1
Asymmetric Synthesis of Chiral Sulfoxides

Henri B. Kagan

Abstract

Enantiopure sulfoxides are important auxiliaries in asymmetric synthesis, and some also have useful biological properties. In this chapter, the various routes to chiral sulfoxides are described, when these are based on asymmetric synthesis. Details are provided of the preparation and use of chiral precursors of sulfoxides such as sulfinates or sulfinamides. The enantioselective catalytic oxidation of sulfides is then discussed, with particular attention being paid to the various metal complexes which have been used. Finally, the stoichiometric oxidation of sulfides by chiral oxaziridines or other chiral organic oxidants is described.

1.1
Chiral Sulfoxides

1.1.1
Introduction

The first example of an optically active sulfoxide was described in 1926 [1]. This discovery was helpful for discussions regarding the nature of the S–O bond and the non-planarity of sulfur. Later, chiral sulfoxides slowly emerged as a class of compounds of interest in asymmetric synthesis (for reviews, see Refs. [2–7]). Enantiopure sulfoxides also became important in the pharmaceutical industry, due mainly to their biological properties. As a result, many types of pharmaceutical agents became of special interest, most notably one class of anti-ulcer drugs. Methods for the efficient preparation of chiral sulfoxides are also of particular interest [8]. Hence, this chapter will focus on approaches based on the asymmetric synthesis of chiral sulfoxides in a broad sense, where a chiral auxiliary is used in either a stoichiometric or catalytic manner and, preferentially, is also reusable.

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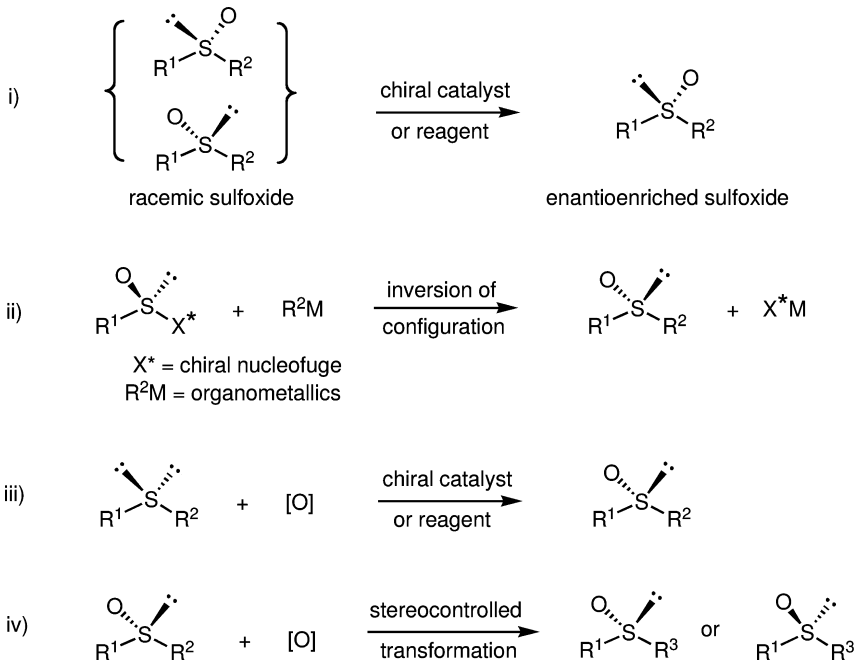
1.1.2
The Main Routes to Chiral Sulfoxides

The main routes to chiral sulfoxides are depicted in Scheme 1.1. The resolution of a racemic mixture (route i) was the first method used to produce chiral sulfoxides, by either a chemical approach or an enzymatic reaction. Since the 1960s, the transformation of a diastereochemically pure sulfinate has been a very useful method by which to obtain sulfoxides with high enantiomeric excess (*ee*) values (route ii). The enantioselective oxidation of prochiral sulfides by enzymatic or non-enzymatic methods represents a relatively direct way (route iii) to prepare enantioenriched sulfoxides. Another preparative method (route iv) is to modify the structure of some chiral sulfoxides without any loss of stereochemistry at the sulfur atom.

In this chapter, attention will be focused on *non-enzymatic asymmetric syntheses of sulfoxides*, excluding the resolution processes. Two classes of reactions will be subsequently presented – the stoichiometric asymmetric syntheses, and the catalytic asymmetric syntheses.

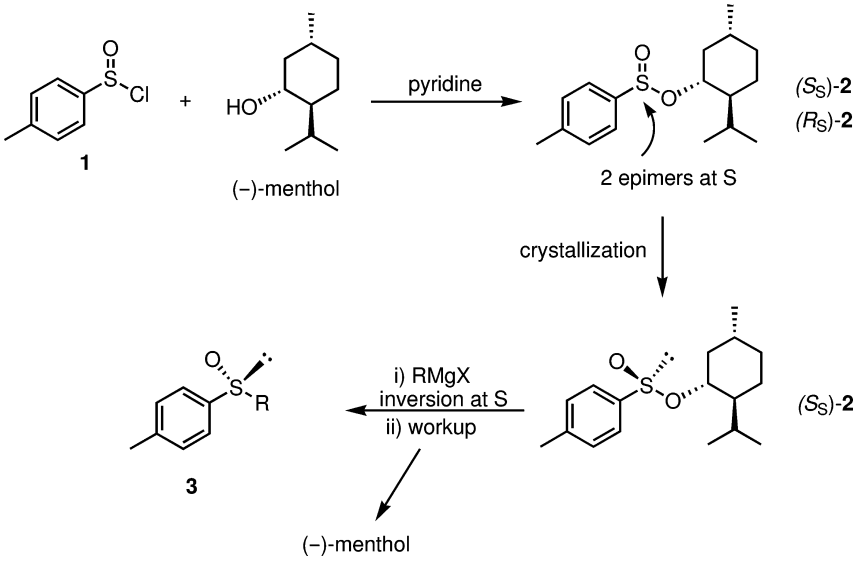


Scheme 1.1 The main routes to chiral sulfoxides.

1.2
Use of Chiral Sulfur Precursors

1.2.1
Sulfinates (Andersen Method)

Chiral sulfinates are excellent precursors of chiral sulfoxides, and this approach was pioneered by Andersen in 1962, using one diastereomer of menthyl *p*-tolylsulfinate prepared from (−)-menthol [9, 10]. The reaction was of preparative interest, and provided sulfoxides of very high *ee*-values. The inversion of configuration for the substitution reaction was firmly established [11, 12]. The now so-called *Andersen method* is illustrated schematically in Scheme 1.2 for the synthesis of the *p*-tolyl sulfoxides **2**. Here, there are two important issues: (1) the need to prepare the menthyl *p*-tolylsulfinates **1** from (−)-menthol; and (2) to separate the two epimers at sulfur. The *p*-tolylsulfinyl chloride (**1**) was prepared *in situ* by the reduction of *p*-tolylsulfonyl chloride according to a known procedure [13]. Subsequent separation of the two epimers could be achieved by crystallization, as (S_S)-**2** is crystalline and (R_S)-**2** is oily. Very soon, the Andersen method became the preferred approach when preparing enantiopure sulfoxides of known absolute configuration. The large majority of examples used as the starting material sulfinate (S_S)-**2** due to the ease of its preparation. An important improvement (giving 90% yield) of the preparation of (−)-menthyl *p*-tolylsulfinate [(S_S)-**2**] was introduced by Mioskowski and Solladié in 1980 [14]. These authors combined the crystallization step in acetone with an *in-situ* epimerization by a catalytic amount



Scheme 1.2 The Andersen method for the preparation of chiral sulfoxides.

of HCl. A modification of the preparation of sulfinates was proposed in 1987 by Sharpless et al. [15], based on the use of arylsulfonyl chlorides which are reduced *in situ* by trimethyl phosphite in the presence of triethylamine. In this way pure (−)-menthyl *p*-toluenesulfinate was prepared at the 0.2 mole scale, with 66% yield.

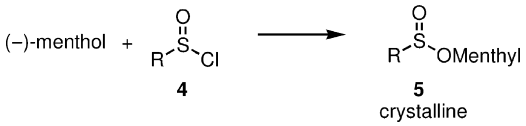
A wide range of sulfoxides **3** has been described in the literature (see Section 1.2.2) and subsequently used as synthetically useful chiral reagents. The reason for this is the ease of preparation of diastereochemically pure menthyl (S_S)-*p*-toluenesulfinate **2**, which is crystalline. Some other crystalline menthyl arylsulfinates have been synthesized for their use in the Andersen method; some examples are listed in Table 1.1.

Menthyl alkylsulfinates (**4**, R = alkyl), generally produce an oily material and are not suitable for the Andersen method. Alternatively, menthol may be replaced with another chiral and available alcohol; for example, cholesterol and methanesulfinyl chloride produce cholesteryl methanesulfinate epimers which may be separated by crystallization with moderate yields [19]. Many methyl alkyl sulfoxides (100% ee) could then be synthesized from these compounds by the addition of an appropriate Grignard reagent.

