Asymmetric Oxidation of Sulfides

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Abstract

This review discusses synthesis of enantiopure sulfoxides through the asymmetric oxidation of prochiral sulfides. The use of metal complexes to promote asymmetric sulfoxidation is described in detail, with a particular emphasis on the synthesis of biologically active sulfoxides. The use of non-metal based systems, such as oxaziridines, chiral hydroperoxides and peracids, as well as biologically-catalyzed sulfoxidations is also examined.

Keywords: Sulfide oxidation, sulfoxides, asymmetric synthesis, enantioselective synthesis, metal-based catalysts.

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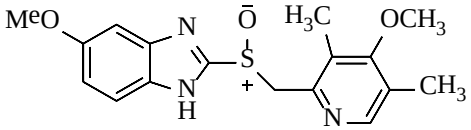
1. Introduction

Enantiopure sulfoxides are important reagents in asymmetric synthesis due to their use as chiral auxiliaries in a broad range of synthetic reactions such as Diels Alder reactions (1-3), Michael addition reactions (4), carbon-carbon (5,6) and carbon-oxygen (7) bond forming reactions. The use of chiral sulfoxides as auxiliaries in asymmetric synthesis has been discussed in a number of reviews.(8-12) A large number of sulfoxides, such as the gastric acid inhibitors omeprazole **[1]**, lansoprazole **[2]**, rabeprazole **[3]** and pantoprazole **[4]** have found use in the pharmaceutical industry.



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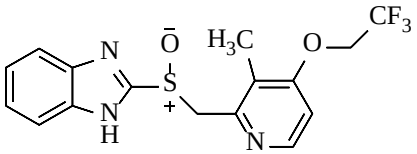

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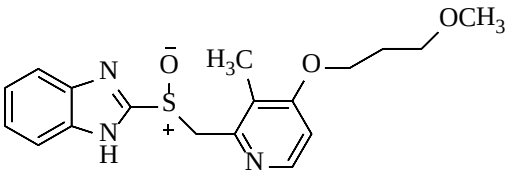

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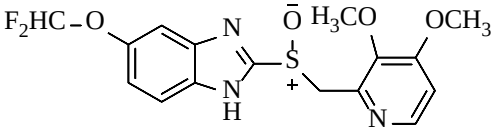

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The three main routes to enantiopure sulfoxides are asymmetric sulfoxidation, nucleophilic substitution using a chiral sulfur precursor and kinetic resolution of racemic sulfoxides (13-17). This review will discuss the asymmetric oxidation of sulfides promoted by metal complexes and non-metal based systems such as chiral oxaziridines, peracids, hydroperoxides, and biological systems, with a particular emphasis on the synthesis of biologically active sulfoxides. It will focus primarily on the asymmetric oxidation of acyclic aryl alkyl sulfides while the oxidation of dialkyl sulfides, cyclic sulfides and disulfides will also be briefly explored.

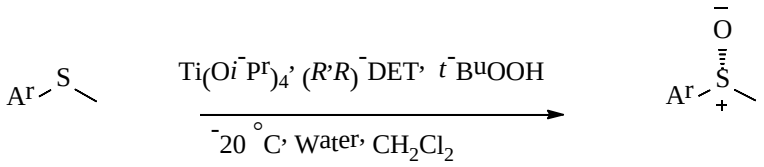
2. Metal-catalyzed asymmetric sulfoxidation

The most attractive method for the preparation of enantiopure sulfoxides is metal-catalyzed asymmetric sulfide oxidation because these oxidizing systems can, in general, be applied to a wide range of substrates and only a catalytic amount of the metal complex is required. Although titanium and vanadium complexes have found the most use in asymmetric sulfoxidation, other metal based systems such as iron and copper have emerged in recent years.

2.1 Titanium complexes

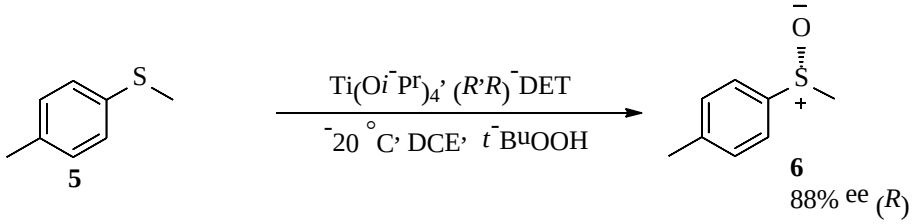
In 1984, the research groups of Kagan (18) and Modena (19) independently reported the use of a titanium complex in the asymmetric oxidation of sulfides. The systems used to carry out the oxidations were based on the Sharpless asymmetric epoxidation procedure. (20) Kagan *et al*. (18,21) used a titanium complex prepared from Ti(O*i*-Pr)$_4$, (*R*,*R*)-diethyl tartrate (DET) and water in the ratio 1:2:1 with *tert*-butyl hydroperoxide (TBHP) as oxidant (**Scheme 1**). Although stoichiometric amounts of the titanium complex were initially required to produce

sulfoxides in high enantioselectivities, a subsequent publication reported the use of a catalytic alternative with only a slight reduction in enantioselectivity (22). Replacement of TBHP with cumyl hydroperoxide (CHP) led to an improvement in enantioselectivity. The Modena method is very similar to Kagan's, but uses Ti(O*i*-Pr)$_4$/DET in a ratio of 1:4, dichloroethane (DCE) as solvent and is carried out in the absence of water (19). The Modena system was used to oxidize methyl *p*-tolyl sulfide **[5]**, producing the corresponding sulfoxide **[6]** in high enantioselectivity (**Scheme 2**).



Ar	Yield (%)	ee (% *R*)
p-Tolyl	90	91
Phenyl	80	89
p-bromophenyl	70	80
p-chlorophenyl	95	78

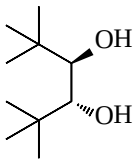
Scheme 1 Kagan Oxidation



Scheme 2 Modena Oxidation

A number of other research groups have carried out titanium-catalyzed sulfoxidations using different chiral ligands to that employed by Kagan. Imamoto *et al.* (23) used the diol **[7]** as a chiral ligand for the asymmetric oxidation of methyl *p*-tolyl sulfide **[5]**. This system used CHP as oxidant and produced methyl *p*-tolyl sulfoxide **[6]** in moderate yield (42%) and excellent enantioselectivity [95% enantiomeric excess (ee)]. Interestingly, Imamoto observed that the oxidation using **[7]** proceeded with the highest degree of enantiopurity when conducted in the presence of molecular sieves. This was in contrast to Kagan's study which

demonstrated that the presence of water was crucial for the enantioselectivity of the oxidation. Uemura *et al.* (24) also investigated the effect of water in the Kagan system and concluded that the presence of too much or too little water in the reaction could impact detrimentally on the enantioselectivity of the oxidation.



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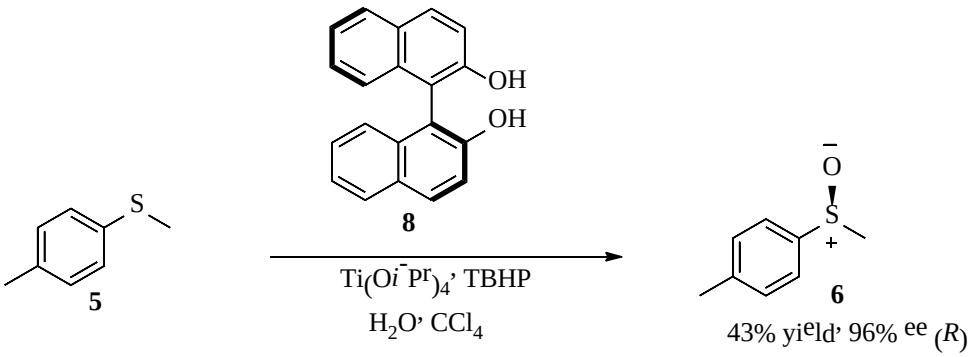
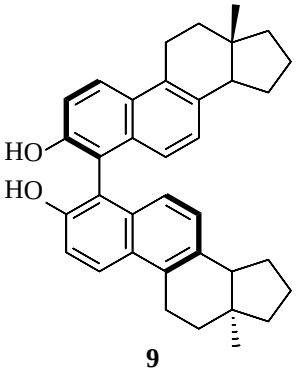
Uemura (25) also reported titanium-catalyzed oxidation using binaphthol (BINOL) **[8]** as chiral ligand and TBHP as oxidant. This system produced methyl *p*-tolyl sulfoxide **[6]** in moderate yield (43%) and excellent enantioselectivity (up to 96% ee, **Scheme 3**).



Scheme 3 Uemura Oxidation

A number of other research groups have also used binaphthol derivatives as chiral ligands to asymmetrically oxidize sulfides. Bolm *et al.* (26) used a steroid derived BINOL derivative **[9]** to oxidize **[5]**, producing sulfoxide **[6]** in excellent enantioselectivity (92% ee). Bolm reported that an addition of water was crucial for the enantioselectivity of the oxidation.

Martyn *et al.* (27) investigated the effect of fluorine substitution at a number of positions of BINOL on its catalytic activity in titanium-mediated sulfide oxidation. Sulfoxide **[6]** was produced in moderate yield (55%) and good enantioselectivity (80% ee) using **[10]**, while the use of **[8]** as chiral auxiliary afforded **[6]** in moderate yield (69%) but poor enantioselectivity (3% ee). Interestingly, the (*R*) enantiomer is preferentially formed using **[10]** while the (*S*) enantiomer is favoured using **[8]**.



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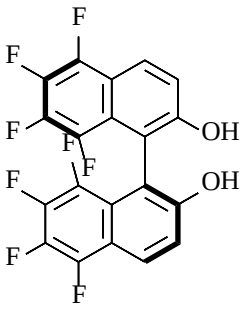

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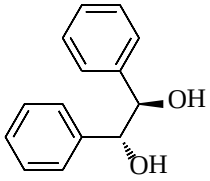
Rosini *et al.* (28) also used a diol **[11]** as chiral ligand to asymmetrically oxidize aryl methyl sulfides. The sulfoxide **[6]** was produced in moderate yield (62%) and good enantioselectivity (80% ee). Recently, Rosini (29) has used a similar diol **[12]** to oxidize benzyl phenyl sulfide **[13]**, producing sulfoxide **[14]** in moderate yield and excellent enantioselectivity (**Scheme 4**).



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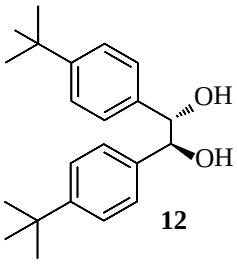

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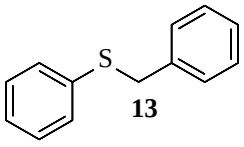

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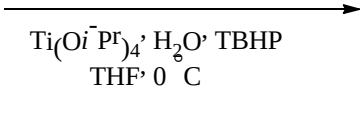

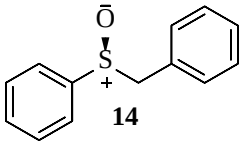

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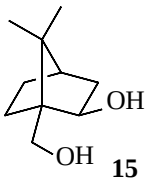
> 99% ee (*S*)
65% Yield

Scheme 4 Chiral Diol as a Ligand

Zeng *et al.* (30) used camphanediols such as **[15]** to oxidize thioanisole **[16]**, producing the sulfoxide of thioanisole **[17]** in poor yield but with excellent enantioselectivity (up to 99% ee). Zeng speculated that the oxidation occurs by an intramolecular nucleophilic oxygen transfer to the coordinated sulfide.

Zhu *et al.* (31) used 2,5-dialkyl cyclohexane-1,4-diols such as **[18]** to produce a variety of enantioenriched aryl methyl sulfoxides (up to 84% ee) in moderate to good yields (up to 79%).



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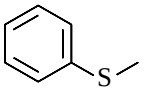

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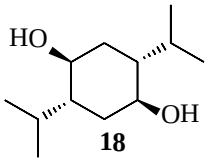

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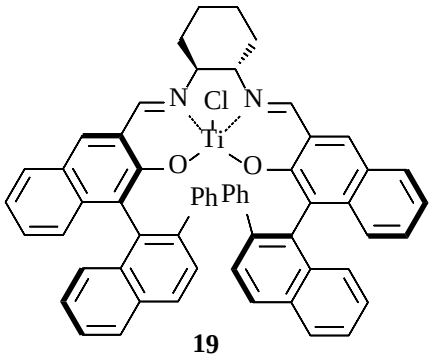
Titanium-salen complexes have also been used to asymmetrically oxidize sulfides. Katsuki reported the use of Ti (salen) complex **[19]** for the asymmetric oxidation of a number of aryl alkyl sulfides. The best results were obtained when the oxidation was carried out at 0 °C using urea hydrogen peroxide adduct (UHP) as oxidant. This system afforded methyl *p*-chlorophenyl sulfoxide **[20]** in excellent yield (88%) and excellent enantioselectivity (99% ee) (32,33).



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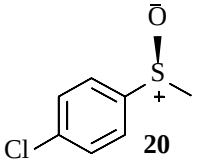

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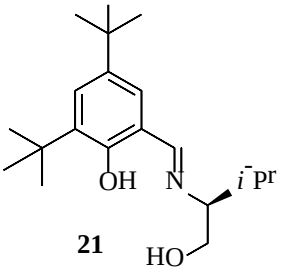
Bryliakov and Talsi (34) reported tiatanium-catatlysed asymmetric sulfoxidation using titanium-salen complexes similar to that used by Katsuki. This system afforded benzyl phenyl sulfoxide **[14]** in a moderate conversion (65%) and excellent enantioselectivity (97% ee) by a combination of asymmetric oxidation and kinetic resolution. Bryliakov (35) also reported a titanium-mediated oxidation using an amino alcohol derived Schiff base ligand **[21]** and hydrogen peroxide as oxidant. This system afforded benzyl phenyl sulfoxide **[14]** in excellent conversion (96%) and modest enantioselectivity (60% ee).



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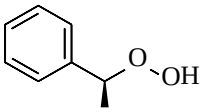
The use of chiral hydroperoxides in titanium-mediated sulfoxidations has been examined. Adam *et al.* (36) used hydroperoxide **[22]** to oxidize methyl *p*-tolyl sulfide **[5]**, producing sulfoxide **[6]** in a moderate conversion (69%) and good enantioselectivity (75% ee). Kinetic resolution accompanied these oxidations which resulted in reduced yield due to over-oxidation, but improved enantioselectivity.



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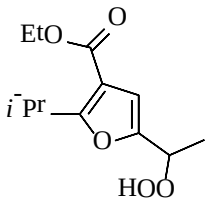
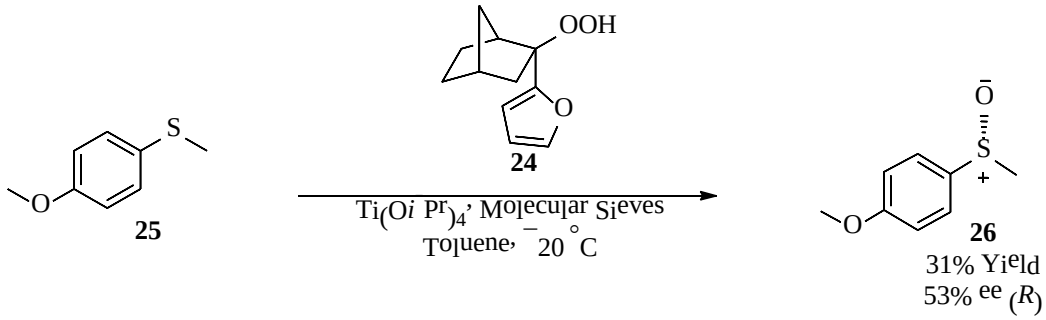


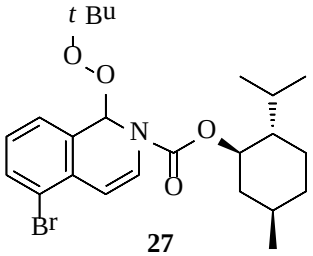
23

Scettri and co-workers (37-40) used an enantioenriched form of the secondary furyl hydroperoxide **[23]** to oxidize thioanisole **[16]**, affording sulfoxide **[17]** in good yield (75%) and excellent enantioselectivity (95% ee). Interestingly, the oxidation of the sulfide resulted in kinetic resolution of **[23]**. This system used DET as the chiral ligand. Scettri *et al.* (41) also used a variety of norcamphor-derived furyl hydroperoxides such as **[24]**. The use of a chiral ligand with these peroxides is not necessary. Scettri speculated that steric interactions between the oxidant and sulfide resulted in preferential formation of one sulfoxide enantiomer. The best result was obtained for the oxidation of *para*-methoxyphenyl methyl sulfide **[25]**, producing sulfoxide **[26]** in poor yield and moderate enantioselectivity (**Scheme 5**). Significant sulfone formation accompanied this oxidation.

