Recent Developments in the Synthesis and Utilization of Chiral Sulfoxides

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I. Introduction

The interest in chiral tricoordinated sulfur compounds in general, and sulfoxides in particular, has shifted from purely academic, directed toward the study of their stereochemical behavior,[1] to a well-established applied synthetic interest. This shift is due to the discovery, at the beginning of the 1980s, that chiral sulfoxides are efficient chiral auxiliaries that are able to bring about important asymmetric transformations.[2] Therefore, the past two decades have witnessed an exponential use of these chiral auxiliaries in asymmetric synthesis, establishing the chiral sulfinyl group as one of the most efficient and versatile chiral controllers in C−C and C−X bond formations.

There are basically three factors that form the basis of the success and effectiveness of the sulfinyl group as a chiral controller: (i) its high optical stability, (ii) its efficiency as a carrier of the chiral information, and (iii) its accessibility in both enantiomeric forms.

(i) In general, the thermal stereomutation of sulfoxides occurs at a significant rate only at about 200 °C, as indicated by the values of the activation parameters of the pyramidal inversion determined for various sulfoxides[3] [from 35 to 42 kcal/mol for $\Delta H^{\#}$, and from −8 to +4 cal/(mol K) for $\Delta S^{\#}$]. There are a few exceptions, such as benzyl and allyl sulfoxides, whose racemization occurs at lower temperatures (130−150 and 50−70 °C, respectively).

(ii) The large stereoelectronic differences between the three substituents at the sulfinyl sulfur—the lone pair of electrons, the oxygen atom, and two alkyl or aryl groups—allow the creation of a well-defined chiral environment around the sulfur atom.[4] Additionally, the polarized S−O bond, with a net positive charge on sulfur, allows both the oxygen and sulfur atoms to coordinate to Lewis acids and transi-

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Inmaculada Fernández was born in Seville, Spain, in 1961. She graduated in chemisttry from the University of Seville (1984), where she obtained her Ph.D. degree (1988) working with Prof. Felipe Alcudia and Prof. Francisco Zorilla on conformational analysis of sulfur compounds. She was subsequently awarded a NATO fellowship and carried out postdoctoral work with Prof. Guy Solladié at the Ecole Européenne des Hautes Etudes des Industries Chimiques de Strasbourg (EHICS), France, working on the total asymmetric synthesis of (–)-aspicillin. In 1990, she took her position as Tenured Professor at the Faculty of Pharmacy at the Universtiy of Seville. She was a visiting Professor (1993–1995) at the Universidad Autonoma de Madrid, Spain, working with Prof. José Luis García-Ruano on the chemistry of chiral sulfinylimines. Her research interests include organic synthetic chemistry and asymmetric synthesis.

Noureddine Khiar was born in 1960 in Khouribga, Morocco, and in 1980 he moved to Strasbourg, France. He was educated mainly at the Université Louis Pasteur, France, where he received his B.S. (1983), his M.S. (1985), and his Ph.D. degrees (1989), the later at the Ecole Européenne des Hautes Etudes des Industries Chimiques de Starsbourg (EHICS) under the guidance of Prof. Arlette Solladié-Cavallo, working on asymmetric synthesis of hydroxy amino acids. In 1990, he carried out postdoctoral work at Kansas State University with Prof. Duy H. Hua. In 1991, he moved to the University of Seville (Departamento de Química Orgánica y Farmaceútica), where he started working on the asymmetric synthesis of chiral sulfoxides (1991–1992) with Prof. Felipe Alcudia. Without leaving totally the area of sulfoxide chemistry, he moved to Madrid to work on oligosaccharide synthesis (1993–1996) at the Instituto de Química Orgánica General (CSIC) with Prof. Manuel Martín-Loma. Back to Seville, to the newly created Instituto de Investigaciounes Químicas (CSIC), he took in 1998 his position as Científico Titular (Tenured Scientist) in the Spanish Reseach Council, Consejo Superior de Investigaciones Cientificas (CSIC). His main research interests are the design and development of new stereoselective reaction methods, asymmetric catalysis, synthesis of natural products, and carbohydrate chemistry.

tion metals, leading to highly rigid and ordered transition-state geometries that permit effective transfer of the chiral information to the α, *β*, or more distant positions.[5]

(iii) The synthesis of chiral nonracemic sulfoxides with high enantiomeric purity has been a subject of constant interest over the past two decades.[7−10] A real breakthrough occurred in the synthesis of chiral sulfoxides at the beginning of the 1990s, when various new methodologies appeared. The new methods allow access to a large number of sulfoxides with different steric and stereoelectronic characteristics, generally in both enantiomeric forms.

Actually, a number of reviews dedicated to the utilization of sulfoxides in numerous asymmetric reactions are available in the literature. These include Michael addition,[11] C−C bond formation,[12,13] carbonyl reduction,[14] Diels−Alder reaction,[15−18] and radical addition.[19,20] These reviews, as well as others dedicated to the utilization of chiral sulfoxides in the synthesis of biologically active molecules,[21,22] should be consulted for details and considered as complementary to this article, as it is not the purpose of this article to review the general chemistry of chiral sulfoxides. The aims of this article are the following: (i) To give an accurate summary of all the recent developments in the preparation of optically pure sulfoxides, mainly from 1992 to date. (ii) To review in detail the recent utilization of chiral sulfoxides in metal-catalyzed enantioselective reactions and in stoichiometric transition-metal-promoted asymmetric reactions. This represents one of the most promising recent applications of chiral sulfoxides and has not been reviewed yet. (iii) To discuss some recent work directed toward the utilization of chiral sulfoxides on solid phases.

On the other hand, a number of biologically significant molecules have in their structure a stereogenic sulfinyl sulfur atom[23] and therefore exist as a pair of enantiomers which may exhibit differential stereochemically dependent metabolism and enzyme inhibition. Due to the FDA policy statement regarding the development of new stereoisomeric drugs,[24] both enantiomers of pharmaceutically interesting chiral sulfoxides need to be synthesized and their biological activity determined.

This important aspect of sulfoxides has been missing from nearly all the monographs discussing the synthesis and utilization of chiral sulfoxides,[25a] even though the world's highest selling drug in 2000 ($6.2 billion U.S.) was the chiral sulfoxide **1**.[25b] Omeprazole **1** (Figure 1), which is marketed under the names of Losec and Prisolec, is the leading gastric proton pump inhibitor (PPI) used as an antiulcer agent. Consequently, a large number of pharmaceutical companies seek to develop their own gastric acid secretion inhibitors based on the framework of omeprazole (Figure 1),[26] and actually some of them are clinically used PPIs (**2**−**4**, Figure 1). In recent years there has been great interest in the synthesis of optically pure (*S*)-omeprazole (esomeprazole) in relation of the chiral switch to single enantiomer launching of omeprazole.[25a,27] Accordingly, esomeprazole (*S*-**1**, Figure 1) was launched throughout Europe in August 2000 and in the United States in February 2001 under the trade name of Nexium as new PPI. Among the other biologically active sulfoxides, it is worth mentioning (Figure 2) the amino acid sulfoxides of

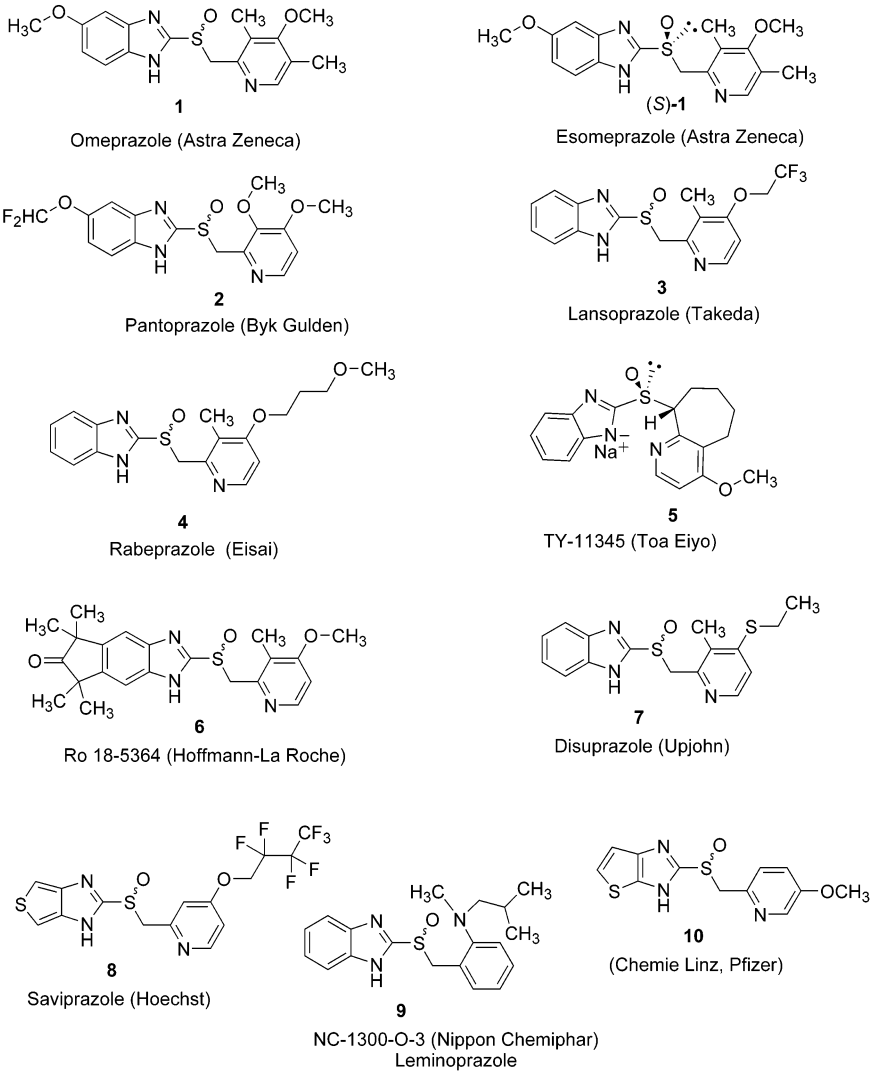


Figure 1.

type **11**, which have demonstrated a wide range of biological activities. These include flavors and aroma precursors as well as the regulation of cholesterol catabolism and antibiotic activities.[28] Other important sulfoxides include the inhibitor of uric acid biosynthesis BOF-4272 (**12**),[27] the ACAT inhibitor RP 73163 (**13**),[28] the potassium channel activator Aprikalim (**14**),[29] the calcium channel antagonists (**15**),[30] the anticancer drugs sulforaphane (**16**),[31] and sparsomycin (**17**),[32] sulfoxide complexes type **18** and **19**,[33,34] the immunosuppressor oxisurane (**20**),[35] and finally, the platelet adhesion inhibitor **21** (OPC-29030).[36]

The review is organized into 16 sections, where all the methods producing chiral sulfoxides actually available (excluding resolution) are discussed in-depth in the first sections. Those methods based on the asymmetric oxidation of prochiral sulfides are given in sections II−VII, and those based on nucleophilic substitution on chiral sulfur derivatives are discussed in sections VIII and IX. Aiming to show the synthetic usefulness of each method, an application part is included with a special emphasis on the synthesis of some of the significant molecules presented in Figures 1 and 2. Subsequently, and after a general discussion on metal−sulfoxide bonding, the utilization of sulfoxides as chiral ligands in metal-catalyzed enantioselective catalysis is given in section XI, pursued by the utilization of sulfoxides as chiral auxiliaries in various processes promoted by transition metals (section XII). Finally, the preliminary works recently developed on the utilization of sulfoxides on solid supports are included in section XIII, preceding the ultimate section of concluding remarks and future directions.

