Copper-Catalysed Asymmetric Sulfide Oxidation

by

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Abstract

The focus of this thesis is the preparation of enantiopure sulfoxides by means of copper-catalysed asymmetric sulfoxidation, with particular emphasis on the synthesis of aryl benzyl and aryl alkyl sulfoxides.

Chapter 1 contains a review of the methods employed for the asymmetric synthesis of sulfoxides, compounds with many applications in stereoselective synthesis and in some cases with pharmaceutical application. Chapter 1 describes asymmetric oxidation, including metal-catalysed, non metal-catalysed and enzyme-catalysed, in addition to synthetic approaches *via* nucleophilic substitution of appropriately substituted precursors. Kinetic resolution in oxidation of sulfoxides to the analogous sulfones is also discussed; in certain cases, access to enantioenriched sulfoxides can be achieved *via* a combination of asymmetric sulfoxidation and complementary kinetic resolution.

The design and synthesis of a series of sulfides to enable exploration of the substituent effects of the copper-mediated oxidation was undertaken, and oxidation to the racemic sulfoxides and sulfones to provide reference samples was conducted. Oxidation of the sulfides using copper-Schiff base catalysis was undertaken leading to enantioenriched sulfoxides. The procedure employed is clean, inexpensive, not air-sensitive and utilises aqueous hydrogen peroxide as oxidant. Extensive investigation of the influence of the reaction conditions such as solvent, temperature, copper salt and ligand was undertaken to lead to the optimised conditions.

While the direct attachment of one aryl substituent to the sulfide is essential for efficient enantiocontrol, in the case of the second substituent the enantiocontol is dependent on the steric rather than electronic features of the substituent. Significantly, use of naphthyl-substituted sulfides results in excellent enantiocontrol; notably 97% ee, obtained in the oxidation of 2-naphthyl benzyl sulfide, represents the highest enantioselectivity reported to date for a copper-mediated sulfur oxidation. Some insight into the mechanistic features of the copper-mediated sulfur oxidation has been developed based on this work, although further investigation is required to establish the precise nature of the catalytic species responsible for asymmetric sulfur oxidation.

Full experimental details, describing the synthesis and structural characterisation, and determination of enantiopurity are included in chapter 3.

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1.1 Introduction

Note: this introduction is reproduced from:

"*Synthesis of Enantioenriched Sulfoxides*"

Graham E. O'Mahony, Padraig Kelly, Simon E. Lawrence, Anita R. Maguire, *ARKIVOC*, **2011**, 1–110.

Padraig Kelly and I were the primary authors of this paper. Simon Lawrence and Anita Maguire provided assistance in terms of proof-reading, and helped with the overall construction of the manuscript

Updates to this review article appear in red type

Enantiopure sulfoxides have attracted a great deal of interest in the past three decades due to their use as chiral auxiliaries in a broad range of synthetic reactions. The sulfinyl group has been shown to be an efficient chiral auxiliary in carbon-carbon[1,2] and carbon-oxygen[3] bond forming reactions, in cycloaddition reactions,[4-6] radical addition reactions[7,8] and in asymmetric catalysis.[9] The sulfinyl group is successful as a chiral controller because: (1) it is configurationally stable at RT (generally stable up to 200 °C), (2) it is accessible in both enantiomeric forms, and (3) it is an excellent carrier of chiral information.[10] A number of reviews have been published dealing with the use of enantiopure sulfoxides in asymmetric synthesis.[11-15]

Enantiopure sulfoxides have also found use in the pharmaceutical industry due to their important biological activity. Omeprazole, the world's highest selling drug in 1997 ($5 billion U.S.),[16] is a proton pump inhibitor used to treat acid-induced inflammation and ulcers of the stomach and duodenum. A number of other acid secretion inhibitors based on the framework of omeprazole have also been developed (Figure 1.1). Esomeprazole, the (*S*)-form of omeprazole, was launched in Europe in 2000 and the USA in 2001 under the trade name Nexium™.

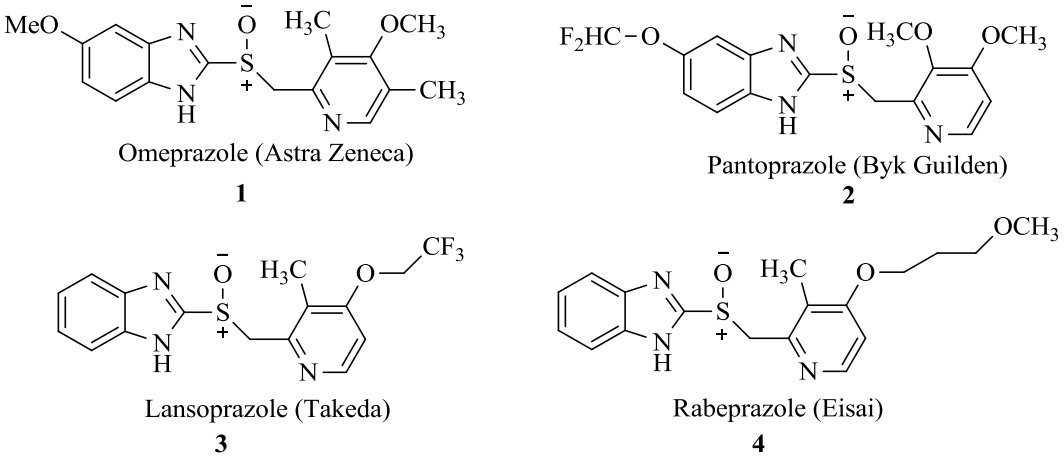


Figure 1.1

Other biologically active compounds containing the sulfinyl moiety include modafinil **5** and sulindac **6**, which have been used to treat narcolepsy and inflammation respectively (Figure 1.2).[17,18] A number of reviews outlining the asymmetric synthesis of biologically active sulfoxides have appeared.[19,20]

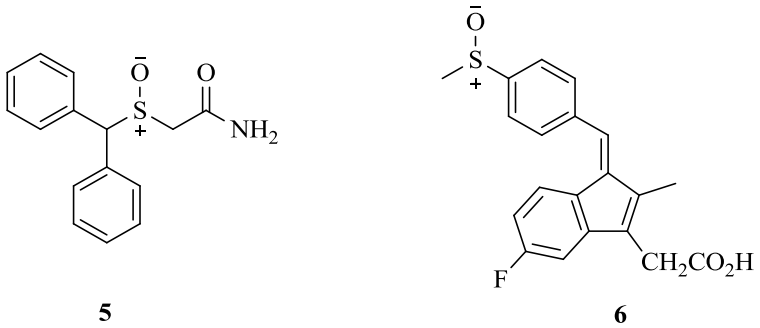


Figure 1.2

There are two principal routes to enantiopure sulfoxides;[10,21-25]

- Oxidation
- Nucleophilic substitution

The oxidation route is by far the most popular because of its versatility in that the same route can be used to oxidise many sulfides.

1.2 Asymmetric sulfide oxidation

The most attractive method for the preparation of enantiopure sulfoxides is asymmetric sulfide oxidation.[21] Developing a novel oxidation method that involves simply treating a

sulfide with an oxidising reagent/complex to form the enantiopure sulfoxide has been, and still is, the goal of many research groups.

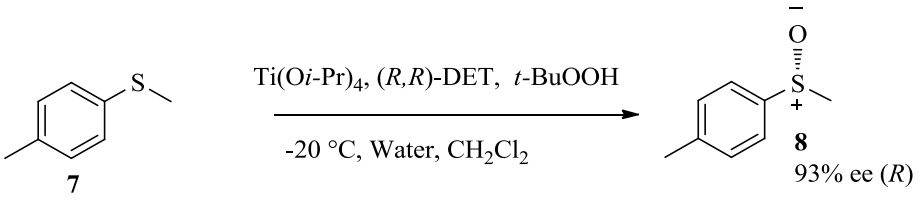
Peracids were used to carry out the first asymmetric sulfide oxidations, however, results obtained were very modest with enantioselectivity rarely greater than 10% ee.[26,27] Since the 1980s a number of practical and efficient asymmetric sulfide oxidation methods have been reported.[28-32] Most asymmetric sulfide oxidations are metal-catalysed though a number of non-metal catalysed oxidations and biological oxidations are known.

1.2.1 Metal-catalysed asymmetric sulfide oxidation

1.2.1.1 Titanium-catalysed oxidation

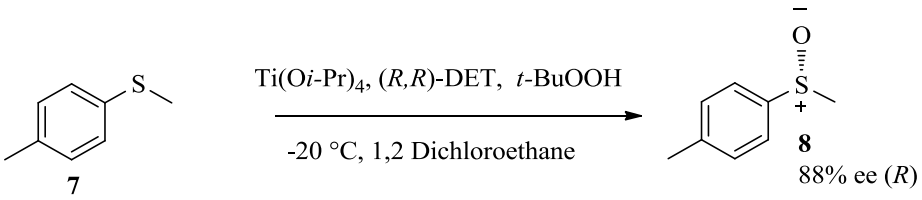
The first major advance in metal-catalysed asymmetric sulfide oxidation was reported by Kagan in 1984 (Scheme 1.1).[33,34] Also in 1984, Modena independently reported a similar oxidation method (Scheme 1.2).[35] Both the Kagan and Modena oxidation methods are based on the Sharpless asymmetric epoxidation.[36,37] These asymmetric sulfide oxidation methods represented the first practical and efficient oxidation methods for the metal-catalysed asymmetric oxidation of sulfides. The methods are not substrate specific and are relatively straightforward.

The differences between the methods are relatively minor. Both methods use a titanium catalyst, diethyl tartrate (DET) as the chiral auxiliary, *tert*-butyl hydrogen peroxide (TBHP) as the oxidant and are carried out at -20 ^{o}C. The Kagan method uses dichloromethane as the solvent and also involves the addition of water to the oxidation. The Modena method uses dichloroethane (DCE) as the solvent but does not involve the addition of water to the oxidation. The fact that these reactions were catalysed by titanium is unsurprising given its pivotal role in so many enantioselective reactions.[38] Elucidation of the structure of the Kagan-Modena catalysts has proved challenging.[39,40]



Kagan Oxidation

Scheme 1.1

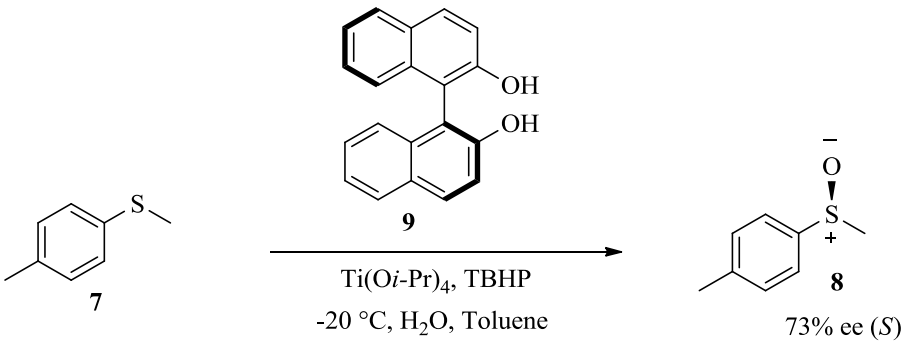


Modena Oxidation

Scheme 1.2

The Kagan oxidation method has received more attention than the Modena oxidation method. Using cumene hydroperoxide (CHP) instead of TBHP with the Kagan oxidation method resulted in higher enantioselectivity in the oxidation of **7**, with **8** being obtained in 96% ee in almost quantitative yield.[41] The role of water in the Kagan oxidation was investigated because it is based on the Sharpless asymmetric epoxidation[36,37] and water is a known catalyst poison in this reaction.[42] In the Kagan oxidation, water deactivates the catalyst for epoxidation but promotes enantioselective sulfide oxidation.[33,34] The effect of water in the Kagan oxidation was also investigated by Uemura, who reported that too little or too much water present in the reaction could impact detrimentally on the enantioselectivity of the reaction.[43]

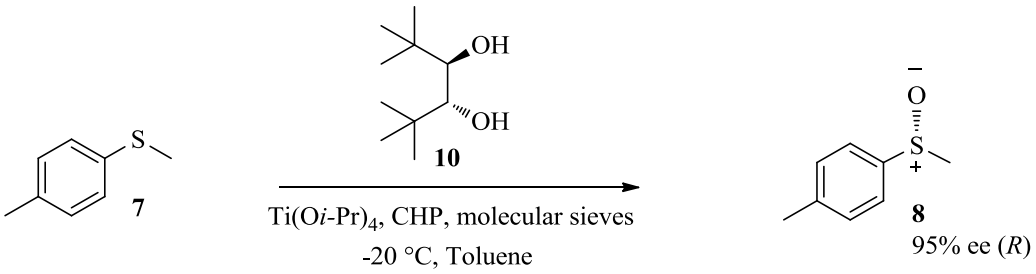
Most of the investigations into titanium mediated sulfur oxidation have focused on using different chiral auxiliaries to establish if the scope and enantioselectivity of the reaction can be improved. Uemura utilised a binaphthol chiral auxiliary, **9**, with the Kagan oxidation method and obtained sulfoxides in good yield and high enantiopurity (Scheme 1.3).[43]



Scheme 1.3

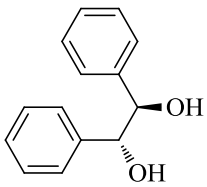
Imamoto used the hexanediol **10** as a chiral auxiliary in a titanium mediated sulfide oxidation.[44] Both Kagan and Uemura demonstrated that water was crucial for the enantioselectivity of the oxidation, however Imamoto observed that the oxidation using **10** as

the chiral auxiliary proceeded with the highest degree of enantiopurity when conducted in the presence of molecular sieves. Sulfoxides were obtained in good yield and with good enantioselectivity by Imamoto using cumene hydroperoxide (CHP) as oxidant (Scheme 1.4). Imamoto developed further diol-type chiral auxiliaries but these were less effective than **10**.[45]



Scheme 1.4

Superchi and Rosini also used diols as chiral auxiliaries following a similar procedure to Uemura; the oxidant used was TBHP and the reaction was carried out in the presence of water.[46] The ligand was (*S*,*S*)-1,2-diphenylethan-1,2-diol **11** with carbon tetrachloride as solvent and the reaction was carried out at 0 ^{o}C. The sulfoxide **8** was obtained with 80% ee in 62% yield.



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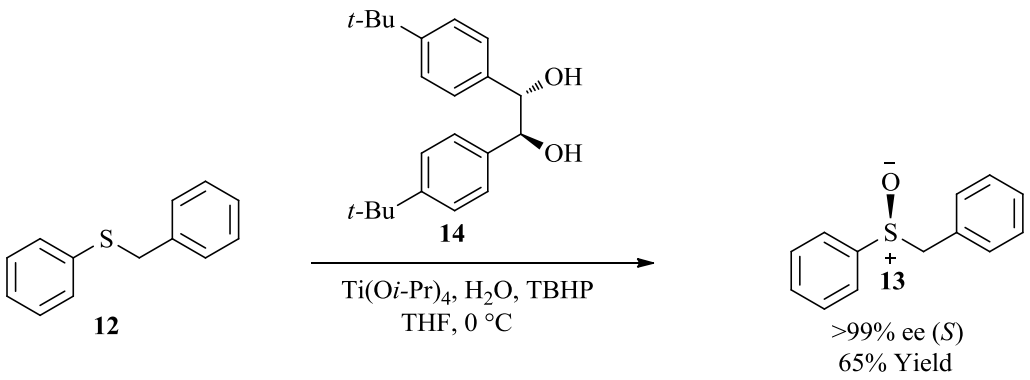
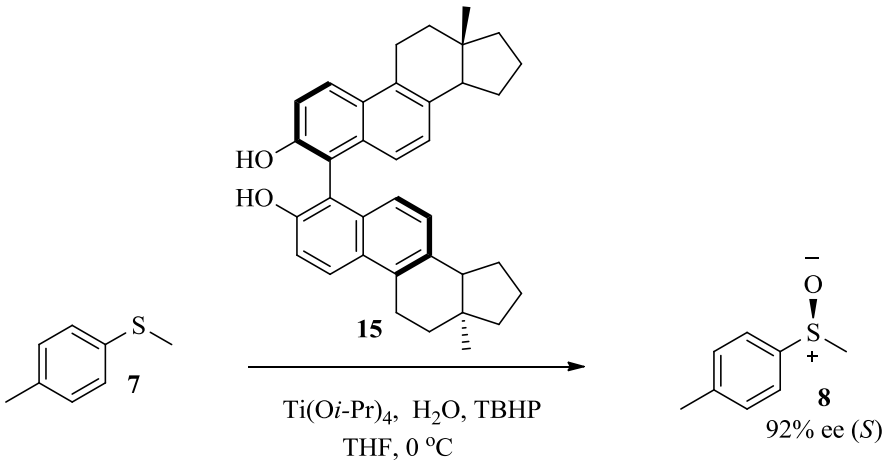
Similar diols **14** have recently been used by the same research group to prepare enantiopure aryl benzyl sulfoxides (Scheme 1.5).[47]



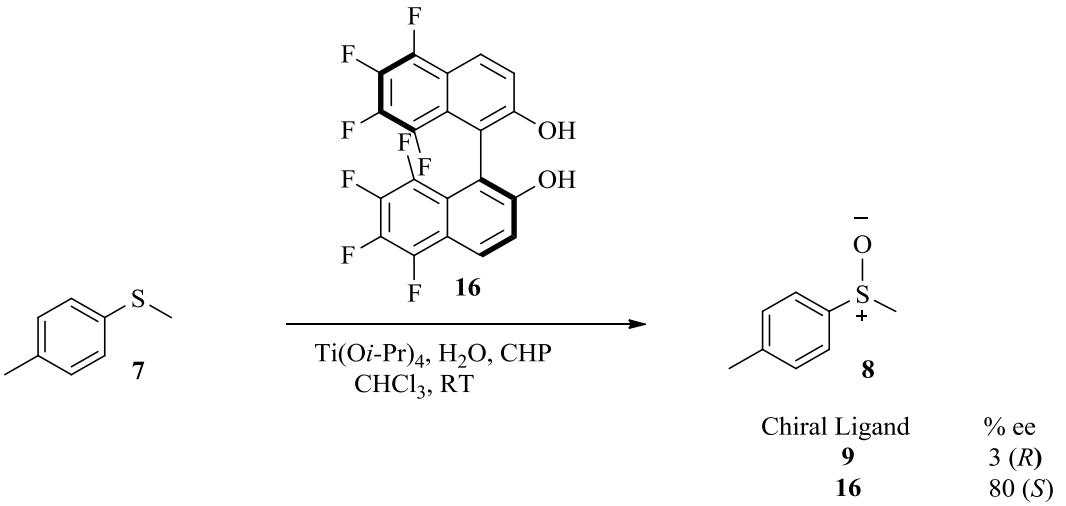
Scheme 1.5

Bolm and Dabard used a steroid derived BINOL derivative **15** as a chiral auxiliary.[48] Similar to Uemura's use of **9**, a water addition was crucial for the enantioselectivity of the oxidation (Scheme 1.6).



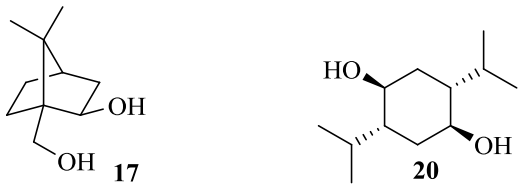
Scheme 1.6

Martyn *et al.* used a fluorinated BINOL (BINOL- F_8) derivative **16**, reasoning that it should interact differently with the titanium catalyst than BINOL (Scheme 1.7).[49] Carrying out the reaction at RT, using chloroform as the solvent and CHP as the oxidising agent, **16** significantly outperformed **9** in terms of enantioselectivity and efficiency. Also significant is the stereoselectivity of the reaction, using **9** the *R*-enantiomer is preferentially formed while using **16** the *S*-enantiomer is preferentially formed. The reason given for the better performance of **16** over **9** was the increased acidity of the hydroxyl groups. Ligand **16** has also been used in other asymmetric synthetic transformations.[50]



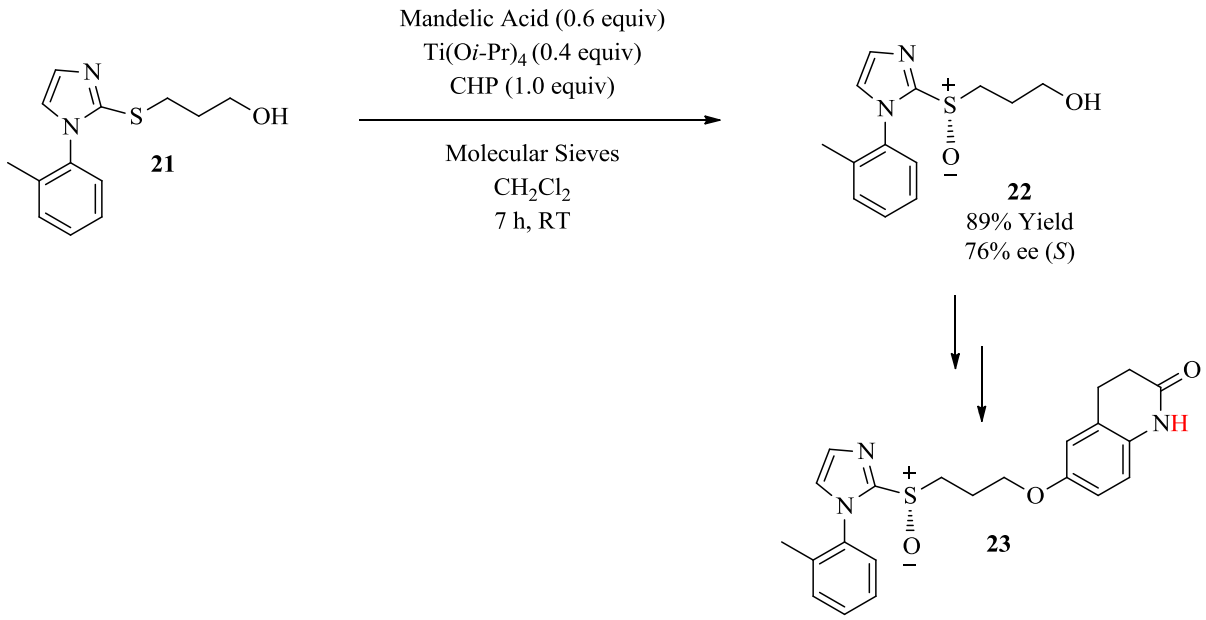
Scheme 1.7

Camphanediols, such as **17**, have also been used to prepare enantioenriched sulfoxides using this methodology.[51] It is proposed that the oxidation in this case occurs by an intramolecular nucleophilic oxygen transfer to the coordinated sulfide. This method oxidised thioanisole **18** to its sulfoxide **19** in poor yield but with excellent enantioselectivity (up to 99% ee).



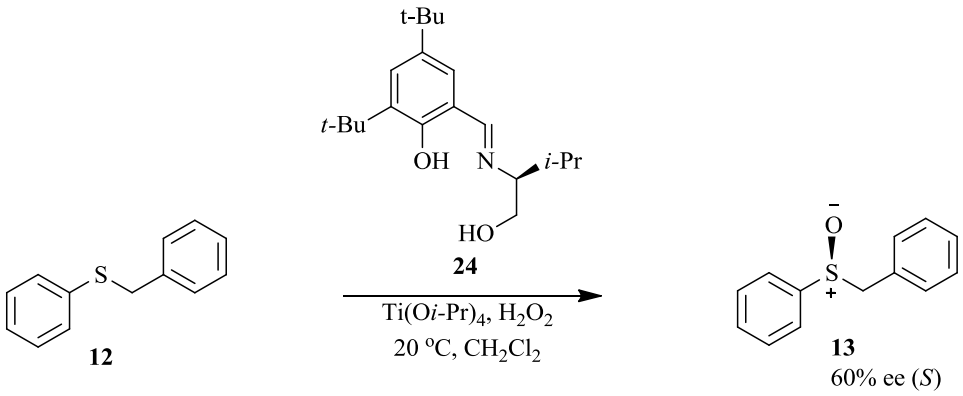
2,5-Dialkylcyclohexane-1,4-diols, e.g. **20**, have been used to generate a variety of enantioenriched aryl methyl sulfoxides (up to 84% ee).[52]

Mandelic acid was used as a chiral auxiliary to synthesise **22** on a large scale.[53-55] Significantly this oxidation can be carried out at RT and is not sensitive to atmospheric moisture, unlike the Kagan and Modena oxidation methods.[54] The sulfoxide **22** was obtained in good yield and high enantiopurity. Recrystallization afforded enantiopure **22**; a key intermediate in the synthesis of the platelet adhesion inhibitor **23** (Scheme 1.8).



Scheme 1.8

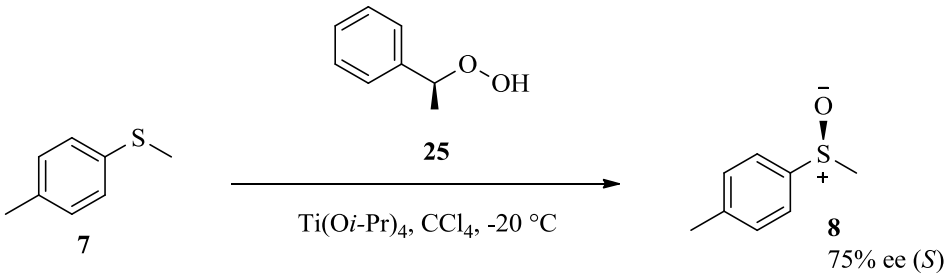
Bryliakov and Talsi employed an amino alcohol derived Schiff base ligand **24** as the chiral auxiliary with hydrogen peroxide as the oxidant (Scheme 1.9).[56] Modest results were obtained.



Scheme 1.9

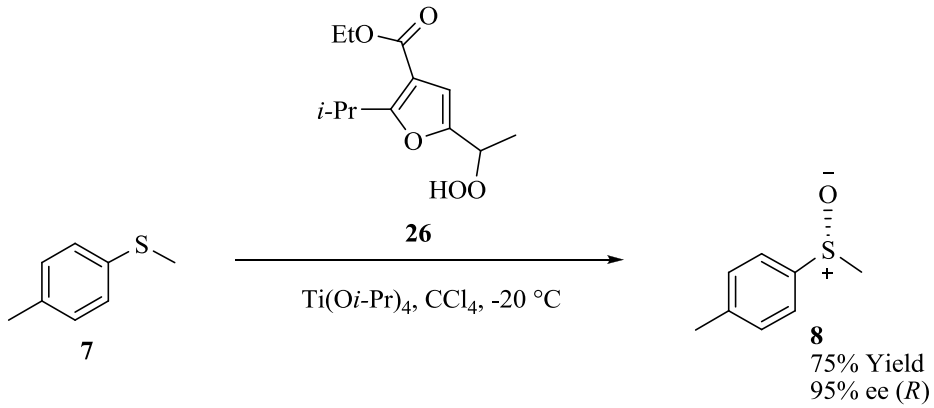
Bryliakov and Talsi have also reported the titanium-salen catalysed oxidation of sulfides that employed hydrogen peroxide as the oxidant.[57] The titanium-salen system reported is best suited to oxidise bulky sulfides such as benzyl phenyl sulfide**.** Poorer results were obtained for the oxidation of aryl alkyl sulfides. Notably, this asymmetric sulfide oxidation is accompanied by complementary kinetic resolution of the sulfoxide.

While most of the research into the Kagan-Modena oxidation methods have focused on the chiral auxiliary used, Adam *et al.* investigated the use of a chiral hydroperoxide **25** (Scheme 1.10).[58] Results obtained were modest, with moderate to good enantiopurities, but considerable sulfone formation accompanied the reactions. The significance of the sulfone formation will be discussed later, see section 3.



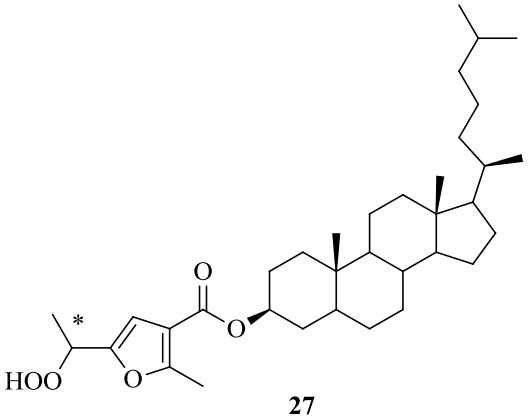
Scheme 1.10

Scettri *et al.* also investigated the effect of using hydroperoxides as the oxidising agents.[59-65] Using the conditions proposed by Modena, with an achiral tertiary furyl hydroperoxide oxidising agent, **8** was obtained in good yield and 90% ee.[59] Secondary furyl hydroperoxides were also investigated to see if enantioselectivity could be improved, and it was found that use of the furyl hydroperoxide **26** resulted in a further improvement in enantioselectivity and yield (Scheme 2.11).[59] Compound **26** possesses a stereocentre and was used in enantioenriched form. During the oxidation, kinetic resolution of **26** occurred.



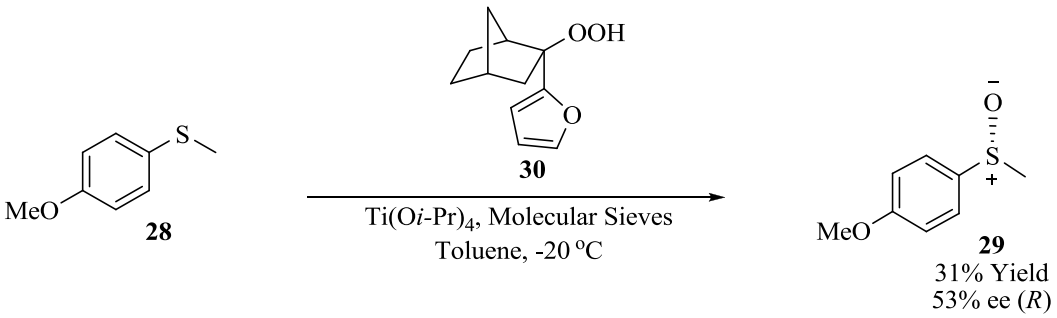
Scheme 1.11

Reaction times were reduced using the steroidal furyl hydroperoxide **27** but this resulted in a decrease in the enantioselectivity of the oxidation.[63]



27

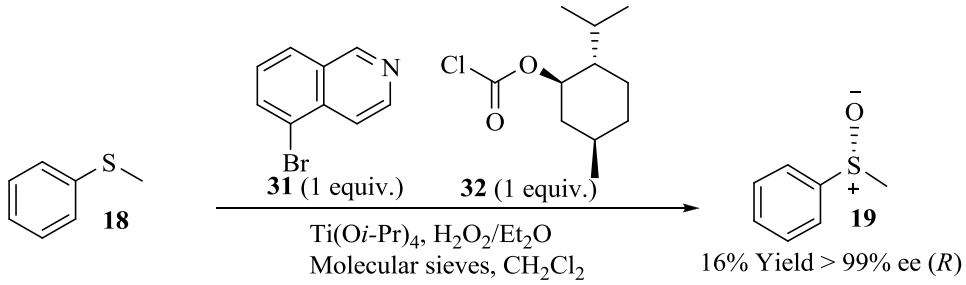
Various camphor derived furyl hydroperoxides have been developed and used by Lattanzi and Scettri.[65-68] Unlike other hydroperoxides, the use of a chiral auxiliary with the camphor furyl hydroperoxides is not necessary. It was proposed that steric interactions between the sulfide and the camphor derived oxidant resulted in the preferential formation of one sulfoxide enantiomer.[66] The furyl hydroperoxides were converted to the alcohol in the oxidation; which can be used to regenerate the hydroperoxide. Overall, the enantioselectivity of the oxidations was only moderate, with the highest enantioselectivity reported in the oxidation of *para*-methoxyphenyl methyl sulfide **28** using the (*S*)-norcamphor derived furyl hydroperoxide **30** (Scheme 1.12).[66] Sulfone formation was a significant feature for all the camphor derived furyl hydroperoxides.



Scheme 1.12

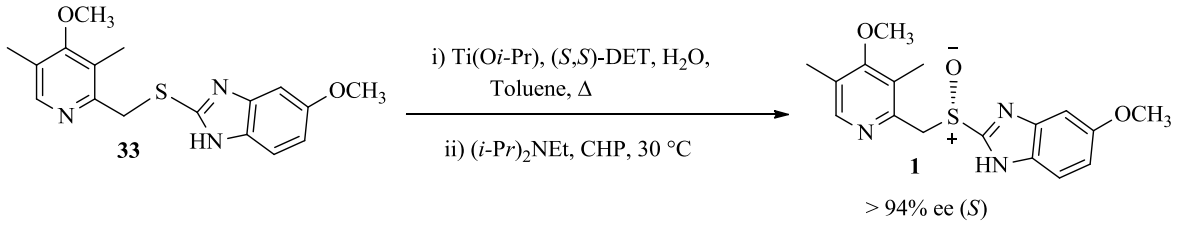
Recently, Liebscher used chiral hydroperoxide moieties for the asymmetric oxidation of aryl methyl sulfides (Scheme 1.13).[69] When 1.1 equivalents of H_2O_2 (oxidant) was used the (*R*)-sulfoxide was obtained in a 55% yield and 23% ee, with some over-oxidation to the sulfone. However, the use of 3.3 equivalents of H_2O_2 produced the (*R*)-sulfoxide in a 16%

yield and > 99% ee with a large amount of over-oxidation, indicating that kinetic resolution was taking place.



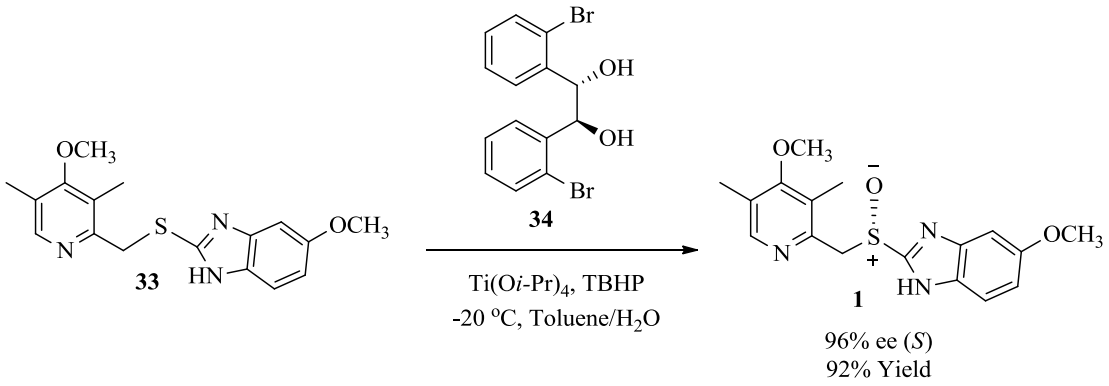
Scheme 1.13

Titanium mediated sulfide oxidation has been successfully used to prepare esomeprazole (Nexium®, **1***S*) which is the enantiopure form of omeprazole **1**.[70] The method used is based on the Kagan method, however the catalyst complex is prepared in the presence of the sulfide at an elevated temperature. The oxidation is carried out in the presence of *N*,*N*-di*iso*propylethylamine at 30 °C (Scheme 1.14). The role of this amine is unclear but is necessary for the enhanced enantioselectivity.



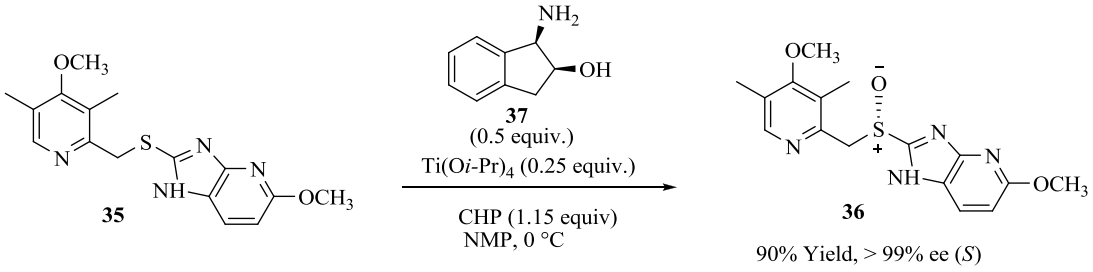
Scheme 1.14

The preparation of esomeprazole using a chiral complex with two chiral ligands (DET and a chiral amine) has been reported.[71] More recently a high yielding and highly enantioselective titanium mediated oxidative preparation of esomeprazole and similar heteroaromatic sulfoxides has been reported by Jiang *et al.*[72] This method employed a brominated aromatic diol **34** as chiral auxiliary and TBHP as the oxidant (Scheme 1.15).



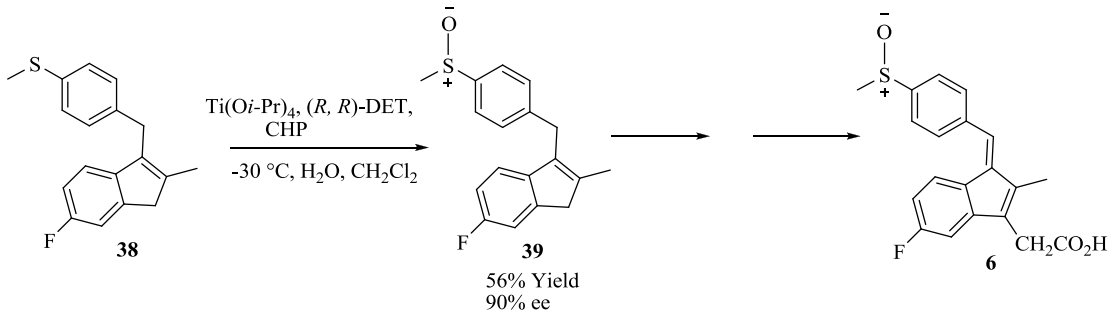
Scheme 1.15

Delamare *et al.* reported a new titanate-(+)-(1*R*, 2*S*)-*cis*-1-amino-2-indanol system **37** for the asymmetric synthesis of (*S*)-tenatoprazole. The procedure involved the use of the polar aprotic solvent *N*-methyl-2-pyrrolidone (NMP) and afforded the sulfoxide in high yield (90%) and enantioselectivity (> 99%) (Scheme 1.16).[73]



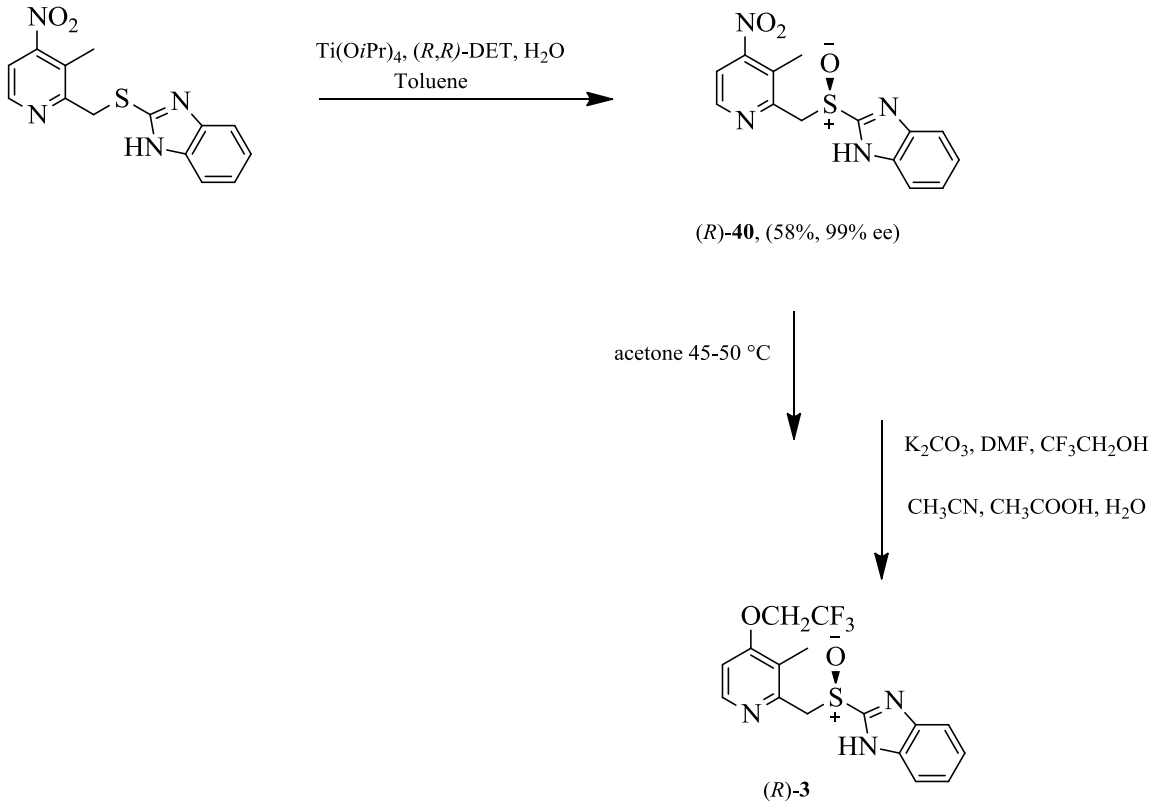
Scheme 1.16

Highly enantioenriched sulindac **6** has been prepared using the Kagan procedure by Maguire *et al.*, Scheme 1.17.[74] Naso *et al.*, employing the oxidant TBHP and a different chiral auxiliary, has also prepared highly enantioenriched **6** using the Kagan procedure.[75]



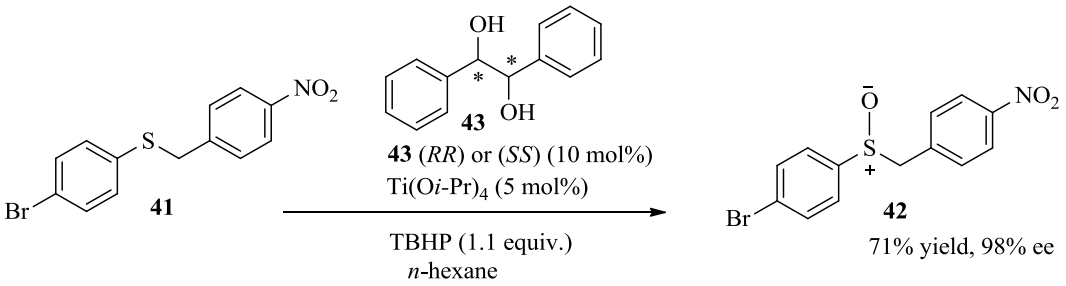
Scheme 1.17

Raju *et al.* used a titanium based system in the asymmetric synthesis of lansoprazole **3**.[76] (*R*)-**40** was obtained in excellent enantioselectivity and then converted to lansoprazole as shown in Scheme 1.18.



Scheme 1.18

Cardellicchio *et al.* investigated aryl benzyl sulfides using the titanium hydrobenzoin complex **43** as the catalyst. Interestingly, the (*R*)-sulfoxide was obtained when (*S*,*S*)-hydrobenzoin was used, whereas the reaction afforded the (*S*)-sulfoxide in the presence of (*R*,*R*)-hydrobenzoin. Aryl benzyl sulfoxides were obtained in excellent yields and enantioselectivities (Scheme 1.19).[77]



Scheme 1.19

Cardellicchio *et al.* hypothesised based on NMR studies of the reaction mixture, that a simple tetrahedral complex between titanium and two molecules of the ligand is formed in solution when titanium tetraisopropoxide and hydrobenzoin are mixed. This tetrahedral complex between titanium and hydrobenzoin is approached first by the sulfide, and then by the oxidant, thus yielding an octahedral complex. A simplified model of the octahedral complex was reported in 2011 and is shown in Figure 1.3.[78]

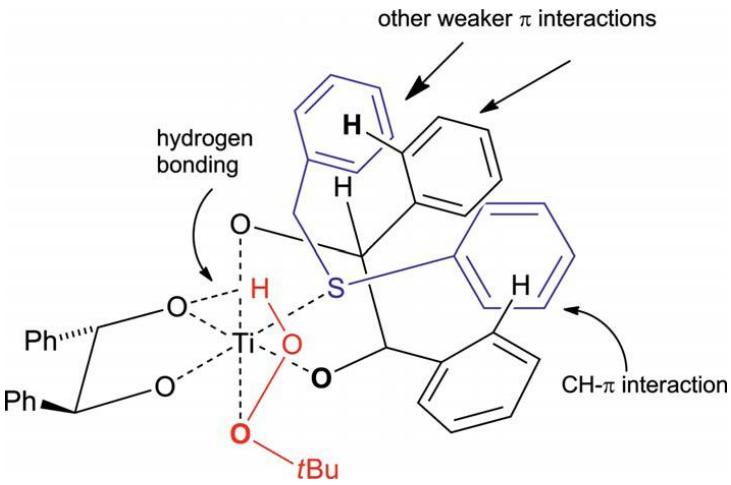


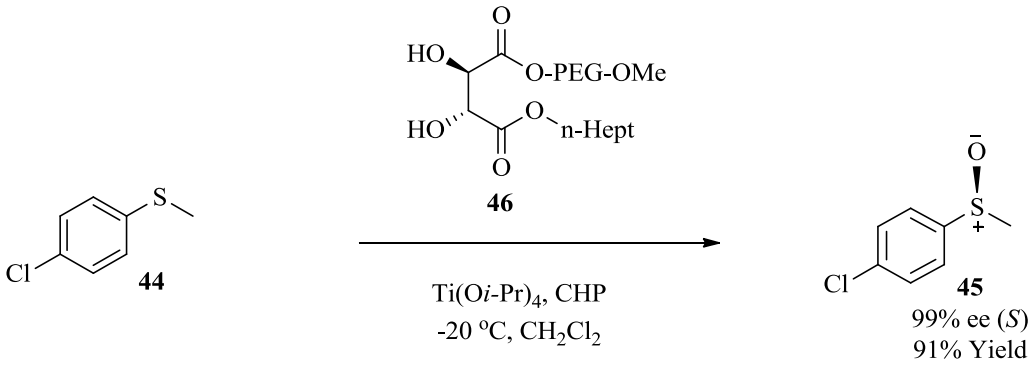
Figure 1.3 Octahedral titanium-hydrobenzoin complex (reproduced from reference[78])

Cardellicchio observed a strong hydrogen bond between the acidic hydrogen atom of the TBHP and one oxygen atom of a hydrobenzoin molectule. A CH-π interaction is present between hydrogen of one hydrobenzoin and a phenyl group of the aryl benzyl sulfide. Weaker interactions between the π aryl group are present in the rear part of the structure. The absence of these stabilizing interactions in the octahedral complex leading to the other enantiomer accounted for the high enantioselectivity achieved using this system.

The Modena oxidation method was re-investigated using a range of different oxidising reagents.[79] High enantioselectivity was achieved using CHP or recyclable furyl hydroperoxides in the presence of reduced amounts of the titanium- DET complex.

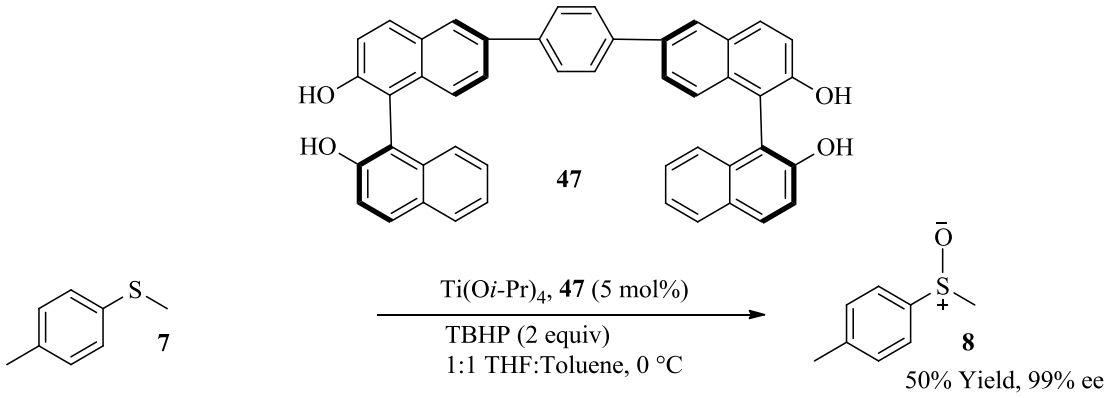
The use of immobilised catalysts is attracting a lot of interest as it may impact favorably on the efficiency of the reaction, as well as addressing environmental concerns by enabling easy recycling of the catalyst and reducing waste.[80] Iwamoto *et al.* carried out the Kagan methodology using a titanium catalyst which was immobilised on mesoporous silica.[81] The results obtained were modest with only moderate enantioselectivity being observed.

Considerably better results were reported by Gao *et al.* using a soluble PEG supported tartrate chiral auxiliary **46** (Scheme 1.20).[82]



Scheme 1.20

Yuan *et al.* designed and synthesised a series of BINOL derived ligands such as **47** and used them as catalysts. A range of sulfides were oxidised by this system, producing sulfoxides in excellent enantioselectivities, albeit in modest yield (Scheme 1.21).[83]

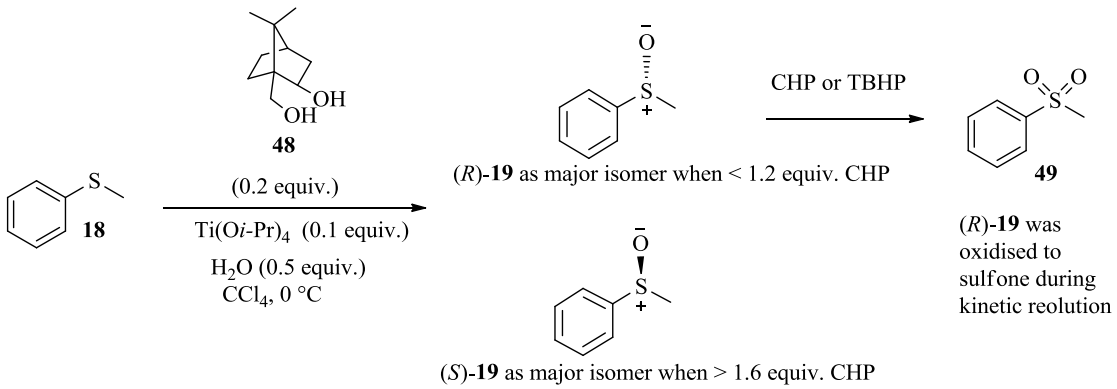


Scheme 1.21

Impressive results were reported by Sahoo *et al.* using an immobilised titanium-binol complex to prepare a variety of enantiopure aryl methyl sulfoxides.[84] This asymmetric oxidation was accompanied by complementary kinetic resolution. The chiral catalyst was immobilised using an ionic liquid modified mesoporous silica SBA 15 support. Essentially enantiopure phenyl methyl sulfoxide was obtained using only 60 % enantiopure catalyst

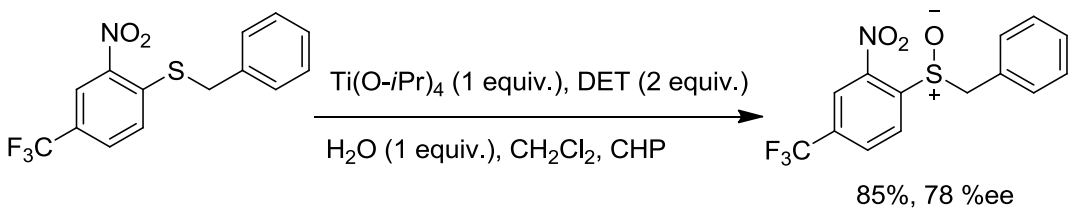
using this system. The immobilized catalyst employed proved to be quite robust and could be recycled without any loss of either enantioselectivity or activity over one month.

Zeng *et al.* used a 2,10-camphanediol derived titanium complex **48** in the asymmetric oxidation of thioanisole **18** (Scheme 1.22). It was discovered that the absolute configuration of the predominant sulfoxide product depended on the amount of CHP that was used. (*R*)-**19** was found to be the major isomer when < 1.2 equivalents of CHP was used while (S)-**19** was the major isomer when > 1.6 equivalents of CHP was used. In contrast, however, the absolute configuration of the predominant sulfoxide product was always the same when TBHP was used as the oxidant.[51] The asymmetric oxidation was accompanied by complementary kinetic resolution, producing the sulfoxide **19** of thioanisole **18** in 99% ee but in poor yield due to formation of the sulfone **49**.[51]



Scheme 1.22

Rodygin *et al.* reported the asymmetric oxidation of a range of fluorine containing sulfides using the Kagan system obtaining excellent yields and good enantioslectivities (up to 78% ee) (Scheme 1.23).[85]



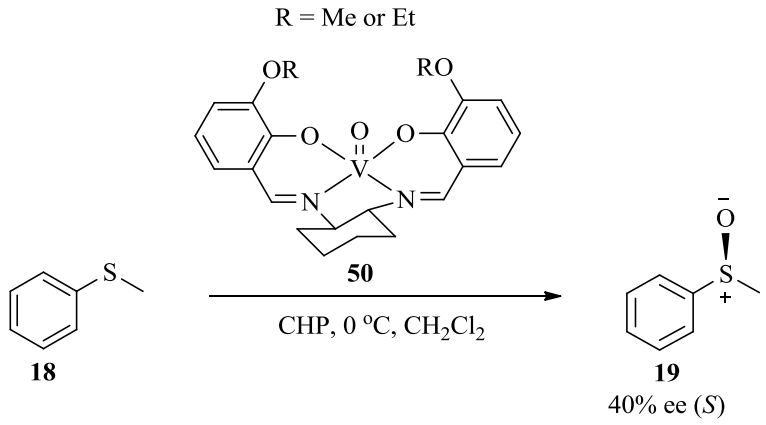
Scheme 1.23

1.2.1.2 Vanadium-catalysed oxidation

After titanium, vanadium is the most popular metal catalysts in asymmetric sulfide oxidation.[86] In one of the earliest reports of vanadium-catalysed sulfur oxidation, Modena successfully prepared racemic sulfoxides using TBHP as the oxidant and vanadyl acetylacetonate [$VO(acac)_2$] as the catalyst, identifying vanadium(IV) as the active oxidising species present.[87]

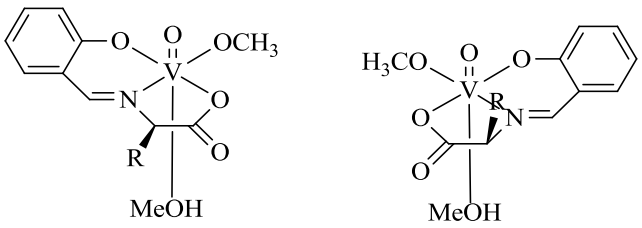
Vanadium catalysts with Schiff base ligands

Vanadium was first successfully used in asymmetric sulfide oxidation by Fujita in the 1980s.[88] Using a vanadium Schiff base complex **50** as the catalyst and CHP as the oxidant, enantioselectivities of up to 40% ee were reported (Scheme 1.24). This oxidation proceeded in the presence of catalytic rather than stoichiometric amounts of the catalyst. The nature and preparation of the complexes has been investigated.[89] The Schiff base ligands used were also used to form titanium Schiff base ligand complexes which were successfully used in asymmetric sulfide oxidation.[90,91]



Scheme 1.24

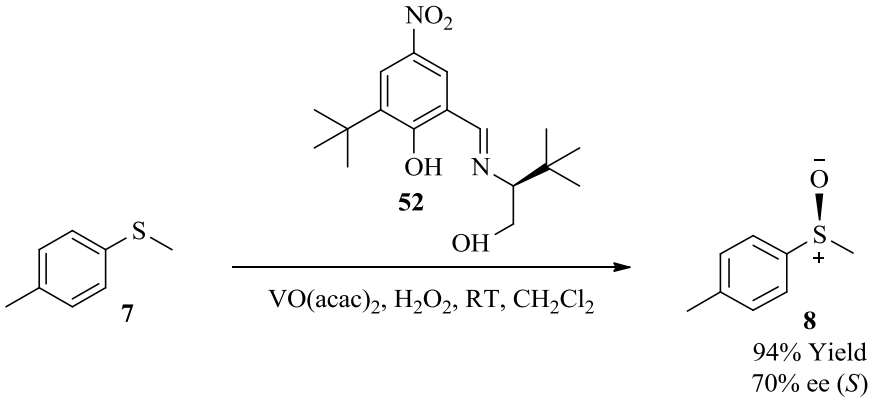
Later work on the vanadium Schiff base ligand catalysts involved the use of L-amino acids and salicylaldehyde to prepare the Schiff base.[92] The results obtained using these complexes for the oxidation of thioanisole **18** were poor, with 14% ee being the highest enantioselectivity observed. The structures of this vanadium Schiff base ligand, complex **51**, are shown below.



51 EXO **51 ENDO**

Colonna *et al.* also used vanadium complexes similar to **51** to prepare racemic **8** in reasonable yield using TBHP as oxidant, although this was accompanied by significant sulfone formation.[93]

Using slightly different Schiff base ligands, Bolm *et al.* reported a very significant improvement, with high levels of enantioselectivity achieved. Most significant was the use of ambient atmospheric conditions for the oxidation, overcoming the extreme sensitivity associated with titanium-catalysed oxidations, and obviating the need for an inert atmosphere.[94] The oxidation was catalysed by a chiral vanadium Schiff base complex formed *in situ* by the reaction of $VO(acac)_2$ and a Schiff base. The oxidant used was aqueous hydrogen peroxide, a cheap and environmentally benign oxidant. Asymmetric oxidation occurred even in the presence of 0.1 mol% of the catalyst.



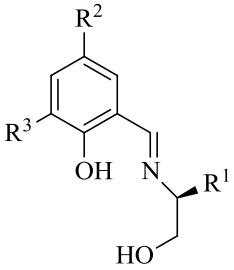
Scheme 1.25

This oxidation method is suitable for the asymmetric oxidation of a variety of sulfides including functionalised sterically hindered disulfides.[95]

Influence of ligand

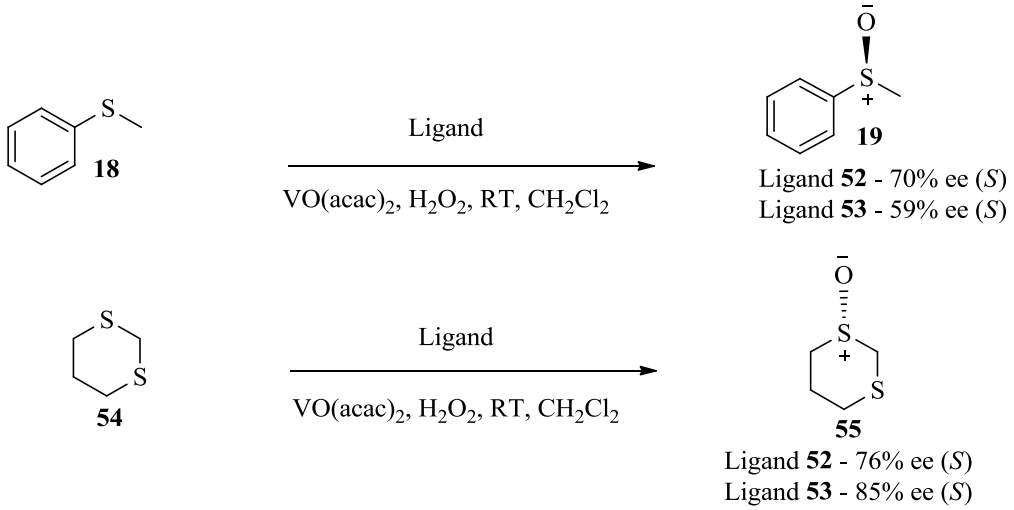
The Schiff base ligands were easily formed by reacting the appropriate salicylaldehyde with enantiopure amino alcohols.[86] In the absence of the ligand no oxidation takes place. The crucial role of the ligand has attracted considerable attention with many groups endeavouring

to identify the optimum ligand for this synthesis. There are three positions in the ligand which are most suited to variation.



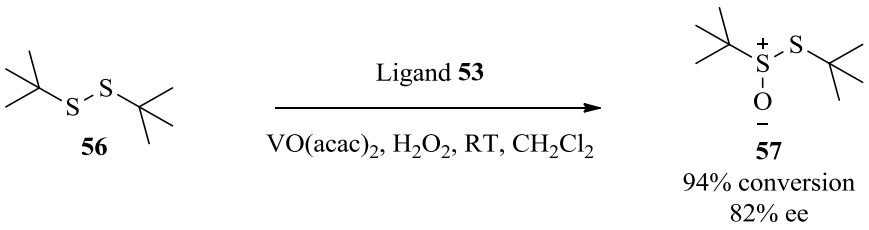
52 : $R^1 = R^3 = t$-Bu, $R^2 = NO_2$
53 : $R^1 = R^2 = R^3 = t$-Bu

Bolm carried out a limited investigation into identifying the optimum ligand and results obtained indicated that the optimum ligand was substrate specific.[94] Thus, the sulfoxide **19** of thioanisole **18** was obtained in 70% ee using **52**, and in 59% ee using ligand **53**. However, oxidation of dithioacetal **54** produced the mono sulfoxide **55** in 76% ee using ligand **52** and 85% ee using ligand **53** (Scheme 1.26).



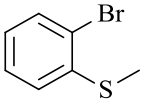
Scheme 1.26

Ellman *et al*., investigating the asymmetric oxidation of *tert*-butyl disulfide **56**,[96] carried out a more extensive study of the Schiff base ligands.[97] It was found that when R^1 = *t*-butyl, optimal results were obtained. Investigations revealed that the R^2 substituent played no steric role in the oxidation, however the electronic effects of this substituent were important, for example when $R^2 = NO_2$ or OMe, there was a decrease in the enantioselectivity of the oxidation. Both the electronic and steric effects of R^3 were significant. Overall, it was found that ligand **53** was the optimum ligand for the asymmetric oxidation of **56**, Scheme 1.27.



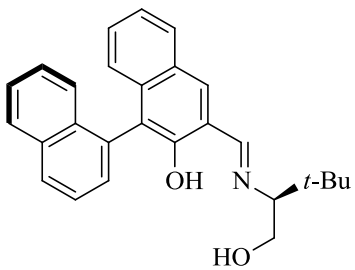
Scheme 1.27

A report by Maseras, based on computational studies and experimental results, confirms that the R^2 substituent of the ligand has little or no effect on the enantioselectivity of the oxidation using this system for the oxidation of **56**.[98] However, both R^1 and R^3 are critical to the selectivity of the oxidation, as these substituents are near the active site of the vanadium Schiff base oxidising complex. This report was based on the oxidation of **56** and only the steric effect of the ligand substituents was investigated.

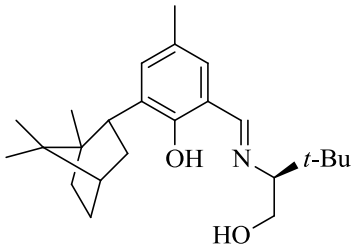


58

Berkessel carried out an extensive study of ligand structure while trying to optimise the asymmetric oxidation of thioanisole **18** and *ortho*-bromo thioanisole **58**.[99] Once again the optimum ligand was substrate specific with ligand **59** being the optimum ligand for the oxidation of **18**, while ligand **60** was optimum for the oxidation of **57**.



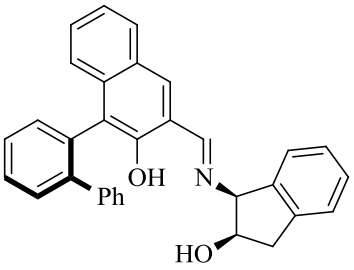
59



60

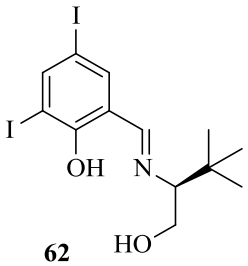
The most significant difference between the ligands used by Berkessel and those used by Ellman and Bolm is that the ligands used by Berkessel possess two elements of chirality. The extra chiral feature was found not to affect the stereoselectivity of the oxidation, and stereoselectivity was determined only by the chiral centre of the amino alcohol moiety.

Katsuki, encouraged by Berkessel's results, investigated more sterically hindered ligands, such as ligand **61**, which gave the sulfoxide **19** of thioanisole **18** in 88% ee.[100]

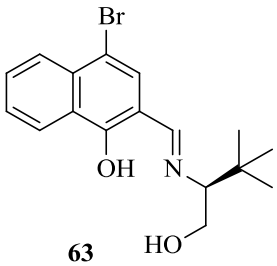


61

Jackson *et al.* utilised a solid phase array approach to identify the optimum ligand for the asymmetric oxidation of aryl alkyl sulfides.[101,102] Synthesizing a variety of Schiff bases mounted on a Merrifield resin solid support, allowed screening of a large number of amino alcohols and salicylaldehydes. Ligands **62** and **63** were identified as the two best ligands. Ligand **61** has become the ligand of choice for this oxidation method and is also used in iron-Schiff base catalysed oxidations.[103-106]

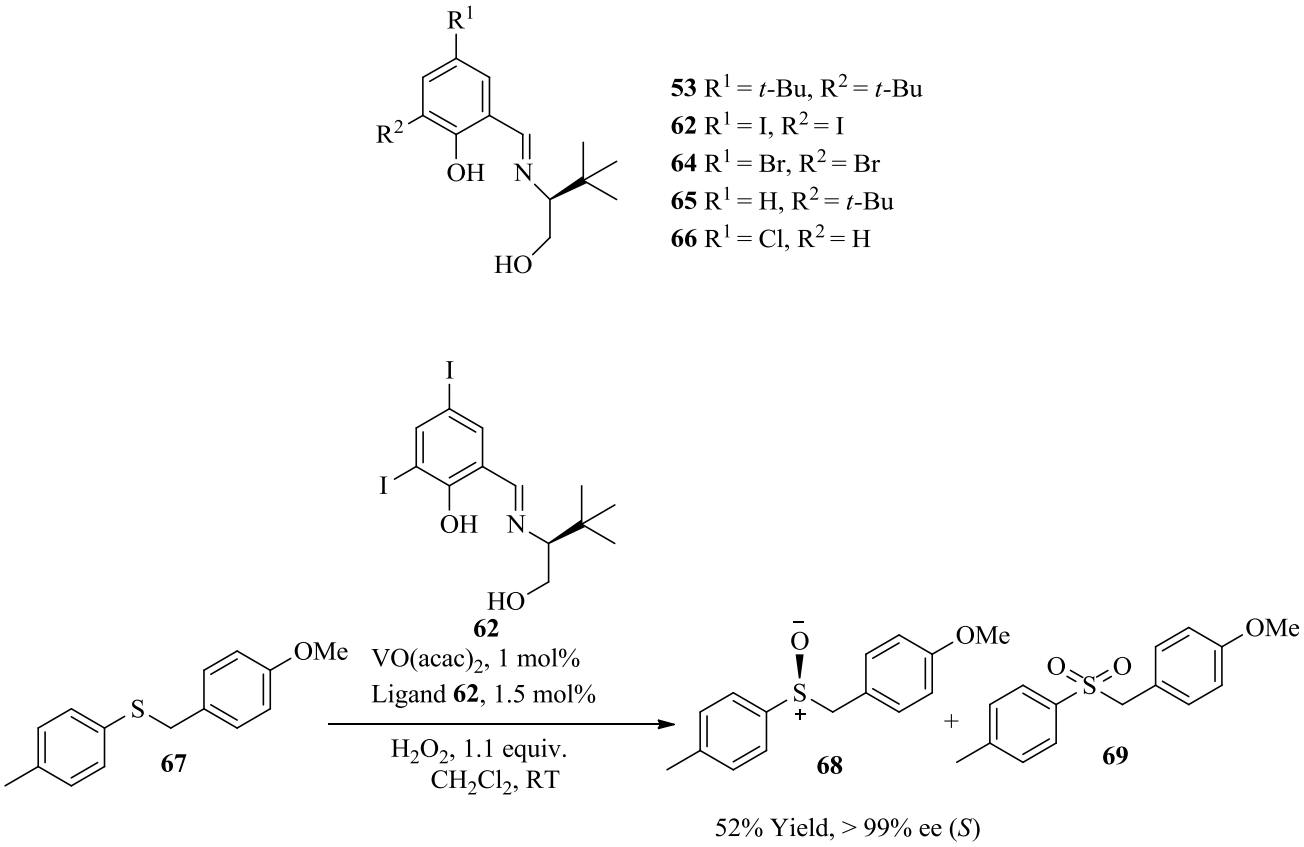


62



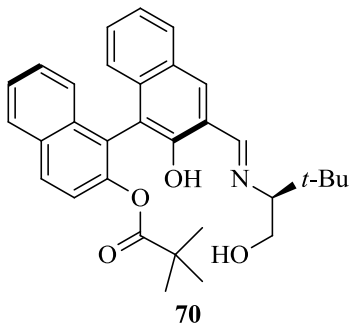
63

A number of Schiff base ligands were investigated by Maguire *et al.* for use in asymmetric oxidation of aryl benzyl sulfides.[107,108] Ligand **62** gave the best results, with excellent enantioselectivities, which were achieved through a combination of asymmetric oxidation and complementary kinetic resolution (Scheme 1.28).



Scheme 1.28

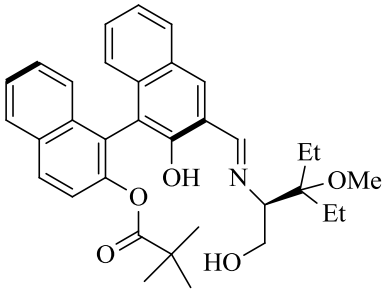
From the results reported by Ellman,[97] Berkessel[99] and Katsuki,[100] it is clear that steric considerations are very important in ligand design. Ahn investigated sterically hindered ligands derived from BINOL,[109] similar to those used by Berkessel and Katsuki. The best ligand identified, **70**, was used to obtain the sulfoxide **19** in 90% yield and 86% ee.



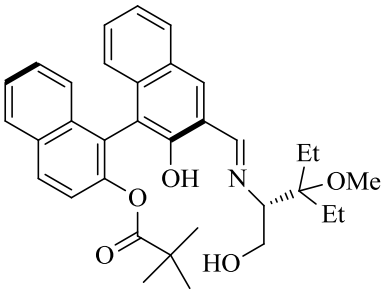
70

Ahn investigated the effect of a more sterically hindered amino acid in the Schiff base ligand, using ligand **71**.[110] No improvement was observed in the oxidation of **18**, however,

benzyl phenyl sulfoxide **13** was obtained in over 80% yield and 96% ee for both enantiomers. Interestingly, (*S*)-**71** produced (*R*)-**13**, while (*R*)-**71** produced (*S*)-**13**.

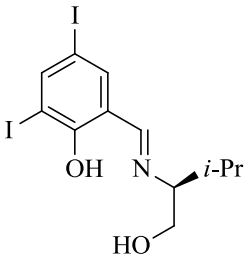


(*S*)-**71**

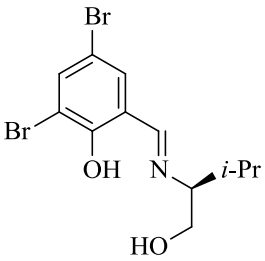


(*R*)-**71**

A report by Gao indicated that using (*S*)-valinol and the *i*-Pr substituted ligands **72** and **73**, resulted in higher enantioselectivity than that achieved with their *i*-Bu analogues for the oxidation of thioanisole **18**.[111]

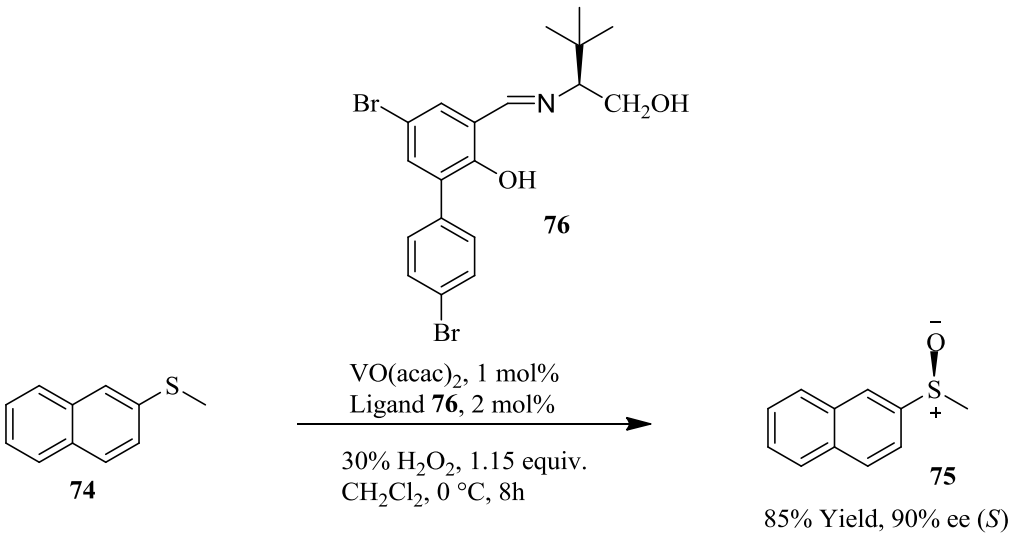


72



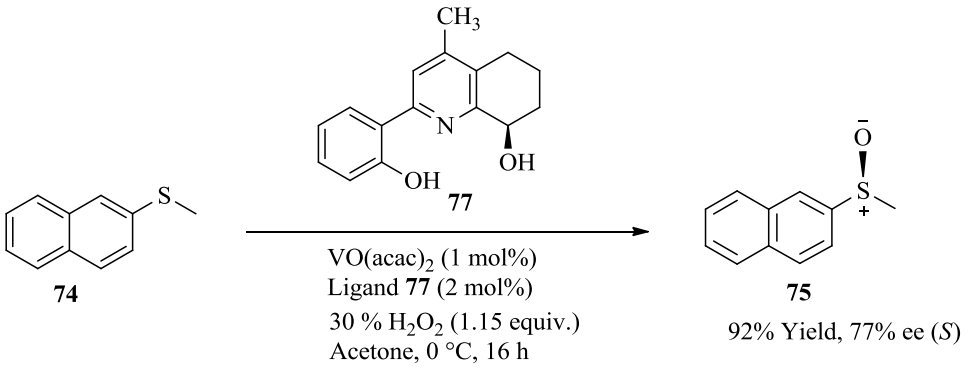
73

Recently, Liu *et al*. investigated a series of salicylaldehyde derived Schiff base ligands for the asymmetric oxidation of aryl methyl sulfides.[112] Ligand **76** gave the best result producing sulfoxide **75** in 85% yield and 90% ee (Scheme 1.29).



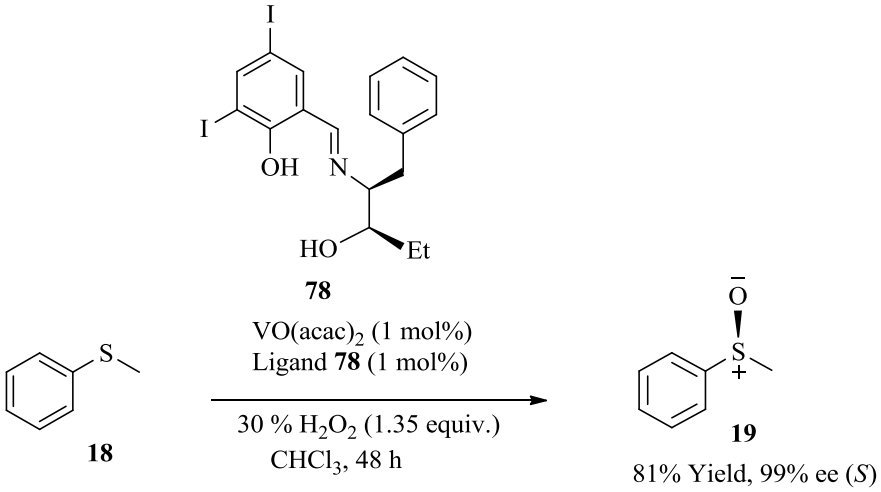
Scheme 1.29

Liu *et al.* produced a novel chiral tridentate ligand **77** bearing a rigid tetrahydroquinoline framework, which was used in the oxidation of aryl methyl sulfides, producing sulfoxide **75** in 92% yield and 77% ee (Scheme 1.30).[113]



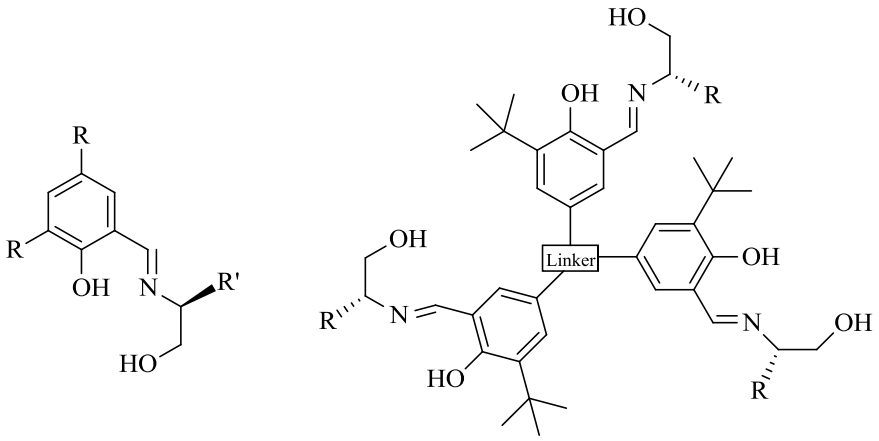
Scheme 1.30

Li *et al.* used Schiff base ligands with two stereogenic centers in the oxidation of aryl alkyl sulfides. Ligand **78** gave the best results, producing sulfoxide **19** in an 81% yield and 99% ee (Scheme 1.30).[114] Complementary kinetic resolution was observed in oxidations using this ligand.



Scheme 1.30

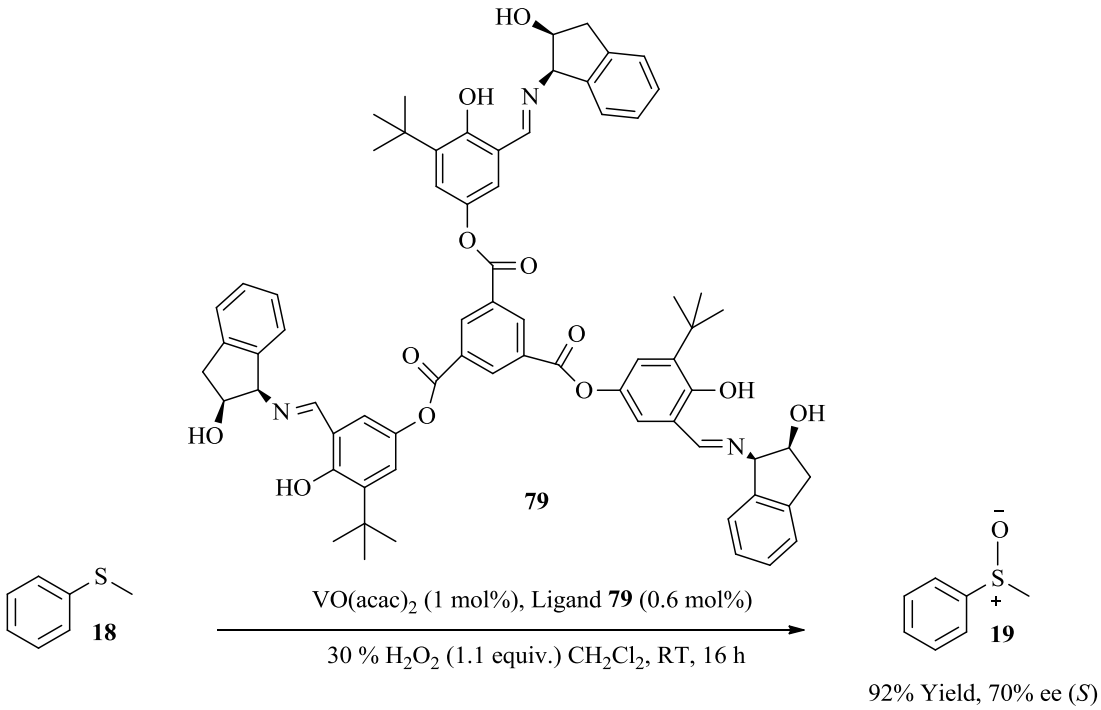
Suresh *et al.* produced a series of trimeric variants of Bolm's original chiral vanadium salen catalysts (Figure 1.4). These C_3-symmetric trinuclear Schiff bases were synthesised by condensing a variety of trialdehydes with optically active amino alcohols.



Bolm's vanadium Schiff base ligands **Trimeric variant of Bolm's ligands**

Figure 1.4

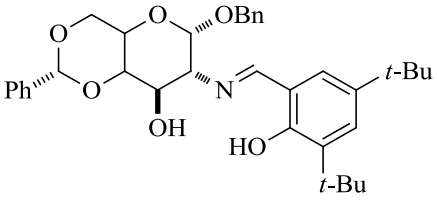
Ligand **79** was used in the oxidation of thioanisole **18,** producing sulfoxide **19** in 92% yield and 70% ee (Scheme 1.32).[115]



Scheme 1.32

Ligand **79** was also employed in the oxidation of **12** using the same conditions as outlined in Scheme 2.30, producing the sulfoxide **13** in 98% yield and 86% ee.

Khiar *et al.* reported enantioselectivities of up to 96% ee oxidising thiosulfinates employing the carbohydrate derived ligand **80**.[95]



80

Volcho *et al*. also investigated Schiff base ligands that possessed more than one chiral centre.[20] The investigations employed α-pinene and 3-carene derived Schiff base ligands (Figure 1.6).[116,117] The results for the oxidation of thioanisole **18** using these ligands was modest. Interestingly, for the 3-carene derived ligand, the extent and direction of the enantioselectivity of the oxidation could be influenced by reaction temperature, while for the α-pinene derived ligand the substituents on the aromatic ring could influence not only the

extent but also the direction of enantioselectivity. It was speculated that these observations arise due to the existence of two distinct oxidative pathways.

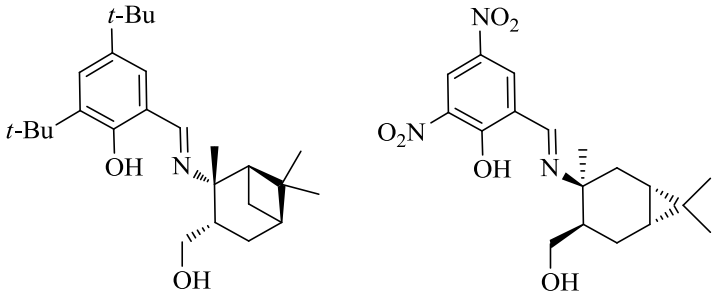
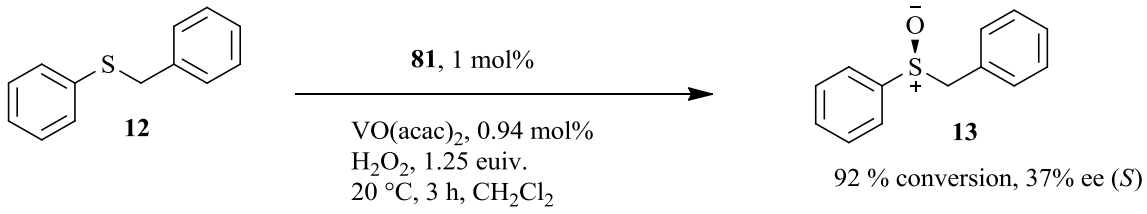


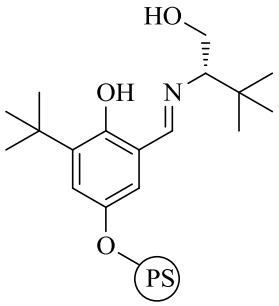
Figure 1.6

Il'ina *et al.* used chiral Schiff bases, such as **81**, in the asymmetric oxidation of benzyl phenyl sulfide obtaining excellent conversions but poor enantioselectivities (Scheme 1.33).[118]



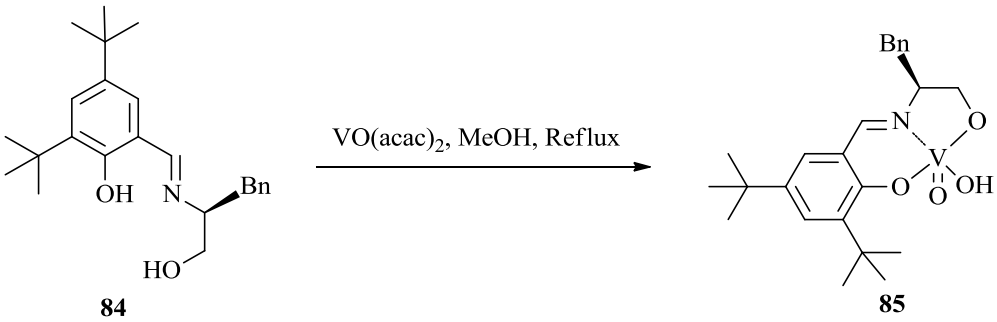
Scheme 1.33

Barbarini *et al.* investigated the use of polymer supported vanadium Schiff base complexes.[119] A number of Schiff base ligands were attached to polystyrene or polyacrylate backbones, and then reacted with $VO(acac)_2$ to form the polymer supported complexes. For the oxidation of thioanisole **18**, the highest enantiopurity reported was 61% ee, significantly poorer than those obtained using the 'free' vanadium Schiff base complex. However, the catalyst was recoverable and could be recycled up to four times without any significant loss in enantioselectivity or efficiency. A possible reason for this poorer enantioselection is that vanadyl acetylacetonate, in the presence of polystyrene, can catalyse non-enantioselective sulfide oxidation to the sulfoxide. The optimum supported Schiff base ligand identified was **83**.



83
PS = polystyrene

Most procedures prepare the vanadium Schiff base ligand catalyst complex *in situ* and do not isolate the complex. In one report, Zeng and co-workers pre-formed and isolated a number of vanadium Schiff base ligand catalyst complexes, and subsequently employed them in asymmetric sulfide oxidation.[120,121] The catalyst complex was prepared by heating the Schiff base ligand with $VO(acac)_2$ in methanol (Scheme 1.34).

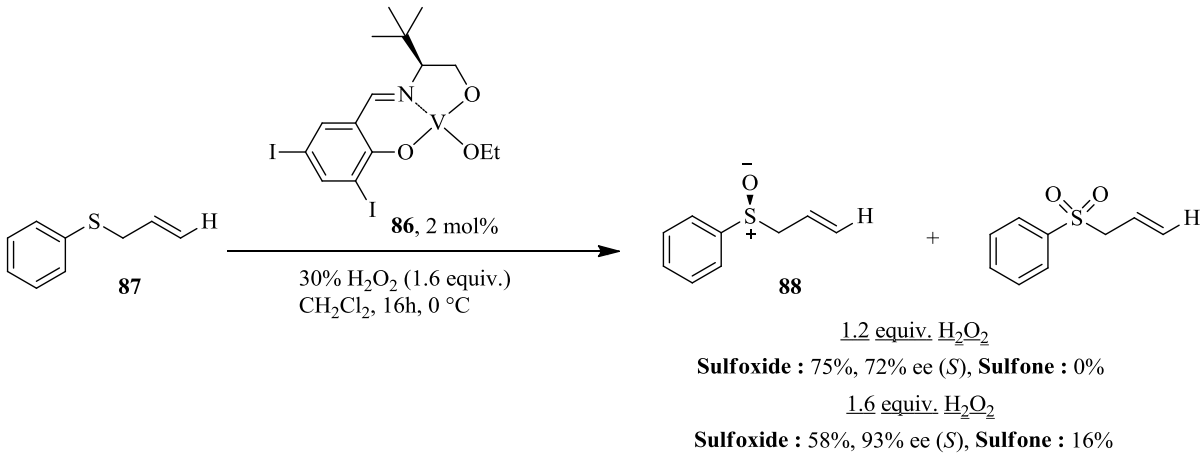


84 **85**

Scheme 1.34

Results obtained by Zeng using these pre-formed catalyst complexes were slightly superior to those obtained using *in situ* formed catalyst. The reason for this was attributed to the presence of unreacted $VO(acac)_2$ in the reaction mixture, when the catalyst was formed *in situ*. Similar results were reported by Gau *et al.* employing pre-formed catalysts.[122]

Zeng used a similar vanadium Schiff base complex **86** to oxidise allyl phenyl sulfide **87**, obtaining the corresponding sulfoxide **88** in moderate yield and excellent enantioselectivity (Scheme 1.35).[123] Carrying out the oxidation using an increased amount of oxidant resulted in reduced yields but an improvement in enantioselectivity indicating that kinetic resolution was taking place.



Scheme 1.35

Pre-formed catalyst complexes, using glucopyranose derived Schiff base ligands, were also investigated by Plass *et al.*[124] Relatively poor enantioselectivity (26% ee) was observed using these catalysts in the asymmetric oxidation of thioanisole **18**.

Romanowski *et al.* prepared and investigated pre-formed catalyst complexes using chiral diamine Schiff base ligands of the type shown in Figure 1.7 for the oxidation of thioanisole **18**.[125,126] Modest enantioselectivity was reported (up to 39% ee).[126]

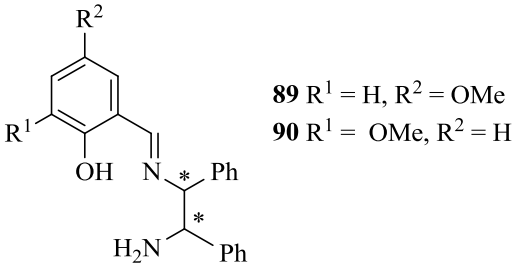
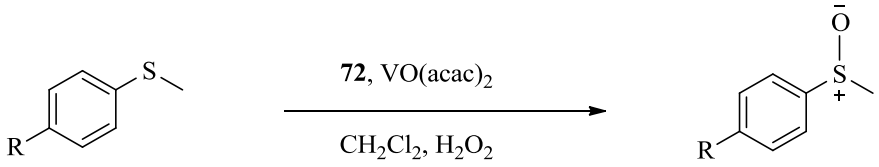


Figure 1.7

Influence of electronic effects of substituents of the sulfide

Investigations by Gao *et al.* indicated that the substituents on the aromatic ring of the sulfide can influence the enantioselectivity and efficiency of the asymmetric oxidations.[111] These investigations showed that the presence of substituents such as the nitro group, resulted in a decline in the efficiency of the overall oxidation in terms of yield and enantioselectivity. Substituents, such as bromine, had the opposite effect (Scheme 1.36).



19 R = H, 84% Yield, 88% ee
27 R = MeO, 64% Yield, 70% ee
91 R = NO_2, 51%Yield, 32% ee
92 R = Br, 82% Yield, 92% ee

Scheme 1.36

This trend has been observed in other investigations,[94,100,109,127] although to a lesser extent, indicating that the influence of the ligand is greater than that of the substituent on the aromatic ring of the sulfide. Interestingly, the report by Barbarini *et al.* employing a polymer supported ligand showed the opposite trend.[119]

Influence of solvent

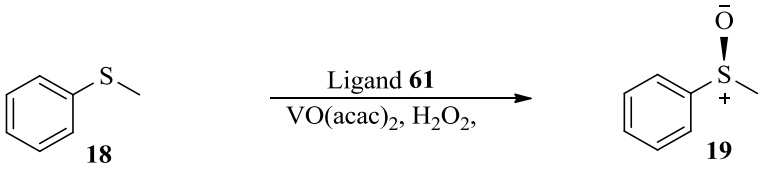
Solvent is another variable that has been investigated. Bolm used dichloromethane as the solvent in his first report.[94] Ellman found that chloroform enhanced the enantioselectivity of the oxidation. The thiosulfinate **57** was obtained in 82% ee when the solvent was dichloromethane and 91% ee when chloroform was the solvent.[96] Ellman also investigated acetonitrile, THF, carbon tetrachloride, toluene, *tert*-butyl alcohol and nitromethane, with inferior results compared to those obtained using either dichloromethane or chloroform. Katsuki *et al.*[100], Liu *et al.*[113] and Li *et al.*[114] also found dichloromethane, and chloroform to be superior to other solvents for this oxidation, confirming Ellman's results.

A 2 : 1 toluene/dichloromethane solvent system was used by Gau *et al.* to oxidise thioanisole **18** using this system at -20 ^{o}C.[122] This gave superior enantioselectivity (98% ee) compared to dichloromethane (90% ee), however, the yield obtained (61%) was lower than when using dichloromethane (75%). It should be noted that this work was carried out using pre-formed rather than *in situ* formed catalyst complexes.

Influence of temperature

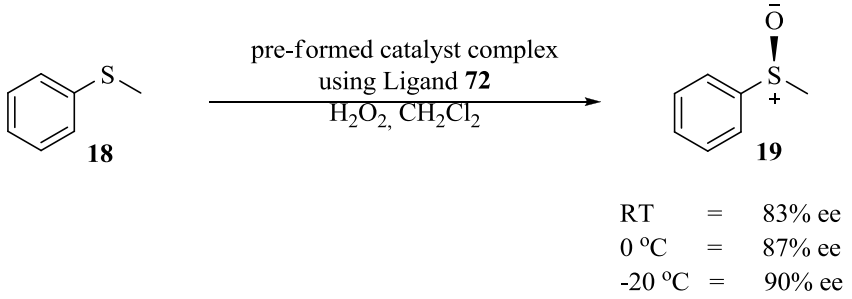
A number of research groups investigated the influence of temperature on the enantioselectivity of the oxidation. Bolm's initial work undertook the oxidation at RT.[94] Berkessel observed an increase in enantioselectivity carrying out the oxidation at 0 ^{o}C[99] and Katsuki also reported similar results,[128] see Table 2.1.

Table 2.1 Results reported by Katsuki at different temperatures.[128]



Solvent	Temperature	Yield %	% ee
CH_2Cl_2	RT	88	77
CH_2Cl_2	0 ^oC	83	86
CH_2Cl_2	-20 ^oC	81	68
$CHCl_3$	RT	66	65
$CHCl_3$	0 ^oC	74	80

Gau *et al.* also reported increased enantioselectivity for the oxidation of thioanisole **18** with decreasing reaction temperature using pre-formed catalysts (Scheme 1.37).[122]

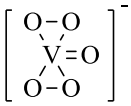


Scheme 1.37

Influence of rate of oxidant addition

The rate of addition of the oxidant has also been investigated for its impact on the enantioselectivity. In the first report using vanadium catalysts, the oxidant was added dropwise in one portion, since rapid addition resulted in an elevated reaction temperatures and led to overoxidation, forming the sulfone.[94] Karpyshev *et al*. carried out a more extensive investigation, observing that rapid addition did cause an elevation in reaction temperature, albeit a small one (< 2 ^oC).[129] It also led to reduced enantioselectivity and sulfoxide yield. They speculated that this was due to the increased presence of an achiral oxidising species formed by the rapid addition of the oxidising reagent. Using ^{51}V NMR three principal

vanadium complexes were identified in the oxidation reaction.[129] Two of these complexes were identified as containing the ligand while the other complex was identified as the achiral oxidising species diperoxovanadium **93**, as previously identified by Conte *et al.*[130] The vanadium complex **93**, $[VO(O_2)_2]^-$ is a water soluble species, and it was confirmed by ^{51}V NMR that its concentration increased when the oxidant was added rapidly.[129]

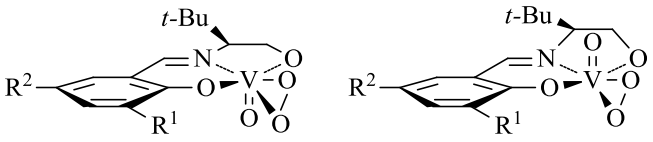


93

Ellman *et al.* investigated whether the effects seen due to different addition rates were influenced by the nature of the solvent.[131] Oxidising **56** in chloroform, Ellman observed that fast addition of the oxidant did not impact on the enantioselectivity. In contrast, with solvents which are miscible with the oxidant, rapid addition of the oxidant produced racemic sulfoxide. This was attributed to the formation of the achiral vanadium species **93**. Using these solvents, coupled with slow addition of oxidant, results in relatively high enantioselectivities (> 50% ee).

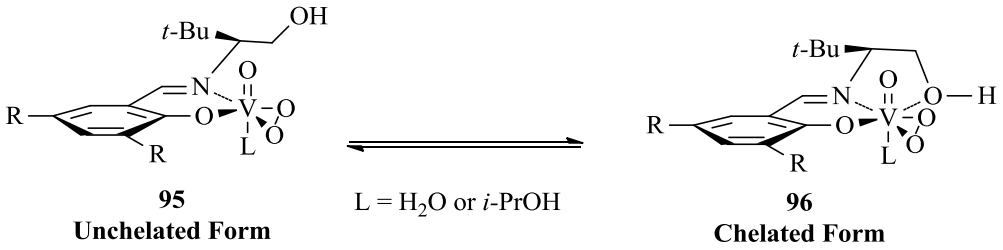
Nature of the catalyst

The exact nature of the oxidising complexes formed in this oxidation has yet to be fully elucidated. Bolm speculated that the oxidising species formed in this oxidation were vanadium(V) species having oxoperoxy groups **94**.[132]



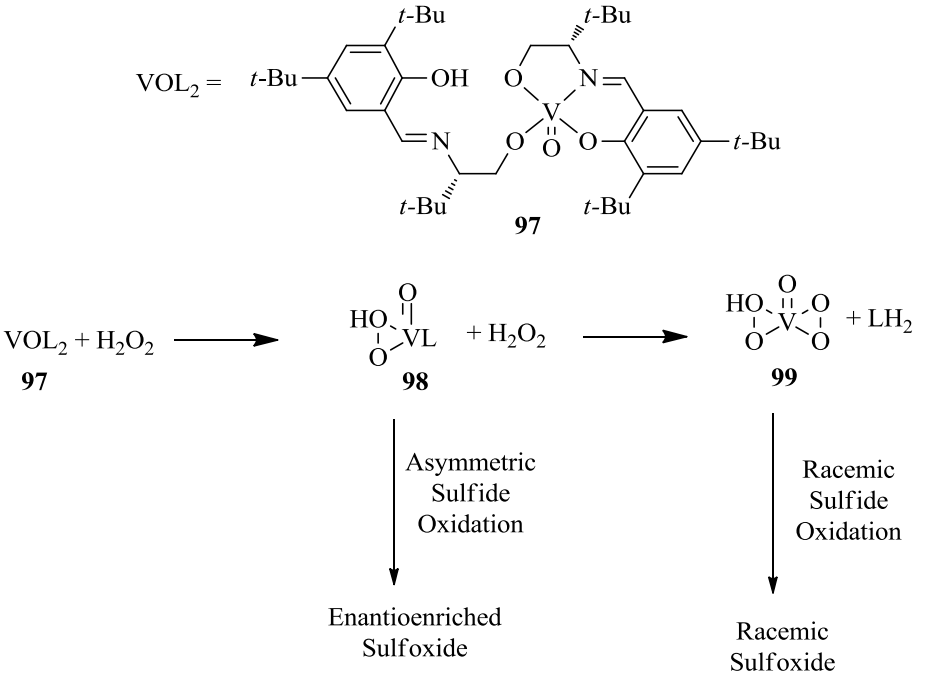
94a **94b**

Bryliakov conducted a more extensive investigation of the vanadium species formed using ^{51}V NMR analysis and found that the monoperoxy species formed can exist in more than one form.[133] Two principal species were proposed to be present in equilibrium with each other – an unchelated form **95** and a chelated form **96**, in which the primary alcohol coordinates to the vanadium (Scheme 1.38). Due to the complicated NMR spectra obtained it was not possible to assign individual NMR signals to either **95** or **96**.



Scheme 1.38

Ellman *et al*. proposed the formation of the vanadium ligand complex **97** (VOL_2), which is then oxidised to form the chiral peroxy oxidising species **98**. This can be further oxidised to form the achiral diperoxy oxidising species **99**, with loss of the chiral ligand (Scheme 1.39).[131] This model suggests why rapid addition of the oxidant might lead to reduced enantioselectivity.



Scheme 1.39

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Zeng *et al*. proposed a mechanism for this oxidation (Scheme 1.40).[120] A peroxide molecule co-ordinates to the vanadium complex, followed by sulfide coordination to the vanadium, oxygen transfer from the peroxide to the sulfur, and dissociation of the sulfoxide product. The oxovanadium complex reforms and the catalytic cycle can continue.

The *tert*-butyl group, the R^2 group and the nature of the sulfide are key to influencing which pair of electrons goes where - the greater this influence, the higher the enantioselectivity of the oxidation. This explains why higher enantioselectivity is observed when oxidising sulfides containing a naphthyl or a bulky group using this method.[100] Thus, for ligand **59** developed by Berkessel,[99] Zeng postulates the naphthyl groups limit the orientation of attack of the sulfide, improving the enantioselectivity of the oxidation, Figure 1.8.

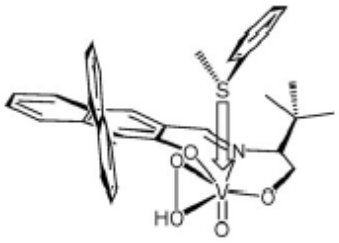
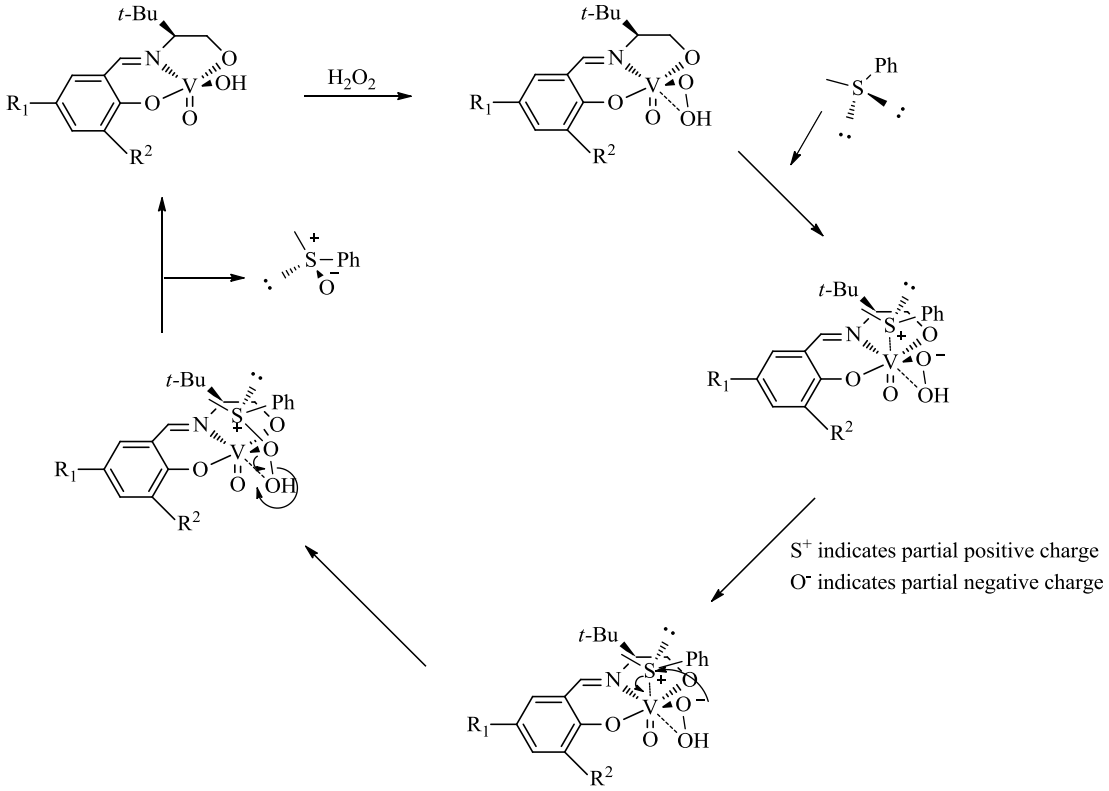


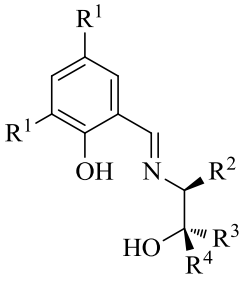
Figure 1.8 (reproduced from ref.[120] by permission of the Royal Society of Chemistry (RSC) for the Centre National de la Recherche Scientifique (CNRS) and the RSC)



Scheme 1.40

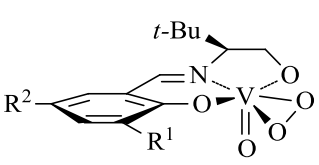
The rate-determining step is the coordination of the sulfide onto the vanadium complex. Studies by Ellman *et al*., using $H_2{}^{18}O$, showed that the oxygen atoms of the sulfoxide and of the hydroxyl group in the oxovanadium complex come from the hydrogen peroxide, in agreement with Zeng's mechanism.

Zeng observed a dramatic drop in enantioselectivity using the sterically hindered ligand **100**,[120] which can be attributed solely to the presence of the phenyl groups. This suggests that the equilibrium between the unchelated **95** and chelated **96** forms of the vanadium complex proposed by Bryliakov is unlikely. However, it is also possible that **100** is simply not capable of asymmetric sulfide oxidation.

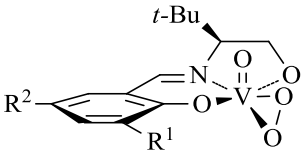


100 R^1 = *t*-Bu, R^2 = *i*-Pr, R^3 = R^4 = Ph
101 R^1 = *t*-Bu, R^2 = *i*-Pr, R^3 = R^4 = H

Maseras *et al.* proposed that there were two diastereomeric forms of the catalyst complex **94a** and **94b** both of which can oxidise sulfides, though with opposite stereoselectivity.[98] Hence, there are two pathways in this reaction, one leading to the major sulfoxide enantiomer and the other to the minor sulfoxide enantiomer.



94a



94b

The stereoselectivity of the oxidation is determined by the configuration of **94**, *i.e.* employing a ligand derived from the *S-tert*-butyl amino alcohol leads to a stereo-outcome opposite to that which is observed employing the same ligand derived from the *R tert*-butyl amino alcohol. The R^1 substituent in **94** plays a role in the stability of the catalyst complex and is critical in determining which diastereomer predominates. Whichever form of the diastereomer predominates will influence the enantioselectivity of the oxidation, *i.e.* if the pro-*S* form of the diastereomer predominates, the *S* sulfoxide will be predominantly formed. It was found for the oxidation of **56** (*tert*-butyl disulfide) that as the steric bulk of R^1

diminished, so too did the enantioselectivity of the oxidation. This was attributed to the possibility that both diastereomers of the oxidising complex were now of similar stability, so the extent to which one diastereomer form predominates over the other is reduced, hence lower enantioselectivity in the sulfide oxidation. Reducing the steric bulk of the R^2 substituent had little effect on the enantioselectivity of the oxidation of **56**. This was attributed to the fact that the R^2 substituent is far away from the active site of the diastereomer unlike R^1 and the *tert*-butyl group, so naturally it exerts a smaller effect on oxidation than the R^2 substituent. Only the steric influence of R^1 and R^2 of the ligand was investigated during this study and only one substrate, **56** *tert*-butyl disulfide, was screened, accordingly the results of this study cannot be regarded as applicable to all ligands and substrates.

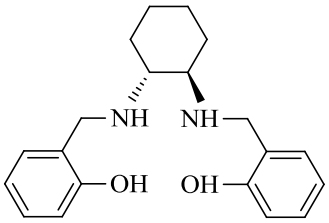
Influence of additives

Katsuki was the first to report an enhancement in the enantioselectivity attributable to the presence of an additive in the oxidation.[100] Carrying out the oxidation of thioanisole **18** in the presence of a small amount of methanol at RT, Katsuki observed a slight improvement in enantioselectivity. Oxidising **18** at 0 $^{\circ}$C in dichloromethane, the enhancement of enantiopurity due to the presence of methanol was up to 2%. At –20 ^{o}C the improvement was 15%. The enantioselectivity was enhanced by up to 8% ee when the solvent was chloroform with a small amount of methanol. This enhancement was seen both at RT and at 0° C. Katsuki surmised the enhancement of enantioselectivity in the presence of methanol was due to its donor effects, which may affect some of the peroxo-vanadium oxidising species present.

Investigations by Gao found that carrying out the vanadium-catalysed oxidation in the presence of 4-methoxybenzoic acid or a number of its salts did not enhance the enantioselectivity.[111] This is in contrast to Bolm's observations with iron Schiff base catalysed reactions.[105,106] Bolm attributed the improved efficiency and enantioselectivity to the formation of a monocarboxylate bridged diiron complex.[106] Gao proposed that the analogous divanadium complex probably cannot form, and thus there is no improvement in enantioselectivity.

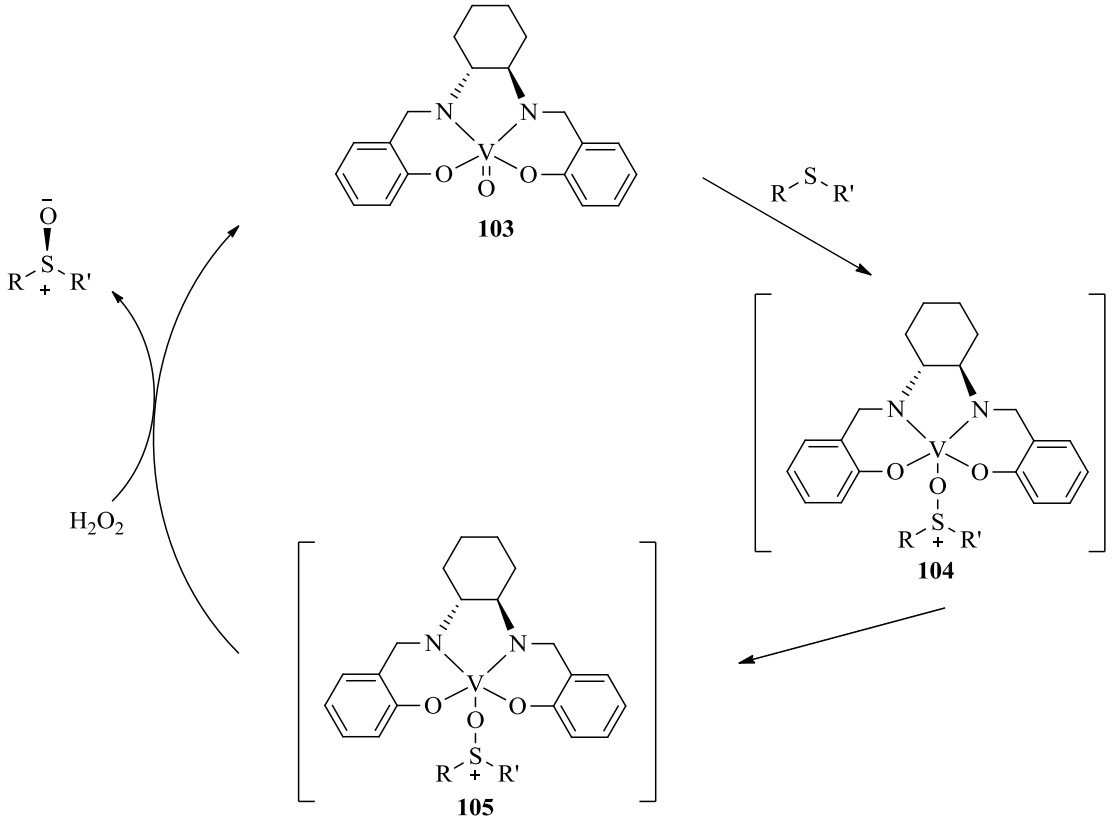
Vanadium salan catalysis

In 2004 Zhu reported that enantioenriched sulfoxides could be successfully prepared by oxidising sulfides in the presence of a vanadium salan complex.[134] After screening a number of salan ligands, ligand **102** was found to be the optimum ligand for this oxidation method.



102

This ligand formed a complex with vanadyl acetylacetonate, which catalysed asymmetric sulfide oxidation. The oxidant used was hydrogen peroxide. The enantioselectivity of the oxidation was very impressive with the sulfoxide **19** of thioanisole **18** obtained in 81% yield and 95% ee. The mechanism proposed involved the nucleophilic attack of the sulfide on the vanadium salen complex to form an intermediate (Scheme 1.41). The reaction of this intermediate with hydrogen peroxide forms the sulfoxide and regenerates the vanadium salen complex.

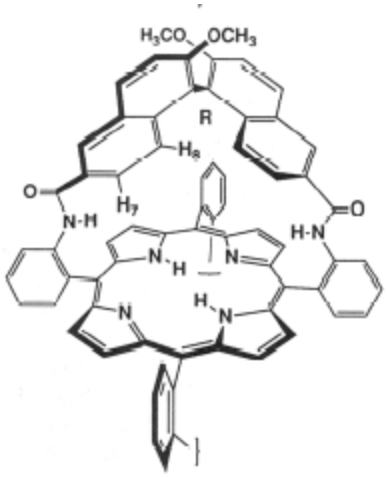


Scheme 1.41

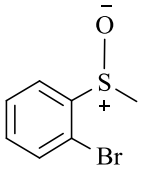
1.2.1.3 Iron-catalysed oxidation

Ideally, in catalysis the catalyst used would be cheap and non-toxic, hence iron is attractive among the transition metals. Iron catalysts have been successfully used in asymmetric sulfide oxidation.

Groves and Viski used vaulted naphthyl metalloporphyrins **106** in a variety of asymmetric reactions, one of which was an asymmetric sulfide oxidation.[135] The results of this oxidation, which employed iodosylbenzene as the oxidant, were modest in terms of enantioselectivity with methyl *ortho*-bromophenyl sulfoxide **107** being obtained in 74% yield with 48% ee. The sulfoxide **19** of thioanisole **18** was obtained in 84% yield with 24% ee.

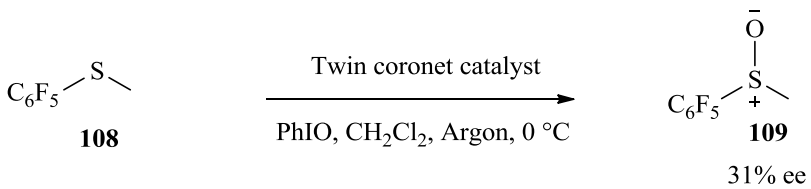


106 (re-produced from ref. [135])



107

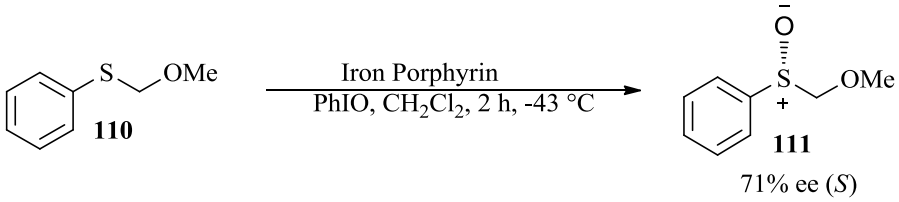
Naruta *et al.* reported an enantioselective iron-catalysed sulfide oxidation.[136,137] The method utilised iron complexes of 'twin coronet' porphyrins as the catalyst and iodosylbenzene as the oxidant (Scheme 1.42).



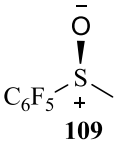
Scheme 1.42

A dramatic improvement occurred when the reaction was conducted in the presence of 1-methylimidazole at –15 °C, with pentafluorophenyl methyl sulfoxide **109** being obtained in lower yield but much higher enantiopurity, 73% ee. The 1-methylimidazole was believed to coordinate to the active metal centre and enhance enantioselectivity by changing the porphyrin structure around the iron and preventing decomposition of the catalyst.

Inoue also successfully used iron porphyrins and reported similar results, with the enantioselectivity considerably enhanced when the oxidation was carried out in the presence of imidazole.[138] Methoxymethyl phenyl sulfoxide **111** was obtained with 71% ee while **109** was obtained in 36% ee (Scheme 1.43).

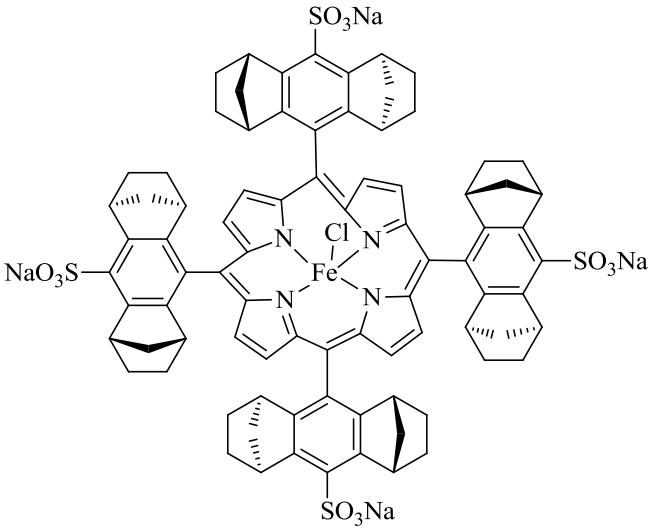


Scheme 1.43

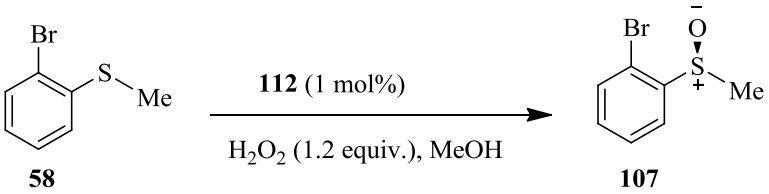


36% ee (*S*)

Le Maux *et al.* recently reported the asymmetric oxidation of sulfides using chiral water-soluble iron porphyrins, such as **112,** as catalyst. Excellent conversions and enantioslectivities were obtained for a range of aryl methyl sulfides.[139] When the oxidation was carried out in the presence of 2-methylimidazole there was a slight improvement in enantioselectivity but a reduction in yield (Scheme 1.44).



112

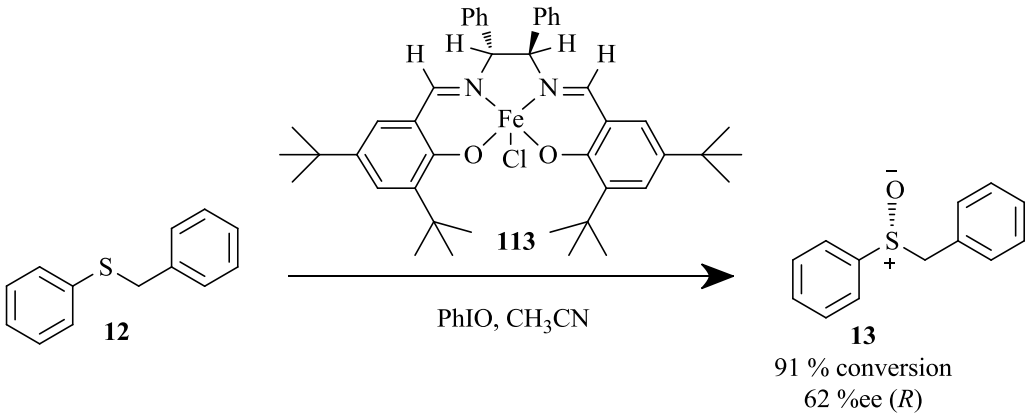


58 **107**

Temperature (°C)	Conversion (%)	ee (%, *S*)
20	100	74
0	98	82
-20	98	87
-20	61	90 (10 mmol 2-methylimidazole)*

Scheme 1.44

Bryliakov reported modest enantioselectivity using the iron complex **113** and established that the active species is an iodosylbenzene(salen)-iron(III) complex (Scheme 1.45).[140] Identification of the active species will possibly enable further improvement of this method.

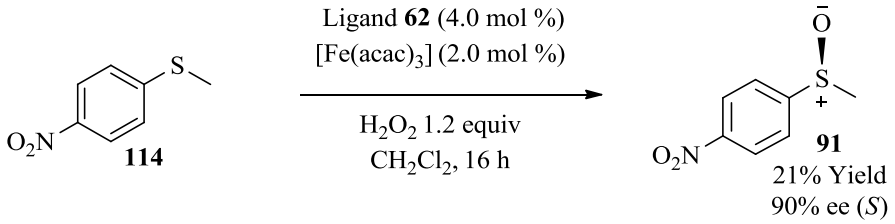


13
91 % conversion
62 %ee (*R*)

Scheme 1.45

In 2003 Bolm reported that the Schiff base ligands developed for vanadium were also successful with iron (Scheme 1.46).[94] This iron-catalysed oxidation is very practical and robust, using readily available reagents, such as aqueous hydrogen peroxide, and the reaction is performed in air, without an inert atmosphere.

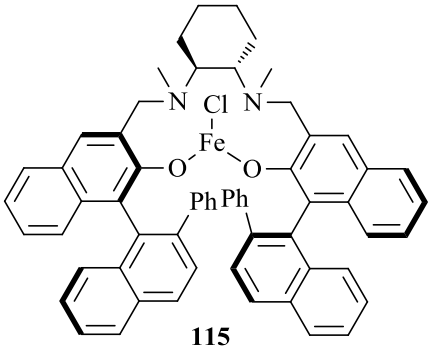
The oxidation reported by Bolm involves the *in situ* formation of an iron Schiff base catalyst followed by the addition of the sulfide and then the oxidising agent. Initial results obtained using this method were modest in terms of chemical yield but enantioselectivity was high.



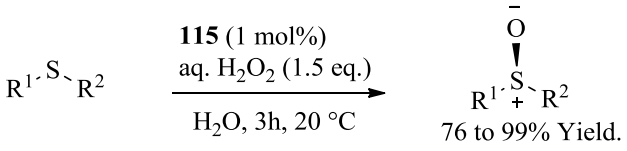
Scheme 1.46

The effect of carrying out the oxidation in the presence of an additive was found to have a beneficial effect on the enantioselectivity of the oxidation.[105,106] Carrying out the oxidation in the presence of 4-methoxybenzoic acid or the lithium salt of 4-methoxybenzoic acid resulted in improvements in both enantioselectivity and yield. For example, **91** was isolated in a yield of 36% and 96% ee when the oxidation was carried out in the presence of the lithium salt of 4-methoxybenzoic acid. Enantioenriched Sulindac has been successfully prepared using this iron-catalysed asymmetric sulfide oxidation.[103]

Katsuki and Egami used a novel chiral Fe (salan) complex **115** for asymmetric oxidation of sulfides using hydrogen peroxide in water.[141-143] This method was used to oxidize both alkyl aryl and methyl alkyl sulfides (Scheme 1.47).



