparison to catalyst **54**; 20 – 30 mol%), yet still affording good yields and high enantioselectivities for a range of olefins.[60]

Enhanced ketone stability and reactivity was shown in ketone catalyst **64**, where the fused ketal moiety in catalyst **54** was replaced with electron withdrawing acetate groups. Catalyst **64** was found to be effective for the epoxidation of challenging substrates such as *α,β*-unsaturated esters, affording ee's up to 98%.[61]

Ketone **65** was found to be highly effective for the epoxidation of a variety of *cis*-olefins and terminal olefins.[62] Mechanistic studies have shown that electronic interactions between the oxazolidinone moiety of ketone **65** and the approaching substituents on the *cis*-olefin substrates play a key role in the transition state of oxygen transfer.

Most recently, the Shi group has reported that ee's of up to 92% have been achieved using catalyst **65** in the epoxidation of various *cis*-olefins as substrates (Table 12).[63]

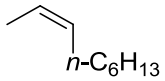
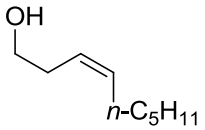
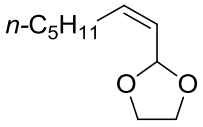
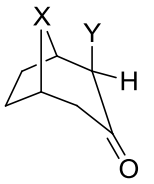
Substrate	R subst. on ketone 40	Temp. / ˚C	Time / h	% Yield	% ee
	*p*-*n*-BuPh	0	8	52	64
	*p*-*n*-BuPh	-10	4	89	82
	BOC	-10	12	76	92

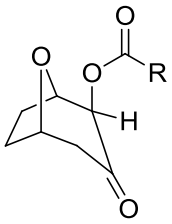
Table 12. Shi's epoxidation of various *cis*-based olefins

1.4.5 Armstrong's Tropinone-Catalysed Epoxidations

Armstrong has shown that a range of α-substituted-*N*-ethoxycarbonyltropinone catalysts (**66-67**,[64] **68** – **76**)[65] is capable of epoxidizing alkenes using Oxone as the terminal oxidant, affording excellent conversions and good enantioselectivities (Figure 14).[64,65]



66 X = NCO_2Et, Y = H
67 X = NCO_2Et, Y = F
68 X = O, Y = F
69 X = O, Y = OH



70 R = CH_3
71 R = CF_3
72 R = Ph
73 R = *p*-NO_2Ph
74 R = *m*-NO_2Ph
75 R = *p*-MeOPh
76 R = *m*-MeOPh

Figure 14. Armstrong's α-substituted-*N*-ethoxycarbonyltropinone ketone catalysts

Initial studies by Armstrong looked into the commercially available racemic *N*-ethoxycarbonyltropinone **66** (Figure 14). Promising initial results showed that the epoxidation of *trans*-stilbene was complete after 3 hours. Armstrong proposed that the introduction of an electron-withdrawing substituent adjacent to the carbonyl group would increase the reactivity of the catalyst, for example racemic α-fluoro-derivative **67**, which at 25 mol% afforded *trans*-stilbene oxide in 100% conversion after 30 minutes (Table 13).

Entry	(±)-67 (mol%)	Conv. (%)	Time (h)
1	100	100	<0.25
2	50	100	<0.25
3	25	100	<0.5
4	10	100	2
5	5	100	≤20
6	1	62	24

Table 13. Oxone derived epoxidation of *trans*-stilbene catalysed by racemic ketone **67**

Armstrong further showed that chiral ketone **67** could be employed for the asymmetric epoxidation of a range of olefins, affording ee's up to 83% (Table 14).

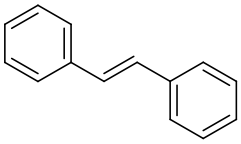
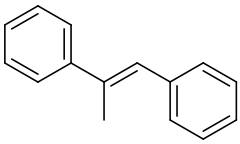
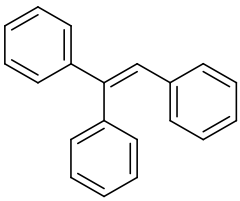
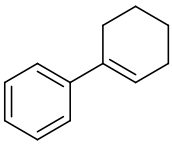
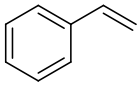
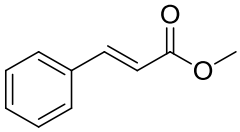
Alkene	(+)-67 (mol%)	% Conv.	Time / h	% Yield	% ee Config.
	10	100	< 3	88	76; *R*,*R*
	10	100	< 4	100	73; *R*,*R*
	10	100	< 4	100	83; *R*
	10	100	<6	97	69; *R*
	10	100	< 2	33	29; *R*
	25	64	24	33	64

Table 14. Asymmetric epoxidation of alkenes catalysed by ketone (+)-**67**

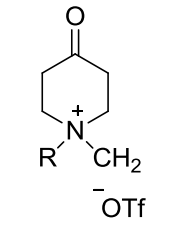
Armstrong subsequently showed that non-racemic esters of hydroxy-8-oxabicyclo[3.2.1]octan-3-one (catalysts **70** – **76**) afforded promising asymmetric epoxidation (98% ee for phenylstilbene with **70**), after initial screening experiments of the corresponding racemic catalysts yielded moderate to good conversions (Table 15).[65]

Ketone	(*E*)-Stilbene		Styrene		α-Methylstyrene	
	Conv.	***ee***	***Conv.***	***ee***	***Conv.***	***ee***
70	85	93	100	48	100	10
72	39	75	100	36	100	11
73	41	78	100	35	100	15
74	46	81	100	40	100	10
75	53	67	100	31	75	19
76	24	46	100	25	65	26

Table 15. Epoxidation results for Armstrong's ester-derived non-racemic ketones **70** – **76** (Figure 14)

1.4.6 Denmark's Ketone-Catalysed Epoxidations

Denmark's first adventures into ketone-derived epoxidations began in 1995, when he investigated a phase-transfer ketone catalyst operating under a new biphasic epoxidation system, utilising Oxone as the oxidant.[66] Optimization of the catalytic system led to a range of olefins oxidized in excellent yields (> 83%) (Table 16). Denmark identified that using the correct pH (7.5 - 8) with an *N*-dodecyl chain present on the catalyst were essential for effective epoxidation reaction.

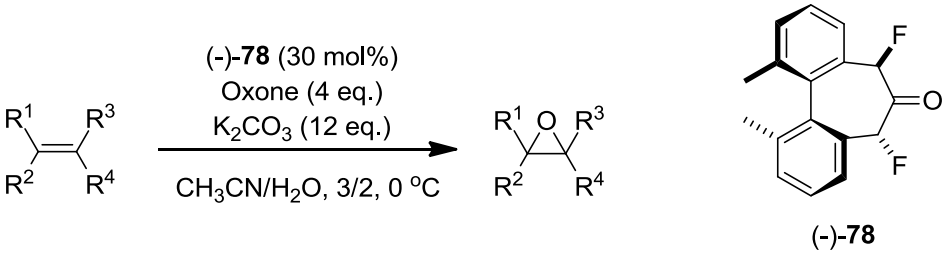


77 R=*n*-C_6H_{13}

Alkene	% Conv.	% Yield
1-octene	100	91
cyclohexene	100	92
2-cyclohexen-1-ol	96	83
(*E*)-2-methylstyrene	100	96

Table 16. Denmark's *N*-alkyl, *N*-methyl piperidinium triflate phase-transfer catalyst **77**

Denmark later reported that a seven-membered ring carbocyclic chiral ketone **78** containing a fluorine substituent at the α-carbon had a dramatic effect on the epoxidation of olefins. Catalyst **78** was found to afford ee's up to 94% (Table 17).[67]



(-)-**78**

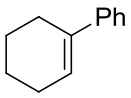
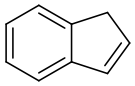
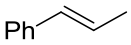
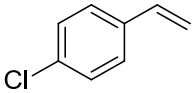
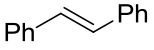
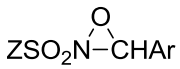
Substrate	% Yield	% ee
	79	59
	67	12
	80	88
	55	43
	46	94

Table 17. Denmark's α-fluorinated ketone mediated epoxidations

1.4.7 Oxaziridine Mediated Epoxidations

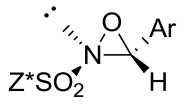
During the eighties, Davis reported the synthesis of optically active 2-sulfonyl- and 2-sulfamyloxaziridines (Figure 15), formed by oxidation of their corresponding sulfonylimine or sulfamylimine using either *m*CPBA or Oxone.[68]



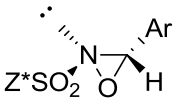
2-sulfonyloxaziridine, Z = alkyl, aryl
2-sulfamyloxaziridine, Z = R_2N

Figure 15. Davis's 2-Sulfonyloxaziridine and 2-Sulfamyloxaziridine

These chiral oxaziridines were reported to oxidize non-functionalized sulfides (enantiomeric excesses up to 91% observed),[69] and to epoxidize olefins (up to 65% ee, Table 18) utilising oxidants **79 – 82**.[70]



(+)-(*R,R*)-79,80



(+)-(*S,S*)-81,82

a. Z* = (-)-3-bromocamphor, Ar = 2-chloro-5-nitrophenyl
b. Z* = (-)-(*S*)-(*N*-benzyl)-1-phenethylamine,
Ar = pentafluorophenyl

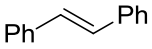
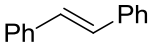
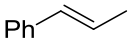
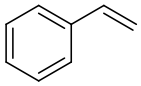
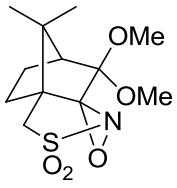
Oxaziridine	Solvent	Temp (˚C)	Alkene	ee (%)	Config.
79	$CHCl_3$	60		34.9	(*R,R*)
80	$CHCl_3$	60		30.3	(*S,S*)
81	$CHCl_3$	25		53	(*R,R*)
82	$CHCl_3$	25		61.1	(*S*)

Table 18. Davis epoxidation using chiral 2-sulfonyl- and 2-sulfamyloxaziridines **79** – **82**

In 1995, Page reported that enantioselectivities as high as 98% ee could be achieved for the enantioselective oxidation of sulfides utilizing [(3,3-dimethoxycamphoryl)sulfonyl]oxaziridine **83** (Figure 16).[71]

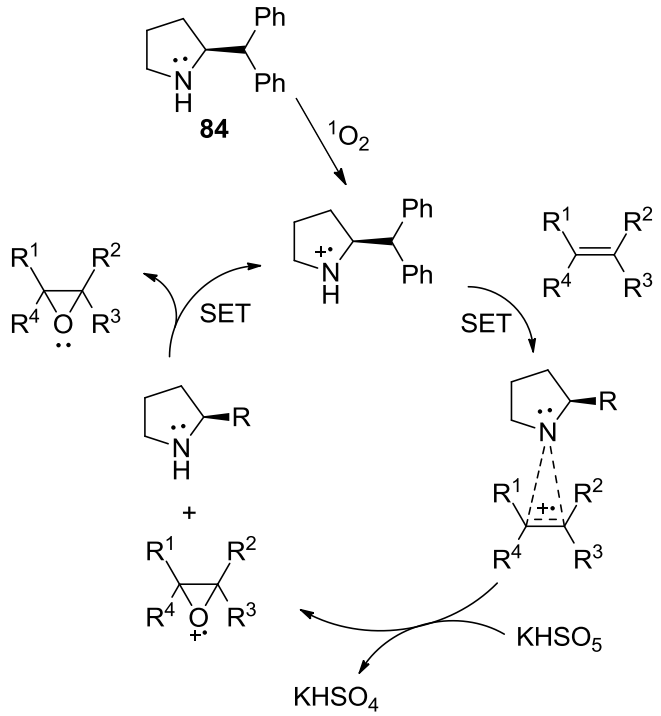


83

Figure 16. Page's highly effective oxaziridine catalyst **83**

1.4.8 Aggarwal's Amine-Catalysed Epoxidations

Chiral amine-catalysed epoxidations of simple olefins were first reported by Aggarwal in 2000.[72] Aggarwal reported that a chiral derivative of pyrrolidine, (*S*)-2-(diphenylmethyl)pyrrolidine **84**, allowed the conversion of 1-phenylcyclohexene into its corresponding epoxide in 57% ee (Scheme 21).

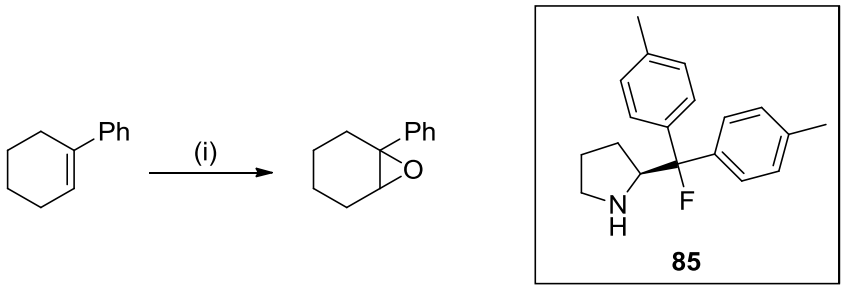


Scheme 21. Aggarwal's epoxidation mechanism utilizing amine **84**

However, the reproducibility of key reactions proposed has led to ongoing research into the exact mechanism for the chiral-amine catalysed reactions.[73] Aggarwal later proposed a new catalytic cycle for the asymmetric epoxidation of various olefins utilizing the hydrochloride salt of amine **84**, affording ee's up to 52%.[74]

1.4.9 Yang's Amine-Catalysed Epoxidations

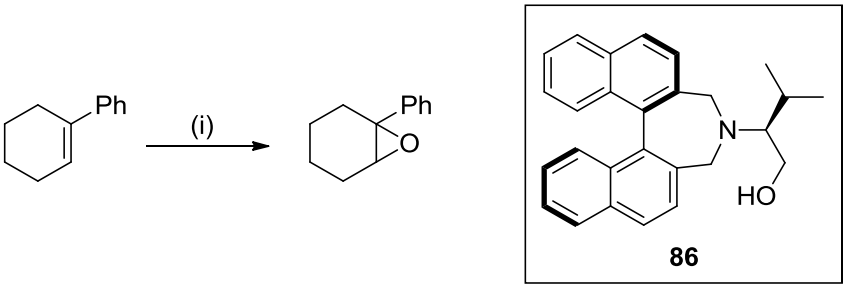
Yang showed that her fluorinated chiral secondary amine catalysts were effective in the epoxidation of 1-phenylcyclohexene, affording ee's as high as 61% when utilizing chiral proline-derived catalyst **85** (Scheme 22).[75]



Scheme 22. *Reagents and conditions*: (i) Amine **85** (5 mol%), Oxone (2 eq.), $NaHCO_3$ (5 eq.), CH_3CN-H_2O (10:1), r.t., 2 h, 92%, 61% ee.

1.4.10 Page & Lacour's Amine-Catalysed Epoxidations

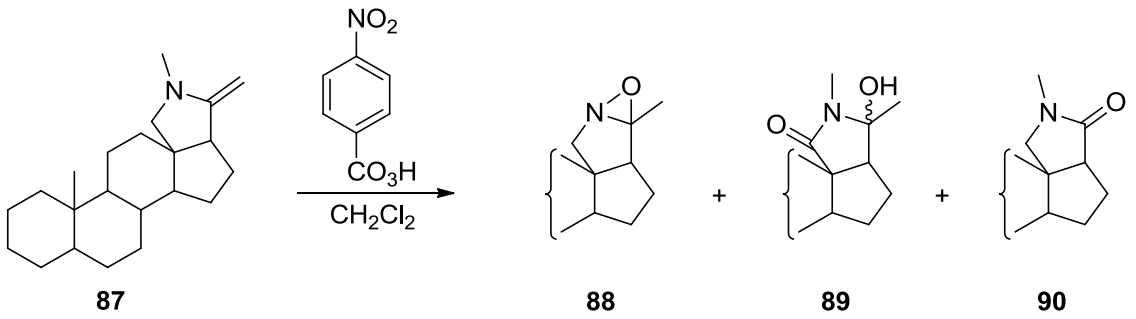
Page & Lacour have recently reported novel binaphthalene–amine catalysts for the asymmetric epoxidation of a range of alkenes. The epoxidation of 1-phenylcyclohexene was achieved in 81% ee under aqueous conditions using chiral binaphthalene amine **86** (Scheme 23).[76]



Scheme 23. *Reagents and conditions*: (i) Amine **86** (10 mol%), Oxone (2 eq.), $NaHCO_3$ (5 eq.), CH_3CN-H_2O (10:1), 0 °C, 2 h, 81% ee.

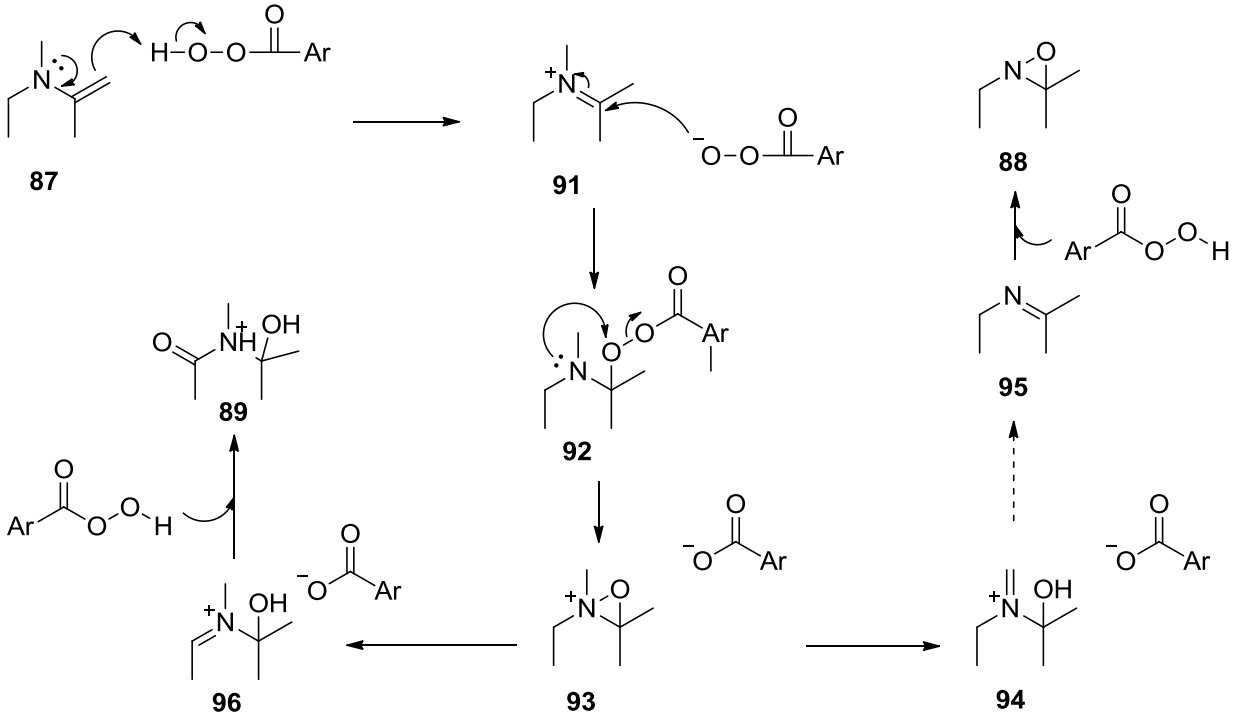
1.4.11 Oxaziridinium Salt-Catalysed Epoxidations

Lusinchi first reported steroid-based oxaziridinium salts in 1976. Lusinchi initially described the formation of an oxaziridine **88** from a reaction between enamine **87** and *p*-nitroperbenzoic acid in dichloromethane, whilst observing two side products, a hydroxylactam **89** and lactam **90** (Scheme 24).[77]



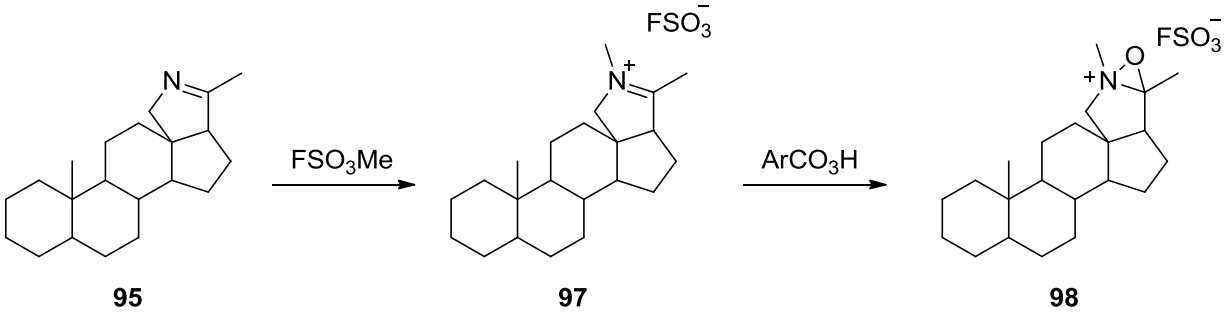
Scheme 24. Lusinchi's primary investigations into oxaziridine formation

They suggested that the hydroxylactam side product **89** is a direct result of elimination reactions occurring in the intermediate oxaziridinium salt (Scheme 25).



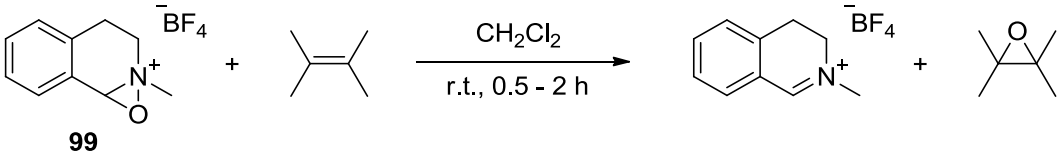
Scheme 25. Mechanism of formation of the oxaziridinium salt and hydroxylactam side products

Lusinchi showed it was possible to methylate imine **95** utilizing 'magic methyl' (methyl fluorosulfonate), yielding iminum salt **97**, which in the presence of *p*-nitroperbenzoic acid, yields steroid-based oxaziridinium salt **98** (Scheme 26).



Scheme 26. Lusinchi's oxaziridinium salt **98**

Dihydroisoquinolinium-derived oxaziridinium salt **99** was later reported to be effective for the epoxidation of various olefins (Table 19).[78]



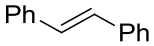
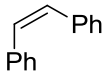
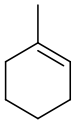
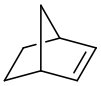
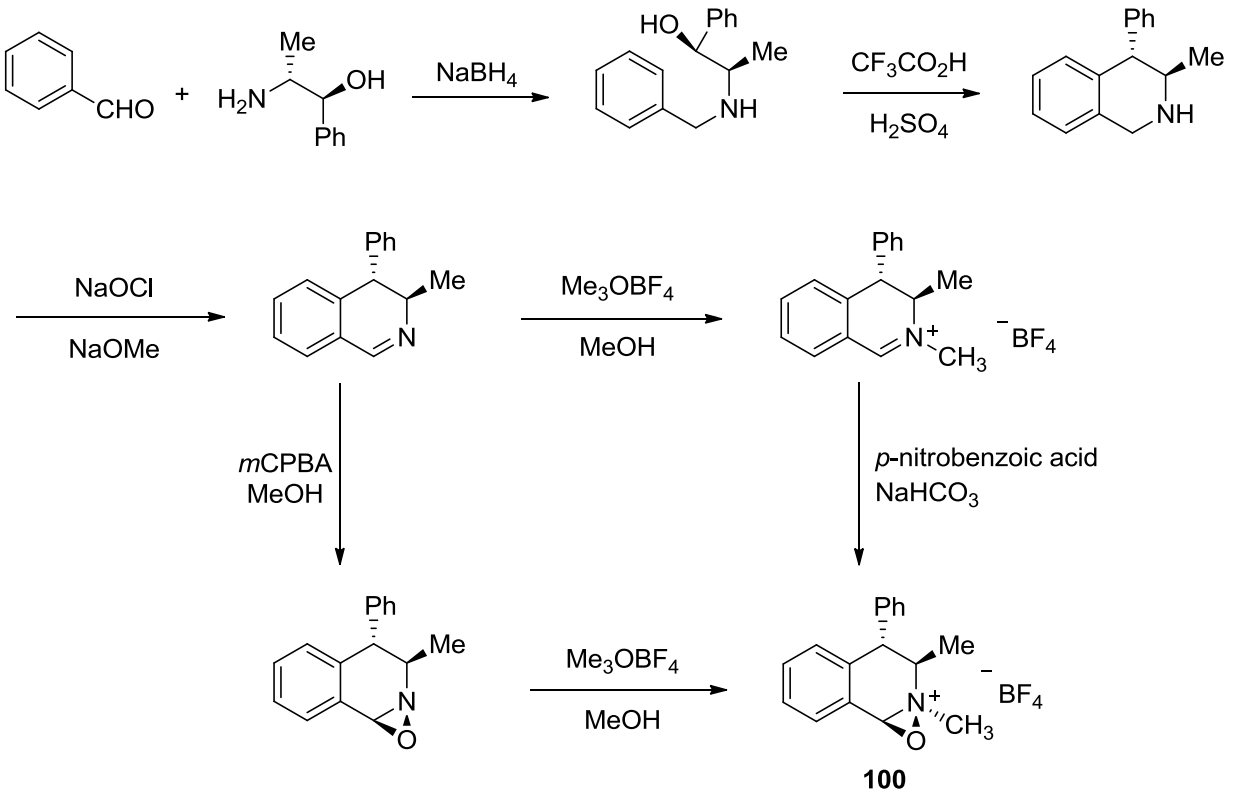
Substrate	Time / mins	Epoxide % Yield
	30	96
	60	89
	10	84
	10	75

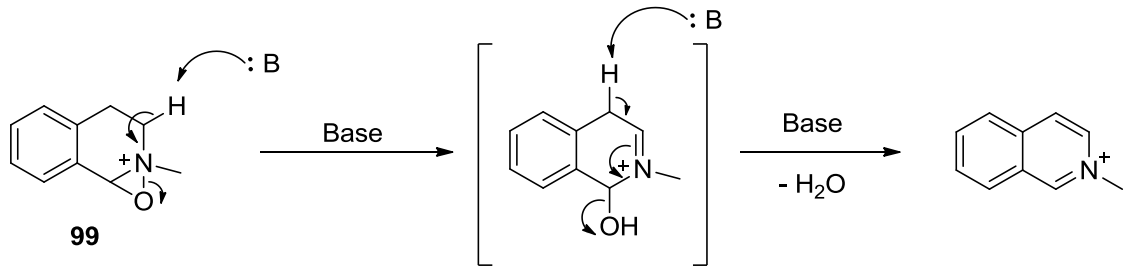
Table 19. Lusinchi's epoxidation utilizing oxaziridinium salt **99**

In 1993, Lusinchi reported the first synthesis of a chiral enantiomerically pure oxaziridinium salt **100** (Scheme 27), which was shown to effect the epoxidation of *trans*-stilbene in 33% ee.[79]



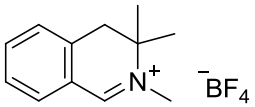
Scheme 27. Lusinchi's synthesis of enantiomerically pure oxaziridinium salt **100** from (1*S*,2*R*)-(+)-norephedrine

Bohé later showed that oxaziridinium salt **99** can be deactivated by *in-situ* base-catalysed dehydration, accounting for the poor catalyst efficiency observed (Scheme 28).[80]



Scheme 28. *In-situ* base catalysed dehydration of oxaziridinium salt **99**

Bohé developed an achiral 3,3-disubstituted-dihydroisoquinolinium catalyst **101** (Figure 17) that, in the presence of Oxone, can generate an oxaziridinium salt with an improved catalyst turnover in comparison to iminium salt **99**, due to the exclusion of the aromatization pathway (Scheme 28). Iminium-salt **101** is capable of epoxidizing *trans*-stilbene in 87% yield in 7 h (in comparison, catalyst **99** completes the same reaction in 16 h).[81]



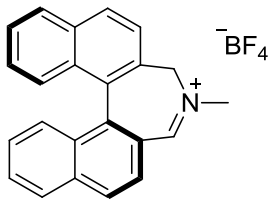
101

Figure 17. Bohé's improved 3,3-disubstituted-dihydroisoquinolinium catalyst **101**

Several research groups have since also reported their individual chiral oxaziridinium-salt catalysts capable of catalyzing epoxidations of various olefins, and are discussed herein.

1.4.12 Aggarwal's Chiral Binaphthalene Azepinium Salt Catalyst

Aggarwal reported an effective chiral binaphthalene azepinium salt catalyst **102**, containing an achiral methyl group as the nitrogen substituent (Table 20), which produced promising results and 71% ee for the epoxidation of 1-phenylcyclohexene.[82]



102

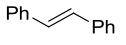
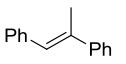
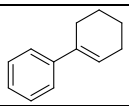
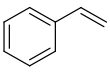
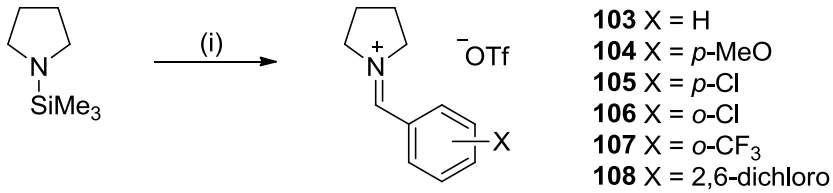
Alkene	Reaction Time / h	% Yield	% ee
	3	71	31 (*R*,*R*)
	2	60	45 (*R*,*R*)
	2	80	71 (*R*,*R*)
	1	80	39 (1*S*,2*R*)
	12	66	8

Table 20. *Reagents and conditions*: Conditions: **102** (5 mol%), Oxone (1 eq.), $NaHCO_3$ (4 eq.), MeCN-H_2O

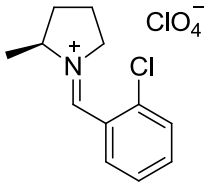
1.4.13 Armstrong's Exocyclic Iminium Salts

In 1997, Armstrong reported a range of exocyclic iminium triflate salts, generated from the condensation of *N*-TMS-pyrrolidine and aromatic aldehydes (Scheme 29). Catalysts **106** and **107**, containing *ortho* electron-withdrawing substituents were found to be most effective, with catalyst **107** affording yields up to 93% for the epoxidation of various olefins with Oxone.[83]



Scheme 29. *Reagents and conditions*: (i) ArCHO (1 eq.), TMSOTf (1 eq.), Et_2O.

Armstrong later reported chiral variants of exocyclic iminium salt catalysts **103 – 108**. These chiral catalysts were difficult to synthesize, and in the best cases, were isolated and used as crude samples. One equivalent of chiral iminium salt **109** was shown to effect the epoxidation of 1-phenylcyclohexene in 22% ee (Figure 18).[84]

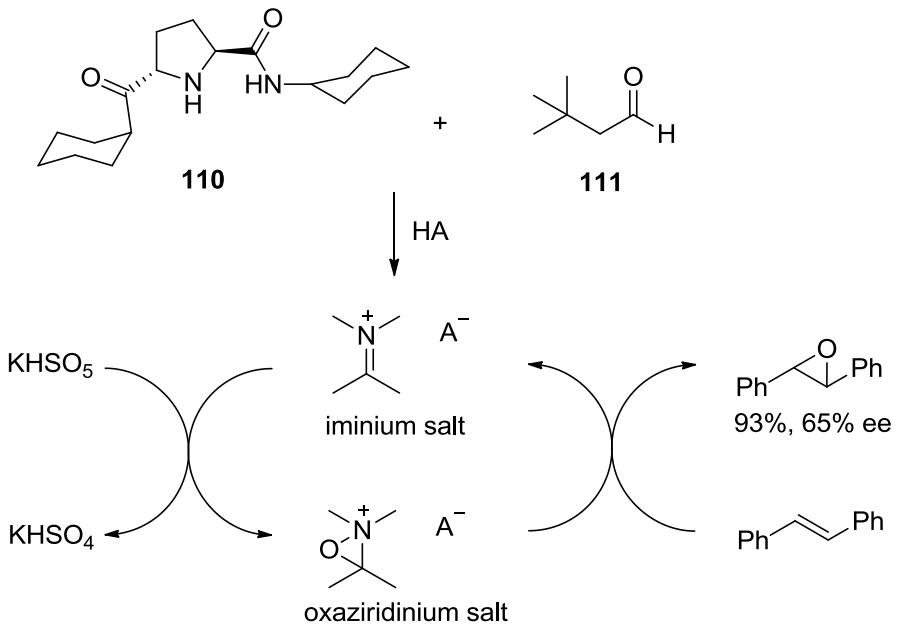


109

Figure 18. Armstrong's chiral pyrrolidine derived iminium salt **109**

1.4.14 Yang's Chiral Iminium Salts

Yang showed that moderate to good enantioselectivities could be achieved for the epoxidation of various olefins, when iminium salts were generated *in situ* from a range of aldehydes and amines.[85] The epoxidation of *trans*-stilbene occurred in 65% ee utilising C_2-symmetric amine **110** and β-branching aldehyde **111** (Scheme 30).



Scheme 30. Yang's asymmetric epoxidation of *trans*-stilbene

1.4.15 Lacour's TRISPHAT Counter Ions

In 2002, Lacour reported a novel biphasic asymmetric epoxidation system for a range of simple olefins, utilizing a biphenyl-derived iminium salt **112** containing a TRISPHAT counterion **113** (Figure 19).[86]

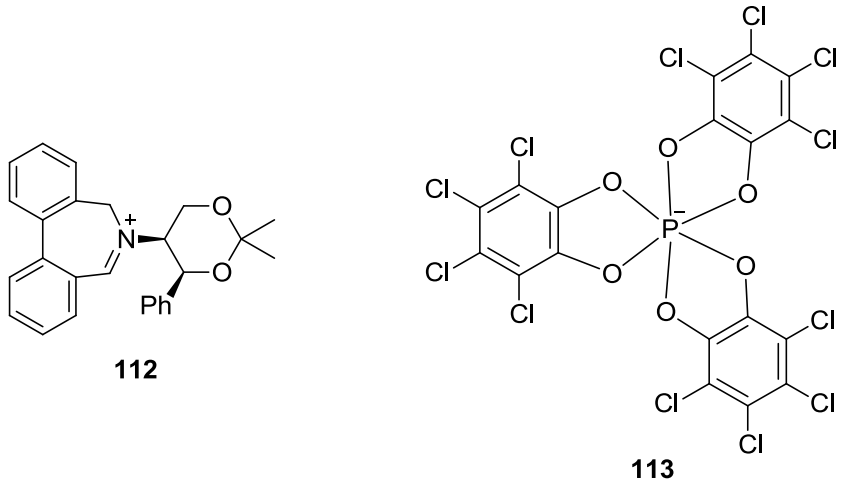
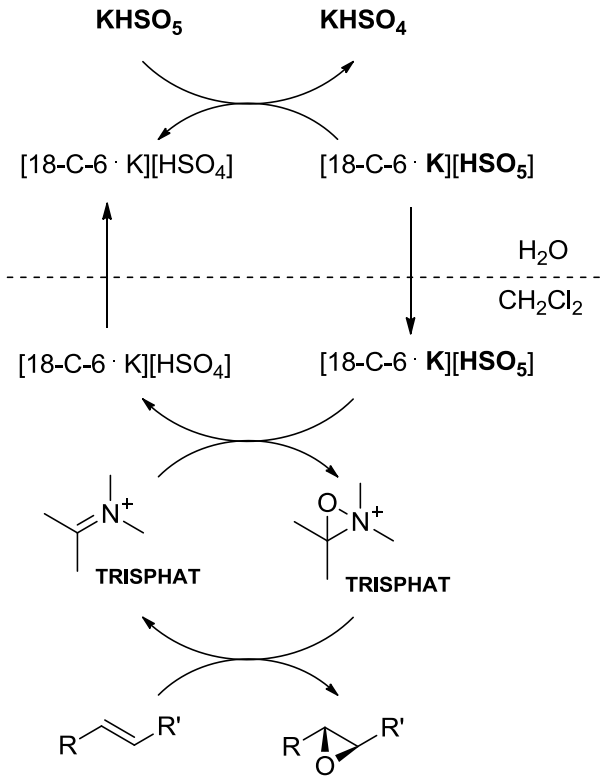


Figure 19. Lacour's biphenyl-derived iminium **112** and TRISPHAT anion **113**

Initial reactions carried out under standard aqueous epoxidation conditions (MeCN:H_2O, 1:1) with the new iminium salt yielded similar results as reported by Page,[87] who utilised a biphenyl azepinium salt with tetraphenylborate as the counterion (both systems affording ee's ~60%).

Lacour then proposed a biphasic solvent system (CH_2Cl_2:H_2O) that was tested in the epoxidation of a range of olefins, but, no sign of epoxidation was observed. They realised the addition of a catalytic amount of 18-C-6 would allow the transportation of $KHSO_5$ (Oxone) between the aqueous and organic layers (Scheme 31).



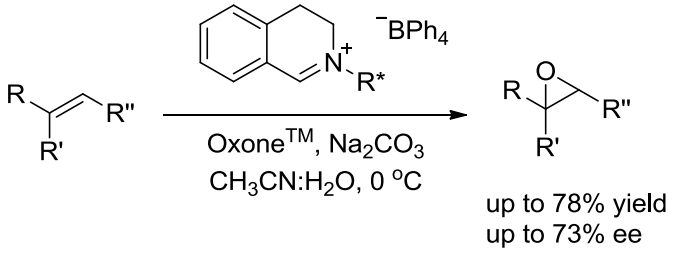
Scheme 31. Lacour's proposed mechanism for the epoxidation of olefins in the presence of catalytic amounts of 18-C-6

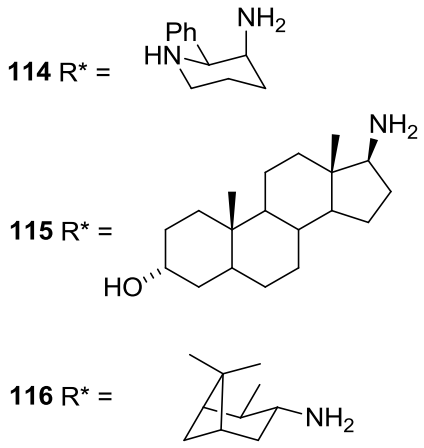
This new methodology allowed the epoxidation of olefins in up to 89% yield, and showed good enantioselectivities; the combination of iminium **112** and TRISPHAT **113** was shown to effect the epoxidation of 1-phenyl-3,4-dihydronaphthalene in 76% ee.

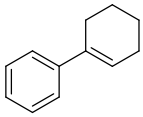
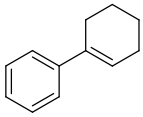
Lacour later reported a range of their biphenyl and binaphthyl tertiary azepines and quaternary iminium salts, and showed both to be effective for the asymmetric epoxidation of unfunctionalized olefins, affording ee's up to 83%.[88]

1.4.16 Page's Iminium Salt-catalyzed Epoxidations

Page was the first to report iminium salt catalysts containing a chiral substituent on the iminium nitrogen atom, exocyclic to the ring containing the iminium unit: by bringing the enantiocontrolling asymmetric centre close to the site of oxygen transfer, the belief was that higher enantioselectivities would be obtained. In 1998, Page reported his new catalytic procedure for the asymmetric epoxidation of olefins, utilizing easily prepared dihydroisoquinolinium iminium salts **114 – 116** (5 – 10 mol%) and Oxone as the oxidant, achieving ee's of up to 73% (Table 21).[89]





Catalyst	Alkene	Catalyst Loading/ mol%	% Yield	% ee
114		1	39	25
115		0.5	47	14

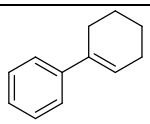
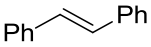
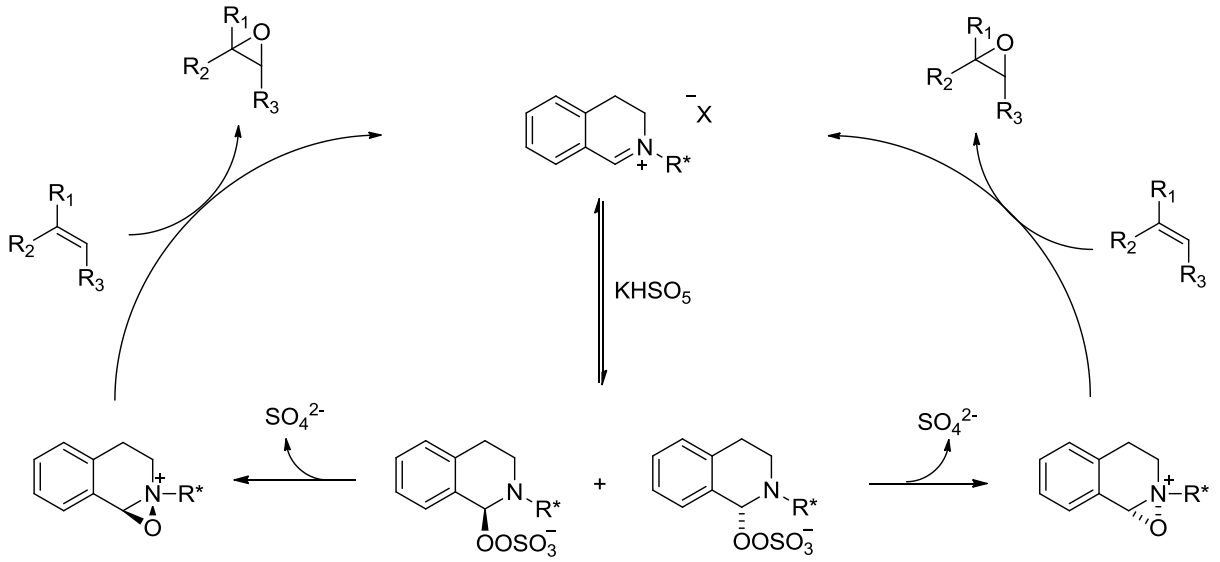
116		5	68	40
116		10	78	73

Table 21. Page's dihydroisoquinoline iminium salts used in the catalytic asymmetric epoxidation of alkenes by Oxone

The novel catalytic procedure reported by Page had some advantages over previously reported chiral iminium salt-catalyzed epoxidations, including;

- The iminium salts can be synthesized with ease; they require no purification *via* chromatography, and most of the starting materials can be purchased or made using simple synthetic steps (catalyst synthesis can be easily scaled up to 70 g)
- Epoxidations require a reduced catalyst loading (<10 mol%); a direct comparison to Shi's general chiral dioxirane-catalyzed epoxidation procedure which requires up to 30 mol% in cases

For these reasons alone, further investigations were undertaken including extending the substrate scope and modifying the existing iminium salt structure. To understand the mechanism of oxygen transfer in these asymmetric epoxidation reactions, Page later proposed a catalytic cycle similar to that previously reported by Hanquet and Lusinchi,[90] in which the oxidative intermediate is an oxaziridinium salt (Scheme 32).[91]



Scheme 32. Page's proposed catalytic cycle for oxaziridinium-mediated asymmetric epoxidation

Analysis of the mechanism shows the likely first step to be nucleophilic attack of the persulfate anion on the carbon of the iminium bond. The generation of two possible diastereoisomers arises from persulfate attack occurring from both the *si* and *re* faces of the iminium bond, and, after irreversible expulsion of sulfate, two diastereomeric oxaziridinium species can be formed. In theory, these diastereomers would afford differing levels of enantioselective oxygen transfer occurring to pro-chiral olefin substrates. Page proposed that the rate determining step in the mechanism is the irreversible expulsion of sulfate.

1.4.17.1 Analysis of the Reaction Parameters

Page further studied the reaction parameters in attempts to optimize the reaction conditions; these included counter ion effect, effect of the solvent system, temperature variation and catalyst loading.[91] Since the *N*-isopinocampheyl-derived iminium salt **116** showed an optimum between reactivity and enantioselectivity, this catalyst was chosen as a model for testing these parameters.

1.4.17.1 Effect of Counter-Ion

Iminium salt **116** was found to be successful in forming precipitates with a variety of counter-ions, which allowed the generation of not only the tetraphenylborate salt, but also the tetrafluoroborate, hexafluorophosphate, perchlorate and periodate salts. Under aqueous conditions (Oxone (2 eq.), Na_2CO_3 (4 eq.), MeCN:H_2O (1:1), 0 °C), the asymmetric epoxidation of 1-phenylcyclohexene was observed with 5 mol% of catalyst **116** with various counter-ions.[91] The periodate salt produced an enantioselectivity (35% ee) comparable to the tetraphenylborate species (40% ee), but the perchlorate species produced the poorest enantioselectivity of all the species tested (20% ee). However, all of the salts afforded the same enantiomer of epoxide product (*R*,*R*) and all reactions were completed after 45 minutes.

1.4.17.2 Effect of Solvent System

Page observed that increasing the ratio of water:acetonitrile from 1:1 to 2:1 had the general effect of increasing the reaction rate, presumably due to increased Oxone solubility and thus increased availability for consumption in the desired oxygen transfer process. Page reasoned that increasing the amount of water would allow quicker nucleophilic attack of the persulfate ion on the iminium bond, and better solvation of the departing sulfate anion.

The effect was noticed to be more pronounced at lower catalyst loadings; for example, the asymmetric epoxidation of 1-phenylcyclohexene utilizing 0.5 mol% of iminium salt **116** with a tetraphenylborate anion under aqueous conditions (H_2O:MeCN, 1:1) afforded only 30% yield of 1-phenylcyclohexene oxide after 1 hour. However, at a 2:1 ratio (H_2O:MeCN) 1-phenylcyclohexene oxide was attained in quantitative yield under similar conditions.[91]

Reducing the amount of Oxone (1 eq.) and sodium carbonate (2 eq.) used in the asymmetric epoxidation reactions by half resulted in incomplete conversion after one hour in the improved (2:1) conditions.

Page later disclosed results linking the effects of co-solvent polarity with any asymmetric induction observed, hoping to clarify the mechanism of the epoxidation reactions (Scheme 32).[91]

The co-solvents were selected so that they differed significantly in dielectric constant (ε, indicated by the values in brackets), including dichloromethane (8.9), trifluoroethanol (26.7), acetonitrile (37.5), water (78.4) and formamide (111). The epoxidation of 1-phenylcyclohexene was studied this time using iminium salt **116** (10 mol%) as both its tetraphenylborate and perchlorate salts using the co-solvents stated above in a 1:1 ratio with water. The perchlorate salt exhibited an interesting trend; when the co-solvent was trifluoroethanol, the reaction was complete in 30 minutes with quantitative conversion and 26% ee. But, in dichloromethane the reaction took three hours to reach 50% conversion, affording the epoxide in an increased 33% ee. In formamide there was no reaction, and this result was the same for the tetraphenylborate salt. Page reasoned that the lack of reactivity in formamide could be linked to the iminium species becoming highly solvated, and potentially leads to the irreversible attack of formamide on the iminium species. When the tetraphenylborate salt was tested under chlorinated co-solvent conditions, no conversion was observed after three hours, which is probably the result of poor miscibility between the two solvents, thus limiting the availability of inorganic oxidant in the organic phase.[91]

1.4.17.3 Effect of Temperature

Oxone is known to be unstable at elevated temperatures under alkaline conditions, and the freezing point of aqueous solvent systems limits the temperature of asymmetric epoxidations to close to 0 °C. Epoxidation experiments conducted at –10 °C under the standard 1:1 conditions were found to be slow due to the insolubility of inorganic Oxone and sodium carbonate. Upon increasing the ratio of water:acetonitrile to 3:1, the epoxidation of 1-phenylcyclohexene using catalyst **116** at –10 °C went to full conversion after 45 minutes, affording 1-phenylcyclohexene oxide in good yield and similar enantioselectivity (35% ee) in comparison to the reaction carried out at 0 °C (40% ee).[91] When the reactions were repeated between 27 – 32 °C, negligible epoxidation was observed after 1 hour, and this is linked to the instability of either Oxone or the oxaziridinium species at elevated temperatures.

1.4.17.4 Effect of Catalyst Loading

The epoxidation of 1-phenylcyclohexene at 0 °C utilizing iminium salt **116** at various catalyst loadings was investigated. Analysis of the data found the optimum loading was 2 mol% for this model (Figure 20). Page further observed in this model that at very low catalyst loadings, lower enantioselectivities were achieved. In this instance, Page didn't report how the conversion was affected by varying the catalyst loading. Through all the evidence accrued, Page proposed that the alkene is not involved in the rate determining step in the mechanism.[91]

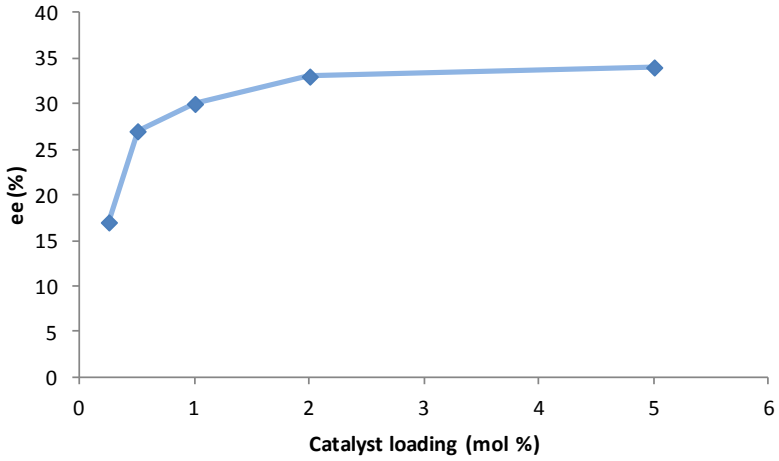


Figure 20. Effect of catalyst loading on the asymmetric epoxidation of 1-phenylcyclohexene utilising iminium salt **116**

1.4.18 Page's Alcohol, Ether and Acetal Derived Dihydroisoquinolinium Salts

In 2001, Page reported a range of iminium salts functionalized at the nitrogen atom, which could be easily prepared from amino alcohols, amino ethers and amino acetals, affording enantiomeric excesses up to 60%. Page reasoned that the extra polar units within the chiral exocyclic substituent might help to control the diastereofacial selectivity of attack of the iminium unit by persulfate and/or the diastereofacial selectivity of approach of the alkene substrate to the reactive oxidizing intermediate.[87]

1.4.18.1 Page's Iminium Salts Derived from Chiral 1,2-Amino Alcohol Precursors Containing a Primary Hydroxyl Group

Readily available α-amino acids can be easily reduced to afford the corresponding chiral 1,2-amino alcohols, which in turn undergo condensation reactions with 2-(2-bromoethyl)benzaldehyde to afford the desired dihydroisoquinolinium salts **117** – **120** (Figure 21).[87]

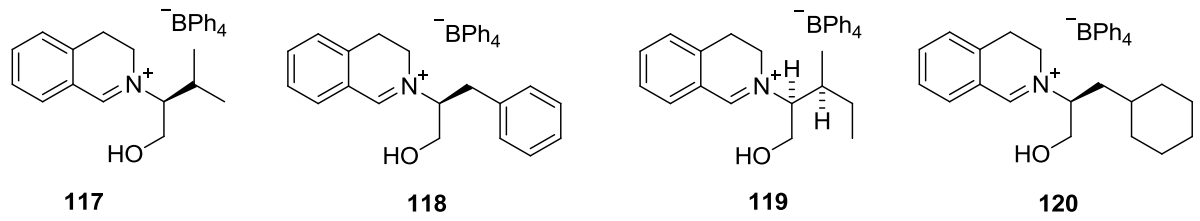
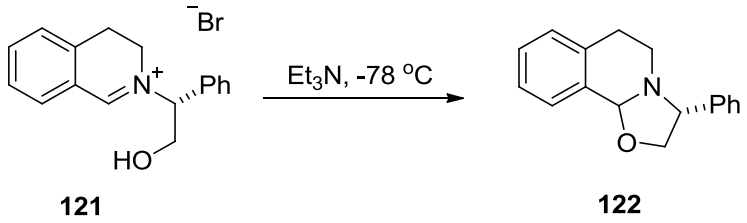


Figure 21. Page's iminium salts derived from chiral 1,2-amino alcohol precursors containing a primary hydroxyl group

Similar dihydroisoquinolinium salts containing a pendent hydroxyl group such as **121** have been reported to undergo base-induced ring closure yielding oxazolidines **122** (Scheme 33),[92] but Page did not observe such problems in the synthesis of his iminium salts.



