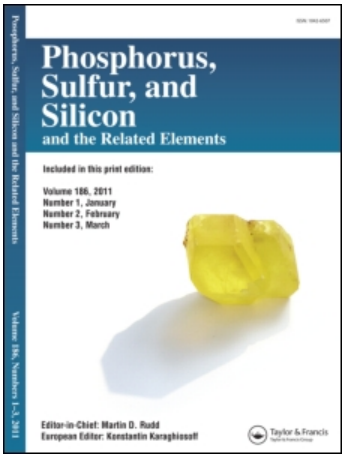

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RECENT ADVANCES IN THE SYNTHESIS OF SULFOXIDES FROM SULFIDES

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Review

RECENT ADVANCES IN THE SYNTHESIS OF SULFOXIDES FROM SULFIDES

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This review deals with the various recent advances in the selective oxidation of sulfides to sulfoxides. Non-stereoselective, diastereoselective as well as enantioselective methods are covered. A considerable number of new oxidizing agents have been reported in the last ten to twelve years including those aiming to replace *m*-chloroperbenzoic acid as the classical sulfide oxidant: Oxone®, dimethyldioxirane, among others. Chiral sulfoxides are especially important in modern asymmetric synthesis, their obtention from prochiral sulfides by Davis' oxaziridines and modifications of Sharpless procedure are discussed, along with other less common methods. The most newly reported microbiological and enzymatic oxidations are also included.

1. INTRODUCTION

The oxidation of sulfides is, undoubtedly, the most widely used route for the synthesis of sulfoxides. Although many methods have been known for decades, the lack of a wide range oxidizing reagent, the usual problem of overoxidation to sulfone, undesired side reactions and the effect over sensitive substrates, have accounted for the large amount of work done in this area in recent years.

Particularly important advances have been made in the enantioselective oxidation of prochiral sulfides to the corresponding chiral sulfoxides. The main reason for this development is that chiral sulfoxides are widely used, due to their high diastereoselectivity, as auxiliaries or reagents in asymmetric synthesis.[1,2] The sulfoxide group is also involved in diverse biological activities and optically pure sulfoxides are of great pharmaceutical interest.[3,4]

This review aims to account the synthetic methods for the preparation of sulfoxides from sulfides and it especially focuses on the last ten to twelve years of synthetic development in this field which is scarcely covered by reviews. An excellent account has been published in the middle eighties.[5]

2. NON-STEREOSELECTIVE OXIDATION

A considerable number of non-stereoselective methods has been reported for the synthesis of sulfoxides from sulfides. The research in this area has been increased during recent years, and one of the main reasons for such a development is the commercial discontinuity of a "classical" sulfide oxidant: *m*-chloroperbenzoic acid (MCPBA).[6]

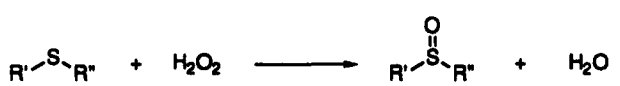
2.1. Peroxidic Reagents

2.1.1. Hydrogen Peroxide

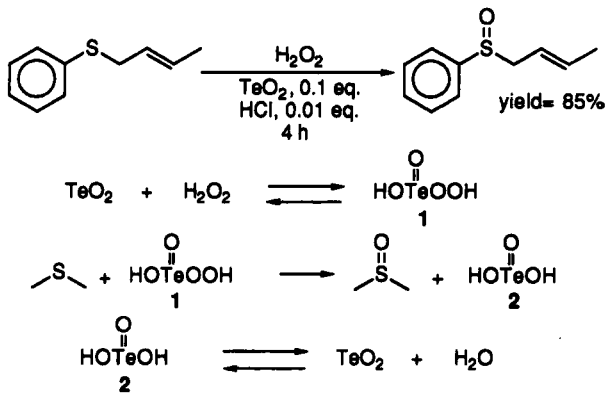
One of the simplest procedures for the oxidation of sulfides to sulfoxides is that involving hydrogen peroxide (H_2O_2) as oxidant, a very cheap reagent (Scheme 1). The major drawback of using this method is the facile overoxidation to sulfone.

The effectiveness of H_2O_2 in different solvents has been extensively studied. Aliphatic, aromatic and heterocyclic sulfoxides have been obtained using H_2O_2 in acetone or aqueous solution at room temperature.[5a]

Many catalysts have been reported to accelerate the sulfoxidation under H_2O_2. Traditionally, acetic acid[7] and formic acid[8] were used as catalyst, but several others have been recently reported. Vanadium peroxide (V_2O_5),[9] selenium oxide (SeO_2),[10] titanium trichloride ($TiCl_3$)[11,12] and tellurium dioxide (TeO_2)[13] are among them. In the last case, oxidation was performed with 0.1 equivalent of TeO_2 giving sulfoxides in high yields (81–95%) without overoxidation. In general, the addition of 0.01 equivalent of concentrated HCl improved reaction rates (Scheme 2),[13] suggesting that the oxidizing species is the peroxytellenious acid (**1**) which would reduce back to tellenious acid (**2**) and quickly regenerate by H_2O_2.



SCHEME 1



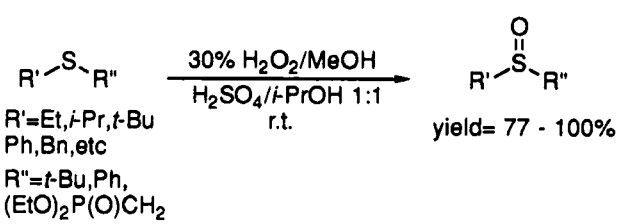
SCHEME 2

Mikolajczyk et al.[14] have reported a new methodology that is especially effective for the oxidation of sterically hindered sulfides to sulfoxides. The reaction was performed in the presence of a catalytic amount of a sulfuric acid/isopropanol mixture (Scheme 3).[14] No overoxidation was observed.

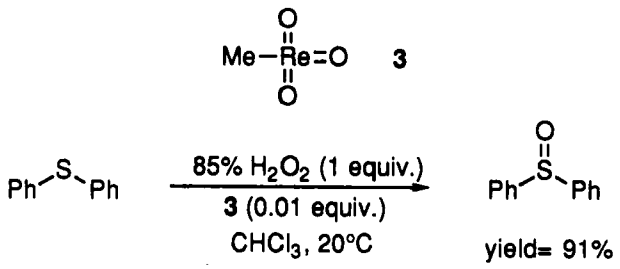
Titanium silicate molecular sieves TS-1 and TS-2 also catalyze the sulfoxidation by H_2O_2[15] but its utility is limited because this methodology is not suitable for bulky sulfides, probably because the active Ti(IV) species are located inside the pores.

Methyltrioxorhenium (MTO) (**3**)[16,17] is another catalyst rendering sulfoxides in high yields and good chemoselectivity (Scheme 4).[16] H_2O_2 (85%) must be used because less concentrated solutions produce overoxidation. This constitutes a clear drawback of the method since 85% H_2O_2 is not an "easy to handle" reagent.

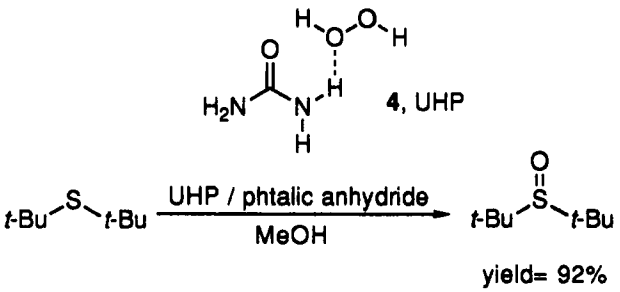
Urea-hydrogen peroxide (UHP) (**4**), a stable, safe and easy to prepare source of pure H_2O_2, has been used in combination with phthalic anhydride to oxidize dialkyl, diaryl and alkyl aryl sulfides to the corresponding sulfoxides in excellent yields (84–96%) (Scheme 5).[18] Optimum molar ratios were 1:4:2 (substrate/UHP/phthalic anhydride); excess of reagent has been found to produce sulfones exclusively.[19]



SCHEME 3



SCHEME 4

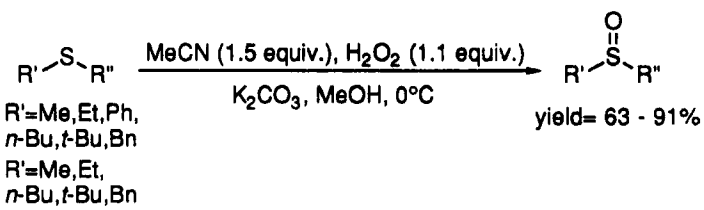


SCHEME 5

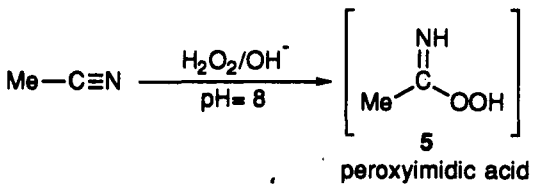
In 1993, Page reported an efficient oxidation of sulfides to sulfoxides by treatment with H_2O_2/acetonitrile/potassium carbonate in methanol (Scheme 6).[20] Excess of the reactive mixture led to sulfone formation. In fact, this reaction consists in the *in situ* formation of a highly reactive peroxyimidic acid (**5**) which is the actual oxidizing species (Scheme 7).[20]

2.1.2. Hydroperoxides

In recent years, the most important development in the field of hydroperoxides as sulfoxidation reagents has been the synthesis of chiral sulfoxides from sulfides (see Section 4). Many hydroperoxides have been used for sulfoxidation, being the *tert*-butyl hydroperoxide (TBHP) the most frequently utilized.



SCHEME 6



SCHEME 7

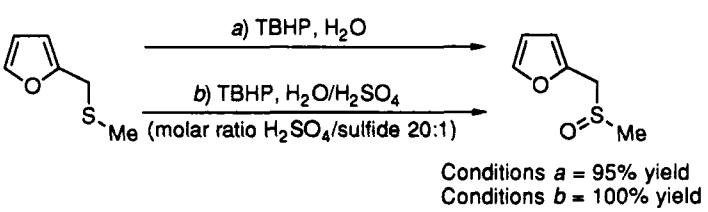
Fringuelli *et al.*[21] have found that sulfoxides can be obtained in excellent yields (90–100%) by oxidation of sulfides with TBHP in heterogeneous aqueous medium (Scheme 8a).[21] The oxidation rate was sometimes increased by addition of sulfuric acid (Scheme 8b).[21]

Recently, silica gel-mediated oxidation by TBHP[22] has been reported as a convenient and "clean" method for sulfide oxidation. Adsorption of TBHP on the silica gel apparently facilitates oxygen atom transfer *via* synchronous hydrogen atom exchange (Scheme 9).[22] Careful stoichiometric control was necessary to avoid the formation of sulfones.

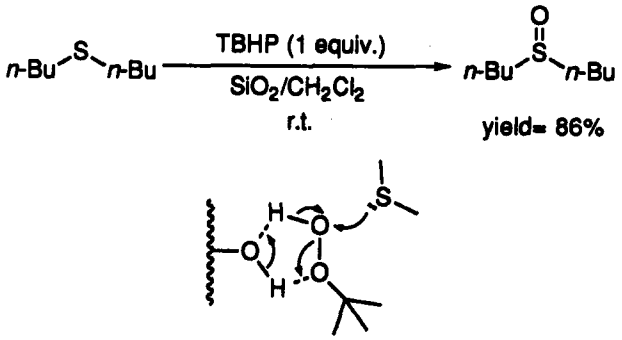
On the other hand, vanadium-pillared montmorillonite have been used as catalyst for the TBHP oxidation of sulfides to sulfoxides in excellent yields.[23]

2.1.3. Other Organic Hydroperoxides

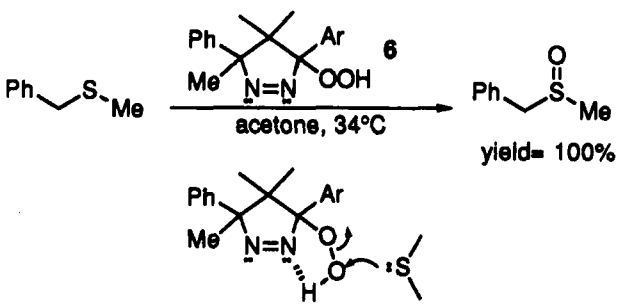
Organic hydroperoxides such as flavin 4a-hydroperoxides[24–27] and α-azohydroperoxides[28–32] are well documented as oxidants of sulfides to sulfoxides. Baunstark[32] reported that cyclic α-azohydroperoxides, such as **6**, behave as highly reactive oxygen transfer reagents performing the oxidation of benzyl methyl sulfide in excellent yield (Scheme 10).[32] The enhanced reactivity of this and similar reagents is likely due to the basicity of the azo function that allows a five-membered intramolecular hydrogen bond.



SCHEME 8



SCHEME 9



SCHEME 10

Unfortunately, these α-azohydroperoxides are photosensitive and rather unstable. However, more recently, Nishio reported that a series of *N*-substituted 3-hydroperoxyindolin-2-ones (7) (Figure 1)[33] are stable reagents for the selective oxidation of different sulfides to the corresponding sulfoxides in generally good yields and without further oxidation to sulfones.

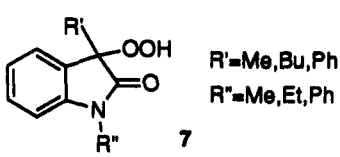
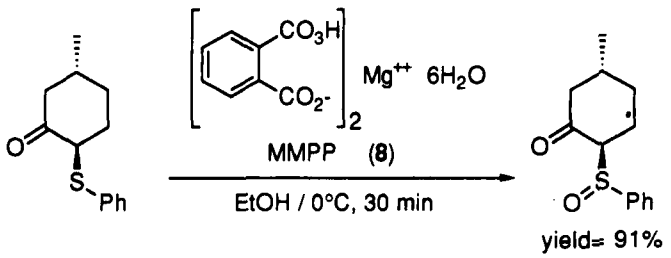


FIGURE 1



SCHEME 11

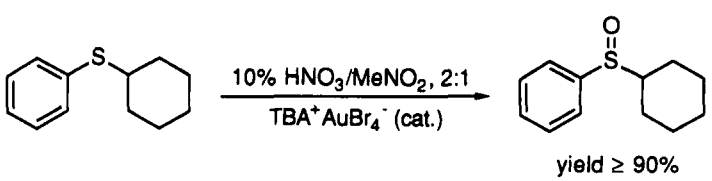
2.1.4. Organic Peroxyacids and Peroxides

m-Chloroperbenzoic acid (MCPBA) was the most widely reported oxidizing reagent in the past thirty years or so but has been withdrawn from market by the major suppliers[6] due to its shock-sensitive and potentially explosive characteristics.

