Asymmetric Synthesis using Sulfimides

by

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Submitted for the Degree of Doctor of Philosophy

Department of Chemistry
University of Warwick
September 1995

Dedicated to my parents

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Acknowledgements

I would like to thank my supervisor Dr. Paul C. Taylor for his encouragement, patience and support. I would also like to thank Dr. Andrew J. Clark for his help and humour and Professor D.H.G. Crout for providing assistance and direction along the way.

Thanks are also due to Mr. Michael Vaughan for helping type my thesis, Dr. J.J. Hastings for running the 400 MHz NMR spectra, Dr W.E. Errington for doing the X-ray crystallography, Mr. I. Katyal and the EPSRC Mass Spectrometry Service for the mass spectra, Mr. Paul Moore for doing the microanalyses, Dr. C.J. Samuel for assistance in interpreting some NMR spectra and the EPSRC for funding my research.

I would like to thank everyone in the department for making life in a laboratory bearable; in particular, Daf and Andy for helping me spend my grant on Guinness and curry and Hardeep and Annie for making me feel sane. Special thanks go to Cathrine for looking after me during writing-up and for putting up with a stubborn old so-and-so who is never wrong and to my parents to whom I am deeply indebted for giving me the opportunity to see the world and for not making me feel as though I should be elsewhere milking cows.

Declaration

The work described in this thesis is the original of the author, except where acknowledgement has been made to results and ideas previously published. The work was carried out at the Department of Chemistry, University of Warwick, between October 1st, 1992 and June 30th, 1995 and has not been previously submitted for a degree at any institution.

Abstract

Asymmetric synthesis, the synthesis of chiral molecules, has developed into one of the most important areas of chemistry. Numerous methods are used to prepare chiral compounds, one of which involves using chiral acyl anion equivalents. The potential of imides of cyclic sulfimides **148** as chiral acyl anion equivalents was found to be limited to simple alkylations using sodium hydride and an alkyl iodide in DMF. Alkylated adducts **154**, **158** and **159** were prepared with good diastereoselectivity, with the *anti* and *anti-anti* geometries being preferred for **154** and **158**, and **159**, respectively. The conformations of the parent sulfimides **148** were investigated. We found that cyclic sulfimides (1,3,4-oxathiazines) **132** were inaccessible, which precluded our investigation into the potential of this new class of compound as chiral acyl anion equivalents. In the course of this work, the BPTM group was developed as a replacement for the troublesome PTM group as a protecting group for primary, secondary and benzylic alcohols.

Vinyl sulfimides **186** were prepared using a modified Wadsworth-Emmons reaction, with good *E* selectivity. Additions of alcohols to give adducts **185** proceeded with good diastereoselectivity. The attempted deprotection of adduct **185b** using hydrogenolysis resulted in reduction of the sulfimide group to yield protected β-hydroxy sulfide **192**. Radical additions to vinyl sulfimides **186** resulted in 2-vinyl oxa-heterocycles **202** and **210**, with THF and THP as solvent, respectively. A radical addition mechanism has been proposed, but uncertainty still exists as this mechanism can not explain both triethylborane and benzoyl peroxide mediated reactions as the *E*/*Z* selectivities are different. At this stage, an ionic mechanism can not be ruled out. 2-Vinyl oxa-heterocycles **202** and **210** have been converted, using Taylor's variant of the Malherbe-Bellus reaction, into 9- and 10-membered

lactones **220** and **221**, respectively, which are closely related to a number of important natural products.

Considerable progress has been made in developing a new asymmetric sulfimidation procedure. Promising enantioselectivites have been observed using a copper-catalysed decompsition of tosyl azide or PhI=NTs **224** into nitrenes. Interception of the nitrenes by sulfide within the chiral influence of C-2 symmetric chiral ligands **225** or **231** yielded sulfimide **65**. A discrete copper-nitrene species is thought to be an intermediate in the catalytic cycle.

Abbreviations

b.p.	Boiling point
BPTM	*p*-Bromophenylthiomethyl
BPTMCl	*p*-Bromophenylthiomethylchloride
br	Broad
n-BuLi	*n*-Butyllithium
cat.	Catalyst
CI	Chemical ionisation
COSY	Correlated spectroscopy
d	Doublet
DAG	Diacetone-D-Glucose
de	Diastereomeric excess
DEPT	Direct enhancement by polarisation transfer
DET	Diethyltartrate
DME	1,2-Dimethoxyethane
ee	Enantiomeric excess
EI	Electron impact
Et	Ethyl
EtOH	Ethanol
FAB	Fast atom bombardment
HOMO	Highest occupied molecular orbital
Hz	Hertz
IR	Infra-red
J	Coupling constant
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
m	Multiplet

Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
mol	Mole
m.p.	Melting point
MS	Mass spectrum
MTM	Methylthiomethyl
NMR	Nuclear Magnetic Resonance
ppm	Parts per miilion
PTM	Phenylthiomethyl
Pr	Propyl
q	Quartet
R	Alkyl or aryl
RT	Room temperature
s	Singlet
SOMO	Singly occupied molecular orbital
t	Triplet
tlc	Thin layer chromatography
THF	Tetrahydrofuran
THP	Tetrahydropyran
TFAA	Trifluoroacetic anhydride
Ts/Tosyl	*p*-Methylbenzenesulfonyl
TMS	Trimethylsilyl
TMSCl	Trimethylsilylchloride
Tol	*p*-Methylphenyl
$[\alpha]_D$	Specific rotation

Chapter 1

Introduction

1.1 Introduction to sulfimides

Sulfimides **1** are the nitrogen analogues of sulfoxides **2**. Although sulfimides have been known for almost eighty years, they remain a rather unexploited class of compound. This is particularly surprising as sulfimides and sulfoxides are equally convenient to prepare. Besides sulfoxides, the other $S^{(IV)}$ analogues of sulfimides worthy of note are the sulfur ylids **3** (**Figure 1.1**).

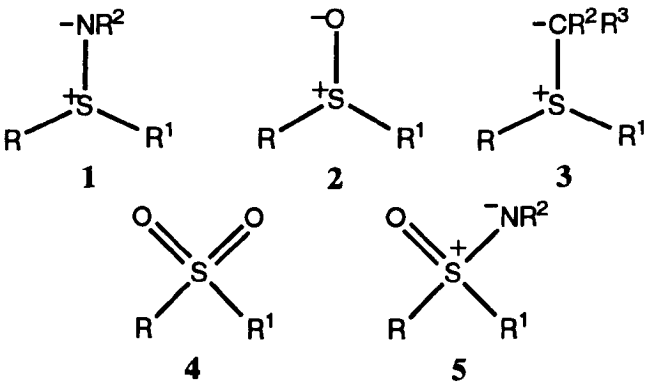


Figure 1.1 General structure of sulfimides and analogues

The most well known $S^{(VI)}$ analogues of sulfimides are sulfones **4** and sulfoximides **5**, although the former are less relevant to this discussion as the sulfur centre is achiral. Three other $S^{(VI)}$ analogues are sulfoximide ylids **6**, sulfur diimides **7** and oxosulfonium salts **8** (**Figure 1.2**).

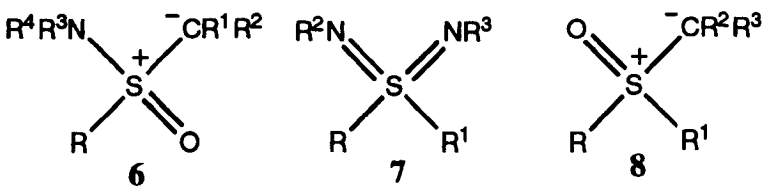
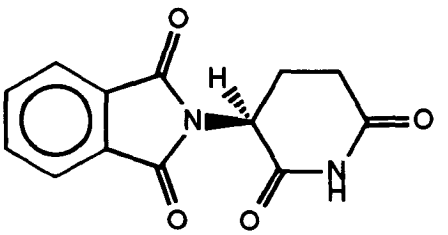


Figure 1.2 Other analogues of sulfimides

The S-X bond (X = CR_2, NR, O) in the classes of sulfur compounds described above can be represented either as S=X or S^+-X^-. The true nature of these bonds will be discussed later, but we propose to use the S=X representation when the definition of stereochemistry at sulfur is not important (eg. sulfones). Otherwise the S^+-X^- representation will be preferred.

1.2 Asymmetric synthesis - a foreword

The development of asymmetric synthesis as a fundamental part of chemistry has been a rapid process, of which the thalidomide tragedy was a defining moment (**Figure 1.3**). The drug **9** was administered in its racemic form, with both enantiomers having the desired sedative effect. However, the (-)-enantiomer (shown here) caused foetal abnormalities which resulted in tremendous suffering for the victims. Since then, asymmetric synthesis has advanced to the stage where nearly all chiral compounds are accessible in high enantiomeric purity.



9

Figure 1.3 Structure of thalidomide

The tightening of controls relating to the administration of chiral drugs by the regulatory authorities has ensured that chiral drugs are not prescribed in the racemic form, unless both enantiomers have been shown to be harmless. The financial incentives to develop new asymmetric methods are thus huge.

There are four main methods of deploying the source of chirality in asymmetric synthesis:

• Chiral building blocks: amino acids such as glutamic acid, and their corresponding reduced derivatives amino alcohols, are widely used chiral building blocks.

• Chiral auxiliaries: Meyers' oxazolines[1] and Evans' oxazolidinones[2] are among the most well known and versatile auxiliaries.

• Chiral reagents: Simpkins' asymmetric deprotonation using chiral amide bases[3] is an example of the use of a chiral reagent.

• Chiral catalysts: the most well known chiral catalytic processes are asymmetric epoxidations, for example by the Sharpless procedure.[4]

1.3 Sulfoxides

1.3.1 Introduction

The extent to which an S-X (X=O, N, C) bond displays single or double bond character has been the focus of much debate.[5] Generally, the bond is accepted as having more double than single bond character. The bond order is heavily influenced by the electronic nature of the substituents on the sulfur.

Sulfoxides contain a tricoordinate sulfur atom. Given dissimilar alkyl/aryl substituents, sulfoxides can thus exist as enantiomers (**Figure 1.4**).

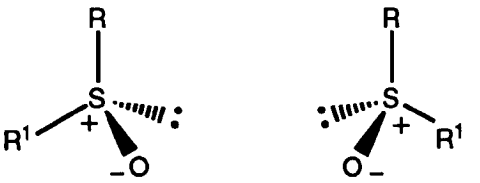


Figure 1.4 An enantiomeric pair of sulfoxides

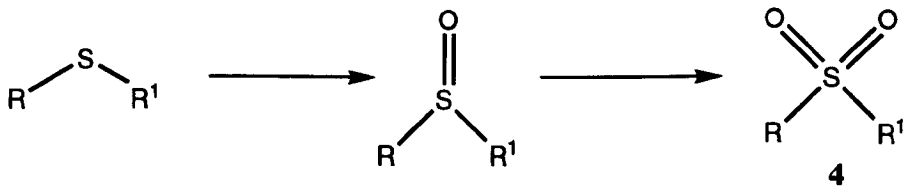
For sulfoxides to be of any use in asymmetric synthesis the chiral sulfur centre must be configurationally stable (thermally, chemically and photochemically). Mislow determined the activation parameters for pyramidal inversion for a series of alkyl/aryl sulfoxides.[6] In most cases, configurational mobility was observed only at about 200 °C, meaning that

sulfoxides can be used in asymmetric synthesis under conventional asymmetric reaction conditions.

1.3.2 Synthesis of sulfoxides

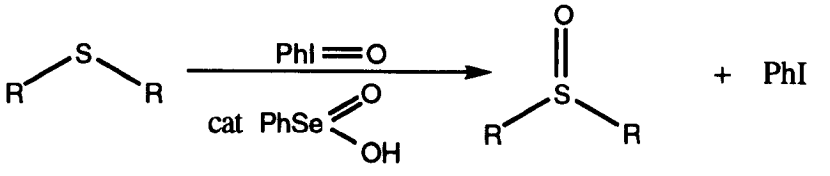
1.3.2.1 Oxidation of a sulfide

Oxidation of a sulfide is the most common approach to sulfoxides. Oxidising agents such as hydrogen peroxide, *m*-chloroperbenzoic acid and *t*-butylhypochlorite are widely used, although almost any oxidising agent will work. However, over-oxidation to sulfones **4** is a problem (**Scheme 1.1**).



Scheme 1.1

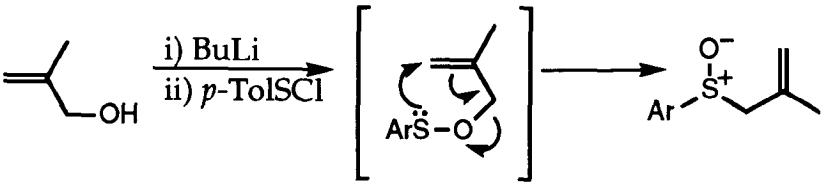
Less common, but perhaps the most effective oxidising agent, is iodosobenzene with benzeneseleninic acid as catalyst (**Scheme 1.2**). Electron deficient alkyl aryl sulfoxides can be isolated in excellent yields, with little or no sulfone present, under mild conditions.[7]



Scheme 1.2

1.3.2.2 Rearrangement of sulfenate esters

Grieco demonstrated how sulfenate esters **10** can undergo a 2,3-sigmatropic rearrangement to give allylic sulfoxides **11** (**Scheme 1.3**).[8]



10 **11**

Scheme 1.3

1.3.3 Asymmetric synthesis of sulfoxides

1.3.3.1 Asymmetric oxidation of sulfides

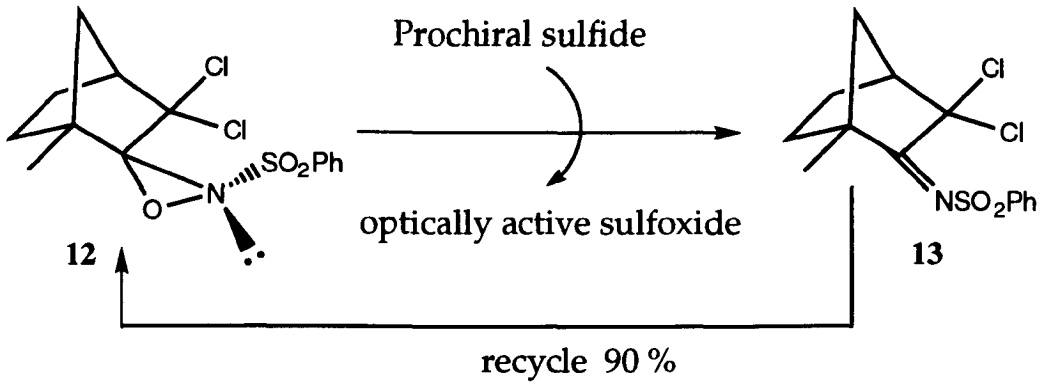
1.3.3.1.1 Kagan's and Modena's modified Sharpless oxidation system

With little expectation, Kagan examined the suitability of the Sharpless epoxidation reagent as an asymmetric sulfoxidation system. Optimisation by both Kagan and Modena (using $Ti(OiPr)_4$: diethyl tartrate :*t*-BuOOH 1:4:2) has given access to aryl methyl sulfoxides of good enantiomeric purity (80-96 % ee).[9,10]

The two drawbacks are the limitation to aryl methyl sulfoxides and the requirement for stoichiometric amounts of titanium reagent. The latter is a major problem as it is both expensive and toxic. Use of cumene hydroperoxide as oxidant has allowed limited progress towards a catalytic procedure.

1.3.3.1.2 Davis' oxaziridines

Davis' oxaziridines **12** give very good asymmetric sulfoxidation results in terms of enantioselectivity, generality and predictability. Davis used a stoichiometric amount of oxaziridine to oxidise a variety of sulfides (**Scheme 1.4**).[11]

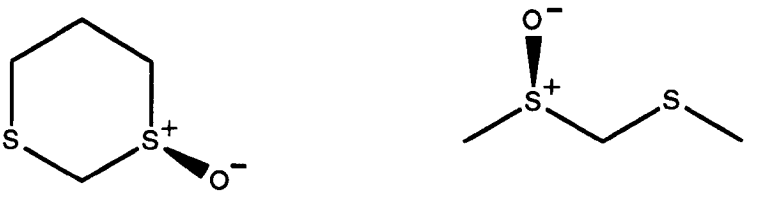


Scheme 1.4

Methyl *p*-tolyl sulfoxide (>95% ee) and benzyl *t*-butyl sulfoxide (94% ee) were the two best results obtained. Generally, the greater the steric difference between the alkyl and aryl substituents on the sulfur, the better the enantioselectivity. Regeneration of the oxaziridine from the sulfonylimine **13** is possible, making this an economic asymmetric sulfoxidation procedure. Either enantiomeric sulfoxide series is accessible as both enantiomeric forms of the oxaziridine are available.

1.3.3.1.3 Enzymatic oxidations

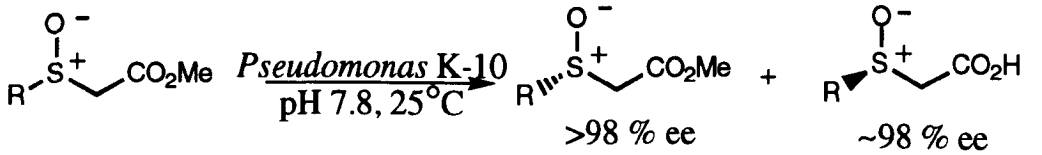
Some impressive enantioselectivities have been observed for biotransformations of sulfides to sulfoxides using enzymes. Most noteworthy has been chloroperoxidase, when used with a stoichiometric amount of either hydrogen peroxide or *t*-butyl peroxide which gave good results with aryl methyl sulfides, eg. methyl phenyl sulfoxide; 100% yield, 98% ee and 2-pyridyl methyl sulfoxide; 100% yield, 99% ee., although this system is limited to aryl methyl sulfides.[12] More recently, Colonna has observed excellent enantioselectivities using cyclohexanone monooxygenase. For example, the dithioacetal oxides **14** and **15** (**Figure 1.5**) were isolated in excellent yields and optical purities (both 98% ee).[13]



14 15

Figure 1.5 Structure of dithioacetals 14 and 15

Kinetic resolution of functionalised racemic sulfoxides **16** provides a useful route to highly optically enriched sulfoxides **17** and **18** (**Scheme 1.5**).[14]



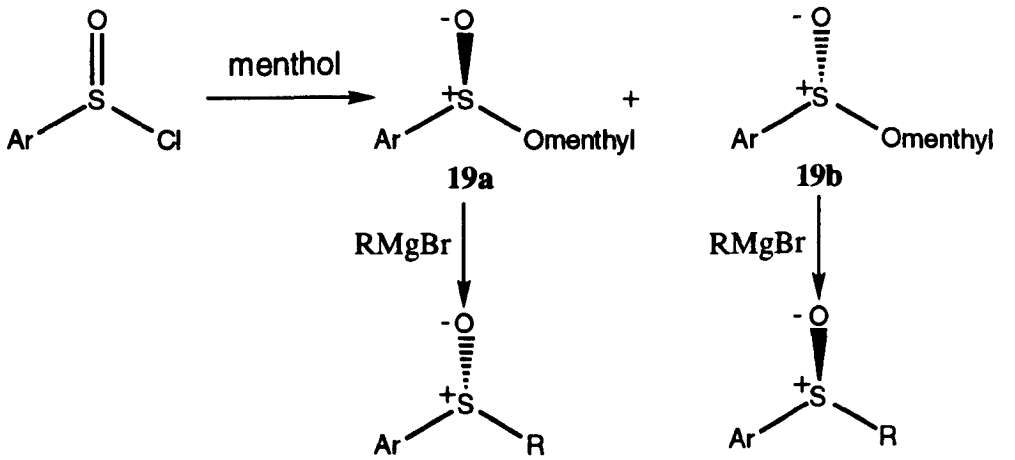
16 17 18

Scheme 1.5

1.3.3.2 Andersen synthesis and related methods

1.3.3.2.1 Andersen synthesis

The Andersen synthesis has been the most popular route to optically active sulfoxides.[15] By using cheap, readily available chiral alcohols, such as menthol, diastereomeric sulfenate esters **19** can be generated (**Scheme 1.6**). Regeneration of menthol by Grignard displacement proceeds with inversion at the sulfur atom.

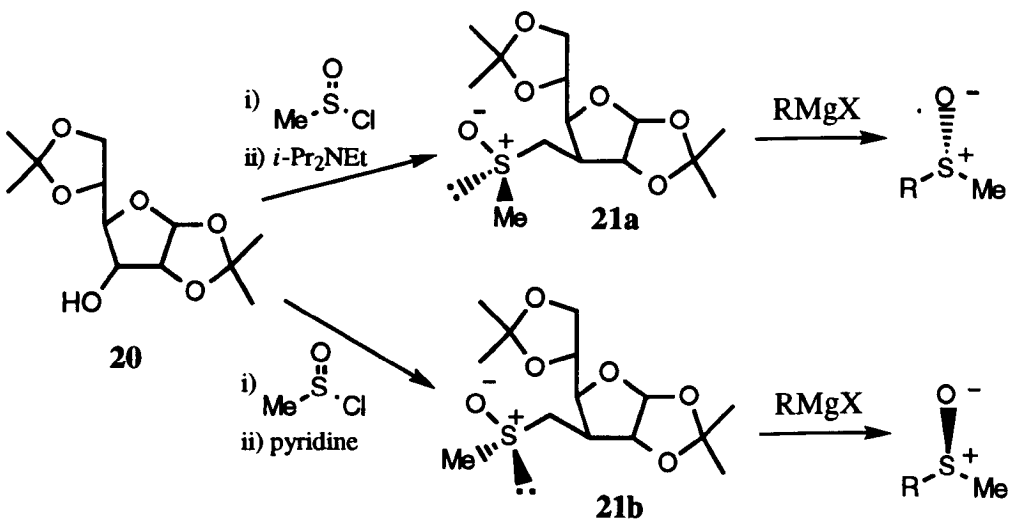


Scheme 1.6

This approach is limited to aromatic (ArSOCl) precursors and to the availability of Grignard reagents. Separation of diastereomeric sulfinate esters **19** may be necessary, depending on the kinetic selectivity during esterification, although this can sometimes be avoided by acid-catalysed epimerisation at the sulfur, when the more crystalline isomer can then be isolated in good yield and high enantiomeric purity.

1.3.3.2.2 Llera's diacetone-D-glucose (DAG) 20

Using cheap readily available DAG **20** as the chiral auxiliary, Llera has found a potentially useful method for generating optically active methyl sulfoxides (**Scheme 1.7**).[16]



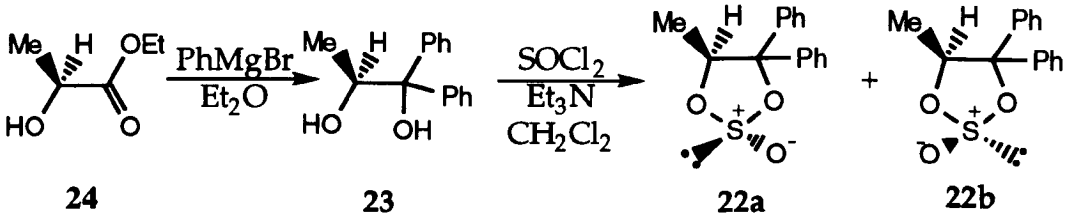
Scheme 1.7

Sulfinate esters **21** can be selectively generated (**21a** by using the sterically hindered Hunig's base and **21b** by using pyridine), in good yields and with high diastereoselectivity. Grignard displacement of the furanose unit liberates homochiral methyl sulfoxides.

1.3.3.2.3 Kagan's cyclic sulfite method

One of the restrictions of the Andersen procedure can be avoided by having two leaving groups on the chiral sulfur precursor, as demonstrated by Kagan's use of chiral sulfites. The only remaining restriction on the range of available chiral sulfoxides is then, in principle, the availability of the Grignard reagents required for the nucleophilic substitution.

Kagan's idea was to place two sterically dissimilar leaving groups either side of the chiral sulfur within the confines of cyclic sulfites **22** (**Scheme 1.8**).[17]



24 **23** **22a** **22b**

Scheme 1.8

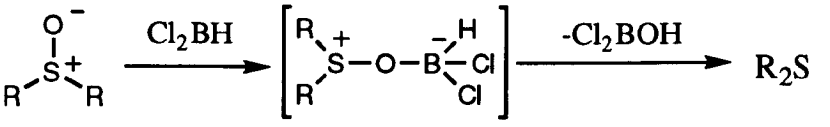
Conversion to chiral sulfoxides of excellent optical purity (100% ee) required two further sequential Grignard additions. The regioselectivity of addition was controlled by the steric properties of both nucleophile and parent diol **23**. Either enantiomeric sulfoxide can be obtained, as both enantiomeric forms of the lactate **24** are now available.

1.3.4 Reactions of sulfoxides

1.3.4.1 Oxidation and reduction

Sulfoxides can easily be reduced to sulfides by many reducing agents. Of greater importance is the chemoselective reduction of a sulfoxide in preference to other reducable functional groups. A simple example is that of dichloroborane, which is capable of selectively reducing aliphatic sulfoxides in minutes in the presence of ester, acid chloride, nitrile or nitro groups. Even

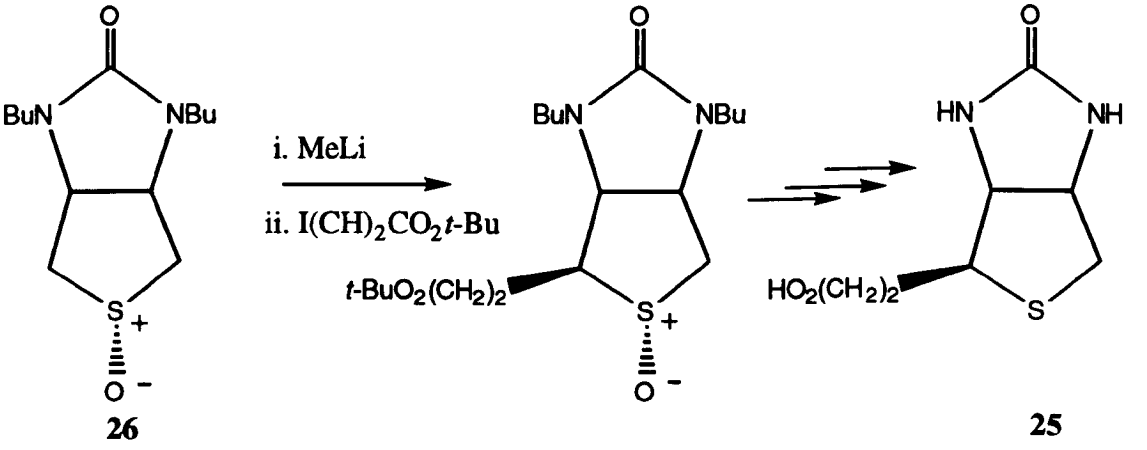
aldehydes, ketones, amides and alkenes are only a slightly reduced (**Scheme 1.9**).[18]



Scheme 1.9

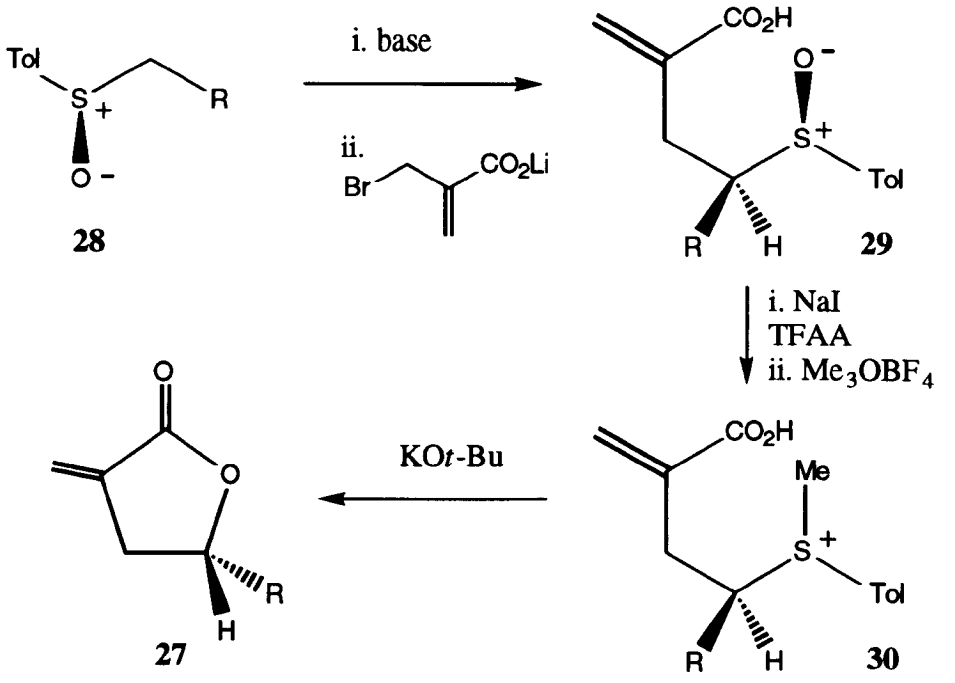
1.3.4.2 Sulfoxides in asymmetric synthesis

The ability of the sulfoxide group to stabilize an α-carbanion enables diastereomeric C-C bond formation to result from electrophilic attack. Sulfoxides have consequently found considerable use as chiral auxiliaries. The first successful stereocontrolled alkylation to be used in a total synthesis was developed by the group of Marquet. They generated dl-biotin **25**, which required the alkylation of the *exo*-sulfoxide **26** as a key step (**Scheme 1.10**).[19]



Scheme 1.10

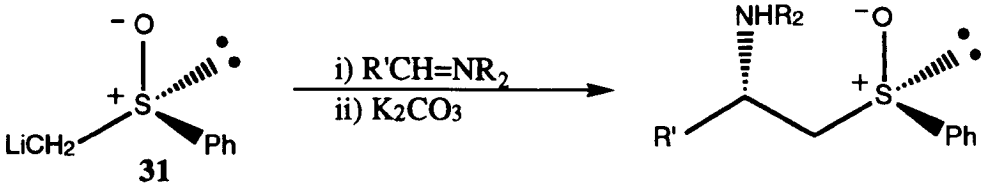
Bravo and co-workers demonstrated the usefulness of sulfoxides as chiral auxiliaries by targeting homochiral α-methylene butyrolactones **27** (**Scheme 1.11**).[20]



Scheme 1.11

Metalation of homochiral sulfoxides **28** with a variety of bases followed by alkylation gave diastereomeric sulfinyl acids **29**. However, removal of the sulfoxide auxiliary required two steps, namely reduction to sulfide and methylation to afford the sulfonium salt **30**, followed by intramolecular displacement of the sulfenate group with inversion the give lactones **27**.

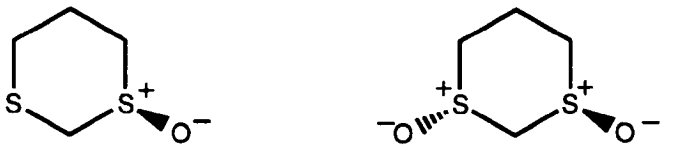
Pyne demonstrated that imines could act as electrophiles with metalated methyl *p*-tolyl sulfoxide **31**. Imines possessing at least one aryl substituent led to good diastereoselectivities (**Scheme 1.12**).[21]



Scheme 1.12

Page's 1,3-dithian-1-oxide **14**[22] and Aggarwal's 1,3-dithian-1,3-dioxide **32**[23] have proven extremely useful as chiral auxiliaries (**Figure 1.6**). The latter possesses C-2 symmetry. This characteristic reduces the number of competing diastereomeric transition states in an asymmetric induction

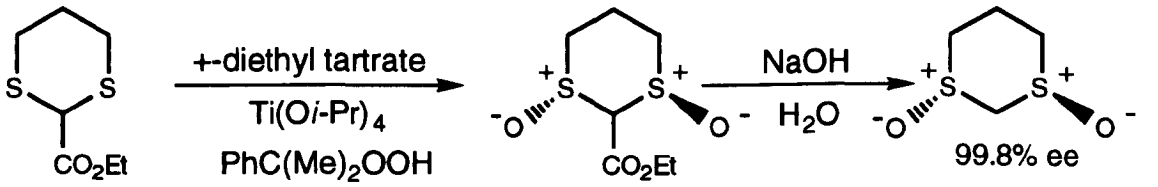
reaction by half, which in turn increases the diastereoselectivity of the reaction.



14 **32**

Figure 1.6 Structure of sulfoxides 14 and 32

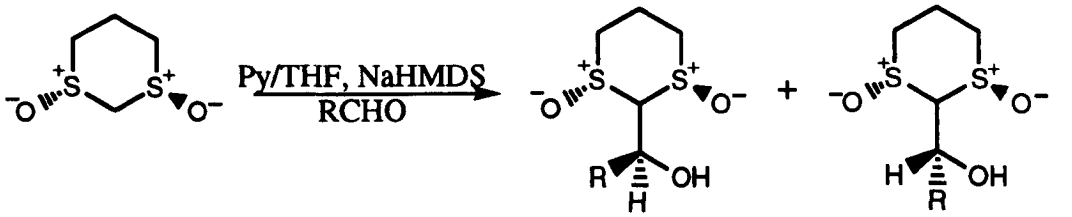
Enantiomerically pure **32** was made available by applying Kagan's C-2 functionalisation strategy to the substrate before using a slight variation of the Modena oxidation conditions (**Scheme 1.13**). Commercially available **33** was found to be the most suitable substrate.



33 **32**

Scheme 1.13

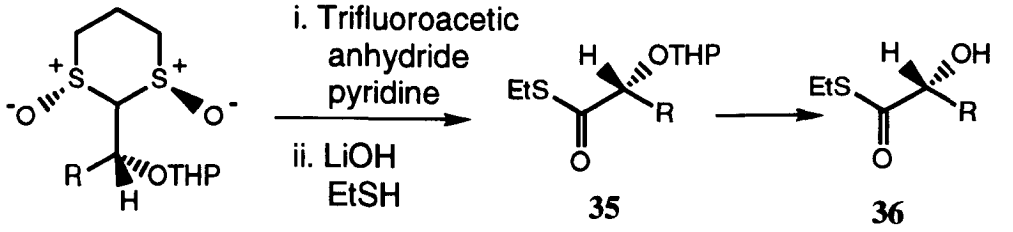
Highly diastereoselective C-C bond forming reactions were observed with metalated **32** and certain aromatic aldehydes (**Scheme 1.14**), particularly with benzaldehyde (R=Ph, 92% de) and anisaldehyde (R=*p*-$MeOC_6H_4$, 90% de), to yield adducts **34**. Both solvent system and metal counter ion were found to be important factors in affecting the yield and diastereoselectivity, respectively.



32 **34a** **34b**

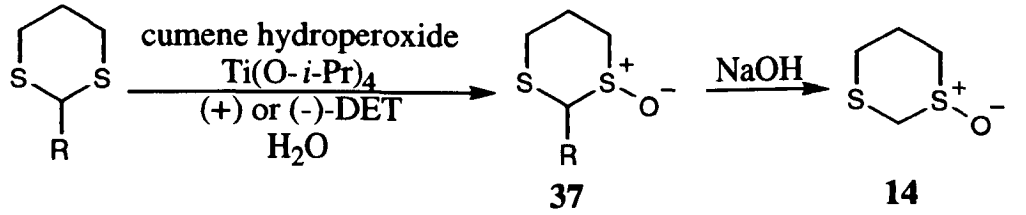
Scheme 1.14

Removal of the chiral sulfoxide auxiliary was effected using the first example of a transthiolesterification reaction (**Scheme 1.15**), to yield, after deprotection of **35** to the alcohol, ethyl thiolester **36** (R=Ph; 97% ee). Ethyl thiolesters **36** could be cleanly converted into acids and esters with excellent enantioselectivities.



Scheme 1.15

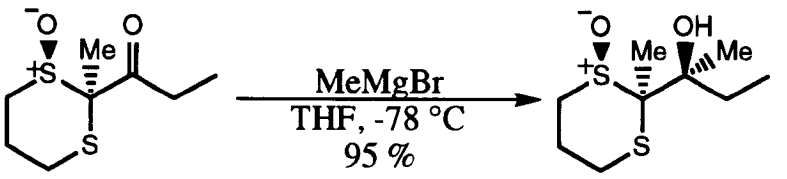
Page has similarly made **14** available in both enantiomeric forms using a slight variation on Kagan and Modena's asymmetric oxidation methodology (**Scheme 1.16**).



Scheme 1.16

2-Substitution was necessary to obtain good enantioselectivities, the best result being with R=pivaloyl giving **37** as a mixture of *anti:syn* 1:1 (92% and 88% ee respectively). Compound **37** (R=Pivaloyl) could be recrystallised to optical purity in one step and the deacylation provided **14** optically pure.

Carbonyl functionalisation of **14** at C-2 has made this derivative extremely useful as both chiral auxiliary and building block. Enolate alkylation, nucleophilic addition, reduction, conjugate addition, cycloaddition and Mannich reactions are all possible, usually with good stereoselectivity. For example, Grignard addition to β-keto sulfoxide **38** proceeds smoothly to yield **39** in excellent diastereoselectivity (**Scheme 1.17**).

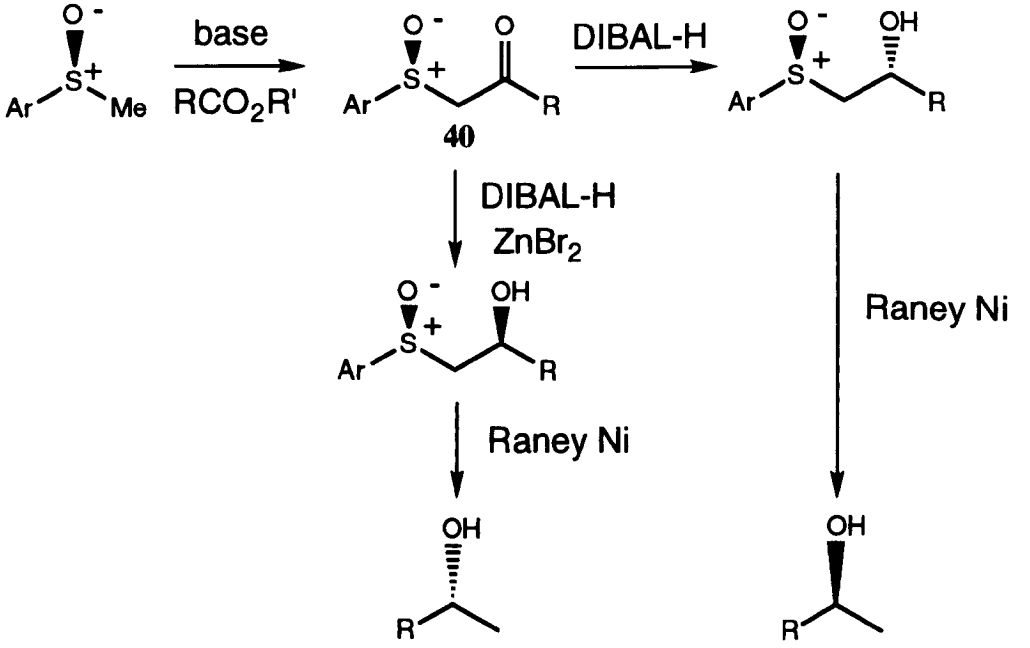


syn exclusive

38 **39**

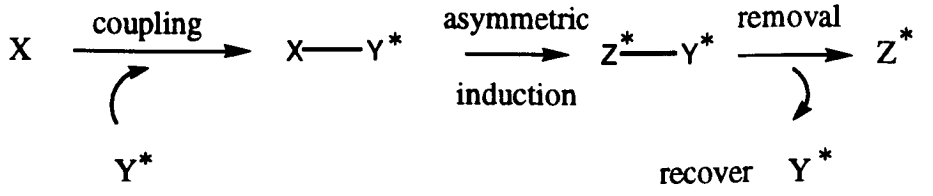
Scheme 1.17

Solladie has extensively utilised α-functionalised methyl sulfoxides such as **40** in various asymmetric syntheses to prepare, for example, chiral alcohols with good enantioselectivities (**Scheme 1.18**).[24]



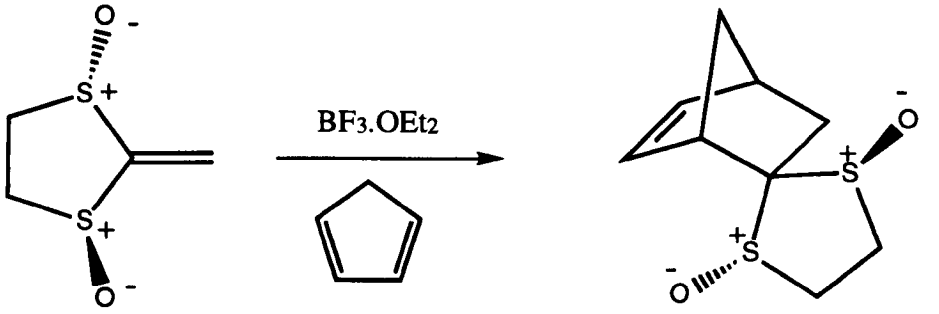
Scheme 1.18

Chiral auxiliaries usually require two extra steps in a synthesis. Both the coupling of the auxiliary Y* to the reactant X, and the removal of the auxiliary, require at least one step each (**Scheme 1.19**).



Scheme 1.19

However, sulfoxide mediated asymmetric processes usually involve a useful C-C bond forming reaction, followed by a diastereoselective transformation then a desulfurisation reaction in which the chirality at sulfur is destroyed. As few target molecules have sulfur functionalities, this desulfurisation step is nearly always required. Solladie's synthesis of chiral alcohols described above illustrates these points. Chiral sulfoxides have also been used in asymmetric versions of the Diels-Alder reaction. For example, Aggarwal's C-2 symmetric dithiolane ketene dithioacetal **41** was reported to give a single diastereomeric adduct **42** with cyclopentadiene as the diene (**Scheme 1.20**).[25]

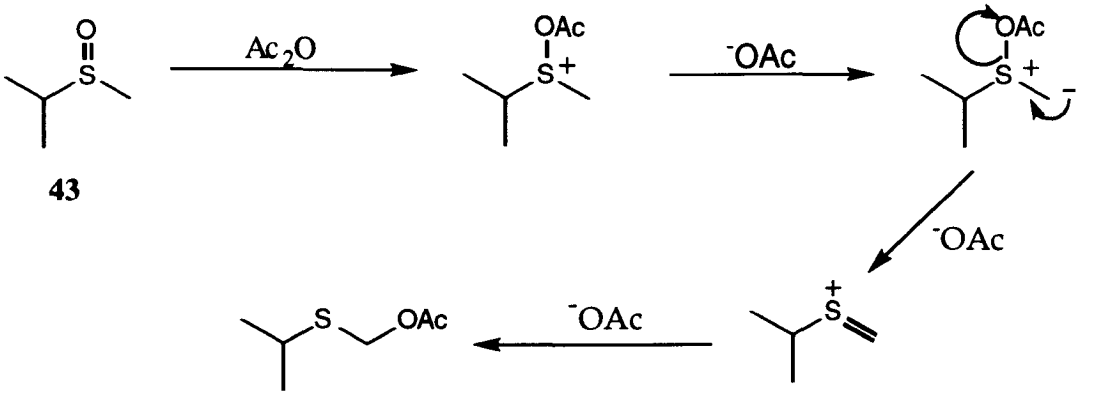


41 **42**

Scheme 1.20

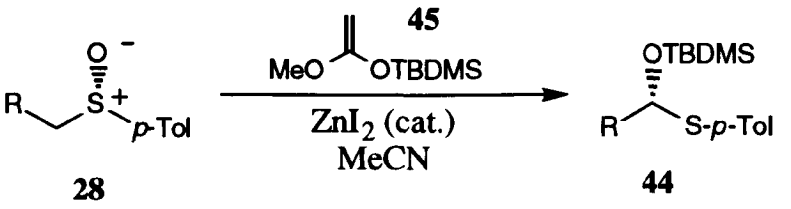
1.3.4.3 Pummerer rearrangements of sulfoxides

Sulfoxides with at least one α-H can be reduced to the sulfide with oxidation at the α-carbon. For example, methyl *i*-propyl sulfoxide **43** can undergo such a rearrangement in the presence of acetic anhydride (**Scheme 1.21**).[26]



Scheme 1.21

Kita prepared optically active sulfides **44** using the first highly asymmetric Pummerer rearrangement. Using *O*-silylated ketene acetal **45** and a catalytic amount of zinc iodide, good enantioselectivies were observed, in particular with R=CO_2Et (87 % ee) and R=$CONMe_2$ (88 % ee) (**Scheme 1.22**).[27]

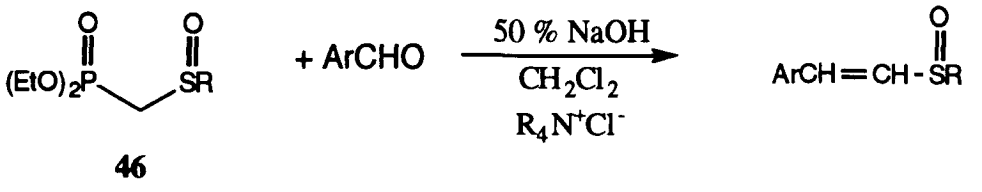


Scheme 1.22

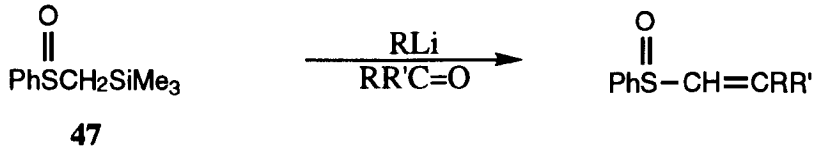
1.3.5 Vinyl sulfoxides

1.3.5.1 Preparation

Two general methods exist for the synthesis of vinyl sulfoxides. Oxidation of the appropriate vinyl sulfoxide is possible using a variety of oxidants, but the most common method is that of condensation of an aldehyde with, for example, functionalised methyl sulfoxides **46** (**Scheme 1.23**)[28] and **47** (**Scheme 1.24**).[29]



Scheme 1.23



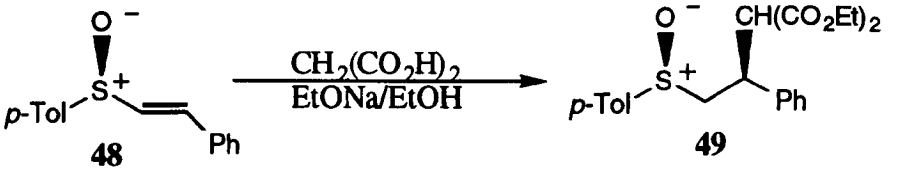
47

Scheme 1.24

The former is a two-phase Wittig-Horner reaction whereas the latter involves a Petersen-type olefination process. Optically active vinyl sulfoxides can also be prepared using the Andersen synthesis (**Section 1.3.3.2.1**).

1.4.5.2 Reactions of vinyl sulfoxides

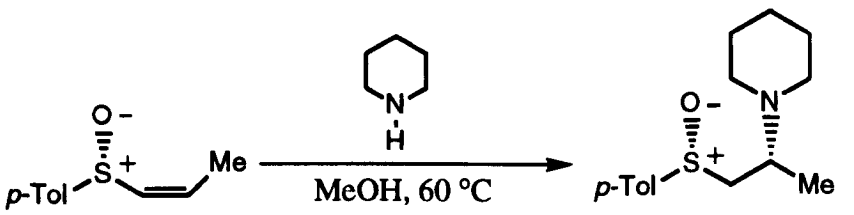
Vinylic sulfoxides are prone to Michael-type addition reactions with carbon nucleophiles or amines. The addition of diethyl malonate to optically active sulfoxide **48** resulted in diastereomeric C-C bond formiation with the *syn*-isomer **49** predominating (8:2) (**Scheme 1.25**).[30]



48 **49**

Scheme 1.25

Amine additions were first investigated by Stirling in 1971, who found that the conjugate addition of piperidine to vinyl sulfoxide **50** followed the same stereochemical course as above, to yield adduct **51** (**Scheme 1.26**).[31]

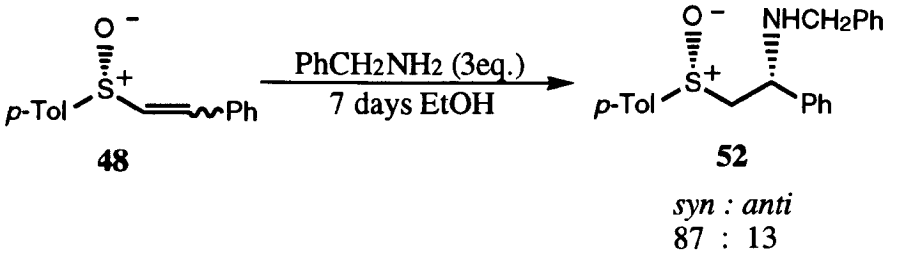


50 **51**

syn : *anti*
87 : 13

Scheme 1.26

Pyne observed that *syn*-diastereoisomer **52** was predominant when either *E*- or Z-substituted vinyl sulfoxides **48** were reacted with benzylamine (**Scheme 1.27**).[32]



48 **52**

syn : anti
87 : 13

Scheme 1.27

1.4 Sulfimides.

1.4.1 Introduction.

As noted for the analogous S-O bond in sulfoxides, the nature of the S-N bond in sulfimides has been the focus of much debate.[5c] The S-N bond has the added influence of a further substituent (on nitrogen). Two extreme representations are given to illustrate the sulfimidyl group (**Figure 1.7**).

Figure 1.7 Two representations of a sulfimide

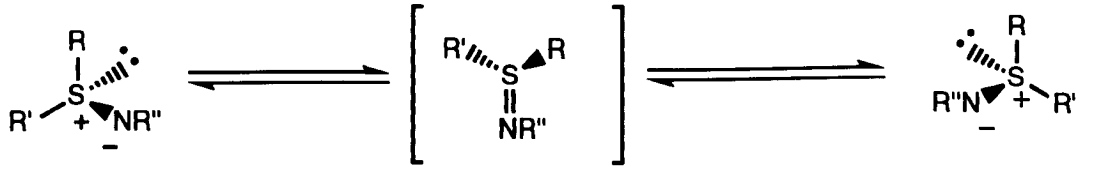
The substituents on sulfur and nitrogen exert a major influence on the polarity of the bond and hence the stability of the sulfimide. As a general rule, electron rich R^2 and electron poor R/R^1 tend to destabilise the sulfimide, whereas electron poor R^2 and electron rich R/R^1 give more stable compounds.

The S-N bond is generally accepted as being a highly polarised bond. A typical S-N bond length (0.163 nm) is less than the sum of the respective covalent radii (0.183 nm) indicating considerable bonding character.[5c]

Koval has summarised the three main explanations of the nature of the bond. In actuality, all three effects may contribute.[5c]

1. A normal double bond with the second bond resulting from overlap between nitrogen atom *p* orbitals and sulfur atom *d* orbitals.
2. A semipolar bond in which the second bond is ionic.
3. A double bond in which the π-system is stabilised by a hyperconjugative effect between the nitrogen bond pair and antibonding σ-orbitals of the neighbouring S-C bond.

An important point to note is that there have been no diastereomeric compounds observed as a result of hindered rotation around the S-N bond. Sulfimides with different substituents on sulfur can exist in enantiomeric forms (**Scheme 1.28**).



53

Scheme 1.28

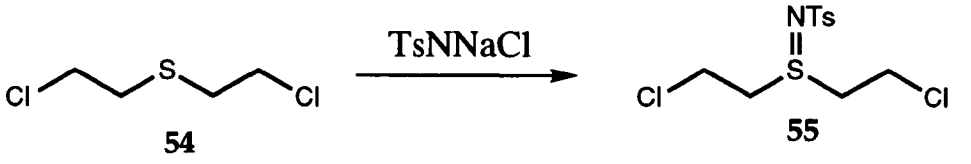
The thermal racemisation of sulfimides is known to proceed *via* a planar transition state **53**. Generally, the more polarised the S-N bond, the higher the barrier to inversion. Studies on a series of optically active sulfimides (R=2-$MeOC_6H_4$, R^1=Ph, R^2= tosyl, MeCO, PhCO, etc.) found that racemisation could occur at ~75°C in $CHCl_3$.[33]

1.4.2 Preparation of sulfimides

1.4.2.1 Racemic syntheses

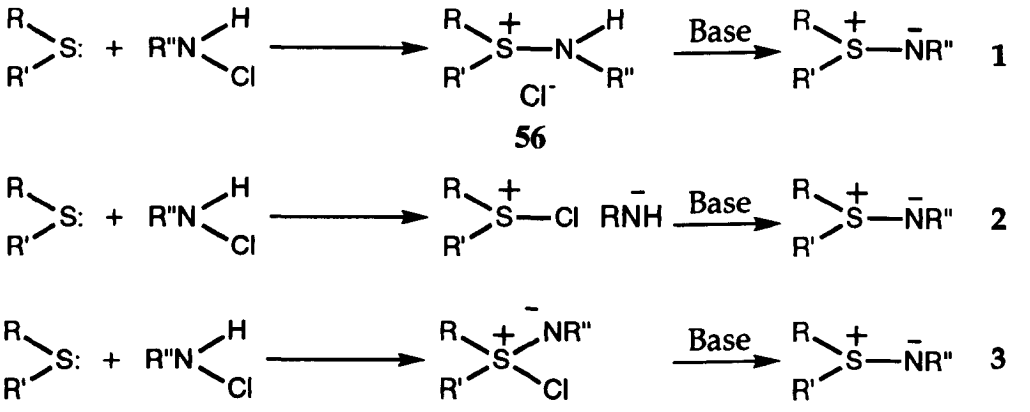
1.4.2.1.1 Oxidative imidation

The first synthesis of a sulfimide was reported by Raper in 1917, who found that mustard gas **54** reacted with Chloramine-T to give sulfimide **55** (**Scheme 1.29**).[34] This method has become the most widely used sulfimidation procedure.



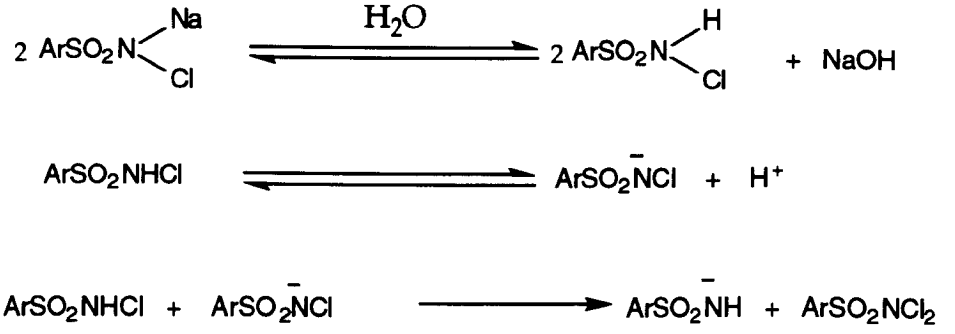
Scheme 1.29

The mechanism of oxidative imination of a sulfide is not fully understood. There are three possible mechanisms to consider (**Scheme 1.30**).[35]



Scheme 1.30

Equation **1** involves attack of the sulfide on the electron poor nitrogen, giving an aza-sulfonium salt **56**, whereas **2** involves nucleophilic attack on electrophilic chlorine and **3** equates to oxidative addition of Chloramine-T to the sulfide. Equation **2** illustrates the mechanism accepted as being reponsible for sulfimidation, although there is uncertainty regarding the source of electrophilic chlorine. Two equilibria and one irreversible reaction are known to occur in oxidative imination involving Chloramine-T (**Scheme 1.31**).[5c]

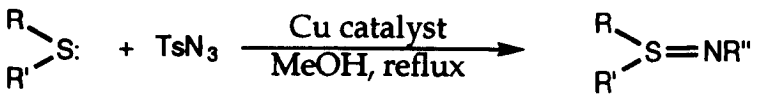


Scheme 1.31

The nucleophilicity of the sulfur atom is important, as electron withdrawing sulfur substituents hinder sulfimidation. Better sources of electrophilic chlorine need to be used in these cases, such as sulfuryl chloride (SO_2Cl_2), chlorine gas and *t*-butyl hypochlorite (*t*-BuOCl). Other *N*-chloro compounds such as *N*-chlorocarboxamides, *N*-chlorourethane and *N*-chlorourea give access to sulfimides with *N*-substituents other than tosyl.

1.4.2.1.2 Sulfimidation using nitrenes.

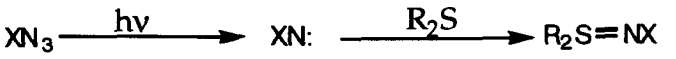
Sulfimidation by both photochemical and thermal nitrene generation is possible, although both methods are problematic. Sulfimides can decompose under photochemical conditions to generate nitrenes themselves and the temperatures needed to generate nitrenes are in the decomposition range of some sulfimides. Both methods can be used successfully though, as demonstrated by Horak, who synthesised eight sulfimides via thermal nitrene generation, with yields comparable to or better than with the traditional Chloramine-T method (**Scheme 1.32**).[36]



Scheme 1.32

The presence of copper powder as catalyst ensured that thermolysis of tosyl azide occurred at lower than normal temperatures. The most widely used

photochemical method is the photolysis of various azides in excess sulfide (**Scheme 1.33**).[37]

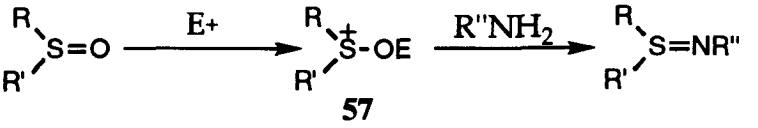


X = $ArSO_2$, PhCO, EtOCO

Scheme 1.33

1.4.2.1.3 Condensation of a sulfoxide with an amine

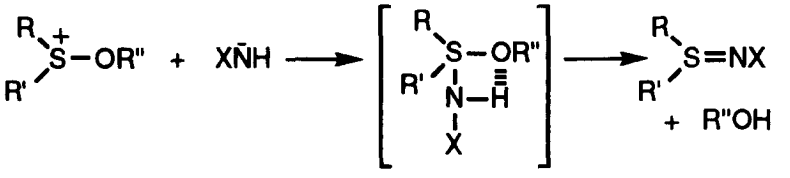
Electrophilic attack on the oxygen atom of a sulfoxide will give a sulfonium salt **57** which can be attacked by an amine (**Scheme 1.34**).