II. Diastereoselective Sulfoxidations

Various groups have been trying to develop efficient methods of asymmetric oxidation of sulfides to optically pure sulfoxides, considered as the most direct synthetic route for this type of compounds. In this way, several optically pure sulfoxides have been obtained by either diastereoselective or enantioselective oxidation of sulfides. In the former approach, the diastereoselectivity achieved has been generally accounted for by invoking either steric- or neighboring-group participation.[39] The basic process makes use of the proximity of a defined chiral center to relay stereochemistry to the newly formed sulfoxide. Ohta reported the diastereoselective oxidation of aryl sulfides to aryl sulfoxides. By using the directing

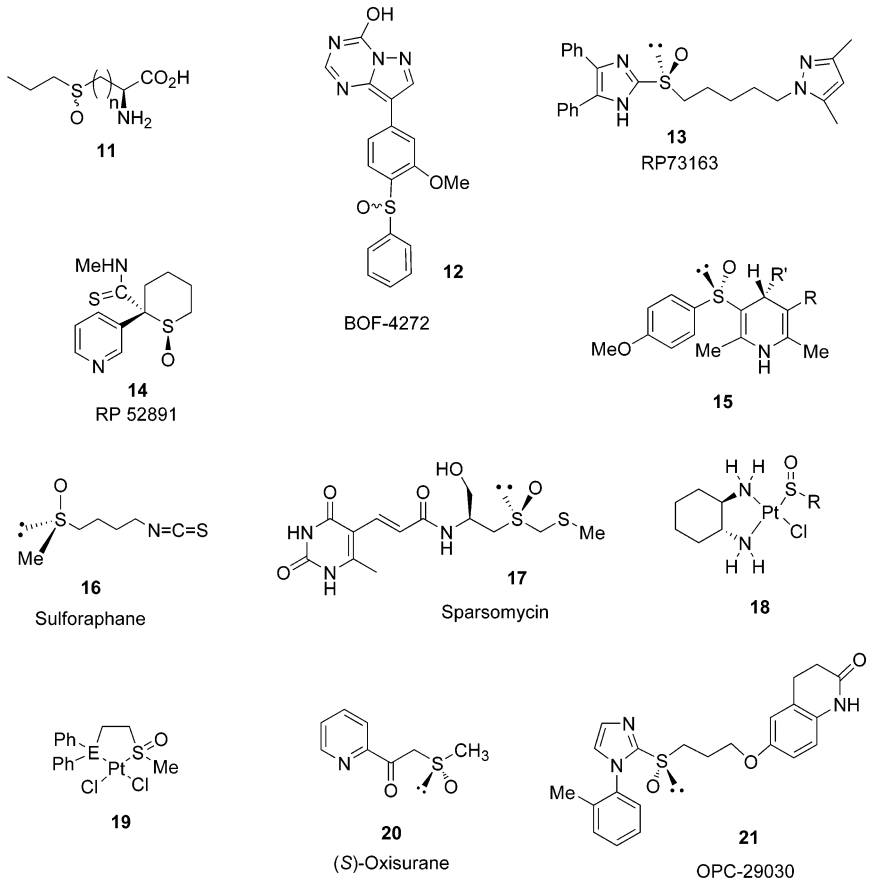
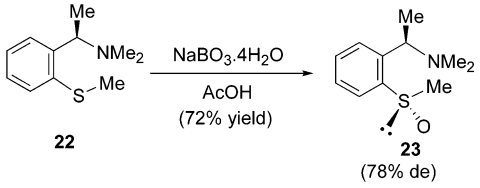


Figure 2.

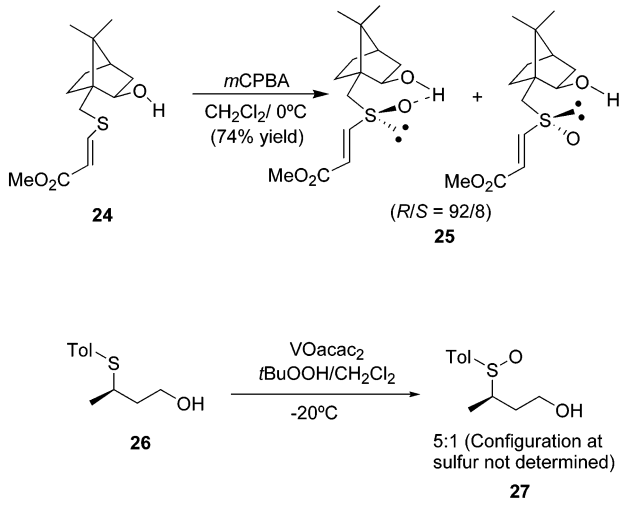
effects of ortho-substituents, these sulfoxides could be designed as chiral ligands for catalytic asymmetric synthesis. It was found that perborate oxidation of the optically active sulfide **22** (Scheme 1), prepared

Scheme 1



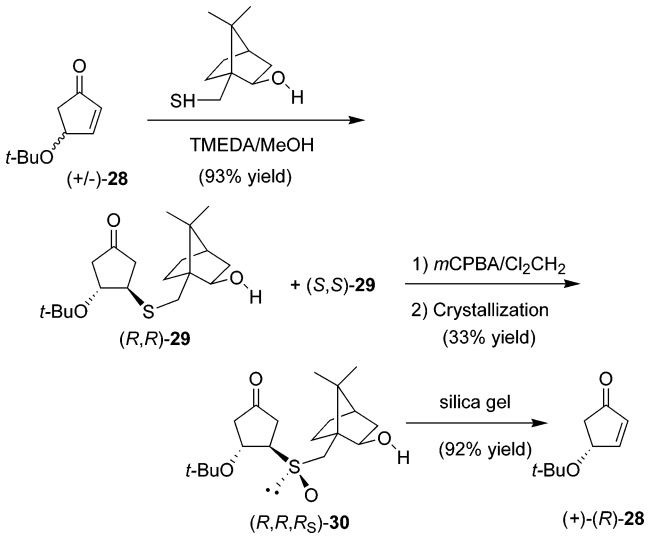
from α-methylbenzylamine by ortho-lithiation and disulfide quench, affords with moderate diastereoselectivity (up to 78% diastereomeric excess, de) the (*R*)-sulfoxide **23**.[40] Interestingly, organic peracids were ineffective as diastereoselective oxidant to obtain **23**. A properly positioned hydroxyl group has been frequently used as a diastereocontrol bias to deliver the electrophilic oxygen of a peracid to the prochiral thioether. De Lucchi applied this principle to direct the diastereoselective oxidation of 10-*exo*-hydroxybornyl derivative **24** for the synthesis of vinyl sulfoxides **25** (Scheme 2).[41,42] Similarly, Seebach and Breitschuh utilized the hydroxyl substituent to direct the oxidation of acyclic hydroxysulfide **26** to the corresponding sulfoxide **27** in 80% de (Scheme 2).[43] An incipient hydrogen bonding between the substrate hydroxyl group and the incoming percarboxylic acid has been proposed,[44] and this is in concordance with the loss of stereoselectivity in the oxidation of **24** with

Scheme 2



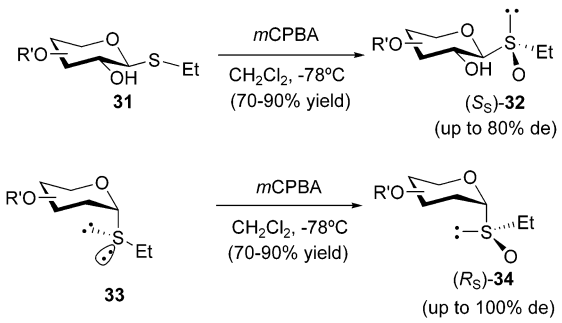
m-CPBA in MeOH or acetone. It is interesting to mention that sulfoxides of type **25** have been shown to be good chiral dienophiles and chiral acceptors in asymmetric Diels−Alder and Michael addition reactions, respectively. Haynes elegantly applied De Lucchi's method in order to resolve racemic 4-*tert*-butoxycyclopentanone **28** (Scheme 3). This was accomplished via a three-step, high-yielding sequence: Michael addition of (−)-10-mercaptoisoborneol to the enone, diastereoselective oxidation of the resulting sulfide **29** followed by recrystallization of sulfoxide **30**, and finally silica gel elimination of the sulfoxide to afford (*R*)-(+)-4-*tert*-butoxycyclopentanone (*R*)-**28**.[45]

Scheme 3



Studies on the diastereoselective oxidation of various thioglycosides have shown that diastereoselection is variable (0−95% de), depending mainly on the stereochemistry of the anomeric carbon (α or β) and on the substituent at the C-2 position in β anomers (Scheme 4).[46]

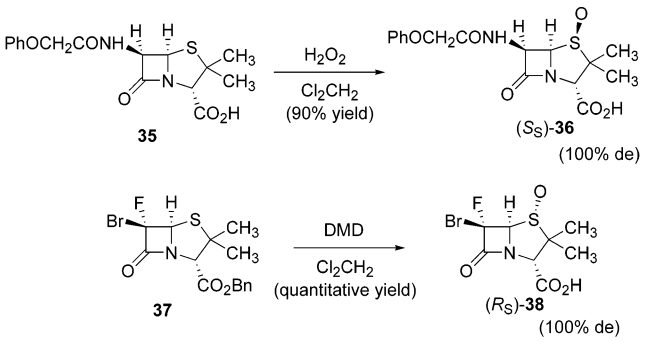
Scheme 4



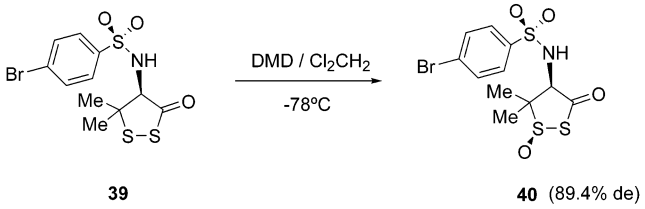
The high diastereoselectivity observed in the synthesis of β-sulfinyl glycosides **32**, with a free OH at C-2, has been rationalized by a hydrogen bonding and the predominance of the exo-anomeric conformation of the starting thioglycoside **31** (Scheme 4).[47] The exo-anomeric effect is also responsible for the high diastereoselectivity observed in the case of α-thioglycosides **33**. In the exo-anomeric conformation, only the *pro-R* Lp of the sulfide is accessible for the peracid, thus affording (R_S)-sulfinyl thioglycosides **34** as a single isomer (Scheme 4).[48]