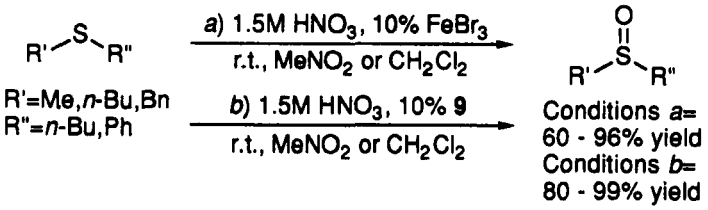
The only other peracid recently reported for sulfide oxidation to sulfoxides is magnesium monoperoxyphthalate hexahydrate (MMPP) (**8**). This non shock-sensitive, non deflagrating oxidant has been used, under stoichiometric control, for the selective synthesis of a large number of sulfoxides from the corresponding sulfides (Scheme 11).[34–37]

2.3. Nitrogen-Containing Oxidants

The "ancient" nitric acid oxidation of sulfides to sulfoxides has been improved through the years. Gasparrini *et al.* have reported the tetrabutylammonium tetrachloroaurate(III) ($TBA^+AuCl_4^-$)[38,39] and, especially tetrabutylammonium tetrabromoaurate(III) ($TBA^+AuBr_4^-$),[40] as catalysts for the selective oxidation by nitric acid of alkyl aryl, dialkyl, diaryl and other sulfides to the corresponding sulfoxides (Scheme 12).[40] The reaction was carried out in a 1:2-biphasic system containing nitromethane and 10% nitric acid.



SCHEME 12



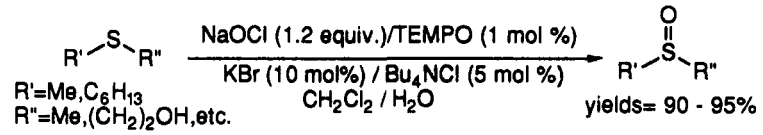
SCHEME 13

Recently, Suárez *et al.* described the efficiency of two catalysts: $FeBr_3$ and $(FeBr_3)_2(DMSO)_3$ (**9**), in the selective sulfoxidation by nitric acid. Reaction under **9** as catalyst gave in general higher yields (Scheme 13).[41] An induction period was observed in reactions catalyzed by **9** denoting that the organic sulfide coordinates to the metal prior to oxidation.

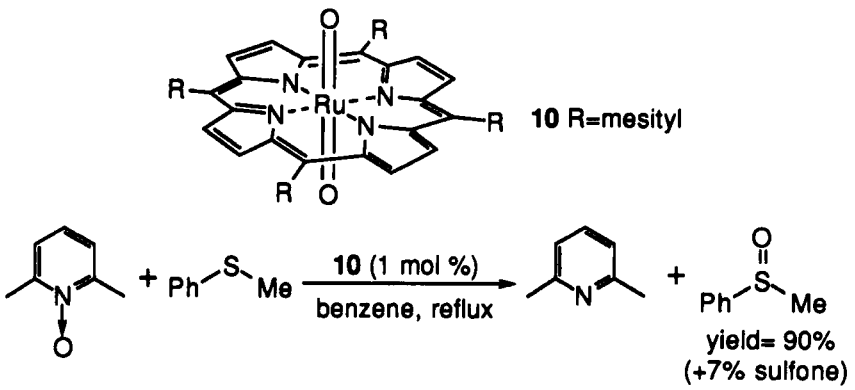
Among nitrates used as oxidant of sulfides, the most popular is Cerium(IV) ammonium nitrate (CAN). Baciocchi found that sulfoxides can be obtained in very high yields (90–100%) by phase transfer catalyzed oxidation of the corresponding sulfides by CAN.[42] Cerium ammonium nitrate, as well as nitrogen oxide, have been used to catalyze sulfide oxidation by dioxygen (see Section 2.8).

Skarzewski[43] has recently investigated the system 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)/sodium hypochlorite for the selective oxidation of sulfides to sulfoxides. The active species is the oxoammonium salt, a mild electrophilic oxidant arising from TEMPO and stoichiometric amounts of NaOCl. When the reaction was co-catalyzed by potassium bromide and tetrabutylammonium chloride (phase transfer conditions), dialkyl and alkyl aryl sulfides were selectively oxidized to the corresponding sulfoxides in excellent yields (Scheme 14).[43]

Hirobe[44,45] has reported the lutidine N-oxide oxidation of phenyl methyl and dibenzyl sulfides to the corresponding sulfoxides catalyzed by ruthenium porphyrin complexes such as **10**. Small amounts of sulfone were also obtained (Scheme 15).[45]



SCHEME 14



SCHEME 15

2.4. Polyvalent Organoiodines

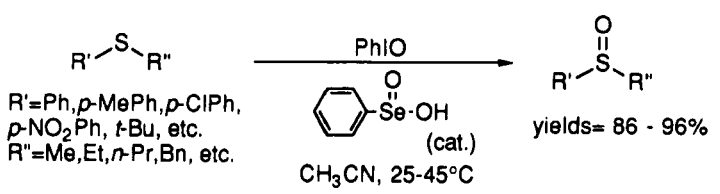
2.4.1. Iodosylbenzene

Iodosylbenzene is known since 1949 as sulfide oxidant.[46] Using methanol as solvent, it has been reported to oxidize vinylsulfides to vinylsulfoxides at room temperature.[47] In recent years, the major development in the area of iodosylbenzene oxidations has been its activation by a catalyst.

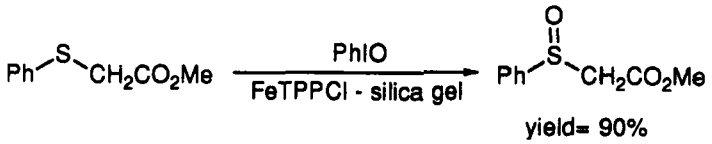
Kim[48] has informed the preparation of sulfoxides from various sulfides in excellent yields under mild conditions, using iodosylbenzene catalyzed with benzeneseleninic acid. No overoxidation was observed (Scheme 16).[48]

Also, the iodosylbenzene oxidation in the presence of catalytic amounts of *p*-toluenesulfonic acid and acetonitrile as solvent has been reported to give sulfoxides in high yields, without overoxidation.[49] For example, a sulfoxide with an electron-withdrawing group, the *p*-nitorphenyl methyl sulfoxide, was obtained in 99% yield.

Iron and manganese porphyrin complexes behave as good catalysts for iodosylbenzene oxidation of sulfides to sulfoxides[50,51] (see also Section 4.4). In 1991, Pautet[52] described a method that used metalloporphyrins immobilized on silica gel, to obtain good chemoselectivity on those oxidations. Thus, with het-



SCHEME 16



SCHEME 17

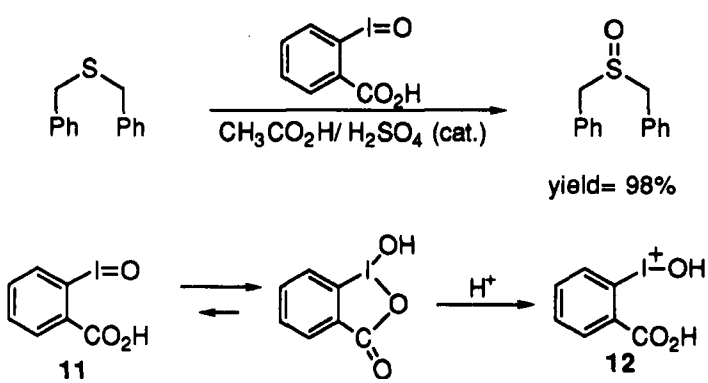
erogenized chloro *meso*-tetraphenylporphyrinato iron(III) (FeTPPCl) on the surface of silica gel as catalyst, several sulfides were oxidized to the corresponding sulfoxides (Scheme 17).[52]

2.4.2 Other Polyvalent Organoiodines

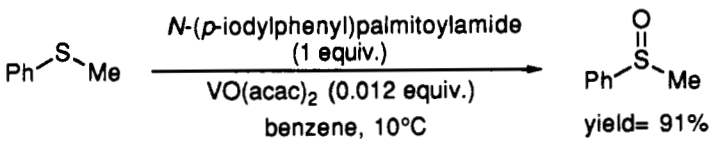
(Ditrifluoroacetoxyiodo)benzene has been described as a better oxidant than its unfluorinated analog (diacetoxyiodo)benzene, although the former appears to be less selective.[53]

o-Iodosylbenzoic acid has been used to oxidize several alkyl aryl, dialkyl and diaryl sulfides to sulfoxides in very good yields (Scheme 18).[54] Since acetic acid was used as solvent and sulfuric acid as catalyst, *o*-iodosylbenzoic acid (**11**) was converted into the protonated form (**12**) which was postulated to be the active species. *o*-Iodosylbenzoic acid is easy to prepare by treatment of *o*-iodobenzoic acid with acetyl nitrate.

m-Iodosylbenzoic acid[55] has also been reported for the oxidation of diphenyl, dibenzyl and phenyl benzyl sulfides to the corresponding sulfoxides in very good yields (82–94%).



SCHEME 18



SCHEME 19

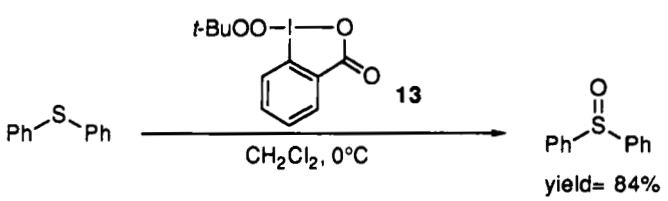
Pautet *et al.*[56] have demonstrated that poor oxidants as the iodylarenes become good oxidants in the presence of vanadyl acetylacetonate [$VO(acac)_2$]. The best result was obtained with *N*-(*p*-iodylphenyl)palmitoylamide,[57] which performed the $VO(acac)_2$ catalyzed selective oxidation of thioanisole to phenyl methyl sulfoxide in 91% yield (Scheme 19).[57]

On the other hand, a new stable crystalline (alkylperoxy)iodinane: 1-(*tert*-butylperoxy)-1,2-benziodoxol-3(1*H*)-one (**13**) (Scheme 20)[58] has been reported to perform diphenyl sulfide oxidation to afford the diphenyl sulfoxide in good yield.

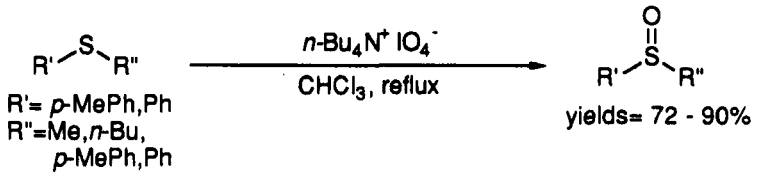
2.5. Metaperiodates

The main problem in non-stereoselective sulfide oxidation to sulfoxides is the overoxidation to sulfones. The most commonly employed reagent in this case is sodium metaperiodate.[59,60] Santaniello *et al.*[61] have reported that this reagent can be used under phase transfer conditions for the oxidation of sulfides to sulfoxides in good yields (70–75%). However, tetrabutylammonium periodate (TBAPI) in refluxing chloroform gave very high yields in shorter reaction times (Scheme 21).[62]

Among the different variations of metaperiodate oxidation can be mentioned silica[63] and alumina[64]-supported sodium metaperiodate and periodate forms of Amberlyst A26 and Amberlyst IRA 904 resins.[65]



SCHEME 20



SCHEME 21

2.6. Bromites

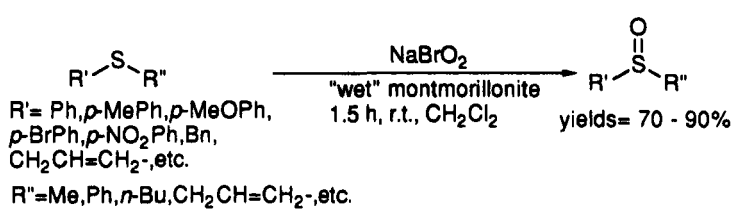
Sodium bromite has been reported for the synthesis of sulfoxides from sulfides in water/dioxane mixtures.[66] Morimoto *et al.* have described that inorganic supports serve as highly reactive sites for sodium bromite oxidation of sulfides in aprotic solvents, avoiding the problem of the negligible solubility of sodium bromite in organic solvents. Thus, "wet" montmorillonite,[67] kaolin and H^+-exchanged zeolite F-9[68] have been used for the oxidation of dialkyl, alkyl aryl and cyclic sulfides in dichloromethane to obtain the corresponding sulfoxides in good yields (Scheme 22).[67]

2.7. Halogenating Reagents

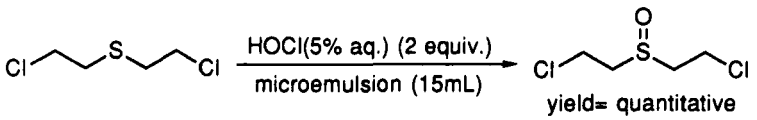
Halogenating reagents work through an initial formation of an halosulfonium ion that subsequently, by hydrolysis or alcoholysis, gives rise to the corresponding sulfoxide. Various of these reagents have been developed in recent years.

2.7.1 N-Halogenated Agents

N-Chlorosuccinimide (NCS) and *N*-bromosuccinimide (NBS) have been used for oxidation of sulfides to sulfoxides for sometime.[69] Monochlorourethane (MCU) in wet tetrahydrofuran[70] have been reported for the efficient chemo- and diastereoselective synthesis of Ceph-3-em (*R*)sulfoxides without overoxidation. Other *N*-halogenated reagents, such as *N*-bromobenzamide[71] and *N*-chloroacetamide,[72] have been also used for the sulfide oxidation to sulfoxides.



SCHEME 22



Microemulsion: 3% cyclohexane, 82% water,
5% surfactant, 10% co-surfactant.