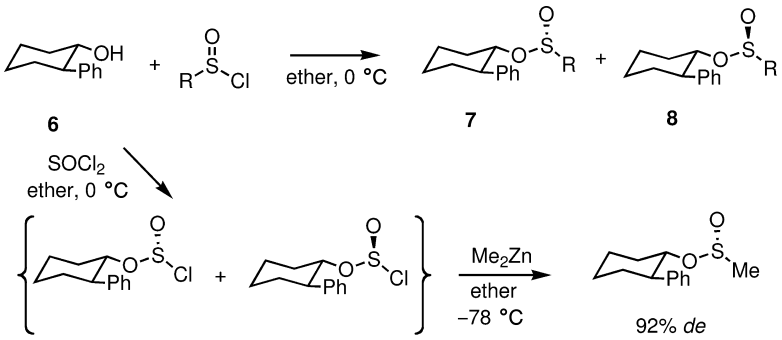
In order to avoid the separation of diastereomeric sulfinates, the best solution is to directly produce one preponderant diastereomer in the esterification step (**4** and chiral alcohol) (Scheme 1.3). Some kinetic diastereoselectivity (up to 10 : 1) has been observed by Whitesell and colleagues in sulfinate formation (**7** and **8**) from 2-phenylcyclohexanol **6** (Scheme 1.3) [20a,b]. One improvement in the synthesis of sulfinates was the intermediate formation of chlorosulfite esters by the action of thionyl chloride on *trans*-phenylcyclohexanol **6** (Scheme 1.3) [20b].

The mixture of diastereomeric chlorosulfites was then treated with various dialkylzincs over a range of conditions, and as a consequence sulfinate ester **7** was obtained with up to 97% yield and 92% diastereomeric excess (*de*). The authors assumed a dynamic kinetic resolution process where the chlorosulfinates were in

Table 1.1 Synthesis of some crystalline menthyl sulfinates.



Entry	R	Reference
1	1-Naphthyl	10
2	1-(2-Naphthyl)	16
3	1-(2-OMe-naphthyl)	17
4	4-Bromophenyl	18



Scheme 1.3 Use of 2-phenylcyclohexanol in the preparation of sulfinates.

rapid equilibrium in respect to the subsequent reaction with dialkylzincs, where one diastereomer reacts faster than the other.

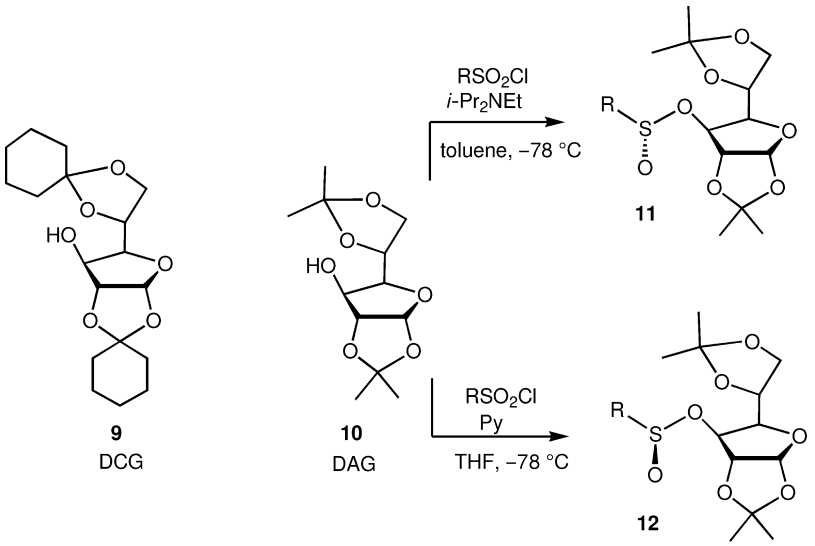
1.2.2
Diastereoselective Formation of Sulfinates

Ridley and Smal prepared various arenesulfinic esters of dicyclohexyl-D-glucofuranose (DCG, **9**) with a modest diastereoselectivity at sulfur (<3 : 1) when the esterification was performed in pyridine–ether at −78 °C [21]. Crystallization led to the formation of one diastereomer, in low yield.

In 1991, Llero, Fernandez and Alcudia made the important discovery that diacetone-D-glucose (DAG, **10**) was converted stereoselectively in 90% yield into either (*S*)- or (*R*)-methanesulfinates from methanesulfinyl chloride, according to the nature of the amine which was taken as base [22]. Moreover, the two sulfinates were crystalline and could easily be purified. This methodology was optimized and extended to various DAG alkyl- or arylsulfinates (Scheme 1.4) [23a]. The isolated yields are excellent in diastereomerically pure sulfinates **11** and **12** (R = Me, Et, *n*-Pr, *p*-Tol), except when R = Cy because of decomposition during the isolation step. The *tert*-butyl sulfinates **11** and **12** were also prepared using the DAG approach, but the initial *de*-values were lower (72% and 84%, respectively) [23b].

The replacement of DAG **10** by other alcohols (menthol, cholesterol, borneol, etc.) surprisingly gave sulfinates with low *de*-values [24].

Metzner et al. used pure sulfinates **11** and **12** (R = Cy) obtained by using the DAG technology [25]. Diastereomerically pure C_2-symmetric bis-sulfinates esters were prepared by Khiar et al. from ethane-1,2-bis-sulfinyl chloride [26]. The *meso*-disulfinate was formed competitively and removed by crystallization. These authors discussed the effect of the base on the stereoselectivity and configuration of sulfinate esters produced using the DAG method, and favored a kinetic resolution mechanism involving the sulfinyl chloride and the base [27].

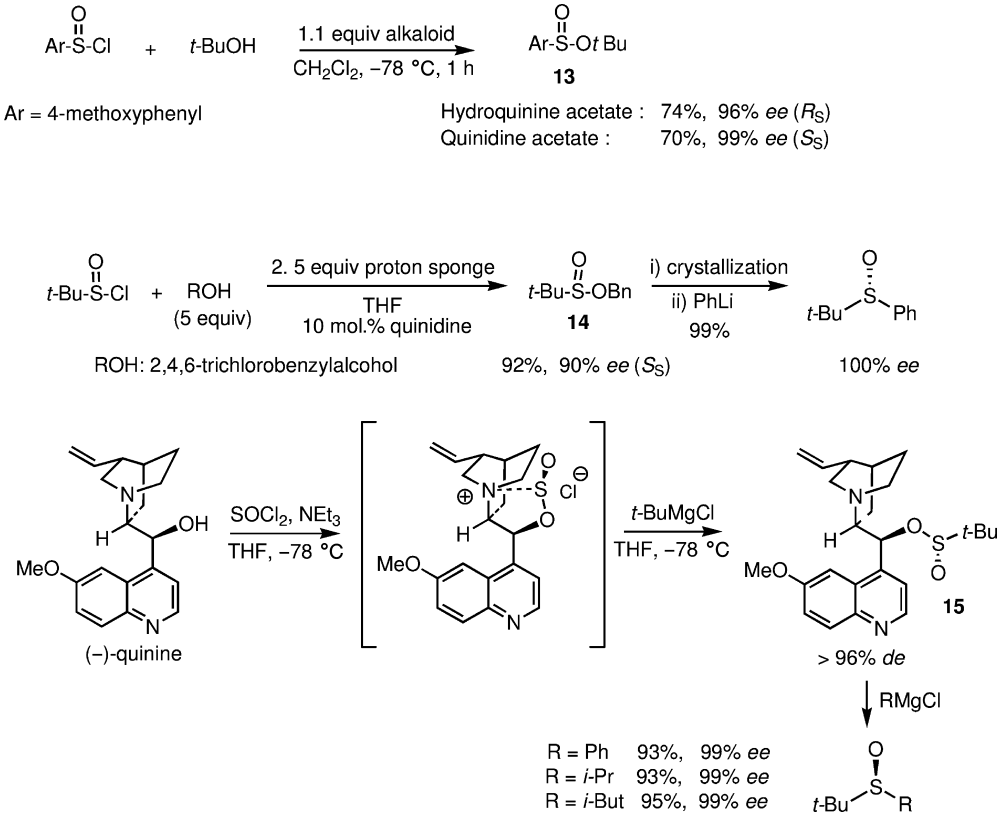


Scheme 1.4 Diastereoselective formation of sugar sulfinates.

Recently, the asymmetric sulfinylation of achiral alcohols has been reported in the presence of stoichiometric or catalytic amounts of chiral tertiary amine. Toru et al. prepared *in situ* a combination of an arylsulfonyl chloride and a cinchona alkaloid (in stoichiometric amounts), acting as a chiral sulfinylating agent [28]. In this way, *tert*-butyl arylsulfinates **13** could be prepared with very high *ee*-values (Scheme 1.5).

Ellman et al. devised a procedure where the cinchona alkaloids were taken as catalysts, in the presence of a proton sponge [29]. Benzyl *tert*-butylsulfinate **14** of 90% *ee* was obtained and its configuration established (after crystallization to upgrade its *ee* to 100%) by its transformation into enantiopure phenyl *tert*-butyl sulfoxide by the action of phenyllithium.