Neighboring-group participation has also been observed in the case of well-positioned amido proton. This effect has been widely used for the synthesis of β-lactamic compounds, penicillin and cephalosporin.[49] The oxidation of 6-acetamido penicillin type **35** afforded exclusively the (S_S)-isomer (*S*)-**36**, in contrast to the oxidation of 6-halopenicillin derivatives **37**, which afforded only the R_S derivatives (*R*)-**38** as a result of steric constraint (Scheme 5).[50] Glass reported on a high diastereoselective oxidation (18:1) of 1,2-dithiolan-3-one **39**, bearing a sulfonamide group at the 4-position, in favor of the cis-isomer **40** (Scheme 6).[51]

Scheme 5

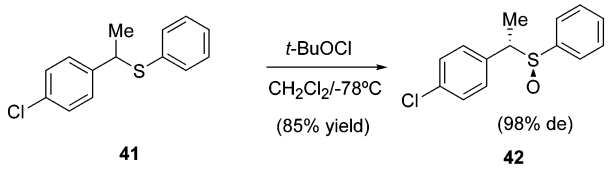


Scheme 6



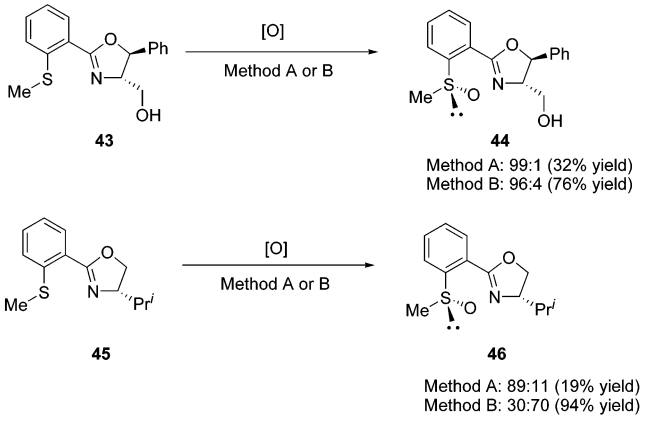
The asymmetric oxidation of acyclic sulfides without neighboring-group participation is more challenging. Otera reported a remarkably high diastereoselective oxidation of acyclic aryl sulfide type **41** using ^{t}BuOCl as oxidant. In contrast, oxidations using *m*-CPBA and $NaIO_4$ were each slightly diastereoselective in favor of the opposite diastereoisomer of **42** (Scheme 7).[52]

Scheme 7



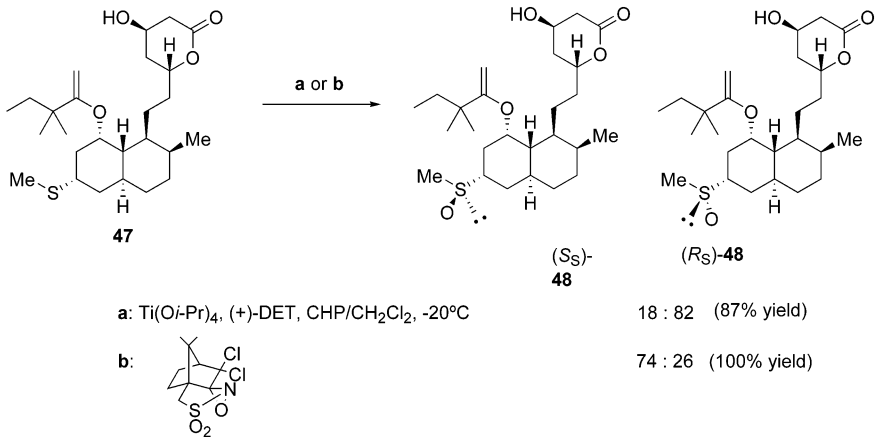
Finally, some of the established enantioselective oxidation systems which will be discussed in the following section have been used to achieve what is, in effect, a diastereoselective oxidation. In this sense, the use of modified Sharpless asymmetric epoxidation conditions in the oxidation of **43** gives slightly higher diastereoselectivity for the production of hydroxysulfoxides **44** than *m*-CPBA (Scheme 8).[53] It is notewor-

Scheme 8[a]



[a] Method A: TBHP/(+)-DET/Ti(O-*i*-Pr)$_4$. Method B: *m*-CPBA.

Scheme 9

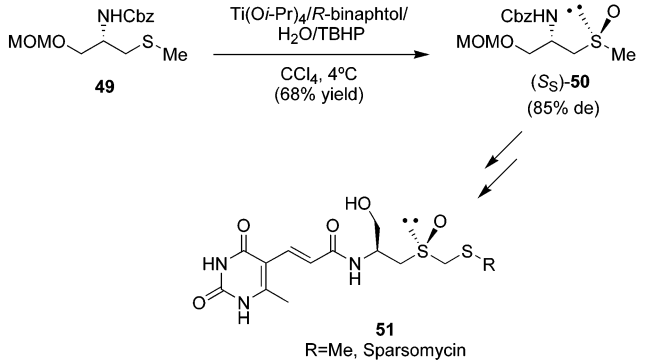


thy that the oxidation of a related thioether tethered to the dihydrooxazole moiety **45** afforded the corresponding sulfoxides **46** with lower diastereoslectivity (Scheme 8), demonstrating the role of the hydroxyl group in the diastereoselection.[54]

Similar reaction conditions also give moderate diastereoselectivity (64%) in the preparation of the novel 6-sulfinyl tetrahydromevinic acid (R_S)-**48** from the corresponding thioether **47** (Scheme 9). The diastereomeric sulfoxide (S_S)-**48** can be prepared by oxidation using an oxaziridine as oxidant (vide infra),[55] but in only 48% de.

Recently, Ubukata's group applied Uemura's enantioselective approach (see section IV.B) for the diastereoselective synthesis of sparsomycin(Scheme 10).[56]

Scheme 10



Sparsomycin **17** (Figure 2) is a unique antibiotic that exhibits antibiotic activity against a variety of gram-positive bacteria; it also shows potent antitumor activity against the KB human epidermoid carcinoma cell in tissue culture.[57] Using Ti(O*i*-Pr)$_4$/(*R*)-(+)-binaphthol/H_2O/TBHP in 0.1:0.2:2:2 ratio, oxidation of **49** afforded the desired (S_S)-sulfoxide (*S*)-**50** in 68% yield and 85% de. Sulfenylation of (*S*)-**50** with various disulfides ultimately led to natural sparsomycin and to sparsomycin analogues **51** (Scheme 10). Interestingly, these authors also reported the synthesis of the (S_S,R_S)-**52** and (S_S,S_S)-**52** bis-sulfoxides, analogues of sparsomycins, named sparoxomycin A_1 and A_2, respectively (Figure 3). These compounds were found to convert the transformed morphology of temperature-sensitive mutant Rous sarcoma virus-infected NKK cells to normal morphology, at a wide range of concentrations, without cytotoxicity.[58]

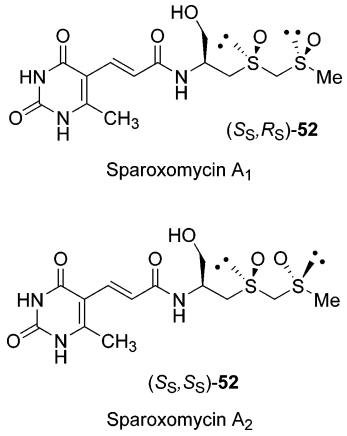


Figure 3.

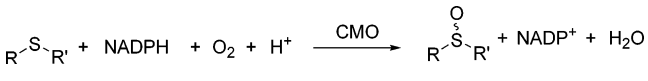
III. Enantioselective Biological Sulfoxidations

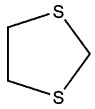
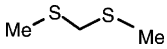
The enantioselective oxidation of a prochiral sulfide is undoubtly the most direct and economical method for the synthesis of enantiomerically pure sulfoxides. It is not surprising that this area has been, and still is, a very active area of research. Nevertheless, most of the pursued sulfoxides are nonfunctionalized. The difficulty thus stems from developing efficient enantioselective methodologies for the oxidation of nonfunctionalized substrates. To control a possible molecular recognition for an efficient oxidation process, enzymatic approaches as well as chemical reagents that act in the same manner as enzymes have been developed. The promising results obtained in biological sulfoxidation in the past decade suggest that this approach will be of synthetic interest in the future. Both isolated enzymes and whole cells have been used in the enantioselective oxidation of prochiral sulfides.[59−63]

A. Enzyme-Catalyzed Sulfoxidation[28]

Isolated enzymes were used in the oxidation of prochiral sulfides for the first time by Walsh et al at the beginning of the 1980s.[64] The use of pig liver FAD-dependent mono-oxygenase afforded (*R*)-ethyl *p*-tolyl sulfoxide in 90% enantiomeric excess (ee), while flavin-containing cyclohexanone mono-oxygenase (CMO) from *Acinetobacter* afforded the opposite enantiomer with 64% ee. In a series of papers, Colonna's group has shown that CMO is the most

Table 1. Enantioselective Cyclohexanone Mono-oxygenase (CMO)-Catalyzed Oxidation of Sulfides



R	R′	yield (%)	ee (%)	sulfoxide configuration
Ph	Me	88	99	*R*
p-FC_6H_4	Me	91	92	*R*
Ph	Et	86	47	*R*
p-FC_6H_4	Et	96	93	*S*
Ph	*i*-Pr	93	3	*S*
t-Bu	Me	98	99	*R*
		81[a]	>98	*R*
		94[a]	>98	*R*
		92[a]	>98	*R*

[a] Monosulfoxides.

effective and general enzyme for the enantioselective synthesis of sulfoxides (Table 1).[65−68] The stereochemical outcome of the enzymatic reactions has been shown to be highly dependent on the sulfide structure. Accordingly, for alkyl aryl sulfides the optical purity of the products ranges from 99% ee for the (R_S)-methyl phenyl sulfoxide to 93% ee for (S_S)-ethyl *p*-fluorophenyl sulfoxide (Table 1).[65] The method is particularly suitable for the preparation of (*R*)-*tert*-butyl methyl sulfoxide (99% ee), as well as for the enantioselective mono-oxidation of dithioacetals (Table 1).[68] An interesting feature of this approach is the use of a second enzyme to regenerate the expensive cosubstrate NADPH, thereby allowing the use of NADPH in catalytic quantity, lowering the cost of the operation. The regenerating system used was either glucose 6-phosphate and glucose 6-phosphate dehydrogenase or L-malate and malic enzyme.