SCHEME 23

2.7.2. Other Halogenating Reagents

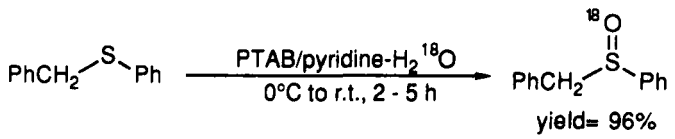
Sodium hypochlorite has been known to oxidize sulfides to sulfoxides under controlled conditions.[73] In 1990, Menger[74,75] showed that oil-in-water microemulsion could remarkably increase the rate of sulfide oxidation with two equivalents of hypochlorite. No sulfone was formed (Scheme 23).[75] Microemulsion would increase the reaction rate due to the formation of large hydrocarbon/water contact area that permits communication between the water-soluble HOCl and the oil-soluble sulfide with an interfacial co-surfactant serving as an intermediate.

Tetraalkylammonium tribromides have been used, as a substitute of bromine, for the selective oxidation of sulfides to sulfoxides. Phenyltrimethylammonium tribromide (PTAB) oxidized a wide range of sulfides to the corresponding sulfoxides in high yields (Scheme 24).[76] This methodology is particularly recommended for the synthesis of ^{18}O-labeled sulfoxides.

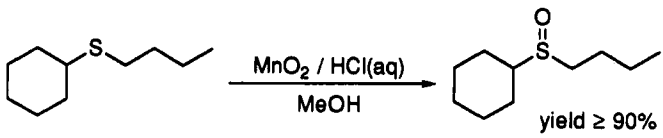
Benzyltrimethylammonium tribromide[77] also oxidizes dialkyl, aryl alkyl and diaryl sulfides to the sulfoxides in high yields.

Ghelfi *et al.*[78,79] have reported that the intermediate reagent Mn(IV)-Cl_x is an effective halogenating agent for the synthesis of sulfoxides from sulfides. This reactive species was generated either by the combination of manganese(IV) oxide-trimethylchlorosilane[78] or manganese(IV)oxide-35% aqueous hydrogen chloride.[79] Some aliphatic, aromatic and cyclic sulfoxides were obtained in very high yields, without overoxidation (Scheme 25).[79]

Very recently, mercury(II) oxide-iodine reagent has been reported to perform mild and selective oxidation of alkyl sulfides to sulfoxides in high yields.[80] The reaction proceeds *via* the formation of an iodosulfinium cation, followed by its replacement by an oxygen from the HgO (Scheme 26).[80]



SCHEME 24



SCHEME 25

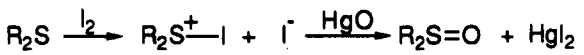
2.8. Oxygen

In 1985, Riley[81] reported a highly selective oxidation of sulfides to sulfoxides using molecular oxygen. This autoxidation, performed at 40-atm pressure in polar solvents, does not require a catalyst, an initiator, or photosensitizer and light. Aliphatic sulfides can be converted to sulfoxides in good yields using this method (Scheme 27a).[81] In contrast, less electron rich phenyl substituents at the sulfur substantially reduce reactivity, since diphenyl sulfide was found to be inert to the reaction conditions. Mechanistically, one electron transfer from the sulfide to the oxygen gives the sulfide radical cation (**14**), which is then oxygenated by triplet oxygen to the radical cation (**15**), a very potent oxidizing intermediate. Finally, conversion to the product is achieved when **15** is reduced to the zwitterion (**16**), followed by a bimolecular reaction with sulfide substrate to generate two molecules of sulfoxide (Scheme 27b).[81]

This author[82–86] has also studied the oxidation of sulfides using oxygen in the presence of catalysts. Autoxidation of sulfides catalyzed by cerium(IV) salts,[82,83] especially ceric ammonium nitrate (CAN), largely enhances the oxidation rate compared with the uncatalyzed one. The rate determining step in these oxidations is the Ce(IV)-promoted oxidation of sulfide to the radical cation **14** (see Scheme 27b). On the other hand, ruthenium[84–86] and palladium[87] complexes were also reported to catalyze autoxidation of sulfides to sulfoxides.

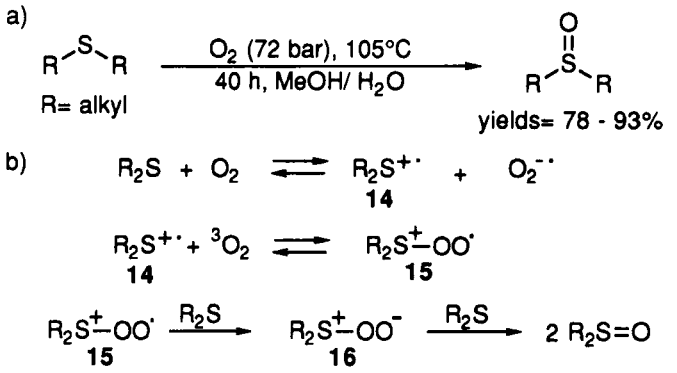
Mixtures of nitrogen dioxide/oxygen have also been studied. Thus, dialkyl, diaryl and cyclic sulfides were converted in high yields to sulfoxides in the presence of oxygen and catalytic amounts of nitrogen oxide.[88,89] No overoxidation was observed in any case (Scheme 28).[88]

Recently, Lion *et al.*[90] reported a new and efficient method for oxidizing sulfides selectively to sulfoxides using atmospheric oxygen in the presence of an aldehyde (isobutyraldehyde) and Ni(II) complexes catalysis (**17**). Controlling the reaction times, quantitative yields were observed since sulfone formation

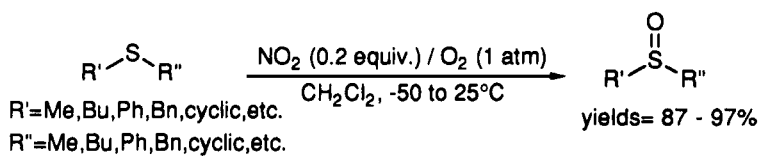


R=Pr,Bu,*i*-Pr,Bn,cyclic,etc.

SCHEME 26



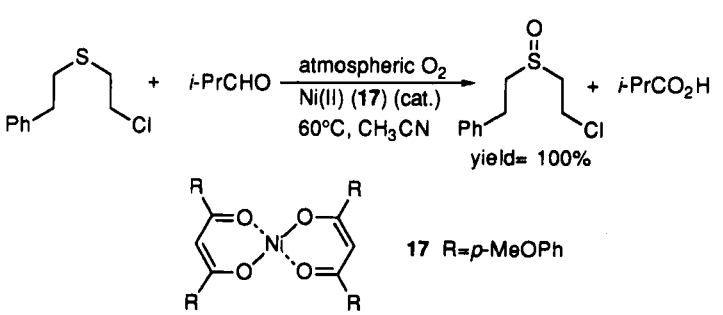
SCHEME 27



SCHEME 28

was avoided (Scheme 29).[90] Aldehydes serve as sacrificial auxiliaries ending up as the corresponding carboxylic acids. Evidences support an acylperoxy radical as the active species.[91]

Polymerizable tris(β-ketoesterate)iron(III) complex[92] has also been used as catalyst for molecular oxygen-sacrificial aldehyde oxidation of sulfides to sulfoxides.



SCHEME 29

2.9. Dioxiranes

In few years since it was first reported,[93] dioxiranes have become one of the most widely used methods for the selective oxidation of sulfides to sulfoxides.[94–97] They show several desirable characteristics: mild reaction conditions, high yields, no sulfone formation and simple work-up, among others. Dimethyldioxirane (DMDO) (**18**) and trifluoromethyl-methyl dioxirane (TMDO) (**19**) are the most common dioxiranes (Scheme 30).[94] Dimethyldioxirane is obtained simply in acetone solution by distilling it from a mixture of Oxone® and acetone at pH 7.4.[98]

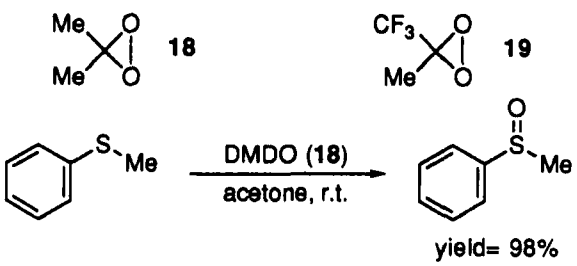
According to recent studies, DMDO is more selective on sulfoxide synthesis than TMDO, since the latter is a stronger oxidant and can oxidize both sulfides and sulfoxides.[99]

2.10. Other Oxygen Transfer Oxidants

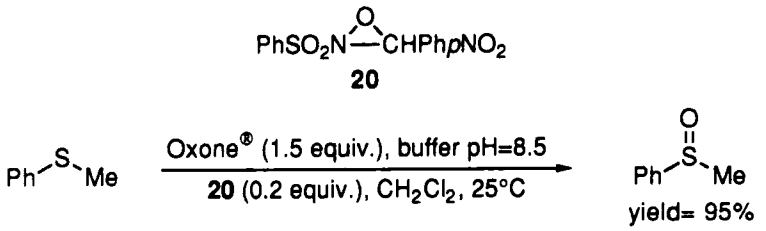
Oxaziridines are also a newly developed type of sulfide oxidant with particular interest in the area of asymmetric synthesis of sulfoxides (see Section 4.2).

In 1988, F.A. Davis[100] described the chemoselective catalytic oxidation of aliphatic and aromatic sulfides to sulfoxides using *N*-sulfonyloxaziridines (**20**) and buffered Oxone® as stoichiometric oxidant. Sulfoxides were obtained in very high yields; even in large excess of **20** overoxidation was extremely slow (Scheme 31).[100] The catalytic cycle involves the continuous regeneration of the oxidizing species **20** by the Oxone®.

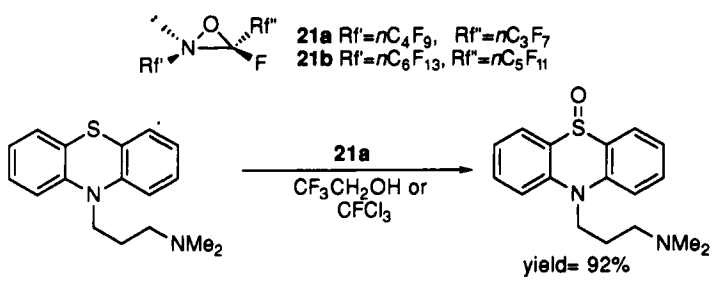
More recently, perfluoro-cis-2,3-dialkyloxaziridines such as **21**,[101] have been used for stoichiometric oxidation of sulfides to sulfoxides. These reagents have strong oxidizing power since oxygen transfer is increased by effect of the electron-withdrawing ability of fluorine atoms. Yields were above 90% if one equivalent of **21** was used. Excess of reagent led to sulfone formation (Scheme 32).[101]



SCHEME 30



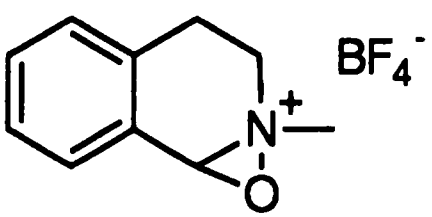
SCHEME 31



SCHEME 32

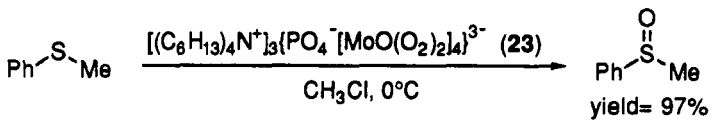
Another kind of oxaziridine, dihydroisoquinolin-derived oxaziridium salt (**22**) (Figure 2),[102] has also been used for sulfoxidation of sulfides. This oxaziridine was prepared *in situ* by the reaction of buffered Oxone® with the corresponding iminium salt.

On the other hand, Mo(VI) peroxopolyoxo complexes such as tetrahexylammonium tetrakis(diperoxomolybdo)phosphate (**23**),[103,104] cetylpyridium tetrakis-(diperoxomolybdo)phosphate[105,106] and others,[107] have been reported to perform the oxidation of some aryl methyl sulfides to the corresponding sulfoxides in high yields (Scheme 33).[103] In each case the complex was prepared by treating the corresponding salt of 12-molybdophosphoric acid with aqueous hydrogen peroxide.



22

FIGURE 2



SCHEME 33

Oxo(phosphine)ruthenium (IV) complexes[108] were also reported to oxidize cleanly sulfides to sulfoxides.

A rather different kind of oxidizing system was reported by Kim:[109] 2-nitrobenzenesulfinyl chloride and potassium superoxide. The active species was the *in situ* generated sulfinylperoxy intermediate (**24**). Several aryl alkyl, aryl benzyl and dibenzyl sulfides were oxidized under these conditions to the corresponding sulfoxides in very high yields (Scheme 34).[109]

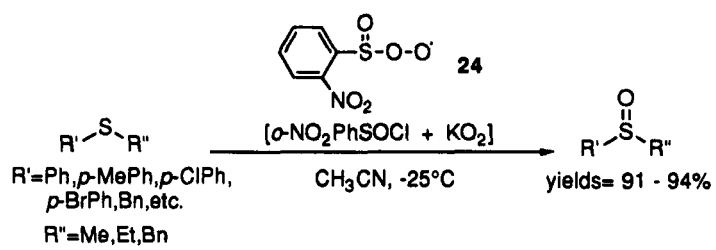
2.11. Other Oxidizing Agents

2.11.1. Organoselenium Reagents

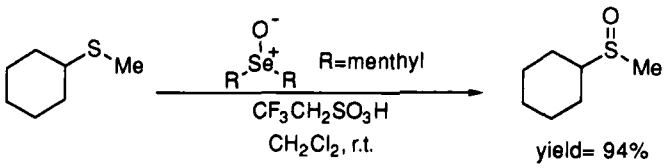
Benzyl selenoxide[110] and (*p*-methoxyphenyl)selenoxide[111] in acetic acid as solvent, have been used for the sulfoxidation of different sulfides. Recently, Rayner reported a mild and selective sulfoxidation using the selenoxide-sulfonic acid system. This combination allowed the use of more practical solvents such as dichloromethane (Scheme 35).[112,113]

2.11.2. Inorganic Peroxyacids and Salts

Oxone® is a stable form of potassium hydrogen persulfate, containing also potassium hydrogen sulfate and potassium sulfate. This oxidizing agent was first reported for the oxidation of sulfides to sulfones.[114] Later studies showed the possibility of using Oxone® for the selective oxidation to sulfoxides under controlled conditions. Thus, diarylsulfides yielded predominantly diarylsulfoxides in a phase transfer controlled oxidation by Oxone® (Tetrabutylammonium



SCHEME 34



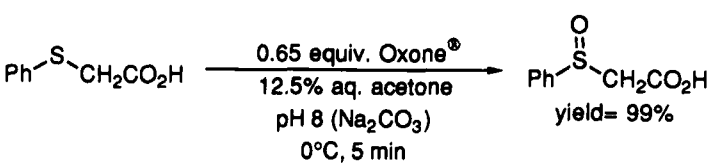
SCHEME 35

bromide, water/CH_2Cl_2 as solvent).[115] In 1990 Quallich[116] reported the selective oxidation of sulfides to sulfoxides using 1.2 equiv. of Oxone® in water/acetone. However, Webb[117] described more recently the sulfoxidation of various sulfides by 0.65 equiv. of Oxone® in 12.5% aqueous acetone, buffered to pH 8, with modest to excellent yields (Scheme 36).[117] In this case, an *in situ* generation of dimethyldioxirane was believed to be involved (see above). Using 1.3 equiv. of Oxone® and room temperature, the corresponding sulfones were obtained in high yields.

