Enantioselective Synthesis of Sulfoxides: 2000−2009

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Contents

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1. Chemical Methods of Nonracemic Sulfoxide Preparation

1.1. Introduction

In the field of asymmetric synthesis, nonracemic sulfoxides are recognized as valuable and efficient reagents. Their extensive use as chiral auxiliaries and intermediates is substantiated by high asymmetric induction exerted by a sulfinyl fragment, and its configurational stability.[1] The numerous applications of chiral sulfoxides in organic synthesis were presented in several review articles.[2−5] A sulfinyl auxiliary was also utilized in procedures leading to the desymmetrization of racemic mixtures.[6−9] The increasing use of chiral sulfur ligands in asymmetric catalysis was recently

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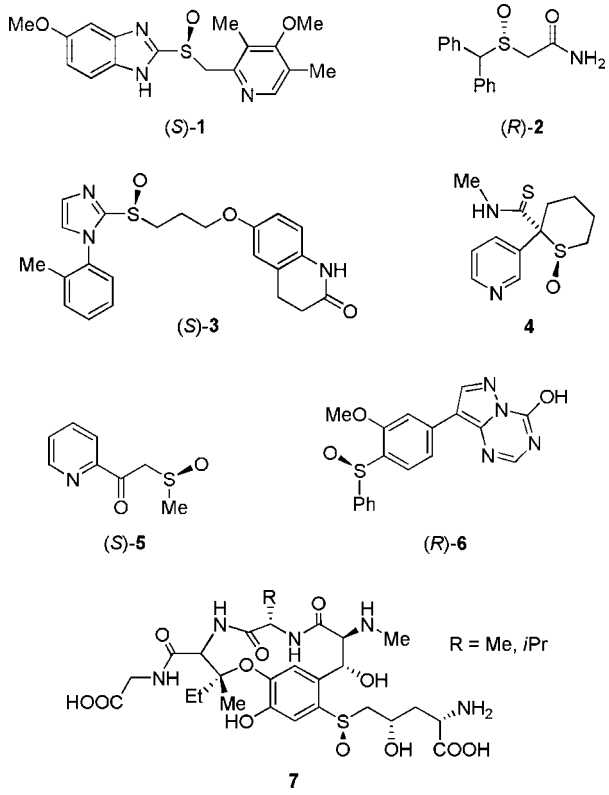
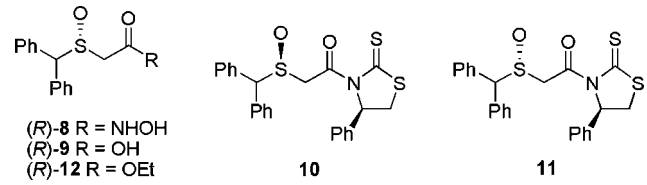
reviewed.[10,11] Nonracemic sulfoxides are also employed in enantioselective organocatalysis.[12−17]

Another aspect of the use of nonracemic sulfoxides is connected with the crucial role played by chiral sulfur-containing compounds in biology.[18] In recent years, the pharmaceutical industry has shown an increasing interest in nonracemic compounds.[19−22] Among them, sulfinyl derivatives are of special importance.[23] Esomeprazole **1**, the (*S*) form of omeprazole, which is used to heal and relieve symptoms of gastric or duodenal ulcers, is counted among the world's most sold pharmaceuticals.[23,24] The manifold activity of chiral sulfoxide-based drugs can be illustrated by armodafinil (the (*R*)-enantiomer of modafinil (**2**), a stimulant drug approved for treatment of sleep disorders);[25,26] OPC-29030 (**3**), a platelet adhesion inhibitor;[27,28] aprikalim (**4**), an activator of the potassium channel;[29] oxisurane (**5**), an immunosuppressor;[30] pyrazolotriazine derivative **6**, effective in hyperuricemia;[31] or ustiloxins **7**, active against human breast and lung cancer lines.[32]



Three principal approaches used for preparation of nonracemic compounds involve separation of a racemic mixture, transformation of a reagent from the chiral pool, or the use of chiral catalyst for enantioselective synthesis. These methods can also be utilized to obtain a chiral sulfoxide. Racemic sulfinyl derivatives were separated using chiral columns[33−35] and by fractional crystallization of the binary compounds formed with a chiral resolving agent; some recent examples make use of formation of inclusion compounds.[36−38] Chemical resolution methods include the reversible reactions with nonracemic compounds. For example, resolution of racemic (2-methylsulfinyl)phenylphosphonic acid was accomplished *via* the formation of the cinchoninium salts.[39] For the synthesis of the (*R*) and (*S*) enantiomers of modafinil (**2**) and adrafinil (**8**), a racemic α-sulfinyl carboxylic acid, **9**, was treated with a chiral thiazolidinethione, and the resulting diastereomers, **10** and **11**, were separated chromatographically.[26] Subsequent displacement with ammonia or hydroxylamine gave both enantiomers of compounds **2** and **8**, while hydrolysis or esterification led to enantiopure modafinic acid (**9**) and ethyl modafinate (**12**). Another approach is illustrated by the preparation of nonracemic hydroxysulfoxides *via* stereoselective reduction of a carbonyl group in chiral or racemic β-ketosulfoxides.[40,41] The enantiomeric enrichment of the racemic mixture can also be achieved by the selective reduction of the sulfinyl group[42−45] or (more often) by its oxidation. Many chiral oxidants used for the preparation of sulfoxides are also able to oxidize the sulfoxides to sulfones. When different reaction rates are observed for the two enantiomers, kinetic resolution can occur (see also section 1.4, Scheme 5).



Different preparation methods utilizing the transformation of nonracemic substrate were developed in the last decades and are frequently used. The synthesis of a chiral sulfoxide requires the formation of a C−S bond (typically by nucleophilic substitution of other nonracemic sulfinyl compounds) or of a S−O bond (oxidation of prochiral sulfides with chiral oxidants or diastereoselective oxidation of chiral substrates). (In principle, other possibilities also come to mind, such as enantioselective reduction of unsymmetrical sulfones to the corresponding sulfoxides.) Finally, the enantioselective transformations using substoichiometric amounts of a chiral catalyst are particularly attractive, since multiplication of chirality may be achieved in these reactions. While catalytic C−S bond formation reactions leading to chiral sulfoxides are rare,[46] various efficient oxidation systems were designed and used for preparation of these compounds in high enantiomeric purity, and in many cases both optical antipodes were accessible.

In this contribution, we shall concentrate our attention on the stoichiometric and catalytic transformations leading to the formation of nonracemic sulfoxides. In general, methods utilizing chiral sulfoxides as substrates will not be considered, although, in some cases, a new C−S bond is formed in such reactions. This review, which covers the years 2000−2009, describes recent achievements in the field and is an extension of a review that appeared in 2000.[47] Since then, several authors have reviewed the subject more or less thoroughly. An essential and comprehensive review concerning the preparation methods and utilization of chiral sulfoxides was published by Fernández and Khiar in 2003.[2] Legros, Dehli, and Bolm concentrated their 2005 paper on the syntheses of biologically active sulfoxides.[23] The application of metal complexes in the asymmetric oxidation of prochiral sulfides was described by Volcho et al.[48,49] and by Bryliakov and Talsi.[50] Holland presented the use of biocatalysts for the preparation of chiral sulfoxides.[51] Sections dedicated to sulfoxide synthesis can be found in books,[52−55] and reviews are available on oxidations mediated by titanium,[56] vanadium,[57,58] iron,[59] peroxy, peroxo, and oxo metal complexes[60] or nonmetal catalysts.[61] The catalytic properties of salen-type ligands (salen = *N*,*N*′-ethylenebis(salicylimine)) were described by Katsuki and co-workers.[62−64] In 2001, Procter reviewed the synthesis of organic derivatives of sulfur and

selenium, including chiral sulfoxides.[65] Two articles on the application of different oxidants to the synthesis of sulfoxides (in most cases nonstereoselective) were published in 2005.[66,67] A review article on the chemistry of C_2-symmetric bissulfoxides also contains the description of preparation methods.[68] Several review articles written in Chinese addressed the preparation of nonracemic sulfoxides as well.[69−71]

The first part of this review, devoted to the chemical methods used for the preparation of nonracemic sulfoxides, is organized as follows: after a short presentation of "state of art" in 2000 (section 1.2), new applications of known synthetic methods are shown (section 1.3), followed by a description of new procedures and compounds (section 1.4). In section 1.5, examples of diastereoselective preparations are given. New developments in heterogenized systems are presented in section 1.6. Section 1.7 briefly summarizes the observed trends. For clarity of presentation, in all stereochemical drawings, the sulfinyl group is drawn with a single bond without charges on S and O atoms.

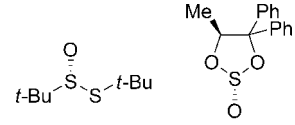
1.2. Overview of Synthetic Methods Developed in the 20th Century

1.2.1. Nucleophilic Substitution (C−S Bond Formation)

Nonracemic sulfoxides can be prepared by the addition of an organometallic reagent to electrophilic derivatives containing a sulfinyl group. The reaction results in the formation of a new carbon−sulfur bond with inversion of configuration at the sulfur atom. For this purpose, various chiral sulfinyl transfer reagents were designed. Among them, chiral sulfinates were recognized to be particularly attractive. The classical Andersen procedure in which optically pure menthyl sulfinate reacted with a desired organometallic compound (Scheme 1) was used with success in the synthesis of different nonracemic sulfoxides.[72,73] However, the original procedure was restricted to the preparation of diaryl or alkyl aryl *S*-oxides, since menthyl alkylsulfinates are typically oils and cannot be obtained in a diastereomerically pure form by recrystallization. The use of carbanionic leaving groups (Scheme 2) opened a route to the enantiomerically pure dialkyl sulfoxides as described by Naso and co-workers.[74,75]

Instead of using menthol derivatives, chiral sulfinates can be formed using *trans*-2-phenylcyclohexanol[76] or chiral carbinols derived from diacetone-D-glucose (DAG). The DAG methodology was extensively developed by Alcudia, Llera, and co-workers.[77,78] This strategy allowed the preparation of a variety of sulfoxides (including dialkyl ones) in both enantiomeric forms. The key intermediates, chiral sulfinates, are prepared from the corresponding sulfinyl chlorides and DAG (Scheme 3). The configuration of the main diastereomer is dependent on the base used for the reaction: ethyl diisopropylamine leads to (*S*)-alkyl- or arylsulfinates, while pyridine affords their (*R*)-epimers. Sulfinamides, formed from sulfinyl chlorides and nitrogen bases, were proposed as active sulfur species in this reaction; their possible interaction with the chiral alcohol (DAG) depends on the steric hindrance exerted by the amine substituents, leading to different reaction pathways for iPr$_2$NEt and pyridine.[77]

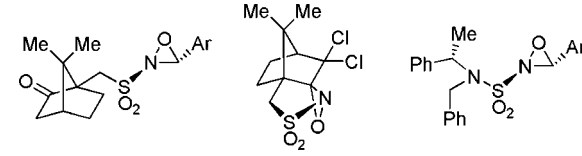
Ellman and co-workers described the reaction of Grignard reagents with chiral *tert*-butyl *tert*-butanethiosulfinate **13**, leading to the corresponding sulfoxides without racemization.[79] Among other chiral sulfinyl transfer reagents, those bearing two leaving groups attached to sulfur are of special interest, since, in principle, they may be used to obtain any desired sulfoxide. There is no need to prepare a new reactant for each kind of substitution. Two organometallic additions, performed in the right sequence, are necessary to introduce two different alkyl or aryl groups. For example, a method developed by Kagan et al. utilized chiral sulfite **14**, which was obtained in two steps from (*S*)-ethyl lactate (Scheme 4).[80,81]



13 **14**

1.2.2. Davis Oxaziridines

Oxaziridines are known for their exceptional ability to transfer an amine group or an oxygen atom to various nucleophiles. For sulfoxidation reaction, derivatives containing a bulky or electron-withdrawing group on the nitrogen atom or both the nitrogen and carbon atoms of the three-membered ring were found to be most effective.[82] Davis and co-workers demonstrated that the chiral *N*-sulfonyl- (for example **15** and **16**) and sulfamyloxaziridines (**17**) gave high yields in the synthesis of various chiral sulfoxides, without the formation of sulfones.[83,84] The enantioselectivities were strongly substrate-dependent, and higher *ee* values were observed for the sterically hindered sulfides. The oxidant was used in stoichiometric amounts, but it can be regenerated from the chiral imine formed in the course of the reaction.



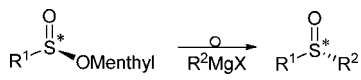
15 **16** **17**

Chiral *N*-alkyl-oxaziridines also appeared to be effective in the enantioselective sulfoxidation, but in this case the oxidant was activated by the addition of acids.[85] Other metal-free oxidations were also described.[86−88] In particular, the organocatalyzed sulfoxidations appeared to be ineffective,[12,89] especially if compared with reactions catalyzed by chiral metal complexes.

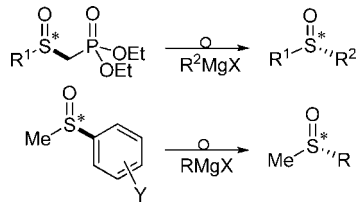
1.2.3. Metal Complexes in Enantioselective Oxidation

Since their introduction in 1984, metal complexes with enantiopure chelating ligands have shown their exceptional

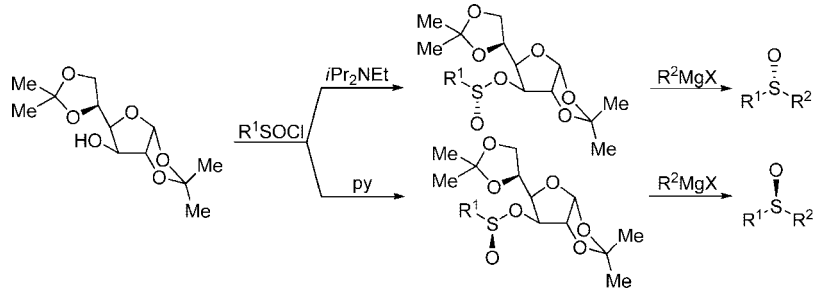
Scheme 1



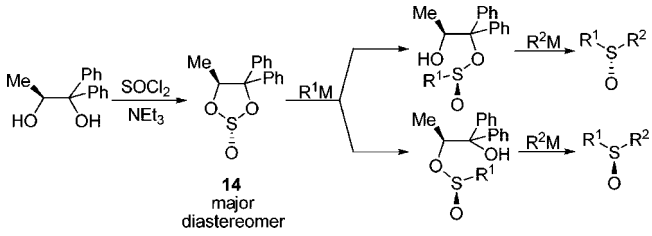
Scheme 2



Scheme 3

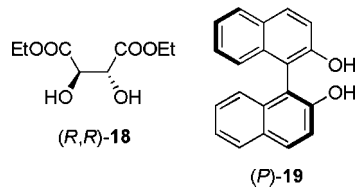


Scheme 4



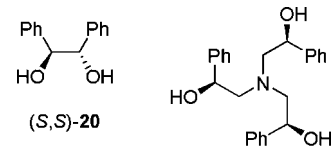
efficiency in the enantioselective oxidation of sulfides. Bidendate diols, tridendate Schiff bases, and tetradendate salen-type ligands have been commonly used, typically in combination with d^0 metal ions: titanium(IV) and vanadium(V).

Twenty-six years ago, the groups of Kagan[90] and Modena[91] independently described their modifications of the Sharpless reagent used for asymmetric epoxidation. The system was based on titanium isopropoxide as the metal source, enantiopure diethyl tartrate **18** as the chiral modifier, and *tert*-butyl hydroperoxide (TBHP) as terminal oxidant. In the Modena version, anhydrous conditions were applied, and the ratio of the system's components was Ti(O-*i*Pr)$_4$/DET/TBHP = 1:4:2. The key feature of Kagan's variant was the addition of a stoichiometric amount of water (Ti/DET/H_2O = 1:2:1). In its original version, Kagan's method suffered from the use of stoichiometric amounts of a titanium complex. However, a catalytic alternative was later developed in which 0.1 equiv of Ti(O-*i*Pr)$_4$ was used.[92] The system was also improved by using cumyl hydroperoxide (CHP) in place of TBHP and by conducting the reaction in 2-propanol in the presence of 4 Å molecular sieves to protect the active catalyst against an excess of water.[92,93] High enantioselectivity (*ee* > 95% for certain substrates) and reasonable yields were achieved for alkyl aryl sulfides. Although the necessity of purification of sulfoxides from the relatively large amount of titanium salts produced during the workup is a serious drawback of this method and the chemoselectivity of the system is in some cases limited, modified Sharpless catalysts are regarded as one of the most effective sulfoxidation systems.



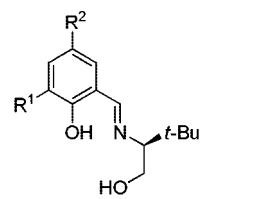
(*R*,*R*)-**18** (*P*)-**19**

The success of Kagan's and Modena's methods encouraged other groups to explore the possibility of replacing diethyl tartrate by other chiral diols. Uemura and co-workers introduced chiral BINOL (**19**) as ligand in Ti-catalyzed sulfoxidations.[94,95] (1*R*,2*R*)- or (1*S*,2*S*)-1,2-Diphenylethane-1,2-diol (hydrobenzoin, HB, **20**) was applied with success by Rosini's group.[96,97] For both ligands, high enantioselectivities (up to 96% *ee*) were observed in the oxidation of alkyl aryl sulfides with TBHP. Ligands of C_3-symmetry were examined as well, as exemplified by the chiral trialkanolamine **21** (where *ee* values up to 84% were obtained).[98] A different approach to Kagan's method, the use of chiral secondary alkyl hydroperoxides, afforded the sulfoxides in low yields (<20%) and up to 79% *ee*.[99]

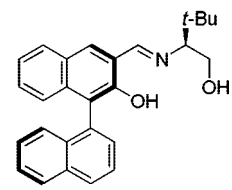


(*S*,*S*)-**20** (*R*,*R*,*R*)-**21**

Oxidation systems based on vanadium complexes also received considerable attention. Fujita and co-workers described the use of a vanadyl complex with tridendate or tetradendate chiral Schiff bases.[100−102] Using organic hydroperoxides (TBHP, CHP, THP), they obtained alkyl aryl sulfoxides with low to moderate enantioselectivities. In 1995, Bolm and Bienewald reported the efficient sulfoxidation of different sulfides using the catalyst formed *in situ* from vanadyl acetylacetonate and chiral Schiff bases **22**−**25**.[103] With 30% hydrogen peroxide as oxidant, they obtained chiral sulfoxides with up to 85% *ee*. Several advantages of Bolm's system are evident: simple preparation of Schiff bases from commercially available enantiopure 1,2-aminoalcohols and salicylaldehydes, low catalyst loadings (<1 mol %, even 0.01 mol % was found sufficient), utilization of a cheap and environmentally benign oxidant, simple reaction conditions, and easy workup. One should also mention the ease of modification of Schiff bases and their availability of both enantiomeric forms, which allows the preparation of sulfoxides of opposite configurations.



(*S*)-**22**: R^1 = *t*-Bu, R^2 = NO_2
(*S*)-**23**: R^1 = R^2 = *t*-Bu
(*S*)-**24**: R^1 = $SiPh_2$*t*-Bu, R^2 = *t*-Bu
(*S*)-**25**: R^1 = H, R^2 = NO_2



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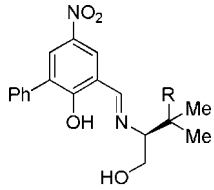
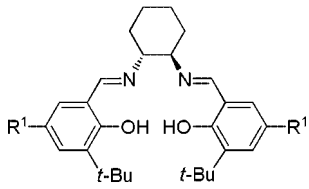
During the following years, Bolm and Bienewald broadened the scope of substrates,[104] while other groups described

modifications of the Schiff base structure. Significant improvements were achieved by Vetter and Berkessel, who prepared ligands with the additional elements of chirality, with compound **26** leading to optimal results.[105] Ellman and co-workers found compound **23** to be the best ligand for the preparation of chiral *tert*-butyl *tert*-butanethiosulfinate (**13**) (94% conversion, 82% *ee*).[79,106] The effects of simple modifications of the ligand structure were investigated in our laboratory.[107,108] We observed the enantioselectivity improvement for the valinol derivative **27**, which catalyzed the oxidation of thioanisole in 90% yield and 75% *ee*, while for the analogous *tert*-leucinol-derived ligand **28** a similar *ee* value (73%) was accompanied by a lower yield (74%, all values at 0 °C).

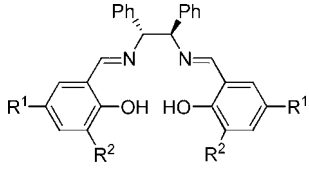


(*S*)-**27**: R = H
(*S*)-**28**: R = Me

Several groups concentrated their efforts on chiral sulfoxidation catalyzed by manganese complexes. Jacobsen and co-workers afforded high yields and moderate *ee* using manganese with salen-type ligands **29**−**36** and PhIO or H_2O_2 as oxidant.[109] The system performance was improved by introducing additional chiral centers (as in ligands **37** and **38**), as described by Katsuki et al.[110,111] An interesting aerobic oxidation of sulfides was also described with the combined use of molecular oxygen, pivalaldehyde, and β-oxo aldiminato manganese(III) complex (ligand **39** gave the highest *ee*) as catalyst.[112]

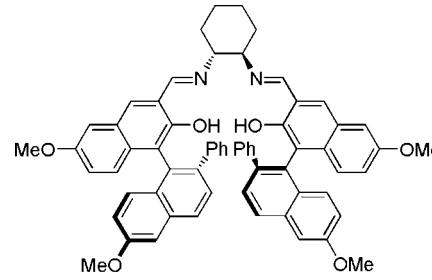


29: R^1 = OMe
30: R^1 = *t*-Bu
31: R^1 = NO_2
32: R^1 = H



33: R^1 = OMe, R^2 = *t*-Bu
34: R^1 = *t*-Bu, R^2 = *t*-Bu
35: R^1 = Me, R^2 = *t*-Bu
36: R^1 = OMe, R^2 = H

Systems based on complexes of other transition metals, such as zirconium,[113] iron,[114,115] copper and nickel,[116] or rhenium,[117] were also examined. Although the results in several cases were quite satisfactory,[113] these catalysts received much less attention than the titanium and vanadium complexes.



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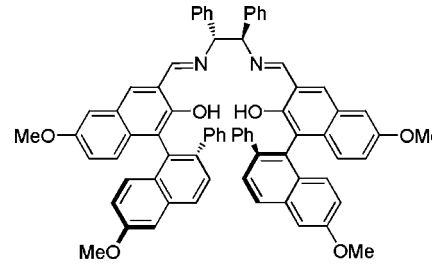

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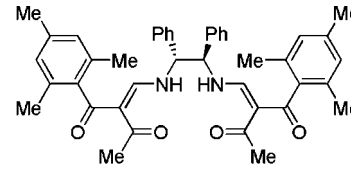

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1.3. New Applications

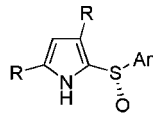
Some of the previously discussed systems were used in recent years in the synthesis of numerous nonracemic sulfoxides. When applied to a wider range of substrates, the "classical" methods showed their possibilities and limitations. In many cases, modification of the original reaction conditions was found necessary to obtain the desired product with a reasonable yield and/or stereoselectivity.

1.3.1. Chiral Sulfinate Method

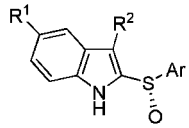
The classical Andersen sulfinylation protocol still provides an attractive alternative for methods based on sulfide oxidation. This one-pot procedure allows the introduction of the arylsulfinyl function into the substrate, which in most cases does not contain sulfur. Conveniently, menthyl *p*-toluenesulfinate, a key reagent typically used for this transformation, is commercially available in both enantiomeric forms. As can be seen from the following examples, high enantiomeric purity of the resulting sulfoxides is often accompanied by reduced yields.

A series of (4-X-benzyl) *p*-tolyl sulfoxides (X = H, CH_3, F, Cl) was prepared in both enantiomeric forms using the Andersen method.[118] The reaction of menthyl *p*-toluenesulfinate with ring-substituted benzyl Grignard reagents proceeded with various yields (13−88%) and a complete inversion of configuration (from 94 to >99% *ee*).

Three chiral menthyl sulfinates, *p*-tolyl, 1-naphthyl, and 2-methoxy-1-naphthyl derivatives, were used in the synthesis of novel *N*-phosphanopyrrolyl and -indolyl sulfoxides.[119] The α-sulfinylation of *N*-protected substrates was achieved using lithium diisopropylamide at −78 °C in THF solution and the corresponding sulfinate in the next step to give (*S*)-sulfoxides **40**−**48** in moderate yields (29−60%, but only 4.6% for the hindered 3-methyl derivative **48**).

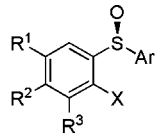


40: R = H, Ar = *p*-Tol
41: R = H, Ar = 1-Naphthyl
42: R = H, Ar = 2-Methoxy-1-naphthyl
43: R = CH_3, Ar = 2-Methoxy-1-naphthyl



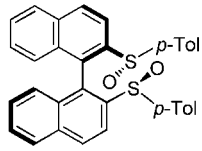
44: $R^1 = R^2$ = H, Ar = 2-Methoxy-1-naphthyl
45: R^1 = Me, R^2 = H, Ar = 2-Methoxy-1-naphthyl
46: R_1 = OMe, R^2 = H, Ar = 2-Methoxy-1-naphthyl
47: R^1 = OMe, R^2 = H, Ar = 1-Naphthyl
48: R^1 = H, R^2 = Me, Ar = 2-Methoxy-1-naphthyl

New chiral sulfoxide ligands **49**−**56** were prepared from the corresponding halogenobenzenes, which were lithiated and reacted with chiral menthyl sulfinates (33−79% yield).[120] Four stereoisomers of bis-sulfoxide binaphthyl or biphenyl derivatives (**57** and **58**) were obtained similarly in 34−60% yield from racemic 2,2′-dibromosubstituted precursors using either (+) or (−)-menthyl-*p*-toluenesulfinate. The resulting diastereomeric pairs were separated chromatographically.[121,122]

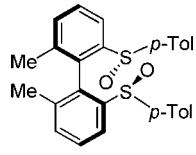


49: $R^1 = R^2 = R^3$ = H, X = F, Ar = *p*-Tol
50: $R^1 = R^2 = R^3$ = H, X = F, Ar = 2-Methoxy-1-naphthyl
51: R^1 = Me, $R^2 = R^3$ = H, X = F, Ar = *p*-Tol
52: $R^1 = R^3$ = H, R^2 = Me, X = F, Ar = *p*-Tol
53: $R^1 = R^2$ = H, R^3 = OMe, X = F, Ar = *p*-Tol
54: $R^1 = R^2$ = H, R^3 = OCH_2Ph, X = F, Ar = *p*-Tol
55: $R^1 = R^2 = R^3$ = H, X = $NHPPh_2$, Ar = *p*-Tol
56: $R^1 = R^2 = R^3$ = H, X = $NHPPh_2$, Ar = 2-Methoxy-1-naphthyl

In their study on the use of the sulfinyl group as a chiral auxiliary to control the stereochemistry of atropisomers, Clayden and co-workers applied the Andersen method for the preparation of nonracemic amides (of type **59**),[123,124] biaryls (**60**−**62**),[125,126] diaryl ethers (**63**),[125,127] and urea derivatives **64** and **65**.[125,128−130] Sulfinylation of the appropriate lithiated substrates was achieved using menthyl *p*-toluenesulfinate, *tert*-butyl *tert*-butanethiosulfinate, isopropyl-isopropanethiosulfinate, or cyclohexylsulfinyl diacetonylglucose (DAG derivative). Under optimal conditions, yields as high as ∼90% were obtained in several cases.

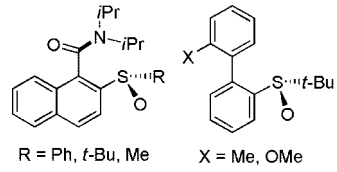


(M,S_S,S_S)-**57**



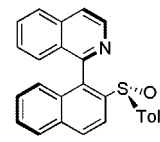
(P,S_S,S_S)-**58**

García Ruano and co-workers thoroughly examined the asymmetric induction exerted by a chiral sulfinyl group which was introduced using the Andersen method.[131−134] Sulfoxides **66**−**68** were prepared from bromoarene derivatives and menthyl *p*-toluenesulfinate in 59 (**66**), 54 (**67**), and

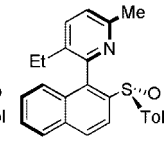


R = Ph, *t*-Bu, Me
59

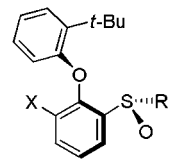
X = Me, OMe
60



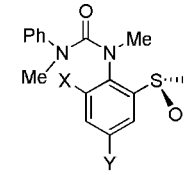
61



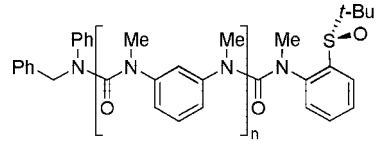
62



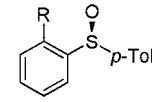
R = *p*-Tol, Me, *i*Pr, *t*-Bu, Cyclohexyl, *etc.*
X = CN, MOM
63



R = Ph, *t*-Bu, Me
X = H, Br, Y = H, Me
64



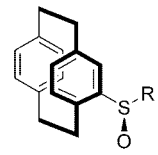
n = 1-6
65



(*S*)-**66**: R = Me
(*S*)-**67**: R = Et
(*S*)-**68**: R = CH_2OTIPS

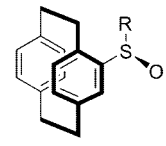
57% yields (**68**), respectively.[131,132] In the enantioselective synthesis of certain bioactive compounds, e.g. centrolobine,[135] *cis*-lauthisan,[136] and α-tocoferol,[137] Carreño, Solladié, and co-workers synthesized the key chiral sulfinyl intermediates using a modified Andersen approach.[138]

To resolve the planar chirality of [2.2]paracyclophane, a sulfinyl moiety was introduced into position-4 *via* the reaction of racemic 4-bromo[2.2]paracyclophane with *n*- or *tert*-butyllithium followed by the addition of (S_S)-menthyl *p*-toluenesulfinate or (*R*)-*tert*-butyl *tert*-butane thiosulfinate **13**.[139−141] The resulting sulfoxides **69** and **70** were obtained as a mixture of diastereomers with a 1:1 or 1:1.4 ratio, and 61% or 72% combined yield, respectively. Their chromatographic separation led to enantiomerically pure 4-tolylsulfinyl or 4-*tert*-butylsulfinyl[2.2]paracyclophanes, which were used to prepare other chiral derivatives.

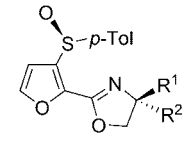


69

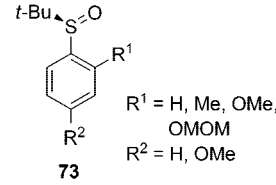
R = *t*-Bu, *p*-Tol



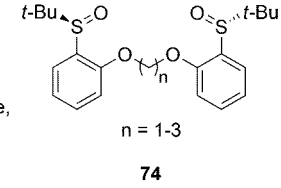
70



71: $R^1 = R^2$ = Me
72: R^1 = *i*Pr, R^2 = H



R^1 = H, Me, OMe, OMOM
R^2 = H, OMe
73

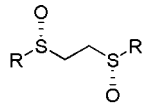


n = 1-3
74

A recent application of menthyl *p*-toluenesulfinate in the synthesis of chiral (3-sulfinyl)furan-2-yl derivatives **71** and **72** was described by Arai et al.[142] For **71**, a 78% yield was noted, but the enantiomeric excess was somehow lowered (80%); compound **72** was obtained in much lower yield (27%), and an alternative procedure of its preparation was developed.

Liao and co-workers developed a novel procedure for the separation of racemic *tert*-butyl *tert*-butane thiosulfinate using inclusion compounds formed with (*R*)-BINOL.[143] (*R*)-thiosulfinate **13** was applied for the synthesis of monomeric (**73**) and dimeric aryl *tert*-butyl sulfoxides (**74**) from the corresponding aryl bromides in 72−92% and 24−42% yield, respectively.[144]

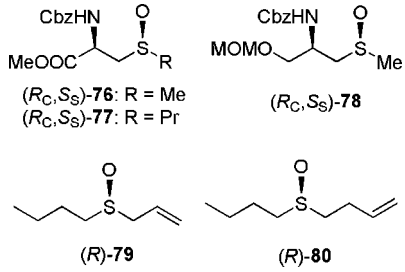
As a further development of the use of glucose-derived carbinols as chiral auxiliaries (DAG method), a series of C_2-symmetric bissulfoxides (*S*,*S*)- and (*R*,*R*)-**75** was obtained in high *de*.[145,146] The key intermediates, bis-sulfinate esters, were selectively formed from the corresponding sulfinyl chlorides by an enantiodivergent dynamic kinetic resolution.



R = Me, Et, *i*Pr, *t*-Bu, *p*-Tol, *o*-Anisyl, CH_2(2-pyridyl), CH_2COO*t*-Bu

75

Using the DAG methodology, both diastereomers of *S*-oxidized *N*-protected *S*-methyl- or *S*-propyl-L-cysteine methyl ester (**76** and **77**) were prepared.[147] The diastereomeric ratio was strongly dependent on the combination of solvent and base; for *S*-methyl derivative **76**, iPr$_2$EtN/toluene gave the best result for the preparation of the S_S isomer, and a pyridine/CH_2Cl_2 combination gave the best result for the R_S one. Further conversions allowed the formation of the sulfoxide **78**, which was considered as a chiral fragment of the antibiotic (*S*)-sparsomycin. A diacetone−glucose auxiliary was also used in the synthesis of the (*R*)- and (*S*)-enantiomers of allylic and homoallylic sulfoxides **79** and **80**.[148,149] These derivatives, which served as models in the investigation of the mechanism of oleic acid desaturation, were obtained in 66−84% yield and 96% *ee*.



(R_C,S_S)-**76**: R = Me
(R_C,S_S)-**77**: R = Pr

(R_C,S_S)-**78**

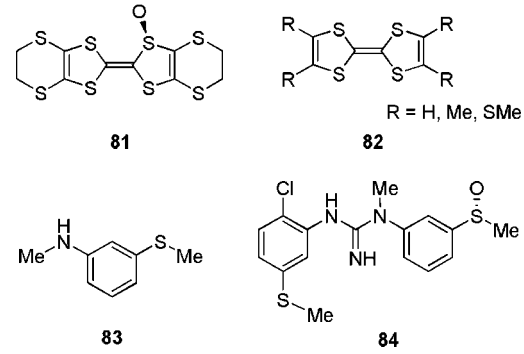
(*R*)-**79**

(*R*)-**80**

The sulfinate approach cannot be regarded as universal, although the introduction of DAG derivatives extended the scope of accessible sulfoxides. Despite several drawbacks of the Andersen method (the need for operation with organometallic compounds, side reactivity that lowered the yield of the desired substitution product), it remains the simplest route to certain groups of sulfoxides (*e.g.* *p*-tolyl, *tert*-butyl, isopropyl, cyclohexyl) in high enantiomeric purity.