115



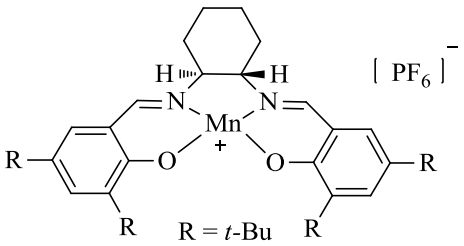
R^1 = aryl or alkyl
R^2 = Me

R^1 = aryl 81-96% ee (*S*)
R^1 = alkyl 87-94% ee (*S*)

Scheme 1.47

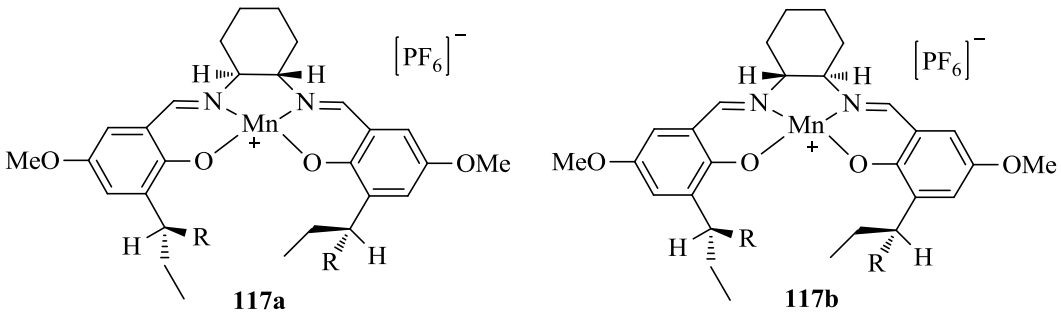
1.2.1.4 Manganese-catalysed oxidation

Manganese has been successfully used in asymmetric sulfide oxidation. Like titanium, manganese catalysts have been successfully used in asymmetric epoxidation reactions.[143] Jacobsen was first to successfully use a manganese catalyst in asymmetric sulfide oxidation using complex **116** that exhibited highly selective asymmetric epoxidation.[144] Results were encouraging in that enantioselectivity was observed, but overall the enantioselectivity was poor.



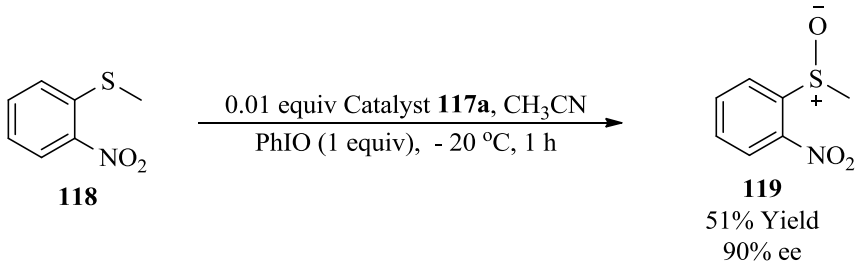
116

Work by Katsuki using a different manganese-salen catalyst **117a** resulted in much improved enantioselectivity.[145,146] Surprisingly the diastereomer of this complex **117b** exhibits only poor enantioselectivity.



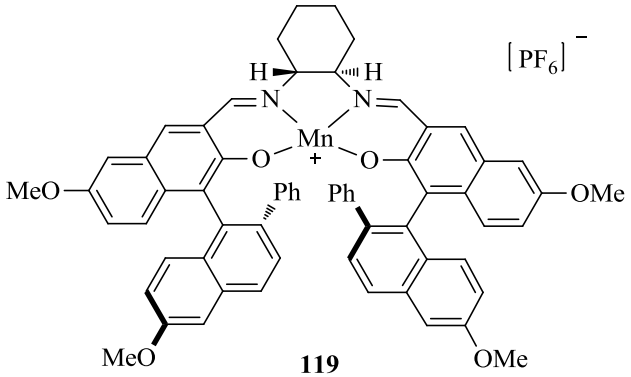
R = *t*-butylphenyl

Different oxidants were evaluated by Katsuki, and overall iodosylbenzene (PhIO) was found to be the optimum oxidising agent (Scheme 1.48).

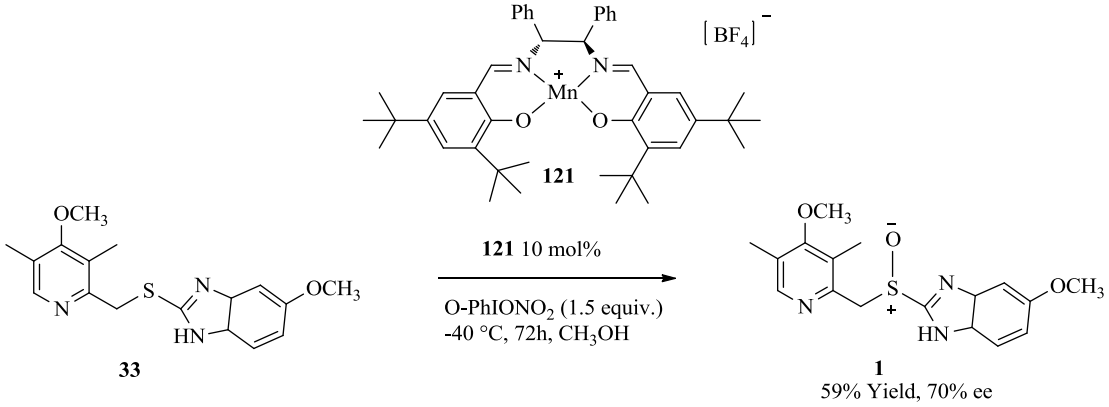


Scheme 1.48

The result obtained in oxidising **119**, 90% ee**,** was described by Katsuki as the highest enantioselectivity obtained at the time using exclusively asymmetric sulfide oxidation.[143] Further work by Katsuki resulted in the preparation of a new manganese complex **120**, that enhanced the enantioselectivity of the oxidation with **119** being obtained in almost quantitative yield in 94% ee at RT.[147] Katsuki also reported that in some cases carrying out the oxidation in the presence of 4-phenylpyridine *N*-oxide (4-PPNO) resulted in improved enantioselectivity.[147] Similar results were obtained when carrying out manganese-salen catalysed epoxidations in the presence of 4-PPNO, where it acts as a donor ligand in the medium.[148]

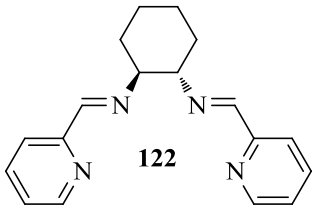


Recently, Ryu *et al.* used a similar manganese complex **121** to synthesize esomeprazole in 59% yield and 70% ee (Scheme 1.49).[149]



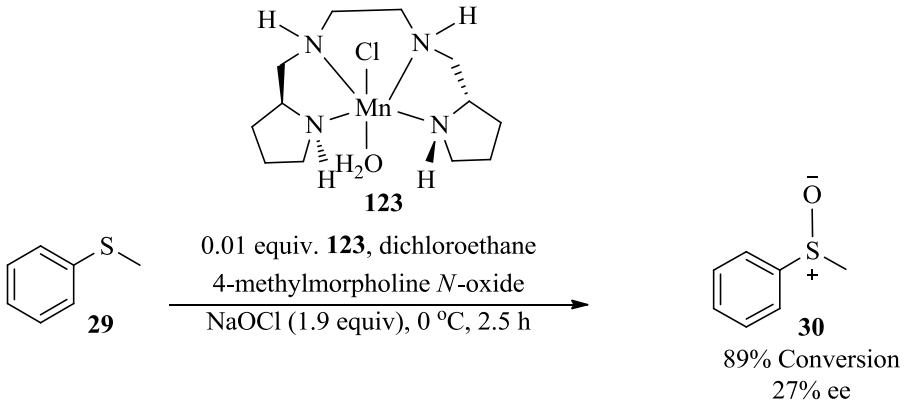
Scheme 1.49

Schoumacker *et al.* also investigated manganese-catalysed sulfide oxidation.[150] Using a catalyst similar to that used by Katsuki, sulfoxides with modest enantioselectivities were prepared. The catalyst comprised of a manganese salt, either $Mn(acac)_2$ or $Mn(ClO_4)_2$ and a salen type ligand **122**.



Manganese-catalysed oxidation has also been reported by Nagata *et al.*[151,152] Enantioselective aerobic oxidation of sulfides into optically active sulfoxides was achieved by using pivalaldehyde in the presence of a catalytic amount of optically active *β*-oxo aldiminatomanganese(III) complexes.

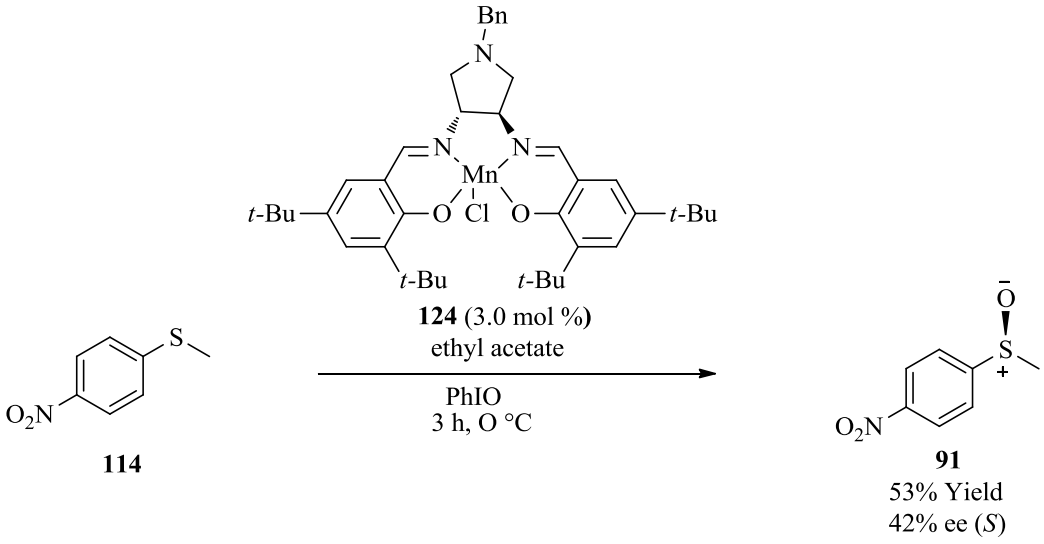
Iglesias reported modest enantioselectivity using the manganese complex **123** (Scheme 1.50).[153] Carrying out the oxidation using **123** under homogeneous conditions resulted in the sulfoxide being isolated with moderate enantioselectivity.



Scheme 1.50

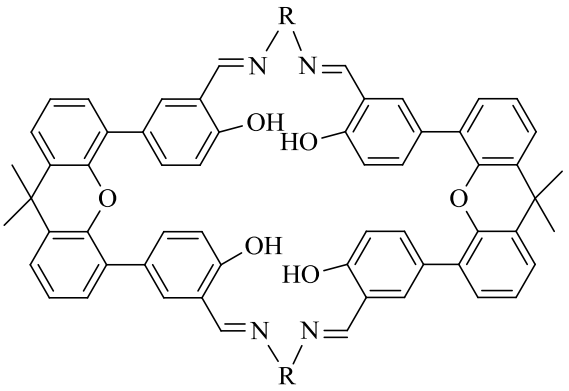
Preparing the catalyst complex using a manganese zeolite resulted in the desired solid phase catalyst being isolated, which could be used in heterogeneous catalysis. Carrying out the oxidation using this solid phase catalyst and employing the same conditions as shown in Scheme 1.51 resulted in sulfoxides with poorer enantioenrichment being isolated. The lower enantioselectivity was attributed to the possible presence of unreacted Mn^{2+} in the zeolite, which could form an achiral oxidising species. The heterogeneous catalyst could be isolated by filtration and recycled without major loss of efficiency or activity.

Gao *et al.* recently reported the use of chiral salen-manganese complexes with a pyrrolidine backbone, **124**.[154] Results reported were modest with the highest enantioselectivity observed for the oxidation of **114**. These type of complexes have proved very efficient catalysts in asymmetric epoxidation reactions.[155]

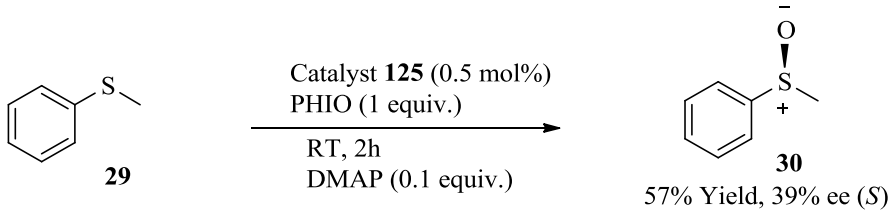


Scheme 1.51

Hirotsu *et al*. recently prepared dimanganese (III) complexes of salen-type ligands anchored by 9,9-dimethylxanthene-4,5-diyl spacers **125**. These complexes were used in the asymmetric oxidation of thioanisole **18**, but only modest enantioselectivities were obtained (Scheme 1.52).[156]



125



29 **30**

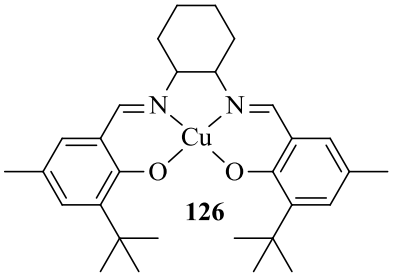
57% Yield, 39% ee (*S*)

Scheme 1.52

1.2.1.5 Copper-catalysed oxidation

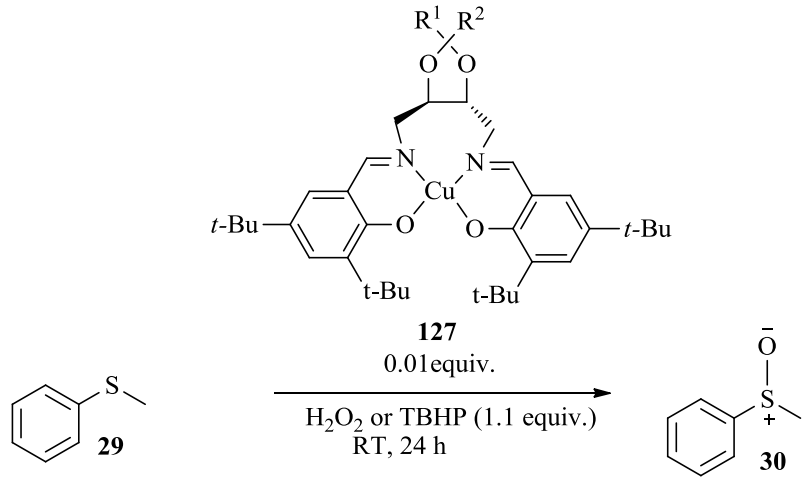
Iglesias investigated a copper catalyst similar to the manganese catalyst **123** used above. Under homogeneous conditions, the sulfoxide **19** of thioanisole **18** was successfully prepared in modest yield and 30% ee.[153] A possible explanation of the modest yields was that the copper-oxo species formed was less stable than the corresponding manganese species, resulting in less oxidation. Attempts to carry out the oxidation using a solid phase copper catalyst were unsuccessful.

Cross reported enantiopurities of up to 14% ee for the oxidation of thioanisole **18** using the copper salen complex **126**.[157] Other copper salen complexes screened proved to be ineffective.



126

Zhu *et al.* used chiral copper(II) complexes of optically active Schiff bases **127**, which have central seven-membered chelate rings. These produced sulfoxides in good yields (> 80%) but relatively low enantioselectivity (up to 17% ee) (Scheme 1.53).[158]

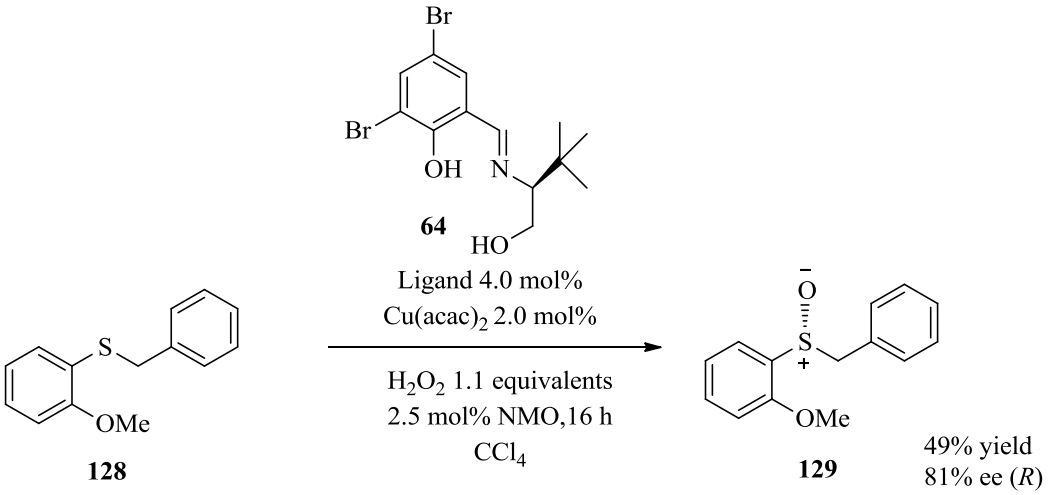


Scheme 1.53

Investigations by Kraemer using copper(II) salen-type complexes in asymmetric sulfide oxidation proved unsuccessful, with all copper complexes investigated proving inactive.[159] Ayala *et al.*, using an immobilized chiral copper salen complex in asymmetric sulfide oxidation, prepared aryl methyl sulfoxides in high yield but with poor enantioselectivity, up to 30% ee.[160] The immobilized catalyst could be recycled and TBHP was employed as the oxidant.

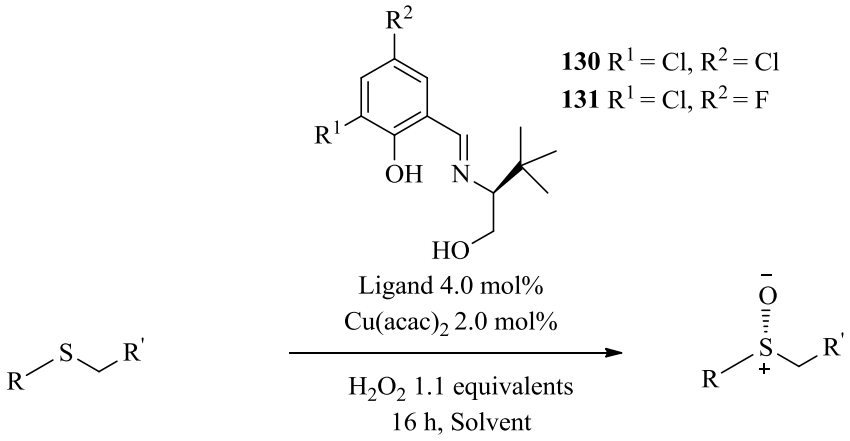
Copper Schiff base mediated asymmetric oxidation of aryl benzyl sulfides has been reported by Maguire *et al.*[161] The results reported compare favourably to other known copper mediated asymmetric sulfide oxidation methods, especially in terms of enantiocontrol (up to 81% ee), but yields and overall enantioselectivities are modest compared to other available methods. The method reported is similar to the vanadium and iron Schiff base mediated

oxidations reported by Bolm in that the same oxidant and ligands are employed. Interestingly, the resulting sulfoxide configuration is opposite to that observed for the iron/vanadium mediated methods. Best results were reported for sterically hindered aryl benzyl sulfides, and an improvement in the yield for this oxidation was observed in the presence of additives. No over-oxidation to the sulfone was observed (Scheme 1.54).



Scheme 1.54

Recently, Maguire *et al.* reported excellent yields and enantioselectivities for the copper-catalysed oxidation of sulfides.[162] The use of solvent mixtures resulted in a dramatic improvement in yields, while maintaining high enantiopurities (Scheme 1.55). A direct relationship between the steric bulk of the sulfide substituents and the enantioselectivity of the oxidation was observed.

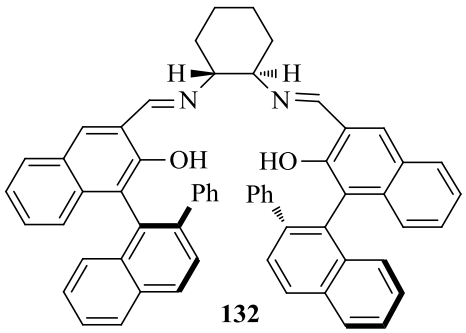


Solvent	R	R'	Ligand	Yield (%)	ee (%, *R*)
toluene	Ph	Ph	**130**	21	58
hexane : MeOH (9:1)	Ph	Ph	**130**	90	79
hexane : MeOH (9:1)	p-Tol	Ph	**130**	91	81
hexane : MeOH (9:1)	p-Tol	Ph	**131**	90	84
toluene	Ph	2-Naphthyl	**130**	23	93

Scheme 1.55

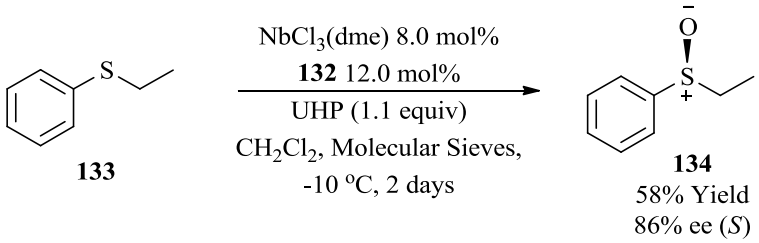
1.2.1.6 Niobium-catalysed oxidation

Katsuki has successfully used a niobium salen, obtained from niobium chloride dimethoxyethane [$NbCl_3$(dme)] and salen **132**, to carry out asymmetric sulfide oxidation.[163] The salen ligand used was very similar to that used by Katsuki in manganese-salen catalysed asymmetric sulfide oxidation.



132

The oxidising reagent used was urea•hydrogen peroxide adduct (UHP). Optimised conditions are as shown in Scheme 1.56. The highest enantiopurity was obtained oxidising ethyl phenyl sulfide **133**.

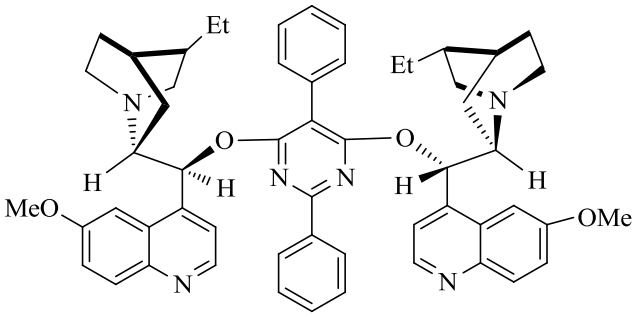


Scheme 1.56

Bolm *et al.* also carried out investigations into niobium-catalysed asymmetric sulfide oxidation but observed poor enantioselectivity (< 2% ee).[94]

1.2.1.7 Tungsten-catalysed oxidation

In 2003, Thakur and Sudalai reported a tungsten-catalysed asymmetric sulfide oxidation.[164] Using WO_3 and a cinchona alkaloid **135** as the catalyst and aqueous hydrogen peroxide as the oxidant, sulfoxides with up to 65% ee were isolated in good yield. While the results obtained were modest in comparison to other oxidation methods, this represented the first successful asymmetric sulfide oxidation catalysed by tungsten.

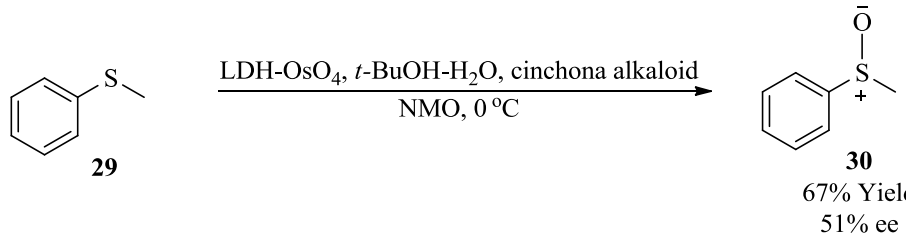


135

1.2.1.8 Osmium-catalysed oxidation

Kantam has reported asymmetric sulfide oxidation using an osmium catalyst supported on layered double hydroxides (LDH), a cinchona alkaloid as the chiral auxiliary and *N*-methylmorpholine *N*-oxide (NMO) as the oxidant.[165] The results obtained were reasonable with good yields and enantiopurities (up to 51% ee, Scheme 1.57). This method is more notable for its use of LDH than the enantioselectivity of the oxidation. The use of the catalyst

supported on LDH permitted recovery of the catalyst, which could then be recycled. Recycled catalyst generally did not perform as well as new catalyst. Sulfone formation also accompanied this reaction.

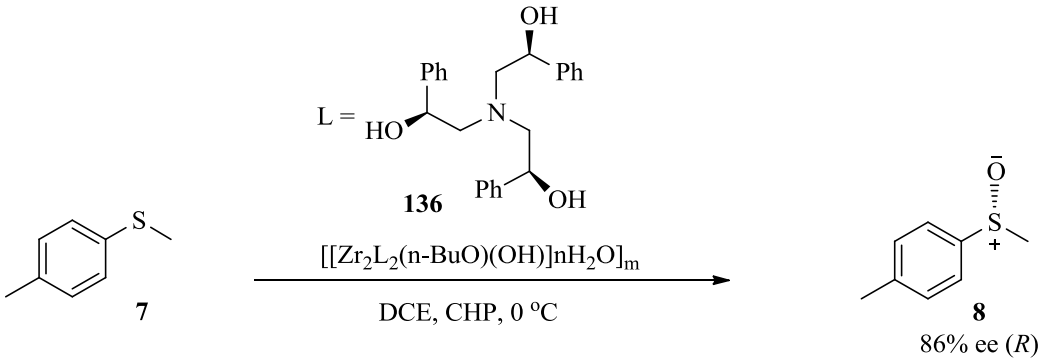


29 → **30**
67% Yield
51% ee

Scheme 1.57

1.2.1.9 Zirconium-catalysed oxidation

Modena reported in 1999 a highly stereoselective sulfide oxidation using a chiral zirconium(IV) catalyst.[166,167] Oxidations of methyl-*p*-tolyl sulfide **7** using this methodology gave enantiopurities of 86% ee (Scheme 1.58). Further stereoselective oxidations of aryl alkyl sulfides typically gave 80-90% ee. The chiral ligand **136** has also been successfully used in titanium-catalysed sulfide oxidations.[168] Unfortunately with this system a significant amount of the corresponding sulfone is also produced. Using less oxidant (CHP) overcomes this problem but the resulting sulfoxide is effectively racemic.



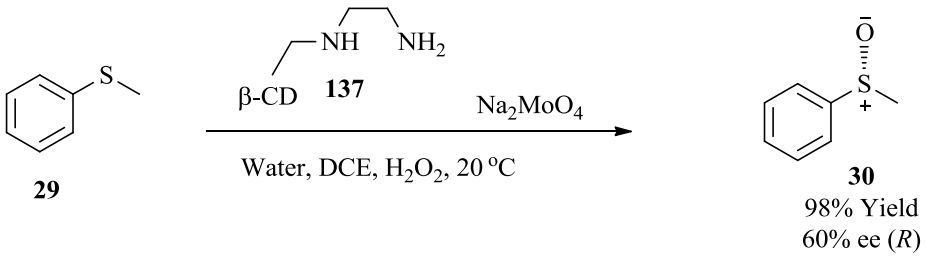
136

7 → **8**
86% ee (*R*)

Scheme 1.58

1.2.1.10 Molybdenum-catalysed oxidation

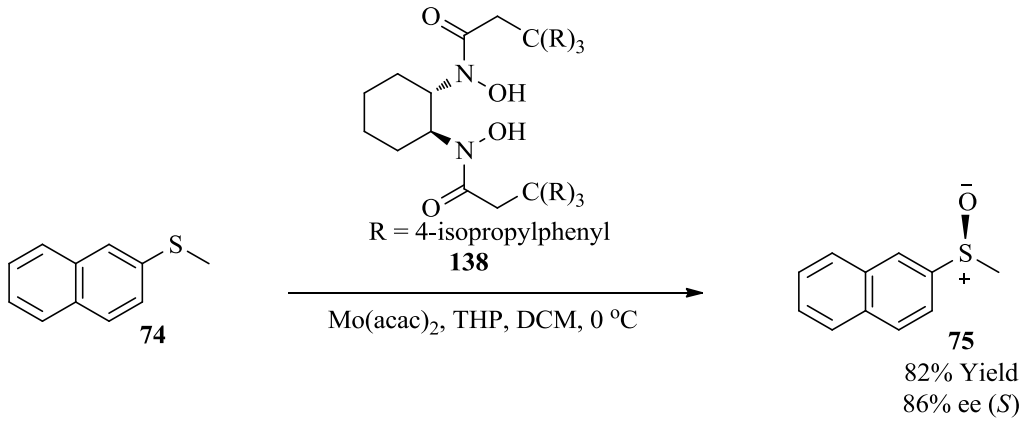
Bonchio has also successfully carried out asymmetric sulfide oxidations catalysed by molybdenum.[169] Chirality is induced by carrying out the oxidation in the presence of a β-cyclodextrin (β-CD) derived ligand **137** (Scheme 1.59).



Scheme 1.59

Ligand **137** (L), hydrogen peroxide and the molybdenum salt form an oxodiperoxomolybdenum species, $MoO(O_2)_2L$ which oxidises the sulfide. The achiral $MoO(O_2)_2$ species is also believed to form in this oxidation, reducing the enantioselectivity of the oxidation. To overcome this problem the oxidation is carried out using a biphasic solvent system. The substrate will preferentially reside in the dichloroethane layer, but it is believed the β-CD catalyst can extract the sulfide from this organic layer into the aqueous layer, where it is oxidised. As the achiral oxidising species is only aqueous soluble, the potential for it to oxidise the sulfide, which is in the organic layer, will be reduced thus improving the overall enantioselectivity of the oxidation.

Basak *et al*. reported another molybdenum catalyst suitable for asymmetric sulfide oxidation.[170] This method employs trityl hydroperoxide (THP) as the oxidant and the chiral auxiliary used is a *bis*-hydroxamic acid derivative **138** (Scheme 1.60).



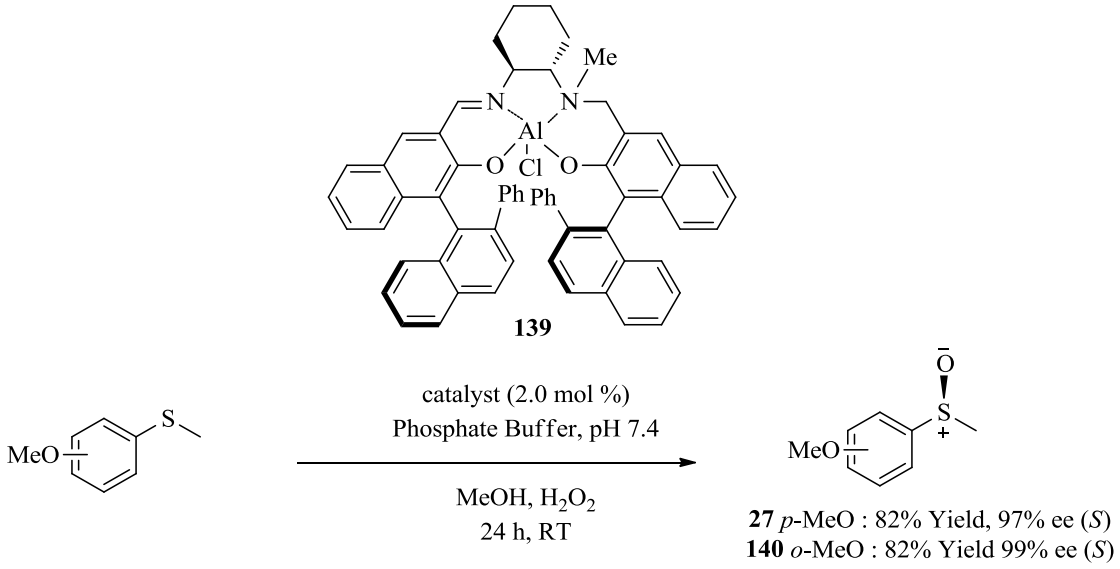
Scheme 1.60

Carrying out the oxidation using a ligand with less bulky groups (R = Ph) resulted in a drop in enantioselectivity. Using TBHP as an oxidant also resulted in decreased

enantioselectivity. The enantioselectivity observed using CHP as the oxidant was similar to that observed using THP as the oxidant.

1.2.1.11 Aluminium-catalysed oxidation

A chiral aluminium catalyst **139** has recently been used in asymmetric sulfide oxidation by Katsuki and co-workers.[171] The results obtained compare very favourably to existing methods, and furthermore the solvents and oxidant employed make this a very 'green' reaction. Some overoxidation to the sulfone occurs using this method to oxidize *para*-substituted aryl methyl sulfides, though the extent of overoxidation is reduced considerably or completely when oxidizing more sterically hindered *meta* or *ortho* substituted aryl methyl sulfides. Interestingly, enantioselectivity improves slightly as the substrate becomes more sterically hindered. This method proved amenable to scale up and was suitable for the oxidation of thioacetals.



Scheme 1.61

1.2.2 Non-metal catalysed asymmetric sulfide oxidations

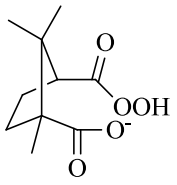
In non-metal catalysed asymmetric sulfide oxidation, enantioselectivity can be controlled either by using a chiral oxidant or by carrying out the oxidation in the presence of a chiral catalyst.

1.2.2.1 Chiral oxidants

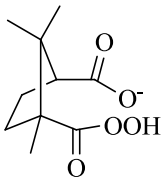
Peracids

Early work on asymmetric sulfide oxidation involved the use of peracids to oxidise sulfides.[26] Montanari investigated the use of optically active peroxy acids in asymmetric sulfide oxidation but results reported were poor.[172]

In 1977 Pirkle and Rinaldi reported that the enantioselectivity of monoperoxycamphoric acid **141** (MPCA) sulfide oxidations could be enhanced by the use of a single isomer of MPCA, rather than a mixture of the two MPCA isomers.[173] Pirkle proposed MPCA could exist as two isomers **141a** and **141b** with opposite stereoselectivity to each other. Pirkle speculated that the results obtained in previous reports, where MPCA was used as the oxidant, could have been improved had only a single isomer of MPCA been used.



141a

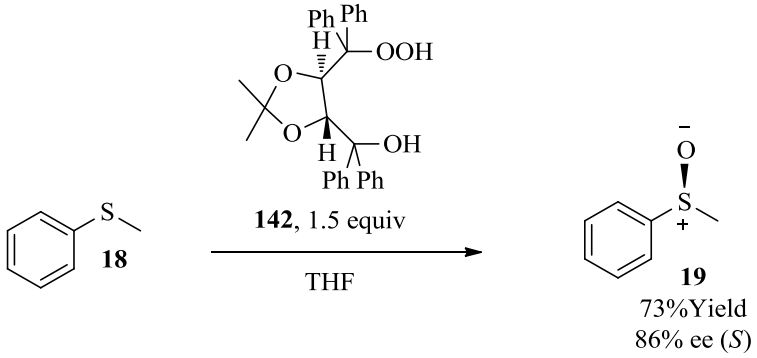


141b

Using MPCA as a mixture of isomers Pirkle obtained **30** in 6% ee, however using the single isomer **141a**, Pirkle obtained **30** in 9% ee. Single isomer MPCA was also successfully used to prepare enantioenriched epoxides and oxaziridines.

Chiral hydroperoxides

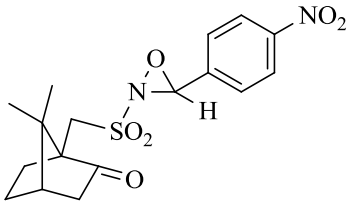
Seebach and Aoki used (4*R*,5*R*)-5-[(hydroperoxydiphenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}diphenylmethanol **142** (TADOOH) derived from H_2O_2 and tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) in asymmetric sulfide oxidation.[174] Using this hydroperoxide as oxidant, **19** was prepared in good yield and high enantiopurity (Scheme 1.62).



Scheme 1.62

Oxaziridines

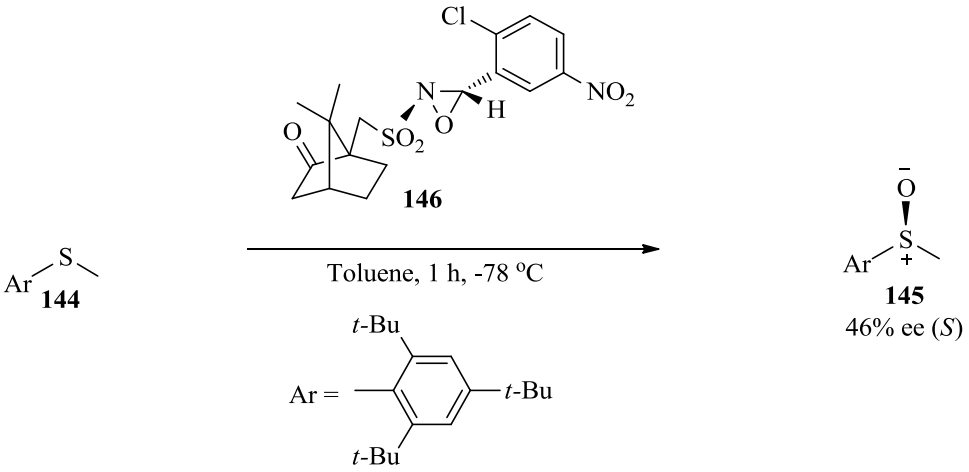
Davis *et al.* reported a new class of aprotic oxidising agents for the oxidation of sulfur compounds in 1978.[175] Using arenesulfonyl oxaziridines Davis successfully oxidised sulfides to sulfoxides in good yield. Subsequent work by Davis using these oxidising agents resulted in the development of a new chiral oxidising agent, 2-[(-)camphor-10-ylsulfonyl]-3-(nitrophenyl)oxaziridine **143**.[176] Oxidising agent **143** was used by Davis to enantioselectively oxidise sulfides, for example the sulfoxide **19** of thioanisole **18** was obtained with modest enantiopurity, 14% ee. In common with Pirkle, Davis used one isomer of the oxidising agent (33% optically pure) rather than a mixture of isomers.



143

Significantly, Davis was able to conclude that the key to enhancing the enantioselectivity using oxaziridine oxidising reagents was the relationship between the electrophilic oxygen and chiral centres of the oxaziridine, as well as the restricted geometry of the oxaziridine.

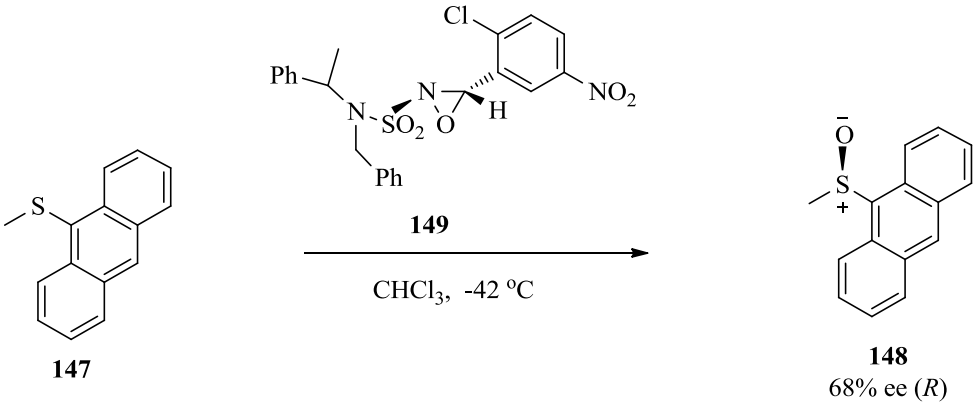
Using the oxaziridine **146** reagent shown below Davis extended the scope of the oxidation, oxidising a variety of aryl alkyl sulfides.[177] Highest enantioselectivity in this study was observed for the oxidation of sulfide **144** (Scheme 1.63).



Scheme 1.63

The mechanism of the oxidation is believed to involve nucleophilic attack by the sulfide on the electrophilic oxygen of the oxaziridine, similar to oxidation with peracids. The stereoselectivity of the oxidation is attributed to the steric factors, with electronic effects and variation of solvent having no effect on the stereoselectivity of the oxidation.

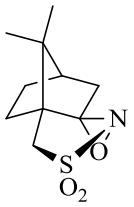
Using the sulfamyl oxaziridine **149**, Davis reported the highest enantioselectivity at the time obtained by asymmetric sulfide oxidation.[178]



Scheme 1.64

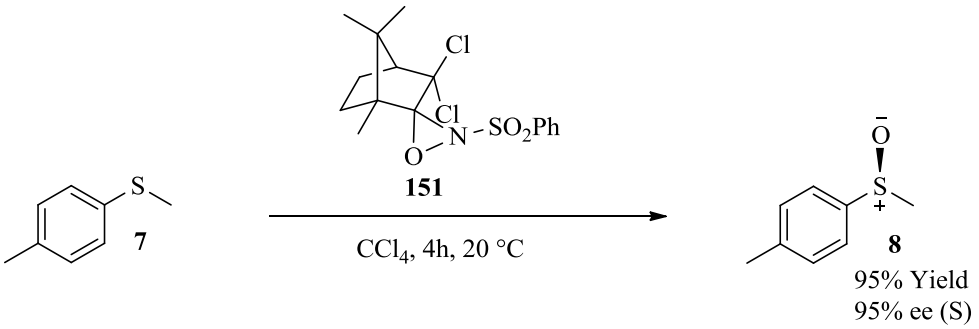
The mechanism of the oxidation using the sulfamyl oxaziridine is believed to be similar to that of the sulfonyl oxaziridine. Sulfamyloxaziridines offer two practical advantages over sulfonyloxaziridines – it is easier to vary the structure and they are chromatographically more stable, and therefore, easier to purify and isolate.[179]

Davis investigated camphorylsulfonyloxaziridine **150** but the results obtained were inferior to those obtained using sulfamyloxaziridines.[180]



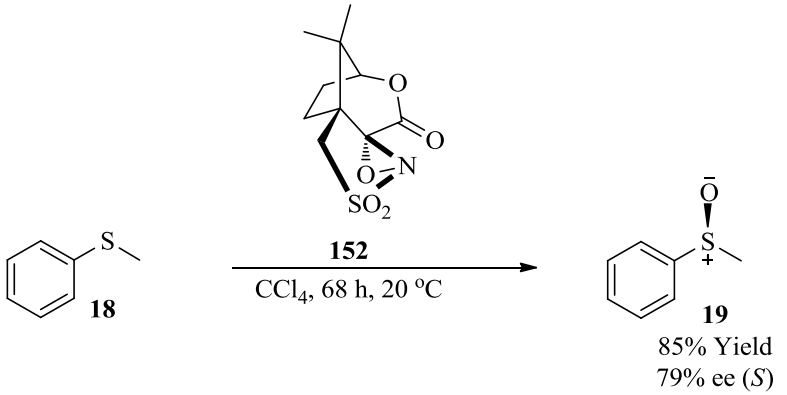
150

Later investigations by Davis using dichlorocamphorylsulfonyloxaziridine **151** were much more successful.[181] Using **151**, sulfoxides with very high enantiopurities could be prepared. Furthermore, the results obtained were at least comparable, if not superior, to those obtained using other available oxidation methods, and the oxidation was carried out at RT (Scheme 1.65).[182]



Scheme 1.65

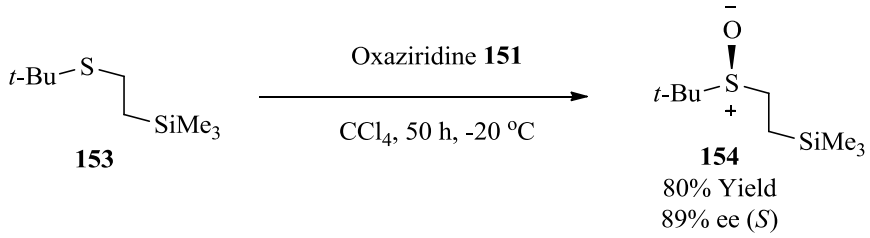
Meladinis *et al.* investigated oxaziridine derivatives such as **152** in asymmetric sulfide oxidation, obtaining **19** in good yield with high enantioselectivity (Scheme 1.66).[183]



Scheme 1.66

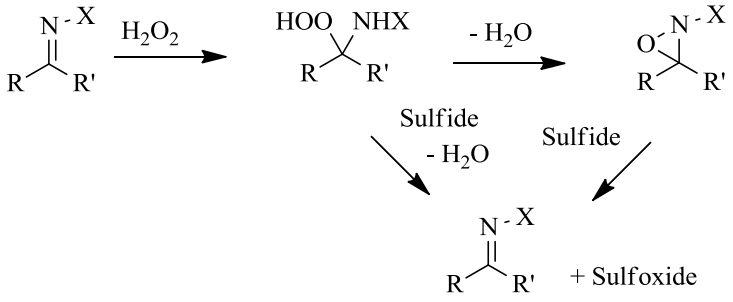
Sulfonyloxaziridines derived from benzothiazole were also investigated by Davis but were found to be inferior to both the sulfamyloxaziridines and 1**51**.[184]

Schwan successfully used **151** to asymmetrically oxidise a number of aryl/alkyl 2-(trimethylsilyl)ethyl sulfides.[185] In almost all of these oxidations the use of **151** as the oxidising agent resulted in higher enantioselectivity than other available asymmetric sulfide oxidation methods. The greatest degree of enantiocontrol was observed in the oxidation of *tert*-butyl sulfide **153**, which was not surprising as investigations by Davis established that the stereocontrol exerted by the oxaziridine during the oxidation was due to steric effects (Scheme 1.67).[177] Sulfides that did not possess a sterically demanding group were less susceptible to stereocontrol during the oxidation.



Scheme 1.67

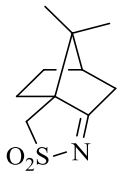
In 1988, Davis reported a selective racemic oxidation of sulfides to sulfoxides, (Scheme 1.68).[186] The significance of the method was that the oxaziridine oxidising reagent used was generated *in situ* by oxidising an imine. Given that some of the chiral oxaziridine oxidising reagents used in asymmetric sulfide oxidation were sensitive, this method offered the possibility of overcoming this problem.



Scheme 1.68

Page *et al.* was first to report the successful asymmetric sulfide oxidation using an *in situ* generated oxidising reagent.[187] Cyclic camphorsulfonylimine **155** was oxidised in a buffered

solution using hydrogen peroxide to form the oxaziridine or hydroperoxide, both of which could act as potential oxidants of the sulfide. The basic buffer used suppressed direct oxidation of the sulfide by the hydrogen peroxide.



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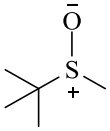
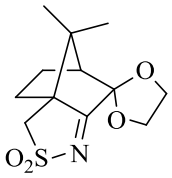
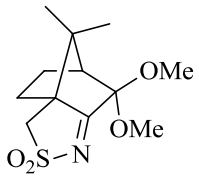


156

Using this *in situ* generated oxidising agent, *tert*-butyl methyl sulfoxide **156** was prepared in 83% yield and 42% ee. Later investigations by Page established that using the imines **157** and **158** resulted in much higher enantioselectivity, with **156** being obtained in quantitative yield and 86% ee when the dimethoxyimine **158** was used in the oxidation.[188]



157

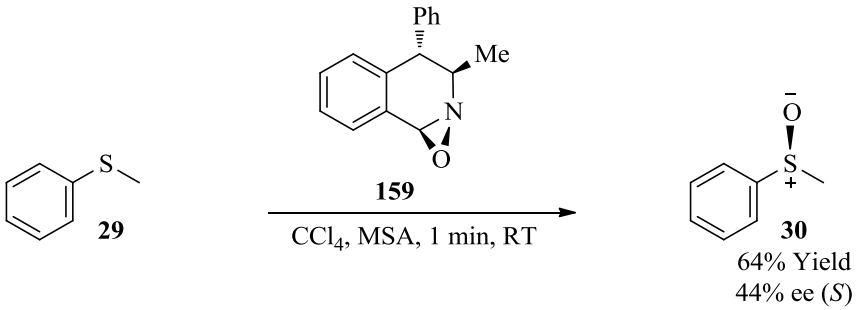


158

Page surmised that the primary oxidative species generated *in situ* using this oxidation method was the hydroperoxyamine as the stereoselectivity of the oxidation was opposite to that which would be expected if the oxidation was carried out using an oxaziridine.[188] Trends observed in the results of the oxidation differed from those that would be expected if the oxaziridine was the oxidising reagent.[187] Despite this, an investigation by Page using the oxaziridine of **158** as the oxidant and the imine **158** to generate oxidant *in situ* gave similar results, which could indicate that the oxaziridine was indeed the primary oxidative species generated *in situ*.[189] Page investigated further imines to see if the enantioselectivity could be improved.[190] However, the results obtained were inferior to those previously achieved.

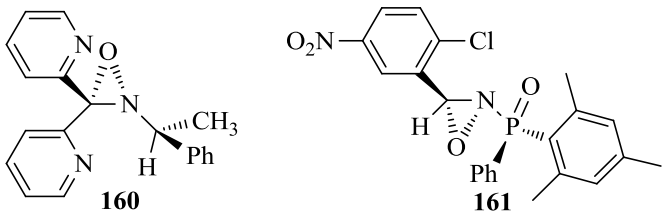
It was first reported in 1988 that acid could catalyse the oxygen transfer from an oxaziridine to a sulfide.[191] Bohé was first to use this knowledge in asymmetric sulfide oxidation using methanesulfonic acid (MSA) and an oxaziridine derived from dihydroisoquinoline **159** to carry out the oxidation (Scheme 1.69).[192] Overall the results

obtained using this method were modest compared to other oxidative methods that were available at that time.

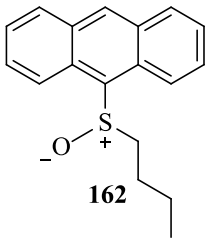


Scheme 1.69

Schoumacker *et al.* also used acids to promote oxygen transfer from oxaziridines in asymmetric sulfide oxidation.[193] Using a Lewis acid with the oxaziridine **160**, benzyl phenyl sulfoxide **13** was isolated in good yield with moderate enantioselectivity, 63% ee. Zinc chloride was found to be the best Lewis acid for these sulfide oxidations. While the results were modest, this represented the first Lewis acid promoted asymmetric oxidation of sulfides by oxaziridines.

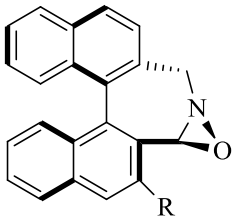


Jennings *et al.* used *N*-phosphinoyloxaziridines **161** to carry out asymmetric sulfide oxidations obtaining 9-anthryl *n*-butyl sulfoxide **162** in 70% ee.[194] The oxidation could be carried out at 0 ^{o}C in dichloromethane and the chiral imine by-product could, in principle, be recycled back to the oxaziridines.



Recently, Bohé *et al*. prepared enantiopure **8** in good yield (88%) using a cholesterol derived oxaziridinium salt as the oxidising agent. The oxaziridinium salt used was the first oxaziridinium salt derived from cholesterol.[195]

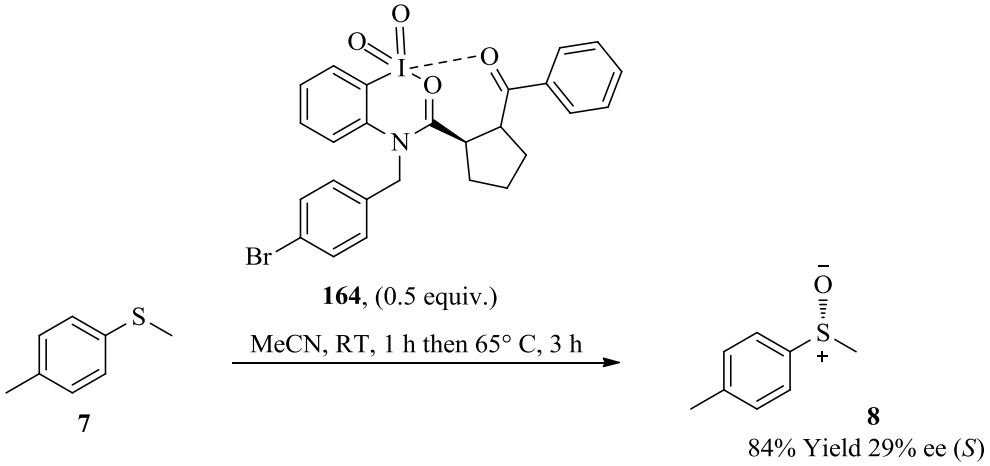
Hanquet *et al*. reported acid promoted asymmetric sulfoxidations using binaphthyl-derived oxaziridines **163**. The oxidations of dialkyl or diaryl sulfides produced the corresponding sulfoxides in good yield (up to 86%) with no sulfone formation and with enantiopurities ranging from 20% to 80% ee.[196] The enantioselectivity varied depending on reaction time, temperature and the acid used. Interestingly, the configuration of the resulting major sulfoxide enantiomer varied with the structure of the sulfide used.



R = H or Ph
163

Iodine based reagents

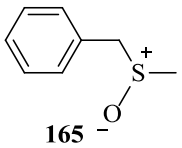
Zhdankin *et al.* reported the racemic and asymmetric oxidation of sulfides using iodine based oxidising reagents.[197-199] In 2006, Zhdankin *et al.* used a chiral benziodoxazine derivative **164**, developed from (*S*)-proline, in the asymmetric oxidation of sulfide **7**, producing sulfoxide **8** in 84% yield and 29% ee (Scheme 1.70).[199]



Scheme 1.70

1.2.2.2 Chiral catalysts

One of the earliest reported uses of a chiral catalyst in the asymmetric oxidation of sulfides was reported by Pitman, who used iodine as the oxidant and *D*-2-methyl-2-phenylsuccinate as the buffer; benzyl methyl sulfoxide **165**, was obtained with just over 6% ee.[200] Repeating the oxidation in the presence of a non-chiral phthalate buffer resulted in the isolation of racemic sulfoxide.

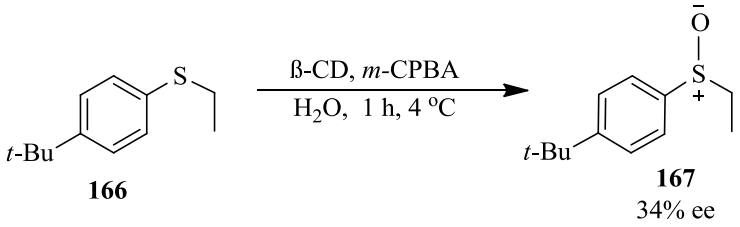


165

Cyclodextrins

Surendra *et al.* investigated a cyclodextrin catalysed sulfide oxidation.[201] The oxidation was accompanied by limited asymmetric induction. The oxidation is catalysed by the chiral auxiliary β-cyclodextrin (β-CD) and the oxidant used is NBS. The enantioselectivity of the oxidation is poor, less than 10% ee. While the results are not very encouraging, this method uses mild conditions and with further development may become an attractive viable asymmetric sulfide oxidation method. Rossi observed similar results while investigating $FeBr_3$ – cyclodextrin catalysed sulfide oxidation obtaining sulfoxides with low enantiopurities.[202]

Earlier work by Czarnik using cyclodextrin as a chiral auxiliary in asymmetric sulfide oxidation yielded more encouraging results.[203] Carrying out the oxidation under the conditions in Scheme 2.65, sulfoxides with over 30% ee were obtained (Scheme 1.71). This compared very favourably to other asymmetric oxidation methods available at the time.



166 **167** 34% ee

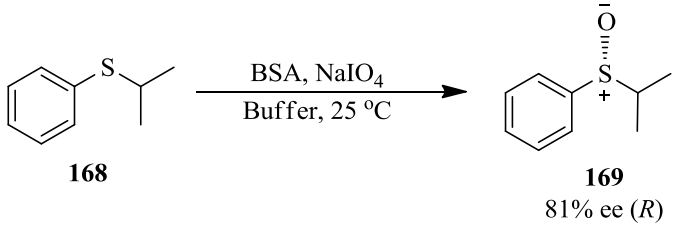
Scheme 1.71

Other oxidising reagents besides *m*-CPBA were screened by Czarnik. Results obtained using hydrogen peroxide, *t*ert-butyl hydroperoxide and $PhI(OAc)_2$ were inferior to those obtained using *m*-CPBA. Drabowicz also reported asymmetric sulfide oxidation catalysed by

β-cyclodextrin, with hydrogen peroxide as oxidant, and enantiopurities up to 30% ee were achieved.[204]

Bovine serum albumin

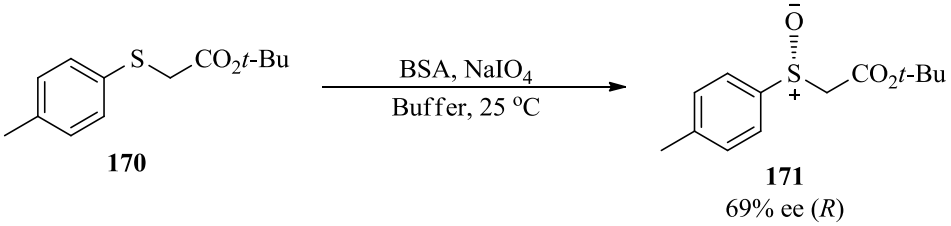
Sugimoto oxidised a number of aromatic sulfides in the presence of bovine serum albumin (BSA) using sodium metaperiodate as the oxidant.[205] The results obtained were impressive with **169** being obtained with an optical purity of 81% (Scheme 1.72).



168 **169**
81% ee (*R*)

Scheme 1.72

Ogura also carried out oxidation in the presence of BSA to obtain the mono sulfoxide of di-*p*-tolyl dithioacetal with an optical purity of 60%.[206] Colonna used similar conditions to Sugimoto and Ogura to obtain **171** in almost 70% ee (Scheme 1.73).[207]



170 **171**
69% ee (*R*)

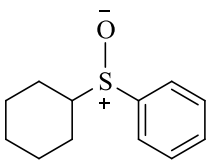
Scheme 1.73

As the results obtained using BSA to induce chirality are highly substrate dependent, the use of BSA in asymmetric sulfide oxidation has received very little attention since these reports.

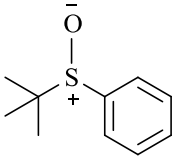
1.2.3 Electrochemical asymmetric sulfide oxidation

In 1976 Firth and Miller reported limited enantioselectivity in the oxidation of sulfides using electrochemical means.[208] While the results obtained were poor (3% ee) it was the first report of electrochemical asymmetric sulfide oxidation.

A few years later Komori and Nonaka reported a more enantioselective electrochemical oxidation.[209] Using poly(L-valine)-coated platinum electrodes, phenyl cyclohexyl sulfoxide **172** was obtained in 31% yield and 54% ee. Later work by Komori and Nonaka using a variety of poly-(amino acid) coated platinum/graphite electrodes established that the best electrode was the L-valine coated electrode.[210] Using this electrode *tert*-butyl phenyl sulfoxide **173** was obtained in 45% yield and 93% ee. This compared very favorably to the Kagan[34] and Modena[35] oxidation methods which were being published at that time.



172



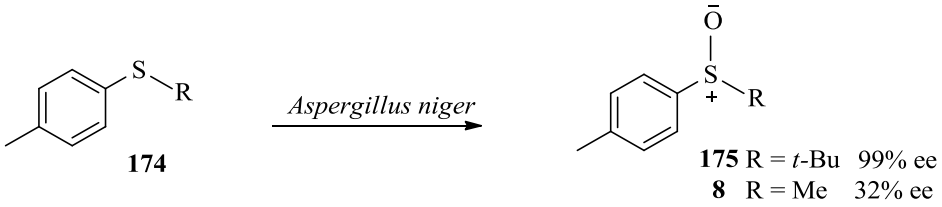
173

1.2.4 Biological asymmetric sulfide oxidation

Biological asymmetric sulfide oxidation is a less popular method for preparing enantioenriched sulfoxides than chemical asymmetric sulfide oxidation. There are many reasons for this but the principal reason is that since the publication of the Kagan and Modena methods, chemical asymmetric sulfide oxidation has proved itself to be the more practical and efficient method for preparing enantioenriched sulfoxides. Generally, the biological oxidation of sulfides, or biotransformation of sulfides, is carried out using whole cell cultures or isolated enzymes. A number of reviews of this area have appeared.[10]

1.2.4.1 Oxidation using whole cells

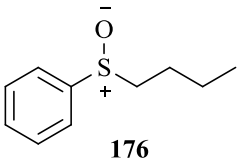
One of the earliest reports of whole cell cultures capable of oxidising sulfides to sulfoxides was in the 1950s when it was discovered that the addition of biotin to the growth culture of *Aspergillus niger* resulted in the formation of a new metabolite biotin *S*-oxide.[211,212] In 1962, benzyl phenyl sulfoxide **13** with 18% optical purity, was successfully prepared by oxidation of the sulfide by fermentation with fungus *Aspergillus niger*.[213] Later work using *Aspergillus niger* established that the efficiency of the sulfide oxidation was substrate specific with enantiopure **175** being isolated from the fermentation; for the less sterically demanding substrate **7**, enantioselectivity was considerably lower, Scheme 1.74.[214]



Scheme 1.74

The biocatalyst present in the fungus *Helminothosporium* sp. NRRL 4671 has been used in the asymmetric oxidation of a variety of sulfides with very high enantioselectivity being observed, similarly *Mortierella isabellina* ATCC 42613 has also been successfully used to prepare highly enantioenriched sulfoxides.[215-222]

Bacterial cells have proven to be very useful in asymmetric sulfide oxidation. The oxidation of the antibiotics, lincomycin and clindamycin to the sulfoxide by *Streptomyces* bacteria was the first indication that bacterial cells were capable of oxidising sulfides.[223,224] Ohta *et al.* prepared a number of aryl alkyl sulfoxides with high enantiopurities using the bacteria, *Corynebacterium equi*. For example enantiopure *n*-butyl phenyl sulfoxide **176** was obtained using this bacteria.[225-227]



176

A *Micrococcus* species was used to prepare the sulfoxide **19** of thioanisole **18** with >90% ee.[228] *Pseudomonas putida* NCIB 9816-4, which expresses the enzyme naphthalene dioxygenase, was used to prepare a variety of enantioenriched aryl alkyl sulfoxides with up to 98% ee being reported.[229]

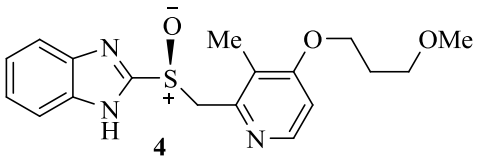
Biocatalytic sulfoxidation using the topsoil bacterium *Pseudomonas frederiksbergensis* has been reported by Adam *et al.*[230] For example **8**, was obtained effectively enantiopure (> 99% ee) in quantitative yield using *Pseudomonas frederiksbergensis* to oxidize the sulfide.

Boyd *et al.* reported the TDO- and NDO-catalysed asymmetric oxidation of a range of sulfides.[231,232] The TDO enzyme system was more reluctant to catalyse oxidation of dialkyl sulfides than aryl alkyl sulfides to the corresponding monosulfoxides.

Yeasts have also been used in asymmetric sulfide oxidation, though to a rather limited extent. Best results were obtained under semi-anaerobic conditions with **8** being obtained with 92-94% ee.[233,234] Roberts successfully used bakers' yeast (*Saccharomyces cerevisiae* NCYC 73) to prepare **8** in high yield and enantiopurity.[233] Given the ease of protocol and relatively low cost of the bakers' yeast catalyst, this result is very significant.

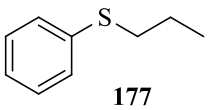
Kayser *et al.* prepared enantiopure sulfoxides *via* biooxidation with engineered yeast (*Saccharomyces cerevisiae*) and E.coli overexpressing enzyme cyclohexanone monooxygenase (CHMO). It had previously been shown that CHMO-catalysed oxidations of sulfides required a combination of a large and a small substituent on the sulfur for maximum enantioselectivity.[235] As a result, this system[236] was used in the oxidation of **18**, producing the sulfoxide **19** in 95% yield and 99% ee.

Nagasawa *et al.* tested over 650 microorganisms in the asymmetric synthesis of the proton pump inhibitor, rabeprazole **4** from the corresponding sulfide.[237] The microorganisms consisted of 300 molds, 200 bacteria, 100 yeasts, and 50 basidiomycetes. The molds produced the best results, with the highest activity exhibited by the newly isolated strain, *Cunninghamella echinulata MK40*. The addition of glucose improved product formation. Rabeprazole was produced in enantiopure form (*S*) and in a 92% conversion from the sulfide with no sulfone formation.



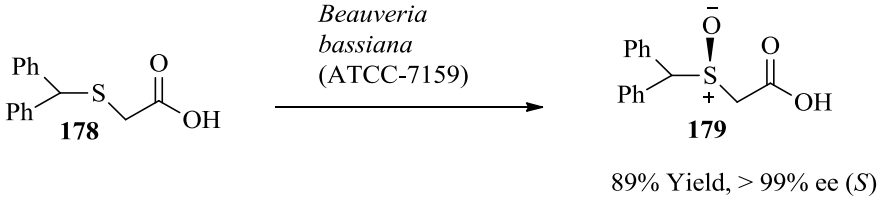
4

Porto *et al.* reported that white rot Basidomycetes promoted the asymmetric oxidation of aromatic pro-chiral sulfides, producing sulfoxides in good yields and enantioselectivities, and with a small amount of sulfone production. The oxidation of phenyl propyl sulfide **177** produced the (*S*)-sulfoxide in enantiopure form.[238]



177

Olivo *et al.* reported a highly enantioselective oxidation of benzhydrylsulfanyl acetic acid to the corresponding (*S*)-sulfinyl carboxylic acid using the fungus *Beauveria bassiana*. The sulfoxide **179** was produced in excellent yield (89%) and enantioselectivity (99%) (Scheme 1.75).[17] The sulfoxide **179** was further amidated using the bacteria *Bacillus niger* to give (*S*)-modafinil **5** in 68% yield.



Scheme 1.75

Collado *et al.* reported the enantiomeric oxidation of a series of substituted sulfides using the filamentous fungi *Botrytis cinerea*, *Eutypa lata* and *Trichoderma viride*. In the oxidation of benzyl phenyl sulfide, *T. viride* gave the best result, producing sulfoxide in 60% yield and > 95% ee (*R*). Interestingly, the (*R*)-enantiomer was favored in biotransformations by *T. viride* and *E. lata* while the (*S*)-enantiomer was favored in those by *B. cinerea*.[239]

Chauvin *et al.* reported the asymmetric oxidation of alkyl aryl and dialkyl sulfides using the microalga, *Chlorella sorokiniana*. These sulfides were converted to sulfoxides in modest yields (up to 67% conversion) and enantioselectivities (up to 58% ee). In the oxidation of alkyl aryl sulfides the formation of the (*R*)-enantiomer was favored while the (*S*)-enantiomer was favored with the dialkyl sulfides.[240]

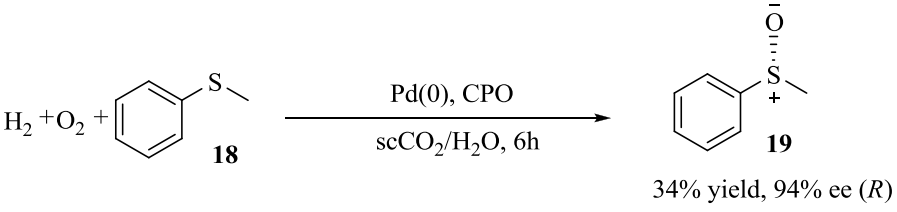
1.2.4.2 Oxidation using isolated enzymes

While the use of whole cells instead of isolated enzymes for asymmetric sulfide oxidation is advantageous for a number of reasons, obviating the need to isolate the enzymes and to add cofactors to the oxidation, the use of isolated enzymes in asymmetric sulfide oxidation has attracted considerable interest. Most enzymes used in asymmetric sulfide oxidation contain a metal centre, usually iron, which facilitates the oxidation of the sulfide in the presence of an oxidant.

The CHMO enzyme has been used to oxidise a variety of aryl alkyl sulfides with high enantioselectivity.[241,242] Chen used CHMO isolated from an engineered yeast strain to prepare **19** in 95% yield and >99% ee from its sulfide **18**.[243]

The chloroperoxidase (CPO) enzyme has shown itself to be a very useful enzyme in the asymmetric oxidation of sulfides.[244] It is the most versatile of the peroxidases.[10] It can be isolated in quantity from the marine fungus *Caldariomyces fumago*. Colonna demonstrated that the optimum oxidant for use with CPO is hydrogen peroxide, obtaining sulfoxides in high yield and enantiopurity.[245] Significant achiral oxidation can occur in these oxidations which is not catalysed by CPO; this can be avoided by the use of conditions proposed by Sheldon.[246,247] The first electroenzymatic asymmetric sulfide oxidation was reported using the CPO enzyme from *Caldariomyces fumago*.[248] A carbon cathode reduces dissolved oxygen to form hydrogen peroxide which, in the presence of CPO can enantioselectively oxidise sulfides to sulfoxides. Thioanisole **18** was oxidised to form **19** with very high enantioselectivity (99% ee) using this method. Selective oxygen transfer by heme-peroxidases like CPO has been investigated.[249] The poor stability of CPO and indeed other peroxidases has limited their use in organic synthesis, however investigations into improving the stability of peroxidases are ongoing.[250]

Leitner and Greiner carried out an enantioselective sulfoxidation by cascade reaction of Pd(0) catalysed formation of H_2O_2 and enzymatic oxidation using chloroperoxidase (CPO) from *Caldariomyces fumago*. Supercritical carbon dioxide (sc CO_2) was used as medium for *in situ* generation of H_2O_2 from H_2 and O_2 using Pd catalysts. The system afforded **19** in 34% yield and 94% ee (Scheme 1.76).[251]



Scheme 1.76

Hollmann and Arends also used CPO enzyme to produce **19** in quantitative yield and 99% ee. This procedure involved light-driven H_2O_2 generation, using flavins as

photocatalysts and EDTA as sacrificial electron donor. The waste product produced from EDTA oxidation (formaldehyde, ethylenediamine) was a major disadvantage with this method. The replacement of EDTA with formate resulted in a decrease in the enantioselectivity to 78%.[252]

Initial investigations using horseradish peroxidase in asymmetric sulfide oxidation were disappointing.[253] The generation of engineered biocatalysts by replacing one of the amino acids in the enzyme, *phenylalanine* with *leucine*, resulted in a major improvement in the performance of the enzyme with (*S*) sulfoxides being obtained with high enantiopurity.[254,255] A variety of aryl alkyl sulfoxides were obtained with >90% ee. Replacing the amino acid with threonine resulted in a drop in enantioselectivity.

An improvement in the performance of the enzyme, *mammalian lactoperoxidase*, was observed when the oxidant was added continuously rather than in aliquots, enabling the sulfoxide **19** of thioanisole **18** to be obtained in 85% yield and 80% ee.[256]

Flavin-dependent monooxygenase 3 (FMO3) was used to prepare enantioenriched sulindac **6** from the analogous sulfide in 90% ee with the *R* enantiomer predominating.[18] Sulfides have been asymmetrically oxidised by toluene dioxygenase (TDO) and naphthalene dioxygenase (NDO) with the resulting sulfoxides being isolated in high yield and enantiopurity.[257]

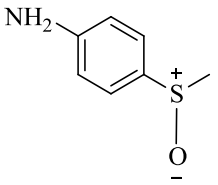
Recombinant 4-hydroxyacetophenone monooxygenase (HAPMO) from *Pseudomonas fluorescens* ACB was reported as an excellent enzyme for asymmetric sulfide oxidation.[258] De Gonzalo *et al.* used this enzyme to prepare a variety of aryl alkyl sulfoxides in high yield and high enantiopurity, for example **19** was obtained in 99% ee with 96% conversion.

Myeloperoxidase mediated asymmetric sulfide oxidation was investigated by Wever[253] and the results obtained were interesting. At pH = 5 maximal sulfoxide yields were reported but optimal enantioselectivity of the oxidation occurred at pH = 6. Overall the results were modest with **19** being obtained with a maximum of 32% ee.

Many enzymes rely on an iron porphyrin system to carry out the oxidation, however the use of non-heme enzymes has also attracted attention. For example manganese peroxidase was successfully used to oxidise **18**.[253] Limited investigations resulted in **19** being isolated in 18% yield but with 91% ee.

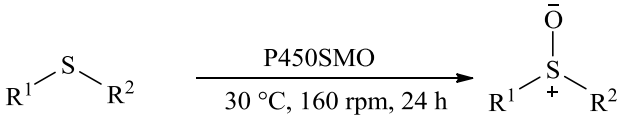
Vanadium haloperoxidases are probably the most investigated non-heme based peroxidases used in asymmetric sulfide oxidation. Anderssen and Allenmark reported moderate enantioselectivity when oxidising aryl alkyl sulfides using vanadium bromoperoxidase.[259] ten Brink reported improved enantioselectivity using vanadium

bromoperoxidase from *Ascophyllum nodosum*.[260] Better enantioselectivity was observed preparing aryl sulfoxides which contained activating substituents at the *para* position of the aromatic ring. The sulfoxide **180** was obtained in 89% ee.



180

Recently, a cytochrome P450 monooxygenase was successfully cloned from *Rhodococcus species ECU0066* and used in asymmetric sulfide oxidations.[261] A number of aryl methyl sulfides were oxidised to sulfoxides with modest to good conversions and excellent enantioselectivities (Scheme 1.77).



Sulfoxides		Conv.(%)	ee (%)
8 R^1 = *p*-Me-C_6H_5	R^2 = Me	69	87 (*S*)
30 R^1 = C_6H_5	R^2 = Me	32	99 (*S*)
181 R^1 = *p*-Cl-C_6H_5	R^2 = Et	89	99 (*S*)

Scheme 1.77

Casella *et al.* reported that mushroom tyrosinase (*Agaricus bisporus*) could catalyse the asymmetric oxidation of sulfides to sulfoxides in the presence of catechol as substrate. Only the oxy-form of the enzyme was capable of oxidising the sulfide in a two electron process. The yield was low (~ 20%) because L-dopamine, which was used as a reductant, competed with the sulfide in the catalytic reaction. However, the enantioselectivity was high (~ 85% ee) and could be further increased when excess ascorbic acid is added to the reaction to limit enzyme inactivation by the quinones produced by L-dopa oxidation.[262]

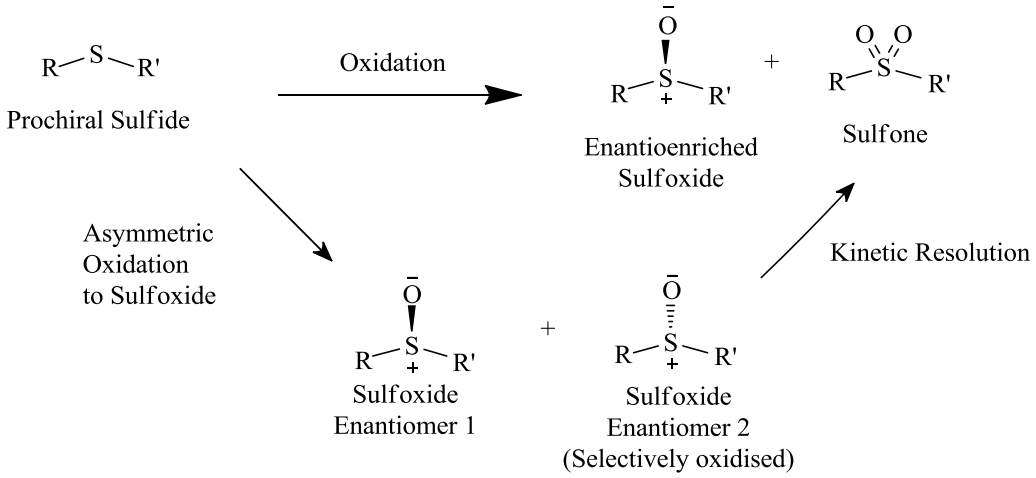
1.3 Kinetic resolution of sulfoxides

While asymmetric sulfide oxidation is more attractive as a route to enantiopure sulfoxides, a second strategy involving kinetic resolution in sulfoxide oxidation has also been explored. Kinetic resolution strategies can be categorised as either oxidative or non-oxidative, with the former being the most popular strategy.

1.3.1 Oxidative kinetic resolution

Most kinetic resolution methods involve the preferential oxidation of one sulfoxide enantiomer to the sulfone, leaving the remaining sulfoxide enantioenriched. Asymmetric sulfide oxidation is often accompanied by stereoselective sulfoxide oxidation called kinetic resolution, which often exhibits complementary stereoselectivity to the asymmetric sulfide oxidation step, enhancing the overall enantioselectivity of the oxidation. Most of the reported kinetic resolution methods are in fact variations of asymmetric sulfide oxidations, with the principal difference being the substrate used is the sulfoxide rather than the sulfide.

While kinetic resolution of racemic sulfoxides is rarely employed as a route to enantioenriched sulfoxides, as the maximum yield is at best 50%, a number of groups engaged in the enantioselective preparation of sulfoxides have successfully used asymmetric sulfide oxidation in tandem with kinetic resolution to prepare enantioenriched sulfoxides (Scheme 1.78).



Scheme 1.78

Various catalysts and oxidants that have been employed in oxidative kinetic resolutions are discussed below. Most research reports regarding kinetic resolution employ aryl methyl sulfoxides while some reports use aryl benzyl sulfoxides.

1.3.1.1 Biological methods

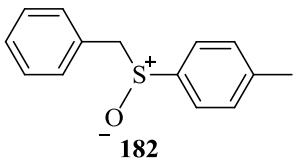
Oxidising racemic *para*-tolyl methyl sulfoxide **8** using an *Aspergillus Niger* culture, resulted in the unreacted sulfoxide being isolated in 57% yield and 30% optical purity.[263] Sugimoto reported that kinetic resolution took place when oxidising racemic sulfoxide with hydrogen peroxide in the presence of BSA.[264] The highest enantioselectivity was observed in the kinetic resolution of *tert*-butyl phenyl sulfoxide **173**, which was isolated with 33% ee after the kinetic resolution experiment. Using a combination of both asymmetric sulfide oxidation and kinetic resolution, Sugimoto obtained phenyl *iso*-propyl sulfoxide **173** in 93% ee.[264]

Overall, compared to the number of biological asymmetric sulfide oxidations reported, relatively few biological kinetic resolutions of sulfoxides have been reported.

1.3.1.2 Chiral oxidants

Peroxy Acids

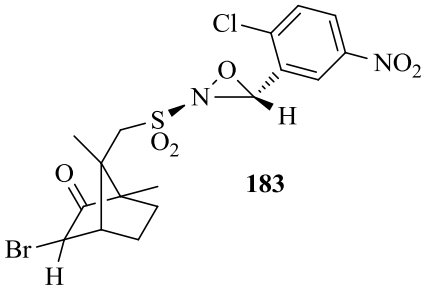
One of the earliest reports of oxidative kinetic resolution was described by Montanari.[172] A chiral peroxy acid, 2,3,3-trimethylperbutyric acid, preferentially oxidised one enantiomer of a racemate while leaving the other sulfoxide enantiomer enantioenriched. Unoxidised **19** was obtained in 3% ee while unoxidised *tert*-butyl phenyl sulfoxide **173** was obtained in 5% ee. Koboyashi described a similar kinetic resolution experiment, using percamphoric acid in the oxidation of racemic benzyl *para*-tolyl sulfoxide **182**; the unoxidised sulfoxide was found to have an optical purity of 3% ee.[265]



182

Oxaziridines

Davis has successfully employed oxaziridines in kinetic resolution experiments.[266] Using chiral 2-sulfonyloxaziridines, such as **183**, sulfoxides were isolated in up to 27% ee, using *para*-tolyl methyl sulfoxide **8** as substrate.

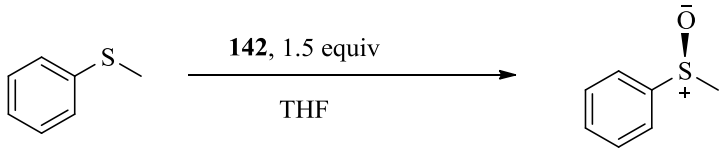


183

Davis proposed that this oxidative kinetic resolution method could be used in conjunction with asymmetric sulfide oxidation and, through multi-step kinetic resolutions, it would be possible to improve the enantiopurity of the sulfoxide.

Hydroperoxides

TADOOH **142** was used by Seebach and Aoki to asymmetrically oxidise sulfides.[174] Significant complementary kinetic resolution of the sulfoxide product accompanied the sulfide oxidation, and this was used to improve the overall enantioselectivity of the oxidation. The contribution of kinetic resolution was temperature dependent; virtually no kinetic resolution was observed at -30 ^{o}C, while it was most efficient at RT (Scheme 1.79).



29 **30**
73% Yield
86% ee (*S*)

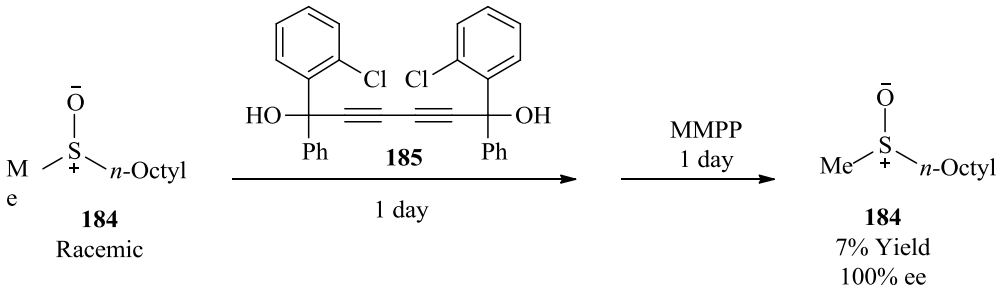
Scheme 1.79

1.3.1.3 Chiral catalysts

Inclusion complexation in the solid state

Toda reported that kinetic resolution occurs when sulfoxides are oxidised in the presence of the optically active host compound, (-)-1,6-di(*o*-chlorophenyl)-l,6-diphenylhexa-2,4-diyne-l,6-diol, **185**.[267] Racemic sulfoxide **184** was mixed with **185** and kept at RT for a day, and then selectively oxidized to the sulfone by mixing with an achiral oxidising agent such as *m*-CPBA or MMPP and leaving for a further day. The sulfoxide recovered was enantioenriched because the optically active host compound selectively binds one sulfoxide enantiomer; the unbound enantiomer is then oxidized to the sulfone. Excellent enantioselectivity was

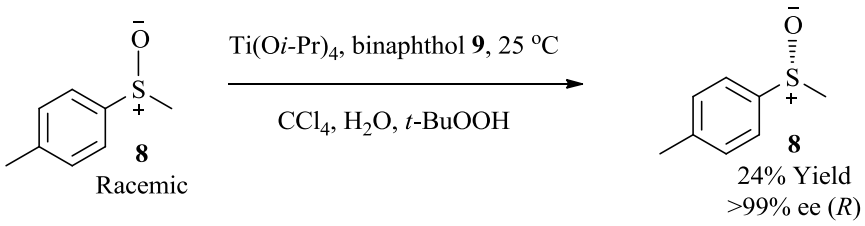
obtained in some cases, albeit at the expense of yield (Scheme 1.80). The absolute stereochemistry of **184** was not identified.



Scheme 1.80

Titanium-catalysed oxidative kinetic resolution

The modified Sharpless reagents developed by Kagan and Modena have both been used in kinetic resolution experiments. Uemura reported a correlation between enantiopurity and sulfone concentration, see section 2.11.[268] Using a combination of both asymmetric sulfide oxidation and kinetic resolution, **8** was obtained in 99% ee (Scheme 1.81). Uemura optimised the conditions for the kinetic resolution which were similar to those used in asymmetric sulfide oxidation. The major difference was that the optimum temperature was found to be 25 ^{o}C for the kinetic resolution compared to -20 ^{o}C for the asymmetric sulfide oxidation.[269]

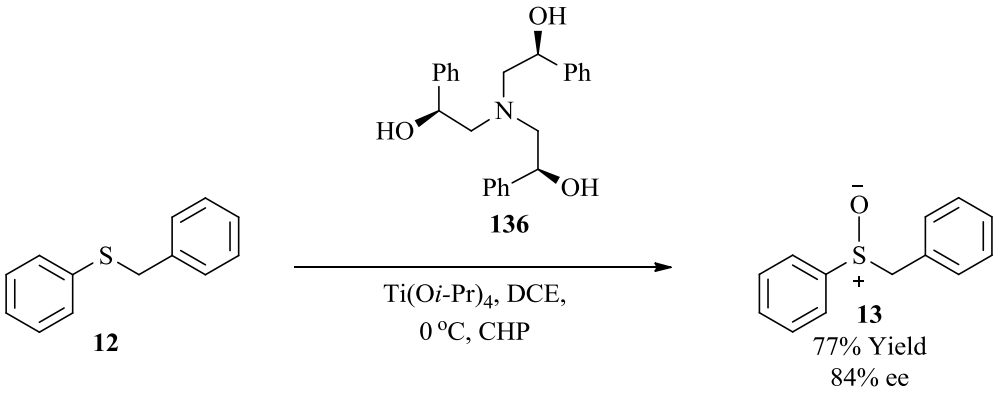


Scheme 1.81

Superchi and Rosini reported that (*S*,*S*)-1,2-diphenylethan-1,2-diol **11** was a suitable ligand for titanium mediated asymmetric sulfide oxidation.[46,270] The oxidation was accompanied by significant sulfone formation due to kinetic resolution. In this case, kinetic resolution did not improve enantioselectivity, and therefore conditions were developed to suppress it. Thus, the reaction time was limited to 2 hours, two equivalents of the oxidant were used and the reaction was carried out at 0 ^{o}C. Carrying out at a lower temperature, - 20

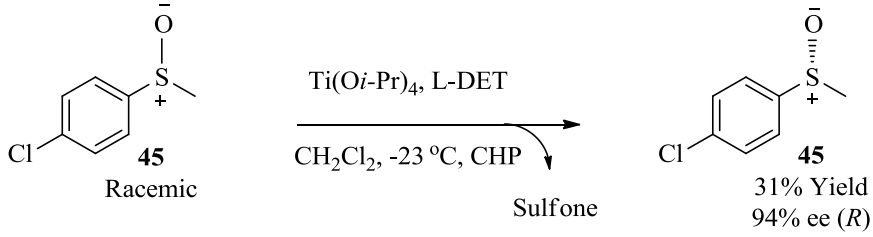
^{o}C, would have perhaps reduced or even eliminated kinetic resolution, as has been shown by Uemura.[269]

Licini employed a trialkanolamine ligand **136** and CHP as oxidant in a titanium mediated sulfide oxidation.[168] Significant sulfone formation was observed, attributable to oxidative kinetic resolution of the sulfoxide (Scheme 1.82).



Scheme 1.82

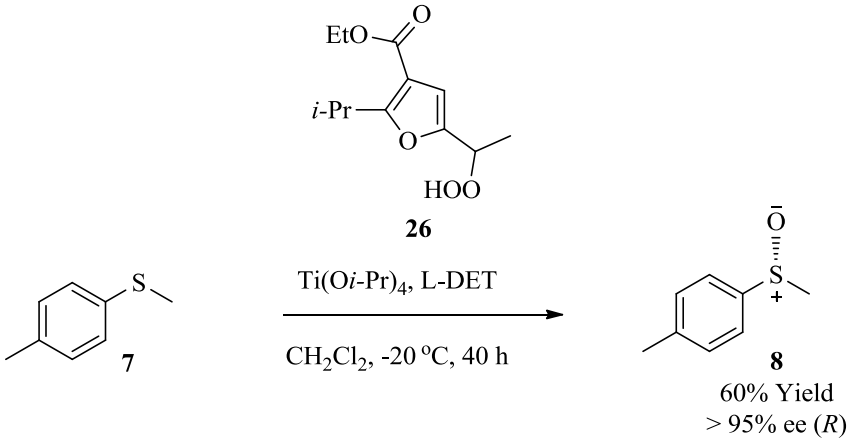
Scettri, using the conditions reported by Modena, reported that racemic sulfoxides could be enantioselectively oxidised to the sulfone.[60] Using CHP, Scettri obtained *para*-chlorophenyl methyl sulfoxide **45** in good yield and high enantioselectivity (Scheme 1.83). Poorer enantioselectivity was observed when TBHP was the oxidant.



Scheme 1.83

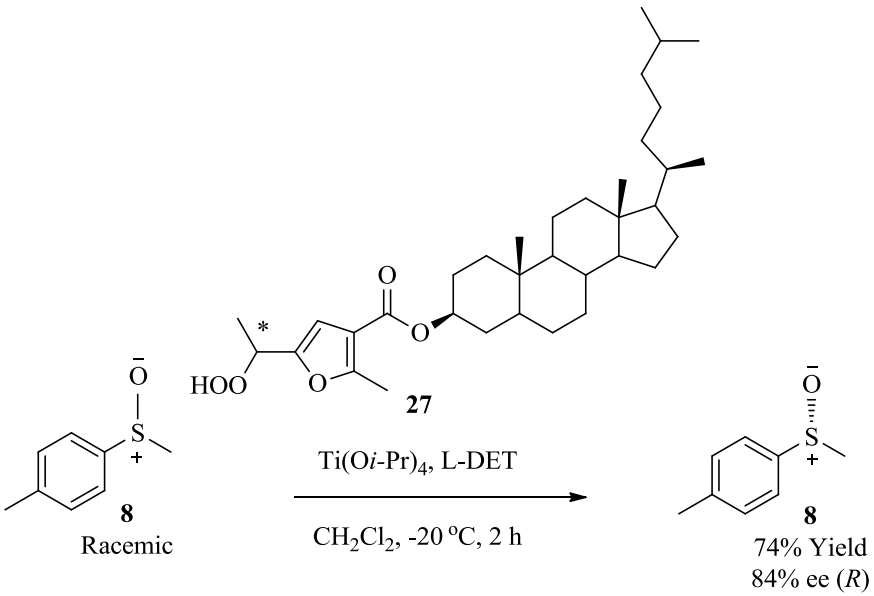
In a later report by Scettri, the enantioselectivity of the oxidation was improved using a racemic furyl hydroperoxide **26** as the oxidant.[61] The hydroperoxide **26** had already been successfully used in asymmetric sulfide oxidation,[59] see section 1.2. The results obtained using the hydroperoxide **26** were superior to those reported using CHP, with sulfoxides being obtained in higher enantiopurity. The enantioenriched sulfoxide **8** was obtained through a combination of asymmetric oxidation and complementary kinetic resolution (Scheme 1.84). Kinetic resolution alone produced enantioenriched **8** in > 95% ee but in a 38% yield, much

lower than the 60% yield obtained through a combination of asymmetric sulfide oxidation and complementary kinetic resolution.



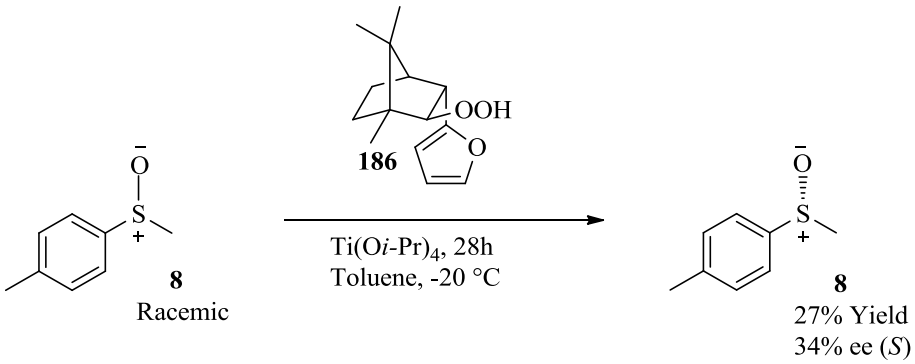
Scheme 1.84

Steroidal furyl hydroperoxides **27** also proved to be very efficient oxidants in the kinetic resolution of sulfoxides, though not as effective as the furyl hydroperoxide oxidant **26** discussed previously.[63] Employing both asymmetric sulfide oxidation and kinetic resolution, sulfoxides were obtained in good yield and high enantiopurity using this oxidant. While the results shown may be inferior in terms of yield and enantioselectivity to those obtained previously by Scettri, the reaction time is considerably shorter (Scheme 1.85).



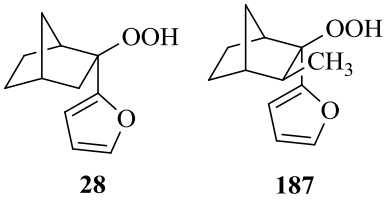
Scheme 1.85

Enantiopure chiral camphor derived furyl hydroperoxides, which obviate the need to use a chiral auxiliary in the oxidation, have also been shown to promote the kinetic resolution of sulfoxides.[65] For example, the enantiopure chiral camphor derived furyl hydroperoxide **186** was found to catalyse kinetic resolution with moderate enantioselectivity (Scheme 1.86).[67]

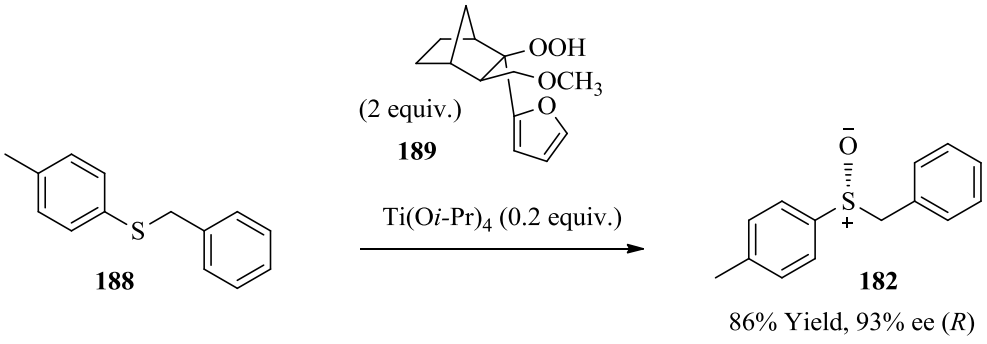


Scheme 1.86

Similar results were reported using the optically pure (*S*)-norcamphor derived tertiary furyl hydroperoxides **28** and **187**.[66,68]



Scettri recently used a functionalised (*S*)-norcamphor-based hydroperoxide/titanium(IV) isopropoxide system **189** in the asymmetric oxidation of a range of aryl benzyl and aryl alkyl sulfides. It was observed that the asymmetric oxidation was accompanied by complementary kinetic resolution (Scheme 1.87). [271]



Scheme 1.87

Adam *et al.* found that titanium mediated asymmetric sulfide oxidation using optically active hydroperoxides as oxidants, was accompanied by the kinetic resolution of the sulfoxide product.[58] The optimum hydroperoxide was found to be (*S*)-1-phenylethyl hydroperoxide **23**. It was proposed that the enantioselectivity is most likely due to steric effects, as shown in Figure 1.9, steric hindrance in complex **190a** between the hydroperoxide and the aromatic group of the *S* sulfoxide would be expected, whereas in complex **190b** less steric hindrance would be expected, hence preferential oxidation of the *R* sulfoxide to the sulfone over the *S* sulfoxide occurs. When the solvent used is *iso*-propanol, which can coordinate to the titanium centre, no kinetic resolution occurs, supporting Adam's proposal.

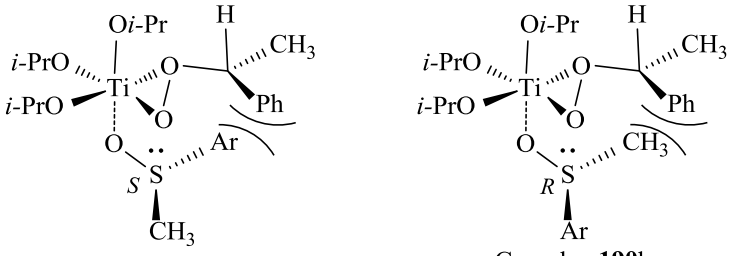
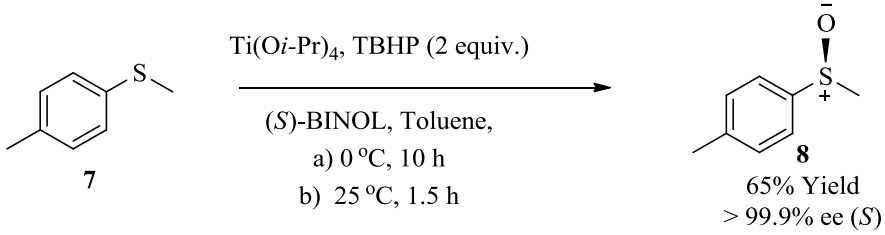


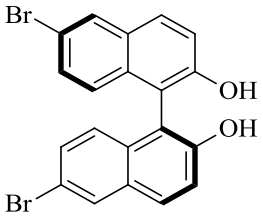
Figure 1.9

Chan *et al.* developed a one pot tandem catalytic oxidation and kinetic resolution process for the enantioselective preparation of sulfoxides.[272] Using conditions slightly different to those used by Uemura, sulfoxides in high yield and good enantiopurity were obtained. The key difference between the Uemura method and this method was that the oxidant (TBHP) was in a decane solution and not an aqueous solution, affording greater control over the water content of the reaction. The oxidation conditions involved temperature control with the asymmetric oxidation step taking place at 0 ^{o}C and the subsequent kinetic resolution step at 25 ^{o}C. The best result was obtained oxidising *para*-tolyl methyl sulfide **8** (Scheme 1.88).



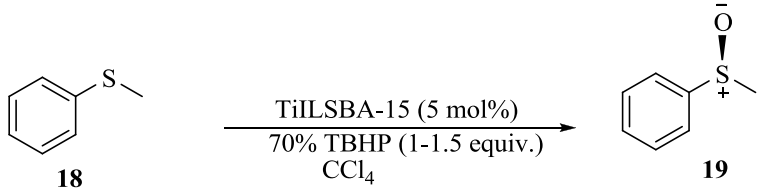
Scheme 1.88

Use of the ligand (*S*)-6,6-dibromobinaphthol **191** was also investigated in this oxidation method and it was found that while enantioselectivity dropped, the rate of sulfur oxidation increased, see section 1.2.1.2.



191

Sahoo *et al*. immobilised a chiral titanium-binol complex onto an ionic liquid modified SBA-15 and prepared a variety of enantiopure aryl methyl sulfoxides with complementary kinetic resolution.[84] When the oxidation was carried out in the presence of 1 equivalent of TBHP, the sulfoxide **19** of thioanisole **18** was obtained in 85% yield and 75% ee after 10 hours. Another 0.5 equivalents of TBHP was then added and the oxidation was monitored for another 10 hours producing sulfoxide in 59% yield and 99% ee. (Scheme 1.89).[84]

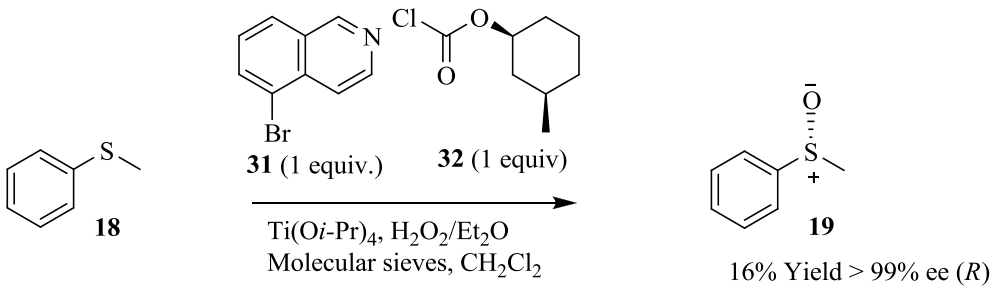


18 **19**

Rxn. time (h)	Sulfoxide Yield (%)	ee (%)	Sulfone Yield
10	85	75	0
16	65	93	20
20	59	99	30

Scheme 1.89

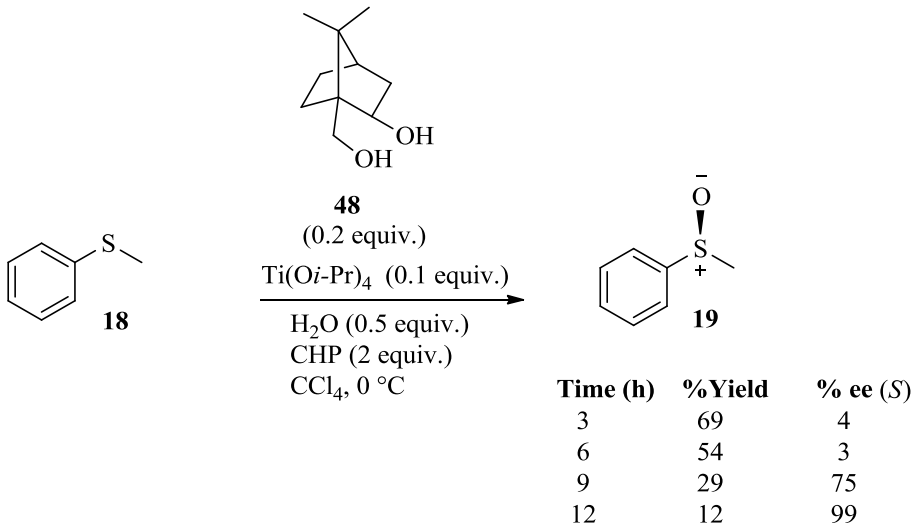
Liebscher *et al.* reported that titanium mediated asymmetric sulfide oxidation, using chiral hydroperoxide moieties, was accompanied by complementary kinetic resolution (Scheme 1.90).[69] Using 1.1 equivalents of aqueous H_2O_2 the (*R*)-sulfoxide was obtained in a 55% yield and 23% ee with some over oxidation to the sulfone. However, the use of 3.3 equivalents of aqueous H_2O_2 produced the (*R*)-sulfoxide in a 16% yield and > 99% ee, with a large amount of over oxidation to the sulfone.



Scheme 1.90

Bryliakov and Talsi also observed kinetic resolution in titanium-salen catalysed asymmetric oxidation of sulfides. When the amount of oxidant (H_2O_2) was reduced to just one equivalent the selectivity increased but the enantioselectivity decreased. This indicated that the high enantioselectivity was attained through both asymmetric oxidation and subsequent kinetic resolution.[56]

Zeng *et al.* reported that the use of a 2,10-camphanediol **48** derived titanium complex, in the asymmetric oxidation of thioanisole **18**, was accompanied by complementary kinetic resolution (Scheme 1.91).[51]



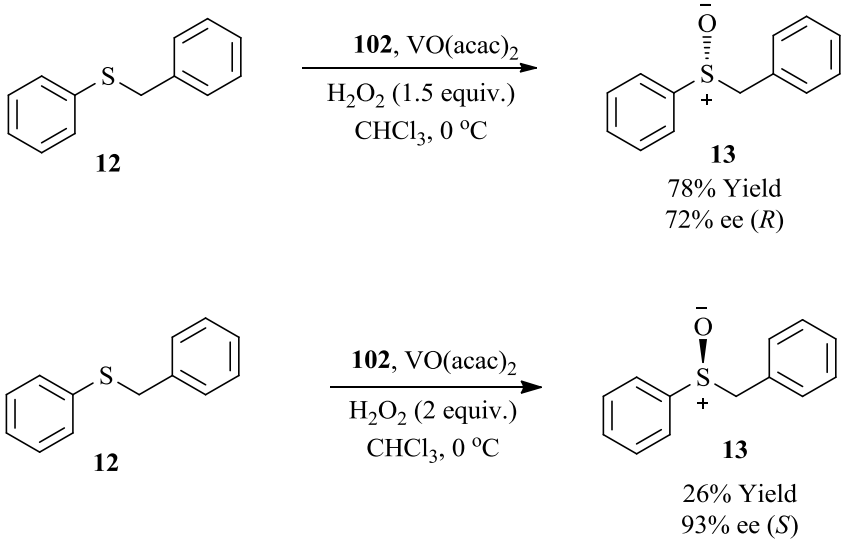
Time (h)	%Yield	% ee (*S*)
3	69	4
6	54	3
9	29	75
12	12	99

Scheme 1.91

When 2 equivalents of CHP were used the sulfoxide **19** of thioanisole **18** was obtained in 99% ee but in very poor yield due to the formation of a large amount of sulfone (Scheme 3.14).

Vanadium-catalysed oxidative kinetic resolution

Zhu reported a very efficient kinetic resolution method utilising a vanadium salen catalyst and hydrogen peroxide as the oxidant for the asymmetric oxidation of aryl methyl and aryl benzyl sulfides.[134] The results obtained using this system compared very favourably with other kinetic resolutions reported. In some cases, the kinetic resolution of the sulfoxide was more enantioselective than the asymm]etric sulfide oxidation (Scheme 1.92). The salen ligand **102** used was the same as that used in the asymmetric sulfide oxidation procedure, see section 1.2.1.2. Kinetic resolution was found to occur most efficiently using a larger amount of oxidant than that required in asymmetric sulfide oxidation.



Scheme 1.92

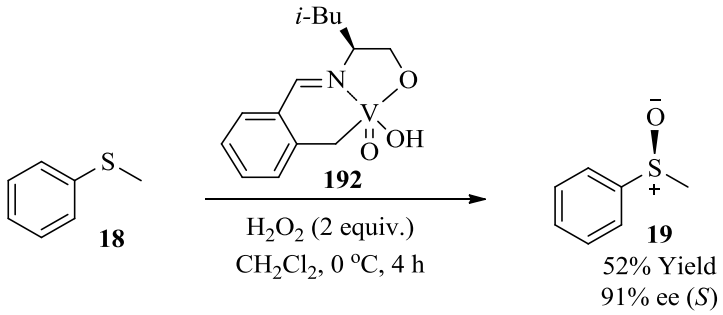
Unusually, the asymmetric sulfide oxidation and kinetic resolution exhibit divergent, hence uncomplementary, stereoselectivity, and any kinetic resolution of the sulfoxide product undermines the enantioselectivity of the asymmetric sulfide oxidation. However, given that the optimal temperature for the kinetic resolution is 25 °C and 0 °C for the asymmetric sulfide oxidation, any such effect is likely to be small.

The vanadium catalyst used in an asymmetric sulfide oxidation method reported by Bolm was initially thought not to promote kinetic resolution of sulfoxides.[94] In the original report of this oxidation, it was deduced that the high enantioselectivity of the oxidation was due

exclusively to asymmetric sulfide oxidation.[94] This was supported by the fact very little sulfone was formed during the oxidation and that the enantiopurity of the sulfoxide product did not change significantly during the reaction. Had kinetic resolution been occurring, it would be expected that enantiopurity of the sulfoxide would decrease or increase relative to increasing sulfone formation. Subsequent reports reinforced the belief that kinetic resolution did not occur using this oxidation method as despite extensive investigation, kinetic resolution was not reported.[86] The existence of the aqueous soluble achiral diperoxovanadium oxidising species, **103**, which was possibly capable of oxidising sulfoxides to sulfones would have explained the formation of small amounts of sulfone during the reaction.

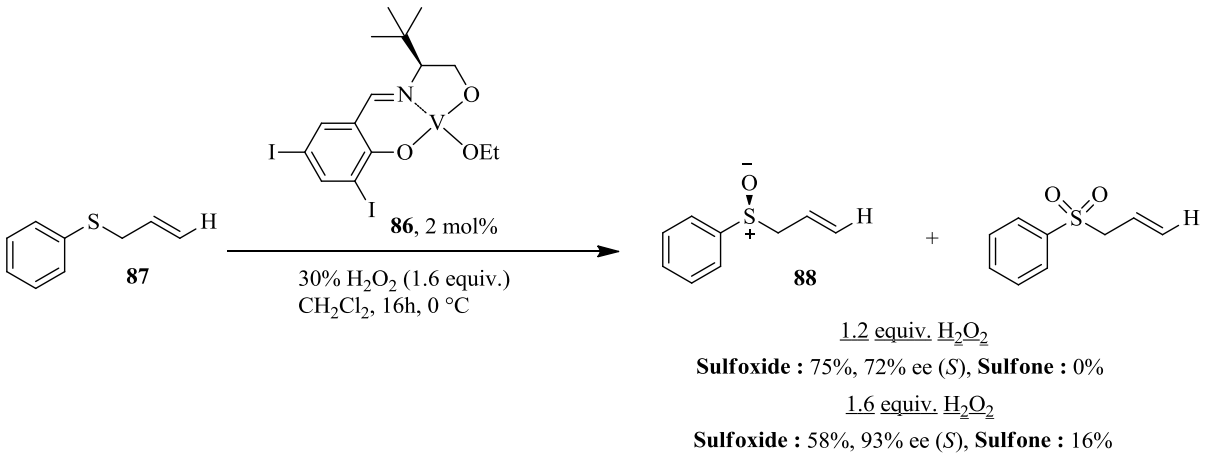
Zeng *et al.* was first to report kinetic resolution using this methodology.[121] Zeng cited considerable sulfone formation (10%) in the oxidation of methyl *para*-nitrophenyl sulfide **114** using the complexes reported by Katsuki, as an indicator of kinetic resolution possibly occuring.[100] The significance of the sulfone formation was not commented on by Katsuki. The fact that Bolm reported significant sulfone formation in a similar iron-catalysed oxidation coupled with high enantioselectivity that may have been due to kinetic resolution, further supported Zeng's suggestion that kinetic resolution could occur during this vanadium-catalysed oxidation.[105]

To establish whether kinetic resolution was taking place Zeng investigated the effects of adding more that one equivalent of the oxidant to the reaction.[121] Zeng used preformed catalyst in this investigation, which performed better than *in situ* generated catalyst.[121] As more oxidant was added, sulfone formation increased and the enantiopurity of the sulfoxide increased, which was attributed to kinetic resolution. The oxidation of the sulfide was modified so that asymmetric sulfide oxidation and concomitant kinetic resolution could take place. The conditions in Scheme 1.93 were found to be the optimum conditions for the oxidation of thioanisole **18**.



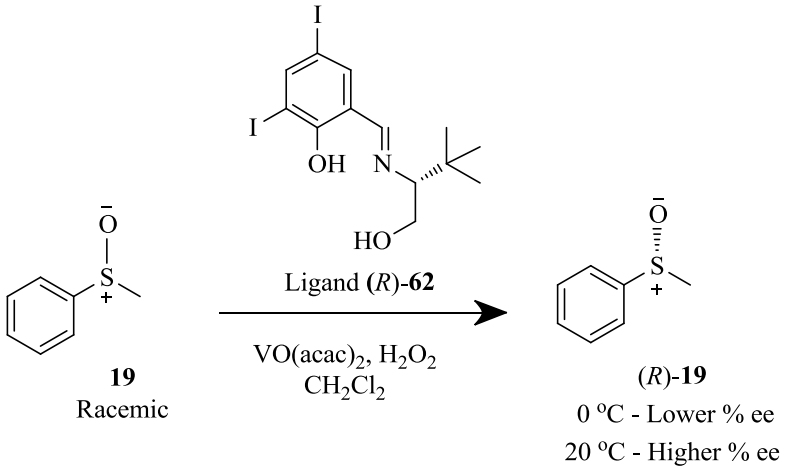
Scheme 1.93

Zeng recently reported kinetic resolution in the vanadium-catalysed oxidation of allyl phenyl sulfide (Scheme 1.94).[123]



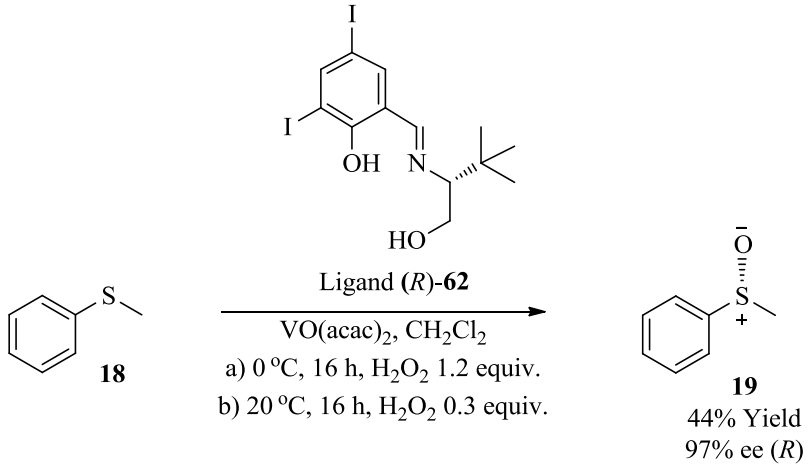
Scheme 1.94

At the same time as Zeng's original paper, Jackson independently reported kinetic resolution using this method.[127] An initial investigation using racemic sulfoxide **19** as substrate under the conditions in Scheme 1.95, yielded only limited amounts of sulfone, indicating that kinetic resolution was not a significant factor. Repeating the reaction at RT (20 ^{o}C) resulted in considerable kinetic resolution being observed.



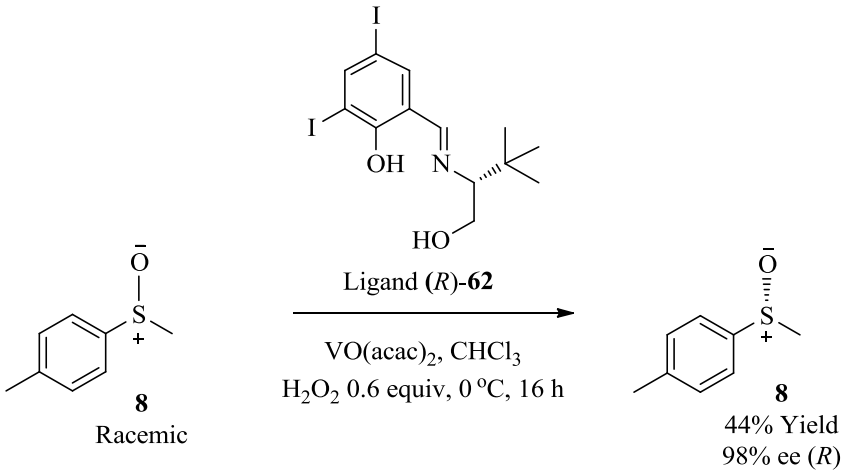
Scheme 1.95

Arising out of these observations, a tandem catalytic approach to the oxidative preparation of enantioenriched sulfoxides was developed (Scheme 1.96). This tandem approach was similar to that used by Chan in a titanium-catalysed oxidation.[272]



Scheme 1.96

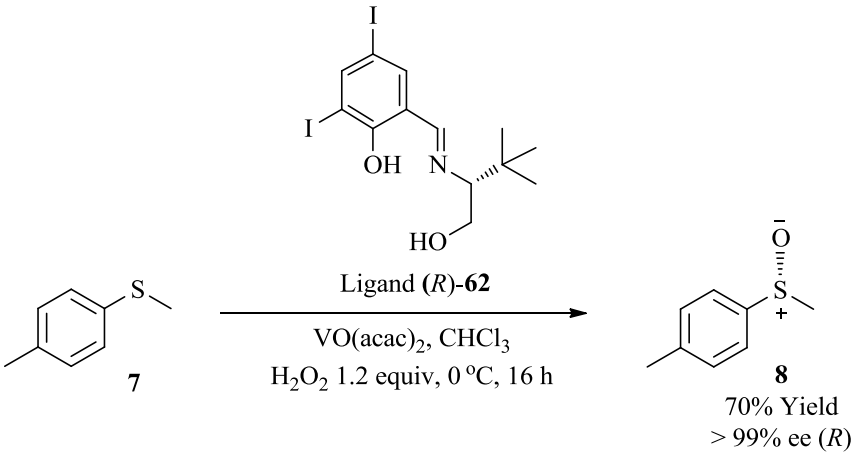
Results obtained by Ellman[96,97] and Zhu[134] employing vanadium catalysts in asymmetric oxidation indicated that chloroform was a good solvent for asymmetric sulfide oxidations. Jackson reported that kinetic resolution was enhanced carrying out the reaction in chloroform rather than dichloromethane at 20 °C and kinetic resolution was improved even further by carrying out the reaction in chloroform at 0 °C (Scheme 1.97).[127]



Scheme 1.97

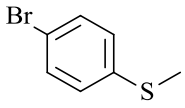
Considering the maximum possible yield is 50%, the 44% yield is exceptional, indicating the high efficiency of the kinetic resolution. Both Ellman and Katsuki carried out asymmetric sulfide oxidations using this catalyst and chloroform as the solvent, in both cases the optimum reaction temperature was 0 °C.[96,97,100] Jackson proposed that carrying out both the asymmetric sulfide oxidation and subsequent kinetic resolution in chloroform at 0 °C would be a very efficient route for the enantioselective preparation of sulfoxides. This proved to be

the case, with a variety of aryl alkyl sulfoxides prepared in good yield and high enantiopurity (Scheme 1.98).[127]



Scheme 1.98

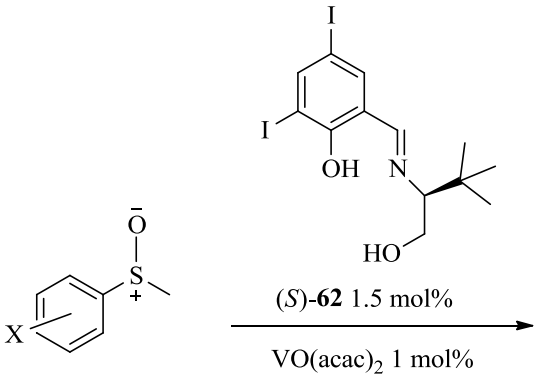
This has been undertaken on a large-scale (60 mmol), with 48 hour reaction time. Using *para*-bromophenyl methyl sulfide **193** and **7** as substrates, gave slightly lower enantioselectivity than the small-scale reactions, though still very high. Recrystallisation of the product yielded the sulfoxides in high yield effectively enantiopure (> 99% ee).



193

Maguire *et al.* reported kinetic resolution in vanadium-catalysed asymmetric oxidation of aryl benzyl sulfides.[107,108] A number of ligands were used in these oxidations with ligand **62** producing the best results. Excellent enantioselectivities were obtained (typically 91-99% ee) albeit in moderate yields. The kinetic resolution experiments produced the best results when carried out at RT. Carrying out the reaction at either higher or lower temperatures (temperature range investigated -20 °C to +30 °C) resulted in a decrease in enantiopurity.

Jackson reported the oxidative kinetic resolution of alkyl aryl sulfoxides using a combination of $VO(acac)_2$ and Schiff base ligand **62** in toluene.[273] Jackson found that most substrates gave almost racemic products at RT but at elevated temperatures (45 °C) high enantioselectivities were obtained (Scheme 1.99).



Sulfoxide X	Temp.(° C)	SX:SF	% ee (*S*)
45 4-Cl	22	55:45	5
45 4-Cl	45	44:56	78
8 4-Me	22	48:52	3
8 4-Me	45	41:59	79

Scheme 1.99

Manganese-catalysed oxidative kinetic resolution

The manganese salen catalyst used by Katsuki in asymmetric sulfide oxidation was also found to catalyse kinetic resolution in the oxidation of sulfoxides (section 1.2.1.4).[146] However, the resolution was inefficient, with high enantiopurity only being observed when the sulfoxide had been oxidised almost entirely to the sulfone.

Enantioselective aerobic asymmetric oxidation of sulfides using pivalaldehyde in the presence of a catalytic amount of optically active *β*-oxo aldiminatomanganese(III) complexes was reported by Nagata.[151,152] Asymmetric sulfide oxidation was accompanied by kinetic resolution of the sulfoxide product, which enhanced the overall enantioselectivity of the oxidation.

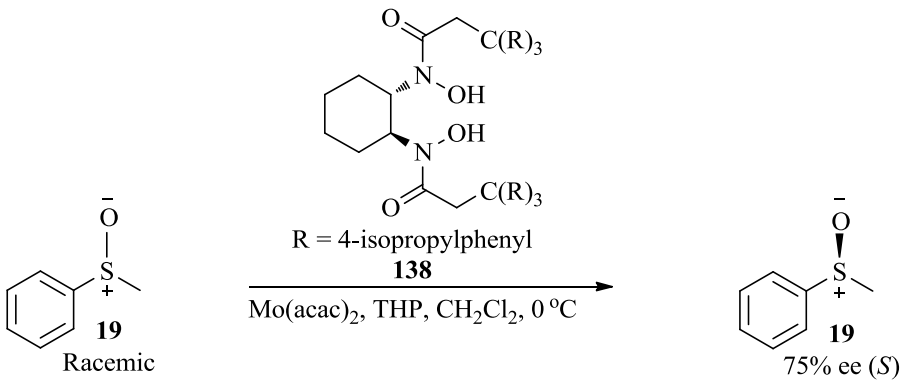
Tungsten-catalysed oxidative kinetic resolution

Similar to Zhu's vanadium salen catalyst, Thakur and Sudalai's tungsten cinchona alkaloid catalyst, see section 1.2.1.7, was a more effective catalyst for the kinetic resolution of sulfoxides than for asymmetric sulfide oxidation.[164] The conditions used for the kinetic resolution were identical to those used for the asymmetric sulfide oxidation with the notable exception of temperature. Like many of the oxidative kinetic resolution methods discussed here the optimal temperature was 25 ^{o}C. The highest enantioselectivity was observed for the

kinetic resolution of racemic *para*-tolyl benzyl sulfoxide **182** which was obtained in 25% yield and 9 % ee.

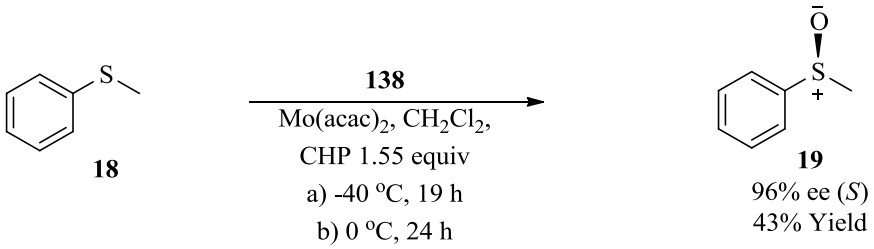
Molybdenum-catalysed oxidative kinetic resolution

Molybdenum-catalysed asymmetric sulfide oxidation reported by Basak was accompanied by kinetic resolution of the sulfoxide product (section 1.2.1.10).[170] The effect of the kinetic resolution was complementary to that of the asymmetric sulfide oxidation. Using racemic sulfoxide as the substrate under the same conditions as the asymmetric sulfide oxidation resulted in the isolation of enantioenriched sulfoxide (Scheme 1.100). Kinetic resolution also occurred efficiently when CHP was used as the oxidising agent.



Scheme 1.100

Using asymmetric sulfide oxidation in combination with kinetic resolution resulted in the isolation of sulfoxides in good yield and high enantiopurity. Again the results obtained using CHP as the oxidant were better than those obtained using THP (Scheme 3.23).