Peroxidases are another important class of enzymes that are able to catalyze sulfoxidation. To date, the most versatile one is a chloroperoxidase from *Caldariomyces fumago* (CPO), isolated in 1961 by Hager,[69] and used for the first time in enantioselective sulfoxidation by Kobayashi, although in low ee (13%).[70] As shown by Colonna's group, H_2O_2 is the best oxidant for CPO-catalyzed enantioselective sulfoxidation, promoting the synthesis of optically pure sulfoxides with high yield and selectivity.[71,72] However, significant uncatalyzed oxidation of the sulfide (10−30%) was observed in blank reactions without catalyst, lowering the enantioselectivity of the enzymatic oxidation. Traces of metal oxides, known to catalyze oxidation of sulfides, have been invoked to explain the oxidation in blank reactions. Interestingly, Sheldon's group recently reported experimental conditions which avoid the uncatalyzed oxidation in water, obtaining enantiopure sulfoxides in water, as well as in a *tert*-butyl alcohol/water mixture (Table 2).[73]

Table 2. Enantioselective Oxidation of Sulfides, R_1SR_2, by Chloroperoxidase (CPO) and H_2O_2[73]

	sulfide		*t*-BuOH/buffer (50:50 v/v)		buffer	
entry	R_1	R_2	convrsn (%)	ee (%)	convrsn (%)	ee (%)
1	Ph	Me	73	99	100	99
2	Ph	Et	52	99	83	99
3	Ph	Pr	1	60	3	27
4	*p*-Tol	Me	66	99	83	99
5	*p*-$MeOC_6H_4$	Me	50	99	53	99
6	*m*-$MeOC_6H_4$	Me	19	99	37	99
7	*o*-$MeOC_6H_4$	Me	2	99	3	99
8	*p*-BrC_6H_4	Me	46	99	15	99
9	*m*-BrC_6H_4	Me	22	99	11	99
10	2-thienyl	Me	91	99	100	99
11	2-(1,3-thiazolyl)	Me	80	99	100	99

A detailed study by Wong's group of the chloroperoxidase-catalyzed oxidation of *para*-substituted alkyl phenyl sulfides by hydrogen peroxide or racemic alkyl hydroperoxides as oxidant in aqueous buffer[74] showed that slow addition of H_2O_2 to the reaction mixture afforded nearly enantiopure sulfoxides (97−99% ee). Interestingly, when racemic alkyl hydroperoxides were used as the oxidants, optically active alcohols and alkyl hydroperoxides were obtained as byproducts (Scheme 11).

Some aromatic bicyclic sulfides have recently been oxidized in high ee (up to 91%) by a vanadium-containing bromoperoxidase (VBrPO) from the alga *Corallina officinalis*.[75] It is interesting to note that the VBrPO produces the (*S*)-bicyclic sulfoxide **53**, with the stereochemistry opposite to that obtained with heme-containing chloroperoxidase (CPO) from *Caldariomyces fumago* (Scheme 12). The enantioselectivity observed was not the result of a kinetic resolution, as no overoxidation to sulfone was detected.

Other heme-peroxidases were found to catalyze the enantioselective sulfoxidation of alkyl aryl sulfides. These include horseradish peroxidase (HRP),[76,77] cytochrome *c* peroxidase (CcP),[78] microsome peroxidase (MP),[79] lactoperoxidase (LPO),[80] and dioxygenase.[81] Yet, their turnover numbers (TONs) and enantioselectivities were lower than those observed with CPO (Table 3).

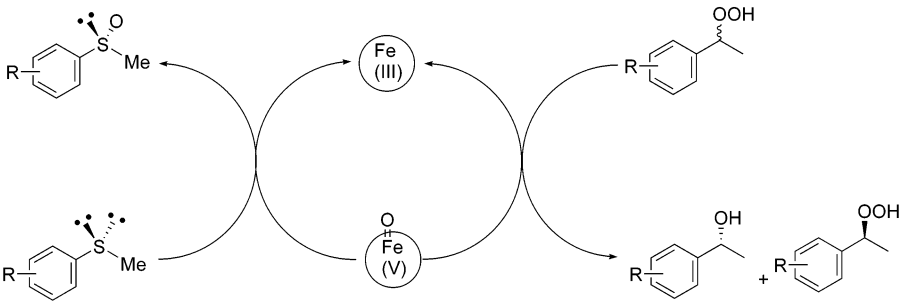
Table 3. Comparative Values of Turnover Number and Enantioselectivity for the Oxidation of Methyl Phenyl Sulfide to Sulfoxide with Peroxidases

enzyme	reaction time (min)	yield (%)	ee (%) (config)	TON[a]
CPO[b]	60	100	98 (*R*)	6.3×10^4
HRP[c]	60	95	46 (*S*)	29
LPO[d]	105	40	52 (*R*)	57
MP-11[e]	45	45	3 (*S*)	3

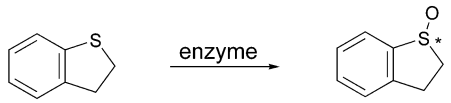
[a] TON (turnover number) = moles of product produced per mole of enzyme used. [b] Chloroperoxidase. [c] Horseradish peroxidase. [d] Lactoperoxidase. [e] Microsome peroxidase.

Finally, an interesting and promising approach is the utilization of molecular engineering in order to improve the efficiency and selectivity of biochemical oxidations. Ozaki produced a HRP mutant in which phenylalanine **41** is replaced by leucine; this led to a

Scheme 11



Scheme 12[a]



53

[a] Enzyme CPO: quantitative yield (97% ee, *R*). Enzyme VBr-PO: 99% yield (90% ee, *S*).

Table 4. Enantioselectivity in the Oxidation of Thioethers Using Native HRP and F41L HRP

substrate	ee (%) native HRP	ee (%) F41L HRP
Ph–S–Et	35	94
Ph–S–cyclopropyl	7	94
2-Naphthyl–S–Me	69	99

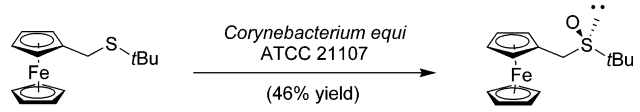
highly enantioselective enzyme, producing (S_S)-sulfoxides with very high ee's (Table 4).[82,83] The double mutant Leu-29-His and His-64-Leu of the oxygen carrier myoglobin gave an enzyme which converted thioanisole to the (R_S)-sulfoxide in 97% ee.[84] The double mutation Ph-43-His and His-64-Leu gave a less enantioselective enzyme—thioanisole was oxidized with 85% ee—however, the rate of oxidation was almost 200 times faster than that of natural myoglobin.[85]

B. Microbiological Oxidation

The great advantage of the utilization of whole-cell biocatalysts comes from avoiding the need for enzyme isolation, as well as the provision of cofactors. Thus, even though the enantioselectivities achieved are less spectacular than with isolated enzymes, for preparative scale the production of chiral sulfoxides is more convenient. Biological oxidation of sulfides to sulfoxides using whole cells has employed mainly fungi and bacteria and, to a lesser extent, yeasts.[59,60,62,63]

Among the bacterial strains screened in the oxidation of metallocene sulfides, *Corynebacterium equi* ATCC 21107 gave the best results (Scheme 13), allowing the oxidation of the ferrocenyl derivative **54** to the (R_S)-sulfoxides **55** with ee > 95%.[86] *Pseudomonas putida* UV4 and an engineered *Escherichia coli* which expresses the toluene dioxygenase (TDO) enzymes oxidize a wide range of alkyl aryl sulfides, substituted dithianes, and dithiolanes to sulfoxides.[87]

Scheme 13



54 **55** (>95% ee)

The sulfoxides are obtained with the R_S absolute configuration with high ee's (up to 97%). Para-substituted aryl alkyl sulfides lead to the (S_S)-sulfoxides in moderate ee, while (R_S)-heteroaryl sulfoxides **56** and **57** (Figure 4) are obtained in very

(*R*)-**56** (*R*)-**57**

Figure 4.

high ee (>98% and 94%, respectively). Strains expressing naphthalene dioxygenase (NDO) activity, such as *P. putida* NCIB8859 and an engineered strain of *E. coli*, oxidize a wide range of prochiral sulfides, leading to sulfoxides with *S* configuration in high ee's.[88]

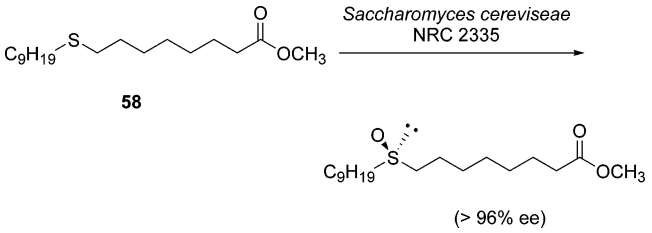
Holland's group has broadly studied the oxidation of prochiral sulfide by the fungi *Helminthosporium* and *Mortierella isabellina*. It was found that phenyl and benzyl alkyl sulfides, *p*-alkylbenzyl methyl sulfides, and isocyanate sulfides are generally oxidized in a complementary manner with good ee (>80%).[89−93] Accordingly, in the oxidation of methyl aryl sulfides, *Helminthosporium* gives the (S_S)-sulfoxide as major isomer (Table 5), while *M. isabellina* produces the (R_S)-enantiomer.

The same group showed that the fungus species NRRL 4671 oxidize a very large number (>40) of prochiral thioethers to the corresponding (S_S)-sulfox-

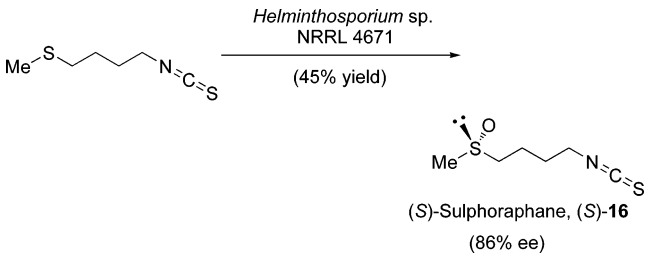
Table 5. Biotransformation of Sulfides, R_1SR_2, to Sulfoxides with *Helminthosporium*

R_1	R_2	yield (%)	ee (%)	config at S
Ph	Et	40	84	*S*
p-Br-C_6H_4	Me	69	90	*S*
p-NC-C_6H_4	Me	80	92	*S*
p-MeO-C_6H_4	Me	83	80	*S*
p-MeS-C_6H_4	Me	64	80	*S*
p-Bu-$C_6H_4CH_2$	Me	74	90	*S*
p-(*i*-Pr)$C_6H_4CH_2$	Me	77	80	*S*
p-$ClC_6H_4CH_2$	Me	71	90	*S*
p-O_2N-$C_6H_4CH_2$	Me	95	92	*S*
p-MeO-$C_6H_4CH_2$	Me	86	80	*S*

Scheme 14



Scheme 15



ides in high ee's (>80%) and very good yields (>75%). A predictive model for chiral sulfoxidation by the fungus was recently proposed from the analysis of the sulfoxidation of a large number (>100) of substrates.