1.3.2. Oxidation with Chiral Oxaziridines

The commercially available (8,8-dichlorocamphorylsulfonyl)oxaziridine **16** was used for the oxidation of bis(ethylenedithio)tetrathiafulvane, a member of a class of sulfur-rich precursors to organic conductors.[150] As a single product, the monosulfoxide **81** was formed with 44% *ee* (74% after recrystallization). Significantly lower asymmetric induction was observed for the less hindered substrates **82** (0−9% *ee*).[151] The enantioselective oxidation of *N*-methyl-3-methylsulfanylaniline **83** with chiral oxaziridines was performed as a key step in the synthesis of a neuroprotective agent CNS 5788 (**84**).[152] Among the three oxidants tested, (8,8-dichlorocamphorylsulfonyl)oxaziridine (**16**) gave the best results (∼95% yield, ∼75% *ee* of the desired sulfoxide). The final product was obtained with 76.5% enantiomeric excess, which was improved to 98% through two crystallizations.



81

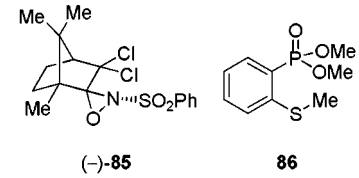
R = H, Me, SMe

82

83

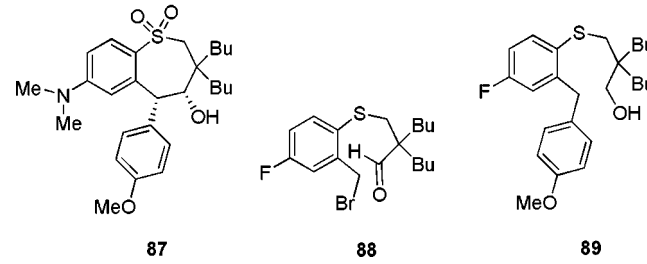
84

In their approach to the synthesis of esomeprazole **1**, von Unge and co-workers tested the chiral oxaziridine **85** for the asymmetric oxidation of the prochiral sulfide.[24] In spite of quite satisfactory results (40% *ee* further improved to 94% by recrystallization), the authors turned their attention to Kagan's method. On the other hand, the Davis oxaziridine was found superior to the Kagan and Bolm oxidizing systems in the conversion of dimethyl (2-methylsulfanyl)phenylphosphonate **86** into the corresponding (*S*)-sulfoxide, which was obtained in 82% yield and 73% *ee*.[39]



(−)-**85**

86



87

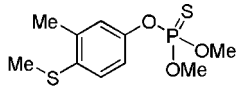
88

89

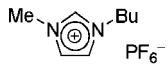
A highly enantioselective synthesis of benzothiepine **87** was described that utilized the oxidation of the sulfide precursor **88** and a ring-closure reaction in which the sulfinyl group served as a chiral auxilary.[153] Among the chiral oxidants tested (Kagan system with TBHP or CHP, Jacobsen's catalyst with CHP, and PhI(OAc)$_2$), (8,8-dichlorocamphorylsulfonyl)oxaziridine (**16**) gave the best results (60% *ee* for sulfide **88**, and 78% for the substrate **89**, for which 95% yield was noted).

In their research concerning the metabolism of fenthion (**90**), Rimoldi, Schlenk, and co-workers used (*N*-phenylsulfonyl)(8,8-dichlorocamphoryl)oxaziridine (**85**) for the oxidation of this pesticide.[154] In this work, (−)-**85** led to the (*S*)-sulfoxide with 81% yield, and (+)-**85** gave the (*R*)-enantiomer (79% yield); in both cases, the *ee* was 82%, and the enatiomeric purity was improved by recrystallization to >99%.

While looking for the best method for the preparation of nonracemic modafinil derivatives (modafinil (**2**), modafinic acid (**9**), and its methyl ester), Guillen, Plaquevent, and co-workers found that chiral oxaziridines gave better results than metal-based systems.[155] Oxaziridine **16** reacted with appropriate sulfides in CCl_4 at 20 °C to give sulfinyl products in 47−90% yield and 60−90% *ee*. The authors replaced the chlorinated solvent with the ionic liquid [bmim][PF_6] (**91**), which enhanced the yield of sulfoxides (73−87%) while generally maintaining the stereochemical outcome of the reaction (55−78% *ee*).



90



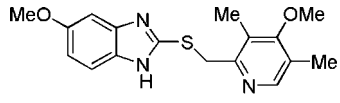
91

Sulfide oxidation with chiral oxaziridines is an operationally simple method which utilizes the commercially available reagents, typically in stoichiometric amounts (a significant question from the economical point of view). In most cases, the stereoselectivity is high, not necessarily excellent, but in the case of certain sensitive substrates, the Davis procedure turned out to be most efficient.

1.3.3. Oxidation Using Metal Complexes

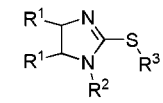
1.3.3.1. Kagan's System. In spite of the availability of numerous catalytic sulfoxidation systems, the efficient and relatively simple Kagan procedure has been applied in many recent preparations, including applications in the pharmaceutical industry. However, in some cases, alterations of the original procedure appeared to be necessary to reach the desired results.

A highly efficient synthesis of esomeprazole **1** via the asymmetric oxidation of the corresponding sulfide **92** was described.[24] Since the application of the original Kagan conditions led to a nearly racemic product, certain modifications that enhanced the enantioselectivity were introduced. When the titanium complex was prepared from DET, Ti(O-*i*Pr)$_4$, and H_2O in the presence of starting sulfide and *N*,*N*-diisopropylethylamine by stirring in toluene at 50−54 °C, the subsequent oxidation with CHP at 30 °C led to esomeprazole at >94% *ee* (its conversion to a sodium salt and recrystallization gave the product with >99.5% *ee*). Interestingly, the high enantioselectivity was retained even when substoichiometric quantities of the titanium complex were employed.[24]



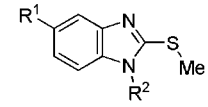
92

In 2005, Cephalon chemists patented a method of enantioselective preparation of (*R*)-modafinil **2** from the corresponding sulfide.[25] Again, the addition of tertiary amine (*N*,*N*-diisopropylethylamine or triethylamine) was found to be essential for the high enantiomeric purity of the isolated product (*ee* = up to 99.8%). CHP was used as the oxidant, and the chiral DET could be used in low amounts (even 5% mol, but optimal results were obtained for 15−30% mol of catalyst). The method worked well for several modafinil analogs (>92% *ee*), but only 10−50% *ee* was observed for diphenylmethylthioacetic (modafinic) acid (**9**), its amide, and its methylated derivative. Similar reaction conditions were also effective in the asymmetric oxidation of sulfides attached to nitrogen-containing heterocycles **92**−**95**.[156,157] High levels of enantioselection (94−98%) were achieved when two unsubstituted nitrogen atoms were present in the structure of the starting sulfide; also compound **92** was converted into esomeprazole **1** in 78% yield and 97% *ee*.



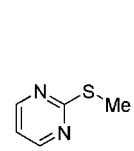
R^1 = H, Ph; R^2 = H, Me; R^3 = Me, Bn

93

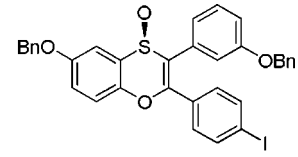


R^1 = H, OMe; R^2 = H, Me

94



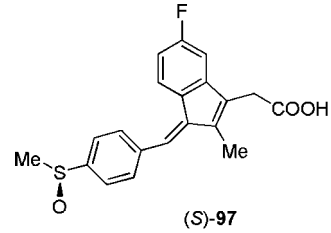
95



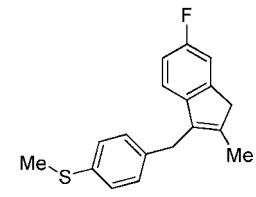
(*S*)-**96**

An efficient asymmetric synthesis of a selective estrogen receptor modulator with a dihydrobenzoxanthiin skeleton reported by Song, King, and co-workers utilized a chiral sulfoxide-directed reduction as an essential step.[158] The key sulfoxide, **96**, was prepared by means of the Kagan procedure, using D-diisopropyl tartrate as the source of chirality, titanium isopropoxide, CHP, and *N*,*N*-diisopropylethylamine in THF solution. For the reaction conducted on a kilogram scale with the catalyst loading reduced to 15 mol %, compound **96** was obtained in 86% yield (95% purity) and 99% *ee*.

The asymmetric Kagan sulfoxidation was also utilized for the highly enantioselective synthesis of Sulindac (**97**), an anti-inflammatory drug.[159] The procedure included the oxidation of sulfide **98** into sulfoxide with CHP (56% yield, 91% *ee*), which was converted to the desired product in three steps; a direct oxidation of Sulindac sulfide was unsuccessful.



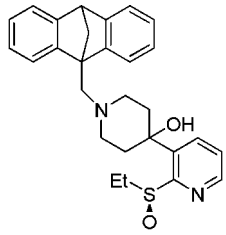
(*S*)-**97**



98

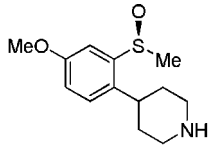
The asymmetric oxidation of sulfide to the (*S*)-sulfoxide using modified Kagan conditions was applied in the synthetic procedure for drug candidate ZD3638 (**99**) within AstraZeneca Pharmaceuticals.[160,161] The amounts and order of addition of reagents were optimized to give the highest *ee* (>99.5% after crystallization), and the yield increased from 58% to 73% by the addition of *N*,*N*-diisopropylethylamine. The DET/Ti(O-*i*Pr)$_4$/H_2O system was also used in the synthesis of ZD2249 methoxy sulfoxide (**100**), but in this case, CHP was used as the oxidant (96.9% yield, 94.4% *ee*).[162]

Volcho and co-workers reported an efficient procedure for the preparation of esomeprazole (**1**) *via* titanium-catalyzed oxidation of the corresponding sulfide **92** with CHP.[163] Besides diethyl D-tartrate, another chiral ligand—the optically



(*S*)-**99**

active (*R*)-*N*,*N*-dimethyl-1-phenylethylamine (**101**)—was applied, leading to the sodium salt of **1** in 64% yield and >99.5% *ee*. The monooxidized product was accompanied by only traces of sulfone. Replacement of (*R*)-**101** with its enantiomer decreased the yield significantly (57%), which proved that the amine acted as the second chiral ligand.



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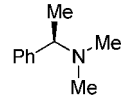
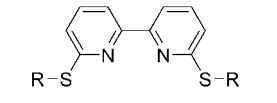


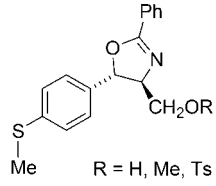
(*R*)-**101**

6,6′-Bis(alkylsulfanyl)-2,2′-bipyridines **102** were converted to the corresponding nonracemic mono- and bis-sulfoxides using the Davis oxaziridine or the Kagan method.[164] The latter method led to higher enantioselectivities (up to 82%), but in most cases the yield was lower.



R = Me, Et, *i*Pr, CH_2COOEt, Bn

102

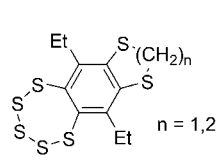


R = H, Me, Ts

103

Several substituted aryl methyl sulfides were oxidized to the corresponding (*R*)-sulfoxides using slightly modified Kagan conditions.[75] Lower amounts of CHP and water gave satisfactory yields (70−94%) and *ee*'s (80−97%) of products which were converted in the next step to methyl alkyl sulfoxides with a modified Andersen method (see section 1.2.1).

Two stereogenic centers present in oxazoline derivatives **103** were found to be insufficient for the effective 1,8-asymmetric induction in the synthesis of the corresponding sulfoxides using achiral oxidants (NaOCl/TEMPO, Br_2/H_2O/$NaHCO_3$, *m*CPBA).[165] These potential chiral methylsulfinyl group transfer reagents were thus obtained using the Kagan methodology in 66−98% yield and with *de*'s exceeding 95%. The (*R*) absolute configuration was assigned to the newly created chiral center.



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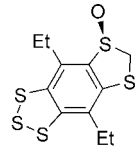
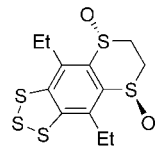


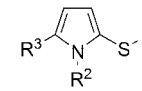
(*R*)-**105**



(*S*,*S*)-**106**

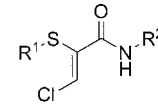
Desulfurization and ring contraction were observed during TBHP oxidation of two benzopentathiepin substrates **104**.[166] Application of Kagan conditions led to products with the mono- and dioxidized dithiin or dithiole ring (crystal structures of (*R*)-**105** and (*S*,*S*)-**106** were determined) with *ee* of 65−90% (which was improved by recrystallization to >99%).

The recent studies on the sulfoxidation of the series of 2-arylsulfanylpyrroles **107** demonstrated that the synthetic Kagan and Modena protocols could be applied with success if the electron-withdrawing groups differentiated the two substituents of the sulfur atom.[167] For highly functionalized substrates, α-thio-β-chloroacrylamides **108**, application of the standard Kagan oxidation method resulted in low to moderate enantioselectivity (up to 53% *ee*).[168] None of the tested modifications of experimental conditions led to the improved stereochemical reaction performance. Only *N*-aryl amides were oxidized. The ethyl and benzyl derivatives were unreactive; their conversion was achieved using the Bolm protocol (*vide infra*).



R^1 = Ph, *p*-Tol, Mes, 4-NO_2Ph, 2,4-NO_2Ph, 1-Naphthyl
R^2 = H, Ts; R^3 = H, CHO

107



R^1 = Me, Bu, *i*Bu, Ph, 4-NO_2Ph, 4-MeOPh
R^2 = Et, Bn, *p*-Tol, 4-FPh

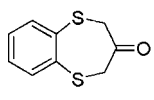
108

The numerous applications of Kagan's oxidation system result from the ready availability of reagents and from the fact that in many cases this procedure leads to high *ee* and reasonable sulfoxide yields, which are sometimes lowered by the overoxidation to the sulfone. This fact may complicate the isolation of the expected monooxygenated product. However, the reaction outcome can be altered by the choice of peroxide, stoichiometry, or conditions (solvent, temperature, order of reagent addition) and by addition of appropriate chiral or achiral substances. Among the possible additives, increasing the enantiomeric purity of oxidation product, *N*,*N*-diisopropylethylamine (Hünig's base), was found to be particularly efficient in several preparations.[24,25,156−158,161] The analysis of the possible mechanism of its action revealed the binding of the amine to titanium that yielded the coordinatively saturated complex.[157] As a consequence, prochiral sulfides do not interact with metal ion, but with the chiral tartrate ligand (at least in the case of nitrogen-containing substrates).

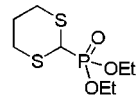
1.3.3.2. Modena's Protocol. Reinvestigation of Modena's protocol by Scettri and co-workers led to the conclusion that high levels of enantioselectivity could be maintained in the oxidation of alkyl aryl sulfides by CHP or furyl hydroperoxides even in the presence of only 10% of Ti(O-*i*Pr)$_4$/(*R*,*R*)-DET (1:4) complex.[169] An additional enhancement of enantioselectivity could be achieved by means of a stereoconvergent kinetic resolution process.

Modena's procedure was found to give the optimal results (ca. 60% yield, 97% *ee*) in the asymmetric oxidation of 1,5-benzodithiepan-3-one (**109**) with CHP.[7] Kagan conditions and Davis oxaziridine were found to be inefficient for this substrate. In their asymmetric synthesis of cispentacin, Aggarwal and co-workers applied Modena's conditions for the preparation of bis-sulfoxide (>98% *ee*) from 1,3-dithiane derivative **110**, bearing a phosphonate moiety in the 2-posi-

tion.[170] Good yields (60−75%) and enantioselectivities (at least 98% *ee*) of (*R*,*R*)-bissulfoxides were also observed in the oxidation of ketene dithioacetals **111** with CHP.[171] Small amounts of monosulfoxide were also isolated; however, the formation of *meso*-dioxidized product was not observed, which was accounted for by its possible tight binding with titanium catalyst. CHP was also applied for the conversion of 2-(methylsulfanyl)benzaldehyde (**112**) into (*R*)-sulfoxide (81% yield, 80% *ee*).[17] The reaction was performed in dichloromethane solution at −20 °C under modified Modena conditions (**112**/Ti(O-*i*Pr)$_4$/(*R*,*R*)-DET/CHP = 3:1:4:6); the product was used for the preparation of bissulfoxide **113**, which was tested as catalyst in the asymmetric allylation of aldehydes.



109



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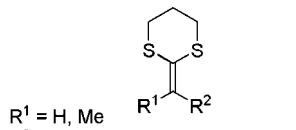
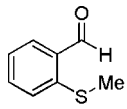


R^1 = H, Me
R^2 = *n*-Bu, *n*-Hexyl, Ph, 4-MeOPh
R^1, R^2 = -$(CH_2)_5$-

111



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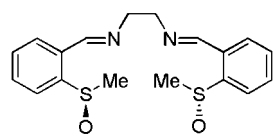
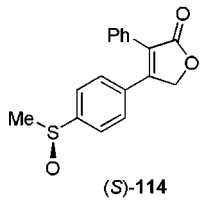
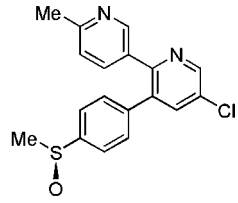


(*R*,*R*)-**113**

In the preparation of enantiomerically pure sulfoxides **114**−**116** as prodrugs of the potent COX-2 inhibitors, the Modena catalytic system (Ti(O-*i*Pr)$_4$/(*R*,*R*)- or (*S*,*S*)-DET (1:4) and TBHP as oxidant) used in 1,2-dichloroethane led to the highest stereoselectivity (88−100% *ee*), with yields in the 17−60% range.[172,173] From the two modifications of the original Sharpless methodology, Modena's approach has been less frequently applied. In our opinion, this oxidation system deserves more attention, since for certain sulfides (for example, dithioacetal derivatives) the results surpassed those obtained under Kagan conditions.

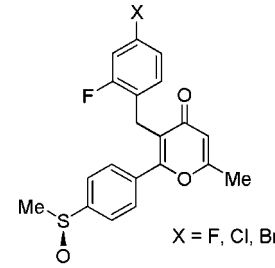


(*S*)-**114**



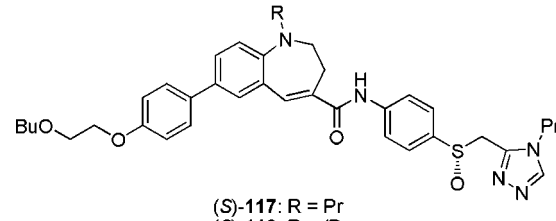
(*S*)-**115**

1.3.3.3. Uemura's Method and Other Titanium-Catalyzed Oxidations. The combination of NMR, CD, and MS methods allowed the identification of the single titanium BINOLate species present in the (*R*)-BINOL/Ti(O-*i*Pr)$_4$/H_2O system in 1:0.5:10 ratio in CCl_4.[174] The tetrahedral (BINOLate)$_6$Ti$_4$(μ_3-OH)$_4$ complex was proposed as a catalytic precursor in the asymmetric sulfoxidation under Uemura's reaction conditions.



(*S*)-**116**

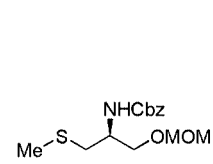
Several 1-benzazepine derivatives containing a sulfoxide moiety bearing a heteroaryl group were prepared as the orally active CCR5 antagonists which could work as anti-HIV-1 agents.[175] Since the absolute configuration of the sulfinyl group was significant for the biological action of these compounds, two derivatives, **117** and **118**, were prepared from the corresponding sulfides by the asymmetric oxidation. From the Ti-based systems tested (DET/H_2O, HB, BINOL), Uemura's method led to the optimal results (84% yield, 96% *ee* for (*S*)-**117**, 45% yield, 84% *ee* for (*S*)-**118**).



(*S*)-**117**: R = Pr
(*S*)-**118**: R = *i*Bu

Modified reaction conditions that combined asymmetric oxidation (at 0 °C) with kinetic resolution (at 25 °C) produced a compromise between yield and selectivity in the (*S*)-BINOL-mediated catalytic oxidation of thioanisole derivatives.[176] The products were isolated in 58−65% yield and 96 to >99.9% *ee*. Adopting these conditions, (*S*)-6,6′-dibromo-BINOL was tested for the oxidation of thioanisole. In this case, shorter reaction times were sufficient to reach 99.9% *ee* and 35% yield of sulfoxide.

Nakajima et al. used (*R*)-BINOL as a chiral ligand to improve the results of the Kagan method applied to the oxidation of sulfide **119**, a sparsomycin precursor **120**, and its analogues (up to 65% *de* and a maximal yield of 86%).[177] Under optimal conditions (0.2 equiv of BINOL, CCl_4 solvent 0 °C/−10 °C, 2.5/9.5 h), an 85−87% *de* was noted, accompanied by 59−75% yield.



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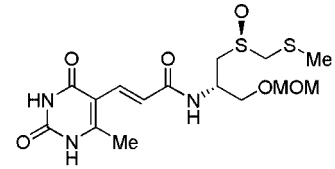
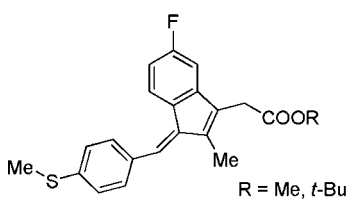


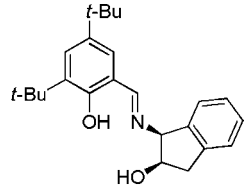
120

Various nonracemic β-ketosulfoxides were obtained in reasonable yields (57−90%) and high enantioselectivity (in most cases *ee* > 98%) by means of the enantioselective oxidation of the corresponding sulfides.[178] TBHP served as the terminal oxidant, and the reactions were mediated by the Ti(O-*i*Pr)$_4$ (5 mol %)/(*S*,*S*)-hydrobenzoin (HB) system, with or without water added, in hexane or CCl_4 at room temperature. Part of the resulting ketosulfoxides were reduced with DIBAL-H to the corresponding β-hydroxysulfoxides with high diaste-

reoselection. A similar oxidation system was applied for the preparation of Sulindac alkyl esters **121** with high *ee* values (94−96%) and moderate yield (48−50%).[179] Both enantiomeric forms of these sulfoxides were prepared using (*S*,*S*)-HB or (*R*,*R*)-HB, and their further hydrolysis led to Sulindac almost quantitatively and without loss of enantiomeric purity.



121



122

In the search for an efficient preparation method of benzyl *p*-bromophenyl sulfoxide, a key substrate for the two carbon-for-carbon substitution approach to chiral sulfoxides (see section 1.4.1.1), various catalysts were tested together with Ti(O-*i*Pr)$_4$ as the metal source and TBHP as the oxidant.[180,181] (*S*,*S*)- and (*R*,*R*)-HB ligands in *n*-hexane gave the best results: (*R*)- and (*S*)-sulfoxides were produced, uniformly, with ~80% yield and *ee* > 98%.

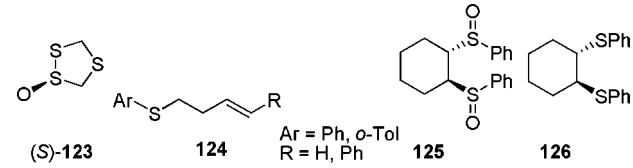
The titanium-catalyzed oxidation of thioethers utilizing the commercially available chiral diols, BINOL and HB (which are used in substoichiometric quantities), appears less popular than methods based on the Ti-tartrate complex. However, this method led to optimal results when applied for various substrates, including dialkyl sulfides.

1.3.3.4. Bolm's Oxidizing System. Several groups investigated the mechanism of vanadium-catalyzed enantioselective sulfoxidation. Using ^{51}V and ^{13}C NMR spectroscopy, Bryliakov, Karpyshev, and co-workers identified two types of monoperoxovanadium(V) species containing one Schiff base ligand present in the system at low temperature.[182−184] They also explained that lowering of enantioselectivity observed when H_2O_2 is added in one portion (instead of dropwise or portionwise addition) is caused by formation of an achiral bis-peroxo complex.[182]

A similar conclusion was drawn from the investigations of di-*tert*-butyl disulfide sulfoxidation with aqueous hydrogen peroxide catalyzed by vanadium complexes of Schiff base (*S*)-**23**.[185] A catalyst precursor, containing a V(V) fragment and two coordinated ligands **23** was isolated from the reaction mixture. Maseras and co-workers performed the computational study on this reaction.[186,187] A good agreement was found between the results of these calculations and the experimental *ee* values observed for four differently substituted ligands (**23** and its less hindered derivatives). Groups present at the 3 position of the aromatic ring and the one at the stereogenic carbon both affect the overall selectivity, although the mechanisms of their action are different.[187] On the basis of the suggested reaction mechanism,[185] Weix and Ellman developed an efficient method for enantioselective oxidation of di-*tert*-butyl disulfide.[188] Using a syringe pump for the dropwise addition of H_2O_2, >97% conversion and up to 83% *ee* were obtained in a homogeneous acetonitrile solution with ligand **23**. Even better performance was achieved using acetone as a solvent and indanol-derived ligand **122**. These conditions allowed the reaction to be conducted at a 2.3 M concentration and on a kilogram scale (99% conversion, >85% *ee*). The resulting thiosulfinate **13** could then be easily converted into *tert*-butanesulfinamide, a versatile chiral reagent used in asymmetric sythesis.[79,106,185,188,189] Compound **13** itself was found to be useful as a chiral (*tert*-butylsulfinyl) group transfer agent in the modification of Andersen's method.[125,140]

The optimized catalytic system developed in our laboratory (VO(acac)$_2$/ligand **27**/H_2O_2)[107,108] was shown to be efficient in the oxidation of various types of sulfides.[8,9,190,191] Encouraged by the promising results obtained for 1,3-dithiane and 1,3-dithiolane derivatives,[107,192] we examined the oxidation of 1,2,4-trithiolane.[192,193] The optically active product (*S*)-**123** was obtained in 20% yield, while the application of the Kagan protocol did not lead to the *S*-oxidized products, and the use of the vanadyl complex of the original Bolm ligand **22** allowed us to isolate only the racemic 1-*S*-oxide in 21% yield.

A series of homoallylic sulfides **124** was converted to the corresponding sulfoxides in 60−90% yield and 66−85% *ee*.[190] These enantioenriched products were then dihydroxylated to examine the possible chiral induction from the sulfinyl center. The resulting diastereomeric dihydroxysulfoxides were also obtained by an alternative route that utilized the diastereoselective oxidation of nonracemic dihydroxysulfides (see section 1.5).



(*S*)-**123** **124** **125** **126**

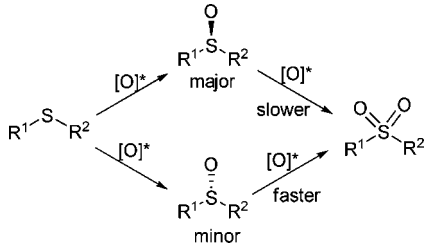
An effective deracemization of *trans*-1,2-bis(phenylsulfanyl)cyclohexane was achieved by the catalyzed enantioselective sulfoxidation with our optimized catalytic system, followed by the chromatographic separation of diastereomeric mono- and bissulfoxides.[9] Subsequent recrystallization of enantiomerically enriched bissulfoxide **125** and its final deoxygenation gave optically pure (1*R*,2*R*)-bis(phenylsulfanyl)cyclohexane **126**.

The Bolm oxidation procedure appeared to be the method of choice for the preparation of nonracemic 2-aryl- or 2-alkylsulfinyl-chloroacrylamides **108**, highly functionalized sulfoxides of significant synthetic potential.[168] Differently substituted Schiff bases led to comparable yields (up to 88%) and enantioselectivities, with maximum *ee* values in the range of 70% (*ca.* 20% higher than observed using the Kagan method). Availability of the original Bolm ligand and easy preparation of similar reagents resulted in their successful application in the vanadium-catalyzed oxidation of various sulfides (including substrates bearing other functional groups). The advantages of this catalytic system inspired other researchers, who concentrated their efforts on the modification of the Schiff base or the reaction conditions (section 1.4.3.2.1).

1.4. New Systems

As can be seen from the previous section, classical synthetic methods were applied with success to the preparation of various sulfoxides in high enantiomeric purity. However, certain limitations are also apparent. For example, most oxidation methods are inefficient for substrates bearing two similar groups, and thus, dialkyl or diaryl sulfoxides are obtained with low asymmetric induction. Another problem (especially important for the titanium-catalyzed oxidations) is connected with limited chemoselectivity. Overoxidation to the sulfone (dependent on the electrophilic character of an oxidant) can lower the yield of the sulfoxide substantially.

Scheme 5

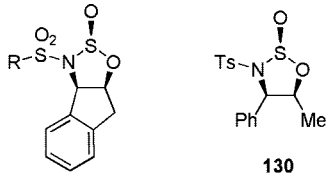


Sometimes the presence of a sulfone can complicate the isolation of the sulfoxide. However, typically, if the oxidation rates of two enantiomeric sulfoxides are different, the stereoconvergence of the two subsequent reactions increases the *ee* of the isolated sulfoxides (kinetic resolution shown in Scheme 5), but still at the expense of chemical yield.

The design of new synthetic methods also addresses these problems. Other aspects, such as the stability and recyclability of catalysts and the environmental issues, are raised as well.

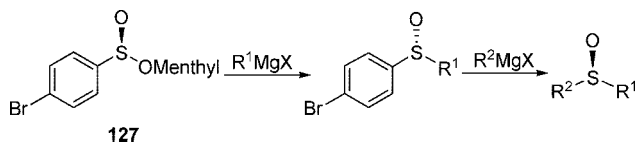
1.4.1. C−S Bond Formation

1.4.1.1. Developments of the Andersen Method. Naso and co-workers combined their protocol including a carbanionic leaving group with the classical Andersen method (Schemes 1−3).[194] Starting from (S_S)-menthyl *p*-bromobenzenesulfinate (**127**), a series of dialkyl sulfoxides was prepared by two successive replacement reactions (the first one was performed at +5 °C, and the second one was performed at −30 °C) with high yields and *ee* > 98% (Scheme 6). The same research group described the use of chiral benzyl *p*-bromophenyl sulfoxide **128**, obtained on a multigram scale from the corresponding sulfide, as a general precursor of dialkyl sulfoxides by a two carbon-for-carbon substitution sequence (Scheme 7).[180] This procedure led to the products with yields in the range of 62−91%, and the *ee* in most cases was very high (>98%). The methodology utilizing the carbanionic leaving group, which extended the scope of available chiral sulfoxides, was reviewed by Naso et al.[181]

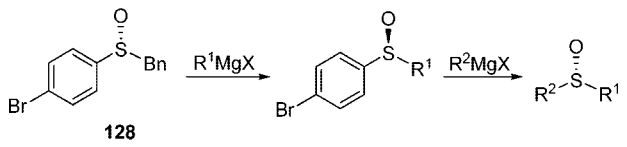


1.4.1.2. New Chiral Sulfinyl Transfer Reagents. In recent years, *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide de-

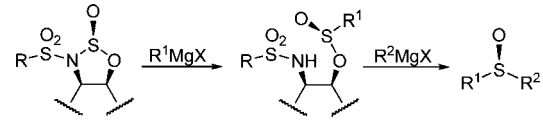
Scheme 6



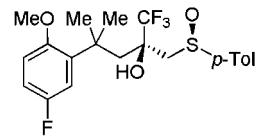
Scheme 7

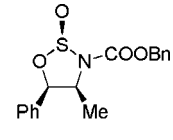


Scheme 8



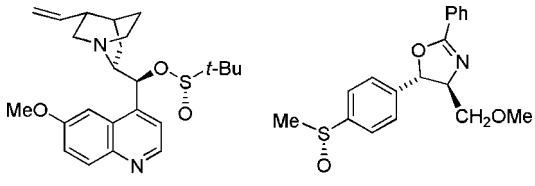
rivatives **129** and **130** were introduced by Senanayake and co-workers as valuable precursors of enantiopure sulfinamides and sulfoxides.[195−198] The synthetic strategy, originally proposed by Wudl and Lee,[199] was substantially improved by the activation of the nitrogen atom in **129** and **130**. These compounds were prepared from thionyl chloride and chiral *N*-activated amino alcohols (IASOO, ITSOO, MIOO) or *N*-tosylnorephedrine (TMPOO) in high quantities and both *endo* and *exo* forms.[195,196] Two subsequent reactions with appropriate organometallic compounds (Scheme 8) yielded a number of structurally diverse sulfoxides with high yields and very high enantioselectivities, with the configuration dependent on the starting form of the sulfinyl transfer agent.[196,197] This strategy was applied to a one-pot synthesis of the drug intermediate **131** in 48% overall yield and >99% *de* after crystallization.[198] A similar *N*-benzyloxy derivative **132** obtained from (1*R*,2*S*)-norephedrine was used for the synthesis of chiral sulfoxides by García Ruano and co-workers.[200] The authors showed the importance of the order in which the organometallic nucleophiles were used, since some of the nucleophiles used in the first step reacted with the sulfinate product, which led to the undesired symmetrical sulfoxide. They also found that the addition of 1.2 equiv of HBF_4 prior to the application of the second Grignard reagent improved the stereoselectivity of the reaction. The electrophilic additive blocked the nitrogen atom of the reaction intermediate and prevented the intramolecular *N*-sulfinylation that was responsible for racemization. Miscellaneous sulfoxides were obtained using this methodology, and in most cases the *ee* exceeded 90%.



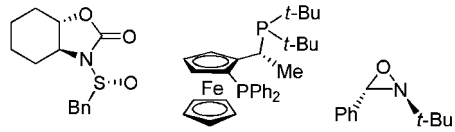


Other sulfinyl transfer reagents containing a pseudo-oxathiazolidine ring **133** were prepared from cinchona alkaloids, quinine, or quinidine.[201] These chiral *tert*-butyl sulfinates were converted into chiral sulfoxides with high yields and >96% *ee*. Sulfoxide **134** bearing the oxazoline ring was used as the chiral methylsulfinyl group transfer agent.[165] Its reaction with butyllithium reagents proceeded with moderate (47−52%) yield, but high enantiomeric purity was preserved (92−99% *ee*).

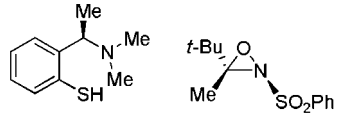
N-Sulfinyloxazolidinones, reported earlier by Evans et al. as effective sulfinyl transfer reagents,[202] were also applied in the synthesis of chiral sulfoxides by Juaristi, Quintero, Anaya de Parrodi, et al.[203] For this purpose, they synthesized a novel compound **135** and its three stereoisomeric derivatives starting from inexpensive cyclohexene oxide and (*S*)-phenylethylamine. Their reaction with methylmagnesium bromide afforded the chiral benzyl methyl sulfoxide (either (*R*) or (*S*) isomer depending on the configuration of the oxazolidine **135**) in 70−75% yield and >98% *ee*. In



133 (R_S)-134



($4S,5S,R_S$)-135 136 137

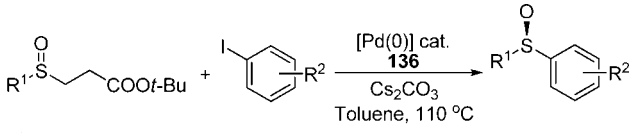


(*R*)-138 139

conclusion, several new chiral sulfinyl transfer reagents based on the oxazolidine or oxathiazolidine skeleton were developed that gave results comparable to those obtained with menthyl sulfinates or DAG derivatives.