Scheme 33. Yamamoto's base induced ring closure

When salts **117 – 120** were employed in the epoxidation of 1-phenylcyclohexene, some interesting observations were made. Firstly, they react slower than catalysts that lack the pendent hydroxyl group, such as iminium salt **116**. Secondly, they all produce racemic 1-phenylcyclohexene oxide. Catalyst **116** (0.5 mol%) afforded the full conversion of 1-phenylcyclohexene to its corresponding epoxide in one hour, yet more than 2 mol% of catalyst **117 – 120** is required to achieve the same effect. Page reasoned the high catalyst loadings were required for **117 – 120** due to equilibrium between the ring-opened active iminium salt

and ring-closed inactive oxazolidine forms of the catalyst occurring under alkaline reaction conditions.[87]

1.4.18.2 Page's Iminium Salts from Chiral 1,2-Amino Alcohol Precursors Containing a Secondary Hydroxyl Group

Iminium salts **123** – **125** (Figure 22) were prepared from chiral 1,2-amino alcohols containing a secondary hydroxyl group, and these salts afforded improved enantioselectivities compared to catalysts **117** – **120** that contain primary hydroxyl group (up to 33% ee for the epoxidation of 1-phenyl-3,4-dihydronaphthalene utilizing iminium salt **125**).[87]

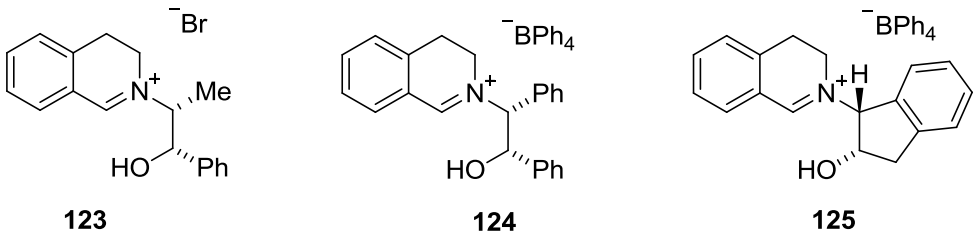
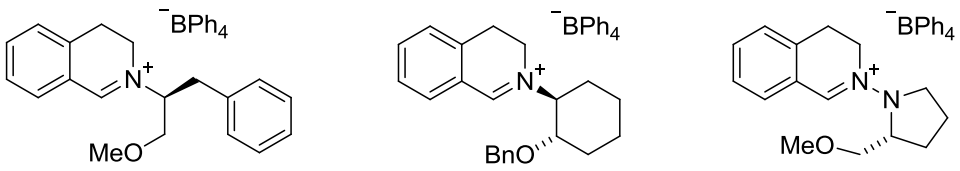


Figure 22. Page's iminium salts derived from chiral 1,2-amino alcohol precursors containing a secondary hydroxyl group

These catalysts containing a secondary hydroxyl group require a higher catalyst loading (5 mol%) for a convenient reaction time, presumably due to the equilibrium favouring the ring-closed inactive oxazolidine iminium form.

1.4.18.3 Page's Iminium Salts from Amino Ether Precursors

Iminium salts **126** – **128** (Figure 23) were prepared from simple amino ethers, and iminium salt **126** afforded poor enantioselectivity in the epoxidation of 1-phenylcyclohexene (7% ee), but was a more reactive salt than its corresponding parent alcohol **118**. This is presumably due to the absence of the ring closing effect observed with the amino alcohol derivative **118**.[87]

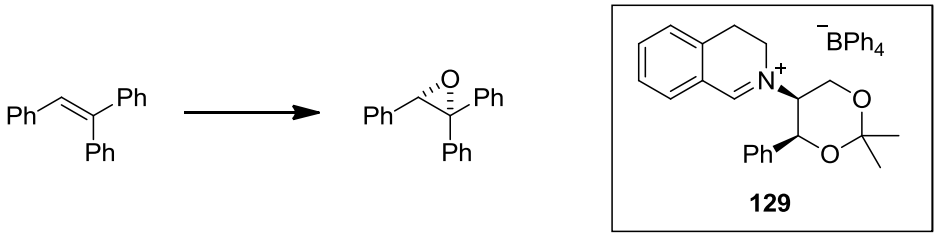


126 127 128

Figure 23. Page's iminium salts derived from amino ether precursors

1.4.18.4 Page's Iminium Salts from Amino Acetal Precursors

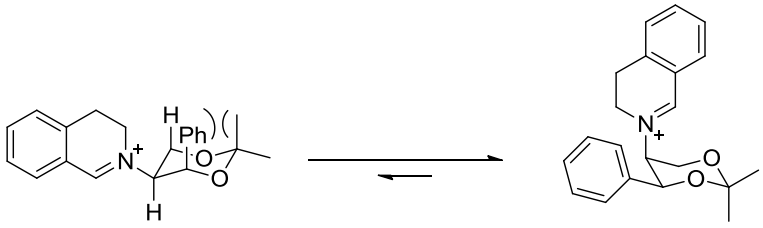
Page prepared an acetonide-derived dihydroisoquinolinium tetraphenylborate salt **129** (Scheme 34) which showed similar enantioselectivities for the epoxidation of various olefins to the isopinocampheyl-derived catalyst **116**. Dihydroisoquinolinium salt **129** containing the dioxane functionality was shown to effect the epoxidation of triphenylethylene in 59% ee (Scheme 34).[87]



129

Scheme 34. *Reagents and conditions*: iminium-salt **129** (5 mol%), Oxone (2 eq.), Na_2CO_3 (4 eq.), CH_3CN-H_2O (1:1), 0 °C

A key feature of compound **129** is the *syn* relationship between the nitrogen heterocycle and the phenyl group. The dioxane unit can adopt two conformations **130** and **131**, in which either the phenyl or dihydroisoquinolinium group must be axial (Scheme 35).

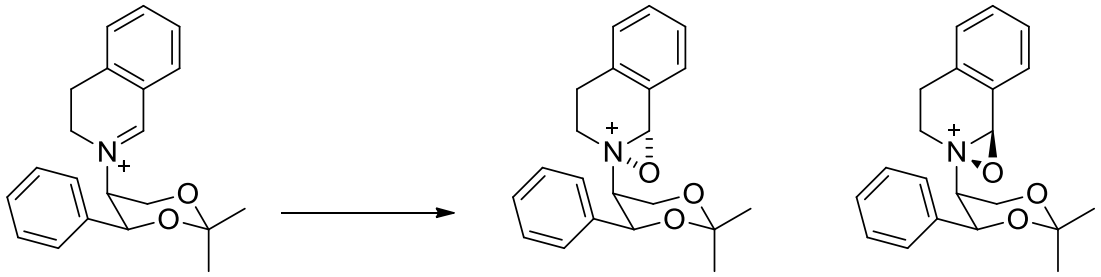


130 131

Scheme 35. Two potential chair conformations of the dioxane ring

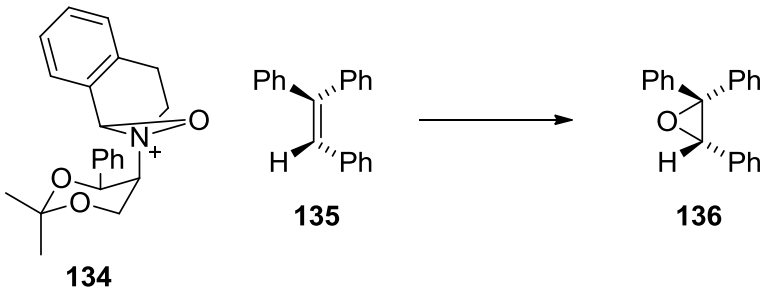
Proof of the 1,3-dioxane ring occupying a chair conformation in the solid state was shown through single crystal X-ray analysis; **131** is expected to be the thermodynamically favoured conformer due to reduced 1,3-diaxial interactions and a double gauche effect.

Page reported that the asymmetric induction in the epoxidation process may arise from conformer **131** hindering attack of the oxidant on the iminium bond from the direction of the phenyl substituent, rendering the opposite side more accessible. This would lead to major **132** and minor **133** diastereoisomeric oxaziridinium species (Scheme 36).



Scheme 36. Hindered attack of the oxidant affords two possible diastereoisomeric species

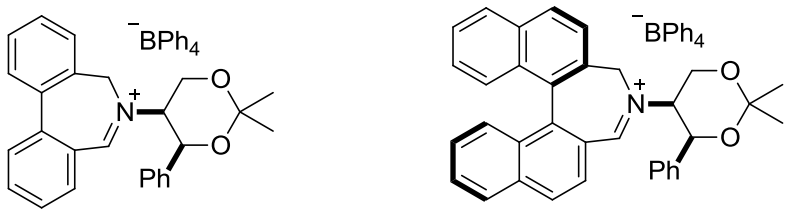
Oxygen transfer is believed to occur *via* a spiro transition state, in which oxaziridinium intermediate **134** (Scheme 37) oxidizes triphenylethylene **135** to its corresponding (*S*)-enantiomer epoxide product **136**.[40,41]



Scheme 37. Olefin approach to oxaziridinium intermediate **134** *via* a spiro transition state

As shown above, it is thought that the alkene approaches the oxaziridinium moiety so that the carbon-carbon double bond is perpendicular to the iminium bond axis.

The dihydroisoquinolinium backbone was later replaced with a biphenyl **12**/binaphthyl **137** fused to a seven-membered azepinium salt, leading to a new generation of iminium salts (Figure 24).[93,94] Under aqueous derived reaction conditions, biphenyl-azepinium salt **12** catalysed the conversion of 1-phenylcyclohexene to its corresponding epoxide in 60% ee in just 3 minutes.[93]



12 **137**

Figure 24. Page's biphenyl/binaphthyl azepinium salt catalysts

1.4.19 Variation of the Oxidant

Page initially reported the use of Oxone as the main stoichiometric oxidant during the iminium salt catalysed asymmetric epoxidation reactions,[87,89] but Oxone has its drawbacks. Oxone is insoluble in most organic solvents, is atom-inefficient, and can be unstable at room temperature. Page has recently reported new organocatalytic epoxidation systems through variation of the oxidant used to oxidize the iminium salts, and these are discussed in detail below.

1.4.19.1 Tetraphenylphosphonium Monoperoxysulfate

Page investigated an alternative to the oxidant Oxone, which was limited to aqueous-based conditions due to low solubility issues of Oxone in many organic solvents, with the terminal oxidant tetraphenylphosphonium monoperoxysulfate (TPPP).[95] This new discovery led to the development of the first ever non-aqueous epoxidation system mediated by iminium salt-catalysts.

The biphenyl-azepinium salt **12** was used in the optimized epoxidation of 1-phenylcyclohexene, affording full conversion within 3 minutes, yielding the epoxide in 67%

ee.[94] In 2012, Page further illustrated this system with the enantioselective total synthesis of (+)-scuteflorin A **10** (Scheme 4, Section 1.0).[5] The key step was the biphenyl-azepinium salt **12**-mediated asymmetric epoxidation of xanthyletin **8** under non-aqueous conditions, yielding the chiral oxirane product **9** in >99% ee.

Page reported a new sulfone-containing analogue of the amino-acetal catalyst **11**, which, under the non-aqueous conditions, afforded high yields (up to 89%). Epoxidation of 6-cyano-2,2-dimethyl chromene **2** with iminium salt **11** afforded the corresponding epoxide in 97% ee, which was subsequently ring-opened to afford the antihypertensive agent levcromakalim **3**.[3] Natural products (−)-(3'*S*)-lomatin **7** and (+)-(3'*S*,4'*R*)-*trans*-khellactone **6** were obtained in 57 and 58% overall yields; a non-aqueous enantioselective epoxidation of seselin afforded the enantioenriched epoxide product in 97% ee using iminium salt **11** as the key step (Figure 25, Scheme 4).[4]

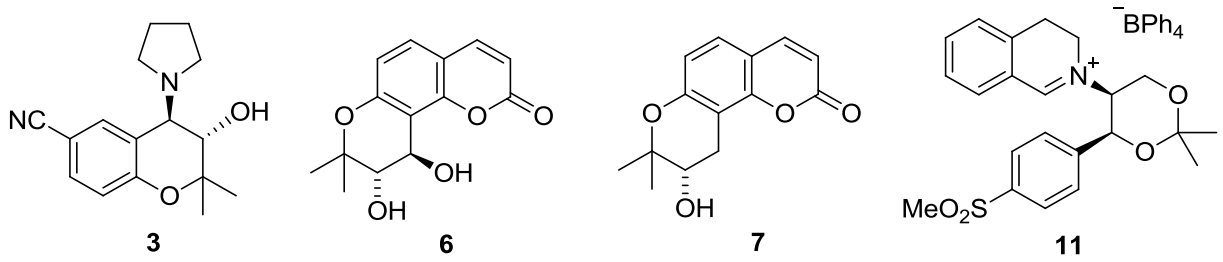


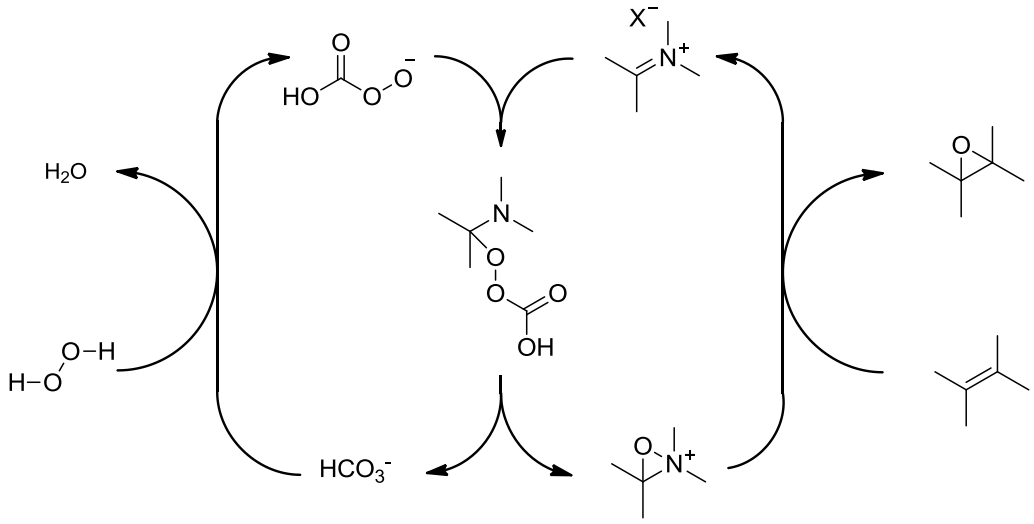
Figure 25. Levcromakalim **3**, (+)-(3'*S*,4'*R*)-*trans*-khellactone **6**, (−)-(3'*S*)-lomatin **7** and Page's sulfone-derived dihydroisoquinoline iminium salt **11**

1.4.19.2 Electrochemical Generation of Persulfate

In 2008, Page showed that a monoperoxysulfate oxidant could be generated through electrochemistry. The results reported using this new system yielded comparable ee's to those observed when using commercially available persulfate; for example, the epoxidation of 1-phenylcyclohexene afforded ee's up to 64%.[96]

1.4.19.3 Utilization of Hydrogen Peroxide as an Oxidant

Page identified that hydrogen peroxide could be used as an alternative stoichiometric oxidant in the presence of carbonate. Optimization of this new system resulted in enantiomeric excesses of up to 56% being achieved for the asymmetric epoxidation of 1-phenylcyclohexene. A double catalytic cycle was proposed; percarbonate is generated by reaction of hydrogen peroxide and hydrogen carbonate anion. This percarbonate species is then thought to oxidize the iminium salt (Scheme 38).[97]



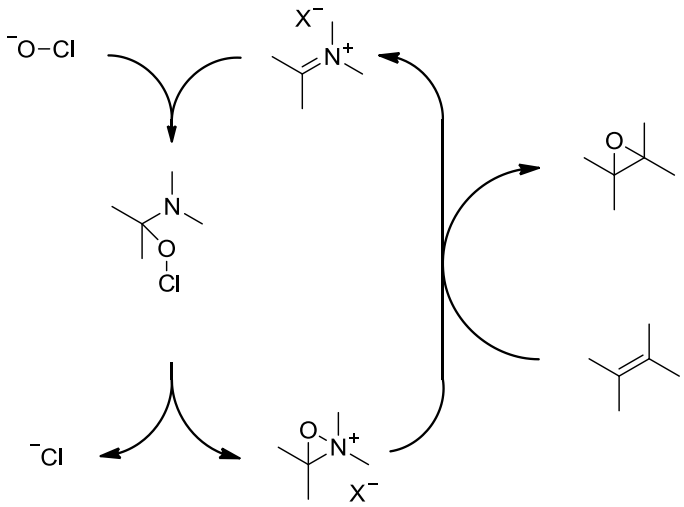
Scheme 38. Page's proposed double catalytic cycle

1.4.19.4 Utilization of Sodium Hypochlorite as an Oxidant

Page reported the first examples of iminium salt-mediated asymmetric epoxidation of olefins utilizing sodium hypochlorite as the stoichiometric oxidant: enantiomeric excesses of up to 68% were obtained for the epoxidation of 1-phenylcyclohexene.[98]

As indicated above, Page observed that carbonate salts co-catalyse the epoxidation process. Two possible mechanisms have been proposed for the asymmetric epoxidation when sodium hypochlorite is used. The first is a double catalytic cycle as shown previously in Scheme 38, where hypochlorite may generate percarbonate, which then acts as the oxygen transfer agent to

oxidize the iminium salt. Alternatively, hypochlorite itself could add directly to the iminium salt (Scheme 39).



Scheme 39. Alternative formation of the oxaziridinium salt

1.5 Kinetic Resolution

Enantioenriched compounds are highly sought after building blocks for asymmetric synthesis and there are a number of methods available to generate them. These include;

- Utilising the chiral pool: This involves the use of relatively simple, potentially cheap enantiopure starting materials (e.g. amino acids, monosaccharides) provided by nature itself to create more complex compounds. The advantage here is that the chirality is 'built-in', which can then be maintained throughout the synthesis.
- The chemical resolution of enantiomers from a racemate.
- Use of a chiral auxiliary.
- Utilisation of a chiral catalyst or reagent that is able to react with achiral starting materials, generating chirality into the product.

In the late twentieth century, Professor Henri Kagan studied kinetic resolution, becoming one of the most published in the field. Kagan defined kinetic resolution as: [99]

"*a process in which one of the enantiomers of a racemic mixture is more readily transformed into a product than is the other*"

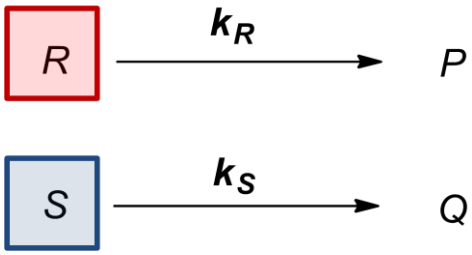


Figure 26. Kagan's explanation of the kinetic resolution of two starting material enantiomers

Kagan stated that kinetic resolution occurs when $k_R \neq k_S$, and the reaction is stopped between zero and 100% conversion. Ideally only one enantiomer reacts, e.g. enantiomer *R*, so that at 50% conversion, a mixture of 50% *S* enantiomer is recovered, and 50% of product *P* is obtained (Figure 26).

One of the major drawbacks associated with kinetic resolutions is that the maximum yield of the desired product is limited to 50%. One of the major advantages of a kinetic resolution is that racemic starting materials are considerably cheaper than their chiral counterparts, and this reason alone makes an effective kinetic resolution attractive.

Jacobsen has most recently reviewed the advances in kinetic resolution reactions for a range of metal-based and organocatalytic epoxidation reactions.[100] He reported a number of conditions that should be met to make kinetic resolutions more attractive for utilizing this methodology on a large scale in asymmetric syntheses of complex molecules;

- The racemic starting material should be cheap, and the product cannot be made using other resolution methodologies.
- The catalyst employed should: (1) be cheap to synthesize, (2) consume only one enantiomer from the racemate, (3) be used at the lowest possible catalyst loading.
- The starting material recovered should be easily separable from the product obtained.
- Both the chiral product obtained from the resolution and the recovered starting material are valuable and are obtained in high enantioselectivities.

1.5.1 Alternative Resolution Methods

Classic resolutions typically utilize a stoichiometric amount of chiral resolving agent that can generate a separable pair of diastereoisomers by formation of complexes, and after removal of the chiral resolving agent, the chiral substrate is produced. The first manual resolution was demonstrated by Louis Pasteur in 1848 without the use of a chiral resolving agent on racemic ammonium sodium tartrate,[101] and later in 1858 he discovered the enantioselective destruction of a racemic mixture (ammonium tartrate) with a chiral reagent (*Penicillium glaucum*).[102]

Chiral chromatography can be applied on a preparative scale, and allows a mobile phase containing the racemate to pass over a chiral stationary phase, thus allowing the separation of enantiomers on a large scale. This method is however limited by costs, including long separation times and high volumes of solvent required.

Dynamic kinetic resolutions utilize a starting material racemization step which occurs at a faster rate than that of the starting material to product transformation (Figure 27). The main advantage this method has over kinetic resolutions is that the product can be isolated in 100% yield, with the enantiomeric excess determined by the magnitude of difference in energy between the diastereomeric transition states in the selectivity determining step.

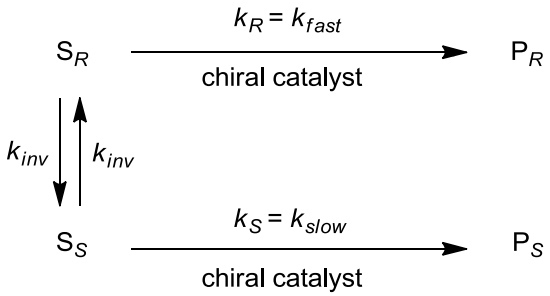


Figure 27. Dynamic kinetic resolution

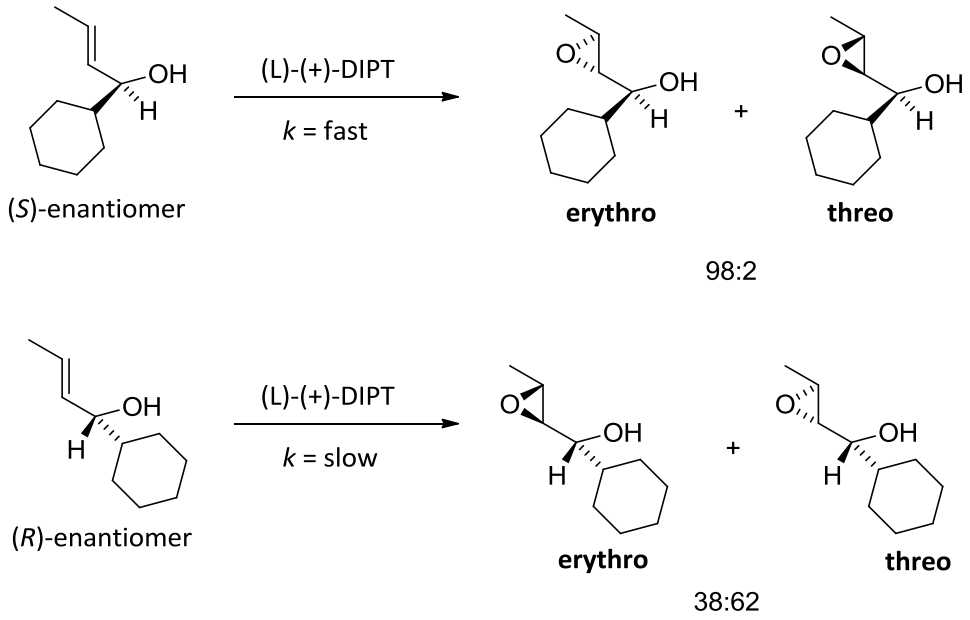
1.5.2 Kinetic Resolution of Racemic Alkenes Using Catalytic Asymmetric Epoxidation

Kinetic resolution of racemic alkenes using asymmetric epoxidation is an attractive topic for asymmetric catalysis, as racemic alkenes are generally cheap and readily available, but is potentially more challenging than the asymmetric epoxidation of prochiral alkenes. Catalytic

kinetic resolutions are attractive because only small amounts of chiral agent are required. Kinetic resolution in asymmetric epoxidation has been observed previously by Sharpless,[103] Jacobsen,[104] Katsuki,[105] Shi[57] and Yang,[107] and is discussed below.

1.5.3 Sharpless's Kinetic Resolution

Some of the first reports of kinetic resolution in asymmetric epoxidation were published by Sharpless in 1981.[103] Sharpless applied his titanium alkoxide tartrate catalysts in the epoxidation of racemic secondary allylic alcohols. Sharpless initially found three variables that defined the kinetic resolution results observed. These include the enantiomeric excess of the recovered starting material, the percentage conversion of racemic substrate, and the relative rate of the reaction. The relative rate can be calculated if the first two factors are already known (e.g. at 50% conversion, and 75% ee starting material retained, relative rates of k_{rel} = 5 – 10 are observed). Sharpless showed that the epoxidation of racemic *trans*-cyclohexylpropenylcarbinol under his epoxidation conditions using L-(+)-diisopropyltartrate afforded some interesting results (Scheme 40).



Scheme 40. Differences observed in erythro-threo selectivity for the enantiomers of *trans*-cyclohexylpropenylcarbinol

The epoxidation of the (*S*)-enantiomer of *trans*-cyclohexylpropenylcarbinol proceeded at a faster rate than its opposite (*R*)-enantiomer, affording the major product as the erythro product (98:2). Scheme 9 shows that L-(+)-tartrates deliver oxygen from the underside of the molecule when posed as in the standard Sharpless mnemonic. The experimental data collected by Sharpless confirm this theory (the (*S*)-enantiomer reacts 104 times faster than the (*R*)-enantiomer). As shown in Scheme 40, the allylic alcohol is drawn so that the alkene carbons and hydroxyl lie in the plane of the paper, with the carbinol carbon positioned at the lower right. Nearly all of the secondary allylic alcohols Sharpless tested adhere to a recurring trend; when L-(+)-tartrates are used the fastest reacting enantiomer is the one in which the substituent on the carbinol carbon is up when the allylic alcohol moiety is drawn ((*S*)-enantiomer, Scheme 40).

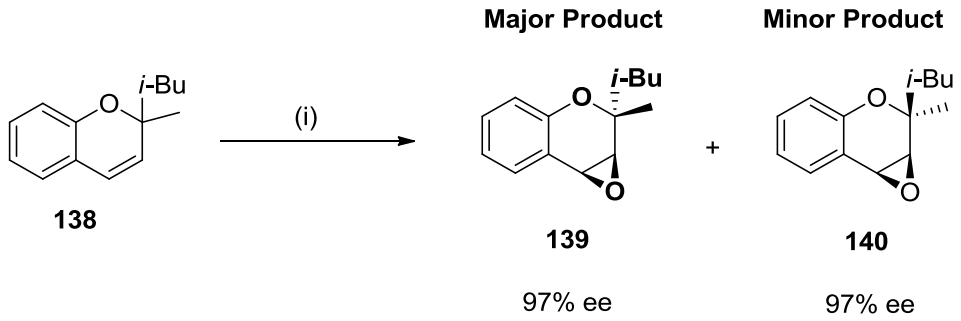
These high erythro:threo ratios obtained when using Sharpless conditions can be compared to those of the achiral vanadium metal-based epoxidation catalyst ($VO(acac)_2$/TBHP/CH_2Cl_2), which is the next best alternative. The ratios are slightly lower for the vanadium-based catalyst (ratios of erythro/threo of 75-80/25-20).[106]

Sharpless also performed epoxidation experiments where the reaction was stopped at 50% and 100% conversion respectively. Followed by GC, at 50% conversion, 49% yield of erythro epoxide product was obtained in 96% ee. Meanwhile, at 100% conversion, after chromatography, the threo product was also isolated in 20% yield and 92% ee.

Interestingly, Sharpless observed that increasing the size of the tartrate ligand (DMT → DET → DIPT) greatly affects the rate difference in epoxidation of the enantiomers from the racemic starting material. He also concluded that an excess of tartrate ligand (1.5:1.0 of tartrate:titanium isopropoxide) was essential in order to detect resolution in complex secondary allylic alcohol substrates, and that, under normal conditions of 1:1 (tartrate:titanium isopropoxide), no kinetic resolution would be observed, presumably due to unwanted epoxidation by non-ligated titanium-alkoxide species.

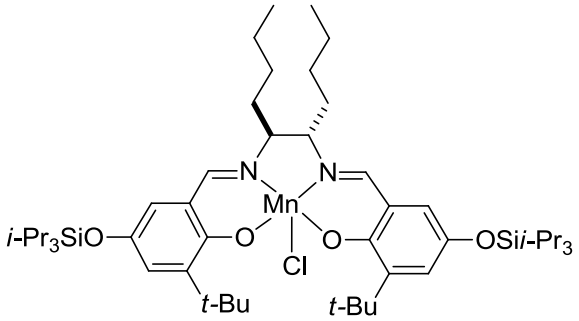
1.5.4 Jacobsen's Kinetic Resolution

In 1995, Jacobsen reported that using his manganese salen catalyst **27**, in the presence of an oxidant (*m*CPBA), under non-aqueous conditions, he was able to oxidize racemic conjugated olefins, more specifically *cis*-chromenes in up to 97% ee. Jacobsen interestingly found that at partial conversions of alkene to epoxide, the major epoxide product **139** (in which the *iso*-butyl group is *trans* to the epoxide, confirmed by circular dichroism and NOE measurements) is generated in preference, and could be separated from the minor product by flash chromatography. This would indicate a difference in reactivity of each of the two alkene enantiomers (Scheme 41). Jacobsen did not report any yields for either the major or minor products of the kinetic resolution reaction.[104]



Scheme 41. *Reagents and conditions*: (i) Catalyst **27**, *m*CPBA, CH_2Cl_2, NMO, -78 °C.

Jacobsen found that these kinetic resolution results could be enhanced further by reducing the temperature to –78 °C and by changing the manganese-salen catalyst's steric and electronic properties. The most pronounced changes occurred when the sterically hindered, electron rich catalyst **141** was used, leading to greater enantioselectivity in the epoxidation and the highest relative rate of 6.9.



141

Jacobsen also observed that the nature of the alkyl substituents on the starting materials was important to obtain high selectivity. He observed a highest rate of selectivity of 9.3, when the alkyl substituent was an isopropyl group, in comparison to a rate of 4.5 for the unbranched n-pentyl alkyl group (Table 22).

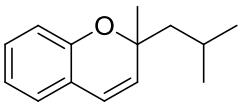
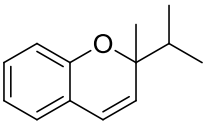
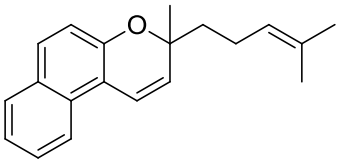
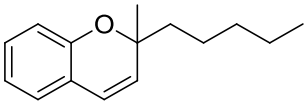
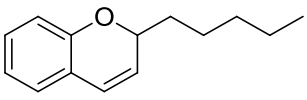
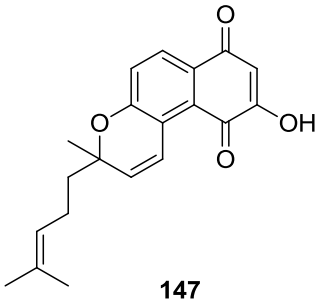
Compound Reference	Substrate	k_{rel}
142		6.9
143		9.3
144		6.1
145		4.5
146		2.7

Table 22. k_{rel} = relative rate, calculated by; ln[(1 - C)(1 - ee)]/ln[(1 - C)(1 + ee)], C is the fraction of remaining olefin, ee is the % enantiomeric excess

Jacobsen also applied his methodology to the epoxidation of tricyclic substrates (**144**, Table 22), but found that the substrates reacted much more slowly, yielding 60% conversion over long reaction times (in comparison bicyclic >80% conversion in 10 minutes).

Interestingly, the lowest selectivity was achieved using 2-pentylchromene, which only providing a rate of 2.7. Jacobsen accounted for this selectivity by proposing that the epoxidation proceeded through a competitive, non-asymmetric aromatization pathway, which in turn yielded multiple complex products. Jacobsen's kinetic resolution was applied to the synthesis of teretifolione B **147**. The key epoxide was isolated at 80% conversion, and only 15% yield (30% theoretical), but more importantly in high enantiomeric excess (91% ee). The observed relative rate was 3.4, which was lower than the one observed for tricyclic chromene **144** (Table 22, k_{rel} = 6.1).[104]



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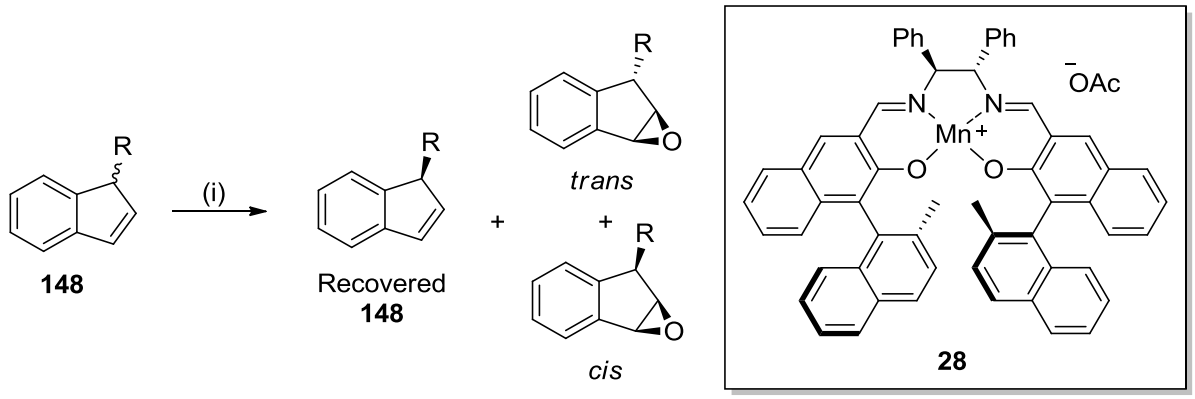
Overall, Jacobsen's kinetic resolution data involves high selectivity, but with moderate substrate-induced selectivity.

1.5.5 Katsuki's Kinetic Resolution

Katsuki reported results of kinetic resolution observed with their manganese-salen based catalysts **28**.[105] Katsuki's substrates for kinetic resolution were all racemic conjugated olefins. Their theory involved the metal centre of the manganese-salen catalyst being capable of differentiating between enantiomers in racemic substrates. As described earlier, they believed that a radical-based mechanism accounts for the formation of the major epoxide product in high enantioselectivity. Their main substrates for epoxidations were 3-alkylindenes **148** (Scheme 42).

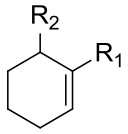


Scheme 42. *Reagents and conditions*: (i) Catalyst **28**, NaOCl, CH_2Cl_2, -20 °C

When these substrates were reacted with *m*CPBA, no *cis*/*trans* selectivity was observed. The ratio of *trans*:*cis* was 2:1 when a bulky optically active manganese-salen catalyst **28** was employed as the catalyst. Katsuki's relative rates of epoxidation were similar to those obtained by Jacobsen (2.6-7.5), depending on the substrate tested.[105]

1.5.6 Shi's Kinetic Resolution

In 1999, Shi reported results of kinetic resolution with his epoxidation procedure using chiral ketone catalyst **54**. Shi used cyclic olefins **149** with the chiral centre at the allylic position for his kinetic resolution test substrates, reasoning that the rigid conformation of the cyclic olefins and proximity of the chiral centre make them key targets for kinetic resolution.[57]



149

Shi proposed that two possible *spiro* transition states could be formed (Figure 28). He proposed a favoured transition state (1), in which steric interaction between R_2 group of the alkene and one of the dioxirane oxygens was minimized, thus allowing one enantiomer of the racemic starting material to be oxidized faster.

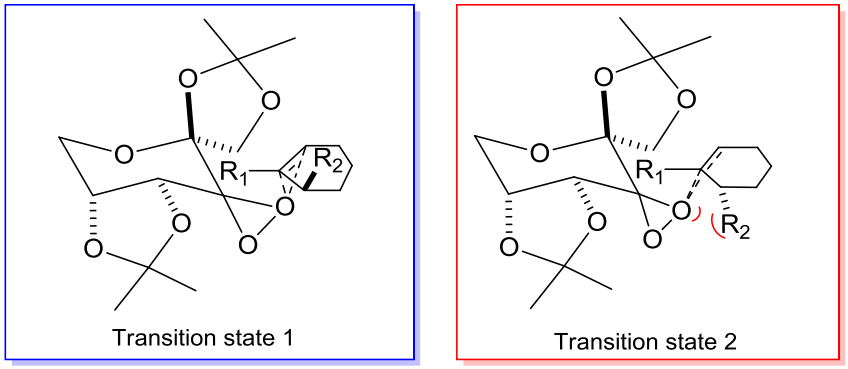
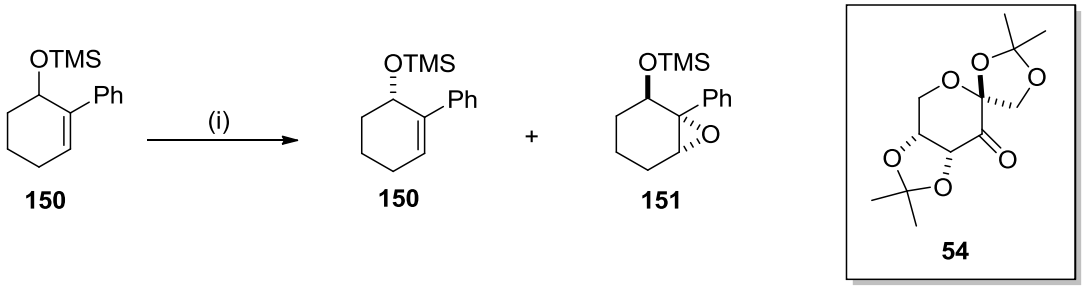


Figure 28. Favoured and disfavoured transition states

This theory was supported by experimental results, when testing kinetic resolution on a range of cyclohexene substrates at 50% conversion. Shi isolated major epoxide **151** as the *trans*-epoxide (>20:1) in 95% ee, and also managed to recover the starting material **150** in similar enantiomeric excesses (96% ee) (Scheme 43). The relative rate values calculated for Shi's kinetic resolution data range from k_{rel} = 4 to >100 for the epoxidation of 1,3 and 1,6 disubstituted cyclohexene substrates.[50]

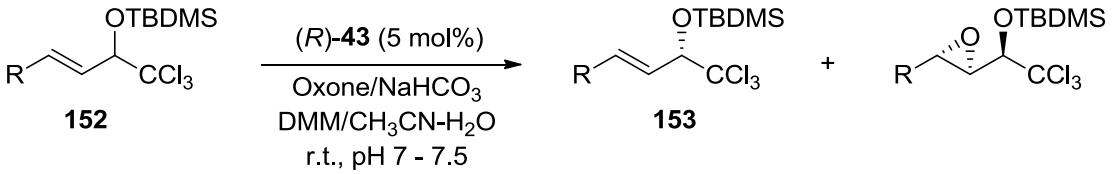


Scheme 43. *Reagents and conditions*: (i) Catalyst **54** (35 mol%), Oxone (2.3 eq.), K_2CO_3 (9.5 eq.), CH_3CN-DMM-0.05M $Na_2B_4O_7{\cdot}10\ H_2O$ in aqueous EDTA solution.

1.5.7 Yang's Kinetic Resolution of Acyclic Secondary Allylic Silyl Ethers

In 2001, Yang reported that chiral chloro ketone epoxidation catalyst (*R*)-**43** was suitable for the kinetic resolution of α-trichloromethyl allylic alcohols **152**. Yang observed that (*R*)-substrates were consumed at a faster rate than the (*S*)-substrates **153**, affording selectivities up

to s = 100 (s = k_{rel}).[107] Yang also showed that diastereoselectivities were excellent, with ratios of *erythro:threo* consistently around 49:1 (Table 23).



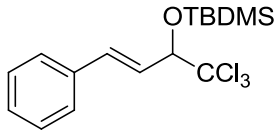
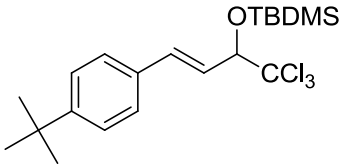
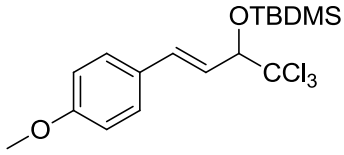
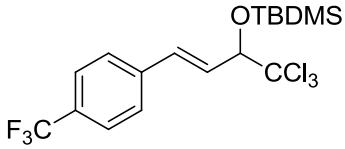
Substrate	Time / h	Conv. (%)	Recovered SM		Epoxide			
			% Yield	% ee	*erythro: threo*	% Yield	% ee	s^i
	10	55	84	96 (*S*)	>49:1	85	77	30
	4	50	87	94 (*S*)	>49:1	82	93	100
	1.5	38	80	58 (*S*)	>49:1	76	-	55
	6	46	94	78 (*S*)	>49:1	85	-	54

Table 23. Yang's kinetic resolution of various α-trichloromethyl allylic alcohols utilising chiral catalyst (*R*)-**43**

1.6 Conclusions

This introduction has covered the most recent advancements in the field of asymmetric epoxidation. The most successful methodologies for asymmetric epoxidation reactions utilize either a metal-based catalyst (Sharpless's titanium-derived catalyst or Jacobsen's manganese-derived catalysts), or a non-metal based catalyst (for example various chiral ketones developed by Shi, Yang, Denmark and Armstrong). Since the earliest advancements by Sharpless in asymmetric epoxidations on allylic alcohol substrates, there have been a number of methodologies developed (using either metal or non-metal based catalysts), that work for a broad range of olefins and maintain excellent enantioselectivity in the oxygen transfer step.

Following on from previous studies in asymmetric catalytic oxygen transfer reactions in the Page group, herein is described two new projects that further extend our understanding of oxaziridinium salts as catalysts.

1.7 References

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CHAPTER TWO: RESULTS

2.0 Chapter Preview

This chapter builds upon the achievements made within the Page group in the field of iminium-salt catalysed asymmetric epoxidation over the last 15 years. The first examples of kinetic resolution of various racemic benzopyrans utilizing Page's iminium salt-mediated non-aqueous asymmetric epoxidation conditions are described. The aims of this particular study are to:

- Prepare a number of racemic chromenes
- Obtain enantioenriched products from the epoxidation reactions
- Recover enantioenriched starting material if the kinetic resolution is successful
- Identify the major epoxide diastereoisomer generated from the reaction

All the information derived from the kinetic resolution experiments should help elucidate the selectivity of the oxygen transfer process.

The second part of this chapter details the first examples of asymmetric epoxidation of dihydroquinoline substrates catalysed by chiral iminium salts. This methodology will allow access to various quinoline-derived natural products and pharmaceuticals, such as helquinoline[1] **1** and virantmycin[2] **2** (Figure 1).

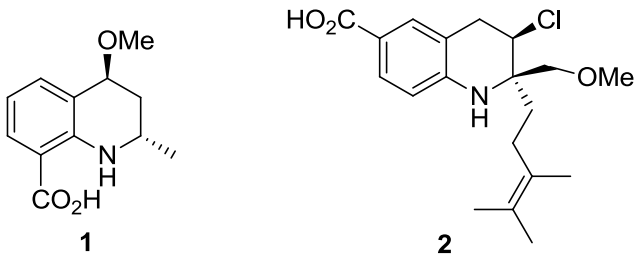


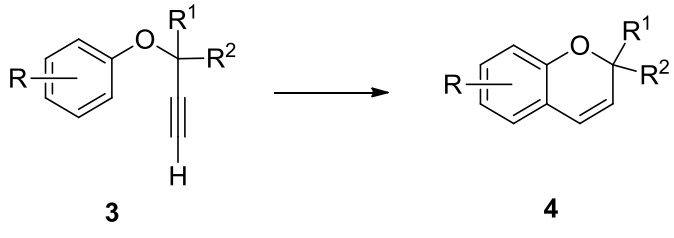
Figure 1. Tetrahydroquinoline-derived natural products

2.1 Reactions Utilized in the Synthesis of 2*H*-Benzopyrans

The resolution of racemic 2*H*-benzopyrans is an attractive research topic that has already received attention from many synthetic groups worldwide. The literature is well documented with many syntheses of 2*H*-benzopyrans, and a number of key reactions are discussed herein.

2.1.1 Claisen Rearrangement

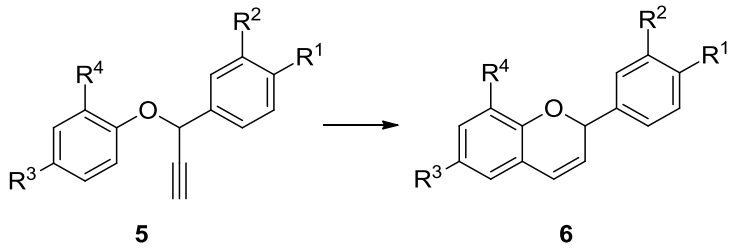
Harfenist first investigated the rearrangement of aryl propargyl ethers **3** to chromenes **4**, investigating the effect of the *gem*-dimethyl moiety on the rate of cyclization. Harfenist reported excellent yields for various 2-methyl- or 2,2-dimethyl-chromenes when *o*-dichlorobenzene was used as the solvent, applying heat if necessary to form a homogeneous solution (Scheme 1).[3]



R = CN, R^1, R^2 = H (0%)
R = CN, R^1 = H, R^2 = CH_3 (99%)
R = NO_2, R^1 = H, R^2 = CH_3 (84%)
R = Cl, R^1 = H, R^2 = CH_3 (0%)
R = OCH_3, R^1, R^2 = CH_3 (83%)
R = NO_2, R^1, R^2 = CH_3 (75%)
R = NHAc, R^1, R^2 = CH_3 (96%)

Scheme 1. *Reagents and conditions*: propargyl ether **3** (1 eq.), *o*-dichlorobenzene, Δ

Subramanian reported the synthesis of various flav-3-enes **6** in excellent yields (up to 95%), utilizing the Claisen rearrangement as the key step under similar conditions to those used by Harfenist (Scheme 2).[4]



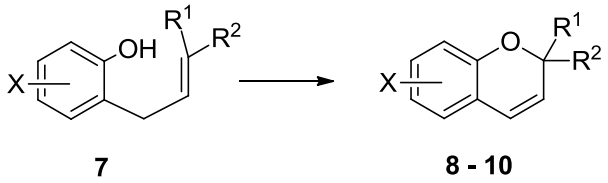
R^1 - R^4 = H (93%)
R^1,R^2,R^4 = H, R^3 = CH_3 (95%)
R^1,R^2 = OCH_3, R^3 = CH_3, R = H (93%)
R^1,R^2,R^4 = H, R^3 = NO_2 (84%)

Scheme 2. *Reagents and conditions*: propargyl ether **5** (1 eq.), solvent; *N*,*N*-diethylaniline or *o*-dichlorobenezene, Δ

The main advantage of this cyclization reaction in both examples shown above is the consistently high levels of yields observed in all cases tested, irrespective of the number of substituents at the C2-position or the size of the substituent. The downside to this method is the need for using elevated temperatures (in excess of >180 °C for Subramanian's examples).

2.1.2 Oxidation of Allylphenols

Cardillo reported the synthesis of various 2,2-substituted chromenes by two methodologies, both proceeding through oxidation of the phenol starting material. The first method involved adding a benzene solution of methyl-trialkyl-ammonium dichromate to a refluxing solution of the required allylphenol **7** in benzene. Reaction completion was observed after one hour, affording chromenes **8** - **10** in moderate to good yields (Scheme 3).[5]

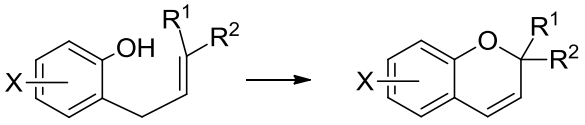


7 **8 - 10**

8; X = 5-CH_3O, R^1, R^2 = CH_3 (83%)
9; X = 4-CH_3, R^1, R^2 = CH_3 (78%)
10; X = 4-CH_3, R^1 = H, R^2 = C_6H_5 (45%)

Scheme 3. *Reagents and conditions*: benzene solution of methyl-trialkyl-ammonium dichromate (1 eq.), allylphenol **7** (1 eq.), benzene, Δ, 1 h

The second method reported by Cardillo involved the oxidation of allylphenols **7** utilizing an etheral DDQ solution. The reaction proceeds at ambient temperature, affording various chromenes in yields up to 90% (Scheme 4).[5]



7 **11-13**

11; X = 4-CH_3O, R^1, R^2 = CH_3 (85%)
12; X = 4-CH_3, R^1, R^2 = CH_3 (90%)
13; X = 4-CH_2CH_3, R^1 = H, R^2 = C_6H_5 (90%)

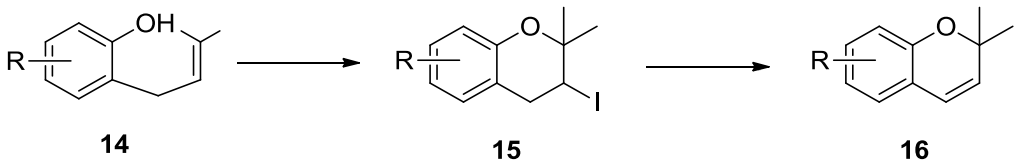
Scheme 4. *Reagents and conditions*: DDQ (1.1 eq.) in ether, allylphenol (1 eq.) in ether, r.t., 2 h

The yields for this reaction remain high in both methods reported; yet the main disadvantage observed with both is the use of potentially toxic materials. DDQ can react with water to yield hydrogen cyanide gas, whilst potassium dichromate and benzene are known carcinogens.

2.1.3 Iodination of Allylphenols

Bongini reported that *N*-iodosuccinimide can be used in the cyclization of various substituted 2-allylphenols **14**, yielding 3-iodochromanes **15**, which in turn may be dehydrohalogenated to give various chromenes **16** in excellent yields (up to 95%) (Scheme

5).[6] The reaction however has to be conducted in the dark due to the instability of NIS in the presence of light.



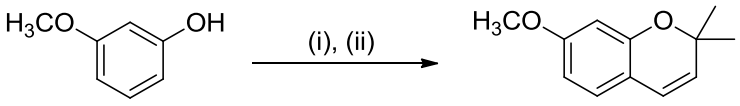
14 **15** **16**

Scheme 5. *Reagents and conditions*: (i) NIS (1.1 eq.), 2-allylphenol **14** (1 eq.), CH_2Cl_2, r.t., 1 h. (ii) 3-iodochromane **15** (1 eq.), KOH/MeOH (10%), 50 °C, 2 h

Jurd later reported a similar protocol for the synthesis of various 2*H*-flavenes, except this time cyclization of 2-cinnamylphenols was achieved using hydrogen peroxide and iodine.[7]

2.1.4 Combination of Metal Phenoxides and Carbonyl Compounds

Casiraghi reported the synthesis of various 2*H*-benzopyrans by reacting various metal phenoxides (titanium(IV) or magnesium phenolates in toluene), with an assortment of *α,β*-unsaturated carbonyl compounds. The isolated yields for various chromene substrates are good to excellent (50–81%), and the methodology could be extended to the synthesis of naturally occurring chromenes, for example, 6-demethoxyageratochromene **18**, which was achieved in 81% yield (Scheme 6).[8]



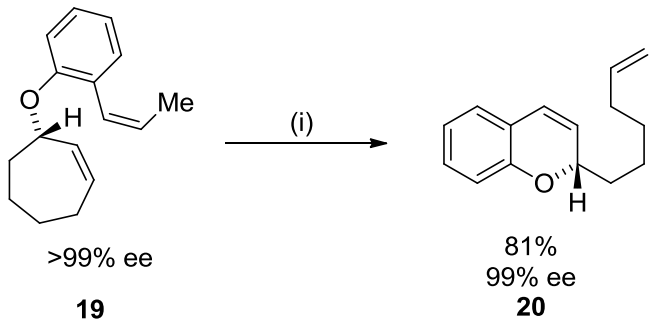
17 **18**

Scheme 6. *Reagents and conditions*: (i) $Ti(OEt)_4$ (1 eq.), **17** (4 eq.), toluene, reflux, ½ h then, removal of excess ethanol (ii) 3-methylbut-2-enal (6 eq.), toluene, reflux, 8 h

2.1.5 Formation of Chromenes by Metathesis: Utilization of a Ruthenium-carbene Catalyst

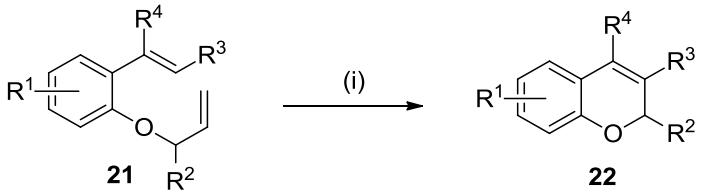
The facile synthesis of chromenes reported by Hoveyda is one of the best examples of chromene synthesis in the literature due to the consistently high percentage yields obtained for various chromene products, in which Grubbs 1st generation catalyst is employed in the ruthenium-catalysed rearrangement of styrenyl ethers.[9,10] Hoveyda showed that under an

ethylene atmosphere, the reaction can be driven to yield only the formation of chromene substrates, and reduce the formation of unwanted dimerization products.[9] When the styrenyl ether is enantioenriched, e.g. **19** (>99% ee), no loss in enantioselectivity is observed during the ruthenium-catalysed rearrangement, affording enantioenriched **20** in 81% yield (Scheme 7).