Scheme 1.101

Zirconium-catalysed sulfoxide oxidation

Bonchio *et al.* reported in 1999 a highly stereoselective sulfide oxidation using a chiral zirconium(IV) catalyst.[166,167] A significant amount of the sulfone formed during the

oxidation. Using less oxidant (CHP) overcomes this problem but the resulting sulfoxide is effectively racemic. This, while not commented on by Bonchio, would seem to indicate that kinetic resolution of the sulfoxide was possibly taking place. The fact that using less oxidant resulted in only racemic sulfoxide being formed would suggest that the kinetic resolution, if it is taking place, is more stereoselective than the asymmetric sulfide oxidation.

1.3.2 Non-oxidative kinetic resolution

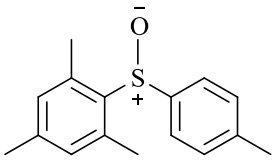
Besides enantioselective oxidation to the sulfone, it is possible to carry out kinetic resolution using other types of methodology.

1.3.2.1 Chemical methods

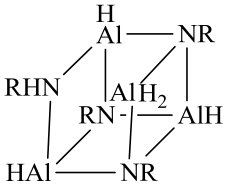
Another approach to enantiopure sulfoxides involves the preferential reduction of one of the sulfoxide enantiomers to the sulfide, leaving the other enantiomer enriched. Mikołajczyk, using *ortho*-ethyl phosphonothioic acid or *ortho*-*iso*-propyl methylphosphonothioic acid as the reducing agent, prepared enantioenriched sulfoxides from racemic sulfoxide.[274] The enantioselectivity of the reduction was moderate with the highest enantioselectivity being observed in the reduction of *n*-butyl methyl sulfoxides with the remaining sulfoxide having 6% ee. The reducing reagent used was *ortho*-*iso*-propyl methylphosphonothioic acid. Mikołajczyk also reported the asymmetric reduction of chiral sulfoxides by optically active lithium aluminium hydride complexes with alcohols, but again low enantiopurities were obtained.[275]

Drabowicz reported the partial kinetic resolution of racemic sulfoxides by reduction using a formamidinesulfinic acid-optically active amine reducing agent. Drabowicz noted that steric hindrance influenced the optical purity of the resolved sulfoxides but only modest enantiopurities were achieved overall.[276]

Montanari reported very high enantioselectivity in the reduction of mesityl *para*-tolyl sulfoxide **194** using chiral poly[*N*-(1-phenylethyl)iminoalanes] obtaining **194** in 78% ee in a reasonable yield.[277] It was found that the open cage tetramer of the chiral poly[*N*-(1-phenylethyl)iminoalanes] **195** was responsible for the enantioselectivity of the reduction.

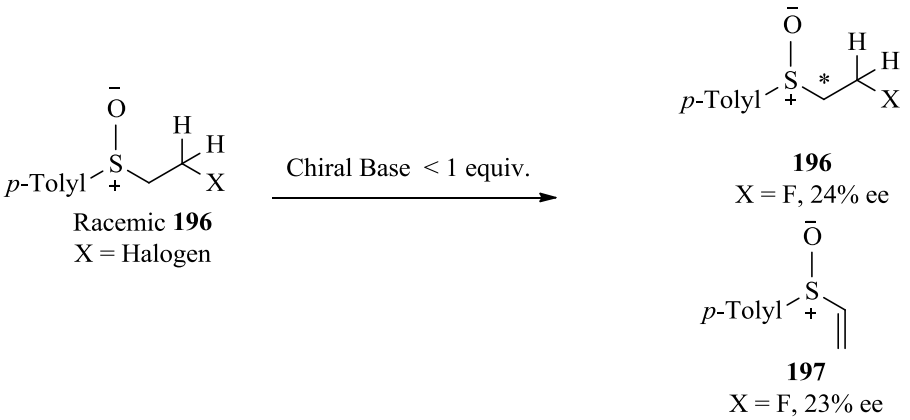


194



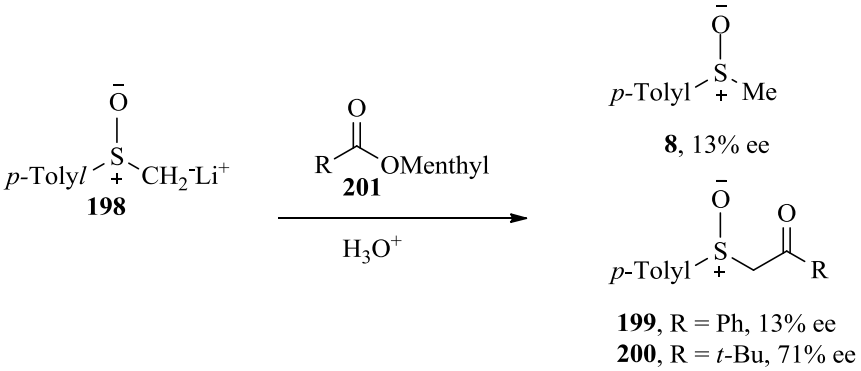
195
R = PhCHMe

Naso resolved sulfoxides using a selective elimination reaction.[278] Racemic β-halosulfoxides **196** were reacted with a chiral base to form a vinyl sulfoxide **197**. When the sulfoxide was reacted with insufficient base the remaining sulfoxide was enantioenriched, indicating one sulfoxide enantiomer was less reactive than the other. Highest enantioenrichment was observed when the *para*-tolyl β-fluoroethyl sulfoxide was used as substrate. The remaining unreacted **196** had 24% ee while the product **197** had 23% ee (Scheme 1.102). The configuration of the sulfoxide is dependent upon the base used.



Scheme 1.102

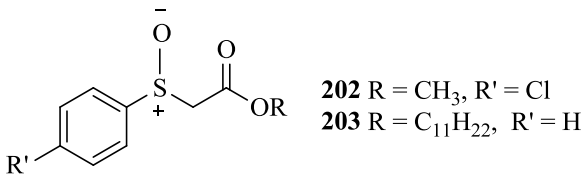
Similar methodology was used to prepare enantioenriched sulfoxide.[279] Reacting the α-sulfinyl carbanion **198** with a menthyl ester **201**, resulted in the formation of enantioenriched β-ketosulfoxide and the remaining unreacted **8** was also enantioenriched (Scheme 1.103).



Scheme 1.103

Conditions were optimised and it was found that the reaction was most efficient when 0.5 equivalents of **201** was used. The results obtained when R = methyl were very poor with very little enantioselectivity in the reaction. When R = *tert*-butyl, there was a significant improvement in enantioselectivity with the product **200** having 71% ee. The highest reported enantiopurity for unreacted starting material was 13% ee when R = phenyl. This methodology was developed from a method used to prepare bissulfoxides, where a menthyl sulfinate ester was used instead of a menthyl carboxylate.[280]

Ohta reported very high enantioselectivity in an enzymatic kinetic resolution.[281] Hydrolysing methyl benzenesulfinylacetate using *Corynebacterium equi*, it was noticed that there was a substantial drop in the rate of the reaction once half the sulfoxide was hydrolysed. This was attributed to the fact that one sulfoxide enantiomer was preferentially hydrolysed by the bacteria. The sulfoxides were recovered in a very high yield for a kinetic resolution reaction, between 30 - 43% with the maximum possible yield being 50%. Enantioselectivity was excellent with **202** obtained in 97% ee. However, this method seems to be limited to certain substrates since when the lipophilic ester **203** was the substrate, enantioselectivity observed was either poor or absent.



Sulfoxide enantiomers effectively do not interconvert at RT; they only do so at an appreciable rate at high temperatures. Pirkle observed that heating sulfoxides at low

concentrations with cholesteryl esters in degassed sealed vessels resulted in a change in the ratio of sulfoxide enantiomers present.[282] The change in the ratio of enantiomers was very small, for example, 1-naphthyl methyl sulfoxide **75** was obtained in 9% ee, using cholesteryl *para*-nitrobenzoate. As the sulfoxides isolated are not obtained in quantitative yield, it is unclear whether the enantioenrichment is due to enantiomer interconversion or otherwise.[283]

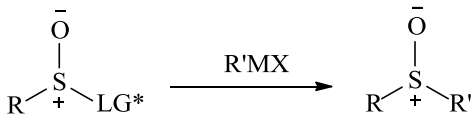
1.3.2.2 Biological methods

While enantioselective oxidation of sulfides to sulfoxides using biological approaches has been explored extensively, see section 1.2.4, the reverse reaction involving the asymmetric reduction of racemic sulfoxides has received much less attention. There have been a number of reports of DMSO reductase enzymes, which can effect kinetic resolution of racemic sulfoxides/substrates.[284-286] Sulfoxide **8** has been obtained with enantioselectivities from 32 to > 98% ee using a range of biocatalysts in asymmetric reductions of racemic **8**.[287]

1.4 Nucleophilic displacement

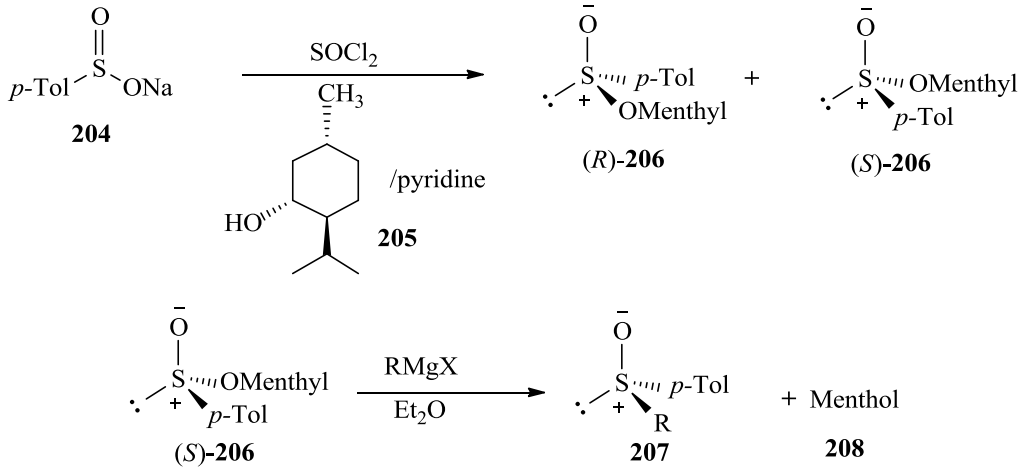
Nucleophilic displacement at the sulfur atom is one of the most popular and efficient methods for the preparation of enantiopure sulfoxides.[10] It was first reported by Andersen[288] and the methodology used in this first nucleophilic displacement is now commonly referred to as the Andersen method.

1.4.1 Single nucleophilic substitution of an enantiomerically pure chiral precursor



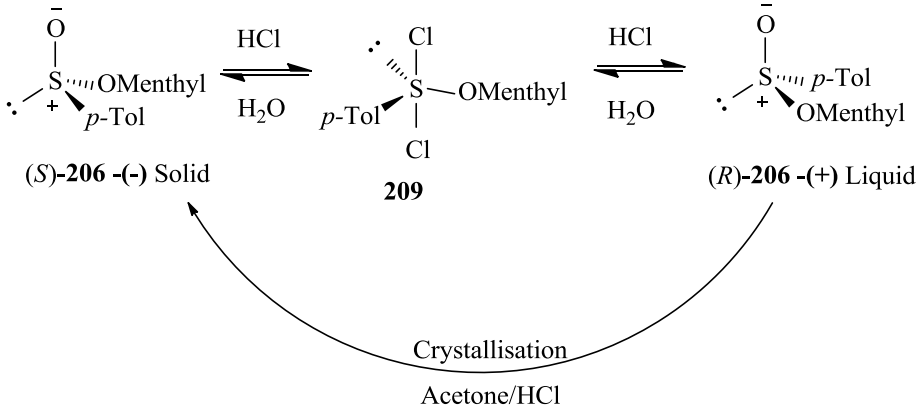
Scheme 1.104

The Andersen method for the preparation of enantiopure sulfoxides employs the use of a enantiomerically pure menthyl sulfinate ester. Nucleophilic attack by a Grignard reagent upon diastereomerically pure sulfinate displaces the O-menthyl leaving group to form the enantiopure sulfoxide in good yield. The reaction proceeds with complete inversion of configuration at sulfur (Scheme 1.104 and 1.105).[289-292]



Scheme 1.105

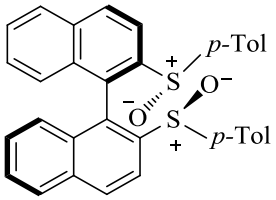
The procedure described above is the method of choice for the large-scale preparation of non-racemic sulfoxides. Both diastereomers of **206** are commercially available. A significant drawback with this procedure is the preparation of the menthyl sulfinate esters. The sulfinate diastereomers require multiple recrystallisations to achieve the high degree of diastereomeric purity necessary for asymmetric synthesis of sulfoxides using the Andersen procedure. Utilising an equilibration technique discovered by Herbrandson (Scheme 1.106), which substantially increased the yields of (*S*)-**206**, resolved this problem to an extent.[293] The Andersen method is suitable for the preparation of alkyl aryl or diaryl sulfoxides, however dialkyl sulfoxides could not be produced using this method, as the required menthyl sulfinate could not be prepared in enantiomerically pure form at the sulfur. Investigations by Drabowicz *et al.* established that benzene is the best solvent for the Andersen procedure.[294]



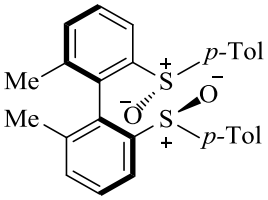
Scheme 1.106

Recently, Dorta *et al.* prepared four stereoisomers of *bis*-sulfoxide binaphthyl or biphenyl derivatives **210** and **211** in 34-60% yield.[295] These new chiral sulfoxide ligands were

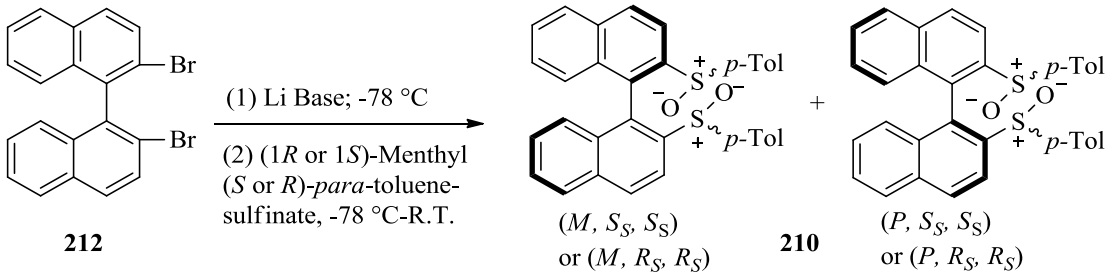
prepared from racemic 2,2'-dibromo substituted precursors using either (+) or (-)-menthyl *para*-toluenesulfinate (Scheme 1.107). The resulting diastereomeric pairs were separated chromatographically.[295,296]



(M, S_S, S_S)-**210**



(P, S_S, S_S,)-**211**



212

(M, S_S, S_S) or (M, R_S, R_S)

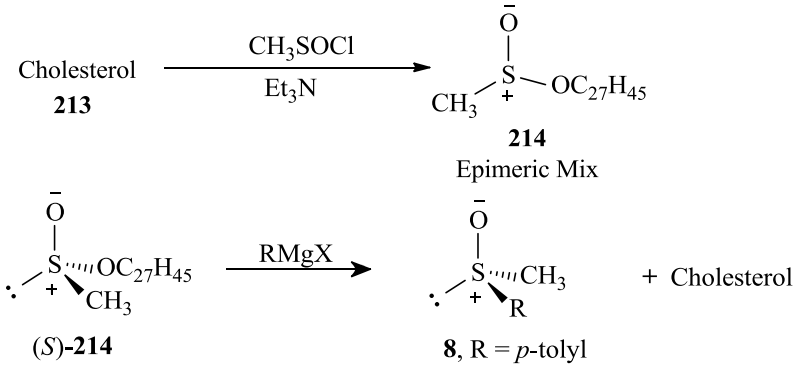
210

(P, S_S, S_S) or (P, R_S, R_S)

Scheme 1.107

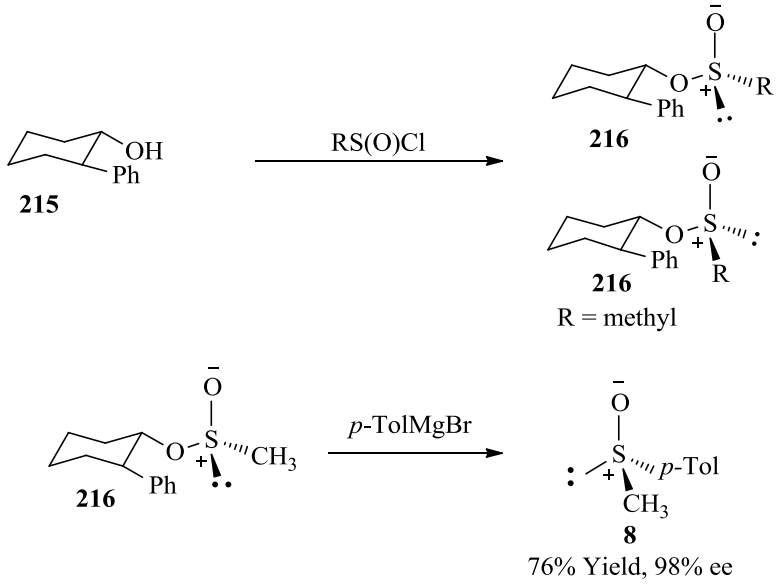
Since the original Andersen procedure was published in the 1960s, a number of groups have proposed adaptations to the procedure. Most of this research has focused on the development of new sulfinate esters.[10]

Andersen *et al.* published a procedure for the synthesis of pure methyl alkyl sulfoxides using cholesterol as the leaving group instead of menthol.[297] Using cholesterol allowed preparation of the epimeric mixture of enantiomerically pure methyl sulfinate esters **214** suitable for nucleophilic substitution (Scheme 1.108). Dialkyl sulfoxides with high enantiomeric purity were obtained, generally in excess of 80% ee, albeit with poor yields; typically less than 50%.



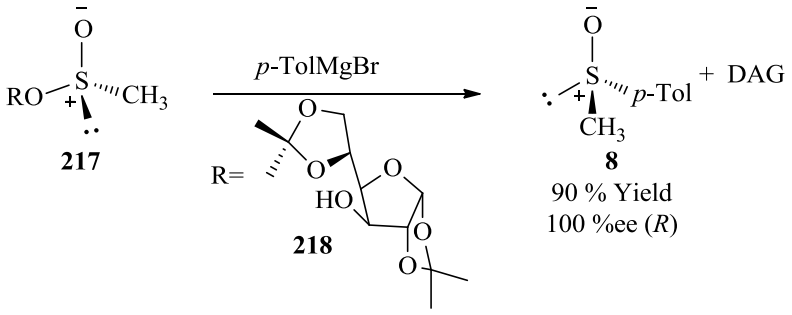
Scheme 1.108

Whitesell *et al.* investigated the use of *trans*-2-phenylcyclohexanol **215** as the leaving group in the sulfinate ester (Scheme 1.109).[298,299] Using **215** in the preparation of the sulfinate ester proved to be more practical than menthol, albeit at higher cost. The two cyclohexanol sulfinate diastereomers **216** formed could be separated by crystallisation or chromatography. Chromatography could not be used to separate the menthyl sulfinate diastereomers.



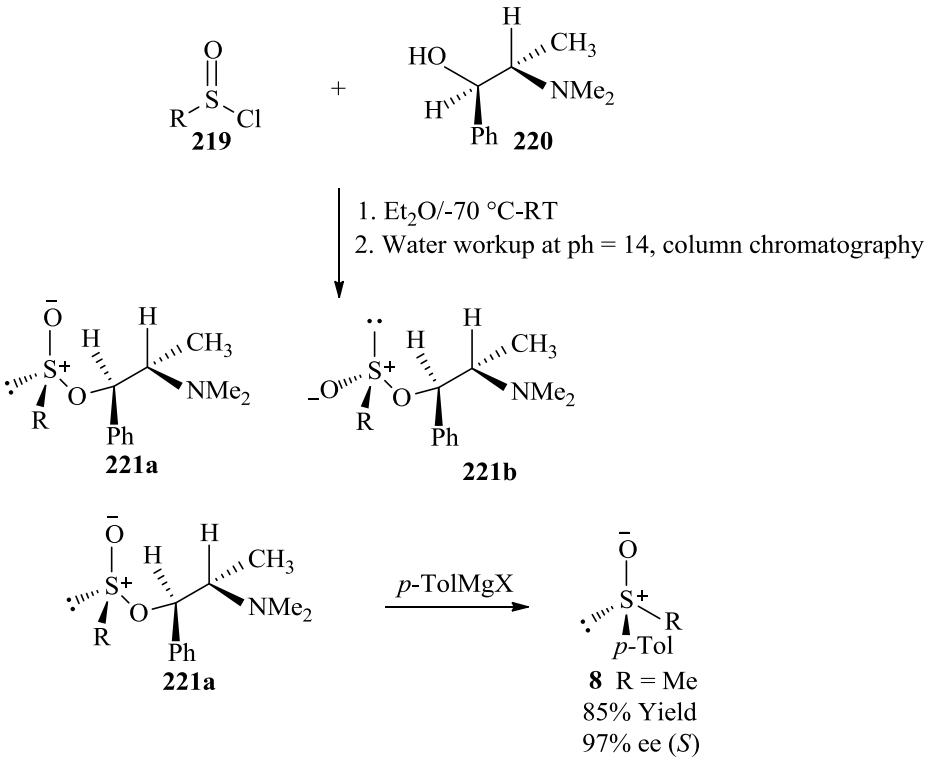
Scheme 1.109

Diacetone-D-glucose (DAG) **218** was also successfully used as an alternative to menthol in the preparation of the sulfinate ester **217**.[300-304] Using different bases in the preparation of the sulfinate, it was possible to obtain either of the two diastereomers of **217** with high diastereoselectivity (Scheme 1.110).



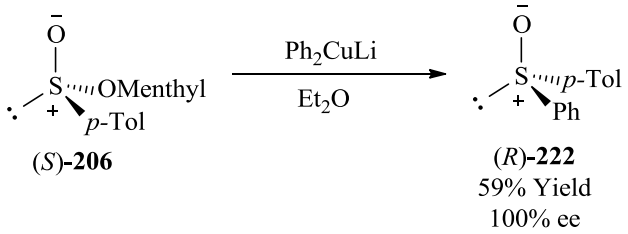
Scheme 1.110

In 1999, Drabowicz reported a method of asymmetric sulfoxide synthesis, which employed the amino alcohol *N*-methylephedrine **220** as the leaving group (Scheme 1.111).[305] The sulfinates **221a** and **221b** were prepared using **220** and could be separated using flash chromatography. High enantioselectivity was observed.



Scheme 1.111

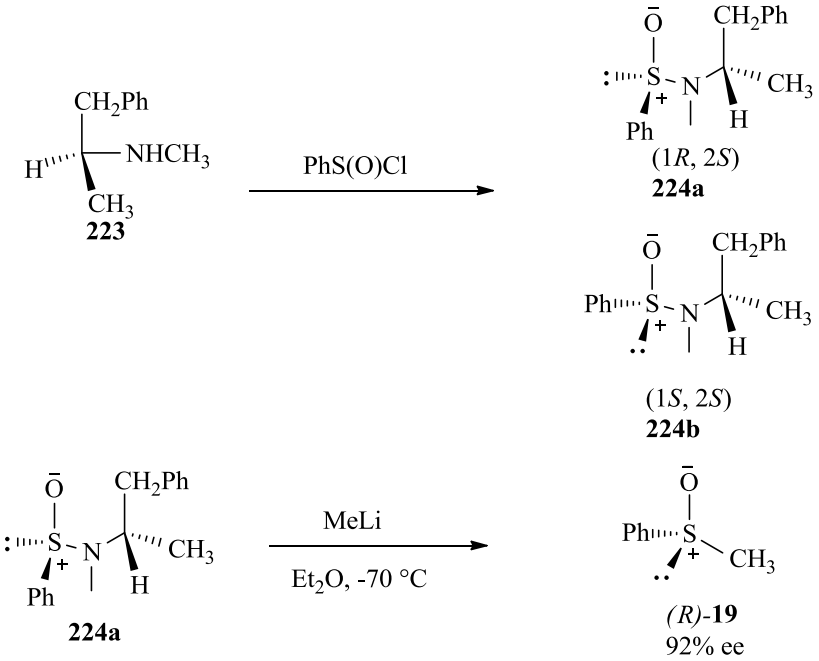
Harpp employed organocopper reagents instead of Grignard reagents using the Andersen procedure.[306] The sulfoxide **222** was obtained in 59% yield and 100% ee using this method (Scheme 1.112).



(*S*)-**206** (*R*)-**222** 59% Yield 100% ee

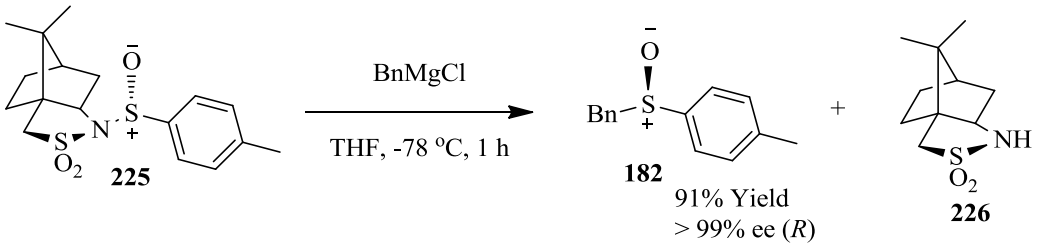
Scheme 1.112

Chiral sulfinamides have also been successfully used as the chiral auxiliaries in nucleophilic substitutions. Jacobus and Mislow reported that the reaction of benzenesulfinyl chloride with (*S*)-(+)-deoxyephredine **223** yielded a 3:1 mixture of sulfinamide diastereomers, **224a** and **224b**, which could be separated by fractional crystallisation (Scheme 1.113).[307] By reacting the appropriate diastereomer with methyl lithium, sulfoxides with up to 92% optical purity could be isolated. Attempts to form the sulfoxides using Grignard reagents instead of lithium reagents proved unsuccessful.



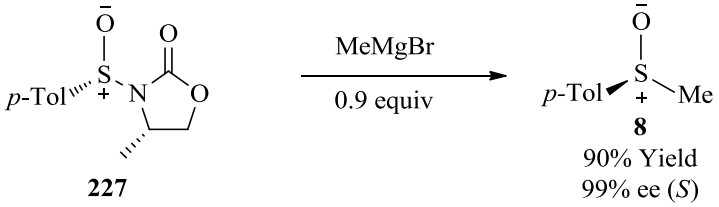
Scheme 1.113

N-Sulfinylsultam **225** has been successfully used by Oppolzer to prepare enantioenriched sulfoxides and sulfinimines.[308] **225** was formed through the 4-dimethylaminopyridine (DMAP) assisted sulfinylation of sultam. Treating **225** with an organometallic reagent in THF at low temperatures resulted in the formation of the sulfoxides, which were obtained in good yield and excellent enantiopurity (Scheme 1.114).



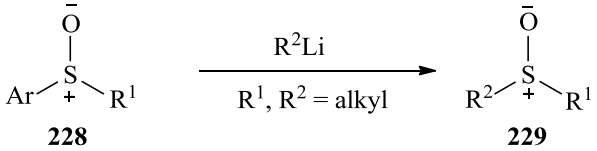
Scheme 1.114

Evans *et al.* used chiral *N*-sulfinyl oxazolidinones **227** in the preparation of enantiopure sulfoxides (Scheme 1.115). Here a number of dialkyl and alkyl aryl sulfoxides were synthesised with very high enantioselectivities.[309]



Scheme 1.115

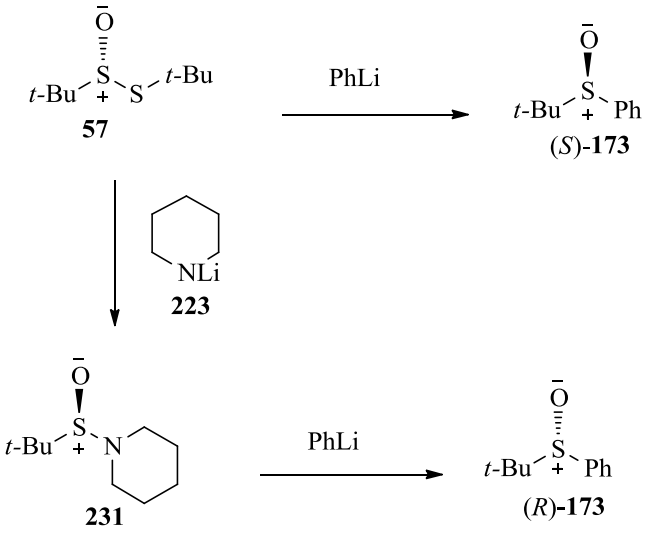
Sulfinate esters and sulfinamides are not the only chiral auxiliaries that have been successfully used in nucleophilic substitution reactions. Johnson reported a general method for the preparation of dialkyl sulfoxides, similar to that proposed by Andersen, with a sulfoxide as the chiral precursor.[310] Alkyllithium or alkylsodium reagents are used to displace an aryl group from the sulfoxide chiral precursor to produce the unsymmetrical enantiopure dialkyl sulfoxide (Scheme 1.116). The chiral sulfoxide precursor could be prepared using the Andersen synthesis.



Scheme 1.116

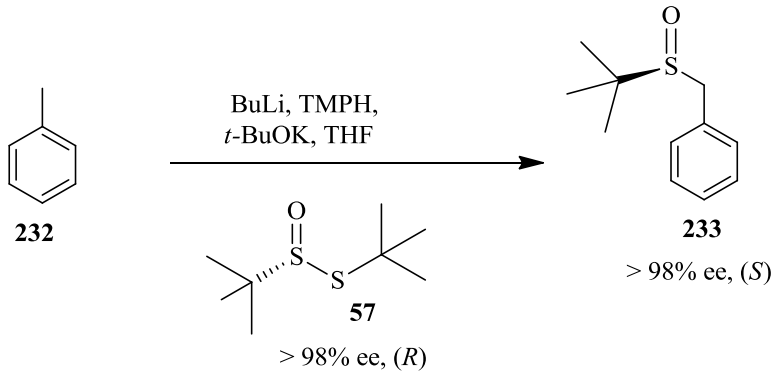
Ellman prepared a limited number of enantiopure *tert*-butyl sulfoxides using an enantiopure *tert*-butanesulfinate ester **57** as the chiral auxiliary.[97] Enantiopure **57** could be prepared by asymmetric sulfide oxidation of the disulfide. Treating **57** with an organolithium

reagent resulted in the formation of the sulfoxide with inversion of stereochemistry. Furthermore, by reacting **57** initially with lithiated piperidine, it was possible to obtain the other sulfoxide enantiomer. Other dialkyl sulfoxides were prepared using this method in good yield and high enantiopurity (Scheme 1.117). *tert*-Butanesulfinamides could also be prepared using this method.



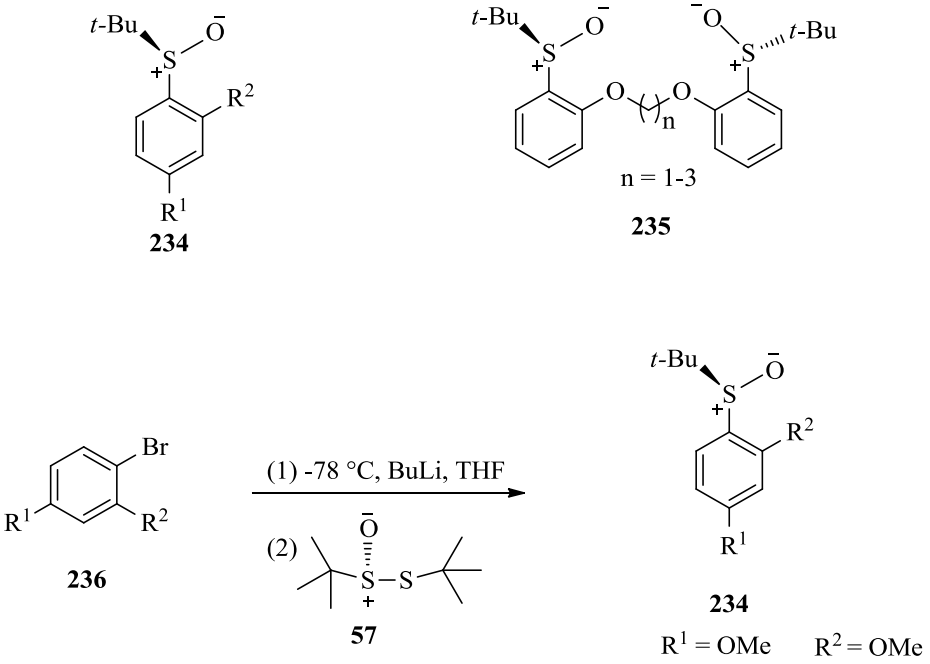
Scheme 1.117

Casey *et al.* synthesised a large variety of highly enantioselective benzyl *tert*-butyl sulfoxides by deprotonation of toluene derivatives, under basic conditions, and the *in situ* reaction of benzyllithium derivatives with *tert*-butyl *tert*-butanethiosulfinate (Scheme 1.118).[311]



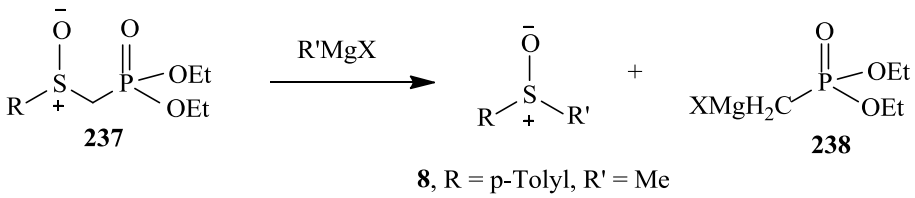
Scheme 1.118

Liao *et al.* synthesised a series of enantiomerically pure mono- and bis-aryl *tert*-butyl sulfoxides to promote the enantioselective allylation of aldehydes with allyltrichlorosilane. (*R*)-Thiosulfinate **57** was used for the synthesis of monomeric **234** and dimeric aryl *tert*-butyl sulfoxides **235** from the corresponding aryl bromides **236** in yields of 24-92% (Scheme 1.119).[312]



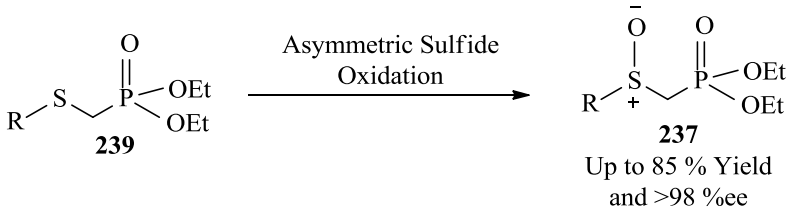
Scheme 1.119

Similar to Johnson's report,[310] work by Cardellicchio with chiral halovinyl sulfoxides and organometallic reagents confirmed that the formation of enantiopure sulfoxides through the displacement of a carbon leaving group was a practical route to sulfoxides.[313] Cardellicchio successfully prepared a variety of sulfoxides with very high enantiopurity through the displacement of methyl dimethylphosphonate using Grignard reagents (Scheme 1.120).[314]



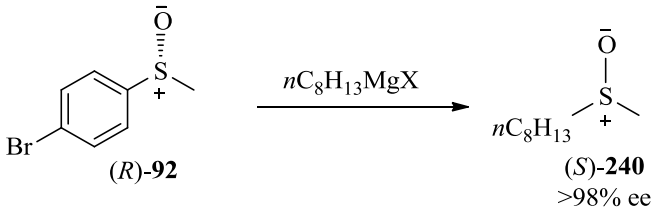
Scheme 1.120

Later investigations focused on preparing different enantiopure chiral auxiliaries for this route to sulfoxides.[315,316] Using a titanium mediated oxidation it was possible to prepare **237** in high enantiopurity from the corresponding sulfide **239** (Scheme 1.121).



Scheme 1.121

Similar to Johnson's report,[310] Cardellicchio prepared enantiopure sulfoxides through the displacement of the aryl group in appropriately substituted aryl methyl sulfoxides using organometallic reagents.[317] *para*-Bromophenyl methyl sulfoxide **92** was identified as the best sulfoxide precursor for this reaction. Enantiopure **92** could be prepared by asymmetric sulfide oxidation followed by recrystallisation. This method worked very well for the preparation of long chain alkyl methyl sulfoxides (Scheme 1.122).



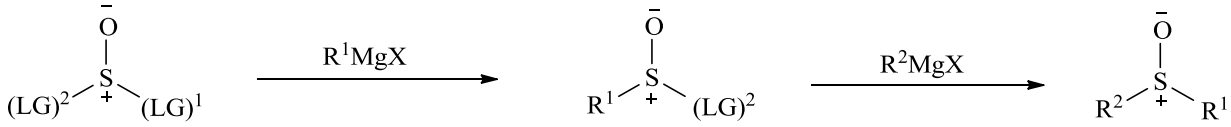
Scheme 1.122

A number of other research groups have reported the enantioselective preparation of sulfoxides through the displacement of carbon leaving groups from sulfinyl chiral auxiliaries.[318-320]

1.4.2 Double nucleophilic substitution of an enantiomerically pure sulfinyl precursor

The nucleophilic substitution methods previously discussed involve only one nucleophilic displacement. Using these methods means that the resulting sulfoxide will contain a substituent from the chiral precursor used. This limits the scope of this route to sulfoxides. This fundamental limitation has curtailed the widespread use of single nucleophilic substitution for the preparation of enantiopure sulfoxides. This limitation could be obviated if the chiral precursor could undergo two sequential nucleophilic displacement reactions to

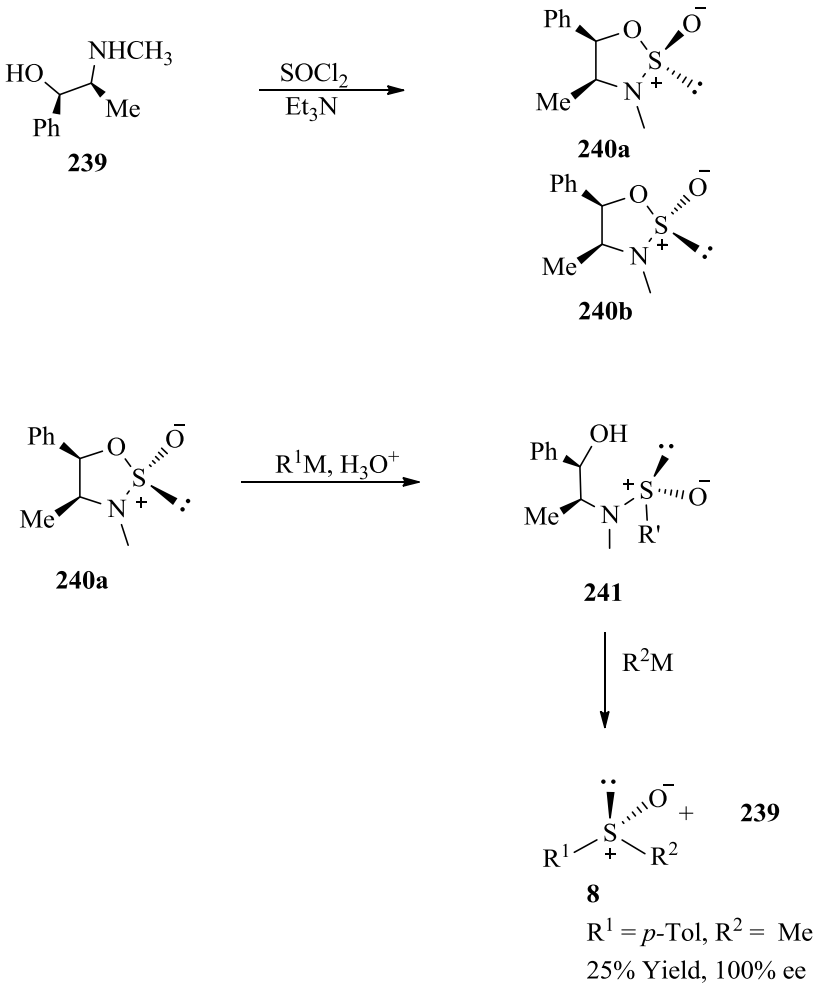
yield the desired sulfoxides in high enantioselectivity and yield. For this to occur the chiral precursor needs to possess two leaving groups of different leaving ability. Cyclic sulfites are the most commonly used chiral precursors that meet this criterion.



LG = carbionic leaving group

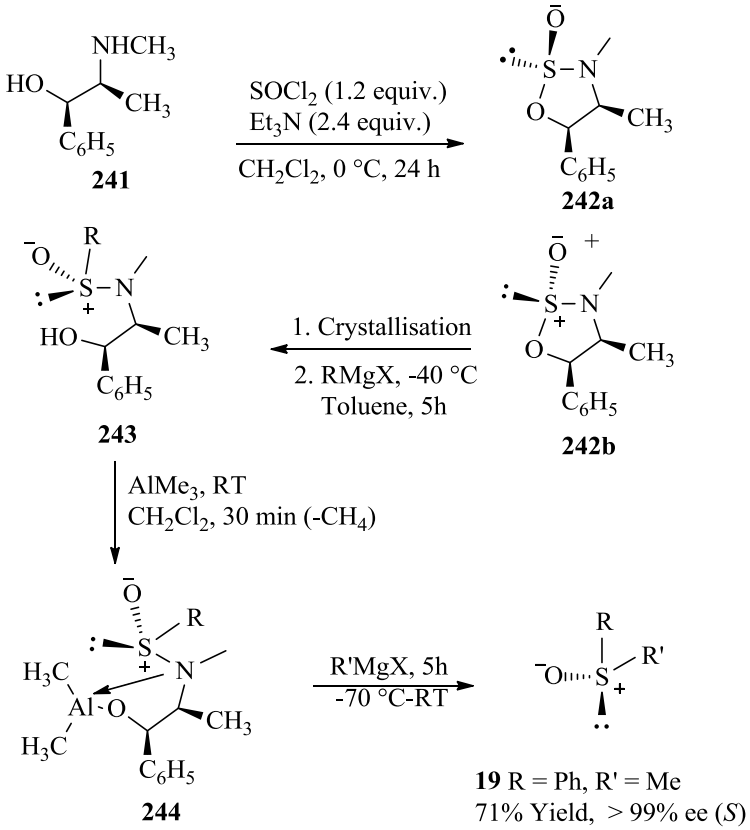
Scheme 1.123

Wudl and Lee were the first to develop a synthesis where the starting reagent possessed two groups of different leaving ability and underwent successive nucleophilic attack from two different nucleophiles (Scheme 1.124).[321,322] Here ephedrine **241** was reacted with thionyl chloride to form two diastereomers **242a** and **242b**, which could be separated. The appropriate diastereomer was reacted with an organometallic reagent to yield a chiral hydroxysulfinamide **241**, which underwent subsequent reaction with another organometallic reagent to yield ephedrine and the sulfoxide. High selectivity was observed when Grignard reagents were used for the final nucleophilic displacement, however low yields were reported. Using organolithium reagents, higher yields were reported but with lower selectivity due to racemisation occurring during the breaking of the S-N bond. The problem of the formation of symmetrical sulfoxides after the first nucleophilic displacement was overcome by the addition of a small amount of tetramethylethylenediamine (TMEDA). The best result obtained was 100% ee (*R*)-**8** in 25% yield.



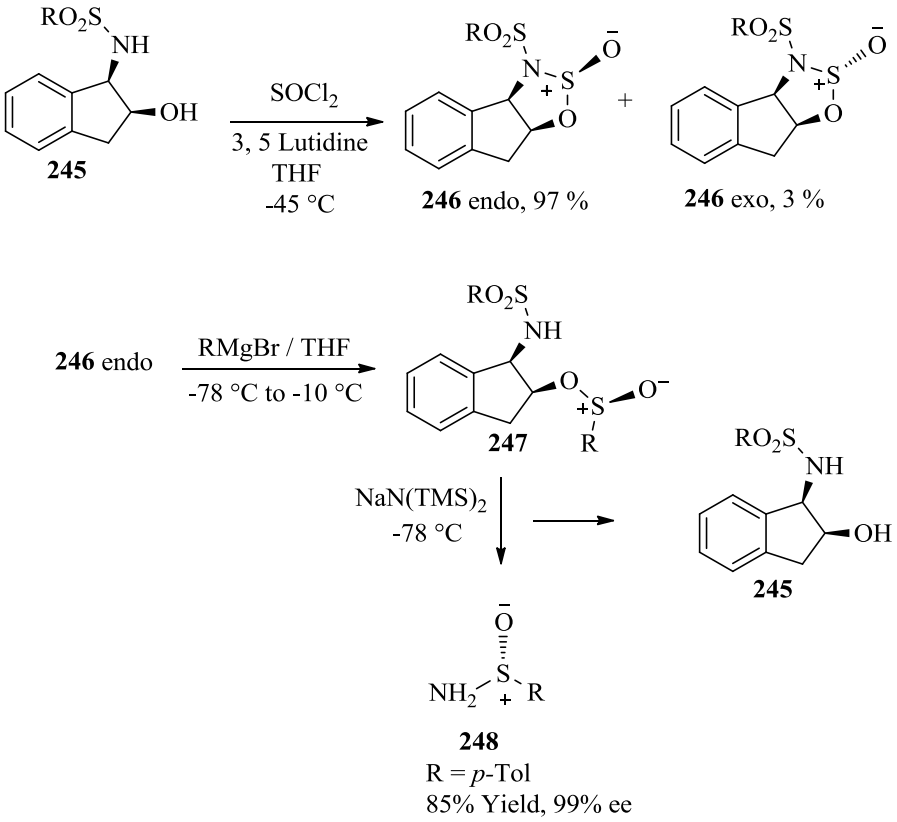
Scheme 1.124

Work by Snyder and Benson improved the method developed by Wudl and Lee.[323] Improvements were made in the preparation of the oxathiazolidine-*S*-oxide, **242a** and **242b**, which resulted in higher yields. The problems with selectivity and yield reported by Wudl and Lee when carrying out the second displacement were solved by the use of an additive. Addition of trimethylaluminium prior to the displacement reaction, resulted in improvements in both the yield and enantioselectivity of the reaction (Scheme 1.125). It was proposed that the intermediate **244** was formed in the presence of the trimethylaluminium, which facilitated the formation of the sulfoxide. The sulfoxide **19** of thioanisole **18** was prepared in a yield of 71% and >99% ee (*S*) while *iso*-propyl phenyl sulfoxide was also prepared in a yield of 82% and >99% ee (*S*) using this method. Both aryl alkyl and dialkyl sulfoxides were prepared using this method. Diaryl sulfoxides were not accessible using this method.



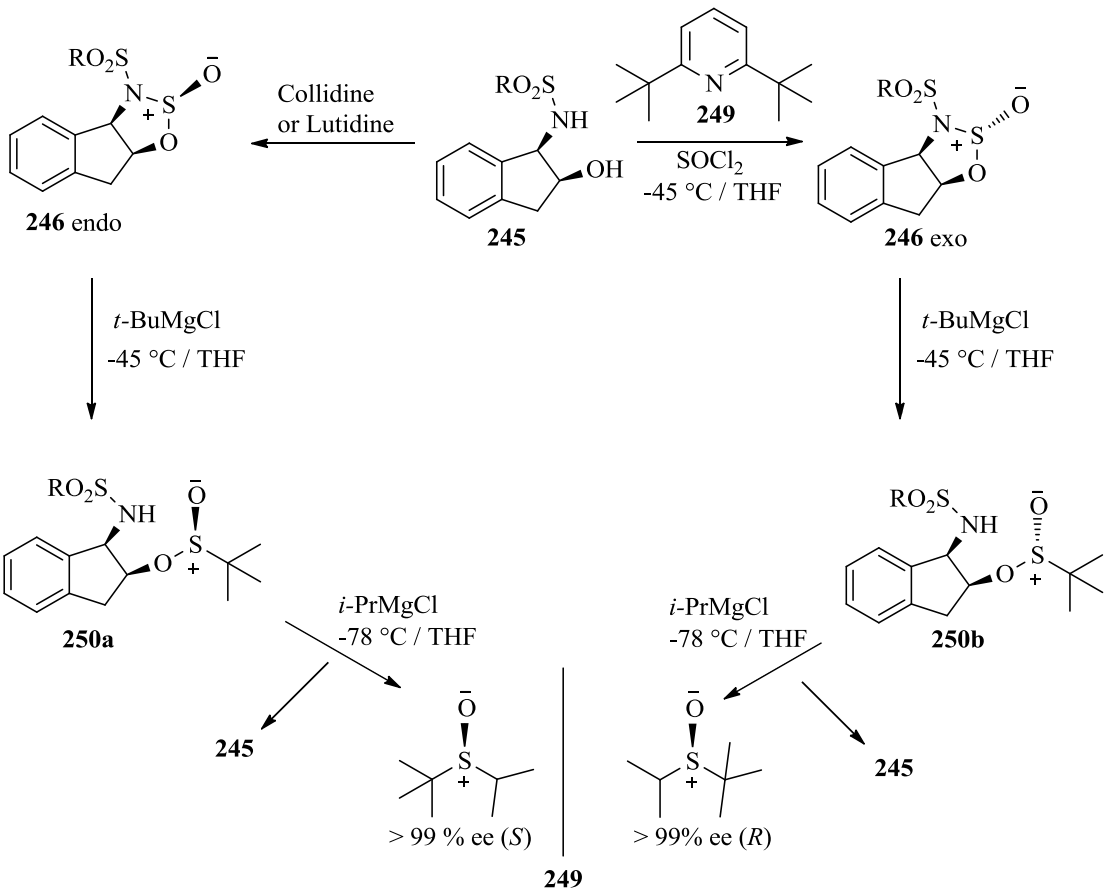
Scheme 1.125

Senanayake *et al.* further improved the Wudl and Lee method.[324] Ephedrine **241**, which had been used by Wudl and Lee was replaced by (1*R*, 2*S*)-(+)-*cis*-amino-2-indanol, **245**. Following the procedure outlined in (Scheme 1.126), high enantioselectivity and high yields were reported for the preparation of sulfinamides.



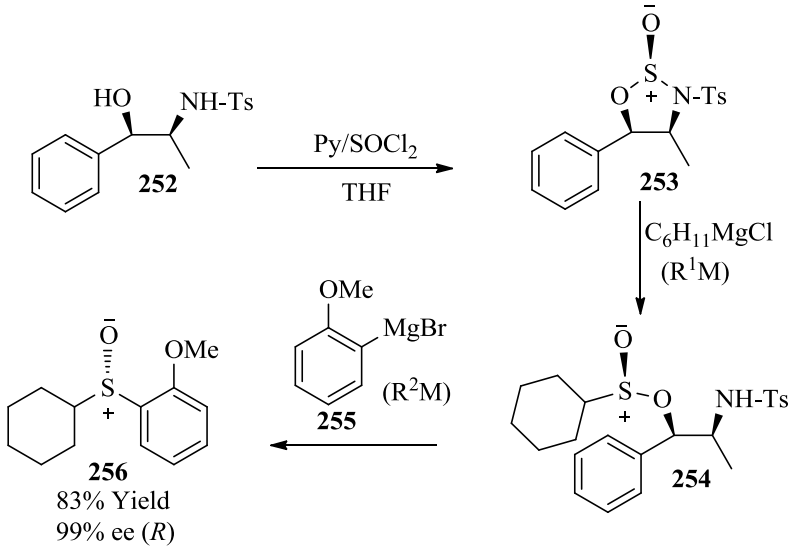
Scheme 1.126

Subsequent work by Senanayake *et al.* resulted in the development of a one pot synthetic route to sulfoxides.[324-326] The method is very similar to that used to prepare sulfinamides shown in Scheme 1.126. Senanayake initially synthesised sulfoxides using *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide **246** *endo* and **246** *exo* where R = *para*-tolyl or 2,4,6-mesityl (Scheme 1.127). Investigations into the preparation of **246** established that employing different bases could induce high selectivity towards **246** *endo* or **246** *exo*. With this information it was possible to isolate enantiomerically pure **246**. The first nucleophilic displacement was carried out at low temperature in THF and the second displacement was carried out at a lower temperature in THF. The results obtained using this method were generally good with high yields and high enantioselectivity.



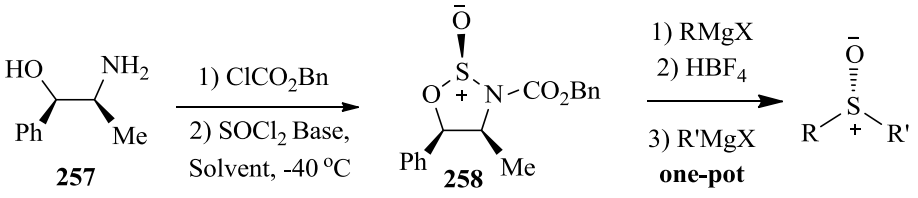
Scheme 1.127

The method shown in Scheme 4.23 involves the use of expensive *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide **245**. Senanayake investigated this method using a more readily available and less expensive amino alcohol, norephedrine **252**. Senanayake identified *N*-tosyl-1,2,3-oxathiazolidine-2-oxide **253** as the most suitable derivative of **241** for the preparation of enantiopure sulfoxides. This template **253** could be used to prepare sulfoxides using a one-pot synthesis. The template could also be isolated from the final reaction mixture and recycled. Overall, the enantioselectivities and yields reported were very high (Scheme 1.128).



Scheme 1.128

García Ruano *et al.* reported a one-pot synthesis of sulfoxides using **257**.[327] *N*-Benzyloxycarbonylsulfamidite **258** was prepared from **257**. By varying the conditions used to prepare **258** the ratio of the resulting diastereomers could be altered so that the preferential formation of one diastereomer would take place. The first displacement was carried out at low temperature in dichloromethane. The addition of HBF_4 to the reaction prior to the second displacement reduced racemisation. The second displacement was also carried out at low temperature in dichloromethane. Overall, the results using this method were quite good, with high enantioselectivity often in excess of 90% ee being reported. García Ruano recommended this one pot synthesis, outlined in Scheme 1.129 for the synthesis of dialkyl, diaryl, aryl vinyl, aryl alkyl sulfoxides. Qin and Jiang used a similar method to prepare sulfinamides.[328]

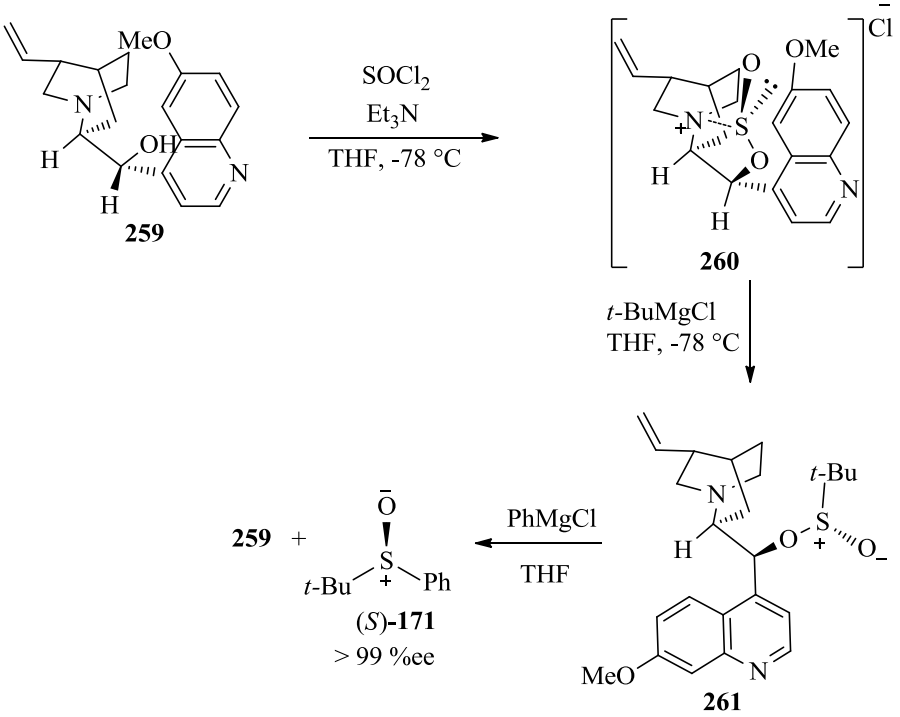


	R	R'	Yield (%)	ee (%)
30	Ph	Me	54	93 (*R*)
145	Mesityl	Me	78	98 (*S*)
194	Mesityl	para-Tolyl	71	97 (*R*)

Scheme 1.129

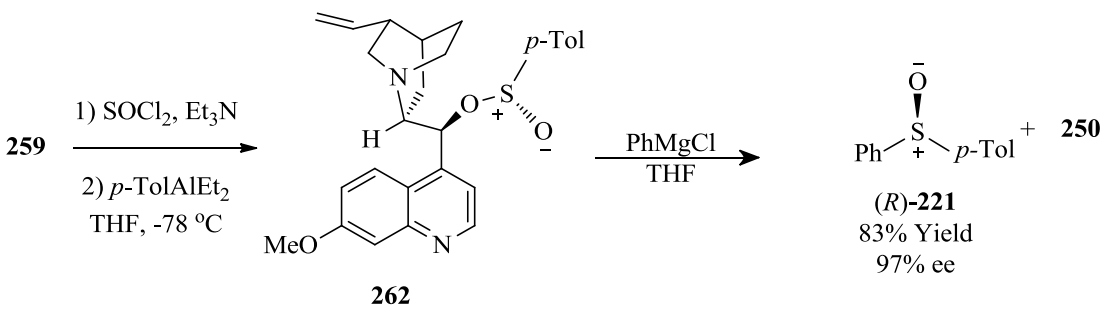
Lu and Senanayake reported another method for the preparation of enantiopure sulfoxides (Scheme 1.130).[329] This method utilised the cinchona alkaloid, quinine **259** to form the chiral

precursor **260**. The S-N bond in **261** is not covalent. The advantage of this is that nucleophilic displacement of the S-O bond is less likely to occur so only one product will form as a result of the first nucleophilic substitution.



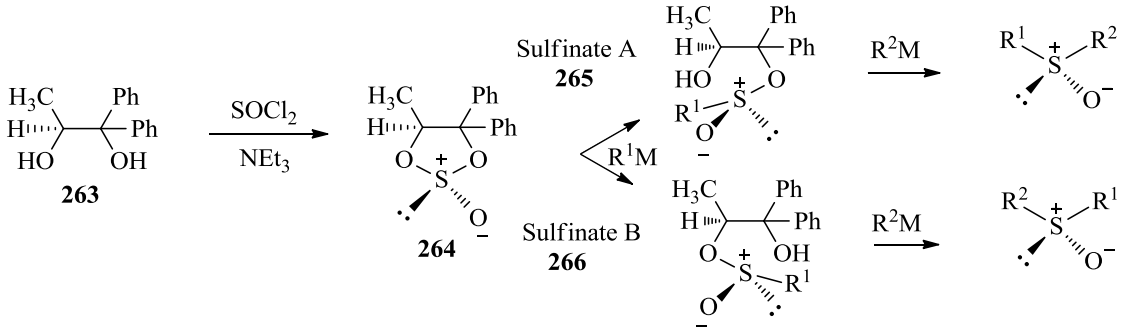
Scheme 1.130

Using a *para*-tolyl Grignard reagent for the first displacement resulted in formation of the ditolyl sulfoxide. This problem was overcome by using a different organometallic reagent, *para*-tolyldiethylaluminum, which was prepared *in situ* using diethylaluminum chloride and *para*-tolylmagnesium bromide. This methodology was also used for the preparation of sulfinamides.



Scheme 1.131

In the early 1990s Kagan developed a route to chiral sulfoxides, shown in Scheme 1.132, involving a double nucleophilic displacement.[330-332] The route was similar to that used by Wudl and Lee. Here a diol **263** was reacted with thionyl chloride to yield cyclic sulfite diastereomers **264**. The diastereomers could be separated by crystallisation and then reacted with suitable organometallic reagents in THF to form sulfinates **265** and **266**. The formation of symmetrical sulfoxide side products was not observed when Grignard reagents were used. An interesting observation was that **265** was preferred when R^1 was small and if R^1 was bulky **266** was preferred. The route was found to be especially suitable for the chiral *tert*-butyl sulfoxides. Unusually, unlike previous chiral precursors discussed, which involved the displacement of an S-N bond followed by the displacement of an S-O bond or vice versa, the sequential breaking of two S-O bonds occurs using this sulfite.

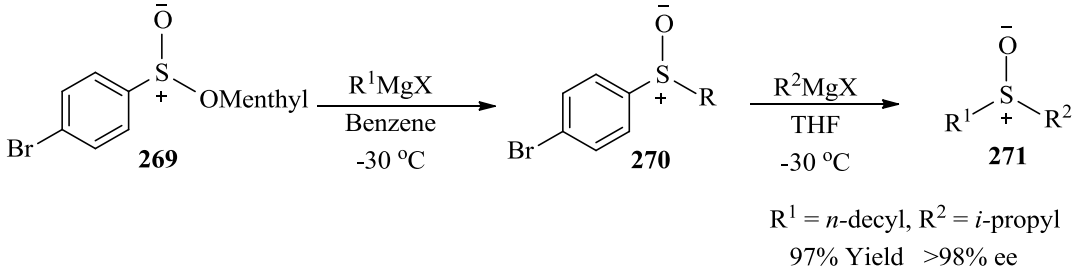


	R^1	R^2	Yield (%)	ee (%)
173	*t*-Bu	Ph	99	100
267	*t*-Bu	n-Bu	99	100
268	*t*-Bu	Vinyl	99	100

Scheme 1.132

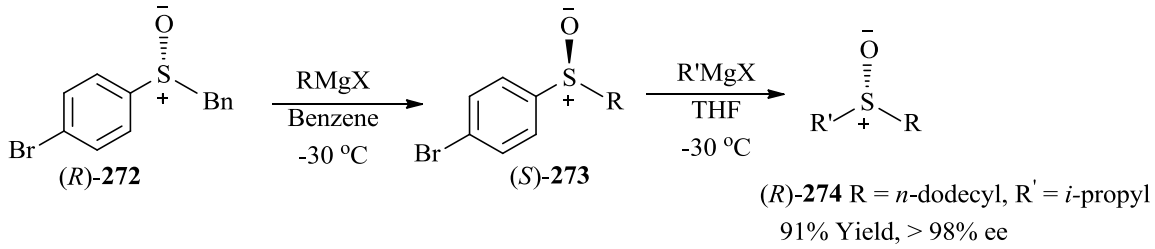
The preparation of the above chiral precursors used in double nucleophilic substitution is quite challenging. This has had the effect of limiting the use of these methods to prepare sulfoxides.

Cardellicchio proposed a novel method for the preparation of dialkyl sulfoxides, using an easily prepared acyclic chiral auxiliary. Cardellicchio made use of both the Andersen method,[288] and the fact that substituted aryl groups can be displaced from sulfoxides using Grignard reagents,[317] to prepare menthyl *para*-bromobenzenesulfinate **269**, a menthyl sulfinate ester that could undergo sequential nucleophilic substitution (Scheme 1.133). The sequential substitution of **269** is possible due to the different leaving abilities of the O-menthyl group and *para*-bromobenzene group.



Scheme 1.133

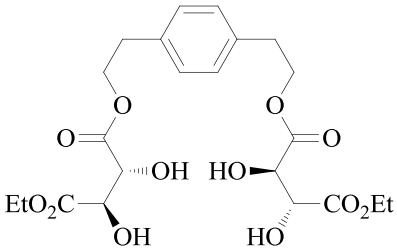
The sulfinate ester **269** can be prepared in good yield using existing methodology,[333] however this method still required the diastereomers of **269** to be separated. Cardellicchio proposed a new chiral precursor to overcome this problem. Thus, benzyl *para*-bromophenyl sulfoxide **272**, which contains two substituents of different leaving abilities and is readily obtainable from the corresponding sulfide using a titanium mediated oxidation method,[334] has been used for the preparation of dialkyl sulfoxides. For example, *n*-dodecyl *iso*-propyl sulfoxide **274** was prepared in 91% yield and >98% ee (Scheme 1.134).



Scheme 1.134

Despite the very high enantioselectivity and yields of these reactions, this approach developed by Cardellicchio has received little attention. This is primarily due to the limited number of sulfoxides, mainly dialkyl sulfoxides, that can be prepared using these precursors.[335] The development of new carbanionic leaving groups may extend the scope of this methodology.

Corey *et al.* recently reported a tetradentate ligand for titanium-catalysed asymmetric sulfide oxidation. This system produced methyl *p*-tolyl sulfoxide **8** in 86% yield and 92% enantioselectivity. Significantly, Corey provided some mechanistic insight into the origin of the enantioselectivity.[336]



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References

(1) Solladie, G.; *Asymmetric Synthesis* **1983**, *2*, 157-199.
(2) Sklute, G.; Amsallem, D.; Shabli, A.; Varghese, J. P.; Marek, I. *J. Am. Chem. Soc.* **2003**, *125*, 11776-11777.
(3) Carreno, M. C.; Garcia, R. J. L.; Martin, A. M.; Pedregal, C.; Rodriguez, J. H.; Rubio, A.; Sanchez, J.; Solladie, G. *J. Org. Chem.* **1990**, *55*, 2120-2128.
(4) Ruano, J. L. G.; De, l. P. B. C. *Top. Curr. Chem.* **1999**, *204*, 1-126.
(5) Lee, A. W. M.; Chan, W. H. *Top. Curr. Chem.* **1997**, *190*, 103-129.
(6) Arai, Y.; Koizumi, T. *Sulfur Rep.* **1993**, *15*, 41-65.
(7) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562-2579.
(8) Toru, T.; Watanabe, Y.; Mase, N.; Tsusaka, M.; Hayakawa, T.; Ueno, Y. *Pure Appl. Chem.* **1996**, *68*, 711-714.
(9) Fernandez, I.; Valdivia, V.; Leal, M. P.; Khiar, N. *Org. Lett.* **2007**, *9*, 2215-2218.
(10) Fernandez, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651-3705.
(11) Carreno, M. C.; Hernandez-Torres, G.; Ribagorda, M.; Urbano, A. *Chem. Commun.* **2009**, 6129-6144.
(12) Hanquet, G.; Colobert, F.; Lanners, S.; Solladie, G. *ARKIVOC* **2003**, 328-401.
(13) Pellissier, H. *Tetrahedron* **2006**, *62*, 5559-5601.
(14) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallou, I. *Aldrichimica. Acta.* **2005**, *38*, 93-104.
(15) Mikolajczyk, M. D., J.; Kielbasinski, P.; *Chiral Sulfur Reagents: Applications in Asymmetric and Stereoselective Synthesis*, CRC press, Boca Raton, USA, 1998, 1-274.
(16) Agranat, I.; Caner, H. *Drug Discovery Today* **1999**, *4*, 313-321.
(17) Olivo, H. F.; Osorio-Lozada, A.; Peeples, T. L. *Tetrahedron: Asymmetry* **2005**, *16*, 3507-3511.
(18) Hamman, M. A.; Haehner-Daniels, B. D.; Wrighton, S. A.; Rettie, A. E.; Hall, S. D. *Biochem. Pharmacol.* **2000**, *60*, 7-17.
(19) Legros, J.; Dehli, J. R.; Bolm, C. *Adv. Synth. Catal.* **2005**, *347*, 19-31.
(20) Volcho, K. P.; Salakhutdinov, N. F. *Russ. Chem. Rev.* **2009**, *78*, 457-464.
(21) Collins, S. G.; Maguire, A. R. *Sci. Synth.* **2007**, *31a*, 907-948.
(22) Mikolajczyk, M. D., J.; Kielbasinski, P.; *Topics in Stereochemistry*, vol. 13, Allinger, M.L.; Eliel, E.L.; Eds. Interscience New York 1982, 333-468.
(23) Drabowicz, J. K., P.; Mikolajczyk.; *Synthesis of Sulfones, Sulfoxides and Cyclic Sulfides*, Eds. Patai, S.; Rappaport, Z.; Wiley, Chichester, 1994 , 109-254.
(24) Wojaczynska, E.; Wojaczynski, J. *Chem. Rev.* **2010**, *110*, 4303-4356.
(25) O'Mahony, G. E.; Kelly, P.; Lawrence, S. E.; Maguire, A. R. *ARKIVOC* **2011**, 1-110.
(26) Maccioni, A.; Montanari, F.; Secci, M.; Tramontini, M. *Tetrahedron Lett.* **1961**, *2*, 607-611.
(27) Balenovic, K.; Bregant, N.; Francetic, D. *Tetrahedron Lett.* **1960**, *1*, 20-22.
(28) Madesclaire, M. *Tetrahedron* **1986**, *42*, 5459-5495.
(29) Baird, C. P.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1973-2003.
(30) Bryliakov, K. P.; Talsi, E. P. *Curr. Org. Chem.* **2008**, *12*, 386-404.

(31) Kagan, H. B.; Luukas, T. O.; *Transition Metals for Organic Synthesis*: Beller, M.; Bolm, C. Eds.; 2nd Edn;Wiley: Weinham. 2004; 30613.
(32) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 335-354.
(33) Pitchen, P.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 1049-1052.
(34) Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188-8193.
(35) Di, F. F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325-326.
(36) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976.
(37) Sharpless, K. B. *Chem. Br.* **1986**, *22*, 38-40.
(38) Ramon, D. J.; Yus, M. *Chem. Rev.* **2006**, *106*, 2126-2208.
(39) Bonchio, M.; Licini, G.; Modena, G.; Moro, S.; Bortolini, O.; Traldi, P.; Nugent, W. *Chem. Commun.* **1997**, 869-870.
(40) Potvin, P. G.; Fieldhouse, B. G. *Tetrahedron: Asymmetry* **1999**, *10*, 1661-1672.
(41) Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135-5144.
(42) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922-1925.
(43) Komatsu, N.; Nishibayashi, Y.; Sugita, T.; Uemura, S. *Tetrahedron Lett.* **1992**, *33*, 5391-5394.
(44) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1997**, *62*, 8560-8564.
(45) Takeda, T.; Imamoto, T. *Tetrahedron: Asymmetry* **1999**, *10*, 3209-3218.
(46) Superchi, S.; Rosini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 349-352.
(47) Superchi, S.; Scafato, P.; Restaino, L.; Rosini, C. *Chirality* **2008**, *20*, 592-596.
(48) Bolm, C.; Dabard, O. A. G. *Synlett* **1999**, 360-362.
(49) Martyn, L. J. P.; Pandiaraju, S.; Yudin, A. K. *J. Organomet. Chem.* **2000**, *603*, 98-104.
(50) Chen, Y.; Yekta, S.; Martyn, L. J. P.; Zheng, J.; Yudin, A. K. *Org. Lett.* **2000**, *2*, 3433-3436.
(51) Zeng, Q.-L.; Tang, H.-Y.; Zhang, S.; Liu, J.-C. *Chin. J. Chem.* **2008**, *26*, 1435-1439.
(52) Sun, J.; Yang, M.; Dai, Z.; Zhu, C.; Hu, H. *Synthesis* **2008**, 2513-2518.
(53) Matsugi, M.; Fukuda, N.; Minamikawa, J.-i.; Otsuka, S. *Tetrahedron Lett.* **1998**, *39*, 5591-5592.
(54) Matsugi, M.; Fukuda, N.; Muguruma, Y.; Yamaguchi, T.; Minamikawa, J.-i.; Otsuka, S. *Tetrahedron* **2001**, *57*, 2739-2744.
(55) Matsugi, M.; Shimada, R.; Ohata, S.; Nojima, M.; Fukuda, N.; Minamikawa, J.-i.; Kita, Y. *Chem. Pharm. Bull.* **2002**, *50*, 1511-1513.
(56) Bryliakov, K. P.; Talsi, E. P. *J. Mol. Catal. A: Chem.* **2007**, *264*, 280-287.
(57) Bryliakov, K. P.; Talsi, E. P. *Eur. J. Org. Chem.* **2008**, 3369-3376.
(58) Adam, W.; Korb, M. N.; Roschmann, K. J.; Saha-Moeller, C. R. *J. Org. Chem.* **1998**, *63*, 3423-3428.
(59) Scettri, A.; Bonadies, F.; Lattanzi, A. *Tetrahedron: Asymmetry* **1996**, *7*, 629-632.
(60) Scettri, A.; Bonadies, F.; Lattanzi, A.; Senatore, A.; Soriente, A. *Tetrahedron: Asymmetry* **1996**, *7*, 657-658.
(61) Lattanzi, A.; Bonadies, F.; Senatore, A.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2473-2478.
(62) Lattanzi, A.; Bonadies, F.; Scettri, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2141-2151.
(63) Palombi, L.; Bonadies, F.; Pazienza, A.; Scettri, A. *Tetrahedron: Asymmetry*

1998, *9*, 1817-1822.
(64) Lattanzi, A.; Bonadies, F.; Schiavo, A.; Scettri, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2619-2625.
(65) Lattanzi, A.; Scettri, A. *J. Organomet. Chem.* **2006**, *691*, 2072-2082.
(66) Lattanzi, A.; Iannece, P.; Scettri, A. *Tetrahedron: Asymmetry* **2004**, *15*, 1779-1785.
(67) Lattanzi, A.; Iannece, P.; Scettri, A. *Tetrahedron: Asymmetry* **2004**, *15*, 413-418.
(68) Lattanzi, A.; Piccirillo, S.; Scettri, A. *Eur. J. Org. Chem.* **2006**, 713-718.
(69) Blumenthal, H.; Liebscher, J. *ARKIVOC* **2009**, 204-220.
(70) Cotton, H.; Elebring, T.; Larsson, M.; Li, L.; Sörensen, H.; von Unge, S. *Tetrahedron: Asymmetry* **2000**, *11*, 3819-3825.
(71) Khomenko, T. M.; Volcho, K. P.; Komarova, N. I.; Salakhutdinov, N. F. *Russ. J. Org. Chem.* **2008**, *44*, 124-127.
(72) Jiang, B.; Zhao, X.-L.; Dong, J.-J.; Wang, W.-J. *Eur. J. Org. Chem.* **2009**, 987-991.
(73) Delamare, M.; Belot, S.; Caille, J.-C.; Martinet, F.; Kagan, H. B.; Henryon, V. *Tetrahedron Lett.* **2009**, *50*, 1702-1704.
(74) Maguire, A. R.; Papot, S.; Ford, A.; Touhey, S.; O'Connor, R.; Clynes, M. *Synlett* **2001**, 41-44.
(75) Naso, F.; Cardellicchio, C.; Affortunato, F.; Capozzi, M. A. M. *Tetrahedron: Asymmetry* **2006**, *17*, 3226-3229.
(76) Raju, M. N.; Kumar, N. U.; Reddy, B. S.; Anitha, N.; Srinivas, G.; Bhattacharya, A.; Mukkanti, K.; Kolla, N.; Bandichhor, R. *Tetrahedron Lett.* **2011**, *52*, 5464-5466.
(77) Naso, F.; Capozzi, M. A. M.; Bottoni, A.; Calvaresi, M.; Bertolasi, V.; Capitelli, F.; Cardellicchio, C. *Chem.--Eur. J.* **2009**, *15*, 13417-13426.
(78) Capozzi, M. A. M.; Centrone, C.; Fracchiolla, G.; Naso, F.; Cardellicchio, C. *Eur. J. Org. Chem.* **2011**, *2011*, 4327-4334.
(79) Massa, A.; Mazza, V.; Scettri, A. *Tetrahedron: Asymmetry* **2005**, *16*, 2271-2275.
(80) Ding, K.; Wang, Z.; Wang, X.; Liang, Y.; Wang, X. *Chemistry* **2006**, *12*, 5188-97.
(81) Iwamoto, M.; Tanaka, Y.; Hirosumi, J.; Kita, N.; Triwahyono, S. *Microporous Mesoporous Mater.* **2001**, *48*, 271-277.
(82) Gao, J.; Guo, H.; Liu, S.; Wang, M. *Tetrahedron Lett.* **2007**, *48*, 8453-8455.
(83) Yuan, X.-y.; Wang, X.-t. *J. Chongqing Univ. (Engl. Ed.)* **2008**, *7*, 179-185.
(84) Sahoo, S.; Kumar, P.; Lefebvre, F.; Halligudi, S. B. *J. Catal.* **2009**, *262*, 111-118.
(85) Rodygin, K. S.; Rubtsova, S. A.; Kutchin, A. V.; Slepukhin, P. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2011**, *186*, 1885-1894.
(86) Bolm, C. *Coord. Chem. Rev.* **2003**, *237*, 245-256.
(87) Curci, R.; Di, F. F.; Testi, R.; Modena, G. *J. Chem. Soc., Perkin Trans. 2* **1974**, 752-757.
(88) Nakajima, K.; Kojima, M.; Fujita, J. *Chem. Lett.* **1986**, 1483-1486.
(89) Nakajima, K.; Kojima, K.; Kojima, M.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2620-2630.
(90) Nakajima, K.; Sasaki, C.; Kojima, M.; Aoyama, T.; Ohba, S.; Saito, Y.; Fujita, J. *Chem. Lett.* **1987**, 2189-2192.
(91) Sasaki, C.; Nakajima, K.; Kojima, M.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1991**,

64, 1318-1324.
(92) Nakajima, K.; Kojima, M.; Toriumi, K.; Saito, K.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 760-767.
(93) Colonna, S.; Manfredi, A.; Spadoni, M.; Casella, L.; Gullotti, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 71-73.
(94) Bolm, C.; Bienewald, F. *Angew. Chem., Int. Ed. Engl.* **1996**, *34*, 2640-2642.
(95) Khiar, N.; Mallouk, S.; Valdivia, V.; Bougrin, K.; Soufiaoui, M.; Fernandez, I. *Org. Lett.* **2007**, *9*, 1255-1258.
(96) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913-9914.
(97) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011-8019.
(98) Balcells, D.; Maseras, F.; Ujaque, G. *J. Am. Chem. Soc.* **2005**, *127*, 3624-3634.
(99) Vetter, A. H.; Berkessel, A. *Tetrahedron Lett.* **1998**, *39*, 1741-1744.
(100) Ohta, C.; Shimizu, H.; Kondo, A.; Katsuki, T. *Synlett* **2002**, 161-163.
(101) Green, S. D.; Monti, C.; Jackson, R. F. W.; Anson, M. S.; MacDonald, S. J. F. *Chem. Commun.* **2001**, 2594-2595.
(102) Pelotier, B.; Anson, M. S.; Campbell, I. B.; MacDonald, S. J. F.; Priem, G.; Jackson, R. F. W. *Synlett* **2002**, 1055-1060.
(103) Korte, A.; Legros, J.; Bolm, C. *Synlett* **2004**, 2397-2399.
(104) Legros, J.; Bolm, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5487-5489.
(105) Legros, J.; Bolm, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4225-4228.
(106) Legros, J.; Bolm, C. *Chem.--Eur. J.* **2005**, *11*, 1086-1092.
(107) Kelly, P.; Lawrence, S. E.; Maguire, A. R. *Synlett* **2006**, 1569-1573.
(108) Kelly, P.; Lawrence, S. E.; Maguire, A. R. *Eur. J. Org. Chem.* **2006**, 4500-4509.
(109) Jeong, Y.-C.; Choi, S.; Hwang, Y. D.; Ahn, K.-H. *Tetrahedron Lett.* **2004**, *45*, 9249-9252.
(110) Jeong, Y.-C.; Huang, Y. D.; Choi, S.; Ahn, K.-H. *Tetrahedron: Asymmetry* **2005**, *16*, 3497-3501.
(111) Gao, A.; Wang, M.; Wang, D.; Zhang, L.; Liu, H.; Tian, W.; Sun, L. *Chinese J. Catal.* **2006**, *27*, 743-748.
(112) Liu, H.; Wang, M.; Wang, Y.; Yin, R.; Tian, W.; Sun, L. *Appl. Organomet. Chem.* **2008**, *22*, 253-257.
(113) Liu, H.-B.; Wang, M.; Wang, Y.; Wang, Y.; Sun, H.; Sun, L.-C. *Catal. Commun.* **2009**, *11*, 294-297.
(114) Wu, Y.; Liu, J.; Li, X.; Chan, A. S. C. *Eur. J. Org. Chem.* **2009**, 2607-2610.
(115) Suresh, P.; Srimurugan, S.; Babu, B.; Pati, H. N. *Tetrahedron: Asymmetry* **2007**, *18*, 2820-2827.
(116) Koneva, E. A.; Volcho, K. P.; Korchagina, D. V.; Komarova, N. I.; Kochnev, A. I.; Salakhutdinov, N. F.; Tolstikov, A. G. *Russ. Chem. Bull.* **2008**, *57*, 108-117.
(117) Koneva, E. A.; Volcho, K. P.; Korchagina, D. V.; Salakhutdinov, N. F.; Tolstikov, A. G. *Russ. J. Org. Chem.* **2009**, *45*, 815-824.
(118) Il'ina, I. V.; Koneva, E. A.; Korchagina, D. V.; Sal'nikov, G. E.; Genaev, A. M.; Volcho, K. P.; Salakhutdinov, N. F. *Russ. J. Org. Chem.* **2012**, *48*, 214-220.
(119) Barbarini, A.; Maggi, R.; Muratori, M.; Sartori, G.; Sartorio, R. *Tetrahedron: Asymmetry* **2004**, *15*, 2467-2473.
(120) Zeng, Q.; Wang, H.; Weng, W.; Lin, W.; Gao, Y.; Huang, X.; Zhao, Y. *New J.*

Chem. **2005**, *29*, 1125-1127.
(121) Zeng, Q.; Wang, H.; Wang, T.; Cai, Y.; Weng, W.; Zhao, Y. *Adv. Synth. Catal.* **2005**, *347*, 1933-1936.
(122) Hsieh, S.-H.; Kuo, Y.-P.; Gau, H.-M. *Dalton Trans.* **2007**, 97-106.
(123) Zeng, Q.; Gao, Y.; Dong, J.; Weng, W.; Zhao, Y. *Tetrahedron: Asymmetry* **2011**, *22*, 717-721.
(124) Lippold, I.; Becher, J.; Klemm, D.; Plass, W. *J. Mol. Catal. A: Chem.* **2009**, *299*, 12-17.
(125) Kwiatkowski, E.; Romanowski, G.; Nowicki, W.; Kwiatkowski, M.; Suwinska, K. *Polyhedron* **2007**, *26*, 2559-2568.
(126) Romanowski, G.; Kwiatkowski, E.; Nowicki, W.; Kwiatkowski, M.; Lis, T. *Polyhedron* **2008**, *27*, 1601-1609.
(127) Drago, C.; Caggiano, L.; Jackson, R. F. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 7221-7223.
(128) Shimizu, M.; Shibuya, K.; Hayakawa, R. *Synlett* **2000**, 1437-1438.
(129) Karpyshev, N. N.; Yakovleva, O. D.; Talsi, E. P.; Bryliakov, K. P.; Tolstikova, O. V.; Tolstikov, A. G. *J. Mol. Catal. A: Chem.* **2000**, *157*, 91-95.
(130) Conte, V.; Di, F. F.; Moro, S. *J. Mol. Catal. A: Chem.* **1997**, *117*, 139-149.
(131) Blum, S. A.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2002**, *68*, 150-155.
(132) Bolm, C.; Bienewald, F. *Synlett* **1998**, 1327-1328.
(133) Bryliakov, K. P.; Karpyshev, N. N.; Fominsky, S. A.; Tolstikov, A. G.; Talsi, E. P. *J. Mol. Catal. A: Chem.* **2001**, *171*, 73-80.
(134) Sun, J.; Zhu, C.; Dai, Z.; Yang, M.; Pan, Y.; Hu, H. *J. of Org. Chem.* **2004**, *69*, 8500-8503.
(135) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628-3634.
(136) Naruta, Y.; Tani, F.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1378-80.
(137) Naruta, Y.; Tani, F.; Maruyama, K. *Tetrahedron: Asymmetry* **1991**, *2*, 533-542.
(138) Chiang, L. C.; Konishi, K.; Aida, T.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1992**, 254-256.
(139) Le, M. P.; Simonneaux, G. *Chem. Commun. (Cambridge, U. K.)* **2011**, *47*, 6957-6959.
(140) Bryliakov, K. P.; Talsi, E. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 5228-5230.
(141) Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 8940-8941.
(142) Egami, H.; Katsuki, T. *Synlett* **2008**, 1543-1546.
(143) Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189-214.
(144) Palucki, M.; Hanson, P.; Jacobsen, E. N. *Tetrahedron Lett.* **1992**, *33*, 7111-7114.
(145) Noda, K.; Hosoya, N.; Yanai, K.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **1994**, *35*, 1887-1890.
(146) Noda, K.; Hosoya, N.; Irie, R.; Yamashita, Y.; Katsuki, T. *Tetrahedron* **1994**, *50*, 9609-9618.
(147) Kokubo, C.; Katsuki, T. *Tetrahedron* **1996**, *52*, 13895-13900.
(148) Irie, R.; Ito, Y.; Katsuki, T. *Synlett* **1991**, 265-266.
(149) Choi, J. Y.; Hwang, G.-S.; Senapati, B. K.; Ryu, D. H. *Bull. Korean Chem. Soc.* **2008**, *29*, 1879-1880.
(150) Schoumacker, S.; Hamelin, O.; Pecaut, J.; Fontecave, M. *Inorg. Chem.* **2003**, *42*, 8110-8116.
(151) Imagawa, K.; Nagata, T.; Yamada, Y.; Mukaiyama, T. *Chem. Lett.* **1995**, 335-

336.
(152) Nagata, T.; Imagawa, K.; Yamada, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3241-3246.
(153) Alcon, M. J.; Corma, A.; Iglesias, M.; Sanchez, F. *J. Mol. Catal. A: Chem.* **2002**, *178*, 253-266.
(154) Gao, A.; Wang, M.; Shi, J.; Wang, D.; Tian, W.; Sun, L. *Appl. Organomet. Chem.* **2006**, *20*, 830-834.
(155) Wang, D.; Wang, M.; Wang, X.; Chen, Y.; Gao, A.; Sun, L. *J. Catal.* **2006**, *237*, 248-254.
(156) Hirotsu, M.; Ohno, N.; Nakajima, T.; Kushibe, C.; Ueno, K.; Kinoshita, I. *Dalton Trans.* **2010**, *39*, 139-148.
(157) Bunce, S.; Cross, R. J.; Farrugia, L. J.; Kunchandy, S.; Meason, L. L.; Muir, K. W.; O'Donnell, M.; Peacock, R. D.; Stirling, D.; Teat, S. J. *Polyhedron* **1998**, *17*, 4179-4187.
(158) Zhu, H.-B.; Dai, Z.-Y.; Huang, W.; Cui, K.; Gou, S.-H.; Zhu, C.-J. *Polyhedron* **2004**, *23*, 1131-1137.
(159) Plitt, P.; Pritzkow, H.; Oeser, T.; Kraemer, R. *J. Inorg. Biochem.* **2005**, *99*, 1230-1237.
(160) Ayala, V.; Corma, A.; Iglesias, M.; Sanchez, F. *J. Mol. Catal. A: Chem.* **2004**, *221*, 201-208.
(161) Kelly, P.; Lawrence, S. E.; Maguire, A. R. *Synlett* **2007**, 1501-1506.
(162) O'Mahony, G. E.; Ford, A.; Maguire, A. R. *J. Org. Chem.* **2012**, *77*, 3288-3296.
(163) Miyazaki, T.; Katsuki, T. *Synlett* **2003**, 1046-1048.
(164) Thakur, V. V.; Sudalai, A. *Tetrahedron: Asymmetry* **2003**, *14*, 407-410.
(165) Kantam, M. L.; Prakash, B. V.; Bharathi, B.; Reddy, C. V. *J. Mol. Catal. A: Chem.* **2005**, *226*, 119-122.
(166) Bonchio, M.; Licini, G.; Mantovani, S.; Modena, G.; Nugent, W. A. *J. Org. Chem.* **1999**, *64*, 1326-1330.
(167) Licini, G.; Bonchio, M.; Modena, G.; Nugent, W. A. *Pure Appl. Chem.* **1999**, *71*, 463-472.
(168) Di, F. F.; Licini, G.; Modena, G.; Motterle, R.; Nugent, W. A. *J. Org. Chem.* **1996**, *61*, 5175-5177.
(169) Bonchio, M.; Carofiglio, T.; Di, F. F.; Fornasier, R. *J. Org. Chem.* **1995**, *60*, 5986-5988.
(170) Basak, A.; Barlan, A. U.; Yamamoto, H. *Tetrahedron: Asymmetry* **2006**, *17*, 508-511.
(171) Matsumoto, K.; Yamaguchi, T.; Fujisaki, J.; Saito, B.; Katsuki, T. *Chem.—Asian J.* **2008**, *3*, 351-358.
(172) Folli, U.; Iarossi, D.; Montanari, F.; Torre, G. *J. Chem. Soc., C.* **1968**, 1317-1322.
(173) Pirkle, W. H.; Rinaldi, P. L. *J. Org. Chem.* **1977**, *42*, 2080-2082.
(174) Aoki, M.; Seebach, D. *Helv. Chim. Acta* **2001**, *84*, 187-207.
(175) Davis, F. A.; Jenkins, R., Jr.; Yocklovich, S. G. *Tetrahedron Lett.* **1978**, 5171-5174.
(176) Davis, F. A.; Jenkins, R., Jr.; Rizvi, S. Q. A.; Panunto, T. W. *J. Chem. Soc., Chem. Commun.* **1979**, 600-601.
(177) Davis, F. A.; Jenkins, R. H., Jr.; Awad, S. B.; Stringer, O. D.; Watson, W. H.; Galloy, J. *J. Am. Chem. Soc.* **1982**, *104*, 5412-5418.
(178) Davis, F. A.; McCauley, J. P., Jr.; Harakal, M. E. *J. Org. Chem.* **1984**, *49*,

1465-1467.
(179) Davis, F. A.; McCauley, J. P., Jr.; Chattopadhyay, S.; Harakal, M. E.; Towson, J. C.; Watson, W. H.; Tavanaiepour, I. *J. Am. Chem. Soc.* **1987**, *109*, 3370-3377.
(180) Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, S.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477-8482.
(181) Davis, F. A.; ThimmaReddy, R.; Weismiller, M. C. *J. Am. Chem. Soc.* **1989**, *111*, 5964-5965.
(182) Davis, F. A.; Reddy, R. T.; Han, W.; Carroll, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 1428-1237.
(183) Meladinis, V.; Verfurth, U.; Herrmann, R. *Z. Naturforsch., B: Chem. Sci.* **1990**, *45*, 1689-1694.
(184) Davis, F. A.; Reddy, R. T.; McCauley, J. P., Jr.; Przeslawski, R. M.; Harakal, M. E.; Carroll, P. J. *J. Org. Chem.* **1991**, *56*, 809-815.
(185) Schwan, A. L.; Pippert, M. F. *Tetrahedron: Asymmetry* **1995**, *6*, 131-138.
(186) Davis, F. A.; Lal, S. G.; Durst, H. D. *J. Org. Chem.* **1988**, *53*, 5004-5007.
(187) Page, P. C. B.; Heer, J. P.; Bethell, D.; Collington, E. W.; Andrews, D. M. *Tetrahedron Lett.* **1994**, *35*, 9629-9632.
(188) Page, P. C. B.; Heer, J. P.; Bethell, D.; Collington, E. W.; Andrews, D. M. *Synlett* **1995**, 773-775.
(189) Bulman Page, P. C.; Heer, J. P.; Bethell, D.; Collington, E. W.; Andrews, D. M. *Tetrahedron: Asymmetry* **1995**, *6*, 2911-2914.
(190) Bethell, D.; Page, P. C. B.; Vahedi, H. *J. Org. Chem.* **2000**, *65*, 6756-6760.
(191) Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1988**, *29*, 2817-2818.
(192) Bohé, L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 155-166.
(193) Schoumacker, S.; Hamelin, O.; Téti, S.; Pécaut, J.; Fontecave, M. *J. Org. Chem.* **2004**, *70*, 301-308.
(194) Jennings, W. B.; Kochanewycz, M. J.; Lovely, C. J.; Boyd, D. R. *J. Chem. Soc., Chem. Commun.* **1994**, 2569-2570.
(195) del Rio, R. E.; Wang, B.; Achab, S.; Bohé, L. *Org. Lett.* **2007**, *9*, 2265-2268.
(196) Akhatou, A.; Rahimi, M.; Cheboub, K.; Ghosez, L.; Hanquet, G. *Tetrahedron* **2007**, *63*, 6232-6240.
(197) Ladziata, U.; Zhdankin, V. V. *Synlett* **2007**, 527-537.
(198) Zhdankin, V. V.; Smart, J. T.; Zhao, P.; Kiprof, P. *Tetrahedron Lett.* **2000**, *41*, 5299-5302.
(199) Ladziata, U.; Carlson, J.; Zhdankin, V. V. *Tetrahedron Lett.* **2006**, *47*, 6301-6304.
(200) Higuchi, T.; Pitman, I. H.; Gensch, K. H. *J. Am. Chem. Soc.* **1966**, *88*, 5676-5677.
(201) Surendra, K.; Krishnaveni, N. S.; Kumar, V. P.; Sridhar, R.; Rao, K. R. *Tetrahedron Lett.* **2005**, *46*, 4581-4583.
(202) Rossi, L. I.; de, R. R. H. *Appl. Catal., A* **2004**, *267*, 267-272.
(203) Czarnik, A. W. *J. Org. Chem.* **1984**, *49*, 924-927.
(204) Drabowicz, J.; Mikolajczyk, M. *Phosphorus Sulfur* **1984**, *21*, 245-248.
(205) Sugimoto, T.; Kokubo, T.; Miyazaki, J.; Tanimoto, S.; Okano, M. *J. Chem. Soc., Chem. Commun.* **1979**, 402-404.
(206) Ogura, K.; Fujita, M.; Iida, H. *Tetrahedron Lett.* **1980**, *21*, 2233-2236.
(207) Colonna, S.; Banfi, S.; Fontana, F.; Sommaruga, M. *J. Org. Chem.* **1985**, *50*, 769-771.
(208) Firth, B. E.; Miller, L. L. *J. Am. Chem. Soc.* **1976**, *98*, 8272-8273.

(209) Komori, T.; Nonaka, T. *J. Am. Chem. Soc.* **1983**, *105*, 5690-5691.
(210) Komori, T.; Nonaka, T. *J. Am. Chem. Soc.* **1984**, *106*, 2656-2659.
(211) Holland, H. L. *Chem. Rev.* **1988**, *88*, 473-485.
(212) Holland, H. L. *Nat. Prod. Rep.* **2001**, *18*, 171-181.
(213) Dodson, R. M.; Newman, N.; Tsuchiya, H. M. *J. Org. Chem.* **1962**, *27*, 2707-2708.
(214) Auret, B. J.; Boyd, D. R.; Henbest, H. B.; Ross, S. *J. Chem. Soc., C* **1968**, 2371-2374.
(215) Holland, H. L.; Brown, F. M.; Larsen, B. G. *Bioorg. Med. Chem.* **1994**, *2*, 647-652.
(216) Holland, H. L.; Brown, F. M.; Larsen, B. G. *Tetrahedron: Asymmetry* **1994**, *5*, 1241-1248.
(217) Holland, H. L.; Brown, F. M.; Larsen, B. G. *Tetrahedron: Asymmetry* **1995**, *6*, 1561-1567.
(218) Holland, H. L.; Brown, F. M.; Larsen, B. G.; Zabic, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1569-1574.
(219) Holland, H. L.; Bornmann, M. J.; Lakshmaiah, G. *J. Mol. Catal. B: Enzym.* **1996**, *1*, 97-102.
(220) Holland, H. L.; Brown, F. M.; Lakshmaiah, G.; Larsen, B. G.; Patel, M. *Tetrahedron: Asymmetry* **1997**, *8*, 683-697.
(221) Holland, H. L.; Brown, F. M.; Kerridge, A.; Turner, C. D. *J. Mol. Catal. B: Enzym.* **1999**, *6*, 463-471.
(222) Holland, H. L.; Gu, J.-X.; Kerridge, A.; Willetts, A. *Biocatal. Biotransform.* **1999**, *17*, 305-317.
(223) Argoudelis, A. D.; Mason, D. J. *J. Antibiot. (Tokyo)* **1969**, *22*, 289-91.
(224) Argoudelis, A. D.; Coats, J. H.; Mason, D. J.; Sebek, O. K. *J. Antibiot.* **1969**, *22*, 309-314.
(225) Ohta, H.; Okamoto, Y.; Tsuchihashi, G. *Chem. Lett.* **1984**, 205-208.
(226) Ohta, H.; Okamoto, Y.; Tsuchihashi, G. *Agric. Biol. Chem.* **1985**, *49*, 671-676.
(227) Ohta, H.; Okamoto, Y.; Tsuchihashi, G. *Agric. Biol. Chem.* **1985**, *49*, 2229-2231.
(228) Mahmoudian, M.; Michael, A. *J. Biotechnol.* **1993**, *27*, 173-179.
(229) Lee, K.; Brand, J. M.; Gibson, D. T. *Biochem. Biophys. Res. Commun.* **1995**, *212*, 9-15.
(230) Adam, W.; Heckel, F.; Saha-Möller, C. R.; Taupp, M.; Schreier, P. *Tetrahedron: Asymmetry* **2004**, *15*, 983-985.
(231) Boyd, D. R.; Sharma, N. D.; Haughey, S. A.; Malone, J. F.; King, A. W. T.; McMurray, B. T.; Alves-Areias, A.; Allen, C. C. R.; Holt, R.; Dalton, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3288-3296.
(232) Boyd, D. R.; Sharma, N. D.; Ljubez, V.; Byrne, B. E.; Shepherd, S. D.; Allen, C. C. R.; Kulakov, L. A.; Larkin, M. J.; Dalton, H. *Chem. Commun.* **2002**, 1914-1915.
(233) Tang, J.; Brackenridge, I.; Roberts, S. M.; Beecher, J.; Willetts, A. J. *Tetrahedron* **1995**, *51*, 13217-13238.
(234) Beecher, J.; Richardson, P.; Roberts, S.; Willetts, A. *Biotechnol. Lett.* **1995**, *17*, 1069-74.
(235) Carrea, G.; Redigolo, B.; Riva, S.; Colonna, S.; Gaggero, N.; Battistel, E.; Bianchi, D. *Tetrahedron: Asymmetry* **1992**, *3*, 1063-1068.
(236) Zhao, H.; Kayser, M. M.; Wang, Y.; Palkovits, R.; Schueth, F. *Microporous Mesoporous Mater.* **2008**, *116*, 196-203.

(237) Yoshida, T.; Kito, M.; Tsujii, M.; Nagasawa, T. *Biotechnol. Lett.* **2001**, *23*, 1217-1222.
(238) Ricci, L. C.; Comasseto, J. V.; Andrade, L. H.; Capelari, M.; Cass, Q. B.; Porto, A. L. M. *Enzyme Microb. Technol.* **2005**, *36*, 937-946.
(239) Pinedo-Rivilla, C.; Aleu, J.; Collado, I. G. *J. Mol. Catal. B: Enzym.* **2007**, *49*, 18-23.
(240) Daligault, F.; Nugier-Chauvin, C.; Patin, H. *Org. Biomol. Chem.* **2006**, *4*, 1474-1477.
(241) Ottolina, G.; Pasta, P.; Carrea, G.; Colonna, S.; Dallavalle, S.; Holland, H. L. *Tetrahedron: Asymmetry* **1995**, *6*, 1375-1386.
(242) Colonna, S.; Gaggero, N.; Carrea, G.; Pasta, P. *Chem. Commun. (Cambridge)* **1997**, 439-440.
(243) Chen, G.; Kayser, M. M.; Mihovilovic, M. D.; Mrstik, M. E.; Martinez, C. A.; Stewart, J. D. *New J. Chem.* **1999**, *23*, 827-832.
(244) Colonna, S.; Del, S. S.; Gaggero, N.; Carrea, G.; Pasta, P. *Heteroat. Chem.* **2002**, *13*, 467-473.
(245) Colonna, S.; Gaggero, N.; Casella, L.; Carrea, G.; Pasta, P. *Tetrahedron: Asymmetry* **1992**, *3*, 95-106.
(246) van Deurzen, M. P. J.; Remkes, I. J.; van Rantwijk, F.; Sheldon, R. A. *J. Mol. Catal. A: Chem.* **1997**, *117*, 329-337.
(247) van Deurzen, M. P. J.; van Rantwijk, F.; Sheldon, R. A. *Tetrahedron* **1997**, *53*, 13183-13220.
(248) Lutz, S.; Steckhan, E.; Liese, A. *Electrochem. Commun.* **2004**, *6*, 583-587.
(249) van Rantwijk, F.; Sheldon, R. A. *Curr. Opin. Biotechnol.* **2000**, *11*, 554-564.
(250) van Deurzen, M. P. J.; van Rantwijk, F.; Sheldon, R. A. *Trends Biotechnol.* **2001**, *19*, 73-80.
(251) Karmee, S. K.; Roosen, C.; Kohlmann, C.; Luetz, S.; Greiner, L.; Leitner, W. *Green Chem.* **2009**, *11*, 1052-1055.
(252) Perez, D. I.; Grau, M. M.; Arends, I. W. C. E.; Hollmann, F. *Chem. Commun.* **2009**, 6848-6850.
(253) Tuynman, A.; Schoemaker, H. E.; Wever, R. *Monatsh. Chem.* **2000**, *131*, 687-695.
(254) Ozaki, S.-I.; Ortiz, d. M. P. R. *J. Am. Chem. Soc.* **1994**, *116*, 4487-4488.
(255) Ozaki, S.-i.; Ortiz, d. M. P. R. *J. Am. Chem. Soc.* **1995**, *117*, 7056-7064.
(256) Tuynman, A.; Vink, M. K. S.; Dekker, H. L.; Schoemaker, H. E.; Wever, R. *Eur. J. Biochem.* **1998**, *258*, 906-913.
(257) Boyd, D. R.; Sharma, N. D.; Haughey, S. A.; Kennedy, M. A.; McMurray, B. T.; Sheldrake, G. N.; Allen, C. C. R.; Dalton, H.; Sproule, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1929-1934.
(258) de Gonzalo, G.; Torres Pazmiño, D. E.; Ottolina, G.; Fraaije, M. W.; Carrea, G. *Tetrahedron: Asymmetry* **2006**, *17*, 130-135.
(259) Andersson, M. A.; Allenmark, S. G. *Tetrahedron* **1998**, *54*, 15293-15304.
(260) ten Brink, H. B.; Holland, H. L.; Schoemaker, H. E.; van Lingen, H.; Wever, R. *Tetrahedron: Asymmetry* **1999**, *10*, 4563-4572.
(261) Zhang, J.-D.; Li, A.-T.; Yang, Y.; Xu, J.-H. *Appl. Microbiol. Biotechnol.* **2010**, *85*, 615-624.
(262) Pievo, R.; Gullotti, M.; Monzani, E.; Casella, L. *Biochemistry* **2008**, *47*, 3493-3498.
(263) Auret, B. J.; Boyd, D. R.; Henbest, H. B. *J. Chem. Soc., C* **1968**, 2374-2376.
(264) Sugimoto, T.; Kokubo, T.; Miyazaki, J.; Tanimoto, S.; Okano, M. *Bioorg.*

Chem. **1981**, *10*, 311-323.
(265) Kobayashi, M.; Yabe, A. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 224-225.
(266) Davis, F. A.; Billmers, J. M. *J. Org. Chem.* **1983**, *48*, 2672-2675.
(267) Toda, F.; Mori, K.; Matsuura, Y.; Akai, H. *J. Chem. Soc., Chem. Commun.* **1990**, 1591-1593.
(268) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529-4533.
(269) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 7624-7626.
(270) Donnoli, M. I.; Superchi, S.; Rosini, C. *J. Org. Chem.* **1998**, *63*, 9392-9395.
(271) Lattanzi, A.; Piccirillo, S.; Scettri, A. *Adv. Synth. Catal.* **2007**, *349*, 357-363.
(272) Jia, X.; Li, X.; Xu, L.; Li, Y.; Shi, Q.; Au-Yeung, T. T. L.; Yip, C. W.; Yao, X.; Chan, A. S. C. *Adv. Synth. Catal.* **2004**, *346*, 723-726.
(273) Mohammadpoor-Baltork, I.; Hill, M.; Caggiano, L.; Jackson, R. F. W. *Synlett* **2006**, 3540-3544.
(274) Mikolajczyk, M.; Para, M. *J. Chem. Soc. D* **1969**, 1192-1193.
(275) Mikolajczyk, M.; Drabowicz, J. *Phosphorus Sulfur* **1976**, *1*, 301-303.
(276) Drabowicz, J.; Pacholczyk, M. *Phosphorus Sulfur* **1981**, *10*, 233-235.
(277) Annunziata, R.; Borgogno, G.; Montanari, F.; Quici, S.; Cucinella, S. *J. Chem. Soc., Perkin Trans. 1* **1981**, 113-118.
(278) Marchese, G.; Naso, F.; Ronzini, L. *J. Chem. Soc., Chem. Commun.* **1974**, 830-831.
(279) Kunieda, N.; Motoki, H.; Kinoshita, M. *Chem. Lett.* **1978**, 713-716.
(280) Kunieda, N.; Nokami, J.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 256-259.
(281) Ohta, H.; Kato, Y.; Tsuchihashi, G. *Chem. Lett.* **1986**, 217-218.
(282) Pirkle, W. H.; Rinaldi, P. L. *J. Am. Chem. Soc.* **1977**, *99*, 3510-3511.
(283) Eskenazi, C.; Nicoud, J. F.; Kagan, H. B. *J. Org. Chem.* **1979**, *44*, 995-999.
(284) Abo, M.; Tachibana, M.; Okubo, A.; Yamazaki, S. *Biosci., Biotechnol., Biochem.* **1994**, *58*, 596-597.
(285) Abo, M.; Tachibana, M.; Okubo, A.; Yamazaki, S. *Bioorg. Med. Chem.* **1995**, *3*, 109-112.
(286) Hanlon, S. P.; Graham, D. L.; Hogan, P. J.; Holt, R. A.; Reeve, C. D.; Shaw, A. L.; McEwan, A. G. *Microbiology* **1998**, *144 (Pt 8)*, 2247-2253.
(287) Boyd, D. R.; Sharma, N. D.; Byrne, B. E.; Haughey, S. A.; Kennedy, M. A.; Allen, C. C. R. *Org. Biomol. Chem.* **2004**, *2*, 2530-2537.
(288) Andersen, K. K. *Tetrahedron Lett.* **1962**, *3*, 93-95.
(289) Andersen, K. K. *J. Org. Chem.* **1964**, *29*, 1953-1956.
(290) Andersen, K. K.; Gaffield, W.; Papanikolaou, N. E.; Foley, J. W.; Perkins, R. I. *J. Am. Chem. Soc.* **1964**, *86*, 5637-46.
(291) Hope, H.; De, l. C. U.; Homer, G. D.; Messing, A. W.; Sommer, L. H. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 612-613.
(292) Axelrod, M.; Bickart, P.; Jacobus, J.; Green, M. M.; Mislow, K. *J. Amer. Chem. Soc.* **1968**, *90*, 4835-4842.
(293) Herbrandson, H. F.; Dickerson, R. T., Jr.; Weinstein, J. *J. Am. Chem. Soc.* **1956**, *78*, 2576-2578.
(294) Drabowicz, J.; Bujnicki, B.; Mikolajczyk, M. *J. Org. Chem.* **1982**, *47*, 3325-3327.
(295) Mariz, R.; Luan, X.; Gatti, M.; Linden, A.; Dorta, R. *J Am Chem Soc* **2008**, *130*, 2172-2173.

(296) Burgi, J. J.; Mariz, R.; Gatti, M.; Drinkel, E.; Luan, X.; Blumentritt, S.; Linden, A.; Dorta, R. *Angew. Chem. Int. Ed.* **2009**, *48*, 2768-2771.
(297) Andersen, K. K.; Bujnicki, B.; Drabowicz, J.; Mikolajczyk, M.; O'Brien, J. B. *J. Org. Chem.* **1984**, *49*, 4070-4072.
(298) Whitesell, J. K.; Wong, M. S. *J. Org. Chem.* **1991**, *56*, 4552-4554.
(299) Whitesell, J. K.; Wong, M.-S. *J. Org. Chem.* **1994**, *59*, 597-601.
(300) Ridley, D. D.; Smal, M. A. *J. Chem. Soc., Chem. Commun.* **1981**, 505-506.
(301) Fernandez, I.; Khiar, N.; Llera, J. M.; Alcudia, F. *J. Org. Chem.* **1992**, *57*, 6789-6796.
(302) Khiar, N.; Fernández, I.; Alcudia, F. *Tetrahedron Lett.* **1994**, *35*, 5719-5722.
(303) Ridley, D. D.; Smal, M. A. *Aust. J. Chem.* **1982**, *35*, 495-507.
(304) Alcudia, F. K., N.; Fernandez, I.; *Tetrahedron Lett.* **1991**, 32, 7299.
(305) Drabowicz, J.; Bujnicki, B.; Biscarini, P.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **1999**, *10*, 3177-3187.
(306) Harpp, D. N.; Vines, S. M.; Montillier, J. P.; Chan, T. H. *J. Org. Chem.* **1976**, *41*, 3987-3992.
(307) Jacobus, J.; Mislow, K. *Chem. Commun.* **1968**, 253-254.
(308) Oppolzer, W.; Froelich, O.; Wiaux-Zamar, C.; Bernardinelli, G. *Tetrahedron Lett.* **1997**, *38*, 2825-2828.
(309) Evans, D. A.; Faul, M. M.; Colombo, L.; Bisaha, J. J.; Clardy, J.; Cherry, D. *J. Am. Chem. Soc.* **1992**, *114*, 5977-5985.
(310) Lockard, J. P.; Schroeck, C. W.; Johnson, C. R. *Synthesis* **1973**, 485-486.
(311) Syed, M. K.; Casey, M. *Eur. J. Org. Chem.* **2011**, *2011*, 7207-7214.
(312) Wang, P.; Chen, J.; Cun, L.; Deng, J.; Zhu, J.; Liao, J. *Org. Biomol. Chem.* **2009**, *7*, 3741-3747.
(313) Cardellicchio, C.; Fiandanese, V.; Naso, F.; Scilimati, A. *Tetrahedron Lett.* **1992**, *33*, 5121-5124.
(314) Cardellicchio, C.; Iacuone, A.; Naso, F.; Tortorella, P. *Tetrahedron Lett.* **1996**, *37*, 6017-6020.
(315) Capozzi, M. A. M.; Cardellicchio, C.; Fracchiolla, G.; Naso, F.; Tortorella, P. *J. Am. Chem. Soc.* **1999**, *121*, 4708-4709.
(316) Cardellicchio, C.; Fracchiolla, G.; Naso, F.; Tortorella, P. *Tetrahedron* **1999**, *55*, 525-532.
(317) Capozzi, M. A. M.; Cardellicchio, C.; Naso, F.; Tortorella, P. *J. Org. Chem.* **2000**, *65*, 2843-2846.
(318) Durst, T.; LeBelle, M. J.; Van, d. E. R.; Tin, K. C. *Can. J. Chem.* **1974**, *52*, 761-766.
(319) Hojo, M.; Masuda, R.; Saeki, T.; Fujimori, K.; Tsutsumi, S. *Synthesis* **1977**, 789-791.
(320) Furukawa, N.; Ogawa, S.; Matsumura, K.; Fujihara, H. *J. Org. Chem.* **1991**, *56*, 6341-6348.
(321) Wudl, F.; Lee, T. B. K. *J. Chem. Soc., Chem. Commun.* **1972**, 61-62.
(322) Wudl, F.; Lee, T. B. K. *J. Am. Chem. Soc.* **1973**, *95*, 6349-6358.
(323) Benson, S. C.; Snyder, J. K. *Tetrahedron Lett.* **1991**, *32*, 5885-5888.
(324) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 7880-7881.
(325) Han, Z.; Krishnamurthy, D.; Grover, P.; Wilkinson, H. S.; Fang, Q. K.; Su, X.; Lu, Z.-H.; Magiera, D.; Senanayake, C. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 2032-2035.
(326) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Su, X.; Wilkinson, H. S.;

Lu, Z.-H.; Magiera, D.; Senanayake, C. H. *Tetrahedron* **2005**, *61*, 6386-6408.
(327) Garcia, R. J. L.; Alemparte, C.; Aranda, M. T.; Zarzuelo, M. M. *Org Lett* **2003**, *5*, 75-78.
(328) Qin, Y.; Wang, C.; Huang, Z.; Xiao, X.; Jiang, Y. *J. Org. Chem.* **2004**, *69*, 8533-8536.
(329) Lu, B. Z.; Jin, F.; Zhang, Y.; Wu, X.; Wald, S. A.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 1465-1468.
(330) Rebiere, F.; Kagan, H. B. *Tetrahedron Lett.* **1989**, *30*, 3659-3662.
(331) Kagan, H. B.; Rebiere, F. *Synlett* **1990**, 643-650.
(332) Rebiere, F.; Samuel, O.; Ricard, L.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 5991-5999.
(333) Capozzi, M. A. M.; Cardellicchio, C.; Naso, F.; Spina, G.; Tortorella, P. *J. Org. Chem.* **2001**, *66*, 5933-5936.
(334) Capozzi, M. A. M.; Cardellicchio, C.; Naso, F.; Rosito, V. *J. Org. Chem.* **2002**, *67*, 7289-7294.
(335) Capozzi, M. A. M.; Cardellicchio, C.; Naso, F. *Eur. J. Org. Chem.* **2004**, 1855-1863.
(336) Newhouse, T. R.; Li, X.; Blewett M. M.; Whitehead, C. M.; Corey, E. J. *J. Am. Chem. Soc.* **2012**, 17354-17357.

Chapter 2

Results and Discussion

2.0 Sulfoxides

Sulfoxides are just one of an array of functional groups of organic compounds involving the sulfur atom; they have the general structure RS(O)R' in which R and R' are aryl or alkyl groups.[1,2] The sulfur to oxygen bond is polarised due to the presence of the electronegative oxygen atom which acts as a hydrogen bond acceptor.[1-4]

The nature of the sulfur to oxygen bond has been extensively investigated. Double bond characteristics were first assigned to the linkage in both sulfoxides and sulfones by Philips *et al.* due to the small dipole moments of the sulfur to oxygen linkage (2.2 to 2.9 D), the short bond length (1.45 Å) and the relatively high bond strength.[5] However the dipole moments of sulfoxides were recalculated by Cumper and Walker; this study found the dipole moments to be in the range 2.8 to 4.3 D.[6] Toshiyasu *et al*. also reported relatively large dipole moments, including 4.0 D for diaryl sulfoxides suggesting that the sulfur to oxygen bond is, in fact, better represented by a single semi-polar bond, rather than a covalent double bond.[7] Later reports demonstrated that the bond dissociation energies of the sulfur to oxygen bond in sulfoxides are lower than those in sulfones (86 kcal/mol average to 112 kcal/mol average, respectively) again indicating that the sulfur to oxygen linkage is best represented by a single semi-polar bond (Figure 2.1) and as a covalent double bond in sulfones.[8,9]

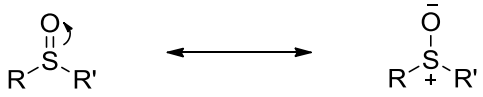


Figure 2.1

Sulfoxides are configurationally stable up to 200 °C, which means that enantiopure sulfoxides can be isolated.[10] The fact that single enantiomers of the sulfoxide can be isolated has placed this group at the centre of many modern asymmetric synthesis strategies in which the sulfoxide group is used to exert stereocontrol over the reaction.

2.1 Project Background

Enantiopure sulfoxides are important reagents in organic chemistry due to their use as chiral auxiliaries in a broad range of synthetic reactions.[11-13] Many sulfoxides exhibit important biological activity and, as a result, they have also found use in pharmaceutical applications.[14,15]

Enantiopure sulfoxides can be synthesised by three main routes:[16]

(1) Nucleophilic substitution (Andersen method)

(2) Kinetic resolution of racemic sulfoxides

(3) Asymmetric oxidation of sulfides

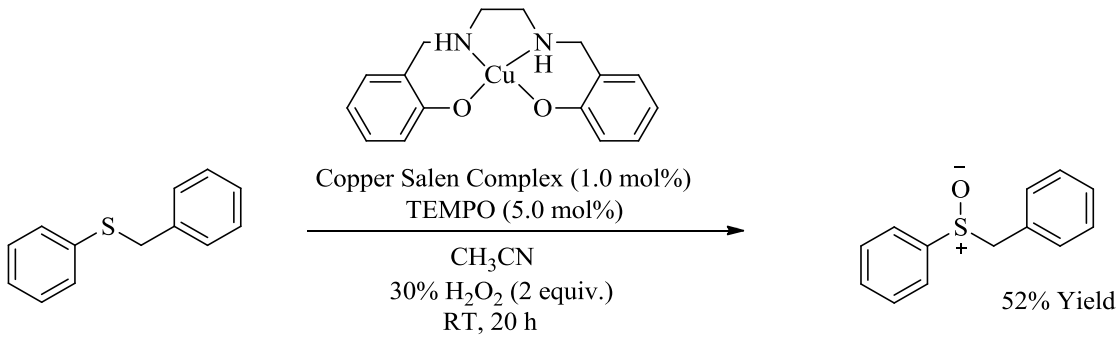
The Andersen method, which involves the use of chiral sulfinates to prepare enantiopure sulfoxides, is limited by the fact that only one sulfinate ester, menthyl *p*-toluenesulfinate, is readily available. The synthesis of enantiopure sulfoxides through kinetic resolution of racemic sulfoxides is also limited, since the maximum obtainable yield is 50%, although the utilisation of asymmetric sulfide oxidation coupled with complementary kinetic resolution is more practical.[16] As a result of these limitations, the most attractive method for the synthesis of enantiopure sulfoxides is asymmetric sulfide oxidation.[16] These oxidations can be promoted by metal and non-metal based systems. Although chiral oxaziridines, hydroperoxides, peracids, iodine based systems, enzymes and whole cell systems can promote asymmetric sulfoxidation, their use has not received the same amount of attention as metal based catalysts for a number of reasons. Firstly, the use of chiral hydroperoxides, peracids and iodine based systems has only afforded sulfoxides in modest enantiopurities.[16] On the other hand, chiral oxaziridines must be used in near stoichiometric amounts which reduces the efficiency of this method on a large scale.[16] Although the use of biological systems, such as isolated enzymes and whole cell systems, to promote asymmetric sulfoxidation has been successful in many cases, its usefulness is reduced by the very limited substrate scope that biological systems tend to have for sulfide substrates.[16]

Complexes of metals such as titanium, vanadium, iron, manganese, copper, aluminium, zirconium, niobium and molybdenum have been used to catalyse the asymmetric oxidation of sulfides.[16,17] The use of titanium (Kagan system) and vanadium complexes (Bolm system) have found the most use in sulfur oxidation, and are now readily employed in the synthesis of a wide range of enantiopure sulfoxides, including biologically active compounds.[16,17]

However, both the Kagan and Bolm methodologies have a number of disadvantages associated with their use. The Kagan system is sensitive to atmospheric moisture, has low

turnover numbers and it employs a complex and expensive catalytic system,[18] while the Bolm system uses vanadium as the metal catalyst, which is known to exert toxic and mutagenic effects on a variety of biological systems.[19]

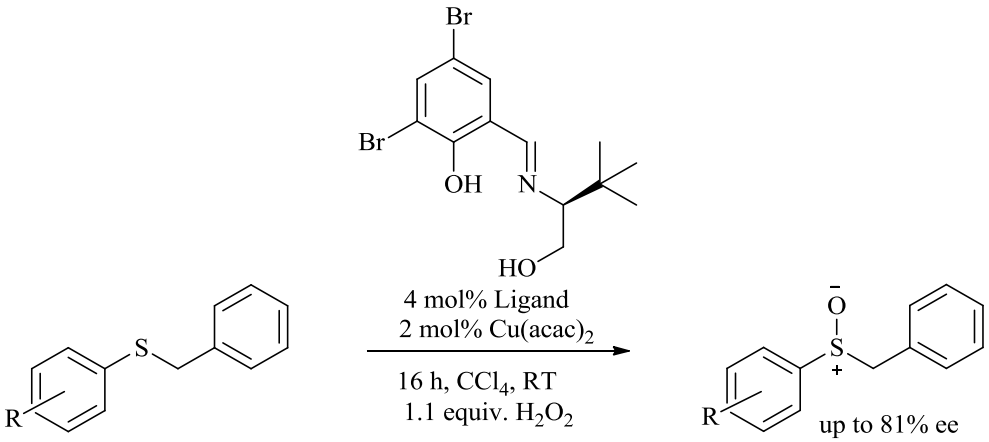
There have been very few reports of the use of copper complexes to promote asymmetric sulfoxidation; the research groups of Cross,[20] Kraemer,[21] Zhu,[22] Iglesias[23] have all used copper-based systems to asymmetrically oxidise sulfides, but with limited success (enantioselectivities of 0-30% ee, see Section 1.2.15). However, the use of copper is advantageous since it is relatively cheap and environmentally benign. In 2005, Velusamy *et al.* reported a chemoselective achiral copper-catalysed route to sulfoxides.[24] This system used TEMPO (2,2,6,6-tetramethyl-1-piperdinyl-oxyl, free radical) in conjunction with a copper-salen catalyst and hydrogen peroxide as oxidant to prepare racemic aryl benzyl, aryl alkyl, benzyl alkyl and alkyl alkyl sulfoxides in moderate to good yields (Scheme 2.1).



Scheme 2.1

Excellent selectivity for sulfoxide formation was observed with the addition of TEMPO, with little, if any, over-oxidation to form sulfone. This oxidising system employed somewhat similar conditions to those used in vanadium-catalysed asymmetric sulfide oxidations reported by Bolm, in that the oxidant used was hydrogen peroxide and an O,N-based ligand was employed. It was considered possible that the use of a chiral ligand rather than the achiral ligand used by Velusamy *et al.* would result in asymmetric induction.

Kelly carried out a preliminary investigation of copper-catalysed asymmetric sulfoxidation using salicylaldehyde derived ligands, focussing primarily on the oxidation of aryl benzyl sulfides.[25] Kelly demonstrated that copper-Schiff base catalysis can been used to produce enantioenriched sulfoxides in good enantiopurities (up to 81% ee), albeit in modest yields (generally 15 to 30%, Scheme 2.2).



Scheme 2.2

2.2 Objectives

The overall objective of this work was to expand the investigation of copper-catalysed asymmetric sulfide oxidation building on Kelly's earlier work.[26]

Specifically, the key objectives of this project were

(1) To improve the efficiency of the oxidation both in terms of yield and enantioselectivity.

(2) To investigate the effect of variation of reaction conditions such as reaction solvent, Schiff base ligand and temperature on the oxidation.