57

Scheme 1.34

This approach was first used by Tarbell and Weaver in 1941 who condensed alkyl and aryl sulfoxides with sulfonamides using phosphorous pentoxide as the electrophile.[38] Other examples of electrophiles include acetic anhydride, boron trifluoride and sulfur trioxide. The nitrogen source can be an amine or an amide. Koval has proposed a four-membered cyclic intermediate **58** stabilised by intramolecular hydrogen bonding to explain the stereospecific nature of the reaction (**Scheme 1.35**).[5c]

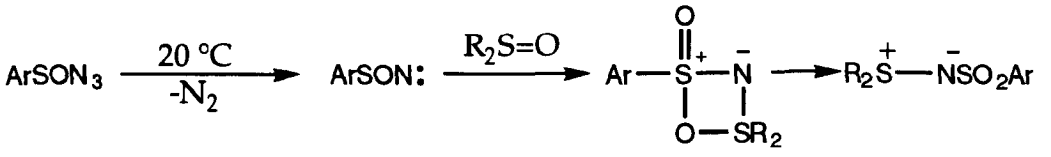


58

Scheme 1.35

1.4.2.1.4 Reaction of sulfoxides with arylsulfinyl azides

In the presence of arylsulfinyl azides **59**, sulfoxides were found to form sulfimides. A four-membered intermediate **60** is thought to be involved (**Scheme 1.36**).[39]

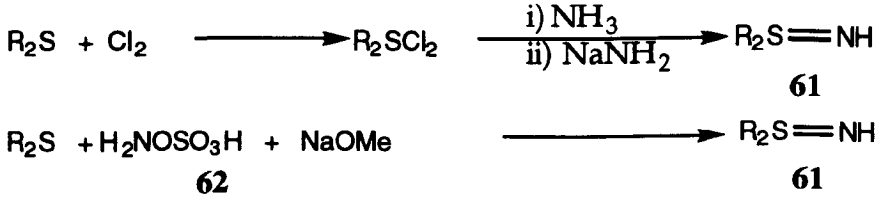


59 **60**

Scheme 1.36

1.4.2.1.5 Sulfimides *via* "free" sulfimides

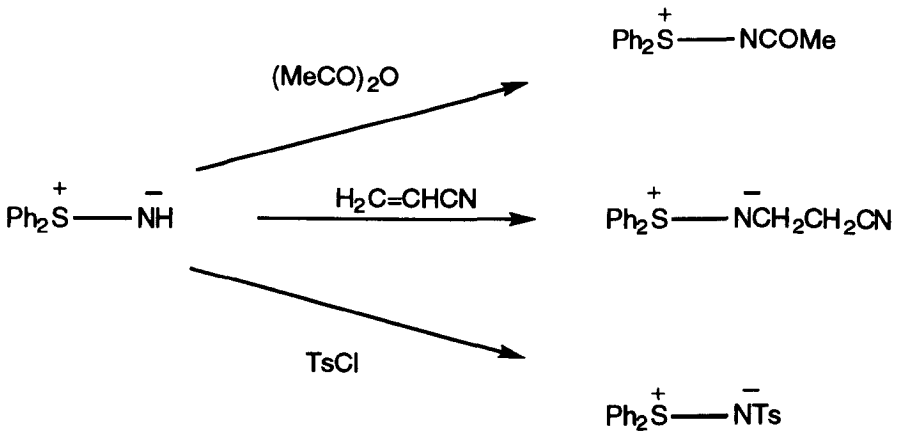
"Free" sulfimides **61** are sulfimides which are unsubstituted at nitrogen. Though generally not as stable as other sulfimides, they are available through oxidation of a sulfide by chlorine to the dichloride, followed by amination with ammonia. A better method of preparation uses hydroxyamine-*O*-sulfinic acid **62** and base (**Scheme 1.37**).[40]



62 **61**

Scheme 1.37

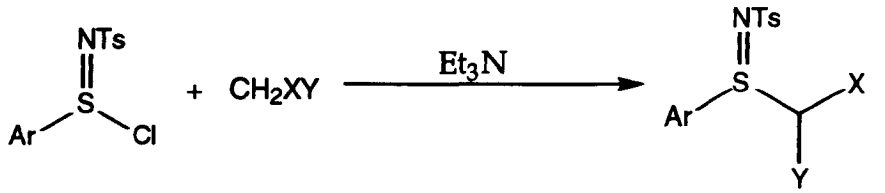
Electrophilic substitution at the nitrogen of free sulfimides leads to substituted sulfimides (**Scheme 1.38**).[35]



Scheme 1.38

1.4.2.1.6 Nucleophilic substitution at sulfur

Sulfimide synthesis by the nucleophilic attack on sulfur with subsequent displacement of a halogen atom is of limited use, as this method requires a sulfimide to make a sulfimide. However, it remains a useful way through to α,α-disubstituted methyl sulfimides **63** (**Scheme 1.39**).[41]



X = CN, MeCO
Y = CN, MeCO

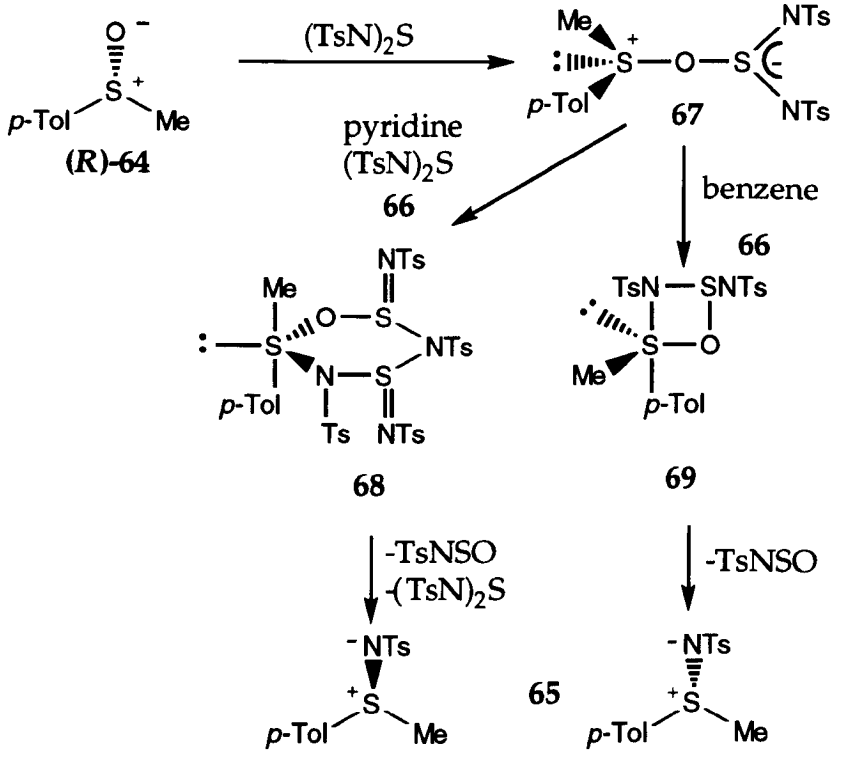
63

Scheme 1.39

1.4.2.2 Asymmetric synthesis of sulfimides

1.4.2.2.1 From sulfoxides

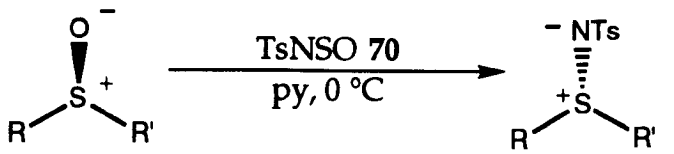
In a mechanistic study, Cram showed that enantiomerically enriched sulfoxide **64** could be converted to enantiomerically enriched sulfimides **65** using *N,N*-bis(tosyl) sulfurdiimide **66** via intermediate sulfonium salt **67** (**Scheme 1.40**).[42]



Scheme 1.40

With **67**, inversion of stereochemistry at sulfur was observed in the presence of pyridine, which stabilises the intermediate so that a second equivalent of diimide can attack giving the six-membered intermediate **68**. However, in benzene the intermediate **67** collapses to a four-membered intermediate **69**, leading to retention of configuration at sulfur in sulfimide **65**.

Cram also used *N*-sulfinyl tosylsulfonamide **70** to generate optically active sulfimides from sulfoxides with inversion of configuration at the sulfur (**Scheme 1.41**). These reactions remain the only effective asymmetric syntheses of sulfimides, although both methods involve the use of *N*-sulfinyl species that are difficult to synthesise and handle, being prone to both hydrolysis and thermal decomposition.[43]

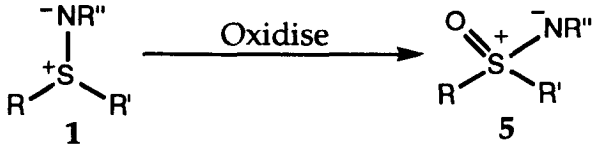


Scheme 1.41

1.4.3 Reactions of sulfimides

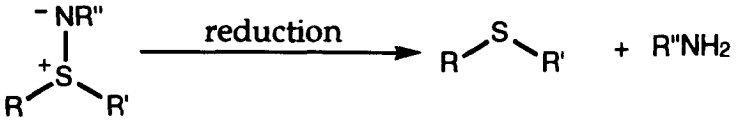
1.4.3.1 Oxidation and reduction

Sulfimides **1** are quite stable towards oxidation, with access to sulfoximides **5** only being possible with strong oxidising agents, such as potassium permanganate and alkaline hydrogen peroxide (**Scheme 1.42**).[5c,35]



Scheme 1.42

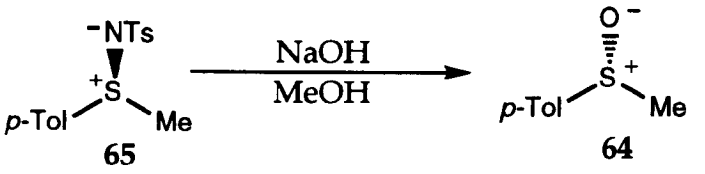
Reduction of sulfimides proceeds readily and provides a convenient method of removing the sulfimidyl group. Reductants such as phosphorous pentasulfide, cysteine and $LiAlH_4$ have been used (**Scheme 1.43**). More recently, boranes have been found to be effective reductants.



Scheme 1.43

1.4.3.2 Hydrolysis

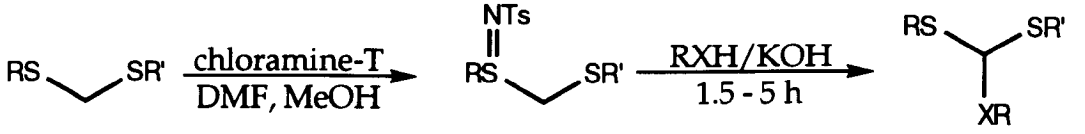
Mineral acids can hydrolyse sulfimides to sulfoxides as mentioned earlier. Cram's group hydrolysed homochiral sulfimide **65** with methanolic sodium hydroxide to give the corresponding sulfoxide **64** with inversion at the sulfur (**Scheme 1.44**), with no loss of optical purity.[44]



65 64

Scheme 1.44

Yoshida reported the hydrolysis of sulfimides **71** under alcoholic and thiolic conditions to yield di- and tri-thioorthoformates **72** (**Scheme 1.45**).[45]



71 **72**
X=O,S

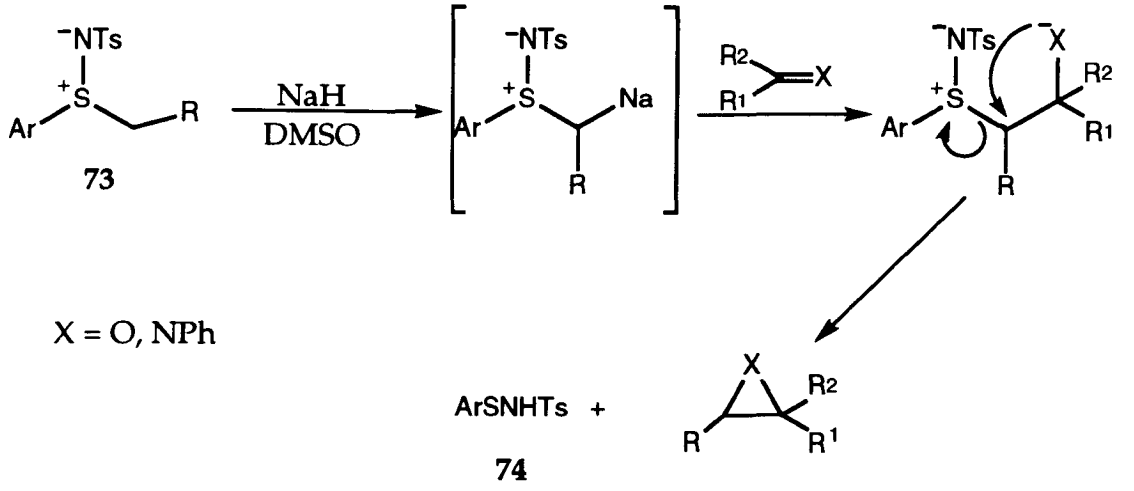
Scheme 1.45

Sulfimides **71** were isolated in good yield and either alcoholysis or thiolysis smoothly generated orthoformates **72**. Gross and Walther further developed this work to synthesise a wider range of orthoformates.[46]

1.4.3.3 Alkylidene transfer agents

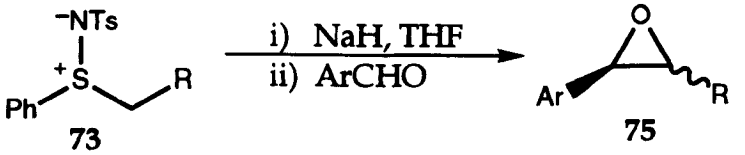
1.4.3.3.1 Intermolecular

In 1976, the group of Tamura extended known alkylidene transfer methodology for sulfur ylids to sulfimides. They demonstrated that oxiranes and aziridines resulted from addition of metalated alkyl sulfimides to carbonyl compounds and imines respectively (**Scheme 1.46**).[47]



Scheme 1.46

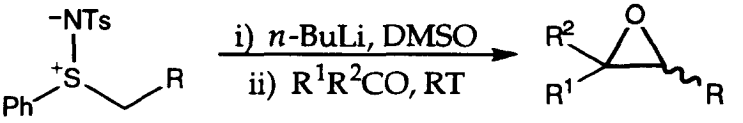
Metalation of **73** followed by condensation with an aldehyde, ketone or imine proceeded *via* intramolecular displacement of *N*-tosyl aryl/alkyl sulfenamide **74** to give an epoxide or aziridine. With benzaldehyde (R^1= Ph, R^2= H, X=O) and *S*-ethyl-*S*-phenyl-*N*-tosylsulfimide (**73** Ar=Ph, R=Me) a mixture of *cis* and *trans* epoxide (3:5) was isolated in reasonable yield (65%). The one example given for aziridination was found to proceed in reasonable yield (Ar=Ph, R=H, X= NPh, R^1= Ph, R^2=H). They developed this method into a high yielding stereoselective synthesis of *trans*-1,2-disubstituted oxiranes **75** (**Scheme 1.47**). By using sodium hydride in THF instead of dimsyl anion in DMSO, increased yields were observed (Ar= Ph, R= Me, 60%, 91:9 *trans:cis*), comparing favourably with the initial results mentioned above.



Scheme 1.47

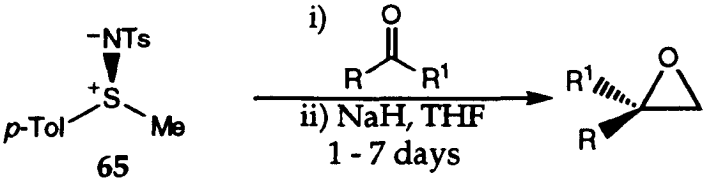
At about the same time, Johnson independently developed a similar epoxidation procedure (**Scheme 1.48**).[48] He found that a lithium counterion gave higher yields than observed with sodium. This procedure was an

improvement on Tamura's work (R= Ph, R^1= Ph, R^2=Me; 100% yield, Tamura 71%).



Scheme 1.48

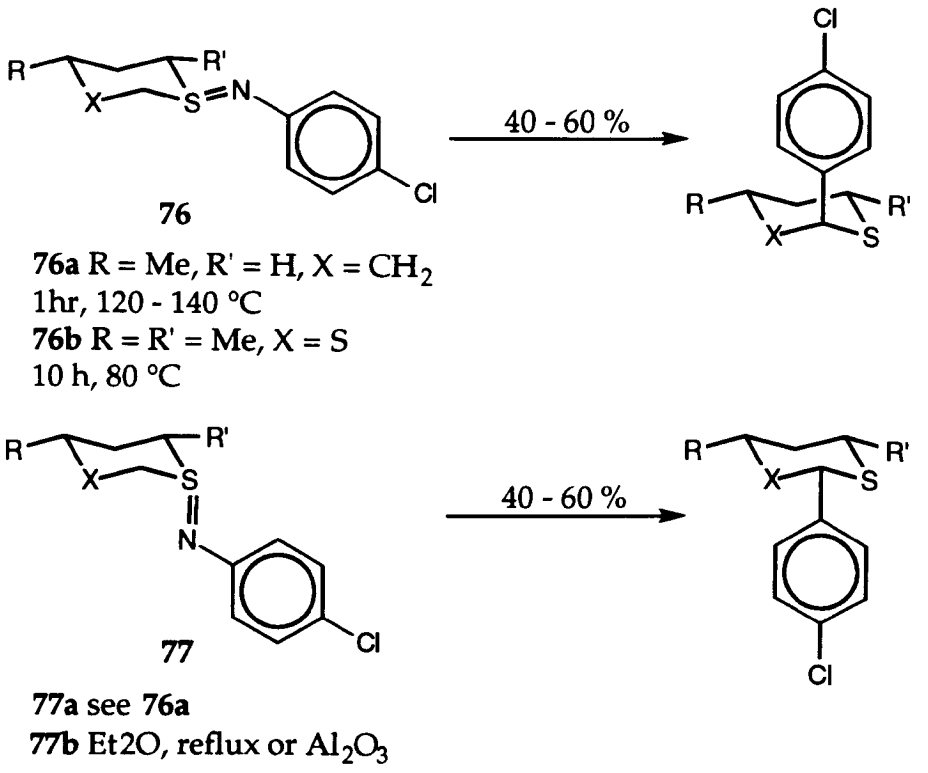
This procedure has been further refined, so that optically active epoxides can be prepared. The asymmetric transfer of a methylidene group from sulfimide analogues to carbonyl compounds had not been reported until our group used chiral non-racemic sulfimide **65** as a chiral transfer agent. On optimisation of the reaction conditions it was found that inverse addition of carbonyl compound before sodium hydride gave better, more consistent yields (**Scheme 1.49**). The best result was reported for benzaldehyde (R=Ph, R^1=H, 70% ee) although some promising enantioselectivities were noted for ketone electrophiles (eg. R=Ph, R^1=Me, 45 % ee).[49]



Scheme 1.49

1.4.3.3.2 Intra-molecular alkylidene transfer

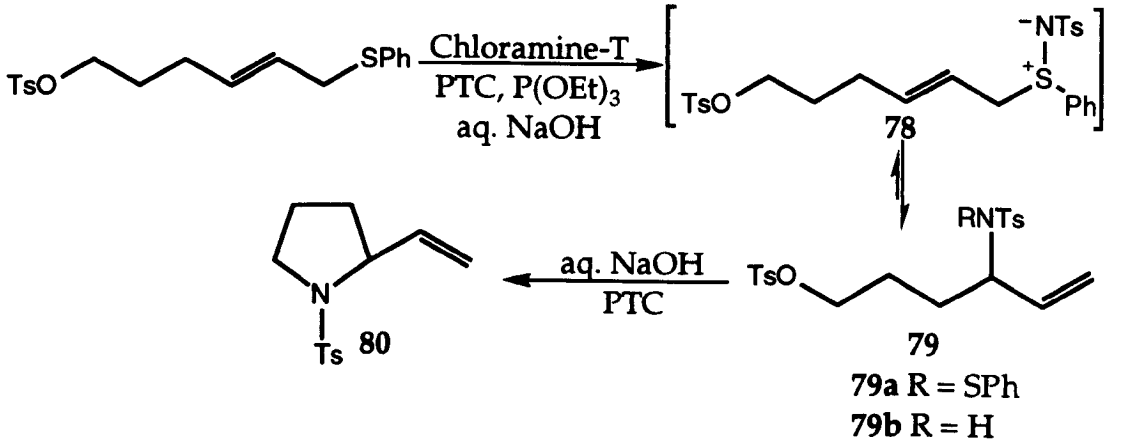
Certain sulfimides can undergo a Sommelet-type 2,3-sigmatropic rearrangement involving intramolecular alkylidene transfer. Claus reported the stereospecific 2,3-sigmatropic rearrangement of cyclic *N*-aryl sulfimides **76** and **77** (**Scheme 1.50**).[50] Sulfimides **76a**, **76b** and **77a** required harsh conditions to induce rearrangement whereas **77b** rearranged rapidly under mild conditions.



Scheme 1.50

1.4.3.4 Rearrangements of sulfimides

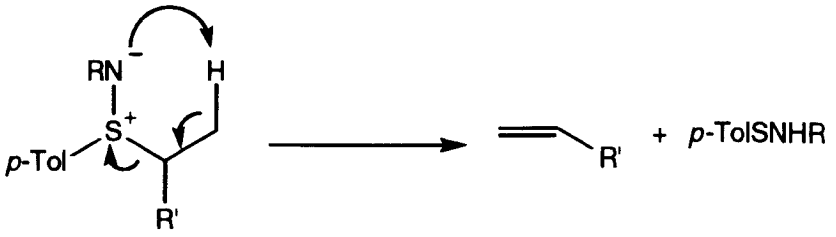
Allyl sulfimides **78** can undergo a 2,3-sigmatropic rearrangement to form sulfenamides **79**. Dolle developed a synthesis of 2-vinyl substituted cyclic amines **80** involving this type of rearrangement as the key step (**Scheme 1.51**).[51]



Scheme 1.51

Sulfimide synthesis using standard conditions results in an equilibrium in which sulfenamide **79a** predominates. Triethylphosphite accelerates conversion of **79a** to **79b**. The intramolecular cyclisation was performed with basic phase transfer catalysis.

S-Alkyl sulfimides that possess a β-H atom, (such as **81**), are prone to a rearrangement that can occur on heating (**Scheme 1.52**).[52]

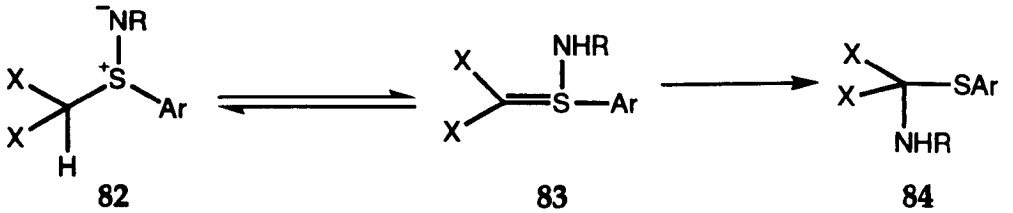


81

R = Ar, MeCO
R' = H, Me

Scheme 1.52

Sulfimides possessing an activated α-H atom, such as **82**, can undergo imido-ylid tautomerism (*ie.* 1,3-sigmatropic shift), depending on the nature of the substituents X (**Scheme 1.53**).[5c] With strongly electron withdrawing groups (X= PhCO or CN, etc.) the α-H acidity is sufficient for the equilibrium to be shifted almost entirely to the amino-sulfonium ylid **83**. A further rearrangement can occur in which migration of the arylsulfenamide group to the carbon atom results in the formation of α-aminosulfides **84**, in an overall Pummerer-type rearrangement

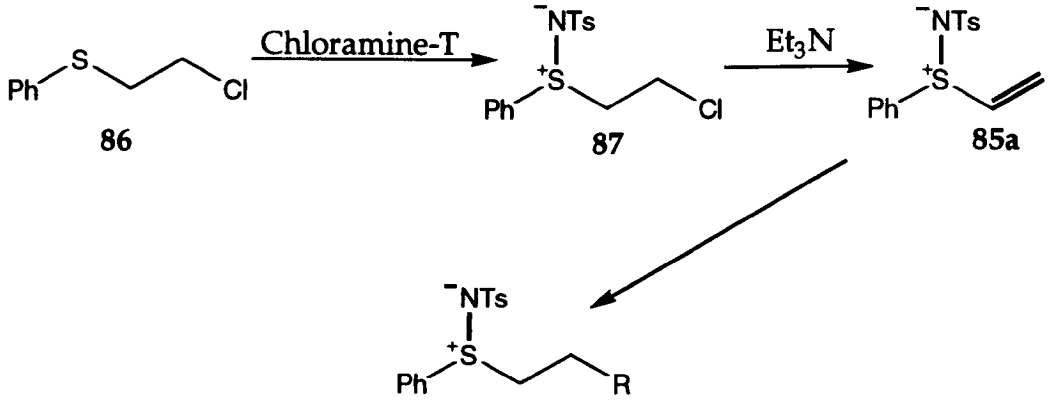


82 **83** **84**

Scheme 1.53

1.4.4 Vinyl sulfimides

Stirling first prepared vinyl sulfimides in 1974 and demonstrated their synthetic utility as Michael acceptors. Vinyl sulfimide **85a** was generated from 2-chloroethyl sulfide **86** and Chloramine-T followed by base-induced elimination from intermediate **87** (**Scheme 1.54**). Conjugate addition of ethoxide or piperidine gave adducts **88a** and **88b** respectively in quantitative yields.[53]



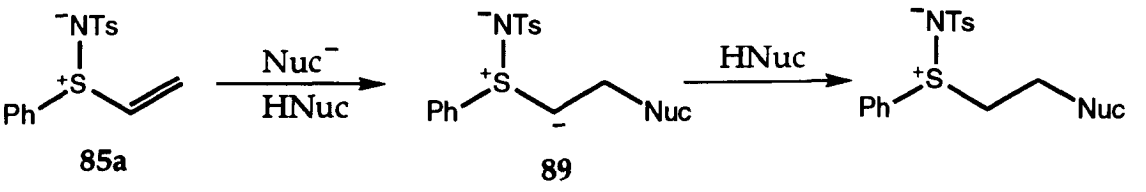
86 **87** **85a**

88a R=OEt
88b R=piperidyl
88c R=PhS
88d R=NPh_2
88e R=$PhCH_2$
88f R=$CH(CN)_2$

Scheme 1.54

Yamamoto and Okowara independently synthesised *S*-phenyl-*S*-vinyl-*N*-tosyl sulfimide **85a** using similar chemistry to Stirling and studied a wide variety of Michael-type additions to this acceptor.[54] Thiols, amines, alcohols and malononitrile added to yield adducts **88c**, **88d**, **88e** and **88f**, respectively. The amount of sodium hydride needed depended on the basicity of the nucleophile. Proposing the mechanism shown below (**Scheme 1.55**), they postulated that acidic nucleophiles such as benzyl alcohol and malononitrile were deprotonated by intermediate **89** and therefore only a catalytic amount of sodium hydride was needed. However, nucleophiles such as

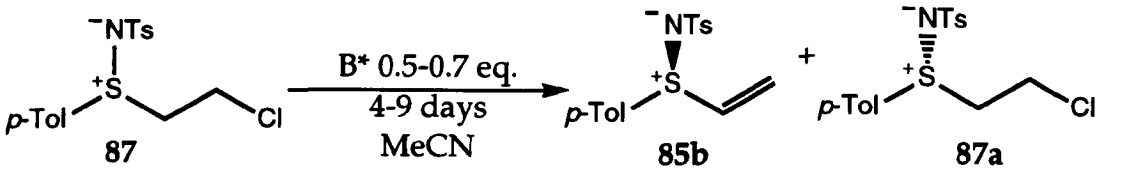
diphenylamine needed equimolar amounts of sodium hydride to propagate the reaction. The addition of organolithium and Grignard nucleophiles to **85a** was also studied.



85a **89**

Scheme 1.55

Optically active vinyl sulfimides **85b** and **87a** were prepared using a chiral base-induced elimination (**Scheme 1.56**).[55]

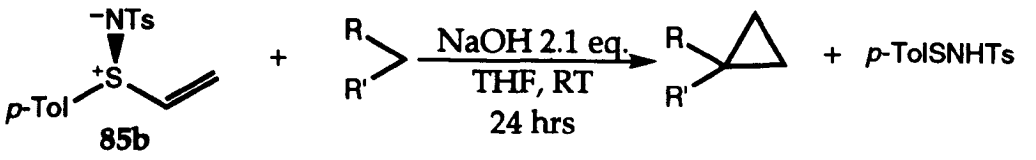


87 **85b** **87a**

Scheme 1.56

Reasonable enantioselectivities were observed with (-)-quinine as base (**85b**, 31% ee; **87a** 32% ee), but the best results were found using (+)-quinidine (**85b**, 29% ee; **87a**, 73% ee using 0.7eq and 50% and 48% using 0.5 eq.). The absolute configuration of **85b** was dependent on the chirality of the amine used; (+)-**85b** and (-)-**85b** from (+)-quinidine and (-)-quinine (the 'quasi-enantiomer' of (+)-quinidine), respectively. Both enantiomers of **85b** are available as **87a** was converted to **85b** using an achiral, base-induced elimination.

Cyclopropanation using vinyl sulfimides **85b** has been studied by Yamamoto (**Scheme 1.57**). Good yields were obtained with R=R'= MeCO (83%), R=R'= PhCO (95%) and diethylmalonate R=R'=EtO_2C (76%) as active methylene nucleophiles.[56]



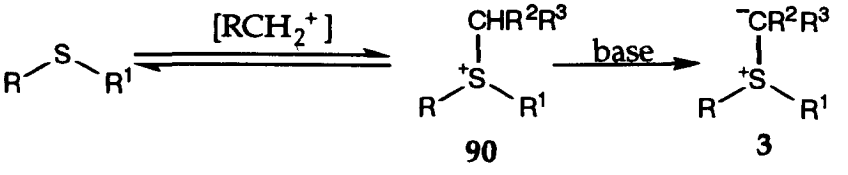
85b

Scheme 1.57

1.5 Sulfonium Ylids

1.5.1 Introduction and preparation

Sulfonium ylids are represented by the general structure **3** and are synthesised from sulfonium salts **90** which are in turn prepared by alkylation of a sulfide (**Scheme 1.58**).[57] Sulfonium ylids are generally less stable than the analogous oxosulfonium ylids. Sulfur ylids, in particular sulfonium ylids, have long been known to undergo alkylidene transfer reactions to carbonyl compounds. The reactivity of these ylids varies, with the more stable oxosulfonium ylid reacting reversibly with carbonyl compounds and the less stable sulfonium ylids undergoing kinetic additions.

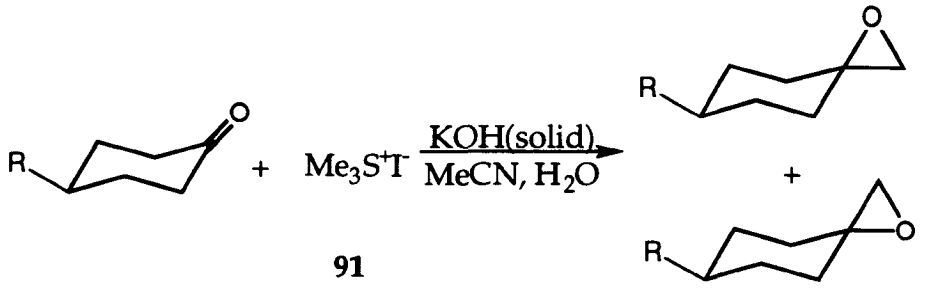


Scheme 1.58

1.5.2 Reactions of sulfonium ylids

1.5.2.1 Formation of epoxides

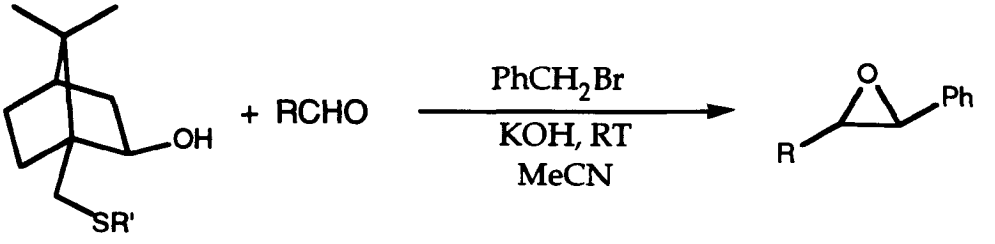
Sulfonium ylids have been widely used as chiral reagents. Corey and Johnson were the first to use sulfur ylids as alkylidene transfer reagents in the early 1960s, to generate epoxides from aldehydes and ketones.[58] Racemic epoxidations have now become highly effective reactions, overcoming early problems of ylid stability and solubility. The *in situ* generation of the ylid of sulfonium salt **91** in the presence of substrate is a useful methylidene transfer method (**Scheme 1.59**).[59]



91

Scheme 1.59

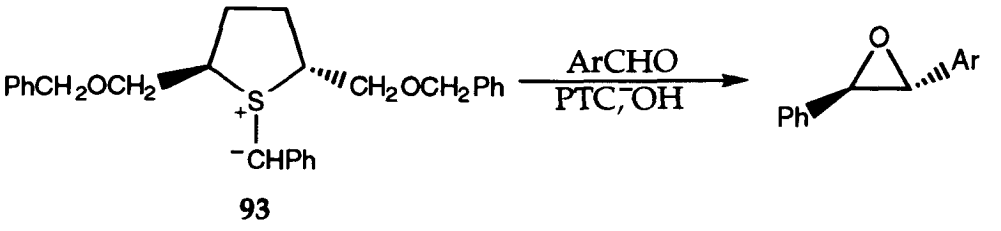
Trost and Hammen were the first to attempt asymmetric alkylidene transfer reactions, but they failed to observe any enantioinduction.[60] Asymmetric variants have now begun to emerge with varying degrees of enantiopurities being observed. Furukawa made the first significant steps towards optically active epoxides *via* alkylidene transfer. Using the optically active sulfide **92** derived from (+)-camphorsulfonic acid, epoxides were formed in good yields and with reasonable enantioselectivities (**Scheme 1.60**).[61] Good results were found with benzaldehyde (R=Ph, 47% ee) and 4-chlorobenzaldehyde (R=4-ClC_6H_4, 43% ee). These optical yields are good when consideration is given to the distance between the chiral centre and the reaction centre.



92

Scheme 1.60

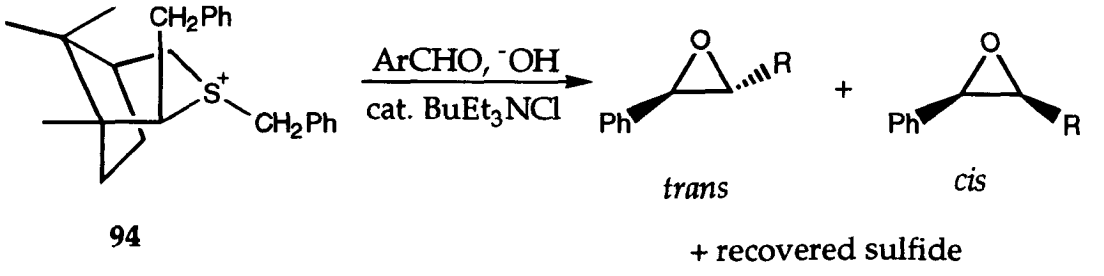
Durst used C-2 symmetric thiolanes and thianes as chiral sources, the former giving good enantioinduction for 4-nitrobenzaldehyde as the carbonyl source using ylid **93** (eg. Ar= 4-$O_2NC_6H_4$, 83% ee) (**Scheme 1.61**).[62]



93

Scheme 1.61

Better enantioselectivities were observed using chiral bicyclic sulfonium salt **94** (**Scheme 1.62**). With benzaldehyde (R=Ph, *trans*(>96% ee) : *cis*(*meso*); 5:1) and cyclohexanone (R'=C_6H_{11} *trans*(84% ee) : *cis*(86% ee); 2:3) mixtures of *cis* and *trans* epoxides were found, whereas with 4-methylbenzaldehyde (R=*p*-tol *trans*(>96% ee)), no *cis* isomer could be observed.[63]



94

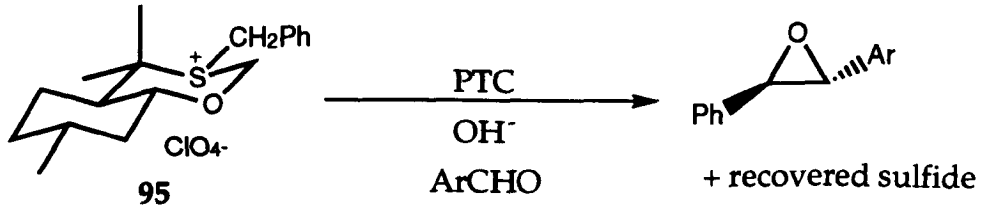
trans

cis

+ recovered sulfide

Scheme 1.62

Solladie-Cavallo developed a similar route to highly enriched *trans* epoxides. In particular, with 4-chlorobenzaldehyde (Ar= 4-ClC_6H_4, 62-100% ee, depending on the reference $[\alpha]_D$ used as standard) and sulfonium salt **95** derived from(+)-*R*-pulegone (**Scheme 1.63**).[64]

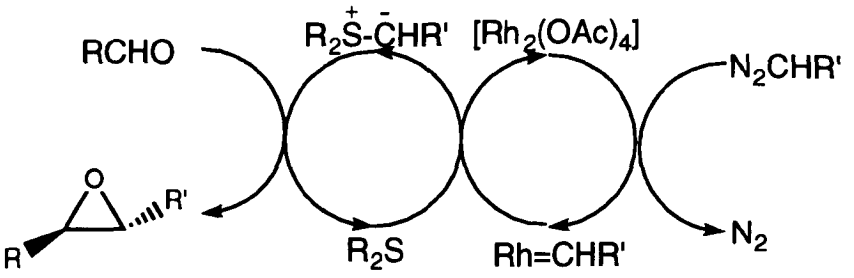


95

+ recovered sulfide

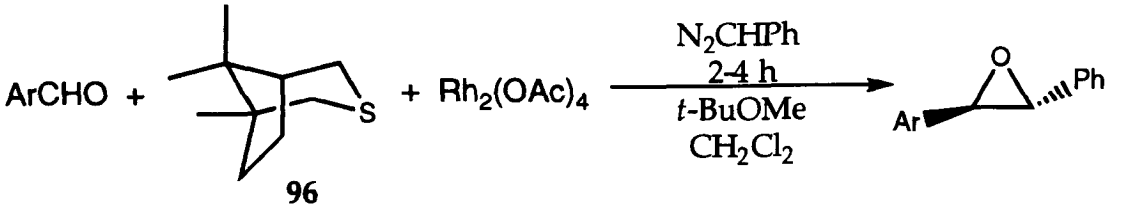
Scheme 1.63

In all three methods mentioned above, the chiral sources are sulfides, which can be recovered in reasonable amounts, making this methodology economic. Aggarwal has developed the first catalytic cycle for asymmetric epoxide synthesis using carbenoids (**Scheme 1.64**).[65]



Scheme 1.64

The optimisation of the reaction conditions was done using achiral sulfides. This included minimising side reactions and making the reaction catalytic in sulfide and rhodium. With chiral sulfide **96**, good yields, but only low enantioselectivities, have been found to date, but other homochiral sulfides are being investigated (**Scheme 1.65**).

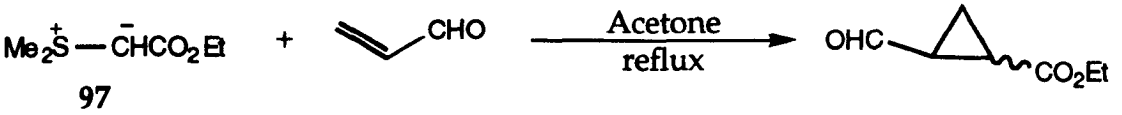


96

Scheme 1.65

1.5.2.2. Formation of cyclopropanes and aziridines

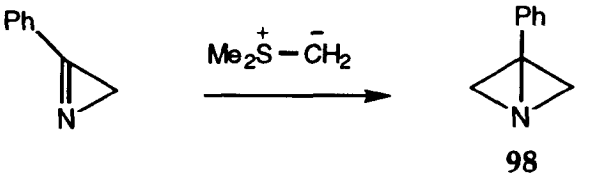
Both cyclopropanes and aziridines are amenable to synthesis from sulfonium ylid alkylidene transfer agents. Stabilised sulfonium ylids, such as **97**, are usually needed to generate cyclopropanes from α,β-unsaturated carbonyl compounds. Otherwise competition from 1,2-addition results in vinyl epoxides as the favoured products (**Scheme 1.66**).[57]



97

Scheme 1.66

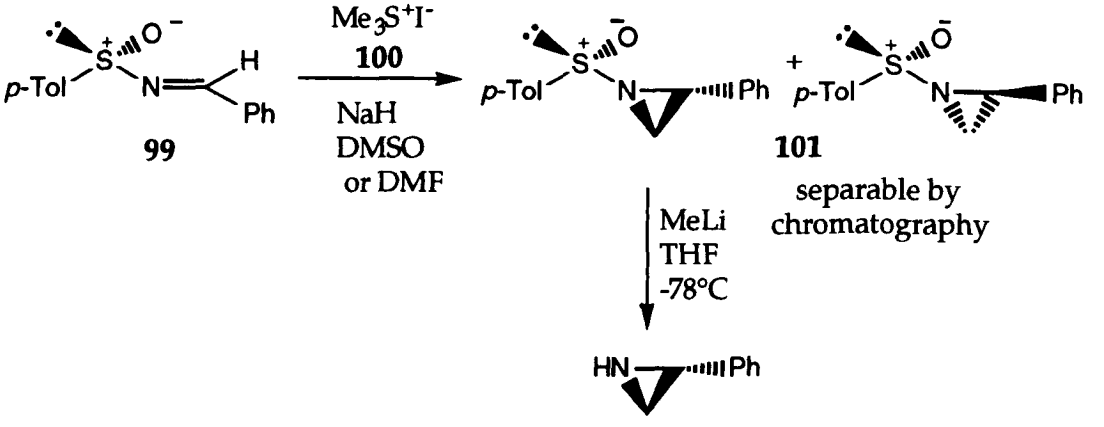
Aziridination *via* sulfonium ylid chemistry is also possible. An interesting example involves formation of bicycloaziridine **98** (**Scheme 1.67**).[66]



98

Scheme 1.67

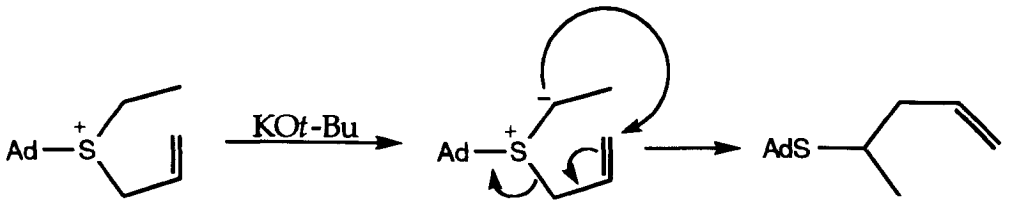
Asymmetric aziridination has been approached using chiral sulfinimine **99** with sulfonium ylid **100** (**Scheme 1.68**). Modest diastereoselectivities were observed in two cases (DMSO, 36:64; DMF 33:67). The diastereomeric *N*-sulfinylaziridines **101** are separable, allowing access to either enantiomer of the aziridines.[67]



Scheme 1.68

1.5.2.3 Ylid rearrangements

Allyl sulfonium ylid **102** can undergo 2,3-sigmatropic rearrangements, usually proceeding with allylic inversion. Chirality transfer from sulfur to carbon has been used to form a C-C bond asymmetrically (**Scheme 1.69**).[68]

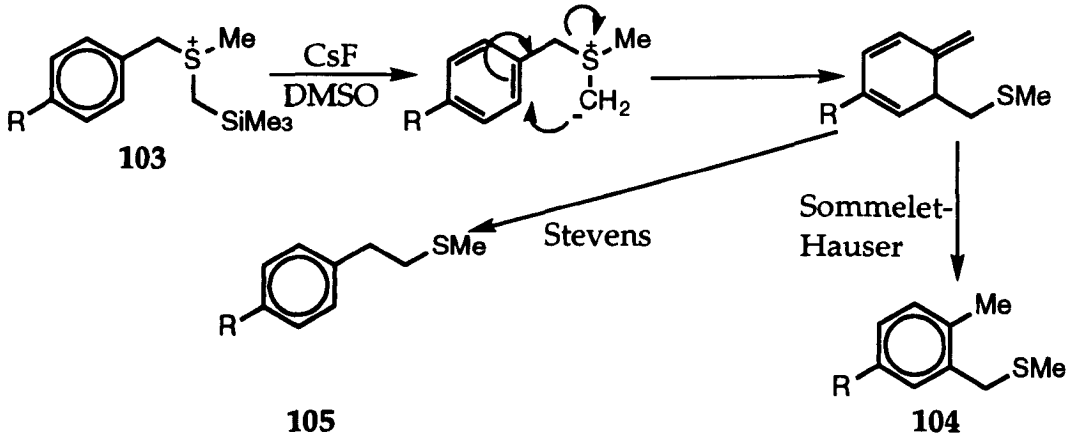


102
chiral-at-sulfur
Ad = 1-Adamantyl

chiral-at-carbon
94% optical
activity retained

Scheme 1.69

S-Methyl benzyl sulfonium ylids **103** can potentially undergo both Stevens and Sommelet-Hauser rearrangements (**Scheme 1.70**). Good yields of Sommelet-Hauser derived products **104** were observed (R=H, 83%, R=Me, 81%), but no Stevens products **105** were detected using these conditions.[69]

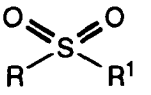


Scheme 1.70

1.6 Sulfones

1.6.1 Introduction

Sulfones have the general formula **4**, in which the carbon substituents can be alkyl, vinyl, alkynyl or aryl (**Figure 1.8**). Sulfones are usually chemically and thermally stable, being resistant to oxidation and reduction in particular. Their preparation and reactions have been reviewed.[70]



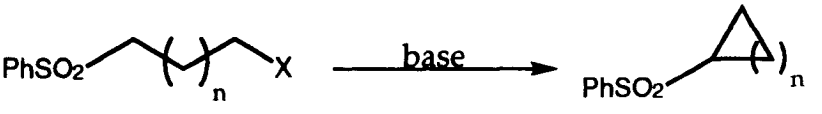
4

Figure 1.8 General structure of a sulfone

As sulfones are not chiral-at-sulfur, only those parts of their extensive chemistry which are most closely related to our work will be discussed.

1.6.2 Alkylations of α-sulfonyl carbanions

A convenient preparation of cycloalkanes is possible *via* internal alkylation of sulfone **106** (**Scheme 1.71**). In addition, carbonyl compounds such as aldehydes, ketones and esters have been shown to be effective electrophiles for metalated sulfones.[71]

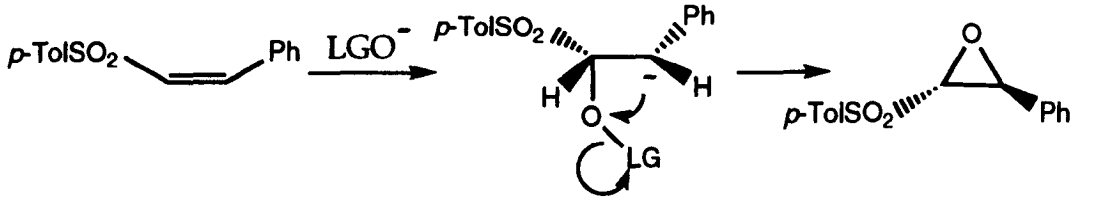


106

Scheme 1.71

1.6.3 Reactions of vinylic sulfones as Michael acceptors

Vinylic sulfone **107** is an excellent Michael acceptor, reacting with amines, alcohols, thiols and organometallics as nucleophiles.[72] Epoxidation of the double bond is also possible, to generate intermediate **108**, using hypochlorite (LG=Cl) or peroxide (LG=OH) (**Scheme 1.71**).[73]

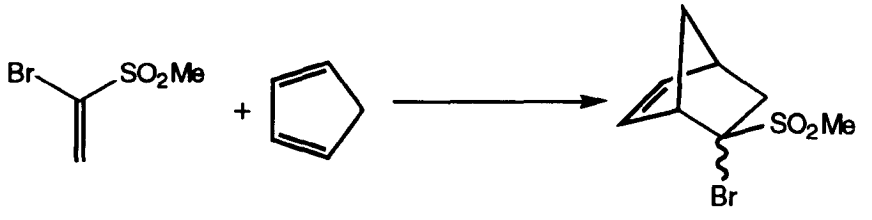


107 **108**

Scheme 1.72

1.6.4 Vinyl sulfones as Diels-Alder dienophilic substrates

Vinylic sulfones are electron deficient alkenes and can undergo Diels-Alder reactions with a variety of dienes. Bicyclic sulfone **109** was formed from cyclopentadiene and α-bromovinyl methyl sulfone **110** (**Scheme 1.73**).[74]



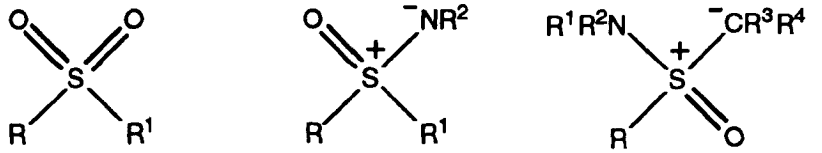
110 **109**

Scheme 1.73

1.7 Sulfoximides and their ylids

1.7.1 Introduction

Sulfoximides **5** and oxosulfonium ylids **6** are the nitrogen analogues of sulfones **4**, and the corresponding sulfone ylids, respectively (**Figure 1.9**).



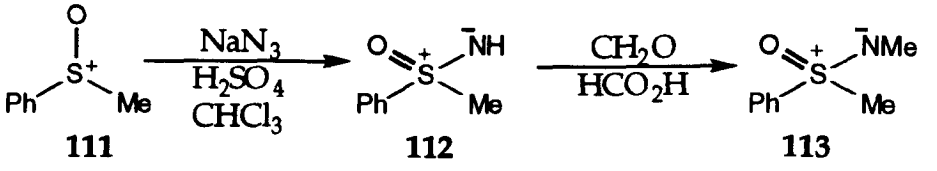
4 **5** **6**

Figure 1.9 General structure of sulfoximides and analogues

Both **5** and **6** are chiral given different substituents on the sulfur. As with sulfimides, the nature of the bonding involved is unclear. The multiplicity of the S-O, S-N and S-C (in **6**) bonds depends on the electronic characteristics of the substituents on the sulfur and nitrogen atoms. Both the ylid **5** and the parent **6** are configurationally stable $S^{(VI)}$compounds.

1.7.2 Racemic preparation of sulfoximides

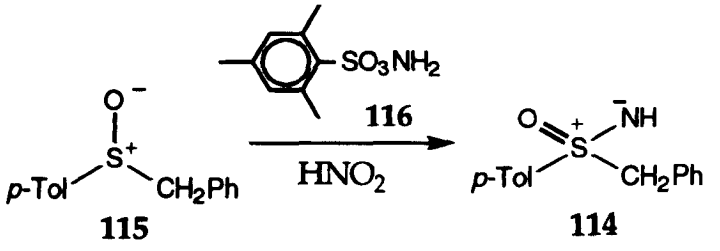
The most popular route to sulfoximides was that developed by Bentley and Whitehead in 1951 (**Scheme 1.74**).[75] Oxidation of sulfoxide **111** with acidified sodium azide gave "free sulfoximide" **112** which was alkylated using formaldehyde to yield sulfoximide **113**.



111 **112** **113**

Scheme 1.74

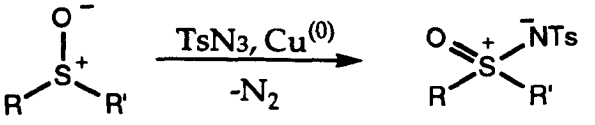
Tamura developed another route to 'free sulfoximide' **114** from sulfoxide **115** using the rather unstable aminating agent mesitylsulfonyloxyamine **116** (**Scheme 1.75**).[76]



115 **114**

Scheme 1.75

Copper-catalysed decomposition of tosyl azide leads to a nitrene, which can be trapped by sulfoxides to yield *N*-tosyl sulfoximides (**Scheme 1.76**).[77]

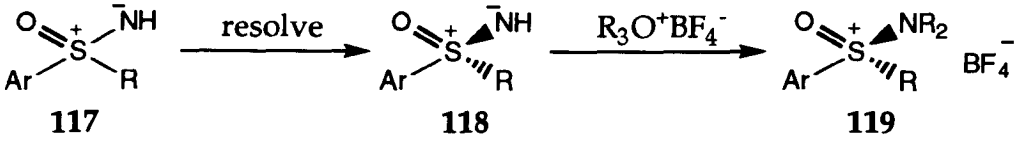


Scheme 1.76

1.7.3 Asymmetric synthesis of sulfoximides

The group of Johnson was able to prepare optically pure "free sulfoximides" after one recrystallisation of the diastereomeric salts from **117** and (+)-10-

camphorsulfonic acid. Alkylation of the "free-sulfoximide" **118** gave optically pure **119** (**Scheme 1.77**).[78]



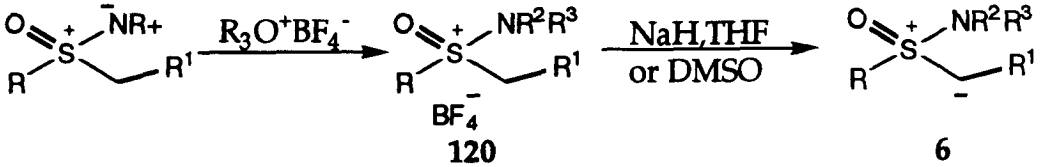
117 **118** **119**

Scheme 1.77

The method of Bentley and Whitehead (**Scheme 1.74**) when applied to optically active sulfoxides results in racemic sulfoximides. Tamura's copper catalysed azide decomposition procedure (**Scheme 1.76**) gives access to optically active sulfoximides from sulfoxides.

1.7.4 Preparation of ylids of sulfoximides

Ylids **6** of sulfoximides can be prepared from sulfoximides by alkylation of **120** followed by deprotonation (**Scheme 1.78**). These ylids are also configurationally stable at sulfur.[78]

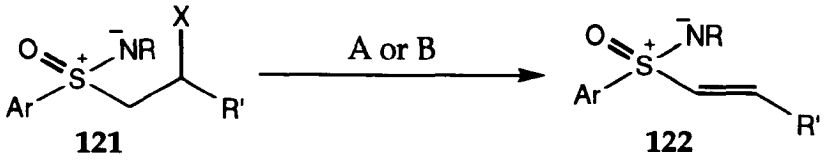


120 **6**

Scheme 1.78

1.7.5 Preparation of vinylic sulfoximides

Base-induced eliminations from β-functionalised *S*-alkyl sulfoximides **121** were used by the groups of Glass and Pyne to generate vinyl sulfoximides **122** (**Scheme 1.79**).[79]



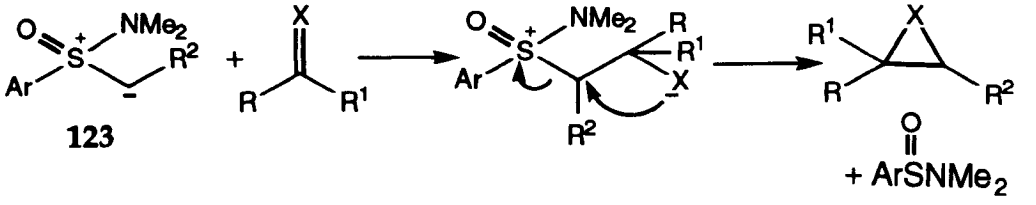
A = NEt_3
B = $MeSO_2Cl/NEt_3/DBU$

Scheme 1.79

Glass used dehydrohalogenation to prepare vinylic sulfoximides **122** (Ar=*p*-tol, R=Ts, X=Cl, R'=H, method A) in good yield.[79] Pyne made substituted vinylic sulfoximides **122** by elimination of methanesulfonic acid (Ar=Ph, R= chiral alkylether, X=OH, R'=Ph, Me, *n*-Bu, $PhCH_2CH_2$, method B).[80] A Peterson-type synthesis of vinylic sulfoximides has also been reported.[81]

1.7.6 Reactions of sulfoximides and corresponding ylids

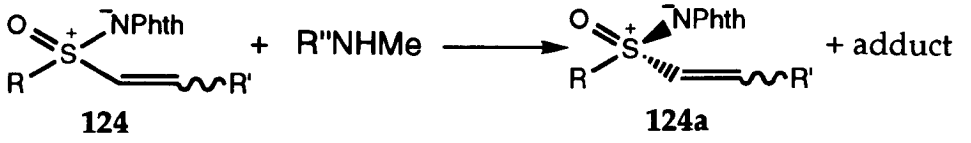
Sulfoximides have been used as both chiral auxiliaries and reagents. Sulfoximide ylid **123** has been shown to be effective chiral reagent for asymmetric alkylidene transfer. Optically active epoxides and cyclopropanes were made from carbonyl compounds and α,β-unsaturated ketones or esters and ylid **123**, respectively (**Scheme 1.80**). *N*-Substituted imines afford aziridines (**Scheme 1.80**). Reasonable optical purities were observed for cyclopropanations with *trans*-benzalacetophenone (*trans*-PhCH=CHCOPh, 35% ee) and methylacrylate (*trans*-$MeCH=CHCO_2H$, 43% ee) as substrates. Epoxidations were not as effective (R=Ph, R^1=H, R^2=Ph, X=O, 20% ee).[78]



Scheme 1.80

1.7.7 Reactions of vinylic derivatives

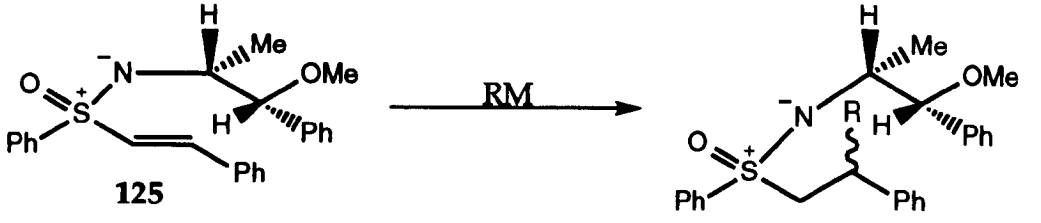
Kinetic resolutions of vinylic sulfoximides **124** by Michael additions of chiral amines gave optically active sulfoximides **124a** (**Scheme 1.81**).[82]



124 **124a**

Scheme 1.81

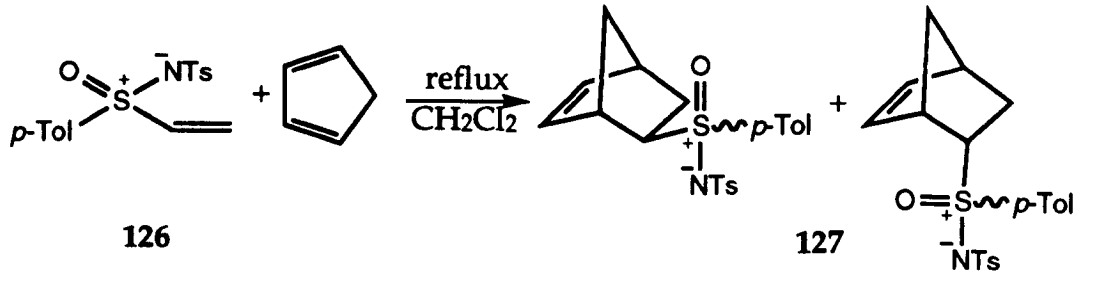
Using a deficiency of (-)-(*1R,2S*)-ephedrine (R"= PhCH(OH)CH(Me)) resulted in recovered vinylic sulfoximide **124a** displaying some optical enrichment (46% ee, R= *p*-tol, R'= H). Pyne used vinylic sulfoximide **125** as a chiral auxiliary in asymmetric conjugate additions of organometallics, which proceeded with good diastereoselectivities (R=Me, M=Li, 93% de; R=*n*-Bu, M=Li, 90% de). Organocopper reagents (M=Cu) also gave good diastereoselectivities (**Scheme 1.82**).[80]



125

Scheme 1.82

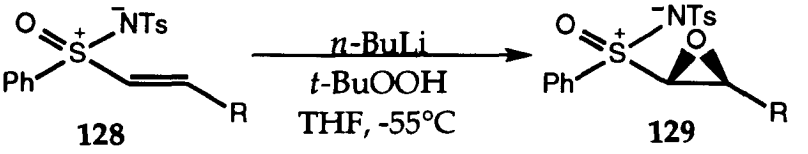
Diels-Alder reactions using vinylic sulfoximide **126** proceed with limited diastereoselectivities, but reasonable *endo/exo* selectivity (**Scheme 1.83**). This particular example gave one diastereoisomer **127** of the major product with overall 9:2 *endo:exo* selectivity.[79]



126 **127**

Scheme 1.83

Nucleophilic epoxidations of sulfoximides **128** were found to proceed with high diastereoselectivity using *t*-butylperoxide (**Scheme 1.84**). High stereoselectivities were observed in the epoxide products **129** (R= Me, *i*-Pr).[83]



128 **129**

Scheme 1.84

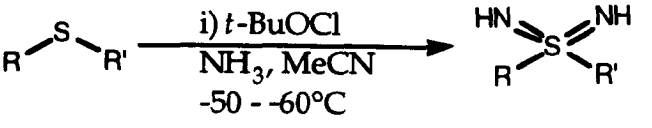
1.8 Sulfodi-imides

Sulfodi-imides **7** are the aza analogues of sulfones **4** (**Figure 1.10**). Unlike sulfones, they are chiral if the *N*-substituents and the sulfur substituents are dissimilar. Although thermally and hydrolytically stable sulfodi-imides have found limited synthetic utility.

4 **7**

Figure 1.10 General structure of a sulfone and a sulfodi-imide

The most convenient synthesis requires the action of *t*-butylhypochlorite and ammonia on the appropriate sulfide (**Scheme 1.85**).[84] Chloramine-T has also been used to make sulfodi-imides from sulfides *via* sulfimides.[85]



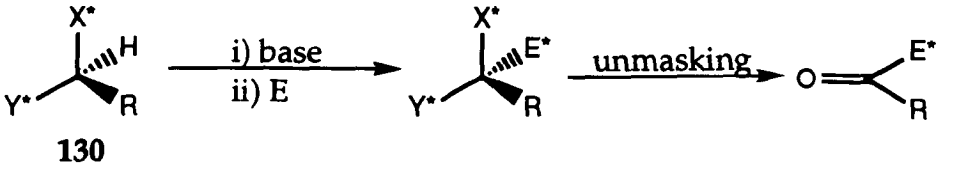
Scheme 1.85

Chapter 2

Attempted synthesis of cyclic sulfimides 132

2.1 Introduction.

Chiral acyl anion equivalents **130**, which are masked aldehydes and ketones, are important synthons in asymmetric synthesis (**Scheme 2.1**).[86]



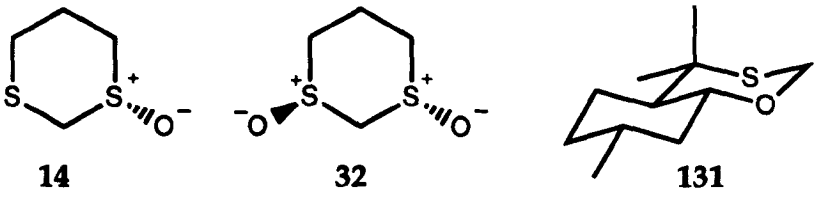
130

Scheme 2.1

The target functional groups are present in many natural products and so the transfer of chirality from the chiral acyl anion equivalent to a compound containing a carbonyl group is an important process. Reaction of the acyl anion equivalent with a base and prochiral electrophile can proceed with high diastereoselectivity. Unmasking yields homochiral aldehydes or ketones if the chiral acyl anion equivalent was enantiomerically pure.

2.2 Strategy.

The most prominent examples of chiral acyl anion equivalents are compounds **14**, **32**, and **131** (**Figure 2.1**).



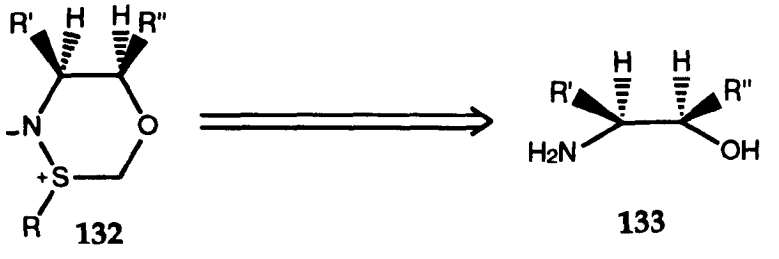
14 **32** **131**

Figure 2.1 Structures of 14, 32 and 131

All three exhibit excellent diastereoselectivities in many reactions, as illustrated by the examples of the sulfoxides discussed in Chapter 1. Page's dithiane monoxide[22] and Aggarwal's dithiane dioxide[23] have both posed recently resolved problems at the unmasking stage and Eliel's oxathiane, derived from natural (+)-pulegone, is only available in one enantiomeric form.[87] To rival current methodology, any new chiral acyl anion equivalent would have to fulfill three criteria:-

1. Be readily available in both enantiomeric forms.
2. Be easily unmasked.
3. Undergo C-C bond formation with excellent diastereoselectivity.