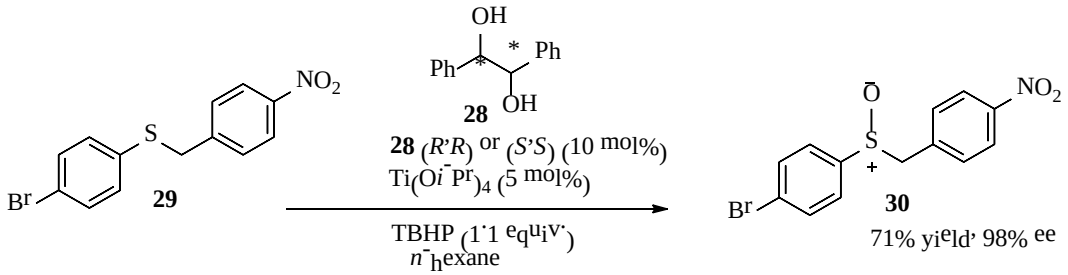


Scheme 5 Chiral Hydroperoxides

Liebscher (42) used a chiral peroxide **[27]** derived from (*R*)-menthyl chloroformate, 4-bromoisoquinoline and TBHP. complementary kinetic resolution accompanied this oxidation. The use of 3.3 equivalents of hydrogen peroxide as oxidant afforded sulfoxide **[17]** in poor yield (16%) and excellent enantioselectivity (>99% ee), with a large amount of over-oxidation to sulfone.



Cardellicchio *et al.* (43) asymmetrically oxidized aryl benzyl sulfides using a titanium complex composed of hydrobenzoin **[28]** as the catalyst. The system was used to oxidize sulfide **[29]**, producing sulfoxide **[30]** in good yield and excellent enantioselectivity (**Scheme 6**).



Scheme 6 Chiral Diol in Titanium-mediated Oxidation

The mechanism of this system has been investigated (44). Cardellicchio *et al.* hypothesized, 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 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**.

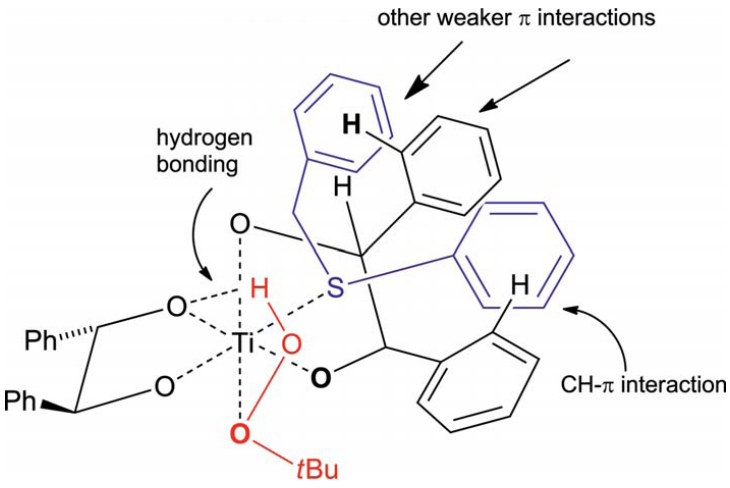
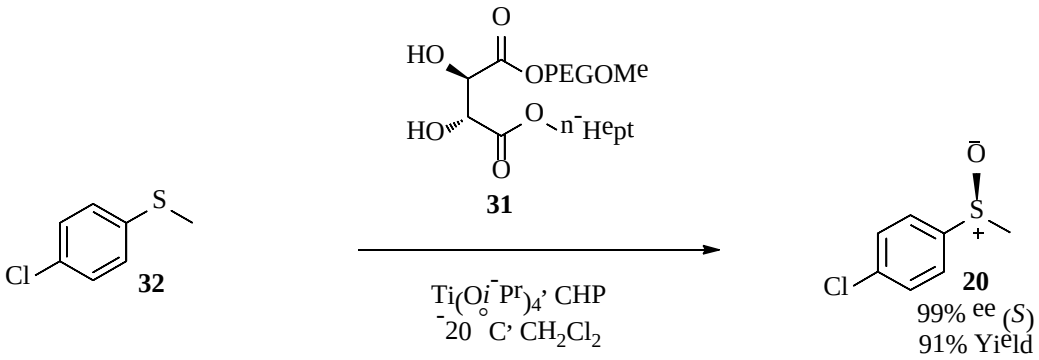


Figure 1 Octahedral titanium-hydrobenzoin complex (reproduced with permission from reference (44)

Cardellicchio reported a strong hydrogen bond between the acidic hydrogen atom of the TBHP and one oxygen atom of a hydrobenzoin ligand. A CH-π interaction was proposed between hydrogen of one hydrobenzoin and a phenyl group of the aryl benzyl sulfide. Weaker interactions between the π systems of other aryl groups 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.

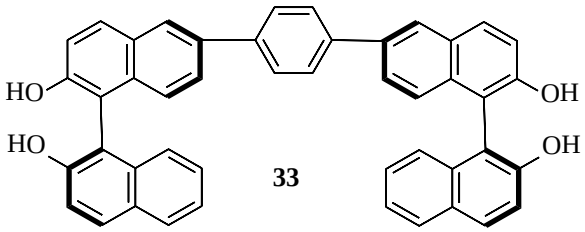
A number of research groups have reported the use of immobilized catalysts. Iwamoto *et al.* (45) used the Kagan methodology employing a titanium catalyst which was immobilized on mesoporous silica. However, only moderate enantioselectivities were obtained (up to 30% ee).

Similarly, Gao *et al.* (46) used a soluble polyethylene glycol (PEG)-supported tartrate chiral ligand **[31]** to oxidize sulfide **[32]**, producing sulfoxide **[20]** in excellent yield and excellent enantioselectivity (**Scheme 7**).



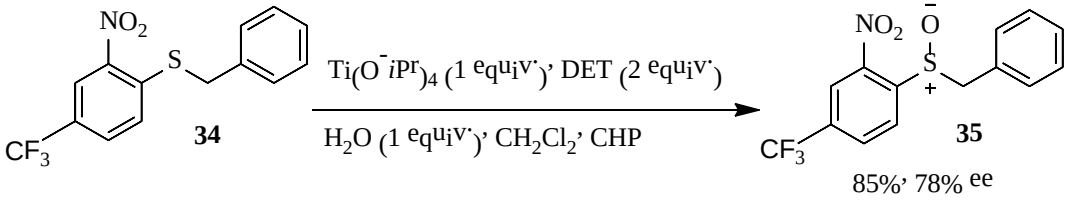
Scheme 7 Use of Immobilized Catalyst by Gao to promote Asymmetric Oxidation

Yuan *et al.* (47) used a titanium complex composed of the naphthol derived compound **[33]** to oxidize methyl *p*-tolyl sulfide **[5],** producing sulfoxide **[6]** in moderate yield (50%) and excellent enantioselectivity (99% ee). TBHP was used as oxidant and the oxidation was carried out in a toluene-tetrahydrofuran (THF) (1:1) solvent mixture.



Sahoo *et al.* (48) used an immobilized titanium-BINOL complex to prepare enantiopure aryl methyl sulfoxides. Complementary kinetic resolution accompanied these oxidations. The immobilized catalyst could be used in multiple runs without any loss of either enantioselectivity or activity.

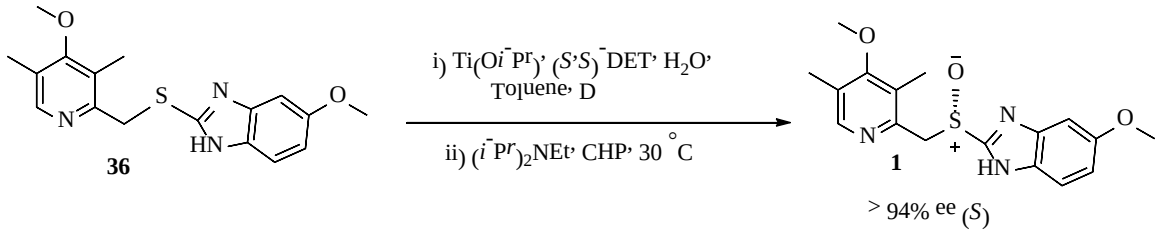
Rodygin *et al.* (49) recently reported the asymmetric oxidation of a range of fluorine containing sulfides using the Kagan system. Sulfide **[34]** was oxidized to sulfoxide **[35]** in good yield and enantioselectivity (**Scheme 8**).



Scheme 8 Titanium-Catalyzed Oxidation of Fluorine-containing Sulfides

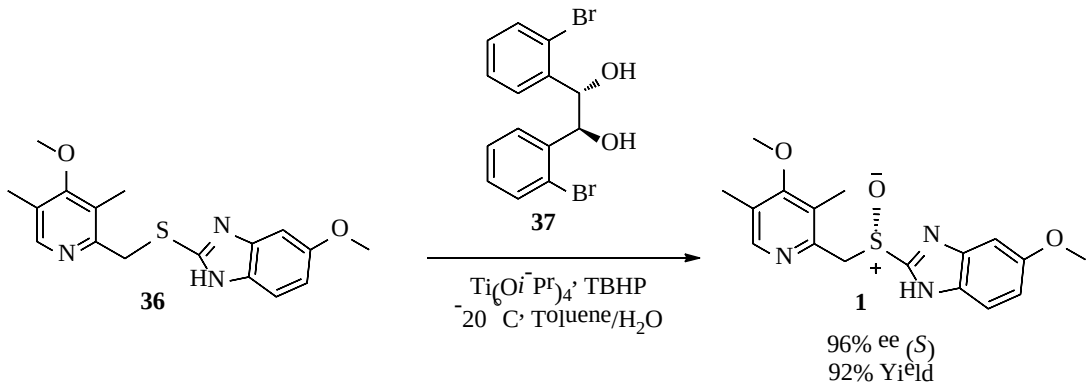
2.1.1 Synthesis of biologically active sulfoxides using titanium complexes

Titanium complexes have been used to synthesise pharmaceutical agents. A modified Kagan system was used by Von Unge (50) to prepare esomeprazole **[1]** in high enantioselectivity from the corresponding sulfide **[36]** (**Scheme 9**). Unlike the original Kagan procedure, the catalyst complex was prepared in the presence of the sulfide at an elevated temperature. The addition of *N*,*N*-diisopropylethylamine to the reaction mixture was necessary for the enhanced enantioselectivity.



Scheme 9 Synthesis of Esomeprazole using a modified Kagan Procedure

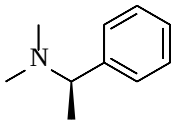
Jiang *et al.* (51) used a brominated aromatic diol **[37]** in the asymmetric synthesis of esomeprazole **[1]**. This system employed TBHP as oxidant and produced esomeprazole in high yield and enantioselectivity (**Scheme 10**).



Scheme 10 Synthesis of Esomeprazole using Brominated Aromatic Diol

Zhu *et al.* (31) used **[18]** as a chiral ligand in the asymmetric oxidation of sulfide **[36]**, affording esomeprazole **[1]** in good yield (72 %) and enantioselectivity (76% ee).

Volcho *et al.* (52) also reported a titanium-catalyzed asymmetric oxidation of omeprazole sulfide **[36]**. This system used CHP as oxidant and (*R*)-*N*,*N*-dimethyl-1-phenylethylamine **[38]** as a chiral ligand, producing the sodium salt of **[1]** in 64% yield and > 99.5% ee.



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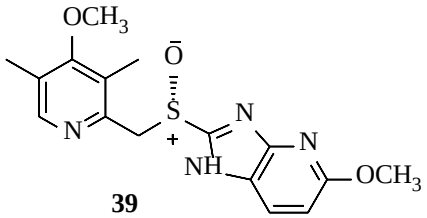
Delamare *et al.* (53) reported the asymmetric synthesis of (*S*)-tenatoprazole **[39]** using a titanium complex with (+)-(1*R*, 2*S*)-*cis*-1-amino-2-indanol **[40]** as the chiral ligand. The procedure involved the use of the polar aprotic solvent *N*-methyl-2-pyrrolidone (NMP) and afforded **[39]** in high yield (90%) and enantioselectivity (> 99% ee).



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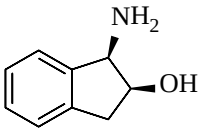
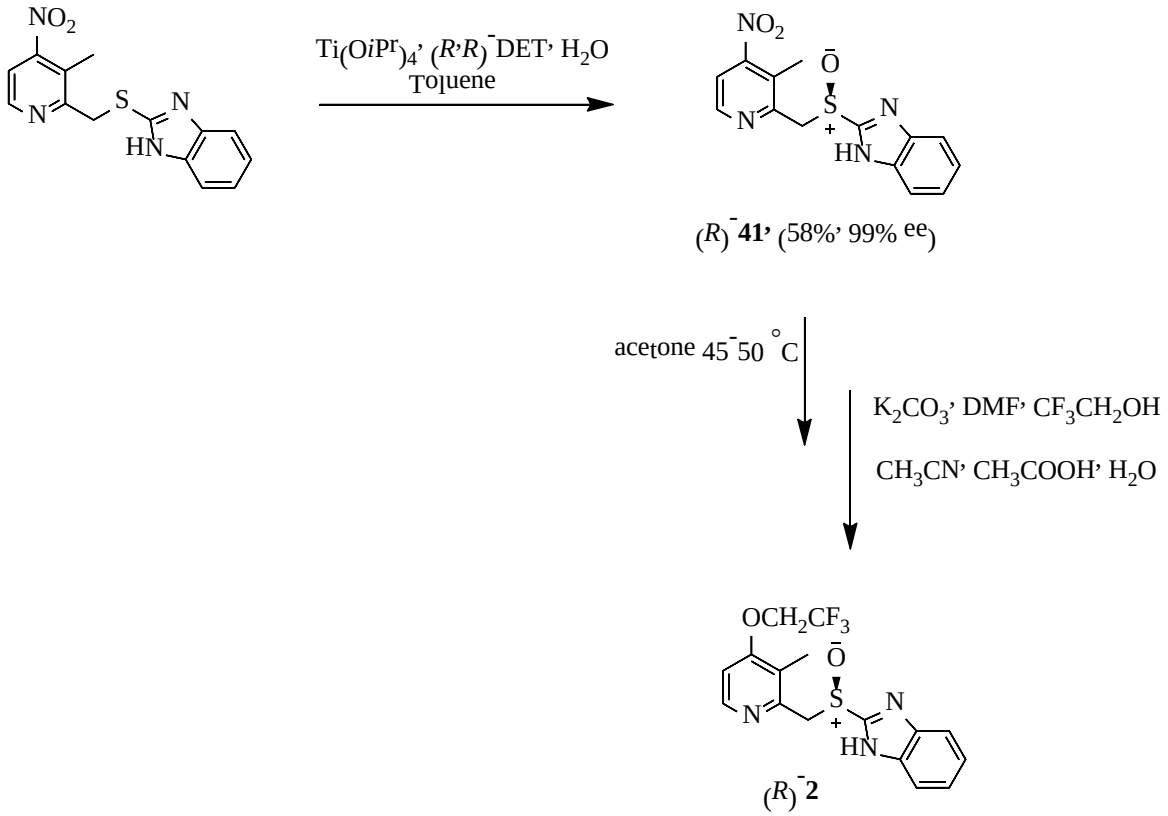


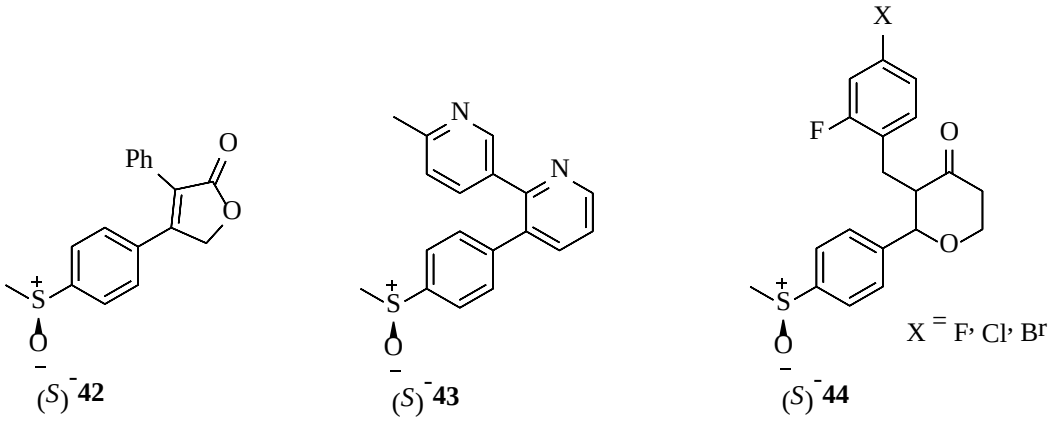
40

Raju *et al.* (54) used the Kagan system in the asymmetric synthesis of dexlansoprazole **[2]**. (*R*)-**[41]** was obtained in excellent enantioselectivity and then converted to **[2]** as shown in **Scheme 11**.