(3) To investigate the steric and electronic effects of the sulfide substituents on the efficiency of the oxidation.

(4) To expand the substrate scope of this methodology.

(5) To apply the copper-mediated oxidation to the synthesis of biologically active sulfoxides.

(6) To understand the nature of the interactions in the copper-ligand substrate complex which lead to enantiocontrol, ultimately with a view to the design of new enantioselective copper catalysis.

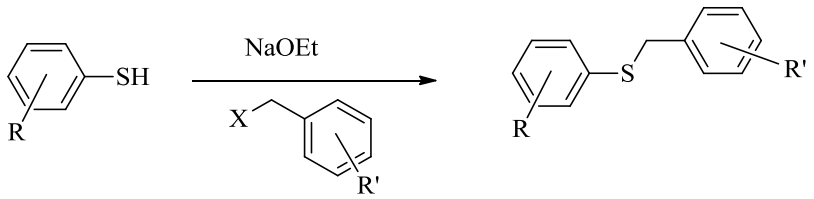
2.3 Preparation of Sulfides

To enable detailed investigation of the influence of sulfide structure on the enantioselective copper-mediated oxidation, 49 sulfides with varying substituents were prepared, as summarised in Figures 2.8, 2.17, 2.18, 2.24, 2.26, 2.27 and 2.28. Methyl *p*-tolyl sulfide, ethyl phenyl sulfide, benzyl phenyl sulfide and benzyl methyl sulfide were obtained commercially. Sulfides were prepared by four distinct methods. *Methods A* and *B* had been used previously in the research group, while *methods C* and *D* were reported in the literature. All of the sulfides were stable at RT over an extended period of time unless otherwise indicated. While in most cases the sulfide odour was relatively mild, care was taken in handling all thiols and sulfides with use of bleach to destroy residual material before disposal.

Method A[26]

This method was used for the synthesis of the majority of sulfides used in this work (Table 2.0, 2.1, 2.2 & 2.3). Sodium thiolates were generated *in situ* by addition of the thiol to freshly prepared sodium ethoxide at 0 °C, followed by addition of a benzyl or alkyl halide leading to efficient formation of the sulfides which were subsequently purified by column chromatography on silica gel.

Table 2.0 Preparation of Aryl Benzyl Sulfides using *Method A*



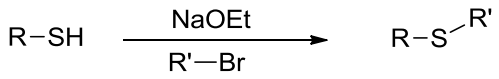
Sulfide	R	X	R'	Yield %[a]	Appearance
[1][26,27]	4-MeO	Br	H	95	White Solid
[2][26,28]	3-MeO	Br	H	83	Clear Oil
[3][26,27]	4-MeO	Br	H	55	White Solid
[4][26,29]	4-Me	Cl	4'-MeO	75	White Solid
[5][30]	2-Me	Br	H	90	Clear Oil

[6]	3-Me	Br	H	91	Clear Oil
[7][26,29]	4-Me	Br	H	76	White Solid
[8]	H	Br	2'-Me	86	Clear Oil
[9]	H	Br	3'-Me	77	Clear Oil
[10][31]	H	Br	4'-Me	87	White Solid
[11][32]	H	Br	2'-Cl	84	Clear Oil
[12][33]	H	Br	3'-Cl	93	Clear Oil
[13][34]	H	Cl	4'-Cl	89	White Solid
[14][44,71]	2-Cl	Br	H	81	Clear Oil
[15]	3-Cl	Br	H	91	White Solid
[16][29]	4-Cl	Br	H	92	White Solid
[17][35]	4-Me	Br	2'-Me	88	Clear Oil
[18]	4-Me	Br	3'-Me	91	Clear Oil
[19][29]	4-Me	Br	4'-Cl	78	White Solid
[20][36]	4-Me	Br	3'-Cl	81	White Solid
[21]	4-Me	Br	2'-Cl	83	Clear Oil
[22]	2-MeO	Br	2'-Cl	73	White Solid

a) Yield of sulfide after purification by column chromatography.

While sulfides **[1]–[5]**, **[7]**, **[10]–[14]**, **[16]**, **[17]**, **[19]** and **[20]** are known compounds prepared following a similar procedure, sulfides **[6]**, **[8]**, **[9]**, **[15]**, **[21]** and **[22]** are novel compounds and are fully characterised in Section 3.2. As summarised in Table 2.0, aryl benzyl sulfides bearing a range of different substituents on each of the aryl rings were efficiently prepared by this method. This method was subsequently extended to a broader range of sulfides as summarised in Table 2.1.

Table 2.1 Preparation of other Sulfides using *Method A*



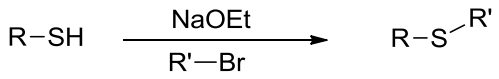
Sulfide	R	R'	Yield %[a]	Appearance
[23][37]	Ph	CH_2-Cyclohexyl	95	Clear Oil
[24][38]	Ph	*i*-Bu	97	Clear Oil
[25][39]	Ph	*i*-Pr	70	Clear Oil
[26][40]	Ph	CH_2-2'-Naphthyl	82	White Solid
[27][41]	Ph	$CH_2(CH_2)_{10}CH_3$	78	White Solid
[28][42]	Ph	$CH_2(CH_2)_6CH_3$	84	Clear Oil
[29][43]	2-Naphthyl	Bn	84	White Solid
[30][44]	1-Naphthyl	Bn	36	White Solid
[31]	2-Naphthyl	4'-Chlorobenzyl	75	White Solid
[32]	1-Naphthyl	4'-Chlorobenzyl	65	White Solid

a) Yield of sulfide after purification by column chromatography.

While sulfides **[23]–[30]** are known compounds prepared following a similar procedure, sulfides **[31]** and **[32]** are novel compounds and are fully characterised in Section 3.2. The only sulfide which was obtained in modest yield was 1-naphthyl benzyl sulfide **[30]** in which case unreacted thiol was recovered.

Interestingly alkyl thiols can also be used in this process leading to efficient sulfide synthesis as illustrated in Table 2.2.

Table 2.2 Preparation of other Sulfides using Alkyl Thiols using *Method A*



Sulfide	R[b]	R'	Yield %[a]	Appearance
[33][45]	$CH_3(CH_2)_{10}CH_2$	Bn	88	Clear Oil
[34][46]	$CH_3(CH_2)_6CH_2$	Bn	83	Clear Oil
[35][47]	*i*-Pr	Bn	88	Clear Oil
[36][48]	Cyclohexyl	Bn	87	Clear Oil
[37][49]	*i*-Bu	Bn	91	Clear Oil
[38][31]	*t*-Bu	Bn	91	Clear Oil

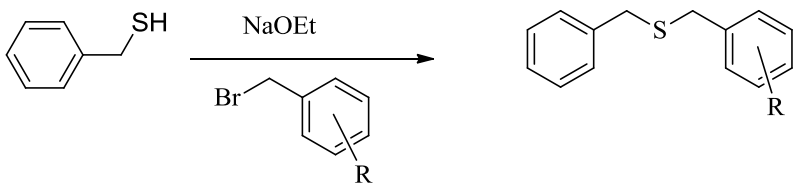
a) Yield of sulfide after purification by column chromatography.

b) Extreme care is taken when using alkyl thiols due to their malodourus nature. These compounds were weighed out in the fumehood, with the fumehood sash kept as low as possible, and all glassware involved with the use of these compounds is soaked in an aqueous bleach bath prior to washing. The containers containing these thiols are sealed using parafilm and are kept in the appropriate safety cupboard.

Sulfides **[33]–[38]** are known compounds prepared following a similar procedure.

A series of substituted dibenzyl sulfides was also prepared in good yields using *Method A* as shown in Table 2.3. Dibenzyl sulfides were prepared as described in Scheme 2.3, except benzyl mercaptan was used instead of the thiophenol derivative.

Table 2.3 Preparation of Dibenzyl Sulfides using *Method A*



Sulfide	R	Yield %[a]	Appearance
[39][50]	2-Me	84	White Solid
[40][50]	3-Me	85	Clear Oil

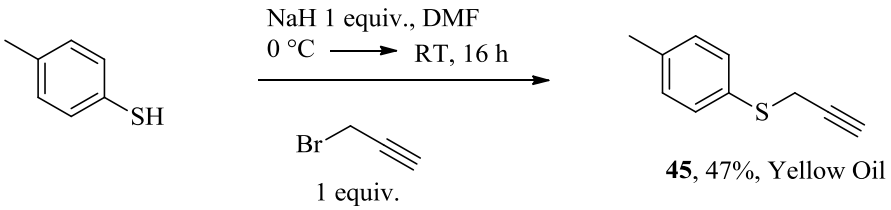
[41][50]	4-Me	80	White Solid
[42]	2-Cl	87	Clear Oil
[43][50]	3-Cl	78	Clear Oil
[44][50]	4-Cl	81	Clear Oil

a) Yield of sulfide after purification by column chromatography.

While sulfides **[39]–[41]**, **[43]** and **[44]** are known compounds prepared following an identical procedure, sulfide **[42]** is a novel compound and is fully characterised in Section 3.2.

Method B[26]

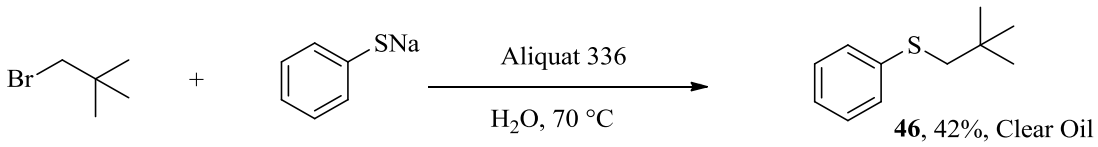
Kelly had described the synthesis of sulfide **[45]** through use of sodium hydride in dimethyl formamide (DMF) rather than sodium ethoxide in ethanol.[26] Accordingly, this method was employed in this work as illustrated in Scheme 2.4. Sulfide **[45]** is unstable at RT and turns a dark colour on storage at RT over approximately two months.



Scheme 2.4

Method C[51]

Sulfide **[46]** had been previously described in the literature employing the conditions described in Scheme 2.5.[51] During this work the neopentyl sulfide **[46]** was prepared in modest yield, significantly lower than the 78% yield reported by Landini *et al.*[51] To separate the sulfide from the diphenyl disulfide and the phase transfer reagent Kugelröhr distillation proved efficient as described in the literature.

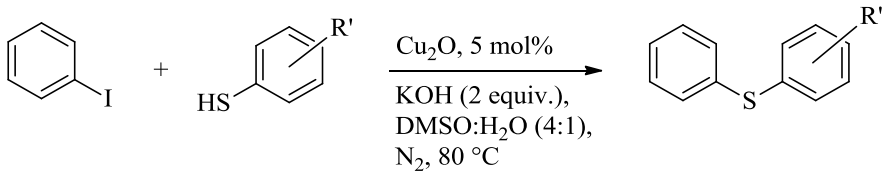


Scheme 2.5

Method D[52]

Synthesis of diaryl sulfides has been described by Xu *et al. via* copper-mediated nucleophilic aromatic substitution as illustrated in Table 2.4.[52] This approach was employed in this work to achieve the synthesis of a series of differentially disubstituted diaryl sulfides in similar yields to that reported in the literature.[52]

Table 2.4 Preparation of Diphenyl Sulfides using *Method D*



Sulfide	R'	Yield %[a]	Appearance
[47][52,53]	2'-MeO	71	Clear Oil
[48][52,53]	4'-MeO	75	White Solid
[49][52,53]	4'-Me	73	Clear Oil

a) Yield of sulfide after purification by column chromatography.

Note: Sulfides **[27]**, **[28]** and **[33]**–**[38]** have an unpleasant odour.

Spectral characteristics agreed with literature data for each of the known sulfides while the novel sulfides were fully characterised including typically ^{1}H and ^{13}C NMR, IR, high and low resolution mass spectrometry, and microanalysis.

As *Methods B* and *C* had previously been described for the synthesis of sulfides **[45]** and **[46]**, this approach was employed in this work; use of sodium ethoxide in ethanol was not explored.

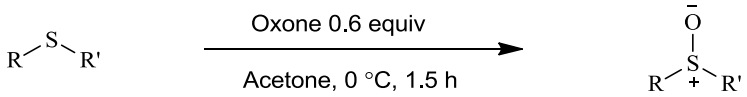
2.4 Preparation of Racemic Sulfoxides

Racemic sulfoxides were prepared by oxidation of the corresponding sulfides to provide reference materials for chiral HPLC (Table 2.5). While there are numerous oxidising agents available for the achiral oxidation of sulfides, Oxone®[54] in acetone was used as oxidant in this project based on previous experience in the research group.[26] The progress of the oxidation was readily monitored by TLC and while over-oxidation to the sulfone can occur it was

readily controlled through use of 0.6 equivalents of Oxone®[54] and careful TLC monitoring. The reaction was terminated as soon as sulfone began to appear by TLC. Typically, the sulfones are slightly more polar than the sulfides, while the sulfoxides are much more polar. Although the generation of dimethyl dioxirane as a reaction intermediate is possible when using Oxone®[54] in acetone, no attempt was made to determine if dimethyl dioxirane was involved in the oxidation during this work.[55]

The pure sulfoxides were readily obtained free of sulfides and sulfones following column chromatography. The sulfoxides are readily characterised by the appearance of the S-O stretch in the IR spectrum at ν_{max} ~ 1030 cm^{-1}.

Table 2.5 Preparation of Racemic Sulfoxides



Sulfoxide	R	R'	Yield %[a]	Appearance
[50][26,56]	Ph	Bn	86	White Solid
[51][26,57]	4-$CH_3C_6H_4$	Bn	84	White Solid
[52][26,58]	4-$CH_3C_6H_4$	4'-Methoxybenzyl	89	White Solid
[53][26,58]	2-$MeOC_6H_4$	Bn	81	White Solid
[54][26,58]	3-$MeOC_6H_4$	Bn	77	Clear Oil
[55][26,58]	4-$MeOC_6H_4$	Bn	79	White Solid
[56][37]	Ph	CH_2-Cyclohexyl	74[b]	White Solid
[57][59]	4-$CH_3C_6H_4$	CH_3	91	Clear Oil
[58][60]	Ph	C_2H_5	90	Clear Oil
[59][61]	Ph	$CH(CH_3)_2$	82	Clear Oil
[60][62]	Ph	$CH_2CH(CH_3)_2$	83	Clear Oil
[61]	Ph	$CH_2C(CH_3)_3$	71	Clear Oil
[62]	Ph	CH_2-2'-Naphthyl	74	White Solid
[63][63]	$(CH_3)_2CH$	Bn	88	Clear Oil

[64][64]	$(CH_3)_2CHCH_2$	Bn	86	White Solid
[65][65,66]	$(CH_3)_3C$	Bn	73	White Solid
[66][67]	2-Naphthyl	Bn	76[b]	White Solid
[67]	1-Naphthyl	Bn	81[b]	White Solid
[68]	2-Naphthyl	4'-Chlorobenzyl	83[b]	White Solid
[69]	1-Naphthyl	4'-Chlorobenzyl	78[b]	White Solid
[70][65]	Cyclohexyl	Bn	89	Clear Oil
[71][68]	Ph	$CH_2(CH_2)_{10}CH_3$	81	White Solid
[72][68]	Ph	$CH_2(CH_2)_6CH_3$	83	White Solid
[73][69]	Bn	$CH_2(CH_2)_{10}CH_3$	77[b]	White Solid
[74][69]	Bn	$CH_2(CH_2)_6CH_3$	85	White Solid
[75][30]	2-$CH_3C_6H_4$	Bn	88	White Solid
[76]	2-$CH_3C_6H_4$	Bn	92	White Solid
[77][70]	Ph	2'-Methylbenzyl	85	White Solid
[78][71]	Ph	3'-Methylbenzyl	84	Clear Oil
[79][72]	Ph	4'-Methylbenzyl	90	White Solid
[80][26,73]	4-$CH_3C_6H_4$	CH_2-C≡CH	71	Clear Oil
[81][56]	Ph	CH_2-CH=CH_2	73	Clear Oil
[82][74]	Bn	CH_2-CH=CH_2	82	Clear Oil
[83]	Bn	CH_3	90	Clear Oil
[84]	Ph	2'-Chlorobenzyl	74	White Solid
[85][71]	Ph	3'-Chlorobenzyl	77	White Solid
[86][71]	Ph	4'-Chlorobenzyl	83	White Solid
[87][75]	2-ClC_6H_4	Bn	81	White Solid
[88][76]	3-ClC_6H_4	Bn	80	White Solid
[89][71]	4-ClC_6H_4	Bn	85	White Solid

[90][26,77]	4-FC_6H_4	Bn	81	White Solid
[91]	4-$CH_3C_6H_4$	2'-Methylbenzyl	89	White Solid
[92][71]	4-$CH_3C_6H_4$	3'-Methylbenzyl	87	White Solid
[93][78]	4-$CH_3C_6H_4$	4'-Chlorobenzyl	75	White Solid
[94][79]	4-$CH_3C_6H_4$	3'-Chlorobenzyl	79	White Solid
[95]	4-$CH_3C_6H_4$	2'-Chlorobenzyl	74	Clear Oil
[96]	2-$MeOC_6H_4$	2'-Chlorobenzyl	71	White Solid
[97]	Bn	2'-Methylbenzyl	88	White Solid
[98]	Bn	3'-Methylbenzyl	82	White Solid
[99][80]	Bn	4'-Methylbenzyl	86	White Solid
[100][81]	Bn	2'-Chlorobenzyl	80	White Solid
[101]	Bn	3'-Chlorobenzyl	74	White Solid
[102][82]	Bn	4'-Chlorobenzyl	83	White Solid
[103][83]	Ph	2'-$MeOC_6H_4$	84	White Solid
[104][84]	Ph	3'-$MeOC_6H_4$	88	White Solid
[105][85]	Ph	4'-MeC_6H_4	82	White Solid

a) Yield of sulfoxide after purification by column chromatography.

b) A significant amount of sulfone formation was observed by TLC analysis during these oxidations.

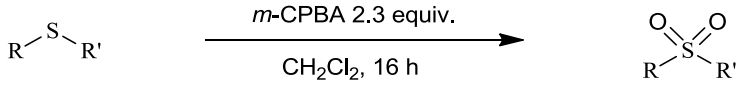
All of the sulfoxides prepared were stable at RT over an extended period of time and did not have a strong odour; most of them were solids and were readily handled.

While sulfoxides **[50]–[60]**, **[63]–[66]**, **[70]–[75]**, **[77]–[82]**, **[85]–[90]**, **[92]–[94]**, **[99]**, **[100]**, **[102]–[105]** are known compounds prepared following a similar procedure, sulfoxides **[61]**, **[62]**, **[67]–[69]**, **[76]**, **[83]**, **[84]**, **[91]**, **[95]–[98]** and **[101]** are novel compounds and are fully characterised in Section 3.4. Spectral characteristics for the known sulfoxides were in agreement with the literature data.

2.5 Preparation of Sulfones

To provide reference material for use in the analysis of copper-mediated oxidation genuine samples of sulfones were prepared by oxidation of the corresponding sulfides (Table 2.6) using 2.3 equivalents of *m*-CPBA to ensure complete oxidation of the sulfide to the sulfone (Table 2.6). A basic workup yielded the crude sulfone which was then purified by column chromatography on silica gel to give the sulfones in good yield. All of the sulfones prepared were stable at RT over an extended period of time and were odourless, and most were solids.

Table 2.6 Preparation of Sulfones



Sulfone	R	R'	Yield %[a]	Appearance
[106][43]	Ph	Bn	94	White Solid
[107][43,86]	4-$CH_3C_6H_4$	Bn	90	White Solid
[108][87,88]	4-$CH_3C_6H_4$	4'-Methoxybenzyl	79	White Solid
[109][89]	4-$MeOC_6H_4$	Bn	84	White Solid
[110][43]	4-$CH_3C_6H_4$	CH_3	91	White Solid
[111][90]	Ph	C_2H_5	88	White Solid
[112][91]	Ph	$CH_2CH(CH_3)_2$	80	White Solid
[113][92]	Ph	$CH_2C(CH_3)_3$	74	White Solid
[114][93]	$(CH_3)_2CH$	Bn	87	Clear Oil
[115][94]	$(CH_3)_2CHCH_2$	Bn	81	White Solid
[116][95]	$(CH_3)_3C$	Bn	77	White Solid
[117][43]	2-Naphthyl	Bn	75	White Solid
[118][96]	1-Naphthyl	Bn	81	White Solid
[119][97]	Cyclohexyl	Bn	82	White Solid
[120][98]	Ph	$CH_2(CH_2)_{10}CH_3$	90	White Solid

[121][99]	Ph	$CH_2(CH_2)_6CH_3$	88	White Solid
[122][100]	Bn	$CH_2(CH_2)_{10}CH_3$	91	White Solid
[123][100]	Bn	$CH_2(CH_2)_6CH_3$	84	White Solid
[124]	2-$CH_3C_6H_4$	Bn	81	White Solid
[125][101]	3-$CH_3C_6H_4$	Bn	89	White Solid
[126][87,102]	Ph	2'-Methylbenzyl	86	White Solid
[127][103]	Ph	3'-Methylbenzyl	92	White Solid
[128][104,103]	Ph	4'-Methylbenzyl	83	White Solid
[129][105]	Ph	CH_2-CH=CH_2	73	Clear Oil
[130][106]	Bn	CH_2-CH=CH_2	81	White Solid
[131][107]	Bn	CH_3	81	White Solid
[132][108]	Ph	2'-Chlorobenzyl	87	White Solid
[133][33]	Ph	3'-Chlorobenzyl	79	White Solid
[134][33,87]	Ph	4'-Chlorobenzyl	80	White Solid
[135][109]	2-ClC_6H_4	Bn	84	White Solid
[136][109]	3-ClC_6H_4	Bn	84	White Solid
[137][110,104]	4-ClC_6H_4	Bn	78	White Solid
[138][111]	4-$CH_3C_6H_4$	2'-Methylbenzyl	90	White Solid
[139]	4-$CH_3C_6H_4$	3'-Methylbenzyl	88	White Solid
[140][112,113]	4-$CH_3C_6H_4$	4'-Chlorobenzyl	79	White Solid
[141][36]	4-$CH_3C_6H_4$	3'-Chlorobenzyl	74	White Solid
[142][114]	4-$CH_3C_6H_4$	2'-Chlorobenzyl	83	White Solid
[143]	2-$MeOC_6H_4$	2'-Chlorobenzyl	77	White Solid
[144][115]	Bn	2'-Methylbenzyl	91	White Solid
[145]	Bn	3'-Methylbenzyl	83	White Solid
[146][115]	Bn	4'-Methylbenzyl	86	White Solid

[147][116]	Bn	2'-Chlorobenzyl	80	White Solid
[148][117]	Bn	3'-Chlorobenzyl	76	White Solid
[149][117]	Bn	4'-Chlorobenzyl	81	White Solid
[150][118]	Ph	2'-$MeOC_6H_4$	85	White Solid
[151][118]	Ph	4'-$MeOC_6H_4$	89	White Solid
[152][119]	Ph	4'-MeC_6H_4	84	White Solid

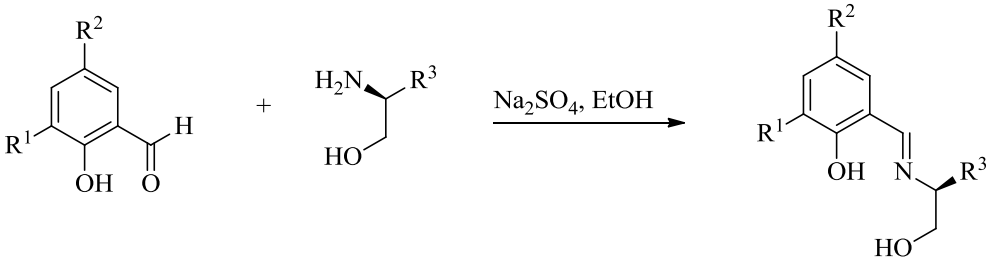
a) Yield of sulfone after purification by column chromatography.

While sulfones **[106]–[123]**, **[125]–[138]**, **[140]–[142]**, **[144]** and **[146]–[152]** are known compounds prepared following a similar procedure, sulfones **[124]**, **[139]**, **[143]** and **[145]** are novel compounds and are fully characterised in Section 3.5. Spectral characteristics for the known sulfones were in agreement with the literature data.

2.6 Preparation of Schiff Base Ligands

Schiff base ligands have been used extensively in asymmetric catalysis and have been reviewed extensively.[120,121] Bolm has explored the nature of steric and electronic effects.[122] Based on Bolm's work, ligands **[153]–[162]** were selected for investigation enabling exploration of both the steric and electronic effects of the aryl substituents R^1 and R^2 and the steric effects of R^3 (Table 2.7). The ligands were prepared by treating a commercially available salicylaldehyde derivative with a commercially available enantiopure amino alcohol in the presence of a drying agent (sodium sulfate), followed by column chromatography to generate the pure ligand. Each of the Schiff base ligands prepared were stable at RT over an extended period of time and were odourless. Multigram quantities of the ligands can be readily prepared following this procedure.

Table 2.7 Preparation of Schiff base ligands



Ligand	R^1	R^2	R^3	Yield %[a]	Appearance	Rotation $[\alpha]_D^{20}$
[153][26,123]	H	*t*-Bu	*t*-Bu	82	Yellow Solid	− 43.4° (c 0.3, acetone); Lit.[26] − 46.8° (c 0.3, acetone).
[154][26,124]	*t*-Bu	H	*t*-Bu	88	Yellow Oil	− 51.2° (c 0.3, acetone); Lit.[26] − 54.3° (c 0.3, acetone).
[155]	Cl	Cl	*t*-Bu	72	Yellow Solid	− 23.6° (c 1.0, acetone)
[156][26,124,125]	Br	Br	*t*-Bu	73	Yellow Solid	− 16.1° (c 1.0, acetone); Lit.[26] − 107.0° (c 0.1, acetone).[b]
[157][26,56,125]	I	I	*t*-Bu	79	Yellow Solid	− 18.5° (c 1.0, acetone); Lit.[126] − 16.6° (c 1.0, acetone).
[158]	Cl	F	*t*-Bu	75	Yellow Solid	− 27.4 (c 1.0, acetone)
[159]	F	F	*t*-Bu	57	Yellow Solid	− 35.6 (c 0.5, acetone)
[160]	Br	Br	*i*-Pr	76	Yellow Solid	− 9.1 (c 1.0, acetone)
[161]	Cl	H	*t*-Bu	77	Yellow Solid	− 60.8 (c 1.0, $CHCl_3$)
[162]	H	Cl	*t*-Bu	70	Yellow Solid	− 48.6 (c 1.0, $CHCl_3$)

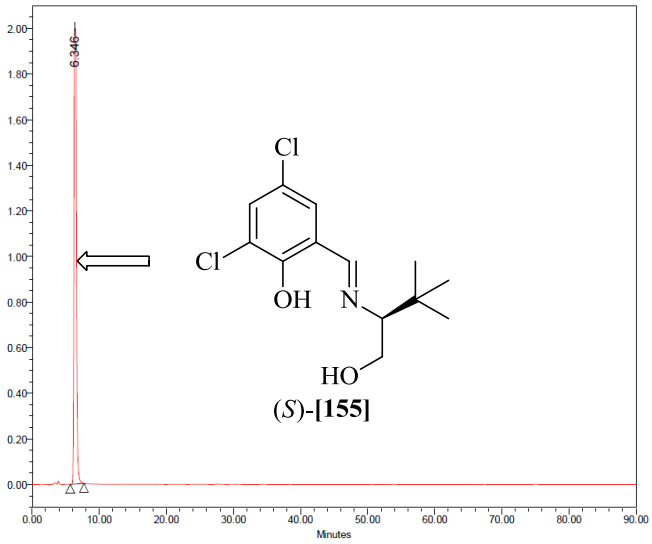
a) Yield of Schiff base ligand after purification by column chromatography.

b) The $[\alpha]_D^{20} = -107°$ reported by Kelly[26] is inconsistent with the rotation value obtained in this work. It is suspected that this is a mistake by Kelly as the other rotations reported by Kelly are of the same order of magnitude as the rotations obtained in this work.

The specific rotation value for ligand **[156]** obtained in this work differed from Kelly's result, although the rotations are measured at different concentrations, while the specific rotations for ligands **[153]**, **[154]** and **[157]** were in agreement with the literature values.

While ligands **[153]**, **[154]**, **[156]** and **[157]** are known compounds prepared following a similar procedure, ligands **[155]** and **[158]–[162]** are novel compounds and are fully characterised in Section 3.6.

The HPLC chromatogram of ligand **[155]** is illustrated in Figure 2.2 supporting retention of enantiopurity in the condensation.



HPLC: t_R (*S*) = 6.3 min, [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C].

Figure 2.2

2.7 Spectral and Chromatographic Analysis of Enantioenriched Sulfoxides

Use of ^{1}H NMR spectroscopy to characterise the level of sulfide oxidation was particularly useful as illustrated in Figures 2.3–2.5. Enhanced deshielding of the of the benzylic and aromatic protons is generally observed on going from sulfide to sulfoxide to sulfone, in addition to characteristic signals for the diastereotopic protons in the sulfoxides. For aryl sulfides the patterns for the aromatic protons were very characteristic depending on the level of sulfide oxidation. As the signals for the sulfide, sulfoxide and sulfone are readily distinguished, determination of the ratio of each of these components in a crude product mixture is readily achieved from either a racemic or enantioselective sulfide oxidation as illustrated in Figures 2.3–2.5.

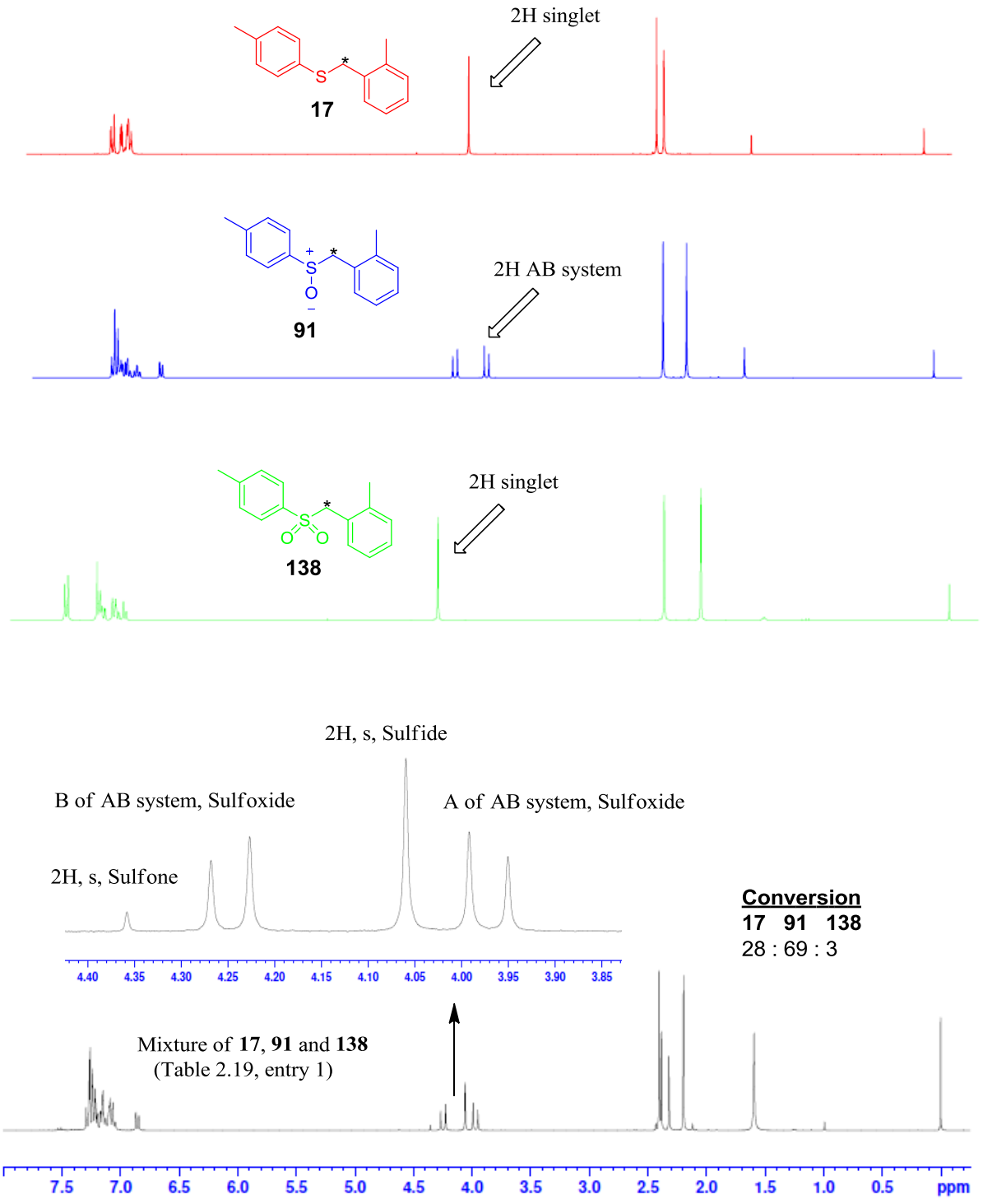
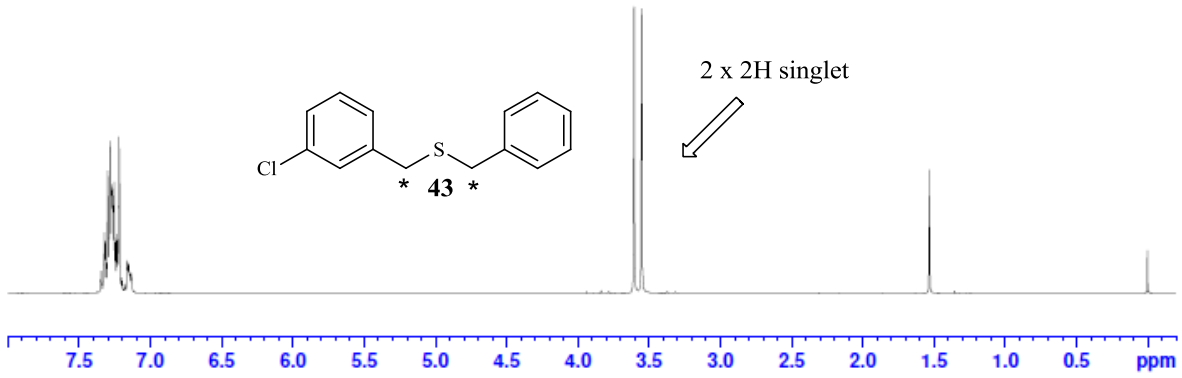
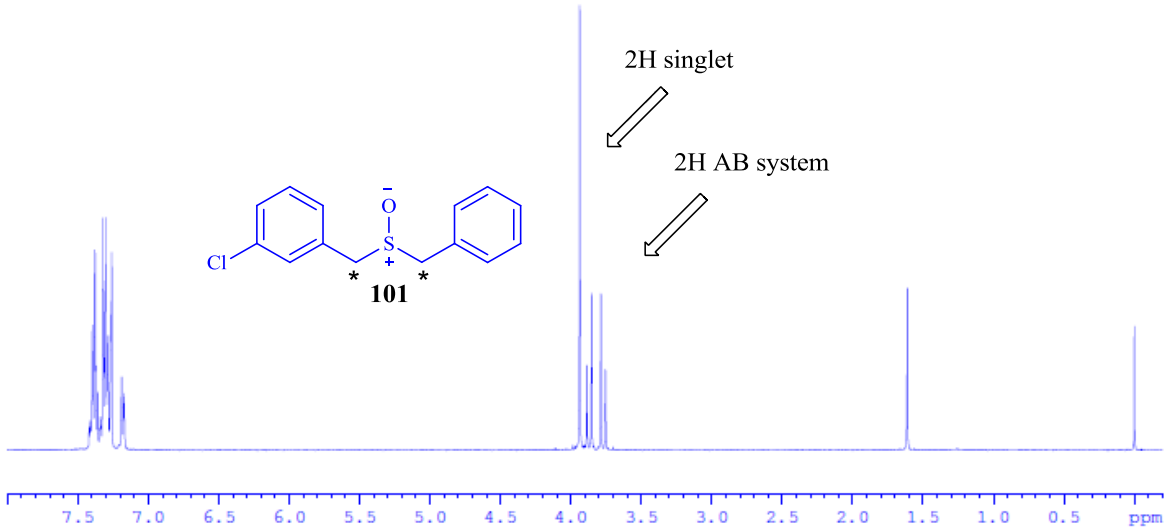


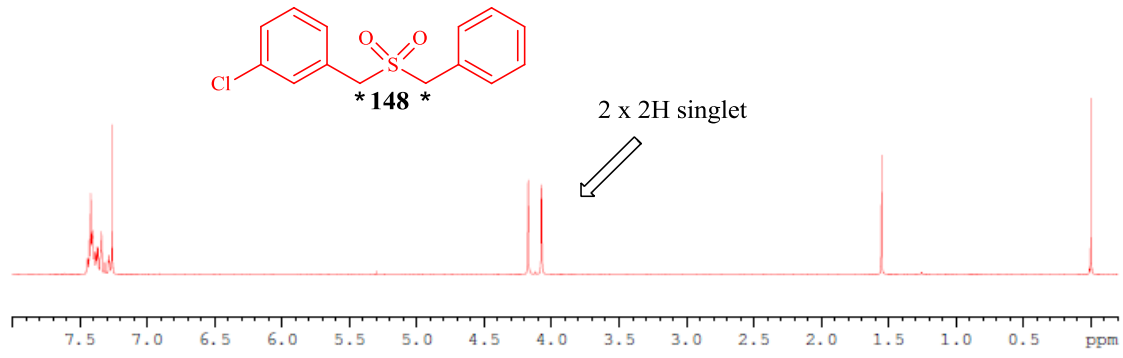
Figure 2.3 ^{1}H NMR spectra of aryl benzyl sulfide, sulfoxide, sulfone and crude mixture (Table 2.19, entry 1).

For the dibenzyl sulfides, there are two SCH_2 peaks which appear as singlets. For the corresponding sulfoxides, the $S(O)CH_2$ peaks appear as either two AB systems or an AB

system plus a singlet (Figure 2.4). The corresponding sulfone SO_2CH_2 peaks appear as singlets further downfield.







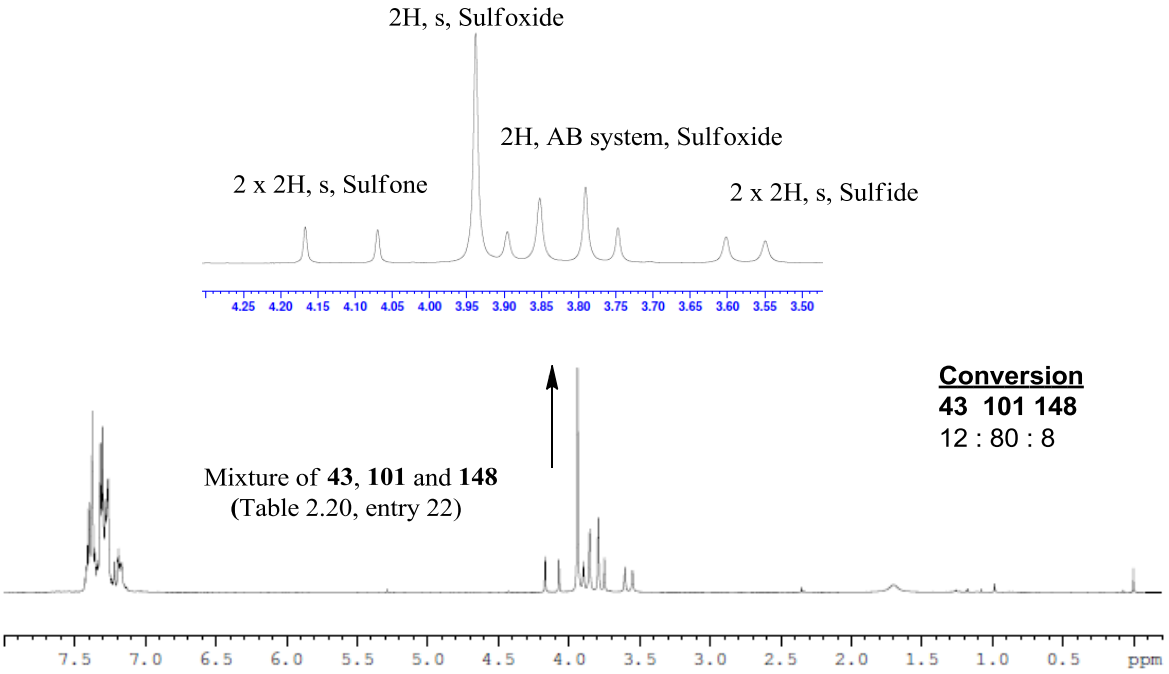
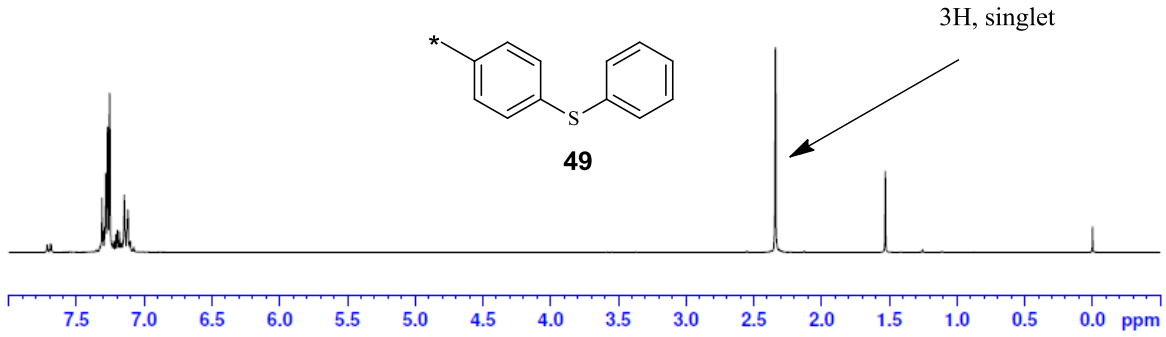


Figure 2.4 ^{1}H NMR spectra of a mixture of dibenzyl sulfide, sulfoxide and sulfone, and crude mixture (Table 2.20, entry 22).

For the diphenyl sulfides and sulfoxides the ratio of the sulfide to sulfoxide was established by analysis of the 3H singlet due to the Ar-CH_3 or Ar-OCH_3 (Figure 2.5).



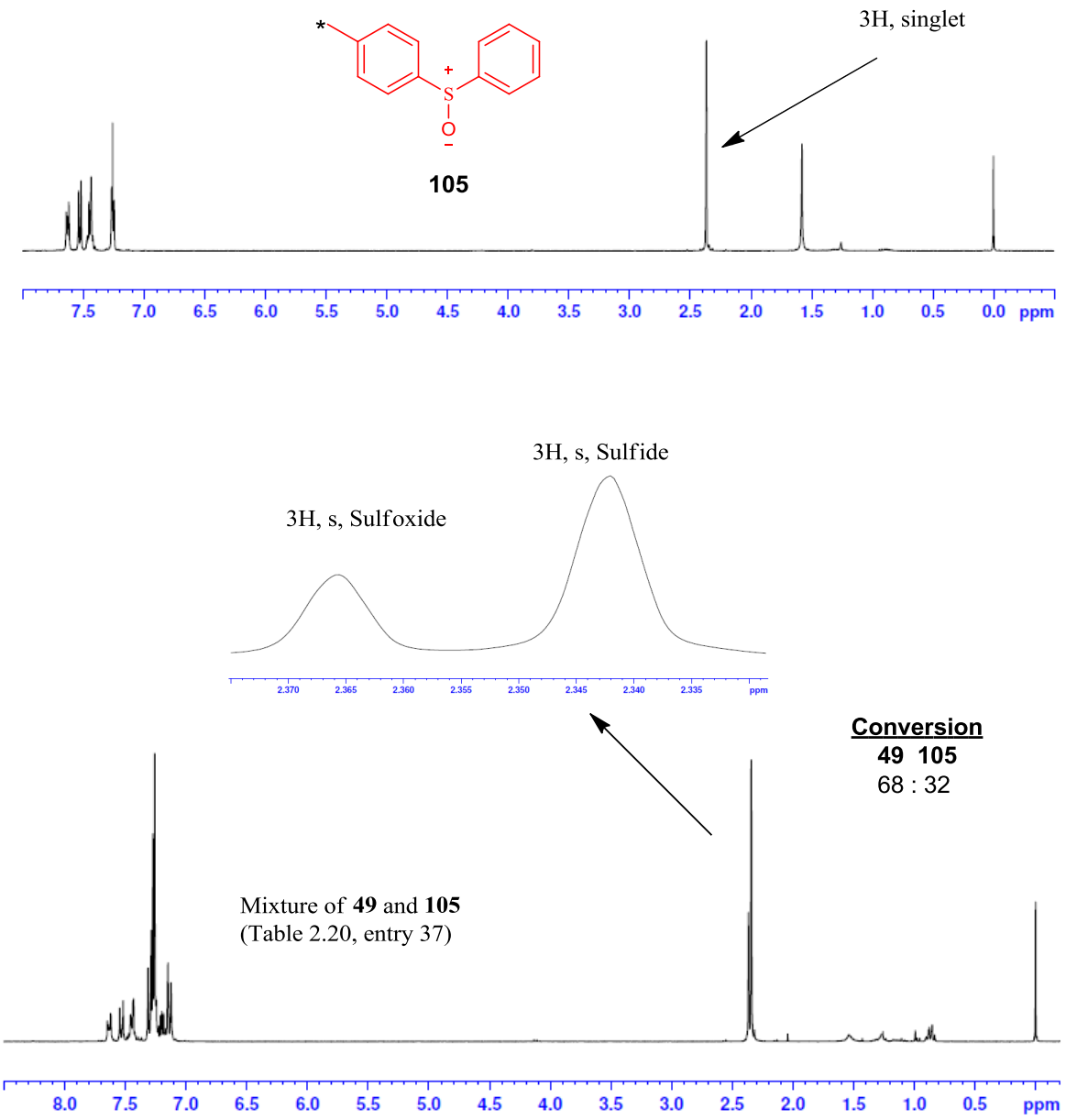
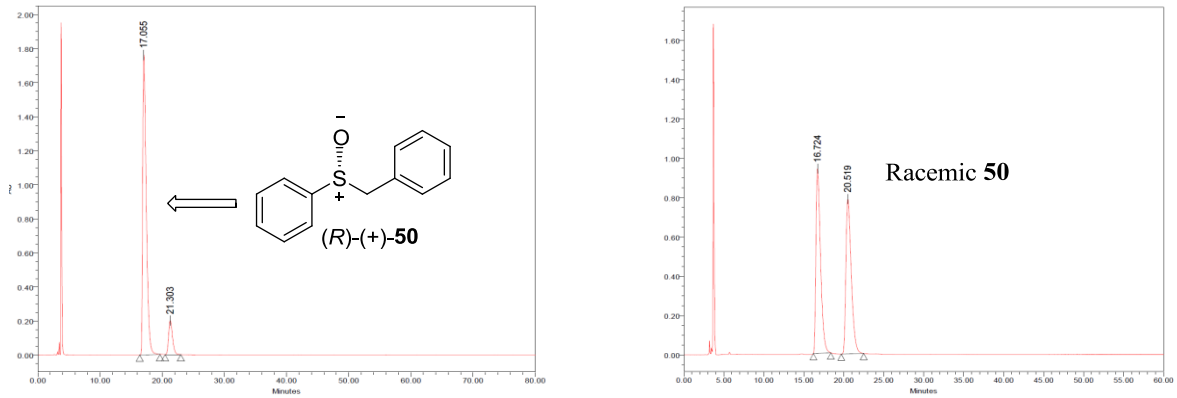


Figure 2.5 ^{1}H NMR spectra of diphenyl sulfide, sulfoxide and crude mixture (Table 2.20, entry 37).

The enantiopurity of sulfoxides was determined using chiral high performance liquid chromatography, see Appendix 1 for conditions. The chromatogram for enantoenriched sulfoxide (*R*)-(+)-**[50]** is illustrated in Figure 2.6.



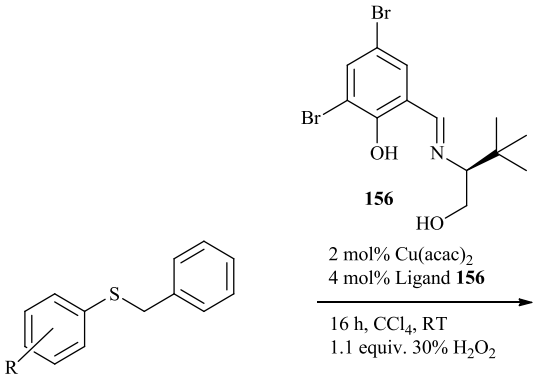
HPLC: 79% ee; t_R (*R*) = 17.1 min, t_R (*S*) = 21.3 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 40 °C]; Table 2.11, entry 5.

Figure 2.6

For sulfoxides **[50]–[55]**, **[57]**, **[58]**, **[65]**, **[81]**, **[87]**, **[93]**, **[94]**, **[105]** the absolute configuration was determined by comparison of the specific rotation values to known literature values (see Section 3.4); for sulfoxides **[56]**, **[59]**, **[60]–[62]**, **[68]**, **[69]**, **[75]**, **[76]**, **[78]–[80]**, **[84]–[86]**, **[88]–[90]**, **[92]**, **[95]** the absolute configuration is the proposed configuration based on the direction of specific rotation values and HPLC elution order (see Section 3.4); for sulfoxides **[63]**, **[64]**, **[70]**, **[77]**, **[82]**, **[91]**, **[97]–[104]** the absolute configuration was not determined; for sulfoxides **[66]** and **[67]** absolute configuration was determined by single crystal X-ray diffraction on a crystalline sample of 1-naphthyl benzyl sulfoxide and 2-naphthyl benzyl sulfoxide recrystallised from CH_2Cl_2;[127] for sulfoxides **[71]** and **[72]** the proposed configuration was based on comparison of optical rotation to known literature value for (*R*)-decyl benzyl sulfoxide;[128] for sulfoxides **[73]** and **[74]** the proposed configuration was based on comparison of optical rotation to known literature values for (*R*)-decyl phenyl sulfoxide[129] and (*R*)-butyl phenyl sulfoxide.[130]

2.8 Copper-Mediated Asymmetric Sulfide Oxidation

As outlined in Section 1.2.15 and 2.1, Kelly carried out a preliminary study of copper-mediated asymmetric sulfoxidation, focussing primarily on the oxidation of aryl benzyl sulfides. A selection of Kelly's oxidations were repeated to ensure comparability, especially of efficiencies and enantioselectivities (Figure 2.7).

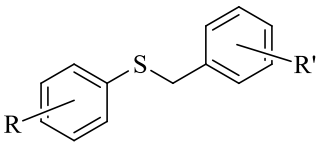


	This Work		Kelly's Work	
	Yield (%)	ee (%)	Yield (%)	ee (%)
R = H,	22	62	27	61
R = 2-MeO	21	81	29	79
R = 3-MeO	20	63	26	67
R = 4-MeO	20	43	17	39

Figure 2.7

2.9 Investigation of CCl_4 and Toluene as Solvent

In general, chlorinated solvents tend to be the most suitable solvents in metal-catalysed asymmetric sulfoxidation.[16] However, as chlorinated solvents are toxic, their replacement with less toxic non-chlorinated solvents is desirable. In a previous study, Kelly carried out a limited investigation of reaction solvent in the copper-catalysed asymmetric oxidation of benzyl phenyl sulfide **[163]** and established that the more chlorinated the solvent used (CH_2Cl_2 to $CHCl_3$ to CCl_4), the higher the enantioselectivity, with CCl_4 giving the best results.[26] A series of aryl benzyl sulfides (Figure 2.8) was oxidised using either CCl_4 or toluene as solvent as shown in Table 2.8.

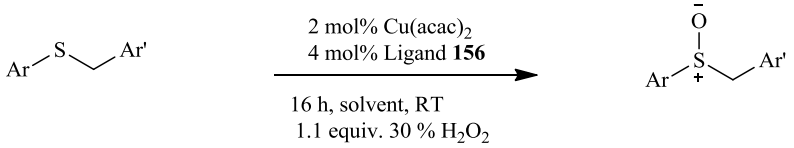


1 R = 4-MeO R' = H
2 R = 3-MeO R' = H
3 R = 2-MeO R' = H
4 R = 4-CH_3 R' = 4-MeO
7 R = 4-CH_3 R' = H
163 R = H R' = H
164 R = 4-F R' =H

Figure 2.8

During this work, each of the oxidations were carried out in toluene and compared to Kelly's results in Table 2.8. The substitution of CCl_4 with toluene as solvent for the asymmetric oxidation of a range of aryl benzyl sulfides proceeded with no significant loss in yield or enantioselectivity. For sulfoxides **[52]** and **[55]** an improvement in enantioselectivity was observed when CCl_4 was substituted with toluene as solvent (entries 3 and 6, Table 2.8).

Table 2.8 Investigation of CCl_4 and Toluene as Solvent in the Oxidation of Aryl Benzyl Sulfides



Entry	Sulfide	Ar	Ar'	Toluene			CCl_4[d]			Sulfoxide
				Sulfide : Sulfoxide	Yield %[b]	%ee[c] (*R*)[d]	Sulfide : Sulfoxide	Yield %[b]	%ee[c] (*R*)	
1	**[163]**[e]	Ph	Ph	73 : 27	21	58	74 : 26	27	61	**[50]**
2	**[7]**	4-MeC_6H_4	Ph	78:22	15	51	46 : 54	38	55	**[51]**
3	**[4]**	4-MeC_6H_4	4'-$MeOC_6H_4$	55 : 45	30	46	47 : 53	42	27	**[52]**
4	**[3]**	2-$MeOC_6H_4$	Ph	74 : 26	19	77	57 : 43	29	79	**[53]**
5	**[2]**	3-$MeOC_6H_4$	Ph	74 : 26	18	73	68 : 32	24	69	**[54]**
6	**[1]**	4-$MeOC_6H_4$	Ph	54 : 46	33	54	63 : 37	17	39	**[55]**
7	**[164]**[f]	4-FC_6H_4	Ph	75 : 25	18	34	71 : 29	13	39	**[90]**

a) Ratio of sulfide : sulfoxide determined by ^1H NMR analysis of the crude product, no sulfone produced. b) Yield of sulfoxide after purification by column chromatography. c) Determined by HPLC analysis on chiral column; absolute configuration determined by comparison of specific rotation values for **[50]**, **[51]** to known literature values; for **[52]**, **[53]**, **[54]**, **[55]**, **[90]** proposed configuration based on HPLC elution order and the direction of the specific rotations. d) Results obtained by Kelly *et al.*[26]

e) Sulfide was obtained commercially from Aldrich. f) Sulfide was obtained from Kelly.[131]

The results of this study are illustrated in Figure 2.9. While in most cases the enantiopurities of the sulfoxides are comparable on replacing CCl_4 with toluene as solvent, for sulfoxides **[52]** and **[55]** there was a significant enhancement in enantioselectivity when CCl_4 was replaced with toluene as solvent. The use of toluene as solvent offers significant safety benefits over CCl_4.

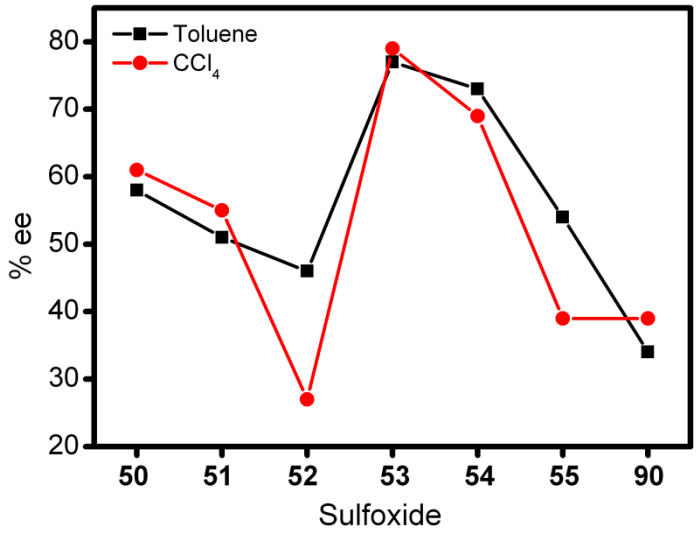


Figure 2.9 Influence of CCl_4 and toluene as solvent on enantioselectivity

2.10 Investigation of Reaction Solvent[132]

Having established that CCl_4 could be replaced with toluene with no significant loss in yield and enantioselectivity, a more detailed investigation of solvent was undertaken.[132] The oxidation of sulfide **[163]** using either ether or dioxane as solvent, afforded sulfoxide **[50]** in poor yield and enantioselectivity (entries 1 and 2, Table 2.9). The use of low polarity solvents such as toluene, CCl_4, and benzene, afforded sulfoxide **[50]** with improved enantioselectivity (entries 3, 4 and 5, Table 2.9), in agreement with Kelly's results.[25,26] The use of methanol (MeOH) as solvent afforded sulfoxide **[50]** with an improved yield but a reduction in enantioselectivity in comparison to the low polarity solvents (entry 7, Table 2.9). No sulfoxide was produced when the oxidation was carried out in hexane (entry 6, Table 2.9). The mixed solvent system of toluene-MeOH resulted in improved yield, but with a reduced enantioselectivity (entries 9-12, Table 2.9). However, carrying out the oxidation using 9:1 hexane/methanol solvent mixture produced sulfoxide **[50]** in excellent yield and good enantioselectivity (entry 13, Table 2.9). Excellent yields and good enantiopurities were also

obtained using solvent mixtures of hexane and ethanol, and cyclohexane and methanol (entries 14 and 15, Table 2.9). Although hexane and methanol are partially miscible, while hexane and ethanol are fully miscible, both solvent systems produce sulfoxide **[50]** in almost identical yield and enantioselectivity (entries 13 and 14, Table 2.9). Interestingly, practically racemic sulfoxide was produced when the oxidation was carried out in a solvent system composed of hexane and IPA (entry 16, Table 2.9). The dramatic improvements in conversion and ultimately sulfoxide yield is illustrated in Figure 2.10 which shows the ^{1}H NMR of the crude product from the oxidation of sulfide **[163]** in different solvents/solvent systems.

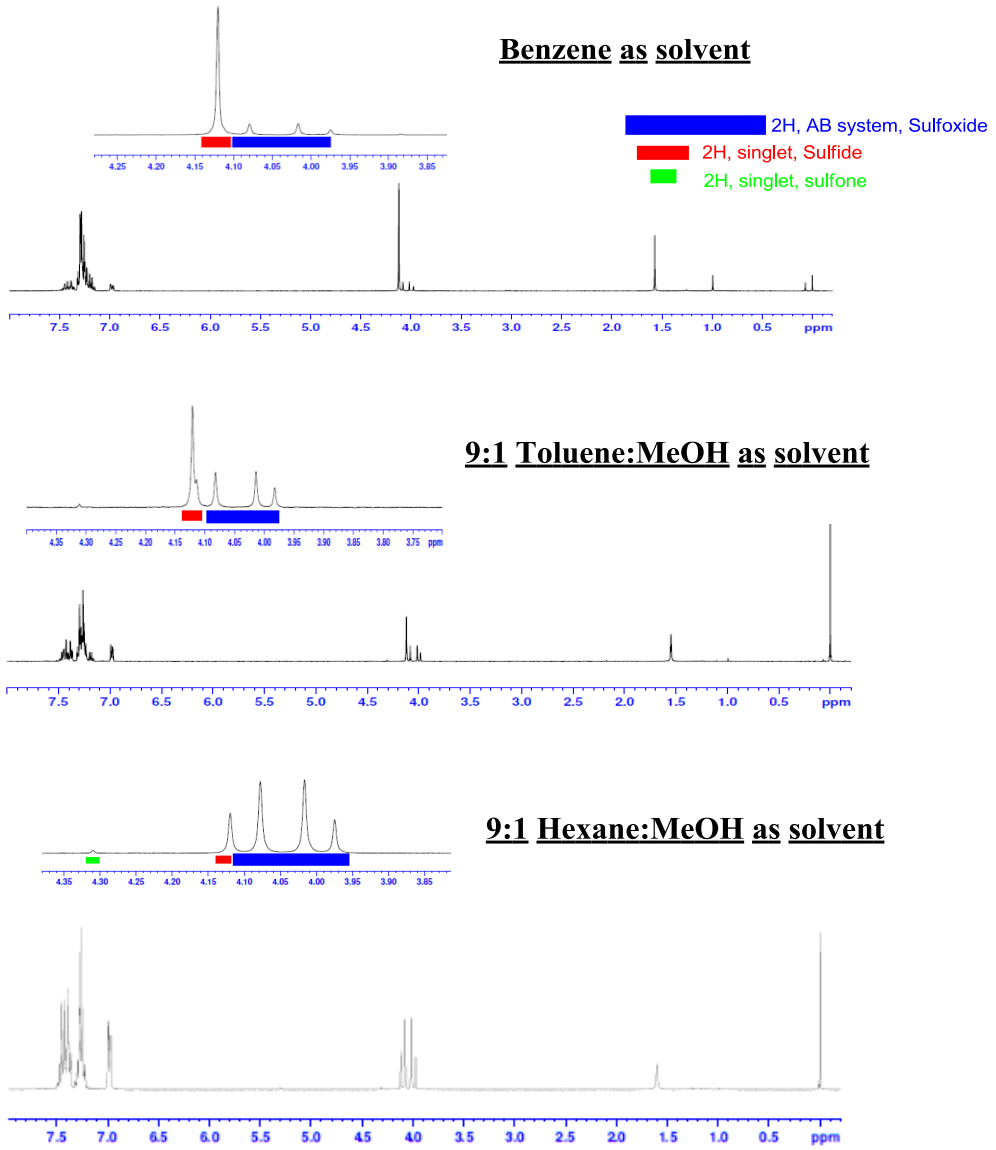
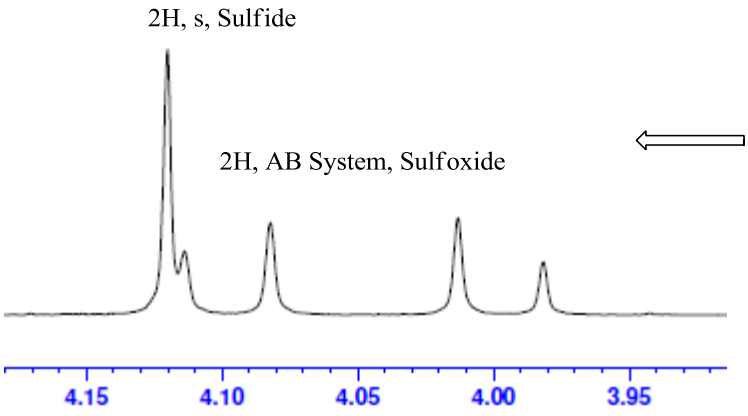


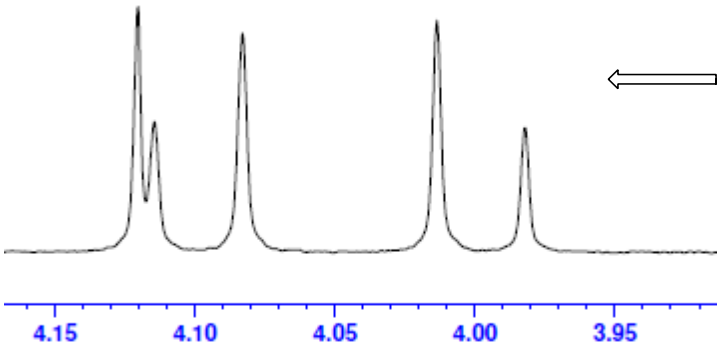
Figure 2.10 ^{1}H NMR of crude product from the oxidation of phenyl benzyl sulfide **[163]** in different solvents

It is likely that the poor yields obtained previously were due to sulfoxide inhibition of the oxidation through complexation with the copper catalyst. However, the use of solvent mixtures of methanol can overcome this inhibition, presumably by co-ordination of methanol to the copper catalyst, thereby displacing the sulfoxide, which results in improved yields. The use of a 9:1 carbon tetrachloride-methanol solvent mixture afforded sulfoxide **[50]** in good yield but with reduced enantioselectivity relative to hexane/methanol (entry 17, Table 2.9). The addition of NMO (2.5 mol%) to this system resulted in an improvement in yield (entry 18, Table 2.9 and Figure 2.11). Interestingly, the use of solvent systems containing bulky alcohols such as IPA, *tert*-butanol and 2-butanol afforded sulfoxide **[50]** in poor enantioselectivity (entries 16, 20 and 21, Table 2.9) but in good yield in the case of IPA. This indicates that the bulky alcohols bind to the copper catalyst in such a way as to inhibit the stereoselectivity of the oxidation. The use of a solvent mixture composed of hexane and benzyl alcohol afforded sulfoxide **[50]** in good yield but poor enantioselectivity (entry 19, Table 2.9). Benzyl alcohol is not a bulky alcohol, yet its use in a mixed solvent system results in very low enantioselectivity which suggests that another factor, other than its size, is influencing the enantioselectivity of the oxidation. Overall, it is apparent that the use of polar low molecular weight alcohols, such as methanol and ethanol, result in excellent enantiopurity whereas the use of higher molecular weight alcohols result in a dramatic reduction in enantioselectivity. Interestingly, the use of each enantiomer of 2-butanol, as well as the racemate, afforded sulfoxide **[50]** in similar yield and enantioselectivity (entries 21–23, Table 2.9).



^{1}H NMR of crude product from oxidation of sulfide 163 (MeOH)

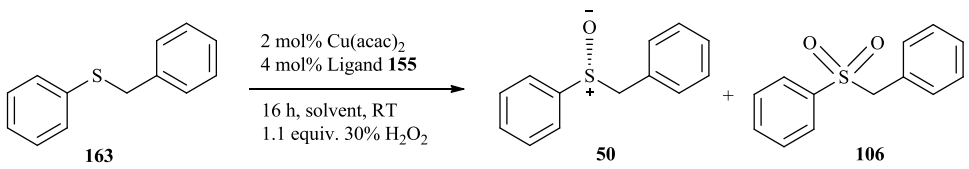
2H, s, Sulfide
2H, AB System, Sulfoxide



^{1}H NMR of crude product from oxidation of sulfide 163 (MeOH + NMO)

Figure 2.11 Improvement in conversion with the addition of NMO to oxidation

Table 2.9 Investigation of Reaction Solvent



Entry	Solvent	[163] : [50] : [106][a]	Yield %[b] [50]	%ee[c] (*R*) [50]
1	Ether	85 : 15 : 0	8	10
2	Dioxane	69 : 31 : 0	25	1
3	Toluene	79 : 21 : 0	17	58
4	CCl_4	65 : 35 : 0	27	61
5	Benzene	66 : 34: 0	26	69
6	Hexane	100 : 0 : 0	0	-
7	MeOH	40 : 60 : 0	50	24
8	MeOH[d]	19 : 81 : 0	73	29
9	50:50 Toluene : MeOH	47 : 53 : 0	48	47
10	75:25 Toluene : MeOH	46 : 54 : 0	47	47
11	90:10 Toluene : MeOH	42 : 58 : trace	52	49
12	95:5 Toluene : MeOH	48 : 52 : 0	45	46

13	90:10 Hexane : MeOH	3 : 96 : 1	87	80[e]
14	90:10 Hexane : EtOH	1 : 98 : 1	90	76
15	90:10 Cyclohexane : MeOH	8 : 91 : 1	85	79
16	90:10 Hexane : IPA	7 : 92 : 1	83	1
17	90:10 CCl_4 : MeOH	21 : 76 : 3	70	62
18	90:10 CCl_4 : MeOH[d]	9 : 89 : 2	82[d]	63
19	90:10 Hexane : benzyl alcohol	4 : 94 : 2	87	7
20	90:10 Hexane : *t*-BuOH	45 : 55 : trace	46	4
21	90:10 Hexane : 2-butanol	57 : 43 : 0	38	8
22	90:10 Hexane : (*S*)-2-butanol	61 : 39 : 0	32	3
23	90:10 Hexane : (*R*)-2-butanol	59 : 41 : 0	35	4

a) Ratio of **[163]:[50]:[106]** determined by ^{1}H NMR analysis of the crude product.

b) After purification by column chromatography.

c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H); Absolute configuration determined by comparison of rotation values to literature values.

d) Oxidation carried out in the presence of NMO (2.5 mol%).

e) Oxidation of **[163]** under the optimised conditions of entry 13 was repeated on a number of occasions with enantiopurities in the range of 71-80% ee reproducibly achieved.

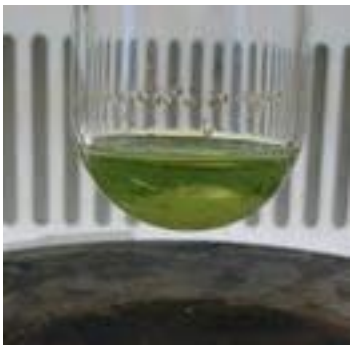
Colour changes and reaction solvent

The addition of copper(II) acetylacetonate (blue) and Schiff base ligand (yellow) to the solvent results in a blue/green solution regardless of which solvent was used. The sulfide is added after 5 min and no colour change is observed with this addition. The oxidant is added next and depending on which solvent/solvent system is employed the resulting mixture can either be homogenous or heterogeneous; again the green/blue colour of the organic layer remains unchanged at this stage. If the solvent is completely immiscible with the oxidant (aqueous hydrogen peroxide), in which case the reaction mixture is heterogeneous, the aqueous layer turns from clear to brown during the oxidation over a few hours. This brown colour presumably indicates that the copper(II) species is reduced to copper(I). Interestingly with the use of mixed solvent systems composed of polar and non-polar solvents, such as

hexane/methanol, no brown colour is observed during the oxidation. This may indicate that the Cu(II) complex is more efficiently regenerated in the presence of methanol.

The sulfide and catalyst are soluble in these mixed solvent systems, however, the sulfoxide is only partially soluble and precipitation occurs when the reaction solvent becomes saturated with the sulfoxide. As a result, the sulfoxide collects around the round bottomed flask during the oxidation using mixed solvent systems (Figure 2.12). This precipitation of the sulfoxide product is also observed, although to a much lesser extent, using non-polar solvents such as CCl_4, benzene and toluene (Figure 2.12). The dramatic improvement in yield can, perhaps, be explained by the fact that the sulfoxide precipitates and hence can no longer bind to the copper-ligand complex and inhibit the oxidation. Interestingly, during the aqueous work up, the aqueous layer is brown when the oxidation is carried out in the low polarity solvents such as toluene, but is colourless when the oxidation is carried out in a mixed solvent system.

Reaction mixture immediately on addition of oxidant
Green/Blue Color : Oxidation in Hexane-MeOH (9:1)



After 16 h oxidation
Sulfoxide precipitates and collects on side of flask during oxidation

Reaction mixture immediately on addition of oxidant
Green/Blue Color : Oxidation in Toluene

After 16 h oxidation
Aqueous layer turns brown during oxidation.
Only a small amount of sulfoxide collects on flask

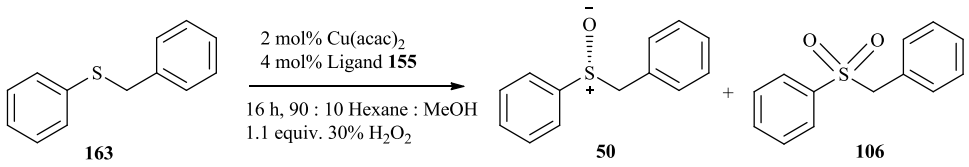
Figure 2.12

Based on Kelly's earlier results which showed a sensitivity to concentrations, the reactions were conducted using a standard concentration of 1 mmol sulfide, 2 mol% $Cu(acac)_2$ and 4 mol% ligand in 2 mL solvent, single or mixed.

2.11 Investigation of Reaction Temperature

The temperature at which the oxidation was carried out was also investigated. Lower temperatures have been reported to enhance the enantioselectivity of vanadium-catalysed sulfoxidations.[126,133] For the titanium-mediated Kagan procedure, the optimum temperature was found to be -20 °C.[134] However, in this copper-catalysed procedure a reduction in temperature below RT resulted in a decrease in both the yield and enantioselectivity of the oxidation (entries 2 and 3, Table 2.10). An increase in temperature above RT also resulted in a reduction in yield and enantioselectivity, although the reduction in yield was modest (entries 4-11, Table 2.10). A direct relationship between sulfone formation and reaction temperature was observed, with increased temperatures resulting in significant sulfone formation (up to 16%, entry 11, Table 2.10).

Table 2.10 Investigation of Reaction Temperature



Entry	Temperature °C	[163] : [50] : [106][a]	Yield %[b] [50]	%ee[c] (*R*) [50]
1	Ambient	3 : 96 : 1	87	80
2	0	82 : 18 : 0	11	28
3	4	65 : 35 : 0	24	34
4	25	0 : 96:4	84	58
5	30	0 : 97 : 3	82	53
6	35	0 : 95 : 5	83	47
7	40	0 : 95 : 5	80	41
8	45	0 : 93 : 7	77	35

9	50	0 : 90 : 10	75	27
10	55	0 : 91 : 9	78	25
11	60	0 : 84 : 16	71	14

a) Ratio of **[163]:[50]:[106]** determined by ^{1}H NMR analysis of the crude product.

b) After purification by column chromatography.

c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H); Absolute configuration determined by comparison of rotation values to literature values.

The results of this study are illustrated in Figure 2.13. This plot shows that the optimum temperature for the asymmetric oxidation is around 20 °C (ambient). In light of these results, the sensitivity to modest variation in temperature is quite significant. While all subsequent experiments were conducted at ambient temperature, it should be noted that the temperature in the laboratory may have varied a little and based on the results in Figure 2.13 this may have influenced the enantioselectivity achieved. It is recommended that future studies are temperature controlled to avoid variation due to temperature. Further investigation to determine the optimum temperature is warranted.

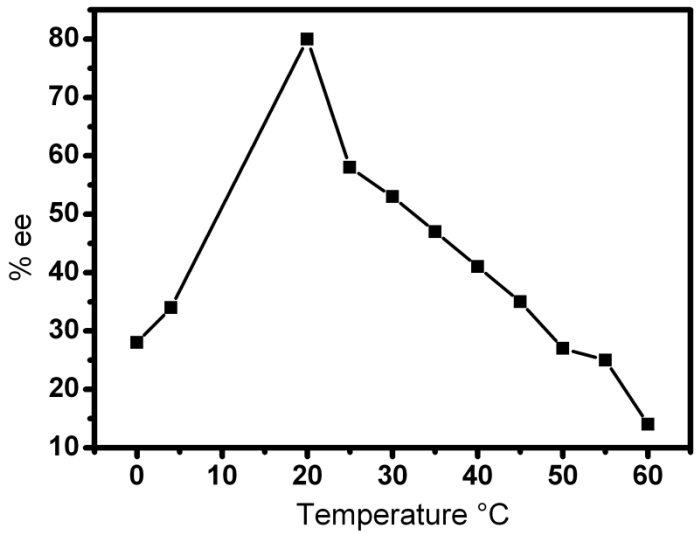
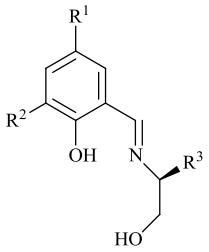


Figure 2.13 Influenece of temperature on enantioselectivity

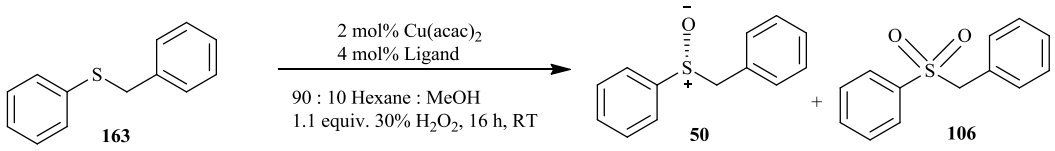
2.12 Investigation of Schiff Base Ligand[132]

The structure of the Schiff base ligand was investigated in an attempt to find the optimum ligand for this system.[132] Ligands **[153]** and **[154]** contain a sterically bulky *tert*-butyl group in either the R^1 or R^2 positions of the ligand. The use of these ligands in the oxidation of benzyl phenyl sulfide **[163]**, afforded sulfoxide **[50]** in poor yield and enantioselectivity (entries 1 and 2, Table 2.11). Ligand **[157]** had previously been shown to be very effective in vanadium-catalysed oxidations;[58] however its use with this copper based system afforded sulfoxide **[50]** with poor yield and enantioselectivity (entry 7, Table 2.11). Substitution of the iodo substituents (ligand **[157]**) with bromo substituents (ligand **[156]**) resulted in a significant enhancement in both yield and enantioselectivity (entries 6 and 7, Table 2.11). A similar improvement was observed on replacing the bromo substituents (ligand **[156]**) with chloro substituents (ligand **[155]**, entries 5 and 6, Table 2.11). However, the use of ligand **[159]**, which contains fluoro substituents in the R^1 and R^2 positions, afforded sulfoxide **[50]** in modest yield and poor enantioselectivity (entry 9, Table 2.11). A reduction in both yield and enantioselectivity is observed with the substitution of the *tert*-butyl with an isopropyl in the R^3 position of the ligand indicating that the steric bulk at the R^3 position is crucial to maintain the enantioselectivity of the oxidation (entries 6 and 10, Table 2.11). The results of the oxidations using ligands **[161]** and **[162]** demonstrate that the presence of a chloro substituent at the R^2 position of the ligand is more important to the yield and enantioselectivity than at the R^1 position (entries 11 and 12, Table 2.11). However, the presence of chloro substituents at both positions results in the highest yield and enantioselectivity (entry 5, Table 2.11).

Table 2.11 Investigation of Schiff Base Ligand



153 R^1 = *t*-Bu, R^2 = H, R^3 = *t*-Bu
154 R^1 = H, R^2 = *t*-Bu, R^3 = *t*-Bu
155 R^1 = Cl, R^2 = Cl, R^3 = *t*-Bu
156 R^1 = Br , R^2 = Br, R^3 = *t*-Bu
157 R^1 = I, R^2 = I, R^3 = *t*-Bu
158 R^1 = F , R^2 = Cl, R^3 = *t*-Bu
159 R^1 = F , R^2 = F, R^3 = *t*-Bu
160 R^1 = Br , R^2 = Br, R^3 = *i*-Pr
161 R^1 = H , R^2 = Cl, R^3 = *t*-Bu
162 R^1 = Cl , R^2 = H, R^3 = *t*-Bu



163 **50** **106**

Entry	Ligand	[163] : [50] : [106]	Yield %[b] [50]	%ee[c] (*R*) [50]
1	**[153]**	64 : 36 : 0	39	2[d]
2	**[154]**	73 : 27 : 0	24	3[d]
3	**[153]**	70 : 30 : 0	28	3
4	**[154]**	71 : 29 : 0	24	1
5	**[155]**	1 : 98 : 1	90	79
6	**[156]**	1 : 96 : 3	86	66
7	**[157]**	68 : 32 : 0	28	3
8	**[158]**	3 : 96 : 1	87	58
9	**[159]**	45 : 55 : trace	47	37
10	**[160]**	50 : 50 : 0	44	6
11	**[161]**	15 : 83 : 2	72	38
12	**[162]**	61 : 39 : 0	30	5

a) Ratio of **[163]:[50]:[106]** determined by ^{1}H NMR analysis of the crude product.

b) After purification by column chromatography.

c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H); Absolute configuration determined by comparison of rotation values to literature values.

d) Results obtained using Kelly's samples of ligands **[153]** and **[154]**.

The results of this study are illustrated in Figure 2.14, which shows that ligand **[155]** performs the best in the oxidation of benzyl phenyl sulfide **[163]**.

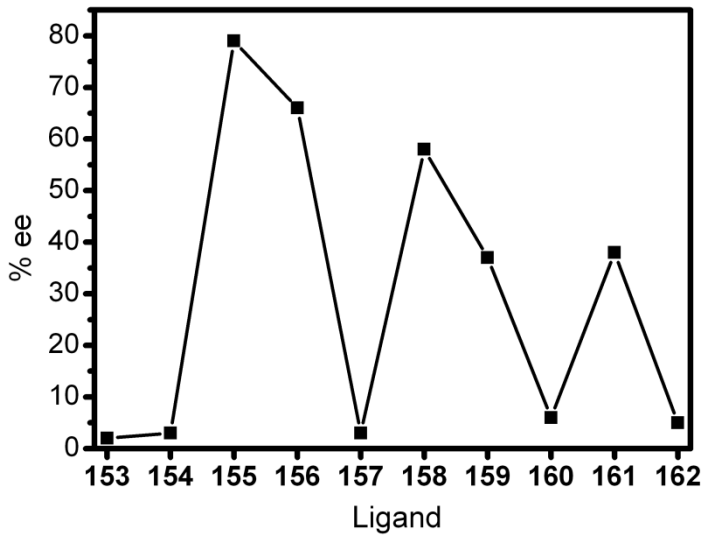
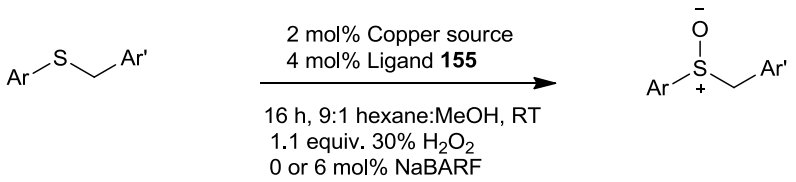


Figure 2.14 Influence of Schiff base ligand on enantioselectivity

2.13 Investigation of Effect of NaBARF and Copper Source[132]

The effects of copper source and the presence of NaBARF as an additive on the asymmetric oxidation was explored. Previous research in our group demonstrated that counter ions and additives can have a large influence on the enantioselectivity in copper-catalysed reactions of α-diazoketones.[135,136] To our knowledge NaBARF has not been previously used as an additive in asymmetric sulfide oxidation. The optimum results, both in terms of yield and enantioselectivity, were obtained when $Cu(acac)_2$ was used as copper source in the absence of NaBARF. A reduction in both yield and enantioselectivity was observed when the oxidations were carried out using $Cu(acac)_2$ in the presence of NaBARF (6 mol%, Table 2.12). However, the presence of NaBARF resulted in improved enantiopurities when CuCl was employed as copper source, although improvements were only very slight (Table 2.12). Interestingly when the copper-ligand complex was stirred in 9:1 hexane/MeOH for 2 h before addition of sulfide, the resulting sulfoxide was obtained with a significant reduction in enantioselectivity (entries 3 and 5, Table 2.12).

Table 2.12 Investigation of Effect of NaBARF and Copper Source



Entry	Sulfide	Ar	Ar′	Copper Source	NaBARF[d]	Sulfide : Sulfoxide : Sulfone[a]	Yield %[b]	%ee[c] (*R*)	Sulfoxide
1	**[163]**	Ph	Ph	CuCl	No	83 : 17 : 0	12	3	**[50]**
2	**[163]**	Ph	Ph	CuCl	Yes	-	13	31	**[50]**
3	**[163]**	Ph	Ph	$Cu(acac)_2$	No	3 : 96 : 1	87	80	**[50]**
4	**[163]**	Ph	Ph	$Cu(acac)_2$	Yes	-	61	41	**[50]**
5	**[163]**	Ph	Ph	$Cu(acac)_2$	No	2 : 93 : 5	85	57	**[50]**[e]
6	**[7]**	*p*-Tol	Ph	CuCl	No	81 : 19 : 0	13	7	**[51]**
7	**[7]**	*p*-Tol	Ph	CuCl	Yes	-	12	9	**[51]**
8	**[7]**	*p*-Tol	Ph	$Cu(acac)_2$	No	2 : 97 : 1	91	81	**[51]**
9	**[7]**	*p*-Tol	Ph	$Cu(acac)_2$	Yes	-	73	37	**[51]**
10	**[11]**	Ph	2′-ClC_6H_4	CuCl	No	85 : 15 : 0	9	6	**[84]**
11	**[11]**	Ph	2′-ClC_6H_4	CuCl	Yes	-	14	9	**[84]**
12	**[11]**	Ph	2′-ClC_6H_4	$Cu(acac)_2$	No	10 : 89 : 1	82	44	**[84]**
13	**[11]**	Ph	2′-ClC_6H_4	$Cu(acac)_2$	Yes	-	71	32	**[84]**
14	**[12]**	Ph	3′-ClC_6H_4	CuCl	No	87 : 13 : 0	7	5	**[85]**
15	**[12]**	Ph	3′-ClC_6H_4	CuCl	Yes	-	13	19	**[85]**
16	**[12]**	Ph	3′-ClC_6H_4	$Cu(acac)_2$	No	18 : 78 : 4	72	27	**[85]**
17	**[12]**	Ph	3′-ClC_6H_4	$Cu(acac)_2$	Yes	-	61	22	**[85]**
18	**[13]**	Ph	4′-ClC_6H_4	CuCl	No	88 : 12 : 0	8	3	**[86]**
19	**[13]**	Ph	4′-ClC_6H_4	CuCl	Yes	-	13	40	**[86]**
20	**[13]**	Ph	4′-ClC_6H_4	$Cu(acac)_2$	No	7 : 91 : 2	85	54	**[86]**
21	**[13]**	Ph	4′-ClC_6H_4	$Cu(acac)_2$	Yes	-	56	37	**[86]**

a) Ratio of sulfide : sulfoxide : sulfone determined by ^{1}H NMR analysis of the crude product. For the experiments carried out in the presence of NaBARF, it was not possible to determine the ratio of sulfide : sulfoxide : sulfone due to signal broadening.

b) After purification by column chromatography.

c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H for **[50]**, **[51]**, **[85]**, **[86]**, Chiracel AS-H for **[84]**); Absolute configuration determined by comparison of rotation values for **[50]** and **[51]** to known literature values; for **[84]**, **[85]**, **[86]** proposed configuration based on HPLC elution order and direction of specific rotations.

d) NaBARF was added prior to addition of sulfide. Copper-ligand complex and NaBARF (6 mol%) was stirred in 9:1 hexane/MeOHfor 2 h before addition of sulfide.

e) Copper-ligand complex was stirred in 9:1 hexane/MeOHfor 2 h before addition of sulfide.

The results of this study are shown in Figure 2.15. Overall, the best results were achieved when the oxidation was carried out using $Cu(acac)_2$ in the absence of NaBARF (green columns). Interestingly, the addition of NaBARF to the reaction mixture using CuCl results in an enhancement in the enantioselectivities (black columns vs red columns). While it is difficult to absolutely rationalise the differing effects of NaBARF with the two different copper sources, it is possible that the naked sodium cation tends to abstract the chloride from the copper complex, thereby generating a more tightly held complex and accordingly higher enantioselectivity, while with $Cu(acac)_2$ the influence of the additive is the opposite.

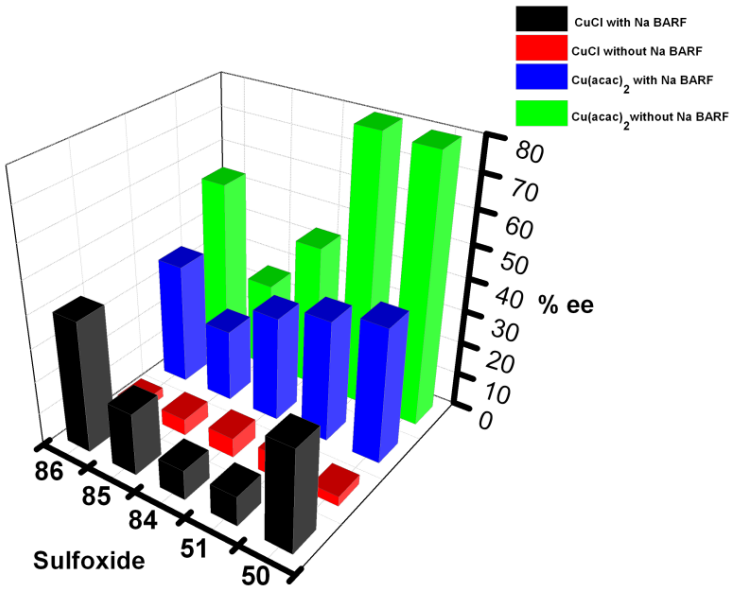


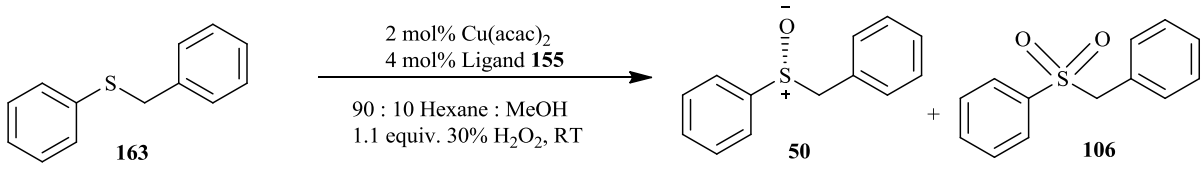
Figure 2.15 Effect of NaBARF and Copper Source on Enantioselectivty

During the *viva* exam use of a base to deprotonate the ligand was discussed. Note $Cu(acac)_2$ has a more basic ligand than CuCl.

2.14 Investigation of Influence of Reaction Time

The influence of reaction time on the efficiency and and enantioselectivity of the oxidation was also investigated (Table 2.13).

Table 2.13 Investigation of Influence of Reaction Time



Entry	Time (h)	[163] : [50] : [106][a]	%ee[b] (*R*) [50]
1	2	16 : 83 : 1	60
2	5	2 : 96 : 2	68
3	7	1 : 97 : 2	69
4	16	1 : 97 : 2	69

a) Ratio of **[163]:[50]:[106]** determined by ^{1}H NMR analysis of the crude product.

b) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H); Absolute configuration determined by comparison of rotation values to literature values.

Kelly undertook a time study in the oxidation of benzyl phenyl sulfide **[163]** in dichloromethane using ligand **[157]** and found that the reaction was effectively complete after 8 hours.[26] As part of the current project, the time profile in the oxidation of **[163]** using ligand **[155]** was undertaken as summarised in Table 2.13. Interestingly, the results indicate that the oxidation is essentially complete with 5 hours. As this time profile was established at a late period during this work, 16 hour reaction periods were used as standard although, in retrospect, shorter times may have been feasible. Signifcantly, leaving the reaction for 16 h had no effect on either the efficiency or the enantioselectivity compared to a 5 h reaction period. More significantly, it appears that the enantiopurity at the early stages of the reaction is slightly lower than that as the reaction proceeds, consistent with co-ordination of the sulfoxide to the copper thereby changing the nature of the catalyst as the reaction proceeds. The ultimate enantiopurity achieved here (69% ee) was slightly lower than the optimum values achieved earlier in this work (71-80% ee), when the reaction is not subjected to

withdrawal of aliquots for analysis. However, the oxidation was repeated using conditions outlined in Table 2.13, without withdrawal of aliquots with stirring for 16 h, and the enantioselectivity obtained was also 69% ee indicating that the reduction in enantiopurity, compared to the optimised values in Table 2.9, entry 13 (71-80% ee), may be due to deterioration of the reagents over time as this study was undertaken near the end of this work.

2.15 Investigation of Steric and Electronic Effects of Sulfide Substituents[132]

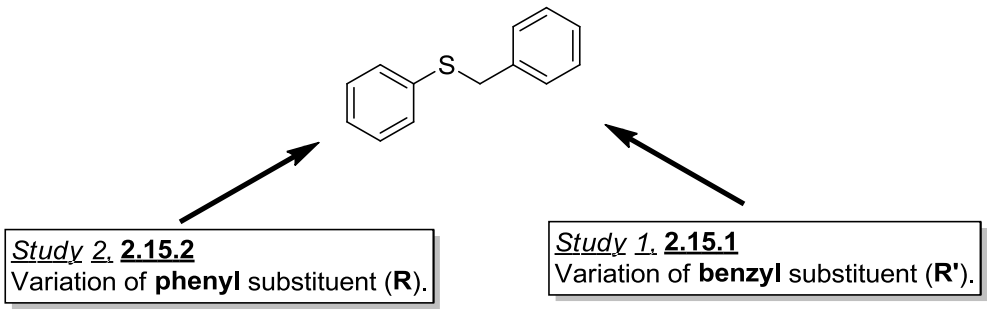


Figure 2.16

The effect of varying sulfide substituents was next examined; in particular the steric and electronic effects of the sulfide substituents on the efficiency and the enantioselectivity of the oxidation was explored.

2.15.1 *Investigation of Steric and Electronic Effects of Benzyl Substituents*

Initially, the benzyl group was varied as shown in Figure 2.17.

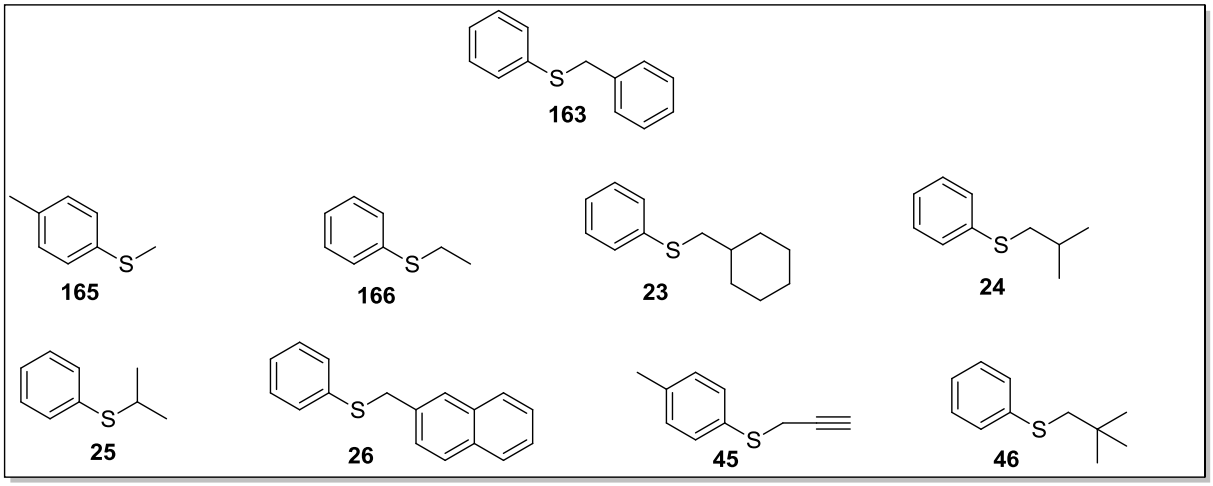
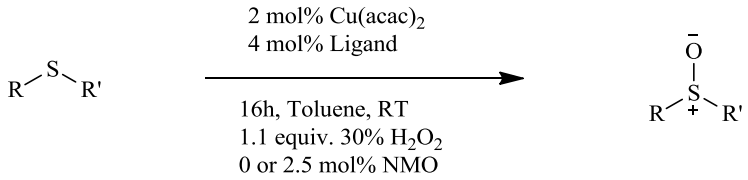


Figure 2.17 Investigation of steric and electronic effects

This study demonstrated that the steric effect of the benzyl substituent of the sulfide had a very strong influence on the enantioselectivity of the oxidation, much more so than the electronic nature of the benzyl substituent (entries 2, 3, 13 and 14, Table 2.14; sulfoxides **[56]** and **[80]**, Scheme 2.6).[132] A direct relationship between the size of the R' substituent and the enantioselectivity of the oxidation was observed, for example substitution of a methyl group with an ethyl group in the R' position results in a relatively large increase in enantioselectivity (22 to 40% ee, entries 4 and 6, Table 2.14; sulfoxides **[57]** and **[58]**, Scheme 2.6). Similarly, the replacement of an isobutyl with a neopentyl group in the R' position results in an improvement in enantioselectivity (61 to 71% ee, entries 9 and 10, Table 2.14; sulfoxides **[60]** and **[61]**, Scheme 2.6). Excellent enantioselectivity was reproducibly achieved in the oxidation of 2'-naphthylmethyl phenyl sulfide **[26]** (93% ee, entry 12, Table 2.14; sulfoxide **[62]**, Scheme 2.6). Kelly has reported that the addition of NMO can result in improved yields in copper-mediated asymmetric sulfoxidation.[25] Carrying out the oxidation in the presence of NMO (2.5 mol%) in either MeOH or CCl_4 resulted in an improvement in yield as discussed in Section 2.10. As a result, the experiments were repeated using NMO as an additive and the results are shown in Table 2.14. The addition of NMO (2.5 mol%) results in an improvement in yield in nearly all cases. It is believed that the NMO can overcome sulfoxide inhibition, which is responsible for the poor yields, by co-ordinating to the copper Schiff base complex thereby displacing the sulfoxide. However, the enhancements in yields are only modest and the use of mixed solvent systems result in much greater improvements in yields as discussed in Section 2.10.

Table 2.14 Investigation of Steric and Electronic Effects of Sulfide Substituents in Toluene, with and without NMO



Entry	Sulfide	R	R′	Ligand	No NMO			NMO[d]			Sulfoxide
					Sulfide : Sulfoxide[a]	Yield %[b]	%ee[c] (*R*)	Sulfide : Sulfoxide[a]	Yield %[b]	%ee[c] (*R*)	
1	**[163]**	Ph	$-CH_2C_6H_5$	**[156]**	79 : 21	17	58	61 : 39	30	60	**[50]**
2	**[23]**	Ph	$-CH_2-$ Cyclohexyl	**[156]**	86 : 14	23	54	78:22	20	60	**[56]**
3	**[23]**	Ph	$-CH_2-$ Cyclohexyl	**[155]**	70 : 30	19	57	71 : 29	24	63	**[56]**
4	**[165]**	*p*-Tol	Me	**[156]**	79 : 21	15	22	65 : 35	37	21	**[57]**
5	**[165]**	*p*-Tol	Me	**[155]**	81 : 19	11	19	64 : 36	36	16	**[57]**
6	**[166]**	Ph	Et	**[156]**	8:2	12	40	6:4	39	49	**[58]**
7	**[166]**	Ph	Et	**[155]**	72 : 28	22	46	59 : 41	40	53	**[58]**
8	**[25]**	Ph	*i*-Pr	**[155]**	72 : 28	19	50	69 : 31	26	64	**[59]**
9	**[24]**	Ph	$-CH_2CH(CH_3)_2$	**[156]**	82 : 18	13	51	78:22	17	56	**[60]**
10	**[24]**	Ph	$-CH_2CH(CH_3)_2$	**[155]**	71 : 29	15	61	76 : 24	18	61	**[60]**
11	**[46]**	Ph	$-CH_2C(CH_3)_3$	**[155]**	8:2	15	71	72 : 28	28	71	**[61]**
12	**[26]**	Ph	$-CH_2-$2'-Naphthyl	**[155]**	73 : 27	23	93[e]	45 : 55	30	93	**[62]**
13	**[45]**	*p*-Tol	$-CH_2C\equiv CH$	**[156]**	84 : 16	8	3	78:22	14	4	**[80]**
14	**[45]**	*p*-Tol	$-CH_2C\equiv CH$	**[155]**	81 : 19	4	5	83 : 17	10	6	**[80]**

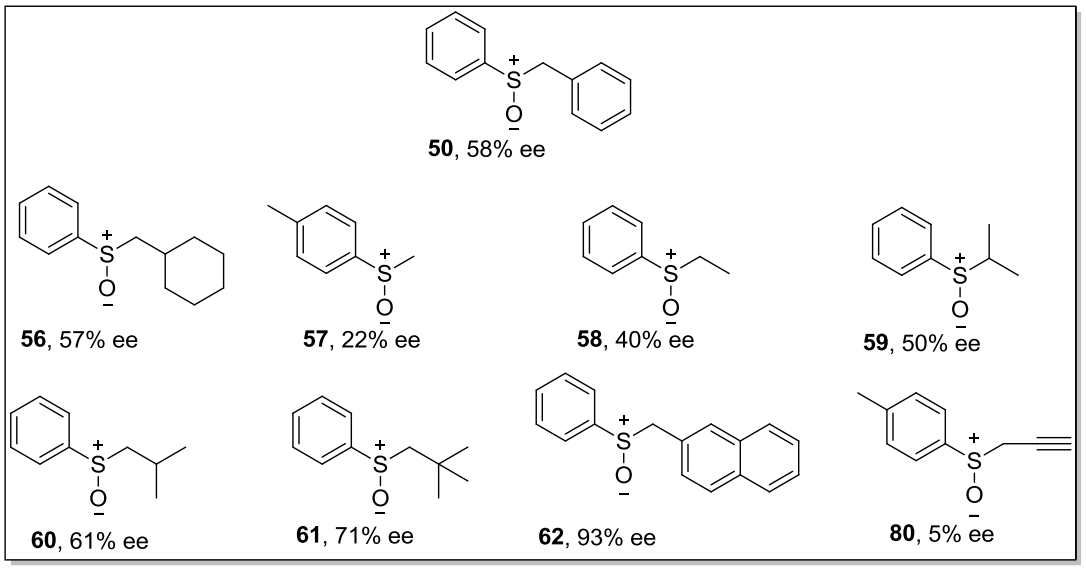
a) Ratio of sulfide : sulfoxide determined by ^1H NMR analysis of the crude product, no sulfone produced.

b) Yield of sulfoxide after purification by column chromatography.

c) Determined by HPLC analysis on chiral column; absolute configuration determined by comparison of specific rotation values for **[50]**, **[57]**, **[58]**, **[59]**, **[60]** to known literature values; for **[56]**, **[61]**, **[62]**, **[80]** proposed configuration based on HPLC elution order and direction of specific rotations.

d) Oxidation carried out in the presence of NMO (2.5 mol%, for 1 mmol sulfide).

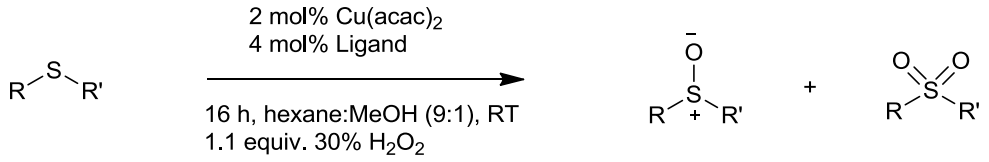
e) The oxidation of sulfide **[26]**, under the conditions indicated in Table 2.14, without NMO, using ligand **[155]** was reproduced several times with enantioselectivities ranging from 90-93% ee respectively.



Scheme 2.6 Influence of steric and electronic effects on enantioselectivity

The optimum reaction conditions (ligands **[155]** and **[158]**, and 9:1 hexane/methanol) were then employed for the oxidation of a number of aryl benzyl and aryl alkyl sulfides as shown in Table 2.15.[132] A dramatic improvement in yield was observed using these conditions (*cf.* Table 2.14, oxidation in toluene). For example, benzyl phenyl sulfoxide **[50]** was obtained in excellent yield (90%) and enantioselectivity (79% ee). Little, if any, over-oxidation to sulfone was observed (no more than 2%). Significant sulfone formation can reduce yields of sulfoxide and leads to difficulties in isolation of the desired product. A direct link between the size of the R' substituent and the enantioselectivity of the oxidation was evident again. An increase in enantioselectivity was observed when the steric bulk of the R' substituent was increased (entries 8, 9, 10 and 12, Table 2.15). The optimum ligand appears to be dependent on the substrate, because while ligand **[155]** was optimum for certain substrates, ligand **[158]** produced superior results with others. Sulfide **[3]** (230 mg, 1 mmol) was not fully soluble in 1 mL of 9:1 hexane/methanol and, as a result, an increased volume of solvent (3 mL) was used. This may have resulted in reduced enantioselectivity as previous work in the group had demonstrated that increasing dilution had a detrimental effect on the enantioselectivity.[26] Sulfide **[26]** was insoluble in 9:1 hexane/methanol, and hence no oxidation was observed.

Table 2.15 Investigation of Steric and Electronic Effects of Sulfide Substituents in 9:1 Hexane-MeOH



Entry	Sulfide	R	R'	Ligand	Sulfide : Sulfoxide : Sulfone	Yield %[b]	%ee[c] (*R*)	Sulfoxide
1	**[163]**	Ph	-$CH_2C_6H_5$	**[155]**	1 : 98 : 1	90	79	**[50]**
2	**[163]**	Ph	-$CH_2C_6H_5$	**[158]**	2 : 98 : 0	91	58	**[50]**
3	**[7]**	4-MeC_6H_4	-$CH_2C_6H_5$	**[155]**	2 : 97 : 1	91	81	**[51]**
4	**[7]**	4-MeC_6H_4	-$CH_2C_6H_5$	**[158]**	4 : 96 : 0	90	84	**[51]**
5	**[4]**	4-MeC_6H_4	4'-$MeOC_6H_4$	**[155]**	2 : 97 : 1	90	47	**[52]**
6	**[3]**	2-$MeOC_6H_4$	-$CH_2C_6H_5$	**[155]**	8 : 92 : trace	85	29	**[53]**
7	**[2]**	3-$MeOC_6H_4$	-$CH_2C_6H_5$	**[155]**	46 : 54 : 0	47	21	**[54]**
8	**[165]**	4-MeC_6H_4	Me	**[155]**	4 : 96 : trace	90	23	**[57]**
9	**[166]**	Ph	Et	**[155]**	2 : 98 : trace	92	44	**[58]**
10	**[25]**	Ph	*i*-Pr	**[155]**	19 : 81 : trace	74	60	**[59]**
11	**[24]**	Ph	-$CH_2CH(CH_3)_2$	**[155]**	10 : 90 : trace	82	48	**[60]**
12	**[46]**	Ph	-$CH_2C(CH_3)_3$	**[155]**	15 : 85 : 0	79	71	**[61]**
13	**[26]**	Ph	-CH_2-2'-Naphthyl	**[155]**	100 : 0 : 0	-	-	**[62]**
14	**[5]**	2-MeC_6H_4	-$CH_2C_6H_5$	**[155]**	1 : 98 : 1	91	64	**[75]**
15	**[5]**	2-MeC_6H_4	-$CH_2C_6H_5$	**[158]**	6 : 94 : 0	88	71	**[75]**
16	**[6]**	3-MeC_6H_4	-$CH_2C_6H_5$	**[155]**	11 : 89 : 0	84	54	**[76]**
17	**[6]**	3-MeC_6H_4	-$CH_2C_6H_5$	**[158]**	10 : 88:2	83	69	**[76]**
18	**[8]**	Ph	-CH_2-*o*-Tol	**[155]**	12 : 85 : 2	80	47[d]	**[77]**

19	**[9]**	Ph	-CH_2-*m*-Tol	**[155]**	7 : 92 : 1	83	50	**[78]**
20	**[9]**	Ph	-CH_2-*m*-Tol	**[158]**	4 : 95 : 1	90	46	**[78]**
21	**[10]**	Ph	-CH_2-*p*-Tol	**[155]**	1 : 97 : 2	89	55	**[79]**

a) Ratio of sulfide : sulfoxide : sulfone determined by ^{1}H NMR analysis of the crude product.

b) Yield of sulfoxide after purification by column chromatography.

c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H for **[50]**, **[51]**, **[52]**, **[53]**, **[54]**, **[57]**, **[58]**, **[59]**, **[60]**, **[61]**, **[62]**, **[75]**, **[76]**, **[78]**, **[79]**; Chiracel AS-H for **[77]**); Absolute configuration determined by comparison of rotation values for **[50]**, **[57]**, **[58]**, **[59]**, **[60]** to known literature values; for **[52]**, **[53]**, **[54]**, **[61]**, **[75]**, **[78]** proposed configuration based on HPLC elution order and direction of specific rotations.

d) Configuration of **[77]** not determined.

2.15.2 *Investigation of Steric and Electronic Effects of Aryl Substituents*

Having investigated the impact of variation of the benzyl substituent on the enantioselectivity of the copper-mediated oxidation, we then focused on the effect of variation of the aryl substituent (Figure 2.16 and Figure 2.18). In this study the steric and electronic nature of the R substituent was explored. The primary objective was to establish if the presence of the aryl ring is critical for efficient enantioselective oxidation (Figure 2.19).

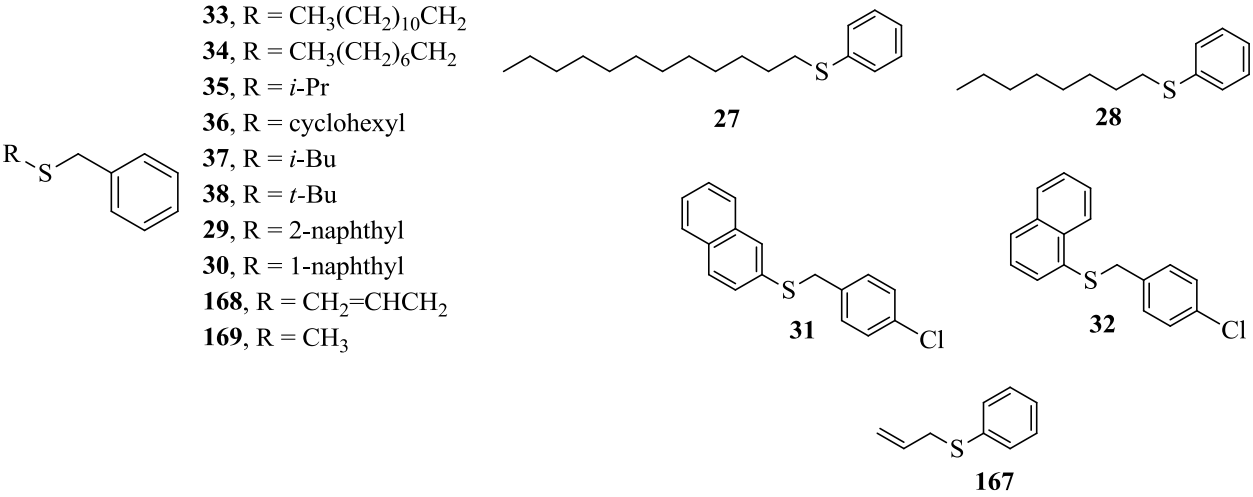
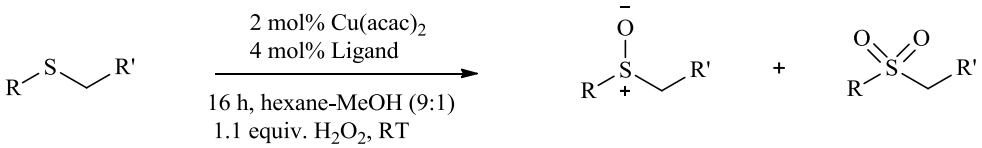


Figure 2.18

A dramatic reduction in enantioselectivity was observed with the replacement of the aryl ring with alkyl substituents even with the most sterically demanding *tert*-butyl group (37% *cf.* 79% for benzyl phenyl sulfide under the same conditions, entry 1, Table 2.15 and entry 7, Table 2.16). This was in contrast to our previous study in which replacement of benzyl with a neopentyl group in the R' position of the sulfide afforded sulfoxides with comparable

enantioselectivity (71 and 79% ee, entries 1 and 12, Table 2.15). Hence, the aryl ring must be directly attached to the sulfur to achieve good enantiocontrol. A steric effect was observed, with enhanced enantioselectivity as the bulk of the R group increases from methyl to isobutyl to isopropyl to *tert*-butyl, although increases in enantioselectivities are only modest (entries 1, 4, 7 and 34, Table 2.16). The oxidation of sulfides **[33]** and **[34]**, which contain long alkyl chains, also proceeded with modest enantioselectivity (entries 24-29, Table 2.16). However, oxidation of sulfides **[27]** and **[28]** proceed with improved enantioselectivity (57-58% ee using ligand **[158]**) highlighting the importance of direct attachment of the sulfur to the aryl ring (entries 21 and 23, Table 2.16). A similar pattern was observed in the oxidation of the allyl phenyl and allyl benzyl sulfides **[167]** and **[168]** with higher, albeit modest enantioselectivity for the phenyl sulfide **[167]** (entries 30-33, Table 2.16). The observation of any enanatioenrichment with the allyl sulfoxides is very suprising as racemisation occurs in these systems *via* the Mislow-Evans rearrangement.[188] Excellent enantioselectivities were achieved in the oxidation of sulfides bearing 2- and 1-naphthyl groups **[29]** and **[30]**. The replacement of the phenyl substituent with a 1-naphthyl group (sulfide **[30]**) afforded comparable levels of asymmetric induction (75% ee using ligand **[155]** entry 13, Table 2.16 *cf.* benzyl phenyl sulfoxide **[50]** entry 1, Table 2.15), while the substitution with a 2-naphthyl group resulted in enhanced levels of enantioinduction, reproducibly up to 97% ee (entries 11 and 12, Table 2.16). Sulfoxides **[68]** and **[69]** were afforded with reduced enantioselectivities relative to their unsubstituted counterparts (71 and 90% ee vs. 75 and 97% ee, entries 13-16, Table 2.16) demonstrating that the *para*-chloro substituent on the phenyl ring has a negative impact on enantioselectivity, although the reduction is only marginal. Sulfides **[29]** to **[32]** were insoluble in 9:1 hexane/methanol and, as a result, 9:1 toluene/methanol was used as solvent in these oxidations. We have shown previously that 9:1 hexane/MeOH could be replaced with 9:1 toluene-MeOH with a slight reduction in enantioselectivity (Section 2.9).

Table 2.16 Investigation of steric effects of sulfide substituents



Entry	Sulfide	R	R'	Ligand	Sulfide : Sulfoxide : Sulfone[a]	Yield %[b]	%ee[c] (*R*)	Sulfoxide
1	**[35]**	*i*-Pr	Ph	**[155]**	0 : 97 : 3	86	27	**[63]**
2	**[35]**	*i*-Pr	Ph	**[158]**	1 : 96 : 3	88	36	**[63]**
3	**[35]**	*i*-Pr	Ph	**[156]**	0 : 98:2	82	13	**[63]**
4	**[37]**	*i*-Bu	Ph	**[155]**	4 : 94 : 2	87	11	**[64]**
5	**[37]**	*i*-Bu	Ph	**[158]**	2 : 97 : 1	89	19	**[64]**
6	**[37]**	*i*-Bu	Ph	**[156]**	10 : 90 : 0	80	8	**[64]**
7	**[38]**	*t*-Bu	Ph	**[155]**	2 : 97 : 1	88	37	**[65]**
8	**[38]**	*t*-Bu	Ph	**[158]**	1 : 98 : 1	90	40	**[65]**
9	**[38]**	*t*-Bu	Ph	**[156]**	11 : 88 : 1	82	16	**[65]**
10	**[29]**	2-Naphthyl	Ph	**[155]**	100 : 0 : 0	-	-	**[66]**
11	**[29]**	2-Naphthyl	Ph	**[155]**	62 : 38 : 0	32	97[e]	**[66]**
12	**[29]**	2-Naphthyl	Ph	**[158]**	58 : 42 : 0	38	95	**[66]**
13	**[30]**	1-Naphthyl	Ph	**[155]**	48 : 52 : 0	46	75	**[67]**
14	**[30]**	1-Naphthyl	Ph	**[158]**	56:44 : 0	37	77	**[67]**
15	**[31]**	2-Naphthyl	4'-ClC_6H_4	**[155]**	23 : 75 : 2	67	90	**[68]**
16	**[32]**	1-Naphthyl	4'-ClC_6H_4	**[155]**	65 : 35 : 0	28	71	**[69]**

17	**[36]**	Cyclohexyl	Ph	**[155]**	3 : 94 : 3	88	27	**[70]**
18	**[36]**	Cyclohexyl	Ph	**[158]**	4 : 93 : 3	85	33	**[70]**
19	**[36]**	Cyclohexyl	Ph	**[156]**	5 : 93 : 2	82	21	**[70]**
20	**[27]**	Ph	$CH_2(CH_2)_9CH_3$	**[155]**	29 : 65 : 6	60	57	**[71]**
21	**[27]**	Ph	$CH_2(CH_2)_9CH_3$	**[158]**	27 : 65 : 8	57	57	**[71]**
22	**[28]**	Ph	$CH_2(CH_2)_5CH_3$	**[155]**	32 : 62 : 6	55	36	**[72]**
23	**[28]**	Ph	$CH_2(CH_2)_5CH_3$	**[158]**	31 : 63 : 6	55	58	**[72]**
24	**[33]**	$CH_3(CH_2)_{10}CH_2$	Ph	**[155]**	2 : 93 : 5	88	21	**[73]**
25	**[33]**	$CH_3(CH_2)_{10}CH_2$	Ph	**[158]**	9 : 86 : 5	79	26	**[73]**
26	**[33]**	$CH_3(CH_2)_{10}CH_2$	Ph	**[156]**	6 : 88 : 6	78	22	**[73]**
27	**[34]**	$CH_3(CH_2)_6CH_2$	Ph	**[155]**	9 : 85 : 6	77	22	**[74]**
28	**[34]**	$CH_3(CH_2)_6CH_2$	Ph	**[158]**	10 : 84 : 6	77	21	**[74]**
29	**[34]**	$CH_3(CH_2)_6CH_2$	Ph	**[156]**	19 : 76 : 5	65	10	**[74]**
30	**[167]**	Ph	$CH=CH_2$	**[155]**	26 : 74 : 0	67	29	**[81]**
31	**[167]**	Ph	$CH=CH_2$	**[158]**	21 : 79 : 0	72	24	**[81]**
32	**[168]**	$CH_2=CHCH_2$	Ph	**[155]**	6 : 94 : 0	87	11[d]	**[82]**
33	**[168]**	$CH_2=CHCH_2$	Ph	**[158]**	6 : 94 : 0	85	13[d]	**[82]**
34	**[169]**	CH_3	Ph	**[155]**	5 : 94 : 1	85	4	**[83]**

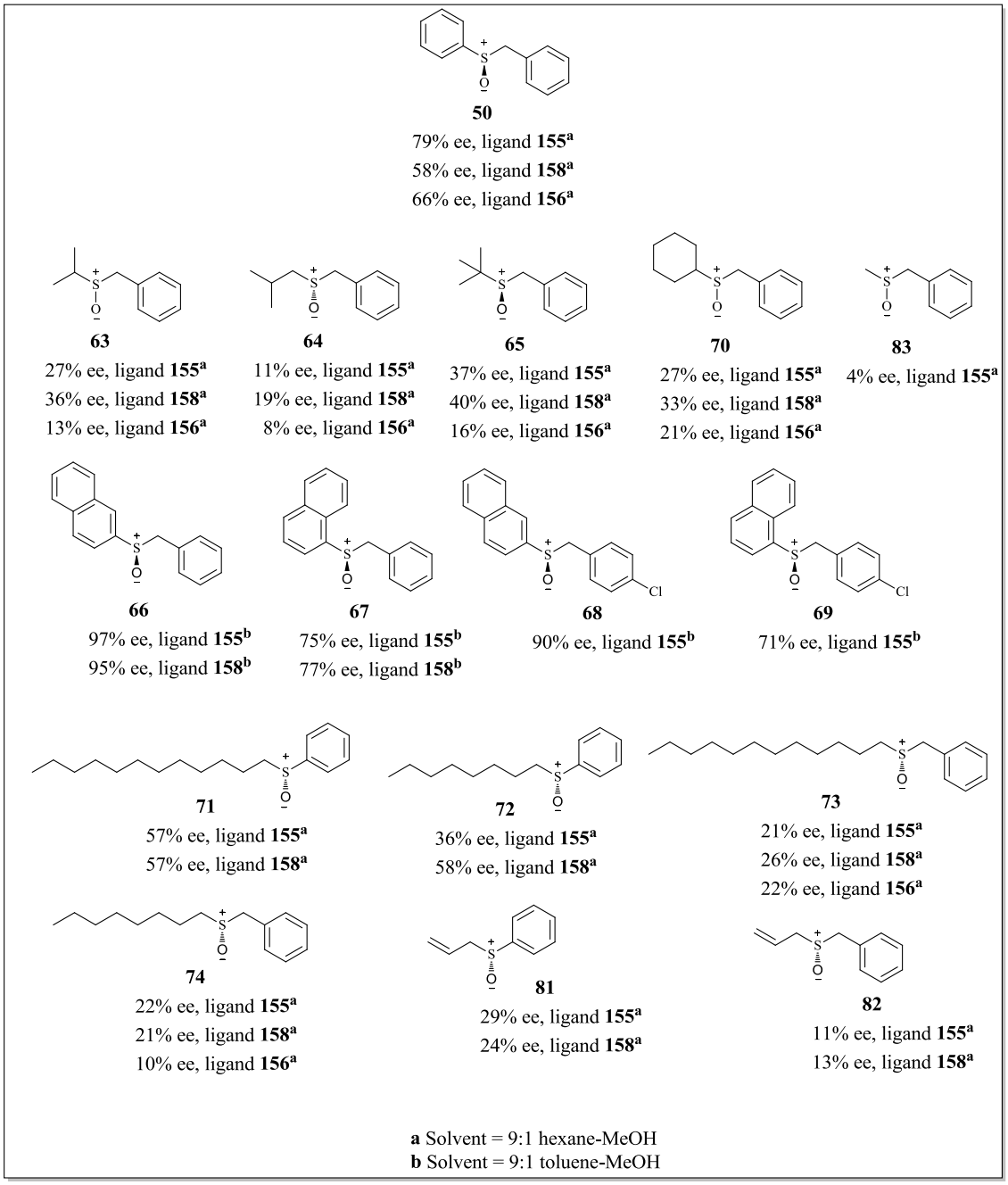
a) Ratio of sulfide : sulfoxide : sulfone determined by ^{1}H NMR analysis of the crude product.

b) Yield of sulfoxide after purification by column chromatography.

c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H for **[65]**, **[66]**, **[68]**, **[69]**, **[83]**; Chiracel AS-H for **[63]**, **[64]**, **[67]**, **[71]**, **[73]**, **[74]**, **[82]**; Chiracel OJ-H for **[81]**; Phenomenex Lux Cellulose-4 for **[72]**, **[83]**; Phenomenex Lux Amylose-2 for **[70]**); **[83]** enantiomers were separated using both OD-H and Phenomenex Lux Cellulose-4 columns, resolution was better using Phenomenex Lux Cellulose-4 column; Absolute configuration determined by comparison of rotation values for **[64]**, **[65]**, **[81]** to known literature values; for **[66]** and **[67]** absolute configuration was determined by single crystal X-ray diffraction on a crystalline sample of 1-naphthyl benzyl sulfoxide and 2-naphthyl benzyl sulfoxide recrystallised from CH_2Cl_2,[127] **[68]** and **[69]** proposed configuration based on HPLC elution order and direction of specific rotations, **[73]** and **[74]** proposed configuration based on comparison of optical rotation to known literature values for (*R*)-decyl phenyl sulfoxide[129] and (*R*)-butyl phenyl sulfoxide,[130] **[71]** and **[72]** proposed configuration based on comparison of optical rotation to known literature value for (*R*)-decyl benzyl sulfoxide.[128]

d) Configuration of **[82]** not determined.

e) The oxidation of sulfide **[29]**, under the conditions indicated in Table 2.16 using ligand **[155]** was reproduced several times with enantioselectivities ranging from 95-97% ee.



