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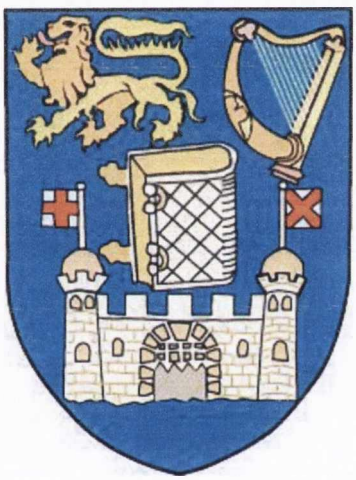
The Development of Novel Organocatalysts for Asymmetric Methylene Transfer in the Corey-Chaykovsky Reaction



Trinity College Dublin

A thesis submitted to the University of Dublin for the degree of Doctor of Philosophy

2012

Sarah Kavanagh

Under the supervision of Professor Stephen Connon

Declaration:

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Acknowledgements

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Abstract

To date, the enantioselective preparation of terminal three-membered heterocycles *via* the Corey-Chaykovsky (CC) reaction has been characterised by unsatisfactory enantioselectivities. In the benchmark literature report involving asymmetric methylene transfer to benzaldehyde, the terminal epoxide product was afforded in 57% *ee*, while in the benchmark literature report involving asymmetric methylene transfer to an imine, the terminal aziridine product was formed in just 19% *ee*. Both of these procedures require the use of (super)stoichiometric quantities (one or two equivalents respectively) of chiral sulfide.

It had twice been reported that *N*-alkyl salts derived from ephedrine act as chiral phase transfer catalysts in CC reactions between sulfonium ylides and benzaldehyde, furnishing the terminal epoxide product in high enantiomeric excess. Having repeated the key experiments detailed in both papers precisely, we found that the epoxide product had been formed as a racemic mixture. Due to the authors' reliance on specific rotation to determine the *ee* of the epoxide product, they failed to recognise that the optical activity that they observed was as a result of the epoxide formed from the base-mediated decomposition of the enantiopure catalysts.

It has been well documented that (thio)urea derivatives are robust and active hydrogen-bond donating catalysts for a variety of addition reactions characterised by an increase in basicity at a heteroatom in the reaction transition state. We therefore considered the development of an organocatalytic strategy based on the use of hydrogen-bond-donating catalysts for an enantioselective variant of the CC reaction involving aldehydes as substrates. It was found that a simple urea could promote the smooth transformation of a range of aldehydes and trimethylsulfonium iodide into terminal epoxides (up to 96%) at 5 mol% loading under biphasic reaction conditions at room temperature. It was, however, found that neither bifunctional (thio)urea derivatives possessing a sulfide moiety (from which the ylide could be generated by alkylation followed by deprotonation), nor 2-monosubstituted thiolane derivatives possessing a hydrogen-bond-donating moiety, are of an appropriate design motif to accommodate hydrogen-bond-mediated catalysis in CC reactions.

We have demonstrated that chiral C_2-symmetric 2,5-disubstituted thiolane derivatives induce enantioselectivity (up to 47% product *ee*) in stoichiometric CC reactions with benzaldehyde as the substrate. We have also shown that similar levels of enantiomeric excess (43% *ee*) can be achieved using 20 mol% loading of the same chiral sulfide. These levels of product enantiomeric excesses are approaching those obtained following the benchmark literature procedures for the enantioselective preparation of terminal epoxides *via* the CC reaction, but require 5-10 times less chiral sulfide catalyst. We have also demonstrated, for the first time, that geminally disubstituted terminal epoxides can be prepared from ketones *via* our catalytic CC methodology using 20 mol% loading of an achiral sulfide.

Chiral C_2-symmetric 2,5-disubstituted thiolane derivatives also proved efficient in the promotion of enantioselective (up to 30% *ee*) methylene transfer to a range of aromatic, aliphatic and α,β-unsaturated imines. The enantioselectivities achievable following our methodology are higher (by up to 11%) than the enantioselectivity that was realised following the benchmark literature procedure for the asymmetric synthesis of a terminal aziridine *via* a chiral sulfonium ylide, but require just one equivalent of the chiral sulfonium salt.

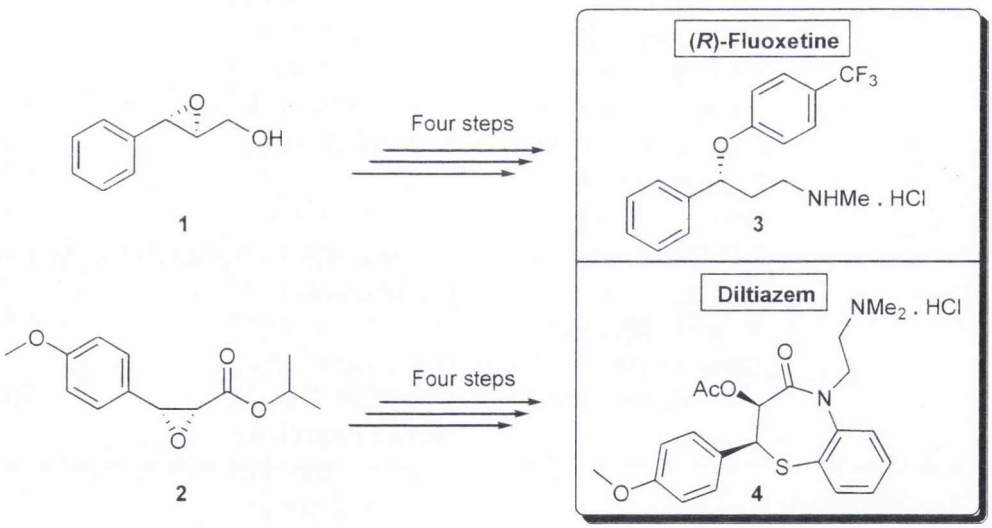
Abbreviations

Å	Angstrom
Ac	Acetyl
AE	Asymmetric Epoxidation
Ar	Aryl
AZ	Asymmetric Aziridination
BINAP	2,2'-*bis*(Diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
BOC	*tert*-Butoxycarbonyl
Bu	Butyl
BUDAM	3,5-Di-*tert*-butyldianisylmethyl
Bz	Benzoyl
cat.	Catalyst
Cbz	Carboxybenzyl
CC	Corey-Chaykovsky
conv.	Conversion
CSP	Chiral stationary phase
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
de	Diastereomeric excess
DET	Diethyl tartrate
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPP	Diphenylphosphoryl
dr	Diastereomeric ratio
EDG	Electron donating group
ee	Enantiomeric excess
ent	Enantiomer
equiv.	Equivalent
Et	Ethyl
EWG	Electron withdrawing group
FDA	Food and Drug Administration
HKR	Hydrolytic Kinetic Resolution
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
IPA	*iso*-Propyl alcohol
IR	Infrared
KR	Kinetic Resolution
k	Rate constant
LDA	Lithium diisopropylamide
LG	Leaving Group
LUMO	Lowest Unoccupied Molecular Orbital
m	*meta*
Me	Methyl
MeCN	Acetonitrile
Ms	Methanesulfonyl

MS	Molecular sieves
NBCC	*N*-Benzylcinchonidinium chloride
NMO	Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
Np	Naphthyl
Ns	Nosyl
Nu	Nucleophile
o	*ortho*
OTf	Trifluoromethanesulfonate
p	*para*
PG	Protecting Group
Ph	Phenyl
PMP	*para*-Methoxyphenyl
P_2-*t*-Bu	1-*tert*-Butyl-2,2,4,4,4-pentakis(dimethylamino)-2λ^5,4λ^5-catenadi(phosphazene)
rac	Racemic
rt	Room temperature
S	Selectivity factor
SAR	Structure Activity Relationship
sec	Secondary
SES	2-(Trimethylsilyl)ethanesulfonyl
TBHP	*tert*-Butyl hydroperoxide
TEA	Triethylamine
tert	Tertiary
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
TON	Turnover number
TPS	2,4,6-Triisopropylbenzenesulfonyl
TS	Transition state
Ts	Tosyl
VANOL	3,3′-Diphenyl-2,2′-bi-1-naphthalol,3,3′-diphenyl-2,2′-bi-1-naphthol
VAPOL	2,2′-Diphenyl-3,3′-(4-biphenanthrol)
XRD	X-ray Diffraction

1.1 Epoxides; general properties and applications

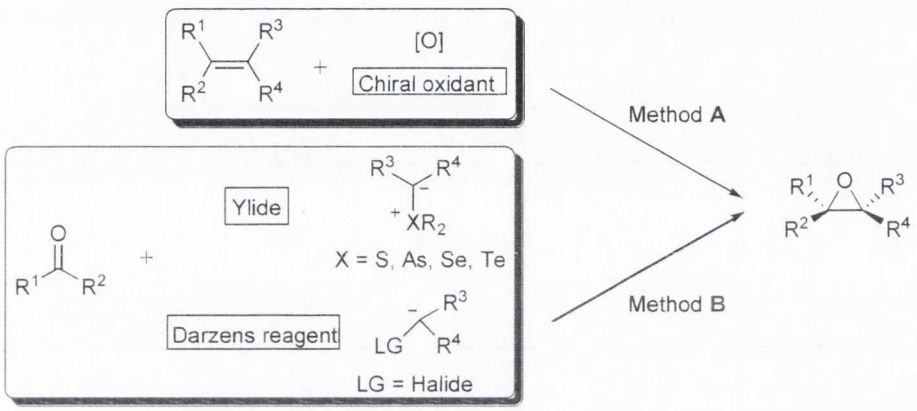
Epoxides are three membered heterocyclic molecules that possess inherent strain energy owing to their internal bond angles of *ca.* 60°.[1] They are typically used as electrophiles which undergo reliable, regio- and stereospecific ring-opening reactions with a wide range of nucleophiles to yield valuable bifunctional molecules.[1] This makes epoxides one of the most important functional groups in the toolbox of the organic chemist.[2] Following the emergence of 'the chiral switch',[3] there has been a surge in demand for single enantiomer drugs, which has consequently led to an increase in demand for epoxides in their enantiomerically pure form. Chiral epoxides (*e.g.* **1** and **2**) have been successfully employed as intermediates in the synthesis of a number of existing marketed drugs *e.g.* fluoxetine (**3**)[4] and diltiazem (**4**)[5] respectively (Scheme 1.1). Given the incessant demand for enantioenriched pharmaceuticals, it is paramount that highly efficient and selective methods for the enantioselective synthesis of these key intermediates be developed. Catalytic asymmetric epoxidation is undoubtedly one of the most attractive methods for the synthesis of these valuable building blocks.[6]



Scheme 1.1 Chiral epoxides **1** and **2** as versatile building blocks in the synthesis of (*R*)-fluoxetine (**3**) and diltiazem (**4**)

1.2 Catalytic asymmetric synthesis of epoxides

Generally speaking, there are two ways by which an epoxide can be prepared enantioselectively from achiral starting materials; the first approach involves enantioselective oxidation of a prochiral alkene (method **A**, Scheme 1.2), while the second approach involves the enantioselective alkylidenation of a prochiral carbonyl compound by using either an ylide or a Darzens reagent (method **B**, Scheme 1.2).[7]



Scheme 1.2 Methods for the enantioselective preparation of epoxides from achiral starting materials

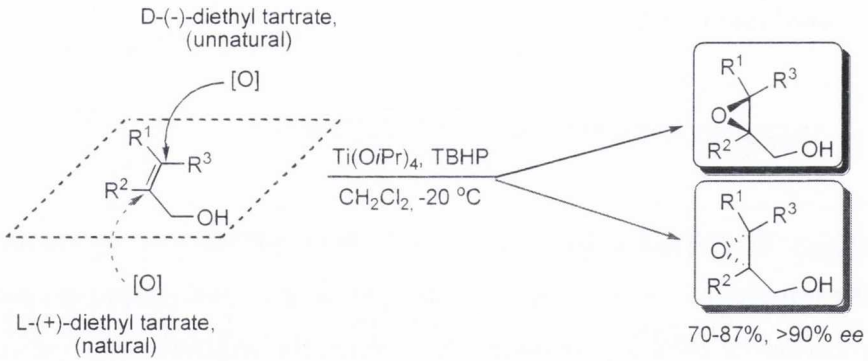
1.2.1 Asymmetric epoxidation (AE) of alkenes

The first example of an asymmetric alkene epoxidation was reported by Henbest *et al.* in 1965.[8] In this example the chiral peracid, percamphoric acid, was employed and a meagre enantiomeric excess of 10% was realised. Since then, the oxidative method of preparing enantioenriched epoxides has received considerable attention and many accomplished protocols have been reported.[9] This method however, is not without its drawbacks; if the starting alkene itself is derived from a carbonyl compound, then the oxidation method represents a two step procedure; the first step involves a Wittig reaction, which governs relative stereochemistry, followed by enantioselective oxidation of the resulting prochiral alkene, which governs absolute stereochemistry. The structural prerequisites of the olefin

substrates are also a limiting factor in the majority of these protocols.[9] The most widely used and efficient methods for the asymmetric epoxidation of alkenes will be discussed.

1.2.1.1 Catalytic AE of allylic alcohols

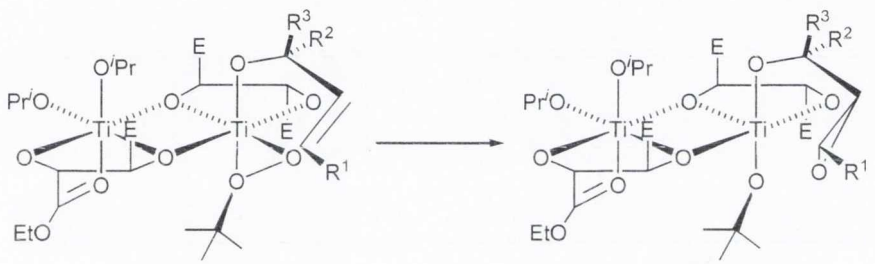
Until the major breakthrough reported by Katsuki and Sharpless in 1980, the field of asymmetric epoxidation had been devoid of methodologies leading to synthetically useful levels of enantiomeric excess.[10] They reported the successful conversion of an allylic alcohol into an asymmetric epoxyalcohol using a chiral titanium ion-based catalyst. This reaction marked the genesis of a new era in asymmetric synthesis and would eventually contribute to Professor Sharpless' receipt of the Nobel Prize in 2001.[11] Using titanium tetraisopropoxide ($Ti(O\textit{i}Pr)_4$) as a transition metal catalyst, diethyl tartrate (DET) as a chiral ligand and *tert*-butyl hydroperoxide (TBHP) as oxidant, they successfully epoxidised a range of allylic alcohols in high chemical yield and high enantiomeric excess (Scheme 1.3). A standout feature of this protocol is that by changing the chirality of the tartrate used *i.e.* (+) or (-)-diethyl tartrate, the sense of enantioenduction can be switched, thus affording both enantiomers of the epoxyalcohol (Scheme 1.3).[10]



Scheme 1.3 The asymmetric epoxidation of allylic alcohols using the Katsuki – Sharpless system

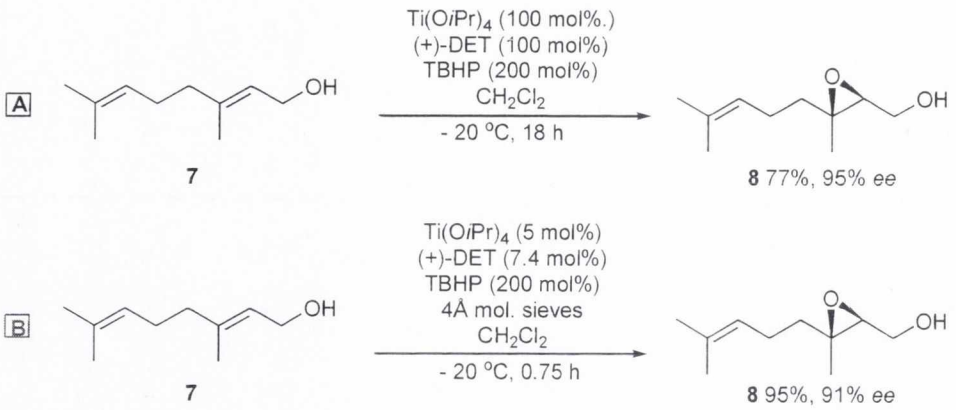
When the alkene is depicted as shown above (Scheme 1.3) with the hydroxymethyl substituent positioned at the bottom right (as drawn), using (-)-diethyl tartrate delivers the

oxygen atom from above the plane of the alkene, and conversely, (+)-diethyl tartrate delivers the oxygen to the bottom face. There has been much debate about the mechanism of the Sharpless asymmetric epoxidation reaction.[12] It is accepted that in solution, two isopropoxide ligands are replaced by $Ti(OiPr)_4$ and the chelating diol DET to form the complex ($Ti(DET)(OiPr)_2$). TBHP and the allylic alcohol then displace the two remaining isopropoxide ligands to form what is referred to as the 'loaded' catalyst (**5**, Scheme 1.4). Face – selective delivery of an oxygen atom from the bound TBHP to the allylic alcohol furnishes an enantioenriched epoxide (**6**, Scheme 1.4). The cycle is perpetuated by addition of further TBHP and allylic alcohol.[12,13]



Scheme 1.4 The transition state of the Sharpless asymmetric epoxidation of allylic alcohols

This process had remained stoichiometric with respect to the titanium tartrate catalyst until 1986, when Sharpless *et al.* established that the presence of water in reactions was inextricably linked to a diminution of both product *ee* and reaction rate.[14] They attributed these findings to the reversible and irreversible interaction of the catalyst with water. To circumvent these negative effects they added molecular sieves to catalysed reactions which accommodated the use of as little as 5% titanium tetraisopropoxide and 6 – 7.5% tartrate (Scheme 1.5).[15] Although the levels of product *ee* are slightly lower than in the stoichiometric reaction (**8**, A and B Scheme 1.5), this process is more economical, the chemical yields are improved and isolation is made less difficult.



Scheme 1.5 A: The stoichiometric Sharpless system; B: The improved, catalytic Sharpless system

It has since been reported that a wide variety of allylic alcohols can be asymmetrically epoxidised *via* this methodology[16] and despite the extensive research that followed,[16,17] the initial, pioneering reaction conditions are still widely used today. The primary limitation associated with these systems is the requirement of the alkene substrate to be functionalised as an allylic alcohol.[9a] With this in mind, considerable efforts have been made towards the development of protocols for the asymmetric epoxidation of unfunctionalised alkenes (*vide infra*).

1.2.1.2 Catalytic AE using chiral manganese-salen catalysts

In the case of the catalytic asymmetric epoxidation of functionalised alkenes, the intricacy of manipulating the alkene's approach to the catalyst is overcome by functional group ligation to the catalyst (as in the case of Sharpless' systems, *vide supra*). The principal obstacle associated with the asymmetric epoxidation of unfunctionalised alkenes however, is the reliance on noncovalent interactions to direct the alkene to the active catalyst.[18]

In 1990, a decade after the discovery of the Sharpless – Katsuki asymmetric epoxidation of allylic alcohols, the next breakthrough in asymmetric epoxidation was unveiled.

Jacobsen *et al.*[19] and Katsuki *et al.*[20] independently reported protocols for the catalytic asymmetric epoxidation of unfunctionalised alkenes using chiral manganese-salen complexes **9** and **10** respectively (Figure 1.0).

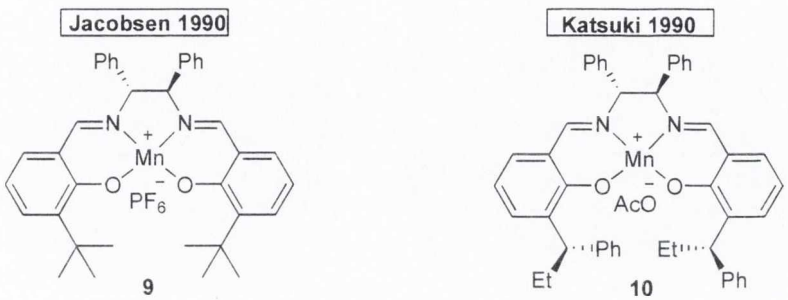
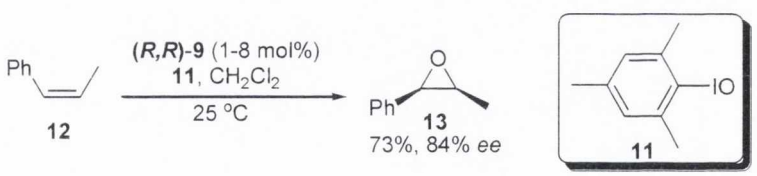


Figure 1.0 The first chiral manganese-salen catalysts reported by Jacobsen and Katsuki

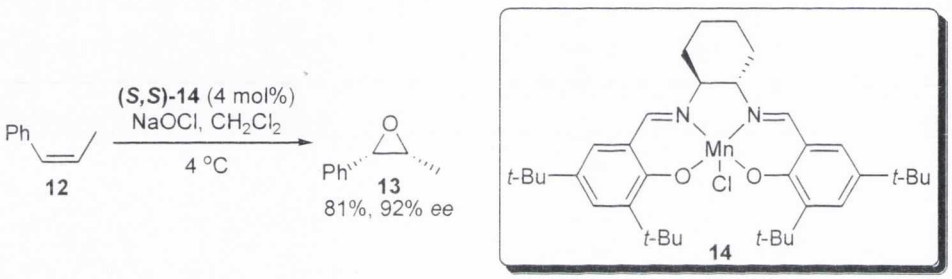
A variety of unfunctionalised alkenes were epoxidised enantioselectively using either catalyst **9** or **10** with an iodosylbenzene derivative as terminal oxidant (the catalytically active species responsible for the transfer of an oxygen atom to the alkene is $O{=}M^{V}(salen)^{+}$).[18,19] Jacobsen's catalyst (*i.e.* **9**) fared better than Katsuki's (*i.e.* **10**), epoxidising monosubstituted – terminal, trisubstituted and (*Z*)-alkenes in good to excellent enantiomeric excess (57-93%) (Scheme 1.6).[19] (*E*)-Alkenes, however proved to be poor substrates for this reaction (20-30% *ee*).



Scheme 1.6 A representative example of the catalytic AE of the (*Z*)-alkene **12** using chiral manganese-salen catalyst **9**

Since the initial reports, there have been numerous structural improvements made to both catalysts.[21] The introduction of *tert*-butyl groups *para* to the salen oxygen atoms in **9** had

a marked effect on enantioselectivity (**14**, Scheme 1.7).[22] To further enhance the practicality of this process, commercial bleach was used as oxidant. This new catalyst, referred to today as 'Jacobsen's catalyst', was evaluated in the oxidation of a range of (*Z*)-alkenes and excellent levels of enantioselectivity were achieved (89-98% *ee*) (Scheme 1.7). To date, further modifications to this catalyst's structure have been made and have led to improved performance;[21] however, due to the ease of preparation of **14** (>90% overall yield from two facile steps), the accessibility of both enantiomers and its commercial availability, it remains in widespread use today.[9b]

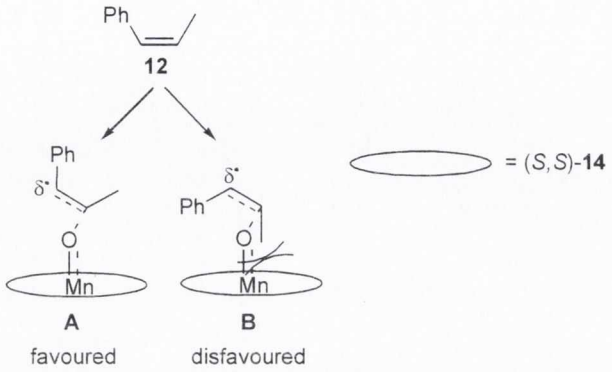


Scheme 1.7 A representative example of the catalytic AE of the (*Z*)-alkene **12** using Jacobsen's catalyst (**14**)

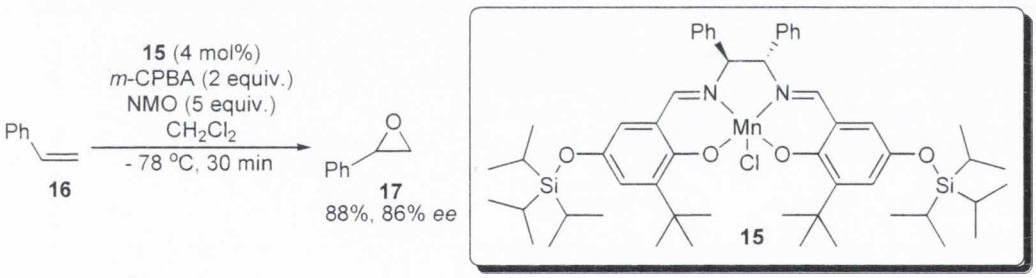
The stereochemical outcome observed with respect to the class of alkene employed as substrate ((*Z*)-di- and trisubstituted alkenes) can be rationalised upon consideration of the transition states (Scheme 1.8). It has been proposed that oxygen atom transfer proceeds *via* a radical intermediate and that the transition state results from a skewed side-on approach of the alkene to the M=O species.[5,23] It is assumed that the asymmetric environment created by the chiral salen ligand can influence the orientation of the radical (*i.e.* to the left in Scheme 1.8): the resulting transition states of (*Z*)-alkene **12** in an epoxidation reaction catalysed by **14** are shown (A and B; Scheme 1.8). Due to the steric clash in transition state B, the reaction occurs *via* transition state A, leading to (*R*,*S*)-**13**.[23]

In a further study, they addressed the issue of low enantioselectivity associated with terminal alkenes. They developed a low temperature (-78 °C) procedure using *N*-

methylmorpholine *N*-oxide (NMO) as oxidant, and using catalyst **15**, they successfully epoxidised styrene (**16**) to styrene oxide (**17**) in 86% *ee* (Scheme 1.9).[24,25]



Scheme 1.8 The origin of enantioinduction in the epoxidation of (*Z*)-alkene **12** with catalyst Jacobsen's catalyst (**14**)



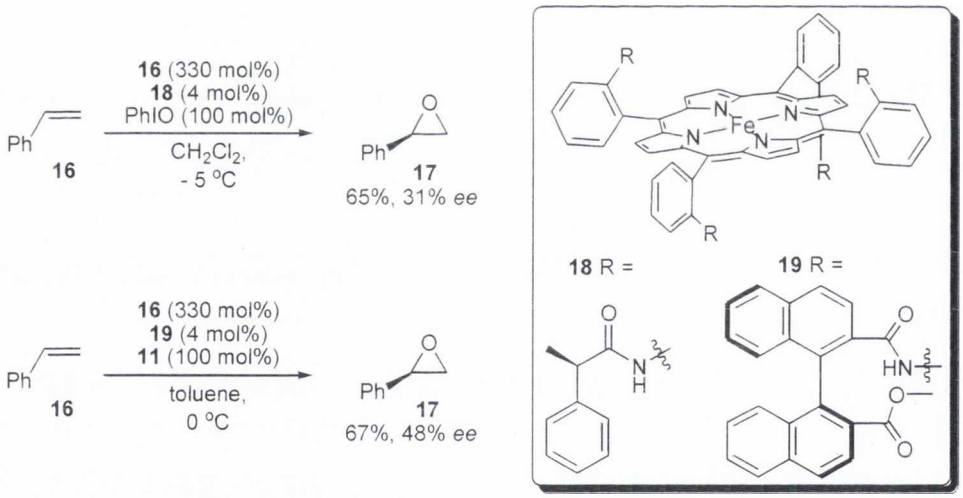
Scheme 1.9 The AE of terminal alkene **16** using chiral Mn(salen) catalyst **15**

As with Sharpless' chiral titanium-ion catalysts, there are limiting factors. Due to decomposition of the catalyst, these systems are generally characterised by low turnover numbers (TON).[26a] Furthermore, these systems are not effective with all classes of alkene: although Gilheany *et al.* reported a highly enantioselective variant of this system for the AE of (*E*)-β-methylstyrene using a chiral Cr(salen) complex,[26b] the aforementioned systems generally only work well for (*Z*)-di- and trisubstituted alkenes,[26a] for chromene and hindered indene derived tetrasubstituted alkenes[27] and styrenes.[24,25]

1.2.1.3 Catalytic AE using chiral metalloporphyrin catalysts

Taking inspiration from one of nature's oxidising enzymes, cytochrome P-450, which has an iron porphyrin complex at its active site,[28] Groves *et al.*, while searching for novel iron catalysts as oxygen transfer agents, discovered that iron porphyrins could catalyse epoxidation reactions using iodosylbenzene as an oxygen source.[29] As in the case of Mn(salen) systems, the epoxidation of alkenes is believed to occur *via* a highly reactive metal-oxo species.[18] They speculated that if a chiral metalloporphyrin were to be employed in the same reaction, epoxidation of the alkene would occur in an asymmetric fashion giving rise to a new class of catalyst for the asymmetric epoxidation of alkenes.

Accordingly, in 1983, Groves *et al.* reported the first example of an asymmetric epoxidation reaction using chiral iron porphyrin catalysts **18** and **19** (Scheme 1.10).[30]

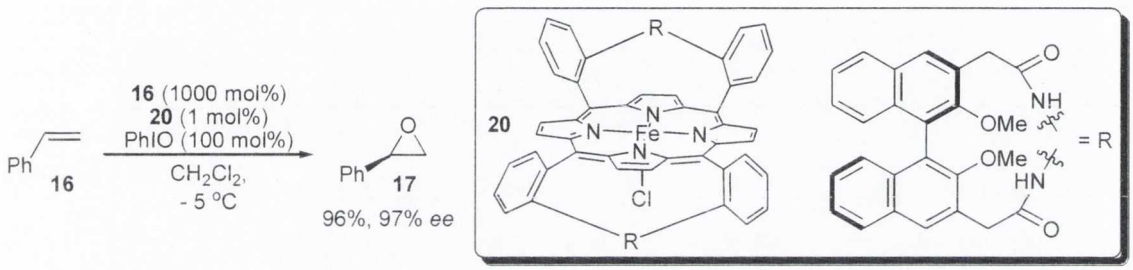


Scheme 1.10 The first example of an asymmetric epoxidation reaction using a chiral metalloporphyrin

Employing these chiral 'picket fence' porphyrins (two chiral 'pickets' above and below the porphyrin unit) in the epoxidation of **16**, they obtained **17** in 31% *ee* using **18** and 48% *ee* using **19** (Scheme 1.10). The greater selectivity observed using binaphthyl substituents (*i.e.* **19**) was believed to arise from a larger, more rigid chiral cavity leading

to improved catalyst-substrate interactions.[18] Since this initial report, there have been numerous reports of chiral metalloporphyrin catalysts aimed at the development of highly enantioselective terminal alkene epoxidation protocols.[9b,31]

One of the most acclaimed procedures to date is that reported by Rose *et al.* in 2004.[32] They proposed the new C_2-symmetrical binaphthyl-strapped iron porphyrin **20** that was capable of discriminating prochiral faces of terminal alkenes through weak, non-bonding interactions.



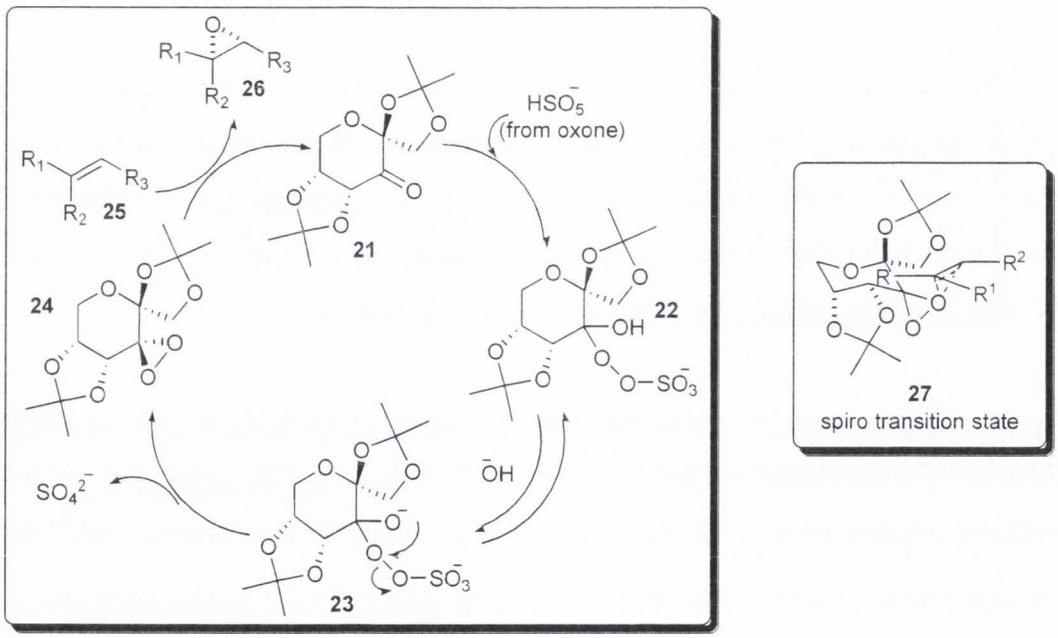
Scheme 1.11 A highly enantioselective chiral porphyrin catalyst for terminal epoxidation

Catalyst **20** exhibited outstanding activity in the enantioselective epoxidation of a range of styrene derivatives, affording excellent chemical yields (84-96%) and enantiomeric excesses (84-97%) of the corresponding styrene oxides (Scheme 1.11). They theorised that the approach of the alkene toward the iron centre is directed by the rigid BINAP 'walls' which in turn induces the transfer of chiral information.

Although chiral porphyrin catalysts are effective promoters of the asymmetric epoxidation of unfunctionalised alkenes (especially terminal), their laborious and overall low yielding preparation (*e.g.* **20**, Scheme 1.11)[32] precludes their widespread application.

1.2.1.4 AE using chiral dioxirane catalysts

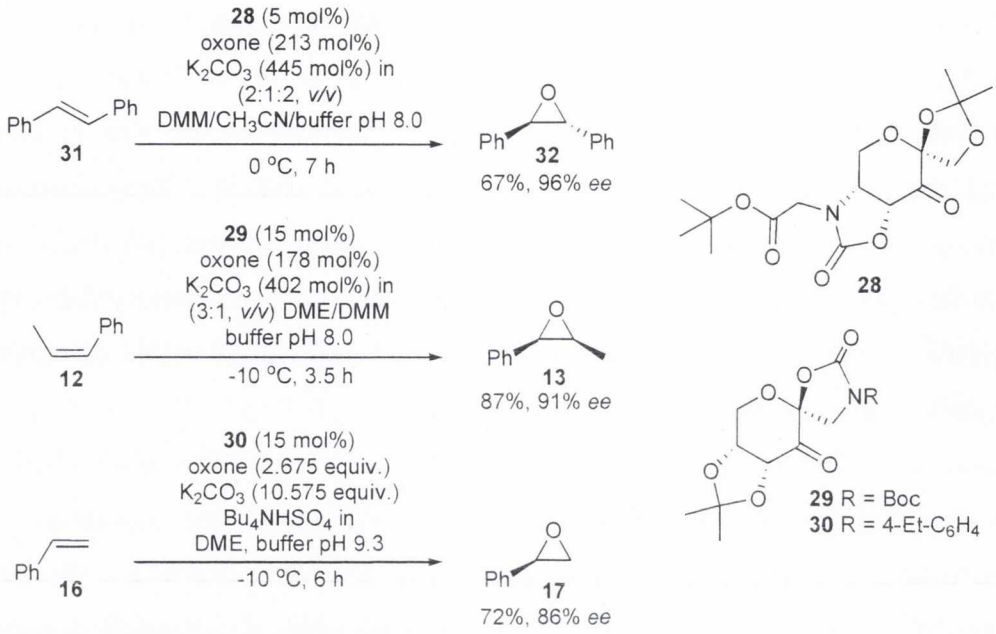
The major drawback associated with the aforementioned asymmetric epoxidation methods is their lack of compatibility with (*E*)-alkenes.[9b,26] This problem was addressed by Shi *et al.* in 1996 when they reported a novel, chiral fructose-derived ketone **21** capable of dioxirane mediated asymmetric epoxidation of a range of trisubstituted and (*E*)-alkenes in moderate to high chemical yield (41-84%) and high *ee* (87-95%).[33] An appealing trait of this system is that both enantiomers of the catalyst can be easily prepared; **21** from D-fructose in two steps, and **ent-21** from L-sorbose in five steps.[34] The active oxidant in this system is a dioxirane (*e.g.* **24**, Scheme 1.12), which had previously proven to be an effective epoxidation reagent.[35] The catalytic cycle for this process is illustrated in Scheme 1.12. The dioxirane **24** is generated *in situ* from oxone and **21**, which then selectively delivers one of its oxygen atoms to the alkene **25** to yield the enantioenriched epoxide **26** (Scheme 1.12). It has been shown that spiro transition state **27** is favoured, delivering the less sterically hindered equatorial oxygen atom of the dioxirane to the alkene.[36]



Scheme 1.12 Catalytic cycle of the asymmetric epoxidation of an alkene using **21**

In the initial report, oxone was used as oxidant; however, due to its rapid autodecomposition at high pH, the reaction was performed at pH 7-8. It was found that at this pH, decomposition of **21** occurred rapidly (seemingly *via* a Baeyer-Villiger oxidation pathway), prescribing the use of three equivalents of chiral catalyst.[33] They subsequently reported a modified procedure in which the reaction was performed at pH 10.5,[37] hoping that a higher pH would favour formation of anion **23** and consequently **24**, over the decomposition pathway. Even with this modified procedure, 20-30 mol% of catalyst **21** was required to achieve similar results.

To overcome this decomposition they designed a new catalyst (**28**) incorporating a more electron-withdrawing oxazolidine group which was hoped would retard the Baeyer-Villiger oxidation reaction (Scheme 1.13).[38] Indeed, this catalyst was required at just 1-5 mol% loadings to obtain results comparable to those obtained using 20-30 mol% of **21**; a variety of trisubstituted and (*E*)-alkenes were epoxidised in good to excellent chemical yield (67-100%) and high *ee* (87-97%). Attempts were made at developing various other catalysts based on this system, for the asymmetric epoxidation of (*Z*)-[39] and terminal alkenes.[39b,40] A selection of the most outstanding results achieved for the AE of (*Z*)-alkenes using **29**,[39b] and terminal alkenes using **30**,[40b] are depicted in Scheme 1.13. Attempts have been made by various other groups to develop alternative chiral ketone catalysts for the catalytic asymmetric epoxidation of alkenes; however, the catalysts that have been reported by Shi *et al.* provide superior results.[36]



Scheme 1.13 Representative examples of asymmetric alkene epoxidation using chiral ketone catalysts

As with all previous methods discussed regarding the asymmetric epoxidation of alkenes, here too exists a limitation. This method has only generated high levels of product enantiomeric excess in the epoxidation of (*E*)- and trisubstituted alkenes.[36] The methodologies that have been discussed for the asymmetric epoxidation of alkenes represent a mere selection of the leading systems that exist for this transformation. This list is by no means exhaustive and there are many other accomplished procedures that have been reported in the literature to date.[9,26,31a,36,41] However, despite this, a readily accessible catalyst system capable of epoxidising terminal alkenes with excellent scope and levels of product enantiomeric excess remains elusive. A representation of the classes of epoxide that are accessible *via* the aforementioned protocols for the AE of alkenes in synthetically useful levels of enantiomeric excess (>90%) is depicted in Figure 1.1.

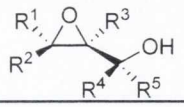
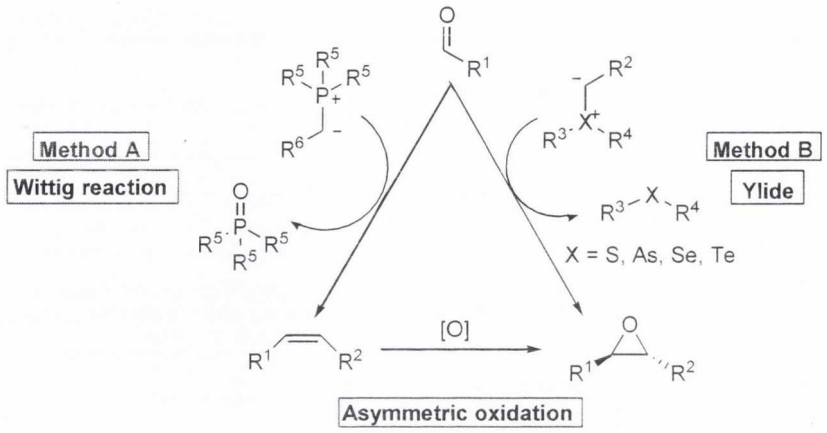
Entry	Epoxide class	Alkene oxidation system	Limitation(s) associated with this system
A		Sharpless systems (chiral Ti ion-based catalysts)	- The substrate must be an allylic alcohol
B		Jacobsen systems (chiral Mn(salen) catalysts)	- Low TON of catalyst - Excellent levels of epoxide *ee* only when alkene is (*Z*) or trisubstituted
C		Shi systems (chiral dioxirane catalysts)	- Excellent levels of epoxide *ee* only when alkene is (*E*), a styrene or trisubstituted
D		Jacobsen and Shi systems (chiral dioxirane catalysts and chiral Mn(salen) catalysts)	- As entries B and C
E		Chiral metalloporphyrin catalysts and Jacobsen system (chiral Mn(salen) catalysts)	- As entry B - Metalloporphyrin catalyst synthesis laborious and low yielding - Excellent levels of epoxide *ee* only when alkene is a styrene

Figure 1.1 The classes of epoxide available in excellent *ee via* AE of alkenes and the limitations associated with each system

1.2.2 Catalytic AE of carbonyl compounds

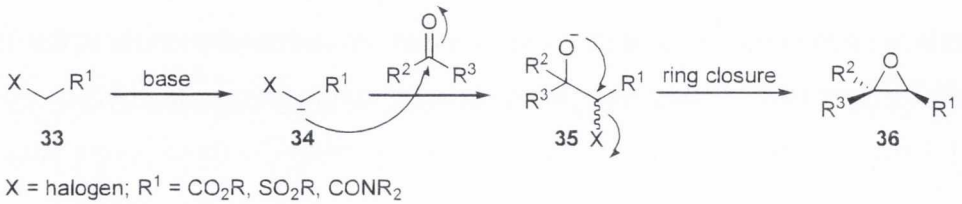
There are two primary methods for the preparation of a chiral epoxide from a carbonyl compound: (a) a two step procedure involving a Wittig reaction, followed by asymmetric oxidation (*vide supra*) of the resulting prochiral alkene (method A, Scheme 1.11), and (b) the asymmetric alkylidenation of a prochiral carbonyl compound using either a Darzens reaction or an ylide (method B, Scheme 1.11). The oxidative approach has proven to be an efficient method for the preparation of chiral epoxides;[9,17,36] however, the structural requirements of the alkene substrates limit its utility (*vide supra*). Moreover, the latter class of reactions represent a more efficient, one-step procedure; however, in this one step there is the difficult task of controlling both diastereo- and enantioselectivity.



Scheme 1.14 Methods for the enantioselective preparation of an epoxide *via* a carbonyl compound

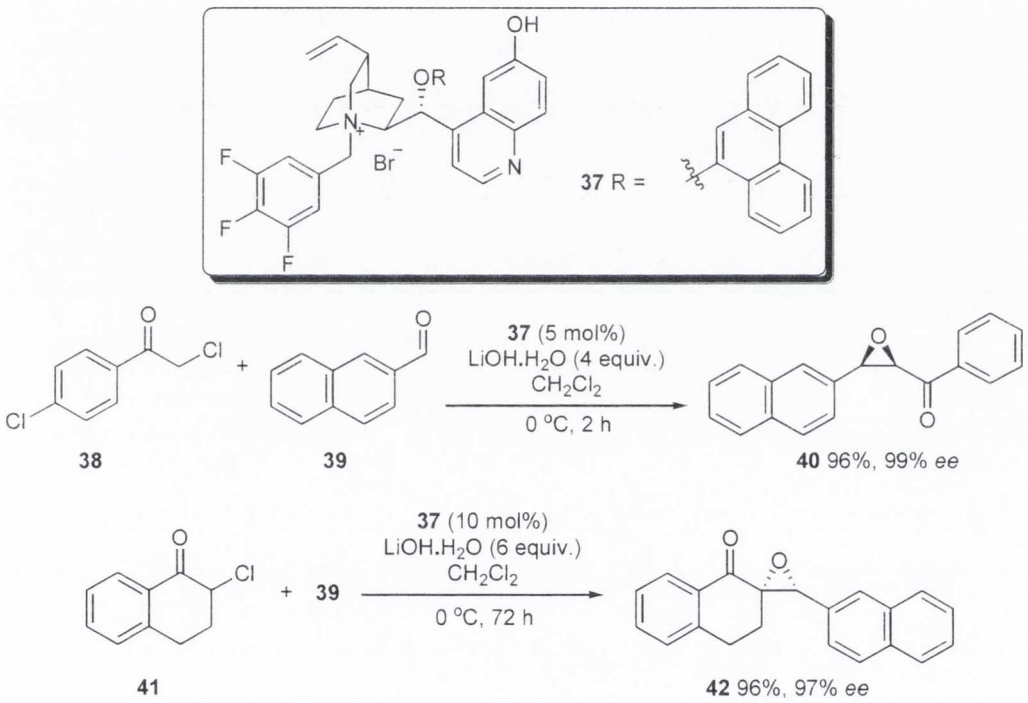
1.2.2.1 Catalytic AE of carbonyl compounds *via* the Darzens reaction

The asymmetric epoxidation of aldehydes and ketones using the Darzens reaction allows the preparation of epoxides bearing electron withdrawing groups (epoxy esters, acids, amides, and sulfones).[42] The reaction was discovered in 1904 by the Russian chemist Auguste Georges Darzens.[43] The reaction involves deprotonation of an α-halo ester, sulfone, or amide **33** to form an α-halo (enolate)anion **34** which then adds to the carbonyl compound. Subsequent ring closure of the adduct **35** affords the epoxide **36** (Scheme 1.15). The most desirable method for inducing asymmetry in the Darzens reaction is the use of a chiral catalyst that could be used in substoichiometric quantities.



Scheme 1.15 Mechanism of the Darzens reaction

Some of the most successful protocols thus far involve the use of chiral phase transfer catalysts (although the use of chiral auxiliaries and chiral reagents has been reported[39]). One of the most notable examples to date is the very recent report from Deng *et al.*, who detailed the development of a highly enantioselective chiral phase transfer catalyst for the Darzens reaction.[44] They demonstrated that a cupreinium salt **37** in as little as 5 mol% loading, could catalyse the asymmetric Darzens reaction between (α-substituted) α-chloro ketones and a range of benzaldehydes. In addition, one example involving an aliphatic aldehyde was reported (Scheme 1.16).



Scheme 1.16 The catalytic asymmetric Darzens reaction reported by Deng *et al.*

In the catalysed reactions between α-chloro ketones (*e.g.* **38**) and aromatic aldehydes (*e.g.* **39**), excellent chemical yields (90-96%) and high levels of enantioselectivity (90-99% *ee*) of the corresponding epoxides (*e.g.* **40**) were observed. In the reaction with an aliphatic substrate, the epoxide was obtained in high chemical yield (81%) and high enantioselectivity (81% *ee*). Similarly, in the reactions between α-substituted α-chloro ketones (*e.g.* **41**) and aromatic (*e.g.* **39**) and aliphatic aldehydes, excellent yields (90-

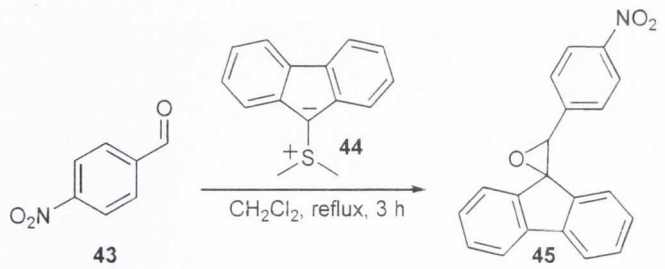
96%) and epoxide *ee* (90-97% for aromatic *e.g.* **42** and 80-87% for aliphatic) were realised. This report is one of few to have detailed a catalytic asymmetric Darzens reaction for the synthesis of epoxides in greater than 90% *ee*.[45] Due to the limited scope and success of the Darzens reaction toward the enantioselective synthesis of epoxides, the ylide approach appears to hold far greater promise.[42]

1.2.2.2 Catalytic AE of carbonyl compounds *via* a ylide

The ylide-mediated procedure for the asymmetric synthesis of epoxides is an attractive one; it represents a one step procedure (Scheme 1.14), however, if it is to rival the more conventional oxidative techniques, it is crucial that this method be made feasible in both an asymmetric and catalytic fashion. If the resulting epoxide is destined to be chiral, the asymmetric influence must be derived from either a chiral substrate or a chiral ylide, and if the reaction is to be catalytic, the chiral ylide must be regenerated in the reaction (method B, Scheme 1.14).

1.3 Sulfonium ylide mediated epoxidation: a historical perspective

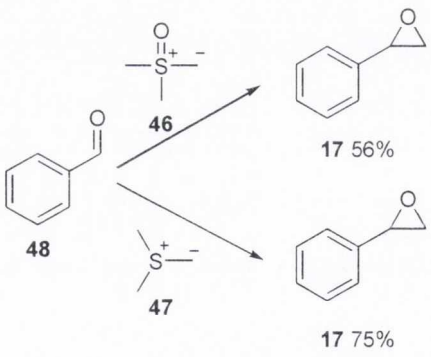
The first example of a sulfur ylide-mediated epoxidation reaction was reported by Johnson and La Count in 1958.[46] This was a serendipitous discovery whereby they set out to investigate the fate of the isolable sulfonium ylide, dimethylsulfonium fluorenylide (**44**), in a reaction with *p*-nitrobenzaldehyde (**43**).



Scheme 1.17 The first reported example of a sulfonium ylide-mediated epoxidation reaction

The authors expected this ylide to behave the same as a phosphonium ylide would in a Wittig reaction and produce an alkene;[46] However, instead of obtaining the anticipated alkene, they obtained epoxide **45** (Scheme 1.17).

In 1962, Corey and Chaykovsky reported the discovery of a new isolable ylide for this reaction, dimethylsulfoxonium methylide (**46**),[47] and in 1965, the same authors disclosed the discovery of a further, less stable ylide, dimethyl sulfonium methylide (**47**).[48] In the latter report, the formation and applications of these ylides was detailed. In both cases, the ylides were formed by deprotonation of either trimethyloxosulfonium iodide/chloride or trimethylsulfonium iodide, and their reaction with a variety of electrophilic, unsaturated functional groups was investigated (C=O, C=C, C=N, C=S). In all cases, the reactions were characterised by methylene transfer from the ylide to the substrate. Benzaldehyde (**48**) was successfully epoxidised using both **46** and **47**, furnishing **17** as desired (Scheme 1.18). This approach toward the synthesis of epoxides has since been referred to as the Corey-Chaykovsky reaction.

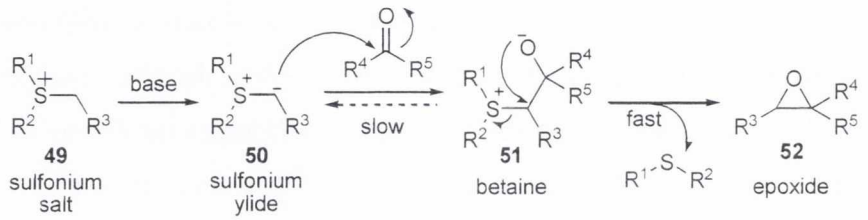


Scheme 1.18 The epoxidation of benzaldehyde using ylides **46** and **47**

1.3.1 The mechanism of the Corey-Chaykovsky (CC) reaction

The mechanism of the Corey-Chaykovsky reaction involves base-mediated deprotonation of a sulfonium salt **49** to generate a sulfonium ylide **50**, which adds to a carbonyl electrophile to form a zwitterionic betaine intermediate **51**, which then undergoes ring

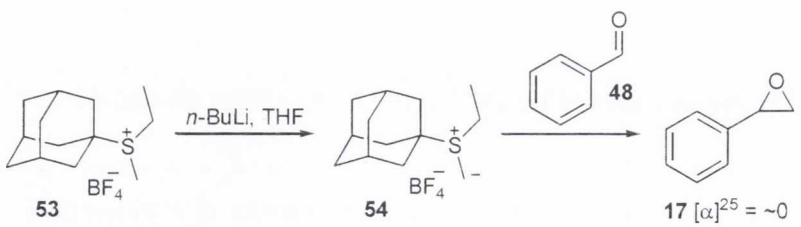
closure to furnish an epoxide **52**, with regeneration of the sulfide (Scheme 1.19).[49] It is noteworthy that recovery of the sulfide is particularly important if a chiral sulfide has been employed in the reaction.



Scheme 1.19 The mechanism of the Corey-Chaykovsky reaction

1.3.2 The enantioselective synthesis of epoxides *via* the Corey-Chaykovsky reaction: the use of chiral sulfide catalysts

The means by which asymmetry can be induced in the Corey-Chaykovsky reaction is by using either a chiral substrate or a chiral ylide.[7] The latter offers the possibility of rendering the process catalytic, and extensive efforts along these lines have been made by many independent groups.[50] The first reported example of the use of a chiral sulfide in the Corey-Chaykovsky epoxidation reaction was that of Trost *et al.* in 1973.[51] In this report, the reaction of the ylide **54** of the chiral sulfonium salt, (+)-adamantylethylmethylsulfonium fluoroborate (**53**), with benzaldehyde (**48**) was described (Scheme 1.20).



Scheme 1.20 The first example of a chiral sulfide in a Corey - Chaykovsky epoxidation reaction

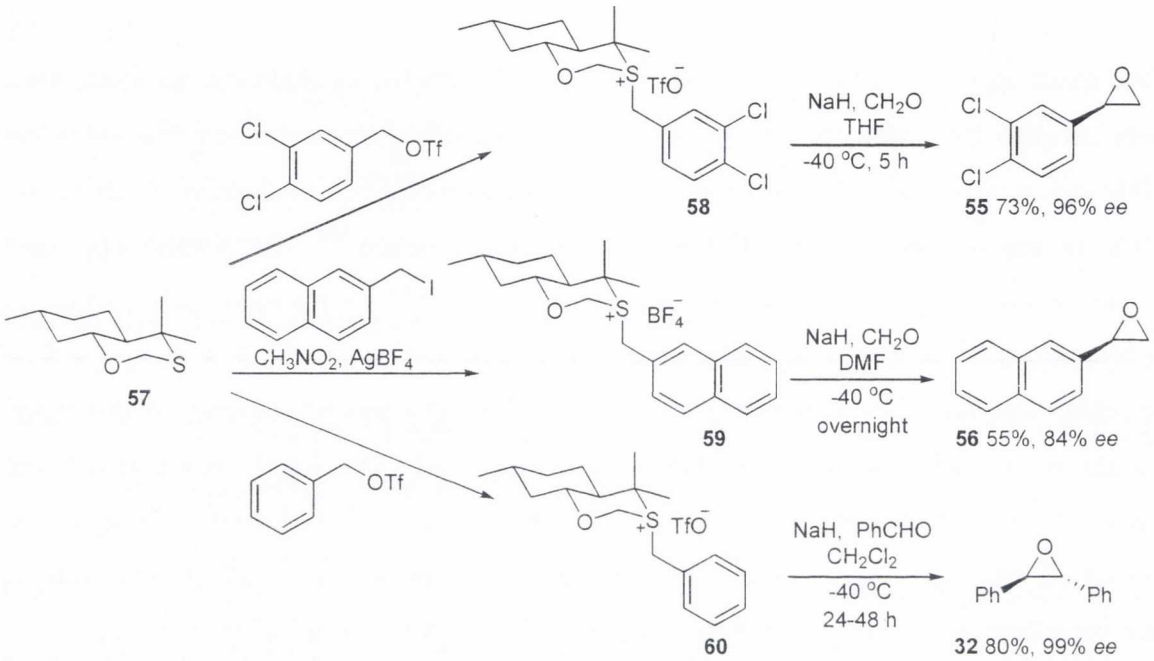
This was not a successful attempt, as the epoxide **17** that was formed in the reaction was optically inactive, *i.e.* a racemate. Despite the discouraging initial result, the development of novel chiral sulfides and catalytic procedures for this reaction has since proven to be an area of great interest.[42,50]

Two main approaches to chiral sulfide-mediated asymmetric epoxidation reactions have been adopted, and these can be categorised into two distinctive groups: those in which the ylide is formed in the reaction from a preformed sulfonium salt, and those in which the ylide is formed in a 'one-pot' procedure from a sulfide.[50b] The former approach prescribes the use of a stoichiometric quantity of chiral sulfonium salt, which is deprotonated to form an ylide, which then reacts with the carbonyl substrate to yield an epoxide. The latter accommodates the use of substoichiometric amounts of the chiral sulfide as the ylide is formed from the sulfide *in situ*, and following the reaction with the carbonyl substrate to form the epoxide, the sulfide is regenerated which can again be converted into the ylide. A variety of the most distinguished chiral catalysts and systems that have been developed for both approaches to date will be discussed (*vide infra*).

1.3.2.1 AE using preformed chiral sulfonium salts: a stoichiometric process

This method entails the formation and isolation of a sulfonium salt, followed by deprotonation with a base to form an ylide which then reacts with a carbonyl compound to yield an epoxide. Although this method necessitates the use of a stoichiometric amount of chiral sulfide, if high diastereoselectivities, enantioselectivities and chemical yields can be achieved, along with clean regeneration and isolation of the chiral sulfide, then this method represents a viable alternative to a substoichiometric (catalytic) process. An exemplary demonstration of the use of preformed chiral sulfonium salts in the asymmetric Corey-Chaykovsky reaction was reported by Solladié-Cavallo *et al.* in 1995.[52] They reported a highly enantioselective synthesis of two terminal epoxides (**55** and **56**) using Eliel's oxathiane (**57**) (prepared from (+)-(*R*)-pulegone in three steps)[53] derived sulfonium salts **58** and **59** respectively (Scheme 1.21). Deprotonation of the sulfonium salts with sodium hydride followed by reaction of the resulting ylides with

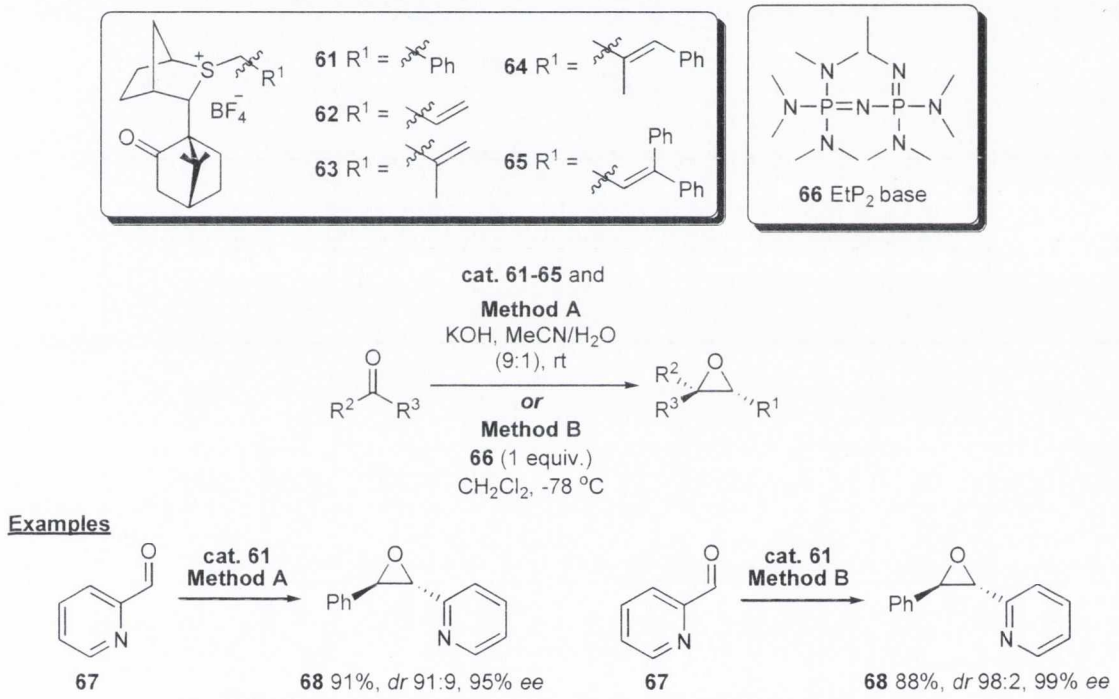
paraformaldehyde afforded epoxides **55** and **56** (Scheme 1.21). It is noteworthy that up to 86% of oxathiane **57** can be recovered in these reactions and can thus be used in subsequent reactions.



Scheme 1.21 The stoichiometric sulfonium salt-mediated epoxidation reaction reported by Solladié-Cavallo *et al.*

In 1996, the same group extended this strategy to the asymmetric epoxidation of aromatic aldehydes using the benzyl sulfonium salt of **57** (**60**, Scheme 1.21).[54] The deprotonation of **60** followed by asymmetric benzylidene transfer to a variety of aromatic aldehydes afforded the corresponding *trans*-diaryl epoxides in good chemical yield (56-84%) and excellent enantiomeric excess (99.0-99.9%) (*e.g.* **32**, Scheme 1.21). As before, up to 92% of oxathiane **57** could be isolated from the reactions and used in subsequent reactions. In 2000 the same group published two independent reports detailing the application of **60** in asymmetric epoxidation reactions with heteroaromatic[55] and α,β-unsaturated aldehydes,[56] furnishing the corresponding epoxides in excellent *ee* (>95% in both cases). They also successfully recovered oxathiane **57** from each reaction.

The major drawback associated with the above strategy is the availability of only one enantiomer of oxathiane **57**.[52-56] This obstacle was overcome by Aggarwal *et al.* in 2003.[57] This report detailed sulfonium salts **61-65** (both enantiomers of the sulfide precursor being prepared from camphorsulfonyl chloride in four steps and the sulfonium salts being prepared from either the appropriate bromide or alcohol) as catalysts in asymmetric epoxidation reactions with aromatic, heteroaromatic, aliphatic, α,β-unsaturated and propargyl aldehydes, and ketone substrates (Scheme 1.22).

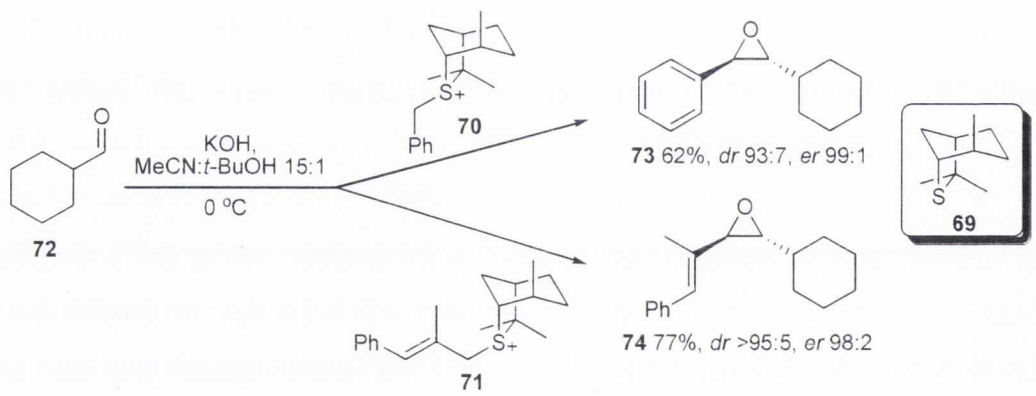


Scheme 1.22 Stoichiometric enantioselective sulfonium ylide epoxidation using sulfonium salts **61-65**

Taking inspiration from Solladié-Cavallo *et al.* who observed that if the homogeneous phosphazene base, EtP_2 (**66**), (*N*,*N*,*N*',*N*'-tetramethyl-*N*''-tris(dimethylamino)phosphoranylidene)phosphoric triamide ethylimine) was used in AE reactions, greater selectivities could be achieved due to its ability to deprotonate the sulfonium salt at low temperatures. They found that even at -78 °C, yields of epoxide were high and that the reaction time was much shorter compared to reactions performed

using sodium hydride as base.[55] Aggarwal *et al.* came to the same conclusion; they found that in all cases, superior results were obtained in reactions using EtP_2 at -78 °C, than those that were performed using KOH/MeCN/H_2O at room temperature (Scheme 1.22). In most cases, they obtained high chemical yields (except when methacrolein (52%) and TIPS-propargyl aldehyde (51%) were employed as substrates and when sulfonium salts **62** (43%), **63** (37%) and **65** (69%) were used as catalysts), high diastereoselectivities (except when TIPS-propargyl aldehyde (60:40) was substrate) and high enantioselectivities (except when *p*-nitroacetophenone (71%) was substrate).[57] A representative example is illustrated in Scheme 1.22. Except in the circumstances where the epoxide was not stable to chromatography, they reported that the chiral sulfide could be recovered in "essentially" quantitative yield.

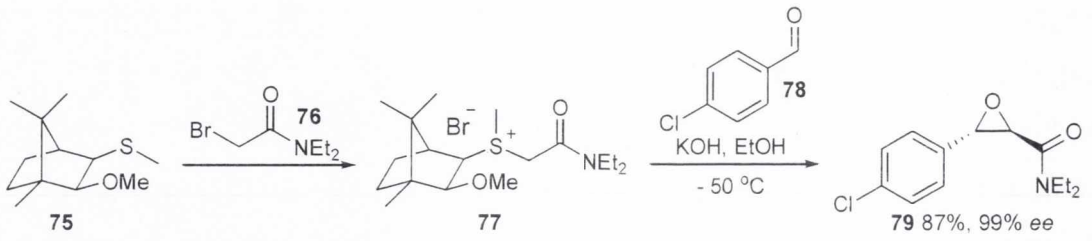
The chiral sulfonium ylide epoxidation technique has been implied as an alternative to the more traditional oxidative technique,[50] however due to its limited scope (α,β-unsaturated and 1,2-arylalkyl aldehydes are not good substrates)[42] and the lengthy, multistep syntheses of the chiral sulfide catalysts,[50,58] this method is rarely used.[59] In 2010, Aggarwal *et al.* reported a novel chiral catalyst, isothiocineole (**69**), that is available in both enantiomeric forms, that can be prepared economically (1g of (-)-**69** can reportedly be prepared for less that 1$) and that can promote the asymmetric epoxidation of a range of aldehydes (including typically troublesome aldehydes) in excellent *ee* (Scheme 1.23).[60]



Scheme 1.23 Stoichiometric enantioselective epoxidation using isothiocineole (**69**) derived catalysts

Sulfonium salts **70** and **71** were prepared from the appropriate bromide or alcohol. The reaction of **70** with aromatic, unsaturated and aliphatic aldehydes (*e.g.* **72**, Scheme 1.23) afforded the corresponding epoxides (*e.g.* **73**) in moderate to high yields (56-88%), excellent diastereoselectivities (up to >95:5) and excellent enantioselectivities (up to 98% *ee*). These are the highest levels of diastereoselectivity and enantioselectivity reported for the synthesis of 1,2-arylalkyl epoxides using chiral sulfides to date (Scheme 1.23).[60] Similarly, a range of allylic sulfonium salts (*e.g.* **71**, Scheme 1.23) were evaluated in epoxidation reactions with benzaldehyde and aliphatic aldehydes, and as before, the corresponding vinylic epoxides (*e.g.* **74**) were obtained in moderate to high yields (65-97%). Excellent diastereoselectivities (>95:5) and enantioselectivities (up to 98% *ee*) were also observed, provided the sulfonium salt had an α-substituent. As was the case for all previous examples, they reported that 95% of the chiral sulfide could be recovered. Representative examples are depicted in Scheme 1.23. This is the most selective method reported to date for the asymmetric synthesis of α,β-unsaturated epoxides.

In a report from Aggarwal *et al.* in 2002, it was outlined that glycidic amides could also be prepared in excellent *ee* using this methodology.[61] In this report, the highly diastereo- and enantioselective epoxidation of a range of aldehydes to glycidic amides using D-camphor-derived chiral sulfide **75** (which had been previously reported by Dai for asymmetric epoxidation reactions[62]) was detailed. Alkylation of **75** with *N,N*-diethyl bromoacetamide (**76**) afforded **77** as a 10:1 mixture of diastereomers: purification by recrystallisation afforded diastereomerically pure **77**. In reactions between aromatic or heteroaromatic aldehydes and **77**, the corresponding epoxides were obtained in high yield (85-93%), complete *trans* diastereoselectivity, and excellent *ee* (92-99%) (*e.g.* **79**, Scheme 1.24). Aliphatic aldehydes also afforded high yields (79-87%) and complete diastereomeric purity of the corresponding epoxides; however, high *ee* (93%) was only observed in the case where a tertiary aliphatic aldehyde was employed as substrate.



Scheme 1.24 A representative example of the asymmetric synthesis of glycidic amides *via* chiral sulfonium salt **77**

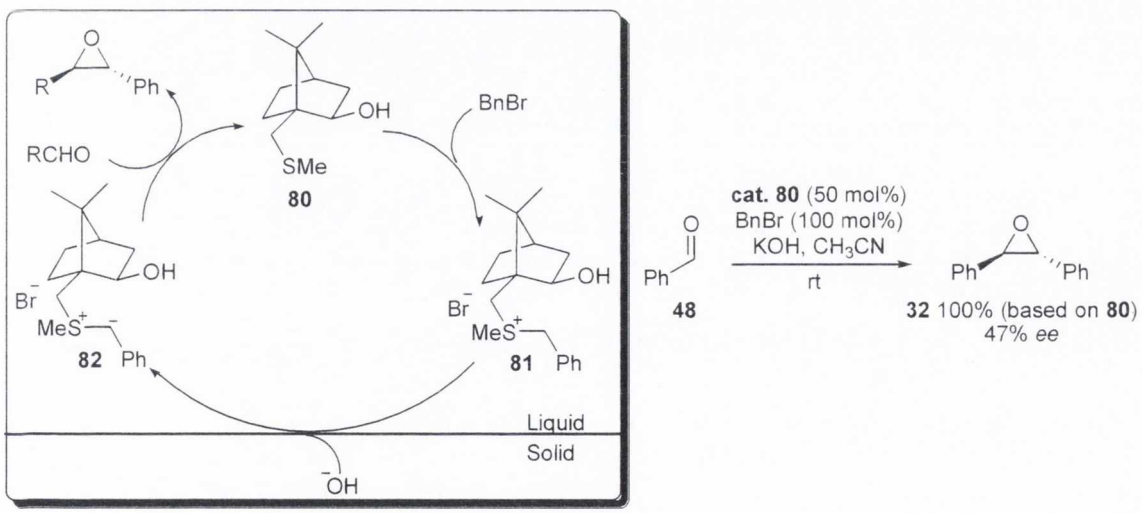
The aforementioned examples are by no means the only representations of stoichiometric chiral sulfonium salt epoxidation reactions;[7,42,50b,58a,63] however, these examples represent some of the most selective catalysts available for this methodology to date.

1.3.2.2 Catalytic AE using chiral sulfides: a substoichiometric process

Although the preceding method for the enantioselective synthesis of epoxides using chiral sulfides necessitates the use of stoichiometric amounts of catalyst, in most cases, they can be recovered after the reaction and used in subsequent epoxidation reactions (*vide supra*); however this approach still represents a two-step procedure: formation and isolation of the sulfonium salt, followed by formation of the ylide and reaction with the carbonyl substrate. A far more efficient method of performing a chiral sulfonium ylide-mediated epoxidation reaction is the 'one-pot' procedure, whereby formation of the ylide from the sulfide, and subsequent reaction of the ylide with the carbonyl substrate occur in the same reaction. In this scenario, if the regenerated sulfide can be transformed back to the ylide, it is possible that the chiral sulfide be used in substoichiometric quantities and act as a *bona fide* catalyst. There are two methods for the preparation of a sulfonium ylide from a sulfide *in situ*: the first method entails alkylation of the sulfide with an appropriate electrophile, followed by deprotonation of the resulting sulfonium salt while the second approach involves the reaction of the sulfide with a carbene or a carbenoid (*vide infra*).

1.3.2.2.1 Catalytic asymmetric sulfonium ylide epoxidation: sulfide alkylation followed by sulfonium salt deprotonation

The first example of a catalytic chiral sulfonium ylide epoxidation was reported by Furukawa *et al.* in 1989.[64] Their catalytic cycle was based upon alkylation of the camphor derived chiral sulfide **80** with an appropriate benzyl bromide, followed by deprotonation of sulfonium salt **81** using powdered potassium hydroxide, and subsequent reaction of ylide **82** with benzaldehyde (**48**) or *p*-chlorobenzaldehyde (**78**) to yield what they hoped would be an enantioenriched epoxide. Their optimum conditions, along with their best result are shown in Scheme 1.25. Using 50 mol% loading of sulfide **80**, they obtained *trans*-**32** in 100% yield (calculated with respect to the stoichiometry of the sulfide) and 47% *ee*. They also performed an epoxidation reaction between *p*-chlorobenzaldehyde (**78**) and **80** at just 10 mol% loading. The corresponding epoxide was reportedly obtained in 230% yield (again, calculated with respect to the stoichiometry of the sulfide) and 31% *ee*.[64]



Scheme 1.25 The first catalytic asymmetric sulfonium ylide epoxidation reaction

Since the publication of this ground-breaking methodology, there have been many contributions from other research groups with the aspiration of improving upon the

original catalytic cycle.[65,66] This research has focussed mainly on broadening the scope of the reaction (with respect to substrates and alkylating agents) and the development of superior chiral sulfides. Benzyl bromide is the alkylating agent that appears most frequently in these reactions and the reactions are often performed using *tert*-butanol/water 9:1 or acetonitrile/water 9:1 as solvent with sodium or potassium hydroxide as base.[65b-d,66a,b,e,f,g] These basic reaction conditions generally preclude the use of substrates with enolisable protons; however aromatic,[66] heteroaromatic[66b,g] and aliphatic aldehydes (low diastereoselectivities were observed)[66a] along with cinnamaldehyde[66b,c,g] have been shown to be compatible substrates. Sulfide alkylation is a slow step[67] and depending on the catalyst (more encumbered sulfides tend to take longer periods of time to alkylate), reaction times can vary greatly (from 1 day to one month). To alleviate this issue, additives such as sodium iodide and tetra-*n*-butylammonium iodide (to promote a Finkelstein reaction)[68] are sometimes used.[66b] A further measure that can be taken to accelerate the reaction is the use of tetrabutylammonium sulfate which acts as a phase transfer catalyst.[58a,66f] Loadings of chiral sulfide range from 100 mol% to as low as 10 mol%. A selection of chiral sulfide catalysts that have delivered some of the best results to date in catalytic epoxidation reactions based on the alkylation and deprotonation system are shown (**83-95**, Figure 1.2). Catalysts **83-85** proved to be moderately selective; in epoxidation reactions using **83**, **84** or **85**, *trans*-epoxides were obtained in up to 60%, 77% or 55% *ee* respectively.[65a,62] In reactions catalysed by **86**, only moderate diastereoselectivities (up to 70:30 *trans*/*cis*) and enantioselectivities (up to 70% *ee*) were achieved.[65c] Conversely, sulfides **87-95** purvey epoxides with excellent levels of enantiomeric excess; all of these sulfides provide epoxides in 90% *ee* or higher.[58,66]

Of these sulfides, the C_2-symmetric variety that have been developed independently by Goodman and Metzner afford the highest levels of diastereo- and enantiocontrol in epoxidation reactions.[66a,b,e,f] In 1998, Metzner *et al.* reported the development of a chiral sulfide **87** capable of the enantioselective epoxidation of aromatic and aliphatic aldehydes.[66a] The reactions were performed at room temperature using a stoichiometric quantity of **87**, and a combination of benzyl bromide, *tert*-butanol/water 9:1 and sodium hydroxide. The corresponding epoxides were obtained in high yield (87-92%), high *de*

(84-86%, except in the case where an aliphatic aldehyde was employed as substrate) and high *ee* (86-94%). Although the chiral sulfide can be recovered from the reaction, this process would be more attractive if a substoichiometric quantity of catalyst could be employed. To this end, using the same conditions as before, they performed a reaction containing just 10 mol% loading of sulfide **87**.[66a] Following one month, the reaction had reached completion; despite the lengthy reaction time, the yield, *de* and *ee* were conserved.