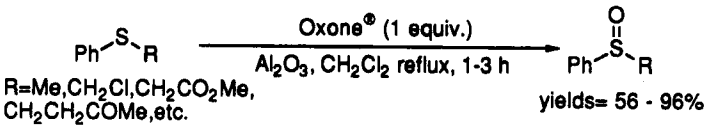
The use of the system Oxone®-wet alumina is another variety reported for this kind of sulfide oxidation. Under stoichiometric control (1 equiv. of Oxone®) sulfoxides were exclusively obtained. Excess of oxidant yielded the sulfones (Scheme 37).[118]

Sodium perborate oxidation, developed by McKillop,[119,120] is one of the best known methods for the selective sulfoxidation of sulfides. This method has been used with a wide variety of substrates,[121,122] and in some cases, such as the selective oxidation of the *N,N*-dimethyl-1-(2-ethylthiophenyl)ethylamine (**25**), it showed to be better than several other oxidants (Scheme 38).[123]

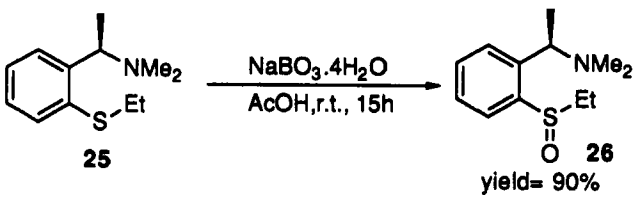
Although permanganate salts are generally used for sulfone synthesis, barium permanganate [$Ba(MnO_4)_2$] in refluxing acetonitrile has been reported for the mild and selective oxidation of sulfides to sulfoxides with modest to high yields.[124] Zinc bismuthate [$Zn(BiO_3)_2$] has also been employed for the sulfoxidation of sulfides.[125]



SCHEME 36



SCHEME 37



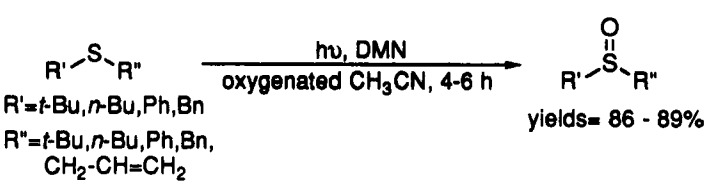
SCHEME 38

2.12. Photochemical Oxidation

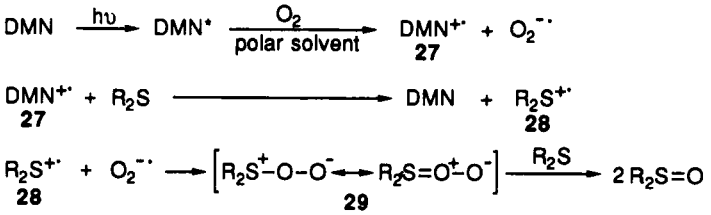
Photooxidation of organic sulfides has been extensively studied under a variety of conditions. Direct photooxidation in the presence of oxygen has been described for some aliphatic and aromatic sulfides.[126,127]

Recently, Bhalerao reported the efficient and selective photooxidation of several sulfides to sulfoxides under 1,4-dimethoxynaphthalene (DMN) sensitization. This reaction is carried out through an electron transfer mechanism without involving singlet oxygen (Scheme 39).[128] The sulfide radical cation (**28**) is generated by a one-electron transfer from the sulfide to the DMN radical cation (**27**), the former reacting with the oxygen radical anion to form the zwitterion (**29**). Finally the bimolecular reaction with a sulfide renders two molecules of sulfoxide (Scheme 40).[128]

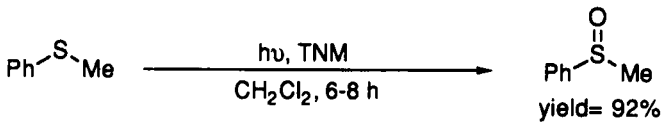
Excellent results have also been obtained using tetranitromethane (TNM) as electron acceptor in photooxidation of sulfides.[129] Various aryl alkyl, dialkyl, diaryl and dibenzyl sulfoxides were obtained in good to excellent yields. Overoxidation to sulfones did not occur even in excess of TNM and prolonged photooxidation (Scheme 41).[129]



SCHEME 39



SCHEME 40



SCHEME 41

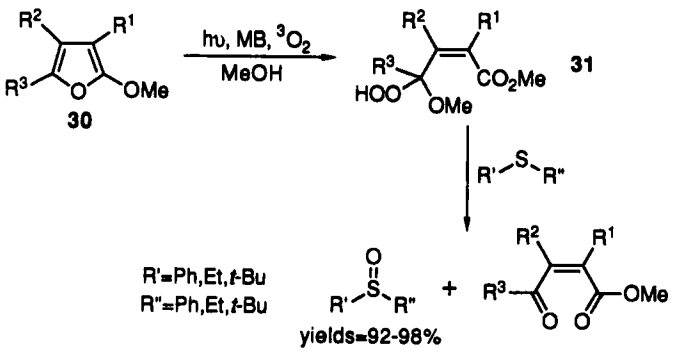
Photooxygenation of substituted diphenyl sulfides on irradiated titanium dioxide (TiO_2) powders suspended in oxygenated acetonitrile, afforded the corresponding sulfoxides in good yields (73–95%).[130,131] However, dibenzyl sulfides suffered C-S cleavage under similar conditions. This TiO_2-photocatalyzed reaction is initiated by the formation of a surface bound radical cation generated by interfacial electron transfer. The photogenerated hole, located at the surface of the irradiated semiconductor, is trapped by an adsorbed sulfide yielding the adsorbed sulfide radical cation.[131]

Photooxidation involving singlet oxygen has been reported using different sensitizers such as rose bengal,[132–134] tetraphenylphosphine (TPP),[132–134] methylene blue (MB), or 10-methylphenothiazine (MPT).[135] The proposed mechanism involves also the zwitterion **29** (see Scheme 40).[136,137] Foote has also reported the synglet oxygen photooxidation of thiiranes,[138] but only alkyl thiiranes in non-nucleophilic solvents gave thiirane oxides as main product.

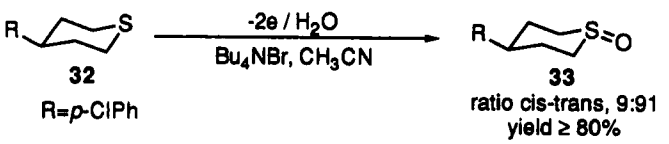
Recently, Scarpati *et al.* described an indirect way to obtain sulfoxides by photooxidation. Oxidation of 2-methoxyfurans (**30**) by methylene blue sensitized photooxidation afforded a strong oxidant (**31**) which concomitantly oxidized sulfides to sulfoxides in high yields (Scheme 42).[139]

2.13. Electrochemical Oxidation

Electrochemical oxidation of sulfides to sulfoxides has obtained the best results using bromide salts as electrolytes.[140,141] Sawaki[142] reported that the electrooxidation of 4(*p*-chlorophenyl)thiane (**32**) in aqueous organic solvent gave predominantly the trans sulfoxide using tetrabutylammonium bromide as electrolyte (Scheme 43).[142]



SCHEME 42



SCHEME 43

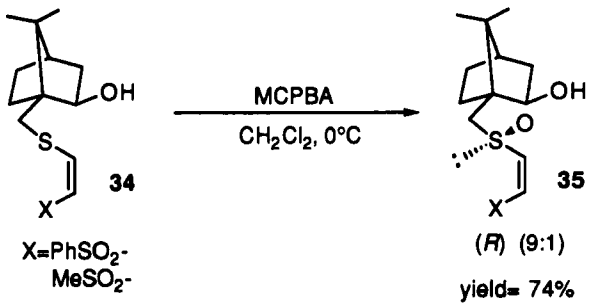
It appears that the electrolysis of **32** in the presence of sulfuric acid gave preference to the cis-isomer (ratio cis-trans, 67:33).

3. DIASTEREOSELECTIVE OXIDATION

In recent years, there has been a variety of reports concerning the diastereoselective oxidation of sulfides to sulfoxides. Steric hindrance or participation of neighboring groups are often involved in this selectivity.

Proximal hydroxy groups have shown to play an important role in promoting the complete stereoselectivity of sulfide oxidation.[143] It has been extensively studied in the case of 10-mercapto-2-*exo*-hydroxybornyl derivatives, since the corresponding sulfoxides have received a great deal of interest in asymmetric Diels Adler reactions[144,145] and Michael additions.[146–148]

Thus, vinyl sulfoxides such as the (1*S*)10-mercaptoisoborneol derivative (**35**) was obtained with high diastereoselectivity by *m*-chloroperbenzoic acid (MCPBA) oxidation in CH_2Cl_2 at 0°C (Scheme 44).[144] This specificity was attributed to the incipient hydrogen bonding between the substrate hydroxy group and the percarboxylic acid. Solvents like acetone or methanol decreased diastereoselectivity by competing for hydrogen bond formation.



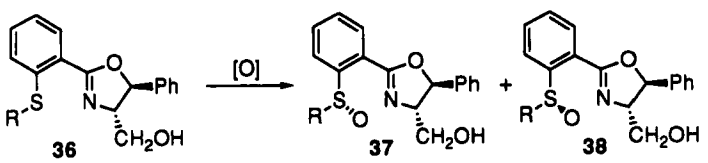
SCHEME 44

Later, Annunziata *et al.*[149] improved the diastereoselectivity by lowering the reaction temperature (−78°C) obtaining only one diastereoisomer in 90% yield. The corresponding acetoxy derivative was also oxidized to give only a 65:35 mixture of the epimers, pointing to the role of the hydroxy group in promoting diastereoselectivity. Related substrates have been investigated by Koizumi[145,150–153] and Ridley.[147]

Aryl sulfides containing enantiomerically pure 4-hydroxymethyl substituted oxazolidines (**36**) gave sulfoxides with good levels of diastereocontrol using MCPBA or TBHP/Ti(O*i*Pr)$_4$[154] (Scheme 45).

It is noteworthy that related aryl sulfides such as **26** (see Scheme 38) were obtained with up to 78% de. In the case of **36**, hydroxy-directing effect contributes greatly on selectivity.

MCBPA and TBHP/Ti(O*i*Pr)$_4$ were reported for the diastereoselective oxidation of 2,4-disubstituted thiazolidines.[155] MCBPA has also been used in other hydroxy-delivered oxidations.[156,157] Ozone is another oxidant which has been described for the highly diastereoselective oxidation of cyclohexenyl methyl sulfides containing a proximal hydroxy group.[158]



SCHEME 45

A directing effect has also been noted in the case of a neighboring amido proton. Glass[159] reported a very high diastereoselectivity for the dimethyldioxirane oxidation of 1,2-dithiolan-3-ones bearing an amide group at position 4 (**39**). The highest diastereoselectivity (trans-cis, 18:1) was achieved at −78°C (Scheme 46).[159]

In contrast, similar studies about the oxidation of 3-substituted thietanes[160] gave only modest diastereoselectivity.

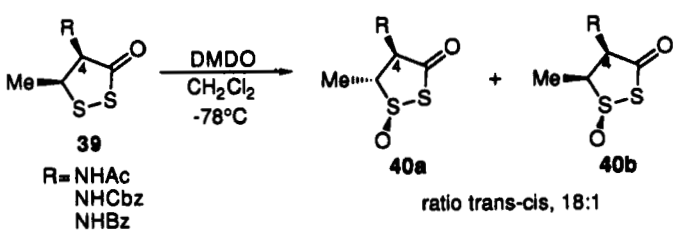
The area of β-lactam compounds, especially penicillins and cephalosporins, is full of examples of diastereoselective oxidation of sulfides. The amide-directed effect on the oxidation of 6-acetamidopenicillin derivatives (i.e.: Penicillin V (**41**)) led exclusively to the corresponding β-sulfoxide (*S*) (**42**), using different oxidants[7,161,162] (Scheme 47).[162] Similar results were reported in the case of cephalosporins.[161,8,70]

Several 6-halopenicillin derivatives have been oxidized by dimethyldioxirane (DMDO) with complete stereocontrol; only one of the corresponding diatereoisomeric sulfoxides was obtained in each case. Steric effects were mainly responsible for this selectivity (Scheme 48).[163]

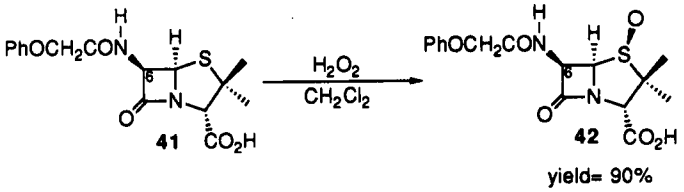
A remarkably high diastereoselectivity has been reported on the use of *tert*-butyl hypochlorite (*t*-BuOCl) as diastereoselective oxidant for simple acyclic sulfides (**43**).[164] Interestingly, for aryl sulfides like **43**, *t*-BuOCl was by far the best diastereoselective oxidant, while MCPBA and $NaIO_4$ gave the opposite diastereoisomer and modest selectivity (Scheme 49).[164]

In contrast, *t*-BuOCl and MCPBA have demonstrated poor diastereoselectivity for the oxidation of *N*-arylthio- and *N*-alkylthioderivatives of Evans oxazolidinones.[165]

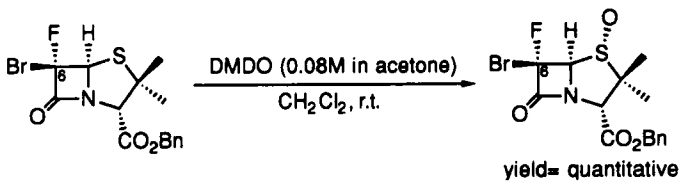
The combination of $MoO_2(acac)_2$/TBHP has been reported for the oxidation of cyclic and open-chain sulfides derived from lactic acid and 3-hydroxybutiric acid. Diastereoselectivity and yields were only modest.[166]



SCHEME 46



SCHEME 47

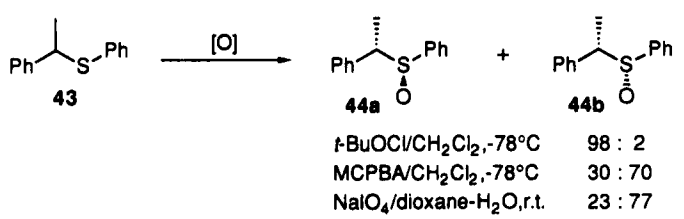


SCHEME 48

4. ENANTIOSELECTIVE OXIDATION

Enantiomerically pure sulfoxides are increasingly used as chiral synthons and are now among the most important intermediates for enantioselective carbon-carbon bond formation. Being the most useful and promising method for the preparation of enantiomerically pure sulfoxides, asymmetric oxidation continues to attract a great deal of attention within the organic chemistry community.