We considered cyclic sulfimides **132**, derived from chiral 1,2-aminoalcohols **133** and a chloromethylalkyl/arylsulfide, to be potential chiral acyl anion equivalents. Cyclic sulfimides are known compounds, although this particular case would be the first example of the 1,3,4-oxathiazine ring system **(Scheme 2.2)**.

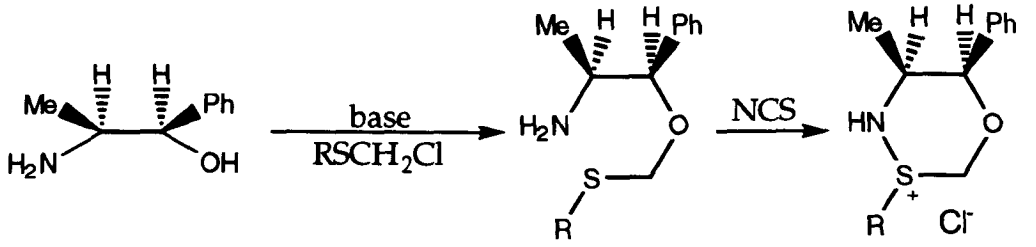


132 **133**

Scheme 2.2

We expected the cyclisation *via* sulfimide formation to result in a single absolute configuration at sulfur, due to conformational constraints. The range of aminoalcohols available is large, being accessed by the reduction of amino acids. We chose norephedrine **133a** as: (i) it is readily available in both enantiomeric forms and (ii) hydrogenation is expected to reduce both the sulfimide and benzylic ether, thereby unmasking the carbonyl group.[88]

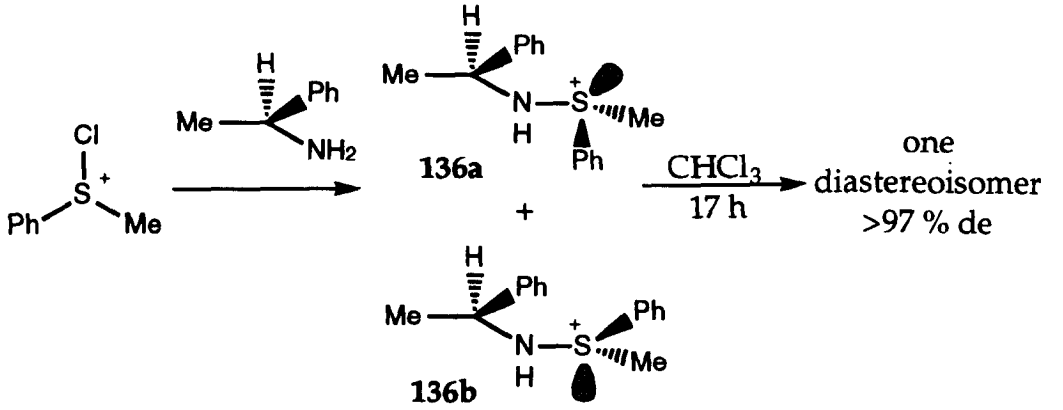
O-Alkylation to yield **134** followed by cyclisation using *N*-chlorosuccinimide would, in principle, yield two diastereomeric imidosulfonium salts **135** (**Scheme 2.3**).



133a **134** **135**

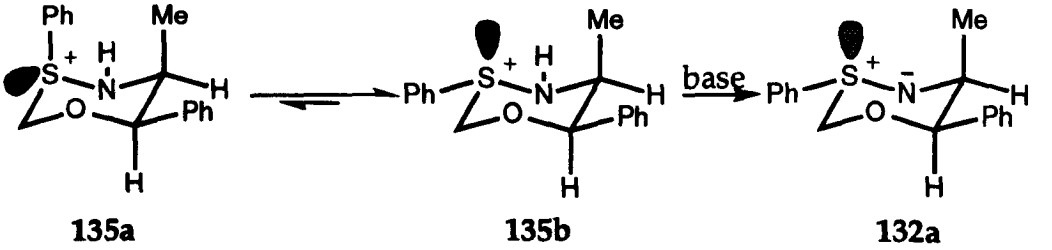
Scheme 2.3

The possible formation of two diastereomeric sulfonium chlorides was little cause for concern, as we had already shown that acyclic analogue **136** underwent inversion at the positively charged sulfur to yield the thermodynamically favoured salt (**Scheme 2.4**).[89]



Scheme 2.4

We speculated that, in the cyclic case, conformer **132a** with one phenyl 'equatorial' and the *S*-alkyl/aryl substituent 'equatorial' would be preferred sterically (**Scheme 2.5**).

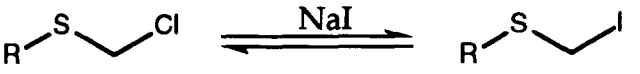


135a **135b** **132a**

Scheme 2.5

Reaction of cyclic sulfimide **132a** with alkylating agents and prochiral carbonyl compounds would allow us to assess the diastereoselectivity of alkylation and to probe the possibility of asymmetric induction in the initial addition, respectively.

The use of chloromethylalkyl/arylsulfides as alkylating agents for use as protecting groups for alcohols is well documented. Corey and Bock introduced the methylthiomethyl MTM group, *via* iodomethylmethylsulfide **137a**, as a new selective protecting group for alcohols.[90] Chloromethylmethylsulfide **138a** and sodium iodide react *in situ* to generate an equilibrium with the iodo-derivative (**Scheme 2.6**).



138 **137a** R=Me
137b R=Ph

Scheme 2.6

Holton and Nelson extended Corey's methodology to the phenylthiomethyl group using chloromethylphenylsulfide **138b** and sodium iodide (**Scheme 2.6**).[91]

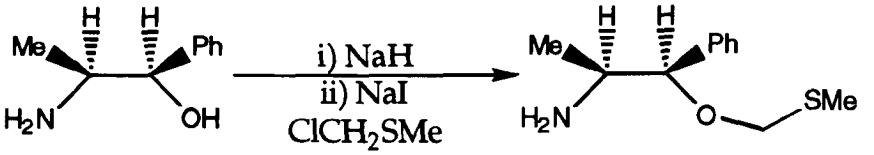
2.3 Results and Discussion

2.3.1 Chemoselective alkylation of aminoalcohols[92]

2.3.1.1 Preparation of (1*R*,2*S*)-1-Methyl-2-(methylsulfanylmethoxy)-phenyl-ethylamine 134a

Deprotonation of (*1R, 2S*)-norephedrine **133a** using sodium hydride in refluxing THF followed by the addition of sodium iodide and chloromethylmethylsulfide afforded a yellow oil upon acid-neutralisation work-up (**Scheme 2.7**). ^{1}H NMR analysis of the crude product mixture showed the presence of signals that we attributed to two compounds. The major product was assigned as being the desired MTM ether on the basis of

the expected signals in the ^1H NMR spectrum, in particular a downfield AB quartet (centred around 4.47 ppm) typical of an *O,S*-acetal methylene group in a chiral environment. The minor compound was assigned as being unreacted norephedrine, by comparison with an NMR spectrum of the starting material. Distillation of the crude yellow oil afforded **134a** as a colourless oil in good yield (80%).

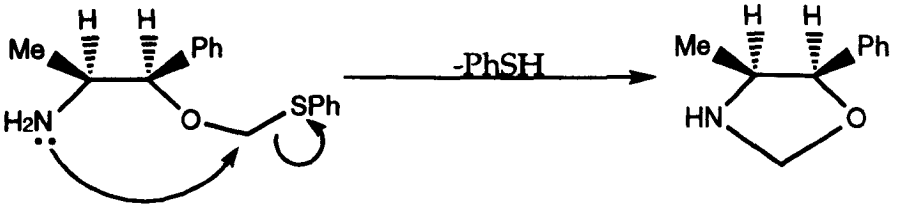


133a **134a**

Scheme 2.7

2.3.1.2 Attempted preparation of (1*R*,2*S*)-1-Methyl-2-(phenylsulfanyl-methoxy)phenylethylamine 134b

We failed to generate the PTM analogue **134b** (**Scheme 2.8**) of the MTM ether **134a**. Using the same procedure as described above, two major products were observed. Analysis of these products by NMR indicated signals present that we attributed to oxazolidine **139** and unreacted norephedrine **133a** (**Scheme 2.8**).



134b **139**

Scheme 2.8

The spectrum contained an AB quartet (centred at 4.97 ppm) and resonances attributable to the benzylic and methine protons of oxazolidine **139**. The molecular ion was also evident in the mass spectrum (MH^+). However, comparison with literature NMR data revealed inconsistencies in chemical

shifts and coupling constants,[93] if our proposed structure was correct. At this stage, considering the 'yield' of oxazolidine (<5 %), we decided that full characterisation would be difficult and unnecessary at this stage. If under different reaction conditions, this compound became more prominent, a full investigation would be warranted.

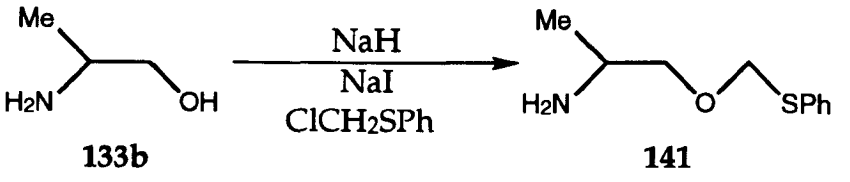
^{1}H NMR analysis of the organic phases left behind after acid extraction revealed signals we assigned to bis(phenylthio)methane **140 (Figure 2.2)**. Our explanation for the formation of this byproduct is discussed later.

140

Figure 2.2 Structure of bisphenylthiomethane 140

2.3.1.3 Preparation of DL-1-Methyl-2-(phenylsulfanyl-methoxy)ethyl-amine 141

It was hoped that reducing the steric demand of the nucleophilic alkoxide would promote alkylation. Therefore, we changed the aminoalcohol to DL-2-amino-1-propanol **133b**, which has a primary alcohol functionality, as opposed to norephedrine's benzylic alcohol group. If this alkylation worked, we envisaged problems later, in that the unmasking stage would become more difficult as the ether linkage would not be benzylic and so would not be cleaved by hydrogenation. Using conditions described above, the PTM ether **141** was isolated *via* distillation of the crude yellow oil obtained after acid-neutralisation work-up (**Scheme 2.9**). Byproduct **140** was also isolated from the organic layers left after the acid-neutralisation work-up.



133b **141**

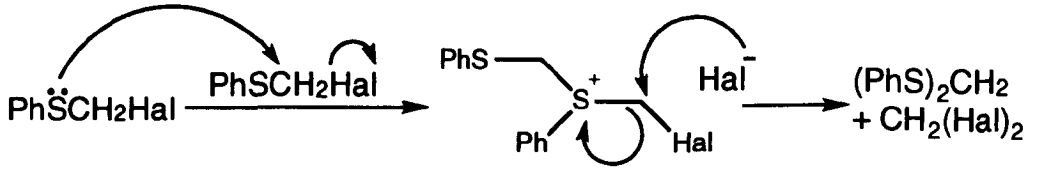
Scheme 2.9

We attempted to try and manipulate the reaction conditions to promote formation of the desired products **134a, 134b** and **141**, and hinder bis(phenylthio)methane **140** generation. In all three cases, making the amount of sodium iodide catalytic (1.0 to 0.01 eq.) did not affect yields or product distributions. Also, the longer the reaction was left stirring at room temperature, the more byproduct was formed.

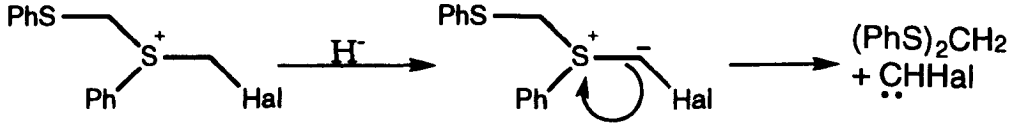
2.3.2 Mechanistic possibilities for the formation of bisphenylthiomethane

Three possible mechanisms have been proposed to explain the formation of byproduct **140** (**Scheme 2.10**).[94]

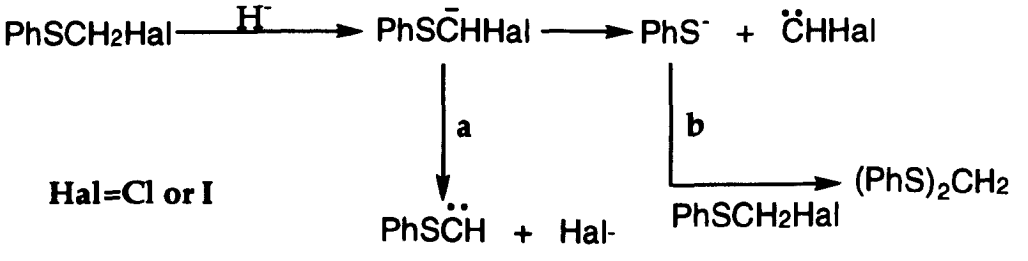
Equation 1



Equation 2



Equation 3

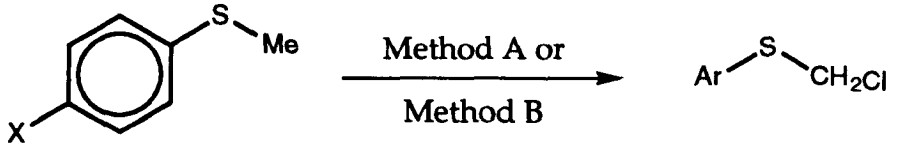


Scheme 2.10

We consider Campbell's mechanism (**equation 1**) to be most likely although the presence of sodium hydride makes sulfonium ylid decomposition (**equation 2**) and carbanion decomposition (**equation 3**), both to carbenes, possible. Should Campbell's mechanism be correct, we postulate that a reduction in the nucleophilicity of sulfur would hinder the formation of bis(phenylthio)methane. We considered changing the electronic nature of the aromatic ring, in such a way as to make ArTMCl **138** a better alkylating group. Our results and literature precedent implied that the MTM group was effective in protecting primary and benzylic alcohols, whereas the PTM group was ineffective for both of the above.

2.3.3 Discovery of the *p*-bromophenylthiomethyl (BPTM) protecting group

Our strategy was to protect a primary, secondary and benzylic alcohol with the most suitable arylthiomethyl group. This necessitated the preparation of three known aromatic thiomethylchlorides **138** from the corresponding aryl methyl sulfides **142** (**Scheme 2.11**), which we achieved in the yields given in the **Table 2.1**.



142 **138**

Scheme 2.11

Table 2.1 Yields of aromatic thiomethylchlorides 138

entry	X	yield %	method
a	MeO	86	A
b	Br	89	A
c	NO_2	99	B

Method A: NCS, CCl_4, filter[95]

Method B: SO_2Cl_2, CH_2Cl_2, reflux[96]

^1H NMR analysis and mass spectra of all products (entries **a**,**b** and **c**) agreed with literature data.[97] Our approach in finding the most suitable aromatic substituent involved four test reactions for each chloride. Each reaction was left for 24 hrs in THF/acetonitrile (10:1.5 ml) at room temperature, thereby providing standard conditions for each reaction, along with the following variables:

Reaction 1 ArTMSCl in solvent only (control).

Reaction 2 ArTMSCl and sodium hydride.

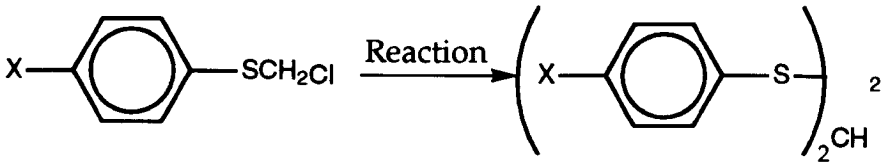
Reaction 3 ArTMSCl and sodium iodide.

Reaction 4 ArTMSCl, sodium iodide and sodium hydride.

These test reactions were designed to assess which ArTMSCl **138** was the least troublesome in terms of stability towards byproduct formation under the alkylation conditions. Our results are presented in **Table 2.2, Scheme 2.12**.

Table 2.2 Distribution of products for Scheme 2.12

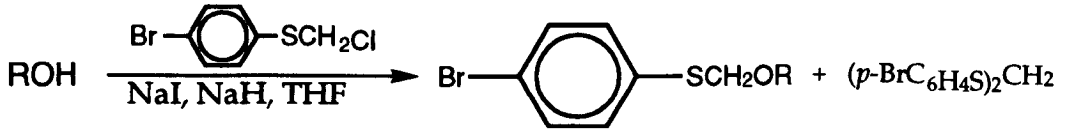
	Product ratio (**142**:**143**)			
X-C$_6$H$_4$-SCH$_2$Cl	**1**	**2**	**3**	**4**
142a X=MeO	**142a**	1:3	1:1	**143a**
142b X=H	**142b**	**142b**	**142b**	1:12
142c X=Br	**142c**	**142c**	**142c**	1:15
142d X=NO_2	**142d**	**142d**	**142d**	**142d**



142 **243**

Scheme 2.12

^{1}H NMR analysis of the crude product mixtures allowed identification of bisarylsulfanyl compounds **243**, by comparison with literature data.[98] Product ratios were determined by NMR of the crude mixtures. The more electron rich sulfide **142a** was considered too reactive (entry **a**) and conversely the more electron poor sulfide **142d** was too unreactive (entry **d**). *p*-Bromophenylthiomethyl choride **142c** (entry **c**) was therefore selected for more rigorous investigation. A range of alcohols were then investigated using our potentially new protecting group (**Scheme 2.13 and Table 2.3**).



143 **243c**

Scheme 2.13

Table 2.3 Yields of BPTM protected alcohols 143 and byproduct 243c

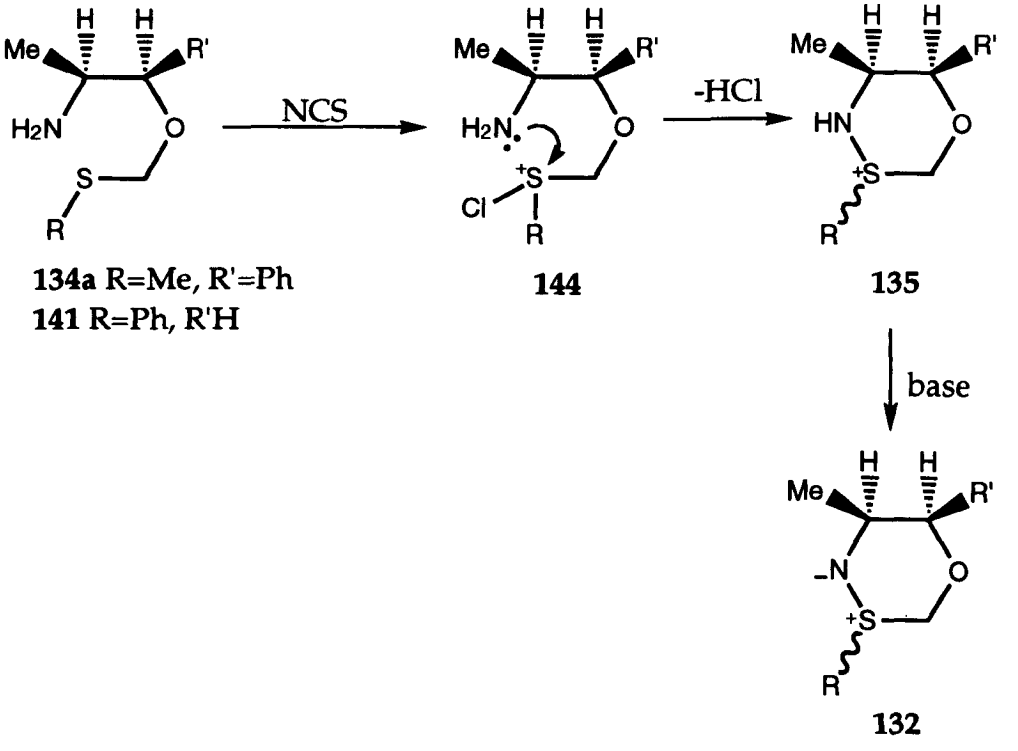
	% Yield **143**	% Yield **243c**
143a R=$PhCH_2$	80	5
143b R=*n*-hexyl	60	10
143c R=$Ph(CH_3)CH$	35	30
143d R=cyclohexyl	55	20

Primary and benzylic alcohols are protected effectively, giving BPTM protected alcohols **143b** and **143a**, respectively, although more sterically

hindered secondary alcohols are not so well protected, as evidenced by lower yields and more byproduct being present for **143c** and **143d**. Deprotection of the benzylic derivative **143a** is under investigation.[99]

2.3.4 Attempted cyclisations of MTM ether 134a and PTM ether 141

Our proposed cyclisation *via* sulfimidation involved sulfonium chloride **144** generation using *N*-chlorosuccinimide, followed by intramolecular nucleophilic attack by amine to yield imidosulfonium salt **135**. It was hoped that subsequent treatment with base would form sulfimide **132** (**Scheme 2.14**).



134a R=Me, R'=Ph
141 R=Ph, R'H

144

135

132

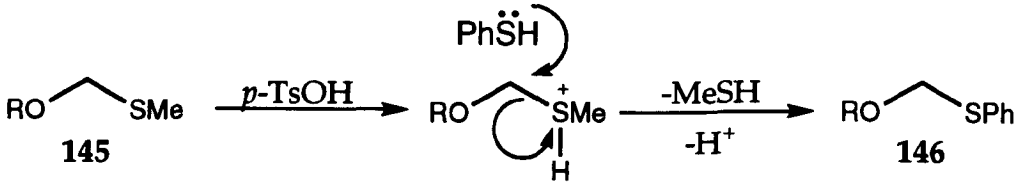
Scheme 2.14

Exposure of both **134a** and **141** to the aforementioned conditions afforded an intractable mixture of products. Analysis by NMR, MS and IR revealed no evidence of either the desired products or the starting materials. Varying the time given for sulfonium chloride **144** formation, the temperature at which both chloride formation and the treatment of base were allowed to occur, as well as a different source of electrophilic chlorine (sulfuryl chloride), all

resulted in similar product mixtures. We have no explanation for these results at this stage.

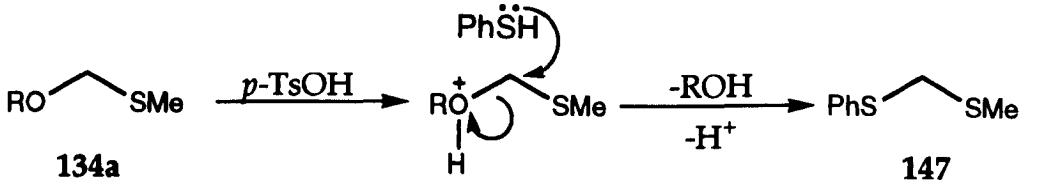
2.3.5 Alternative attempts at generating the preferred PTM ether 134b

As we considered the norephedrine PTM ether **134b** to be the most suitable cyclic sulfimide precursor, due to its benzylic ether linkage, we attempted two alternative alkylation procedures. Dieter and Datar developed the controlled exchange of MTM ethers **145** with thiophenol to prepare PTM ethers **146**.[100] We thus tried adapting this methodology to the exchange of an MTM ether with thiophenol (**Scheme 2.15**).



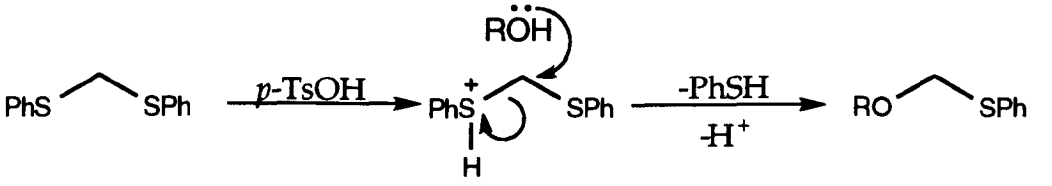
Scheme 2.15

Therefore, we reacted MTM ether **134a** with thiophenol and *p*-tosic acid in dichloromethane in a Soxhlet apparatus, containing molecular sieves (4Å) to mop up methanethiol byproduct. The consumption of thiophenol was monitored by tlc, and after work-up, ^{1}H NMR analysis suggested signals were present attributable to methylthiophenylthiomethane **147** and some *bis*(phenylthio)methane **140** as the minor product. We propose that elimination of norephedrine as the alkoxide is preferred (**Scheme 2.16**).



Scheme 2.16

Our second attempt at preparing **134b** involved distilling under reduced pressure a mixture of *p*-tosic acid, *bis*(phenylthio)methane (molten solvent) and norephedrine (**Scheme 2.17**).



Scheme 2.17

We expected thiophenol to distil over leaving PTM ether **134b** as the residue. However, ^{1}H NMR analysis indicated signals present attributable to one minor compound besides unreacted norephedrine, this being the tentatively identified oxazolidine **139** we generated earlier.

2.4 Summary

The preparations of two new protected alcohols **134a** and **141** are reported, although the attempted cyclisations to 1,3,4-oxathiazines **132** were unsuccessful. A replacement for the PTM moiety as a protecting group for alcohols has been discovered. The BPTM group was shown to protect primary, secondary and benzylic alcohols, an improvement on both the PTM group, which is only suitable for phenols and to some extent for primary alcohols and the MTM group which is suitable for primary alcohols only.

Chapter 3

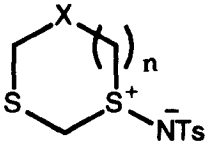
Synthesis and reactions of imides of cyclic sulfides

3.1 Aim

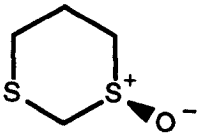
Our unsuccessful attempt at preparing 1,3,4-oxathiazines **132** (cyclic sulfimides) precluded our investigation into the potential of this new class of compound as chiral acyl anion equivalents. Our interest in sulfimides as chiral acyl anion equivalents remained, but we reconsidered our approach. We decided to study a class of compounds, known as imides of cyclic sulfides, the syntheses of which have been reported,[45,101] but had received limited attention as synthetically useful compounds. Our aim was to investigate the potential of these compounds as chiral acyl anion equivalents.

3.2 Review of methodology

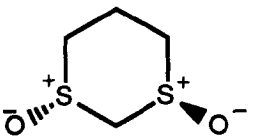
The relevant methodology has been discussed in the introduction to Chapter 2. Imides of cyclic sulfides **148** are closely related to Page's dithiane monoxide **14** and Aggarwal's dithiane dioxide **32** (**Figure 3.1**).



148a X=CH_2, n=0
148b X=CH_2, n=1
148c X=S, n=1



14

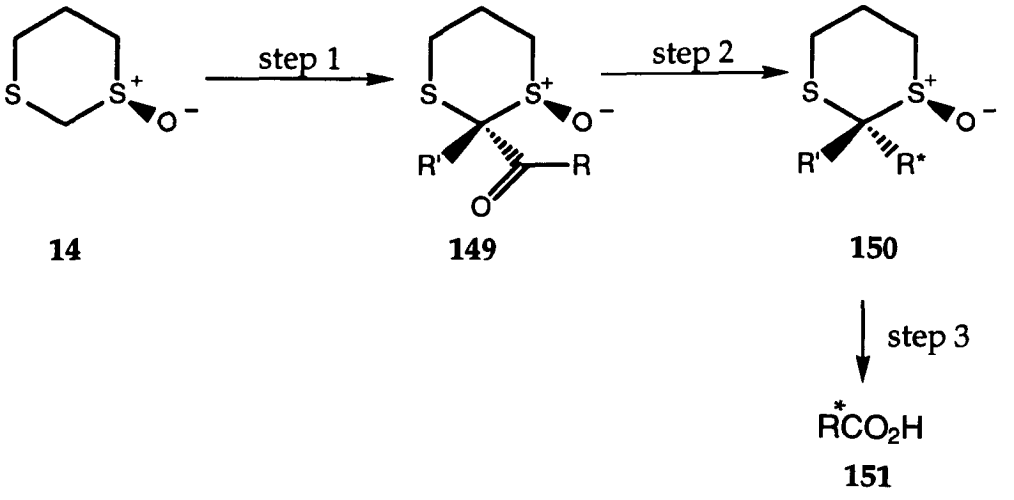


32

Figure 3.1 Structures of sulfimides 148 and sulfoxides 14 and 32

Dithiane monoxide acyl anion equivalency is demonstrated by the preparation of chiral carboxylic acids (**Scheme 3.1**). Diastereoselective

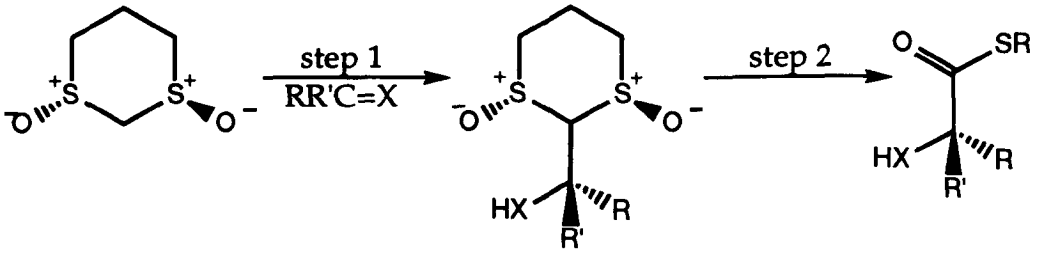
condensation of the C-2 carbanion with an acylating agent results in a new chiral centre at C-2, which is further functionalised by alkylation to yield **149** (**step 1**). The diastereoselective transformation of the prochiral acyl substituent RCO into a chiral substituent R* in **150** (**step 2**) followed by unmasking of the carbonyl group (**step 3**) yields chiral carboxylic acids **151**.[22]



14 **149** **150** **151**

Scheme 3.1

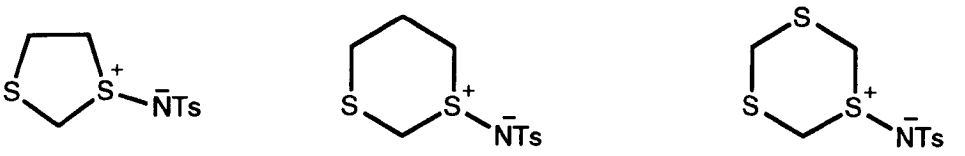
Dithiane dioxide methodology typically involves fewer steps (**Scheme 3.2**). Diastereoselective addition of the C-2 carbanion of **32** to a prochiral electrophile to prepare **152** (**step 1**) establishes the chirality of alkyl thioester **153**, isolated by unmasking (**step 2**).[23]



32 **152** **153**

Scheme 3.2

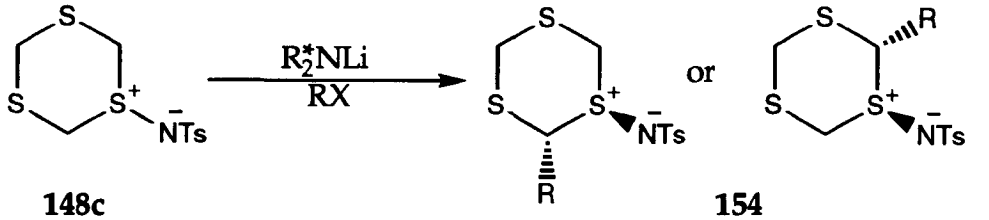
We speculated that the sulfimide analogues **148a** and **148b** of sulfoxide **14** (diimide analogues of **32** have only been reported speculatively as mechanistic intermediates) would lead to improved diastereoselectivities in the methodology above (**Scheme 3.2**).



148a **148b** **148c**

Figure 3.2 Structures of sulfimides 148

We also considered the achiral acyl anion equivalent **148c**, derived from trithiane, to be of interest, as we hoped to break the symmetry of **148c** with a chiral base, yielding enantiomerically enriched products **154** (**Scheme 3.3**). The preparations of **148** are described in Chapter 4.



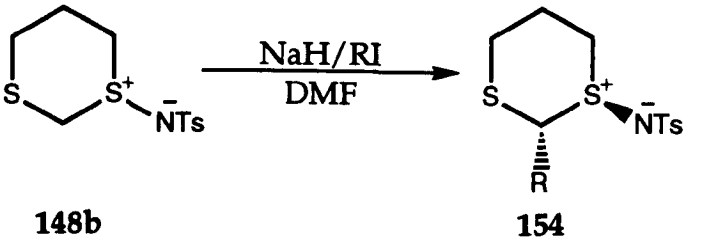
148c **154**

Scheme 3.3

3.3 Results and discussion

3.3.1 Preparation of alkylated adducts 154 of imide of cyclic sulfide 148b

Our initial assessment of the potential of racemic imides of cyclic sulfides as chiral acyl anion equivalents involved studying the diastereoselectivity of alkylation. We found the sodium salt of dithiane imide **148b** to react smoothly with alkyl iodides in DMF to yield **154** (**Scheme 3.4**).



148b **154**

Scheme 3.4

The reactions were highly diastereoselective, leading predominantly to the *anti* products in all cases, as judged by comparison of their NMR data with these of compound **156a** (**Table 3.1**).

Table 3.1 Yields and diastereoselectivities for alkylations of sulfimides 148b and 148c

Sulfimide	R	Equivs. NaH/RI	Product	Yield %	de[a] %
148b	Me	1	**154a**	55	93
	Et	1	**154b**	b	75
148c	Me	4	**159a**	55	>75
	Et	1	**158b**	20	>85
			159b	15	>70
	n-Pr	1	**158c**	25	>85
			159c	23	>80

[a] des were assessed from ^{1}H NMR spectra of crude product mixtures

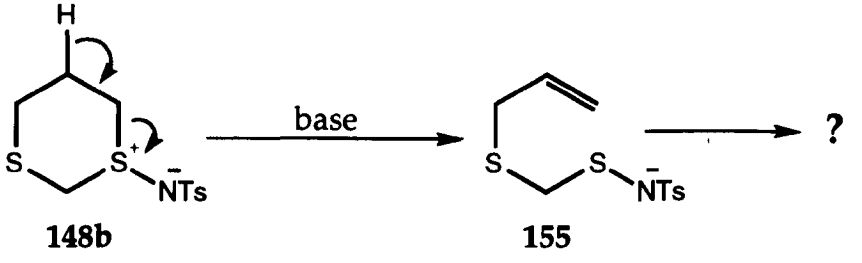
[b] not isolated

Unfortunately, these conditions proved to be the only conditions applicable to alkylations, as with other bases (alkyllithiums, LDA or NaHMDS), solvents, temperatures or alkyl halides (chlorides or bromides) the reactions failed. More importantly the carbanion of **148b** failed to react successfully with prochiral electrophiles such as aldehydes or ketones. In each case complex mixtures of products were observed, with one major byproduct present, namely tosyl amide. This was also the case with bifunctional alkyl iodides ICH_2Z (Z=COCl, CO_2H, $SiMe_3$), which we hoped would alkylate the carbanion of **148b**, thereby functionalising the acyl anion equivalent by way of iodide displacement.

Sulfimide **148a** was found to decompose into tosyl amide and other unidentified products under all of the above conditions, including those successful for **148b**.

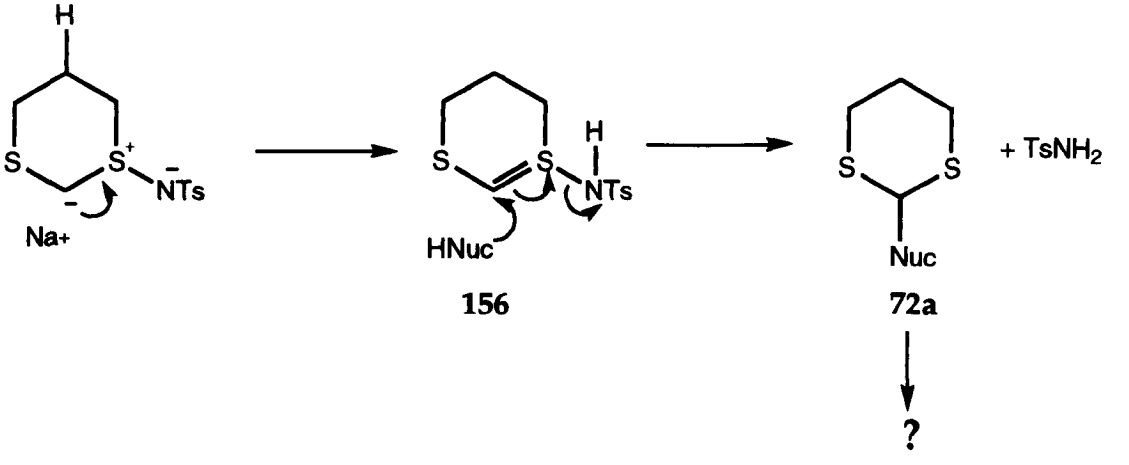
3.3.2 Possible mechanisms to explain formation of tosyl amide

We identified the byproduct as being *p*-tosyl amide by comparison wth ^1H NMR and mass spectra of pure material.[102] We proposed that tosyl amide was generated in two possible ways (**Schemes 3.5 and 3.6**).[103]



148b **155**

Scheme 3.5



156 **72a**

Scheme 3.6

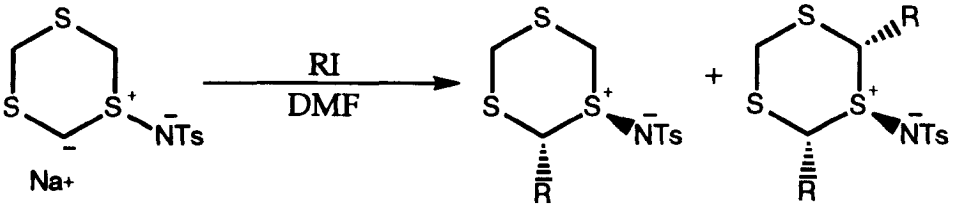
An elimination reaction from **148b** (**Scheme 3.5**) would give sulfenamide **155**, which under aqueous workup, could lead to tosyl amide, although, besides tosyl amide, the remnants of such a reaction were never observed. However, there is precedent for such a decomposition.[103]

Nucleophilic interception of sulfimide **156** could also give tosyl amide. Hydrolysis of these compounds were noted by Walther and Gross,[46] as

discussed in the introduction, but again, the dithiane derivative **72a**, or decomposition products thereof, were never isolated.

3.3.3 Preparation of alkylated adducts 158 and 159 of imide of cyclic sulfide 148c

If the former explanation applied, then we predicted that the sodium salt **157** of trithiane imide **148c** would potentially be a better substrate under these conditions, as no β-protons are present. Exposing the sodium salt to the alkylating conditions used above gave the desired products **158**, but disappointingly along with roughly equal amounts of the *meso* compounds **159** resulting from alkylation at both acidic α-sites (**Scheme 3.7, Table 3.1**).



157 **158** **159**

Scheme 3.7

With careful chromatography it was possible to separate monoalkylated compounds, **158b** and **158c** from dialkylated products **159b** and **159c**, respectively, although the purification of the dialkylated products proved difficult. The diastereoselectivities were estimated from crude spectra. We have only ambiguous NMR evidence for monomethyl compound **158a**, which could not be isolated.

The dialkylated compound **159a** was prepared free of **158a** by reaction with excess sodium hydride and excess methyl iodide, with good diastereoslectivity. The expected *anti,anti* relative stereochemistry was confirmed for the dimethyl derivative **159a** by a single crystal X-ray diffraction study.[104] Subsequent comparison of the ^{1}H NMR spectrum of

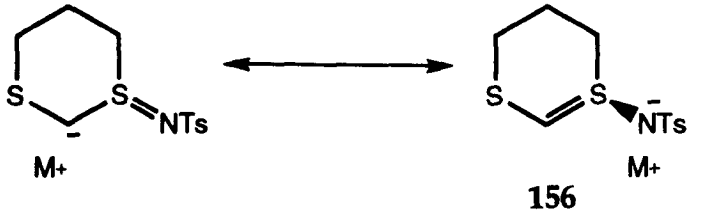
159a with those of the other alkylated sulfimides **159b, 159c, 158a, 158b and 158c** enabled us to deduce that in all cases the major diastereoisomer has the *anti* stereochemistry as shown. The *meso* products **159** were of no use in our asymmetric synthesis programme and so we attempted to stop the alkylation at the chiral monoalkylated products **158**, but even reducing the amounts of both sodium hydride and methyl iodide still resulted in mixtures of mono- **158** and dialkylated **159** products.

3.4 Conclusion

The potential of sulfimides **148a** and **148b** as chiral acyl anion equivalents is limited by the stability of the C-2 metalated derivatives. In the presence of a dipolar aprotic solvent such as DMF with an *in situ* quench by an electrophile (RI), mono- and dialkylated products result, possessing *anti* and *anti,anti* stereochemistry, respectively. However, other base systems and prochiral electrophiles result in decomposition of the anion **157** and the anion of **148b** into byproducts. The introduction of chirality into sulfimide **148c** is prevented by facile dialkylation to *meso* products.

3.5 Preparation and reactions of sulfimides 160 and 162

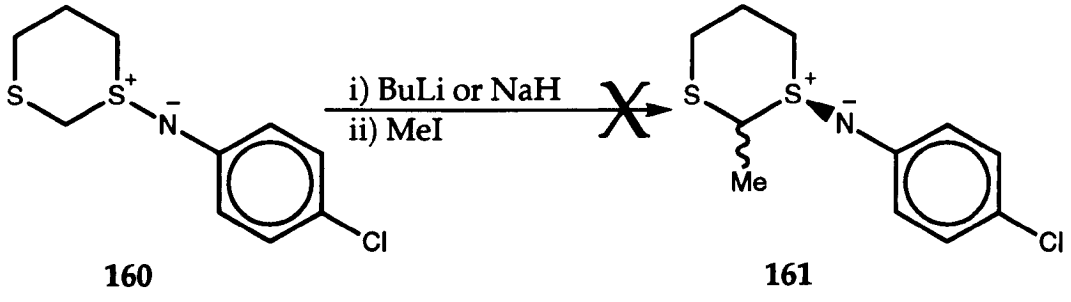
The *N*-tosyl substituent of sulfimide **148b** was thought to be too electron withdrawing, as we observed decomposition products attributable to the canonical form **156** (**Scheme 3.9**) in reactions of metalated **148b**.



156

Scheme 3.9

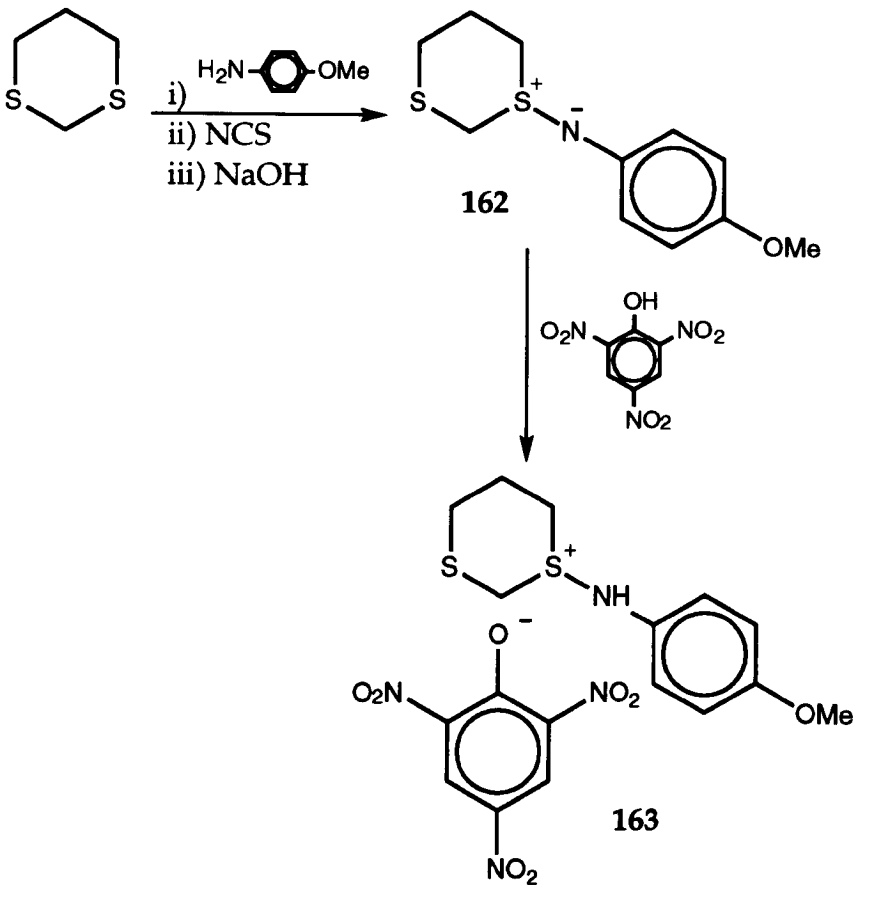
The significant contribution made by this form was thought to be sufficient to make the C-2 carbon electrophilic, as opposed to nucleophilic in the anion form, and therefore prone to nucleophilic attack. We proposed to make the *N*-substituent less electron withdrawing compared to *N*-tosyl. Therefore, sulfimide **160** was prepared using known methodology from *N*-chlorosuccinimide, to form the chlorosulfonium salt, and amine, followed by a base wash.[101a] Exposure of the sulfimide to methylation conditions did not result in methylated adducts **161**, but instead gave a complicated mixture of unidentified products (**Scheme 3.10**).



160 **161**

Scheme 3.10

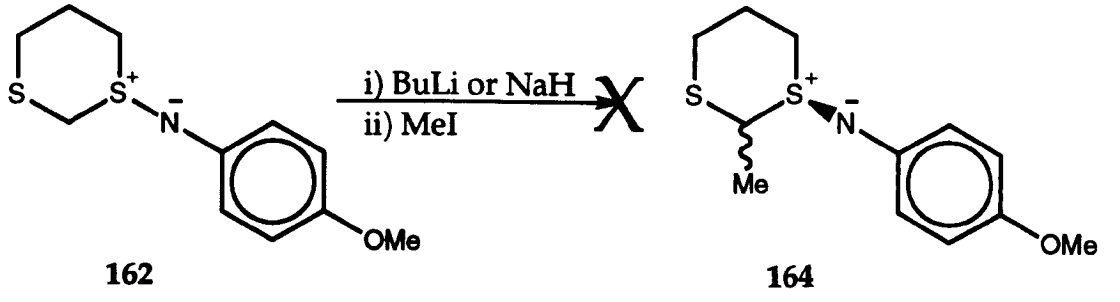
Sulfimide **160** is known to undergo a rearrangement as discussed in the introduction (**Scheme 1.50**). We observed neither a rearrangement product **76** or **77** nor methylated adduct **161** in the product mixtures. We did not observe any amine decomposition product, as was the case with the *N*-tosyl sulfimides, but we could not explain the results at this stage. The other electron rich *N*-aryl sulfimide we considered worthy of investigation was sulfimide **162** (**Scheme 3.11**).[101a]



Scheme 3.11

As above, formation of the chlorosulfonium salt was achieved using *N*-chlorosuccinimide. Attack by amine and a base wash yielded sulfimide. However, sulfimide **162** had limited stability at room temperature in air, and so was isolated as a stable brown powder as the picrate **163**.

Methylation to yield **164** was attempted by two different methods. Using the unstable sulfimide **162** at -78°C, with base and methyl iodide, resulted in a very complicated mixture of products, from which only very limited analytical evidence for the desired adduct could be obtained (**Scheme 3.12**).



162 **164**

Scheme 3.12

Starting from picrate **163**, one equivalent of base was used to generate sulfimide **162** *in situ*, then a second equivalent was needed for deprotonation at C-2. Unfortunately, a similar negative result was observed.

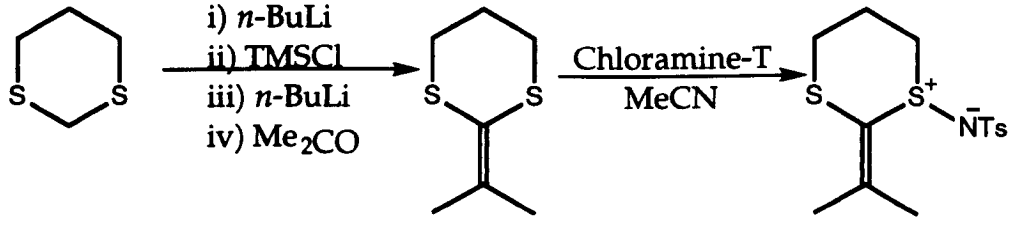
3.5 Imides of ketene dithioacetals 166

3.5.1 Strategy

The availability of imides of ketene dithioacetals enabled us to study Michael additions and Diels-Alder reactions of these compounds, in conjunction with our investigations into the potential of imides of cyclic sulfides as chiral acyl anion equivalents and vinyl sulfimides as chiral Michael acceptors (**chapter 5**).

3.5.2 Preparation of imides of ketene dithioacetals 166

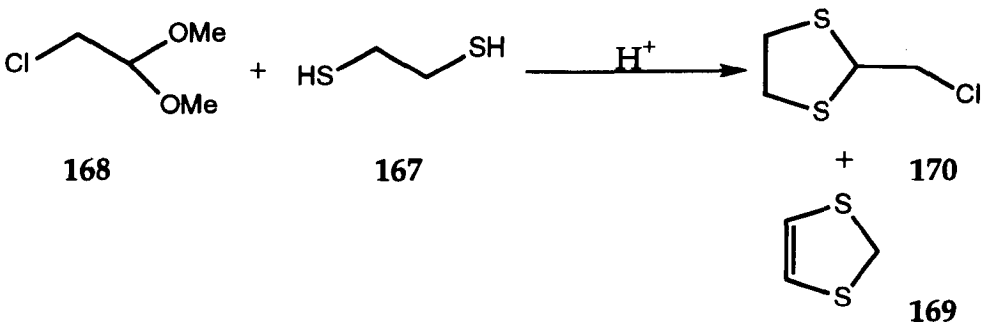
Claus prepared several imides of ketene dithioacetals, one of which was of interest to us.[105] Peterson olefination conditions gave ketene dithioacetal **165** in good yield,[106] which, on reaction with Chloramine-T, yielded imide **166** (**Scheme 3.13**).



165 **166**

Scheme 3.13

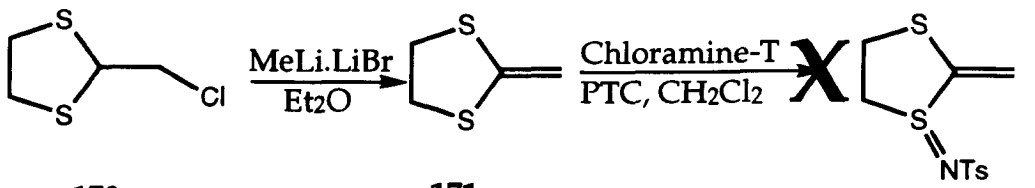
We also considered the five-membered analogue to be of interest. This compound required a different synthetic approach. The instability of 2-lithiodithiolane necessitated starting from dithiol **167** and acetal **168** (**Scheme 3.14**).[107]



168 167 170 169

Scheme 3.14

Two products resulted, the minor one being 2,3-dihydro-1,4-dithiolane **169** and the major product being 2-chloromethyl-1,3-dithiolane **170**. Base-induced elimination of HCl yielded 2-methylene-1,3-dithiolane **171** (**Scheme 3.15**).



170 **171**

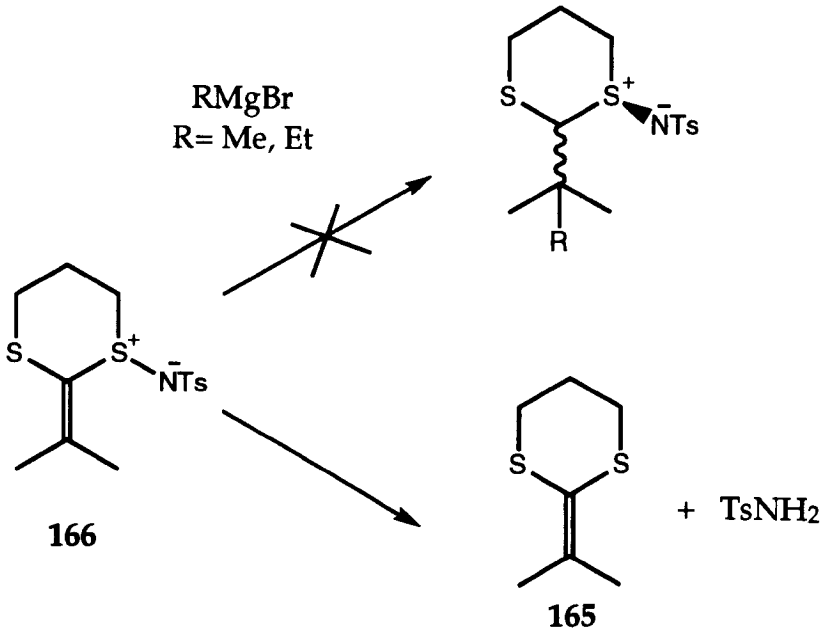
Scheme 3.15

Unfortunately, reaction of **171** with Chloramine-T resulted in a complicated mixture of products, with no analytical evidence for either the starting material or the desired product.

3.5.3 Attempted Michael-type additions to sulfimide 166

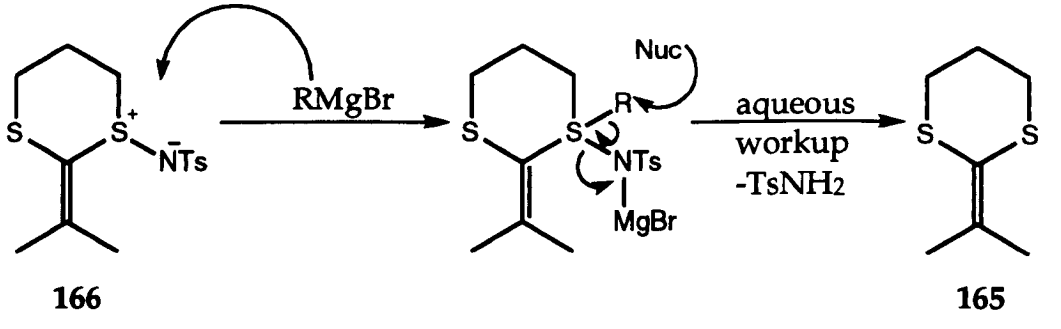
3.5.3.1 Grignard additions

The addition of a Grignard reagent to imide **166** resulted in the starting ketene dithioacetal **165** and tosyl amide (**Scheme 3.16**).[108]



Scheme 3.16

We consider this fragmentation to occur *via* nucleophilic attack at sulfur followed by reduction to **165** (**Scheme 3.17**).



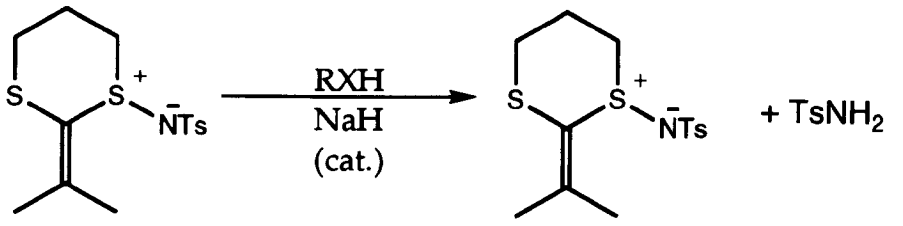
Scheme 3.17

3.5.3.2 Other carbon nucleophiles

The attempted addition of either diethylzinc or the anion of diethyl malonate to **166** resulted in unreacted starting material **166** being recovered.

3.5.3.3 Addition of RXH (X=O,S)

Using methodology described more fully in Chapter 5, sodium hydride catalysed Michael-type additions of RXH failed (**Scheme 3.18**).



166 **166**

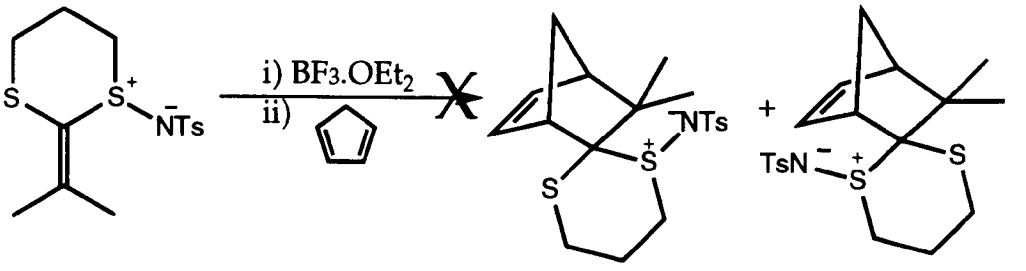
X = O, R = Et, Bu minor major
X = S, R = Ph in EtOH

Scheme 3.18

Unreacted starting material **166** was recovered as a minor component, but the major product of each reaction was tosyl amide. For a nucleophilic attack at the sulfimide sulfur to occur with subsequent displacement of the tosyl amide and concomitant reduction of sulfide, the corresponding ketene dithioacetal **165** would have to be present. We could not find any analytical evidence for this byproduct. A fragmentation reaction was presumably occuring, the nature of which we were unable to determine. In any case, this sulfimide was considered unsuitable as a Michael-type acceptor.

3.5.3.4 Attempted Diels-Alder reaction

We had hoped that Diels-Alder reaction of sulfimide **166**, by analogy with the work of Aggarwal,[109] would lead to cycloadducts **172** (**Scheme 3.19**). However, when freshly distilled cyclopentadiene and boron trifluoride etherate were reacted with sulfimide **166**, starting sulfimide **166** was recovered unreacted.



166 172

Scheme 3.19

3.5.4 Conclusion

We speculate that Michael-type and Diels-Alder additions to this ketene dithioacetal imide **166** are hindered by the steric requirements of the isopropylidene group. Perhaps the ethylidene group, or some other monofunctionalised alkylidene group would be a more suitable Michael-type acceptor and Diels-Alder dienophile.

3.6 Summary

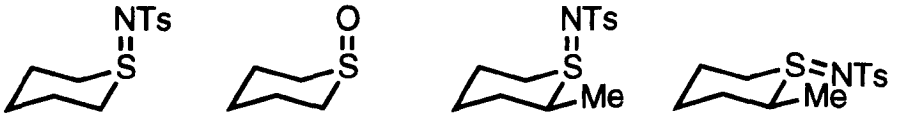
Imides of cyclic sulfides **148** have been shown to be of limited use as chiral acyl anion equivalents. Alkylations were found to give predominantly *anti*-products **154** with the dithiane sulfimide and *anti-anti*-products with the trithiane sulfimide **158** and **159**. Reactions with prochiral electrophiles such as aldehydes failed. Imides of ketene dithioacetals **166** failed as both Michael-type acceptors and Diels-Alder dienophiles.

Chapter 4

Conformational analysis of imides of cyclic sulfides

4.1 Introduction

During our studies into the potential of tosyl imides of 1,3-dithiane **148b** and 1,3-dithiolane **148a** s chiral acyl anion equivalents, we noticed that predicting the conformations of such compounds was extremely difficult from literature precedent. This problem was also evident in the sulfoxide sereies.[110] There has been a considerable amount of work done using X-ray and NMR studies into the conformations of related compounds, but no clear predictive guidelines have yet emerged. Molecular modelling is of limited use in addressing this problem, mainly because the necessary parameters for representation of the sulfimide bond have yet to be defined.



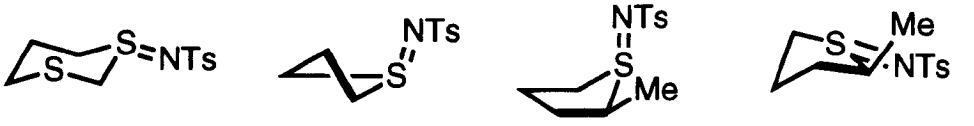
173 **174** **175** **176**

Figure 4.1 Structures of sulfimides 173, 175 and 176 and sulfoxide 174

The sulfimidyl bond in thiane 1-tosylimide **173** has a clear preference for the axial position, as judged by NMR studies and confirmed by X-ray crystallography.[111] This is consistent with the axial preference of the sulfinyl bond in thiane 1-oxide **174**.[111,112] However, competition from even a sterically undemanding alkyl group desiring its preferred equatorial position is sufficient to force the sulfimide to adopt the equatorial conformation.[111] This indicates how small the energy

difference between the axial and equatorial conformers must be. Hence, for example, *cis* 2-methylthiane 1-tosylimide **175** has the methyl group in its preferred equatorial position and the sulfimide bond in its preferred axial position, whereas the *trans* isomer **176** has both substituents equatorial, *ie.* with the methyl group in its favoured equatorial position and the sulfimide bond, uncharacteristically, also equatorial.[111]

Less electron withdrawing substituents on nitrogen (eg. aryl) show a clear preference for the equatorial form,[113] as does the tosylimide group in the 1,3-dithiane derivative **148b**,[111,114] these results being deduced from NMR data alone. It should be noted that equilibria (equatorial/axial) are usually observed by NMR but, in all cases where crystallographic data are also available, the dominant conformer in solution is that found in the solid state.[111-115]



148b **177** **178** **179**

Figure 4.2 Structures of sulfimides 148b, 177, 178 and 179

The thiolane analogues exhibit similar trends, although conformational distinctions are less marked in the more flexible 5-membered rings. For example, the sulfimidyl bond has been shown, by NMR and X-ray analysis, to be pseudoaxial in thiolane 1-tosylimide **177**, axial in the *cis* 2-methyl compound **178** and *endo-isoclinal* in the *trans* 2-methyl analogue **179**, where the methyl group is also *endo-isoclinal*.[115] Neither the conformational preferences of *N*-aryl thiolane derivatives nor those of 1,3-dithiolane derivatives have been examined.

148c **148a**

Figure 4.3 Structures of sulfimides **148c** and **148a**

We reasoned that confirmation of the NMR studies on the dithiane imide **148b** by X-ray crystallography, along with parallel investigations of 1,3,5-trithiane 1-tosylimide **148c** and 1,3-dithiolane 1-tosylimide **148a** would help to clarify the continuing uncertainty regarding the reasons for the various conformational preferences.