The enantioselective oxidation of thia fatty acid **58** (Scheme 14) and analogues to the corresponding (R_S)-sulfoxide was first achieved by Buist[94] using baker's yeast (*Saccharomyces cerevisae* NRC 2335) under aerobic conditions in high ee (>96%). A later work by Roberts,[95,96] using *S. cerevisae* NCYC 73, succeeded in the oxidation of methyl *p*-tolyl sulfide (92% ee and 60% yield). Boyd and Dalton reported that microbial oxidation of aryl alkyl and diaryl sulfides to optically pure sulfoxides by selected strains of the bacterium *P. putida* UV4 gave (R_S)-sulfoxides with high ee, while *P. putida* NCIMB 8859 preferentially produced (S_S)-sulfoxides.[97]

Some Applications. Sulforaphane (**16**, Figure 2) is an aliphatic isothiocyanate sulfoxide that is abundant in certain varieties of broccoli and broccoli sprouts. Sulforaphane is a monofunctional inducer of Phase II detoxification enzymes and was shown to significantly inhibit DMBA-induced mammary carcinogenesis in rats. Interesentingly, sulforaphane has been found recently to act as a potent bacterisotatic agent against various strains of *Helicobacter pylori*, irrespective of their resistance to conventional antibiotics.[98] It is important to note that *H. pylori* infections are known to cause gastritis and peptic ulcers and to dramatically enhance the risk of gastric cancers. The (S_S)-sulforaphane (*S*)-**16** was prepared by Holland's group from the corresponding sulfide using *Helminthosporium* sp. NRRL 4671 (Scheme 15).[99]

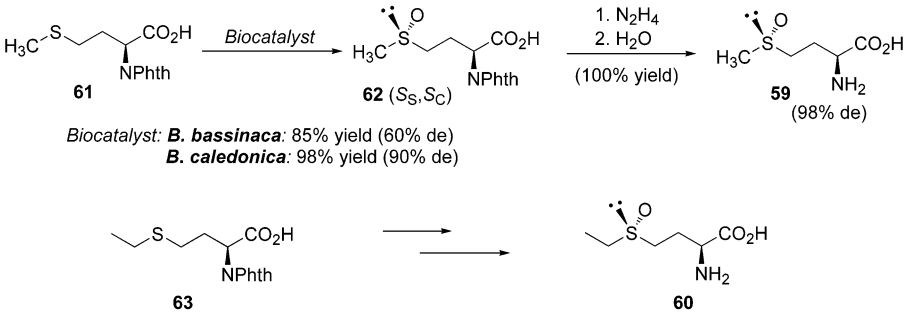
The same group also reported the biocatalytic route to the (S_S)-diastereoisomer of methionine sulfoxide (*S*)-**59** and the carcinogenic ethionine sulfoxides (*S*)-**60** (Scheme 16).[100,101] Biooxidation of the *N*-phthaloyl derivatives of either D- or L-methionine **61** by *Beauvaria bassinaca* ATCC 7159 produces the corresponding (S_S)-**62** sulfoxides in good yields (85−88%) and moderate diastereomeric excesses (60 and 70%). The use of *Beauvaria caledonica* ATCC 64970 allows the preparation of (S_C,S_S)-**62** in almost quantitative yield and in 90% diastereomeric excess, and (R_C,S_S)-**62** in 60% yield and 92% de. The biotransformation of *N*-phthaloyl ethionine **63** parallels those obtained from the corresponding methionines in terms of stereoselectivity of oxidation, but in this instance no significant differences were observed between the two *Beauvaria* strains employed. Recently, a patent application described the synthesis of both enantiomers of omeprazole (**1**) using a variety of fungal and bacterial biocatalysts.[102]

C. Antibodies-Catalyzed Sulfoxidation

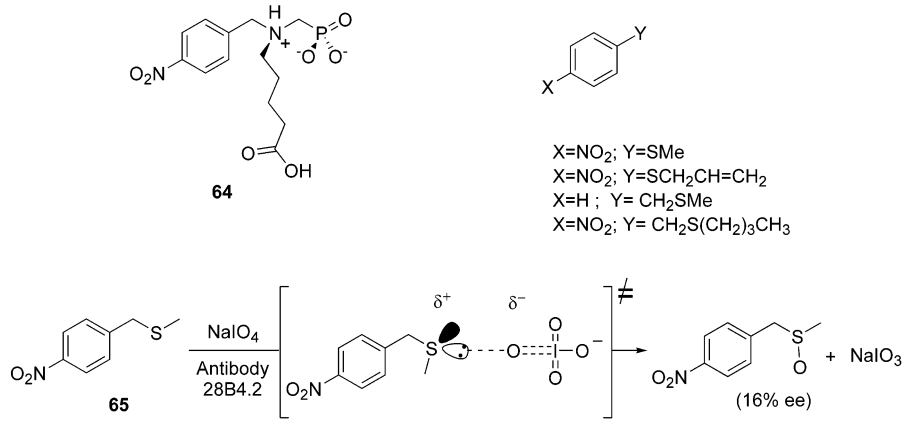
Schultz reported the synthesis of an antibody[103] directed to the oxidation of thioethers with sodium periodate. The antibody was raised against the aminophosphonic acid hapten **64** (Scheme 17). Since the hapten **64** contains a protonated amine at physiological pH, antibodies specific for **64** were expected to stabilize the incipient positive charge on sulfur present in the transition state in Scheme 17.[104] The obtained antibody 28B4.2 was shown to accelerate the oxidation of sulfide **65** by a factor of 2.2×10^5, validating the synthetic design. The turnover and rate acceleration for antibody 28B4.2 reveal that this antibody is as efficient as numerous monoxygenase enzymes. The X-ray structure of the antibody with and without the hapten has been resolved at 1.9 and 2.2 Å, which has permitted the determination of the structural parameters responsible for the catalysis and the low ee (16%) observed.

Recently, Keinan and Nimri reported an interesting antibody−metalloporphyrin that mimics natural oxidation enzyme.[105] On the basis of the catalytic

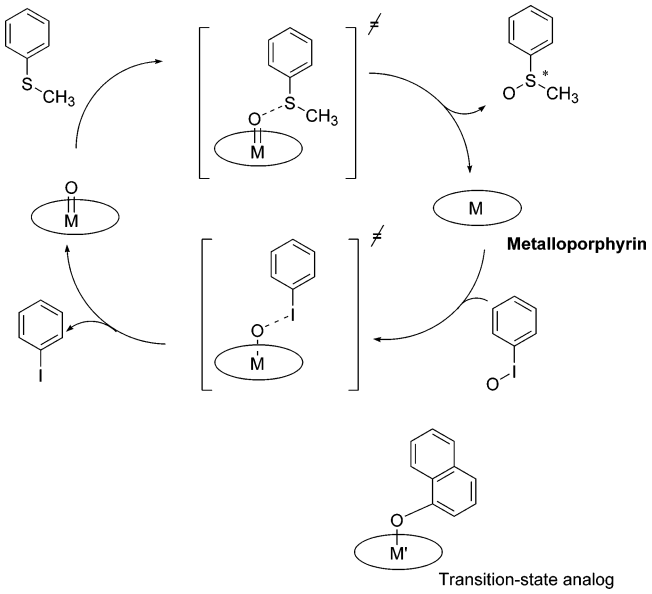
Scheme 16



Scheme 17



Scheme 18



cycle of metalloporphyrin-catalyzed sulfoxidation of thioanisole (Scheme 18), the authors designed a hapten with an α-naphthoxy ligand as the transition-state analogue.[106]

The antibody SN37.4 was raised against a water-soluble tin(IV) porphyrin **66** (Figure 5) containing an axial α-naphthoxy ligand. The catalytic assembly comprising antibody SN37.4 and a ruthenium(II) porphyrin cofactor **67** exhibited typical enzyme characteristics. The oxidation reaction of various aryl alkyl sulfides was carried out using PhIO as the co-oxidant to afford the corresponding sulfoxides in up to 43% ee (for thioanisole).[105]

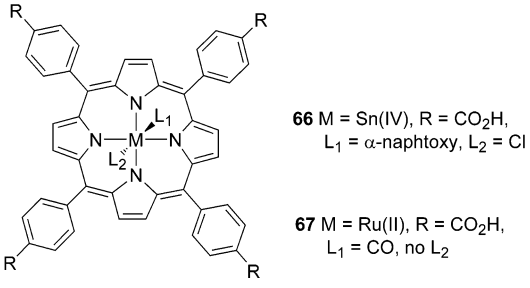


Figure 5.

IV. Metal-Catalyzed Enantioselective Chemical Sulfoxidation

Enantioselective chemical sulfoxidation is one of the most challenging approaches to chiral sulfoxides.[107−110] Nevertheless, its importance for the large-scale production of biologically significant molecules makes it attractive from both academic and industrial points of view. Basically, two methods have been used in the chemical oxidation of sulfides: those based on metal-catalyzed asymmetric sulfoxidation and those based on chiral oxaziridines. While both methodologies lead to specific sulfoxides with high enantioselectivities, the latter routes (as well as some of the metal-catalyzed routes) suffer from the utilization of the chiral controller in stoichiometric amount. To solve this problem, various catalytic systems have recently been reported. These systems are based on the use of different C_2-symmetric diols, C_3-symmetric aminotriol−titanium complexes, or metal−salen complexes (Mn, V, Ti) with moderate to good success. These approaches are discussed in detail in the following section, where priority has been given to their industrial application for the preparation of biologically active sulfoxides.

A. Modified Sharpless Method: Oxidation in the Presence of Chiral Titanium Tartrate

The outstanding successes of the Sharpless epoxidation[111] of allylic alcohols prompted various applications of the titanium alcoholate for the enantioselective oxidation of various substrates. Along this line, pioneering works on the enantioselective oxidation of sulfides came almost at the same time from Kagan's and Modena's groups.