Senanayake et al. described a very general sulfinylating process which allowed the asymmetric synthesis of sulfinates and sulfoxides from a stoichiometric amount of quinine or quinidine [30]. This is exemplified in Scheme 1.5 for the case of quinine. Quinine and thionyl chloride, in the presence of 2 equivalents of triethylamine at −78 °C, afforded a chlorosulfite the structure of which was modified by the formation of a pseudo five-membered ring through interaction with a vicinal tertiary nitrogen (''ate'' complex). The addition of a Grignard reagent (*tert*-butylMgCl) led to the formation of sulfinate **15** in high *de*. The subsequent addition of various alkylmagnesium chlorides generated almost enantiopure *tert*-butyl alkyl sulfoxides The addition of *p*-tolylmagnesium bromide to the ''ate'' complex generated the di-(*p*-tolyl)sulfoxide rather than the expected *p*-tolylsulfinate. Fortunately, *p*-tolylAlEt$_2$ (prepared *in situ* from *p*-tolylMgBr and Et$_2$AlCl) provided the *p*-tolylsulfinate derived from quinine (78% yield, 98% *de*, R_S configuration) which could be transformed into various sulfoxides. For example, MeMgCl gave (*S*)-methyl *p*-tolyl sulfoxide (88% yield, 96% *ee*).

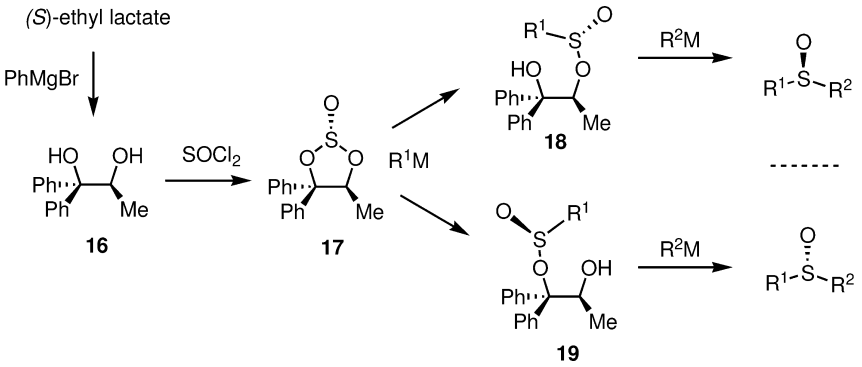


Scheme 1.5 Use of alkaloids in the preparation of sulfinates.

1.2.3
Sulfinates from Sulfites

Dissymmetrical sulfites have a stereogenic sulfur center and two different potential OR leaving groups. A degree of regioselectivity might be expected in the attack by 1 equivalent of an organometallic reagent, and this approach was investigated in 1991 by Kagan et al. (for a description, see Scheme 1.6) [31]. Crystalline cyclic sulfite **17** was prepared in 70% yield from diol **16** which itself was issued from (*S*)-ethyl lactate. The *trans* stereochemistry in sulfite **17** was established using X-ray crystallography. The addition of various Grignard reagents resulted in a clean monosubstitution reaction, with the formation of sulfinates **18**, **19**. The regioselectivity of the reaction was seen to depend on the Grignard reagent used; organometallics, such PhMgBr or BnMgBr did not provide any preferential ring cleavage of the sulfite **17**.

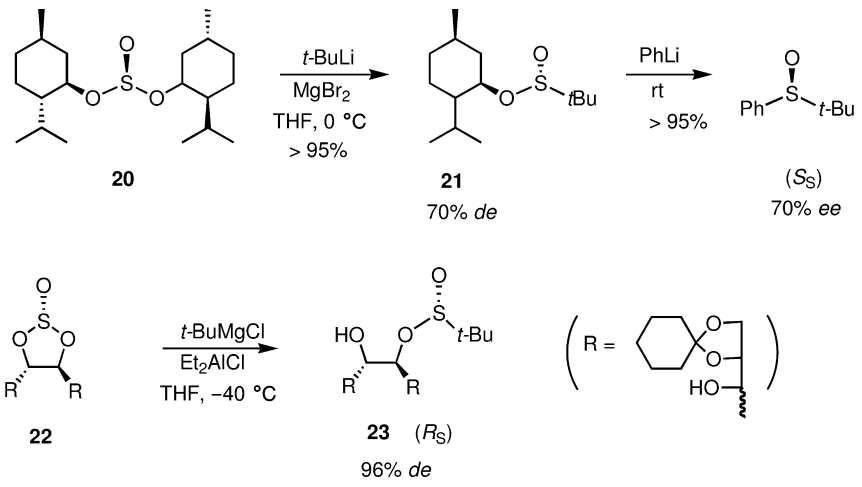
A hindered reagent such as *t*-BuMgBr or MesitylMgBr provided sulfinates (S_S)-**18** (**18**:**19** = 95:5 and 88:12, respectively) which were easily purified by crystallization. MeMgI afforded an excess of **19** (**19**:**18** = 80:20). This approach was



Scheme 1.6 From a chiral sulfite to chiral sulfinates.

useful for preparing *tert*-butylsulfinate **18** ($R^1 = t$-Bu), which in turn gave access to a variety of enantiopure sulfoxides. The stereochemistry of each substitution step was proved to occur with inversion of configuration.

Cyclic sulfites derived from some C_2-symmetric alcohols have been used as precursors of sulfinates. The two oxygen atoms of such sulfites are diastereotopic and should have different reactivities towards an achiral nucleophilic reagent. Kagan et al. established that sulfite **20**, prepared from menthol and $SOCl_2$, allowed production of the menthyl *tert*-butylsulfinate **21** in a monosubstitution process by using the combination t-BuLi : $MgBr_2 = 2:1$ (Scheme 1.7) [31]. The competitive reaction is the disubstitution giving directly the bis-*tert*-butyl sulfoxide (as observed with *t*-BuLi alone). Sulfinate formation could not be achieved with *n*-BuMgBr, which gave the di-*n*-butyl sulfoxide.

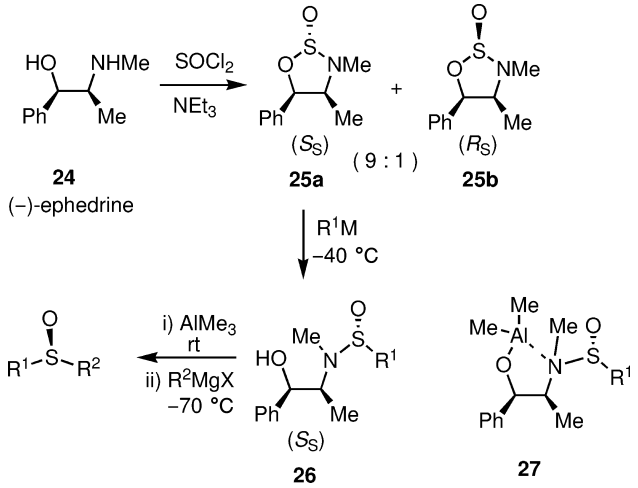


Scheme 1.7 Transformation of C_2-symmetric sulfites into sulfinates.

Vallée et al. found that the cyclic sulfite **22** prepared from mannitol biscyclohexylidene could generate *tert*-butylsulfinates **23** with substantial stereoselectivity when it was attacked by *tert*-BuMgCl (Scheme 1.7) [32]. The *de*-values (prevalent R_S configuration) were much improved (up to 96% *de*) by the addition of 1 equivalent of Et_2AlCl, presumably due to the chelation of a magnesium atom at the sulfinyl group. The diasteroselectivity was moderate, with *i*-PrMgCl and BnMgCl (70 and 78% *de*, respectively). The sulfite of the bis-acetonide of mannitol was also investigated, but this led to a lower diastereoselectivity in the sulfinate formation.

1.2.4
Sulfinamides

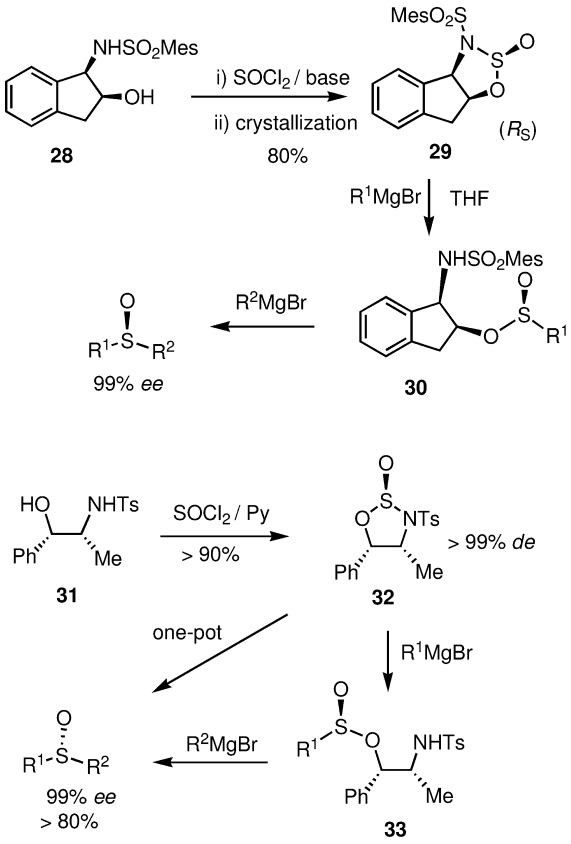
It was established at an early stage that sulfoxides could be obtained from sulfinamides by the addition of methyllithium, with an inversion of configuration at sulfur [33]. Wudl and Lee prepared 1,2,3-oxathiazolidine-2-oxide **25** from (−)-ephedrine **24** and thionyl chloride in 80% yield as a mixture of diastereomers **25a** and **25b** (72 : 28) (Scheme 1.8) [34]. By using a combination of crystallization and HCl-catalyzed equilibration, pure **25a** (100% *de*) could be isolated in 65% yield. The addition of a Grignard reagent or organolithiums gave sulfinamides **26** in good yields, but with only about 50% *ee*. The ring cleavage had occurred regioselectively. These authors discussed the stereochemical and mechanistic aspects of this reaction. The diastereochemically pure sulfinamide **26** was transformed into various enantiopure sulfoxides in excellent yields after treatment with CH_3MgBr, CH_3Li or PhLi. This approach to sulfoxides, using ephedrine as



Scheme 1.8 Use of 1,2,3-oxathiazolidine-2-oxide derived from ephedrine for the asymmetric synthesis of sulfoxides.

a chiral auxiliary, was reinvestigated by Snyder and Benson in 1991 [35], and an improvement in the epimerization step generated **25** in 70% isolated yield. These authors optimized the transformation of **25** into sulfinamides **26** by using the Grignard reagents (to avoid epimerization at sulfur). In that way, various sulfinates **26** with *de*-values ranging between 95 and 99% could be isolated in excellent yields. In order to recover various dialkyl or alkyl aryl sulfoxides (>99% *ee*) in good yields, the authors introduced $AlMe_3$ before adding the Grignard reagents at −70 °C. Presumably, the $AlMe_3$ generates an aluminum complex **27** prior to the attack by the Grignard reagent.