4.2 Results and discussion

The conformations of compounds **148a, 148b** and **148c**, as determined by X-ray crystallography, are shown in **Figure 4.4**, with the previously determined structures of **173** and **177** for comparison.[111,115] The result for the dithiane derivative **148b** confirms the equatorial preference indicated by the NMR studies.[114] The trithiane imide **148c** also shows the equatorial preference but the dithiolane imide **148a** clearly has an axial sulfimidyl bond. The envelope conformation of the latter example is different to the half-chair adopted by the simple thiolane analogue **177**, but similar to some more substituted examples (eg. **178**).[115]

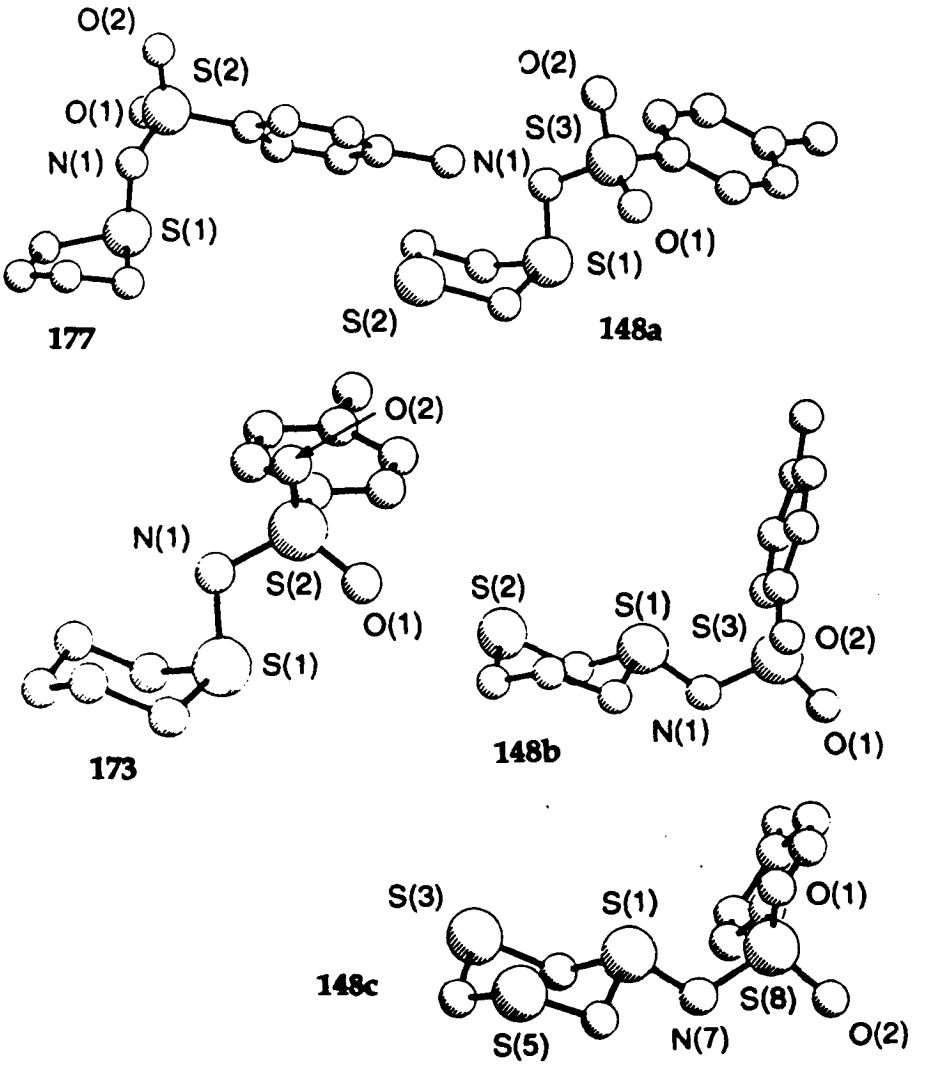


Figure 4.4 Conformations of sulfimides 148 as determined by X-ray crystallography

It has been demonstrated that the conformational preference of sulfinyl and sulfimidyl bonds depends on the relative magnitudes of the entropic contribution, which favours equatorial, and the thermochemical factor which favours axial.[116] Three classes of interaction have been invoked to explain the thermochemical preference for the axial position:

1. *gauche* effects;
2. 1,3-*syn* attractive interactions;
3. long range molecular orbital interactions.

These effects will be discussed in turn below.

4.2.1 *Gauche* effects

It has been suggested on a number of occasions that the axial preference of both sulfinyl and sulfimidyl bonds is due to unfavourable *gauche* interactions with vicinal C-H bonds (**Figure 4.5**).[117] Claus pointed out, however, that, should this effect be important, all examples should show the axial preference.[111] His results showed clearly that this was not the case as there are many examples of equatorial sufimidyl bonds, this being confirmed by our structures of **148b** and **148c**. In addition, Claus demonstrated that steric interactions with the sulfimide bond are unimportant, as significant increases in the bulk of the *N*-substituent (eg. phenyl to 2,6-dimethylphenyl) produced no noticable change in conformational preference.[111]

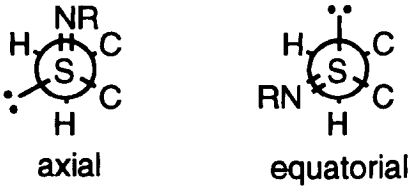


Figure 4.5 Newman representation of *gauche* interactions between the S=N bond and vicinal C-H bonds

Having shown that the unfavourable *gauche* effects described above were not responsible for the axial preference, Claus proposed an attractive *gauche* effect between the highly polarised S-N bond and the *gauche* C-C bonds, which he suggested would be more polarisable than the C-H bonds.[111] This explanation seemed plausible, as increasing the polarisation of the sulfimide bond by increasing the electronegativity of the *N*-substituent (eg. aryl to tosyl) increases the proportion of the axial conformer.[111] We sought to investigate this effect by replacing the vicinal C-C bonds by C-S bonds, which should be rather more polarisable.

Compounds **148b** and **148c** would be expected to have axial sulfimide bonds, maximising the *gauche* interactions with C-S bonds. In fact, in both **148b** and **148c** the equatorial sulfimide bond is *anti* to the C-S bond or bonds (**Figure 4,6**). There seems little evidence, therefore, for an attractive *gauche* effect based on bond polarisability.

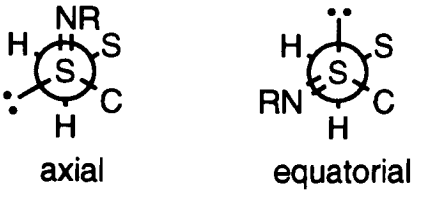


Figure 4.6 Newman representation of *gauche* interactions between the S=N bond and C-S bonds

Although we believe the *gauche* effects thus far used to explain the conformational preferences of sulfimides to be unimportant, other *gauche* effects can be used to rationalise our results. These are discussed later.

4.2.2 1,3-*Syn* attractive interactions

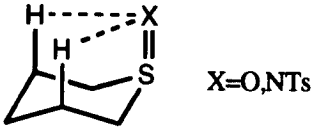
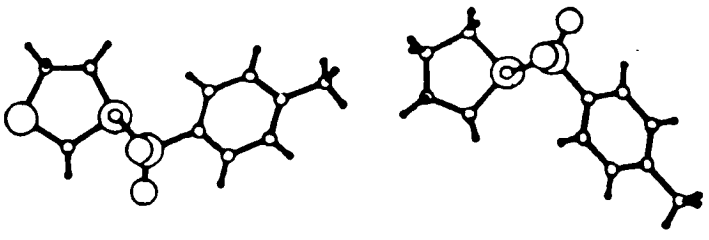


Figure 4.7 Representation of 1,3-interactions between S-X substituent and axial 3,5 protons

Another popular explanation for the axial preference of some sulfoxides and sulfimides is an attractive interaction between the oxygen or nitrogen, respectively, and the axial hydrogen on C-3 (**Figure 4.7**).[117,118] Our results seem, at first sight, to support this idea. The thiolane compounds **177** and **148a**, which both have the possibility of 1,3-interactions, both have axial

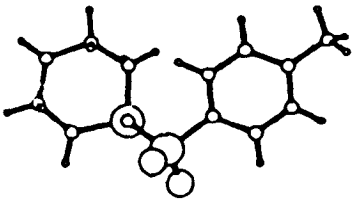
sulfimidyl bonds. In addition, examination of the orientation of the lone pair on nitrogen shows that it is correctly disposed for such an interaction in both cases (Figure 4.8), clearly pointing towards a C-3 hydrogen.



148a **177**

Figure 4.8 Orientation of the nitrogen lone pair in sulfimides 177 and 148a

The behaviour of the thiane series **173**, **148b** and **148c** cannot, however, be rationalised in this manner. Although removing all possibility of 1,3-*syn* attractive interactions, as in **148c**, does result in the sulfimide adopting the equatorial form, the dithiane derivative **148b**, which does offer an opportunity for 1,3-interactions, also has an equatorial preference. More convincingly, examination of the crystal structure of the thiane derivative **173** suggests that N-H interactions cannot be responsible for its axial preference. Two geometries are found for **173**,[111] one is shown in **Figure 4.9**, neither of which has the nitrogen lone pair oriented for an attractive 1,3-interaction.



173

Figure 4.9 Orientation of nitrogen lone pair in the two geometries of sulfimide 173

We propose, therefore, that, although attractive *syn* 1,3-interactions may be responsible for the axial preference of the sulfimidyl bond in the thiolane series, this effect is not of significance in the thiane series.

4.2.3. Long range molecular orbital interactions

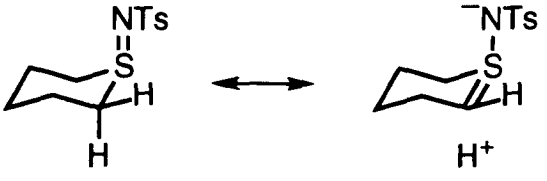
Zefirov concluded that long range molecular orbital interactions could be used to rationalise axial preferences in oxides of six-membered cyclic sulfides. However, we and others have observed axial preferences in five-membered sulfimide analogues, where these molecular orbital interactions can not be invoked. We therefore discount this explanation in the case of sulfimides.[119]

4.2.4 Special *gauche* effects

There is substantial evidence for the existence of two special *gauche* effects, namely (a) the attractive *gauche* effect and (b) the repulsive *gauche* effect.[120] We feel that most of the observations on conformational preferences of sulfimides can be rationalised by invoking these two effects as explained below.

4.2.4.1 The attractive *gauche* effect

It has been calculated that, when bond-bond interactions (either steric or electrostatic) are not too large, bond-antibond interactions can exert an effect on conformational preference.[121] The result is a tendency for polarised A-X bonds (where X is strongly electronegative) to lie *trans* to the best donor bonds (in this case C-H) to maximise the $\sigma_{CH} - \sigma^*_{AX}$ interaction. In the case of cyclic sulfimides this would result in an axial sulfimidyl bond, as the equatorial example would have the polar A-X bond *trans* to a C-C bond. This effect can be represented by a considering a contribution from the resonance form **180** (**Scheme 4.1**).



173 **180**

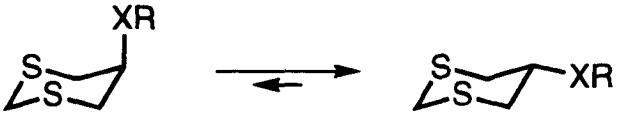
Scheme 4.1

The existence of an attractive *gauche* effect is an appealing explanation for the axial preference of sulfimidyl bonds, especially if the results from the group of Claus[111] are reexamined. As mentioned in Section 1 there is an increasing tendency for the sulfimidyl bond to be axial as the electron

demand of the *N*-substituent increases. This is consistent with the literature observations and calculations which show that the attractive *gauche* effect only applies when X in the A-X bond is highly electronegative. We conclude that increasing the electron demand of the *N*-substituent renders the nitrogen sufficiently electronegative for bond-antibond interactions to be important in determining the conformation.

4.2.4.2 The repulsive *gauche* effect

The repulsive *gauche* effect is observed when one or both *gauche* substituents have lone pairs in diffuse orbitals and is probably due, therefore, to repulsive overlap of these orbitals.[120] This effect has most frequently been measured in compounds which have sulfur containing substituents in vicinal sites, eg. **181**, or a sulfur vicinal to another heteroatom, usually oxygen, eg. **182 (Scheme 4.2).**[122] In these cases the preference for the equatorial conformer is much greater than would be predicted from conventional steric and electrostatic considerations.



181 X = S
182 X = O

Scheme 4.2

It is not surprising, then, to observe that the sulfimidyl bond has a strong equatorial preference in compounds **148b** and **148c**, as an axial orientation would place it *gauche* to one or two sulfur atoms, respectively. The apparent lack of a repulsive *gauche* effect in the dithiolane derivative **148a** is, however, puzzling. It may be that *syn* 1,3-attractive interactions, as discussed in Section 2, are more important in this case, but we can not exclude a perturbation due to crystal packing forces.

4.3 Conclusion

The unusual conformational preferences of sulfimides of six-membered cyclic sulfides can be satisfactorily explained by invoking so-called special *gauche* effects. The attractive *gauche* effect favours the axial conformer and becomes important with strongly electron demanding groups on nitrogen. Otherwise, conventional steric and electrostatic interactions, which favour the equatorial conformer, prevail. Even with strongly electron demanding groups on nitrogen, 3-thia analogues show a marked equatorial preference. This is a manifestation of the repulsive *gauche* effect which is due to interactions with the diffuse filled *3p* orbitals on sulfur.

The conformational preferences of sulfimides of five-membered cyclic sulfides require further investigation. Although the attractive *gauche* effect can be used to explain the axial preference, the reason for the apparent absence of a repulsive *gauche* effect in the dithiolane derivative **148a** remains unclear.

Finally, we remark that caution is required in extrapolating these conclusions to sulfoxide analogues where other combinations of interactions may be important.

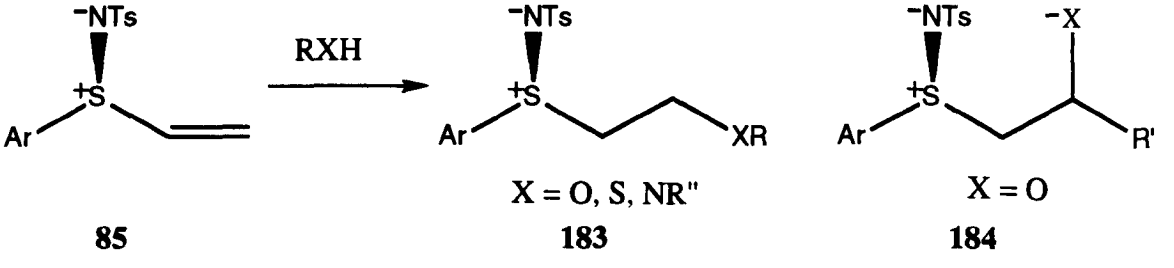
Chapter 5

Synthesis and reactions of vinyl sulfimides

5.1 Aim

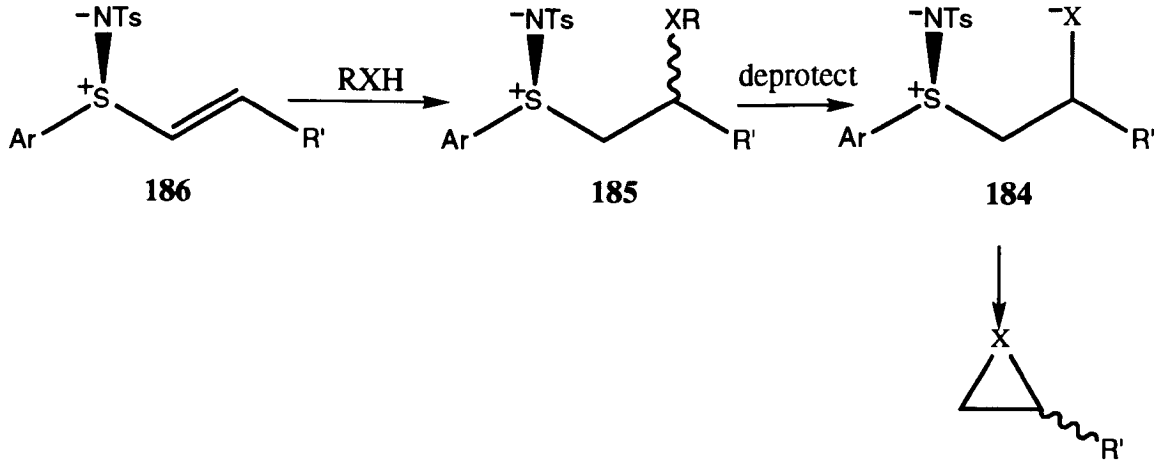
The chemistry of α,β-unsaturated sulfur$^{(IV)}$ and sulfur$^{(VI)}$ species was discussed in Chapter 1. Vinylic sulfoxides, sulfones and sulfoximides are all well known compounds that have been widely used, in particular in Michael-type addition and Diels-Alder reactions. Vinylic sulfimides are also known, but only as unsubstituted vinylic species.[53,54,123]

As the Michael-type additions of various nucleophiles to unsubstituted vinyl sulfimides **85** to yield adducts **183** had been reported (**Scheme 5.1**)[53,54] and the elimination from intermediates **184** to yield three-membered heterocycles is well known, as discussed in Chapter 1. We proposed to combine these two reactions to create a diastereoselective route to epoxides, aziridines and thiiranes (**Scheme 5.2**).



85 **183** **184**

Scheme 5.1



Scheme 5.2

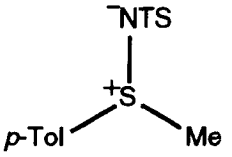
We hoped that the significant steric and electronic effects of the NTs group would lead to a reasonable diastereoselectivity in the formation of **185** from substituted vinyl sulfimides **186**. Our strategy thus required us to develop a synthesis of the previously unknown β-functionalised vinyl sulfimides **186** and to devise a method of removing R from **185** to generate **184**.

The synthesis of vinyl sulfimides will be discussed first, in **section 5.2**, followed by their reactions, in **section 5.3**.

5.2 Synthesis of vinyl sulfimides 186

5.2.1 Synthetic strategy

As the methods described in this chapter are intended for applications in asymmetric synthesis, we needed a route which allowed preparation of enantiomerically enriched vinyl sulfimides. For this reason we were restricted to sulfimide **65**, which is the only available enantiomerically pure sulfimide, as starting material (**Figure 5.1**). This led naturally to a choice of Wittig or Peterson type chemistry.



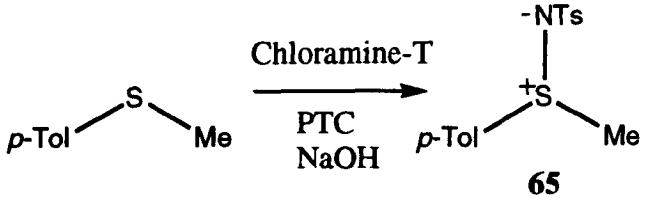
65

Figure 5.1 Structure of sulfimide 65

Vinyl sulfoxides, sulfoximides and sulfones have all been prepared by Wittig-type reactions. Of these routes, we selected the modified Wadsworth-Emmons approach used by Craig's group to prepare vinyl sulfoximides, as this method gave high yields and excellent *E*-selectivity.[124]

5.2.2 Results and discussion

Racemic *S*-methyl-*S*-*p*-tosyl-*N*-*p*-tosylsulfimide **65** was prepared, using a literature procedure,[125] from Chloramine-T and thioanisole under phase transfer conditions (**Scheme 5.3**).

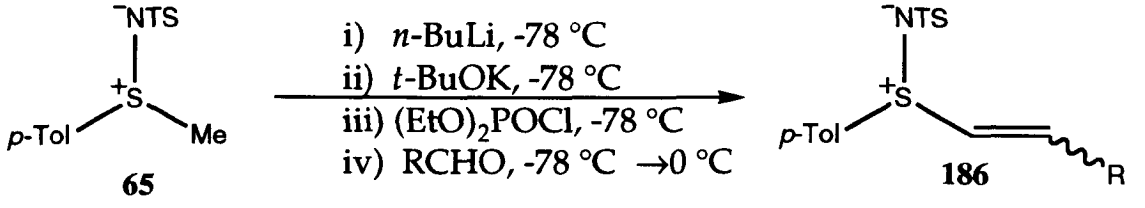


65

Scheme 5.3

The addition of two equivalents of base, one each of *n*-BuLi and KO*t*-Bu, to sulfimide **65**, followed by diethylchlorophosphate and aldehyde yielded vinylic sulfimides **186** in moderate yields, but good *E*/*Z* selectivities (**Scheme 5.4, Table 5.1**). Particularly impressive selectivities were observed with aldehydes possessing a bulky substituent R (**186e and 186f**). With benzaldehyde as electrophile, one reaction resulted in excellent *E*/*Z* selectivity (**186b 96:4**), but this result could not be repeated and the selectivity otherwise was good (**186b**). Using optically enriched sulfimide (14% ee), chiral shift ^{1}H NMR on *E*-styryl sulfimide using Pirkle's reagent indicated

that no racemisation of the chiral sulfur centre had occurred during the reaction (**186c, 16% ee**). This is a crucial result, as it demonstrates that optically pure sulfimide could be used to prepare optically pure vinyl sulfimides with no loss of optical activity.

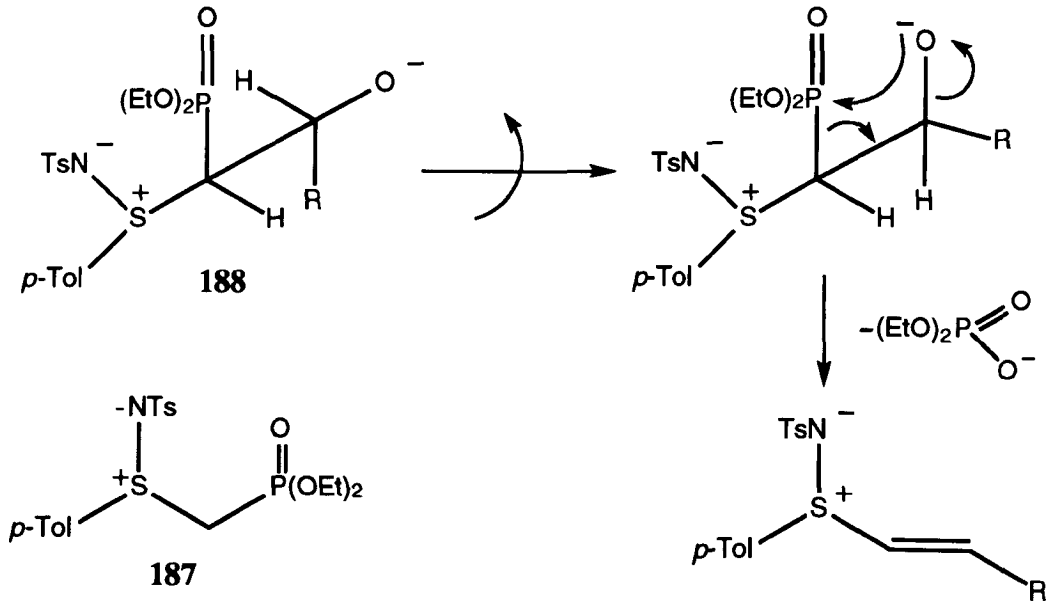


Scheme 5.4

Table 5.1 Yields and stereoselectivities of vinyl sulfimides 186

186	R	%Yield	*E*:Z
a	*p*-$MeOC_6H_4$	60	80:20
b	Ph	48	87:13
c	Ph	39	87:13
d	cyclopropyl	32	53:47
e	*t*-Bu	39	>98:2
f	*i*-Pr	64	>98:2

This reaction involves generation of *S*-[(diethylphosphonyl)methyl]-*S*-*p*-tosyl-*N*-tosyl sulfimide **187** *in situ*, followed by metalation and subsequent electrophilic attack by aldehyde. Elimination from betaine intermediate **188** is preceded by relief of the steric interactions between R and the sulfimidyl group, leading predominantly to *E*-vinyl sulfimides **186** (**Scheme 5.5**). The selectivities observed indicate that bulky R groups lead to excellent *E*-selectivity, in agreement with the mechanism illustrated in **Scheme 5.5**.



Scheme 5.5

The yields were somewhat disappointing. To address this problem, we tried changing one of the bases. We tried various mixtures of *n*-BuLi, sodium hydride and KO*t*-Bu, all to no avail, as the yields were at best the same. We also allowed the intermediate **187** to warm to higher temperatures (-78 °C to 0 °C and -78 °C to room temperature) before aldehyde addition, both with no effect. Also this intermediate was given longer at -78 °C before aldehyde addition (1 hr and 3 hrs), again with no improvement in yield. However, sufficient quantities of vinyl sulfimides **186** were obtained, although this reaction is currently under further review.

5.3 Reactions of β-functionalised vinyl sulfimides 186

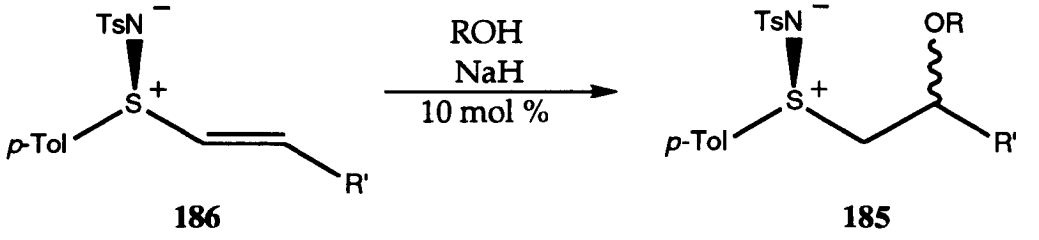
5.3.1 Review

Michael-type additions to unsubstituted vinylic sulfimides **85** are known to occur readily using amines, alcohols and thiols, as discussed in **Chapter 1**. In these examples, the β-carbon is an electrophilic, sterically unhindered site β to a chiral centre and so potentially under considerable chiral influence. It was hoped that substitution would not alter the steric characteristics of this

site dramatically, as nucleophilic additions may be hindered by bulky β-substituents.

5.3.2 Results and discussion

Using conditions developed by Yamamoto for nucleophilic additions to unsubstituted vinyl sulfimides,[54] we allowed three substituted vinyl sulfimides **186** to react with alcohols (ROH) and 10 mol% of sodium hydride to prepare adducts **185** (**Scheme 5.6, Table 5.2**).



186 **185**

Scheme 5.6

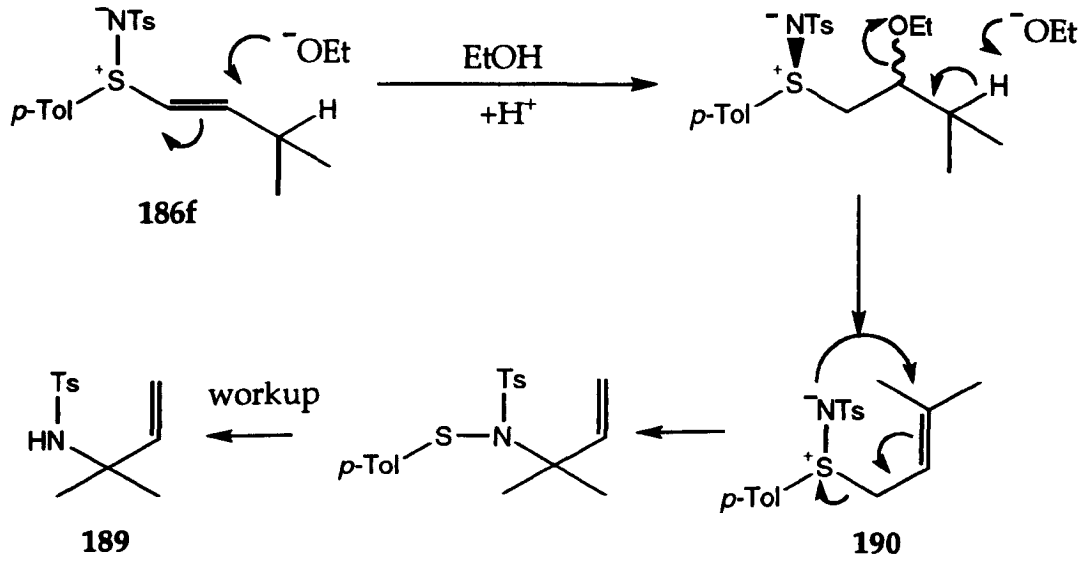
Table 5.2 Yields and diastereoselectivities for adducts 185

185	R'	R	Time d	%Yield	%de	mp. /°C
a	Ph	Et	7	85	80	127-129
b	Ph	$PhCH_2$	3	56	>95	146-148
c	*p*-$MeOC_6H_4$	Et	3	46	80	-
d	*t*-Bu	Et	-	-	-	-
e	*i*-Pr	Et	-	-	-	-

Good diastereoselectivities were observed, especially with benzylalcohol (**185a**), although the reaction was incomplete after three days, which accounted for the moderate yield. One recrystallisation of **185a** resulted in one diastereoisomer being observed by NMR. Knowing that optically enriched vinyl sulfimides are accessible (**Table 5.1, 186c**), a route through to

optically enriched adducts is therefore possible. This will then allow the preparation of optically enriched β-hydroxy sulfides (**section 5.3.4**), and potentially, optically enriched three-membered heterocycles, such as epoxides. No reaction occurred when the β-substituent was sterically demanding (**185d**) even after heating for several days, when decomposition of the vinylic sulfimide into a mixture of unidentified products resulted. ^{1}H NMR evidence only was obtained for adduct **185c**.

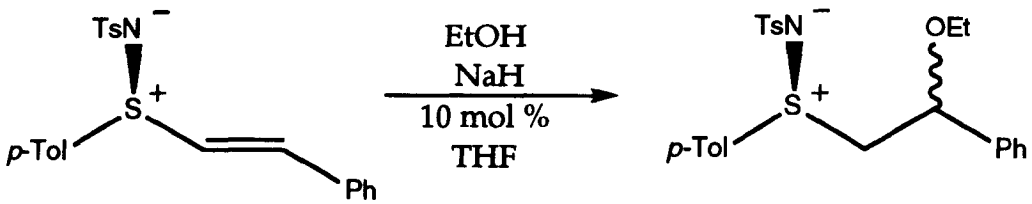
An interesting result was observed in the reaction of ethanol and sulfimide **185e**. No β-adduct was observed, but analytical evidence indicated the presence of, in particular, a mono-substituted alkene (^{1}H NMR) and a quaternary carbon (^{13}C NMR). Structural elucidation implied sulfenamide **189** had been formed. We propose that addition of ethoxide occurred followed by elimination of ethanol to give the allyl sulfimide **190**. Allyl sulfimides are known to undergo 2,3-sigmatropic rearrangements (**Scheme 5.7**).



Scheme 5.7

The limitation to the methodology at this stage was to cheap, volatile alcohols which act both as nucleophile and solvent. We hoped to move away from this restriction so as to widen the scope of the reaction. We therefore tried

using THF as solvent, with one equivalent of ethanol and a small amount of sodium hydride to generate sodium ethoxide(**Scheme 5.8**). However, exposure of sulfimide **186b** to these conditions resulted in no reaction at all, even after being left at room temperature for ten days. Heating the mixture resulted in a mixture of unidentified products. Even increasing the amount of ethanol to ten equivalents gave no product.

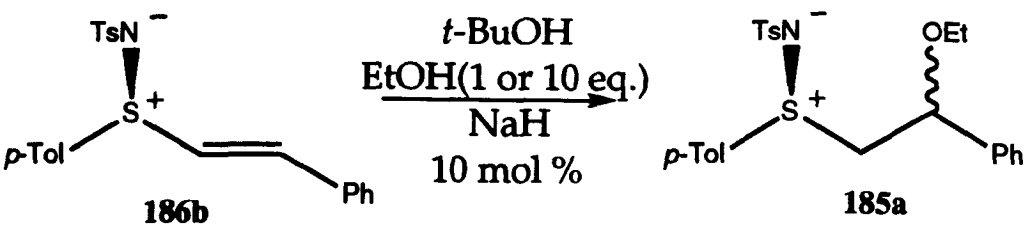


186a **185a**

Scheme 5.8

Other nucleophiles such as sodium cyanide, thiophenol and ethanethiol in THF gave no reaction at all at room temperature, with starting sulfimide recovered unchanged.

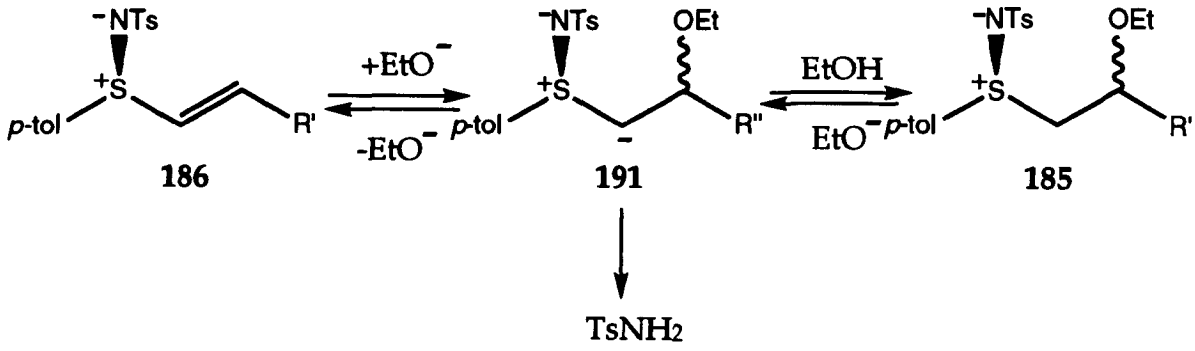
We speculated that a universal non-nucleophilic protic solvent may provide protons to the intermediate anion **191** (see **Scheme 5.10**) and therefore promote reactivity. We tried *t*-butylalcohol, which necessitated maintaining the reactions at about 30°C to prevent the alcohol from freezing. One reaction was attempted using sulfimide **186b**, one equivalent of ethanol and a small amount of sodium hydride and another under the same conditions, but with ten equivalents of ethanol (**Scheme 5.9**). Both reactions resulted in one identifiable product, namely tosyl amide, and recovered sulfimide **186b**.



186b **185a**

Scheme 5.9

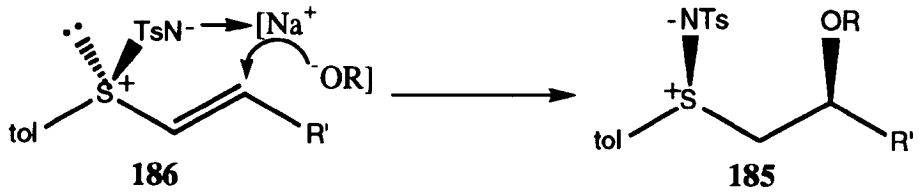
We suggest that the tosyl amide may have resulted from decomposition of intermediate carbanion **191** by analogy with some of our other work (**Scheme 5.10**). This implies that addition of a nucleophile had occured, although we have no other evidence for such an addition. We tentatively propose that the three species illustrated are in an equilibrium, which lies to the left. Excess amounts of ethanol would push the equilibrium to the desired adduct. Otherwise an alternative slow side reaction of anion **191** would result in the formation of tosyl amide.



Scheme 5.10

5.3.3 Stereochemistry of β-adducts 185

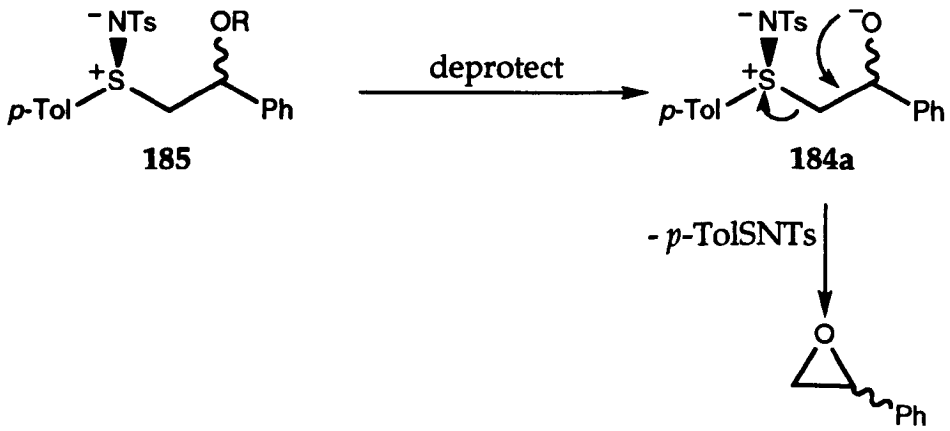
We have no evidence to support an assignment of the relative stereochemistry of adducts **185** at this stage. By analogy to the adducts obtained from additions of amines to vinyl sulfoxides as reported by Stirling and Pyne,[31,32] the *syn* diastereoisomer would be expected to be the preferred product. However, a tentative alternative to their proposals would involve coordination of the incoming alkoxide through the sodium counterion to the NTs group, and hence attack would occur from the same side of the alkene as the NTs group (**Scheme 5.11**). This would again lead to the *syn* diastereoisomer.



Scheme 5.11

5.3.4 Attempted conversion of β-adducts 185 to epoxides

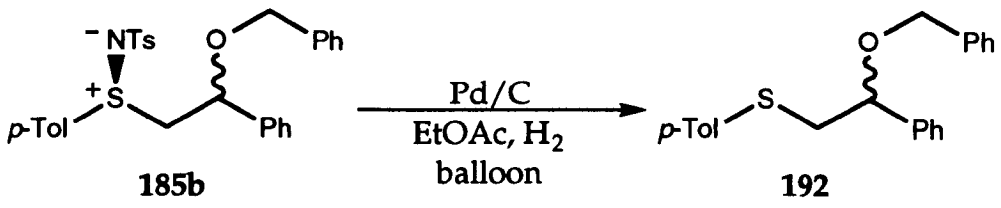
As mentioned above, we had envisaged conversion of adducts **185** to epoxides as being possilbe *via* the alkoxide, which by analogy with known methodology,[49] would undergo intramolecular displacement of a sulfenamide. A deprotection step was therefore needed to generate the alkoxide **184a** from adducts **185** (**Scheme 5.12**).



Scheme 5.12

Adduct **185a** was expected to be difficult to deprotect and so we undertook preliminary hydrogenation studies on benzyl alcohol adduct **185b**. Two catalysts were used, the first being palladium on carbon, which reduced the sulfimidyl group rather than the benzyl group, giving the β-(phenylmethoxy)sulfide **192** in good yield as well as a little unreacted sulfimide (**Scheme 5.13**). Palladium hydroxide gave a mixture of unidentified products. In both cases, ethyl acetate was used as solvent, because methanol

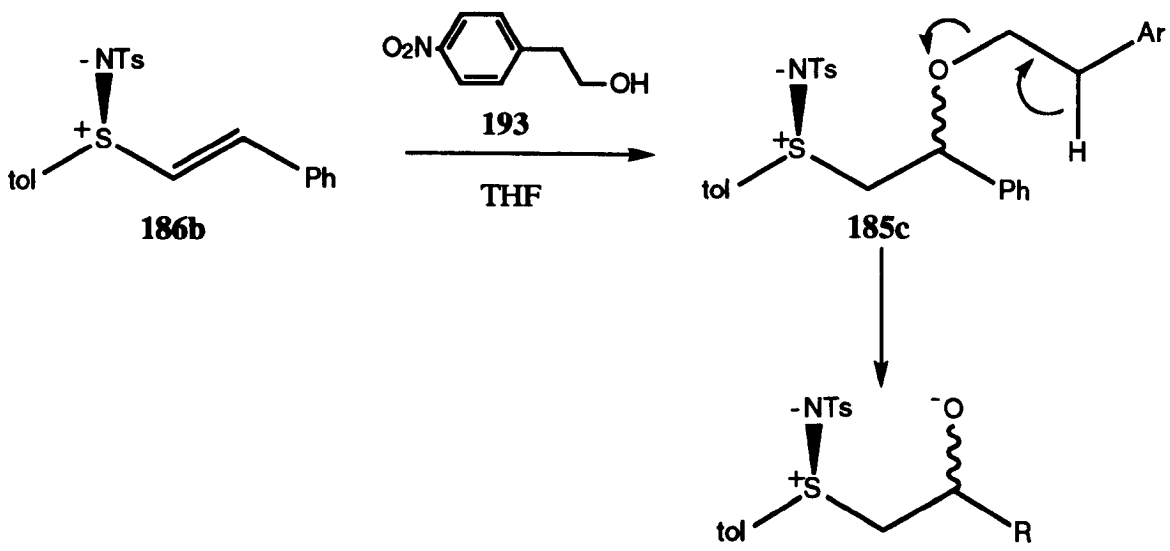
was expected to lead to elimination of benzyl alcohol and result in mixtures of alcohol adducts.



Scheme 5.13

The first reaction provides a route to chiral, non-racemic protected β-hydroxy sulfides (starting from enantiomerically enriched sulfimide). The deprotected β-hydroxy sulfides are under investigation as metaloselective chiral ligands.[126]

We had always suspected that benzyl would not be a suitable masking group for this strategy, due to the facile hydrogenolysis of sulfimides. The two other alternatives we had considered were the β–4-nitrophenylethyl and the 2,2,2-trichloroethyl groups. As expected from our other results, β–4-nitrophenylethanol **193** did not add to vinyl sulfimide **185b** to yield adduct **185c** (**Scheme 5.14**), as it could not be used as solvent.[127]



Scheme 5.14

Trichloroethanol, which could be and was used as solvent, also failed to react with sulfimide **186b**. This is consistent with the mechanism shown in **Scheme 5.10**. The equilibrium would lie even further to the left with the less nucleophilic trichloroethoxide.[128]

Our group has also observed amine additions to the sulfimides used above that proceed with similar yields and diastereoselectivities.

5.4 Summary

A new synthesis of β–substituted vinyl sulfimides **186** has been developed using a modified Wadsworth-Emmons procedure.[124] The yields are moderate, but the *E*-selectivities are good to excellent in all but one case. The addition of alcohols to these vinyl sulfimides afforded adducts **185** in good yields and good to excellent diastereoselectivities. The target epoxides have not yet been realised, but a new synthesis of protected β-hydroxy sulfide **192** has been achieved.

Further development is necessary if a diastereoselective synthesis of three-membered heterocycles is to be realised. In particular, there is a need to move away from the need for the alcohol to be the solvent as well as nucleophile. Furthermore, the subsequent adduct **185** should possess an ether linkage that is amenable to deprotection to the alkoxide, allowing cyclisation *via* elimination of sulfenamide. Extension of this methodology to amines, which is underway, and thiols would then give access to aziridines and thiiranes, respectively.

Chapter 6

Radical additions to chiral vinyl sulfimides

6.1 Introduction to intermolecular radical additions

The intermolecular addition of a carbon-centred radical to an alkene (or alkyne) (**Scheme 6.1**) is a highly favourable exothermic process. The formation of a new C-C bond (368 kJ mol^{-1}) outweighs the loss of a π C-C bond (~230 kJ mol^{-1}) thermodynamically. This reaction is reversible only in certain cases.[129]

Scheme 6.1

Carbon-centred radicals can be classified as ambiphilic, electrophilic and most common of all, nucleophilic, depending on the electronic contribution of substituents attached to the carbon radical.

6.1.1 Nucleophilic radicals

Frontier Molecular Orbital (FMO) theory can be used to rationalise orbital interactions for radical additions.[130] The Singly Occupied Molecular Orbital (SOMO) of a nucleophilic radical will combine with the Lowest Unoccupied Molecular Orbital (LUMO) of an alkene (**Figure 6.1**). Electron-withdrawing substituents attached to the alkene lower the LUMO and can therefore increase the rate of reaction.

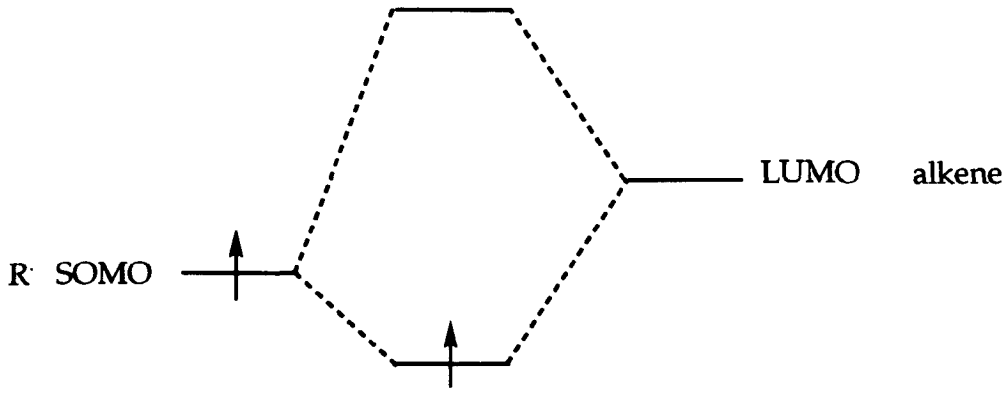
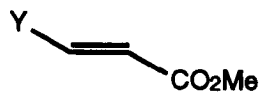


Figure 6.1 Representation of the relative energies of the SOMO of a nucleophilic radical and the LUMO of an alkene

The addition of alkyl substituents at the radical centre can increase the rate of addition to alkenes, despite the increased steric demand of the radical centre. The electron-donating alkyl substituents raise the energy of the SOMO, thereby increasing the rate of reaction.[131]

The most useful intermolecular radical addition is to the β-position of an activated alkene or alkyne. Substitution at the β-position of the alkene usually slows the rate of addition due to steric effects, as demonstrated by the influence of substituents Y on the rate of addition of cyclohexyl radical to acrylates **194** (**Table 6.1**).[132]



194

Table 6.1 Relative rates of addition of cyclohexyl radical to acrylates 194

Y	K_{rel}
CN	6.0
H	1.0
Me	0.01

The regioselectivity of addition is markedly affected by substitution at the β-position, in that as the β group gets larger, the tendency for addition at the α-position increases (**Figure 6.2**).[132]

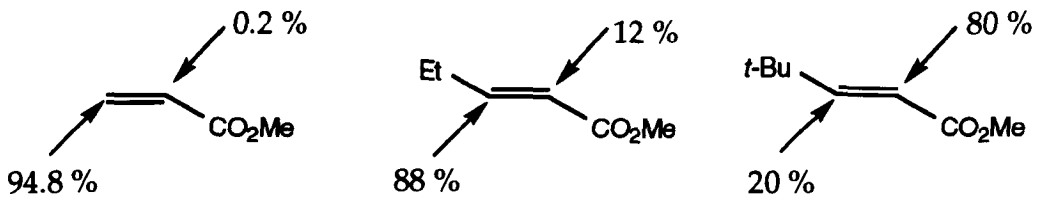


Figure 6.2 Regioselectivities of additions to β-substituted acrylates

Intramolecular radical additions, though a very important method of ring formation, are beyond the scope of this introduction.

6.1.2 Electrophilic radicals

Carbon-centred radicals possessing two electron-withdrawing substituents have relatively low-lying SOMOs and therefore require electron-rich alkenes that contain high energy HOMOs, for successful addition. The rate of addition of the malonyl radical **195** to substituted styrenes **196** illustrates this point (**Scheme 6.2, Table 6.2**).[133]

195 **196**

Scheme 6.2

Table 6.2 Relative rates of addition of malonyl radical 195 to styrenes 196

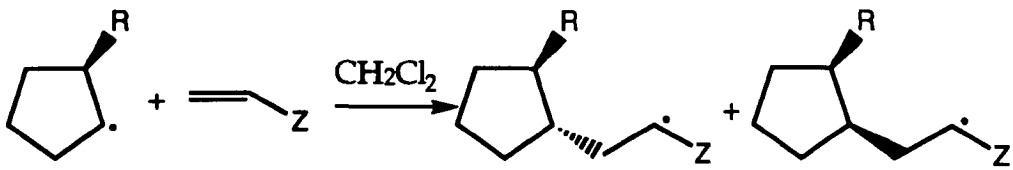
Z	K_{rel}
OMe	2.1
Me	1.0
CO_2Et	0.27

6.1.3 Ambiphilic radicals

Ambiphilic radicals have SOMO energies intermediate between that of nucleophilic and electrophilic radicals. They can add to both electron rich and electron poor alkenes.

6.2 Stereoselectivity of radical addition

Stereocontrol in radical additions is generally attained in two ways. The source of chirality can be present in the form of a chiral auxiliary on the alkene or within the radical species itself (chiral building block). The latter is illustrated by carbon-centred radicals that contain a chiral centre α to the radical. For example, cyclic radicals **197** exhibit a high degree of *trans* diastereoselectivity in the addition to activated alkenes (**Scheme 6.3, Table 6.3**).[134]



197

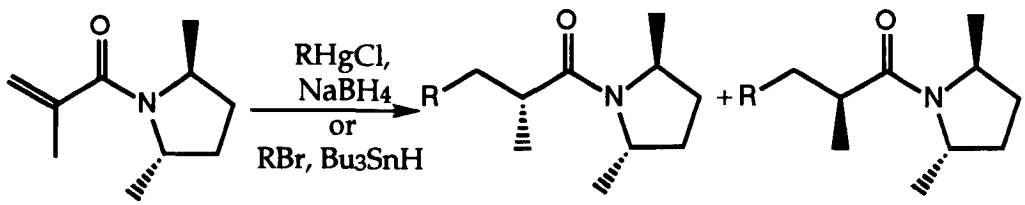
Scheme 6.3

Table 6.3 Diastereoselectivity of addition of cyclic radicals 197 to activated alkenes

Z	R	*antisyn*
Ph	OEt	90:10
CN	OEt	77:23
CN	Me	92:8

Chiral auxiliaries have led to considerable success in providing diastereoselective control in radical additions. For example, Giese has

demonstrated that radical additions to methylacrylamides **198**, followed by trapping of the intermediate radical, proceed with high diastereoselectivities (**Scheme 6.4**).[135]



198

R = t-Bu **90 : 10**
R = Me **67 : 33**

Scheme 6.4

6.3 Methods of generating radicals

6.3.1 Initiators

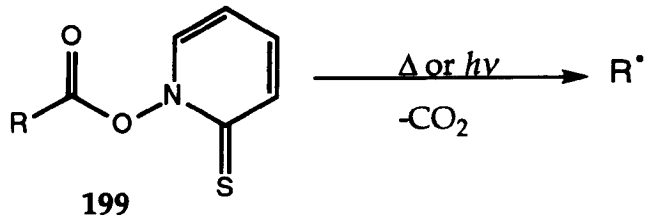
Initiators are often needed to set-off a radical reaction. Thermolytic or photolytic homolysis of a chemical initiator, such as a peroxide or an azo compound, for example 2,2'-azobisisobutyronitrile (AIBN), are the usual methods for initiating a radical reaction.

6.3.2 Tin hydrides

Tin hydrides, such as tributyl tin hydride, are the most common reagents used to propagate radical chain reactions. AIBN is required to initiate the reaction, then the Bu_3Sn radical acts as the chain carrier.[136]

6.3.3 Barton method

The homolysis of thiohydroxamate esters **199** either photolytically or thermally was developed by Barton, and gives access to primary, secondary and tertiary radicals (**Scheme 6.5**).[137]

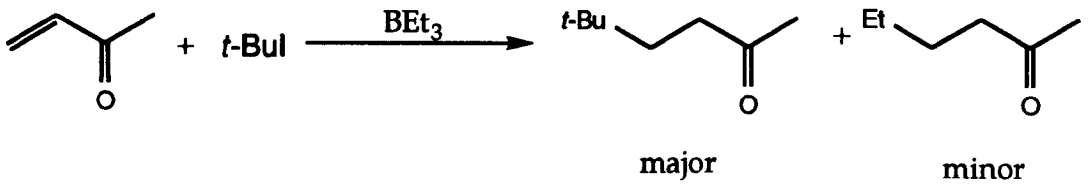


199

Scheme 6.5

6.3.4 Borane method

Alkyl radicals can also be generated from trialkyl boranes and alkyl iodides (**Scheme 6.6**). The minor product arises from ethyl radical addition to the unsaturated ketone.[138]



major minor

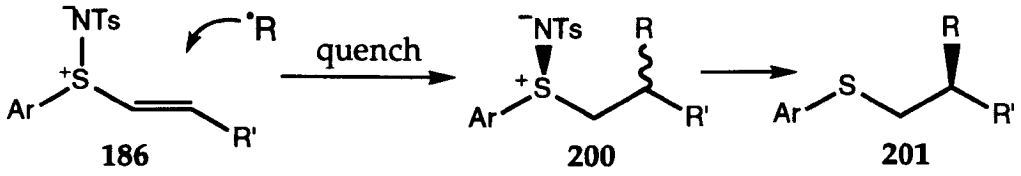
Scheme 6.6

6.3.5 Carbon hydrides

Due to the strength of the C-H bond, only activated bonds such as those adjacent to carbonyl groups and heteroatoms are capable of sustaining a radical chain process

6.4 Strategy

Following the success of our Michael-type additions of alcohols to β-functionalised vinylsulfimides **186**, we proposed to investigate radical additions to these compounds to prepare adducts **200**. We hoped that C-C bond formation, as opposed to C-X (X = O, N) bond formation described in Chapter 5, would occur diastereoselectively (**Scheme 6.7**).



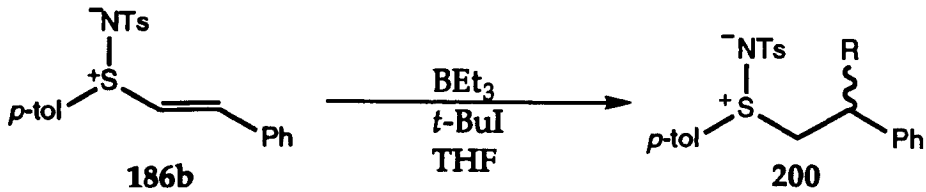
Scheme 6.7

Using similar reductive methodology as proposed in Chapter 5, removal of the sulfimidyl group would allow access to homochiral sulfides **201** (if the starting vinyl sulfimide was optically pure).

6.5 Results and discussion

6.5.1 Preparation of 2-*E*-styryltetrahydrofuran 202

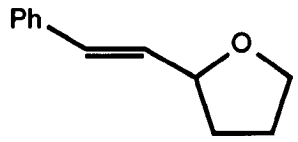
The tin hydride and mercuric halide[139] mediated radical generating methods were considered unsuitable in our case, because of the susceptibility of sulfimides to reduction under these conditions. Therefore, the most suitable method of radical generation was considered to be the alkyl borane method, as the radical addition could then be performed at room temperature, thereby discounting any possibility of thermal racemisation of the chiral sulfur centre. Therefore, vinyl sulfimide **186b** was allowed to react with triethylborane and *t*-butyl iodide in THF at room temperature (**Scheme 6.8**).



Scheme 6.8

Consumption of the vinyl sulfimide was monitored by tlc, and on completion of the reaction, quenching with 10% disodium hydrogenphosphate and ethereal work-up, followed by evaporation gave a pale yellow oil. Analysis by NMR revealed resonances attributable to an *E*-substituted alkene, not the

expected alkyl spin system of the adduct **200**. Mass spectroscopic analysis gave a considerably lower than expected molecular ion (m/z = 174), from which we deduced that no sulfur atoms were present (insufficient M+2). Further analysis by NMR (COSY and DEPT) enabled assignment as 2-*E*-vinyltetrahydrofuran **202** (**Figure 6.3**).

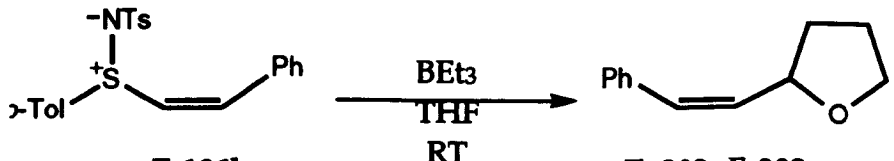


202

Figure 6.3 Structure of 2-*E*-stryryltetrahydrofuran 202

As no *t*-butyl substituted adducts were observed using the standard borane-mediated radical generating conditions used above, we investigated the reaction of triethylborane with vinylsulfimide **186b** in THF (**Scheme 6.8**, except no *t*-butyl iodide). We reasoned that the *t*-butyl radical would be too sterically hindered to add to our styryl group, and so we hoped that ethyl radicals would undergo the addition, if just triethylborane was present. However, compound **202** was isolated, as was the case with the triethylborane and *t*-butyl iodide reaction (**Scheme 6.8**).

To investigate if the geometry of the starting vinyl sulfimide was reflected in the product alkene, we reacted *Z*-vinyl sulfimide **Z-186b** with triethylborane under the same conditions as used for the *E*-isomer (**Scheme 6.9**). A mixture of *E*:*Z* isomers (13:87) was formed, with no ethyl radical adducts present in the product mixture. This reaction was repeated, with the same selectivity being observed.

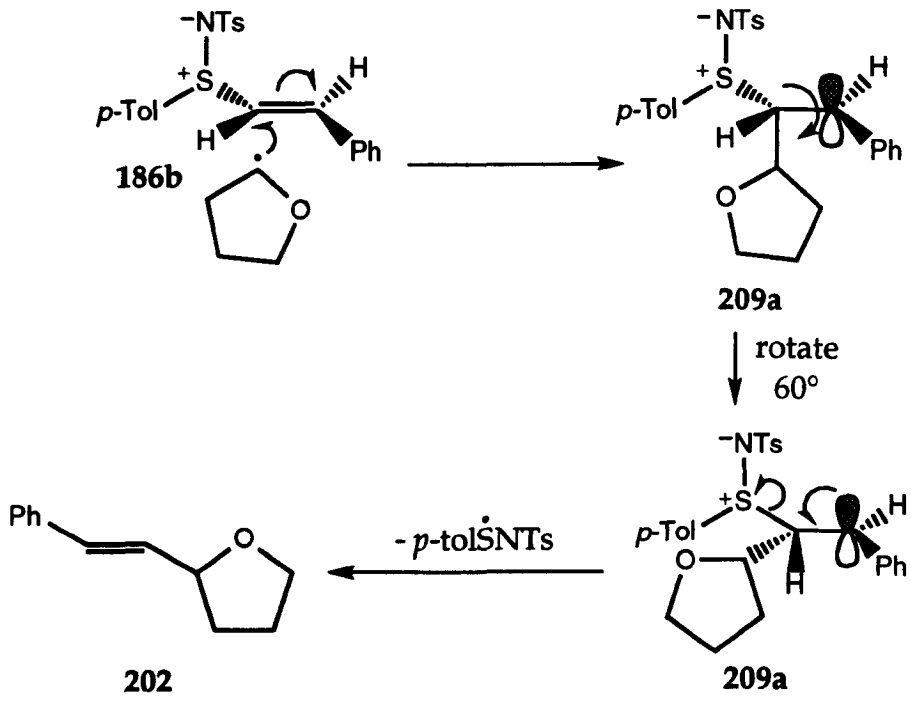


Z-186b → **Z-202: E-202** 87:13

Scheme 6.9

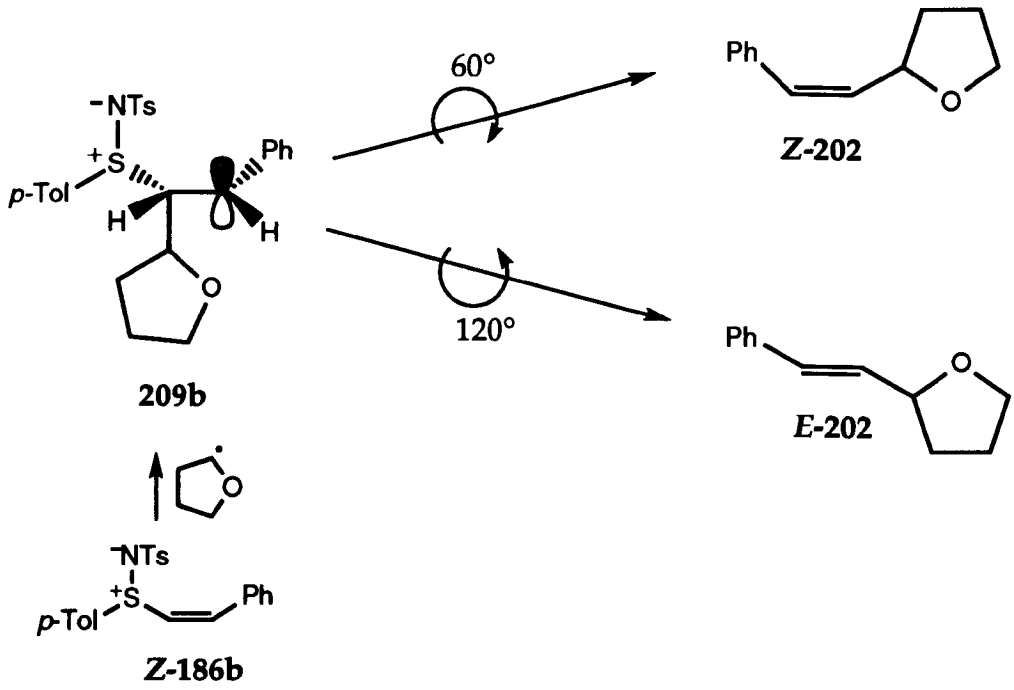
6.5.2 Mechanistic considerations

From the structures of products *E*- and **Z-202**, it was clear that THF, or a derivative, must have been involved in the mechanism. We propose a Michael-type addition mechanism of a THF radical to sulfimide **186b** to account for the above observations (**Scheme 6.10**).