There are two main methods used for this asymmetric oxidation, those based on modified Sharpless asymmetric epoxidation conditions and those based on chiral oxaziridines. The metallo(salen) complexes- and metallo porphyrin-catalyzed oxidations are among the other methods developed in recent years for the enantioselective oxidation of sulfides.



SCHEME 49

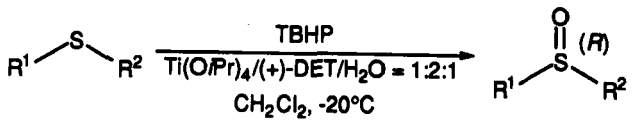


TABLE I Asymmetric oxidation of aryl akyl and dialkyl sulfides by TBHP and $Ti(OiPr)_4/(+)$-DET/H_2O.[176,177]

Entry	R^1	R^2	*yield(%)*	*ee(%)*
1	*p*-tolyl	methyl	90	89
2	*o*-anisyl	methyl	70	84
3	*p*-anisyl	methyl	58	86
4	1-naphthyl	methyl	98	89
5	2-naphthyl	methyl	88	90
6	*p*-tolyl	ethyl	71	74
7	*p*-tolyl	*n*-butyl	75	20
8	2-naphthyl	*n*-propyl	78	24
9	*t*-butyl	methyl	72	53
10	*n*-octyl	methyl	77	53
11	cyclohexyl	*n*-butyl	67	54
12	methyl	CH_2CO_2Me	84	63

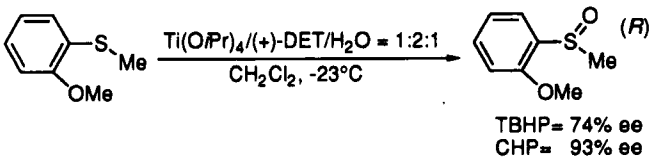
4.1. Modified Sharpless Methodology

Modification of the Sharpless epoxidation procedure was first reported independently by Kagan[167] and Modena.[191]

Kagan[167–177] discovered by serendipity that deactivated Sharpless reagent was excellent to promote asymmetric oxidation of sulfides to sulfoxides. Thus, *tert*-butyl hydroperoxide (TBHP) (1.1 equiv.) and titanium tetraisopropoxide [$Ti(O$-$iPr)_4$]—diethyltartrate (DET)—water (1:2:1) reagent, in dichloromethane, at −20°C afforded sulfoxides in good yields and with an enantiomeric excess (ee) often in the range of 80–90%. In Table I are summarized the results obtained by Kagan.

High enantioselectivity (80–90%) was obtained for aryl methyl sulfides (Entries 1–5). Bulky alkyl groups decreased ee's (Entries 6–8). Dialkylsulfides led to optically active sulfoxides with lower enantiomeric excess (<60%) (Entries 9–12).

A further improvement was obtained when cumene hydroperoxide (CHP) was used instead of TBHP. Asymmetric induction was significantly increased for all the reactions and the use of CHP allowed to reduce the amount of Ti complex to 0.2 mol equiv. (Scheme 50).[178,179]



SCHEME 50

More recently, Kagan[180] has described very well defined experimental conditions for the preparation of the titanium complex, which are needed to ensure reproducibility. It is noteworthy that the same author has also reported that further enrichment of optically active sulfoxides can be achieved by preparative flash chromatography.[181]

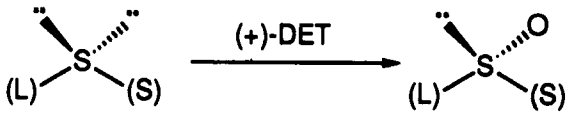
While the mechanism of this asymmetric oxidation of sulfides by water-modified Ti reagent remains a matter of debate, prediction of the absolute configuration of the sulfoxide is well established. Being the large group (L) an aromatic ring and the small group (S) an alkyl group, sulfoxides have *R* configuration when (+) DET is used (Scheme 51).[177]

Figure 3[176] shows a tentative model for this asymmetric oxidation, assuming that the reaction goes through a bititanium species and that tartrate acts as a tridentate ligand.

1,3-Dithiane 1-oxide derivatives (**47**) serve as chiral acyl anions equivalent for the enantioselective synthesis of a wide range of products.[182] During the development of an efficient synthesis of optically pure **47**, Page[183–187] found that 2-acyl-1,3-dithianes (**45**) undergo Kagan's sulfoxidation with a higher enantioselectivity than simple 2-alkyl dithianes. Steric differentiation between the two groups attached to the sulfur atom and the effect of the presence of a polar group within the molecule may be the cause of this improvement.[183] After sulfoxidation, the acyl group can be eliminated cleanly with NaOH to afford the desired 1,3-dithiane 1-oxide (**47**) (Scheme 52).[183]

Kagan's reagent has also been used for the asymmetric oxidation of aryl ferrocenyl sulfides to reach the corresponding sulfoxides in very high enantioselectivity (>99% ee), as long as the aryl groups were devoid of electron-withdrawing groups (Scheme 53).[188]

In a similar approach, Thomas *et al.* have described the oxidation of methylthio substituted tricarbonyl(η^6-arene)chromium(0) complexes under Kagan's conditions giving the corresponding sulfoxides in 90–95% ee. The reaction conditions were ineffective for other alkylthio and arylthio substituents (Scheme 54).[189,190]



SCHEME 51

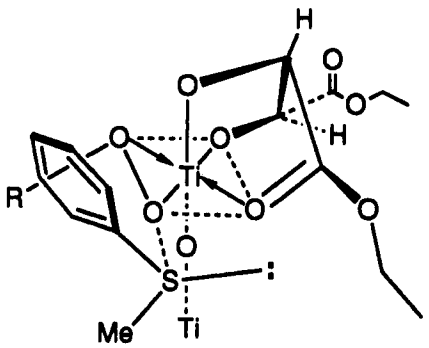
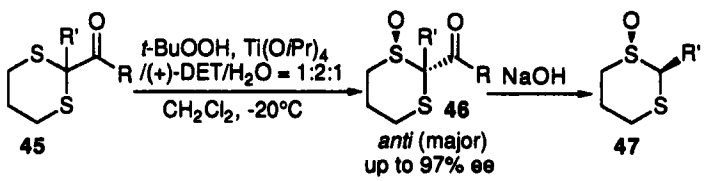
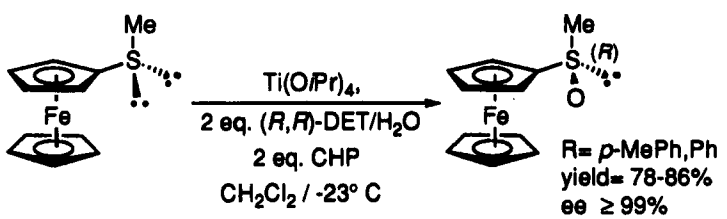


FIGURE 3



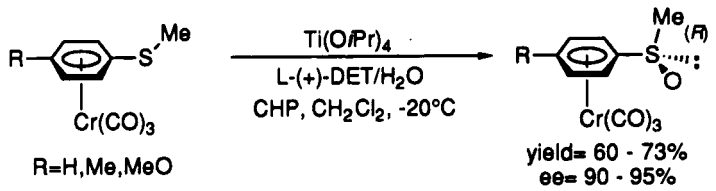
SCHEME 52



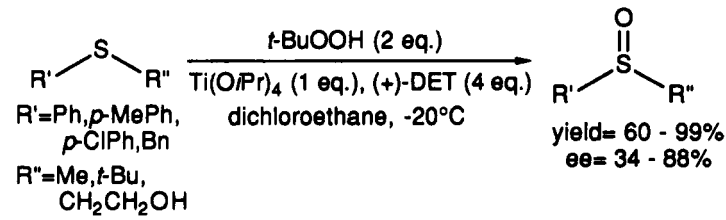
SCHEME 53

Contemporaneous with Kagan's work, Modena *et al.*[191–199] described the asymmetric oxidation of sulfides using several Ti complexes [($Ti(OiPr)_4$, $VO(OiPr)_3$, $MoO_2(acac)_2$] with a larger excess of DET (4 eq. molar) and without adding water. The best results were found when $Ti(OiPr)_4$ was used (Scheme 55).[191]

Modena also noted that for asymmetric oxidation of S-methyl β-hydroxysulfides, protection of the hydroxy group improved yields and enantioselectivity.[195]



SCHEME 54

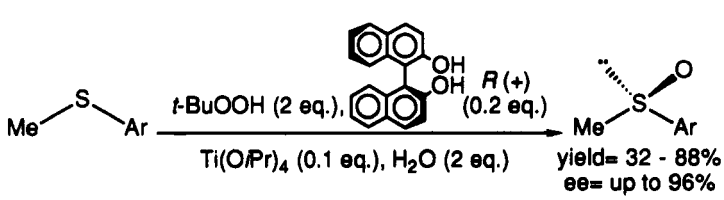


SCHEME 55

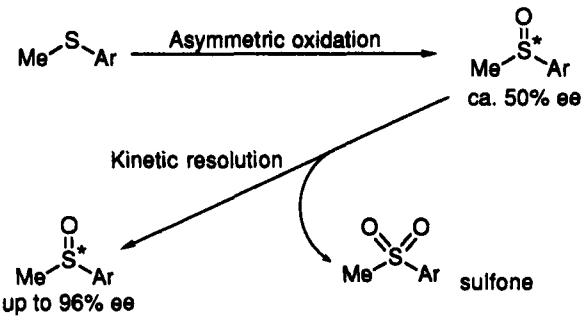
In a modification of Kagan's procedure, Uemura *et al.*[200,201] have reported the use of *R*(+)-binaphthol instead of diethyltartrate as the chiral source. The highest enantioselectivities (up to 96% ee) were obtained with TBHP at 25°C and 2 mol% of the catalyst (Scheme 56).[200] All the sulfoxides obtained had the *R* configuration.

As in the case of Kagan's reagent, 0.5 to 3.0 eq. of water was necessary, not only to produce an effective catalyst but also to maintain the catalyst activity of the Ti-binaphthol complex for longer time. Interestingly, mechanistic studies revealed that the initial asymmetric oxidation (≈50% ee) is followed by a selective sulfoxide oxidation, resulting in an enhancement of the ee's values around 84–96% (Scheme 57).[201] Consequently, the complex $Ti(OiPr)_4$-binaphthol catalyzes not only the asymmetric oxidation of sulfides but also the kinetic resolution of sulfoxides.

Choudary *et al.* have also adapted Kagan's methodology using titanium catalysts supported on Al_2O_3, SiO_2, ZrO_2 and montmorillonite. Thus, high enantioselectivity has been achieved using montmorillonite K10 as solid support.[202]



SCHEME 56



SCHEME 57

4.2. Chiral Oxaziridines

An important class of synthetically useful stoichiometric chiral sulfide oxidizing reagents are the *N*-sulfamyloxaziridines and *N*-sulfonyloxaziridines, which have been developed by Davis.[203–211]

Chiral 2-sulfamyloxaziridines (**48**) afforded high asymmetric oxidation of nonfunctionalized sulfides to sulfoxides (53–91% ee) (Scheme 58).[205] Enantioselectivities were comparable to those using Kagan's methodology.

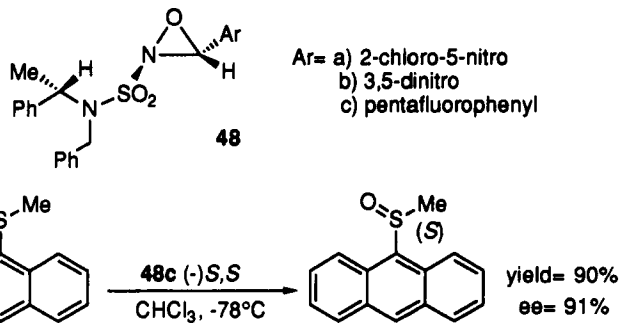
The rate of oxygen transfer by the oxaziridine was slower when bulky and/or electron-donating substituents were attached to the nitrogen and carbon atoms of the oxaziridine ring.[205]

Many *N*-sulfonyloxaziridines have been developed in recent years. Thus, the first report for the asymmetric sulfide oxidation was the (10-camphorsulfonyl)oxaziridine (**49**) (Figure 4), but the levels of enantioselectivity were only modest (13–40% ee).[203,204]

Later, oxaziridines like (+) (2*R*,8a*S*)-(camphorylsulfonyl)oxaziridine (**50**),[206,207] (2,2-dichlorocamphorylsulfonyl)oxaziridine (**51**),[211] (3-oxocamphorylsulfonyl)oxaziridine (**52**)[212] and related lactone **53**[213,214] were developed (Figure 5). The ee's were at best only modest (5–74%).

The best result up to date for the asymmetric oxidation of sulfides was obtained with *N*-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine (**54**) (Figure 5).[208,209] This reagent was very efficient for the enantioselective oxidation of alkyl aryl sulfides, functionalized sulfides and for *tert*-butyl methyl and *tert*-butyl benzyl sulfides. The corresponding sulfoxides were obtained in very high and predictable stereoselectivities (66–>95% ee). In most cases ee's values were higher than using Kagan's reagent.