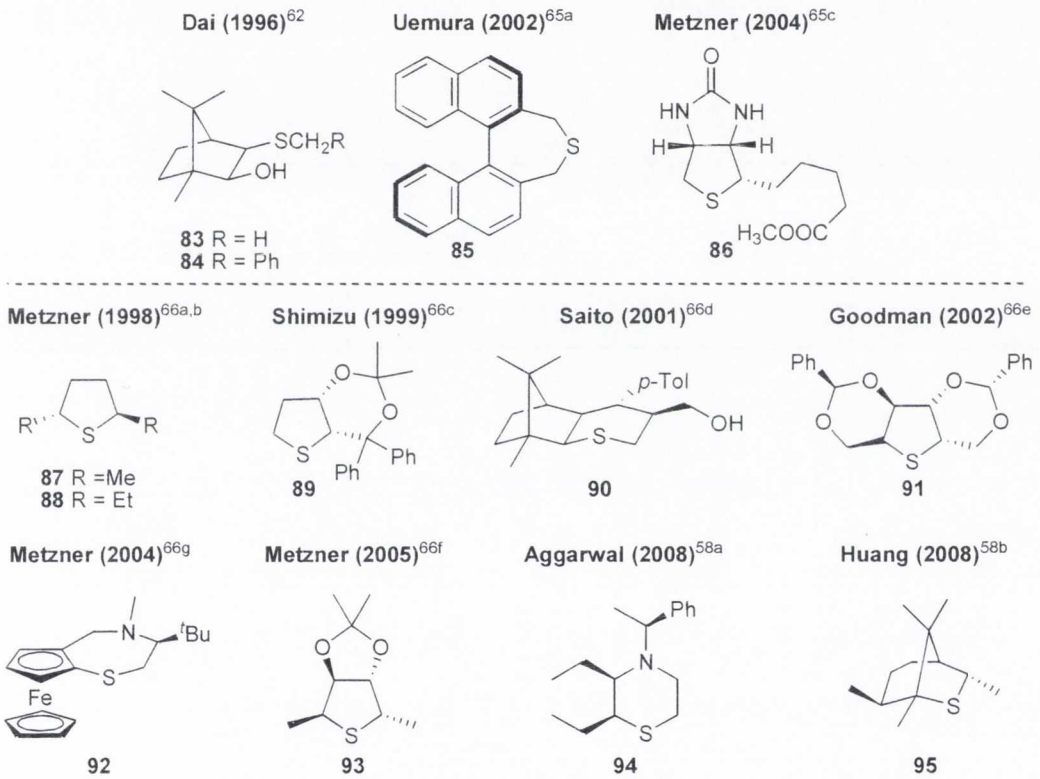
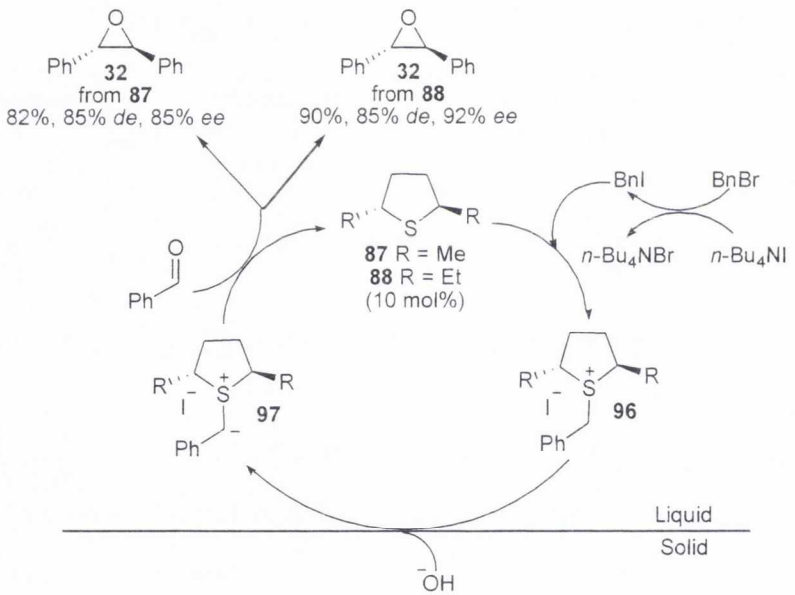


Figure 1.2 A selection of benchmark chiral sulfides that have been developed for epoxidation reactions using the alkylation and deprotonation system

In 2001, the same group reported improvements to this process, along with the development of the bulkier sulfide **88**, which could furnish stilbene oxide in up to 93% *ee* (when used stoichiometrically).[66b] They found that by doubling the concentration of the reaction (with respect to the aldehyde) and adding one equivalent of tetra-*n*-butylammonium iodide or sodium iodide, they could lower the loading of **87** to just 10

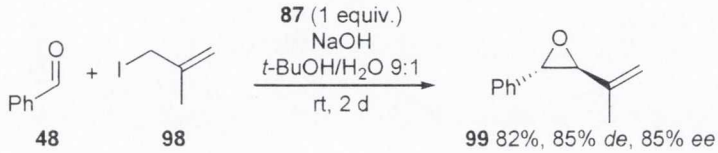
mol% and still effectuate shorter reaction times (up to six days) than before (one month) without too great a diminution in either yield or selectivity (except when cinnamaldehyde was used as substrate; a loss of 18% *ee* was observed). Their new procedure was applied to the epoxidation of a range of aromatic, α,β-unsaturated and heteroaromatic aldehydes using 10 mol% of **87**: the corresponding epoxides were obtained in good yield (60-82%), *de* (75-85%) and *ee* (64-89%). They also discovered that **88** could be used in substoichiometric amounts (10 mol%) and that it exhibited greater selectivity than **87** in the epoxidation of a variety of aromatic aldehydes; for example, stilbene oxide (**32**) that was isolated from a reaction that had been catalysed by 10 mol% **88** showed an increase of 7% *ee* compared to **32** that had been isolated from a reaction that had been performed under the same conditions but had been catalysed by **87** (Scheme 1.26).



Scheme 1.26 Catalytic cycle of the asymmetric epoxidation of benzaldehyde using chiral sulfides **87** and **88**

To further enhance the utility of this procedure, the same group applied this protocol to the asymmetric synthesis of vinyl epoxides *via* allyl transfer from chiral sulfides **87** and **88** to aldehydes.[69] This process was found only to be compatible with β-substituted allyl halides (due to the various reaction pathways that are possible if non β-substituted allyl

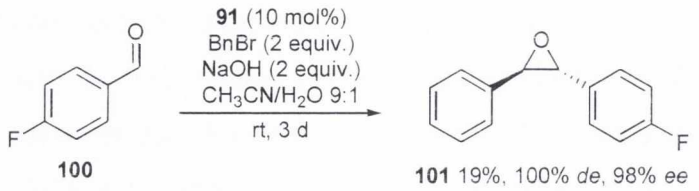
halides are employed).[70] A series of reactions were performed between a selection of β-substituted allyl halides and aromatic and heteroaromatic aldehydes using one equivalent of either **87** or **88** as catalyst. The corresponding vinyl epoxides were returned in good yield (55-85%), poor to moderate *dr* (2.3:1 to >50:1) and poor to high *ee* (45-90%). The best result achieved is illustrated in Scheme 1.27.



Scheme 1.27 The best result obtained in the asymmetric synthesis of vinyl epoxides catalysed by sulfide **87**

The catalyst that has delivered the highest enantioselectivities *via* this system is the C_2-symmetric sulfide **91**, that was developed by Goodman *et al.* in 2002.[66e] This catalyst proved to be highly selective and could furnish stilbene oxide (**32**) in 97% *ee* using one equivalent of **91**; however, the reaction time was seven days and even after this time a yield of just 59% was achieved. They demonstrated that high enantioselectivities could be realised using loadings of as little as 10 mol% of **91**: stilbene oxide (**32**) was obtained in 16% yield and 98% *ee* after two days. The scope of the reaction was also evaluated: it was revealed that only electron deficient aromatic aldehydes were appropriate substrates for this reaction. The most notable result is depicted in Scheme 1.28.

Although the selectivities achieved using sulfide **91** are higher than those achieved using either **87** or **88**, due to the attainment of meagre yields of epoxide after extended reaction times, the catalysts proposed by Metzner offer a more well-balanced combination of chemical yield and enantioselectivity.



Scheme 1.28 The best result obtained in the asymmetric epoxidation of aromatic aldehydes catalysed by **91**

The catalysts that have been developed for this system to date have enjoyed great success; they have displayed great levels of selectivity in many instances and have found application in the synthesis of a variety of classes of epoxide, including vinyl epoxides and glycidic amides.[58,62,65-67,69,71,72]

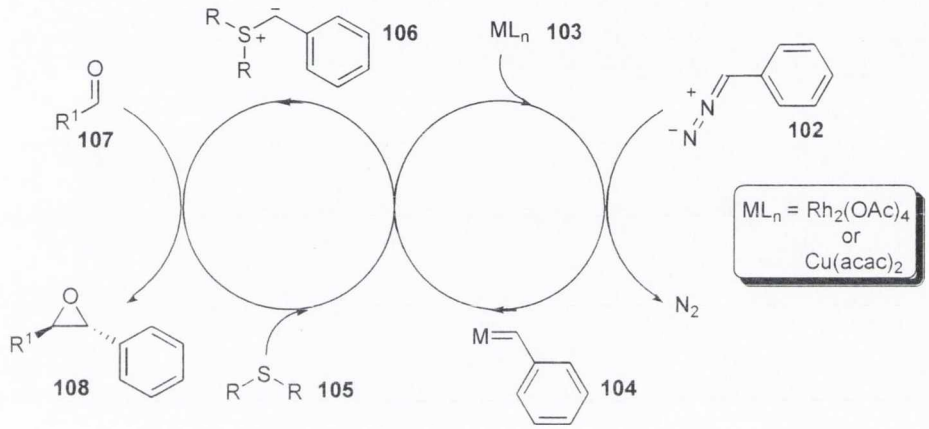
1.3.2.2.2 Catalysis *via* ylide formation from a carbene source

Due to the sluggish nature of the alkylation step in catalytic asymmetric epoxidation reactions *via* the sulfide alkylation and subsequent deprotonation system (*vide supra*), the development of alternative methods for the formation of the sulfonium ylide *in situ* has been an area of great interest (*vide infra*). An alternative system that can be employed to perform a catalytic sulfonium ylide-mediated epoxidation reaction involves the reaction of a sulfide with either a carbene or carbenoid to form an ylide *in situ*. There are two primary advantages associated with the preparation of an ylide using this methodology: the deprotonation step discussed in Section 1.3.2.2.1 is bypassed, and the conditions under which the reactions are conducted are neutral. There are three methods by which the carbene can be generated (*vide infra*).

1.3.2.2.2.1 Catalytic asymmetric sulfonium ylide epoxidation: the generation of a carbene from a diazo compound

One of the methods that can be employed to form a sulfonium ylide is the transition metal-mediated decomposition of a diazo compound (rhodium and copper salts have

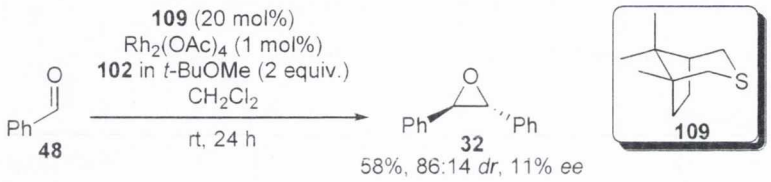
proven to be particularly efficient in this process).[73] If the resulting rhodium or copper carbenoid is trapped with a sulfide, a sulfonium ylide will result. Attempts have been made to exploit this strategy toward the development of a catalytic asymmetric epoxidation protocol.[74-84] In 1994, Aggarwal *et al.* reported the first example of a catalytic transition metal-mediated sulfonium ylide epoxidation reaction.[74] This procedure was based on the catalytic cycle illustrated below (Scheme 1.29).



Scheme 1.29 The catalytic cycle for the catalytic sulfonium ylide-mediated epoxidation *via* a carbene derived from a diazo compound

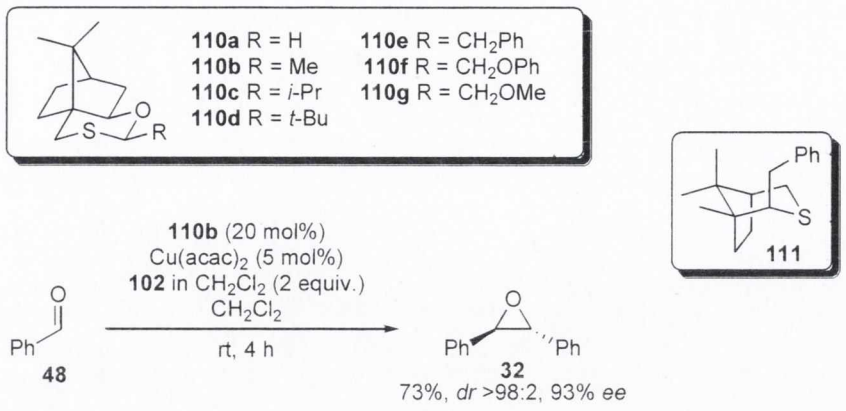
Their original catalytic cycle, which required one equivalent of sulfide, involved the decomposition of phenyl diazomethane (**102**) with rhodium acetate (*e.g.* **103**) to form a rhodium carbenoid (*e.g.* **104**) which was trapped with dimethyl sulfide (*e.g.* **105**) to form a sulfonium ylide (*e.g.* **106**) which subsequently reacted with an aldehyde (*e.g.* **107**) to produce an epoxide (*e.g.* **108**). By taking precautions to minimise unwanted reaction pathways such as the reaction of **102** with the aldehyde or the dimerisation of **102** in the presence of the metal carbenoid (which can be achieved by adding **102** over a period of time so as to keep its concentration as low as possible), they succeeded in developing a catalytic (in sulfide) procedure. This was achieved by adding **102** (2 equiv. in methyl *tert*-butyl ether) to a reaction containing dimethyl sulfide (20 mol%), rhodium acetate (1 mol%) and aldehyde (1 equiv.) in dichloromethane over a 24 hour period. A range of aromatic and aliphatic aldehydes were successfully epoxidised affording good yields of

epoxide (45-89%). In the same report, they detailed the application of chiral sulfide **109** (which had previously been reported by Durst *et al.*[63e] in a stoichiometric sulfonium ylide epoxidation reaction) in this cycle. Using the same procedure just described, employing 20 mol% of **109**, they obtained **32** in 58% yield and 11% *ee* (Scheme 1.30). It is noteworthy that the yield that was realised in this instance is higher than that obtained by Durst (39% *trans*, 16% *cis*) using a stoichiometric quantity of the preformed sulfonium salt of **109** (however, Durst observed product *ee* of 15% of *trans* **32**).[63e,74]



Scheme 1.30 The first example of a catalytic asymmetric epoxidation reaction *via* a metal carbenoid and a substoichiometric quantity of chiral sulfide

Since the unveiling of this pioneering catalytic cycle, there have been efforts made to develop this into a more enantioselective process.[77-80] In 1996, Aggarwal *et al.* accomplished this task by developing a range of chiral thioacetals (**110a-g**), and to accommodate the use of more sterically hindered sulfides, a modified version of the original catalytic cycle.[79] They found that when the more encumbered sulfide **111**[63e] (1 equiv.) was employed in the catalytic cycle with benzaldehyde as substrate (under the same reaction conditions that were employed in Scheme 1.30), **32** was not observed. However, they found that by replacing $Rh_2(OAc)_4$ with $Cu(acac)_2$, **32** could be prepared in 40% yield. They attributed this to $Cu(acac)_2$ and **102** leading to the formation of a less hindered copper carbenoid which is capable of reacting with more sterically challenging sulfides. Having optimised the catalytic cycle, thioacetals **110a-g** were employed in reactions with benzaldehyde as the substrate: thioacetal **110b** provided the best yield (73%), *dr* (>98:2) and *ee* (93%) (Scheme 1.31).



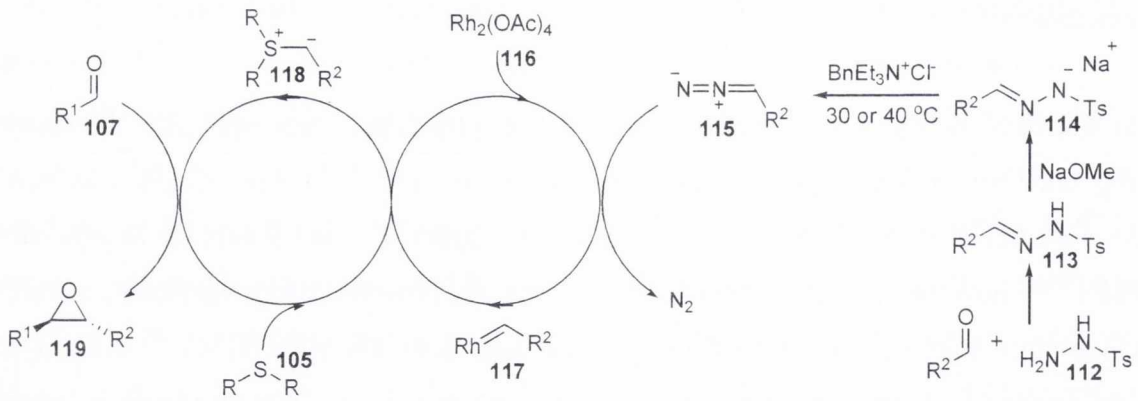
Scheme 1.31 The catalytic asymmetric epoxidation of benzaldehyde *via* a copper carbenoid and a substoichiometric quantity of chiral sulfide

Having identified the optimum catalyst, the scope of the reaction was investigated: **110b** successfully catalysed the epoxidation of a range of aromatic and α,β-unsaturated aldehydes in good yield (64-73%), excellent *dr* (>98:2) and *ee* (89-92%). Aliphatic aldehydes led to lower yields (32-35%), diastereoselectivities (70:30-92:8) and enantioselectivities (68-90% *ee*) of epoxide.

This catalytic procedure using the transition metal-mediated decomposition of diazo compounds has proven to be a useful methodology for the synthesis of epoxides derived from base sensitive aldehydes.[75,76] It has also been applied to the synthesis of glycidic amides;[83,84] however, greater enantioselectivities can be achieved using the stoichiometric methodology involving preformed chiral sulfonium salts (Scheme 1.24).[61b] Although promising results have been obtained in catalytic asymmetric epoxidation reactions using this methodology, there is one major issue that inhibits its synthetic utility: diazo compounds are hazardous materials that are both toxic and explosive.[85] Furthermore, phenyl diazomethane alone has been successfully employed as the diazo component in asymmetric epoxidation reactions based on this catalytic cycle[86] which inevitably restricts the scope of epoxides that can be prepared. For example, it has been reported that *p*-methoxyphenyl diazomethane decomposes at -80 °C and may detonate when isolated.[87]

1.3.2.2.2.2 Catalytic asymmetric sulfonium ylide epoxidation: the generation of a carbene from *N*-tosylhydrazone salts

To circumvent the restrictions posed by the diazo-mediated epoxidation process (*vide supra*), Aggarwal *et al.* developed a modification of this procedure, based on the Bamford-Stevens reaction,[88] involving the *in situ* generation of the diazo compound from *N*-tosylhydrazone salts (**114**, Scheme 1.32).[89] After extensive optimisation studies using the achiral sulfide tetrahydrothiophene (counterion, metal catalyst, solvent, temperature, scope *etc.*), the modified catalytic procedure depicted in Scheme 1.32 was developed.[89,90] The *N*-tosylhydrazones **113** were prepared from an appropriate aldehyde and tosylhydrazine (**112**): subsequent treatment of the newly formed *N*-tosylhydrazone **113** with a base (sodium methoxide) afforded the *N*-tosylhydrazone sodium salt **114**. Heating a suspension of the *N*-tosylhydrazone salt and a phase transfer catalyst (benzyl triethylammonium chloride) effectuated the smooth generation of the diazo compound **115**.[89]



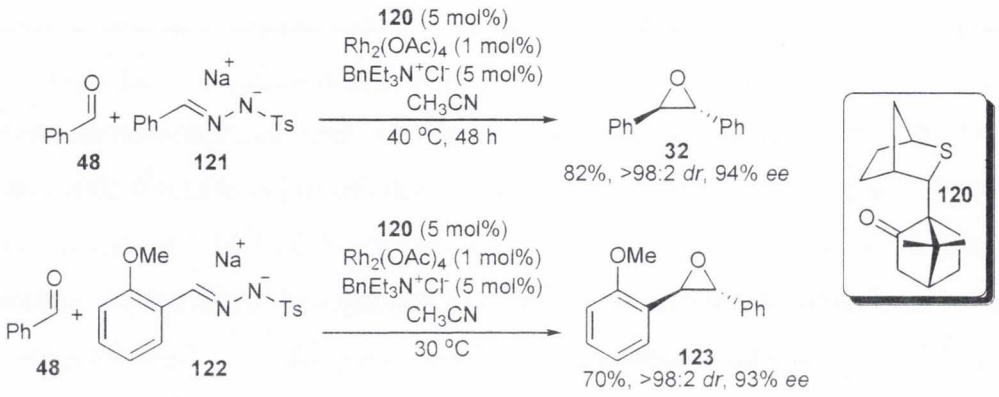
Scheme 1.32 The catalytic cycle for the catalytic asymmetric epoxidation of carbonyl compounds *via* *N*-tosylhydrazone salts

Rhodium acetate was found to be the optimum metal catalyst in this improved procedure. The investigations into the scope of this process using tetrahydrothiophene as sulfide component revealed that a broad range of carbonyl compounds, and indeed tosylhydrazone salts, were compatible with this process.[90] Aromatic aldehydes afforded

high yields of epoxide (87-98%) and excellent diastereoselectivities, while both heteroaromatic (33-90%) and α,β-unsaturated aldehydes (33-97%) returned poor to high yields of the corresponding epoxides and very good to excellent levels of diastereocontrol. Aliphatic aldehydes also proved to be suitable substrates, yielding epoxides in moderate yield (49-70%) and diastereoselectivity, as did propargylic aldehydes (60%), in which case no diastereocontrol was observed. Ketones however did not fare as well as aldehydes as the carbonyl component in this reaction.[90] The scope of the tosylhydrazone salt component was also investigated and it was found that in reactions with benzaldehyde as substrate, a variety of differently substituted tosylhydrazone salts were compatible. Tosylhydrazone salts derived from both electron deficient and electron rich aldehydes afforded the corresponding epoxides in high yield (73-95%) and diastereoselectivities, except when mesitaldehyde was used as substrate, which gave a yield of epoxide of just 17%. *N*-Tosylhydrazone salts derived from heteroaromatic aldehydes also gave good results and the corresponding epoxides were obtained in moderate to high yield (51-96%) and poor to high diastereoselectivity. Again, the ketone derived tosylhydrazone salt fared worse than those derived from aldehydes as it gave irreproducible results. The prospect of preparing vinyl epoxides *via* this methodology was also explored and it was found that in reactions with benzaldehyde, α,β-unsaturated tosylhydrazone salts, the corresponding epoxides could be obtained in poor to moderate yield: high diastereoselectivities were only observed when both the α- and β-positions were substituted.

In order to make this process asymmetric, a number of chiral sulfides were prepared and their performance in epoxidation reactions based on this catalytic cycle were evaluated;[90,91] however, of all the sulfides that were screened, sulfide **120** provided the best results. Some of the best results achieved are illustrated in Scheme 1.33. Aromatic and heteroaromatic aldehydes proved to be good substrates affording moderate to excellent yields (30-100%), excellent diastereo- (>98:2) and enantioselectivities (89-94%) of the corresponding epoxides (*e.g.* **32**, Scheme 1.33). The yields obtained when aliphatic aldehydes were substrates were moderate (46-58%), the *dr*'s varied from >98:2-75:25, and the enantioselectivities were uniformly high (89-94% *ee*). α,β-Unsaturated

aldehydes also proved to be good substrates: epoxides were returned in low to good yield (21-70%), high *dr* (>98:2) and good *ee* (87-88%).

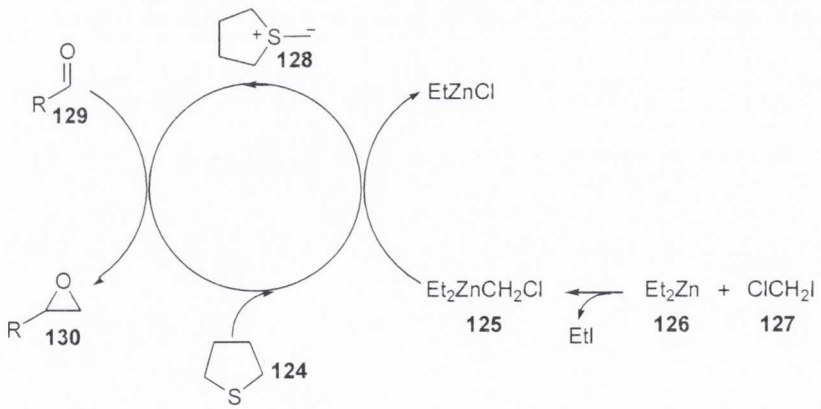


Scheme 1.33 Representative results obtained in the evaluation of reaction scope using chiral sulfide **120**

They also investigated the scope of the tosylhydrazone salt component in reactions with benzaldehyde as substrate: tosylhydrazone salts derived from both electron deficient and electron rich aldehydes afforded the corresponding epoxides in moderate to high yield (64-95%, except when mesitaldehyde was used as substrate; a yield of 10% was obtained using 100 mol% of **120**), high *dr* (80:20->98:2) and moderate to high *ee* (64-94%) (*e.g.* **123**, Scheme 1.33).[90] Tosylhydrazone salts derived from heteroaromatic aldehydes did not fare as well: the corresponding epoxides were obtained in moderate yield (46-53%), poor to good *dr* (63:37-90:10) and moderate *ee* (61-63%). They also attempted to apply this asymmetric protocol to the synthesis of vinyl epoxides *via* α,β-unsaturated tosylhydrazone salts: in reactions with benzaldehyde, poor yields were obtained (12-56%) and high *dr*'s (>98:2) were only observed when the α-position was substituted and required either 20 or 100 mol% of **120**. Likewise, high *ee* (88%) was only achieved in one instance, when the α-position was substituted, and again this required 100 mol% loading of **120**. It should be noted that in the aforementioned reactions, depending on the carbonyl component and tosylhydrazone salt that were employed in the reaction, varying quantities of **120**, phase transfer catalyst and temperature were required for epoxidation reactions to occur.[90]

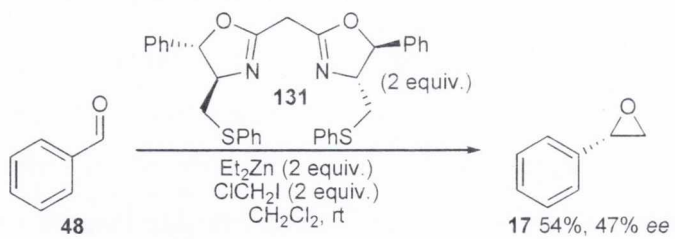
1.3.2.2.2.3 Catalytic asymmetric sulfonium ylide epoxidation: the generation of a carbene from a Simmons-Smith reagent. The enantioselective synthesis of terminal epoxides

The chiral sulfonium ylide-mediated method for the asymmetric synthesis of epoxides has proven to be successful thus far for a variety of different classes of epoxide (*vide supra*). The enantioselective synthesis of terminal epoxides *via* this methodology however, has not enjoyed the same success. The most useful procedures to date have relied on Simmons-Smith reagents for the formation of the sulfonium ylide (*vide infra*). In 1997, Aggarwal *et al.* reported the first example of such a reaction using an achiral sulfide, tetrahydrothiophene (**124**).[92] The catalytic cycle which they envisioned and successfully developed is depicted in Scheme 1.34. The reaction involves the formation of a zinc carbenoid **125** from diethyl zinc (**126**) and chloroiodomethane (**127**), followed by reaction with **124** to form sulfonium ylide **128** which subsequently adds to an aldehyde to yield the desired epoxide. Aromatic and aliphatic aldehydes proved to be suitable substrates in reactions with **124** (3 equiv.) affording moderate to excellent yields (58-95%) of the corresponding epoxides.



Scheme 1.34 The catalytic cycle for the Simmons-Smith mediated asymmetric sulfonium ylide epoxidation

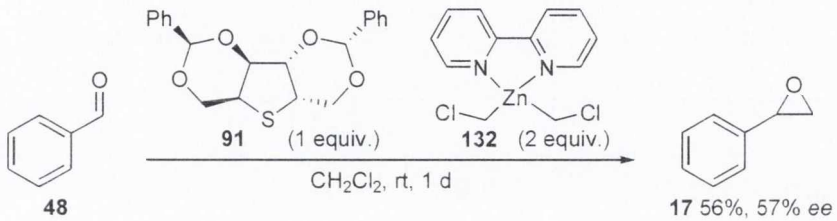
It was proven that the former method involving the transition metal mediated decomposition of diazo compounds (Section 1.3.2.2.2.1 and 1.3.2.2.2.2) could not be applied to the synthesis of terminal epoxides: it is postulated that diazomethane undergoes facile transformation to ethylene under these conditions.[50b,93] Thus, the development of the Simmons-Smith-mediated epoxidation reaction into an enantioselective process was desirable. This was achieved by Aggarwal *et al.* in 2002.[93] A variety of chiral sulfides were prepared and their performance in epoxidation reactions with benzaldehyde was evaluated. The results obtained were interesting: both chiral sulfides **87** and **120** had previously returned racemic styrene oxide under conventional Corey-Chaykovsky reaction conditions, however under Simmons-Smith conditions, styrene oxide was obtained in 12% and 16% *ee* respectively. This implies that the zinc ion is in close proximity to the ylide in the transition state of the reaction.[93] Inspired by this, they sought to develop a chiral catalyst incorporating both a ligand capable of binding the zinc ion and a sulfide moiety from which the ylide could be generated *in situ*. It was hoped that the bound metal would complex the aldehydic oxygen atom and addition of the ylide to the aldehyde would occur in an intramolecular fashion, thus giving rise to greater enantioselectivity of the resulting epoxide. To this end, a range of oxazolines and *bis*(oxazolines) were prepared: **131** proved to be the optimum catalyst in a reaction with benzaldehyde, affording **17** in 54% yield and 47% *ee* (Scheme 1.35).



Scheme 1.35 Simmons-Smith-mediated asymmetric methylene transfer to benzaldehyde using **131**

In 2004, Goodman *et al.* reported a modified version of this protocol, along with the superior chiral sulfide **91**.[94] Due to the capricious results obtained using diethyl zinc, they

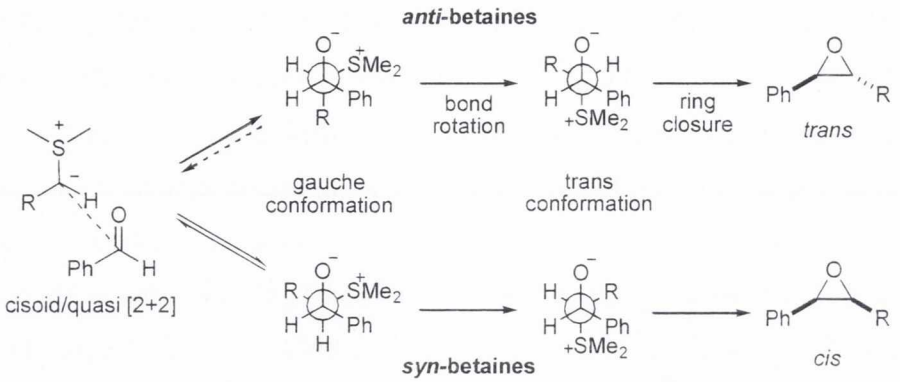
developed the stable, isolable zinc complex **132**. In a reaction performed with benzaldehyde, **91** (1 equiv.) and **132** (2 equiv.), styrene oxide was obtained in 56% yield and 57% *ee*, which is the highest enantioselectivity reported to date in an asymmetric sulfonium ylide-mediated epoxidation reaction involving benzaldehyde as substrate.[94]



Scheme 1.36 Simmons-Smith-mediated asymmetric methylene transfer to benzaldehyde using **91**

1.3.3 Delving deeper into the mechanism of the CC reaction: the origin of diastereo- and enantioselectivity

The chiral sulfonium ylide-mediated epoxidation reaction has proven to be unpredictable with respect to the observed selectivities; in some instances poor selectivities are observed, whilst in others, excellent levels of epoxide diastereo- and enantioselectivity are observed (*vide supra*). To enable the development of new, improved procedures and the design of more selective catalysts, it is paramount that the underlying factors governing the stereochemical outcome of these reactions be fully understood. There are three explicit steps involved in the Corey-Chaykovsky reaction: addition of the ylide to the aldehyde in a cisoid (quasi [2+2]) fashion[49] leading to the formation of a betaine with charges adjacent (gauche) to each other,[49] followed by torsional C-C bond rotation to the *trans*-conformation (with charges *anti*) and final ring closure to afford the epoxide (Scheme 1.37). Overall, the *syn* pathway leads to a *cis*-epoxide and conversely, the *anti* pathway leads to a *trans*-epoxide. Therefore, the key question is - what are the factors that influence the outcome of this reaction from a selectivity standpoint?



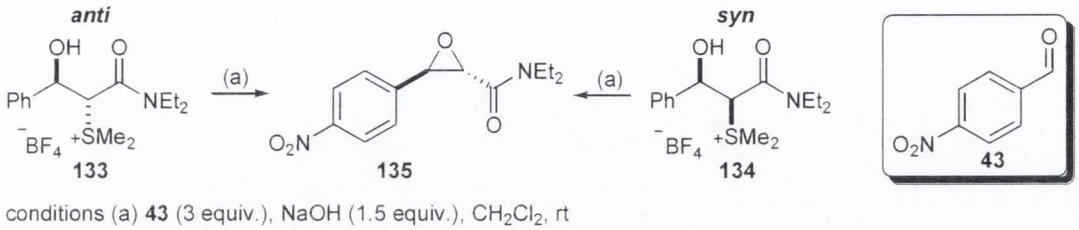
Scheme 1.37 The Corey-Chaykovsky reaction mechanism from a stereochemical perspective

1.3.3.1 The origin of diastereoselectivity (and enantioselectivity): stabilised ylides

There are three general classes of ylides: stabilised, semi-stabilised and non-stabilised. Stabilised ylides are those that have an adjacent anion-stabilising group (*e.g.* an ester or amide), semi-stabilised ylides are those that have a weakly anion stabilising group (*e.g.* benzyl or allyl) and non-stabilised ylides are those that are unable to stabilise negative charge (*i.e.* alkyl or H). The levels of epoxide diastereo- and enantioselectivity observed in epoxidation reactions are inextricably linked to the nature of the ylide employed in the reaction (*vide infra*). For example, complete diastereocontrol (and almost complete enantiocontrol[61a]) has been achieved employing amide-stabilised ylides in this reaction, purveying *trans*-glycidic amides exclusively (*vide supra*, Scheme 1.24).[61,63b,83,84]

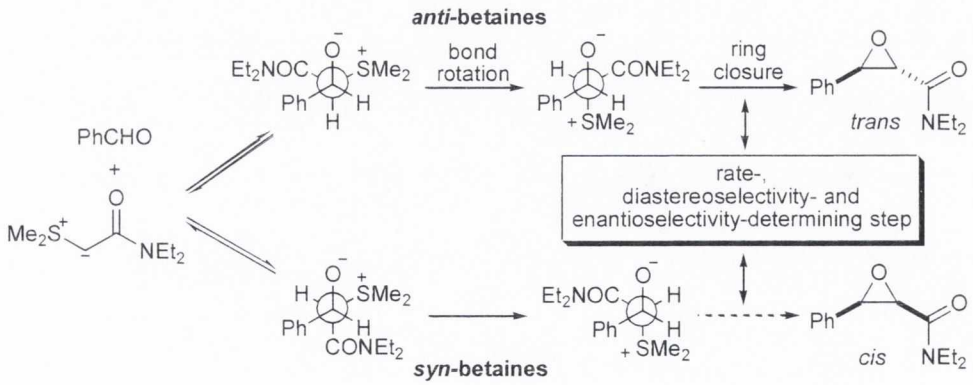
It has been found (in general) that the diastereoselectivity of this process is dependent upon the degree of reversibility of betaine formation.[49] To elucidate the reversibility of the betaine intermediates that result from the addition of an amide-stabilised ylide to benzaldehyde, crossover studies were performed (Scheme 1.38).[95] The deprotonation of the diastereomeric hydroxysulfonium salts **133** and **134** (in separate reactions) in the presence of the more reactive aldehyde **43** afforded *trans*-**135** exclusively. This insinuates that both *syn*- and *anti*-betaines derived from amide-stabilised ylides are formed

reversibly; therefore the rate determining step in this reaction is either bond rotation or ring closure.



Scheme 1.38 Crossover experiment performed to elucidate the reversibility of *syn*- and *anti*-betaines derived from amide-stabilised ylides **133** and **134**

To probe this uncertainty, the energy profile was calculated computationally and it was found that in the case of both *syn*- and *anti*-betaines, the energy barrier for reversion to starting materials was very close in magnitude to that of bond rotation.[61b] The step that was determined to be highest in energy, *i.e.* the rate- and diastereoselectivity-determining step, is ring closure of the *syn*-betaine (Scheme 1.39).



Scheme 1.39 CC epoxidation using stabilised ylides: stereochemical rationale

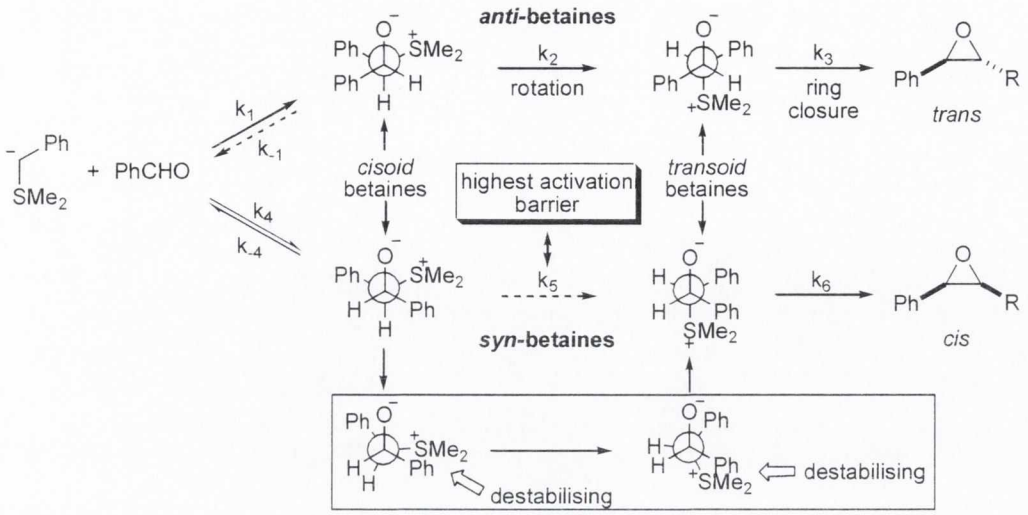
Ring closure of the *syn*-betaine is disfavoured (this is reportedly due to developing steric interactions between the phenyl substituent of the aldehyde and the amide substituent of the ylide) and therefore unproductive. This gives rise to the exclusive production of

trans-epoxide. This is also the enantiodifferentiating step; however, the precise interactions that occur in this transition state that result in excellent levels of epoxide *ee* are not fully understood.[61] Scheme 1.39 is representative of this process.

1.3.3.2 The origin of diastereoselectivity: semi-stabilised ylides

Compared with the aforementioned epoxidation reactions involving stabilised ylides, those that involve semi-stabilised ylides (*e.g.* benzyl- and allyl-stabilised ylides) represent a more intricate class of reactions with respect to the factors governing stereocontrol. Unlike the preceding class of ylides (stabilised), the betaines (*syn* and *anti*) that result from the addition of semi-stabilised ylides to aldehydes are not all formed reversibly: only *syn*-betaine formation is reversible while *anti*-betaine formation is irreversible (as before, this was elucidated from crossover experiments).[96] Therefore, the high *trans* selectivity that is often observed in epoxidation reactions involving semi-stabilised ylides and aromatic aldehydes[54,55,57,58,60,62,65a,d,66,74,76,79,80,90,91,97,98] (*vide supra*) is due to the unproductive reversible formation of *syn*-betaines and the productive irreversible formation of *trans*-betaines.

DFT calculations validated these observations;[49] it was observed that the highest activation barriers in Scheme 1.40 were those corresponding to C-C bond rotation (k_2 and k_5). In the case of the *syn*-betaine, the barrier for reversion to starting materials (k_{-4}) was lower than the barrier to bond rotation (k_5), whereas in the case of the *anti*-betaine, the barrier to bond rotation (k_2) was lower than the barrier for reversion to starting materials (k_{-1}). The highest activation barrier in the reaction was found to be k_5, *i.e.* bond rotation of the *syn*-betaine, thus explaining the high *trans* selectivity observed in the resulting epoxides. Upon inspection of the bond rotation step of the *syn*-betaine in Scheme 1.40, it becomes apparent why this step has the highest energy barrier: the eclipsed interaction between the phenyl group of the aldehyde and the dimethylsulfonium group of the ylide is destabilising.[49]



Scheme 1.40 CC epoxidation using benzyl-stabilised ylides: stereochemical rationale

In certain circumstances, *e.g.* when other substrates or sulfonium salts are employed, a diminution in diastereoselectivity is observed. This occurs if *syn*-betaine formation is either no longer, or less reversible, leading to the formation of *cis*-epoxide and consequently reduced *trans* selectivity. There are four factors that can affect the reversibility of betaine formation: [42,50b, 95] 1) if a less thermodynamically stable carbonyl substrate is employed in the reaction, the resulting ylide is less likely to revert back to it and the ylide. For example, aliphatic aldehydes are usually associated with lower diastereoselectivities than their aromatic counterparts (*vide supra*),[58b,66a,90] 2) the reversibility will also be decreased if a less thermodynamically stable ylide is employed in the reaction, *i.e.* one that is less capable of stabilising a negative charge such as an electron donating group on the aromatic ring,[90] 3) if sterically unencumbered ylides (*e.g.* allylic sulfonium ylides with an α-H substituent[60,69,90]) and/or carbonyl substrates (*e.g.* propargylic aldehydes[57,90]) are employed, k_5 in Scheme 1.40 will be lowered as the destabilisation associated with the interaction between the aldehydic substituent and the substituents on the sulfur atom of the ylide will be reduced, thus favouring formation of *cis*-epoxide, 4) the use of polar solvents and lithium salts have also been shown to lower the barrier to rotation (k_5 in Scheme 1.40).[49,90] *Transoid*-betaines are less thermodynamically stable than cisoid betaines (Scheme 1.40). It has been observed that

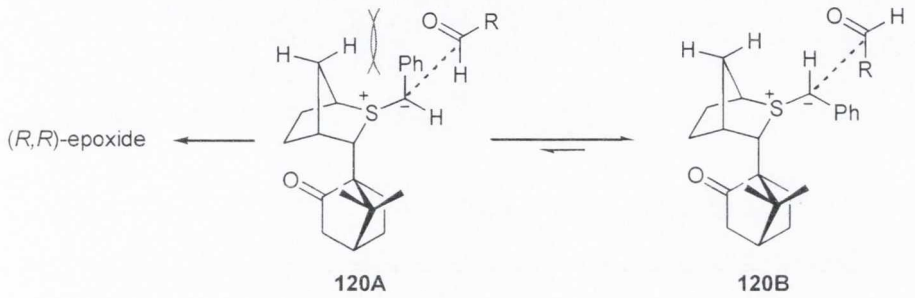
solvation of the charges by protic solvents or lithium salts results in the stabilisation of these transoid-betaines which will lead to a lowering of k_5 and thus an increase in *cis*-epoxide production.[49,95] With the above considerations in mind, many procedures have been developed to date (utilising both chiral and achiral sulfides) that have led to excellent,[58,60,65c,66a-d,f,g,79,91] and in some cases complete,[54,55,57,62,65a,66c,66e,74,76,80,90,97,98] diastereocontrol.

1.3.3.3 The origin of enantioselectivity

Enantiocontrol in sulfonium ylide-mediated epoxidation reactions with prochiral carbonyl substrates depends entirely on the use of chiral sulfides.[49] As epoxidation reactions involving semi-stabilised ylides predominantly occur *via* the non-reversible addition of the ylide to the carbonyl compound leading to a *anti*-betaine intermediate (*vide supra*), it is the transition state leading to this that is the enantiodifferentiating step.[49] The sense of enantioinduction is dependent upon which of the two enantiotopic faces of the ylide the reaction with the aldehyde occurs. There are four fundamental criteria that must be fulfilled to achieve high levels of enantioselectivity in these reactions.[49,95] 1) Only one of the lone pairs on the sulfur atom of the sulfide should react to generate only one diastereomeric sulfonium salt/ylide. 2) There must be control over the conformation of the resulting ylide. 3) The reaction with the carbonyl compound should occur from only one enantiotopic face of the ylide. 4) The formation of the *anti*-betaine should be non-reversible.

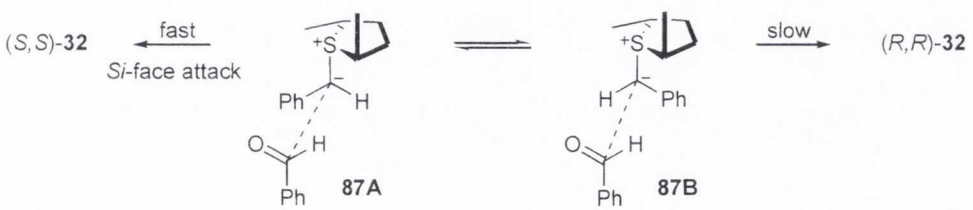
One example where control over the four aforementioned criteria was accomplished was in epoxidation reactions using chiral sulfide **120**, which led to high levels of diastereo- and enantiocontrol.[89-91] Control over the first criterion is achieved as the bulky camphoryl moiety allows only the *exo* lone pair on the sulfide to react, leading to only one diastereomeric sulfonium ylide (Scheme 1.41).[89] There are two possible conformations the resulting ylide can adopt: **120A** or **120B**. The conformation that prevails is **120B** as the 1,4-steric interactions in conformation **120A** render it unfavourable. As the *Si* face of the ylide is blocked by the bulky camphoryl moiety, the aldehyde can only approach the

ylide from the less hindered *Re* face, thereby leading to just one major isomer. To satisfy the fourth criterion, it is vital that *anti*-betaine formation remain non-reversible; however, if the ylide becomes too hindered or stable, *anti*-betaine formation can become reversible.[95] A balance must be struck such that the steric hindrance of the ylide is sufficient to satisfy criterion 2), but not so much that *anti*-betaine formation becomes an issue.



Scheme 1.41 Successful control over the four criteria necessary to achieve high enantioselectivity exhibited by **120**

Another stratagem that can be employed to achieve control over the four criteria is the use of a C_2-symmetric sulfide such as **87** reported by Metzner *et al.*[66a,b] Using a C_2-symmetric sulfide guarantees formation of just one diastereomeric sulfonium ylide. The two possible conformations that the resulting ylide can adopt are shown below (**87A** and **87B**, Scheme 1.42).

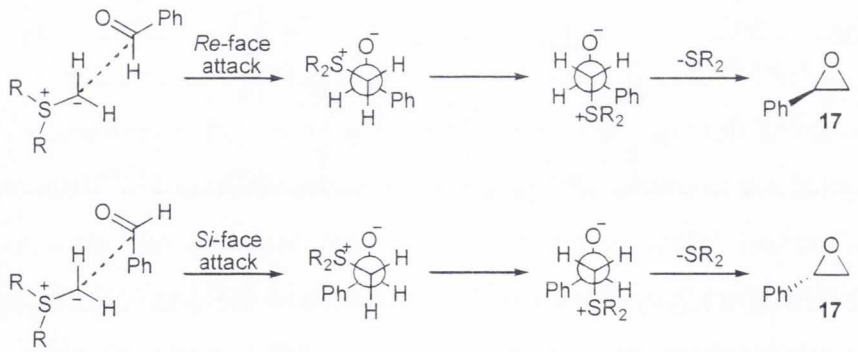


Scheme 1.42 Using a C_2-symmetric sulfide to control the four criteria necessary to achieve high enantioselectivity

In this case, the conformation of the ylide is not stringently controlled as before; the two conformations **87A** and **87B** are in rapid equilibrium but **87A** is considerably more reactive than **87B** leading to the observed high enantioselectivities.[99] The aldehyde approaches **87A** from the *Si* face of the ylide as the *Re* face is blocked by the methyl group on the carbon atom α to sulfur. As previously mentioned, to satisfy the fourth criterion, a balance should be struck regarding ylide hindrance and stability such that *anti*-betaine formation remains non-reversible. **87** And **120** are a mere two examples of chiral sulfides that have been employed in epoxidation reactions where excellent levels of product enantiomeric excess have been achieved through control over the four aforementioned requisite criteria, and indeed, many other accomplished chiral sulfides have been reported to date.[52,54,55,57,58a,60,66,79,80,89,90,91,97,100]

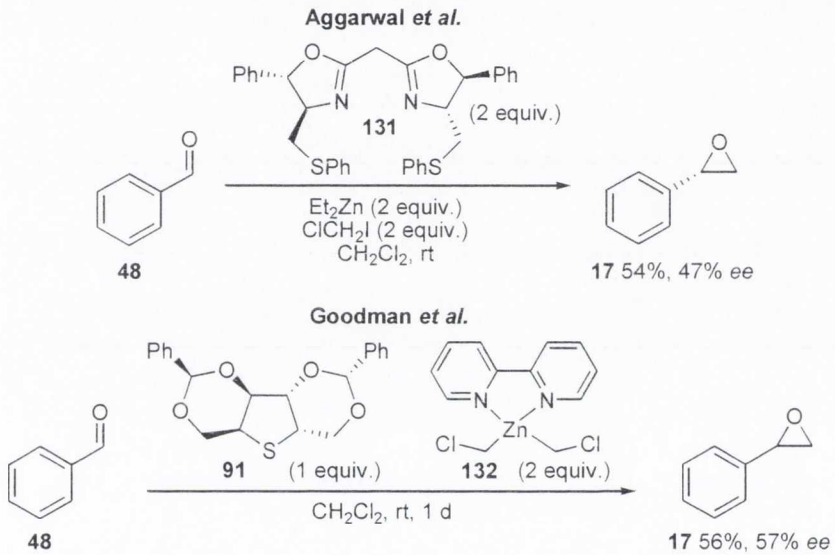
1.3.3.4 The origin of enantioselectivity: non-stabilised ylides. The asymmetric synthesis of terminal epoxides

Great success has been enjoyed in the catalytic asymmetric synthesis of epoxides *via* stabilised and semi-stabilised ylides (*vide supra*); however, the synthesis of terminal epoxides *via* asymmetric methylene transfer using non-stabilised ylides is thus far void of protocols leading to high levels of enantioselectivity.[51,63e] In the case of non-stabilised ylides, betaine formation is non-reversible and enantioselectivity is derived solely from which face of the aldehyde is attacked by the ylide (Scheme 1.43).[95]



Scheme 1.43 The origin of enantioselectivity in the asymmetric synthesis of terminal epoxides *via* methylene transfer from non-stabilised ylides

The protocols that have achieved the highest levels of enantioselectivity to date involve the use of a Simmons-Smith reagent (Section 1.3.2.2.2.3).[93,94] Using chiral sulfide **131** (2 equiv.) and a Simmons-Smith reagent, Aggarwal *et al.* epoxidised benzaldehyde to styrene oxide in 47% *ee* (Scheme 1.44).[93] The highest enantioselectivity that has been reported to date for the epoxidation of benzaldehyde *via* methylene transfer was achieved by Goodman *et al.* using chiral sulfide **91** (1 equiv.) and a Simmons-Smith reagent. Using this protocol, styrene oxide was obtained in 57% *ee* (Scheme 1.44).[94]

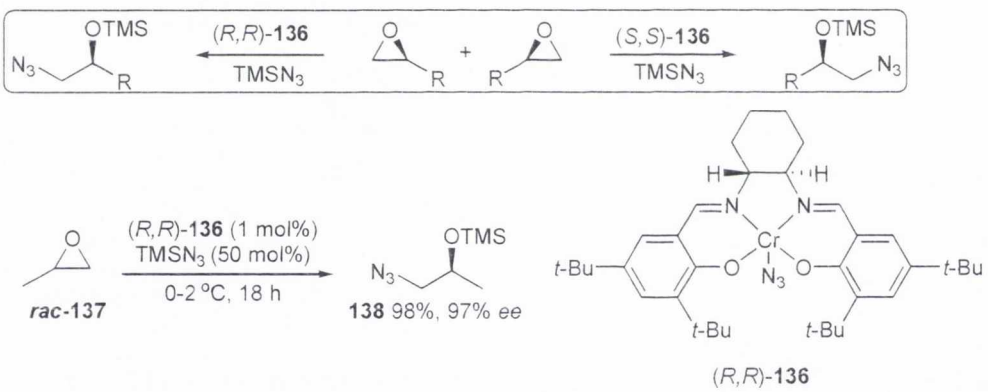


Scheme 1.44 Benchmark protocols for the synthesis of styrene oxide (**17**) *via* asymmetric methylene transfer

An alternative approach was taken by Solladié-Cavallo *et al.* in which two functionalised ylides **58** and **59** were reacted with paraformaldehyde to furnish the corresponding terminal epoxides **55** and **56** in 96% and 84% *ee* respectively (Scheme 1.21).[52] This methodology however, does not accommodate the synthesis of a broad scope of terminal epoxides. It is therefore evident that asymmetric methylene transfer to carbonyl compounds represents the route to enantioenriched terminal epoxides that has greatest potential.

1.4 The most efficient method for the enantioselective preparation of terminal epoxides: kinetic resolution (KR) of terminal epoxides

Of the methods that have been reported to date for the preparation of enantioenriched terminal epoxides, the method reported by Jacobsen *et al.* involving KR *via* ring-opening using either $TMSN_3$[101] or H_2O[102,104,105] is the most efficient. The preliminary reports detailed KR *via* the addition of $TMSN_3$ to terminal epoxides, catalysed by a modified version of the previously reported salen **14** (Scheme 1.45).[101] A range of terminal epoxides were ring-opened in the presence of **136** to furnish the enantioenriched unreacted epoxide and the corresponding 1-azido-2-trimethylsiloxyalkanes in high yield (74-98%, yields based on $TMSN_3$) and enantiomeric excess (89-98%, *e.g.* **138**, Scheme 1.45).[101c]



Scheme 1.45 KR of terminal epoxides using $TMSN_3$ and **136**

The reaction is believed to operate *via* a bimetallic mechanism: one Lewis acidic metal(salen) complex activates the electrophile (epoxide) and a second activates the nucleophile, thus providing a chiral environment for the addition of the nucleophile to only one enantiomer of the electrophile, *i.e.* epoxide (Figure 1.3).[103]

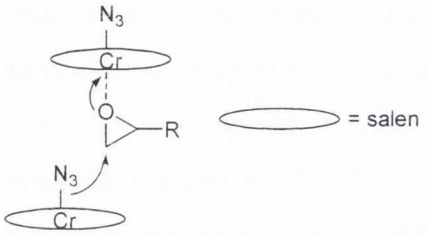
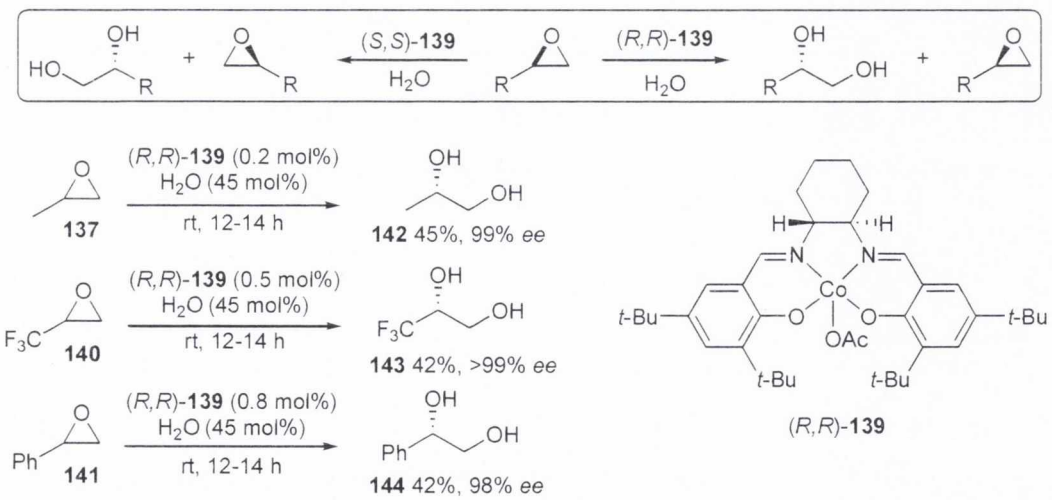


Figure 1.3 Proposed dual activation mechanism for the KR of terminal epoxides using $TMSN_3$

A major improvement was subsequently made to this protocol: developments were made to allow the use of water as the nucleophile, thereby yielding enantiopure terminal epoxides and 1,2-diols in a process termed 'hydrolytic kinetic resolution' (HKR).[102,104,105] Using catalyst **139**, a broad spectrum of terminal epoxides (*e.g.* **137**, **140** and **141**) were successfully resolved, affording the unreacted epoxide and 1,2-diol (*e.g.* **142**, **143** and **144**) in good to high yield (33-45%, yield based on the stoichiometry of nucleophile, thus the maximum yield attainable is 45%) and almost complete enantiomeric purity in many instances (Scheme 1.46).[105]



Scheme 1.46 HKR of terminal epoxides using **139**

Although this methods furnishes high yields (with respect to the stoichiometry of the nucleophile) and enantiomeric excesses of both the unreacted terminal epoxides and 1,2-diols, if the enantioenriched terminal epoxide is the only material that is required from the reaction mixture, then based on the above protocol (Scheme 1.46), the maximum yield achievable from the HKR is 45%.[105]

1.5 The catalytic asymmetric synthesis of disubstituted terminal epoxides *via* the CC reaction

There are two methods for the catalytic asymmetric synthesis of disubstituted terminal epoxides: *via* asymmetric oxidation of a prochiral geminally disubstituted terminal alkene or by asymmetric alkylidenation of a prochiral ketone (Figure 1.4). A highly enantioselective protocol for the asymmetric oxidation of geminally disubstituted terminal alkenes has thus far proven elusive.[9b,17c,106,107]

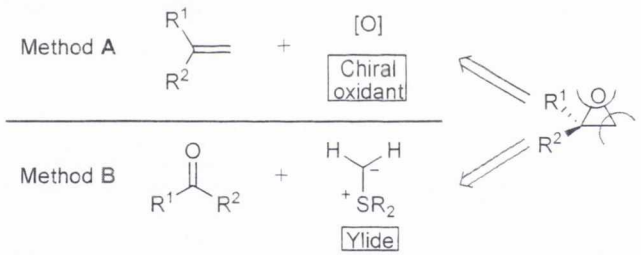
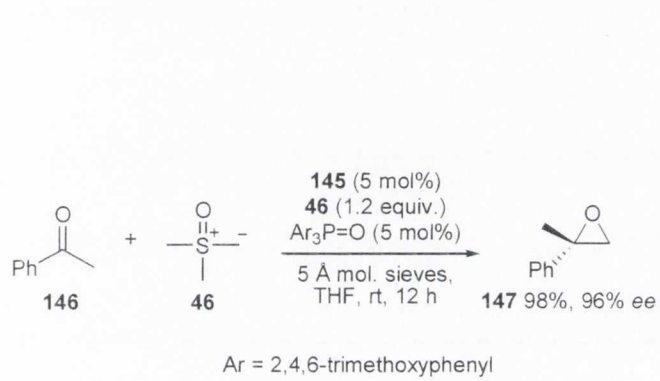
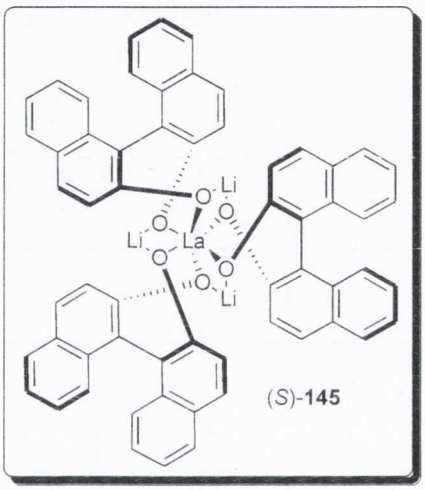


Figure 1.4 Retrosynthetic analysis of an enantioenriched disubstituted terminal epoxide

Since the oxidative approach has failed to provide a route to this class of epoxide with excellent levels of product enantiomeric excess, it is prudent that an alternative route be explored - the sulfonium ylide route. There are numerous reported examples of methylene transfer to ketones; however, none of these procedures are enantioselective and all require the use of (super)stoichiometric sulfide loadings.[108] To date, there has been just one report detailing the highly enantioselective synthesis of disubstituted terminal epoxides *via* the Corey-Chaykovsky reaction.[109] This reported protocol involves the addition of

dimethylsulfoxonium methylide (**46**) to a variety of ketones promoted by the heterobimetallic rare earth-alkali metal complex, La-Li_3-tris(binaphthoxide) (**145**), and a triarylphosphine oxide additive (Ar = 2,4,6-trimethoxyphenyl, Scheme 1.47). A range of methyl ketones, including aromatic, heteroaromatic and aliphatic analogues were successfully epoxidised in high yield (88->99%) and high *ee* (91-97%) using 1-5 mol% loading of **145** (use of 1 mol% of **145** led to a five-fold increase in reaction time). A representative example is outlined in Scheme 1.47.





Scheme 1.47 The asymmetric synthesis of disubstituted terminal epoxides using the heterobimetallic rare earth-alkali metal complex **145** and superstoichiometric sulfide loadings

Indeed, this method involves the use of a catalytic amount of chiral catalyst; however, a superstoichiometric loading of sulfide is required. The possibility of using of a catalytic quantity of chiral sulfide in this reaction would represent a far more efficient protocol for the synthesis of this problematic class of epoxide, which has hitherto proven elusive.

1.6 Aziridines: general properties and applications

Aziridines are epoxides' nitrogen counterparts. Like epoxides, aziridines are highly ring-strained (*ca.* 111 kJ mol^{-1})[110] and undergo regio- and stereospecific ring-opening

reactions with nucleophiles to yield valuable nitrogen containing building blocks such as 1,2-amino alcohols and 1,2-diamines.[110,111] However, as the electronegativity of nitrogen is less than that of oxygen, aziridines do not undergo ring-opening as readily as epoxides.[110] Aziridines can be categorised into two distinctive groups: 'non-activated' and 'activated' (**148** and **149**; Figure 1.5).[112] The former category usually only successfully participate in ring-opening reactions following protonation, quaternisation or formation of a Lewis-acidic adduct.[113] The aziridines that belong to the latter category already contain an electron withdrawing group (EWG) that is capable of conjugatively stabilising the developing negative charge on the nitrogen atom following the ring-opening reaction.[113]

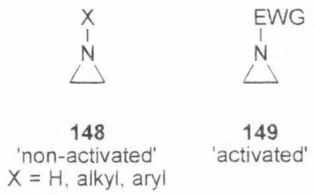
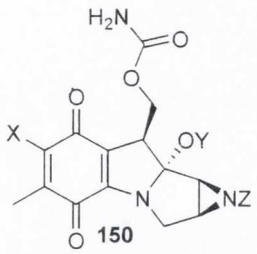


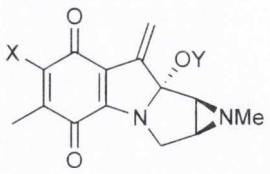
Figure 1.5 'Non-activated' **148** and 'activated' **149** aziridines

Aziridines are biologically active compounds and exhibit antitumour and antibiotic activity.[110] One important class of aziridine-containing natural products that exhibit both antitumour and antibiotic activity are the mitomycins (**150** and **151**; Figure 1.6).[114] It has been elucidated from structure activity relationship (SAR) studies that the aziridine functionality is essential for activity: it is responsible for their DNA cross-linking mode of action.[112]



150

Mitomycin A X = OMe, Y = Me, Z = H
Mitomycin B X = OMe, Y = H, Z = Me
Mitomycin C X = NH_2, Y = Me, Z = H
Porfiromycin X = NH_2, Y = Me, Z = Me



151

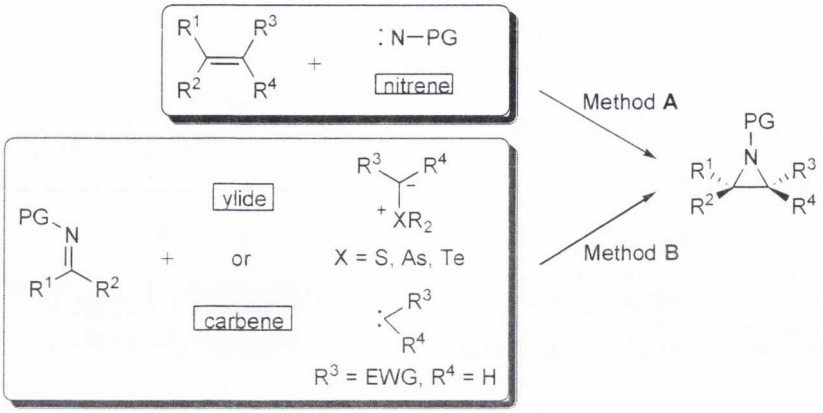
Mitomycin G X = NH_2, Y = Me
Mitomycin H X = OMe, Y = H
Mitomycin K X = OMe, Y = Me

Figure 1.6 The mitomycin family of aziridine-containing antitumour and antibiotic natural products (**150** and **151**)

By virtue of the biological activity and importance of non-racemic aziridines as intermediates in the synthesis of chiral molecules, it is imperative that methods for the asymmetric synthesis of this valuable class of compounds be developed. The most desirable method for the enantioselective preparation of these valuable compounds is *via* catalytic asymmetric aziridination.

1.6.1 Catalytic asymmetric synthesis of aziridines

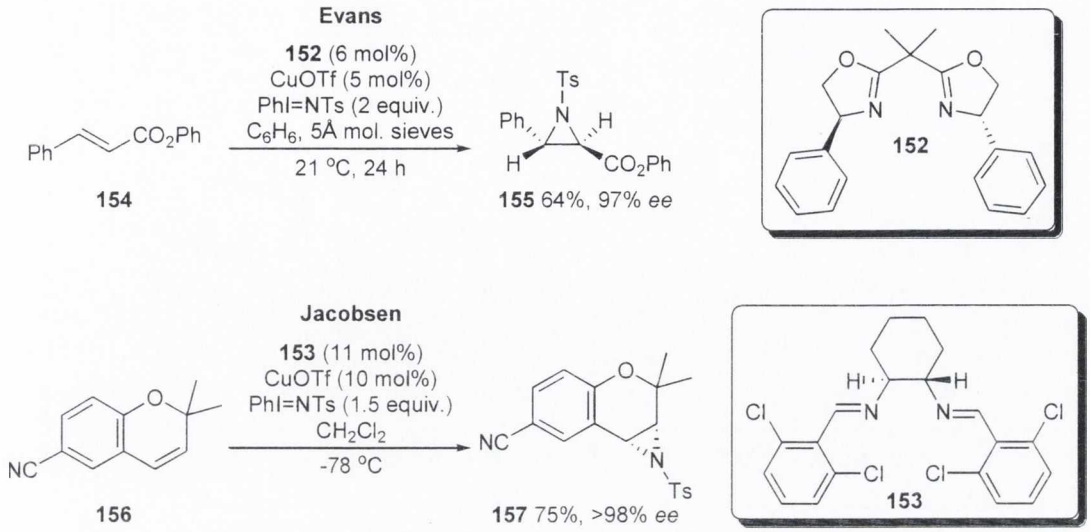
In stark contrast to the success that has been realised in the area of catalytic asymmetric epoxidation, progress in the corresponding field of catalytic asymmetric aziridination (AZ) has been relatively slow. It is because of this deficiency that enantioselective aziridination has been branded "epoxidation's poor relation".[111] There are two main routes towards the catalytic asymmetric synthesis of aziridines: the first involves the addition of a nitrene to an alkene (method A; Scheme 1.48) while the second involves alkylidenation of an imine using either a carbene or an ylide (method B; Scheme 1.48).[7,110,115]



Scheme 1.48 Methods for the catalytic asymmetric synthesis of aziridines

1.6.1.1 Catalytic AZ of prochiral alkenes: metal catalysed asymmetric nitrene transfer to alkenes

The majority of the methods that have been reported to date for the catalytic asymmetric synthesis of aziridines are based on this class of reaction.[110,115] In 1993, Evans *et al.* and Jacobsen *et al.* simultaneously reported the first examples of catalytic asymmetric nitrene transfer to alkenes.[116,117] These processes were based on the asymmetric aziridination of alkenes using PhI=NTs as the nitrene precursor and a chiral copper complex which was derived from a chiral *bis*-oxazoline ligand and Cu(I)OTf in Evans' system and from a chiral 1,2-diamine ligand and Cu(I)OTf in Jacobsen's system (Scheme 1.49). In Evans' system, using chiral ligand **152**, high enantioselectivity was only achieved when cinnamate esters were used as substrates. A representative example is depicted in Scheme 1.49. In Jacobsen's system, using chiral ligand **153**, high enantioselectivity was only achieved when chromene derivative **156** was used as substrate (Scheme 1.49).

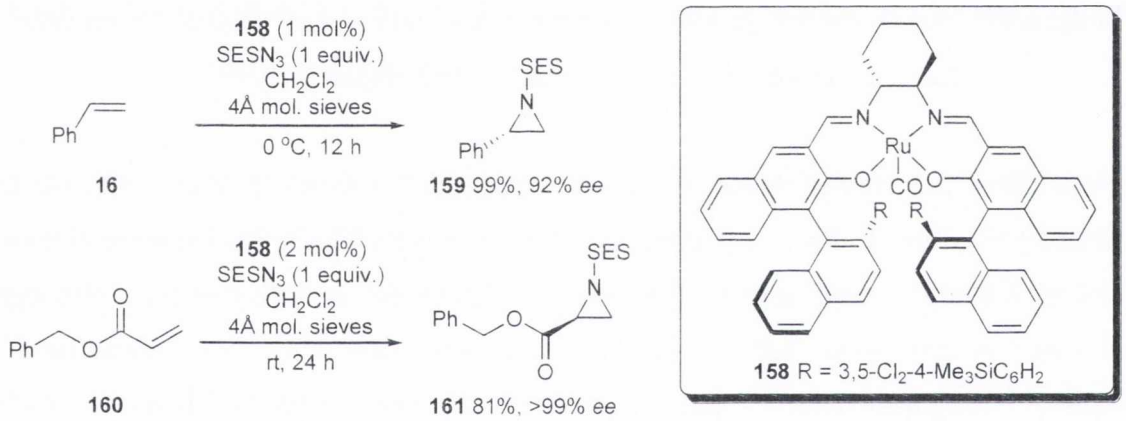


Scheme 1.49 The catalytic asymmetric aziridination of alkenes reported by Evans and Jacobsen using chiral ligands **152** and **153** respectively

Various other procedures based on the aforementioned systems detailing the use of modified procedures and/or chiral metal catalysts have been reported, with some of these protocols leading to high levels of aziridine enantiomeric excess; however, although individual modifications led to different substrate specificity, *e.g.* chalcones,[118] styrenes,[119] cinnamate esters[120] and chromene,[121] a general procedure based on these systems has not yet been developed.[110,115,122,123] Furthermore, these two procedures, and indeed the majority of procedures that have been reported based on this approach, have involved the use of PhI=NTs as the nitrene source. This imposes three drawbacks: 1) environmentally unfriendly iodobenzene is generated as a waste product in the reaction, 2) this is undesirable from an atom economy standpoint and 3) the *p*-toluenesulfonyl (tosyl) group on the nitrene precursor ultimately becomes the protecting group (PG) on the aziridine, which is notoriously difficult to remove.[110,122,123,124]

Katsuki *et al.* overcame these drawbacks by developing a procedure based on the use of a Ru(salen)(CO) complex **158** and 2-(trimethylsilyl)ethanesulfonyl azide ($SESN_3$) as a nitrene precursor (which is undoubtedly one of the most notable examples to date based on this route) for the asymmetric synthesis of SES-protected azides (Scheme 1.50).[124,125]

In contrast to the methods previously reported (*vide supra*), using $SESN_3$ as a nitrene source renders this process both atom economical and more environmentally friendly as molecular nitrogen is generated as a by-product. In contrast to the tosyl protecting group that had been employed previously, the (trimethylsilyl)ethanesulfonyl (SES) protecting group can be deprotected under mild reaction conditions without incurring a diminution in enantiomeric excess.[124,126] Complex **158** successfully promoted the aziridination of terminal, terminal conjugated and α,β-unsaturated esters and amides using $SESN_3$ as the nitrene source providing the corresponding aziridines in moderate to excellent yield (50-99%) and excellent *ee* (92->99%) (except when 1-octene was employed as substrate).[124] Two representative examples are illustrated in Scheme 1.50.

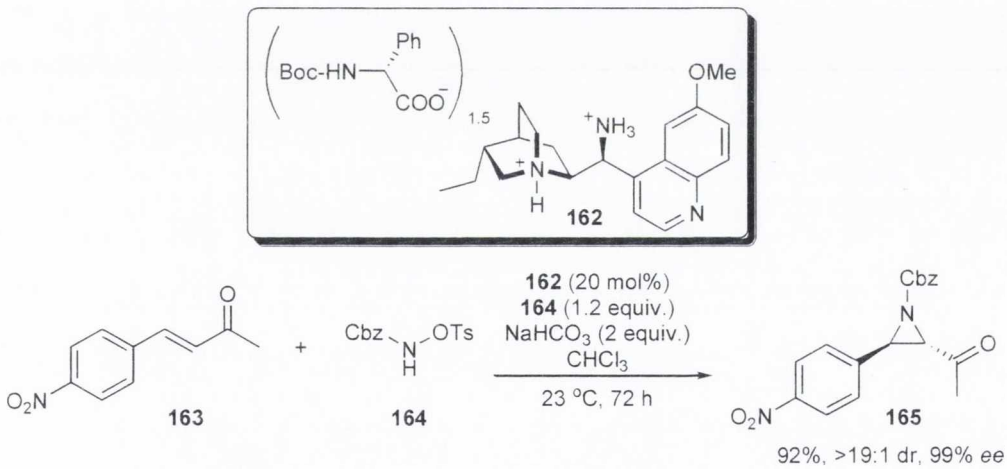


Scheme 1.50 The asymmetric aziridination of terminal alkenes **16** and **160** promoted by **158**

1.6.1.2 Catalytic AZ of prochiral alkenes: organocatalysed asymmetric nitrene transfer to alkenes

Over the past decade, a number of reports have emerged detailing the use of organocatalysts to promote the AZ of alkenes.[115] The majority of these protocols rely on quaternary salts of cinchona alkaloids as the source of asymmetric induction. By means of these catalysts, enantioselective procedures have been developed for the aziridination of cycloalkenones,[127] electron deficient terminal alkenes[128] and chalcones.[129] One of the

most successful, and indeed impressive protocols to date has been contributed by Melchiorre *et al.* (inspired by a report that had disclosed the highly chemo- and stereoselective aziridination of α,β-unsaturated aldehydes),[130] who reported a highly enantioselective protocol for the asymmetric aziridination of enones based on a domino conjugate-cyclisation sequence, catalysed by primary amine salt **162**.[131] They speculated that **162** would activate the enone *via* iminium ion catalysis toward nucleophilic addition of a nitrogen-based reagent, which would be followed in sequence by an enamine-catalysed intramolecular cyclisation step to afford an enantioenriched aziridine. Essentially, the ideal nitrogen-based reagent should initially behave as a nucleophile to effect conjugate addition, while subsequently becoming sufficiently electrophilic to facilitate cyclisation. Indeed, **162** (5-20 mol% loading) promoted the AZ of a range of enones, with **164** as the nitrogen-based reagent.



Scheme 1.51 The AZ of enone **163** catalysed by **162** *via* a domino iminium-enamine intramolecular process

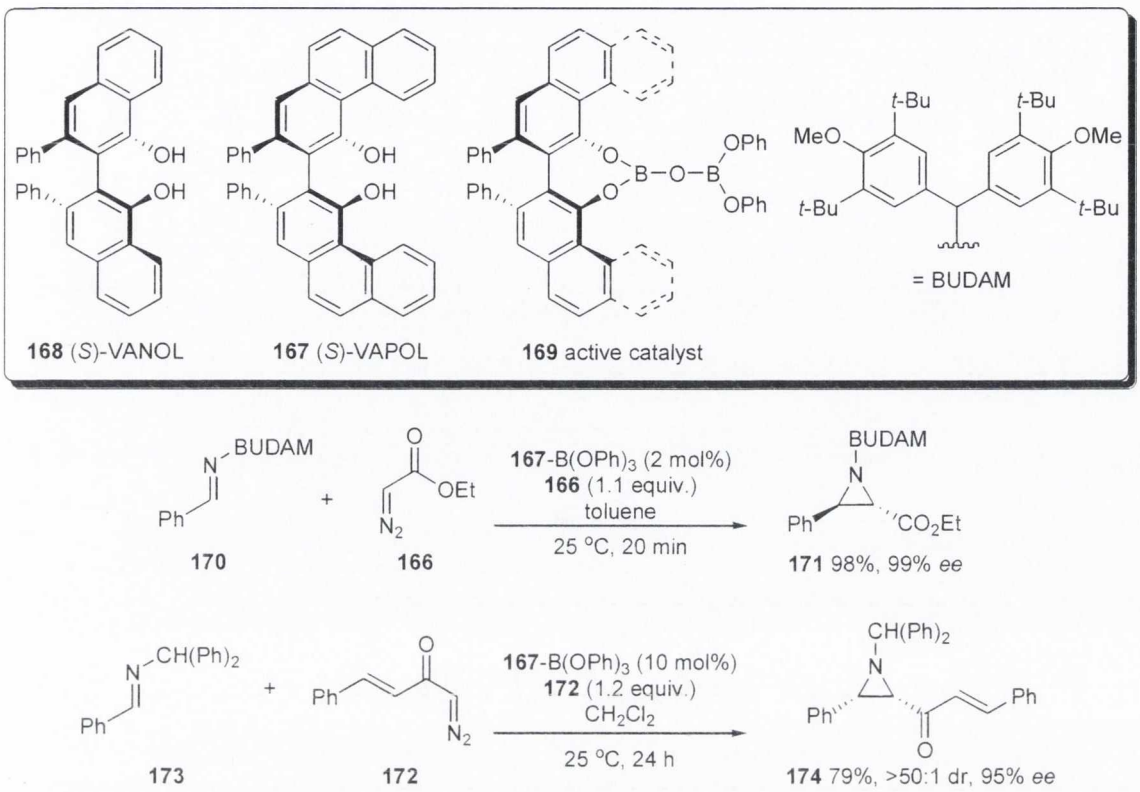
A variety of *N*-Cbz aziridines and an *N*-Boc aziridine were obtained in good yield (74-96%), high diastereo- (19:1->19:1) and high enantiomeric excess (93-99%, except when benzalacetone was employed as substrate). A representative example of this domino iminium-enamine intramolecular process is shown in Scheme 1.51.