Scheme 2.7

For each compound where the absolute configuration was confirmed, the (*R*)-sulfoxide predominates with use of ligand derived form (*S*)-*tert*-leucinol, thus the sense of asymmetric

induction was the same for the majority of the sulfides. In the oxidation of sulfides **[33]**, **[34]** and **[37]** the (*R*)-sulfoxides again predominated, but in this case correspond to the opposite sense of oxygen approach to the prochiral sulfide, albeit at low levels of enantiopurity.

Peak Broadening

In contrast to the clearly-resolved spectra obtained for the racemic sulfoxides, peak broadening was evident in the ^{1}H NMR spectra of the crude product that resulted from the asymmetric oxidation of sulfides **[33]**, **[34]** and **[37]**. Interestingly, for the corresponding sulfides bearing a phenyl substituent no peak broadening was observed (Figure 2.19). It may indicate complexation in the crude product. Following column chromatography, the spectroscopic features were again fully resolved (Figure 2.23).

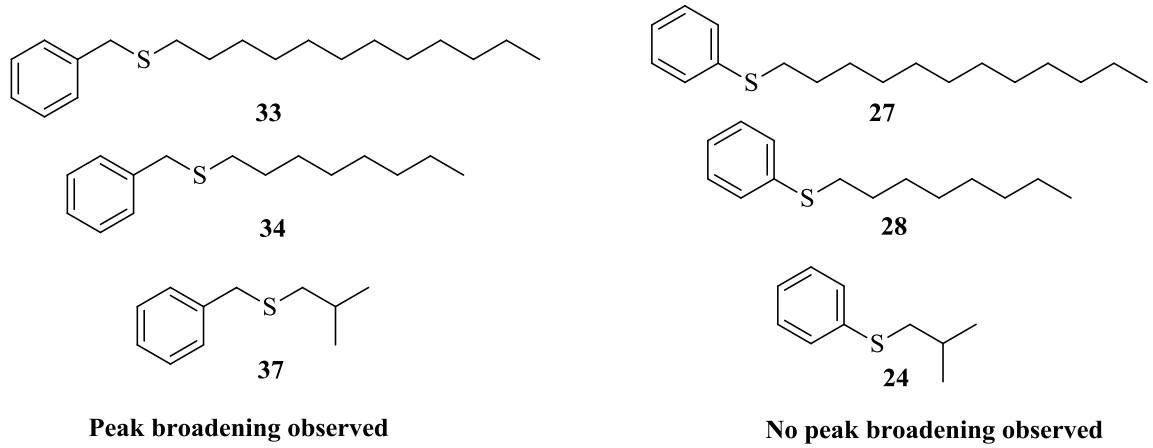


Figure 2.19

During the *viva* examination an alternative explanation for the limited extent of oxidation was discussed. The spectra in Figure 2.20 and 2.21 illustrate broadening in the peaks of the sulfide more so than the sulfoxide. This would indicate preferential complexation of the soft sulfide to copper rather than the hard sulfoxide. If this is the case then catalyst poisoning by sulfoxide is less likely and the role of methanol may relate instead to catalyst stability by providing a reservoir for a stable catalyst possibly with co-ordinating methanol. Investigation using an *in-situ* IR probe may shed light on this.

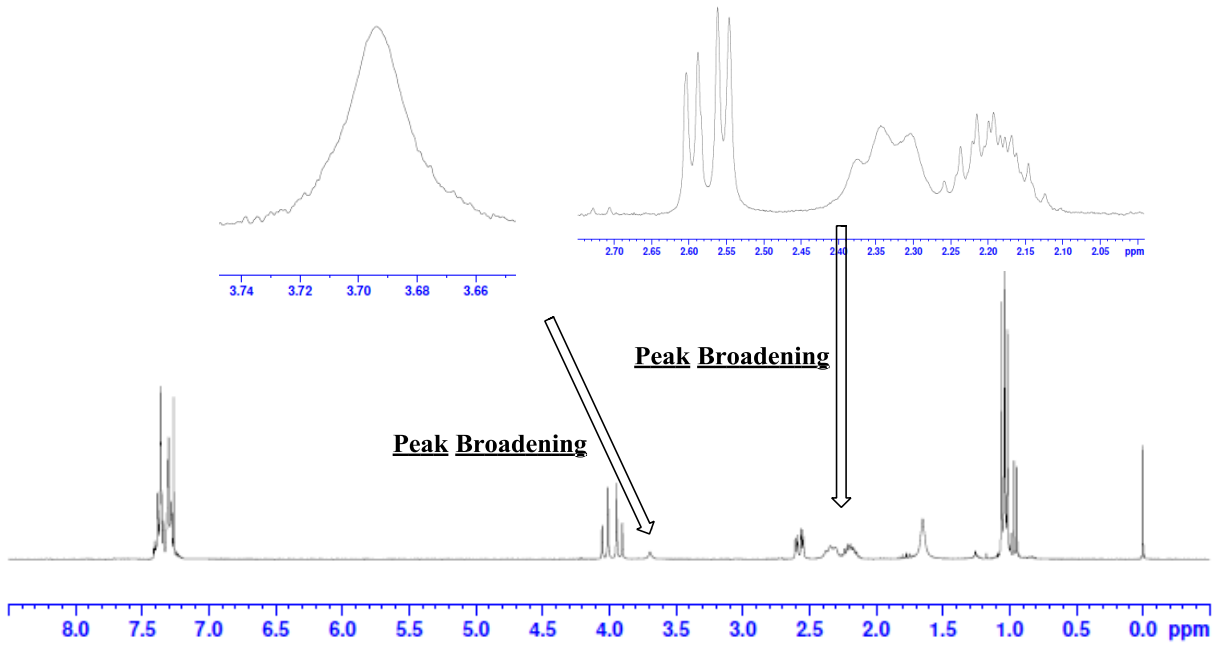


Figure 2.20 Peak broadening in oxidation of sulfide **[37]**

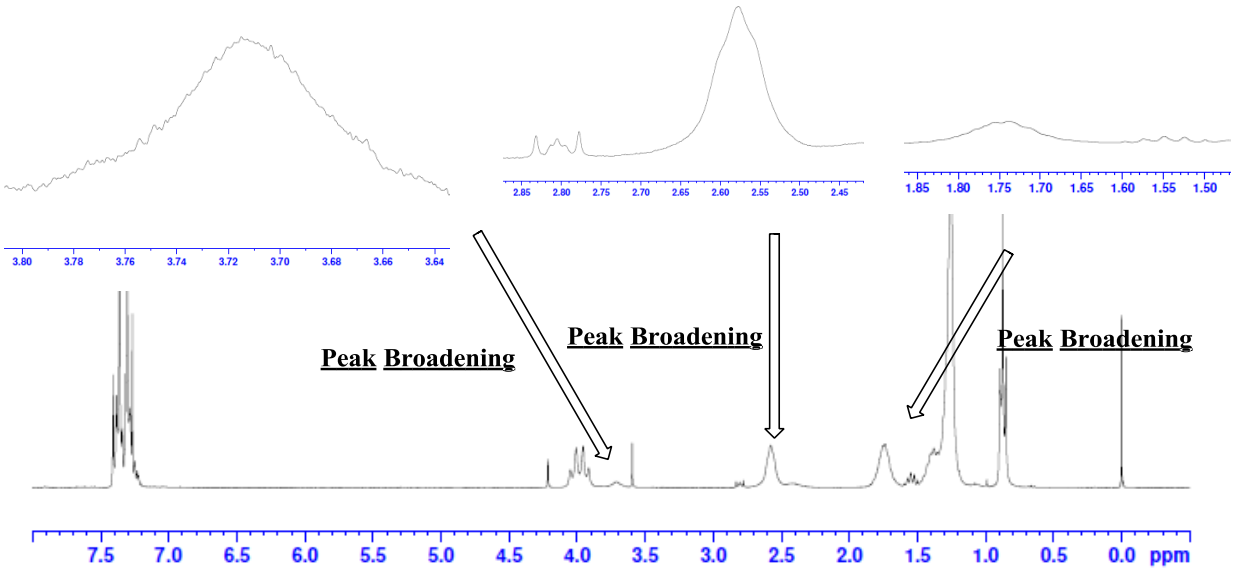


Figure 2.21 Peak broadening in oxidation of sulfide **[34]**

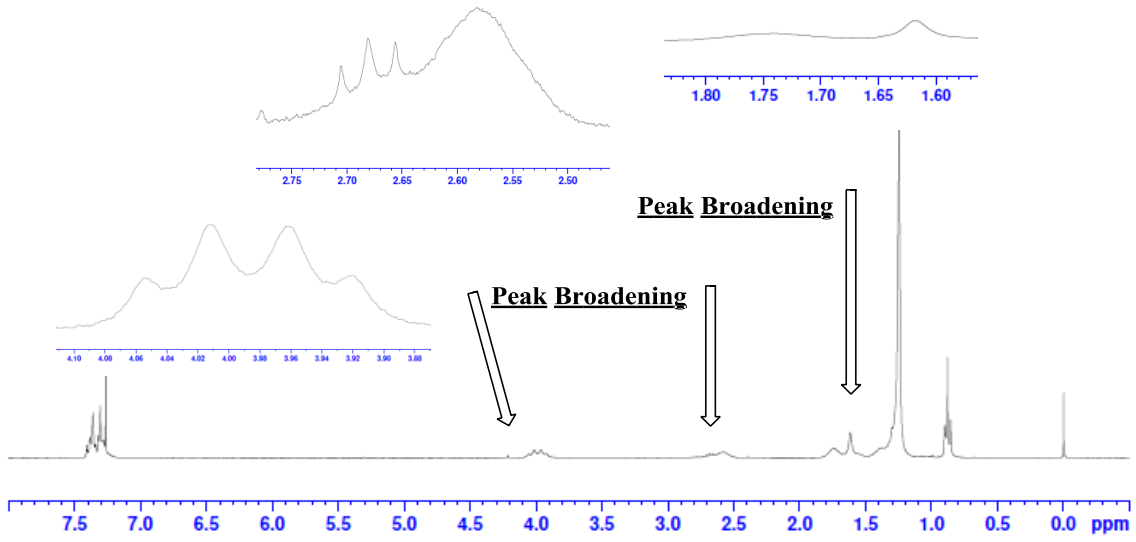


Figure 2.22 Peak broadening in oxidation of sulfide **[33]**

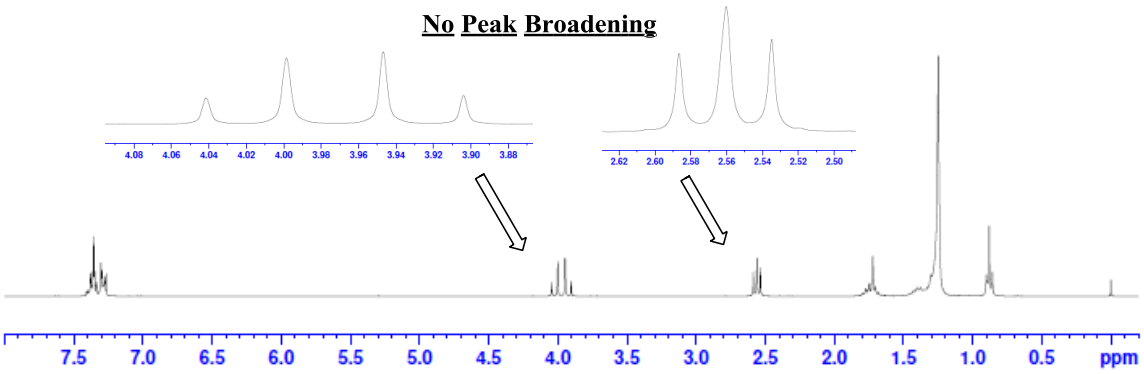
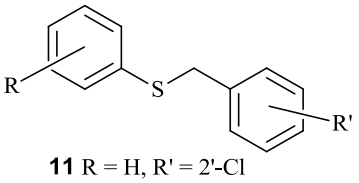


Figure 2.23 No peak broadening observed with purified sulfoxide **[73]** produced from oxidation of sulfide **[33]**, this is the same sulfoxide sample from Figure 2.22 following purification by column chromatography

2.16 Oxidation of Chloro Substituted Aryl Benzyl Sulfides

A number of chloro substituted aryl benzyl sulfides were prepared and oxidised by this system as shown in Figure 2.24 and Table 2.17. The chloro substituent was moved from the *ortho*- to *meta*- to *para*- positions of both rings to investigate its effect on the yield and enantioselectivity of the oxidation.

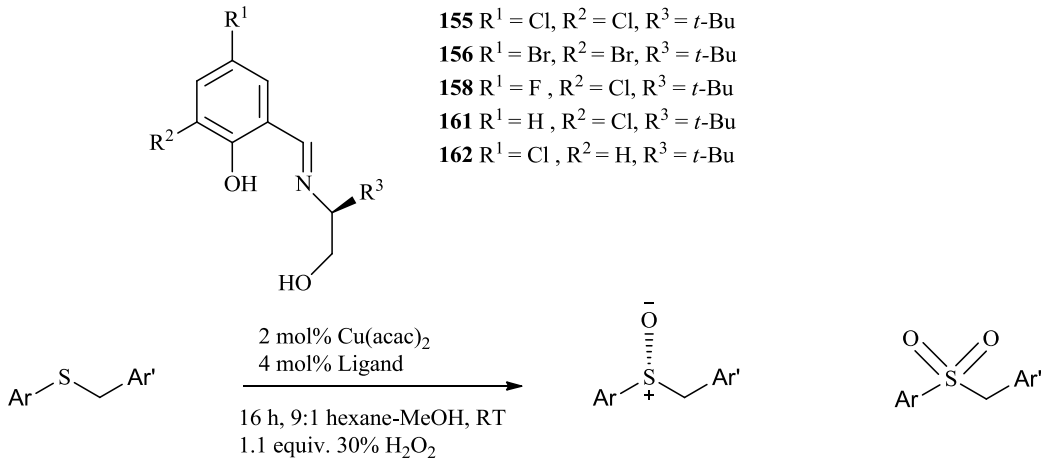


11 R = H, R' = 2'-Cl
12 R = H, R' = 3'-Cl
13 R = H, R' = 4'-Cl
14 R = 2-Cl, R' = H
15 R = 3-Cl, R' = H
16 R = 4-Cl, R' = H

Figure 2.24 Chloro substituted aryl benzyl sulfides

Overall, the oxidation of the chloro substituted derivatives proceeded with lower enantioselectivity than that obtained with benzyl phenyl sulfide **[163]** (Table 2.17 and Scheme 2.8; *cf.* Table 2.9, entry 13). Interestingly for chloro substituted derivatives **[14]**, **[15]** and **[16]**, in which the chloro substituent is on the phenyl ring, the efficiency of the oxidation decreases (entries 12-25, Table 2.17, sulfoxides **[87]**, **[88]** and **[89]**, Scheme 2.8). This reduction in efficiency is not as evident for sulfides **[11]**, **[12]** and **[13]**, in which the chloro substituent is on the benzyl group (entries 1-11, Table 2.17, sulfoxides **[84]**, **[85]** and **[86]**, Scheme 2.8). Ligands **[155]** and **[158]** generally gave the best results both in terms of yield and enantioselectivity in agreement with our earlier results. (Table 2.17).

Table 2.17 Oxidation of aryl benzyl sulfides bearing an electron withdrawing group



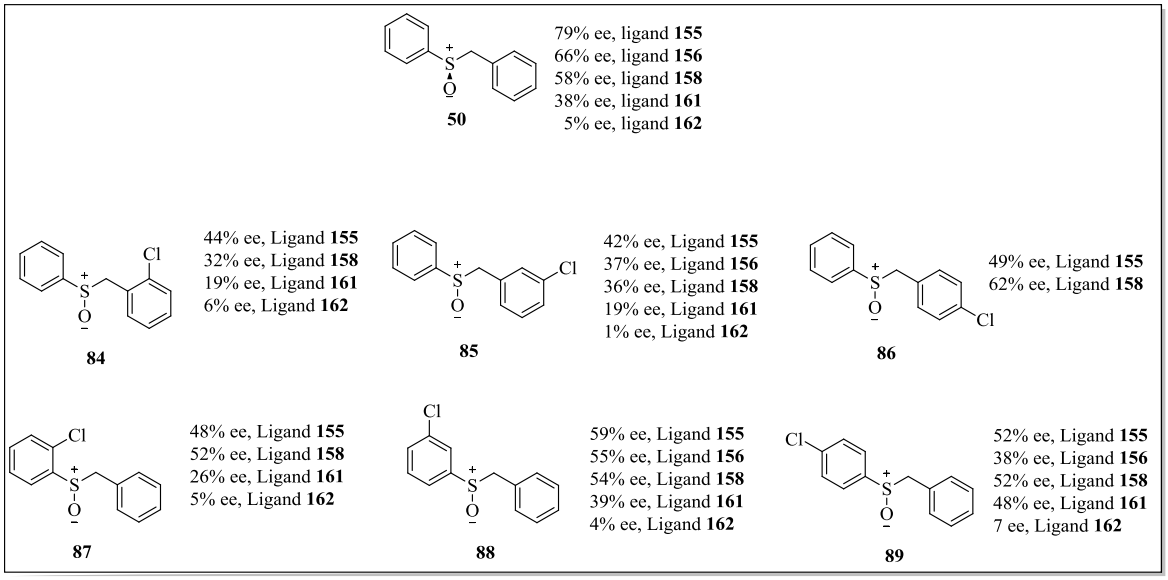
Entry	Sulfide	Ar	Ar'	Ligand	Sulfide : Sulfoxide : Sulfone[a]	Yield %[b]	%ee[c] (*R*)	Sulfoxide
1	**[11]**	Ph	2'-ClC_6H_4	**[155]**	18 : 78 : 4	72	44	**[84]**
2	**[11]**	Ph	2'-ClC_6H_4	**[158]**	19 : 77 : 4	72	32	**[84]**
3	**[11]**	Ph	2'-ClC_6H_4	**[161]**	29 : 67 : 4	58	19	**[84]**
4	**[11]**	Ph	2'-ClC_6H_4	**[162]**	76 : 24 : 0	17	6	**[84]**
5	**[12]**	Ph	3'-ClC_6H_4	**[155]**	10 : 89 : 1	82	42	**[85]**
6	**[12]**	Ph	3'-ClC_6H_4	**[156]**	38 : 62 : 0	57	36	**[85]**
7	**[12]**	Ph	3'-ClC_6H_4	**[158]**	17 : 81 : 2	75	37	**[85]**
8	**[12]**	Ph	3'-ClC_6H_4	**[161]**	47 : 51 : 2	43	19	**[85]**
9	**[12]**	Ph	3'-ClC_6H_4	**[162]**	68 : 31 : 1	21	1	**[85]**
10	**[13]**	Ph	4'-ClC_6H_4	**[155]**	9 : 90 : 1	85	49	**[86]**
11	**[13]**	Ph	4'-ClC_6H_4	**[158]**	12 : 87 : 1	80	62	**[86]**
12	**[14]**	2-ClC_6H_4	Ph	**[155]**	67 : 32 : 1	26	48	**[87]**
13	**[14]**	2-ClC_6H_4	Ph	**[158]**	47 : 51 : 2	46	52	**[87]**
14	**[14]**	2-ClC_6H_4	Ph	**[161]**	73 : 26 : 1	21	26	**[87]**
15	**[14]**	2-ClC_6H_4	Ph	**[162]**	88 : 12 : 0	7	5	**[87]**
16	**[15]**	3-ClC_6H_4	Ph	**[155]**	60 : 39 : 1	33	59	**[88]**
17	**[15]**	3-ClC_6H_4	Ph	**[156]**	77 : 23 : 0	17	55	**[88]**
18	**[15]**	3-ClC_6H_4	Ph	**[158]**	57 : 42 : 1	36	54	**[88]**
19	**[15]**	3-ClC_6H_4	Ph	**[161]**	63 : 36 : 1	24	39	**[88]**
20	**[15]**	3-ClC_6H_4	Ph	**[162]**	70 : 30 : 0	22	4	**[88]**
21	**[16]**	4-ClC_6H_4	Ph	**[155]**	28 : 72 : 0	67	52	**[89]**
22	**[16]**	4-ClC_6H_4	Ph	**[156]**	66 : 34 : 0	27	38	**[89]**
23	**[16]**	4-ClC_6H_4	Ph	**[158]**	20 : 80 : 0	71	52	**[89]**

24	**[16]**	4-ClC_6H_4	Ph	**[161]**	34 : 66 : 0	57	48	**[89]**
25	**[16]**	4-ClC_6H_4	Ph	**[162]**	76 : 24 : 0	16	7	**[89]**

a) Ratio of sulfide : sulfoxide : sulfone determined by ^{1}H NMR analysis of the crude product.

b) Sulfoxide yield after purification by column chromatography.

c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H for **[85]**, **[86]**, **[89]**, Chiracel OJ-H for **[87]**, **[88]**, Chiracel AS-H for **[84]**); Absolute configuration determined by comparison of rotation values for **[87]** to known literature values; for **[84]**, **[85]**, **[86] [88]**, **[89]** proposed configuration based on HPLC elution order and direction of specific rotations.



Scheme 2.8

S(O)CH_2 Protons

For the majority of aryl benzyl sulfoxides an AB system is observed for the S(O)CH_2 protons see Section 2.7. However for sulfoxide **[85]**, the S(O)CH_2 signal appears as a 2H singlet (Figure 2.25).

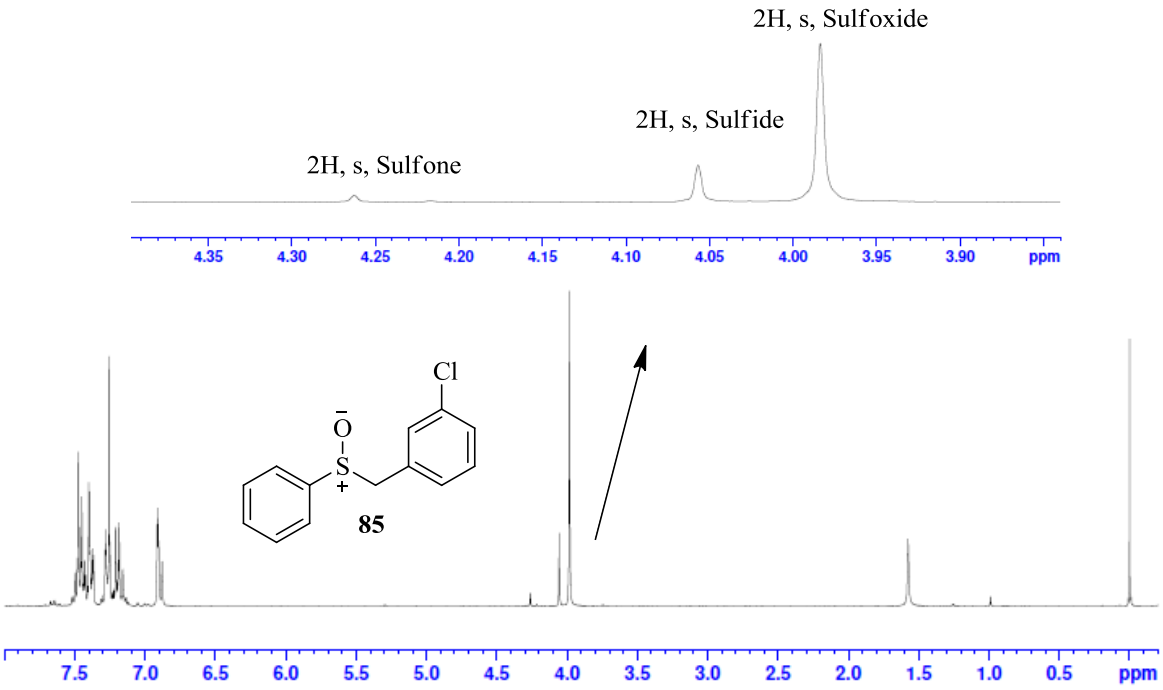
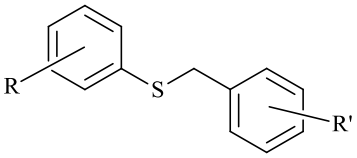


Figure 2.25 ^{1}H NMR of the crude product in the synthesis of sulfoxide **[85]**

2.17 Oxidation of Methyl Substituted Aryl Benzyl Sulfides

A number of methyl substituted aryl benzyl sulfides were synthesised and oxidised by this system as shown in Figure 2.26 and Table 2.18.



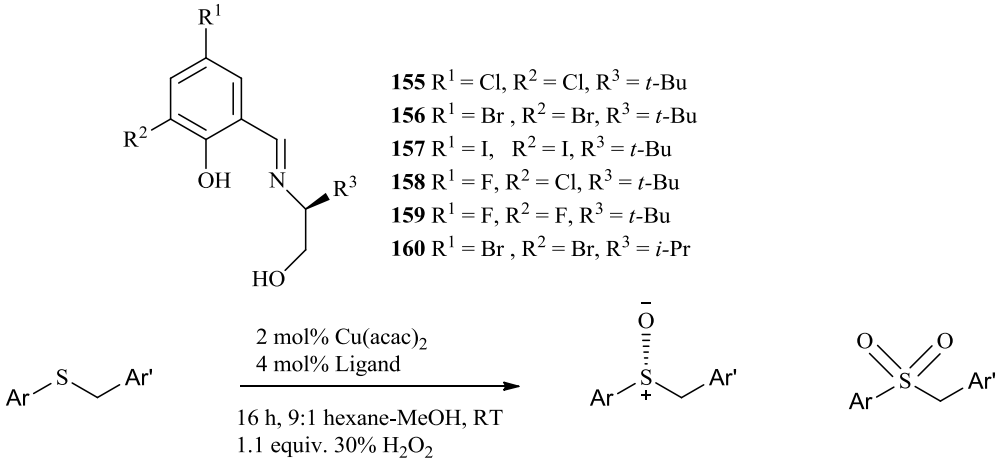
5 R = 2-CH_3, R' = H
6 R = 3-CH_3, R' = H
7 R = 4-CH_3, R' = H
8 R = H, R' = 2'-CH_3
9 R = H, R' = 3'-CH_3
10 R = H, R' = 4'-CH_3

Figure 2.26 Methyl substituted aryl benzyl sulfides

Overall, the enantioselectivities obtained in the oxidation of the methyl substituted derivatives proceeded with comparable or lower enantioselectivity than that obtained with benzyl phenyl sulfide **[163]**. For sulfides **[5]**, **[6]** and **[7]**, in which the methyl substitiuent is on the phenyl ring, the corresponding sulfoxides were obtained in excellent yields (up to 91%) and good enantiopurities (up to 84% ee). Of note, the 84% ee obtained in the oxidation of sulfide **[7]** is the highest achieved to date in the aryl benzyl series. The oxidation of

sulfides **[8]**, **[9]** and **[10]** proceeded with lower enantioselectivity than that obtained for benzyl phenyl sulfide **[163]**, although the yields obtained using ligands **[155]** and **[158]** were excellent in most cases (Table 2.18). In terms of a methyl substituent on either the aryl or benzyl ring the enantioselectivity increases slightly with ligand **[155]** on going from *ortho* to *meta* to *para* substitution (entries 1,7,13 and entries 19, 25, 31, Table 2.18 and sulfoxides **[75]**– Scheme 2.9). Again, the efficiency of the oxidation was largely ligand dependant, with ligands **[155]** and **[158]** producing the best results. Ligands **[157]** and **[160]** performed very poorly, in agreement with our previous results.

Table 2.18 Oxidation of aryl benzyl sulfides bearing an electron donating group



Entry	Sulfide	Ar	Ar'	Ligand	Sulfide : Sulfoxide : Sulfone[a]	Yield %[b]	%ee[c] (*R*)	Sulfoxide
1	**[5]**	2-MeC_6H_4	Ph	**[155]**	1 : 98 : 1	91	64	**[75]**
2	**[5]**	2-MeC_6H_4	Ph	**[156]**	40 : 60 : 0	51	55	**[75]**
3	**[5]**	2-MeC_6H_4	Ph	**[157]**	79 : 21 : 0	16	11	**[75]**
4	**[5]**	2-MeC_6H_4	Ph	**[158]**	6 : 94 : 0	88	71	**[75]**
5	**[5]**	2-MeC_6H_4	Ph	**[159]**	70 : 30 : 0	24	60	**[75]**
6	**[5]**	2-MeC_6H_4	Ph	**[160]**	88 : 12 : 0	10	9	**[75]**
7	**[6]**	3-MeC_6H_4	Ph	**[155]**	11 : 89 : 0	84	65	**[76]**
8	**[6]**	3-MeC_6H_4	Ph	**[156]**	15 : 85 : 0	77	49	**[76]**
9	**[6]**	3-MeC_6H_4	Ph	**[157]**	83 : 17 : 0	16	16	**[76]**

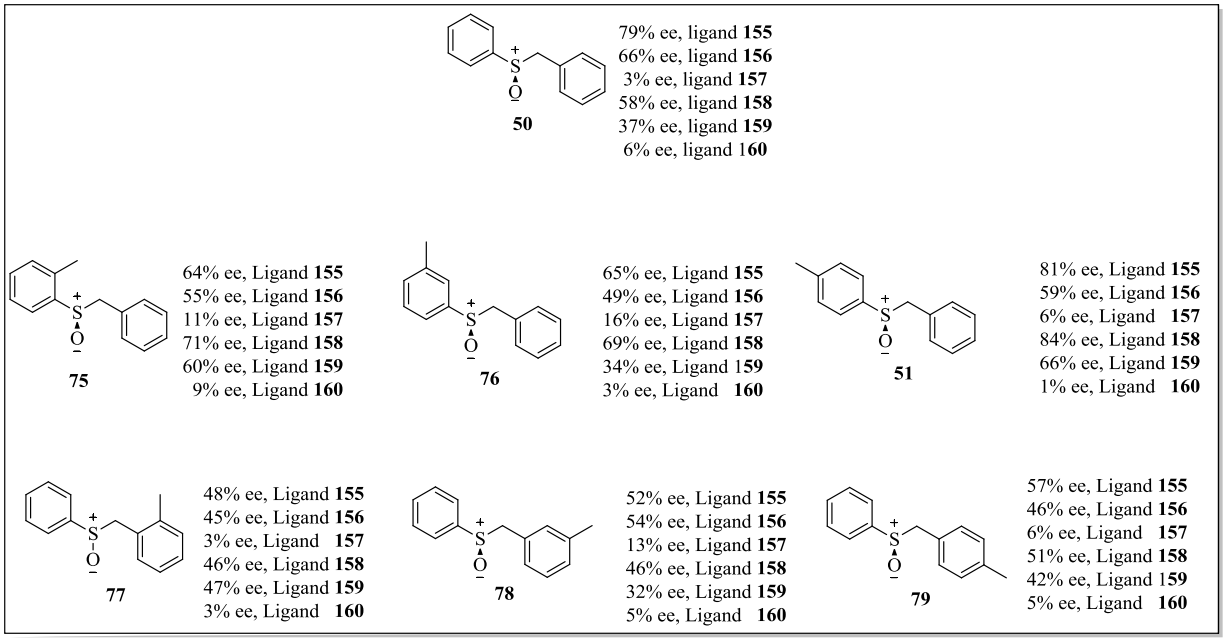
10	**[6]**	3-MeC_6H_4	Ph	**[158]**	10 : 88:2	83	69	**[76]**
11	**[6]**	3-MeC_6H_4	Ph	**[159]**	49 : 51 : 0	45	34	**[76]**
12	**[6]**	3-MeC_6H_4	Ph	**[160]**	76 : 24 : 0	17	3	**[76]**
13	**[7]**	4-MeC_6H_4	Ph	**[155]**	2 : 97 : 1	91	81	**[51]**
14	**[7]**	4-MeC_6H_4	Ph	**[156]**	2 : 98 : 0	90	59	**[51]**
15	**[7]**	4-MeC_6H_4	Ph	**[157]**	81 : 19 : 0	12	6	**[51]**
16	**[7]**	4-MeC_6H_4	Ph	**[158]**	4 : 96 : 0	90	84	**[51]**
17	**[7]**	4-MeC_6H_4	Ph	**[159]**	33 : 67 : 0	60	66	**[51]**
18	**[7]**	4-MeC_6H_4	Ph	**[160]**	71 : 29 : 0	23	1	**[51]**
19	**[8]**	Ph	2'-MeC_6H_4	**[155]**	12 : 85 : 2	80	48	**[77]**
20	**[8]**	Ph	2'-MeC_6H_4	**[156]**	23 : 76 : 1	69	45	**[77]**
21	**[8]**	Ph	2'-MeC_6H_4	**[157]**	87 : 13 : 0	9	3	**[77]**
22	**[8]**	Ph	2'-MeC_6H_4	**[158]**	19 : 81 : 0	74	46	**[77]**
23	**[8]**	Ph	2'-MeC_6H_4	**[159]**	55 : 45 : 0	40	47	**[77]**
24	**[8]**	Ph	2'-MeC_6H_4	**[160]**	72 : 28 : 0	21	3	**[77]**
25	**[9]**	Ph	3'-MeC_6H_4	**[155]**	9 : 90 : 1	81	52	**[78]**
26	**[9]**	Ph	3'-MeC_6H_4	**[156]**	7 : 92 : 1	83	54	**[78]**
27	**[9]**	Ph	3'-MeC_6H_4	**[157]**	81 : 19 : 0	15	13	**[78]**
28	**[9]**	Ph	3'-MeC_6H_4	**[158]**	4 : 95 : 1	90	46	**[78]**
29	**[9]**	Ph	3'-MeC_6H_4	**[159]**	56:44 : 0	36	32	**[78]**
30	**[9]**	Ph	3'-MeC_6H_4	**[160]**	78:22 : 0	17	5	**[78]**
31	**[10]**	Ph	4'-MeC_6H_4	**[155]**	1 : 97 : 2	89	57	**[79]**
32	**[10]**	Ph	4'-MeC_6H_4	**[156]**	14 : 85 : 1	80	46	**[79]**

33	**[10]**	Ph	4'-MeC_6H_4	**[157]**	91 : 9 : 0	5	6	**[79]**
34	**[10]**	Ph	4'-MeC_6H_4	**[158]**	34 : 75 : 1	68	51	**[79]**
35	**[10]**	Ph	4'-MeC_6H_4	**[159]**	66 : 34 : 0	28	42	**[79]**
36	**[10]**	Ph	4'-MeC_6H_4	**[160]**	75 : 25 : 0	16	5	**[79]**

a) Ratio of sulfide : sulfoxide : sulfone determined by ^1H NMR analysis of the crude product.

b) Sulfoxide yield after purification by column chromatography.

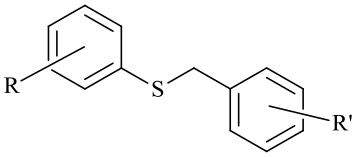
c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H for **[51]**, **[75]**, **[76]**, **[78]**, **[79]**, Chiracel AS-H for **[77]**); Absolute configuration determined by comparison of rotation values for **[51]** to known literature values; for **[75]**, **[76]**, **[77]**, **[78]**, **[79]** proposed configuration based on HPLC elution order and direction of specific rotations.



Scheme 2.9

2.18 Oxidation of Disubstituted Aryl Benzyl Sulfides

A number of disubstituted aryl benzyl sulfides were synthesised and oxidised by this system as shown in Figure 2.27 and Table 2.19.

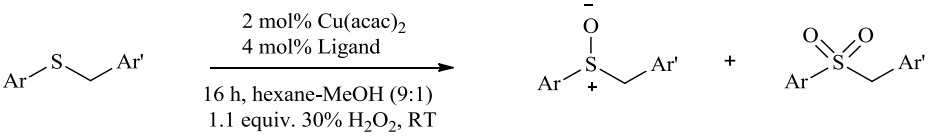


17 R = 4-CH_3, R' = 2'-CH_3
18 R = 4-CH_3, R' = 3'-CH_3
19 R = 4-CH_3, R' = 4'-Cl
20 R = 4-CH_3, R' = 3'-Cl
21 R = 4-CH_3, R' = 2'-Cl
22 R = 2-MeO, R' = 2'-Cl

Figure 2.27 Disubstituted aryl benzyl sulfides

The enantioselectivity obtained in the oxidation of the disubstituted aryl benzyl sulfides was lower than that obtained in the oxidation of benzyl phenyl sulfide **[163]**. An increase in enantioselectivity is observed on moving the chloro substituent from *ortho*- to *meta*- to *para*-position of the benzyl ring using ligand **[155]** (entries 7, 9 and 12, Table 2.19 and sulfoxides **[93]–[95]**, Scheme 2.10), in agreement with our previous results for the methyl substituted sulfides. Interestingly, oxidation of sulfide **[22]** with the *ortho*-methoxyphenyl substituent, in addition to the *ortho*-chloro benzyl substituent, proceeded with good enantiocontrol (entries 15-17, Table 2.19, sulfoxide **[96]**, Scheme 2.10).

Table 2.19 Oxidation of disubstituted aryl benzyl sulfides



Entry	Sulfide	Ar	Ar'	Ligand	Sulfide : Sulfoxide : Sulfone[a]	Yield %[b]	%ee[c] (*R*)	Sulfoxide
1	**[17]**	4-MeC_6H_4	2'-MeC_6H_4	**[155]**	28 : 69 : 3	62	32[d]	**[91]**
2	**[17]**	4-MeC_6H_4	2'-MeC_6H_4	**[158]**	29 : 69 : 2	64	28[d]	**[91]**
3	**[17]**	4-MeC_6H_4	2'-MeC_6H_4	**[156]**	47 : 52 : 1	47	35[d]	**[91]**
4	**[18]**	4-MeC_6H_4	3'-MeC_6H_4	**[155]**	17 : 81 : 2	76	52	**[92]**
5	**[18]**	4-MeC_6H_4	3'-MeC_6H_4	**[158]**	21 : 78 : 1	70	49	**[92]**
6	**[18]**	4-MeC_6H_4	3'-MeC_6H_4	**[156]**	54 : 46 : 0	40	43	**[92]**
7	**[19]**	4-MeC_6H_4	4'-ClC_6H_4	**[155]**	13 : 87 : 0	81	69	**[93]**

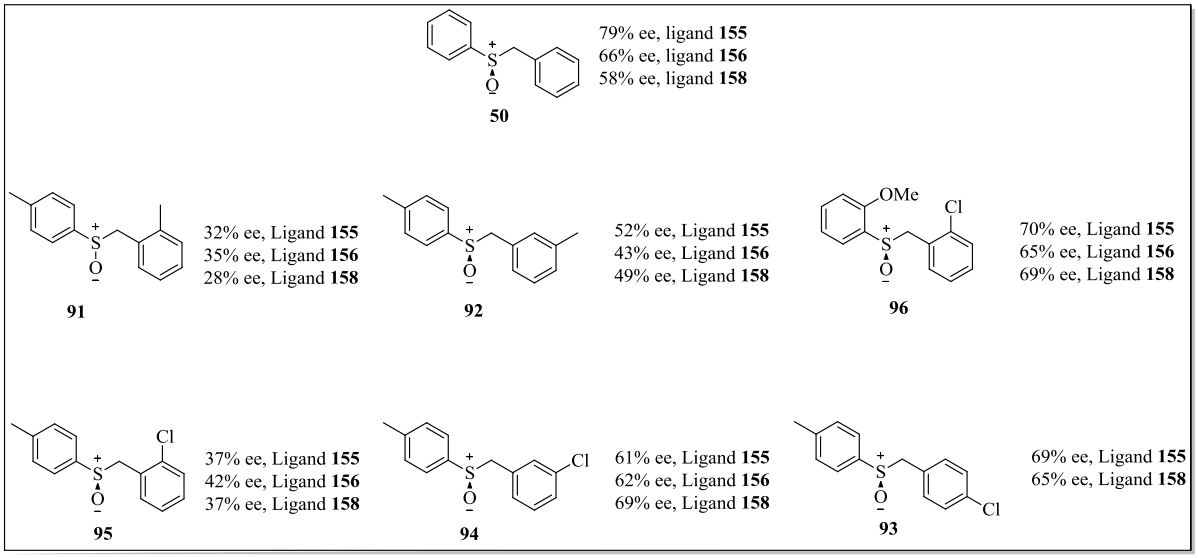
8	**[19]**	4-MeC_6H_4	4'-ClC_6H_4	**[158]**	63 : 37 : 0	32	65	**[93]**
9	**[20]**	4-MeC_6H_4	3'-ClC_6H_4	**[155]**	24 : 75 : 1	70	61	**[94]**
10	**[20]**	4-MeC_6H_4	3'-ClC_6H_4	**[158]**	23 : 76 : 1	68	69	**[94]**
11	**[20]**	4-MeC_6H_4	3'-ClC_6H_4	**[156]**	38 : 61 : 1	55	62	**[94]**
12	**[21]**	4-MeC_6H_4	2'-ClC_6H_4	**[155]**	19 : 80 : 1	74	37	**[95]**
13	**[21]**	4-MeC_6H_4	2'-ClC_6H_4	**[158]**	25 : 74 : 1	65	37	**[95]**
14	**[21]**	4-MeC_6H_4	2'-ClC_6H_4	**[156]**	57 : 43 : 0	39	42	**[95]**
15	**[22]**	2-$MeOC_6H_4$	2'-ClC_6H_4	**[155]**	19 : 80 : 1	75	70	**[96]**
16	**[22]**	2-$MeOC_6H_4$	2'-ClC_6H_4	**[158]**	24 : 75 : 1	71	69	**[96]**
17	**[22]**	2-$MeOC_6H_4$	2'-ClC_6H_4	**[156]**	46 : 54 : 0	48	65	**[96]**

a) Ratio of sulfide : sulfoxide : sulfone determined by ^1H NMR analysis of the crude product.

b) Yield of sulfoxide after purification by column chromatography.

c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H for **[92]** and **[93]**, Chiracel AS-H for **[91]**, **[94]**, **[95]**, **[96]**); **[92]** enantiomers were separated using both OD-H and Phenomenex Lux Cellulose-4 columns, resolution was better using Phenomenex Lux Cellulose-4 column; Absolute configuration determined by comparison of rotation values for **[93]** to known literature values; for **[92]**, **[94]** ,**[95]**, **[96]** proposed configuration based on HPLC elution order and direction of specific rotations.

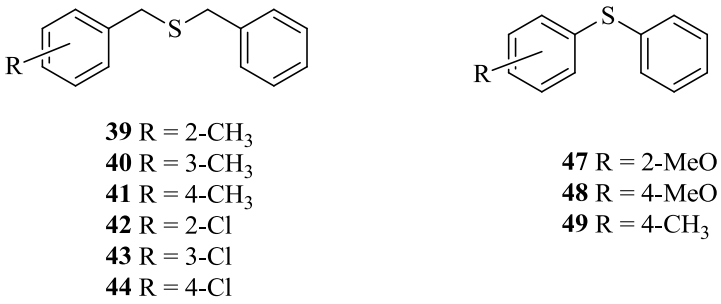
d) Configuration of **[91]** not determined.



Scheme 2.10

2.19 Oxidation of Dibenzyl and Diphenyl Sulfides

A series of diphenyl and dibenzyl sulfides differentially substituted on the two aryl rings was next explored (Figure 2.28).



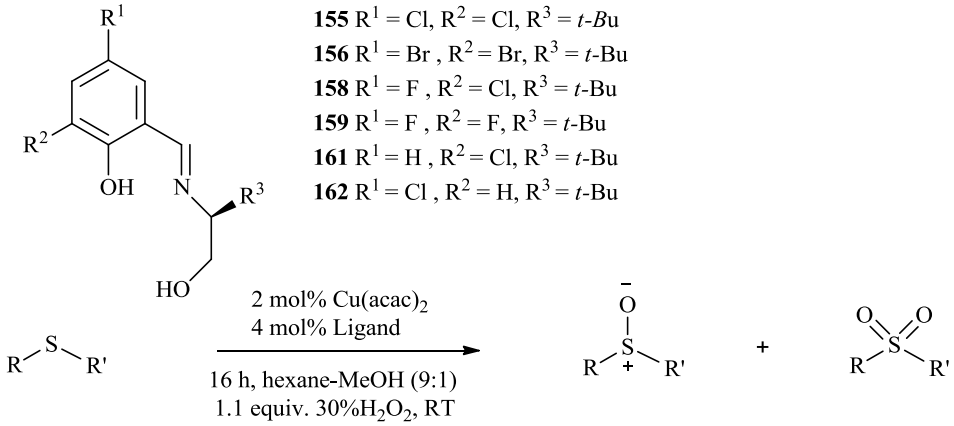
39 R = 2-CH_3
40 R = 3-CH_3
41 R = 4-CH_3
42 R = 2-Cl
43 R = 3-Cl
44 R = 4-Cl

47 R = 2-MeO
48 R = 4-MeO
49 R = 4-CH_3

Figure 2.28 dibenzyl and diphenyl sulfides

However, very poor enantiopurities were achieved; presumably due to poor differentiation between the enantiotopic faces of the sulfide. Interestingly, the efficiencies of oxidations of the dibenzyl derivatives were high, but much lower with the diphenyl derivatives. The oxidation of the dibenzyl derivatives using the difluoro substituted ligand **[159]** resulted in reduced yields compared to the other ligands used in this study, in agreement with our previous observations. Small amounts of sulfone (up to 12%) were evident in the dibenzyl sulfide oxidations in contrast to our earlier studies in which very little or no sulfone was detected in the crude products.

Table 2.20 Oxidation of dibenzyl and diphenyl sulfides



155 R^1 = Cl, R^2 = Cl, R^3 = *t-Bu*
156 R^1 = Br , R^2 = Br, R^3 = *t*-Bu
158 R^1 = F , R^2 = Cl, R^3 = *t*-Bu
159 R^1 = F , R^2 = F, R^3 = *t*-Bu
161 R^1 = H , R^2 = Cl, R^3 = *t*-Bu
162 R^1 = Cl , R^2 = H, R^3 = *t*-Bu

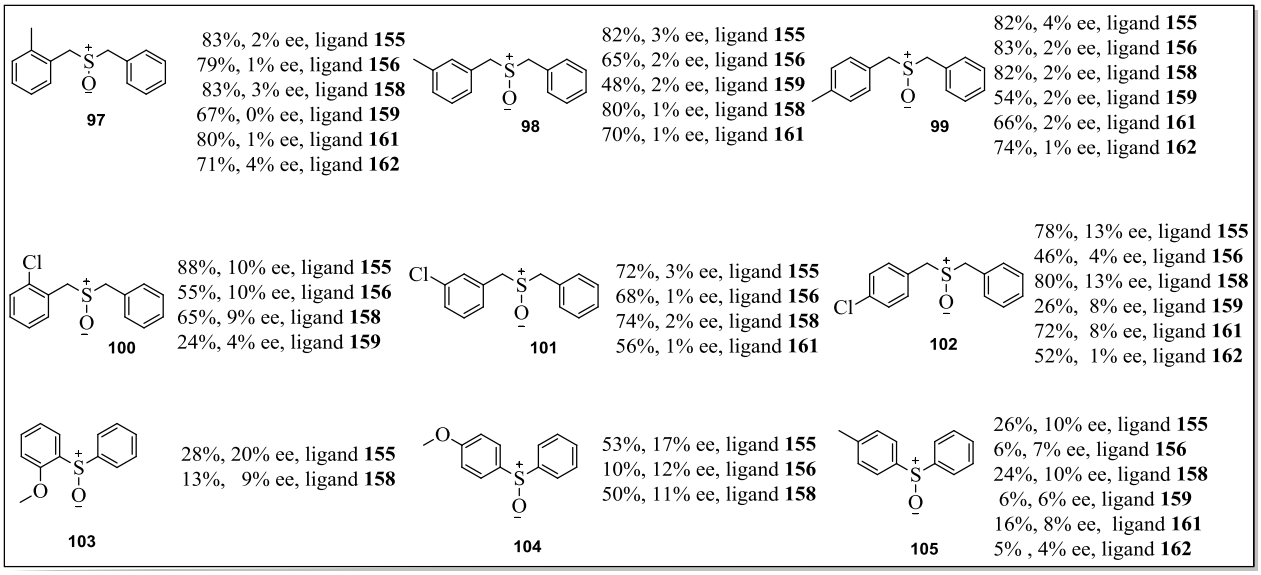
Entry	Sulfide	R	R′	Ligand	Sulfide : Sulfoxide : Sulfone[a]	Yield %[b]	%ee[c]	Sulfoxide
1	**[39]**	2-Methylbenzyl	Bn	**[155]**	2 : 91 : 7	83	2	**[97]**
2	**[39]**	2-Methylbenzyl	Bn	**[158]**	3 : 92 : 5	83	3	**[97]**
3	**[39]**	2-Methylbenzyl	Bn	**[156]**	12 : 87 : 1	79	1	**[97]**
4	**[39]**	2-Methylbenzyl	Bn	**[161]**	10 : 87 : 3	80	1	**[97]**
5	**[39]**	2-Methylbenzyl	Bn	**[162]**	19 : 79 : 2	71	4	**[97]**
6	**[39]**	2-Methylbenzyl	Bn	**[159]**	24 : 73 : 3	67	0	**[97]**
7	**[40]**	3-Methylbenzyl	Bn	**[155]**	1 : 89 : 10	82	3	**[98]**
8	**[40]**	3-Methylbenzyl	Bn	**[158]**	1 : 88 : 11	80	1	**[98]**
9	**[40]**	3-Methylbenzyl	Bn	**[156]**	23 : 75 : 2	65	2	**[98]**
10	**[40]**	3-Methylbenzyl	Bn	**[161]**	9 : 80 : 11	70	1	**[98]**
11	**[40]**	3-Methylbenzyl	Bn	**[159]**	44 : 55 : 1	48	2	**[98]**
12	**[41]**	4-Methylbenzyl	Bn	**[155]**	2 : 89 : 9	82	4	**[99]**
13	**[41]**	4-Methylbenzyl	Bn	**[158]**	3 : 89 : 8	82	2	**[99]**
14	**[41]**	4-Methylbenzyl	Bn	**[156]**	5 : 90 : 5	83	2	**[99]**
15	**[41]**	4-Methylbenzyl	Bn	**[161]**	26 : 72 : 2	66	2	**[99]**
16	**[41]**	4-Methylbenzyl	Bn	**[162]**	10 : 78 : 12	74	1	**[99]**
17	**[41]**	4-Methylbenzyl	Bn	**[159]**	35 : 62 : 3	54	2	**[99]**
18	**[42]**	2-Chlorobenzyl	Bn	**[155]**	3 : 92 : 5	88	10	**[100]**
19	**[42]**	2-Chlorobenzyl	Bn	**[158]**	15 : 81 : 4	65	9	**[100]**
20	**[42]**	2-Chlorobenzyl	Bn	**[156]**	18 : 77 : 5	55	10	**[100]**
21	**[42]**	2-Chlorobenzyl	Bn	**[159]**	64 : 36 : 0	24	4	**[100]**
22	**[43]**	3-Chlorobenzyl	Bn	**[155]**	12 : 80 : 8	72	3	**[101]**
23	**[43]**	3-Chlorobenzyl	Bn	**[158]**	8 : 81 : 11	74	2	**[101]**

24	**[43]**	3-Chlorobenzyl	Bn	**[156]**	20 : 74 : 6	68	1	**[101]**
25	**[43]**	3-Chlorobenzyl	Bn	**[161]**	31 : 65 : 4	56	1	**[101]**
26	**[44]**	4-Chlorobenzyl	Bn	**[155]**	12 : 86 : 2	78	13	**[102]**
27	**[44]**	4-Chlorobenzyl	Bn	**[158]**	11 : 87 : 2	80	13	**[102]**
28	**[44]**	4-Chlorobenzyl	Bn	**[156]**	45 : 54 : 1	46	4	**[102]**
29	**[44]**	4-Chlorobenzyl	Bn	**[161]**	11 : 83 : 6	72	8	**[102]**
30	**[44]**	4-Chlorobenzyl	Bn	**[162]**	40 : 58:2	52	1	**[102]**
31	**[44]**	4-Chlorobenzyl	Bn	**[159]**	67 : 32 : 1	26	8	**[102]**
32	**[47]**	2-Methoxyphenyl	Ph	**[155]**	70 : 30 : 0	28	20	**[103]**
33	**[47]**	2-Methoxyphenyl	Ph	**[158]**	65 : 35 : 0	13	9	**[103]**
34	**[48]**	4-Methoxyphenyl	Ph	**[155]**	41 : 59 : 0	53	17	**[104]**
35	**[48]**	4-Methoxyphenyl	Ph	**[158]**	46 : 54 : 0	50	11	**[104]**
36	**[48]**	4-Methoxyphenyl	Ph	**[156]**	86 : 14 : 0	10	12	**[104]**
37	**[49]**	4-Methylphenyl	Ph	**[155]**	68 : 32 : 0	26	10	**[105]**
38	**[49]**	4-Methylphenyl	Ph	**[158]**	68 : 32 : 0	24	10	**[105]**
39	**[49]**	4-Methylphenyl	Ph	**[156]**	91 : 9 : 0	6	7	**[105]**
40	**[49]**	4-Methylphenyl	Ph	**[161]**	79 : 21 : 0	16	8	**[105]**
41	**[49]**	4-Methylphenyl	Ph	**[162]**	93 : 7 : 0	5	4	**[105]**
42	**[49]**	4-Methylphenyl	Ph	**[159]**	93 : 10 : 0	6	6	**[105]**

a) Ratio of Sulfide : Sulfoxide : Sulfone determined by ^{1}H NMR analysis of the crude product.

b) Yield of Sulfoxide after purification by column chromatography.

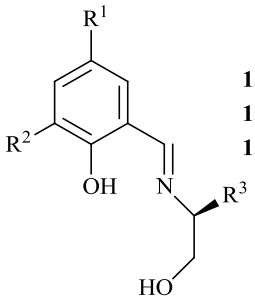
c) Enantioselectivities determined by HPLC analysis on chiral column (Daicel Chiracel OD-H for **[97]**, **[99]**, **[102]** Chiracel OJ-H for **[100]**, **[114]**; Chiracel AS-H for **[98]**, **[105]**; Phenomenex Lux Cellulose-4 for **[101]**, **[104]**; Absolute configuration of sulfoxides **[97]** to **[105]** were not determined.



Scheme 2.11

2.20 Investigation of Pre-Formed Catalyst and Mechanism of Oxidation

For the corresponding vanadium Schiff base catalysed oxidations, it was possible to pre-form and isolate the catalyst and subsequently use this catalyst in the oxidation.[26,137] The pre-formed catalyst was prepared by refluxing the metal salt with the Schiff base ligand in methanol, the catalyst complex was isolated by filtration of the reaction mixture. Kelly attempted to pre-form the copper catalyst complex using this method but was unsuccessful.[26] Further attempts to isolate the copper-ligand complex as a crystalline solid were made during this project, but these also proved unsuccessful. Ligands **[155]**, **[156]** and **[158]** were each, in turn, refluxed in methanol with copper acetylacetonate [2 mmol ligand and 1 mmol $Cu(acac)_2$]; however in each case, no crystalline copper-ligand complex was isolated. It was apparent that the resulting blue-yellow precipitate, isolated by filtration after the solution was cooled, was a mixture composed mainly of Schiff base ligand although some $Cu(acac)_2$ was present. On addition of CH_2Cl_2 (10 mL) and water (10 mL) the ligand went into the organic layer while the remaining $Cu(acac)_2$ went into the aqueous layer. ^{1}H NMR spectra of the recovered ligands were identical to previously obtained data for the pure ligands. The fact that the copper catalyst complex cannot be easily isolated as a solid suggests that the interaction between the copper and the Schiff base ligand is weak and hence the catalyst used in this study may be unstable.



155 R^1 = Cl, R^2 = Cl, R^3 = *t*-Bu
156 R^1 = Br , R^2 = Br, R^3 = *t*-Bu
158 R^1 = F , R^2 = Cl, R^3 = *t*-Bu

It is possible that the copper complex shown in Figure 2.29 is the catalyst precursor, as Ellman isolated a similar vanadium complex while investigating vanadium-catalysed asymmetric sulfoxidation.[138] However, there are no structural reports of copper Schiff base complexes similar to that shown in Figure 2.29.

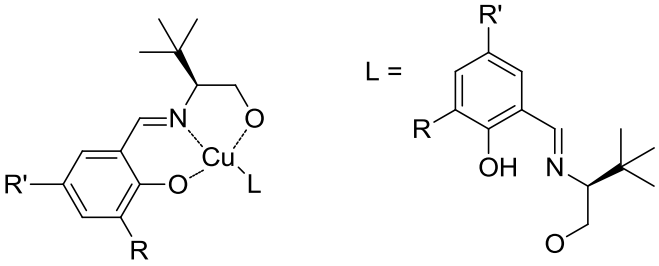
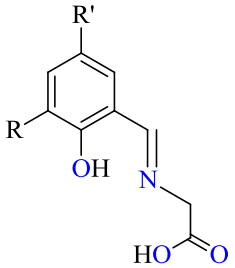
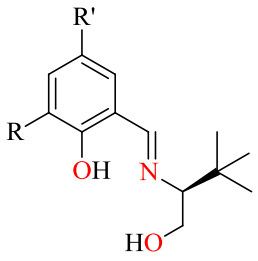


Figure 2.29

The catalytically active complex may also be a dicopper species. Zhu *et al.* reported a dicopper Schiff base ligand complex, $[(CuL)_2{}^1/_3CH_3OH]_n$ derived from an amino acid and a salicylaldehyde derivative.[139] The ligands employed by Zhu possess 4 atoms than can co-ordinate to copper in contrast to the ligands prepared in this study which only possess three such atoms.



Ligands used by Zhu



Ligands used during this study

It is unclear what copper species are formed during the oxidation. Bryliakov *et al.* reported the formation of vanadium species of a higher oxidation number in the analogous vanadium (IV) Schiff base catalysed oxidation. Cross *et al.* has investigated copper(II) and copper(III)

Schiff base complexes.[20] It is possible that the copper(II) Schiff base complex is converted to a peroxo-copper(III) complex, by the oxidant, which is then responsible for the oxidation of the sulfide. The copper(III) complex transfers an oxygen to the sulfide and is reduced back to the copper(II) Schiff base complex which can begin the catalytic cycle again (Figure 2.30).

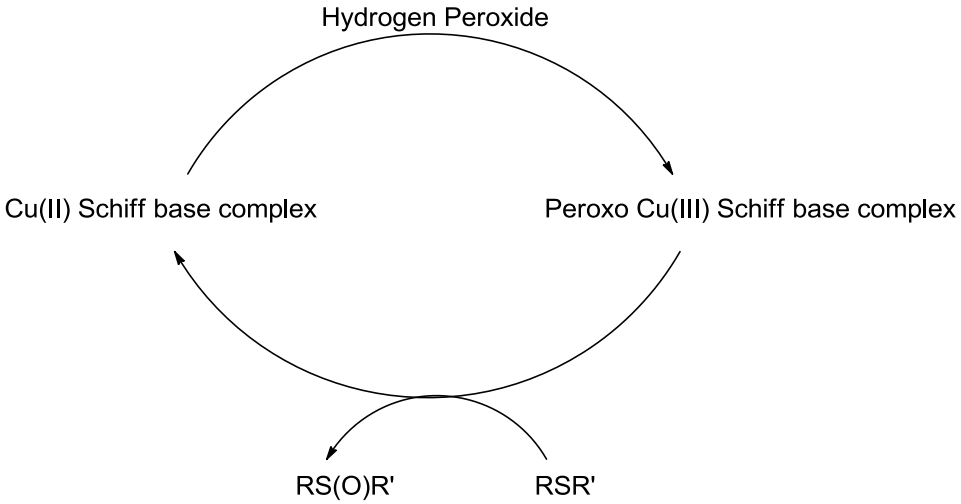
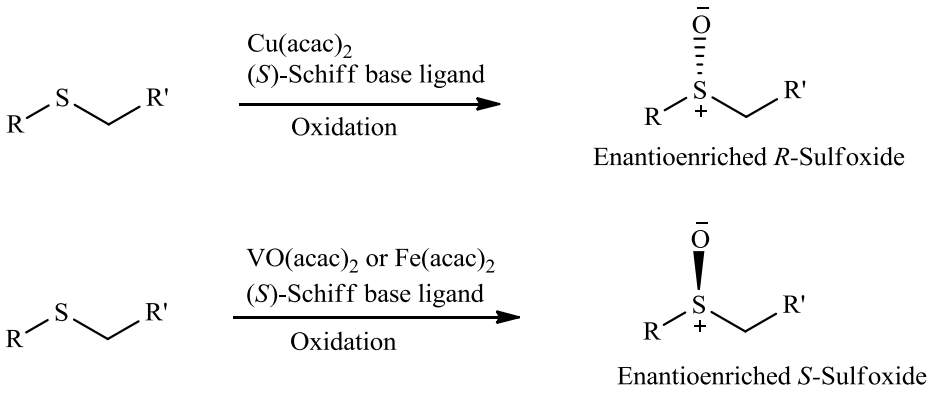


Figure 2.30

The configuration of the sulfoxide product in the copper-mediated sulfoxidation is opposite to that which is observed employing the same ligand with the analogous vanadium or iron-mediated oxidations, *i.e.* use of (*S*)-Schiff base ligand in the vanadium or iron-catalysed systems affords (*S*)-sulfoxides whereas the (*S*)-ligand produces (*R*)-sulfoxides for the copper system (Scheme 2.12).



Scheme 2.12

This implies that the key structural features of the oxidising catalyst formed with copper are different to that formed with vanadium or iron. Zeng *et al.* proposed a mechanism of oxygen

transfer and a template that explains the stereo-outcome (oirigin of stereoselectivity) of the analogous vanadium system.[140] In this proposed template the substituents of the Schiff base ligand align the sulfide with the oxidising complex so that one sulfoxide enantiomer is preferentially formed. However given that the resulting configuration of the sulfoxidation using the copper catalyst is opposite to that obtained with the vanadium system, the structure of the copper complex must differ significantly from the vanadium complex shown in Figure 2.31.

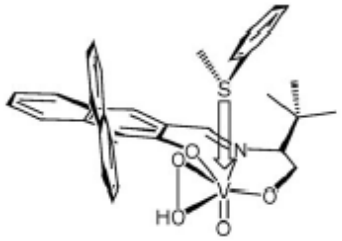
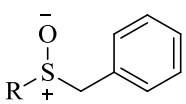


Figure 2.31 (reproduced from reference[140]).

Concluding Remarks on the Influence of Nature of Sulfide and Sulfide Substituents on Enantioselectivity, and its Mechanistic Significance

The results of these studies on the influence of steric and electronic effects of the sulfide substituents lead to a number of conclusions.

(1) At least one aryl moiety is required on the sulfide to achieve good enantiopurity in the copper-catalysed oxidation, with the highest enantiopurity achieved when the aryl moiety is a 2-naphthyl substituent (R, Figure 2.32).



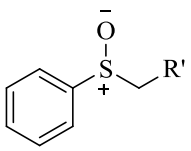
83 R = Me	4% ee[a]
63 R = *i*-Pr	27% ee[a]
64 R = *i*-Bu	11% ee[a]
65 R = *t*-Bu	37% ee[a]
70 R = Cyclohexyl	27% ee[a]
50 R = Ph	79% ee[a]
67 R = 1-Naphthyl	75% ee[b]
66 R = 2-Naphthyl	97% ee[b]

Solvent = Hexane-MeOH (9:1)[a] or Toluene-MeOH (9:1)[b] (See Table 2.16)

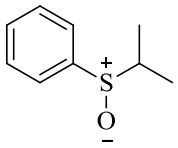
Figure 2.32

(2) The second substituent on the sulfide does not need to be an aryl or a benzyl group. However, it is clear that the steric properties of this group influence very strongly the

outcome of the oxidation in terms of enantioselectivity (R', Figure 2.33). It is evident that good enantioselectivity is achieved when the sulfide substituent is β-branched *i.e.* R' = *i*-Pr or larger.



57	R' = H	22% ee
58	R' = Me	40% ee
60	R' = *i*-Pr	61% ee
61	R' = *t*-Bu	71% ee
62	R' = 2-Naphthyl	93% ee
50	R' = Ph	58% ee
56	R' = Cyclohexyl	57% ee
80	R' = -C°CH	5% ee



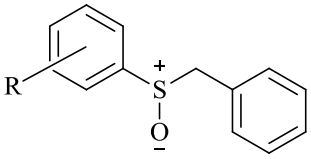
59, 50% ee

Solvent = Toluene (See Table 2.14)

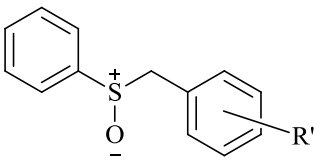
Figure 2.33

(3) *Electronic/steric modification of aryl and benzyl substituents*

The presence of a chloro or methyl substituent on the aryl and benzyl moieties result in some interesting trends. The presence of a chloro substituent (electron withdrawing group) on the aryl substituent results in a significant reduction in both the yield and enantioselectivity compared to the oxidation of benzyl phenyl sulfide under identical conditions (sulfoxides **[87]-[89]**, Figure 2.34).



87	R = 2-Cl	26%, 48% ee
88	R = 3-Cl	33%, 59% ee
89	R = 4-Cl	67%, 52% ee
50	R = H	90%, 79% ee



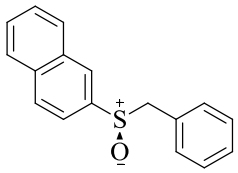
84	R' = 2-Cl	72%, 44% ee
85	R' = 3-Cl	82%, 42% ee
86	R' = 4-Cl	85%, 49% ee
50	R' = H	90%, 79% ee

See Table 2.17

Figure 2.34

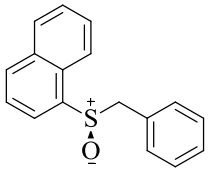
The presence of a chloro substituent on the phenyl ring of the benzyl moiety does not result in a significant reduction in yield, in line with our earlier results which demonstrated that the electronic nature of the benzyl moiety did not significantly affect the efficiency of the oxidation (sulfoxides **[84]-[86]**, Figure 2.34). However, a reduction in enantioselectivity is observed in the synthesis of sulfoxides **[84]-[86]** relative to benzyl phenyl sulfoxide (Figure

2.34). Interestingly, the presence of a chloro substituent on the phenyl ring of the benzyl substituent in sulfides **[31]** and **[32]** also results in a reduction in enantioselectivity in the corresponding sulfoxides **[68]** and **[69]** compared to their unsubstitututed counterparts, although the reduction in enantioselectivity is not as significant in this case (Figure 2.35). A large increase in yield was observed in the synthesis of sulfoxide **[68]** relative to its unsubstituted counterpart **[66]**. However, the opposite trend was observed with sulfoxides **[67]** and **[69]**, with sulfoxide **[69]** afforded in lower yield than its unsubstituted counterpart **[67]**.



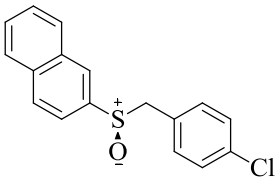
66

32%, 97% ee, ligand **155**[b]
38%, 95% ee, ligand **158**[b]



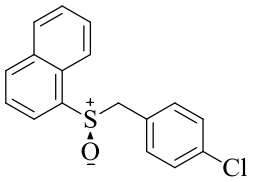
67

46%, 75% ee, ligand **155**[b]
37%, 77% ee, ligand **158**[b]



68

67%, 90% ee, ligand **155**[b]



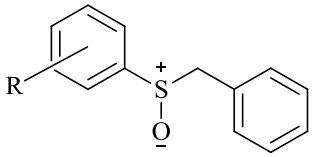
69

28%, 71% ee, ligand **155**[b]

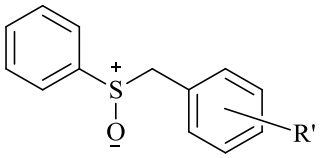
Figure 2.35

The oxidation of aryl benzyl sulfides containing a methyl substituent (electron donating group) on the aryl moiety proceeded with comparable yields and enantioselectivities to the oxidation of benzyl phenyl sulfide (Figure 2.36). The reduction in efficiency observed in the oxidation of sulfides **[14]-[16]**, affording sulfoxides **[87]-[89]**, in which the aryl moiety contains a chloro substituent, is not apparent here, suggesting that while the presence of an electron withdrawing group such as a chloro substituent may impact unfavourably on the asymmetric oxidation, the presence of a methyl substituent on the aryl moiety has no such effect, although a slight reduction in enantioselectivity is observed.

The presence of a methyl substituent on the phenyl ring of the benzyl substituent affords sulfoxides with similar yields to benzyl phenyl sulfoxide, but a significant reduction in enantioselectivity is observed, in line with our results above which demonstrate that the presence of a substituent on the phenyl ring of the benzyl moiety impacts deleteriously on the enantioselectivity of the oxidation.



75 R = 2-Me 91%, 64% ee
76 R = 3-Me 84%, 65% ee
51 R = 4-Me 91%, 81% ee
50 R = H 90%, 79% ee



77 R' = 2-Me 80%, 48% ee
78 R' = 3-Me 81%, 52% ee
79 R' = 4-Me 89%, 57% ee
50 R' = H 90%, 79% ee

See Table 2.18

Figure 2.36

The influence of substituents on the aryl and benzyl moieties is quite different. In the case of the aryl moiety, a clear electronic effect is evident with a decrease in both efficiency and enantioselectivity on introduction of an electron withdrawing chloro substituent (sulfoxides **[87]**-**[89]**, Figure 2.34), while the inductively electron donating methyl substituent has much less impact, leading in the case of sulfoxide **[51]** to a very slight increase in enantioselectivity (Figure 2.36). In the case of the benzyl substituent only a steric effect is evident with a general decrease in enantioselectivity on introduction of either a chloro or methyl substituent, with no visible impact on reaction efficiency.

These results can perhaps be rationalised on the basis of decreased efficiency of co-ordination of the sulfide to the copper complex in the presence of the electronegative chloro substituent in sulfoxides **[87]**-**[89]** compared to sulfoxide **[50]**.

The oxidation of the substituted diphenyl sulfides **[47]**-**[49]** afforded the corresponding sulfoxides **[103]**-**[105]** in poor yields and enantioselectivities, in contrast to a study by Islam *et al.* who obtained both aryl benzyl and diaryl sulfoxides in good yields in a copper-catalysed racemic oxidation procedure, indicating a different catalytically active complex in this case.[141] While the poor enantioselectivities achieved are likely due to poor differentiation between the enantiotopic faces of the sulfide, the poor yields are perhaps due to the poor co-ordination of these diaryl sulfides to the copper complex. The oxidation of the substituted dibenzyl sulfides **[39]**-**[44]** afforded the corresponding sulfoxides **[97]**-**[102]** in good yields but poor enantioselectivities, again indicating poor differentiation between the enantiotopic faces of these sulfides. Similarly, the attempted oxidation of the β-chloroacrylamides was unsuccessful, perhaps due to poor co-ordination of these sulfides to the copper complex (see Section 2.22). These results are summarised in Figure 2.37

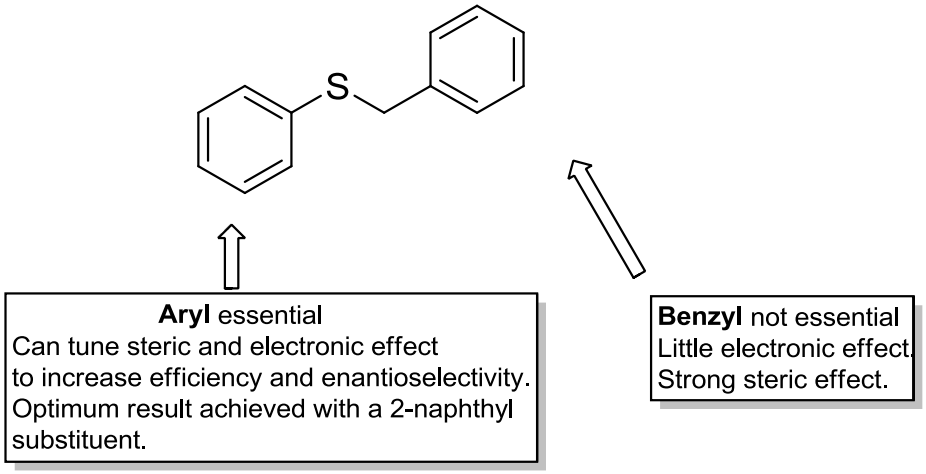
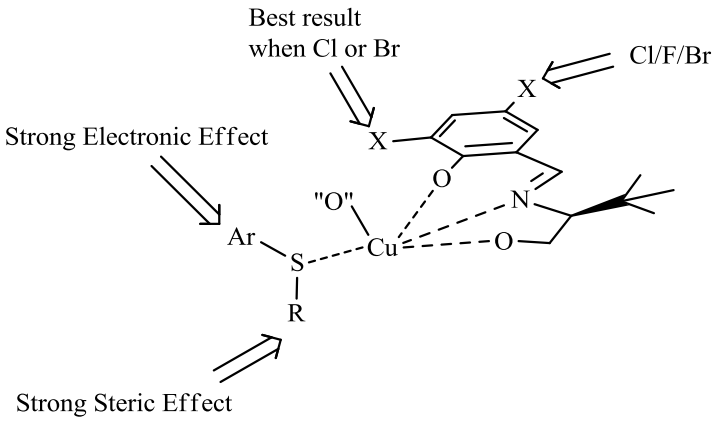


Figure 2.37

In terms of developing a mechanistic understanding of the asymmetric sulfur oxidation employing the copper Schiff base complex, the trends seen in this study are very helpful in providing some insight in this regard. A review of the literature reveals very limited knowledge of the mechanistic nature of copper mediated sulfur oxidation and the intermediates involved.[16,17,132,141,142] In earlier work, Kelly achieved optimum results using 2 equivalents of the ligand to the copper source in CCl_4;[26] this approach was used throughout this current study and critically has not been verified in the optimised hexane/methanol mixture used in this work. Accordingly it is reasonable to assume a 2:1 Schiff base : copper complex in solution, although the nature of the active enantioselective catalyst cannot be inferred on the basis of this experimental observation alone. Furthermore it is evident that a diverse range of copper complexes can be envisaged as the catalytically active species, including mononuclear and dinuclear copper complexes, with peroxo, oxo or superoxo species.[143,144]

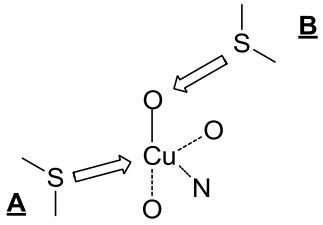
Accordingly at this stage it is difficult to definitively propose a mechanistic model but the results to date indicate quite clearly both steric and electronic factors are critical in determining the enanitoselectivity in the sufur oxidation process. It is possible to envisage co-ordination of the sulfide to a copper complex of the nature illustrated in Fig 2.38 whereby the efficiency of the complexation is directly influenced by the electronic properties of the sulfide with optimum results with mono aryl sulfides, but noticeably decreased efficiency with diaryl sulfides in contrast to Islam's study.[141] The enantiofacial control in transfer of the oxygen to the sulfide is strongly influenced in addition by steric factors, especially on the second sufur substituent.



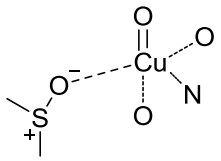
"O" = peroxo, oxo or superoxo potentially including bridging oxo in dinuclear species

Figure 2.38

It is believed that the sulfide binds directly to the copper as shown in Figure 2.39 (**A** rather than **B**), because the electronic properties of the sulfide are crucial to the overall efficiency of the oxidation. Factors that reduce the electron density at sulfur (chloro substituent on the phenyl ring) are expected to reduce the efficiency of co-ordination to the copper complex, and hence a reduction in yield is observed. There is direct evidence for sulfoxide inhibition of the oxidation. Kelly demonstrated that when carrying out the oxidation of benzyl phenyl sulfide in the presence of increasing amounts of DMSO, a corresponding reduction in yield was observed, indicating that the sulfoxide was perhaps competing with the sulfide to bind to the copper complex.[26] The enhancements in efficiency obtained when the oxidation is carried out in the presence of NMO or methanol further demonstrate that the sulfoxide binds to the copper complex and can be displaced by the co-ordination of NMO (partial) or methanol (more effective) to the copper complex, thereby overcoming sulfoxide inhibition (Figure 2.39). In the absence of methanol or another polar solvent the catalyst turnover is very limited with typically only 15–30% yield with 2 mol% of the copper complex. The dramatic decrease in enantioselectivity with use of pure methanol as the solvent medium indicates a dramatic alteration in the nature of the copper complex present in solution in this environment. Interestingly, the efficiency of the oxidation in methanol is much better than in the non-polar toluene, presumably reflecting decomplexation of the sulfoxide from the copper catalyst post oxidation.



A) Sulfide binds directly to copper complex
B) Sulfide binds at different site



Sulfoxide inhibition : addition of NMO or MeOH reduces the extent of sulfoxide inhibition by displacing the sulfoxide

Figure 2.39

Optimum results in terms of enantiocontrol are obtained with the sulfides when R is at least β-branched, indicating the interaction between this moiety and the chiral ligand is critical in delivering reasonable enantiofacial control. Optimum enantioselectivity has been obtained to date with the dichloro **[155]** and dibromo **[156]** or mixed halogenated **[158]** ligands. Furthermore, experiments with the 3' and 5' monochloro ligands **[161]** and **[162]** show very clearly that the 3' halo substituent has a greater impact on the enantiocontrol than the 5' halo substituent. Again this can be rationalised as a combination of electronic effects, varying the ligand-copper-sulfide complex, and steric effects, influencing interactions in the three dimensional transition state (TS) for oxygen transfer.

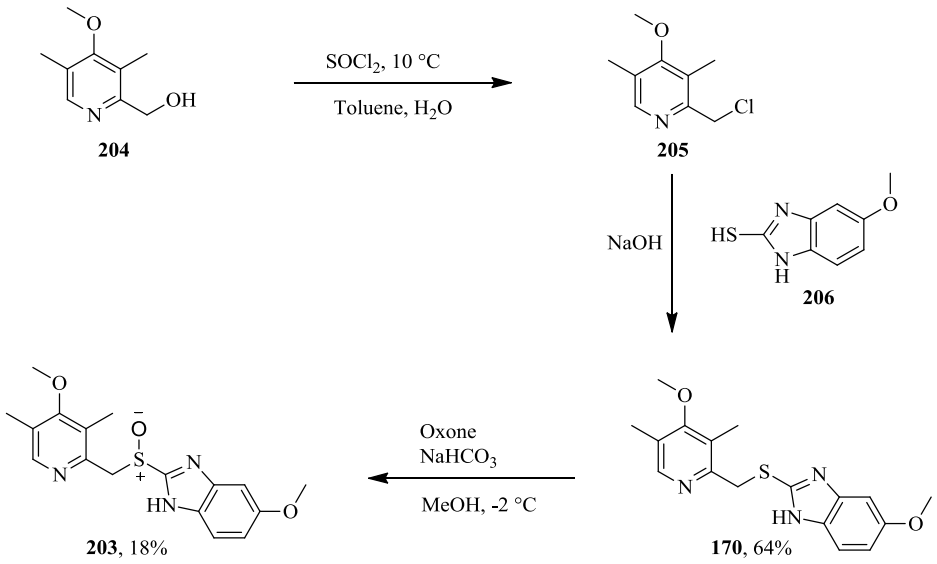
The decrease in both efficiency and enantioselectivity with the chloro substitued sulfoxides **[87]-[89]** can be rationalised using this model, as reflecting decreased efficiency of complexation of the less electron rich sulfide to the copper centre, and, accordingly resulting in decreased efficiency, but, in addition, decreased enantiocontrol due to increased bond lengths in the copper-sulfide-ligand complex resulting in decreased interaction in the critical TS for oxygen transfer.

Further experimental work will be required to explore the nature of the catalytic species in more detail. All attempts to isolate crystalline complexes with or without sulfide have proved unsuccessful to date.

2.21 Asymmetric Synthesis of Biologically Active Sulfoxides

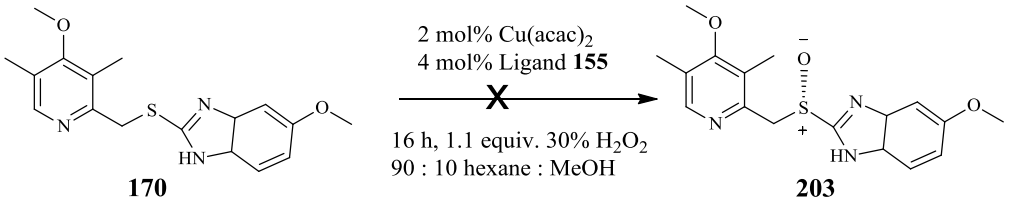
Enantiopure sulfoxides have found use in the pharmaceutical industry due to their important biological activity;[14] for example, esomeprazole, the *S*-enantiomer of omeprazole, has been one of the world's best-selling drugs since its launch in 2001. Omeprazole was prepared following a descibed procedure, by the racemic oxidation of pyrmetazole in a much lower

yield than that reported (18% compared to 99% conversion).[145] Pyrmetazole **[170]** can be obtained by the chlorination of pyrmethyl alcohol, followed by the reaction of the aryl chloride with an alkaline solution of the metmercazole indicated (Scheme 2.13).[145]



Scheme 2.13

The copper-catalysed oxidation procedure was then applied to the synthesis of esomeprazole (Scheme 2.14). However, TLC analysis and analysis of the crude ^{1}H NMR indicated that no oxidation had taken place. During the attempted oxidation a dark colour was observed, perhaps indicating complexation of sulfide **[170]** to the copper Schiff base complex. In another experiment, the amount of the copper-complex [sulfide **[170]**, 1 mmol, 329 mg, $Cu(acac)_2$, 1 mmol, 260 mg and ligand **[155]**, 2 mmol, 580 mg] was increased to stoichiometric amounts, but once again no oxidation was observed.

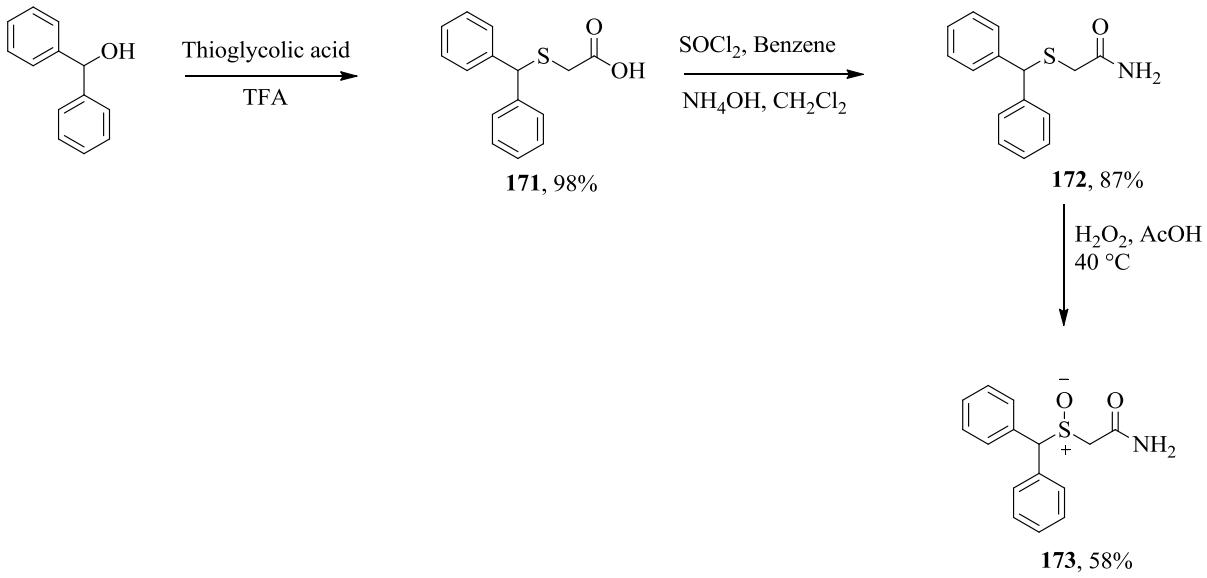


Scheme 2.14

Modafinil is a psychostimulant agent that has been used for the treatment of narcolepsy; it is manufactured by Cephalon and is marketed in the racemic form as Provigil.[15] Interestingly,

modafinil, unlike other CNS stimulants such as amphetamine and methylphenidate, has been reported to have little abuse liability.[146]

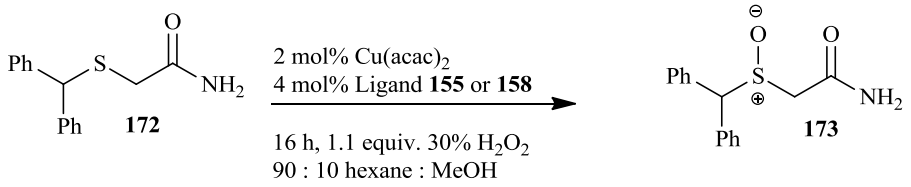
Racemic modafinil was prepared according to a procedure described by Prisinzano *et al.*[147] The synthesis of racemic modafinil begins with the reaction of benzhydrol and thioglycolic acid in trifluoroacetic acid to afford benzhydrylsulfanyl acetic acid **[171]**. The acid is then treated with thionyl chloride in benzene followed by the reaction of the corresponding acid chloride with concentrated ammonium hydroxide to give crude acetamide **[172]**, which is then recrystallised from isopropyl ether to give pure **[172]**. Oxidation of sulfide **[172]** using 30% H_2O_2 in acetic acid produced modafinil **[173]** as shown in Scheme 2.15.[147]



Scheme 2.15 Synthesis of racemic modafinil

Having synthesised modafinil in racemic form, we next attempted the asymmetric oxidation of sulfide **[172]** using copper Schiff base catalysis. Cephalon have patented the use of the Kagan system for the preparation of (*R*)-modafinil; this method produces (*R*)-modafinil in good yield (70%) and excellent enantioselectivity (99% ee).[148] Vanadium and iron Schiff base complexes have also been employed in the synthesis of (*R*)-modafinil but the yields (10 and 45% respectively) and enantioselectivities (15 and 12% ee respectively) were very poor.[149] In this work, benzhydrylsulfanyl acetamide **[172]** was oxidised using the copper Schiff base system and the results are shown in Table 2.21. Although the enantioselectivity of **[173]** was very small, this reaction represents the first time that copper Schiff base catalysis has been used in the asymmetric synthesis of modafinil.

Table 2.21 Asymmetric oxidation of benzhydrylsulfanyl acetamide **[172]**



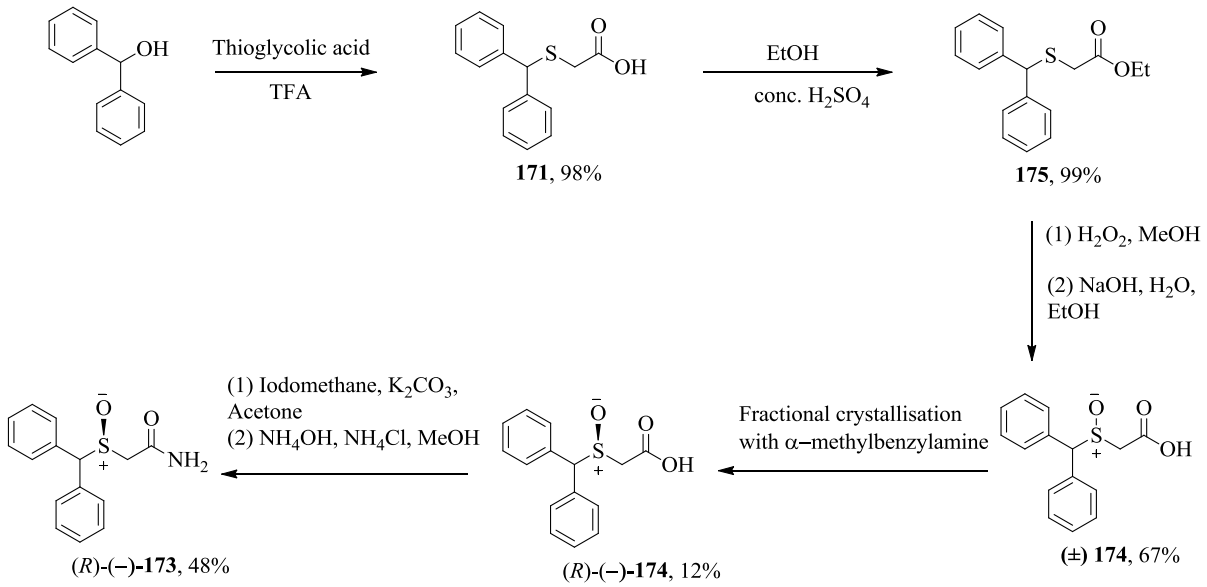
Ligand	[172] : [173][a]	% ee[b] [173] (*S*)[c]
[155]	29 : 71	5
[158]	55 : 45	5

a) Ratio of **[172] : [173]** determined by ^{1}H NMR analysis of the crude product. **[173]** was not isolated.

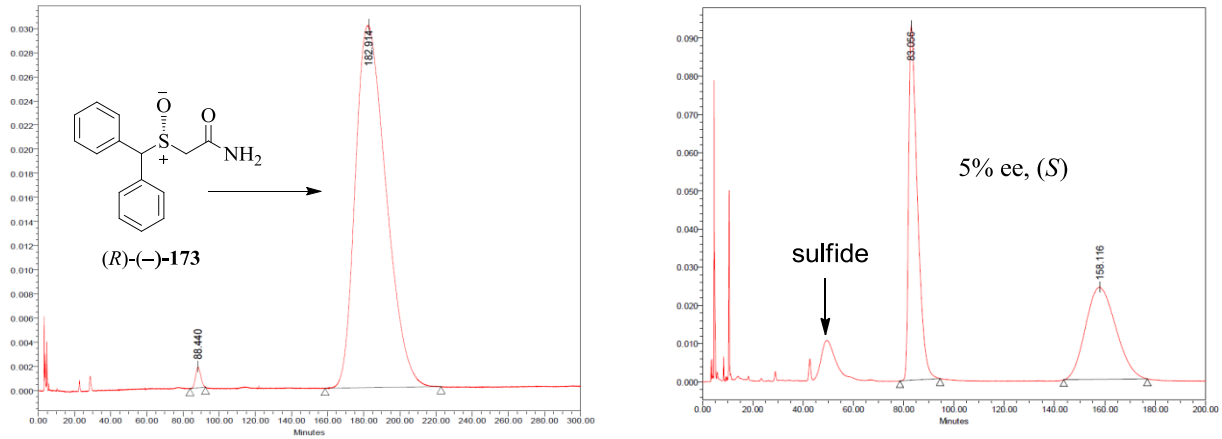
b) Based on HPLC of crude product from the oxidation.

c) Absolute configuration determined by comparison of HPLC retention times of sample with an enantiopure (*R*) sample of modafinil, prepared by a procedure described by Prisinzano *et al.*[147]

The next goal of this study focused on the preparation of (*R*)-(-)-**[173]** in order to establish which enantiomer was formed preferentially. It was decided that resolution *via* diastereomeric salt formation with α-methylbenzylamine and a carboxylic acid derived from racemic **[173]** would be the best route to prepare (*R*)-(-)-**[173]**. This procedure was described by Prisinzano *et al.*[147] who reported that the hydrolysis of amide **[173]**, under both basic and acidic conditions resulted in mainly decomposition. Additionally, attempts at direct oxidation of **[171]** to **[174]**, by Prisinzano, were unsuccessful. To overcome this problem, the carboxyl group was protected as an ester **[175]**. Prisinzano reported that the oxidation of ester **[175]** to the corresponding sulfoxide using 30% H_2O_2, followed by ester hydrolysis gave racemic modafinic acid **[174]** in good yield.[147] Racemic **[174]** was resolved using fractional crystallisation with α-methylbenzylamine. Compound (−)-**[174]** was then converted to its ester followed by ammonolysis to give **(*R*)**-(−)-**[173]**. This procedure was repeated as part of this study and the results, which are consistent with the results obtained by Prisinzano, are shown in Scheme 2.16.



Scheme 2.16



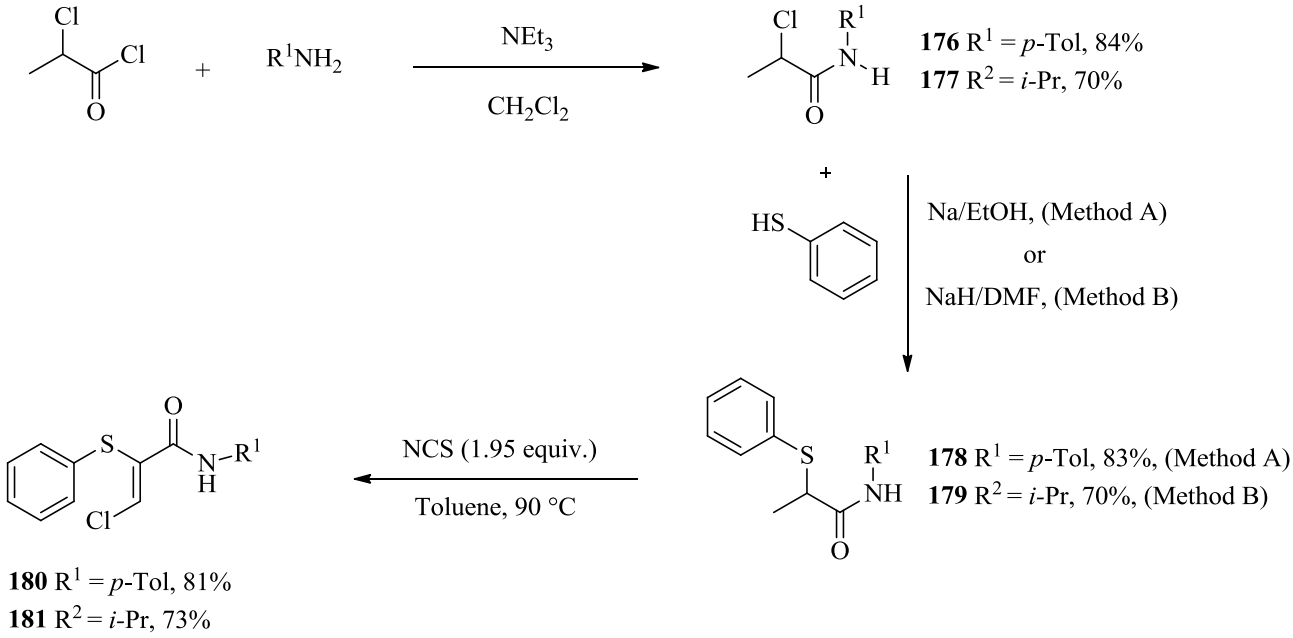
HPLC: t_R = (*S*) 88.4 min, t_R (*R*) = 182.9 min, 98% ee (*R*),
[OJ-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]

Figure 2.40 HPLC of (*R*)-(−)-**[173]** and enantioenriched (*S*)-(+)-**[173]**

2.22 Synthesis and Attempted Oxidation of β-Chloroacrylamides

Based on the results achieved in the enantioselective oxidation of simple sulfides, exploration of the extension to more complex systems was undertaken. The β-chloroacrylamides were synthesised following a procedure described by Lynch and Chopra.[150,151,152] The α-chloroamides **[176]** and **[177]** were prepared first by reacting the acid chloride with the appropriate amine in the presence of triethylamine, in comparable yields to those reported by Chopra (Scheme 2.17).[151] Both amides have previously been prepared in the group and their

spectral characteristics were identical to those described by Lynch.[150] Next, the α-thioamides **[178]** and **[179]** were prepared by the reaction of the thiophenolate anion, generated *in situ*, with the α-chloroamides, in similar yields to those reported by Chopra[151], and with identical spectral characteristics to those described by Lynch.[150] Finally, the β-chloroacrylamides **[180]** and **[181]** were prepared from the reaction of 1.95 equivalents of *N*-chlorosuccinimide (NCS) with the α-thioamides at 90 °C, with comparable yields to those reported by Chopra,[151] and with identical spectral characteristics to those described by Lynch[150] (Scheme 2.17). The α-chloroamides, α-thioamides and β-chloroacrylamides were stable at RT over an extended period of time.

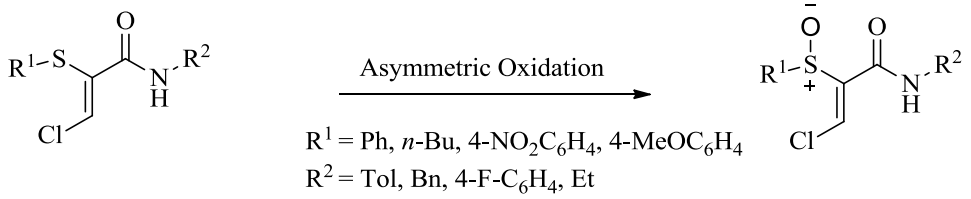


Note: yields after purification by column chromatography on silica gel.

Scheme 2.17

Attempted oxidation of the β-chloroacrylamides

Lynch and Chopra have previously examined the asymmetric sulfoxidation of the β-chloroacrylamides.[150,151] Lynch's work focused primarily on the Kagan oxidation; however Lynch also briefly explored the Modena and Page oxidations as well as an enzymatic oxidation using CPO.[150] The results of Lynch's study are summarised in Scheme 2.18.



Kagan Oxidation: Yields up to 71% and enantiopurities up to 52% ee

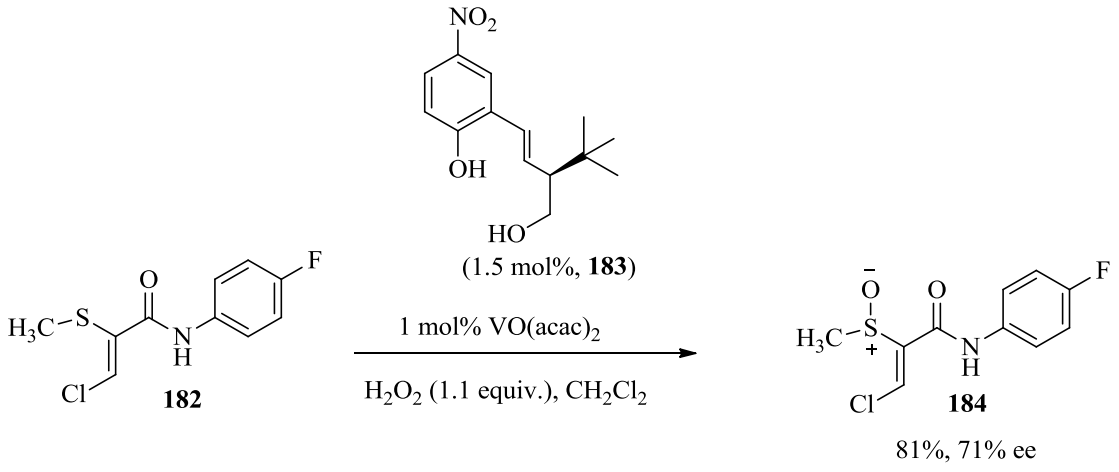
Modena Oxidation: No Conversion

Page Oxidation: Yields up to 21% and enantiopurities up to 29% ee

CPO Oxidation: No Conversion

Scheme 2.18

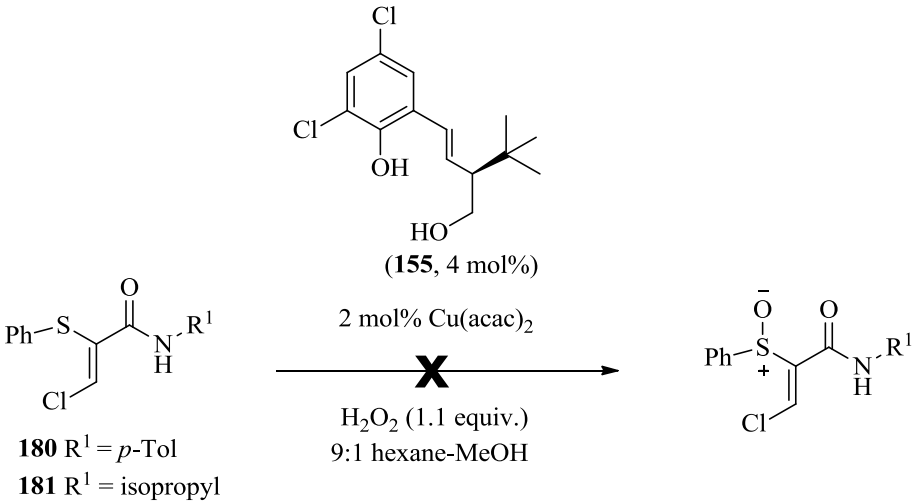
Chopra's work focused primarily on the Bolm oxidation method.[151] Reaction conditions such as temperature and nature of the Schiff base ligand were explored. The best results were obtained in the oxidation of the *S*-methyl β-chloroacrylamide **[182]**, using ligand **[183]**, with sulfoxide **[184]** afforded in good yield and enantioselectivity as shown in Scheme 2.19.



Scheme 2.19

To follow on from the early investigations by Lynch and Chopra, copper-catalysed oxidation of β-chloroacrylamides **[180]** and **[181]** was attempted (Scheme 2.20). These β-

chloroacrylamides were chosen because in our study of the oxidation of aryl benzyl sulfides, an aryl group directly attached to the sulfur was required to achieve high enantioselectivities.

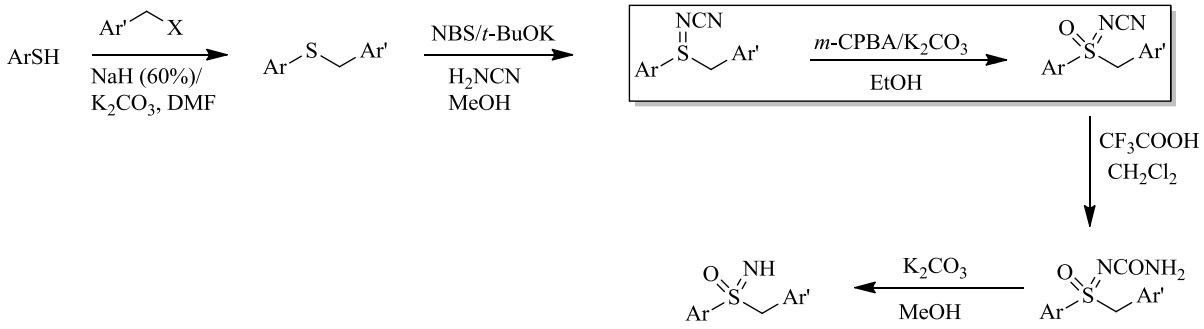


Scheme 2.20

However, TLC analysis of the reaction mixture and analysis of the ^{1}H NMR spectra of the crude products indicated that no oxidation had taken place, with good recovery of unreacted starting material (over 90% in both cases). This copper based oxidation system is particularly useful in the oxidation of aryl benzyl sulfides as previously discussed. However, sulfides **[180]** and **[181]** have significantly different electronic properties to aryl benzyl sulfides and it is possible that these sulfides, comparable to the diphenyl sulfides, co-ordinate very poorly to the copper complex, and, as a result no oxidation is observed.

2.23 Preparation of Aryl Benzyl Sulfoximines

Sulfoximines have attracted considerable interest in the past few decades due to their use as chiral auxiliaries,[153,154] backbones in pseudopeptides[155,156] and applications as chiral ligands in asymmetric synthesis.[157,158] In 2009, Barry *et al.* reported an efficient synthesis of a series of aryl benzyl NH-sulfoximines (Scheme 2.21).[27] The use of *N*-cyanosulfoximines as key intermediates overcomes the difficulties in the deprotections which had previously been encountered, leading to an effective synthetic route to these compounds.



Scheme 2.21

This study focused on the attempted kinetic resolution in the oxidation of a series of aryl benzyl sulfilimines using copper Schiff base catalysis. As a result, the final two steps in this scheme were not explored. A series of aryl benzyl sulfides was selected for this study as shown in Figure 2.41. Sulfides **[1]** and **[16]** were prepared *via* thiolate alkylation as discussed in Section 2.3, while sulfide **[163]** was obtained commercially and sulfide **[185]** was obtained from Nicola Barry, a former member of the research group.[159]

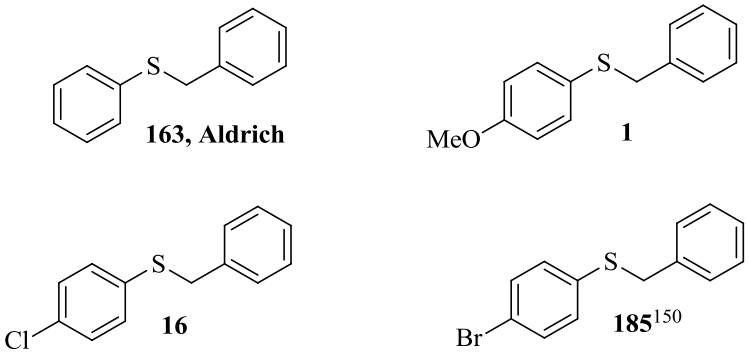
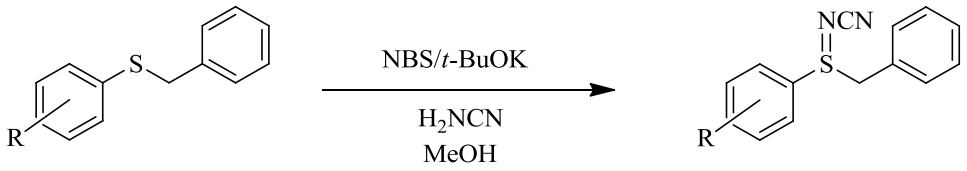


Figure 2.41

The treatment of the sulfides with NBS, cyanamine and potassium *tert*-butoxide in methanol led efficiently to the *N*-cyanosulfilimines (Table 2.25). An aqueous work up gave the crude sulfilimines which were then purified by column chromatography on silica gel to remove traces of residual sulfide. The *N*-cyanosulfilimines had previously been synthesised by Barry and spectral characteristics were in agreement in all cases.[27] The *N*-cyanosulfilimines are stable compounds, which are easily handled and stored without degradation.

Table 2.25 Preparation of aryl benzyl sulfilimines

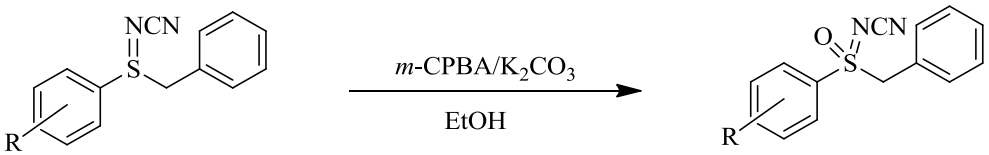


N-Cyanosulfilimines	R	Yield (%)[a]	Appearance
[186]	H	68	White solid
[187]	4-Br	69	White Solid
[188]	4-Cl	73	White Solid
[189]	4-MeO	71	White Solid

a) After purification by column chromatography.

The *m*-CPBA mediated oxidation of the *N*-cyanosulfilimines to the analogous racemic *N*-cyanosulfoximines was undertaken in the presence of potassium carbonate in ethanol according to a procedure described by Barry (Table 2.26).[27] The crude *N*-cyanosulfoximines were purified by column chromatography on silica gel to remove unreacted *N*-cyanosulfilimine. The racemic *N*-cyanosulfoximines had previously been synthesised by Barry and spectral characteristics were in agreement in all cases.[27] The *N*-cyanosulfoximines were stable over an extended period of time.

Table 2.26 Preparation of aryl benzyl sulfoximines

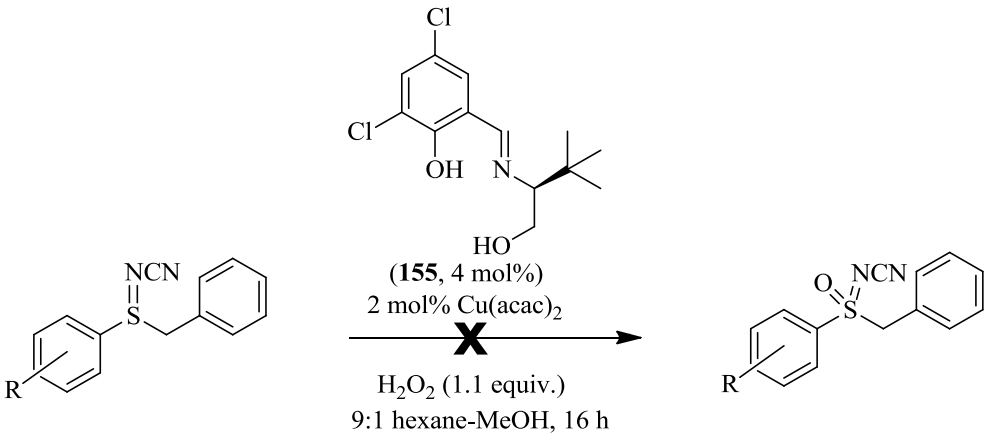


N-Cyanosulfoximines	R	Yield (%)[a]	Appearance
[190]	H	71	White solid
[191]	4-Br	74	White Solid
[192]	4-Cl	61	White Solid
[193]	4-MeO	62	White Solid

a) After purification by column chromatography.

Copper-catalysed kinetic resolution of the aryl benzyl *N*-cyano sulfilimines was then attempted. However, TLC and ^{1}H NMR analysis of the crude products indicated that no

oxygen transfer to sulfur had occurred (Figure 2.42). Thus, the copper system does not effect sulfilimine oxidation.



Scheme 2.22

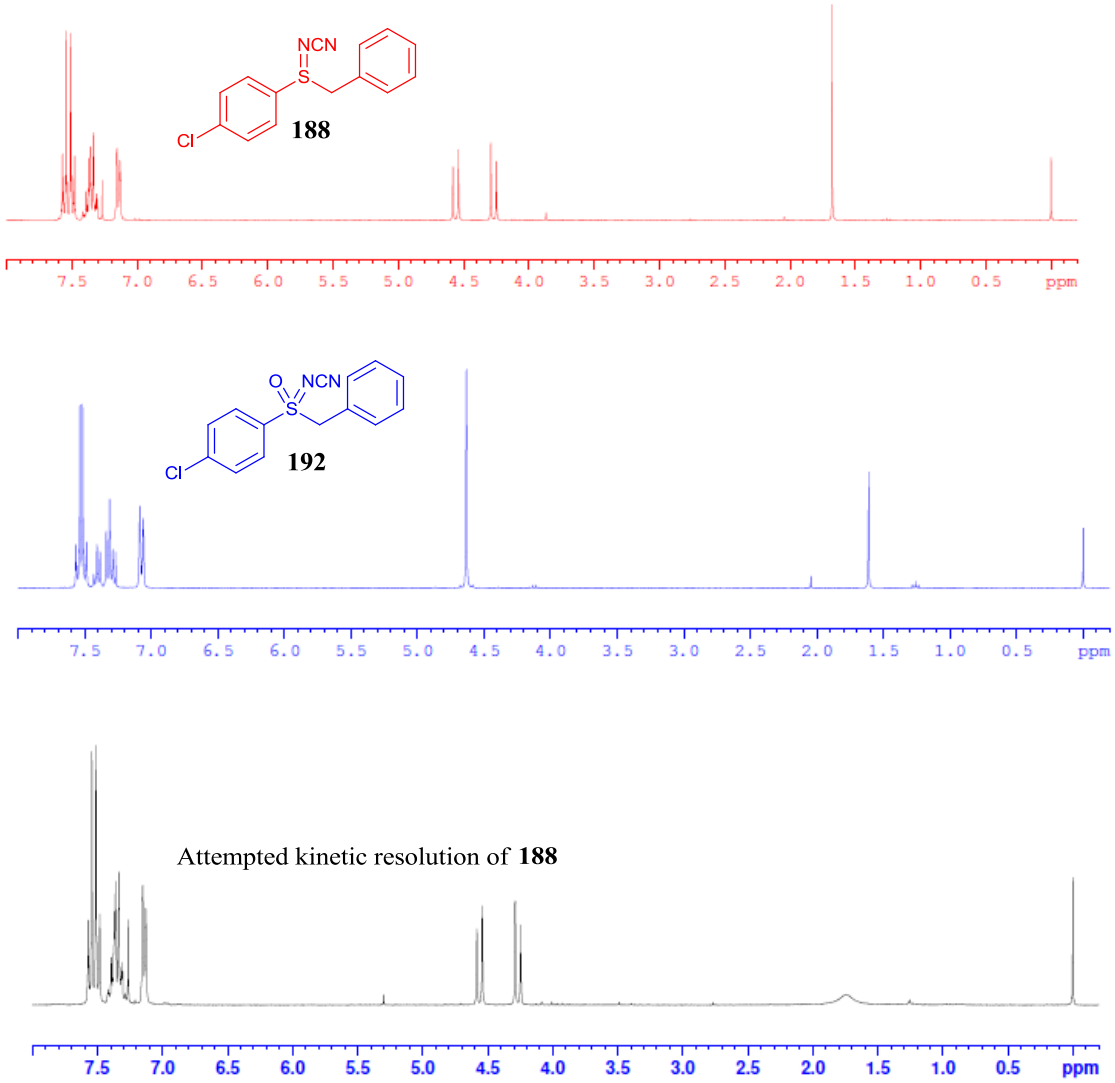


Figure 2.42 ^{1}H NMR spectra for sulfilimine, sulfoximine and attempted resolution of sulfilimine **[188]**

For sulfoximines **[190]** and **[191]** the S(O)CH_2 protons appear to be singlets, however on close inspection of the spectra, these peaks are actually 2H AB systems (Figure 2.43).

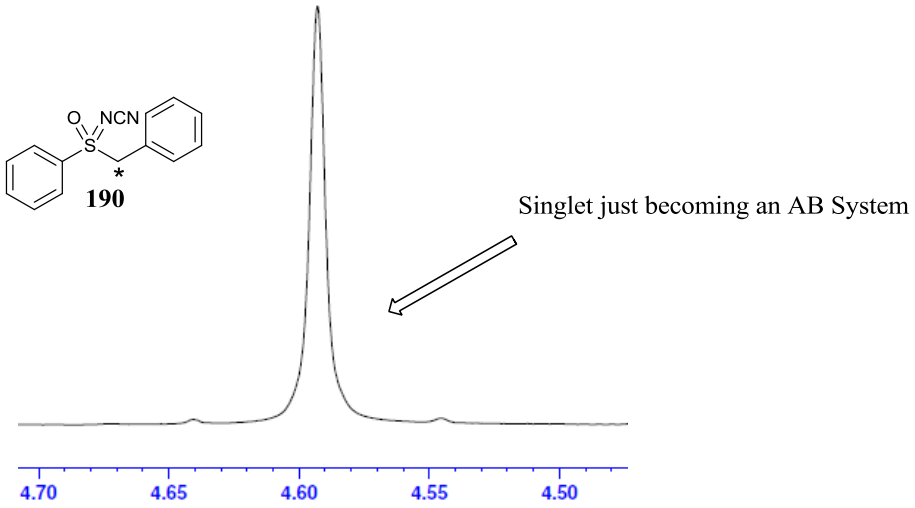
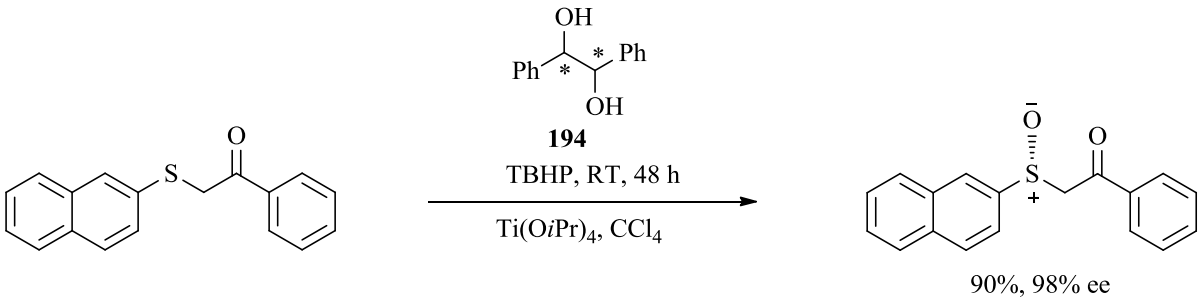


Figure 2.43 $SOCH_2$ signal in sulfoximine **[190]**

2.24 Asymmetric Synthesis of β-Keto Sulfoxides

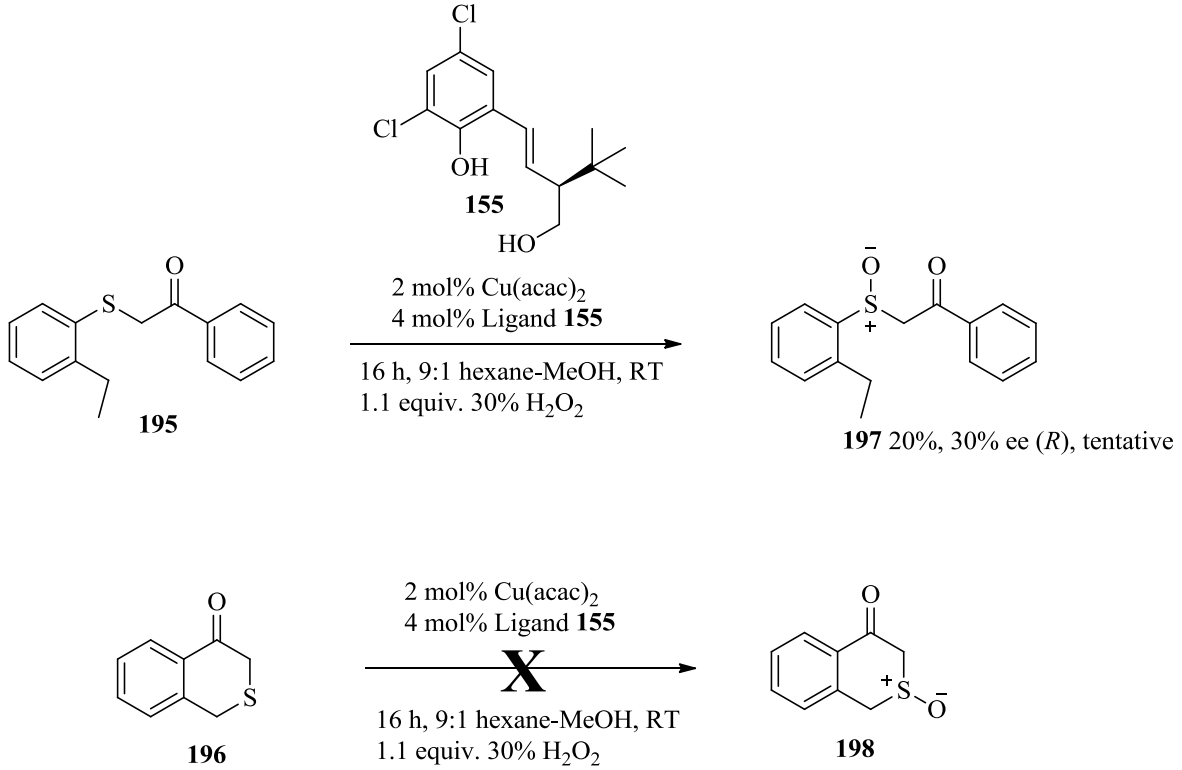
The copper-catalysed asymmetric oxidation of β-keto sulfides was next explored. β-Keto sulfides have been successfully oxidised by a titanium-catalysed procedure, employing hydrobenzoin **[194]** affording β-keto sulfoxides in modest to excellent yields (57-90%) and excellent enantiopurities (in most cases > 98% ee, Scheme 2.23).[160]



Scheme 2.23

Sulfides **[195]** and **[196]** were obtained from other workers in the research group to undertake this study.[161,162] Sulfide **[195]** was successfully oxidised using copper catalysis, affording sulfoxide **[197]** in modest yield and enantiopurity (Scheme 2.24). To our knowledge, this represents the first reported preparation of an enantioenenriched β-keto sulfoxide through copper-catalysed asymmetric sulfoxidation. The absolute configuration of **[197]** is the

proposed configuration based on the comparison of its specific rotation value {$[\alpha]_D^{20}$ = + 42.1° (c 1.0, $CHCl_3$)} to literature value of (+)-(*R*)-2-(phenyl-1'-sulfinyl)-acetophenone { $[\alpha]_D^{20}$ = + 161.7° ($CHCl_3$)}[163] and warrants confirmation. However, the attempted oxidation of sulfide **[196]** to produce sulfoxide **[198]** was unsuccessful. TLC of the crude mixture and analysis of the ^1H NMR of the crude product indicated that no oxidation had taken place with good recovery of unreacted starting material.



Scheme 2.24

2.25 Conclusions

Efficient enantioselective sulfide oxidation is effected using copper-Schiff base catalysis. A range of aryl benzyl and aryl alkyl sulfoxides can be prepared in excellent yields in most cases (up to 92%) and excellent enantioselectivities in certain cases (up to 97% ee). The procedure used is clean, inexpensive, and is not air-sensitive, utilising aqueous hydrogen peroxide as oxidant. A major advantage of this oxidising system is the use of copper as the transition metal which offers significant safety benefits over established methods. The Kagan system is limited by its sensitivity to atmospheric moisture and low turnover numbers, and it

utilises a complex and expensive catalytic system.[18] Although the Bolm system is robust and operationally straightforward, the use of vanadium is not advantageous since vanadium is known to exert toxic, mutagenic and genotoxic effects on a variety of biological systems.[19]

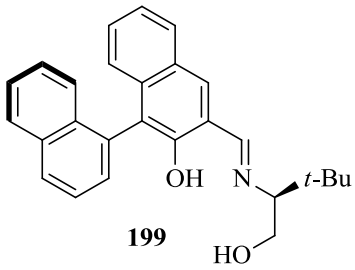
Another important feature of the copper system is the absence or very limited amount of over-oxidation to produce sulfones. The presence of sulfone in the crude product can make isolation of the pure sulfoxide tedious. Sulfone formation also impacts deteriously on the overall yield of the oxidation.

This system is particularly useful for the oxidation of aryl benzyl and aryl branched alkyl sulfides. The aryl ring directly attached to the sulfide is essential for high enantiocontrol, while the benzyl substituent can be replaced by substituents with similar steric demands, without a detrimental effect on enantiocontrol. Significantly, use of naphthyl sulfides results in excellent enantiocontrol with comparable enantioselectivities for the 1-naphthyl benzyl sulfide (75% ee) to phenyl benzyl sulfide (79% ee), but substantially enhanced asymmetric induction in the oxidation of the 2-naphthyl benzyl sulfide (97% ee), presumably *via* a combination of steric and electronic effects. Notably, the 97% ee obtained for the oxidation of 2-naphthyl benzyl sulfide is the highest enantioselectivity reported to date for a copper-mediated sulfur oxidation. Excellent enantioselectivity was also obtained in the oxidation of phenyl 2-naphthyl methyl sulfide (93% ee). In the oxidation of substituted aryl benzyl sulfides, the outcome is influenced, to a certain extent, by the presence of substituents on each of the two aryl rings, with both steric and electronic effects evident.