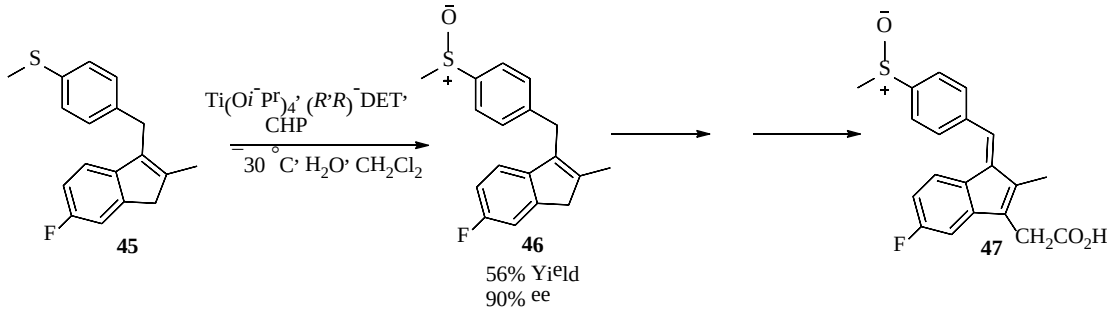
Scheme 11 Asymmetric Synthesis of Dexlansoprazole using a Titanium Complex

Caturla *et al.* (55,56) used the Modena system for the asymmetric synthesis of sulfoxides **[42]**, **[43]** and **[44]** in modest yield (17-60%) and excellent enantioselectivity (88-100% ee). These sulfoxides have the potential to act as prodrugs of the corresponding sulfones which are potent COX-2 inhibitors.



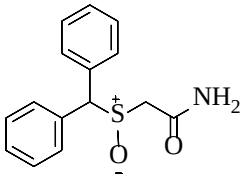
Maguire *et al.* (57) used the Kagan system for the asymmetric oxidation of sulfide **[45]**. Sulfoxide **[46]** was obtained in modest yield and excellent enantioselectivity, and was then converted to sulindac **[47]** as shown in **Scheme 12**.

Naso *et al.* (58) reported high ee (94-96% ee) and moderate yields (48-50%) in the preparation of sulindac alkyl esters using the hydrobenzoin complex **[28]**.



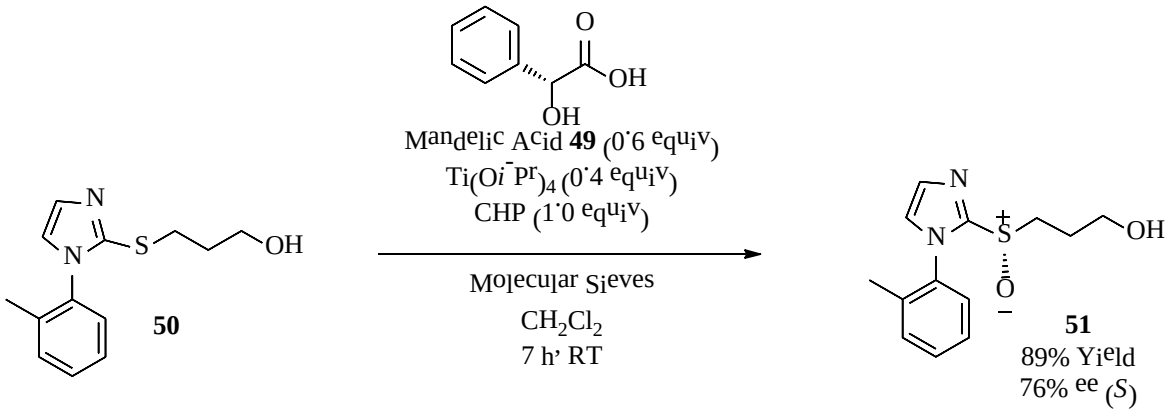
Scheme 12 Asymmetric Synthesis of Sulindac using a Titanium Complex

Cephalon (59) has reported the enantioselelctive synthesis of ®-modafinil **[48]** (up to 99% ee) from the corresponding sulfide. This system used CHP as oxidant and DET as the chiral ligand. The addition of a tertiary amine to the reaction was crucial to achieve high enantioselectivities.

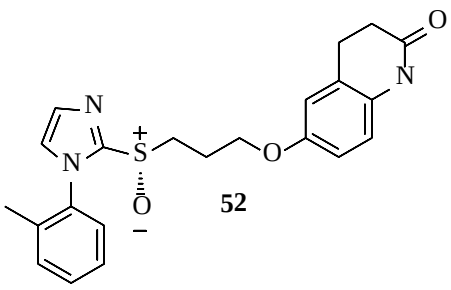


48

Matsugi *et al.* (60-62) used mandelic acid **[49]** as a chiral ligand to oxidize sulfide **[50]** to produce sulfoxide **[51]** on a large scale (**Scheme 13**). Sulfoxide **[51]**, which is a key intermediate in the synthesis of the platelet adhesion inhibitor **[52]**, was obtained in excellent yield and good enantioselectivity from the corresponding sulfide **[50]**, and was subsequently recrystallized to afford enantiopure **[52]**. This system is extremely useful because the reaction proceeds at ambient temperature and mandelic acid **[49]** can be readily recovered by extracting with a weak base.



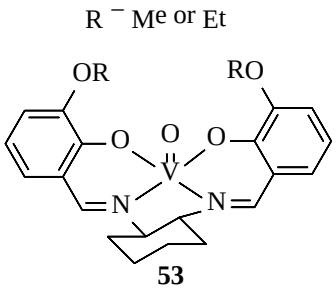
Scheme 13 Use of Mandelic Acid in Titanium-mediated Oxidation



52

2.2 Vanadium complexes

Vanadium complexes composed of tridentate Schiff bases have been used to catalyze asymmetric sulfoxidation. Fujita *et al.* (63) used vanadium Schiff base complex **[53]** as the catalyst and CHP as oxidant for the oxidation of thioanisole **[16]** producing sulfoxide **[17]** in modest enantiopurity (up to 40% ee). Fujita (64) later reported the use of Schiff base ligands derived from salicylaldehyde and L-amino acids, such as **[54]**, however, enantioselectivities remained poor for the oxidation of thioanisole (up to 14% ee).



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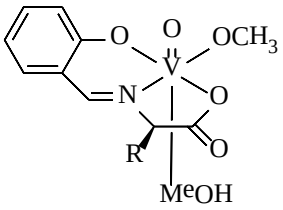
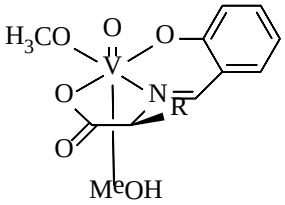


54 EXO

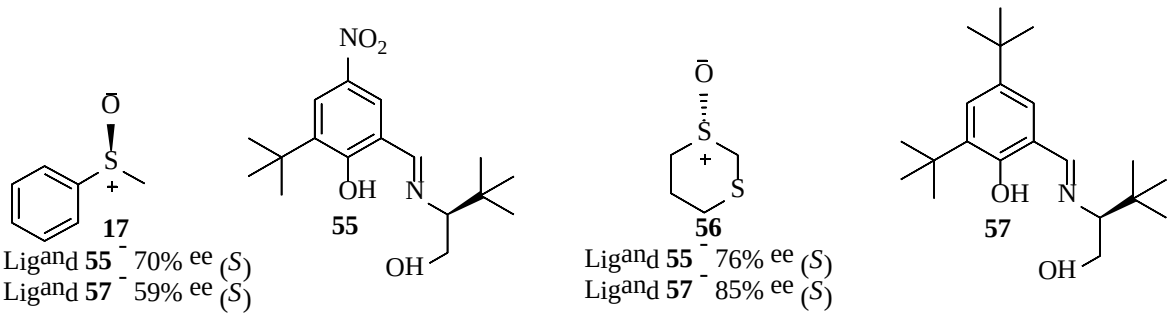


54 ENDO

A dramatic improvement to this oxidizing system was reported by Bolm *et al.* (65) in 1995. Vanadium complexes derived from Schiff bases such as **[55]** and $VO(acac)_2$ were used to catalyze the oxidation of a variety of aryl alkyl sulfides, producing sulfoxides in modest to good enantiopurities (50 to 70% ee). In a subsequent publication (66), Bolm reported the asymmetric monooxidation of dithioketals and dithioacetals, producing monosulfoxides with very good enantiopurities (up to 85% ee).

The Bolm system is superior to other oxidation methods because it employs hydrogen peroxide, a cheap and environmentally benign oxidant, and the oxidizing species is extremely active, with asymmetric oxidation occurring even in the presence of 0.1 mol% of the catalyst. The Schiff base ligands can be synthesized very easily by reacting the appropriate salicylaldehyde with enantiopure aminoalcohols such as L-*tert* leucinol.

Bolm investigated the effect of ligand structure on the oxidation, and reported that the optimum ligand was substrate specific. The use of ligand **[55]** afforded methyl phenyl sulfoxide **[17]** in 70% ee and the dithioacetal monosulfoxide **[56]** in 76% ee. However, use of ligand **[57]** produced sulfoxides **[17]** and **[56]** in 59% and 85% ee respectively (66) (**Scheme 14**).



Scheme 14 Optimum Ligand is Substrate Specific

Ellman *et al.* (67,68) also investigated the effect of ligand structure on the asymmetric oxidation of *tert*-butyl disulfide **[58]**. A *tert*-butyl group was required in the R^1 position of the ligand to achieve the highest enantiopurities, while the substituent at the R^2 position played no steric role in the oxidation although its electronic effects were important (**Figure 2**). The steric and electronic effects of the substituent in the R^3 position of the Schiff base ligand were significant. Overall, ligand **[57]** was optimum for the oxidation of disulfide **[58]**, producing the monosulfoxide **[59]** in good enantioselectivity as shown in **Scheme 15**. Ellman (67) reported improved enantioselectivity (91% ee) on carrying out the oxidation of **[58]** in $CHCl_3$ rather than CH_2Cl_2.

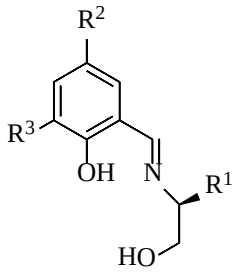
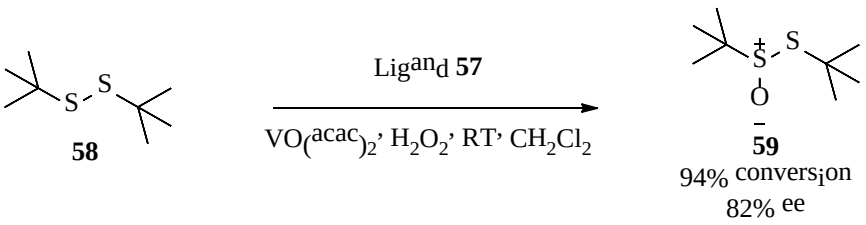
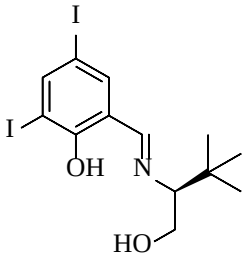


Figure 2 Structure of Schiff Base Ligand



Scheme 15 Asymmetric Oxidation of a Disulfide

Jackson *et al.* (69,70) screened a library of ligands obtained from a solid-supported aldehyde and different amino alcohols. A large number of ligands were tested for the oxidation of thioanisole with ligands **[60]** and **[61]** producing the best results.



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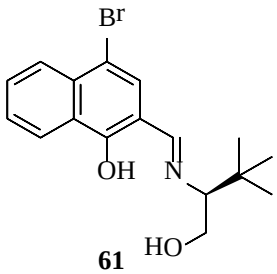
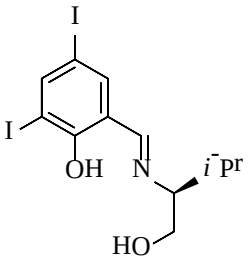


61

Gao *et al.* (71) also investigated the effect of ligand structure on the asymmetric oxidation of sulfides. The results of this study demonstrated that using the isopropyl substituted Schiff base ligands **[62]** and **[63]**, derived from (*S*)-valinol, resulted in higher enantioselectivity than that achieved with their isobutyl analogues (81% ee using **[62]**, 88% ee using **[63],** and 71% ee and 75% ee for their respective isobutyl analogues)for the oxidation of thioanisole **[16]**.



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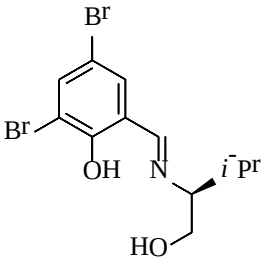
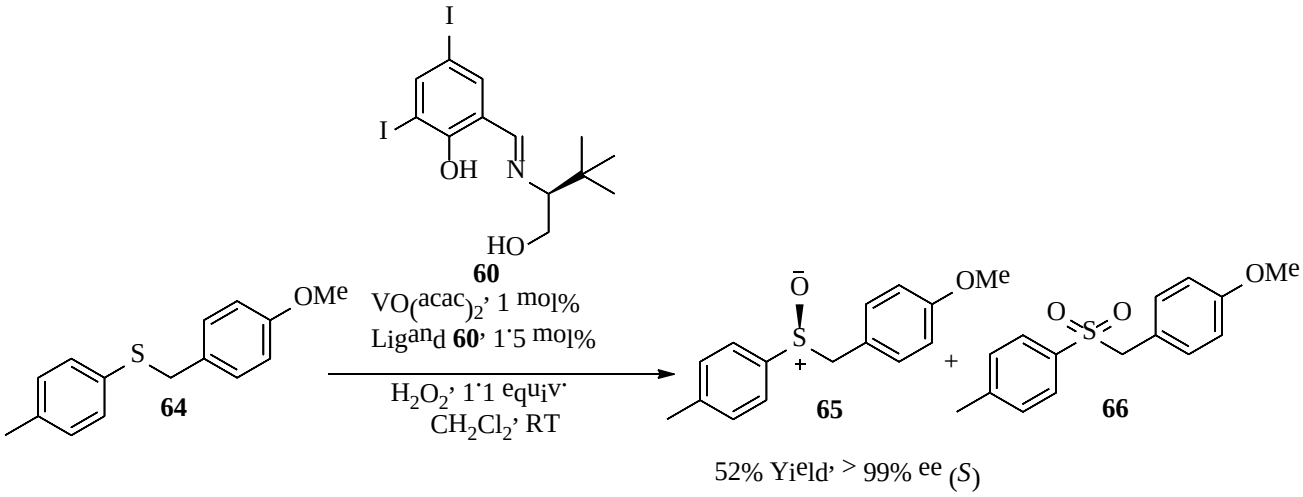


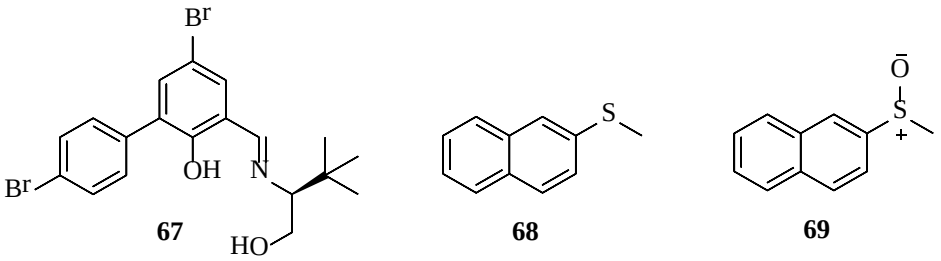
63

Maguire *et al.* (72,73) carried out vanadium-catalyzed oxidations using ligands similar to those used by Bolm. This report focussed on the asymmetric oxidation of aryl benzyl sulfides, in contrast to Bolm's study of aryl alkyl sulfides. An important feature of this oxidation is that it is accompanied by complementary kinetic resolution which resulted in improved enantioselectivities, albeit with reduced yields as a result of over oxidation. A number of Schiff base ligands was investigated with ligand **[60]** producing the best results. Sulfide **[64]** was oxidized to the corresponding sulfoxide **[65]** in modest yield but excellent enantioselectivity with significant over oxidation to sulfone **[66]** as shown in **Scheme 16**.

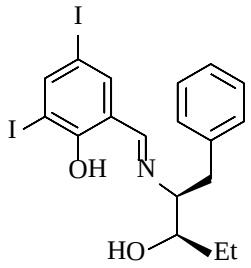


Scheme 16 Vanadium-Catalyzed Oxidation of Aryl Benzyl Sulfides

Liu *et al.* (74) synthesized a series of chiral Schiff bases with different substituents on the salicylidenyl unit. Schiff base **[67]** produced the best results in the oxidation of 2-naphthyl methyl sulfide **[68]**, affording sulfoxide **[69]** in good yield (85%) and excellent enantioselectivity (90% ee). An investigation of solvent indicated that chlorinated solvents such as CH_2Cl_2 and $CHCl_3$ produced sulfoxides with the highest enantiopurities.

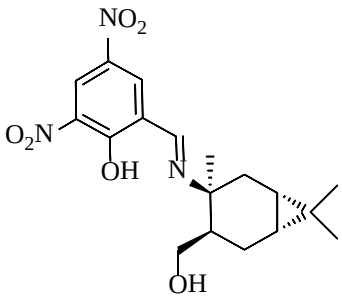


Li *et al.* (75) synthesized a number of novel Schiff base ligands with two stereogenic centres. Ligand **[70]** was used to convert a variety aryl alkyl sulfides into the corresponding sulfoxides with good yields and excellent enantioselectivities (up to 99% ee). The choice of solvent had a large influence on enantioselectivity, with $CHCl_3$ significantly outperforming CH_2Cl_2. Complementary kinetic resolution accompanied this oxidation which led to a slight enhancement in enantioselectivity.