Scheme 7. *Reagents and conditions*: (i) $(PCy_3)_2Cl_2Ru{=}CHCH{=}CPh_2$ (5 mol%), r.t., 24 h, ethylene atm.

Grubbs later reported the use of his ruthenium-carbene catalyst in the ring-closing metathesis of 2-styrenyl allyl ethers (such as **21**), affording an assortment of chromenes in up to 99% yield, as shown below for the formation of 6-bromo-2*H*-1-benzopyran **22** (99%) (Scheme 8).[11]

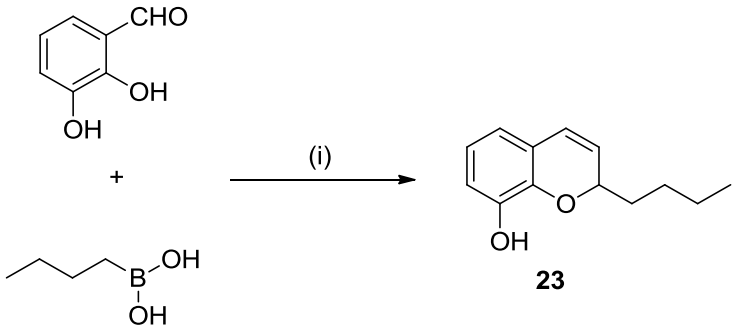


Scheme 8. *Reagents and conditions*: (i) $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (2 mol%), CH_2Cl_2, r.t., 2 h.

However, one of the limiting factors of this reaction is the cost of the catalyst employed. Weighing up the advantages and disadvantages of ruthenium-carbene catalysts, one has to compare the price of the catalyst against the high reaction yields this catalyst affords, in comparison to other methods in the literature that utilize much cheaper reagents but ultimately provide lower reaction yields. For this reason, we chose not to consider using this approach to synthesize our racemic chromene substrates.

2.1.6 The Petasis Reaction: Formation of Chromenes

Finn reported the first examples of catalytic 2*H*-benzopyran formation using the Petasis reaction with the inclusion of a resin-bound amine, and generated substituted chromenes in excellent yields. For example, **23** was formed in 99% yield from the corresponding alkenylboronic acid and *o*-hydroxyaromatic aldehyde (Scheme 9).[12] Finn observed the reaction proceeded well when the aromatic aldehyde has the hydroxy group at the *ortho*-position; no reaction was observed when the hydroxy group was situated *meta* or *para* to the aldehyde functionality.



Scheme 9. *Reagents and conditions*: (i) alkenylboronic acid (1 eq.), *o*-hydroxyaromatic aldehyde (1 eq.), resin-bound amine (40 mol%), dioxane, 90 °C, 24 h

Das,[13] Petasis,[14] and Gois[15] later reported their own individual adjustments to the reaction by either modifying the boron component (potassium vinylic borates),[13,14] or by changing the reaction solvent (water),[15] yet they all report good to excellent yields for various 2*H*-benzopyran substrates.

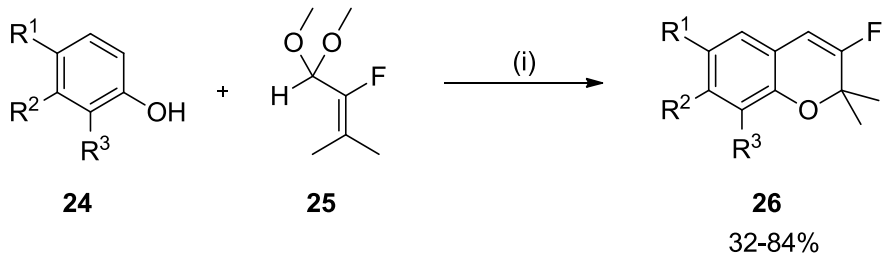
2.2 Base-catalysed Synthesis of Racemic 2*H*-Benzopyran Substrates

To the best of our knowledge, the kinetic resolution of racemic chromenes utilizing iminium salt-catalysed epoxidation processes has not yet been reported. Given the high levels of enantioselectivities observed in the epoxidation of various 2,2-substituted benzopyrans utilizing chiral iminium salts reported by Page in recent years, [16,17,18] we decided to evaluate chromene substrates as possible candidates for kinetic resolution.

The reactions described above afford 2,2-substituted benzopyrans or alternatively provide racemic 2-substituted benzopyrans in good yields. The most enantioselective synthesis of 2-substituted chromenes was reported by Hoveyda as described above (Scheme 7).[9,10]

Our approach to the synthesis of chromenes required us to allow variation of the chromene structure at the 2- and 6- position, but we wished to avoid the use of expensive transition metal complexes such as Grubbs ruthenium-carbene derived catalyst. At the same time, we desired high yields of racemic benzopyrans as observed in the most successful metal-catalysed reactions.

We first looked into the procedures reported by Crombie[19] and Camps[20], both of whom reported similar cyclization procedures in which a substituted phenol **24**, a conjugated aldehyde or its corresponding dimethyl acetal **25**, and a base (such as pyridine) were combined in one flask and heated under reflux, affording various -C5, -C6, -C7 & -C8 substituted benzopyrans **26** in moderate to good yields. Scheme 10 below highlights the conditions reported by Camps and co-workers in their synthesis of various 2*H*-benzopyrans.



Scheme 10. *Reagents and conditions*: (i) **24** (1 eq.), **25** (2 eq.), pyridine (1 eq.), 140 °C.

North later modified and optimized the conditions initially proposed by Crombie and Camps.[21] He investigated the various factors that affect the yield of chromene formed; these included adjustments to the ratio of reagents used in the reaction, changing the base-catalysts employed and introducing various acid additives to activate the acetal towards nucleophilic attack. The optimized conditions for the formation of 6-cyano-2,2-dimethyl chromene **29** are shown below (Scheme 11).[21]

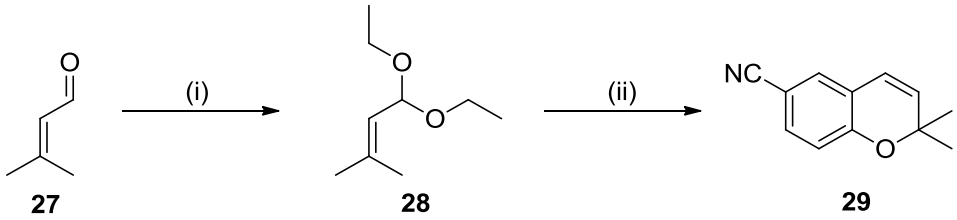
North's methodology appealed to us for a number of reasons:

- All starting materials for the two step procedure are cheap and commercially available
- The acetals are formed under mild conditions and can be easily purified by vacuum distillation
- The chromenes are formed using Dean-Stark conditions in good yields (>60%), and can be purified by crystallization or chromatography
- North shows that the procedure works remarkably well for 4-substituted phenols (>60% yield), allowing us to modify the chromene's electronic properties at the C6 position

Based upon these advantages, we decided to employ the optimized conditions described by North for the synthesis of our own library of -C2, -C6 substituted racemic chromenes.[21]

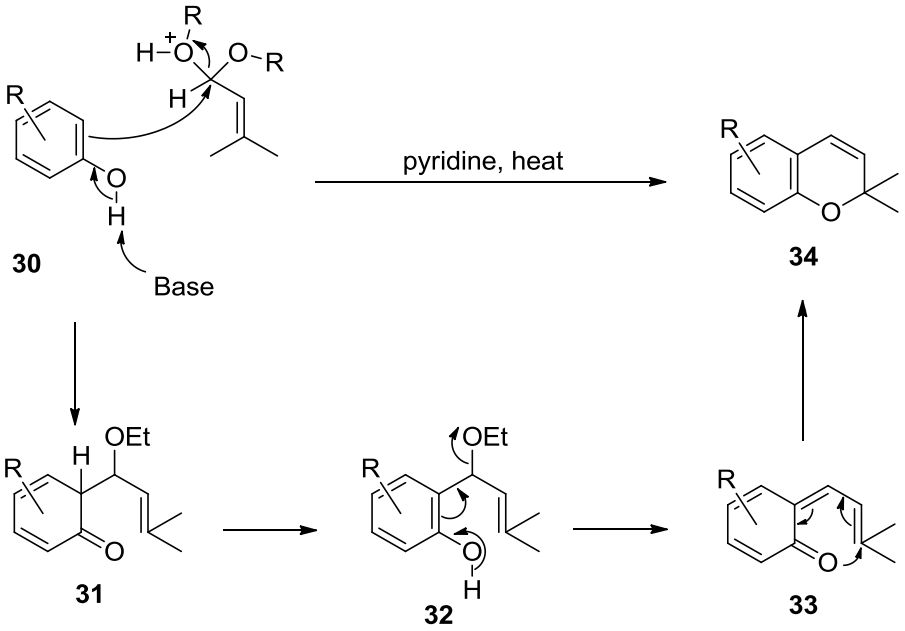
2.2.1 North's Synthesis of Substituted 2,2-Dimethyl-2*H*-1-Benzopyrans

In 1995, North reported a procedure for the formation of the benzopyran core structure in a quick two-step synthesis. The first step involves the acetalization of 3-methyl-2-butenal **27** in the presence of triethylorthoformate, yielding diethyl acetal **28**, which can be purified by vacuum distillation or used directly as a crude mixture in the next step without a significant loss of yield.[22] The second step of North's reported synthesis of 6-cyano-2,2-dimethyl chromene **29** is a base-catalysed condensation reaction between diethyl acetal **28** with 4-cyanophenol in xylene at an elevated temperature (Scheme 11).[19]



Scheme 11. *Reagents and conditions:* (i) **27** (1 eq.), triethylorthoformate (1 eq.), potassium hydrogen sulfate (0.05 eq.), r.t., 1 h. (ii) 4-cyanophenol (1 eq.), **28** (1.4 eq.), 3-picoline (0.25 eq.), *p*-xylene, 115 ˚C, 24 h

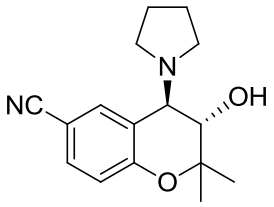
North reported the following mechanism for the base-catalysed synthesis of 2,2-Dimethyl-2*H*-1-Benzopyrans (Scheme 12).



Scheme 12. North's proposed mechanism for the base-catalysed synthesis of benzopyrans

North postulated that the starting phenol has a dual role; initially it is a reactant with the catalytic amount of base, but also acts as an acid catalyst in the activation of the acetal (presumably to an oxonium species). The base-catalysed alkylation of **30** by the activated acetal (oxonium ion) affords dienone **31**. Following this, tautomerization gives **32**, followed by elimination of ethanol forming **33**. Electrocyclic ring closure of **33** affords chromene **34**.

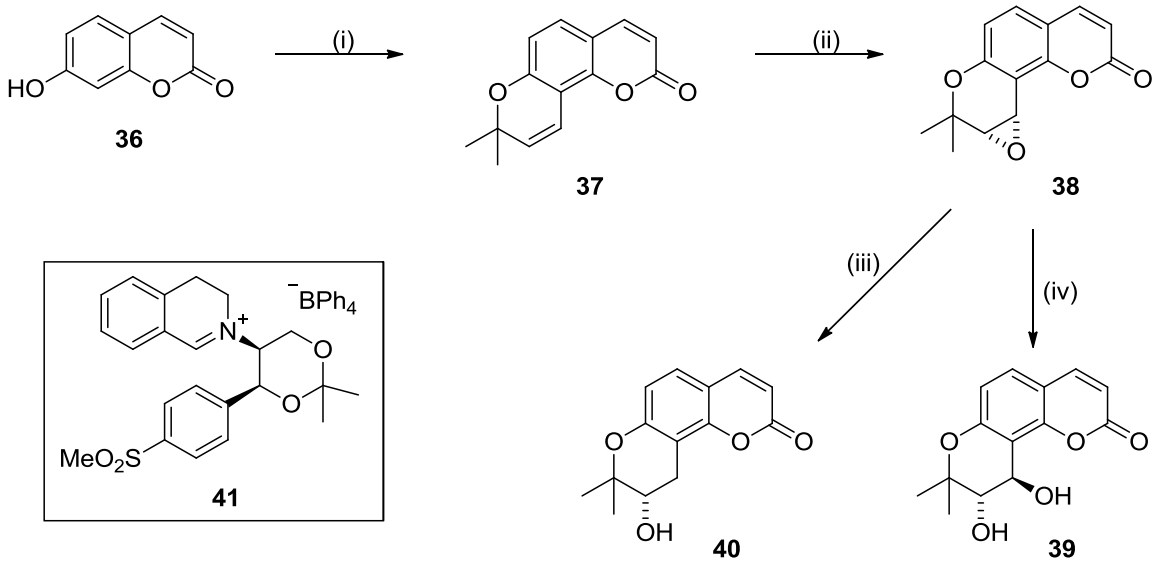
North's route allows easy variation of the substituents at both the C2 and C6 positions of the chromenes using the corresponding dialkylacetals and 4-substituted phenols. This methodology has been most recently employed within the Page group for the synthesis of various chromene structures, including the precursor to the anti-hypertensive agent levcromakalim **35**.[16]



35

Page utilized North's methodology to synthesize the natural product seselin **37** from 7-hydroxycoumarin **36** and 1,1-diethoxy-3-methyl-but-2-ene, which in turn was the olefin

intermediate used in the non-aqueous asymmetric epoxidation reaction utilizing iminium-salt catalyst **41** to access natural products *trans*-khellactone **39** and lomatin **40** (Scheme 13).[17]



Scheme 13. *Reagents and condition:* (i) 1,1-diethoxy-3-methyl-but-2-ene (1.2 eq.), 3-picoline (0.25 eq.), *p*-xylene, reflux, 24 h, 73%; (ii) Catalyst **41** (10 mol%), TPPP (2 eq.), $CHCl_3$, -30 °C, 24 h, 65%, 97% ee; (iii) $NaBH_3CN$ (1 eq.), $BF_3.OEt_2$, THF, 0 °C, 0.5 h, 92%; (iv) 1M aq. H_2SO_4 (5.5 eq.), acetone (1:2 ratio), r.t., 1 h, 95%.

Page showed that North's procedure could alternatively be carried out neat under microwave conditions, and encouragingly seselin **37** was formed in an increased yield (94%) in comparison to 73% yield utilizing the conventional heating method.[17]

2.3 Kinetic Resolution in Asymmetric Epoxidation: The First Examples Using an Iminium Salt-catalyst

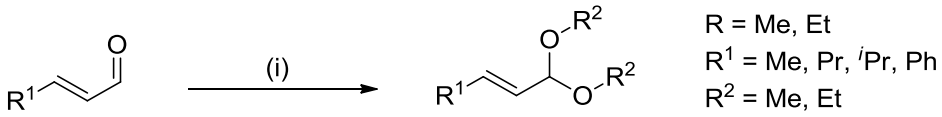
The results reported herein show the first examples of the kinetic resolution of racemic chromene substrates utilizing iminium-salt catalysed asymmetric epoxidations as the key step. The synthesis of various –C2,–C6 substituted chromenes utilizing North's procedure are discussed initially, leading onto the epoxidation of a library of chromene substrates.

The outcomes of the epoxidation reactions are influenced by two key variables; these are the steric effects of alkyl or aryl substituents at the C2 position and the electron-withdrawing/donating substituents at the C6 position.

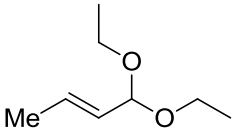
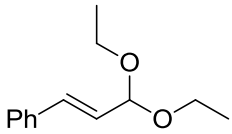
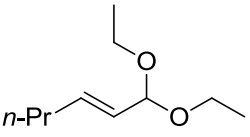
The discussion begins with the synthesis of various acetal substrates.

2.3.1 Formation of Dialkyl Acetals

Four diethyl acetals **42**-**45** were synthesized according to the procedure proposed by Trost,[22] starting from the corresponding commercially available aldehydes (Scheme 14, Table 1). The diethyl acetals were formed in good to excellent yields after purification by vacuum distillation, and could be stored at 0 °C for long periods of time without signs of decomposition. The corresponding dimethyl acetal **46**, as used by Crombie[19] and Camps[20], was also synthesized under similar conditions, but was formed in much lower yield. Dimethyl acetal **46** decomposed over the period of a week when stored at 0 °C.



Scheme 14. *Reagents and Conditions:* (i) $(RO)_3CH$ (1.2 eq.), NH_4NO_3 (0.25 eq.), ROH, 24 h, r.t.

Starting Material	Compound No.	Product Structure	Yield (%)
Crotonaldehyde	**42**		52
Cinnamaldehyde	**43**		83
(2*E*)-2-Hexenal	**44**		47

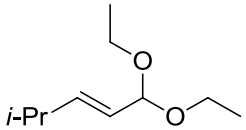
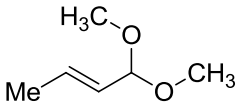
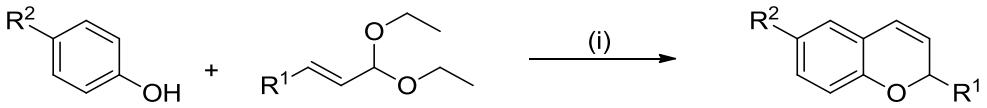
4-Methylpent-2-enal	**45**		78
Crotonaldehyde	**46**		31

Table 1. Formation of various dialkyl acetals

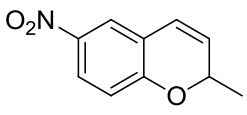
With a range of dialkyl acetals to hand, the synthesis of various chromene based substrates could be approached using North's methodology.

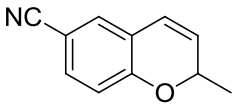
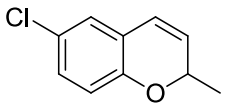
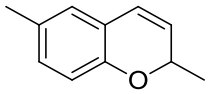
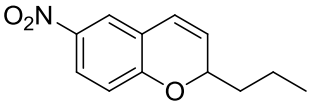
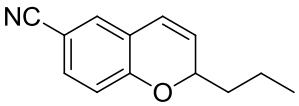
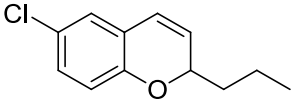
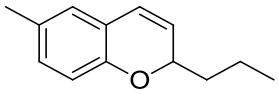
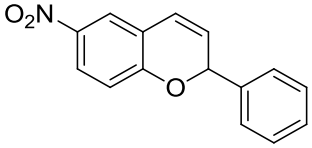
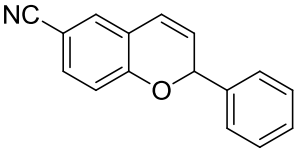
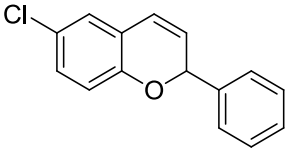
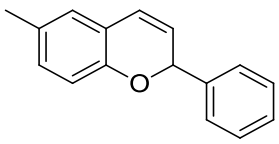
2.3.2 Formation of -C2,-C6 Substituted Racemic 2*H*-Benzopyran Substrates

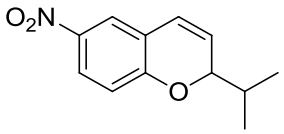
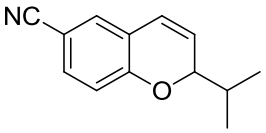
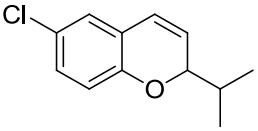
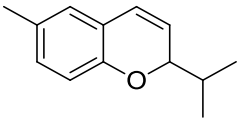
Acetals **42-46** were then subjected to the base-catalysed conditions reported by North,[21] with an interesting trend being observed. When the dimethyl acetal **46** was utilized, the benzopyran products were obtained in low yields (entries 3 and 5, Table 2), possibly due to decomposition of the dimethyl acetal. Pleasingly, the diethyl acetal derivatives **42-45** were found to be more stable under the base-catalysed conditions, and reacted well with 4-chloro-, 4-cyano-, 4-methyl- and 4-nitro-phenols to afford chromenes **47-62** in good to excellent yields after purification using silica gel flash column chromatography of the crude reaction mixture (Scheme 15).



Scheme 15. *Reagents and Conditions*: (i) phenol (2 eq.), alkyl acetal (1 eq., diethyl acetal unless stated otherwise), 3-picoline (0.25 eq.), *p*-xylene, reflux, 24 h.

Entry	Compound No.	Product Structure	Yield (%)
1	**47**		46

2	**48**		76
3			5 [a]
4	**49**		43
5			0 [a]
6	**50**		0
7	**51**		89
8	**52**		97
9	**53**		74
10	**54**		5
11	**55**		55
12	**56**		44
13	**57**		13
14	**58**		11

15	**59**		33
16	**60**		31
17	**61**		16
18	**62**		43

[a] Yields when the dimethyl acetal was utilized

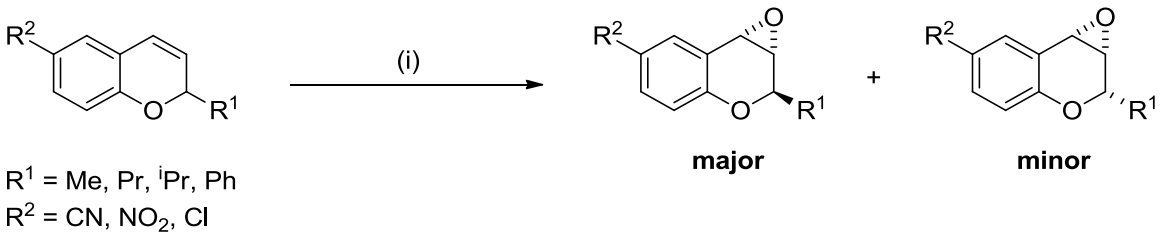
Table 2. Formation of various -C2, -C6 substituted chromenes utilizing North's methodology

The stability of the chromenes varies dramatically depending on the substituents at the C6 position. When the group at C6 contains an electron withdrawing substituent, such as cyano or nitro, these were found to be the most stable chromenes when stored at room temperature. The chromenes containing methyl or chloro substituents at C6 formed viscous oils in all cases and had to be stored at 0 °C and used within a week to avoid decomposition.

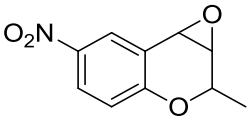
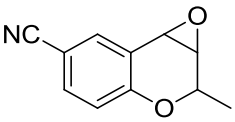
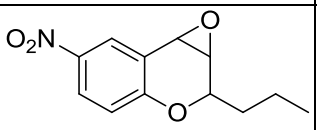
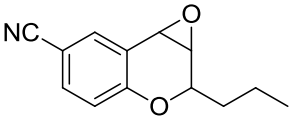
For each of the chromenes **47**-**62**, full characterization of each of the compounds was required since nearly all of them are new compounds. The kinetic resolution experiments require resolved HPLC traces for the two enantiomers of the racemic chromene substrates, and these HPLC traces were used in direct comparison with HPLC traces from asymmetric epoxidation experiments. Examples of racemic substrate traces can be found in Appendix B.

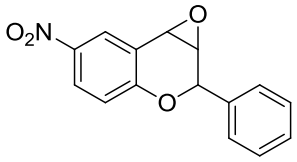
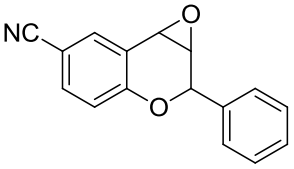
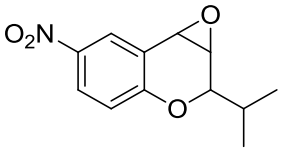
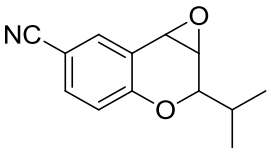
2.3.3 Epoxidation of Racemic Chromenes Utilizing *m*CPBA

Each of the chromenes synthesized was then submitted to standard epoxidation conditions using *m*CPBA (Scheme 16, Table 3). The diastereoisomeric ratios for the epoxide products were calculated from ^{1}H NMR analysis of the inseparable mixture of diastereoisomers. The configuration of the major diastereoisomer was assigned as *trans* based on the epoxidation of more rapid addition of the electrophile to the less hindered face of the alkene and in accordance with related cyclohexene systems. The results show that increasing the bulk size of the substituent at the C2-position, e.g. methyl to phenyl, leads to a dramatic increase in the d.r., from 1:1 to *trans* only.



Scheme 16. *Reagents and Conditions:* (i) *m*CPBA, CH_2Cl_2, 1-8 h, 0 °C

Starting material	Product Reference	Product Structure	Conv. (%)	Epoxide d.r.[a]
47	**63**		100	1.8:1
48	**64**		100	1:1
51	**65**		100	2:1
52	**66**		100	3.5:1

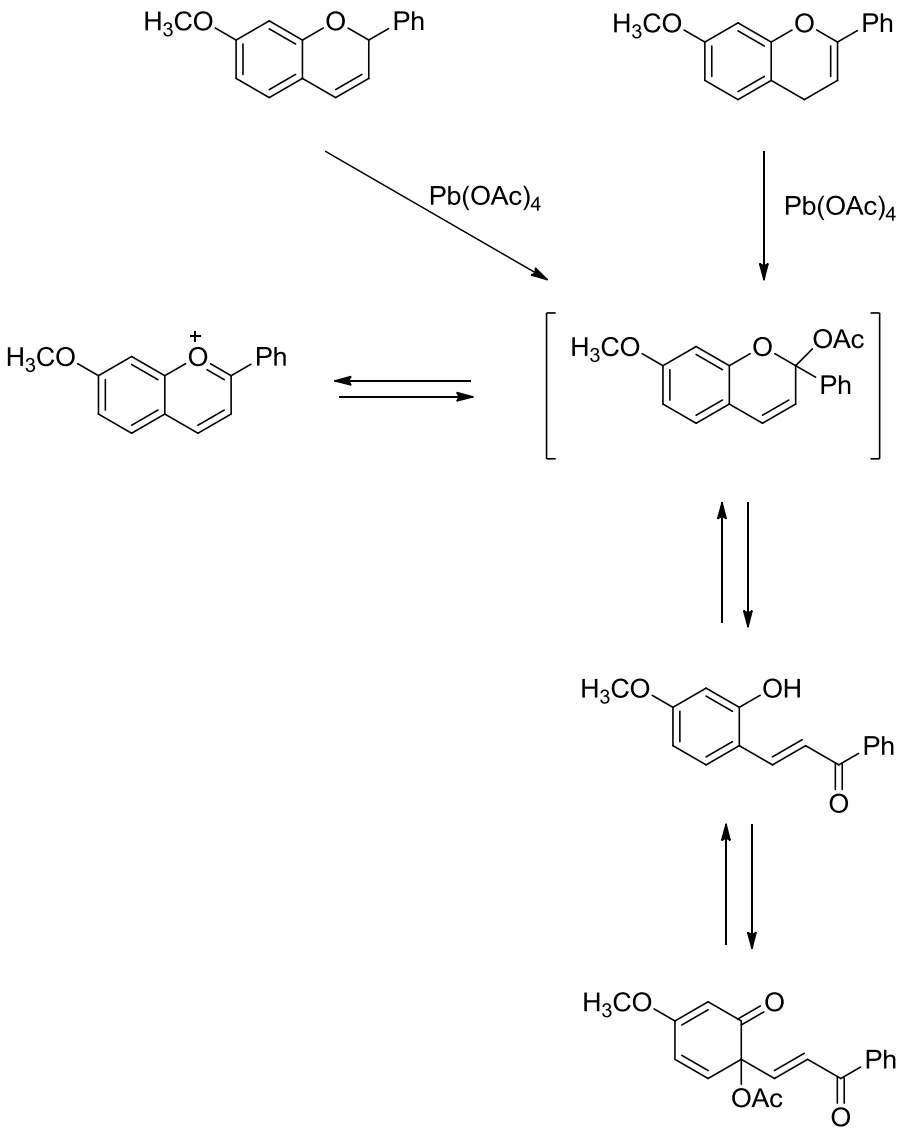
55	**67**		100	*trans* only
56	**68**		100	*trans* only
59	**69**		81	4:1
60	**70**		80	4:1

[a] epoxide diastereoisomeric ratios were determined from the ^{1}H NMR spectra of the reaction mixture after work-up.

Table 3. Racemic chromene epoxides generated from *m*CPBA epoxidations

Unfortunately, all chromenes containing a chlorine or methyl substituent at the C6 position were highly unstable under the standard epoxidation conditions using *m*CPBA, decomposing readily, and yielding neither epoxide nor diol from their respective reaction mixtures as analysed by ^{1}H NMR spectroscopy. Addition of one equivalent or two equivalents of sodium hydrogen carbonate with respect to *m*CPBA to the reaction mixture to neutralize excess acid failed to yield any further success for the epoxidation of these substrates.

This unusual behaviour we have observed for electron-rich chromenes has been observed before in the work reported by Ohki, in which *cis*-chromene substrates readily decomposed when in the presence of an oxidant.[23] The conditions are different from ours, but Ohki has postulated a possible mechanism for the decomposition of these electron-rich chromene substrates (Scheme 17).



Scheme 17. Potential decomposition of *cis*-chromenes by lead acetate as the oxidant

2.4 Asymmetric Epoxidation Utilizing Iminium-Salt Catalysts

Page has recently shown that catalyst **41** can be employed in the asymmetric epoxidation of various *cis*-alkenes, affording high enantioselectivities (up to 97% ee).[16,17] Iminium salt **41** has been highly effective under non-aqueous epoxidation conditions, where the terminal oxidant employed is TPPP **71** (tetraphenylphosphonium monoperoxysulfate) (Figure 2).[16,17]

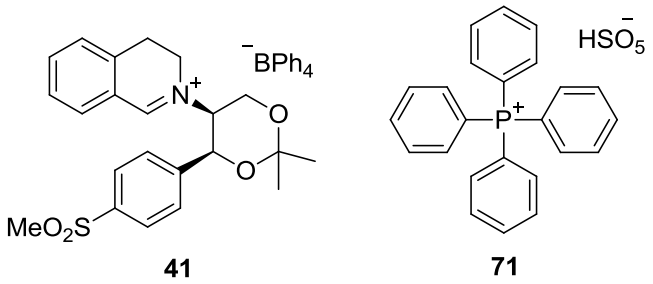
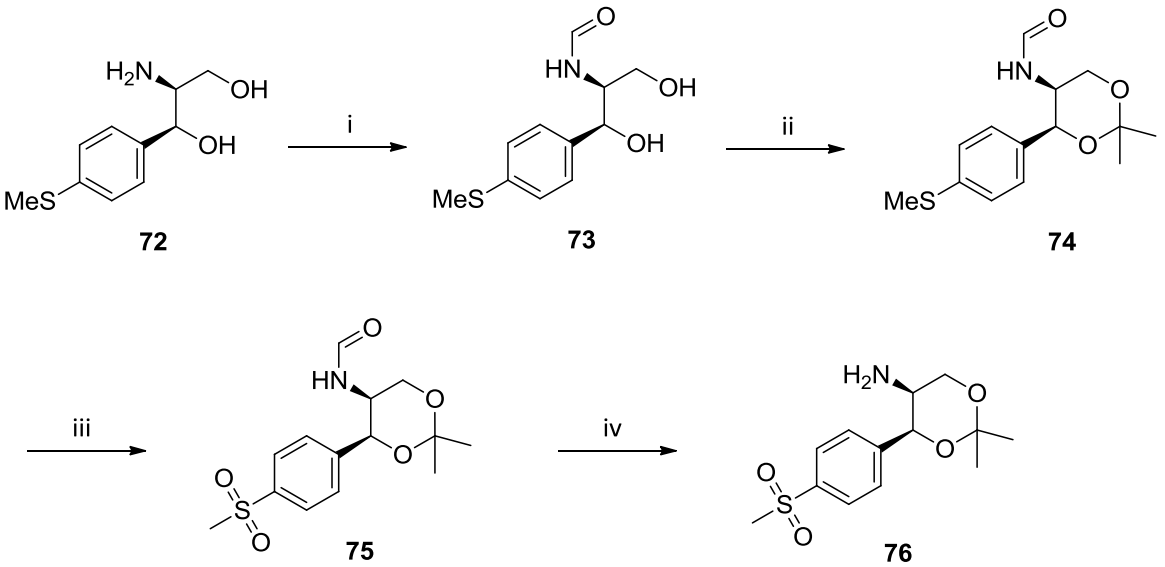


Figure 2. Iminium-salt catalyst **41** and oxidant Tetraphenylphosphonium monoperoxysulfate (TPPP) **71**

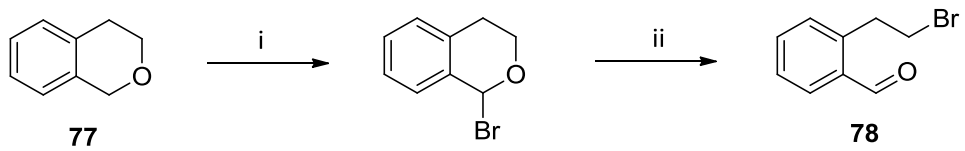
2.4.1 Synthesis of Iminium salt Catalyst 41

The synthesis of iminium salt **41** was divided into two parts; formation of chiral amine **76** (4*S*,5*S*)-2,2-dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-amine from thiomicamine **72**, and the formation of 2-(2-bromoethyl)benzaldehyde **78**. To prepare (4*S*,5*S*)-2,2-dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-amine **76**, thiomicamine **72** was protected using methyl formate to give diol **73** and then treated with 2,2-dimethoxypropane in the presence of *p*-TSA to give sulfide **74**. Sulfide **74** was oxidized to sulfone **75** with *m*CPBA followed by removal of the formyl protecting group using hydrazine monohydrate to yield aminodioxane sulfone **76** in four steps (Scheme 18).[16]



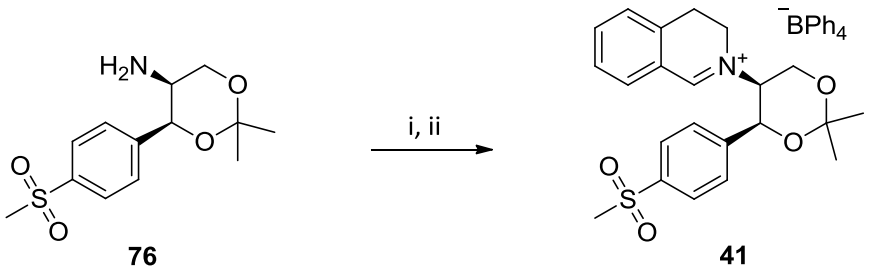
Scheme 18. *Reagents and conditions:* (i) NaOMe (25% in MeOH), CH_3OCHO (1.5 eq.), CH_3OH, r.t., 12 h. (ii) DMP (5 eq.), *p*TSA (0.2 eq.), $PhCH_3$, reflux, 12 h. (iii) *m*CPBA (3 eq.), CH_2Cl_2, 0 °C – r.t., 2 h. (iv) $H_2N\text{-}NH_2.H_2O$ (85%, 20 mL/g), reflux, 2.5 h, 88%

The second part of the catalyst synthesis involved the formation of 2-(2-bromoethyl)benzaldehyde **78**, which was easily prepared from isochroman **77** in two steps followed by distillation of the crude mixture to afford bromo-aldehyde **78** as a colourless liquid (Scheme 19).[24]



Scheme 19. *Reagents and conditions:* (i): Bromine (1.1 eq.), cyclohexene, reflux, 15 mins; (ii): HBr, reflux, 10 mins, 50%

With both 2-(2-bromoethyl)benzaldehyde **78** and (4*S*,5*S*)-2,2-dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-amine **76** in hand, a condensation reaction followed by an anion exchange yielded catalyst **41** in good yield (Scheme 20).[16]



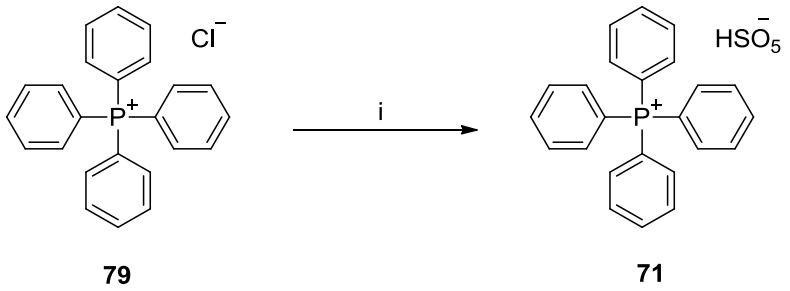
Scheme 20. *Reagents and conditions:* (i) **78** (1.1 eq.), EtOH, 0 °C → r.t., 12 h; (ii) $NaBPh_4$ (1.1 eq.), MeCN, r.t., 5 min, 89%

2.4.2 Synthesis of Tetraphenylphosphonium Monoperoxysulfate (TPPP) 71

Page has shown that a range of oxidants can be implemented in the catalytic iminium-salt mediated asymmetric epoxidation of olefins, including Oxone™,[25] sodium hypochlorite,[26] hydrogen peroxide,[27] and, most recently, tetraphenylphosphonium monoperoxysulfate (TPPP) under non-aqueous conditions.[16,17,18,28]

Di Furia first reported the synthesis of TPPP in 1994. He showed that TPPP could be utilized in the oxidation of manganese-based porphyrins in the presence of imidazole. The oxidized metallo-porphyrins were then shown to epoxidize olefins. We prepared

Tetraphenylphosphonium monoperoxysulfate **72** in 83% yield by an anion exchange reaction between tetraphenylphosphonium chloride **79** and Oxone™ (Scheme 21).[29]



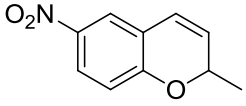
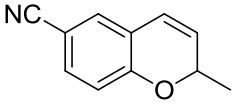
79 **71**

Scheme 21. *Reagents and conditions:* (i): Oxone (1 eq.), $CHCl_3$:H_2O, 10 °C, 0.5 h

With both the oxidant and catalyst prepared, the kinetic resolution experiments could be conducted. However, it was important to identify sources of background oxidation, if any, from the oxidant alone.

2.4.3 Control Experiments: The Absence of Iminium Salt 41

Di Furia reported that tetraphenylphosphonium monoperoxysulfate alone is not capable of epoxidizing cyclooctene or styrene in the absence of manganese porphyrins.[29] To confirm that there would be no background oxidation from TPPP in our catalytic procedure, a small number of control experiments were run in the absence of iminium salt **41** (Table 4). Pleasingly, we observed in most cases no background epoxidation to occur (trace epoxidation observed for compounds **48** and **51**), as shown by the ^{1}H NMR spectra of the crude reaction mixtures (Figure 3).

Chromene substrate	Substrate number	Epoxide present
	**47**	No
	**48**	epoxide region obscured by unidentified impurity

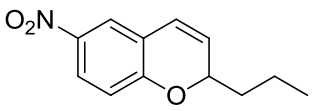
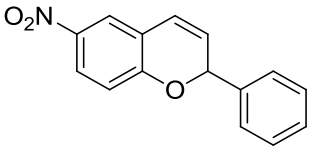
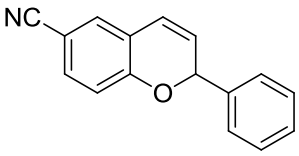
	**51**	epoxide region obscured by unidentified impurity
	**55**	No
	**56**	No

Table 4. Control experiments conducted under standard non-aqueous conditions: TPPP (2 eq.), $CHCl_3$, -30 °C, 24 h

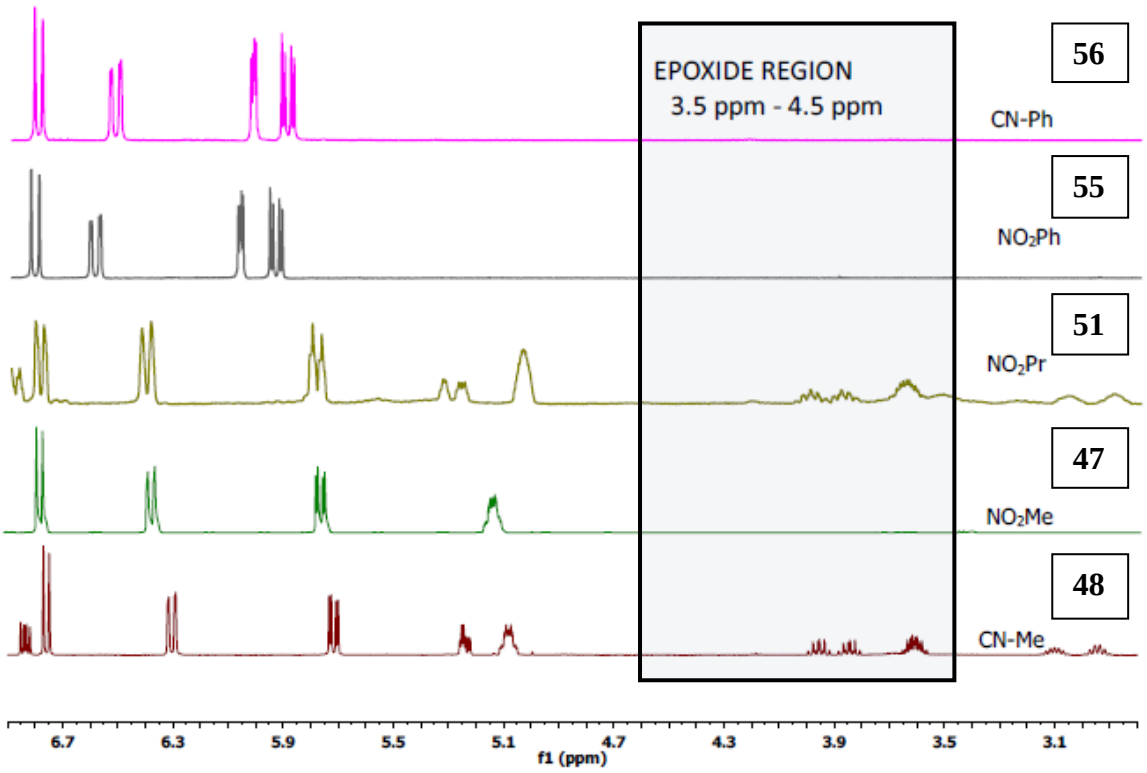
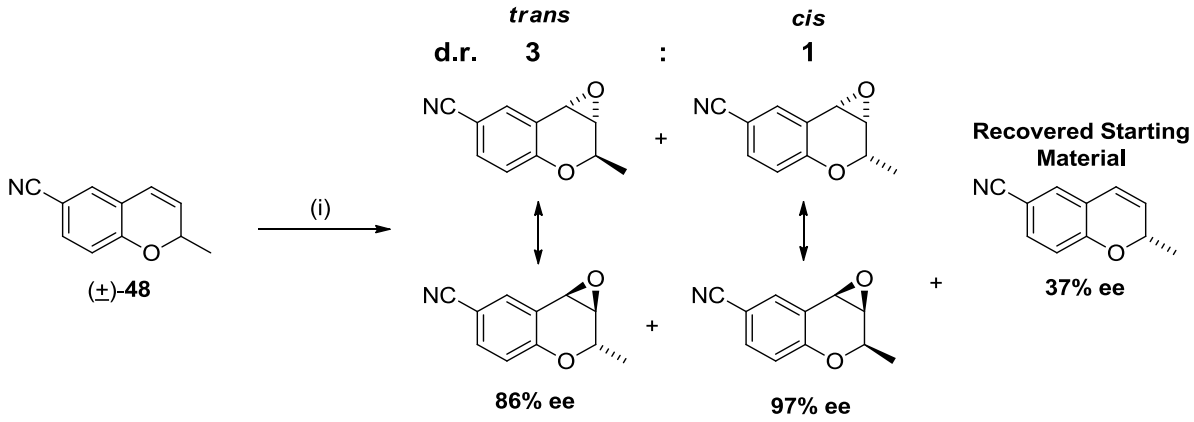


Figure 3. ^1H NMR spectra plots to test if epoxide was produced by the racemic non-catalysed reaction conditions (see table 4)

2.4.4 Trial Run: Asymmetric Epoxidation of (±)-6-cyano-2-methyl-chromene 48

A preliminary experiment was conducted on (±)-6-cyano-2-methyl-chromene **48** under non-aqueous reaction conditions utilizing iminium salt **41**, and provided a promising initial result (Scheme 22).



Scheme 22. *Reagents and conditions*: (i) iminium salt **41** (10 mol%), TPPP (4 eq.), $CHCl_3$, –30 °C, 24 h. (The upper structures of each pair are the major isomers in each case). Epoxide d.r.'s were determined from the ^{1}H NMR spectra of the reaction mixture after work-up.

The reaction showed a number of encouraging signs; most notably, a higher selectivity towards the product where the methyl group at C2 is *trans* to the epoxide moiety was observed than when *m*CPBA is used. At 52% conversion, ^{1}H NMR spectroscopic data of the mixture of inseparable diastereoisomers indicated a 3:1 d.r. (Scheme 22). Chiral HPLC analysis showed the enantiomeric excess of the major epoxide diastereoisomer (*trans*) was 86% ee, and 97% ee for the minor epoxide diastereoisomer (*cis*) (Figure 4). The recovered starting material **48** was measured as 37% ee.

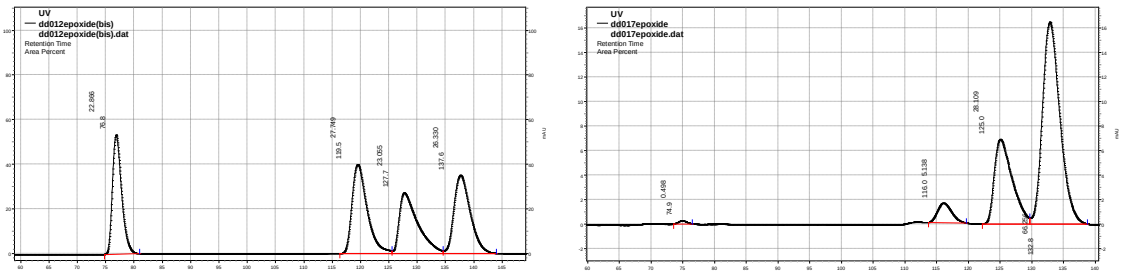


Figure 4. HPLC traces for racemic epoxide **64** (above left, table 3) and enantioenriched epoxide **64** (above right, scheme 22)

2.4.5 Kinetic Resolution of Racemic Benzopyrans 47 - 60 Utilizing Iminium Salt 41

Encouraged by the preliminary result gained for compound **48**, we tested the full library of benzopyran substrates **47** – **60** under the original conditions (iminium salt **41** (10 mol %), TPPP (4 eq.), $CHCl_3$, −30 °C), allowing us to analyse the electronic effects by variation of groups at the C6 position on the chromene, and steric influences by varying the alkyl/aryl substituent at the C2 position (Table 5).

Starting material	**Product No.**	**Conv. (%)**[b]	**Epox d.r.** ***(trans: cis)***[d]	**Major epoxide Diastereo-isomer ee (%)**[c]	**Minor epoxide Diastereo-isomer ee (%)**[c]	**Recovered chromene ee (%)**[c]	**Rotation of recovered chromene**	k_{rel}[e]
47	**63**	48	2.5:1	87	97	26	(+)	2.3
48	**64**	52	3:1	86	97	37	(+)	2.9
51	**65**	50	4:1	87	98	40	(+)	3.4
52	**66**	56	3.5:1	73	92	41	(+)	2.8
55	**67**	26	*trans* only	76	/	17	(+)	3.4
56	**68**	37	*trans* only	78	/	14	(+)	1.9
59	**69**	38	10:1	76	82	42	(+)	8.0
60	**70**	36	16:1	64	95	50	(+)	27.9

[a] All reactions were carried out with substrate (1 eq.), catalyst (10 mol%) and tetraphenylphosphonium monoperoxysulfate (TPPP) (4 eq.) in $CHCl_3$ at −30 °C.

[b] Conversion was determined from the ^{1}H NMR spectra of the crude reaction mixture.

[c] Enantioselectivity was determined using chiral stationary phase HPLC with a Chiralcel OD-H column.

[d] Diastereoisomeric ratios were determined from the ^{1}H NMR spectra of the reaction mixture after work-up.

[e] k_{rel} = ln[(1 - C)(1 - ee)]/ln[(1 -C)(1 + ee)] where **C** is the fraction of **47, 48, 51, 52, 55, 56, 59, 60** consumed (or conversion) and ee is the percentage enantiomeric excess of the recovered starting material/100. The k_{rel} indicates the difference in reactivity between the two competing starting material enantiomers in the form of a rate constant.

Table 5. Kinetic resolution of olefins using asymmetric epoxidation mediated using catalyst **41**

Looking at the electronic effects of various substituents on the benzopyrans core, in all cases, we again found that the compounds **49, 50, 53, 54, 57, 58, 61, 62** containing the chloro or methyl substituent at C6 on the benzopyran were unstable under the epoxidation reaction conditions, and yielded neither epoxide nor diol. The best results were obtained with those compounds containing nitro and cyano substituents on the aromatic ring; presumably their presence stabilizes the epoxide product, preventing decomposition.

As we expected, increasing the bulk size of the alkyl/aryl substituent at C2, from methyl → propyl → phenyl, leads to an increase in the diastereoselectivity and enantioselectivity observed. When C2 is phenyl, we observe only the epoxide product that has the epoxide moiety *trans* with respect to the C2 substituent. The enantioselectivities were good in all cases for the major epoxide diastereoisomer, and were generally higher still for the minor diastereoisomer, with moderate enantioselectivity observed in the recovered starting material (15-50% ee).

Taking the reaction past 50% conversion and near to completion was also investigated. For example, chromene **47** was submitted to the general asymmetric epoxidation conditions, but allowed to reach 84% conversion over one week. Analysis of the reaction mixture showed that the diastereoisomeric ratio remained at 2.5:1 for the major:minor epoxide, with the major epoxide attaining 70% ee, and the minor epoxide with 80% ee. The recovered starting material was <5 mg, but still provided a (+)-rotation and 64% ee.

2.4.6 Determination of the Absolute Configuration of the Major Epoxide Product

With a number of asymmetric epoxidation experiments now complete, we wished to isolate the major epoxide products from our reactions in order to fully determine the absolute configuration of the epoxide products observed.

In order to assign the absolute configuration of the major epoxide product, we first investigated the recovered starting material. In the literature, there are a number of chiral chromenes that have been previously synthesized as single enantiomers.[30] Based upon these reports and the optical rotations of our recovered chromene starting materials (Table 5), we were able to assign the absolute configuration of the products obtained.

Further confirmation of our assignments of the absolute stereochemistry is based on previous outcomes observed within our group for the epoxidation of prochiral olefins with catalyst **41**. We observe the same diastereofacial selectivity in our kinetic resolution experiments as previously observed in the epoxidation of prochiral chromenes.[16,17,18] A simple reaction mnemonic (Figure 5) shows the favoured approach of oxygen transfer between catalyst **41** and racemic chromene substrates.

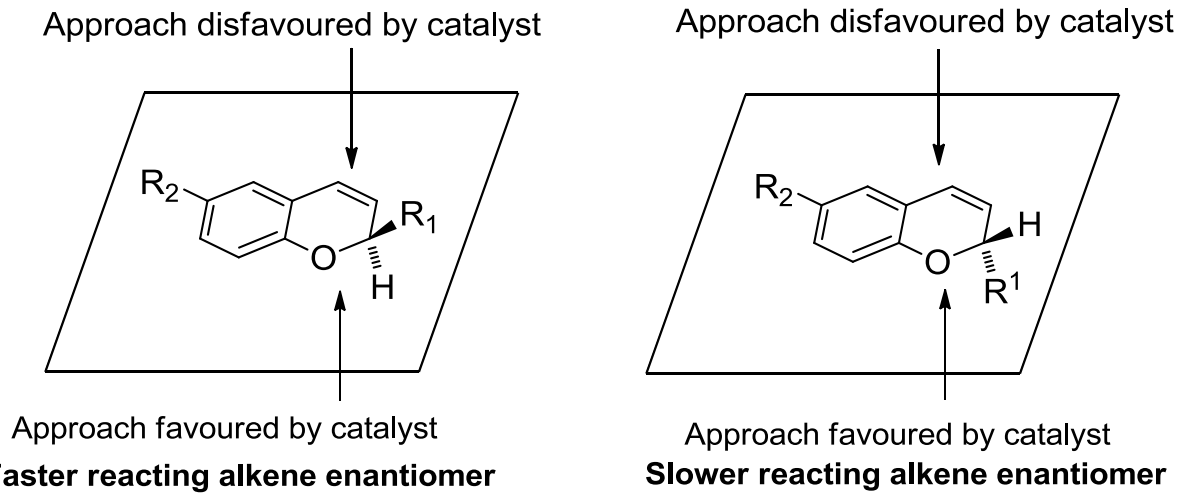
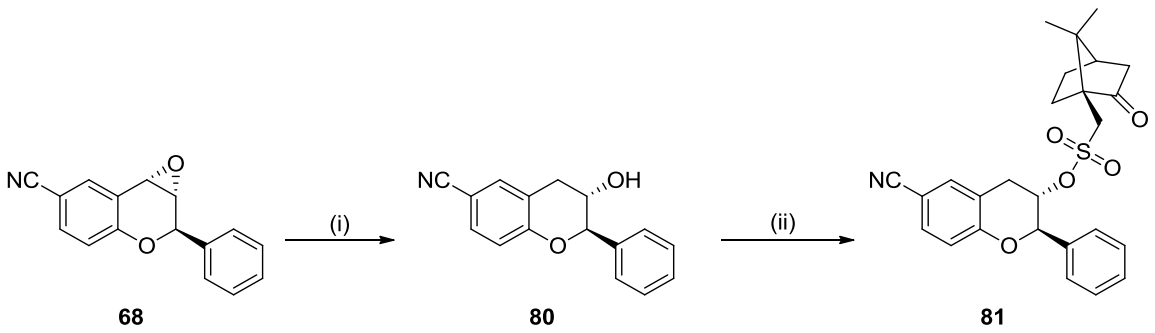


Figure 5. Reaction mnemonic indicating the preferred trajectory of oxidation with catalyst **41**

In order to confirm unequivocally the absolute configuration of the major enantiomer obtained in these reactions, we tried to isolate the major epoxide. We initially attempted separating the epoxide diastereoisomers of 6-cyano-2-methylchromene by column chromatography, but this proved to be unsuccessful. Separation of the diastereoisomers by chiral HPLC was trialled in the laboratory previously, but only small quantities of each isomer were attained (< 1 mg), and so proved unfruitful for the determination of accurate optical rotations.