1.6.1.3 Catalytic AZ of prochiral imines: asymmetric carbene transfer to imines

Although the majority of catalytic asymmetric protocols that have been developed to date for the asymmetric synthesis of aziridines have involved asymmetric nitrene addition to alkenes, some outstanding methods based on carbene transfer to imines have been developed.[115] In the majority of instances, these protocols involve the asymmetric aziridination of imines using a chiral Lewis acid catalyst and ethyl diazoacetate, favouring the formation of the *cis*-ester-substituted aziridine (Maruoka has reported an enantioselective protocol for the synthesis of *trans*-amide substituted aziridines).[115]

The most successful protocol that has been developed to date based on this approach is that reported by Wulff *et al.*.[123,132-136] This protocol involves the asymmetric aziridination of *N*-diarylmethyl imines using ethyl diazoacetate (**166**) and chiral boron Lewis acid catalysts derived from chiral ligands VAPOL (**167**) or VANOL (**168**) and triphenylborate (the active catalyst species **169** is illustrated in Scheme 1.52). Having screened various diarylmethyl *N*-substituents on the imine substrate, it was found that the highest levels of enantiocontrol were achieved with 3,5-di-*tert*-butyldianisylmethyl (BUDAM) as the *N*-substituent.[135] Using 2 mol% loading of active catalyst **167**-$B(OPh)_3$, a range of aromatic and aliphatic BUDAM-substituted imines were transformed into the corresponding ester-substituted aziridines with exclusive *cis* selectivity, in good yield (57-99%) and in the majority of cases, excellent *ee* (80-99%). A representative example is illustrated in Scheme 1.52.

The scope of this protocol was extended to accommodate the synthesis of aziridinyl vinyl ketones (*e.g.* **174**, Scheme 1.52).[136] On this occasion, using 10 mol% loading of active catalyst **167**-$B(OPh)_3$ and various vinyl diazomethyl ketones, a range of aromatic and aliphatic benzhydryl imines were transformed into the corresponding aziridinyl vinyl ketones in moderate yield (35-90%), poor to high *cis*-diastereoselectivity (5:1->50:1) and in the majority of cases, excellent *ee* (81-99.7%). A representative example is illustrated in Scheme 1.52.



Scheme 1.52 The AZ of *N*-diarylmethyl imines **170** and **173** catalysed by **167**-$B(OPh)_3$

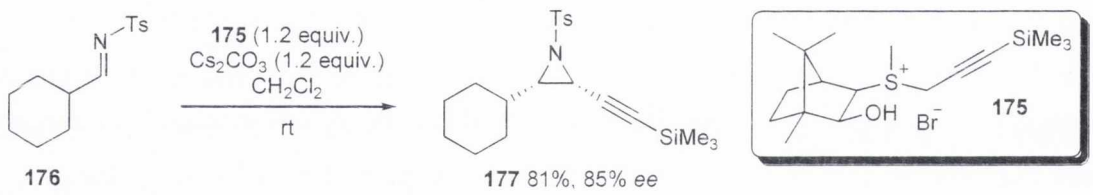
1.6.1.4 Catalytic AZ of prochiral imines: chiral sulfonium ylide-mediated aziridination

Although successful protocols have been developed for the AZ of prochiral alkenes and imines *via* nitrenes and carbenes respectively, the scope still remains quite limited. A route that has proven to be successful towards the asymmetric synthesis of epoxides is the chiral sulfonium ylide route, *via* the Corey-Chaykovsky reaction (*vide supra*). As it has been demonstrated that imines are suitable substrates for the Corey-Chaykovsky reaction,[48] it is possible that chiral sulfonium ylides could lead to highly enantioselective aziridination protocols, giving aziridines the opportunity to enjoy the same success as their oxygen counterparts. Indeed, investigations along these lines have gotten underway (*vide infra*). As was the case for chiral sulfonium ylide-mediated AE reactions, there is both a stoichiometric process involving the use of a preformed sulfonium salt and a sub-

stoichiometric process whereby the sulfonium ylide is formed *in situ*. As before, there are two ways to prepare the sulfonium ylide *in situ*: 1) alkylation of the sulfide followed by deprotonation of the sulfonium salt and 2) the reaction of the sulfide with a carbene or a carbenoid to generate the ylide *in situ*.

1.6.1.4.1 AZ using preformed chiral sulfonium salts: a stoichiometric process

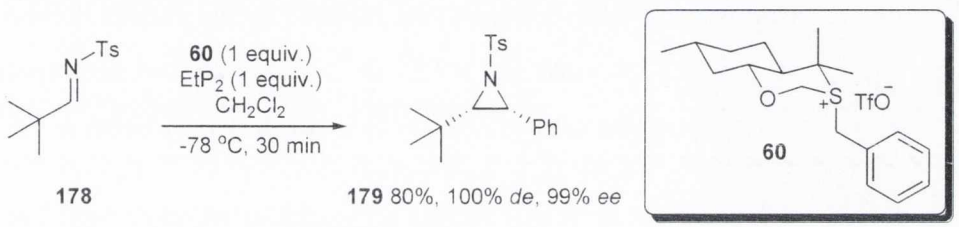
In 1997, Dai *et al.* reported the asymmetric aziridination of prochiral *N*-tosyl imines using chiral propargylic sulfonium salt **175** derived from D-(+)-camphor (two other stereoisomers were also employed) under solid-liquid phase-transfer conditions.[137] A range of *N*-tosyl imines, including aromatic, heteroaromatic, α,β-unsaturated and aliphatic aldimines (*e.g.* **176**) and ketimines all proved to be compatible substrates in this reaction, affording the corresponding acetylenylaziridines in high yield (82-95%), exclusive *cis* diastereoselectivity, and very poor to good enantioselectivity (14-85% *ee*), depending on the substrate employed. The best result obtained is illustrated in Scheme 1.53. Although this process prescribes the use of 1.2 equivalents of chiral sulfide, the authors report that the sulfide can be recovered from the reaction in greater than 80% yield.



Scheme 1.53 The AZ of aliphatic aldimine **176** using propargylic sulfonium salt **175**

A further example of the use of a preformed chiral sulfonium salt-mediated AZ reaction was reported by Solladié-Cavallo *et al.*[138] This report also detailed the AZ of *N*-tosyl imines; however, these reactions were performed using chiral sulfonium salt **60**, derived from Eliel's oxathiane (Section 1.3.2.1). A range of aromatic and aliphatic *N*-tosyl imines underwent AZ with **60** under homogeneous reaction conditions using the liquid base EtP_2

(Section 1.3.2.1) at -78 °C. The aziridines derived from aliphatic substrates were obtained in moderate to good yield (60-80%), excellent diastereo- (96:4-100:0 in favour of *cis*) and enantioselectivity (99-100% *ee*). The aziridines derived from aromatic imines were also obtained in good yield (70-88%) and exceptional enantioselectivity (100% *ee*); however, the diastereoselectivities proved to be capricious, ranging from 50:50 to 70:30 with *cis*:*trans* preference depending on the substrate. A representative example is depicted in Scheme 1.54.



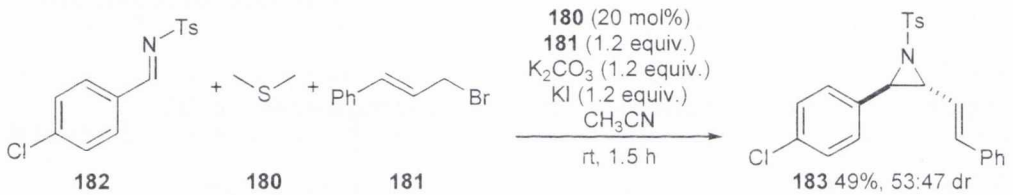
Scheme 1.54 The AZ of aliphatic aldimine **178** using sulfonium salt **60**

A major drawback associated with this procedure is the use of the expensive EtP_2 base (**66**). To circumvent this issue and to improve the synthetic feasibility of this process, Hameršak *et al.* reported that by using sodium hydride in tetrahydrofuran at -40 °C in conjunction with chiral sulfonium salt **60**, *N*-tosyl, *N*-SES and *N*-Boc aldimines could be aziridinated without a marked diminution in either yield, diastereo- or enantioselectivity compared to reactions performed with **60** in dichloromethane using **66** as base at -78 °C.[139] For example, the transformation of **178** to **179** in Scheme 1.54 performed using sodium hydride in tetrahydrofuran at -40 °C afforded **179** in 68% yield, 100% *de* and 97% *ee*. One issue associated with this protocol is that the reaction time required increased from four hours to twenty hours.

1.6.1.4.2 AZ *via* sulfide alkylation and deprotonation: a substoichiometric process

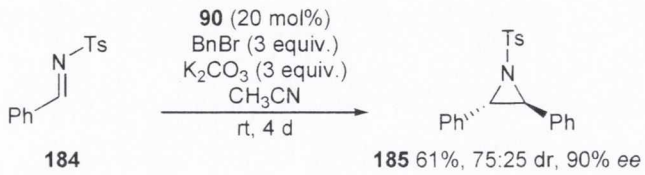
In 1996, Dai *et al.* reported the first example of a catalytic sulfonium ylide-mediated aziridination reaction.[140] The catalytic protocol that was developed (see Scheme 1.25)

involved the use of achiral dimethyl sulfide (**180**) and cinnamyl bromide (**181**) with acetonitrile as solvent and potassium carbonate as base. Under these conditions, using 20 mol% loading of **180**, a range of aromatic *N*-sulfonyl imines successfully underwent aziridination to afford the corresponding β-phenylvinyl aziridines in poor yield (30-49%) and poor diastereoselectivity (43:57-29:71, *trans*:*cis*). Under the same conditions, but using 1.2 equivalents of potassium iodide, a yield of 49% could be achieved compared to the same reaction performed in the absence of potassium iodide. Increasing the loading of **180** to 1 equivalent led to an increase in yield (72%) and diastereomeric ratio (31:69). **83** (at 20 mol% loading, Figure 1.2) also proved to be suitable as the sulfide component in this reaction affording **183** in 23% yield and 49:51 dr (product *ee* was not reported). A representative example based on this catalytic protocol is illustrated in Scheme 1.55.



Scheme 1.55 A representative example of the first catalytic sulfonium ylide-mediated aziridination of imines

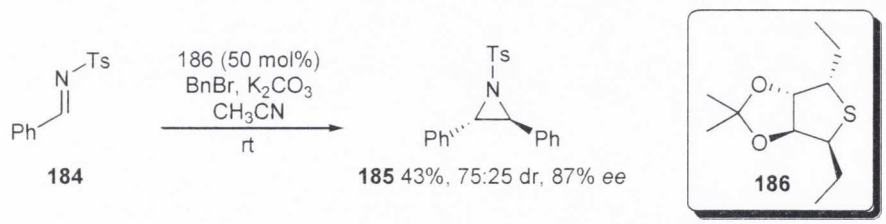
In 2001, Saito *et al.* reported their development of an enantioselective version of this catalytic cycle using chiral sulfide **90** (Figure 1.2) in the AZ of aryl- and vinyl-substituted *N*-sulfonyl imines, again using acetonitrile as solvent and potassium carbonate as base.[141] Employing one equivalent of **90** and arylmethyl bromides, aryl-substituted *N*-sulfonyl imines underwent AZ in good yield (79->99%), modest diastereoselectivity (63:37-79:21 in favour of *trans*) and high enantioselectivity (84-98% *ee*). They demonstrated that high enantioselectivities could be achieved by decreasing the loading of **90** to just 20 mol% (Scheme 1.56) or even 10 mol%; however, at the latter loading, the yield of aziridine was <10% after one week reaction time.



Scheme 1.56 A representative example of the AZ of aryl-substituted *N*-sulfonyl imines catalysed by **90**

Similar results were obtained in the AZ of cinnamylidene-*N*-tosylamine. Using 50 mol% loading of **90** and benzyl bromide, good yield (73%), diastereoselectivity (80:20) and excellent enantioselectivity (93%) were achieved.

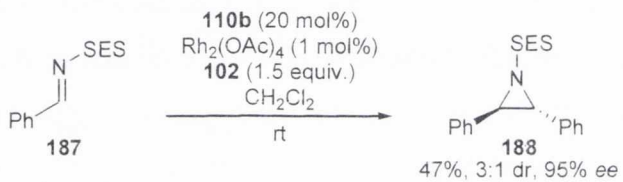
A third and final example of the AZ of imines based on this approach has been developed by Huang *et al.*[142] Under the same conditions that were associated with the previous two examples, the C_2-symmetric sulfide **186** derived from L-tartaric acid promoted the highly enantioselective aziridination of aromatic and α,β-unsaturated *N*-tosyl imines. Using one equivalent of **186** and benzyl bromide, the corresponding α,β-unsaturated and aryl-substituted *N*-tosyl aziridines were obtained in moderate yield (50-75%), poor to high *trans*:*cis* selectivity (60:40-90:10) and high enantioselectivity (80-96% *ee*). They also demonstrated a substoichiometric reaction using 50 mol% loading of **186**: a diminution (of 29%) in yield and *ee* (9%) of **185** was observed (compared to the stoichiometric reaction, Scheme 1.57).



Scheme 1.57 The catalytic AZ of **184** promoted by **186**

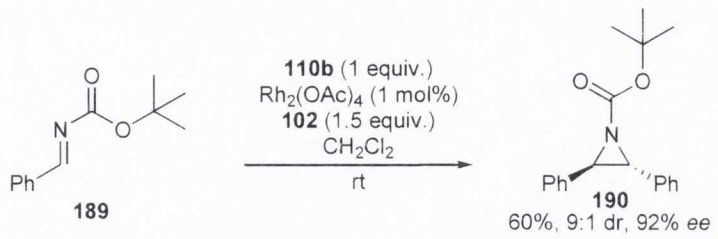
1.6.1.4.3 Catalytic sulfonium ylide-mediated AZ: carbene-mediated ylide formation *via* a diazo compound

Aggarwal *et al.* successfully applied the catalytic cycle that they had developed for the asymmetric synthesis of epoxides (Scheme 1.29) to the asymmetric synthesis of aziridines.[143,122] They found that decomposition of phenyl diazomethane (**102**) in the presence of $Rh_2(OAc)_4$ (**116**) led to the formation of a metallocarbene, which subsequently reacted with chiral sulfide **110b** to generate a ylide that led to the enantioselective aziridination of a range of variously *N*-substituted aromatic and aliphatic imines. Using 20-100 mol% loading of **110b**, aromatic and aliphatic *N*-SES imines were successfully aziridinated in low to high yield (47-91%), modest dr (1:1-5:1 in favour of *trans*) and high *ee* (88-95%). A representative example is illustrated in Scheme 1.58.



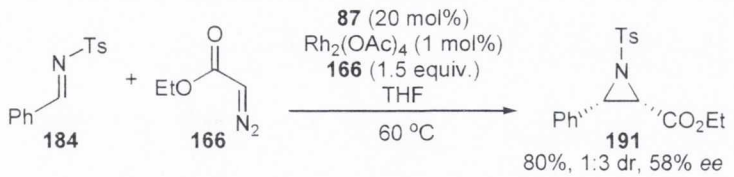
Scheme 1.58 A representative example of the catalytic AZ of *N*-SES imine **187** promoted by **110b**

The same authors also demonstrated that variously *N*-substituted benzaldehyde-derived imines such as *N*-tosyl and *N*-alkoxycarbonyl substituted imines could be aziridinated under these conditions using one equivalent of **110b** in moderate to high yield (55-86%), improved dr (3:1->10:1) and high *ee* (90-92%).[122] A representative example is depicted in Scheme 1.59.



Scheme 1.59 A representative example of the catalytic AZ of *N*-Boc imine **189** promoted by **110b**

To further enhance the synthetic utility of this process, the same authors extended the scope of this reaction toward the asymmetric synthesis of ester- and amide-substituted *N*-tosyl aziridines.[122] To effect these asymmetric transformations, chiral sulfide **87** was employed at 20-100 mol% loading, along with either a diazoester or a diazoacetamide and $Rh_2(OAc)_4$. To accomplish diazo decomposition of these more stable compounds, the reactions were performed at 60 °C. This process was compatible with a variety of *N*-tosyl aromatic and aliphatic aldimines and afforded the corresponding aziridines in moderate to high yield (53-98%), poor to good dr (2:3-1:12 *trans*:*cis*) and modest *ee* (30-58%). A representative example is illustrated in Scheme 1.60.

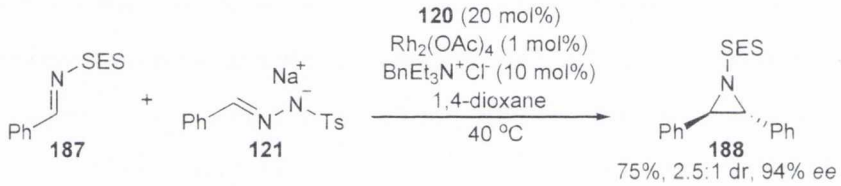


Scheme 1.60 A representative example of the catalytic asymmetric synthesis of ester-substituted aziridine **191** using chiral sulfide **87**, **166** and $Rh_2(OAc)_4$

1.6.1.4.4 Catalytic sulfonium ylide-mediated AZ: carbene-mediated ylide formation *via* *N*-tosylhydrazone salts

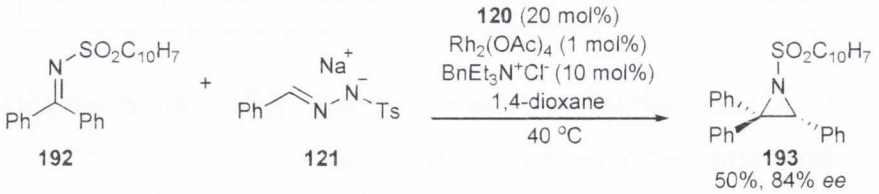
For reasons previously discussed (Section 1.3.2.2.2.2), Aggarwal *et al.* extended the catalytic cycle (Scheme 1.32) that they developed for the AE of aldehydes, in which the

diazo compound is generated *in situ* from an *N*-tosylhydrazone salt, to the AZ of imines.[144] In these reactions, the phenyl salt of phenyl *N*-tosylhydrazone (**121**) was employed as the carbene source. In the presence of 20 mol% loading of **121**, $Rh_2(OAc)_4$ and chiral sulfide **120**, a range of aliphatic, aromatic, cinnamyl and heteroaromatic variously *N*-substituted imines such as *N*-sulfonyl imines (*N*-tosyl, *N*-SES and *N*-$SO_2C_{10}H_7$) and carbamoyl imines (*N*-TcBoc and *N*-Boc) successfully underwent AZ, affording moderate to good yields (50-82%, 30% in the case of *N*-Boc imine), modest diastereoselectivities (2:1-8:1, in favour of *trans*) and, in general, excellent enantioselectivities (73-98% *ee*) of the corresponding aziridines. A representative example is illustrated in Scheme 1.61. They also demonstrated one example where just 5 mol% loading of **120** was employed: the dr was retained and a diminution of 9% yield and 1% *ee* was observed.



Scheme 1.61 A representative example of the catalytic AZ of imines mediated by **121**, $Rh_2(OAc)_4$ and **120**

In this report, the AZ of ketimine **192** to furnish a trisubstituted aziridine **193** was also demonstrated (Scheme 1.62). This represented the first example of the AZ of a symmetrical ketimine to furnish a trisubstituted aziridine.[144]

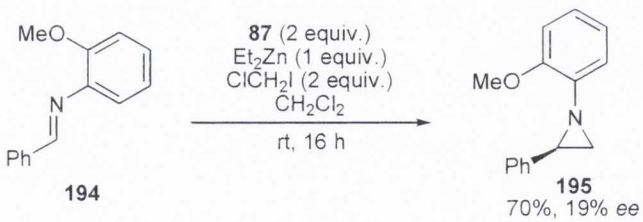


Scheme 1.62 The catalytic AZ of ketimine **192** to furnish trisubstituted aziridine **193**

1.6.1.4.5 Catalytic sulfonium ylide-mediated AZ: the generation of a carbene from a Simmons-Smith reagent. The enantioselective synthesis of terminal aziridines

Aggarwal *et al.* extended the Simmons-Smith carbenoid-mediated procedure which they had developed for the asymmetric synthesis of terminal epoxides (Section 1.3.2.2.2.3), to the asymmetric synthesis of terminal aziridines.[93,145] Using the same Simmons-Smith reagent as before, achiral sulfide **124**, and an imine with either an electron-withdrawing group (tosyl or SES) or a group facilitating bidentate co-ordination (*o*-methoxyphenyl, *e.g.* **194**) as the *N*-substituent, a range of aromatic and aliphatic aldimines were successfully aziridinated in poor to moderate yield (33-79%).[145]

To render this process asymmetric, a variety of chiral sulfides (**87**, **120** and **131**) that had proven to be successful for the AE of aldehydes were evaluated as catalysts in the AZ of imines.[93] The best result was obtained using **87** and is illustrated in Scheme 1.63. This example also represents the highest enantioselectivity that has been achieved to date for the asymmetric synthesis of terminal aziridines *via* an imine and a chiral sulfonium ylide.



Scheme 1.63 The highest enantioselectivity achieved to date for the asymmetric synthesis of a terminal aziridine *via* an imine and a chiral sulfonium ylide

It is noteworthy that although two equivalents of chiral sulfide **87** are required for this transformation, a meagre enantiomeric excess of just 19% results.

1.6.1.4.6 The origin of diastereoselectivity in sulfur ylide-mediated aziridination reactions

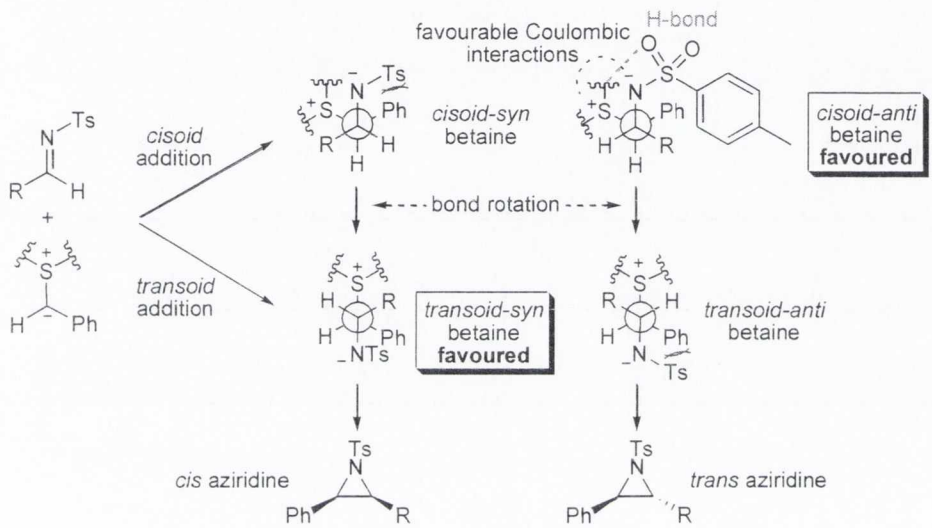
The chiral sulfonium ylide-mediated asymmetric synthesis of aziridines has thus far proven to be an efficient route toward the synthesis of these valuable building blocks. Due to the presence of the ancillary factor to be considered in the AZ of imines, namely the protecting group on the nitrogen atom of the imine substrate, the factors that govern diastereoselectivity in the aziridination of imines are more intricate compared with those to be considered in the corresponding epoxidation reactions involving carbonyl compounds (Sections 1.3.3-1.3.3.4). It is because of these intricacies that the same levels of diastereocontrol that have been observed in the epoxidation of carbonyl compounds have rarely been observed in the corresponding aziridination of imines. The stereochemical outcome varies depending on the nature of the ylide in question (semi-stabilised or stabilised). The nature of the *N*-protecting group, imine substituent and sulfide structure also influence the diastereochemical outcome of these reactions.

1.6.1.4.6.1 The origin of diastereoselectivity in sulfur ylide-mediated aziridination reactions: semi-stabilised ylides

The steps that are involved in the sulfonium ylide-mediated synthesis of aziridines are the same as those that are involved in the sulfonium ylide-mediated synthesis of epoxides (Section 1.3.3). Addition of the ylide to the imine leads to *syn*- and *anti*-betaine intermediates. From crossover studies, Aggarwal *et al.* determined that the betaine intermediates that result from the addition of semi-stabilised ylides to *N*-sulfonyl imines are formed nonreversibly and suggested that this may be due to the stabilising effect that the electron withdrawing group on the nitrogen atom has on the anion of the betaine intermediate.[146] They therefore proposed that the selectivity observed in these reactions is derived from which face of the imine is attacked by the ylide.[146]

The ylide can approach the imine in either a *cisoid* or *transoid* fashion leading to four possible betaine structures: *cisoid-syn*, *transoid-syn*, *cisoid-anti* and *transoid-anti*

(Scheme 1.64).[147] Independent computational studies by Robiette *et al.*[148] and Hameršak *et al.*[147] involving *N*-sulfonyl imines revealed that the pathway leading to the *anti*-betaine occurs with the ylide approaching the imine in a *cisoid* fashion, and conversely, the pathway leading to the *syn*-betaine occurs with the ylide approaching the imine in a *transoid* fashion. Therefore, only two betaines are formed: the *cisoid-anti* and the *transoid-syn*.

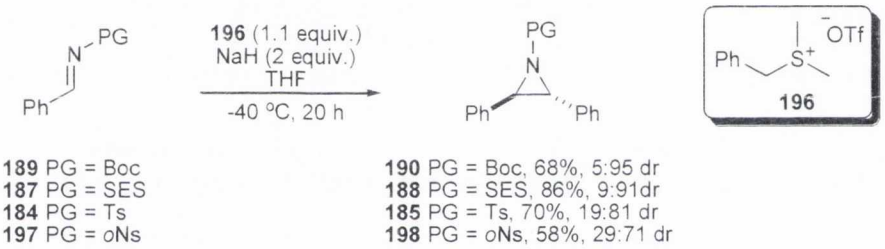


Scheme 1.64 A detailed account of the mechanism accounting for the observed diastereoselectivity in reactions between imines and semi-stabilised ylides[147]

For *anti*-betaine formation, the *cisoid-anti* is favoured due to the favourable Coulombic interactions between the aza anion and the sulfonium cation (highlighted in blue, Scheme 1.64).[147,148] A stabilising C-H···O hydrogen bond between the oxygen atom of the *N*-Ts group and an ylidic hydrogen atom also favours this approach (highlighted in green, Scheme 1.64).[147,148] The unfavourable steric interactions between the *N*-Ts group and the ylidic phenyl group that occur during the *transoid* approach toward the formation of the *anti*-betaine also contribute to the prevalence of the *cisoid-anti* approach.[147,148] In the case of *syn*-betaine formation, the unfavourable steric interactions between the *N*-Ts group and the ylidic phenyl group overrule the aforementioned Coulombic interactions, therefore

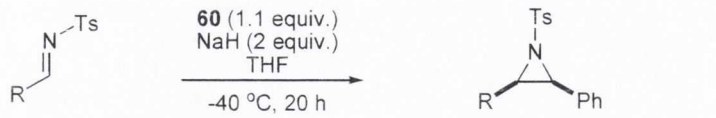
leading to a *transoid* approach.[147,148] Robiette suggested that the low *trans* selectivity that is often observed in reactions between semi-stabilised ylides and *N*-sulfonyl imines (Schemes 1.56, 1.57, 1.58 and 1.61) is due to a lower energy barrier for the formation of the *anti*-betaine in comparison to the energy barrier associated with the formation of the *syn*-betaine.[148]

In the report from Hameršak *et al.*, they attempted to elucidate the correlation between the *trans* selectivity observed in the resulting aziridine and the *N*-protecting group. In reactions between sulfonium salt **196** and variously *N*-substituted imines derived from benzaldehyde, *i.e.* *N*-Boc (**189**), *N*-SES (**187**), *N*-Ts (**184**) and *N*-*o*-nitrobenzenesulfonamide (*N*-*o*Ns (**197**)), they found that the *trans* selectivity decreased as follows: Boc > SES > Ts > *o*Ns (Scheme 1.65).



Scheme 1.65 The observed dependence of diastereoselectivity on the nature of the *N*-substituent on the imine

They also observed that the imine substituent affects the diastereochemical outcome. For example, a series of reactions were performed between sulfonium salt **60** and a range of aromatic and aliphatic aldimines containing the *N*-protecting groups illustrated in Scheme 1.66: two outcomes were particularly intriguing. The reaction between imine **178** and sulfonium salt **60** under the conditions outlined in Scheme 1.65 gave rise to the exclusive formation of *cis*-aziridine **179** (Solladié-Cavallo *et al.* observed the same result,[138] Scheme 1.54) whereas the reaction between **60** and **199** gave rise to a dr of 31:69 of aziridine **200** in favour of *trans* (Scheme 1.66).[147]



178 R = *t*-Bu
199 R = 1-naphthyl

179 R = *t*-Bu, 68%, 100% *cis*
200 R = 1-naphthyl, 60%, 31:69 dr

Scheme 1.66 The observed dependence of diastereoselectivity on the nature of the imine substituent

In the case of reaction of **199** with **60**, the observed *trans*-diastereoselectivity is as previously described, *i.e.* due to a lower energy barrier for the formation of the *anti*-betaine. However, in the reaction between **177** and **60**, both the *cisoid-anti* and the *transoid-syn* intermediate betaines can form. As the *transoid-syn* betaine is already in the correct conformation for elimination, it can directly ring-close to yield the *cis*-aziridine. In order for a *trans*-aziridine to result, the *cisoid-anti* betaine must undergo bond rotation to the *transoid-syn* conformation. Due to the bulky nature of the *tert*-butyl group, the barrier for this rotation is too high and reversion to starting materials occurs, therefore, the *syn* pathway dominates. This is reminiscent of the rate-determining step in epoxidation reactions between semi-stabilised ylides and aldehydes. This is the first demonstration of a reversible reaction between a semi-stabilised ylide and an imine.

1.6.1.4.6.2 The origin of diastereoselectivity in sulfur ylide-mediated aziridination reactions: stabilised ylides

The computational studies performed by Robiette (*vide supra*) involving the addition of stabilised (ester and amide stabilised) ylides to *N*-sulfonyl imines have revealed that the addition of the ylide to the imine is reversible (indeed, this has also been proven through crossover experiments that were performed by Aggarwal *et al.*[146]).[148] This is attributed to the increased stability of the starting materials, *i.e.* the imine and the ester, or amide stabilised ylide. There is therefore a higher energy barrier associated with the addition of stabilised ylides to imines compared with the energy barrier that is associated with the

addition of semi-stabilised ylides to imines.[148] It has also been proven that the bond rotation step is reversible in this class of reactions.

In the study by Robiette, it was observed that the highest point on the energy profile in reactions between stabilised ylides and imines is the energy barrier that corresponds to ring-closure of the intermediate betaines: therefore, the ring-closure step is both the rate- and diastereoselectivity-determining step in these reactions. It was calculated that the transition state associated with *syn* elimination is slightly lower in energy than that associated with *anti* elimination, thus explaining the low *cis* selectivity often observed in these reactions (see Scheme 1.60 for an example).[122]

1.6.1.4.7 The origin of enantioselectivity in sulfur ylide-mediated aziridination reactions

The same four factors that govern enantioselectivity in semi-stabilised ylide epoxidation reactions govern enantioselectivity in semi-stabilised ylide aziridination reactions (Section 1.3.3.3). [95] The enantioselectivity-determining step is the irreversible betaine formation step. These factors have been controlled effectively in asymmetric aziridination reactions using chiral sulfides **60**, **90**, **110b** and **120** resulting in the formation of aziridines in excellent levels of enantiomeric excess (see Schemes 1.54, 1.56, 1.58, 1.59 and 1.61 for examples).[122,138,141,144]

In the case of stabilised ylides, the same levels of control and therefore aziridine enantiomeric excess have not been realised.[122] In reactions between stabilised ylides and imines, betaine formation is reversible and the enantiodifferentiating step is the ring-closing step. To date, poor levels of enantiocontrol have been achieved in these reactions (see Scheme 1.60 for an example).[122]

As discussed in Section 1.6.1.4.5, the highest enantiomeric excess that has been realised for the asymmetric synthesis of terminal aziridines *via* a non-stabilised ylide and an imine is 19%. The same problem that exists in the asymmetric synthesis of terminal epoxides

via non-stable ylides and aldehydes exists for the corresponding synthesis of terminal aziridines: betaine formation is non-reversible and enantioselectivity is derived solely from which face of the imine is attacked by the ylide.

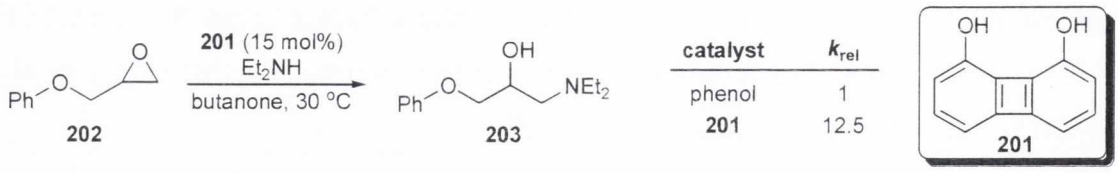
1.7 The evolution of (thio)urea-derived organocatalysts

1.7.1 Hydrogen bond-mediated organocatalysis: general considerations

Hydrogen bond-mediated catalysis is an extremely valuable strategy, and over the past decade, has revolutionised the field of synthetic organic chemistry.[149-151] The nascence of this field is derived from inspiration that has been provided by nature: catalytic systems, *e.g.* enzymes, which utilise hydrogen bonding as a source of weak acid-base interaction.[149,152] Chemists have attempted to mimic this process by developing 'enzyme mimetics'.[153] These hydrogen bond-donating organocatalysts can be considered as Lewis acids, and can therefore interact with a Lewis base (usually a heteroatom) to effect a lowering of the energy of the lowest unoccupied molecular orbital (LUMO) of a catalyst-bound electrophile. This ultimately leads to the activation of the electrophile towards nucleophilic attack and thus results in an improvement in both the rate and selectivity of reactions in which these catalysts are employed.[151] A plethora of synthetically valuable reactions exhibit the characteristics that are required for compatibility with this mode of catalysis, *i.e.* reactions where a significant change in heteroatom basicity is observed over the course of the reaction, such as in nucleophilic addition to C=O and C=N bonds.[154]

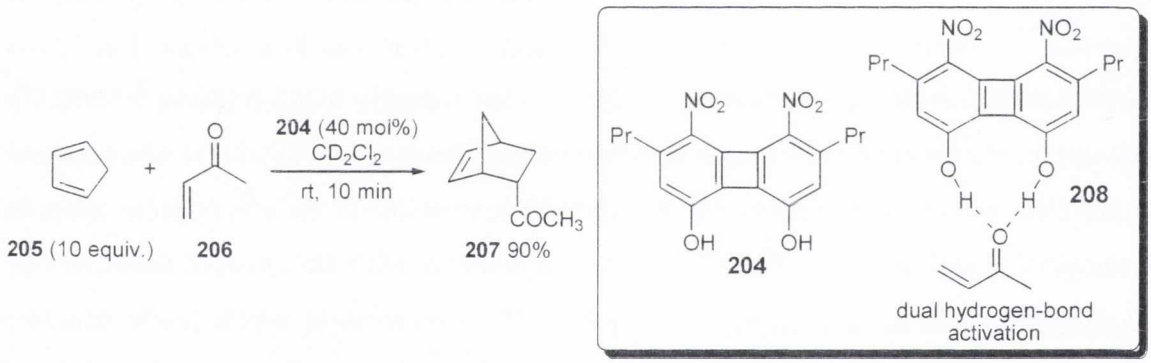
1.7.2 Hydrogen bond-mediated organocatalysis: pioneering studies

Over the course of a pioneering series of studies,[155] Hine *et al.* discovered that both *meta*- and *para*-substituted phenols, and conformationally rigid biphenylenediols such as **201**, could promote the addition of diethylamine to phenyl glycidyl ether (**202**) in butanone (Scheme 1.67). The improved catalysis observed in reactions catalysed by **201** is attributable to the simultaneous donation of two hydrogen bonds to the oxygen atom of the electrophile.



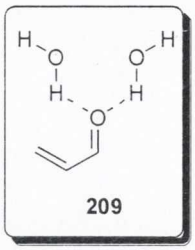
Scheme 1.67 Aminolysis of **202** *via* double hydrogen-bond donation

Kelly *et al.* later validated the findings of Hine *et al.* in a report detailing the use of biphenylenediol **204** as a promoter of Diels-Alder reactions between cyclopentadiene (**205**) and aldehydic and ketonic dienophiles (Scheme 1.68).[156] They too proposed dual hydrogen-bond donation (to the dienophile) as the source of the observed catalysis (**208**, Scheme 1.68).



Scheme 1.68 The promotion of the Diels-Alder reaction by a dual hydrogen-bond donor **204**

The findings subsequently reported by Jorgensen *et al.* supported those of Kelly *et al.* whereby they demonstrated *via* computational studies that the acceleration of Diels-Alder reactions[157] and Claisen rearrangements[158] when water was employed as the reaction solvent was due to the donation of two hydrogen-bonds by two water molecules (**209**, Scheme 1.69).

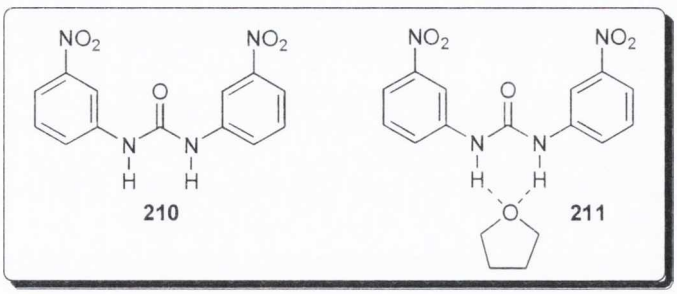


209

Scheme 1.69 The acceleration of the Diels-Alder reaction by two water molecules proposed by Jorgensen *et al.*

1.7.3 The development of (thio)urea derivatives as organocatalysts

In 1988, Etter *et al.* laid the foundations for the impending exploitation of *N,N'*-diarylureas as organocatalysts.[159] *Via* cocrystallisation, they demonstrated (using XRD techniques) the hydrogen-bond directed molecular recognition between a range *N,N'*-diarylureas, especially those with *meta*-electron-withdrawing substituents such as **210**, and compounds containing Lewis basic functionalities such as ethers, ketones, aromatic nitro compounds, sulfoxides and phosphine oxides. The binding mode was characterised by each urea donating two hydrogen-bonds to the Lewis base (*e.g.* **211**, Scheme 1.70).



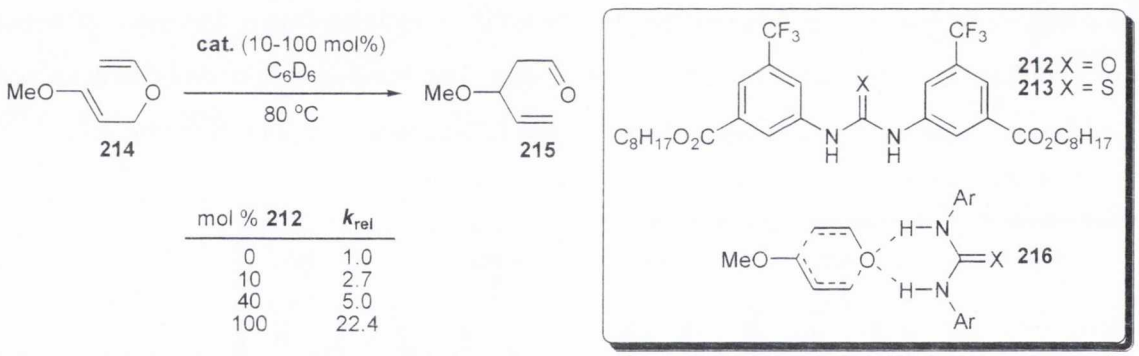
210 **211**

Scheme 1.70 **210**: 1,3-*Bis*(*m*-nitrophenyl)urea; **211**: the bidentate binding between **210** and THF

In 1994, by combining the findings of Kelly, Etter and Jorgensen, Curran *et al.* developed the first urea derivative to be successfully employed as an organocatalyst. They found

that catalytic quantities of a modified version of urea **210** (*i.e.* **212**) could augment both the yield and diastereochemical outcome of reactions involving the allylation of cyclic α-sulfinyl radicals with allyltributylstannane.[160] Replacement of the nitro group (which is a radical inhibitor) of **210** with a trifluoromethyl group, and addition of a lipophilic octyl ester substituent to facilitate solubility, led to the development of **212** (Scheme 1.71).

In a subsequent report, the same group detailed the application of both **212** and its thiourea analogue **213** as promoters of the Claisen rearrangement of 6-methoxy allyl vinyl ether (**214**).[161] This represented the first example of a thiourea derivative as an organocatalyst. The observed rate enhancement in these reactions was reportedly due to a *bis*-hydrogen-bonded transition state (**216**, Scheme 1.71). Due to the decomposition of **213** under the reaction conditions, **212** proved to be superior as a promoter of these reactions. Notable rate acceleration could only be achieved when medium to high loadings of **212** were employed (Scheme 1.71).

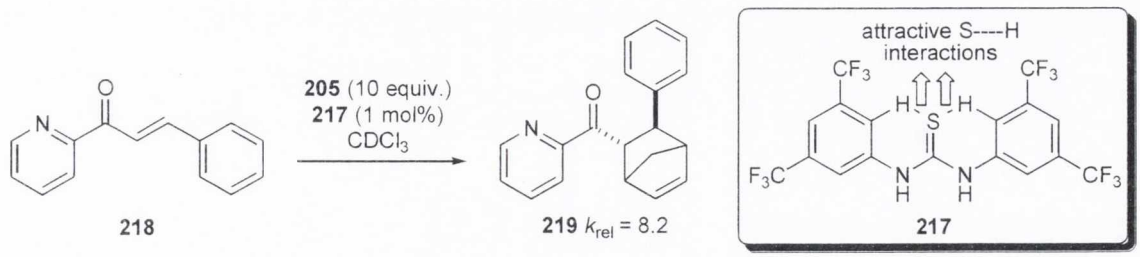


Scheme 1.71 Promotion of the Claisen rearrangement of **214** by **212** and the resulting *bis*-hydrogen-bonded transition state **216**

Schreiner *et al.* later recognised that diarylthioureas could catalyse the Diels–Alder reaction between cyclopentadiene and α,β-unsaturated carbonyl compounds.[162,163] As diarylureas are often associated with poor solubility, more soluble thiourea derivatives were considered, eliminating the necessity for octyl ester substituents (such as **212** and **213**).

Ideally, a hydrogen-bond donating catalyst should have a greater affinity for the transition state than for itself, the substrate or the product. Elimination of the catalyst's lipophilic octyl ester substituent (*vide supra*) eradicates a binding site that can compete with the substrate for the hydrogen-bond donating moiety of the catalyst, thus negating self-association. Also, due to the lower electronegativity of sulfur in comparison to oxygen, self-association of thiourea analogues is less likely to occur. The acidity of the N-H protons should be sufficient such that binding to the Lewis basic substrate be facilitated: this can be achieved by the installation of electron-withdrawing groups on the aromatic rings of the diarylthiourea. As the trifluoromethyl group is both electron-withdrawing and is a poor hydrogen-bond acceptor (removing the possibility of self-association), it was viewed as an attractive possibility.[162]

It was also established that a rigid catalyst structure is necessary to avoid entropic loss upon coordination.[163] Rigidifying internal interactions between the Lewis-basic sulfur and the *ortho*-hydrogen atoms (which hinder rotation, minimising the entropic penalty upon complexation) can be achieved if the electron-withdrawing substituents are located in the *meta*- or *para*-positions (Scheme 1.27). Having screened derivatives with electron-donating and electron-withdrawing groups in various ring positions, the trifluoro-substituted thiourea **217** was found to be the most effective catalyst in Diels-Alder reactions between **205** and a range of five various dienophiles. A representative example is illustrated in Scheme 1.72.[163]



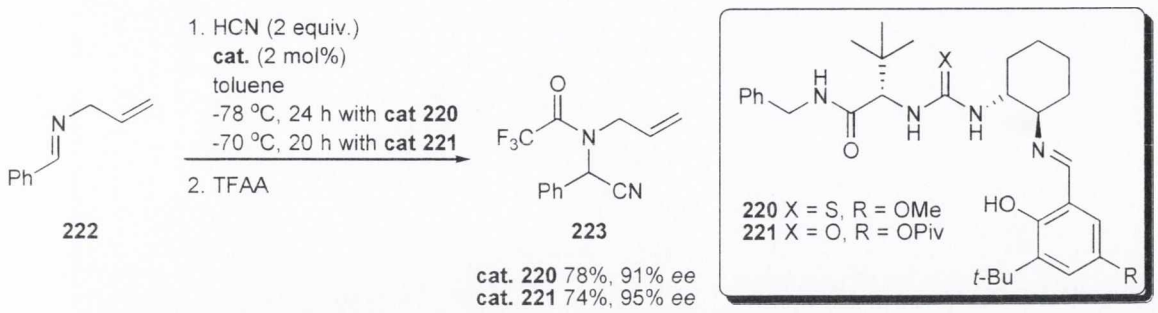
Scheme 1.72 The catalysis of the Diels-Alder reaction by thiourea **217**

Since these groundbreaking findings, diarylureas and –thioureas have proven to be efficient promoters of a number of other synthetically useful reactions such as the cyanation of nitrones,[164] the Baylis-Hillman reaction[165] and Friedel–Crafts alkylations.[149,151,166]

1.7.4 Chiral (thio)urea-derived organocatalysts

In 1998, Jacobsen *et al.* made a fortuitous discovery while preparing parallel combinatorial libraries of chiral Schiff base catalysts for the metal-ion-mediated asymmetric Strecker reaction.[167] During the screening process, they found that the ligand itself, in the absence of a metal ion (*i.e.* the control reaction) provided the highest product *ee* (19%). Subsequent optimisation studies revealed that chiral Schiff base **220** was the optimum catalyst, which efficiently promoted the Strecker reaction between hydrogen cyanide (HCN) and both aromatic and aliphatic *N*-allyl aldimines: the corresponding Strecker adducts were obtained in moderate to high chemical yield (65-92%) and high enantiomeric excess (70-91%). A representative example is illustrated in Scheme 1.73.

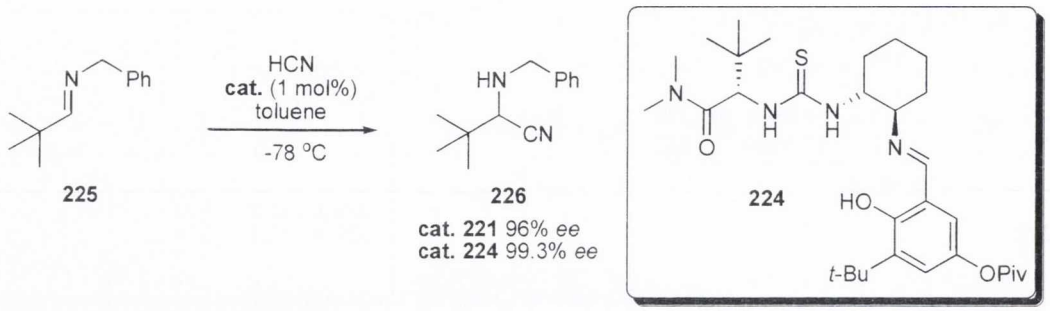
Based on their promising preliminary findings, a further library of chiral Schiff base candidates were prepared and evaluated in Strecker reactions between HCN and both *N*-allyl and *N*-benzyl aromatic and aliphatic aldimines.[168] The soluble, readily prepared[169] 5-pivaloyl-substituted Schiff base **221** proved to be the most efficient catalyst affording the corresponding Strecker adducts in good to excellent yield (65-99%) and generally excellent enantioselectivity (77-97% *ee*).[168] A representative example is depicted in Scheme 1.73. Methylketimines protected with various *N*-benzyl groups also proved to be compatible with **221**, providing the corresponding Strecker adducts in high yield (95%-quantitative) and *ee* (70-95%).[170]



Scheme 1.73 Jacobsen's *et al.* asymmetric Strecker reaction catalysed by Schiff bases **220** and **221**

Structural and mechanistic studies performed by the same group provided valuable insight into the role of **221** in the aforementioned reactions.[171] They elucidated that Michaelis-Menten kinetics are obeyed in these reactions, *i.e.* the formation of the imine-catalyst complex is formed reversibly. Having prepared and evaluated a variety of analogues of **221**, it was found that the interactions responsible for the formation of the imine-catalyst complex is a double hydrogen bond between the imine nitrogen's lone pair and the two urea N-H protons.[171] They also determined that it is the *Z*-stereoisomer of the imine substrate that is involved in the imine-catalyst complex and that the interaction occurs in such a way that both the large imine substituent and the *N*-substituent are directed away from the catalyst.

Based on the observed sense of enantioinduction, they hypothesised that HCN adds over the diaminocyclohexane moiety (from the right of **221**, Scheme 1.73), avoiding the amino acid moiety. To prove this hypothesis, they prepared a variety of Schiff base catalysts bearing more sterically encumbered amino acid portions: indeed they found that **224** furnished the desired Strecker adducts with higher enantioselectivity than reactions catalysed by **221** (Scheme 1.74).[171]



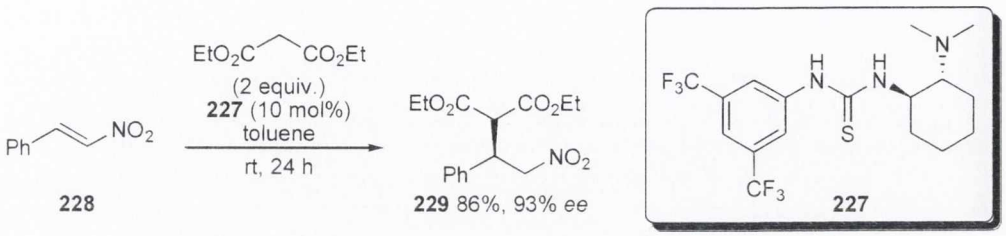
Scheme 1.74 Comparison of the enantioselectivity achieved in the asymmetric Strecker reaction using either **221** or **224**

In the aftermath of the aforementioned seminal studies, many reports have emerged detailing the development of highly enantioselective protocols based on the use of these, and modified versions of these catalysts in an array of other synthetically useful reactions such as the Mannich, imine hydrophosphonylation, aza Baylis-Hillman, Pictet-Spengler, nitro Mannich and acyl Mannich reactions.[151,154]

1.7.5 Chiral bifunctional (thio)urea-derived organocatalysts

The possibility of enhancing the stereochemical outcome of organocatalysed reactions by using chiral bifunctional thiourea-derived catalysts incorporating functionality capable of activating both the nucleophile and electrophile was realised by Takemoto *et al.* in 2003.[172] Taking on board the findings of Curran, Jacobsen and Schreiner (*vide supra*) that positioning a readily tunable (from both a rigidity and a hydrogen-bond donating perspective) aromatic group on one (thio)urea nitrogen atom, and a chiral (Lewis basic) group on the other, they undertook the development of a chiral bifunctional thiourea-derived catalyst for the asymmetric addition of malonate esters to β-nitrostyrenes. They posited that by incorporating a thiourea moiety to activate the nitroolefin and a basic tertiary amine moiety to activate the pro-nucleophile, excellent levels of addition product *ee* should ensue. They therefore prepared and evaluated tertiary amine **227** which proved to be an efficient promoter of the Michael reaction of malonates to various nitroolefins

providing the addition products in high yield (74-95%) and *ee* (81-93%).[172] A representative example is illustrated in Scheme 1.75.



Scheme 1.75 The enantioselective addition of diethyl malonate to nitroolefin **228** catalysed by the chiral bifunctional thiourea **227**

The authors deduced that both the thiourea and tertiary amine functionalities were of vital importance to the activity of the catalyst. They proposed a mechanism to explain the stereochemical outcome of the reactions: they postulated that the amino group deprotonates the acidic proton of the malonate ester. Concurrently, a hydrogen bonding interaction between the nitroolefin and the N-H protons of the thiourea moiety activates the electrophile. Face selective addition of the malonate nucleophile to the selectively-bound nitroolefin leads to the observed stereoinduction (**230**, Figure 1.7).[173]

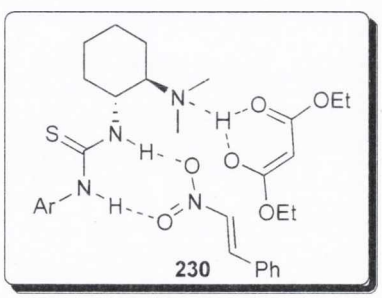


Figure 1.7 The mechanism proposed by Takemoto *et al.* which explains the sense of stereoinduction observed in the asymmetric addition of diethyl malonate to nitroolefins

Further studies revealed that a variety of β-ketoesters were also compatible pronucleophiles in these reactions.[173]

Less than a decade has passed since the emergence of the first report detailing the application of a bifunctional (thio)urea-derived organocatalyst in an asymmetric transformation.[172] Since then, vast progress has been made in this field with the appearance of many landmark publications from an array of independent research groups. For example, **227** has been shown to successfully promote the aza Henry reaction[174] while both **227** and its urea analogue have been employed as catalysts in the dynamic kinetic resolution (DKR) of racemic azalactones.[175] (Thio)urea-substituted cinchona alkaloids have also been shown to exhibit excellent enantioselectivity in a variety of addition reactions.[151,154] Due to the outstanding levels of control that can be achieved using this class of catalyst, this area is likely to continue to flourish as it has done over the past decade.[151,154,176]

2.1 The development of novel hydrogen bond-donating organocatalysts toward the highly enantioselective synthesis of terminal epoxides *via* the Corey-Chaykovsky reaction

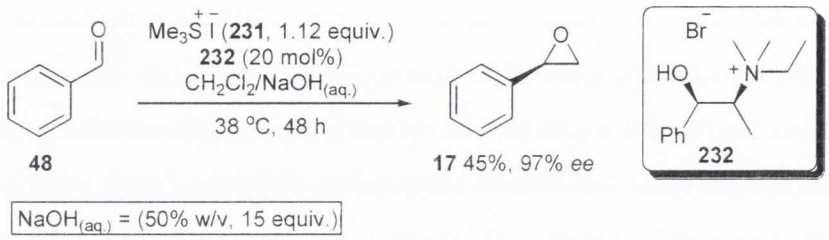
Over the past five decades the Corey-Chaykovsky reaction[46-48] has blossomed, becoming a highly synthetically useful route for the synthesis of enantioenriched epoxides.[7,42,50] Excellent enantioselectivities have been achieved in reactions involving the addition of both stabilised and semi-stabilised sulfonium ylides to aldehydes to furnish 1,2-disubstituted epoxides (*vide supra*); however, the corresponding reactions involving the addition of non-stabilised sulfonium ylides to aldehydes to yield terminal epoxides is characterised by moderate enantioselectivities (see Sections 1.3.2.1, 1.3.2.2.1, 1.3.2.2.2.1, 1.3.2.2.2.2 and 1.3.2.2.2.3).[93,94] As the archetypal strategy involving chiral sulfonium ylides has failed to supply these valuable materials in high optical purity,[93,94] we decided to develop a novel class of organocatalyst based on the exploitation of hydrogen-bonding in an attempt to plug this significant gap in the technology.

2.1.1 *N*-Alkyl salts derived from ephedrine as promoters of enantioselective methylene transfer to aldehydes: a historical perspective

During the course of a research programme aimed at the design of novel hydrogen-bond-donating organocatalysts for asymmetric methylene transfer to aldehydes, we were intrigued to discover that *N*-alkyl salts derived from ephedrine had twice been reported to act as chiral phase transfer catalysts in Corey-Chaykovsky reactions between sulfonium ylides and benzaldehyde, reportedly furnishing the terminal epoxide product in moderate-excellent enantiomeric excess.[177,178]

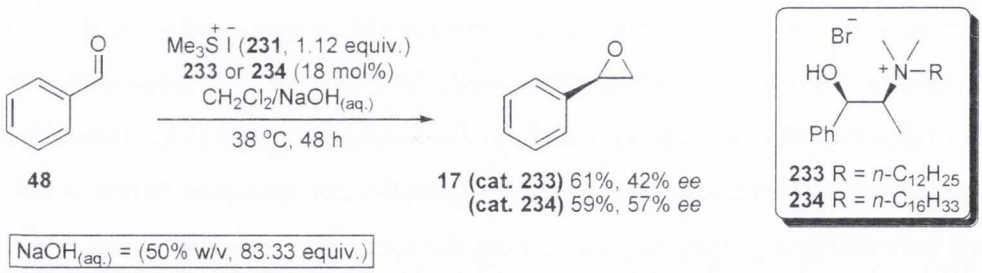
In 1975, Hiyama *et al.* disclosed that in a reaction between benzaldehyde (**48**) and trimethylsulfonium iodide (**231**) under biphasic reaction conditions (CH_2Cl_2/$NaOH_{(aq.)}$) in the presence of the ephedrine-derived salt **232**, styrene oxide (**17**) was furnished in moderate yield and excellent enantioselectivity (Scheme 2.1). They reported an

enhancement in enantioselectivity with increased catalyst loading (35% *ee* at 1 mol% loading and 97% *ee* at 20% loading).



Scheme 2.1 Conditions employed and results obtained by Hiyama *et al.* using **232**

Over 20 years later, Zhang *et al.* reported a similar study detailing the use of the lipophilic catalysts **233** and **234** (Scheme 2.2).[178] Again significant enantioselectivity of the resulting epoxide products was reported. In this instance, a dependence of enantioselectivity on both reaction temperature and time was observed: in general product *ee* increased with temperature (up to 40 °C), and reaction time (up to 60 h). The authors attributed the observed enantioselectivities to hydrophobic-lipophilic interactions between the substrate and the chiral micelle formed by the chiral surfactants **233** and **234**.

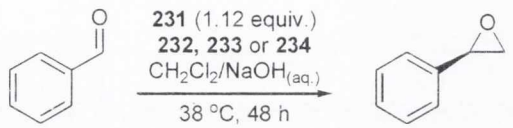


Scheme 2.2 Conditions employed and results obtained by Zhang *et al.* using **233** and **234**

It is noteworthy that in both reports, the authors relied on optical rotation to both assign the absolute configuration, and to determine the *ee* of the epoxide product.

2.1.1.1 Our investigation into an underexploited methodology for the enantioselective preparation of terminal epoxides

Given the difficulties associated with the catalytic asymmetric synthesis of terminal epoxides (*vide supra*), we viewed this as a significant opportunity to develop this hitherto underexploited methodology by means of the design of new phase-transfer catalysts for this reaction. We began by repeating the key experiments detailed in both papers precisely.[179] Our findings are outlined in Table 2.1.



48 **17**

entry	conditions	cat.	yield 17 (%)[a]	$[\alpha]_D^{20}$	*ee* (%)[b]
1	Hiyama	**232**	100	+9.3 (*c* 1.00)	0
2	Zhang	**233**	77	+12.0 (*c* 0.38)	0
3	Zhang	**234**	78	+17.4 (*c* 0.32)	0

[a]Determined using ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. [b]CSP-HPLC analysis (Chiralcel OD-H column 4.6 x 250 mm, 99.9/0.1 hexane:i-PrOH).

Table 2.1 Results obtained in our laboratory upon replication of the experiments reported Hiyama *et al.*[177] and Zhang *et al.*[178]

Catalysis was observed in reactions containing **232**, **233**, and **234** (the control reaction devoid of catalyst afforded **17** in 16% chemical yield under identical reaction conditions). The optical activity of **17** was also determined following chromatography of the catalysed reactions (Table 2.1); however, to our surprise, CSP-HPLC analysis of the purified epoxide product obtained from the catalysed reactions revealed that **17** had been formed as a racemic mixture.[180] Several repetitions of these experiments yielded reproducible results. The CSP-HPLC chromatograms obtained from these reactions, together with that

of ***rac*-17** are shown (**A**, **B**, and **C**, Figure 2.1). Although the catalysed reactions had been purified by chromatography prior to HPLC analysis, a peak not derived from **17** appeared at 15.6-16 min retention time in the HPLC chromatograms (**B**, and **C**, Figure 2.1).

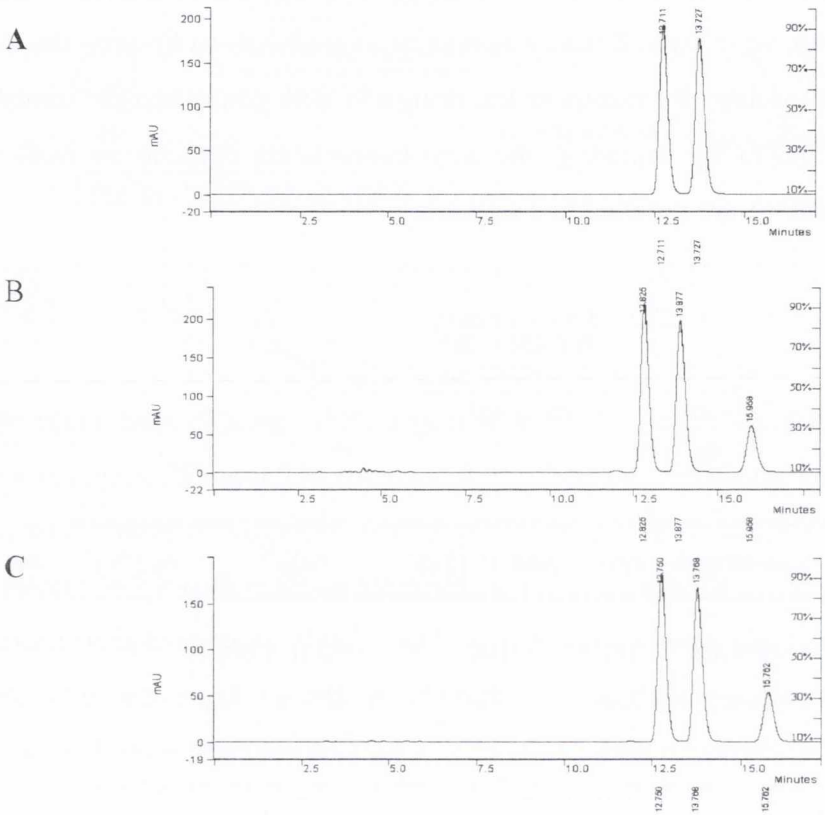


Figure 2.1 CSP-HPLC analysis of the reactions outlined in Table 2.1. (**A**) Racemic **17**. Chromatographed epoxide product obtained from the reaction catalysed by **232** under Hiyama's conditions (**B**) and by **233** under Zhang's conditions (**C**).

The identity of this impurity was elucidated using ^{1}H NMR analysis and was found to be epoxide **235** (Scheme 2.3), presumably formed in high enantiomeric excess *via* the base-mediated ring-closure of **232**, **233**, and **234**. Figure 2.2 shows that this impurity is present in both the crude and isolated (after column chromatography) ^{1}H NMR spectra of the reaction catalysed by **234**. Very similar spectra were obtained from the other reactions outlined in Table 2.1. This indicates that **235** is inseparable from **17** by column chromatography and is thus responsible for the observed optical activity.

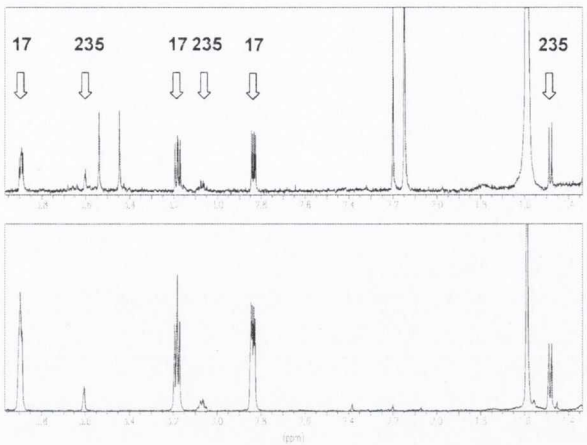
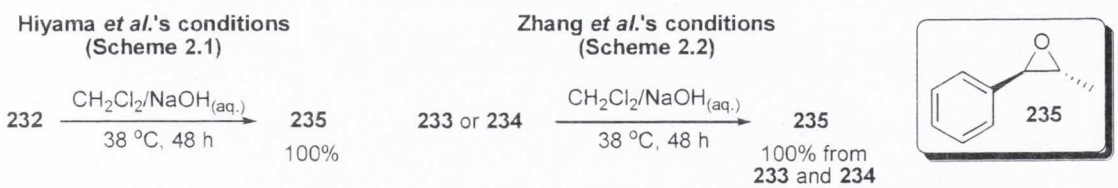


Figure 2.2 ^{1}H NMR analysis (400 MHz, $CDCl_3$) of the reaction catalysed by **234** (Table 2.1). (**A**) Sample taken from the crude reaction after 48 h. (**B**) Sample taken after purification by chromatography.

To verify the assumption that **235** is formed under these basic conditions, and that the optical activity of the chromatographed products is ascribable to **235**, catalysts **232**, **233** and **234** were subjected to the reaction conditions outlined in Schemes 2.1 and 2.2 in the absence of both benzaldehyde (**48**) and trimethylsulfonium iodide (**231**) (Scheme 2.3).



Scheme 2.3 The decomposition of **232**, **233** and **234** in the absence of **48** or **231** under the specified reaction conditions

Each of **232**, **233** and **234** completely decomposed to form **235** in quantitative yield (Scheme 2.3). This explains the strong dependence of the enantioselectivity on reaction temperature, time and loading that was observed in the two earlier reports:[177,178] factors likely to induce greater decomposition of enantiopure catalyst to afford higher levels of enantiopure **235** would ultimately lead to a product with a greater specific rotation.

It was found that isolated **235** had a high specific rotation ($[\alpha]_D^{20} = +64.6$ $c = 0.71$) and an identical retention time (15.7 min) to the previously unidentified component in the chromatograms shown in Figure 2.1 (Figure 2.3).

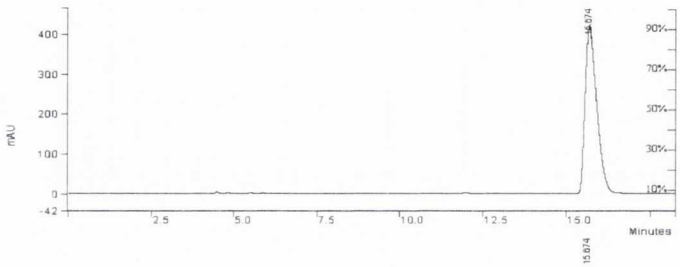


Figure 2.3 CSP-HPLC analysis of the decomposition of **234** under Zhang *et al.*'s conditions (Scheme 2.3)

To confirm that **17** was actually formed as a racemic mixture in this reaction, and that epoxide racemisation did not occur during chromatography or under the reaction conditions, a sample of commercially available enantiopure **(*R*)-17** was purified by the same column chromatography methodology used throughout this study. In a second experiment, pure **(*R*)-17** (1.0 equiv.) was added at t = 0 h to a Corey-Chaykovsky reaction. Upon completion of the reaction, the products were isolated and analysed by CSP-HPLC. In both cases, no evidence of racemisation was observed with **17** being detected in >99% *ee* and 53% *ee* respectively. Hence, it is certain that the error in reporting **232**, **233** and **234** in the earlier studies as being capable of inducing asymmetry in the Corey-Chaykovsky reaction is due to their reliance on specific rotation to both assign absolute configuration and determine *ee*. The authors were unfortunate that the epoxide formed from the decomposition of the catalyst (*i.e.* **235**), which is responsible for the observed optical activity, is difficult to separate from styrene oxide (**17**). Using the low-field NMR instrumentation available to Hiyama and Zhang, it may not have been possible to identify **235** at low levels (max. 20%). With the benefit of CSP-HPLC analysis and high-field NMR (400-600 MHz) it can be unequivocally shown that these ammonium salt-catalysed methylene transfer reactions furnish racemic products exclusively. It was therefore decided to discontinue this project and focus our attention on

the development of alternative hydrogen-bond donating catalysts for the asymmetric synthesis of terminal epoxides.

2.1.2 The development of (thio)urea-derivatives for the catalytic asymmetric synthesis of terminal epoxides: precedents and proposed mode of action

As discussed in Section 1.3.2.2.2.3, the hitherto most common strategy for the asymmetric synthesis of terminal epoxides involving the use of chiral sulfonium ions has failed to lead to highly enantioselective methylene transfer protocols for the CC reaction. For the past four years, our group has been interested in the design and exploitation of (thio)urea derivatives as robust and active hydrogen-bond donating catalysts for a variety of addition reactions characterised by an increase in basicity at a heteroatom in the reaction transition state.[181] Curran[160,161] and Schreiner[162,163] (Section 1.7.3) made the milestone discoveries that readily prepared, tunable and relatively rigid *N,N'*-diarylureas and –thioureas, possessing two *syn*-periplanar N-H bonds available for hydrogen-bond-donation, are efficient catalysts for Claisen rearrangements and Diels-Alder reactions respectively. It was later shown that these compounds are also active and versatile promoters of the addition of cyanide and silyl ketene acetals to nitrones,[164] the Baylis-Hillman reaction,[165] Friedel-Crafts type reactions,[166] acetalisations,[182] Claisen rearrangements,[165,183] epoxide ring-opening reactions,[184] acyl Strecker reactions,[185] tetrahydropyranylations[186] and imine reductions,[187] *inter alia*.[188]

We therefore became interested in the development of an organocatalytic strategy based on the use of hydrogen-bond-donating catalysts, specifically, chiral bifunctional (thio)urea derivatives for an enantioselective variant of the CC reaction (Figure 2.4).

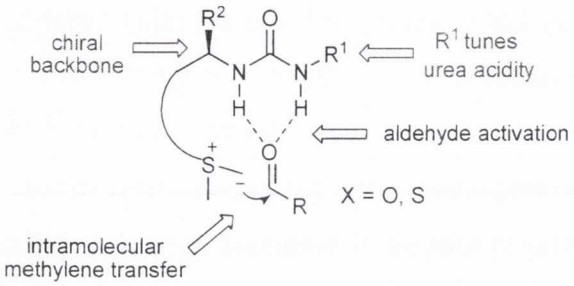
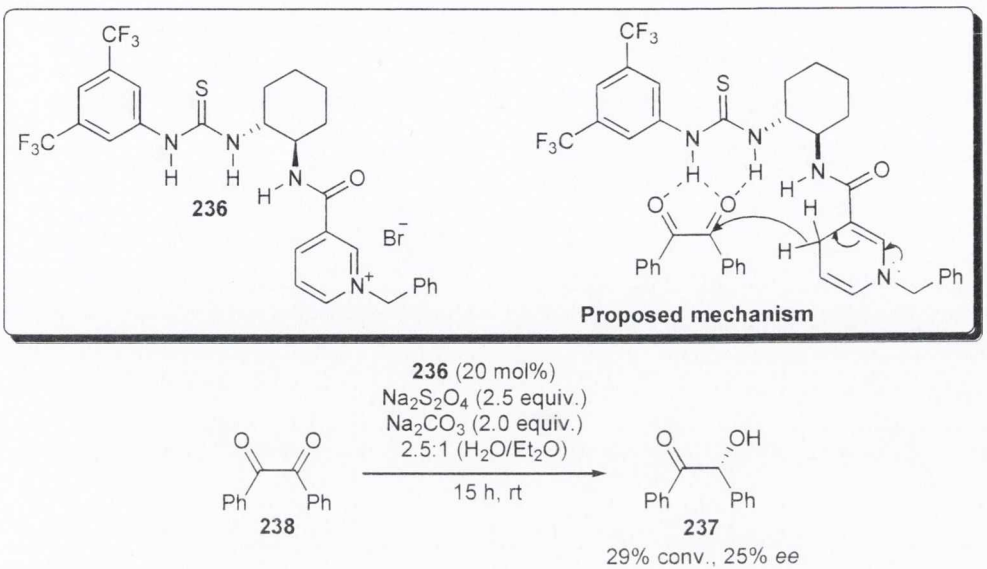


Figure 2.4 Rationale for chiral bifunctional (thio)urea catalyst activity

These bifunctional catalysts possess both an electrophile activating unit ((thio)urea) and a sulfide group (from which the ylide can be generated *via* alkylation to the corresponding sulfonium salt with subsequent deprotonation) linked together by a chiral tether. Conceptually, the (thio)urea moiety should activate the aldehyde towards nucleophilic attack by the ylide through a hydrogen bonding interaction between the oxygen of the aldehydic carbonyl group and the N-H protons of the (thio)urea (the acidity of which being readily tunable). Subsequent intramolecular delivery of the methylene group to the bound aldehyde in a face-selective manner should furnish an enantioenriched terminal epoxide.

We were encouraged by a recent report from our group detailing the development of a new class of bifunctional catalyst incorporating both a substrate activating (thio)urea moiety and an organic hydride donor (**236**, Scheme 2.4). This bifunctional thiourea-based pyridinium salt precatalyst could promote the reduction of diketones in the presence of aqueous base in a biphasic system without decomposition.[189] It was found that **(*R*,*R*)-236** could furnish **(*R*)-237** from **238** with moderate enantioselectivity (Scheme 2.4).



Scheme 2.4 The asymmetric reduction of diketone **238** using bifunctional thiourea derivative **236**

We therefore posited that (thio)urea derivatives could accelerate CC reactions under these conditions through the stabilisation of developing negative charge on the oxygen heteroatom in the rate determining addition step transition state (Figure 2.5).

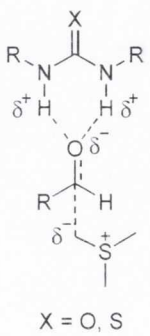
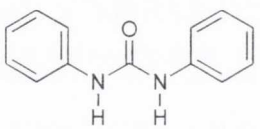


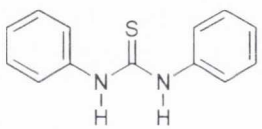
Figure 2.5 Proposed mode of (thio)urea catalyst activity

We were also intrigued by the lack of activity of readily available and inexpensive (€22.90/25g, TCI Europe) trimethylsulfonium iodide in CC reactions. It has proven to be unreactive under convenient biphasic conditions ($CH_2Cl_2/NaOH_{(aq.)}$, rt) and only gives

appreciable product yields upon heating in the presence of a phase transfer catalyst.[177,178,190] These conditions are not conducive to either hydrogen bond-mediated catalysis or, arguably, hydrogen bond-mediated asymmetric induction. Furthermore, solid-liquid two-phase systems have been developed (NaOH or KOH(s)/MeCN),[191-193] however heating is involved and the formation of cinnamonitrile is a problem.[67] One further issue which was considered before catalyst development commenced (which is in fact the issue we speculated to be the reason for the paucity of studies on the use of hydrogen bond donating catalysts in the CC reaction) was the issue regarding the reasonably basic conditions required to form the sulfonium ylide, which would preclude the use of hydrogen-bond-donating catalysts of strong to medium acidity. We were therefore pleased to find that the pK_a (DMSO) of *N,N'*-diphenylurea (**239**, Scheme 2.5), its thiourea analogue *N,N'*-diphenylthiourea (**240**, Scheme 2.5) and trimethylsulfonium iodide (**231**) are 19.55, 13.4 and 18.2 respectively.[194] Thus, at a minimum we expected urea derivatives to be compatible with the deprotonated sulfonium methylide.



239



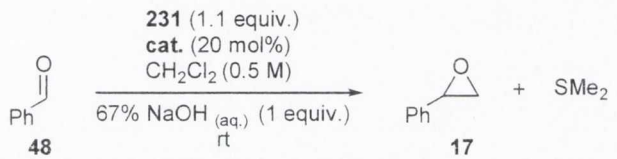
240

Scheme 2.5 *N,N'*-diphenylurea (**239**) and its thiourea analogue *N,N'*-diphenylthiourea (**240**)

2.1.2.1 Evaluation of the aldehyde-activating capability of symmetrical (thio)urea derivatives in the CC reaction: preliminary investigations and optimisation studies (performed by Dr. Eimear Fleming)

Prior to the development of a bifunctional catalyst (*vide supra*) for the asymmetric synthesis of terminal epoxides *via* the CC reaction (Figure 2.4), evaluation of the aldehyde-activating capability of the urea moiety under simple CC reaction conditions was deemed prudent. With the preliminary insight previously mentioned, and with the

knowledge that precatalyst **236** could promote the reduction of diketones in the presence of aqueous base in a biphasic system without decomposition,[189] Dr. Eimear Fleming[195] began catalyst screening and optimisation studies. A set of (thio)urea derivatives were prepared and their efficiency as promoters of the CC reaction with **48** as substrate was evaluated. Dr. Fleming's findings are summarised in Table 2.2. Under the conditions outlined in Table 2.2, catalysis was observed, with urea **239** proving to be more efficient than its thiourea counterpart **240** (entries 4 and 6) affording 12% conversion of **17**.

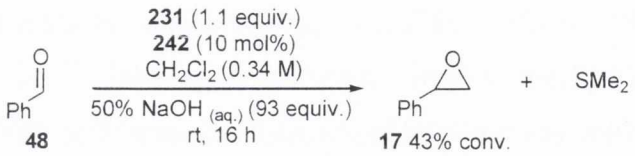


entry	cat.	time (h)	conv. (%)[a]
1	-	24	0
2	-	94	9
3	**239**	16	<2
4	**239**	94	12
5	**240**	24	0
6	**240**	94	0

[a]Determined using ^{1}H NMR spectroscopy.