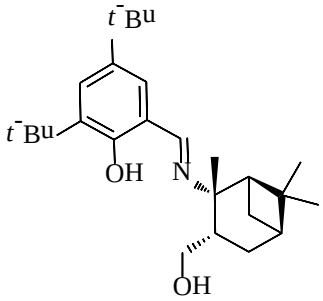


70

In 2009, Koneva *et al.* (76) reported the synthesis of a series of new chiral Schiff bases, such as **[71]**, derived from the monoterpene, (+)-3-carene. However the use of these ligands in the asymmetric oxidation of thioanisole **[16]** afforded sulfoxide **[17]** with very poor enantiopurities (up to 20% ee). In another publication (77), Koneva outlined the use of α-pinene derived ligands **[72]** for asymmetric sulfoxidation; however enantioselectivities remained low (up to 32% ee).



3-carene ligand 71

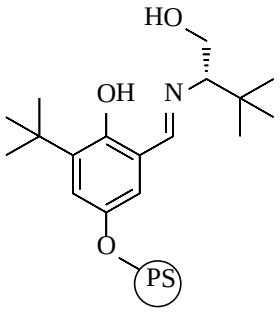


pinene ligand 72

Barbarini *et al.* (78) synthesized a series of polymer-supported chiral Schiff bases, such as **[73]**, composed of salicylaldehyde deivatives and optically active amino alcohols. Moderate enantioselectivities were obtained, in the oxidation of thioanisole, when the ligand was supported on a polystyrene matrix (~56% ee), while the use of polyester supports resulted in a significant reduction in enantioselectivity (~39% ee). However, overall the enantioselectivities were considerably lower than those obtained using the "free" vanadium complex.

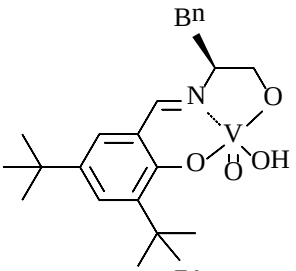
Zeng *et al.* (79) reported the use of pre-formed complexes, such as **[74]**, in asymmetric sulfoxidation. Schiff bases were prepared by condensation of a salicylaldehyde derivative with a chiral amino alcohol. $VO(acac)_2$ and the Schiff base were then refluxed for 3 hours in methanol to generate the complex, which appears as a brown precipitate. The use of these complexes, with hydrogen peroxide as oxidant, afforded sulfoxide **[17]** in excellent yield but poor enantioselectivity. However, increasing the amount of oxidant afforded **[17]** in modest

yield (41%) and excellent enantioselectivity (up to 99% ee) as a result of complementary kinetic resolution. The pre-formed complexes were also used to oxidize various substituted sulfides with good enantiocontrol.



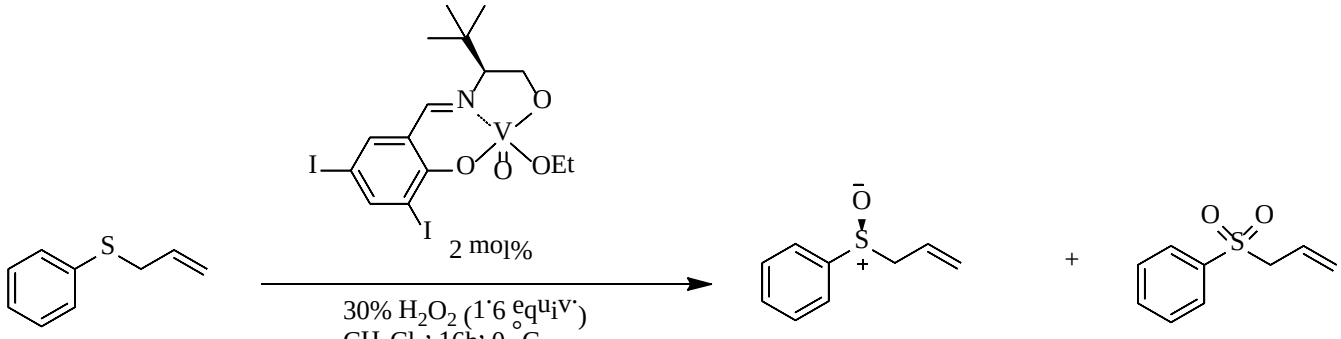
73

PS = polystyrene



74

Recently, Zeng (80) used a vanadium Schiff base complex to oxidize allyl phenyl sulfide, obtaining the corresponding sulfoxide in moderate yield and excellent enantioselectivity (**Scheme 17**). 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.



1·2 equiv· H_2O_2

Sulfoxide : 75%, 72% ee (*S*), **Sulfone :** 0%

1·6 equiv· H_2O_2

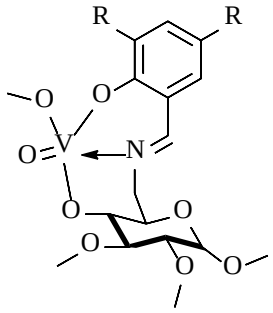
Sulfoxide : 58%, 93% ee (*S*), **Sulfone :** 16%

Scheme 17 Asymmetric Oxidation of Allyl Phenyl Sulfide using a Vanadium Complex

Lippold *et al.* (81) reported the use of pre-formed vanadium complexes, such as **[75]**, derived from 6-amino-6-deoxyglucopyranoside. Complex **[75]** was used to oxidize thioanisole **[16]** and benzyl phenyl sulfide **[13]**, producing the corresponding sulfoxides in good to excellent yields (91% for **[17]** and 77% for **[14]**) but poor enantioselectivity (26% ee for **[17]** and 16%

ee for **[14]**). Interestingly, the use of TBHP as oxidant, instead of hydrogen peroxide, afforded racemic sulfoxide.

Romanowski and co-workers (82,83) investigated asymmetric sulfoxidation using pre-formed complexes, derived from chiral diamine Schiff bases **[76]** and **[77]**; however, only modest enantiopurities were achieved (up to 39% ee).



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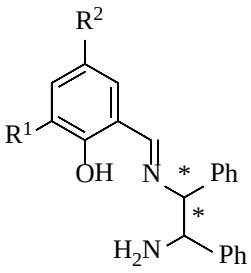
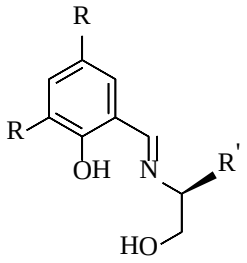
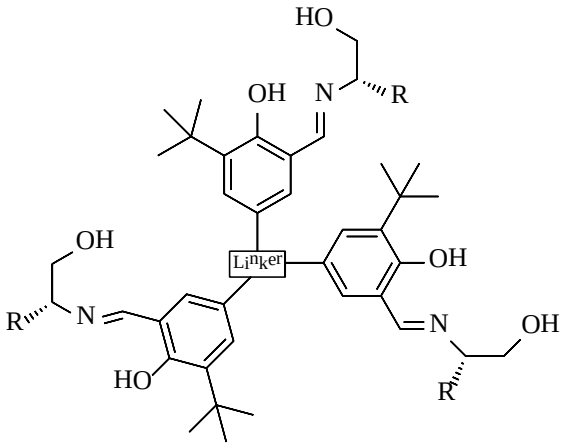


76 R^1 = H, R^2 = OMe
77 R^1 = OMe, R^2 = H

Trimeric variants of Bolm's catalysts were synthesized by Pati *et al*. (84) (**Figure 3**) and used in the oxidation of both aryl methyl and aryl benzyl sulfides. Pati *et al*. reported improved enantioselectivities using vanadium catalysts derived from ligands with the three salen moieties separated from one another by a tether. Benzyl phenyl sulfoxide **[14]** was afforded in excellent yield (92%) and enantioselectivity (89% ee) using this oxidizing system.



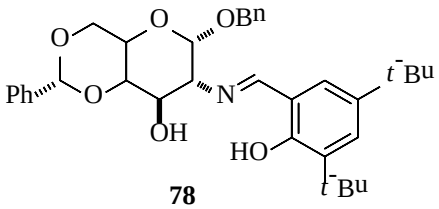
Bolm's vanadium Schiff base ligands



Trimeric variant of Bolm's catalyst

Figure 3 Bolm's Ligand and Trimeric Variant prepared by Pati

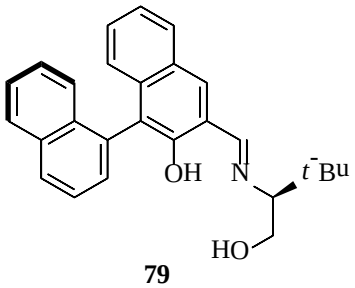
Khiar and Fernandez (85) reported the first study on asymmetric oxidation of functionalized sterically hindered disulfides. Excellent enantioselectivities (up to 96% ee) were obtained using the carbohydrate ligand **[78]**.



78

A number of research groups have used sterically bulky ligands in vanadium-catalyzed oxidations. Berkessel *et al.* (86) used ligands **[79]** and **[80]** to oxidize thioanisole **[16]** and ortho-bromo thioanisole **[81]**, producing the corresponding sulfoxides in good enantiopurities (up to 78%). Although these ligands possess two elements of chirality, the extra chiral feature does not affect the stereoselectivity of the oxidation, and stereoselectivity was determined only by the chiral centre of the amino alcohol moiety.

Katsuki *et al.* (87) used a modified version of Berkessel's ligand **[82]** in the oxidation of thioanisole **[16]**, producing the corresponding sulfoxide **[17]** in good yield (83%) and good enantioselectivity (86% ee). An addition of methanol resulted in improved enantioselectivity (88% ee). Katsuki speculated that coordination of methanol affected the equilibrium of the peroxo vanadium species.



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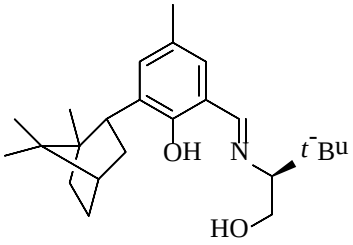

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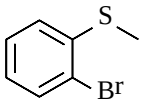

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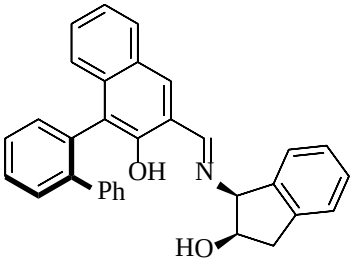
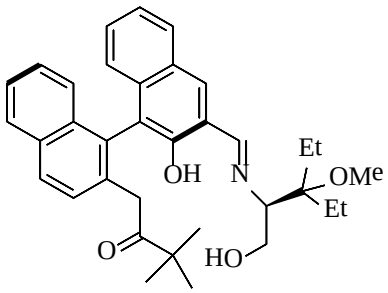
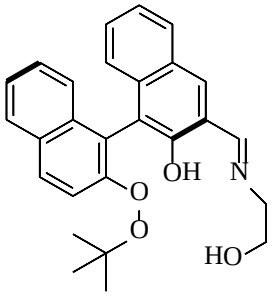


82

Ahn *et al.* (88,89) synthesized a number of ligands that were based on **[79]**. The use of **[83]** as chiral ligand afforded benzyl phenyl sulfoxide **[14]** in excellent enantiopurity (96% ee). Ahn demonstrated that a chiral centre was required in the imine to achieve asymmetric induction as only racemic sulfoxide was generated using **[84]**.

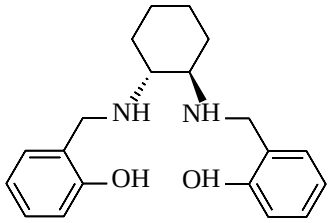


83



84

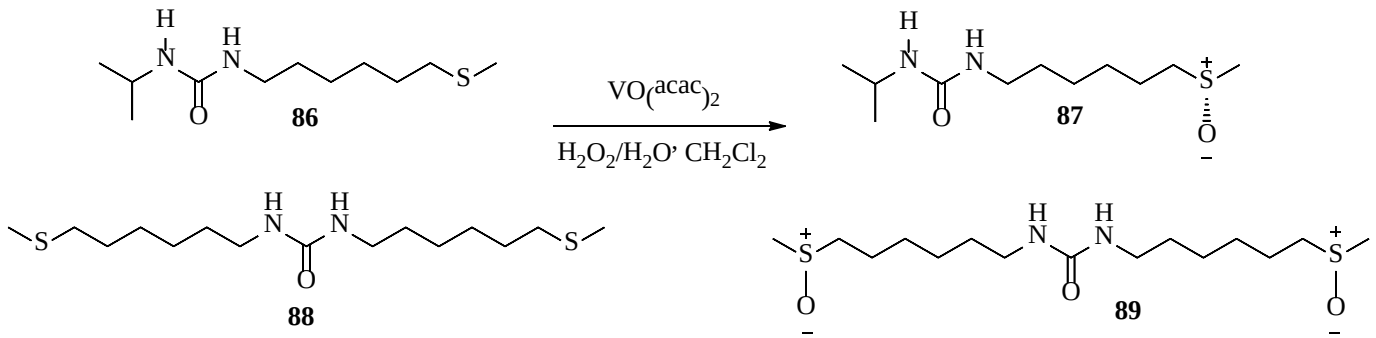
Zhu *et al.* (90) reported asymmetric sulfoxidation using vanadium complexes composed of salen ligands such as **[85]**. A solvent study indicated that $CHCl_3$ was optimal for the oxidation, while hydrogen peroxide was used as oxidant. Salen ligand **[85]** was used to catalyze the oxidation of a range of sulfides, affording sulfoxides in good yields (up to 86%) and excellent enantioselectivities (up to 95% ee), in certain cases.



85

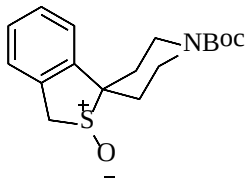
2.2.1 Synthesis of biologically active sulfoxides using vanadium complexes

A vanadium complex composed of Schiff base **[57]** was used to oxidize sulfide **[86]** producing sulfoxide **[87]** in excellent yield (91%) but moderate enantioselectivity (45% ee). Similarly, oxidation of bis-sulfide **[88]** using ligand **[57]** afforded the bis-sulfoxide **[89]**, (-)-diptocarpidin, in poor enantioselectivity (91) (28% ee, **Scheme 18**). Both sulfoxides exhibit antihypoxic activity.



Scheme 18 Synthesis of Biologically Active Sulfoxides using a Vanadium Complex

Nishi *et al.* (92) used a vanadium complex with ligand **[57]** to prepare sulfoxide **[90]**, a key intermediate in the synthesis of a tachykinin receptor anatagonist, in good yield (80%) and moderate enantioselectivity (54% ee).

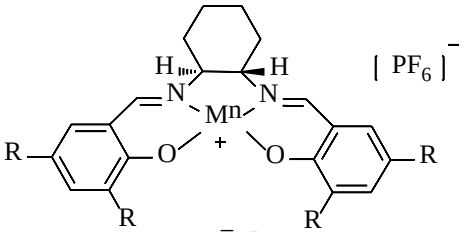


90

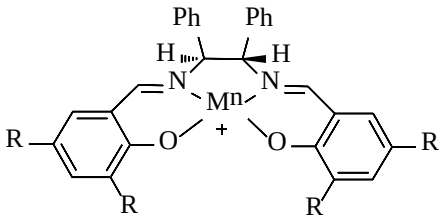
®-Modafinil **[48]** was prepared in moderate yield (45%) and poor enantioselectivity (12% ee) using a vanadium-catalyzed sulfoxidation, employing **[60]** as chiral ligand (93).

2.3 Manganese complexes

In the last two decades there have been numerous reports of the use of manganese-salen complexes in asymmetric sulfoxidation. 1n 1992, Jacobsen *et al.* (94) used manganese complex **[91]** to catalyze sulfide oxidation but only very modest enantioselectivities were achieved. Quici *et al.* (95) used manganese complexes **[92]** and **[93]**, which are composed of quadridentate Schiff base ligands, for asymmetric sulfoxidation. These ligands are derived from 1,2-diamines and fluorous derivatives of salicylaldehyde. Chiral ligands **[92]** and **[93]** were tested in the oxidation of methyl aryl sulfides, using iodosylbenzene as oxidant, but afforded the corresponding sulfoxides in poor enantiopurities (up to 17% ee).

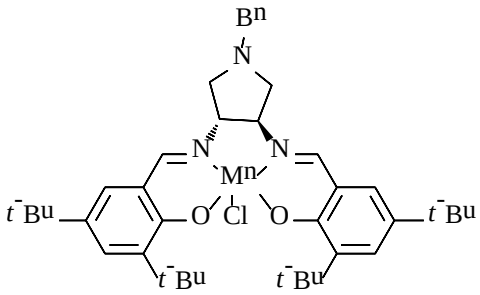


91 R = *t*-Bu
92 R = C_8F_{17}

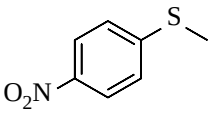


93 R = C_8F_{17}

Gao *et al.* (96) investigated the use of manganese complexes bearing a pyrollidine backbone such as **[94]**. However, only modest enantioselectivities were achieved (up to 42% ee). Iodosylbenzene was used as oxidant as the use of hydrogen peroxide led to catalyst decomposition, while *m*-CPBA afforded significant amounts of sulfone. The best results were obtained for electron-deficient substrates such as *para*-nitrophenyl methyl sulfide **[95]**.