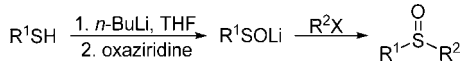
1.4.1.3. Chiral Sulfoxide by Electrophilic Attack. A new C−S bond can also be formed as a consequence of electrophilic attack on a sulfur atom. The generation of a sulfenate anion serves as the first step in these preparations. Such an anion can be derived from sulfenate esters, sulfines, or functionalized sulfoxides.[46,204−211] Madec, Poli, and co-workers described an enantioselective arylation of sulfenate anions generated from β-sulfinyl esters in the presence of palladium(0) and a chiral Josiphos-type ligand **136** (Scheme 9).[46] Using different aryl iodides and Cs_2CO_3 as a base, they obtained a series of aryl tolyl, aryl 2-naphthyl, and aryl benzyl sulfoxides in 67−98% yield and 40−80% *ee*. Perrio and co-workers developed a new method in which aliphatic thiols were converted into the corresponding thiolates, which in turn were oxidized with oxaziridine to the sulfenate salts.[212−215] These salts were treated *in situ* with aliphatic halides (Scheme 10) to produce the desired sulfoxides. Interestingly, a mild oxidant, *trans*-2-*tert*-butyl-3-phenyloxaziridine **137**, was found to be particularly efficient in this procedure. In the asymmetric version, using an enantiopure thiol **138** as substrate, and the racemic oxidant **139**, diastereomeric mixtures of sulfoxides were obtained with a high *de* (62−96%, depending on the halide used).[213] The preparation of chiral sulfoxides from sulfenate anions extends the palette of methods based on stereoselective substitution.

Scheme 9



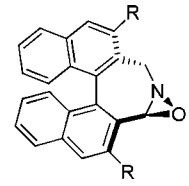
R^1 = *p*-Tol, 2-Naphthyl, Bn
R^2 = Me, OMe, CF_3, NO_2

Scheme 10

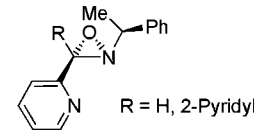


1.4.2. Organic Oxidants

1.4.2.1. Oxaziridines. New chiral binaphthyl-derived oxaziridines **140** were synthesized and tested in the methanesulfonic acid-promoted oxidation of several sulfides.[216] No sulfone was formed in the course of thesw reactions, and the yield of the corresponding sulfoxides was in the range of 64−86%. The enantioselectivity was rather moderate (*ee* ≤ 33%), but it was further improved by varying the acids (methanesulfonic or trifluoroacetic acid) and reaction time (up to 80% *ee*).



R = H, Ph

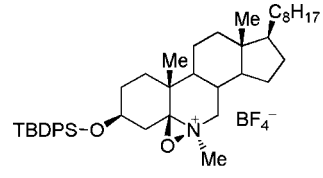


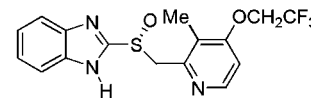
R = H, 2-Pyridyl

140 141

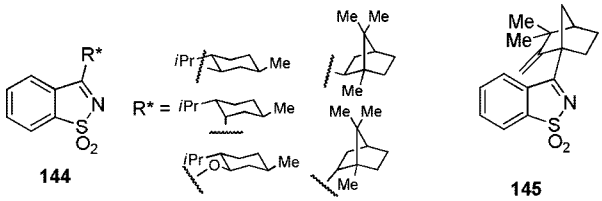
To avoid the use of strong Brønsted acids for the activation of oxaziridines, Fontecave and co-workers designed the 2-pyridyl-substituted derivatives **141**, which could be used with Lewis acid such as $ZnCl_2$.[217] The coordination of the Zn^{2+} ion by a pyridyl substituent and oxaziridine nitrogen atom led to the formation of a 1:1 adduct, which increased the electrophilic character of the oxygen atom. For a series of aryl alkyl sulfides, this system gave chiral sulfoxides with 23−85% yield and 22−45% *ee*. The configuration of the main enantiomer was dependent on the chirality of the oxaziridine ring.

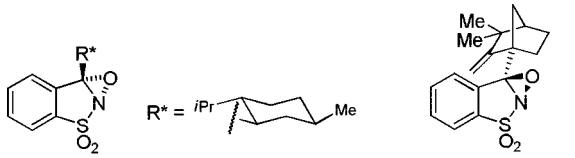
The new oxaziridinium salt **142**, which was prepared in two steps from the protected 6-azacholesterol, was tested in the oxidation of alkyl aryl sulfides and afforded (*R*)-sulfoxides with high enantioselectivities (for example, *ee* > 99% for methyl *p*-tolyl sulfide at −70 °C) and yields.[218] These results encouraged the authors to use their system for the preparation of (*R*)-lansoprazole (**143**) (60% yield, 97% *ee*).[218] Oxaziridinium-like intermediates were believed to be the possible active species in the chiral sulfoxidation promoted by certain organocatalysts.[219,220] Chiral sulfonylimines **144** and **145** were used in stoichiometric amounts in the oxidation of various sulfides (including cyclic ones) by hydrogen peroxide.[219] The yields were in the range 31−100%, while the enantioselectivity was rather moderate (*ee* = 2−38%). The tertiary alkyl derivative **145**, which exhibited the highest activity, was also used in substoichiometric quantities (10% and 20%). The (*R*)-enantiomers of phenyl methyl sulfoxide and *p*-tolyl methyl sulfoxide were obtained almost quantitatively, but the enantioselectivity was only 14% in both cases. The two oxaziridines **146** and **147** were synthesized to check their potential participation in the sulfonylimine-catalyzed reaction.[219] With these new oxidants, sulfoxides with identical configurations were obtained, but the enantiomeric excess was lower. These observations indicated that oxaziridine could be the main but not the sole oxygen atom-transfer reagent in the process.

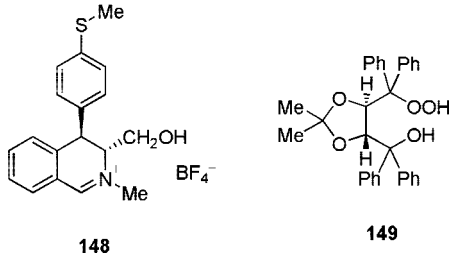




142 (*R*)-143







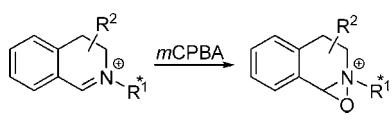
Various chiral dihydroisoquinolinium salts were also used for the generation of the corresponding oxaziridines (Scheme 11).[85,220] Starting from (1*S*,2*S*)-thiomicamine, a new, enantiomerically pure tetrafluoroborate salt **148** was prepared.[220] Using 10 mol % of **148**, and oxone as oxidant, methyl-*p*-tolyl sulfide was converted to the (*R*)-sulfoxide with 50−84% yield (depending on reaction conditions) and up to 42% *ee*. Among the new chiral oxaziridine derivatives, compound **142**, which can be prepared from cholesterol, led to optimal results. Still, there is a need for an effective, easily obtainable and thus cheaper alternative for the previously developed reagents.

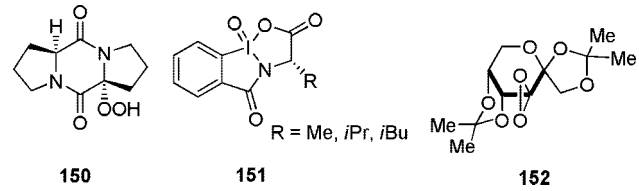
1.4.2.2. Hydroperoxides and Other Chiral Organic Oxidants. Chiral hydroperoxides were used not only in titanium-catalyzed sulfoxidations (see section 1.4.3.1.1)[221−225] but also in metal-free oxidations of prochiral sulfides. Aoki and Seebach prepared a stable, crystalline hydroperoxy alcohol, TADOOH (**149**).[226] Thioanisole was oxidized by TADOOH without any catalysts in THF solution to produce mainly the (*S*)-sulfoxide in 73% yield and 86% *ee* under optimized conditions (1.5 equiv of oxidant, 96 h, −30 °C → RT). The enantiomeric purity of the resulting sulfoxide was enhanced by kinetic resolution.

Another chiral, diketopiperazine-derived hydroperoxide **150** was recently described and used in different oxidation reactions.[227] Various sulfides were converted to the corresponding sulfoxides with a complete chemoselectivity (no sulfone was formed) and moderate to high yields, but no enantioselectivity was observed.

As new organic oxygen transfer reagents for the enantioselective sulfoxidation, benziodazole oxides **151** were prepared from the corresponding 2-iodobenzamides and potassium bromate.[228] Thioanisole was almost quantitatively (90−92% yield) converted into the S-oxide by these chiral

Scheme 11

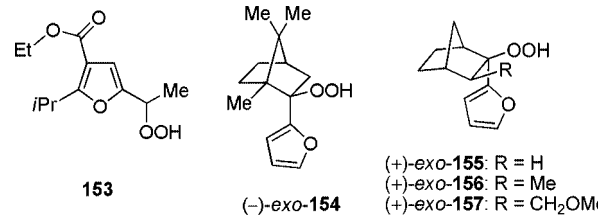




oxidants, but the *ee* was rather unsatisfactory (11−16%). Low enantioselectivity (2−26% *ee*) and moderate yields (47−60%) were observed when chiral dioxirane **152** generated *in situ* from pyranose-derived ketone was used for the oxidation of alkyl aryl sulfides.[229] These examples, and the previous attempts with chiral peracids (up to 20% *ee*)[230−232] and *N*-chlorocaprolactam (*ee* below 3%)[233] clearly show that although, in principle, each organic oxidant can be converted into a nonracemic derivative, the asymmetric induction can be disappointingly inefficient. As a result, chiral oxaziridines remain unrivaled in the field of metal-free enantioselective sulfoxidation.

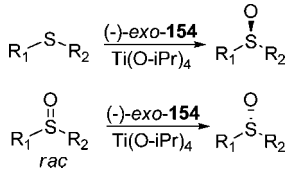
1.4.3. Oxidations Catalyzed by Metal Complexes

1.4.3.1. Titanium-Mediated Oxidations. *1.4.3.1.1. Modifications of Kagan's System. Chiral Furyl Hydroperoxides.* As a modification of the Kagan/Modena protocol of sulfide oxidation, Lattanzi, Scettri, and co-workers introduced a new class of hydroperoxides derived from furan.[221−225,234−237] They found that racemic furyl hydroperoxides of type **153** can be used in place of the commonly used *tert*-butyl or cumyl hydroperoxides in the Ti(O-*i*Pr)$_4$/DET or Ti(O-*i*Pr)$_4$/BINOL-catalyzed sulfoxidations, leading to high enantioselectivities due to enantioconvergence of asymmetric oxidation and kinetic resolution.[234−237] The oxidants were easily synthesized from furan and carbonyl compounds in satisfactory yields. Moreover, their recovery after the catalytic reaction was possible because the tertiary furyl alcohol formed as the side-product could be isolated from the reaction mixture and reoxidized back to the starting hydroperoxide.



Following these observations, the authors concentrated their attention on the investigation of the Ti-catalyzed asymmetric oxidation mediated by chiral furyl hydroperoxides. The results were collected in a review article.[224] A renewable chiral hydroperoxide (−)-*exo*-**154** was prepared starting from (1*R*)-camphor and tested in the oxidation of various sulfides.[221] Using 0.2 equiv of Ti(O-*i*Pr)$_4$, 1 equiv of **154**, and 4 Å molecular sieves at −20 °C in toluene, the corresponding sulfoxides (in most cases (*S*)-enantiomers) were obtained in moderate yields (up to 68%) and enantioselectivities (*ee* ≤ 51%). Sulfone production was negligible under these conditions, and no kinetic resolution was observed. Sulfoxides of the opposite configuration were prepared as well with the use of the (1*S*)-camphor-derived hydroperoxide. Interestingly, a stereodivergent kinetic process observed with the use of a stoichiometric amount of

Scheme 12



metal complex and prolonged reaction time can be utilized to obtain sulfoxides enriched in both enantiomeric forms by means of the same chiral promoter (Scheme 12).[221,222]

Another optically pure tertiary hydroperoxide **155** derived from (+)-norcamphor was prepared by the same group.[222] Reduction of steric hindrance as compared to the case of compound **154** resulted in an increase of the sulfoxidation rate, but the enantioselectivities were remarkably lowered (for example, 23% *ee* against 47% for methyl *p*-tolyl sulfoxide). In this case, significant amounts of sulfones were also produced, and the *ee*'s could be improved using the enantioconvergent kinetic resolution process.

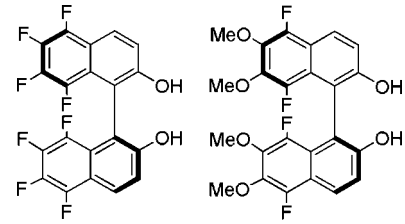
To enhance the asymmetric induction of the norcamphor derivative, an additional chiral center close to the hydroperoxy group was introduced in the new hydroperoxide **156**.[223] The methylation increased the enantioselectivity of sulfoxidations as compared to the case of **155** (*ee*'s were higher by about 20%) under similar conditions. In this case, however, only traces of sulfones were observed and further enantiomeric enrichment of sulfoxides due to kinetic resolution did not take place.

Much better results were obtained when the methyl substituent was replaced by a methoxymethyl group bearing the additional donor atom (compound **157**).[225] For a series of alkyl aryl sulfides, the combined enantioselective oxidation and kinetic resolution led to moderate yields (typically 30−57%) but high enantioselectivities: (*R*)-sulfoxides were isolated with 68−99% *ee*.

The proposed transition states for the titanium-mediated sulfoxidations using chiral furyl hydroperoxides suggest that the furan ring is not directly engaged in the catalytic action.[224] In principle, the synthetic strategy developed by Lattanzi, Scettri, and co-workers can be applied for the synthesis of various chiral hydroperoxides, with the furyl substituent replaced, for example, by other heterocycles.

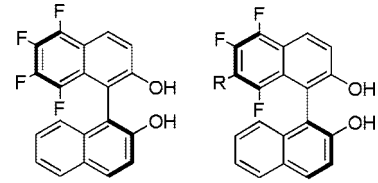
1.4.3.1.2. New BINOL Derivatives and Other Diols. The effect of BINOL ring substitution on its catalytic properties was investigated by Yudin and co-workers.[238−240] The octafluorosubstituted derivative (F_8BINOL, **158**) of increased configurational stability exhibited higher activity in the oxidation of methyl *p*-tolyl sulfide with CHP as compared to (*S*)-BINOL itself and produced the sulfoxide of the opposite configuration (*S*) with up to 86% *ee*.[238] The methoxylated derivative **159**, which was prepared from F_8BINOL by the nucleophilic substitution, retained the sense of chiral induction, but the enantioselectivity was substantially lower.[239] F_4BINOL **160**, bearing fluorine atoms on a single naphthyl ring, gave similar yields and *ee*'s in the thioanisole oxidation as F_8BINOL.[240] In contrast, for its two 7-substituted derivatives **161**, both yield and enantioselectivity were dramatically decreased.

Scettri and co-workers described the first application of commercially available titanocenes, Cp_2TiCl_2 and $Cp_2Ti(OTf)_2$, as the titanium source in the oxidation of prochiral sulfides by TBHP.[241] With (*R*)-BINOL as the chiral ligand and the addition of 4 Å molecular sieves, the reaction carried out at −20 °C led to (*R*)-methyl aryl sulfoxides in good yields and moderate *ee*'s (up to 45%).



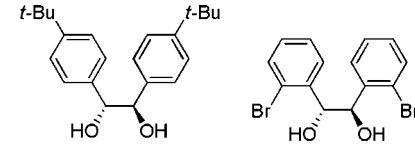
158 **159**

A series of enantiopure (*R*,*R*)-1,2-arylethane-1,2-diols was prepared[242] and used in the titanium-catalyzed enantioselective oxidation of alkyl aryl sulfides with TBHP.[243] The promising results obtained for the bis-*tert*-butyl derivative **162** in the conversion of *p*-tolyl methyl sulfide (70% yield, 90% *ee* compared with 62% yield and 80% *ee* for unsubstituted (*R*,*R*)-HB) prompted the authors to perform further reactions with this ligand. In most cases, the yields were comparable to those of the parent HB ligand, and better *ee*'s were observed for unhindered substrates. In addition, diol **162** could be applied in *n*-hexane solution instead of the CCl_4 that was used in the original method. This modification made the procedure safer and more ecologically sound. In the enantioselective preparation of esomeprazole **1** from the corresponding sulfide **92**, dibromosubstituted ligand **163** appeared to be optimal (92% yield, 96% *ee* for the reaction performed in toluene at −20 °C).[244] Similar results were obtained in the course of oxidation of other 1*H*-benzimidazolyl sulfides (e.g., pantoprazole, rabeprazole, or lansoprazole) with TBHP, which was catalyzed by the titanium complex of **163**.



160 **161**

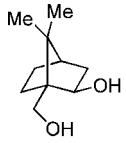
The study of thioanisole oxidation by the titanium complex formed *in situ* from $Ti(O\text{-}iPr)_4$ and a chiral 2,10-camphanediol **164** showed that the absolute configuration of the product was dependent on the oxidant used.[245] TBHP yielded (*S*)-sulfoxide with up to 92% *ee*, which was reached due to a stereoconvergent kinetic resolution. In the case of CHP, the (*R*)-enantiomer was formed preferentially when the amount of oxidant did not exceed 1.2 equiv. Higher amounts or prolonged reaction time reversed the stereochemical preference, and the (*S*)-isomer was isolated with up to 99% *ee*. This observation was rationalized by the stereodivergent kinetic process in which the main sulfoxide product was oxidized to the sulfone faster than the minor one.



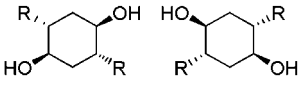
(*R*,*R*)-**162** (*R*,*R*)-**163**

The enantiopure 2,5-dialkylcyclohexane-1,4-diols **165**–**168** were examined as ligands for titanium in the oxidation of thioanisole.[246] The best results were obtained when

CHP was used as oxidant, and the reaction was conducted in CCl_4 at 0 °C in the presence of 4 Å molecular sieves. Under these conditions, similar yields (72−75%) and an enantiomeric excess equal to 65% (methyl derivatives) or 76−77% (isopropyl-substituted ligands) were noted for the four diols. For other alkyl aryl sulfides, the Ti(O-*i*Pr)$_4$/**168** system worked equally well (up to 84% *ee* was observed). The authors found that the reaction's enantioselectivity originated only from the asymmetric oxidation, since kinetic resolution was not efficient in this process. Diol **166** was applied as the ligand in the Ti-catalyzed oxidation of sulfide **92**, leading to esomeprazole **1** in 72% yield and 76% *ee*.



164

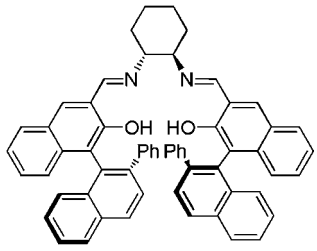


165: R = Me
166: R = *i*Pr
167: R = Me
168: R = *i*Pr

169

The previously discussed alterations of the chiral diols used as ligands in titanium-mediated sulfoxidations influenced their reactivity, configurational stability, and solubility (which allowed variation of the reaction conditions). Ligand **163** (which was found to be efficient in the synthesis of omeprazole derivatives) and compound **164** (which showed the unusual oxidant-dependent enantioselectivity switch) seem to be of particular interest.

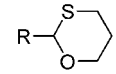
1.4.3.1.3. Other Titanium Complexes. Searching for efficient and environmentally friendly salen-based systems for enantioselective sulfoxidation, Saito and Katsuki prepared two di-μ-oxo titanium complexes **169** with ligands **30** and **170**.[247−250] Using the catalyst derived from compound **170** and aqueous hydrogen peroxide in methanol, they obtained methyl phenyl sulfoxide with 76% *ee*, which was significantly improved to 94% when the urea−H_2O_2 adduct (UHP) was used as an oxidant.[247] Similar results were obtained for the oxidation of other methyl aryl sulfides (78−95% yield, 92−99% *ee*). With the *tert*-butyl substituted ligand, the enantioselectivity was considerably smaller. The reaction was shown to proceed through a monomeric Ti(salen) complex, which was converted by H_2O_2 to an active peroxoTi(salen) species.[248] The new system was then applied to the oxidation of cyclic dithioacetals (dithiolane and dithiane derivatives **171**−**180**) and produced monosulfoxides in high diastereomeric ratios (72−98% *de*) and enantioselectivities (typically 79−99% *ee* for the major diastereomer).[249] Complex **169** was also able to catalyze the oxidative kinetic resolution of racemic 2-substituted 1,3-oxathianes **181**, while the UHP oxidation of 2-phenyl-1,3-oxathiolane **182** also produced a single diastereomer, but the relative ratio of the two enantiomers was much lower.[250]

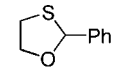


170

171: R^1 = *t*-Bu, R^2 = H
172: R^1 = Bn, R^2 = H
173: R^1 = CH_2CH_2Ph, R^2 = H
174: R^1 = C≡CPh, R^2 = H
175: R^1 = Ph, R^2 = Me

176: R^1 = *t*-Bu, R^2 = H
177: R^1 = Bn, R^2 = H
178: R^1 = CH_2CH_2Ph, R^2 = H
179: R^1 = C≡CPh, R^2 = H
180: R^1 = Ph, R^2 = Me

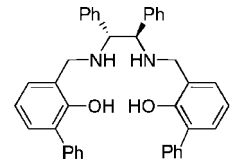




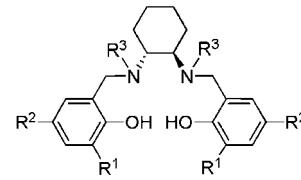
R = Ph, CH_2CH_2Ph, CH=CHPh

181 **182**

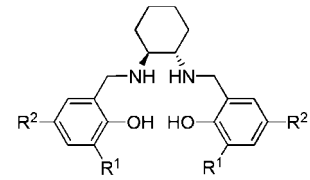
Prompted by the results obtained by Katsuki et al., who used the Ti^{IV} complexes with a reduced form of salen as epoxidation catalysts,[251,252] which also led to the development of Fe^{III}-salan[253,254] and Al^{III}-salalen[255−258] sulfoxidation systems (*vide infra*), Bryliakov and Talsi prepared a series of chiral titanium(IV) complexes with (*N*,*N*′-bissalicylamine)-ethylene (salan, **183**−**191**) for the enantioselective oxidation of sulfides with hydrogen peroxide.[259] For the ligand/Ti(O-*i*Pr)$_4$ ratio equal to 1.0 (found to be optimal), the enantioselectivity was low to moderate, but when the most promising ligands were converted into the corresponding di-μ-oxo dimeric titanium complexes, the *ee*'s increased substantially. With the higher excess of oxidant to make use of kinetic resolution, enantiomeric excesses up to 97% were achieved.



(*S*,*S*)-**183**

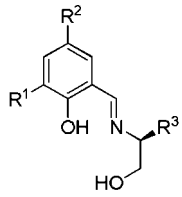


(*R*,*R*)-**184**: R^1 = R^2 = *t*-Bu, R^3 = H
(*R*,*R*)-**185**: R^1 = *t*-Bu, R^2 = NO_2, R^3 = H
(*R*,*R*)-**186**: R^1 = R^2 = R^3 = H
(*R*,*R*)-**187**: R^1 = R^3 = H, R^2 = Br
(*R*,*R*)-**188**: R^1 = Ph R^2 = NO_2, R^3 = H
(*R*,*R*)-**189**: R^1 = Ph R^2 = H, R^3 = Me

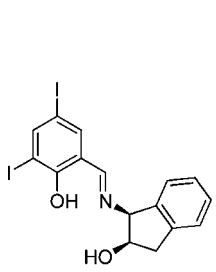


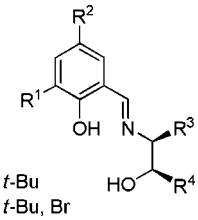
(*S*,*S*)-**190**: R^1 = Adamantyl, R^2 = Me
(*S*,*S*)-**191**: R^1 = Ph, R^2 = H

The same authors adapted the tridendate Schiff base−H_2O_2 system, which was previously used in vanadium-catalyzed sulfoxidations,[183] for the construction of titanium-based catalysts.[260] Six ligands, **23**, **122**, and **192**−**195**, were prepared from enantiopure 2-aminoalcohols and disubstituted salicylaldehydes, and they were tested in the oxidation of three alkyl aryl sulfoxides using Ti(O-*i*Pr)$_4$ as the metal source and 30% aqueous hydrogen peroxide. Reasonable chemoselectivities, but rather moderate enantioselectivities (up to 60% *ee*), were observed in these oxidations, with ligand **193** giving the best results. For Schiff bases **196** investigated by Somanathan et al., similar yields and *ee*'s (40−64%) were observed in the Ti-catalyzed sulfoxidation of thioanisole.[261]



192: $R^1 = R^2 = I$, $R^3 = t$-Bu
193: $R^1 = R^2 = t$-Bu, $R^3 = i$Pr
194: $R^1 = t$-Bu, $R^2 = H$, $R^3 = Ph$

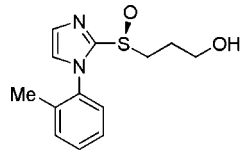




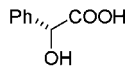
R^1 = H, *t*-Bu
R^2 = H, *t*-Bu, Br
R^3 = CH_2OH, CH_2OMe, CH_2SBn, $(CH_2)_2SMe$
R^4 = H, Ph

195 **196**

The key intermediate in the synthesis of compound OPC-29030 (**3**), (*S*)-3-[1-(2-methylphenyl)imidazol-2-ylsulfinyl]-propan-1-ol (**197**), was obtained through the titanium-catalyzed enantioselective oxidation of the corresponding sulfide.[27] As the original Kagan conditions yielded the product in 78% yield and with only 54% *ee* (which could be raised by a single crystallization to >99.5%), other chiral ligands were tested in this oxidation. (*R*)-Mandelic acid **198** appeared to be the optimal promoter, leading to (*S*)-sulfoxide in 74% yield and 76% *ee*. The proposed reaction mechanism involved a rigid, chiral intermediate in which α-hydroxy-carboxylate was coordinated to titanium.

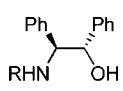


(*S*)-**197**



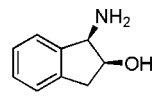
(*R*)-**198**

A series of chiral *N*-alkyl-(1*S*,2*S*)-1,2-diphenylaminoethanol ligands **199** was investigated in the oxidation of alkyl aryl sulfides.[262] The active complexes were formed *in situ* from Ti(O-*i*Pr)$_4$, aminoalcohols, and water, and TBHP was used as an oxidant. For most ligands tested, almost racemic sulfoxides were obtained. Only the *N*-methyl-substituted derivative led to a (*S*) product with a moderate *ee* (up to 56%). Another aminoalcohol, (1*R*,2*S*)-*cis*-1-amino-2-indanol (**200**), led to the optimal results (90% yield, 99% *ee*) in the synthesis of (*S*)-tenatoprazole **201**.[263] The reaction was carried out in 1-methyl-2-pyrrolidine as a solvent at 0 °C in the presence of 0.5 equiv of Ti(O-*i*Pr)$_4$ and 2.32 equiv of CHP.

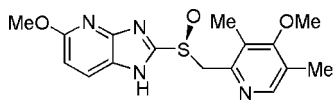


(*S*,*S*)-**199**

R = H, Me, Et, Pr, *i*Pr, Cyclohexyl, Bn

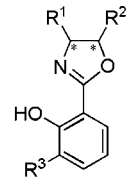


200

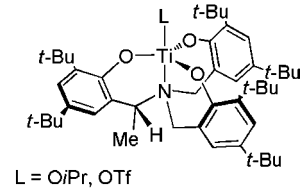


(*S*)-**201**

Starting from chiral 1,2-aminoalcohols, Jiang and co-workers prepared the corresponding oxazoline derivatives **202**−**205**.[264] Using the best ligand (4*S*,5*S*)-**202**, Ti(O-*i*Pr)$_4$ in CH_2Cl_2/CCl_4 (3:7 v/v) at 0 °C, and TBHP (70% solution in water) as the oxidant, (*R*)-alkyl aryl sulfoxides were obtained with high enantioselectivity (typically 70−96% *ee*). Low yields were connected with the overoxidation to the sulfone; this phenomenon had a beneficial influence on *ee* values due to kinetic resolution.



202: $R^1 = R^2 = Ph$, $R^3 = t$-Bu
203: $R^1 = R^2 = Ph$, $R^3 = H$
204: $R^1 = Ph$, $R^2 = H$, $R^3 = t$-Bu
205: $R^1 = Bn$, $R^2 = H$, $R^3 = t$-Bu



L = O*i*Pr, OTf

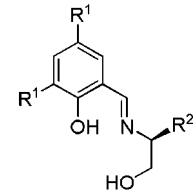
(*R*,*M*)-**206**

Novel pseudo-C_3-symmetric titanium complexes exhibiting propeller chirality (*R*,*M*)-**206** were employed as catalysts for the oxidation of benzyl phenyl sulfide with CHP.[265] Under optimal conditions (2 equiv of oxidant, 10 mol % of triflate catalyst, toluene as solvent), (*R*)-sulfoxide was obtained in 78% yield and 37% *ee*; the enantioselectivity was further improved to 47% *ee* utilizing kinetic resolution.

Among the novel titanium catalysts, complexes with tetradendate (NNOO)-donating ligands (salen and salan derivatives **30**, **37**, and **183**−**191**) were found to be the most appropriate for the preparation of miscellaneous sulfoxides. Other promising systems (e.g., aminoalcohol **200**) deserve further testing with a wider range of substrates.

1.4.3.2. Vanadium-Catalyzed Oxidations. *1.4.3.2.1. Tridendate Schiff Bases.* Prompted by the results of Bolm and Bienewald,[103,104] many research groups explored the possibility of the relatively easy modification of the original Schiff bases.

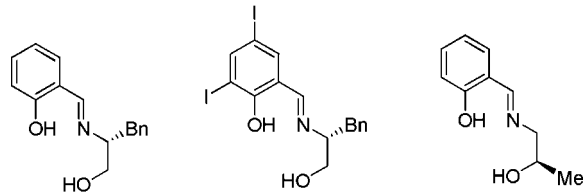
During the study on reactive intermediates in vanadium-catalyzed enantioselective sulfoxidation, Bryliakov and co-workers analyzed the conversion of thioanisole by means of hydrogen peroxide and the complex generated *in situ* from VO(acac)$_2$ or VO(O-*i*Pr)$_3$ and Schiff bases **23**, **193**, **207**, and **208**.[183] Replacing the *tert*-butyl group in the ligand used by Bolm and Binewald[103] by other substituents led to a significant loss of enantioselectivity.



(*S*)-**207**: $R^1 = t$-Bu, $R^2 = Ph$
(*S*)-**208**: $R^1 = t$-Bu, $R^2 = Bn$

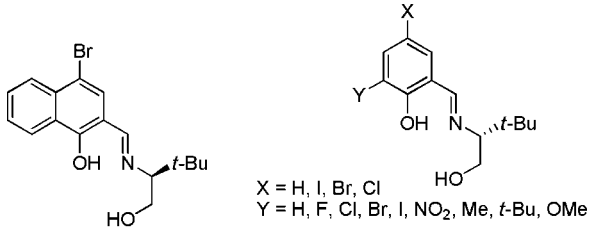
Rozwadowska and co-workers tested several ligands obtained from (1*S*,2*S*)-1-aryl-2-amino-1,3-propanediols and salicylaldehydes in the V-catalyzed oxidation of methyl *p*-tolyl sulfide with 30% aqueous hydrogen peroxide.[266] Among these Schiff bases, the best yield (97%) and enantiomeric excess (43%, increased by recrystallization to >99%) were observed for compound **209**, bearing only one

stereogenic center. Other Schiff bases (two of them, **210** and **211**, prepared for the first time) were used by this group for the oxidation of oxazoline-derived sulfides **103**.[165] The *de* values ranged from 0 to 99%, with diiodo-substituted leucinol derivative **192** being most efficient.



(*R*)-**209** (*R*)-**210** (*R*)-**211**

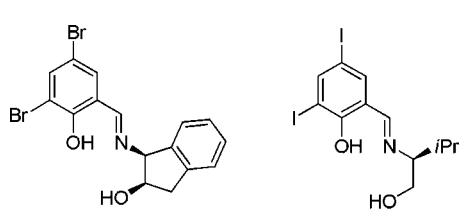
The optimization of the Schiff base structure was performed through screening of a library of ligands obtained from a solid-supported aldehyde and different 1,2-aminoalcohols (see also section 1.6).[267] Then a series of Schiff bases was prepared using (1*R*,2*S*)-*cis*-aminoindanol, one of two aminoalcohols leading to the best results, and diversely substituted salicylaldehydes. Fourty-one of these ligands were tested in the oxidation of thioanisole. Finally, by combining the most promising aldehydes with the best aminoalcohols, two ligands, **192** and **212**, were found to be optimal. When used for the vanadium-catalyzed oxidation of alkyl aryl sulfides with 1.2 equiv of H_2O_2 in dichloromethane at 0 °C, they gave highly enriched sulfoxides (*ee* = 89−97%) in high yields (74−86%).



(*S*)-**212** (*R*)-**213**

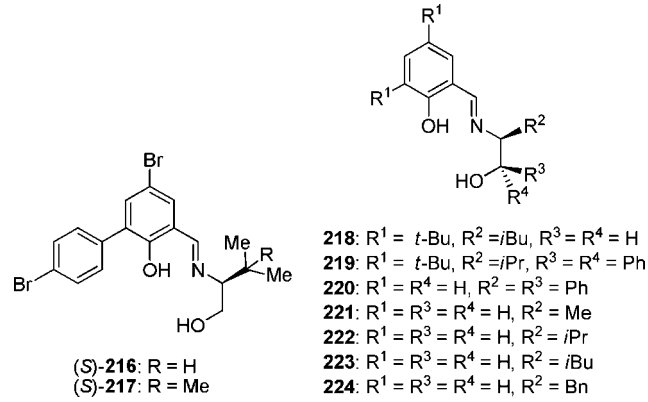
Further comparison with other (*R*)-leucinol-based ligands bearing halogen substituents **213**, some of which were also quite effective in the thioanisole oxidation (for example, 88% *ee* was noted for dichloro and chloroiodo derivatives), confirmed the superiority of diiodo-substituted Schiff base **192** (92% *ee*).[268]

A library of 41 Schiff bases created by Somanathan's group from differently substituted salicylaldehydes and enantiopure 1,2-aminoalcohols was tested in the thioanisole sulfoxidation by H_2O_2 using $VO(acac)_2$ as the metal source.[261,269] Yields ranging from 41 to 98% and *ee* values between 9 and 61% were noted, and 3,5-dibromosalicylidene ligand **214** gave the best results.



214 (*S*)-**215**

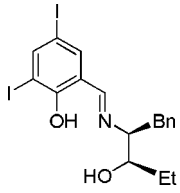
A systematic study of chiral Schiff bases containing a 3,5-dibromo- or 3,5-diiodosalicylidene fragment confirmed the beneficial effects of halogen substituents on the enantioselectivity of sulfide oxidation, with iodo-derivatives performing slightly better.[270] Together with a bulky group (*tert*-butyl, isopropyl) attached to a chiral carbon atom, such a substitution resulted in high *ee* values for (*S*)-methyl phenyl sulfoxide (88% for **215** and 90% for **192**, respectively). An influence of the 3-aryl substituent on the reaction performance was also investigated.[271] From the ligands tested, those bearing a 4-bromophenyl group, **216** and **217**, showed the highest *ee* values in the thioanisole oxidation (74 and 77%, respectively). In the case of 2-naphthyl methyl sulfide, the enantioselectivity was even higher (90% *ee* for Schiff base **217**).