Scheme 6.10

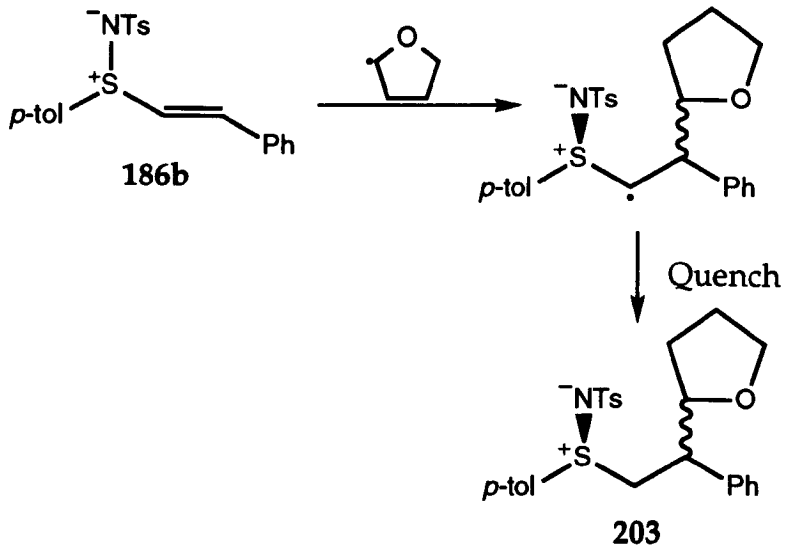
There is literature precedent for the Michael-type addition of THF radicals to alkynes, giving 2-vinyl- and 3-vinyl tetrahydrofuran products.[140] Our proposal involves the Michael-type addition of a THF radical to the electron deficient styrene derivative, ie. α-addition to the vinyl sulfimide **186b**. With the *E*-substrate, subsequent steric relief by rotation of 60° around the C-C bond in intermediate **209a** followed by elimination would give *E*-alkene **202**.



Scheme 6.11

Similarly, Z-vinyl sulfimide **Z-186b** would give Z-styryl tetrahydrofuran **Z-202** predominantly (**Scheme 6.11**). Invoking the principle of least motion would favour formation of Z-alkene **Z-202** (60°) whereas E-alkene **E-202** is disfavoured (120°). Competition between the two rotations would result in a mixture of products, with the kinetic product predominating in this case.

Other radical mechanisms are also possible in principle. Supposing that a THF radical attacked vinyl sulfimide **186b** in a Michael-type addition in the manner we hoped for as described in the strategy (**6.4**), adduct **203** would be a possible product (**Scheme 6.12**).

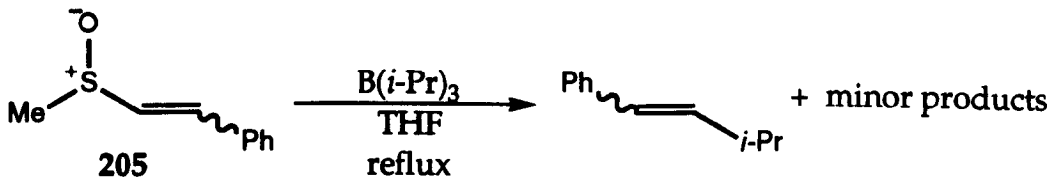


Scheme 6.12

Alkene generation from adduct **203** is then in principle possible, if triethylborane acts as a Lewis acid, promoting elimination of sulfenamide **74a** (**Scheme 6.13**). This route would give a geminally disubstituted alkene **204**. However, this compound was not observed in the product mixtures by NMR.

Scheme 6.13

There is literature evidence for both an ionic mechanism and a radical mechanism involving trialkylboranes, which have been proposed to explain the results of the reactions of styryl sulfoxides (**Scheme 6.14**) and styryl sulfones with boranes in THF.[141]



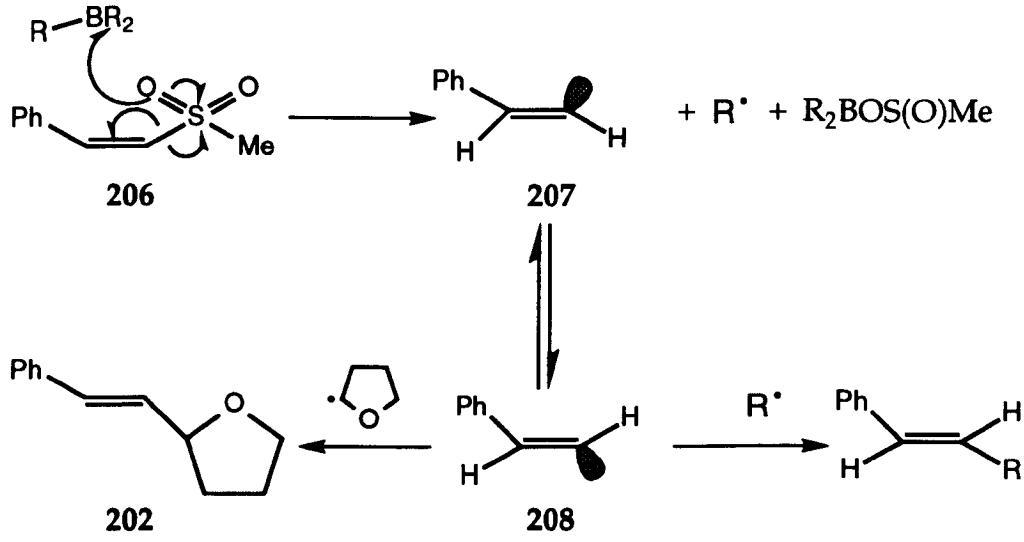
Scheme 6.14

With *E*-vinyl sulfoxide **205**, exclusively *E*-alkene was isolated, whereas a mixture of *E*:*Z* (1:1.8) isomers was generated from *Z*-vinyl sulfoxide **205**. The result for the *Z*-vinyl sulfoxide **205** was rationalised using an ionic mechanism (**Scheme 6.15**).

205

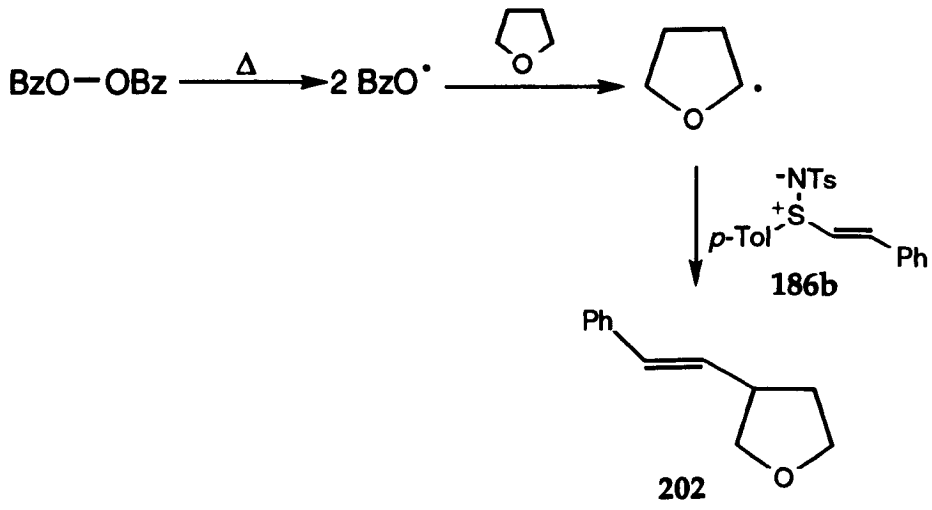
Scheme 6.15

With methyl *E*- or *Z*-styryl sulfone **206**, exclusive *E*-alkene formation resulted (**Scheme 6.16**). The sulfone chemistry was explained using a radical mechanism, which also explained the formation of *E*-product in the sulfoxide case, as here, competition from the two mechanisms would account for the mixtures observed. Exclusive *E*-product formation would result from equilibration between the sterically-hindered *Z*-vinyl radical **207** and the more reactive *E*-isomer **208**. One of the minor products observed was vinyl tetrahydrofuran **202**. A mechanism similar to the one proposed by us (**Scheme 6.10**) was rejected because methyl styryl sulfide, which is more electron rich than the methyl styryl sulfoxide **205**, failed to react with triethylborane. We instead ascribe this observation to coordination of the sulfide to the electron deficient borane.



Scheme 6.16

Before postulating a radical mechanism to explain the formation of alkene **202**, we had to rule out the possibility of a non-radical mechanism, such as the ionic mechanism illustrated above (**Scheme 6.15**). A more traditional method of radical generation was needed, so we used benzoyl peroxide in refluxing THF (**Scheme 6.17**).

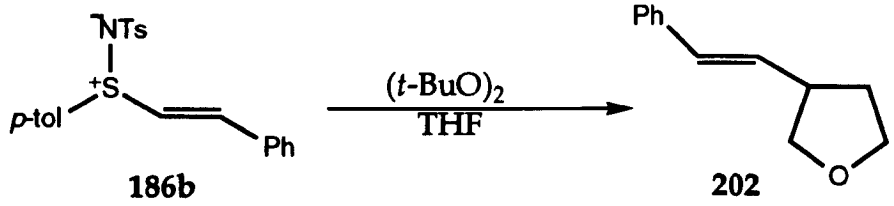


Scheme 6.17

Exclusively E-alkene **202** was isolated by distillation of the crude yellow oil (63%) obtained after concentration of the reaction mixture under reduced pressure. Under the same conditions (**Scheme 6.17**), Z-vinyl sulfimide **Z-186b** gave a ratio of *E*:Z isomers of **202** which was found to be inconsistent when the reaction was repeated. We can not confidently report a reaction time and

ratio of products observed after this time (this aspect of the work is currently under further investigation).

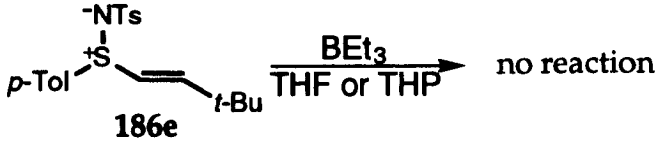
Further evidence for a radical-based reaction was obtained from reacting sulfimide *E*-**186b** with *t*-butylperoxide in an autoclave (50 atm, 150°C), from which E-alkene **202** was isolated in better yield (77%) (**Scheme 6.18**).



186b **202**

Scheme 6.18

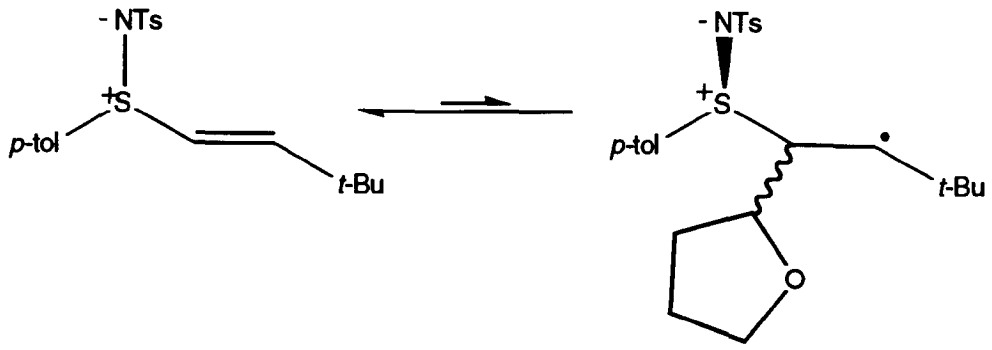
We decided to change the alkene aryl substituent to an alkyl substituent to investigate if changing the stereoelectronic and steric characteristics of this site would affect the product distribution. Therefore, vinyl sulfimide **186e** was reacted with triethylborane in both THF and THP (**Scheme 6.19**).



186e

Scheme 6.19

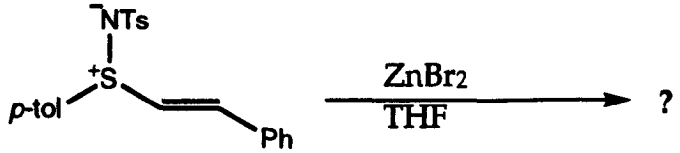
Steric hindrance of the α-position (to the sulfimide) by the *t*-butyl group is unlikely, as even the steric requirements of this bulky group are unlikely to prevent an addition reaction at this site. The electronic characteristics of the β-vinyl carbon are also different in sulfimide **186e** to sulfimide **186b**. The intermediate **209a** is a benzylic radical species and therefore stabilised in relation to the corresponding intermediate **209b** which would arise if sulfimide **186e** reacted in the same way. The addition may be reversible and as the *t*-butyl group would not provide stabilisation relative to the benzylic species **209a**, the equilibrium would lie to the left (**Scheme 6.20**).



186e **209b**

Scheme 6.20

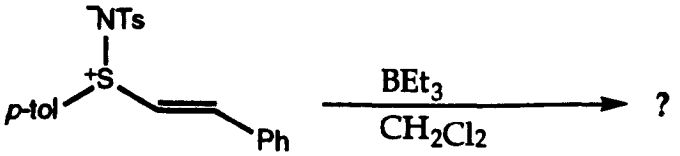
At this stage, we had not exposed any of the vinyl sulfimides **186** to truly ionic conditions. Therefore, we decided to investigate the stability of sulfimide ***E*-186b** to Lewis acid conditions, which we hoped would encourage an ionic mechanism. Thus, we exposed sulfimide ***E*-186b** to zinc bromide in THF (**Scheme 6.21**). No reaction occured after 7 days, with sulfimide ***E*-186b** recovered. This implied that sulfimide ***E*-186b** was unreactive under these conditions.



186b

Scheme 6.21

We also needed to establish whether sulfimide ***E*-186b** was reactive towards triethylborane in a non-radical precursor solvent. Therefore, sulfimide ***E*-186b** was stirred in CH_2Cl_2 and triethylborane for 7 days (**Scheme 6.22**). No reaction occured with sulfimide ***E*-186b** recovered unreacted.

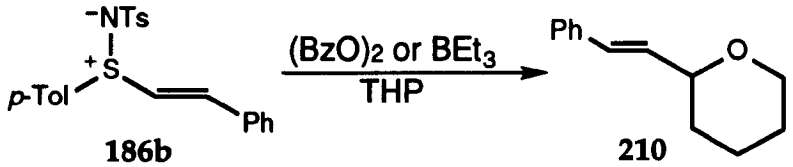


186b

Scheme 6.22

6.5.3 Preparation of 2-*E*-styryltetrahydropyran 210

We then considered attempting to extend the scope of the reaction from five-membered heterocycles to tetrahydropyran derivatives. Using the same conditions, but with tetrahydropyran as solvent, with either triethylborane or benzoyl peroxide as mediator, alkene **210** was prepared in good yield (**Scheme 6.23**).

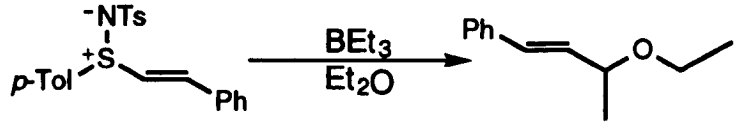


186b **210**

Scheme 6.23

6.5.4 Preparation of styryl derivative 211

We only have ^{1}H NMR evidence for an acyclic version of this reaction, using ether as solvent to prepare alkene **211** (**Scheme 6.24**).

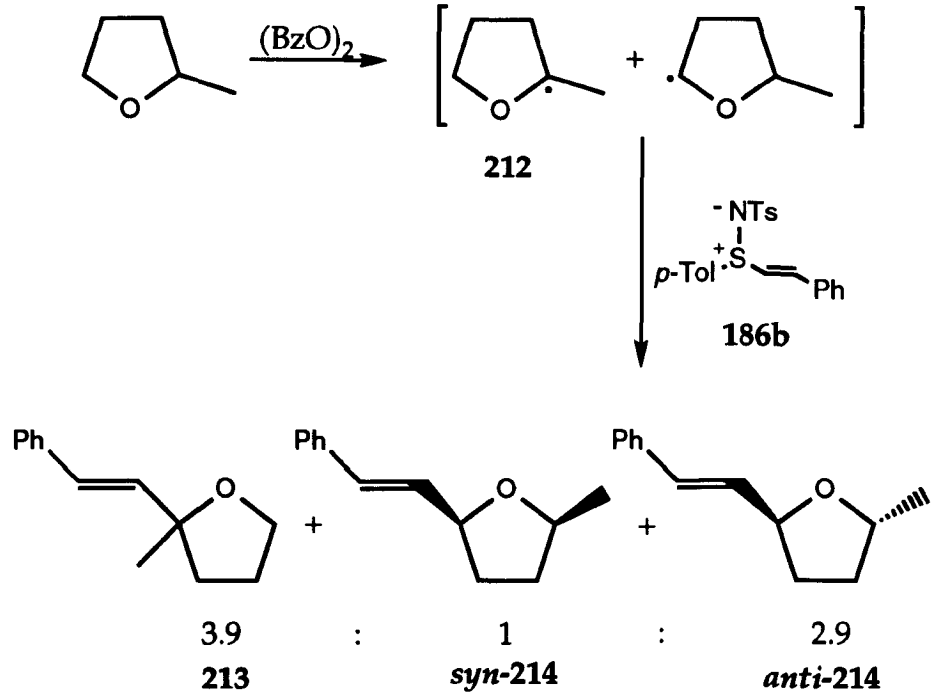


186b **211**

Scheme 6.24

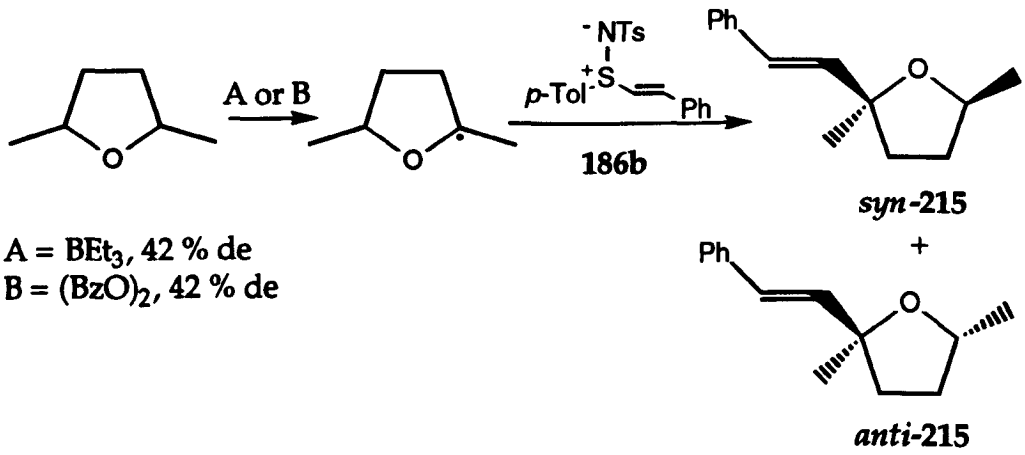
6.5.5 Preparations of other THF derivatives

With 2-methyltetrahydrofuran as radical precursor, we were able to study regioselectivity of the radical addition, although the regioselectivity is dependent on radical stability, which in this case should favour the more stable tertiary radical **212** (**Scheme 6.25**).



Scheme 6.25

The overall ratio of 2°:3° radical adducts **213:214** was 1:1, which implies that the more stable tertiary radical **212** was sufficiently sterically encumbered to allow the less stable secondary radical to react. The diastereoselectivity was good (50%, 1:2.9, ***syn*-214**:***anti*-214**). The assignment of the major diastereomer was determined by overnight nOe NMR experiments as being the ***anti*-214**, as expected due to steric interactions between the vinyl and methyl groups. To further investigate the diastereoselectivity of this reaction, we used 2,5-dimethyltetrahydrofuran as radical precursor (**Scheme 6.26**).

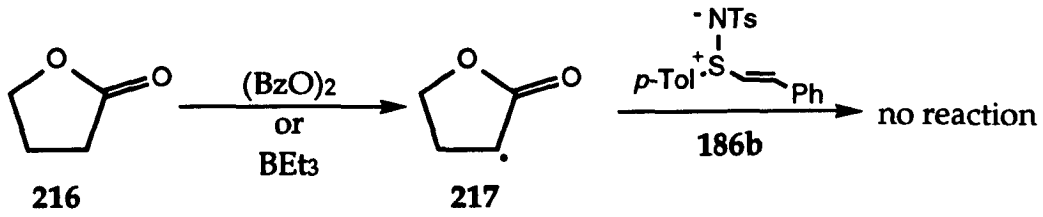


Scheme 6.26

Both methods (A and B) gave reasonable yields and diastereoselectivities. The major diastereomer was presumed to be ***anti*-215**, by analogy with the 2-methyltetrahydrofuran reaction, although we have no NMR evidence to support this analogy. The fact that both reagents (triethylborane and benzoyl peroxide) gave the same diastereoselectivity, gives further support to our conclusion that both reagents react by the same mechanism.

6.5.6 Attempted electrophilic radical additions to vinyl sulfimide 186b

The reaction of γ-butyrolactone **216** with either triethylborane or benzoyl peroxide and sulfimide **186b** resulted in **186b** being recovered unchanged (**Scheme 6.27**). This was as expected as the vinyl sulfimide **186b** is an electron deficient alkene, and therefore unlikely to react with electrophilic radicals such as **217**.

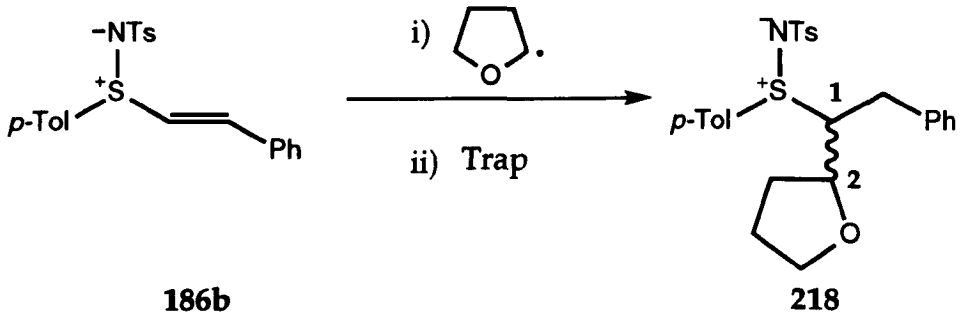


Scheme 6.27

6.5.7 Attempted trapping of the radical intermediate 209a

6.5.7.1 As adducts 218

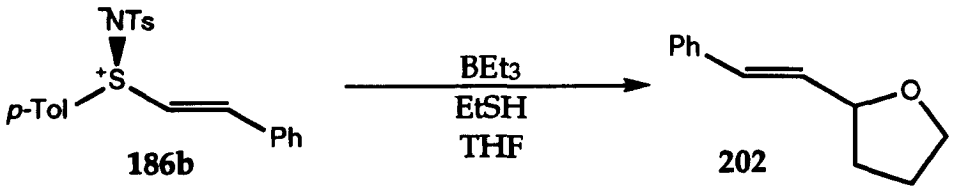
The diastereoselectivity of radical addition to vinyl sulfimide ***E*-186b** could only be assessed if we could trap out the intermediate **209a**, to allow isolation of the adducts **218** (**Scheme 6.28**). The chirality of the sulfimide group may only affect chiral centre **1** in adduct **218**, with chiral centre **2** affected by the radical itself. Also, trapping out **218** may give more evidence to support one or other of the mechanisms.



186b **218**

Scheme 6.28

Our first attempted trapping reactions involved using ethanethiol as a hydrogen source, in the presence of vinyl sulfimide **186b**, triethylborane and THF. Unfortunately, alkene **202** was still generated in reasonable yield (**Scheme 6.29**).

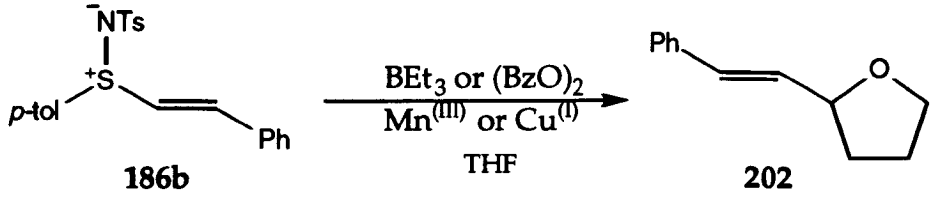


186b **202**

Scheme 6.29

6.5.7.2 As oxidised or reduced derivatives

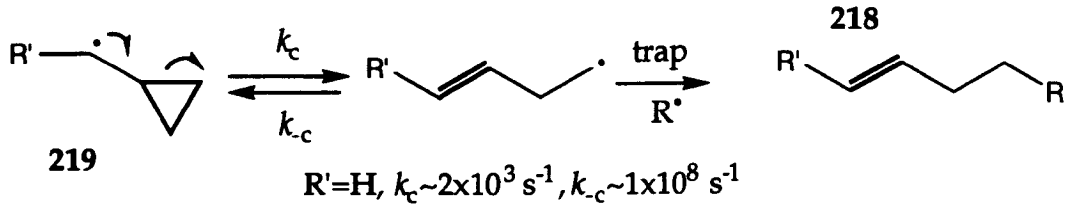
Reduction of radical intermediate **209a** was thought impractical in the presence of the readily reduced sulfimide group. Oxidation of the radical to a cation was therefore an option. Copper$^{(I)}$ and manganese$^{(III)}$ salts are known to oxidise radicals,[142] so two complementary sets of reactions were studied. Vinyl sulfimide **186b**, triethylborane and both manganese$^{(III)}$ acetate and copper$^{(I)}$ chloride were used in turn, in THF as solvent at room temperature (**Scheme 6.30**). In both cases, alkene **202** was prepared in reasonable yield. Under the same conditions, but using $(BzO)_2$ in refluxing THF, the same results were observed(**Scheme 6.30**).



Scheme 6.30

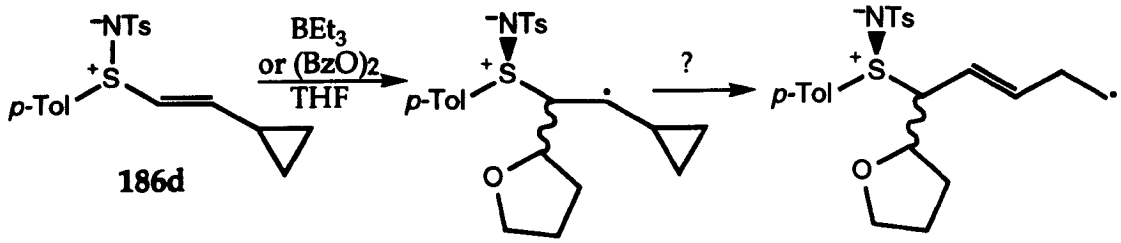
6.5.7.3 As an isomerised derivative

The isomerisations of radical species of the type **219** shown below are known (**Scheme 6.31**).[143]



Scheme 6.31

We therefore proposed to allow radical additions to *E*- and *Z*-vinyl sulfimide **186d** and to investigate if the elimination or the isomerisation was the more favoured process (**Scheme 6.32**).

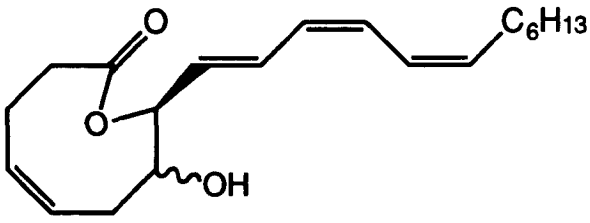


Scheme 6.32

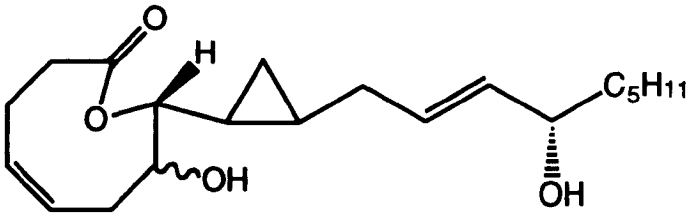
An unidentified mixture of products was found in both cases. There was no evidence for starting material, adducts or isomerised products by NMR or mass spectroscopic analysis.

6.5.8 Preparation of 9- and 10-membered lactones

Medium ring lactones are important natural products.[144] In particular, the marine metabolites such as halicholactone and ascidiatrienolide A and B are 9-membered lactones that have attracted much interest, as they are bioactive compounds (**Figure 6.4**).[145] Taylor has developed a new route to 9-membered lactones using vinyltetrahydrofurans[145] in a variation of the Malherbe-Bellus reaction.[146]



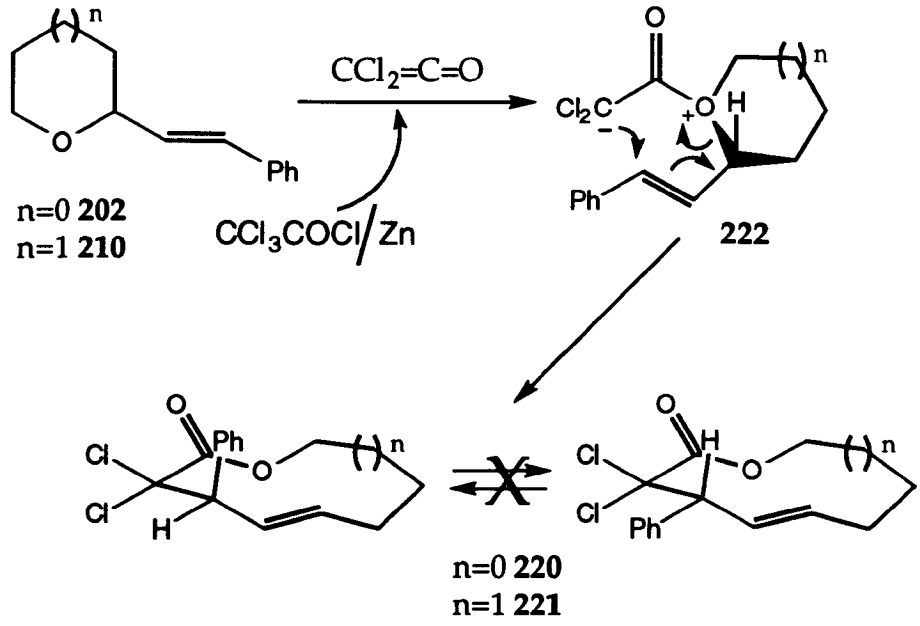
Ascidiatrienolide (A=α-OH, B=β-OH)



Halicholactone

Figure 6.4 Proposed structures of marine metabolites ascidiatrienolide and halicholactone

We considered expanding the range of lactones available by allowing 2-*E*-styryltetrahydro-furan ***E*-202** and -pyran ***E*-210** to react under Taylor's conditions (**Scheme 6.33**), enabling isolation of the corresponding new lactones **220** and **221**, respectively, in the conformer ratios and yields given in **Table 6.4**. The conformers were found not to interconvert at room temperature, a result also observed by Taylor.[145]



Scheme 6.33

Table 6.4 Conformer isomer ratios and yields of lactones 220 and 221

n	lactone	*eq:ax*	yield
0	**220**	85:15	23
1	**221**	>98:2	60

Activated zinc and trichloroacetylchloride form dichloroketene *in situ* , which is then attacked by the oxygen of the oxa-heterocycle. The reactions are thought to proceed *via* a six-membered transition state **222** in which the phenyl group would prefer to be equatorial, as observed by NMR in the conformer isomer distributions.

6.6 Summary

A new, synthetically versatile reaction of vinyl sulfimides **186** allows access to 2-vinyl substituted THF **202, 213, 214** and **215** and THP **210** compounds. If triethyl borane is used to mediate the reactions, then a high degree of stereocontrol is attained. *E*-Vinyl sulfimide ***E*-186b** stereospecifically gave the *E*-alkene **202** and *Z*-vinyl sulfimide ***Z*-186b** undergoes the reaction giving the

Z:*E* isomers of **202** in good stereoselectivity (87:13). With benzoyl peroxide, *E*-vinyl sulfimide ***E*-186b** gave exclusively *E*-alkene **202**, whereas ***Z*-186b** gave unrepeatable results. A radical mechanism is proposed to explain the α-addition products, but if both the triethylborane and benzoyl peroxide mediated reactions proceed *via* the same mechanism, then the same selectivities should be observed. At this stage, we can not rule out an ionic mechanism as an alternative, as such a mechanism may explain the different selectivities we observed.

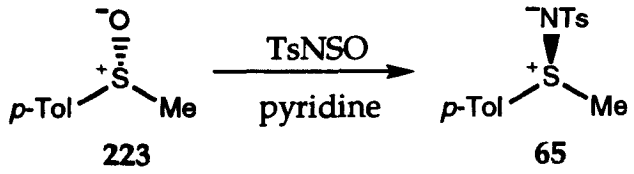
Future work would involve using enantiomerically enriched vinyl sulfimides, which we know are available (**Chapter 5, Table 5.1, 186c**), to investigate if enantiomerically enriched vinyl oxa-heterocycles and 9- and 10- membered lactones can be prepared. Also, further investigations into the stereoselectivity of the benzoyl peroxide mediated reaction of Z-vinyl sulfimide**Z-186b** may lead to a more satisfactory conclusion regarding the mechanism of these addition reactions.

CHAPTER 7

Asymmetric synthesis of sulfimides

7.1 Introduction

In chapters 5 and 6 we have described new methods for the preparation of chiral β-*O*-alkyl sulfides, such as **201**, which are precursors to β-hydroxy sulfides, and vinyl oxa-heterocycles **202** and **210**, as well as the first steps towards enantiomerically pure epoxides, aziridines and thiiranes. These routes have been designed to exploit the only available enantiomerically pure sulfimide **65**.



223 **65**

Scheme 7.1

However, our group has found that the procedure described by Cram for conversion of sulfoxide **223** to sulfimide **65** (**Scheme 7.1**)[43] gave inconsistent yields and enantiomeric purities.[148] In addition, enantiomerically pure sulfoxide **223** is rather costly.

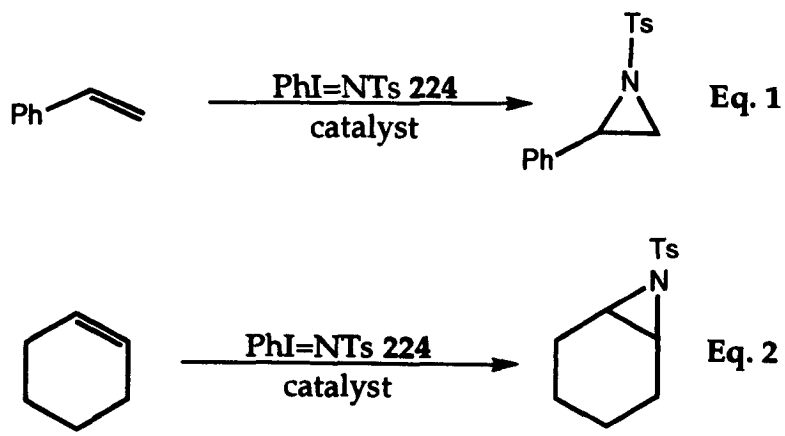
We decided to attempt to develop an asymmetric synthesis of sulfimide **65** which is:

- inexpensive.
- high yielding.
- highly enantioselective.
- applicable to the synthesis of a wide range of chiral sulfimides.

7.2 Strategy

We speculated that sulfimidation by *in situ* nitrene generation in the presence of a sulfide and a metal catalyst (**Chapter 1, Scheme 1.32**)[36] should be amenable to asymmetric modification. We hoped that use of a chiral metal complex to catalyse nitrene generation would enable sulfimidation to occur within the chiral influence of the ligand.

This approach was inspired by the work of Jacobsen, Evans and Masamune on asymmetric aziridation chemistry using chiral metal catalysts.[149] As so little is known regarding the intermediates involved and the mechanism of sulfimide formation from nitrenes in our proposed methodology, we had to work by analogy to related methodology. The study by Evans on asymmetric aziridation was particularly useful.[149b] They found that copper(I) catalysts gave optimal yields in aziridinations of alkenes with *N-p*-tosyliminophenyliodinane (PhI=NTs) **224** as nitrene precursor (**Scheme 7.2**). Copper(I) perchlorate, copper(I) triflate and copper(II) triflate all gave superior yields (>90 %, equation **1** and 75 %, equation **2**) compared to the salts of the other metals tried.



Scheme 7.2

Evans' results, along with Horak's observation that both copper(I) acetyl acetonate and copper(I) phthalocyanin could both catalyse the thermal nitrene generation from azide to prepare sulfimides from sulfides,[36] indicated that a

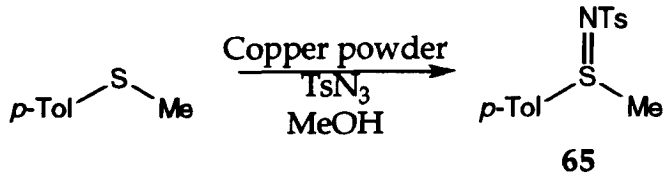
copper(I) species would be a good starting point. Evans noted that the oxidations state of the catalyst was in fact unknown. Using *N*-*p*-tosyliminophenyliodinane **224**, a known oxidant, oxidation of $Cu^{(I)}$ to $Cu^{(II)}$ would be expected. Therefore, the catalyst could be in the +2 oxidation state, even when using $Cu^{(I)}$ species.[149b]

Although *N*-*p*-tosyliminophenyliodinane **224** was found to be more successful than tosyl azide as a nitrene precursor in asymmetric aziridination, we decided to start by studying tosyl azide, as this was the nitrene precursor used by Horak for copper catalysed sulfimidation.[36]

We initially selected the C-2 symmetric oxazoline based ligands, as initially used by Masamune for asymmetric cyclopropanations[149c] and Evans for asymmetric aziridations,[149b] although we did not discount Jacobsen's chiral diimine-based ligands.[149a] We chose to study methyl *p*-tolyl sulfide, both as it leads to our principal target sulfimide **65** and because the optically pure sulfimide has been fully characterised. Comparison of the $[\alpha]_D$ value[44] provided us with a convenient measure of the extent of enantioinduction in our reactions.

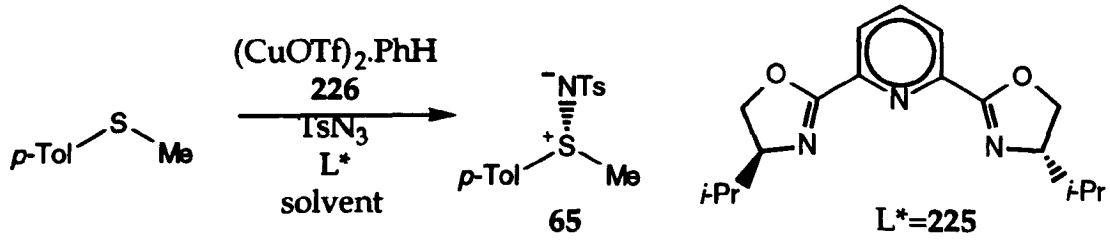
7.3 Results and Discussion

Horak did not prepare methyl *p*-tosyl sulfimide **65** using the copper-catalysed thermal nitrene generation method,[36] so we thought a convenient place to start would be to use the conditions used for methyl phenyl sulfide. Therefore, sulfide, copper powder ('activated' by washing with oxalic acid) and *p*-tosyl azide (prepared from tosyl chloride and sodium azide using a literature procedure) were heated to reflux in methanol (**Scheme 7.3**). The reaction progress was monitored by consumption of tosyl azide or formation of the product. Although incomplete consumption of tosyl azide was observed, even after 24 hours, we isolated the sulfimide (56 %).



Scheme 7.3

Knowing the method worked, we introduced a chiral ligand. We tried (-)-2,6-bis[(4*S*)-isopropyl-2-oxazolin-2-yl]pyridine **225** and copper$^{(I)}$ triflate (as benzene complex **226**) as ligand and metal source, respectively (**Scheme 7.4**). Adding the ligand to the metal in methanol resulted in the green solution turning pale brown after five minutes, indicating that a new complex had been formed. Addition of sulfide and tosyl azide followed by heating to reflux resulted in 56% yield of the sulfimide **65** with promising optical purity (10% ee). The procedure was then repeated with a number of different solvents. The results are presented in **Table 7.1**.



Scheme 7.4

Table 7.1 Yields and enantioselectivities for sulfimide 65 using TsN_3 as nitrene precursor

Entry	Solvent	b.p. (°C)	Time (h)	Yield (%)	ee (%)
a	MeOH	65	9	56	10
b	CH_2CCl_2	40	120	-	-
c	$CHCl_3$	61	72	-	-
d	$ClCH_2CH_2Cl$	83	12	-	-
e	THF	65-67	144	-	-
f	MeCN	81-82	12	55	5
g	DMF	(80-90)[a]	120	10	0
h	Acetone	56	60	60	12
i	Benzene	80	72	90	0

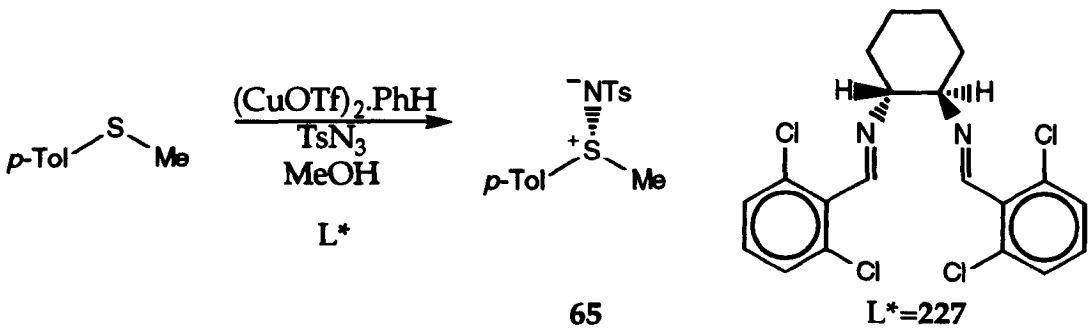
a: maintained at this temperature

We had hoped that a change in the solvent would bring about an improvement on the result observed with methanol as solvent (**entry a**). However, consideration of the boiling point of the solvent was important. The rate of thermolysis of tosyl azide is rather slow below 60°C and so solvent choice is limited to solvents boiling at or above this temperature. It was also important to keep the reaction temperature below 100°C, to avoid epimerisation of the product sulfimide **65**. For this reason, solvents with boiling points between 55°C and 85°C are ideal.

The range of solvents employed is shown in the table. Our observations were that halogenated solvents (**entries b, c and d**) are useless, benzene was best for yield (90 % **entry i**), but that methanol, acetonitrile and acetone were the most encouraging in terms of yield and enantioselectivity (**entries a, f and h**). Conclusions at this stage were difficult, but some coordinating ability seems necessary in the ligand, as the polarised solvents gave the best results,

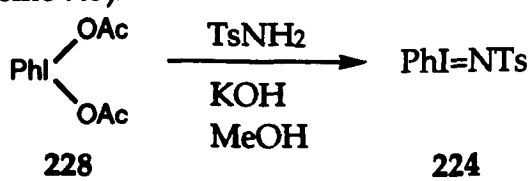
although THF did not work. The absolute configuration indicated in **Scheme 7.4** was deduced by the comparison of the sign of optical rotation compared to the literature value.

Changing the solvent did not drastically improve the enantioselectivity, so we tried changing the ligand. Using Jacobsen's ligand **227**,[149a] standard Horak conditions,[36] with methanol as solvent, resulted in no product at all (**Scheme 7.5**), with unreacted sulfide recovered. There was no analytical evidence for unchanged ligand. We speculated that the imine moiety had been methanolysed under the reaction conditions, although no methanolysed products were observed, but we would still have expected a racemic product.



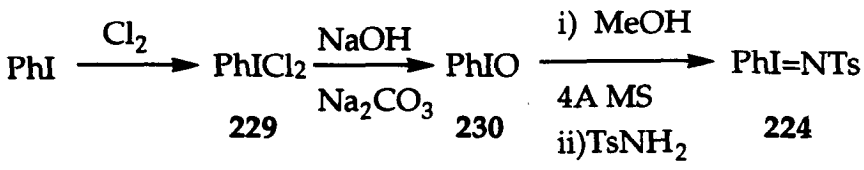
Scheme 7.5

The low enantioselectivities observed at this stage could be attributed to some racemisation of optically active sulfimide at the relatively elevated reaction temperatures. We therefore planned a lower temperature synthesis, thus precluding use of tosyl azide as nitrene precursor. We thus turned to *N*-*p*-tosyliminophenyliodinane (PhI=NTs) **224** as a nitrene precursor, the synthesis of which has been reported. Using the first reported synthesis of this compound, developed by the group of Yamada, whereby phenyliodo diacetate **228** was reacted with tosyl amide,[150] we found inconsistent, low yields resulted (**Scheme 7.6**).



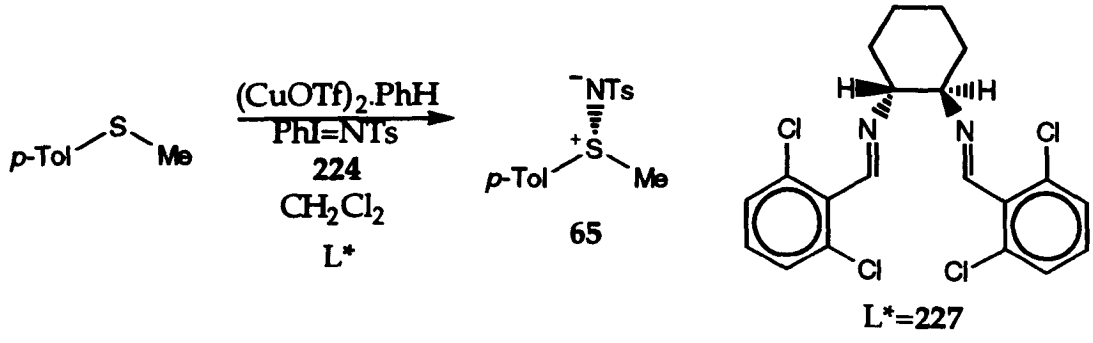
Scheme 7.6

We also tried the method reported by the group of Simandi, where iodobenzene was oxidised to phenyliodo dichloride **229**.[151] Hydrolysis of **229** gave iodosobenzene **230**, which was reacted with tosyl amide to give **224** (**Scheme 7.7**). However, similarly inconsistent yields were observed. Solvent dryness was not thought to be a problem, as the methanol had been 'super-dried'. The molecular sieves used in the first preparation were thoroughly dried under vacuum. However, sufficient quantities of **224** were obtained using both methods to carry out our study.



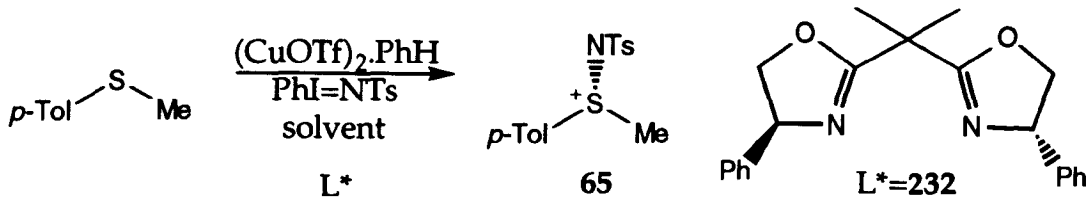
Scheme 7.7

With Jacobsen's ligand **227** and PhI=NTs **224**, we obtained a good yield of sulfimide **65** (73%), but it proved to be racemic (**Scheme 7.8**).



Scheme 7.8

We therefore tried a new ligand, which was commercially available in both enantiomeric forms. Ligand **231**, (*R*)-(+)-2,2'-isopropylidene-bis(4-phenyl-2-oxazoline, was tried under a variety of temperatures (**Scheme 7.9**). These results are presented in **Table 7.2**.



Scheme 7.9

Table 7.2 Yields and enantioselectivities for sulfimide 65 (Scheme 7.8)

Entry	Solvent	T (°C)	Time (h)	ee (%)	Yield (%)
a	CH_2Cl_2	-90	12	14	79
b	CH_2Cl_2	-78	5	18	75
c	CH_2Cl_2	0	4.5	15	87
d	MeOH	reflux	12	4	51

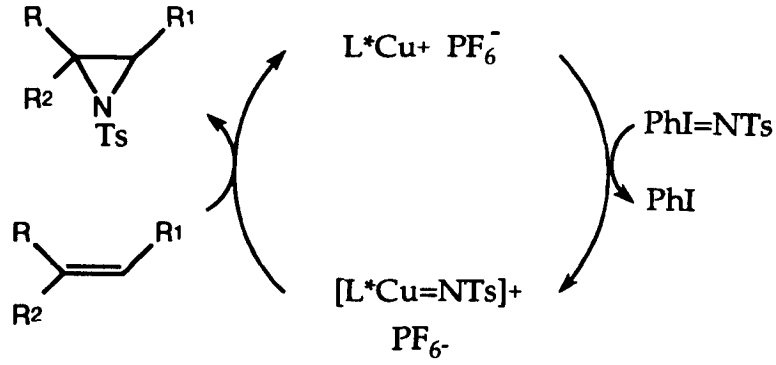
Good yields and promising enantioselectivities were observed (**entries a,b and c**), although one anomalous case resulted in the formation of the other enantiomer of the sulfimide (**entry d**).

Preliminary studies were also undertaken into the potential of Chloramine-T as a nitrene-precursor. We observed that sulfimidation using sulfide and Chloramine-T could be catalysed by copper(I) triflate, and so further studies into making this reaction asymmetric are in progress.

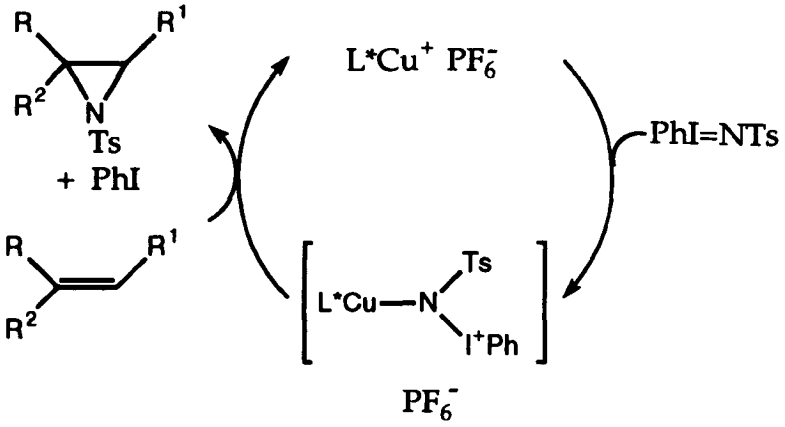
7.3.1 Mechanistic conclusions

The mechanism of asymmetric sulfimidation is unknown. Following our study in this area, and other recently proposed mechanisms for asymmetric aziridinations, we feel able to make some tentative comments on this subject. Jacobsen suggested two mechanisms to explain the copper-catalysed asymmetric aziridinations observed by his group (**Schemes 7.10 and 7.11**).[152] Both mechanisms involve a discrete copper(III)-nitrene as a reactive

intermediate, but differ in the role of *N-p*-tosyliminophenyliodinane **224** as nitrene precursor.



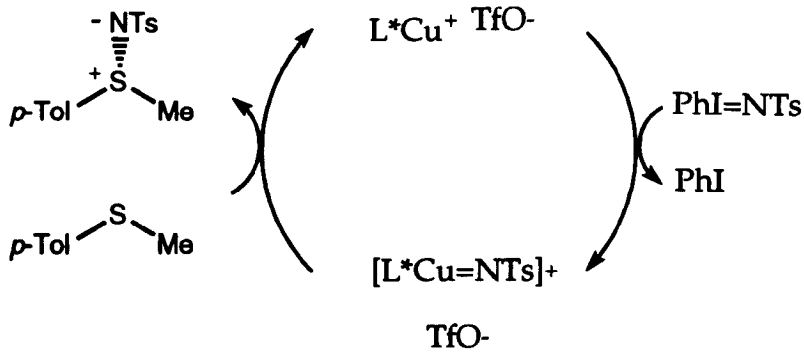
Scheme 7.10



Scheme 7.11

The redox mechanism (**Scheme 7.10**) involves iodobenzene being fully dissociated from the aziridinating species. The Lewis acid catalysis mechanism (**Scheme 7.11**) proposes that iodobenzene is an integral component of the active intermediate. Jacobsen found that structural modifications on iodobenzene made no difference to the enantioselectivities observed in a series of aziridinations of alkenes. This implied that the latter mechanism was perhaps the least likely of the two proposed. A comparison of the observed enantioselectivities in the aziridination of styrene by either PhI=NTs **224** or tosyl azide catalysed by a chiral $CuPF_6$ complex found them to be identical. This supports the idea of a common copper-nitrene intermediate. Jacobsen's own study supported a discrete $Cu^{(III)}$-nitrene

intermediate. Using Jacobsen's mechanism as a direct comparison, we propose a similar catalytic cycle to explain our asymmetric sulfimidation. As mentioned earlier, PhI=NTs **224** is known to react with sulfides without the need for a catalyst, so the order of addition of sulfide and nitrene precursor could be important. Our proposal involves a discrete copper-nitrene intermediate similar to Jacobsen's discrete species (**Scheme 7.12**). However, Jacobsen's mechanism whereby covalently bonded nitrene precursor (**Scheme 7.11**) is involved is not unlikely.

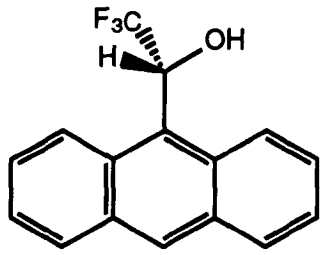


Scheme 7.12

The mechanism of asymmetric sulfimidation using tosyl azide as nitrene precursor is presumed to involve a similar copper-nitrene intermediate by analogy with the styrene examples discussed above.

7.3.2 Determination of enantiomeric purity

Enantiomeric purity was initially assessed by the determination of optical rotation and then comparison with the literature value for optically pure sulfimide. Promising enantioselectivities were then checked by addition of (*R*)-(-)-trifluoro-1-(9-anthryl)-ethanol (Pirkle's reagent) **232** (**Figure 7.1**) and analysis by 400 MHz ^{1}H NMR. Comparison of the *S*-methyl integrals of the diastereomeric complexes gave the enantiomeric excess. Close agreement was always observed between the enantioselectivities calculated from optical rotations and chiral shift ^{1}H NMR (+/- 2% ee).



232

Figure 7.1 Structure of Pirkle's reagent 232

7.4 Summary

Some progress has been made towards a new asymmetric sulfimidation procedure and some promising enantioselectivities have been observed. Further developments are in progress to try and establish which nitrene precursor, temperature, solvent, metal catalyst and chiral ligand will result in optimal enantioselectivities.

Chapter 8

Experimental

8.1 General experimental

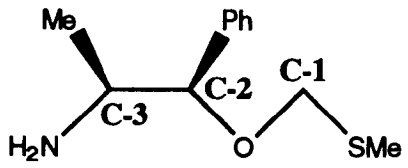
Melting points were determined using a Stuart Scientific SMP 1 melting point apparatus and are uncorrected. Optical rotations were recorded on an Optical Activity Ltd. model AA-1000 polarimeter at 546 nm with a path length of 2 dm. Microanalyses were performed at the University of Warwick. Accurate masses and some mass spectra were performed by the EPSRC Mass Spectrometry Service at Swansea University. Other mass spectra were recorded on a Kratos MS90 spectrometer with only molecular ions (M^+ or MH^+) and major peaks being reported, with intensities quoted as percentages of the base peak. Infra-red spectra were recorded neat, as nujol mulls or as a KBr disc, as indicated, on a Perkin-Elmer 1720X fourier transform spectrometer. Only selected absorbances (υ_{max}) are reported. ^1H NMR spectra were recorded at either 250 MHz or 400 MHz on Bruker ACF 250 or Bruker ACP instruments, respectively. Chemical shifts (δ)are quoted in parts per million (ppm) and referenced to the appropriate solvent peak. ^{13}C NMR spectra were recorded at 62.9 MHz on a Bruker ACF 250 or 100.6 MHz on a Bruker ACP 400 instrument. Chemical shifts (δ) are qouted in ppm and referenced to the appropriate solvent peak. Chemicals were purchased from Aldrich. Fluka or Sigma at the highest available grade. All solvents were purchased from Fisons Scientific Equipment at SLR grade and purified, when required, by literature methods. Anhydrous solvents were obtained as follows: dichloromethane, distilled from calcium hydride under nitrogen; THF and THP, distilled from sodium-benzophenone ketal under nitrogen; DMF, distilled from calcium hydide under nitrogen and acetone , distilled

from magnesium sulfate under nitrogen, MeOH and EtOH, distilled from magnesium methoxide and magnesium ethoxide under nitrogen, respectively. Tlc was performed on aluminium backed plates precoated with silica (0.2 mm, $60F_{254}$) which were developed using one or more of the following agents: UV fluorescence (254 nm), iodine vapour or *p*-anisaldehyde (2.5% *v/v*). Flash chromatography was performed on silica gel (Merck Kieselgel $60F_{254}$, 230-400 mesh).

X-Ray crystallographic measurements were made with a Siemens P3R3 four-circle diffractometer equipped with an Oxford Cryosystems Cooler (version 2.4). Graphite monochromated Mo-Kα radiation (λ 0.71073Å) was used to collect the intensity data in the ω-2θ mode Unit cell parameters and orientation were obtained by least-squares refinement of the setting angles of 20 high angle reflections. The crystallographic program system was SHELXTL-93. The structures were solved by direct methods and refined using full-matrix least-squares on F^2. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were given isotropic thermal parameters equal to 1.2 (or 1.5 for methyl groups) times the equivalent isotropic displacement parameter of the atom to which it is attached. A summary of the crystal dat, refinement details, bond lengths and angles are given in the appendices.

8.2 Experimental for Chapter 2

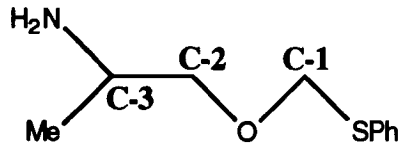
8.2.1 (1*R*,2*S*)-1-Methyl-2-(methylsulfanylmethoxy)-phenyl-ethylamine 134a



134a

(1*R*,2*S*)-(-)-Norephedrine (1.51 g, 10 mmol) and sodium hydride (60%, hexane washed, 0.48 g, 20 mmol) were heated to reflux in THF (20 ml) for 2 hrs. The reaction was cooled to 0°C. Sodium iodide (1.50 g, 10 mmol) and chloromethylphenylsulfide (0.84 ml, 10 mmol) were added, then stirring was continued at room temperature for 20 hrs. The reaction was quenched with water (20 ml) and extracted with ether (3x20 ml). The combined ethereal layers were then extracted with 5% HCl (3x20 ml), neutralised with 10% aqueous sodium carbonate and extracted with ether (3x20 ml). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford a pale yellow oil. Bulb-to-bulb distillation under reduced pressure afforded a colourless oil (1.41 g, 67%). b.p. 110°C /10 mmHg; (Found M^+ 212.1109. MH^+ requires 212.1110); υ_{max} (neat) /cm^{-1} 3366, 1493, 1302, 1054, 960; δ_H(250 MHz; $CDCl_3$) 7.27 (m, 5H, Ph), 4.67 (d, J=11.5 Hz, 1H, H-1), 4.46 (d, J=6.0 Hz, 1H, H-2), 4.27 (d, J=11.5 Hz, 1H, H-1), 3.13 (dq, 6.3 1H, H-3), 2.14 (s, 3H, MeS), 1.5 (brs, 2H, NH_2), 1.09 (d, J=6.3 Hz, 3H, Me); δ_C (62.9 MHz; $CDCl_3$) 138.1 (Ph), 128.3 (Ph),127.95 (Ph), 126.1 (Ph), 83.0 (C-1), 72.6 (C-2), 51.4 (C-3), 19.4 (Me), 14.0 (MeS); *m/z* (CI) 212 (100 MH^+%), 164 (25).

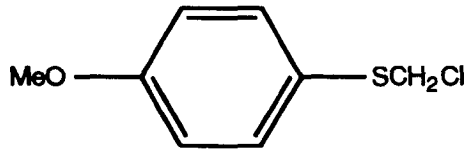
8.2.2 DL-1-Methyl-2-(phenylsulfanylmethoxy)ethylamine 141



141

A mixture of DL-2-amino-1-propanol (150 mg, 2.0 mmol), sodium hydride (51 mg, 2.1 mmol), chloromethylphenylsulfide (301 mg, 1.9 mmol) and sodium iodide (28 mg, 0.19 mmol) in THF/acetonitrile (16 ml/2 ml) was stirred at 0°C for 1 hr. The reaction was then stirred at room temperature for 24 hrs, poured into water (30 ml) and extracted with ether (3x20 ml). The combined ethereal extracts were extracted with 5% aqueous HCl (3x30 ml) and the combined aqueous phases neutralised with 10% aqueous sodium carbonate. The aqueous phases were extracted with ether (3x20 ml), dried over magnesium sulfate and concentrated under reduced pressure to afford a pale yellow oil. Bulb-to-bulb distillation under reduced pressure afforded a colourless oil (90 mg, 24%). bp. 85°C (10 mmHg); (Found M^+ 198.0953. MH^+ requires 198.0949); υ_{max} (neat) /cm^{-1} 3368, 2964, 2924, 1734, 1584, 1481, 1457, 1440, 1374, 1245, 1076, 1026, 740, 704, 692; δ_H(250 MHz; $CDCl_3$) 7.26 (m, 5H, Ph), 5.02 (brs, 2H, H-1), 3.58 (dd, J=3.4, 8.9 Hz, 1H, H-2), 3.34 (dd, J=8.9, 8.9 Hz, 1H, H-2), 3.16 (m, 1H, H-3), 2.20 (brs, 2H, NH_2), 1.07 (d, J=6.3 Hz, 3H, Me); δ_C (62.9 MHz; $CDCl_3$) 135.7 (Ph), 130.0 (Ph), 128.9 (Ph), 126.6 (Ph), 76.2 (C-1), 74.7 (C_2), 46.3 (C-3), 19.4 (Me); *m/z* (CI/NH_3) 198 (100 MH^+%), 123 (64).