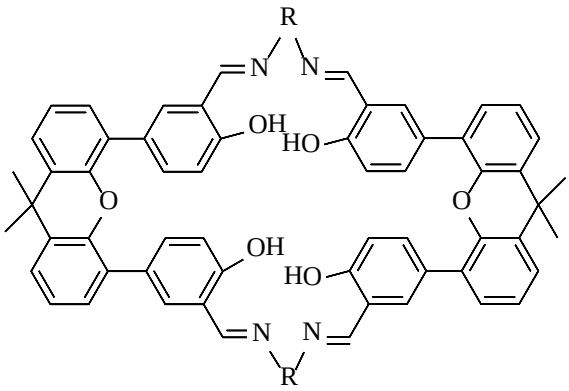


94



95

Hirotsu *et al.* (97) used dimanagnese(III) complexes composed of salen ligands **[96]** for the oxidation of thioanisole **[16]** reporting modest enantioselectivities (up to 39% ee). Iglesias *et al*. (98) used manganese complex **[97]** for the asymmetric oxidation of **[16]**, but again enantioselectivities achieved were poor (up to 27% ee).



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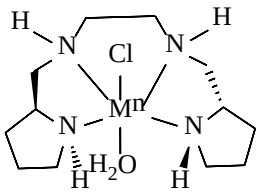
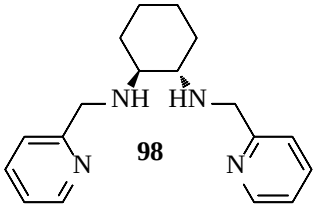
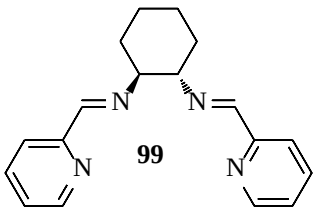


97

Fontecave *et al.* (99) synthesized manganese complexes bearing perchlorate or acetylacetenoate anions. The use of chiral ligand **[98]** afforded the sulfoxide of thioanisole **[17]** in very poor enantioselectivity (~ 5% ee). However, use of its derivative **[99]** led to improved asymmetric induction (up to 62% ee). Interestingly, the configuration of the sulfoxide was dependant on the metal source used, with $Mn(ClO_4)_2$ producing the (*S*)-enantiomer while the use of $Mn(acac)_2$ gave the ®-enantiomer.



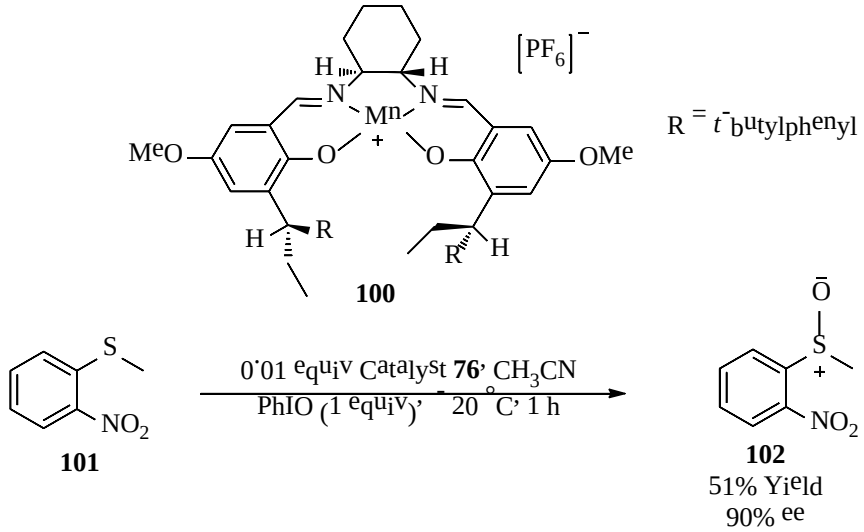
98



99

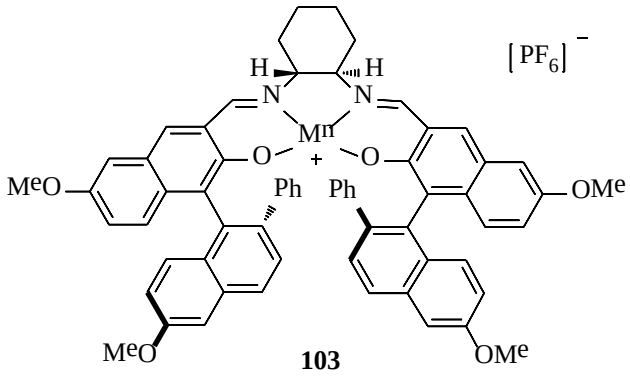
Katsuki *et al.* (32,100) has obtained the best results in manganese-catalyzed asymmetric sulfoxidation. Manganese complex **[100]** was used to oxidize *ortho*-nitrophenyl methyl

sulfide **[101]**, producing the corresponding sulfoxide **[102]** in moderate yield and excellent enantioselectivity as shown in **Scheme 19**.



Scheme 19 Katsuki Oxidation

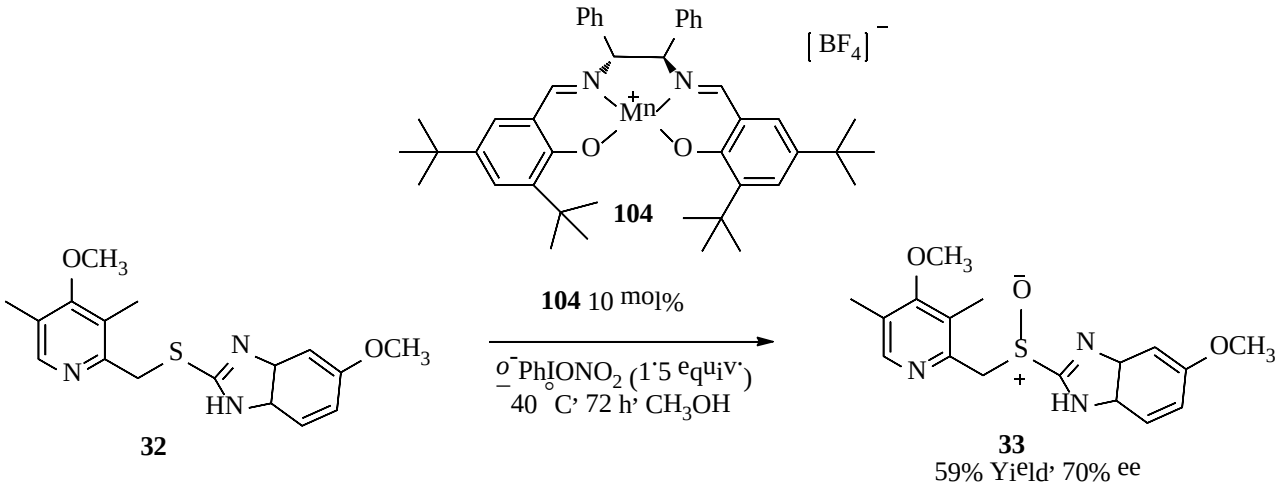
Subsequently, Katsuki (33) reported improved yields and enantioselectivities using manganese complex **[103]**. Sulfoxide **[102]** was now produced in quantitative yield and excellent enantioselectivity (up to 94% ee). The addition of 4-phenylpyridine *N*-oxide to the oxidizing system resulted in improved enantioselectivities in certain cases.



2.3.1 Synthesis of biologically active sulfoxides using manganese complexes

In 2008, Ryu *et al.* (101) reported the asymmetric oxidation of omeprazole sulfide **[36]** using a manganese complex **[104]**. Esomeprazole **[1]** was afforded in moderate yield and good enantioselectivity as shown in **Scheme 20**. This system was also used to oxidize a range of

aryl alkyl sulfides, producing *para*-nitrophenyl methyl sulfoxide **[105]** in good yield (76%) and good enantioselectivity (80% ee).

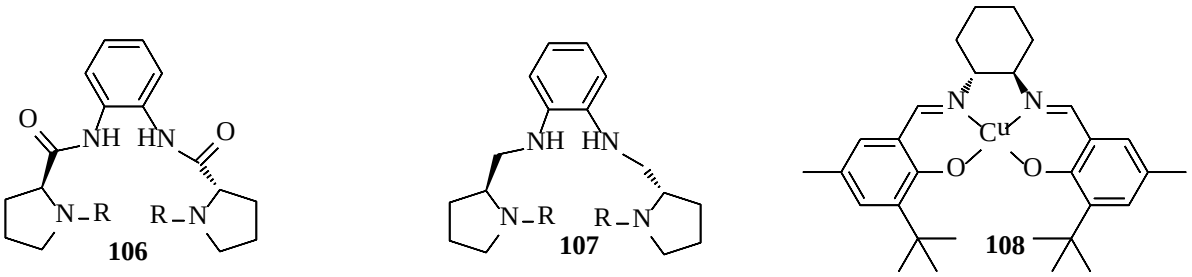


Scheme 20 Synthesis of Esomeprazole using a Manganese Complex

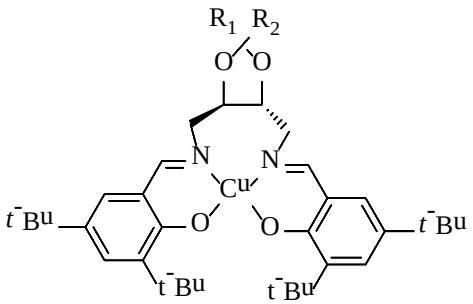
2.4 Copper complexes

Copper complexes of proline based ligands **[106]** and **[107]** have been used by Sanchez *et al.* (98) to oxidize thioanisole **[16]** using NaOCl as oxidant, producing sulfoxide **[17]** in poor enanantioselectivty (up to 25% ee). These complexes exhibited similar chemo- and stereoselectivities but lower activies compared to their manganese analogs. Sanchez *et al.* (102) also reported the preparation of enantioenriched aryl methyl sulfoxides (up to 30% ee) using immobilized copper(II) salen-type complexes and TBHP as oxidant.

Cross *et al.* (103) oxidized **[16]** using the copper salen complex **[108]**, producing sulfoxide **[17]** in poor enantioselectivity (up to 14% ee).

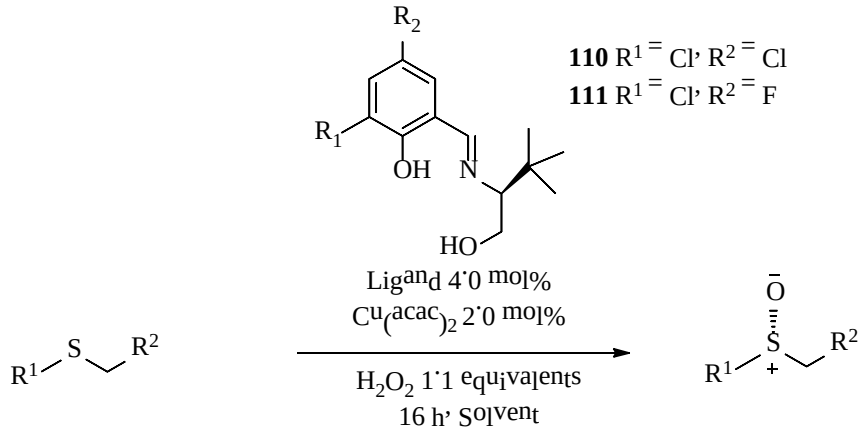


Zhu *et al.* (104) used complexes composed of optically active Schiff bases such as **[109]**. These afforded sulfoxides in good yields (> 80%) but poor enantioselectivities (up to 17% ee).



109

Maguire *et al.* (105,106) has reported the highest enantioselectivities achieved in copper-catalyzed asymmetric sulfide oxidation. A series of chiral Schiff bases were used to oxidize a number of aryl benzyl sulfoxides in modest yield (up to 49%) but good enantioselectivity (up to 81% ee) (105). The addition of *N*-methylmorpholine-*N*-oxide (NMO) to the oxidizing system resulted in an improvement in yield in all cases and an improvement in enantioselectivity in certain cases. This system is similar to Bolm's vanadium- (65) and iron-catalyzed oxidations (107,108) in that the same oxidant and similar ligands are employed. Interestingly, the direction of stereoselectivity observed is opposite to that observed for iron/vanadium-catalyzed oxidations. Recently, Maguire *et al.* (106) reported a dramatic improvement in yields and also an improvement in enantioselectivities using mixed solvent systems (**Scheme 21**). Carrying out the oxidation in mixtures composed of polar, low molecular weight alcohols such as methanol or ethanol in conjuction with a non-polar alkane such as hexane produced sulfoxides in excellent yields (up to 92%) and excellent enantioselectivities (up to 93% ee). Schiff base ligands **[110]** and **[111]** produced the best results. Interestingly, the use of bulkier alcohols such as isopropyl alcohol (IPA) afforded only racemic sulfoxide. 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	**110**	21	58
hexane : MeOH (9:1)	Ph	Ph	**110**	90	79
hexane : MeOH (9:1)	*p*-Tol	Ph	**110**	91	81
hexane : MeOH (9:1)	*p*-Tol	Ph	**111**	90	84
toluene	Ph	2-Naphthyl	**110**	23	93

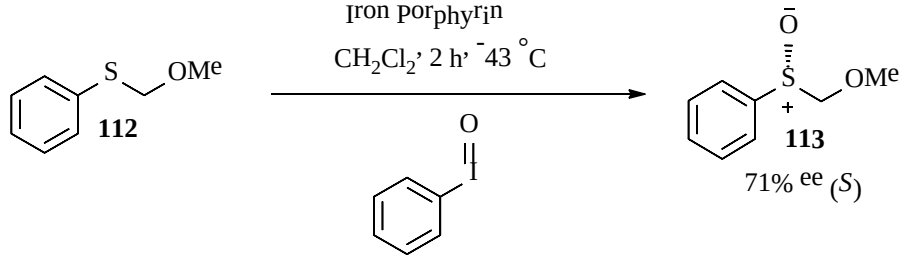
Scheme 21 Asymmetric Oxidation of Sulfides using a Copper Complex

2.5 Iron complexes

In 2003, Bolm (107) reported an iron-catalyzed asymmetric sulfoxidation. This system was based on the vanadium methodology in that the same oxidant and Schiff base ligands were employed. The initial results were poor both in terms of yield and enantioselectivity; the sulfoxide of thioanisole **[17]** was produced in low yield (36%) and moderate enantioselectivity (59% ee). However, the use of additives led to an improvement in the efficiency of the oxidation (108,109). The oxidation of thioanisole **[16]**, in the presence of lithium 4-methoxybenzoate, afforded sulfoxide **[17]** in moderate yield (63%) and excellent enantioselectivity (90% ee). Similar improvements were obtained for a range of aryl alkyl sulfides. As with vanadium, the use of Schiff base ligands with (*S*)-configuration produced sulfoxides with (*S*)-configuration and *vice versa*.

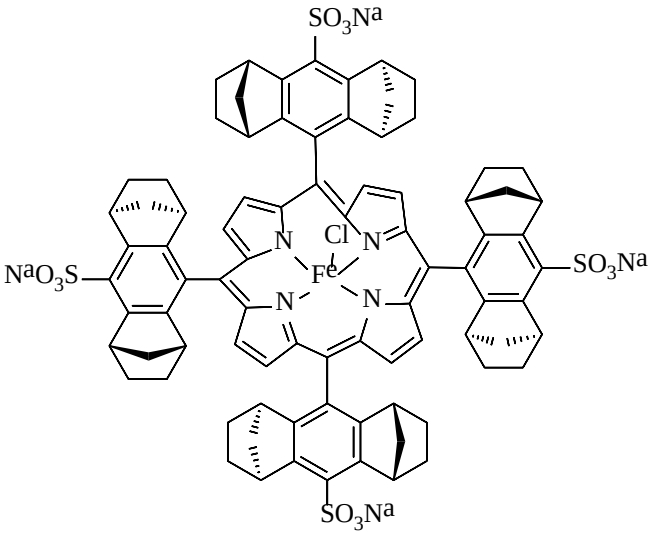
A number of research groups have reported the use of iron porphyrins in asymmetric sulfoxidation. Groves and Viski (110) used vaulted naphthyl metalloporphyrins with iodosylbenzene as oxidant. This system produced *ortho*-bromo phenyl sulfoxide in good yield (74%) and moderate enantioselectivity (48% ee). Naruta *et al.* (111,112) employed iron complexes of “twin coronet” porphyrins as the catalyst and iodosylbenzene as oxidant

producing sulfoxides in modest enantioselectivities (up to 31% ee). A dramatic improvement in enantioselectivity (up to 73% ee) was obtained when the oxidation was carried out in the presence 1-methylimidazole at –15 °C. It is believed that the 1-methylimidazole binds to the active metal centre and enhances the enantioselectivity by changing the porphyrin structure around the iron which prevents decomposition of the catalyst. Inoue *et al.* (113) also reported enhanced enantioselectivity on carrying out an iron porphyrin-catalyzed catalyzed oxidation in the presence of imidazole. This system was used to oxidize methoxymethyl phenyl sulfide **[112]** producing the corresponding sulfoxide **[113]** in good enantioselectivity (**Scheme 22**).