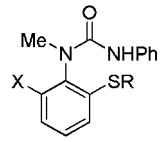
In another series of Schiff bases, **218**−**224**, prepared by Zhao and co-workers, a general (and somehow surprising) tendency was observed that *tert*-butyl substituents present in the aryl ring decreased the *ee* value of sulfoxidation when compared to unsubstituted systems.[272] The authors pointed out that the ligand bearing bulky substituents in the ring performed better when the smaller group was present at the 2 position and *vice versa*. In the oxidation of thioanisole with aqueous H_2O_2, up to 68% *ee* (ligand **222**) was noted; for most of the remaining derivatives, the *ee* was in the range 45−60%. Similar values were obtained for complexes formed *in situ* from the Schiff bases **193**, **208**, and **222**−**224** and vanadyl acetylacetonate.[273] When the corresponding preformed, isolated complexes were used (to avoid the waste of the Schiff base, which is typically used in 50% mol excess as compared to $VO(acac)_2$), in most cases the *ee* was slightly raised. Yields between 31 and 77% and *ee*'s ranging from 77 to 99% were achieved. An increase of oxidant amount and the reaction time enhanced the enantioselectivity. This observation suggested the possibility of utilizing kinetic resolution in this oxidation. In the original report from Bolm and in most of the subsequent papers dealing with the oxidation of prochiral sulfides catalyzed by the vanadium-Schiff base system, the induction of chirality was typically attributed exclusively to asymmetric oxidation, and the kinetic resolution of resulting sulfoxides was not observed. Apparently, with the ligands and substrates tested, the overoxidation of sulfoxide to sulfone was found to be negligible. However, for certain combinations of reactants, catalyst, and reaction conditions (temperature, solvent, amount of oxidant, and reaction time), this phenomenon can become important and its influence on the enantioselectivity would be meaningful. Taking into consideration the possible kinetic resolution in the oxidation of alkyl aryl sulfides using their optimized ligand **192**, Jackson and co-workers examined the vanadium-catalyzed reaction of racemic methyl phenyl

sulfoxide with aqueous H_2O_2.[268,274] While in dichloromethane at 0 °C the effect was negligible, raising the temperature to 20 °C allowed reasonable enantioenrichment. An even more pronounced effect was observed when the reaction was conducted in chloroform, with 0 °C being the optimal temperature. Using these conditions, various alkyl aryl sulfides were oxidized with hydrogen peroxide using $VO(acac)_2$ and ligand (*R*)-**192**. Very high enantioselectivity (typically 95.5 to >99.5% *ee*) and reasonable yields (70−86%) were observed. For selected substrates, the reaction was carried out on a 60.0 mmol scale, and (*R*)-methyl phenyl sulfoxide was obtained in 87% yield and 93% *ee*, while the (*R*)-*para*-tolyl and (*R*)-*para*-bromophenyl derivatives were almost enantiopure (>99.5% *ee* after one recrystallization, 82% and 77% yield, respectively). The kinetic resolution (although less effective) was also observed for this system using toluene as solvent at higher temperature and this observation suggested its synthetic utility.[275]

Novel Schiff bases prepared from β-aminoalcohols containing two stereogenic centers were tested as ligands in vanadium-catalyzed oxidation of thioanisole with 30% aqueous H_2O_2.[276] A preliminary screening showed that compound **225** led to (*S*)-sulfoxide in 98% yield and the highest *ee* of 67%, for the reaction carried out in CH_2Cl_2 at room temperature, using 1.1 equiv of oxidant. Also, in the case of this ligand, changing of the solvent to chloroform, lowering the temperature to 0 °C, and increasing the amount of H_2O_2 to 1.35 equiv allowed a significant improvement of the reaction stereoselectivity due to kinetic resolution. The enantiomeric excess of the product was raised to 99%, while the yield remained reasonable (81%); similar results were obtained for other alkyl aryl sulfides tested.



225



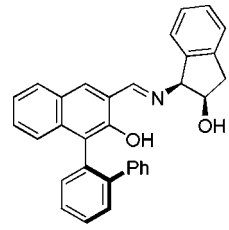
X = *t*-Bu, $(Me_3Si)_2CH$
R = Me, *p*-Tol, Cyclohexyl

226

Another illustration of the kinetic resolution taking place during oxidation of aryl benzyl sulfides was reported by Kelly et al.[118,277] The conversion of these substrates using different Schiff bases led to significant amounts of sulfones, and the optical purity of the sulfoxides increased with the use of excess oxidant. Very high enantiomeric excesses (typically 91 to >99%), accompanied by a moderate yield (~50%), were observed when ligand **192** and only 0.8 equiv of H_2O_2 were used for the reaction, which was carried out in dichloromethane at room temperature.

The kinetic resolution of 2-sulfanyl ureas **226** was achieved by means of vanadium-catalyzed oxidation with hydrogen peroxide and chiral Schiff base **192**.[130] The reaction led preferentially to *anti*-diastereomer in a high *ee*, and the remaining unreacted sulfide was also significantly enantiomerically enriched.

A modification of the ligand introduced by Vetter and Berkessel[105] was reported by Katsuki and co-workers, who replaced the naphthyl moiety with a 2-biphenyl substituent.[278] Among the three ligands **227**−**229** prepared by this group, **227** was chosen as the most efficient auxiliary, giving (*S*)-methyl phenyl sulfoxide in 83% yield and 86% *ee*. A slight improvement in enantioselectivity was observed when a small amount of methanol was added to the reaction mixture (*ee* = 88%). The authors suggested that coordination of the alcohol molecule affected the equilibration of peroxo vanadium species present in the reaction mixture.



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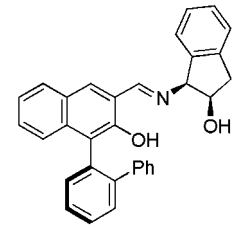
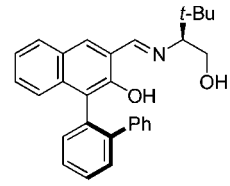


228

Ahn and co-workers changed the substituents of the binaphthyl part of the Berkessel ligan and obtained Schiff bases **230**−**232**.[279] They found that compound **230** used for thioanisole oxidation performed better than the original ligand (90% yield, 86% *ee* at 0 °C). They also showed that chirality in the imine fragment was necessary for the asymmetric induction (a racemic product was obtained for ligand **233**), and it determined the absolute configuration of the resulting sulfoxide (the (*S*)-isomer was obtained using diastereomeric ligands (*R*,*S*)-**230** and (*S*,*S*)-**230** differing in the configuration of the binaphthyl subunit; albeit, the *ee* was only 72% for the second case). Oxidation of other methyl aryl sulfides also gave satisfactory results (except for the case of methyl *o*-bromophenyl sulfide, for which up to 42% *ee* was noted), and for benzyl phenyl sulfide and its 4-bromo derivative, the *ee* values reached 99 and 98%, respectively. Other sterically hindered Schiff bases, **234** and **235**, prepared by this group exhibited similar enantioselectivities in the sulfide oxidation.[280]



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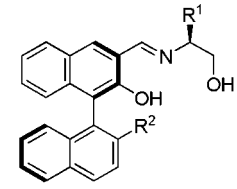
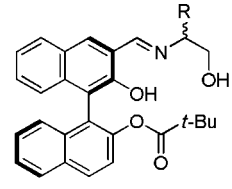
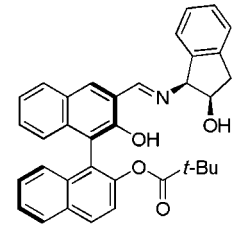


230: R^1 = *t*-Bu, R^2 = OOC*t*-Bu
231: R^1 = *t*-Bu, R^2 = OOCMe
232: R^1 = *t*-Bu, R^2 = O-$SiPh_2$(*t*-Bu)
233: R^1 = H, R^2 = OOC*t*-Bu



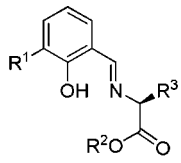
234: R = $C(Et)_2OMe$, $C(i\text{-}Bu)_2OMe$



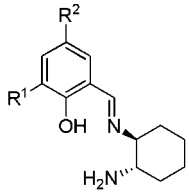
(*R*,*S*,*R*)-**235**

A series of Schiff bases **236** was obtained from amino acids or amino acid esters and salicylaldehydes.[281] Thioanisole oxidation with TBHP catalyzed by oxovanadium complexes of these ligands afforded (*R*)-sulfoxides with high yields (up to 90%), but the enantiomeric excess was small (5−20%). Chiral dioxovanadium(V) Schiff base complexes were prepared from salicylaldehydes and enantiomerically pure (1*S*,2*S*)- or (1*R*,2*R*)-1,2-diamines: 1,2-diphenyl-1,2-

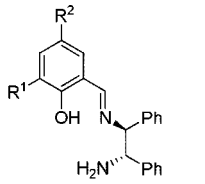
diaminoethane or *trans*-1,2-diaminocyclohexane.[282,283] Selected complexes were used as catalysts in the thioanisole oxidation with CHP, and lower enantioselectivity was observed for the cyclohexane derivatives (19−23% *ee* for ligands **237** and **238** vs 34−39% noted for **239** and **240**). Schiff bases derived from differently substituted enantiopure 1,2-aminoalcohols and salicylaldehydes were converted to the oxovanadium(V) complexes bearing the alkoxy group **241**.[284] These chiral complexes were used as catalyst precursors for the oxidation of thioanisole, and for the ethoxy derivative and ligand **192**, very high *ee* values were observed (83−98%, depending on reaction conditions).



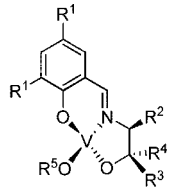
(*S*)-**236**: R^1 = H, Cl, NO_2, R^2 = H, Me
R^3 = Me, *i*Pr, *i*Bu, *s*-Bu, Bn,
CH_2CH_2SMe, $(CH_2)_4NH_2$,



(*S*,*S*)-**237**: R^1 = H, R^2 = OMe
(*S*,*S*)-**238**: R^1 = OMe, R^2 = H



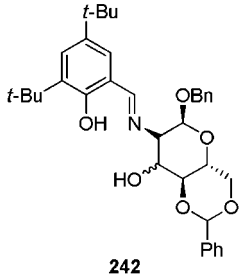
(*S*,*S*)-**239**: R^1 = H, R^2 = OMe
(*S*,*S*)-**240**: R^1 = OMe, R^2 = H



R^1 = H, *t*-Bu, I, R^2 = Ph, Bn, *i*Bu, *t*-Bu
R^3 = H, Ph, *t*-Bu, R^4 = H, Ph; R^5 = Et, *i*Pr, *i*Bu, *t*-Bu

241

The carbohydrate-derived Schiff bases **242** and **243** were also prepared from 3,5-disubstituted salicylaldehydes and 2-aminopyranoses.[285] Glucose-based ligands exhibited low to medium enantioselectivity in the vanadium-catalyzed oxidation of thioanisole, with the *ee* value reaching 60%. Vanadium complexes prepared from 6-amino-6-deoxyglucopyranoside-based ligands **244** were even less selective (up to 26% *ee* in thioanisole oxidation with H_2O_2).[286]



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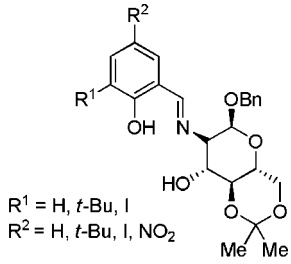
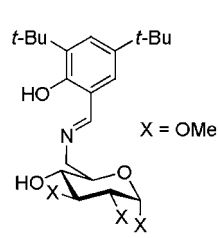


R^1 = H, *t*-Bu, I
R^2 = H, *t*-Bu, I, NO_2

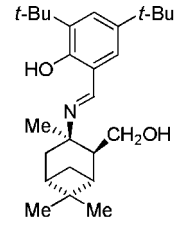
243

Low asymmetric induction (up to 32% *ee* for ligand **245**) was observed during sulfide oxidation with Schiff bases prepared from the chiral terpene compounds: myrtenal, caryophyllene, pinene, or carene.[287−289] Comparable results were obtained in the oxidation of phenacyl phenyl sulfide **246** with the use of terpene-derived ligand **247** and ClO_2 as oxidant (32% *ee*, 78% yield).[290] Cyclodextrin inclusion compounds of the vanadium complex with Schiff base-derived hydrazone ligand **248** were tested in the oxidation of thioanisole with hydrogen peroxide in water/ethanol.[291] A very small *ee* (2%) was only observed for the 1:2 K[VO_2(**248**)]−α-CD complex.



X = OMe

244



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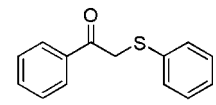
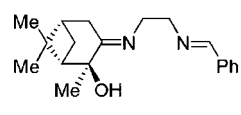


246

A novel chiral ligand bearing a rigid tetrahydroquinoline framework **249** was applied in the vanadium-catalyzed preparation of aryl methyl sulfoxides which were obtained in 80−95% yield and 66−77% *ee*.[292] Interesting trimeric variants of Bolm's catalysts were prepared and used in the oxidation of prochiral sulfides.[293] Two of eight ligands, **250** and **251**, with a sufficiently expanded linker to keep the catalytic centers apart, yielded reasonable catalytic properties (88/92% yield, 70/72% *ee* for the oxidation of thioanisole, and 98/92% yield, 86/89% *ee* for benzyl phenyl sulfide).



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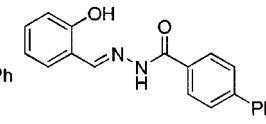

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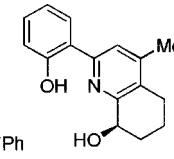
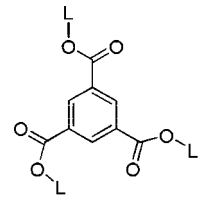
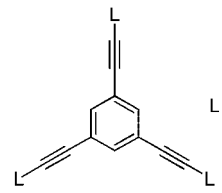


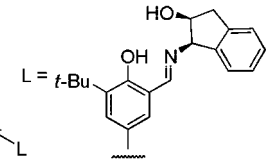
249



250

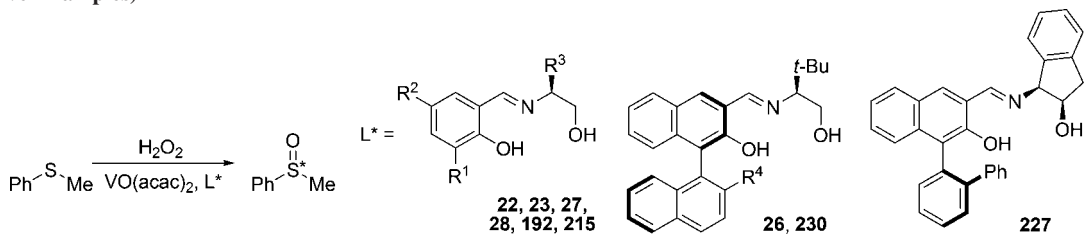


251



Since the seminal work of Bolm and Bienewald, a great library of chiral Schiff bases has become available. The relatively simple synthesis of these ligands (a reaction of an appropriately substituted salicylaldehyde with an amine chosen from the chiral pool) that can be readily tested in catalytic reactions resulted in contributions from a number of research groups. The progress made is illustrated by the representative results of thioanisole oxidation collected in Table 1. One should be aware that such comparisons are fully reliable only for reactions carried out under identical conditions and preferably repeated in one laboratory. Such factors as temperature, concentration, amount of H_2O_2 and mode of its addition, reaction time, and solvent used are extremely important. In particular, the kinetic resolution observed in $CHCl_3$ solution can result in increased stereo-

Table 1. Oxidation of Thioanisole with Aqueous Hydrogen Peroxide Catalyzed by Vanadium Complexes with Chiral Schiff Bases (Representative Examples)[a]



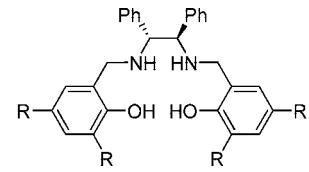
ligand	R^1	R^2	R^3	R^4	temp	time (h)	yield (%)	ee (%) (conf)	ref
22	*t*-Bu	NO_2	*t*-Bu		RT	12	94	70 (*S*)	103
23	*t*-Bu	*t*-Bu	*t*-Bu		RT	12	73	59 (*S*)	103
27	Ph	NO_2	*i*Pr		RT	20	80	58 (*S*)	107
					0 °C		90	75 (*S*)	
28	Ph	NO_2	*t*-Bu		RT	20	78	62 (*S*)	107
					0 °C		74	73 (*S*)	
192	I	I	*t*-Bu		0 °C	16	75−81	90−92 (*S*)	267, 268
192	I	I	*t*-Bu		20 °C	16	81	90 (*S*)	270
215	I	I	*i*-Pr		20 °C	16	84	88 (*S*)	270
26				H	RT	12	85	71 (*S*)	105
					0 °C		92	78 (*S*)	
227					0 °C	12	83	86 (*S*)	278
					0 °C		81	88 (*S*)[b]	
230				OOC*t*-Bu	RT	24	86	82 (*S*)	258
					0 °C		90	86 (*S*)	

[a] Common reaction conditions: 1−2 mol % of ligand, 1% of $VO(acac)_2$, solvent CH_2Cl_2, 1.1−1.2 equiv of aqueous hydrogen peroxide added. [b] MeOH added to the reaction mixture.

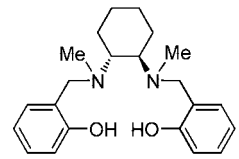
selectivity when compared to the case of the reaction performed in CH_2Cl_2.[274,276]

The results presented in Table 1 show the influence of the pattern of ligand substitution on both the yield and stereochemical outcome of the catalytic reaction. The presence of bulky substituents, especially at the R^1 and R^3 positions, seems to be of key importance for the observed stereodifferentiation. The role of these groups was also pointed out by the calculations.[187] However, their size should be controlled, since these substituents could hinder the access of the prochiral sulfide to the coordinated peroxide. The electronic factor that can alter the donating properties of the Schiff base should not be neglected either. In the diiodosubstituted ligand **192**, the most effective combination can be found that was successful in preparation of various sulfoxides. Although certain ligands seem to be optimal for the oxidation of alkyl aryl sulfides, several examples show that even a small modification of substrate structure could require the use of a catalyst with a different substitution pattern.

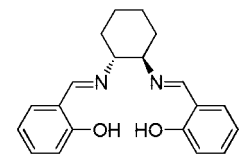
1.4.3.2.2. Other Vanadium Complexes. Several groups reported the use of vanadium(IV) or vanadium(V) complexes of tetradentate (NNOO)-donating ligands as catalysts for enantioselective sulfoxidation. Striking discrepancies between the results presented in the relevant papers can be clearly seen. Zhu and co-workers described the application of salan derivatives **184**, **186**, and **252**−**254** based on the (1*R*,2*R*)-1,2-diaminocyclohexane or (1*S*,2*S*)-1,2-diamino-1,2-diphenylethane skeleton.[294] Following Bolm's conditions (with a catalyst formed *in situ* from $VO(acac)_2$ and a chiral ligand) and using thioanisole as a model substrate, they observed high yields (71−91%) and varying selectivities (21−95% *ee*) of methyl phenyl sulfoxide. The best result (81% yield, 95% *ee*) was obtained with ligand **186** and chloroform as solvent at 0 °C. Interestingly, the analogous salen ligands **30** and **255** led to very poor enantioselectivities and a reverse asymmetric induction (*S* configuration of product) as compared with the case of salan (*R*-sulfoxides formed preferentially). The selected salan ligand (**186**) was used in the vanadium-catalyzed oxidation of various sulfides. The *ee* values (51−92%) were lower than those for methyl phenyl sulfoxide, but quite fair enantioselectivities were observed for dialkyl sulfides. It was also shown that kinetic resolution of racemic sulfoxides can be achieved with a system based on ligand **186** which led preferentially to (*S*)-sulfoxides with up to 98% *ee*.[294]



(*S*,*S*)-**252**: R = H
(*S*,*S*)-**253**: R = *t*-Bu



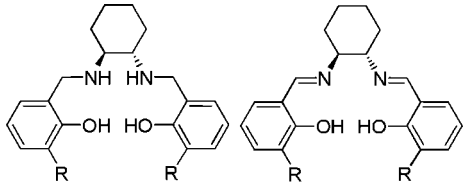
(*R*,*R*)-**254**



(*R*,*R*)-**255**

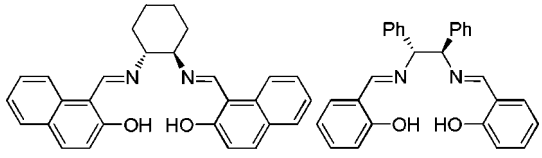
In contrast to those findings, combining vanadium ($VO(acac)_2$ or $VO(OBu)_3$ was used as the metal source) together with salan-type ligands **184**−**187** and **191**, Bryliakov and Talsi observed poor to medium enantioselectivities in the oxidation of alkyl aryl sulfides with aqueous hydrogen peroxide.[259] The reaction was carried out in CH_2Cl_2 at room temperature, but the highest *ee* value of 37.5% was obtained in $CHCl_3$ solution at −12 °C with the ligand (*R*,*R*)-**186** (oxidation of *p*-bromophenyl methyl sulfide; (*R*)-sulfoxide formed preferentially). Costa Pessoa, Correia, and co-workers prepared vanadium(IV) complexes of salan-type ligands **184**, **186**, **252**, **256**, and **257** and tested their catalytic activity in the oxidation of thioanisole with H_2O_2.[295] Again, the results

contrasted with the high enantioselectivity reported by Zhu et al.[294] The best *ee* value (50%) was observed for ligand **256** used in 1,2-dichloroethane at 0 °C. A general preference for (*R*)-sulfoxide formation found for ligands bearing the (*S*,*S*)-configuration differed from previous results obtained with vanadium−salan catalysts.[259,294] Attempts with the oxidized (salen-type) ligands **224** and **258**−**261** resulted in significantly lower enantioselectivities (0−26% *ee*); the results were explained by the lower hydrolytic stability of the corresponding vanadium complexes in comparison to the case of the analogous salan species.

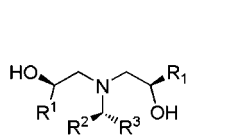


(*S*,*S*)-**256**: R = OMe
(*S*,*S*)-**257**: R = OEt
(*S*,*S*)-**258**: R = OMe
(*S*,*S*)-**259**: R = OEt

Several groups concentrated their efforts on the investigations of vanadium complexes as models of active sites of vanadium-dependent haloperoxidases.[296−299] Rehder and coworkers reported on the synthesis of chiral oxovanadium(V) complexes with amino-bis(alcoholates) bearing two or three stereogenic centers (**262**) and their use in the enantioselective oxidation of thioanisole using CHP or TBHP (with the latter giving worse results which were explained by steric hindrance in the intermediate peroxo species).[297,298] A maximum value of *ee* of 31% was observed in the formation of (*S*)-methyl *p*-tolyl sulfoxide.[298] Slightly better effects were obtained (*ee* up to 38%) for the sulfide oxidation with CHP catalyzed by vanadium complexes of chiral mono- and diethanolamines derived from glycine-*tert*-butyl ester or sarcosine.[299] Both isolated oxovanadium(V) complexes and *in situ* formed catalysts were tested, and **263** was found to yield the most efficient catalyst.

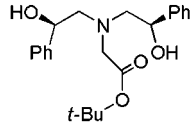


(*R*,*R*)-**260** (*S*,*S*)-**261**

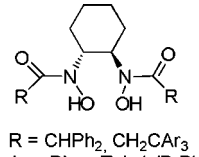


R^1,R^2 = Me, Ph, R^3 = H, Me

262



263

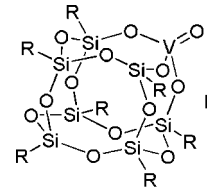


R = $CHPh_2$, CH_2CAr_3
Ar = Ph, *p*-Tol, 4-*i*PrPh

264

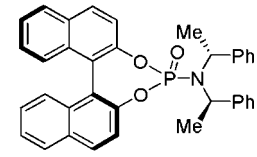
The use of hydroxamic acids **264** as ligands in vanadium-catalyzed sulfoxidation was explored.[300] Thioanisole conversion by trityl hydroperoxide (THP) proceeded in modest yield (17−20%), and the *ee* values were moderate (30% and 47%), especially when compared with those of the analogous molybdenum system (*vide infra*). Only 14% *ee* was noted when the polyhedral silsesquioxane trisilanolate vanadium(V) complex **265** with a chiral amine **266** as a cocatalyst was used in the oxidation of thioanisole with CHP.[301]

The contradictory results described in the cited papers concerning vanadium salan complexes require explanation.



R = *i*Bu

265

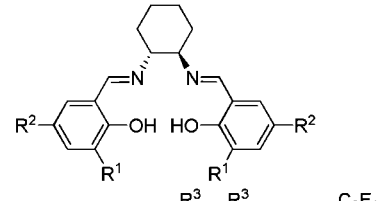


266

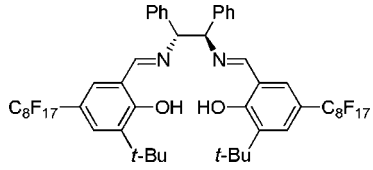
To make them really comparable, all experimental conditions should be identical, including solvent, temperature, stoichiometry, and concentration of reagents, mode of oxidant addition, reaction time, *etc*. It is possible that the reaction outcome is governed by an overlooked, subtle factor. Nevertheless, such an irreproducibility does not encourage further practical applications of the system, especially in the context of the effectiveness of tridendate Schiff bases as chiral ligands for vanadium-catalyzed sulfoxidations.

1.4.3.3. Manganese-Catalyzed Oxidations. When applied for model substrates, the original Jacobsen Mn catalyst was inferior to titanium- and vanadium-based systems. Consequently, its applications for more elaborated sulfides were only marginally reported.[153] However, in recent years, several papers appeared describing the use of modified (salen)manganese(III) as catalyst for the preparation of chiral sulfoxides. Five chiral fluorinated derivatives **267** and **268** were tested in the oxidation of methyl aryl sulfides with iodosylbenzene under homogeneous conditions or in a acetonitrile/perfluorooctane biphasic system.[302] In the latter case, the chemoselectivity was higher and the catalysts could be easily recovered and used up to four times without significant loss of activity. However, in all experiments, the *ee* of the resulting sulfoxides did not exceed 17%. Comparable results were obtained when the dimanganese(III) complex of a dimeric salen-type ligand anchored by two 9,9-dimethylxanthenediyl spacers (**269**) was used for thioanisole oxidation by PhIO (6% *ee* improved to 22% by the addition of 4-(dimethylamino)pyridine).[303]

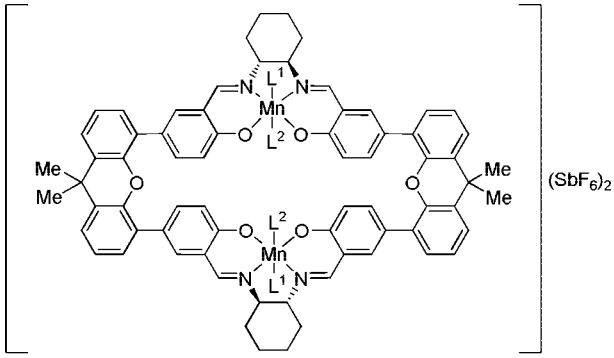
Significantly better, though still moderate, *ee* values (up to 42%) were observed in the course of sulfoxidation mediated by (salen)Mn(III) complexes with a pyrrolidine backbone **270**.[304] Also in these reactions, iodosylbenzene was used, since hydrogen peroxide led to catalyst decomposition, and *m*CPBA afforded mainly sulfones. With 1.1 equiv of PhIO, methyl aryl sulfides were converted to the corresponding (*S*)-sulfoxides in 30−71% yield (higher values were obtained with chlorobenzene or acetonitrile used as a solvent), and the highest enantioselectivity was observed for electron-deficient substrates. This effect was also previously observed for the original Jacobsen catalysts bearing ligands **29**−**36** and was explained by the higher reactivity of electron-rich sulfides which led to the lowered selectivity.[109]



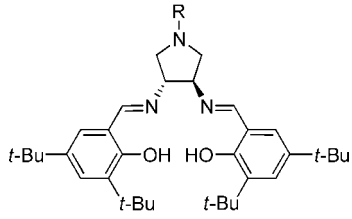
(*R*,*R*)-**267**



(*R*,*R*)-**268**

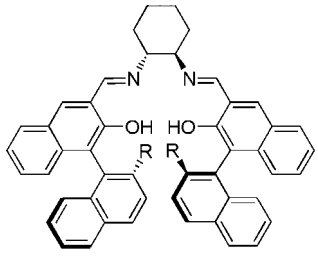


269



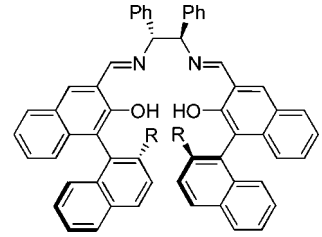
(*R*,*R*)-**270**

Among the manganese complexes of salen derivatives **30**, **34**, **271**, and **272** tested as catalysts in the synthesis of esomeprazole, Mn(III) coordinated with **30** and a tetrafluoroborate anion led to optimal results (58% yield, 69% *ee* after 14 h) with iodosylbenzene as oxidant and methanol as solvent.[305] On the other hand, ligand **271** and acetonitrile as solvent were found to be advantageous for oxidation of simple alkyl aryl sulfides. The corresponding (*S*)-sulfoxides were formed in 68−90% yield and 30−80% *ee*, while 77% yield and 76% *ee* were also obtained in the oxidation of methyl *tert*-butyl sulfide.



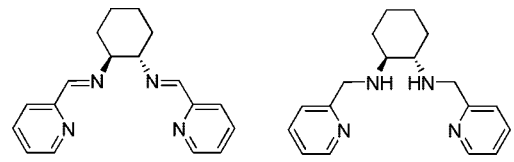
271

A tetravalent Schiff base **273** and its reduced derivative **274** were prepared by Fontecave and co-workers and converted into the manganese(II) complexes bearing perchlorate or acetylacetonate anions.[306] While the use of ligand **274** in the Mn-catalyzed thioanisole oxidation by hydrogen peroxide led to the sulfoxide with 0−5% *ee*, higher enantioselectivity was achieved with ligand **273**. Interestingly,



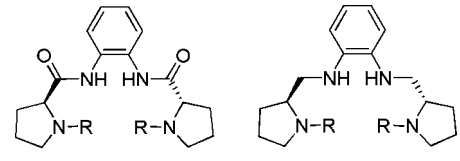
272

the choice of metal source—$Mn(ClO_4)_2$ or $Mn(acac)_2$—had a great influence on the stereochemical outcome of the reaction: (*S*)-sulfoxide was formed with *ee* = 10% when the perchlorate complex was used, but the use of the acetylacetonate complex led mainly to the (*R*)-isomer with 34% *ee*. Thus, the achiral anion caused an interesting switch in the chirality of the product. This observation can be explained by a different structure of the active species, as suggested by the crystal structures of the precursor complexes, Mn(**273**)$(ClO_4)_2$ and Mn(**273**)$(acac)_2$, in which diverse modes of coordination of ligand **273** were found. Again, with these manganese catalysts, a better stereoselectivity was found for *p*-bromo- and *p*-nitro-substituted sulfides (38 and 62% *ee*, respectively). The system could be further improved through the modification of the mode of addition of H_2O_2 and by the use of excess of ligand **273**. Under these conditions, higher yields (25−70%) and *ee* values (31−61%) were observed.



(*S*,*S*)-**273** (*S*,*S*)-**274**

Four C_2-symmetric, tetradendate ligands **275** and **276** containing two (*S*)-proline fragments (reduced in compounds **276**) were prepared, and their cationic manganese(II) complexes were examined in the oxidation of thioanisole and (3-ethylbutyl)phenylsulfide.[307] An aqueous solution of sodium hypochlorite was used as the terminal oxidant, and the reaction was carried out in dichloromethane with the addition of 4-methylmorpholine *N*-oxide monohydrate to stabilize the Mn(V)=O complex formed in the oxidation cycle. Higher chemoselectivity was observed for the substituted substrate (75−80% yield of sulfoxide), and the enantioselectivity was rather moderate (up to 28% *ee*) but was slightly increased for amide **275** compared to the case for amine ligands **276**.

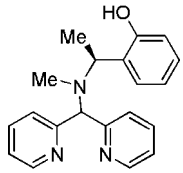


R = H, Bn

(*S*,*S*)-**275** (*S*,*S*)-**276**

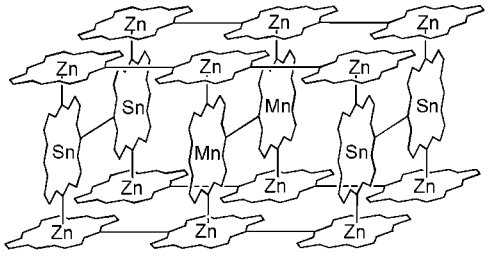
As can be clearly seen, in manganese-catalyzed oxidations, tetradendate, C_2-symmetric ligands were preferred. A rare example employing a C_1-symmetry ligand (*S*)-**277** is thus worth mentioning.[308] The Mn(II) complex formed *in situ* from **277**

and $Mn(OAc)_2$ was used as a catalyst in the reaction of alkyl aryl sulfides with 30% aqueous H_2O_2 carried out in acetone solution. (*R*)-Sulfoxides were formed with good yields (48−55%), but the enantioselectivity of this conversion was unsatisfactory. The highest *ee* value of 18% was observed for thioanisole, and the remaining sulfides gave only 5−8% *ee*.



(*S*)-**277**

Low *ee* values (12−14%) were observed in the oxidation of methyl *p*-tolyl sulfide with 2-(*tert*-butylsulfonyl)iodosylbenzene catalyzed by the supramolecular box **278**.[309] The 18-porphyrin assembly was constructed from four zinc triporphyrins, with two Sn(IV) diporphyrins bearing (D)- or (L)-*N*-acetylphenylalanine axial ligands (the source of chirality) and a manganese(III) diporphyrin. The newly elaborated systems based on Mn complexes, though interesting from the structural point of view, seem to be of limited practical use.



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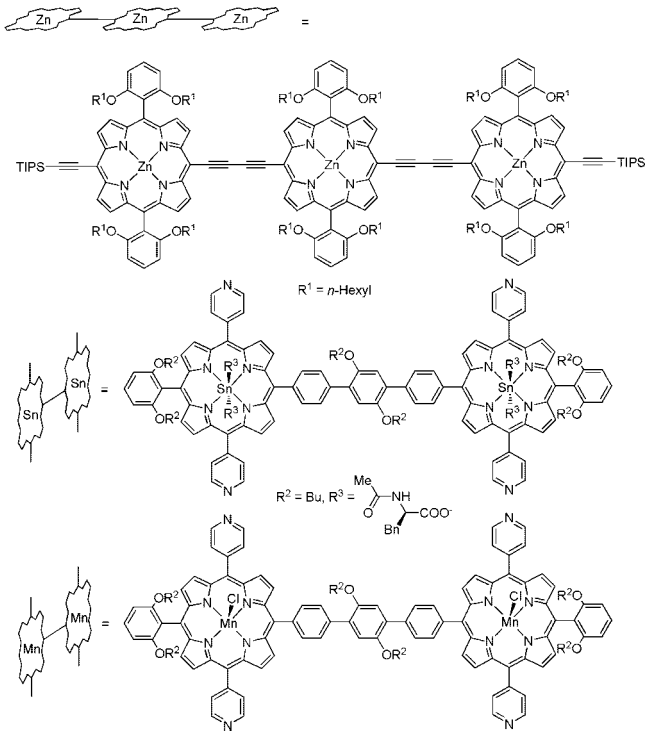


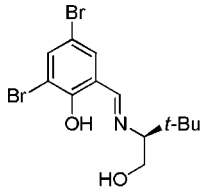
1.4.3.4. Iron-Catalyzed Oxidations. Following the success of the chiral Schiff base−vanadium systems, Legros and Bolm decided to use ligands of this kind with iron(III) acetylacetonate instead of $VO(acac)_2$.[310−313] The idea was to use a metal which would be more environmentally friendly (less toxic) and relatively abundant and, therefore, also more convenient from the economical point of view.