Likewise other oxaziridines, steric effects are primarily responsible for the enantiofacial recognition. Thus, high ee's (>90%) were observed when the difference in size of groups bonded to the sulfur was large, i.e., *t*-Bu vs. methyl,



SCHEME 58

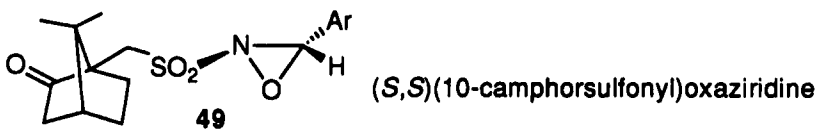


FIGURE 4

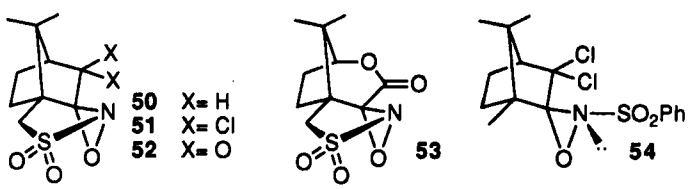
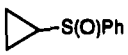
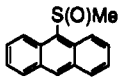
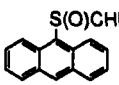


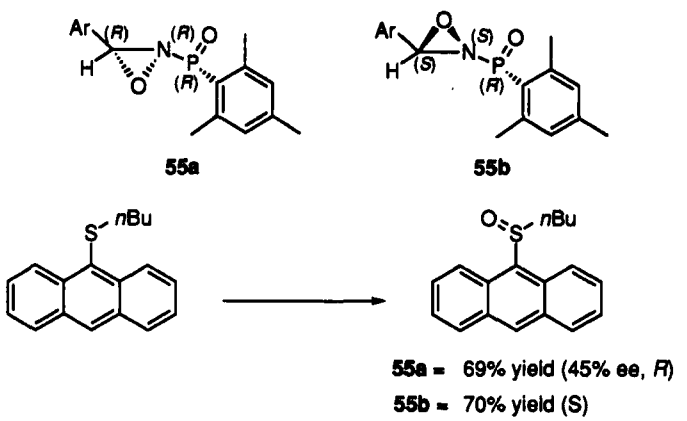
FIGURE 5

benzyl, etc. (entries 7 and 8, Table II), meanwhile similar size in both substituents gave poor selectivity (entry 9). However, high ee's in non polar solvents for aryl alkyl sulfides suggest that also a stereoelectronic component is contributing to the process.

A different kind of oxaziridines, chiral *N*-phosphinoyloxaziridines, have also been shown to produce asymmetry in sulfide oxidation.[215] Both diastereoisomeric *N*-phosphinoyloxaziridines **55a** (configuration $R_CR_NR_P$) and **55b** (config. $S_CS_NR_P$) (Scheme 59)[215] converted sulfides into chiral sulfoxides at 0–20°C with little or no sulfone formation. In all cases, enantioselectivity was moderate and the opposite configuration of the sulfoxide was obtained with each diastereoisomer. Having both diastereoisomers the same configuration at the phosphorus atom, these results indicate, against any prediction, that the rather bulky mesitylphenylphosphinoyl group is not relevant for chiral recognition.

TABLE II Asymmetric oxidation of sulfides to sulfoxides by *N*-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine (−) **54**, in CCl_4 at 20°C.[209]

Entry	*Sulfoxide*	*%ee(config.)*	*yield*
1	*p*-MePh-S(O)-Me	>95 (*S*)	95%
2	*p*-MeOPh-S(O)-Me	80 (*S*)	74%
3	*p*-MePh-S(O)-CH_2Ph	94 (*S*)	94%
4		92 (*S*)	90%
5		95 (*S*)	60%
6		94 (*S*)	60%
7	Me-S(O)-CMe_3	94 (*S*)	84%
8	$PhCH_2$-S(O)-CMe_3	91 (*S*)	80%
9	Me-S(O)-$(CH_2)_7CH_3$	13 (*S*)	94%



SCHEME 59

In terms of selectivity and efficiency, Davis' and Kagan's asymmetric sulfoxidation procedures seem to be complementary. Direct comparison of the oxidation of 2,3-epoxy sulfides,[216] showed that Davis' reagent gave good selectivity when phenyl epoxy sulfide was used as substrate, while Kagan's method was better for the methyl epoxy sulfide. In another comparative study, Davis' oxaziridines proved to be clearly superior for the asymmetric oxidation of aryl and alkyl 2-(trimethylsilyl)ethyl sulfides;[217] however, it must be mentioned that simple methyl and ethyl substituents at the sulfur atom were not included in this comparison.

Recently, Page *et al.*[218,219] have reported a new system for the asymmetric oxidation of dialkyl sulfides using hydrogen peroxide and catalytic sulfonylimines. The highest enantioselectivities (from 40 to 98% ee) were obtained using the oxocamphorsulfonylimine acetal (**56**) (Scheme 60).[219]

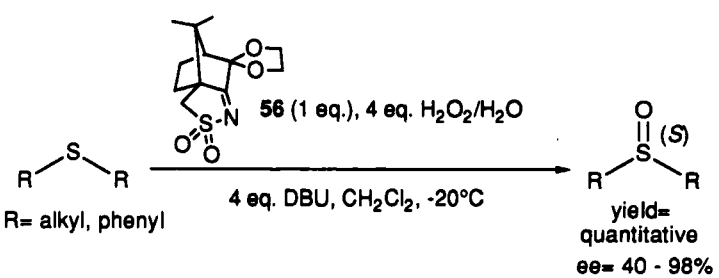
Addition of hydrogen peroxide to the sulfonylimine (**56**) in basic conditions produces a highly reactive hydroperoxyamine (**57**) that transfers oxygen to the sulfide in an enantioselective manner. The catalytic cycle restarts when the sulfonylimine (**56**) is regenerated by dehydration of hydroxyamine (**58**) (Scheme 61).[219] Formation *in situ* of Davis' oxaziridine (**59**) is possible, but authors rule out **59** as the oxidizing species because the stereochemical outcome is opposite to that observed using directly Davis' oxaziridine.

4.3. Metallo(salen)-Catalyzed Oxidation

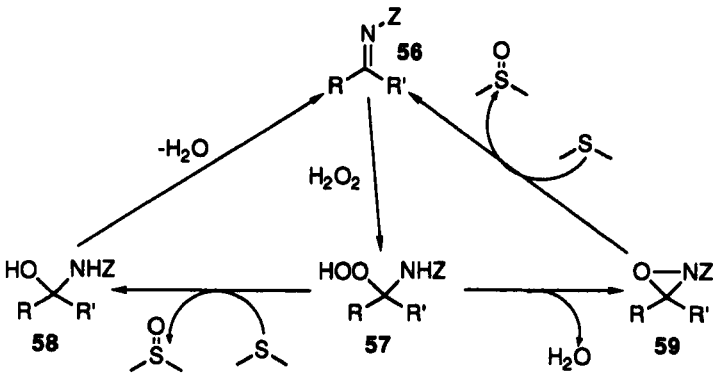
Chiral disalicylaldehyde ethylenimine (salen) Ti and V complexes have been used as catalysts for enantioselective sulfide oxidation.

In 1986, Fujita reported the asymmetric oxidation of aryl methyl sulfides by hydroperoxides (THBP and CHP) with optically active (salen)oxovanadium(IV) complexes as catalysts.[220,221] The best result was obtained with complex **60**, giving (*S*)-sulfoxides in optical yields that ranged from 7 to 40% ee. Fujita has also developed a binuclear (salen)titanium(IV) complex (**61**)[222,223] which was used to catalyze asymmetric oxidation of methyl phenyl sulfide by trityl hydroperoxide in methanol at 0°C. The methyl phenyl (*R*)-sulfoxide was obtained in very high yields and 60% ee (Scheme 62).[223]

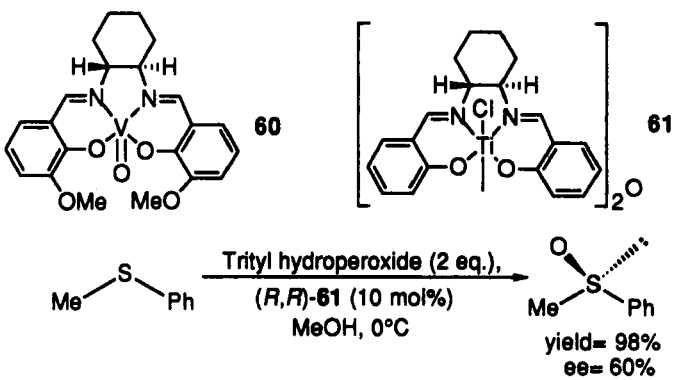
The related *N*-salicyldene-L-aminoacids(sal-L-aa) titanium(IV) complexes have also been used in combination with *t*-butyl hydroperoxide to obtain sulfoxides in ee's up to 21%.[224]



SCHEME 60



SCHEME 61



SCHEME 62

Taking into account the clear homology between epoxidation and sulfide oxidation, Jacobsen *et al.* have reported the asymmetric oxidation of sulfide with H_2O_2 catalyzed by the chiral (salen)manganese complex (**62**) (Figure 6),[225]

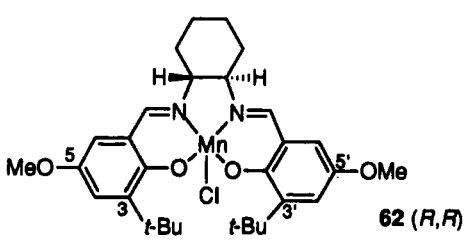
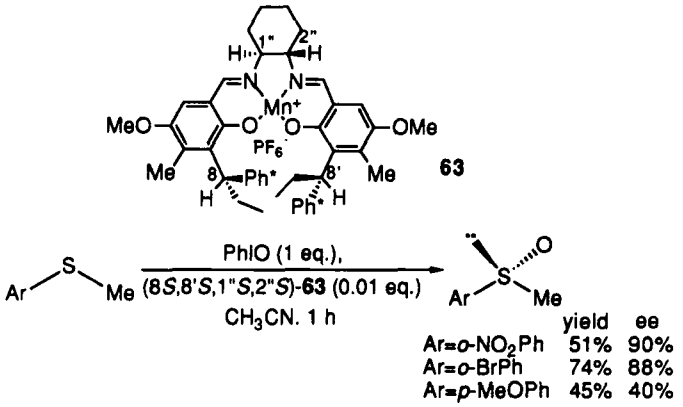


FIGURE 6



SCHEME 64

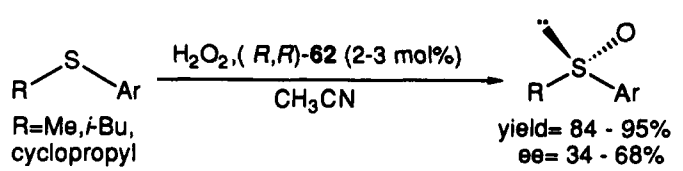
which had been previously used with great success in epoxidation of conjugated olefins.

Unbuffered hydrogen peroxide oxidation of aryl sulfides, catalyzed by 2–3 mol% of **62** in acetonitrile, rendered the corresponding sulfoxides with high yield and moderate enantioselectivity (Scheme 63).[225]

It was not surprising to observe that ligand characteristics for increasing enantioselectivity in sulfide oxidation were similar to those for optimal selectivity in epoxidation,[226] i.e., the presence of bulky substituents on 3,3′ and 5,5′ positions of **62** favored substrate approach closer to the disymmetric diimine affecting selectivity.

In 1994, Katsuki *et al.* reported the asymmetric synthesis of chiral sulfoxides using different (salen)manganese(III) complexes.[227–229] They found that complex **63** showed high asymmetric induction up to 90% ee (Scheme 64).[227] Unlike Jacobsen's work,[225] iodosylbenzene was the best oxidant in all cases.

Aryl substituents bearing electron-withdrawing groups showed higher enantioselectivity than those bearing electron-donating groups; Katsuki *et al.* suggested that the reaction proceeded *via* a charge transfer complex.



SCHEME 63

More recently, the asymmetric oxidation of sulfides with molecular oxygen and catalyzed by other Mn(III) complexes, the β-oxo aldiminato Mn(III) complexes (i.e.: **64**, R = 2,4,6-trimethylphenyl), was informed by Mukaiyama *et al.*[230] They found that addition of a sacrificial aldehyde bearing a bulky alkyl group, such as *t*-butyl, can improve optical purity (Scheme 65).[230]

It should be noted that the opposite absolute configuration (*S*) was obtained when *N*-methylimidazole was added. These results were in agreement with those obtained for the asymmetric epoxidation of olefins by a similar procedure.[231]

4.4. Metallo Porphyrin-Catalyzed Oxidation

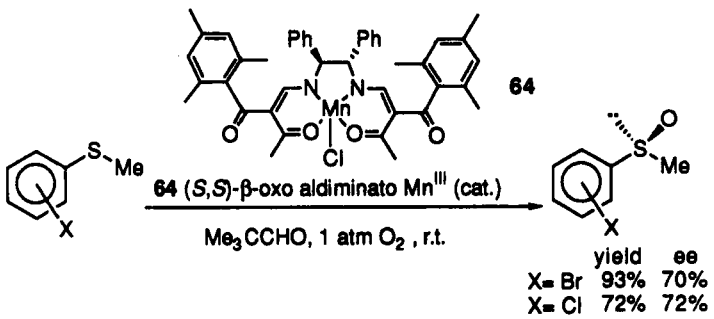
Synthetic chiral porphyrins as cytochrome P-450 models have been reported to catalyze enantioselective sulfide oxidations.[232–241]

In 1990, Groves and Viski described the synthesis and applicability of chiral binaphthyl chloroiron(III) porphyrin complex (**65**-$Fe^{III}Cl$) (Figure 7).[236]

This binaphthyl-bridged metalloporphyrin exhibited strong asymmetric interaction with substrates and robustness to endure the course of catalytic oxygenation. Unfortunately, good results in terms of enantioselectivity in epoxidation and hydroxylation were not followed by similar results in sulfoxidation, since aryl methyl (*R*)-sulfoxides were obtained with only 14–48% ee. Iodosylbenzene was used as stoichiometric oxidant (Scheme 66).[236]

In a related work Naruta and Maruyama[237,238] have reported the obtention of chiral sulfoxides in moderate to good enantioselectivities by iodosylbenzene as oxidant with "twin coronet" porphyrins (**66**) as catalyst, in the presence of 1-methylimidazole (Scheme 67).[237]

These "twin coronet" porphyrins bear chiral binaphthalene moieties rigidly linked to both faces of the porphyrin ring to form chiral substrate binding sites. The addition of 1-methylimidazole as an axial ligand, remarkably increased stereoselectivity, probably due to changes on porphyrin structure in the vicinity