Table 2.2 Preliminary (thio)urea catalyst screening conducted by Dr. Eimear Fleming

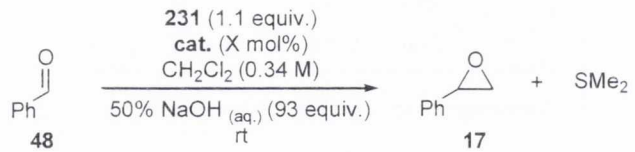
Encouraged by this, optimisation studies (with respect to solvent, base and organic phase concentration) were performed to identify reaction conditions that would lead to both high levels of epoxide product in the presence of catalyst and background reaction suppression in the absence of catalyst. A set of conditions were developed that satisfied these criteria: under biphasic reaction conditions (CH_2Cl_2/50% $NaOH_{(aq.)}$) using 93 equivalents of base and 5 mol% of urea **242**, styrene oxide (**17**) was furnished in 43% conv. (Scheme 2.6). It is noteworthy that under the same conditions but in the absence of catalyst, **17** was not formed.



Scheme 2.6 Preliminary reaction conditions developed by Dr. Eimear Fleming

2.1.2.2 Building on the preliminary optimisation studies: optimisation of reaction agitation

Initial experiments performed under the preliminary reaction conditions developed above between benzaldehyde (**48**) and trimethylsulfonium iodide (**231**) under biphasic reaction conditions (CH_2Cl_2/50% $NaOH_{(aq.)}$) using 93 equivalents of base, indicated that, although good levels of conversion of **48** to **17** were occurring in the reactions catalysed by **242** (entry 3, Table 2.3), appreciable levels of **17** were also being formed in the control reactions (entries 1 and 2, Table 2.3) which is undesirable from an enantioselectivity perspective.



entry	cat.	cat. loading (X mol%)	stirring plate setting[a]	time (h)	conv. (%)[b]
1	-	0	4	24	9
2	-	0	8	24	27
3	**242**	2	8	24	77
4	**242**	5	4	24	100

[a]Radley's Carousel Stirring Hotplate (No. RR98072). [b]Determined using ^{1}H NMR spectroscopy.

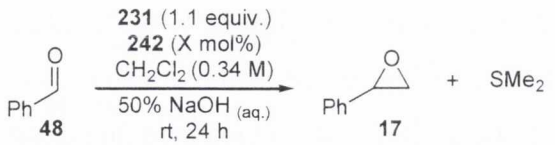
Table 2.3 Optimisation of reaction agitation

Stirring rigour was found to be inextricably linked to the quantity of **17** that was formed in reactions (Table 2.3). The background reaction became more prominent with more rigorous stirring (entries 1 and 2). It was also elucidated that using **242** at 5 mol% loading afforded the highest levels of **17**. It was therefore decided that subsequent reactions should be performed with the stirring hotplate set at stirring setting 4 using **242** catalyst loadings of 5 mol%.

2.1.2.3 Building on the preliminary optimisation studies: optimisation of base loadings for the CC reaction

Due to the persistence of the background reaction, optimisation of the reaction conditions was required until its abolition was achieved without causing a diminution of the levels of **17** formed in catalysed reactions. Our first port of call was the re-evaluation of base equivalents. It was hoped that employing lower loadings of base would lead to attenuation of the background reaction. Our findings are documented in Table 2.4. Using either 5 or 10 equivalents of the base led to suppression of the background reaction (entries 1 and 3); however, the levels of **17** obtained from the corresponding catalysed reactions proved to be poor (entries 2 and 4). The catalysed reaction performed with 46.5 equivalents of the base furnished higher levels of **17** with simultaneous suppression of the formation of **17** in the background reaction (entries 5 and 6).

The highest levels of **17** were obtained from catalysed reactions performed using 60 or 70 equivalents of the base (entries 8 and 10); however, the control reaction containing 70 equivalents of the base (entry 9) afforded a greater quantity of **17** than did the reaction performed using 60 equivalents (entry 7). Therefore, reactions performed using 60 equivalents of 50% $NaOH_{(aq.)}$ provide the optimum combination of both yield of **17** in the catalysed reaction and suppression of the background reaction.



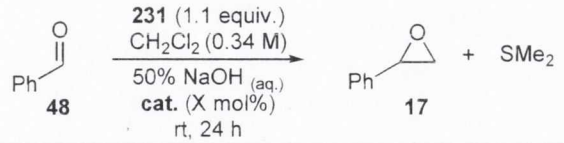
entry	242 (X mol%)	base equiv.	conv. (%)[a]
1	0	5	0
2	5	5	9
3	0	10	0
4	5	10	16
5	0	46.5	0
6	5	46.5	73
7	0	60	1
8	5	60	96
9	0	70	4
10	5	70	96

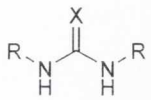
[a]Determined using ^{1}H NMR spectroscopy.

Table 2.4 Optimisation of base loadings for the CC reaction

2.1.2.4 The evaluation of a range of (thio)urea derivatives as promoters of the CC reaction

Having identified the optimum conditions for hydrogen-bond-mediated CC reactions using (thio)urea derivatives with respect to solvent, agitation (Table 2.3) and base (Scheme 2.6 and Table 2.4), attention subsequently turned to the elucidation of the optimum (thio)urea catalyst structure in the CC reaction. A range of urea and thiourea derivatives, **217**, **239**, **240** and **242-249** were prepared as potential promoters of the CC reaction between **48** and **231** under biphasic conditions (CH_2Cl_2/$NaOH_{(aq.)}$) at room temperature. The performance of each of these catalysts was evaluated and the results are presented in Table 2.5.





243 X = O, R = H
244 X = S, R = H
245 X = O, R = Me
246 X = O, R = C_6H_{11}
239 X = O, R = C_6H_5
240 X = S, R = C_6H_5
247 X = O, R = 4-OMe-C_6H_4
248 X = O, R = 4-NO_2-C_6H_4
249 X = O, R = 3,5-$(F)_2$-C_6H_3
242 X = O, R = 3,5-$(CF_3)_2$-C_6H_3
217 X = S, R = 3,5-$(CF_3)_2$-C_6H_3

entry	cat.	cat. loading (X mol%)	CH_2Cl_2:NaOH (v/v)[a]	conv. (%)[b,c]	yield (%)[d]
1	-	-	1.23:1	1.5	0
2	**243**	5	1.23:1	3	0
3	**244**	5	1.23:1	1	0
4	**245**	5	1.23:1	7	0
5	**246**	5	1.23:1	2	0
6	**239**	5	1.23:1	50	39
7	**240**	5	1.23:1	35	22
8	**247**	5	1.23:1	14	0
9	**248**[e]	5	1.23:1	22	11
10	**249**	5	1.23:1	99	99
11	**242**	5	1.23:1	97	97
12	**217**	5	1.23:1	67	50
13	**242**	5	7.37:1	42	29
14	**242**	5	14.7:1	15	0
15[f]	**242**	10	1.23:1	100	100
16	**242**	2	1.23:1	85	85
17	**NBCC**[g]	5	1.23:1	69	60
18[h]	**NBCC**[g]	5	1.23:1	95	83

[a]2.18 cm^3 used. [b]Determined using ^1H NMR spectroscopy. [c]The only species detected by ^1H NMR spectroscopy were **48**, **17** and intermediate. [d]Determined by ^1H NMR spectroscopy using (*E*)-stilbene as internal standard. [e]**248** Was only partially soluble in the reaction medium. [f]21 h reaction time. [g]NBCC = *N*-benzylcinchonidinium chloride. [h]NBCC and **242** used together, both at 5 mol% loading.

Table 2.5 (Thio)urea catalysis of the CC reaction

In the absence of catalyst, styrene oxide (**17**) was not observed (entry 1). Surprisingly, trace amounts of an unidentified intermediate were detected by ^{1}H NMR (this intermediate was also observed when lower loadings of base were employed in reactions (Table 2.4)), which was converted to **17** after extended reaction times. At low catalyst loadings of 5 mol%, urea (**243**), thiourea (**244**) and *N*-alkyl urea derivatives **245–246** failed to promote the formation of **17** effectively, although significant levels of the intermediate were observed using *N,N'*-dimethylurea (**245**). Integration of the resonances associated with the intermediate supports the assumption that its presence is responsible for the discrepancy between the conversion and yield involving inefficient catalysts.

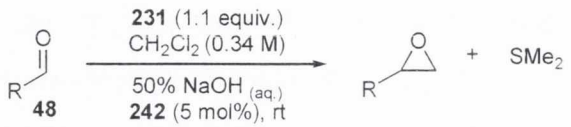
Use of the more acidic *N*-phenylurea and -thioureas (**239** and **240** respectively) resulted in substantial improvements in both rate and efficiency, furnishing **17** in moderate yield (entries 6 and 7). An electron-rich analogue of urea **239** (*i.e.* **247**, entry 8) proved inferior to more acidic analogues incorporating electron deficient aromatic substituents (even the insoluble **248**, entries 9–11). Gratifyingly, *bis*-fluoro- and *bis*-trifluoromethylphenyl substituted ureas **249** and **242** proved to be highly active, both producing **17** in excellent yields after 24 h at 5 mol% loading (entries 10 and 11). As expected (*vide supra*), urea **242** is a more active catalyst than the more acidic thiourea **217** (entry 12), just as **239** is a better catalyst in this reaction than **240**. This observed superiority of urea over thiourea derivatives is unusual;[160,170] in this case we would propose that it is related to the high acidity of the thiourea derivatives relative to the sulfonium ion (*vide supra*, the pK_a (DMSO) of thiourea *N,N'*-diphenylthiourea (**240**) and trimethylsulfonium iodide (**231**) are 13.4 and 18.2 respectively. Reducing the amount of base led to lower conversions (entries 13 and 14), whilst increasing the catalyst loading (to 10 mol%) resulted in faster reactions and quantitative yields (entry 15). In addition, efficient catalysis was observed with catalyst loadings as low as 2 mol% after 24 h (entry 16). We also found that **242** is superior to the cinchona alkaloid-derived phase transfer catalyst *N*-benzylcinchonidinium chloride (NBCC), however little synergy was observed when both catalysts were employed together (entries 11, 17 and 18).

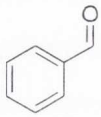
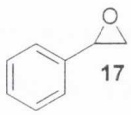
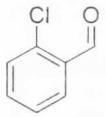
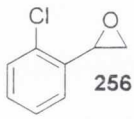
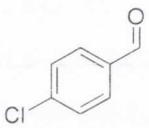
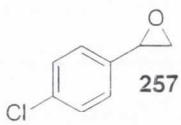
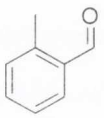
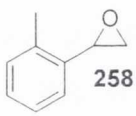
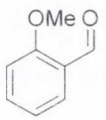
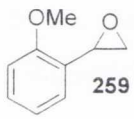
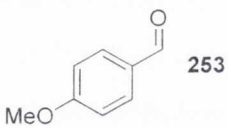
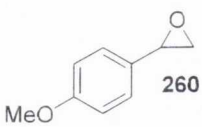
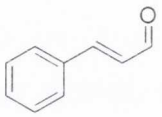
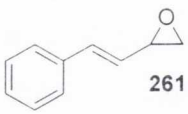
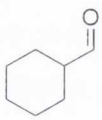
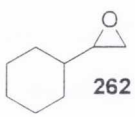
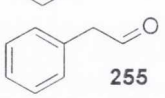
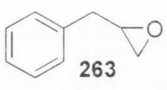
2.1.2.5 The synthesis of epoxides 17 and 256-263 *via* catalysis of the CC reaction by urea 242: evaluation of substrate scope

Having identified an active catalyst, *i.e.* **242** (although **249** also proved to be a highly active catalyst in the CC reaction, urea **242** was chosen as the candidate for further study as it has already been shown to promote a range of transformations effectively whereas **249** is less widely used) attention subsequently turned to the question of substrate scope.

We were pleased to find that the catalytic procedure proved robust: catalyst **242** promoted the smooth transformation of a range of aldehydes **48**, **72**, **78** and **250-255** into epoxides **17** and **256-263** at 5 mol% loadings (Table 2.6). In addition to styrene oxide (**17**) (entry 1), epoxides derived from activated (entries 2 and 3), hindered (entry 4) and electron-rich (entries 5 and 6) aromatic aldehydes could be prepared in excellent yields (synthesis of epoxides **17**, **257**, **259**, **260** and **263** was performed by Mr. Alessandro Piccinini). α,β-Unsaturated and α-substituted aliphatic aldehydes (but not unbranched analogues which underwent competitive aldol reactions) were also amenable to epoxidation under these conditions (entries 7-9).

We have therefore shown for the first time that appropriately substituted *N*,*N*'-diarylureas and thioureas are capable of the efficient catalysis of the Corey–Chaykovsky reaction involving the inexpensive trimethylsulfonium iodide at ambient temperature.[196] Rather unusually, urea derivatives are clearly superior catalysts in comparison to their thiourea analogues in these processes. These catalysed reactions are of wide scope with respect to the aldehyde component, with clean formation of the epoxide being observed under optimum conditions.



Entry	Substrate	Time (h)	Product	Yield (%)[a]
1[e]	 **48**	20	 **17**	93
2	 **250**	16	 **256**	93
3[e]	 **78**	15	 **257**	91
4	 **251**	85	 **258**	96
5[e]	 **252**	40	 **259**	57 (95)[b]
6[e]	 **253**	92	 **260**	75 (98)[b]
7	 **254**	38	 **261**	91
8	 **72**	133[c]	 **262**	90
9[e]	 **255**	40[d]	 **263**	0

[a]Isolated yield. [b]Crude epoxide decomposes during either Kugelrohr distillation or chromatography, the figure in parentheses represents the crude yield of spectroscopically pure product. [c]98% Of **72** had been consumed after 69 h. [d]Time taken for complete consumption of **255**. [e]Synthesis of epoxide performed by Mr. Alessandro Piccinini.

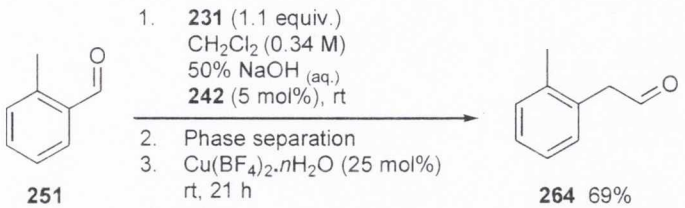
Table 2.6 Evaluation of the substrate scope

The efficient catalysis observed in this study (5 mol% catalyst loading is generally sufficient) offers the possibility of developing an enantioselective variant of the reaction using chiral urea derivatives. Investigations along these lines will now be discussed (*vide infra*).

2.1.2.5.1 The homologation of aldehydes *via* the Meinwald rearrangement of epoxides

The clean catalysis observed in these reactions, combined with the electrophilic nature of the epoxide products, inspired us to develop a tandem organocatalytic epoxidation–transition metal catalysed ring opening process. Coppertetrafluoroborate had previously been reported as being a highly efficient reagent for the catalysis of the Meinwald rearrangement. It was demonstrated that a range of epoxides could undergo rearrangement to furnish carbonyl compounds under mild reaction conditions.[197] We therefore proposed combining the aforementioned epoxidation process with a Cu(II) ion-catalysed Meinwald rearrangement to provide a convenient protocol for the homologation of aldehydes (Scheme 2.7) for the first time.

Organocatalysed epoxidation of **251**, followed by separation of the phases and addition of $Cu(BF4)_2 \cdot nH_2O$ (25 mol%) to the organic phase, resulted in the isolation of the chain-extended phenyl acetaldehyde derivative **264** in good overall yield.



Scheme 2.7 Tandem organocatalytic epoxidation–transition metal catalysed Meinwald rearrangement

2.1.2.6 The development of bifunctional urea derivatives as promoters of the CC reaction: preliminary considerations

As the fundamental aldehyde activating unit of the proposed bifunctional chiral urea derived catalyst, *i.e.* the urea component, did efficiently promote CC reactions between **231** and a range of aldehydes (*vide supra*), we set about the development of a bifunctional urea-derived catalyst for this reaction, *i.e.* by incorporating a sulfide moiety (from which the ylide can be generated by alkylation followed by deprotonation) which is linked to the urea moiety *via* a chiral backbone and an alkyl tether of an appropriate length (*vide infra*).

The success of this class of catalyst (from an enantioselectivity standpoint) is reliant upon intramolecular delivery of the methylene group from the sulfur ylide to the bound aldehyde, and due to the presence of a chiral backbone, it is hypothesised that this will occur in a face selective manner. Therefore, before attempting to develop a chiral variant of this bifunctional urea derived catalyst, validation that the catalyst would indeed be bifunctional, *i.e.* that methylene transfer from the sulfonium ylide would proceed in an intramolecular fashion to the activated aldehyde rather than in an intermolecular fashion, was considered paramount (Figure 2.6).

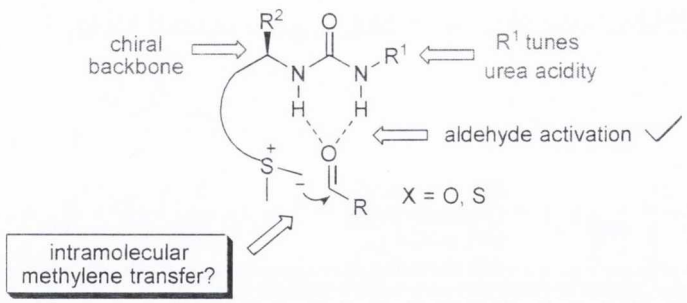


Figure 2.6 Proposed intramolecular CC reaction promoted by bifunctional urea derivatives

To accommodate intramolecular methylene transfer from the ylide to the bound aldehyde, the length of the alkyl chain should be such that the Bürgi-Dunitz angle is attainable in a scenario in which the aldehyde is bound to both the urea N-H hydrogen atoms (the most plausible binding mode). We therefore felt that it was crucial to elucidate the optimum alkyl chain/tether length to accommodate these requirements.

2.1.2.7 The development of bifunctional urea derivatives as promoters of the CC reaction: early developments

In a parallel study, both Mr. Alessandro Piccinini and Dr. Eimear Fleming were involved in the development of chiral urea-derived bifunctional catalysts for the CC reaction based on modified amino acids, namely *S*-adenosyl methionine (nature's alkylating agent). They realised that the structural requirements of the proposed bifunctional urea-derived catalysts were fulfilled by a methionine-derived catalyst system. They speculated that incorporation of a urea moiety in a sulfide-containing long-chain α-amino acid, specifically L-methionine (**265**), would lead to a successful catalyst candidate (Figure 2.7). This led to the development of three L-methionine-derived urea-based prototypes of varying acidity (**266-268**, Figure 2.7).[195]

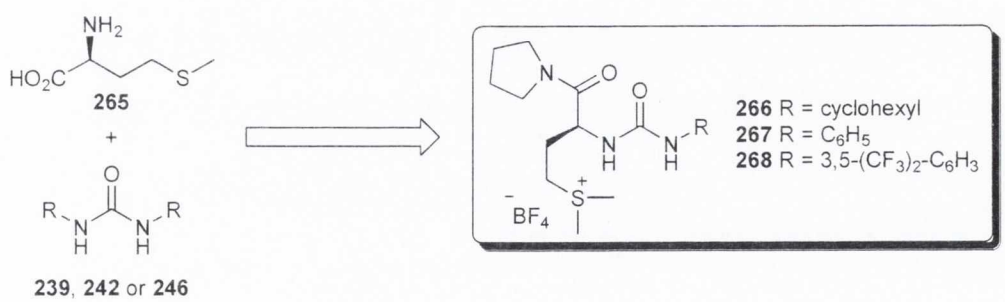
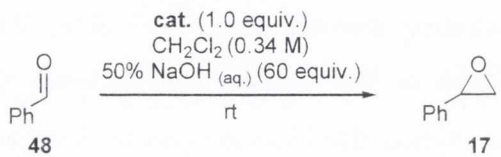


Figure 2.7 Integration of a urea moiety and L-methionine: the development of three L-methionine-derived urea-based catalysts/reagents **266-268**

Experiments were subsequently performed by Dr. Eimear Fleming to evaluate the performance of each of **266-268** in CC reactions with **48** as substrate using the optimum

conditions previously developed (Table 2.5) for symmetrical urea derivatives (entries 1-3, Table 2.7). The reaction containing the most acidic analogue **268** did not afford any **17** (Table 2.7, entry 1), whilst the reactions containing the less acidic **266** and **267** afforded modest levels of **17** (entries 2 and 3). The failure of **268** to furnish **17** in the CC reaction was attributed to the base mediated decomposition of **268** (it was later found that **267** is also susceptible to this decomposition pathway).



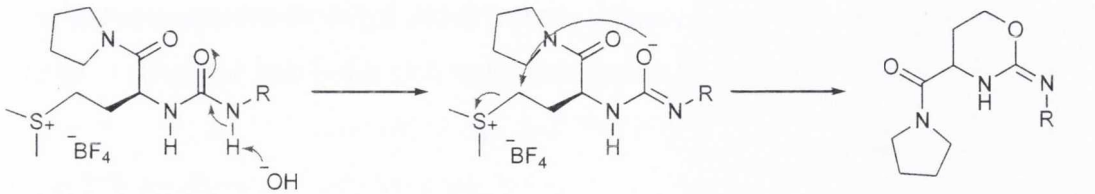
48 **17**

entry	cat.	time (h)	conv. (%)[a]	*ee* (%)[b]
1	**266**	1	39	-
2	**267**	1	51	0
3	**268**	1	0	0

[a]Determined using ^{1}H NMR spectroscopy. [b]Determined by CSP-HPLC analysis (Chiralcel OD-H column).

Table 2.7 The evaluation of **266-268** as bifunctional catalysts/reagents in the CC reaction

Abstraction of a urea N-H proton from either **267** or **268**, followed by ring-closure of the intermediates **269** or **270**, resulted in the formation of **271** or **272** respectively. The proposed mechanism is illustrated in Scheme 2.8.



267 R = C_6H_5
268 R = 3,5-$(CF_3)_2$-C_6H_3

269 R = C_6H_5
270 R = 3,5-$(CF_3)_2$-C_6H_3

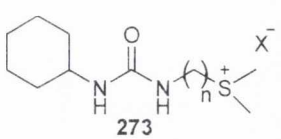
271 R = C_6H_5
272 R = 3,5-$(CF_3)_2$-C_6H_3

Scheme 2.8 The base-mediated decomposition of **267** and **268**

Having identified that cyclohexyl-substituted bifunctional derivative **266** could promote CC reactions without decomposition, tether length optimisation studies would be performed on a cyclohexyl-substituted urea derivative. A further crucial finding was unveiled by Mr. Alessandro Piccinini: X-ray analysis of **266** revealed that the boron tetrafluoroborate counterion, resulting from alkylation of the preceding sulfide using Meerwein's salt, was binding to the urea moiety thus occupying the aldehyde activation functionality - the crux of these bifunctional catalysts.

2.1.2.8 The preparation of three bifunctional urea-derived sulfonium salts (274-276) for tether length optimisation studies

Having elucidated that a cyclohexyl substituent is the optimum substituent for these urea-derived bifunctional catalysts, the achiral prototype **273** was conceived, whereby the tether length can be readily modified (Figure 2.8). As it was also discovered that the boron trifluoride counterion is not conducive to hydrogen bond-mediated catalysis, an alternative counterion was required.



273

Figure 2.8 Fundamental bifunctional catalyst design for the optimisation of tether length

With these preliminary findings in mind, three achiral, bifunctional urea derivatives of varying tether length were prepared: where n (Figure 2.8) = 2, 3 and 4 and the counterion is iodide (Figure 2.9).

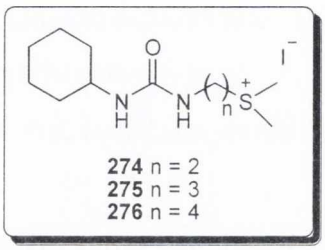
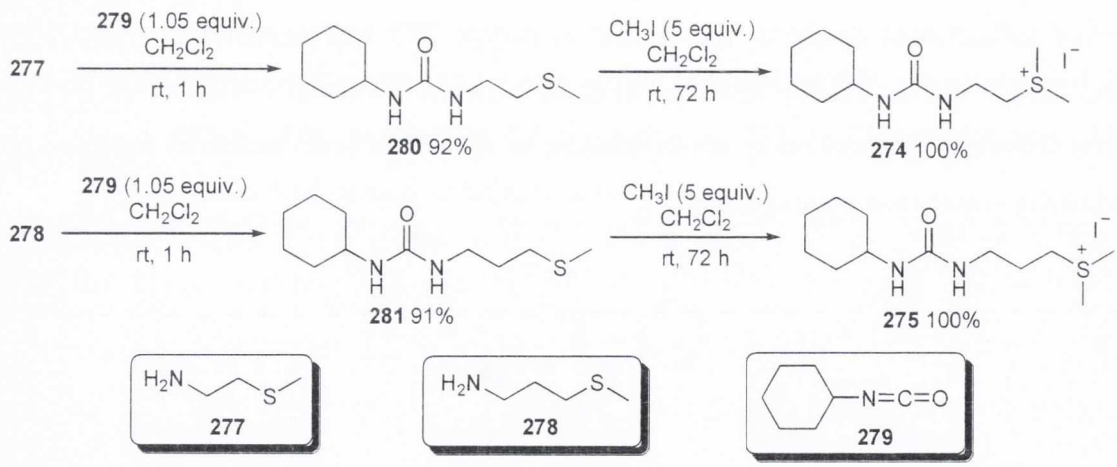


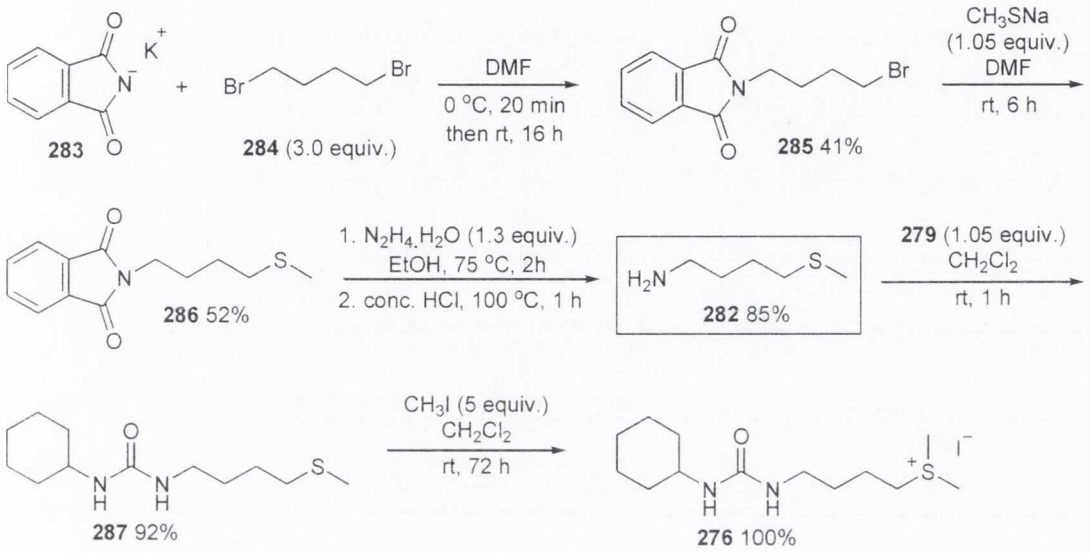
Figure 2.9 Three bifunctional urea derivatives of varying tether length for the evaluation of optimum tether length

The preparation of both **274** and **275** was straightforward: reaction of either 2-(methylthio)ethyl amine (**277**) for **274**, or 2-(methylthio)propyl amine (**278**) for **275** with cyclohexyl isocyanate (**279**) using CH_2Cl_2 as solvent, afforded urea-derived sulfides **280** and **281** respectively (Scheme 2.9). Subsequent alkylation of **278** and **279** with iodomethane using CH_2Cl_2 as solvent furnished the desired sulfonium salts **274** and **275** in quantitative yield.



Scheme 2.9 Synthesis of sulfonium salts **274** and **275**

The amine components **277** and **278** for the synthesis of **274** and **275** are commercially available. The amine component 4-methylthiobutylamine (**282**) for the synthesis of **276** (where n = 4, Figure 2.9) however, is not and thus required synthesis. The preparation of **282** and **276** are shown in Scheme 2.10.



Scheme 2.10 Synthesis of sulfonium salts **274** and **275**

Reaction of potassium phthalimide (**283**) with 1,4-dibromobutane (**284**) in *N*,*N*-dimethylformamide (DMF) afforded **285** in 41% yield. Subsequent treatment of **285** with sodium methanethiolate in DMF furnished **286** in 52% yield. Heating **286** under reflux in the presence of hydrazine monohydrate with ethanol as solvent, followed by treatment with conc. HCl and further heating at 100 °C provided **282** in 82% yield. Subsequent reaction of **282** with **279** afforded urea **287** in 92% yield which, upon treatment with iodomethane, furnished the desired sulfonium salt **276** in quantitative yield (Scheme 2.10).

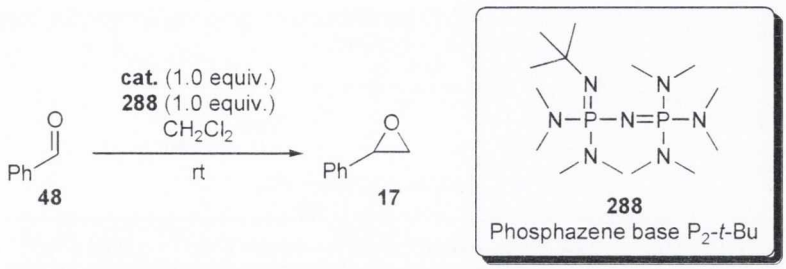
2.1.2.8.1 Evaluation of 274-276 as bifunctional promoters of the CC reaction

Having prepared three sulfonium salts of varying tether length (*i.e.* n = 2, 3 and 4, Figure 2.9), attention subsequently turned to their evaluation as stoichiometric bifunctional

promoters of the CC reaction. It was hoped that following these studies, an optimum length of the alkyl chain linking the sulfonium salt to the aldehyde activating moiety (urea) would be unequivocally identified. It was envisaged that this well-defined alkyl chain length would ultimately be incorporated into a chiral variant of these bifunctional urea derivatives and that a highly enantioselective terminal epoxidation protocol would ensue.

Taking inspiration from both Solladié-Cavallo *et al.*[55] and Aggarwal *et al.*[57] (Section 1.3.2.1), whereby it was found that the use of a phosphazene base (**66**) in CH_2Cl_2 accommodated the execution of low temperature (-78 °C) reactions, leading to higher product enantioselectivities and much shorter reaction times in comparison with reactions performed using other bases and higher temperatures, it was decided that our tether length optimisation studies would be performed under these same conditions (using the *tert*-butyl analogue of **66**, **288**). Results obtained from our optimisation studies are displayed in Table 2.8.

Initial experimentation began with reactions being performed under the aforementioned conditions at room temperature, 0.25 M reaction concentration and using benzaldehyde (**48**) as substrate (entries 1, 2 and 3, Table 2.8). Reactions containing either **275** or **276** furnished **17** in excellent yields (entries 2 and 3), whereas in the reaction containing **274**, **17** was obtained in only moderate yield (entry 1). We deemed these results to be inconclusive, as reactions under these conditions proved too rapid to determine the most efficient candidate. To this end, in an attempt to hamper the reaction rate, the reaction was diluted to 0.01 M. As previously, reactions containing **275** and **276** afforded **17** in excellent yields (entries 5 and 6), whilst the reaction catalysed by **274** afforded **17** in only moderate yield (entry 4). From the crude ^{1}H NMR spectrum, it was observed that catalyst **274** was decomposing under the reaction conditions. For this reason **274** was discarded as a possible candidate.

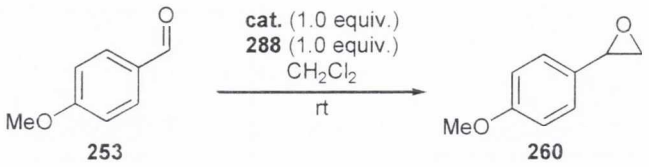


entry	cat.	conc. (M)	time (min)	conv. (%)[a]	yield (%)[b]
1	**274**	0.25	10	87	48
2	**275**	0.25	10	100	95
3	**276**	0.25	10	97	93
4	**274**	0.01	10	36	30
5	**275**	0.01	10	100	98
6	**276**	0.01	10	100	99

[a]Determined using ^{1}H NMR spectroscopy. [b]Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as internal standard.

Table 2.8 Preliminary studies: evaluation of **274-276** as promoters of the CC reaction using **48** as substrate

Attention was then focussed on differentiating between **275** and **276** as to which is the catalyst of optimum tether length for the effectuation of intramolecular CC reactions. In a further attempt to decrease the rate of epoxidation, a less reactive aldehyde was chosen as substrate, *para*-anisaldehyde (**253**). With a 0.01 M reaction concentration, reactions containing **275** and **276** again afforded similarly high yields of epoxide product (entries 1 and 2, Table 2.9). As the reaction rate was still too rapid to identify the optimum chain length, the reaction concentration was further decreased (to 0.005 M) and the reaction was monitored after a shorter period of time (entries 3 and 4). Again the reaction conditions were conducive to reaction rates too rapid to allow discrimination between **275** and **276** (entries 3 and 4).



253 260

entry	cat.	conc. (M)	time (min)	conv. (%)[a]	yield (%)[b]
1	**275**	0.01	10	87	75
2	**276**	0.01	10	86	71
3	**275**	0.005	5	91	70
4	**276**	0.005	5	83	52

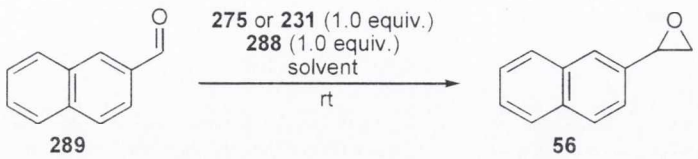
[a]Determined using ^{1}H NMR spectroscopy. [b]Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as internal standard.

Table 2.9 Evaluation of **275** and **276** as promoters of the CC reaction using the less reactive substrate **253**

At this dilution, ^{1}H NMR spectroscopic analysis of the crude reaction mixture was proving problematic. To circumvent this issue, quenching the reaction with a weak acid (silica gel) at a fixed time, with subsequent concentration of the reaction mixture *in vacuo* prior to crude ^{1}H NMR analysis was considered. For this technique to be feasible, it is prudent that a substrate that will lead to the formation of a non-volatile, non-electron-rich epoxide product be employed. An electron rich epoxide would lead to unwanted rearrangement (Section 2.1.2.5.1). A volatile epoxide product, upon concentration of the reaction mixture *in vacuo*, would lead to loss of product, thus providing an inaccurate result. With these considerations in mind, solid 2-naphthaldehyde was chosen as substrate for subsequent reactions.

At this point it was also considered prudent to ascertain whether intramolecular methylene transfer was in fact occurring. An experiment was thus devised whereby along with a reaction containing **275** as the methylene source, a concurrent reaction would also be performed (under identical reaction conditions) containing trimethylsulfonium iodide (**231**) as the methylene source. Due to the fact that neither **231** nor its ylide are soluble in

dichloromethane, acetonitrile was chosen as solvent. Our findings are illustrated in Table 2.10.



289 56

entry	cat.	solvent	conc. (M)	time (min)	conv. (%)[a]	yield (%)[b]
1	**275**	CH_3CN	0.005	1	100	57
2	-	CH_3CN	0.005	1	100	81

[a]Determined using ^1H NMR spectroscopy. [b]Determined by ^1H NMR spectroscopy using (*E*)-stilbene as internal standard.

Table 2.10 Bifunctional **275** *versus* **231** in the CC reaction

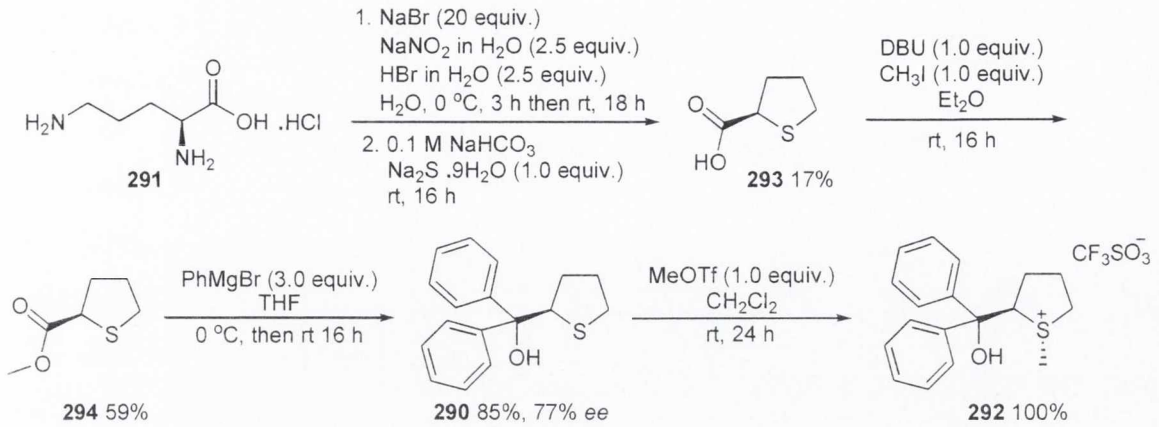
We were amazed to find that the reaction containing **231** as the methylene source (leading to an intermolecular reaction pathway in the absence of catalysis by hydrogen bonding) afforded **17** in high yield after 1 min (entry 2, Table 2.10), whilst the reaction containing **275** afforded **17** in only moderate yield (entry 1). As an *ee* of >6% was never achieved in reactions employing L-methionine-derived urea-based catalysts/reagents **266-268**[195] coupled with the evidence from Table 2.13 that intramolecular methylene transfer may not be occurring, it was decided to pursue alternative departures in hydrogen bond-mediated catalyst design for the asymmetric synthesis of terminal epoxides *via* the CC reaction.

2.1.2.9 Chiral 2-monosubstituted thiolane derivatives as hydrogen bond donating catalysts for the asymmetric synthesis of terminal epoxides *via* the CC reaction: preliminary considerations and synthesis of 292

Intrigued by the success that has been enjoyed by chiral sulfides in catalytic asymmetric CC reactions involving stabilised and semi-stabilised ylides (Sections 1.3.2.1-1.3.3.3), and the lack thereof in reactions involving their non-stabilised counterparts (Section

1.3.3.4), we speculated as to whether the enantioselectivity of the latter process could be improved by incorporating an aldehyde-activating functionality into these chiral molecules, thus rendering them bifunctional. It was hoped that these bifunctional catalysts would lead to a highly enantioselective methodology for the synthesis of terminal epoxides *via* non-stabilised ylides based on the same premise discussed in previous sections (Figure 2.6, Section 2.1.2.6), *i.e.* by manipulating the aldehyde's orientation *via* hydrogen bonding to effect face selective intramolecular methylene transfer.

Given the documented asymmetric synthesis of chiral 2-monosubstituted thiolane derivatives such as **290**,[198,199] in conjunction with their high tunability (from both a steric and a hydrogen bond donation standpoint, (*vide infra*), we viewed **290** as a good platform upon which to commence proof of concept studies. The synthesis of **290** from L-(+)-ornithine hydrochloride (**291**), and its sulfonium salt **292**, is outlined in Scheme 2.11. The *ee* of **290** was ascertained by CSP-HPLC analysis (Chiralpak OJ-H, hexane/IPA 9.75:0.25, 0.5 mL min^{-1}) and was found to be 77% *ee*. It had previously been reported that resolution of **293** (using brucine as a chiral resolving agent) could afford enantiopure **293** (which is the step responsible for the observed enantioselectivity of the catalyst);[199] however, as the purpose of our preliminary studies was to elucidate whether or not **292** would be a suitable methylene source and hence promote CC reactions, the optical purity of the catalyst was considered extraneous at this point. Preliminary proof of concept studies would be performed using the preformed sulfonium salt **292** in stoichiometric quantities with the aspiration to later modify the procedure to accommodate the use of catalytic quantities of **290**.



Scheme 2.11 Synthesis of **290** from L-(+)-ornithine hydrochloride

The penultimate step in this synthesis, *i.e.* the addition of an organometallic reagent (*i.e.* a Grignard or an alkyl/aryl lithium reagent) to **294**, renders this class of compound highly versatile in terms of the steric environment that can be created adjacent to the site of reaction, the factor ultimately governing the approach of the aldehyde to the ylide and thus the enantioselectivity of the process. For example, addition of more, or indeed less sterically encumbered organometallic reagents to ester **294** would facilitate the synthesis of a range of catalysts of varying steric properties (Figure 2.10).

The addition of a hydrogen bond donating moiety to this type of catalyst offers an additional control mechanism with respect to face selectivity upon approach of the aldehyde to the ylide (Figure 2.10). It was hoped that subsequent to the stringently controlled approach of the aldehyde to the ylide (by means of steric interactions, *vide supra*), that the aldehyde would bind to the hydrogen bond donating functionality and that intramolecular methylene transfer would occur, yielding an optically active terminal epoxide. This hydrogen bond donating moiety is also readily tunable, for example, it was anticipated that the hydroxyl (OH) group could be readily transformed into various other hydrogen bond donating groups such as a urea or an amido group (*vide infra*).

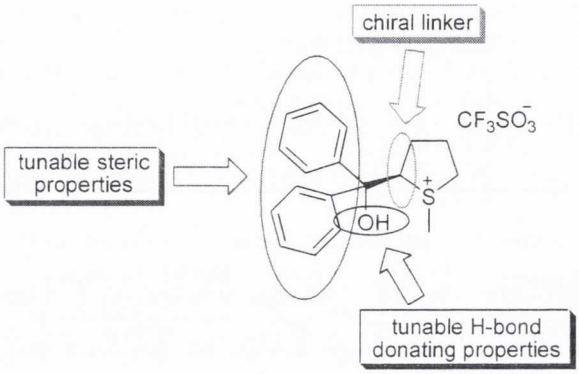
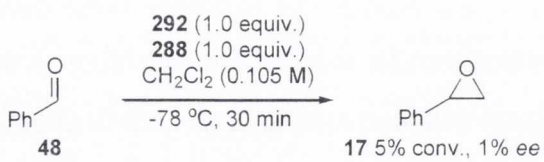


Figure 2.10 Illustration of the highly tunable nature of **292** and its derivatives from both a steric and an H-bond donating standpoint

2.1.2.9.1 Evaluation of 292 as a bifunctional promoter of the CC reaction

Having prepared **292** (although not in its enantiopure form, *vide supra*), experimentation commenced to evaluate its efficiency as a promoter of the CC reaction. In a related study (*vide infra*), it was found that the reaction conditions affording the best combination of both yield and enantioinduction in these systems involved the use of **288** as base, CH_2Cl_2 as solvent, a reaction concentration of 0.105 M and a temperature of -78 °C (Scheme 2.12). Under these conditions, and with benzaldehyde (**48**) as substrate, it was found that only trace amounts of **17** were formed after 30 min reaction time. CSP-HPLC analysis (Chiralcel AS column, 99/1 hexane:*i*-PrOH, 1 cm^3 min^{-1}) of isolated **17** revealed that it had been formed in 1% *ee*.



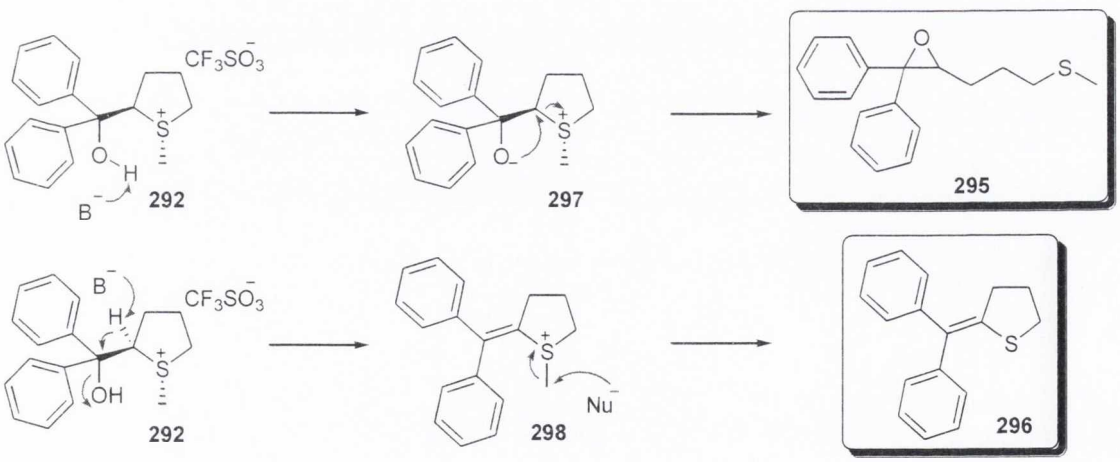
Scheme 2.12 Evaluation of **292** as a promoter of the CC reaction with **48** as substrate

We were intrigued to find that neither sulfonium salt **292** nor its sulfide precursor **290** were present in the crude ^1H NMR spectrum following the reaction: however, two species

(one major and one minor) not derived from **48** were detected. Following column chromatography and subsequent analysis using both NMR spectroscopy and high resolution mass spectrometry (HRMS), the identities of these two compounds were elucidated. The major component was found to be **295** while the minor compound was **296** (Scheme 2.13). Both **295** and **296** are believed to result from the base-mediated decomposition of **292** (Scheme 2.13). To further validate this observation, in the absence of an electrophile (*e.g.* **48**), **292** was treated with **288** under otherwise identical reaction conditions: both **295** and **296** were observed in the ^{1}H NMR spectrum of the crude reaction mixture.

Deprotonation of the hydroxyl group in **292**, followed by ring closure (to form the epoxide) and subsequent ring opening of the alkylated thiolane affords the major decomposition product **295**.

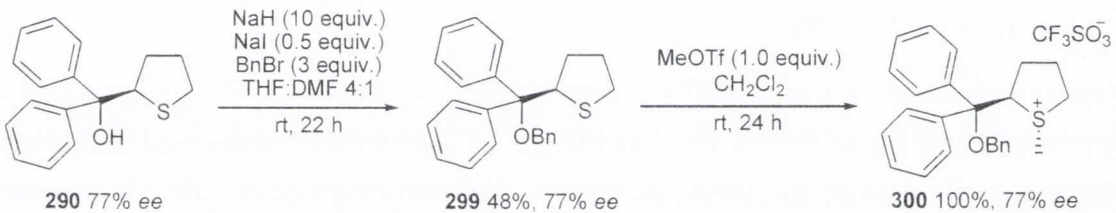
Deprotonation of the proton at the 2-position on the five-membered ring followed by elimination of the hydroxyl group yields the alkylated intermediate **298**. Subsequent demethylation of **298** by a nucleophile (presumably hydroxide) furnishes the minor decomposition product **296**.



Scheme 2.13 The proposed mechanisms for the base-mediated decomposition of **292** to **295** and **296**

2.1.2.9.2 Re-evaluation of catalyst design: protection of 290 as its benzyl ether

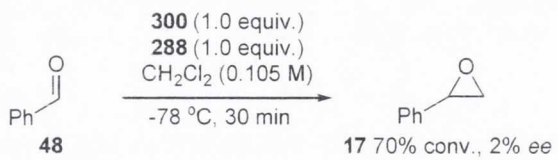
Having observed that the major product formed in the CC reaction between **48** and **292** is the base-mediated decomposition product **295**, protection of the hydroxyl group was considered. **290** Was thus protected as its benzyl ether (Scheme 2.14). Benzyl ether **299** was prepared from **290** *via* a Williamson ether synthesis using sodium hydride as base and benzyl iodide (prepared *in situ via* a Finkelstein reaction using benzyl bromide and sodium iodide) as the alkyl halide. The triflate salt **300** was prepared from **299** using methyl triflate as shown in Scheme 2.12. (It is worthy of note that in this instance, precursor **290** was formed in 77% *ee* following the synthetic route outlined in Scheme 2.11.)



Scheme 2.14 The preparation of benzyl protected sulfonium salt **300**

2.1.2.9.3 Evaluation of benzyl ether 300 in the CC reaction

To ascertain whether benzyl protected **300** was indeed a more efficient promoter of CC reactions than **292**, its performance was evaluated under the same reaction conditions that were employed for the evaluation of **292** (Scheme 2.15).

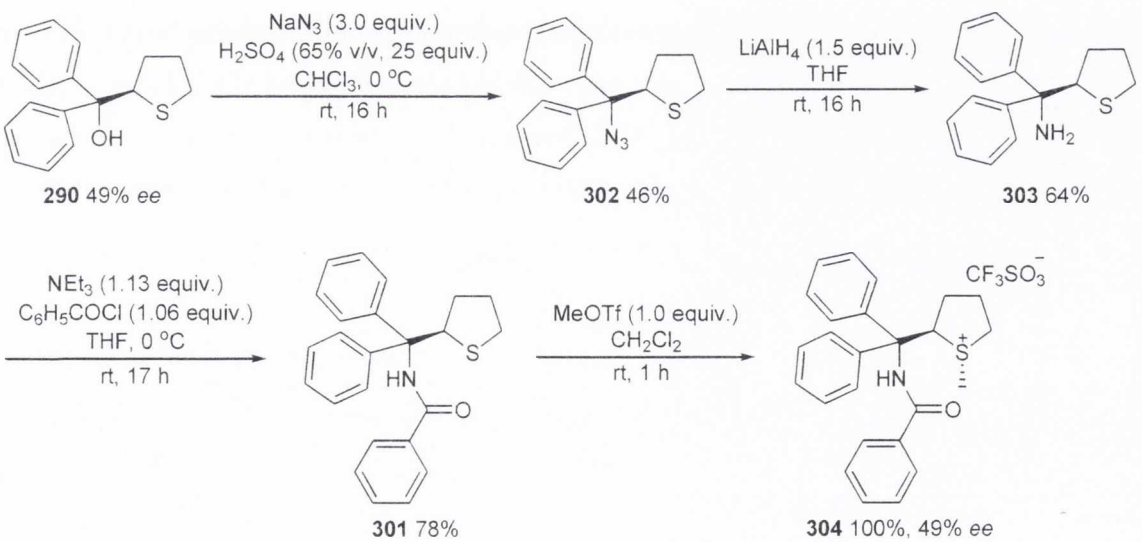


Scheme 2.15 Evaluation of **300** as a promoter of the CC reaction with **48** as substrate

In a CC reaction between **48** and **300**, following 30 minutes at -78 °C, **17** was indeed formed in greater abundance than before; however, the product *ee* was still negligible. In this instance, as the hydroxyl group was protected, base-mediated decomposition product **295** was not observed in the ^{1}H NMR spectrum of the crude reaction. The base-mediated decomposition product **296** (after elimination of benzyl alcohol) on the other hand was observed, thus indicating that **300** is also not an appropriate catalyst for this system.

2.1.2.9.4 The installation of an alternative hydrogen bond donating group: the preparation of amide 301

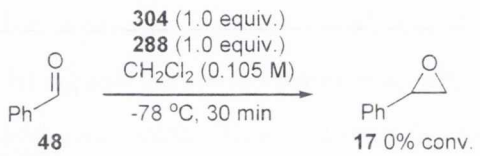
Due to the failure of both **292** and **300** to mediate enantioselective CC reactions and their decomposition under basic reaction conditions, the design of a catalyst possessing an alternative hydrogen bond donating motif was contemplated. Given the facile transformation of an alcohol into an amide, along with the known hydrogen bond donating ability of amides,[200] we viewed **301** as a plausible bifunctional catalyst for this system. The synthesis of **301** is outlined in Scheme 2.16. It is worthy of note that in this instance, precursor **290** was formed in 49% *ee* following the synthetic route outlined in Scheme 2.11.



Scheme 2.16 The preparation of the sulfonium salt **304** of amide **301** from **290**

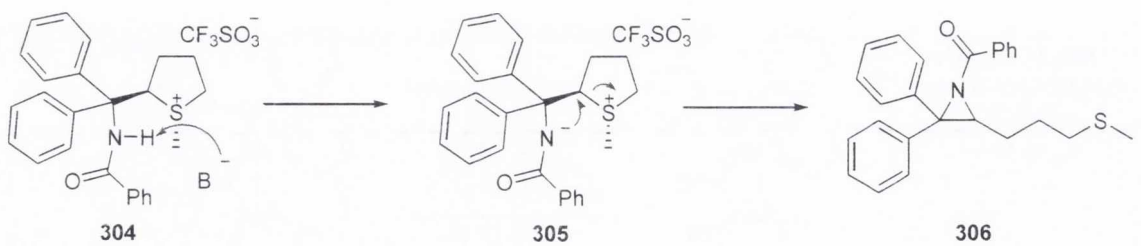
2.1.2.9.5 The evaluation of 301 as a promoter of the CC reaction

As before, in order to determine the efficiency of **301** as a promoter of the CC reaction in comparison to both **292** and **300**, the reaction was carried out under the same reaction conditions that were employed in the evaluation of both **292** and **300** (Scheme 2.17). In a reaction with **48** as substrate at -78 °C, after 30 minutes, it was determined from the ^{1}H NMR spectrum of the crude reaction that **17** had not been formed. Both the sulfide precursor **301** (trace amounts) and a second compound not derived from **48**, however, were detected.



Scheme 2.17 The evaluation of **304** as a promoter of the CC reaction using **48** as substrate

Using both NMR spectroscopy and HRMS, the identity of the unknown compound was revealed: similar to the fate of **292**, **304** too underwent base-mediated decomposition, leading to the formation of **306** (Scheme 2.18). Deprotonation of the amide N-H proton to form **305**, followed by ring closure and ring opening (of the alkylated thiolane) resulted in the formation of the *N*-acyl aziridine **306**.



Scheme 2.18 The base-mediated decomposition of **304**

Due to the preferential deprotonation of the hydrogen bond donors in these systems instead of the methyl group of the sulfonium salt, and the propensity of the sulfonium salts of these thiolane derivatives to ring-open, it seemed clear that 2-monosubstituted thiolane derivatives are not conducive to bifunctional hydrogen bond-mediated catalysis under these basic reaction conditions.

2.2 Conclusion: Chapter 2

We have unequivocally demonstrated that *N*-alkyl salts derived from ephedrine **232**, **233** and **234** do not promote enantioselective CC reactions under phase transfer conditions to afford enantioenriched terminal epoxides.[179] The precedents upon which we based this study[177,178] appear to have mistakenly attributed product optical activity to asymmetric catalysis. Due to the authors' reliance on specific rotation to determine the *ee* of the epoxide product, they failed to recognise that the optical activity that they observed was as a result of the epoxide formed **235** from the base-mediated decomposition of the enantiopure catalysts. We have corrected the literature to this end.[179]

We have also shown that urea derivatives are active catalysts for the base-mediated generation of terminal epoxides from aldehydes and trimethylsulfonium iodide.[196] Catalyst **242** proved to be the most efficient promoter of CC reactions and proved robust, promoting the smooth transformation of a range of aromatic (**48**, **78** and **250-253**), α-substituted aliphatic (**72**) and α,β-unsaturated (**254**) aldehydes into epoxides (**17** and **256-262**) at 5 mol% loading. We also demonstrated the homologation of aromatic aldehyde **251** *via* a tandem epoxidation-Meinwald rearrangement process.

Our attempts to develop a novel class of bifunctional urea derivatives as promoters of the CC reaction have revealed that **274-276** are not of an appropriate design to accommodate enantioselective (intramolecular) methylene transfer to aldehydes toward the synthesis of enantioenriched terminal epoxides.

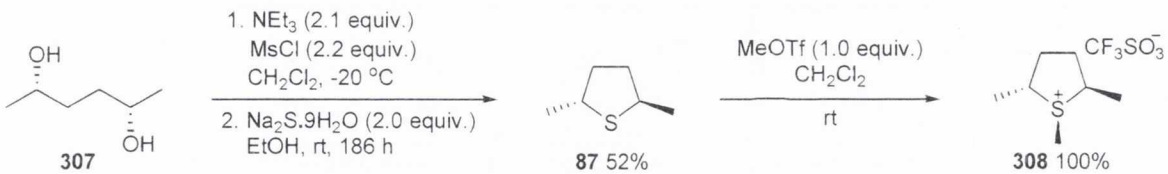
We have also established that 2-monosubstituted thiolane derivatives possessing a hydrogen-bond-donating moiety are also not conducive to a system leading to high levels of terminal epoxide enantiomeric excess due to the relatively low pK_a of the hydrogen bond donor relative to the methyl group on the sulfonium salt and the propensity of the five-membered heterocyclic ring to open upon deprotonation of the hydrogen atom on the heteroatom of the hydrogen bond donor.

3.1 The development of novel C_2-symmetric sulfides for the catalytic asymmetric synthesis of terminal epoxides *via* the CC reaction: preliminary considerations

Having elucidated that hydrogen bond-mediated catalysis is not compatible with chiral thiolane derivatives (see Scheme 2.11 and Scheme 2.16) due to their propensity to decompose under basic reaction conditions, the development of catalysts based on an alternative design motif was investigated. Given the success of the C_2-symmetric sulfides **87** and **88** employed by Metzner *et al.*[66a,b] and **91** devised by Goodman *et al.*[66e,94] (due to their fulfilment of the four criteria necessary to achieve high levels of enantioselectivity in epoxidation reactions (see Section 1.3.3.3)), coupled with their successful application in catalytic (as little as 10 mol% catalyst loading) epoxidation reactions involving semi-stabilised sulfonium ylides (Scheme 1.26), we considered these C_2-symmetric sulfides a good foundation upon which to begin the development of novel variants of these catalysts for the promotion of enantioselective methylene transfer.

3.1.1 The synthesis of C_2-symmetric sulfide 87

Proof of concept studies commenced with the preparation of C_2-symmetric sulfide **87** (Scheme 3.1), the preparation of which had previously been reported by Metzner *et al.*[66a,66b,67] (2*R*,5*R*)-2,5-Dimethylthiolane (**87**) was prepared in two simple steps from commercially available, enantiopure (2*S*,5*S*)-2,5-hexanediol (**307**, Scheme 3.1).



Scheme 3.1 The preparation of sulfonium salt **308**

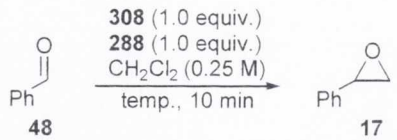
Treatment of **307** with triethylamine and methanesulfonyl chloride in methylene chloride afforded the dimesylate which, without the necessity for further purification, underwent

cyclisation with sodium sulfide to afford enantiopure **87** (determined using specific rotation, see experimental section) in 52% yield.

To elucidate whether or not **87** was capable of inducing enantioselectivity in CC reactions, it was decided to perform the preliminary evaluation reactions stoichiometrically, *i.e.* using one equivalent of preformed sulfonium salt **308**. Thus, sulfonium salt **308** was prepared form **87** using methyl triflate as alkylating agent (Scheme 3.1).

3.1.2 The evaluation of 308 as a promoter of CC reactions with benzaldehyde as substrate

Having prepared **308**, attention subsequently turned to its evaluation in epoxidation reactions with benzaldehyde as substrate. Under the same reaction conditions that were employed in the evaluation of hydrogen bond-donating catalysts **274**, **275**, **276**, **292**, **300** and **304**, *i.e.* using P_2-*t*-Bu **288** as base and CH_2Cl_2 as solvent, the performance of **308** as an enantioselective promoter of the CC reaction was evaluated. The initial reaction was performed at 0.25 M concentration at room temperature (entry 1, Table 3.1).



48 **17**

entry	temp. (°C)	conv. (%)[a]	yield (%)[b]	*ee* (%)[c]
1	rt	100	100	2.6
2	-72	100	100	1.7

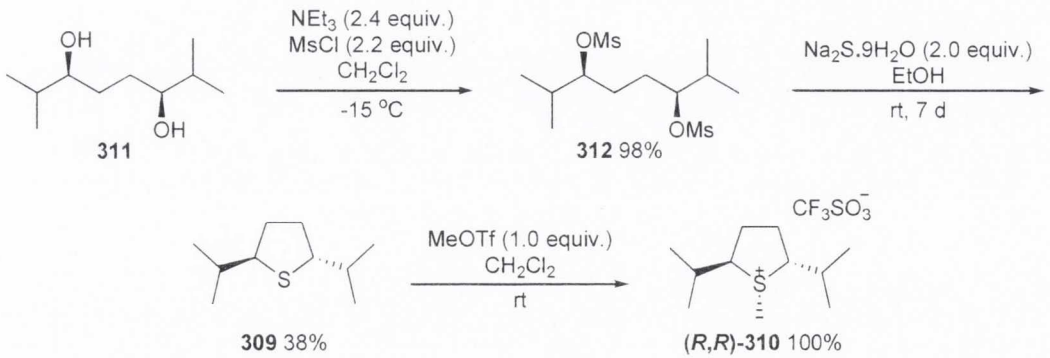
[a]Determined using ^{1}H NMR spectroscopy. [b]Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. [c]CSP-HPLC analysis (Chiralcel AS column, 99/1 hexane:*i*-PrOH).

Table 3.1 The evaluation of **308** as an enantioselective promoter of the CC reaction

Under these reaction conditions, **17** was furnished in excellent yield; however, an *ee* of just 2.6% was achieved (entry 1, Table 3.1). This was in good agreement with the findings of Aggarwal *et al.* who also found that **87** gave 0% *ee* in "conventional Corey-Chaykovsky sulfur ylide chemistry".[93] In an attempt to improve the enantioselectivity of this process, the same reaction was repeated at -72 °C (entry 2, Table 3.1). As was the case in the previous reaction, **17** was returned in excellent yield and negligible *ee*.

3.1.3 The development and synthesis of the bulkier C_2-symmetric sulfide 309

Metzner *et al.* demonstrated that by replacing the methyl groups of **87** with more sterically demanding ethyl groups (*i.e.* **88**), *i.e.* by increasing the steric bulk around the sulfur atom, an increase in the enantioselectivity of the epoxidation process ensued (Scheme 1.26).[66b] Intrigued by this, we considered replacing the methyl groups of **87** with bulkier isopropyl groups to yield the more sterically encumbered derivative (2*R*,5*R*)-2,5-diisopropyl-thiolane (**309**). It was hoped that the larger isopropyl groups would provide greater control over the approach of the aldehyde to the ylide and thus improve the enantioselectivity of the process. As before, initial experimentation would be performed using a stoichiometric protocol to elucidate whether enantioinduction was occurring, thus sulfonium salt **310** was prepared (Scheme 3.2).

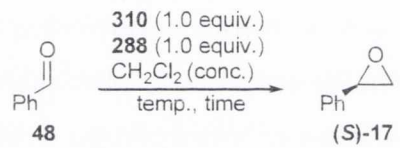


Scheme 3.2 The preparation of sulfonium salt **310**

Sulfonium salt **310** was prepared according to the same synthetic route that was outlined for the preparation of sulfonium salt **308**; however, on this occasion, commercially available, enantiopure (3*S*,6*S*)-2,7-dimethyl-3,6-octanediol (**311**) was employed as starting material.

3.1.4 The evaluation of C_2-symmetric thiolane 309 as an enantioselective promoter of the CC reaction

Subsequent to the successful preparation of the more sterically encumbered sulfonium salt **310**, our attention was subsequently focused on its evaluation as an enantioselective promoter of the CC reaction under the same reaction conditions as before (Table 3.1), using benzaldehyde as substrate. Our findings are outlined in Table 3.2.



48 **(*S*)-17**

entry	conc. (M)	temp. (°C)	time (min)	conv. (%)[a]	yield (%)[b]	*ee* (%)[c,d]
1	0.25	rt	10	95	95	20
2	0.25	-72	60	100	95	29
3	0.05	rt	10	97	97	24

[a]Determined using ^{1}H NMR spectroscopy. [b]Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. [c]CSP-HPLC analysis (Chiralcel AS column, 99/1 hexane:*i*-PrOH). [d]The absolute configuration of **17** is (*S*).

Table 3.2 The evaluation of sulfonium salt **310** as an enantioselective promoter of the CC reaction

To our delight, the hypothesis that increasing the steric bulk of the substituents at the 2- and 5-positions in these C_2-symmetric sulfides held true, with **17** being furnished in excellent yield and 20% *ee* at room temperature (Table 3.2, entry 1) – conditions that

afforded **17** in just 2.6% *ee* when the less sterically encumbered chiral sulfonium salt **308** was employed as the promoter (Table 3.1, entry 1).

The effect of lowering the temperature on the enantioselectivity of the epoxidation process was then evaluated: under the same conditions as before, at -72 °C, **17** was formed in excellent yield and 29% *ee* (Table 3.2, entry 2), representing an increase of 9% *ee* in comparison to the reaction that was performed at room temperature (Table 3.2, entry 1). It is noteworthy that under identical reaction conditions, using chiral sulfonium salt **308** as the promoter, **17** was afforded in 1.7% *ee* (Table 3.1, entry 2).

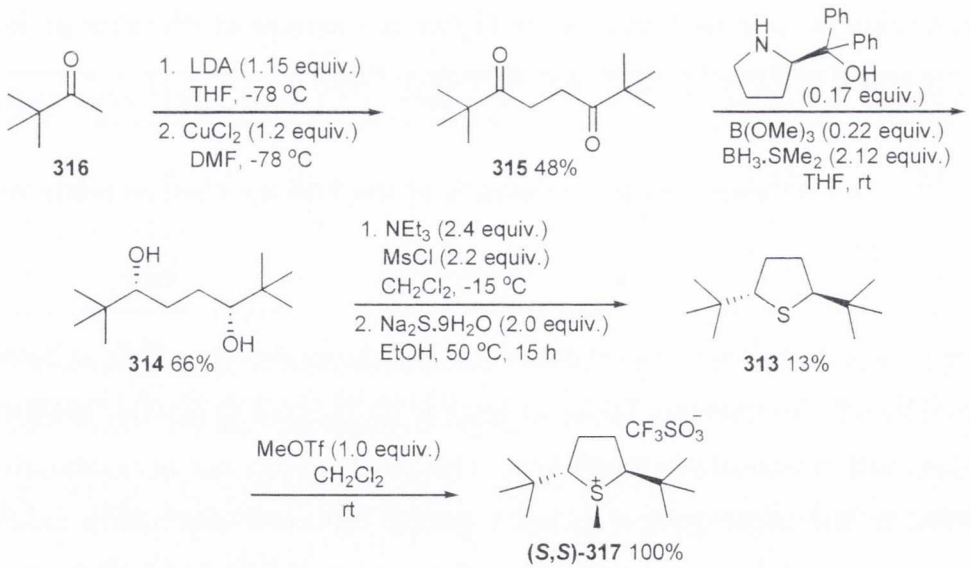
The effect of concentration on enantioselectivity was also investigated (Table 3.2, entry 3). Under the same reaction conditions that were previously employed, but decreasing the reaction concentration to 0.05 M, **17** was again formed in excellent yield; however, on this occasion, **17** was furnished in 24% *ee*. It is therefore evident that decreasing the reaction concentration also has a positive effect on the enantioselectivity of these reactions, leading to the formation of **17** in higher *ee* (increase of 4%) than in the same reaction performed at higher (0.25 M) concentration (Table 3.2, entry 1).

3.1.5 The development and synthesis of the bulkier C_2-symmetric thiolane 313

In the previous section, it was demonstrated that increasing the steric bulk at both the 2- and 5-positions of C_2-symmetric thiolanes leads to an increase in epoxide product *ee* in CC reactions with benzaldehyde as substrate. This observed increase in enantioselectivity is ascribable to the larger groups having a greater influence over which face of the aldehyde is attacked by the ylide. Therefore, in a bid to further improve the enantioselectivity of the CC reaction toward the synthesis of enantioenriched terminal epoxides, the development of a more sterically encumbered analogue of the C_2-symmetric sulfide **309** commenced. As the *tert*-butyl group is significantly more sterically demanding than the isopropyl group, the preparation of (2*S*,5*S*)-2,5-di-*tert*-butylthiolane (**313**) was pursued.

The starting materials for the syntheses of the aforementioned C_2-symmetric thiolanes, *i.e.* **87** and **309**, were the commercially available, enantiopure diols (2*S*,5*S*)-2,5-hexanediol (**307**) and (3*S*,6*S*)-2,7-dimethyl-3,6-octanediol (**311**) respectively (Schemes 3.1 and 3.2). As the corresponding enantiopure diol (**314**) for the synthesis of the *tert*-butyl analogue **313** is not commercially available, its synthesis was required. The preparation of **313** is outlined in Scheme 3.3.

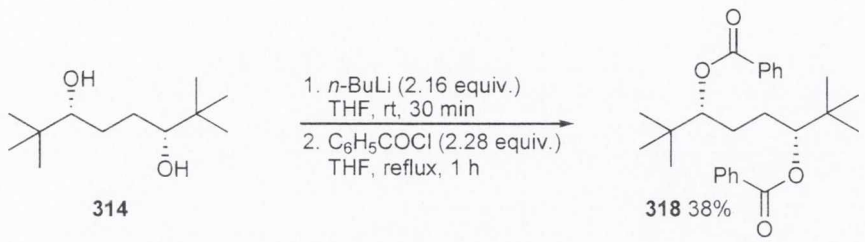
Following a literature procedure,[201] 1,4-diketone **315** was prepared from pinacolone (**316**), lithium diisopropylamide and anhydrous copper(II) chloride. Asymmetric reduction[202] of **315** afforded enantiopure (*vide infra*) **314** in good yield. From **314**, sulfide **313** was prepared following the same methodology that was implemented for the synthesis of both **308** and **310** (Schemes 3.1 and 3.2); however, in this case, due to the instability of the intermediate dimesylate,[202] cyclisation with sodium sulfide to enantiopure **313** was performed without its prior isolation.



Scheme 3.3 The preparation of sulfonium salt **317**

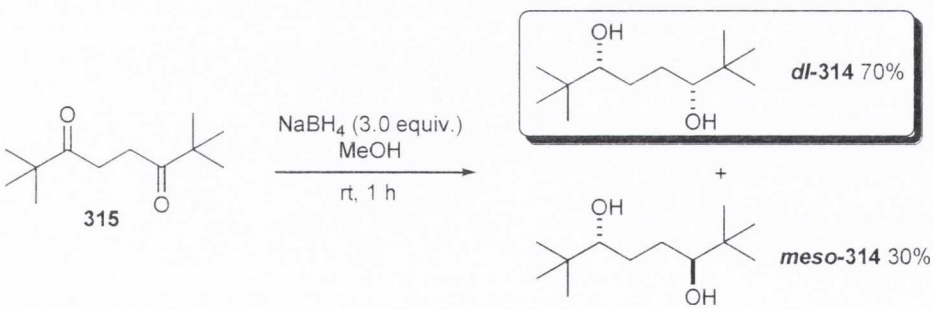
To accurately measure the enantiomeric excess in which **314** had been formed following the asymmetric reduction of 1,4-diketone **315**, it was crucial that CSP-HPLC analysis be

performed. As CSP-HPLC analysis relies upon UV for detection, due to the fact that diol **314** does not contain a chromophore, it was derivatised (according to a literature procedure[203]) as its benzoyl ester **318** (Scheme 3.4).



Scheme 3.4 The derivatisation of **314** as its benzoyl ester **318** for HPLC-UV analysis

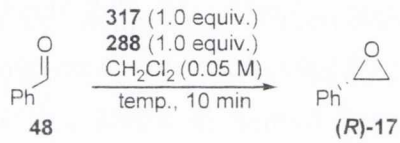
Having derivatised **314** as its benzoyl ester **318**, CSP-HPLC analysis (Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA 99.9:0.1, 1 mL min^{-1}) revealed that following asymmetric reduction of **315**, **314** had been formed in >99% *ee*. Note: ***rac*-318** was prepared following the same procedure that was outlined for the preparation of **318**; however, $NaBH_4$ was employed to reduce **315** to diol **314** (Scheme 3.5). The resulting diol was formed in a 70:30 mixture of ***dl*-314**:***meso*-314**. Isolation of ***dl*-314** was possible *via* column chromatography.



Scheme 3.5 The synthesis of ***dl*-314** from **315**

3.1.6 The evaluation of the bulky C_2-symmetric thiolane 313 as an enantioselective promoter of the CC reaction

To elucidate whether **313** would emerge superior to the less sterically encumbered 2,5-disubstituted thiolanes **87** and **309** as a promoter of enantioselective CC reactions, its performance was evaluated stoichiometrically (using **317**) with benzaldehyde as substrate. (It is worthy of note that due to the low yield obtained in the overall synthesis of **313** and its tacky nature (rendering it difficult to manipulate), in stoichiometric epoxidation reactions, alkylation of **313** to **317** was performed *in situ*. The resulting reaction mixture was concentrated *in vacuo* and the resulting sulfonium salt was used directly without purification). The findings are presented in Table 3.3.



entry	temp. (°C)	conv. (%)[a]	yield (%)[b]	*ee* (%)[c,d]
1	rt	95	95	42
2	-72	89	89	47

[a]Determined using ^{1}H NMR spectroscopy. [b]Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. [c]CSP-HPLC analysis (Chiralcel AS column, 99/1 hexane:*i*-PrOH). [d]The absolute configuration of **17** is (*R*).

Table 3.3 The evaluation of **317** as an enantioselective promoter of the CC reaction

The first reaction was performed under the reaction conditions that afforded the highest levels of enantiomeric excess of **17** when **310** was employed as promoter (Table 3.3, entry 1). Under these reaction conditions, **17** was prepared in excellent yield and an encouraging *ee* of 42% (considering the enantioselectivities realised following the benchmark protocols,[93,94] Scheme 1.44) was achieved (Table 3.3, entry 1). As we had previously demonstrated that decreasing the reaction temperature led to higher levels of

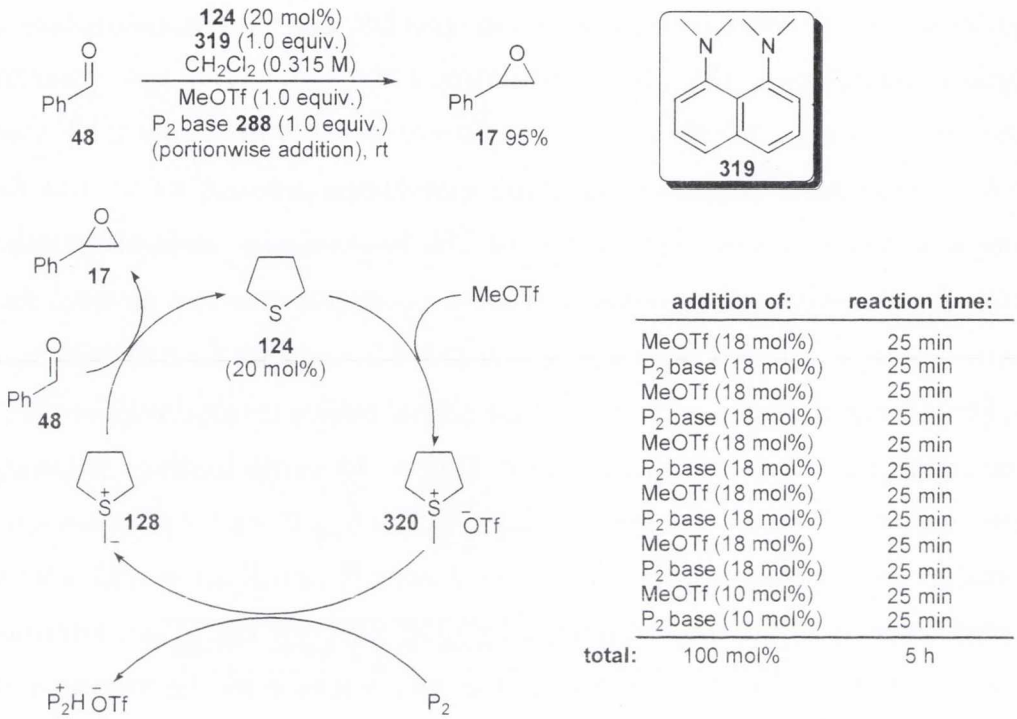
epoxide *ee* in these reactions (entry 2, Table 3.2), the subsequent reaction employing **317** as promoter was performed at both low concentration (0.05 M) and low temperature (-72 °C): to our delight, **17** was furnished in high yield and in 47% *ee* (which is the same *ee* that was achieved following the next best protocol in the literature for the synthesis of terminal epoxides *via* the CC reaction – this process also prescribes the use of 2 equivalents of chiral sulfide **131**,[93] Scheme 1.44).

3.1.7 The development of a catalytic epoxidation protocol

The ultimate objective of our endeavour was to develop a catalytic protocol for the asymmetric synthesis of terminal epoxides *via* the CC reaction. In a related research project, Mr. Alessandro Piccinini found that the achiral sulfide tetrahydrothiophene (**124**) could be employed in catalytic quantities (as little as 10 mol% loading) following an epoxidation protocol based on the 'sulfide alkylation followed by sulfonium salt deprotonation' methodology (Section 1.3.2.2.1). Extensive optimisation studies revealed that methyl triflate was the most efficient alkylating agent for the *in situ* formation of sulfonium salt **320** and that P_2-*t*-Bu **288** was the optimum base for the formation of the sulfonium ylide **128**.