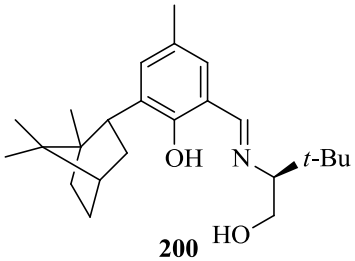
The generalisation of this procedure to β-keto sulfoxides was successful, albeit with modest levels of enantiopurities (30% ee), although the attempted copper-catalysed oxidation of sulfilimines and β-chloroacrylamides was unsuccessful. Modafinil was obtained in good conversion (71%) but very poor enantioselectivity (5% ee) using this system, while the attempted asymmetric oxidation of pyrmetazole was unsuccessful. Some insight into the mechanistic features of the copper-mediated sulfur oxidation has been developed based on this work, although further investigation is required to establish the precise nature of the catalytic species responsible for asymmetric sulfur oxidation.

2.26 Future Work

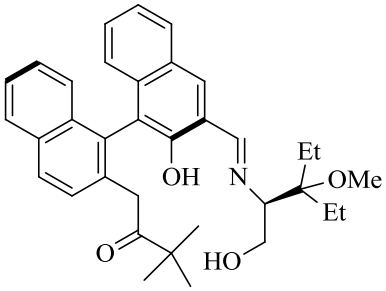
Future work to develop this oxidation method further should focus on identification of the catalyst precursor to assist in the understanding of the mechanism of enantioselective oxidation and the nature of the catalyst. A broader ligand study should be carried out, in particular the sterically hindered ligands used by Berkessel and Ahn **[199]** and **[200]**,[164,165] and ligands bearing two stereogenic centres, **[201]** and **[202]** developed by Li *et al.* should be investigated.[166]



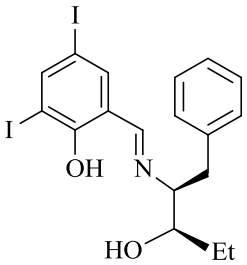
199



200

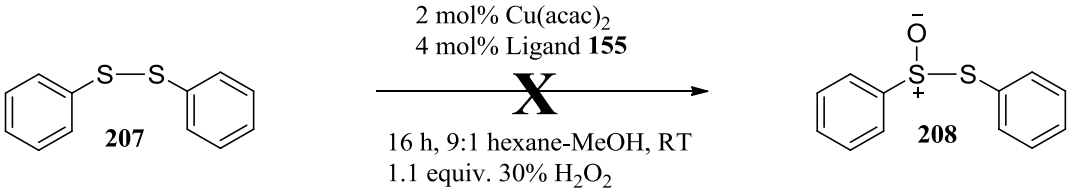


201



202

During the *viva* exam extension of the copper-catalysed oxidation to the Ellman system was discussed. While Ellman oxidised di-*tert*-butyl disulfide, preliminary investigation of diphenyl disulfide was undertaken as illustrated in Scheme 2.25. Following workup it was clear that no oxidation had taken place.



Scheme 2.25

Chapter 3

Experimental

3. Experimental Section

3.1 General Procedures

All solvents were distilled prior to use by the following methods: dichloromethane was distilled from phosphorus pentoxide, ethyl acetate was distilled from potassium carbonate or phosphorus pentoxide, hexane was distilled prior to use, ethanol and methanol were distilled from the corresponding magnesium alkoxide and stored over 3 Å molecular sieves. Organic phases were dried using anhydrous magnesium sulfate. Hydrogen peroxide was standardized by titration using potassium iodide, sodium thiosulfate and a starch indicator. The majority of reagents were supplied by Sigma-Aldrich. 1- and 2-naphthylthiol were obtained from TCI. All commercial reagents were used without further purification.

^{1}H (300 MHz), ^{1}H (400 MHz), ^{13}C (75.5 MHz) NMR and ^{13}C DEPT spectra were recorded on either a Bruker Avance 300 or 400 NMR spectrometer. All spectra were recorded at 20 °C in deuterated chloroform ($CDCl_3$) using tetramethylsilane (TMS) as an internal standard unless otherwise stated. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) relative to TMS and coupling constants are expressed in Hertz (Hz). Splitting patterns in ^{1}H spectra are designated as s (singlet), bs (broad singlet), d (doublet), bd (broad doublet), t (triplet), q (quartet), dd (doublet of doublets), AB (AB system), ABX (ABX system), (m) multiplet and bm (broad multiplet). DEPT spectra were recorded for all ^{13}C NMR spectra.

Infra red spectra were recorded as thin films on sodium chloride plates for oils or as potassium bromide (KBr) discs for solids, on a Perkin Elmer Paragon 1000 FT-IR spectrometer and Perkin Elmer Spectrum 100.

Melting points were measured on an Electrothermal 9100 capillary melting point apparatus and are uncorrected.

Flash column chromatography was carried out using Kieselgel 60, 0.040-0.063 mm; Thin layer chromatography (TLC) was carried out on precoated silica gel plates. Visualisation was achieved by UV light detection (254 nm).

Enantiopurities of the chiral compounds were determined by chiral HPLC performed on Chiralcel OD-H, AS-H and OJ-H columns, and Phenomenex Lux Cellulose 4 and Amylose 2 columns. Details of the column conditions and mobile phases employed are

included in appendix 1. Low and high temperature chiral HPLC analysis was obtained using an Igloo-Cil® column heater/cooler.

Single-crystal X-ray diffraction data were collected on a Bruker APEX II DUO with monochromated Mo Kα radiation (λ = 0.7107 Å) fitted with an Oxford Cryosystems Cobra low temperature device. All calculations and refinement were made using the APEX software.[i] All diagrams were prepared using Mercury software.

Optical rotations were recorded on a Perkin Elmer 341 polarimeter, at 20 °C in the solvents indicated. The sodium–D line (589 nm) was used in all cases. Samples were analysed in a 1 mL dual walled, thermostatted glass cell (PE part number: 631136) of path length 10 cm. Sample temperature control was maintained using a Julabo F25-MV immersion circulator. Results were processed on a Dell Optiplex GX260 PC using Bio Light Pol Winlab software (version number 1.00.01). The units of α are 10^{-1} deg cm^2g^{-1}. Specific rotations were employed to indicate the direction of enantioselection. Optically active samples are numbered as for the corresponding racemate with either (+)- or (−)- as prefix.

The Microanalysis Laboratory, National University of Ireland, Cork, performed elemental analysis using the Perkin-Elmer 240 and Exeter Analytical CE440 elemental analysers.

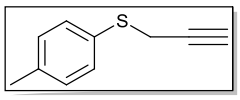
Mass spectra were recorded on a Waters/Micromass LCT Premier time of flight spectrometer (ESI) and a Waters/Micromass Quattron Micro triple quadrupole spectrometer (ESI).

CAUTION- Thiols and certain sulfides (**[27]**, **[28]**, **[33]** and **[34]**) used in this research are malodorous compounds. These compounds were dispensed in the fumehood and all glassware involved with the use of these compounds are soaked in an aqueous bleach bath prior to washing. The benzyl halides used are lachrymatory and therefore care is required in their use. They are weighed out in the fumehood and solutions containing these compounds are concentrated using a rotary evaporator in a fumehood.

3.2 Preparation of Sulfides

Method A

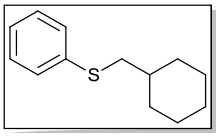
4-Methylphenyl prop-2'-ynyl sulfide [45][26,167]



NaH (716 mg of 67% dispersion in mineral oil, 20 mmol) was added to a two neck flask under nitrogen. After washing with hexane (3 × 5 mL), dry DMF (15 mL) was added to the flask and the mixture was stirred for 5 min. The reaction mixture was cooled to 0 °C, and 4-methylbenzene thiol (2.48 g, 20 mmol) was added slowly. The mixture was stirred for 5 min, a solution of propargyl bromide (1.72 mL, 20 mmol) in DMF (10 mL) was added. The mixture was removed from the ice bath, allowed to return to RT and stirred for 16 h under nitrogen. HCl (2 M, 20 mL) and CH_2Cl_2 (20 mL) were added to the flask. The layers were separated, and the organic layers were washed with HCl (2 M, 3 × 20 mL) and brine (15 mL), dried and concentrated under reduced pressure, to yield the crude product as yellow oil. This was purified by column chromatography on silica gel (100% hexane) to yield 4-methylphenyl prop-2'-ynyl sulfide **[45]** as a yellow oil (763 mg, 47%); ^{1}H NMR δ_H (400 MHz) 2.23 (1H, t, *J* 2.6 Hz, C≡C-H), 2.34 (3H, s, $ArCH_3$), 3.56 (2H, d, *J* 2.6 Hz, SCH_2), 7.14 (2H, d, *J* 8.5 Hz, Ar-H), 7.38 (2H, d, *J* 8.5 Hz, Ar-H); IR (film) ν_{max}/cm^{-1} 2117, 1231, 643.

Method B

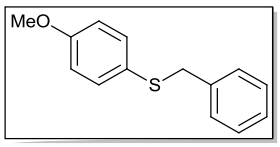
Cyclohexylmethyl phenyl sulfide [23][37]



Thiophenol (1.32 g, 1.23 mL, 12 mmol) was added to sodium ethoxide, [made from sodium (0.46 g, 20 mmol) in ethanol (20 mL) at 0 °C (ice bath), while stirring under nitrogen]. The mixture was stirred for 5 min at 0 °C, then (bromomethyl)cyclohexane (1.77 g, 1.40 mL, 10 mmol) was added. The reaction mixture was removed from the bath and stirred for 16 h at RT under nitrogen. Water (20 mL) and CH_2Cl_2 (20 mL) were added to the flask. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed with aqueous sodium hydroxide (2 M, 3 × 20 mL) and brine (20 mL), dried, filtered and concentrated under reduced pressure to give the crude sulfide which was purified by column chromatography (100% hexane) to give cyclohexylmethyl phenyl sulfide **[23]** as a clear oil (1.940 g, 95%); ^{1}H NMR δ_H (400 MHz) 0.89–1.08 (2H, m, cyclohexyl protons), 1.10–1.32 (3H, m, cyclohexyl protons), 1.45–1.80 (4H, m, cyclohexyl protons), 1.82–1.94 (2H, m,

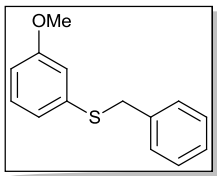
cyclohexyl protons), 2.80 (2H, d, *J* 6.8 Hz, SCH_2) 7.09–7.18 (1H, m, Ar-H), 7.21–7.38 (4H, m, Ar-H); IR (film) ν_{max}/cm^{-1} 2924, 1584, 1480, 1448, 736.

Benzyl 4-methoxyphenyl sulfide [1][26,27]



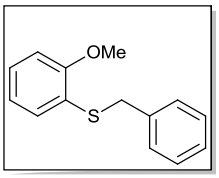
4-Methoxybenzenethiol (2.94 g, 2.58 mL, 21 mmol), sodium ethoxide [made *in situ* from sodium (0.56 g 24.0 mmol) in ethanol (30 mL) while stirring under nitrogen] and benzyl bromide (3.42 g, 2.4 mL, 20.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (8:2 hexane:ethylacetate) to give benzyl 4-methoxyphenyl sulfide **[1]** as a white solid (4.39 g, 95 %); m.p. 47–49 °C, (Lit.[28] 48–49 °C); ^{1}H NMR δ_H (300 MHz) 3.77 (3H, s, O-CH_3), 3.98 (2H, s, SCH_2), 6.73–6.83 (2H, m, Ar-H), 7.13–7.31 (7H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 41.2 (SCH_2), 55.3 (OCH_3), 114.4 (CH_{Ar}), 126.1 ($C_{Ar(q)}$), 127.0 (CH_{Ar}), 128.4 (CH_{Ar}), 128.9 (CH_{Ar}), 134.1 (CH_{Ar}), 138.1 ($C_{Ar(q)}$), 159.2 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2920, 2834, 1595, 1493, 1288, 1246, 1179, 1026, 810.

Benzyl 3-methoxyphenyl sulfide [2][26,28]



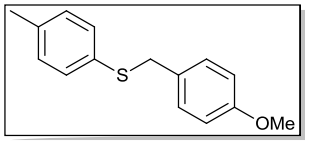
3-Methoxybenzenethiol (2.94 g, 2.58 mL, 21 mmol), sodium ethoxide [made *in situ* from sodium (0.56 g 24.0 mmol) in ethanol (30 mL) while stirring under nitrogen] and benzyl bromide (3.42 g, 2.4 mL, 20.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (8:2 hexane:ethylacetate) to give benzyl 3-methoxyphenyl sulfide **[2]** as a clear oil (3.80 g, 83 %); ^{1}H NMR δ_H (300 MHz) 3.73 (3H, s, O-CH_3), 4.12 (2H, s, SCH_2), 6.67–6.75 (1H, m, Ar-H), 6.80–6.85 (1H, m, Ar-H), 6.87–6.94 (1H, m, Ar-H), 7.12–7.35 (6H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 38.9 (SCH_2), 55.2 (OCH_3), 112.2 (CH_{Ar}), 114.8 (CH_{Ar}), 121.8 (CH_{Ar}), 127.2 (CH_{Ar}), 128.5 (CH_{Ar}), 128.8 (CH_{Ar}), 129.7 (CH_{Ar}), 137.4 ($C_{Ar(q)}$), 137.8 ($C_{Ar(q)}$), 159.7 ($C_{Ar(q)}$); IR (film) ν_{max}/cm^{-1} 3062, 3029, 2936, 1590, 1479, 1249, 1043, 769; m/z (ESI) [$(M+OH)^+$] 247 (90%), 231 (8), 181 (8), 152 (10), 94 (4), 80 (10), 64 (14), 42 (100); HRMS (ESI): Exact mass calculated for $C_{14}H_{15}O_2S$ [$(M+OH)^+$] 247.0793, Found 247.0796.

Benzyl 2-methoxyphenyl sulfide [3][26,27]



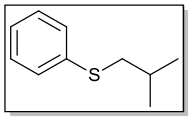
2-Methoxybenzenethiol (2.80 g, 2.52 mL, 20.0 mmol), sodium ethoxide [made *in situ* from sodium (0.56 g 24.0 mmol) in ethanol (30 mL) while stirring under nitrogen] and benzyl bromide (3.36 g, 2.36 mL, 19.6 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (8:2 hexane:ethylacetate) to give benzyl 2-methoxyphenyl sulfide **[3]** as a white solid (2.50 g, 55 %); m.p. 68–70 °C; ^{1}H NMR δ_H (300 MHz) 3.88 (3H, s, O-CH_3), 4.09 (2H, s, SCH_2), 6.79–6.91 (2H, m, Ar-H), 7.12–7.35 (7H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 37.3 (SCH_2), 55.8 (OCH_3), 110.5 (CH_{Ar}), 121.0 (CH_{Ar}), 124.5 ($C_{Ar(q)}$), 127.0 (CH_{Ar}), 127.6 (CH_{Ar}), 128.4 (CH_{Ar}), 128.9 (CH_{Ar}), 130.5 (CH_{Ar}), 137.5 ($C_{Ar(q)}$), 157.6 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2934, 1577, 1476, 1245, 1071, 1025, 747; m/z (ESI) [$(M+OH)^+$] 247 (100%), 231 (6), 181 (8), 145 (3), 122 (3), 91 (4), 80 (12); HRMS (ESI): Exact mass calculated for $C_{14}H_{15}O_2S$ [$(M+OH)^+$] 247.0793, Found 247.0799.

4-Methylphenyl 4'-methoxybenzyl sulfide [4][26,29]



4-Methylbenzenethiol (1.24 g, 10.0 mmol), sodium ethoxide [made *in situ* from sodium (0.28 g, 12.0 mmol) in ethanol (30 mL) while stirring under nitrogen] and 4-methoxybenzyl chloride (1.56 g, 1.45 mL, 10 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (8:2 hexane:ethylacetate) to give 4-methoxyphenyl 4'-methylbenzyl sulfide **[4]** as a white solid (1.83 g, 75%); m.p. 65–67 °C, (Lit.[168] 67 °C); ^{1}H NMR δ_H (300 MHz) 2.30 (3H, s, Ar-CH_3), 3.78 (3H, s, O-CH_3), 4.03 (2H, s, SCH_2), 6.76–6.84 (2H, m, Ar-H), 7.03–7.11 (2H, m, Ar-H), 7.13–7.28 (4H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 21.0 ($ArCH_3$), 39.2 (SCH_2), 55.3 (OCH_3), 113.9 (CH_{Ar}), 129.6 (CH_{Ar}), 129.8 ($C_{Ar(q)}$), 129.9 (CH_{Ar}), 130.7 (CH_{Ar}), 132.7 ($C_{Ar(q)}$), 136.5 ($C_{Ar(q)}$), 158.7 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2958, 2833, 1609, 1510, 1492, 1241, 1174, 1030, 799; m/z (ESI) [$(M+OH)^+$] 261 (10%), 153.2 (4), 122.2 (12), 121.2 (84), 94 (4), 80, (4); HRMS (ESI): Exact mass calculated for $C_{15}H_{17}O_2S$ [$(M+OH)^+$] 261.0949, Found 261.0937.

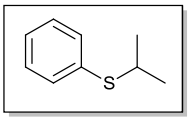
Isobutyl phenyl sulfide [24][38]



Thiophenol (1.10 g, 1.03 mL, 10 mmol), sodium ethoxide [made *in situ* from sodium (0.28 g 12.0 mmol) in ethanol (20 mL) while stirring under nitrogen] and 1-bromo-2-methylpropane (1.37 g, 10 mmol) were used as described for

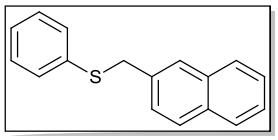
[23] to give the crude sulfide which was purified by column chromatography (100% hexane) to give isobutyl phenyl sulfide **[24]** as a clear oil (1.61 g, 97%); ^{1}H NMR δ_H (300 MHz) 1.03 [6H, d, *J* 6.6 Hz, CH(C*H*$_3$)$_2$], 1.79–1.94 [1H, m, C*H*(CH$_3$)$_2$], 2.81 (2H, d, *J* 6.6 Hz, SCH$_2$), 7.11–7.19 (1H, m, Ar-H), 7.22–7.35 (4H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 22.1 [CH(*C*H$_3$)$_2$], 28.3 [*C*H(CH$_3$)$_2$], 42.6 (SCH$_2$), 125.6 (CH$_{Ar}$), 128.80 (CH$_{Ar}$), 128.84 (CH$_{Ar}$), 137.4 (C$_{Ar(q)}$); IR (film) ν_{max}/cm^{-1} 2958, 2927, 1586, 1481, 1438, 1026, 737, 690.

Isopropyl phenyl sulfide [25][39]



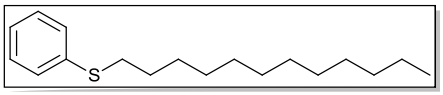
Thiophenol (1.10 g, 1.03 mL, 10 mmol), sodium ethoxide [made *in situ* from sodium (0.28 g 12.0 mmol) in ethanol (20 mL) while stirring under nitrogen] and 2-bromopropane (1.23 g, 10 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give isopropyl phenyl sulfide **[25]** as a clear oil (1.06 g, 70%); ^{1}H NMR δ_H (300 MHz) 1.29 [6H, d, *J* 6.9 Hz, CH(C*H*$_3$)$_2$], 3.30–3.45 [1H, m, C*H*(CH$_3$)$_2$], 7.18–7.33 (3H, m, Ar-H), 7.38–7.42 (2H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 23.1 [CH(*C*H$_3$)$_2$], 38.2 (SCH), 126.7 (CH$_{Ar}$), 128.8 (CH$_{Ar}$), 131.9 (CH$_{Ar}$), 135.5 (C$_{Ar(q)}$); IR (film) ν_{max}/cm^{-1} 2962, 2925, 1584, 1480, 1439, 1026, 741, 692.

2-Naphthylmethyl phenyl sulfide [26][40]



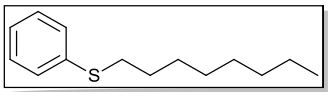
Thiophenol (1.10 g, 10 mmol), sodium ethoxide [made *in situ* from sodium (0.28 g 12.0 mmol) in ethanol (20 mL) while stirring under nitrogen] and (2-bromomethyl)naphthalene (2.21 g, 10 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give 2-naphthylmethyl phenyl sulfide **[26]** as a white solid (2.05 g, 82%); m.p. 102–104 °C, (Lit.[40] 99.5–100.5 °C); ^{1}H NMR δ_H (300 MHz) 4.26 (2H, s, SCH$_2$), 7.11–7.27 (3H, m, Ar-H), 7.28–7.36 (2H, m, Ar-H), 7.38–7.51 (3H, m, Ar-H), 7.63–7.85 (4H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 39.5 (SCH$_2$), 125.8 (CH$_{Ar}$), 126.1 (CH$_{Ar}$), 126.5 (CH$_{Ar}$), 127.0 (CH$_{Ar}$), 127.4 (CH$_{Ar}$), 127.7 (CH$_{Ar}$), 127.7 (CH$_{Ar}$), 128.3 (CH$_{Ar}$), 128.9 (CH$_{Ar}$), 130.1 (CH$_{Ar}$), 132.6 (C$_{Ar(q)}$), 133.3 (C$_{Ar(q)}$), 134.9 (C$_{Ar(q)}$), 136.3 (C$_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 3048, 2917, 1438, 832, 738.

Dodecyl phenyl sulfide [27][41]



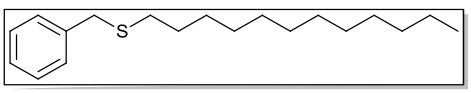
Thiophenol (3.97 g, 3.70 mL, 36.0 mmol), sodium ethoxide [made *in situ* from sodium (0.828 g 36.0 mmol) in ethanol (30 mL) while stirring under nitrogen] and 1-bromododecane (7.48 g, 7.14 mL, 30.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give dodecyl phenyl sulfide **[27]** as a white solid (6.5 g, 78%); m.p. 29–32 °C, (Lit.[41] m.p. 31–33 °C); ^{1}H NMR δ_H (300 MHz) 0.88 (3H, t, *J* 6.3 Hz, CH_3), 1.15–1.72 (20H, m), 2.91 (2H, t, *J* 7.2 Hz, $SOCH_2$), 7.10–7.36 (5H, m, Ar-H); IR (film) ν_{max}/cm^{-1} = 2919, 1439, 730, 689.

Octyl phenyl sulfide [28][42]



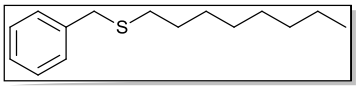
Thiophenol (3.97 g, 3.70 mL, 36.0 mmol), sodium ethoxide [made *in situ* from sodium (0.828 g 36.0 mmol) in ethanol (30 mL) while stirring under nitrogen] and 1-bromooctane (5.79 g, 5.18 mL, 30.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give octyl phenyl sulfide **[28]** as a clear oil (5.59 g, 84%); ^{1}H NMR δ_H (300 MHz) 0.88 (3H, t, *J* 6.6 Hz, CH_3), 1.15–1.72 (12H, m), 2.95 (2H, t, *J* 7.2 Hz, SCH_2), 7.10–7.37 (5H, m, Ar-H); IR (film) ν_{max}/cm^{-1} = 2926, 1480, 1439, 737, 690.

Dodecyl benzyl sulfide [33][45]



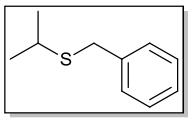
Dodecanethiol (7.92 g, 8.62 mL, 36.0 mmol), sodium ethoxide [made *in situ* from sodium (0.828 g 36.0 mmol) in ethanol (30 mL) while stirring under nitrogen] and benzyl bromide (5.13 g, 3.6 mL, 30.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give dodecyl benzyl sulfide **[33]** as a clear oil (7.72 g, 88%); ^{1}H NMR δ_H (300 MHz) 0.88 (3H, t, *J* 6.9 Hz, CH_3), 1.15–1.41 (18H, m), 1.48–1.63 (2H, m), 2.41 (2H, t, *J* 7.2 Hz, SCH_2), 3.70 (2H, s, SCH_2-Ar), 7.19–7.35 (5H, m, Ar-H); IR (film) ν_{max}/cm^{-1} = 2925, 1494, 1465, 1454, 767, 699.

Octyl benzyl sulfide [34][46]



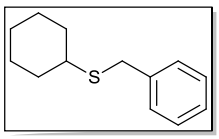
Octanethiol (4.39 g, 5.21 mL 36.0 mmol), sodium ethoxide [made *in situ* from sodium (0.828 g 36.0 mmol) in ethanol (30 mL) while stirring under nitrogen] and benzyl bromide (5.13 g, 3.6 mL, 30.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give octyl benzyl sulfide **[34]** as a clear oil (5.89 g, 83%); ^{1}H NMR δ_H (300 MHz) 0.88 (3H, t, *J* 6.3 Hz, CH_3), 1.13–1.41 (10H, m), 1.47–1.63 (2H, m), 2.41 (2H, t, *J* 7.2 Hz, SCH_2), 3.70 (2H, s, SCH_2-Ar), 7.17–7.38 (5H, m, Ar-H); IR (film) ν_{max}/cm^{-1} = 2854, 1494, 1454, 767, 699.

Isopropyl benzyl sulfide [35][47]



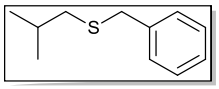
2-Propanethiol (2.74 g, 3.34 mL, 36 mmol), sodium ethoxide [made *in situ* from sodium (0.828 g 36.0 mmol) in ethanol (30 mL) while stirring under nitrogen] and benzyl bromide (5.13 g, 3.6 mL, 30.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give isopropyl benzyl sulfide **[35]** as a clear oil (4.39 g, 88%); ^{1}H NMR δ_H (300 MHz) 1.25 [6H, d, *J* 6.7 Hz, CH(C*H*$_3$)$_2$], 2.71–2.88 [1H, m, C*H*(CH$_3$)$_2$], 3.74 (2H, s, Ar-CH_3), 7.18–7.39 (5H, m, Ar-H); IR (film) ν_{max}/cm^{-1} = 2959, 1495, 1453, 1236, 703.

Cyclohexyl benzyl sulfide [36][48]



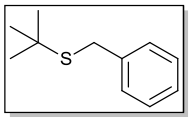
Cyclohexanethiol (4.18 g, 4.50 mL, 36 mmol), sodium ethoxide [made *in situ* from sodium (0.828 g 36.0 mmol) in ethanol (30 mL) while stirring under nitrogen] and benzyl bromide (5.13 g, 3.6 mL, 30.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give cyclohexyl benzyl sulfide **[36]** as a clear oil (5.39 g, 87%); ^{1}H NMR δ_H (300 MHz) 1.13–1.43 (5H, m, cyclohexyl protons), 1.48–1.83 (3H, m, cyclohexyl protons), 1.86–2.02 (2H, m, cyclohexyl protons), 2.48–2.63 (1H, m, cyclohexyl protons) 3.74 (2H, s, SCH_2), 7.15–7.38 (5H, m, Ar-H); IR (film) ν_{max}/cm^{-1} = 2929, 1494, 1449, 1202, 700.

Isobutyl benzyl sulfide [37][49]



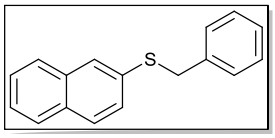
2-Methyl-1-propanethiol (3.25 g, 3.87 mL, 36 mmol), sodium ethoxide [made *in situ* from sodium (0.828 g 36.0 mmol) in ethanol (30 mL) while stirring under nitrogen] and benzyl bromide (5.13 g, 3.6 mL, 30.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give isobutyl benzyl sulfide **[37]** as a clear oil (4.92 g, 91%); ^{1}H NMR δ_H (300 MHz) 0.95 [6H, d, *J* 6.6 Hz, CH(C*H*$_3$)$_2$], 1.69–1.86 [1H, m, C*H*(CH$_3$)$_2$], 2.31 (2H, d, *J* 6.9 Hz, SCH$_2$), 3.69 (2H, s, SCH$_2$-Ar), 7.18–7.37 (5H, m, Ar-H); IR (film): ν_{max}/cm^{-1} = 2957, 1494, 1453, 733, 700.

***tert*-Butyl benzyl sulfide [38]**[31]



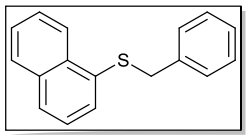
2-Methyl-2-propanethiol (3.25 g, 4.06 mL, 36 mmol), sodium ethoxide [made *in situ* from sodium (0.828 g 36.0 mmol) in ethanol (30 mL) while stirring under nitrogen] and benzyl bromide (5.13 g, 3.6 mL, 30.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give *tert*-butyl benzyl sulfide **[38]** as a clear oil (4.92 g, 91%); ^{1}H NMR δ_H (300 MHz) 1.35 [9H, s C(C*H*$_3$)$_3$], 3.77 (2H, s, SCH$_2$), 7.16–7.40 (5H, m, Ar-H); IR (film) ν_{max}/cm^{-1} = 2941, 1495, 1455, 1364, 1168, 713, 696.

2-Naphthyl benzyl sulfide [29][43]



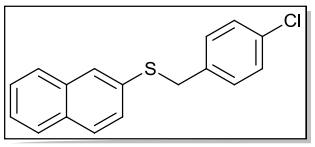
2-Naphthylthiol (5.77 g, 36 mmol), sodium ethoxide [made *in situ* from sodium (0.828 g 36.0 mmol) in ethanol (30 mL) while stirring under nitrogen] and benzyl bromide (5.13 g, 3.6 mL, 30.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give 2-naphthyl benzyl sulfide **[29]** as a white solid (6.31 g, 84%); m.p. 89–91 °C, (Lit.[30] m.p. 88 °C); ^{1}H NMR δ_H (300 MHz) 4.22 (2H, s, SCH$_2$), 7.18–7.51 (8H, m, Ar-H), 7.63–7.83 (4H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} = 2923, 1582, 814, 738.

1-Naphthyl benzyl sulfide [30][44]



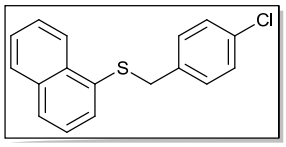
1-Naphthylthiol (5.77 g, 36 mmol), sodium ethoxide [made *in situ* from sodium (0.828 g 36.0 mmol) in ethanol (30 mL) while stirring under nitrogen] and benzyl bromide (5.13 g, 3.6 mL, 30.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give 1-naphthyl benzyl sulfide **[30]** as a white solid (2.70 g, 36%); m.p. 82–85 °C, (Lit.[169] m.p. 84 °C); ^{1}H NMR δ_H (300 MHz) 4.14 (2H, s, SCH_2), 7.12–7.39 (6H, m, Ar-H), 7.41–7.60 (3H, m, Ar-H), 7.72 (1H, d, *J* 8.1 Hz, Ar-H), 7.83 (1H, dd, *J* 7.2 Hz and 2.7 Hz, Ar-H), 8.42 (1H, dd, *J* 7.8 Hz and 1.5 Hz, Ar-H); IR (KBr): ν_{max}/cm^{-1} = 2924, 1455, 785, 765; (Found: C, 81.33; H, 5.74. $C_7H_{14}S$ Requires C, 81.56; H, 5.64).

2-Naphthyl 4-chlorobenzyl sulfide [31]



2-Naphthylthiol (5.77 g, 36 mmol), sodium ethoxide [made *in situ* from sodium (0.828 g 36.0 mmol) in ethanol (30 mL) while stirring under nitrogen] and 4-chlorobenzyl bromide (6.16 g, 30.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give 2-naphthyl 4-chlorobenzyl sulfide **[31]** as a white solid (6.40 g, 75%); m.p. 77–79 °C; ^{1}H NMR δ_H (300 MHz) 4.16 (2H, s, SCH_2), 7.14–7.29 (4H, m, Ar-H), 7.32–7.52 (3H, m, Ar-H), 7.64–7.83 (4H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 38.4 (SCH_2), 126.0 (CH_{Ar}), 126.6 (CH_{Ar}), 127.2 (CH_{Ar}), 127.7 (CH_{Ar}), 127.9 (CH_{Ar}), 128.3 (CH_{Ar}), 128.5 (CH_{Ar}), 128.7 (CH_{Ar}), 130.2 (CH_{Ar}), 132.0 ($C_{Ar(q)}$), 133.0 ($C_{Ar(q)}$), 133.2 ($C_{Ar(q)}$), 133.7 ($C_{Ar(q)}$), 136.0 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} = 2904, 1491, 1405, 818, 741; (Found: C, 71.30; H, 4.68. $C_{17}H_{13}ClS$ Requires C, 71.69; H, 4.60).

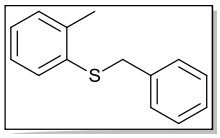
1-Naphthyl 4-chlorobenzyl sulfide [32]



1-Naphthylthiol (5.77 g, 36 mmol), sodium ethoxide [made *in situ* from sodium (0.828 g 36.0 mmol) in ethanol (30 mL) while stirring under nitrogen] and 4-chlorobenzyl bromide (6.16 g, 30.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give 1-naphthyl 4-chlorobenzyl sulfide **[32]** as a white solid (5.55 g, 65%); m.p. 79–81 °C; ^{1}H NMR δ_H (300 MHz) 4.07 (2H, s, SCH_2), 7.02–7.60 (8H, m, Ar-H), 7.74 (1H, d, *J* 8.1 Hz, Ar-H), 7.84 (1H, dd, *J* 8.1 Hz and 2.4 Hz, Ar-H), 8.34–8.46 (1H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 38.8 (SCH_2), 125.1 (CH_{Ar}), 125.5 (CH_{Ar}), 126.3

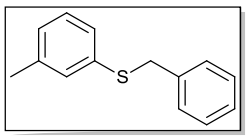
(CH_{Ar}), 126.6 (CH_{Ar}), 128.1 (CH_{Ar}), 128.5 (CH_{Ar}), 128.7 (CH_{Ar}), 130.0 (CH_{Ar}), 130.2 (CH_{Ar}), 132.5 ($C_{Ar(q)}$), 132.9 ($C_{Ar(q)}$), 133.2 ($C_{Ar(q)}$), 134.0 ($C_{Ar(q)}$), 136.1 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} = 3051, 1490, 1405, 788, 767; (Found: C, 71.33; H, 4.52. $C_{17}H_{13}ClS$ Requires C, 71.69; H, 4.60).

Benzyl *o*-tolyl sulfide [5][30]



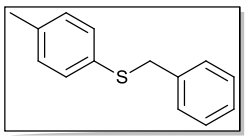
2-Methylbenzenethiol (1.25 g, 1.19 mL, 10 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.28 g, 12.0 mmol) in ethanol (20 mL)] and benzyl bromide (1.71 g, 1.19 mL, 10.0 mmol) were used as described for **[23]** to give the crude product which was purified by column chromatography (100% hexane) to give benzyl *o*-tolyl sulfide **[5]** as a clear oil (1.93 g, 90%); ^{1}H NMR δ_H (300 MHz) 2.32 (3H, s, Ar-CH_3), 4.08 (2H, s, SCH_2), 7.04–7.18 (3H, m, Ar-H), 7.19–7.33 (6H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 20.3 ($ArCH_3$), 38.3 (SCH_2), 126.1 (CH_{Ar}), 126.4 (CH_{Ar}), 127.2 (CH_{Ar}), 128.5 (CH_{Ar}), 128.8 (CH_{Ar}), 128.9 (CH_{Ar}), 130.1 (CH_{Ar}), 135.8 ($C_{Ar(q)}$), 137.2 ($C_{Ar(q)}$), 137.9 ($C_{Ar(q)}$); IR (film) ν_{max}/cm^{-1} 3061, 3029, 1469, 1454, 1066, 744, 697; (Found C, 78.50; H, 6.62; $C_{14}H_{14}S$ requires C, 78.46; H, 6.58); m/z (ESI) [$(M+OH)^+$] 231 (66%), 215 (4), 181 (6), 153 (16), 152 (38), 131 (14), 80 (40), 64 (56); HRMS (ESI): Exact mass calculated for $C_{14}H_{15}SO$ [$(M+OH)^+$] 231.0844, Found 231.0848.

Benzyl *m*-tolyl sulfide [6]



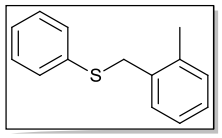
3-Methylbenzenethiol (1.25 g, 1.20 mL, 10 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.28 g, 12.0 mmol) in ethanol (20 mL)] and benzyl bromide (1.71 g, 1.19 mL, 10.0 mmol) were used as described for **[23]** to give the crude product as a white solid which was purified by column chromatography (100% hexane) to give benzyl *m*-tolyl sulfide **[6]** as a clear oil (1.95 g, 91%); ^{1}H NMR δ_H (300 MHz) 2.29 (3H, s, Ar-CH_3), 4.11 (2H, s, SCH_2), 6.95–7.02 (1H, m, Ar-H), 7.07–7.34 (8H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 21.4 ($ArCH_3$), 39.0 (SCH_2), 126.7 (CH_{Ar}), 127.2 (CH_{Ar}), 128.5 (CH_{Ar}), 128.8 (CH_{Ar}), 128.9 (CH_{Ar}), 130.4 (CH_{Ar}), 136.2 ($C_{Ar(q)}$), 137.6 ($C_{Ar(q)}$), 138.6 ($C_{Ar(q)}$); IR (film) ν_{max}/cm^{-1} 3029, 2921, 1592, 1495, 1453, 770, 693; (Found C, 78.55; H, 6.62; S, 14.93; $C_{14}H_{14}S$ requires C, 78.46; H, 6.58; S 14.96); m/z (ESI) [$(M+OH)^+$] 231 (100%), 215 (4), 183 (6), 145 (12), 132 (24), 91 (8), 80 (8); HRMS (ESI): Exact mass calculated for $C_{14}H_{15}SO$ [$(M+OH)^+$] 231.0844, Found 231.0843.

Benzyl *p*-tolyl sulfide [7][26,29]



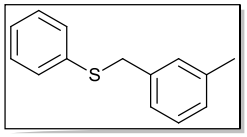
4-Methylbenzenethiol (1.25 g, 10 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.28 g, 12.0 mmol) in ethanol (20 mL)] and benzyl bromide (1.71 g, 1.19 mL, 10.0 mmol) were used as described for **[23]** to give the crude product as a white solid which was purified by column chromatography (100% hexane) to give benzyl *p*-tolyl sulfide **[7]** as a white solid (1.63 g, 76%); m.p. 42–43 °C, (Lit.[101] 45 °C); ^{1}H NMR δ_H (300 MHz) 2.30 (3H, s, Ar-CH_3), 4.06 (2H, s, SCH_2), 7.05 (2H, d, *J* 8.2 Hz, Ar-H), 7.15–7.32 (7H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 21.0 ($ArCH_3$), 39.7 (SCH_2), 127.1 (CH_{Ar}), 128.4 (CH_{Ar}), 128.8 (CH_{Ar}), 129.6 (CH_{Ar}), 130.7 (CH_{Ar}), 132.4 ($C_{Ar(q)}$), 136.5 ($C_{Ar(q)}$), 137.8 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2921, 1494, 1454, 1265, 740, 697.

2-Methylbenzyl phenyl sulfide [8]



Thiophenol (1.10 g, 1.03 mL, 10 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.28 g, 12.0 mmol) in ethanol (20 mL)] and 2-methylbenzyl bromide (1.85 g, 1.34 mL, 10.0 mmol) were used as described for **[23]** to give the crude product as a white solid which was purified by column chromatography (100% hexane) to give 2-methylbenzyl phenyl sulfide **[8]** as a clear oil (1.84 g, 86%); ^{1}H NMR δ_H (300 MHz) 2.39 (3H, s, Ar-CH_3), 4.10 (2H, s, SCH_2), 7.02–7.37 (9H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 19.2 ($ArCH_3$), 37.4 (SCH_2), 126.0 (CH_{Ar}), 126.5 (CH_{Ar}), 127.5 (CH_{Ar}), 128.9 (CH_{Ar}), 129.8 (CH_{Ar}), 130.3 (CH_{Ar}), 130.5 (CH_{Ar}), 135.1 ($C_{Ar(q)}$), 136.7 ($C_{Ar(q)}$), 136.8 ($C_{Ar(q)}$); IR (film) ν_{max}/cm^{-1} 3060, 2929, 1583, 1479, 1438, 737, 690; (Found C, 78.61; H, 6.32; S, 15.02; $C_{14}H_{14}S$ requires C, 78.46; H, 6.58; S 14.96); m/z (ESI) [$(M+OH)^+$] 231 (100%), 106 (8%, 105 (72), 80 (8), 64 (20), 42 (24); HRMS (ESI): Exact mass calculated for $C_{14}H_{15}SO$ [$(M+OH)^+$] 231.0844, Found 231.0844.

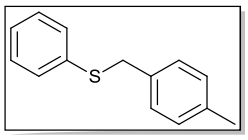
3-Methylbenzyl phenyl sulfide [9]



Thiophenol (1.10 g, 1.03 mL, 10 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.28 g, 12.0 mmol) in ethanol (20 mL)] and 3-methylbenzyl bromide (1.85 g, 1.35 mL, 10.0 mmol) were used as described for **[23]** to give the crude product as a white solid which was purified by column

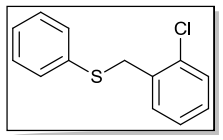
chromatography (100% hexane) to give 3-methylbenzyl phenyl sulfide **[9]** as a clear oil (1.65 g, 77%); ^{1}H NMR δ_H (300 MHz) 2.31 (3H, s, Ar-CH_3), 4.09 (2H, s, SCH_2), 7.00–7.37 (9H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 21.3 ($ArCH_3$), 39.0 (SCH_2), 125.9 (CH_{Ar}), 126.3 (CH_{Ar}), 128.0 (CH_{Ar}), 128.4 (CH_{Ar}), 128.8 (CH_{Ar}), 129.6 (CH_{Ar}), 129.7 (CH_{Ar}), 136.6 ($C_{Ar(q)}$), 137.3 ($C_{Ar(q)}$), 138.2 ($C_{Ar(q)}$); IR (film) ν_{max}/cm^{-1} 3057, 2920, 1584, 1480, 1438, 1089, 738, 690; (Found C, 78.20; H, 6.51; S, 15.3; $C_{14}H_{14}S$ requires C, 78.46; H, 6.58; S 14.96); m/z (ESI) [$(M+OH)^+$] 231 (100%), 215 (8), 183 (8), 145 (12), 132 (26), 105 (8), 91 (8); HRMS (ESI): Exact mass calculated for $C_{14}H_{15}SO$ [$(M+OH)^+$] 231.0844, Found 231.0843.

4-Methylbenzyl phenyl sulfide [10][31]



Thiophenol (1.10 g, 1.03 mL, 10 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.28 g, 12.0 mmol) in ethanol (20 mL)] and 4-methylbenzyl bromide (1.85 g, 10.0 mmol) were used as described for **[23]** to give the crude product as a white solid which was purified by column chromatography (100% hexane) to give 4-methylbenzyl phenyl sulfide **[10]** as a white solid (1.86 g, 87%); m.p. 69–71 °C, (Lit.[31] 63.5–64.4 °C); ^{1}H NMR δ_H (300 MHz) 2.32 (3H, s, Ar-CH_3), 4.09 (2H, s, SCH_2), 7.03–7.36 (9H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 21.1 ($ArCH_3$), 38.7 (SCH_2), 126.2 (CH_{Ar}), 128.7 (CH_{Ar}), 128.8 (CH_{Ar}), 129.2 (CH_{Ar}), 129.6 (CH_{Ar}), 134.3 ($C_{Ar(q)}$), 136.7 ($C_{Ar(q)}$) 136.8 ($C_{Ar(q)}$); IR (film) ν_{max}/cm^{-1} 3058, 2918, 1582, 1479, 1435, 1090, 738, 690; (Found C, 78.13; H, 6.59; S, 15.30; $C_{14}H_{14}S$ requires C, 78.46; H, 6.58; S 14.96); m/z (ESI) [$(M+OH)^+$] 231 (60%), 213 (6), 145 (6), 106 (10), 105 (100). 80 (18), 64 (14); HRMS (ESI): Exact mass calculated for $C_{14}H_{15}SO$ [$(M+OH)^+$] 231.0844, Found 231.0849.

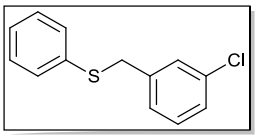
2-Chlorobenzyl phenyl sulfide [11][32]



Thiophenol (2.42 g, 2.26 mL, 22.0 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.51 g, 22.0 mmol) in ethanol (30 mL)] and 2-chlorobenzyl bromide (4.11 g, 2.60 mL, 20.0 mmol) were used as described for **[23]** to give the crude product as a white solid which was purified by column chromatography (100% hexane) to give 2-chlorobenzyl phenyl sulfide **[11]** as a clear oil (3.94 g, 84%); ^{1}H NMR δ_H (300 MHz) 4.21 (2H, s, SCH_2), 7.09–7.40 (9H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 37.0 (SCH_2), 126.8 (CH_{Ar}), 128.6 (CH_{Ar}), 128.9 (CH_{Ar}), 129.7 (CH_{Ar}),

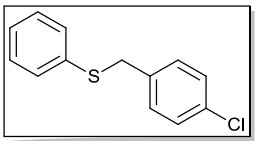
130.7 (CH_{Ar}), 134.1 ($C_{Ar(q)}$), 135.2 ($C_{Ar(q)}$), 135.7 ($C_{Ar(q)}$), 5 CH_{Ar} seen for 7 CH_{Ar}; IR (film) ν_{max}/cm^{-1} 3059, 1582, 1480, 1473, 1439, 1052, 736, 690.

3-Chlorobenzyl phenyl sulfide [12][33]



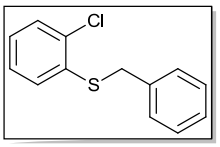
Thiophenol (2.42 g, 2.26 mL, 22.0 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.51 g, 22.0 mmol) in ethanol (30 mL)] and 3-chlorobenzyl bromide (4.11 g, 2.63 mL, 20.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give 3-chlorobenzyl phenyl sulfide **[12]** as a clear oil (4.37 g, 93%); ^{1}H NMR δ_H (300 MHz) 4.06 (2H, s, SCH_2), 7.10–7.34 (9H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 38.8 (SCH_2), 126.8 (CH_{Ar}), 126.9 (CH_{Ar}), 127.4 (CH_{Ar}), 128.91 (CH_{Ar}), 128.94 (CH_{Ar}), 129.7 (CH_{Ar}), 130.3 (CH_{Ar}), 134.3 ($C_{Ar(q)}$), 135.6 ($C_{Ar(q)}$), 139.7 ($C_{Ar(q)}$), 5 CH_{Ar} seen for 7 CH_{Ar}; IR (film) ν_{max}/cm^{-1} 3059, 1597, 1574, 1479, 1438, 1089, 1072, 739, 690.

4-Chlorobenzyl phenyl sulfide [13][34]



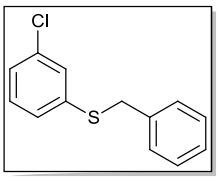
Thiophenol (2.42 g, 2.26 mL, 22.0 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.51 g, 22.0 mmol) in ethanol (30 mL)] and 4-chlorobenzyl chloride (3.22 g, 20.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give 4-chlorobenzyl phenyl sulfide **[13]** as a white solid (4.18 g, 89%); m.p. 75–77 °C, (Lit.[170] 78–78.5 °C); ^{1}H NMR δ_H (300 MHz) 4.05 (2H, s, SCH_2), 7.12–7.33 (9H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2917, 1576, 1437, 1405, 1090, 734.

Benzyl 2-chlorophenyl sulfide [14][27,171]



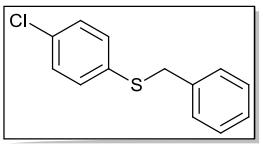
2-Chlorobenzenethiol (3.18 g, 22.0 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.51 g, 22.0 mmol) in ethanol (30 mL)] and benzyl bromide (3.42 g, 2.38 mL, 20.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give benzyl 2-chlorophenyl sulfide **[14]** as a clear oil (3.80 g, 81%); ^{1}H NMR δ_H (400 MHz) 4.12 (2H, s), 7.07–7.19 (2H, m, Ar-H), 7.20–7.41 (7H, m, Ar-H); IR (film) ν_{max}/cm^{-1} 2918, 1490, 1390, 1097, 810.

Benzyl 3-chlorophenyl sulfide [15]



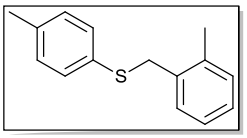
3-Chlorobenzenethiol (3.18 g, 2.56 mL, 22.0 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.51 g, 22.0 mmol) in ethanol (30 mL)] and benzyl bromide (3.42 g, 2.38 mL, 20.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give benzyl 3-chlorophenyl sulfide **[15]** as a white solid (4.27 g, 91%); m.p. 34–36 °C; ^{1}H NMR δ_H (300 MHz) 4.10 (2H, s, SCH_2), 7.08–7.34 (9H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 38.7 (SCH_2), 126.3 (CH_{Ar}), 127.4 (CH_{Ar}), 127.5 (CH_{Ar}), 128.6 (CH_{Ar}), 128.9 (CH_{Ar}), 129.0 (CH_{Ar}), 129.9 (CH_{Ar}), 134.6 ($C_{Ar(q)}$), 136.8 ($C_{Ar(q)}$), 138.7 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 3030, 1578, 1495, 1454, 1406, 1072, 776; (Found C, 66.32; H, 4.81; $C_{13}H_{11}ClS$ requires C, 66.51; H, 4.72).

Benzyl 4-chlorophenyl sulfide [16][29]



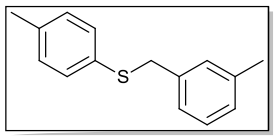
4-Chlorobenzenethiol (3.18 g, 22.0 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.51 g, 22.0 mmol) in ethanol (30 mL)] and benzyl bromide (3.42 g, 2.38 mL, 20.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give benzyl 4-chlorophenyl sulfide **[16]** as a white solid (4.32 g, 92%); m.p. 46–48 °C, (Lit.[170] 43–44 °C); ^{1}H NMR δ_H (300 MHz) 4.07 (2H, s, SCH_2), 7.11–7.32 (9H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 3059, 1598, 1575, 1479, 1438 1089, 738, 690.

2'-Methylbenzyl 4-methylphenyl sulfide [17][35]



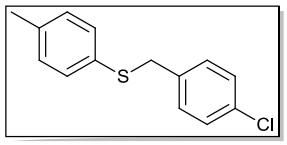
4-Methylbenzenethiol (4.47 g, 36.0 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.83 g, 36.0 mmol) in ethanol (30 mL)] and 2-methylbenzyl bromide (5.55 g, 4.02 mL, 30.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give 2'-methylbenzyl 4-methylphenyl sulfide **[17]** as a clear oil (6.03 g, 88%); ^{1}H NMR δ_H (300 MHz) 2.32 (3H, s, Ar-CH_3), 2.38 (3H, s, Ar-CH_3), 4.06 (2H, s, SCH_2), 7.00–7.28 (8H, m, Ar-H); IR (film) ν_{max}/cm^{-1} = 2921, 1493, 1091, 807.

3'-Methylbenzyl 4-methylphenyl sulfide [18]



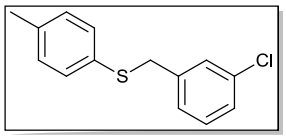
4-Methylbenzenethiol (4.47 g, 36.0 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.83 g, 36.0 mmol) in ethanol (30 mL)] and 3-methylbenzyl bromide (5.55 g, 4.05 mL, 30.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give 3'-methylbenzyl 4-methylphenyl sulfide **[18]** as a clear oil (6.23 g, 91%); ^{1}H NMR δ_H (300 MHz) 2.31 (6H, 2 overlapping s, Ar-CH_3), 4.04 (2H, s SCH_2), 6.99–7.29 (8H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 21.1 (Ar-CH_3), 21.4 (Ar-CH_3), 39.7 (SCH_2), 125.9 (CH_{Ar}), 127.9 (CH_{Ar}), 128.3 (CH_{Ar}), 129.6 (CH_{Ar}), 130.5 (CH_{Ar}), 132.7 ($C_{Ar(q)}$), 136.5 ($C_{Ar(q)}$), 137.6 ($C_{Ar(q)}$), 138.1 ($C_{Ar(q)}$), 5 CH_{Ar} signals seen for 6 CH_{Ar}; IR (film) ν_{max}/cm^{-1} = 2920, 1608, 1492, 1091, 802; m/z (ESI) [$(M+OH)^+$] 245 (50%), 91 (20), 83 (50); HRMS (ESI): Exact mass calculated for $C_{15}H_{17}SO$ [$(M+OH)^+$] 245.1000, Found 245.0994; (Found: C, 78.71; H, 7.14. $C_{15}H_{16}S$ Requires C, 78.90; H, 7.06).

4'-Chlorobenzyl 4-methylphenyl sulfide [19][29]



4-Methylbenzenethiol (4.47 g, 36.0 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.83 g, 36.0 mmol) in ethanol (30 mL)] and 4-chlorobenzyl bromide (6.16 g, 30.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give 4'-chlorobenzyl 4-methylphenyl sulfide **[19]** as a white solid (5.82, 78%); m.p. 66–68 °C, (Lit.[29] m.p. 64–65 °C); ^{1}H NMR δ_H (300 MHz) 2.30 (3H s, Ar-CH_3), 3.99 (2H, s, SCH_2), 7.00–7.29 (8H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} = 2926, 1490, 1405, 1090, 803.

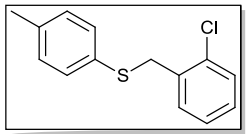
3'-Chlorobenzyl 4-methylphenyl sulfide [20][36]



4-Methylbenzenethiol (4.47 g, 36.0 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.83 g, 36.0 mmol) in ethanol (30 mL)] and 3-chlorobenzyl bromide (6.16 g, 30.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give 3'-chlorobenzyl 4-methylphenyl sulfide **[20]** as a white solid (6.05 g,

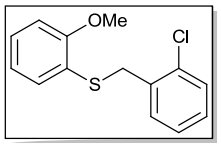
81%); m.p. 35–36 °C; ^{1}H NMR δ_H (300 MHz) 2.31 (3H s, Ar-CH_3), 4.00 (2H, s, SCH_2), 7.00–7.28 (8H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} = 2921, 1597, 1492, 1201, 1091, 806.

2'-Chlorobenzyl 4-methylphenyl sulfide [21]



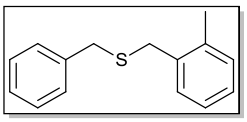
4-Methylbenzenethiol (4.47 g, 36.0 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.83 g, 36.0 mmol) in ethanol (30 mL)] and 2-chlorobenzyl bromide (6.16 g, 30.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give 2'-chlorobenzyl 4-methylphenyl sulfide **[21]** as a clear oil (6.19 g, 83%); ^{1}H NMR δ_H (300 MHz) 2.31 (3H s, Ar-CH_3), 4.16 (2H, s, SCH_2), 7.00–7.28 (7H, m, Ar-H), 7.30–7.41 (1H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 21.1 (Ar-CH_3), 37.7 (Ar-CH_3), 39.7 (SCH_2), 126.7 (CH_{Ar}), 128.5 (CH_{Ar}), 129.6 (CH_{Ar}), 129.7 (CH_{Ar}), 130.7 (CH_{Ar}), 131.5 (CH_{Ar}), 131.9 ($C_{Ar(q)}$), 134.0 ($C_{Ar(q)}$), 135.5 ($C_{Ar(q)}$), 137.0 ($C_{Ar(q)}$); IR (film) ν_{max}/cm^{-1} = 2921, 1492, 1444, 1052, 807; m/z (ESI) 239 (60%), 235 (30), 130 (50), 102 (74), 59 (62); HRMS (ESI): Exact mass calculated for $C_{14}H_{14}ClSO$ [$(M+OH)^+$] 265.0532, Found 265.0532; (Found: C, 67.76; H, 5.30. $C_{14}H_{13}ClS$ Requires C, 67.59; H, 5.27).

2'-Methoxyphenyl 2-chlorobenzyl sulfide [22]



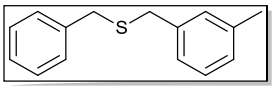
2-Methoxybenzenethiol (5.05 g, 36.0 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.83 g, 36.0 mmol) in ethanol (30 mL)] and 2-chlorobenzyl bromide (6.16 g, 30.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give 2'-methoxybenzyl 2-chlorophenyl sulfide **[22]** as a white solid (5.80 g, 73%); m.p. 44–46 °C; ^{1}H NMR δ_H (300 MHz) 3.89 (3H s, Ar-OCH_3), 4.19 (2H, s, SCH_2), 6.80–6.90 (2H, m, Ar-H), 7.07–7.28 (5H, m, Ar-H), 7.30–7.40 (1H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 35.0 (Ar-CH_3), 55.8 (SCH_2), 110.5 (CH_{Ar}), 121.0 (CH_{Ar}), 123.6 ($C_{Ar(q)}$), 126.7 (CH_{Ar}), 128.2 (CH_{Ar}), 128.4 (CH_{Ar}), 129.5 (CH_{Ar}), 130.8 (CH_{Ar}), 131.5 (CH_{Ar}), 134.1 ($C_{Ar(q)}$), 135.3 ($C_{Ar(q)}$), 158.0 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} = 2854, 1579, 1463, 1027, 743; m/z (ESI) [$(M+OH)^+$] 281 (100), 245 (24), 239 (8), 195 (6), 142 (8), 141 (50), 130 (10), 105 (6), 64 (20); HRMS (ESI): Exact mass calculated for $C_{14}H_{14}ClO_2S$ [$(M+OH)^+$] 281.0403, Found 281.0391; (Found: C, 63.64; H, 4.99. $C_{14}H_{13}ClOS$ Requires C, 63.51; H, 4.95).

Benzyl 2-methylbenzyl sulfide [39][50]



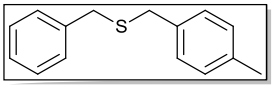
Benzyl mercaptan (2.73 g, 2.58 mL, 22.0 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.51 g, 22.0 mmol) in ethanol (30 mL)] and 2-methylbenzyl bromide (3.70 g, 2.68 mL, 20.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give benzyl 2-methylbenzyl sulfide **[39]** as a white solid (4.22 g, 84%); m.p. 31–32 °C, (Lit.[50] m.p. 31–32 °C); ^{1}H NMR δ_H (300 MHz) 2.30 (3H, s, Ar-CH_3), 3.61 (2H, s, SCH_2), 3.66 (2H, s, SCH_2), 7.07–7.36 (9H, m, Ar-H); IR (film) ν_{max}/cm^{-1} = 2916, 1608, 1493, 1453, 1228, 716, 702.

Benzyl 3-methylbenzyl sulfide [40][50]



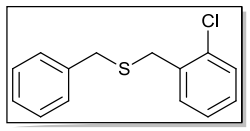
Benzyl mercaptan (2.73 g, 2.58 mL, 22.0 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.51 g, 22.0 mmol) in ethanol (30 mL)] and 3-methylbenzyl bromide (3.70 g, 2.7 mL, 20.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give benzyl 3-methylbenzyl sulfide **[40]** as a clear oil (4.27 g, 85%); ^{1}H NMR δ_H (300 MHz) 2.34 (3H, s, Ar-CH_3), 3.57 (2H, s, SCH_2), 3.61 (2H, s, SCH_2), 7.00–7.13 (3H, m, Ar-H), 7.15–7.37 (6H, m, Ar-H); IR (film) ν_{max}/cm^{-1} = 3028, 1608, 1493, 1453, 716, 702.

Benzyl 4-methylbenzyl sulfide [41][50]



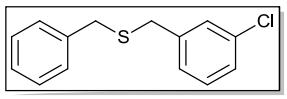
Benzyl mercaptan (2.73 g, 2.58 mL, 22.0 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.51 g, 22.0 mmol) in ethanol (30 mL)] and 4-methylbenzyl bromide (3.70 g, 20.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give benzyl 4-methylbenzyl sulfide **[41]** as a white solid (4.02 g, 80%); m.p. 29–30 °C, (Lit.[50] m.p. 29–31 °C); ^{1}H NMR δ_H (300 MHz) 2.33 (3H, s, Ar-CH_3), 3.56 (2H, s, SCH_2), 3.59 (2H, s, SCH_2), 7.07–7.36 (5H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} = 2917, 1616, 1511, 1454, 697.

Benzyl 2-chlorobenzyl sulfide [42]



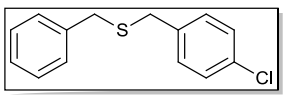
Benzyl mercaptan (2.73 g, 2.58 mL, 22.0 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.51 g, 22.0 mmol) in ethanol (30 mL)] and 2-chlorobenzyl bromide (4.11 g, 2.60 mL, 20.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give benzyl 2-chlorobenzyl sulfide **[42]** as a clear oil (4.76 g, 87%); ^{1}H NMR δ_H (300 MHz) 3.69 (2H, s, SCH_2), 3.74 (2H, s, SCH_2), 7.12–7.40 (9H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 33.4 (SCH_2), 36.2 (SCH_2), 126.7 (CH_{Ar}), 127.1 (CH_{Ar}), 128.4 (CH_{Ar}), 128.5 (CH_{Ar}), 129.0 (CH_{Ar}), 129.8 (CH_{Ar}), 130.7 (CH_{Ar}), 134.2 ($C_{Ar(q)}$), 135.9 ($C_{Ar(q)}$), 137.9 ($C_{Ar(q)}$); IR (film) ν_{max}/cm^{-1} = 3028, 1494, 1472, 1453, 1444, 1052, 739, 698; (Found: C, 67.50; H, 5.47. $C_{14}H_{13}ClS$ Requires C, 67.59; H, 5.27).

Benzyl 3-chlorobenzyl sulfide [43][50]



Benzyl mercaptan (2.73 g, 2.58 mL, 22.0 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.51 g, 22.0 mmol) in ethanol (30 mL)] and 3-chlorobenzyl bromide (4.11 g, 2.63 mL, 20.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give benzyl 3-chlorobenzyl sulfide **[43]** as a clear oil (4.27 g, 78%); ^{1}H NMR δ_H (300 MHz) 3.55 (2H, s, SCH_2), 3.60 (2H, s, SCH_2), 7.10–7.38 (9H, m, Ar-H); IR (film) ν_{max}/cm^{-1} = 3028, 1598, 1494, 1475, 1453, 1431, 1076, 724, 702.

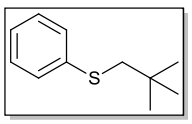
Benzyl 4-chlorobenzyl sulfide [44][50]



Benzyl mercaptan (2.73 g, 2.58 mL, 22.0 mmol), sodium ethoxide [freshly made *in situ* from sodium (0.51 g, 22.0 mmol) in ethanol (30 mL)] and 4-chlorobenzyl bromide (4.11 g, 20.0 mmol) were used as described for **[23]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give benzyl 4-chlorobenzyl sulfide **[44]** as a clear oil (4.43 g, 81%); ^{1}H NMR δ_H (300 MHz) 3.55 (2H, s, SCH_2), 3.60 (2H, s, SCH_2), 7.13–7.38 (9H, m, Ar-H); IR (film) ν_{max}/cm^{-1} = 3028, 1490, 1453, 1092, 1015, 705.

Method C

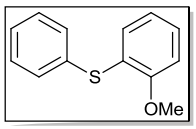
Neopentyl phenyl sulfide [46][51]



1-Bromo-2,2-dimethylpropane (3.02 g, 20 mmol), aqueous benzenethiolate (20 mmol) [prepared by the addition of thiophenol (2.22 g, 2.07 mL, 20 mmol) to an ice-cold solution of sodium hydroxide (1 g in 15 mL water)] and Aliquat-336 (0.033 mol equiv.) were added to a 2-neck round bottomed flask under nitrogen. The mixture was heated at 70 °C with vigorous stirring for 16 h. After the mixture had cooled to RT, the organic layer was separated and the aqueous phase was extracted with two 20 mL portions of diethyl ether. The combined organic phases were washed with 20 mL of 10% aqueous sodium chloride and dried over magnesium sulfate. After removal of the solvent the resulting residual oil was distilled using a Kugelröhr apparatus to give neopentyl phenyl sulfide **[46]** as a clear oil (1.33 g, 37%); bp 145–147 °C (0.1 mm Hg); ^{1}H NMR δ_H (300 MHz) 1.04 [9H, s, C(C*H*$_3$)$_3$], 2.90 (2H, s, SCH$_2$), 7.10–7.18 (1H, m, Ar-H), 7.21–7.30 (2H, m, Ar-H), 7.32-7.38 (2H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 29.1 [C(*C*H$_3$)$_3$], 32.5[*C*(CH$_3$)$_3$], 48.6 (SCH$_2$), 125.5 (CH$_{Ar}$), 128.8 (CH$_{Ar}$), 128.9 (CH$_{Ar}$), 138.5 (C$_{Ar(q)}$); IR (film) ν_{max}/cm^{-1} 2958, 2907, 1584, 1480, 1438, 1026, 736, 690.

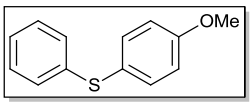
Method D

2-Methoxyphenyl phenyl sulfide [47][52,53]



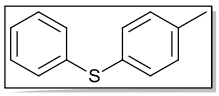
Cu_2O (0.286 g, 2 mmol) and KOH (2.24 g, 40 mmol) were added to a 250 mL round bottom flask under N_2. Iodobenzene (4.48 mL, 8.16 g, 40 mmol), 2-methoxybenzenethiol (5.44 mL, 6.27 g, 44 mmol) and solvent (40 mL DMSO, 10 mL H_2O) were added and the flask was placed in an oil bath and warmed at 80 °C, with stirring under N_2 for 24 h. The resulting suspension was cooled to RT and filtered with the addition of ethyl acetate (30 mL). The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (100% hexane) to give 2-methoxyphenyl phenyl sulfide **[47]** as a clear oil (6.14 g, 71%); ^{1}H NMR δ_H (400 MHz) 3.87 (2H, s, SCH$_2$), 3.60 (2H, s, SCH$_2$), 6.82–6.94 (2H, m, Ar-H), 7.07–7.15 (2H, m, Ar-H), 7.20–7.39 (4H, m, Ar-H), 7.69–7.73 (1H, m, Ar-H); IR (film) ν_{max}/cm^{-1} = 3062, 1453, 1432, 1036, 744, 697.

4-Methoxyphenyl phenyl sulfide [48][52,53]



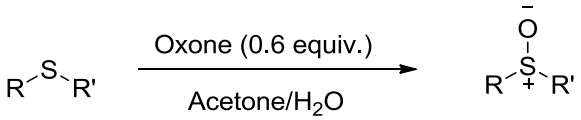
Cu_2O (0.286 g, 2 mmol), KOH (2.24 g, 40 mmol), iodobenzene (5.00 mL, 8.72 g, 40 mmol), 4-methoxybenzenethiol (5.50 mL, 6.27 g, 44 mmol) and solvent (40 mL DMSO, 10 mL H_2O) were used as described for **[47]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give 4-methoxyphenyl phenyl sulfide **[48]** as a white solid (6.49 g, 75%); m.p. 29–30 °C, (Lit.[172] m.p. 30–30.5 °C); ^{1}H NMR δ_H (300 MHz) 3.81 (3H, s, Ar-OCH_3), 6.84–6.93 (2H, m, Ar-H), 7.09–7.28 (5H, m, Ar-H), 7.37–7.45 (2H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2835, 1592, 1493, 1478, 1439, 1246, 1031, 739, 689.

4-Methylphenyl phenyl sulfide [49][52,53]



Cu_2O (0.286 g, 2 mmol), KOH (2.24 g, 40 mmol), iodobenzene (4.48 mL, 8.16 g, 40 mmol), 4-methylbenzenethiol (5.46 g, 44 mmol) and solvent (40 mL DMSO, 10 mL H_2O) were used as described for **[47]** to give the crude sulfide which was purified by column chromatography (100% hexane) to give 4-methylphenyl phenyl sulfide **[49]** as a clear oil (5.84 g, 73%); ^{1}H NMR δ_H (300 MHz) 2.34 (3H, s, Ar-CH_3), 7.05–7.35 (9H, m, Ar-H); IR (film) ν_{max}/cm^{-1} 3058, 1582, 1491, 1477, 1439, 1083, 737, 690.

3.3 Preparation of Racemic Sulfoxides



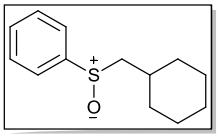
General Procedure

Oxone®[54] (370 mg, 0.6 equiv.) in water (10 mL) was added dropwise to a stirred solution of the sulfide (1 mmol) in acetone (10 mL), over a 15 minute period, at 0 °C (ice-bath). The reaction mixture was stirred at 0 °C for 1.5 h, while being monitored by TLC (6:4 hexane: ethyl acetate). The solution was concentrated under reduced pressure, after which CH_2Cl_2 (10 mL) was added to the residue. The layers were separated, and the organic layer was washed with water (3 × 10 mL). The aqueous layers were washed with CH_2Cl_2 (10 mL), and the

combined organic layers were washed with brine (15 mL), dried, filtered and concentrated under reduced pressure to give the crude product. This was purified by column chromatography on silica gel to yield the pure sulfoxide. In all cases, spectroscopic data were in agreement with data for the enantioenriched samples.

3.4 Preparation of Enantioenriched Sulfoxides

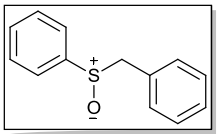
(*R*)-(+)-Cyclohexylmethyl phenyl sulfoxide [56][37] (**Table 3.2, entry 2**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a round bottomed flask containing Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and toluene (1 mL). The resulting solution was stirred at RT for 5 min, and then a solution of sulfide **[23]** (206 mg, 1 mmol) in toluene (1 mL) was added. Stirring was continued for 5 min, at RT, then aqueous H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution. The reaction mixture was stirred at RT for a further 16 h. Water (10 mL) and CH_2Cl_2 (10 mL) were added to the reaction mixture and the phases were separated. The organic layer was washed with water (3 × 10 mL) and brine (10 mL), dried and concentrated under reduced pressure to give the crude product as a yellow solid. The crude product contained a mixture of sulfide and sulfoxide (70:30). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane: ethyl acetate) to yield (*R*)-(+)-cyclohexylmethyl phenyl sulfoxide **[56]** as a white solid (42 mg, 19%, 57% ee); ^{1}H NMR δ_H (300 MHz) 1.01–1.41 (5H, m, cyclohexyl protons), 1.60–1.83 (4H, m, cyclohexyl protons), 1.89–2.08 (1H, m, cyclohexyl protons), 2.09–2.17 (1H, m, cyclohexyl protons), 2.45–2.52 (1H, A of ABX system, *J* 12.9 Hz and 9.0 Hz, SCH_2), 2.76–2.82 (1H, B of ABX system, *J* 12.9 Hz and 4.8 Hz, SCH_2), 7.42–7.72 (5H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2920, 1443, 1034, 752; HPLC: t_R (*R*) = 17.3 min, t_R (*S*) = 20.3 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 47.8° (*c* 1.0, $CHCl_3$).

Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

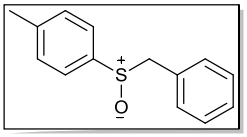
(*R*)-(+)-Benzyl phenyl sulfoxide [50][26,56] (**Table 3.8, entry 1**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and benzyl phenyl sulfide (200 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (1:98:1). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-benzyl phenyl sulfoxide **[50]** as a white solid (194 mg, 90%, 79% ee); m.p. 125–126 °C (Lit.[27] m.p. 121–122 °C, racemic); ^{1}H NMR δ_H (300 MHz) 4.00 (1H, A of AB system, *J* 12.5 Hz, $SOCH_2$), 4.10 (1H, B of AB system, *J* 12.5 Hz, $SOCH_2$), 6.90–7.04 (2H, m, Ar-H), 7.19–7.32 (3H, m, Ar-H), 7.33–7.52 (5H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} = 2961, 1455, 1442, 1084, 1033, 746; HPLC: t_R (*R*) = 17.1 min, t_R (*S*) = 21.3 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 146.5° (*c* 1.0, acetone) {ref.[56] $[\alpha]_D^{20}$ = − 169.8° (*c* 1.0, acetone) for (*S*) = 79% ee}.

Absolute configuration was determined by comparison of specific rotation value to known literature value.

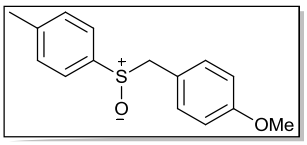
(*R*)-(+)-Benzyl *p*-tolyl sulfoxide [51][26,57] (**Table 3.8, entry 3**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[7]** (214 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (2:97:1). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-benzyl *p*-tolyl sulfoxide **[51]** as a white solid (210 mg, 91%, 81% ee); ^{1}H NMR δ_H (300 MHz) 2.40 (3H, s, $ArCH_3$), 3.97 (1H, A of AB system, *J* 12.6 Hz, $SOCH_2$), 4.09 (1H, B of AB system, *J* 12.6 Hz, $SOCH_2$), 7.00 (2H, dd, *J* 7.5 Hz and 1.5 Hz, Ar-H), 7.17–7.37 (7H, m, Ar-H); m/z (ESI) [$(M+H)^+$] 231 (4%), 183 (8), 182 (40), 141 (100), 100 (30), 59 (6), 46 (8); HRMS (ESI): Exact mass calculated for $C_{14}H_{15}SO$ [$(M+H)^+$] 231.0844, Found 231.0839; IR (KBr) ν_{max}/cm^{-1} 2912, 1494, 1456, 1083, 1014, 768; HPLC: t_R (*R*) = 16.3 min, t_R (*S*) = 19.9 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 106.0° (*c* 1.0, acetone), {ref.[72] $[\alpha]_D^{20}$ = − 254.0° (*c* 0.7, acetone) for (*S*) > 99% ee}.

Absolute configuration was determined by comparison of specific rotation value to known literature value.

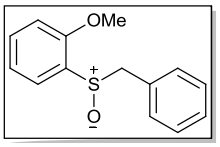
(*R*)-(+)-4-Methoxybenzyl 4'-methylphenyl sulfoxide [52][26,58] (**Table 3.8, entry 5**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[4]** (244 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (2:97:1). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-4-methoxybenzyl 4'-methylphenyl sulfoxide **[52]** as a white solid (234 mg, 90%, 47% ee); m.p. 123–124 °C; ^{1}H NMR δ_H (300 MHz) 2.40 (3H, s, $ArCH_3$), 3.79 (3H, s, OCH_3), 3.93 (1H, A of AB system, *J* 12.6 Hz, $SOCH_2$), 4.03 (1H, B of AB system, *J* 12.6 Hz, $SOCH_2$), 6.75–6.81 (2H, m, Ar-H), 6.87–6.94 (2H, m, Ar-H), 7.19–7.32 (4H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 21.5 ($ArCH_3$), 55.3 (OCH_3), 63.0 ($SOCH_2$), 113.9 (CH_{Ar}), 121.2 ($C_{Ar(q)}$), 124.5 (CH_{Ar}), 129.6 (CH_{Ar}), 131.6 (CH_{Ar}), 139.6 ($C_{Ar(q)}$), 141.5 ($C_{Ar(q)}$), 159.6 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2961, 1610, 1514, 1036, 809; m/z (ESI) [$(M+H)^+$] 261 (8%), 183 (3), 182 (50), 141 (14), 100 (70), 60 (4), 59 (100); HRMS (ESI): Exact mass calculated for $C_{15}H_{17}SO_2$ [$(M+H)^+$] 261.0949, Found 261.0947; HPLC: t_R (*R*) = 12.7 min, t_R (*S*) = 15.9 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 37.9° (*c* 1.0, $CHCl_3$), {ref.[58] $[\alpha]_D^{20}$ = − 87° (*c* 0.2, $CHCl_3$) for (*S*) > 99% ee}.

Absolute configuration was determined by comparison of specific rotation value to known literature value.

(*R*)-(+)-Benzyl 2-methoxyphenyl sulfoxide [53][26,25] (**Table 3.8, entry 6**)

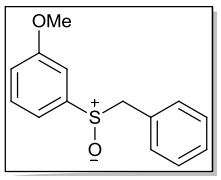


Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[3]** (230 mg, 1 mmol) in hexane/methanol (9:1, 5 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide and sulfoxide (8:92:trace). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-benzyl 2-methoxyphenyl sulfoxide **[53]** as a white

solid (209 mg, 85%, 29% ee); m.p. 31–33 °C; ^{1}H NMR δ_H (300 MHz) 3.87 (3H, s, OCH_3), 3.98 (1H, A of AB system, *J* 12.0 Hz, $SOCH_2$), 4.24 (1H, B of AB system, *J* 12.0 Hz, $SOCH_2$), 6.90 (1H, d, J 7.8 Hz, Ar-H), 6.99–7.11 (3H, m, Ar-H), 7.17–7.30 (3H, m, Ar-H), 7.36-7.49 (2H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 55.8 (OCH_3), 59.7 ($SOCH_2$), 110.3 (CH_{Ar}), 121.5 (CH_{Ar}), 125.8 (CH_{Ar}), 127.9 (CH_{Ar}), 128.2 (CH_{Ar}), 130.2 ($C_{Ar(q)}$), 130.3 (CH_{Ar}), 130.4 ($C_{Ar(q)}$), 132.0 (CH_{Ar}), 155.1 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2959, 1596, 1496, 1086, 1032, 697; m/z (ESI) [$(M+H)^+$] 247 (6%), 207 (8), 142 (6), 141 (100) 100 (10), 87 (4), 59 (20), 46 (4); HRMS (ESI): Exact mass calculated for $C_{14}H_{15}SO_2$ [$(M+H)^+$] 247.0793, Found 247.0783; HPLC: t_R (*R*) = 16.2 min, t_R (*S*) = 18.6 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 60.3° (*c* 1.0, acetone), {ref.[25] $[\alpha]_D^{20}$ = + 351° (*c* 0.32, $CHCl_3$) for (*R*) = 81% ee}.

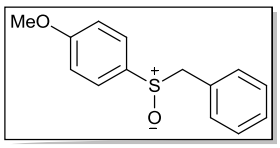
Absolute configuration was determined by comparison of specific rotation value to known literature value.

(*R*)-(+)-Benzyl 3-methoxyphenyl sulfoxide [54][25,26] (**Table 3.8, entry 7**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[2]** (230 mg, 1 mmol) in hexane/methanol (9:1, 5 mL) were used as described for **[56]** to give the crude product as a yellow oil. The crude product contained a mixture of sulfide and sulfoxide (46:54). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-benzyl 3-methoxyphenyl sulfoxide **[54]** as a clear oil (116 mg, 47%, 21% ee); ^{1}H NMR δ_H (300 MHz) 3.72 (3H, s, OCH_3), 4.00 (1H, A of AB system, *J* 12.5 Hz, $SOCH_2$), 4.07 (1H, B of AB system, *J* 12.5 Hz, $SOCH_2$) 6.87–7.03 (5H, m, Ar-H), 7.20–7.37 (4H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 55.5 (OCH_3), 63.5 ($SOCH_2$), 108.4 (CH_{Ar}), 116.5 (CH_{Ar}), 118.1 (CH_{Ar}), 128.3 (CH_{Ar}), 128.5 (CH_{Ar}), 129.1 ($C_{Ar(q)}$), 129.8 (CH_{Ar}), 130.4 (CH_{Ar}), 144.0 ($C_{Ar(q)}$), 160.1 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2907, 1594, 1481, 1248, 1031, 697; m/z (ESI) [$(M+H)^+$] 247 (2%), 87 (6), 59 (100); HRMS (ESI): Exact mass calculated for $C_{14}H_{15}SO_2$ [$(M+H)^+$] 247.0793, Found 247.0789; HPLC: t_R (*R*) = 12.2 min, t_R (*S*) = 14.0 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 68.5° (*c* 1.0, acetone), {ref.[25] $[\alpha]_D^{20}$ = + 73.5° (*c* 0.17, acetone) for (*R*) = 69% ee}. Absolute configuration was determined by comparison of specific rotation value to known literature value.

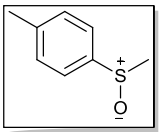
(*R*)-(+)-Benzyl 4-methoxyphenyl sulfoxide [55][25,76] (**Table 3.1, entry 2**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[156]** (15.2 mg, 4.0 mol%), and sulfide **[1]** (230 mg, 1 mmol) in toluene (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide and sulfoxide (54:46). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-benzyl 4-methoxyphenyl sulfoxide **[55]** as a white solid (81 mg, 33%, 54% ee); ^{1}H NMR δ_H (300 MHz) 3.84 (3H, s, OCH_3), 3.95 (1H, A of AB system, *J* 12.0, $SOCH_2$), 4.11 (1H, B of AB system, *J* 12.0, $SOCH_2$), 6.89–7.02 (4H, m, Ar-H), 7.20-7.33 (5H, m, Ar-H), ^{13}C NMR δ_C (75.5 MHz) 55.5 (OCH_3), 63.8 ($SOCH_2$), 114.4 (CH_{Ar}), 126.4 (CH_{Ar}), 128.2 (CH_{Ar}), 128.5 (CH_{Ar}), 129.3 ($C_{Ar(q)}$) 130.4 (CH_{Ar}), 133.6 ($C_{Ar(q)}$), 162.0 ($C_{Ar(q)}$); HPLC: t_R (*R*) = 15.5 min, t_R (*S*) = 18.4 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 48.2° (*c* 1.0, acetone), {ref.[25] $[\alpha]_D^{20}$ = + 31.9° (*c* 0.28, acetone) for (*R*) = 44% ee}.

Absolute configuration was determined by comparison of specific rotation value to known literature value.

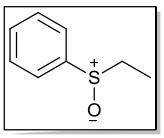
(*R*)-(+)-Methyl *p*-tolyl sulfoxide [57][59] (**Table 3.8, entry 8**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and methyl *p*-tolyl sulfide (138 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow oil. The crude product contained a mixture of sulfide, sulfoxide and sulfone (4:96:trace). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-methyl *p*-tolyl sulfoxide **[57]** as a clear oil (139 mg, 90%, 23% ee); ^{1}H NMR δ_H (400 MHz) 2.42 (3H, s, $ArCH_3$), 2.71 (3H, s, $SOCH_3$), 7.34 (2H, d, *J* 8.4 Hz, Ar-H), 7.54 (2H, d, *J* 8.4 Hz, Ar-H); m/z (ESI) [$(M+H)^+$] 155 (8%), 141 (80), 105 (2), 100 (28); HRMS (ESI): Exact mass calculated for $C_8H_{11}OS$ [$(M+H)^+$] 155.0531, Found 155.0526; HPLC: t_R (*R*) = 20.1 min, t_R (*S*) = 23.8 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (95:5); 20 °C]; $[\alpha]_D^{20}$ = + 43.6° (*c* 1.0, acetone) {ref.[59] $[\alpha]_D^{20}$ = + 150.4° (*c* 1.17, acetone) for (*R*) > 99% ee}.

Absolute configuration was determined by comparison of specific rotation value to known literature value.

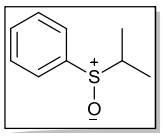
(*R*)-(+)-Ethyl phenyl sulfoxide [58][60] (**Table 3.8, entry 9**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and ethyl phenyl sulfide (138 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow oil. The crude product contained a mixture of sulfide, sulfoxide and sulfone (2:98:trace). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-ethyl phenyl sulfoxide **[58]** as a clear oil (142 mg, 92%, 44% ee); ^{1}H NMR δ_H (400 MHz) 1.20 (3H, t, *J* 3.5 Hz), 2.70–3.00 (2H, m, $SOCH_2$), 7.46–7.57 (3H, m, Ar-H), 7.58–7.66 (2H, m, Ar-H); IR (film) ν_{max}/cm^{-1} 2935, 1479, 1444, 1087, 1021, 749; m/z (ESI) [$(M+H)^+$] 155 (20%), 100 (24); HRMS (ESI): Exact mass calculated for $C_8H_{11}OS$ [$(M+H)^+$] 155.0531, Found 155.0532; HPLC: t_R (*R*) = 8.1 min, t_R (*S*) = 9.8 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 40 °C]; = + 96.1° (*c* 1.0, acetone) {ref.[60] $[\alpha]_D^{20}$ = + 185.6° (*c* 0.71, acetone) for (*R*) > 99% ee}.

Absolute configuration was determined by comparison of specific rotation value to known literature value.

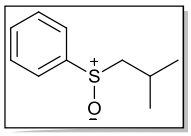
(*R*)-(+)-Isopropyl phenyl sulfoxide [59][61] (**Table 3.8, entry 10**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[25]** (152 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow oil. The crude product contained a mixture of sulfide, sulfoxide and sulfone (19:81:trace). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-isopropyl phenyl sulfoxide **[59]** as a clear oil (125 mg, 74%, 60% ee); ^{1}H NMR δ_H (400 MHz) 1.15 [3H, d, *J* 6.6 Hz, one of $CH(CH_3)_2$], 1.23 [3H, d, *J* 6.6 Hz, one of $CH(CH_3)_2$], 2.75–2.91 (1H, m, SOCH), 7.44–7.62 (5H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 14.0 [$CH(CH_3)_2$, one of CH_3], 15.9 [$CH(CH_3)_2$, one of CH_3], 54.6 (SOCH), 125.0 (CH_{Ar}), 128.9 (CH_{Ar}), 131.0 (CH_{Ar}), 141.7 ($C_{Ar(q)}$); IR (film) ν_{max}/cm^{-1} 2970, 1464, 1444, 1088, 1023; HPLC: t_R (*R*) = 6.6 min, t_R (*S*) = 7.5 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 112.8° (*c* 1.0, $CHCl_3$).

Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

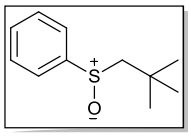
(*R*)-(+)-Isobutyl phenyl sulfoxide [60][62] (**Table 3.8, entry 11**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[24]** (166 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow oil. The crude product contained a mixture of sulfide, sulfoxide and sulfone (10:90:trace). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-isobutyl phenyl sulfoxide **[60]** as a clear oil (149 mg, 82%, 48% ee); ^{1}H NMR δ_H (400 MHz) 1.07 (3H, d, *J* 6.6 Hz, one of CH_3), 1.17 (3H, d, *J* 6.6 Hz, one of CH_3), 2.14–2.33 [1H, m, C*H*$(CH_3)_2$)], 2.45 (1H, A of ABX system, *J* 12.0 Hz and 4.8 Hz, $SOCH_2$), 2.82 (1H, B of ABX system, *J* 12.0 Hz and 4.8 Hz, $SOCH_2$), 7.43–7.58 (3H, m, Ar-H), 7.59–7.69 (2H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 21.7 [CH(*C*$H_3)_2$, one of CH_3], 22.8 [CH(*C*$H_3)_2$, one of CH_3], 24.2 [*C*H$(CH_3)_2$, CH], 67.6 ($SOCH_2$), 123.9 (CH_{Ar}), 129.3 (CH_{Ar}), 130.9 (CH_{Ar}), 144.7 ($C_{Ar(q)}$); m/z (ESI) 142 (14%), 141 (100); HRMS (ESI): Exact mass calculated for $C_{10}H_{15}SO$ [$(M+H)^+$] 183.0844, Found 183.0850; IR (film) ν_{max}/cm^{-1} 2960, 1465, 1444, 1090, 1038, 750; HPLC: t_R (*R*) = 5.9 min, t_R (*S*) = 6.7 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 129.0° (*c* 1.0, $CHCl_3$).

Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

(*R*)-(+)-Neopentyl phenyl sulfoxide [61] (**Table 3.8, entry 12**)

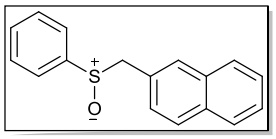


Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[46]** (166 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide and sulfoxide (15:85). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-neopentyl phenyl sulfoxide **[61]** as a clear oil (155 mg ,79%, 71% ee); ^{1}H NMR δ_H (300 MHz) 1.21 [9H, s C(C*H*$_3)_3$], 2.54 (1H, A of AB system, *J* 13.5 Hz, $SOCH_2$), 2.81 (1H, B of AB system, *J* 13.8 Hz, $SOCH_2$), 7.43–7.56 (3H, m, Ar-H), 7.59–7.66 (2H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 29.8 [(C(*C*$H_3)_3$)], 32.0 [(*C*$(CH_3)_3$], 73.9 ($SOCH_2$) 123.8 (CH_{Ar}), 129.2 (CH_{Ar}), 130.7 (CH_{Ar}), 145.6 ($C_{Ar(q)}$); (Found C, 67.10; H, 8.37; S, 16.29; $C_{11}H_{16}OS$ requires C, 67.30; H, 8.22; S 16.33); IR (KBr) ν_{max}/cm^{-1} 2958, 1474,

1448, 1084, 1045, 709; HPLC: t_R (*R*) = 6.6 min, t_R (*S*) = 7.6 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 87.9° (*c* 1.0, $CHCl_3$).

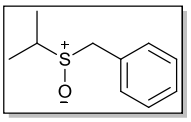
Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

(*R*)-(+)-2-Naphthylmethyl phenyl sulfoxide [62] (**Table 3.2, entry 12**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[26]** (250 mg, 1 mmol) in toluene (2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide and sulfoxide (73:27). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-2-naphthylmethyl phenyl sulfoxide **[62]** as a white solid (61 mg, 23%, 93% ee). m.p. 85–87 °C; ^{1}H NMR δ_H (400 MHz) 4.15 (1H, A of AB system, *J* 12.4 Hz, $SOCH_2$), 4.26 (1H, B of AB system, *J* 12.4 Hz, $SOCH_2$), 7.08 (1H, dd, *J* 8.6 Hz and 1.6 Hz, Ar-H), 7.31–7.53 (8H, m, Ar-H), 7.66–7.85 (3H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 64.0 ($SOCH_2$), 124.5 (CH_{Ar}), 126.3 (CH_{Ar}), 126.4 (CH_{Ar}), 126.7 ($C_{Ar(q)}$), 127.7 (CH_{Ar}), 127.75 (CH_{Ar}), 127.9 (CH_{Ar}), 128.1 (CH_{Ar}), 128.9 (CH_{Ar}), 129.8 (CH_{Ar}), 131.2 (CH_{Ar}), 132.9 ($C_{Ar(q)}$), 133.1 ($C_{Ar(q)}$), 142.9 ($C_{Ar(q)}$); (Found C, 76.43; H, 5.58; S, 12.10; $C_{17}H_{14}OS$ requires C, 76.66; H, 5.30; S, 12.04); HPLC: t_R (*R*) = 32.1 min, t_R (*S*) = 40.6 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = +75.4° (*c* 1.0, $CHCl_3$). Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

(−)-Isopropyl benzyl sulfoxide [63][63] (**Table 3.9, entry 1**)

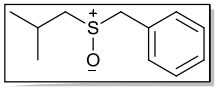


Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[35]** (166 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow oil. The crude product contained a mixture of sulfoxide and sulfone (97:3). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (−)-isopropyl benzyl sulfoxide **[63]** as a clear oil (157 mg, 86%, 27% ee); ^{1}H NMR δ_H (300 MHz) 1.29 [3H, d, *J* 7.2 Hz, $CH(CH_3)_2$], 1.33 [3H, d, *J* 6.6 Hz, $CH(CH_3)_2$], 2.59–2.76

[1H, m, C*H*(CH_3)$_2$)], 3.91 (2H, s, $SOCH_2$), 7.22–7.43 (5H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 13.8 [CH(*C*H_3)$_2$, one of CH_3], 16.7 [CH(*C*H_3)$_2$, one of CH_3], 48.2 [*C*H(CH_3)$_2$], 54.9 ($SOCH_2$), 128.2 (CH_{Ar}), 129.0 (CH_{Ar}), 129.9 (CH_{Ar}), 130.5 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2968, 1497, 1455, 1051, 1020, 700; HPLC: t_R (+) = 36.4 min, t_R (−) = 63.6 min [Chiracel AS-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = − 11.1° (*c* 1.27, $CHCl_3$).

Absolute configuration was not determined.

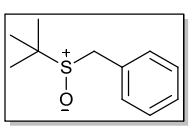
(*R*)-(+)-Isobutyl benzyl sulfoxide [64][64] (**Table 3.9, entry 4**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[37]** (180 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (4:94:2). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-isobutyl benzyl sulfoxide **[64]** as a white solid (171 mg, 87%, 11% ee); m.p. 66–68 °C; ^{1}H NMR δ_H (300 MHz) 1.04 [6H, 2 overlapping d, *J* 6.6 Hz and *J* 6.6 Hz, CH(C*H*$_3$)$_2$], 2.09–2.27 [1H, m, C of ABC system, C*H*(CH_3)$_2$)], 2.33 (1H, A of ABC system, *J* 12.6 Hz and 9.3 Hz, $SOCH_2$), 2.57 (1H, B of ABC system, *J* 12.6 Hz and 4.8 Hz, $SOCH_2$), 3.92 (1H, A of AB system, *J* 12.9 Hz, $SOCH_2$), 4.03 (1H, B of AB system, *J* 12.9 Hz, $SOCH_2$), 7.22–7.43 (5H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 21.6 [CH(*C*H_3)$_2$, one of CH_3], 22.9 [CH(*C*H_3)$_2$, one of CH_3], 23.8 [*C*H(CH_3)$_2$], 59.0 ($SOCH_2$), 60.6 ($SOCH_2$), 128.3 (CH_{Ar}), 128.9 (CH_{Ar}), 130.0 (CH_{Ar}), One C(q) not seen; IR (KBr) ν_{max}/cm^{-1} 2960, 1455, 1076, 1028, 699; HPLC: t_R (*S*) = 43.1 min, t_R (*R*) = 47.7 min [Chiracel AS-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 15.9° (*c* 1.0, $CHCl_3$), {ref[64] $[\alpha]_D^{20}$ = − 110° (*c* 0.9, $CHCl_3$) for (*S*) > 99% ee}. Peak broadening is evident in the ^{1}H NMR spectrum of the crude product at δ 2.33, 2.09–2.27, and 3.69 ppm.

Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

(*R*)-(−)-*tert*-Butyl benzyl sulfoxide [65][65,66] (**Table 3.9, entry 7**)

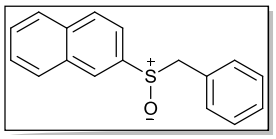


Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[38]** (180 mg, 1 mmol) in

hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (2:97:1). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(−)-*tert*-butyl benzyl sulfoxide **[65]** as a white solid (173 mg, 88%, 37% ee); m.p. 73–75 °C, (Lit.[65] m.p. 74–75 °C, racemic); ^{1}H NMR δ_H (300 MHz) 1.32 [9H, s, C(C*H*$_3$)$_3$], 3.63 (1H, A of AB system, *J* 12.9 Hz, SOC*H*$_2$), 3.83 (1H, B of AB system, *J* 12.9 Hz, SOC*H*$_2$), 7.28–7.41 (5H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 23.1 [(C(*C*H$_3$)$_3$)], 53.0 (SOC*H*$_2$), 53.7 [(*C*(CH$_3$)$_3$], 128.0 (CH$_{Ar}$), 128.9 (CH$_{Ar}$), 130.0 (CH$_{Ar}$), 132.1 (C$_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2962, 1456, 1366, 1034, 700; HPLC: t_R (*R*) = 14.3 min, t_R (*S*) = 19.0 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = − 83.6° (*c* 0.92, CHCl$_3$), $[\alpha]_D^{20}$ = − 48.6° (*c* 1.01, ethanol); {$[\alpha]_D^{20}$ = + 140° (*c* 1.1, EtOH) for (*S*) > 99% ee}[138,66].

Absolute configuration was determined by comparison of specific rotation value to known literature value.

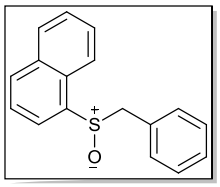
(*R*)-(+)-2-Naphthyl benzyl sulfoxide [66][67] (Table 3.9, entry 10)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[29]** (250 mg, 1 mmol) in toluene/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide and sulfoxide (62:38). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-2-naphthyl benzyl sulfoxide **[66]** as a white solid (85 mg, 32%, 97% ee); m.p. 155–157 °C; A racemic sample was prepared with m.p. 186–187 °C, (Lit.[67] m.p. 189–190 °C, racemic); ^{1}H NMR δ_H (300 MHz) 4.08 (1H, A of AB system, *J* 12.6 Hz, SOC*H*$_2$), 4.16 (1H, B of AB system, *J* 12.6 Hz, SOC*H*$_2$), 6.90–7.07 (2H, m, Ar-H), 7.12–7.34 (3H, m, Ar-H), 7.36–7.47 (1H, m, Ar-H), 7.49–7.62 (2H, m, Ar-H), 7.74–7.99 (4H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 63.4 (SOC*H*$_2$), 120.2 (CH$_{Ar}$), 125.3 (CH$_{Ar}$), 127.2 (CH$_{Ar}$), 127.8 (CH$_{Ar}$), 128.0 (CH$_{Ar}$), 128.3 (CH$_{Ar}$), 128.5 (CH$_{Ar}$), 129.0 (CH$_{Ar}$), 129.2 (C$_{Ar(q)}$), 130.4 (CH$_{Ar}$), 132.7 (C$_{Ar(q)}$), 134.5 (C$_{Ar(q)}$), 139.9 (C$_{Ar(q)}$), 9 CH$_{Ar}$ signals seen for 10 CH$_{Ar}$; IR (KBr) ν_{max}/cm^{-1} 2955, 1452, 1076, 1039, 695; HPLC: t_R (*R*) = 27.0 min, t_R (*S*) = 38.1 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 63.7° (*c* 1.02, CHCl$_3$); The absolute stereochemistry was determined by single crystal X-ray

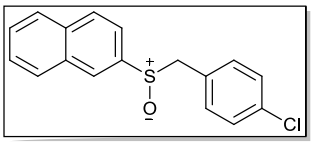
diffraction on a crystalline sample of 2-naphthyl benzyl sulfoxide recrystallised from CH_2Cl_2;[127] Crystal data: $C_{17}H_{14}OS$, M = 266.34, triclinic, space group *P1*, a = 5.7020(9), b = 8.4251(13), c = 14.510(2) Å, V = 675.96(18) Å^3, Z = 2, D_c = 1.309 g cm^{-3}, F_{000} = 280, Mo Kα radiation, λ = 0.7107 Å, T = 296(2) K, $2\theta_{max}$ = 25.78°, μ = 0.227 mm^{-1}. 13658 reflections collected, 4784 unique (R_{int} = 0.0 68). Final GooF = 0.90, R_1 = 0.043, [3208 obs. data: $I > 2\sigma(I)$]; wR_2 = 0.094 (all data). CCDC 891525.

(*R*)-(+)-1-Naphthyl benzyl sulfoxide [67] (**Table 3.9, entry 12**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[30]** (250 mg, 1 mmol) in toluene/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide and sulfoxide (48:52). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-1-naphthyl benzyl sulfoxide **[67]** as a white solid (123 mg, 46%, 75% ee); m.p. 104–106 °C; ^{1}H NMR δ_H (300 MHz) 4.06 (1H, A of AB system, J 12.6 Hz, $SOCH_2$), 4.26 (1H, B of AB system, J 12.6 Hz, $SOCH_2$), 6.81–6.97 (2H, m, Ar-H), 7.10–7.32 (3H, m, Ar-H), 7.43–7.62 (3H, m, Ar-H), 7.77 (1H, dd, J 8.6 Hz and 1.6 Hz, Ar-H), 7.84–8.01 (3H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 61.7 ($SOCH_2$), 121.5 (CH_{Ar}), 123.8 (CH_{Ar}), 125.4 (CH_{Ar}), 126.5 (CH_{Ar}), 127.2 (CH_{Ar}), 128.2 (CH_{Ar}), 128.3 (CH_{Ar}), 129.0 (CH_{Ar}), 129.2 ($C_{Ar(q)}$), 129.5 ($C_{Ar(q)}$), 130.3 (CH_{Ar}), 131.2 (CH_{Ar}), 133.2 ($C_{Ar(q)}$), 138.6 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 3058, 1506, 1454, 1049, 770, 698; m/z (ESI) [(M+H)$^+$] 267 (44%), 91 (4), 64 (100), 60 (10), 46 (10); HRMS (ESI): Exact mass calculated for $C_{17}H_{15}OS$ [(M+H)$^+$] 267.0844, Found 267.0838; (Found: C, 76.38; H, 5.24. $C_7H_{14}OS$ Requires C, 76.66; H, 5.30); HPLC: t_R (*S*) = 21.6 min, t_R (*R*) = 42.2 min [Chiracel AS-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 335.8° (*c* 1.03, $CHCl_3$). The absolute stereochemistry was determined by single crystal X-ray diffraction on a crystalline sample of 1-naphthyl benzyl sulfoxide recrystallised from CH_2Cl_2;[127] Crystal data: $C_{17}H_{14}OS$, M = 266.34, orthorhombic, space group $P2_12_12_1$, a = 5.6554(8), b = 14.536(2), c = 16.378(2) Å, V = 1346.4(3) Å^3, Z = 4, D_c = 1.314 g cm^{-3}, F_{000} = 560, Mo Kα radiation, λ = 0.7107 Å, T = 300(2) K, $2\theta_{max}$ = 26.58°, μ = 0.228 mm^{-1}. 25499 reflections collected, 2764 unique (R_{int} = 0.073). Final GooF = 1.02, R_1 = 0.040, [2122 obs. data: $I > 2\sigma(I)$]; wR_2 = 0.088 (all data). CCDC 891524.

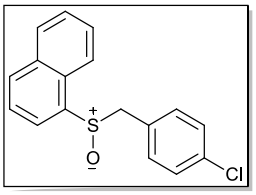
(*R*)-(+)-2-Naphthyl 4-chlorobenzyl sulfoxide [68] (Table 3.9, entry 14)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[31]** (285 mg, 1 mmol) in toluene/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (23:75:2). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-2-naphthyl 4-chlorobenzyl sulfoxide **[68]** as a white solid (202 mg, 67%, 90% ee); m.p. 196–198 °C; ^{1}H NMR δ_H (300 MHz) 4.05 (1H, A of AB system, *J* 12.6 Hz, $SOCH_2$), 4.11 (1H, B of AB system, *J* 12.9 Hz, $SOCH_2$), 6.90 (2H, d, *J* 8.1 Hz, Ar-H), 7.09–7.31 (2H, m, Ar-H), 7.41 (1H, dd, *J* 8.4 Hz and 1.5 Hz, Ar-H), 7.49–7.68 (2H, m, Ar-H), 7.74–8.01 (4H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 62.2 ($SOCH_2$), 120.1 (CH_{Ar}), 125.2 (CH_{Ar}), 127.4 (CH_{Ar}), 127.5 ($C_{Ar(q)}$), 127.9 (CH_{Ar}), 128.1 (CH_{Ar}), 128.5 (CH_{Ar}), 128.6 (CH_{Ar}), 129.2 (CH_{Ar}), 131.7 (CH_{Ar}), 132.7 ($C_{Ar(q)}$), 134.47 ($C_{Ar(q)}$), 134.54 ($C_{Ar(q)}$), 139.5 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2958, 1490, 1038, 823, 749; m/z (ESI) [$(M+H)^+$] 301 (70%), 303 (32), 283 (30), 256 (22), 240 (16), 197 (8), 195 (12), 130 (20), 74 (14), 64 (100) 60 (46), 46 (18), 42 (8); HRMS (ESI): Exact mass calculated for $C_{17}H_{14}{}^{35}ClOS$ [$(M+H)^+$] 301.0454, Found 301.0445; HPLC: t_R (*R*) = 33.0 min, t_R (*S*) = 49.4 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 117.0° (*c* 1.0, $CHCl_3$).

Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

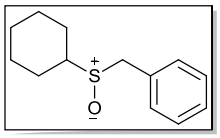
(*R*)-(+)-1-Naphthyl 4-chlorobenzyl sulfoxide [69] (Table 3.9, entry 15)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[32]** (285 mg, 1 mmol) in toluene/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide and sulfoxide (65:35). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-1-naphthyl 4-chlorobenzyl sulfoxide **[69]** as a white solid (84 mg, 28%, 71% ee): m.p. 123–125 °C; ^{1}H NMR δ_H (300 MHz) 4.00 (1H, A of AB system, *J* 12.9 Hz, $SOCH_2$), 4.25 (1H, B of AB system, *J* 12.9 Hz, $SOCH_2$), 6.68–6.82 (2H, m, Ar-H), 7.07–7.20 (2H, m, Ar-H), 7.45–7.72

(4H, m, Ar-H), 7.86–8.01 (3H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 60.1 ($SOCH_2$), 121.3 (CH_{Ar}), 123.9 (CH_{Ar}), 125.4 (CH_{Ar}), 126.6 (CH_{Ar}), 127.3 (CH_{Ar}), 127.6 ($C_{Ar(q)}$) 128.3 (CH_{Ar}), 129.0 ($C_{Ar(q)}$), 129.1 (CH_{Ar}), 131.4 (CH_{Ar}), 131.6 (CH_{Ar}), 133.2 ($C_{Ar(q)}$), 134.4 ($C_{Ar(q)}$), 137.8 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 3056, 1491, 1051, 801, 770; m/z (ESI) [$(M+H)^+$] 301 (80%), 303 (20), 300 (12), 217 (8), 141 (4), 64 (100), 39 (4); HRMS (ESI): Exact mass calculated for $C_{17}H_{14}{}^{35}ClOS$ [$(M+H)^+$] 301.0454, Found 301.0450; HPLC: t_R (*S*) = 21.2 min, t_R (*R*) = 53.3 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 355.4° (*c* 1.06, $CHCl_3$). Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

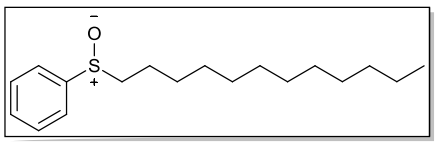
(+)-Cyclohexyl benzyl sulfoxide [70][65] (**Table 3.9, entry 16**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[36]** (206 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (3:94:3). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (+)-cyclohexyl benzyl sulfoxide **[70]** as a clear oil (196 mg, 88%, 27% ee); ^{1}H NMR δ_H (300 MHz) 1.17–1.76 (5H, m, cyclohexyl protons), 1.77–2.01 (4H, m, cyclohexyl protons), 2.02–2.19 (1H, m, cyclohexyl protons), 2.38–2.54 (1H, m, CHSO of cyclohexyl protons) 3.90 (1H, A of AB system, *J* 12.9 Hz, $SOCH_2$), 3.99 (1H, B of AB system, *J* 12.9 Hz, $SOCH_2$), 7.20–7.45 (5H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 24.0, 25.2, 25.48, 25.50, 26.9 (5 × CH_2, cyclohexyl protons), 54.8 ($SOCH_2$), 56.9 (CHSO), 128.2 (CH_{Ar}), 128.9 (CH_{Ar}), 130.0 (CH_{Ar}), 130.7 ($C_{Ar(q)}$); IR (film) ν_{max}/cm^{-1} 2929, 1453, 1028, 698; HPLC: t_R (−) = 32.4 min, t_R (+) = 39.7 min [Phenomenex Lux Amylose-2; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 4.7° (*c* 1.0, $CHCl_3$).

Absolute configuration was not determined.

(*R*)-(+)-Dodecyl phenyl sulfoxide [71][68] (**Table 3.9, entry 19**)

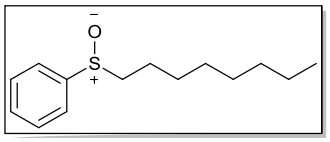


Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[27]** (279 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were

used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (29:65:6). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-dodecyl phenyl sulfoxide **[71]** as a white solid (167 mg, 60%, 57% ee); m.p. 50–53 °C; ^{1}H NMR δ_H (300 MHz) 0.88 (3H, t, *J* 6.3 Hz, CH_3), 1.16–1.84 (20H, m), 2.70–2.84 (2H, m, $SOCH_2$), 7.43–7.67 (5H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 14.1 (CH_3), 22.2 (CH_2), 22.7 (CH_2), 28.7 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 31.9 (CH_2), 57.4 ($SOCH_2$), 124.0 (CH_{Ar}), 129.2 (CH_{Ar}), 130.9 (CH_{Ar}), 144.2 ($C_{Ar(q)}$), 8 signals seen for 10 CH_2; IR (KBr) ν_{max}/cm^{-1} 2918, 1442, 1036, 1022, 687; HPLC: t_R (*S*) = 27.5 min, t_R (*R*) = 34.8 min [Chiracel AS-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 69.5° (*c* 1.26, $CHCl_3$), $[\alpha]_D^{20}$ = + 76.4° (*c* 1.36, acetone), $[\alpha]_D^{20}$ = + 88.4° (*c* 1.00, ethanol).

Absolute configuration determined by comparison of optical rotation to literature value of (*R*)-decyl phenyl sulfoxide $[\alpha]_D^{20}$ = + 140° (acetone) for (*R*) > 98% ee[129] and (*R*)-butyl phenyl sulfoxide $[\alpha]_D^{20}$ = + 181° (*c* 9.42, ethanol) for (*R*) > 99% ee.[130]

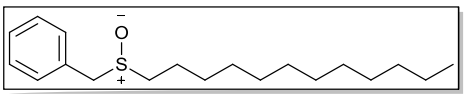
(*R*)-(+)-Octyl phenyl sulfoxide [72][68] (**Table 3.9, entry 21**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[28]** (222 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (32:62:6). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-octyl phenyl sulfoxide **[72]** as a white solid (122 mg, 55%, 36% ee); ^{1}H NMR δ_H (300 MHz) 0.87 (3H, t, *J* 6.6 Hz, CH_3), 1.12–1.83 (12H, m), 2.70–2.86 (2H, m, $SOCH_2$), 7.43–7.68 (5H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 14.0 (CH_3), 22.2 (CH_2), 22.6 (CH_2), 28.7 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 31.7 (CH_2), 57.4 ($SOCH_2$), 124.0 (CH_{Ar}), 129.2 (CH_{Ar}), 130.9 (CH_{Ar}), 144.1 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2927, 1443, 1088, 1046, 748, 693; HPLC: t_R (*S*) = 18.8 min, t_R (*R*) = 23.4 min [Chiracel AS-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 65.1° (*c* 1.0, $CHCl_3$), $[\alpha]_D^{20}$ = + 57.5° (*c* 1.03, acetone), $[\alpha]_D^{20}$ = + 61.2° (*c* 1.00, ethanol).

Absolute configuration determined by comparison of optical rotation to literature value of (*R*)-decyl phenyl sulfoxide $[\alpha]_D^{20}$ = + 140° (acetone) for (*R*) > 98% ee[129] and (*R*)-butyl phenyl sulfoxide $[\alpha]_D^{20}$ = + 181° (*c* 9.42, ethanol) for (*R*) > 99% ee.[130]

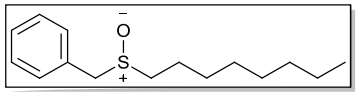
(*R*)-(+)-Dodecyl benzyl sulfoxide [73][69] (**Table 3.9, entry 23**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[33]** (293 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[155]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (2:93:5). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-dodecyl benzyl sulfoxide **[73]** as a white solid (271 mg, 88%, 21% ee); m.p. 77–79 °C, (Lit.[69] m.p. 80–80.5 °C, racemic); ^{1}H NMR δ_H (300 MHz) 0.88 (3H, t, *J* 6.6 Hz, CH_3), 1.15–1.51 (18H, m), 1.62–1.86 (2H, m), 2.56 (2H, t, *J* 7.5 Hz, $SOCH_2$), 3.93 (1H, A of AB system, *J* 12.9 Hz, $SOCH_2$), 4.02 (1H, B of AB system, *J* 12.9 Hz, $SOCH_2$), 7.21–7.52 (5H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 14.1 (CH_3), 22.4 (CH_2), 22.7 (CH_2), 28.8 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 31.9 (CH_2), 51.0 ($SOCH_2$), 58.3 ($SOCH_2$), 128.3 (CH_{Ar}), 128.9 (CH_{Ar}), 129.9 (CH_{Ar}), 130.0 ($C_{Ar(q)}$), 8 signals seen for 10 CH_2; IR (KBr) ν_{max}/cm^{-1} 2916, 1454, 1020, 698; HPLC: t_R (*S*) = 48.3 min, t_R (*R*) = 66.0 min [Chiracel AS-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 13.1° (*c* 1.0, $CHCl_3$).

Absolute configuration determined by comparison of optical rotation to literature value of (*R*)-decyl benzyl sulfoxide $[\alpha]_D^{20}$ = + 76.9° (*c* 1.9, $CHCl_3$) for (*R*) > 99% ee.[128] Peak broadening is evident in the ^{1}H NMR spectrum of the crude product at δ 1.62–1.86 (sulfoxide), 2.41 (sulfide), 2.56 (sulfoxide) and 3.70 (sulfide) ppm.

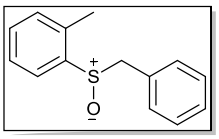
(*R*)-(+)-Octyl benzyl sulfoxide [74][69] (**Table 3.9, entry 26**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[34]** (236 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (9:85:6). The sulfoxide was purified by column

chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-octyl benzyl sulfoxide **[74]** as a white solid (194 mg, 77%, 22% ee); m.p. 72–74 °C, (Lit.[69] m.p. 71–71.5 °C, racemic); ^{1}H NMR δ_H (300 MHz) 0.87 (3H, t, *J* 6.3 Hz, CH_3), 1.12–1.53 (10H, m), 1.60–1.86 (2H, m), 2.56 (2H, t, *J* 7.8 Hz, $SOCH_2$), 3.93 (1H, A of AB system, *J* 12.9 Hz, $SOCH_2$), 4.02 (1H, B of AB system, *J* 12.9 Hz, $SOCH_2$), 7.20–7.52 (5H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 14.1 (CH_3), 22.4 (CH_2), 22.6 (CH_2), 28.8 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 31.7 (CH_2), 51.0 ($SOCH_2$), 58.3 ($SOCH_2$), 128.3 (CH_{Ar}), 128.9 (CH_{Ar}), 129.9 (CH_{Ar}), 130.0 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2918, 1455, 1026, 698; HPLC: t_R (*S*) = 24.1 min, t_R (*R*) = 34.8 min [Cellulose 4; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 9.4° (*c* 1.0, $CHCl_3$). Absolute configuration determined by comparison of optical rotation to literature value of (*R*)-decyl benzyl sulfoxide $[\alpha]_D^{20}$ = + 76.9° (*c* 1.9, $CHCl_3$) for (*R*) > 99% ee.[128] Peak broadening is evident in the ^{1}H NMR spectrum of the crude product at δ 1.60–1.86 (sulfoxide), 2.41 (sulfide), 2.56 (sulfoxide) and 3.70 (sulfide) ppm.

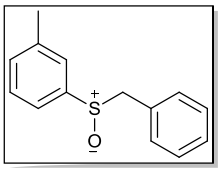
(*R*)-(+)-Benzyl *o*-tolyl sulfoxide [75][30] (**Table 3.8, entry 14**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[5]** (214 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (1:98:1). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-benzyl *o*-tolyl sulfoxide **[75]** as a white solid (209 mg, 91%, 64% ee); m.p. 69–71 °C; ^{1}H NMR δ_H (300 MHz) 2.06 (3H, s, $ArCH_3$), 4.00 (1H, A of AB system, *J* 12.3 Hz, $SOCH_2$), 4.10 (1H, B of AB system, *J* 12.6 Hz, $SOCH_2$), 6.97 (2H, dd, *J* 7.8 Hz and 1.3 Hz, Ar-H), 7.06–7.16 (1H, m, Ar-H), 7.19–7.41 (5H, m, Ar-H), 7.67–7.78 (1H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 18.0 ($ArCH_3$), 62.3 ($SOCH_2$), 124.2 (CH_{Ar}), 127.1 (CH_{Ar}), 128.3 (CH_{Ar}), 128.5 (CH_{Ar}), 129.3 ($C_{Ar(q)}$), 130.2 (CH_{Ar}), 130.4 (CH_{Ar}), 130.9 (CH_{Ar}), 135.6 ($C_{Ar(q)}$), 141.3 ($C_{Ar(q)}$); m/z (ESI) [$(M+H)^+$] 231 (70%), 105 (2%); ESI-HRMS: Exact mass calculated for $C_{14}H_{15}OS$: 231.0844; found: 231.0855; (Found C, 73.06; H, 6.12; S, 14.20; $C_{14}H_{14}OS$ requires C, 73.01; H, 6.13; S 13.92); HPLC: t_R (*R*) = 11.2 min, t_R (*S*) = 13.2 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 18.5°

(c 1.0, $CHCl_3$). Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

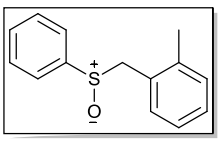
(*R*)-(+)-Benzyl *m*-tolyl sulfoxide [76] (**Table 3.8, entry 16**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[6]** (214 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide and sulfoxide (11:89). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-benzyl *m*-tolyl sulfoxide **[76]** as a white solid (193 mg, 84%, 62% ee); ^{1}H NMR δ_H (300 MHz) 2.34 (3H, s, $ArCH_3$), 3.97 (1H, A of AB system, J 12.6 Hz, $SOCH_2$), 4.08 (1H, B of AB system, J 12.3 Hz, $SOCH_2$), 7.00 (2H, dd, J 7.8 Hz and 2.1 Hz, Ar-H), 7.10–7.34 (7H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 21.3 ($ArCH_3$), 63.7 ($SOCH_2$), 121.5 (CH_{Ar}), 124.7 (CH_{Ar}), 128.2 (CH_{Ar}), 128.4 (CH_{Ar}), 128.6 (CH_{Ar}), 129.3 ($C_{Ar(q)}$), 130.4 (CH_{Ar}), 131.9 (CH_{Ar}), 139.1 ($C_{Ar(q)}$), 142.7 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2919, 1454, 1038, 766; m/z (ESI) [$(M+H)^+$] 231 (80%), 105 (2%); ESI-HRMS: Exact mass calculated for $C_{14}H_{15}OS$: 231.0844; found: 231.0840; (Found C, 72.96; H, 6.28; S, 14.0; $C_{14}H_{14}OS$ requires C, 73.01; H, 6.13; S 13.92); HPLC: t_R (*R*) = 15.1 min, t_R (*S*) = 18.9 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 48.6° (c 1.0, $CHCl_3$).

Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

(−)-2-Methylbenzyl phenyl sulfoxide [77][70] (**Table 3.8, entry 18**)

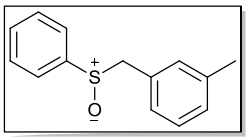


Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[8]** (214 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (13:85:2). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (−)-2-methylbenzyl phenyl sulfoxide **[77]** as a white solid (184 mg, 80%, 47% ee); ^{1}H NMR δ_H (300 MHz) 2.18 (3H, s $ArCH_3$), 3.99 (1H, A of AB

system, *J* 12.3 Hz, $SOCH_2$), 4.27 (1H, B of AB system, *J* 12.3 Hz, $SOCH_2$), 6.85 (1H, d, *J* 6.6 Hz, Ar-H), 7.02–7.25 (3H, m, Ar-H), 7.35–7.52 (5H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2926, 1443, 1094, 1030, 750; (Found C, 73.19; H, 6.02; S, 13.85; $C_{14}H_{14}OS$ requires C, 73.01; H, 6.13; S, 13.92); HPLC: t_R (+) = 67.1 min, t_R (−) = 85.3 min [Chiracel AS-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = − 16.5° (*c* 1.0, $CHCl_3$).

Absolute configuration was not determined.

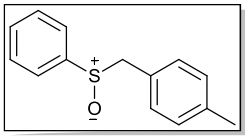
(*R*)-(+)-3-Methylbenzyl phenyl sulfoxide [78][71] (**Table 3.8, entry 19**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[9]** (214 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow oil. The crude product contained a mixture of sulfide, sulfoxide and sulfone (7:92:1). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-3-methylbenzyl phenyl sulfoxide **[78]** as a clear oil (191 mg, 83%, 50% ee); ^1H NMR δ_H (300 MHz) 2.27 (3H, s $ArCH_3$), 3.94 (1H, A of AB system, *J* 12.3 Hz, $SOCH_2$), 4.08 (1H, B of AB system, *J* 12.6 Hz, $SOCH_2$), 6.80 (2H, d, *J* 5.7 Hz, Ar-H), 7.06–7.19 (2H, m, Ar-H), 7.36–7.51 (5H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 21.3 (Ar-CH_3), 63.9 ($SOCH_2$), 124.5 (CH_{Ar}), 127.4 (CH_{Ar}), 128.4 (CH_{Ar}), 128.8 (CH_{Ar}), 129.0 (CH_{Ar}), 129.1 ($C_{Ar(q)}$), 131.1 (CH_{Ar}), 131.2 (CH_{Ar}), 138.2 ($C_{Ar(q)}$), 143.0 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2967, 1604, 1444, 1040, 736; m/z (ESI) [$(M+H)^+$] 231 (6%), 183 (16), 182 (100), 100 (10), 59 (54), 46 (32); ESI-HRMS: Exact mass calculated for $C_{14}H_{15}OS$: 231.0844; found: 231.0846; (Found C, 73.42; H, 6.13; S, 13.97; $C_{14}H_{14}OS$ requires C, 73.01; H, 6.13; S, 13.92); HPLC: t_R (*R*) = 16.2 min, t_R (*S*) = 18.7 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 36.8° (*c* 1.0, $CHCl_3$).

Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

(*R*)-4-Methylbenzyl phenyl sulfoxide [79][72] (**Table 3.8, entry 21**)

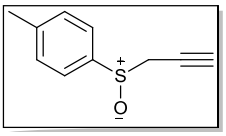


Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[10]** (214 mg, 1 mmol) in

hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (1:97:2). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-4-methylbenzyl phenyl sulfoxide **[79]** as a white solid (205 mg, 89%, 55% ee); ^{1}H NMR δ_H (300 MHz) 2.32 (3H, s $ArCH_3$), 3.96 (1H, A of AB system, *J* 12.6 Hz, $SOCH_2$), 4.07 (1H, B of AB system, *J* 12.6 Hz, $SOCH_2$), 6.87 (2H, d, *J* 7.8 Hz, Ar-H), 7.06 (2H, d, *J* 7.8 Hz, Ar-H), 7.36–7.51 (5H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2959, 1512, 1442, 1043, 687; (Found C, 73.12; H, 6.33; S, 13.94; $C_{14}H_{14}OS$ requires C, 73.01; H, 6.13; S 13.92); HPLC: t_R (*R*) = 12.7 min, t_R (*S*) = 14.3 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 42.2° (*c* 1.0, $CHCl_3$).