1. The Kagan System

Kagan's group at Orsay (France) discovered by serendipity that 1 mol equivalent of water was necessary to produce the active catalyst able to oxidize prochiral sulfides to sulfoxides with high ee.[112−116] The combination Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET/H_2O (1:2:1) at −20 °C in CH_2Cl_2 was determined as the optimal conditions to achieve high enantioselectivity. In this system, a stoichiometric amount of the titanium complex with regard to the prochiral sulfide was needed. Tables 6 and 7 show some representative

Table 6. Asymmetric Oxidation of Aryl Alkyl Sulfides, ArSR, by *t*-BuOOH and the Water-Modified Titanium Reagent [Ti(O*i*-Pr)$_4$/(+)-DET/H$_2$O = 1:2:1]

entry	Ar	R	isolated yield (%)	ee (%)
1	*p*-tolyl	methyl	90	89
2	*p*-tolyl	ethyl	71	74
3	*p*-tolyl	*n*-butyl	75	75
4	1-naphthyl	methyl	98	89
5	2-naphthyl	methyl	88	90
6	2-naphthyl	*n*-propyl	78	24
7	9-anthracenyl	methyl	33	86
8	*o*-tolyl	methyl	77	89
9	*p*-MeOC$_6$H$_4$	methyl	72	86
10	*o*-MeOC$_6$H$_4$	methyl	70	84
11	phenyl	*c*-propyl	73	95
12	phenyl	CH_2Cl	60	47
13	phenyl	CH_2CN	85	34
14	2-pyridyl	methyl	63	77

Table 7. Asymmetric Oxidation of Dialkyl Sulfides, R$_1$SR$_2$, by *t*-BuOOH and the Water-Modified Titanium Reagent [Ti(O*i*-Pr)$_4$/(+)-DET/H$_2$O = 1:2:1]

entry	R_1	R_2	isolated yield (%)	ee (%)
1	*t*-Bu	Me	72	53
2	octyl	Me	77	53
3	cyclohexyl	Bu	67	54
4	$PhCH_2$	Me	88	35
5	$PhCH_2CH_2CH_2$	Me	84	50
6	Me	CH_2CO_2Me	84	63
7	Me	$CH_2CH_2CO_2Me$	85	64
8	Me	CH_2SMe	81	40

results obtained in the oxidation of several thioethers with *tert*-butyl hydroperoxide (TBHP) under these conditions.[113]

After a good method was found for the oxidation of sulfides, attention was directed toward the development of a catalytic version of it. The best improvement achieved by Kagan's group was the substitution of TBHP for cumene hydroperoxide (CHP). The utilization of CHP, associated with the addition of molecular sieves before catalyst formation, allowed the amount of titanium complex to be reduced to 0.2 mol equiv without loss of the ee (Table 8).[117] The use

Table 8. Catalyzed Stereoselective Oxidation of Alkyl Aryl and Dialkyl Sulfides, RSR', by CHP and the Kagan System

entry	R	R′	time (h)	convrsn (%)	SO:SO$_2$ ratio	ee (%) (config)
1	Ph	Me	5	100	27:71	89 (*R*)
2	*p*-MeC$_6$H$_4$	Me	5	100	25:75	86 (*R*)
3	*p*-MeC$_6$H$_4$	Me	4	100	32:68	89 (*R*)
4	*p*-ClC$_6$H$_4$	Me	6	100	32:68	86 (*R*)
5	2-Naph	Me	6	100	52:48	88 (*R*)
6	*p*-MeC$_6$H$_4$	*n*-Bu	6	94	37:63	91 (*R*)
7	*p*-MeC$_6$H$_4$	*i*-Pr	21	100	28:72	91 (*R*)
8	Ph	*t*-Bu	19	33	44:56	77 (*R*)
9	Ph	Bn	6	95	22:78	79 (*R*)
10	Bn	Me	2	100	60:40	14 (*R*)
11	*n*-Oct	Me	2	100	60:40	8 (*R*)

of molecular sieves, as moisture scavengers, permits a better control of the amount of water in the reaction mixture.

Though the exact mechanism of enantioselective oxidation of sulfide with the water-modified Sharpless catalyst is still unknown, the very good correlation between the absolute configuration of tartrate and the sulfoxides formed[108,113] allows the proposition that the catalytically active species is a dimer with two titanium atoms connected via an η-oxo bridge (Figure 6). Thus, the approach of the incoming sulfide

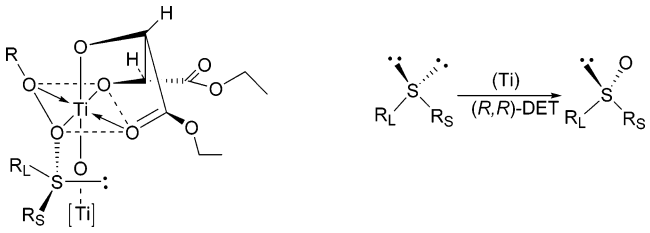


Figure 6.

is determined by an efficient distinction between the larger (R_L) and the smaller (R_S) substituents at the sulfur atom.

Further improvement of the catalytic process has recently been achieved. A systematic study of the roles played by titanium alkoxide, 2-propanol, and molecular sieves (MS) has permitted the decrease of the catalyst loading to 10 mol %.[118,119] This catalyst has a new composition, Ti(O-*i*-Pr)$_4$/(*R*,*R*)-DET/*i*-PrOH (1:4:4), in the presence of 4-Å MS, which can be considered as a combination of the Modena (vide infra) and Kagan systems. The new system furnishes chiral sulfoxides with very high ee (75−95%, Table 9).

Table 9. Asymmetric Oxidation of Sulfides, R$_1$SR$_2$, by CHP in the Presence of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET/*i*-PrOH (1:4:4) and Molecular Sieves

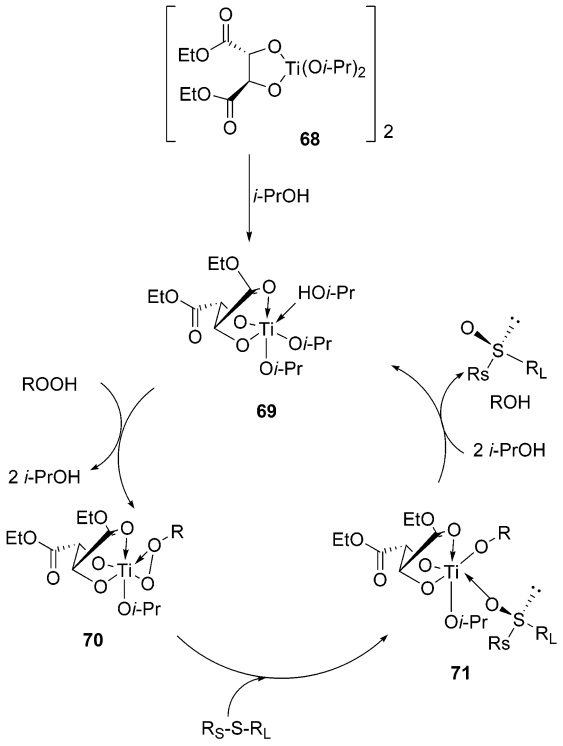
entry	R_1	R_2	yield (%)	ee (%) (*R*)
1	phenyl	Me	81	91.2
2	*p*-tolyl	Me	77	95.6
3	*p*-anisyl	Me	73	92.1
4	*o*-anisyl	Me	72	89.3
5	*o*-nitrophenyl	Me	51	75.0
6	phenyl	$CH{=}CH_2$	58	55.4
7	*p*-tolyl	Et	68	78.1
8	*p*-tolyl	*n*-butyl	70	25.0
9	*o*-anisyl	phenyl	64	6.2
10	benzyl	Me	72	90.3
11	*n*-octyl	Me	69	70.7

In the mechanism proposed for the oxidation of sulfides with the new system (Scheme 19), the active species is the monomeric titanium complex **70**, bearing a simple isopropoxide instead of the η-oxo group proposed in the original system (Figure 6). The monomeric complex **70** is formed from **69**, which is generated from the dimeric titanium compound **68** by the action of 2-propanol. The alcohol has also a beneficial effect by displacing the sulfoxide formed, inducing the formation of **69** from **71**, thereby permitting a catalytic cycle.[67]

2. The Modena System

The group headed by Modena at Padua (Italy) developed a different system that is able to oxidize sulfides to sulfoxides with high selectivity.[120] This system is also based on a modification of the Sharpless conditions. Modena's group used a 1:1:4 ratio of

Scheme 19



TBHP/Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET at −20 °C (toluene or 1,2-dichloroethane).[121] The results are in general similar, in both yield and selectivity, to those obtained using the water-modified reagent, but this system gives better results in the asymmetric oxidation of 1,3-dithiolane (Table 10). This latter finding has been successfully applied to the resolution of racemic ketones through their transformation into 1,3-dithiolanes, followed by asymmetric monosulfoxidation, subsequent separation of diastereomers, and ultimate regeneration of the parent ketone.[122]

Table 10. Asymmetric Oxidation of Sulfides by TBHP in the Presence of Ti(O*i*-Pr)$_4$/(+)DET (1:4)

sulfide	yield (%)	diastereomers ratio	ee (%)
p-Tol-S-Me	60		88
p-Tol-S-*t*-Bu	99		34
p-ClC$_6$H$_4$-S-CH$_2$CH$_2$OH	41		14
PhCH$_2$-S-Me	70		46
2-Ph-2-Me-1,3-dithiolane	66[a]	97:3	83[b]
2-Ph-1,3-dithiolane	76[a]	94:6	76[b]
2-*t*-Bu-1,3-dithiolane	82[a]	99:1	70[b]
2-*t*-Bu-2-Me-1,3-dithiolane	61[a]	99:1	68[b]

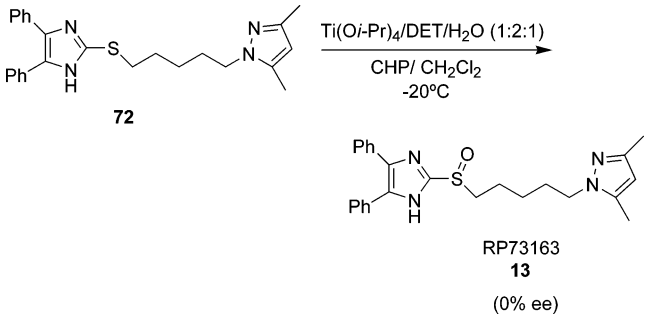
[a] Mono-oxidation. [b] For the major diastereomer.

The observation that the Modena system produces racemic sulfoxides by addition of molecular sieves was interpretted as indicative that identical species could be involved in each of the two systems. Accordingly, the role of an excess of tartrate would be to bring an uncontrolled amount of water.