During the development process, in a reaction performed whereby one equivalent (with respect to the stoichiometry of sulfide **124**) of both methyl triflate and P_2 base were added simultaneously to a solution containing benzaldehyde, **124** (20 mol%) and CH_2Cl_2, phenylacetaldehyde was detected in the ^1H NMR spectrum of the crude reaction mixture. This was postulated to arise from either the presence of adventitious water leading to a triflic acid-catalysed Meinwald rearrangement, or the incompatibility of methyl triflate and P_2 base whilst in solution simultaneously.[205] It was found that the use of one equivalent of proton sponge (**319**) circumvented the deleterious Meinwald rearrangement process, while portionwise addition (with a 25 min interval) of methyl triflate and P_2 base prevented the simultaneous existence of both methyl triflate and P_2 base in solution. Having elucidated reagents and conditions that were conducive to efficient alkylation, deprotonation and thus epoxidation, a catalytic procedure involving the sequential,

portionwise addition of methyl triflate and P_2-*t*-Bu **288** at room temperature to a reaction mixture containing benzaldehyde, proton sponge and **124** with CH_2Cl_2 as solvent was developed (Scheme 3.6).[204]



addition of:	reaction time:
MeOTf (18 mol%)	25 min
P_2 base (18 mol%)	25 min
MeOTf (18 mol%)	25 min
P_2 base (18 mol%)	25 min
MeOTf (18 mol%)	25 min
P_2 base (18 mol%)	25 min
MeOTf (18 mol%)	25 min
P_2 base (18 mol%)	25 min
MeOTf (18 mol%)	25 min
P_2 base (18 mol%)	25 min
MeOTf (10 mol%)	25 min
P_2 base (10 mol%)	25 min
total: 100 mol%	5 h

Scheme 3.6 The catalytic epoxidation protocol developed by Mr. Alessandro Piccinini involving the achiral sulfide **124**

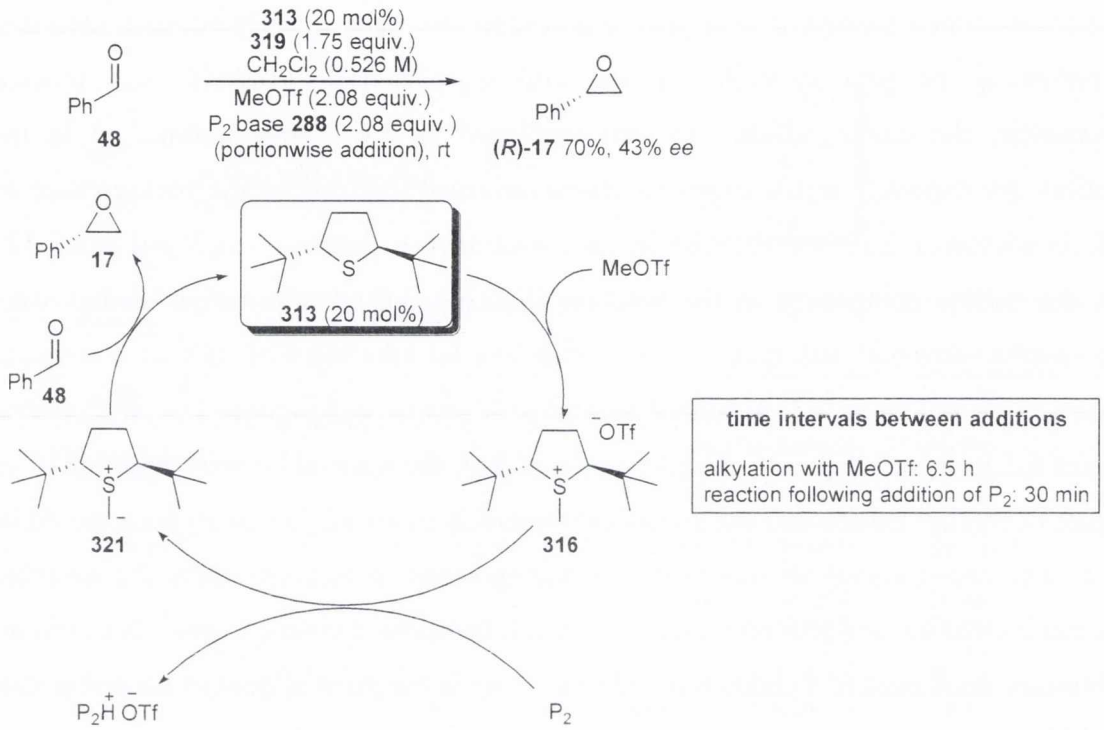
Addition of methyl triflate (18 mol%) to a solution containing **124** (20 mol%), **48** and **319** leads to the *in situ* formation of sulfonium salt **320**. After 25 min (time required for the complete formation of sulfonium salt **320** from **124**), treatment of the resulting solution with P_2-*t*-Bu base yields sulfonium ylide **128**, which subsequently reacts with benzaldehyde to furnish both **17** (95%) and regenerated sulfide **124** (after a further 25 min interval). This sequence is repeated until conversion of benzaldehyde (**48**) to styrene oxide (**17**) is complete (Scheme 3.6). A typical catalytic cycle is depicted in Scheme 3.6.

3.1.7.1 The application of 313 in the catalytic epoxidation protocol: the catalytic asymmetric synthesis of terminal epoxide 17

Having developed a catalytic epoxidation procedure, we subsequently became interested in rendering the process both catalytic and asymmetric. To render this process asymmetric, the chiral sulfide **313** was employed as the sulfide component in the reaction. As expected, initial experimentation revealed that due to the bulky nature of **313**, its alkylation rate was sluggish at the concentration that was employed when **124** was the sulfide component in the reaction (Scheme 3.6). Optimisation studies were performed to this end and the optimum conditions for alkylation of **313** were found to require an overall reaction concentration of 0.526 M, which corresponded to an alkylation time of 6.5 h; therefore, in the catalytic cycle of **313**, the interval between addition of an aliquot of methyl triflate and the subsequent addition of an aliquot of P_2 base would be 6.5 h. The time interval for completion of the epoxidation reaction under the modified reaction conditions was also determined (30 min), therefore, the time interval between the addition of an aliquot of P_2 base and addition of the subsequent aliquot of methyl triflate would be 30 min.

After successfully tailoring the conditions to the requirements of the more sterically encumbered chiral sulfide **313**, an epoxidation reaction was performed using 20 mol% of **313** with benzaldehyde as substrate. Following the portionwise addition sequence outlined in Scheme 3.6, having added 100 mol% of both methyl triflate and P_2 base, upon analysis using ^{1}H NMR spectroscopy, the reaction was adjudged to be incomplete. To ensure the continued prevention of the Meinwald rearrangement, an additional 0.75 equivalents of proton sponge was added to the reaction mixture. This was accompanied by the portionwise addition of supplementary methyl triflate and P_2 base until such time as conversion of **48** to **17** ceased to increase by ^{1}H NMR analysis. Completion of the reaction corresponded to the portionwise addition of a total of 2.08 equivalents of both methyl triflate and P_2 base. (*R*)-Styrene oxide was obtained in high yield (70%) and CSP-HPLC analysis (Chiralpak AS (4.6 mm x 25 cm), hexane/IPA 99:1, 1 mL min^{-1}) revealed that it had been formed in 43% *ee* (Scheme 3.7).[204] The catalytic cycle representing the

asymmetric epoxidation of benzaldehyde using **313** as catalyst is illustrated in Scheme 3.7.



Scheme 3.7 The catalytic asymmetric epoxidation of benzaldehyde using **313**

This methodology affords levels of product enantiomeric excess approaching those obtainable using the benchmark literature procedures for asymmetric methylene transfer (Section 1.3.2.2.2.3),[93,94] but requires 5-10 times less catalyst and provides the product in significantly higher yield.[204] It also represents the first example of an asymmetric terminal epoxidation protocol for the CC reaction not to necessitate the use of (super)stoichiometric quantities of chiral sulfide.

3.1.8 Proposed stereochemical rationale for the catalytic epoxidation of 48 by 313

The major issue associated with the asymmetric synthesis of terminal epoxides *via* unstabilised sulfonium ylides is the irreversible nature of betaine formation (*vide supra*). Enantioselectivity in these reactions is derived solely from which enantiotopic face of the aldehyde is attacked by the ylide. This process has hitherto been characterised by poor facial selectivity, and consequently, enantioselectivity. Figure 3.1 depicts our rationale for the poor selectivity observed in epoxidation reactions catalysed by C_2-symmetric sulfide **313**.

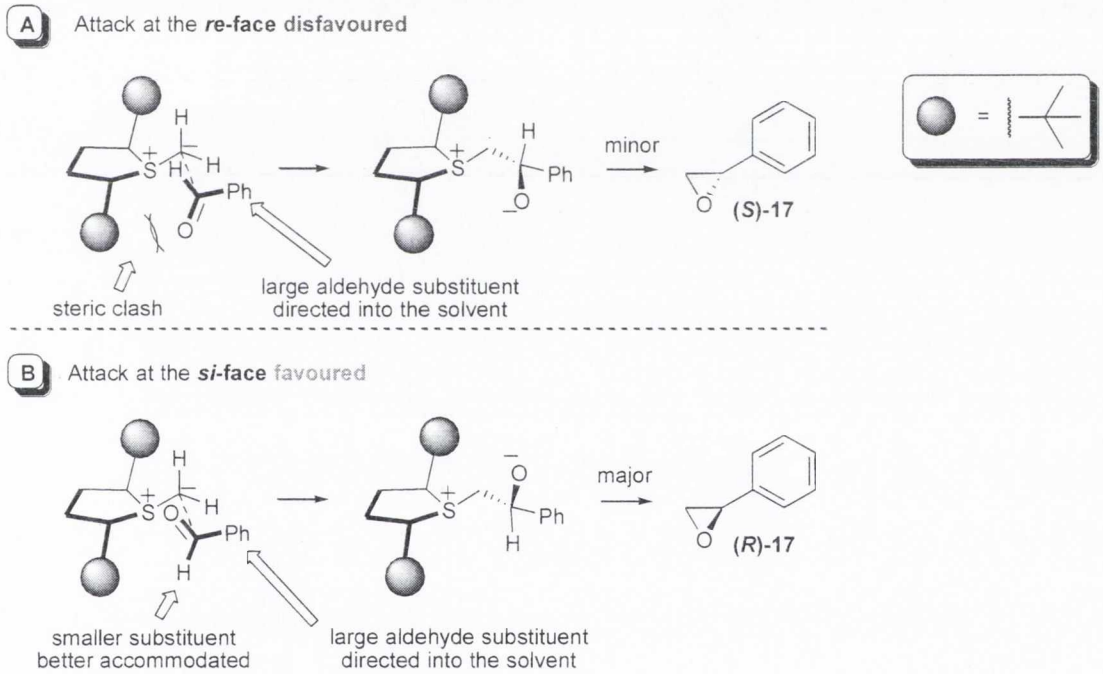


Figure 3.1 Rationale for the stereochemical outcome in epoxidation reactions catalysed by **313**

It is assumed that the aldehyde will approach the ylide in such a way that a) it avoids the large catalyst substituent directed upwards (as drawn, **A** and **B**), b) charge separation/ *gauche* interactions are minimised in the transition state and c) that the large aldehydic

substituent is directed into the solvent. In this scenario, attack at the aldehyde *Si*-face (**B**, Figure 3.1) appears more favourable than attack at the *Re*-face (**A**, Figure 3.1) due to the impending steric clash between the aldehydic carbonyl group and the catalyst *tert*-butyl substituent. This factor may explain why enantioselectivity is consistently unsatisfactory in these systems. The steric discrepancy between the aldehydic C=O and C-H bond is relatively small and the catalyst *tert*-butyl substituent is seemingly not of sufficient steric bulk to allow efficient discrimination between the two possible Bürgi-Dunitz trajectories based on the relatively small steric discrepancy posed by the aldehyde substrate.

As *Si*-facial attack is favoured (in the system outlined in Figure 3.1 involving C_2-symmetric sulfide **(*S*,*S*)-313**), a greater abundance of **(*R*)-17** should result. This is in good agreement with the enantiomeric excess of **17** which we observed in the epoxidation reaction catalysed by **313** (Scheme 3.7).

3.1.9 The logical development of C_2-symmetric sulfide 322

In our quest to develop novel organocatalysts for the asymmetric synthesis of terminal epoxides *via* the CC reaction, we have accumulated valuable information regarding catalyst design - information that has ultimately contributed to the logical design of a novel catalyst for this reaction (*vide infra*).

During the course of a research project aimed at the development of novel, chiral 2-monosubstituted thiolane derivatives as hydrogen bond donating catalysts (*i.e.* **290** and **301**), it was found that due to the relatively low pK_a of the hydrogen bond donor relative to the methyl group on the alkylated thiolane, preferential deprotonation of the hydrogen bond donor occurred, leading to ring-opening of the 5-membered heterocycle (Schemes 2.13 and 2.18). Base-mediated elimination was also found to occur at the 2-position (α to the sulfur atom) of these hydrogen bond donating alkylated thiolanes (**296**, Scheme 2.13).

To circumvent the base-mediated decomposition pathway associated with deprotonation of the hydrogen atom on the heteroatom of the hydrogen bond donor in **292**, it was

protected as its benzyl ether (**300**, Scheme 2.14). This protection strategy was successful and did indeed prevent the undesired decomposition pathway associated with deprotonation of the hydrogen bond donor; however, deprotonation at the 2-position of alkylated thiolane **300** (with elimination of benzyl alcohol) persisted as before (Section 2.1.2.9.3).

It has also been demonstrated that these chiral 2-monosubstituted thiolane derivatives do not lead to appreciable levels of product *ee* in CC reactions: CSP-HPLC analysis of **17** that had been isolated from an epoxidation reaction promoted by **300** revealed that it had been formed in 2% *ee* (Scheme 2.15). It was however demonstrated that good levels (up to 47% *ee*) of enantioselectivity can be achieved in CC reactions when C_2-symmetric thiolanes such as **309** and **313** are employed as promoters (Tables 3.2 and 3.3). It was also shown that more sterically encumbered thiolanes lead to higher levels of enantioinduction in CC reactions (Tables 3.2 and 3.3).

Our experience in catalyst design culminated in the development of a C_2-symmetric thiolane (for the induction of asymmetry) not susceptible to either base-mediated deprotonation on the heteroatom of the hydrogen bond donor (by protecting the hydroxyl groups as methyl ethers) or base-mediated deprotonation at the 2- or 5-positions (by replacing the two hydrogen atoms with methyl groups). C_2-symmetric thiolane **322** and its design rationale are illustrated in Figure 3.2.

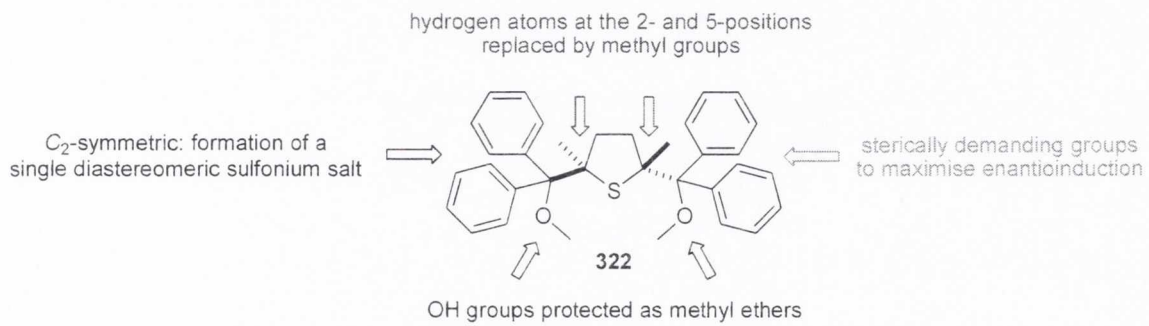
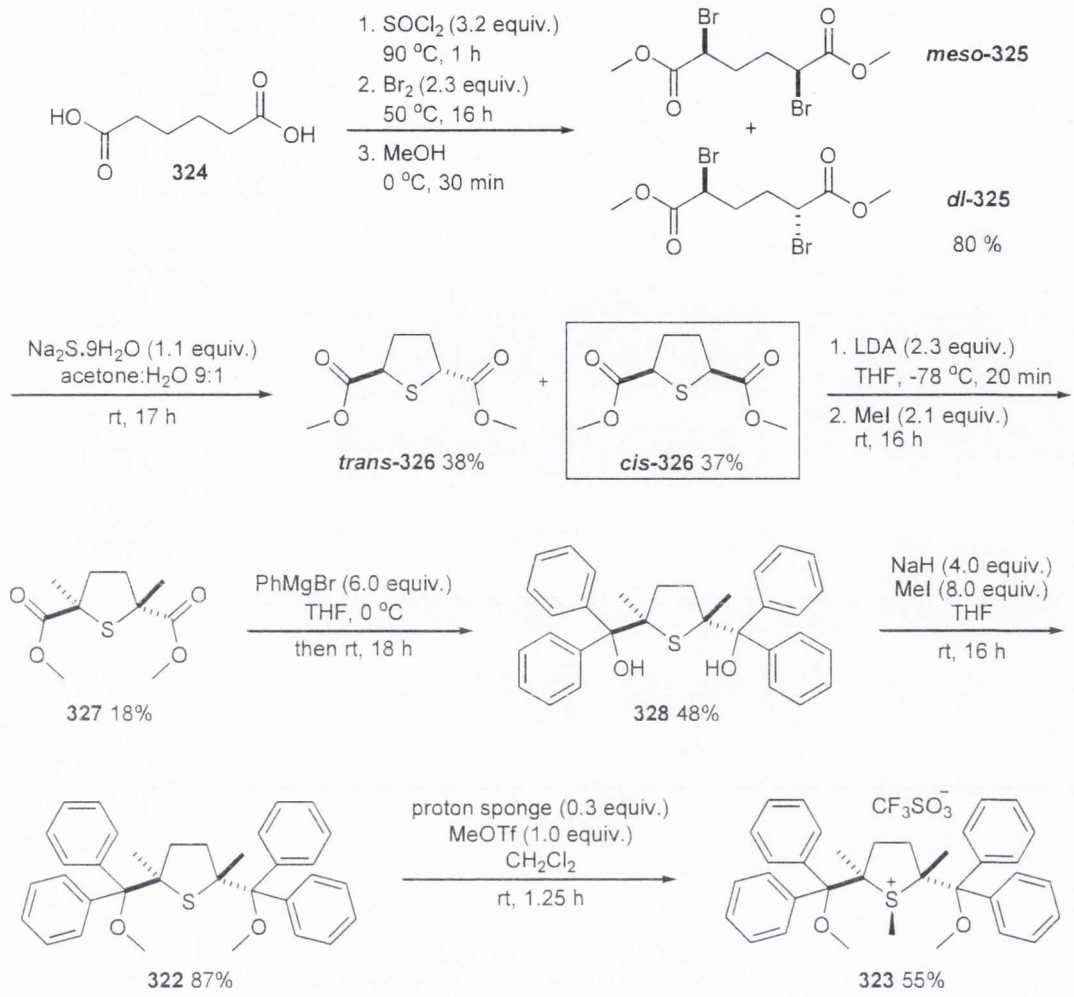


Figure 3.2 Rationale for the design of C_2-symmetric thiolane **322**

3.1.10 The synthesis of sulfonium salt 323

Preliminary proof of concept studies would be performed using a stoichiometric quantity of the preformed sulfonium salt (*i.e.* **323**) of **322** with the aspiration of later modifying the procedure to accommodate the use of catalytic quantities of **322**. Furthermore, as the purpose of these preliminary studies was to ascertain whether or not **322** would be a suitable methylene source and hence promote CC reactions, the optical purity of **322** was considered extraneous at this point. The racemic synthesis of **323** is outlined in Scheme 3.8.

Consecutive treatment of adipic acid (**324**) with thionyl chloride, bromine and methanol afforded *meso*- and *dl*-dimethyl 2,5-dibromoadipate (**325**), which were inseparable by column chromatography. Cyclisation of **325** using sodium sulfide in an acetone:H_2O (9:1) mixture afforded both *cis*-**326** (37%) and *trans*-**326** (38%), which were separable by column chromatography. Treatment of *cis*-**326** with LDA in THF at -78 °C, followed by iodomethane furnished both *cis*-**327** and *trans*-**327** (18%); however, as only the *trans* isomer was required, it was the only product isolated after purification by column chromatography. To *trans*-**327** in THF, phenylmagnesium bromide was added, affording diol **328** (48%). **328** Was then treated with sodium hydride and methyl iodide in THF to furnish **322** (87%). Finally, **322** was transformed into sulfonium salt **323** (55%) by treatment with proton sponge and methyl triflate in methylene chloride.



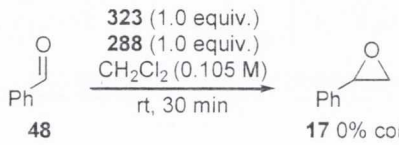
Scheme 3.8 The synthesis of **323**

3.1.11 The evaluation of 323 as a promoter of the CC reaction

Having prepared **323**, attention was subsequently focused on its evaluation as a promoter of the CC reaction. Evaluation would be performed under the same reaction conditions that were employed in stoichiometric epoxidation reactions using chiral sulfonium salts **310** and **317** as promoters (Tables 3.2 and 3.3). The concentration however would differ: as our ultimate goal is to employ this chiral sulfide in catalytic quantities, the reaction would be performed using the same concentration that was employed in the catalytic

epoxidation reaction when **313** was employed as chiral sulfide (*i.e.* 0.105 M with respect to the stoichiometry of **313**, Scheme 3.7).

In an epoxidation reaction with **323** (1.0 equiv.) as promoter and benzaldehyde (**48**) as substrate, after 30 min reaction time at room temperature, no conversion to **17** had occurred (Scheme 3.9).



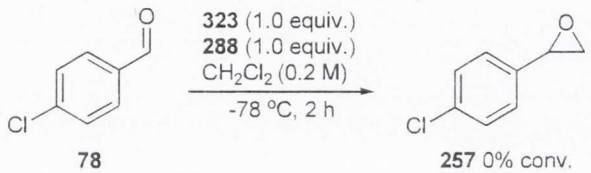
Scheme 3.9 Evaluation of **323** as a promoter of the CC reaction

Furthermore, the ^{1}H NMR spectrum of the crude reaction indicated that neither the sulfonium salt **323** nor its sulfide precursor **322** were present. The major component (apart from benzaldehyde) in the the ^{1}H NMR spectrum of the crude reaction was an unidentified species not related to benzaldehyde and was assumed to be derived from **323**. Isolation of this material by column chromatography and subsequent analysis using both NMR spectroscopy and HRMS revealed that **329** was the major component present in the ^{1}H NMR spectrum of the crude reaction. It is believed that **329** is formed *via* the base-mediated decomposition of **323** (Scheme 3.10).

323 **329**

Scheme 3.10 The base-mediated decomposition of **323**

In an attempt to both promote the CC reaction and circumvent the decomposition pathway outlined in Scheme 3.10, a reaction was performed using a more reactive aldehyde (**78**) as substrate, a lower temperature (-78 °C) and a concentration more conducive to epoxidation (rather than decomposition), *i.e.* the higher concentration of 0.2 M (Scheme 3.11).



Scheme 3.11 Evaluation of **323** as a promoter of the CC reaction under the new reaction conditions

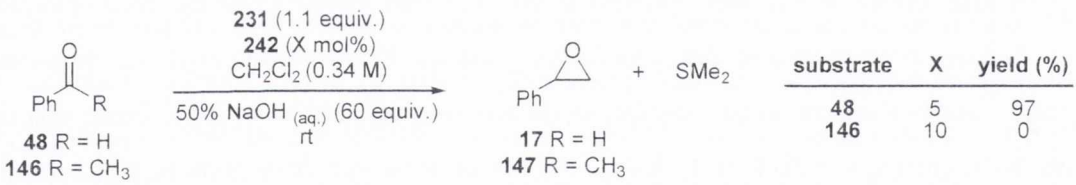
Unfortunately, the outcome was the same as before (Scheme 3.9): after two hours reaction time, no conversion to **257** had occurred. In addition, neither sulfonium salt **323**, nor its sulfide precursor **322** were present in the ^{1}H NMR spectrum of the crude reaction, and as before, base-mediated decomposition product **329** was detected. As it seemed clear that catalysts based on this design motif are not compatible with the basic reaction conditions required, we decided to focus our research on the development of alternative catalysts for the asymmetric synthesis of terminal epoxides for the CC reaction.

3.2 The synthesis of geminally disubstituted terminal epoxides from ketones *via* the catalytic CC reaction: early considerations

On completion of the above study involving the successful development of a catalytic protocol for methylene transfer to aldehydes, we realised that for this methodology to be considered genuinely useful, it was deemed paramount that it also be compatible with ketone substrates. Although there are numerous reported examples of methylene transfer to ketones, all of these procedures require (super)stoichiometric sulfide loadings.[108] The possibility of using a catalytic quantity of sulfide in this reaction would represent a far

more efficient protocol (from an atom-economy perspective) for the synthesis of this problematic class of epoxide, which has thus far proven elusive.

An initial cause of concern regarding the development of a catalytic protocol for the epoxidation of ketones based on the procedure that had been developed for the epoxidation of aldehydes, is the greatly reduced electrophilicity of simple ketones relative to their aldehyde counterparts. Preliminary experimentation in this regard was not encouraging. During the course of a previous research programme aimed at the design of novel hydrogen-bond-donating organocatalysts for methylene transfer in the CC reaction employing a biphasic solvent system (Section 2.1.2.4), we discovered that benzaldehyde (**48**) could be converted to **17** in excellent yield (97%) in the presence of catalyst **242** (5 mol% loading), trimethylsulfonium iodide and base.[196] For the purposes of the current study, this reaction was repeated using acetophenone (**146**) as the substrate. The difference in reactivity was striking: no conversion of **146** to **147** was observed, even when catalyst loadings were elevated to 10 mol% (Scheme 3.12).



substrate	X	yield (%)
48	5	97
146	10	0

Scheme 3.12 The urea-catalysed epoxidation of **48** and the attempted epoxidation of **146**

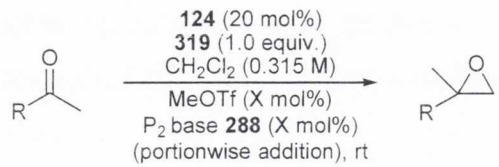
While it was thus obvious that ketones represent a challenge from an electrophilicity standpoint, the key question now was whether or not ketones would be unreactive enough towards ylide **128** under the conditions that had been optimised for the catalytic epoxidation of aldehydes (Scheme 3.6) to render C-C bond formation (as opposed to sulfide alkylation) the rate determining step. If this were the case, it would be unlikely that a practical catalytic procedure would be possible. However, we envisaged that the homogeneous nature of the catalytic methodology (Scheme 3.6), which involves the rapid and clean formation of **128** in the same phase as the ketone electrophile (thus the

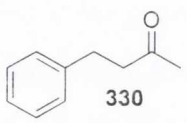
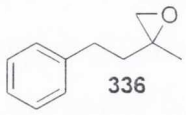
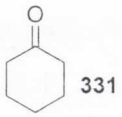
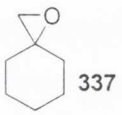
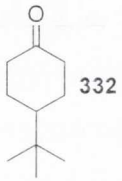
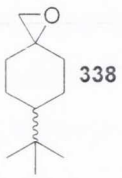
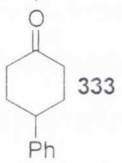
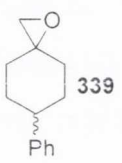
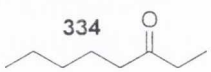
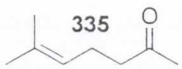
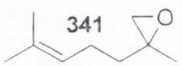
concentration of both could be carefully controlled), could (at least partially) compensate for the inherent lack of electrophilicity associated with ketone substrates.

3.2.1 The synthesis of geminally disubstituted terminal epoxides from ketones *via* the catalytic CC reaction

To test this hypothesis, we applied our catalytic protocol to the epoxidation of a variety of aromatic (performed by Mr. Alessandro Piccinini) and aliphatic ketones. To our delight, in the presence of catalyst **124** (20 mol%), a range of aromatic ketones underwent smooth reaction to the corresponding terminal epoxides in high yield (85-94%).[206] Aliphatic ketones were also susceptible to catalytic epoxidation under these reaction conditions (Table 3.4). Benzyl acetone (**330**) proved to be a good substrate in this reaction, producing the corresponding epoxide **336** in high yield (Table 3.4, entry 1). Cyclohexanone and 4-substituted cyclohexanone derivatives (**331**, and **332-333** respectively, entries 2-4) also furnished the corresponding epoxide products **337-339** in excellent yield. Epoxides derived from long chain aliphatic ethyl- (**334**, entry 5) and methyl- (**335**, entry 6) ketones could also be prepared without difficulty. Undesired aldol-derived side products were not detected in any of the above reactions.[206]

It has, therefore, been demonstrated for the first time that ketones can be converted to terminal epoxides *via* a CC reaction involving methylene transfer in the presence of substoichiometric loadings of a sulfide catalyst. The method is of broad scope, as a diverse array of aromatic and aliphatic aldehydes are amenable to epoxidation. Product yields are invariably high using this convenient, room temperature protocol.



Entry	Substrate	X	Product	Yield (%)[a]
1	 330	100	 336	89
2	 331	144	 337	95
3	 332	118	 338	93
4	 333 Ph	118	 339 Ph	94
5	334 	136	340 	83[b]
6	335 	118	341 	90

[a]Isolated yield. [b]Determined by ^{1}H NMR spectroscopy using styrene as an internal standard.

Table 3.4 The catalytic epoxidation of aliphatic ketones

3.2.2 The attempted asymmetric synthesis of geminally disubstituted terminal epoxides from ketones *via* the CC reaction

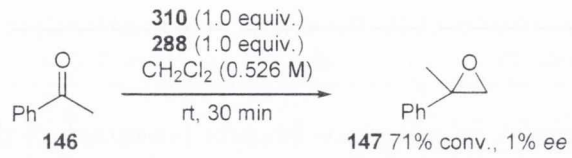
As discussed in Section 1.5, a highly enantioselective protocol for the asymmetric synthesis of geminally disubstituted terminal epoxides *via* the asymmetric oxidation of geminally disubstituted alkenes has thus far proven elusive.[9b,17c,106,107] A similar dearth exists regarding the synthesis of geminally disubstituted terminal epoxides *via* the

asymmetric CC reaction: to date, there has been just one report detailing the highly enantioselective synthesis of this class of epoxide using the sulfonium ylide-mediated methodology and it prescribes the use of both a superstoichiometric quantity of sulfide **46** and a heterobimetallic rare earth-alkali metal complex **145** (Scheme 1.47).[109]

With this significant paucity in mind, we became interested in the application of our recently developed methodology for the asymmetric epoxidation of aldehydes, to the enantioselective preparation of geminally disubstituted terminal epoxides using ketones as substrates. Having previously shown that the chiral C_2-symmetric thiolane **309** can be prepared in two simple steps from commercially available, enantiopure diol **311**, and having demonstrated that it affords appreciable levels of epoxide enantiomeric excess in stoichiometric epoxidation reactions (using sulfonium salt **310**) with benzaldehyde as substrate, we decided to evaluate whether or not it could induce enantioselectivity in epoxidation reactions using ketones as substrates. The ultimate idea of this undertaking being that if enantioselectivity could be achieved in the stoichiometric epoxidation reaction using a ketone as substrate, our catalytic asymmetric aldehyde epoxidation methodology (Scheme 3.7) could be applied to the catalytic asymmetric epoxidation of ketones.

A stoichiometric reaction was therefore performed using preformed sulfonium salt **310**. Bearing in mind the ultimate aim of this endeavour (*i.e.* to apply the catalytic asymmetric protocol to the epoxidation of ketones), the same reaction concentration that was employed in the catalytic asymmetric epoxidation of benzaldehyde (**48**) using chiral C_2-symmetric thiolane **313** (Scheme 3.7), was used in this reaction, as it was anticipated that the alkylation rate of **309** would be similar to that of **313**. Under these conditions, and with acetophenone (**146**) as substrate, it was found that **147** was formed in good conversion (71%) after 30 minutes reaction time. CSP-HPLC analysis (Chiralcel OD column, 99/1 hexane:*i*-PrOH, 0.5 cm^3 min^{-1}) of isolated **147** revealed that it had been formed in 1% *ee* (Scheme 3.13, ***rac*-147** was provided by Mr. Alessandro Piccinini). This decrease in *ee* is ascribable to the smaller steric difference between the methyl and phenyl

groups of ketone **146** relative to the large discrepancy between the hydrogen atom and phenyl group of benzaldehyde (**48**, **B**, Figure 3.1).



146 **147** 71% conv., 1% *ee*

Scheme 3.13 Evaluation of **310** as a promoter of the asymmetric CC reaction with **146** as substrate

Although **310** did promote the CC reaction, it did not do so in an enantioselective fashion, therefore, the development of a catalytic asymmetric variant of this procedure was not explored further.

3.3 Conclusion: Chapter 3

We have demonstrated that chiral C_2-symmetric 2,5-disubstituted thiolane derivatives induce enantioselectivity in stoichiometric CC reactions with benzaldehyde as substrate. This enantioselectivity however, is dependent upon the steric properties of the substituents at the 2- and 5-positions on the thiolane ring. For example, the dimethyl analogue **308** affords negligible levels of enantiomeric excess of **17** (Table 3.1) in CC reactions with benzaldehyde as substrate, while the more sterically encumbered isopropyl and *tert*-butyl analogues both provide **17** with appreciable levels of enantiomeric excess (up to 29% and 47% *ee* respectively, Tables 3.2 and 3.3). This observed increase in selectivity with increase in steric bulk (of the substituents at the 2- and 5-positions) is attributable to these groups exerting greater control over the approach of the aldehyde to the ylide. It is noteworthy that the 47% *ee* that was achieved using **317** (one equivalent) as promoter is the same *ee* that was achieved following the next best protocol in the literature to date[93] (using two equivalents of **131**, Scheme 1.44) for the asymmetric synthesis of terminal epoxides *via* the CC reaction.

We have shown that this enantioselectivity can also be achieved using catalytic (20 mol% loading) quantities of chiral sulfide **313** (Scheme 3.7): **17** was furnished in 70% yield and 43% *ee* following our catalytic protocol.[204] This methodology affords levels of product enantiomeric excess approaching those obtained following the benchmark literature procedures for the enantioselective preparation of terminal epoxides *via* the CC reaction (Section 1.3.2.2.2.3).[93,94] The protocol which we have developed requires 5-10 times less catalyst than the benchmark procedures and provides the product in significantly higher yield.[204] Our methodology is also the first example of an asymmetric terminal epoxidation protocol for the CC reaction not to necessitate the use of (super)stoichiometric quantities of chiral sulfide.

During the course of various research projects aimed at the development of novel organocatalysts for the asymmetric synthesis of terminal epoxides *via* the CC reaction, key realisations with respect to the compatibility of certain aspects of catalyst design led us to the development of sulfide **322** (Section 3.1.9); however, like **292**, **300** and **304** (Sections 2.1.2.9.1, 2.1.2.9.3, 2.1.2.9.5), **322** also proved susceptible to base-mediated decomposition (Scheme 3.10).

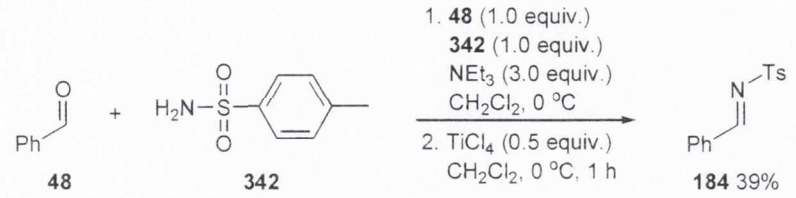
We have also demonstrated, for the first time, that geminally disubstituted terminal epoxides can be prepared from ketones *via* the CC reaction using catalytic quantities (20 mol%) of sulfide. Both aromatic and aliphatic ketones proved to be appropriate substrates for this reaction affording the corresponding geminally disubstituted terminal epoxides in high yield (Section 3.2.1).[206] Our attempt to render this process both catalytic asymmetric and asymmetric however, was not successful: in an epoxidation reaction using chiral sulfonium salt **310** with **146** as substrate furnished terminal epoxide **147** in 1% *ee* (Section 3.2.2).

4.1 The AZ of imines *via* the CC reaction: early considerations

As discussed in Section 1.3.3.4, a methylene transfer protocol leading to excellent levels of terminal epoxide enantiomeric excess *via* the CC reaction has yet to be developed.[93,94,204] The same paucity exists for the enantioselective synthesis of terminal aziridines *via* this methodology, with the benchmark literature protocol affording terminal aziridine **195** in 70% yield and just 19% *ee* (despite the use of 2 equivalents of the chiral sulfide **87**, Scheme 1.63). As the mechanisms associated with asymmetric methylene transfer reactions (*via* non-stabilised ylides) involving both aldehydes and imines as substrates are identical, we pondered as to whether our previously developed protocol for the AE of aldehydes (Sections 3.1.4 and 3.1.6) could be successfully applied to the AZ of imines.

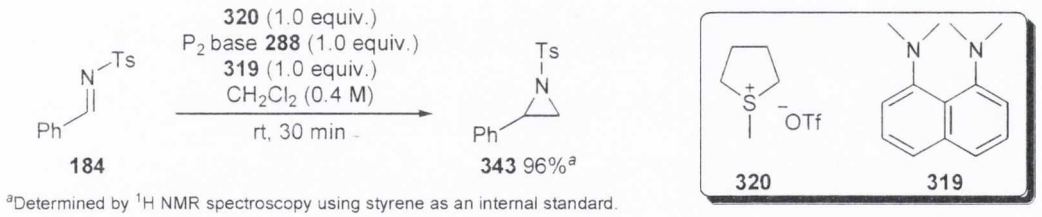
4.2 Imines as substrates in achiral stoichiometric CC reactions: the optimisation of reaction conditions

The main cause of concern at this point was not whether asymmetry would be induced in this reaction, but rather whether methylene transfer to imine substrates would occur. Therefore, proof of concept studies would be performed using achiral methyltetrahydrothiophene triflate (**320**) as the methylene source. As many of the reports in the literature to date detailing the efficient addition of semi-stabilised ylides (Sections 1.6.1.4.1 to 1.6.1.4.3) to imines involve substrates that are activated by means of a tosyl group on the nitrogen atom of the imine, our preliminary experiments would be performed using imine **184** as substrate (the preparation of which is outlined in Scheme 4.1).



Scheme 4.1 The preparation of *N*-tosyl imine **184**

The initial aziridination reaction was performed by addition of methyl triflate (1 equiv.) to a solution (0.4 M in CH_2Cl_2) containing tetrahydrothiophene (1 equiv.). Upon completion of the *in situ* formation of sulfonium salt **320** (30 min), proton sponge (1 equiv.), imine **184** and P_2-*t*-Bu (1 equiv.) were added sequentially. Although the corresponding aziridine **343** had been formed in the reaction (^{1}H NMR spectroscopic analysis of the crude reaction after 40 min), so too had both benzaldehyde (**48**) and styrene oxide (**17**). This is thought to have occurred due to the presence of adventitious water, leading to the hydrolysis of imine **184**, with the resulting benzaldehyde (**48**) being epoxidised to styrene oxide (**17**) by reaction with ylide **128**. Having elucidated the detrimental effect of water on the aziridination reaction, a modified procedure was developed (Scheme 4.2).



[a]Determined by ^{1}H NMR spectroscopy using styrene as an internal standard.

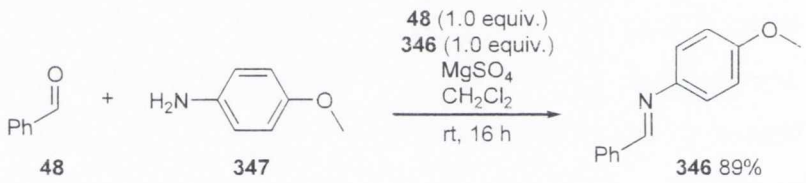
Scheme 4.2 The modified aziridination procedure using pre-formed sulfonium salt **320**

The reaction vessel was charged with sulfonium salt **320**, proton sponge (**319**), imine **184** and placed under vacuum on a Schlenk line for 1 h prior to reaction. The flask was then immediately flushed with argon, fitted with a rubber septum and placed under an atmosphere of argon (balloon). Freshly distilled CH_2Cl_2 (0.4 M) was then added,

followed by P_2-*t*-Bu (**288**). Employing this modified procedure, **343** was furnished in 96% yield.

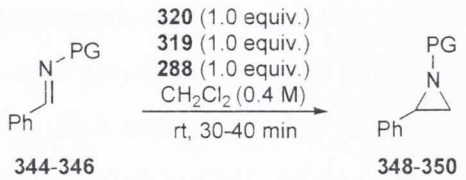
4.3 Identifying the requisites of the imine *N*-substituent

Having established reaction conditions that are conducive to the efficient aziridination of imine **184** (Scheme 4.2), attention was subsequently focussed on investigating the influence of the *N*-substituent (from an electronic perspective) on these reactions. Therefore, a range of *N*-substituted benzaldimines (**344-346**) were prepared: *P*,*P*-diphenyl-*N*-(phenylmethylene)phosphinic amide (**344**) was prepared following the same procedure as outlined for the synthesis of **184** (Scheme 4.1), *N*-phenyl benzaldehyde imine (**345**) was available within the group while *N*-benzylidene-4-methoxybenzenamine (**346**) was prepared as outlined in Scheme 4.3.



Scheme 4.3 The preparation of imine **345**

The suitability of these imines as substrates in CC reactions under the reaction conditions outlined in Scheme 4.2 was then evaluated. The results obtained are illustrated in Table 4.1. As expected (due to the reduced electrophilicity of imines compared with aldehydes), imines possessing an electron withdrawing group as an *N*-substituent (*e.g.* diphenylphosphoryl (DPP), entry 1, Table 4.1) proved the best substrates, with imine **344** being aziridinated to **348** in high yield (86%). Imine **345**, possessing a phenyl group as *N*-substituent, was aziridinated to the corresponding aziridine **349** in slightly lower yield (76%, entry 2), while imine **346**, possessing an electron donating *p*-methoxyphenyl (PMP) group as the *N*-substituent, was aziridinated to **350** in significantly lower yield (55%, entry 3).



344-346 348-350

entry	PG	imine	aziridine	conv. (%)[a]	yield (%)[b]
1	DPP	**344**	**348**	85	86
2	Ph	**345**	**349**	75	76
3	PMP	**346**	**350**	55	55

[a]Determined using ^{1}H NMR spectroscopy. [b]Determined by ^{1}H NMR spectroscopy using styrene as an internal standard.

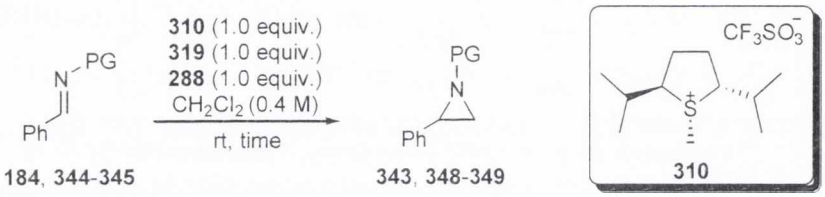
Table 4.1 Evaluation of the influence of imine *N*-substituent in CC aziridination reactions

In summary, of the imine substrates evaluated thus far under the reaction conditions outlined in both Scheme 4.2 and Table 4.1, the *N*-substituents giving rise to the highest levels of aziridine product are, in ascending order, PMP (55%, entry 3, Table 4.1), Ph (76%, entry 2, Table 4.1), DPP (86%, entry 1, Table 4.1) and Ts (96%, Scheme 4.2).

4.4 The AZ of imines 334-346 promoted by chiral sulfonium salt 310

Having established that 'activated' imines, *i.e.* imines that have an electron withdrawing group on their nitrogen atom (**184** and **344**), are aziridinated in higher yields than imines that possess deactivating groups (*e.g.* **346**, entry 3, Table 4.1), attention subsequently turned to rendering the aziridination of these 'activated' imines asymmetric. Due to the ease of preparation of **310** (relative to the *tert*-butyl analogue **317**, Section 3.1.5) and its ability to induce asymmetry in epoxidation reactions (Table 3.2), preliminary AZ reactions would be performed with **310** as the promoter. It was also hoped that the dependency of enantioselectivity on *N*-substituent would be revealed during this evaluation study.

Due to the adverse effect exhibited by water on the outcome of these aziridination reactions, reactions performed with **310** as sulfonium salt were performed under the same stringently anhydrous conditions as before (Section 4.2). The results obtained in CC reactions performed involving imines **184**, **344** and **345** as substrates and **310** as promoter are outlined in Table 4.2.



entry	PG	imine	aziridine	time (min)	conv. (%)[a]	yield (%)[b]	*ee* (%)[c]
1	Ph	**345**	**349**	90	32	31	13
2	Ts	**184**	**343**	40	88	87	6
3	DPP	**344**	**348**	30	82	n.d.[d]	9

[a]Determined using ^{1}H NMR spectroscopy. [b]Determined by ^{1}H NMR spectroscopy using styrene as an internal standard. [c]Determined using CSP-HPLC analysis. [d]Not determined due to overlap with internal standard signal.

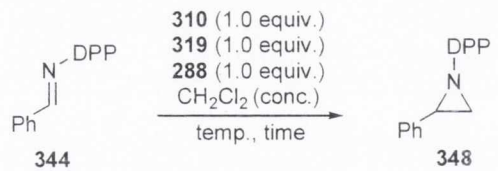
Table 4.2 Evaluation of **310** as an enantioselective promoter of CC reactions with imines as substrates

The highest *ee* that was achieved under these conditions, with **310** as promoter, corresponds to the aziridination of imine **345** to aziridine **349** (entry 1, Table 4.2), *i.e.* where the *N*-substituent is Ph. The yield of this reaction however, was poor, affording **349** in just 31% yield. This low yield is ascribable to a combination of both the poor electrophilicity of the imine and the steric hindrance, and thus reactivity, of **310**. The highest yield (87%), but lowest *ee* (6%), was achieved when 'activated' imine **184** was employed as the substrate (entry 2, Table 4.2). Upon inspection of Table 4.2, it is clear that imine **344**, possessing a DPP group as *N*-substituent, provided the terminal aziridine with the best combination of both yield (82% conv.) and *ee* (9%, entry 3). This high yield is, as previously mentioned, attributable to the electron withdrawing properties of the

DPP *N*-substituent, thus activating the imine toward nucleophilic attack by the ylide. The higher *ee* achieved when **344** was employed as the substrate compared to that achieved when **184** was employed is presumably due to the size of the DPP group relative to the Ts group (entries 2 and 3, Table 4.2).

4.5 Optimising the reaction conditions for the optimum imine *N*-substituent

Having identified the imine *N*-substituent that leads to the best combination of both yield and *ee* in these CC reactions (under the preliminary reaction conditions), *i.e.* **344** (possessing a DPP group as *N*-substituent), we became interested in developing reaction conditions that would lead to an improvement in the enantioselectivity of the aziridination process. Initial experimentation along these lines involved the modification of the same factors that led to an increase in *ee* in the corresponding epoxidation reactions (Tables 3.2 and 3.3), *i.e.* decreasing the reaction concentration, the reaction temperature, or a combination of both. The results obtained are illustrated in Table 4.3.



entry	conc. (M)	temp. (°C)	time (h)	conv. (%)[a]	*ee* (%)[b]
1	0.4	-78	16	87	2
2	0.08	-78	16	96	1.4
3	0.4	60	0.5	98	10[c]

[a]Determined using ^{1}H NMR spectroscopy. [b]Determined using CSP-HPLC analysis. [c]The absolute configuration of aziridine **348** was determined to be (*R*) using specific rotation (see the experimental section).

Table 4.3 Optimising the reaction conditions for the enantioselective aziridination of imine **344**

To our surprise, while lowering the reaction temperature had little effect on the conversion (87%) of imine **344** to aziridine **348**, a deleterious effect on the enantioselectivity (2% *ee*) of the process was observed (entry 1, Table 4.3). A similar temperature modification in a related epoxidation reaction promoted by **310** had led to a 9% increase in *ee* (compared to the same reaction performed at room temperature) of the resulting epoxide (entry 2, Table 3.2). As it was also observed in related epoxidation reactions that decreasing both the concentration and temperature of the reaction leads to an increase in epoxide *ee* (Tables 3.2 and 3.3), the subsequent aziridination reaction was performed at both low temperature (-78 °C) and low concentration (0.08 M, entry 2, Table 4.3). As before, these conditions were found to have a negative effect on the enantioselectivity of the aziridination process (entry 2), with **348** being furnished in just 1.4% *ee*.

To ensure that these anomalous results were not due to experimental error, both the room temperature reaction performed at 0.4 M (entry 3, Table 4.2) and the low temperature (-78 °C) reaction performed at 0.08 M (entry 2, Table 4.3) were repeated. Upon repetition of the former reaction, **348** was again afforded in 9% *ee*. Similarly, upon repetition of the latter reaction, **348** was furnished in 0.4% *ee*. Therefore, the results obtained from the reactions documented in Table 4.3 are due to an unusual temperature dependence and not experimental error.

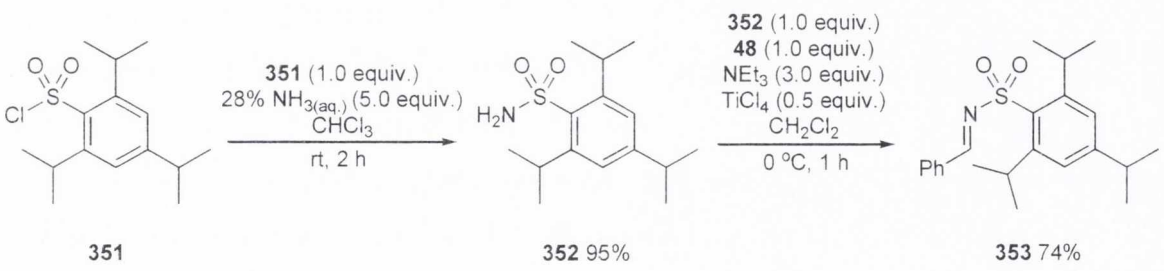
Having observed a decrease in enantioselectivity in aziridination reactions performed at low temperature, we speculated whether performing the same reaction at an elevated temperature would have an opposite effect, *i.e.* lead to higher levels of aziridine *ee*. Thus, the subsequent reaction was performed at 60 °C (entry 3, Table 4.3). We were intrigued to find that an increase in enantioselectivity did indeed occur, with **348** being formed in 10% *ee* (entry 3). Although there have been reports detailing asymmetric reactions whereby a diminution in enantioselectivity is observed at lower temperatures with an increase in enantioselectivity being observed at elevated temperatures, this temperature dependence is rare.[207] Most catalytic asymmetric reactions exhibit the opposite

temperature dependence, *i.e.* whereby an increase in temperature is associated with a diminution in enantioselectivity.

4.6 Re-evaluation of the imine *N*-substituent

Due to the anomaly associated with the temperature dependence of DPP imine **344** in asymmetric aziridination reactions, and the fact that it seemed unlikely that further optimisation (of reaction conditions) studies would lead to higher enantioselectivities in the aziridination of **344** to **348**, we considered the evaluation of alternative groups as imine *N*-substituent.

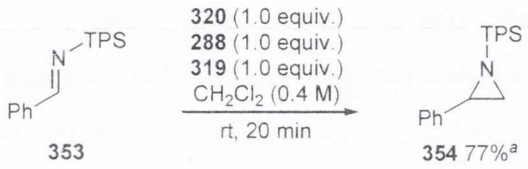
Thus far, we have identified that 1) higher yields of the aziridine product are achieved in CC reactions when the imine *N*-substituent is electron withdrawing and 2) that increasing the size of this group leads to higher levels of enantioinduction in these reactions. One such group that is an amalgamation of these two requisite properties (*i.e.* electron withdrawing and sterically hindered) is the 2,4,6-triisopropylbenzenesulfonyl group (TPS). Prior to the evaluation of this group as a suitable imine *N*-substituent, benzaldimine **353** was prepared in two facile steps from 2,4,6-triisopropylbenzenesulfonyl chloride (**351**, Scheme 4.4). Treatment of sulfonyl chloride **351** with ammonia in chloroform afforded 2,4,6-triisopropylbenzenesulfonamide (**352**) in 95% yield. Imine **353** was prepared from the preceding sulfonamide and **48** using triethylamine and titanium(IV) chloride in methylene chloride in 74% yield.



Scheme 4.4 The synthesis of imine **353** from **351**

4.7 Evaluation of the TPS group as imine *N*-substituent in CC reactions promoted by achiral sulfonium salt 320

Having prepared *N*-TPS imine **353**, attention was subsequently turned to the evaluation of this group as imine *N*-substituent in CC reactions. As our primary aim at this point was to investigate the suitability of this group in CC reactions from a reactivity (rather than enantioselectivity) perspective, *i.e.* the conversion of imine **353** to aziridine **354**, initial experimentation was performed using achiral sulfonium salt **320** under the reaction conditions that were previously employed in achiral aziridination reactions (Scheme 4.5).



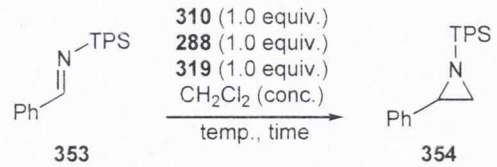
[a]Determined by ^{1}H NMR spectroscopy using styrene as an internal standard.

Scheme 4.5 The aziridination of *N*-TPS imine **353** using sulfonium salt **320**

We were pleased to find that under these reaction conditions, aziridine **354** had been formed in 77% yield after 20 minutes reaction time at room temperature.

4.8 Evaluation of the TPS group as imine *N*-substituent in CC reactions promoted by chiral sulfonium salt 310

As it has been shown that *N*-TPS imine **353** is sufficiently activated to undergo efficient CC reactions with sulfonium methylide **128** (Scheme 4.5), we became interested in establishing whether or not this *N*-substituent would lead to higher levels of aziridine enantiomeric excess in CC reactions than those previously evaluated (Tables 4.2 and 4.3). To satisfy our curiosity, chiral sulfonium salt **310** was employed as promoter in CC reactions with *N*-TPS imine **353** as substrate (Table 4.4).



entry	conc. (M)	temp. (°C)	time (h)	conv. (%)[a]	yield (%)[b]	*ee* (%)[c]
1	0.4	rt	0.66	84	85	14
2	0.4	-78	17	91	90	18
3	0.08	-78	16	74	72	22

[a]Determined using ^{1}H NMR spectroscopy. [b]Determined by ^{1}H NMR spectroscopy using styrene as an internal standard. [c]Determined using CSP-HPLC analysis.

Table 4.4 The evaluation of **310** as an enantioselective promoter of CC reactions with *N*-TPS imine **353** as substrate

The initial reaction was performed under the same conditions that were employed when achiral **320** was promoter. After 40 minutes reaction time at room temperature, **354** was formed in 85% yield and 14% *ee* (entry 1, Table 4.4): this represented the highest *ee* we had hitherto obtained in an aziridination reaction (see Tables 4.2 and 4.3). Interestingly, under identical reaction conditions, the tosyl imine **184** was aziridinated in just 6% *ee* (entry 2, Table 4.2). We propose that the increase in enantioselectivity observed in the aziridination of *N*-TPS imine **353** to **354** is attributable to the greater steric bulk of the TPS group relative to the Ts group (*vide infra*, Figure 4.2).

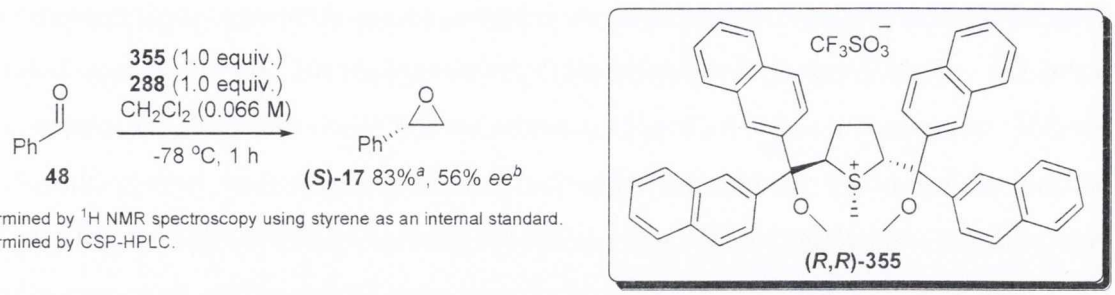
As a decrease in temperature was accompanied by an increase in enantioselectivity in epoxidation reactions promoted by **310** (Table 3.2), the subsequent aziridination reaction was performed at the lower temperature of -78 °C (entry 2, Table 4.4). To our delight, aziridine **354** was furnished in 90% yield and 18% *ee* - just 1% *ee* lower than the benchmark methodology for the synthesis of terminal aziridines *via* the CC reaction.[93]

It was also observed in related asymmetric epoxidation reactions (entry 2, Table 3.3) that a combination of both low temperature and low concentration afforded the epoxide product with the highest levels of enantioselectivity. Therefore, in an attempt to further

enhance the enantioselectivity of the aziridination process, a reaction was performed at -78 °C with a reaction concentration of 0.08 M (entry 3, Table 4.4). These conditions proved conducive to enantioselective aziridination with **354** being furnished in 72% yield and 22% *ee*. The enantioselectivity realised in this reaction is higher than that achieved following the benchmark methodology for the asymmetric synthesis of a terminal aziridine in a CC reaction involving an imine and a chiral sulfonium ylide.[93] It is also worthy of note that the benchmark protocol prescribes the use of two equivalents of chiral sulfide **87**.

4.9 Alternative C_2-symmetric sulfides for the AZ of imines *via* the CC reaction: preliminary considerations

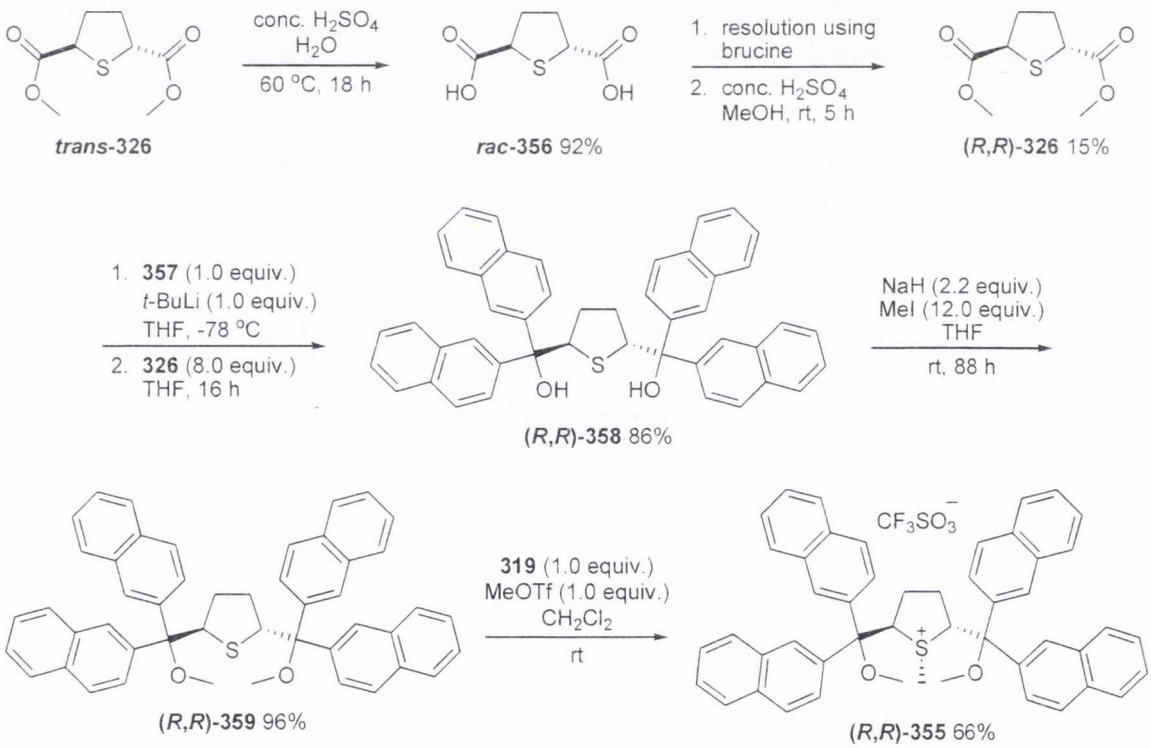
Having identified the optimum imine *N*-substituent (TPS) and the optimum conditions (entry 3, Table 4.4) for these aziridination reactions, we became interested in improving the enantioselectivity of this terminal aziridination process further by determining the optimum chiral sulfonium salt component in these reactions. In a related project aimed at the development of novel C_2-symmetric sulfides for the asymmetric synthesis of terminal epoxides, it was found that sulfonium salts with more sterically encumbered groups at the 2- and 5-positions (*e.g.* **355**) afforded styrene oxide in higher *ee* than those with less sterically demanding groups (*e.g.* **313**, which is in accordance with the proposed model in Figure 3.1, Section 3.1.8). For example, Mr. A. Piccinini discovered that in a reaction with benzaldehyde (**48**) and the 2-naphthyl analogue **355**, styrene oxide (**17**) was furnished in 56% *ee* (Scheme 4.6).



[a]Determined by ^1H NMR spectroscopy using styrene as an internal standard.
[b]Determined by CSP-HPLC.

Scheme 4.6 The asymmetric epoxidation of **48** promoted by **355** (performed by Mr. A. Piccinini)

Hoping that the same increase in enantioselectivity that was observed in epoxidation reactions would be mirrored in aziridination reactions, sulfonium salt **355** was prepared (Scheme 4.7).



Scheme 4.7 The preparation of sulfonium salt ***(R,R)*-355**

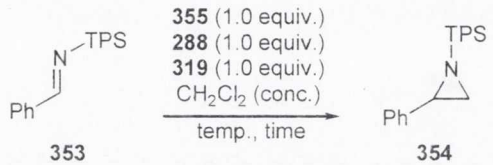
Trans*-326** was prepared as outlined in Section 3.1.10. Acid-catalysed hydrolysis of ***trans*-326** afforded tetrahydrothiophene-2,5-dicarboxylic acid (rac*-356**). Resolution of ***rac*-356** using brucine (for a detailed account of the resolution, see the experimental section), followed by treatment of the resulting dicarboxylic acid with methanol and conc. sulfuric acid afforded **(*R*,*R*)-326** (92% *ee*, the *ee* of **326** was determined by CSP-HPLC analysis).

Recrystallisation of the preceding dimethyl ester (92% *ee*) afforded enantiopure **(*R*,*R*)-326** (the *ee* of which was determined by CSP-HPLC analysis). Addition of **(*R*,*R*)-326** to a cooled solution containing 2-naphthyllithium (formed *in situ* from 2-bromonaphthalene (**357**) and *tert*-butyllithium) afforded diol **(*R*,*R*)-358** (86%). Sequential treatment of this diol with sodium hydride and iodomethane in THF furnished **(*R*,*R*)-359** (96%). Alkylation of **(*R*,*R*)-359** in methylene chloride with methyl triflate (in the presence of proton sponge **319** to circumvent the acid catalysed elimination of methanol from **(*R*,*R*)-359**) afforded sulfonium salt **(*R*,*R*)-355** (66%).

4.10 The evaluation of (*R*,*R*)-355 as a promoter of CC reactions with *N*-TPS imine 353 as substrate

Having successfully prepared the sulfonium salt **(*R*,*R*)-355**, and having identified the imine *N*-substituent affording the highest levels of enantiomeric excess in these aziridination reactions, we then wished to identify whether or not the more sterically hindered 2-naphthyl analogue **355** would induce higher levels of enantioselectivity in these reactions than the isopropyl analogue **310**. To test this hypothesis, a reaction was performed using **(*R*,*R*)-355** as the promoter and imine **353** as substrate under the same reaction conditions that were employed when achiral sulfonium salt **320** was promoter (entry 1, Table 4.5). Gratifyingly, **355** proved to be a superior enantioselective promoter than **310** under these reactions conditions, furnishing **354** in 70% yield and 25% *ee* (entry 1).

In a bid to further improve the enantioselectivity of this process, the subsequent reaction was performed under the conditions (-78 °C, 0.08 M) that afforded the highest levels of enantiomeric excess of **354** when **310** was employed as the promoter (see entry 3, Table 4.4). To our dismay, under these (formerly optimum) conditions, **354** was furnished in 15% *ee* (entry 2, Table 4.5) representing a decrease in *ee* of 10% in comparison with the preceding reaction performed at room temperature and higher concentration (entry 1, Table 4.5).



353 354

entry	conc. (M)	temp. (°C)	time (h)	conv. (%)[a]	yield (%)[b]	*ee* (%)[c]
1	0.4	rt	1.25	69	70	25
2	0.08	-78	17	69	n.d.[d]	15
3	0.01	rt	1.25	n.d.[e]	n.d.[d]	19

[a]Determined using ^{1}H NMR spectroscopy. [b]Determined by ^{1}H NMR spectroscopy using styrene as an internal standard. [c]Determined using CSP-HPLC analysis. [d]Not determined due to overlap with internal standard signal. [e]Not determined due to the dilute and unclean (*vide infra*) nature of the crude reaction mixture.

Table 4.5 The evaluation of **355** as an enantioselective promoter of CC reactions with *N*-TPS imine **353** as substrate

Hoping that a similar diminution in *ee* would not be observed, a reaction was performed at room temperature but at high dilution (0.01 M, entry 3, Table 4.5). As before, **354** was formed in lower *ee* (19%) than in the reaction performed at higher temperature and higher concentration.

4.11 A hypothesis for the anomalous results obtained in AZ reactions promoted by 355

Intrigued by our findings, investigations were performed to help explain why conditions that had previously led to an improvement in enantioselectivity in aziridination reactions when the isopropyl substituted sulfonium salt **310** was employed as the methylene source and **353** as the substrate (*i.e.* decreasing reaction temperature and concentration, see Table 4.4) subsequently led to a diminution in enantioselectivity in the same reaction when the carbinol analogue **355** was employed (see Table 4.5).

Upon closer inspection of the ^{1}H NMR spectra obtained from the crude reactions corresponding to entries 1, 2 and 3 in Table 4.5, along with recovered C_2-symmetric sulfide **359**, resonances not derived from imine **353** were detected. Three species responsible for these signals were successfully isolated from the reactions after column chromatography. Following extensive analysis using both NMR spectroscopy and HRMS, the identities of these materials were revealed (**360-362**, Figure 4.1). Each of **360-362** is derived from the decomposition of **355** (*vide infra*).

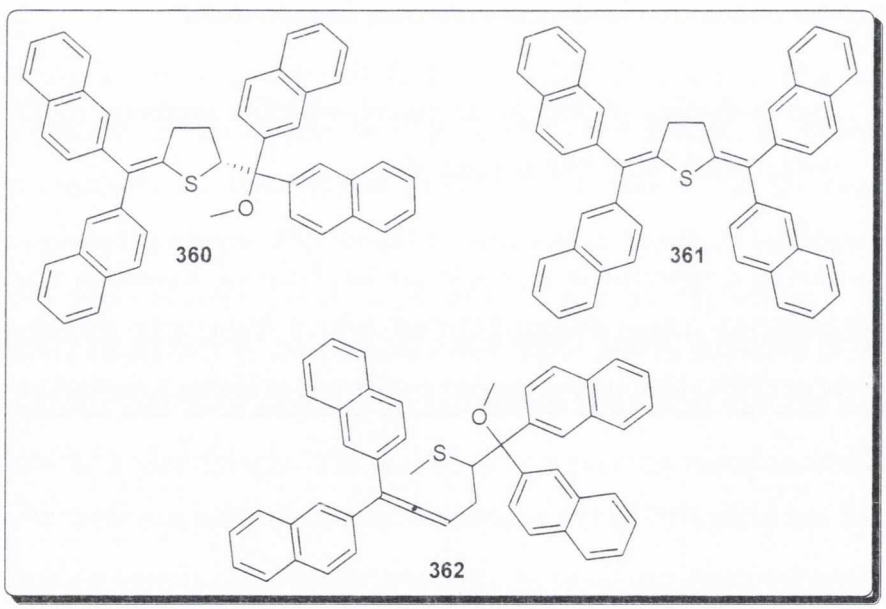


Figure 4.1 Decomposition products **360-362** derived from **355**

In related epoxidation reactions promoted by **355**, this decomposition and accompanying diminution in enantioselectivity was not observed (see Scheme 4.6). In epoxidation reactions promoted by the isopropyl analogue **310**, styrene oxide was obtained in up to 29% *ee* (entry 2, Table 3.2), whilst in epoxidation reactions promoted by **355**, styrene oxide was furnished in up to 56% *ee* (Scheme 4.6).

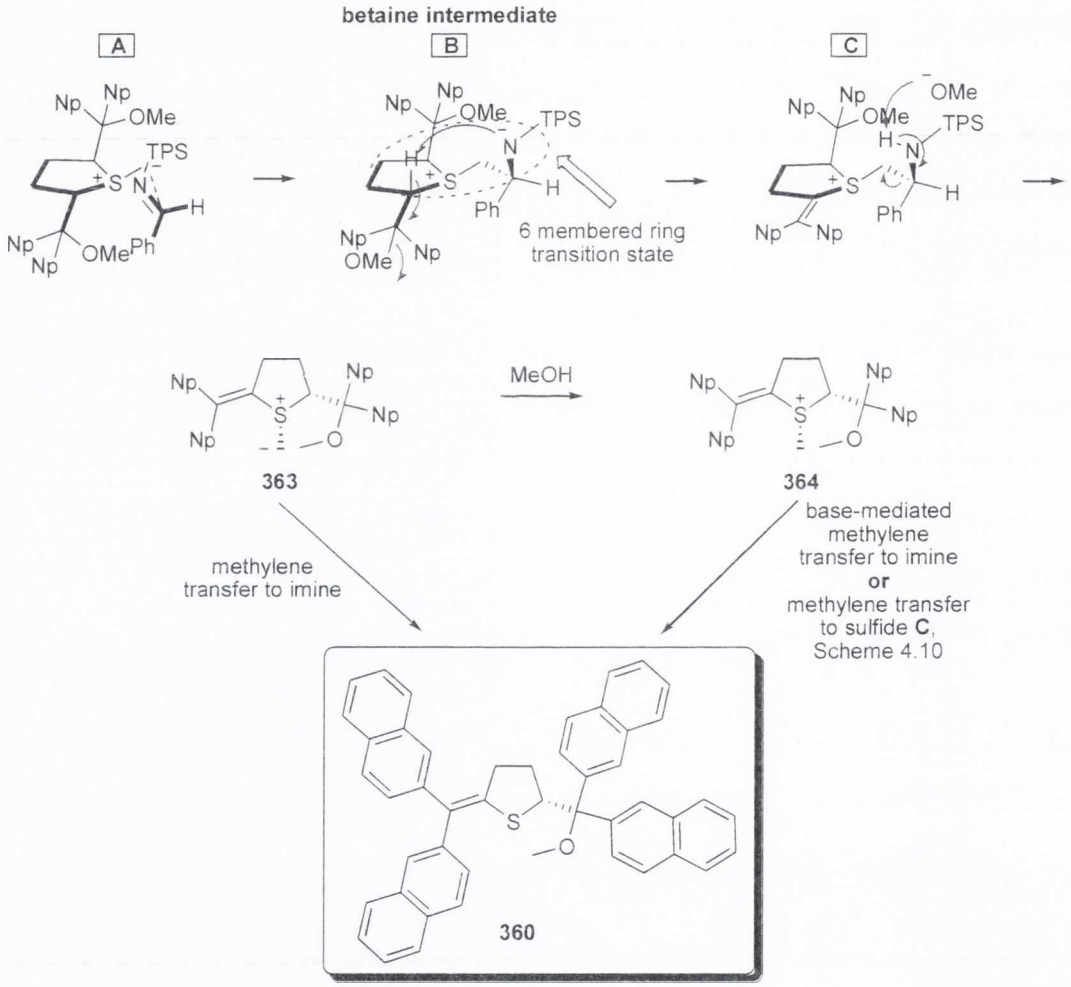
This increase in enantioselectivity was not observed in related aziridination reactions: under otherwise identical reaction conditions (-78 °C, 0.08 M), aziridine **354** was furnished in 22% *ee* in the reaction promoted by the isopropyl analogue **310** (entry 3, Table 4.4) while an *ee* of just 15% was achieved in the reaction promoted by the 2-naphthyl analogue **355** (entry 2, Table 4.5). It is noteworthy that an *ee* of 25% was achieved when a reaction promoted by **355** was performed at higher temperature and concentration (rt, 0.4 M).

This therefore led us to believe that the same levels of enantioselectivity that had been achieved in epoxidation reactions promoted by **355** were not realised in related aziridination reactions due to the ancillary mediation of the aziridination process by a decomposed variant of **355** (*i.e.* **360-362**) whereby one or both of the stereocenters had been lost prior to methylene transfer - a process that is possibly exacerbated at lower reaction temperature and concentration (see Table 4.5).

4.11.1 The fate of sulfonium salt 355: outcome 1 – the formation of sulfide 360

As *N*-sulfonyl imines are more electrophilic, and thus more reactive than their benzaldehyde counterparts,[208] decomposition of **355** must occur subsequent to the addition of the ylide to the imine. Therefore, we propose that this decomposition occurs subsequent to addition of the ylide to the imine, but prior to ring closure of the resulting betaine intermediate to the aziridine. Our hypothesis for the formation of sulfide **360** is outlined in Scheme 4.8.

Addition of the ylide to the imine occurs in the usual manner to yield the betaine intermediate (**B**, Scheme 4.8). As the negative charge on the nitrogen atom is stabilised due to the presence of the sulfonyl group, one would assume that its lifetime is longer than that of the alkoxide anion of the betaine intermediate in corresponding epoxidation reactions. The nitrogen anion now has the choice to either a) form a three membered ring (aziridine) or b) to proceed *via* a six membered ring transition state (by abstracting a proton from the carbon atom α to the sulfur atom, **B**, Scheme 4.8).



Scheme 4.8 The decomposition of **355** to **360**

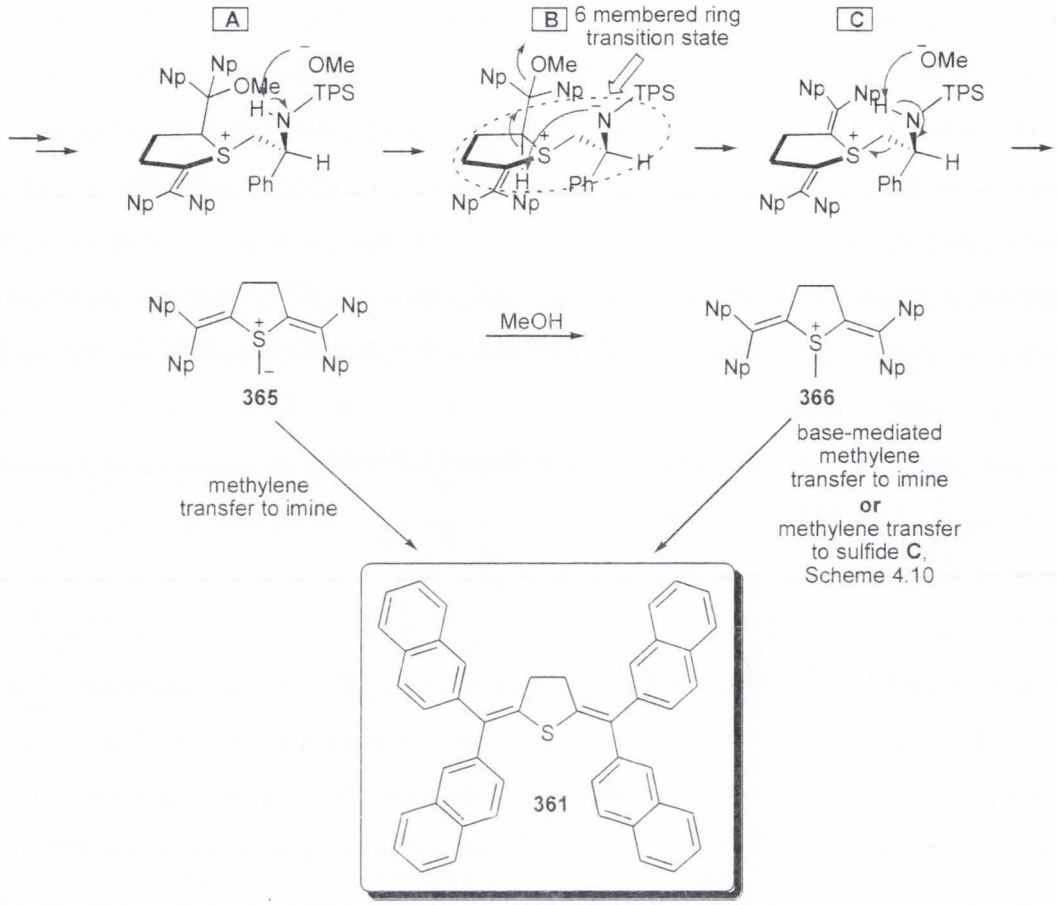
The former option a), *i.e.* formation of the aziridine, requires the formation of a strained three membered ring which, during the ring closure process, would require the *N*-TPS

group of the imine to come into close proximity with the large catalyst substituent – a factor that is not present in the epoxidation process. Undoubtedly, this reaction does occur. Evidence for this is the presence of regenerated **359** in the ^{1}H NMR spectra obtained from the crude reactions. The latter option b) involves the formation of a six membered ring transition state. As the relative rate of formation of a six membered ring is generally faster than that of a three membered (aziridine) ring,[209] it is assumed that option b) occurs (in conjunction with scenario a): intramolecular deprotonation at the carbon atom α to sulfur followed by elimination of methoxide yields **C** in Scheme 4.8. Deprotonation of the N-H bond of **C** by methoxide leads to the regeneration of imine **353** and sulfonium ylide **363**. Ylide **363** can either transfer its methylene group to an imine substrate or abstract a proton to form sulfonium salt **364**.

Treatment of **364** with P_2 base in the presence of imine **353** yielded aziridine **354** and sulfide **360**. It is worthy of note that ring closure of the betaine intermediate resulting from addition of ylide **363** to imine **353** should be more facile than ring closure of the betaine derived from the reaction of imine **353** and the ylide of sulfonium salt **355** as the newly formed C=C bond of **363** is planar, and as such the steric clash between the large imine *N*-substituent and the catalyst's large substituent should be diminished. Furthermore, in this scenario, as methylene transfer to the imine occurs after the loss of a stereocenter in sulfonium salt **355**, the enantioselectivity of this process should be decreased (as was observed in Table 4.5).