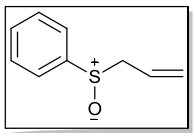
Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

4-Methylphenyl prop-2'-ynyl sulfoxide [80][73] (**Table 3.2, entry 14**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[45]** (162 mg, 1 mmol) in toluene (2 mL) were used as described for **[56]** to give the crude product as a yellow oil. The crude product contained a mixture of sulfide and sulfoxide (81:19). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield 4-methylphenyl prop-2'-ynyl sulfoxide **[80]** as a clear oil (7 mg, 4%, 5% ee); ^{1}H NMR δ_H (300 MHz) 2.33 (1H, t, *J* 2.7 Hz, C≡C-H), 2.44 (3H, s, Ar-CH_3), 3.59 (1H, A of ABX system, J_{AB} 14.2 Hz, J_{AX} 2.6 Hz, $SOCH_2$), 3.67 (1H, B of ABX system, J_{AB} 14.4 Hz, J_{BX} 2.6 Hz, $SOCH_2$), 7.35 (2H, d, *J* 8.3 Hz, Ar-H), 7.61 (2H, d, *J* 8.2 Hz, Ar-H); HPLC: t_R (*R*) = 14.6 min, t_R (*S*) = 17.5 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 5.2° (*c* 1.0, $CHCl_3$). Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

(*R*)-(+)-Allyl phenyl sulfoxide [81][56] (**Table 3.9, entry 29**)

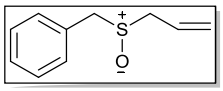


Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and allyl phenyl sulfide (150 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the

crude product as a yellow oil. The crude product contained a mixture of sulfide and sulfoxide (26:74). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-allyl phenyl sulfoxide **[81]** as a clear oil (113 mg, 68%, 29% ee); ^{1}H NMR δ_H (300 MHz) 3.43–3.65 (2H, m, $SOCH_2$), 5.20 (1H, d, *J* 16.4 Hz, -CH=CH_2), 5.39 (1H, d, *J* 10.5 Hz, -CH=CH_2) 5.57–5.75 (1H, m, -C*H*=CH_2), 7.42–7.69 (5H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 60.9 ($SOCH_2$), 123.9 (-CH=*C*H_2), 124.4 (CH_{Ar}), 125.3 (-*C*H=CH_2), 129.0 (CH_{Ar}), 131.0 (CH_{Ar}), 143.0 ($CH_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 3058, 1635, 1444, 1090, 1042, 692; HPLC: t_R (*R*) = 11.3 min, t_R (*S*) = 14.1 min [Chiracel OJ-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 24.2° (c 1.0, $CHCl_3$), {ref[173] $[\alpha]_D^{20}$ = − 160.2° (*c* 0.9, $CHCl_3$) for (*S*) > 97% ee}.

Absolute configuration was determined by comparison of specific rotation value to known literature value.

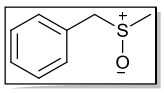
(+)-Allyl benzyl sulfoxide [82][74] (**Table 3.9, entry 31**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[168]** (164 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow oil. The crude product contained a mixture of sulfide and sulfoxide (6:94). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (+)-allyl benzyl sulfoxide **[82]** as a clear oil (157 mg, 87%, 11% ee); ^{1}H NMR δ_H (300 MHz) 3.20–3.33 (1H, m, SOCH_2-CH=CH_2), 3.36–3.50 (1H, m, SOCH_2-CH=CH_2), 3.96 (1H, A of AB system, *J* 12.9 Hz, SOCH_2-Ar), 4.01 (1H, B of AB system, *J* 13.2 Hz, SOCH_2-Ar), 5.39 (1H, d, *J* 17 Hz, -CH=CH_2), 5.49 (1H, d, *J* 10.2 Hz, -CH=CH_2), 5.82–6.02 (1H, m, -C*H*=CH_2), 7.21–7.43 (5H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 54.2 ($SOCH_2$), 56.9 ($SOCH_2$), 123.7 (-CH=*C*H_2), 125.8 (-*C*H=CH_2), 128.4 (CH_{Ar}), 129.0 (CH_{Ar}), 129.9 ($C_{Ar(q)}$), 130.1 (CH_{Ar}); IR (KBr) ν_{max}/cm^{-1} 2963, 1455, 1031, 700; HPLC: t_R (−) = 81.8 min, t_R (+) = 112.9 min [Chiracel As-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 2.3° (*c* 1.0, $CHCl_3$).

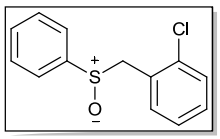
Absolute configuration was not determined.

Benzyl methyl sulfoxide [83] (Table 3.9, entry 33)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and benzyl methyl sulfide **[169]** (138 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow oil. The crude product contained a mixture of sulfide, sulfoxide and sulfone (5:94:1). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield benzyl methyl sulfoxide **[83]** as a clear oil (134 mg, 87%, 4% ee); ^{1}H NMR δ_H (300 MHz) 2.46 (3H, s, Ar-CH_3), 3.93 (1H, A of AB system, *J* 12.6 Hz, $SOCH_2$), 4.07 (1H, B of AB system, *J* 12.6 Hz, $SOCH_2$), 7.20–7.43 (5H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 37.3 (Ar-CH_3), 60.3 ($SOCH_2$), 128.5 (CH_{Ar}), 129.0 (CH_{Ar}), 129.7 ($C_{Ar(q)}$), 130.0 (CH_{Ar}); IR (film) ν_{max}/cm^{-1} 3032, 2150, 1497, 1455, 1028, 700; HPLC: t_R = 53.4 min, t_R = 60.0 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (95:5); 20 °C], t_R = 50.7 min, t_R = 63.1 min [Phenomenex Lux Cellulose-4; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C], better resolution was obtained using Phenomenex Lux Cellulose-4 column; $[\alpha]_D^{20}$ ~ 0° (*c* 1.0, $CHCl_3$).

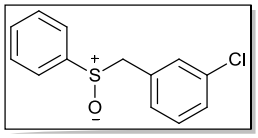
(*R*)-(+)-2-Chlorobenzyl phenyl sulfoxide [84] (Table 3.10, entry 1)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[11]** (235 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (18:78:4). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield 2-chlorobenzyl phenyl sulfoxide **[84]** as a white solid (181 mg, 72%, 44% ee); m.p. 62–64 °C; ^{1}H NMR δ_H (300 MHz) 4.17 (1H, A of AB system, *J* 12.6 Hz, $SOCH_2$), 4.25 (1H, B of AB system, *J* 12.6 Hz, $SOCH_2$), 7.03–7.30 (3H, m, Ar-H); 7.32–7.53 (6H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 61.8 ($SOCH_2$), 124.3 (CH_{Ar}), 126.9 (CH_{Ar}), 128.1 ($C_{Ar(q)}$), 129.0 (CH_{Ar}), 129.6 (CH_{Ar}), 129.8 (CH_{Ar}), 131.4 (CH_{Ar}), 132.7 (CH_{Ar}), 134.9 ($C_{Ar(q)}$), 143.2 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 3056, 1474, 1444, 1047, 748; (Found: C, 62.35; H, 4.35. $C_{13}H_{11}ClOS$ Requires C, 62.27; H, 4.42); HPLC: t_R (*S)* = 64.4 min, t_R (*R*) = 71.3 min [Chiracel AS-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 23.8° (*c* 1.0, $CHCl_3$).

Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

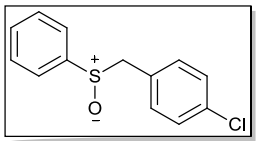
(*R*)-(+)-3-Chlorobenzyl phenyl sulfoxide [85][71] (**Table 3.10, entry 6**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[12]** (235 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (10:89:1). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield 3-chlorobenzyl phenyl sulfoxide **[85]** as a white solid (206 mg, 82%, 42% ee); m.p. 79–82 °C; ^{1}H NMR δ_H (300 MHz) 3.98 (2H, s, $SOCH_2$), 6.84–6.94 (2H, m, Ar-H), 7.13–7.31 (2H, m, Ar-H), 7.35–7.52 (5H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 62.8 ($SOCH_2$), 124.3 (CH_{Ar}), 128.4 (CH_{Ar}), 128.6 (CH_{Ar}), 129.0 (CH_{Ar}), 129.6 (CH_{Ar}), 130.3 (CH_{Ar}), 131.1 ($C_{Ar(q)}$), 131.4 (CH_{Ar}), 134.2 ($C_{Ar(q)}$), 142.4 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2970, 1472, 1444, 1428, 1086, 1039, 704; HPLC: t_R (*R)* = 18.0 min, t_R (*S*) = 22.8 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 24.1° (*c* 1.2, $CHCl_3$).

Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

(*R*)-(+)-4-Chlorobenzyl phenyl sulfoxide [86][71] (**Table 3.10, entry 12**)

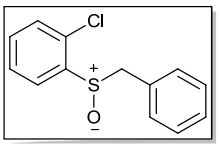


Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[13]** (235 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (9:90:1). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield 4-chlorobenzyl phenyl sulfoxide **[86]** as a white solid (213 mg, 85%, 49% ee); m.p. 167–169 °C, (Lit.[77] 173 °C); ^{1}H NMR δ_H (400 MHz) 3.99 (1H, A of AB system, *J* 12.8 Hz, $SOCH_2$), 4.08 (1H, B of AB system, *J* 12.6 Hz, $SOCH_2$), 6.92–7.05 (2H, m, Ar-H), 7.18–7.52 (7H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2962, 1455, 1442, 1034, 745; HPLC: t_R (*R)* = 15.9 min, t_R (*S*) = 19.4 min [Chiracel

OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 52.7° (*c* 1.2, $CHCl_3$).

Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

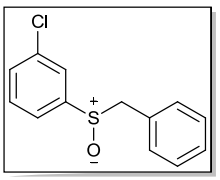
(*R*)-(+)-Benzyl 2-chlorophenyl sulfoxide [87][75] (**Table 3.10, entry 14**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[14]** (235 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (67:32:1). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield benzyl 2-chlorophenyl sulfoxide **[87]** as a white solid (65 mg, 26%, 48% ee); m.p. 59–61 °C, (Lit.[174] 60 °C); ^{1}H NMR δ_H (300 MHz) 3.96 (1H, A of AB system, *J* 12.9 Hz, $SOCH_2$), 4.01 (1H, B of AB system, *J* 12.6 Hz, $SOCH_2$), 6.84–6.93 (2H, m, Ar-H), 7.18–7.33 (5H, m, Ar-H), 7.36–7.48 (2H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 62.3 ($SOCH_2$), 125.8 (CH_{Ar}), 128.7 (CH_{Ar}), 129.3 (CH_{Ar}), 131.7 (CH_{Ar}), 134.6 ($C_{Ar(q)}$), 137.6 ($C_{Ar(q)}$), 140.9 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2963, 1476, 1408, 1390, 1097, 1037, 1013, 824; HPLC: t_R (*S)* = 27.1 min, t_R (*R*) = 32.2 min [Chiracel OJ-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 162.6 (c 1.05, $CHCl_3$), {ref[75] $[\alpha]_D^{20}$ = + 397.1° (*c* 1.0, $CHCl_3$) for (*R*) = 95% ee}.

Absolute configuration was determined by comparison of specific rotation value to known literature value.

(*R*)-(+)-Benzyl 3-chlorophenyl sulfoxide [88][76] (**Table 3.10, entry 18**)

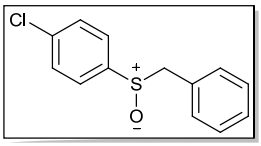


Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[15]** (235 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (60:39:1). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield benzyl 3-chlorophenyl sulfoxide **[88]** as a white solid (83 mg, 33%, 59% ee); m.p. 106–108 °C, (Lit.[76] 106–107 °C,

racemic); ^{1}H NMR δ_H (300 MHz) 4.00 (1H, A of AB system, *J* 12.6 Hz, $SOCH_2$), 4.10 (1H, B of AB system, *J* 12.6 Hz, $SOCH_2$), 6.90–7.05 (2H, m, Ar-H), 7.14–7.50 (7H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 63.6 ($SOCH_2$), 122.6 (CH_{Ar}), 124.5 (CH_{Ar}), 128.53 (CH_{Ar}), 128.56 (CH_{Ar}), 128.62 ($C_{Ar(q)}$), 130.4 (CH_{Ar}), 131.3 (CH_{Ar}), 135.3 ($C_{Ar(q)}$), 144.9 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2957, 1455, 1409, 1073, 1039, 695; HPLC: t_R (*S)* = 15.9 min, t_R (*R*) = 22.3 min [Chiracel OJ-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C];$[\alpha]_D^{20}$ = + 142.0° (*c* 1.0, $CHCl_3$).

Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

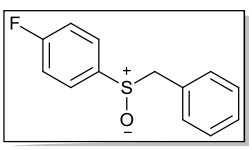
(*R*)-(+)-Benzyl 4-chlorophenyl sulfoxide [89][71] (**Table 3.10, entry 23**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[16]** (235 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide and sulfoxide (28:72). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield benzyl 4-chlorophenyl sulfoxide **[89]** as a white solid (155 mg, 67%, 52% ee); m.p. 126–129 °C, (Lit.[110] 120–122 °C, racemic); ^{1}H NMR δ_H (400 MHz) 3.90 (1H, A of AB system, *J* 12.8 Hz, $SOCH_2$), 4.02 (1H, B of AB system, *J* 12.6 Hz, $SOCH_2$), 6.81–6.96 (2H, m, Ar-H), 7.12–7.36 (7H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2966, 1474, 1454, 1389, 1035, 698; HPLC: t_R (*R)* = 41.2 min, t_R (*S*) = 46.3 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (95:5); 20 °C]; $[\alpha]_D^{20}$ = + 131.5° (*c* 1.0, $CHCl_3$).

Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

Benzyl 4-fluorophenyl sulfoxide [90][77] (**Table 3.1, entry 7**)

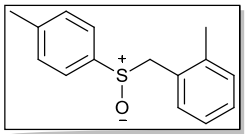


Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[164]** (213 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide and sulfoxide (75:25). The sulfoxide was purified by column

chromatography on silica gel (6:4 hexane/ethyl acetate) to yield benzyl 4-fluorophenyl sulfoxide **[90]** as a white solid; (42 mg, 18%, 34% ee); m.p. 138–140 °C (Lit.[26] m.p. 137–139 °C); ^{1}H NMR δ_H (300 MHz) 2.40 (3H, s, Ar-CH_3), 3.96 (1H, A of AB system, *J* 12.6 Hz, $SOCH_2$), 4.16 (1H, B of AB system, *J* 12.6 Hz, $SOCH_2$), 6.92–6.99 (2H, m, Ar-H), 7.03–7.26 (2H, m, Ar-H), 7.15–7.43 (5H, m, Ar-H); HPLC: t_R (*R)* = 34.5 min, t_R (*S*) = 39.9 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (98:2); 20 °C]; $[\alpha]_D^{20}$ = + 60.0° (*c* 0.19, acetone).

Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

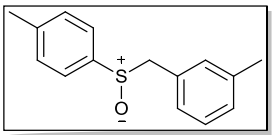
(−)-2'-Methylbenzyl 4-methylphenyl sulfoxide [91] (**Table 3.12, entry 1**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[17]** (228 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (28:69:3). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (−)-2'-methylbenzyl 4-methylphenyl sulfoxide **[91]** as a white solid (151 mg, 62%, 32% ee); m.p. 83–85 °C; ^{1}H NMR δ_H (300 MHz) 2.19 (3H, s, Ar-CH_3), 2.40 (3H, s, Ar-CH_3), 3.97 (1H, A of AB system, *J* 12.6 Hz, $SOCH_2$), 4.25 (1H, B of AB system, *J* 12.6 Hz, $SOCH_2$), 6.86 (1H, d, *J* 7.5 Hz, Ar-H), 7.01–7.42 (7H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 19.5 (Ar-CH_3), 21.5 (Ar-CH_3), 62.1 ($SOCH_2$), 124.5 (CH_{Ar}), 126.1 (CH_{Ar}), 128.1 ($C_{Ar(q)}$), 128.5 (CH_{Ar}), 129.6 (CH_{Ar}), 130.5 (CH_{Ar}), 131.5 (CH_{Ar}), 137.7 ($C_{Ar(q)}$), 139.9 ($C_{Ar(q)}$), 141.7 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2922, 1494, 1083, 1045, 809, 771; m/z (ESI) 141 (12%), 64 (16); HRMS (ESI): Exact mass calculated for $C_{15}H_{17}OS$ [$(M+H)^+$] 245.1000, Found 245.0988; (Found: C, 73.54; H, 6.66. $C_{15}H_{16}OS$ Requires C, 73.73; H, 6.60); HPLC: t_R (*+)* = 27.1 min, t_R (−) = 32.2 min [Chiracel OJ-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; HPLC: t_R (+) = 48.2 min, t_R (−) = 63.0 min [Chiracel AS-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = − 3.7° (*c* 1.65, $CHCl_3$).

Absolute configuration was not determined.

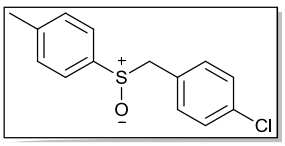
(*R*)-(+)-3'-Methylbenzyl 4-methylphenyl sulfoxide [92][71] (**Table 3.12, entry 4**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[18]** (228 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (17:81:2). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-3'-methylbenzyl 4-methylphenyl sulfoxide **[92]** as a white solid (185 mg, 76%, 52% ee); m.p. 65–68 °C; ^{1}H NMR δ_H (300 MHz) 2.27 (3H, s, Ar-CH_3), 2.40 (3H, s, Ar-CH_3), 3.91 (1H, A of AB system, *J* 12.3 Hz, $SOCH_2$), 4.06 (1H, B of AB system, *J* 12.6 Hz, $SOCH_2$), 6.74–6.85 (2H, m, Ar-H), 7.03–7.33 (6H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 21.3 (Ar-CH_3), 21.5 (Ar-CH_3), 64.0 ($SOCH_2$), 124.5 (CH_{Ar}), 127.4 (CH_{Ar}), 128.4 (CH_{Ar}), 129.0 (CH_{Ar}), 129.3 ($C_{Ar(q)}$), 129.5 (CH_{Ar}), 131.1 (CH_{Ar}), 138.2 ($C_{Ar(q)}$), 139.8 ($C_{Ar(q)}$), 141.6 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2919, 1493, 1085, 1044, 789; HPLC: t_R (*R*) = 25.9 min, t_R (*S*) = 29.8 min, 51% ee, [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C], t_R (*S*) = 45.3 min, t_R (*R*) = 60.0 min, 52% ee, [Phenomenex Lux Cellulose-4; flow rate 1 mL min^{-1}; hexane/2-PrOH (95:5); 20 °C], better resolution was achieved using Phenomenex Lux Cellulose-4 column; $[\alpha]_D^{20}$ = + 45.6° (*c* 1.0, $CHCl_3$).

Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

(*R*)-(+)-4'-Chlorobenzyl 4-methylphenyl sulfoxide [93][78] (**Table 3.12, entry 7**)

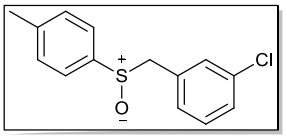


Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[19]** (249 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide and sulfoxide (13:87). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-4'-chlorobenzyl 4-methylphenyl sulfoxide **[93]** as a white solid (214 mg, 81%, 69% ee); m.p. 155–157 °C; ^{1}H NMR δ_H (300 MHz) 2.40 (3H, s, Ar-CH_3), 3.97 (2H, s, $SOCH_2$), 6.90 (2H, d, *J* 8.4 Hz, Ar-H), 7.16–7.33 (6H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 21.5 (Ar-CH_3), 62.5 ($SOCH_2$), 124.4 (CH_{Ar}), 127.7 ($C_{Ar(q)}$), 128.6 (CH_{Ar}), 129.7 (CH_{Ar}), 131.7 (CH_{Ar}), 134.3 ($C_{Ar(q)}$), 139.2 ($C_{Ar(q)}$), 141.8 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1}

2966, 1493, 1034, 812; HPLC: t_R (*R*) = 28.8 min, t_R (*S*) = 33.0 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 83.5° (*c* 1.0, $CHCl_3$), {ref[58] $[\alpha]_D^{20}$ = − 140° (*c* 0.5, $CHCl_3$) for (*S*) = 98% ee}.

Absolute configuration was determined by comparison of specific rotation value to known literature value.

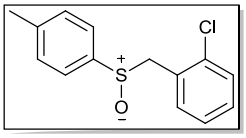
(*R*)-(+)-3'-Chlorobenzyl 4-methylphenyl sulfoxide [94][79] (**Table 3.12, entry 9**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[20]** (249 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (24:75:1). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield (*R*)-(+)-3'-chlorobenzyl 4-methylphenyl sulfoxide **[94]** as a white solid (185 mg, 70%, 61% ee); m.p. 90–93 °C [Lit. m.p. 88-88.5 °C, (+)-enantiomer, enantiopure][79]; ^{1}H NMR δ_H (300 MHz) 2.40 (3H, s, Ar-CH_3), 3.94 (1H, A of AB system, *J* 12.6 Hz, $SOCH_2$), 3.99 (1H, B of AB system, *J* 12.9 Hz, $SOCH_2$), 6.84–6.95 (2H, m, Ar-H), 7.13–7.33 (6H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 21.5 (Ar-CH_3), 62.9 ($SOCH_2$), 124.4 (CH_{Ar}), 128.3 (CH_{Ar}), 128.6 (CH_{Ar}), 129.6 (CH_{Ar}), 129.7 (CH_{Ar}), 130.3 (CH_{Ar}), 131.3 ($C_{Ar(q)}$), 134.2 ($C_{Ar(q)}$), 139.2 ($C_{Ar(q)}$), 142.0 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2917, 1431, 1085, 1034, 817, 789; HPLC: t_R (*R*) = 46.8 min, t_R (*S*) = 61.9 min [Chiracel AS-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 72.0° (*c* 1.0, $CHCl_3$), $[\alpha]_D^{20}$ = + 135.1° (*c* 1.0, acetone) {ref[79] $[\alpha]_D^{20}$ = + 295° (acetone) for (+) > 99% ee}.

Absolute configuration was determined by comparison of specific rotation value to known literature value.

(*R*)-(+)-2'-Chlorobenzyl 4-methylphenyl sulfoxide [95] (**Table 3.12, entry 12**)

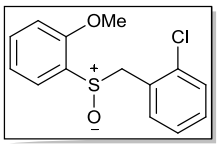


Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[21]** (249 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (19:80:1). The sulfoxide was purified by column

chromatography on silica gel (6:4 hexane/ethyl acetate) to yield 2'-chlorobenzyl 4-methylphenyl sulfoxide **[95]** as a clear oil (196 mg, 74%, 37% ee); ^{1}H NMR δ_H (300 MHz) 2.41 (3H, s, Ar-CH_3), 4.15 (1H, A of AB system, *J* 12.6 Hz, $SOCH_2$), 4.24 (1H, B of AB system, *J* 12.6 Hz, $SOCH_2$), 7.02–7.44 (8H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 21.5 (Ar-CH_3), 61.9 ($SOCH_2$), 124.3 (CH_{Ar}), 126.9 (CH_{Ar}), 128.3 ($C_{Ar(q)}$), 129.6 (CH_{Ar}), 129.7 (CH_{Ar}), 129.8 (CH_{Ar}), 132.7 (CH_{Ar}), 134.9 ($C_{Ar(q)}$), 140.0 ($C_{Ar(q)}$), 141.8 ($C_{Ar(q)}$); IR (film) ν_{max}/cm^{-1} 2923, 1474, 1084, 1054, 808, 762; m/z (ESI) 289 (10%), 287 (50), 245, 153 (12), 105 (14), 90 (6), 64 (20), 60 (8), 32 (8), ion corresponding to parent molecular ion at 265 not seen in nominal but detected in high resolution mass spectrum; HRMS (ESI): Exact mass calculated for $C_{14}H_{14}{}^{35}ClOS$ [$(M+H)^+$] 265.0454, Found 265.0442; (Found: C, 63.44; H, 5.03. $C_{14}H_{13}ClOS$ Requires C, 63.51; H, 4.95); HPLC: t_R (*S*) = 51.5 min, t_R (*R*) = 60.3 min [Chiracel AS-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 29.0° (*c* 1.1, $CHCl_3$).

Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

(*R*)-(+)-2'-Chlorobenzyl 2-methoxyphenyl sulfoxide [96] (**Table 3.12, entry 15**)

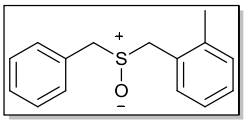


Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[22]** (265 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (19:80:1). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield 2'-chlorobenzyl 2-methoxyphenyl sulfoxide **[96]** as a white solid (211 mg, 75%, 70% ee); m.p. 71–73 °C; ^{1}H NMR δ_H (300 MHz) 3.83 (3H, s, Ar-OCH_3), 4.13 (1H, A of AB system, *J* 12.6 Hz, $SOCH_2$), 4.53 (1H, B of AB system, *J* 12.6 Hz, $SOCH_2$), 6.88 (1H, d, *J* 8.4 Hz, Ar-H), 7.03–7.15 (1H, m, Ar-H), 7.16–7.37 (4H, m, Ar-H), 7.38–7.50 (1H, m, Ar-H), 7.59 (1H, dd, *J* 7.8 Hz and 1.5 Hz, Ar-H); ^{13}C NMR δ_C (75 MHz) 55.6 (Ar-OCH_3), 57.8 ($SOCH_2$), 110.3 (CH_{Ar}), 121.4 (CH_{Ar}), 125.4 (CH_{Ar}), 126.6 (CH_{Ar}), 128.8 ($C_{Ar(q)}$), 129.4 (CH_{Ar}), 129.5 (CH_{Ar}), 130.6 ($C_{Ar(q)}$), 132.2 (CH_{Ar}), 132.9 (CH_{Ar}), 134.9 ($C_{Ar(q)}$), 155.5 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2938, 1477, 1274, 1040, 757; m/z (ESI) [$(M+H)^+$] 281 (20%), 283 (10), 142 (6), 100 (6); HRMS (ESI): Exact mass calculated for $C_{14}H_{14}{}^{35}ClO_2S$ [$(M+H)^+$] 281.0403, Found 281.0402; (Found: C, 59.79; H, 4.71. $C_{14}H_{13}ClO_2S$ Requires C, 59.89; H, 4.67); HPLC: t_R (*S*) = 39.6

min, t_R (*R*) = 61.3 min [Chiracel AS-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 228.3° (*c* 1.0, $CHCl_3$). Absolute configuration is the proposed configuration based on HPLC elution order and direction of specific rotation.

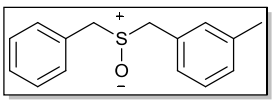
Specific rotations were recorded on a selection of the essentially racemic dibenzyl sulfoxide series and were very close to zero and hence are not reported.

Benzyl 2-methylbenzyl sulfoxide [97] (**Table 3.13, entry 1**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[39]** (228 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (2:91:7). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield benzyl 2-methylbenzyl sulfoxide **[97]** as a white solid (203 mg, 83%, 2% ee); m.p. 107–109 °C; ^{1}H NMR δ_H (300 MHz) 2.26 (3H, s, Ar-CH_3), 3.90–4.08 (4H, m, $SOCH_2$), 7.13–7.43 (9H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 19.7 (Ar-CH_3), 56.4 ($SOCH_2$), 58.3 ($SOCH_2$), 126.5 (CH_{Ar}), 128.4 (CH_{Ar}), 128.6 (CH_{Ar}), 129.0 (CH_{Ar}), 129.1 ($C_{Ar(q)}$), 130.1 (CH_{Ar}), 130.4 ($C_{Ar(q)}$), 130.8 (CH_{Ar}), 131.1 (CH_{Ar}), 137.4 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2971, 1495, 1455, 1029, 1012, 698; (Found: C, 73.64; H, 6.81. $C_{15}H_{16}OS$ Requires C, 73.73; H, 6.60); HPLC: t_R = 49.6 min, t_R = 56.4 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C].

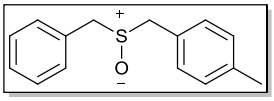
Benzyl 3-methylbenzyl sulfoxide [98] (**Table 3.13, entry 7**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[40]** (228 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (1:89:10). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield benzyl 3-methylbenzyl sulfoxide **[98]** as a white solid (200 mg, 82%, 3% ee); m.p. 83–85 °C; ^{1}H NMR δ_H (300 MHz) 2.35 (3H, m, Ar-CH_3), 3.79–3.99 (4H, m, $SOCH_2$), 7.03–7.43 (9H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 21.4 (Ar-CH_3),

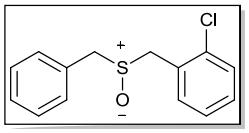
57.4 ($SOCH_2$), 57.5 ($SOCH_2$), 127.1 (CH_{Ar}), 128.3 (CH_{Ar}), 128.8 (CH_{Ar}), 128.9 (CH_{Ar}), 129.2 (CH_{Ar}), 130.1 ($C_{Ar(q)}$), 130.15 (CH_{Ar}), 130.23 ($C_{Ar(q)}$), 130.8 (CH_{Ar}), 138.7 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2916, 1495, 1454, 1029, 699; (Found: C, 73.82; H, 6.74. $C_{15}H_{16}OS$ Requires C, 73.73; H, 6.60); HPLC: t_R = 94.4 min, t_R = 112.9 min [Chiracel AS-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C].

Benzyl 4-methylbenzyl sulfoxide [99][80] (**Table 3.13, entry 12**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[41]** (228 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (2:89:9). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield benzyl 4-methylbenzyl sulfoxide **[99]** as a white solid (200 mg, 82%, 4% ee); m.p. 97–99 °C (Lit.[80] m.p. 94 °C); ^1H NMR δ_H (300 MHz) 2.35 (3H, m, Ar-CH_3), 3.79–3.95 (4H, m, $SOCH_2$), 7.18 (4H, s, Ar-H), 7.23–7.43 (5H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 21.2 (Ar-CH_3), 57.0 ($SOCH_2$), 57.2 ($SOCH_2$), 126.9 ($C_{Ar(q)}$), 128.3 (CH_{Ar}), 128.9 (CH_{Ar}), 129.7 (CH_{Ar}), 130.0 (CH_{Ar}), 130.2 (CH_{Ar}), 130.3 ($C_{Ar(q)}$), 138.3 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2957, 1495, 1454, 1036, 699; HPLC: t_R = 40.9 min, t_R = 44.9 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C].

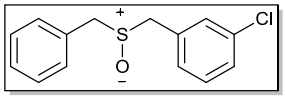
Benzyl 2-chlorobenzyl sulfoxide [100][81] (**Table 3.13, entry 18**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[42]** (249 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (12:80:8). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield benzyl 2-chlorobenzyl sulfoxide **[100]** as a white solid (180 mg, 68%, 10% ee); m.p. 116–119 °C (Lit.[81] m.p. 112–113 °C, racemic); ^1H NMR δ_H (300 MHz) 3.91 (1H, A of AB system, *J* 12.9 Hz, $SOCH_2$), 3.98 (1H, A of AB system, *J* 12.9 Hz, $SOCH_2$), 4.03 (1H, B of AB system, *J* 12.9 Hz, $SOCH_2$), 4.23 (1H, B of AB system, *J* 12.9 Hz, $SOCH_2$), 7.19–7.46 (9H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 55.8 ($SOCH_2$), 58.4 ($SOCH_2$), 127.3 (CH_{Ar}), 128.4 (CH_{Ar}), 128.9 ($C_{Ar(q)}$), 129.0 (CH_{Ar}), 129.8 (CH_{Ar}), 129.9

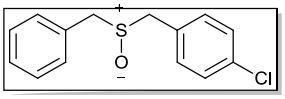
(CH_{Ar}), 130.1 (CH_{Ar}), 132.5 (CH_{Ar}), 134.5 ($C_{Ar(q)}$), one $C_{Ar(q)}$ not seen; IR (KBr) ν_{max}/cm^{-1} 3061, 1496, 1474, 1454, 1042, 699; HPLC: t_R = 24.6 min, t_R = 30.7 min [Chiracel OJ-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C].

Benzyl 3-chlorobenzyl sulfoxide [101] (**Table 3.13, entry 22**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[43]** (249 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (12:80:8). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield benzyl 3-chlorobenzyl sulfoxide **[101]** as a white solid (191 mg, 72%, 3% ee); m.p. 72–74 °C; ^{1}H NMR δ_H (400 MHz) 3.77 (1H, A of AB system, *J* 12.9 Hz, $SOCH_2$), 3.90 (1H, B of AB system, *J* 12.9 Hz, $SOCH_2$), 3.97 (2H, s, $SOCH_2$), 7.13–7.44 (9H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2918, 1495, 1476, 1455, 1040, 699; (Found: C, 63.37; H, 5.07. $C_{14}H_{13}ClOS$ Requires C, 63.51; H, 4.95); HPLC: t_R = 33.9 min, t_R = 54.5 min [Phenomenex Lux Cellulose-4; flow rate 1 mL min^{-1}; hexane/2-PrOH (8:2); 20 °C].

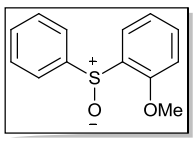
Benzyl 4-chlorobenzyl sulfoxide [102][82] (**Table 3.13, entry 26**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[44]** (249 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide, sulfoxide and sulfone (12:86:2). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield benzyl 4-chlorobenzyl sulfoxide **[102]** as a white solid (207 mg, 78%, 13% ee); m.p. 127–130 °C; ^{1}H NMR δ_H (300 MHz) 3.76 (1H, A of AB system, *J* 13.2 Hz, $SOCH_2$), 3.88 (1H, B of AB system, *J* 13.2 Hz, $SOCH_2$), 3.91 (2H, s, $SOCH_2$), 7.16–7.43 (9H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 56.2 ($SOCH_2$), 57.6 ($SOCH_2$), 128.5 (CH_{Ar}), 128.8 ($C_{Ar(q)}$), 128.4 (CH_{Ar}), 129.1 (CH_{Ar}), 129.9 ($C_{Ar(q)}$), 130.1 (CH_{Ar}), 131.5 (CH_{Ar}), 134.5 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2918, 1496, 1474, 1445, 1043, 763, 698; HPLC: t_R

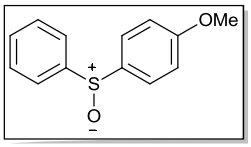
= 28.7 min, t_R = 32.7 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C].

(+)-2-Methoxyphenyl phenyl sulfoxide [103][83] (**Table 3.13, entry 32**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[47]** (216 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide and sulfoxide (70:30). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield 2-methoxyphenyl phenyl sulfoxide **[103]** as a white solid (65 mg, 28%, 20% ee); m.p. 96–98 °C (Lit.[175] m.p. 98–99 °C, racemic); ^{1}H NMR δ_H (300 MHz) 3.82 (3H, s, Ar-OCH$_3$), 6.93–6.98 (1H, m, Ar-H), 7.14–7.19 (1H, m, Ar-H), 7.22–7.25 (1H, m, Ar-H), 7.35 (1H, t, *J* 7.6 Hz, Ar-H), 7.40–7.50 (3H, m, Ar-H), 7.61–7.69 (2H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 55.6 (Ar-OCH$_3$), 109.1 (CH$_{Ar}$), 117.0 (CH$_{Ar}$), 117.4 (CH$_{Ar}$), 124.8 (CH$_{Ar}$), 129.3 (CH$_{Ar}$), 130.3 (CH$_{Ar}$), 131.1 (CH$_{Ar}$), 145.6 (C$_{Ar(q)}$), 147.0 (C$_{Ar(q)}$), 160.4 (C$_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2937, 1477, 1443, 1038, 751; HPLC: t_R = 16.0 min (+), t_R = 21.9 min (−) [Chiracel OJ-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 19.2° (*c* 1.0, CHCl$_3$).

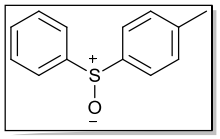
(+)-4-Methoxyphenyl phenyl sulfoxide [104][84] (**Table 3.13, entry 34**)



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[48]** (216 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow solid. The crude product contained a mixture of sulfide and sulfoxide (41:59). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield 4-methoxyphenyl phenyl sulfoxide **[104]** as a white solid (123 mg, 53%, 17% ee); m.p. 67–69 °C (Lit.[175] m.p. 61–62 °C, racemic); ^{1}H NMR δ_H (400 MHz) 3.82 (3H, s, O-CH$_3$), 6.91–7.00 (2H, m, Ar-H), 7.39–7.50 (3H, m, Ar-H), 7.53–7.65 (4H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 55.5 (Ar-OCH$_3$), 114.8 (CH$_{Ar}$), 124.6 (CH$_{Ar}$), 127.3 (CH$_{Ar}$), 129.2 (CH$_{Ar}$), 130.7 (CH$_{Ar}$), 136.8 (C$_{Ar(q)}$), 145.9 (C$_{Ar(q)}$), 162.1 (C$_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1}

2838, 1594, 1496, 1255, 1090, 1042, 751; HPLC: t_R = 81.1 min (+), t_R = 87.8 min (−) [Phenomenex Lux Cellulose-4; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 11.8° (*c* 1.0, $CHCl_3$).

(*R*)-(+)-4-Methylphenyl phenyl sulfoxide [105][85] (**Table 3.13, entry 37**)

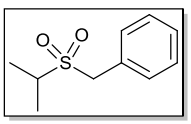


Copper(II) acetylacetonate (5.2 mg, 2.0 mol%), Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and sulfide **[49]** (200 mg, 1 mmol) in hexane/methanol (9:1, 2 mL) were used as described for **[56]** to give the crude product as a yellow oil. The crude product contained a mixture of sulfide and sulfoxide (68:32). The sulfoxide was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield 4-methylphenyl phenyl sulfoxide **[105]** as a white solid (56 mg, 26%, 10% ee); m.p. 73–76 °C (Lit.[176] m.p. 78–82 °C; ^{1}H NMR δ_H (400 MHz) 2.67 (3H, s, Ar-CH_3), 7.22–7.29 (3H, m, Ar-H), 7.40–7.57 (4H, m, Ar-H), 7.60–7.66 (2H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2920, 1443, 1090, 1044; HPLC: t_R (*S*) = 60.2 min, t_R = 87.8 min (*R*) [Chiracel AS-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 3.2° (*c* 1.0, $CHCl_3$), {ref[177] $[\alpha]_D^{20}$ = − 24.0° ($CHCl_3$) for (*S*)-enantiomer}.

Absolute configuration was determined by comparison of specific rotation value to known literature value.

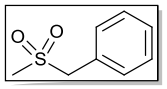
3.5 Preparation of Sulfones

Isopropyl benzyl sulfone [114][93]



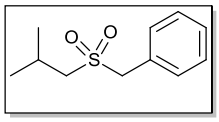
Isopropyl benzyl sulfide **[35]** (1 mmol, 166 mg), *m*-CPBA (77%, 2.3 mmol, 517 mg) and CH_2Cl_2 (20 mL) were added to a round bottomed flask and stirred for 16 h. Water (10 mL) was added to the flask and the layers were separated. The organic layer was washed with aqueous sodium hydroxide (2M, 3 × 10 mL) and brine (20 mL), dried, filtered and concentrated under reduced pressure to give isopropyl benzyl sulfone **[114]** as a white solid (172 mg, 87%); m.p. 66–67 °C, (Lit.[94] m.p. 65 °C); ^{1}H NMR δ_H (300 MHz) 1.37 (6H, d, *J* 6.9 Hz, [CH(C*H*$_3$)$_2$)], 2.90–3.09 (1H, m, [C*H*(CH$_3$)$_2$)], 4.23 (2H, s, SO_2CH_2), 7.33–7.48 (5H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2924, 1456, 1304, 1115, 699.

Methyl benzyl sulfone [131][107]



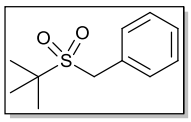
Methyl benzyl sulfide **[169]** (138 mg, 1 mmol) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to methyl benzyl sulfone **[131]** as a white solid (172 mg, 81%); 119–121 °C, (Lit.[107] m.p. 127 °C); ^{1}H NMR δ_H (300 MHz) 2.76 (3H, s, CH_3), 4.26 (2H, s, SO_2CH_2), 7.31–7.48 (5H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2931, 1306, 1253, 1120, 788, 701.

Isobutyl benzyl sulfone [115][94]



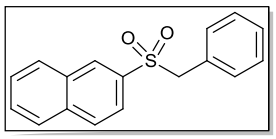
Isobutyl benzyl sulfide **[37]** (1 mmol, 180 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give isobutyl benzyl sulfone **[115]** as a white solid (172 mg, 81%); m.p. 84–85 °C, (Lit.[94] m.p. 87 °C); ^{1}H NMR δ_H (300 MHz) 1.08 (6H, d, *J* 6.9 Hz, [CH(C*H*$_3$)$_2$)], 2.23–2.40 (1H, m, [C*H*(CH$_3$)$_2$)], 2.72 (2H, d, *J* 6.6 Hz, SO_2CH_2-CH), 4.21 (2H, s, SO_2CH_2Ar), 7.41 (5H, m, appears as a singlet, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2965, 1456, 1304, 1114, 699.

***tert*-Butyl benzyl sulfone [116]**[95]



Tert-butyl benzyl sulfide **[38]** (1 mmol, 180 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give *tert*-butyl benzyl sulfone **[116]** as a white solid (163 mg, 77%); m.p. 124–126 °C, (Lit.[95] m.p. 122 °C); ^{1}H NMR δ_H (300 MHz) 1.44 [9H, s C(C*H*$_3$)$_3$], 4.20 (2H, s, SO_2CH_2), 7.33–7.47 (5H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2973, 1457, 1295, 1282, 1022, 1113.1, 701.

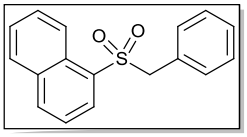
2-Naphthyl benzyl sulfone [117][43]



2-Naphthyl benzyl sulfide **[29]** (1 mmol, 250 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 2-naphthyl benzyl sulfone **[117]** as a white solid (211 mg, 75%); m.p. 194–195 °C, (Lit.[96] m.p. 193 °C); ^{1}H NMR δ_H (300 MHz) 4.38 (2H, s,

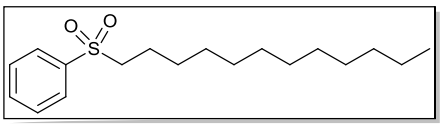
SO_2CH_2), 7.03–7.14 (2H, m, Ar-H), 7.17–7.36 (3H, m, Ar-H), 7.53–7.71 (3H, m, Ar-H), 7.81–7.96 (3H, m, Ar-H), 8.16–8.23 (1H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 3063, 1456, 1312, 1117, 697.

1-Naphthyl benzyl sulfone [118][96]



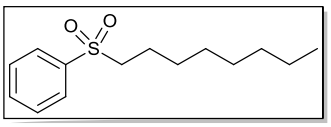
1-Naphthyl benzyl sulfide **[30]** (1 mmol, 250 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 1-naphthyl benzyl sulfone **[118]** as a white solid (228 mg, 81%); m.p. 114–115 °C, (Lit.[96] m.p. 111.5–112.5 °C); ^{1}H NMR δ_H (300 MHz) 4.51 (2H, s, SO_2CH_2), 6.88–7.00 (2H, m, Ar-H), 7.09–7.30 (3H, m, Ar-H), 7.39–7.49 (1H, m, Ar-H), 7.56–7.74 (2H, m, Ar-H), 7.90-8.01 (2H, m, Ar-H), 8.03-8.12 (1H, m, Ar-H), 8.77 (1H, d, *J* 8.7 Hz, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2938, 1454, 1314, 1149, 696.

Dodecyl phenyl sulfone [120][98]



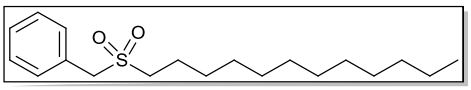
Dodecyl phenyl sulfide **[27]** (1 mmol, 279 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give dodecyl phenyl sulfone **[114]** as a white solid (279 mg, 90%); m.p. 62–63 °C, (Lit.[98] m.p. 62 °C); ^{1}H NMR δ_H (300 MHz) 0.88 (3H, t, *J* 6.6 Hz, CH_3), 1.12–1.52 (18H, m), 1.62–1.80 (2H, m), 3.00–3.14 (2H, m, SO_2CH_2), 7.50–7.70 (3H, m, Ar-H), 7.87–7.96 (2H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2917, 1287, 1153, 689.

Octyl phenyl sulfone [121][99]



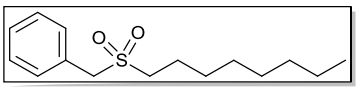
Octyl phenyl sulfide **[28]** (1 mmol, 222 mg) and (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give octyl phenyl sulfone **[121]** as a white solid (224 mg, 88%); m.p. 48–51 °C; ^{1}H NMR δ_H (300 MHz) 0.86 (3H, t, *J* 6.6 Hz, CH_3), 1.12–1.43 (10H, m), 1.63–1.79 (2H, m), 3.00–3.12 (2H, m, SO_2CH_2), 7.50–7.71 (3H, m, Ar-H), 7.84–7.95 (2H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2917, 2847, 1283, 1272, 1137, 1125, 696.

Dodecyl benzyl sulfone [122][100]



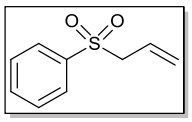
Dodecyl benzyl sulfide **[33]** (1 mmol, 293 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give dodecyl benzyl sulfone **[122]** as a white solid (295 mg, 91%); m.p. 80–81 °C, (Lit.[100] m.p. 77–78 °C); ^{1}H NMR δ_H (300 MHz) 0.88 (3H, t, *J* 6.6 Hz, CH_3), 1.15–1.41 (18H, m), 1.70–1.88 (2H, m), 2.73–2.88 (2H, m, SO_2CH_2), 4.21 (2H, s, SO_2CH_2-Ar), 7.40 (5H, m, appears as a singlet, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2917, 1464, 1303, 1126, 696.

Octyl benzyl sulfone [123][100]



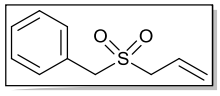
Octyl benzyl sulfide **[34]** (1 mmol, 236 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give octyl benzyl sulfone **[123]** as a white solid (225 mg, 84%); m.p. 66–67 °C, (Lit.[100] m.p. 65–66 °C); ^{1}H NMR δ_H (300 MHz) 0.87 (3H, t, *J* 6.3 Hz, CH_3), 1.15–1.42 (10H, m), 1.70–1.88 (2H, m), 2.73–2.86 (2H, m, SO_2CH_2), 4.21 (2H, s, SO_2CH_2-Ar), 7.40 (5H, m, appears as a singlet, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2916, 1457, 1278, 1123, 695.

Allyl phenyl sulfone [129][105]



Allyl phenyl sulfide (1 mmol, 150 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give allyl phenyl sulfone **[129]** as a clear oil (133 mg, 73%); ^{1}H NMR δ_H (300 MHz) 3.82 (2H, d, *J* 7.2 Hz, SO_2CH_2), 5.15 (1H, d, *J* 17.0 Hz, -CH=CH_2), 5.34 (1H, d, *J* 10.2 Hz, -CH=CH_2), 5.70–5.90 (1H, m, -C*H*=CH_2), 7.49–7.71 (3H, m, Ar-H), 7.80–7.92 (2H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 3068, 1448, 1309, 1147, 1086, 689.

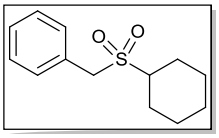
Allyl benzyl sulfone [130][106]



Allyl benzyl sulfide **[168]** (1 mmol, 164 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give allyl benzyl sulfone **[130]** as a white solid (159 mg, 81%); m.p. 63–64 °C, (Lit.[178] m.p.

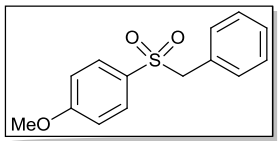
60.5–61.5 °C); ^{1}H NMR δ_H (300 MHz) 3.59 (2H, d, *J* 7.2 Hz, $SOCH_2$), 4.22 (2H, s, $SOCH_2$-Ar), 5.42 (1H, d, *J* 17.1 Hz, -CH=CH_2), 5.53 (1H, d, *J* 10.2 Hz, -CH=CH_2), 5.83–6.01 (1H, m, -C*H*=CH_2), 7.41 (5H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2922, 1456, 1316, 1119, 699.

Cyclohexyl benzyl sulfone [119][97]



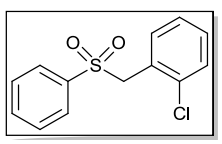
Cyclohexyl benzyl sulfide **[36]** (206 mg, 1 mmol) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give cyclohexyl benzyl sulfone **[119]** as a white solid (195 mg, 82%); m.p. 103–105 °C, (Lit.[97] m.p. 99–101 °C); ^{1}H NMR δ_H (300 MHz) 1.10–1.32 (3H, m, cyclohexyl protons), 1.47–1.76 (3H, m, cyclohexyl protons), 1.81–1.99 (2H, m, cyclohexyl protons), 2.06–2.20 (2H, m, cyclohexyl protons), 2.68–2.81 (1H, m, $CHSO_2$ of cyclohexyl protons) 4.19 (2H, s, SO_2CH_2), 7.33–7.49 (5H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2925, 1447, 1306, 1149, 1087.

4-Methoxyphenyl benzyl sulfone [109][89]



4-Methoxyphenyl benzyl sulfide **[1]** (1 mmol, 230 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 4-methoxyphenyl benzyl sulfone **[109]** as a white solid (193 mg, 84%); m.p. 88–92 °C, (Lit.[89] m.p. 96–98 °C) ^{1}H NMR δ_H (400 MHz) 3.85 (3H, s, Ar-OCH_3), 4.28 (2H, s, SO_2CH_2), 6.84–6.93 (2H, m, Ar-H), 7.04–7.13 (2H, m, Ar-H), 7.21–7.35 (2H, m, Ar-H), 7.48–7.55 (2H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2943, 1316, 1295, 1285, 1149, 696.

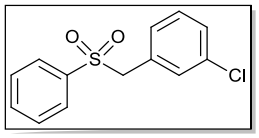
2-Chlorobenzyl phenyl sulfone [132][108]



2-Chlorobenzyl phenyl sulfide **[11]** (1 mmol, 235 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 2-chlorobenzyl phenyl sulfone **[132]** as a white solid (232

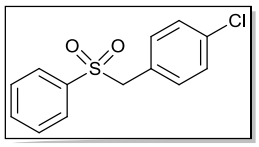
mg, 87%); m.p. 66–68 °C; ^{1}H NMR δ_H (300 MHz) 4.56 (2H, s, SO_2CH_2), 7.20–7.31 (3H, m, Ar-H), 7.39–7.50 (3H, m, Ar-H), 7.53–7.70 (3H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2930, 1447, 1320, 1310, 1157, 1139, 1085, 758, 556.

3-Chlorobenzyl phenyl sulfone [133][33]



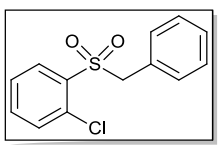
3-Chlorobenzyl phenyl sulfide **[12]** (1 mmol, 235 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 3-chlorobenzyl phenyl sulfone **[133]** as a white solid (211 mg, 79%); m.p. 106–108 °C, (Lit.[33] m.p. 110–111 °C); ^{1}H NMR δ_H (300 MHz) 4.27 (2H, s, SO_2CH_2), 6.94–7.10 (2H, m, Ar-H), 7.15–7.33 (2H, m, Ar-H), 7.42–7.52 (2H, m, Ar-H), 7.59–7.71 (3H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2941, 1446, 1309, 1151, 1087, 736, 689.

4-Chlorobenzyl phenyl sulfone [134][33,87]



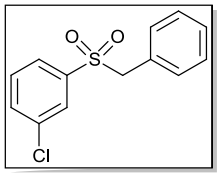
4-Chlorobenzyl phenyl sulfide **[13]** (1 mmol, 235 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 4-chlorobenzyl phenyl sulfone **[134]** as a white solid (213 mg, 80%); m.p. 189–191 °C, (Lit.[33] m.p. 189–191 °C); ^{1}H NMR δ_H (300 MHz) 4.27 (2H, s, SO_2CH_2), 7.02 (2H, d, *J* 8.4 Hz, Ar-H), 7.16–7.32 (2H, m, Ar-H), 7.41–7.53 (2H, m, Ar-H), 7.54–7.70 (3H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2941, 1309, 1280, 1151, 1087, 736, 689.

2-Chlorophenyl benzyl sulfone [135][109]



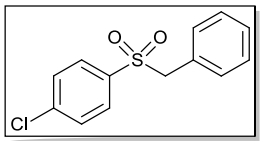
2-Chlorophenyl benzyl sulfide **[14]** (1 mmol, 235 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 2-chlorophenyl benzyl sulfone **[136]** as a white solid (224 mg, 84%); m.p. 101–103 °C, (Lit.[109] m.p. 102–103 °C); ^{1}H NMR δ_H (400 MHz) 4.65 (2H, s, SO_2CH_2), 7.13–7.32 (6H, m, Ar-H), 7.44–7.60 (2H, m, Ar-H), 7.73–7.80 (1H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2944, 1300, 1277, 1118, 694.

3-Chlorophenyl benzyl sulfone [136][109]



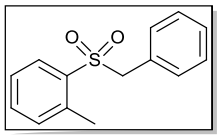
3-Chlorophenyl benzyl sulfide **[15]** (1 mmol, 235 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 3-chlorophenyl benzyl sulfone **[136]** as a white solid (224 mg, 84%); m.p. 109–111 °C ^{1}H NMR δ_H (300 MHz), 4.32 (2H, s, SO_2CH_2), 7.10 (2H, d, *J* 8.4 Hz, Ar-H), 7.23–7.68 (7H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2936, 1318, 1296, 1155, 695.

4-Chlorophenyl benzyl sulfone [137][110,104]



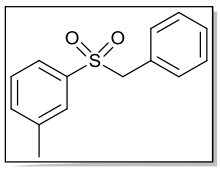
4-Chlorophenyl benzyl sulfide **[16]** (1 mmol, 235 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 4-chlorophenyl benzyl sulfone **[137]** as a white solid (208 mg, 78%); m.p. 144–146 °C, (Lit.[110] m.p. 142–145 °C); ^{1}H NMR δ_H (300 MHz) 4.31 (2H, s, SO_2CH_2), 7.01–7.13 (2H, m, Ar-H), 7.21–7.45 (5H, m, Ar-H), 7.48–7.59 (2H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2943, 1314, 1151, 1091, 698.

Benzyl *o*-tolyl sulfone [124][179]



Benzyl *o*-tolyl sulfide **[5]** (1 mmol, 214 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give benzyl *o*-tolyl sulfone **[124]** as a white solid (199 mg, 81%); m.p. 94–97 °C, (Lit.[179] m.p. 94–94.5 °C); ^{1}H NMR δ_H (300 MHz) 2.52 (3H, s, Ar-H), 4.33 (2H, s, SO_2CH_2), 7.01–7.12 (2H, m, Ar-H), 7.18–7.34 (5H, m, Ar-H), 7.40–7.51 (1H, m, Ar-H), 7.70 (1H, dd, *J* 7.8 Hz and 1.2 Hz); IR (KBr) ν_{max}/cm^{-1} 2928, 1456, 1312, 1154, 1120, 698.

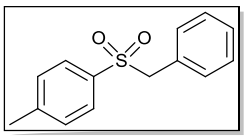
Benzyl *m*-tolyl sulfone [125][101]



Benzyl *m*-tolyl sulfide **[6]** (1 mmol, 214 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give benzyl *m*-tolyl sulfone **[125]** as a white solid (219 mg, 89%); m.p.

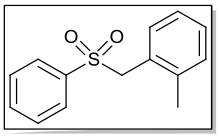
91–94 °C, (Lit.[101] m.p. 95 °C); ^{1}H NMR δ_H (300 MHz) 2.35 (3H, s, Ar-H), 4.29 (2H, s, SO_2CH_2), 7.02–7.13 (2H, m, Ar-H), 7.20–7.48 (7H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2923, 1456, 1402, 1316, 1301, 1128, 690.

Benzyl *p*-tolyl sulfone [107][43,86]



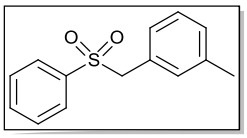
Benzyl *p*-tolyl sulfide **[7]** (1 mmol, 214 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give benzyl *p*-tolyl sulfone **[107]** as a white solid (221 mg, 90%); m.p. 142–144 °C, (Lit.[86] m.p. 140–141 °C); ^{1}H NMR δ_H (300 MHz) 2.42 (3H, s, Ar-H), 4.29 (2H, s, SO_2CH_2), 7.03–7.13 (2H, m, Ar-H), 7.19–7.37 (5H, m, Ar-H), 7.45–7.53 (2H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2925, 1596, 1456, 1410, 1311, 1303, 1153, 1130, 1085, 702.

2-Methylbenzyl phenyl sulfone [126][87,102]



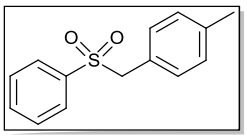
2-Methylbenzyl phenyl sulfide **[8]** (1 mmol, 214 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 2-methylbenzyl phenyl sulfone **[126]** as a white solid (212 mg, 86%); m.p. 69–71 °C, (Lit.[102] m.p. 73–75 °C); ^{1}H NMR δ_H (300 MHz) 2.11 (3H, s, Ar-H), 4.38 (2H, s, SO_2CH_2), 6.99–7.30 (4H, m, Ar-H), 7.40–7.53 (2H, m, Ar-H), 7.59–7.70 (3H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2925, 1445, 1305, 1288, 1143, 1081, 601.

3-Methylbenzyl phenyl sulfone [127][103]



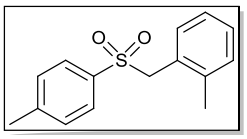
3-Methylbenzyl phenyl sulfide **[9]** (1 mmol, 214 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 3-methylbenzyl phenyl sulfone **[127]** as a white solid (226 mg, 92%); m.p. 121–123 °C, (Lit.[103] m.p. 120–121 °C); ^{1}H NMR δ_H (300 MHz) 2.26 (3H, s, Ar-H), 4.26 (2H, s, SO_2CH_2), 6.80–6.92 (2H, m, Ar-H), 7.08–7.19 (2H, m, Ar-H), 7.40–7.52 (2H, m, Ar-H), 7.53–7.70 (3H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2920, 1456, 1308, 1287, 1152, 1122, 698.

4-Methylbenzyl phenyl sulfone [128][104,103]



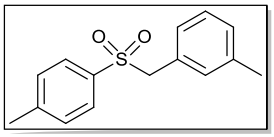
4-Methylbenzyl phenyl sulfide **[10]** (1 mmol, 214 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 4-methylbenzyl phenyl sulfone **[128]** as a white solid (204 mg, 83%); m.p. 146–148 °C, (Lit.[103] m.p. 151–152 °C); ^{1}H NMR δ_H (300 MHz) 2.32 (3H, s, Ar-H), 4.27 (2H, s, SO_2CH_2), 6.96 (2H, d, *J* 8.1 Hz, Ar-H), 7.06 (2H, d, *J* 7.8 Hz, Ar-H), 7.40–7.51 (2H, m, Ar-H), 7.53–7.70 (3H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2919, 1308, 1155, 1120, 701, 526.

2'-Methylbenzyl 4-methylphenyl sulfone [138][111]



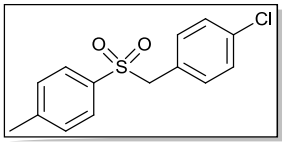
2′-Methylbenzyl 4-methylphenyl sulfide **[17]** (1 mmol, 228 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 2'-methylbenzyl 4-methylphenyl sulfone **[138]** as a white solid (234 mg, 90%); m.p. 168–172 °C; ^{1}H NMR δ_H (300 MHz) 2.12 (3H, s, Ar-CH_3), 2.43 (3H, s, Ar-CH_3), 4.36 (2H, s SO_2CH_2), 6.99–7.31 (6H, m, Ar-H), 7.52 (2H, d, *J* 8.4 Hz, Ar-H), 7.52 (2H, d, *J* 8.4 Hz, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2925, 1317, 1156, 1135, 1086, 566.

3'-Methylbenzyl 4-methylphenyl sulfone [139]



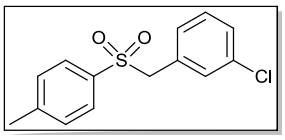
3'-Methylbenzyl 4-methylphenyl sulfide **[18]** (1 mmol, 228 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 3'-methylbenzyl 4-methylphenyl sulfone **[139]** as a white solid (229 mg, 88%); m.p. 151–154 °C; ^{1}H NMR δ_H (300 MHz) 2.27 (3H, s, Ar-CH_3), 2.42 (3H, s, Ar-CH_3), 4.24 (2H, s SO_2CH_2), 6.79–6.95 (2H, m, Ar-H), 7.08–7.30 (4H, m, Ar-H), 7.52 (2H, d, *J* 8.4 Hz, Ar-H); ^{13}C NMR δ_C (75 MHz) 21.2 (Ar-CH_3), 21.6 (Ar-CH_3), 63.0 (SO_2CH_2), 127.9 (CH_{Ar}), 128.1 ($C_{Ar(q)}$), 128.4 (CH_{Ar}), 128.7 (CH_{Ar}), 129.4 (CH_{Ar}), 131.6 (CH_{Ar}), 135.2 ($C_{Ar(q)}$), 138.3 ($C_{Ar(q)}$), 144.6 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2926, 1597, 1309, 1155, 1089, 750; (Found: C, 69.26; H, 6.08. $C_{15}H_{16}O_2S$ Requires C, 69.20; H, 6.19).

4'-Chlorobenzyl 4-methylphenyl sulfone [140][112,113]



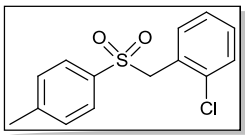
4'-Chlorobenzyl 4-methylphenyl sulfide **[19]** (1 mmol, 249 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 4'-chlorobenzyl 4-methylphenyl sulfone **[140]** as a white solid (222 mg, 79%); m.p. 166–168 °C, (Lit.[113] m.p. 167–168 °C); ^{1}H NMR δ_H (300 MHz) 2.43 (3H, s, Ar-CH_3), 4.25 (2H, s SO_2CH_2), 7.03 (2H, d, *J* 8.7 Hz, Ar-H), 7.17–7.31 (4H, m, Ar-H), 7.52 (2H, d, *J* 8.4 Hz, Ar-H); IR (KBr) ν_{max}/cm^{-1} 3067, 1448, 1319, 1147, 689.

3'-Chlorobenzyl 4-methylphenyl sulfone [141][36]



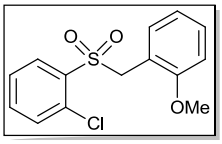
3'-Chlorobenzyl 4-methylphenyl sulfide **[20]** (1 mmol, 249 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 3'-chlorobenzyl 4-methylphenyl sulfone **[141]** as a white solid (208 mg, 74%); m.p. 116–118 °C, (Lit.[36] m.p. 120–121 °C); ^{1}H NMR δ_H (300 MHz) 2.43 (3H, s, Ar-CH_3), 4.25 (2H, s SO_2CH_2), 6.91–7.13 (2H, m, Ar-H), 7.14–7.38 (4H, m, Ar-H), 7.40–7.61 (2H, d, *J* 8.4 Hz, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2928, 1598, 1317, 1151, 667.

2'-Chlorobenzyl 4-methylphenyl sulfone [142][114]



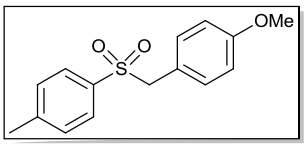
2'-Chlorobenzyl 4-methylphenyl sulfide **[21]** (1 mmol, 249 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 2'-chlorobenzyl 4-methylphenyl sulfone **[142]** as a white solid (233 mg, 83%); m.p. 133–135 °C; ^{1}H NMR δ_H (300 MHz) 2.43 (3H, s, Ar-CH_3) 4.54 (3H, s, SO_2CH_2), 7.19-7.33 (5H, m, Ar-H); 7.40-7.55 (3H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2925, 1596, 1320, 1156, 555.

2'-Methoxybenzyl 2-chlorophenyl sulfone [143]



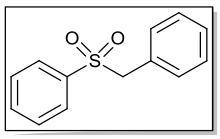
2'-Methoxybenzyl 2-chlorophenyl sulfide **[22]** (1 mmol, 265 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 2'-methoxybenzyl 2-chlorophenyl sulfone **[143]** as a white solid (228 mg, 77%); m.p. 122–124 °C; ^{1}H NMR δ_H (300 MHz) 4.02 (3H, s, O-CH_3), 4.83 (2H, s, SO_2CH_2), 6.93–7.10 (2H, m, Ar-H); 7.15–7.35 (3H, m, Ar-H), 7.37–7.46 (1H, m, Ar-H), 7.52–7.62 (1H, m, Ar-H), 7.72 (1H, dd, *J* 7.8 Hz and 1.8 Hz, Ar-H); ^{13}C NMR δ_C (75 MHz) 56.3 (Ar-OCH_3), 57.1 (SO_2CH_2), 112.2 (CH_{Ar}), 120.5 (CH_{Ar}), 126.4 ($C_{Ar(q)}$), 126.6 ($C_{Ar(q)}$), 126.9 (CH_{Ar}), 129.7 (CH_{Ar}), 130.0 (CH_{Ar}), 131.2 (CH_{Ar}), 133.0 (CH_{Ar}), 135.3 ($C_{Ar(q)}$), 135.9 (CH_{Ar}), 157.8 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 2941, 1592, 1480, 1317, 1130, 760; (Found: C, 56.84; H, 4.56. $C_{14}H_{13}ClO_2S$ Requires C, 56.66; H, 4.42).

4-Methylphenyl 4'-methoxybenzyl sulfone [108][87,88]



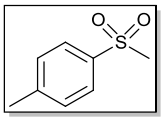
4-Methylphenyl 4'-methoxybenzyl sulfide **[4]** (1 mmol, 276 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 4-methylphenyl 4'-methoxybenzyl sulfone **[108]** as a white solid (218 mg, 79%); m.p. 114–118 °C, (Lit.[88] m.p. 119–121 °C); ^{1}H NMR δ_H (400 MHz) 2.42 (3H, s, Ar-H), 3.79 (3H, s, Ar-OCH_3), 4.26 (2H, s, SO_2CH_2), 6.74–6.82 (2H, m, Ar-H), 6.95–7.05 (2H, m, Ar-H), 7.21–7.29 (2H, m, Ar-H), 7.48–7.55 (2H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2941, 1448, 1306, 1144, 1086, 733.

Benzyl phenyl sulfone [106][43]



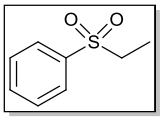
Benzyl phenyl sulfide (1 mmol, 200 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give benzyl phenyl sulfone **[106]** as a white solid (218 mg, 94%); m.p. 146–148 °C, (Lit.[33] m.p. 147–148 °C); ^{1}H NMR δ_H (400 MHz) 4.31 (2H, s, SO_2CH_2), 7.01–7.13 (2H, m, Ar-H), 7.19–7.33 (3H, m, Ar-H), 7.38–7.49 (2H, m, Ar-H), 7.53–7.65 (3H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2944, 1309, 1152, 689.

Methyl *p*-tolyl sulfone [110][43]



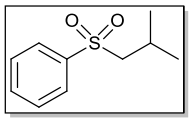
Methyl *p*-tolyl sulfide (1 mmol, 138 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give methyl *p*-tolyl sulfone **[110]** as a white solid (155 mg, 91%); m.p. 84–86 °C, (Lit.[180] m.p. 85–86 °C); ^{1}H NMR δ_H (400 MHz) 2.46 (3H, Ar-CH_3), 3.03 (3H, s, SO_2CH_3), 7.37 (2H, d, *J* 8.0 Hz, Ar-H), 7.83 (2H, d, *J* 8.4 Hz, Ar-H); IR (KBr) ν_{max}/cm^{-1} 3018, 1320, 1301, 1289, 1148, 762, 538.

Ethyl phenyl sulfone [111][90]



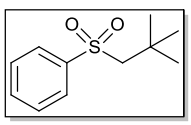
Ethyl phenyl sulfide (1 mmol, 138 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give ethyl phenyl sulfone **[111]** as a white solid (150 mg, 88%); m.p. 40–42 °C, (Lit.[181] m.p. 43 °C); ^{1}H NMR δ_H (400 MHz) 1.28 (3H, t, *J* 7.2 Hz, CH_2CH_3), 3.12 (2H, q, *J* 7.6 Hz, CH_2CH_3), 7.53–7.71 (3H, m, Ar-H), 7.87–7.95 (2H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2919, 1455, 1320, 1153, 1039, 697.

Isobutyl phenyl sulfone [112][91]



Isobutyl phenyl sulfide **[24]** (1 mmol, 166 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give isobutyl phenyl sulfone **[112]** as a white solid (159 mg, 80%); m.p. 74–77 °C; ^{1}H NMR δ_H (400 MHz) 1.06 [6H, d, *J* 6.8 Hz, $CH(CH_3)_2$], 2.18–2.31 [1H, m, $CH(CH_3)_2$)], 2.99 (2H, d, *J* 6.4 Hz, SO_2CH_2), 7.51–7.69 (3H, m, Ar-H), 7.89–7.96 (2H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2941, 1447, 1306, 1145, 1087, 731, 586.

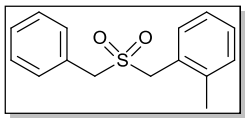
Neopentyl phenyl sulfone [113][92]



Neopentyl phenyl sulfide **[46]** (1 mmol, 180 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give neopentyl phenyl sulfone **[113]** as a white solid (157 mg, 74%); m.p. 38–40 °C, (Lit.[92] m.p. 38–39 °C); ^{1}H NMR δ_H (400 MHz) 1.14 [9H, s, $C(CH_3)_3$], 3.04 (2H, s,

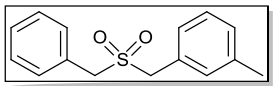
SO_2CH_2), 7.51–7.60 (2H, m, Ar-H), 7.61–7.67 (1H, m, Ar-H), 7.89–7.96 (2H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2962, 1477, 1447, 1370, 1306, 1242, 1149, 1086.

Benzyl 2-methylbenzyl sulfone [144][115]



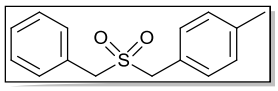
Benzyl 2-methylbenzyl sulfide **[39] (**1 mmol, 228 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give benzyl 2-methylbenzyl sulfone **[144]** as a white solid (237 mg, 91%); m.p. 137–139 °C; ^{1}H NMR δ_H (300 MHz) 2.34 (3H, s, Ar-CH_3), 4.08 (2H, s, SO_2CH_2), 4.11 (2H, s, SO_2CH_2), 7.09–7.45 (9H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2944, 1413, 1283, 1117, 753, 692.

Benzyl 3-methylbenzyl sulfone [145]



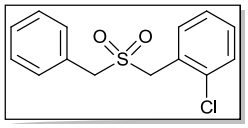
Benzyl 3-methylbenzyl sulfide **[40] (**1 mmol, 228 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give benzyl 3-methylbenzyl sulfone **[145]** as a white solid (216 mg, 83%); m.p. 146–148 °C; ^{1}H NMR δ_H (300 MHz) 2.37 (3H, s, Ar-CH_3), 4.10 (2H, s, SO_2CH_2), 4.13 (2H, s, SO_2CH_2), 7.11–7.47 (9H, m, Ar-H); ^{13}C NMR δ_C (75 MHz) 21.4 (Ar-CH_3), 58.0 (SO_2CH_2), 58.1 (SO_2CH_2), 127.4 ($C_{Ar(q)}$), 127.6 ($C_{Ar(q)}$), 127.9 (CH_{Ar}), 128.9 (CH_{Ar}), 129.0 (CH_{Ar}), 129.8 (CH_{Ar}), 130.9 (CH_{Ar}), 131.6 (CH_{Ar}), 138.8 ($C_{Ar(q)}$), one CH_{Ar} not seen; IR (KBr) ν_{max}/cm^{-1} 2941, 1282, 1305, 1124, 1114, 693; (Found: C, 69.31; H, 6.11. $C_{15}H_{16}O_2S$ Requires C, 69.20; H, 6.19).

Benzyl 4-methylbenzyl sulfone [146][115]



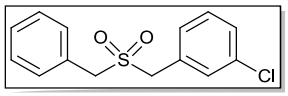
Benzyl 4-methylbenzyl sulfide **[41] (**1 mmol, 228 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give benzyl 4-methylbenzyl sulfone **[146]** as a white solid (224 mg, 86%); m.p. 162–164 °C; ^{1}H NMR δ_H (300 MHz) 2.37 (3H, s, Ar-CH_3), 4.09 (2H, s, SO_2CH_2), 4.11 (2H, s, SO_2CH_2), 7.14–7.30 (4H, m, Ar-H), 7.32–7.47 (5H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2941, 1280, 1116, 690, 505.

Benzyl 2-chlorobenzyl sulfone [147][116]



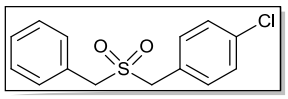
Benzyl 2-chlorobenzyl sulfide **[42] (**1 mmol, 249 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give benzyl 2-chlorobenzyl sulfone **[147]** as a white solid (225 mg, 80%); m.p. 104–108 °C, (Lit.[116] m.p. 120.5–122 °C); ^{1}H NMR δ_H (300 MHz) 4.22 (2H, s, SO_2CH_2), 4.45 (2H, s, SO_2CH_2), 7.21–7.60 (9H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2987, 1416, 1317, 1124, 702, 511.

Benzyl 3-chlorobenzyl sulfone [148][117]



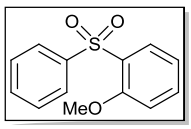
Benzyl 3-chlorobenzyl sulfide **[43] (**1 mmol, 249 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give benzyl 3-chlorobenzyl sulfone **[148]** as a white solid (213 mg, 76%); m.p. 131–133 °C; ^{1}H NMR δ_H (300 MHz) 4.08 (2H, s, SO_2CH_2), 4.17 (2H, s, SO_2CH_2), 7.21–7.48 (9H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2944, 1300, 1276, 1118, 737, 694.

Benzyl 4-chlorobenzyl sulfone [149][117]



Benzyl 4-chlorobenzyl sulfide **[44] (**1 mmol, 249 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give benzyl 4-chlorobenzyl sulfone **[149]** as a white solid (227 mg, 81%); m.p. 168–170 °C; ^{1}H NMR δ_H (300 MHz) 4.08 (2H, s, SO_2CH_2), 4.16 (2H, s, SO_2CH_2), 7.20–7.49 (9H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2944, 1417, 1300, 1276, 1116, 694, 505.

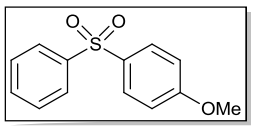
2-Methoxyphenyl phenyl sulfone [150][118]



2-Methoxyphenyl phenyl sulfide **[47] (**1 mmol, 249 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 2-methoxyphenyl phenyl sulfone **[150]** as a white solid (211 mg, 85%); ^{1}H NMR δ_H (300 MHz) 3.84 (3H, s, Ar-OCH_3), 7.08 (1H, dd, *J* 7.5 and 1.8 Hz,

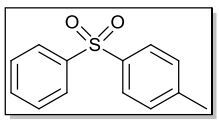
Ar-H), 7.33–7.61 (6H, m, Ar-H), 7.89–8.00 (2H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2919, 1593, 1497, 1260, 1150, 1106, 730, 577.

4-Methoxyphenyl phenyl sulfone [151][118]



4-Methoxyphenyl phenyl sulfide **[48] (**1 mmol, 249 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 4-methoxyphenyl phenyl sulfone **[151]** as a white solid (221 mg, 89%); ^{1}H NMR δ_H (300 MHz) 3.84 (3H, s, Ar-OCH_3), 6.90–7.02 (2H, m, Ar-H), 7.42–7.61 (3H, m, Ar-H), 7.82–7.99 (4H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2939, 1598, 1479, 1307, 1242, 1152, 726, 580.

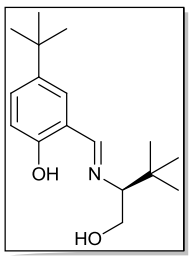
4-Methylphenyl phenyl sulfone [152][119]



4-Methylphenyl phenyl sulfide **[49] (**1 mmol, 200 mg) and *m*-CPBA (77%, 2.3 mmol, 517 mg) in CH_2Cl_2 (20 mL) were used as described for **[114]** to give 4-methylphenyl phenyl sulfone **[152]** as a white solid (195 mg, 84%); ^{1}H NMR δ_H (300 MHz) 2.40 (3H, s, Ar-CH_3), 7.30 (2H, d, *J* 8.1 Hz, Ar-H), 7.42–7.61 (3H, m, Ar-H), 7.79–7.88 (2H, m, Ar-H), 7.89–7.99 (2H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2925, 1447, 1318, 1295, 1308, 1157, 548.

3.6 Synthesis of Schiff Base Ligands

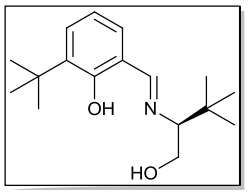
(*S*)-2-(*N*-5'-*tert*-Butylsalicylidene)-amino-3,3-dimethyl-1-butanol [153][26,123]



5-*tert*-Butyl-2-hydroxybenzaldehyde (342 mg, 0.32 mL, 1.836 mmol) and anhydrous sodium sulfate (0.65 g) were added to a solution of (*S*)-*tert*-leucinol (215 mg, 1.836 mmol) in ethanol (20 mL) stirring at RT. The resulting mixture turned a yellow colour upon addition of leucinol. The reaction mixture was then stirred under reflux for 16 h, cooled to RT, filtered and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and washed with water (3 × 10 mL) and brine (15 mL). The organic layer was dried and concentrated under reduced pressure to leave the crude product as a yellow crystalline solid

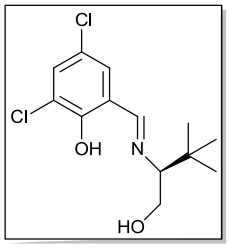
which was purified by column chromatography on silica gel (8:2, hexane/ethyl acetate) to yield **[153]** as a yellow crystalline solid (372 mg, 82 %); m.p. 119-120 °C (Lit.[26] m.p. 119–120 °C); ^{1}H NMR δ_H (300 MHz) 0.96 [9H, s, AlkC(CH_3)$_3$], 1.31 [9H, s, Ar-C(CH_3)$_3$], 1.62 (1H, bs, OH), 2.93 (1H, dd, *J* 9.5 and 2.8 Hz, CHN), 3.75 (1H, dd, *J* 11.0 and 9.6 Hz, one of C*H*$_2$OH), 3.92 (1H, dd, *J* 11.1 and 2.8 Hz, one of C*H*$_2$OH), 6.91 (1H, d, *J* 8.6 Hz, Ar-H), 7.26-7.28 (1H, m, Ar-H), 7.36 (1H, dd, *J* 8.6 and 2.5 Hz, Ar-H), 8.36 (1H, s, HC=N); ^{13}C NMR δ_C (75.5 MHz) 27.0 [C(*C*H$_3$)$_3$], 31.4 [C(*C*H$_3$)$_3$], 33.2 [*C*(CH$_3$)$_3$], 34.0 [*C*(CH$_3$)$_3$], 62.5 (CH$_2$OH), 81.3 (NCH), 116.5 (CH$_{Ar}$), 117.8 (C$_{Ar(q)}$), 128.0 (CH$_{Ar}$), 129.8 (CH$_{Ar}$), 141.5 (C$_{Ar(q)}$), 158.9 (C$_{Ar(q)}$), 166.4 (HC=N); IR (KBr) ν_{max}/cm^{-1} 3422, 2958, 1633, 1493; (Found: C, 73.31; H, 9.89; N, 5.12 $C_{17}H_{27}NO_2$ Requires C, 73.34; H, 10.14; N, 5.03), $[\alpha]_D^{20}$ = - 43.4° (*c* 0.3 in acetone).

(*S*)-2-(*N*-3'-*tert*-Butylsalicylidene)-amino-3,3-dimethyl-1-butanol [154][26,124]



3-*tert*-Butyl-2-hydroxybenzaldehyde (107 mg, 0.102 mL, 0.6 mmol), sodium sulfate (0.3 g) and (*S*)-*tert*-leucinol (70 mg, 0.60 mmol) in ethanol (10 mL) were used as described for **[153]** to give the crude product as a yellow oil which was purified by column chromatography on silica gel (8:2, hexane/ethyl acetate) to yield **[154]** as a yellow oil (146 mg, 88%); ^{1}H NMR δ_H (300 MHz) 0.99 [9H, s, Alk-C(CH_3)$_3$], 1.44 [9H, s, Ar-C(CH_3)$_3$], 2.93 (1H, dd, *J* 9.4 and 2.7 Hz, CHN), 3.73 (1H, dd, *J* 11.0 and 9.5 Hz, one of C*H*$_2$OH), 3.90 (1H, dd, *J* 11.1 and 2.8 Hz, one of C*H*$_2$OH), 6.84 (1H, t, *J* 7.5 Hz, Ar-H), 7.15 (1H, dd, *J* 7.6 and 1.6 Hz, Ar-H), 7.35 (1H, dd, *J* 7.6 and 1.6 Hz, Ar-H), 8.42 (1H, s, HC=N); IR (film) ν_{max}/cm^{-1} 3367, 2959, 1633, 1458, 1436; $[\alpha]_D^{20}$ = − 51.2° (*c* 0.3 in acetone).

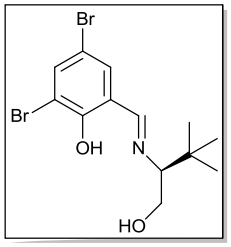
(*S*)-2-(*N*-3',5'-Dichlorosalicylidene)-amino-3,3-dimethyl-1-butanol [155]



3,5-Dichlorosalicylaldehyde (191 mg, 1 mmol), sodium sulfate (0.5 g) and (*S*)-*tert*-leucinol (117 mg, 1 mmol) in ethanol (15 mL), were used as described for **[153]** to give the crude product as a yellow solid which was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield **[155]** as a bright yellow crystalline solid (209 mg, 72%); m.p. 153-156 °C; ^{1}H NMR δ_H (300 MHz) 1.01 [9H, s, C(C*H*$_3$)$_3$], 3.10 (1H, dd, *J* 9.5 and 2.4 Hz, CHN), 3.11 (1H, bs, OH), 3.70 (1H, dd, *J* 11.2 and 9.8 Hz, one of C*H*$_2$OH), 3.98–4.08

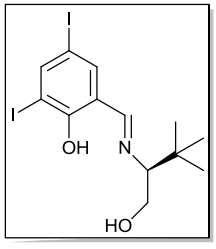
(1H, bm, one of C*H*$_2$OH), 7.35 (1H, d, *J* 2.5 Hz, Ar-H), 7.58 (1H, d, *J* 2.4 Hz, Ar-H), 8.12 (1H, s, HC=N); ^{13}C NMR δ_C (75.5 MHz) 27.3 [C(*C*H$_3$)$_3$], 33.4 [*C*(CH$_3$)$_3$], 62.2 (CH$_2$OH), 79.2 (NCH), 107.9 (C$_{Ar(q)}$), 114.8 (C$_{Ar(q)}$), 118.2 (C$_{Ar(q)}$), 133.8 (CH$_{Ar}$), 139.1 (CH$_{Ar}$), 162.9 (C$_{Ar(q)}$), 164.9 (HC=N); m/z (ESI) [(M+H)$^+$] 290 (100%), 292 (68), 294 (11), expected ^{35}Cl/^{37}Cl pattern seen; HRMS (ESI): Exact mass calculated for $C_{13}H_{18}{}^{35}Cl_2NO_2$ [(M+H)$^+$] 290.0715, Found 290.0723; IR (KBr) ν_{max}/cm^{-1} 3322, 2971, 1645, 1502 1209, 1058; (Found: C, 54.07; H, 5.91; N, 4.64. $C_{13}H_{17}Cl_2NO_2$ Requires C, 53.81; H, 5.90; N, 4.64); HPLC: t_R (*S*) = 6.3 min, [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = − 23.6° (*c* 1.0, acetone).

(*S*)-2-(*N*-3', 5'-Dibromosalicylidene)-amino-3,3-dimethyl-1-butanol [156][26,124,125]



3,5-Dibromosalicylaldehyde (0.129 g, 0.45 mmol) and sodium sulfate (0.25 g) and (*S*)-*tert*-leucinol (53.9 mg, 0.45 mmol) in ethanol (10 mL), were used as described for **[153]** to give the crude product as a yellow solid which was purified by column chromatography on silica gel (8:2 hexane/ethyl acetate) to yield **[156]** as a bright yellow crystalline solid (125 mg, 73%); m.p. 159–161 °C (Lit.[26] m.p. 160–162 °C); ^{1}H NMR δ_H (300 MHz) 1.01 [9H, s, C(CH$_3$)$_3$], 3.10 (1H, dd, *J* 9.5 and 2.4 Hz, CHN), 3.11 (1H, bs, OH), 3.70 (1H, dd, *J* 11.2 and 9.8 Hz, one of C*H*$_2$OH), 3.98–4.08 (1H, bm, one of C*H*$_2$OH), 7.35 (1H, d, *J* 2.5 Hz, Ar-H), 7.58 (1H, d, *J* 2.4 Hz, Ar-H), 8.12 (1H, s, HC=N); ^{13}C NMR δ_C (75.5 MHz) 27.3 [C(*C*H$_3$)$_3$], 33.4 [*C*(CH$_3$)$_3$], 62.2 (CH$_2$OH), 79.2 (NCH), 107.9 (C$_{Ar(q)}$), 114.8 (C$_{Ar(q)}$), 118.2 (C$_{Ar(q)}$), 133.8 (CH$_{Ar}$), 139.1 (CH$_{Ar}$), 162.9 (C$_{Ar(q)}$), 164.9 (HC=N); m/z (ESI) 383 (6%), 382 (50), 380 (100), [(M+H)$^+$] 378 (50), 118 (6), expected ^{79}Br/^{81}Br pattern seen; HRMS (ESI): Exact mass calculated for $C_{13}H_{18}{}^{79}Br_2NO_2$ [(M+H)$^+$] 377.9704, Found 377.9710; $[\alpha]_D^{20}$ = − 16.1° (*c* 1.0 in acetone).

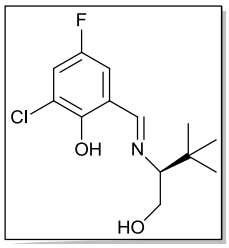
(*S*)-2-(*N*-3', 5'-Diiodosalicylidene)-amino-3,3-dimethyl-1-butanol [157][26,56,125]



3,5-Diiodosalicylaldehyde (374 mg, 1 mmol), sodium sulfate (0.5 g) and (*S*)-*tert*-leucinol (117 mg, 1 mmol) in ethanol (15 mL), were used as described for **[153]** to give the crude product as a yellow solid which was purified by column chromatography on silica gel (8:2 hexane/ethyl

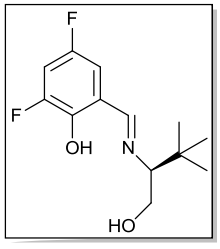
acetate) to yield **[157]** as a bright yellow crystalline solid (374 mg, 79%); m.p. 164–165 °C (Lit.[56] m.p. 163–164 °C); ^{1}H NMR δ_H (300 MHz) 1.00 [9H, s, C(CH$_3$)$_3$], 2.53 (1H, bs, OH), 3.08 (1H, dd, *J* 9.5 and 2.5 Hz, CHN), 3.68 (1H, dd, *J* 11.1 and 9.8 Hz, one of C*H*$_2$OH), 3.93–4.07 (1H, bm, one of C*H*$_2$OH), 7.51 (1H, d, *J* 2.1 Hz, Ar-H), 8.01 (1H, d, *J* 2.1 Hz, Ar-H), 8.10 (1H, s, HC=N); m.p. 164–165 ^{o}C, IR (KBr) ν_{max}/cm^{-1} 3320, 2965, 1638, 1479, 1217, 1060; $[\alpha]_D^{20} = -18.5°$ (c 0.1 in acetone), Lit. $[\alpha]_D^{20} = -16.6°$ (*c* 1.0 for *S* in acetone).[56]

(*S*)-2-(*N*-3'-Chloro-5'-fluorosalicylidene)-amino-3,3-dimethyl-1-butanol [158]



3-Chloro-5-fluoro-2-hydroxybenzaldehyde (0.87 g, 5 mmol), sodium sulfate (1.5 g) and (*S*)-*tert*-leucinol (0.59 g, 5 mmol) were used as described for **[153]** to give the crude product as a yellow-orange solid which was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield **[158]** as a yellow solid (1.03 g, 75%); m.p. 103–105 °C ; ^{1}H NMR δ_H (300 MHz) 1.00 [9H, s, C(CH$_3$)$_3$], 2.81 (1H, bs, OH), 3.06 (1H, dd, *J* 9.6 and 2.4 Hz, CHN), 3.70 (1H, overlapping dd, *J* 11.1 and 9.6 Hz, one of C*H*$_2$OH), 3.99 (1H, dd, *J* 11.4 and 2.7 Hz, one of C*H*$_2$OH), 6.87 (1H, dd, *J* 8.1 and 3.0 Hz, Ar-H), 7.14 (1H, dd, *J* 8.1 and 3.0 Hz, Ar-H), 8.22 (1H, s, HC=N); ^{13}C NMR δ_C (75.5 MHz) 26.9 [C(*C*H$_3$)$_3$], 33.0 [*C*(CH$_3$)$_3$], 61.9 (CH$_2$OH), 79.8 (NCH), 115.2 (CH$_{Ar}$, d, $^2J_{CF}$ 23 Hz), 117.0 (C$_{Ar(q)}$, d, $^3J_{CF}$ 8 Hz), 121.0 (CH$_{Ar}$, d, $^2J_{CF}$ 26 Hz), 122.8 (C$_{Ar(q)}$, d, $^3J_{CF}$ 10 Hz), 153.4 (C$_{Ar(q)}$, d, $^1J_{CF}$ 239 Hz), 157.0 (C$_{Ar(q)}$), 164.6 (C$_{Ar(q)}$, d, $^4J_{CF}$ 3 Hz, HC=N); m/z (ESI) [(M+H)$^+$] 274 (100%), 276 (46), 277 (6); HRMS (ESI): Exact mass calculated for $C_{13}H_{18}F^{35}ClNO_2$ [(M+H)$^+$] 274.1010, Found 274.1006; IR (KBr) ν_{max}/cm^{-1} 3288, 2973, 1643, 1471, 1366, 1209, 1063, 803; (Found: C, 57.41; H, 6.30; N, 5.24. $C_{13}H_{17}ClFNO_2$ Requires C, 57.04; H, 6.26; N, 5.12); $[\alpha]_D^{20} = -27.4°$ (*c* 1.0, acetone).

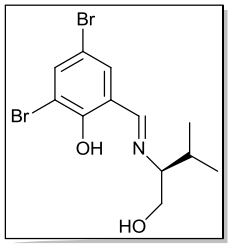
(*S*)-2-(*N*-3',5'-Difluorosalicylidene)-amino-3,3-dimethyl-1-butanol [159]



3,5-Difluorosalicylaldehye (0.79 g, 5 mmol), sodium sulfate (1.5 g) and (*S*)-*tert*-leucinol (0.59 g, 5 mmol) were used as described for **[153]** to give the crude product as a yellow-orange solid which was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield **[159]** as a

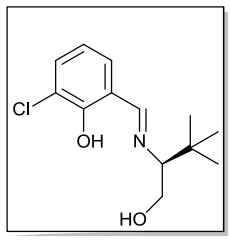
yellow solid (0.73 g, 57%); ^{1}H NMR δ_H (300 MHz) 0.99 [9H, s, C(C*H*$_3$)$_3$], 2.08 (1H, brs, OH), 3.01 (1H, dd, *J* 9.6 and 2.7 Hz, CHN), 3.70 (1H, dd, seen as t, *J* 9.9 and 9.9 Hz, one of C*H*$_2$OH), 3.99 (1H, brd, *J* 9.8 Hz, one of C*H*$_2$OH), 6.75–6.82 (1H, m, Ar-H), 6.86–6.96 (1H, m Ar-H), 8.26 (1H, s, HC=N); ^{13}C NMR δ_C (75.5 MHz) 26.9 [C(*C*H$_3$)$_3$], 33.1 [*C*(CH$_3$)$_3$], 62.0 (CH$_2$OH), 80.4 (NCH), 107.4–108.0 (m, CH$_{(Ar)}$), 111.2–111.5 (m, CH$_{(Ar)}$); 164.6 (C$_{Ar(q)}$, HC=N); m/z (ESI) 118 (8%); HRMS (ESI): Exact mass calculated for $C_{13}H_{18}F_2NO_2$ [(M+H)$^+$] 258.1328, Found 258.1317; IR (KBr) ν_{max}/cm^{-1} 3308, 2966, 1638, 1479, 1215, 1059, 857; $[\alpha]_D^{20} = -35.6°$ (*c* 0.5, acetone).

(*S*)-2-(*N*-3', 5'-Dibromosalicylidene)-amino-3-methyl-1-butanol [160]



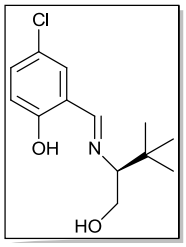
3,5-Dibromosalicylaldehye (280 mg, 1 mmol), sodium sulfate (0.5 g) and (*S*)-*tert*-leucinol (117 mg, 1 mmol) were used as described for **[153]** to give the crude product as a yellow-orange solid which was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield **[160]** as a yellow solid (277 mg, 76%); m.p. 136−138 °C; ^{1}H NMR δ_H (300 MHz) 1.01 [6H, d, *J* 6.7 Hz, CH(CH$_3$)$_2$], 1.88–2.06 [1H, m, C*H*(CH$_3$)$_2$], 3.17–3.29 (1H, m, CHN), 3.72 (1H, dd, seen as t, *J* 9.2 Hz, one of C*H*$_2$OH), 3.99 (1H, dd, *J* 2.6 and 11.4 Hz, one of C*H*$_2$OH), 7.25 (1H, d, *J* 2.5 Hz, Ar-H), 7.67 (1H, d, *J* 2.5 Hz, Ar-H), 8.14 (1H, s, HC=N); ^{13}C NMR δ_C (75.5 MHz) 18.4 [CH(*C*H$_3$)$_2$, one of CH$_3$], 19.8 [CH(*C*H$_3$)$_2$, one of CH$_3$], 29.6 [*C*H(CH$_3$)$_2$,] 64.0 (CH$_2$OH), 74.8 (NCH), 107.2 (C$_{Ar(q)}$), 114.8 (C$_{Ar(q)}$), 117.6 (C$_{Ar(q)}$), 133.5 (CH$_{Ar}$), 138.8 (CH$_{Ar}$), 163.0 (C$_{Ar(q)}$), 164.6 (HC=N); m/z (ESI) 366 (100%), 368 (50), [(M+H)$^+$] 364 (50), 369 (4); HRMS (ESI): Exact mass calculated for $C_{12}H_{16}{}^{79}Br_2NO_2$ [(M+H)$^+$] 363.9379, Found 363.9384; IR (KBr) ν_{max}/cm^{-1} 3259, 2965, 1645, 1497, 1212, 1043, 857, 690; (Found: C, 40.03; H, 4.14; N, 3.57. $C_{12}H_{15}Br_2NO_2$ Requires C, 39.48; H, 4.14; N, 3.84) $[\alpha]_D^{20} = -9.1°$ (*c* 1.0, acetone).

(*S*)-2-(*N*-3'-Chlorosalicylidene)-amino-3,3-dimethyl-1-butanol [161]



3-Chlorosalicylaldehyde (157 mg, 1 mmol), sodium sulfate (0.5 g) and (*S*)-*tert*-leucinol (117 mg, 1 mmol) were used as described for **[153]** to give the crude product as a yellow-orange solid which was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield **[161]** as a yellow solid (197 mg, 77%); m.p. 93–95 °C; ^{1}H NMR δ_H (300 MHz) 1.01 [9H, s, C(CH$_3$)$_3$], 1.62 (1H, bs, OH), 2.83 (1H, bs, OH), 3.05 (1H, dd, *J* 9.5 and 3.0 Hz, CHN), 3.72 (1H, overlapping dd, *J* 11.1 and 9.6 Hz, one of C*H*$_2$OH), 3.99 (1H, dd, *J* 11.1 and 2.4 Hz, one of C*H*$_2$OH), 6.64 (1H, dd, appears as t, *J* 7.8 and 7.8 Hz, Ar-H), 7.13 (1H, dd, *J* 7.7 and 1.8 Hz, Ar-H), 7.33 (1H, dd, *J* 7.8 and 1.8 Hz, Ar-H), 8.25 (1H, s, HC=N); ^{13}C NMR δ_C (75.5 MHz) 26.9 [C(*C*H$_3$)$_3$], 33.1 [*C*(CH$_3$)$_3$], 62.0 (CH$_2$OH), 79.5 (NCH), 117.3 (CH$_{Ar}$), 118.1 (C$_{Ar(q)}$), 122.7 (C$_{Ar(q)}$), 130.4 (CH$_{Ar}$), 133.3 (CH$_{Ar}$), 160.9 (C$_{Ar(q)}$), 165.6 (HC=N); (Found: C, 60.80; H, 7.04; N, 5.38. C$_{13}$H$_{18}$ClNO$_2$ Requires C, 61.05; H, 7.09; N, 5.48); $[\alpha]_D^{20} = -60.8°$ (*c* 1.0, CHCl$_3$).

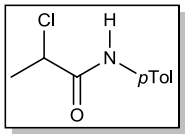
(*S*)-2-(*N*-5'-Chlorosalicylidene)-amino-3,3-dimethyl-1-butanol [162]



5-Chlorosalicylaldehyde (157 mg, 1 mmol), sodium sulfate (0.5 g) and (*S*)-*tert*-leucinol (117 mg, 1 mmol) were used as described for **[153]** to give the crude product as a yellow-orange solid which was purified by column chromatography on silica gel (6:4 hexane/ethyl acetate) to yield **[162]** as a yellow solid (179 mg, 70%); 117–120 °C; ^{1}H NMR δ_H (300 MHz) 0.97 [9H, s, C(CH$_3$)$_3$], 1.62 (1H, bs, OH), 2.93 (1H, dd, *J* 9.0 and 2.7 Hz, CHN), 3.71 (1H, overlapping dd, *J* 11.2 and 9.8 Hz, one of C*H*$_2$OH), 3.95 (1H, dd, *J* 11.0 and 2.1 Hz, one of C*H*$_2$OH), 6.86–6.93 (1H, m, Ar-H), 7.20-7.31 (2H, m, Ar-H), 8.26 (1H, s, HC=N); ^{13}C NMR δ_C (75.5 MHz) 27.0 [C(CH$_3$)$_3$], 33.2 [C(CH$_3$)$_3$], 62.3 (CH$_2$OH), 81.1 (NCH), 118.6 (CH$_{Ar}$), 119.3 (C$_{Ar(q)}$), 123.2 (C$_{Ar(q)}$), 130.7 (CH$_{Ar}$), 132.3 (CH$_{Ar}$), 160.0 (C$_{Ar(q)}$), 164.7 (HC=N); IR (KBr) ν_{max}/cm^{-1} 3259, 2962, 1634, 1046; (Found: C, 60.99; H, 6.80; N, 5.33. C$_{13}$H$_{18}$ClNO$_2$ Requires C, 61.05; H, 7.09; N, 5.48); $[\alpha]_D^{20} = -48.6°$ (*c* 1.0, CHCl$_3$).

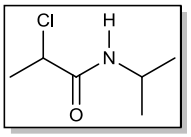
3.7 Preparation of α-Haloamides

N-4'-Methylphenyl-2-chloropropanamide [176][150,152,182]



2-Chloropropionyl chloride (5.00 g, 3.83 mL, 38.89 mmol) in CH_2Cl_2 (25 mL) was added dropwise over 20 min to a solution of *p*-toluidine (4.16 g, 38.89 mmol) and triethylamine (3.97 g, 5.77 mL, 39.25 mmol) in CH_2Cl_2 (45 mL) at 0 °C, while stirring under nitrogen. The solution was then removed from the ice bath and the reaction was allowed to warm to RT and stirred at RT for 4 h. Then, water (50 mL) was added and the layers separated. The organic layer was washed with a saturated solution of sodium bicarbonate (2 × 30 mL), water (50 mL) and brine (50 mL), dried and evaporated under reduced pressure to give the amide **[176]** as a white solid (6.53 g, 84%) which required no further purification; ^{1}H NMR δ_H (300 MHz) 1.82 (3H, d, *J* 7.2 Hz, H_3C-CHCl), 2.33 (3H, s, Ar-CH_3), 4.54 (1H, q, *J* 6.9 Hz, CHCl), 7.15 (2H, d, *J* 8.1 Hz, Ar-H), 7.42 (2H, d, *J* 8.4 Hz, Ar-H), 8.23 (1H, bs, NH); IR (KBr) ν_{max}/cm^{-1} 3251, 2983, 1663, 1550, 1076, 815.

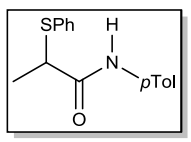
N-Isopropyl-2-chloropropanamide [177][150,182,140]



This was obtained following the procedure described for **[176]** from 2-chloropropionyl chloride (6.35 g, 4.86 mL, 49.83 mmol), isopropylamine (2.95 g, 4.28 mL, 49.83 mmol) and triethylamine (5.05 g, 6.96 mL, 49.83 mmol) in CH_2Cl_2 (62.5 mL) to give the amide **[177]** as a white solid which required no further purification (5.37 g, 72%); ^{1}H NMR δ_H (400 MHz) 1.20 [6H, d, *J* 7.0, CH(CH_3)$_2$], 1.74 (3H, d, *J* 7.2 Hz, H_3C-CHCl), 3.97–4.12 [1H, symmetrical m, C*H*(CH_3)$_2$], 4.39 (1H, q, *J* 6.8 Hz, CHCl), 6.39 (1H, bs, NH); IR (KBr) ν_{max}/cm^{-1} 3280, 2975, 1654, 1561, 1371.

3.8 Preparation of α-Phenylthioamides

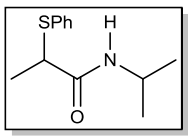
N-4'-Methylphenyl-2-(phenylthio)propanamide [178][117,182,140]



Thiophenol (2.5 mL, 24.3 mmol) was added to a solution of freshly prepared sodium ethoxide [made from sodium (0.56 g, 24.3 mmol) in dry

ethanol (45 mL) at 0 °C] while stirring under nitogen. The resulting solution was stirred for 20 min at 0 °C and *N*-4′-methylphenyl-2-chloropropanamide **[176]** (4.00 g, 20.25 mmol) was added over 15 min at 0 °C. The reaction mixture was then removed from the ice bath and following stirring for 16 h, the reaction was quenched by addition of water (50 mL) and CH_2Cl_2 (35 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with aqueous NaOH (1M, 2 × 50 mL), water (100 mL) and brine (100 mL), dried and concentrated under reduced pressure to give the crude sulfide which was purified by chromatography on silica gel using hexane-ethyl acetate as the eluent (gradient elution 0%-2% ethyl acetate in hexane) to give the sulfide **[178]** as an off-white solid (4.24 g, 83%); m.p. 112–114 °C (Lit.[150] m.p. 112–114 °C); ^{1}H NMR δ_H (400 MHz) 1.63 (3H, d, *J* 7.0 Hz, H_3C-CHSPh), 2.30 (3H, s, Ar-CH_3), 3.90 (1H, q, *J* 6.9 Hz, CHS), 7.08–7.13 (2H, m, Ar-H), 7.20–7.43 (7H, m, Ar-H), 8.35 (1H, bs, NH); IR (KBr) ν_{max}/cm^{-1} 3295, 2926, 1657, 1604, 1514, 1439, 816.

N-Isopropyl-2-(phenylthio)propanamide [179][182,140]

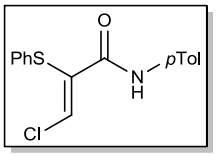


Sodium hydride (1.41 g of 60% dispersion in mineral oil, 35.12 mmol), was placed in a 3-necked round bottom flask under a flow of nitrogen. Following washing with hexane (3 × 20 mL), anhydrous DMF (150 mL) was added and the resulting suspension was stirred for 10 min. The reaction mixture was cooled to 0 °C and thiophenol (3.80 mL, 36.80 mL) was added slowly *via* syringe. The mixture was stirred for 20 min at 0 °C, then a solution of *N*-isopropyl-2-chloropropanamide **[177]** (5.00 g, 33.45 mmol) in DMF (15 mL) was added. On completion of the addition, the ice bath was removed and the reaction mixture was stirred at RT for 4 h. Water (100 mL) and CH_2Cl_2 (100 mL) were then added and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic layers washed with aqueous NaOH (1M, 100 mL), water (2 × 100 mL) and brine (100 mL), dried and concentrated under reduced pressure to give the crude sulfide. After chromatography on silica gel using hexane/ethyl acetate (97:3), *N*-isopropyl-2-(phenylthio)propanamide **[179]** was isolated as a colourless solid (6.13g, 82%); m.p. 43–45 °C (Lit.[182] m.p. 42–44 °C); ^{1}H NMR δ_H (400 MHz) 0.99 [3H, d, *J* 6.6 Hz, one of CH(CH_3)$_2$], 1.09 [3H, d, *J* 6.6 Hz, one of CH(CH_3)$_2$], 1.54 (3H, d, *J* 7.1 Hz, H_3C-CHCl), 3.78 (1H, q, *J* 6.8 Hz, CHCl) 3.92–4.10 [1H, symmetrical m,

C*H*$(CH_3)_2$], 6.38 (1H, bs, NH), 7.20–7.41 (5H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 3282, 2972, 1643, 1551, 1439.

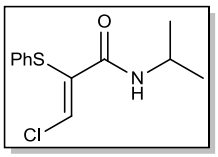
3.9 Preparation of α-phenylthioβ-chloroacrylamides

_N_-4'-Methylphenyl-_Z_-3-chloro-2-(phenylthio)propenamide [180][117,182,140]



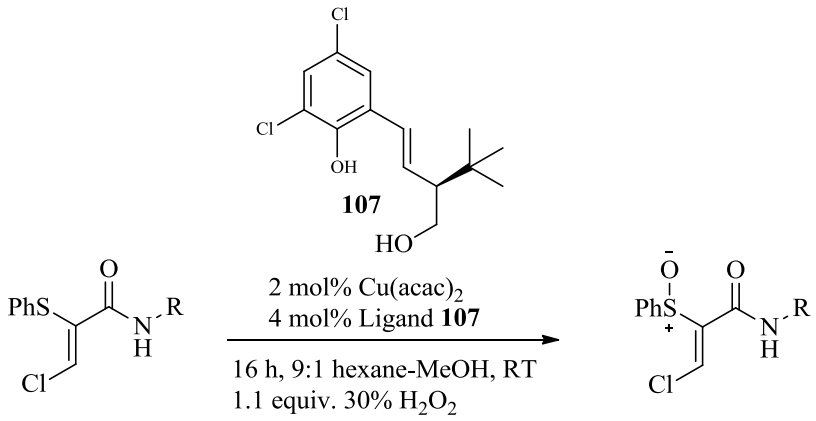
Unrecrystallised *N*-chlorosuccinimide (NCS) (2.79 g, 20.87 mmol) was added in one portion to a solution of *N*-4′-methylphenyl-2-(phenylthio)propanamide **[178]** (2.9 g, 10.7 mmol) in toluene (60 mL). The flask was immediately immersed in an oil bath at 90 °C and heating was maintained for 2 h with stirring. The reaction mixture was cooled to 0 °C and the succinimide by-product removed by filtration. The solvent was evaporated at reduced pressure to give the crude β-chloroacrylamide as an off-white solid. The crude product was purified by chromatography on silica gel using hexane/ethyl acetate (98:2) to give β-chloroacrylamide **[180]** as a white solid (1.82 g, 80%); m.p. 111–113 °C (Lit.[150] m.p. 110–111 °C); ^{1}H NMR δ_H (400 MHz) 2.29 (3H, s, Ar-CH_3), 7.03–7.14 (2H, m, Ar-H), 7.20–7.37 (7H, m, Ar-H), 8.05 (1H, s, CHCl), 8.62 (1H, bs, NH); IR (KBr) ν_{max}/cm^{-1} 3338, 3065, 1656, 1523, 1406, 751.

_N_-Isopropyl-_Z_-3-chloro-2-(phenylthio)propenamide [181][150,182,140]



β-Chloroacrylamide **[181]** was prepared following the procedure described for β-chloroacrylamide **[180]** using *N*-isopropyl-2-(phenylthio)propanamide **[179]** (2.30 g, 15.86 mmol), NCS (3.81 g, 28.55 mmol) and toluene (60 mL). Following filtration and evaporation of the solvent at reduced pressure, the crude β-chloroacrylamide **[181]** was isolated. The crude product was purified by chromatography on silica gel using hexane/ethyl acetate (98:2) to give β-chloroacrylamide **[181]** as an off-white solid (3.04 g, 75%); m.p. 73–76 °C (Lit.[150] m.p. 74–76 °C); ^{1}H NMR δ_H (400 MHz) 0.97 [6H, d, *J* 6.6 Hz, CH(C*H*$_3)_2$], 3.88–4.05 [1H, symmetrical m, C*H*$(CH_3)_2$], 6.51 (1H, bd, NH), 7.18–7.37 (5H, m, Ar-H), 7.83 (1H, s, CHCl); IR (KBr) ν_{max}/cm^{-1} 3259, 2975, 1640, 1542, 1440, 886, 752.

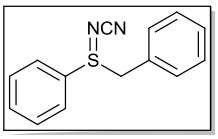
Attempted Oxidation of β-chloroacrylamides



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a solution of Schiff base ligand **[155]** (11.6 mg, 4.0 mol%) in 9:1 hexane/MeOH (1 mL). The resulting solution was stirred at RT for 5 min, and then a solution of the β-chloroacrylamide (1 mmol) in 9:1 hexane/MeOH (3 mL) was added. After 5 min stirring at RT, H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution. The reaction mixture was stirred at RT for a further 16 h. TLC and ^{1}H NMR analysis of the crude product indicated that no oxidation had taken place.

3.10 Preparation of Aryl Benzyl Sulfilimines

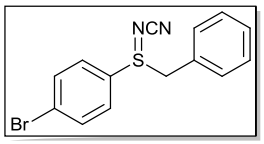
_N_-Cyano-_S_-benzyl-_S_-phenyl sulfilimine [186][27]



Benzyl phenyl sulfide **[163]** (3.0 g, 15 mmol), cyanamide (0.82 g, 19.4 mmol.) and potassium *tert*-butoxide (2.18 g, 18 mmol) were stirred in methanol (60 mL) at RT. *N*-Bromosuccinimide (4.0 g, 22 mmol) was added to this solution. The reaction progress was monitored by TLC analysis. Once the starting sulfide had been consumed, the reaction mixture was concentrated under reduced pressure. Saturated $Na_2S_2O_3$ solution (30 mL) and CH_2Cl_2 (30 mL) were added to the crude mixture and the phases separated. The aqueous layer was further washed with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give the crude product which was purified using column chromatography on silica gel using CH_2Cl_2/acetone (9:1) to give *N*-cyano-*S*-benzyl-*S*-phenyl sulfilimine **[186]** as a white solid (2.45 g, 68%); m.p. 72–74 °C (Lit.[27] m.p. 72–73 °C); ^{1}H NMR δ_H (300 MHz) 4.28 (1H, A of AB system, *J* 12.6 Hz, one of CH_2), 4.55 (1H, B

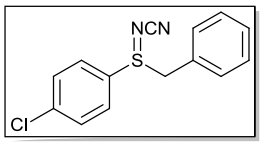
of AB system, *J* 12.6 Hz, one of CH_2), 7.09–7.21 (2H, m, Ar-H), 7.23–7.42 (3H, m, Ar-H), 7.46–7.69 (5H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2922, 2149, 1496, 1445, 1156, 748.

N-Cyano-S-benzyl-*S*-(4-bromophenyl) sulfilimine [187][27]



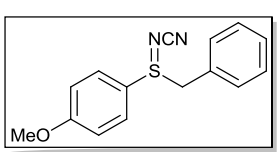
The reaction of benzyl 4-bromophenyl sulfide[161] **[185]** (4.17 g, 15 mmol), cyanamide (0.82 g, 19.4 mmol) and potassium *tert*-butoxide (2.18 g, 18 mmol) and *N*-bromosuccinimide (4.0 g, 22 mmol), as described for **[186]**, and subsequent purification by column chromatography on silica gel using CH_2Cl_2/acetone (9:1) afforded *N*-cyano-*S*-benzyl-*S*-(4-bromophenyl) sulfilimine **[187]** as a white solid (3.30 g, 69%); m.p. 122–125 °C (Lit.[27] m.p. 121–125 °C); ^{1}H NMR δ_H (300 MHz) 4.28 (1H, A of AB system, *J* 12.6 Hz, one of CH_2), 4.54 (1H, B of AB system, *J* 12.6 Hz, one of CH_2), 7.08–7.21 (2H, m, Ar-H), 7.23–7.52 (5H, m, Ar-H), 7.59–7.71 (2H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 3080, 2151, 1474, 1455, 1388, 1158, 1067.

N-Cyano-S-benzyl-S-(4-chlorophenyl) sulfilimine [188][27]



The reaction of benzyl 4-chlorophenyl sulfide **[16]** (3.53 g, 15 mmol), cyanamide (0.82 g, 19.4 mmol) and potassium *tert*-butoxide (2.18 g, 18 mmol) and *N*-bromosuccinimide (4.0 g, 22 mmol), as described for **[186]**, and subsequent purification by column chromatography on silica gel using hexane/ethyl acetate (6:4) afforded *N*-cyano-*S*-benzyl-*S*-(4-chlorophenyl) sulfilimine **[188]** as a white solid (3.01 g, 73%); m.p. 124–126 °C (Lit.[27] m.p. 122–125 °C); ^{1}H NMR δ_H (300 MHz) 4.27 (1H, A of AB system, *J* 12.6 Hz, one of CH_2), 4.56 (1H, B of AB system, *J* 12.6 Hz, one of CH_2), 7.09–7.20 (2H, m, Ar-H), 7.28–7.42 (3H, m, Ar-H), 7.42–7.61 (5H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 3063, 2152, 1456, 1393, 1182, 1091, unexplained broad band at 1710 cm^{-1}.

N-Cyano-*S*-benzyl-*S*-(4-methoxyphenyl) sulfilimine [189][27]

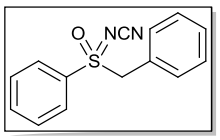


The reaction of benzyl 4-methoxyphenyl sulfide **[1]** (3.45 g, 15 mmol), cyanamide (0.82 g, 19.4 mmol) and potassium *tert*-butoxide

(2.18 g, 18 mmol) and *N*-bromosuccinimide (4.0 g, 22 mmol), as described for **[186]**, and subsequent purification by column chromatography on silica gel using hexane/ethyl acetate (6:4) afforded *N*-cyano-*S*-benzyl-*S*-(4-methoxyphenyl) sulfilimine **[189]** as a white solid (2.88 g, 71%); m.p. 72–75 °C (Lit.[27] m.p. 72–75 °C); ^{1}H NMR δ_H (300 MHz) 3.87 (3H, s, Ar-OCH_3), 4.27 (1H, A of AB system, *J* 12.6 Hz, one of CH_2), 4.57 (1H, B of AB system, *J* 12.6 Hz, one of CH_2), 6.93–7.03 (2H, m, Ar-H), 7.11–7.19 (2H, m, Ar-H), 7.26–7.40 (3H, m, Ar-H), 7.54–7.63 (2H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2974, 2146, 1591, 1497, 1456, 1261, 1180, 1084.

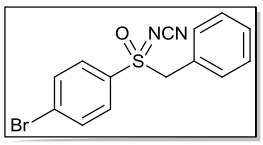
3.11 Preparation of Aryl Benzyl Sulfoximines

N-Cyano-*S*-benzyl-*S*-phenyl sulfoximine [190][27]



N-Cyano-*S*-benzyl-*S*-phenyl sulfilimine **[186]** (240 mg, 1 mmol) was stirred in ethanol (30 mL) at 0 °C. *m*-CPBA (77%, 260 mg, 1.16 mmol) and K_2CO_3 (414 mg, 3 mmol) were added to the solution. The solution was then removed from the ice bath and stirred until TLC indicated that all of the starting sulfilimine had been consumed. The reaction mixture was concentrated under reduced pressure. Water (10 mL) and CH_2Cl_2 (10 mL) were added to the reaction residue and the phases separated. The aqueous layer was further washed with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product which was purified by column chromatography using hexane/ethyl acetate (6:4) to give *N*-cyano-*S*-benzyl-*S*-phenyl sulfoximine **[190]** as a white solid (172 mg, 67%); m.p. 172–174 °C (Lit.[27] m.p. 169–173 °C); ^{1}H NMR δ_H (300 MHz) 4.59 (2H, s, CH_2), 6.92–7.06 (2H, m, Ar-H), 7.20–7.33 (2H, m, Ar-H), 7.50–7.80 (5H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2921, 2197, 1493, 1447, 1251, 1187, 1089.

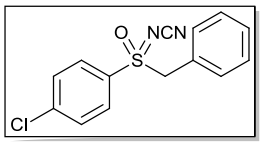
N-Cyano-*S*-benzyl-*S*-(4-bromophenyl) sulfoximine [191][27]



The reaction of *N*-cyano-*S*-benzyl-*S*-(4-bromophenyl) sulfilimine **[187]** (319 mg, 1 mmol), *m*-CPBA (77%, 260 mg, 1.16 mmol) and

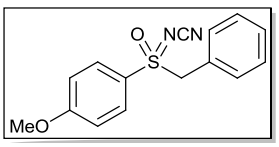
K_2CO_3 (414 mg, 3 mmol), as described for **[190]**, and subsequent purification by column chromatography using hexane/ethyl acetate (6:4) afforded *N*-cyano-*S*-benzyl-*S*-(4-bromophenyl) sulfoximine **[191]** as a white solid (248 mg, 74%); m.p. 140–141 °C (Lit.[27] m.p. 141–143 °C); ^{1}H NMR δ_H (300 MHz) 4.62 (2H, s, CH_2), 7.02–7.11 (2H, m, Ar-H), 7.23–7.50 (5H, m, Ar-H), 7.62–7.71 (2H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 2920, 2197, 1571, 1456, 1390, 1253, 1068.

N-Cyano-*S*-benzyl-*S*-(4-chlorophenyl) sulfoximine [192][27]



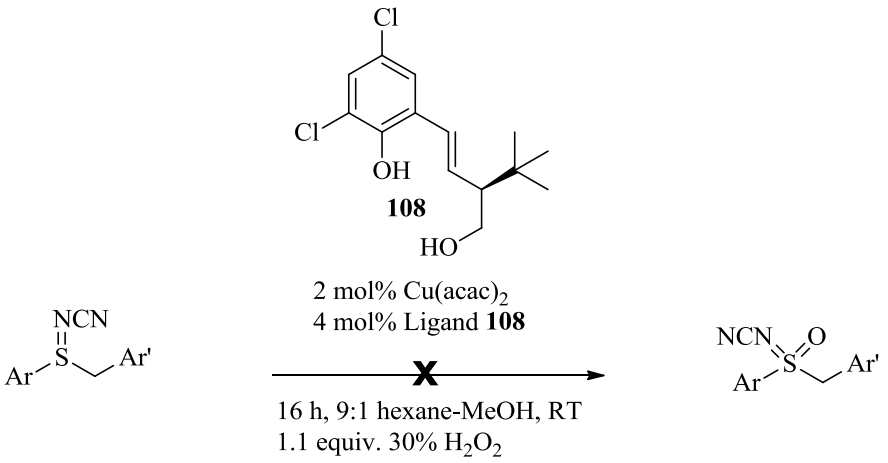
The reaction of *N*-cyano-*S*-benzyl-*S*-(4-chlorophenyl) sulfilimine **[188]** (275 mg, 1 mmol), *m*-CPBA (77%, 260 mg, 1.16 mmol) and K_2CO_3 (414 mg, 3 mmol), as described for **[190]**, and subsequent purification by column chromatography using hexane/ethyl acetate (6:4) afforded *N*-cyano-*S*-benzyl-*S*-(4-chlorophenyl) sulfoximine **[192]** as a white solid (177 mg, 61%); m.p. 122–126 °C (Lit.[27] m.p. 123–126 °C); ^{1}H NMR δ_H (300 MHz) 4.63 (2H, s, CH_2), 7.01–7.12 (2H, m, Ar-H), 7.22–7.60 (7H, m, Ar-H); IR (KBr): ν_{max}/cm^{-1} 2920, 2197, 1572, 1475, 1396, 1253, 1184, 1084.

N-Cyano-*S*-benzyl-*S*-(4-methoxyphenyl) sulfoximine [193][27]



The reaction of *N*-cyano-*S*-benzyl-*S*-(4-methoxyphenyl) sulfilimine **[189]** (270 mg, 1 mmol), *m*-CPBA (77%, 260 mg, 1.16 mmol) and K_2CO_3 (414 mg, 3 mmol), as described for **[190]**, and subsequent purification by column chromatography using hexane/ethyl acetate (8:2) afforded *N*-cyano-*S*-benzyl-*S*-(4-methoxyphenyl) sulfoximine **[193]** as a white solid (178 mg, 62%); m.p. 129–133 °C (Lit.[27] m.p. 129–133 °C); ^{1}H NMR δ_H (300 MHz) 3.89 (3H, s, Ar-OCH_3), 4.59 (2H, s, CH_2), 6.90–7.00 (2H, m, Ar-H), 7.01–7.10 (2H, m, Ar-H), 7.22–7.41 (3H, m, Ar-H), 7.47–7.56 (2H, m, Ar-H); IR (KBr): ν_{max}/cm^{-1} 2922, 2194, 1592, 1496, 1247, 1175, 1092.

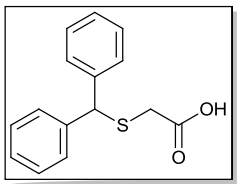
Attempted Oxidation/Resolution of Aryl Benzyl Sulfilimines



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a solution of Schiff base ligand **[155]** (11.6 mg, 4.0 mol%) in 9:1 hexane/MeOH (1 mL). The resulting solution was stirred at RT for 5 min, and then a solution of the sulfilimine (1 mmol) in 9:1 hexane/MeOH (2 mL) was added. After 5 min stirring at RT, H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution. The reaction mixture was stirred at RT for a further 16 h. TLC and ^{1}H NMR analysis of the crude product indicated that no oxidation had taken place.