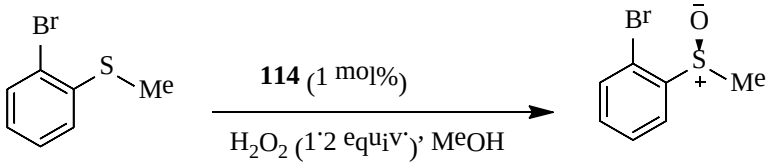


Scheme 22 Iron Porphyrin-Catalyzed Asymmetric Oxidation of Sulfides

Le Maux *et al.* (114) recently reported the asymmetric oxidation of sulfides using chiral water-soluble iron porphyrins **[114]** as catalysts. Excellent conversions and enantioselectivities were obtained for a range of aryl methyl sulfides. 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 23**).



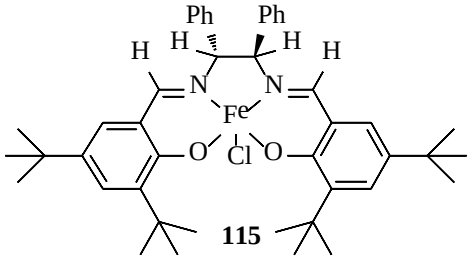
114



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

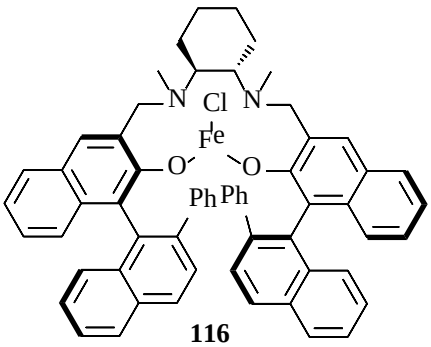
Scheme 23 Asymmetric Sulfoxidation using Iron Porphyrin **114**

Bryliakov and Talsi (115) reported the use of Fe(III)-salen systems, such as **[115]**, for the oxidation of a range of sulfides. This system produced benzyl phenyl sulfoxide **[14]** in excellent conversion (91%) and moderate enantioselectivity (62% ee).

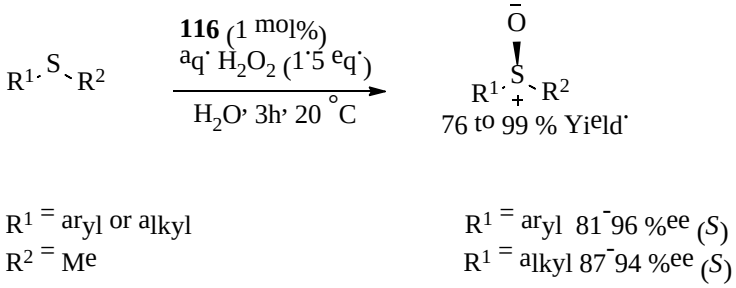


115

Egami and Katsuki (116,117) reported improved enenatioselectivities using salen derivatives, such as **[116]**, bearing chiral binaphthyl fragments. This system used hydrogen peroxide as oxidant and water as solvent, and was used to oxidize a number of aryl alkyl and methyl alkyl sulfides (**Scheme 24**).

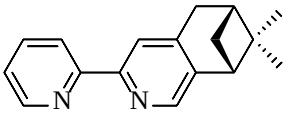


116



Scheme 24 Asymmetric Sulfoxidation using an Iron Salen Derivative

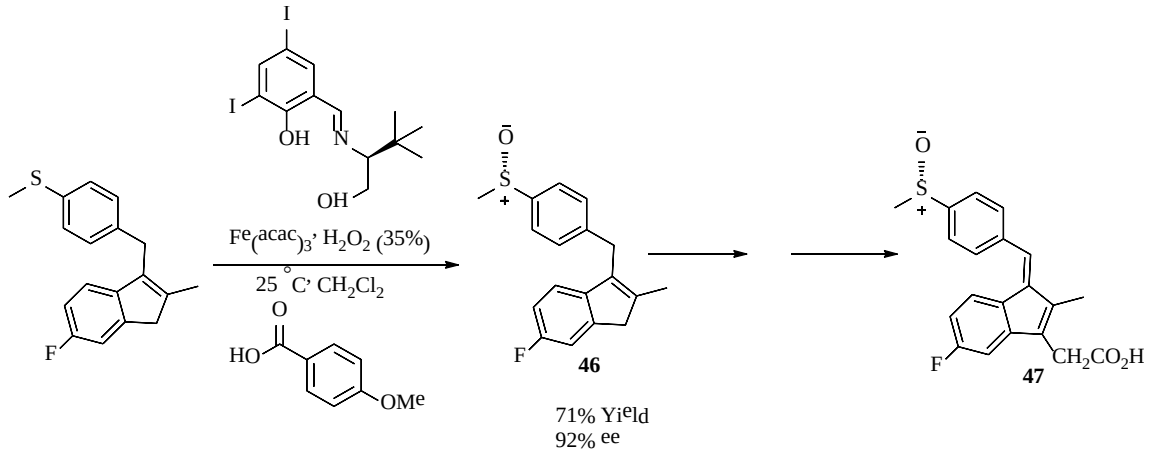
Fontecave *et al.* (118) formed an iron complex using the chiral bipyridyl derivative **[117]**. However, the application of this complex to the oxidation of aryl methyl sulfides, afforded essentially racemic sulfoxides.



117

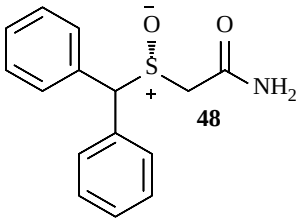
2.5.1 Synthesis of biologically active sulfoxides using iron complexes

Bolm (119) applied the iron-mediated oxidation system to the asymmetric synthesis of sulindac **[47]** (**Scheme 25**). In the absence of additives, sulfoxide **[46]** was obtained in moderate yield (53%) and enantioselectivity (58% ee).



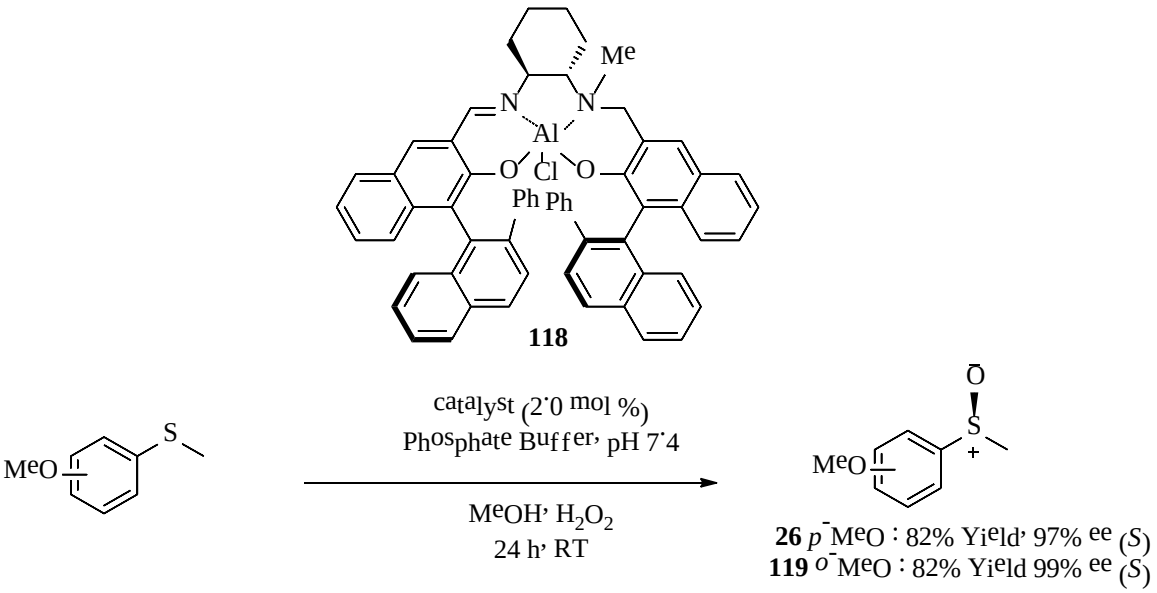
Scheme 25 Asymmetric Synthesis of Sulindac using an Iron Complex

Ternois *et al.* (93) reported an iron-catalyzed asymmetric sulfoxidation in the synthesis (*R*)-modafinil **[48]**; however poor yields (10%) and enantioselectivities (15% ee) were obtained.



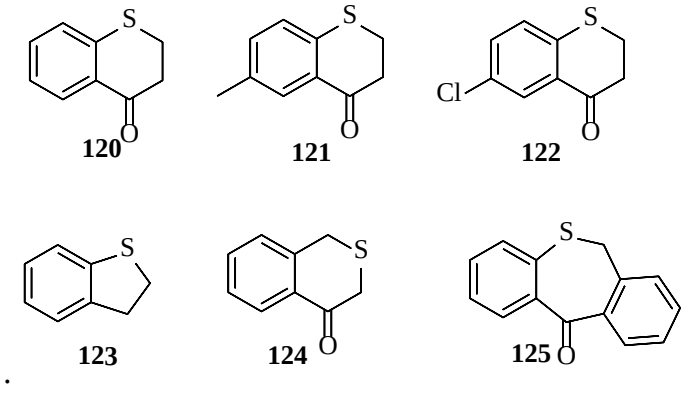
2.6 Aluminum complexes

A highly efficient aluminium-catalyzed oxidation was reported by Katsuki *et al.* (120). The aluminium complex **[118]** was used to oxidize a number of sulfides, affording sulfoxides such **[119]** and **[26]** in good yields and excellent enantioselectivities as shown in **Scheme 26**. This oxidizing system is superior to many established methods because the solvent and oxidant used make this a very green reaction. High enantioselectivities were maintained under modified reaction conditions such as low catalyst loadings and high substrate concentrations.



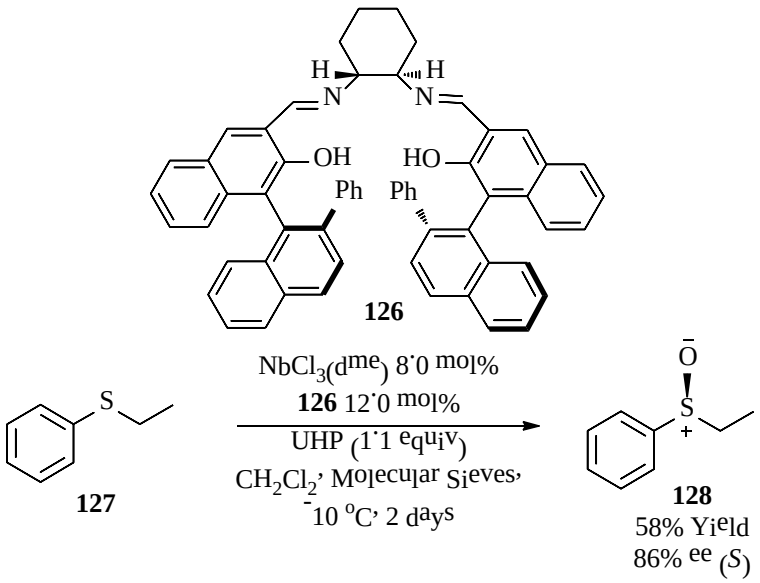
Scheme 26 Asymmetric Sulfoxidation using an Aluminum Catalyst

A number of bicyclic sulfur compounds **[120-125]** were also oxidized using **[118]** affording the corresponding sulfoxides in excellent enantiopurities (87-99% ee) (121).



2.7 Niobium complexes

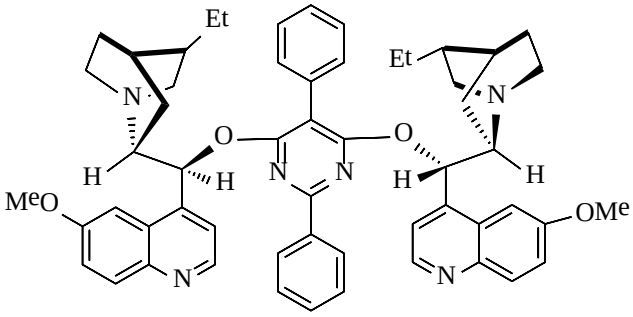
Katsuki *et al.* (122) has also investigated the asymmetric oxidation of sulfides using niobium complexes. The use of salen complex **[126]** afforded the highest enantioselectivities (up to 86% ee). This system used urea-hydrogen peroxide adduct as oxidant and the addition of molecular sieves was necessary to achieve high enantiopurites. The best results were achieved with ethyl phenyl sulfide **[127]**, with sulfoxide **[128]** produced in moderate yield and excellent enantioselectivity as shown in **Scheme 27**.



Scheme 27 Asymmetric Sulfoxidation using an Niobium Catalyst

2.8 Tungsten complexes

In 2003, Sudalai *et al.* (123) reported a tungsten-catalyzed asymmetric sulfoxidation, affording sulfoxides in moderate enantiopurities (up to 65% ee). The cinchona alkaloid derivative **[129]** was used as the chiral ligand and hydrogen peroxide was used as oxidant.



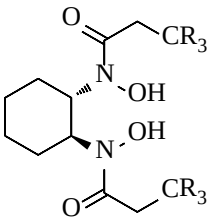
129

2.9 Osmium complexes

In 2005, Kantam *et al.* (124) carried out asymmetric sulfoxidation of aryl alkyl sulfides using an OsO_4 catalyst supported on layered double hydroxides, a cinchona alkaloid derivative and NMO as co-oxidant. Sulfoxide **[17]** was afforded in moderate yield (67%) and enantioselectivity (51% ee) using this system.

2.10 Molybdenum complexes

There have been numerous reports of molybdenum-catalyzed asymmetric sulfoxidation in recent years. Complexes prepared from $Mo(acac)_2$ and bis-hydroxamic acids, such as **[130]**, and trityl hydrogen peroxide (THP) as oxidant, afforded sulfoxides with good yields (66–99%) and enantiopurities (54–86% ee), in certain cases. An increase in the amount of oxidant and reaction time resulted in a considerable enhancement in enantioselectivities (92–99% ee), as a result of kinetic resolution (125).

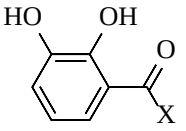


R = 4-isopropylphenyl

130

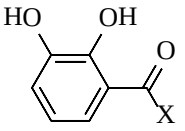
Molybdenum complexes composed of cyclodextrin derived ligands **[131]** and **[132]** were used to oxidize aryl alkyl sulfides, with hydrogen peroxide as oxidant. Modest enantioselectivities were obtained (35–65% ee) (126).

Bonchio *et al.* (127) used a molybdenum complex composed of a cyclodextrin derived ligand **[133]** in the oxidation of thioanisole **[16]**, affording sulfoxide **[17]** in excellent yield (98%) and moderate enantioselectivity (60% ee). A biphasic solvent system (water-DCE) was employed to overcome racemic oxidation by $MoO(O_2)_2$ which is also present in the reaction mixture.

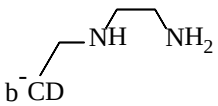


131

X = mono-6-O-b-CD



132



133

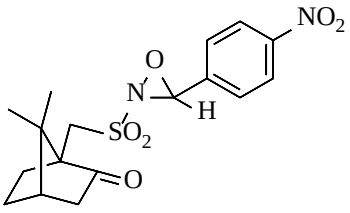
3. Non-metal based systems in asymmetric sulfoxidation

3.1 Chiral oxaziridines

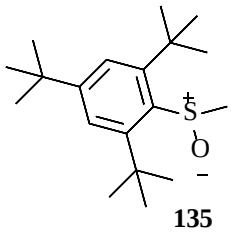
In 1979, Davis *et al.* (128) reported the use of chiral oxaziridine **[134]** in asymmetric sulfoxidation. Although enantioselectivities were very low (~ 14% ee), this represented the

first time an oxaziridine had been used in the preparation of enantioenriched sulfoxides. Davis's study indicated that the relationship between the electrophilic oxygen and the chiral centre of the reagent, and the restricted geometry of the oxidizing agent, were important in obtaining higher enantioselectivities.

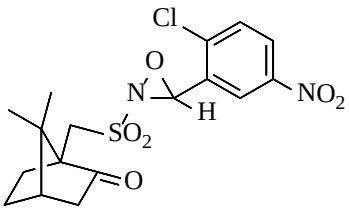
Davis (129) extended the scope of this methodology to include disulfides and thiosulfinates. Sulfoxide **[135]** was prepared in moderate enantioselectivity (46% ee) using oxaziridine **[136]**. This study indicated that factors controlling the absolute configuration of the product and the extent of asymmetric induction were largely steric in nature.