Five *tert*-leucinol derived (*S*)-ligands (e.g., **22**, **23**, or **192**) were tested in the enantioselective sulfoxidation of thioanisole as a model substrate, using conditions similar to those applied previously in vanadium-catalyzed oxidations (CH_2Cl_2, 1.2 equiv of 30% aqueous H_2O_2, 16 h at room temperature).[310] The best results were observed for two dihalogenosubstituted derivatives: **279** (30% yield, 55% *ee*) and **192** (36% yield, 59% *ee*). In the Fe-catalyzed reaction, in analogy to the vanadium-based systems, all Schiff bases having the (*S*)-configuration led preferentially to the (*S*)-sulfoxide. When applied to other methyl aryl sulfides, the ligand **192**/$Fe(acac)_3$ catalytic system afforded sulfoxides with high *ee* values (65−90%; for ethyl phenyl sulfoxide and butyl phenyl sulfoxide, *ee*'s were remarkably lower). Under the conditions described, no sulfone formation was observed; conversely, the unreacted substrates were recovered in significant amounts and the sulfoxide yields were below 44%. A significant improvement of the method that increased both yields and enantioselectivities was achieved by means of additives.[311,312] Legros and Bolm found that carboxylic acids and their salts were able to markedly affect the oxidation, and the best results were observed for the additive/$[Fe(acac)_3]$ ratio of 0.5 to 1. In the presence of lithium 4-methoxybenzoate, which led to the most pronounced effects, thioanisole was formed in 90% *ee* and 63% yield. Similar values (with *ee* up to 96%) were noted for other alkyl aryl sulfides tested when 4-methoxybenzoic acid or its lithium salt was added to the reaction mixture. Further screening, extended to the use of nonaromatic additives, did not reveal any better compounds for this purpose.[312] Significant amounts of sulfones (9−16%) were also formed in the course of the reaction, but the possible kinetic resolution was found to have a negligible effect on the marked enantioselectivity. Based on the observed positive nonlinear effect and on the optimal Fe-additive ratio (2:1), a monocarboxylate-bridged diiron(III) complex was postulated as a key intermediate in the catalytic cycle.

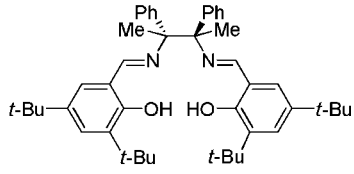
The new $Fe(acac)_3$−Schiff base (*S*)-**192** catalytic system was applied in the synthesis of Sulindac (**97**).[313] Without additives, the oxidation of the corresponding sulfide proceeded with moderate yield (53%) and *ee* (58%). Also in this case the use of 4-methoxybenzoic acid raised both the yield (71%) and the enantioselectivity (*ee* = 92%). Using (*R*)-**192**, (*R*)-sulfoxide **97** was obtained under these conditions in 70% yield and 90% *ee*.

The asymmetric Fe(III)−salen systems were applied by Bryliakov and Talsi for the oxidation of sulfides with iodosylarenes.[314,315] Among the monomeric complexes prepared, those with ligands **30** and **280** gave the best *ee* value of benzyl phenyl sulfoxide (62%), with yields of 86 and 77%, respectively, from reactions conducted in acetonitrile solution at 0 °C with PhIO as a terminal oxidant. Interestingly, a μ-oxo dimer **281** appeared to be a better catalyst than its monomeric precursor (92% yield, 65% *ee* at −20 °C). For other substrates, oxidation proceeded with a similar or lower (as in the case of thioanisole) stereoselectivity, but for the optimal combination of sulfide (PhS*i*Pr), oxidant (MesIO), and conditions (−21 °C), the *ee* value of 84% was reached. The active intermediate of general formula $[Fe^{III}(ArIO)$-

(salen)] was detected by means of ^{1}H NMR, which was in agreement with the observed dependence of the reaction performance on the nature of the iodosylarene used.



(*S*)-**279**



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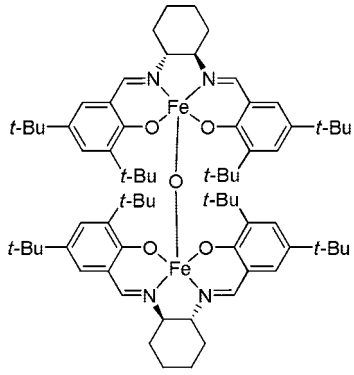
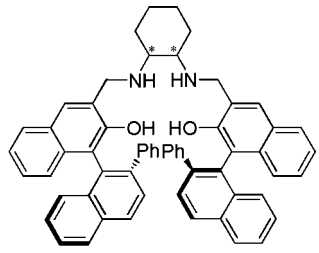


281

Significantly better enantioselectivity was observed by Egami and Katsuki for the reaction in which salan (a reduced salen) derivatives bearing chiral binaphthyl fragments **282** and **283** complexed with Fe(III) were used in thioanisole oxidation by 30% aqueous H_2O_2.[253,254] For the reactions carried out in water at 20 °C, a *ee* as high as 96% was noted (ligand **283**) together with a yield of 90−92%. The complex with **283** as ligand proved to be a very effective catalyst of the asymmetric oxidation of various prochiral substrates, including methyl alkyl sulfides, and the corresponding sulfoxides were formed with 87−94% *ee*.[253] Since considerable amounts of sulfones (up to 24%) were formed during the oxidation process, the authors worked out a modification of the reaction conditions that suppressed the overoxidation without loss of enantioselectivity.[254] This was achieved by lowering the temperature to 0 °C and reducing the amount of water as solvent and decreasing the catalyst loading.



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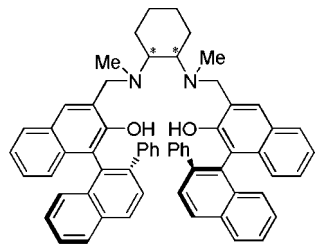
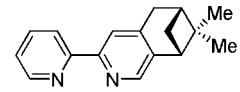


283

Fontecave and co-workers investigated the catalytic properties of the iron(II) complex with the chiral bipyridyl derivative **284**.[316] This compound gave essentially racemic products when it was used for the oxidation of methyl aryl sulfides with aqueous hydrogen peroxide. This performance was significantly worse than that previously found for the analogous μ-oxo dimeric system (4−40% *ee*).[317]



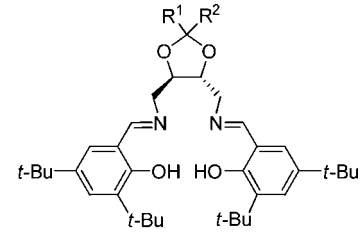
284

Iron-based catalysts with H_2O_2 as oxidant, which are beneficial from ecological and economical points of view, seem to be the most promising among new systems developed in the 21st century. Sulfoxidations catalyzed by Bolm's system (Fe(acac)$_3$/ligand **192**/4-methoxybenzoic acid) and Katsuki's complex of compound **283** led to results approaching those obtained with titanium and vanadium catalysts. The main problem, which can be in part eliminated by choosing the appropriate reaction conditions, is connected with sulfone formation. These systems, which have already been used by other chemists,[155,168] should find wider application in the future.

1.4.3.5. Copper-Based Systems. The highest enantioselectivity obtained in the copper-catalyzed enantioselective oxidations was reported by Maguire and co-workers.[318] They prepared a series of chiral tridendate Schiff base complexes using *tert*-leucinol derived ligands (*S*)-**213**. Under optimal reaction conditions (4 mol % of ligand, 2 mol % of Cu(acac)$_2$, 1.1. equiv of 30% H_2O_2, 16 h at room temperature, CCl_4 as a solvent), the complex with ligand **279** appeared to be the best catalyst for the oxidation of benzyl aryl sulfides. Yields were not high (13−42%), but *ee*'s up to 79% were observed; both maximal values were further enhanced by the addition of 4-methylmorpholine-*N*-oxide. A yield of 49% and a 81% *ee* for the formation of 2-methoxyphenyl benzyl sulfoxide were noted. No sulfone was formed during the reaction, which is in contrast with the case of the vanadium-catalyzed oxidation of similar sulfides (see section 1.4.3.2).[118,277]

Copper complexes of proline-based ligands **275** and **276** were used as catalysts in the oxidation of alkyl phenyl sulfides with NaOCl and exhibited similar chemo- and stereoselectivities (up to 25% *ee*) but lower activities when compared to their manganese analogs (see section 1.4.3.3).[307]

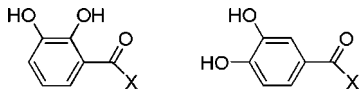
Chiral salen-type ligands (*R*,*R*)-**285** were converted into the corresponding copper(II) complexes, which were examined as catalysts in the thioanisole oxidation.[319] While good yields (>80%) were observed in all reactions, only the use of the dimethyl derivative, aqueous hydrogen peroxide, and acetonitrile as a solvent led to the nonnegligible enantiomeric excess (17%).



R^1 = H, Me, R^2 = Ph, *i*Pr, Me

(*R*,*R*)-**285**

The interesting β-cyclodextrin-based catechol-type ligands **286** and **287** were prepared by Sakuraba and Maekawa.[320] Their copper(II) complexes were examined in the oxidation of alkyl aryl sulfides by aqueous hydrogen peroxide. Both catalysts efficiently accelerated the reaction, leading to the sulfoxides of opposite configuration with *ee*'s in the range of 26−52%.



X = mono-6-O-β-CD

286 **287**

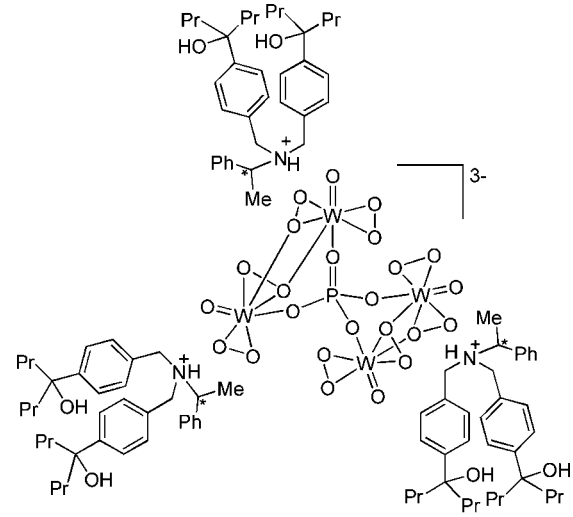
1.4.3.6. Molybdenum and Tungsten Catalysts. Several reports on the use of molybdenum catalysts in the catalytic asymmetric sulfoxidation appeared in recent years. Interestingly, the best results were obtained using ligands which were otherwise rarely combined with other metal ions, while typical ones such as BINOL were found inefficient.[321] Also, salan-type ligands **184** and **191** applied with $MoO_2(acac)_2$ as catalysts in the oxidation of sulfides with H_2O_2 gave unsatisfactory results (0−8.5% *ee*).[259]

Much better reaction outcomes were observed for the molybdenum complexes prepared from $MoO_2(acac)_2$ and hydroxamic acids **264**.[300,322] Oxidation of alkyl aryl sulfides with THP in dichloromethane solution led to the corresponding sulfoxides (in most cases the (*S*)-isomers) in high yield (66−99%) and with 54−86% *ee*, with better results observed for the bulkier ligand. Also di(*tert*-butyl) disulfide was efficiently converted into thiosulfinate **13** (79% yield, 90% *ee*) by this catalytic system. Although no sulfone was formed under the standard reaction conditions, increasing the amount of oxidant (THP or CHP) and reaction time resulted in significant enhancement of *ee* values (92−99%) of (*S*)-sulfoxides, indicating that asymmetric oxidation was followed by the stereoconvergent kinetic resolution.

The cyclodextrin-derived ligands **286** and **287** described in section 1.4.3.5 were also combined with molybdenum(V).[320] Compared with copper(II) complexes, Mo(V) derivatives resulted in slightly better optical yields (35−65% *ee*) in the oxidation of alkyl aryl sulfides with H_2O_2, leading to the opposite enantiomers of the corresponding sulfoxides.

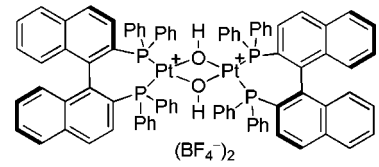
Enantiopure dendritic polyoxometallates **288** were prepared through combination of the chiral amines and the heteropolyacid $H_3PW_{12}O_{40}$ in the presence of an excess of H_2O_2.[323] Compound **288** catalyzed the oxidation of thioanisole by aqueous hydrogen peroxide in chloroform; the methyl phenyl sulfoxide was formed in 93% yield and 14% *ee*, which proved the effective chirality transfer from the periphery to the catalytic center.

1.4.3.7. Niobium, Platinum, Aluminum, and Ruthenium Catalysts. Miyazaki and Katsuki explored the asymmetric oxidation of sulfides catalyzed by niobium complexes.[324] Among the ligands tested, salen derivatives exhibited the highest enantioselectivities (17−68% *ee*) in the conversion of thioanisole with urea−hydrogen peroxide in dichloromethane solution at room temperature. Lowering the temperature to −10 °C together with increasing the catalyst loading (8 mol %) and using an excess of ligand (diastereomer of compound **170** with an opposite configuration of binaphthyl fragments; 1.5−2 equiv with respect to niobium) allowed the *ee* value to improve to 86%. For other sulfides, the corresponding (*S*)-sulfoxides were formed under these optimized conditions with 77−86% *ee* and 58−94% yield.



288

A dimeric platinum(II) complex {[(*R*)-BINAP]Pt(μ-OH)}$_2$(BF$_4$)$_2$ (**289**) was applied to a catalytic sulfoxidation performed in water−surfactant solutions.[325] Various alkyl aryl sulfides were oxidized using 35% aqueous hydrogen peroxide. Sodium dodecyl sulfate (SDS) in 75 mM concentration was found to give the highest chemo- and enantioselectivity in the conversion of thioanisole (the (*R*)-sulfoxide was formed in 98% yield and 40% *ee*). The function of SDS was thought to involve solubilization of the substrate and the catalyst in water. After the reaction, the products could be easily isolated by extraction with diethyl ether; the catalyst, however, could not be reused, since its activity and enantioselectivity were significantly reduced by the oxidant. Nevertheless, the methodology showed its efficiency, especially for electron-deficient substrates for which highest values of *ee*'s were observed (up to 88%); albeit, the yields were rather moderate (63−68%).



289

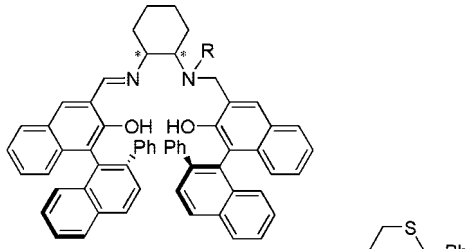
The first use of chiral salalen (1-(*N*-salicylamine)-2-(*N*-salicylimine)ethane, the partially reduced salen) aluminum complexes as catalysts for the enantioselective oxidation of thioethers was reported by Katsuki et al.[255−258] Thioanisole conversion using 2 mol % of salen (**30**) or salalen derivatives (**290** and **291**) and 30% aqueous hydrogen peroxide as an oxidant was examined. The high asymmetric induction was observed for BINOL-derived compounds **290** and **291** and, in particular, (*aR*,*S*,*S*,*aR*)-**291**.[255] The highest yield of the (*S*)-sulfoxide (90%) with an *ee* of 98% was noted when methanol containing phosphate buffer (pH = 7.4) was used as a solvent. The overoxidation to sulfone appeared to increase the *ee* value of (*S*)-sulfoxide due to the enantioconvergent kinetic resolution. Other methyl aryl sulfides were also oxidized with the excellent enantioselectivity (*ee* = 97−99%) and reasonable yields (81−91%); up to 10% of corresponding sulfones were isolated. For benzyl methyl sulfoxide, the *ee* value was slightly lower (80%). An efficient desymme-

Table 2. Chiral Complexes Used as Catalysts in Enantioselective Oxidation of Sulfides[a]

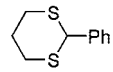
metal ligand	Ti^{IV}	V^{IV}/V^{V}	Mn^{II}/Mn^{III}	Fe^{III}	Cu^{II}	Mo^{V}/Mo^{VI}	Al^{III}	Nb^{III}
bidendate diol	++				++	+		
tridendate Schiff bases	++	++		++	++			
tetradentate salen, salan, salalen	++	++	++	++	+	+	++	++

[a] Legend: +, low *ee*; ++, moderate or high *ee*.

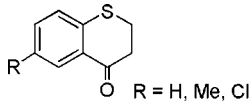
trization of 1,3-dithiane derivatives **177**, **180**, and **292** was also achieved by means of Al-catalyzed oxidation with (*aR*,*S*,*S*,*aR*)-**291** as the chiral ligand.[257] The reaction was performed at 10 °C to suppress the production of the bissulfoxide and sulfone observed at room temperature, and the desired monooxidation products were isolated in 86−92% yield and 98−99% *ee*. The oxidation system based on the Al(salalen) complex was also applied to the transformation of various bicyclic sulfur compounds **293**−**297**.[258] The corresponding sulfoxides were formed in reasonable yields (64−86%) and high enantioselectivities (87−99%); the only exception was found for sulfide **295** (18% yield, 62% *ee*), which was attributed to the inhibition of the catalyst by the sulfoxide product.



290: R = H
291: R = Me

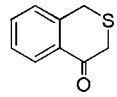


292



R = H, Me, Cl

293



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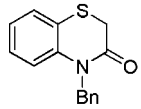

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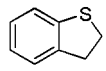

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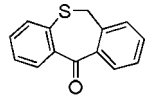
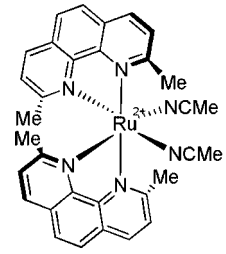


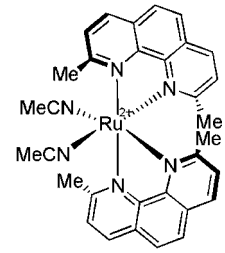
297

Katsuki's group analyzed the thioanisole oxidation using the Al−salalen (**291**) system under modified reaction conditions, including low catalyst loadings and high substrate concentrations.[256] When a 5 M solution of thioanisole (instead of the original 0.1 M) and 0.2 mol % of aluminum complex were used, 95% yield and 97% *ee* were observed. Even under solvent-free conditions and for 0.002 mol % of catalyst, both the isolated yield (86%) and *ee* (96%) remained satisfactory. Similar outcomes were noted for other methyl aryl sulfides, while dialkyl sulfides were oxidized without solvent or using high concentrations with only slightly lowered enantioselectivity (69−91% *ee*). As mentioned by the authors, the use of the corresponding aluminum salan and salen complexes led to significantly lower enantioselectivity in the thioanisole oxidation.[255]

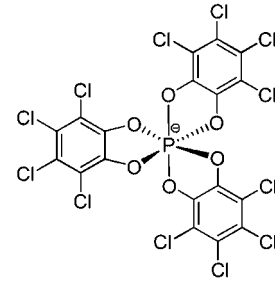
A completely different approach, using a chiral-at-metal complex with achiral ligands as a sulfoxidation catalyst, was described by Fontecave and co-workers.[326] Two enantiomeric forms of the cationic octahedral ruthenium(II) complex with 2,9-dimethyl-1,10-phenantroline (**298**) were separated by crystallization with the chiral trisphosphate anion Δ-**299**. Their use in the oxidation of alkyl aryl sulfides with aqueous hydrogen peroxide performed in methanol resulted in a complete conversion (after 8 h at room temperature) with high chemoselectivity (sulfoxide/sulfone = 9:1) and enantiomeric excess in the range of 7−18%. The (*S*)-sulfoxides were preferentially obtained when the Δ-enantiomer was applied as catalyst. Although the stereoselectivity appeared to be modest, the possibility of chirality transfer directly from the stereogenic metal center opened a new perspective of catalytic asymmetric sulfoxidation.



Λ-**298**



Δ-**298**



Δ-**299**

Certainly, the use of enantiopure ligands remains the most straightforward route to the construction of sulfoxidation catalysts. Among metals other than titanium, vanadium, manganese, and iron, aluminum (complexed with salalen **291**) and molybdenum (with hydroxamic acid **264**) showed the largest potential for further applications and developments.

1.4.3.8. Summary. During the last few years, numerous new complexes were examined as catalysts for enantiocatalytic oxidation of prochiral sulfides. Including previous investigations and heterogenized systems (section 1.6), representatives of a majority of the transition metals were tried: titanium and zirconium (group 4), vanadium and niobium (5), molybdenum and tungsten (6), manganese and rhenium (7), iron, ruthenium, osmium (8), nickel, platinum (10), copper (11), and, in addition, zinc (12) and aluminum (13). Three kinds of chiral ligands were commonly used: bidendate diols, tridendate Schiff bases, and tetradendate salen-type compounds. The combinations examined so far are given in Table 2.

As can be seen from Table 2, several systems using different metals were found to be effective as sulfoxidation catalysts. Still, there are gaps which may be filled in the

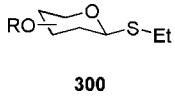
future (for example, bidendate ligands have not been combined with vanadium, manganese, and iron). The table does not show, however, which compounds were most frequently used. Within new literature cited in sections 1.3.3 and 1.4.3, ca. 60 papers concerning titanium complexes (the majority of them possessed bidendate ligands) can be found. The application of vanadium complexes (typically, with tridendate Schiff bases) was also described in ca. 60 articles. Iron and manganese systems appeared in 10 and 9 papers, respectively, while the remaining metals received less attention (4 and less examples). These numbers show the tendencies which will probably persist for some time.

1.5. Diastereoselective Oxidations

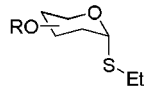
In diastereoselective oxidations, the sulfide itself serves as the source of asymmetric induction if another stereogenic element (center, axis, or plane) is present in the molecule. Four situations can be distinguished, since both substrate and oxidant used can be in nonracemic or racemic/achiral form.

In the first case (nonracemic substrate + achiral oxidant), one can expect the preference in the production of one diastereomer, which can also be significantly enantiomerically enriched. Typically, a diastereomeric mixture is then separated to give nonracemic sulfoxides. In the second case (both substrate and oxidant in nonracemic form), a double induction can lead to improved selectivity as compared with the use of achiral oxidant. However, a mismatched combination can decrease the level of stereocontrol. The third case (achiral or racemic substrate + nonracemic oxidant) can also result in dia- and enantioselection, and we describe such reactions in sections devoted to the respective oxidizing systems. The fourth case (achiral/racemic substrate + achiral oxidant) can only provide racemic diastereomers. A few examples of this situation will be given at the end of this section.

Various nonracemic sulfides bearing diverse chiral functions were examined as substrates of diastereoselective oxidation. Khiar used *m*-chloroperoxobenzoic acid for the conversion of α- or β-ethylthioglycosides **300** and **301** into the corresponding sulfoxides with the diastereoselectivity ranging from 0 to >95%.[327] Interestingly, the α-anomers favored the R_S configuration of the newly formed stereogenic center, while for the β-anomers a preference of the S_S configuration was observed.

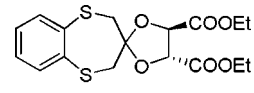


300



301

The *m*CPBA oxidation of the cyclic chiral dithioacetal **302** led to a separable mixture of diastereomers **303** (45% yield) and **304** (52%).[7] The further oxidation of the deprotected (*S*)- or (*R*)-mono-*S*-oxide with *m*CPBA, DMDO, or H_2O_2 led preferably to the *meso* product, while ozonation led mainly to the (*S*,*S*)- or (*R*,*R*)-isomers, respectively (*de* = 41−52%). Oxidation of sulfide (−)-**305** with mCPBA, leading to the separable mixture of diastereomers in 89% and 5% yields, was applied in the synthesis of the potential agonists of metabotropic glutamate receptors.[328] The preparation of four stereoisomeric β-hydroxysulfoxides involved the lipase-catalyzed enantioselective resolution of the corresponding hydroxysulfides **306** and oxidation of the resulting enantiomeric substrates with *m*CPBA.[329] The fractional crystallization of the obtained diastereomeric pairs allowed the isolation of enantiopure (R,S_S)-**307** and (S,R_S)-**307** (each in 40% yield) as white crystals, while the corresponding mother liquors contained mainly (R,R_S)-**307** and (S,S_S)-**307**, respectively. Similar results were obtained for the *p*-tolyl derivative **308**. A β-hydroxysulfide (*R*)-**309** was also used as a substrate in the improved synthesis of OPC-29030 (**3**), a platelet adhesion inhibitor.[28] Among various stoichiometric and catalytic oxidation methods, the best results were reached using 5 mol % of $VO(acac)_2$, 1.05 equiv of CHP, and 4 Å molecular sieves. The desired sulfoxide was formed in 91% yield and 72% *de* (61% yield and 98% *de* after recrystallization).



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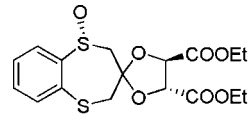

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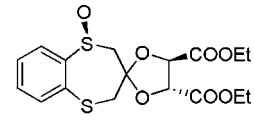

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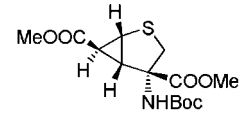
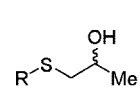
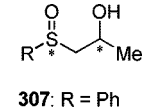


(-)-**305**

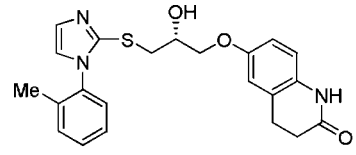


306

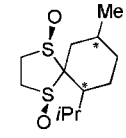
R = Ph, *p*-Tol, 2-Naphthyl, Cyclohexyl, Et, Bn, CH_2CH_2Ph



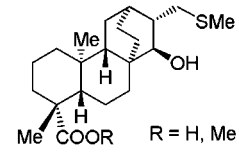
307: R = Ph
308: R = *p*-Tol



(*R*)-**309**



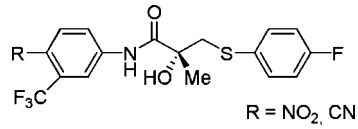
310



R = H, Me

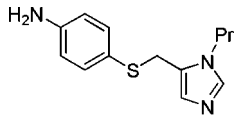
311

The oxidation of chiral menthone dithiolanes with TBHP led to bis-sulfoxides **310** in 50−55% yield and *de* > 95%.[330] Sulfinyl−sulfonyl derivatives, which also contained four stereogenic centers, were produced in 65−70% yield and *de* > 98% when an excess of H_2O_2 was used as oxidant. Oxidation of sulfide **311** with racemic 2-benzenesulfonyl-3-phenyloxaziridine yielded separable diastereomers of serofendic acid or its methyl ester (16% and 23% *de*, respectively), candidate drugs for neurological disorders.[331] Sodium periodate was used for the oxidation of the chiral bicalutamide derivatives **312**.[332] The main product (48% yield) was established by X-ray analysis to have the (R,S_S)-configuration; the minor diastereomer (R,R_S) was formed in 27% yield.



(*R*)-**312**

Ikemoto described the oxidation of prochiral sulfide **313**, which was initially converted into a chiral crystalline salt with di-*p*-toluoyl-D-tartaric acid.[333] Its treatment with 30% aqueous H_2O_2, without any catalyst, led to the formation of sulfoxide salt **314**·H_2O (42% conversion, 52% *de*). Recrystallization and reaction with 1 M HCl led to the desired (*S*)-sulfoxide of high enantiomeric purity.



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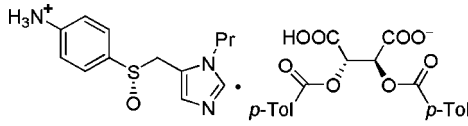
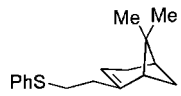


314

In some cases, in addition to the use of a nonracemic substrate, chiral oxidizing systems were applied as well. The reason for doing so could be the remote localization of the existing stereogenic element with respect to the newly formed sulfinyl center. This arrangement may cause the asymmetric induction to be inefficient. Besides, such a procedure could limit the number of the isomers formed in the course of reaction (*vide infra*).

In the course of our investigations on the possible applications of the modified Bolm catalytic system (H_2O_2/VO(acac)$_2$/(*S*)-**27**), we prepared the chiral nopol derivative **315** and subjected it to diastereoselective sulfoxidation.[192] We observed selective formation of one diastereomer in 44% yield, and the enantiomeric excess was equal to 80%.



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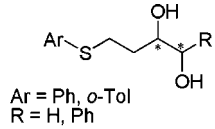
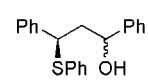


316

The vanadium−chiral Schiff base **27** catalytic system was also applied in the oxidation of enantioenriched diols **316** obtained in the course of stereoselective dihydroxylation of homoallylic sulfides **124**.[190] We observed the preferential formation of *unlike* (R_S,3*S*,4*S*/S_S,3*R*,4*R*) diastereomer in 73−90% yield and 18−26% *de*. The configuration of the sulfinyl group was found to be dependent on the configuration of the diol substrate. Interestingly, the oxidation using the TEMPO/NaOCl system yielded mainly *like* (S_S,3*S*,4*S*/R_S,3*R*,4*R*) diastereoisomer, with 62% *de* but in significantly lower yields (40−46%).

The oxidizing system based on the vanadyl complexes of the chiral salicylidenevalinol derivative was also used for the conversion of a mixture of diastereomers of γ-hydroxysulfide **317** with a fixed (3*R*)-configuration.[8] When $NaIO_4$ was used as oxidant, all four possible diastereomeric γ-hydroxysulfoxides were formed in comparable yields. Another achiral oxidizing system, TEMPO/NaOCl, led to a mixture of two diastereomers. Finally, the use of 30% H_2O_2/VO(acac)$_2$/(*S*)-**27** resulted in the production of three isomers in a 63:32:5 ratio. The dominant product was separated by column chromatography and exhibited the (S_S)-configuration at the new stereogenic center. In a full analogy, when (*R*)-**27** was used, the main components of the resulting mixture (67:21:12 ratio was observed) were found to have the (R_S)-configuration. The complete configurational assignment was based on the analysis of the CD spectra and on the chemical correlation with the corresponding sulfones.



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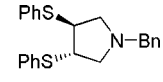
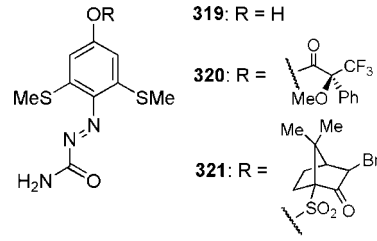
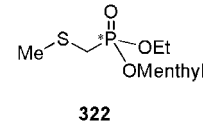


(*S*,*S*)-**318**

Chiral (3*S*,4*S*)-*N*-benzyl-3,4-bis(phenylsulfanyl)pyrrolidine (**318**) was oxidized using the VO(acac)$_2$−Schiff base (*S*)-**27** system to give the (R_S,3*S*,4*S*)-monosulfoxide and the (R_S,R_S,3*S*,4*S*)-bissulfoxide, which were isolated as pure diastereomers in 45 and 40% yield, respectively.[191] Typically, the (*S*)-valinol derivative **27** led to (*S*)-sulfoxides; therefore, the absolute configuration of the newly created stereogenic center(s) presumably resulted from the asymmetric induction caused by the substrate itself.

Kagan's conditions were applied to the diastereoselective oxidation of rubroflavin derivatives.[334] As the direct oxidation of sulfide **319** was unsatisfactory, it was converted to a chiral ester **320** or sulfinate **321**. Their oxidation led to the corresponding monosulfoxides in 38%/35% yield and 67%/72% *de*, respectively, and after chromatographic separation and hydrolysis, the enantiopure (*S*)-rubroflavin was obtained.



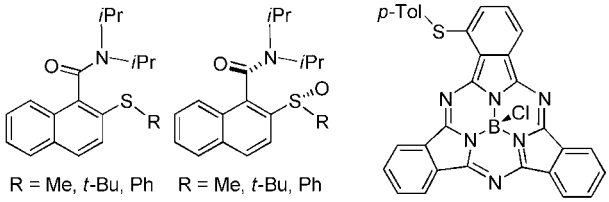


322

Naso and co-workers prepared four stereoisomers of ethyl menthyl (methylsulfinyl)methylphosphonate *via* the diastereoselective oxidation of the corresponding sulfides (R_P)-**322** and (S_P)-**322**.[335] Using TBHP as the oxidant and a titanium complex of (*S*)-BINOL as catalyst, they obtained (R_P,R_S)- and (S_P,R_S)-sulfoxides, respectively, in high yields (82−88%) and diastereomeric purity (>95% *de*). Similar results were observed for the oxidation catalyzed by the Ti−(*R*)-BINOL system, but in this case a mixture of sulfides was subjected to oxidation, and (R_P,S_S)- and (S_P,S_S)-sulfoxides were easily isolated by column chromatography.

Treatment of racemic or achiral substrates with *m*CPBA, DMDO, or other achiral oxidants may result in the preferential formation of one diastereoisomer, and in some cases, *de* values are higher than 99%. Clayden and co-workers examined the *m*CPBA oxidation of atropisomeric 2-sulfanyl-substituted aromatic amides.[123,125,336] For substrates **323**, only the *anti* diastereomer **324** was isolated after workup as a result of rapid epimerization of the less stable *syn* isomer. A diastereoselective process of the oxidation of thioether-substituted subphthalocyanine **325** with *m*CPBA was described by González-Rodríguez and Torres.[337] A high

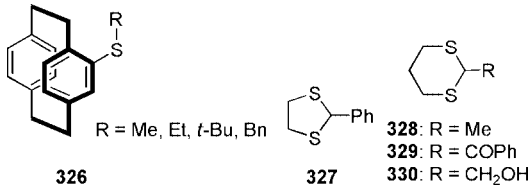
diastereomeric ratio (95:5) was observed together with a ca. 80% yield; interestingly, when the thia-substituent was attached to the β-position, two corresponding diastereomers were formed in equal amounts.



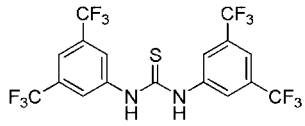
323 324 325

The oxidation of the racemic 4-alkylsulfanyl[2.2]paracyclophanes **326** with $NaIO_4$ and *m*CPBA was investigated as well. While benzyl, methyl, and ethyl derivatives led to diastereomeric mixtures, with the highest *de* equal to 82%,[338] *tert*-butyl sulfoxide was formed as a single diastereoisomer in 80% ($NaIO_4$ as oxidant) or 94% yield (*m*CPBA).[140]

Racemic β-hydroxysulfoxides were oxidized using TBHP and titanium catalysts: Ti(O*i*-Pr)$_4$ or titanocenes with *de* in the range 12−76%.[339] Cp_2TiCl_2 was also found to be an efficient catalyst of the conversion of achiral 2-substituted-1,3-dithianes and 1,3-dithiolanes **180**, **292**, and **327**−**329**.[340] Using TBHP as oxidant and 4 Å molecular sieves, 2-phenyl-1,3-dithiane was oxidized in 86% yield and 96% *de*. A similar or lower preference for the *trans* diastereomer was observed for other substrates. A comparable diastereoselectivity was observed in the oxidation of **292** and **327** (92% and 62% *de*, respectively) with TBHP when a thiourea derivative **331** was used as a catalyst.[341]

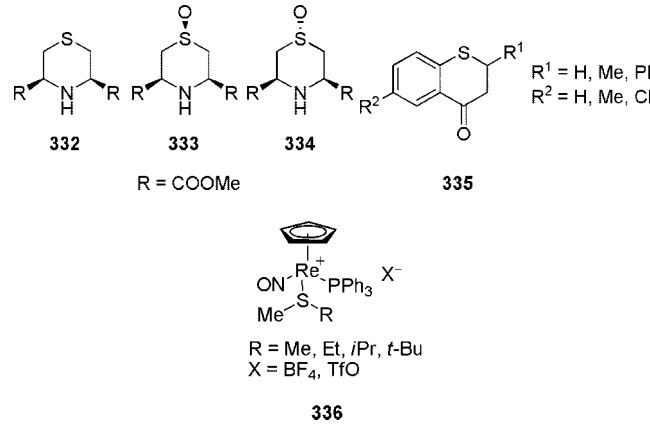


326 327



331

An interesting oxidant-dependent diastereoselectivity was observed in the sulfoxidation of 3,5-substituted *meso*-1,4-thiazane **332**.[342] Isomer **333** was preferentially formed by using H_2O_2, *m*CPBA, or $NaIO_4$ (for which the highest *de* = 67% was found), while aqueous bromine led mainly to compound **334** (*de* = 82%). 2-Substituted 1-thiochroman-4-ones **335** were converted into the corresponding sulfoxides using various oxidants, and the best chemoselectivity was obtained for dimethyl dioxirane.[343] However, rather low diastereoselectivity was observed (19−40% *de*). DMDO was also used for the oxidation of the rhenium sulfide complexes **336** to give the sulfur-bound sulfoxide complexes.[344] The combined yields of the two diastereomers were high in most cases, but a competing oxidation of the coordinated triphenylphosphine was also significant. For the complex with *tert*-butyl methyl sulfide and BF_4^- as counterion, the formation of a single diastereomer was observed. For other substrates, the *de* value was in the range of 25−74%.