Senananyake et al. synthesized the 1,2,3-oxathiazolidine-2-oxide system **29** from aminoalcohol **28** and thionyl chloride in 80% yield at the kilogram scale (Scheme 1.9) [36]. Here, nitrogen is connected to a sulfonyl moiety which acts as an electron-withdrawing group. As a consequence, the Grignard reagents cleave the ring with the release of nitrogen and formation of sulfinate **30** in excel-

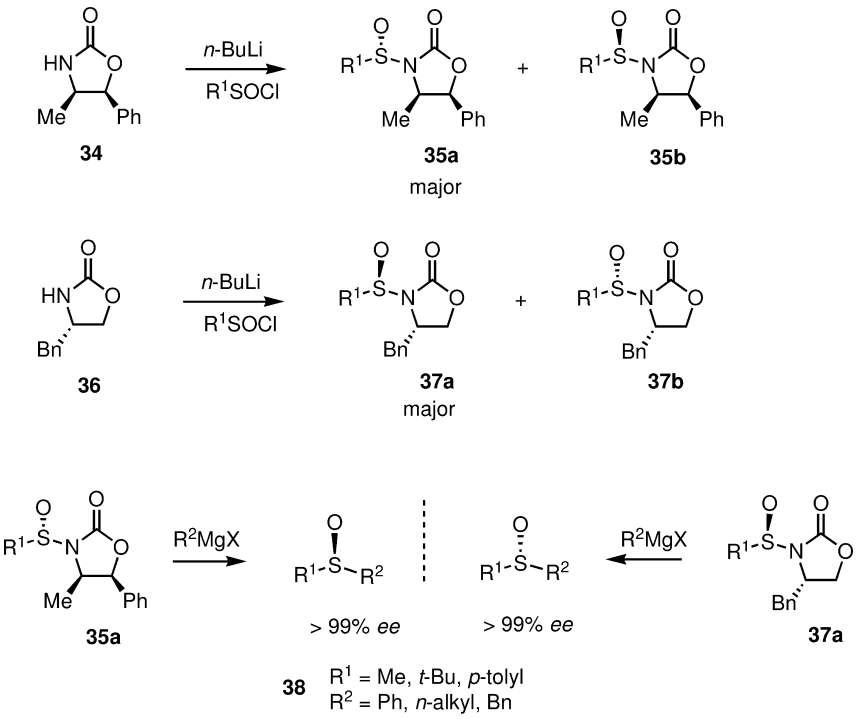


Scheme 1.9 Use of 1,2,3-oxathiazolidine-2-oxide derived from a *β*-aminoalcohol for the asymmetric synthesis of sulfoxides.

lent yields and inversion of configuration. Enantiopure sulfoxides or sulfinamides were easily obtained subsequently.

One interesting observation was the direct stereoselective transformation of alcohol **28** into **29** (diastereomeric ratio, $dr = 97:3$) by using collidine or lutidine [tetrahydrofuran (THF), −45 °C] [37]. The epimer (at sulfur) of **29** was also diastereoselectively produced ($dr = 7:93$) with 2,6-di-*tert*-butyl pyridine as base. The easy access to (R_S)-**29** or (S_S-**29**) allowed the production of a large variety of chiral sulfoxides (>95% *ee*) such as R^1 = *t*-Bu, R^2 = *i*-Pr.

A further improvement was the selection of *N*-tosylnorephedrine **31** for the preparation of heterocyclic compound **32**. The sequential addition of R^1MgX and R^2MgX generated, in a one-pot procedure, the sulfoxides (99% *ee*) with a configuration which depended on the order of introduction of the two Grignard reagents. Many types of sulfoxide have been synthesized using this approach. Likewise, *t*-Bu-S(O)-CH_2CO_2*t*-Bu (a useful reagent in asymmetric synthesis [38]) was prepared by the sequential addition of *t*-BuMgCl and Li enolate of *tert*-butyl acetate. The chiral templates **28** or **31** could be isolated and recycled, and the subsequent large-scale production of methyl *p*-tolyl sulfoxide from **32** has been described [39].



Scheme 1.10 Use of an Evans auxiliary for the synthesis of sulfoxides.

Evans's oxazolidinones, such as **34** and **36**, represent starting materials for preparing a mixture of sulfinamides **35a**, **35b** or **37a**, **37b** which are crystalline and easy to separate by chromatography (Scheme 1.10) [40]. Another approach which has been investigated is based on the *m*-CPBA oxidation of *N*-arylthio- and *N*-(alkylthio)oxazolidinones deriving from **36**.

The conversion of sulfinamides into sulfoxides **38** (>95% *ee*) is excellent when using Grignard reagents or Reformatzky reagent (Zn + *tert*-butyl bromoacetate). The only limitation is the initial separation step to obtain the diastereochemically pure sulfinamides **35a** and **37a**. These sulfinyl donors are complementary, as they afford sulfoxides of opposite absolute configuration. The chiral auxiliary **17** or **18** is released and could be recovered.

1.3 Catalytic Enantioselective Sulfide Oxidation

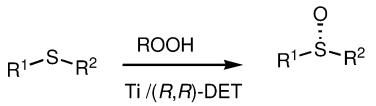
The catalytic enantioselective oxidation of sulfides represents the most direct approach to sulfoxides. Over the past 20 years a variety of catalytic systems have been developed, and some of these are now used at the industrial scale. There are, however, no fully generalized methods as the enantioselectivity is highly sensitive to the substrate structure. On occasion, a competitive overoxidation to sulfone is observed, together with some kinetic resolution which increases the *ee*-value of the isolated sulfoxide. This case will be not considered as the increase in *ee* is realized with a simultaneous decrease in the yield. The various families of chiral catalysts will be briefly presented below, the details and developments of which are available in various reviews [4, 8, 41–45].

1.3.1 Titanium Complexes

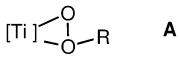
1.3.1.1 Diesters of Tartaric Acid

In 1984, the catalysts for the Sharpless asymmetric epoxidation of allylic alcohols were modified by the groups of Kagan and Modena in order that they may be applied to enantioselective sulfide oxidations. Kagan and colleagues used a titanium complex prepared from $Ti(O\textit{i}\text{-}Pr)_4$, (*R*,*R*)-diethyl tartrate (DET), water (1 : 2 : 1) with *tert*-butyl hydroperoxide (TBHP) [46, 47]. The reaction was run at −22 °C in methylene chloride. Initially, the titanium complex was taken in stoichiometric amounts, but a subsequent procedure was devised to function with substoichiometric amounts (50 to 10 mol.%) [48]. The replacement of TBHP with cumyl hydroperoxide led to a general improvement in the enantiomeric excess of the sulfoxide [48, 49]. By contrast, Modena et al. used a slightly different titanium system, with the combination $Ti(O\textit{i}\text{-}Pr)_4$/(*R*,*R*)-DET = 1 : 4 [50].

Optimization of the Kagan procedure with cumene hydroperoxide (CHP) as oxidant and stoichiometric amounts of the titanium complex allowed the preparation of ferrocenyl *p*-tolyl sulfoxide or methyl *p*-tolyl sulfoxide with >99% *ee* [51,



R^1 = *p*-tolyl	R^2 = Me	89% *ee* [47, 50]
R^1 = *p*-tolyl	R^2 = Me	99% *ee* [52a]
R^1 = Ph	R^2 = Me	91% *ee* [53]
R^1 = Me	R^2 = CH_2CO_2Et	63% *ee* [47]
R^1 = *p*-tolyl	R^2 = ferrocenyl	99% *ee* [51]
R^1 = *t*-Bu	R^2 = ferrocenyl	99% *ee* [51, 54a]
R^1 = $Cr(CO)_3C_6H_6$	R^2 = Me	95% *ee* [54b]



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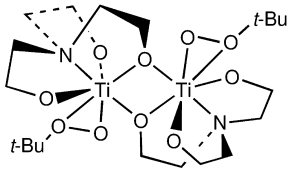
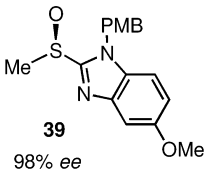


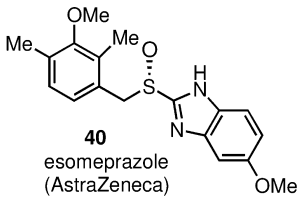
B

Scheme 1.11 Sulfoxidation in the presence of a Ti/DET complex.