3. Some Applications

Kagan's water-modified titanium system has been frequently used for the production of specific sulfoxides with synthetic as well as biological interest. The most impressive are those producing optically pure sulfoxides in kilogram scale for industrial production of a final or intermediate sulfoxide. A common scenario in the pharmaceutical discovery of biologically active sulfoxides is the discovery that a preselected thioether lead compound is metabolized into the corresponding sulfoxide. In many cases, the biological activity is sustained by one enantiomeric sulfoxide, making necessary its production in enantiomerically pure form. In an interesting paper, Pitchen discusses the discovery and the industrial production of two biologically active sulfoxides discovered at the former French pharmaceutical company Rhone Polenc.[123] RP 73163 (**13**, Figure 2) is a hypocholesterolemic agent which acts by inhibiting the enzyme ACAT. From the two enantiomeric sulfoxides, only the (S_S)-isomer exhibited useful biological activity. However, a first attempt to oxidize sulfide **72** in the presence of Ti(O*i*-Pr)$_4$/DET/H$_2$O (1:2:1) using CHP as final oxidant gave RP 73163 in racemic form (Scheme 20).[123]

Scheme 20



This result is due in part to the fact that the sulfide **72** is not a good substrate for the enantioselective oxidation, as there is no steric-group difference. Sulfide **73** (Scheme 21), with two sterically different substituents on the sulfur, was used as starting material.[124] Using CHP as the oxidant, with 1 equiv of the unnatural and expensive D-DET and 0.5 equiv of Ti(O-*i*-Pr)$_4$, afforded the desired (*S*)-sulfoxide (*S*)-**74** in 98−99% ee and 75% yield. The approach consisted of the synthesis of the sulfoxide **75** by alkylation of (*S*)-**74**. Finally, deprotection of the *p*-methoxybenzyl group in refluxing trifluroacetic acid followed by recrystallization gave RP 73163 in >99% ee.[124]

The second sulfoxide, RP 52891 (**14**, Figure 2), was discovered in the same manner. 2-(3-Pyridyl)tetrahydrothiopyran **76** has been synthesized in the optimization process of antisecretary and antiulcer activity of 2-(2-pyridyl)tetrahydrothiophene-2-carbothioamides such as picartamide (Figure 7).[125] In general screening, compound **76** was shown to have antihypertensive activity in the spontaneously hypertensive rats (SHAR) screen. This activity was later shown to be due to the corresponding sulfoxide **14**.

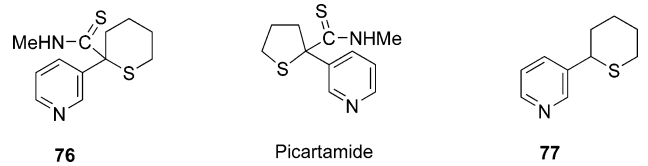
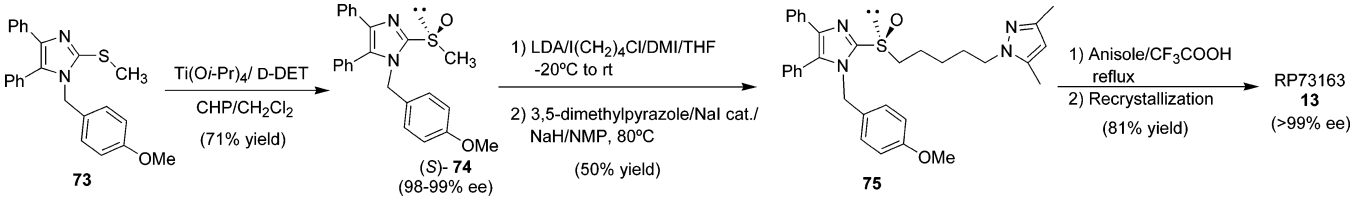
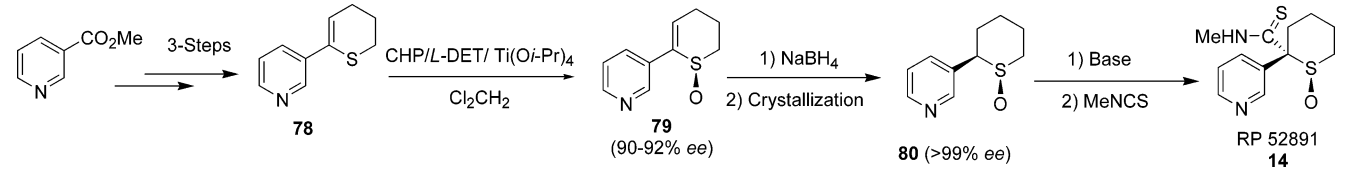


Figure 7.

Scheme 21



Scheme 22



The (R_S)-sulfoxide **14** (Figure 2) is a potent hypotensive agent which acts as an opener of the ATP-sensitive K^+ channel, while the (S_S)-enantiomer and the sulfide lack activities. The oxidation of **77** (Figure 7) using the best conditions found for the synthesis of the ACAT inhibitor RP 73163 (vide supra) led to the corresponding sulfoxide in only 20% ee. However, the oxidation of the more rigid vinylic sulfide **78** (Scheme 22) gave the desired (R_S)-sulfoxide **79** in 90−92% ee using the natural L-DET as the chiral ligand. Reduction of the vinyl sulfoxide with sodium borohydride afforded sulfoxide **80**, which after recrystallization allowed the isolation of the desired isomer (*R*,*R*)-**80** in high diastereomeric excess. Finally, diastereoselective alkylation with methyl isocyanate followed by recrystallization gave RP 52891 **14** in >99% ee.[123]

As stated in the introductory section, 5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1*H*-benzimidazole **1** (Figure 1), which has the generic name omeprazole, occupies a pre-eminent place within the synthetic sulfoxide drugs. Omeprazole and the recently launched esomeprazole (Nexium) are the leading gastric proton pump inhibitors used clinically as a antiulcer agents.[126]

The first syntheses of optically pure omeprazole, as well as the determination of its absolute configuration (Figure 8), have been done via resolution of

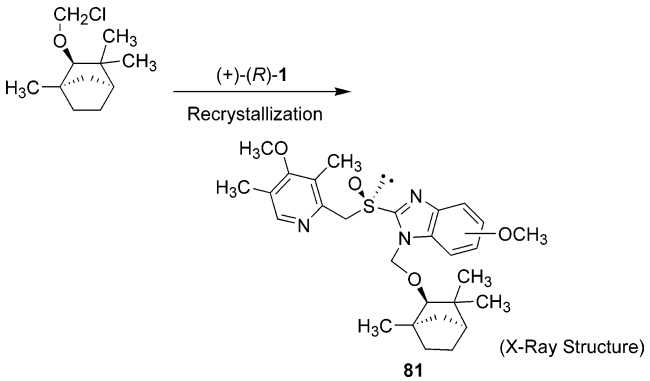


Figure 8.

the racemate.[127−129] Recently, an asymmetric oxidation of the corresponding prochiral sulfide was described, [130] in which various oxidants were tried for the direct synthesis of esomeprazole (*S*)-**1** from the sulfide **82** with dissimilar results. As there is no steric-group difference in the starting sulfide, the use of the standard Kagan protocol leads to a nearly racemic mixture of the sulfoxide. Interestingly, researchers from AstraZeneca recently found specific conditions of Kagan's protocol which afforded esomeprazole with high enantioselectivity (Scheme 23).[130]

These variations entail (i) the preparation of the titanium complex with the sulfide, (ii) the equilibration of the mixture of the catalyst and the sulfide at elevated temperature, and most importantly (iii) the addition of Hunig's base together with the CHP used as terminal oxidant. Additionally, the catalyst can be used in a substoichiometric amount (4 mol %), even though 30 mol % was usually used to afford reproducibility on macroscale production (6.2 kg of the starting sulfide). The AstraZeneca conditions gave various biologically active sulfoxides with high ee, provided the starting sulfide carried a benzimidazole N−H group. Interestingly, when applied to the sulfide **72** (Scheme 23), these conditions afforded (*S*)-RP 73163, (*S*)-**13**, in 92% ee. This result seems to reinforce the interpretation of the authors on the importance of an NH function in the molecule for the high enantioselectivity observed.

Kagan's approach was also applied by Davis and Pfister from Synthex for the preparation of (*R*,*S*)-**84** and (*S*,*S*)-**84**, chiral analogues of Hantzsh esters 4-aryl-1,4-dihydropyridine-3,5-carboxylic acid diesters **83** (Figure 9).[131] Hantzsh esters are used as cardiovascular drugs; they inhibit smooth and cardiac muscle contractions by blocking the influx of calcium ions through plasma membrane channels.[132]

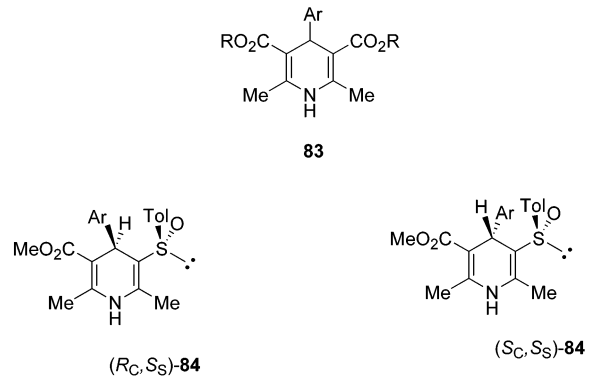
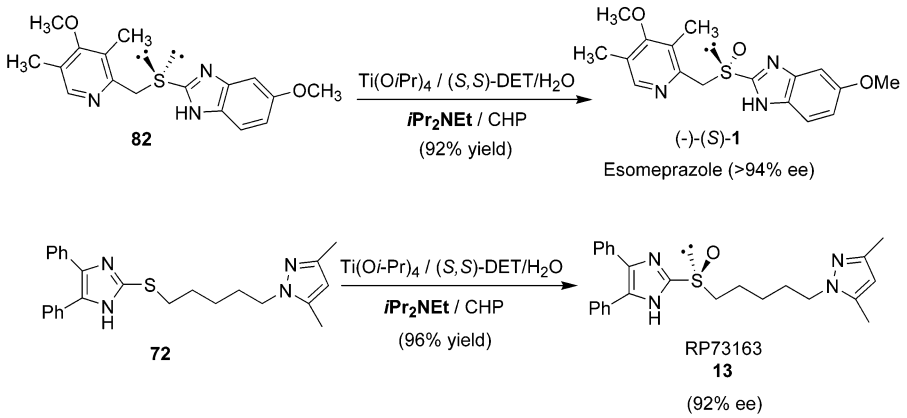
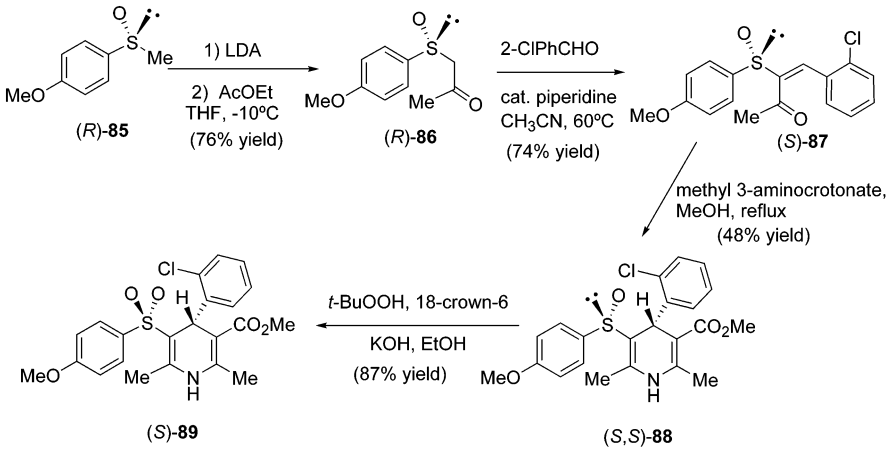


Figure 9.