332 333 334 335

336

A large variety of functionalized sulfides was subjected to diastereoselective oxidation. A common feature of these reactions is the remarkable dependence of the observed chemo- and stereoselectivity on the nature of the oxidant. This fact is not surprising, since different reaction mechanisms are possible, and this variation in mechanisms should be taken into account when such oxidations are planned.

1.6. Heterogenized Systems

Although the oxidations described in the previous sections make use of homogeneous catalysts, the overall system in many cases is heterogeneous. Reactions in which aqueous hydrogen peroxide serves as oxidant are typically conducted under biphasic conditions. In certain titanium-catalyzed oxidations, the addition of 4 Å molecular sieves has a beneficial effect on the yield and stereochemical outcome.[28,92,221,241,340] However, there are only a few examples of the application of heterogeneous catalysts in the preparation of nonracemic sulfoxides. Preliminary studies performed on sulfide oxidation with urea−H_2O_2 catalyzed by cinchonine and cinchonidine salts with a Keggin-type structure heteropolyacid suggested the possibility of applying this system for the enantioselective synthesis of sulfoxides.[345] Thakur and Sudalai described the use of chiral cinchona alkaloids in combination with WO_3 and 30% H_2O_2 in THF for the efficient conversion of alkyl aryl sulfides.[346] $(DHQD)_2PYR$ afforded the desired (*R*)-sulfoxides in 79−90% yield and 35−65% *ee*, and $(DHQ)_2PYR$ yielded the (*S*)-enantiomers (in up to 52% *ee*). (*R*)-Lansoprazole **143** was also obtained by this methodology in 84% yield and 88% *ee*. WO_3 was also combined with salan-type ligands **184**, **186**, and **252**−**254**.[347] Using aqueous hydrogen peroxide as the terminal oxidant and dichloromethane as solvent, different methyl aryl sulfides were converted into (*R*)-sulfoxides in 65−86% yield and 27−67% *ee*. The catalyst could be recovered by filtration after the reaction and used in the subsequent runs.

The ease of separating the heterogeneous catalyst from the reactants and the possibility of its recycling are very important features from an ecological point of view (waste minimizing). These advantages are also a driving force for the immobilization of the chiral homogeneous catalysts.[348,349] Such an approach can result in the increased stability of a supported complex, as some unwanted processes (e.g., dimerization) are impossible due to the separation of active molecules one from another. One may also expect a kind of substrate selectivity because bulkier sulfides would have limited accessibility to the catalyst when it is hidden in the pores or channels of the support. Such diffusion problems

would typically lead to lowered reaction rates. In some cases, certain unselective reaction routes that influence the stereoselectivity should also be taken into account.

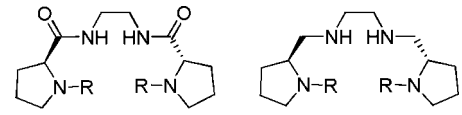
Different kinds of materials were employed as supports for the chiral complexes. Inorganic solids involved zeolites, clays (e.g., montmorilonite), and silica, and immobilization methods included encapsulation (ship-in-the-bottle method), adsorption on the surface, ion exchange, and covalent anchoring of the catalytic species. In the case of organic polymeric supports, two methods were applied: covalent attachment to the preformed polymer or a copolymerization of the functionalized complex with styrene or other monomers. A new interesting approach makes use of self-supported coordination polymers formed directly from metal ions and bridging ligands.

In general, the metal catalysts used for sulfide oxidation are immobilized. As a recent exception, a polymer-supported *N*-phenylsulfonyloxaziridine (Davis reagent) was prepared and used for the selective oxidation of different substrates, including sulfides, though not in a stereoselective manner.[350]

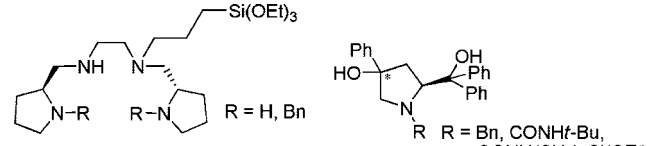
The heterogeneous catalyst was prepared from Mg−Al layered-double hydroxides exchanged with osmate (K_2OsO_4).[351] Using $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$ as chiral ligands and *N*-methylmorpholine oxide as the cooxidant, alkyl aryl sulfides were converted into the corresponding (*R*)- or (*S*)-sulfoxides in 71−76% yield and 23−28% *ee*. Significant amounts of sulfones were also observed (the sulfoxide/sulfone ratios were close to 4:1). In the recycling experiments, the isolated yield of the sulfoxide decreased only slightly, but a significant drop of enantioselectivity was noted as well.

The immobilization of the Ti-BINOL complex onto ionic liquid-modified mesoporous silica resulted in high enantioselectivity (up to 99.9% *ee*) and reasonable yields in the oxidation of alkyl aryl sulfides by TBHP.[352] A high enantiomeric excess was connected with the observed kinetic resolution. In addition, a positive nonlinear effect was noted (the catalyst of 60% *ee* led to an almost enantiomerically pure sulfoxide), indicating the involvement of an active complex bearing two ligands of identical chirality. Kheder and co-workers prepared a titanium(IV)-exchanged K10-montmorillonite and used this system in the oxidation of thioanisole with TBHP or H_2O_2.[353] Among the chiral ligands tested (diethyl tartrate, diisopropyl tartrate, BINOL), only (*R*)-BINOL led to a reasonable enantioselectivity (up to 18% *ee*).

In a biomimetic design of a vanadium peroxidase model, Sheldon and co-workers encapsulated the vanadyl complex of Bolm's Schiff base **22** into zeolite Y.[354] Although the catalyst remained active in the sulfoxidation of thioanisole, the product appeared to be racemic. Better results were obtained by Iglesias and co-workers, who used ion exchange to introduce chiral manganese complexes with C_2-symmetry ligands **337** and **338** into the supercages of zeolite Y.[355,356] Oxidation of thioanisole and (2-ethylbutyl)phenylsulfide with NaOCl in dichloromethane proceeded with a modest enantioselectivity (up to 19% *ee*). The chemoselectivity was high for the bulkier substrate, which gave the corresponding sulfoxide as the sole product. Higher enantioselectivities (up to 32% *ee* for PhIO as oxidant) were observed for the analogous manganese and copper complexes with ligands **339** bearing a triethoxysilyl group, which were covalently attached to zeolite Y or MCM-41.[356] The heterogenized systems exhibited higher activity and stability than their homogeneous analogs: the catalysts could be reused without any loss of activity. A similar attachment to zeolites was also examined for dioxomolybdenum(VI) and oxovanadium(V) complexes with chiral diols **340**.[357] High sulfoxide yields in the oxidation of thioanisole with hydrogen peroxide or TBHP were accompanied by low *ee* values (<10%). Additionally, in the case of the vanadium complex, a catalyst leaching was detected.



(*S*,*S*)-**337** (*S*,*S*)-**338**

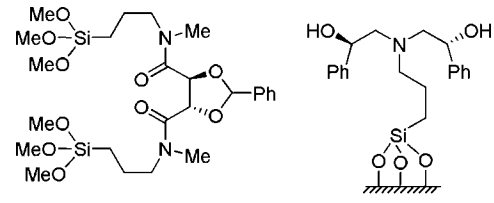


(*S*,*S*)-**339** **340**

Several groups used mesoporous silica for the catalyst immobilization. Salen manganese(II) and copper(II) complexes were modified with a triethoxysilyl substituent, which allowed them to be covalently attached to the support (silica gel or MCM-41).[358] In most cases, the enantioselectivity of the sulfide oxidation catalyzed by these systems was low, and the maximum *ee* values (up to 26%) were found for PhIO as oxidant.

Iwamoto and co-workers applied a template ion-exchange method for the titanium(IV) ion incorporation into the structure of silica.[359−361] This system was used for the oxidation of *p*-tolyl methyl sulfide with hydrogen peroxide or TBHP. The highest *ee* value (30%) was reached with (*R*,*R*)-tartaric acid as a chiral modifier. Other metal ions (chromium, aluminum, iron, zirconium, zinc) which were also incorporated into MCM-41 led to unsatisfactory results (the sulfoxide yield did not exceed 24%).[360,361]

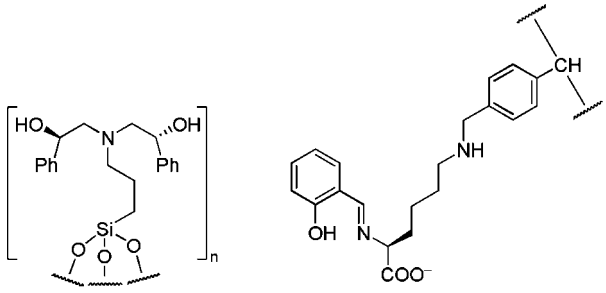
Another approach, based on the preparation of chiral mesostructured organosilica, was described by García et al.[362] A chiral tartrate was converted into a bis-silylated amide **341** and incorporated into the framework of the support. Using this material as a chiral ligand for titanium, and CHP as oxidant, the authors obtained methyl phenyl sulfoxide in 70% yield and 31% *ee*. The catalysts could be reused (58% yield and 26% *ee* were obtained for the second run), and no leaching of tartramide was observed.



341 **342**

Rehder's group investigated the heterogeneous catalytic systems obtained by immobilization of vanadium catalysts on silica gel or mesoporous silicas.[363] Vanadyl complexes of supported ligand **342** and the aggregate **343** formed by a polymerization of the carbasilatrane were used for the oxidation of thioanisole by cumyl hydroperoxide. High

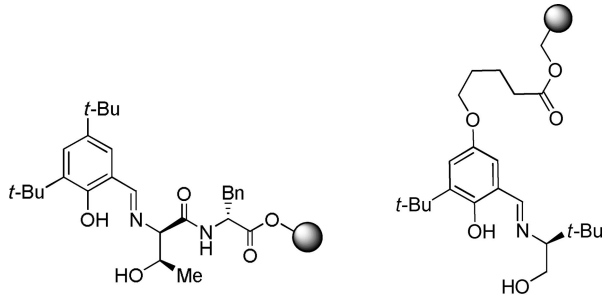
chemoselectivity but only moderate stereoselectivity (up to 26% *ee*) were observed.



343 344

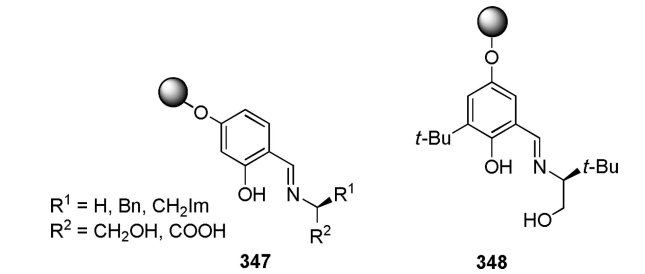
Organic supports used for the catalyst immobilization were in most cases based on styrene copolymers. For example, the lysine-derived Schiff base prepared by Rehder and co-workers was covalently attached to Merrifield and Barlos resins (structure **344** and its analogs).[364] In thioanisole oxidations catalyzed by vanadium complexes of these systems, the (*S*)-sulfoxide was obtained in high yield, but the maximal *ee* was only 19%.

A library screening performed on the vanadium complexes of Schiff bases attached to the Wang resin led to the identification of the optimized structure **345**.[365] Vanadium catalyzed oxidation of thioanisole with H_2O_2 using this ligand led to a product with 23% *ee*. Interestingly, when $VO(acac)_2$ was replaced with titanium isopropoxide, the (*R*)-sulfoxide was formed with a considerably higher enantioselectivity (*ee* = 64%). Other alkyl aryl sulfides were also converted by this system with *ee* values in the 45−72% range. Improved performance in the vanadium-catalyzed sulfoxidation was accomplished by the construction of another library of Schiff bases.[267] An *ee* of 52% was observed for the *tert*-leucinol derivative **346**, which appeared to be the optimal ligand for the enantioselective oxidation of thioanisole with aqueous hydrogen peroxide.

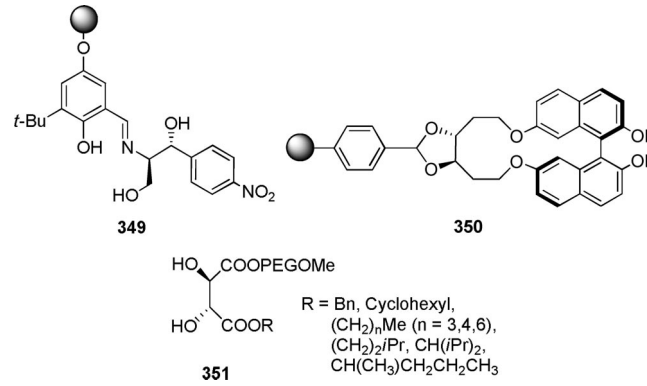


345 346

Other vanadium-based catalysts containing chiral Schiff bases **347** bound to Merrifield resin were examined in the thioanisole oxidation using TBHP as the oxygen source.[366] High conversion yields were accompanied by moderate enantioselectivity (*ee* ≤ 40%). Sartori and co-workers investigated the oxidation of thioanisole by H_2O_2 catalyzed by vanadium complexes of Schiff bases **348** and **349** which were supported on polystyrene and polyacrylate.[367] The latter attachment resulted in systematically lower yields and *ee*'s as compared with the cases of the homogeneous analogs, while for polystyrene-tethered systems the differences were lower. For the optimal ligand **348**, methyl aryl sulfides were oxidized in 54−80% yield and 45−57% *ee*. A polymer-supported *cyclo*-BINOL derivative **350** appeared efficient in the titanium-catalyzed oxidation of thioanisole (67% yield, 78% *ee*) and *p*-tolyl methyl sulfide (65% yield, 88% *ee*) with TBHP.[368] The system retained its activity and selectivity in successive runs.



347 348

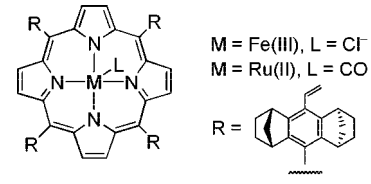


349 350

351

The use of the soluble polymer (polyethylene glycol monomethyl ether, MeOPEGOH) for the attachment of chiral tartrate ligands (structure **351**) coupled the advantages of homogeneous catalysis (high activity and accessibility) with the benefit of the solid phase method. The catalyst could be precipitated and easily recovered by filtration.[369] Some of the ligands tested exhibited a high enantioselectivity in the titanium-catalyzed sulfoxidation of thioanisole (up to 98% *ee*) and other alkyl aryl sulfides (33−99% *ee* for *n*-heptyl-substituted ligand) with cumyl hydroperoxide.

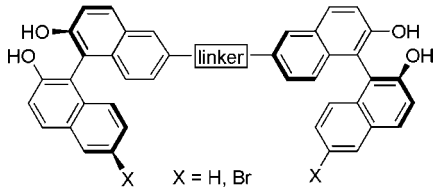
A copolymerization approach was utilized by Simonneaux and co-workers, who prepared chiral iron(III) and ruthenium(II) porphyrins **352** bearing the vinyl functions.[370] Different polymers were obtained by copolymerization of these complexes with styrene and divinylbenzene or ethyleneglycol dimethacrylate. When tested in the oxidation of alkyl aryl sulfides with PhIO, the iron systems retained a moderate enantioselectivity (49−75% *ee*) of their homogeneous counterparts, but the yields were significantly higher (up to 89%). In the case of Ru, the preoxidation of the catalysts to form the dioxoruthenium complex was found necessary, and the latter compound catalyzed the oxidation of thioanisole by 2,6-dichloropyridine *N*-oxide at 60 °C (92% yield, 48% *ee*).



352

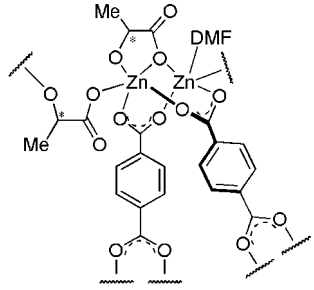
Catalysis by coordination polymers eliminates the need for an additional support. Properly designed bridging ligands

interconnect metal ions to form a 1D, 2D, or 3D system. In such a network, the active species are arranged in a regular way (as compared with the random distribution in a typical support) and their high concentration induces high activity for the whole system. This self-supporting strategy was applied for the heterogenization of chiral titanium complexes containing bridged BINOL ligands **353**.[371−373] The resulting coordinating polymers catalyzed the enantioselective oxidation of alkyl aryl sulfides with cumyl hydroperoxide. Very high *ee* values (75.5 to >99.9%) and moderate yields were observed, which resulted from the stereoconvergent kinetic resolution. To test the possibility of catalyst reuse, eight cycles of thioanisole oxidation were performed using this system without significant lowering of the yield and with a fully preserved enantioselectivity.



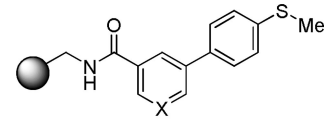
353

A homochiral coordination polymer **354** was constructed from Zn^{2+} ions, L-lactate ligand, and *p*-benzenedicarboxylic acid.[374,375] 1D chains were formed by zinc ions bridged by lactate anions and dicarboxylates, which also interconnected the linear polymers. The resulting 3D network with an open architecture was examined as catalyst for the oxidation of alkyl aryl sulfides with hydrogen peroxide or UHP. Interestingly, the conversions of thioanisole and methyl *p*-bromophenyl sulfide were almost quantitative when H_2O_2 was used, while more bulky sulfides were almost unreactive because they were not able to penetrate the pores. No asymmetric induction was observed in the reaction. However, the enantioenrichment of the product sulfoxides (*ee* = 20%) resulted from their selective sorption in the chiral porous material. Therefore, a unique method of preparation of nonracemic sulfoxides was proposed that utilized the catalytic oxidation of sulfides and the separation of the products with the same chiral column containing the homochiral zinc polymer.[375]



354

A reverse approach to the solid phase sulfoxidation was also described.[376] Two sulfides, **355** and **356**, chosen for the study, were attached to a solid support (Rink Amide resin), and the efficiencies of different methods of oxidation were compared. Modena's system worked better than Kagan's, but the Davis oxaziridine (−)-**85** appeared optimal for these substrates: **355** led to the corresponding sulfoxide in 99% yield and 70% *ee*, while for pyridine derivative **356** a 90% yield and 84% *ee* were observed. Interestingly, the results obtained for solid-state sulfoxidation were better than those found for the conversion of analogous nonbound sulfides, performed in a homogeneous manner using the Davis and Modena procedures.



355: X = CH
356: X = N

Although substantial progress has been made, in most cases the immobilization of homogeneous sulfoxidation catalysts resulted in a significant lowering of their activity and selectivity: *ee* values, with a few exceptions, did not exceed 30−40%. One should also remember that, typically, test reactions were limited to the oxidation of thioanisole or its monosubstituted derivatives, and the straightforward application of these systems to more bulky sulfides could be difficult. On the other hand, these examples demonstrated the possibility of catalyst recovery and reuse. Such advantages of heterogenized systems are important from both ecological and economical points of view.

1.7. Summary

Recent years have shown a remarkable development of new synthetic methods in the area of nonracemic sulfoxides. Still, the striking confidence in the well-tried, classical procedures is reflected by their numerous applications. In particular, the Kagan, Andersen, and Davis reagents are frequently used in the stoichiometric preparations of various sulfoxides, including intermediates important for the pharmaceutical industry.

Since none of the known methods can be regarded as universal, there is room for improvement and new systems with a better performance are required. Certain aspects, such as efforts to reach higher yields and enantioselectivities, and wider applicability (for example, for dialkyl and diaryl sulfides or substrates with sensitive groups), are important, but other tendencies are also clearly seen. The practical and economic issues are taken into account: processes should be simple, easily scaled-up, and reproducible. Mild (ambient) conditions with cheap, easily available reagents are preferred. Energy consumption and waste production should be minimized. Last but not least, the procedures should be environmentally friendly ("green") and safe. Thus, hydrogen peroxide (or, less commonly used, dioxygen) is preferred as oxidant due to low price, safe handling, and "clean" reduction products. Iron and titanium catalysts are regarded as more ecologically benign than the more toxic vanadium. Chlorinated solvents should be avoided, and performing the reactions in water is recommended.

Certain fields (such as the use of vanadium Schiff bases as catalysts) seem to be well explored, and one should not expect significant progress there. Other areas have received relatively less attention, and their further development is possible. For example, the organocatalytic methods of sulfoxide synthesis have been only marginally studied[208,209] and deserve reconsideration. In this regard, the successful application of a chiral ketone as catalyst for disulfide oxidation with oxone is significant.[377]

2. Biological Oxidations

2.1. Introduction

Different aspects need to be taken into account when the asymmetric organic synthesis is planned. While the yield of the process and its stereoselectivity remain the most important criteria, safety, health, and environmental aspects are of increasing interest. In this context, the application of biocatalysts to perform the desired chemical transformation has gained considerable attention.[378−380] The use of enzymes allows reactions to be conducted under mild conditions, typically with water as solvent, so that in many cases hazardous reagents can be avoided. Moreover, the nonracemic product may be readily obtained due to the built-in chirality of the catalyst. In addition to stereoselectivity, also regio- and chemoselectivity (the tolerance for different functional groups), as well as high substrate specificity, are frequently observed.

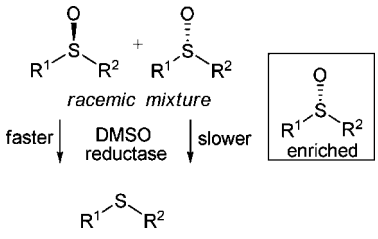
On the other hand, one should be aware of several drawbacks of the application of biocatalysts. The high specificity means a narrow operational range, since certain substrates would not be accepted by the enzyme. The range of reactions that can be catalyzed is restricted when compared with the case of typical homogeneous catalysts, which also offer easier access to both enantiomeric forms of the desired product. Additionally, the limited stability and relative sensitivity of biocatalysts should also be mentioned.

In spite of these limitations, the progress of biotechnology results in a better availability, also on a large scale, of biocatalysts of improved stability and performance. Consequently, enzymes are widely used in many different chemical transformations, including the enantioselective synthesis of chiral sulfoxides.[51]

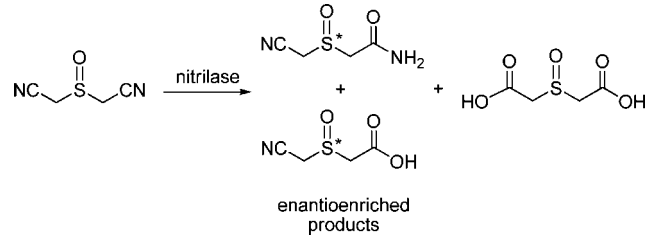
In most cases, different oxidases are applied that are able to convert prochiral sulfides into the corresponding S-oxides. The rare examples of a diverse approach employing the kinetic resolution of sulfoxides by dimethyl sulfoxide reductase[42−44] or methionine sulfoxide reductase[381] (Scheme 13) are also worth mentioning. A procedure utilizing the electrochemical regeneration of the enzyme yielded various sulfoxides with high *ee* (>97%).[45] The stereoselective oxidation of (*S*)-isomers of sulfoxides catalyzed by cytochrome *c*-crown ether complexes was also reported.[382] An interesting desymmetrization of bis(cyanomethyl) sulfoxide and bis(2-hydroxymethylphenyl) sulfoxide was recently described, exploiting the nitrilase-promoted hydrolysis or lipase-catalyzed acetylation, respectively (Schemes 14 and 15).[383,384]

Some of the oxidizing biocatalysts participate in the naturally occurring sulfoxidations, including the metabolism of certain drugs or xenobiotics and synthesis of chiral sulfoxides (in most cases derivatives of amino acids such as methionine or *S*-alkylcysteine) involved in different biochemical processes.[385,386] The majority of these enzymes, however, have a different physiological function but are also

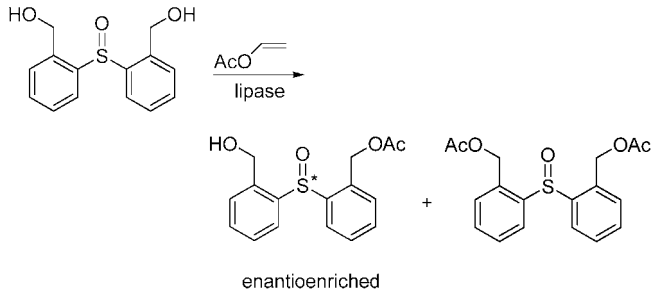
Scheme 13



Scheme 14



Scheme 15



able to catalyze the oxidation of heteroatoms, including sulfur. These reactions can be performed under mild conditions with dioxygen or hydrogen peroxide as oxidants, without further oxidation of sulfoxide to the corresponding sulfone.

Two general ways of performing sulfide biooxidation will be described in the following sections: the use of enzymes (either isolated from their natural sources or cloned and overexpressed) and the utilization of whole-cell systems. In section 2.4, the use of nonaqueous media and the aspect of enzyme immobilization are addressed, and the final part is devoted to new concepts, including the application of artificial metalloenzymes in the enantioselective sulfoxidation.

2.2. Isolated Enzymes

2.2.1. Peroxidases

Peroxidases constitute a heterogeneous group of redox enzymes capable of catalyzing different oxidations utilizing hydrogen peroxide or hydroperoxides as the oxygen source.[378] These ubiquitous biocatalysts are found in animals, plants, and microorganisms, and they are typically classified into three groups: heme peroxidases, vanadium peroxidases, and nonmetal peroxidases.[387] From the first class, horseradish peroxidase (HRP) was the most thoroughly investigated; other examples include lactoperoxidase, *Coprinus cinereus* peroxidase (CiP), cytochrome *c* peroxidase, or microperoxidase-11 (the heme peptide obtained by digestion of cytochrome *c* with proteolytic enzymes).[378] Several aspects of the utilization of peroxidases in the asymmetric sulfoxidation were recently reviewed.[387,388] HRP was first used for this purpose by Colonna and co-workers.[389] For methyl aryl sulfides, they were able to reach up to 95% yield and 0−68% *ee* ((*S*)-sulfoxide dominated), and even under optimal conditions, the stereoselectivity of the reaction catalyzed by wild-type enzyme remained moderate.[390] The stereoselectivity was substantially improved (*ee* > 94%) by the replacement of the phenylalanine-41 residue by smaller amino acids such as leucine.[391,392]

Several other peroxidases have been recently tested in the enantioselective sulfoxidation. In thioanisole oxidation catalyzed by myeloperoxidase, stepwise addition of H_2O_2 resulted

in the maximal yield (78%) at pH = 5.0, while the best stereoselectivity was reached at pH = 6.0 (*ee* = 32%).[390] The (*R*)-sulfoxide was formed preferentially, while another enzyme from the family, manganese peroxidase, led to the (*S*)-enantiomer with a very high *ee* (91% at pH = 5.0 and 87% at pH = 7.0), albeit in low yield (18% at pH = 5.0 and 36% at pH = 7.0).[390]

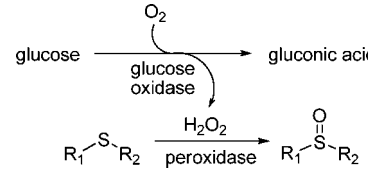
Lignin peroxidase from *Phanerochaete chrysosporium* was tested in the oxidation of alkyl aryl sulfides by H_2O_2.[393] The results suggested that the reaction proceeded through a sulfide radical cation which then formed the desired sulfoxide (up to 98% yield) or a disulfide (up to 7%). The yield of sulfoxide increased with an increase of the electron-donating properties of the aryl ring substituent. This effect was, however, accompanied by a decrease of the enantiomeric excess of the sulfoxide; the highest value (62%, *S* configuration) was observed for *p*-bromophenyl methyl sulfoxide.

The oxidation of several alkyl aryl sulfides by a recombinant pea cytosolic ascorbate peroxidase (rAPX) and its site-directed mutant (W41A) was examined by Raven and coworkers.[394] For rAPX, essentially racemic mixtures were formed, while the substitution of tryptophan 41 with an alanine residue enhanced the *ee* up to 60%. These results were correlated with modeling studies that used the known crystal structure of rAPX. They showed that mutation opened access of the substrate to the heme and changed the conformation of the arginine 38 residue responsible for the control of the substrate binding orientation.

Haloperoxidases, enzymes that are responsible for the conversion of halide anions by hydrogen peroxide, were also widely used in various oxidation reactions.[395,396] Heme-containing chloroperoxidase (CPO), isolated from the marine fungi *Caldariomyces fumago*, exhibited very high enantioselectivity and versatility in sulfoxidation reactions.[388,397,398] For instance, thioanisole was quantitatively converted to the (*R*)-sulfoxide with 99% *ee*. Recently, CPO was used by Holland's group for the oxidation of methionine derivatives with hydrogen peroxide.[399] Substituted L and D-methionine and L-ethionine were converted to the corresponding (*R*)-sulfoxides with *de* values ranging from 0 to 91%. *S*-Methyl- and *S*-ethyl-L-cysteine derivatives were also oxidized to give the (*R*)-products with 12−90% *de*.[385]

Vanadium-containing peroxidases, although being more stable than their heme counterparts, in most cases are not readily available and exhibit low activities and a narrow scope in enantioselective oxidations.[51,400] However, vanadium chloroperoxidase (VCPO) from the fungus *Curvularia inaequalis* and vanadium bromoperoxidases (VBPOs) from the seaweeds *Corallina pilulifera* and *Ascophyllum nodosum* were shown to oxidize thioanisole.[401] While VCPO led to racemic product, VBPO enzymes yielded the enantioenriched sulfoxide with up to 91% *ee* (in the case of *A. nodosum*, which gave mainly the (*R*)-enantiomer). Further optimization of reaction conditions improved this value up to 96%.[402] The authors also showed that the VBPO from *Ascophyllum nodosum* remained active at temperatures up to 70 °C. VBPO from *Corallina officinalis* was found to be effective in the oxidation of bicyclic sulfides,[403] and it exhibited high selectivity (over 95% *ee*) in the conversion of substrates with a *cis*-carboxyl group.[404] For instance, (*S*)-2-methylsulfinylbenzoic acid was prepared with high enantiomeric purity, which was retained (*ee* = 97%) after an increase of the reaction scale.[405] These encouraging results, however, did not lead to the wider use of vanadium-dependent peroxidases, in contrast to the heme-dependent biocatalysts.

Scheme 16

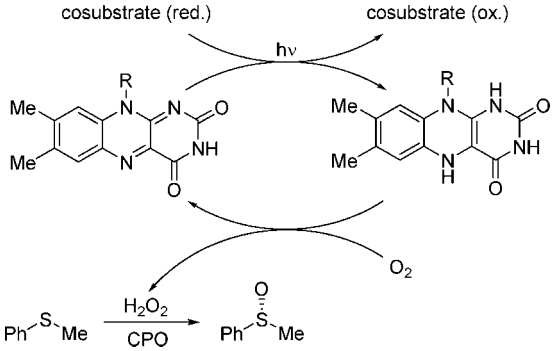


The possible industrial application of heme peroxidases is, however, limited due to their relatively high price and low stability. In general, these enzymes are not resistant to elevated temperature and organic solvents, but the main disadvantage is connected with the heme degradation caused by peroxide used as the oxidant. Another problem is connected with the catalase activity of CPO, which can be responsible for the excessive consumption of peroxide.[406] Methods of improving the catalytic performance of peroxidases were reviewed by Sheldon et al.[387] In particular, the enzyme turnover number can be increased by feed-on-demand addition of hydrogen peroxide. Its concentration can be maintained at a desired level using a peroxide−stat system.[407] On the other hand, the optimization of the performance of HRP in thioanisole oxidation (the *S*-sulfoxide obtained with 100% yield and 60% *ee*) was achieved with spectroscopic monitoring of the concentration of the enzyme intermediates during the continuous addition of H_2O_2.[390]

With feed-on-demand methods, a local concentration of peroxide at the point of addition can still be high. This problem can be overcome by the *in situ* generation of H_2O_2 by enzymatic[408−413] or electrochemical methods.[414−416] A commercially available, inexpensive glucose oxidase (GOX or GOD) was used for this purpose.[408,409] Utilizing glucose as a sacrificial reductant, this enzyme converts dioxygen into hydrogen peroxide, which can then be utilized by a peroxidase (Scheme 16). This tandem system was applied with success for the oxidation of aryl methyl sulfides, leading preferentially to (*S*)-sulfoxides (65−95% conversion, up to 90% *ee*).[409] Plant peroxidase from *C. cinereus* (CiP) and horseradish peroxidase was used in these transformations. Other peroxidases, chloroperoxidase from *C. fumago*, soybean peroxidase (SBP), and microperoxidase-11 as well as phytase from *Aspergillus ficuum*, were coimmobilized with GOX into polyuretane foam.[408] These systems showed increased operational stability and total turnover number in the oxidation of thioanisole, with *ee* values reaching 99% (CPO), 69% (phytase), and 50% (SBP) for (*S*)-sulfoxide. The use of the bienzymatic GOX/CiP system was extended for a group of heteroaryl-methyl sulfides.[412] Substrates bearing electron-rich heterocycles were readily oxidized to form (*S*)-sulfoxides (40−100% conversion, 41 to >99% *ee*), while those containing electron-deficient rings were unreactive. The tandem system worked well in an ionic liquid (1-butyl-3-methylimidazolium hexafluorophosphate) containing 5−10% of water.[411] Thioanisole and methyl-2-naphthyl sulfide were oxidized with a stereoselectivity similar to that observed for aqueous solutions (up to 92% *ee* for the latter substrate).

Other oxidases were also tested in tandem with CiP by the Therisod group, includng D-amino acid oxidase (DAOx) immobilized on a polymeric support, and alcohol oxidase (AOX) with DL-alanine or methanol as a substrate, respectively.[410,413] Aryl methyl sulfides were efficiently converted into *S*-oxidized products, with reasonable yields and *ee*'s.