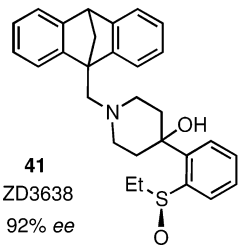
52a]. A catalytic version, by decreasing the amount of the titanium complex (>10 mol.%) was set up by replacing water with isopropanol in the combination $Ti(Oi\text{-}Pr)_4/(R,R)$-DET/*i*-PrOH. *Ee*-values up of to 95% were observed for some aryl methyl sulfoxides [52b]. When the Modena protocol was recently reinvestigated [53] it gave interesting results for the enantioselective synthesis of sulfoxides using furylhydroperoxides instead of CHP. Some examples of the oxidation with both systems are included in Scheme 1.11. The mechanisms of the Kagan or Modena systems are, presumably, very similar, and NMR studies have demon-



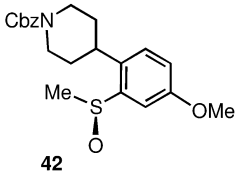
39
98% *ee*



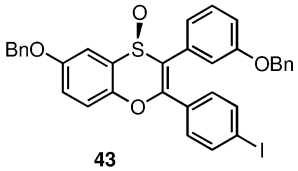
40
esomeprazole
(AstraZeneca)
> 91% *ee*



41
ZD3638
92% *ee*



42
ZD2249
94% *ee*



43
(Merck)
92% *ee*

Scheme 1.12 Industrial applications of the Ti/DET methodology.

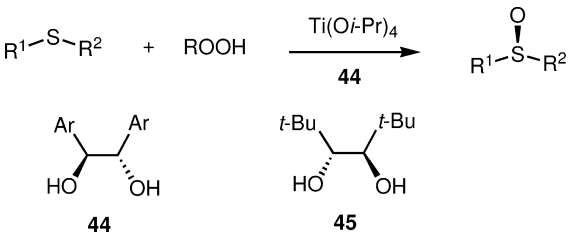
strated a great complexity for the species in equilibrium in solution [55]. The existence of a peroxotitanium species A (Scheme 1.11) has been postulated, and this has been well supported by the X-ray crystal structure of a peroxotitanium complex B [56].

The Kagan oxidation has been used on quite large scales to prepare sulfoxides of industrial interest, either as intermediates or products. Some examples (**39** [57], **40** [58a], **41** [59], **42** [60], **43** [61]) are listed in Scheme 1.12. Von Unge et al. prepared esomeprazole **40** on a multi-kilogram scale using a modification of the Kagan procedure but with the addition of *N*,*N*-diisopropylethylamine to the titanium catalyst (4 mol.%) [58a].

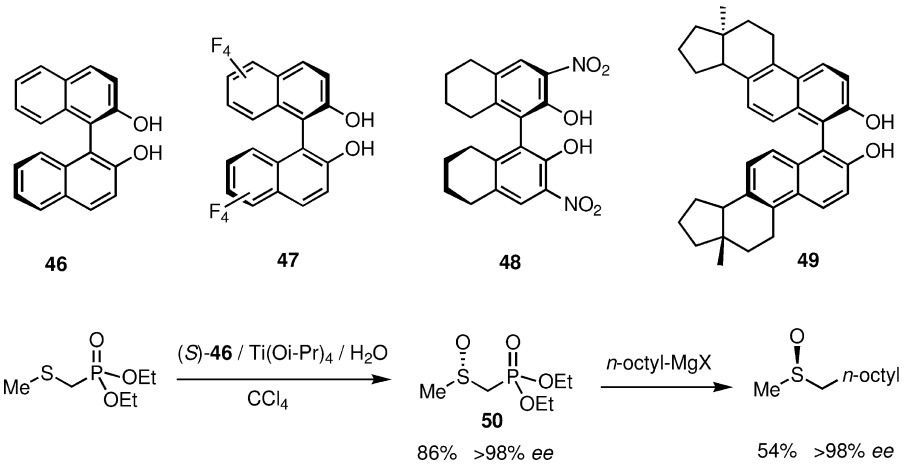
The mechanism of this procedure, as recently discussed, is related to that proposed by Kagan et al.; however, it was suggested that the amine was present in the transition state because of hydrogen bonding to one of the reactants [58b]. The importance of the imidazole fragment was established, presumably because of an H-bonding (the NH of imidazole) to both the ester carbonyl of DET and the peroxo oxygen.

1.3.1.2 C_2-Symmetric 1,2-Diols as Ligands

In the water-modified Kagan reagent, the DET ligand was replaced by a variety of chiral diols. For example, 1,2-diarylethane 1,2-diols **44** (Ar = 2-methoxyphenyl) (Scheme 1.13) allowed stoichiometric, enantioselective oxidations of sulfides to be performed, sometimes with high *ee*-values [62a]. An asymmetric synthesis of sulindac esters (up to 94–96% *ee*, 50% yield) was recently described [62b]. Of special interest are the catalytic conditions developed by Rosini et al., using **44** (Ar = Ph) [63]. Conditions have been identified which avoid the overoxidation of sulfides into sulfones. For example, aryl methyl or benzyl sulfides (*ee*-values up to 99%) are cleanly oxidized at 0 °C by TBHP in the presence of 10 mol.% of the combination $Ti(Oi\text{-}Pr)_4$/**44**/H_2O. The aryl benzyl sulfoxides represent a good starting material for the preparation of many sulfoxides, as the benzyl group can be displaced (with inversion of configuration) by various organometallics [64]. Among the C_2 symmetric diols which were used instead of DET, mention might also be made of diol **45**, as prepared by Imamoto et al. [65]. This gave moderate *ee*-values in the preparation of some sulfoxides, unless some subsequent kinetic resolution was allowed.



Scheme 1.13 Sulfoxidation in the presence of some Ti/1,2-diol complexes.



Scheme 1.14 Sulfoxidation in presence of some Ti/binaphthol complexes.

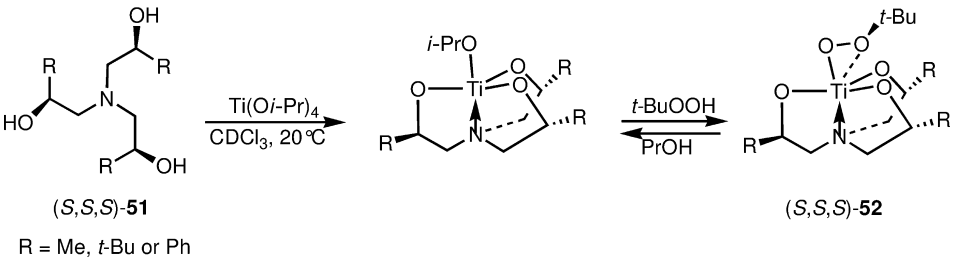
1.3.1.3 Binaphthol and Derivatives

Uemura et al. developed a procedure for catalytic enantioselective oxidation by the *in-situ* formation of a Ti(IV) complex from binol **46**, a titanium alkoxide and a large excess of water (Scheme 1.14) [66a]. For example, methyl *p*-tolyl sulfoxide was produced in 90% yield and 73% *ee*. Higher *ee*-values (but lower yields) could be achieved by combining this with a kinetic resolution [66b]; chiral diphenols **47** [67], **48** [68] and **49** [69] have been used instead of binol itself.

One interesting application of the binol system is the formation of **50** (98% *ee*) under catalytic conditions [70]. Compound **50** is a good precursor of a variety of sulfoxides by a displacement reaction of $CH_2P(O)(OEt)_2$ by organometallics.

1.3.1.4 C_3-Symmetric Triethanolamine Ligands

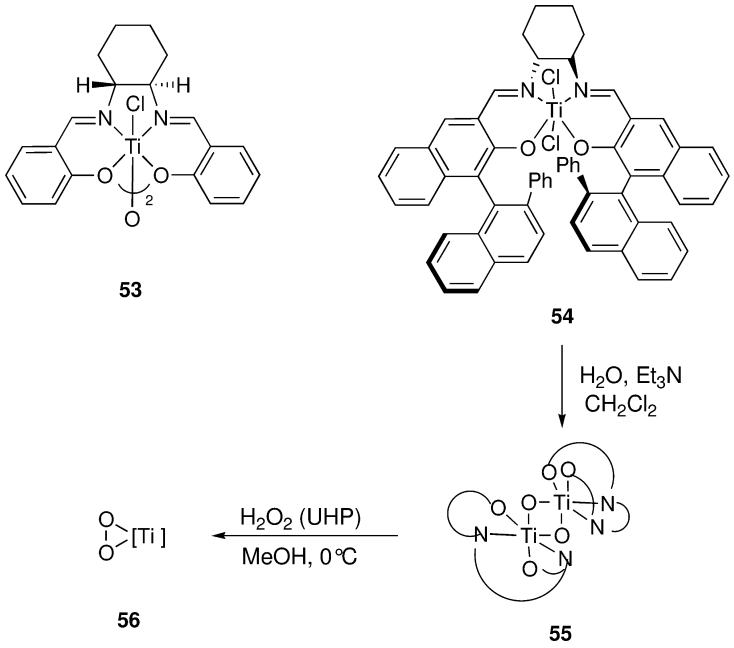
Licini and Nugent investigated the use of **51** as ligand of a titanium catalyst of sulfoxidation (Scheme 1.15) [71]. The catalytic activity was good (1 mol.% catalyst could be used) and the *ee*-values were up to 85%. In this respect, an interesting mechanistic study has been conducted and a peroxo complex **52** isolated.