We next looked at isolation of the major epoxide from the asymmetric epoxidation of 6-cyano-2-phenylbenzopyran **56**. Epoxide **68** was reductively ring-opened by hydrogenation over a palladium on carbon catalyst to give alcohol **80** in quantitative yield.[31] Alcohol **80** was then converted to the corresponding 10*S*-camphorsulfonyl ester **81** in 43% yield (Scheme 23).[32]



Scheme 23. *Reagents and conditions*: (i) Pd/C, H_2 (1 atm), MeOH, r.t., 20 min, 99%; (ii) (10*S*)-(+)-camphorsulfonyl chloride (1 eq.), Et_3N (2 eq.), PhMe, r.t., 24 h, 43%.

Excitingly, recrystallization of 6-cyano-(2*R*)-phenyl-(3*S*)-camphor(16*S*,19*R*)-sulfonylester chromene from a petroleum ether-dichloromethane two layered solvent system yielded long colourless crystals, that were suitable for X-ray analysis. Single crystal X-ray analysis of **81** confirmed our assignment of absolute and relative configuration (Figure 6, Appendix A).

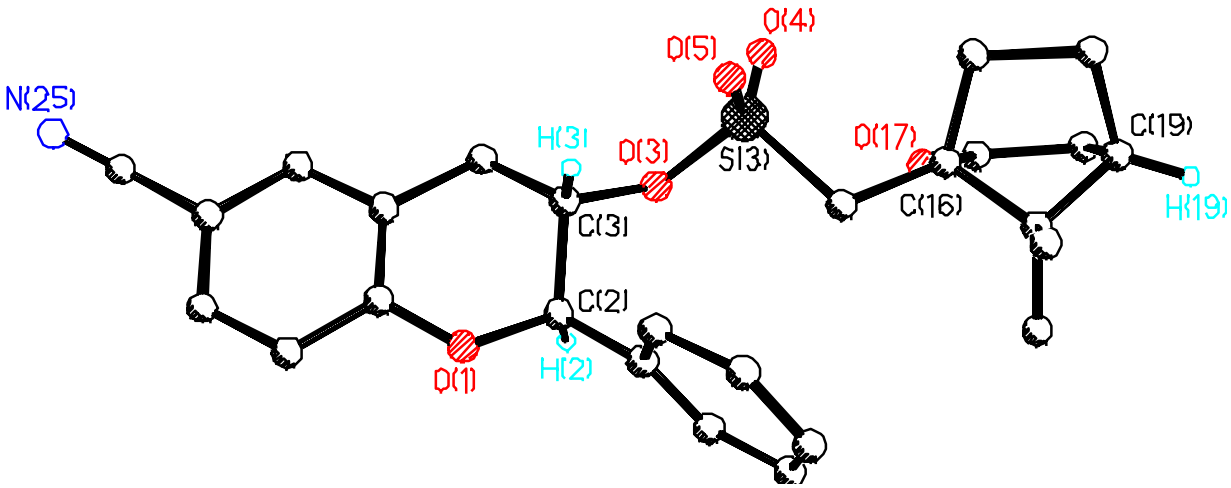


Figure 6. Single crystal X-Ray structure of sulfonyl ester **81**

Analysis of the crystal structure data gives some key information: the mean bond length of the C2-C9 (phenyl substituent) is 1.540(13) Å, whilst the mean bond length of the C3-O3 bond is 1.477(9) Å. The bond angle between C3-C2-C9 is 113.0(7)°, whilst that of C3-O3-S3 is much larger at 123.2(5)°.

In order to assign the absolute stereochemistry, we must look at the chromene core structure as lying flat in the plane of the page. From here, we can see that the phenyl substituent at C2 is coming out towards the reader, with the proton H2 going away from the reader. Looking at the oxygen atom O3, we observe it heading away from the reader, with the hydrogen H3 coming out of the plane of the paper towards the reader. The addition of (+)-camphorsulfonyl ester moiety to the oxygen O3, which has known stereochemistry at C16 and C19 respectively, enabled us to make the assignment unequivocally.

With this information in hand, firstly, we can see that the major epoxide product is the one that has the epoxide moiety *trans* to the R substituent at the C2 position. Secondly, the stereochemistry observed would indicate that the oxygen transfer process is more selective for the alkene enantiomer where the phenyl or R substituent at C2 is coming out of the plane of the paper towards the reader, allowing the catalytic oxygen transfer step to occur from the opposite side/underneath.

Analysis of this oxygen transfer step from the crystallographic data collected agrees directly with the same diastereofacial selectivity previously observed when our group has conducted the epoxidation of various prochiral chromenes.

2.5 Conclusions and Future Applications

The results accumulated within this research project have shown that the resolution of racemic benzopyrans by iminium-salt mediated asymmetric epoxidation with catalyst **41** can be achieved with excellent enantioselectivities for the minor epoxide and good enantioselectivites for the major epoxide product. The recovered starting material can also be isolated in moderate enantioselectivities (15-50% ee). The methodology works well for those chromenes containing electron-withdrawing substituents at the C6 position on the chromene, but fails when electron-rich chromenes are subjected to the same reaction conditions.

Future aims should look towards developing a new catalytic system, maybe utilizing another iminium-salt catalyst developed within the group that is more favoured towards sensitive olefin substrates, or adapting the methodology to work under Page's aqueous epoxidation conditions.

Catalyst **82** and **83** (Figure 7) have recently shown great promise within the Page group for the epoxidation of various *cis*-olefins under aqueous and non-aqueous conditions.[33] In another project I have been involved in the Page group, we reported the epoxidation of various 2,2-substituted benzopyrans under non-aqueous conditions affording ee's up to 98% ee (Table 6, Appendix C).

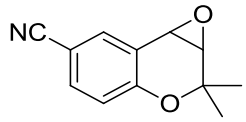
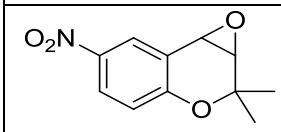
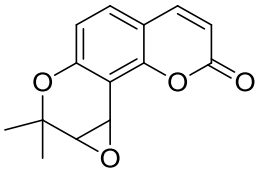
Epoxide	**Catalyst**	**Conv /%**	**Reaction time (h)**	**ee/ %**	**Major enantiomer**
	**82**	90	20	97	(−)-1*S*,2*S*
	83	100	48	98	(−)-1*S*,2*S*
	**83**	74	120	94	(−)-1*S*,2*S*
	**83**	100	45	86	(+)-(3'*S*,4'*S*)

Table 6. *Epoxidation conditions*: iminium salt catalyst **82**/**83** (10 mol%), TPPP (2 eq.), $CHCl_3$, 0 °C

Applications of this methodology to natural product syntheses can be envisaged for those target molecules containing a chromen-3-ol core, such as catechin **84**, containing a proton and phenyl substituent at C2.

Some key examples found in the literature include green tea catechins such as EGCG **85** (Figure 7), which are known to exert excellent bio-activities,[34] but many syntheses of

various green tea catechins are achieved in low overall yield,[35] either following tedious and in some cases expensive asymmetric synthesis.

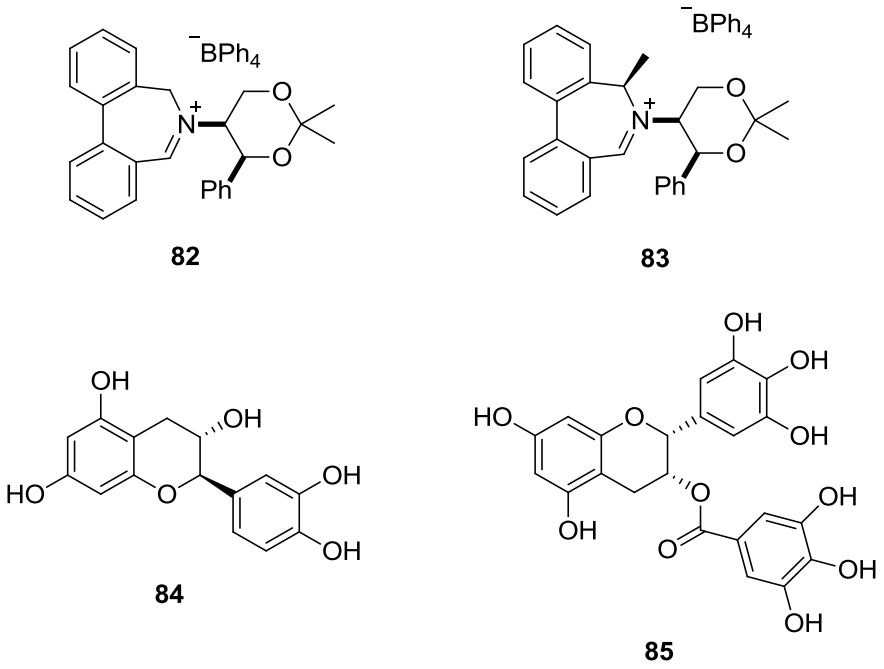
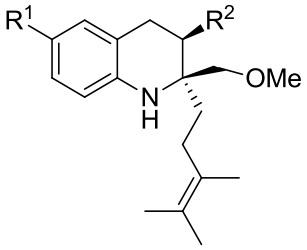


Figure 7. Iminium-salt catalysts **82** and **83**, Green tea compounds Catechin **84** and EGCG **85**

Current projects within the Page research group are investigating implementing this kinetic resolution methodology to gain access to generate these chromen-3-ol green tea catechins.

2.6 The First Examples of Asymmetric Epoxidation on Dihydroquinoline Substrates catalysed by Chiral Iminium-salts

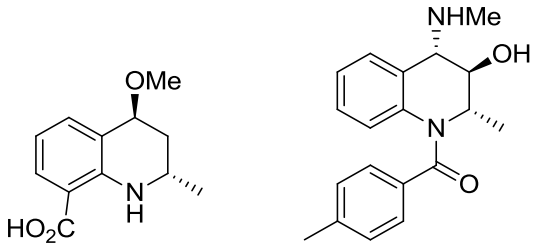
The tetrahydroquinoline motif is a key moiety found in a number of natural products and pharmaceuticals, for example, benzastatins C & D **86-87**, and virantmycin **2**, all of which exhibit potent biological activity (Figure 8).[2]



86 Benzastatin C; $R^1 = CONH_2$, $R^2 = Cl$
87 Benzastatin D; $R^1 = CONH_2$, $R^2 = OH$
2 Virantmycin; $R^1 = CO_2H$, $R^2 = Cl$

Figure 8. Tetrahydroquinoline-derived natural products

This particular area of heterocyclic chemistry has been reviewed by Menéndez in 2011,[36] and has allowed us to identify some natural products and drug molecules that could be synthesized within the Page group, such as helquinoline **1** and tetrahydroquinoline drug molecule **88** (Figure 9).[1,37]



1 **88**

Figure 9. Potential synthetic target molecules helquinoline **1** and drug molecule **88**

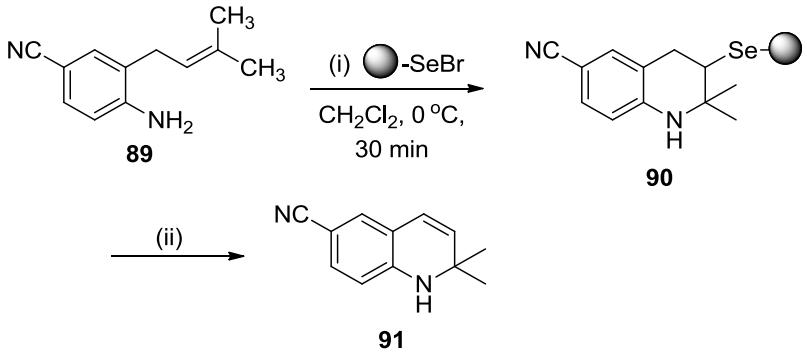
2.6.1 Reactions Utilized in the Synthesis of Dihydroquinoline Substrates

Our strategy to develop a methodology to access tetrahydroquinoline natural products such as helquinoline **1**, would start with the synthesis of the dihydroquinoline motif followed by enantioselective epoxidation to obtain chiral non-racemic tetrahydroquinolines.

Some of the most successful reactions employed in the generation of dihydroquinolines are discussed herein.

2.6.2 Nicolaou's Polymer-Supported Selenium Cyclizations

Nicolaou reported the cyclization of a limited number of *para*-substituted *ortho*-prenyl anilines in the presence of a polymer-bound selenenyl bromide resin. When Nicolaou utilized the unprotected aniline **89**, he observed a 6-*endo*-trig cyclization to afford the 2,2-dimethyldihydroquinoline nucleus **90** in just 30 minutes. The final product, 6-cyano-2,2-dimethyldihydroquinoline **91**, was formed in 85% yield after oxidative cleavage of the selenenyl resin.[38]



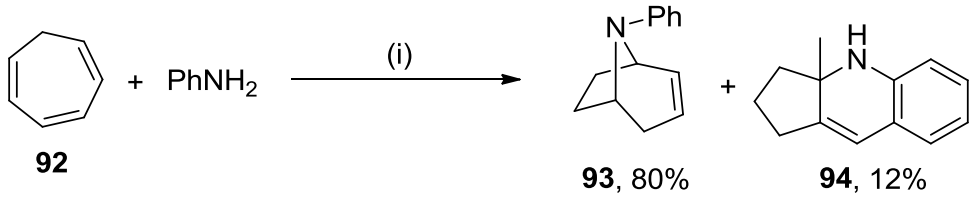
Scheme 24. *Reagents and conditions*: (i) Polymer-bound selenenyl bromide resin, Aniline (2 eq.), Dichloromethane, 0 °C, 30 min. (ii) Hydrogen Peroxide, THF.

However, the methodology has a few important drawbacks to note; Nicolaou's attempts to derivatize the nitrogen of the dihydroquinoline scaffold failed due to severe steric encumbrance of the position by the adjacent *gem*-dimethyl group. Secondly, the methodology only afforded clean conversion to the quinoline motif when *para*-substituted electron-deficient substituents (such as cyano or nitro substituents) were present on the aniline.

2.6.3 Hartwig's Palladium-catalysed Hydroamination

Hartwig has recently reported a palladium-catalysed hydroamination reaction of cyclic trienes, in which he proposes that the bridged bicyclic products of the reaction are

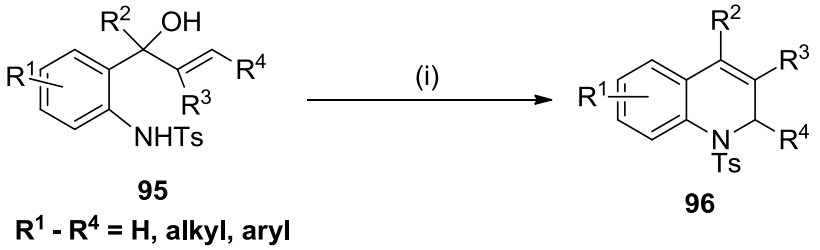
generated from a consecutive intermolecular hydroamination and transannular intramolecular hydroamination reaction.[39] The major products in each example reported are the tropene products, such as **93** (Scheme 25), which are all formed in good to excellent yields. However, the main drawback of this methodology is that the dihydroquinoline side-products, such as **94**, are formed in much lower yields (9 – 38%). Interestingly, Hartwig showed that heating **93** with just the catalyst components of the system, and without the amine present, gave 87% unreacted starting material after 1.5 hours, showing that tropene **93** is not a direct precursor to quinoline **94**.



Scheme 25. *Reagents and conditions*: (i) Cycloheptatriene **92** (2.0-4.0 mmol, 4 eq.), Aniline (0.5-1 mmol), $Pd(TFA)_2$ (2%), Xantphos (4%), Benzoic Acid (10%), Toluene, 110 °C

2.6.4 Gold Catalysed Intramolecular Allylic Amination

Chan has shown that various 1,2-dihydroquinolines (**96**) can be synthesized from 2-tosylaminophenylprop-1-en-3-ols (**95**) in good to excellent yields when reacted specifically at room temperature, in toluene, catalysed by a specific gold-silver catalyst combination (Scheme 26).[40] This intramolecular allylic amination reaction works best when the 2-tosylaminophenylprop-1-en-3-ol starting materials contain electron-donating substituents.

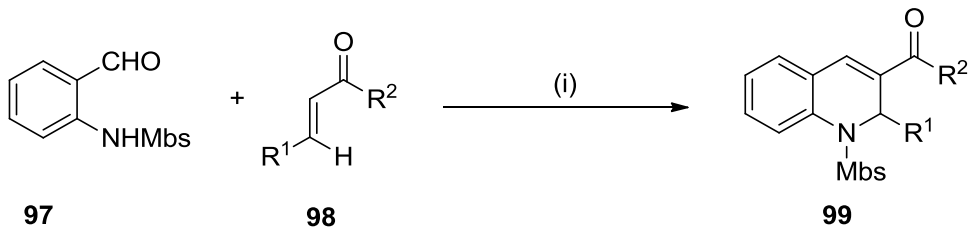


Scheme 26. *Reagents and conditions*: (i) $AuCl_3$ (5 mol%), $AgSbF_6$ (10 mol%), Toluene, r.t., 1 h

Chan's methodology, however, has its drawbacks. Firstly, the reaction only proceeds efficiently in toluene (acetonitrile and 1,4-dioxane were tested as solvents, yet showed no sign of reaction). Secondly, the catalyst mixture employed in the reaction is limited to using a gold trichloride-silver antimony hexafluoride mixture (at relatively high catalyst loadings), with other precious metals such as ytterbium triflate and indium trichloride affording relatively low yields (up to 11%).

2.6.5 Tandem Michael-aldol additions

Hamada showed that a base-catalysed tandem Michael-aldol reaction was feasible starting from *N*-protected *o*-aminobenzaldehydes **97** and α,β-unsaturated carbonyl compounds **98**, affording various 3-substituted dihydroquinolines **99** in good yields (Scheme 27).[41] They observed that under these reaction conditions a base-catalysed dehydration was taking place. In the absence of benzyltriethylammonium chloride, no reaction was observed at all.



97 **98** **99**

Scheme 27. *Reagents and conditions*: (i) $BnEt_3NCl$ (0.2 eq.), 4M K_2CO_3, $CHCl_3$, r.t., 64 h (Mbs: 4-MeOPhSO_2)

The reaction is, however, limited to two specific examples in the report, and no further expansion of substrate scope was reported by the authors. The inclusion of a substituent at the 3-position on the dihydroquinoline core may hinder our efforts to conduct successful epoxidation reactions on the C3-C4 alkene moiety, and for this reason this methodology was not considered as a suitable method to access our dihydroquinoline substrates.

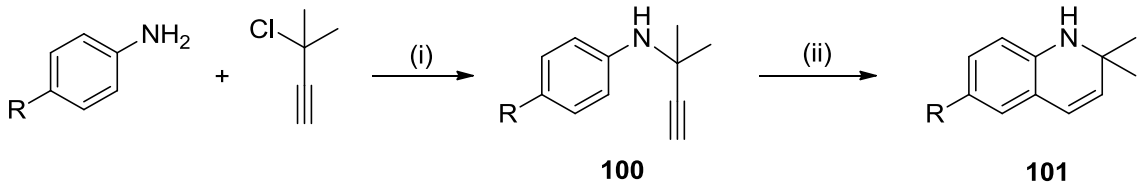
The examples described above do not include the enantioselective syntheses of 2-substituted dihydroquinolines, but it is worth noting that excellent enantioselectivities have been reported independently by Shibasaki (96 % ee)[42], Takemoto (97% ee)[43] and Alexakis (75% ee) respectively.[44] The work reported in this chapter looks to employ an

enantioselective iminium-salt catalysed epoxidation step to form enantioenriched tetrahydroquinoline products from various prochiral dihydroquinoline substrates.

2.6.6 Copper catalysed cyclization of *N*-(1,1-disubstitutedpropargyl)anilines

In 1960, Hennion reported the first examples of alkylation of aromatic amines with tertiary acetylinic chlorides catalysed by cuprous chloride. The methodology reported by Hennion allowed various *N*-(1,1-disubstitutedpropargyl)anilines **100** to be synthesized in good yields (up to 56%). The addition of a catalytic amount of cuprous chloride was found to be essential for the reaction to proceed within a reasonable reaction time (≤ 3 hours), since the aromatic amines react very poorly in its absence.[45]

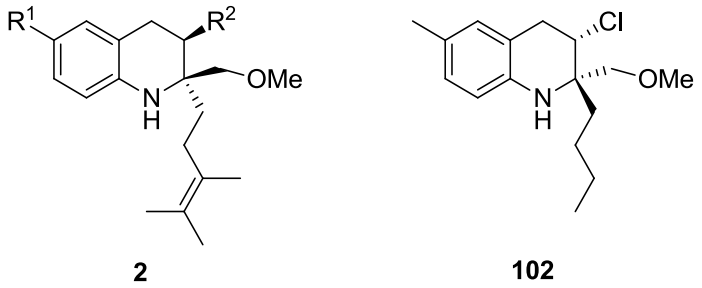
Ward later showed that these *N*-(1,1-disubstitutedpropargyl)anilines **100** could be cyclised by refluxing them in toluene in the presence of cuprous chloride, affording various 2,2-disubstituted-1,2-dihydroquinolines **101** in good yields (up to 82%). He showed that electron donating groups at the *para*-position of the ring (such as methyl or methoxy moieties) enhanced the rate of reaction, whilst electron withdrawing substituents slowed the reaction rate (Scheme 28).[46]



Scheme 28. *Reagents and conditions*: (i) Aniline (1 eq.), Triethylamine (1.3 eq.), 3-Chloro-3-methyl-1-butyne (1 eq.), Copper(I) chloride, Copper bronze powder, Diethyl ether, r.t., 3 h.[45] (ii) Copper(I) chloride (10% by weight), reflux, toluene, 0.5 – 16 h.[46]

Ward's aim was to find a quick route to synthesizing 2,2-disubstituted-3-chlorotetrahydroquinolines, compounds that are close in structure to the known natural product virantmycin **2**.[2] He showed that his 2,2-disubstituted-1,2-dihydroquinoline

substrates could be *cis*-dichlorinated, followed by selective monodechlorination at the benzylic position to afford 3-chlorotetrahydroquinolines **102** (Figure 10).[46,47]



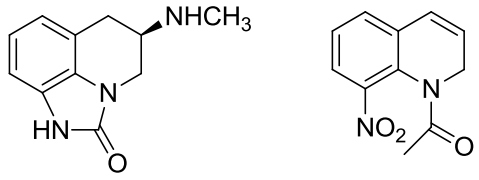
2 **102**

Figure 10. Tetrahydroquinoline-derived natural product Virantmycin **2** and Ward's 3-chlorotetrahydroquinoline **102**

We decided to implement Ward's methodology as it would allow us to generate a library of 2,2-disubstituted-1,2-dihydroquinolines with various electron-withdrawing or electron-donating substituents at the *para*-position on the aniline used to construct the quinoline core. The synthesis can be achieved in two simple steps from relatively inexpensive commercially available starting materials. Encouraged by the results reported by Ward for the *cis*-dichlorination of dihydroquinolines, we envisaged the possibility of applying our iminium-salt catalysts to effect an asymmetric epoxidation reaction on the alkene moiety of the dihydroquinoline substrate.

Ward has already reported that *m*CPBA can be used to prepare non-chiral epoxides of various nitrogen-protected dihydroquinoline substrates.[47] Smith has alternatively shown that the hydrobromination of dihydroquinolines using aqueous NBS followed by base catalysed elimination affords the subsequent non-chiral epoxides.[48]

The asymmetric epoxidation of dihydroquinolines has only been very rarely reported. The only examples in the literature are shown by Wuts,[49] in which intermediates towards the synthesis of sumanirole **103**,[48] include chiral 3,4-epoxy-tetrahydroquinoline substrates (Figure 11). The two methodologies utilized by Wuts for the epoxidation of 1-acetyl-8-nitrodihydroquinoline **104** (Figure 11) include Shi's epoxidation conditions,[50] and Jacobsen's epoxidation conditions,[51] with the chiral epoxide ee determined as 13% and 97% in each case, respectively.



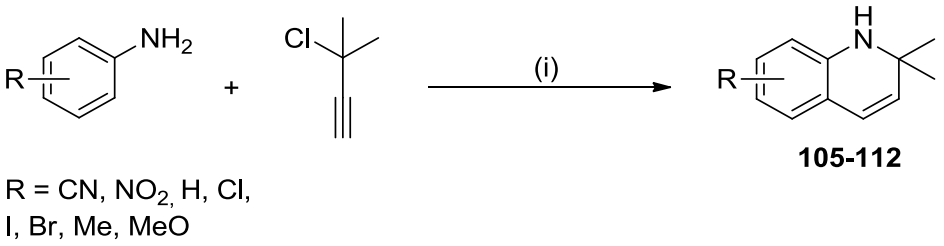
103 **104**

Figure 11. Anti-parkinson's drug molecule sumanirole **103** and 1-acetyl-8-nitrodihydroquinoline **104**

The results discussed herein are the first examples of organocatalytic iminium-salt derived asymmetric epoxidation reactions of 1,2-dihydroquinoline substrates to afford chiral 3,4-epoxytetrahydroquinoline products.

2.7 Preparation of Dihydroquinoline Substrates 105-112

Encouraged by Ward's methodology, we found that dihydroquinoline substrates **105-112** could be synthesized in moderate yields (Scheme 29, Table 7). During the reaction, the intermediate *N*-(1,1-disubstitutedpropargyl)anilines **100** were not observed as a product. Isolation of dihydroquinolines **105-112** was achieved by refluxing the anilines and 3-chloro-3-methyl-1-butyne in toluene until complete consumption of starting material was observed by thin layer chromatography.



Scheme 29. *Reagents and conditions*: 3-Chloro-3-methyl-1-butyne (1 eq.), Aniline (1 eq.), Copper Bronze powder (0.1 eq.), Copper (I) chloride (1 eq.), toluene, reflux, 24 h.

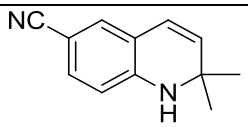
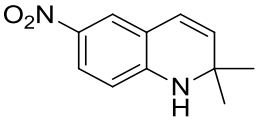
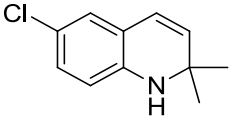
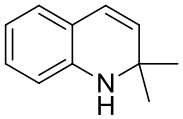
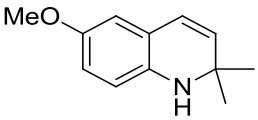
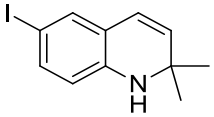
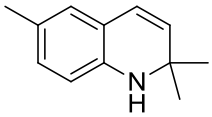
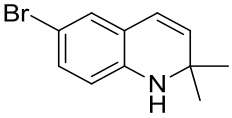
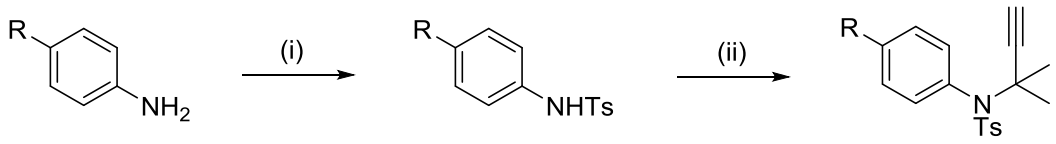
Product	Dihydroquinoline	Yield (%)
105		30
106		32
107		25
108		14
109		0
110		0
111		0
112		0

Table 7. Various 6-substituted dihydroquinolines synthesised according to Scheme 29

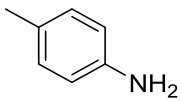
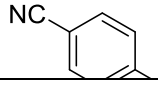
In an attempt to increase the yields of compounds **105-108**, the methodology was repeated in a sealed glass vial and submitted to microwave irridation for 20 minutes, previously utilized in the group for increasing the yield of seselin **37** (Scheme 13) when changing from the conventional reflux conditions to microwave conditions.[17] This methodology however proved to be unsuitable for this particular copper-catalysed cyclisation reaction, and in two cases tested, compounds **105** and **107** were not observed after 1 hour of irridation, either by thin layer chromatography of the reaction mixture, or by analysis of the ^{1}H NMR spectra of the crude reaction mixture.

The yields of dihydroquinolines **105-108** are only moderate at best, and further attempts were made to increase the yields of this cyclization reaction. We first looked at protecting the aniline with a protecting group, such as a tosyl-protecting group as used in Chan's gold-catalysed intramolecular allylic amination reactions.[40] This would then be followed by alkylating with 3-chloro-3-methyl-1-butyne in the same fashion as Hennion's procedure,[45] and finally cyclization by refluxing in toluene in the presence of cuprous chloride (Scheme 30). We hoped that this would not only increase the yields of the 1,2-dihydroquinoline products, but would also result in the protection of the secondary amine, which could prove to be necessary for a successful epoxidation of the alkene moiety.

The results from this procedure are indicated below (Table 8). The tosylation of three aromatic amines occurred in nearly quantitative yield after stirring at room temperature for 24 hours under base catalysed conditions. However, attempts to alkylate the protected aromatic amines with 3-chloro-3-methyl-1-butyne failed under numerous base-catalysed conditions tested (Table 8).



Scheme 30. *Reagents and conditions*: (i) Aniline (1 eq.), Triethylamine (1.5 eq.), *p*-Toluenesulfonyl chloride (1.2 eq.), r.t., 24 h; (ii) 3-Chloro-3-methyl-1-butyne (1 eq.), See Table 8.

Aniline Starting Material	**Yield of Tosyl-Protected Product (%)**	**Conditions Utilized for Attempted Alkylation Step**	**Yield of Alkylated Aniline (%)**
	97	Triethylamine (1.5 eq.), THF, r.t., 24 h	0
		n-BuLi (1.5 eq.), THF, -78 C – r.t., 3 h	0
		Pyridine (1.5 eq.), CH_2Cl_2, r.t., 24 h	0
	96	Triethylamine (1.5 eq.), THF, r.t., 24 h	0

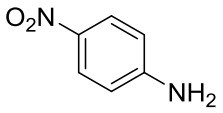
		n-BuLi (1.5 eq.), THF, -78 C – r.t., 3 h	0
	95	Triethylamine (1.5 eq.), THF, r.t., 24 h	0

Table 8. Attempted synthesis of alkylated aromatic amines

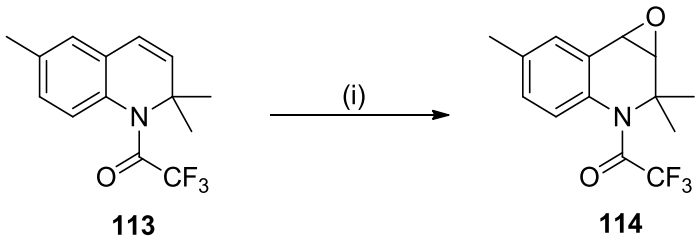
Since the results obtained from this modified method proved to be unfruitful, we decided to proceed to the next stage of our methodology using our original conditions to synthesize the 1,2-dihydroquinoline substrates.

With the dihydroquinolines in hand, a number of trial epoxidations were conducted utilizing either *m*CPBA or various iminium salt catalysts under aqueous and non-aqueous conditions upon the dihydroquinolines **105-112** above (Table 9). We found that consumption of alkene starting material was observed in most cases, but, the desired epoxide product was not isolated. From ^{1}H NMR spectra of the crude reaction mixtures conducted in $CDCl_3$, only peaks in the aromatic region were seen, at approximately the same chemical shifts as the starting material aniline.

Starting material	**Oxidation system**	**Epoxide product detected**
105	*m*CPBA, CH_2Cl_2, 0 °C	No, complex mixture observed
106	*m*CPBA, CH_2Cl_2, 0 °C	No, complex mixture observed
107	*m*CPBA, CH_2Cl_2, 0 °C	Aniline SM observed
	TPPP (2 eq.), Iminium-salt **82** (10 mol%), $CHCl_3$, 0 °C	Aniline SM observed
108	*m*CPBA, CH_2Cl_2, 0 °C	Aniline SM observed

Table 9. Epoxidation of dihydroquinoline substrates with various oxidizing agents

The instability of the dihydroquinolines towards oxidants such as *meta*-chloroperbenzoic acid made us re-think our strategy. Ward had reported that protecting the secondary amine of his 1,2-dihydroquinolines with a trifluoroacetyl protecting group allowed only the alkene moiety to be dichlorinated to give various 3,4-dichlorotetrahydroquinolines, with no sign of aromatic chlorination taking place. He also showed that *N*-trifluoroacetyl protected **113** can react with *m*CPBA, affording the racemic epoxide **114** in good yield (70%) (Scheme 17).[47]

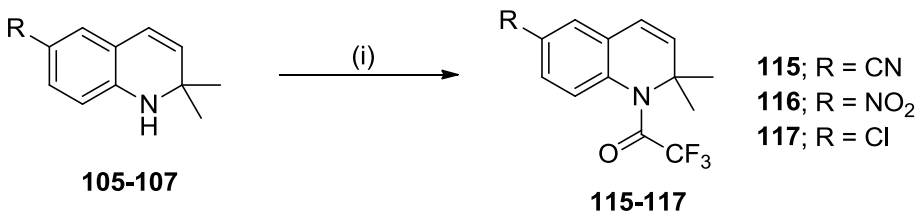


Scheme 31. *Reagents and conditions:* (i) *m*CPBA (1 eq.), $NaHCO_3$ (1.25 eq.), CH_2Cl_2, r.t., 41 h

Encouraged by Ward's findings, we looked at potential protecting groups for the secondary amine of the dihydroquinolines we had generated in order to perform successful epoxidation reactions.

2.7.1 Preparation of Nitrogen-protected Dihydroquinoline Substrates

Our first attempt at protecting the secondary amine of our dihydroquinolines with a trifluoroacetyl moiety was achieved by following the same procedure as reported by Ward (Scheme 32).[47]



Scheme 32. *Reagents and conditions*: (i) Pyridine (1 eq.), trifluoroacetic anhydride (2 eq.), CH_2Cl_2, 0 °C → r.t., 1 h

The best methodology in our hands involved the use of trifluoroacetic anhydride under basic conditions (pyridine), which afforded yields up to 97% (Table 10).[47] Other bases were tested, for example, triethylamine and *n*-butyl lithium, on compounds **105** and **107**, but in both cases of these bases tested the yields of product obtained of **115** and **117** were lower than that observed when pyridine was used (Table 10).

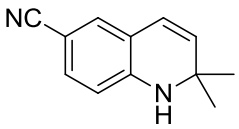
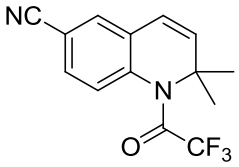
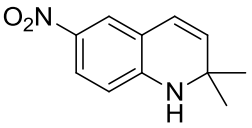
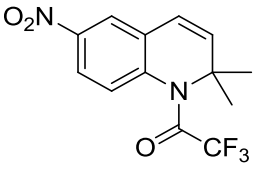
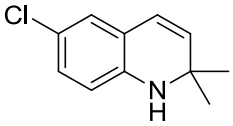
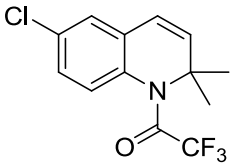
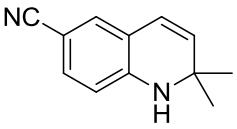
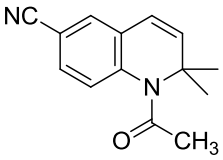
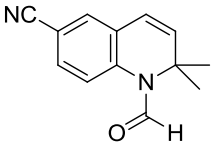
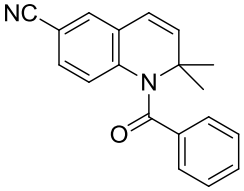
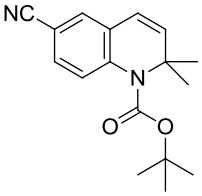
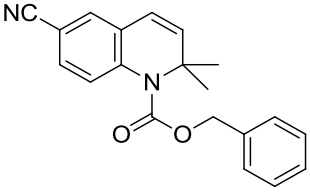
Starting Material	Product Reference	Conditions used	Time (h)	Yield (%)
 **105**	 **115**	(a)	1	97
		(b)	12	65
		(c)	4	40
 **106**	 **116**	(a)	1.5	0
 **107**	 **117**	(a)	1	68
		(b)	12	43
		(c)	4.5	40

Table 10. *Reagents and conditions:* (a) dihydroquinoline (1 eq.), trifluoroacetic anhydride (2 eq.), pyridine (1 eq.), CH_2Cl_2, 0 °C → r.t., 1 h; (b) dihydroquinoline (1 eq.), trifluoroacetic anhydride (2 eq.), triethylamine (1 eq.), CH_2Cl_2, r.t., overnight (12 h); (c) dihydroquinoline (1 eq.), *n*-BuLi (1.4 eq.), THF, -78 °C, 1 h, then, trifluoroacetic anhydride (2 eq.) dissolved in minimum amount of THF, -78 °C → r.t., 3 h.

Following on from the success of the trifluoroacetyl protecting group, we decided to try a range of protecting groups under various conditions. Our best results were obtained when a strong base such as *n*-butyl lithium was used to deprotonate the dihydroquinoline nitrogen (Table 11). This time, however, bases such as triethylamine and pyridine resulted in the isolation of the products in much lower yields, if at all. Protection of dihydroquinolines **105** and **107** with acetyl moieties using the same procedure as reported by Ward resulted in

isolation of only the starting material in both cases.[47] An attempt to formylate the nitrogen atom of dihydroquinoline **105** under similar conditions used for the synthesis of our iminium salt catalysts **41** and **82** as reported by Thomas *et al.* failed.[52] 6-nitro-substituted 1,2-dihydroquinoline **106** also failed to react with a benzoyl moiety when using *n*-butyl lithium as base.

Starting Material	**Product**	**Conditions Used**	**Yield (%)**
 **105**	 **118**	(a)	0
		(b)	0
	 **119**	(c)	0
	 **120**	(d)	41
	 **121**	(e)	33
	 **122**	(f)	55

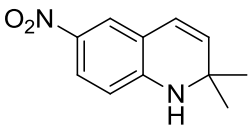
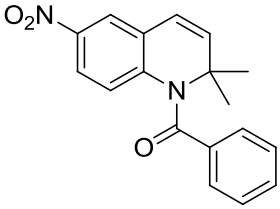
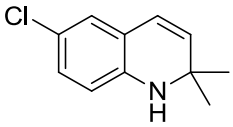
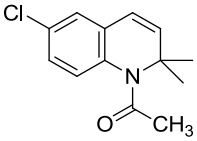
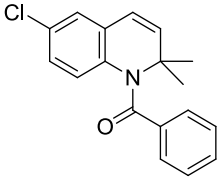
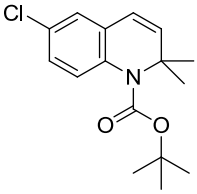
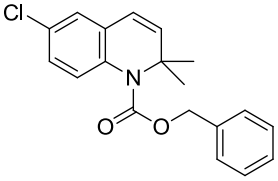
 **106**	 **123**	(d)	0
 **107**	 **124**	(a)	0
	 **125**	(d)	0
	 **126**	(e)	40
	 **127**	(f)	14

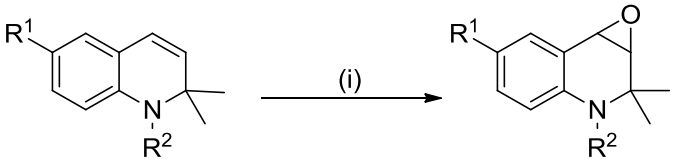
Table 11. *Reagents and conditions*: Each starting with 1 equivalent of 1,2-dihydroquinoline (a) Ac_2O (1.5 eq.), pyridine (0.5 mL), CH_2Cl_2, 0 ˚C → r.t., 3 h.; (b) AcCl (1.5 eq.), triethylamine (1.3 eq.), CH_2Cl_2, 0 ˚C → r.t., 1 h.[47]; (c) NaOMe (1 eq.), CH_3CHO (1.5 eq.), MeOH, r.t., 24 h.[52]; (d) *n*-BuLi (1.4 eq.), benzoyl chloride (1.5 eq.), THF, -78 °C → r.t., 4 h.; (e) *n*-BuLi (1.4 eq.), di-*tert*-butyl dicarbonate (1.5 eq.), THF, -78 °C → r.t.; (f) *n*-BuLi (1.4 eq.), benzyl chloroformate (1.5 eq.), THF, -78 °C → r.t.

The dihydroquinolines that contained a -chloro or -cyano substituent at the C6 position were most stable during the nitrogen protection reactions, with nitro substituted dihydroquinolines being the least stable. The least favourable group to protect the dihydroquinolines was found to be the acetate protecting group, despite repeating Ward's successful methodology of dihydroquinoline acetate protections.[47] Protecting the dihydroquinolines **105** and **107** with *tert*-butoxycarbonyl or carbobenzoxy moieties proceeded in moderate yields (≤55%), but nevertheless it provided five new compounds that could be tested for reactivity in subsequent epoxidation reactions, alongside the two compounds generated from trifluoroacetyl protection.

The results obtained for the non-chiral and chiral epoxidations of these new nitrogen-protected 1,2-dihydroquinoline substrates are detailed below.

2.7.2 Non-chiral Epoxidations of Dihydroquinoline Substrates 120-127 utilizing *meta*-Chloroperbenzoic Acid

The new nitrogen-protected dihydroquinoline substrates **120-127** were subjected to achiral epoxidation conditions using *m*CPBA as the oxidant, to determine their reactivity towards oxidative species, their stability, and to provide racemic standards (Table 12).



115-127 **128-134**

R^1 = CN, NO_2, Cl
R^2 = $C(O)CF_3$, C(O)Ph, $C(O)O^tBu$, $C(O)OCH_2Ph$

R^1	R^2	Substrate	Product no.	Conversion (%)	Yield (%)
CN	$C(O)CF_3$	**115**	**128**	100	60
Cl	$C(O)CF_3$	**117**	**129**	100	52
CN	C(O)Ph	**120**	**130**	100	53

CN	C(O)O^{t}Bu	**121**	**131**	100	71
CN	C(O)OCH$_2$Ph	**122**	**132**	100	78
Cl	C(O)O^{t}Bu	**126**	**133**	100	53
Cl	C(O)OCH$_2$Ph	**127**	**134**	-	0

Table 12. *Reagents and conditions: m*CPBA (2 eq.), $NaHCO_3$ (4 eq.), CH_2Cl_2, 0 °C, 24 h

The epoxide products generated were surprisingly stable (no decomposition was observed after being left at room temperature for 2 months) and could be easily purified by flash column chromatography on silica gel. The epoxidation of various *N*-protected dihydroquinolines with *m*CPBA showed that the olefin double bond is reactive towards electrophilic oxygen sources, and the products appear to be stabilized by the electron-withdrawing nature of the protecting groups. The conversion of olefin to epoxide in each reaction reported above (Table 12) was followed by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

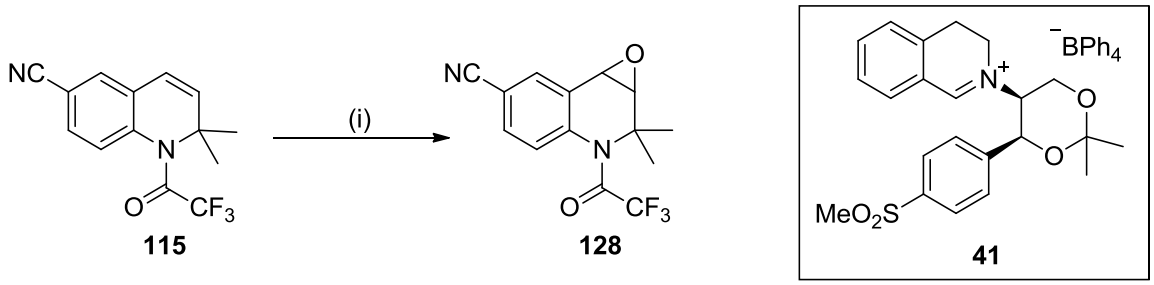
The isolated yields of epoxide products **128**-**133** after chromatography were good. It should be noted that all the successful results were achieved when the dihydroquinolines contained a cyano or chloro moiety at C6 on the quinoline core structure. Since there were no successful protection reactions on the nitro-containing dihydroquinoline **106** (previously shown in tables 10 and 11), the subsequent epoxidation reactions on these substrates could not be tested. Encouraged by these results, we felt that an asymmetric variant of the epoxidation reaction could be attempted. It is important to note that most of the racemic samples obtained could be analysed using chiral HPLC or using a chiral shift reagent in ^{1}H NMR spectroscopy.

2.7.3 Initial Attempt at the Asymmetric Epoxidation of Dihydroquinoline Substrate 115 under non-aqueous conditions

The asymmetric epoxidation of *N*-protected dihydroquinoline substrates **115**-**126** could be approached in two ways, both of which have been previously developed within the group: The first method attempted would be under non-aqueous conditions, where TPPP is

employed as the primary oxidant, and the second, uses aqueous conditions utilizing Oxone as the oxidant.

Our first attempt at an asymmetric epoxidation of these substrates involved non-aqueous conditions with iminium salt **41**, previously shown to be highly effective in the asymmetric epoxidation of the complementary chromene-derived substrates (Scheme 33). Our initial test substrate was dihydroquinoline **115**, containing a cyano moiety at the C6 position of the core structure, and also a trifluoroacetyl protecting group on the nitrogen atom. Dihydroquinoline **115** was observed to be extremely unreactive under these oxidative conditions, and the reaction achieved 37% conversion after 5 days. Excitingly, the corresponding epoxide product **128** was isolated with excellent enantioselectivity (73% ee).



Scheme 33. *Reagents and conditions*: iminium-salt **41** (10 mol%), TPPP (2 eq.), CH_2Cl_2, 0 °C, 5 days

To test whether the conversion of this reaction could be improved under these non-aqueous conditions, the reaction was repeated two more times in the same solvent (dichloromethane), initially leaving the reaction for a longer time period (1 week), and secondly by increasing the number of equivalents of oxidant added (5 equivalents of TPPP). In both cases attempted the reaction maintained a low conversion (each time achieving <40%), yet the enantioselectivity remained consistent (~73% ee).

Attempting this reaction in another non-aqueous solvent, for example chloroform (the preferred solvent for the non-aqueous iminium salt-catalysed asymmetric epoxidation reactions of the corresponding racemic chromene substrates used in the kinetic resolution experiments), proved to be unfruitful, yielding only trace amounts of the epoxide product as detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

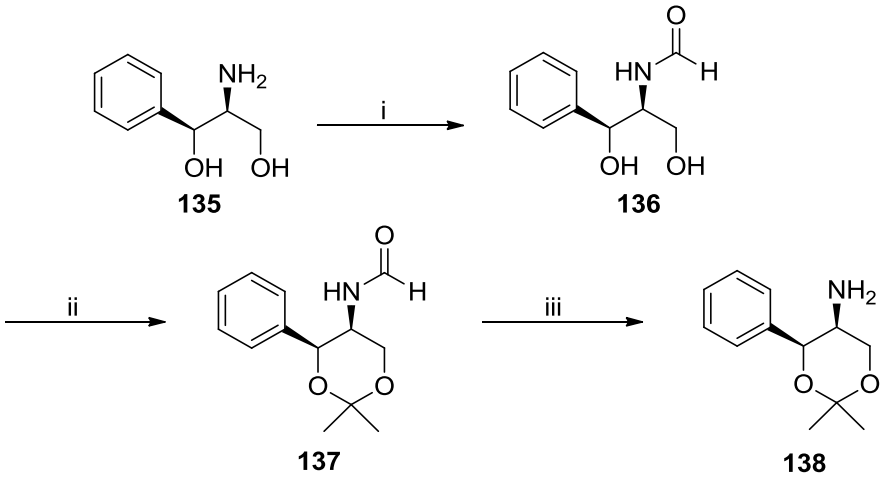
We turned our attention to improving the conversion of this reaction; in order to achieve this we would require a much more reactive catalyst, perhaps changing the reaction

conditions to aqueous conditions. Biphenylazepinium-derived iminium salt **82** was previously reported by Page to be much more reactive than various dihydroisoquinolinium salts in the epoxidation of simple olefins under both aqueous conditions[53] and non-aqueous conditions.[33]

2.7.4 Synthesis of Biphenyl Azepinium Iminium-salt 82

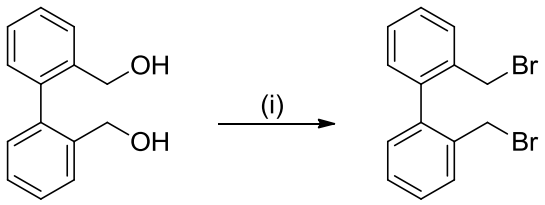
The preparation of iminium salt **82** was achieved by a similar procedure to that shown above in this chapter for iminium salt **41** (Schemes 18-20), starting this time from known chiral (*S*)-(−)-2-amino-3-phenyl-1-propanediol **135** (Scheme 34). The procedure reported by Thomas could be employed to synthesize the aminodioxane part of the catalyst, which can be formed in a 3 step synthesis from chiral amine **135** (Scheme 34).[52]

The synthesis started from the commercially available amine **135**, and was first protected using methyl formate to give diol **136**, and then treated with 2,2-dimethoxypropane in the presence of camphorsulfonic acid to afford *N*-((4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)formamide **137** in quantitative yield. Removal of the formyl protecting group was achieved using hydrazine monohydrate, and after extraction with ethyl acetate, aminodioxane **138** was isolated in good yield (88%).