SCHEME 65

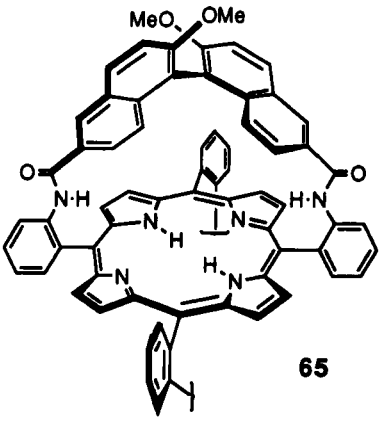
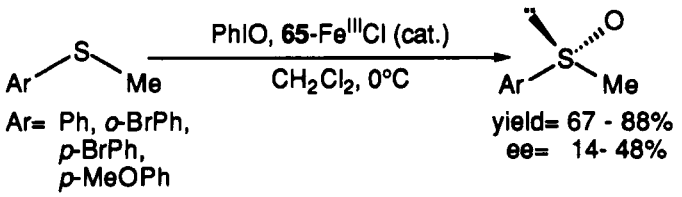
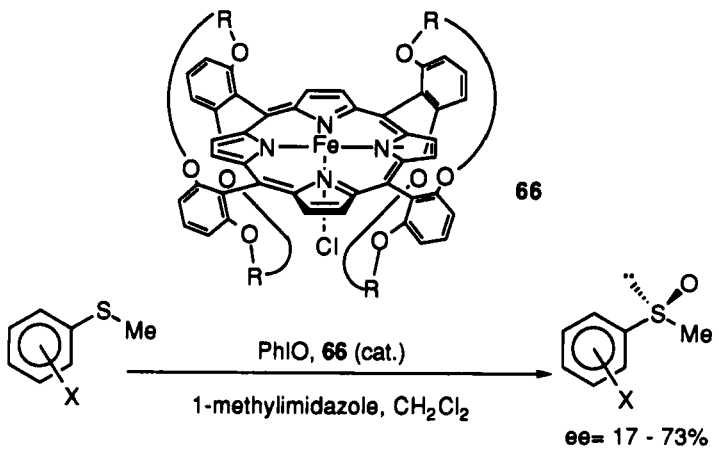


FIGURE 7



SCHEME 66



SCHEME 67

of the iron. Alike other asymmetric oxidants, steric hindrance around the sulfur atom rather than the electronic character of the substituents is dominant for the enantiofacial recognition.

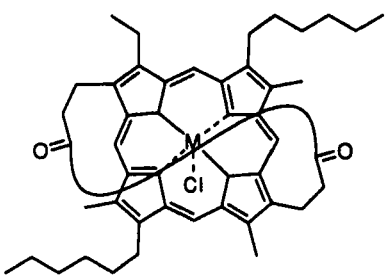
In 1992, Inoue[239,240] reported the oxidation of aryl methyl sulfides by iodosylbenzene using a C_2-chiral 1,4-xylylene-strapped chloroiron porphyrin complex (**67**-$Fe^{III}Cl$) as catalyst, yielding the corresponding sulfoxides in 18–71% ee. Porphyrin moiety has no chiral substituents but diastereotopic faces due to the strap (Scheme 68).[239]

The effect of increasing selectivity by adding imidazole as axial ligand was also observed. It was speculated that imidazole may block the unstrapped face of the porphyrin leaving only the most sterically demanding face available for the oxygen transfer reaction.

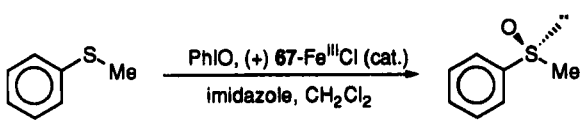
In the other hand, Halterman *et al.* used catalytic amounts of a D_4-symmetrical chloromanganese tetra(dimethanoanthracenyl)porphyrin complex (**68**) (Figure 8)[241] for the iodosylbenzene oxidation of aryl alkyl sulfides. Good chemical yields were obtained and enantioselectivities ranged from 40 to 68% ee.

4.5. Miscellaneous Asymmetric Oxidation

Chiral flavins have also been described to obtain chiral sulfoxides.[27] *N*(5)-Ethylflavinium derivative (**69**) was reported as an asymmetric catalyst for the oxidation of methyl aryl sulfides in the presence of hydrogen peroxide. The degree of enantioselectivity ranged from modest to good (19–65% ee). In fact, the oxidizing species is the hydroperoxyflavin (**70**) which is regenerated by the



67, Strap= -$NHCH_2C_6H_4CH_2NH$-



yield= 68%
ee= 43%

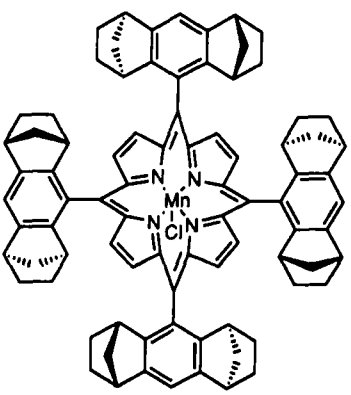
SCHEME 68

hydrogen peroxide (Scheme 69).[27] The stereoselectivity obtained can be explained by the planar chirality of **69**, which is maintained during the oxygenation cycle.

In an original approach, Adam[242] opened up a new route for asymmetric sulfoxidations, i.e., the use of metal-coordinated sulfides. The prochiral sulfide was first coordinated to an optically pure ruthenium complex fragment (**72**), and then oxidized by dimethyldioxirane.[243] Oxidation of the coordinated sulfides gave the corresponding coordinated sulfoxides (**73**) in high chemical yields. The latter was then decomplexed with sodium iodide, affording the chiral sulfoxides (**74**) in variable ee's (Scheme 70).[242]

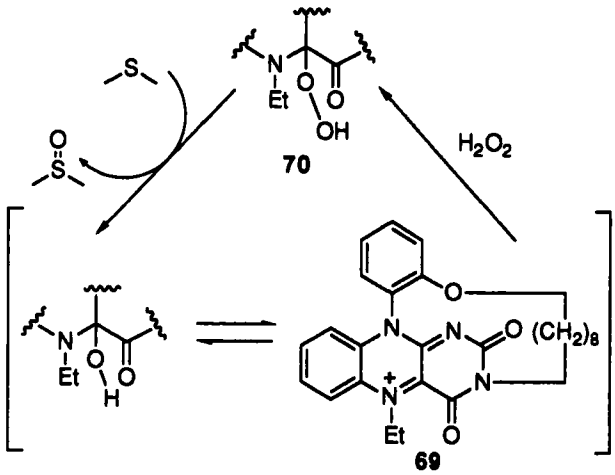
Cyclodextrins (CDs) also provide a chiral binding site capable of including several kinds of hydrophobic compounds and have been used to increase enantioselectivity of sulfoxidation.[244–250] In a comprehensive study, Sakuraba and Tanaka[250] reported that, for alkyl phenyl sulfide oxidation, β-cyclodextrin (β-CD) complexes gave higher chiral induction than α-CD complexes, with ee's ranging from 15 to 81%. The best optical yield was achieved when methyl 1-naphtyl sulfide (**75**) was treated with crystalline β-CD complex suspended in water at 0°C and using peracetic acid as oxidant. The corresponding (*S*)-sulfoxide (**76**) was obtained in an excellent chemical yield (Scheme 71).[250]

Other methods for asymmetric sulfoxidation can also be mentioned. Chiral micelles formed from chiral surfactants such as *N*-dodecyl-*N*,*N*-dimethylephedrine bromide, have been used for enantiomeric discrimination in oxidation of phenyl alkyl sulfides by sodium periodate (ee: 1.6 to 15%).[251] In 1990, a Russian group reported the use of ozonides of chiral phosphites as oxidant in combination with $Ti(OiPr)_4$.[252]

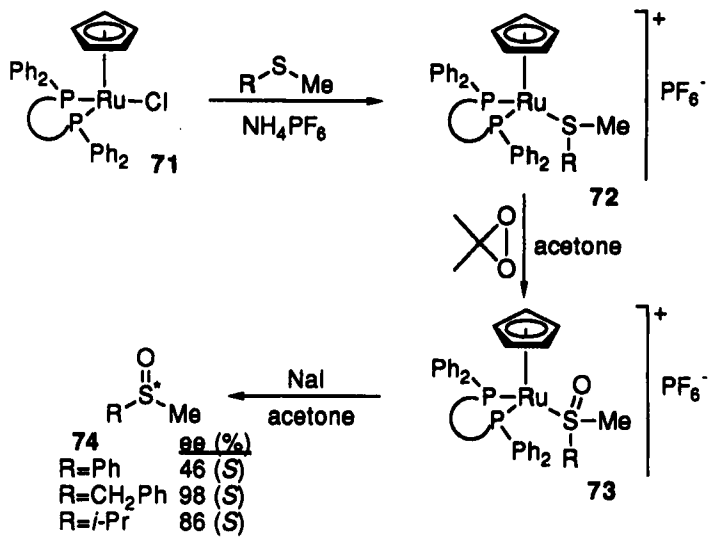


68

FIGURE 8

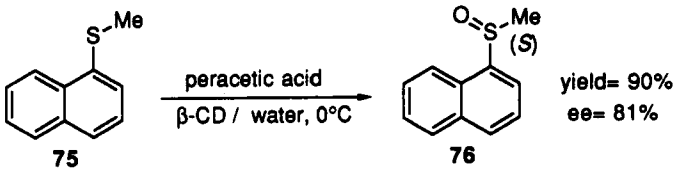


SCHEME 69



SCHEME 70

Imamoto *et al.*[253] first reported the use of polyvalent organoiodine compounds as asymmetric oxidizing agents. New iodosylbenzene-derived chiral reagents such as **77** (Figure 9),[253] oxidized cleanly prochiral aryl methyl sulfides to the corresponding optically active sulfoxides in moderate enantioselectivity (30–53% ee).



SCHEME 71

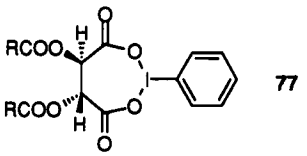


FIGURE 9

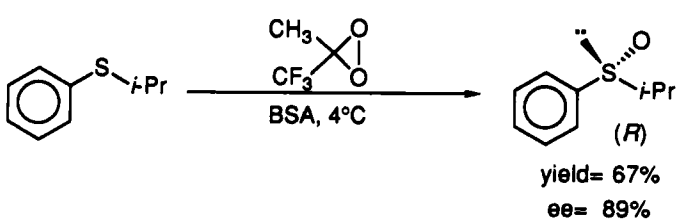
Bovine serum albumin (BSA), used as natural chiral auxiliary, has been used in combination with different oxidants[254–259] to prepare chiral sulfoxides (Scheme 72).[258]

5. BIOLOGICAL OXIDATION

5.1. Microbiological Oxidation

Since the first reported method in 1954,[260] many fungi and strains have been employed for the microbiological oxidation of sulfides to sulfoxides.[261]

Holland *et al.*[262–268] have extensively investigated the use of fungi such as *Helminthosporium* and *Mortierella isabellina* for the asymmetric oxidation of sulfides. *Helminthosporium* efficiently oxidized phenyl and benzyl alkyl sulfides,[262,263] *p*-alkylbenzyl methyl sulfides,[264] and isothiocyanate sulfides (**78–80**)[265,266] to the corresponding (*S*)-sulfoxides. Although chemical yields were not always good (sulfone was also obtained in some cases), ee's were generally above 80%.



SCHEME 72

Mortierella isabellina and *Helminthosporium* were complementary since the former produced the opposite *R* configuration at the sulfur,[266–269] albeit yields and enantioselectivities were sometimes lower than when using the latter (Scheme 73).[266]

Oxidation of alkyl aryl and allyl aryl sulfides by *Corynebacterium equi* was described by Otha.[270–272] Results showed high ee's (*R* configuration) and some overoxidation to sulfone, especially in cases where the alkyl chains were long (n-$C_{10}H_{21}$, n-C_4H_9) (Scheme 74).[270]

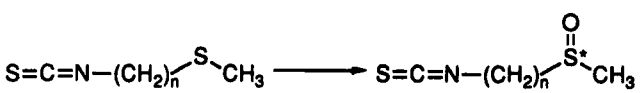
More recently, the same author[273] reported that 2-alkylethyl phenyl sulfides could be oxidized by *Rhodococcus equi* to afford the corresponding (*R*)-sulfoxide in high enantiomeric excess.

Buist *et al.*[274,275] demonstrated that Baker's Yeast (*Saccharomyces cerevisiae* NRC 2335) was capable of enantioselective sulfoxidation of fatty acid analogues. Thus, methyl *S*-benzyl-8-mercaptooctanoate (**81**)[275] was converted by Baker's Yeast to the (*S*)-sulfoxide **82** with 70% ee (Scheme 75a).[275]

Very recently, Roberts *et al.*[276,277] have described a highly enantioselective oxidation of methyl *p*-tolylsulfide (**83**) to the corresponding (*R*)-sulfoxide (**84**) using Baker's Yeast (in this case, *S. cerevisiae* NCYC 73) (Scheme 75b).[276] This transformation was performed with 92% ee and 60% yield, and the product was used as chiral auxiliary in the synthesis of key intermediates in the preparation of mevinic acid analogues.

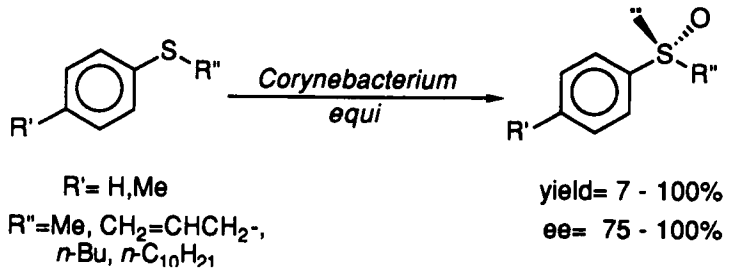
In 1995, Boyd and Dalton[279] reported the microbial oxidation of aryl alkyl and diaryl sulfides to optically active sulfoxides by selected strains of the bacterium *Pseudomonas putida*. For example, *P. putida* UV4 gave (*R*)-sulfoxides with very high enantioselectivity, although chemical yields for diaryl sulfoxides were extremely low (Scheme 76).[279] Dioxygenase enzymes were found to be responsible for this catalytic sulfoxidation. Interestingly, when another strain of *P. putida* was employed (NCIMB 8859), (*S*)-sulfoxides were obtained preferentially.