Scheme 1.15 A Ti/triethanolamine complex.

1.3.1.5 Ti (Salen) Catalysts

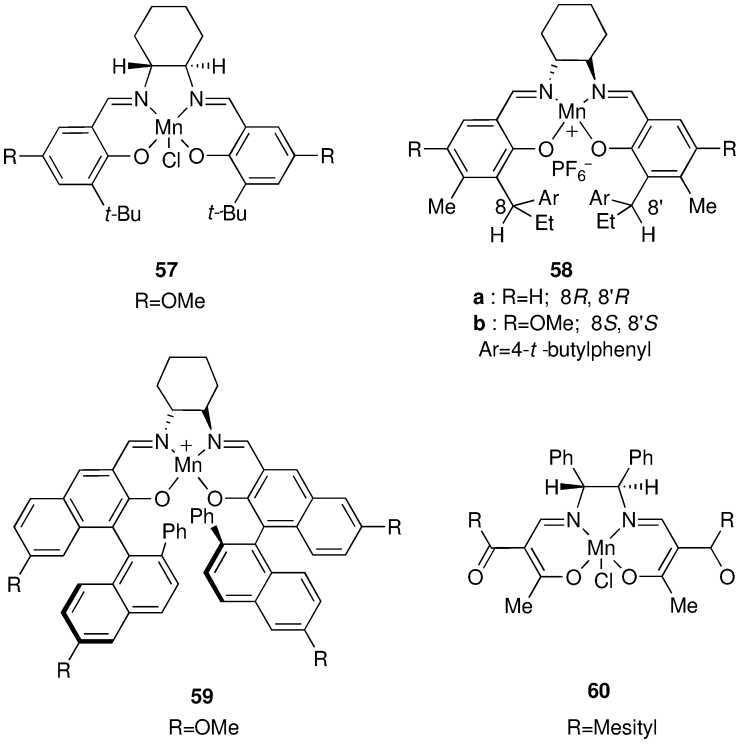
The Ti complexes with chiral salen ligands such as **53** (Scheme 1.16) were first investigated by Fujita et al. [72], although more recently Katsuki and colleagues have conducted extensive studies of new Salen–Ti(IV) catalysts for sulfoxidation by hydrogen peroxide [73]. Complex **54** was transformed, according to a procedure described by Belokon et al. [74] on another Salen–Ti(IV) complex, to a *cis*-μ-dioxo dimer **55**. This complex is an excellent catalyst precursor for the oxidation of sulfides at room temperature. For example, methyl phenyl sulfoxide was prepared at room temperature in 76% *ee* with aqueous H_2O_2, and in 94% *ee* with the urea hydrogen peroxide adduct (UHP). The procedure with UHP in methanol at 0 °C gave the best results, and was used for the oxidation of many aryl methyl sulfides (with *ee*-values in the range of 92–99%) in 80 to 90% yield. Benzyl ethyl sulfoxide was obtained with 93% *ee* and 72% yield. Presumably, UHP cleanly transforms complex **55** into the active peroxo complex **56**. In the presence of water, **56** is in equilibrium with the less-stereoselective hydroperoxo(hydroxo)-titanium species.



Scheme 1.16 Ti/salen catalysts for sulfoxidation.

1.3.2
Manganese Complexes

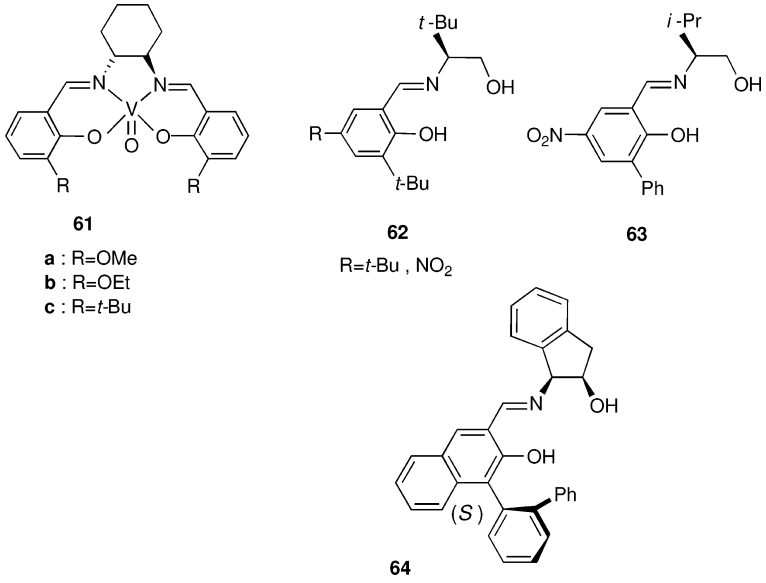
In 1991, Halterman et al. developed a D_4 symmetric manganese tetraphenylporphyrin catalyst for the enantioselective oxidation of sulfides by iodosylbenzene [75]; subsequently *ee*-values of up to 68% have been obtained. The family of Salen manganese (III) provided some active enantioselective catalysts. For example, Jacobsen et al. prepared complex **57** (Scheme 1.17) which showed good catalytic activity (2 mol.%) for the oxidation alkyl aryl sulfides into sulfoxides (*ee*-values up to 68%) [76]. Later, Katsuki et al. prepared the Salen–manganese complexes **58–59** [77] and catalyzed the enantioselective oxidation of sulfides with *ee*-values of up to 90% (2-nitrophenyl methyl sulfoxide) with iodosobenzene as oxidant. Mukaiyama et al. have also studied the family of *β*-oxo aldiminato Mn(III) complex **60** using the combination pivaladehyde/molecular oxygen as an oxidant system [78]. In this way, methyl *ortho*-bromophenyl sulfoxide was obtained in 70% *ee*.



Scheme 1.17 Manganese catalysts for sulfoxidation.

1.3.3
Vanadium Complexes

Nakajima et al. prepared oxo vanadium complexes derived from chiral Schiff bases such as **61** (Scheme 1.18), and which were catalysts for the oxidation of sulfides by CHP [79]. The enantioselectivity was at best 40% *ee*, although the catalytic activity was excellent (0.1 mol.% catalyst). A significant improvement was introduced by Bolm et al. in 1995 by the preparation of highly active vanadium catalysts (used at 0.01 mol.% amounts) derived from Schiff bases **62** and $[VO(acac)_2]$ [80a]. The oxidant was aqueous H_2O_2 (30%), and the sulfoxides were formed in 50 to 70% *ee* from aryl alkyl sulfides. These authors extended the reaction to the monooxidation of dithioketals or dithioacetals, and monosulfoxides could be obtained with *ee*-values up to 85% [80b]. Skarzewski et al. screened several Schiff bases (e.g. **63**) deriving from (*S*)-valinol in the oxidation of thioanisol and acyclic disulfides [81], and the enantioselectivity was in the region of that achieved by Bolm et al. A bis-sulfoxide of 95% *ee* and 60% *de* has been obtained in 41% yield with ligand **63**. This high *ee* was the result of the known amplification which arose from the two identical asymmetric reactions on a substrate with two prochiral centers. Katsuki et al. attempted to improve Bolm's procedure by using new Schiff base tridentate ligands [82a]. The best of these ligands was **64**, which gave 87% *ee* in methyl phenyl sulfoxide (for 1 mol.% catalyst). The Bolm procedure, when applied to the asymmetric synthesis of aryl ben-



Scheme 1.18 Vanadium catalysts for sulfoxidation.

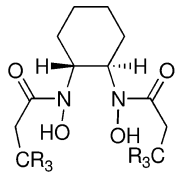
zyl sulfoxides and some other sulfoxides (*ee*-values >90%), is often accompanied by a kinetic resolution [82b,c].

Ellman et al. used the Bolm catalyst for the monooxidation of di-*tert*-butyldisulfide into *tert*-butyl *tert*-butanesulfinate (90% *ee*) [83a]. The reaction was subsequently optimized for large-scale production [83b]. Salan–oxovanadium complexes were also shown to be excellent catalysts in asymmetric sulfoxidations using hydrogen peroxide as oxidant [84].

1.3.4
Molybdenum Complexes

Molybdenum complexes as catalysts of enantioselective sulfoxidation have been explored but provided results inferior to those of the titanium or vanadium complexes [85].

Recently, Yamamoto and colleagues investigated the potential of a chiral Mo complex of a bis-hydroxamic acid **65** (Scheme 1.19) [86]. The best results were obtained with trityl hydroperoxide as oxidant at 0 °C in dichloromethane. The catalyst (2 mol.%) was prepared from $MoO_2(acac)_2$ and **65**. In this way, *p*-tolyl methyl sulfoxide and 1-naphthyl methyl sulfoxide were prepared in good yields with 81% *ee* and 86% *ee*, respectively. Higher *ee*-values may be obtained by combining with a kinetic resolution through overoxidation to sulfone, albeit at the expense of the yield.