Scheme 34. *Reagents and conditions*: (i) NaOMe (25% in MeOH), methyl formate (1.5 eq.), MeOH, r.t., 12 h; (ii) 2,2-Dimethoxypropane (10 eq.), CSA (0.1 eq.), acetone, reflux, 4 h, quant.%; (iii) Hydrazine monohydrate (85%, 20 mL/g of **137**), reflux, 2.5 h, 88%

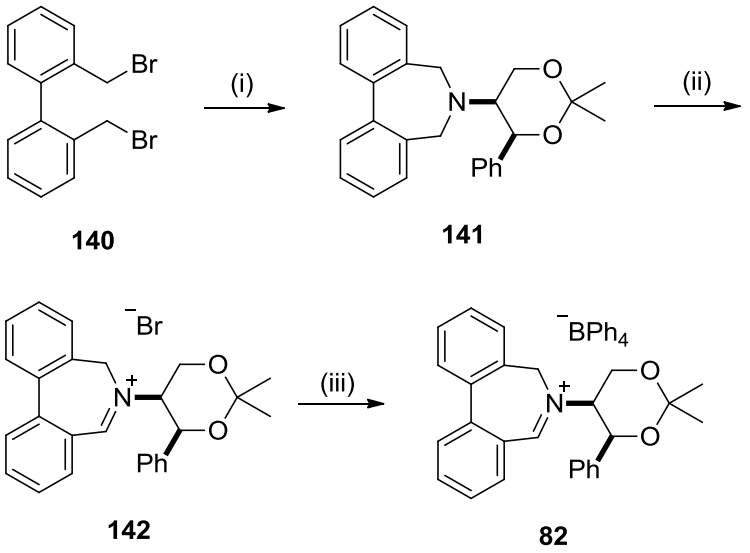
With aminodioxane **138** to hand, the other half of the catalyst, the biphenyl backbone, was required. 2,2'-*bis*(Bromomethyl)biphenyl **140** was formed by refluxing 2,2'-biphenyl-dimethanol **139** in hydrobromic acid according to the literature procedure reported by Lygo (Scheme 35).[54]



139 **140**

Scheme 35. *Reagents and conditions*: (i) 2,2'-biphenyldimethanol (1 eq.), HBr (48% wt. in H_2O), reflux, 2 h

2,2'-*Bis*(bromomethyl)biphenyl **140** was then subsequently condensed with aminodioxane **138** under basic conditions (potassium carbonate) in refluxing acetonitrile for 24 hours, with the reaction progress monitored by thin layer chromatography. Upon completion, the resulting amine **141** could be used directly in the next step without further need for purification. The addition of *N*-bromosuccinimide to a solution of amine **141** yielded iminium salt **142** with a bromide counter ion, which was then exchanged for a tetraphenylborate anion by the addition of sodium tetraphenylborate dissolved in a minimum amount of acetonitrile. Catalyst **82** could be isolated by filtration, and its purity could be further increased by recrystallization from hot ethanol (Scheme 36).[53]

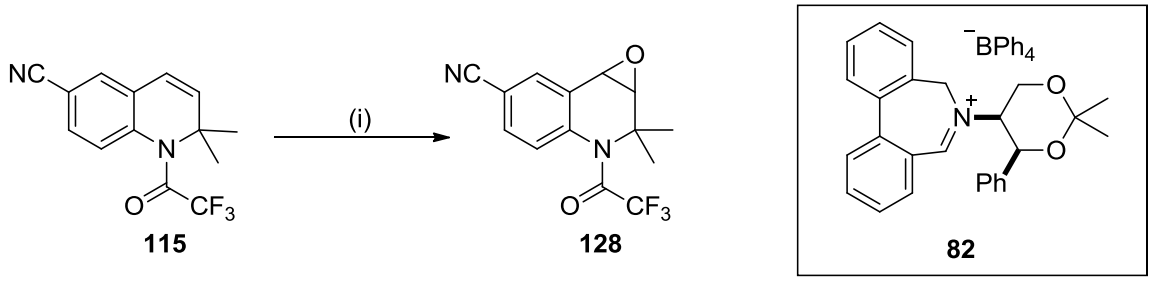


Scheme 36. *Reagents and conditions*: (i) 2,2'-*Bis*(bromomethyl)biphenyl (1 eq.), aminodioxane **138** (1 eq.), K_2CO_3 (2 eq.), CH_3CN, reflux, 24 h (ii) **141** (1 eq.), NBS (1.1 eq.), EtOH, r.t., 1 h; then (iii) $NaBPh_4$ (1.2 eq.) in minimum CH_3CN, r.t., 5 min

With both iminium-salts **41** and **82** to hand, we could now test a range of nitrogen protected dihydroquinoline substrates **115-126** under both aqueous and non-aqueous conditions.

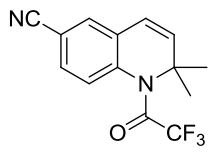
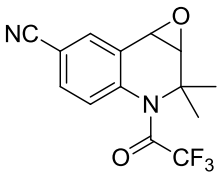
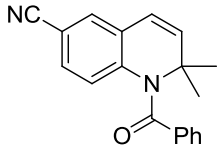
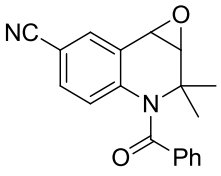
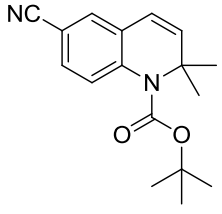
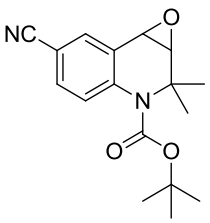
2.7.5 Asymmetric Epoxidation of *N*-Protected Dihydroquinoline Substrates 115-126: Comparing Aqueous and Non-aqueous conditions

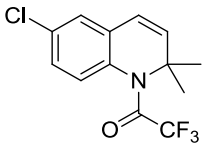
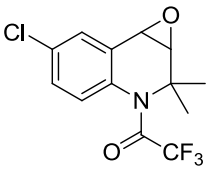
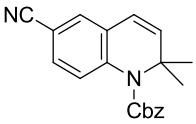
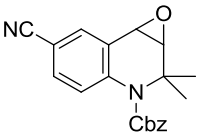
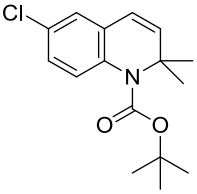
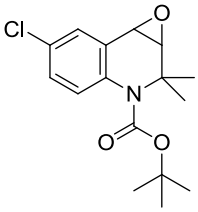
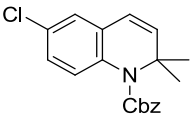
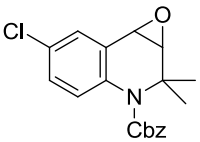
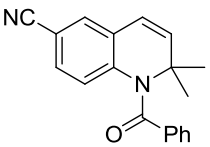
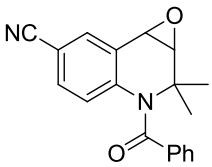
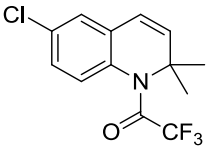
After the initial success of the non-aqueous epoxidation conditions, we next looked at employing catalyst **82** and utilizing aqueous conditions for the asymmetric epoxidation of dihydroquinoline **115**. Page has previously shown that both catalysts **41** and **82** can be used under the aqueous conditions reported by Yang (acetonitrile:water in a 10:1 ratio).[55] The combination of catalyst **82** with aqueous conditions allowed full conversion of alkene **115** to its corresponding epoxide **128** in under 2 hours (in comparison to the non-aqueous conditions; 5 days for 37% conversion), yet the enantioselectivity was only moderate at 37% ee (Scheme 37).



Scheme 37. *Reagents and conditions*: (i) Dihydroquinoline (1 eq.), Oxone (2 eq.), $NaHCO_3$ (5 eq.), catalyst **82** (5 mol%), CH_3CN:H_2O (10:1), 0 °C, 2 h.

Encouraged by this result, we submitted the protected dihydroquinolines **115-126** to non-aqueous and aqueous conditions with catalysts **41** and **82**; the results are reported below (Table 13). Enantioselectivities range from low to good, depending upon the epoxidation conditions, protecting group, and catalyst used.

Substrate	Product no.	Epox. cond.	Time (h)	Conv. (%)	Yield (%)	ee (%)	Rotation of epoxide
 **115**	 **128**	(a)	24	97	76	37	(–)
 **120**	 **130**	(a)	24	89	68	66	(–)
 **121**		(a)	2	100	90	12	(–)

	131						
 **117**	 **129**	(a)	24	100	87	22	(–)
 **122**	 **132**	(a)	48	-	0	-	n/a
 **126**	 **133**	(a)	0.5	100	0	<5%	n/a
 **127**	 **134**	(a)	24	-	0	-	n/a
 **120**	 **130**	(b)	120	<5	0	-	n/a
 **117**		(b)	120	46	13	62	(–)

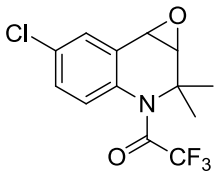
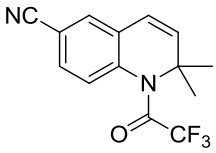
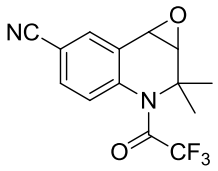
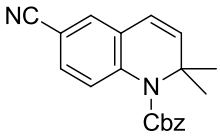
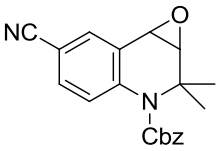
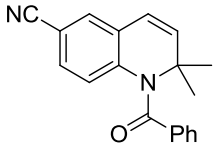
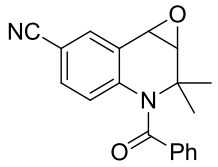
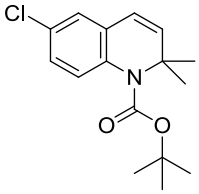
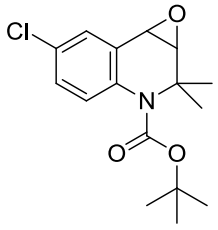
	 **129**						
 **115**	 **128**	(b)	120	37	10	73	(–)
 **122**	 **132**	(b)	120	-	0	-	n/a
 **120**	 **130**	(c)	120	-	0	-	n/a
 **126**	 **133**	(c)	18	-	0	-	n/a

Table 13. *Reagents and conditions*: System (a) = Catalyst **82**; 5 mol%, Oxidant; Oxone (2 eq.), $NaHCO_3$ (5 eq.), Solvent system; Acetonitrile:Water (10:1), Temperature; 0 °C (Yang's conditions).[55] System (b) = Catalyst **41**; 10 mol%, Oxidant; TPPP (2 eq.), Solvent

system; Dichloromethane, Temperature; 0 °C. System (c) = Catalyst **82**; 10 mol%, Oxidant; TPPP (2 eq.), Solvent system; Dichloromethane, Temperature; 0 °C.

The results presented in Table 13 show a range in enantioselectivity and conversion. Focusing on those reactions conducted under aqueous conditions, where each reaction proceeds to full completion, we observe the following effects.

Utilizing biphenyl-derived iminium salt **82** in each of the aqueous reactions the enantioselectivity dramatically varied depending on the protecting group attached to the nitrogen atom. When the protecting group is BOC, the enantioselectivity obtained was low (12% ee). When this group was replaced with a benzoyl protecting group, we observed a dramatic increase in enantioselectivity; for example, the enantioenriched epoxide product **130** of substrate **120** was achieved in 66% ee under the aqueous conditions.

Investigating the effect of changing the solvent system to a non-aqueous system with a different complementary catalyst, in this case utilizing dichloromethane with dihydroisoquinolinium iminium salt **41**, we observed some of the best enantioselectivities, at the cost of sacrificing conversion towards the product. The most successful substrates tested were those that contain a trifluoroacetyl protecting group; for example the non-aqueous asymmetric epoxidation of **115** (cyano) and **117** (chloro) afforded higher enantioselectivities for the epoxide products (73 and 62% ee respectively), but both were obtained at a low conversion (<50%). When the protecting group was changed from a trifluoroacetyl group to a carbobenzoxy or a benzoyl protecting group, the conversion was extremely poor under the non-aqueous conditions, even after 5 days. In an attempt to increase the conversion in these non-aqueous epoxidation reactions, some reactions were trialled utilizing non-aqueous conditions and the more reactive iminium salt **82** (System C, Table 13). However, we were disappointed to see that in both cases tested, the system afforded either just starting material in the case of substrate **120** (after 5 days), and decomposition products from substrate **126** (^{1}H NMR analysis of the crude reaction mixture showed no sign of epoxide nor alkene after 18 hours).

As shown in table 13, the non-aqueous epoxidations only proceeded when dichloromethane was the chosen solvent. When testing this reaction with a number of

substrates using chloroform or acetonitrile, no sign of epoxidation was recorded, with only starting material recovered.

We have shown that the organocatalytic asymmetric epoxidation reaction can be applied to these *N*-protected dihydroquinoline substrates under both aqueous and non-aqueous conditions. The use of two different iminium salt catalysts was trialled, and in both cases, the chiral epoxide products from these asymmetric epoxidation reactions were afforded in moderate to good enantioselectivities. There has only been one example in the literature to date, for this asymmetric epoxidation reaction of dihydroquinoline substrates,[49] and the results we report here show that this unusual methodology may have future applications in inducing chirality at the C3 and C4 positions of the quinoline structure, and thus, a useful tool in the total synthesis of natural products.

2.8 Overall Conclusions and Future Work

The results accumulated within this part of the project have shown the first successful examples of the asymmetric epoxidation reaction on nitrogen-protected dihydroquinoline substrates using iminium salt catalysis, providing moderate to good enantioselectivities (highest being 73% ee).

These results are encouraging, and have shown the clear potential for this methodology to be utilized in the total synthesis of tetrahydroquinoline natural products such as helquinoline **1**[1] and virantmycin **2**[2].

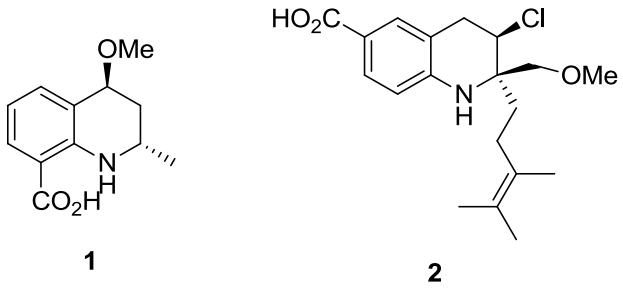


Figure 12. Future applications: tetrahydroquinoline-derived natural products

2.9 References

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CHAPTER THREE: EXPERIMENTAL

3.0 Experimental

3.1 General experimental details

Infrared spectra were acquired using a Perkin Elmer System 2000 FT-IR spectrophotometer. Solid samples were run as nujol mulls or as thin films of their solution in DCM on sodium chloride plates. Liquid samples were run neat.

^{1}H and ^{13}C NMR spectra were measured respectively at 400.13 and 100.62 MHz using Varian Unity Plus (400 MHz) spectrometers, at 300.05 and 75.45 MHz using a Varian Gemini 200 (300 MHz) instrument, at 400.13 and 100.03 MHz using a 400 MHz Bruker Avance III 2 channel nanobay NMR spectrometer, or at 500.21 and 125.05 MHz using a Bruker Avance III 500 MHz NMR spectrometer. The solvent used for NMR spectroscopy was deuteriated chloroform unless stated otherwise, using tetramethylsilane as the internal reference. Chemical shifts are given in parts per million (ppm) and *J* values are given in Hertz (Hz).

High resolution mass spectra were obtained from the EPSRC Mass Spectrometry Service at the University of Swansea. Melting points were recorded using a Büchi B-545 melting point instrument and are reported uncorrected. Optical rotation values were measured with a Bellingham and Stanley ADP-440+ instrument, operating at λ=589 nm, corresponding to the sodium D line at room temperature. The solvents used for these measurements were of spectrophotometric grade. The solutions for these measurements were prepared in volumetric flasks for maximum accuracy of the volume of solvent used.

Enantiomeric excesses were determined by chiral high performance liquid chromatography, (chiral HPLC). HPLC samples were prepared by silica gel-based chromatography or using silica gel preparative TLC plates. Data was recorded using a Hitachi Elite LaChrom instrument fitted with a L2400 UV detector (256 nm unless stated otherwise), L2300 column oven, L2200 autosampler, L2130 pump, a chiracel OD-H 5µm particle size column. All HPLC samples were run under hexane – isopropanol conditions with varying methods.

Except where noted, all chemicals were used as received from Sigma Aldrich. Organic solvents were dried prior to use: diethyl ether and tetrahydrofuran were dried over sodium benzophenone ketyl and distilled; toluene was dried over sodium wire and distilled; petroleum ether 40/60 was distilled over calcium hydride.

Diethyl acetal reaction products were purified under vacuum distillation of the crude reaction mixture; chromenes, chromene epoxides, dihydroquinolines, *N*-protected dihydroquinolines and *N*-protected dihydroquinoline epoxides were eluted using flash column chromatography with various eluents.

3.2 Numbering systems

The NMR spectroscopic measurements have been assigned in accordance with the numbering system shown in Figure 1. The systems use standard nomenclature. Aromatic systems are numbered according to standard protocol. Aromatic carbon atoms bearing a substituent are indicated *C* quat., arom.. All aromatic carbon atoms which are attached to a hydrogen atom are called *C* arom in ^{13}C spectra, or C*H* arom. in ^{1}H spectra. The dihydroisoquinolinium carbon atoms are termed *isoq*. except carbon atoms C3 and C4, which are termed CH_2N *isoq*-3 and Ar-CH_2 *isoq*-4 in the assignment. The biphenyl system is numbered (Figure 1) with carbon atoms termed as *biphenyl*. Chromene and dihydroquinoline compounds are labelled (Figure 1) in accordance with standard protocol.

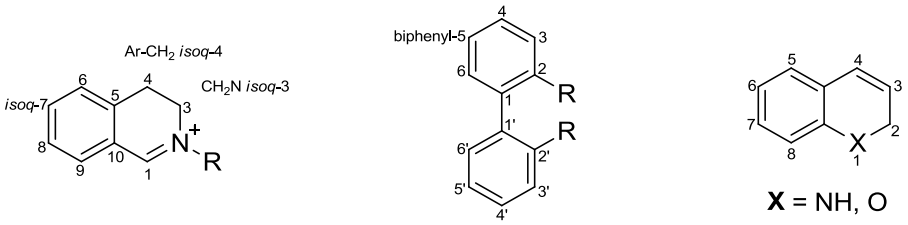
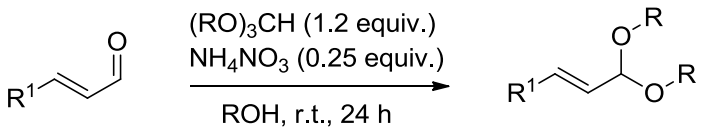


Figure 1. Numbering systems employed in the experimental procedures.

3.3 Individual experiments

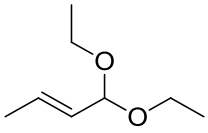
3.3.1 Kinetic resolution section

General Procedure for Acetal Formation[1]



The aldehyde was dissolved in anhydrous alcohol (20 mL/gram of aldehyde). Solid ammonium nitrate (0.25 equiv.) and the corresponding trialkylorthoformate (1.2 equiv.) were added directly to the solution. The solution was allowed to stir under a nitrogen atmosphere at room temperature for 24 h, and quenched with saturated aqueous sodium hydrogen carbonate (20 mL/gram of aldehyde). The acetal product was extracted three times using dichloromethane (10 mL/gram of aldehyde), the combined organic extracts were dried over magnesium sulfate, and the organic solvents removed under reduced pressure. The crude acetal products were purified using vacuum distillation (35 – 45 °C, 2 mbar) to afford pure colourless products.

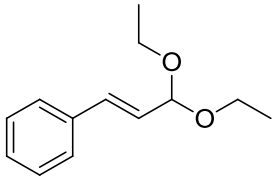
1,1-Diethyoxybut-2-ene (42): [1,2,3]



1,1-Diethyoxybut-2-ene was prepared using the general procedure for acetal formation from crotonaldehyde (10 g, 143 mmol), yielding the desired compound as a colourless liquid (10.6 g, 51%) after purification using vacuum distillation (2 mbar, 35-38 °C). ν_{max} (film) / cm^{-1}: 2976, 2880, 1677, 1446, 1371, 1125. ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.17 (6H, t, *J* = 7 Hz, 2x $OCH_2C\underline{H}_3$), 1.65 (3H, dd, *J* = 7, 2 Hz, $C\underline{H}_3$), 3.38 – 3.45 (2H, m, $OC\underline{H}_2CH_3$), 3.50 – 3.61 (2H, m, $OC\underline{H}_2CH_3$), 4.77 (1H, d, *J* = 6 Hz), 5.48 (1H, ddq, *J* = 16,

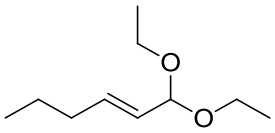
6, 2 Hz), 5.78 (1H, dqd, *J* = 16, 7, 1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 14.9, 17.2, 60.7, 101.7, 128.9, 129.5.

(3,3-Diethoxyprop-1-enyl)benzene (43): [4,5]



(3,3-diethoxyprop-1-enyl)benzene was prepared using the general procedure for acetal formation from *trans*-cinnamaldehyde (12 g, 91.0 mmol), yielding the desired compound as a colourless liquid (15.6 g, 83%) after purification using vacuum distillation (2 mbar, 37-40 °C). ν_{max} (film) / cm^{-1}: 2975, 2877, 1949, 1655, 1449. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.25 (6H, t, *J* = 7 Hz, 2x $OCH_2C\underline{H}_3$), 3.40 – 3.83 (4H, m, 2x $OC\underline{H}_2CH_3$), 5.06 (1H, dd, *J* = 5, 1 Hz), 6.21 (1H, dd, *J* =16, 5 Hz), 6.71 (1H, d, *J* = 16 Hz), 7.08 – 7.47 (5H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 15.1, 60.9, 101.5, 126.8, 126.8, 128.0, 128.6, 132.9, 136.3.

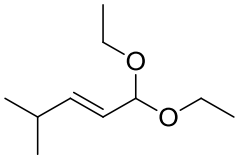
1,1-Diethoxyhex-2-ene (44): [6]



1,1-Diethoxyhex-2-ene was prepared using the general procedure for acetal formation from hex-2-enal (3 g, 30.6 mmol), yielding the desired compound as a colourless liquid (2.1 g, 40%) after purification using vacuum distillation (2 mbar, 35-37 °C). ν_{max} (film) / cm^{-1}: 3105, 2799, 1587, 1491, 1301. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.79 (3H, t, *J* = 7 Hz, propyl-$C\underline{H}_3$), 1.09 (6H, t, *J* = 7 Hz, 2x <u>ethyl</u>-$C\underline{H}_3$), 1.24 – 1.37 (2H, m, propyl-$C\underline{H}_2$), 1.93 (2H, dd, *J* = 8, 15 Hz, <u>propyl</u>-$C\underline{H}_2$), 3.31 – 3.51 (4H, m, 2x <u>ethyl</u>-$C\underline{H}_2CH_3$), 4.71 (1H, d, *J*

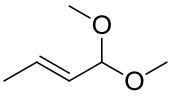
= 6 Hz), 5.37 (1H, dd, *J* = 6, 16 Hz), 5.68 (1H, dt, *J* = 7, 16 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.3, 14.9, 21.7, 33.9, 60.6, 101.7, 127.5, 134.6

1,1-Diethoxy-4-methylpent-2-ene (45): [7]



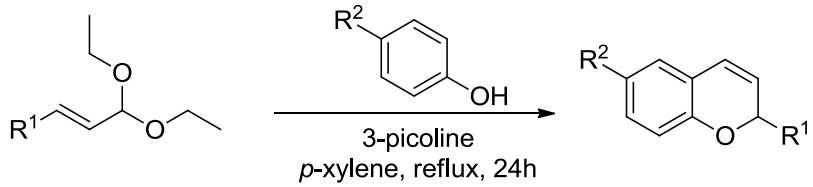
1,1-Diethoxy-4-methylpent-2-ene was prepared from 4-methyl-2-pentenal (2.0 g, 20.4 mmol), using the general procedure for acetal formation, yielding the desired compound as a pale yellow liquid (2.75 g, 78%) after purification using vacuum distillation (2 mbar, 42-45 °C). ν_{max} (film) / cm^{-1}: 3092, 2887, 1560, 1505, 1275, 1150. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.88 (6H, d, *J* = 7 Hz, 2x *iso*-propyl-C$\underline{H}_3$), 1.08 (6H, t, *J* = 6 Hz, 2x ethyl-$CH_2C\underline{H}_3$), 2.10 – 2.28 (1H, m, *iso*-propyl-C$\underline{H}(CH_3)_2$), 3.23 – 3.41 (2H, m, 2x ethyl-C$\underline{H}_2CH_3$), 3.40 – 3.55 (2H, m, 2x ethyl-C$\underline{H}_2CH_3$), 4.69 (1H, d, *J* = 6 Hz), 5.30 (1H, dd, *J* = 16, 6 Hz), 5.65 (1H, dd, *J* = 16, 6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 14.5, 21.4, 30.0, 60.0, 101.3, 124.3, 140.8.

1,1-Dimethyoxybut-2-ene (46): [1]



1,1-Dimethyoxybut-2-ene was prepared using the general procedure for acetal formation from crotonaldehyde (2.54 g, 36.2 mmol), ammonium nitrate (0.72 g, 9.1 mmol) and trimethylorthoformate (4.61 g, 43.5 mmol), yielding the desired compound as a light yellow volatile liquid (1.3 g, 31%) after purification using vacuum distillation (2 mbar, 35-38 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.75 (3H, d, *J* = 6 Hz, C$\underline{H}_3$), 3.30 (6H, s, 2x O$C\underline{H}_3$), 4.72 (1H, d, *J* = 6 Hz), 5.44 (1H, dd, *J* = 16, 6 Hz), 5.83 (1H, dq, *J* = 16, 7 Hz).

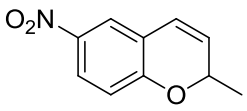
General Procedure for the Formation of Chromenes



R^1 = Me, Pr, ^{i}Pr, Ph
R^2 = CN, NO_2, Cl, CH_3

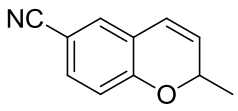
The required phenol (2 equiv.) was dissolved in *p*-xylene (15 mL per gram of phenol), and 3-picoline (0.25 equiv.) and the corresponding acetal (1 equiv.) were added. The reaction mixture was heated under reflux under nitrogen for 24 h. The solvent was removed under reduced pressure. The product was purified using column chromatography using a petroleum ether:toluene mixture as the eluent, yielding chromenes as pure crystals or oils.

6-Nitro-2-methyl-chromene (47): [8]



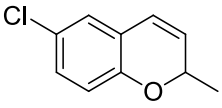
The compound was prepared using the general procedure for chromene formation from 4-nitrophenol (3.19 g, 23.0 mmol) and 1,1-Diethoxybut-2-ene (1.65 g, 11.49 mmol), yielding the compound as a yellow crystalline solid (1.01 g, 46%; mp 67-69 °C, lit.[8] 66-66.5 °C) after purification using column chromatography (Eluent: 1:1, petroleum ether: toluene). ν_{max} (film) / cm^{-1}: 1575, 1506, 1480, 1373, 911. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.49 (3H, d, *J* = 7 Hz, C<u>H</u>$_3$), 5.14 – 5.22 (1H, m, C2-<u>H</u>), 5.80 (1H, dd, *J* = 10, 3 Hz, C3-<u>H</u>), 6.41 (1H, dd, *J* = 10 Hz, 2 Hz, C4-<u>H</u>), 6.81 (1H, d, *J* = 9 Hz, C8-<u>H</u>), 7.87 (1H, d, *J* = 3 Hz, C5-<u>H</u>), 8.02 (1H, dd, *J* = 9, 3 Hz, C7-<u>H</u>). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 22.0, 73.2, 116.4, 121.4, 122.3, 125.5, 128.7, 159.2. HRMS *m/z*: 191.0578 [M^+]; $C_{10}H_9NO_3$ requires 191.0577. HPLC trace (90:10, 30 min, 1 mL/min); 5.7 min (48.76%), 5.97 (51.24%).

6-Cyano-2-methyl-chromene (48): [8]



The compound was prepared using the general procedure for chromene formation from 4-cyanophenol (1.65 g, 13.9 mmol) and 1,1-Diethoxybut-2-ene (1.0 g, 6.93 mmol), yielding the compound as a cream solid (0.90 g, 76%; mp 53-55 °C, lit.[8] 55.5-56 °C) after purification using column chromatography (Eluent: 1:1, petroleum ether: toluene). ν_{max} (film) / cm^{-1}: 2360, 2342, 2225, 1605, 1488, 1373, 1253, 765. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.46 (3H, d, *J* = 7 Hz, C<u>H</u>$_3$), 5.08 – 5.14 (1H, m, C2-<u>H</u>), 5.75 (1H, dd, *J* = 10, 3 Hz, C3-<u>H</u>), 6.33 (1H, dd, *J* = 10, 2 Hz, C4-<u>H</u>), 6.79 (1H, d, *J* = 8 Hz, C8-<u>H</u>), 7.22 (1H, d, *J* = 2 Hz, C5-<u>H</u>), 7.38 (1H, dd, *J* = 8, 2 Hz, C7-<u>H</u>). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 21.9, 72.7, 104.2, 117.1, 119.4, 122.1, 122.3, 128.6, 130.4, 133.6, 157.3. HRMS *m/z*: 171.0678 [M^+]; $C_{11}H_9NO$ requires 171.0679. HPLC trace (90:10, 30 min, 1 mL/min); 5.93 min (49.45%), 6.41 (50.55%).

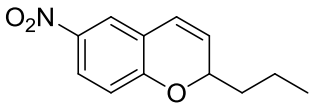
6-Chloro-2-methyl-chromene (49): [8]



The compound was prepared using the general procedure for chromene formation from 4-chlorophenol (2.95 g, 23.04 mmol) and 1,1-diethoxybut-2-ene (1.66 g, 11.52 mmol), yielding the compound as a yellow oil (0.89 g, 43 %) after purification using column chromatography (Eluent: 1:1, petroleum ether: toluene). ν_{max} (film) / cm^{-1}: 3050, 2977, 2932, 1767, 1645, 1481, 1368, 1208. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.44 (3H, d, *J* = 7 Hz, C<u>H</u>$_3$), 4.95-5.03 (1H, m, C2-<u>H</u>), 5.70 (1H, dd, *J* = 10, 3 Hz, C3-<u>H</u>), 6.31 (1H, dd, *J* = 10, 2 Hz, C4-<u>H</u>), 6.71 (1H, d, *J* = 9 Hz, C8-<u>H</u>), 6.94 (1H, d, *J* = 3 Hz, C5-<u>H</u>), 7.05 (1H, dd,

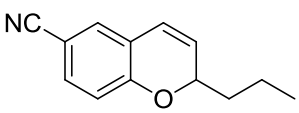
J = 9, 3 Hz, C7-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.4, 71.8, 117.5, 123.0, 123.3, 125.8, 126.2, 128.4, 128.8, 152.2. HRMS *m/z*: 180.0338 [M^+]; $C_{10}H_9ClO$ requires 180.0342. HPLC trace (98:2 hexane:iso-propanol, 0.5 mL/min); inseperable: 10.20 min (100 %).

6-Nitro-2-propyl-chromene (51): [8]



The compound was prepared using the general procedure for chromene formation from 4-nitrophenol (1.0 g, 7.18 mmol) and 1,1-diethoxyhex-2-ene (0.62 g, 3.59 mmol), yielding the compound as a viscous orange oil (0.7 g, 89%) after purification using column chromatography (Eluent: 1:1, petroleum ether: toluene). ν_{max} (film) / cm^{-1}: 2961, 1614, 1580, 1515, 1483, 1342, 1242, 1091, 1002, 747. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.96 (3H, t, *J* = 7 Hz, propyl-CH_3), 1.40-1.85 (4H, m, propyl-CH_2-CH_2), 4.99-5.11 (1H, m, C2-H), 5.79 (1H, dd, *J* = 10, 3 Hz, C3-H), 6.40 (1H, dd, *J* = 10, 3 Hz, C4-H), 6.79 (1H, d, *J* = 9 Hz, C8-H), 7.84 (1H, d, *J* = 3 Hz, C5-H), 8.00 (1H, dd, *J* = 9, 3 Hz, C7-H). ^{13}C NMR (100 MHz, $CDCl_3$): 13.7, 17.7, 37.9, 76.5, 116.1, 121.5, 122.1, 123.3, 125.3, 127.6, 141.6, 159.3. HRMS *m/z*: 220.0962 [M + H]+; [$C_{12}H_{13}NO_3$+H]+ requires 220.0968. HPLC trace (90:10, 30 min, 1 mL/min); 4.89 min (49.49%), 5.18 min (50.51%).

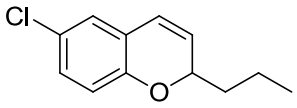
6-Cyano-2-propyl-chromene (52):



The compound was prepared using the general procedure for chromene formation from 4-cyanophenol (1.73 g, 14.5 mmol) and 1,1-Diethoxyhex-2-ene (1.25 g, 7.25 mmol), yielding the compound as a yellow oil (1.40 g, 97%) after purification using column

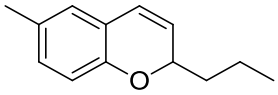
chromatography (Eluent: 1:1, petroleum ether: toluene). ν_{max} (film) / cm^{-1}: 2960, 2874, 2225, 1605, 1489, 1381, 1253, 1130, 1005. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.94 (3H, t, *J* = 7 Hz, propyl-C<u>H</u>$_3$), 1.40-1.84 (4H, m, propyl-C<u>H</u>$_2$C<u>H</u>$_2$), 4.91-5.04 (1H, m, C2-<u>H</u>), 5.74 (1H, dd, *J* = 10, 3 Hz, C3-<u>H</u>), 6.33 (1H, dd, *J* = 10, 2 Hz, C4-<u>H</u>), 6.77 (1H, d, *J* = 8 Hz, C8-<u>H</u>), 7.19 (1H, d, *J* = 2 Hz, C5-<u>H</u>), 7.35 (1H, dd, *J* = 8, 2 Hz, C7-<u>H</u>). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.7, 17.7, 37.8, 76.0, 103.9, 116.8, 119.2, 122.2, 122.4, 127.5, 130.1, 133.4, 157.4. HRMS *m/z*: 200.1065 [M + H]+; [$C_{13}H_{13}NO$ + H]+ requires 200.1070. HPLC trace (90:10, 30 min, 1 mL/min); 5.11 min (50.47%), 5.47 min (49.53%).

6-Chloro-2-propyl-chromene (53):



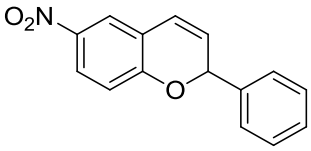
The compound was prepared using the general procedure for chromene formation from 4-chlorophenol (1.50 g, 11.7 mmol) and 1,1-Diethoxyhex-2-ene (1.0 g, 5.85 mmol), yielding the compound as a yellow oil (0.9 g, 74%) after purification using column chromatography (Eluent: 1:1, petroleum ether: toluene). ν_{max} (film) / cm^{-1}: 2960, 2873, 1481, 1378, 1235, 1010, 878. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.95 (3H, t, *J* = 7 Hz, propyl-C<u>H</u>$_3$), 1.42-1.82 (4H, m, propyl-C<u>H</u>$_2$C<u>H</u>$_2$), 4.80-4.89 (1H, m, C2-<u>H</u>), 5.72 (1H, dd, *J* = 10, 3 Hz, C3-<u>H</u>), 6.32 (1H, dd, *J* = 10, 2 Hz, C4-<u>H</u>), 6.70 (1H, d, *J* = 9 Hz, C8-<u>H</u>), 6.93 (1H, d, *J* = 3 Hz, C5-<u>H</u>), 7.03 (1H, dd, *J* = 9, 3 Hz, C7-<u>H</u>). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.8, 17.9, 37.3, 75.1, 117.2, 123.0, 123.3, 125.5, 126.0, 127.3, 128.6, 152.1. HRMS *m/z*: 209.0722 [M + H]+; [$C_{12}H_{13}ClO$ + H]+ requires 209.0728. HPLC trace (99:1 hexane:*iso*-propanol, 30 min, 0.5 mL/min); 7.61 min (56.49%), 7.90 min (43.51%).

6-Methyl-2-propyl-chromene (54):



The compound was prepared via the general procedure for chromene formation from *para*-cresol (4.6 g, 42.6 mmol) and 1,1-Diethoxyhex-2-ene (3.66 g, 21.3 mmol), yielding the compound as a yellow viscous oil (0.2 g, 5%) after purification via column chromatography (Eluent: 3:2, petroleum ether:toluene). ν_{max} (film) / cm^{-1}: 3018, 2959, 2932, 2872, 1636, 1493, 1225, 1151, 1016, 813. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.86 (3H, t, *J* = 7 Hz, propyl-C$\underline{H}_3$), 1.34-1.76 (4H, m, propyl-C$\underline{H}_2$-C$\underline{H}_2$), 2.15 (3H, s, Ar-C$\underline{H}_3$), 4.69-4.75 (1H, m, C2-$\underline{H}$), 5.57 (1H, dd, *J* = 3, 10 Hz, C3-$\underline{H}$), 6.26 (1H, dd, *J* = 1, 10 Hz, C4-$\underline{H}$), 6.59 (1H, d, *J* = 8 Hz, C8-$\underline{H}$), 6.68 (1H, d, *J* = 2 Hz, C5-$\underline{H}$), 6.81 (1H, dd, *J* = 2, 8 Hz, C7-$\underline{H}$). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.9, 18.1, 20.4, 37.3, 74.8, 115.7, 121.9, 124.0, 126.2, 127.0, 129.5, 130.1, 151.4. HPLC trace (99.9:0.1, 120 min, 0.25 mL/min); 64.00 min (50.43%), 73.47 min (49.57%).

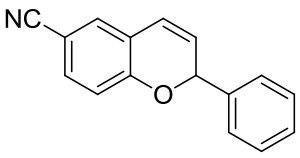
6-Nitro-2-phenyl-chromene (55):



The compound was prepared using the general procedure for chromene formation from 4-nitrophenol (1.0 g, 7.2 mmol) and (3,3-diethoxyprop-1-enyl)benzene (0.73 g, 3.56 mmol), yielding the compound as a cream solid (0.496 g, 55%; mp 104-106 °C) after purification using column chromatography (Eluent: 3:2, petroleum ether:toluene). ν_{max} (film) / cm^{-1}: 3063, 3034, 1647, 1612, 1576, 1480, 1343, 1261, 913. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 5.94 (1H, dd, *J* = 10, 3 Hz, C3-$\underline{H}$), 6.07 (1H, dd, *J* = 3, 2 Hz, C2-$\underline{H}$), 6.59 (1H, dd, *J* = 10, 2 Hz, C4-$\underline{H}$), 6.81 (1H, d, *J* = 9 Hz, C8-$\underline{H}$), 7.35-7.46 (5H, m, Ph-$\underline{H}$), 7.93 (1H, d, *J* = 3 Hz,

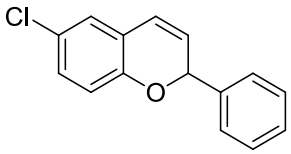
C5-H), 8.01 (1H, dd, *J* = 9, 3 Hz, C7-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 78.5, 116.3, 120.9, 122.3, 122.4, 125.6, 127.2, 129.0, 129.1, 139.5, 141.8, 158.6. HRMS *m/z*: 254.0799 [M + H]+; $[C_{15}H_{11}NO_3 + H]$+ requires 254.0812. HPLC trace (95:5, 80 min, 0.5 mL/min); 23.55 min (49.20%), 24.66 (50.80%).

6-Cyano-2-phenyl-chromene (56): [9]



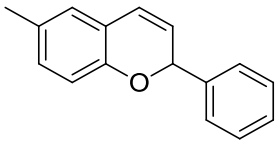
The compound was prepared using the general procedure for chromene formation from 4-cyanophenol (1.0 g, 8.4 mmol) and (3,3-diethoxyprop-1-enyl)benzene (0.86 g, 4.16 mmol), yielding the compound as a white crystalline powder (0.43 g, 44%, mp 123-125 °C) after purification using column chromatography (Eluent: 1:1, petroleum ether:toluene). ν_{max} (film) / cm^{-1}: 3033, 2222, 1677, 1602, 1570, 1489, 1374, 1251, 1229, 1128, 893, 825. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 5.90 (1H, dd, *J* = 10, 3 Hz, C3-H), 6.02 (1H, dd, *J* = 3, 2 Hz, C2-H), 6.52 (1H, dd, *J* = 10, 2 Hz, C4-H), 6.80 (1H, d, *J* = 8 Hz, C8-H), 7.29 (1H, d, *J* = 2 Hz, C5-H), 7.35-7.45 (6H, m, C7-H & Ph-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 78.0, 104.4, 117.0, 119.1, 121.7, 122.2, 126.3, 127.1, 128.9, 129.0, 130.4, 133.8, 139.7, 156.8. HRMS *m/z*: 251.1180 [M + NH_4]+; $C_{16}H_{11}NO + NH_4$]+ requires 251.1179. HPLC trace (99.5:0.5, 180 min, 0.5 mL/min, 230 nm); 41.34 min (47.94%), 43.47 (52.06%).

6-Chloro-2-phenyl-chromene (57): [8]



The compound was prepared using the general procedure for chromene formation from 4-chlorophenol (1.0 g, 7.62 mmol) and (3,3-diethoxyprop-1-enyl)benzene (0.78 g, 3.81 mmol) yielding the compound as a viscous colourless oil (0.12 g, 13%) after purification using column chromatography (Eluent: 1:1, petroleum ether: toluene). ν_{max} (film) / cm^{-1}: 3032, 1639, 1477, 1424, 1368, 1261, 1231, 1200, 1121, 1034, 814, 755, 697. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 5.88 (1H, dd, *J* = 10, 3 Hz, C3-H), 5.94 (1H, dd, *J* = 3, 2 Hz, C2-H), 6.47 (1H, dd, *J* = 10, 2 Hz, C4-H), 6.72 (1H, d, *J* = 9 Hz, C8-H), 7.02 (1H, d, *J* = 3 Hz, C5-H), 7.08 (1H, dd, *J* = 9, 3 Hz, C7-H), 7.37-7.49 (5H, m, Ph-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 77.4, 117.5, 122.8, 123.3, 126.0, 126.2, 126.3, 127.2, 128.8, 128.9, 129.2, 140.4, 151.8. HRMS *m/z*: 243.0561 [M + H]+; $[C_{15}H_{11}ClO + H]+$ requires 243.0571. HPLC trace (99.9:0.1 hexane:*iso*-propanol, 0.25 mL/min); inseparable: 104.77 min (100 %).

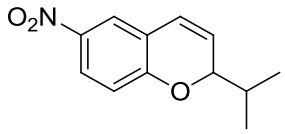
6-Methyl-2-phenyl-chromene (58):



The compound was prepared via the general procedure for chromene formation from *para*-cresol (3 g, 27.8 mmol) and (3,3-diethoxyprop-1-enyl)benzene (2.87 g, 13.9 mmol), yielding the compound as a colourless oil (0.34 g, 11%) after purification via column chromatography (Eluent: 3:2, petroleum ether:toluene). ν_{max} (film) / cm^{-1}: 3086, 3062, 3030, 2920, 2864, 1639, 1489, 1456, 1253, 1219, 1126, 1036, 875, 815, 702. ^{1}H NMR

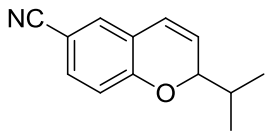
(300 MHz, $CDCl_3$): δ_H 2.40 (3H, s, Ar-C<u>H</u>$_3$), 5.91 (1H, dd, *J* = 10, 3 Hz, C3-<u>H</u>), 6.00-6.02 (1H, m, C2-<u>H</u>), 6.62 (1H, dd, *J* = 10, 2 Hz, C4-<u>H</u>), 6.88 (1H, d, *J* = 8 Hz, C8-<u>H</u>), 6.96 (1H, d, *J* = 2 Hz, C5-<u>H</u>), 7.06 (1H, dd, *J* = 8, 2 Hz, C7-<u>H</u>), 7.45-7.62 (5H, m, Ph-<u>H</u>). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.6, 77.2, 115.9, 121.4, 124.3, 125.2, 127.2, 127.3, 128.5, 128.9, 130.1, 130.5, 141.2, 151.3. HRMS *m/z*: 223.1116 [M + H]+; $[C_{16}H_{14}O + H]$+ requires 223.1117. HPLC trace (90:10, 30 min, 1 mL/min); 4.77 min (48.10%), 4.99 min (51.90%).

6-Nitro-2-*iso*propyl-chromene (59):



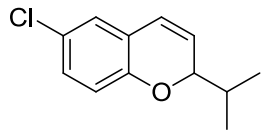
The compound was prepared using the general procedure for chromene formation from 4-nitrophenol (0.80 g, 5.54 mmol) and 1,1-diethoxy-4-methylpent-2-ene (0.475 g, 2.77 mmol), yielding the compound as pale yellow viscous oil (0.2 g, 33%) after purification using column chromatography (Eluent: 3:2, petroleum ether:toluene). ν_{max} (film) / cm^{-1}: 3073, 2965, 2874, 1613, 1579, 1335, 1241, 1089. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.00 (6H, dd, *J* = 8, 7 Hz, (2x) ^{i}Pr-CH_3), 1.95-2.03 (1H, m, ^{i}Pr-C<u>H</u>$(CH_3)_2$), 4.82-4.84 (1H, m, C2-<u>H</u>), 5.77 (1H, dd, *J* = 10, 3 Hz, C3-<u>H</u>), 6.43 (1H, dd, *J* = 10, 2 Hz, C4-<u>H</u>), 6.77 (1H, d, *J* = 9 Hz, C8-<u>H</u>), 7.81 (1H, d, *J* = 3 Hz, C5-<u>H</u>), 7.97 (1H, dd, *J* = 9, 3 Hz, C7-<u>H</u>). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 17.1, 17.6, 34.2, 81.6, 115.9, 121.5, 122.2, 123.1, 125.5, 126.1, 141.5, 160.0. HRMS *m/z*: 237.1229 [M + NH_4]+; $[C_{12}H_{13}NO_3 + NH_4]$+ requires 237.1234. HPLC trace (90:10, 30 min, 1 mL/min); 4.843 min (48.91%), 5.117 min (51.09%).

6-Cyano-2-*iso*propyl-chromene (60):



The compound was prepared using the general procedure for chromene formation from 4-cyanophenol (0.97 g, 8.1 mmol) and 1,1-diethoxy-4-methylpent-2-ene (0.7 g, 4.05 mmol), yielding the compound as a colourless viscous oil (0.25 g, 31%) after purification using column chromatography (Eluent: 3:2, petroleum ether:toluene). ν_{max} (film) / cm^{-1}: 3053, 2965, 2931, 2874, 2225, 1603, 1489, 1379, 1252, 1130. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.97 (6H, dd, *J* = 7, 5 Hz, (2x) ^{i}Pr-CH_3), 1.90-2.01 (1H, m, ^{i}Pr-C<u>H</u>$(CH_3)_2$), 4.74-4.77 (1H, m, C2-<u>H</u>), 5.72 (1H, dd, *J* = 10, 3 Hz, C3-<u>H</u>), 6.35 (1H, dd, *J* = 10, 2 Hz, C4-<u>H</u>), 6.75 (1H, d, *J* = 8 Hz, C8-<u>H</u>), 7.16 (1H, d, *J* = 2 Hz, C5-<u>H</u>), 7.32 (1H, dd, *J* = 8, 2 Hz, C7-<u>H</u>). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 17.1, 17.5, 33.9, 81.0, 103.7, 116.5, 119.3, 122.3, 122.9, 125.9, 130.2, 133.5, 158.0. HRMS *m/z*: 200.1062 [M + H]+; $[C_{13}H_{13}NO + H]+$ requires 200.1070. HPLC trace (90:10, 30 min, 1 mL/min); 5.023 min (49.90%), 5.417 min (50.10%).

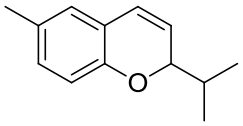
6-Chloro-2-*iso*propyl-chromene (61):



The compound was prepared using the general procedure for chromene formation from 4-chlorophenol (1.59 g, 12.4 mmol) and 1,1-Diethoxy-4-methylpent-2-ene (1.06 g, 6.2 mmol), yielding the compound as a colourless oil (0.206 g, 16%) after purification using column chromatography (Eluent: 3:2, petroleum ether:toluene). ν_{max} (film) / cm^{-1}: 3050, 2963, 2931, 2873, 1637, 1481, 1234, 1203, 1123, 1019, 997, 878, 814, 698. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.00 (6H, dd, *J* = 7, 1 Hz, 2x ^{i}Pr-CH_3), 1.93-2.04 (1H, m, ^{i}Pr-C<u>H</u>$(CH_3)_2$), 4.61-4.65 (1H, m, C2-<u>H</u>), 5.73 (1H, dd, *J* = 10, 3 Hz, C3-<u>H</u>), 6.36 (1H, dd, *J* = 10, 2 Hz,

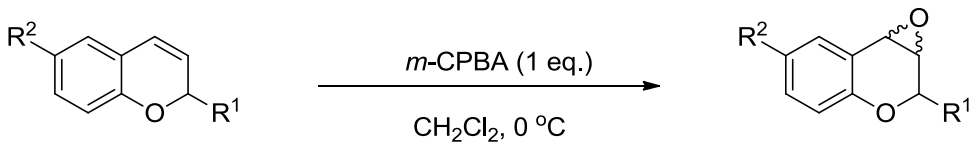
C4-H), 6.70 (1H, d, *J* = 9 Hz, C8-H), 6.92 (1H, d, *J* = 3 Hz, C5-H), 7.03 (1H, dd, *J* = 9, 3 Hz, C7-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 17.5, 17.6, 33.4, 80.2, 116.9, 123.3, 123.6, 125.3, 125.6, 126.0, 128.7, 152.7. HPLC trace (99.9:0.1, 120 min, 0.25 mL/min); 14.80 min (49.74%), 15.87 min (50.26%).

6-Methyl--2-*iso*propyl-chromene (62):



The compound was prepared via the general procedure for chromene formation from *para*-cresol (1.0 g, 9.2 mmol) and 1,1-diethoxy-4-methylpent-2-ene (0.79 g, 4.6 mmol), yielding the compound as a yellow oil (0.37 g, 43%) after purification via column chromatography (Eluent: 3:2, petroleum ether:toluene). ν_{max} (film) / cm^{-1}: 3018, 2961, 2929, 2872, 1636, 1492, 1226, 1152, 999, 814. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.92 (6H, dd, *J* = 7, 6 Hz, 2x ^{i}Pr-CH_3), 1.87-1.95 (1H, m, ^{i}Pr-C<u>H</u>$(CH_3)_2$), 2.16 (3H, s, Ar-C<u>H</u>$_3$), 4.48-4.51 (1H, m, C2-<u>H</u>), 5.61 (1H, dd, *J* = 10, 3 Hz, C3-<u>H</u>), 6.31 (1H, dd, *J* = 10, 2 Hz, C4-<u>H</u>), 6.60 (1H, d, *J* = 8 Hz, C8-<u>H</u>), 6.68 (1H, d, *J* = 2 Hz, C5-<u>H</u>), 6.81 (1H, dd, *J* = 8, 2 Hz, C7-<u>H</u>). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 17.6, 17.7, 20.4, 33.2, 79.9, 115.4, 121.8, 124.4, 124.6, 126.9, 129.5, 129.9, 151.9. HPLC trace (99.9:0.1, 120 min, 0.25 mL/min); 33.46 min (50.27%), 35.47 min (49.73%).

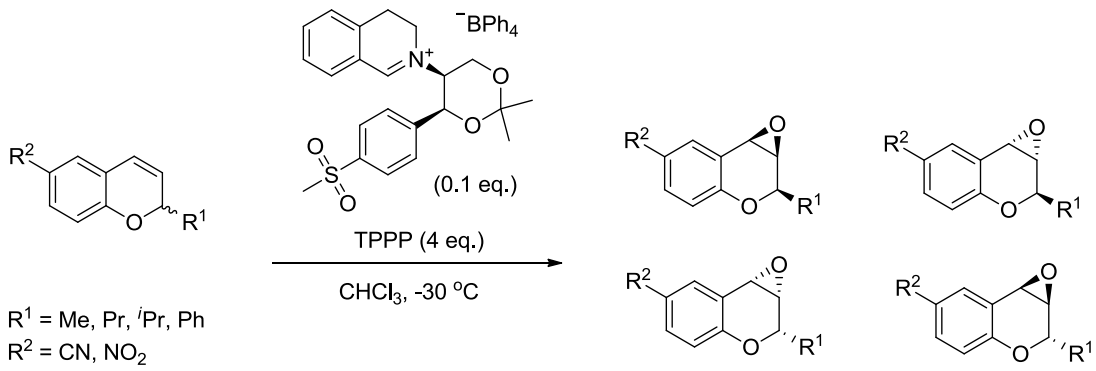
General Procedure for the Formation of Racemic Epoxides (A)



R^1 = Me, Pr, ^{i}Pr, Ph
R^2 = CN, NO_2

The required chromene (1 equiv.) and *meta*-chloroperbenzoic acid (1 equiv.) were dissolved in dichloromethane (20 mL per 100 mg of chromene) at 0 °C, and allowed to stir until reaction completion. Saturated aqueous sodium hydrogen carbonate solution (5 mL per 100 mg of chromene) was added to quench the reaction. The organic layer was extracted against water and brine washes (10 mL per 100 mg of chromene), and combined with further dichloromethane extracts of the aqueous layer. The combined organic extracts were dried over magnesium sulfate, and excess solvent was removed under reduced pressure. The crude product was purified using column chromatography (ethyl acetate: petroleum ether: triethylamine).

General Procedure for the Formation of Chiral Epoxides (B)

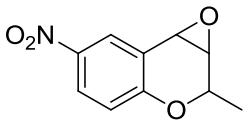


R^1 = Me, Pr, ^{i}Pr, Ph
R^2 = CN, NO_2

Tetraphenylphosphonium monoperoxysulfate (4 equiv.) and iminium salt **41** (10 mol%) were dissolved in chloroform (20 mL per 100 mg of chromene) and cooled to −30 °C. The required chromene (1 equiv.) dissolved in chloroform (2 mL per 100 mg of chromene) was

then added slowly over 10 minutes to the reaction mixture. The reaction progress was monitored by ^{1}H NMR spectroscopy of the crude reaction mixture. At 50% conversion, the reactions were quenched by the addition of diethyl ether (20 mL per 100 mg of chromene). The catalyst was removed by filtration through celite, washed with diethyl ether (10 mL per 100 mg of chromene), and solvents removed under reduced pressure. The crude product was purified using column chromatography (ethyl acetate: petroleum ether: triethylamine) to yield the chiral epoxide as a colourless solid or oil.