Scheme 17

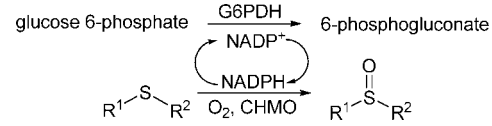


(*S*)-Thioanisole sulfoxide was also prepared on a gram scale (86% yield, 75% *ee* for DAOx; 72% yield, 75% *ee* for AOX).[413]

Hydrogen peroxide used in peroxidase-catalyzed oxidation of sulfides can also be generated *in situ* by electrochemical methods.[414−416] This offers two main advantages over the tandem systems: no side products are formed from the reaction of the sacrificial reductant (e.g., gluconic acid formed from glucose), and it is possible to control the rate of H_2O_2 production by applying the desired current and voltage. An electroenzymatic sulfoxidation of thioanisole was performed using chloroperoxidase from *C. fumago* and H_2O_2 obtained by cathodic reduction of dioxygen. A high enantiomeric excess of (*R*)-methyl phenyl sulfoxide (>98.5%) was observed.[414] The method was applied to three other substrates; for methyl *p*-tolyl sulfide and methyl *p*-methoxyphenyl sulfide, the *ee* values were equal to 93% and 99%, respectively, while the *N*-MOC-L-methionine methyl ester was oxidized with the diastereomeric ratio 81:19.[415] The use of three-dimensional electrode and optimized reaction conditions (10% (v/v) *tert*-butanol as a cosolvent) allowed the thioanisole oxidation to be performed on a gram scale.[416]

A recent example of thioanisole oxidation with CPO from *C. Fumago* involved *in situ* H_2O_2 generation directly from H_2 and O_2 using Pd(0) catalysts performed in supercritical carbon dioxide.[417] The enzyme was found to be stable in $scCO_2/H_2O$ biphasic media, and the optically enriched (*R*)-sulfoxide was obtained with an *ee* up to 94%. Another approach involved light-driven H_2O_2 generation, using flavins as photocatalysts and EDTA as sacrificial electron donor (cosubstrate, Scheme 17).[418] Illumination of a solution containing EDTA (8 mM), flavin mononucleotide (FMN, 80 μM), CPO (0.357 μM), and thioanisole (8 mM) with a 250 W bulb resulted in the quantitative conversion of sulfide into (*R*)-sulfoxide with *ee* > 99%. The enzyme remained active for at least 7 h without loss of selectivity. The total turnover number of CPO exceeded 22 000. The new method offered several advantages over the previous approaches which utilized specialized equipment or a second, costly enzyme. The main problem was connected with the undesirable waste products (formaldehyde, ethylene diamine) formed from EDTA oxidation. When this sacrificial electron donor was replaced by formate, the reaction enantioselectivity was diminished to *ee* = 78%. This effect was attributed to the interaction of formate with heme iron. Still, the photocatalytic method of peroxide generation opens a new perspective for the wider application of chloroperoxidase for the preparation of nonracemic sulfoxides.

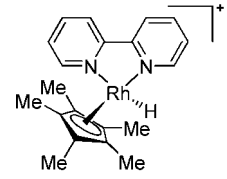
Scheme 18



2.2.2. Monooxygenases

Monooxygenases are defined as biocatalysts capable of an efficient and selective insertion of one oxygen atom from O_2 to the substrate, while the other is reduced to water.[388] Different kinds of oxidative reactions are catalyzed by these enzymes, with π-bond epoxidations, carbon hydroxylations, and heteroatom (N, S, P) oxidations being the most typical. Several classes of monooxygenases are distinguished based on the redox cofactor: cytochrome P450-dependent, flavin-dependent, copper-dependent, and Fe-pterin enzymes.[419] Under the physiological conditions, the enzyme prosthetic group is regenerated in the catalytic cycle by NADH/NADPH, and the necessity for the use of stoichiometric amounts of this expensive cofactor complicates the applications of monooxygenases.[388] Another difficulty is connected with the low stability of the isolated enzymes. These problems can be overcome by using whole cells for the monooxygenase-catalyzed reactions, since the living cells provide the natural recycling systems. However, to avoid the possibility of competing reactions that could lower the yield and *ee* of the formed sulfoxide, the use of isolated enzymes is preferred. Efficient coenzyme regeneration is therefore necessary, and it is usually performed by the second enzyme. The glucose-6-phosphate dehydrogenase (G6PDH)/glucose-6-phosphate pair is commonly used (Scheme 18) and can lead to a high rate of sulfide oxidations.[420] This system can be replaced by alcohol dehydrogensase/2-propanol or formate dehydrogenase/formate pairs.

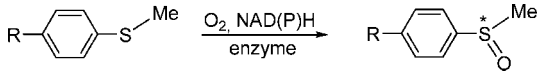
As an interesting alternative, instead of using NADPH/NADH for the flavin reduction, an organorhodium derivative $[Cp^*Rh(bpy)H]^+$ (**357**) was tested for this purpose.[421] This hydride complex reduces the FAD cofactor and is regenerated by formate or with the use of electrochemical methods.[422] Unfortunately, for all monooxygenases used, the **357**/formate system led to a drastic drop of enantioselectivity of sulfide oxidation, suggesting that NADPH is also important for the stereochemical outcome of the reaction by properly shaping the active site of these enzymes. Recently, the possible use of the rhodium complex for the regeneration of P450-dependent monooxygenases was demonstrated, though a racemic sulfoxide was formed in the process.[423]



357

In recent years, the application of flavin-dependent monooxygenases in enantioselective sulfoxidation has received considerable attention. Since several flavoenzymes can catalyze the Baeyer−Villiger oxidation of cyclic or acyclic ketones, yielding chiral esters, these proteins are usually termed Baeyer−Villiger monooxygenases (BVMOs).[424−427] The widely investigated Baeyer−Villiger enzyme, cyclo-

Table 3. Comparison of Stereochemical Outcomes of BVMO-Catalyzed Sulfoxidations



	sulfoxide, *ee* (conf)		
enzyme	R = H	R = CH_3	ref
CHMO	37% (*S*)	99% (*R*)	428 and 429
HAPMO	>99% (*S*)	>99% (*S*)	433
EtaA		55% (*S*)	435
PAMO (WT)	44/41% (*R*)	10/6% (*R*)	436 and 438
M446G PAMO	93% (*R*)	92% (*R*)	439

hexanone monooxygenase (CHMO) from *Acinetobacter* sp., was used previously for the enantioselective oxidation of various sulfides.[397,428−430] Both whole-cell systems and the isolated enzyme were applied for this purpose. CHMO can now be produced on a large scale in *Escherichia coli* by expressing the recombinant protein.[431] While it exhibits satisfactory activity and selectivity, CHMO suffers from the limited stability and the need for NADPH regeneration. The performance of isolated CHMO (cloned and overexpressed in *E. coli*) was examined to improve enzyme stability and reuse, and cofactor recycling.[420] The half-life of CHMO was increased from about 1 day to ca. 1 week by the addition of 1 M sodium sulfate, but the additive caused a moderate decrease of enzyme activity. The stability of CHMO was also improved by its immobilization (section 2.4.2).

In recent years, several novel flavoenzymes were isolated and applied for the synthesis of chiral sulfoxides. 4-Hydroxyacetophenone monooxygenase (HAPMO) from *Pseudomonas fluorescens* ACB was purified, characterized, and used in the oxidation of a range of aromatic ketones.[432] This enzyme was also shown to accept thioanisole and methyl *p*-tolyl sulfide as substrates, giving the corresponding (*S*)-sulfoxides with >99% *ee*.[433] Several other alkyl aryl and dialkyl sulfides were also converted into *S*-oxides with high enantioselectivity (51−99%) and 31−96% conversion.[434] The absolute configuration of the main enantiomer was strongly dependent on the substrate structure. In general, phenyl sulfides were found to be the best substrates for the enzyme, which correlated with the structure of its physiological substrate, acetophenone.

Another FAD-containing monooxygenase was found in *Mycobacterium tuberculosis*, in which it is responsible for the activation of thioamide prodrugs (e.g., ethionamide) used to treat the infection.[435] This specific protein, ethionamide monooxygenase (EtaA), was also able to catalyze the enantioselective sulfoxidation of methyl-*p*-tolyl sulfide, yielding the *S*-product with 55% *ee*.

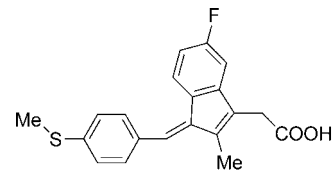
The recognition of the protein sequence motif common for the known BVMOs allowed a new monooxygenase to be identified in the thermophilic actinomycete *Thermobifida fusca*.[436] This biocatalyst, named phenylacetone monooxygenase (PAMO), exhibited a remarkable thermostability and a tolerance toward organic solvents,[437] making it an attractive candidate for practical applications. Like other BVMOs, PAMO catalyzed the sulfoxidation reaction; however, for alkyl phenyl sulfides, the enantioselectivities were only low to moderate (see Table 3). Much better results (up to 98% *ee*) were obtained for the benzylic sulfides (whose structure resembles the best enzyme substrate, phenylacetone).[438] In this case, the high stereoselectivity was in part due to the kinetic resolution process, as PAMO catalyzed the further oxidation of the corresponding sulfoxides to sulfones. The substrate specificity was altered by site-directed mutagenesis.[439] Among several single, double, and triple mutants (their preparation was preceded by analysis of the crystal structure of the enzyme[440]), the M446G variant displayed an increased enantioselectivity in the oxidation of phenyl sulfides (Table 3), while for methyl benzyl sulfide the *ee* decreased from 98% to 59% (*S*-sulfoxide dominated for this substrate). A similar stereoselectivity improvement in the conversion of thioanisole derivatives was also observed when methanol was used as a cosolvent in the wild-type PAMO oxidations.[437]

The term flavin-containing monooxidases (FMOs) is used for a family of microsomal enzymes catalyzing O_2- and NADPH-dependent oxidation of many drugs and xenobiotics containing heteroatoms.[441−443] At least five isoforms of FMOs were identified in numerous vertebrate species. FMO3 is the major liver isoform in adult humans, and FMO1 is the main form found in the liver of most other mammals and the fetal liver.

FMO enzymes were shown to catalyze enantioselective sulfoxidation reactions. For example, detergent-treated hepatic microsomes from rainbow trout catalyzed the conversion of different substrates, including methyl-*p*-tolyl sulfide (*S*-product with 48% *ee* was obtained).[443] Using liver microsomes from various species, Elfarra and Krause showed that FMOs can oxidize L-methionine.[441] For cDNA-expressed rabbit and human moooxygenases, FMO3 exhibited the highest activity and stereoselectivity (90−100% of (*S*)-sulfoxide). Small peptides containing methionine were also able to serve as FMO substrates, but only if the Met amino group was not modified or engaged in the peptide bond. Several FMO1 variants found in humans were expressed in the baculovirus system and used for the N- and S-oxidation.[442] All mutants preserved their catalytic activity and yielded (*R*)-methyl-*p*-tolyl sulfoxide and (*R*)-fenthion sulfoxide (a product obtained from the common insecticide fenthion **90**) with >95% *ee*.

The involvement of FMOs in drug metabolism was investigated by several groups.[444,445] The oxidation of Sulindac sulfide **358**, a physiological metabolite of sulindac **97**, was performed by human liver and kidney microsomes, as well as cDNA-expressed microsomes.[444] The metabolism of this compound was entirely FMO-dependent, and the major product, (*R*)-sulfoxide **97**, was formed with up to 97% *ee*. Similar results were obtained using isolated FMO1, FMO2, and FMO3 enzymes, while FMO5 lacked catalytic activity.

Albendazole (ABZ, **359**) and fenbendazole (FBZ, **360**) are prochiral benzimidazole derivatives that are effective against different parasitic worms.[445] These compounds are converted *in vivo* to the corresponding sulfoxides, which retain the anthelmintic activity. The oxidation of ABZ and FBZ by liver, lung, and intestinal microsomes from sheep and cattle was described by Virkel and co-workers.[445] Inactivation and inhibition experiments allowed the estimation of the contribution of FMO and cytochrome P450 systems in the sulfoxidation. These two enzymatic pathways showed different enantioselectivities, therefore limiting the observed *ee* of the formed sulfoxides. The metabolism of ABZ and FBZ and the distribution of the corresponding sulfoxide enantiomers in various species were widely investigated.[446,447]



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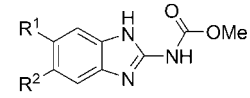
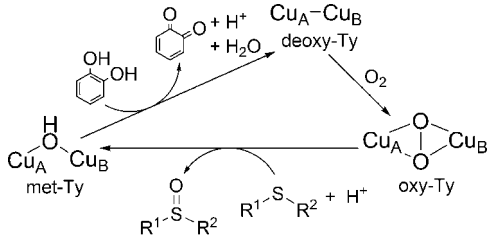


359: R^1 = SPr, R^2 = H
360: R^1 = H; R^2 = SPh

Scheme 19



Toluene monooxygenases (TMOs) are soluble, non-heme four-component enzymes catalyzing the hydroxylation of toluene derivatives. Fishman and co-workers investigated the ability of TMOs to selectively oxidize alkyl aryl sulfides, using both wild-type enzymes and their variants obtained by site-directed mutagenesis.[448] Among the four biocatalysts studied, toluene *o*-monooxygenase (TOM) from *Burkholderia cepacia* G4 showed the highest oxidation rate for thioanisole and methyl *p*-tolyl sulfide, leading to the (*S*)-sulfoxides with 51% *ee* and 11% *ee*, respectively. The stereoselectivity was much higher for toluene 4-monooxygenase (T4MO) of *Pseudomonas mendocina* KR1: 86% *ee* for thioanisole and ~42% *ee* for the *p*-tolyl derivative (in this case the (*R*)-product dominated) were noted. By a screening of a library of mutants, several variants of TOM and T4MO were identified showing improved activity and selectivity (up to 98% *ee*) which the authors connected with the better accessibility of the diiron center of the enzyme.

Casella and co-workers examined the possible use of mushroom (*Agaricus bisporus*) tyrosinase (polyphenol oxidase, Ty) in the enantioselective sulfoxidation.[449,450] This dicopper enzyme is strongly active toward phenolic substrates, catalyzing their *o*-hydroxylation and the further oxidation of *o*-diphenols to quinones by dioxygen. This catalytic activity can be broadened by the use of a suitable reducing agent, such as catechol (Scheme 19). The cosubstrate converts tyrosinase to the deoxy form, which binds O_2 with high affinity, and the resulting oxy-Ty is capable of oxidizing thioanisole in a two-electron process. The observed yield of (*S*)-sulfoxide was rather moderate (ca. 20%) due to the fact that L-dopamine used as a reductant was also competing with the sulfide in the catalytic reaction.[450] The enzyme inactivation by the quinones formed in the course of the reaction was limited by adding an excess of ascorbate, which allowed us to raise the *ee* of product up to 94%. Other sulfide substrates were also tested; albeit, the yields were rather unsatisfactory.[450]

Various newly isolated monooxygenases exhibited high efficiency in the oxidation of prochiral sulfides. The results of catalytic reactions were found to be substrate-dependent. Future works will probably concentrate on further modifications of reaction conditions and the structure of CHMO and other enzymes of comparable activity and increased stability (e.g., PAMO).

2.2.3. Other Enzymes and Nonenzymatic Proteins

The high activity and selectivity exhibited in sulfide oxidation by heme enzymes (peroxidases and monooxygenases) directed the biochemists' attention to other hemoproteins, such as myoglobin, hemoglobin, or cytochrome *c*.[451] Though their natural, physiological role is nonenzymatic, they all bear iron protoporphyrin IX as the prosthetic group, which can be appropriately tuned to show peroxidase-like activity. Myoglobin (Mb), normally responsible for the storage and transfer of molecular oxygen, catalyzes the one- and two-electron oxidation of a variety of substrates by peroxide. Since this protein was not tailored to exhibit such oxidase activity, the oxidation rates are very low, and thioanisole is converted into (*R*)-sulfoxide with rather modest stereoselectivity (*ee* = 25%).[452,453] The effect can be connected with a difference of the heme cavity of peroxidases and myoglobin in which the access of potential substrates is much more limited. To change this situation, an engineering of the distal side of the heme pocket was performed by the construction of several single and double sperm whale Mb mutants.[454] Among them, L29H, L29H/H64L, and F43H/H64L Mb variants showed a substantial increase of both rate and enantiomeric excess in thioanisole oxidation (Table 4).[452−458]

Table 4. Oxidation of Thioanisole by Sperm Whale Mb Variants[452−458]

variant	rate (turnover/min)	*ee*[a]
wild-type Mb	0.25	25
L29H	3.9	91
F43H	3.5	59
H64L	0.072	27
H64D	145	6
H64D/V68A	121	84
H64D/V68S	64	88
H64D/V68I	410	25
L29H/H64L	5.5	97
F43H/H64L	47	85

[a] The absolute configuration of the dominant isomer was *R* in each case, except for the H64D/V68I Mb variant.

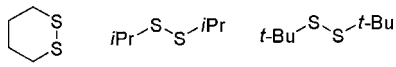
Myoglobin mutants were tested in the oxidation of various sulfides,[452,455] including bicyclic ones for which the (*S*)-enantiomer was the dominant product. Two variants of human Mb (C110A and Y103F) were also investigated to establish the role of tyrosine-103 and cysteine-110 in the peroxidase-like activity.[459] Casella and co-workers showed the effect of nitrite on the oxidation of aromatic sulfides catalyzed by horse heart Mb, sperm whale Mb, and their mutated versions involving threonine-67.[460,461] The enantioselectivity and yields were improved, although they remained below the values obtained for H64D/V68A or H64D/V68S mutant proteins.

Another possible strategy of Mb modification, involving the prosthetic group replacement, was also widely utilized and is described in section 2.5.

The promising results obtained in the oxidations catalyzed by modified Mb connected with the fact that, compared with peroxidases, myoglobin is cheaper and more stable (the problem of stability change caused by mutation was seldom addressed[460]) should lead to wider application of this hemoprotein in the field of sulfoxide synthesis.

Interestingly, also several redox-innocent, ubiquitous proteins which lack readily oxidizible/reducible functionalities can be used as catalysts in the enantioselective sulfoxidation.[451] While the oxidation of sulfides by hydrogen peroxide in aqueous solution takes place without catalyst, the possible substrate activation upon binding in the hydrophobic cavity and the chiral environment provided by the protein may facilitate the reaction by improving its yield and making the process stereoselective. Bovine and human serum albumins (BSA, HSA) and hydrolytic enzymes (chymotrypsin, subtilisin Carlsberg) were described as catalysts of the oxidations of various sulfides.[462−465] Recently, the monooxidation of model disulfides **361**−**363** with peroxides

catalyzed by bovine serum albumin (BSA) was investigated by Dzyuba and Klibanov.[466] The best results were achieved for the most hydrophobic substrate **363**. Interestingly, the absolute configuration of the resulting sulfinate depended on the oxidant used: the (*S*)-enantiomer for H_2O_2, and the (*R*)-isomer in the case of TBHP dominated in the reaction mixture. Another hydrophobic substrate, phenyl isobutyl sulfide, was chosen as an appropriate candidate for the α-chymotrypsin-mediated sulfoxidation with hydrogen peroxide.[465] Its high affinity for the hydrophobic enzyme binding site together with low solubility in water (further diminished by addition of Na_2SO_4 to the reaction medium), which reduced the rate of noncatalytic oxidation, resulted in an accelerated and highly stereoselective oxidation. The ratio of the initial rates of the production of (*S*)- and (*R*)-sulfoxide was estimated as about 80, while, for another hydrolytic enzyme, subtilisin Carlsberg, this ratio of initial rates was 4.5. Other sulfides exhibited much worse results in the chymotrypsin-catalyzed reaction, and this observation was explained by computer modeling studies showing binding of substrates in the pocket and their accessibility by the oxidant.[465]



361 **362** **363**

2.3. Whole-Cell Systems

Although a lot of the isolated enzymes exhibit high chemo-, regio-, and enantioselectivity, in some cases, removal of enzymes from their natural environment results in the lowering of their activity, selectivity, and even stability.[467] This is particularly true for the membrane-bound biocatalysts, which may lose their good catalytic properties when isolated from the cell. Besides, some enzymes cooperate with other biomolecules, cofactors, and can utilize metabolites present in the cytoplasm (e.g., ATP, $NAD(P)^+$/NAD(P)H). Even if there are no such factors that may affect the action of a purified enzyme, the use of whole cells can be the method of choice because the isolation procedure can be tedious and expensive.

However, a living cell (also dead, if such is used) presents a complex system, making the nature of the real catalytic species uncertain. Even in the cases in which the enzyme engaged in the substrate conversion is well-established, its activity can be modified by other compounds present in the culture, and the desired product may be further metabolized. For instance, the prolonged oxidation of sulfides by toluene dioxygenase of *Pseudomonas putida* is accompanied by the partial reduction catalyzed by a specific reductase (*vide infra*).[468,469] A preliminary screening can be performed on model substrates prior to system application for the more demanding ones.[470]

Another problem in whole-cell biocatalysis is connected with a low reaction rate. The cell envelopes containing the enzyme are not quite easily penetrated by the substrate molecules, and this permeation barrier can limit the rate of the catalytic process.

Taking into account the above-mentioned pros and cons, the whole-cell systems are thoroughly examined for the different biotransformations, including the enantioselective sulfoxidation.[467] Bacteria, fungi, and yeasts are commonly used because of their rapid growth and ease of handling. A well-established DNA technology makes them readily available in sufficient quantities for preparative purposes. Less commonly, plant cells and organ cultures are also studied,[471] with a special interest in microalgae, the fastest growing plants.[472]

In this section, the recent advances in the use of whole-cell systems in the sulfide oxidation will be presented, starting from those in which the oxidizing enzyme is known.

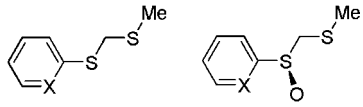
2.3.1. Identified Enzymes

2.3.1.1. Monooxygenases. The new bacterial species *Rhodococcus erythropolis* was previously applied in the biocatalytic desulfurization of fuels (conversion of dibenzothiophenes to the corresponding sulfoxides). A version of this microorganism expressing the monooxygenase DszC was shown to catalyze the stereoselective sulfoxidation of a variety of sulfides.[473] With only several exceptions, the yield of sulfoxide was moderate to high, the sulfone formation was negligible, and the predominant (*R*)-product was obtained with a varying enantioselectivity. A comparative molecular field analysis was applied for the prediction of the enantiomeric excess of the reaction.[474]

Enantiopure (*ee* > 96%) aryl methyl sulfoxides prepared with the recombinant strains of baker's yeast (*Saccharomyces cerevisiae*) and *E. coli* overexpressing CHMO were covalently bound to a mesoporous silica and used as heterogeneous catalysts for asymmetric allylation.[475] In general, the monooxygenases and peroxidases were used as isolated enzymes, in contrast to the situation with dioxygenases described in the following section.

2.3.1.2. Dioxygenases. Dioxygenases are enzymes catalyzing oxygenation reactions in which both atoms of dioxygen are incorporated into the product.[476] These biocatalysts are involved in the aerobic degradation of aromatic substrates and are responsible for *cis*-dihydroxylation of arenes or aromatic ring cleavage. Nevertheless, dioxygenases can also catalyze single and tandem oxygenation of various substrates. Typically, these enzymes contain three components: iron–sulfur flavoprotein reductase, an iron−sulfur ferredoxin, and an oxygenase bearing a mononuclear iron site. The complex nature and cofactor dependence of dioxygenases are responsible for the fact that in most cases whole cell oxidations are performed. Two enzymes found in *P. putida* species, toluene dioxygenase (TDO) and naphthalene dioxygenase (NDO), were widely used for enantioselective sulfoxidation.[477−479] With different strains of *P. putida*, UV4 (a TDO source) or NCIMB 8859 (NDO-containing strain), a range of substrates was converted to the corresponding sulfoxides with high *ee* values. For certain substrates, the two enzymes exhibited different stereochemical preferences. For instance, for thioanisole oxidation with *P. putida* UV4, the (*R*)-sulfoxide was formed with *ee* > 98%, while the NCIMB 8859 strain led to the (*S*)-product with 91% *ee*.[479]

Boyd and co-workers showed that the oxidation of substrates **364** bearing three possible reaction centers (alkyl aryl sulfur, dialkyl sulfur, or arene ring) led preferentially to the enantiopure (*ee* > 98%) alkyl aryl sulfoxides (**365**).[480] For the dialkyl sulfides containing an aromatic ring (**292**, **327**, **366**), TDO yielded mainly *cis*-dihydroxylated products. However, the enantiopure diol sulfoxides resulting from the substrate trioxygenations were also formed. Similar products were also obtained in good yields in the prolonged biotransformation (over 18 h) of alkyl aryl sulfides using whole cells of *P. putida* UV4.[481] The enantiopure sulfoxides were further converted to the corresponding catechols **367** using the *E. coli narB* strain.



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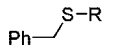

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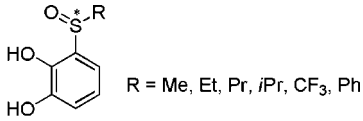

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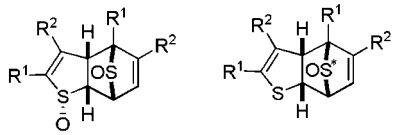
The competition between sulfoxidation and *cis*-dihydroxylation reactions was further examined for the TDO-catalyzed oxidation of monosubstituted thiophenes.[468] For 2-substituted derivatives, the heterocyclic sulfur atom was the preferred oxidation site. The initially formed thiophene oxides dimerized spontaneously to give disulfoxide products **368**, which were found to be racemic. However, their deoxygenation catalyzed by a reductase enzyme present in the cell of *P. putida* led to the corresponding monosulfoxides **369** with 3−77% *ee*, which was due to the kinetic resolution. Biotransformation of 3-substituted thiophenes yielded both dihydroxylation and sulfoxidation products (e.g., a monosulfoxide). For the substrates bearing a sulfur atom in the acyclic 2-substituent, this additional center was preferentially oxidized to give the corresponding monosulfoxides at 18−52% yield and up to ≥98% *ee*.[468]



368 369

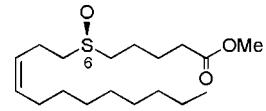
R^1 = H, R^2 = Me, Ph, Cl, Br
R^1 = H, Me, Et, Ph, Cl, Br, I, SMe, SPh, S-2-thienyl, R^2 = H

TDO- and NDO-catalyzed oxidation of the series of methyl aryl sulfides allowed both the *cis*-dihydroxylated and sulfur-monooxidized products to be isolated.[469] In most cases, the *ee* values for *S*-oxides were higher (≥90%) for the NDO enzyme. Further enantiomeric enrichment of methyl *p*-tolyl sulfoxide was observed in the *P. putida* UV4 and was assigned to the partial conversion of the (*S*) enantiomer to the dihydroxysulfide. This observation served as additional evidence of the activity of a stereoselective sulfoxide reductase in *P. putida* UV4.

The biotransformation of methyl-*o*-bromophenyl sulfide with *E. coli*-overexpressed toluene dioxygenase led to the mixture of diol and (*R*)-sulfoxide in a ratio of 2.5:1, while for the *meta*-substituted substrate the ratio changed to 1:18.[482] The authors explained this difference by the influence of substitution on the substrate fit in the active site of the dioxygenase.

Bicyclic substrates containing one or two sulfur atoms were biotransformed to the corresponding monosulfoxides using *P. putida* UV4 (yielding (*R*)-products) and *P. putida* 8859 (to (*S*)-products).[483] In several cases, the *ee* exceeded 98%, but the yields were low, especially for the TDO-catalyzed reactions. Boyd and co-workers thoroughly explored the transformations of various sulfides by dioxygenase-expressing microorganisms. In general, the competitive oxidation pathways resulted in moderate yields of the desired sulfoxides, although the products of tandem oxidation may also be of special interest.

2.3.1.3. Desaturases. Fatty acid desaturases constitute a group of redox metalloenzymes engaged in lipid biosynthesis. These membrane-bound or soluble proteins catalyze the NADPH- and O_2-dependent insertion of double bonds into fatty acyl chains.[484] Their catalytic behavior can be, however, much more diverse, including the enantioselective sulfoxidation of thia derivatives.[484,485] The possibility of sulfide oxidation is utilized in the so-called thia test, which gives insight into the mechanism of the enzymatic reaction, showing the position of the initial attack of the diiron cofactor.[486,487] It was shown that, for an effective sulfoxidation, the thia substrate should bear a sulfur atom in the site at which the dehydrogenation reaction of the corresponding fatty acyl analogue is initiated.[486,487] The configuration of the product sulfoxide was found to be consistent with the preference of pro-*R* hydrogen removal for the parent enzymatic reaction. For example, only a 6-thia-derivative was converted by the Δ^6 desaturase from *Tetrahymena thermophila* into the (*S*)-sulfoxide **370** with 9% yield and >95% *ee*.[487] The (*S*)-sulfoxide was also produced by Δ^9 desaturase-catalyzed oxidation of the sulfide (whole cells of *S. cerevisiae* were used in this experiment), but in this case the *ee* was significantly lower (32%). This observation was rationalized by the fact that the enzyme oxo-transfer activity is reduced for substrates with the sulfur atom in a position different than position 9 or 10.[488,489] The effect of substrate chain length was investigated using a series of 9-thia fatty acid methyl esters which were incubated with cultures of *S. cerevisiae*.[490] Acceptable levels of conversion (11−90%) were observed for the derivatives possessing from 14 to 19 atoms in the chain. The C-16 product **371** was obtained on a preparative scale (200 mg, 40% yield) and appeared to contain almost pure (*R*)-sulfoxide (ca. 95% *ee*).[490]



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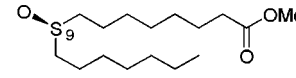

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The microalgae *Chlorella vulgaris* desaturating system was also applied for the enantioselective sulfoxidation.[491] Methyl 6-, 7-, 12-, and 13-thiastearates were first converted intracellularly by Δ^9-desaturase to give products with a double bond at C-9. These thiaoleoyl esters were found to be good substrates for oleate Δ^{12}-desaturase, which oxidized 12- and 13-thiasubstituted derivatives into the corresponding sulfoxides with a high enantioselectivity (*ee* ≥ 90%), while 6- and 7-thiaoleates were desaturated at the 12 position.

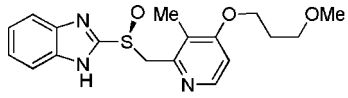
By a combination of chemical and enzymatic processes, the synthesis of novel chiral sulfoxide-containing lipids and phospholipids can be achieved.[490] Still, the synthetic utility of desaturases in the enantioselective sulfoxidation seems to be rather limited by their substrate specificity.

2.3.2. Unknown Enzymes

A topsoil bacterium *Pseudomonas frederiksbergensis* was tested for the very first time by Adam et al. in the oxidation

of prochiral sulfides.[492] For several aryl-methyl and cyclohexyl methyl sulfides, a high enantiomeric excess of the (*S*)-sulfoxide (70 to >99%) was observed, and unoptimized yields were in the range 4−48%. Benzyl methyl sulfide and phenyl isopropyl sulfide were barely consumed by the bacterium. Surprisingly, the stereochemical outcomes for commercially available *P. frederiksbergensis* DSM 13002 and a strain 33 isolated directly from the soil samples were different: the latter led to *R* isomers with significantly lower *ee* (up to 89%).[493] This observation was explained by the possible difference of the structure of the sulfoxidation enzymes, whose nature, however, was not established. A new bacterial strain (ECU0066) exhibiting the sulfide monooxygenase activity was isolated from soil samples and identified as *Rhodococcus* sp.[494] Asymmetric oxidation of thioanisole performed by this isolate led to the (*S*)-sulfoxide in 44% yield and 99% *ee*; the high enantioselectivity was partially due to the kinetic resolution. The stereochemical preference suggested the action of an enzyme different from monooxygenase found in *Rhodocoeccus erythropolis*[473] (see section 2.3.1.1). Oxidation of seven other alkyl aryl sulfides yielded *S*-oxides mostly as (*S*)-enantiomers, with yields ranging from 14 to 86% and *ee*'s equal to 17−97%.

About 650 strains comprising bacteria, fungi, yeasts, and molds were tested for their potential of catalyzing the formation of a proton pump inhibitor, rabeprazole (**372**) *via* oxidation of the corresponding sulfide.[495] The highest activity was exhibited by the newly isolated strain, the mold *Cunninghamella echinulata* MK40. The product formation was improved by adding 0.5% of detergent and 0.25% glucose to the culture broth. The reaction led almost exclusively to the (*S*)-enantiomer of the sulfoxide (>99% *ee*) without any overoxidation to the sulfone. Interestingly, the system exhibited a marked substrate specificity: simple sulfides such as thioanisole, 4-methylthiophenol, or methionine derivatives were not oxidized, and for other proton pump inhibitors—omeprazole (**1**) and lansoprazole (**143**)—the conversion was 49% and only 0.6% of rabeprazole formation, respectively.



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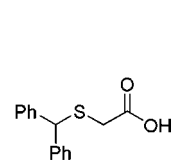
Six white-rot *Basidiomycetes* fungi that promote the biodegradation of lignin using nonspecific extracellular peroxidases and laccases were examined as catalysts in the oxidation of four alkyl phenyl sulfides.[496] Whole cells in a buffer solution were applied, resulting in 42−96% conversion and 12 up to ≥99% *ee* (the (*S*)-product dominated in each case) after 48 h. With expanding reaction time, the stereoselectivity increased due to kinetic resolution during the oxidation of sulfoxides to the corresponding sulfones. Similar behavior was observed previously for the oxidation of methyl aryl or ethyl aryl sulfides using *Aspergillus terreus* CCT 3320, giving the best *ee* (≥95%) after 96 h.[497]

Alkyl aryl and dialkyl sulfides were treated with the filamentous fungi *Botrytis cinerea*, *Trichoderma viride*, and *Eutypa lata*.[498] Only thioanisole and butyl phenyl sulfide were converted to the desired sulfoxides, with the (*S*)-enantiomer favored by *B. cinerea*, and the (*R*)-product favored by two other fungi. The decrease of sulfoxide yield with time, together with the increase of the enantiomeric excess (up to >95%) suggested that also in this case the stereoselectivity is in part due the overoxidation of the minority sulfoxide to sulfone.

Olivo and co-workers described a highly enantioselective oxidation of benzhydrylsulfanyl acetic acid **373** performed by the cultures of the fungus *Beauveria bassiana*.[499] The resulting sulfoxide was obtained in 89% yield and 99% *ee* and was further amidated using the bacteria *Bacillus niger* to give (*S*)-modafinil, (*S*)-**2** (68% yield). Interestingly, a direct oxidation of the appropriate amide by *B. bassiana* led to (*R*)-modafinil in 67% yield, but with low stereoselectivity (*ee* = 22%).



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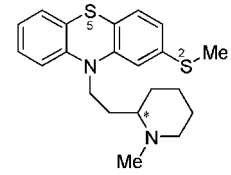

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Thioridazine **374**, a neuroleptic drug containing a phenothiazine ring, was subjected to sulfoxidation catalyzed by 12 different endophytic fungi.[500,501] Two sulfoxides (2-sulfoxide and 5-sulfoxide) were formed, which are also important metabolites of the drug. In general, the 2-oxidation was faster and led preferentially to the (*R*) configuration of the newly formed center.[500]

Holland and co-workers used different fungi for the bioconversion of substrates bearing both sulfide and carbonyl functions into products containing two chiral centers.[502,503] Here, β-ketosulfides were incubated with *Helminthosporium* sp. NRRL 4671, *Mortierella isabellina* ATCC 42613, and *Rhodococcus erythropolis* IGTS8. *M. isabelina* was capable of converting the widest range of substrates, giving yields in the range of 3−75% and *de* values up to 90%. The main products of type **307** had a (S_C, R_S) configuration, similar to those obtained with *Rhodococcus*. In contrast, use of *Helminthosporium* led to the hydroxysulfoxide bearing the (*S*) configuration on the sulfur atom.[503]

The microalgae *Chlorella sorokiniana* (*Chlorella vulgaris*) were already mentioned because of the use of their desaturating system.[491] As a nondesaturase oxidation of certain thiastearates had also been noticed, a series of alkyl aryl sulfides and several prochiral dialkyl sulfides was tested as the substrates for the 24-h incubation with the whole cells of *C. sorokiniana*.[472] Indeed, these sulfides were converted into the *S*-oxides with modest yields (1−67% conversion) and *ee*'s (up to 58%). A reversed enantioselectivity was observed between the alkyl aryl sulfides ((*R*)-sulfoxides were preferentially formed) and dialkyl ones (*S* product). Based on inhibition experiments, the participation of NADPH/H^+-dependent enzymes different from cytochrome P450 was believed to be responsible for the observed transformations.