4.11.2 The fate of sulfonium salt 355: outcome 2 – the formation of sulfide 361

The initial two steps in the mechanism leading to sulfide **361** are the same as **A** and **B** outlined in Scheme 4.8 (Scheme 4.9). Deprotonation of sulfonamide **A** leads to a nitrogen anion (**B**) which deprotonates α to the sulfur atom (*via* a six membered ring) causing the subsequent elimination of methoxide. Deprotonation of sulfonamide **C** leads to the regeneration of imine **353** and sulfonium ylide **365**. The fate of ylide **365** is as described for **363** and is outlined in Scheme 4.9.

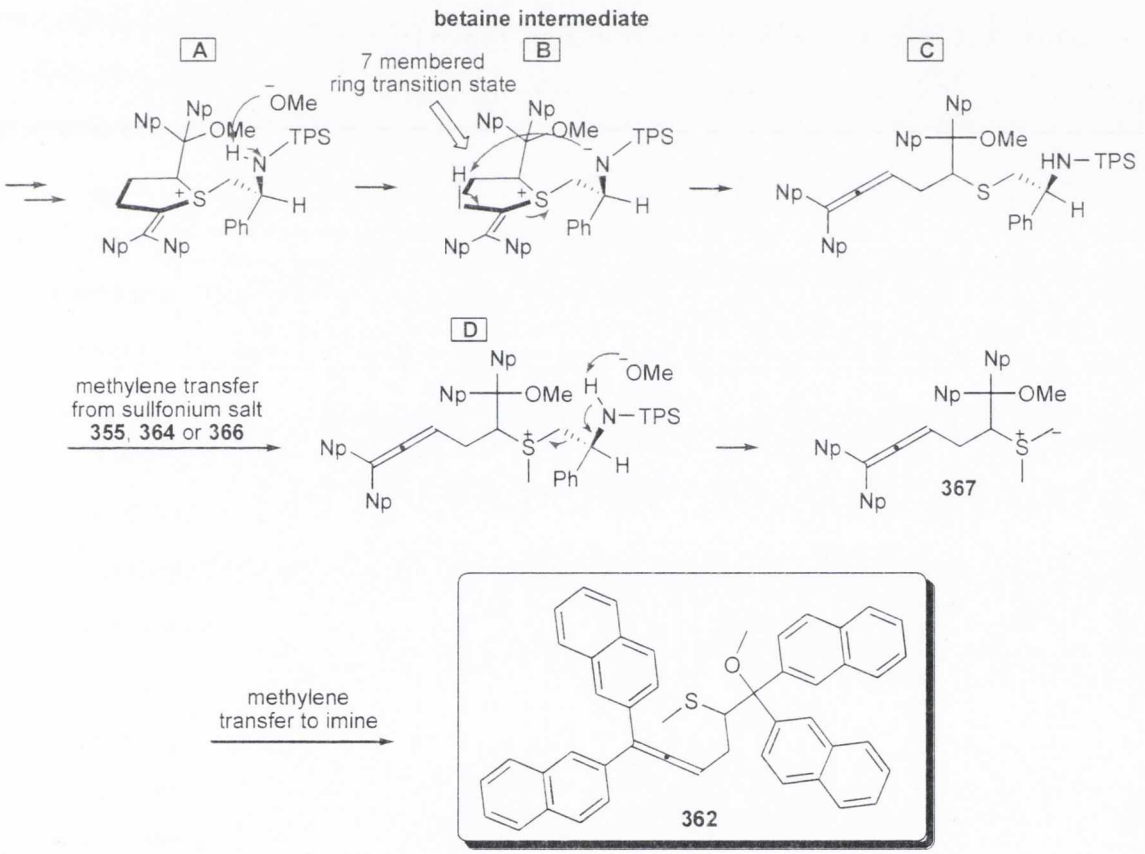


Scheme 4.9 The decomposition of **355** to **361**

As previously mentioned, due to the planar nature of the resulting C=C bonds α to sulfur, ring closure (to the product aziridine) of the betaine resulting from addition of ylide **365** to imine **353** should be more facile (from a steric encumbrance perspective) in comparison to the ring closure of betaine **B**, Scheme 4.8. As the aziridine product is ultimately derived from a methylene transfer process that has occurred *via* **365** (Scheme 4.9) where both stereocenters have been destroyed, a diminution in *ee* of the overall process should ensue (as was observed in Table 4.5).

4.11.3 The fate of sulfonium salt 355: outcome 3 – the formation of sulfide 362

Our hypothesis for the formation of sulfide **362** is outlined in Scheme 4.10. The initial steps in this mechanism are the same as steps **A** and **B** outlined in Scheme 4.8. Although the subsequent step in this decomposition process involves the formation of a seven membered ring (**B**, Scheme 4.10), the unfavourable steric interactions imminent upon ring closure of the betaine to form the three membered aziridine ring (*i.e.* between the *N*-TPS group of the imine and the large catalyst substituent) makes this pathway a viable possibility. The decreased stability of the sulfur cation due to the formation of the C=C bond also makes this process more favourable. Ring opened product **C** results.



Scheme 4.10 The decomposition of **355** to **362**

The next step in this mechanism involves methylene transfer from a sulfonium salt in solution (**355**, **364** or **366**) to sulfide **C** to yield sulfonium salt **D**. This type of methylene transfer from a sulfonium salt to a sulfide has been well documented, especially those that occur in biological systems like the sulfonium metabolite *S*-adenosyl-L-methionine.[210] Deprotonation of the sulfonamide N-H of **D** by methoxide affords regenerated imine **353** and sulfonium ylide **367** which can transfer its methylene group to an imine to yield an aziridine. Although one stereocenter α to the sulfur atom has been retained, it should not be sufficient to direct the approach of the imine.

As was the case in both Scheme 4.8 and 4.9, due to the relatively unhindered nature of the betaine intermediate that would result from addition of ylide **367** to imine **353** relative to betaine **B**, ring closure (to the product aziridine) should be facilitated as the steric clash with the large imine *N*-TPS group and the promoter would be diminished. As methylene transfer to the imine occurs after the loss of a stereocenter and C_2-symmetry (*via* **367**), a reduction in enantioselectivity of the aziridination process should result (as was observed in Table 4.5).

4.11.4 Rationale for the diminution in enantioselectivity observed: a summary

The same increase in enantioselectivity that was observed in epoxidation reactions when isopropyl analogue **310** was employed as the sulfonium salt component (up to 29% *ee*) compared to reactions that were performed when 2-naphthyl analogue **355** was employed (up to 56% *ee*) was not observed in related aziridination reactions (up to 22% *ee* using **310** and 25% *ee* using **355**).

It was also observed that conditions that led to an increase in enantioselectivity in aziridination reactions promoted by **310** with *N*-TPS imine **353** as substrate (*i.e.* lower temperature and concentration, Table 4.4) led to a diminution in *ee* in reactions promoted by sulfonium salt **355** (see Table 4.5).

The isolation of decomposition products **360-362** from the aziridination reactions promoted by **355** led us to believe that methylene transfer to the imine substrate was not only occurring *via* C_2-symmetric **355**, but that this process was also being mediated by sulfonium ylides **363** (Scheme 4.8), **365** (Scheme 4.9) and **367** (Scheme 4.10).

These decomposition products were not, however, isolated from the related epoxidation reactions. As *N*-sulfonyl imines are more electrophilic, and thus more reactive than their benzaldehyde counterparts,[208] we believe that decomposition of **355** occurs subsequent to the addition of the ylide to the imine, *i.e.* subsequent to betaine formation. We posited that due to the imminent steric clash between the large imine *N*-TPS substituent and one or both of the large catalyst substituents at the 2- and 5-positions upon ring closure of the betaine to form the strained three membered aziridine ring (a factor that is not present in the corresponding epoxidation process), the pathway involving the formation of a six membered ring, *i.e.* intramolecular deprotonation of the thiolane ring α to the sulfur atom, also occurs.

The proposed intramolecular decomposition mechanisms (Schemes 4.8-4.10) are in good agreement with the observed correlation between the decrease in both temperature and concentration and the resulting diminution in enantioselectivity (see Table 4.5). If the mechanism for this decomposition process involved an intermolecular process, at higher dilution this process should be less persistent and no diminution in *ee* should ensue. However, as a decrease in *ee* is observed at higher dilution - conditions that are conducive to intramolecular reactions - one can assume that this reaction proceeds *via* an intramolecular pathway.

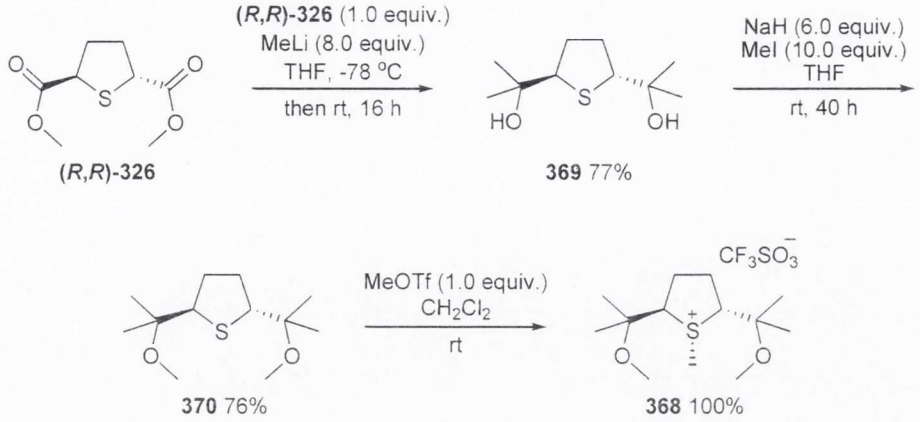
Upon depression of the reaction temperature a diminution in *ee* is observed. This diminution in *ee* is presumably due to a greater proportion of the betaine intermediate proceeding *via* the decomposition pathway at this temperature, thus leading to a greater proportion of methylene transfer to the imine substrate occurring *via* sulfonium ylides **363** (Scheme 4.8), **365** (Scheme 4.9) and **367** (Scheme 4.10).

(***N.B.*** The intermediates in the mechanisms outlined for the decomposition of sulfonium salt **355** were not detected by NMR analysis. Sulfides **360-362** were, however, detected and isolated. The mechanisms outlined in Schemes 4.8-4.10 are merely hypotheses that have been conceived in an attempt to rationalise their derivation.)

4.12 Development of the less sterically encumbered sulfonium salt 368

As previously discussed, our rationale as to the why the 2-naphthyl sulfonium salt **355** induced only marginally higher levels of enantioselectivity in aziridination reactions than did the isopropyl analogue **310**, is that methylene transfer to imine **353** occurs *via* decomposed sulfonium ylides **363** (Scheme 4.8), **365** (Scheme 4.9) and **367** (Scheme 4.10). in conjunction with the ylide of C_2-symmetric sulfonium salt **355**. We believe that decomposition of **355** occurs due to the requirement of the *N*-TPS group of the imine to come into close proximity with the large catalyst substituent during the formation of the aziridine ring from the betaine intermediate. We therefore speculated as to whether a sulfonium salt of intermediate steric bulk (with respect to the isopropyl analogue **310** and the 2-naphthyl analogue **355**) would induce higher levels of enantioselectivity in CC reactions involving imine **353** as substrate, whereby the steric interactions between the imine and catalyst would be reduced, thus eliminating the decomposition pathway.

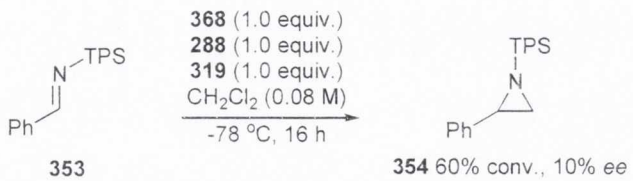
To this end, sulfonium salt **366**, which is intermediate in size and readily prepared from ***(R,R)*-326** (Scheme 4.7), was synthesised as illustrated in Scheme 4.11. Furthermore, the C=C that results from the elimination reaction that occurs during decomposition of sulfonium salt **355** is favourable as a stable conjugated system results. If the same elimination reaction were to occur in sulfonium salt **368**, a conjugated system would not result. It was therefore hoped that this elimination reaction would not be observed in aziridination reactions promoted by **368**.



Scheme 4.11 The preparation of sulfonium salt **368**

4.13 The evaluation of sulfonium salt 368 as an enantioselective promoter of the CC reaction

The evaluation of **368** as an enantioselective promoter of the CC reaction involving *N*-TPS imine **353** as substrate was performed under the conditions that were found to be optimum for the aziridination of **353** promoted by sulfonium salt **310** (see entry 3, Table 4.4). The result obtained is outlined in Scheme 4.12.



Scheme 4.12 The evaluation of sulfonium salt **368** as an enantioselective promoter of the CC reaction involving imine **353** as substrate

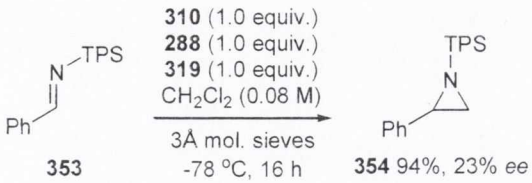
Both the isopropyl and 2-naphthyl analogues (**310** and **355** respectively) proved to be superior enantioselective promoters of this reaction as **368** furnished aziridine **354** in just 10% *ee* (Scheme 4.12). Under identical reaction conditions, **310** furnished **354** in 22% *ee* (entry 3, Table 4.4). From the ^{1}H NMR spectrum of the crude reaction mixture, the fate

of sulfonium salt **368** appeared to be similar to that of **355**: although signals associated with regenerated sulfide **370** were present, it appeared that decomposition had again occurred as signals similar to those associated with decomposed sulfide **362** were observed.

At this juncture, it seemed clear that C_2-symmetric sulfonium salts such as **355** and **368** possessing a leaving group (methoxide) were unlikely to lead to highly enantioselective aziridination protocols for the CC reaction. The hitherto highest enantiomeric excess that we achieved in an aziridination reaction was 25%, and this was achieved using **355** as promoter (entry 1, Table 4.5). An *ee* of 22% was realised in a reaction promoted by sulfonium salt **310** (entry 3, Table 4.4), which is just 3% less than was achieved in the reaction promoted by **355**. Due to the laborious (and impractically inefficient) nature of the preparation of sulfonium salt **355** (Scheme 4.7) in comparison with the preparation of sulfonium salt **310** (Scheme 3.2), all future aziridination reactions would be performed using **310** as promoter.

4.14 Yield optimisation: the elimination of deleterious water

Prior to the evaluation of substrate scope, optimisation of the reaction conditions to maximise the yield of aziridine obtained from these reactions was deemed paramount. It appears that the yield of aziridine in these reactions is inextricably linked to the stringency of the exclusion of water. Therefore, in a bid to obtain the maximum possible yield of aziridine *via* the elimination of adventitious water, a reaction was performed whereby the freshly distilled (over calcium hydride) methylene chloride solvent was initially stored over activated 3Å molecular sieves and stored under an atmosphere of argon. The required amount of methylene chloride was subsequently added *via* an oven dried syringe to the reaction vessel containing the solid reagents in addition to activated 3Å molecular sieves. The result obtained from this reaction is outlined in Scheme 4.13.

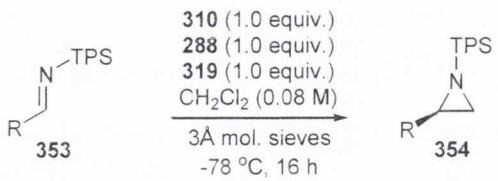


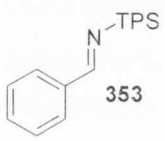
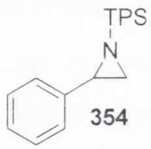
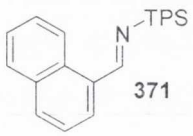
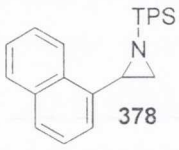
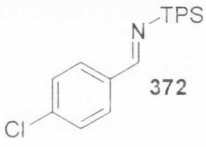
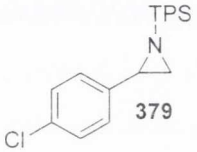
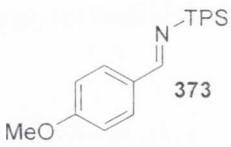
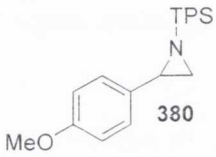
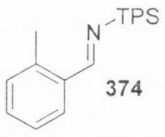
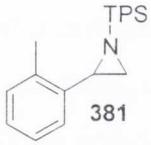
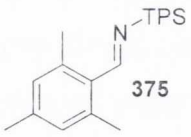
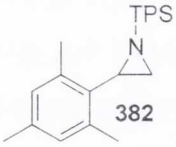
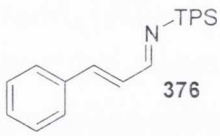
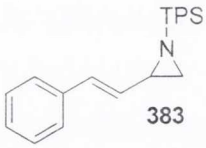
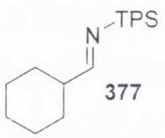
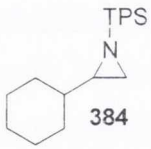
Scheme 4.13 Optimising the yield of the aziridination process

Gratifyingly, the yield of aziridine obtained from the reaction performed under these conditions (94%) involving the use of activated 3Å molecular sieves was greater than that achieved in the reaction performed under identical conditions not containing activated 3Å molecular sieves (72%, entry 3, Table 4.4). Therefore, all subsequent aziridination reactions would be performed under these stringently anhydrous conditions (*vide infra*, Table 4.6).

4.15 The evaluation of reaction scope in aziridination reactions promoted by 310

Having identified the optimum *N*-substituent, the optimum sulfonium salt promoter and the optimum conditions for these AZ reactions, we became interested in evaluating the scope of this reaction with respect to imine substrates. The results obtained are outlined in Table 4.6. We were pleased to find that our asymmetric aziridination procedure proved robust with sulfonium salt **310** promoting methylene transfer to a range of aromatic (**353** and **371-375**), aliphatic (**377**) and α,β-unsaturated imines (**376**). Aziridines derived from electron-neutral aromatic imines were furnished in excellent yield and 23% *ee* (entries 1 and 2). Aziridines derived from both electron-withdrawing and electron-deficient imines were also furnished in high yield and in 18% and 25% *ee* respectively (entries 3 and 4). More sterically hindered aromatic imines were also aziridinated to the corresponding aziridines in high yield and up to 30% *ee* (entries 5 and 6). The α,β-unsaturated imine **376** also underwent aziridination, furnishing aziridine **383** in high yield and 18% *ee* (entry 7). Aliphatic imine **377** was also aziridinated in high yield and 20% *ee* (entry 8).



Entry	Substrate	Product	Yield (%)[a]	*ee* (%)[b]
1			91	23
2			92	23
3			88	18
4			92	25
5			87	30
6			87	25
7			92	18
8			91	20

[a]Isolated yield. [b]Determined by CSP-HPLC.

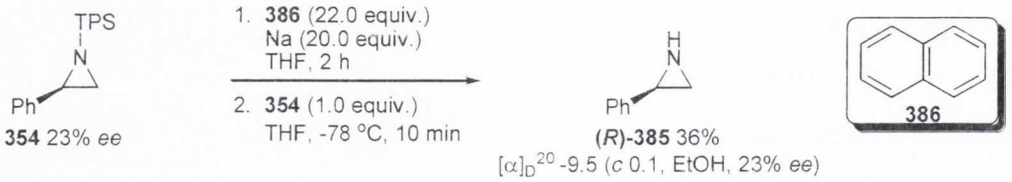
Table 4.6 The AZ of imines using sulfonium salt **310**

The enantioselectivities realised in the aziridination reactions outlined in Table 4.6 (with the exception of entries 3 and 7) are higher (by up to 11%, entry 5) than the enantioselectivity that was achieved following the benchmark literature procedure for the asymmetric synthesis of a terminal aziridine *via* a chiral sulfonium ylide.[93] The benchmark protocol requires the use of two equivalents of chiral sulfide **87** and the resulting aziridine **195** is obtained in 70% yield and just 19% *ee* (Scheme 1.63).[93] Our methodology involves the use of just one equivalent of chiral sulfonium salt **310** which furnishes the aziridine product with yields of up 92% and *ee*s of up to 30%.

4.16 The determination of configuration of *N*-TPS aziridines derived from reactions promoted by 310: the deprotection of 354

Having prepared a range of non-racemic terminal aziridines (Table 4.6), we became interested in ascertaining which enantiomer had been formed in greater abundance in these reactions. As no data regarding the terminal aziridine products (**354** and **378-384**) that result from methylene transfer to *N*-TPS imines (**353** and **371-377**) has been reported in the literature to date, we could neither rely on specific rotation nor CSP-HPLC analysis to assign the absolute configuration of the aziridine products that had been formed in greater abundance. Optical rotation data for the deprotected analogue of aziridine **354**, *i.e.* **385**, however, has been reported in the literature.[211] We therefore began investigating methods for the deprotection of *N*-2,4,6-triisopropylbenzenesulfonyl aziridines.

As there is no data in the literature regarding *N*-TPS aziridines, there are no reported methods for their deprotection. There are, however, reports detailing the deprotection of structurally related *N*-toluenesulfonyl aziridines. One such method which proved successful involved the use of sodium naphthalenide as a one-electron reductant.[212] We repeated the procedure outlined in this report: the outcome is illustrated in Scheme 4.14.



Scheme 4.14 The deprotection of **354**

To our delight, deprotection of **354** did occur, furnishing deprotected *N*-H aziridine **385** in 36% yield. It is noteworthy that the starting material for this reaction, *i.e.* **354**, was prepared *via* the procedure outlined in Table 4.6 and was formed in 23% *ee*; thus, the *ee* of deprotected aziridine **385** is also 23%.

The specific rotation of **385** was then measured (Scheme 4.14). Comparing the specific rotation obtained for **385** with the literature data, it was found that **(-)-385** possesses the (*R*)-absolute configuration.[211] It was therefore assumed that aziridines obtained from the reactions outlined in Table 4.6 were formed with a small preference for the (*R*)-enantiomer.

4.17 The stereochemical rationale for the aziridination of 353 by 310

The poor enantiocontrol that has been achieved in epoxidation reactions involving non-stabilised sulfonium ylides seems accomplished in comparison to the enantiocontrol that has been achieved in related aziridination reactions. A meagre enantiomeric excess of just 19% has been achieved following the benchmark literature protocol for the preparation of terminal aziridines *via* the CC reaction, and two equivalents of chiral sulfide were required to achieve this inadequate result.[93] We have developed a method for this transformation in which an *ee* of up to 30% can be achieved using just one equivalent of a chiral sulfonium ylide (entry 5, Table 4.6). Although this is an improvement, it does not represent a system that is under stringent control. Nonetheless, this system is under some control as one enantiomer of aziridine (*R*) is formed in a greater amount than the other.

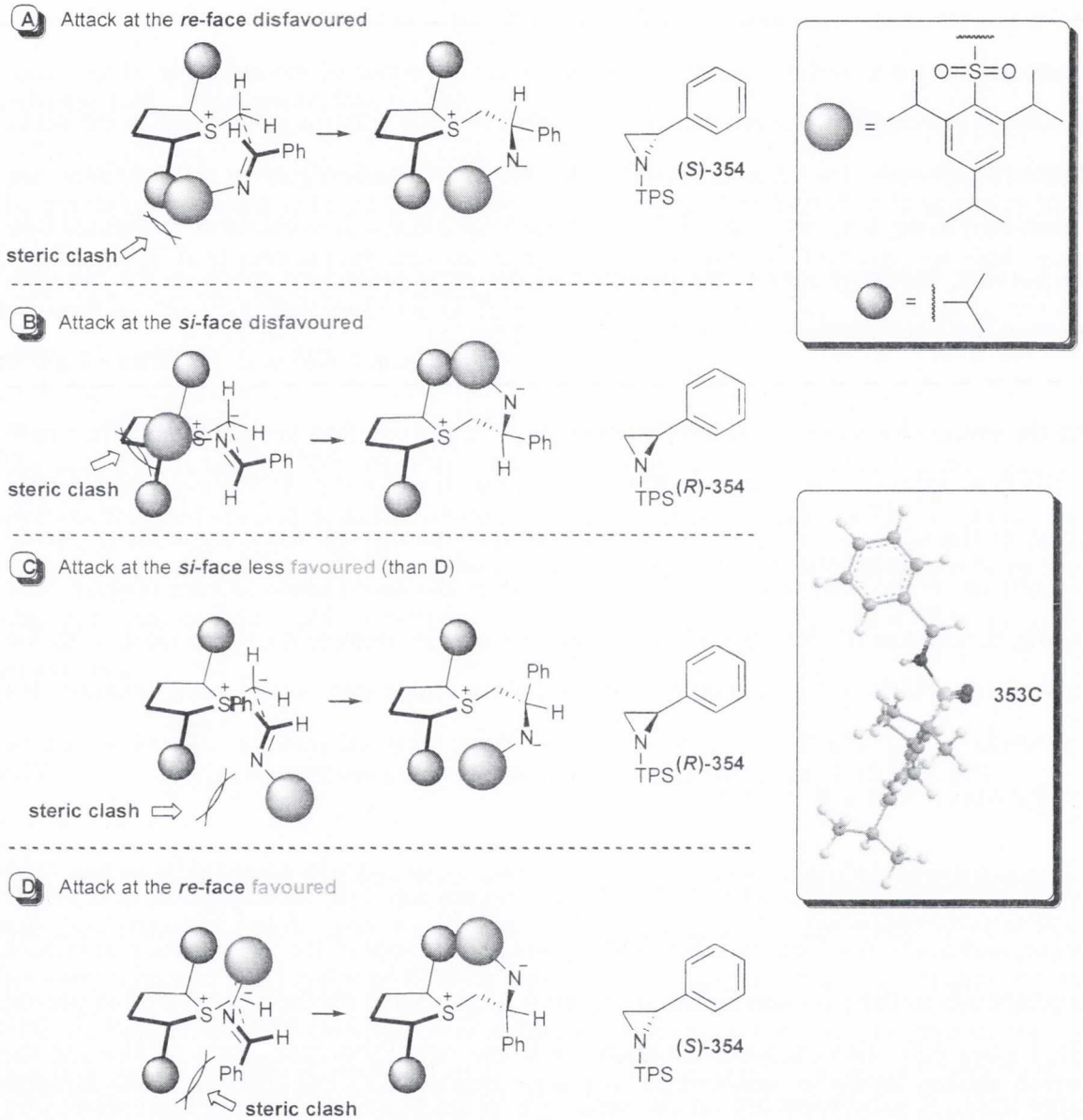
Figure 4.2 is a depiction of our hypothesis regarding the stereochemical outcome of these reactions.

As was previously mentioned in Section 3.1.8, we assume that the imine is likely to approach the ylide in the manner described for the approach of the aldehyde to the ylide in related epoxidation reactions *i.e.* a) it avoids the large catalyst substituent to the back, directed upwards (as drawn, **A-D**), b) charge separation/*gauche* interactions are minimised in the transition state and c) that the large aldehydic substituent is directed into the solvent. However, due to the presence of the large protecting group on the nitrogen atom of the imine substrate, c) no longer holds true.

As the imine (*E*)-isomer is generally preferred,[213] there are four possible ways the imine is likely to approach the ylide (**A-D**, Figure 4.2) with either the aldehyde-derived phenyl group or the imine *N*-TPS group being directed into the solvent. Contrary to the preferred orientation of the phenyl group of the aldehyde in the epoxidation system (Figure 3.1), owing to the size of the aziridine *N*-substituent and its impending steric clash with the sulfonium ylide's large substituent (isopropyl in this case), one would assume that approaches involving the large *N*-TPS group being directed into the solvent would be preferred (*i.e.* **C** and **D**, Figure 4.2).

As imine **353** is aziridinated in 23% *ee* by sulfonium salt **310**, both approaches **C** and **D** occur, and as the resulting aziridine **354** is formed in favour of the (*R*)-enantiomer (which corresponds to the (*S*)-enantiomer in Figure 4.2, see ***N.B.***) *Re*-facial attack must prevail (**D**, Figure 4.2). This outcome is logical: in **C** the large isopropyl group of **310** and the large imine *N*-substituent are on the same side of the ylide and suffer a steric clash (see the energy minimised (MM2) imine **353C** for a true representation of the magnitude of the TPS group). Approach **D** suffers the least significant steric clash as the large isopropyl group of **310** (furthest from the reader, as drawn) and the large imine *N*-TPS group are on opposite sides of the ylide. Furthermore, the large isopropyl group of **310** (nearest the reader, as drawn) and the large imine *N*-TPS group avoid one another;

however, the steric clash involving the phenyl group of the imine and the isopropyl group of **310** is also a factor, leading to poor discrimination and thus poor enantioselectivity.



N.B. The conformation of the isopropyl salt **310** employed as promoter in the reactions outlined in Table 4.4 is (*R*,*R*). This yielded (*R*)-aziridines (see Scheme 4.14).
In the above Figure, for ease of illustration, the conformation of the promoter is (*S*,*S*) and should therefore yield (*S*)-aziridine products.

Figure 4.2 Our hypothesis for the stereochemical outcome of aziridination reactions

4.18 Conclusion: Chapter 4

We have established that 'activated' imines, *i.e.* imines that have an electron withdrawing group on their nitrogen atom, *i.e.* *N*-Ts, *N*-DPP, and *N*-TPS (**184**, **344** and **353** respectively), afford the highest yields of aziridine products in CC reactions performed according to our methodology (Tables 4.2 and 4.5). Of these variously *N*-substituted imine substrates, the best combination of both product yield and *ee* was achieved when the TPS group was employed as *N*-substituent (entry 3, Table 4.4).

Sulfonium salt **310** was found to be the optimum (of those evaluated) enantioselective promoter of these reactions. Our attempts to improve the enantioselectivity of aziridination reactions by employing the more sterically hindered sulfonium salt **355** failed. This was due to the propensity of **355** to undergo undesired elimination reactions in favour of aziridination reactions, leading to the mediation of the methylene transfer process by decomposed sulfonium ylides **363**, **365** and **367**. This in turn had a detrimental effect on the enantioselectivities of these reactions.

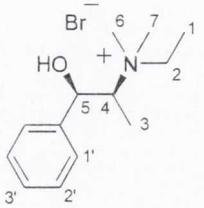
Our asymmetric aziridination procedure proved robust, with sulfonium salt **310** efficiently promoting enantioselective methylene transfer to a range of aromatic, aliphatic and α,β-unsaturated imines (Table 4.6). The enantioselectivities achievable following our methodology are higher (by up to 11%, entry 5, Table 4.6) than the enantioselectivity that was realised following the benchmark literature procedure for the asymmetric synthesis of a terminal aziridine *via* a chiral sulfonium ylide.[93] The benchmark protocol requires the use of two equivalents of chiral sulfide **87**, whilst our methodology requires the use of just one equivalent of chiral sulfonium salt **310** which furnishes the aziridine products in both higher yields and enantiomeric excesses. Although poor levels of enantiocontrol are achieved in these reactions, we have advanced a hypothesis to account for the stereochemical outcome of these reactions (Figure 4.2).

5.1 General experimental data

Proton Nuclear Magnetic Resonance spectra were recorded on a Bruker Avance 400 or 600 MHz spectrometer in $CDCl_3$ referenced relative to residual $CHCl_3$ (δ = 7.26 ppm) or DMSO-d_6 referenced relative to residual DMSO-d_6 (δ = 2.50 ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. Carbon NMR spectra were recorded on the same instruments (100 or 150 MHz) with total proton decoupling. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum One spectrophotometer. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualised by UV irradiation, $KMnO_4$, phosphomolybdic acid, or anisaldehyde staining. Specific rotation measurements were made on a Rudolph research analytical Autopol IV instrument, and are quoted in units of $10^{-1}degcm^2g^{-1}$. Anhydrous THF was distilled over sodium-benzophenone ketyl radical before use. Methylene chloride, toluene and triethylamine were distilled from calcium hydride. All reactions were carried out under a protective argon atmosphere. Analytical CSP-HPLC was performed on Daicel CHIRALCEL OD (4.6 mm x 25 cm), CHIRALCEL OD-H (4.6 mm x 25 cm), CHIRALCEL OJ-H (4.6 mm x 25 cm), CHIRALPAK AD-H (4.6 mm x 25 cm) and CHIRALPAK AS (4.6 mm x 25 cm) columns. Solid reagents for all catalysed reactions were weighed using a Precisa balance, series 320XR, model XR125SM-FR (readability 0.01 mg/0.1 mg). For all known compounds the spectral characteristics were in agreement with those reported in the literature.

5.2 Experimental data for Chapter 2

5.2.1 (1*R*,2*S*)-(-)-*N*-Ethyl-*N*,*N*-dimethylephedrinium bromide (232)



A 10 cm^3 round bottomed flask was charged with (1*R*,2*S*)-(-)-*N*-methylephedrine (1.0 g, 5.58 mmol). The flask was fitted with a rubber septum and placed under an atmosphere of argon (balloon). THF (5 cm^3) was added *via* syringe, followed by bromoethane (416 μL, 5.58 mmol). The reaction was allowed to stir at ambient temperature for 96 h. The precipitated salt was filtered, washed with hexane, followed by CH_2Cl_2 and dried under high vacuum to yield **(1*R*,2*S*)-232** (1.576 g, 98%) as a white solid. M.p. 189-191 °C. $[\alpha]_D^{20} = -16.2$ (*c* 2.45, H_2O).

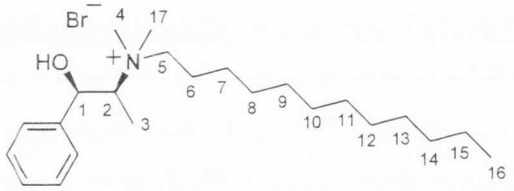
δ_H (400 MHz, $(CD_3)_2SO$): 1.11 (d, J 6.6, 3H, H-3), 1.32 (t, J 7.1, 3H, H-1), 3.12 (s, 3H, H-6), 3.19 (s, 3H, H-7), 3.48-3.56 (m, 1H, H-2a), 3.59-3.67 (m, 2H, H-2b and H-4), 5.46 (app. d, 1H, H-5), 6.07 (d, J 4.6, 1H, OH), 7.30 (t, J 7.3, 1H, H-3'), 7.40 (app. t, 2H, H-2'), 7.45 (d, J 7.3, 2H, H-1').

δ_C (100 MHz, $(CD_3)_2SO$): 6.5, 8.1, 48.0, 48.2, 58.1, 68.1, 71.9, 125.9, 127.4, 128.2, 142.1 (q).

υ (cm^{-1}): 717, 771, 1011, 1042, 1447, 1478, 3012, 3212 (O-H).

HRMS (ESI): $[M+H]^+$ Calcd. for $C_{13}H_{22}NO$ 208.1701; found 208.1706.

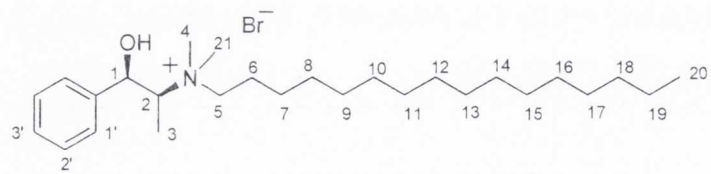
5.2.2 (1*R*,2*S*)-*N*-Dodecyl-*N*,*N*-dimethyl ephedrine bromide (233)



A 10 cm^3 round bottomed flask was charged with (1*R*,2*S*)-(−)-*N*-methylephedrine (300 mg, 1.67 mmol). 1-Bromododecane (401 μL, 1.67 mmol) was subsequently added *via* warm syringe and the reaction was stirred at 100 °C for 24 h. The crude product was purified by recrystallisation (CH_2Cl_2:hexane) to afford **(1*R*,2*S*)-233** (658 mg, 92%) as a light brown solid. M.p. 88-89 °C; lit.,[178] 88-89 °C. $[\alpha]_D^{20}$ = -11.0 (*c* 0.14, EtOH); lit.,[178] $[\alpha]_D^{20}$ = -11.4 (EtOH). The NMR spectra of **233** were consistent with those previously reported.[214]

δ_H (600 MHz, D_2O): 0.82 (t, J 7.1, 3H, H-16), 1.19-1.30 (m, 17H, H-3 and H-9, H-10, H-11, H-12, H-13, H-14 and H-15), 1.36 (br s, 4H, H-7 and H-8), 1.77-1.84 (m, 2H, H-6), 3.15 (s, 3H, H-4), 3.22 (s, 3H, H-17), 3.41-3.46 (m, 1H, H-5a), 3.51-3.56 (m, 1H, H-5b), 3.66 (m, 1H, H-2), 5.57 (app. s, 1H, H-1), 7.37-7.41 (m, 5H, H-Aryl).

5.2.3 (1*R*,2*S*)-*N*-Hexadecyl-*N*,*N*-dimethyl ephedrine bromide (234)



A 10 cm^3 round bottomed flask was charged with (1*R*,2*S*)-(-)-*N*-methylephedrine (1.000 g, 5.58 mmol). 1-Bromohexadecane (1.71 cm^3, 5.58 mmol) was subsequently added *via* warm syringe and the reaction was stirred at 100 °C for 24 h. The crude product was

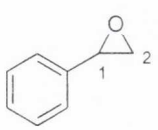
purified by recrystallisation (CH_2Cl_2:hexane) to afford **(1*R*,2*S*)-234** (2.463 g, 94%) as a white solid. M.p. 112-113 °C; lit.,[178] 112-113 °C. $[\alpha]_D^{20}$ = -9.5 (*c* 0.07, EtOH); lit.,[178] $[\alpha]_D^{20}$ = -9.1 (EtOH). The NMR spectra of **234** were consistent with those previously reported.[215]

δ_H (400 MHz, $CDCl_3$): 0.88 (t, J 6.9, 3H, H-20), 1.19 (d, J 6.4, 3H, H-3), 1.23-1.45 (m, 26H, H-7, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15, H-16, H-17, H-18 and H-19), 1.61-1.84 (br m, 2H, H-6), 3.34 (s, 3H, H-4), 3.48-3.54 (m, 1H, H-5a), 3.52 (s, 3H, H-21), 3.64 (m, 1H, H-2), 3.81-3.90 (m, 1H, H-5b), 5.46-5.54 (br m, 1H, OH), 5.81 (app. s, 1H, H-1), 7.26 (t, J 7.3, 1H, H-3'), 7.35 (app. t, 2H, H-2'), 7.51 (d, J 7.7, 2H, H-1').

5.2.4 General procedure A: the epoxidation of benzaldehyde (48) by 232, 233 and 234 (Table 2.1)

A carousel flask (*vide supra*) containing a magnetic stirring bar was charged with trimethylsulfonium iodide (1.1 equiv.) followed by 50% NaOH/H_2O solution *via* syringe. (*E*)-Stilbene (0.5 equiv.) and **232**, **233** or **234** (0.2 equiv.) were then added, the flask was fitted with a cap and placed under an atmosphere of argon (balloon). CH_2Cl_2 and freshly distilled benzaldehyde (1.0 equiv.) were then added sequentially *via* syringe and the reaction was stirred at 38 °C for 48 h. The crude material was purified by flash chromatography.

5.2.4.1 Styrene oxide (17)



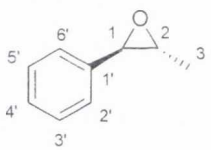
Prepared according to general procedure A using **48** (100 μL, 0.984 mmol), trimethylsulfonium iodide (224.89 mg, 1.102 mmol), **234** (92.41 mg, 0.197 mmol), (*E*)-

stilbene (88.66 mg, 0.492 mmol), 50% $NaOH/H_2O$ solution (3.67 g/3.67 cm^3, 91.75 mmol) and CH_2Cl_2 (3.67 cm^3). Purification of the crude material by flash chromatography (7:3 hexane:CH_2Cl_2) afforded styrene oxide (**17**) as a pale yellow liquid (78%, the yield was determined by ^1H NMR spectroscopy using (*E*)-stilbene as an internal standard).The NMR spectra of **17** were consistent with those previously reported.[216]

δ_H (400 MHz, $CDCl_3$): 2.81 (dd, J 2.7, 5.5, 1H, H-2a), 3.16 (dd, J 4.2, 5.5, 1H, H-2b), 3.87 (dd, J 2.7, 4.2, 1H, H-1), 7.27-7.38 (m, 5H, H-Ar).

HRMS (ESI): $[M+H]^+$ Calcd. for C_8H_9O 121.0653; found 121.0659.

5.2.5 (1*R*,2*R*)-1,2-Epoxy-1-phenyl-propane (235)



A 100 cm^3 round bottomed flask was charged with 50% $NaOH/H_2O$ solution (794 mmol, 467 equiv.) *via* syringe. **234** (800 mg, 1.70 mmol) Was then added to the flask followed by CH_2Cl_2 (31.8 cm^3) *via* syringe. The reaction was stirred at 50 °C under reflux for 38 h. The reaction mixture was then diluted with water (20 cm^3) and extracted with CH_2Cl_2 (4 x 50 cm^3). The organic extracts were combined and washed with brine (50 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by column chromatography (7:3 hexane:CH_2Cl_2, 5% triethylamine) to afford **(1*R*,2*R*)-235** (224 mg, 98%) as a colourless oil. $[\alpha]_D^{20}$ = +64.6 (*c* 0.71, acetone); lit.,[180] $[\alpha]_D^{25}$ = +71.8 (*c* 1.546, acetone). The NMR spectra of **235** were consistent with those previously reported.[217]

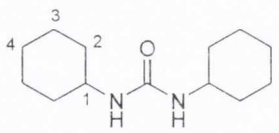
δ_H (400 MHz, $CDCl_3$): 1.48 (d, J 5.2, 3H, H-3), 3.05 (qd, J 5.2, 2.1, 1H, H-2), 3.60 (d, J 2.1, 1H, H-1), 7.28-7.30 (m, 5H, H-Aryl).

δ_C (100 MHz, $CDCl_3$): 17.5, 58.6, 59.1, 125.1, 127.6, 128.0, 137.3 (q).

5.2.6 General procedure B: the synthesis of symmetrical urea catalysts 217 and 242-249 (Table 2.5)

An oven dried 50 cm^3 round bottomed flask was charged with 1,1-carbonyldiimidazole (500 mg, 3.084 mmol). The flask was fitted with a rubber septum and placed under an atmosphere of argon (balloon). CH_2Cl_2 (15 cm^3) Was then added *via* syringe and the mixture was stirred until 1,1-carbonyldiimidazole dissolved. The appropriate primary amine (6.476 mmol) was then added *via* syringe and the resulting solution was stirred at ambient temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2:hexane and the precipitate was filtered to afford the crude product, which was purified by recrystallisation from the appropriate solvents to yield the corresponding pure symmetrical urea. (Thio)ureas **239** and **240** were readily available within the group.

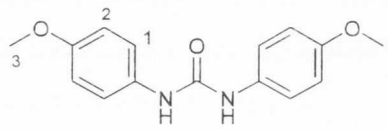
5.2.6.1 *N,N'*-Dicyclohexylurea (246)



Prepared according to general procedure B using cyclohexylamine (741 μL, 6.476 mmol). The crude product was purified by recrystallisation from ethanol to yield **246** (590 mg, 86%) as colourless crystals. M.p. 236-237 °C; lit.,[218] 235-236 °C. The NMR spectra of **246** were consistent with those previously reported.[218]

δ_H (600 MHz, $CDCl_3$): 1.10-1.19 (m, 6H, H-2a and H-4a), 1.32-1.38 (m, 4H, H-3a), 1.59-1.61 (m, 2H, H-4b), 1.69-1.72 (m, 4H, H-3b), 1.93 (app. d, 4H, H-2b).

5.2.6.2 *N,N'-bis*-(*p*-Methoxyphenyl)urea (247)

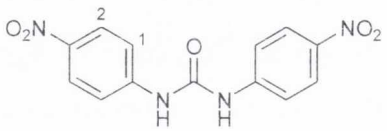


Prepared according to general procedure B using *p*-anisidine (544 mg, 6.476 mmol). The crude product was purified by recrystallisation from acetone to yield **247** (366 mg, 44%) as a white solid. M.p. 241-243 °C; lit.,[159b] 240-241 °C. The NMR spectra of **247** were consistent with those previously reported.[159b]

δ_H (400 MHz, $(CD_3)_2SO$): 3.71 (s, 6H, H-3), 6.85 (d, J 9.0, 4H, H-2), 7.33 (d, J 9.0, 4H, H-1), 8.39 (s, 2H, NH).

δ_C (150 MHz, $(CD_3)_2SO$): 55.1, 113.9, 119.9, 132.9 (q), 152.9 (C=O), 154.3 (q).

5.2.6.3 *N,N'-bis*-(*p*-Nitrophenyl)urea (248)

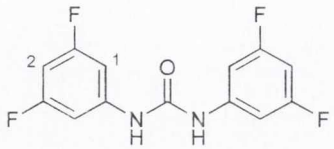


Prepared according to general procedure B using *p*-nitroaniline (894 mg, 6.476 mmol). The crude product was purified by recrystallisation from ethanol to yield **248** (1.037 g, 53%) as a yellow solid. M.p. 307-309 °C; lit.,[159b] >300 °C. The NMR spectra of **248** were consistent with those previously reported.[159b]

δ_H (600 MHz, $(CD_3)_2SO$): 7.73 (d, J 9.0, 4H, H-1), 8.19 (d, J 9.0, 4H, H-2), 9.80 (br s, 2H, NH).

δ_C (150 MHz, $(CD_3)_2SO$): 118.3, 125.4, 141.4, 147.0, 152.8 (C=O).

5.2.6.4 *N,N'-bis*-(3,5-Difluoro-phenyl)-urea (249)



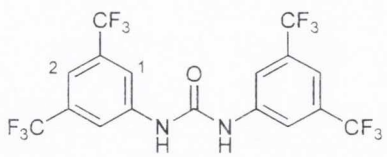
Prepared according to procedure B using 3,5-difluoroaniline (836 mg, 6.476 mmol). The crude product was purified by recrystallisation from EtOAc:hexane to yield **249** (553 mg, 53%) as white crystals. M.p. 210-212 °C; lit.,[195] 210 °C. The NMR spectra of **249** were consistent with those previously reported.[195]

δ_H (400 MHz, $(CD_3)_2SO$): 6.83 (t, J 9.3, 2H, H-2), 7.19 (d, J 7.8, 4H, H-1), 9.27 (br s, 2H, NH).

δ_C (100 MHz, $(CD_3)_2SO$): 97.2 (t, J 26.0), 101.3 (d, J 29.2), 142.0 (t, J 14.2), 152.0 (C=O), 162.6 (dd, J 241.2, 15.5).

δ_F (100 MHz, $(CD_3)_2SO$): -110.1 (s, 4F).

5.2.6.5 *N,N'-bis*-(3,5-*bis*-Trifluoromethyl-phenyl)urea (242)



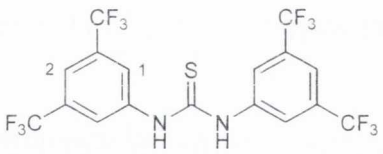
An oven dried 100 cm^3 round bottomed flask was charged with 1,1-carbonyldiimidazole (1.000 g, 6.167 mmol). The flask was fitted with a rubber septum and placed under an atmosphere of argon (balloon). CH_2Cl_2 (30 cm^3) was then added *via* syringe and the

reaction was stirred until 1,1-carboxylimidazole dissolved. 3,5-*bis*-(Trifluoromethyl)aniline (12.951 mmol) was then added *via* syringe and the reaction was stirred at ambient temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2:hexane and the precipitate was filtered to afford the crude product, which was purified by recrystallisation from EtOAc:hexane to yield **242** (1.286 g, 43%) as a white solid. M.p. 241-242 °C; lit.,[165] 240-242 °C. The NMR spectra of **242** were consistent with those previously reported.[165]

δ_H (600 MHz, $CDCl_3$): 7.63 (s, 2H, H-2), 7.98 (s, 4H, H-1).

δ_F (100 MHz, $(CD_3)_2SO$): -62.1 (s, 12F).

5.2.6.6 *N,N'-bis*-(3,5-*bis*-Trifluoromethyl-phenyl)thiourea (217)



An oven dried 25 cm^3 round bottomed flask was charged with 1,1'-thiocarbonyldiimidazole (300 mg, 1.683 mmol). The flask was fitted with a rubber septum and placed under an atmosphere of argon (balloon). CH_2Cl_2 (9 cm^3) was then added *via* syringe and the reaction was stirred until 1,1'-thiocarbonyldiimidazole dissolved. 3,5-*bis*-(Trifluoromethyl)aniline (548 μL, 3.535 mmol) was then added *via* syringe and the reaction was stirred at ambient temperature for 16 h. The crude reaction mixture was concentrated *in vacuo* and the crude residue was purified by column chromatography (6:4 CH_2Cl_2:hexane) to yield **217** (522 mg, 62%) as a white solid. M.p. 179-180 °C; lit.,[219] 180-181 °C. The NMR spectra of **217** were consistent with those previously reported.[219]

δ_H (400 MHz, $(CD_3)_2SO$): 7.87 (s, 2H, H-2), 8.21 (s, 4H, H-1), 10.64 (s, 2H, NH).

5.2.7 General procedure C: (thio)urea derivatives 217, 239, 240 and 242-249 as catalysts in the epoxidation of 48 (Table 2.5)

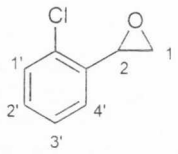
Note: These reactions must be carried out under rigorously identical conditions (flask- and stirring bar size, stirring rate and temperature) to achieve reproducible results.

The carousel flasks (*vide supra*) containing a magnetic stirring bar were placed on the carousel. Trimethylsulfonium iodide (165.7 mg, 0.81 mmol) was added to each flask. 50% $NaOH/H_2O$ solution (1.77 cm^3, 44.3 mmol) was then added *via* syringe and the resulting suspension was allowed to stir for 10 min. (*E*)-Stilbene (66.5 mg, 0.37 mmol) and catalyst (0.037 mmol) were then added and the flask was fitted with a cap and placed under an atmosphere of argon (balloon). CH_2Cl_2 (2.175 cm^3) and freshly distilled aldehyde (0.74 mmol) were then added sequentially *via* syringe and the reaction stirred at ambient temperature for 24 h.

5.2.8 General procedure D: the synthesis of epoxides 17 and 256-263 catalysed by 242 (Table 2.6)

An oven dried 50 cm^3 round bottomed flask was charged with trimethylsulfonium iodide (828.32 mg, 4.059 mmol) followed by addition of 50% $NaOH/H_2O$ solution (8.856 cm^3, 221.4 mmol) *via* syringe. **242** (89.34 mg, 0.185 mmol) Was then added and the flask was fitted with a septum and placed under an atmosphere of argon (balloon). CH_2Cl_2 (10.9 cm^3) and freshly distilled aldehyde (3.69 mmol) were then added sequentially *via* syringe and the reaction stirred at ambient temperature until complete (TLC). The reaction mixture was diluted with water (5 cm^3) and extracted with CH_2Cl_2 (4 x 30 cm^3). The organic extracts were combined and washed with brine (20 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by column chromatography.

5.2.8.1 *ortho*-Chlorostyrene oxide (256)



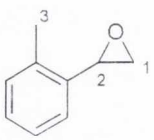
Prepared according to general procedure D using **250** (416 μL, 3.69 mmol). After work-up, flash chromatography (6:4 hexane:CH_2Cl_2) yielded **256** (531 mg, 93%) as a yellow oil. The NMR spectra of **256** were consistent with those previously reported.[220]

δ_H (400 MHz, $CDCl_3$): 2.67 (dd, J 5.6, 2.4, 1H, H-1a), 3.20 (dd, J 5.6, 3.9, 1H, H-1b), 4.22 (dd, J 3.9, 2.4, 1H, H-2), 7.21-7.27 (m, 3H, H-2', H-3' and H-4'), 7.34-7.38 (m, 1H, H-1').

δ_C (100 MHz, $CDCl_3$): 49.6, 50.3, 125.2, 126.6, 128.5, 128.7, 132.8 (q), 135.2 (q).

HRMS (EI): $[M]^+$ calcd. for C_8H_7ClO 154.0185; found 154.0191.

5.2.8.2 *ortho*-Methylstyrene oxide (258)



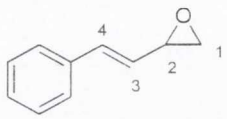
Prepared according to general procedure D using **251** (427 μL, 3.69 mmol). After work-up, flash chromatography (9.5:0.5 hexane: EtOAc, 4% triethylamine) yielded **258** (476 mg, 96%) as a yellow oil. The NMR spectra of **258** were consistent with those previously reported.[221]

δ_H (400 MHz, $CDCl_3$): 2.45 (s, 3H, H-3), 2.71 (dd, J 5.7, 2.8, 1H, H-1a), 3.18 (dd, J 5.7, 4.0, 1H, H-1b), 4.02 (dd, J 4.0, 2.8, 1H, H-2), 7.19 (m, 4H, H-Aryl).

δ_C (100 MHz, $CDCl_3$): 18.3, 49.7, 50.0, 123.6, 125.7, 127.2, 129.4, 135.4 (q), 135.7 (q).

HRMS (EI): $[M]^+$ calcd. for $C_9H_{10}O$ 134.0732; found 134.0734.

5.2.8.3 2-((*E*)-Styryl-oxirane) (261)



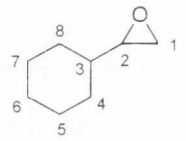
Prepared according to general procedure D using **254** (465 μL, 3.69 mmol). After work-up, flash chromatography (7:3 EtOAc:hexane, 4% triethylamine) yielded **261** (490 mg, 91%) as a yellow oil. The NMR spectra of **261** were consistent with those previously reported.[222]

δ_H (400 MHz, $CDCl_3$): 2.80 (dd, J 5.1, 2.6, 1H, H-1a), 3.08 (app. t, 1H, H-1b), 3.54 (m, 1H, H-2), 5.88 (dd, J 16.0, 8.0, 1H, H-3), 6.83 (d, J 16.0, 1H, H-4), 7.29-7.42 (m, 5H, H-Aryl).

δ_C (100 MHz, $CDCl_3$): 48.8, 52.2, 126.0, 126.5, 127.6, 128.2, 134.2, 135.6 (q).

HRMS (EI): $[M]^+$ calcd. for $C_{10}H_{10}O$ 146.0732; found 146.0732.

5.2.8.4 2-Cyclohexyloxirane (262)



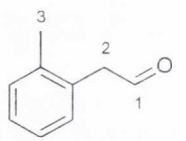
Prepared according to general procedure D using **72** (447 μL, 3.69 mmol). After work-up, flash chromatography (6:4 hexane:CH_2Cl_2) yielded **262** (425 mg, 91%) as a yellow oil. The NMR spectra of **262** were consistent with those previously reported.[223]

δ_H (400 MHz, $CDCl_3$): 1.07-1.32 (m, 6H, H-3, H-4a, H-5a, H-6a, H-7a and H-8a), 1.68-1.72 (m, 2H, H-6b and H-8b), 1.76-1.80 (m, 2H, H-5b and H-7b), 1.89-1.92 (m, 1H, H-4b), 2.55 (dd, J 4.4, 3.8, 1H, H-1b), 2.72-2.76 (m, 2H, H-2 and H-1a).

δ_C (100 MHz, $CDCl_3$): 25.1, 25.2, 25.9, 28.4, 29.3, 40.0, 45.6, 56.3.

HRMS (EI): $[M]^+$ calcd. for $C_8H_{14}O$ 126.1045; found 126.1041.

5.2.9 *o*-Tolylacetaldehyde (264)



The synthesis of epoxide **258** was performed according to general procedure D on 3.70 mmol scale with 11 cm^3 of CH_2Cl_2 as solvent. When the reaction was complete (analysis by ^1H NMR spectroscopy) the mixture was diluted with water (20 cm^3) and transferred to a separating funnel. As the molarity of the organic phase of the subsequent reaction is 0.095 M, the work up was carried out so that the final organic phase volume was 39 cm^3.

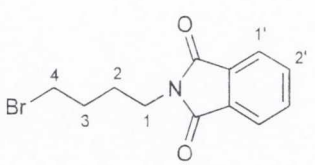
The aqueous phase was extracted with CH_2Cl_2 (3 x 8 cm^3), leaving 4 cm^3 for washings. The combined organic extracts were then washed with water (2 x 30 cm^3) and brine (1 x 30 cm^3). The organic phase was then dried ($MgSO_4$) and the solution filtered. An oven dried 50 cm^3 round bottomed flask containing a stirring bar and molecular sieves (4 Å) was fitted with a septum and placed under argon. Using an oven dried glass syringe, the filtrate was then transferred to the flask. The catalyst, copper tetrafluoroborate hydrate (218.8 mg, 0.923 mmol, 0.25 equiv.), was then added to the reaction flask and the resulting mixture stirred for 21 h at ambient temperature. The reaction mixture was diluted with CH_2Cl_2 (50 cm^3) and filtered to remove the molecular sieves. The organic phase was then washed with water (3 x 50 cm^3) and brine (3 x 50 cm^3). The organic phase was then dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The product was purified by column chromatography (6:4 hexane:CH_2Cl_2) to yield **264** as a colourless oil (342 mg, 69%). The NMR spectra of **264** were consistent with those previously reported.[224]

δ_H (400 MHz, $CDCl_3$): 2.30 (s, 3H, H-3), 3.73 (d, J 2.2, 2H, H-2), 7.19-7.29 (m, 4H, H-Ar), 9.73 (t, J 2.2, 1H, H-1).

δ_C (100 MHz, $CDCl_3$): 19.3, 48.3, 126.1, 127.4, 130.1, 130.2, 136.7 (2 x q), 198.9 (C=O).

HRMS (EI): $[M]^+$ calcd. for $C_9H_{10}O$ 134.0732; found 134.0734.

5.2.10 *N*-(4-Bromobutyl)-phthalimide (285)



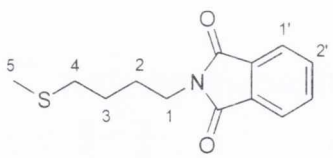
An oven dried 100 cm^3 round bottomed flask was charged with dimethylformamide (27 cm^3) *via* syringe followed by 1,4-dibromobutane (8.96 cm^3, 75.030 mmol). The flask was

fitted with a septum and placed under an atmosphere of argon (balloon). The resulting solution was cooled to 0 °C with an ice-bath. To this solution was slowly added phthalimide potassium salt (4.6305 g, 25.000 mmol). After 20 min the ice bath was removed and the resulting solution was allowed to stir at room temperature for 16 h. The reaction mixture was then diluted with diethyl ether (150 cm^3) and the organic layer was washed with H_2O (2 x 100 cm^3). The combined aqueous layers were extracted again with diethyl ether (150 cm^3). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by column chromatography (1:1 hexane:CH_2Cl_2) to afford **285** (2.89 g, 41%) as white needle-shaped crystals. M.p. 81-82 °C; lit.,[225] 80-81 °C. The NMR spectra of **285** were consistent with those previously reported.[226]

δ_H (400 MHz, $CDCl_3$): 1.86-1.95 (m, 4H, H-2 and H-3), 3.45 (t, J 6.4, 2H, H-4), 3.74 (t, J 6.3, 2H, H-1), 7.74 (dd, J 5.5, 3.1, 2H, H-2'), 7.86 (app. dd, 2H, H-1').

δ_C (100 MHz, $CDCl_3$): 26.8, 29.4, 32.4, 36.5, 122.8, 131.6 (q), 133.6, 167.9 (C=O).

5.2.11 *N*-(4-Methylthiobutyl)-phthalimide (286)



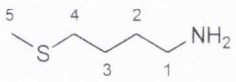
An oven dried 25 cm^3 round bottomed flask was charged with ice-cooled dimethylformamide (7 cm^3) *via* syringe followed by sodium thiomethoxide (741.3 mg, 10.576 mmol). The flask was fitted with a septum and placed under an atmosphere of argon (balloon). **285** Was slowly added to the solution. The resulting solution was allowed to stir for 6 h. The reaction mixture was then diluted with diethyl ether (50 cm^3)

and the organic layer was washed with H_2O (2 x 30 cm^3). The combined aqueous layers were extracted again with diethyl ether (50 cm^3). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by column chromatography (1:1 hexane:CH_2Cl_2) to afford **286** (1.297 g, 52%) as white needle-shaped crystals. M.p. 58-59 °C; lit.,[225] 56-59 °C. The NMR spectra of **286** were consistent with those previously reported.[226]

δ_H (400 MHz, $CDCl_3$): 1.66 (m, 2H, H-3), 1.78 (m, 2H, H-2), 2.11 (s, 3H, H-5), 2.54 (t, J 7.2, 2H, H-4), 3.72 (t, J 7.1, 2H, H-1), 7.72 (app. dd, 2H, H-2'), 7.85 (app. dd, 2H, H-1').

δ_C (100 MHz, $CDCl_3$): 15.1, 25.9, 27.3, 33.2, 37.1, 122.8, 131.6 (q), 133.5, 168.0 (C=O).

5.2.12 4-Methylthiobutylamine (282)



An oven dried 25 cm^3 round bottomed flask was charged with **286** (1.279 g, 5.130 mmol) and ethanol (7 cm^3). Hydrazine monohydrate (324 μL, 6.669 mmol) was added *via* syringe to the resulting solution under an atmosphere of argon (balloon). The reaction was heated under reflux at 75 °C and after 2 h conc. HCl (1 cm^3) was added. The reaction was heated at 100 °C for a further 1 h and left to cool overnight. The reaction mixture was then filtered and the residue washed with H_2O (100 cm^3). The filtrate was then transferred to a separating funnel, adjusted to pH 13 and extracted with diethyl ether (3 x 100 cm^3). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to yield **282** (520 mg, 85%) as a light yellow oil without requiring further purification. The NMR spectra of **282** were consistent with those previously reported.[226]

δ_H (400 MHz, $CDCl_3$): 1.43 (br s, 2H, NH), 1.55-1.68 (m, 4H, H-2 and H-3), 2.11 (s, 3H, H-5), 2.51 (t, J 7.5, 2H, H-4), 2.72 (t, J 6.7, 2H, H-1).

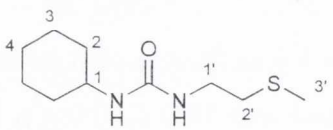
δ_C (100 MHz, $CDCl_3$): 15.1, 25.8, 29.3, 33.3, 40.2.

HRMS (EI): $[M]^+$ calcd. for $C_5H_{13}NS$ 119.0769; found 119.0770.

5.2.13 General procedure E: synthesis of unsymmetrical ureas 280, 281 and 287

An oven dried round bottomed flask containing a stirring bar was charged with the appropriate primary amine (1 equiv.) followed by CH_2Cl_2 (0.75 M) *via* syringe. Cyclohexyl isocyanate (1.05 equiv.) was then slowly added *via* syringe. The resulting solution was allowed to stir at room temperature for 1 h. The reaction mixture was extracted with CH_2Cl_2 (3 30 cm^3). The combined organic extracts were washed with saturated brine solution, dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product which was purified using flash chromatography to afford the desired unsymmetrical urea.

5.2.13.1 *N*-Cyclohexyl-*N*'-(2'-(methylthio)ethyl)urea (280)



Prepared according to general procedure E using 2-(methylthio)ethyl amine (214 μL, 2.300 mmol), CH_2Cl_2 (3 cm^3) and cyclohexyl isocyanate (309 μL, 2.415 mmol). Column chromatography (1:1 hexane:EtOAc) afforded **280** (458 mg, 92%) as a white solid. M.p. 107-109 °C.

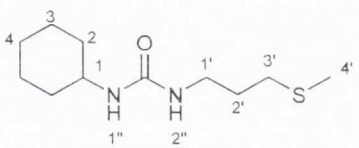
δ_H (400 MHz, $CDCl_3$): 1.07-1.20 (m, 3H, H-2a and H-4a), 1.29-1.40 (m, 2H, H-3a), 1.57-1.62 (m, 1H, H-4b), 1.68-1.73 (m, 2H, H-3b), 1.91-1.95 (m, 2H, H-2b), 2.11 (s, 3H, H-3'), 2.65 (t, J 6.5, 2H, H-2'), 3.40 (t, J 6.3, 2H, H-1'), 3.48 (tt, J 10.4, 3.9, 1H, H-1), 4.41 (br s, 2H, NH).

δ_C (100 MHz, $CDCl_3$): 15.0, 24.9, 25.6, 33.9, 34.6, 38.6, 49.4, 157.4 (C=O).

υ (cm^{-1}): 893, 1077, 1246, 1306, 1566, 1623 (C=O), 2853, 2932, 3319 (N-H).

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_{10}H_{20}N_2OSNa$ 239.1194; found 239.1200.

5.2.13.2 *N*-Cyclohexyl-*N'*-(3'-(methylthio)propyl)urea (281)



Prepared according to general procedure E using 2-(methylthio)propyl amine (800 μL, 7.300 mmol), CH_2Cl_2 (10 ml) and cyclohexyl isocyanate (980 μL, 7.665 mmol). Column chromatography (7:3 hexane:EtOAc) afforded **281** (739 mg, 91%) as a white solid. M.p. 90-92 °C.

δ_H (600 MHz, $(CD_3)_2SO$): 1.04-1.16 (m, 3H, H-2a and H-4a), 1.22-1.28 (m, 2H, H-3a), 1.51-1.53 (m, 1H, H-4b), 1.59-1.64 (m, 4H, H-2' and H-3b), 1.72-1.75 (m, 2H, H-2b), 2.04 (s, 3H, H-4'), 2.44 (t, J 7.4, 2H, H-3'), 3.04 (app. q, 2H, H-1'), 3.32 (m, overlap

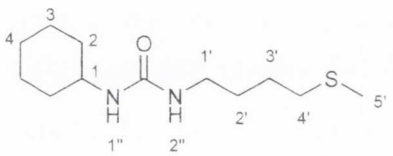
with H_2O resonance, 1H, H-1), 5.65 (d, J 7.9, 1H, NH-1"), 5.73 (t, J 5.4, 1H, NH-2").

δ_C (150 MHz, $(CD_3)_2SO$): 14.6, 24.4, 25.3, 29.5, 30.6, 33.3, 38.1, 47.7, 157.3 (C=O).

υ (cm^{-1}): 1083, 1234, 1246, 1523, 1567, 1623 (C=O), 2851, 2915, 2932, 3311 (N-H).

HRMS (ESI): $[M+H]^+$ Calcd. for $C_{11}H_{23}N_2OS$ 231.1531; found 231.1535.

5.2.13.3 *N*-Cyclohexyl-*N'*-(4'-(methylthio)butyl)urea (287)



Prepared according to general procedure E using **282** (518 mg, 4.345 mmol), CH_2Cl_2 (5.7 cm^3) and cyclohexyl isocyanate (583 µL, 4.562 mmol). Column chromatography (1:1 hexane:EtOAc) afforded **287** (977 mg, 92%) as a white solid. M.p. 89-90 °C.

δ_H (600 MHz, $(CD_3)_2SO$): 1.03-1.16 (m, 3H, H-2a and H-4a), 1.22-1.29 (m, 2H, H-3a), 1.40-1.45 (m, 2H, H-2'), 1.49-1.54 (m, 3H, H-3' and H-4b), 1.62-1.65 (m, 2H, H-3b), 1.72-1.75 (m, 2H, H-2b), 2.04 (s, 3H, H-5'), 2.46 (t, J 7.3, 2H, H-4'), 2.98 (app. q, 2H, H-1'), 3.35 (m, overlap with H_2O resonance, 1H, H-1), 5.63 (d, J 7.9, 1H, NH-1"), 5.67 (t, J 5.5, 1H, NH-2").

δ_C (150 MHz, $(CD_3)_2SO$): 14.6, 24.4, 25.3, 26.0, 29.2, 32.9, 33.3, 38.6, 47.6, 157.3 (C=O).

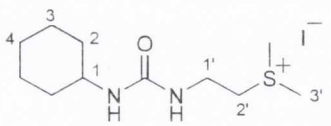
υ (cm^{-1}): 1082, 1213, 1244, 1305, 1571, 1621 (C=O), 2852, 2929, 3319 (N-H).

HRMS (ESI): $[M+H]^+$ Calcd. for $C_{12}H_{25}N_2OS$ 245.1688; found 245.1696.

5.2.14 General procedure F: synthesis of urea salts 274, 275, 276

A 5 cm^3 round bottomed flask was charged with the appropriate urea (1 equiv.) followed by CH_2Cl_2 (1.1 M). Iodomethane (5 equiv.) was then added and the flask was fitted with a glass stopper. The resulting solution was allowed to stir at room temperature for 72 h. The solvent was removed *in vacuo* and dried under high vacuum to yield the corresponding iodide salt.

5.2.14.1 *N*-Cyclohexyl-*N*'-(2'-(methylthio)ethyl)urea methiodide salt (274)



Prepared according to general procedure F using **280** (300 mg, 1.387 mmol), CH_2Cl_2 (1.5 cm^3) and iodomethane (432 μL, 6.934 mmol) to afford **274** as a yellow solid (496.9 mg, 100%). M.p. 102-103 °C.

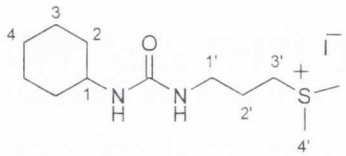
δ_H (600 MHz, $(CD_3)_2SO$): 1.09-1.17 (m, 3H, H-2a and H-4a), 1.23-1.29 (m, 2H, H-3a), 1.52-1.55 (m, 1H, H-4b), 1.64-1.66 (m, 2H, H-3b), 1.73-1.74 (m, 2H, H-2b), 2.90 (s, 6H, H-3'), 3.36 (m, 3H, H-1 and H-2'), 3.45 (app. q, 2H, H-1'), 6.16 (app. d, 2H, NH).

δ_C (150 MHz, $(CD_3)_2SO$): 24.4, 24.6, 25.2, 33.1, 34.1, 45.8, 48.0, 157.6 (C=O).

υ (cm^{-1}): 1038, 1092, 1235, 1252, 1554, 1619 (C=O), 2851, 2924, 2972, 3303 (N-H).

HRMS (ESI): $[M]^+$ Calcd. for $C_{11}H_{23}N_2OS$ 231.1531; found 231.1536.

5.2.14.2 *N*-Cyclohexyl-*N'*-(3'-(methylthio)propyl)urea methiodide salt (275)



Prepared according to general procedure F using **281** (650 mg, 2.822 mmol), CH_2Cl_2 (3.0 cm^3) and iodomethane (880 μL, 14.110 mmol) to afford **275** as a yellow solid (1.051 g, 100%). M.p. 78-80 °C.

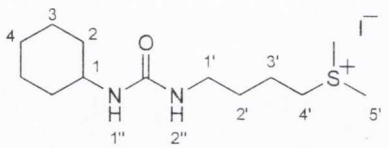
δ_H (600 MHz, $(CD_3)_2SO$): 1.11-1.16 (m, 3H, H-2a and H-4a), 1.23-1.29 (m, 2H, H-3a), 1.52-1.54 (m, 1H, H-4b), 1.63-1.67 (m, 2H, H-3b), 1.73-1.76 (m, 2H, H-2b), 1.82 (app. quintet, 2H, H-2'), 2.88, (s, 6H, H-4'), 3.11 (app. q, 2H, H-1'), 3.24 (t, J 7.6, 2H, H-3'), 3.35 (m, overlap with H_2O resonance, 1H, H-1), 5.84-5.88 (m, 2H, NH).

δ_C (150 MHz, $(CD_3)_2SO$): 24.3, 24.5, 24.7, 25.2, 33.2, 37.7, 47.8, 54.8, 157.5 (C=O).

υ (cm^{-1}): 1236, 1252, 1447, 1556, 1619 (C=O), 2851, 2926, 2975, 3304 (N-H).

HRMS (ESI): $[M]^+$ Calcd. for $C_{12}H_{25}N_2OS$ 245.1688; found 245.1686.

5.2.14.3 *N*-Cyclohexyl-*N*'-(4'-(methylthio)butyl)urea methiodide salt (276)



Prepared according to general procedure F using **287** (150 mg, 0.614 mmol), CH_2Cl_2 (0.7 cm^3) and iodomethane (191 μL, 3.069 mmol) to afford **276** as a yellow solid (237 mg, 100%). M.p. 110-112 °C.

δ_H (600 MHz, $(CD_3)_2SO$): 1.05-1.17 (m, 3H, H-2a and H-4a), 1.23-1.29 (m, 2H, H-3a), 1.46-1.54 (m, 3H, H-2' and H-4b), 1.63-1.75 (m, 6H, H-2b, H-3' and H-3b), 2.88 (s, 6H, H-5'), 3.03 (m, 2H, H-1'), 3.30 (overlap with H_2O resonance, 2H, H-4'), 3.35 (m, overlap with H_2O resonance, 1H, H-1), 5.70 (d, J 7.9, 1H, NH-1"), 5.75 (t, J 5.3, 1H, NH-2").

δ_C (150 MHz, $(CD_3)_2SO$): 21.0, 24.6, 25.0, 25.8, 29.3, 33.8, 38.7, 42.2, 48.2, 157.9 (C=O).

υ (cm^{-1}): 1229, 1248, 1569, 1618 (C=O), 2358, 2851, 2932, 2983, 3299 (N-H).

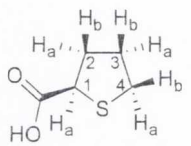
HRMS (ESI): $[M]^+$ Calcd. for $C_{13}H_{27}N_2OS$ 259.1844; found 259.1850.

5.2.15 General procedure G: the epoxidation of benzaldehyde (48) by 274, 275 and 276 (entries 1, 2 and 3, Table 2.8)

An oven dried 5 cm^3 round bottomed flask was charged with **274, 275** or **276** (1 equiv.) followed by (*E*)-stilbene (0.5 equiv.). The flask was fitted with a septum and placed under

an atmosphere of argon (balloon). CH_2Cl_2 (0.25 M) and freshly distilled benzaldehyde (1 equiv.) were then added sequentially *via* syringe. The resulting solution was treated with P_2-*t*-butyl solution (2.0 M in THF, 1 equiv.) and allowed to stir at ambient temperature.

5.2.16 (*R*)-(-)-Tetrahydrothiophene-2-carboxylic acid (293)



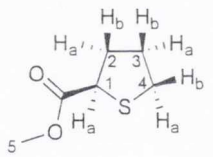
A 250 cm^3 three necked round bottomed flask containing a magnetic stirring bar, with one dropping funnel connected to each side neck and a gas outlet connected to central neck, was charged with L-(+)-ornithine hydrochloride (3.4 g, 20 mmol), sodium bromide (41.3 g, 400 mmol) and H_2O (100 cm^3). One dropping funnel was charged with sodium nitrite (3.5 g, 50 mmol) in H_2O (15 cm^3) and the other was charged with hydrobromic acid (5.6 cm^3, 50 mmol) in H_2O (15 cm^3). The resulting solution was cooled to 0 °C using an ice-bath and the solutions of sodium nitrite and hydrobromic acid were added dropwise from the dropping funnels. The rate of reaction was monitored by gas evolution *via* the gas outlet, which was placed in a graduated cylinder containing H_2O. Initially, the solutions were added slowly over a period of 3 h. As the reaction rate had decreased considerably after this time, the ice-bath was removed and the remaining solutions were added dropwise over an additional 2 h. The solution was allowed to stir at room temperature overnight. The resulting solution was transferred to a separating funnel and extracted with Et_2O (3 x 100 cm^3). The combined organic extracts were then extracted with 0.1 M $NaHCO_3$ (200 cm^3) and collected in a 500 cm^3 round bottomed flask containing a magnetic stirring bar. The resulting solution was treated with sodium sulfide nonahydrate (4.8 g, 20 mmol) and allowed to stir overnight. After this time, the reaction volume was reduced to *ca.* 50 cm^3 *in vacuo*. The reaction mixture was then transferred to a 250 cm^3 three necked round bottomed flask with a dropping funnel charged with 2 M HCl connected to one side neck, a glass stopper fitted to the other and a gas outlet connected to central neck which was fed into a solution of 10 M NaOH. The reaction

mixture was acidified by dropwise addition of the HCl solution from the dropping funnel. The acidified solution was transferred to a separating funnel, extracted with Et_2O (5 x 50 cm^3), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (7:3 hexane:EtOAc) afforded **293** as a white solid (460 mg, 17%). M.p. 51-53 °C; lit.,[227] 50-51 °C. $[\alpha]_D^{20}$ = -13.5 (*c* 0.6, EtOH, 77% *ee*); lit.,[228] $[\alpha]_D^{20}$ = -14.2 (*c* 13, EtOH). The NMR spectra of **293** were consistent with those previously reported.[227]

δ_H (400 MHz, $CDCl_3$): 1.98-2.23 (m, 3H, H-2b, H-3a and H-3b), 2.30-2.36 (m, 1H, H-2a), 2.87-2.92 (m, 1H, H-4a), 2.98-3.04 (m, 1H, H-4b), 3.96 (dd, J 7.3, 4.4, 1H, H-1a).

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_5H_8O_2SNa$ 155.0143; found 155.0143.