134

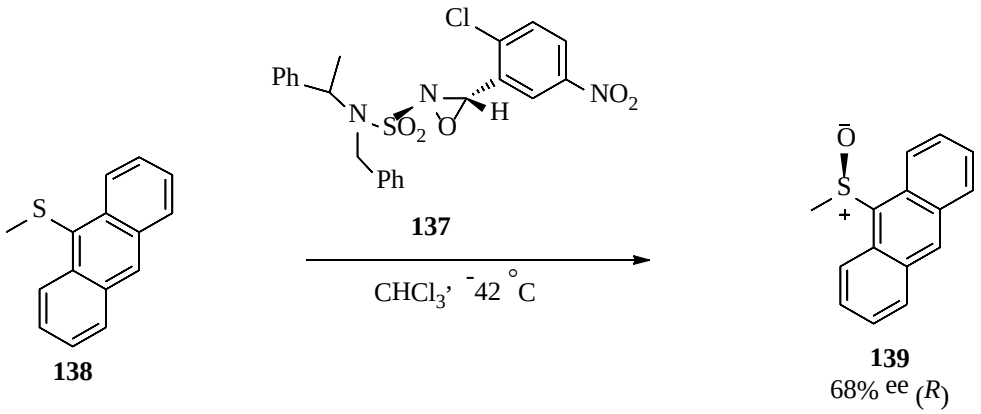


135



136

In 1984, Davis (130) reported the use of chiral sulfamyloxaziridines in asymmetric sulfoxidation. Oxaziridine **[137]** was used to oxidize sulfide **[138]**, affording sulfoxide **[139]** in moderate enantioselectivity (68% ee) as shown in **Scheme 28**.



138

139
68% ^{ee} (*R*)

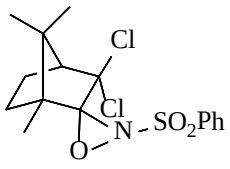
Scheme 28 Asymmetric Sulfoxidation promoted by a Chiral Oxaziridine

Davis speculated that the increased enantioselectivity obtained using 2-sulfonyl and 2-sulfamylozaziridines, compared with peracids or hydroperoxides, was due to the closer proximity of the oxaziridine substituents to the active site.

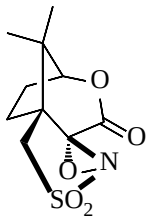
In 1989, Davis (131) reported dramatic improvements in enantioselectivities using dichlorocamphorylsulfonyloxaziridine **[140]**. Methyl *p*-tolyl sulfoxide **[6]** was obtained in

excellent yield (95%) and enantioselectivity (95% ee) using **[140]**. The uniformily high enantioselectivities obatained for a variety of sulfides indicated that factors, other than steric, were important using this system.

Meladinis *et al.* (132) used a similar camphor-based ozaziridine **[141]** to oxidize thioanisole **[16]**, producing sulfoxide **[17]** in good yield (85%) and enantioselectivity (79% ee).

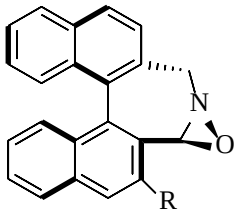


140



141

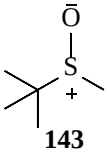
Binaphthyl-derived oxaziridines, such as **[142]**, have been used to oxidize both dialkyl and diaryl sulfides, affording sulfoxides in good yields (up to 86%) and modest to good enantiopurities (20% to 80% ee) (133). The configuration of the resulting sulfoxide was dependant on the sulfide used.



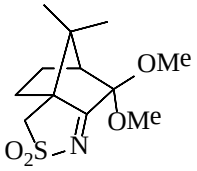
R = H or Ph

142

In 1994, Page *et al.* (134) reported the use of an oxidizing agent, generated *in situ*, to promote asymmetric sulfoxidation. *tert*-Butyl methyl sulfoxide **[143]** was generated in good yield (83%) and moderate enantiopurity (42% ee) using this system. The use of imine **[144]** afforded sulfoxide **[143]** with improved yield (quantitative) and enantioselectivity (86% ee) (135). A major advantage of this system comes from the simplicity by which **[144]** can be prepared in enantiopure form.

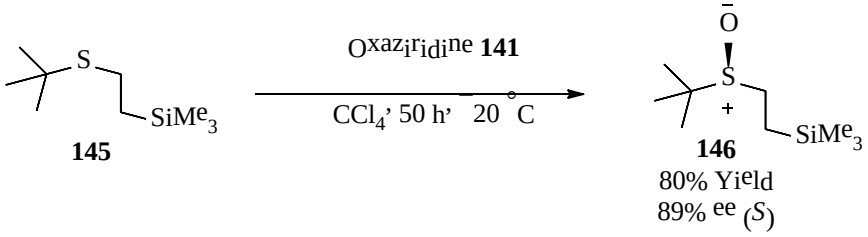


143



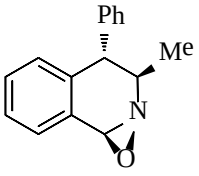
144

Schwan and Pippert (136) asymmetrically oxidized a number of aryl and alkyl 2-(trimethylsilyl)ethyl sulfides to their corresponding sulfoxides using chiral oxaziridine **[140]**. This system gave superior results to other established asymmetric oxidation methods available at the time. The oxidation of sulfide **[145]** afforded sulfoxide **[146]** in good yield (80%) and excellent enantioselectivity (89% ee) as shown in **Scheme 29**. A steric effect was evident, with sterically bulky sulfides affording sulfoxides with higher enantiopurities.



Scheme 29 Asymmetric Sulfoxidation of Sterically Bulky Sulfides using a Chiral Oxaziridine

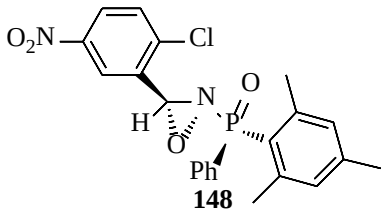
In 1999, Bohé *et al.* (137) used methanesulfonic acid (MSA) and an oxaziridine derived from **[147]** to asymmetrically oxidize thioanisole **[16]**; however, moderate yields (up to 64%) and poor enantioselectivities (up to 44% ee) were obtained.



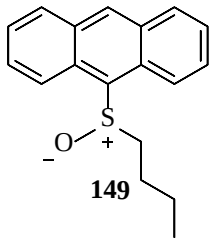
147

Jennings *et al*. (138) used optically active *N*-phosphinoyloxaziridines **[148]** to promote asymmetric sulfide oxidation. 9-Anthryl *n*-butyl sulfoxide **[149]** was obtained in good enantiopurity (70% ee) using this system. Jennings reported that the configuration at phosphorus had little influence on the asymmetric induction.

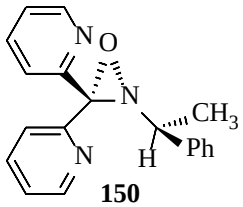
In 2005, Schoumacker *et al.* (139) reported the synthesis of new chiral *N*-alkyloxaziridines, such as **[150]**, for asymmetric sulfoxidation. Although these oxaziridines were initially inert towards oxidation, they can be activated by Lewis acids such as zinc chloride. Overall, results were modest with enantioselectivities ranging from 22 to 63% ee.



148



149

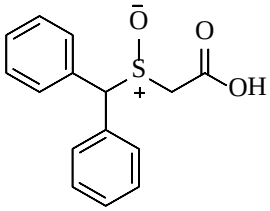


150

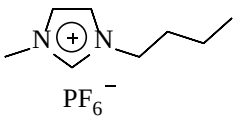
3.11 Synthesis of biologically active sulfoxides using chiral oxaziridines

Chiral oxaziridine **[140]** was used by Von Unge *et al.* (50) in the asymmetric oxidation of omeprazole sulfide **[36]**, affording esomeprazole **[1]** in poor enantioselectivity (40% ee), which was improved by recrystallization (94% ee). Despite the high enantioselectivities obtained, Von Unge focussed instead on a titanium-mediated process for the synthesis of **[1]** as this metal-catalyzed procedure had greater potential to be used in production scale.

Ternois *et al.* (93) reported the asymmetric synthesis of modafinil and its derivatives. The use of chiral oxaziridine **[140]** gave superior results to a number of metal-catalyzed systems both in terms of yield and enantioselectivity. (*S*)-Modafinil **[48]** and (*S*)-modafinic acid **[151]** were obtained in moderate yields and moderate to good enantioselectivities (66% and 60% ee for **[48]**, 47% and 90% ee for **[151]**). The replacement of CCl_4 as solvent with ionic liquid **[152]**, resulted in improved yields but a reduction in enantioselectivities (73% and 55% ee for **[48]**, 73% and 78% ee for **[151]**).

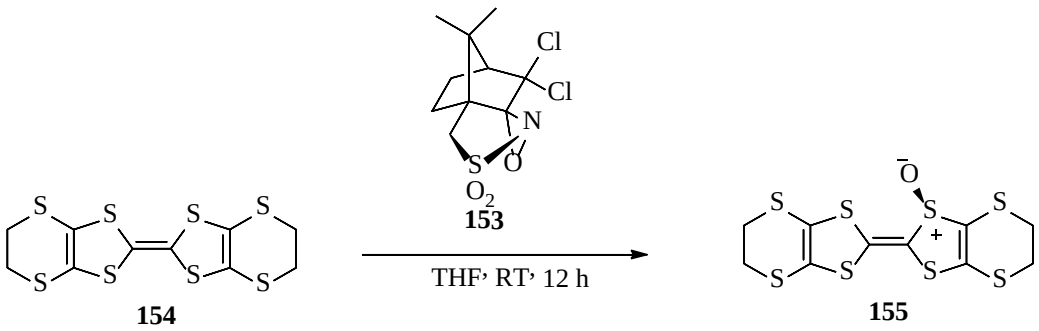


151



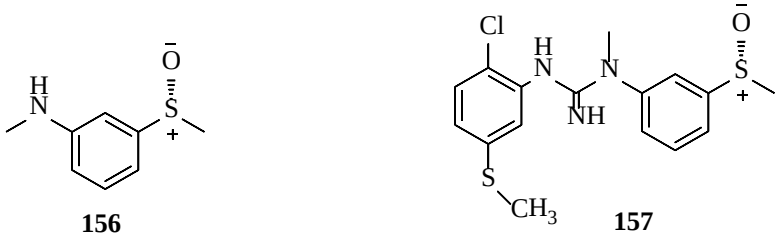
152

Avarvari *et al.* (140) reported the use of chiral oxaziridine **[153]** for the asymmetric oxidation of sulfide **[154]**, a precursor in the synthesis of organic conductors. The inner monosulfoxide **[155]** was isolated in poor enantioselectivity (44% ee) as shown in **Scheme 30**, which was subsequently improved by recrystallization (74% ee). A direct relationship was observed between the steric bulk of sulfide substrates and the enantioselectivity of the oxidation, with less sterically hindered sulfides oxidized with negligible enantioselectivity.



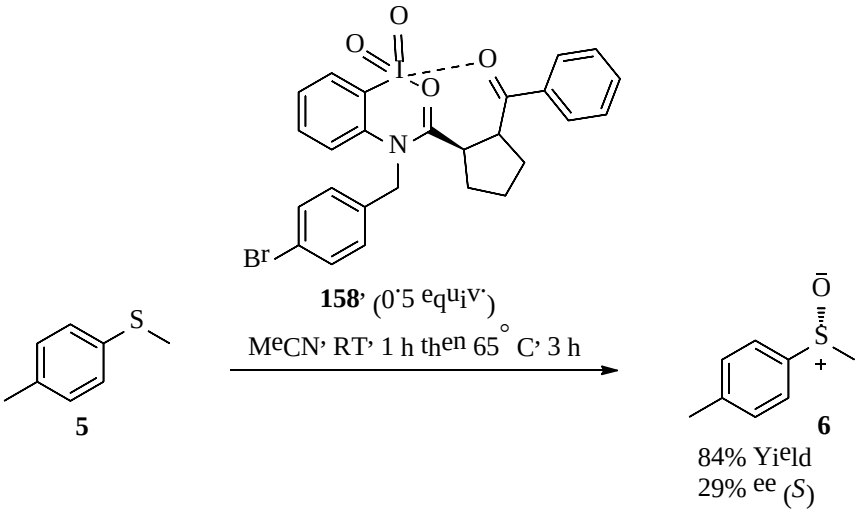
Scheme 30 Synthesis of a Biologically Active Sulfoxide using a Chiral Oxaziridine

Padmanabhan *et al.* (141) used oxaziridine **[153]** to prepare sulfoxide **[156]** in excellent yield (95%) and good enantioselectivity (75% ee). Sulfoxide **[156]** is a precursor to CNS 5788 **[157]**, a neuroprotective agent.



3.2 Iodine complexes

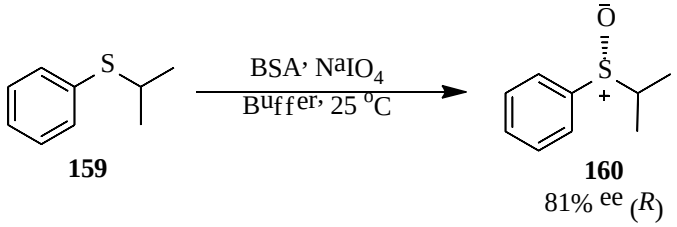
In 2006, Zhdankin *et al.* (142) used an iodine complex **[158]**, derived from (*S*)-proline, to catalyze the oxidation of methyl *p*-tolyl sulfide **[5]**. Sulfoxide **[6]** was generated in good yield but poor enantioselectivity as shown in **Scheme 31**.



Scheme 31 Asymmetric Sulfoxidation promoted by an Iron Complex

3.3 Bovine serum albumin

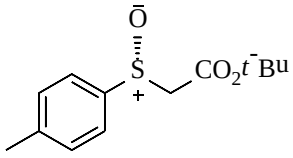
Sugimoto *et al.* (143) reported the asymmetric oxidation of a large number of aromatic sulfides in the presence of bovine serum albumin (BSA), with sodium metaperiodate as oxidant. Although yields and enantioselectivities were generally modest, the oxidation of sulfide **[159]** to produce sulfoxide **[160]** proceeded with good efficiency as shown in **Scheme 32**.



159 **160**
81% ee (*R*)

Scheme 32 Asymmetric Sulfoxidation using BSA

Ogura *et al.* (144) carried out the asymmetric oxidation of dithioacetals in the presence of BSA, reporting modest enantioselectivities (up to 60% ee). Colonna *et al.* (145) carried out a similar oxidation to obtain sulfoxide **[161]** in 69% ee.

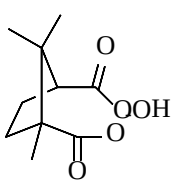


161

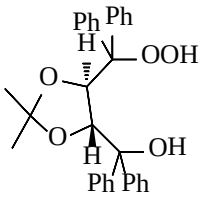
3.4 Chiral hydroperoxides and peracids

Peracids have been known to promote asymmetric sulfoxidation since the 1960s (146). Although subsequent publications have reported the use of peracids, such as **[162]**, the enantioselectivities achieved have been poor (less than 10% ee) (147).

Superior results have been achieved using chiral hydroperoxides. Aoki and Seebach (148) used hydroperoxide **[163]** to promote asymmetric sulfoxidation. Sulfoxide **[17]** was obtained in good yield (73%) and enantioselectivity (86% ee) using this method.



162

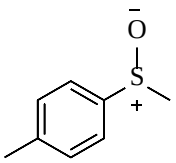


163

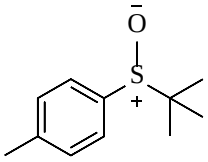
4. Enzyme-catalyzed asymmetric sulfoxidation

4.1 Whole cell systems

The use of whole cell systems to catalyze asymmetric sulfoxidation has been known for many decades. In 1962, Dodson *et al.* (149) reported the oxidation of benzyl phenyl sulfide **[13]** using *Aspergillus niger*, affording sulfoxide **[14]** in modest enantiopurity (18% ee). In a later report, Boyd *et al.* (150) described the oxidation of a range of alkyl and aryl benzyl sulfides using *Aspergillus niger*. The enantioselectivity of the oxidation was largely substrate specific, with sterically bulky sulfides affording sulfoxides, such as **[164]**, with higher enantiopurities.



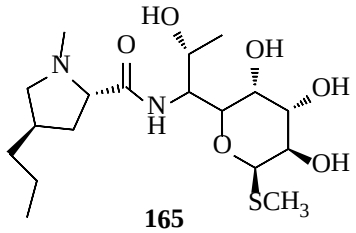
6, 32% ee



164, 99% ee

Holland and co-workers (151-158) have reported the asymmetric oxidation of a large number of sulfides by the fungus *Helminthosporium* species NRRL 4671. Excellent enantioselectivities were obtained in certain cases (>96% ee, after recrystallization). Holland (158) also employed the fungus *Mortierella isabellina* for asymmetric sulfoxidation, reporting modest to good enantiopurities. Interestingly, the use of *Helminthosporium* species NRRL 4671 produced (*S*)-sulfoxides, while *Mortierella isabellina* favoured the production of the (*R*)-enantiomer.

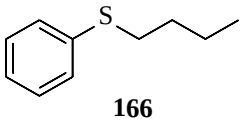
There have been numerous reports of the use of bacterial cells to promote asymmetric sulfide oxidation. In 1969, Argoudelis *et al.* (159) reported the transformation of lincomycin **[165]** to the corresponding sulfoxide by *Streptomyces lincolnensis*.



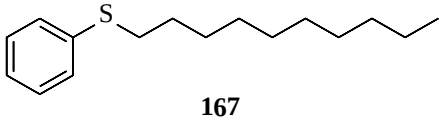
165

Ohta *et al.* (160-162) also synthesized chiral sulfoxides via microbial oxidation of sulfides. Incubation of a range of aryl alkyl sulfides with growing cells of *Corynebacterium equi* IFO 3730 afforded sulfoxides with excellent enantioselectivities (up to 100% ee). The length of the alkyl chain in the sulfide had a strong influence on the efficiency of the oxidation. While

the oxidation of aryl methyl sulfides gave sulfoxides exclusively, a significant amount of sulfone accompanied the oxidation of sulfides bearing a long alkyl chain (sulfides **[166]** and **[167]**).