6-Nitro-2-methyl-chromene epoxide (63):

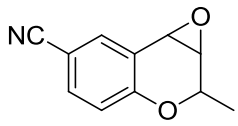


General procedure A: 6-Nitro-2-methyl-chromene **47** (0.205 g, 1.07 mmol) and *meta*-chloroperbenzoic acid (0.184 g, 1.07 mmol) were dissolved in dichloromethane (40 mL) at 0 °C, and left to react for 8 h. The racemic epoxide was isolated as a cream solid (0.20 g, 90%; mp 86-88 °C) after purification using column chromatography (Eluent: 3:1:0.1, petroleum ether:ethyl acetate:triethylamine). ν_{max} (film) / cm^{-1}: 3075, 2984, 2935, 1620, 1591, 1521, 1487, 1341, 1257, 1094, 878, 746. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ratio of *trans:cis*, 1.8:1) 1.36 (3H, d, *J* = 7 Hz, C$\underline{H}_3$, *trans*), 1.61 (3H, d, *J* = 7 Hz, C$\underline{H}_3$, *cis*), 3.66 (1H, dd, *J* = 4, 1 Hz, C3-$\underline{H}$, *trans*), 3.73 (1H, d, *J* = 4 Hz, C3-$\underline{H}$, *cis*), 3.95 (1H, d, *J* = 4 Hz, C4-$\underline{H}$, *trans*), 4.00 (1H, d, *J* = 4 Hz, C4-$\underline{H}$, *cis*), 4.43 (1H, q, *J* = 7 Hz, C2-$\underline{H}$, *cis*), 4.87 (1H, q, *J* = 7 Hz, C2-$\underline{H}$, *trans*), 6.90 (2H, d, *J* = 9 Hz, C8-$\underline{H}$, *cis* & *trans*), 8.14 (2H, dd, *J* = 9, 3 Hz, C7-$\underline{H}$, *cis* & *trans*), 8.28 (1H, d, *J* = 3 Hz, C5-$\underline{H}$, *trans*), 8.31 (1H, d, *J* = 3 Hz, C5-$\underline{H}$, *cis*). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 16.6, 18.3, 48.1, 49.5, 58.6, 58.8, 69.7, 69.9, 117.9, 118.6, 120.3, 120.6, 125.9, 126.0, 126.2, 126.4, 141.5, 141.6, 157.6, 159.4. HRMS *m/z*: 206.0461 $[M - H]^-$; $[C_{10}H_9NO_4 - H]^-$ requires 206.0459. HPLC trace (99.5:0.5 hexane:*iso*-

propanol, 180 min, 0.5 mL/min); 60.31 min (21.22%), 74.09 min (21.79%), 95.06 min (28.69%), 100.87 min (28.29%).

General procedure B: Tetraphenylphosphonium monoperoxysulfate (1.71 g, 3.8 mmol) and iminium salt **41** (0.068 g, 0.095 mmol) were dissolved in chloroform (40 mL) and cooled to −30 °C. 6-nitro-2-methyl-chromene **47** (0.182 g, 0.95 mmol) dissolved in chloroform (4 mL) was then added slowly over 10 minutes to the reaction mixture. The reaction was quenched at 48% conversion, and enantioenriched 6-nitro-2-methyl-chromene epoxide was isolated as a cream solid (0.065 g, 33%) after purification using column chromatography (Eluent: 3:1:0.1, petroleum ether: ethyl acetate: triethylamine). $[\alpha]_D$ = −58.4, (*c* 0.005 g/mL CH_2Cl_2). HPLC trace (99.5:0.5, 180 min, 0.5 mL/min); 58.29 min (0.40%) *cis*, 70.71 min (26.78%) *cis*, 91.36 min (68.02%) *trans*, 97.75 min (4.79%) *trans*.

6-Cyano-2-methyl-chromene epoxide (64): [10]

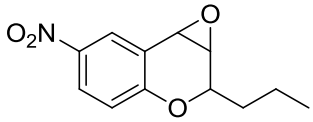


General procedure A: 6-Cyano-2-methyl-chromene **48** (1.10 g, 6.42 mmol) and *meta*-chloroperbenzoic acid (1.10 g, 6.42 mmol) were dissolved in dichloromethane (100 mL) at 0 °C, and left to react for 6 h. The racemic epoxide was isolated as a cream solid (1.02 g, 85%) after purification using column chromatography (Eluent: 3:1:0.1, petroleum ether:ethyl acetate:triethylamine). ν_{max} (film) / cm^{-1}: 2917, 2849, 2227, 1615, 1581, 1495, 1253, 1229, 1159, 873. ^1H NMR (300 MHz, $CDCl_3$): δ_H (ratio of *trans:cis* = 1:1) 1.33 (3H, d, *J* = 7 Hz, C<u>H</u>$_3$, *trans*), 1.58 (3H, d, *J* = 7 Hz, C<u>H</u>$_3$, *cis*), 3.63 (1H, dd, *J* = 4, 1 Hz, C3-<u>H</u>, *trans*), 3.69 (1H, dd, *J* = 4, 1 Hz, C3-<u>H</u>, *cis*), 3.87 (1H, d, *J* = 4 Hz, C4-<u>H</u>, *trans*), 3.92 (1H, d, *J* = 4 Hz, C4-<u>H</u>, *cis*), 4.37 (1H, q, *J* = 6 Hz, C2-<u>H</u>, *cis*), 4.82 (1H, q, *J* = 6 Hz, C2-<u>H</u>,

trans), 6.88 (2H, d, *J* = 9 Hz, C8-H, *cis* & *trans*), 7.52 (2H, dd, *J* = 9, 2 Hz, C7-H, *cis* & *trans*), 7.64 (1H, d, *J* = 2 Hz, C5-H, *trans*), 7.66 (1H, d, *J* = 2 Hz, C5-H, *cis*). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 16.5, 18.4, 48.0, 49.4, 58.8, 59.1, 69.3, 69.5, 104.4, 104.5, 118.4, 118.7, 119.2, 121.1, 121.4, 133.9, 134.1, 134.3, 134.5, 155.7, 157.7. HRMS *m/z*: 187.0628 [M^+]; $C_{11}H_9NO_2$ requires 187.0633. HPLC trace (99.5:0.5, 180 min, 0.5 mL/min); 76.82 min (22.87%), 119.490 min (27.75%), 127.70 min (23.05%), 137.62 min (26.33%).

General procedure B: Tetraphenylphosphonium monoperoxysulfate (0.9 g, 2 mmol) and iminium salt **41** (0.036 g, 0.05 mmol) were dissolved in chloroform (20 mL) and cooled to −30 °C. 6-cyano-2-methyl-chromene **48** (0.085 g, 0.50 mmol) dissolved in chloroform (2 mL) was then added slowly over 10 minutes to the reaction mixture. The reaction was quenched at 52% conversion, and enantioenriched 6-cyano-2-methyl-chromene epoxide was isolated as a cream solid (0.031 g, 33 %, mp = 77-79 °C) after column chromatography (Eluent: 3:1:0.1, petroleum ether: ethyl acetate: triethylamine). $[\alpha]_D$ = -74, (*c* 0.01 g/mL $CHCl_3$). HPLC trace (99.5:0.5, 180 min, 0.5 mL/min); 74.88 min (0.50%) *cis*, 116.04 min (5.14%) *trans*, 125.01 min (28.11%) *cis*, 132.81 min (66.26%) *trans*.

6-Nitro-2-propyl-chromene epoxide (65):

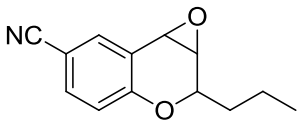


General procedure A: 6-Nitro-2-propyl-chromene **51** (0.310 g, 1.43 mmol) and *meta*-chloroperbenzoic acid (0.245 g, 1.43 mmol) were dissolved in dichloromethane (50 mL) at 0 °C, and left to react for 5 h. The racemic epoxide was isolated as a yellow oil (0.265 g, 79%) after purification using column chromatography (Eluent; 10:1:0.1, petroleum ether: ethyl acetate: triethylamine). ν_{max} (film) / cm^{-1}: 2961, 2874, 1619, 1591, 1516, 1486, 1340,

1244, 1088. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ratio of *trans:cis* = 2:1) 0.96 (3H, t, *J* = 7 Hz, propyl-C<u>H</u>$_3$, *trans*), 1.04 (3H, t, *J* = 7 Hz, propyl-C<u>H</u>$_3$, *cis*), 1.45-2.02 (8H, m, propyl-C<u>H</u>$_2$-C<u>H</u>$_2$, *cis* & *trans*), 3.67 (1H, dd, *J* = 4, 1 Hz, C3-<u>H</u>, *trans*), 3.76 (1H, dd, *J* = 4, 1 Hz, C3-<u>H</u>, *cis*), 3.94 (1H, d, *J* = 4 Hz, C4-<u>H</u>, *trans*), 3.99 (1H, d, *J* = 4 Hz, C4-<u>H</u>, *cis*), 4.26-4.30 (1H, m, C2-<u>H</u>, *cis*), 4.70-4.73 (1H, m, C2-<u>H</u>, *trans*), 6.91 (1H, d, *J* = 9 Hz, C8-<u>H</u>, *trans*), 6.92 (1H, d, *J* = 9 Hz, C8-<u>H</u>, *cis*), 8.14 (1H, dd, *J* = 9, 3 Hz, C7-<u>H</u>, *cis*), 8.15 (1H, dd, *J* = 9, 3 Hz, C7-<u>H</u>, *trans*), 8.28 (1H, d, *J* = 3 Hz, C5-<u>H</u>, *trans*), 8.31 (1H, d, *J* = 3 Hz, C5-<u>H</u>, *cis*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 14.0, 14.1, 18.4, 19.0, 33.3, 35.1, 48.6, 49.4, 58.4, 73.3, 73.6, 118.1, 118.7, 120.7, 121.1, 126.1, 126.2, 126.3, 126.6, 141.6, 141.7, 157.9, 159.6. HRMS *m/z*: 236.0911 [M + H]+; $[C_{12}H_{13}NO_4 + H]$+ requires 236.0918. HPLC trace (99.5:0.5, 180 min, 0.5 mL/min); 41.77 min (13.78%), 51.76 min (13.55%), 59.50 min (39.42%), 65.630 min (33.25%).

General procedure B: Tetraphenylphosphonium monoperoxysulfate (2.31 g, 5.12 mmol) and iminium salt **41** (0.092 g, 0.128 mmol) were dissolved in chloroform (60 mL) and cooled to −30 °C. 6-nitro-2-propyl-chromene **51** (0.28 g, 1.28 mmol) dissolved in chloroform (6 mL) was then added slowly over 10 minutes to the reaction mixture. The reaction was quenched at 50% conversion, and enantioenriched 6-nitro-2-propyl-chromene epoxide was isolated as a yellow oil (0.12 g, 40%) after purification using column chromatography (Eluent: 10:1:0.1, petroleum ether: ethyl acetate: triethylamine). $[\alpha]_D$ = −35, (*c* 0.01 g/mL $CHCl_3$). HPLC trace (99.5:0.5, 180 min, 0.5 mL/min); 40.45 min (0.37%), 49.52 min (17.40%), 57.23 min (72.28%), 61.39 min (9.96%).

6-Cyano-2-propyl-chromene epoxide (66):

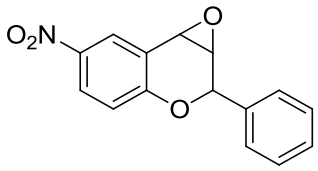


General procedure A: 6-Cyano-2-propyl-chromene **52** (0.150 g, 0.75 mmol) and *meta*-chloroperbenzoic acid (0.130 g, 0.75 mmol) were dissolved in dichloromethane (25 mL) at 0 °C, and left to react for 5 h. The racemic epoxide was isolated as a colourless oil (0.13 g, 81%) after purification using column chromatography (Eluent: 5:1:0.1, petroleum ether: ethyl acetate: triethylamine). ν_{max} (film) / cm^{-1}: 2963, 2925, 2224, 1745, 1610, 1579, 1494, 1247, 1170. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ratio of *trans*:*cis* = 3.5:1) 0.96 (3H, t, *J* = 7 Hz, Propyl-C<u>H</u>$_3$, *trans*), 1.03 (3H, t, *J* = 7 Hz, Propyl-C<u>H</u>$_3$, *cis*), 1.45-1.85 (8H, m, Propyl-C<u>H</u>$_2$C<u>H</u>$_2$, *cis* & *trans*), 3.65 (1H, dd, *J* = 4, 1 Hz, C3-<u>H</u>, *trans*), 3.74 (1H, d, *J* = 4 Hz, C3-<u>H</u>, *cis*), 3.87 (1H, d, *J* = 4 Hz, C4-<u>H</u>, *trans*), 3.91 (1H, d, *J* = 4 Hz, C4-<u>H</u>, *cis*), 4.20-4.23 (1H, m, C2-<u>H</u>, *cis*), 4.66-4.69 (1H, m, C2-<u>H</u>, *trans*), 6.89 (1H, d, *J* = 9 Hz, C8-<u>H</u>, *trans*), 6.90 (1H, d, *J* = 9 Hz, C8-<u>H</u>, *cis*), 7.52-7.55 (2H, m, C7-<u>H</u>, *cis* & *trans*), 7.64 (1H, d, *J* = 2 Hz, C5-<u>H</u>, *trans*), 7.67 (1H, d, *J* = 2 Hz, C5-<u>H</u>, *cis*). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 13.6, 13.8, 18.1, 18.6, 32.9, 34.9, 48.1, 49.0, 58.3, 72.7, 73.0, 104.5, 118.4, 118.7, 119.1, 121.7, 133.9, 134.0, 134.3, 134.6, 156.0. HRMS *m/z*: 238.0840 $[M+Na]^+$; $[C_{13}H_{13}NO_2+Na]^+$ requires 238.0838. HPLC trace (99.5:0.5, 180 min, 0.5 mL/min); 27.14 min (10.86%), 36.32 min (38.48%), 38.24 min (10.67%), 39.82 min (39.99%).

General procedure B: Tetraphenylphosphonium monoperoxysulfate (2.15 g, 4.76 mmol) and iminium salt **41** (0.086 g, 0.12 mmol) were dissolved in chloroform (50 mL) and cooled to −30 °C. 6-cyano-2-propyl-chromene **52** (0.24 g, 1.19 mmol) dissolved in chloroform (5 mL) was then added slowly over 10 minutes to the reaction mixture. The reaction was quenched at 56% conversion, and enantioenriched 6-cyano-2-propyl-

chromene epoxide was isolated as a colourless oil (0.100 g, 39%) after purification using flash column chromatography (Eluent: 5:1:0.1, petroleum ether: ethyl acetate: triethylamine), $[\alpha]_D$ = −22, (0.004 g/mL, CH_2Cl_2). HPLC trace (99.5:0.5, 180 min, 0.5 mL/min); 27.10 min (0.93%), 36.17 min (10.56%), 37.63 min (21.42%), 39.38 min (67.09%).

6-Nitro-2-phenyl chromene epoxide (67):

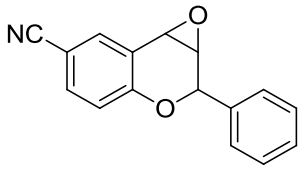


General procedure A: 6-Nitro-2-phenyl-chromene **55** (0.22 g, 0.87 mmol) and *meta*-chloroperbenzoic acid (0.15 g, 0.87 mmol) were dissolved in dichloromethane (40 mL) at 0 °C, and left to react for 8 h. The racemic epoxide was isolated as a colourless solid (0.22 g, 94%; mp = 120-122 °C) after purification using column chromatography (Eluent: 4:1:0.1, petroleum ether: ethyl acetate: triethylamine). ν_{max} (film) / cm^{-1}: 3071, 2928, 1620, 1591, 1515, 1485, 1339, 1236, 1041. ^{1}H NMR (300 MHz, $CDCl_3$): (*only trans observed*) δ_H 3.94 (1H, dd, *J* = 4, 1 Hz, C3-H, *trans*), 4.13 (1H, d, *J* = 4 Hz, C4-H, *trans*), 5.73 (1H, s, C2-H, *trans*), 6.92 (1H, d, *J* = 9 Hz, C8-H, *trans*), 7.27-7.38 (5H, m, Ar-H), 8.17 (1H, dd, *J* = 9, 3 Hz, C7-H, *trans*), 8.36 (1H, d, *J* = 3 Hz, C5-H, *trans*). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 48.8, 58.1, 75.7, 100.4, 118.6, 120.7, 126.2, 126.9, 127.2, 129.4, 129.6, 136.3, 158.1. HRMS *m/z*: 287.1025 [M + NH_4]+; [$C_{15}H_{11}NO_4$ + NH_4]+ requires 287.1026. HPLC trace (90:10, 60 min, 1 mL/min); 26.63 min (48.44%), 43.18 min (51.56%).

General procedure B: Tetraphenylphosphonium monoperoxysulfate (3.36 g, 7.44 mmol) and iminium salt **41** (0.132 g, 0.186 mmol) were dissolved in chloroform (100 mL) and

cooled to −30 °C. 6-nitro-2-phenyl-chromene **55** (0.47 g, 1.86 mmol) dissolved in chloroform (10 mL) was then added slowly over 10 minutes to the reaction mixture. The reaction was quenched at 26% conversion, and enantioenriched 6-nitro-2-phenyl-chromene epoxide was isolated as a colourless solid (0.075 g, 15%) after purification using column chromatography (Eluent: 4:1:0.1, petroleum ether: ethyl acetate: triethylamine), $[\alpha]_D$ = +51, (*c* 0.01 g/mL, CH_2Cl_2); HPLC trace (90:10, 60 min, 1 mL/min); 23.97 min (88.13%), 37.01 min (11.87%).

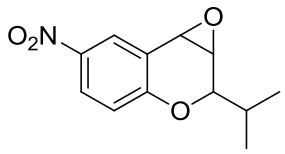
6-Cyano-2-phenyl-chromene Epoxide (68):



General procedure A: 6-Cyano-2-phenyl-chromene **56** (0.165 g, 0.71 mmol) and *meta*-chloroperbenzoic acid (0.12 g, 0.71 mmol) were dissolved in dichloromethane (30 mL) at 0 °C, and left to react for 8 h. The racemic epoxide was isolated as a cream solid (0.160 g, 90%) after purification using column chromatography, (4:1:0.1, petroleum ether: ethyl acetate: triethylamine). ν_{max} (film) / cm^{-1}: 3057, 2903, 2223, 1610, 1577, 1491, 1242, 997. ^1H NMR (500 MHz, $CDCl_3$) δ_H (*only trans observed*) 3.94 (1H, dd, *J* = 4, 1 Hz, C3-H, *trans*), 4.08 (1H, d, *J* = 4 Hz, C4-H, *trans*), 5.73 (1H, s, C2-H, *trans*), 6.93 (1H, d, *J* = 9 Hz, C8-H, *trans*), 7.28-7.39 (5H, m, Ar-H), 7.58 (1H, dd, *J* = 9, 2 Hz, C7-H, *trans*), 7.74 (1H, d, *J* = 2 Hz, C5-H, *trans*). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 48.5, 58.2, 75.2, 104.7, 118.6, 118.9, 121.3, 127.0, 129.1, 129.3, 134.0, 134.8, 136.3, 156.1. HRMS *m*/*z*: 250.0859 $[M + H]^+$; $[C_{16}H_{11}NO_2+H]^+$ requires 250.0863. HPLC trace (90:10, 60 min, 1 mL/min); 29.21 min (48.01%), 38.23 min (51.99%).

General procedure B: Tetraphenylphosphonium monoperoxysulfate (3.61 g, 8.0 mmol) and iminium salt **41** (0.144 g, 0.2 mmol) were dissolved in chloroform (100 mL) and cooled to −30 °C. 6-cyano-2-phenyl-chromene **56** (0.47 g, 2.0 mmol) dissolved in chloroform (10 mL) was then added slowly over 10 minutes to the reaction mixture. The reaction was quenched at 37% conversion, and enantioenriched 6-cyano-2-phenyl-chromene epoxide was isolated as a cream solid (0.12 g, 24%; mp 136-138 °C) after purification using column chromatography (Eluent: 4:1:0.1, petroleum ether: ethyl acetate: triethylamine), $[\alpha]_D$ = +72, (*c* 0.01 g/mL, CH_2Cl_2); HPLC trace (90:10, 60 min, 1 mL/min); 26.23 min (88.99%), 34.17 min (11.01%).

6-Nitro-2-isopropyl-chromene Epoxide (69):

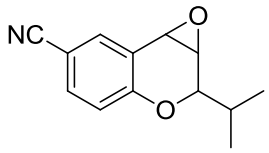


General procedure A: 6-Nitro-2-isopropyl-chromene **59** (0.26 g, 1.2 mmol) and *meta*-chloroperbenzoic acid (0.2 g, 1.2 mmol) were dissolved in dichloromethane (50 mL) at 0 °C, and left to react for 8 h. The racemic epoxide was isolated as a yellow oil (0.14 g, 50%) after purification using column chromatography (Eluent: 5:1:0.1, petroleum ether: ethyl acetate: triethylamine). ν_{max} (film) / cm^{-1}: 2965, 2923, 1620, 1591, 1520, 1486, 1341, 1256, 1089. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ratio of *trans:cis*, 4:1) 0.97 (6H, d, *J* = 9 Hz, ^{i}Pr-C<u>H</u>$_3$, *cis* or *trans*), 1.09 (6H, d, *J* = 9 Hz, ^{i}Pr-C<u>H</u>$_3$, *cis* or *trans*), 1.99-2.09 (1H, m, C<u>H</u>$(CH_3)_2$, *trans*), 2.20-2.28 (1H, m, C<u>H</u>$(CH_3)_2$, *cis*), 3.73 (1H, dd, *J* = 6, 1 Hz, C3-<u>H</u>, *trans*), 3.85 (1H, d, *J* = 6 Hz, C3-<u>H</u>, *cis*), 3.94 (1H, d, *J* = 6 Hz, C4-<u>H</u>, *cis*), 3.96 (1H, d, *J* = 6 Hz, C4-<u>H</u>, *trans*), 4.00 (1H, d, *J* = 8 Hz, C2-<u>H</u>, *cis*), 4.47 (1H, d, *J* = 8 Hz, C2-<u>H</u>, *trans*), 6.91 (1H, d, *J* = 12 Hz, C8-<u>H</u>, *trans*), 6.94 (1H, d, *J* = 12 Hz, C8-<u>H</u>, *cis*), 8.15 (2H, dd, *J* = 12, 4 Hz, C7-<u>H</u>, *cis* & *trans*), 8.28 (1H, d, *J* = 4 Hz, C5-<u>H</u>, *trans*), 8.31 (1H, d, *J* = 4 Hz,

C5-H, *cis*). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.2, 18.3, 18.4, 19.1, 31.5, 31.8, 48.5, 48.7, 56.2, 56.9, 78.1, 78.8, 117.9, 118.2, 120.6, 121.0, 126.1, 126.2, 126.3, 126.7, 141.4, 159.0, 160.2, 169.5. HRMS *m/z*: 236.0915 [M + H]+; $[C_{12}H_{13}NO_4 + H]+$ requires 236.0918. HPLC trace (99.5:0.5, 180 min, 0.5 mL/min); 35.78 min (8.19% *cis*), 52.39 min (9.52% *cis*), 60.19 min (41.27% *trans*), 65.78 min (41.02% *trans*)

General procedure B: Tetraphenylphosphonium monoperoxysulfate (1.17 g, 2.6 mmol) and iminium salt **41** (0.046 g, 0.065 mmol) were dissolved in chloroform (30 mL) and cooled to −30 °C. 6-nitro-2-isopropyl-chromene **59** (0.14 g, 0.65 mmol) dissolved in chloroform (3 mL) was then added slowly over 10 minutes to the reaction mixture. The reaction was quenched at 38% conversion, and enantioenriched 6-nitro-2-isopropyl-chromene epoxide was isolated as a yellow oil (0.035 g, 25%) after purification using column chromatography (Eluent: 5:1:0.1, petroleum ether: ethyl acetate: triethylamine). $[\alpha]_D$ = −63, (*c* 0.004 g/mL CH_2Cl_2). HPLC trace (99.5:0.5, 180 min, 0.5 mL/min); 35.74 min (0.73% *cis*), 56.13 min (7.46% *cis*), 63.05 min (11.07% *trans*), 68.42 min (80.73% *trans*).

6-Cyano-2-isopropyl-chromene epoxide (70):

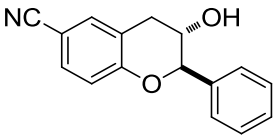


General procedure A: 6-Cyano-2-isopropyl-chromene **60** (0.29 g, 1.44 mmol) and *meta*-chloroperbenzoic acid (0.25 g, 1.44 mmol) were dissolved in dichloromethane (60 mL) at 0 °C, and left to react for 5 h. The racemic epoxide was isolated as a colourless oil (0.17 g, 55%) after purification using column chromatography (Eluent: 5:1:0.1, petroleum ether: ethyl acetate: triethylamine). ν_{max} (film) / cm^{-1}: 2967, 2932, 2877, 2226, 1616, 1582, 1495,

1251, 1134, 1008, 876. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ratio of *trans:cis* = 4:1) 0.97 (6H, d, *J* = 7 Hz, (2x)^{i}Pr-C<u>H</u>$_3$, *cis* or *trans*), 1.08 (6H, d, *J* = 7 Hz, (2x)^{i}Pr-C<u>H</u>$_3$, *cis* or *trans*), 1.97-2.06 (1H, m, ^{i}Pr-C<u>H</u>$(CH_3)_2$, *trans*), 2.20-2.27 (1H, m, ^{i}Pr-C<u>H</u>$(CH_3)_2$, *cis*), 3.72 (1H, dd, *J* = 4, 1 Hz, C3-<u>H</u>, *trans*), 3.83 (1H, d, *J* = 4 Hz, C3-<u>H</u>, *cis*), 3.87 (1H, d, *J* = 4 Hz, C4-<u>H</u>, *cis*), 3.89 (1H, d, *J* = 4 Hz, C4-<u>H</u>, *trans*), 3.95 (1H, d, *J* = 6 Hz, C2-<u>H</u>, *cis*), 4.42 (1H, d, *J* = 6 Hz, C2-<u>H</u>, *trans*), 6.89 (2H, d, *J* = 9 Hz, C8-<u>H</u>, *cis* & *trans*), 7.53 (2H, dd, *J* = 9, 2 Hz, C7-<u>H</u>, *cis* & *trans*), 7.63 (1H, d, *J* = 2 Hz, *trans*), 7.67 (1H, d, *J* = 2 Hz, *cis*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 18.7, 19.3, 31.5, 48.6, 56.6, 77.8, 78.5, 118.5, 118.9, 134.2, 134.8. HRMS *m/z*: 216.1021 [M + H]+; $[C_{13}H_{13}NO_2 + H]+$ requires 216.1022. HPLC trace (99.5:0.5, 180 min, 0.5 mL/min); 42.44 min (10.10%), 64.01 min (39.00%), 80.14 min (9.96%), 84.10 min (40.94%).

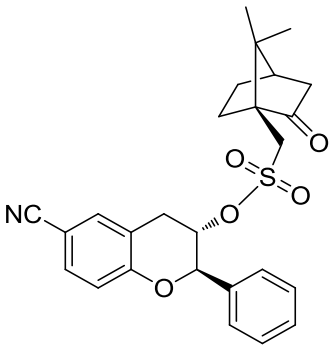
General procedure B: Tetraphenylphosphonium monoperoxysulfate (27.4 g, 60.8 mmol) and iminium salt **41** (1.09 g, 1.52 mmol) were dissolved in chloroform (300 mL) and cooled to −30 °C. 6-cyano-2-isopropyl-chromene **60** (3.0 g, 15.2 mmol) dissolved in chloroform (30 mL) was then added slowly over 10 minutes to the reaction mixture. The reaction was quenched at 36% conversion, and enantioenriched 6-cyano-2-isopropyl-chromene epoxide was isolated as a colourless oil (0.75 g, 23%) after purification using column chromatography (Eluent: 5:1:0.1, petroleum ether: ethyl acetate: triethylamine). $[\alpha]_D$ = −52, (*c* 0.01 g/mL CH_2Cl_2); HPLC trace (99.5:0.5, 180 min, 0.5 mL/min); 43.17 min (0.12%), 71.15 min (17.11%), 81.47 min (5.04%), 89.15 min (77.73%).

Formation of Alcohol (+)-80: [11]



6-Cyano-2-phenyl-chromene epoxide **68** (1 g, 4.02 mmol) was dissolved in anhydrous methanol (50 mL) in a flame-dried round-bottomed flask. The solution was then purged with nitrogen, and a catalytic amount of palladium/carbon was added to the stirring solution, followed by the addition of hydrogen gas (1 atm). The reaction was allowed to stir at room temperature, with the reaction progress monitored by thin layer chromatography. Upon reaction completion, the reaction mixture was filtered through celite, and remaining organic solvents removed under reduced pressure. Alcohol **80** (1 g, 99%) was isolated as a colourless oil after column chromatography (Eluent: 1:1, petrol:ethyl acetate). $[\alpha]_D$ = + 28.0 (0.01 g/mL, CH_2Cl_2). ν_{max} (film) / cm^{-1}: 3424, 2224, 1579, 1492, 1245. ^{1}H NMR (400 MHz, $CDCl_3$): 1.84 (1H, d, *J* = 4 Hz, O<u>H</u>), 2.92 (1H, dd, *J* = 16, 9 Hz, C4-<u>H</u>), 3.09 (1H, dd, *J* = 16, 5 Hz, C4-<u>H</u>), 4.08-4.22 (1H, m, C3-<u>H</u>), 4.91 (1H, d, *J* = 8 Hz, C2-<u>H</u>), 6.99 (1H, d, *J* = 8 Hz, C8-<u>H</u>), 7.35-7.49 (7H, m, Ar-<u>H</u> & C5-<u>H,</u> C7-<u>H</u>). ^{13}C NMR (100 MHz, $CDCl_3$): 32.2, 67.4, 82.4, 104.4, 117.6, 119.1, 121.5, 126.9, 129.0, 129.1, 132.0, 134.4, 137.1, 157.7; *m/z* found $[M + Na]^+$ 274.0842; $[C_{16}H_{13}NO_2+Na]^+$ requires 274.0838.

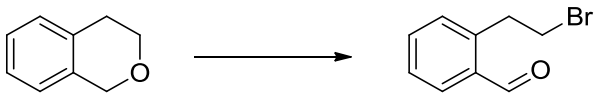
Formation of (10*S*)-camphorsulfonyl ester (+)-81: [12]



To a flame-dried round bottom flask was added alcohol **80** (1.0 g, 3.98 mmol), (10*S*)-(+)-camphorsulfonyl chloride (996 mg, 3.98 mmol) and dry toluene (50 mL). Triethylamine (1.1 mL, 7.96 mmol) was slowly added over 10 minutes and the reaction was left to stir under a nitrogen atmosphere for 24 h. Upon reaction completion, excess organic solvents were removed under reduced pressure. Purification *via* column chromatography (Eluent: 6:1, petroleum ether:ethyl acetate) affords colourless crystalline **81**. Slow recrystallization from dichloromethane/hexane afforded ester **81** (6-cyano-(2*R*)-phenyl-(3*S*)-camphor(16*S*,19*R*)-sulfonylester chromene), as long colourless crystals (0.8 g, 43%, mp = 153 – 155 °C); $[\alpha]_D$ = + 44.0 (*c* 0.02 g/mL, CH_2Cl_2). ν_{max} (film) / cm^{-1}: 2963, 2226, 1743, 1493, 1246, 906, 726. ^{1}H NMR (400 MHz, $CDCl_3$): 0.77 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.35-1.41 (1H, m), 1.52-1.59 (1H, m), 1.88-2.01 (2H, m), 2.08 (1H, t, *J* = 4 Hz), 2.22-2.37 (2H, m), 2.65 (1H, d, *J* = 15 Hz, AB system C15), 3.11 (2H, m), 3.35 (1H, d, *J* = 15 Hz, AB system C15), 5.22-5.25 (1H, m), 5.45 (1H, d, *J* = 5 Hz), 7.05 (1H, d, *J* = 9 Hz, C8-H), 7.33-7.38 (6H, m, Ar-H & C5-H), 7.48 (1H, d, *J* = 9 Hz, C7-H). ^{13}C NMR (100 MHz, $CDCl_3$): 19.6, 19.7, 24.9, 26.8, 28.9, 42.4, 42.7, 47.9, 48.3, 57.9, 75.3, 78.9, 104.7, 117.6, 118.9, 119.5, 126.0, 129.0, 129.1, 132.4, 134.2, 136.7, 157.0, 214.0; *m/z* found $[M + NH_4]^+$: 483.1945; $[C_{26}H_{27}NO_5S+NH_4]^+$ requires 483.1948.

3.3.2 Iminium-salt Catalyst 41 Synthesis and Oxidant Formation

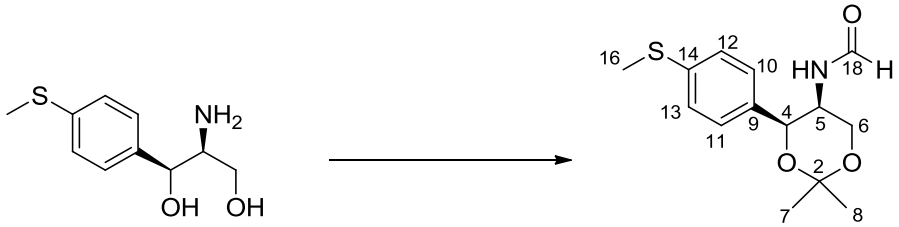
2-(2-Bromoethyl)benzaldehyde (78): [13]



77 **78**

Bromine (4.2 mL, 81.97 mmol) was added to an ice-cooled solution of isochroman **77** (10 g, 74.52 mmol) in cyclohexane (70 mL) slowly down a reflux condenser over 5 minutes with stirring. After the vigorous reaction had calmed, the solution was refluxed until the reaction turned pale yellow and the liberation of hydrogen bromide gas had ceased. The solution was cooled to room temperature, and then solvents were removed *in vacuo.* The remaining oil was dissolved in hydrobromic acid (25 mL, 48% aq.) and heated under reflux for 10 minutes. The solution was then cooled and extracted with diethyl ether (3 x 100 mL). The organic extracts were washed with water (2 x 30 mL), dilute sodium hydrogen carbonate (2 x 30 mL), and dried over $MgSO_4$. Removal of the solvents under reduced pressure afforded crude **78** as a orange-brown oil. Purification of crude **78** by vacuum distillation (2 mbar, 50-54 °C) afforded **78** as a colourless liquid (7.015 g, 47%). ν_{max} (film) / cm^{-1}: 3021, 2969, 2743, 1703, 1599, 1291. δ_H (500 MHz, $CDCl_3$) 3.36-3.64 (4H, m, Ph(C*H*$_2$)$_2$Br), 7.34 (1H, d, *J* = 8 Hz, C*H* arom., *ortho* to bromoethyl group), 7.49 (1H, t, *J* = 8 Hz, *para* to bromoethyl group), 7.56 (1H, t, *J* = 8 Hz, C*H* arom., *para* to formyl group), 7.83 (1H, d, *J* = 8 Hz, C*H* arom., *ortho* to formyl group), 10.15 (1H, s, C*H*O). δ_H (125 MHz, $CDCl_3$) 32.8 (Ph*C*H$_2$), 36.3 (*C*H$_2$Br), 127.7, 132.1, 133.7, 133.9, 134.5, 140.5 (Ph), 192.9 (*C*HO).

***N*-((4*S*,5*S*)-2,2-Dimethyl-4-[4-(methylsulfanyl)-phenyl]-1,3-dioxan-5-yl]formamide (74):** [14]

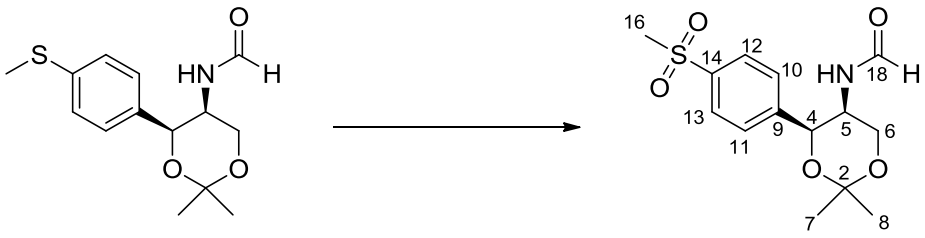


72 **74**

Sodium methoxide in methanol (0.5 mL, 2.3 mmol) was added to a solution of (1*S*,2*S*)-(+)-2-amino-1-(4-(methylthio)phenyl)-1,3-propandiol **72** (5 g, 23.4 mmol) in methanol (50 mL), followed by the addition of methyl formate (1.4 mL, 25.7 mmol). The reaction was stirred at room temperature for 3.5 h, and the solvent removed under reduced pressure to yield *N*-(1*S*,2*S*)-1,3-dihydroxy-1-(4-(methylthio)phenyl)propan-2-yl)formamide as a yellow oil. The resulting formamide was dissolved in acetone (250 mL) followed by the addition of *p*-toluenesulfonic acid (0.5 g, 2.9 mmol) and 2,2-dimethoxypropane (30 mL). The reaction was stirred for 4 h at room temperature and monitored by TLC. The solvents were removed under reduced pressure and the residue was re-dissolved in ethyl acetate (250 mL) followed by washes with water (100 mL), Brine (100 mL) and saturated aqueous sodium hydrogen carbonate solution (2 x 100 mL). The combined organic layers were dried over magnesium sulfate, and the solvents removed under reduced pressure to give **74** as a colourless oil (5.5 g, 84%); $[\alpha]_D$ = + 0.9 (*c* 1.00, $CHCl_3$) [Lit.[14] $[\alpha]_D$ = + 1.3 ° (*c* 1.27, $CHCl_3$)]; ν_{max} (film) / cm^{-1}: 3310, 2991, 2251, 1668, 1496, 1382, 1165; ^{1}H NMR (500 MHz, $CDCl_3$): 1.54 (3H, s, C*H*$_3$, C7), 1.57 (3H, s, C*H*$_3$, C8), 2.44 (3H, s, SC*H*$_3$, C16), 3.83 (1H, d, *J* = 12 Hz, NCHC*H*H-O, H6), 4.24 (1H, dd, *J* = 12 Hz, NCHC*H*H-O, H6'), 4.24-4.30 (1H, m, NC*H*, H5), 5.15 (1H, s, Ar-C*H*, H4), 6.68 (1H, d, *J* = 9 Hz, N*H*), 7.21-7.24 (4H, m, 4 x C*H* arom., H10, H11, H12, H13), 7.91 (1H, s, NC*H*O, H18). ^{13}C NMR (125 MHz, $CDCl_3$): 15.7 (S*C*H$_3$, C16), 18.6 (CH$_3$, C7), 29.7 (*C*H$_3$, C8), 45.3, (*C*HNH, C5), 64.6

(CH_2, C6), 71.4 (*C*H arom., C4), 99.7 (*C* quat., C2), 125.9 (2 x *C*H arom., C10, C11), 126.3 (2 x *C*H arom., C12, C13), 135.1 (*C* quat. arom., C14), 137.7 (*C* quat. arom., C9), 160.7 (*C*HO, C18).

_N_-((4*S*,5*S*)-2,2-Dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-yl]formamide (75): [14]

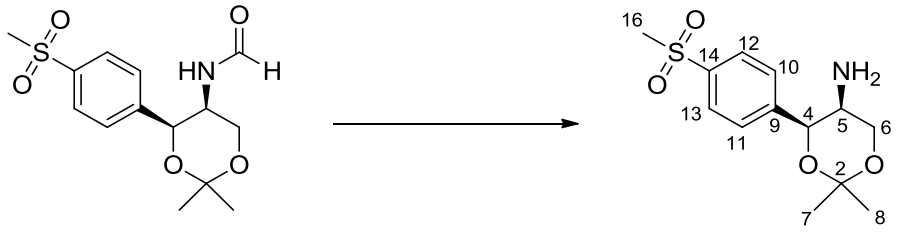


74 **75**

N-((4*S*,5*S*)-2,2-Dimethyl-4-[4-(methylsulfanyl)-phenyl]-1,3-dioxan-5-yl]formamide **74** (4.0 g, 14.2 mmol) was dissolved in dichloromethane (100 mL) and cooled to 0 °C. A solution of *m*-CPBA (7.03 g, 31.0 mmol) in chloroform (20 mL) was added slowly to the reaction over 10 minutes. The mixture was stirred for 2 h, with the progress monitored by TLC. The organic layer was transferred to a separating funnel, and washed with saturated aqueous sodium hydrogen carbonate (2 x 50 mL), and dried over magnesium sulfate. The solvents were then removed under reduced pressure to yield **75** as a colourless oil. Recrystallization from chloroform/diethyl ether yielded **75** as colourless crystals (3.6 g, 81%, mp = 145 – 146 °C, [Lit.[14] mp 146 – 147 °C]); $[\alpha]_D$ = −14.5 ° (*c* 1.11, $CHCl_3$) [Lit. $[\alpha]_D^{20}$ = −11.6 ° (*c* 1.21, $CHCl_3$)]; ν_{max} (film) / cm^{-1}: 2995, 1674, 1515, 1383, 1301, 1239, 1203, 1150, 1087. ^{1}H NMR (500 MHz, $CDCl_3$): 1.54 (3H, s, CH_3, C7), 1.57 (3H, s, CH_3, C8), 3.00 (3H, s, SCH_3, C16), 3.82 (1H, dd, *J* = 12, 2 Hz, NCHC*H*HO, H6), 4.29 (1H, dd, *J* = 12, 2 Hz, NCHC*H*HO, H6'), 4.39 (1H, dd, J = 10, 2 Hz, NC*H*, H5), 5.25 (1H, s, Ar-C*H*, H4), 6.48 (1H, d, *J* = 10 Hz, N*H*), 7.52 (2H, d, *J* = 8 Hz, 2 x C*H* arom., H10, H11), 7.86 (2H, d, *J* = 9 Hz, 2 x C*H* arom., H12, H13), 7.91 (1H, s, NC*H*O, H18). ^{13}C NMR (125

MHz, $CDCl_3$): 18.9 (*C*H_3, C7), 30.0 (*C*H_3, C8), 44.8 (S*C*H_3, C16), 45.5 (N*C*H, C5), 64.9 (*C*H_2, C6), 71.9 (*C*H arom., C4), 100.4 (*C* quat., C2), 127.0 (2 x *C*H, arom., C12, C13), 127.6 (2 x *C*H arom., C11, C10), 140.0 (*C* quat., arom., C14), 144.9 (*C* quat., arom., C9), 161.0 (N*C*HO, C18).

(4*S*,5*S*)-2,2-Dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-amine (76): [14]

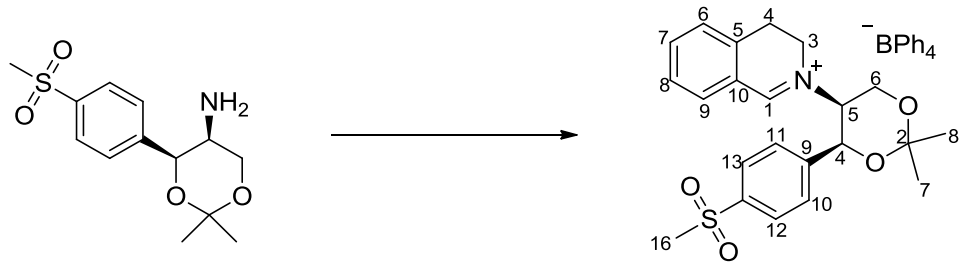


75 **76**

N-((4*S*,5*S*)-2,2-Dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-yl]formamide **75** (1.8 g, 5.8 mmol) was dissolved in aqueous hydrazine monohydrate (80 mL, 85%) and heated to reflux for 2.5 h. The reaction was cooled to room temperature, and extracted with ethyl acetate (3 x 50 mL). The organic layers were washed with water (100 mL), brine (100 mL), dried over magnesium sulfate and the solvents removed under reduced pressure to afford a colourless oil. Recrystallization of crude **76** from ethyl acetate/diethyl ether gave the product as colourless crystals (1.45 g, 88%, mp 120-121 °C [Lit.[14] mp 120-122 °C]); $[\alpha]_D$ = + 65.3 (*c* 1.05, $CHCl_3$), [Lit.[14] $[\alpha]_D$ = +50 (*c* 1.00 $CHCl_3$)]. ν_{max} (film) / cm^{-1}: 3383, 2993, 1602, 1407, 1383, 1151, 1077, 913; ^{1}H NMR (500 MHz, $CDCl_3$): 1.55 (6H, s, 2 x C*H*$_3$, H7, H8), 2.85 (1H, m, C*H*NH_2, H5), 3.06 (3H, s, SC*H*$_3$, H16), 3.83 (1H, d, *J* = 11Hz, NCC*H*$_2$, H6), 4.32 (1H, dd, *J* = 12, 2 Hz, NCC*H*$_2$, H6'), 5.20 (1H, m, ArC*H*, H4), 7.57 (2H, d, *J* = 8 Hz, 2 x C*H* arom., H10, H11), 7.93 (2H, d, *J* = 8 Hz, 2 x C*H* arom., H12, H13); ^{13}C NMR (125 MHz, $CDCl_3$): 18.9 (*C*H_3, C7), 29.9 (*C*H_3, C8), 44.7 (S*C*H_3, C16), 49.5 (N*C*H, C5), 66.6 (*C*H_2, C6), 73.6 (Ar-C*H*, C4), 99.6 (*C* quat., C2), 127.1 (2 x *C*H

arom., C12, C13), 127.5 (2 x C*H* arom., C10, C11), 139.6 (*C* quat., arom., C14), 146.5 (*C* quat., arom., C9).

(+)-*N*-(4*S*,5*S*)-2,2-Dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-yl)-3,4-dihydroisoquinolinium tetraphenylborate (41): [14]

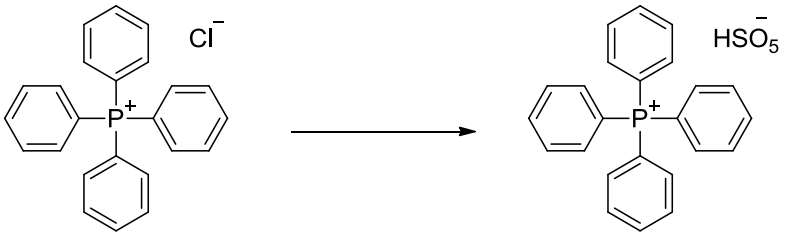


76 **41**

A solution of (4*S*,5*S*)-2,2-dimethyl-4-[4-(methylsulfonyl)-phenyl]-1,3-dioxan-5-amine **76** (0.75 g, 3.0 mmol) in ethanol (7.5 mL) was added dropwise to an ice-cooled flask containing 2-(2-bromoethyl)benzaldehyde **78** (0.69 g, 3.3 mmol). The reaction was allowed to reach ambient temperature then stirred for 24h at room temperature. A solution of sodium tetraphenylborate (1.1 g, 3.3 mmol) in acetonitrile (1 mL) was added in one portion and the reaction was stirred for 5 minutes, followed by the removal of organic solvents under reduced pressure. Ethanol (10 mL) was added to the residue, followed by a few drops of water. The resulting solid was collected by filtration, washed with cold ethanol (10 mL) followed by diethyl ether (10 mL), affording a light yellow powder **41** (1.4 g, 65%, mp 199 – 200 °C; $[\alpha]_D$ = + 195 (*c* 1.06, Acetone) [Lit.[14] $[\alpha]_D$ = +126.7 (*c* 1.20 acetone)]; ν_{max} (film) / cm^{-1}: 1635, 1600, 1574, 1480, 1384, 1315, 1264, 1203, 1151. ^{1}H NMR (500 MHz, Acetone-d_6): 1.69 (3H, s, CH_3, H7 eq.), 1.73 (3H, s, CH_3, H8 ax.), [2.61-2.68 (1H, m), 2.86-2.93 (1H, m), Ar-CH_2, *isoq*-4], 3.01 (3H, s, CH_3, H16), [3.63-3.69 (1H, m), 4.11-4.17 (1H, m), CH_2N, *isoq*-3], 4.50 (1H, d, *J* = 14 Hz, NCHCH_2, H6 eq.), 4.55-4.56 (1H, m, NC*H*CH_2, H5), 4.77 (1H, dd, *J* = 14, 3 Hz, H6 ax.), 6.06 (1H, d, J = 3 Hz, ArC*H*, H4), 6.79 (4H, t, *J* = 7 Hz, 4 x C*H* arom., *para* in BPh_4 gp.), 6.94 (8H, t, *J* = 7 Hz,

8 x C*H* arom., ortho in BPh_4 gp.), 7.33-7.36 (8H, m, 8 x C*H* arom., *meta* in BPh_4 gp.), 7.49 (1H, t, *J* = 8 Hz, C*H* arom., *isoq*-8), 7.74-7.84 (3H, m, 3 x C*H* arom., *isoq*-6,7,9), 7.80 (2H, d, *J* = 8 Hz, 2 x C*H* arom., H10, H11), 7.96 (2H, d, *J* = 9 Hz, 2 x C*H* arom., H12, H13), 9.28 (1H, s, NC*H*, *isoq*-1). ^{13}C NMR (125 MHz, acetone-d_6): 18.8 (*C*H_3, C7), 25.3 (Ar-*C*H_2, *isoq*-4), 29.4 (*C*H_3, C8), 44.2 (S*C*H_3, C16), 52.3 (*C*H_2N, *isoq*-3), 62.8 (*C*H_2, C6), 66.0 (N*C*H_2, C5), 71.5 (Ar-*C*H, C4), 101.6 (*C* quat., C2), 122.3 (8 x *C*H arom., *ortho* in BPh_4 gp.), 125.3 (*C* quat., arom., *isoq*-10), 126.0 (2 x *C*H arom., C12, C13), 127.5 (2 x *C*H arom., C10, C11), 128.8 (*C*H arom., *isoq*-6), 129.2 (*C*H arom., *isoq*-8), 129.3 (4 x *C*H arom., *para* in BPh_4 gp.), 135.4 (*C*H arom., *isoq*-7), 137.0 (8 x *C*H arom., *meta* in BPh_4 gp.), 137.9 (*C*H arom., *isoq*-9), 139.6 (*C*H arom., C14), 142.3 (*C* quat., arom., *isoq*-5), 143.1 (*C* quat., arom., C9), 165.0 (4 x *C* quat., arom., *ipso* in BPh_4 gp.), 168.9 (N*C*H, *isoq*-1).

Tetraphenylphosphonium monoperoxysulfate (71): [15]

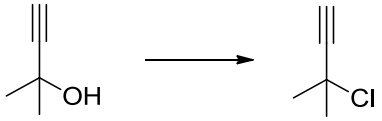


79 **71**

Oxone™ triple salt (2 $KHSO_5$:$KHSO_4$:K_2SO_4) (15.0 g, 48.8 mmol w.r.t. $KHSO_5$) was dissolved in deionized water (300 mL), and the solution stirred at 10-15 °C (water bath). A solution of tetraphenylphosphonium chloride **79** (15.0 g, 40.0 mmol) in distilled dichloromethane (300 mL) was added over 5 minutes, and the mixture stirred for an additional 30 minutes. The organic layer was separated, and the solvent removed under reduced pressure at room temperature. Colourless **71** was transferred to a fritted glass funnel, and washed with distilled water (2 x 75 mL). The solid was dissolved in dichloromethane (180 mL), and the solution dried ($MgSO_4$). Hexane was added until cloudiness developed, and the flask was placed in the freezer (- 20°C) for 2 h, producing a colourless precipitate of the salt about 85% pure in peroxide (15.4g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.64 (8H, m), 7.78 (8H, m), 7.89 (4H, m), 8.92 (1H, s).