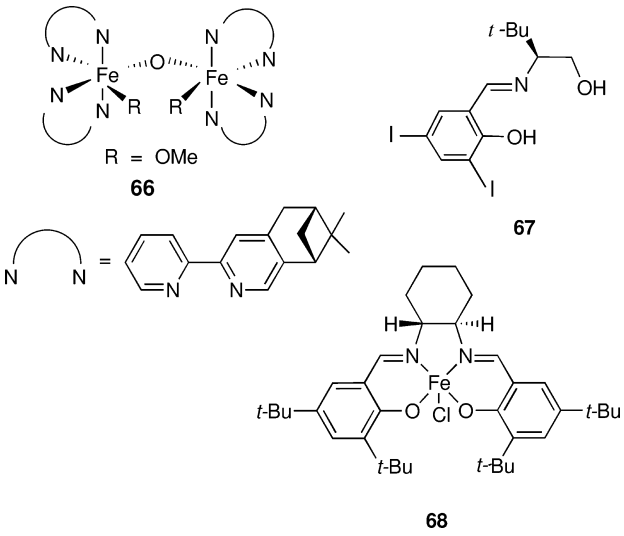


65
R=4-isopropylphenyl

Scheme 1.19 A chiral bis-hydroxamic acid, ligand of molybdenum.

1.3.5
Iron Complexes

Although chiral iron(III) porphyrins are highly active catalysts of sulfoxidation, the enantiomeric excesses of the sulfoxides are modest [87]. Fontecave and colleagues studied the binuclear complex **66** (Scheme 1.20) compared to its mononuclear analogue, using hydrogen peroxide as oxidant, and found the *ee*-values of aryl methyl sulfoxides not to exceed 40% [88]. A successful approach was developed by Bolm et al. in 2003, who used 35% aqueous hydrogen peroxide and an iron complex (2 mol.%) derived from $Fe(acac)_3$ and the Schiff base **67** [89a]. This protocol was improved by the introduction of an additive (10 mol.%) as



Scheme 1.20 Chiral iron catalysts for sulfoxidation.

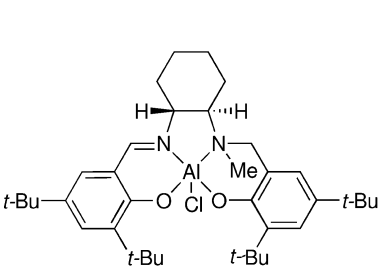
p-methoxybenzoic acid [89b,c]. The oxidation of methyl *p*-chlorophenyl sulfide produced the corresponding sulfoxide in 92% *ee* and 60% yield. In some cases, kinetic resolution was also observed when the sulfone was produced.

A mechanistic study of the iron-catalyzed oxidation of thioethers by iodosylarenes was recently reported by Bryliakov and Talsi [90b]. Iron complexes such as **68** and analogues have been screened, and are very active (0.02 mol.%) at room temperature. The highest enantioselectivity (77% *ee*) was achieved in the oxidation of isopropyl phenyl sulfide; the structure of the reaction intermediates has been established.

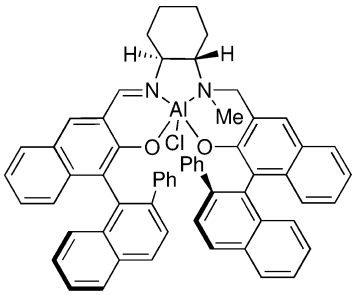
1.3.6 Miscellaneous

Recently, a chiral aluminum (salalen) complex **69a** (Scheme 1.21) has been used as the catalyst of sulfoxidation by 30% hydrogen peroxide [90b]. The enantioselectivity was modest, after which the authors examined the binol-derived complex **69b** [90]. The oxidation was run in methanol with 2 mol.% catalyst, a phosphate buffer (pH 7.4) and 1.1 equiv. 30% (v/v) H_2O_2. Many aryl methyl sulfoxides were produced with *ee*-values in the range of 97 to 99%, with sulfone formation between <1% and 10% according to the substrate. Some kinetic resolution was apparent if there was any overoxidation to sulfones.

Polymeric chiral metalloporphyrin (Fe or Ru) complexes were used as insoluble catalysts of sulfide oxidation in toluene by 2,6-dichloropyridine *N*-oxide [91a], and *ee*-values of up to 75% were observed. A heterogeneous tungsten catalyst (WO_3–L*–30% aq. H_2O–THF; 0 °C or 25 °C) has been reported [91b], where



69a



69b

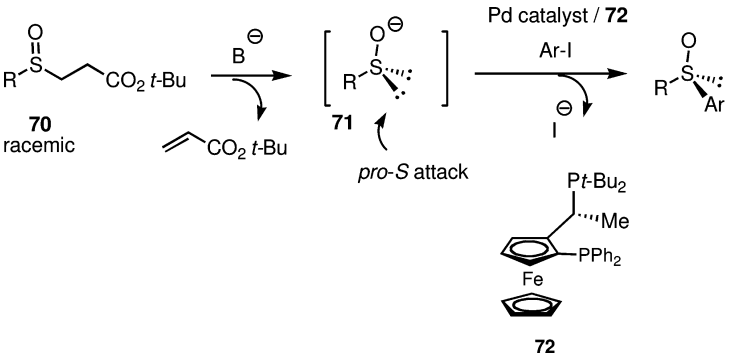
Scheme 1.21 Chiral Al catalysts for sulfoxidation.

L* = $(DHQD)_2$-PYR, a derivative of dihydroquinidine. This system allowed the asymmetric synthesis (84% yield, 88% *ee*) of (*R*)-lansoprazole, an anti-ulcer drug. Heterogeneous titanium complexes derived from multitopic binol ligands are excellent and robust catalysts of sulfoxidation [91c].

A new approach to catalytic sulfoxidation has been proposed by Fontecave and colleagues [91d] which is based on the preparation of "chiral-at-metal" octahedral Ru (III) catalysts, bearing only achiral ligands. Only modest enantioselectivities were reported, although some chiral copper catalysts permitted the production of sulfoxides (up to 81% *ee*) from aryl benzyl sulfides [91d].

1.4
Catalytic Arylation of Sulfenate Anions

A new approach has been devised by Poli, Madec and colleagues for the catalytic synthesis of sulfoxides, as described in Scheme 1.22 [92]. Racemic sulfoxide **70** underwent a retro-Michael reaction under the influence of a base, which gener-

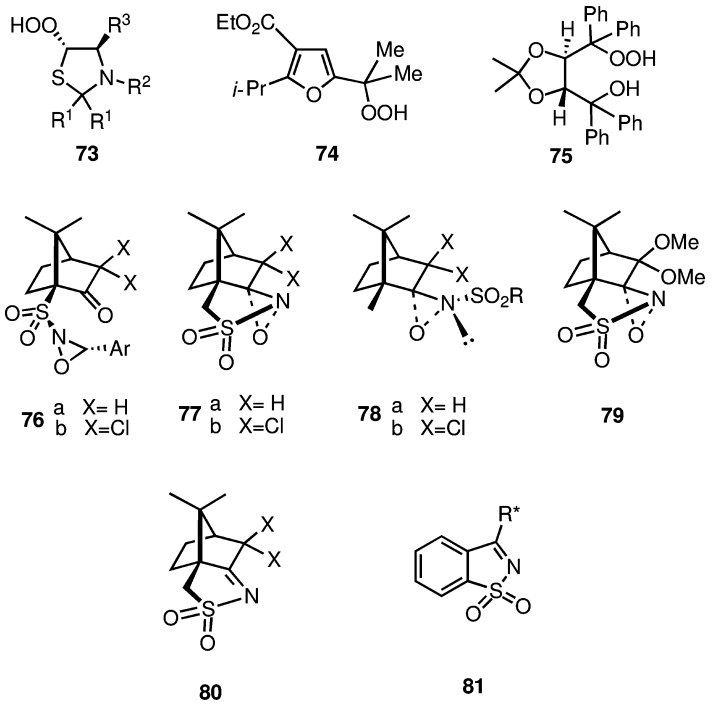


Scheme 1.22 Asymmetric arylation of sulfenate ions.

ated *in situ* sulfenate ion **71**. This prochiral substrate is then coupled to an aryl iodide under the influence of a palladium(0) catalyst bearing a chiral diphosphine **72**. Under optimized conditions (2 mol.% [Pd] and 2 mol.% **72**, 4 equiv. Cs_2CO_3 in refluxing toluene) the isolated yields were excellent, with *ee*-values of up to 80% (*p*-tolyl *p*-nitrophenyl sulfoxide).