166



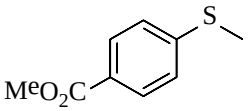
167

Ethene-grown *Micrococcus sp.* M90C was used to catalyze the asymmetric oxidation of thioanisole **[16]**, producing sulfoxide **[17]** in excellent enantioselectivity (> 90% ee) (163).

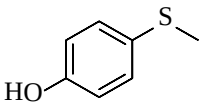
A range of aryl alkyl sulfides was oxidized by the topsoil bacterium *Pseudomonas frederiksbergensis* (164). Excellent conversions (100%) and enantioselectivities (> 99% ee) were obtained. Sulfides bearing a long alkyl chain were oxidized with a reduction in both yield and enantioselectivity.

Brackenridge *et al.* (165) reported the asymmetric oxidation of methyl *p*-tolyl sulfide **[5]**, using bakers yeast (*Saccharomyces cerevisiae* NCYC73). Sulfoxide (*R*)-**[6]** was prepared in enantiopure form in a 60% yield.

Kayser *et al.* (166) also reported the use of engineered yeast in the oxidation of aryl alkyl sulfides. Sulfoxide **[17]** was prepared in excellent yield (95%) and enantioselectivity (99% ee). Interestingly, sulfides bearing a *para* substituent on the phenyl ring, such as **[168]** and **[169]**, were converted to sulfoxides with high enantiopurities (96% ee for **[168]**, 98% ee for **[169]**), albeit with a reduction in yield (45% for **[168]**, 33% ee for **[169]**).

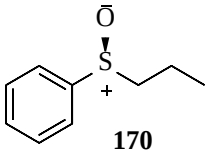


168



169

White-rot basidomycetes promote the asymmetric oxidation of sulfides into sulfoxides with good enantiopurities and conversions, although minor sulfone production is also observed (159). (*S*)-n-propylphenyl sulfoxide **[170]** was obtained in enantiopure form using six different forms of Basidomycetes (167).



170

Filamentous fungi *Botrytis Cinerea*, *Eutypa lata* and *Trichoderma Viride* have been used in the asymmetric oxidation of sulfides, affording sulfoxides with modest to good enantiopurities (168). Oxidations using *T. viride* and *E. lata* gave the (*R*)-sulfoxide, while the use of *B. cinerea* favoured the formation of the (*S*)-enantiomer.

Whole cells of the microalga *Chlorella sorokiniana* were used in the oxidation of a large number of sulfides. Overall, modest yields (up to 67%) and enantioselectivities (up to 58% ee) were obtained (169). The structure of the sulfide had a strong influence on the efficiency of the oxidation, with aryl alkyl sulfoxides generally produced in higher yields and enantioselectivities than benzyl alkyl sulfoxides.

4.2 Isolated Enzymes

There have been numerous reports of the use of a chloroperoxidase (CPO) enzyme in the asymmetric oxidation of sulfides. These methods generally differ by the method in which the oxidant is generated. Colonna *et al.* (170) used CPO from the marine fungus *Caldariomyces fumago*, with hydrogen peroxide as oxidant, to catalyze asymmetric sulfoxidation. Sulfoxides were produced in good yields and enantiopurities (up to 99% ee).

Lutz *et al.* (171) reported the first asymmetric electroenzymatic oxidation catalyzed by a CPO enzyme. Hydrogen peroxide is generated *in situ* by cathodic reduction of oxygen. Overall, excellent enantioselectivities were obtained for the oxidation of thioanisole **[16]** (> 98.5% ee).

Leitner *et al.* (172) also reported a CPO-catalyzed oxidation of thioanisole **[16]**, affording sulfoxide **[17]** in poor yield (34%) and excellent enantioselectivity (94% ee). The oxidant, hydrogen peroxide, was generated *in situ* directly from hydrogen and oxygen using palladium catalysis in supercritical carbon dioxide (sc. CO_2). Hydrogen peroxide was then used by the CPO enzyme to oxidize thioanisole **[16]** in the aqueous phase as shown in **Figure 4**.

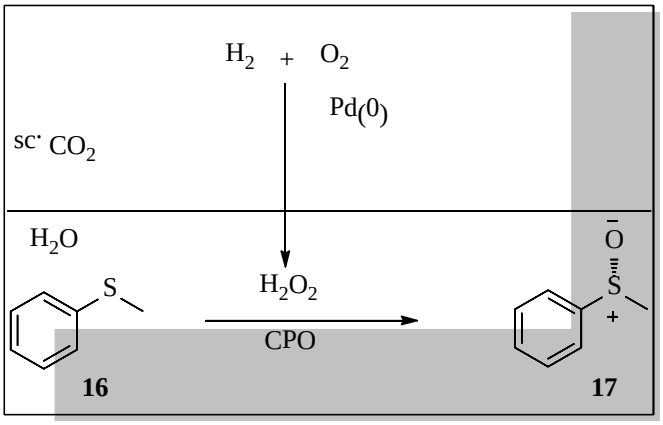
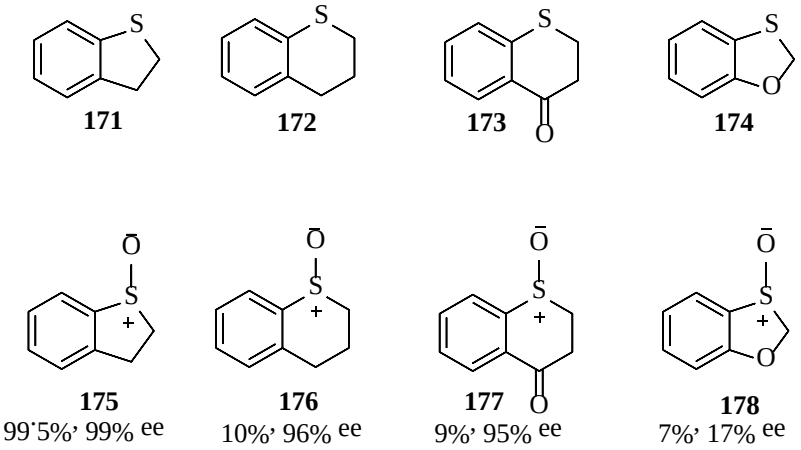


Figure 4 Asymmetric Electroenzymatic Sulfoxidation

Sulfoxide **[17]** was afforded in quantitative yield and excellent enantioselectivity (99% ee) in a procedure described by Arends *et al* (173). In this case, hydrogen peroxide was generated by light, using flavins as photocatalysts and ethylendiaminetetraacetic acid (EDTA) as an electron donor. Unfortunately, the oxidation was accompanied by waste product from EDTA such as formaldehyde and ethylenediamine. Replacement of EDTA with formate resulted in reduced enantiopurities.

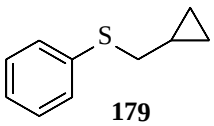
Allenmark and Andersson (174) carried out asymmetric sulfoxidation using a CPO from *Caldariomyces fumago* and hydrogen peroxide as oxidant. The oxidation of 2,3-dihydrobenzothiophene **[171]** proceeded with excellent yield (99.5%) and enantioselectivity (99% ee). The introduction of increased steric bulk (sulfides **[172]** and **[173]**) or a heteroatom (sulfide **[174]**) to the sulfide resulted in a reduction in yield or a reduction in both yield and enantioselectivity relative to sulfoxide **[175]**. Further studies indicated that sulfides **[172]** and **[173]** were too sterically demanding to compete for the active site of the enzyme, while sulfide **[174]** acted as a competitive inhibitor of the enzyme. As a result, sulfoxides **[175-178]** were obtained in poor yield as shown in **Scheme 33**.



Scheme 33 Asymmetric Sulfoxidation using a CPO Enzyme

In 1995, Ottolina *et al.* (175) reported the preparation of enantioenriched sulfoxides by asymmetric oxidation, catalyzed by cyclohexanone monooxygenase (CHMO) from *Acinetobacter NCIB 9871*. This system afforded a range of aryl alkyl sulfoxides in excellent yields and enantioselectivities. Ottolina established an active site model to explain and predict the stereoselectivity of the oxidation.

Ozaki and de Montellano (176,177) reported an efficient horseradish peroxidase (HRP)-catalyzed asymmetric sulfoxidation. Interestingly, the replacement of *phenylalanine-41* with *leucine* increases both the rate and the enantioselectivity of the oxidation. The greatest improvement, using this modified enzyme, was observed for cyclopropylmethyl phenyl sulfide **[179]**, which is oxidized ten times faster and with an increase in enantioselectivity from 7 to 94% ee. Replacement of *phenylalanine-41* with *threonine* resulted in an improvement in rate but a reduction in enantioselectivity for the oxidation of thioanisole **[16]** and *para*-chlorothioanisole **[32]**. The results indicated that *phenylalanine-41* is a major determinant of peroxygenase substrate binding in the HRP active site.



Wever *et al.* (178) reported the asymmetric oxidation of **[16]** using both lactoperoxidase (LPO) and *Coprinus cinereus* peroxidase (CiP), affording sulfoxide **[17]** in good yields (85%

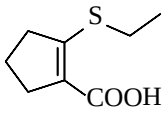
for LPO and 84% for CiP) and enantioselectivities (80% ee for LPO and 73% ee for CiP). Interestingly, the use of LPO afforded (*R*)-**[17]** while CiP yielded the (*S*)-enantiomer. Wever *et al.* (179) reported the use of vanadium haloperoxidases in asymmetric sulfoxidation. The vanadium bromoperoxidase from the brown seaweed *Ascphyllum nodosum* afforded (*R*)-**[17]** in modest yield (55%) and good enantioselectivity (85% ee). The optimum pH range for this enzyme was pH 5–6. Interestingly, the vanadium bromoperoxidase from the red seaweed *Corallina pilulifera* afforded sulfoxide (*S*)-**[17]** in poor yield (18%) and modest enantioselectivity (55% ee), while use of the vanadium chloroperoxidase from the fungus *Curvularia inaequalis* catalyzes the formation of racemic **[17]** in a 54% yield. Wever (180) also used Myeloperoxidase (MPO) to catalyze sulfide oxidation; however, only modest enantiopurities were obtained (up to 32% ee).

Boyd *et al.* (181) reported the asymmetric oxidation of a series of aryl alkyl sulfides, using selected strains of the soil bacterium *Pseudomonas putida*, containing either toluene dioxygenase (TDO) or naphthalene dioxygenase (NDO). Enantioselectivities were excellent in most cases (up to >98% ee) although the yields varied significantly. Interestingly, the TDO-catalyzed oxidation favoured the (*R*)-enantiomer while use of NDO favoured the (*S*)-enantiomer. Gibson *et al.* (182) reported similar results for the oxidation of unsubstituted aryl alkyl sulfides. However, the presence of substituents at the *para* position, resulted in a reduction in both yield and enantioselectivity (sulfides **[25]** and **[105]**).

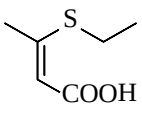
4-Hydroxyacetophenone monooxygenase (HAMPO) from *Pseudomonas fluorescens* ACB has been used to catalyze the oxidation of a range of phenyl and benzyl alkyl sulfides (183). Excellent conversions (up to 96%) and enantioselectivities (up to 99% ee) were achieved for the majority of the phenyl alkyl sulfoxides. However, the oxidation of the benzyl alkyl sulfides proceeded with a reduction in both conversion and enantioselectivity. This was in contrast to the use of phenylacetone monooxygenase (PAMO) which afforded benzyl alkyl sulfoxides with higher enantiopurities than the corresponding phenyl analogues (184). The absolute configuration of the products was strongly dependent on the size of the alkyl group, using HAMPO, with the (*S*)-enantiomer predominating in the case of small alkyl substituents, wheras a bulkyl alkyl chain resulted in preferential formation of the (*R*)-enantiomer.

Allenmark and Andersson (185) used vanadium bromoperoxidase from *Corallina officinalis* in asymmetric sulfide oxidation, with hydrogen peroxide as oxidant. This study indicated that sulfides bearing a *cis*-substituted carboxyl group such as **[180]** and **[181]** are oxidized rapidly

producing sulfoxides in excellent enantioselectivities (>95% ee). Interestingly, a rapid loss of stereoselectivity was observed when the oxidation was carried out in the presence of bromide ions.

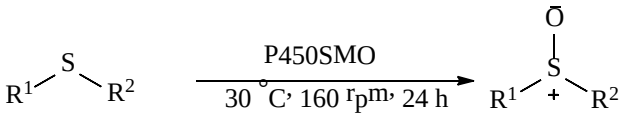


180



181

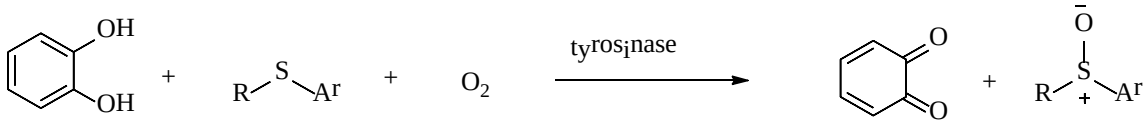
Zhang *et al.* (186) used a cytochrome P450 monooxygenase in asymmetric sulfoxidation, producing sulfoxides **[17]** and **[182]** in excellent enantioiselectivities as shown in **Scheme 34**.



Sulfoxides		Conv. (%)	ee (%)
17 R_1 = C_6H_5	R_2 = Me	32	99 (*S*)
182 R_1 = *p*-Cl-C_6H_5	R_2 = Et	89	99 (*S*)

Scheme 34 Asymmetric Sulfoxidation using a Cytochrome P450 Monooxygenase Enzyme

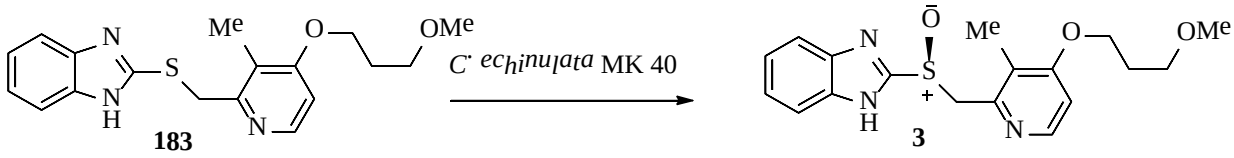
Casella *et al.* (187) reported the asymmetric oxidation of sulfides using mushroom tyrosinase in the presence of catechol as co-substrate as shown in **Scheme 35**. Catechol competes with the sulfide in the reaction which limits the efficiency of the process (yields of ~ 20%). Casella demonstrated that the mechanism of the sulfoxidation involves oxygen transfer from oxy-tyrosinase to the sulfide.



Scheme 35 Asymmetric Sulfoxidation using a Tyrosinase Enzyme

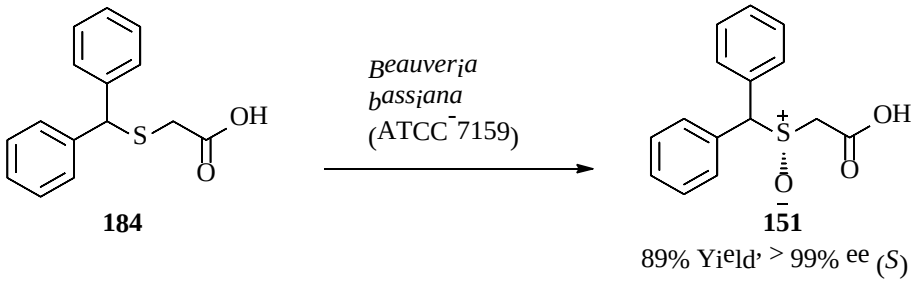
4.3 Synthesis of biologically active sulfoxides using biological oxidations

A large number of microorganisms (~650) were tested for their potentiality to convert rabeprazole sulfide **[183]** to the corresponding sulfoxide **[3]** (188). A newly isolated strain of mold, *Cunninghamella echinulata* MK 40, gave the best result with **[3]** produced in enantiopure form (*S*) and in a 92% conversion (**Scheme 36**). Omeprazole and Lansoprazole were also prepared by this method, although the conversions were significantly lower.



Scheme 36 Synthesis of Rabeprazole using a Microorganism

Olivo *et al.* (189) reported the asymmetric synthesis of sulfoxide **[151]** from benzhydralsulfanyl acetic acid **[184]** using the fungus *Beauveria bassiana*. Excellent yield (89%) and enantioselectivity (99% ee) were obtained as shown in **Scheme 37**. Sulfoxide **[151]** was then converted to modafinil **[48]**.



Scheme 37 Asymmetric Synthesis of Modafinil using a Fungus

Hamman *et al*. (190) reported the use of flavin-dependent monooxygenase 3 (FMO3) to prepare enantioenriched sulindac **[47]** from the corresponding sulfide in 90% ee (*R*).

5. Conclusion

In conclusion, substantial progress has been made over the past two decades in asymmetric sulfide oxidation using metal catalysts, enzymatic oxidation and non-metal based systems. However, substrate scope remains limited with best results for aryl methyl sulfides.

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