5.2.17 (*R*)-Tetrahydrothiophene-2-carboxylic acid methyl ester (294)



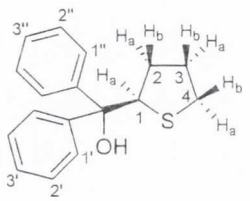
To a 25 cm^3 round bottomed flask containing **293** (630 mg, 4.766 mmol) and a magnetic stirring bar was added anhydrous Et_2O (12 cm^3) *via* syringe, followed by the dropwise addition of DBU (713 µL, 4.766 mmol). The resulting solution was allowed to stir for 5 min, after which time methyl iodide (297 µL, 4.766 mmol) was added dropwise. The reaction mixture was allowed to stir overnight. The crude reaction was concentrated *in vacuo* and purification by flash chromatography (9:1 hexane:Et_2O) afforded **294** as a yellow liquid (408 mg, 59%). $[\alpha]_D^{20}$ = -24.3 (*c* 0.5, $CHCl_3$, 77% *ee*).

δ_H (600 MHz, $CDCl_3$): 1.95-2.12 (m, 2H, H-2b and H-3a), 2.15-2.25 (m, 1H, H-3b), 2.28-2.35 (m, 1H, H-2a), 2.89 (br s, 1H, H-4a), 2.97 (br s, 1H, H-4b), 3.72 (s, 3H, H-5), 3.93 (br s, 1H, H-1a).

δ_C (150 MHz, $CDCl_3$): 31.0, 33.3, 33.5, 47.5, 52.5, 174.3 (C=O).

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_6H_{10}O_2SNa$ 169.0299; found 169.0293.

5.2.18 (*R*)-(Thiolan-2-yl)diphenylmethanol (290)



An oven dried 50 cm^3 round bottomed flask containing **294** (730 mg, 4.992 mmol) and a magnetic stirring bar was fitted with a rubber septum and placed under an atmosphere of argon (balloon). Anhydrous THF (25 cm^3) was added *via* syringe. The resulting solution was cooled to 0 °C using an ice-bath when phenylmagnesium bromide (3.0 M in Et_2O, 5 cm^3, 14.979 mmol) was added dropwise *via* syringe. The resulting solution was allowed to reach room temperature and stir overnight. The reaction mixture was cooled to 0 °C and quenched by the addition of sat. $NH_4Cl_{(aq)}$ (10 cm^3). The resulting solution was transferred to a separating funnel, extracted with Et_2O (3 x 50 cm^3), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (8:2 hexane:CH_2Cl_2) afforded **290** as a white solid (1.145 g, 85%). M.p. 60-62 °C. $[\alpha]_D^{20}$ = +260 (*c* 0.2, acetone, 77% *ee*).

CSP-HPLC analysis: CHIRALCEL OJ-H (4.6 mm x 25 cm), hexane/IPA: 9.75/0.25, 0.5 mL min^{-1}, RT, UV detection at 220 nm, retention times: 47.2 min (minor enantiomer) and 68.9 min (major enantiomer).

δ_H (600 MHz, $CDCl_3$): 1.61-1.65 (m, 1H, H-2a), 1.77-1.86 (m, 2H, H-2b and H-3a), 2.17-2.20 (m, 1H, H-3b), 2.85-2.87 (m, 2H, H-4a and H-4b), 3.55 (br s, 1H, OH), 4.67 (m, 1H, H-1a), 7.16 (t, J

7.3, 1H, H-3'), 7.21 (t, J 7.3, 1H, H-3''), 7.26 (app. t, 2H, H-2'), 7.30 (app. t, 2H, H-2''), 7.45 (d, J 7.6, 2H, H-1'), 7.54 (d, J 7.6, 2H, H-1'').

δ_C (150 MHz, $CDCl_3$): 31.76, 31.78, 33.4, 59.5, 77.8 (q), 125.4, 126.1, 126.5, 127.1, 128.0, 128.2, 145.0 (q), 148.0 (q).

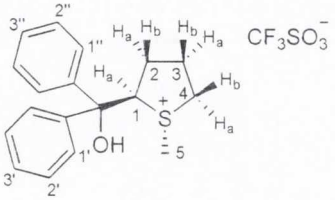
υ (cm^{-1}): 692, 748, 979, 1166, 1447, 1489, 2857, 2933, 3451 (O-H).

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_{17}H_{18}OSNa$ 293.0976; found 293.0977.

5.2.19 General procedure H: the synthesis of sulfonium salts 292, 300, 304, 308, 310, 320, 355 and 368

An oven dried round bottomed flask was charged with the appropriate sulfide (1 equiv.). The flask was fitted with a septum and placed under an atmosphere of argon (balloon) when CH_2Cl_2 was added *via* syringe. Methyl triflate (1 equiv.) was then added and the resulting solution was allowed to stir at room temperature. The solvent was removed *in vacuo* and the resulting sulfonium salt was purified as required.

5.2.20 (*R*)-(Thiolan-2-yl)diphenylmethanol triflate (292)



Prepared according to general procedure H using **290** (40.0 mg, 0.148 mmol), CH_2Cl_2 (1.4 cm^3) and methyl triflate (16.7 μL, 0.148 mmol). After 24 h reaction time, **292** was

furnished as a white solid in quantitative yield (64.30 mg). M.p. 120-122 °C. $[\alpha]_D^{20} = -7.3$ (*c* 0.26, CH_2Cl_2, 77% *ee*).

δ_H (600 MHz, $CDCl_3$): 2.12-2.19 (br m, 1H, H-2b), 2.46-2.52 (br m, 1H, H-3b), 2.59-2.65 (br m, 1H, H-3a), 2.68 (s, 3H, H-5), 2.69-2.75 (br m, 1H, H-2a), 3.25-3.30 (m, 1H, H-4a), 3.35-3.40 (m, 1H, H-4b), 4.26 (br s, 1H, OH), 5.51 (app. t, 1H, H-1a), 7.28-7.31 (m, 2H, H-3' and H-3''), 7.37-7.40 (m, 4H, H-2' and H-2''), 7.56 (d, J 7.7, 2H, H-1'), 7.58 (d, J 7.7, 2H, H-1'').

δ_C (150 MHz, $CDCl_3$): 24.7, 29.5, 31.3, 44.0, 78.5 (q), 78.6, 125.2, 125.8, 128.3, 128.5, 129.0, 129.2, 142.3 (q), 144.3 (q).

δ_F (376 MHz, $CDCl_3$): -78.8 (s, 3F).

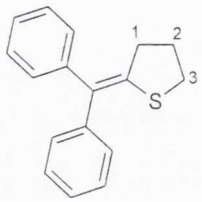
υ (cm^{-1}): 706, 734, 1001, 1028, 1156, 1224, 1250, 1449, 3028, 3418.

HRMS (ESI): $[M]^+$ Calcd. for $C_{18}H_{21}OS$ 285.1313; found 285.1323.

5.2.21 General procedure I: the epoxidation of benzaldehyde (48) by 292, 300 and 304 (Schemes 2.12, 2.15 and 2.17)

An oven dried 5 cm^3 round bottomed flask was charged with either **292**, **300** or **304** (1 equiv.). The flask was then fitted with a septum and placed under an atmosphere of argon (balloon). CH_2Cl_2 (0.105 M) and freshly distilled benzaldehyde (1 equiv.) were then added sequentially *via* syringe. The resulting solution was cooled to -78 °C when it was treated with P_2-*t*-butyl solution (2.0 M in THF, 1 equiv.). The reaction mixture was allowed to stir at this temperature for 30 min.

5.2.22 Base-mediated decomposition product 296 derived from sulfonium salt 292: tetrahydro-2-(diphenylmethylene)thiophene (296)



296 Was obtained from the epoxidation reaction after purification by column chromatography (8:2 hexane:CH_2Cl_2) as a colourless solid. M.p. 73-74 °C.

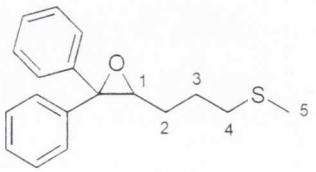
δ_H (600 MHz, $CDCl_3$): 2.10 (app. quintet, 2H, H-2), 2.73 (t, J 6.8, 2H, H-3), 3.06 (t, J 6.4, 2H, H-1), 7.19-7.38 (m, 10 H, H-Ar).

δ_C (150 MHz, $CDCl_3$): 30.4, 33.9, 36.3, 74.7 (q), 126.0, 126.5, 127.9, 128.0, 129.0, 129.1, 142.2 (q), 142.8 (q), 143.1 (q).

υ (cm^{-1}): 696, 750, 766, 1073, 1260, 1440, 1490, 1591, 2852, 2922, 3052.

HRMS (ESI): $[M+H]^+$ Calcd. for $C_{17}H_{17}S$ 253.1051; found 253.1046.

5.2.23 Base-mediated decomposition product 295 derived from sulfonium salt 292: 3-(3-(methylthio)propyl)-2,2-diphenyloxirane (295)



295 Was obtained from the epoxidation reaction after purification by column chromatography (8:2 hexane:CH_2Cl_2) as a colourless oil.

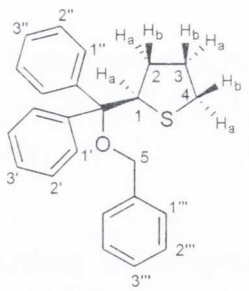
δ_H (600 MHz, $CDCl_3$): 1.35-1.41 (m, 1H, H-2a), 1.62-1.68 (m, 1H, H-2b), 1.74-1.89 (m, 2H, H-3), 2.06 (br s, 3H, H-5), 2.47-2.54 (m, 2H, H-4), 3.42 (m, 1H, H-1), 7.26-7.42 (m, 10H, H-Ar).

δ_C (150 MHz, $CDCl_3$): 15.3, 25.9, 28.7, 33.8, 66.0, 66.1 (q), 127.0, 127.6, 127.7, 127.9, 128.1, 128.3, 137.5 (q), 141.0 (q).

υ (cm^{-1}): 696, 731, 907, 1243, 1447, 1495, 1735, 2858, 2916, 3029, 3060.

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_{18}H_{20}OSNa$ 307.1133; found 307.1144.

5.2.24 (*R*)-2-((Benzyloxy)diphenylmethyl)-tetrahydrothiophene (299)



An oven dried 5 cm^3 round bottomed flask containing a magnetic stirring bar was charged with **290** (50.0 mg, 0.185 mmol), sodium iodide (13.9 mg, 0.092 mmol) and sodium hydride (60% dispersion in mineral oil, 74.0 mg, 1.849 mmol). The flask was fitted with a rubber septum and placed under an atmosphere of argon (balloon). Anhydrous THF (0.4 cm^3) was added *via* syringe, followed by DMF (0.1 cm^3). The resulting solution was treated with benzyl bromide (66 μL, 0.555 mmol) and allowed to

stir at ambient temperature for 22 h. The reaction mixture was quenched with H_2O (2 cm^3), transferred to a separating funnel and extracted with Et_2O (3 x 5 cm^3). The combined organic layers were washed with H_2O (5 x 10 cm^3), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (9:1 hexane:CH_2Cl_2) afforded **299** as a pale yellow, viscous oil (31.97 mg, 48%). $[\alpha]_D^{20}$ = -333.3 (*c* 0.3, CH_2Cl_2, 77% *ee*).

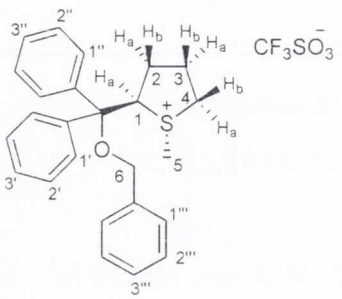
δ_H (400 MHz, $CDCl_3$): 1.37-1.45 (m, 1H, H-3a), 1.66-1.76 (m, 1H, H-3b), 1.81-1.90 (m, 1H, H-2a), 1.99-2.08 (m, 1H, H-2b), 2.35-2.44 (br m, 1H, H-4a), 2.67-2.74 (br m, 1H, H-4b), 4.22 (d, J 11.5, 1H, H-5a), 4.39 (d, J 11.5, 1H, H-5b), 4.66-4.72 (br m, 1H, H-1a), 7.25-7.33 (m, 11H, H-2', H-3', H-2'', H-3'', H-1''', H-2''' and H-3'''), 7.45 (d, J 6.9, 2H, H-1'), 7.56 (d, J 7.6, 2H, H-1'').

δ_C (100 MHz, $CDCl_3$): 30.4, 31.8, 32.8, 53.9, 65.6, 86.0 (q), 127.04, 127.07, 127.1, 127.2, 127.4, 127.6, 128.2, 129.0, 129.5, 139.3 (q), 141.7 (q), 143.3 (q).

υ (cm^{-1}): 696, 733, 756, 1027, 1061, 1085, 1444, 1493, 2858, 2927, 3030, 3058, 3087.

HRMS (ESI): $[M+K]^+$ Calcd. for $C_{24}H_{24}OSK$ 399.1185; found 399.1199.

5.2.25 (*R*)-2-((Benzyloxy)diphenylmethyl)-tetrahydrothiophene triflate (300)



Prepared according to general procedure H using **299** (130 mg, 0.361 mmol), CH_2Cl_2 (3.4 cm^3) and methyl triflate (40.8 μL, 0.361 mmol). **300** Was obtained as a colourless semi-solid in quantitative yield (189.39 mg). $[\alpha]_D^{20}$ = -41.3 (*c* 0.1, acetone, 77% *ee*).

δ_H (600 MHz, $CDCl_3$): 1.85-1.89 (m, 1H, H-2b), 1.95-1.99 (m, 1H, H-3b), 2.62-2.69 (m, 2H, H-3a and H-4b), 2.76-2.81 (m, 1H, H-2a), 3.04 (s, 3H, H-5), 3.41-3.46 (m, 1H, H-4a), 3.99 (d, J 11.0, 1H, H-6a), 4.24 (d, J 11.0, 1H, H-6b), 5.55 (app. t, 1H, H-1a), 7.25 (d, J 6.7, 2H, H-1'''), 7.30 (t, J 7.2, 1H, H-3'''), 7.35 (app. t, 2H, H-2'''), 7.44-7.49 (m, 8H, H-2', H-3', H-1'', H-2'' and H-3''), 7.57 (d, J 7.4, 2H, H-1').

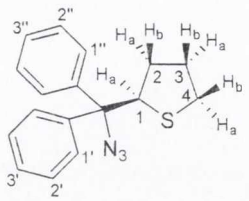
δ_C (150 MHz, $CDCl_3$): 26.6, 28.1, 30.9, 42.7, 67.0, 75.9, 85.1 (q), 127.5, 128.1, 128.3, 128.7, 128.9, 129.2, 129.5 (C-1' and C-2''), 129.6, 136.4 (q), 136.5 (q), 137.0 (q).

δ_F (376 MHz, $CDCl_3$): -78.8 (s, 3F).

υ (cm^{-1}): 705, 764, 1029, 1166, 1226, 1240, 1448, 1713, 3032, 3492.

HRMS (ESI): $[M]^+$ Calcd. for $C_{25}H_{27}OS$ 375.1783; found 375.1767.

5.2.26 (*R*)-2-(Azidodiphenylmethyl)-tetrahydrothiophene (302)



A 50 cm^3 round bottomed flask containing a magnetic stirring bar was charged with **290** (1.085 g, 4.013 mmol), $CHCl_3$ (8 cm^3) *via* syringe and sodium azide (783 mg, 12.038 mmol). The reaction mixture was cooled to 0 °C using an ice-bath when H_2SO_4 (65% v/v, 8 cm^3) was added dropwise. The resulting solution was allowed to stir at room temperature for 16 h. The reaction mixture was brought to pH 10 by treatment with 2M NaOH, transferred to a separating funnel and extracted with Et_2O (30 cm^3). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude azide which was purified by flash chromatography (8:2 hexane:CH_2Cl_2) to afford **302** (542 mg, 46%) as a colourless oil. $[\alpha]_D^{20} = +19.8$ (*c* 0.6, CH_2Cl_2, 77% *ee*).

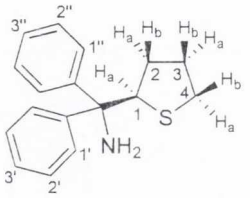
δ_H (600 MHz, $CDCl_3$): 1.70-1.74 (m, 1H, H-2a), 1.76-1.85 (m, 2H, H-2b and H-3a), 1.96-1.99 (m, 1H, H-3b), 2.80-2.88 (m, 2H, H-4a and H-4b), 4.57 (app. t, 1H, H-1a), 7.22 (t, J 6.6, 1H, H-3'), 7.25-7.32 (m, 5H, H-1', H-2' and H-3''), 7.38 (app. t, 2H, H-2''), 7.48 (d, J 7.7, 2H, H-1'').

δ_C (150 MHz, $CDCl_3$): 31.1, 32.8, 33.7, 58.3, 75.8 (q), 127.0, 127.5, 128.0, 128.3, 128.4, 128.5, 141.9 (q), 143.4 (q).

υ (cm^{-1}): 739, 895, 1034, 1263, 1445, 1492, 2105, 2858, 1927, 3058.

HRMS (GC-CI): $[M+H-N_2]^+$ Calcd. for $C_{17}H_{18}NS$ 268.1160; found 268.1154.

5.2.27 ((*R*)-Tetrahydrothiophen-2-yl)diphenylmethanamine (303)



An oven dried 5 cm^3 round bottomed flask containing a magnetic stirring bar and preceding azide **302** (432 mg, 1.462 mmol) was fitted with a rubber septum and placed under an atmosphere of argon (balloon). Anhydrous THF (2 cm^3) was then added *via* syringe. This solution was then added dropwise to an oven dried 10 cm^3 round bottomed flask containing a magnetic stirring bar and a solution of $LiAlH_4$ (83 mg, 2.193 mmol) in anhydrous THF (2 cm^3) under an atmosphere of argon (balloon). The resulting solution was allowed to stir for 16 h. The reaction mixture was quenched with 2M NaOH (1 cm^3) and filtered through a pad of celite. The resulting solution was then transferred to a separating funnel, extracted with Et_2O (4 x 20 cm^3) and dried over $MgSO_4$. The crude product was purified by flash chromatography (8:2 hexane:EtOAc) to afford **303** as a colourless oil (254 mg, 64%). $[\alpha]_D^{20} = +13.3$ (*c* 0.2, acetone, 77% *ee*).

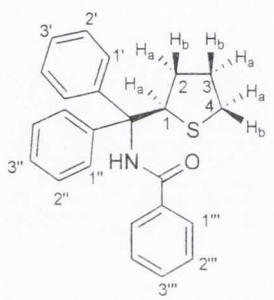
δ_H (600 MHz, $CDCl_3$): 1.63-1.68 (m, 1H, H-2a), 1.78-1.85 (m, 2H, H-2b and H-3a), 2.14-2.17 (m, 1H, H-3b), 2.86 (m, 2H, H-4a and H-4b), 4.60 (dd, J 9.5, 6.7, 1H, H-1a), 7.17-7.21 (m, 2H, H-3' and H-3''), 7.25-7.31 (m, 4H, H-2' and H-2''), 7.42 (d, J 7.6, 2H, H-1'), 7.50 (d, J 7.6, 2H, H-1'').

δ_C (150 MHz, $CDCl_3$): 31.5, 32.1, 33.3, 58.6, 63.9 (q), 126.3, 126.4, 126.56, 126.60, 128.0, 128.1, 146.1 (q), 148.4 (q).

υ (cm^{-1}): 699, 755, 831, 1181, 1445, 1490, 1596, 2857, 2929, 3020, 3055.

HRMS (ESI): $[M\text{-}NH_2]^+$ Calcd. for $C_{17}H_{17}S$ 253.1051; found 253.1041.

5.2.28 *N*-(((*R*)-Tetrahydrothiophen-2-yl)diphenylmethyl)benzamide (301)



An oven dried 10 cm^3 round bottomed flask containing **303** (250 mg, 0.928 mmol) and a magnetic stirring bar was fitted with a rubber septum and placed under an atmosphere of argon (balloon). Anhydrous THF (3.1 cm^3) was added *via* syringe. The resulting solution was cooled to 0 °C using an ice-bath when triethylamine (150 μL, 1.044 mmol) was added *via* syringe, followed by dropwise addition of benzoyl chloride (115 μL, 0.984 mmol). The resulting solution was allowed to reach room temperature and stir for 17 h. The reaction mixture was then transferred to a separating funnel and extraction was performed using H_2O (10 cm^3) and CH_2Cl_2 (3 x 20 cm^3). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (9:1 hexane:EtOAc) afforded **301** as a white solid (271 mg, 78%). M.p. 119-121 °C. $[\alpha]_D^{20}$ = -32.9 (*c* 0.2, acetone, 49% *ee*).

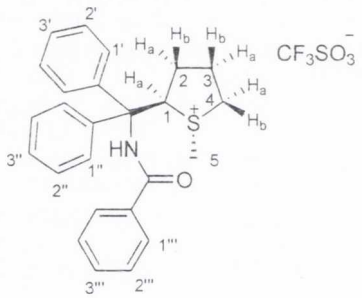
δ_H (400 MHz, $CDCl_3$): 1.71-1.87 (m, 4H, H-2a, H-2b, H-3a and H-3b), 2.75-2.91 (m, 2H, H-4a and H-4b), 4.74-4.79 (m, 1H, H-1a), 7.22-7.27 (m, 6H, H-1', H-2', H-3' and H-3''), 7.32 (app. t, 2H, H-2'''), 7.49 (t, J 7.3, 1H, H-3'''), 7.65 (d, J 7.6, 2H, H-1''), 7.69 (br s, 1H, NH), 7.84 (d, J 7.5, 2H, H-1''').

δ_C (100 MHz, $CDCl_3$): 30.6, 33.2, 33.9, 59.4, 67.3 (q), 127.1, 127.2, 127.7, 128.1, 128.3, 128.6, 128.8, 131.6, 135.8 (q), 142.2 (q), 144.8 (q), 166.6 (C=O).

υ (cm^{-1}): 694, 768, 1029, 1180, 1286, 1479, 1499, 1672, 2858, 2922, 3055, 3321.

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_{24}H_{23}NOSNa$ 396.1398; found 396.1385.

5.2.29 *N*-(((*R*)-Tetrahydrothiophen-2-yl)diphenylmethyl)benzamide triflate (304)



Prepared according to general procedure H using **301** (20.0 mg, 0.054 mmol), CH_2Cl_2 (0.5 cm^3) and methyl triflate (6 μL, 0.054 mmol) to afford **304**, after 1 h, as a white solid in quantitative yield. M.p. 81-83 °C. $[\alpha]_D^{20}$ = -44.1 (*c* 0.3, CH_2Cl_2, 49% *ee*).

δ_H (600 MHz, $CDCl_3$): 1.94-2.02 (m, 1H, H-2b), 2.48-2.54 (m, 1H, H-3b), 2.78 (s, 3H, H-5), 2.92-2.99 (m, 1H, H-3a), 3.03-3.07 (m, 1H, H-2a), 3.16-3.21 (m, 1H, H-4b), 3.50-3.55 (m, 1H, H-4a), 5.88 (app. t, 1H, H-1a), 7.30 (d, J 7.5, 2H, H-1''), 7.32-7.35 (m, 1H, H-3''), 7.37-7.42 (m, 3H, H-3' and H-2''), 7.47

(app. t, 2H, H-2'), 7.51-7.55 (m, 4H, H-1' and H-2'''), 7.63 (t, J 7.5, 1H, H-3'''), 7.82 (d, J 7.4, 2H, H-1''').

δ_C (150 MHz, $CDCl_3$): 27.1, 29.9, 32.5, 44.0, 68.5 (q), 75.5, 126.3, 126.8, 127.2, 128.9, 129.2, 129.4, 129.5, 130.1, 132.6 (q), 133.2, 142.6 (q), 143.8 (q), 168.6 (C=O).

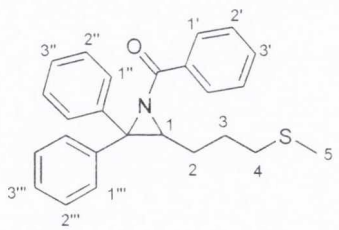
δ_F (376 MHz, $CDCl_3$): -78.8

υ (cm^{-1}): 701, 909, 1028, 1151, 1223, 1253, 1481, 1656, 2250, 2959, 3027, 3060, 3310.

HRMS (ESI): $[M^+]$ Calcd. for $C_{25}H_{26}NOS$ 388.1735; found 388.1738.

5.2.30 Base mediated decomposition product 306 derived from sulfonium salt 304:

3-(3-(Methylthio)propyl)-2,2-diphenylaziridin-1-yl)(phenyl)methanone (306)



306 Was obtained from the epoxidation reaction after purification by column chromatography (7:3 hexane:CH_2Cl_2) as an off-white solid. M.p. 75-77 °C.

δ_H (600 MHz, $(CD_3)_2SO$): 1.08-1.14 (m, 1H, H-2a), 1.41-1.46 (m, 1H, H-2b), 1.76 (app. quintet, 2H, H-3), 1.97 (s, 3H, H-5), 2.45 (dt, J 6.9, 3.6, 2H, H-4), 5.43 (dd, J 10.9, 2.5, 1H, H-1), 7.18 (d, J 7.3,

2H, H-1''), 7.24 (app. t, 1H, H-3''), 7.27-7.32 (m, 3H, H-2'' and H-3'''), 7.39 (app. t, 2H, H-2'''), 7.54 (app. t, 2H, H-2'), 7.58 (d, J 7.4, 2H, H-1'''), 7.62 (app. t, 1H, H-3'), 8.04 (d, J 7.1, 2H, H-1').

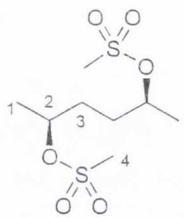
δ_C (150 MHz, $(CD_3)_2SO$): 14.5, 25.6, 31.5, 32.8, 80.4 (q), 86.7, 126.7, 126.9, 127.0, 127.3 (q), 127.4, 127.8, 128.0, 128.3, 128.7, 131.9, 142.0 (q), 145.9 (q), 161.4 (C=O).

υ (cm^{-1}): 684, 701, 759, 898, 1023, 1068, 1285, 1449, 1647, 2849, 2917, 2954, 3017, 3058.

HRMS (ESI): $[M+H]^+$ Calcd. for $C_{25}H_{26}NOS$ 388.1735; found 388.1725.

5.3 Experimental data for Chapter 3

5.3.1 (1*S*,4*S*)-4-Methanesulfonyloxy-1-methylpentyl methanesulfonate (387)



A solution of (2*S*,5*S*)-2,5-hexanediol (1.00 g, 8.462 mmol) and triethylamine (2.87 cm^3, 17.51 mmol) in CH_2Cl_2 (17.2 cm^3) was cooled to –20 °C. Methanesulfonyl chloride (1.44 cm^3, 18.616 mmol) was added dropwise at this temperature. The reaction mixture was allowed to warm to 0 °C at which time 1 M HCl (2.9 cm^3) was added. The resulting solution was transferred to a separating funnel and extracted with CH_2Cl_2 (3 x 20 cm^3). The combined organic extracts were washed with sat. $NaHCO_{3(aq)}$ and dried over $MgSO_4$. The product (1*S*,4*S*)-4-methanesulfonyloxy-1-methylpentyl methanesulfonate (**387**) was

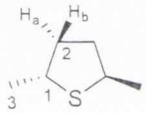
obtained as a pale yellow oil (2.32 g) which was sufficiently pure to be used directly in the next step. $[\alpha]_D^{20}$ = +17.1 (*c* 0.54, $CHCl_3$). The NMR spectra of **387** were consistent with those previously reported.[66a]

δ_H (400 MHz, $CDCl_3$): 1.44 (d, J 6.4, 6H, H-1), 1.72-1.87 (m, 4H, H-3), 3.02 (s, 6H, H-4), 4.85-4.88 (m, 2H, H-2).

δ_C (100 MHz, $CDCl_3$): 20.8, 31.6, 38.3, 78.4.

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_8H_{18}O_6S_2Na$ 297.0443; found 297.0455.

5.3.2 (2*R*,5*R*)-2,5-Dimethylthiolane (87)



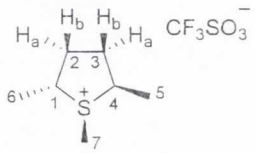
Sodium sulfide nonahydrate (4.120 g, 17.152 mmol) was added to a solution of the preceding dimesylate **387** (2.322 g, 8.462 mmol) in ethanol (22 cm^3). The reaction mixture was stirred at room temperature for 186 h. The resulting solution was poured into water (15 cm^3) and extracted with pentane (4 x 15 cm^3). The combined organic extracts were washed with brine (15 cm^3) and dried over $MgSO_4$. The crude product was purified by flash chromatography (100 % pentane) to afford **87** as a yellow oil (781 mg, 52%). Note: due to the volatile nature of the product, the solvent was removed with the water bath set at 0 °C. $[\alpha]_D^{20}$ = +152.0 (*c* 1.1, Et_2O); lit.,[229] $[\alpha]_D^{20}$ = +139 (*c* 1.22, Et_2O). The NMR spectra of **87** were consistent with those previously reported.[66a]

δ_H (400 MHz, $CDCl_3$): 1.29 (d, J 6.6, 6H, H-3), 1.50-1.55 (m, 2H, H-2a), 2.14-2.21 (m, 2H, H-2b), 3.56-3.60 (m, 2H, H-1).

δ_C (100 MHz, $CDCl_3$): 22.7, 39.5, 44.5.

HRMS (CI): $[M+H]^+$ Calcd. for $C_6H_{13}S$ 117.0738; found 117.0738.

5.3.3 (2*R*,5*R*)-2,5-Dimethylthiolane triflate (308)



Prepared according to general procedure H using **87** (58 mg, 0.501 mmol), CH_2Cl_2 (0.5 cm^3) and methyl triflate (56 μL, 0.501 mmol). **308** Was obtained as a pale yellow oil in quantitative yield. $[\alpha]_D^{20} = +28.2$ (*c* 0.5, $CHCl_3$).

δ_H (600 MHz, $CDCl_3$): 1.59 (d, J 6.8, 3H, H-5), 1.70 (d, J 7.0, 3H, H-6), 1.87-1.94 (m, 1H, H-2b), 2.21-2.28 (m, 1H, H-3b), 2.52-2.57 (m, 1H, H-3a), 2.65-2.70 (m, 1H, H-2a), 2.88 (s, 3H, H-7), 4.12-4.21 (m, 2H, H-1 and H-4).

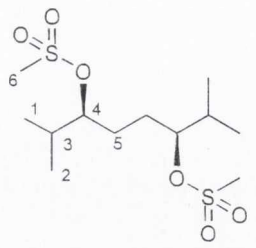
δ_C (100 MHz, $CDCl_3$): 13.5, 18.6, 18.8, 36.0, 36.7, 54.6, 62.5.

δ_F (376 MHz, $CDCl_3$): -78.4 (s, 3F).

υ (cm^{-1}): 757, 1027, 1152, 1223, 1249, 1460, 2939.

HRMS (ESI): $[M]^+$ Calcd. for $C_7H_{15}S$ 131.0894; found 131.0888.

5.3.4 (3*S*,6*S*)-2,7-Dimethyl-3,6-di-O-methanesulfonyloxyoctane (312)



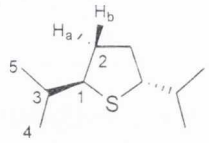
A solution of (3*S*,6*S*)-2,7-dimethyl-3,6-octanediol (1.256 g, 7.21 mmol) and triethylamine (2.44 cm^3, 17.51 mmol) in CH_2Cl_2 (15 cm^3) was cooled to –15 °C. Methanesulfonyl chloride (1.23 cm^3, 15.86 mmol) was added dropwise at this temperature. The reaction mixture was allowed to warm to 0 °C at which time 1 M HCl (2.2 cm^3) was added. The resulting solution was transferred to a separating funnel, extracted with CH_2Cl_2 (3 x 15 cm^3) and dried over $MgSO_4$. The product was purified by flash chromatography (7:3 hexane:EtOAc) to afford **312** as a pale yellow oil (2.334 g, 98%). $[\alpha]_D^{20}$ = -2.9 (*c* 0.51, $CHCl_3$). The NMR spectra of **312** were consistent with those previously reported.[230]

δ_H (400 MHz, $CDCl_3$): 0.99 (app. t, 12H, H-1 and H-2), 1.74-1.89 (m, 4H, H-5), 1.98-2.06 (m, 2H, H-3), 3.03 (s, 6H, H-6), 4.59-4.63 (m, 2H, H-4).

δ_C (100 MHz, $CDCl_3$): 17.2, 17.6, 26.2, 31.2, 38.3, 86.9.

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_{12}H_{26}O_6S_2Na$ 353.1069; found 353.1072.

5.3.5 (2*R*,5*R*)-2,5-Diisopropyl-thiolane (309)



Sodium sulfide nonahydrate (2.839 g, 11.822 mmol) was added to a solution of the preceding dimesylate **312** (1.915 g, 5.795 mmol) in ethanol (29 cm^3). The reaction mixture was stirred at room temperature for 7 days. The resulting solution was transferred to a separating funnel, extracted with CH_2Cl_2 (3 x 30 cm^3) and dried over $MgSO_4$. The product was purified by flash chromatography (100% hexane) to afford **309** as a yellow oil (382 mg, 38%). Note: due to the volatile nature of the product, the solvent was removed with the water bath set at 0 °C. $[\alpha]_D^{20} = -141.3$ (*c* 0.75, Et_2O).

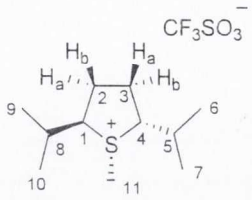
δ_H (400 MHz, $CDCl_3$): 0.94 (d, J 6.6, 6H, H-4), 0.99 (d, J 6.6, 6H, H-5), 1.47-1.52 (m, 2H, H-2b), 1.61-1.70 (m, 2H, H-3), 2.18-2.21 (m, 2H, H-2a), 3.11-3.17 (m, 2H, H-1).

δ_C (100 MHz, $CDCl_3$): 20.6, 22.0, 34.8, 35.6, 57.0.

υ (cm^{-1}): 969, 1043, 1156, 1228, 1366, 1383, 1467, 2868, 2956.

HRMS (CI): $[M+H]^+$ Calcd. for $C_{10}H_{21}S$ 173.1364; found 173.1362.

5.3.6 (2*R*,5*R*)-2,5-Diisopropyl-thiolane triflate (310)



Prepared according to general procedure H using **309** (17 mg, 0.099 mmol), CH_2Cl_2 (0.5 cm^3) and methyl triflate (10.8 μL, 0.099 mmol). After 2 h reaction time, **310** was obtained as a viscous yellow oil in quantitative yield. $[\alpha]_D^{20} = -168.3$ (*c* 0.3, CH_2Cl_2).

δ_H (600 MHz, $CDCl_3$): 1.12 (d, J 6.4, 3-H, H-9), 1.16-1.18 (m, 9H, H-10, H-6 and H-7), 1.87 (ddd, J 27.3, 12.3, 5.5, 1H, H-2b), 2.10 (m, 1H, H-5), 2.21 (qd, J 7.1, 6.8, 1H, H-8), 2.45 (ddd, J 27.6, 13.2, 5.5, 1H, H-3b), 2.56 (m, 1H, H-3a), 2.73 (m, 1H, H-2a), 2.91 (s, 3H, H-11), 3.42 (m, 1H, H-4), 4.26 (m, 1H, H-1).

δ_C (150 MHz, $CDCl_3$): 19.8, 20.3, 20.9, 21.1, 22.9, 28.2, 31.7, 32.8, 32.9, 68.5, 75.1.

δ_F (376 MHz, $CDCl_3$): -78.9 (s, 3F).

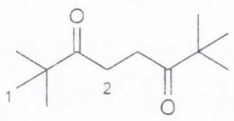
υ (cm^{-1}): 755, 841, 952, 968, 1027, 1158, 1224, 1260, 1371, 1389, 1425, 1449, 1471, 2877, 2961.

HRMS (ESI): $[M]^+$ Calcd. for $C_{11}H_{23}S$ 187.1520; found 187.1517.

5.3.7 General procedure J: the epoxidation of benzaldehyde (48) by 308 and 310 (Tables 3.1 and 3.2)

An oven dried 5 cm^3 round bottomed flask was charged with **308** or **310** (1 equiv.) and (*E*)-stilbene (0.5 equiv.). The flask was fitted with a septum and placed under an atmosphere of argon (balloon). CH_2Cl_2 and freshly distilled benzaldehyde (1 equiv.) were then added sequentially *via* syringe. At the required temperature, the resulting solution was treated with P_2-*t*-butyl solution (2.0 M in THF, 1 equiv.). The reaction mixture was allowed to stir at this temperature for the required period of time.

5.3.8 2,2,7,7-Tetramethyl-3,6-octanedione (315)



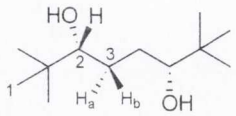
3-Methylbutan-2-one (**316**, 2.48 cm^3, 19.98 mmol) was added dropwise to a solution of dry THF (27 cm^3) and LDA (1.8 M in THF/heptane/ethylbenzene, 12.8 cm^3, 22.98 mmol) at -78 °C. After 15 min, anhydrous $CuCl_2$ (3.224 g, 23.98 mmol) in dry DMF (22 cm^3) was added simultaneously at the same temperature. The dark green solution was stirred for an additional 30 min and then allowed to reach room temperature. The solution was transferred to a separating funnel. The solution was acidified and extracted with Et_2O (4 x 50 cm^3). The combined organic extracts were combined, washed with H_2O (5 x 50 cm^3) and dried over $MgSO_4$. Purification by flash chromatography (6:4 hexane:$CHCl_2$) afforded **315** as a pale yellow oil (1.911 g, 48%). The NMR spectra of **315** were consistent with those previously reported.[231]

δ_H (400 MHz, $CDCl_3$): 1.20 (s, 18H, H-1), 2.79 (s, 4H, H-2).

δ_C (100 MHz, $CDCl_3$): 26.2, 30.0, 43.5 (q), 214.4 (C=O).

HRMS (ESI): $[M+H]^+$ Calcd. for $C_{12}H_{23}O_2$ 199.1698; found 199.1696.

5.3.9 (3*R*,6*R*)-2,2,7,7-Tetramethyloctan-3,6-diol (314)

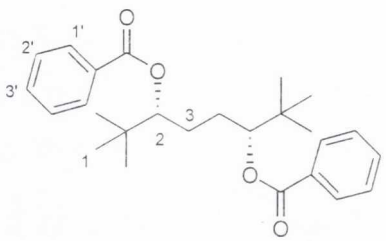


Trimethyl borate (174 μL, 1.55 mmol) was added to a stirred solution of (*S*)-α,α-diphenyl-2-pyrrolidine methanol (302.6 mg, 1.19 mmol) in THF (8.5 cm^3) and stirred for 1 h. After borane-dimethyl sulfide complex (1.42 cm^3, 14.89 mmol) was added, a solution of **315** (1.393 g, 7.03 mmol) in THF (19 cm^3) was added over an hour. After a further hour, the resulting mixture was slowly quenched with 2 M HCl (10.5 cm^3). The aqueous layer was extracted with Et_2O (4 x 30 cm^3). The combined organic extracts were washed with H_2O and brine and dried over $MgSO_4$. The product was purified by flash chromatography (9:1 hexane:EtOAc) to afford the title compound **314** as a white solid (938 mg, 66%). M.p. 162-163 °C; lit.,[202] 142-143 °C. $[\alpha]_D^{20}$ = +55.6 (*c* 0.3, MeOH); lit.,[202] $[\alpha]_D^{25}$ = +37 (c 1.0, MeOH). The enantiomeric excess of the diol was determined to be >99% *ee* (*vide infra*, CSP-HPLC analysis of **318**). The NMR spectra of **314** were consistent with those previously reported.[202]

δ_H (400 MHz, $CDCl_3$): 0.90 (s, 18H, H-1), 1.37-1.46 (m, 2H, H-3a), 1.70-1.78 (m, 2H, H-3b), 2.13 (br, 2H, OH), 3.21 (app.d, 2H, H-2).

δ_C (100 MHz, $CDCl_3$): 25.7, 29.1, 35.0 (q), 80.5.

5.3.10 (3*R*,6*R*)-2,2,7,7-Tetramethyloctan-3,6-diol-benzoyl ester (318): benzoyl ester derivative of 314 for determination of enantiomeric excess by CSP-HPLC analysis.



To a solution of **314** (50 mg, 0.25 mmol) in THF (0.8 cm^3), was added under argon over 5 min, *n*-butyllithium (1.6 M in hexane, 340 μL, 0.54 mmol). After 30 min, the resulting solution was treated with the dropwise addition of a solution of benzoyl chloride (66 μL, 0.57 mmol) in THF (0.6 cm^3). The resulting solution was heated under reflux for 1 h and was subsequently cooled to 0 °C, at which time H_2O (1 cm^3) was added. The aqueous phase was extracted with Et_2O (3 x 5 cm^3), the combined organic phase dried over $MgSO_4$ and purified by flash chromatography (6:4 hexane:CH_2Cl_2) to afford **318** as a white solid (38.55 mg, 38%). M.p. 119-120 °C. $[\alpha]_D^{20}$ = -20.9 (*c* 0.07, $CHCl_3$).

CSP-HPLC analysis: CHIRALPAK AD-H (4.6 mm x 25 cm), hexane/IPA: 99.9/0.1, 1 mL min^{-1}, RT, UV detection at 220 nm, retention times: 12.1 min (single enantiomer).

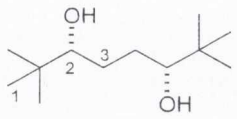
δ_H (400 MHz, $CDCl_3$): 0.92 (s, 18H, H-1), 1.59-1.69 (m, 4H, H-3), 5.10 (app.d, 2H, H-2), 7.45 (app.t, 4H, H-2'), 7.57 (t, J 7.4, 2H, H-3'), 8.05 (d, J 7.2, 4H, H-1').

δ_C (100 MHz, $CDCl_3$): 26.0, 26.4, 35.0 (q), 80.8, 128.4, 129.7, 130.6 (q), 132.8, 166.5 (C=O).

υ (cm^{-1}): 704, 929, 1113, 1268, 1708, 2872, 2961, 3069.

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_{26}H_{34}O_4Na$ 433.2355, found 433.2361.

5.3.11 (±)-2,2,7,7-Tetramethyloctan-3,6-diol (*dl*-314)



A 10 cm^3 round bottomed flask containing a magnetic stirring bar was charged with **315** (184 mg, 0.925 mmol) and methanol (5.6 cm^3) *via* syringe. The flask was fitted with a rubber septum when sodium borohydride (105 mg, 2.776 mmol) was added. The resulting solution was allowed to stir at room temperature for 1 h. The reaction mixture was quenched with H_2O (10 cm^3), transferred to a separating funnel and extracted with CH_2Cl_2 (3 x 20 cm^3). The combined organic phase was dried over $MgSO_4$, concentrated *in vacuo* and used in the next step without further purification. The title diol was obtained as a white solid in quantitative yield (*dl*:*meso* 70:30). M.p. 155-156 °C; lit.,[202] 142-143 °C. The NMR spectra of **(*dl*-314)** were consistent with those previously reported.[202]

***meso*-314**;

δ_H (400 MHz, $CDCl_3$): 0.91 (s, 18H, H-1), 1.29-1.34 (m, 2H, H-3a), 1.78-1.82 (m, 2H, H-3b), 3.27 (app. d, 2H, H-2).

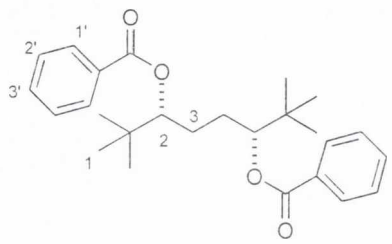
δ_C (100 MHz, CD_3OD): 81.4, 36.1 (q), 30.5, 26.4.

***dl*-314**;

δ_H (400 MHz, $CDCl_3$): 0.91 (s, 18H, H-1), 1.39-1.46 (m, 2H, H-3a), 1.72-1.78 (m, 2H, H-3b), 3.22 (app. d, 2H, H-2).

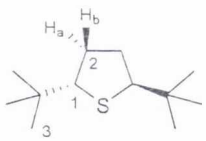
δ_C (100 MHz, CD_3OD): 80.2, 36.0 (q), 29.4, 26.4.

5.3.12 (±)-2,2,7,7-Tetramethyloctan-3,6-diol-benzoyl ester (*rac*-318)



To a solution of ***dl*-314** (79 mg, 0.391 mmol) in THF (1.2 cm^3), was added under argon over 5 min, *n*-butyllithium (1.6 M in hexane, 537 μL, 0.859 mmol). After 30 min, the resulting solution was treated with the dropwise addition of a solution of benzoyl chloride (100 μL, 0.859 mmol) in THF (0.86 cm^3). The resulting solution was heated under reflux for 1 h and was subsequently cooled to 0 °C, at which time H_2O (1 cm^3) was added. The aqueous phase was extracted with Et_2O (3 x 5 cm^3), dried over $MgSO_4$ and purified by flash chromatography (6:4 hexane:CH_2Cl_2) to afford ***rac*-318** as a white solid (35.27 mg, 22%). M.p. 117-119 °C. The spectroscopic data of ***rac*-318** were identical to those reported for **(*R*,*R*)-318**.

5.3.13 (2*S*,5*S*)-2,5-Di-*tert*-butylthiolane (313)



A solution of **(*R*,*R*)-314** (887 mg, 4.38 mmol) and triethylamine (1.48 cm^3, 10.65 mmol) in CH_2Cl_2 (9 cm^3) was cooled to −15 °C. Methanesulfonyl chloride (0.75 cm^3, 9.65 mmol) was added dropwise at this temperature. The reaction mixture was allowed to warm to 0 °C at which time 1 M HCl (1.5 cm^3) was added. The resulting solution was transferred to a separating funnel, extracted with CH_2Cl_2 (3 x 15 cm^3) and dried over $MgSO_4$. The product was purified by flash chromatography (8:2 hexane:EtOAc). The

resulting moderately unstable dimesylate[202] was not concentrated to dryness and was used directly in the next step.

Sodium sulfide nonahydrate (952 mg, 3.96 mmol) was added to a solution of the preceding dimesylate (700 mg, 1.95 mmol) in ethanol (8.7 cm^3). The reaction mixture was stirred at 50 °C for 15 h and after allowing the resulting solution to reach room temperature, it was poured into water (6 cm^3), extracted with pentane (4 x 15 cm^3) and dried over $MgSO_4$. The crude product was purified by flash chromatography (100 % hexane) to afford **313** as a yellow liquid (50 mg, 13%). $[\alpha]_D^{20} = +55.7$ (*c* 0.06, $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 0.98 (s, 18H, H-3), 1.55-1.60 (m, 2H, H-2a), 2.04-2.07 (m, 2H, H-2b), 3.29-3.33 (m, 2H, H-1).

δ_C (100 MHz, $CDCl_3$): 27.3, 32.1, 33.2 (q), 61.1.

HRMS (CI): $[M+H]^+$ Calcd. for $C_{12}H_{25}S$ 201.1677, found 201.1669.

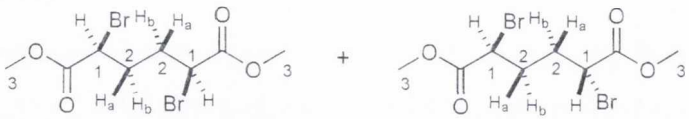
5.3.14 General procedure K: Catalytic asymmetric methylene transfer to benzaldehyde using sulfide 313 (Scheme 3.7)

A 5 cm^3 round bottomed flask containing a stirring bar was charged with **313** (9.9 mg, 0.049 mmol). The flask was fitted with a septum and placed under an atmosphere of argon (balloon). CH_2Cl_2 (0.47 cm^3) and styrene (28.3 μL, 0.247 mmol) were added consecutively *via* syringe. Proton sponge (52.9 mg, 0.247 mmol) was then added, followed by benzaldehyde (25.0 μL, 0.325 mmol). The first aliquot of methyl triflate (5.0 μL, 0.18 equiv.) was added and the resulting solution was allowed to stir at room temperature for 6.5 h. After this time, the first aliquot of P_2 base was added (2.0 M in THF, 22.2 μL, 0.18 equiv.) and allowed to stir for 30 min. The consecutive additions of methyl triflate and P_2 base were repeated four times (0.9 equiv. in total, *vide supra*). The remaining methyl triflate (3.6 μL, 0.1 equiv.) and P_2 base (2.0 M in THF, 16.2 μL, 0.1

equiv.) were then added following the same portionwise procedure (*vide supra*). Upon completion of this cycle, the reaction was analysed by ^{1}H NMR. The reaction was adjudged to be incomplete, thus the cycle was continued (*vide supra*) adding additional proton sponge (39.7 mg, 0.75 equiv.), methyl triflate (30.2 μL, 1.08 equiv.) and P_2 base (2.0 M in THF, 133.4 μL, 1.08 equiv.). Upon completion, the reaction mixture was diluted with water (5 cm^3) and extracted with CH_2Cl_2 (4 x 30 cm^3). The organic extracts were combined, washed with brine (20 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. After purification of the crude material by flash chromatography (6:4 hexane:CH_2Cl_2), the product **(*R*)-17** was obtained as a pale yellow liquid (20.8 mg, 70%, 43% *ee*).

CSP-HPLC analysis: CHIRALPAK AS (4.6 mm x 25 cm), hexane/IPA: 9.9/0.1, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: 6.6 min (major enantiomer) and 7.6 (minor enantiomer).

5.3.15 Dimethyl 2,5-dibromoadipate (325)



A 250 cm^3 round bottomed flask containing a magnetic stirring bar was charged with adipic acid (10 g, 68.428 mmol) and freshly distilled thionyl chloride (16 cm^3, 219.349 mmol) *via* syringe. A reflux condenser connected to a gas outlet, which was placed in a conical flask containing 5 M KOH solution, was attached to the flask and the reaction mixture was allowed to stir in an oil bath set at 90 °C for 1 h. The flask was then removed from the oil bath and allowed to reach room temperature when bromine (8 cm^3, 156.134 mmol) was added in two portions. The resulting solution was allowed to stir in an oil bath set at 50 °C overnight. The flask was removed from the oil bath and allowed to reach room temperature. A separate 500 cm^3 round bottomed flask containing a magnetic stirring bar was charged with methanol (150 cm^3) and cooled to 0 °C using an ice bath. The cooled reaction mixture was slowly poured into the methanol and allowed to stir for

30 min. The resulting solution was transferred to a separating funnel and extracted with H_2O (200 cm^3) and CH_2Cl_2 (4 x 150 cm^3). The combined organic extracts were washed with 1 M sodium thiosulfate solution (100 cm^3), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (6:4 CH_2Cl_2:hexane) afforded **325** as a colourless solid (19.967 g, 88%). M.p. 75-76 °C; lit.,[232] 76-77 °C. The NMR spectra of **325** were consistent with those previously reported.[232] Note; both ***meso*-325** and ***dl*-325** were formed in the reaction and were inseparable by flash chromatography.

***meso*-325**;

δ_H (600 MHz, $CDCl_3$): 2.05-2.09 (m 2H, H-2a), 2.29-2.32 (m, 2H, H-2b), 3.795 (s, 6H, H-3), 4.24-4.27 (m, 2H, H-1).

δ_C (150 MHz, $CDCl_3$): 32.6, 44.4, 53.3, 169.79 (C=O).

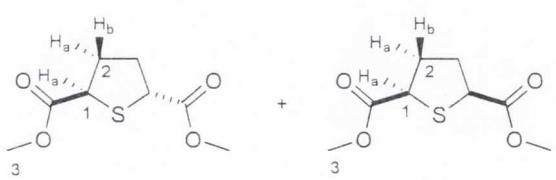
***dl*-325**;

δ_H (600 MHz, $CDCl_3$): 2.12-2.17 (m, 2H, H-2a), 2.19-2.25 (m, 2H, H-2b), 3.792 (s, 6H, H-3), 4.24-4.27 (m, 2H, H-1).

δ_C (150 MHz, $CDCl_3$): 32.4, 44.3, 53.3, 169.81 (C=O).

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_8H_{12}O_4BrNa$ 352.9000, found 352.8983.

5.3.16 Dimethyl tetrahydrothiophene-2,5-dicarboxylate (326)



Sodium sulfide nonahydrate (15.167 g, 63.151 mmol) was added to a solution of **325** (19.967 g, 60.143 mmol) in acetone (216 cm^3) and H_2O (24 cm^3). The reaction mixture was stirred at room temperature for 17 h. The resulting solution was poured into water (200 cm^3) and extracted with CH_2Cl_2 (3 x 200 cm^3). The combined organic extracts were washed with brine (200 cm^3) and dried over $MgSO_4$. The crude product was purified by flash chromatography (9:1 hexane:Et_2O) to afford both ***cis*-326** (4.532 g, 37%) and ***trans*-326** (4.640 g, 38%) as yellow liquids. The NMR spectra of **326** were consistent with those previously reported.[233]

***cis*-326**;

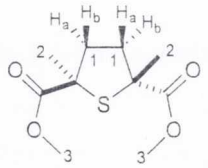
δ_H (400 MHz, $CDCl_3$): 2.11-2.19 (m, 2H, H-2b), 2.49-2.56 (m, 2H, H-2a), 3.72 (s, 6H, H-3), 3.98-4.01 (m, 2H, H-1a).

***trans*-326**;

δ_H (400 MHz, $CDCl_3$): 2.26-2.32 (m, 2H, H-2b), 2.39-2.45 (m, 2H, H-2a), 3.72 (s, 6H, H-3), 4.03-4.05 (m, 2H, H-1a).

HRMS (EI): $[M]^+$ calcd. for $C_8H_{12}O_4S$ 204.0456, found 204.0453.

5.3.17 *trans*-Dimethyl tetrahydro-2,5-dimethylthiophene-2,5-dicarboxylate (327)



An oven dried 100 cm^3 round bottomed flask containing a magnetic stirring bar was fitted with a rubber septum and placed under an atmosphere of argon (balloon). The flask was charged with diisopropylamine (1.58 cm^3, 11.261 mmol) followed by anhydrous THF (19.6 cm^3) *via* syringe. The solution was cooled to -78 °C when *n*-BuLi (1.6 M in

hexanes, 7 cm^3, 11.261 mmol) was added dropwise *via* syringe. The resulting solution was allowed to stir at this temperature for 20 min. The reaction mixture was then treated with ***cis*-326** (1.0 g, 4.896 mmol) in anhydrous THF (9.6 cm^3). The resulting solution was allowed to stir at this temperature for 20 min when methyl iodide (0.64 cm^3, 10.282 mmol) was added dropwise. The reaction mixture was allowed to stir in the cooling bath and reach room temperature overnight. The reaction mixture was quenched by the addition of H_2O (20 cm^3). The resulting solution was transferred to a separating funnel, extracted with CH_2Cl_2 (3 x 100 cm^3), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (9:1 hexane:Et_2O) afforded **327** as a yellow oil (203.7 mg, 18%).

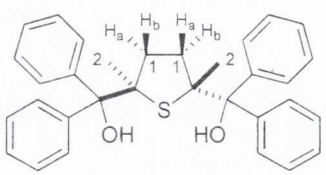
δ_H (600 MHz, $CDCl_3$): 1.61 (s, 6H, H-2), 2.07-2.13 (m, 2H, H-1a), 2.62-2.69 (m, 2H, H-1b), 3.73 (s, 6H, H-3).

δ_C (150 MHz, $CDCl_3$): 26.9, 41.3, 52.8, 59.9 (q), 175.6 (q).

υ (cm^{-1}): 768, 805, 987, 1091, 1138, 1167, 1253, 1277, 1434, 1457, 1727, 2867, 2953.

HRMS (GC-CI): $[M+H]^+$ Calcd. for $C_{10}H_{17}O_4S$ 233.0848; found 233.0840.

5.3.18 (*trans*-Tetrahydro-2,5-dimethylthiophen-2,5-yl)diphenylmethanol (328)



An oven dried 25 cm^3 round bottomed flask containing **327** (204 mg, 0.878 mmol) and a magnetic stirring bar was fitted with a rubber septum and placed under an atmosphere of

argon (balloon). Anhydrous THF (4.4 cm^3) was added *via* syringe. The resulting solution was cooled to 0 °C using an ice-bath when phenylmagnesium bromide (3.0 M in Et_2O, 1.76 cm^3, 5.269 mmol) was added dropwise *via* syringe. The resulting solution was allowed to reach room temperature and stir for 18 h. The reaction mixture was cooled to 0 °C and quenched by the addition of sat. $NH_4Cl_{(aq)}$ (2 cm^3). The resulting solution was transferred to a separating funnel, extracted using H_2O (30 cm^3) and Et_2O (4 x 25 cm^3), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (1:1 hexane:CH_2Cl_2) afforded **328** as a white solid (202 mg, 48%). M.p. 124-126 °C.

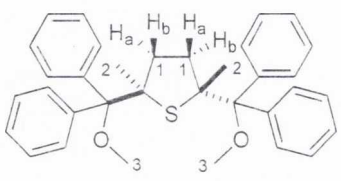
δ_H (400 MHz, $CDCl_3$): 1.18 (br s, 2H, H-1b), 1.81 (s, 6H, H-2), 2.80 (br s, 2H, H-1a), 3.90 (br s, 2H, OH), 7.25-7.50 (m, 20H, H-Ar).

δ_C (100 MHz, $CDCl_3$): 28.0, 37.9, 69.7 (q), 82.4 (q), 126.9, 127.0, 127.2, 127.7, 128.8, 129.5, 143.2 (q), 146.8 (q).

υ (cm^{-1}): 696, 735, 759, 878, 971, 1031, 1163, 1445, 1490, 2938, 3055, 3473, 3547.

HRMS (MALDI): $[M+Na]^+$ Calcd. for $C_{32}H_{32}O_2SNa$ 503.2021; found 503.2030.

5.3.19 *trans*-Tetrahydro-2,5-(methoxydiphenylmethyl)-2,5-dimethylthiophene (322)



An oven dried 10 cm^3 round bottomed flask containing a magnetic stirring bar was charged with **328** (157 mg, 0.327 mmol). The flask was fitted with a rubber septum and placed under an atmosphere of argon (balloon). Anhydrous THF (3.5 cm^3) was added *via*

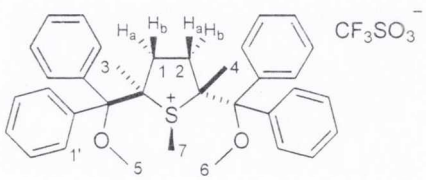
syringe. The resulting solution was treated with sodium hydride (60% dispersion in mineral oil, 52 mg, 1.307 mmol), followed by methyl iodide (160 μL, 2.613 mmol). The resulting solution was allowed to stir at room temperature for 16 h. The reaction mixture was quenched with H_2O (2 cm^3) and transferred to a separating funnel. Extraction was performed using H_2O (10 cm^3) and Et_2O (3 x 30 cm^3). The combined organic extracts were dried over $MgSO_4$. The crude product was purified by flash chromatography (7:3 hexane:CH_2Cl_2) to afford **322** as a pale yellow solid (144.2 mg, 87%). M.p. 93-94 °C.

δ_H (400 MHz, $CDCl_3$): 1.07 (br s, 2H, H-1b), 1.52 (s, 6H, H-2), 2.51 (br s, 2H, H-1a), 3.15 (s, 6H, H-3), 7.24-7.56 (m, 20H, H-Ar).

δ_C (100 MHz, $CDCl_3$): 28.7, 37.7, 54.5, 64.4 (q), 91.1 (q), 126.7, 126.9, 127.0, 127.1, 127.3, 127.8, 144.3 (q), 150.1.

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_{34}H_{36}O_2SNa$ 531.2334; found 531.2339.

5.3.20 *trans*-Tetrahydro-2,5-(methoxydiphenylmethyl)-2,5-dimethylthiophene triflate (323)



Prepared according to general procedure G, using **322** (100 mg, 0.197 mmol), proton sponge (12.64 mg, 0.059 mmol), CH_2Cl_2 (0.4 cm^3) and methyl triflate (22.3 μL, 0.197 mmol). The crude product was purified by flash chromatography (100% EtOAc) followed by recrystallisation from CH_2Cl_2:hexane to afford **323** as a white solid (72 mg, 55%). M.p. 102-103 °C.

δ_H (600 MHz, $CDCl_3$): 1.40-1.43 (m, 1H, H-1b), 1.79 (s, 6H, H-3 and H-4), 2.27 (s, 3H, H-7), 2.31 (dd, J 13.2, 5.3, 1H, H-2b), 2.96 (app. br t, 1H, H-2a), 3.03 (s, 3H, H-5), 3.13 (s, 3H, H-6), 3.33-3.39 (m, 1H, H-1a), 7.24 (d, J 7.5, 2H, H-1'), 7.38-7.64 (m, 18H, H-Ar).

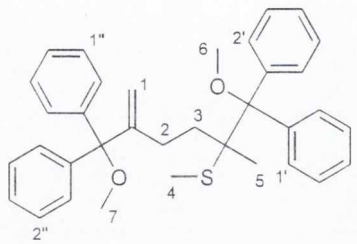
δ_C (150 MHz, $CDCl_3$): 21.0, 23.3, 24.5, 34.9, 40.6, 52.1, 53.9, 77.2 (q), 87.2 (q), 88.3 (q), 91.0 (q), 127.9, 128.4 (2 x C), 128.6, 128.7, 128.9, 129.4 (3 x C), 130.0, 130.4, 131.5, 134.3 (q), 135.2 (q), 137.1 (q), 138.1 (q).

HRMS (ESI): $[M]^+$ Calcd. for $C_{35}H_{39}O_2S$ 523.2671; found 523.2656.

5.3.21 General procedure L: the epoxidation of 48 and 78 by 323 (Schemes 3.9 and 3.11)

An oven dried 5 cm^3 round bottomed flask was charged with **323** (1.0 equiv.). The flask was fitted with a septum and placed under an atmosphere of argon (balloon). CH_2Cl_2 and the appropriate aldehyde (1.0 equiv.) were then added sequentially *via* syringe. At the required temperature, the resulting solution was treated with P_2-*t*-butyl solution (2.0 M in THF, 1.0 equiv.). The reaction mixture was allowed to stir at this temperature for the required period of time.

5.3.22 (1-Methoxy-5-(methoxydiphenylmethyl)-2-methyl-1,1-diphenylhex-5-en-2-yl)(methyl)sulfane (329)



329 Was obtained from the epoxidation reaction after purification by column chromatography (7:3 hexane:CH_2Cl_2) as a yellow oil.

δ_H (600 MHz, $CDCl_3$): 1.13 (s, 3H, H-5), 1.43-1.47 (m, 1H, H-3a), 1.63-1.67 (m, 1H, H-3b), 1.68 (s, 3H, H-4), 1.89-1.95 (m, 1H, H-2a), 2.23-2.29 (m, 1H, H-2b), 2.97 (s, 3H, H-6), 3.00 (s, 3H, H-7), 5.04 (s, 1H, H-1a), 5.35 (s, 1H, H-1b), 7.25-7.33 (m, 12H, H-Ar), 7.41 (app. t, 4H, H-1'' and H-2''), 7.61 (d, J 6.8, 2H, H-1'), 7.70-7.72 (m, 2H, H-2').

δ_C (150 MHz, $CDCl_3$): 13.8, 22.5, 27.4, 37.1, 52.0, 53.5, 56.8 (q), 88.3 (q), 91.6 (q), 113.1, 126.8, 126.89 (2xC), 126.93, 127.0, 127.1, 127.6, 128.9, 129.1, 130.6, 131.0, 140.2 (q), 140.4 (q), 141.5 (q), 141.6 (q), 151.6 (q).

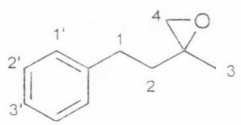
υ (cm^{-1}): 700, 752, 903, 1071, 1444, 1490, 2826, 2936, 3021, 3056.

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_{35}H_{38}O_2SNa$ 545.2490; found 545.2482.

5.3.23 General procedure M: catalytic methylene transfer to ketones using sulfide 124 (Table 3.4)

A 5 cm^3 round bottomed flask containing a stirring bar was charged with proton sponge (121.5 mg, 0.57 mmol). The flask was fitted with a rubber septum and placed under an atmosphere of argon (balloon). CH_2Cl_2 (1.80 cm^3) and styrene (65 μL, 0.57 mmol) were added sequentially *via* syringe. **124** (10 μL, 0.11 mmol, 0.2 equiv.) Was then added, followed by the appropriate ketone (0.57 mmol). The first aliquot of methyl triflate (11.6 μL, 0.18 equiv.) was added and the resulting solution was allowed to stir at room temperature for 25 min. The first aliquot of P_2 base was then added (2.0 M in THF, 51.0 μL, 0.18 equiv.) and allowed to stir for 25 min. The portionwise addition of methyl triflate and P_2 base was repeated four times with the same 25 minute intervals. The remaining methyl triflate (6.4 μL, 0.1 equiv.) and P_2 base (2.0 M in THF, 28.0 μL, 0.1 equiv.) were then added (*vide supra*). After 25 minutes, the reaction was analysed by ^1H NMR spectroscopy. If necessary, the remaining methyl triflate and P_2 base required for the reaction to reach completion was added. Upon completion, the crude material was purified by column chromatography to furnish the corresponding epoxide.

5.3.23.1 2-Methyl-2-(2-phenylethyl)oxirane (336)



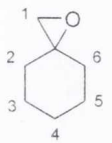
The desired epoxide was obtained following general procedure M using **330** (85 μL, 0.57 mmol), CH_2Cl_2 (1.80 cm^3), proton sponge (121.5 mg, 0.57 mmol), styrene (65 μL, 0.57 mmol), methyl triflate (64.2 μL, 0.57 mmol) and P_2 base (2.0 M in THF, 284 μL, 0.57 mmol). After purification of the crude material by flash chromatography (7:3 hexane:CH_2Cl_2) the product **336** was obtained as a colourless liquid (81.9 mg, 89%). The NMR spectra of **336** were consistent with those previously reported.[109a]

δ_H (400 MHz, $CDCl_3$): 1.38 (s, 3H, H-3), 1.80-1.97 (m, 2H, H-2), 2.58-2.61 (m, 2H, H-4), 2.70-2.74 (m, 2H, H-1), 7.18-7.21 (m, 3H, H-1' and H-3'), 7.26-7.30 (app. t, 2H, H-2').

δ_C (100 MHz, $CDCl_3$): 21.1, 31.5, 38.6, 54.0, 56.7 (q), 126.0, 128.3, 128.5, 141.6 (q).

HRMS (CI): $[M+H]^+$ Calcd. for $C_{11}H_{15}O$ 163.1123, found 163.1123.

5.3.23.2 1-Oxaspiro[2.5]octane (337)



The desired epoxide was obtained following general procedure M using **331** (58.7 μL, 0.57 mmol), CH_2Cl_2 (1.80 cm^3), proton sponge (121.5 mg, 0.57 mmol), styrene (65 μL, 0.57 mmol), methyl triflate (92.4 μL, 0.82 mmol) and P_2 base (2.0 M in THF, 408 μL, 0.82 mmol). To allow chromatography to be performed using 100% CH_2Cl_2 (desirable due to the volatile nature of **337**), upon completion of the reaction, methyl triflate (11.6 μL, 0.18 equiv.) was added (to ensure the formation of **320**) and allowed to stir for 25 min. After purification of the crude material by flash chromatography (100% CH_2Cl_2) with the water bath of the rotary evaporator set to 0 °C, the product **337** was obtained as a pale yellow liquid (60.4 mg, 95%). The NMR spectra of **337** were consistent with those previously reported.[234]

δ_H (400 MHz, $CDCl_3$): 1.48-1.59 (m, 8H, H-2b, H-3, H-4, H-5 and H-6b), 1.71-1.77 (m, 2H, H-2a and H-6a), 2.59 (s, 2H, H-1).

δ_C (100 MHz, $CDCl_3$): 24.5 (2 x CH_2), 24.8, 33.2 (2 x CH_2), 54.0, 58.6 (q).

HRMS (EI): $[M]^+$ calcd. for $C_7H_{12}O$ 112.0888; found 112.0888.

5.3.23.3 6-*tert*-Butyl-1-oxaspiro[2.5]octane (338)

The desired epoxide was obtained following general procedure M using **332** (87.47 mg, 0.57 mmol), CH_2Cl_2 (1.80 cm^3), proton sponge (121.5 mg, 0.57 mmol), styrene (65 μL, 0.57 mmol), methyl triflate (75.7 μL, 0.67 mmol) and P_2 base (2.0 M in THF, 334.6 μL, 0.67 mmol). After purification of the crude material by flash chromatography (7:3 hexane:CH_2Cl_2) the product **338** was obtained as a pale yellow liquid: *dr* (O-*eq*:O-*ax*) 60:40; (89.2 mg, 93%). The NMR spectra of **338** were consistent with those previously reported.[234]

O-*ax*-338;

δ_H (600 MHz, $CDCl_3$): 0.88 (s, 9H, H-5), 1.07-1.08 (m, 1H, H-4), 1.27-1.31 (m, 2H,H-2a), 1.32-1.40 (m, 2H, H-3a), 1.76-1.81 (m, 2H, H-3b), 1.83-1.90 (m, 2H, H-2b), 2.63 (s, 2H, H-1).

δ_C (150 MHz, $CDCl_3$): 24.9, 27.7, 32.5 (q), 33.4, 47.2, 53.9, 58.4 (q).

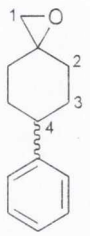
O-*eq*-338;

δ_H (600 MHz, $CDCl_3$): 0.88 (s, 9H, H-5), 1.07-1.08 (m, 1H, H-4), 1.15-1.23 (m, 2H, H-3a), 1.29-1.34 (m, 2H, H-2a), 1.82-1.88 (m, 2H, H-2b), 1.88-1.93 (m, 2H, H-3b), 2.59 (s, 2H,H-1).

δ_C (150 MHz, $CDCl_3$): 26.6, 27.6, 32.4 (q), 33.9, 47.2, 55.1, 59.9 (q).

HRMS (EI): $[M]^+$ calcd. for $C_{11}H_{20}O$ 168.1514; found 168.1506.

5.3.23.4 6-Phenyl-1-oxaspiro[2.5]octane (339)



The desired epoxide was obtained following general procedure M using **333** (98.81 mg, 0.57 mmol), CH_2Cl_2 (1.80 cm^3), proton sponge (121.5 mg, 0.57 mmol), styrene (65 μL, 0.57 mmol), methyl triflate (75.7 μL, 0.67 mmol) and P_2 base (2.0 M in THF, 334.6 μL, 0.67 mmol). After purification of the crude material by flash chromatography (8:2 hexane:CH_2Cl_2), the product **339** was obtained as a pale yellow liquid: *dr* (O-*eq*:O-*ax*) 60:40; (100.4 mg, 94%). The NMR spectra of **339** were consistent with those previously reported.[108f]

O-*ax*-339;

δ_H (600 MHz, $CDCl_3$): 1.37-1.41 (m, 2H, H-2a), 1.84-1.94 (m, 4H, H-3), 2.03-2.09 (m, 2H, H-2b), 2.59-2.65 (m, 1H, H-4), 2.70 (s, 2H, H-1), 7.19-7.32 (m, 5H, H-Ar).

δ_C (150 MHz, $CDCl_3$): 31.7, 33.4, 43.49, 54.1, 57.9 (q), 126.3, 127.0, 128.57, 146.8 (q).

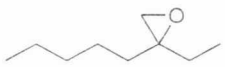
O-*eq*-339;

δ_H (600 MHz, $CDCl_3$): 1.41-1.44 (m, 2H, H-2a), 1.67-1.75 (m, 2H, H-3a), 2.03-2.09 (m, 4H, H-2b and H-3b), 2.59-2.65 (m, 1H, H-4), 2.67 (s, 2H, H-1), 7.19-7.32 (m, 5H, H-Ar).

δ_C (150 MHz, $CDCl_3$): 33.4, 34.0, 43.46, 55.1, 59.4 (q), 126.4, 126.9, 128.6, 146.3 (q).

HRMS (EI): $[M]^+$ calcd. for $C_{13}H_{16}O$ 188.1201; found 188.1204.

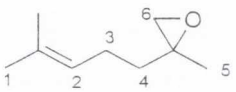
5.3.23.5 2-Ethyl-1,2-epoxyheptane (340)



The desired epoxide was obtained following general procedure M using **334** (88.5 μL, 0.57 mmol), CH_2Cl_2 (1.80 cm^3), proton sponge (121.5 mg, 0.57 mmol), styrene (65 μL, 0.57 mmol), methyl triflate (87.3 μL, 0.77 mmol) and P_2 base (2.0 M in THF, 385.5 μL, 0.77 mmol). Completion of the reaction afforded **340** (83%, the yield was determined by ^1H NMR spectroscopy using styrene as an internal standard).

HRMS (EI): $[M]^+$ calcd. for $C_9H_{18}O$ 142.1358; found 142.1361.

5.3.23.6 2-Methyl-2-(4-methyl-pent-3-enyl)-oxirane (341)



The desired epoxide was obtained following general procedure M using **335** (83.7 μL, 0.57 mmol), CH_2Cl_2 (1.80 cm^3), proton sponge (121.5 mg, 0.57 mmol), styrene (65 μL, 0.57 mmol), methyl triflate (75.7 μL, 0.67 mmol) and P_2 base (2.0 M in THF, 334.6 μL, 0.67 mmol). After purification of the crude material by flash chromatography (8:2 hexane:CH_2Cl_2), the product **341** was obtained as a pale yellow liquid (71.6 mg, 90%). The NMR spectra of **341** were consistent with those previously reported.[235]

δ_H (400 MHz, $CDCl_3$): 1.32 (s, 3H, H-5), 1.47-1.65 (m, 5H, H-1b and H-4), 1.68 (s, 3H, H-1a), 2.07 (app. q, 2H, H-3), 2.57 (d, J 4.9, 1H, H-6a), 2.62 (d, J 4.9, 1H, H-6b), 5.09 (t, 7.0, 1H, H-2).

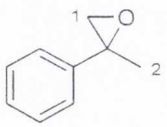
δ_C (100 MHz, $CDCl_3$): 25.7, 17.7, 21.0, 23.9, 36.8, 54.0, 56.9 (q), 123.6, 132.0 (q).

HRMS (EI): $[M]^+$ calcd. for $C_9H_{16}O$ 140.1201; found 140.1201.

5.3.24 General procedure N: the epoxidation of 146 by 310 (Scheme 3.13)

An oven dried 5 cm^3 round bottomed flask containing **310** (68.0 mg, 0.203 mmol) in CH_2Cl_2 (1.9 cm^3) was fitted with a septum and placed under an atmosphere of argon (balloon). **146** (23 μL, 0.203 mmol) and P_2 (2.0 M in THF, 102 μL, 0.203 mmol) were added sequentially *via* syringe. The reaction mixture was allowed to stir for 30 min. The crude material was purified by flash chromatography on deactivated silica gel (silica slurry prepared using 8:2:2 hexane:CH_2Cl_2:triethylamine) (9:1 hexane:CH_2Cl_2 used as eluent).

5.3.24.1 α-Methylstyrene oxide (147)



Prepared according to general procedure N using **310** (68 mg, 0.203 mmol), acetophenone (23 μL, 0.203 mmol), CH_2Cl_2 (1.9 cm^3) and P_2 base (2.0 M in THF, 102 μL, 0.203 mmol). **147** Was obtained as a pale yellow liquid (71% conversion, determined by ^1H NMR spectroscopy). The NMR spectra of **147** were consistent with those previously reported.[109a]

CSP-HPLC analysis: CHIRALCEL OD (4.6 mm x 25 cm), hexane/IPA: 99/1, 0.5 mL min^{-1}, RT, UV detection at 220 nm, retention times: 10.6 min (minor enantiomer) and 11.9 min (major enantiomer).

δ_H (400 MHz, $CDCl_3$): 1.75 (s, 3H, H-2), 2.83 (d, J 5.5, 1H, H-1a), 3.00 (d, J 5.5, 1H, H-1b), 7.28-7.40 (m, 5H, H-Ar).

δ_C (100 MHz, $CDCl_3$): 21.4, 56.3 (q), 56.6, 124.8, 127.0, 127.8, 140.7 (q).

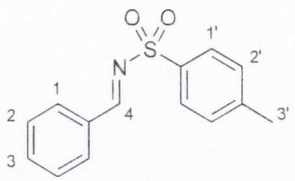
HRMS (EI): $[M]^+$ calcd. for $C_9H_{10}O$ 134.0732; found 134.0730.

5.4 Experimental data for Chapter 4

5.4.1 General procedure O: the preparation of imines 184, 344 and 353

An oven dried round bottomed flask was charged with the appropriate sulfonamide or phosphinamide (1 equiv.), fitted with a septum and placed under an atmosphere of argon (balloon). CH_2Cl_2 was then added *via* syringe followed by triethylamine (3 equiv.) and the appropriate aldehyde (1 equiv.). The resulting solution was cooled to 0 °C. Titanium(IV) chloride (0.5 equiv.) in CH_2Cl_2 was then added dropwise to the cooled solution and the resulting solution was allowed to stir for 1 h at this temperature. The reaction mixture was filtered through celite and washed with CH_2Cl_2. The filtrate was concentrated *in vacuo* and the resulting solid was suspended in toluene and then filtered. The filtrate was then concentrated under reduced pressure to afford the desired imine which was purified as required.

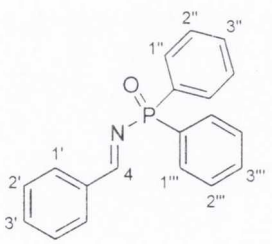
5.4.2 *N*-(Benzylidene)-4-methylbenzenesulfonamide (184)



Prepared according to general procedure O using *p*-toleunesulfonamide (3.253 g, 19 mmol), triethylamine (7.9 cm^3, 57 mmol), benzaldehyde (1.92 cm^3, 19 mmol), CH_2Cl_2 (40 cm^3) and titanium(IV) chloride (1.04 cm^3, 9.5 mmol) in CH_2Cl_2 (10 cm^3). The crude product was recrystallised from CH_2Cl_2:hexane to afford **184** as an off-white solid (1.9 g, 39%). M.p. 103-104 °C; lit.,[236] 110-111 °C. The NMR spectra of **184** were consistent with those previously reported.[236]

δ_H (400 MHz, $CDCl_3$): 2.44 (s, 3H, H-3'), 7.35 (d, J 8.0, 2H, H-1), 7.49 (app. t, J 8.0, 2H, H-2), 7.62 (t, J 7.5, 1H, H-3), 7.88-7.94 (m, 4H, H-1' and H-2'), 9.03 (s, 1H, H-4).