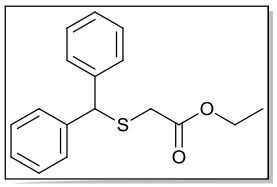
3.12 Preparation of (*R*)-Modafinil

(Benzhydrylsulfanyl)acetic acid [171][147]



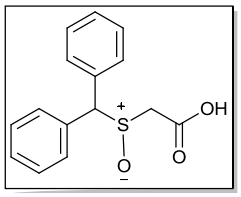
Benzhydrol (10.0 g, 54.3 mmol) and thioglycolic acid (5.0 g, 54.3 mmol) were added to a 250 mL round bottom flask. Trifluoroacetic acid (60 mL) was added and the resulting solution was stirred at RT for 3 h. The solvent was removed under reduced pressure to give an off white solid. Water (60 mL) was added and the resulting precipitate was collected by filtration. The solid was washed with hexane (100 mL) and dried to give (benzhydrylsulfanyl)acetic acid **[171]** as a white solid (13.75 g, 98%); m.p. 125–127 °C (Lit.[147] m.p. 126–129 °C); ^{1}H NMR δ_H (400 MHz) 3.11 (2H, s, SCH_2), 5.43 (1H, s, SCH), 7.18–7.57 (10H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 3423, 1703, 1648, 1450, 749.

Ethyl (benzhydrylsulfanyl)acetate [175][147]



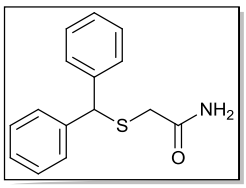
(Benzhydrylsulfanyl)acetic acid **[171]** (7 g, 27.1 mmol) and concentrated sulfuric acid (H_2SO_4) (2 mL) were added to a 250 mL round bottom flask containing absolute ethanol (60 mL), and the solution was heated under reflux overnight. The solvent was removed under reduced pressure and diethyl ether (Et_2O) (50 mL) was added to the residue. The mixture was washed with H_2O (2 × 15 mL), $NaHCO_3$ (15 mL, 5%) and brine (20 mL) and then dried over $MgSO_4$. The solvent was removed under reduced pressure to give ethyl (benzhydrylsulfanyl)acetate **[175]** as a clear oil (7.69 g, 99%); ^{1}H NMR δ_H (300 MHz) 1.27 (2H, t, *J* 7.2 Hz, OC*H*$_2$CH$_3$), 3.07 (2H, s, SCH$_2$), 4.14 (3H, q, *J* 6.9 Hz, OCH$_2$C*H*$_3$), 5.41 (1H, s, SCH) 7.16–7.50 (10H, m, Ar-H); IR (film) ν_{max}/cm^{-1} 2981, 1733, 1276, 1128, 1030, 702.

(±)-(Diphenylmethanesulfinyl)acetic acid [174][147]



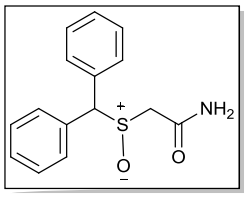
A solution of 30% aqueous H_2O_2 (9.07 g, 27.1 mmol) was added dropwise to a solution of ethyl (benzhydrylsulfanyl)acetate **[175]** (7.64 g, 26.7 mmol), absolute methanol (60 mL) and acid catalyst [6.16 mL, prepared from 2-propanol (9 g) and conc. H_2SO_4 (4 g)] at RT and the resulting solution stirred overnight. NaCl (20 g) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give an off-white solid that was used without further purification. A mixture of the crude solid, NaOH (3.3 g, 82.5 mmol), absolute ethanol (80 mL) and water (10 mL) was stirred at RT for 1 h. The solvent was removed under reduced pressure. Water (80 mL) was added to the residue and the aqueous mixture was washed with Et_2O (2 × 20 mL). The mixture was acidified (pH 2) by the addition of conc. HCl and the resulting precipitate collected by filtration and dried to give (±)-(diphenylmethanesulfinyl)acetic acid **[174]** as a white solid (4.98 g, 67%); m.p. 146–151 °C (Lit.[147] m.p. 148–149 °C); ^{1}H NMR δ_H (400 MHz) 3.25 (1H, A of AB system, *J* 12.0 Hz, SOCH$_2$), 3.64 (1H, B of AB system, *J* 12.1 Hz, SOCH$_2$), 5.36 (1H, s, SOCH), 7.29–7.56 (10H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 3411, 1716, 1637, 1451, 749, 698.

(2-Benzhydrylsulfanyl)acetamide [172][147]



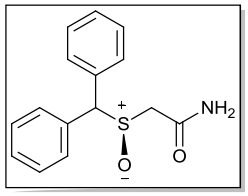
A solution of thionyl chloride (5.0 mL, 91.6 mmol) in benzene (5 mL) was added in a dropwise manner to a solution of **[171]** (4.88 g, 18.9 mmol) in benzene (30 mL) and the resulting mixture heated under reflux for 1.5 h. The solvent was removed under reduced pressure to afford an orange oil. A solution of the oil in CH_2Cl_2 (25 mL) was added cautiously to a vigorously stirred solution of concentrated NH_4OH (62.5 mL). The mixture was stirred vigorously for 2 h and the layers were separated. The aqueous mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined CH_2Cl_2 portion was washed with 5% $NaHCO_3$ (3 × 15 mL) and saturated NaCl (20 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded a crude solid that was recrystallised from isopropyl ether to give **[172]** as a white solid (4.25 g, 87%); m.p. 108–110 °C (Lit.[147] m.p. 109–110 °C); ^{1}H NMR δ_H (400 MHz) 3.01 (2H, s, SCH_2), 5.11 (1H, s, SOCH), 5.63 (1H, bs, one of NH_2), 6.43 (1H, bs, one of NH_2), 7.12–7.51 (10H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 3380, 1651, 1449, 697.

(±)-[2-(Diphenyl)methanesulfinyl]acetamide (Modafinil) (±)-[173][147]



A solution of **[172]** (1.44 g, 5.6 mmol) and 30% H_2O_2 (0.56 mL, 4.94 mmol) in acetic acid (10 mL) was stirred at 40 °C overnight. The mixture was poured into H_2O (200 mL) and a white precipitate formed. The solid was collected by filtration and recrystallised from MeOH to afford **(±)-[173]** as a white solid (0.89 g, 58%); m.p. 160–163 °C (Lit.[147] m.p. 162–163 °C); ^{1}H NMR δ_H (400 MHz) 3.11 (1H, A of AB system, *J* 14.5 Hz, $SOCH_2$), 3.49 (1H, B of AB system, *J* 14.5 Hz, $SOCH_2$), 5.21 (1H, s, SOCH), 5.72 (1H, bs, one of NH_2), 7.06 (1H, bs, one of NH_2), 7.25–7.59 (10H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 3364, 1676, 1413, 1030, 701. HPLC: t_R = (*S*) 82.2 min, t_R (*R*) = 155.1 min [OJ-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C].

(*R*)-(−)-[2-(Diphenyl)methanesulfinyl]acetamide [(*R*)-(−)Modafinil] [173][147]

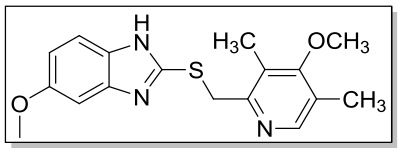


A mixture of (*S*)-(−)-α-methylbenzylamine (2.13 g, 17.55 mmol) and (±)-(diphenylmethanesulfinyl)acetic acid **[174]** (4.5 g, 13.8 mmol) in water (50 mL) was heated to reflux and then filtered. The filtrate was cooled slowly to RT. The resulting solid was collected by filtration and recrystallised two times from water to give a white solid. A suspension of the salt in water

was made acidic (pH 2) by the addition of conc. HCl. The resulting precipitate was collected by filtration and dried to give (*R*)-(−)-(diphenylmethanesulfinyl)acetic acid (*R*)-(−)-**[174]** a white solid (454 mg, 12%). A mixture of (*R*)-(−)-(diphenylmethanesulfinyl)acetic acid (454 mg, 1.65 mmol) (*R*)-(−)-**[174]**, iodomethane (257 mg, 1.81 mmol), and K_2CO_3 (249 mg, 1.81 mmol) in acetone was heated at reflux overnight. The solvent was removed under reduced pressure and water (15 mL) was added to the residue. The aqueous mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a crude solid that was recrystallised from isopropyl ether to give the methyl ester as a white solid (355 mg, 68%). A mixture of the ester (355 mg, 1.23 mmol), NH_4Cl (81 mg, 1.51 mmol), conc. NH_4OH (7 mL) and MeOH (2 mL) was stirred at RT overnight. The resulting precipitate was collected by filtration and recrystallised from diisopropyl ether to give (*R*)-(−)-[2-(diphenyl)methanesulfinyl]acetamide **[173]** as a white solid (237 mg, 48%); m.p. 154–157 °C (Lit.[147] m.p. 156–157 °C); $[\alpha]_D^{20}$ = − 72.4° (c 1.0 in $CHCl_3$), Lit.[147] $[\alpha]_D^{20}$ = − 76.6° (c 1.0 for *R* in $CHCl_3$); ^{1}H NMR δ_H (300 MHz) 3.10 (1H, A of AB system, *J* 14.7 Hz, $SOCH_2$), 3.49 (1H, B of AB system, *J* 14.4 Hz, $SOCH_2$), 5.19 (1H, s, SOCH), 5.57 (1H, bs, one of NH_2), 7.04 (1H, bs, one of NH_2), 7.27–7.56 (10H, m, Ar-H); IR (KBr) ν_{max}/cm^{-1} 3422, 1668, 1451, 750; HPLC: t_R = (*S*) 88.4 min, t_R (*R*) = 182.9 min, 98% ee (*R*), [OJ-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C].

3.12.1 Preparation of Omeprazole

Pyrmetazole [170][183,184]

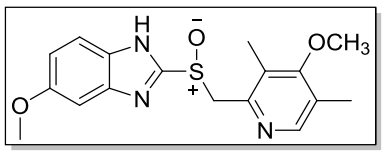


Pyrmethyl alcohol (4.4 g, 26.3 mmol) was dissolved in toluene (38 mL) and water (5 mL) was added at RT. To the stirred mixture at 30 °C, thionyl chloride (4.08 g, 34.3 mmol) was added slowly over 60 min and the formation of product was monitored by TLC analysis. Water (1.5 mL) was added to quench any excess of thionyl chloride. An alkaline solution composed of NaOH (50%, 40 mL) and metmercazole (4.9 g, 27.1 mmol) was added, followed by additional NaOH (50%, ~8 mL) to reach pH > 12.5. The temperature was allowed to increase to 45 °C during the additions. The reaction mixture was left with vigorous stirring for 2 h at 45 °C. The agitation was interrupted and the phases were left to

separate. The organic phase, containing pyrmetazole, was washed with water (20 mL) and was analysed (TLC) for residues of pyrmethyl alcohol. The product was dissolved in CH_2Cl_2, dried over $MgSO_4$ and concentrated under reduced pressure to give **[170]** as a sticky off-white solid (5.5 g, 64%); (Lit.[184] m.p. 47–50 °C); ^{1}H NMR δ_H (400 MHz) 2.08 (3H, s, Ar-CH_3), 2.12 (3H, s, Ar-CH_3), 3.60 (3H, s, Ar-OCH_3), 3.65 (3H, s, Ar-OCH_3), 4.32 (2H, s, SCH_2), 6.62–6.70 (1H, m, Ar-H), 6.90 (1H, bs, Ar-H), 7.23–7.31 (1H, m, Ar-H), 8.07 (1H, s, Ar-H); IR (film) ν_{max}/cm^{-1} 3420, 1630, 1403, 1155.

A m.p. was not obtained due to the sticky nature of the product.

Omeprazole [203][185,186]



A mixture of pyrmetazole (3 g, 9.1 mmol), $NaHCO_3$ (3 g) and aqueous methanol (20 mL) was cooled to – 2 °C and Oxone®[54] (3.50 g, 5.69 mmol) was added. The mixture was stirred for 4 h at 0 °C and a further 1 g (1.63 mmol) of Oxone®[54] was added and stirring continued for 1.5 h. A solution of sodium metabisulfite (0.8 g) in water (20 mL) was added over 5-10 min. After stirring, the resulting precipitate was filtered, washed with water and aqueous methanol (50%) and dried to give **[203]** as a white solid (566 mg, 18%); m.p. 154–159 °C (Lit.[186] m.p. 157 °C); ^{1}H NMR δ_H (300 MHz) 2.19 (3H, s, Ar-CH_3), 2.24 (3H, s, Ar-CH_3), 3.68 (3H, s, Ar-OCH_3), 3.86 (3H, s, Ar-OCH_3), 4.66 (1H, A of AB system, *J* 14.6 Hz, $SOCH_2$), 4.76 (1H, B of AB system, *J* 14.6 Hz, $SOCH_2$), 6.83–7.05 (1H, bm, Ar-H), 7.31–7.42 (1H, bm, Ar-H), 7.59–7.72 (1H, bm, Ar-H), 8.23 (1H, s, Ar-H).

3.13 Copper-Catalysed Asymmetric Sulfide Oxidation

1. Copper(II) acetylacetonate used was as commercially obtained for the preparation of the copper-Schiff base ligand complex.

2. The nature of the reaction mixture is dependent on the solvent used in the oxidation, for example when CCl_4 or toluene are used the reaction mixture is heterogeneous but when methanol or ethanol are used the reaction mixture is homogeneous. When mixed solvent systems are employed the reaction mixture can either be heterogeneous or homogeneous depending on the miscibility of the solvents that make up the mixed solvent system (see section 2.10).

3. The organic layer of the reaction mixture is a blue/green colour. The change in colour of the aqueous layer, during the oxidation, is dependent on the solvent used. The aqueous layer of the reaction mixture turns from clear to brown with the majority of the solvents employed. However, when methanol, ethanol and mixed solvent systems are used this colour change is not observed (see section 2.10). When mixed solvent systems such as hexane/methanol or hexane/ethanol are used the sulfoxide precipitates out of solution during the oxidation, and sticks to the side of the round bottomed flask. This also occurs in benzene, toluene and CCl_4, albeit to a much lesser extent.

4. The crude product was isolated from the reaction mixture as follows. Water (10 mL) and CH_2Cl_2 (10 mL) were added to the reaction mixture. The phases were separated. The organic layer was washed with water (3 × 10 mL) and brine (10 mL), dried and concentrated under reduced pressure to give the crude product as a mixture of sulfide, sulfoxide and sulfone.

5. The ratio of sulfide : sulfoxide : sulfone in the crude product was determined by ^{1}H NMR.

6. The product was purified by column chromatography on silica gel (see section 3.4 for conditions).

7. The enantiopurity of the sulfoxide was determined after purification and isolation of product. Since there is a literature precedent for the separation of sulfoxide enantiomers during column chromatography,[187] in all cases, all fractions of the sulfoxide product were combined and used when determining enantiopurity. Accordingly % ee results reported are due entirely to asymmetric sulfide oxidation and are not enhanced due to separation of the sulfoxide enantiomers during chromatography.

8. In principle, the enantiopurity of an enantioenriched sample can be enhanced by recrystallization. In all instances during this work, chromatographed samples were used for the determination of enantiopurity with no recrystallisation.

9. Only the *S* form of the Schiff base ligands were employed during this work.

10. A 30% aqueous hydrogen peroxide solution was used as oxidant. The concentration of this solution was determined by titration to be 30% on one occasion and the same bottle was then employed for the duration of the project.

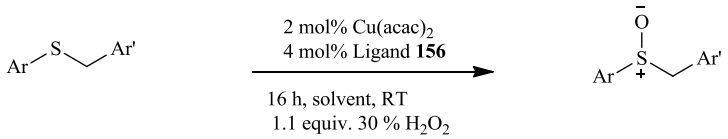
11. The oxidation of sulfide **[163]** at RT in toluene using ligand **[156]** and in hexane/MeOH using ligand **[155]** was reproduced several times with enantioselectivities ranging from 56-61% ee in toluene and 71-81% ee in hexane/MeOH. The oxidations of sulfides **[26]** and **[29]**, under the conditions indicated in Table 3.2 and Table 3.8, were also reproduced several times with enantioselectivities ranging from 90-93% ee and 95-97% ee respectively. All other

experiments were carried out once. The yields of the oxidations were also reproducible and any differences in yield, in the repeated experiments, were very minor.

3.13.1 Investigation of CCl_4 and Toluene as Solvent

Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a round bottomed flask containing Schiff base ligand **[156]** (15.2 mg, 4.0 mol%), and solvent (1 mL). The resulting solution was stirred at RT for 5 min, and then a solution of sulfide (1 mmol) in solvent (1 mL) was added. After 5 min stirring at RT, H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution. The reaction mixture was stirred at RT for a further 16 h.

Table 3.1 Investigation of CCl_4 and Toluene as Solvent



Entry	Sulfide	Ar	Ar′	Toluene			CCl_4[d]			Sulfoxide
				Sulfide : Sulfoxide[a]	Yield %[b]	%ee[c] (*R*)[d]	Sulfide : Sulfoxide	Yield %[b]	%ee[c] (*R*)	
1	**[163]**	Ph	Ph	73 : 27	21	58	74 : 26	27	61	**[50]**
2	**[7]**	4-MeC_6H_4	Ph	78:22	15	51	46 : 54	38	55	**[51]**
3	**[4]**	4-MeC_6H_4	4'-$MeOC_6H_4$	55 : 45	30	46	47 : 53	42	27	**[52]**
4	**[3]**	2-$MeOC_6H_4$	Ph	74 : 26	19	77	57 : 43	29	79	**[53]**
5	**[2]**	3-$MeOC_6H_4$	Ph	74 : 26	18	73	68 : 32	24	69	**[54]**
6	**[1]**	4-$MeOC_6H_4$	Ph	54 : 46	33	54	63 : 37	17	39	**[55]**
7	**[164]**	4-FC_6H_4	Ph	75 : 25	18	34	71 : 29	13	39	**[90]**

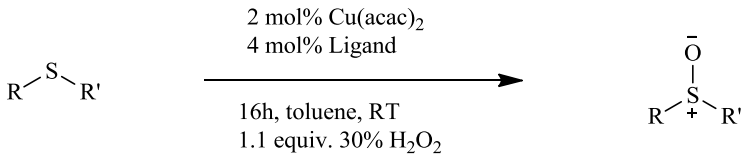
a) Ratio of sulfide : sulfoxide determined by ^{1}H NMR analysis of the crude product, no sulfone produced. b) Yield of sulfoxide after purification by column chromatography. c) Determined by HPLC analysis on chiral column; absolute configuration determined by comparison of specific rotation values for **[50]**, **[51]** to known literature values; for **[52]**, **[53]**, **[54]**, **[55]**, **[90]** proposed configuration based on HPLC elution order and the direction of the specific rotations. d) Results obtained by Kelly *et al.*[26]

3.13.2 Investigation of Steric and Electronic Effects of Sulfide Substituents

Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a round bottomed flask containing Schiff base ligand **[156]** (15.2 mg, 4.0 mol%) or **[155]** (11.6 mg, 4.0 mol%), and toluene (1 mL). The resulting solution was stirred at RT for 5 min, and then a solution of sulfide (200 mg, 1 mmol) in toluene (1 mL) was added. After 5 min stirring at RT, H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution. The reaction mixture was stirred at RT for a further 16 h.

From the reactions including NMO, once the sulfide was added the mixture was stirred for 5 min, then NMO (2.5 mol%, 2.9 mg) was added and the mixture stirred for a further 5 min before addition of hydrogen peroxide.

Table 3.2 Investigation of Steric and Electronic Effects of Sulfide Substituents



Entry	Sulfide	R	R'	Ligand	No NMO			NMO[d]			Sulfoxide
					Sulfide : Sulfoxide[a]	Yield %[b]	%ee[c] (*R*)	Sulfide : Sulfoxide[a]	Yield %[b]	%ee[c] (*R*)	
1	**[23]**	Ph	-CH_2-Cyclohexyl	**[156]**	86 : 14	23	54	78:22	20	60	**[56]**
2	**[23]**	Ph	-CH_2-Cyclohexyl	**[155]**	70 : 30	19	57	71 : 29	24	63	**[56]**
3	**[163]**	Ph	-$CH_2C_6H_5$	**[156]**	79 : 21	17	58	61 : 39	30	60	**[50]**
4	**[165]**	*p*-Tol	Me	**[156]**	79 : 21	15	22	65 : 35	37	21	**[57]**
5	**[165]**	*p*-Tol	Me	**[155]**	81 : 19	11	19	64 : 36	36	16	**[57]**
6	**[166]**	Ph	Et	**[156]**	8:2	12	40	6:4	39	49	**[58]**
7	**[166]**	Ph	Et	**[155]**	72 : 28	22	46	59 : 41	40	53	**[58]**
8	**[25]**	Ph	*i*-Pr	**[155]**	72 : 28	19	50	69 : 31	26	64	**[59]**
9	**[24]**	Ph	-$CH_2CH(CH_3)_2$	**[156]**	82 : 18	13	51	78:22	17	56	**[60]**
10	**[24]**	Ph	-$CH_2CH(CH_3)_2$	**[155]**	71 : 29	15	61	76 : 24	18	61	**[60]**

11	**[46]**	Ph	$-CH_2C(CH_3)_3$	**[155]**	8:2	15	71	72 : 28	28	71	**[61]**
12	**[26]**	Ph	$-CH_2$-2'-Naphthyl	**[155]**	73 : 27	23	93	45 : 55	30	93	**[62]**
13	**[45]**	*p*-Tol	$-CH_2C\equiv CH$	**[156]**	84 : 16	8	3	78:22	14	4	**[80]**
14	**[45]**	*p*-Tol	$-CH_2C\equiv CH$	**[155]**	81 : 19	4	5	83 : 17	10	6	**[80]**

a) Ratio of sulfide : sulfoxide determined by ^1H NMR analysis of the crude product, no sulfone produced.

b) Yield of sulfoxide after purification by column chromatography.

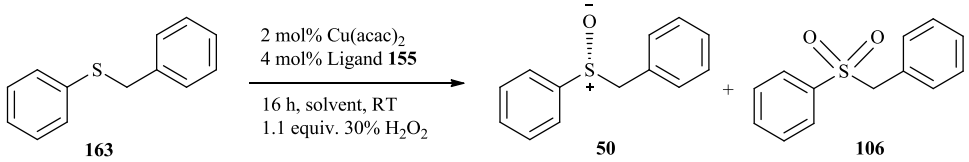
c) Determined by HPLC analysis on chiral column; absolute configuration determined by comparison of specific rotation values for **[50]**, **[57]**, **[58]**, **[59]**, **[60]** to known literature values; for **[56]**, **[61]**, **[62]**, **[80]** proposed configuration based on HPLC elution order and direction of specific rotations.

d) Results obtained when oxidation was carried out in the presence of 2.5 mol% NMO added 5 min after the addition of the sulfide.

3.13.3 Investigation of Reaction Solvent

Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a round bottomed flask containing Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and solvent (1 mL). The resulting solution was stirred at RT for 5 min, and then a solution of sulfide (200 mg, 1 mmol) in solvent (1 mL) was added. After 5 min stirring at RT, H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution. The reaction mixture was stirred at RT for a further 16 h.

Table 3.3 Investigation of Reaction Solvent



Entry	Solvent	[163] : [50] : [106][a]	Yield %[b] [50]	%ee[c] (*R*) [50]
1	Ether	85 : 15 : 0	8	10
2	Dioxane	69 : 31 : 0	25	1
3	Toluene	79 : 21 : 0	17	58
4	CCl_4	65 : 35 : 0	27	61
5	Benzene	66 : 34: 0	26	69

6	Hexane	100 : 0 : 0	0	-
7	MeOH	40 : 60 : 0	50	24
8	MeOH[d]	19 : 81 : 0	73	29
9	50:50 Toluene : MeOH	47 : 53 : 0	48	47
10	75:25 Toluene : MeOH	46 : 54 : 0	47	47
11	90:10 Toluene : MeOH	42 : 58 : trace	52	49
12	95:5 Toluene : MeOH	48 : 52 : 0	45	46
13	90:10 Hexane : MeOH	3 : 96 : 1	87	80
14	90:10 Hexane : EtOH	1 : 98 : 1	90	76
15	90:10 Cyclohexane : MeOH	8 : 91 : 1	85	79
16	90:10 Hexane : IPA	7 : 92 : 1	83	1
17	90:10 CCl_4 : MeOH	21 : 76 : 3	70	62
18	90:10 CCl_4 : MeOH[d]	9 : 89 : 2	82[d]	63
19	90:10 Hexane : benzyl alcohol	4 : 94 : 2	87	7
20	90:10 Hexane : *t*-BuOH	45 : 55 : trace	46	4
21	90:10 Hexane : 2-butanol	57 : 43 : 0	38	8

a) Ratio of **[163]:[50]:[106]** determined by ^{1}H NMR analysis of the crude product.

b) After purification by column chromatography.

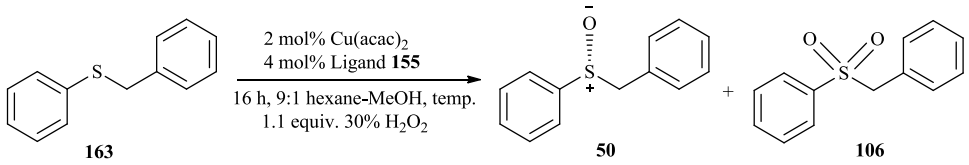
c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H); Absolute configuration determined by comparison of rotation values to literature values.

d) Oxidation carried out in the presence of NMO (2.5 mol%).

3.13.4 Investigation of Reaction Temperature

Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a round bottomed flask containing Schiff base ligand **[155]** (11.6 mg, 4.0 mol%), and 9:1 hexane/methanol (1 mL) at the temperature indicated in Table 3.4. The resulting solution was stirred at the indicated temperature for 5 min, and then a solution of sulfide (200 mg, 1 mmol) in 9:1 hexane/methanol (1 mL) was added. After 5 min stirring at RT, H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution.

Table 3.4 Investigation of Reaction Temperature



Entry	Temperature °C	[163] : [50] : [106][a]	Yield %[b] [50]	%ee[c] (*R*) [50]
1	Ambient	3 : 96 : 1	87	80[d]
2	0	82 : 18 : 0	11	28
3	4	65 : 35 : 0	24	34
4	25	0 : 96:4	84	58
5	30	0 : 97 : 3	82	53
6	35	0 : 95 : 5	83	47
7	40	0 : 95 : 5	80	41
8	45	0 : 93 : 7	77	35
9	50	0 : 90 : 10	75	27
10	55	0 : 91 : 9	78	25
11	60	0 : 84 : 16	71	14

a) Ratio of **[163]:[50]:[106]** determined by ^{1}H NMR analysis of the crude product.

b) After purification by column chromatography.

c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H); Absolute configuration determined by comparison of rotation values to literature values.

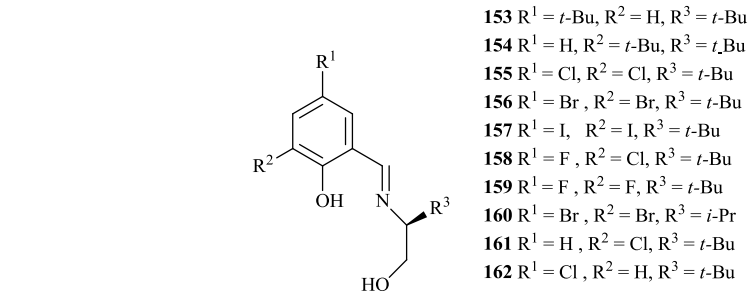
d) This oxidation was carried out numerous times and the enantioselectivity ranged from 71% to 80% ee. Hence the results, in terms of % ee, are variable to a minor extent. The other oxidations in this table were only carried out once.

3.13.5 Investigation of Influence of Ligand Structure

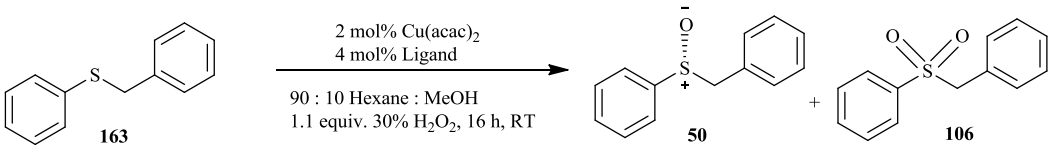
Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a round bottomed flask containing Schiff base ligand (0.04 mmol, 4 mol%), and 9:1 hexane/MeOH (1 mL). The resulting solution was stirred at RT for 5 min, and then a solution of sulfide (200 mg, 1 mmol) in 9:1 hexane/MeOH (1 mL) was added. After 5 min stirring at RT, H_2O_2 (0.130 mL,

30%, 1.1 mmol) was added in one portion, dropwise to the solution. The reaction mixture was stirred at RT for a further 16 h.

Table 3.5 Investigation of Influence of Ligand Structure



153 R^1 = *t*-Bu, R^2 = H, R^3 = *t*-Bu
154 R^1 = H, R^2 = *t*-Bu, R^3 = *t*-Bu
155 R^1 = Cl, R^2 = Cl, R^3 = *t*-Bu
156 R^1 = Br , R^2 = Br, R^3 = *t*-Bu
157 R^1 = I, R^2 = I, R^3 = *t*-Bu
158 R^1 = F , R^2 = Cl, R^3 = *t*-Bu
159 R^1 = F , R^2 = F, R^3 = *t*-Bu
160 R^1 = Br , R^2 = Br, R^3 = *i*-Pr
161 R^1 = H , R^2 = Cl, R^3 = *t*-Bu
162 R^1 = Cl , R^2 = H, R^3 = *t*-Bu



Entry	Ligand	[163] : [50] : [106][a]	Yield %[b] [50]	%ee[c] (*R*) [50]
1	**[153]**	74 : 36 : 0	39	2
2	**[154]**	73 : 27 : 0	24	3
3	**[155]**	1 : 98 : 1	90	79
4	**[156]**	1 : 96 : 3	86	66
5	**[157]**	68 : 32 : 0	28	3
6	**[158]**	3 : 96 : 1	87	58
7	**[159]**	45 : 55 : trace	47	37
8	**[160]**	50 : 50 : 0	44	6
9	**[161]**	15 : 83 : 2	72	38
10	**[162]**	61 : 39 : 0	30	5

a) Ratio of **[163]:[50]:[106]** determined by ^{1}H NMR analysis of the crude product.

b) After purification by column chromatography.

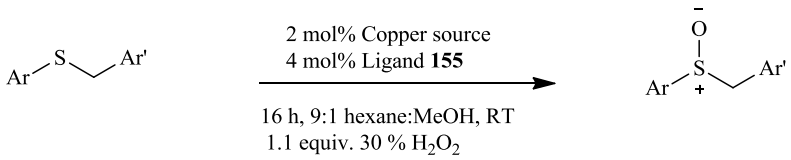
c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H); Absolute configuration determined by comparison of rotation values to literature values.

3.13.6 Investigation of Effect of NaBARF and Copper Source

Copper source (0.02 mmol, 2.0 mol%) was added to a round bottomed flask containing Schiff base ligand **[155]** (11.6 mg, 4 mol%), and 9:1 hexane/MeOH (1 mL). The resulting solution was stirred at RT for 5 min, and then a solution of sulfide (1 mmol) in 9:1 hexane/MeOH (1 mL) was added. After 5 min stirring at RT, H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution. The reaction mixture was stirred at RT for a further 16 h.

NaBARF (6 mol%, 53 mg) was added 5 min after the addition of the copper source. The copper-ligand complex and NaBARF were stirred in 9:1 hexane/MeOH for 2 h before the addition of the sulfide.

Table 3.6 Investigation of Effect of NaBARF and Copper Source



Entry	Sulfide	Ar	Ar'	Copper source	Na BARF[d]	Sulfide : Sulfoxide : Sulfone[a]	Yield %[b]	%ee[c] (*R*)	Sulfoxide
1	**[163]**	Ph	Ph	CuCl	No	83 : 17 : 0	12	3	**[50]**
2	**[163]**	Ph	Ph	CuCl	Yes	-	13	31	**[50]**
3	**[163]**	Ph	Ph	$Cu(acac)_2$	No	3 : 96 : 1	87	80	**[50]**
4	**[163]**	Ph	Ph	$Cu(acac)_2$	Yes	-	61	41	**[50]**
5	**[163]**	Ph	Ph	$Cu(acac)_2$	Yes	2 : 93 : 5	85		**[50]**
6	**[7]**	*p*-Tol	Ph	CuCl	No	81 : 19 : 0	13	7	**[51]**
7	**[7]**	*p*-Tol	Ph	CuCl	Yes	-	12	9	**[51]**
8	**[7]**	*p*-Tol	Ph	$Cu(acac)_2$	No	2 : 97 : 1	91	81	**[51]**
9	**[7]**	*p*-Tol	Ph	$Cu(acac)_2$	Yes	-	73	37	**[51]**
10	**[11]**	Ph	2'-ClC_6H_4	CuCl	No	85 : 15 : 0	9	6	**[84]**
11	**[11]**	Ph	2'-ClC_6H_4	CuCl	Yes	-	14	9	**[84]**

12	**[11]**	Ph	2'-ClC_6H_4	$Cu(acac)_2$	No	10 : 89 : 1	82	44	**[84]**
13	**[11]**	Ph	2'-ClC_6H_4	$Cu(acac)_2$	Yes	-	71	32	**[84]**
14	**[12]**	Ph	3'-ClC_6H_4	CuCl	No	87 : 13 : 0	7	5	**[85]**
15	**[12]**	Ph	3'-ClC_6H_4	CuCl	Yes	-	13	19	**[85]**
16	**[12]**	Ph	3'-ClC_6H_4	$Cu(acac)_2$	No	18 : 78 : 4	72	27	**[85]**
17	**[12]**	Ph	3'-ClC_6H_4	$Cu(acac)_2$	Yes	-	61	22	**[85]**
18	**[13]**	Ph	4'-ClC_6H_4	CuCl	No	88 : 12 : 0	8	3	**[86]**
19	**[13]**	Ph	4'-ClC_6H_4	CuCl	Yes	-	13	40	**[86]**
20	**[13]**	Ph	4'-ClC_6H_4	$Cu(acac)_2$	No	7 : 91 : 2	85	54	**[86]**
21	**[13]**	Ph	4'-ClC_6H_4	$Cu(acac)_2$	Yes	-	56	37	**[86]**

a) Ratio of sulfide : sulfoxide : sulfone determined by ^{1}H NMR analysis of the crude product.

b) After purification by column chromatography.

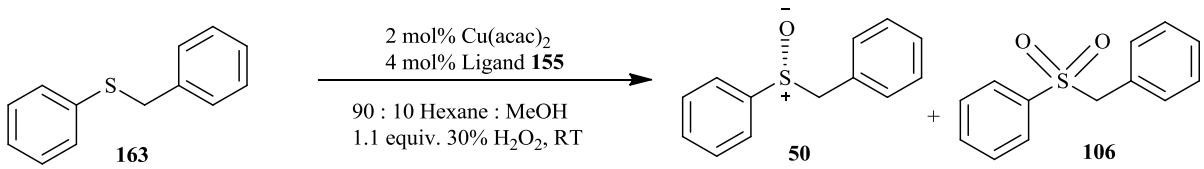
c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H for **[50]**, **[51]**, **[85]**, **[86]**, Chiracel AS-H for **[84]**); Absolute configuration determined by comparison of rotation values for **[50]** and **[51]** to known literature values; for **[84]**, **[85]**, **[86]** proposed configuration based on HPLC elution order and direction of specific rotations.

d) NaBARF was added prior to addition of sulfide. Copper-ligand complex and NaBARF (6 mol%) were stirred in 9:1 hexane/MeOHfor 2 h before addition of sulfide.

3.13.7 Investigation of Influence of Reaction Time

Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a round bottomed flask containing Schiff base ligand **[155]** (11.6 mg, 4.0 mol%) and 9:1 hexane/MeOH (1 mL). The resulting solution was stirred at RT for 5 min, and then a solution of sulfide in 9:1 hexane/MeOH (1 mL) was added. After 5 min stirring at RT, H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution. A sample of the solution was removed at the time indicated and the conversion was determined by ^{1}H NMR analysis.

Table 3.7 Investigation of Influence of Reaction Time



Entry	Time (h)	[163] : [50] : [106][a]	%ee[b] (*R*) [50]
1	2	16 : 83 : 1	60
2	5	2 : 96 : 2	68
3	7	1 : 97 : 2	69
4	16	1 : 97 : 2	69

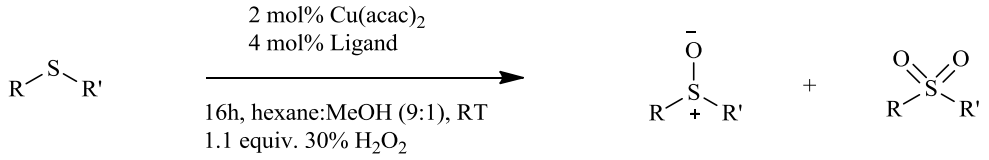
a) Ratio of **[163]:[50]:[106]** determined by ^{1}H NMR analysis of the crude product.

b) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H); Absolute configuration determined by comparison of rotation values to literature values.

3.13.8 Investigation of Steric Effects of Benzyl Substituent using Optimised Conditions

Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a round bottomed flask containing Schiff base ligand **[155]** (11.6 mg, 4.0 mol%) or **[158]** (11.0 mg, 4.0 mol%), and 9:1 hexane/MeOH (1 mL). The resulting solution was stirred at RT for 5 min, and then a solution of sulfide in 9:1 hexane/MeOH (1 mL) was added. After 5 min stirring at RT, H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution. The reaction mixture was stirred at RT for a further 16 h.

Table 3.8 Investigation of Steric Effects of Benzyl Substituent



Entry	Sulfide	Ar	Ar′	Ligand	Sulfide : Sulfoxide : Sulfone	Yield %[b]	%ee[c] (*R*)	Sulfoxide
1	**[163]**	Ph	-$CH_2C_6H_5$	**[155]**	1 : 98 : 1	90	79	**[50]**
2	**[163]**	Ph	-$CH_2C_6H_5$	**[158]**	2 : 98 : 0	91	58	**[50]**
3	**[7]**	4-MeC_6H_4	-$CH_2C_6H_5$	**[155]**	2 : 97 : 1	91	81	**[51]**
4	**[7]**	4-MeC_6H_4	-$CH_2C_6H_5$	**[158]**	4 : 96 : 0	90	84	**[51]**
5	**[4]**	4-MeC_6H_4	4-$MeOC_6H_4$	**[155]**	2 : 97 : 1	90	47	**[52]**
6	**[3]**	2-$MeOC_6H_4$	-$CH_2C_6H_5$	**[155]**	8 : 92 : trace	85	29	**[53]**
7	**[2]**	3-$MeOC_6H_4$	-$CH_2C_6H_5$	**[155]**	46 : 54 : 0	47	21	**[54]**
8	**[165]**	4-MeC_6H_4	Me	**[155]**	4 : 96 : trace	90	23	**[57]**
9	**[166]**	Ph	Et	**[155]**	2 : 98 : trace	92	44	**[58]**
10	**[25]**	Ph	*i*-Pr	**[155]**	19 : 81 : trace	74	60	**[59]**
11	**[24]**	Ph	-$CH_2CH(CH_3)_2$	**[155]**	10 : 90 : trace	82	48	**[60]**
12	**[46]**	Ph	-$CH_2C(CH_3)_3$	**[155]**	15 : 85 : 0	79	71	**[61]**
13	**[26]**	Ph	-CH_2-2'-Naphthyl	**[155]**	100 : 0 : 0	-	-	**[62]**
14	**[5]**	2-MeC_6H_4	-$CH_2C_6H_5$	**[155]**	1 : 98 : 1	91	64	**[75]**
15	**[5]**	2-MeC_6H_4	-$CH_2C_6H_5$	**[158]**	6 : 94 : 0	88	71	**[75]**
16	**[6]**	3-MeC_6H_4	-$CH_2C_6H_5$	**[155]**	11 : 89 : 0	84	54	**[76]**
17	**[6]**	3-MeC_6H_4	-$CH_2C_6H_5$	**[158]**	10 : 88:2	83	69	**[76]**
18	**[8]**	Ph	-CH_2-*o*-Tol	**[155]**	13 : 85 : 2	80	47[d]	**[77]**
19	**[9]**	Ph	-CH_2-*m*-Tol	**[155]**	7 : 92 : 1	83	50	**[78]**
20	**[9]**	Ph	-CH_2-*m*-Tol	**[158]**	4 : 95 : 1	90	46	**[78]**

21	**[10]**	Ph	-CH_2-*p*-Tol	**[155]**	1 : 97 : 2	89	55	**[79]**

a) Ratio of sulfide : sulfoxide : sulfone determined by ^{1}H NMR analysis of the crude product.

b) Yield of sulfoxide after purification by column chromatography.

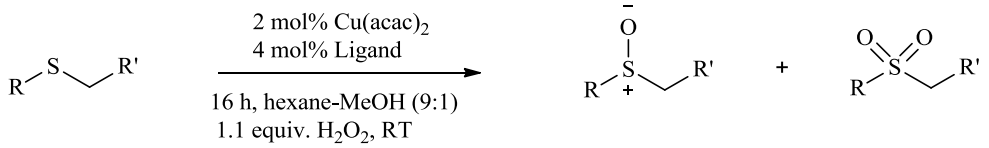
c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H for **[50]**, **[51]**, **[52]**, **[53]**, **[54]**, **[57]**, **[58]**, **[59]**, **[60]**, **[61]**, **[62]**, **[75]**, **[76]**, **[78]**, **[79]**; Chiracel AS-H for **[77]**); Absolute configuration determined by comparison of rotation values for **[50]**, **[57]**, **[58]**, **[59]**, **[60]** to known literature values; for **[52]**, **[53]**, **[54]**, **[61]**, **[75]**, **[78]** proposed configuration based on HPLC elution order and direction of specific rotations.

d) Configuration of **[77]** not determined.

3.13.9 Investigation of Steric and Electronic Effects of Aryl Substituent using Optimised Conditions

Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a round bottomed flask containing Schiff base ligand **[155]** (11.6 mg, 4.0 mol%) or **[158]** (11.0 mg, 4.0 mol%) or **[156]** (15.2 mg, 4.0 mol%) and 9:1 hexane/MeOH (1 mL). The resulting solution was stirred at RT for 5 min, and then a solution of sulfide (1 mmol) in 9:1 hexane/MeOH (1 mL) was added. After 5 min stirring at RT, H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution. The reaction mixture was stirred at RT for a further 16 h.

Table 3.9 Investigation of Steric and Electronic Effects of Aryl Substituent using Optimised Conditions



Entry	Sulfide	R	R'	Ligand	Sulfide : Sulfoxide : Sulfone[a]	Yield %[b]	%ee[c] (*R*)	Sulfoxide
1	**[35]**	*i*-Pr	Ph	**[155]**	0 : 97 : 3	86	27	**[63]**[d]
2	**[35]**	*i*-Pr	Ph	**[158]**	1 : 96 : 3	88	36	**[63]**[d]
3	**[35]**	*i*-Pr	Ph	**[156]**	0 : 98:2	82	13	**[63]**[d]
4	**[37]**	*i*-Bu	Ph	**[155]**	4 : 94 : 2	87	11	**[64]**
5	**[37]**	*i*-Bu	Ph	**[158]**	2 : 97 : 1	89	19	**[64]**

6	**[37]**	*i*-Bu	Ph	**[156]**	10 : 90 : 0	80	8	**[64]**
7	**[38]**	*t*-Bu	Ph	**[155]**	2 : 97 : 1	88	37	**[65]**
8	**[38]**	*t*-Bu	Ph	**[158]**	1 : 98 : 1	90	40	**[65]**
9	**[38]**	*t*-Bu	Ph	**[156]**	11 : 88 : 1	82	16	**[65]**
10	**[29]**	2-Naphthyl	Ph	**[155]**	100 : 0 : 0	-	-	**[66]**
11	**[29]**	2-Naphthyl	Ph	**[155]**	62 : 38 : 0	32[e]	97	**[66]**
12	**[29]**	2-Naphthyl	Ph	**[158]**	58 : 42 : 0	38[e]	95	**[66]**
13	**[30]**	1-Naphthyl	Ph	**[155]**	48 : 52 : 0	46[e]	75	**[67]**
14	**[30]**	1-Naphthyl	Ph	**[158]**	56:44 : 0	37[e]	77	**[67]**
15	**[31]**	2-Naphthyl	4'-ClC_6H_4	**[155]**	23 : 75 : 2	67[e]	90	**[68]**
16	**[32]**	1-Naphthyl	4'-ClC_6H_4	**[155]**	65 : 35 : 0	28[e]	71	**[69]**
17	**[36]**	Cyclohexyl	Ph	**[155]**	3 : 94 : 3	88	27	**[70]**[d]
18	**[36]**	Cyclohexyl	Ph	**[158]**	4 : 93 : 3	85	33	**[70]**[d]
19	**[36]**	Cyclohexyl	Ph	**[156]**	5 : 93 : 2	82	21	**[70]**[d]
20	**[27]**	Ph	$CH_2(CH_2)_9CH_3$	**[155]**	29 : 65 : 6	60	57	**[71]**
21	**[27]**	Ph	$CH_2(CH_2)_9CH_3$	**[158]**	27 : 65 : 8	57	57	**[71]**
22	**[28]**	Ph	$CH_2(CH_2)_5CH_3$	**[155]**	32 : 62 : 6	55	36	**[72]**
23	**[28]**	Ph	$CH_2(CH_2)_5CH_3$	**[158]**	31 : 63 : 6	55	58	**[72]**
24	**[33]**	$CH_3(CH_2)_{10}CH_2$	Ph	**[155]**	2 : 93 : 5	88	21	**[73]**
25	**[33]**	$CH_3(CH_2)_{10}CH_2$	Ph	**[158]**	9 : 86 : 5	79	26	**[73]**
26	**[33]**	$CH_3(CH_2)_{10}CH_2$	Ph	**[156]**	6 : 88 : 6	78	22	**[73]**
27	**[34]**	$CH_3(CH_2)_6CH_2$	Ph	**[155]**	9 : 85 : 6	77	22	**[74]**
28	**[34]**	$CH_3(CH_2)_6CH_2$	Ph	**[158]**	10 : 84 : 6	77	21	**[74]**
29	**[34]**	$CH_3(CH_2)_6CH_2$	Ph	**[156]**	19 : 76 : 5	65	10	**[74]**
30	**[167]**	Ph	$CH=CH_2$	**[155]**	26 : 74 : 0	67	29	**[81]**

31	**[167]**	Ph	$CH=CH_2$	**[158]**	21 : 79 : 0	72	24	**[81]**
32	**[168]**	$CH_2=CHCH_2$	Ph	**[155]**	6 : 94 : 0	87	11	**[82]**[d]
33	**[168]**	$CH_2=CHCH_2$	Ph	**[158]**	6 : 94 : 0	85	13	**[82]**[d]
34	**[169]**	CH_3	Ph	**[155]**	5 : 94 : 1	85	4[f]	**[83]**

a) Ratio of sulfide : sulfoxide : sulfone determined by ^1H NMR analysis of the crude product.

b) Yield of sulfoxide after purification by column chromatography.

c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H for **[65]**, **[66]**, **[68]**, **[69]**, **[83]**; Chiracel AS-H for **[63]**, **[64]**, **[67]**, **[71]**, **[73]**, **[74]**, **[82]**; Chiracel OJ-H for **[81]**; Phenomenex Lux Cellulose-4 for **[72]**, **[83]**; Phenomenex Lux Amylose-2 for **[70]**); **[83]** enantiomers were separated using both OD-H and Phenomenex Lux Cellulose-4 columns, resolution was better using Phenomenex Lux Cellulose-4 column; Absolute configuration determined by comparison of rotation values for **[64]**, **[65]**, **[81]** to known literature values; for **[66]** and **[67]** absolute configuration was determined by single crystal X-ray diffraction on a crystalline sample of 1-naphthyl benzyl sulfoxide and 2-naphthyl benzyl sulfoxide recrystallised from CH_2Cl_2,[127] **[68]** and **[69]** proposed configuration based on HPLC elution order and direction of specific rotations, **[73]** and **[74]** proposed configuration based on comparison of optical rotation to known literature values for (*R*)-decyl phenyl sulfoxide[129] and (*R*)-butyl phenyl sulfoxide,[130] **[71]** and **[72]** proposed configuration based on comparison of optical rotation to known literature value for (*R*)-decyl benzyl sulfoxide.[128]

d) Configuration of **[63]**, **[70]**, **[82]** not determined.

e) These oxidations were carried out in 9:1 toluene/MeOH, due to lack of solubility in 9:1 hexane/MeOH (up to 3 mL of 9:1 hexane/MeOH was used).

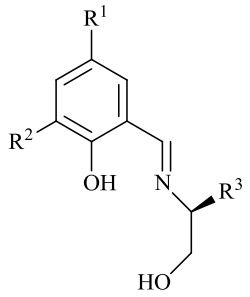
f) Sulfoxide **[83]** was essentially racemic.

3.13.10 Oxidation of Chloro Substituted Aryl Benzyl Sulfides

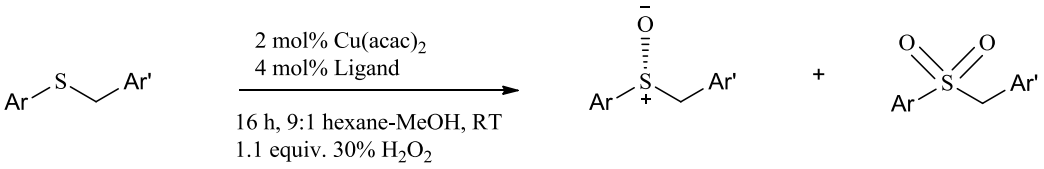
Oxidation of Sulfides [11] to [16]

Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a round bottomed flask containing Schiff base ligand (0.04 mmol, 4 mol%) and 9:1 hexane/MeOH (1 mL). The resulting solution was stirred at RT for 5 min, and then a solution of sulfide (235 mg, 1 mmol) in 9:1 hexane/MeOH (1 mL) was added. After 5 min stirring at RT, H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution. The reaction mixture was stirred at RT for a further 16 h.

Table 3.10 Oxidation of Chloro Substituted Aryl Benzyl Sulfides



155 R^1 = Cl, R^2 = Cl, R^3 = t-*B*u
156 R^1 = Br, R^2 = Br, R^3 = t-*B*u
158 R^1 = F , R^2 = Cl, R^3 = *t*-Bu
161 R^1 = H , R^2 = Cl, R^3 = *t*-Bu
162 R^1 = Cl , R^2 = H, R^3 = *t*-Bu



Entry	Sulfide	Ar	Ar'	Ligand	Sulfide : Sulfoxide : Sulfone[a]	Yield %[b]	%ee[c] (*R*)	Sulfoxide
1	**[11]**	Ph	2'-ClC_6H_4	**[155]**	18 : 78 : 4	72	44	**[84]**
2	**[11]**	Ph	2'-ClC_6H_4	**[158]**	19 : 77 : 4	72	32	**[84]**
3	**[11]**	Ph	2'-ClC_6H_4	**[161]**	29 : 67 : 4	58	19	**[84]**
4	**[11]**	Ph	2'-ClC_6H_4	**[162]**	76 : 24 : 0	17	6	**[84]**
5	**[12]**	Ph	3'-ClC_6H_4	**[155]**	10 : 89 : 1	82	42	**[85]**
6	**[12]**	Ph	3'-ClC_6H_4	**[156]**	38 : 62 : 0	57	36	**[85]**
7	**[12]**	Ph	3'-ClC_6H_4	**[158]**	17 : 81 : 2	75	37	**[85]**
8	**[12]**	Ph	3'-ClC_6H_4	**[161]**	47 : 51 : 2	43	19	**[85]**
9	**[12]**	Ph	3'-ClC_6H_4	**[162]**	68 : 31 : 1	21	1	**[85]**
10	**[13]**	Ph	4'-ClC_6H_4	**[155]**	9 : 90 : 1	85	49	**[86]**
11	**[13]**	Ph	4'-ClC_6H_4	**[158]**	12 : 87 : 1	80	62	**[86]**
12	**[14]**	2-ClC_6H_4	Ph	**[155]**	67 : 32 : 1	26	48	**[87]**

13	**[14]**	2-ClC_6H_4	Ph	**[158]**	47 : 51 : 2	46	52	**[87]**
14	**[14]**	2-ClC_6H_4	Ph	**[161]**	73 : 26 : 1	21	26	**[87]**
15	**[14]**	2-ClC_6H_4	Ph	**[162]**	88 : 12 : 0	7	5	**[87]**
16	**[15]**	3-ClC_6H_4	Ph	**[155]**	60 : 39 : 1	33	59	**[88]**
17	**[15]**	3-ClC_6H_4	Ph	**[156]**	77 : 23 : 0	17	55	**[88]**
18	**[15]**	3-ClC_6H_4	Ph	**[158]**	57 : 42 : 1	36	54	**[88]**
19	**[15]**	3-ClC_6H_4	Ph	**[161]**	63 : 36 : 1	24	39	**[88]**
20	**[15]**	3-ClC_6H_4	Ph	**[162]**	70 : 30 : 0	22	4	**[88]**
21	**[16]**	4-ClC_6H_4	Ph	**[155]**	28 : 72 : 0	67	52	**[89]**
22	**[16]**	4-ClC_6H_4	Ph	**[156]**	66 : 34 : 0	27	38	**[89]**
23	**[16]**	4-ClC_6H_4	Ph	**[158]**	20 : 80 : 0	71	52	**[89]**
24	**[16]**	4-ClC_6H_4	Ph	**[161]**	34 : 66 : 0	57	48	**[89]**
25	**[16]**	4-ClC_6H_4	Ph	**[162]**	76 : 24 : 0	16	7	**[89]**

a) Ratio of sulfide : sulfoxide : sulfone determined by ^1H NMR analysis of the crude product.

b) Sulfoxide yield after purification by column chromatography.

c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H for **[85]**, **[86]**, **[89]**, Chiracel OJ-H for **[87]**, **[88]**, Chiracel AS-H for **[84]**); Absolute configuration determined by comparison of rotation values for **[87]** to known literature values; for **[84]**, **[85]**, **[86] [88]**, **[89]** proposed configuration based on HPLC elution order and direction of specific rotations.

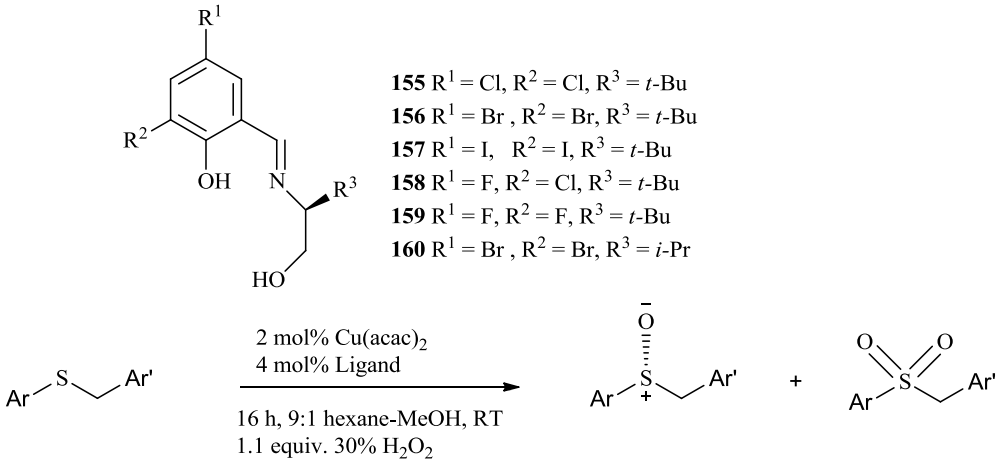
3.13.11 Oxidation of Methyl Substituted Aryl Benzyl Sulfides

Oxidation of Sulfide [5] to [10]

Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a round bottomed flask containing Schiff base ligand (4 mol%) and 9:1 hexane/MeOH (1 mL). The resulting solution was stirred at RT for 5 min, and then a solution of sulfide (214 mg, 1 mmol) in 9:1

hexane/MeOH (1 mL) was added. After 5 min stirring at RT, H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution. The reaction mixture was stirred at RT for a further 16 h.

Table 3.11 Oxidation of Methyl Substituted Aryl Benzyl Sulfides



Entry	Sulfide	Ar	Ar'	Ligand	Sulfide : Sulfoxide : Sulfone[a]	Yield %[b]	%ee[c] (*R*)	Sulfoxide
1	**[5]**	2-MeC_6H_4	Ph	**[155]**	1 : 98 : 1	91	64	**[75]**
2	**[5]**	2-MeC_6H_4	Ph	**[156]**	40 : 60 : 0	51	55	**[75]**
3	**[5]**	2-MeC_6H_4	Ph	**[157]**	79 : 21 : 0	16	11	**[75]**
4	**[5]**	2-MeC_6H_4	Ph	**[158]**	6 : 94 : 0	88	71	**[75]**
5	**[5]**	2-MeC_6H_4	Ph	**[159]**	70 : 30 : 0	24	60	**[75]**
6	**[5]**	2-MeC_6H_4	Ph	**[160]**	88 : 12 : 0	10	9	**[75]**
7	**[6]**	3-MeC_6H_4	Ph	**[155]**	11 : 89 : 0	84	65	**[76]**
8	**[6]**	3-MeC_6H_4	Ph	**[156]**	15 : 85 : 0	77	49	**[76]**
9	**[6]**	3-MeC_6H_4	Ph	**[157]**	83 : 17 : 0	16	16	**[76]**
10	**[6]**	3-MeC_6H_4	Ph	**[158]**	10 : 88:2	83	69	**[76]**
11	**[6]**	3-MeC_6H_4	Ph	**[159]**	49 : 51 : 0	45	34	**[76]**
12	**[6]**	3-MeC_6H_4	Ph	**[160]**	76 : 24 : 0	17	3	**[76]**

13	**[7]**	4-MeC_6H_4	Ph	**[155]**	2 : 97 : 1	91	81	**[51]**
14	**[7]**	4-MeC_6H_4	Ph	**[156]**	2 : 98 : 0	90	59	**[51]**
15	**[7]**	4-MeC_6H_4	Ph	**[157]**	81 : 19 : 0	12	6	**[51]**
16	**[7]**	4-MeC_6H_4	Ph	**[158]**	4 : 96 : 0	90	84	**[51]**
17	**[7]**	4-MeC_6H_4	Ph	**[159]**	33 : 67 : 0	60	66	**[51]**
18	**[7]**	4-MeC_6H_4	Ph	**[160]**	71 : 29 : 0	23	1	**[51]**
19	**[8]**	Ph	2'-MeC_6H_4	**[155]**	12 : 85 : 2	80	48	**[77]**
20	**[8]**	Ph	2'-MeC_6H_4	**[156]**	23 : 76 : 1	69	45	**[77]**
21	**[8]**	Ph	2'-MeC_6H_4	**[157]**	87 : 13 : 0	9	3	**[77]**
22	**[8]**	Ph	2'-MeC_6H_4	**[158]**	19 : 81 : 0	74	46	**[77]**
23	**[8]**	Ph	2'-MeC_6H_4	**[159]**	55 : 45 : 0	40	47	**[77]**
24	**[8]**	Ph	2'-MeC_6H_4	**[160]**	72 : 28 : 0	21	3	**[77]**
25	**[9]**	Ph	3'-MeC_6H_4	**[155]**	9 : 90 : 1	81	52	**[78]**
26	**[9]**	Ph	3'-MeC_6H_4	**[156]**	7 : 92 : 1	83	54	**[78]**
27	**[9]**	Ph	3'-MeC_6H_4	**[157]**	81 : 19 : 0	15	13	**[78]**
28	**[9]**	Ph	3'-MeC_6H_4	**[158]**	4 : 95 : 1	90	46	**[78]**
29	**[9]**	Ph	3'-MeC_6H_4	**[159]**	56:44 : 0	36	32	**[78]**
30	**[9]**	Ph	3'-MeC_6H_4	**[160]**	78:22 : 0	17	5	**[78]**
31	**[10]**	Ph	4'-MeC_6H_4	**[155]**	1 : 97 : 2	89	57	**[79]**
32	**[10]**	Ph	4'-MeC_6H_4	**[156]**	14 : 85 : 1	80	46	**[79]**
33	**[10]**	Ph	4'-MeC_6H_4	**[157]**	91 : 9 : 0	5	6	**[79]**
34	**[10]**	Ph	4'-MeC_6H_4	**[158]**	34 : 75 : 1	68	51	**[79]**
35	**[10]**	Ph	4'-MeC_6H_4	**[159]**	66 : 34 : 0	28	42	**[79]**
36	**[10]**	Ph	4'-MeC_6H_4	**[160]**	75 : 25 : 0	16	5	**[79]**

a) Ratio of sulfide : sulfoxide : sulfone determined by ^{1}H NMR analysis of the crude product.

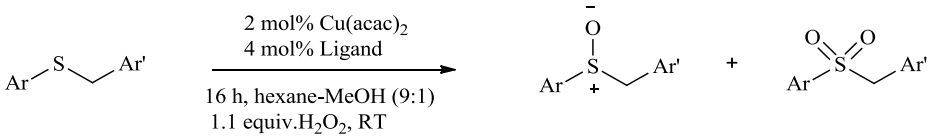
b) Sulfoxide yield after purification by column chromatography.

c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H for **[51]**, **[75]**, **[76]**, **[78]**, **[79]**, Chiracel AS-H for **[77]**); Absolute configuration determined by comparison of rotation values for **[51]** to known literature values; for **[75]**, **[76]**, **[77]**, **[78]**, **[79]** proposed configuration based on HPLC elution order and direction of specific rotations.

3.13.12 Oxidation of Disubstituted Aryl Benzyl Sulfides

Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a round bottomed flask containing Schiff base ligand **[155]** (11.6 mg, 4.0 mol%) or **[158]** (11.0 mg, 4.0 mol%) or **[156]** (15.2 mg, 4.0 mol%) and 9:1 hexane/MeOH (1 mL). The resulting solution was stirred at RT for 5 min, and then a solution of sulfide (1 mmol) in 9:1 hexane/MeOH (1 mL) was added. After 5 min stirring at RT, H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution. The reaction mixture was stirred at RT for a further 16 h.

Table 3.12 Oxidation of Disubstituted Aryl Benzyl Sulfides



Entry	Sulfide	Ar	Ar'	Ligand	Sulfide : Sulfoxide : Sulfone[a]	Yield %[b]	%ee[c] (*R*)	Sulfoxide
1	**[17]**	4-MeC_6H_4	2'-MeC_6H_4	**[155]**	28 : 69 : 3	62	32[d]	**[91]**
2	**[17]**	4-MeC_6H_4	2'-MeC_6H_4	**[158]**	29 : 69 : 2	64	28[d]	**[91]**
3	**[17]**	4-MeC_6H_4	2'-MeC_6H_4	**[156]**	47 : 52 : 1	47	35[d]	**[91]**
4	**[18]**	4-MeC_6H_4	3'-MeC_6H_4	**[155]**	17 : 81 : 2	76	52	**[92]**
5	**[18]**	4-MeC_6H_4	3'-MeC_6H_4	**[158]**	21 : 78 : 1	70	49	**[92]**
6	**[18]**	4-MeC_6H_4	3'-MeC_6H_4	**[156]**	54 : 46 : 0	40	43	**[92]**
7	**[19]**	4-MeC_6H_4	4'-ClC_6H_4	**[155]**	13 : 87 : 0	81	69	**[93]**
8	**[19]**	4-MeC_6H_4	4'-ClC_6H_4	**[158]**	63 : 37 : 0	32	65	**[93]**
9	**[20]**	4-MeC_6H_4	3'-ClC_6H_4	**[155]**	24 : 75 : 1	70	61	**[94]**
10	**[20]**	4-MeC_6H_4	3'-ClC_6H_4	**[158]**	23 : 76 : 1	68	69	**[94]**
11	**[20]**	4-MeC_6H_4	3'-ClC_6H_4	**[156]**	38 : 61 : 1	55	62	**[94]**
12	**[21]**	4-MeC_6H_4	2'-ClC_6H_4	**[155]**	19 : 80 : 1	74	37	**[95]**

13	**[21]**	4-MeC_6H_4	2'-ClC_6H_4	**[158]**	25 : 74 : 1	65	37	**[95]**
14	**[21]**	4-MeC_6H_4	2'-ClC_6H_4	**[156]**	57 : 43 : 0	39	42	**[95]**
15	**[22]**	2-$MeOC_6H_4$	2'-ClC_6H_4	**[155]**	19 : 80 : 1	75	70	**[96]**
16	**[22]**	2-$MeOC_6H_4$	2'-ClC_6H_4	**[158]**	24 : 75 : 1	71	69	**[96]**
17	**[22]**	2-$MeOC_6H_4$	2'-ClC_6H_4	**[156]**	46 : 54 : 0	48	65	**[96]**

a) Ratio of sulfide : sulfoxide : sulfone determined by ^{1}H NMR analysis of the crude product.

b) Yield of sulfoxide after purification by column chromatography.

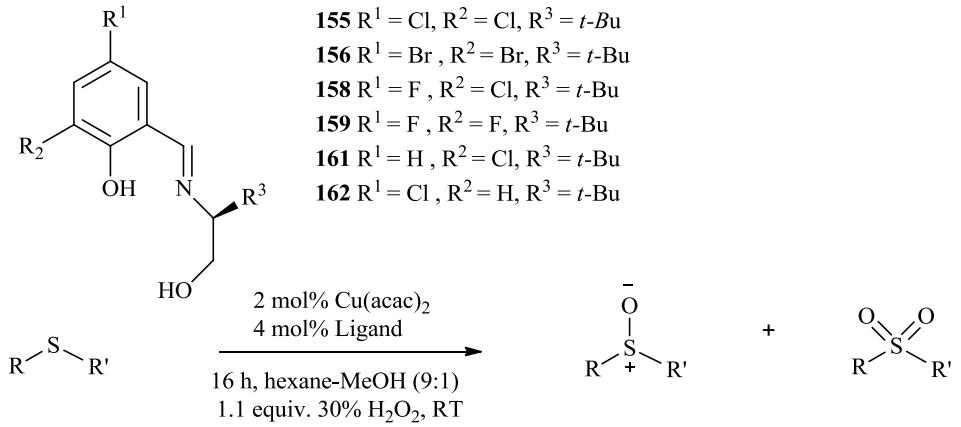
c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H for **[92]** and **[93]**, Chiracel AS-H for **[91]**, **[94]**, **[95]**, **[96]**); **[92]** enantiomers were separated using both OD-H and Phenomenex Lux Cellulose-4 columns, resolution was better using Phenomenex Lux Cellulose-4 column; Absolute configuration determined by comparison of rotation values for **[93]** to known literature values; for **[92]**, **[94]** ,**[95]**, **[96]** proposed configuration based on HPLC elution order and direction of specific rotations.

d) Configuration of **[91]** not determined.

3.13.13 Oxidation of Dibenzyl and Diphenyl Sulfides

Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a round bottomed flask containing Schiff base ligand in 9:1 hexane/MeOH (1 mL). The resulting solution was stirred at RT for 5 min, and then a solution of sulfide (1 mmol) in 9:1 hexane/MeOH (1 mL) was added. After 5 min stirring at RT, H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution. The reaction mixture was stirred at RT for a further 16 h.

Table 3.13 Oxidation of Dibenzyl and Diphenyl Sulfides



155 R^1 = Cl, R^2 = Cl, R^3 = *t-Bu*
156 R^1 = Br , R^2 = Br, R^3 = *t*-Bu
158 R^1 = F , R^2 = Cl, R^3 = *t*-Bu
159 R^1 = F , R^2 = F, R^3 = *t*-Bu
161 R^1 = H , R^2 = Cl, R^3 = *t*-Bu
162 R^1 = Cl , R^2 = H, R^3 = *t*-Bu

Entry	Sulfide	R	R'	Ligand	Sulfide : Sulfoxide : Sulfone[a]	Yield %[b]	%ee[c]	Sulfoxide
1	**[39]**	2-Methylbenzyl	Bn	**[155]**	2 : 91 : 7	83	2	**[97]**
2	**[39]**	2-Methylbenzyl	Bn	**[158]**	3 : 92 : 5	83	3	**[97]**
3	**[39]**	2-Methylbenzyl	Bn	**[156]**	12 : 87 : 1	79	1	**[97]**
4	**[39]**	2-Methylbenzyl	Bn	**[161]**	10 : 87 : 3	80	1	**[97]**
5	**[39]**	2-Methylbenzyl	Bn	**[162]**	19 : 79 : 2	71	4	**[97]**
6	**[39]**	2-Methylbenzyl	Bn	**[159]**	24 : 73 : 3	67	0	**[97]**
7	**[40]**	3-Methylbenzyl	Bn	**[155]**	1 : 89 : 10	82	3	**[98]**
8	**[40]**	3-Methylbenzyl	Bn	**[158]**	1 : 88 : 11	80	1	**[98]**
9	**[40]**	3-Methylbenzyl	Bn	**[156]**	23 : 75 : 2	65	2	**[98]**
10	**[40]**	3-Methylbenzyl	Bn	**[161]**	9 : 80 : 11	70	1	**[98]**
11	**[40]**	3-Methylbenzyl	Bn	**[159]**	44 : 55 : 1	48	2	**[98]**
12	**[41]**	4-Methylbenzyl	Bn	**[155]**	2 : 89 : 9	82	4	**[99]**
13	**[41]**	4-Methylbenzyl	Bn	**[158]**	3 : 89 : 8	82	2	**[99]**
14	**[41]**	4-Methylbenzyl	Bn	**[156]**	5 : 90 : 5	83	2	**[99]**
15	**[41]**	4-Methylbenzyl	Bn	**[161]**	26 : 72 : 2	66	2	**[99]**
16	**[41]**	4-Methylbenzyl	Bn	**[162]**	10 : 78 : 12	74	1	**[99]**
17	**[41]**	4-Methylbenzyl	Bn	**[159]**	35 : 62 : 3	54	2	**[99]**
18	**[42]**	2-Chlorobenzyl	Bn	**[155]**	3 : 92 : 5	88	10	**[100]**
19	**[42]**	2-Chlorobenzyl	Bn	**[158]**	15 : 81 : 4	65	9	**[100]**
20	**[42]**	2-Chlorobenzyl	Bn	**[156]**	18 : 77 : 5	55	10	**[100]**
21	**[42]**	2-Chlorobenzyl	Bn	**[159]**	64 : 36 : 0	24	4	**[100]**
22	**[43]**	3-Chlorobenzyl	Bn	**[155]**	12 : 80 : 8	72	3	**[101]**
23	**[43]**	3-Chlorobenzyl	Bn	**[158]**	8 : 81 : 11	74	2	**[101]**

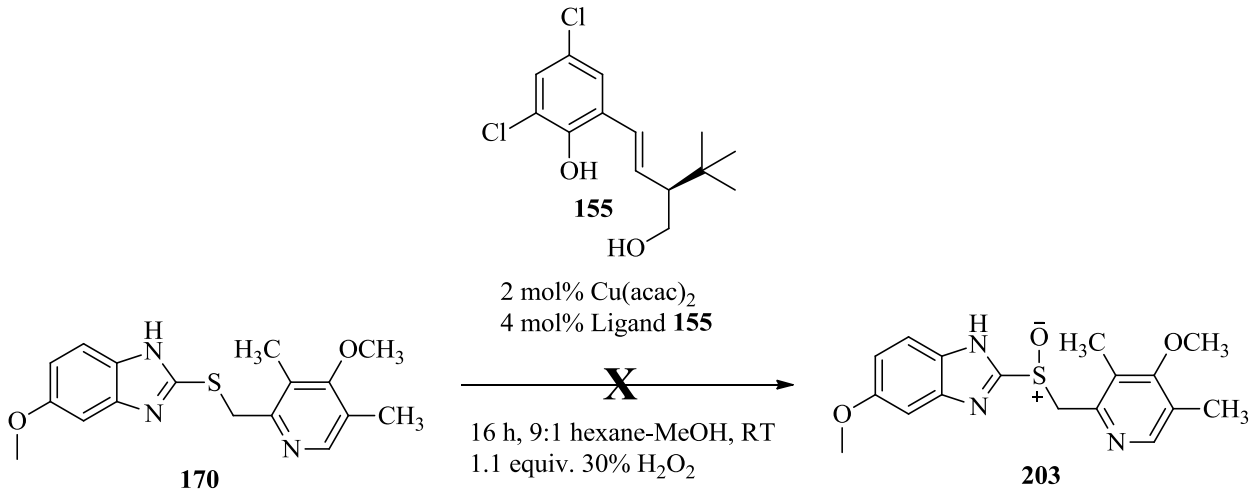
24	**[43]**	3-Chlorobenzyl	Bn	**[156]**	20 : 74 : 6	68	1	**[101]**
25	**[43]**	3-Chlorobenzyl	Bn	**[161]**	31 : 65 : 4	56	1	**[101]**
26	**[44]**	4-Chlorobenzyl	Bn	**[155]**	12 : 86 : 2	78	13	**[102]**
27	**[44]**	4-Chlorobenzyl	Bn	**[158]**	11 : 87 : 2	80	13	**[102]**
28	**[44]**	4-Chlorobenzyl	Bn	**[156]**	45 : 54 : 1	46	4	**[102]**
29	**[44]**	4-Chlorobenzyl	Bn	**[161]**	11 : 83 : 6	72	8	**[102]**
30	**[44]**	4-Chlorobenzyl	Bn	**[162]**	40 : 58:2	52	1	**[102]**
31	**[44]**	4-Chlorobenzyl	Bn	**[159]**	67 : 32 : 1	26	8	**[102]**
32	**[47]**	2-Methoxyphenyl	Ph	**[155]**	70 : 30 : 0	28	20	**[103]**
33	**[47]**	2-Methoxyphenyl	Ph	**[158]**	65 : 35 : 0	13	9	**[114]**
34	**[48]**	4-Methoxyphenyl	Ph	**[155]**	41 : 59 : 0	53	17	**[104]**
35	**[48]**	4-Methoxyphenyl	Ph	**[158]**	46 : 54 : 0	50	11	**[104]**
36	**[48]**	4-Methoxyphenyl	Ph	**[156]**	86 : 14 : 0	10	12	**[104]**
37	**[49]**	4-Methylphenyl	Ph	**[155]**	68 : 32 : 0	26	10	**[105]**
38	**[49]**	4-Methylphenyl	Ph	**[158]**	68 : 32 : 0	24	10	**[105]**
39	**[49]**	4-Methylphenyl	Ph	**[156]**	91 : 9 : 0	6	7	**[105]**
40	**[49]**	4-Methylphenyl	Ph	**[161]**	79 : 21 : 0	16	8	**[105]**
41	**[49]**	4-Methylphenyl	Ph	**[162]**	93 : 7 : 0	5	4	**[105]**
42	**[49]**	4-Methylphenyl	Ph	**[159]**	93 : 10 : 0	6	6	**[105]**

a) Ratio of Sulfide : Sulfoxide : Sulfone determined by ^{1}H NMR analysis of the crude product.

b) Yield of Sulfoxide after purification by column chromatography.

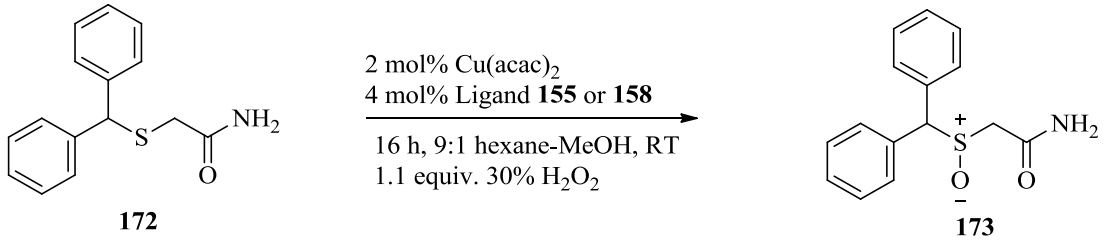
c) Enantioselectivities determined by HPLC analysis on chiral column (Daicel Chiracel OD-H for **[97]**, **[99]**, **[102]** Chiracel OJ-H for **[100]**, **[114]**; Chiracel AS-H for **[98]**, **[105]**; Phenomenex Lux Cellulose-4 for **[101]**, **[104]**; Absolute configuration of sulfoxides **[97]** to **[105]** were not determined.

Attempted Oxidation of Pyrmetazole



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a round bottomed flask containing Schiff base ligand **[155]** (11.6 mg, 4.0 mol%) and 9:1 hexane/MeOH (1 mL). The resulting solution was stirred at RT for 5 min, and then a solution of pyrmetazole (329 mg, 1 mmol) in 9:1 hexane/MeOH (3 mL) was added. After 5 min stirring at RT, H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution. The reaction mixture was stirred at RT for a further 16 h. TLC and ^{1}H NMR analysis of the crude product indicated that no oxidation had taken place. In another experiment, the amount of the copper-complex [$Cu(acac)_2$, 1 mmol, 260 mg and ligand **[155]**, 2 mmol, 580 mg] was increased to stoichiometric amounts, but once again no oxidation was observed.

Oxidation of (2-Benzhydrylsulfanyl)acetamide



Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a round bottomed flask containing Schiff base ligand **[155]** (11.6 mg, 4.0 mol%) or ligand **[158]** (11.0 mg, 4.0 mol%) and 9:1 hexane/MeOH (1 mL). The resulting solution was stirred at RT for 5 min, and then a solution of (2-benzhydrylsulfanyl)acetamide (257 mg, 1 mmol) in 9:1 hexane/MeOH (3 mL)

was added. After 5 min stirring at RT, H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution. The reaction mixture was stirred at RT for a further 16 h.

Table 3.14 Asymmetric oxidation of **[172]**

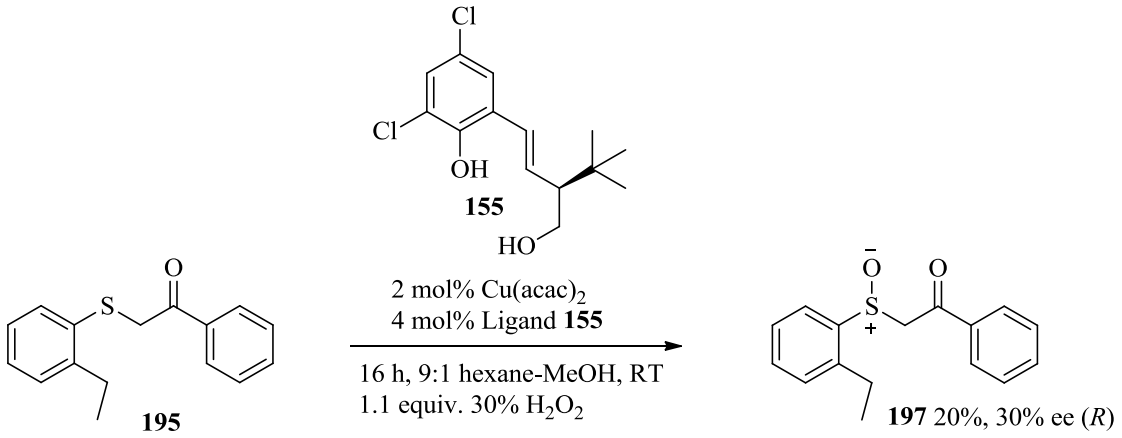
Ligand	**[172] : [173]**[a]	**% ee**[b] **[173] (*S*)**[c]
[155]	29 : 71	5
[158]	55 : 45	5

a) Ratio of **[172] : [173]** determined by ^{1}H NMR analysis of the crude product. **[173]** was not isolated.

b) Based on HPLC of crude product from the oxidation.

c) Absolute configuration determined by comparison of HPLC retention times of sample with an enantiopure sample of (*R*)-modafinil, prepared by a procedure described by Prisinzano *et al.*[147]

Oxidation of β-Keto sulfide [195]

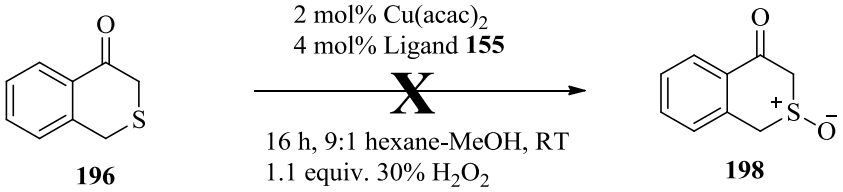


Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a round bottomed flask containing Schiff base ligand **[155]** (11.6 mg, 4.0 mol%) and 9:1 hexane/MeOH (1 mL). The resulting solution was stirred at RT for 5 min, and then a solution of β-keto sulfide **[195]** (256 mg, 1 mmol)[161] in 9:1 hexane/MeOH (1 mL) was added. After 5 min stirring at RT, H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution. The reaction mixture was stirred at RT for a further 16 h. The crude product contained a mixture of sulfide and sulfoxide (68:32). Workup and purification was carried out as described in section 3.13 to give (*R*)-(+)-**[197]** as a white solid (49 mg, 20%, 30% ee); m.p. 92–94 °C; ^{1}H NMR δ_H (400 MHz) 1.30 (3H, t, *J* 8.2 Hz, $ArCH_3$), 2.60–2.72 (1H, A of ABX system, CH_2CH_3), 2.75–2.90 (1H, B of ABX system, CH_2CH_3), 4.24 (1H, A of AB system, *J* 13.2

Hz, $SOCH_2$), 4.45 (1H, B of AB system, *J* 13.2 Hz, $SOCH_2$), 7.21–7.32 (1H, m, Ar-H), 7.35–7.63 (5H, m, Ar-H), 7.84–8.02 (3H, m, Ar-H); ^{13}C NMR δ_C (75.5 MHz) 15.1 (CH_2CH_3), 24.7 (CH_2CH_3), 62.3 ($SOCH_2$), 124.0 (CH_{Ar}), 127.5 (CH_{Ar}), 128.8 (CH_{Ar}), 128.9 (CH_{Ar}), 129.0 (CH_{Ar}), 131.6 (CH_{Ar}), 134.1 (CH_{Ar}), 136.2 ($C_{Ar(q)}$), 141.15 ($C_{Ar(q)}$), 141.20 ($C_{Ar(q)}$), 191.36 ($C_{Ar(q)}$, C=O); (Found C, 70.36; H, 6.11; $C_{16}H_{16}O_2S$ requires C, 70.56; H, 5.92); HPLC: t_R (*R*) = 25.6 min, t_R (*S*) = 34.3 min [Chiracel OD-H; flow rate 1 mL min^{-1}; hexane/2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = + 42.1° (c 1.0, $CHCl_3$). Absolute configuration is the proposed configuration based on comparison of optical rotation to literature value of (+)-(*R*)-2-(phenyl-1'-sulfinyl)-acetophenone $[\alpha]_D^{20}$ = + 161.7° ($CHCl_3$).[163]

Oxidation of β-Keto sulfide [196]

The same procedure as above was used for the oxidation of β-keto sulfide **[196]** (164 mg, 1 mmol).[162] However, TLC analysis and analysis of the ^1H NMR spectrum of the crude product indicated that no oxidation had taken place. The crude product (158 mg) was isolated as a yellow solid, which was composed mainly of recovered sulfide and a small amount of ligand by ^1H NMR.



Attempted Preparation of Pre-Formed Catalyst

Schiff base ligand **[155]** (580 mg, 2 mmol) and $Cu(acac)_2$ (260 mg, 1 mmol) were stirred together in methanol (10 mL) and heated at reflux for 1 h. The solution was cooled and the resulting precipitate was collected by filtration. It was apparent that the resulting precipitate was a mixture composed mainly of ligand **[155]** although some $Cu(acac)_2$ was present. On addition of CH_2Cl_2 (10 mL) and water (10 mL) the ligand went into the organic layer while the remaining $Cu(acac)_2$ went into the aqueous layer.

References

(1) Patai, S.; Rappoport, Z.; Stirling, C.; *The Chemistry of Sulphones and Sulphoxides*, Wiley: **1988**, 109.
(2) Page, P.; Editor *Organosulfur Chemistry, Volume 2: Synthetic and Stereochemical Aspects*; Academic, 1998.
(3) Geremia, S.; Calligaris, M.; Kukushkin, Y. N.; Zinchenko, A. V.; Kukushkin, V. Y. *J. Mol. Struct.* **2000**, *516*, 49-56.
(4) Markarian, S. A.; Asatryan, A. M.; Zatikyan, A. L. J. Chem Thermodyn. **2005**, 768-777.
(5) Phillips, G. M.; Hunter, J. S.; Sutton, L. E. *J. Chem. Soc.* **1945**, 146-162.
(6) Cumper, C. W. N.; Walker, S. *Trans. Faraday Soc.* **1956**, *52*, 193-199.
(7) Toshiyasu, Y.; Taniguchi, Y.; Kimura, K.; Fujishiro, R.; Yoshihara, M.; Tagaki, W.; Oae, S. *Bull. Chem. Soc. Jap.* **1969**, *42*, 1878-1881.
(8) Price, C. C.; Oae, S. *Sulfur Bonding*; Ronald Press, 1962.
(9) Oae, S.; Yoshihara, M.; Tagaki, W. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 951-958.
(10) Longuet-Higgens, H. C. *Trans Faraday Soc.* **1949**, *45*, 173.
(11) Fernandez, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651-3705.
(12) Carreno, M. C.; Hernandez-Torres, G.; Ribagorda, M.; Urbano, A. *Chem. Commun.* **2009**, 6129-6144.
(13) Toru, T.; Bolm, C.; Editors *Organosulfur Chemistry in Asymmetric Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA, 2008.
(14) Volcho, K. P.; Salakhutdinov, N. F. *Russ. Chem. Rev.* **2009**, *78*, 457-464.
(15) Myrick, H.; Malcolm, R.; Taylor, B.; LaRowe, S. *Ann Clin Psychiatry* **2004**, *16*, 101-109.
(16) O'Mahony, G. E.; Kelly, P.; Lawrence, S. E.; Maguire, A. R. *ARKIVOC* **2011**, 1-110.
(17) Wojaczynska, E.; Wojaczynski, J. *Chem. Rev.* **2010**, *110*, 4303-4356.
(18) Bryliakov, K. P.; Talsi, E. P. *Curr. Org. Chem.* **2008**, *12*, 386-404.
(19) Willsky, G. R.; Vanadium in the Biosphere. In *Vanadium in Biological Systems: Physiology and Biochemistry*; Chasteen, N. D., Ed.; Kluwer Academic Publishers; Dordrecht, The Netherlands, 1990; 1-24.
(20) Bunce, S.; Cross, R. J.; Farrugia, L. J.; Kunchandy, S.; Meason, L. L.; Muir, K. W.; O'Donnell, M.; Peacock, R. D.; Stirling, D.; Teat, S. J. *Polyhedron* **1998**, *17*, 4179-4187.
(21) Plitt, P.; Pritzkow, H.; Oeser, T.; Kraemer, R. *J. Inorg. Biochem.* **2005**, *99*, 1230-1237.
(22) Zhu, H.-B.; Dai, Z.-Y.; Huang, W.; Cui, K.; Gou, S.-H.; Zhu, C.-J. *Polyhedron* **2004**, *23*, 1131-1137.
(23) Alcon, M. J.; Corma, A.; Iglesias, M.; Sanchez, F. *J. Mol. Catal. A: Chem.* **2002**, *178*, 253-266.
(24) Velusamy, S.; Kumar, A. V.; Saini, R.; Punniyamurthy, T. *Tetrahedron Lett.* **2005**, *36*, 3819-3822.
(25) Kelly, P.; Lawrence, S. E.; Maguire, A. R. *Synlett* **2007**, 1501-1506.
(26) Kelly, P. *PhD Thesis, National University of Ireland, Cork* **2008**.
(27) Barry, N.; Brondel, N.; Lawrence, S. E.; Maguire, A. R. *Tetrahedron* **2009**, *65*, 10660-10670.
(28) Ham, J.; Yang, I.; Kang, H. *J. Org. Chem.* **2004**, *69*, 3236-3239.

(29) Ding, Q.; Cao, B.; Yuan, J.; Liu, X.; Peng, Y. *Org. Biomol. Chem.* **2011**, *9*, 748-751.
(30) Vowinkel, E. *Synthesis* **1974**, 430-432.
(31) Sakai, N.; Moritaka, K.; Konakahara, T. *Eur. J. Org. Chem.* **2009**, 4123-4127.
(32) Jumar, A.; Schulze, W. *J. Prakt. Chem.* **1957**, *5*, 83-90.
(33) Jarvis, B. B.; Saukaitis, J. C. *J. Amer. Chem. Soc.* **1973**, *95*, 7708-7715.
(34) Gul, K.; Narayanaperumal, S.; Dornelles, L.; Rodrigues, O. E. D.; Braga, A. L. *Tetrahedron Lett.* **2011**, *52*, 3592-3596.
(35) Davies, D. I.; Parfitt, L. T. *J. Chem. Soc. C* **1969**, 1401-1408.
(36) Calo, V.; Melloni, G.; Scorrano, G. *Gazz. Chim. Ital.* **1968**, *98*, 535-44.
(37) King, J. F.; Coppen, M. J. *Can. J. Chem.* **1971**, *49*, 3714-23.
(38) Russell, G. A.; Ngoviwatchai, P.; Tashtoush, H. I.; Pla-Dalmau, A.; Khanna, R. K. *J. Am. Chem. Soc.* **1988**, *110*, 3530-3538.
(39) Jean, M.; Renault, J.; van, d. W. P.; Asao, N. *Tetrahedron Lett.* **2010**, *51*, 378-381.
(40) Chai, C. L. L.; Christen, D.; Halton, B.; Neidlein, R.; Starr, M. A. E. *Aust. J. Chem.* **1995**, *48*, 577-91.
(41) She, J.; Jiang, Z.; Wang, Y. *Tetrahedron Lett.* **2009**, *50*, 593-596.
(42) Cano, R.; Ramon, D. J.; Yus, M. *J. Org. Chem.* **2011**, *76*, 654-660.
(43) Bryliakov, K. P.; Talsi, E. P. *Eur. J. Org. Chem.* **2011**, *2011*, 4693-4698.
(44) Eichman, C. C.; Stambuli, J. P. *J. Org. Chem.* **2009**, *74*, 4005-4008.
(45) Ajiki, K.; Hirano, M.; Tanaka, K. *Org. Lett.* **2005**, *7*, 4193-4195.
(46) Tanaka, K.; Ajiki, K. *Org. Lett.* **2005**, *7*, 1537-1539.
(47) Gellert, B. A.; Kahlcke, N.; Feurer, M.; Roth, S. *Chem.--Eur. J.* **2011**, *17*, 12203-12209.
(48) Firouzabadi, H.; Iranpoor, N.; Jafarpour, M. *Tetrahedron Lett.* **2006**, *47*, 93-97.
(49) Modena, G. *Gazz. Chim. Ital.* **1959**, *89*, 834-842.
(50) Eccles, K. S.; Elcoate, C. J.; Lawrence, S. E.; Maguire, A. R. *ARKIVOC* **2010**, 216-228.
(51) Landini, D.; Rolla, F. *Org. Synth.* **1978**, *58*, 143.
(52) Xu, H.-J.; Zhao, X.-Y.; Fu, Y.; Feng, Y.-S. *Synlett* **2008**, 3063-3067.
(53) Park, N.; Park, K.; Jang, M.; Lee, S. *J. Org. Chem.* **2011**, *76*, 4371-4378.
(54) Caro's Salt, C. a., 2 : 1 : 1 $KHSO_5$, $KHSO_4$, K_2SO_4, L.F. Fieser & M. Fieser, "Reagents for Organic Synthesis", John Wiley & Sons, New York (1967), 1, 952.
(55) Travis, B. R.; Ciaramitaro, B. P.; Borhan, B. *Eur. J. Org. Chem.* **2002**, 3429-3434.
(56) Legros, J.; Bolm, C. *Chem.--Eur. J.* **2005**, *11*, 1086-1092.
(57) Davis, F. A.; Reddy, R. T.; Han, W.; Carroll, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 1428-37.
(58) Kelly, P.; Lawrence, S. E.; Maguire, A. R. *Eur. J. Org. Chem.* **2006**, 4500-4509.
(59) Mancheno, O. G.; Dallimore, J.; Plant, A.; Bolm, C. *Org. Lett.* **2009**, *11*, 2429-2432.
(60) Umemura, K.; Matsuyama, H.; Watanabe, N.; Kobayashi, M.; Kamigata, N. *J. Org. Chem.* **1989**, *54*, 2374-83.
(61) Benson, S. C.; Snyder, J. K. *Tetrahedron Lett.* **1991**, *32*, 5885-5888.
(62) Duddeck, H.; Korek, U.; Rosenbaum, D.; Drabowicz, J. *Magn. Reson. Chem.* **1986**, *24*, 792-797.

(63) Akasaka, T.; Haranaka, M.; Ando, W. *J. Am. Chem. Soc.* **1991**, *113*, 9898-9900.
(64) Mikolajczyk, M.; Drabowicz, J. *J. Am. Chem. Soc.* **1978**, *100*, 2510-2515.
(65) Boudou, C.; Berges, M.; Sagnes, C.; Sopkova-de, O. S. J.; Perrio, S.; Metzner, P. *J. Org. Chem.* **2007**, *72*, 5403-5406.
(66) Nakamura, K.; Higaki, M.; Adachi, S.; Oka, S.; Ohno, A. *J. Org. Chem.* **1987**, *52*, 1414-1417.
(67) Guo, Y.; Darmanyan, A. P.; Jenks, W. S. *Tetrahedron Lett.* **1997**, *38*, 8619-8622.
(68) Xu, H.-J.; Lin, Y.-C.; Wan, X.; Yang, C.-Y.; Feng, Y.-S. *Tetrahedron* **2010**, *66*, 8823-8827.
(69) Ostrowski, Z.; Lesnianski, W. *Rocz. Chem.* **1956**, *30*, 981-983.
(70) Rodriguez, N.; Cuenca, A.; Ramirez, d. A. C.; Medio-Simon, M.; Asensio, G. *Org. Lett.* **2003**, *5*, 1705-1708.
(71) Samanta, R.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 5217-5220.
(72) Guo, Y.; Jenks, W. S. *J. Org. Chem.* **1995**, *60*, 5480-5486.
(73) Shimizu, M.; Shibuya, K.; Hayakawa, R. *Synlett* **2000**, 1437-1438.
(74) Turks, M.; Lawrence, A. K.; Vogel, P. *Tetrahedron Lett.* **2006**, *47*, 2783-2786.
(75) Naso, F.; Capozzi, M. A. M.; Bottoni, A.; Calvaresi, M.; Bertolasi, V.; Capitelli, F.; Cardellicchio, C. *Chem.--Eur. J.* **2009**, *15*, 13417-13426.
(76) Baciocchi, E.; Rol, C.; Scamosci, E.; Sebastiani, G. V. *J. Org. Chem.* **1991**, *56*, 5498-5502.
(77) Clark, N. G.; Cranham, J. E.; Greenwood, D.; Marshall, J. R.; Stevenson, H. A. *J. Sci. Food Agric.* **1957**, *8*, 566-570.
(78) Kelly, P.; Lawrence, S. E.; Maguire, A. R. *Synlett* **2006**, 1569-1573.
(79) Itoh, O.; Numata, T.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 266-269.
(80) Rajanikanth, B.; Ravindranath, B. *Indian J. Chem., Sect. B* **1984**, *23B*, 877-878.
(81) Tuleen, D. L.; White, R. M. *J. Tenn. Acad. Sci.* **1967**, *42*, 111.
(82) Tajbakhsh, M.; Hosseinzadeh, R.; Shakoori, A. *Tetrahedron Lett.* **2004**, *45*, 1889-1893.
(83) Bartlett, P. D.; Aida, T.; Chu, H.-K.; Fang, T.-S. *J. Am. Chem. Soc.* **1980**, *102*, 3515-3524.
(84) Bernoud, E.; Le, D. G.; Bantreil, X.; Prestat, G.; Madec, D.; Poli, G. *Org. Lett.* **2010**, *12*, 320-323.
(85) Emerson, C. R.; Zakharov, L. N.; Blakemore, P. R. *Org. Lett.* **2011**, *13*, 1318-1321.
(86) Harpp, D. N.; Gleason, J. G.; Ash, D. K. *J. Org. Chem.* **1971**, *36*, 322-26.
(87) Kuwano, R.; Kondo, Y.; Shirahama, T. *Org. Lett.* **2005**, *7*, 2973-2975.
(88) Reddy, M. A.; Reddy, P. S.; Sreedhar, B. *Adv. Synth. Catal.* **2010**, *352*, 1861-1869.
(89) Van, L. A. M.; Mulder, R. J.; Strating, J. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 225-234.
(90) Judka, M.; Wojtasiewicz, A.; Danikiewicz, W.; Makosza, M. *Tetrahedron* **2007**, *63*, 8902-8909.
(91) Gannett, P. M.; Nagel, D. L.; Reilly, P. J.; Lawson, T.; Sharpe, J.; Toth, B. *J. Org. Chem.* **1988**, *53*, 1064-1071.
(92) Parham, W. E.; Edwards, L. D. *J. Org. Chem.* **1968**, *33*, 4150-4154.
(93) Rudolph, F. A. M.; Fuller, A. L.; Slawin, A. M. Z.; Buehl, M.; Alan, A. R.;

Derek, W. J. *J. Chem. Crystallogr.* **2010**, *40*, 253-265.
(94) Buchi, I. J.; Prost, M.; Eichenberger, H.; Lieberherr, R. *Helv. Chim. Acta* **1952**, *35*, 1527-1536.
(95) Scholz, R.; Hellmann, G.; Rohs, S.; Oezdemir, D.; Raabe, G.; Vermeeren, C.; Gais, H.-J. *Eur. J. Org. Chem.* **2010**, 4588-4616.
(96) Lamm, B.; Ankner, K. *Acta Chem. Scand., Ser. B* **1978**, *B32*, 264-268.
(97) Mokhtary, M.; Lakouraj, M. M.; Niaki, M. R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2012**, *187*, 321-326.
(98) Kandula, S. R. V.; Kumar, P. *Tetrahedron* **2006**, *62*, 9942-9948.
(99) Shukla, P.; Hsu, Y.-C.; Cheng, C.-H. *J. Org. Chem.* **2006**, *71*, 655-658.
(100) Uchino, M.; Suzuki, K.; Sekiya, M. *Chem. Pharm. Bull.* **1978**, *26*, 1837-1845.
(101) Bogoslovskii, N. V.; Lapkin, I. I. *Uch. Zap., Perm. Gos. Univ.* **1966**, *141*, 300-304.
(102) Wildeman, J.; Van, L. A. M. *Synthesis* **1979**, 733-734.
(103) Dalrymple, D. L.; Reinheimer, J. D.; Barnes, D.; Baker, R. *J. Org. Chem.* **1964**, *29*, 2647-2651.
(104) Mohammadpoor-Baltork, I.; Memarian, H. R.; Bahrami, K.; Esmayilpour, K. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 2751-2766.
(105) Piffl, M.; Weston, J.; Guenther, W.; Anders, E. *J. Org. Chem.* **2000**, *65*, 5942-5950.
(106) Raper, A. H.; Rothstein, E. *J. Chem. Soc.* **1963**, 1027-1035.
(107) Kirihara, M.; Yamamoto, J.; Noguchi, T.; Itou, A.; Naito, S.; Hirai, Y. *Tetrahedron* **2009**, *65*, 10477-10484.
(108) Asthana, R. S.; Misra, G. S. *J. Indian Chem. Soc.* **1954**, *31*, 459-460.
(109) Kessar, S. V.; Nadir, U. K.; Singh, P.; Gupta, Y. P. *Tetrahedron* **1978**, *34*, 449-451.
(110) Choudary, B. M.; Bharathi, B.; Reddy, C. V.; Kantam, M. L. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2069-2074.
(111) Ashcroft, M. R.; Bougeard, P.; Bury, A.; Cooksey, C. J.; Johnson, M. D. *J. Organomet. Chem.* **1985**, *289*, 403-415.
(112) Li, H.; Wang, H.; Pan, Y.; Shi, Y. *Synthetic Commun* **1998**, *28*, 409-415.
(113) Vennstra, G. E.; Zwaneburg, B. *Synthesis* **1975**, 519-520.
(114) Zhang, J.-L.; Hong Chan, P. W.; Che, C.-M. *Tetrahedron Lett.* **2003**, *44*, 8733-8737.
(115) Gould, I. R.; Tung, C. H.; Turro, N. J. *J. Am. Chem. Soc.* **1984**, *106*, 1789-1793.
(116) Lewis, T. R.; Archer, S. *J. Am. Chem. Soc.* **1951**, *73*, 2109-2113.
(117) Al-Bashir, R. F.; Al-Awadi, N. A.; El-Dusouqui, O. M. E. *Can. J. Chem.* **2005**, *83*, 1543-1553.
(118) Bandgar, B. P.; Bettigeri, S. V.; Phopase, J. *Org. Lett.* **2004**, *6*, 2105-2108.
(119) Bandgar, B. P.; Kamble, V. T.; Fulse, D. B.; Deshmukh, M. V. *New J. Chem.* **2002**, *26*, 1105-1107.
(120) Takao, I. M., S *Bifucntional Molecular Catalysis* **2011**.
(121) Moreno, R. M.; Rosol, M.; Moyano, A. *Tetrahedron: Asymmetry* **2006**, *17*, 1089-1103.
(122) Bolm, C.; Bienewald, F. *Angew. Chem., Int. Ed. Engl.* **1996**, *34*, 2640-2642.
(123) Balcells, D.; Maseras, F.; Ujaque, G. *J. Am. Chem. Soc.* **2005**, *127*, 3624-3634.
(124) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011-8019.

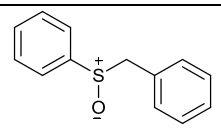
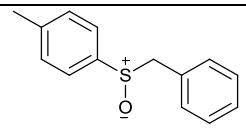
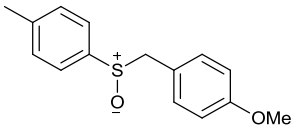
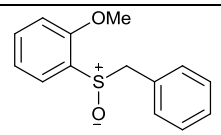
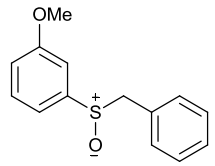
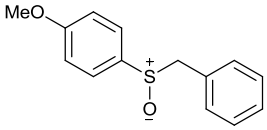
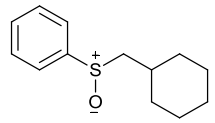
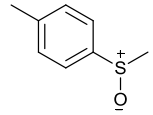
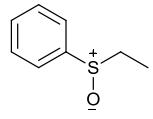
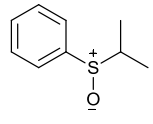
(125) Pelotier, B.; Anson, M. S.; Campbell, I. B.; MacDonald, S. J. F.; Priem, G.; Jackson, R. F. W. *Synlett* **2002**, 1055-1060.
(126) Drago, C.; Caggiano, L.; Jackson, R. F. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 7221-7223.
(127) X-ray structure determination was conducted by Dr. S.E. Lawrence, *Department of Chemistry, University College Cork.*
(128) Buist, P. H.; Marecak, D. M. *J. Am. Chem. Soc.* **1992**, *114*, 5073-5080.
(129) Ohta, H.; Okamoto, Y.; Tsuchihashi, G. *Chem. Lett.* **1984**, 205-208.
(130) Davies, S. G.; Gravatt, G. L. *J. Chem. Soc., Chem. Commun.* **1988**, 780-781.
(131) This compound was obtained from Padraig Kelly, a former member of the research group.
(132) O'Mahony, G. E.; Ford, A.; Maguire, A. R. *J. Org. Chem.* **2012**, *77*, 3288-3296.
(133) Ohta, C.; Shimizu, H.; Kondo, A.; Katsuki, T. *Synlett* **2002**, 161-163.
(134) Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188-8193.
(135) Slattery, C. N.; Clarke, L.-A.; O'Neill, S.; Ring, A.; Ford, A.; Maguire, A. R. *Synlett* **2012**, *23*, 765-767.
(136) O'Neill, S.; O'Keeffe, S.; Harrington, F.; Maguire, A. R. *Synlett* **2009**, 2312-2314.
(137) Zeng, Q.; Wang, H.; Wang, T.; Cai, Y.; Weng, W.; Zhao, Y. *Adv. Synth. Catal.* **2005**, *347*, 1933-1936.
(138) Blum, S. A.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2002**, *68*, 150-155.
(139) Li, Y.-G.; Shi, D.-H.; Zhu, H.-L.; Yan, H.; Ng, S. W. *Inorg. Chim. Acta* **2007**, *360*, 2881-2889.
(140) Zeng, Q.; Wang, H.; Weng, W.; Lin, W.; Gao, Y.; Huang, X.; Zhao, Y. *New J. Chem.* **2005**, *29*, 1125-1127.
(141) Islam, S. M.; Roy, A. S.; Mondal, P.; Tuhina, K.; Mobarak, M.; Mondal, J. *Tetrahedron Lett.* **2012**, *53*, 127-131.
(142) Bryliakov, K. P.; Talsi, E. P. *Curr. Org. Chem.* **2012**, *16*, 1215-1242.
(143) Kim, E.; Helton, M. E.; Wasser, I. M.; Karlin, K. D.; Lu, S.; Huang, H.-w.; Moenne-Loccoz, P.; Incarvito, C. D.; Rheingold, A. L.; Honecker, M.; Kaderli, S.; Zuberbuhler, A. D. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*, 3623-3628.
(144) Tahsini, L.; Kotani, H.; Lee, Y.-M.; Cho, J.; Nam, W.; Karlin, K. D.; Fukuzumi, S. *Chem.--Eur. J.* **2012**, *18*, 1084-1093.
(145) Gustavsson, A.; Kallstrom, A.; Astra Aktiebolag, Swed. . 1997; 17.
(146) Gold, L. H.; Balster, R. L. *Psychopharmacology* **1996**, *126*, 286-292.
(147) Prisinzano, T.; Podobinski, J.; Tidgewell, K.; Luo, M.; Swenson, D. *Tetrahedron: Asymmetry* **2004**, *15*, 1053-1058.
(148) Cephalon Inc, E. U. P., 516,869, 2005. W.O. Patent 028,428, 2005.
(149) Ternois, J.; Guillen, F.; Plaquevent, J.-C.; Coquerel, G. *Tetrahedron: Asymmetry* **2008**, *18*, 2959-2964.
(150) Lynch, D. *PhD Thesis, National University of Ireland, Cork* **2000**.
(151) Chopra, J. *PhD Thesis, National University of Ireland, Cork* **2007**.
(152) Murphy, M.; Lynch, D.; Schaeffer, M.; Kissane, M.; Chopra, J.; O'Brien, E.; Ford, A.; Ferguson, G.; Maguire, A. R. *Org. Biomol. Chem.* **2007**, *5*, 1228-1241.
(153) Pyne, S. G. *Sulfur Rep.* **1992**, *12*, 57-89.
(154) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1-64.

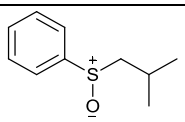
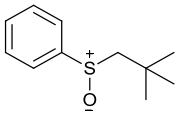
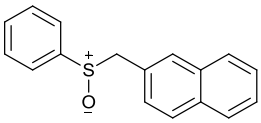
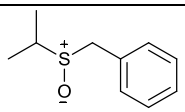
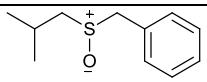
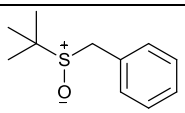
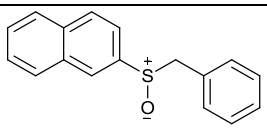
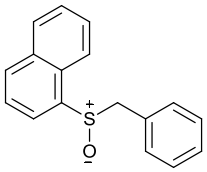
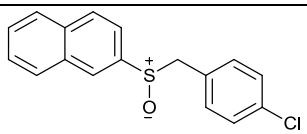
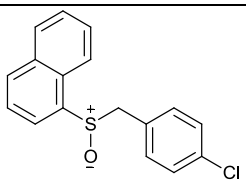
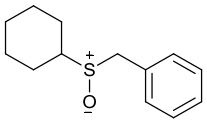
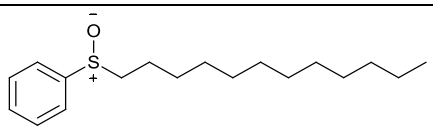
(155) Dehli, J. R.; Bolm, C. *Adv. Synth. Catal.* **2005**, *347*, 239-242.
(156) Bolm, C.; Kahmann, J. D.; Moll, G. *Tetrahedron Lett.* **1997**, *38*, 1169-1172.
(157) Sedelmeier, J.; Hammerer, T.; Bolm, C. *Org. Lett.* **2008**, *10*, 917-920.
(158) Lemasson, F.; Gais, H.-J.; Raabe, G. *Tetrahedron Lett.* **2007**, *48*, 8752-8756.
(159) This compound was obtained from Nicola Barry, a former member of the research group.
(160) Cardellicchio, C.; Omar, O. H.; Naso, F.; Capozzi, M. A. M.; Capitelli, F.; Bertolasi, V. *Tetrahedron: Asymmetry* **2006**, *17*, 223-229.
(161) This compound was obtained from Leslie Ann Clarke, a member of the research group.
(162) This compound was obtained from Naomi Buckley, a member of the research group.
(163) Hajipour, A. R.; Mahboobkhah, N. *Synth. Commun.* **1998**, *28*, 3143-3149.
(164) Vetter, A. H.; Berkessel, A. *Tetrahedron Lett.* **1998**, *39*, 1741-1744.
(165) Jeong, Y.-C.; Choi, S.; Hwang, Y. D.; Ahn, K.-H. *Tetrahedron Lett.* **2004**, *45*, 9249-9252.
(166) Wu, Y.; Liu, J.; Li, X.; Chan, A. S. C. *Eur. J. Org. Chem.* **2009**, 2607-2610.
(167) Glaspy, P. E.; Hancock, R. A.; Thyagarajan, B. S. *Org. Mass Spectrom.* **1985**, *20*, 281-287.
(168) Lapkin, I. I.; Bogoslovskii, N. V.; Mozhova, N. F. *Probl. Organ. Sinteza, Akad. Nauk SSSR, Otd. Obshch. i Tekhn. Khim.* **1965**, 89-91.
(169) Phadnis, S. P. *Indian J. Chem.* **1972**, *10*, 699-702.
(170) Tuleen, D. L.; Marcum, V. C. *J. Org. Chem.* **1967**, *32*, 204-206.
(171) Narayanaperumal, S.; Alberto, E. E.; Gul, K.; Kawasoko, C. Y.; Dornelles, L.; Rodrigues, O. E. D.; Braga, A. L. *Tetrahedron* **2011**, *67*, 4723-4730.
(172) Qian, D.-Q.; Liu, B.; Shine, H. J.; Guzman-Jimenez, I. Y.; Whitmire, K. H. *Journal of Phys. Org. Chem.* **2002**, *15*, 139-147.
(173) Zeng, Q.; Gao, Y.; Dong, J.; Weng, W.; Zhao, Y. *Tetrahedron: Asymmetry* **2011**, *22*, 717-721.
(174) Gadwood, R. C.; Mallick, I. M.; DeWinter, A. J. *J. Org. Chem.* **1987**, *52*, 774-782.
(175) Meyers, C. Y. *Gazz. Chim. Ital.* **1963**, *93*, 1206-1221.
(176) Ridley, D. D.; Smal, M. A. *Aust. J. Chem.* **1982**, *35*, 495-507.
(177) Furukawa, N.; Shibutani, T.; Matsumura, K.; Fujihara, H.; Oae, S. *Tetrahedron Lett.* **1986**, *27*, 3899-3902.
(178) Kaslova, A.; Palecek, M.; Prochazka, M. *Collect. Czech. Chem. Commun.* **1969**, *34*, 1826-1828.
(179) Lamm, B.; Simonet, J. *Acta Chem. Scand., Ser. B* **1974**, *28*, 147-152.
(180) Bahrami, K.; Khodaei, M. M.; Sohrabnezhad, S. *Tetrahedron Lett.* **2011**, *52*, 6420-6423.
(181) Supale, A. R.; Gokavi, G. S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2010**, *185*, 725-731.
(182) Murphy, M. E. *PhD Thesis, National University of Ireland, Cork* **1998**.
(183) Gustavsson, A.; Astrazeneca AB, Swed. 2004; 15.
(184) Oelschlager, H.; Seeling, A.; Seeling, B.; Westesen, K.; Bunjes, H. *Pharmazie* **1999**, *54*, 734-737.
(185) Avrutov, I.; Mendelovici, M.; Finkelstein, N.; Can. . 2004; 8, Cont.-in-part of U.S. Ser. No. 66,850.
(186) Tanaka, Y.; Inkyo, M.; Yumoto, R.; Nagai, J.; Takano, M.; Nagata, S. *Chem. Pharm. Bull.* **2009**, *57*, 1050-1057.

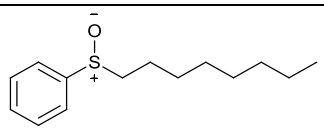
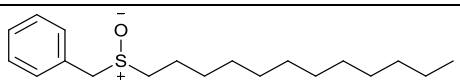
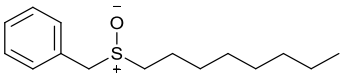
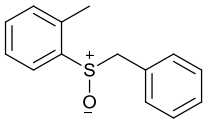
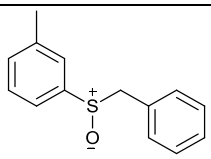
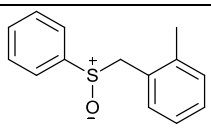
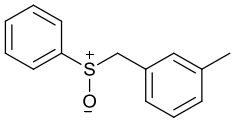
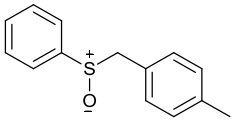
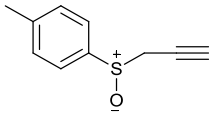
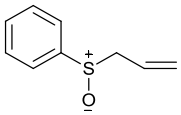
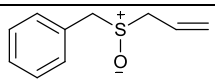
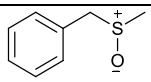
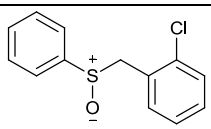
(187) Diter, P.; Taudien, S.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1994**, *59*, 370.
(188) Evans, D. A.; Andrews, G. C.; *Acc. and Chem Res.* **1974**, *7*, 147-155.

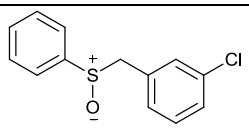
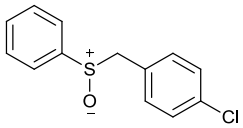
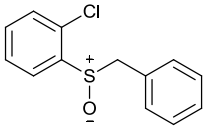
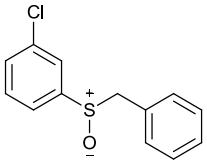
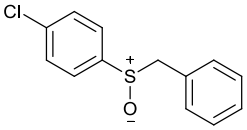
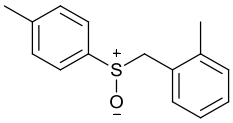
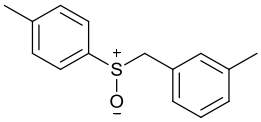
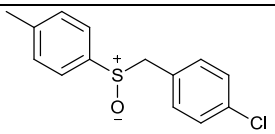
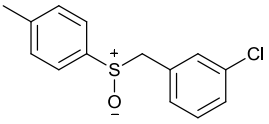
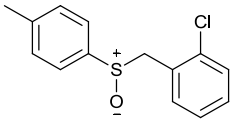
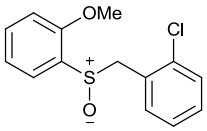
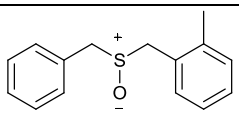
Appendix 1

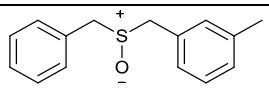
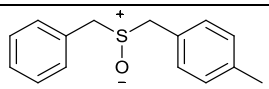
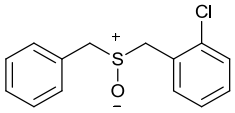
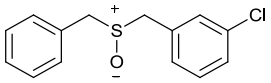
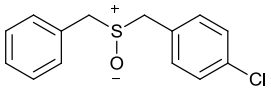
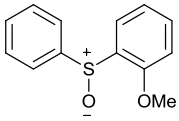
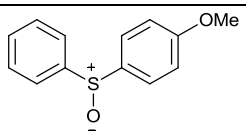
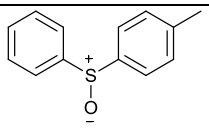
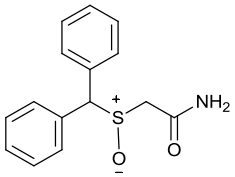
HPLC conditions for determination of enantiopurity (% ee) of sulfoxides.

Sulfoxide	λ (nm)	Flow Rate (mL min^{-1})	Temp. (°C)	Mobile Phase Hexane: IPA	$T_{ret.}$ (min)	Column
	254	1	40	90:10	17.1 *R* 21.3 *S*	OD-H
	254	1	40	90:10	16.3 *R* 19.9 *S*	OD-H
	254	1	40	90:10	12.7 *R* 15.9 *S*	OD-H
	254	1	40	90:10	16.2 *R* 18.6 *S*	OD-H
	254	1	40	90:10	12.2 *R* 14.0 *S*	OD-H
	254	1	40	90:10	15.5 *R* 18.4 *S*	OD-H
	254	1	20	90:10	17.3 *R* 20.3 *S*	OD-H
	254	1	20	95:5	20.1 *R* 23.8 *S*	OD-H
	254	1	40	90:10	8.1 *R* 9.8 *S*	OD-H
	254	1	40	90:10	6.6 *R* 7.5 *S*	OD-H

	254	1	40	90:10	5.9 *R* 6.7 *S*	OD-H
	254	1	40	90:10	6.6 *R* 7.6 *S*	OD-H
	254	1	20	90:10	32.1 *R* 40.6 *S*	OD-H
	254	1	20	90:10	36.4 (+) 63.6 (−)	AS-H
	254	1	20	90:10	43.1 *S* 47.7 *R*	AS-H
	254	1	20	90:10	14.3 *R* 19.0 *S*	OD-H
	254	1	20	90:10	27.0 *R* 38.1 *S*	OD-H
	254	1	20	90:10	21.6 *S* 42.2 *R*	OD-H
	254	1	20	90:10	33.0 *R* 49.4 *S*	OD-H
	254	1	20	90:10	21.2 *S* 53.3 *R*	OD-H
	254	1	20	90:10	32.4 (−) 39.7 (+)	Amylose-2
	254	1	20	90:10	27.5 *S* 34.8 *R*	AS-H

	254	1	20	90:10	18.8 *S* 23.4 *R*	AS-H
	254	1	20	90:10	48.3 *S* 66.0 *R*	AS-H
	254	1	20	90:10	24.1 *S* 34.8 *R*	Cellulose-4
	254	1	40	90:10	11.2 *R* 13.2 *S*	OD-H
	254	1	40	90:10	15.1 *R* 18.9 *S*	OD-H
	254	1	20	90:10	67.1 85.3	AS-H
	254	1	40	90:10	16.2 *R* 18.7 *S*	OD-H
	254	1	40	90:10	12.7 *R* 14.3 *S*	OD-H
	254	1	20	90:10	14.6 *R* 17.5 *S*	OD-H
	254	1	20	90:10	11.3 *R* 14.1 *S*	OJ-H
	254	1	20	90:10	81.8 (−) 112.9 (+)	AS-H
	254	1	20	90:10	50.7 60.1	Cellulose-4
	254	1	20	90:10	64.4 *S* 71.3 *R*	AS-H

	254	1	20	90:10	18.0 *R* 22.8 *S*	OD-H
	254	1	20	95:5	15.9 *R* 19.4 *S*	OD-H
	254	1	20	90:10	27.1 *S* 32.2 *R*	OJ-H
	254	1	20	90:10	15.9 *S* 22.3 *R*	OJ-H
	254	1	20	95:5	41.2 *R* 46.3 *S*	OD-H
	254	1	20	90:10	27.1 (+) 32.2 (−)	OJ-H
	254	1	20	95:5	45.3 *S* 60.0 *R*	Cellulose-4
	254	1	20	90:10	28.8 *R* 33.0 *S*	OD-H
	254	1	20	90:10	46.8 *S* 61.9 *R*	AS-H
	254	1	20	90:10	51.5 *S* 60.3 *R*	AS-H
	254	1	20	90:10	39.6 *S* 61.3 *R*	AS-H
	254	1	20	90:10	49.6 56.4	OD-H

	254	1	20	90:10	94.4 112.9	AS-H
	254	1	20	90:10	40.9 44.9	OD-H
	254	1	20	90:10	24.6 30.7	OJ-H
	254	1	20	8:2	33.9 54.5	Cellulose-4
	254	1	20	90:10	28.7 32.7	OD-H
	254	1	20	90:10	16.0 (+) 21.9 (−)	OJ-H
	254	1	20	90:10	81.1 (+) 87.8 (−)	Cellulose-4
	254	1	20	90:10	60.2 (*S*) 87.8 (*R*)	AS-H
	254	1	20	90:10	88.4 (*S*) 182.9 (*R*)	OJ-H

Appendix 2

Abbreviations/Formulae

% ee	% enantiomeric excess
°	Degrees
acac	Acetylacetonate
Alk	Alkyl
aq.	Aqueous
Ar	Aromatic
BINOL	1,2'-Binaphthol
BSA	Bovine Serum Albumin
CCl_4	Carbon tetrachloride
CD	Cyclodextrin
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
CHP	Cumene hydroperoxide
CMO	Cyclohexanone monooxygenase
CPO	Chloroperoxidase
DAG	Diacetone-D-glucose
DCE	Dichloroethane
DCM	Dichloromethane
DET	Diethyltartrate
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
equiv	Equivalents
Et_2O	Diethyl Ether
EtOH	Ethanol

h	Hours
H_2O_2	Hydrogen Peroxide
HCl	Hydrochloric Acid
HPLC	High Performance Liquid Chromatography
i-	*iso*
IPA	Isopropylalcohol
KOH	Potassium Hydroxide
LDA	Lithium Diisopropylamide
$LiAlH_4$	Lithium Aluminium Hydride
m-	*meta*
m-CPBA	*meta*-Chloroperoxybenzoic acid
MeI	Methyl Iodide
MeOH	Methanol
min	Minutes
mmol	Millimole
m.p.	Melting Point
NaBARF	Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
$NaBH_4$	Sodium Borohydride
NMO	4-Methylmorpholine *N*-oxide
o-	*ortho*
OAc	Acetate
p-	*para*
PhIO	Iodosyl benzene
RT	RT
TBAF	Tetrabutyl Ammonium Fluoride
TBHP	*tert*-Butyl Hydroperoxide
t-Bu	*tert*-Butyl

TDO	Toluene Dioxygenase
TEA	Triethylamine
TEMPO	2,2,6,6-Tetramethylpiperidin-1-oxyl Free Radical
THF	Tetrahydrofuran
THP	Trityl Hydroperoxide
Tolyl	4-Methylphenyl
VO	Vanadyl

[i]. (a) APEX2 v2009.3-0; Bruker AXS: **2009**. (b) Sheldrick, G. M. Acta Crystallogr. **2008**, *A64*, 112−122