1.5
Enantioselective Oxidation of Sulfides

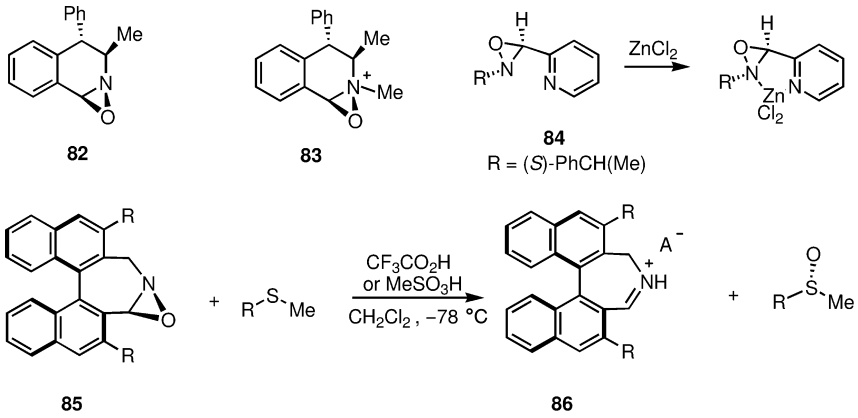
Classical oxygen donors are optically active peracids, and this approach has been monitored in the oxidation of sulfides, albeit without great success (*ee*-values <10%) [93]. Chiral hydroperoxides such as **73** represent another class of reagent which has provided higher enantiomeric excesses (Scheme 1.23), but the addition of Ti(O*i*-Pr)$_4$ enhanced the *ee*-values to some extent [94]. Hydroperoxides such as **74** were also used as excellent chiral oxidants, with Ti(O*i*-Pr)$_4$ as promoter [95]. (*S*)-Phenylethyl hydroperoxide oxidized methyl *p*-tolyl sulfide in the presence of a catalytic quantity of Ti(O*i*-Pr)$_4$ [96]. The enantioselectivity was modest at low conversion, and increased with a subsequent kinetic resolution.



Scheme 1.23 Chiral hydroperoxides and oxaziridines.

An interesting chiral hydroperoxide **75** was briefly investigated by Seebach and Aoki for enantioselective sulfoxidation [97], whereby methyl phenyl sulfoxide was produced in 80% *ee* after oxidation at −30 °C in THF in 60% yield, but without sulfone formation.

Davis and colleagues found several *N*-sulfonyloxazaridines to be interesting reagents for the transformation of sulfides into enantioenriched sulfoxides, with *ee*-values in excess of 95% in some cases [98]. These reagents are derived from camphor (for a review, see Ref. [99]), and some are currently available commercially. One crucial structural factor here is the presence of a *gem*-dihalo system in the vicinity of the oxaziridine ring (as in **76–77**, Scheme 1.23). Typically, the reaction was carried out in CCl_4 at room temperature. As an example, methyl *p*-tolyl sulfide provided the corresponding sulfoxide in 26% *ee* and >95% *ee* with **78b** and **77b**, respectively [98b], whereas **78a** and **77a** furnished methyl *p*-tolyl sulfoxide in 8% *ee* and 67% *ee*, respectively [98a]. Compound **78b** proved to be an excellent reagent of quite broad applicability, and allowed the preparation of both benzyl *tert*-butyl sulfoxide (91% *ee* (*S*)) and methyl *tert*-butyl sulfoxide (94% *ee* (*S*)) [98a]. Bulman Page et al. prepared the dimethoxy analogue **79**, which is a good enantioselective oxidant for non-aryl sulfides, and complementary of the Davis reagents [100]. The same authors also used the sulfonylimines **80** and aqueous hydrogen peroxide (30%) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2 [101a]. In principle, this procedure should give rise to a catalytic version by respect to **80**, with the *in-situ* generation of oxaziridines. In fact, the reaction was run under stoichiometric conditions, and in this way both methyl *p*-tolyl sulfoxide (60% *ee*) and methyl *tert*-butyl sulfoxide (86% *ee*) were prepared quantitatively. Bulman Page and colleagues also prepared and studied the pseudosaccharin derivatives **81** as chiral mediators in the hydrogen peroxide-mediated oxidation of sulfides, although the *ee*-values remained below 35% [101b]. The imine **81** could be quantitatively recovered, however. A family of *N*-phosphinooxaziridines synthesized by Jennings et al. [102] proved capable of oxidizing various aryl alkyl sulfides with *ee*-values of between 35% and 70% (dichoromethane, 0 °C), without sulfone formation. The oxaziridine **82** and its oxaziridinium salt **83** (see Scheme 1.24) were easily prepared by Lusinchi and colleagues from norephedrine [103]. These authors oxidized methyl *p*-tolyl sulfide with an *ee*-value of less than 43%. In the presence of Brönsted acids, some oxaziridines oxidize sulfides into sulfoxides without overoxidation to sulfones, presumably through an oxaziridinium intermediate. Thus, methanesulfonic acid catalyzes the oxygen transfer from **82** to an aryl methyl sulfide (*ee* <44%) [104]. Fontecave and colleagues, by using Lewis acids such as $ZnCl_2$, were able to catalyze the enantioselective transfer of oxygen to sulfides from oxaziridine **84** [105]. This reaction was recently reinvestigated by Hanquet and coworkers with oxaziridines **85** (R = H or Ph) containing a binaphthyl fragment [106], with the best results being observed for **85** (R = H). With $MeSO_3H$ the oxygen transfer was very rapid (<5 min), thus producing the sulfoxide and the iminium **86**; *tert*-butyl methyl sulfoxide and methyl *p*-tolyl sulfoxide were formed in good yield with 60% *ee* and 47% *ee*, respectively. Replacement of the $MeSO_3H$ by triflic acid

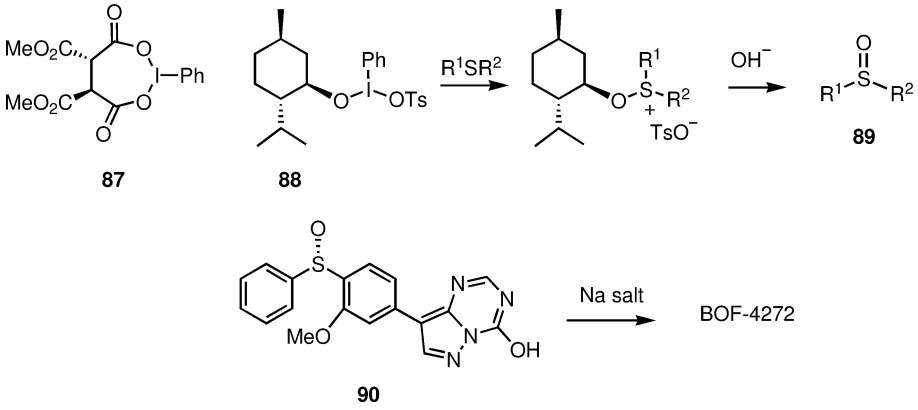


Scheme 1.24 Chiral oxaziridines.

greatly reduced the reaction rate but improved the *ee*-values (to 80% and 70%, respectively).

The imine deriving from **86** could be recovered and recycled. It was of interest to note that, in the absence of acid, oxaziridine **85** (R = H) may slowly oxidize *tert*-butyl methyl sulfide at room temperature, with a good enantioselectivity (70% *ee*).

A completely different approach is the preparation of chiral hypervalent iodo compounds such as **87** [107] or **88** [108] (Scheme 1.25). These reagents are able to oxidize sulfides, thus providing sulfoxides **89** (*ee*-values <60%) following a basic hydrolytic work-up. Oae and coworkers described a method for the asymmetric oxidation of diaryl sulfides using (−)-menthol, pyridine and *t*-butylhypochlorite, followed by basic hydrolysis, giving modest *ee*-values [109]. Bromine oxidation of



Scheme 1.25 Some chiral oxidants.

an aryl methyl sulfide in the presence of (−)-menthol also represents a means of preparing sulfoxonium compounds which are subsequently hydrolyzed into enantiomerically enriched sulfoxides [110]. The method of Oae was modified at the Otsuka Pharmaceutical company in order to prepare sulfoxide **90**, the sodium salt of which (BOF-4272) will inhibit the enzyme, xanthine dehydrogenase [111]. With 4-cyanopyridine as base and 1-chlorobenzotriazole as oxidant, the crude sulfoxide was obtained almost quantitatively with 63% *ee*.

1.6 Summary

As illustrated by the above-described examples, the asymmetric synthesis of sulfoxides of very high *ee*-value is now possible using a wide variety of approaches. The stereochemically pure sulfinates serve as an excellent starting material for preparing enantiopure chiral sulfoxides, the key stage being to obtain a sulfinate of one epimer at sulfur, either by dynamic kinetic resolution induced by crystallization, or by the stereocontrolled sulfinylation of alcohols. The cyclic sulfites or the 1,2,3-oxathiazolidine-2-oxide systems are cyclic structures with two different leaving groups. The nucleophilic displacement of one of these groups can give rise to sulfinates or sulfinamides with a sulfur-defined stereochemistry, and such compounds may then easily be transformed into sulfoxides. The stoichiometric oxidation of sulfides is of preparative interest only in a limited number of cases. Whilst catalytic enantioselective oxidation is highly desirable, and can be used to generate sulfoxides with excellent *ee*-values, it suffers from a lack of generality, and the catalyst must also be optimized and able to adjust to the structure of the sulfide. Another problem is the competitive oxidation of sulfoxide into sulfone, which leads to a decrease in yield, although the *ee*-values may be increased by kinetic resolution (for some additional examples to those mentioned above, see Refs. [112–114]). The sulfinate approach and sulfide oxidation are complementary methods, as shown in Scheme 1.1. In the first of these methods at least one of the two groups of the sulfoxide is introduced as a nucleophile (organometallic chemistry), whereas the precursor of one group of the sulfide is usually of electrophilic character. It is remarkable that, when required, the large-scale asymmetric syntheses of sulfoxides has been realized in either stoichiometric or catalytic mode.

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