5.4.3 *P,P*-Diphenyl-*N*-(phenylmethylene)phosphinic amide (344)



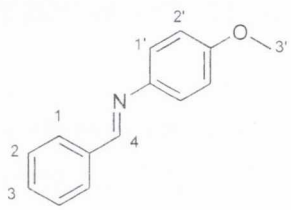
Prepared according to general procedure O using diphenylphosphinamide (651 mg, 3 mmol), triethylamine (1.25 cm^3, 9 mmol), benzaldehyde (303 μL, 3 mmol), CH_2Cl_2 (20 cm^3) and titanium(IV) chloride (110 μL, 1 mmol) in, CH_2Cl_2 (5 cm^3). The crude product was recrystallised from CH_2Cl_2:hexane to afford **344** as a white solid (509.89 mg, 56%).

M.p. 123-125 °C; lit.,[237] 124-126 °C. The NMR spectra of **344** were consistent with those previously reported.[238]

δ_H (400 MHz, $CDCl_3$): 7.43-7.53 (m, 8H, H-2', H-2'', H-2''', H-3'' and H-3'''), 7.59 (t, J 7.4, 1H, H-3'), 7.92-7.97 (m, 4H, H-1'' and H-1'''), 8.02 (d, J 7.2, 2H, H-1'), 9.33 (d, J 32.1, 1H, H-4).

δ_P (162 MHz, $CDCl_3$): 24.9 (s, 1P).

5.4.4 *N*-Benzylidene-4-methoxybenzenamine (346)

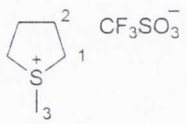


A 50 cm^3 round bottomed flask containing a magnetic stirring bar was charged with anhydrous magnesium sulfate, followed by CH_2Cl_2 (15 cm^3) *via* syringe. The flask was fitted with a rubber septum and placed under an atmosphere of argon (balloon). *p*-Anisidine (738.9 mg, 6.00 mmol) and benzaldehyde (606 μL, 6.00 mmol) were then added and the resulting solution was allowed to stir at ambient temperature for 16 h. The resulting solution was filtered and the filtrate was concentrated *in vacuo*. The resulting solid was washed several times with hexane which afforded pure **346** (1.128 g, 89%) as pale brown crystalline flakes. M.p. 78-80 °C; lit.,[239] 70-71 °C. The NMR spectra of **346** were consistent with those previously reported.[239]

δ_H (400 MHz, $CDCl_3$): 3.84 (s, 3H, H-3'), 6.95 (d, J 8.9, 2H, H-2'), 7.25 (d, J 8.9, 2H, H-1'), 7.46-7.49 (m, 3H, H-2 and H-3), 7.89-7.91 (m, 2H, H-1), 8.49 (s, 1H, H-4).

δ_C (100 MHz, $CDCl_3$): 55.6, 114.5, 122.3, 128.7, 128.9, 131.2, 136.5 (q), 145.0 (q), 158.4 (q), 158.6.

5.4.5 Methyltetrahydrothiophene triflate (320)



Prepared according to general procedure H using tetrahydrothiophene (80.0 μL, 0.907 mmol), CH_2Cl_2 (4.5 cm^3) and methyl triflate (99.5 μL, 0.907 mmol). Purification by recrystallisation from CH_2Cl_2:hexane afforded **320** as a white solid (199.14 mg, 87%). M.p. 246-247 °C.

δ_H (400 MHz, $CDCl_3$): 2.35-2.47 (m, 4H, H-2), 2.93 (s, 3H, H-3), 3.38-3.44 (m, 2H, H-1a), 3.71-3.77 (m, 2H, H-1b).

δ_C (100 MHz, $CDCl_3$): 26.2, 28.5, 45.4.

δ_F (376 MHz, $CDCl_3$): -79.0 (s, 3F).

υ (cm^{-1}): 756, 879, 1028, 1151, 1224, 1254, 1421, 2969, 3029.

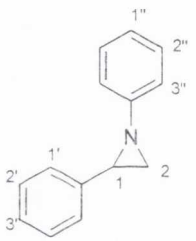
HRMS (ESI): $[M]^+$ Calcd. for $C_5H_{11}S$ 103.0581; found 103.0580.

5.4.6 General procedure P: the aziridination of imines 184, 344-346 and 353 by 310, 320, 355 or 368 (Scheme 4.2, 4.5 and 4.12 and Tables 4.1-4.5)

An oven dried round bottomed flask containing a magnetic stirring bar and sulfonium salt **310** or **320** (1 equiv.) was charged with proton sponge (1 equiv.) and the appropriate

imine (1 equiv.). The flask was placed on a Schlenk line for 1 h. The flask was then immediately flushed with argon, fitted with a rubber septum and placed under an atmosphere of argon (balloon). Freshly distilled CH_2Cl_2 and styrene (1 equiv.) were then added sequentially *via* syringe. The resulting solution was allowed to stir at the appropriate temperature until such time as temperature equilibration was reached. P_2 base (2.0 M in THF, 1 equiv.) was then added dropwise. Upon completion (analysis by ^1H NMR spectroscopy), the crude material was purified by column chromatography to furnish the corresponding aziridine.

5.4.7 (-)-1,2-Diphenylaziridine (349)



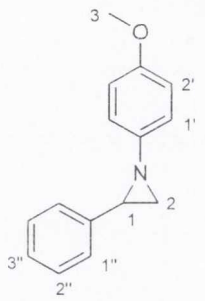
Prepared according to general procedure P at ambient temperature using **310** (86.23 mg, 0.256 mmol), proton sponge (54.93, 0.256 mmol), **345** (46.45 mg, 0.256 mmol), CH_2Cl_2 (0.64 cm^3), styrene (29.4 μL, 0.256 mmol) and P_2 base (128.2 μL, 0.256 mmol). Upon completion, *i.e.* 1.5 h, the crude material was purified by column chromatography (6:4 hexane:CH_2Cl_2) to furnish **349** as a light yellow oil (31%, 13% *ee*, the yield was determined by ^1H NMR spectroscopy using styrene as an internal standard). $[\alpha]_D^{20}$ = -59.3 (*c* 0.1, $CHCl_3$, 13% *ee*); lit.,[240] $[\alpha]_D$ = -381.2 (*c* 0.25, $CHCl_3$). The NMR spectra of **349** were consistent with those previously reported.[240]

CSP-HPLC analysis: CHIRALCEL OJ-H (4.6 mm x 25 cm), hexane/IPA: 7/3, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 11.7 min (minor enantiomer) and 13.9 min (major enantiomer).

δ_H (400 MHz, $CDCl_3$): 2.41 (app. d, 1H, H-2a), 2.47 (app. d, 1H, H-2b), 3.11 (dd, J 6.6, 3.3, 1H, H-1), 6.99 (t, J 7.4, 1H, H-1''), 7.05 (d, J 7.7, 2H, H-3''), 7.24-7.40 (m, 7H, H-2'', H-1', H-2' and H-3').

HRMS (ESI): $[M+H]^+$ Calcd. for $C_{14}H_{14}N$ 196.1126; found 196.1120.

5.4.8 1-(4'-Methoxyphenyl)-2-phenylaziridine (350)

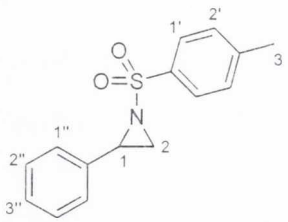


Prepared according to general procedure P at ambient temperature using **320** (60.00 mg, 0.238 mmol), proton sponge (50.97 mg, 0.238 mmol), **346** (50.25 mg, 0.238 mmol), CH_2Cl_2 (0.6 cm^3), styrene (27.3 μL, 0.238 mmol) and P_2 base (119.0 μL, 0.238 mmol). Upon completion, *i.e.* 40 min, the crude material was purified by column chromatography (95:5 hexane:Et_2O) to furnish **350** as a pale yellow oil (55%, the yield was determined by ^1H NMR spectroscopy using styrene as an internal standard). The NMR spectra of **350** were consistent with those previously reported.[240]

δ_H (400 MHz, $CDCl_3$): 2.37 (app. d, 1H, H-2a), 2.41 (app. d, 1H, H-2b), 3.03 (dd, J 6.6, 3.3, 1H, H-1), 3.77 (s, 3H, H-3), 6.80 (d, J 8.8, 2H, H-2'), 6.99 (d, J 8.7, 2H, H-1'), 7.28-7.39 (m, 5H, H-1'', H-2'' and H-3'').

HRMS (ESI): $[M+H]^+$ Calcd. for $C_{15}H_{16}NO$ 226.1232; found 226.1224.

5.4.9 (*R*)-2-Phenyl-1-(*p*-toluenesulfonyl)aziridine (343)

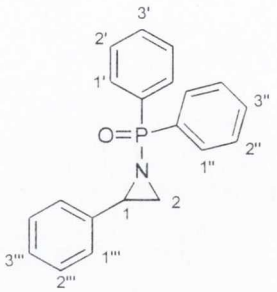


Prepared according to general procedure P at ambient temperature using **310** (80.04 mg, 0.238 mmol), proton sponge (50.99, 0.238 mmol), **184** (61.64 mg, 0.238 mmol), CH_2Cl_2 (0.60 cm^3), styrene (27.3 μL, 0.238 mmol) and P_2 base (119.0 μL, 0.238 mmol). Upon completion, *i.e.* 40 min, the crude material was purified by column chromatography (9:1 hexane:EtOAc) to furnish **343** as a white solid (87%, 6% *ee*, the yield was determined by ^1H NMR spectroscopy using styrene as an internal standard). M.p. 93-95 °C; lit.,[241] 92-93 °C. $[\alpha]_D^{20}$ = -15.3 (*c* 0.25, $CHCl_3$, 6% *ee*); lit.,[241] $[\alpha]_D^{24}$ = -80.25 (*c* 0.8, $CHCl_3$). The NMR spectra of **343** were consistent with those previously reported.[241]

CSP-HPLC analysis: CHIRALCEL OJ-H (4.6 mm x 25 cm), hexane/IPA: 1/1, 0.7 mL min^{-1}, RT, UV detection at 220 nm, retention times: 17.5 min (minor enantiomer) and 21.1 min (major enantiomer).

δ_H (400 MHz, $CDCl_3$): 2.39 (d, J 4.4, 1H, H-2a), 2.43 (s, 3H, H-3), 2.99 (d, J 7.1, 1H, H-2b), 3.77 (dd, J 7.1, 4.4, 1H, H-1), 7.20-7.34 (m, 7H, H-2', H-1'', H-2'' and H-3''), 7.87 (d, J 8.3, 2H, H-1').

5.4.10 *N*-Diphenylphosphinyl-2-phenyl aziridine (348)



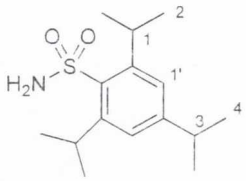
Prepared according to general procedure P at 60 °C using **310** (31.41 mg, 0.093 mmol), proton sponge (20.00 mg, 0.093 mmol), **344** (28.50 mg, 0.093 mmol), CH_2Cl_2 (0.23 cm^3), styrene (10.7 μL, 0.093 mmol) and P_2 base (47.0 μL, 0.093 mmol). Upon completion, *i.e.* 30 min, the crude material was purified by column chromatography (7:3 hexane:EtOAc) to furnish **348** as a white solid (98%, 10% *ee*, the yield was determined by ^1H NMR spectroscopy using styrene as an internal standard). M.p. 92-93 °C; lit.,[242] 91 °C. $[\alpha]_D^{20}$ = +25.3 (*c* 0.12, CH_2Cl_2, 10% *ee*); lit.,[242] (**(*S*)-348**) $[\alpha]_D^{23}$ = -4.6 (*c* 5, CH_2Cl_2). The NMR spectra of **348** were consistent with those previously reported.[242]

CSP-HPLC analysis: CHIRALPAK AD-H (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: 18.8 min (major enantiomer) and 28.9 (minor enantiomer).

δ_H (600 MHz, $CDCl_3$): 2.22 (ddd, J 13.1, 3.4, 1.6, 1H, H-2a), 2.94 (ddd, J 17.8, 6.2, 1.6, 1H, H-2b), 3.77 (ddd, J 15.6, 6.2, 3.4, 1H, H-1), 7.29-7.40 (m, 7H, H-1''',H-2''', H-3''' and H-2'), 7.44-7.56 (m, 4H, H-2'', H-3' and H-3''), 7.87-7.92 (m, 2H, H-1'), 7.97-8.03 (m, 2H, H-1'').

δ_P (162 MHz, $CDCl_3$): 33.9 (s, 1P).

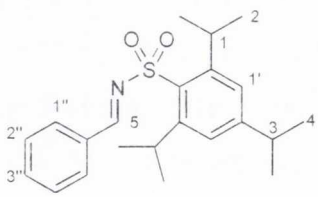
5.4.11 2,4,6-Triisopropylbenzenesulfonamide (352)



A 100 cm^3 round bottomed flask containing a stirring bar was charged with **351** (6.057 g, 20.00 mmol) followed by $CHCl_3$ (30 cm^3, 0.66 M). The solution was then treated with $NH_{3(aq)}$ (28% solution, 5.5 cm^3, 100 mmol) and allowed to stir at room temperature for 2 h. The reaction mixture was transferred to a separating funnel and extracted with $CHCl_3$ (3 x 30 cm^3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was placed on a frit, washed with hexane and dried by suction filtration to afford **352** (5.385 g, 95%) as a white solid. M.p. 130-131 °C; lit.,[243] 118.5-119.5 °C. The NMR spectra of **352** were consistent with those previously reported.[244]

δ_H (400 MHz, $CDCl_3$): 1.25 (d, J 6.8, 6H, H-4), 1.29 (d, J 6.8, 12H, H-2), 2.90 (septet, J 6.9, 1H, H-3), 4.11 (septet, J 6.7, 2H, H-1), 4.80 (br s, 2H, NH), 7.17 (s, 2H, H-1').

5.4.12 *N*-Phenylmethylidene-2-4-6-triisopropylbenzenesulfonamide (353)

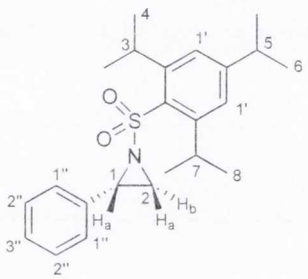


Prepared according to general procedure O using **352** (1 g, 3.528 mmol), triethylamine (1.5 cm^3, 10.585 mmol), benzaldehyde (357 μL, 3.528 mmol), CH_2Cl_2 (7 cm^3) and titanium(IV) chloride (195 μL, 1.764 mmol) in CH_2Cl_2 (2 cm^3). The product **353** was

obtained as an off-white solid (976 mg, 74%). M.p. 128-129 °C; lit.,[245] 128-130 °C. The NMR spectra of **353** were consistent with those previously reported.[245]

δ_H (400 MHz, $CDCl_3$): 1.26 (d, J 7.0, 6H, H-4), 1.29 (d, J 6.7, 12H, H-2), 2.91 (septet, J 7.0, 1H, H-3), 4.36 (septet, J 6.7, 2H, H-1), 7.20 (s, 2H, H-1'), 7.49 (app. t, 2H, H-2''), 7.61 (t, J 7.5, 1H, H-3''), 7.92 (d, J 7.1, 2H, H-1''), 9.02 (s, 1H, H-5).

5.4.13 (*R*)-2-Phenyl-1-(2-4-6-triisopropylbenzenesulfonyl)aziridine (354)



Prepared according to general procedure P at -78 °C using **310** (71.22 mg, 0.212 mmol), **353** (78.65 mg, 0.212 mmol), proton sponge (45.37 mg, 0.212 mmol), CH_2Cl_2 (2.65 cm^3), styrene (24.3 μL, 0.212 mmol) and P_2 base (2.0 M in THF, 106 μL, 0.212 mmol). Upon completion, *i.e.* 16 h, the crude material was purified by column chromatography (98:2 hexane:Et_2O) to furnish **354** as a white solid (72%, 22% *ee*, the yield was determined by ^1H NMR spectroscopy using styrene as an internal standard). M.p. 82-84 °C. $[\alpha]_D^{20} = -7.9$ (*c* 0.16, CH_2Cl_2, 23% *ee*).

CSP-HPLC analysis: CHIRALPAK AD-H (4.6 mm x 25 cm), hexane/IPA: 9.5/0.5, 0.5 mL min^{-1}, RT, UV detection at 220 nm, retention times: 10.0 min (minor enantiomer) and 12.2 (major enantiomer).

δ_H (400 MHz, $CDCl_3$): 1.23-1.28 (m, 18H, H-4, H-6 and H-8), 2.37 (d, J 4.4, 1H, H-2b), 2.90 (septet, J 6.9, 1H, H-5), 3.04 (d, J 7.2, 1H, H-

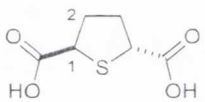
2a), 3.80 (dd, J 7.2, 4.4, 1H, H-1a), 4.40 (septet, J 6.8, 2H, H3 and H-7), 7.17 (s, 2H, H-1'), 7.18-7.21 (m, 2H, H-2''), 7.26-7.32 (m, 3H, H-1'' and H-3'').

δ_C (100 MHz, $CDCl_3$): 23.7, 24.9, 25.1, 29.9, 34.4, 36.3, 40.7, 124.0, 126.6, 128.3, 128.6, 131.4 (q), 135.8 (q), 151.4 (q), 153.7 (q).

υ (cm^{-1}): 694, 758, 1151, 1313, 1462, 1562, 1602, 2869, 2929, 2957.

HRMS (EI): $[M]^+$ Calcd. for $C_{23}H_{31}NO_2S$ 385.2076; found 385.2061.

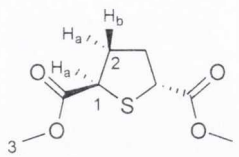
5.4.14 Tetrahydrothiophene-2,5-dicarboxylic acid (*rac*-356)



To a 100 cm^3 round bottomed flask containing ***trans*-326** (8.607 g, 42.141 mmol) and a magnetic stirring bar was added H_2O (50 cm^3) followed by conc. H_2SO_4 (2 cm^3). The flask was fitted with a reflux condenser and the reaction mixture was allowed to stir in an oil-bath set at 60 °C for 18 h. The resulting solution was cooled to 0 °C using an ice-bath and treated with 2 M $NaOH_{(aq)}$ until pH 10 was reached. The resulting solution was transferred to a separating funnel and extracted CH_2Cl_2 (3 x 100 cm^3). The aqueous phase was then treated with 1 M $HCl_{(aq)}$ until pH 1 was reached and extracted with Et_2O (4 x 200 cm^3). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford ***rac*-356** as a white solid (6.842 g, 92%). M.p. 167-169 °C; lit.,[233] 148-149 °C. The NMR spectra of ***rac*-356** were consistent with those previously reported.[233]

δ_H (400 MHz, (D_2O): 2.23-2.30 (m, 4H, H-2), 4.13-4.18 (m, 2H, H-1).

5.4.15 (*R,R*)-Dimethyl tetrahydrothiophene-2,5-dicarboxylate ((*R,R*)-326)



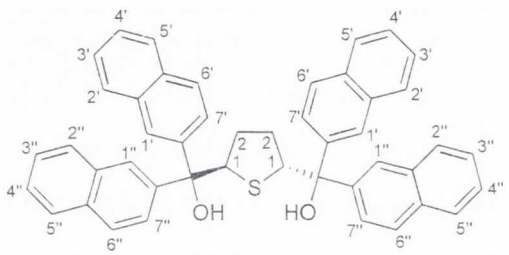
An equimolar amount of brucine dihydrate (15.314 g, 38.830 mmol) and ***rac*-356** (6.842 g, 38.830 mmol) were placed in a 500 cm^3 conical flask containing a magnetic stirring bar. Hot methanol was added along with and a few drops of H_2O (total volume *ca.* 200 cm^3) until fully dissolved. The resulting solution was allowed to stand at room temperature. The resulting crystals were recovered by decanting the mother liquor. The crystals (diacid/brucine salt) were decomposed with 2 M $NaOH_{(aq)}$ and the resulting solution was transferred to a separating funnel. Extraction of brucine was performed with CH_2Cl_2 (3 x 150 cm^3). The aqueous phase was then acidified to pH 1 using 1 M $HCl_{(aq)}$ and extracted with Et_2O (6 x 150 cm^3). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford **356**. This resolution process was repeated exactly (*vide supra*) and after the second resolution, **356** was obtained as a white solid (1.131 g, 17%).

To a 100 cm^3 round bottomed flask containing **(*R,R*)-356** (1.105 g, 6.272 mmol) and a magnetic stirring bar was added methanol (40 cm^3) followed by conc. H_2SO_4 (5 cm^3). The flask was fitted with a rubber septum and the reaction mixture was allowed to stir for 5 h. The resulting solution was transferred to a separating funnel and extracted with sat. $NaHCO_{3(aq)}$ (5 cm^3), H_2O (15 cm^3) and CH_2Cl_2 (3 x 50 cm^3). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford **326** as a white solid which was determined by CSP-HPLC analysis (*vide infra*), to be 92% *ee*. Recrystallisation of this material from CH_2Cl_2:hexane afforded enantiopure **(*R,R*)-326** as a crystalline white solid (1.088 g, 85%). M.p. 56-57 °C. $[\alpha]_D^{20} = -474.76$ (*c* 0.21, $CHCl_3$); lit.,[233] $[\alpha]_D^{23} = -17.27$ (*c* 3.52, $CHCl_3$). The NMR spectra of **(*R,R*)-326** were consistent with those previously reported.[233]

CSP-HPLC analysis: CHIRALCEL OD-H (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: 9.0 min (major enantiomer) and 6.8 (minor enantiomer)

δ_H (400 MHz, $CDCl_3$): 2.11-2.19 (m, 2H, H-2b), 2.49-2.56 (m, 2H, H-2a), 3.72 (s, 6H, H-3), 3.98-4.01 (m, 2H, H-1a).

5.4.16 ((2*R*,5*R*)-Tetrahydrothiophen-2,5-yl)di(naphthalen-3-yl)methanol ((*R*,*R*)-358)



An oven dried 50 cm^3 round bottomed flask containing a magnetic stirring bar was charged with 2-bromonaphthalene (2.433 g, 11.751 mmol). The flask was fitted with a rubber septum and placed under an atmosphere of argon (balloon). Anhydrous THF (15 cm^3) was added *via* syringe and the resulting solution was cooled to -78 °C. The resulting solution was treated, by dropwise addition, with *tert*-butyllithium solution (1.7 M in pentane, 6.9 cm^3, 11.75 mmol) and allowed to stir at this temperature for 30 min. An oven dried 5 cm^3 round bottomed flask containing a magnetic stirring bar was charged with **(*R*,*R*)-326** (300 mg, 1.469 mmol), fitted with a rubber septum and placed under an atmosphere of argon (balloon). Anhydrous THF (4 cm^3) was added *via* syringe. This solution was then added dropwise to the solution at -78 °C *via* syringe. The resulting solution was allowed to stir in the cooling bath and warm to room temperature overnight. The reaction mixture was quenched with sat. $NH_4Cl_{(aq)}$ (5 cm^3), transferred to a separating funnel, extracted with CH_2Cl_2 (4 x 150 cm^3) and dried over $MgSO_4$. The crude product was recrystallised from CH_2Cl_2:hexane to afford **358** as a white amorphous solid (826 mg, 86%). M.p. >282 °C (dec.). $[\alpha]_D^{20}$ = +769.7 (*c* 0.1, $CHCl_3$).

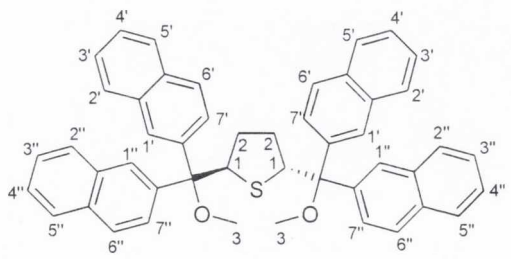
δ_H (600 MHz, $CDCl_3$): 1.60-1.68 (m, 2H, H-2b and H-3b), 2.06-2.15 (m, 2H, H-2a and H-3a), 3.85 (br s, 2H, OH), 4.97-5.04 (m, 2H, H-1), 7.42-7.50 (m, 10H, H-3', H-4', H-5', H-4'' and H-7''), 7.66 (dd, J 8.7, 1.8, 2H, H-7'), 7.72-7.76 (m, 6H, H-6', H-3'' and H-6''), 7.77 (d, J 8.0, 2H, H-5''), 7.86 (d, J 8.0, H-2''), 7.87 (d, J 7.5, 2H, H-2'), 8.11 (s, 2H, H-1''), 8.13 (s, 2H, H-1').

δ_C (150 MHz, $CDCl_3$): 31.7, 60.2, 78.0 (q), 123.9, 124.0, 124.1, 125.3, 125.9, 126.0, 126.15, 126.16, 127.4, 127.5, 127.8, 128.2, 128.3, 128.4, 132.2 (q), 132.5 (q), 132.7 (q), 133.0 (q), 141.5 (q), 144.5 (q).

υ (cm^{-1}): 745, 790, 823, 859, 1113, 1356, 1600, 2955, 3054, 3488.

HRMS (ESI): $[M+Na]^+$ calcd. for $C_{46}H_{36}O_2SNa$ 675.2334, found 675.2316.

5.4.17 (2*R*,5*R*)-tetrahydro-2,5-(methoxydi(naphthalen-3-yl)methyl)thiophene ((*R*,*R*)-359)



An oven dried 100 cm^3 round bottomed flask containing a magnetic stirring bar was charged with **(*R*,*R*)-358** (775 mg, 1.187 mmol). The flask was fitted with a rubber septum and placed under an atmosphere of argon (balloon). Anhydrous THF (55 cm^3) was added *via* syringe. The resulting solution was treated with sodium hydride (60% dispersion in

mineral oil, 105 mg, 2.612 mmol), followed by methyl iodide (887 μL, 14.245 mmol). The resulting solution was allowed to stir at room temperature for 88 h. The reaction mixture was quenched with H_2O (5 cm^3) and concentrated *in vacuo*. The resulting residue was transferred to a separating funnel using CH_2Cl_2. Extraction was performed using H_2O (50 cm^3) and CH_2Cl_2 (4 x 150 cm^3). The combined organic extracts were dried over $MgSO_4$. The crude product was purified by flash chromatography (7:3 hexane:CH_2Cl_2) to afford **(*R*,*R*)-359** as a white solid (774 mg, 96%). M.p. 108-110 °C. $[\alpha]_D^{20} = -31.3$ (*c* 0.1, CH_2Cl_2).

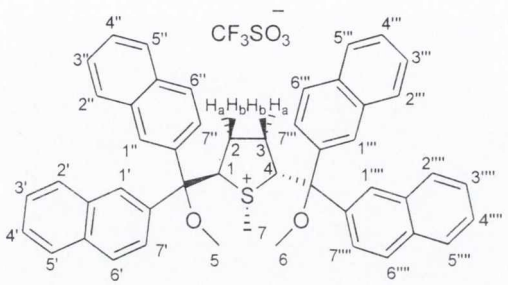
δ_H (600 MHz, $CDCl_3$): 1.73-1.82 (m, 4H, H-2), 3.02 (s, 6H, H-3), 4.20-4.24 (m, 2H, H-1), 7.26 (d, J 8.6, 2H, H-7''), 7.47-7.52 (m, 10H, H-3', H-4', H-7', H-3'' and H-4''), 7.69 (d, J 8.6, 2H, H-6''), 7.76 (d, J 8.7, 2H, H-6'), 7.79-7.87 (m, 8H, H-2', H-5', H-2'' and H-5''), 7.94 (s, 2H, H-1''), 8.02 (s, 2H, H-1').

δ_C (150 MHz, $CDCl_3$): 31.3, 51.7, 53.5, 86.1 (q), 126.0, 126.1, 126.3, 126.4, 126.5, 127.3, 127.52, 127.55, 127.61, 128.2, 128.3, 128.4, 128.7, 128.8, 132.5 (q), 132.6 (q), 132.79 (q), 132.83 (q), 139.3, 140.1.

υ (cm^{-1}): 743, 799, 821, 856, 1071, 1123, 1352, 1598, 2853, 2923, 3054.

HRMS (ESI): $[M+Na]^+$ calcd. for $C_{48}H_{40}O_2SNa$ 703.2647, found 703.2645.

5.4.18 (2*R*,5*R*)-tetrahydro-2,5-(methoxydi(naphthalen-3-yl)methyl)thiophene triflate ((*R*,*R*)-355)



Prepared according to general procedure H, using **(*R*,*R*)-359** (674 mg, 0.990 mmol), proton sponge (212 mg, 0.990 mmol), CH_2Cl_2 (3.3 cm^3) and methyl triflate (109 μL, 0.990 mmol). Purification by flash chromatography using 7:3 hexane:EtOAc initially to remove proton sponge, followed by 100% EtOAc afforded **(*R*,*R*)-355** as an off-white solid (551 mg, 66%). M.p. 179-180 °C. $[\alpha]_D^{20}$ = -76.3 (*c* 1.0, $CHCl_3$).

δ_H (600 MHz, $CDCl_3$): 2.28-2.35 (m, 1H, H-2b), 2.61-2.67 (m, 1H, H-3b), 3.04 (s, 3H, H-5), 3.10 (s, 3H, H-7), 3.25 (s, 3H, H-6), 3.12-3.22 (m, 2H, H-3a and H-4), 3.34-3.42 (m, 1H, H-2a), 5.95 (app. t, 1H, H-1), 6.24 (d, J 8.8, 1H, H-7'''), 7.01 (d, J 9.0, 1H, H-7''''), 7.34 (s, 1H, H-1''''), 7.38-7.45 (m, 3H, H-6''', H-7' and H-7''), 7.51-7.71 (m, 11H, H-3', H-5', H-3'', H-4'', H-5'', H-3''', H-4''', H-2'''', H-3'''', H-4'''' and H-6''''), 7.76-7.83 (m, 3H, H-1''', H-5''' and H-5''''), 7.84-7.92 (m, 3H, H-4', H-2''' and H-2''), 7.95-7.97 (m, 2H, H-6' and H-6''), 8.01 (s, 1H, H-1''), 8.09-8.11 (m, 1H, H-2'), 8.28 (s, 1 H, H-1').

δ_C (150 MHz, $CDCl_3$): 22.6, 29.6, 29.8, 52.3, 55.5, 68.6, 71.8, 83.1 (q), 85.3 (q), 123.5, 124.1, 125.4, 125.8, 126.8, 126.9, 126.9 (2 x C), 127.0, 127.1, 127.2, 127.3, 127.38, 127.40, 127.5, 127.6 (2

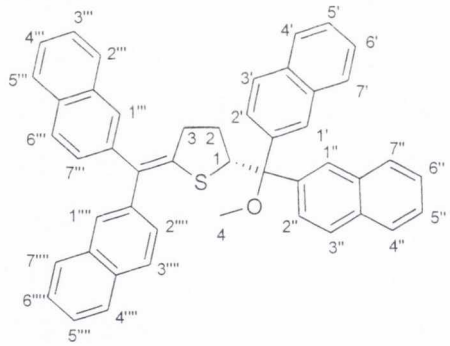
x C), 127.66, 127.70, 128.2, 128.5, 128.6, 128.7, 128.8, 128.9, 129.0, 129.2, 130.0, 132.4 (q), 132.5 (q), 132.6 (q), 132.70 (q), 132.72 (q), 132.8 (q), 132.9 (q), 133.2 (q), 134.9 (q), 135.4 (2 x q), 139.5 (q).

δ_F (376 MHz, $CDCl_3$): -78.5

υ (cm^{-1}): 730, 755, 1029, 1075, 1156, 1255, 2852, 2924, 2957, 3066.

HRMS (ESI): $[M+H]^+$ calcd. for $C_{49}H_{43}O_2S$ 695.2984; found 695.2981.

5.4.19 Decomposition product 360 derived from sulfonium salt 355 (Scheme 4.8)



360 Was isolated from the aziridination reaction performed according to general procedure P using **355**. Purification using flash chromatography (8:2 hexane:CH_2Cl_2) afforded **360** as a yellow solid. M.p. 109-110 °C.

δ_H (600 MHz, $CDCl_3$): 2.04-2.13 (m, 2H, H-2a and H-3a), 2.32-2.37 (m, 1H, H-2b), 2.55-2.59 (m, 1H, H-3b), 3.15 (s, 3H, H-4), 5.02 (app. t, 1H, H-1), 6.90 (d, J 7.7, 1H, H-7'''), 7.14 (s, 1H, H-1'''), 7.29 (d, J 9.7, 1H, H-7''''), 7.35 (d, J 8.8, 1H, H-2''), 7.37-7.60 (m, 11H, H-2', H-5', H-7', H-4'', H-5'', H-6'', H-4''',

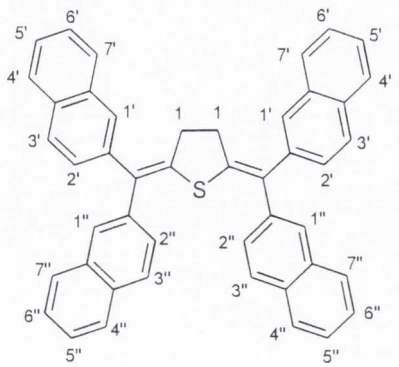
H-6''', H-2'''', H-4'''' and H-6''''), 7.69-7.85 (m, 9H, H-6', H-3'', H-3''', H-1'''', H-3'''' and H-5'''', H-3', H-2''' and H-5'''), 7.91 (d, J 7.9, 1H, H-7''), 7.95 (d, J 7.9, 1H, H-4'), 8.03 (s, 1H, H-1''), 8.12 (s, 1H, H-1').

δ_C (150 MHz, $CDCl_3$): 31.4, 35.7, 51.7, 55.1, 85.6 (q), 125.6, 125.7, 125.80, 125.82, 126.0, 126.1, 126.37, 126.39, 126.8, 127.2, 127.3, 127.4 (2 x C), 127.45, 127.51, 127.56, 127.64 (2 x C), 127.7, 127.79, 127.84, 128.0, 128.1, 128.2, 128.3, 128.4, 128.62, 128.63 (C + C(q)), 131.9 (q), 132.3 (q), 132.49 (q), 132.54 (q), 132.77 (q), 132.80 (q), 133.1 (q), 133.3 (q), 138.4 (q), 139.1 (q), 139.9 (q), 140.5 (q), 143.0 (q).

υ (cm^{-1}): 745, 799, 819, 856, 1073, 1124, 1504, 1597, 2854, 2925, 3053.

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_{47}H_{36}OSNa$ 671.2385; found 671.2370.

5.4.20 Decomposition product 361 derived from sulfonium salt 355 (Scheme 4.9)



361 Was isolated from the aziridination reaction performed according to general procedure P using **355**. Purification using flash chromatography (8:2 hexane:CH_2Cl_2) afforded **361** as an orange solid. M.p. 253-255 °C.

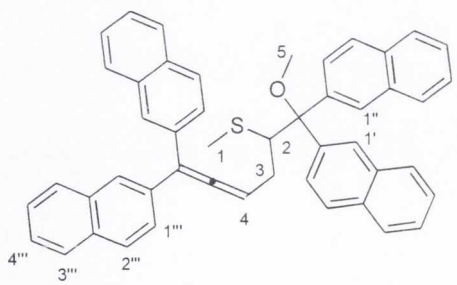
δ_H (600 MHz, $CDCl_3$): 3.07 (s, 4H, H-1), 7.29-7.31 (m, 2H, H-2''), 7.39-7.47 (m, 10H, H-2', H-5', H-6', H-5'' and H-6''), 7.71-7.82 (m, 16H, H-1', H-3', H-4', H-7', H-1'', H-3'', H-4'' and H-7'').

δ_C (100 MHz, $CDCl_3$): 36.4, 126.18, 126.22 (2 x C), 126.5, 127.87, 127.93 (2 x C), 128.0, 128.1, 128.2 (2 x C), 128.4, 128.6, 128.8, 131.2 (q), 132.5 (q), 132.7 (q), 133.5 (q), 133.6 (q), 139.9 (q), 140.2 (q), 141.7 (q).

υ (cm^{-1}): 745, 799, 819, 856, 1073, 1124, 1504, 1597, 2854, 2925, 3053.

HRMS (MALDI): $[M]^+$ Calcd. for $C_{46}H_{32}S$ 616.2225; found 616.2199.

5.4.21 Decomposition product 362 derived from sulfonium salt 355 (Scheme 4.10)



362 Was isolated from the aziridination reaction performed according to general procedure P using **355**. Purification using flash chromatography (8:2 hexane:CH_2Cl_2) afforded **362** as a yellow solid. M.p. 133-134 °C.

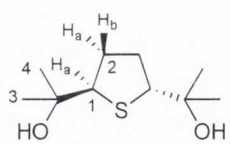
δ_H (600 MHz, $CDCl_3$): 1.87 (s, 3H, H-1), 2.09-2.14 (m, 1H, H-3a), 3.08 (s, 3H, H-5), 3.15-3.19 (m, 1H, H-3b), 4.02 (dd, J 11.0, 1.7, 1H, H-2), 6.04 (app. t, 1H, H-4), 7.3 (app.t, 1H, H-4'''), 7.46-7.92 (m, H-25, H-Ar), 8.05 (s, 2H, H-1' and H-1'').

δ_C (150 MHz, $CDCl_3$): 14.09, 31.7, 51.8, 53.6, 87.2 (q), 92.9, 110.6 (q), 125.88, 125.93 (2 x CH), 125.99, 126.1, 126.17, 126.25, 126.27, 126.89, 126.92, 127.1(2 x CH), 127.23, 127.24, 127.27 (2 x CH), 127.34, 127.4, 127.60, 127.64, 127.92, 127.98, 127.99, 128.02, 128.3, 128.49, 128.53, 128.7, 132.49 (q), 132.53 (q), 132.6 (q), 132.67 (q), 132.71 (2 x C(q)), 133.48 (q), 133.52 (q), 134.3 (q), 134.4 (q), 137.7 (q), 137.9 (q), 206.9 ((q) allene),

υ (cm^{-1}): 744, 818, 951, 1125, 1504, 1596, 2854, 2923, 3054, 3338.

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_{48}H_{38}OSNa$ 685.2541; found 685.2542.

5.4.22 2,5-((2*R*,5*R*)-Tetrahydrothiophen-2,5-yl)propan-2-ol ((*R*,*R*)-369)



An oven dried 25 cm^3 round bottomed flask containing **(*R*,*R*)-326** (150 mg, 0.7344 mmol) and a magnetic stirring bar was fitted with a rubber septum and placed under an

atmosphere of argon (balloon). Anhydrous THF (4 cm^3) was added *via* syringe. The resulting solution was cooled to -78 °C when methyllithium (1.6 M in Et_2O, 3.67 cm^3, 5.875 mmol) was added dropwise *via* syringe. The resulting solution was allowed to stir at this temperature for 30 min and allowed to reach room temperature overnight. The reaction mixture was cooled to 0 °C and quenched by the addition of sat. $NH_4Cl_{(aq)}$ (5 cm^3). The resulting solution was transferred to a separating funnel, extracted with CH_2Cl_2 (3 x 30 cm^3), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (4:6 hexane:EtOAc) afforded **(*R*,*R*)-369** as a white solid (115.7 mg, 77%). M.p. 96-98 °C. $[\alpha]_D^{20}$ = -92.8 (*c* 0.2, $CHCl_3$).

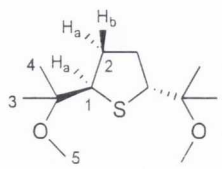
δ_H (600 MHz, $CDCl_3$): 1.23 (s, 6H, H-3), 1.25 (s, 6H, H-4), 1.80-1.88 (m, 2H, H-2b), 2.10-2.17 (m, 2H, H-2a), 2.36 (br s, 2H, OH), 3.52-3.55 (m, 2H, H-1a).

δ_C (150 MHz, $CDCl_3$): 26.3, 31.5, 32.3, 62.2, 70.5 (q).

υ (cm^{-1}): 682, 871, 933, 1122, 1137, 1286, 1359, 1463, 2893, 2970, 3296.

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_{10}H_{20}O_2SNa$ 227.1082; found 227.1083.

5.4.23 (2*R*,5*R*)-Tetrahydro-2,5-(2-methoxypropan-2-yl)thiophene ((*R*,*R*)-370)



An oven dried 100 cm^3 round bottomed flask containing a magnetic stirring bar was charged with **(*R*,*R*)-369** (115.7 mg, 0.566 mmol). The flask was fitted with a rubber

septum and placed under an atmosphere of argon (balloon). Anhydrous THF (2.8 cm^3) was added *via* syringe. The resulting solution was treated with sodium hydride (60% dispersion in mineral oil, 135.9 mg, 3.397 mmol), followed by methyl iodide (353 μL, 5.662 mmol). The resulting solution was allowed to stir at room temperature for 40 h. The reaction mixture was quenched with H_2O (5 cm^3) and concentrated *in vacuo*. The resulting residue was transferred to a separating funnel using CH_2Cl_2. Extraction was performed using H_2O (5 cm^3) and CH_2Cl_2 (3 x 15 cm^3). The combined organic extracts were dried over $MgSO_4$. The crude product was purified by flash chromatography (8:2 hexane:CH_2Cl_2, then 100% CH_2Cl_2) to afford **(*R*,*R*)-370** as a pale yellow oil (131.6 mg, 76%). $[\alpha]_D^{20} = -214.75$ (*c* 0.2, CH_2Cl_2).

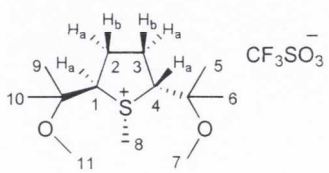
δ_H (400 MHz, $CDCl_3$): 1.21 (s, 6H, H-3), 1.22 (s, 6H, H-4), 1.62-1.73 (m, 2H, H-2b), 2.05-2.14 (m, 2H, H-2a), 3.23 (s, 6H, H-5), 3.59-3.63 (m, 2H, H-1a).

δ_C (100 MHz, $CDCl_3$): 22.4, 22.6, 32.4, 49.7, 58.3, 76.9 (q).

υ (cm^{-1}): 759, 841, 1071, 1134, 1185, 1362, 1378, 1466, 2826, 2898, 2937, 2971.

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_{12}H_{24}O_2SNa$ 255.1395; found 255.1390.

5.4.24 (2*R*,5*R*)-Tetrahydro-2,5-(2-methoxypropan-2-yl)thiophene triflate ((*R*,*R*)- 368)



Prepared according to general procedure H using **(*R*,*R*)-370** (91 mg, 0.392 mmol), CH_2Cl_2 (1.3 cm^3) and methyl triflate (43 μL, 0.392 mmol) to afford **368** as a light brown solid in quantitative yield. M.p. 76-77 °C. $[\alpha]_D^{20}$ = -101.7 (*c* 0.2, CH_2Cl_2).

δ_H (400 MHz, $CDCl_3$): 1.29 (s, 3H, H-10), 1.37 (s, 3H, H-6), 1.41 (s, 3H, H-9), 1.46 (s, 3H, H-5), 2.05-2.13 (m, 1H, H-2b), 2.42-2.47 (m, 1H, H-3a), 2.56-2.67 (m, 2H, H-2a and H-3b), 2.92 (s, 3H, H-8), 3.24 (s, 3H, H-7), 3.25 (s, 3H, H-11), 3.68 (dd, J 12.6, 4.6, 1H, H-4a), 4.39-4.44 (m, 1H, H-1a).

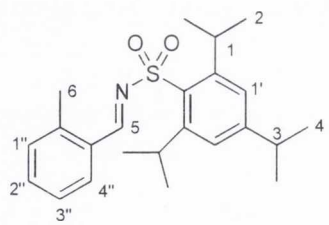
δ_C (100 MHz, $CDCl_3$): 20.3, 23.5, 23.7, 24.3, 26.3, 28.8, 29.2, 49.8, 50.1, 70.0, 75.5 (q), 75.7 (q), 76.9.

δ_F (376 MHz, $CDCl_3$): -78.9 (s, 3F).

υ (cm^{-1}): 756, 851, 1029, 1148, 1225, 1255, 1371, 1472, 2839, 2957, 2985, 3455.

HRMS (ESI): $[M]^+$ Calcd. for $C_{13}H_{27}O_2S$ 247.1732; found 247.1735.

5.4.25 *N*-(2-Methylphenyl)methylidene-2-4-6-triisopropylbenzenesulfonamide (374)



Prepared according to general procedure O using **352** (500 mg, 1.764 mmol), triethylamine (738 μL, 5.292 mmol), *o*-tolualdehyde (204 μL, 1.764 mmol), CH_2Cl_2 (6

cm^3) and titanium(IV) chloride (97 μL, 0.882 mmol) in CH_2Cl_2 (1 cm^3). After purification of the crude material by flash chromatography (1:1 hexane:$CHCl_2$), **374** was obtained as a yellow solid (551 mg, 81%). M.p. 79-81 °C. The NMR spectra of **374** were consistent with those previously reported.[244]

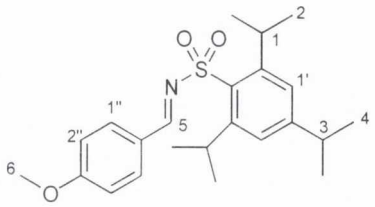
δ_H (400 MHz, $CDCl_3$): 1.25 (d, J 6.4, 6H, H-4), 1.29 (d, J 6.8, 12H, H-2), 2.60 (s, 3H, H-6), 2.91 (septet, J 6.4, 1H, H-3), 4.37 (septet, J 6.8, 2H, H-1), 7.19 (s, 2H, H-1'), 7.26-7.31 (m, 2H, H-1'' and H-2''), 7.47 (app. t, 1H, H-3''), 8.01 (d, J 7.6, 1H, H-4''), 9.35 (s, 1H, H-5).

5.4.26 *N*-(4-Chlorophenyl)methylidene-2-4-6-triisopropylbenzenesulfonamide (372)

Prepared according to general procedure O using **352** (500 mg, 1.764 mmol), triethylamine (738 μL, 5.292 mmol), *p*-chlorobenzaldehyde (248 mg, 1.764 mmol), CH_2Cl_2 (3.5 cm^3) and titanium(IV) chloride (97 μL, 0.882 mmol) in CH_2Cl_2 (1 cm^3). The crude product was recrystallised from CH_2Cl_2:hexane to afford **372** as an amorphous white solid (130 mg, 18%). M.p. 198-199 °C. The NMR spectra of **372** were consistent with those previously reported.[244]

δ_H (400 MHz, $CDCl_3$): 1.26 (d, J 7.0, 6H, H-4), 1.28 (d, J 6.5, 12H, H-2), 2.91 (septet, J 7.0, 1H, H-3), 4.32 (septet, J 6.5, 2H, H-1), 7.20 (s, 2H, H-1'), 7.48 (d, J 8.5, 2H, H-2''), 7.86 (d, J 8.5, 2H, H-1''), 8.98 (s, 1H, H-5).

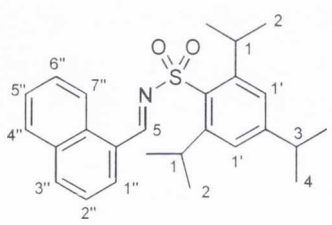
5.4.27 *N*-(4-Methoxyphenyl)methylidene-2-4-6-triisopropylbenzenesulfonamide (373)



Prepared according to general procedure O using **352** (500 mg, 1.764 mmol), triethylamine (738 μL, 5.292 mmol), *p*-anisaldehyde (215 μL, 1.764 mmol), CH_2Cl_2 (6 cm^3) and titanium(IV) chloride (97 μL, 0.882 mmol) in CH_2Cl_2 (1 cm^3). The crude product was recrystallised from EtOAc:hexane to afford **373** as a yellow crystalline solid (403 mg, 57%). M.p. 189-190 °C. The NMR spectra of **373** were consistent with those previously reported.[244]

δ_H (400 MHz, $CDCl_3$): 1.25 (d, J 7.0, 6H, H-4), 1.28 (d, J 6.8, 12H, H-2), 2.90 (septet, J 7.0, 1H, H-3), 3.88 (s, 3H, H-6), 4.36 (septet, J 6.8, 2H, H-1), 6.97 (d, J 8.8, 2H, H-2''), 7.18 (s, 2H, H-1'), 7.88 (d, J 8.8, 2H, H-1''), 8.92 (s, 1H, H-5).

5.4.28 *N*-(1-Naphthyl)methylidene-2-4-6-triisopropylbenzenesulfonamide (371)

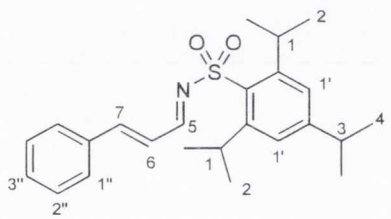


Prepared according to general procedure O using **352** (400 mg, 1.411 mmol), triethylamine (590 μL, 4.234 mmol), 1-naphthaldehyde (193 μL, 1.411 mmol), CH_2Cl_2

(10 cm^3) and titanium(IV) chloride (78 μL, 0.705 mmol). The crude product was recrystallised from CH_2Cl_2:hexane to afford **371** as a yellow solid (412 mg, 69%). M.p. 169-170 °C. The NMR spectra of **371** were consistent with those previously reported.[244]

δ_H (600 MHz, $CDCl_3$): 1.26 (d, J 6.9, 6H, H-4), 1.32 (d, J 6.7, 12H, H-2), 2.91 (septet, J 6.9, 1H, H-3), 4.46 (septet, J 6.7, 2H, H-1), 7.21 (s, 2H, H-1'), 7.59 (app. q, 2H, H-2'' and H-5''), 7.66 (app. t, 1H, H-6''), 7.92 (d, J 8.1, 1H, H-4''), 8.10 (d, J 8.2, 1H, H-3''), 8.12 (d, J 7.1, 1H, H-1''), 9.09 (d, J 8.5, 1H, H-7''), 9.59 (s, 1H, H-5).

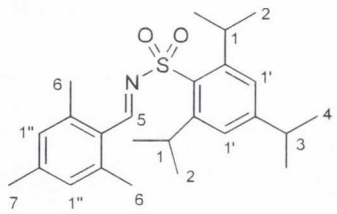
5.4.29 2,4,6-Triisopropyl-*N*-(3-phenylallylidene)benzenesulfonamide (376)



Prepared according to general procedure O using **352** (400 mg, 1.411 mmol), triethylamine (590 μL, 4.234 mmol), *trans*-cinnamaldehyde (178 μL, 1.411 mmol), CH_2Cl_2 (10 cm^3) and titanium(IV) chloride (78 μL, 0.705 mmol). The crude product was recrystallised from EtOAc:hexane to afford **376** as a yellow solid (239 mg, 43%). M.p. 164-165 °C; lit.,[245] 166-167 °C. The NMR spectra of **376** were consistent with those previously reported.[245]

δ_H (400 MHz, $CDCl_3$): 1.25 (d, J 7.0, 6H, H-4), 1.27 (d, J 6.8, 12H, H-2), 2.91 (septet, J 7.0, 1H, H-3), 4.24 (septet, J 6.8, 2H, H-1), 7.00 (dd, J 15.8, 9.3, 1H, H-6), 7.19 (s, 2H, H-1'), 7.41-7.48 (m, 4H, H-7, H-2'' and H-3''), 7.55-7.58 (m, 2H, H-1''), 8.75 (d, J 9.3, 1H, H-5).

5.4.30 *N*-(Mesityl)methylidene-2-4-6-triisopropylbenzenesulfonamide (375)



Prepared according to general procedure O using **352** (400 mg, 1.411 mmol), triethylamine (590 μL, 4.234 mmol), mesitaldehyde (205 μL, 1.411 mmol), CH_2Cl_2 (10 cm^3) and titanium(IV) chloride (78 μL, 0.705 mmol). The product was purified by column chromatography (7:3 hexane:CH_2Cl_2) to yield **375** as a white crystalline solid (378 mg, 65%). M.p. 64-66 °C.

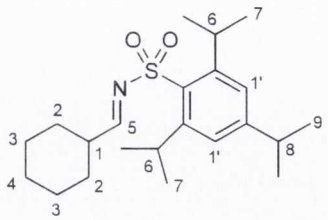
δ_H (400 MHz, $CDCl_3$): 1.25 (d, J 7.0, 6H, H-4), 1.28 (d, J 6.7, 12H, H-2), 2.32 (s, 3H, H-7), 2.55 (s, 6H, H-6), 2.91 (septet, J 7.0, 1H, H-3), 4.36 (septet, J 6.7, 2H, H-1), 6.93 (s, 2H, H-1''), 7.18 (s, 2H, H-1'), 9.49 (s, 1H, H-5).

δ_C (100 MHz, $CDCl_3$): 21.7, 21.9, 23.7, 24.9, 29.9, 34.4, 123.9, 126.4 (q), 130.8, 131.6 (q), 142.8 (q), 144.5 (q), 151.4 (q), 153.6 (q), 168.0.

υ (cm^{-1}): 667, 772, 829, 1041, 1148, 1294, 1314, 1560, 1594, 2871, 2926, 2960.

HRMS (ESI): $[M+H]^+$ Calcd. for $C_{25}H_{36}NO_2S$ 414.2467; found 414.2477.

5.4.31 *N*-(Cyclohexyl)methylidene-2-4-6-triisopropylbenzenesulfonamide (377)



Prepared according to general procedure O using **352** (400 mg, 1.411 mmol), triethylamine (590 μL, 4.234 mmol), cyclohexanecarboxaldehyde (171 μL, 1.411 mmol), CH_2Cl_2 (10 cm^3) and titanium(IV) chloride (78 μL, 0.705 mmol). The crude product was recrystallised from CH_2Cl_2:hexane to afford **377** as a white solid (214 mg, 40%). M.p. 93-95 °C.

δ_H (400 MHz, $CDCl_3$): 1.24-1.36 (m, 23H, H-2a, H-3a, H-4a, H-7 and H-9), 1.66-1.69 (m, 1H, H-4b), 1.74-1.80 (m, 2H, H-3b), 1.87-1.93 (m, 2H, H-2b), 2.42-2.45 (m, 1H, H-1), 2.90 (septet, J 6.9, 1H, H-8), 4.16 (septet, J 6.8, 2H, H-6), 7.17 (s, 2H, H-1'), 8.45 (d, J 4.2, 1H, H-5).

δ_C (100 MHz, $CDCl_3$): 23.7, 24.9, 25.3, 25.8, 28.5, 29.9, 34.4, 43.8, 123.9, 151.5 (q), 153.8 (q), 179.1.

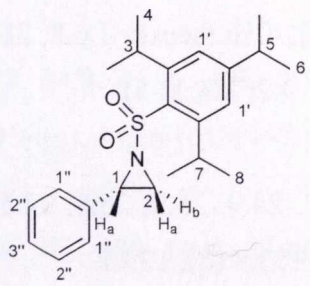
υ (cm^{-1}): 671, 778, 799, 1152, 1295, 1312, 1621, 2852, 2926, 2953.

HRMS (ESI): $[M+H]^+$ Calcd. for $C_{22}H_{36}NO_2S$ 378.2467; found 378.2451.

5.4.32 General procedure Q: the synthesis of aziridines 354 and 378-384 using 310 under the optimised reaction conditions outlined in Scheme 4.13 (Table 4.6)

An oven dried round bottomed flask containing a magnetic stirring bar and **310** (1 equiv.) was charged with proton sponge (1 equiv.), the appropriate imine (1 equiv.) and activated 3Å molecular sieves. The flask was placed on a Schlenk line for 1 h. The flask was then immediately flushed with argon, fitted with a rubber septum and placed under an atmosphere of argon (balloon). Freshly distilled CH_2Cl_2 (0.08 M, that had been stored over activated 3Å molecular sieves) and styrene (1 equiv.), were then added sequentially *via* syringe. The resulting solution was cooled to -78 °C. P_2 base (2.0 M in THF, 1 equiv.) was then added dropwise. Upon completion (analysis by ^1H NMR spectroscopy), the crude material was purified by column chromatography to furnish the corresponding aziridine.

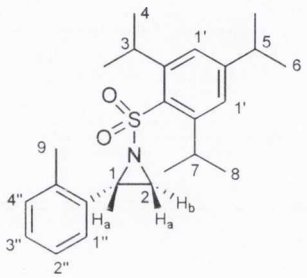
5.4.32.1 (*R*)-2-Phenyl-1-(2-4-6-triisopropylbenzenesulfonyl)aziridine (354)



Prepared according to general procedure Q using **310** (21.36 mg, 0.063 mmol), **353** (23.58 mg, 0.063 mmol), proton sponge (13.60 mg, 0.063 mmol), CH_2Cl_2 (0.79 cm^3), styrene (7.3 μL, 0.063 mmol) and P_2 base (2.0 M in THF, 31.7 μL, 0.063 mmol). Upon completion, *i.e.* 16 h, the crude material was purified by column chromatography (8:2 hexane:CH_2Cl_2) to furnish **354** as a white solid (22.20 mg, 91%, 23% *ee*). M.p. 82-84 °C. $[\alpha]_D^{20} = -7.9$ (*c* 0.16, CH_2Cl_2, 23% *ee*).

CSP-HPLC analysis: CHIRALPAK AD-H (4.6 mm x 25 cm), hexane/IPA: 9.5/0.5, 0.5 mL min^{-1}, RT, UV detection at 220 nm, retention times: 10.0 min (minor enantiomer) and 12.2 (major enantiomer).

5.4.32.2 (*R*)-2-(2-Methylphenyl)-1-(2-4-6-triisopropylbenzenesulfonyl)aziridine (381)



Prepared according to general procedure Q using **310** (22.18 mg, 0.066 mmol), **374** (25.42 mg, 0.066 mmol), proton sponge (14.13 mg, 0.066 mmol), CH_2Cl_2 (0.82 cm^3), styrene (7.6 μL, 0.066 mmol) and P_2 base (2.0 M in THF, 33.0 μL, 0.066 mmol). Upon completion, *i.e.* 16 h, the crude material was purified by column chromatography (8:2 hexane:CH_2Cl_2) to furnish **381** as a white solid (22.90 mg, 87%, 30% *ee*). M.p. 68-70 °C. $[\alpha]_D^{20}$ = -16.19 (*c* 0.21, CH_2Cl_2, 30% *ee*).

CSP-HPLC analysis: CHIRALPAK AD-H (4.6 mm x 25 cm), hexane/IPA: 9.8/0.2, 0.5 mL min^{-1}, RT, UV detection at 220 nm, retention times: 11.3 min (minor enantiomer) and 13.0 (major enantiomer).

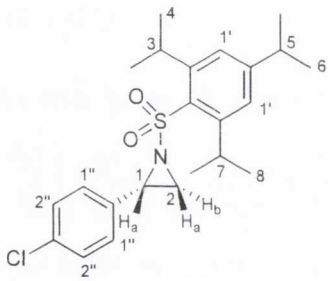
δ_H (600 MHz, $CDCl_3$): 1.25-1.28 (m, 18H, H-4, H-6 and H-8), 2.29 (d, J 4.5, 1H, H-2b), 2.34 (s, 3H, H-9), 2.91 (septet, J 6.9, 1H, H-5), 3.02 (d, J 7.2, 1H, H-2a), 3.94 (dd, J 7.3, 4.5, 1H, H-1a), 4.42 (septet, J 6.8, 2H, H-3 and H-7), 7.12-7.19 (m, 6H, H-1', H-1'', H-2'', H-3'' and H-4'').

δ_C (150 MHz, $CDCl_3$): 19.1, 23.7, 25.0, 25.1, 30.0, 34.4, 35.5, 38.8, 124.0, 125.9, 126.3, 128.0, 130.1, 131.5 (q), 134.0 (q), 136.8 (q), 151.4 (q), 153.7 (q).

υ (cm^{-1}): 661, 773, 894, 1105, 1319, 1460, 1601, 2865, 2925, 2959.

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_{24}H_{33}NO_2SNa$ 422.2130; found 422.2111.

5.4.32.3 (*R*)-2-(4-Chlorophenyl)-1-(2-4-6-triisopropylbenzenesulfonyl)aziridine (379)



Prepared according to general procedure Q using **310** (22.47 mg, 0.067 mmol), **372** (27.11 mg, 0.067 mmol), proton sponge (14.31 mg, 0.067 mmol), CH_2Cl_2 (0.84 cm^3), styrene (7.7 μL, 0.067 mmol) and P_2 base (2.0 M in THF, 33.4 μL, 0.067 mmol). Upon completion, *i.e.* 16 h, the crude material was purified by column chromatography (7:3 hexane:CH_2Cl_2) to furnish **379** as a white solid (24.68 mg, 88%, 18% *ee*). M.p. 122-124 °C. $[\alpha]_D^{20} = -11.8$ (*c* 0.18, CH_2Cl_2, 18% *ee*).

CSP-HPLC analysis: CHIRALPAK AD-H (4.6 mm x 25 cm), hexane/IPA: 9/1, 0.5 mL min^{-1}, RT, UV detection at 220 nm, retention times: 9.1 min (minor enantiomer) and 13.0 (major enantiomer).

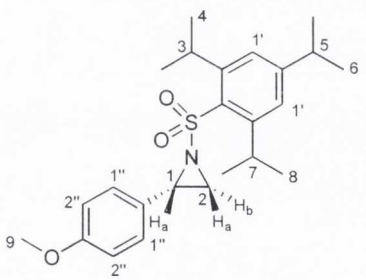
δ_H (600 MHz, $CDCl_3$): 1.24-1.27 (m, 18H, H-4, H-6 and H-8), 2.33 (d, J 4.3, 1H, H-2b), 2.90 (septet, J 6.9, 1H, H-5), 3.03 (d, J 7.2, 1H, H-2a), 3.76 (dd, J 7.2, 4.3, 1H, H-1a), 4.37 (septet, J 6.8, 2H, H-3 and H-7), 7.13 (d, J 8.5, 2H, H-1''), 7.18 (s, 2H, H-1'), 7.27 (d, J 8.5, 2H, H-2'').

δ_C (150 MHz, $CDCl_3$): 23.7, 25.0, 25.1, 29.9, 34.4, 36.4, 39.9, 124.1, 128.0, 128.9, 131.2 (q), 134.3 (q), 134.4 (q), 151.4 (q), 153.9 (q).

υ (cm^{-1}): 694, 811, 914, 1151, 1310, 1494, 1602, 2869, 2928, 2960.

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_{23}H_{30}NO_2ClSNa$ 442.1583; found 442.1564.

5.4.32.4 (*R*)-2-(4-Methoxyphenyl)-1-(2-4-6-triisopropylbenzenesulfonyl) aziridine (380)



Prepared according to general procedure Q using **310** (29.24 mg, 0.087 mmol), **373** (34.90 mg, 0.087 mmol), CH_2Cl_2 (1.09 cm^3), styrene (10.0 μL, 0.087 mmol) and P_2 base (2.0 M in THF, 44.0 μL, 0.087 mmol). Upon completion, *i.e.* 16 h, the crude material was purified by column chromatography on silica that had been deactivated by preparing the silica slurry using 7:3:0.5 hexane:CH_2Cl_2:triethylamine, and using 8:2 hexane:CH_2Cl_2 as eluent. **380** Was obtained as a white solid (33.23 mg, 92%, 25% *ee*). M.p. 86-88 °C. $[\alpha]_D^{20}$ = -29.2 (*c* 0.22, CH_2Cl_2, 25% *ee*).

CSP-HPLC analysis: CHIRALPAK AD-H (4.6 mm x 25 cm), hexane/IPA: 9.5/0.5, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: 6.7 min (minor enantiomer) and 9.4 (major enantiomer).

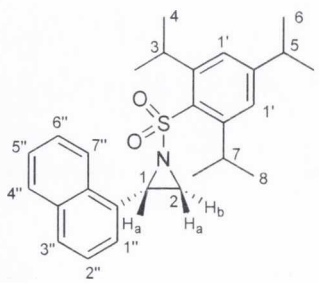
δ_H (600 MHz, $CDCl_3$): 1.23-1.27 (m, 18H, H-4, H-6 and H-8), 2.35 (d, J 4.5, 1H, H-2b), 2.90 (septet, J 6.9, 1H, H-5), 3.01 (d, J 7.2, 1H, H-2a), 3.75 (dd, J 7.2, 4.5, 1H, H-1a), 3.78 (s, 3H, H-9), 4.39 (septet, J 6.8, 2H, H-3 and H-7), 6.82 (d, J 8.7, 2H, H-2''), 7.11 (d, J 8.7, 2H, H-1''), 7.17 (s, 2H, H-1').

δ_C (150 MHz, $CDCl_3$): 23.7, 25.0, 25.1, 29.9, 34.4, 36.1, 40.5, 55.4, 114.1, 124.0, 127.7 (q), 127.9, 131.5 (q), 151.3 (q), 153.6 (q), 159.8 (q).

υ (cm^{-1}): 668, 695, 818, 902, 1152, 1256, 1303, 1519, 1601, 2868, 2929, 2959.

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_{24}H_{33}NO_3SNa$ 438.2079; found 438.2077.

5.4.32.5 (*R*)-2-(1-Naphthyl)-1-(2-4-6-triisopropylbenzenesulfonyl)aziridine (378)



Prepared according to general procedure Q using **310** (27.37 mg, 0.081 mmol), **371** (34.30 mg, 0.081 mmol), proton sponge (17.43 mg, 0.081 mmol), CH_2Cl_2 (1.00 cm^3),

styrene (9.3 μL, 0.081 mmol) and P_2 base (2.0 M in THF, 40.7 μL, 0.081 mmol). Upon completion, *i.e.* 16 h, the crude material was purified by column chromatography (7:3 hexane:CH_2Cl_2) to furnish **378** as a white solid (32.60 mg, 92%, 23% *ee*). M.p. 66-68 °C. $[\alpha]_D^{20}$ = -2.3 (*c* 0.18, CH_2Cl_2, 23% *ee*).

CSP-HPLC analysis: CHIRALPAK AD-H (4.6 mm x 25 cm), hexane/IPA: 9.9/0.1, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: 10.8 min (minor enantiomer) and 12.1 (major enantiomer).

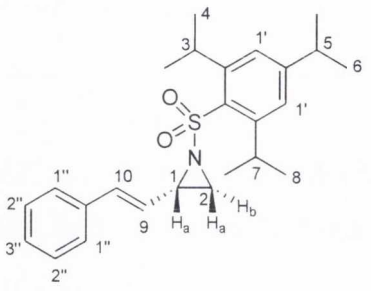
δ_H (600 MHz, $CDCl_3$): 1.27 (app. d, 18H, H-4, H-6 and H-8), 2.44 (d, J 4.5, 1H, H-2b), 2.92 (septet, J 6.9, 1H, H-5), 3.18 (d, J 7.1, 1H, H-2a), 4.42 (dd, J 7.1, 4.5, 1H, H-1a), 4.48 (septet, J 6.7, 2H, H-3 and H-7), 7.20 (s, 2H, H-1'), 7.37-7.43 (m, 2H, H-2'' and H-3''), 7.46-7.51 (m, 2H, H-5'' and H-6''), 7.79 (d, J 7.7, 1H, H-1''), 7.86 (d, J 7.4, 1H, H-4''), 8.09 (d, J 8.0, 1H, H-7'').

δ_C (100 MHz, $CDCl_3$): 23.7, 25.0, 25.1, 30.0, 34.4, 35.2, 39.1, 123.1, 124.1, 124.4, 125.4, 126.1, 126.6, 128.7, 128.8, 131.4 (q), 131.6 (q), 131.7 (q), 133.4 (q), 151.4 (q), 153.8 (q).

υ (cm^{-1}): 670, 699, 779, 903, 1151, 1313, 1601, 2868, 2927, 2959.

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_{27}H_{33}NO_2SNa$ 458.2130; found 458.2130.

5.4.32.6 (*R*)-2-(Styryl)-1-(2-4-6-triisopropylbenzenesulfonyl)aziridine (383)



Prepared according to general procedure Q using **310** (28.25 mg, 0.084 mmol), **376** (33.38 mg, 0.084 mmol), CH_2Cl_2 (1.05 cm^3), styrene (9.6 μL, 0.084 mmol) and P_2 base (2.0 M in THF, 42.0 μL, 0.084 mmol). Upon completion, *i.e.* 16 h, the crude material was purified by column chromatography on silica that had been deactivated by preparing the silica slurry using 7:3:0.5 hexane:CH_2Cl_2:triethylamine and using 8:2 hexane:CH_2Cl_2 as eluent. **383** Was obtained as a white solid (31.79 mg, 92%, 18% *ee*). M.p. 134-136 °C. $[\alpha]_D^{20}$ = -20.6 (*c* 0.17, CH_2Cl_2, 18% *ee*).

CSP-HPLC analysis: CHIRALPAK AD-H (4.6 mm x 25 cm), hexane/IPA: 9.9/0.1, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: 10.4 min (minor enantiomer) and 17.2 (major enantiomer).

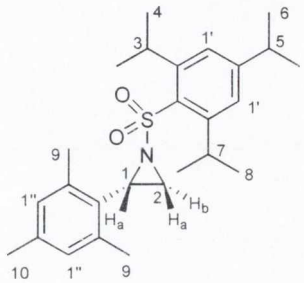
δ_H (400 MHz, $CDCl_3$): 1.24-1.29 (m, 18H, H-4, H-6 and H-8), 2.30 (d, J 4.4, 1H, H-2b), 2.85-2.91 (m, 2H, H-2a and H-5), 3.45-3.50 (m, 1H, H-1a), 4.36 (septet, J 6.8, 2H, H-3 and H-7), 5.86 (dd, J 16.1, 7.7, 1H, H-9), 6.69 (d, J 16.1, 1H, H-10), 7.18 (s, 2H, H-1'), 7.24-7.32 (m, 5H, H-1'', H-2'' and H-3'').

δ_C (100 MHz, $CDCl_3$): 23.7, 25.0, 25.1, 29.9, 34.4, 34.8, 40.8, 124.0, 124.8, 126.5, 128.3, 128.8, 131.6 (q), 134.7 , 136.0 (q), 151.2 (q), 153.6 (q).

υ (cm^{-1}): 663, 700, 755, 786, 939, 973, 1145, 1308, 1602, 2868, 2956.

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_{25}H_{33}NO_2SNa$ 434.2130; found 434.2135.

5.4.32.7 (*R*)-2-Mesityl-1-(2-4-6-triisopropylbenzenesulfonyl)aziridine (382)



Prepared according to general procedure Q using **310** (27.27 mg, 0.081 mmol), **375** (33.53 mg, 0.081 mmol), proton sponge (17.37 mg, 0.081 mmol), CH_2Cl_2 (1.01 cm^3), styrene (9.3 μL, 0.081 mmol) and P_2 base (2.0 M in THF, 40.5 μL, 0.081 mmol). Upon completion, *i.e.* 16 h, the crude material was purified by column chromatography (7:3 hexane:CH_2Cl_2) to furnish **382** as a white solid (30.16 mg, 87%, 25% *ee*). M.p. 87-89 °C. $[\alpha]_D^{20} = -8.6$ (*c* 0.26, CH_2Cl_2, 25% *ee*).

CSP-HPLC analysis: CHIRALPAK AD-H (4.6 mm x 25 cm), hexane/IPA: 9.9/0.1, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: 5.2 min (minor enantiomer) and 6.1 (major enantiomer).

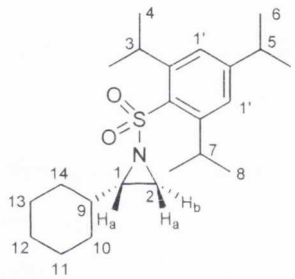
δ_H (600 MHz, $CDCl_3$): 1.24-1.29 (m 18H, H-4, H-6 and H-8), 2.16 (d, J 4.9, 1H, H-2b), 2.24 (s, 3H, H-10), 2.29 (s, 6H, H-9), 2.89 (d, J 7.2, 1H, H-2a), 2.92 (septet, J 6.9, 1H, H-5), 3.96 (dd, J 7.2, 4.9, 1H, H-1a), 4.40 (septet, J 6.8, 2H, H-3 and H-7), 6.80 (s, 2H, H-1''), 7.19 (s, 2H, H-1').

δ_C (100 MHz, $CDCl_3$): 20.2, 21.0, 23.7, 24.9, 25.3, 29.9, 34.37, 34.41, 39.9, 124.0, 128.8 (q), 129.3, 131.6 (q), 137.5 (q), 137.6 (q), 151.4 (q), 153.7 (q).

υ (cm^{-1}): 660, 699, 716, 834, 911, 1152, 1313, 1460, 1599, 2869, 2927, 2960.

HRMS (ESI): $[M+Na]^+$ Calcd. for $C_{26}H_{37}NO_2SNa$ 450.2443; found 450.2453.

5.4.32.8 (*R*)-2-Cyclohexyl-1-(2-4-6-triisopropylbenzenesulfonyl)aziridine (384)



Prepared according to general procedure Q using **310** (30.05 mg, 0.089 mmol), **377** (33.72 mg, 0.089 mmol), proton sponge (19.14 mg, 0.089 mmol), CH_2Cl_2 (1.12 cm^3), styrene (10.2 μL, 0.089 mmol) and P_2 base (2.0 M in THF, 45.0 μL, 0.089 mmol). Upon completion, *i.e.* 16 h, the crude material was purified by column chromatography (7:3 hexane:CH_2Cl_2) to furnish **384** as a white solid (31.82 mg, 91%, 20% *ee*). M.p. 111-113 °C. $[\alpha]_D^{20}$ = -9.5 (*c* 0.23, CH_2Cl_2, 20% *ee*).

CSP-HPLC analysis: CHIRALPAK AD-H (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: 3.6 min (major enantiomer) and 4.4 (minor enantiomer).

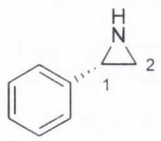
δ_H (600 MHz, $CDCl_3$): 0.85-0.91 (m, 1H, H-12a), 0.95-1.02 (m, 1H, H-10a), 1.08-1.21 (m, 4H, H-9, H-11a, H-13a and H-14a), 1.25-1.27 (m, 18H, H-4, H-6 and H-8), 1.40-1.43 (m, 1H, H-12b), 1.60-1.70 (m, 4H, H-10b, H-11b, H-13b and H-14b), 2.09 (d, J 4.6, 1H, H-2b), 2.55-2.58 (m, 1H, H-1a), 2.62 (d, J 7.0, 1H, H-2a), 2.91 (septet, J 6.9, 1H, H-5), 4.36 (septet, J 6.7, 2H, H-3 and H-7), 7.17 (s, 2H, H-1').

δ_C (100 MHz, $CDCl_3$): 23.73, 23.74, 25.0, 25.1, 25.6, 25.8, 26.2, 29.8 (2xC), 30.0, 31.9, 34.4, 39.3, 44.6, 123.8, 131.6 (q), 151.2 (q), 153.4 (q).

υ (cm^{-1}): 666, 716, 884, 948, 1153, 1312, 1445, 1601, 2863, 2928, 2952, 2965.

HRMS (ESI): $[M+H]^+$ Calcd. for $C_{23}H_{38}NO_2S$ 392.2623; found 392.2630.

5.4.33 (*R*)-2-Diphenylaziridine ((*R*)-385)



An oven dried 25 cm^3 round bottomed flask containing a magnetic stirring bar was charged with naphthalene (912 mg, 7.112 mmol) and finely chopped sodium (149 mg, 6.465 mmol). The flask was fitted with a rubber septum and placed under an atmosphere of argon (balloon). Anhydrous THF (6.4 cm^3) was added *via* syringe. The resulting solution was allowed to stir at ambient temperature for 2 h. An oven dried 25 cm^3 round bottomed flask containing a magnetic stirring bar was then charged with **354** (124.64 mg, 0.323 mmol), fitted with a rubber septum and placed under an atmosphere of argon (balloon). Anhydrous THF (1.8 cm^3) was added *via* syringe and the resulting solution

was cooled to -78 °C. The sodium naphthalide solution was then added dropwise *via* syringe to the cooled solution and allowed to stir at this temperature for 10 min. The reaction mixture was then quenched by the addition of H_2O (1 cm^3). The resulting solution was diluted with Et_2O (10 cm^3), poured onto $MgSO_4$, filtered and concentrated *in vacuo*. Note; due to the volatile nature of the product, the water bath of the rotary evaporator was set at 15 °C. Purification by flash chromatography using 100% hexane initially to remove excess naphthalene, followed by 100% Et_2O, afforded **(*R*)-385** as a colourless oil (14.03 mg, 36%). $[\alpha]_D^{20} = -9.5$ (*c* 0.1, EtOH, 23% *ee*); lit.,[246] $[\alpha]_D^{20} = -43.2$ (*c* 1.07, EtOH). The NMR spectra of **385** were consistent with those previously reported.[247,248]

δ_H (400 MHz, $CDCl_3$): 1.04 (br s, 1H, NH), 1.84 (br s, 1H, H-2a), 2.20-2.30 (m, 1H, H-2b), 3.05 (br s, 1H, H-1), 7.25-7.36 (m, 5H, H-Ar).

δ_C (100 MHz, $CDCl_3$): 29.4, 32.2, 125.8, 127.2, 128.6, 140.6 (q).

HRMS (ESI): $[M+H]^+$ Calcd. for $C_8H_{10}N$ 120.0813; found 120.0810.

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