In the enantioselective sulfoxide preparations with whole cells of bacteria, fungi, and algae, the diversity of oxidized sulfides is particularly remarkable. The pronounced substrate specifity exhibited by most systems suggests their restricted applicability.

2.4. Modification of Reaction Conditions

2.4.1. Nonaqueous Media

Two important limitations hinder the biotechnological applications of oxidative enzymes in the synthesis of chiral

sulfoxides.[504] Many sulfides, including thioanisole, which is commonly used as a model substrate, are sparingly soluble in water. This phenomenon can be responsible for the relatively low reaction rates observed for enzymatic sulfoxidations. Moreover, the enantiomeric purity of the desired product is sometimes lowered by the nonenzymatic (spontaneous) reaction of substrate with the oxidant (e.g., H_2O_2).

These problems can be at least in part overcome by simply changing the reaction medium. It is now well established that many enzymes retain their catalytic properties when switching the solvent from water to an organic one.[505−507] Such a change has a great impact on a structure and stability of a biocatalyst and on the catalytic action itself: the activity and selectivity of the enzyme are significantly altered. The stereochemical preference is strongly solvent dependent and can even be reversed from one solvent to another.[505] The use of organic media instead of water leads to suppression of undesired side reactions and increases the solubility of hydrophobic reactants. Along with the ease of recovery of some products and of insoluble biocatalyst, these advantages make nonaqueous systems an attractive alternative for water-conducted biotransformations.

Dai and Klibanov examined the sulfoxidation of thioanisole with hydrogen peroxide in several anhydrous organic solvents. They found that the rate of spontaneous reaction of these compounds is substantially lower than that in water (from 80 to over 1000 times).[504] For the sulfoxidation catalyzed with horseradish peroxidase, the highest enzyme activity (measured as the initial rate of product formation) was observed in alcohols, and the selectivity was highest in the branched alcohols, isopropanol and *tert*-butanol, as well as in methanol. Other heme proteins were also checked for their peroxidase reactivity in isopropyl alcohol. Soybean peroxidase, myoglobin, hemoglobin, and cytochrome *c* were all more active and selective in isopropyl alcohol than in water, but the improvement of their catalytic properties was not fully satisfactory.[504] Later, it was shown that the higher stereoselectivity can be achieved by the proper biocatalyst preparation.[508−510] The colyophilization of horseradish peroxidase with certain excipients (lyoprotectants) led to an increase of the ratio of the (*S*/*R*) formation rates. The best results were observed for tris(hydroxymethyl)aminomethane (Tris), which increased the stereoselectivity nearly 4 times for the HRP-catalyzed oxidation of thioanisole with TBHP performed in isopropanol.[508] In another experiment, a series of amino acids was colyophilized with HRP, and among them, D-proline was found to cause the maximal increase of the stereoselectivity of sulfoxidation in 2-propanol. A similar beneficial effect was observed for the complexation of HRP with hydrophobic hydroxamic acids.[511] In this case, however, the formation of both enantiomeric products is strongly inhibited, with the more pronounced effect found for the (*R*)-sulfoxide.

To increase the solubility of substrates, the thioanisole oxidation with hydrogen peroxide catalyzed by chloroperoxidase (CPO) from *C. fumago* was performed in aqueous solutions containing short-chain polyethylene glycols.[512] A complete enantioselective conversion (*ee* = 99%) to the (*R*)-sulfoxide was noted in the presence of PEG 200 and tri(ethylene glycol). In addition, the enzyme retained more of its initial activity, as it was protected from denaturation with H_2O_2.

Seven different hydrophilic ionic liquids were tested as cosolvents in the CPO-catalyzed sulfoxidation of thioanisole.[513] For three of them, 1,3-dimethylimidazolium dimethylphosphate, cholinium acetate, and cholinium citrate, all mixed with aqueous citrate buffer (1:1 v/v), it was possible to obtain (*R*)-sulfoxide in yields reaching 74% and high stereoselectivity (*ee* > 99%).

A comparison of the HRP-catalyzed thiosulfination of two disulfides **361** and **363** with hydrogen peroxide in aqueous and in methanolic solution showed that the use of alcohol increased the reaction rate.[466] This effect was, however, accompanied by a considerable lowering of stereoselectivity. Sulfide oxidations by three isolated Baeyer−Villiger monooxygenases, PAMO, HAPMO, and EtaA in water containing 30% of organic cosolvent, were also investigated.[437] While the activity of all enzymes was generally lower than that in buffer alone, the enantioselectivity of thioanisole conversion by PAMO and EtaA substantially increased when the reaction was conducted in methanol−water solution (*ee* changed from 43 to 89% and from 33 to 84%, respectively). For the other substrates tested, a similar effect of methanol addition was found, and for ethyl phenyl and propyl phenyl sulfides, this was accompanied by the change of the stereochemical preference of PAMO from (*S*)- to (*R*)-sulfoxide.

In some cases, the enzyme action can be improved by an appropriate modification which increases its activity in organic solvents.[506] Both chemical and genetic ways of biocatalyst optimization can be utilized. For instance, using random mutagenesis, Sheldon and co-workers achieved a 3.4-fold increase of the catalytic activity of chloroperoxidase in 40% aqueous *tert*-butanol.[514] The use of mixed water−organic solvents as media for enzymatic sulfoxidation should no longer be considered as an exotic idea, but rather as a useful means of tuning the course and effect of the catalytic reaction worth testing.

2.4.2. Enzyme Immobilization

The low operational stability of biocatalysts hampers their widespread application for industrially relevant chemical transformations, which may require quite "unnatural" conditions, such as elevated temperature or the use of organic solvents. Enzyme immobilization can serve as a suitable method of improving the robustness of the bioactive species. Attached to a support which provides the protecting environment, the biocatalysts are less prone to thermal and/or microbial degradation. For example, horseradish peroxidase fused with a cellulose-binding domain and bound to cellulose beads exhibited an increased half-life in buffer solution, and greater stability to organic solvents and elevated temperature.[515]

In addition, such an environment can have a beneficial influence on the partition of substrates and products, and it offers the possibility of enzyme recyclability. A biocatalyst can be recovered by centrifugation or filtration, hopefully without losing a significant amount of activity. Immobilization may improve the enzymatic activity by separating the biomolecules, which in some cases have a tendency to aggregate, especially when lyophilized enzyme powders are used in organic solvents.[516] On the other hand, the improper size of the pores and channels of the support used may cause limited access of substrates to the active sites of immobilized biocatalysts. This would imply a lower activity of the enzyme. This problem can be solved by using a material with a well-defined channel network, e.g. a mesocellular silicate applied for the immobilization of chloroperoxidase.[517]

Various techniques were used for the immobilization of biomolecules in inorganic and organic matrices, including chemisorption, encapsulation, covalent anchoring, and cross-linking. Among other methods, the sol−gel enzyme encapsulation received considerable attention due to the relative simplicity of the entrapment methods. Sol−gel matrices are prepared by hydrolytic polymerization of silicon alkoxide precursors under mild conditions. These silicon oxide glasses exhibit high chemical, mechanical, and thermal stability. Various enzymes were entrapped using this technique, showing an increased resistance to degradation and, in some cases, a considerably higher activity than that of nonimmobilized systems.[516]

Ferrer and co-workers studied the effect of horseradish peroxidase encapsulation by the sol−gel method on the catalytic activity of this enzyme in the asymmetric oxidation of thioanisole with H_2O_2.[518] For the reaction conducted in acetonitrile, they observed an increase of HRP stability (as measured by the value of the total turnover number), activity, and chemo- and stereoselectivity. (*S*)-Sulfoxide was obtained with 31% *ee*; this value can be compared with 11−15% obtained for free HRP. The stereoselectivity was further enhanced with the use of the tandem glucose oxidase−horseradish peroxidase system (56% *ee*).[518] In contrast, a reverse trend was observed for the oxidation of thioanisole and its *para*-substituted derivatives performed in the aqueous buffer solution.[519] A significant drop of the enantiomeric excess of dissolved HRP (91% at 22 °C, and 86% at 40 °C) after encapsulation (68% at 22 °C, and 43% at 40 °C) was noted, while the yield remained essentially the same. These observations were rationalized by the fact that silica gel itself catalyzes a nonenantioselective oxidation of sulfides, and this background reaction lowered the *ee* of the desired product.[519] However, this effect can be reduced by a careful selection of reaction conditions.[518]

Kadnikova and Kostić reported a comparison of the catalytic properties of microperoxidase-11 in solution and immobilized with various techniques.[520] Encapsulation, physisorption, chemisorption, or covalent attachment of the enzyme resulted in the increase of the yield of the sulfoxidation of thioanisole from 15% (free MP-11) to even 95%. However, in each case, the immobilization was connected with the lowering of enantioselectivity: the *ee* values did not exceed 30%, while for free enzyme in solution the (*S*)-sulfoxide with 36% *ee* was obtained. With the exception of the encapsulated species, the enzyme was recycled without a significant drop in activity, at least in the second cycle.

The immobilization of chloroperoxidase in a polyurethane foam was reported by Sheldon et al.[408,514] The supported enzyme mediated the oxidation of thioanisole to (*R*)-sulfoxide by H_2O_2 performed in 50% aqueous *tert*-butanol or by TBHP in isooctane saturated with water with *ee* exceeding 99%.[514] Coimmobilization of CPO with glucose oxidase into PUR foams resulted in a tandem heterogeneous catalyst efficient in enantioselective sulfoxidation of thioanisole by hydrogen peroxide generated from glucose and O_2.[408] In this case, 100% conversion with 99% *ee* and the increase of enzyme stability were reached. Also the catalytic performances of two other peroxidases, phytase and soybean peroxidase, were significantly improved by a similar procedure (increase of *ee* from 24 to 69%, and from 0 to 50%, respectively).[408] Chloroperoxidase was also encapsulated in xerogels and used as a catalyst in the oxidation of different aryl methyl sulfides, yielding 40−85% conversion and >99% *ee*.[521] The catalyst could be recycled up to four times without a significant loss of activity. Encapsulation of CPO in nanosized polymersomes assembled from polystyrene-*b*-poly(L-isocyanoalanine(2-thiophene-3-yl-ethyl)amide) resulted in a 50-fold increase of the enzyme concentration.[522] Consequently, the immobilized chloroperoxidase retained its high activity in the oxidation of thioanisole with high *ee* (99%). The kinetic studies indicated that the substrate molecules readily penetrated the membrane of nanoreactors; more bulky sulfides, however, were not examined in the study. In a recent contribution, Li and co-workers demonstrated the preparation of CPO-coated magnetic nanoparticles containing an iron oxide core and a polymer shell.[523] The resulting nanobiocatalyst, applied for the oxidation of thioanisole with H_2O_2, exhibited activity and enantioselectivity comparable to those of free enzyme (*ee* > 99%). In addition, it could be simply recovered with the external magnetic field and retained its activity after 11 cycles.

Coimmobilization of cyclohexanone monooxygenase with alcohol dehydrogenase (used for NADPH regeneration) into Eupergit C allowed the system to be used for up to 16 cycles with a complete conversion of thioanisole into (*R*)-sulfoxide.[420] Whole cells used for sulfide oxidation can be immobilized as well.[475] In order to improve the process of transformation of aryl methyl sulfides using *Aspergillus terreus*, chrysotile and cellulose/TiO_2 were tested as the support.[497] The immobilized cells retained their catalytic activity, even after 3 months of storage. Scanning electron microscopy showed that the cells were intertwined with the support fibers, providing the ease of their separation from the reactants and its further reuse.

The immobilization of biocatalysts can be regarded as an important method for overcoming their sensitivity, which is one of the factors limiting possible applications. The most attractive modifications ensure the increase of enzyme durability without the loss of activity and stereoselectivity, at least during the oxidation of model substrates.

2.5. New Developments. Artificial Metalloenzymes

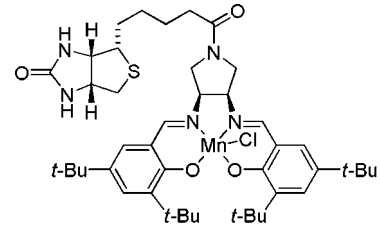
As can be seen from the previous section, significant performance improvements of the naturally occurring biocatalysts can be achieved by the proper modification of reaction conditions. However, protein engineering remains the principal method of construction of refined enzymes for chemical production.[524] In the field of enantioselective sulfoxidation, different variants of peroxidases,[394,514] monooxygenases,[439,442,448] and, in particular, myoglobins,[452−461] constructed using site-directed mutagenesis, exhibited significantly altered catalytic activity, stereoselectivity, and substrate specificity. Typically, the site of modification is planned on the basis of the available structural data concerning the active site of the enzyme. Another approach utilizes the random mutagenesis and screening of the large library of modified proteins for the enzymatic activity. In most cases, the mutations appear far from the active site of the biocatalyst, but they may change its thermal stability or tolerance toward organic solvents.[525] The chosen enzyme variants can be subjected to the subsequent mutation cycle, leading to the next generation of modified biocatalysts, which are again tested for the desired property (activity, selectivity, and stability). This idea of directed evolution, originally introduced in 1997 by Reetz and co-workers,[526] was applied in the optimization of various enzymes,[527,528] including oxidizing ones such as peroxidases[529] or monooxygenases.[530] In

2003, this approach was applied to the engineering of flavin monooxygenases that were used as sulfoxidation catalysts. Mutants that exhibited higher activity and the retained high enantioselectivity of the original wild-type rabbit FMO1 enzyme were identified.[531] Reetz and co-workers chose the cyclohexanone monooxygenase from *Acinetobacter* sp. NCIMB 9871 for the optimization procedure.[532] The wild-type enzyme, applied to the oxidation of the *p*-methylbenzyl methyl sulfide, led to the (*R*)-sulfoxide in 75% yield but only 14% *ee*. By screening of the 10 000-membered library, five mutants (two (*R*)- and three (*S*)-selective) that yielded *ee* values higher than 95% were identified. The high enantioselectivity was connected with the stereoconvergent kinetic resolution, which led to the formation of 5.6−26.6% of sulfone. To reduce this amount, a second evolutionary step was performed. A CHMO variant was identified with seven amino acid exchanges as compared with the wild-type enzyme, which catalyzed the (*S*)-sulfoxide formation in 99.8% *ee* and led to negligible (<5%) sulfone production. These results confirmed the utility of directed evolution to the improvement of enzymes used in stereoselective sulfoxidation.

Besides amino acid substitution, the new biocatalysts can be constructed *via* the covalent modification of existing proteins[533] or by introduction of various cofactors that may substantially change the enzymatic activity or even create it *ex nihilo*.[460,533,534] The most promising results were obtained with the use of metal complexes attached to the protein hosts by covalent or coordination bonds, as well as using supramolecular anchoring.[380,535−537] Such hybrid catalysts or artificial metalloenzymes could in principle inherit the important and desired features of biocatalysts (well-defined chiral environment, large chemo- and regioselectivity, mild reaction conditions) and homogeneous catalysts (large substrate scope and reaction repertoire, access to both enantiomers of product), hopefully without sharing their shortcomings. Actually, since the pioneering research of Kaiser[538] and Whitesides,[539] many research groups designed numerous hybrid catalysts that appeared effective in various types of transformations, including reactions unavailable by "ordinary" biocatalysts.[536]

The concept of artificial metalloenzymes was also applied for the preparation of nonracemic sulfoxides. Sheldon and co-workers, exploiting the similarity of the active site structures of vanadium haloperoxidases and phytase (*myo*-inositol-hexakisphosphate 3-phosphohydrolase), incorporated different oxoanions (MoO_4^{2-}, SeO_4^{2-}, VO_4^{3-}, WO_4^{2-}, ReO_4^-) into this enzyme isolated from *Aspergillus ficuum*, *Aspergillus fumigatus*, and *Aspergillus nidulans*.[354,540−542] The resulting semisynthetic peroxidase catalyzed the oxidation of thioanisole with hydrogen peroxide, yielding the (*S*)-sulfoxide with up to 55% *ee*, as observed for vanadate anion. Other vanadium-incorporated hydrolases (acid phosphatase, sulfatase) and other proteins (albumin, apoferritin) exhibited lower stereoselectivity. The selected catalyst was applied to the oxidation of various alkyl aryl sulfides, for which the corresponding (*S*)-sulfoxides were obtained with 28−65% *ee*. Vanadate-substituted phytase, immobilized by forming a cross-linked enzyme aggregate (CLEA), retained its activity and stereoselectivity and could be recycled at least three times.[542] Wever and co-workers demonstrated that vanadate-incorporated acid phosphatases from *Shigella flexneri* and *Salmonella enterica* ser. *typhimurium* expressed in *E. coli* catalyzed the enantioselective oxidation of thioanisole as well.[543] The enzymes led to the opposite enantiomers of methyl phenyl sulfoxide with *ee*'s in the range of 36−57%. On the other hand, the replacement of the zinc cation in the active site of thermolysin supported on Eupergit C by molybdenate or selenate anions did not result in peroxidase-like activity.[544] Only the incorporation of the tungstate(VI) anion WO_4^{2-} yielded a moderately active catalyst capable of thioanisole conversion into the racemic product.

Ward and co-workers incorporated vanadyl ion, VO^{2+}, into a biotin binding site of streptavidin.[545] The resulting hybrid catalyst appeared effective in the oxidation of methyl aryl sulfides and methyl cyclohexyl sulfide with TBHP, yielding (*R*)-sulfoxides of 46−93% *ee* (with the highest value obtained for the bulky methyl 2-naphthyl sulfide). Evidence provided by EPR measurements, mutagenesis studies, and computer docking simulation allowed identification of the residues responsible for vanadyl binding. On the basis of the structural model, a chimeric straptavidin bearing the fragment of avidin was prepared that preserved the vanadyl binding ability. The novel metalloenzyme exhibited enhanced stereoselectivity in the oxidation of thioanisole (60% *ee*) and cyclohexyl methyl sulfide (90% *ee*). The high affinity of streptavidin for biotin was recently applied to the construction of new sulfoxidation catalysts.[546] The biotinylated manganese(III) salen complexes **375** combined with several Sav mutants were only moderately active in the H_2O_2 conversion of thioanisole with a maximum *ee* value of 13%.



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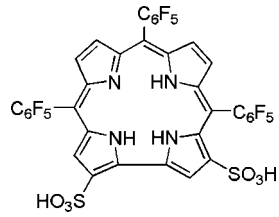
As described in section 2.2.3, serum albumins can catalyze the enantioselective sulfoxidation processes.[462−464,466] A significant improvement of their performance was achieved by Mahammed and Gross, who utilized the ability of these proteins to bind different guest molecules.[547] They used iron(II) and manganese(III) complexes of amphiphilic bis-sulfonated corrole **376**, which were shown to form 1:1 conjugates with different albumins (human, bovine, porcine, sheep, and rabbit serum albumins were tested). These artificial metalloenzymes catalyzed the enantioselective sulfoxidation of thioanisole derivatives and produced *ee*'s up to 74%. The Mn complexes exhibited higher activity, selectivity, and stability of the catalyst as compared with their Fe analogs. Iodosylbenzene and hydrogen peroxide were used as oxidants, with the latter resulting in lower sulfoxide yields but also in higher enantioselectivity. The recent report on the incorporation of Mn(III) salen complexes into HSA showed the ability of these assemblies to catalyze the oxidation of thioanisole by NaOCl with a high chemoselectivity, but only racemic sulfoxide was formed.[548]

The use of site-directed mutagenesis for the design of myoglobins as catalysts for enantioselective sulfoxidations was described in section 2.2.3. In addition, heme, the prosthetic group of Mb, can be replaced by another metalloporphyrin or by a quite different complex. Hayashi and co-workers reported an enhancement of the peroxidase

activity of horse heart Mb caused by modification of heme-propionate side chains.[549] Similarly, an iron complex of porphycene, a porphyrin isomer, caused a 5-fold acceleration of thioanisole oxidation as compared with wild-type Mb.[550] Unfortunately, the stereochemical outcome of these reactions was not discussed. Watanabe et al. described the use of achiral Cr(III) or Mn(III) Schiff bases **377** in the myoglobin-catalyzed sulfoxidations.[551−554] The unsatisfactory result obtained for thioanisole conversion with hydrogen peroxide and the conjugate of a chromium complex with a wild-type Mb (4.3% *ee*) prompted the authors to modify the structure of the binding pocket. Mutants were prepared with an increased access of substrate and oxidant to the metal ion, which resulted in an improvement of the *ee* value up to 13%.[551] Further modifications were supported by analysis of the crystal structures of the artificial metalloproteins.[552,553] The Schiff base Mn(III) and Cr(III) complexes **378** were obtained in which the phenylenediamine unit was substituted with ethylenediamine. This alteration resulted in an additional increase of the protein cavity and raised the enantiomeric excess up to 33%.[553] Interestingly, both enantiomers of the sulfoxide could be prepared with the use of either a Cr(III) or a Mn(III) complex.



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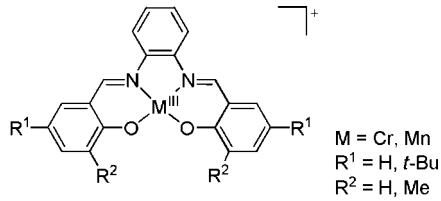

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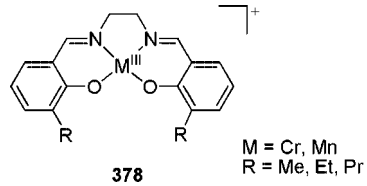

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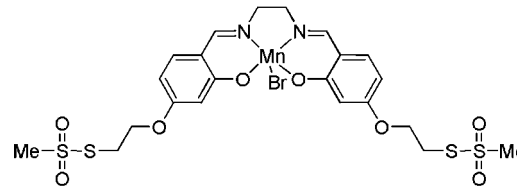
Watanabe's Schiff base complexes were held in the heme cavity by a coordination bond with a proximal histidine residue.[552,553] A covalent anchoring strategy was applied by Lu and co-workers, who prepared a Mn(salen) complex bearing methane thiosulfonate groups, **379**.[555] This compound was attached to one or two cysteine residues which were introduced into apoMb in the positions selected on the basis of computer modeling studies. The resulting hybrid catalysts were tested in the oxidation of thioanisole with aqueous hydrogen peroxide. An *ee* of 12.3% was observed for the Y103C mutant, providing a single-point binding, while the dual covalent attachment possible for L72C/Y103C and T39C/L72C variants resulted in a significant increase of both the reaction rate and the enantioselectivity (51% and 60% *ee*, respectively).[555,556] The polar and proton-donating environment surrounding the manganese cofactor was shown to be critical for enhancing its reactivity and chemoselectivity (no sulfone was detected for the T39C/L72C mutant).[556] The modulation of reactivity caused by an additional H64X mutation (X = R, F) proved the crucial role of distal axial histidine engaged in activation of a H_2O_2 molecule.[557]



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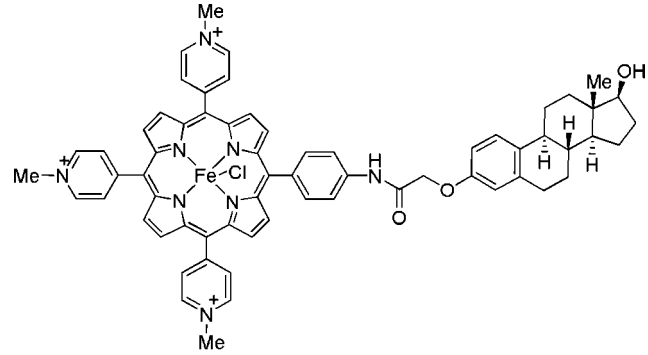
Hemoabzymes, catalytic antibodies with a metalloporphyrin cofactor,[558] were also appropriately modified for use in enantioselective sulfoxidation. A tin porphyrin hapten with an α-naphthoxy axial ligand was applied by Nimri and Keinan to raise a monoclonal antibody capable of specific binding of ruthenium porphyrin.[559] The resulting assembly catalyzed the transformation of alkyl aryl sulfides with iodosylbenzene, yielding (*S*)-sulfoxides with *ee*'s ranging from 20 to 43% (the latter value relates to thioanisole oxidation). A slightly higher enantiomeric excess (45% of (*R*)-methyl phenyl sulfoxide) was obtained by Mahy and co-workers with the 3A3 antibody−microperoxidase 8 (MP8) conjugate that was used for the sulfide oxidation with H_2O_2 conducted with the addition of 5% *tert*-butanol as cosolvent.[560] The use of MP8 alone led to a racemic product with a significantly lowered yield (23% vs 49%). This effect was connected with the protection of microperoxidase from degradation provided by antibody, which also provided a chiral environment that contributed to enantioselection. Similar effects were observed for a new iron porphyrin−estradiol conjugate, **380**, associated with an antiestradiol antibody 7A3.[561] The antibody not only prevented the cofactor from self-oxidation but also led to a nonnegligible enantioselectivity of the thioanisole oxidation by H_2O_2 (8% excess of *S*-sulfoxide). Mahy and co-workers prepared another artificial metalloprotein using a thermoresistant xylanase A, a protein of global positive charge and a wide enough active site to accommodate metalloporphyrins that possess negatively charged substituents.[562] A conjugate with (*meso*-tetra(*p*-carboxyphenyl)porphyrinato)iron(III), **381**, catalyzed the oxidation of thioanisole with H_2O_2 in 24% yield and 36% *ee*; the addition of imidazole improved these values to 85% and 40%, respectively, and resulted in the 3.5-fold increase of the turnover number of the catalyst. These results remain the best achievements obtained with hybrid catalyst containing an iron complex.



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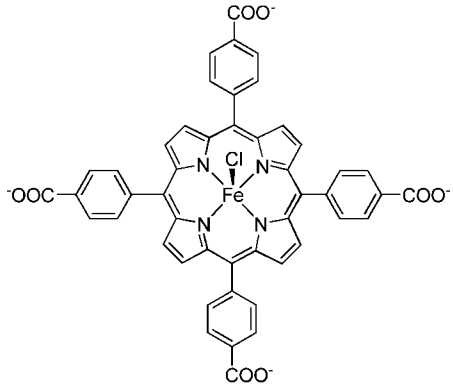

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As could be seen from these examples, both chemical (cofactor modification) and genetic methods (mutations) were applied for the optimization of artificial metalloenzymes. Quite recently, their improvement *via* directed evolution was also described.[563,564] As for now, the performance of these biocatalysts is inferior to that of the "classical" ones. In spite of this fact and the relatively high cost, which both preclude the direct practical application of hybrid catalysts, it is believed that they will be eventually applied in the pharmaceutical industry.[565]

2.6. Perspectives

The biological oxidations described in section 2 illustrate well the typical features of biocatalysts used for the preparation of chiral sulfoxides: high activity and chemo- and stereoselectivity connected with relatively low stability. Moreover, as part of new systems was only tested using thioanisole as a model sulfide, also their substrate scope remains unknown. However, significant progress has been made toward relatively cheap, versatile, and robust biocatalysts, including such approaches as enzyme immobilization, the use of mixed water−organic solvents, or construction of hybrid systems. Various research groups have explored the possibility of controlling the enzymatic activity *via* site-directed mutagenesis, which is more and more often associated with computer simulation based on the known structure of the active site (docking experiments). The relatively new concept of rational *de novo* design of biocatalysts has recently attracted considerable attention.[566,567] The possibility of the construction of a polypeptide with a more or less predicted structure that is tailored to perform the desired chemical transformation has not been, as far as we know, applied to the preparation of new sulfoxidation catalysts. However, new strategies should play an increasing role in the search for high-performance biocatalysts with potential application in the synthesis of nonracemic sulfoxides.

3. Conclusions

The great number of contributions published by numerous groups in the years 2000−2009 proves the unabated interest in the synthesis of nonracemic sulfoxides. Now, the chemist intending to prepare a new compound of this kind would face the *embarras de richesses*, having numerous synthetic methods at his or her disposal. Certainly, the choice of the appropriate procedure would be primarily dependent on personal laboratory experience. In most cases, a simple method using commercially available reagents would be preferred, especially when the sulfoxide is not a final synthetic goal. For the preparation of a series of compounds, a more versatile route accepting various substrates would be sought, while a more sophisticated technique can be applied for the preparation of one particular sulfoxide. In any case, several methods should be tested, as their utility for the specific, desired compound can be predicted only to a limited extent. And making the choice is only half of the way. The careful adjustment of the reaction conditions is then necessary to optimize the yield and the stereochemical outcome.

The comparison of methods used for the preparation of physiologically active sulfoxides is presented in Tables 5−7. The data for these compounds suggest a particular effectiveness of titanium reagents. This is mostly because much effort has been made to work out the optimized conditions under which these complexes could be applied, even on an industrial scale.[22−24,568] Nevertheless, we wish to stress that no synthetic method can be considered to be really universal. Each one has its advantages and disadvantages, especially when various aspects (not only the yield and stereoselectivity of the process) are taken into account. Accordingly, many challenges remain, and one can await further developments in the field of nonracemic sulfoxide synthesis.

Table 5. New Approaches to the Synthesis of Esomeprazole 1 *via* Oxidation of Sulfide 92

oxidation system	yield (%)	*ee* (%)	ref
oxaziridine **85**	78	40 (94)[a]	24
Ti(O-*i*Pr)$_4$/(*S*,*S*)-DET/CHP/Hünig's base	64	>94 (>99.5)[a]	24
Ti(O-*i*Pr)$_4$/(*S*,*S*)-DET/CHP/Hünig's base	78	97	156 and 157
Ti(O-*i*Pr)$_4$/(*S*,*S*)-DET/CHP/(*R*)-**101**	72	>99.5	163
Ti(O-*i*Pr)$_4$/**163**/TBHP	92	96	244
Ti(O-*i*Pr)$_4$/**166**/CHP	72	76	246
30-MnBF$_4$/PhIO	58	69	305

[a] After recrystallization.

Table 6. Syntheses of Modafinil 2 *via* Oxidation of the Corresponding Sulfide

oxidation system	yield (%)	*ee* (%)	ref
Ti(O-*i*Pr)$_4$/(*S*,*S*)-DET/CHP/Hünig's base	88.4	>99.8 (*R*)	25
oxaziridine **16**, CCl_4	66	60 (*S*)	155
oxaziridine **16**, [bmim][PF_6] **91**	73	55 (*S*)	155
[VO(acac)$_2$]/Schiff base (*S*)-**192**/H_2O_2	45	12 (*R*)	155
Fe(acac)$_3$/Schiff base (*S*)-**192**/H_2O_2	10	15 (*R*)	155
30-MnCl/H_2O_2	40	18 (*S*)	155
Beauveria bassiana cultures	67	22 (*R*)[a]	499

[a] (*S*)-Isomer prepared in >99% *ee* via oxidation of sulfide **373** and its amidation.[499]

Table 7. Preparations of Sulindac (*R*)-97

synthetic method	*ee* (%)	ref
oxidation of sulfide **98** with Ti(O-*i*Pr)$_4$/(*S*,*S*)-DET/CHP, followed by 3 synthetic steps	91	159
oxidation with Ti(O-*i*Pr)$_4$/(*S*,*S*)-HB/TBHP, followed by hydrolysis of esters **121**	94−96	179
oxidation of **358** with Fe(acac)$_3$/Schiff base (*S*)-**192**/H_2O_2	58	313
oxidation of **358** with Fe(acac)$_3$/Schiff base (*S*)-**192**/H_2O_2 with the addition of 4-methoxybenzoic acid	92	313
oxidation of **358** with microsomes	up to 97	444

4. Abbreviations

ABZ	albendazole
acac	acetylacetonate
AOX	alcohol oxidase
BINOL	1,1′-bi-2-naphthol
Bn	benzyl, $C_6H_5CH_2-$
Boc	*tert*-butoxycarbonyl
bpy	2,2′-bipyridyl
BSA	bovine serum albumin
Bu	*n*-butyl, C_4H_9
BVMOs	Baeyer−Villiger monooxygenases
Cbz	benzyloxycarbonyl
CD	circular dichroism
α-CD	α-cyclodextrin
CHMO	cyclohexanone monooxygenase
CHP	cumyl hydroperoxide
CiP	*Coprinus cinereus* peroxidase
Cp	cyclopentadienyl
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
CPO	chloroperoxidase
DAG	diacetone-D-glucose
DAOx	D-amino acid oxidase
de	diastereomeric excess
DET	diethyl tartrate
$(DHQ)_2PHAL$	hydroquinine 1,4-phthalazinediyl diether
$(DHQD)_2PHAL$	hydroquinidine 1,4-phthalazinediyl diether
$(DHQ)_2PYR$	hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether
$(DHQD)_2PYR$	hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether
DIBAL-H	diisobutylaluminium hydride
DMDO	dimethyl dioxirane
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EDTA	ethylenediaminetetraacetate
Et	ethyl, C_2H_5
EtaA	ethionamide monooxygenase
FBZ	fenbendazole
FMN	flavin mononucleotide
FMO	flavin-containing monooxidase
G6PDH	glucose-6-phosphate dehyhdrogenase
GOX	glucose oxidase
HAPMO	4-hydroxyacetophenone monooxygenase
HB	hydrobenzoin, 1,2-diphenyl-1,2-ethanediol
HRP	horseradish peroxidase
HSA	human serum albumin
*i*Bu	isobutyl
Im	imidazolyl
*i*Pr	isopropyl
Mb	myoglobin
MCM 41	mesostructured montmorillonite
*m*CPBA	*meta*-chloroperbenzoic acid
MeOPEGOH	polyethylene glycol monomethyl ether
Mes	mesityl, 2,4,6-trimethylphenyl
MOC	methoxycarbonyl
MOM	methoxymethyl, CH_3OCH_2
MP	microperoxidase
NDO	naphthalene dioxygenase
OTf	triflate, trifluoromethanesulfonate
PAMO	phenylacetone monooxygenase
PEG	polyethylene glycol
Ph	phenyl, C_6H_5
Pr	propyl, C_3H_7
PUR	polyurethane
rAPX	pea cytosolic ascorbate peroxidase
salalen	1-(*N*-salicylamine)-2-(*N*-salicylimine)ethane
salan	*N*,*N*′-ethylenebis(salicylamine)
salen	*N*,*N*′-ethylenebis(salicylimine)
Sav	streptavidin
SBP	soybean peroxidase
s-Bu	*sec*-butyl
$scCO_2$	supercritical carbon dioxide
TADOOH	[(4*R*,5*R*)-5-[(hydroperoxydiphenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl]diphenylmethanol
t-Bu	*tert*-butyl
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TDO	toluene dioxygenase
TEMPO	2,2,6,6-tetramethylpiperidyne-1-oxyl
THF	tetrahydrofuran
THP	trityl hydroperoxide
$Ti(O\text{-}iPr)_4$	titanium tetraisopropoxide
TIPS	triisopropylsiloxymethyl
TMO	toluene monooxygenase
T4MO	toluene 4-monooxygenase
p-Tol	*p*-tolyl
TOM	toluene *o*-monooxygenase
Ts	tosyl, *p*-toluenesulfonyl
Ty	tyrosinase
UHP	urea hydroperoxide
VBPO	vanadium bromoperoxidase
VCPO	vanadium chloroperoxidase
WT	wild-type

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