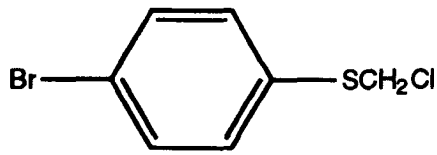
8.2.3 1-(Choromethylsulfanyl)-4-methoxybenzene 138a[97b]



138a

A solution of 1-methoxy-4-(methylthio)benzene (3.08 g, 20 mmol) and *N*-chlorosuccinimide (2.67 g, 20 mmol) in CCl_4 (100 ml) was stirred overnight at room temperature. Succinimide byproduct was filtered off and the filtrate evaporated to dryness under reduced pressure to give a yellow residue. Recrystallisation from petroleum ether/hexane gave a yellow crystalline solid (352 mg, 93%). δ_H(250 MHz; $CDCl_3$) 7.50 (AA' of AA'BB', 2H, Ar), 6.91 (BB' of AA'BB', 2H, Ar), 4.86 (s, 2H, CH_2), 3.82 (s, 3H, MeO); δ_C (62.9 MHz; $CDCl_3$) 160.2 (Ar), 134.7 (Ar), 123.3 (Ar), 114.7 (Ar), 55.3 (MeO), 53.0 (CH_2); *m/z* (EI) 188 (73 M^+%), 153 (73), 139 (100), 124 (13).

8.2.4 1-Bromo-4-(chloromethylsulfanyl)benzene 138b[97a]

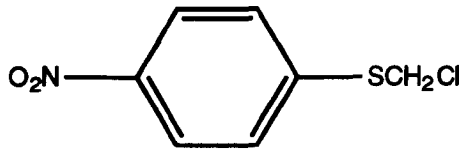


138b

A solution of 1-bromo-4-(methylthio)benzene (2.03 g, 10 mmol) and *N*-chlorosuccinimide (1.34 g, 10 mmol) in CCl_4 (50 ml) was stirred for 48 hrs at room temperature. Succinimide byproduct was filtered off and the filtrate evaporated to dryness under reduced pressure to give a pale yellow residue. Recrystallisation from PE/hexane gave a white crystalline solid (2.24 g, 94%). δ_H(250 MHz; $CDCl_3$) 7.49 (AA' of AA'BB', 2H, Ar), 7.37 (BB'

of AA'BB', 2H, Ar), 4.91 (s, 2H, CH_2); δ_C (62.9 MHz; $CDCl_3$) 137.0 (Ar), 132.3 (Ar), 132.2 (Ar), 122.2 (Ar), 50.5 (CH_2); *m/z* (EI) 236 (77 MH^+%), 201 (92), 122 (100), 108 (87).

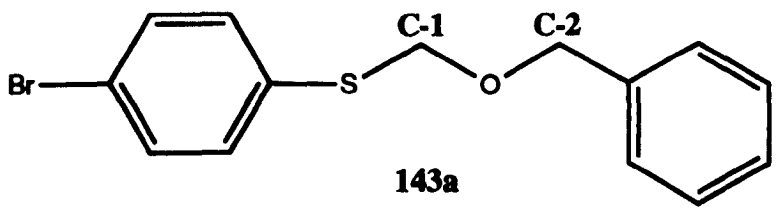
8.2.5 1-(Chloromethylsulfanyl)-4-nitrobenzene 138c[97b]



138c

To a refluxing solution of 4-nitrothioanisole (169 mg, 1.0 mmol) in CH_2Cl_2 (12 ml) was added sulfuryl chloride (84 µl, 1.05 mmol) in CH_2Cl_2 (3 ml) dropwise over 60 mins. Heating was then continued for a further 60 mins before the reaction was concentrated under reduced pressure. The yellow residue was recrystallised from ether to give a yellow crystalline solid (183 mg, 90%). δ_H(250 MHz; $CDCl_3$) 8.16(AA' of AA'BB', 2H, Ar), 7.51 (BB' of AA'BB', 2H, Ar) 5.05 (s, 2H, CH_2); δ_C (62.9 MHz; $CDCl_3$) 143.0 (Ar), 127.7 (Ar), 124.2 (Ar), 124.1 (Ar), 48.7 (CH_2); *m/z* (EI) 203 (55 M^+%), 168 (100), 122 (52), 108 (54).

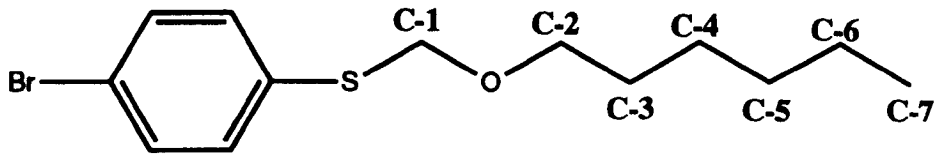
8.2.6 1-Bromo-4-((phenylmethoxy)methylsulfanyl)-benzene 143a



143a

Sodium hydride (0.75 g, 0.031 mol) was added to benzyl alcohol (1.35 ml, 0.031 mol) in dimethoxyethane (DME) (7.5 ml) at 0°C under nitrogen. BPTMCl (3.0 g, 0.0126 mol) in DME (7.5 ml) was then added and the mixture was then stirred for an hour at 0°C followed by 40 hrs at room temperature. Water (40 ml) was added and the mixture was then extracted with ether (3x25 ml). The combined ethereal layers were washed with brine (25 ml) and dried over magnesium sulfate. Filtration followed by concentration under reduced pressure afforded a yellow oil. Column chromatography on silica using 40% dichloromethane in petroleum ether gave a colourless oil (3.12 g, 80%). Found C: 54.09%, H: 4.40%, expected C: 54.38%, H:4.24%; υ_{max} (neat) /cm^{-1} 3064, 3031, 2926, 1474, 1095, 1068, 1029, 1009, 698; δ_H(250 MHz; $CDCl_3$) 7.3-7.5 (m, 9H, Ar), 5.04 (s, 2H, H-1), 4.72 (s, 2H, H-2); δ_C (62.9 MHz; $CDCl_3$) 136.9 (Ar), 135.1 (Ar), 131.9 (Ar), 131.5 (Ar), 128.5 (Ar), 128.2 (Ar), 127.95 (Ar), 120.7 (Ar), 74.8 (C-1), 69.8 (C-2); *m/z* (EI) 310 (7, [^{81}Br]M$^+$), 308 (7, [^{79}Br]M$^+$), 280 (19), 278 (18), 108 (10), 91 (100), 65 (11).

8.2.7 1-Bromo-4-(hexyloxymethylsulfanyl)benzene 143b

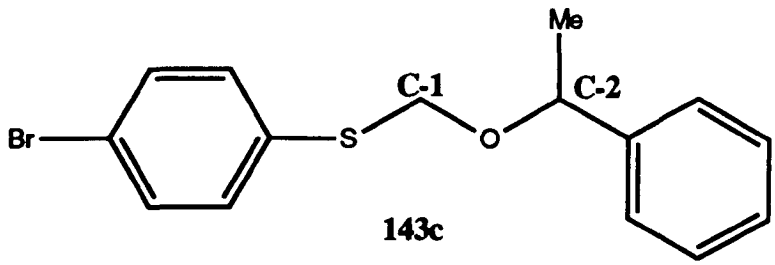


143b

Sodium hydride (0.80 g, 0.033 mol) was added to hexan-1-ol (1.58 ml, 0.012 mol) in dimethoxyethane (DME) (7.5 ml) at 0°C under nitrogen. BPTMCl (3.0 g, 0.0126 mol) in DME (7.5 ml) was then added and the mixture was then stirred for an hour at 0°C followed by 80 hrs at romm temperature. Water (40 ml) was added and the mixture was then extracted with ether (3x25 ml). The combined ethereal layers were

washed with brine (25 ml) and dried over magnesium sulfate. Filtration followed by concentration under reduced pressure afforded a yellow oil Column chromatography on silica using 1% ethyl acetate in petroleum ether gave a pale yellow oil, which afforded a colourless oil upon bulb-to-bulb distillation under reduced pressure (2.18 g, 60%). b.p. 140°C /10 mmHg; Found C: 51.64%, H: 6.51%, expected C: 51.49%, H: 6.31%; υ_{max} (neat) /cm^{-1} 2955, 2930, 2858, 1474, 1099, 1084, 1009, 813; δ_H(250 MHz; $CDCl_3$) 7.50 (AA' of AA'BB', 2H, Ar), 7.22 (BB' of AA'BB', 2H, Ar), 4.97 (s, 2H, H-1), 3.59 (t, J=6.7 Hz, 1H, H-2) 1.59 (~quintet, J=7.0 Hz, 2H, H-3), 1.29 (m, 6H, H-4/5/6), 0.88 (t, J=6.8 Hz, 3H, H-7); δ_C (62.9 MHz; $CDCl_3$) 135.4 (Ar), 131.8 (Ar), 131.4 (Ar), 120.5 (Ar), 75.90 (C-1), 65.6 (C-2), 31.5 (C-3), 29.2 (C-4), 25.8 (C-5), 22.5 (C-6), 14.0 (C-7); *m/z* (EI) 304 (71, [^{81}Br]M^+), 302 (71, [^{79}Br]M^+), 203 (44), 201 (45), 190 (71), 188 (70), 115 (71), 85 (100), 69 (23), 57 (62), 43 (94).

8.2.8 1-Bromo-4-((1-phenylethoxy)methylsulfanyl)-benzene 143c

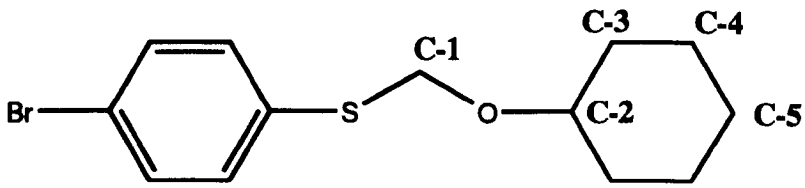


143c

Sodium hydride (0.80 g, 0.033 mol) was added to 1-phenylethanol (1.54 ml, 0.0126 mol) in dimethoxyethane (DME) (7.5 ml) at 0°C under nitrogen. BPTMCl (3.0 g, 0.0126 mol) in DME (7.5 ml) was then added and the mixture was then stirred for an hour at 0°C followed by 24 hrs at romm temperature. Water (40 ml) was added and the mixture was then extracted with ether (3x25 ml). The combined ethereal layers were

washed with brine (25 ml) and dried over magnesium sulfate. Filtration followed by concentration under reduced pressure afforded a yellow oil Column chromatography on silica using 25% dichloromethane in petroleum ether gave a pale yellow oil, which afforded a colourless oil upon bulb-to-bulb distillation under reduced pressure (1.27 g, 35%). b.p. 145°C /10 mmHg; υ_{max} (neat) /cm^{-1} 3062, 3029, 2975, 2928, 1474, 1094, 1070, 1049, 1009, 813; δ_H(250 MHz; $CDCl_3$) 7.35 (m, 9H, Ar), 5.04 (d, J=11.6 Hz, 1H, H-1), 4.95 (q, J=6.4 Hz, 1H, H-2) 4.64 (doublet, J=11.6 Hz, 1H, H-1), 1.48 (d, J=6.4 Hz, 3H, Me); δ_C (62.9 MHz; $CDCl_3$) 142.1 (Ar), 135.3 (Ar), 131.9 (Ar), 131.5 (Ar), 128.6 (Ar), 127.9 (Ar), 126.7 (Ar), 120.6 (Ar), 74.6 (C-1), 72.9 (C-2), 23.6.2 (Me); *m/z* (EI) 324 (7, [^{81}Br]M$^+$), 322 (7, [^{79}Br]M$^+$), 294 (25), 292 (25), 203 (12), 201 (12), 122 (10), 105 (100), 77 (38), 51 (11).

8.2.9 1-Bromo-4-(cyclohexyloxymethylsulfanyl)benzene 143d



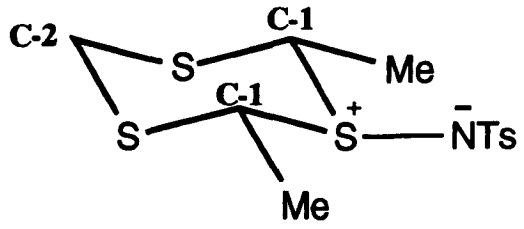
143d

Sodium hydride (0.75 g, 0.031 mol) was added to cyclohexanol (1.31 ml, 0.0126 mol) in dimethoxyethane (DME) (7.5 ml) at 0°C under nitrogen. BPTMCl (3.0 g, 0.0126 mol) in DME (7.5 ml) was then added and the mixture was then stirred for an hour at 0°C followed by 60 hrs at romm temperature. Water (40 ml) was added and the mixture was then extracted with ether (3x25 ml). The combined ethereal layers were washed with brine (25 ml) and dried over magnesium sulfate. Filtration

followed by concentration under reduced pressure afforded a yellow oil Column chromatography on silica using 1% acetone in petroleum ether gave a pale yellow oil, which afforded a colourless oil upon bulb-to-bulb distillation under reduced pressure (2.09 g, 55%). b.p. 145°C /10 mmHg; υ_{max} (neat) /cm^{-1} 2932, 2856, 1474, 1094, 1068, 1035, 1009, 813; δ_H(250 MHz; $CDCl_3$) 7.41 (AA' of AA'BB', 2H, Ar), 7.32 (BB' of AA'BB', 2H, Ar), 5.00 (s, 2H, H-1), 3.69 (m, 1H, H-2) 1.80 (m, 2H, H-3/4), 1.55 (m, 2H, H-3/4), 1.25 (m, 4H, H-3/4), 0.87 (m, 2H, H-5); δ_C (62.9 MHz; $CDCl_3$) 135.5 (Ar), 131.7 (Ar), 131.3 (Ar), 120.3 (Ar), 74.8 (C-1), 72.7 (C-2), 31.7 (C-3/4), 25.5 (C-5), 23.9 (C-3/4); *m/z* (EI) 302 (43, [^{81}Br]M$^+$), 300 (41, [^{79}Br]M$^+$), 203 (52), 201 (51), 190 (85), 188 (85), 113 (77), 83 (100), 69 (29), 55 (86), 41 (59).

8.3 Experimental for Chapter 3

8.3.1 *N*-(2,6-Dimethyl-[1,3,5]trithian-1-ylidene)-4-methyl benzenesulfonamide 159a

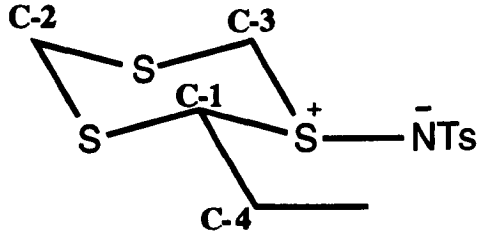


159a

N-[1,3,5]Trithian-1-ylidene-4-methylbenzenesulfonamide (614 mg, 2.0 mmol), sodium hydride (135 mg, 4.5 mmol) and methyl iodide (262 µl, 4.2 mmol) were stirred in dry DMF (60 ml) at room temperature under nitrogen for 15 hrs. After careful addition of water (150 ml) followed by extraction with ethyl acetate (3x60 ml), the combined organic layers were washed with water (3x120 ml). Drying over anhydrous magnesium

sulfate, filtration and evaporation under reduced pressure gave a yellow residue. The product was obtained as a white solid by crystallisation from chloroform/petroleum ether followed by suction filtration (369 mg, 55%). m.p. 100-103°C; (Found: C, 42.70; H, 5.07; N, 4.09. $C_{12}H_{17}NO_2S_4$ requires C, 42.96; H, 5.11; N, 4.17); υ_{max} (Nujol) /cm^{-1} 1714, 1300, 1157, 1097, 974, 902, 817, 722; δ_H(250 MHz; $CDCl_3$) 7.73 (AA' of AA'BB', 2H, Ar), 7.23 (BB' of AA'BB', 2H, Ar), 4.50 (d, J=14.8 Hz, 1H, H-2e), 4.48 (q, 2, J=7.0 Hz, 1H, H-1a), 3.48 (d, J=14.8 Hz, 1H, H-2a), 2.36 (s, 3H, ArMe), 1.42 (d, J=7.0 Hz, 6H, Me); δ_C (62.9 MHz; $CDCl_3$) 142.0 (Ar), 140.7 (Ar), 129.3 (Ar), 126.1 (Ar), 61.5 (C-1), 34.0 (C-2), 21.4 (ArMe), 16.1 (Me); *m/z* (CI/NH_3) 336 (MH^+ %).

8.3.2 *N*-(2-Ethyl-[1,3,5]trithian-1-ylidene)-4-methyl benzenesulfonamide 158b

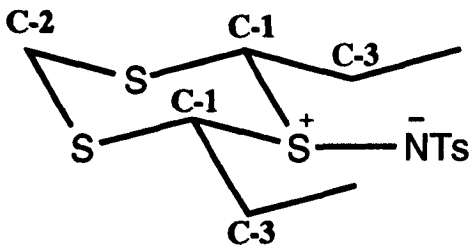


158b

N-[1,3,5]Trithian-1-ylidene-4-methylbenzenesulfonamide (154 mg, 0.5 mmol), sodium hydride (21 mg, 0.7 mmol) and ethyl iodide (48 µl, 0.6 mmol) were stirred in dry DMF (15 ml) at room temperature under nitrogen for 5 hrs. After careful addition of water (40 ml), followed by extraction with ethyl acetate (3x20 ml), the combined organic layers were washed with water (3x50 ml). Drying over anhydrous magnesium sulfate, filtration and evaporation under reduced pressure gave a yellow residue. Separation of mono- and di- alkylated products using flash

chromatography on silica with ethyl acetate as eluant gave the desired product (34 mg, 20%). Rf 0.34 (EtOAc/petroleum ether 3:1); δ_H(250 MHz; $CDCl_3$) 7.77 (AA' of AA'BB', 2H, Ar), 7.24 (BB' of AA'BB', 2H, Ar), 4.53 (d, J=13.2 Hz, 1H, H-3a), 4.50 (dd, J=3.2, 7.9 Hz, 1H, H-1a), 4.36 (d, J=14.5 Hz, 1H, H-2a), 4.15 (d, J=2.3, 13.2 Hz, 1H, H-3e), 3.47 (dd, J=2.3, 14.5 Hz, 1H, H-2e), 2.38 (s, 3H, ArMe), 2.11 (~dq, J=3.2, 7.9 Hz, 1H, H-4), 1.79 (~dq, J=3.2, 7.9 Hz, 1H, H-4), 0.86 (t, J=7.6 Hz, 3H, Me); δ_C (62.9 MHz; $CDCl_3$) 141.9 (Ar,), 140.8 (Ar), 129.3 (Ar), 126.1 (Ar), 67.8 (C-1), 52.2 (C-3), 33.6 (C-2), 22.4 (C-4), 21.4 (ArMe), 9.3 (Me).

8.3.3 *N*-(2,6-Diethyl-[1,3,5]trithian-1-ylidene)-4-methyl benzenesulfonamide 159b

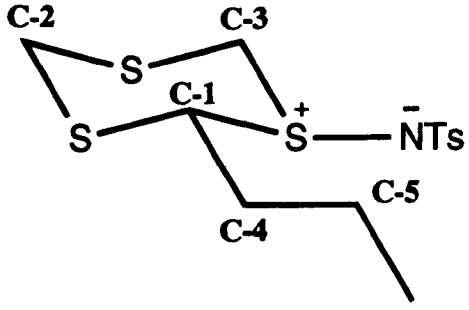


159b

N-[1,3,5]Trithian-1-ylidene-4-methylbenzenesulfonamide (154 mg, 0.5 mmol), sodium hydride (36 mg, 1.2 mmol) and ethyliodide (89 ml, 1.1 mmol) were stirred in dry DMF (15 ml) at room temperature under nitrogen for 10 hrs. After careful addition of water (50 ml) followed by extraction with ethyl acetate (3x20 ml), the combined organic layers were washed with water (3x60 ml). Drying over anhydrous magnesium sulfate, filtration and evaporation under reduced pressure gave a yellow residue. Flash chromatography on silica with ethyl acetate/petroleum ether 3:1 failed to purify the product, as some tosyl amide remained. Further purification on silica gave the same result. The stability of the product is

therefore doudtful. A crude estimate of yield is therfore given (15%, 28 mg). Rf 0.56 (EtOAc/petroleum ether 3:1); δ_H(250 MHz; $CDCl_3$) 7.76 (AA' of AA;BB', 2, Ar), 7.24 (BB' of AA'BB', 2H, Ar), 4.25 (dd, J=3.2, 7.6 Hz, 2H, H-1a), 4.24 (d, J=14.7 Hz, 1H, H-2e), 3.53 (d, J=14.7 Hz, 1H, H-2a), 2.38 (s, 3H, ArMe), 2.12 (~dq, J=3.2, 7.6 Hz, 2H, H-3), 1.79 (~dq, J=3.2, 7.6 Hz, 2H, H-3), 0.89 (t, J=7.6 Hz, 6H, Me); δ_C (62.9 MHz; $CDCl_3$) 141.9 (Ar), 140.7 (Ar), 129.2 (Ar), 126.2 (Ar), 69.6 (C-1), 33.7 (C-2), 22.7 (C-3), 21.4 (ArMe), 9.8 (Me).

8.3.4 *N*-(2-*n*-Propyl-[1,3,5]trithian-1-ylidene)-4-methyl benzenesulfonamide 158c

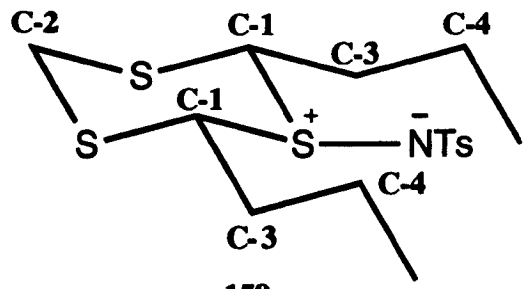


158c

N-[1,3,5]Trithian-1-ylidene-4-methylbenzenesulfonamide (307 mg, 1.0 mmol), sodium hydride (36 mg, 1.2 mmol) and *n*-propyl iodide (107 µl, 1.1 mmol) were stirred in dry DMF (30 ml) at room temperature under nitrogen for 8 hrs. After careful addition of water (50 ml) followed by extraction with ethyl acetate (3x20 ml), the combined organic layers were washed with water (3x60 ml). Drying over anhydrous magnesium sulfate, filtration and evaporation under reduced pressure gave a yellow residue. Separation of mono- and di- alkylated products using flash chromatography on silica with ethyl acetate/CH_2Cl_2 as eluant gave the desired product (87 mg, 25%). Mpt. 119-122°C; Rf 0.35 (CH_2Cl_2:EtOAc 3:1); (Found: C, 44.67; H, 5.48; N, 4.01. $C_{10}H_{19}NO_2S_4$ requires C, 44.75;

H, 5.54; N, 3.93); δ_H(250 MHz; $CDCl_3$) 7.77 (AA' of AA'BB', 2H, Ar), 7.25 (BB' of AA'BB', 2H, Ar), 4.50 (d, J=13.3 Hz, 1H, H-3a), 4.48 (dd, J=3.2, 8.4 Hz, 1H, H-1a), 4.31 (d, J=14.5 Hz, 1H, H-2a), 4.19 (d, J=2.2, 13.3 Hz, 1H, H-3e), 3.46 (dd, J=2.2, 14.5 Hz, 1H, H-2e), 2.38 (s, 3H, ArMe), 1.9 (m, 1H, H-4), 1.6 (m, 1H, H-4), 1.27 (m, 2H, H-5), 0.75 (t, J=7.3 Hz, 3H, Me); δ_C (62.9 MHz; $CDCl_3$) 142.1 (Ar,), 140.8 (Ar,), 129.4 (Ar,), 126.1 (Ar), 66.3 (C-1), 52.4 (C-3), 33.8 (C-2), 30.7 (C-4), 21.3 (ArMe), 18.2 (C-5), 13.4 (Me).

8.3.5 *N*-(2,6-Di-*n*-propyl-[1,3,5]trithian-1-ylidene)-4-methylbenzenesulfonamide 159c

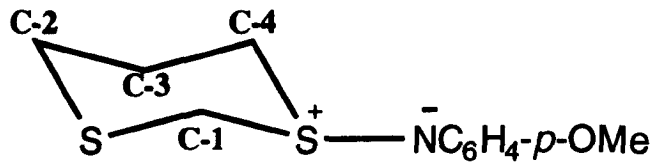


159c

N-[1,3,5]Trithian-1-ylidene-4-methylbenzenesulfonamide (307 mg, 1.0 mmol), sodium hydride (36 mg, 1.2 mmol) and *n*-propyl iodide (107 µl, 1.1 mmol) were stirred in dry DMF (30 ml) at room temperature under nitrogen for 8 hrs. After careful addition of water (50 ml) followed by extraction with ethyl acetate (3x20 ml), the combined organic layers were washed with water (3x60 ml). Drying over anhydrous magnesium sulfate, filtration and evaporation under reduced pressure gave a yellow residue. Flash chromatography on silica with CH_2Cl_2/ethyl acetate as eluant failed to cleanly separate mono- and di- alkylated products, as a minor amount of mono-product remained. A crude estimate of yield is therefore given (90 mg, 23%). Rf 0.64 (CH_2Cl_2/EtOAc); δ_H(250 MHz; $CDCl_3$) 7.76 (AA' of AA'BB', 2H, Ar), 7.24 (BB' of AA'BB', 2H, Ar), 4.23 (dd, J=3.5, 12.2 Hz, 2H,

H-1a), 4.19 (d, J=14.7 Hz, 1H, H-2e), 3.50 (d, J=14.7 Hz, 1H, H-2a), 2.38 (s, 3H, ArMe), 1.98 (m, 2H, H-3), 1.60 (m, 2H, H-3/4), 1.44 (m, 2H, H-3/4), 1.25 (m, 2H, H-3/4), 0.77 (t, J=7.3 Hz, 6H, Me); δ_C (62.9 MHz; $CDCl_3$) 141.9 (Ar), 140.8 (Ar), 129.3 (Ar), 126.2 (Ar), 68.0 (C-1), 33.6 (C-2), 30.98 (C-3), 21.3 (ArMe), 18.7 (C-4), 13.4 (Me).

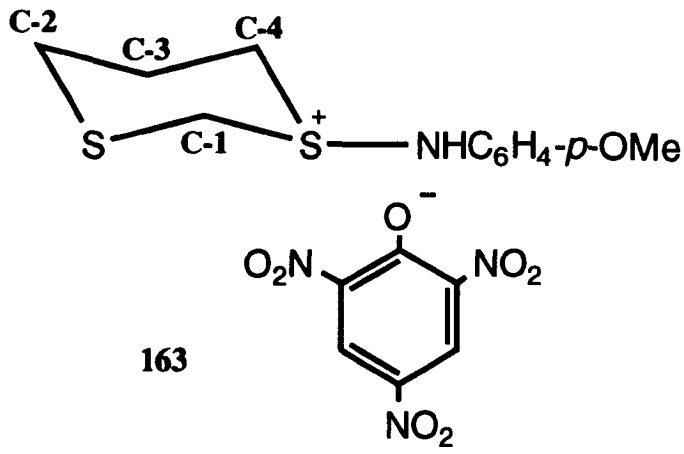
8.3.6 *N*-[1,3]Dithian-1-ylidene-4-methoxybenzene 162[101a]



162

A solution of *N*-chlorosuccinimide (267 mg, 2.0 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a mixture of 1,3-dithiane (240 mg, 2.0 mmol) and *p*-methoxyaniline (246 mg, 2.0 mmol) in CH_2Cl_2 (20 ml) at -20°C. After complete addition, the reaction was stirred for a further 60 mins at -20°C and then allowed to warm to room temperature over 30 mins. The reaction was washed with 5% aqueous NaOH (20 ml), water (20 ml) and then dried over magnesium sulfate. Filtration and evaporation to dryness under reduced pressure gave a red residue (160 mg, 33%) . A ^1H NMR spectrum of the residue indicated the presence of product, but even storage of the product in a freezer could not prevent decomposition to unidentified products. δ_H(250 MHz; $CDCl_3$) 6.82 (AA' of AA'BB', 2H, Ar), 6.73 (BB' of AA'BB', 2H, Ar), 3.92 (brd, J=12.7 Hz, 1H, H-1e), 3.72 (s, 3H, Me), 3.63 (d, J=12.7 Hz, 1H, H-1a), 3.27 (m, 1H, H-2e), 3.03 (dt, J=2.6, 13.0 Hz, 1H, H-2a), 2.60 (m, 3H, H-3,4e), 2.35 (m, 1H, H-4a); δ_C (62.9 MHz; $CDCl_3$) 152.6 (Ar), 146.5 (Ar), 119.8 (Ar), 114.6 (Ar), 55.7 (OMe), 49.3 (C-1), 49.1 (C-4), 29.4 (C-2), 28.1 (C-3).

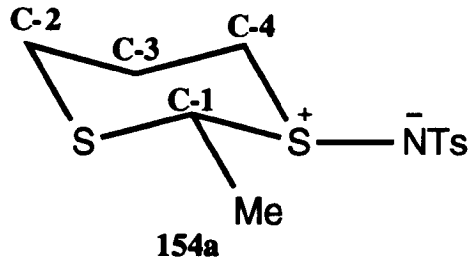
8.3.7 Picrate 163[101a]



163

A solution of *N*-chlorosuccinimide (534 mg, 4.0 mmol) in CH_2Cl_2 (20 ml) was added dropwise to a mixture of 1,3-dithiane (480 mg, 4.0 mmol) and *p*-methoxyaniline (480 mg, 3.9 mmol) in CH_2Cl_2 (50 ml) at -20°C. After complete addition, the reaction was stirred for a further 60 mins at -20°C and then allowed to warm to room temperature over 30 mins. The reaction was washed with 5% aqueous NaOH (20 ml), water (20 ml) and then dried over magnesium sulfate. Filtration and then concentration of the organic phase to ~10 ml followed by addition of a saturated solution of picric acid (~1.0 g, 40 mmol) in ether precipitated a brown solid (1.25 g, 68%). δ_H(250 MHz; DMSO-d_6) 9.12 (brs, 1H, NH), 8.59 (s, 2H, picrate), 7.16 (AA' of AA'BB', 2H, Ar), 6.91 (BB' of AA'BB', 2H, Ar), 4.95 (brd, J=12.9 Hz, 1H, H-1e), 4.62 (d, J=12.9 Hz, 1H, H-1a), 3.90 (m, 1H, H-4e), 3.70 (s, 3H, OMe), 3.61 (m, 1H, H-4a), 2.77 (m, 3H, H-3,4e), 2.32 (m, 1H, H-4a); δ_C (62.9 MHz; DMSO-d_6) 161.0 (Ar), 156.8 (Ar), 141.8 (Ar), 131.9 (Ar), 125.4 (Ar), 124.6 (Ar), 122.4 (Ar), 114.8 (Ar), 55.4 (OMe), 45.1 (C-1), 44.5 (C-4), 27.5 (C-2), 26.6 (C-3).

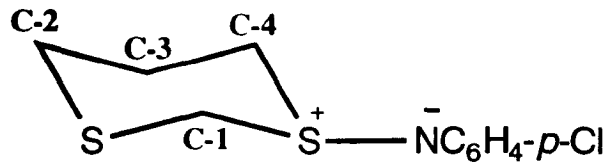
8.3.8 *N*-(2-methyl-[1,3]dithian-1-ylidene)-4-methyl-benzenesulfonamide 154a



154a

N-[1,3]Dithian-1-ylidene-4-methylbenzenesulfonamide (289 mg, 1.0mmol), sodium hydride (33 mg, 1.1 mmol) and methyl iodide (69 ml, 1.1 mmol) were stirred in dry DMF (30 ml) at room temperature under nitrogen for 8 hrs. After careful addition of water (80 ml), followed by extraction with ethyl acetate (3x40 ml), the combined organic layers were washed with water (3x100 ml) and dried over anhydrous magnesium sulfate. Filtration followed by evaporation under reduced pressure gave a yellow residue from which the product was obtained as a white solid by crystallisation from chloroform/petroleum ether followed by suction filtration (167 mg, 55%). δ_H(400 MHz; $CDCl_3$) 7.71 (AA' of AA'BB', 2H, Ar), 7.19 (BB' of AA'BB', 2H, Ar), 3.99 (q, J=6.9 Hz, 1H, H-1), 3.25 (brm, 1H, H-4e), 3.10 (ddd, J=2.8, 13.2, 13.2 Hz, 1H, H-4a), 2.81 (ddd, J=2.3, 12.4, 14.5 Hz, 1H, H-2a), 2.53 (brm, 1H, H-2e), 2.46 (brm, 1H, H-3e), 2.36 (s, 3H, ArMe), 2.20 (brm, 1H, H-3a), 1.38 (d, J=6.96 Hz, 3H, Me); δ_C (100.6 MHz; $CDCl_3$) 141.6 (Ar), 141.2 (Ar), 129.1 (Ar), 125.9 (Ar), 58.6 (C-1), 50.3 (C-4), 29.4 (C-2/3), 29.2 (C2/3), 21.2 (ArMe), 15.5 (Me); *m/z* (CI/NH_3) 304 (MH^+ %).

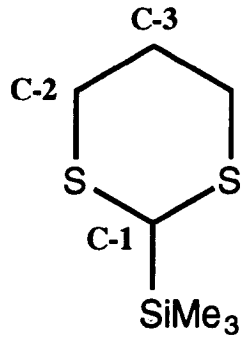
8.3.9 *N*-[1,3]Dithian-1-ylidene-4-chlorobenzene 160[101a]



160

A solution of *N*-chlorosuccinimide (267 mg, 2.0 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a mixture of 1,3-dithiane (240 mg, 2.0 mmol) and *p*-chloroaniline (255 mg, 2.0 mmol) in CH_2Cl_2 (17 ml) at -20°C. After complete addition, the reaction was stirred for a further 60 mins at -20°C and then allowed to warm to room temperature over 30 mins. The reaction was washed with 5% aqueous NaOH (20 ml), water (20 ml) and then dried over magnesium sulfate. Filtration and evaporation to dryness under reduced pressure gave a red residue. Recrystallisation from ether gave a red crystalline solid (450 mg, 92 %). δ_H(250 MHz; $CDCl_3$) 7.03 (AA' of AA'BB', 2H, Ar), 6.76 (BB' of AA'BB', 2H, Ar), 3.95 (brd, J=12.9 Hz, 1H, H-1e), 3.61 (d, J=12.9 Hz, 1H, H-2a), 3.29 (brm, 1H, H-4e), 3.00 (ddd, J=2.6, 13.0, 13.0 Hz, 1H, H-4a), 2.6 (m, 3H, H-2a,e,3e), 2.3 (m, 1H, H-3a); δ_C (62.9 MHz; $CDCl_3$) 152.4 (Ar), 128.8 (Ar), 122.2 (Ar), 119.1 (Ar), 49.2 (C-1), 48.8 (C-4), 28.9 (C-2/3), 28.1 (C-2/3).

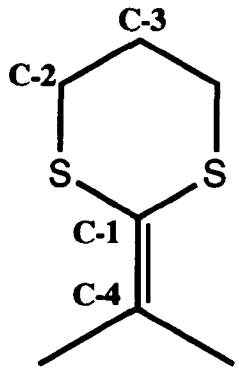
8.3.10 2-Trimethylsilyl-1,3-dithiane 233[153]



233

To a solution of 1,3-dithiane (9.6 g, 0.08 mol) in THF at -60°C under nitrogen was added *n*-BuLi (2.5 m, 32.8 ml) dropwise. The yellow solution was then warmed to 0°C and left stirring for 3 hrs. After cooling to -50°C, trimethylsilylchloride (16.1 ml, 0.126 mol) was added dropwise and the reaction left at room temperature overnight. The reaction was quenched with water and then extracted with pentane. The organic phase was then washed with water and dried over magnesium sulfate. Filtration and evaporation to dryness, followed by distillation under reduced pressure afforded a colourless oil (13.61 g, 89%). b.p. 96-97°C, 5 mmHg, (lit. 75-77°C, 2 Torr.); δ_H(250 MHz; $CDCl_3$) 3.68 (s, 1H, H-1), 2.77 (m, 4H, H-2), 2.03 (m, 2H, H-3), 0.14 (s, 9H, $SiMe_3$).

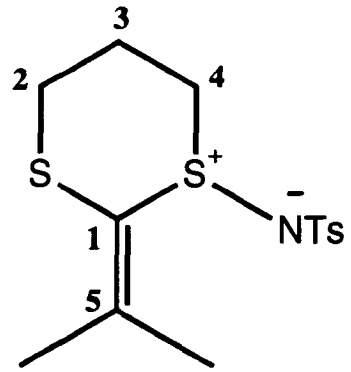
8.3.11 2-Isopropylidene-1,3 dithiane 165[154]



165

To a solution of 2-trimethylsilyl-1,3-dithiane (500mg, 481 μl, 2.6 mmol) in THF (50 ml) at 0°C under nitrogen was added *n*-BuLi (2.5 M, 1.04 ml, 2.6 mmol) dropwise and the reaction left for 20 mins. Then acetone (191 μl, 2.6 mmol) was added dropwise to the solution and the mixture was left for a further 20 mins. After allowing the reaction to warm to room temperature over 2 hrs, saturated aqueous brine (50 ml) was added, and then the mixture was extracted with ether (3x30 ml). After drying the combined ethereal extracts with magnesium sulfate and filtration, evaporation under reduced pressure gave a white solid (150 mg, 36%); δ_H(250 MHz; $CDCl_3$) 2.83 (m, 4H, H-2), 2.07 (m, 2H, H3), 1.90 (s, 6H, Me); δ_C (62.9 MHz; $CDCl_3$) 136.7 (C-1), 118.1 (C-4), 30.1 (C-2), 24.9 (C-3), 22.1 (Me).

8.3.12 *N*-(2-Isopropylidene-[1,3]-dithian-1-ylidene)-4-methylbenzenesulfonamide 166[105]

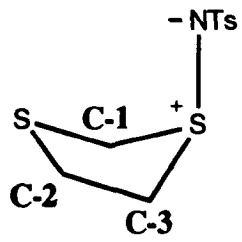


166

Chloramine-T (9.35 g, 0.038 mol) was added to a solution of 2-isopropylidene-1,3-dithiane (5.0 g, 0.031 mmol) and *n*-hexadecyl tri-*n*-butylphosphonium bromide (300 mg, 2 mol%) in CH_2Cl_2 (200 ml) at room temperature over 30 mins. The reaction was stirred for a further 2 hrs and then washed with 5% aqueous sodium hydroxide (200 ml), water (200 ml) and saturated brine (100 ml). The organic phase was dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure to give a white residue. Recrystallisation from CH_2Cl_2 gave a white crystalline solid (3.66 g, 36 %). m.p. 171-173°C, (lit. 172-175°C); δ_H(400 MHz; $CDCl_3$) 7.76 (AA' of AA'BB', 2H, tosyl), 7.17 (BB' of AA'BB', 2H, tosyl), 3.46 (m, 1H, H-4a/e), 3.07 (m, 1H, H-4a/e), 2.86 (m, 2H, H-2), 2.67 (m, 1H, H-3e), 2.35 (s, 3H, ArMe), 1.95 (s, 3H, Me), 1.92 (m, 1H, H-3a), 1.88 (s, 3H, Me'); δ_C (100.6 MHz; $CDCl_3$) 154.3 (C-1), 141.7 (Ar), 141.3 (Ar), 128.7 (Ar), 126.3 (Ar), 121.9 (C-5), 44.7 (C-4), 29.1 (C-2), 23.4 (C-3), 22.3 (Me), 21.0 (ArMe), 15.2 (Me').

8.4 Experimental for Chapter 4

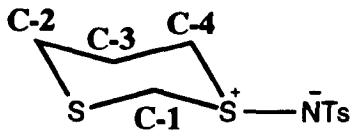
8.4.1 *N*-[1,3]Dithiolan-1-ylidene-4-methylbenzene sulfonamide 148a[101]



148a

To a 100 ml round-bottomed flask equipped with a condenser and magnetic stirrer were added dichloromethane (50 ml), 1,3-dithiolane (4.2 mmol) and *n*-hexadecyl tri-*n*-butylphosphonium bromide (~0.2 mmol). Solid Chloramine-T (1.02 g, 4.5 mmol) was slowly added with stirring and cooling with a water bath. After addition was complete the water bath was removed and stirring was continued for 2 hrs. The reaction mixture was washed with cold aqueous sodium hydroxide (5%, 100 ml) followed by two washes with water (100 ml). The dichloromethane layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was recrystallised from chloroform-ether (3:1) and isolated as a white crystalline solid (0.6 g, 52%). m.p. 159-161°C; (Found: C, 43.61; H, 4.76; N, 5.09. $C_{10}H_{13}NO_2S_3$ requires C, 43.46; H, 4.62; N, 4.91); υ_{max} ($CDCl_3$) /cm^{-1} 1274, 1138, 1087, 979; δ_H(250 MHz; $CDCl_3$) 7.64 (AA' of AA'BB', 2H, Ar), 7.33 (BB' of AA'BB', 2H, Ar), 4.38 (d, J=12.1 Hz, 1H , H-1e), 3.90 (d, J=12.1 Hz, 1H, H-1a), 3.40 (m, 4H, H-2,3), 2.35 (s, 3H, ArMe); δ_C (62.9 MHz; $CDCl_3$) 141.7 (Ar), 141.4 (Ar), 129.5 (Ar), 125.9 (Ar), 53.3 (C-3), 51.8 (C-1), 32.1 (C-2), 21.0 (Me); *m/z* (CI (NH_3)) 276 (73 MH^+ %), 201 (40), 189 (56), 184 (55), 171 (7), 155 (41), 92 (100), 91 (60).

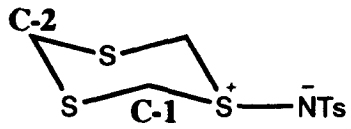
8.4.2 *N*-[1,3]Dithian-1-ylidene-4-methylbenzene sulfonamide 148b[101]



148b

To a 100 ml round-bottomed flask was equipped with a condenser and magnetic stirrer were added dichloromethane (50 ml), 1,3-dithiane (0.5 g,4.2 mmol) and *n*-hexadecyl tri-*n*-butylphosphonium bromide (~0.2 mmol). Solid Chloramine-T (1.02 g, 4.5 mmol) was slowly added with stirring and cooling with a water bath. After addition was complete the water bath was removed and stirring was continued for 2 hrs. The reaction mixture was washed with cold aqueous sodium hydroxide (5%, 100 ml) followed by two washes with water (100 ml). The dichloromethane layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was recrystallised from chloroform-ether (2:1) and isolated as a white crystalline solid (0.95 g, 78%). m.p. 164-165°C (Found: C, 45.49; H, 5.17; N, 4.71. $C_{11}H_{15}NO_2S_3$ requires C, 45.65; H, 5.22; N, 4.84); υ_{max} ($CHCl_3$) /cm^{-1} 1279, 1139, 1090, 969; δ_H(250 MHz; DMSO-d_6) 7.63 (AA' of AA'BB', 2H, Ar), 7.30 (BB' of AA'BB', 2H, Ar), 4.29 (brd, J=12.5 Hz, 1H, H-1e), 4.24 (d, J=12.5 Hz, 1H, H-1a), 3.27 (m, 1H, H-4e), 3.14 (ddd, J=2.9, 12.3, 12.3 Hz, 1H, H-4a), 2.75 (ddd, J=2.6, 11.3, 12.5 Hz, 1H, H-2a), 2.60 (m, 1H, H-2e), 2.41 (m, 1H, H-3e), 2.05 (dddt, J=3.1, 11.7, 11.7, 14.9 Hz, 1H, H-3a), 2.35 (s, 3H, Me); δ_C (62.9 MHz; DMSO-d_6) 142.2 (Ar), 141.3 (Ar), 129.4 (Ar), 125.8 (Ar), 46.7 (C-4), 46.6 (C-2), 26.8 (C-3), 26.4 (C-4), 21.0 (Me); *m/z* (CI (NH_3)) 290 (44 MH^+%), 120 (59), 106 (100).

8.4.3 *N*-[1,3,5]-Trithian-1-ylidene-4-methylbenzene sulfonamide 148c[45]

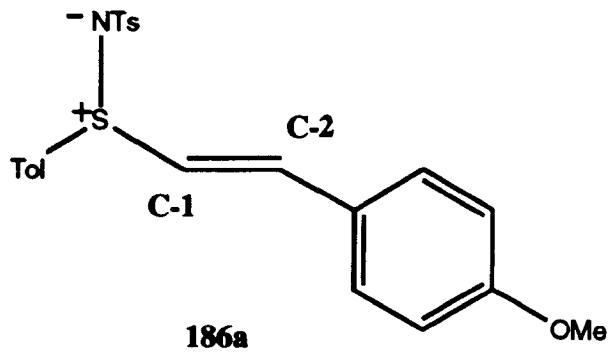


148c

A suspension of 1,3,5-trithiane (1.0 g,7.24 mmol) in a solution of Chloramine-T (2.0 g,8.76 mmol) in dimethylformamide (30 ml) was stirred at room temperature for 1 hr to give a clear solution, which was then poured into cold water. The resultant white precipitate was isolated by filtration and recrystallised from acetonitrile (1.78 g, 80%). m.p. 196-199°C; (Found: C, 38.92; H, 4.18; N, 4.36. $C_{10}H_{13}NO_2S_4$ requires C, 39.06; H, 4.26; N, 4.56); ν_{max} ($CHCl_3$)/cm^{-1} 1280, 1136,1090, 986; δ_H(400 MHz; d_6-DMSO) 7.65 (AA' of AA'BB', 2H, Ar), 7.31 (BB' of AA'BB', 2H, Ar), 4.76 (d, J=12.4 Hz, 2H, H-1e), 4.50 (d, J=12.4 Hz, 2H, H-1a), 4.35 (d, J=14.0 Hz, 1H, H-2e), 3.75 (d, J=14.0 Hz, 1H, H-2a), 2.35 (s, 3H, Me); δ_C (62.9 MHz; d_6-DMSO) 141.9 (Ar), 141.5 (Ar), 129.5 (Ar), 125.9 (Ar), 49.1 (C-1), 30.5 (C-2), 21.0 (Me); *m/z* (CI (NH_3)) 308 (1, MH^+ %), 232 (27), 201 (66), 189 (100), 155 (10).

8.5 Experimental for Chapter 5

8.5.1 *S*-*E*-(*p*-Methoxyphenyl)vinyl-*S*-*p*-tolyl-*N*-*p*-tosyl sulfimide 186a

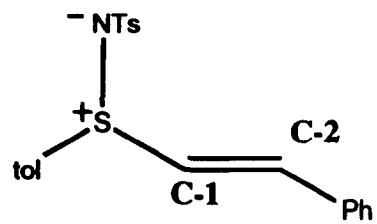


186a

To a solution of *S*-methyl-*S*-*p*-tolyl-*N*-*p*-tosyl sulfimide (1.0 g, 3.26 mmol) in THF (100 ml) at -78'C under nitrogen were added dropwise *n*-BuLi (2.5 M, 1.3 ml, 3.26 mmol), potassium *t*-butoxide (1.0 M, 3.27 ml, 3.26 mmol) and diethylchlorophosphate (0.47 mml, 3.26 mol). After stirring for 10 mins, *p*-anisaldehyde (0.4 ml, 3.26 mmol) in THF (2 ml) was added dropwise and the reaction left to warm to 0°C over 30 mins. Saturated aqueous ammonium chloride (100ml) was added, along with sufficient water to dissolve any salts precipitated, and the reaction extracted with CH_2Cl_2 (3x80 ml). The combined organic layers were washed with water (150 ml) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. A ^1H NMR spectrum of the crude product showed an E:Z ratio of 87:13. Column chromatography of the yellow oil on silica using ether as eluant gave a white solid (0.81 g, 58%). m.p. 122-124°C; Rf 0.30 (ether); (Found: C, 64.91; H, 5.45; N, 3.29. $C_{23}H_{23}NO_3S_2$ requires C, 64.81; H, 5.39; N, 3.23); ν_{max} (Nujol) /cm^{-1} 1602, 1512, 1465, 1307, 1293, 1170, 1136, 1087, 959, 802; δ_H(250 MHz; $CDCl_3$) 7.76 (AA' of AA'BB', 2H,

tosyl), 7.55 (AA' of AA'BB', 2H, tolyl), 7.30 (AA' of AA'BB', 2H, *p*-$MeOC_6H_4$), 7.26 (d, J=15.1 Hz, 1H, H-1), 7.25 (BB' of AA'BB', 2H, tosyl), 7.13 (BB' of AA'BB', 2H, tolyl), 6.85 (BB' of AA'BB, 2H, *p*-$MeOC_6H_4$), 6.42 (dd, J=0.9, 15.1 Hz, 1H, H-2), 3.79 (s, 3H, MeO), 2.36 (s, 3H, tosylMe), 2.29 (s, 3H, tolylMe); δ_C (62.9 MHz; $CDCl_3$) 161.6 (C-1), 142.9 (Ar), 141.5 (Ar), 141.45 (Ar), 141.3 (Ar), 132.3 (Ar), 130.5 (Ar), 129.7 (Ar), 129.0 (Ar), 126.6 (Ar), 126.2 (Ar), 125.3 (Ar), 119.8 (C-2), 114.3 (Ar), 55.4 (MeO), 21.3 (ArMe); *m/z* (EI) 426 (2 MH^+%), 256 (100), 241 21), 211 (35), 91 (76).

8.5.2 *S*-*E*-Styryl-*S*-*p*-tolyl-*N*-*p*-tosyl sulfimide *E*-186b

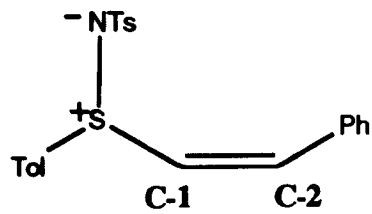


***E*-186b**

To a solution of *S*-methyl-*S*-*p*-tolyl-*N*-*p*-tosyl sulfimide (4.0 g, 0.013 mol) in THF (300 ml) at -78°C under nitrogen were added dropwise *n*-BuLi (2.5 M, 5.2 ml, 0.013 mol), potassium *t*-butoxide (1.0 M, 13 ml, 0.013 mol) and diethylchlorophosphate (1.88 ml, 2.0 mol). After stirring for 10 mins, benzaldehyde (1.32 ml, 0.013 mmol) in THF (5 ml) was added dropwise and the reaction left to warm to 0°C over 30 mins. Saturated aqueous ammonium chloride (300ml) was added, along with sufficient water to dissolve any salts precipitated, and the reaction extracted with CH_2Cl_2 (3x150 ml). The combined organic layers were washed with water (300 ml) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. A ^1H NMR spectrum of the crude product showed an E:Z ratio of 96:4, although this exceptional result could not be repeated, with the normal ratio being 87:13. Column chromatography of the yellow

oil on silica using $CHCl_3$:EtOAc 4:1 as eluant separated the stereoisomers (1.95 g, 38%). m.p. 121-122°C; Rf 0.33 (ether); (Found: C, 66.80; H, 5.35; N, 3.54. $C_{22}H_{21}NO_2S_2$ requires C, 66.90; H, 5.33; N, 3.46); δ_H(400 MHz; $CDCl_3$) 7.76 (AA' of AA'BB', 2H, tosyl), 7.55 (AA' of AA'BB', 2H, tolyl), 7.35 (m, 5H, Ph), 7.32 (d, J=15.2 Hz, 1H, H-1), 7.26 (BB' of AA'BB', 2H, tosyl), 7.14 (BB' of AA'BB', 2H, tolyl), 6.55 (d, J=15.2 Hz, 1H, H-2), 2.37 (s, 3H, tosylMe), 2.30 (s, 3H, tolylMe); δ_C (100.6 MHz; $CDCl_3$) 143.2 (Ar), 141.5 (Ar), 141.4 (Ar), 141.1 (C-1), 132.7 (Ar), 132.0 (Ar), 130.7 (Ar), 130.6 (Ar), 129.1 (Ar), 129.0 (Ar), 128.0 (Ar), 126.9 (Ar), 126.2 (Ar), 122.7 (C-2), 21.3 (2xArMe); *m/z* (CI/NH_3) 396 (8 MH^+%), 227 (92), 226 (100).

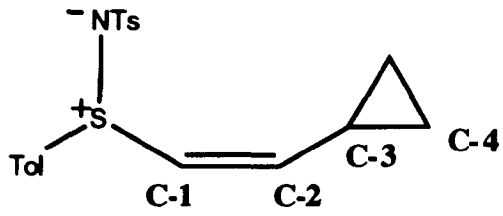
8.5.3 *S-Z*-Styryl-*S-p*-tolyl-*N-p*-tosyl sulfimide *Z*-186b



***Z*-186b**

The minor isomer was isolated by column chromatography (9%). m.p. 124-125°C; ν_{max} (Nujol) /cm^{-1} 1715, 1596, 1305, 1293, 1142, 1084, 955, 819, 814, 755, 724 δ_H(250 MHz; $CDCl_3$) 7.69 (AA' of AA'BB', 2H, tosyl), 7.53 (AA' of AA'BB', 2H, tolyl), 7.36 (m, 5H, Ph), 7.25 (BB' of AA'BB', 2H, tosyl), 7.13 (d, J=10.1 Hz, 1H, H-1), 7.09 (BB' of AA'BB, 2H, tolyl), 6.34 (d, J=10.1 Hz, 1H, H-2), 2.36 (s, 3H, tosMe), 2.32 (s, 3H, tolMe); δ_C (62.9 MHz; $CDCl_3$) 142.8 (Ar), 141.4 (Ar), 141.3 (Ar), 141.2 (C-1), 132.6 (Ar), 132.4 (Ar), 130.5 (Ar), 130.1 (Ar), 129.4 (Ar), 129.0 (Ar), 128.8 (Ar), 126.3 (Ar), 126.2 (Ar), 126.1 (C-2), 21.3 (2xArMe).

8.5.4 *S-Z*-Cyclopropyl-*S*-*p*-tolyl-*N*-*p*-tosyl sulfimide *Z*-186d

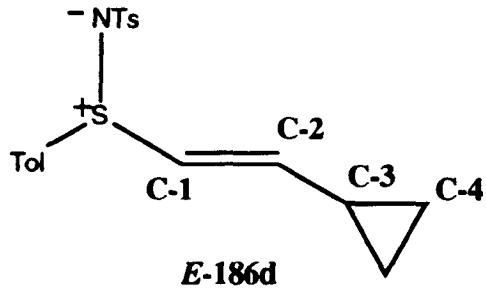


Z-186d

To a solution of *S*-methyl-*S*-*p*-tolyl-*N*-*p*-tosyl sulfimide (614 mg, 2.0 mmol) in THF (40 ml) at -78°C under nitrogen were added dropwise *n*-BuLi (2.5 M, 0.80 ml, 2.0 mmol), potassium *t*-butoxide (1.0 M, 2 ml, 2.0 mmol) and diethylchlorophosphate (0.29 ml, 2.0 mmol). After stirring for 10 mins, cyclopropane carboxyaldehyde (0.149 ml, 2.0 mmol) in THF (1 ml) was added dropwise and the reaction left to warm to 0°C over 30 mins. Saturated aqueous ammonium chloride (40 ml) was added, along with sufficient water to dissolve any salts precipitated, and the reaction extracted with CH_2Cl_2 (3x50 ml). The combined organic layers were washed with water (100 ml) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. A ^1H nmr spectrum of the crude product showed a product E:Z of 53:47. Column chromatography of the yellow oil on silica using $CHCl_3$:EtOAc (4:1) as eluant separated the stereoisomers (total yield 280 mg, 39%). Found MH^+ 360.1104, $C_{19}H_{22}NO_2S_2$ MH^+ requires 360.1092 υ_{max} (nujol) /cm^{-1} 1606, 1292, 1280, 1142, 1089, 981, 734, 661; δ_H(250 MHz; $CDCl_3$) 7.79 (AA' of AA'BB', 2H, tosyl), 7.57 (AA' of AA'BB', 2H, tolyl), 7.28 (BB' of AA'BB, 2H, tosyl), 7.18 (AA' of AA'BB, 2H, tolyl), 6.04 (dd, J=0.6, 9.0 Hz, 1H, H-1), 5.58 (dd, J=9.0, 10.8 Hz, 1H, H-2), 2.39 (s, 3H, tosyl Me), 2.36 (s, 3H, tolyl Me), 2.03 (m, 1H, H-3), 0.99 (m, 2H, H-4), 0.59 (m, 2H, H-4'); δ_C (62.9 MHz; $CDCl_3$) 150.6 (C-1), 142.3 (Ar), 141.7 (Ar), 141.3 (Ar), 132.6 (Ar), 130.4 (Ar), 129.0

(Ar), 126.3 (Ar), 125.9 (Ar), 123.9 (C-2), 21.3 (2xArMe), 12.4 (C-3), 9.1 (C-4), 8.7 (C-4'); *m/z* (FAB) 360 (100 MH+%), 190 (14), 123 (46).

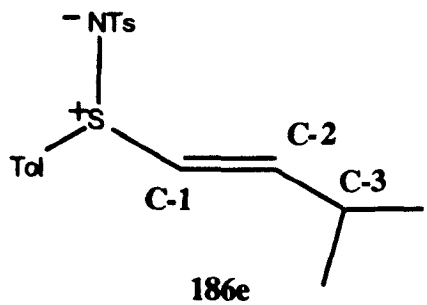
8.5.5 *S*-*E*-Cyclopropyl-*S*-*p*-tolyl-*N*-*p*-tosyl sulfimide *E*-186d



E-186d

Rf 0.32 ($CHCl_3$:EtOAc 4:1); δ_H(250 MHz; $CDCl_3$) 7.74 (AA' of AA'BB', 2H, tosyl), 7.49 (AA' of AA'BB', 2H, tolyl), 7.26 (BB' of AA'BB, 2H, tosyl), 7.16 (AA' of AA'BB, 2H, tolyl), 6.02 (d, J=14.5 Hz, 1H, H-1), 6.01 (dd, J=10.8, 14.5 Hz, 1H, H-2), 2.38 (s, 3H, tosMe), 2.35 (s, 3H, tolMe), 1.53 (m, 1H, H-3), 0.93 (m, 2H, H-4), 0.58 (m, 2H, H-4); δ_C (62.9 MHz; $CDCl_3$) 150.7 (C-1), 142.7 (tol), 141.6 (tos), 141.3 (tos), 132.3 (tol), 130.4 (tol), 129.0 (tos), 126.5 (tol), 126.2 (tos), 121.2 (C-2), 21.3 (2xArMe), 14.5 (C-3), 8.7 (C-4).

8.5.6 *S*-*E*-*i*-Propyl-*S*-*p*-tolyl-*N*-*p*-tosyl sulfimide 186e

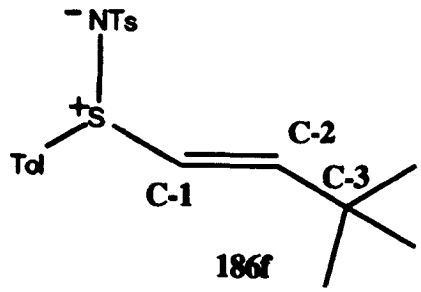


186e

To a solution of *S*-methyl-*S*-*p*-tolyl-*N*-*p*-tosyl sulfimide (1.0 g, 3.26 mmol) in THF (100 ml) at -78°C under nitrogen were added dropwise *n*-BuLi (2.5 M, 1.30 ml, 3.26 mmol), potassium *t*-butoxide (1.0 M, 3.26 ml, 3.26 mmol)

and diethylchlorophosphate (0.47 ml, 3.26 mmol). After stirring for 10 mins, isobutyraldehyde (0.30 ml, 3.26 mmol) in THF (1 ml) was added dropwise and the reaction left to warm to 0°C over 30 mins. Saturated aqueous ammonium chloride (100 ml) was added, along with sufficient water to dissolve any salts precipitated, and the reaction extracted with CH_2Cl_2 (3x80 ml). The combined organic layers were washed with water (200 ml) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. A ^1H nmr spectrum of the crude product showed an E:Z ratio of >98:2. Column chromatography of the yellow oil on silica using ether as eluant gave a white crystalline solid (412 mg, 35%). m.p. 108-110°C; Rf 0.37 (ether); υ_{max} (Nujol) /cm^{-1} 1602, 1490, 1284, 1138, 1088, 1021, 962; δ_H(250 MHz; $CDCl_3$) 7.72 (AA' of AA'BB', 2H, tosyl), 7.47 (AA' of AA'BB', 2H, tolyl), 7.25 (BB' of AA'BB', 2H, tosyl), 7.15 (BB' of AA'BB', 2H, tolyl), 6.55 (dd, 6.4, J=15.1 Hz, 1H, H-2), 5.94 (dd, J=1.3, 14.8 Hz, 1H, H-1), 2.41 (dseptet, J=1.3, 6.8 Hz, 1H, H-3), 2.36 (s, 3H, tosylMe), 2.33 (s, 3H, tolylMe), 0.97 (d, J=7.0 Hz, 6H, Me); δ_C (62.9 MHz; $CDCl_3$) 151.7 (C-1), 142.9 (Ar), 141.5 (Ar), 141.4 (Ar), 132.0 (Ar), 130.4 (Ar), 129.0 (Ar), 126.5 (Ar), 126.2 (Ar), 123.1 (C-2), 31.3 (C-3), 21.3 (ArMe), 20.9 (Me), 20.8 (Me'); *m/z* (CI/NH_3) 362 (100 MH^+%).