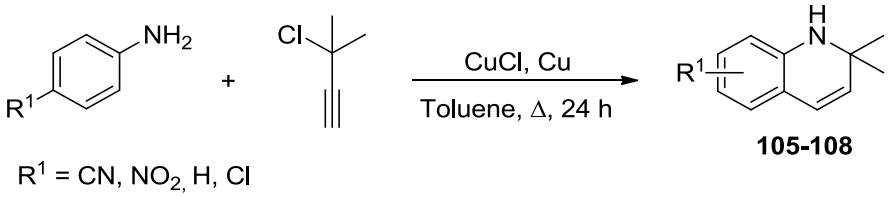
3.3.3 Dihydroquinoline Epoxidation Section

General Procedure for the formation of 3-chloro-3-methylbut-1-yne: [16]



To a 2L three neck flask, equipped with stirrer flea, at 0 °C, was added calcium dichloride (23 g, 209 mmol), cuprous chloride (20 g, 204 mmol), copper powder (0.4 g, 6.67 mmol) and cold concentrated hydrochloric acid (250 mL). The solution was left to stir for 5 minutes at 0 °C followed by purging the reaction with argon for 10 minutes. The corresponding tertiary alcohol (56 g, 667 mmol) was added dropwise over 30 minutes, and the reaction was left to stir for 1 hour at 0 – 5 °C. The upper organic layer was extracted directly from the reaction, and washed three times with cold concentrated hydrochloric acid (150 mL). The organic layer was further extracted with cold water (150 mL), saturated sodium hydrogen carbonate solution (150 mL) and dried on magnesium sulfate to afford the product as a colourless liquid (40 g, 58%). ν_{max} (neat) / cm^{-1}: 2984, 1448, 1368, 1226, 1118, 786. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.82 (6H, s, (2x)-$\underline{CH_3}$), 2.59 (1H, s, C≡C-H). ^{13}C NMR (75 MHz, $CDCl_3$): 34.6, 56.9, 71.9, 86.5. *The NMR data collected matches that found for commercially available 3-chloro-3-methylbut-1-yne.*

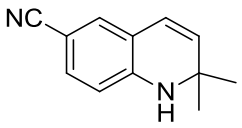
General Procedure for the formation of Dihydroquinolines



R^1 = CN, NO_2, H, Cl

The required aniline and 3-chloro-3-methyl-but-1-yne (1 equiv.) were dissolved in toluene (15 mL/gram of aniline), to which cuprous chloride (1 equiv.) and fine copper powder (1 equiv.) were added to the stirring solution. The reaction was submitted to reflux for 24 h. The reaction was allowed to cool, and water (10 mL/gram of aniline) added. The organic layer was extracted, and dichloromethane extracts from the aqueous phase were combined with the organic layer, and then dried over magnesium sulfate. Remaining solvents were removed under reduced pressure. Purification of the crude material using column chromatography (ethyl acetate:petroleum ether) afforded the dihydroquinolines as crystalline solids or oils.

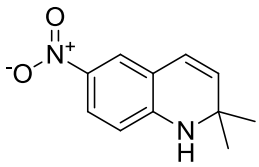
6-Cyano-2,2-dimethyl-1,2-dihydroquinoline (105): [17]



6-Cyano-2,2-dimethyl-1,2-dihydroquinoline **105** was prepared via the general procedure for dihydroquinoline formation from 4-aminobenzonitrile (0.13 g, 1.0 mmol) and 3-chloro-3-methyl-but-1-yne (0.11 g, 1.0 mmol), yielding compound **105** as a yellow solid (0.06 g, 30%; mp 107-109 °C) after purification via column chromatography (Eluent: 2:1:0.1, (petroleum ether:ethyl acetate:triethylamine). ν_{max} (film) / cm^{-1}: 3346, 3038, 2981, 2960, 2921, 2215, 1644, 1601, 1513, 1342, 1278, 1161. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.33 (6H, s, 2x C$\underline{H}_3$), 4.27 (1H, bs, N$\underline{H}$), 5.49 (1H, d, *J* = 10 Hz, C3-$\underline{H}$), 6.17 (1H, d, *J* = 10 Hz, C4-$\underline{H}$), 6.34 (1H, d, *J* = 8 Hz, C8-$\underline{H}$), 7.06 (1H, d, *J* = 2 Hz, C5-$\underline{H}$), 7.17 (1H, dd, *J* = 8, 2

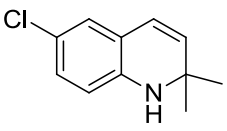
Hz, C7-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 31.9 (2x CH_3), 52.9, 98.0, 112.4, 119.3, 120.7, 122.0, 130.3, 131.8, 133.0, 146.7. HRMS *m/z* 185.1072 $[M + H]^+$; $[C_{12}H_{12}N_2+H]^+$ requires 185.1073.

6-Nitro-2,2-dimethyl-1,2-dihydroquinoline (106): [18]



6-Nitro-2,2-dimethyl-1,2-dihydroquinoline **106** was prepared via the general procedure for dihydroquinoline formation from 4-nitroaniline (1.23 g, 8.88 mmol) and 3-chloro-3-methyl-but-1-yne (0.9 g, 8.88 mmol), yielding compound **106** as a brown crystalline solid (0.58 g, 32%; mp 180-184 °C) after purification via column chromatography (Eluent: 3:1:0.1, petroleum ether:ethyl acetate:triethylamine). ν_{max} (film) / cm^{-1}: 3330, 2969, 1648, 1600, 1580, 1297, 1264, 1126, 1086. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.38 (6H, s, 2x CH_3), 4.47 (1H, bs, NH), 5.54 (1H, dd, *J* = 10, 2 Hz, C3-H), 6.26 (1H, d, *J* = 10 Hz, C4-H), 6.31 (1H, d, *J* = 9 Hz, C8-H), 7.77 (1H, d, *J* = 3 Hz, C5-H), 7.88 (1H, dd, *J* = 9, 3 Hz, C7-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 25.6, 26.8, 28.0, 49.5, 107.1, 118.2, 118.9, 121.8, 127.6. HRMS *m/z* 205.0966 $[M + H]^+$; $[C_{11}H_{12}N_2O_2 + H]^+$ requires 205.0972.

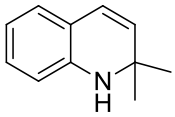
6-Chloro-2,2-dimethyl-1,2-dihydroquinoline (107): [19]



6-Chloro-2,2-dimethyl-1,2-dihydroquinoline **107** was prepared via the general procedure for dihydroquinoline formation from 4-chloroaniline (0.26 g, 2.0 mmol) and 3-chloro-3-methyl-but-1-yne (0.21 g, 2.0 mmol), yielding compound **107** as a yellow solid (0.100 g, 25%; mp 59-61 ˚C) after purification via column chromatography (Eluent: 6:1:0.1,

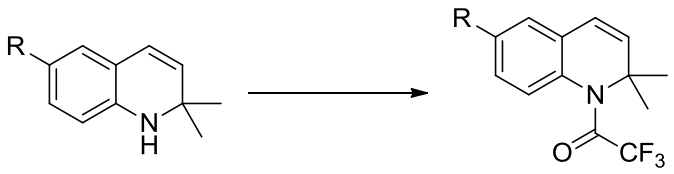
petroleum ether:ethyl acetate:triethylamine). ν_{max} (film) / cm^{-1}: 3388, 3037, 2964, 2925, 1639, 1599, 1489, 1445, 1381, 1359, 1302, 1211, 1084. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.30 (6H, s, (2x)-CH_3), 3.66 (1H, bs, NH), 5.52 (1H, d, *J* = 10 Hz, C3-H), 6.20 (1H, d, *J* = 10 Hz, C4-H), 6.34 (1H, d, *J* = 8 Hz, C8-H), 6.86 (1H, d, *J* = 2 Hz, C5-H), 6.91 (1H, dd, *J* = 8, 2 Hz, C7-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 30.9 (2x CH_3), 52.2, 113.8, 121.4, 121.6, 122.8, 126.1, 128.1, 132.3, 141.7. HRMS *m/z* 194.0728 $[M + H]^+$; $[C_{11}H_{12}NCl + H]^+$ requires 194.0731.

2,2-Dimethyl-1,2-dihydroquinoline (108): [20]



2,2-Dimethyl-1,2-dihydroquinoline **108** was prepared via the general procedure for dihydroquinoline formation from aniline (0.51 g, 5.5 mmol) and 3-chloro-3-methyl-but-1-yne (0.56 g, 5.5 mmol), yielding compound **108** as a brown oil (0.123 g, 14 %) after purification via column chromatography (Eluent: 6:1:0.1, petroleum ether: ethyl acetate:triethylamine). ν_{max} (film) / cm^{-1}: 3377, 3030, 2963, 1637, 1605, 1464, 1318, 1135, 1036, 974, 774, 744. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.33 (6H, s, 2x CH_3), 3.59 (1H, bs, NH), 5.49 (1H, d, *J* = 10 Hz, C3-H), 6.30 (1H, d, *J* = 10 Hz, C4-H), 6.43 (1H, d, *J* = 8 Hz, C8-H), 6.62 (1H, t, *J* = 8 Hz, C7-H), 6.92 (1H, d, *J* = 8 Hz, C6-H), 7.00 (1H, t, *J* = 8 Hz, C5-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 31.1 (2x CH_3), 52.1, 112.9, 117.3, 120.1, 123.8, 126.7, 128.7, 131.0, 143.3. HRMS *m/z* 159.1043 $[M]^+$; $[C_{11}H_{13}N]^+$ requires 159.1043.

General Procedure for the synthesis of *N*-Trifluoroacetyl Dihydroquinolines

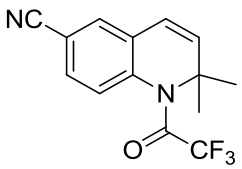


105,107 **115,117**

R = CN, Cl

Trifluoroacetic anhydride (2 equiv.) was added dropwise to a stirring solution of dihydroquinoline dissolved in dichloromethane (10 mL/100 mg of dihydroquinoline) and pyridine (1 equiv.) at 0 °C. The reaction was allowed to reach ambient temperature, and after further stirring for one hour, the reaction was quenched with water (5 mL/100 mg of dihydroquinoline). The organic phase was washed with copper sulfate solution, brine, and combined with dichloromethane extracts taken from the aqueous phase. The combined organic extracts were dried over magnesium sulfate, and remaining organic solvent removed under reduced pressure. The crude organic mixture was purified via column chromatography (ethyl acetate:petroleum ether).

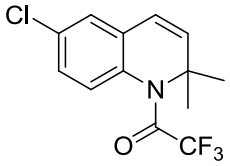
2,2-dimethyl-1-(trifluoroethanoyl)-1,2-dihydroquinoline-6-carbonitrile (115):



Compound **115** was prepared via the general procedure for *N*-trifluoro-acetyl dihydroquinoline protection from 6-cyano-2,2-dimethyl-1,2-dihydroquinoline **105** (0.05 g, 0.27 mmol), trifluoroacetic anhydride (0.11 g, 0.54 mmol) and pyridine (0.02 g, 0.27 mmol), yielding compound **115** as a bright yellow crystalline solid (0.074 g, 97%; mp 97-99 °C) after purification via column chromatography (Eluent: 6:1 petroleum ether:ethyl acetate). ν_{max} (film) / cm^{-1}: 2976, 2231, 1709, 1494, 1362, 1201, 1153. ^{1}H NMR (300 MHz,

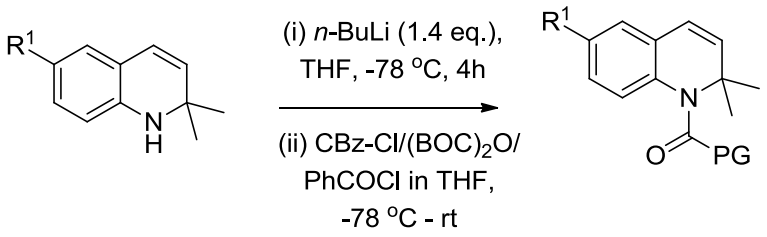
$CDCl_3$): δ_H 1.57 (6H, s, 2x C<u>H</u>$_3$), 5.88 (1H, d, *J* = 10 Hz, C3-<u>H</u>), 6.40 (1H, d, *J* = 10 Hz, C4-<u>H</u>), 6.89 (1H, d, *J* = 8 Hz, C8-<u>H</u>), 7.38 (1H, d, *J* = 2 Hz, C5-<u>H</u>), 7.46 (1H, dd, *J* = 8, 2 Hz, C7-<u>H</u>). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 25.4 (2x *C*H3), 60.5 (*C*2), 110.0, 117.9 (q, J_{C-F} = 265 Hz, <u>C</u>F$_3$), 121.5, 122.3, 122.4, 127.5, 129.7, 131.7, 137.8, 139.4, 159.4 (q, J_{C-F} = 33 Hz, <u>C</u>OCF$_3$). HRMS *m/z* found 281.0894 $[M + H]^+$; $[C_{14}H_{11}F_3N_2O+H]^+$ requires 281.0896.

1-(6-chloro-2,2-dimethylquinolin-1(*2H*)-yl)-2,2,2-trifluoroethanone (117):



Compound **117** was prepared via the general procedure for *N*-trifluoro-acetyl dihydroquinoline protection from 6-chloro-2,2-dimethyl-1,2-dihydroquinoline **107** (0.052 g, 0.27 mmol), trifluoroacetic anhydride (0.11 g, 0.54 mmol) and pyridine (0.02 g, 0.27 mmol), yielding compound **117** as a yellow crystalline solid (0.052 g, 68%; mp 65-67 °C) after purification via column chromatography (Eluent: 6:1, petroleum ether:ethyl acetate). ν_{max} (film) / cm^{-1}: 2974, 2932, 1704, 1489, 1359, 1200, 1177, 892, 717. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.54 (6H, s, 2x C<u>H</u>$_3$), 5.81 (1H, d, *J* = 10 Hz, C3-<u>H</u>), 6.34 (1H, d, *J* = 10 Hz, C4-<u>H</u>), 6.79 (1H, d, *J* = 8 Hz, C8-<u>H</u>), 7.09 (1H, d, *J* = 2 Hz, C5-<u>H</u>), 7.13 (1H, dd, *J* = 8, 2 Hz, C7-<u>H</u>). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 25.3 (2x C<u>H</u>$_3$), 60.2 (*C*2), 117.2 (q, J_{C-F} = 289 Hz, <u>C</u>F$_3$), 122.1, 123.5, 123.6, 126.3, 127.5, 128.5, 132.2, 139.1, 158.6 (q, J_{C-F} = 36 Hz, <u>C</u>OCF$_3$). HRMS *m/z* found 290.0552 $[M + H]^+$; $[C_{13}H_{11}F_3NClO+H]^+$ requires 290.0554.

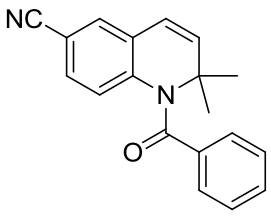
General procedure for the preparation of various nitrogen protected dihydroquinolines



R^1 = CN, Cl
PG = CBz/Ph/BOC

To a flame dried round bottom flask under an atmosphere of nitrogen was added dihydroquinoline (1 equiv.) and anhydrous THF (50 mL/gram of dihydroquinoline). The reaction mixture was cooled to -78 °C, to which *n*-BuLi (1.4 equiv.) was added slowly over 15 minutes, and left to stir for 2 h. This was followed by the slow addition of a solution of *tert*-butylcarboxyl anhydride/benzoyl chloride/benzyl chloroformate (1.5 equiv.) in THF (10 mL/gram of dihydroquinoline) over 15 minutes. Reaction progress was monitored by TLC, then quenched with ammonium chloride solution (10 mL/gram of dihydroquinoline). Ethyl acetate (20 mL/gram of dihydroquinoline) was added, and the organic layers were separated. The combined organic layers were then washed with brine (10 mL/gram of dihydroquinoline), dried over sodium sulfate and concentrated under reduced pressure to afford the title compounds as viscous oils/solids.

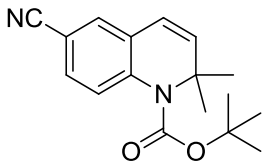
1-benzoyl-2,2-dimethyl-6-cyano-dihydroquinoline (120):



Compound **120** was prepared via the general procedure for dihydroquinoline protection from 6-cyano-2,2-dimethyl-1,2-dihydroquinoline **105** (0.2 g, 1.1 mmol) and benzoyl chloride (0.23 g, 1.65 mmol), yielding compound **120** as a bright yellow luminescent oil

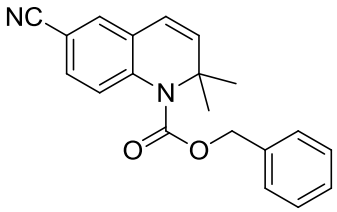
(0.127 g, 40%) after purification via column chromatography (Eluent: 6:1, petroleum ether:ethyl acetate). ν_{max} (film) / cm^{-1}: 2970, 2225, 1664, 1599, 1562, 1487, 1319, 1297, 1242, 1147, 905. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.53 (6H, s, 2x C<u>H</u>$_3$), 5.75 (1H, d, *J* = 10 Hz, C3-<u>H</u>), 6.24 (1H, d, *J* = 8 Hz, C8-<u>H</u>), 6.28 (1H, d, *J* = 10 Hz, C4-<u>H</u>), 6.87 (1H, dd, *J* = 8, 2 Hz, C7-<u>H</u>), 7.14 (1H, d, *J* = 2 Hz, C5-<u>H</u>), 7.18 (2H, t, *J* = 8 Hz, 2x Ph-C*H meta*), 7.25-7.35 (1H, m, Ph-C*H para*), 7.45 (2H, d, *J* = 8 Hz, 2x Ph-C*H ortho*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 26.8 (2x *C*H3), 59.1 (*C*2), 106.1, 119.0, 121.5, 124.5, 126.3, 128.9 (2x Ph*C*H), 129.7, 130.1 (2x Ph*C*H), 130.9, 132.4, 136.2, 139.3, 142.5, 172.3. HRMS *m/z* 289.1330 $[M + H]^+$; $[C_{19}H_{16}N_2O+H]^+$ requires 289.1335.

1-*tert*-butyoxycarbonyl-2,2-dimethyl-6-cyano-dihydroquinoline (121):



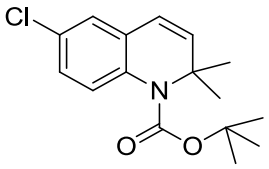
Compound **121** was prepared via the general procedure for dihydroquinoline protection from 6-cyano-2,2-dimethyl-1,2-dihydroquinoline **105** (0.2 g, 1.1 mmol) and *tert*-butoxycarboxyl anhydride (0.35 g, 1.65 mmol), yielding compound **121** as a bright yellow luminescent oil (0.1 g, 33%) after purification via column chromatography (Eluent: 6:1, petroleum ether:ethyl acetate). ν_{max} (film) / cm^{-1}: 2976, 2932, 2225, 1714, 1602, 1491, 1369, 1304, 1224, 1145, 1065, 823. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.54 (9H, s, 3x CH_3, *t*-Bu), 1.55 (6H, s, 2x CH_3), 5.64 (1H, d, *J* = 10 Hz, C3-<u>H</u>), 6.23 (1H, d, *J* = 10 Hz, C4-<u>H</u>), 7.19 (1H, d, *J* = 9 Hz, C8-<u>H</u>), 7.21 (1H, d, *J* = 2 Hz, C5-<u>H</u>), 7.33 (1H, dd, *J* = 9, 2 Hz, C7-<u>H</u>). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 28.0 (2x *C*H3), 28.3 (3x *C*H3, *t*-Bu), 58.1, 82.7, 104.9, 119.4, 121.4, 121.8, 125.6, 129.9, 131.3, 137.9, 141.9, 153.8. HRMS *m/z* 285.1600 $[M + H]^+$; $[C_{17}H_{20}N_2O_2+H]^+$ requires 285.1598.

1-carboxybenzyl-2,2-dimethyl-6-cyano-dihydroquinoline (122):



Compound **122** was prepared via the general procedure for dihydroquinoline protection from 6-cyano-2,2-dimethyl-1,2-dihydroquinoline **105** (0.2 g, 1.1 mmol) and benzyl chloroformate (0.35 g, 1.65 mmol), yielding compound **122** as a colourless powder (0.174 g, 55%; mp 116-118 °C) after purification via column chromatography (Eluent: 6:1, petroleum ether:ethyl acetate). ν_{max} (film) / cm^{-1}: 2963, 2224, 1711, 1602, 1490, 1300, 1216, 1059. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.55 (6H, s, 2x C$\underline{H}_3$), 5.26 (2H, s, Cbz-C$\underline{H}_2$), 5.69 (1H, d, *J* = 10 Hz, C3-$\underline{H}$), 6.26 (1H, d, *J* = 10 Hz, C4-$\underline{H}$), 7.07 (1H, d, *J* = 9 Hz, C8-$\underline{H}$), 7.23 (1H, d, *J* = 2 Hz, C5-$\underline{H}$), 7.27 (1H, dd, *J* = 9, 2 Hz, C7-$\underline{H}$), 7.34-7.42 (5H, m, 5x PhCH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.5 (2x *C*H_3), 58.3, 68.2, 105.8, 114.0, 118.9, 121.3, 122.5, 126.0, 128.7 (2x *C*), 128.7 (2x *C*), 129.6, 131.1, 135.1, 138.1, 140.9, 154.5. HRMS *m/z* found 318.1362 $[M + H]^+$; $[C_{20}H_{18}N_2O_2+H]^+$ requires 318.1368.

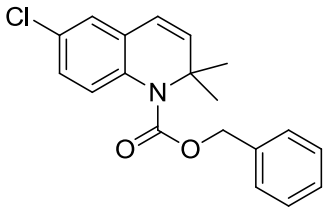
1-*tert*-butyoxycarbonyl-2,2-dimethyl-6-chloro-dihydroquinoline (126):



Compound **126** was prepared via the general procedure for dihydroquinoline protection from 6-chloro-2,2-dimethyl-1,2-dihydroquinoline **107** (0.2 g, 1.04 mmol) and *tert*-butoxycarboxyl anhydride (0.34 g, 1.55 mmol), yielding compound **126** as a brown oil (0.12 g, 40%) after purification via column chromatography (Eluent: 10:1, petroleum ether:ethyl acetate). ν_{max} (film) / cm^{-1}: 2974, 1710, 1487, 1315, 1248, 1156. ^{1}H NMR (400

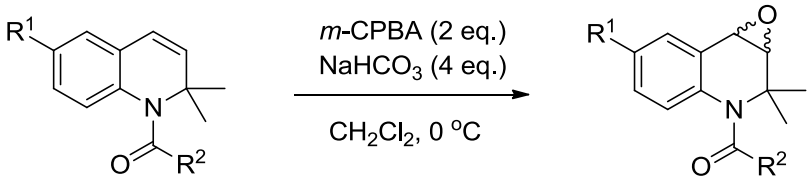
MHz, $CDCl_3$): δ_H 1.51 (9H, s, 3x CH_3, *t*-Bu), 1.52 (6H, s, 2x CH_3), 5.64 (1H, d, *J* = 10 Hz, C3-H), 6.21 (1H, d, *J* = 10 Hz, C4-H), 6.94 (1H, d, *J* = 2 Hz, C5-H), 7.03 (1H, dd, *J* = 9, 2 Hz, C7-H), 7.11 (1H, d, *J* = 9 Hz, C8-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 27.6 (2x CH_3), 28.4 (3C, *t*-Bu), 57.4 (*C*2), 81.6, 122.2, 124.0, 125.6, 127.0, 127.3, 127.6, 136.1, 138.3, 154.0. HRMS *m/z* 294.1259 $[M + H]^+$; $[C_{16}H_{20}ClNO_2+H]^+$ requires 294.1255.

1-carboxybenzyl-2,2-dimethyl-6-cyano-dihydroquinoline (127):



Compound **127** was prepared via the general procedure for dihydroquinoline protection from 6-chloro-2,2-dimethyl-1,2-dihydroquinoline **107** (0.3 g, 0.92 mmol) and benzyl chloroformate (0.3 g, 1.38 mmol), yielding compound **127** as a yellow oil (0.072 g, 14%) after purification via column chromatography (Eluent: 10:1, petroleum ether:ethyl acetate). ν_{max} (film) / cm^{-1}: 2969, 1706, 1485, 1305, 1239, 1209, 1057. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.54 (6H, s, 2x CH_3), 5.22 (2H, s, benzyl-CH_2), 5.69 (1H, d, *J* = 10 Hz, C3-H), 6.24 (1H, d, *J* = 10 Hz, C4-H), 6.96-7.00 (3H, m, C5-H, C7-H, C8-H), 7.33-7.39 (5H, m, Cbz-PhCH). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 27.1 (2x CH_3), 57.7, 67.6, 122.1, 124.6, 125.5, 127.0, 127.7, 128.35, 128.38, 128.5 (2C), 128.6 (2C), 135.2, 135.6, 138.4, 154.6. HRMS *m/z* 328.1104 $[M + H]^+$; $[C_{19}H_{18}ClNO_2+H]^+$ requires 328.1099.

General Procedure for the formation of Racemic Epoxides

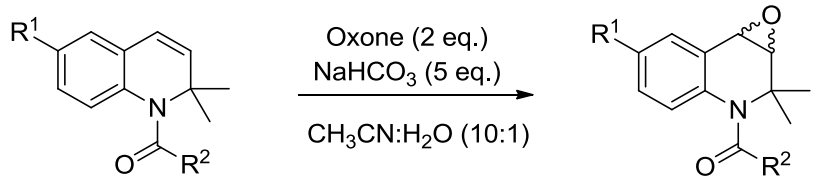


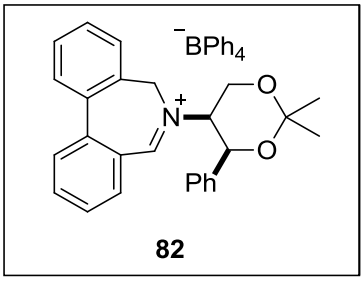
R^1 = CN, Cl
R^2 = CF_3, Ph, BOC, Cbz

The required nitrogen protected dihydroquinoline (1 equiv.) was dissolved in dichloromethane (5 mL/0.02 g of dihydroquinoline) and cooled to 0 °C, to which *meta*-chloroperbenzoic acid (2 equiv.) and sodium hydrogen carbonate (4 equiv.) were added as solids. The reaction was allowed to stir at 0 °C until reaction completion was observed by TLC. Saturated aqueous sodium hydrogen carbonate solution (2 mL/0.02 g of dihydroquinoline) was added to quench the reaction. The organic layer was extracted against water and brine washes, and combined with further dichloromethane extracts of the aqueous layer. The combined organic extracts were dried over magnesium sulfate, and excess solvent was removed under reduced pressure. The crude product was purified using flash column chromatography, utilising various ethyl acetate:petroleum ether:triethylamine eluents.

General Procedure for the Formation of Chiral Epoxides

Aqueous conditions [21]





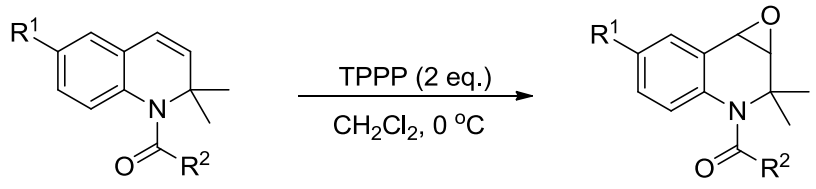
82

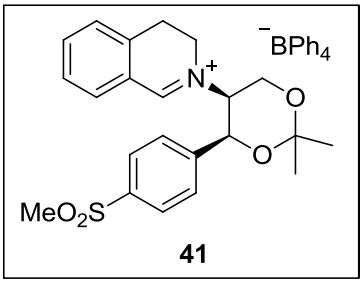
R^1 = CN, Cl
R^2 = CF_3, Ph, $(O)C(CH_3)_3$, $(O)CH_2Ph$

The required nitrogen protected dihydroquinoline (1 equiv.) and catalyst **82** (5 mol%) was dissolved in acetonitrile (1 mL/0.05 g of nitrogen protected dihydroquinoline) and water (0.1 mL/0.05 g of nitrogen protected dihydroquinoline) and the mixture cooled to 0 °C. A mixture of Oxone (2 equiv.) and sodium hydrogen carbonate (5 equiv.) was added as a solid in one portion to the mixture with vigorous stirring. The mixture was stirred at 0 °C until complete conversion of the alkene was observed by TLC. Diethyl ether (10 mL/0.05 g of nitrogen protected dihydroquinoline) was added, and the reaction mixture was filtered through a pad of mixed $MgSO_4$ and sodium bisulfite. The solvent was removed in *vacuo*. Pure epoxides were obtained by column chromatography using ethyl acetate: petroleum ether: triethylamine as eluents.

General Procedure for the Formation of Chiral Epoxides

Non-aqueous conditions [22]

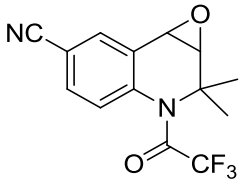




R^1 = CN, Cl
R^2 = CF_3, Ph, $(O)C(CH_3)_3$, $(O)CH_2Ph$

Tetraphenylphosphonium monoperoxysulfate (2 equiv.) was dissolved in dichloromethane (2 mL/0.05 g TPPP) and the solution cooled to 0 °C. A solution of the iminium salt **41** (10 mol%) in dichloromethane (0.5 mL/0.05 g TPPP) was cooled to 0 °C and added dropwise to the solution containing the TPPP over 20 minutes. The temperature of the reaction vessel was monitored to minimize the increase in temperature during the addition. A solution of the alkene in dichloromethane (0.5 mL/0.05 g TPPP) was added dropwise. The mixture was stirred at 0 °C with the reaction progress monitored by TLC. Diethyl ether (pre-cooled to the reaction temperature) (20 mL/0.05 g TPPP) was added to induce precipitation of the remaining oxidant, and the mixture filtered through Celite. The solvents were removed in *vacuo*. If the reaction does not reach completion the epoxide can be separated from the alkene by column chromatography, eluting with ethyl acetate/light petroleum.

3,4-epoxy-2,2-dimethyl-1-(trifluoroethanoyl)-1,2-tetrahydroquinoline-6-carbonitrile (128):



Non-chiral Epoxidation: Following the general procedure for the formation of racemic epoxides, compound **115** (0.06 g, 0.21 mmol), *m*-CPBA (0.07 g, 0.43 mmol) and $NaHCO_3$ (0.07 g, 0.86 mmol) were left to react at 0 °C for 24 hours. The crude reaction mixture was purified by flash column chromatography (eluents; petroleum ether: ethyl acetate: triethylamine, 6:1:0.1), affording **128** as a yellow-orange solid (0.038 g, 60%; mp 114-118 °C). ν_{max} (film) / cm^{-1}: 2927, 2232, 1712, 1501, 1367, 1201, 1172, 1136, 832. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.28 (3H, s, CH_3), 1.84 (3H, s, CH_3), 3.50 (1H, d, *J* = 4 Hz, C3-H), 3.94 (1H, d, *J* = 4 Hz, C4-H), 6.91 (1H, d, *J* = 8 Hz, C8-H), 7.63 (1H, dd, *J* = 2, 8 Hz, C7-H), 7.77 (1H, d, *J* = 2 Hz, C5-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.6, 24.3, 50.6, 58.0, 64.6, 110.3, 117.6, 125.6 (q, $J_{C\text{-}F}$ = 197 Hz, CF_3), 127.2, 127.3, 133.3, 133.4, 138.4, 160.7 (q, $J_{C\text{-}F}$ = 42 Hz, $COCF_3$). HRMS *m/z* found 297.0841 $[M + H]^+$; $[C_{14}H_{11}F_3N_2O_2+H]^+$ requires 297.0845. HPLC trace (90:10 hexane:*iso*-propanol, flow rate: 1 mL/min); 14.75 min (50.02 %), 16.80 min (49.98 %).

Asymmetric Epoxidation

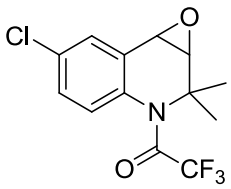
Aqueous conditions: Following the general procedure for the formation of enantioenriched epoxides under aqueous conditions, compound **115** (0.05 g, 0.18 mmol) and catalyst **82** (0.006 g, 5 mol%) was dissolved in acetonitrile:water (10:1, 1 mL) and cooled to 0 °C. Oxone (0.22 g, 0.36 mmol) and sodium hydrogen carbonate (0.08 g, 0.9 mmol) were added in one portion, and the reaction progress was monitored by TLC. The reaction mixture was purified by flash column chromatography (eluents; petroleum ether:

ethyl acetate: triethylamine, 6:1:0.1), affording **128** as a yellow-orange solid (0.041 g, 76%). $[\alpha]_D$ = −219.3 (*c* 0.017 g/mL, CH_2Cl_2); Chiral HPLC trace (90:10, hexane:isopropanol, flow rate: 1 mL/min); 14.80 min (31.32 %), 16.83 min (68.68 %).

Non-Aqueous conditions: Tetraphenylphosphonium monoperoxysulfate (0.64 g, 1.42 mmol) was dissolved in dichloromethane (8 mL) and the solution cooled to 0 °C. A solution of iminium-salt **41** (0.05 g, 10 mol%) in dichloromethane (2 mL) was cooled to 0 °C and added dropwise to the solution containing the TPPP over 20 minutes. The temperature of the reaction vessel was monitored to minimize the increase in temperature during the addition. A solution of compound **115** (0.2 g, 0.71 mmol) in dichloromethane (2 mL) was added dropwise. The mixture was stirred at 0 °C for 120 hours, and quenched at this point to avoid any decomposition of the epoxide product being formed. The reaction mixture was purified by flash column chromatography (eluents; petroleum ether: ethyl acetate: triethylamine, 6:1:0.1), affording **128** as a yellow-orange solid (0.02 g, 10%). $[\alpha]_D$ = −142.4 (*c* 0.01 g/mL, CH_2Cl_2); Chiral HPLC trace (90:10, hexane:isopropanol, flow rate: 1 mL/min); 14.84 min (13.20%), 16.76 min (86.80%).

(The discrepancy between the e.r. by HPLC and the relative magnitudes of the specific rotation measurements was noted in the viva)

3,4-epoxy-2,2-dimethyl-1-(trifluoroethanoyl)-6-chloro-1,2-tetrahydroquinoline (129):



Non-chiral Epoxidation: Following the general procedure for the formation of racemic epoxides, compound **117** (0.1 g, 0.35 mmol), *m*-CPBA (0.12 g, 0.70 mmol) and $NaHCO_3$ (0.115 g, 1.38 mmol) were left to react at 0 °C for 24 hours. The crude reaction mixture was purified by flash column chromatography (eluent mixture, petroleum ether: ethyl acetate: triethylamine; 8:1:0.1), affording **129** as a yellow oil (0.055 g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.22 (3H, s, CH_3), 1.87 (3H, s, CH_3), 3.44 (1H, d, *J* = 4 Hz, C3-H), 3.86 (1H, d, *J* = 4 Hz, C4-H), 6.81 (1H, d, *J* = 8 Hz, C8-H), 7.30 (1H, dd, *J* = 2, 8 Hz, C7-H), 7.45 (1H, d, *J* = 2 Hz, C5-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.6, 23.6, 51.0, 56.9, 63.5, 116.1 (q, $J_{C\text{-}F}$ = 290 Hz, CF_3), 124.6, 126.7, 128.1, 129.0, 131.4, 131.7, 158.7 (q, $J_{C\text{-}F}$ = 36 Hz, $COCF_3$). HRMS *m/z* found 306.0506 $[M + H]^+$; $[C_{13}H_{11}ClF_3NO_2 + H]^+$ requires 306.0503. Resolution of the enantiomers was achieved using 3 mg of europium(III) chelate/10 mg of epoxide (Appendix B).

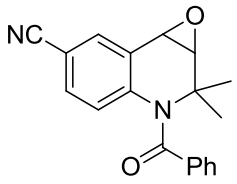
Asymmetric Epoxidation

Aqueous conditions: Following the general procedure for the formation of enantioenriched epoxides under aqueous conditions, compound **117** (0.1 g, 0.34 mmol) and catalyst **82** (0.012 g, 5 mol%) was dissolved in acetonitrile:water (10:1, 2 mL) and cooled to 0 °C. Oxone (0.42 g, 0.68 mmol) and sodium hydrogen carbonate (0.15 g, 1.72 mmol) were added in one portion, and the reaction progress was monitored by TLC. The reaction mixture was purified by flash column chromatography (eluents; petroleum ether: ethyl acetate: triethylamine, 8:1:0.1), affording **129** as a yellow oil (0.091 g, 87%). $[\alpha]_D = -77.6$

(*c* 0.01 g/mL, CH_2Cl_2); Resolution of enantiomers was achieved using 3 mg of europium (III) chelate/10 mg of epoxide (Appendix B).

Non-Aqueous conditions: Tetraphenylphosphonium monoperoxysulfate (0.62 g, 1.38 mmol) was dissolved in dichloromethane (8 mL) and the solution cooled to 0 °C. A solution of iminium-salt **41** (0.05 g, 10 mol%) in dichloromethane (2 mL) was cooled to 0 °C and added dropwise to the solution containing the TPPP over 20 minutes. The temperature of the reaction vessel was monitored to minimize the increase in temperature during the addition. A solution of compound **117** (0.2 g, 0.69 mmol) in dichloromethane (2 mL) was added dropwise. The mixture was stirred at 0 °C for 120 hours, and quenched at this point to avoid any decomposition of the epoxide product being formed. The reaction mixture was purified by flash column chromatography (eluents; petroleum ether: ethyl acetate: triethylamine, 8:1:0.1), affording **129** as a yellow oil (0.028 g, 13%). $[\alpha]_D = -82$ (*c* 0.01 g/mL, CH_2Cl_2); Resolution of enantiomers was achieved using 3 mg of europium(III) chelate/10 mg of epoxide.

3,4-epoxy-2,2-dimethyl-1-(benzoyl)-1,2-tetrahydroquinoline-6-carbonitrile (130):



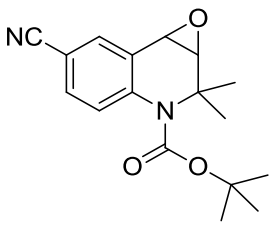
Non-chiral epoxidation: Following the general procedure for the formation of racemic epoxides, Compound **120** (0.06 g, 0.21 mmol), *m*-CPBA (0.07 g, 0.42 mmol) and $NaHCO_3$ (0.07 g, 0.86 mmol) were left to react at 0 °C for 24 hours. The crude reaction mixture was purified by flash column chromatography (eluent mixture, petroleum ether: ethyl acetate: triethylamine; 7:1:0.1), affording **130** as a colourless oil (0.034 g, 53%). ν_{max} (film) / cm^{-1}: 3058, 2972, 2930, 2227, 1665, 1610, 1571, 1497, 1298, 1232, 827, 730. ^1H NMR (300

MHz, $CDCl_3$): δ_H 1.45 (3H, s, C<u>H</u>$_3$), 1.84 (3H, s, C<u>H</u>$_3$), 3.59 (1H, d, *J* = 4 Hz, C3-<u>H</u>), 3.97 (1H, d, *J* = 4 Hz, C4-<u>H</u>), 6.41 (1H, d, *J* = 9 Hz, C8-<u>H</u>), 7.16 (1H, dd, *J* = 2, 9 Hz, C7-<u>H</u>), 7.30 (2H, d, *J* = 8 Hz, Ar-<u>H</u>), 7.41 (1H, t, *J* = 8 Hz, Ar-<u>H</u>), 7.59-7.72 (3H, m, C5-<u>H</u> & 2x Ar-<u>H</u>). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 23.4, 24.9, 51.6, 55.8, 67.3, 106.1, 118.4, 124.4, 125.5, 128.8, 130.3, 132.4, 132.5, 133.3, 136.5, 142.7, 173.3. HRMS *m/z* found 305.1288 $[M + H]^+$; $[C_{19}H_{16}N_2O_2+H]^+$ requires 305.1285. Racemic HPLC trace (98:2, hexane:*iso*-propanol, flow rate; 1 mL/min); 27.31 min (47.11 %), 30.40 min (52.89 %).

Asymmetric Epoxidation

Aqueous conditions: Following the general procedure for the formation of enantioenriched epoxides under aqueous conditions, compound **120** (0.05 g, 0.17 mmol) and catalyst **82** (0.006 g, 5 mol%) was dissolved in acetonitrile:water (10:1, 1 mL) and cooled to 0 °C. Oxone (0.21 g, 0.34 mmol) and sodium hydrogen carbonate (0.07 g, 0.87 mmol) were added in one portion, and the reaction progress was monitored by TLC. The reaction mixture was purified by flash column chromatography (eluents; petroleum ether: ethyl acetate: triethylamine, 7:1:0.1), affording **130** as a colourless oil (0.035 g, 68%). $[\alpha]_D$ = −197.6 (*c* 0.01 g/mL, CH_2Cl_2); Chiral HPLC trace (98:2, hexane:iso-propanol, flow rate; 1 mL/min); 27.36 min (16.78 %), 30.10 min (83.22 %).

3,4-epoxy-1-*tert*-butyoxycarbonyl-2,2-dimethyl-6-cyano-tetrahydroquinoline (131):



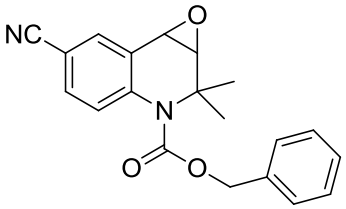
Non-chiral Epoxidation: Following the general procedure for the formation of racemic epoxides, compound **121** (0.07 g, 0.25 mmol), *m*-CPBA (0.09 g, 0.50 mmol) and $NaHCO_3$

(0.08 g, 1.0 mmol) were left to react at 0 °C for 24 hours. The crude reaction mixture was purified by flash column chromatography (eluents; petroleum ether: ethyl acetate: triethylamine, 10:1:0.1), affording epoxide **131** as a colourless oil (0.053 g, 71%). ν_{max} (film) / cm^{-1}: 2965, 2925, 2853, 2227, 1717, 1612, 1574, 1499, 1369, 1316, 1148. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.29 (3H, s, CH_3), 1.49 (9H, s, *t*-Bu), 1.80 (3H, s, CH_3), 3.47 (1H, d, *J* = 4 Hz, C3-H), 3.82 (1H, d, *J* = 4 Hz, C4-H), 7.14 (1H, d, *J* = 9 Hz, C8-H), 7.47 (1H, dd, J = 2, 9 Hz, C7-H), 7.60 (1H, d, *J* = 2 Hz, C5-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 22.7 (*C*H3), 26.2 (*C*H3), 28.2 (3x *C*H3, *t*-Bu), 51.6, 55.3, 67.6, 82.7, 105.7, 118.8, 120.2, 124.1, 124.3, 132.6, 133.4, 142.5. *m/z* found 301.1549 [M + H]+; $C_{17}H_{21}O_3N_2$ requires 301.1547. Racemic HPLC trace (99:1, hexane:iso-propanol, flow rate; 0.5 mL/min); 35.37 min (49.61 %), 37.46 min (50.39 %).

Asymmetric Epoxidation

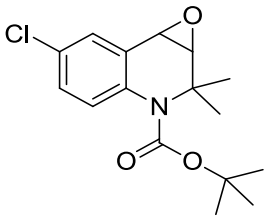
Aqueous conditions: Following the general procedure for the formation of enantioenriched epoxides under aqueous conditions, compound **121** (0.06 g, 0.21 mmol) and catalyst **82** (0.007 g, 5 mol%) was dissolved in acetonitrile:water (10:1, 1 mL) and cooled to 0 °C. Oxone (0.26 g, 0.42 mmol) and sodium hydrogen carbonate (0.09 g, 0.87 mmol) were added in one portion, and the reaction progress was monitored by TLC. The reaction mixture was purified by flash column chromatography (eluents; petroleum ether: ethyl acetate: triethylamine, 10:1:0.1), affording **131** as a colourless oil (0.057 g, 90%). $[\alpha]_D$ = −56.2 (*c* 0.02 g/mL, CH_2Cl_2); Chiral HPLC trace (99:1, hexane:iso-propanol, flow rate; 0.5 mL/min); 35.82 min (43.82 %), 37.88 min (56.18 %).

3,4-epoxy-1-carboxybenzyl-2,2-dimethyl-6-cyano-tetrahydroquinoline (132):



Non-chiral Epoxidation: Following the general procedure for the formation of racemic epoxides, compound **122** (0.16 g, 0.50 mmol), *m*-CPBA (0.17 g, 1 mmol) and $NaHCO_3$ (0.17 g, 2.0 mmol) were left to react at 0 °C for 24 hours. The crude reaction mixture was purified by flash column chromatography (eluents; petroleum ether: ethyl acetate: triethylamine, 6:1:0.1), affording **132** as a colourless oil (0.13 g, 78%). ν_{max} (film) / cm^{-1}: 2975, 2226, 1721, 1612, 1574, 1499, 1306, 1254, 1224, 1069. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.25 (3H, s, C<u>H</u>$_3$), 1.84 (3H, s, C<u>H</u>$_3$), 3.48 (1H, d, *J* = 4 Hz, C3-<u>H</u>), 3.83 (1H, d, *J* = 4 Hz, C4-<u>H</u>), 5.09 & 5.29 (2H, dd, *J* = 12, 79 Hz, C<u>H</u>$_2$-benzyl), 6.95 (1H, d, *J* = 9 Hz, C8-<u>H</u>), 7.25-7.45 (6H, m, C7-<u>H</u> & 5x Ar-<u>H</u>), 7.61 (1H, d, *J* = 2 Hz, C5-<u>H</u>). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 22.4 (*C*H3), 25.7 (*C*H3), 51.1, 55.6, 67.1, 68.1, 106.7, 118.4, 125.2, 125.3, 128.6 (3*C*), 128.7 (2*C*), 132.5, 133.0, 135.1, 141.7, 155.2. HRMS *m/z* found 335.1393 $[M + H]^+$; $[C_{20}H_{18}N_2O_3+H]^+$ requires 335.1390. Enantiomers could not be resolved *via* chiral HPLC nor using chiral shift reagent in the ^{1}H NMR of **132**.

3,4-epoxy-1-*tert*-butyoxycarbonyl-2,2-dimethyl-6-chloro-tetrahydroquinoline (133):

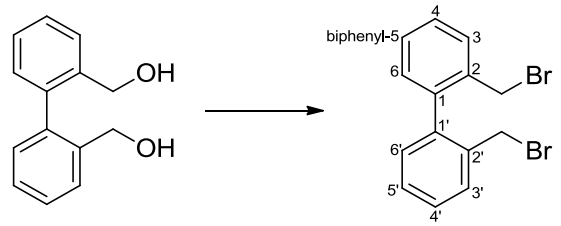


Non-chiral Epoxidation: Following the general procedure for the formation of racemic epoxides, compound **126** (0.1 g, 0.34 mmol), *m*-CPBA (0.12 g, 0.68 mmol) and $NaHCO_3$

(0.11 g, 1.36 mmol) were left to react at 0 °C for 24 hours. The crude reaction mixture was purified by flash column chromatography (eluents; petroleum ether: ethyl acetate: triethylamine, 10:1:0.1), affording **133** as a yellow oil (0.055 g, 53%). ν_{max} (film) / cm^{-1}: 2978, 1709, 1489, 1313, 1240, 1161, 1145. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.18 (3H, s, C<u>H</u>$_3$), 1.45 (9H, s, *t*-Bu), 1.85 (3H, s, C<u>H</u>$_3$), 3.42 (1H, d, *J* = 4 Hz, C3-<u>H</u>), 3.74 (1H, d, *J* = 4 Hz, C4-<u>H</u>), 7.02 (1H, d, *J* = 9 Hz, C8-<u>H</u>), 7.18 (1H, dd, *J* = 3, 9 Hz, C7-<u>H</u>), 7.28 (1H, d, *J* = 3 Hz, C5-<u>H</u>). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 22.6 (*C*H3), 26.1 (*C*H3), 28.0 (3x *C*H3, *t*-Bu), 51.2, 54.8, 67.4, 81.2, 126.1, 126.7, 128.4, 128.5, 128.7, 137.0, 154.7. HRMS *m/z* found 310.1208 $[M + H]^+$; $[C_{16}H_{20}ClNO_3+H]^+$ requires 310.1204. Resolution of enantiomers was achieved using 3 mg of europium (III) chelate/10 mg of epoxide.

3.3.4 Iminium-salt Catalyst 82 Synthesis

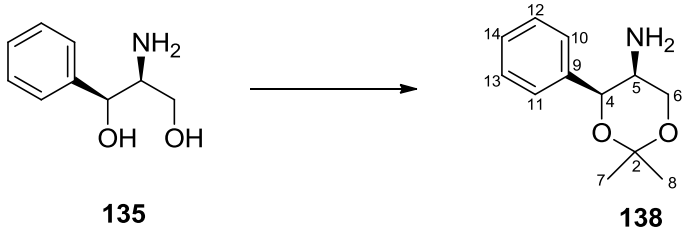
2,2'-*bis*(bromomethyl)biphenyl (140): [23]



139 **140**

2,2'-Biphenyldimethanol **139** (3 g, 14.0 mmol) was dissolved in neat hydrobromic acid (50 mL) at room temperature, and then submitted to reflux for 2.5 h. Reaction progress was monitored by TLC, and upon reaction completion, the solution was cooled, toluene (100 mL) added, and the organic layer was extracted. The organic extract was washed with saturated sodium hydrogen carbonate (100 mL), brine (100 mL), dried ($MgSO_4$), and excess organic solvents removed under reduced pressure, affording 2,2'-*bis*(bromomethyl)biphenyl **140** as a colourless solid (4.5 g, 95%; mp 92-94 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 4.22 (2H, d, *J* = 10 Hz, 2x CH*H*-Br)), 4.37 (2H, d, *J* = 10 Hz, 2x C*H*H-Br), 7.30 (2H, dd, *J* = 8, 2 Hz, Ar-H), 7.40 (2H, ddd, *J* = 8, 8, 2 Hz, Ar-H), 7.44 (2H, dd, *J* = 8, 8, 2 Hz, Ar-H), 7.57 (2H, dd, *J* = 8, 2 Hz, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 32.0, 128.3, 128.7, 130.2, 130.7, 135.9, 139.4.

(4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-amine (138): [24]

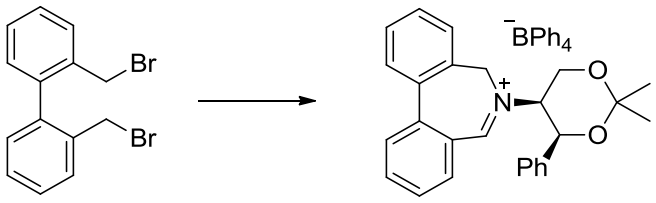


135 **138**

Compound **138** was prepared according to the procedure reported by Thomas.[20] (1*S*,2*S*)–(+)–2-amino-1-phenyl-1,3-propanediol **135** (5.00 g, 29.9 mmol) was dissolved in MeOH

(50 mL), and methyl formate (2.77 mL, 44.85 mmol) and sodium methoxide (1.37 mL, 25% in methanol) were added. The mixture was stirred for 3.5 h and the solvent removed under reduced pressure. Diol **136** (5.80 g, 29.71 mmol) was then dissolved with acetone (250 mL), and 2,2-dimethoxypropane (31.39 mL, 297.10 mmol) and camphorsulfonic acid (0.68 g, 2.97 mmol) were added. The reaction was stirred for 4 h and progress was monitored by TLC. The solvents were removed under reduced pressure, and the residue was re-dissolved in ethyl acetate. The solution was washed with saturated sodium hydrogen carbonate solution, dried ($MgSO_4$), and the solvents were removed under reduced pressure to afford formamide **137** as a colourless oil (6.61 g, 94%). *N*-((4*S*,5*S*)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)formamide **137** (6.58 g, 28.1 mmol), was dissolved in aqueous hydrazine hydrate (140 mL, 85%) and the solution heated under reflux for 3 h. The solution was allowed to reach ambient temperature and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with water (2 x 200 mL) and brine (2 x 200 mL), dried (Na_2SO_4), and the solvents were removed under reduced pressure to afford aminodioxane **138** as a yellow oil (5.39 g, 87%). ν_{max} (film)/cm^{-1}: 3365, 2990, 1663, 1498. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (6H, m, 2x CH_3), 2.66 (1H, dd, *J* = 4, 2 Hz, NC*H*, H5), 3.80 (1H, dd, *J* = 12, 2 Hz, NCHC*H*H-O, H6), 4.20 (1H, dd, *J* = 12, 2 Hz, NCHCH*H*-O, H6'), 5.01 (1H, s, PhC*H*, H4), 7.16-7.28 (5H, m, 5C*H* arom., Ph gp.). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5 (*C*H_3, C7 or C8), 29.6 (*C*H_3, C7 or C8), 49.6 (*C*H, NCH, C5), 66.0 (*C*H_2, C6), 73.7 (Ar-*C*H, C4), 99.2 (*C* quat., C2), 125.7 (2 *C*H arom., C10, C11), 127.5 (*C*H arom., C14), 128.5 (2 *C*H arom., C12, C13), 139.6 (*C* quat., arom., C9).