Recently, a comparative study of Kagan's and Davis' procedures and microbiological methods for the synthesis of optically active vinyl (*S*)-sulfoxides was reported (Figure 10).[280] The conclusion reached was that the three methods were

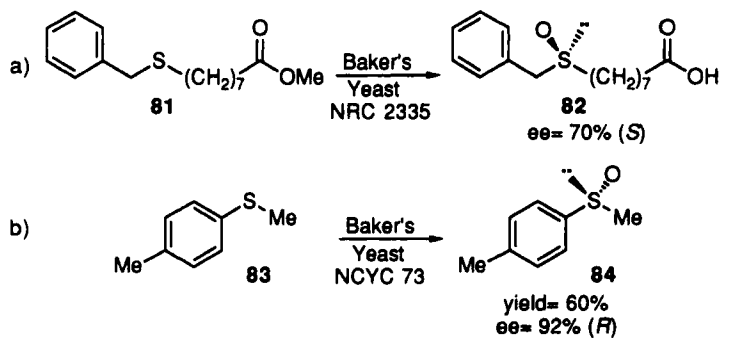


	Helminthosporium	*Mortierella isabellina*
78 n=3	24%(*S*) 68%ee	6%(*R*) 63%ee
79 n=4	45%(*S*) 93%ee	9%(*R*) 58%ee
80 n=5	34%(*S*) 88%ee	7%(*R*) 82%ee

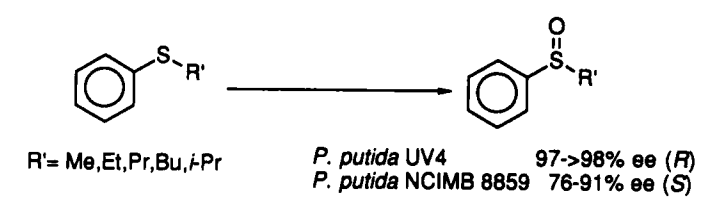
SCHEME 73



SCHEME 74



SCHEME 75



SCHEME 76

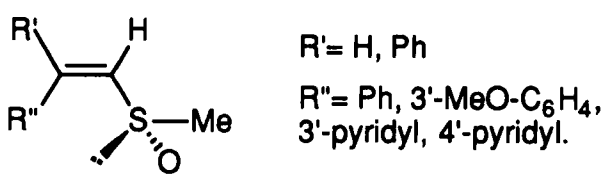


FIGURE 10

complementary. Thus, there is no general method for the preparation of vinyl (*S*)-sulfoxides since the enantioselectivity observed for each method strongly depends on the structure of the substrate.

5.2. Enzymatic Oxidation

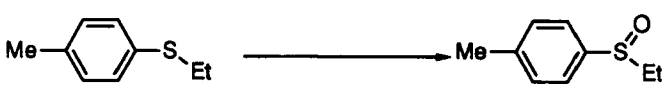
Walsh *et al.* have described the synthesis of both enantiomers of ethyl *p*-tolyl sulfoxide by the use of hog liver flavin adenine dinucleotide (FAD) containing monooxygenase (*R*-sulfoxide, 90% ee),[281] or both, purified cytochrome P-450 isozymes (*S*-sulfoxide, 58–68% ee),[282] or flavin-containing cyclohexanone monooxygenase (CMO) from *Acinetobacter* (*S*-sulfoxide, 64% ee)[281] (Scheme 77).

Enzymatic oxidation by microsomal cytochrome P-450 has been studied quite extensively. Mechanistically, this reaction can involve an oxygen transfer to the sulfur atom from the iron-oxo complex (**85**) suggested to be the active species (path i, Scheme 78).[283] Alternatively, an electron transfer step is also possible leading to a cation radical (**88**), which then collapses to the products (paths ii and iii). Although there is not a clear decision between these two pathways, a recent report[283] suggests that an oxygen transfer mechanism is more likely.

Colonna *et al.*[284–288] extended the investigation of the cyclohexanone monooxygenase (CMO) to a collection of different sulfides. They found that enantioselectivity was dramatically influenced by the structure of the sulfide. Thus, optical purities ranged from 99% ee and *R* configuration to 93% ee and *S* configuration depending on the sulfide used.[284] Phenyl methyl sulfide was oxidized to the corresponding (*R*)-sulfoxide with 99% ee, but when the size of the alkyl chain was increased and *p*-substituents in the phenyl group were present, the corresponding (*S*)-sulfoxides were obtained in high optical purity, i.e., *p*-fluorophenyl ethyl (*S*)-sulfoxide was prepared with 93% ee (Scheme 79).[284]

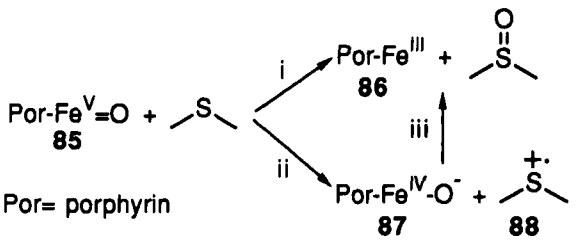
Being the CMO a flavin-containing enzyme, the proposed mechanism[289] involves the formation of a 4a-hydroperoxy flavoenzyme complex which acts as the oxygen transfer species.

Later, the same authors successfully developed an active site model to explain and predict the stereoselectivity of this enzymatic sulfoxidation.[287] CMO seems to be the oxidant system of choice for 1,3-dithioacetals,[288] since the corresponding (*R*)-monosulfoxides were obtained in 81–94% chemical yield and >98% ee. These results were clearly better than chemical and microbial oxidation in terms

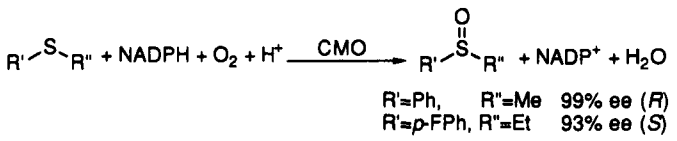


FAD	90% ee (*R*)
CMO	64% ee (*S*)
cytochrome P-450	58 - 68% ee (*S*)

SCHEME 77



SCHEME 78



SCHEME 79

of enantioselectivity. The very high ee's were due to a combination of asymmetric synthesis and kinetic resolution, since the (*S*)-monosulfoxide was oxidized faster than its (*R*)-enantiomer (Scheme 80).[288]

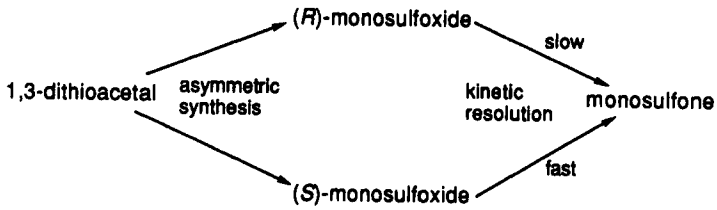
Chloroperoxidase (CPO) from *Caldariomyces fumago* is a heme-containing glycoprotein that has been used in the peroxide dependent enantioselective oxidation of sulfides to the corresponding sulfoxides having the (*R*) absolute configuration.[290–296]

In 1992, Wong *et al.*[295] reported the CPO-catalyzed oxidation of substituted aryl methyl sulfides using hydrogen peroxide as oxidant to obtain the (*R*)-sulfoxides in high chemical and optical yield (Scheme 81).[295]

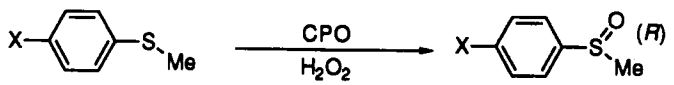
When racemic 1-phenyl ethyl hydroperoxide (**89**) was used as oxidant, the enzyme selectively accepted the (*R*)-hydroperoxide as substrate and oxidized sulfides exclusively to the (*R*)-sulfoxide (**90**), leaving also the corresponding (*S*)-hydroperoxide (**91**) and the (*R*)-alcohol (**92**) (Scheme 82).[295]

CPO-catalyzed oxidation is in competition with the spontaneous oxidation of the sulfides by the peroxide, which leads to racemic sulfoxides. This undesirable reaction can be minimized by reducing the concentration of the substrates (sulfide-hydroperoxide), adding them to the CPO containing solution in small fractions every hour.[295]

Horseradish peroxidase (HRP) has been the most investigated heme-containing peroxidase. Although its use in peroxidase-catalyzed sulfoxidation has been known for some time, HRP seems to be limited in terms of inducing chirality.[291–293,297–299]



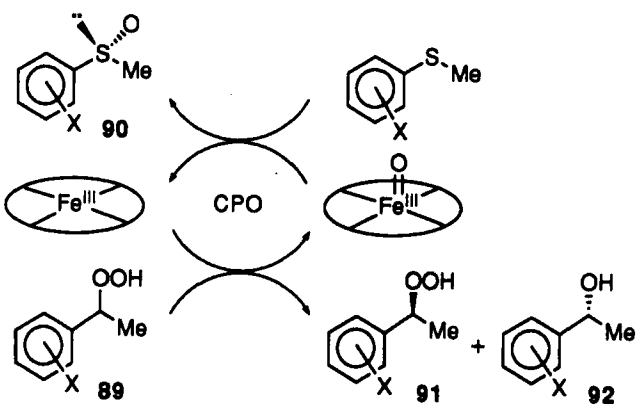
SCHEME 80



X= H, Cl, F, Me, MeO

yield= 66 - 92%
ee= 97 - 100%

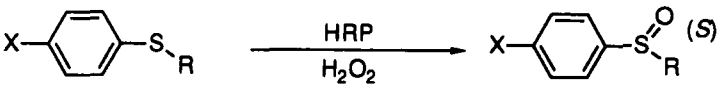
SCHEME 81



SCHEME 82

In 1992, Colonna *et al.*[300] reported for the first time some enantioselectivity (30–68% ee) in the HRP catalyzed oxidation of *p*-substituted phenyl methyl sulfides by H_2O_2. Asymmetric induction was not observed for *o*-substituted phenyl, benzyl, and 2-pyridyl methyl sulfides. Interestingly, the *S* configuration was obtained in all cases in contrast to that observed with CPO (*vide supra*).

Some months later, Ortiz de Montellano[301] obtained similar results for the same substrates, although the ee's were better (62–70%). More recently, this author[302] reported that the mutant F41L HRP, obtained by replacing Phe-41 on the HRP for a leucine, oxidized sulfides with invariably higher enantioselectivity than the native HRP. The largest increase in enantioselectivity was for cyclopropylmethyl phenyl sulfide from 7% by native HRP to 94% by F41L HRP (Scheme 83).[302]



	NativeHRP	F41L HRP
X=H, R=Me	72%ee	97%ee
X=H, R=Et	35%ee	94%ee
X=Cl, R=Me	68%ee	88%ee
X=Me, R=Me	67%ee	97%ee

SCHEME 83

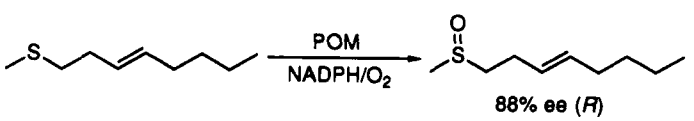
These results suggest that the replacement of Phe-41 by a smaller aminoacid probably increases the access of the sulfide to the ferryl oxygen of the ironporphyrin.

Several other hemoproteins have been shown to catalyze sulfoxidation. Thus, microperoxidase-11[303,304] catalyzed the oxidation by H_2O_2 to (*S*)-sulfoxide albeit with poor enantioselectivity. Soybean hydroperoxide-dependent oxygenase[305] gave methyl *p*-tolyl (*S*)-sulfoxide with about 95% ee.

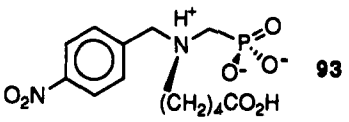
In one of the few reports regarding enzymatic oxidation of aliphatic sulfides, May[306] informed that *Pseudomonas oleovorans* monooxygenase (POM), a nonheme iron monooxygenase, catalyzed the stereoselective sulfoxidation of aliphatic methyl sulfides with varying efficiency (2–88% ee) (Scheme 84).[306]

5.3. Other Biological Oxidations

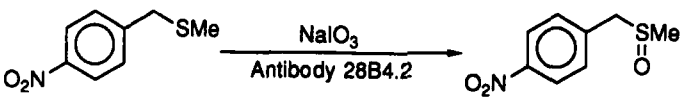
In a very different and novel approach, Schultz *et al.*[307] recently reported preliminary results that suggest the possibility of using antibodies as catalysts for chemo- and stereoselective sulfoxidation. Since the aminophosphonic acid hapten (**93**) is protonated at physiological pH, antibodies specific for **93** were used to stabilize the incipient positive charge on sulfur at the transition state. Thus, high rate of enhancement was noticed for the antibody-catalyzed sodium periodate oxidation of *p*-nitrobenzyl and *p*-nitrophenyl alkyl sulfides (Scheme 85).[307]



SCHEME 84



93



SCHEME 85

6. CONCLUSIONS

Sulfide oxidations to sulfoxides have attracted the interest of many research groups worldwide, and this has been reflected in the numerous and varied methods developed and reported in recent years.

With MCPBA out of the market, sodium metaperiodate, iodosylbenzene and the McKillop's reagent are competing to be the most successful among the traditional oxidants. To this list, Oxone® and dimethyldioxirane have to be added as newly developed successful methods.

However, none of the above mentioned methods can be considered of general applicability and, considering the every day increase in functionalization and complexity of the sulfoxides required in modern organic synthesis, the probability of developing a general method seems to be remote. Therefore, these methods might be considered as complementary.

Undoubtedly, the most important development in recent years has been related to the achievement of methods for the enantioselective oxidation of prochiral sulfides to the corresponding sulfoxides. Among these methods, Davis' oxaziridines and Kagan's and Modena's modifications of Sharpless procedure are the most widely used. These are well-established and "first choice" procedures. Nevertheless, many new methodologies and modifications of those already known have been recently reported, including metallo(salen) complexes- and metallo porphyrin-catalyzed oxidations. Also, newly reported microbiological and enzymatic methods focus on the highly enantioselective synthesis of sulfoxides.

Regarding the degree of enantioselectivity, while the oxidation of alkyl aryl sulfides can be performed with high enantioselectivity, dialkyl sulfides are generally oxidized with only poor enantioselectivity. Consequently, more work has to be done in the area.

Asymmetric oxidation is potentially the most useful method for the preparation of enantiomerically pure sulfoxides and will surely continue to attract attention in the future.

Acknowledgments

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