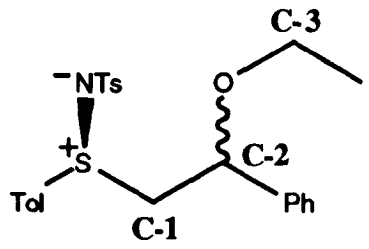
8.5.7 *S-E-t*-Butyl-*S*-*p*-tolyl-*N*-*p*-tosyl sulfimide 186f



186f

To a solution of *S*-methyl-*S*-*p*-tolyl-*N*-*p*-tosyl sulfimide (1.0 g, 3.26 mmol) in THF (100 ml) at -78'C under nitrogen were added dropwise *n*-BuLi (2.5 M, 1.30 ml, 3.26 mmol), potassium *t*-butoxide (1.0 M, 3.26 ml, 3.26 mmol) and diethylchlorophosphate (0.47 ml, 3.26 mmol). After stirring for 10 mins, trimethylacetaldehyde (pivalaldehyde) (0.354 ml, 3.26 mmol) in THF (1 ml) was added dropwise and the reaction left to warm to 0°C over 30 mins. Saturated aqueous ammonium chloride (100 ml) was added, along with sufficient water to dissolve any salts precipitated, and the reaction extracted with CH_2Cl_2 (3x80 ml). The combined organic layers were washed with water (200 ml) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. A ^1H NMR spctrum of the crude product showed an E:Z ratio of >98:2. Column chromatography of the yellow oil on silica using ether as eluant gave a white crystalline solid (480 mg, 39%). m.p. 146-147°C; Rf 0.46 (ether); (Found: C, 63.96; H, 6.76; N, 3.73. $C_{20}H_{25}NO_2S_2$ requires C, 63.82; H, 6.66; N, 3.71); υ_{max} (Nujol) /cm^{-1} 1598, 1492, 1284, 1141, 1089, 1021, 962; δ_H(250 MHz; $CDCl_3$) 7.73 (AA' of AA'BB', 2H, tosyl), 7.47 (AA' of AA'BB', 2H, tolyl), 7.25 (BB' of AA'BB', 2H, tosyl), 7.15 (BB' of AA'BB', 2H, tolyl), 6.53 (d, J=15.0 Hz, 1H, H-2), 5.89 (d, 15.0, 1H, H-1), 2.36 (s, 3H, tosylMe), 2.32 (s, 3H, tolylMe), 0.98 (s, 9H, *t*-Bu); δ_C (62.9 MHz; $CDCl_3$) 155.3 (C-1), 142.9 (Ar), 141.6 (Ar), 141.4 (Ar), 132.1 (Ar), 130.4 (Ar), 129.0 (Ar), 126.6 (Ar), 126.5 (Ar), 126.2 (C-2), 34.7 (C-3), 28.3 (*t*-Bu), 21.3 (2xArMe); *m/z* (CI/NH_3) 376 (100 MH^+%), 220 (43), 207 (26), 206 (17).

8.5.8 *S*-(2-Ethoxy-2-phenylethyl)-*S*-*p*-tolyl-*N*-*p*-tosyl sulfimide 185a

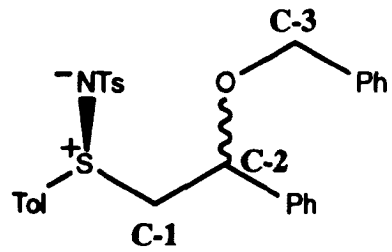


185a

A solution of phenyl vinyl sulfimide (200 mg,0.51 mmol) and sodium hydride (60%; hexane washed, 4 mg, 0.1 mmol, 20 mol%) in ethanol (40 ml) was stirred at room temperature for 5 days. Water (40ml) was added and then the aqueous solution was extracted with CH_2Cl_2 (3 x 40 ml). The combined organic extracts were dried over magnesium sulfate and evaporated to dryness to leave a white residue (80% de). Column chromatography over silica with ether:petroleum ether (8:1) as eluant followed by recrystallisation from ether:petroleum ether gave a white powder (165 mg, 73%). m.p. 127-129°C; Rf 0.33 (ether:petroleum ether); (Found: C, 64.96; H, 6.04; N, 3.34). $C_{24}H_{27}NO_3S_2$ requires C, 65.28; H, 6.16; N, 3.17); ν_{max} (Nujol) /cm^{-1} 1295, 1282, 1140, 1090, 969, 722, 656; δ_H(400 MHz; $CDCl_3$) 7.82 (AA' of AA'BB', 2H, tosyl), 7.60 (AA' of AA'BB', 2H, tolyl), 7.25 (m, 5H, Ph), 7.24 (BB' of AA'BB', 2H, tosyl), 7.18 (BB' of AA'BB', 2H, tolyl), 4.60 (dd, J=2.2, 10.9 Hz, 1H, H-2), 3.23 (dq, J=7.0, 8.8 Hz, 1H, H-3a), 3.19 (dd, J=2.3, 12.9 Hz, 1H, H-1a), 3.05 (dd, J=10.9, 12.9 Hz, 1H, H-1b), 2.96 (dq, J=7.0, 8.8 Hz, 1H, H-3b), 2.35 (s, 3H, tosylMe), 2.33 (s, 3H, tolylMe), 1.07 (t, J=7.0 Hz, 3H, H-4); δ_C (100.6 MHz; $CDCl_3$) 142.9 (Ar), 141.4 (Ar), 141.36 (Ar), 138.5 (Ar), 132.4 (Ar), 130.4 (Ar), 129.0 (Ar), 108.7 (Ar), 128.4 (Ar), 126.3 (Ar), 125.9 (Ar), 74.6 (C-2), 64.6 (C-3),

62.3 (C-1), 21.3 (tosylMe), 21.2 (tolylMe), 14.97 (Me); *m/z* (CI/NH_3) 442 (12 MH^+%).

8.5.9 *S*-(2-Phenyl-2-(phenylmethoxy)ethyl)-*S*-*p*-tolyl-*N*-*p*-tosyl sulfimide 185b

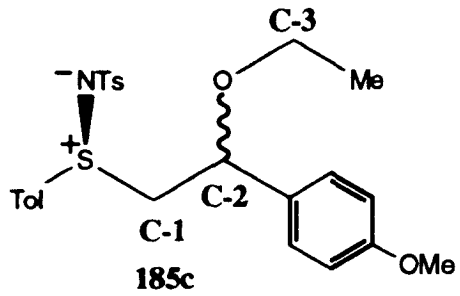


185b

A solution of phenyl vinyl sulfimide (400 mg, 1.0 mmol) and sodium hydride (60%; hexane washed, 8 mg, 20 mol%) in benzyl alcohol (60 ml) was stirred at room temperature for 3 days. Water (100ml) was added and then the aqueous solution was extracted with CH_2Cl_2 (3 x 60 ml). The combined organic extracts were dried over magnesium sulfate and evaporated to dryness to leave a white residue (>95% de). Column chromatography on silica with 10% EtOAc:$CHCl_3$ as eluant followed by recrystallisation from ether:petroleum ether gave one diastereoisomer as a white powder (325 mg, 63%). m.p. 146-148°C; Rf 0.29 (10% EtOAc:$CHCl_3$); $C_{29}H_{29}NO_3S_2$ (Found: C, 68.83; H, 5.79; N, 2.77; requires C, 69.15; H, 5.80; N, 2.78; (Found MH^+ 504.1670. MH^+ requires 504.1669) υ_{max} (Nujol) /cm^{-1} 1283, 1140, 1116, 1090, 967, 725, 656; δ_H(400 MHz; $CDCl_3$) 7.81 (AA' of AA'BB', 2H, tosyl), 7.60 (AA' of AA'BB', 2H, tolyl), 7.30 (m, 10H, Ph), 7.24 (BB' of AA'BB', 2H, tosyl), 7.10 (BB' of AA'BB', 2H, tolyl), 4.81 (dd, J=2.2, 10.9 Hz, 1H, H-2), 4.20 (d, J=10.5 Hz, 1H, H-3), 4.06 (d, J=10.5 Hz, 1H, H3'), 3.27 (dd, J=2.2, 12.9 Hz, 1H, H-1a), 3.15 (dd, J=10.9,

12.8 Hz, 1H, H-1b), 2.35 (3s, 3H, tosylMe), 2.25 (s, 3H, tolylMe); δ_C (100.6 MHz; $CDCl_3$) 142.96 (Ar), 141.4 (Ar), 141.3 (Ar), 138.0 (Ar), 137.4 (Ar), 132.2 (Ar), 130.4 (Ar), 129.1 (Ar), 128.9 (Ar), 128.7 (Ar), 128.3 (Ar), 127.8 (Ar), 127.7 (Ar), 126.5 (Ar), 126.3 (Ar), 125.9 (Ar), 74.96 (C-2), 71.0 (C-3), 62.5 (C-1), 21.3 (ArMe), 21.2 (ArMe); *m/z* (CI/NH_3) 504 (3 MH^+%), 311 (42), 211 (53), 189 (100).

8.5.10 *S*-(2-(*p*-Methoxyphenyl)-2-(ethoxy)ethyl)-*S*-*p*-tolyl-*N*-*p*-tosyl sulfimide 185c

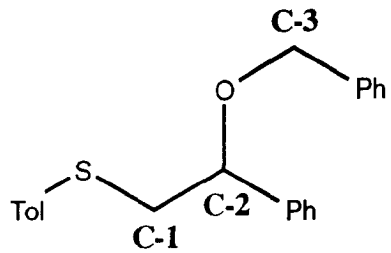


185c

To a solution of vinyl sulfimide (50 mg, 0.12 mmol) in ethanol (5 ml) was added sodium hydride (~1 mg, 20 mol%) and the solution stirred for 5 days at room temperature under nitrogen. Water (10 ml) was added and then the mixture was extracted with CH_2Cl_2 (3x10 ml). The combined organic layers were dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. A ^1H NMR spectrum of the crude residue gave a de of 78%. Column chromatography on silica using petroleum ether:EtOAc (3:2) as eluant gave a white residue (18 mg, 32%). Rf 0.33 (3:2 petroleum ether:EtOAc); δ_H(400 MHz; $CDCl_3$) 7.81 (AA' of AA'BB', 2H, tosyl), 7.60 (AA' of AA'BB', 2H, tolyl), 7.25 (BB' of AA'BB', 2H, tosyl), 7.18 (BB' of AA'BB', 2H, tolyl), 7.17 (AA' of AA'BB', 2H, *p*-$MeOC_6H_4$), 6.83 (BB' of AA'BB, 2H, *p*-$MeOC_6H_4$), 4.55 (dd, J=1.8, 10.9 Hz, 1H, H-2), 3.76 (s, 3H, MeO), 3.20 (dq, J=7.0, 8.8 Hz, 1H, H-3), 3.17 (dd, J=1.8, 12.8 Hz,

1H, H-1b), 3.04 (dd, J=10.9, 12.8 Hz, 1H, H-1a), 2.92 (dq, J=7.0, 8.8 Hz, 1H, $H_{3'}$), 2.35 (s, 3H, tosylMe), 2.33 (s, 3H, tolylMe), 1.05 (t, J=7.0 Hz, 3H, Me);.

8.5.11 4-Methyl-1-(2-phenyl-2–(phenylmethoxy)ethyl sulfanyl)benzene 192

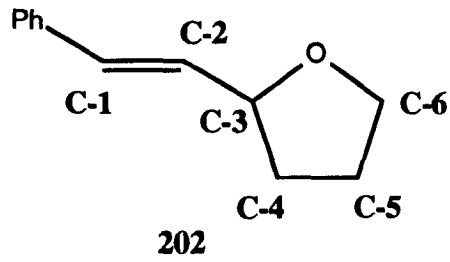


192

A solution of sulfimide **185b** (8 mg, 0.016 mmol) and 10% palladium on carbon (1 mg, 1 eq.) in degassed EtOAc (2 ml) was stirred at room temperature under a positive pressure of hydrogen gas for 5 days. Filtration through celite using EtOAc as eluant and concentration under reduced pressure afforded a yellow oil. Column chromatography on silica using 10% EtOAc:$CHCl_3$ as eluant gave a pale yellow oil (3 mg, 56%). (Found M+NH_4^+ 352.1737. M+NH_4^+ requires 352.1737); δ_H(400 MHz; $CDCl_3$) 7.30 (m, 10H, Ar), 7.21 (AA' of AA'BB', 2H, tolyl), 7.04 (BB' of AA'BB', 2H, tolyl), 4.48 (d, J=11.8 Hz, 1H, H-3a), 4.47 (dd, J=5.2, 8.0 Hz, 1H, H-2), 4.29 (d, J=11.8 Hz, 1H, H-3b), 3.35 (dd, J=8.0, 13.4 Hz, 1H, H-1a), 3.10 (dd, J=5.2, 13.4 Hz, 1H, H-1b), 2.30 (s, 3H, ArMe); δ_C (100.6 MHz; $CDCl_3$) 140.6 (Ar), 137.96 (Ar), 136.0 (Ar), 132.7 (Ar), 130.0 (Ar), 129.5 (Ar), 128.5 (Ar), 128.2 (Ar), 128.0 (Ar), 127.7 (Ar), 127.5 (Ar), 126.8 (Ar), 79.98 (C-2), 70.7 (C-1), 42.3 (C-3), 20.9 (ArMe); *m/z* (CI/NH_3) 352 (100 M+NH_4^+%).

8.6 Experimental for Chapter 6

8.6.1 2-*E*-Styryltetrahydrofuran 202[140]



202

Method A

A solution of vinyl sulfimide ***E*-186b** (50 mg, 0.13 mmol) and benzoyl peroxide (2 mg, 5 mol%) in THF (8 ml) was refluxed for 2 hrs. Four subsequent additions of benzoyl peroxide (2 mg, 5 mol%) over 24 hrs followed by concentration of the mixture under reduced pressure gave a pale yellow oil. Column chromatography on silica using 30% PE:EtOAc as eluant afforded a colourless oil (10 mg, 45%).

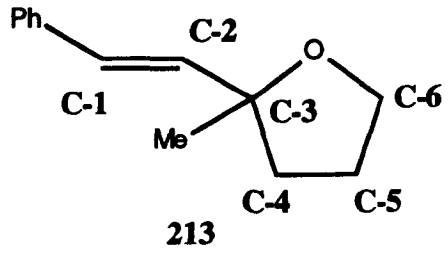
Method B

A solution of vinyl sulfimide ***E*-186b** (50 mg, 0.01 M) and triethyl borane (in THF; 1.0 M, 1.27 ml) in THF (11.4 ml) was stirred at room temperature for 18 hrs. Quenching with 10% aqueous sodium dihydrogen phosphate (10 ml) and extraction with ether (3x20 ml) was followed by drying over magnesium sulfate and filtration. Concentration under reduced pressure afforded a pale yellow oil, which was purified as in Method A (14 mg, 63%).

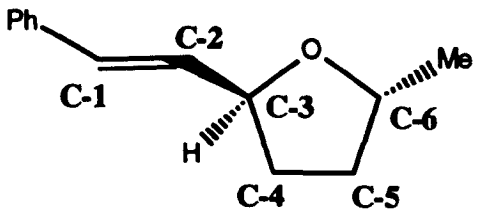
Method C

A solution of vinyl sulfimide ***E*-186b** (700 mg, 1.77 mmol) and *t*-butyl peroxide (65 μl, 20 mol%) in THF (40 ml) was heated in an autoclave at 150°C at ~20 atm for 6 hrs. Concentration of the reaction mixture followed by bulb-to-bulb distillation under reduced pressure afforded a colourless oil (240 mg, 77%); Rf 0.28 (30% petroleum ether:EtOAc); δ_H(400 MHz; $CDCl_3$) 7.27 (m, 5H, Ph), 6.57 (d, J=15.9 Hz, 1H, H-1), 6.20 (dd, J=6.6, 15.9 Hz, 1H, H-2), 4.47 (q, J=6.6 Hz, 1H, H-3), 3.96 (d, J=6.5 Hz, 1H, H-6a), 3.83 (dt, J=6.5, 7.8 Hz, 1H, H-6b), 2.12 (m, 1H, H-4a), 1.95 (m, 2H, H-5), 1.71 (m, 1H, H-4b); δ_C (100.6 MHz; $CDCl_3$) 136.8 (Ar), 130.4 (C-1/2), 130.3 (C-1/2), 128.4 (Ar), 127.4 (Ar), 126.3 (Ar), 79.6 (C-3), 68.1 (C-6), 32.3 (C-4), 25.8 (C-5); *m/z* (EI) 174 (56 M^+%), 131 (100), 91 (64), 77 (93).

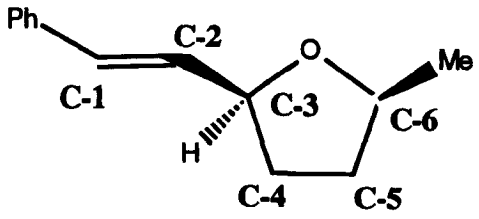
8.6.2 2-Methyl-2-*E*-styryltetrahydrofuran 213 and anti/syn 5-methyl-2-*E*-styryltetrahydrofuran 214



213



anti-214

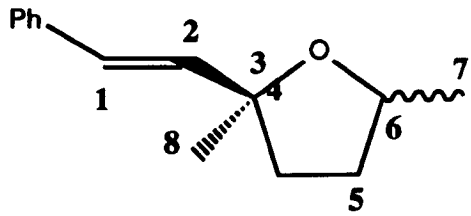


syn-214

A solution of vinyl sulfimide ***E*-186b** (50 mg, 0.13 mmol) and benzoyl peroxide (2 mg, 5 mol%) in 2-methyltetrahydrofuran (8 ml) was heated to reflux for 48 hrs. Concentration under reduced pressure gave a yellow oil.

Column chromatography on silica using 30% petroleum ether:CH_2Cl_2 as eluant afforded an inseparable mixture of regio- and diastereoisomers as a colourless oil (19 mg, 79%). The ratio of stereoisomers was determined by ^1H NMR (*syn* **214** : *anti* **214** : **213** 1:2.9:3.9), with selected chemical shifts for each isomer presented below. Rf 0.24); δ_H(250 MHz; $CDCl_3$); *anti* isomer: 6.57 (d, J=16.3 Hz, 1H, H-1), 6.21 (dd, J=6.7, 15.7 Hz, 1H, H-2), 4.46 (~q, J=6.8 Hz, 1H, H-3), 4.22 (m, 1H, H-6), 1.28 (d, J=6.1 Hz, 3H, Me); *syn* isomer: 6.59 (d, J=15.7 Hz, 1H, H-1), 6.20 (dd, J=6.7, 15.6 Hz, 1H, H-2), 4.62 (dq, J=1.2, 6.7 Hz, 1H, H-3), 4.09 (m, 1H, H-6), 1.31 (d, J=6.1 Hz, 3H, Me); x: 6.56 (d, J=15.98 Hz, 1H, H-1), 6.25 (d, J=15.98 Hz, 1H, H-2), 3.95 (m, 2H, H-6), 1.41 (s, 3H, Me); *m/z* (CI/NH_3) 189 (62 MH^+%), 173 (15), 162 (23), 131 (35), 124 (40), 105 (48), 91 (56), 85 (100).

8.6.3 2,5-Dimethyl-2-*E*-styryltetrahydrofuran 215

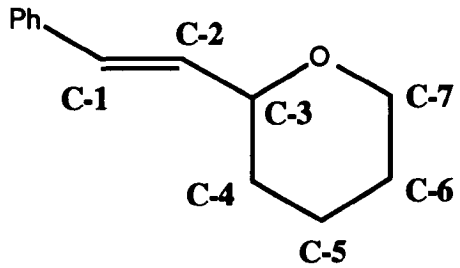


215

A solution of vinyl sulfimide ***E*-186b** (50 mg, 0.13 mmol) and benzoyl peroxide (2 mg, 5 mol%) in 2,5-dimethyltetrahydrofuran (8 ml) was heated to reflux for 30 hrs. Concentration under reduced pressure gave a yellow oil. Column chromatography on silica using 30% petroleum ether:CH_2Cl_2 as eluant afforded a colourless oil as a mixture of diastereoisomers (*anti*:*syn* 71:29, 12 mg, 47%). Rf 0.34; δ_H(250 MHz; $CDCl_3$); *anti* isomer: 7.27 (m, 5H, Ph), 6.55 (d, J=16.0 Hz, 1H, H-1), 6.24 (d, J=16.0 Hz, 1H, H-2), 4.17 (~q, J=6.1 Hz, 1H, H-6), 2.02 (m, 2H, H-4/5), 1.88 (m, 2H, H-4/5), 1.42 (s, 3H, H-8), 1.28 (d, J=6.1 Hz, 3H, H-7); *syn* isomer: 7.27 (m, 5H,

Ph), 6.60 (d, J=15.98 Hz, 1H, H-1), 6.29 (d, J=15.98 Hz, 1H, H-2), 4.19 (~q, J=6.1 Hz, 1H, H-6), 2.02 (m, 2H, H-4/5), 1.88 (m, 2H, H-4/5), 1.40 (s, 3H, H-8), 1.32 (d, 6.1, 3H, H-7); *m/z* (EI) 202 (33 M+%), 187 (82), 131 (85), 91 (64), 77 (25).

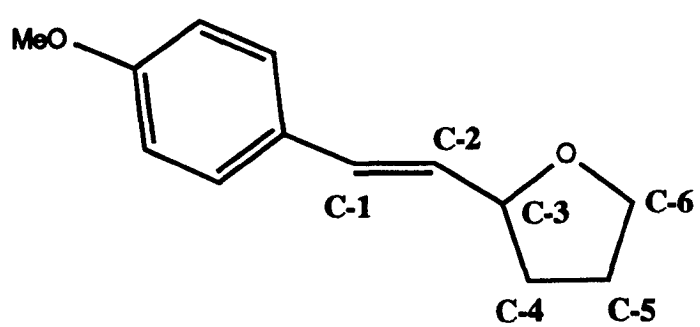
8.6.4 2-*E*-Styryltetrahydropyran 210[140]



210

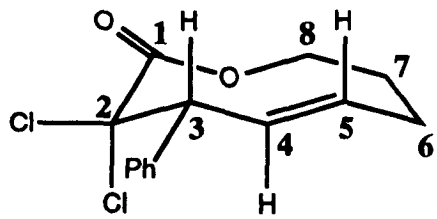
A solution of vinyl sulfimide ***E*-186b** (50 mg, 0.13 mmol) and benzoyl peroxide (4 mg, 10 mol%) in THP (8 ml) was refluxed for 48 hrs. Concentration of the mixture under reduced pressure gave a pale yellow oil. Column chromatography on silica using 30% petroleum ether:CH_2Cl_2 as eluant afforded a colourless oil (21 mg, 87%). δ_H(250 MHz; $CDCl_3$) 7.27 (m, 5H, Ph), 6.29 (dd, J=1.2, 15.98 Hz, 1H, H-1), 6.21 (dd, J=5.8, 16.3 Hz, 1H, H-2), 4.07 (m, 1H, H-7a), 3.97 (m, 1H, H-7b), 3.54 (m, 1H, H-3), 1.90 (m, 1H, H-4a), 1.74 (m, 1H, H-4b), 1.59 (m, 4H, H-5,6); *m/z* (EI) 188 (88 M+%), 131 (65), 104 (100), 91 (92), 77 (40).

8.6.5 2-*E*-2-(*p*-Methoxyphenyl)ethenyltetrahydrofuran



A solution of vinyl sulfimide **186a** (0.012 M, 50 mg, 1.18 x 10^{-4} mmol) and benzoyl peroxide (2mg, 5 mol%) in THF (10 ml) was heated to reflux for 16 hrs, during which time 4 further additions of 2 mg of benzoyl peroxide were made. Concentration under reduced pressure yielded a yellow oil. Column chromatography on silica using petroleum ether:dichloromethane (3:7) as eluant afforded a colourless oil (20 mg, 84%). (Found M^+ 204.1146 $C_{13}H_{16}O_2$ requires 204.1150); υ_{max} (neat) /cm^{-1} 2925, 1734, 1605, 1512, 1282, 1256, 1175, 1164, 1143, 1110, 1089, 1032, 968, 812, 756; δ_H(250 MHz; $CDCl_3$) 7.31 (AA' of AA'BB', 2H, Ar), 6.84 (BB' of AA'BB', 2H, Ar), 6.53 (d, J=15.9 Hz, 1H, H-1), 6.07 (dd, J=6.9, 15.9 Hz, 1H, H-2), 4.47 (brq, J=6.9 Hz, 1H, H-3), 3.96 (m, 1H, H-6a), 3.83 (dt, J=6.2, 7.8 Hz, 1H, H-6b), 3.80 (s, 3H, MeO), 2.12 (m, 1H, H-4a), 1.95 (m, 2H, H-5), 1.69 (m, 1H, H-4b); *m/z* (CI/NH_3) 205 (100 MH^+%), 173 (15), 147 (21), 137 (43), 83 (85).

8.6.6 *E*-3,3-Dichloro-4-phenyl-4,7,8,9-tetrahydro-3H-oxoin-2-one 220

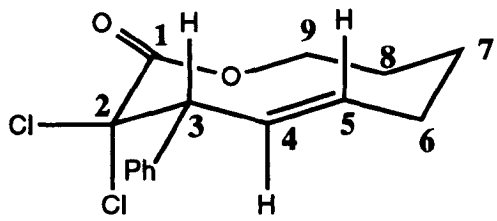


220

2-*E*-Styryltetrahydrofuran (50 mg, 0.29 mmol) and activated zinc (as zinc/copper couple, 23 mg, 0.35 mmol) in ether:hexane (1:1, 8 ml) were stirred at room temperature under nitrogen. Trichloroacetylchloride (36 ul, 0.32 mmol) in ether:hexane (2 ml) was then added and the reaction heated to reflux for 12 hrs. Filtration through a short pad of celite using EtOAc as eluant removed zinc residues. Evaporation to dryness and

subsequent column chromatography of the pale yellow oil using silica and Dichloromethane as eluant afforded a colourless oil (40 mg, 23%); Rf 0.58 (CH_2Cl_2); Found M+NH_4^+ 302.0715; M+NH_4^+ requires 302.0716); υ_{max} (Nujol) /cm^{-1} 1750, 1496, 1263, 1222, 1005, 976, 847, 801, 747, 697; δ_H(400 MHz; $CDCl_3$) 7.38 (m, 5H, Ph), 6.06 (dd, J=10.5, 15.9 Hz, 1H, H-5), 5.76 (ddd, J=6.1, 9.2, 15.9 Hz, 1H, H-6a), 4.91 (ddd, J=3.3, 6.9, 11.5 Hz, 1H, H-8a), 4.21 (ddd, J=3.3, 6.9, 11.5 Hz, 1H, H-8e), 4.04 (d, J=10.5 Hz, 1H, H-4), 2.40 (m, 1H, H-6b), 2.26 (m, 1H, H-6b), 1.95 (m, 2H, H-7); δ_C (100.6 MHz; $CDCl_3$) 167.3 (C-2), 135.1 (C-6,), 130.3 (Ph), 128.9 (C-5), 128.1 (Ph), 127.8 (Ph), 127.3 (Ph), 89.0 (C-3), 69.8 (C-9), 61.9 (C-4), 27.9 (C-7), 26.9 (C-8); *m/z* (CI/NH_3) 302 (19 M+NH_4^+%), 268 (24), 232 (22), 198 (100), 88 (85).

8.6.7*E*-3,3-Dichloro-4-phenyl-3,4,7,8,9,10-hexahydro-oxecin-2-one 221



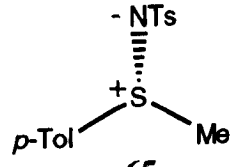
221

2-*E*-Styryltetrahydropyran (15 mg, 0.08 mmol) and activated zinc (as zinc/copper couple, 7 mg, 0.1 mmol) in ether:hexane (1:1, 2 ml) were stirred at room temperature under nitrogen. Trichloroacetylchloride (10 µl, 0.09 mmol) in ether:hexane (1 ml) was then added and the reaction heated to reflux for 10 hrs. Filtration through a short pad of celite using EtOAc as eluant removed zinc residues. Evaporation to dryness afforded a pale yellow oil (9 mg, 37%);. (Found M+NH_4^+ 316.0871; M+NH_4^+ requires 316.0873); υ_{max} (neat) /cm^{-1} 2983, 2936, 1699, 1375, 1341, 1261, 1046, 840; δ_H(400 MHz; $CDCl_3$) 7.50 (m, 2H, ortho-Ar), 7.35 (m, 3H, Ar),

5.97 (ddd, J=1.2, 10.3, 15.3 Hz, 1H, H-5), 5.58 (ddd, J=4.4, 10.5, 15.3 Hz, 1H, H-6), 4.70 (ddd, J=1.2, 8.5, 11.4 Hz, 1H, H-9a), 4.08 (m, 1H, H-9e), 4.01 (d, J=10.3 Hz, 1H, H-4), 2.27 (m, 1H, H-7a), 1.97 (m, 3H, H-7b,8a,9a), 1.70 (m, 1H, H-9b), 1.53 (m, 1H, H-8b); δ_C (100.6 MHz; $CDCl_3$) 167.0 (C-2), 136.9 (C-6), 134.7 (Ph), 130.4 (Ph), 128.1 (Ph), 127.8 (Ph), 127.2 (C-5), 89.9 (C-3), 68.8 (C-10), 62.1 (C-4), 32.7 (C-7), 29.2 (C-8/9), 28.2 (C-8/9); *m/z* (CI/NH_3) 316 (10 M+NH_4^+%), 229 (21).

8.7 Experimental for Chapter 7

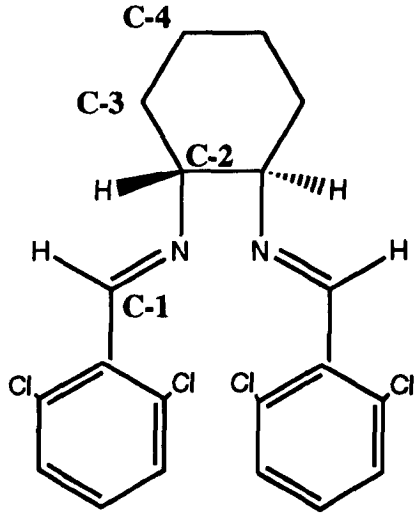
8.7.1 General procedure for asymmetric sulfimidation



65

Copper(I) triflate (5 mol%) and chiral ligand (5 mol%) were stirred in solvent (see Tables) for an hour at room temperature. After this time, the solution was cooled to the desired temperature (see Tables), and methyl *p*-tolyl sulfide and PhI=NTs or tosyl azide (in which case the solution was then heated to reflux) were added. After completion of the reaction, as judged by tlc, the solvent was removed by evaporation under reduced pressure. Filtration through a short pad of silica using ethyl acetate as eluant removed any insoluble copper species. Evaporation under reduced pressure gave crude solid. Column chromatography on silica using dichloromethane0 as eluant afforded a white crystalline solid.

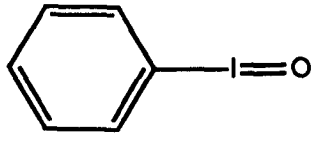
8.7.2 (1*S*,2*S*)-*N*,*N*-Bis-(2,6-dichlorobenzylidene)-diamino-cyclohexane 227[149a]



227

A solution of 2,6-dichlorobenzaldehyde (232 mg, 1.33 mmol) and (-)-(1*R*, 2*R*)-diaminocyclohexane (76 mg, 0.66 mmol) in absolute ethanol (5 ml) was heated to reflux for 1 hr and then allowed to cool to room temperature. The product crystallised from the cooled solution and was collected by suction filtration. The white crystalline solid was dried in a dessicator (230 mg, 81%). mp. 148-150°C, lit. 150-151°C; δ_H(250 MHz; $CDCl_3$); 8.46 (s, 2H, H-1), 7.23 (m, 6H, Ar), 3.60 (brm, 2H, H-2), 1.89 (brm, 6H, H-3/4), 1.57 (brm, 2H, H-3/4).

8.7.3 Iodosobenzene 230[155,156]

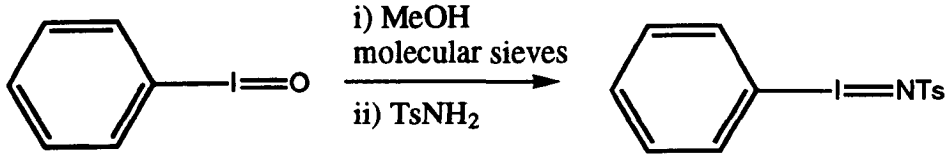


230

A solution of iodobenzene (10.2 g, 5.2 ml, 0.05 mol) in chloroform, protected from the light, was cooled in an ice-salt bath. Dry chlorine gas was bubbled into the flask, just above the surface of the liquid, for about 3

hrs. Iodobenzene dichloride crystallised from the solution and was collected by suction filtration. After washing with a little chloroform, the yellow, crystalline solid was dried in air (10.3 g, 75%). To a large mortar chilled in an ice bath were added iodobenzene dichloride (10.3 g, 0.038 mol), sodium carbonate (10 g) and finely crushed ice (20 g). The mixture was ground thoroughly until a thick paste resulted, and then 5M sodium hydroxide (60 ml) was added in small portions (15 ml), with repeated trituration after each addition. Water (40 ml) was added and the paste was allowed to stand overnight. The product was collected by suction filtration, stirred twice with water (100 ml) in a beaker and collected by suction filtration each time. After drying in air, the product was stirred to a thin mush in a little chloroform, to remove iodobenzene, and collected by suction filtration. The creamy powder was allowed to dry in a dessicator (6.0 g, 73%) and used without any analysis.

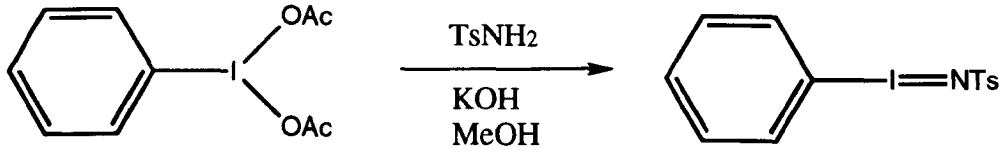
8.7.4 *p*-Tosyliminoiodobenzene 224[150,151]



230 **224**

Iodosobenzene (1.1 g, 5 mmol) was stirred in dry methanol (40 ml) under nitrogen for 15 mins. Activated, powdered molecular sieves (3Å, 3 g) were added and the suspension stirred for 2 hrs. Filtration under nitrogen to remove the sieves was followed by the addition of the same amount of sieves and stirring for a further 2 hrs. Filtration under nitrogen, followed by addition of tosyl amide (846 mg, 4.95 mmol) resulted in a pale yellow solution from which a white precipitate separated afer 30 mins. After a total of 90 mins stirring, most of the solvent was removed by evaporation

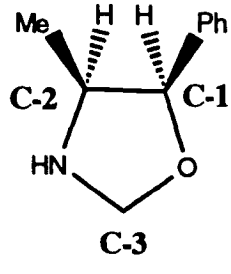
under reduced pressure. Dichloromethane (5 ml) was added and the product was collected by suction filtration. After washing with a little dichloromethane, the pale yellow solid was dried in a dessicator (600 mg, 65%).



228 **224**

Phenyliodo diacetate **228** (3.22 g, 10 mmol) was added to a stirred solution of tosyl amide (1.71 g, 10 mmol) and potassium hydroxide (1.4 g, 25 mmol) in methanol (50 ml) maintained below 10°C. The resultant pale yellow solution was stirred for three hours at room temperature. The mixture was poured into water and left to crystallise overnight. Isolation by suction filtration followed by recrystallisation from methanol yielded a pale yellow solid (1.19 g, 32%). υ_{max} (KBr disc) /cm^{-1} 1266, 1133, 1081, 866, 742, 666; δ_H(250 MHz; $CDCl_3$) 7.74 (m, 4H, Ar), 7.33 (m, 3H, Ar), 7.12 (m, 2H, Ar), 2.35 (s, 3H, Me).

8.7.5 Data for oxazolidine **139**

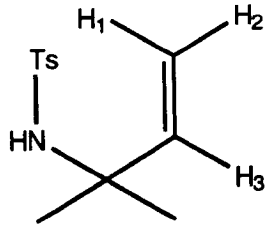


139

δ_H(250 MHz; $CDCl_3$) 7.29 (m, 5H, Ph), 5.47 (d, J=6.3 Hz, 1H, H-1), 5.11 (d, J=8.2 Hz, 1H, H-3a), 4.83 (d, J=8.2 Hz, 1H, H-3b), 3.79 (m, 1H, H-2),

0.78 (d, J=7.1 Hz, 3H, Me); δ_C(100.6 MHz; $CDCl_3$) 137.9 (Ph), 128.2 (Ph), 127.5 (Ph), 126.2 (Ph), 91.6 (C-1), 79.9 (C-3), 70.8 (C-2), 15.2 (Me); CI(NH_3) 164 (85, MH^+).

8.7.6 Data for allyl amine **189**



189

δ_H(250 MHz; $CDCl_3$) 7.77 (AA' of AA'BB', 2H, Ts), 7.26 (BB' of AA'BB', 2H, Ts), 5.76 (dd, J=10.7, 17.4 Hz, 1H, H-3), 5..09 (dd, J=0.6, 17.4 Hz, 1H, H-1), 4.95 (dd, J=0.6, 10.7 Hz, 1H, H-2), 4.77 (brs, 1H, NH), 2.41 (s, 3H, TsMe), 1.28 (s, 6H, Me).

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Appendix 1 Crystal data and structure refinement for *N*-[1,3]dithiolan-1-ylidene-4-methylbenzenesulfonamide **148a**

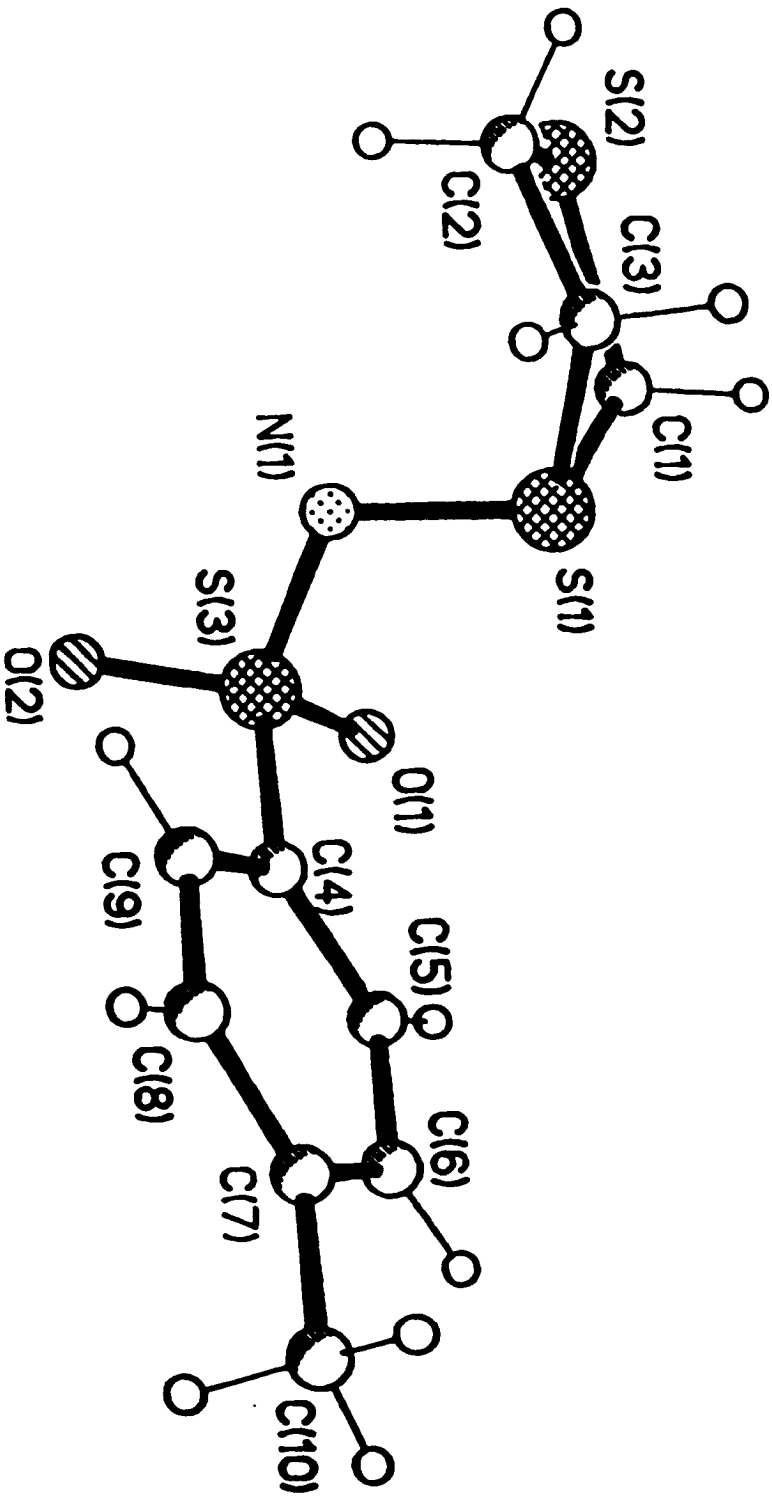


Table 1. Crystal data and structure refinement for 3.

Identification code	tspa3
Empirical formula	C10 H13 N O2 S3
Formula weight	275.39
Temperature	220(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 6.428(4) A alpha = 90 deg. b = 20.216(12) A beta = 100.21(4) de c = 9.515(5) A gamma = 90 deg.
Volume	1216.9(12) A^3
Z	4
Density (calculated)	1.503 Mg/m^3
Absorption coefficient	0.593 mm^-1
F(000)	576
Crystal size	0.25 x 0.23 x 0.16 mm
Theta range for data collection	2.01 to 25.04 deg.
Index ranges	0<=h<=7, -23<=k<=24, -11<=l<=11
Reflections collected	2977
Independent reflections	2012 [R(int) = 0.0361]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2012 / 0 / 146
Goodness-of-fit on F^2	1.068
Final R indices [I>2sigma(I)]	R1 = 0.0386, wR2 = 0.0906
R indices (all data)	R1 = 0.0558, wR2 = 0.1013
Largest diff. peak and hole	0.234 and -0.344 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 3. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	667(1)	7382(1)	4774(1)	27(1)
S(2)	-1498(2)	6414(1)	6287(1)	42(1)
S(3)	2197(1)	8379(1)	6495(1)	28(1)
N(1)	161(4)	7952(1)	5884(3)	28(1)
O(1)	4041(3)	7975(1)	6903(2)	38(1)
O(2)	1579(4)	8798(1)	7573(2)	39(1)
C(1)	968(5)	6632(2)	5784(3)	34(1)
C(2)	-3163(5)	6928(2)	5033(3)	34(1)
C(3)	-1932(5)	7180(2)	3918(3)	32(1)
C(4)	2720(5)	8897(1)	5101(3)	25(1)
C(5)	4661(5)	8891(2)	4684(3)	34(1)
C(6)	4978(6)	9309(2)	3587(4)	41(1)
C(7)	3419(6)	9725(2)	2915(3)	39(1)
C(8)	1496(6)	9717(2)	3362(3)	38(1)
C(9)	1134(5)	9307(2)	4443(3)	33(1)
C(10)	3791(7)	10168(2)	1717(4)	66(1)

Table 3. Selected bond lengths [A] and angles [deg] for 3.

S(1)-N(1)	1.634(3)
S(1)-C(3)	1.772(3)
S(1)-C(1)	1.788(3)
S(2)-C(2)	1.786(3)
S(2)-C(1)	1.790(4)
S(3)-O(1)	1.435(2)
S(3)-O(2)	1.439(2)
S(3)-N(1)	1.590(3)
S(3)-C(4)	1.767(3)
C(2)-C(3)	1.520(4)
C(4)-C(5)	1.374(4)
C(4)-C(9)	1.376(4)
C(5)-C(6)	1.385(5)
C(6)-C(7)	1.377(5)
C(7)-C(8)	1.376(5)
C(7)-C(10)	1.502(5)
C(8)-C(9)	1.373(5)
N(1)-S(1)-C(3)	100.4(2)
N(1)-S(1)-C(1)	105.4(2)
C(3)-S(1)-C(1)	93.1(2)
C(2)-S(2)-C(1)	97.7(2)
O(1)-S(3)-O(2)	117.44(14)
O(1)-S(3)-N(1)	112.12(14)
O(2)-S(3)-N(1)	105.47(14)
O(1)-S(3)-C(4)	106.38(14)
O(2)-S(3)-C(4)	107.47(14)
N(1)-S(3)-C(4)	107.52(14)
S(3)-N(1)-S(1)	112.0(2)
S(1)-C(1)-S(2)	109.6(2)
C(3)-C(2)-S(2)	109.7(2)
C(2)-C(3)-S(1)	108.8(2)
C(5)-C(4)-C(9)	120.7(3)
C(5)-C(4)-S(3)	121.0(2)
C(9)-C(4)-S(3)	118.3(2)
C(4)-C(5)-C(6)	118.4(3)
C(7)-C(6)-C(5)	122.0(3)
C(8)-C(7)-C(6)	118.0(3)
C(8)-C(7)-C(10)	120.9(4)
C(6)-C(7)-C(10)	121.1(3)
C(9)-C(8)-C(7)	121.3(3)
C(8)-C(9)-C(4)	119.7(3)

Symmetry transformations used to generate equivalent atoms:

Table 5. Anisotropic displacement parameters (A^2 x 10^3) for 3. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
S(1)	24(1)	35(1)	24(1)	-1(1)	7(1)	-3(1)
S(2)	49(1)	43(1)	36(1)	10(1)	11(1)	-6(1)
S(3)	29(1)	33(1)	23(1)	0(1)	6(1)	-3(1)
N(1)	25(1)	32(1)	28(1)	-2(1)	9(1)	-3(1)
O(1)	30(1)	43(1)	36(1)	8(1)	-4(1)	3(1)
O(2)	52(2)	39(1)	28(1)	-8(1)	16(1)	-10(1)
C(1)	34(2)	36(2)	32(2)	4(1)	3(1)	6(2)
C(2)	23(2)	50(2)	29(2)	-6(2)	8(1)	-5(2)
C(3)	27(2)	44(2)	23(2)	2(1)	1(1)	-4(2)
C(4)	26(2)	27(2)	24(2)	-1(1)	9(1)	-4(1)
C(5)	26(2)	42(2)	37(2)	-1(2)	10(1)	0(2)
C(6)	38(2)	51(2)	40(2)	-8(2)	22(2)	-13(2)
C(7)	53(2)	36(2)	28(2)	-3(1)	9(2)	-15(2)
C(8)	46(2)	33(2)	34(2)	3(1)	3(2)	3(2)
C(9)	30(2)	40(2)	31(2)	-1(1)	9(1)	3(2)
C(10)	92(3)	66(3)	42(2)	10(2)	18(2)	-28(3)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 3.

	x	y	z	U(eq)
H(1A)	2049(5)	6690(2)	6640(3)	41
H(1B)	1428(5)	6276(2)	5210(3)	41
H(2A)	-4392(5)	6674(2)	4567(3)	40
H(2B)	-3671(5)	7302(2)	5531(3)	40
H(3A)	-2628(5)	7572(2)	3444(3)	38
H(3B)	-1884(5)	6839(2)	3192(3)	38
H(5)	5746(5)	8611(2)	5132(3)	41
H(6)	6299(6)	9307(2)	3292(4)	49
H(8)	410(6)	9998(2)	2918(3)	46
H(9)	-190(5)	9307(2)	4732(3)	40
H(10A)	3281(44)	10610(4)	1867(17)	99
H(10B)	3040(40)	9995(9)	817(5)	99
H(10C)	5292(9)	10186(12)	1692(21)	99

Appendix 2 Crystal data and structure refinement for *N*-[1,3]dithian-1-ylidene-4-methylbenzenesulfonamide **148b**

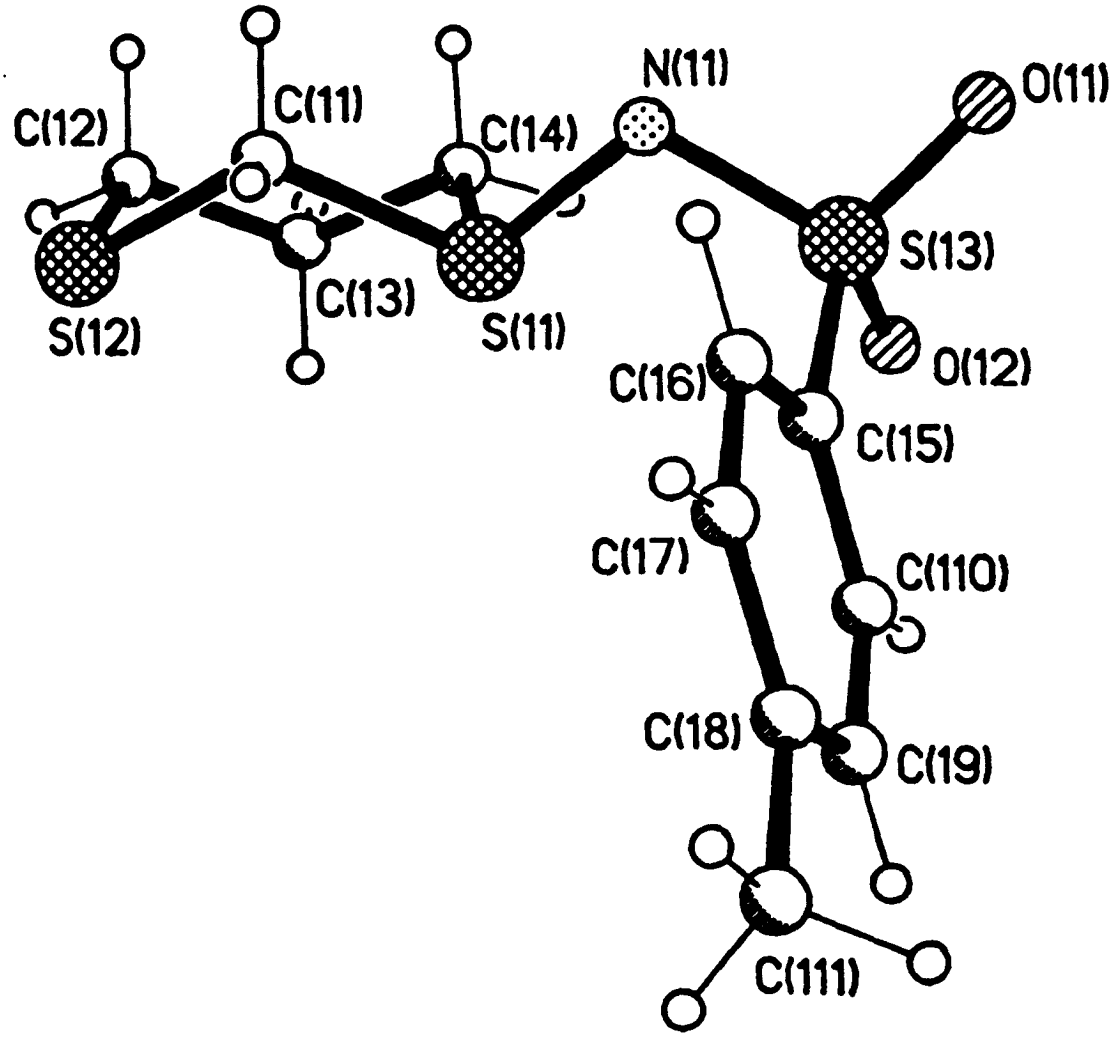


Table 1. Crystal data and structure refinement for 2.

Identification code	tims81
Empirical formula	C11 H15 N O2 S3
Formula weight	289.42
Temperature	230(2) K
Wavelength	0.71073 A
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 6.168(6) A alpha = 110.79(4) deg b = 12.909(8) A beta = 96.92(6) deg c = 17.608(9) A gamma = 94.42(7) deg
Volume	1290(2) A^3
Z	4
Density (calculated)	1.490 Mg/m^3
Absorption coefficient	0.563 mm^-1
F(000)	608
Crystal size	0.39 x 0.23 x 0.10 mm
Theta range for data collection	1.70 to 25.05 deg.
Index ranges	0<=h<=7, -15<=k<=15, -20<=l<=20
Reflections collected	5030
Independent reflections	4568 [R(int) = 0.0203]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4566 / 0 / 309
Goodness-of-fit on F^2	1.007
Final R indices [I>2sigma(I)]	R1 = 0.0396, wR2 = 0.0962
R indices (all data)	R1 = 0.0645, wR2 = 0.1110
Largest diff. peak and hole	0.304 and -0.344 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 2. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(11)	1712(1)	4754(1)	3638(1)	29(1)
S(12)	5348(1)	6314(1)	4809(1)	42(1)
S(13)	-547(1)	2886(1)	2471(1)	30(1)
S(21)	-5225(1)	-4499(1)	1359(1)	29(1)
S(22)	-8806(2)	-6070(1)	192(1)	45(1)
S(23)	-3090(1)	-2586(1)	2518(1)	31(1)
O(11)	-738(4)	2279(2)	1603(1)	40(1)
O(12)	-2531(4)	3236(2)	2786(2)	44(1)
O(21)	-2845(4)	-1983(2)	3385(1)	43(1)
O(22)	-1099(3)	-2871(2)	2183(2)	46(1)
N(11)	1342(4)	3913(2)	2673(1)	34(1)
N(21)	-4839(4)	-3667(2)	2324(1)	31(1)
C(11)	4612(5)	5231(3)	3816(2)	34(1)
C(12)	3804(5)	7355(3)	4627(2)	38(1)
C(13)	1328(5)	6989(2)	4416(2)	35(1)
C(14)	692(5)	6001(2)	3593(2)	34(1)
C(15)	433(5)	2017(2)	2983(2)	26(1)
C(16)	2439(5)	1620(2)	2860(2)	33(1)
C(17)	3096(5)	875(2)	3215(2)	33(1)
C(18)	1798(5)	524(2)	3692(2)	33(1)
C(19)	-178(5)	948(3)	3808(2)	36(1)
C(110)	-866(5)	1690(2)	3462(2)	31(1)
C(111)	2513(6)	-304(3)	4056(2)	53(1)
C(21)	-8097(5)	-5018(2)	1193(2)	31(1)
C(22)	-7213(5)	-7109(3)	345(2)	41(1)
C(23)	-4727(5)	-6738(3)	546(2)	34(1)
C(24)	-4123(5)	-5738(2)	1380(2)	35(1)
C(25)	-4275(5)	-1757(2)	2004(2)	26(1)
C(26)	-2901(5)	-950(2)	1883(2)	31(1)
C(27)	-3783(5)	-309(2)	1468(2)	35(1)
C(28)	-6019(5)	-473(3)	1161(2)	37(1)
C(29)	-7347(5)	-1278(3)	1297(2)	39(1)
C(210)	-6517(5)	-1910(2)	1720(2)	33(1)
C(211)	-6982(7)	212(3)	699(2)	60(1)

Table 3. Selected bond lengths [A] and angles [deg] for 2.

S(11)-N(11)	1.636(3)
S(11)-C(14)	1.796(3)
S(11)-C(11)	1.799(4)
S(12)-C(11)	1.787(3)
S(12)-C(12)	1.800(3)
S(13)-O(11)	1.433(2)
S(13)-O(12)	1.442(3)
S(13)-N(11)	1.602(3)
S(13)-C(15)	1.769(3)
S(21)-N(21)	1.632(3)
S(21)-C(24)	1.796(3)
S(21)-C(21)	1.796(3)
S(22)-C(21)	1.780(3)
S(22)-C(22)	1.797(3)
S(23)-O(21)	1.430(2)
S(23)-O(22)	1.442(3)
S(23)-N(21)	1.602(3)
S(23)-C(25)	1.774(3)
C(12)-C(13)	1.523(5)
C(13)-C(14)	1.534(4)
C(15)-C(110)	1.377(4)
C(15)-C(16)	1.388(4)
C(16)-C(17)	1.380(4)
C(17)-C(18)	1.389(4)
C(18)-C(19)	1.383(5)
C(18)-C(111)	1.495(4)
C(19)-C(110)	1.373(4)
C(22)-C(23)	1.530(5)
C(23)-C(24)	1.553(4)
C(25)-C(26)	1.383(4)
C(25)-C(210)	1.386(4)
C(26)-C(27)	1.386(4)
C(27)-C(28)	1.390(5)
C(28)-C(29)	1.378(5)
C(28)-C(211)	1.508(4)
N(11)-S(11)-C(14)	103.52(14)
N(11)-S(11)-C(11)	101.4(2)
C(14)-S(11)-C(11)	98.4(2)
C(11)-S(12)-C(12)	98.7(2)
O(11)-S(13)-O(12)	117.2(2)
O(11)-S(13)-N(11)	105.12(14)
O(12)-S(13)-N(11)	112.6(2)
O(11)-S(13)-C(15)	107.86(14)
O(12)-S(13)-C(15)	106.03(14)
N(11)-S(13)-C(15)	107.6(2)
N(21)-S(21)-C(24)	104.04(14)
N(21)-S(21)-C(21)	101.7(2)
C(24)-S(21)-C(21)	98.1(2)
C(21)-S(22)-C(22)	98.8(2)
O(21)-S(23)-O(22)	116.5(2)
O(21)-S(23)-N(21)	106.08(14)
O(22)-S(23)-N(21)	112.2(2)
O(21)-S(23)-C(25)	108.55(14)
O(22)-S(23)-C(25)	105.70(14)
N(21)-S(23)-C(25)	107.4(2)

S(13)-N(11)-S(11)	112.5(2)
S(23)-N(21)-S(21)	112.9(2)
S(12)-C(11)-S(11)	109.6(2)
C(13)-C(12)-S(12)	113.3(2)
C(12)-C(13)-C(14)	112.1(3)
C(13)-C(14)-S(11)	111.9(2)
C(110)-C(15)-C(16)	120.7(3)
C(110)-C(15)-S(13)	119.5(2)
C(16)-C(15)-S(13)	119.7(2)
C(17)-C(16)-C(15)	118.9(3)
C(16)-C(17)-C(18)	121.4(3)
C(19)-C(18)-C(17)	118.0(3)
C(19)-C(18)-C(111)	121.3(3)
C(17)-C(18)-C(111)	120.6(3)
C(110)-C(19)-C(18)	121.7(3)
C(19)-C(110)-C(15)	119.4(3)
S(22)-C(21)-S(21)	109.0(2)
C(23)-C(22)-S(22)	113.9(2)
C(22)-C(23)-C(24)	110.8(3)
C(23)-C(24)-S(21)	112.8(2)
C(26)-C(25)-C(210)	120.1(3)
C(26)-C(25)-S(23)	118.4(2)
C(210)-C(25)-S(23)	121.5(2)
C(25)-C(26)-C(27)	119.4(3)
C(26)-C(27)-C(28)	121.1(3)
C(29)-C(28)-C(27)	118.1(3)
C(29)-C(28)-C(211)	120.6(3)
C(27)-C(28)-C(211)	121.3(3)
C(210)-C(29)-C(28)	121.8(3)
C(29)-C(210)-C(25)	119.4(3)

Symmetry transformations used to generate equivalent atoms:

Table 5. Anisotropic displacement parameters (A^2 x 10^3) for 2. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
S(11)	36(1)	26(1)	30(1)	15(1)	9(1)	6(1)
S(12)	40(1)	46(1)	38(1)	19(1)	-3(1)	4(1)
S(13)	33(1)	27(1)	34(1)	16(1)	6(1)	7(1)
S(21)	32(1)	31(1)	30(1)	16(1)	8(1)	3(1)
S(22)	45(1)	45(1)	39(1)	11(1)	-6(1)	12(1)
S(23)	27(1)	32(1)	36(1)	17(1)	3(1)	2(1)
O(11)	51(1)	36(1)	30(1)	13(1)	-4(1)	2(1)
O(12)	34(1)	48(1)	64(2)	33(1)	14(1)	17(1)
O(21)	50(1)	42(1)	33(1)	14(1)	-6(1)	-5(1)
O(22)	30(1)	50(1)	74(2)	38(1)	16(1)	14(1)
N(11)	48(2)	26(1)	30(1)	14(1)	10(1)	3(1)
N(21)	36(1)	29(1)	29(1)	14(1)	8(1)	0(1)
C(11)	32(2)	43(2)	35(2)	21(2)	9(1)	12(1)
C(12)	44(2)	31(2)	36(2)	12(1)	4(2)	0(1)
C(13)	38(2)	25(2)	41(2)	11(1)	5(1)	8(1)
C(14)	35(2)	30(2)	40(2)	16(1)	3(1)	11(1)
C(15)	31(2)	19(1)	25(2)	7(1)	1(1)	3(1)
C(16)	33(2)	34(2)	36(2)	17(1)	11(1)	7(1)
C(17)	28(2)	30(2)	42(2)	14(1)	4(1)	8(1)
C(18)	38(2)	26(2)	32(2)	14(1)	-6(1)	1(1)
C(19)	41(2)	38(2)	36(2)	20(2)	11(1)	3(2)
C(110)	32(2)	32(2)	33(2)	14(1)	9(1)	6(1)
C(111)	56(2)	51(2)	63(2)	39(2)	-8(2)	4(2)
C(21)	28(2)	32(2)	33(2)	15(1)	1(1)	8(1)
C(22)	48(2)	33(2)	37(2)	7(1)	1(2)	13(2)
C(23)	29(2)	35(2)	39(2)	15(1)	2(1)	12(1)
C(24)	27(2)	37(2)	41(2)	15(2)	3(1)	11(1)
C(25)	29(2)	26(2)	26(2)	10(1)	8(1)	4(1)
C(26)	30(2)	30(2)	31(2)	11(1)	6(1)	0(1)
C(27)	46(2)	28(2)	37(2)	16(1)	15(2)	2(1)
C(28)	48(2)	34(2)	31(2)	11(1)	10(2)	16(2)
C(29)	30(2)	41(2)	41(2)	10(2)	2(1)	11(2)
C(210)	30(2)	27(2)	43(2)	13(1)	6(1)	2(1)
C(211)	77(3)	72(3)	53(2)	39(2)	21(2)	38(2)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 2.

	x	y	z	U(eq)
H(11A)	5454(5)	4608(3)	3786(2)	41
H(11B)	4967(5)	5515(3)	3392(2)	41
H(12A)	4106(5)	8040(3)	5120(2)	45
H(12B)	4308(5)	7529(3)	4174(2)	45
H(13A)	576(5)	7620(2)	4389(2)	42
H(13B)	829(5)	6776(2)	4854(2)	42
H(14A)	1288(5)	6193(2)	3162(2)	41
H(14B)	-916(5)	5861(2)	3447(2)	41
H(16)	3335(5)	1853(2)	2540(2)	39
H(17)	4450(5)	600(2)	3132(2)	40
H(19)	-1073(5)	723(3)	4132(2)	44
H(110)	-2211(5)	1973(2)	3552(2)	38
H(11C)	3962(18)	-477(16)	3931(13)	80
H(11D)	1471(23)	-981(8)	3825(12)	80
H(11E)	2568(40)	11(9)	4648(3)	80
H(21A)	-8395(5)	-5330(2)	1608(2)	37
H(21B)	-8986(5)	-4406(2)	1243(2)	37
H(22A)	-7685(5)	-7302(3)	795(2)	49
H(22B)	-7523(5)	-7785(3)	-155(2)	49
H(23A)	-4244(5)	-6518(3)	108(2)	41
H(23B)	-3957(5)	-7363(3)	572(2)	41
H(24A)	-2516(5)	-5575(2)	1524(2)	42
H(24B)	-4684(5)	-5950(2)	1810(2)	42
H(26)	-1383(5)	-839(2)	2080(2)	37
H(27)	-2854(5)	247(2)	1393(2)	42
H(29)	-8862(5)	-1398(3)	1094(2)	46
H(210)	-7461(5)	-2441(2)	1816(2)	40
H(21C)	-5847(13)	781(15)	706(14)	90
H(21D)	-8171(30)	567(19)	959(10)	90
H(21E)	-7546(41)	-270(5)	134(5)	90

Appendix 3 Crystal data and structure refinement for *N*-[1,3,5]-trithian-1-ylidene-4-methylbenzenesulfonamide **148c**

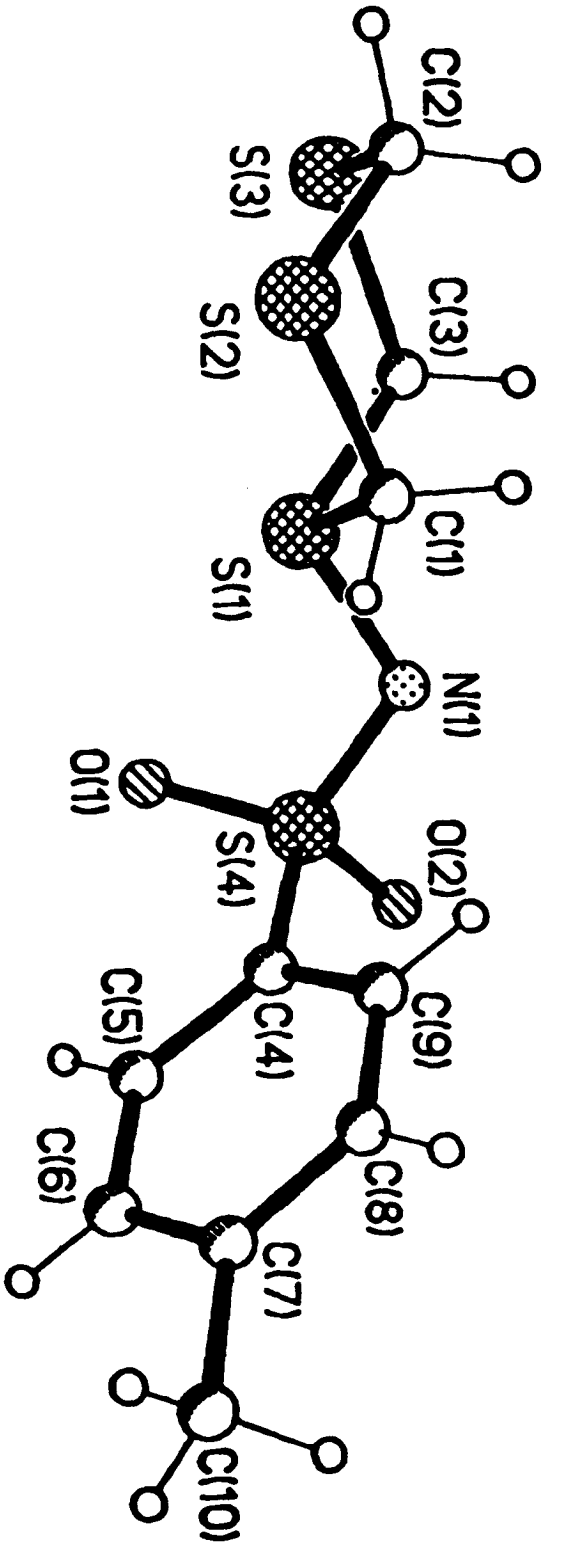


Table 1. Crystal data and structure refinement for 1.