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



140 **82**

2,2'-*Bis*(bromomethyl)biphenyl **140** (4.24g, 12.5 mmol) and amine **138** (3.1 g, 13.8 mmol) were dissolved in MeCN (30 mL), to which K_2CO_3 (5.2g, 37.6 mmol) was added at room temperature. The reaction was submitted to reflux for 24 h, cooled, diluted with CH_2Cl_2 (100 mL), extracted with water (2x 50 mL), brine (2x 50 mL), and dried over $MgSO_4$. Excess solvents were removed under reduced pressure, affording amine **141** (4.87 g, 92%). Amine **141** (3 g, 7.79 mmol) was then dissolved in CH_2Cl_2 (15 mL), to which *N*-bromosuccinimide (1.66 g, 9.35 mmol) was added, and left to stir for 5 minutes. Excess dichloromethane was removed under reduced pressure, and the remaining solid was re-dissolved in ethanol (30 mL). Sodium tetraphenylborate (2.93 g, 8.50 mmol) was dissolved in a minimum amount of acetonitrile (4 mL), and added to the stirring solution at room temperature. After 5 minutes, the reaction was stopped and excess organic solvents removed under reduced pressure, affording **82** as a pale orange powder (3.72 g, 68%, mp 187-188 °C). Further purification of **82** can be achieved by recrystallization from hot ethanol. $[\alpha]^{20}_{D}$ – 44.0° (*c* 1.01, CH_3CN). ν_{max} (film)/cm^{-1}: 3055, 3038, 2999, 1633, 1579, 1480, 1451, 1385. ^{1}H NMR (400 MHz, DMSO-d_6, 115 °C): δ = 1.71 (3H, s), 1.74 (3H, s), 4.32 (1H, d, *J* = 22 Hz), 4.49 (1H, d, *J* = 22 Hz), 4.68–4.77 (1H, m), 4.72 (1H, dd, *J* = 22, 5 Hz), 5.15 (1H, d, *J* = 22 Hz). 5.82 (1H, d, *J* = 4 Hz), 6.75 (4H, t, *J* = 12 Hz), 6.88 (8H, t, *J* = 12 Hz), 7.11-7.16 (5H, m), 7.20-7.25 (8H, m), 7.55-7.63 (3H, m), 7.64-7.69 (3H, m), 7.92-7.94 (2H, m), 9.03 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6, 120 °C): δ = 18.1, 28.4,

42.7, 60.8, 66.1, 70.5, 99.9, 120.4, 124.1, 129.4, 132.6, 133.6, 135.0, 135.2, 140.5, 163.3, 171.1.

3.4 References

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CHAPTER FOUR: APPENDIX

4.0 Appendix A: X-ray Data

The crystallographic data for the structures presented in the text are given in this section. Crystallographic analyses were carried out at the University of St. Andrews by Dr. A. M. Z. Slawin (**Compound 81**).

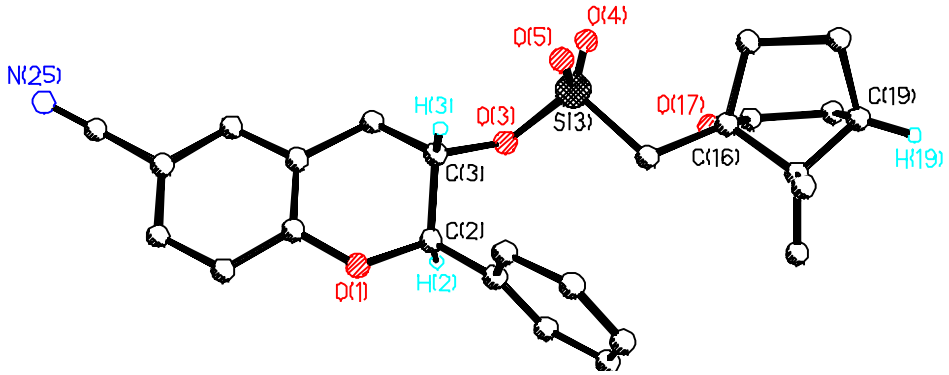


Table 1. Crystal data and structure refinement for **81**.

Data Collection method	Rigaku Mercury70 diffractometer
Empirical Formula	$C_{26}H_{27}NO_5S$
Formula Weight	465.56
Crystal Color, Habit	colorless, prism
Crystal Dimensions	0.050 X 0.050 X 0.050 mm
Crystal System	triclinic
Lattice Type	Primitive
Lattice Parameters	a = 8.081(2) Å
	b = 10.686(4) Å
	c = 14.044(5) Å
	α = 86.22(3) ^{o}
	β = 75.19(2) ^{o}
	γ = 79.31(2) ^{o}
	V = 1151.9(6) Å^3
Space Group	P1 (#1)

Z value	2
D_{calc}	1.342 g/cm^3
F_{000}	492.00
μ(MoKα)	1.787 cm^{-1}

B. Intensity Measurements

Diffractometer	Mercury70
Radiation	MoKα (λ = 0.71075 Å)
Voltage, Current	50kV, 16mA
Temperature	-180.0^{o}C
Detector Aperture	70 x 70 mm
Pixel Size	0.068 mm
$2\theta_{max}$	50.7^o
No. of Reflections Measured	Total: 7444
	Unique: 5471 (R_{int} = 0.0607)
	Friedel pairs: 1388
Corrections	Lorentz-polarization
	Absorption
	(trans. factors: 0.753 - 0.991)

C. Structure Solution and Refinement

Structure Solution	Direct Methods
Refinement	Full-matrix least-squares on F^2
Function Minimized	Σ w $(Fo^2 - Fc^2)^2$
Least Squares Weights	w = 1/ [$\sigma^2(Fo^2)$ + $(0.1214 \cdot P)^2$
	+ 0.0000 $\cdot$ P]
	where P = $(Max(Fo^2,0) + 2Fc^2)/3$
$2\theta_{max}$ cutoff	50.7^o
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	5471

No. Variables	595
Reflection/Parameter Ratio	9.19
Residuals: R1 (I>2.00σ(I))	0.0683
Residuals: R (All reflections)	0.1067
Residuals: wR2 (All reflections)	0.1993
Goodness of Fit Indicator	0.804
Flack Parameter (Friedel pairs = 1388)	-0.08(14)
Max Shift/Error in Final Cycle	0.063
Maximum peak in Final Diff. Map	0.45 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.30 $e^-/Å^3$

Table 2. Atomic coordinates and equivalent isotopic displacement parameters ($Å^2$) for **81**

atom	x	y	z	B_{eq}
S3	-0.0811(3)	0.4327(2)	0.7115(2)	3.53(5)
S33	0.4920(3)	0.6206(2)	0.4160(2)	3.75(5)
O1	0.0467(7)	0.8693(5)	0.6573(4)	3.31(11)
O3	-0.1449(7)	0.5804(5)	0.7049(5)	4.18(12)
O4	-0.2100(11)	0.3705(7)	0.6956(6)	7.8(3)
O5	0.0916(10)	0.4010(6)	0.6538(5)	5.8(2)
O17	-0.3959(8)	0.3209(7)	0.9146(5)	5.5(2)
O31	0.4102(7)	0.1724(5)	0.4543(4)	3.05(10)
O33	0.3961(7)	0.5119(5)	0.4775(4)	3.35(11)
O34	0.6649(8)	0.5686(8)	0.3743(7)	7.9(3)
O35	0.4528(12)	0.7209(6)	0.4830(6)	7.5(3)
O47	0.0929(8)	0.7651(6)	0.2470(5)	5.4(2)
N25	-0.1823(10)	1.1199(7)	0.2485(6)	4.7(2)
N55	0.5853(9)	-0.0759(7)	0.8767(6)	4.3(2)
C2	-0.0285(11)	0.7657(8)	0.7100(6)	3.6(2)

C3	-0.0406(10)	0.6672(7)	0.6403(6)	2.6(2)
C4	-0.1344(11)	0.7218(8)	0.5641(7)	4.0(2)
C5	-0.1371(9)	0.9034(8)	0.4411(6)	3.2(2)
C6	-0.1062(9)	1.0263(8)	0.4104(6)	2.8(2)
C7	-0.0340(10)	1.0937(8)	0.4633(7)	3.5(2)
C8	0.0140(11)	1.0418(8)	0.5472(7)	3.8(2)
C9	0.0848(10)	0.7116(7)	0.7813(7)	3.1(2)
C10	0.0160(12)	0.7154(8)	0.8801(7)	3.9(2)
C11	0.1139(13)	0.6640(8)	0.9446(7)	4.1(2)
C12	0.2832(13)	0.6046(8)	0.9098(7)	4.0(2)
C13	0.3570(12)	0.5964(9)	0.8101(8)	4.5(2)
C14	0.2561(12)	0.6516(8)	0.7444(7)	4.1(2)
C15	-0.0729(10)	0.4148(7)	0.8354(6)	2.9(2)
C16	-0.0761(9)	0.2815(7)	0.8782(6)	2.6(2)
C17	-0.2617(11)	0.2545(8)	0.9252(6)	3.5(2)
C18	-0.2446(10)	0.1423(8)	0.9930(7)	3.8(2)
C19	-0.0481(10)	0.1145(8)	0.9856(7)	3.4(2)
C20	-0.0010(10)	0.2482(7)	0.9701(6)	3.0(2)
C21	0.0378(12)	0.0518(8)	0.8845(7)	4.1(2)
C22	0.0126(11)	0.1634(7)	0.8118(7)	3.4(2)
C23	0.1963(9)	0.2462(8)	0.9494(7)	3.8(2)
C24	-0.0889(10)	0.3389(8)	1.0562(7)	3.9(2)
C25	-0.1502(10)	1.0786(8)	0.3201(7)	3.7(2)
C27	-0.0907(9)	0.8504(8)	0.5255(6)	3.1(2)
C28	-0.0114(10)	0.9186(7)	0.5766(6)	2.8(2)
C29	0.4464(10)	0.1268(7)	0.5398(6)	2.9(2)
C30	0.5011(9)	0.2029(7)	0.5995(6)	2.5(2)

C32	0.3412(11)	0.3058(7)	0.4520(6)	3.2(2)
C33	0.4752(9)	0.3775(7)	0.4716(6)	2.30(13)
C34	0.5182(12)	0.3392(7)	0.5706(7)	3.7(2)
C35	0.5372(9)	0.1504(8)	0.6880(6)	3.0(2)
C36	0.5152(10)	0.0249(8)	0.7164(6)	3.0(2)
C37	0.4617(10)	-0.0504(7)	0.6540(6)	2.9(2)
C38	0.4279(10)	0.0019(7)	0.5685(6)	3.2(2)
C39	0.2944(11)	0.3450(7)	0.3573(6)	3.1(2)
C40	0.4136(11)	0.3217(7)	0.2670(7)	3.3(2)
C41	0.3690(11)	0.3646(8)	0.1782(7)	3.6(2)
C42	0.2012(12)	0.4307(8)	0.1832(7)	3.9(2)
C43	0.0821(12)	0.4525(8)	0.2723(7)	3.9(2)
C44	0.1260(11)	0.4081(8)	0.3579(7)	3.8(2)
C45	0.3722(11)	0.6570(7)	0.3273(6)	3.5(2)
C46	0.3850(10)	0.7751(8)	0.2614(6)	3.2(2)
C47	0.2307(11)	0.8043(9)	0.2136(8)	4.2(2)
C48	0.2722(12)	0.8920(9)	0.1286(8)	5.1(2)
C49	0.4563(11)	0.9120(9)	0.1331(7)	4.2(2)
C50	0.5355(11)	0.7792(8)	0.1675(6)	3.4(2)
C51	0.4254(13)	0.9953(9)	0.2219(7)	4.6(2)
C52	0.3822(11)	0.9016(8)	0.3112(7)	3.6(2)
C53	0.7121(11)	0.7778(10)	0.1867(8)	4.9(2)
C54	0.5518(12)	0.6715(9)	0.0958(7)	4.6(2)
C55	0.5560(10)	-0.0307(8)	0.8054(7)	3.3(2)

$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$

Table 3. Bond Lengths [Å] for **81**.

atom	atom	distance	atom	atom	distance
S3	O3	1.570(6)	S3	O4	1.404(10)
S3	O5	1.416(7)	S3	C15	1.755(9)
S33	O33	1.599(6)	S33	O34	1.393(7)
S33	O35	1.411(7)	S33	C45	1.747(10)
O1	C2	1.432(10)	O1	C28	1.373(10)
O3	C3	1.477(9)	O17	C17	1.219(11)
O31	C29	1.347(10)	O31	C32	1.432(9)
O33	C33	1.458(8)	O47	C47	1.231(11)
N25	C25	1.142(13)	N55	C55	1.144(12)
C2	C3	1.516(13)	C2	C9	1.540(13)
C3	C4	1.494(13)	C4	C27	1.514(12)
C5	C6	1.401(11)	C5	C27	1.388(12)
C6	C7	1.364(13)	C6	C25	1.452(13)
C7	C8	1.384(13)	C8	C28	1.389(11)
C9	C10	1.357(12)	C9	C14	1.395(11)
C10	C11	1.375(14)	C11	C12	1.374(13)
C12	C13	1.377(13)	C13	C14	1.413(15)
C15	C16	1.511(10)	C16	C17	1.549(11)
C16	C20	1.556(12)	C16	C22	1.567(10)
C17	C18	1.489(12)	C18	C19	1.538(12)
C19	C20	1.533(12)	C19	C21	1.549(12)
C20	C23	1.542(11)	C20	C24	1.538(11)
C21	C22	1.537(12)	C27	C28	1.391(13)
C29	C30	1.405(12)	C29	C38	1.392(11)
C30	C34	1.507(11)	C30	C35	1.406(11)
C32	C33	1.524(13)	C32	C39	1.487(12)
C33	C34	1.530(13)	C35	C36	1.404(12)

C36	C37	1.421(13)	C36	C55	1.436(13)
C37	C38	1.361(12)	C39	C40	1.387(11)
C39	C44	1.400(12)	C40	C41	1.410(13)
C41	C42	1.395(12)	C42	C43	1.373(12)
C43	C44	1.370(15)	C45	C46	1.518(11)
C46	C47	1.536(14)	C46	C50	1.554(10)
C46	C52	1.556(12)	C47	C48	1.476(14)
C48	C49	1.560(15)	C49	C50	1.545(12)
C49	C51	1.521(14)	C50	C53	1.515(14)
C50	C54	1.544(13)	C51	C52	1.561(13)

Table 4. Bond Angles [^{o}] for **81**.

atom	atom	atom	angle	atom	atom	atom	angle
O3	S3	O4	108.5(4)	O3	S3	O5	109.6(4)
O3	S3	C15	100.6(4)	O4	S3	O5	119.4(5)
O4	S3	C15	110.0(4)	O5	S3	C15	107.1(4)
O33	S33	O34	109.1(4)	O33	S33	O35	103.8(4)
O33	S33	C45	99.8(4)	O34	S33	O35	119.6(6)
O34	S33	C45	111.9(5)	O35	S33	C45	110.4(5)
C2	O1	C28	117.4(7)	S3	O3	C3	123.2(5)
C29	O31	C32	115.5(6)	S33	O33	C33	122.5(4)
O1	C2	C3	111.4(7)	O1	C2	C9	106.2(7)
C3	C2	C9	113.0(7)	O3	C3	C2	103.9(6)
O3	C3	C4	107.9(7)	C2	C3	C4	113.3(7)
C3	C4	C27	112.1(8)	C6	C5	C27	119.0(9)
C5	C6	C7	120.6(8)	C5	C6	C25	118.3(8)
C7	C6	C25	121.1(8)	C6	C7	C8	121.1(8)
C7	C8	C28	118.8(9)	C2	C9	C10	120.3(7)
C2	C9	C14	120.0(8)	C10	C9	C14	119.5(9)
C9	C10	C11	121.1(8)	C10	C11	C12	120.3(8)

C11	C12	C13	120.5(10)	C12	C13	C14	118.7(8)
C9	C14	C13	119.9(8)	S3	C15	C16	115.2(6)
C15	C16	C17	113.6(6)	C15	C16	C20	116.7(7)
C15	C16	C22	120.2(6)	C17	C16	C20	97.6(6)
C17	C16	C22	103.7(7)	C20	C16	C22	101.9(6)
O17	C17	C16	125.3(8)	O17	C17	C18	127.2(8)
C16	C17	C18	107.2(7)	C17	C18	C19	102.3(7)
C18	C19	C20	102.2(6)	C18	C19	C21	105.8(8)
C20	C19	C21	103.4(6)	C16	C20	C19	94.9(7)
C16	C20	C23	114.1(6)	C16	C20	C24	113.4(6)
C19	C20	C23	112.8(6)	C19	C20	C24	114.8(6)
C23	C20	C24	106.9(8)	C19	C21	C22	102.5(6)
C16	C22	C21	104.9(7)	N25	C25	C6	179.0(9)
C4	C27	C5	119.9(8)	C4	C27	C28	120.4(8)
C5	C27	C28	119.6(8)	O1	C28	C8	116.4(8)
O1	C28	C27	122.7(7)	C8	C28	C27	120.9(8)
O31	C29	C30	121.2(7)	O31	C29	C38	118.6(8)
C30	C29	C38	120.2(8)	C29	C30	C34	120.9(8)
C29	C30	C35	118.8(7)	C34	C30	C35	120.3(8)
O31	C32	C33	107.6(7)	O31	C32	C39	111.3(7)
C33	C32	C39	112.8(7)	O33	C33	C32	106.6(6)
O33	C33	C34	106.8(6)	C32	C33	C34	112.3(7)
C30	C34	C33	112.2(8)	C30	C35	C36	120.1(8)
C35	C36	C37	119.9(8)	C35	C36	C55	120.5(9)
C37	C36	C55	119.5(8)	C36	C37	C38	119.2(7)
C29	C38	C37	121.8(9)	C32	C39	C40	122.0(8)
C32	C39	C44	119.8(7)	C40	C39	C44	118.3(8)
C39	C40	C41	121.1(8)	C40	C41	C42	118.3(7)
C41	C42	C43	120.8(9)	C42	C43	C44	120.3(8)
C39	C44	C43	121.1(8)	S33	C45	C46	121.7(7)

C45	C46	C47	110.1(8)	C45	C46	C50	122.0(6)
C45	C46	C52	117.1(7)	C47	C46	C50	99.0(7)
C47	C46	C52	104.5(7)	C50	C46	C52	101.4(7)
O47	C47	C46	123.5(9)	O47	C47	C48	127.4(10)
C46	C47	C48	108.9(8)	C47	C48	C49	100.9(8)
C48	C49	C50	102.2(8)	C48	C49	C51	105.2(7)
C50	C49	C51	103.9(8)	C46	C50	C49	94.2(6)
C46	C50	C53	114.9(8)	C46	C50	C54	112.5(7)
C49	C50	C53	112.1(8)	C49	C50	C54	114.0(8)
C53	C50	C54	108.7(7)	C49	C51	C52	103.3(7)
C46	C52	C51	103.3(7)	N55	C55	C36	178.6(9)

Table 5. Anisotropic displacement parameters for **81**.

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S3	0.063(2)	0.0399(13)	0.0358(13)	-0.0196(11)	-0.0169(11)	0.0115(9)
S33	0.071(2)	0.0340(12)	0.050(2)	-0.0234(11)	-0.0309(12)	0.0127(10)
O1	0.067(4)	0.027(3)	0.035(4)	-0.013(3)	-0.019(3)	0.012(3)
O3	0.060(4)	0.043(4)	0.062(4)	-0.020(3)	-0.024(3)	0.021(3)
O4	0.172(8)	0.086(6)	0.098(6)	-0.092(6)	-0.102(6)	0.039(5)
O5	0.104(5)	0.047(4)	0.059(5)	-0.017(4)	0.000(4)	0.008(3)
O17	0.040(4)	0.092(5)	0.080(5)	-0.015(4)	-0.027(4)	0.034(4)
O31	0.056(4)	0.026(3)	0.037(4)	-0.009(3)	-0.016(3)	0.002(3)
O33	0.057(4)	0.033(3)	0.036(4)	-0.012(3)	-0.006(3)	0.002(3)
O34	0.043(4)	0.114(6)	0.138(8)	-0.019(4)	-0.026(5)	0.077(6)
O35	0.208(9)	0.042(4)	0.067(5)	-0.035(5)	-0.082(6)	0.012(4)
O47	0.057(4)	0.071(5)	0.085(6)	-0.015(4)	-0.032(4)	0.007(4)
N25	0.066(5)	0.058(5)	0.058(6)	-0.020(4)	-0.024(5)	0.028(5)
N55	0.063(5)	0.055(5)	0.044(5)	-0.002(4)	-0.021(4)	0.005(4)
C2	0.055(5)	0.044(5)	0.043(6)	-0.018(4)	-0.021(5)	0.013(4)
C3	0.041(4)	0.034(5)	0.031(5)	-0.012(4)	-0.021(4)	0.013(4)

C4	0.060(5)	0.053(6)	0.049(6)	-0.019(5)	-0.032(5)	0.019(5)
C5	0.038(5)	0.034(5)	0.050(6)	-0.011(4)	-0.014(4)	0.015(4)
C6	0.032(4)	0.041(5)	0.029(5)	-0.003(4)	-0.007(4)	0.009(4)
C7	0.040(5)	0.033(5)	0.051(6)	-0.002(4)	-0.004(4)	0.019(4)
C8	0.058(5)	0.029(5)	0.052(7)	-0.003(4)	-0.009(5)	0.001(4)
C9	0.048(5)	0.028(5)	0.043(6)	-0.007(4)	-0.016(5)	0.010(4)
C10	0.072(6)	0.026(5)	0.049(7)	-0.011(4)	-0.013(5)	-0.005(4)
C11	0.097(8)	0.039(5)	0.027(5)	-0.018(5)	-0.021(5)	0.006(4)
C12	0.076(7)	0.043(6)	0.042(6)	-0.016(5)	-0.033(5)	0.007(5)
C13	0.064(6)	0.046(6)	0.067(8)	-0.009(5)	-0.025(6)	-0.005(5)
C14	0.079(7)	0.053(6)	0.029(5)	-0.037(5)	-0.010(5)	0.006(4)
C15	0.040(4)	0.028(4)	0.047(5)	-0.008(4)	-0.020(4)	0.009(4)
C16	0.039(4)	0.029(4)	0.035(5)	-0.009(4)	-0.013(4)	0.010(4)
C17	0.059(6)	0.051(6)	0.030(5)	-0.024(5)	-0.016(4)	0.008(4)
C18	0.053(5)	0.057(6)	0.042(6)	-0.026(5)	-0.015(5)	0.016(5)
C19	0.056(5)	0.034(5)	0.039(6)	-0.013(4)	-0.012(4)	0.009(4)
C20	0.046(5)	0.032(5)	0.038(5)	-0.007(4)	-0.016(4)	0.011(4)
C21	0.076(6)	0.026(5)	0.053(7)	-0.004(5)	-0.018(5)	0.005(4)
C22	0.059(5)	0.025(5)	0.046(6)	-0.008(4)	-0.015(5)	0.001(4)
C23	0.037(5)	0.055(6)	0.053(6)	-0.010(4)	-0.012(4)	0.003(5)
C24	0.052(5)	0.050(6)	0.052(6)	-0.021(4)	-0.011(5)	-0.012(5)
C25	0.040(5)	0.045(6)	0.053(7)	-0.010(4)	-0.013(5)	0.023(5)
C27	0.034(4)	0.043(5)	0.037(6)	-0.005(4)	-0.007(4)	0.016(4)
C28	0.045(5)	0.034(5)	0.030(5)	-0.011(4)	-0.012(4)	0.010(4)
C29	0.043(5)	0.033(5)	0.030(5)	-0.001(4)	-0.006(4)	0.003(4)
C30	0.036(4)	0.029(5)	0.028(5)	-0.003(4)	-0.006(4)	-0.003(4)
C32	0.060(5)	0.034(5)	0.032(5)	-0.009(4)	-0.017(4)	0.005(4)
C33	0.036(4)	0.017(4)	0.033(5)	-0.008(3)	-0.003(4)	0.004(3)
C34	0.073(6)	0.023(5)	0.052(6)	-0.015(4)	-0.029(5)	0.014(4)
C35	0.038(4)	0.045(6)	0.032(5)	-0.002(4)	-0.013(4)	0.005(4)

C36	0.035(4)	0.041(5)	0.035(5)	-0.007(4)	-0.004(4)	0.005(4)
C37	0.051(5)	0.028(5)	0.035(5)	-0.013(4)	-0.013(4)	0.003(4)
C38	0.051(5)	0.033(5)	0.038(6)	-0.009(4)	-0.014(4)	0.004(4)
C39	0.066(6)	0.027(5)	0.032(5)	-0.025(4)	-0.016(4)	0.004(4)
C40	0.053(5)	0.030(5)	0.044(6)	-0.010(4)	-0.017(5)	0.005(4)
C41	0.062(6)	0.040(5)	0.042(6)	-0.021(5)	-0.019(5)	0.001(4)
C42	0.072(6)	0.050(6)	0.034(6)	-0.022(5)	-0.022(5)	0.014(4)
C43	0.060(6)	0.042(5)	0.061(7)	-0.023(5)	-0.031(6)	0.005(5)
C44	0.054(6)	0.039(5)	0.056(7)	-0.020(5)	-0.013(5)	0.003(5)
C45	0.073(6)	0.029(5)	0.040(5)	-0.022(4)	-0.026(5)	0.010(4)
C46	0.050(5)	0.042(5)	0.028(5)	-0.005(4)	-0.010(4)	0.002(4)
C47	0.045(5)	0.050(6)	0.071(7)	-0.013(5)	-0.027(5)	0.005(5)
C48	0.082(7)	0.060(6)	0.063(7)	-0.018(5)	-0.038(6)	0.017(5)
C49	0.070(6)	0.059(6)	0.037(6)	-0.019(5)	-0.026(5)	0.015(5)
C50	0.060(5)	0.036(5)	0.031(5)	-0.005(4)	-0.008(4)	0.002(4)
C51	0.085(7)	0.042(6)	0.060(7)	-0.020(5)	-0.038(6)	0.004(5)
C52	0.056(5)	0.042(5)	0.044(6)	-0.011(4)	-0.016(5)	-0.006(4)
C53	0.048(5)	0.075(7)	0.067(7)	-0.026(5)	-0.008(5)	-0.007(6)
C54	0.066(6)	0.065(6)	0.039(6)	-0.029(5)	0.008(5)	-0.013(5)
C55	0.046(5)	0.050(6)	0.035(6)	-0.011(4)	-0.016(4)	0.005(5)

The general temperature factor expression: $\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$

Table 6. Hydrogen coordinates for **81**.

Atom	x	y	z	B_{iso}
H2	-0.1484	0.8001	0.7494	4.28
H3	0.0778	0.6202	0.6085	3.14
H4A	-0.1032	0.6624	0.5086	4.77
H4B	-0.2612	0.7308	0.5929	4.77

H5	-0.1889	0.8571	0.4047	3.81
H7	-0.0164	1.1776	0.4422	4.22
H8	0.0633	1.0895	0.5841	4.52
H10	-0.1018	0.7542	0.9050	4.63
H11	0.0644	0.6695	1.0136	4.97
H12	0.3497	0.5689	0.9549	4.75
H13	0.4735	0.5544	0.7859	5.45
H14	0.3050	0.6478	0.6753	4.86
H15A	0.0344	0.4418	0.8418	3.48
H15B	-0.1729	0.4729	0.8752	3.48
H18A	-0.2833	0.0691	0.9707	4.61
H18B	-0.3121	0.1630	1.0611	4.61
H19	-0.0144	0.0654	1.0429	4.04
H21A	-0.0213	-0.0178	0.8744	4.92
H21B	0.1626	0.0176	0.8780	4.92
H22A	0.1259	0.1773	0.7688	4.08
H22B	-0.0626	0.1469	0.7700	4.08
H23A	0.2364	0.2157	1.0084	4.55
H23B	0.2205	0.3325	0.9320	4.55
H23C	0.2573	0.1893	0.8947	4.55
H24A	-0.0534	0.3037	1.1156	4.72
H24B	-0.2154	0.3486	1.0680	4.72
H24C	-0.0537	0.4223	1.0398	4.72
H32	0.2334	0.3235	0.5066	3.90
H33	0.5834	0.3642	0.4169	2.76
H34A	0.6387	0.3506	0.5666	4.41
H34B	0.4391	0.3960	0.6222	4.41

H35	0.5766	0.1999	0.7287	3.65
H37	0.4497	-0.1362	0.6717	3.50
H38	0.3906	-0.0482	0.5272	3.80
H40	0.5271	0.2760	0.2650	3.91
H41	0.4511	0.3489	0.1166	4.31
H42	0.1688	0.4611	0.1242	4.69
H43	-0.0313	0.4985	0.2746	4.73
H44	0.0407	0.4203	0.4187	4.58
H45A	0.4028	0.5830	0.2834	4.16
H45B	0.2482	0.6620	0.3623	4.16
H48A	0.1881	0.9731	0.1369	6.12
H48B	0.2754	0.8528	0.0661	6.12
H49	0.5270	0.9448	0.0704	5.00
H51A	0.5305	1.0305	0.2216	5.48
H51B	0.3270	1.0664	0.2233	5.48
H52A	0.2664	0.9321	0.3550	4.34
H52B	0.4708	0.8908	0.3498	4.34
H53A	0.7441	0.7001	0.2239	5.88
H53B	0.7072	0.8525	0.2249	5.88
H53C	0.7990	0.7799	0.1238	5.88
H54A	0.4425	0.6783	0.0761	5.48
H54B	0.5766	0.5888	0.1286	5.48
H54C	0.6466	0.6791	0.0374	5.48

Table 7. Bond lengths involving hydrogens (Å) for **81**.

Atom	atom	distance	atom	atom	distance
C2	H2	1.000	C3	H3	1.000

C4	H4A	0.990	C4	H4B	0.990
C5	H5	0.950	C7	H7	0.950
C8	H8	0.950	C10	H10	0.950
C11	H11	0.950	C12	H12	0.950
C13	H13	0.950	C14	H14	0.950
C15	H15A	0.990	C15	H15B	0.990
C18	H18A	0.990	C18	H18B	0.990
C19	H19	1.000	C21	H21A	0.990
C21	H21B	0.990	C22	H22A	0.990
C22	H22B	0.990	C23	H23A	0.980
C23	H23B	0.980	C23	H23C	0.980
C24	H24A	0.980	C24	H24B	0.980
C24	H24C	0.980	C32	H32	1.000
C33	H33	1.000	C34	H34A	0.990
C34	H34B	0.990	C35	H35	0.950
C37	H37	0.950	C38	H38	0.950
C40	H40	0.950	C41	H41	0.950
C42	H42	0.950	C43	H43	0.950
C44	H44	0.950	C45	H45A	0.990
C45	H45B	0.990	C48	H48A	0.990
C48	H48B	0.990	C49	H49	1.000
C51	H51A	0.990	C51	H51B	0.990
C52	H52A	0.990	C52	H52B	0.990
C53	H53A	0.980	C53	H53B	0.980
C53	H53C	0.980	C54	H54A	0.980
C54	H54B	0.980	C54	H54C	0.980

Table 8. Torsion Angles (^{o}) for **81**.

(Those having bond angles > 160 or < 20 degrees are excluded.)

atom1	atom2	atom3	atom4	angle	atom1	atom2	atom3	atom4	angle
O4	S3	O3	C3	-127.3(6)	O5	S3	O3	C3	4.8(7)
O3	S3	C15	C16	159.9(5)	C15	S3	O3	C3	117.3(6)
O4	S3	C15	C16	45.6(6)	O5	S3	C15	C16	85.6(6)
O34	S33	O33	C33	-10.8(7)	O35	S33	O33	C33	-139.4(6)
O33	S33	C45	C46	167.0(5)	C45	S33	O33	C33	106.6(5)
O34	S33	C45	C46	-77.7(7)	O35	S33	C45	C46	58.2(7)
C2	O1	C28	C8	158.4(5)	C2	O1	C28	C27	-21.9(8)
C28	O1	C2	C3	44.8(8)	C28	O1	C2	C9	168.3(5)
S3	O3	C3	C2	-124.7(6)	S3	O3	C3	C4	114.7(6)
C29	O31	C32	C33	59.7(7)	C29	O31	C32	C39	-176.1(6)
C32	O31	C29	C30	-31.9(9)	C32	O31	C29	C38	147.8(6)
S33	O33	C33	C32	-129.5(5)	S33	O33	C33	C34	110.2(5)
O1	C2	C3	O3	-171.2(6)	O1	C2	C3	C4	-54.3(8)
O1	C2	C9	C10	117.1(7)	O1	C2	C9	C14	-66.7(8)
C3	C2	C9	C10	-120.4(7)	C3	C2	C9	C14	55.8(9)
C9	C2	C3	O3	69.2(7)	C9	C2	C3	C4	-173.9(6)
O3	C3	C4	C27	153.7(5)	C2	C3	C4	C27	39.2(8)
C3	C4	C27	C5	166.9(6)	C3	C4	C27	C28	-16.0(9)
C6	C5	C27	C4	175.7(5)	C6	C5	C27	C28	-1.4(9)
C27	C5	C6	C7	-0.9(9)	C27	C5	C6	C25	178.0(6)
C5	C6	C7	C8	1.4(10)	C25	C6	C7	C8	-177.5(6)
C6	C7	C8	C28	0.5(10)	C7	C8	C28	O1	176.7(6)
C7	C8	C28	C27	-2.9(10)	C2	C9	C10	C11	178.0(7)
C2	C9	C14	C13	-176.8(7)	C10	C9	C14	C13	-0.6(13)
C14	C9	C10	C11	1.8(13)	C9	C10	C11	C12	-1.6(14)

C10	C11	C12	C13	0.3(14)	C11	C12	C13	C14	0.8(14)
C12	C13	C14	C9	-0.6(14)	S3	C15	C16	C17	-89.9(6)
S3	C15	C16	C20	157.7(4)	S3	C15	C16	C22	33.6(9)
C15	C16	C17	O17	13.5(12)	C15	C16	C17	C18	-160.5(6)
C15	C16	C20	C19	175.9(5)	C15	C16	C20	C23	-66.4(7)
C15	C16	C20	C24	56.2(8)	C15	C16	C22	C21	161.5(7)
C17	C16	C20	C19	54.6(6)	C17	C16	C20	C23	172.3(6)
C17	C16	C20	C24	-65.1(7)	C20	C16	C17	O17	137.1(8)
C20	C16	C17	C18	-36.9(7)	C17	C16	C22	C21	-70.3(7)
C22	C16	C17	O17	-118.6(9)	C22	C16	C17	C18	67.4(8)
C20	C16	C22	C21	30.6(7)	C22	C16	C20	C19	-51.1(6)
C22	C16	C20	C23	66.5(7)	C22	C16	C20	C24	-170.8(6)
O17	C17	C18	C19	-170.9(9)	C16	C17	C18	C19	3.0(8)
C17	C18	C19	C20	33.1(8)	C17	C18	C19	C21	-74.8(7)
C18	C19	C20	C16	-55.3(6)	C18	C19	C20	C23	-174.0(6)
C18	C19	C20	C24	63.2(8)	C18	C19	C21	C22	70.4(8)
C20	C19	C21	C22	-36.7(8)	C21	C19	C20	C16	54.4(7)
C21	C19	C20	C23	-64.3(8)	C21	C19	C20	C24	173.0(6)
C19	C21	C22	C16	3.1(9)	C4	C27	C28	O1	6.7(10)
C4	C27	C28	C8	-173.7(6)	C5	C27	C28	O1	-176.2(6)
C5	C27	C28	C8	3.4(10)	O31	C29	C30	C34	1.1(9)
O31	C29	C30	C35	-180.0(5)	O31	C29	C38	C37	-179.8(5)
C30	C29	C38	C37	-0.1(10)	C38	C29	C30	C34	-178.7(6)
C38	C29	C30	C35	0.3(9)	C29	C30	C34	C33	-1.7(9)
C29	C30	C35	C36	-1.2(9)	C34	C30	C35	C36	177.7(6)
C35	C30	C34	C33	179.4(6)	O31	C32	C33	O33	-175.1(5)
O31	C32	C33	C34	-58.5(7)	O31	C32	C39	C40	-55.1(10)

O31	C32	C39	C44	125.3(7)	C33	C32	C39	C40	66.1(9)
C33	C32	C39	C44	-113.5(7)	C39	C32	C33	O33	61.6(7)
C39	C32	C33	C34	178.3(5)	O33	C33	C34	C30	146.9(6)
C32	C33	C34	C30	30.3(8)	C30	C35	C36	C37	2.0(9)
C30	C35	C36	C55	178.4(6)	C35	C36	C37	C38	-1.8(10)
C55	C36	C37	C38	-178.2(6)	C36	C37	C38	C29	0.9(10)
C32	C39	C40	C41	-177.1(7)	C32	C39	C44	C43	175.8(7)
C40	C39	C44	C43	-3.8(12)	C44	C39	C40	C41	2.5(12)
C39	C40	C41	C42	-0.4(12)	C40	C41	C42	C43	-0.5(13)
C41	C42	C43	C44	-0.7(14)	C42	C43	C44	C39	2.9(14)
S33	C45	C46	C47	-163.4(5)	S33	C45	C46	C50	81.4(9)
S33	C45	C46	C52	-44.2(8)	C45	C46	C47	O47	21.4(11)
C45	C46	C47	C48	-162.7(6)	C45	C46	C50	C49	173.3(8)
C45	C46	C50	C53	-69.9(10)	C45	C46	C50	C54	55.2(11)
C45	C46	C52	C51	171.8(6)	C47	C46	C50	C49	52.6(7)
C47	C46	C50	C53	169.4(6)	C47	C46	C50	C54	-65.5(7)
C50	C46	C47	O47	150.5(8)	C50	C46	C47	C48	-33.6(8)
C47	C46	C52	C51	-66.1(7)	C52	C46	C47	O47	-105.2(9)
C52	C46	C47	C48	70.7(7)	C50	C46	C52	C51	36.4(7)
C52	C46	C50	C49	-54.2(7)	C52	C46	C50	C53	62.6(8)
C52	C46	C50	C54	-172.3(6)	O47	C47	C48	C49	174.6(9)
C46	C47	C48	C49	-1.0(9)	C47	C48	C49	C50	36.0(8)
C47	C48	C49	C51	-72.3(8)	C48	C49	C50	C46	-55.6(7)
C48	C49	C50	C53	-174.7(6)	C48	C49	C50	C54	61.3(8)
C48	C49	C51	C52	74.6(8)	C50	C49	C51	C52	-32.4(8)
C51	C49	C50	C46	53.7(8)	C51	C49	C50	C53	-65.4(8)
C51	C49	C50	C54	170.6(7)	C49	C51	C52	C46	-2.7(9)

4.1 Appendix B: Determining enantiomeric excesses by HPLC or by Chiral Shift Experiments of ^{1}H NMR spectra

Determination of enantiomeric excess of **56**, **60**, **68**, **70** by HPLC.

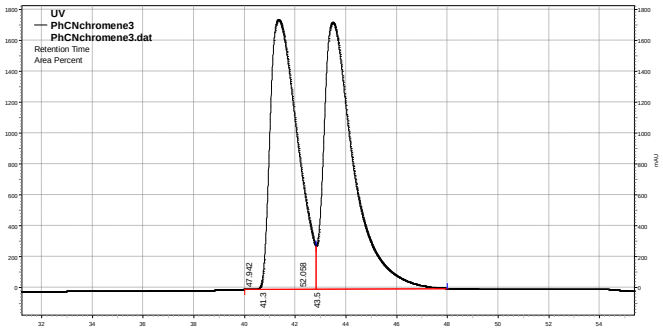
HPLC conditions: Column Eurocel 01 280 x 4.6 mm, 5 µm particle size.

Flow: 0.5 mL / min

Hexane:Isopropanol: 99.5:0.5

Area % Report for racemic 56

Data File: C:\EZChrom Elite\Enterprise\Projects\Dave\PhCNchromene3.dat

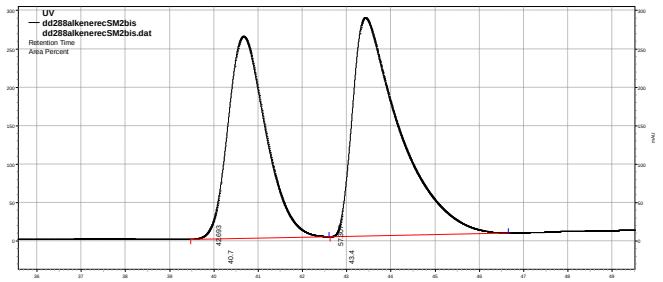


UV Results

Retention Time	Area	Area %	Height	Height %
41.337	514307753	47.94	6969959	50.28
43.470	558463298	52.06	6891331	49.72
Totals	1072771051	100.00	13861290	100.00

Area % Report for enantioenriched 56

Data File: C:\EZChrom Elite\Enterprise\Projects\Dave\paper2011\dd288alkenerecSM2bis.dat



UV Results

Retention Time	Area	Area %	Height	Height %
40.663	62108870	42.69	1051182	48.05
43.417	83370682	57.31	1136548	51.95
Totals	145479552	100.00	2187730	100.00

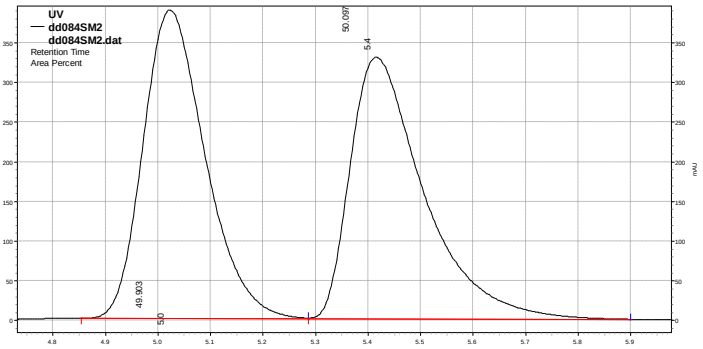
HPLC conditions: Column Eurocel 01 280 x 4.6 mm, 5 µm particle size.

Flow: 1 mL / min

Hexane:Isopropanol: 90:10

Area % Report for racemic 60

Data File: C:\EZChrom Elite\Enterprise\Projects\Dave\1st year phd\dd084SM2.dat

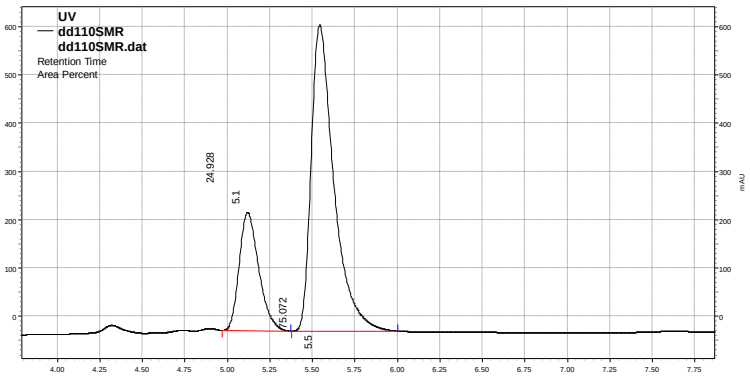


UV Results

Retention Time	Area	Area %	Height	Height %
5.023	12826528	49.90	1555434	54.11
5.417	12876177	50.10	1319204	45.89
Totals	25702705	100.00	2874638	100.00

Area % Report for enantioenriched 60

Data File: C:\EZChrom Elite\Enterprise\Projects\Dave\1st year phd\dd110SMR.dat



UV Results

Retention Time	Area	Area %	Height	Height %
5.117	7847582	24.93	979532	27.86
5.543	23633357	75.07	2535759	72.14
Totals	31480939	100.00	3515291	100.00

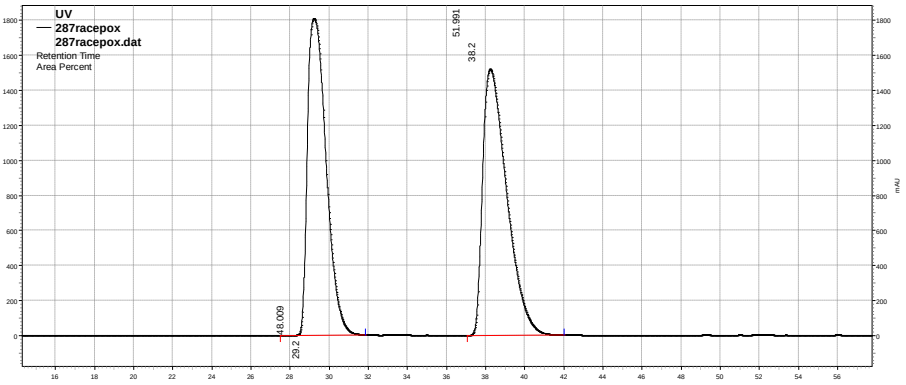
HPLC conditions: Column Eurocel 01 280 x 4.6 mm, 5 µm particle size.

Flow: 1 mL / min

Hexane:Isopropanol: 90:10

Area % Report for racemic 68

Data File: C:\EZChrom Elite\Enterprise\Projects\Dave\paper2011\287racepox.dat

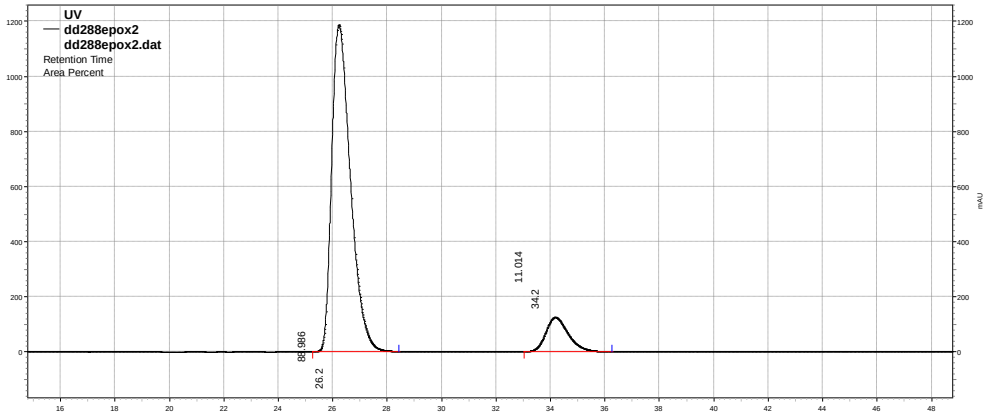


UV Results

Retention Time	Area	Area %	Height	Height %
29.213	479698387	48.01	7228572	54.34
38.227	519477371	51.99	6072709	45.66
Totals	999175758	100.00	13301281	100.00

Area % Report for enantioenriched 68

Data File: C:\EZChrom Elite\Enterprise\Projects\Dave\paper2011\dd288epox.dat



UV Results

Retention Time	Area	Area %	Height	Height %
26.227	227664852	88.99	4739603	90.55
34.170	28179676	11.01	494739	9.45
Totals	255844528	100.00	5234342	100.00

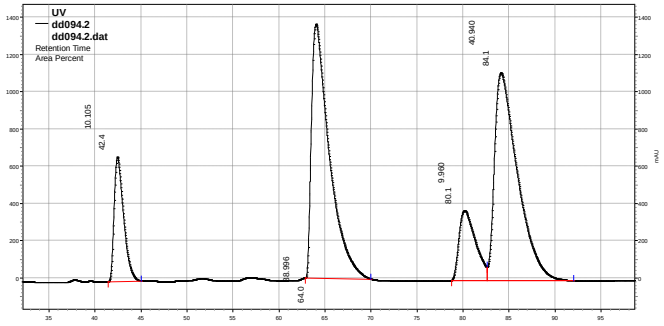
HPLC conditions: Column Eurocel 01 280 x 4.6 mm, 5 µm particle size.

Flow: 0.5 mL / min

Hexane:Isopropanol: 99.5:0.5

Area % Report for racemic 70

Data File: C:\EZChrom Elite\Enterprise\Projects\Dave\1st year phd\dd094.2.dat

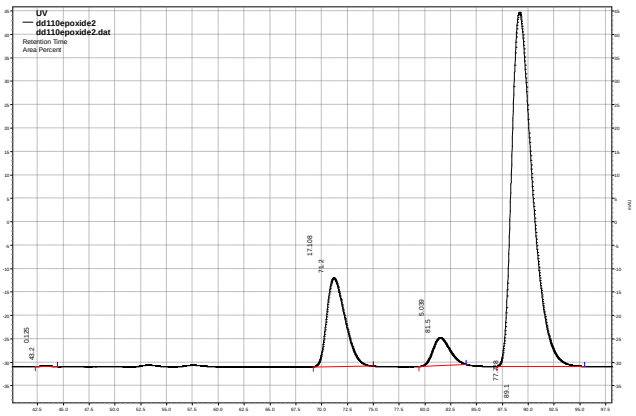


UV Results

Retention Time	Area	Area %	Height	Height %
42.440	190699438	10.10	2671724	18.95
64.013	735938851	39.00	5454226	38.69
80.140	187967029	9.96	1504738	10.68
84.103	772625826	40.94	4465081	31.68
Totals	1887231144	100.00	14095769	100.00

Area % Report for enantioenriched 70

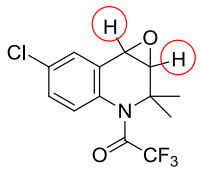
Data File: C:\EZChrom Elite\Enterprise\Projects\Dave\1st year phd\dd110epoxide2.dat



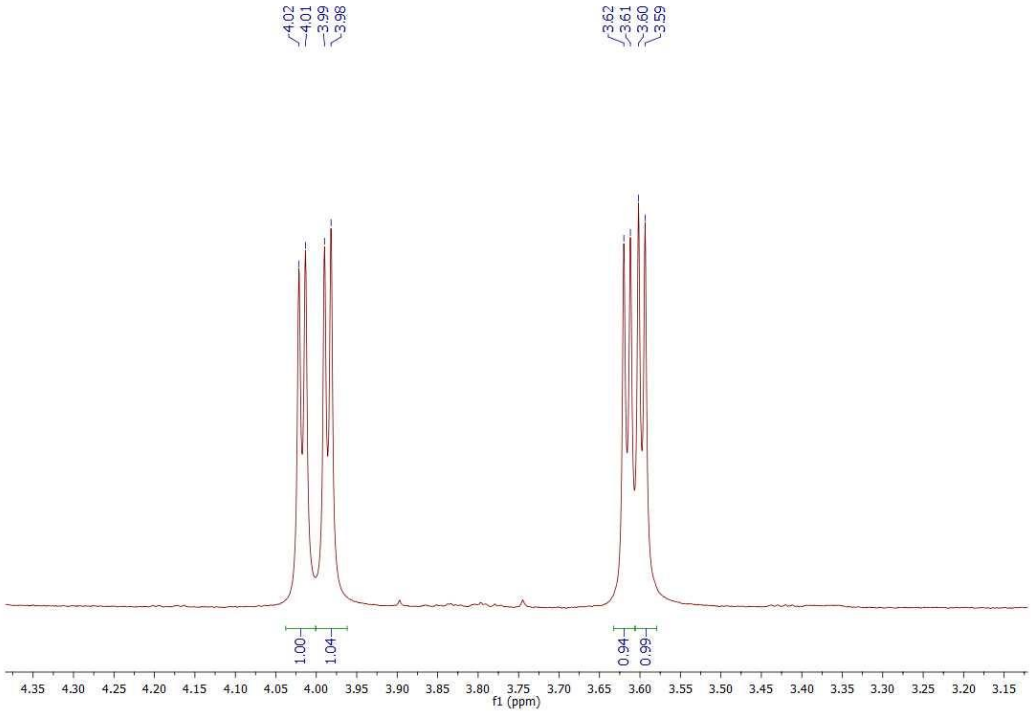
UV Results

Retention Time	Area	Area %	Height	Height %
43.173	67588	0.12	1184	0.29
71.150	9270749	17.11	75500	18.73
81.470	2730918	5.04	23856	5.92
89.147	42121596	77.73	302562	75.06
Totals	54190851	100.00	403102	100.00

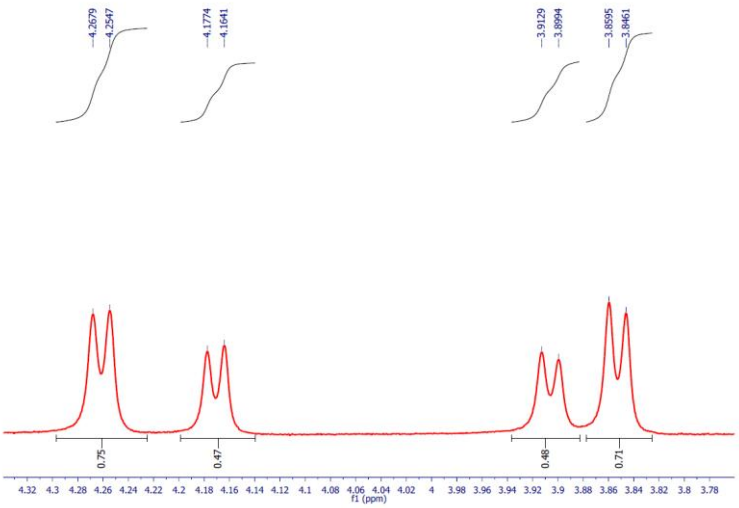
Determination of enantiomeric excess of epoxide 129 using chiral europium shift reagent (europium (III) tris[3-(hepta-fluropropylhydroxymethylene)-(+)-camphorate]



Racemic epoxide 129 resolved using 3 mg [(+)-Eu(hfc)3] per 10 mg of compound 129



Enantioenriched epoxide 129; (aqueous conditions, catalyst 83, ee = 22%)



Enantioenriched epoxide 129; (non-aqueous conditions, catalyst 41, ee = 62%)