Identification code	spare
Empirical formula	C10 H13 N O2 S4
Formula weight	307.45
Temperature	230(2) K
Wavelength	0.71073 A
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 6.159(3) A alpha = 110.92(3) deg. b = 9.709(4) A beta = 93.47(3) deg. c = 12.417(4) A gamma = 104.52(3) deg
Volume	662.1(5) A^3
Z	2
Density (calculated)	1.542 Mg/m^3
Absorption coefficient	0.706 mm^-1
F(000)	320
Crystal size	0.51 x 0.38 x 0.29 mm
Theta range for data collection	1.78 to 25.05 deg.
Index ranges	0<=h<=7, -11<=k<=11, -14<=l<=14
Reflections collected	2591
Independent reflections	2350 [R(int) = 0.0277]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2350 / 0 / 156
Goodness-of-fit on F^2	0.987
Final R indices [I>2sigma(I)]	R1 = 0.0323, wR2 = 0.0913
R indices (all data)	R1 = 0.0356, wR2 = 0.0949
Extinction coefficient	0.133(7)
Largest diff. peak and hole	0.358 and -0.360 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	2756(1)	3054(1)	8092(1)	29(1)
S(2)	5914(1)	1125(1)	7608(1)	54(1)
S(3)	2060(1)	483(1)	8932(1)	46(1)
S(4)	1697(1)	5558(1)	7963(1)	30(1)
O(1)	-250(2)	4416(2)	7156(1)	43(1)
O(2)	1314(3)	6914(2)	8796(1)	44(1)
N(1)	3019(3)	4891(2)	8718(1)	31(1)
C(1)	5673(4)	3037(3)	8136(2)	40(1)
C(2)	4960(4)	579(3)	8775(2)	48(1)
C(3)	2203(4)	2458(2)	9287(2)	33(1)
C(4)	3575(3)	6202(2)	7111(2)	27(1)
C(5)	2656(4)	6331(3)	6118(2)	38(1)
C(6)	4082(4)	6982(3)	5501(2)	44(1)
C(7)	6392(4)	7507(2)	5850(2)	37(1)
C(8)	7281(4)	7348(2)	6831(2)	36(1)
C(9)	5891(3)	6689(2)	7460(2)	33(1)
C(10)	7949(5)	8262(3)	5200(2)	58(1)

Table 3. Selected bond lengths [A] and angles [deg] for 1.

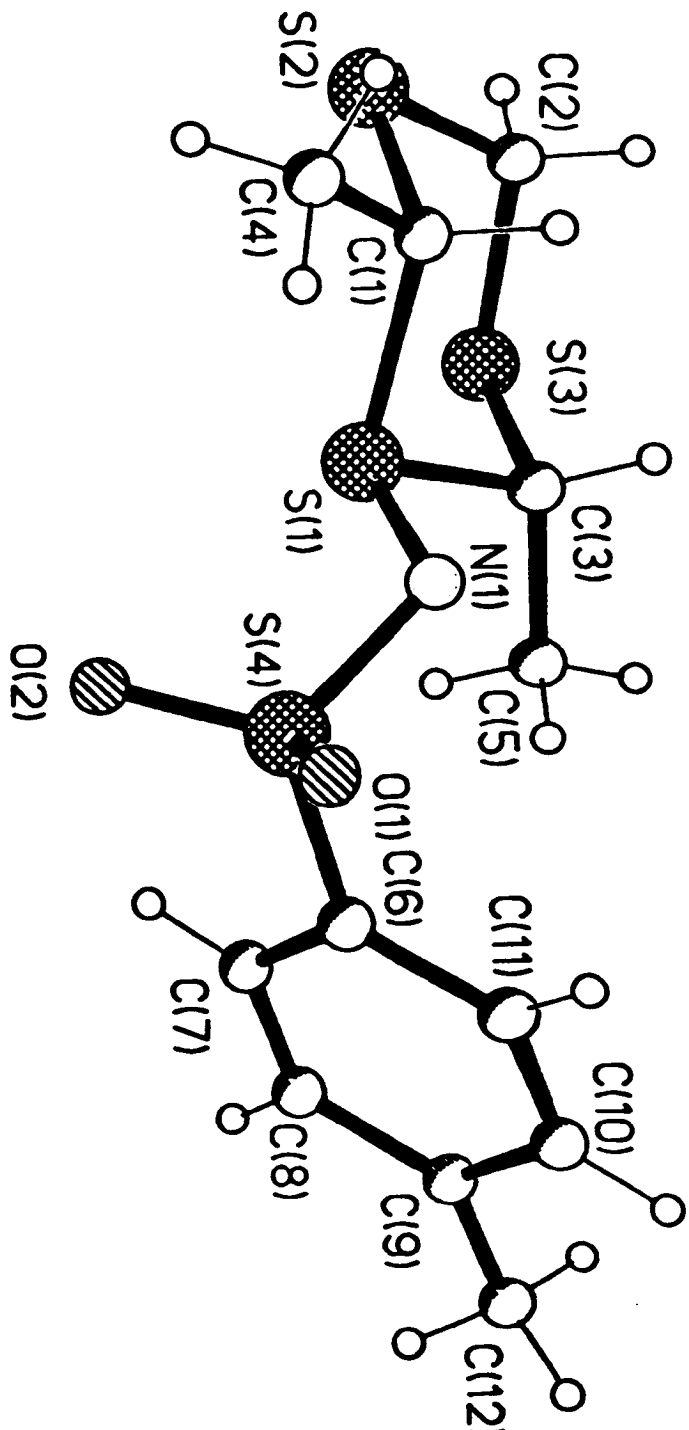
S(1)-N(1)	1.631(2)
S(1)-C(3)	1.796(2)
S(1)-C(1)	1.799(2)
S(2)-C(1)	1.783(2)
S(2)-C(2)	1.794(3)
S(3)-C(3)	1.785(2)
S(3)-C(2)	1.791(3)
S(4)-O(1)	1.437(2)
S(4)-O(2)	1.439(2)
S(4)-N(1)	1.601(2)
S(4)-C(4)	1.763(2)
C(4)-C(9)	1.374(3)
C(4)-C(5)	1.384(3)
C(5)-C(6)	1.381(3)
C(6)-C(7)	1.370(3)
C(7)-C(8)	1.380(3)
C(7)-C(10)	1.508(3)
C(8)-C(9)	1.384(3)
N(1)-S(1)-C(3)	100.66(10)
N(1)-S(1)-C(1)	102.09(10)
C(3)-S(1)-C(1)	97.16(11)
C(1)-S(2)-C(2)	98.90(11)
C(3)-S(3)-C(2)	99.68(11)
O(1)-S(4)-O(2)	117.09(11)
O(1)-S(4)-N(1)	113.30(10)
O(2)-S(4)-N(1)	105.67(10)
O(1)-S(4)-C(4)	106.28(10)
O(2)-S(4)-C(4)	106.20(10)
N(1)-S(4)-C(4)	107.79(10)
S(4)-N(1)-S(1)	114.84(11)
S(2)-C(1)-S(1)	112.00(13)
S(3)-C(2)-S(2)	115.45(14)
S(3)-C(3)-S(1)	112.65(11)
C(9)-C(4)-C(5)	120.0(2)
C(9)-C(4)-S(4)	121.6(2)
C(5)-C(4)-S(4)	118.2(2)
C(6)-C(5)-C(4)	119.5(2)
C(7)-C(6)-C(5)	121.4(2)
C(6)-C(7)-C(8)	118.3(2)
C(6)-C(7)-C(10)	121.6(2)
C(8)-C(7)-C(10)	120.1(2)
C(7)-C(8)-C(9)	121.4(2)
C(4)-C(9)-C(8)	119.4(2)

Symmetry transformations used to generate equivalent atoms:

Table 5. Anisotropic displacement parameters (A^2 x 10^3) for 1. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
S(1)	34(1)	27(1)	29(1)	12(1)	6(1)	10(1)
S(2)	63(1)	44(1)	65(1)	21(1)	28(1)	33(1)
S(3)	48(1)	31(1)	64(1)	26(1)	9(1)	5(1)
S(4)	28(1)	33(1)	38(1)	19(1)	10(1)	13(1)
O(1)	27(1)	50(1)	55(1)	30(1)	2(1)	5(1)
O(2)	56(1)	46(1)	50(1)	24(1)	26(1)	33(1)
N(1)	36(1)	26(1)	32(1)	13(1)	6(1)	11(1)
C(1)	36(1)	36(1)	57(1)	23(1)	23(1)	16(1)
C(2)	54(1)	35(1)	61(2)	22(1)	5(1)	20(1)
C(3)	34(1)	31(1)	38(1)	19(1)	11(1)	8(1)
C(4)	29(1)	24(1)	29(1)	11(1)	7(1)	9(1)
C(5)	34(1)	45(1)	35(1)	17(1)	1(1)	10(1)
C(6)	54(1)	54(1)	31(1)	23(1)	6(1)	18(1)
C(7)	48(1)	33(1)	32(1)	13(1)	15(1)	12(1)
C(8)	30(1)	39(1)	37(1)	13(1)	8(1)	6(1)
C(9)	30(1)	40(1)	34(1)	19(1)	5(1)	11(1)
C(10)	70(2)	64(2)	50(1)	33(1)	30(1)	16(1)

Appendix 4 Crystal data and structure refinement for *N*-(2,6-dimethyl-[1,3,5]trithian-1-ylidene)-4-methyl-benzenesulfonamide **159a**



```
**********************************************************************
  SHELXL-93 - CRYSTAL STRUCTURE REFINEMENT - MSDOS 32-BIT VERSION  *
  tstwo                          started at 11:18:14 on 22-Apr-1994  *
**********************************************************************

TITL TS163 in P-1
CELL 0.71073   7.486   8.965  11.323  98.91  92.71  98.82
ZERR    2.00   0.006   0.006   0.008   0.05   0.06   0.06
LATT  1
SFAC C H N O S
UNIT 24 34 2 4 8

L.S.      739.90     F(000) =     352.0     Mu =   0.64 mm-1      Cell Wt =      671.01    Rho =  1.506

L.S. 4
TEMP -53
ACTA
SIZE 0.18 0.16 0.27
PLAN 20
SFLAT C6 C8 C10 C7 C11 C9 C12
WGHT    0.076300    0.320600
EXTI       1.05257
S1    5    0.02914   0.23127   0.44695  11.00000   0.02497   0.01833 =
     0.02392   0.00408  -0.00299   0.00308
S2    5    0.09021   0.18226   0.69943  11.00000   0.03280   0.02915 =
     0.02727   0.01041  -0.00559   0.00403
S3    5   -0.28043   0.09508   0.56689  11.00000   0.02714   0.02632 =
     0.03365   0.00715  -0.00169  -0.00025
S4    5    0.16448   0.33092   0.24818  11.00000   0.02746   0.02842 =
     0.02573   0.00747  -0.00143   0.00332
N1    3    0.08171   0.37428   0.37518  11.00000   0.03628   0.01875 =
     0.02421   0.00661  -0.00107   0.00341
O1    4    0.27714   0.46827   0.22930  11.00000   0.03604   0.04290 =
     0.03811   0.01557  -0.00359  -0.00744
O2    4    0.24215   0.19269   0.23906  11.00000   0.03552   0.04007 =
     0.03654   0.00614   0.00061   0.01611
C1    1    0.13605   0.31503   0.59653  11.00000   0.02800   0.02161 =
     0.02326   0.00324  -0.00524   0.00244
AFIX  3
H1    2    0.08840   0.40849   0.62549  11.00000  -1.20000
AFIX  0
C2    1   -0.14959   0.17273   0.70600  11.00000   0.03368   0.02991 =
     0.02616   0.00648   0.00255   0.00361
AFIX  3
H2A   2   -0.18859   0.10917   0.76453  11.00000  -1.20000
H2B   2   -0.17531   0.27432   0.73354  11.00000  -1.20000
AFIX  0
C3    1   -0.20675   0.23970   0.47830  11.00000   0.02364   0.02614 =
     0.02991   0.00478   0.00089   0.00439
AFIX  3
H3    2   -0.21693   0.34112   0.52099  11.00000  -1.20000
AFIX  0
C4    1    0.33817   0.35243   0.59064  11.00000   0.02777   0.04101 =
     0.04015   0.01224  -0.00617   0.00019
AFIX  3
H4A   2    0.38823   0.42818   0.65805  11.00000  -1.50000
H4B   2    0.36528   0.39063   0.51812  11.00000  -1.50000
H4C   2    0.38985   0.26152   0.59277  11.00000  -1.50000
AFIX  0
C5    1   -0.32167   0.20745   0.36060  11.00000   0.03143   0.04675 =
     0.03841   0.01025  -0.00499   0.00475
AFIX  3
H5A   2   -0.44120   0.22721   0.37627  11.00000  -1.50000
H5B   2   -0.32777   0.10249   0.32520  11.00000  -1.50000
H5C   2   -0.27099   0.27194   0.30672  11.00000  -1.50000
AFIX  0
C6    1   -0.02232   0.29715   0.14060  11.00000   0.03014   0.02744 =
     0.02060   0.00572  -0.00075   0.00233
C7    1   -0.09503   0.14941   0.08750  11.00000   0.04226   0.02445 =
     0.02971   0.00606  -0.00149   0.00713
AFIX  3
H7    2   -0.04469   0.06760   0.10761  11.00000  -1.20000
AFIX  0
C8    1   -0.24834   0.12569   0.00958  11.00000   0.04105   0.03172 =
     0.02957   0.00277  -0.00330  -0.00276
AFIX  3
H8    2   -0.29143   0.02708  -0.02975  11.00000  -1.20000
AFIX  0
C9    1   -0.33137   0.24577  -0.01571  11.00000   0.03133   0.04014 =
     0.02573   0.00915  -0.00227   0.00171
C10   1   -0.25444   0.39265   0.03798  11.00000   0.04291   0.03455 =
     0.03475   0.01154  -0.00506   0.01055
AFIX  3
H10   2   -0.30507   0.47527   0.01987  11.00000  -1.20000
AFIX  0
C11   1   -0.10088   0.41860   0.11493  11.00000   0.04189   0.02475 =
     0.03008   0.00490  -0.00473   0.00246
AFIX  3
H11   2   -0.05131   0.51812   0.14901  11.00000  -1.20000
AFIX  0
C12   1   -0.49904   0.22059  -0.09834  11.00000   0.04148   0.05703 =
     0.04762   0.01868  -0.01257  -0.00211
AFIX  3
H12A  2   -0.60511   0.21546  -0.05423  11.00000  -1.50000
H12B  2   -0.50328   0.12655  -0.15212  11.00000  -1.50000
H12C  2   -0.49468   0.30582  -0.14316  11.00000  -1.50000

HKLF 4
```

ovalent radii and connectivity table for TS163 in P-1

```
C    0.770
N    0.320
O    0.700
S    1.030

M1 - M1 C3 C1
C2 - C2 C1
C3 - C3 C2
O1 - O1 O2 M1 C6
S4 - S4 S1
S1 - S4
S2 - S4
C4 - C4 S2 S1
S3 - S2 S3
C5 - C5 S3 S1
C1 - C1
C3 - C3
C11 - C11 C7 S4
C8 - C8 C6
C9 - C9 C7
C7 - C8 C10 C12
C10 - C11 C9
C11 - C6 C10
C12 - C9
```

Summary of restraints for TS163 in P-1

Sigma and atoms for FLAT

0.2000 C6 C8 C10 C7 C11 C9 C12

2836 Reflections read, of which 0 rejected

0 =< h =< 8, -10 =< k =< 10, -13 =< l =< 13, Max. 2-theta = 50.11

0 Systematic absence violations

Inconsistent equivalents etc.

h	k	l	Fo^2	Sigma(Fo^2)	N	Esd of mean(Fo^2)
0	2	0	9858.83	38.05	2	299.48
0	3	0	1372.16	10.19	2	52.53
0	4	0	177.97	3.55	2	27.81
0	5	0	155.53	3.80	2	19.96
0	-7	1	1099.17	12.03	2	161.73
0	2	1	7389.95	33.11	2	282.55
0	-8	2	2078.44	19.51	2	340.23
0	6	2	817.56	10.03	2	58.08
0	-6	3	2394.64	20.81	2	188.89
0	-4	3	6256.11	38.34	2	336.16
0	4	3	575.97	7.01	2	57.65
0	4	4	775.27	8.96	2	67.02

12 Inconsistent equivalents

2614 Unique reflections, of which 0 suppressed

R(int) = 0.0324 R(sigma) = 0.0255 Friedel opposites merged

Maximum memory for data reduction = 1719 / 25749

5.7 seconds elapsed time

Least-squares cycle 1 Maximum vector length = 511 Memory required = 2185 / 214512

wR2 = 0.1146 before cycle 1 for 2614 data and 172 / 172 parameters

Summary of restraints applied in cycle 1

	DFIX-	DFIX+	SAME/SADI	CHIV	FLAT	DELU	SIMU	ISOR	SUMP
Number	0.	0.	0.	0.	4.	0.	0.	0.	0.
Mean(w*del^2)	0.000	0.000	0.000	0.000	0.243	0.000	0.000	0.000	0.000
Mean sigma	0.000	0.000	0.000	0.000	0.200	0.000	0.000	0.000	0.000
Mean deviation	0.000	0.000	0.000	0.000	0.076	0.000	0.000	0.000	0.000

GooF = S = 1.045; Restrained GooF = 1.044 for 4 restraints

Weight = 1 / [sigma^2(Fo^2) + (0.0783 * P)^2 + 0.32 * P] where P = (Max (Fo^2, 0) + 2 * Fc^2) / 3

N value esd shift/esd parameter

```
  1      1.05251      0.00274     -0.021    OSF

Mean shift/esd =   0.020    Maximum =   0.069 for   z  S3

Max. shift = 0.000 A for C2       Max. dU = 0.000 for C9

   30.3 seconds elapsed time

Least-squares cycle  2      Maximum vector length =  511      Memory required =   2185 /  214512

wR2 =  0.1146 before cycle  2 for   2614 data and   172 /   172 parameters

Summary of restraints applied in cycle   2

                  DFIX-     DFIX+   SAME/SADI     CHIV      FLAT      DELU      SIMU      ISOR      SUMP

      Number         0.        0.        0.        0.        4.        0.        0.        0.        0.

Mean(w*del^2)    0.000     0.000     0.000     0.000     0.243     0.000     0.000     0.000     0.000

Mean sigma       0.000     0.000     0.000     0.000     0.200     0.000     0.000     0.000     0.000

Mean deviation   0.000     0.000     0.000     0.000     0.076     0.000     0.000     0.000     0.000

Goof = S =      1.045;      Restrained Goof =      1.044  for      4 restraints

Weight = 1 / [ sigma^2(Fo^2) + ( 0.0763 * P )^2 +   0.32 * P ]   where  P = ( Max ( Fo^2, 0 ) + 2 * Fc^2 ) / 3

   N      value        esd    shift/esd  parameter

   1      1.05251      0.00274      0.000    OSF

Mean shift/esd =   0.001    Maximum =  -0.003 for  U13 C3

Max. shift = 0.000 A for C10      Max. dU = 0.000 for O2

    27.1 seconds elapsed time

Least-squares cycle  3      Maximum vector length =  511      Memory required =   2185 /  214512

wR2 =  0.1146 before cycle  3 for   2614 data and   172 /   172 parameters

Summary of restraints applied in cycle   3

                  DFIX-     DFIX+   SAME/SADI     CHIV      FLAT      DELU      SIMU      ISOR      SUMP

      Number         0.        0.        0.        0.        4.        0.        0.        0.        0.

Mean(w*del^2)    0.000     0.000     0.000     0.000     0.243     0.000     0.000     0.000     0.000

Mean sigma       0.000     0.000     0.000     0.000     0.200     0.000     0.000     0.000     0.000

Mean deviation   0.000     0.000     0.000     0.000     0.076     0.000     0.000     0.000     0.000

Goof = S =      1.045;      Restrained Goof =      1.044  for      4 restraints

Weight = 1 / [ sigma^2(Fo^2) + ( 0.0763 * P )^2 +   0.32 * P ]   where  P = ( Max ( Fo^2, 0 ) + 2 * Fc^2 ) / 3

   N      value        esd    shift/esd  parameter

   1      1.05251      0.00274      0.001    OSF

Mean shift/esd =   0.000    Maximum =  -0.002 for  U13 C2

Max. shift = 0.000 A for C1       Max. dU = 0.000 for C11

    27.1 seconds elapsed time

Least-squares cycle  4      Maximum vector length =  511      Memory required =   2185 /  214512

wR2 =  0.1146 before cycle  4 for   2614 data and   172 /   172 parameters

Summary of restraints applied in cycle   4

                  DFIX-     DFIX+   SAME/SADI     CHIV      FLAT      DELU      SIMU      ISOR      SUMP

      Number         0.        0.        0.        0.        4.        0.        0.        0.        0.

Mean(w*del^2)    0.000     0.000     0.000     0.000     0.243     0.000     0.000     0.000     0.000

Mean sigma       0.000     0.000     0.000     0.000     0.200     0.000     0.000     0.000     0.000

Mean deviation   0.000     0.000     0.000     0.000     0.076     0.000     0.000     0.000     0.000

Goof = S =      1.045;      Restrained Goof =      1.044  for      4 restraints

Weight = 1 / [ sigma^2(Fo^2) + ( 0.0763 * P )^2 +   0.32 * P ]   where  P = ( Max ( Fo^2, 0 ) + 2 * Fc^2 ) / 3

   N      value        esd    shift/esd  parameter
```

1 1.05251 0.00274 0.000 OSF

Mean shift/esd = 0.000 Maximum = 0.000 for OSF

Max. shift = 0.000 A for C3 Max. dU = 0.000 for C2

No correlation matrix elements larger than 0.500

27.2 seconds elapsed time

IS163 in P-1

atom	x	y	z	sof	U11	U22	U33	U23	U13	U12	Ueq
N1	0.02914 0.00008	0.23127 0.00007	0.44695 0.00005	1.00000 0.00000	0.02497 0.00034	0.01833 0.00032	0.02391 0.00033	0.00408 0.00024	-0.00300 0.00024	0.00308 0.00024	0.02254 0.00018
N2	0.09021 0.00009	0.18226 0.00007	0.69943 0.00006	1.00000 0.00000	0.03281 0.00038	0.02914 0.00037	0.02726 0.00035	0.01041 0.00027	-0.00558 0.00027	0.00403 0.00028	0.02948 0.00020
N3	-0.28043 0.00009	0.09508 0.00007	0.56689 0.00006	1.00000 0.00000	0.02714 0.00036	0.02631 0.00036	0.03363 0.00038	0.00714 0.00027	-0.00168 0.00027	-0.00025 0.00026	0.02940 0.00020
N4	0.16447 0.00009	0.33092 0.00007	0.24818 0.00006	1.00000 0.00000	0.02745 0.00036	0.02843 0.00036	0.02573 0.00035	0.00746 0.00026	-0.00143 0.00026	0.00333 0.00026	0.02712 0.00020
N1	0.08171 0.00030	0.37428 0.00022	0.37518 0.00018	1.00000 0.00000	0.03626 0.00126	0.01875 0.00107	0.02420 0.00111	0.00662 0.00085	-0.00107 0.00092	0.00339 0.00090	0.02629 0.00049
N1	0.27713 0.00027	0.46827 0.00023	0.22931 0.00018	1.00000 0.00000	0.03599 0.00113	0.04290 0.00121	0.03810 0.00113	0.01555 0.00091	-0.00354 0.00088	-0.00746 0.00091	0.03972 0.00051
O2	0.24216 0.00027	0.19269 0.00023	0.23907 0.00017	1.00000 0.00000	0.03554 0.00109	0.04000 0.00114	0.03655 0.00108	0.00614 0.00087	0.00065 0.00083	0.01615 0.00088	0.03638 0.00047
C1	0.13606 0.00034	0.31502 0.00028	0.59653 0.00022	1.00000 0.00000	0.02797 0.00135	0.02156 0.00124	0.02323 0.00123	0.00324 0.00097	-0.00526 0.00100	0.00242 0.00100	0.02470 0.00054
N1	0.08841 0.00034	0.40848 0.00028	0.62549 0.00022	1.00000 0.00000	0.02964 0.00000						
C2	-0.14957 0.00036	0.17272 0.00031	0.70600 0.00023	1.00000 0.00000	0.03371 0.00147	0.02990 0.00140	0.02612 0.00131	0.00646 0.00106	0.00257 0.00109	0.00360 0.00113	0.02986 0.00059
N2A	-0.18857 0.00036	0.10916 0.00031	0.76453 0.00023	1.00000 0.00000	0.03584 0.00000						
N2B	-0.17529 0.00036	0.27431 0.00031	0.73354 0.00023	1.00000 0.00000	0.03584 0.00000						
C3	-0.20674 0.00034	0.23971 0.00030	0.47830 0.00023	1.00000 0.00000	0.02362 0.00130	0.02610 0.00132	0.02992 0.00136	0.00477 0.00105	0.00089 0.00104	0.00439 0.00103	0.02653 0.00055
N3	-0.21692 0.00034	0.34113 0.00030	0.52099 0.00023	1.00000 0.00000	0.03183 0.00000						
C4	0.33817 0.00036	0.35243 0.00034	0.59064 0.00027	1.00000 0.00000	0.02776 0.00146	0.04102 0.00165	0.04014 0.00162	0.01226 0.00130	-0.00613 0.00120	0.00019 0.00122	0.03656 0.00067
N4A	0.38823 0.00036	0.42818 0.00034	0.65805 0.00027	1.00000 0.00000	0.05484 0.00000						
N4B	0.36528 0.00036	0.39063 0.00034	0.51812 0.00027	1.00000 0.00000	0.05484 0.00000						
N4C	0.38985 0.00036	0.26152 0.00034	0.59277 0.00027	1.00000 0.00000	0.05484 0.00000						
C5	-0.32167 0.00039	0.20746 0.00036	0.36060 0.00026	1.00000 0.00000	0.03143 0.00153	0.04677 0.00178	0.03840 0.00162	0.01031 0.00134	-0.00502 0.00123	0.00476 0.00129	0.03893 0.00069
N5A	-0.44120 0.00039	0.22722 0.00036	0.37627 0.00026	1.00000 0.00000	0.05839 0.00000						
N5B	-0.32777 0.00039	0.10250 0.00036	0.32520 0.00026	1.00000 0.00000	0.05839 0.00000						
N5C	-0.27099 0.00039	0.27195 0.00036	0.30672 0.00026	1.00000 0.00000	0.05839 0.00000						
C6	-0.02232 0.00035	0.29715 0.00029	0.14060 0.00021	1.00000 0.00000	0.03013 0.00140	0.02741 0.00134	0.02063 0.00123	0.00570 0.00101	-0.00068 0.00102	0.00233 0.00106	0.02620 0.00056
C7	-0.09504 0.00039	0.14941 0.00030	0.08750 0.00024	1.00000 0.00000	0.04225 0.00161	0.02451 0.00136	0.02966 0.00140	0.00605 0.00107	-0.00154 0.00117	0.00713 0.00116	0.03192 0.00061
N7	-0.04470 0.00039	0.06760 0.00030	0.10761 0.00024	1.00000 0.00000	0.03830 0.00000						
C8	-0.24834 0.00040	0.12569 0.00033	0.00958 0.00024	1.00000 0.00000	0.04106 0.00163	0.03169 0.00149	0.02957 0.00144	0.00275 0.00116	-0.00327 0.00121	-0.00273 0.00122	0.03546 0.00065
N8	-0.29143 0.00040	0.02708 0.00033	-0.02975 0.00024	1.00000 0.00000	0.04255 0.00000						
C9	-0.33137 0.00038	0.26578 0.00033	-0.01571 0.00024	1.00000 0.00000	0.05130 0.00144	0.04087 0.00158	0.02570 0.00133	0.00908 0.00114	-0.00222 0.00108	0.00178 0.00110	0.03253 0.00061
C10	-0.25444 0.00041	0.39265 0.00034	0.05798 0.00026	1.00000 0.00000	0.04294 0.00169	0.05450 0.00193	0.03475 0.00152	0.01134 0.00120	-0.00582 0.00125	0.01485 0.00127	0.03657 0.00066

O	-0.30507	0.47527	0.01987	1.00000	0.04388						
	0.00041	0.00034	0.00026	0.00000	0.00000						
N1	-0.10089	0.41859	0.11492	1.00000	0.04186	0.02474	0.03005	0.00486	-0.00468	0.00251	0.03273
	0.00039	0.00031	0.00024	0.00000	0.00163	0.00133	0.00142	0.00108	0.00119	0.00116	0.00062
N1	-0.05132	0.51811	0.14900	1.00000	0.03927						
	0.00039	0.00031	0.00024	0.00000	0.00000						
N2	-0.49904	0.22059	-0.09835	1.00000	0.04146	0.05698	0.04762	0.01861	-0.01257	-0.00210	0.04920
	0.00045	0.00041	0.00031	0.00000	0.00185	0.00211	0.00190	0.00158	0.00145	0.00150	0.00084
N2A	-0.60511	0.21546	-0.05424	1.00000	0.07380						
	0.00045	0.00041	0.00031	0.00000	0.00000						
N2B	-0.50328	0.12633	-0.15213	1.00000	0.07380						
	0.00045	0.00041	0.00031	0.00000	0.00000						
N2C	-0.49468	0.30302	-0.14317	1.00000	0.07380						
	0.00045	0.00041	0.00031	0.00000	0.00000						

Final Structure Factor Calculation for TS163 in P-1

Total number of l.s. parameters = 172 Maximum vector length = 511 Memory required = 2013 / 23506

R2 = 0.1146 before cycle 5 for 2614 data and 0 / 172 parameters

Summary of restraints applied in cycle 5

	DFIX-	DFIX+	SAME/SADI	CHIV	FLAT	DELU	SIMU	ISOR	SUMP
Number	0.	0.	0.	0.	4.	0.	0.	0.	0.
Mean(w*del^2)	0.000	0.000	0.000	0.000	0.243	0.000	0.000	0.000	0.000
Mean sigma	0.000	0.000	0.000	0.000	0.200	0.000	0.000	0.000	0.000
Mean deviation	0.000	0.000	0.000	0.000	0.076	0.000	0.000	0.000	0.000

GooF = S = 1.045; Restrained GooF = 1.044 for 4 restraints

Weight = 1 / [sigma^2(Fo^2) + (0.0763 * P)^2 + 0.32 * P] where P = (Max (Fo^2, 0) + 2 * Fc^2) / 3

R1 = 0.0382 for 2240 Fo > 4.sigma(Fo) and 0.0453 for all 2614 data
wR2 = 0.1146, GooF = S = 1.045, Restrained GooF = 1.044 for all data

4.6 seconds elapsed time

Principal mean square atomic displacements U

0.0297	0.0201	0.0179	S1
0.0406	0.0296	0.0182	S2
0.0374	0.0280	0.0227	S3
0.0325	0.0269	0.0219	S4
0.0378	0.0245	0.0166	N1
0.0610	0.0319	0.0263	O1
0.0473	0.0367	0.0251	O2
0.0338	0.0218	0.0186	C1
0.0346	0.0301	0.0249	C2
0.0302	0.0261	0.0233	C3
0.0513	0.0344	0.0239	C4
0.0494	0.0409	0.0265	C5
0.0327	0.0264	0.0195	C6
0.0438	0.0293	0.0226	C7
0.0485	0.0330	0.0249	C8
0.0436	0.0313	0.0228	C9
0.0483	0.0391	0.0223	C10
0.0465	0.0271	0.0246	C11
0.0746	0.0440	0.0290	C12

Analysis of variance for reflections employed in refinement K = Mean[Fo^2] / Mean[Fc^2] for group

Fc/Fc(max)	0.000	0.016	0.033	0.049	0.067	0.086	0.109	0.139	0.178	0.243	1.000
Number in group	271.	261.	258.	256.	260.	266.	257.	261.	262.	262.	
GooF	0.867	1.052	1.138	1.189	0.991	1.099	1.040	1.020	1.041	0.987	
K	1.020	0.947	0.962	1.024	1.010	1.020	0.994	1.001	1.018	0.999	

Resolution(A)	0.84	0.87	0.90	0.95	1.00	1.06	1.14	1.25	1.43	1.79	inf
Number in group	273.	250.	266.	264.	258.	257.	261.	262.	262.	261.	
GooF	1.056	0.894	0.899	0.900	0.862	1.012	1.102	0.976	1.227	1.429	
K	1.025	1.008	1.001	1.016	0.994	1.017	0.985	0.995	1.061	0.992	
R1	0.074	0.057	0.050	0.053	0.049	0.045	0.040	0.035	0.061	0.057	

ommended weighting scheme: WGHT 0.0763 0.3204

t Disagreeable Reflections (* if suppressed)

h	k	l	Fo^2	Fc^2	Delta(F^2)/esd	Fc/Fc(max)	Resolution(A)
0	-4	2	435.09	289.62	5.08	0.148	2.16
-5	2	5	175.76	290.12	5.08	0.148	1.24
1	-3	1	96.54	56.91	5.03	0.066	2.88
1	-5	3	773.56	533.11	4.73	0.201	1.70
0	-2	1	803.56	524.02	4.69	0.199	4.32
-1	9	5	115.98	193.67	4.67	0.121	0.85
1	4	2	23.14	46.95	4.55	0.060	1.79
1	-6	2	2632.15	1885.69	4.41	0.378	1.48
-1	3	1	67.52	109.54	4.37	0.091	2.70
1	-8	1	896.76	642.18	4.22	0.221	1.12
0	-5	2	904.10	650.68	4.19	0.222	1.75
0	-6	2	7305.57	5258.12	4.15	0.632	1.47
1	-4	2	142.53	96.00	4.09	0.085	2.15
-3	1	5	152.00	104.04	3.93	0.089	1.68
2	-6	1	187.60	129.98	3.89	0.099	1.45
3	-1	2	19.95	8.24	3.84	0.025	2.24
1	-6	3	5017.25	3772.89	3.78	0.535	1.45
1	-3	3	66.65	43.05	3.77	0.057	2.44
1	-7	3	76.15	46.78	3.72	0.060	1.26
2	-7	3	200.79	142.39	3.58	0.104	1.23
-6	6	5	29.81	55.70	3.54	0.065	0.91
-2	-4	1	9.88	21.87	3.54	0.041	1.78
1	-8	3	509.23	384.23	3.37	0.171	1.11
-2	1	5	92.16	130.00	3.28	0.099	1.90
-3	-4	2	6.70	17.44	3.28	0.036	1.52
1	-7	5	137.87	98.11	3.26	0.086	1.18
-6	0	1	0.75	14.65	3.19	0.033	1.23
3	-2	3	40.45	25.30	3.19	0.044	1.98
5	0	7	85.69	57.54	3.19	0.066	1.05
1	2	4	72.23	49.94	3.15	0.062	2.03
-1	3	4	26.62	14.62	3.10	0.033	1.88
1	-8	2	2885.64	2281.12	3.06	0.416	1.12
-3	-4	8	20.90	36.56	3.00	0.053	1.12
0	-3	2	3391.03	2679.59	2.98	0.451	2.78
0	-6	3	2161.65	1512.02	2.97	0.339	1.44
-1	-2	2	104.50	77.30	2.94	0.077	3.23
1	-9	1	382.93	296.90	2.92	0.150	0.99
2	-8	3	1102.02	877.19	2.89	0.258	1.10
-5	7	6	58.52	88.68	2.87	0.082	0.88
1	-10	5	131.02	94.80	2.87	0.085	0.87
-1	-10	4	241.81	184.09	2.85	0.118	0.86
3	0	9	10.06	21.77	2.85	0.041	1.08
-6	0	2	17.62	7.24	2.84	0.023	1.22
2	-4	1	627.38	499.73	2.84	0.195	2.04
2	-6	3	509.06	403.43	2.82	0.175	1.41
-1	3	2	70.74	95.82	2.76	0.085	2.43
-6	2	10	-5.35	3.14	2.75	0.015	0.84
0	-1	5	61.47	83.17	2.65	0.079	2.25
1	-10	6	301.19	236.83	2.63	0.134	0.85
2	3	0	304.23	243.89	2.59	0.136	2.12

ond lengths and angles

S1 -	Distance	Angles			
	1.630 (0.002)				
	1.828 (0.003)	103.18 (0.13)			
	1.835 (0.003)	100.48 (0.13)	98.48 (0.14)		
	S1 -	N1	C3		
S2 -	Distance	Angles			
	1.790 (0.003)				
	1.798 (0.003)	100.78 (0.14)			
	S2 -	C2			
S3 -	Distance	Angles			
	1.797 (0.003)				
	1.797 (0.003)	100.59 (0.14)			
	S3 -	C3			
S4 -	Distance	Angles			
	1.433 (0.002)				
	1.439 (0.002)	118.19 (0.14)			
	1.609 (0.002)	105.33 (0.13)	112.96 (0.12)		
	1.768 (0.003)	106.79 (0.13)	107.45 (0.13)	105.26 (0.13)	
	S4 -	O1	O2	N1	
N1 -	Distance	Angles			
	1.609 (0.002)				
	1.630 (0.002)	114.87 (0.13)			
	N1 -	S4			
O1 -	Distance	Angles			
	1.433 (0.002)				
	O1 -				
O2 -	Distance	Angles			
	1.439 (0.002)				
	O2 -				
C3 -	Distance	Angles			
	1.506 (0.004)				
	1.798 (0.003)	100.51 (0.19)			
	1.835 (0.003)	109.80 (0.20)	110.41 (0.14)		

```
                C1 -          C4              S2

S2 -          Distance      Angles
S2          1.790 (0.003)
S3          1.797 (0.003)   114.88 (0.16)
                C2 -          S2

C3 -          Distance      Angles
C5          1.515 (0.004)
S3          1.797 (0.003)   109.29 (0.19)
S1          1.828 (0.003)   108.76 (0.20) 108.46 (0.14)
                C3 -          C5              S3

C4 -          Distance      Angles
C1          1.506 (0.004)
                C4 -

C5 -          Distance      Angles
C3          1.515 (0.004)
                C5 -

C6 -          Distance      Angles
C11         1.376 (0.004)
C7          1.383 (0.004)   120.22 (0.25)
S4          1.768 (0.003)   119.33 (0.20) 120.37 (0.21)
                C6 -          C11             C7

C7 -          Distance      Angles
C8          1.383 (0.004)
C6          1.383 (0.004)   119.09 (0.26)
                C7 -          C8

C8 -          Distance      Angles
C9          1.383 (0.004)
C7          1.383 (0.004)   121.62 (0.26)
                C8 -          C9

C9 -          Distance      Angles
C8          1.383 (0.004)
C10         1.386 (0.004)   117.97 (0.26)
C12         1.496 (0.004)   121.87 (0.27) 120.16 (0.28)
                C9 -          C8              C10

C10 -         Distance      Angles
C11         1.377 (0.004)
C9          1.386 (0.004)   121.22 (0.28)
                C10 -         C11

C11 -         Distance      Angles
C6          1.376 (0.004)
C10         1.377 (0.004)   119.87 (0.26)
                C11 -         C6

C12 -         Distance      Angles
C9          1.496 (0.004)
                C12 -

     4.4 seconds elapsed time

FMAP and GRID set by program

FMAP   2   1  18
GRID    -3.333  -2  -2     3.333   2   2

R1 =  0.0451 for   2614 unique reflections after merging

Electron density synthesis with coefficients Fo-Fc

Maximum =     0.51,     Minimum =    -0.46 e/A^3,     Highest memory used =  1098 / 16491
Mean =    0.00,     Rms deviation from mean =     0.08 e/A^3

Fourier peaks appended to .res file

              x       y       z       sof     U       Peak   Distances to nearest atoms (including symmetry equivalents)
Q1    1   0.0727  0.2719  0.5211  1.00000  0.05    0.51   0.89 S1  0.95 C1  1.55 H1  2.01 H1
Q2    1   0.0713  0.2996  0.1809  1.00000  0.05    0.44   0.81 C6  0.98 S4  1.84 C7  1.87 O2
Q3    1  -0.2158  0.1333  0.6382  1.00000  0.05    0.44   0.89 C2  0.91 S3  1.49 H2A  1.51 H2B
Q4    1  -0.0985  0.2335  0.4586  1.00000  0.05    0.42   0.86 C3  0.97 S1  1.53 H3  1.92 C5
Q5    1  -0.0573  0.1568  0.6790  1.00000  0.05    0.42   0.79 C2  1.10 S2  1.67 H2A  1.55 H2B
Q6    1   0.0539  0.1381  0.6011  1.00000  0.05    0.34   1.13 S2  1.62 C1  2.01 C2  2.06 S1
Q7    1  -0.4019  0.0729  0.5379  1.00000  0.05    0.33   0.93 S3  2.14 C3  2.49 H5A  2.50 H4C
Q8    1   0.3662  0.4432  0.5621  1.00000  0.05    0.32   0.63 H4B  0.92 C4  1.12 H4A  1.75 H4C
Q9    1   0.0401  0.3358  0.3000  1.00000  0.05    0.30   0.89 N1  1.13 S4  1.81 C6  2.03 S1
Q10   1   0.1125  0.2175  0.7814  1.00000  0.05    0.27   0.93 S2  2.06 C2  2.30 H2A  2.35 H2B
Q11   1  -0.2021  0.1938  0.7783  1.00000  0.05    0.25   0.77 H2A  0.93 C2  0.95 H2B  2.41 S2
Q12   1  -0.4428  0.2074 -0.2021  1.00000  0.05    0.24   1.05 H12B  1.13 H12C  1.26 C12  2.11 H12A
Q13   1   0.0561  0.0573  0.5010  1.00000  0.05    0.24   1.80 S1  2.33 S2  2.37 C1  2.40 S3
Q14   1  -0.1750  0.1846  0.7384  1.00000  0.05    0.23   0.42 C2  0.77 H2A  0.82 H2B  2.04 S2
Q15   1   0.4172  0.2556  0.5421  1.00000  0.05    0.23   0.62 H4C  1.20 C4  1.39 H4B  1.91 H4A
Q16   1   0.2699  0.4442  0.1619  1.00000  0.05    0.23   0.76 O1  1.44 S4  2.30 H10  2.36 C6
Q17   1  -0.1330  0.0832  0.4785  1.00000  0.05    0.23   1.53 S3  1.58 C3  1.75 O1  2.26 H5B
Q18   1  -0.4578  0.1437  0.3578  1.00000  0.05    0.23   0.57 H5A  1.05 C5  1.23 H5B  1.75 H5C
Q19   1  -0.1270  0.3437  0.3385  1.00000  0.05    0.23   1.18 H5C  1.57 H1  1.81 C5  2.05 C5
Q20   1  -0.3107  0.1750  0.7380  1.00000  0.05    0.22   1.21 H2A  1.25 H2B  1.28 C2  1.99 H12B

Shortest distances between peaks (including symmetry equivalents)

   11  14  0.51     11  20  0.89     14  20  1.02      5  14  1.15      3  14  1.17     13  13  1.22      3   5  1.23
```

6	13	1.25	5	6	1.25	12	20	1.27	9	19	1.35	2	9	1.38	4	17	1.39	3	20	1.39
1	4	1.40	13	17	1.49	13	17	1.51	3	11	1.59	1	6	1.60	5	11	1.63	5	10	1.65
3	7	1.72	8	15	1.76	4	19	1.82	11	12	1.85	2	16	1.86	6	17	1.88	7	7	1.88
1	13	1.89	3	17	1.95	6	13	1.98	6	10	2.06	5	20	2.06	3	6	2.08	1	17	2.08
10	14	2.13	7	17	2.14	12	14	2.19	4	13	2.19	6	17	2.23	7	15	2.28	4	6	2.28
5	17	2.28	5	13	2.33	10	11	2.33	7	20	2.34	7	18	2.35	4	9	2.35	1	5	2.37
6	14	2.40	2	19	2.40	15	18	2.41	1	8	2.46	3	4	2.49	9	16	2.56	5	13	2.58
1	15	2.61	3	13	2.61	3	12	2.62	1	9	2.66	8	8	2.67	7	18	2.68	4	5	2.71
1	19	2.71	3	13	2.72	17	17	2.73	7	14	2.74	4	7	2.76	4	13	2.78	18	19	2.78
4	18	2.81	3	10	2.81	1	3	2.81	6	11	2.88	5	7	2.90	6	15	2.91	7	15	2.93
1	13	2.93	8	19	2.95	17	18	2.97	13	15	2.97	14	17	2.99						

4.3 seconds elapsed time

```
++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
 tstwo          finished at 11:20:25   Total elapsed time:      130.7 secs  +
++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
```

Appendix 5 Crystal data and structure refinement for *S*-*E*-styryl-*S*-*p*-tolyl-*N*-*p*-tosyl sulfimide ***E*-186b**

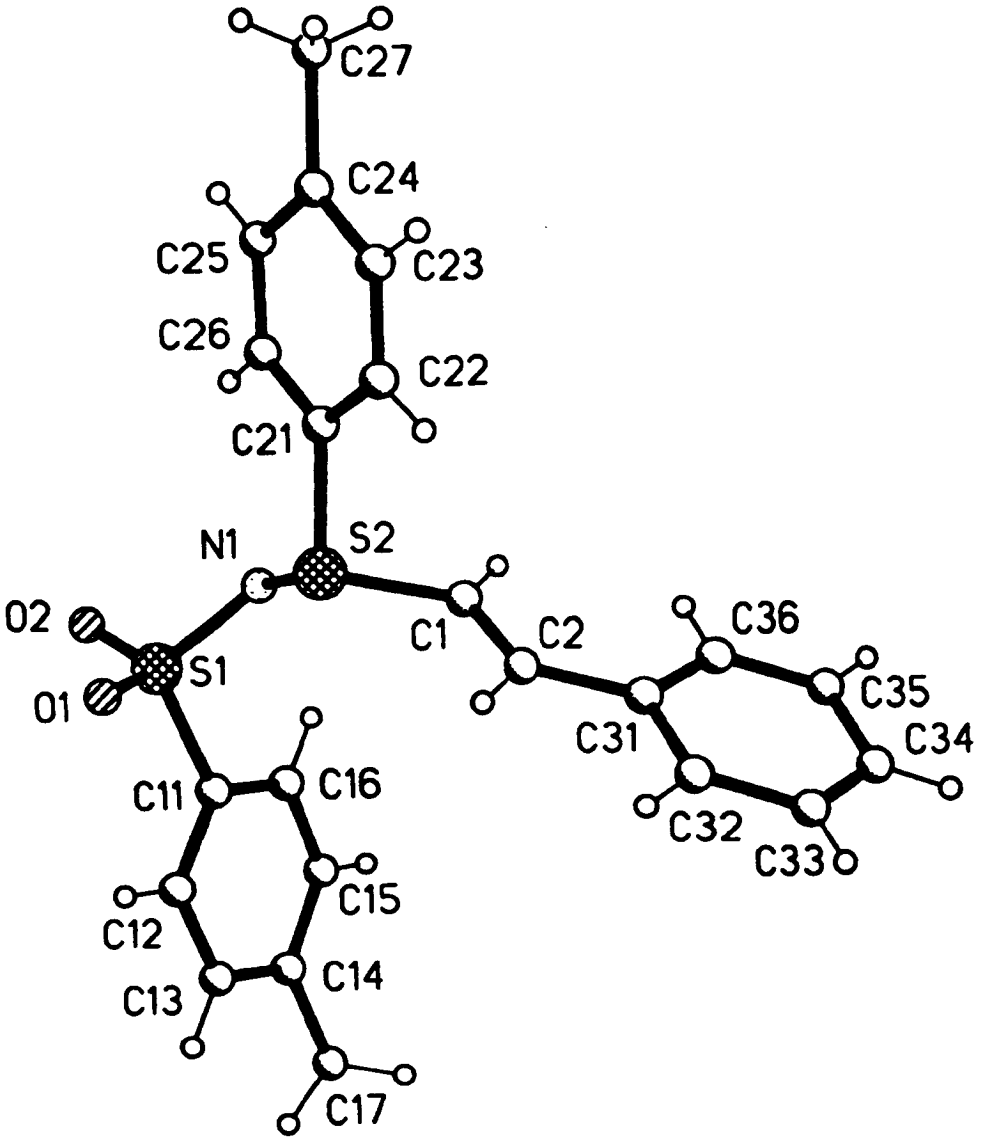


Table 1. Crystal data and structure refinement for 1.

Identification code	pans
Empirical formula	$C_{22}H_{21}NO_2S_2$
Formula weight	395.52
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 15.48(2) Å α = 90° b = 14.93(2) Å β = 110.62(8)° c = 18.67(2) Å γ = 90°
Volume	4038(7) Å^3
Z	8
Density (calculated)	1.301 Mg/m^3
Absorption coefficient	0.280 mm^{-1}
F(000)	1664
Crystal size	0.45 x 0.09 x 0.04 mm
θ range for data collection	2.01 to 22.55°
Index ranges	$0 \le h \le 16$, $0 \le k \le 16$, $-20 \le l \le 18$
Reflections collected	2772
Independent reflections	2658 [R(int) = 0.0381]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2656 / 24 / 246
Goodness-of-fit on F^2	0.940
Final R indices [I>2sigma(I)]	R1 = 0.0799, wR2 = 0.1826
R indices (all data)	R1 = 0.1845, wR2 = 0.2405
Largest diff. peak and hole	0.532 and -0.383 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	7647(2)	1786(2)	7037(1)	69(1)
S(2)	8876(2)	2542(2)	6513(1)	77(1)
O(1)	8408(4)	1732(4)	7739(3)	95(2)
O(2)	6785(4)	2093(4)	7084(4)	95(2)
N(1)	7807(4)	2369(5)	6395(4)	75(2)
C(1)	9019(6)	2207(6)	5688(5)	78(3)
C(2)	9724(6)	1723(5)	5716(6)	72(3)
C(11)	7444(5)	684(5)	6656(4)	54(2)
C(12)	7787(5)	-33(6)	7113(4)	68(2)
C(13)	7585(6)	-881(5)	6819(5)	77(3)
C(14)	7034(6)	-1022(6)	6076(5)	70(3)
C(15)	6695(6)	-287(7)	5630(5)	84(3)
C(16)	6913(6)	564(5)	5913(5)	72(3)
C(17)	6852(7)	-1952(6)	5765(6)	111(4)
C(21)	8971(5)	3718(5)	6466(4)	58(2)
C(22)	9792(6)	4072(6)	6495(5)	82(3)
C(23)	9920(6)	4968(7)	6516(5)	84(3)
C(24)	9214(6)	5544(7)	6493(5)	86(3)
C(25)	8389(6)	5179(6)	6468(5)	80(3)
C(26)	8261(6)	4280(6)	6443(5)	75(3)
C(27)	9334(7)	6547(6)	6495(6)	109(4)
C(31)	9972(5)	1410(5)	5080(6)	65(2)
C(32)	10762(5)	902(6)	5256(5)	72(3)
C(33)	11058(6)	578(6)	4701(8)	101(4)
C(34)	10560(7)	741(7)	3943(7)	100(4)
C(35)	9774(8)	1252(7)	3759(5)	95(3)
C(36)	9482(6)	1568(6)	4318(6)	74(3)

Table 3. Bond lengths [Å] and angles [deg] for 1.

S(1)-O(1)	1.423(6)
S(1)-O(2)	1.442(6)
S(1)-N(1)	1.569(7)
S(1)-C(11)	1.775(8)
S(2)-N(1)	1.611(7)
S(2)-C(1)	1.705(10)
S(2)-C(21)	1.768(8)
C(1)-C(2)	1.296(11)
C(2)-C(31)	1.448(11)
C(11)-C(16)	1.353(7)
C(11)-C(12)	1.355(7)
C(12)-C(13)	1.372(9)
C(13)-C(14)	1.366(8)
C(14)-C(15)	1.366(8)
C(14)-C(17)	1.494(12)
C(15)-C(16)	1.371(9)
C(21)-C(22)	1.360(8)
C(21)-C(26)	1.371(8)
C(22)-C(23)	1.352(9)
C(23)-C(24)	1.379(9)
C(24)-C(25)	1.373(9)
C(24)-C(27)	1.510(12)
C(25)-C(26)	1.356(9)
C(31)-C(36)	1.375(8)
C(31)-C(32)	1.377(8)
C(32)-C(33)	1.360(9)
C(33)-C(34)	1.373(10)
C(34)-C(35)	1.372(9)
C(35)-C(36)	1.361(9)

O(1)-S(1)-O(2)	116.4(4)
O(1)-S(1)-N(1)	115.7(4)
O(2)-S(1)-N(1)	105.5(4)
O(1)-S(1)-C(11)	106.8(4)
O(2)-S(1)-C(11)	106.4(4)
N(1)-S(1)-C(11)	105.2(4)
N(1)-S(2)-C(1)	106.4(4)
N(1)-S(2)-C(21)	104.6(4)
C(1)-S(2)-C(21)	101.9(4)
S(1)-N(1)-S(2)	114.5(4)
C(2)-C(1)-S(2)	120.2(8)
C(1)-C(2)-C(31)	127.6(9)
C(16)-C(11)-C(12)	120.1(8)
C(16)-C(11)-S(1)	119.5(6)
C(12)-C(11)-S(1)	120.4(6)
C(11)-C(12)-C(13)	119.7(6)
C(14)-C(13)-C(12)	121.4(7)
C(13)-C(14)-C(15)	117.6(9)
C(13)-C(14)-C(17)	120.2(8)
C(15)-C(14)-C(17)	122.1(8)
C(14)-C(15)-C(16)	121.3(7)
C(11)-C(16)-C(15)	119.8(6)
C(22)-C(21)-C(26)	119.4(8)
C(22)-C(21)-S(2)	118.5(6)

C(26)-C(21)-S(2)	122.0(6)
C(23)-C(22)-C(21)	120.7(8)
C(22)-C(23)-C(24)	120.7(8)
C(25)-C(24)-C(23)	118.1(10)
C(25)-C(24)-C(27)	120.4(9)
C(23)-C(24)-C(27)	121.5(9)
C(26)-C(25)-C(24)	121.1(8)
C(25)-C(26)-C(21)	120.0(7)
C(36)-C(31)-C(32)	117.5(9)
C(36)-C(31)-C(2)	125.7(8)
C(32)-C(31)-C(2)	116.9(9)
C(33)-C(32)-C(31)	121.5(8)
C(32)-C(33)-C(34)	120.2(9)
C(35)-C(34)-C(33)	118.9(11)
C(36)-C(35)-C(34)	120.3(9)
C(35)-C(36)-C(31)	121.5(8)

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for 1. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$

	U11	U22	U33	U23	U13	U12
S(1)	75(2)	62(2)	72(2)	2(1)	30(1)	-8(1)
S(2)	63(2)	85(2)	86(2)	1(2)	32(1)	2(1)
O(1)	98(5)	99(5)	64(4)	4(4)	-2(4)	-19(4)
O(2)	94(5)	78(4)	131(6)	-6(4)	63(4)	12(4)
N(1)	61(4)	76(5)	83(5)	-5(4)	20(4)	-15(4)
C(1)	60(6)	81(7)	85(7)	-7(5)	15(5)	-9(5)
C(2)	63(6)	52(6)	93(7)	7(5)	18(5)	4(5)
C(11)	53(5)	59(6)	56(6)	3(5)	25(4)	0(4)
C(12)	73(6)	68(6)	58(6)	5(5)	17(5)	7(5)
C(13)	84(7)	62(7)	87(8)	25(6)	31(6)	10(5)
C(14)	72(6)	75(7)	77(7)	-12(6)	43(6)	0(5)
C(15)	82(7)	97(8)	65(6)	-5(6)	14(5)	-8(6)
C(16)	78(6)	70(7)	67(7)	14(5)	23(5)	-2(5)
C(17)	144(10)	71(7)	125(9)	-15(7)	54(8)	-14(7)
C(21)	45(5)	60(6)	75(6)	-8(5)	29(4)	-12(5)
C(22)	61(6)	87(8)	101(8)	-13(6)	34(5)	-15(6)
C(23)	59(6)	93(8)	111(8)	-39(7)	43(6)	-30(6)
C(24)	101(8)	91(8)	62(6)	-8(6)	27(6)	-34(7)
C(25)	66(6)	74(7)	103(8)	5(6)	35(5)	-9(5)
C(26)	58(6)	62(7)	107(8)	-5(6)	32(5)	-2(5)
C(27)	125(9)	93(9)	102(8)	-12(7)	29(7)	-41(7)
C(31)	63(6)	42(5)	101(8)	-12(5)	43(6)	-12(5)
C(32)	45(5)	63(6)	101(8)	-3(6)	16(5)	4(5)
C(33)	56(7)	83(8)	166(12)	-13(9)	41(8)	2(6)
C(34)	89(9)	85(8)	149(12)	-25(8)	72(8)	-20(7)
C(35)	98(9)	102(9)	90(8)	-1(7)	41(7)	-34(7)
C(36)	67(6)	76(7)	82(7)	9(6)	30(6)	-13(5)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(1)	8589(6)	2373(6)	5217(5)	94
H(2)	10117(6)	1557(5)	6201(6)	86
H(12)	8157(5)	50(6)	7623(4)	81
H(13)	7830(6)	-1370(5)	7134(5)	93
H(15)	6309(6)	-364(7)	5124(5)	101
H(16)	6696(6)	1056(5)	5595(5)	87
H(17A)	7201(41)	-2061(18)	5439(35)	167
H(17B)	6206(11)	-2020(17)	5475(37)	167
H(17C)	7031(49)	-2373(7)	6180(6)	167
H(22)	10271(6)	3693(6)	6500(5)	98
H(23)	10489(6)	5199(7)	6546(5)	101
H(25)	7910(6)	5556(6)	6467(5)	95
H(26)	7693(6)	4045(6)	6412(5)	89
H(27A)	8937(37)	6826(7)	6725(37)	164
H(27B)	9176(49)	6756(9)	5978(7)	164
H(27C)	9964(13)	6698(7)	6782(36)	164
H(32)	11102(5)	777(6)	5766(5)	87
H(33)	11599(6)	245(6)	4835(8)	122
H(34)	10751(7)	509(7)	3562(7)	120
H(35)	9441(8)	1383(7)	3249(5)	114
H(36)	8938(6)	1897(6)	4183(6)	89