Scheme 23



Scheme 24



Davis and Pfister prepared both enantiomers of *p*-anisyl methyl sulfoxide **86** (Scheme 24) by the Kagan protocol in >98% ee, using cumene hydroperoxide in the presence of the titanium complex. Hantzsh reaction of (*E*)-vinyl-*β*-keto sulfoxide (S_S)-**87** gave dihydropyridine (*S,S*)-**88** in 45% yield as a single isomer (Scheme 24). In spontaneously hypertensive rats, the corresponding sulfone (*S*)-**89** was about 10 times more potent in lowering blood pressure than (*R*)-**89**, obtained following a similar synthetic scheme from (*S*)-**86**. Recently, Imanishi's group, in a series of papers on the synthesis of dihydropyridines bearing a chiral sulfoxide, structurally related to those of Davis (Figure 9), reported that the sulfoxides themselves are active calcium channel antagonists.[133]

A new biologically interesting molecule is (*S*)-(+)-3,4-dihydro-6-[3-(1-*o*-tolyl-2-imidazoyl)sulfinylpropoxy]-2(1*H*)-quinolinone **21** (Figure 2), named OPC-29030. This chiral sulfoxide is actually under clinical trials as a new platelet adhesion inhibitor which suppresses the production of 12-(*S*)-hydroxyeicosatetraenoic acid (12-HETE) from platelets.[134] A patent is reported for a method using Kagan's protocol in the oxidation of 3-[1-(2-methylphenyl)imidazol-2-ylthio]propan-1-ol **90**, albeit the yield of sulfoxide **91** is low (Scheme 25).[135] Interestingly, Matsugi recently found that the use of chiral mandelic acid in the presence of Ti(O*i*-Pr)$_4$, molecular sieves, and cumene hydroperoxide (Scheme 25f) afforded (*S*)-**91** (a key intermediate in the synthesis of OPC-29030) in high optical purity (up to 75% ee). Neither the conditions of Uemura, Modena, and Davis nor those of Jacobsen allow OPC-29030 to be accessed in an acceptable optical yield.[136]

Beside the synthesis of biologically active molecules, various groups have applied Kagan's approach for the synthesis of synthetically useful sulfoxides. Page et al. prepared the chiral acyl anion equivalent 1,3-dithiane-1-oxide **92** (Figure 10)[137] by oxidation of

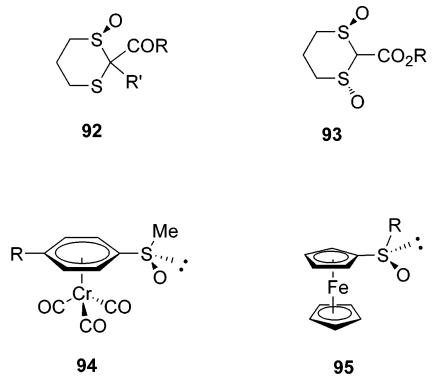
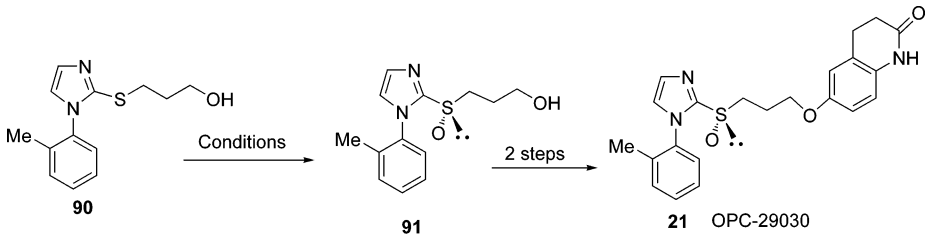


Figure 10.

the corresponding 1,3-dithiane, finding that the introduction of a polar group in the 2 position of the 1,3-dithiane was responsible for the high enantiomeric excess (99% ee).[138] The same results were reported by Aggarvall, who later found that Modena's system was superior to Kagan's system for the

Scheme 25



Conditions	ee (%)
a) (+)-DET(2eq.), CHP (1eq), Ti(O*i*-Pr)$_4$, (0.5eq.), MS 4Å:	54
b) (+)-DET(1eq.), CHP (1eq), Ti(O*i*-Pr)$_4$, (0.5eq.), H_2O (0.5 eq) MS 4Å:	4
c) (+)-binaphtol (1eq.), CHP (1eq), Ti(O*i*-Pr)$_4$, (0.5eq.), MS 4Å:	36
d) Davis Oxaziridine:	12
e) Jacobsen salen complex:	14
f) Ph, CO_2H, OH (0.6 eq.), CHP (1eq), Ti(O*i*-Pr)$_4$, (0.4eq.), MS 4Å	75

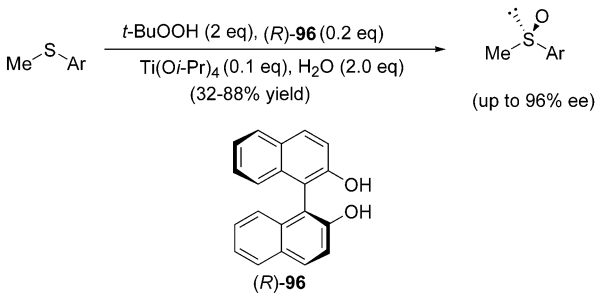
enantioselective oxidation of the 2-ethoxycarbonyl-1,3-dithiane, leading to the C_2-symmetric bis-sulfoxide **93** (Figure 10).[139]

Thomas et al. described the synthesis of the methylsulfinyl-substituted tricarbonyl-(η^6-arene)chromium(0) complex **94** (Figure 10) by oxidation of the corresponding sulfide with CHP in the presence of Ti(O*i*-Pr)$_4$/DET/H_2O (90−95% ee),[140] in an approach similar to that used by Kagan for the preparation of aryl ferrocenyl sulfoxide **95** (Figure 10).[141] Enantiopure **94** and **95** are important building blocks, as the sulfoxide moiety can efficiently direct the ortholithiation, leading to diastereomerically pure compounds with planar chirality (vide infra).

B. Other C_2-Symmetric Titanium-Catalyzed Sulfide Oxidation Systems

One of the most important improvements in the catalytic asymmetric oxidation of prochiral sulfides using chiral titanium complexes was developed by Uemura.[142,143] This catalytic system uses Ti(O*i*-Pr)$_4$ in the presence of (*R*)-(+)-binaphthol (**96**, Scheme 26)

Scheme 26



instead of DET as a chiral source. The highest ee was obtained with TBHP at 25 °C, with as little as 5 mol % of the chiral ligand leading to sulfoxides with R_S absolute configuration, and up to 96% ee (Scheme 26).

An important characteristic feature of the Uemura system is the large positive nonlinear effect observed, indicating that the actual catalyst consists of a titanium species with more than one (*R*)-BINOL ligand coordinated to the metal. It has also been shown that the %ee of the final sulfoxide depends on the reaction time: there is an increase in the enantiomeric excess with an increase in the reaction time, accompanied by an increase in the sulfone formation. Taken together, these results imply that a kinetic resolution is removing the (S_S)-sulfoxide, thereby raising the amount of the (R_S)-sulfoxide.[143]

Various groups have followed the strategy of Uemura to develop an effective chiral Ti(IV) catalyst, using different C_2-symmetric diols with variable steric and stereoelectronic features (Figure 11). In

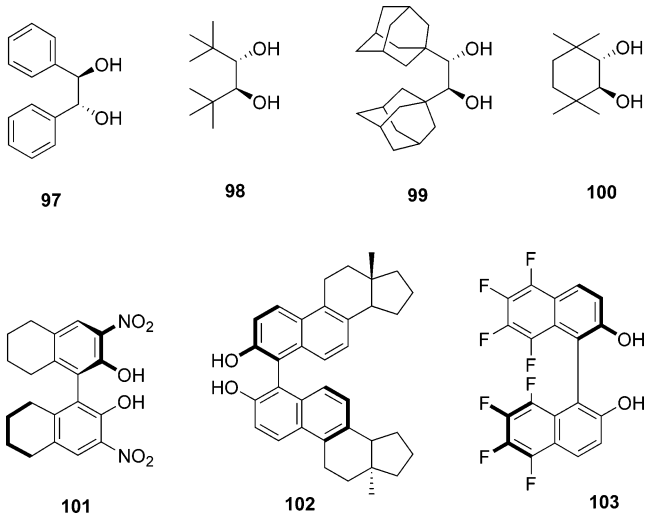


Figure 11.

this sense, Rosini developed a system using 10 mol % of (*S*,*S*)-1,2-diphenylethane-1,2-diol **97** as chiral ligand and TBHP as oxidant.[144−146] Nevertheless, this system was shown to be less effective than the former, as it allows the synthesis of phenyl methyl sulfoxide in 60% yield and 80% ee. The system is nevertheless particularly useful for the oxidation of aryl benzyl sulfides (up to 99% ee), which are normally bad substrates for titanium-based oxidations with diethyl tartrate ligands. In a related study using similar ligands, the observed stereoselectivity was found to be highly dependent on the substituent at the *para* position of the aryl groups in the ligand. In one example, an interesting reversal of selectivity was observed on introduction of a *p*-trifluoromethyl group.[146]

At the same time, Imamoto reported the synthesis of the (*R*,*R*)- and (*S*,*S*)-2,2,5,5-tetramethyl-3,4-hexanediol **98** (Figure 11) and its utilization in a Ti-catalyzed enantioselective sulfoxidation.[147] Using Ti(O*i*-Pr)$_4$/(*S*,*S*)-**98** in a 1:2 ratio, with 4-Å MS and CHP, a variety of methyl aryl sulfoxides were synthesized in up to 95% ee. It was again demonstrated that a combination of asymmetric oxidation and kinetic resolution is responsible for the high ee's obtained. Although the mechanistic details of the reaction are unknown, the authors propose mononuclear titanium with two diol units and one CHP as the active catalyst. Other C_2-symmetric diols, such as **99** and **100** (Figure 11), have been prepared and screened as ligands in the titanium(IV)-mediated asymmetric oxidation of aryl alkyl sulfides. The new ligands were found to be much less effective than the previously cited ligands.[148] Reetz reported the synthesis of (*R*)-3,3′-dinitrooctahydrobinaphthol **101** (Figure 11) and its utilization in the asymmetric oxidation of methyl *p*-tolyl sulfide.[149] An 86% ee was obtained when using 2:1 mixture of **101** and Ti(O*i*-Pr)$_4$, together with CHP as oxidant.

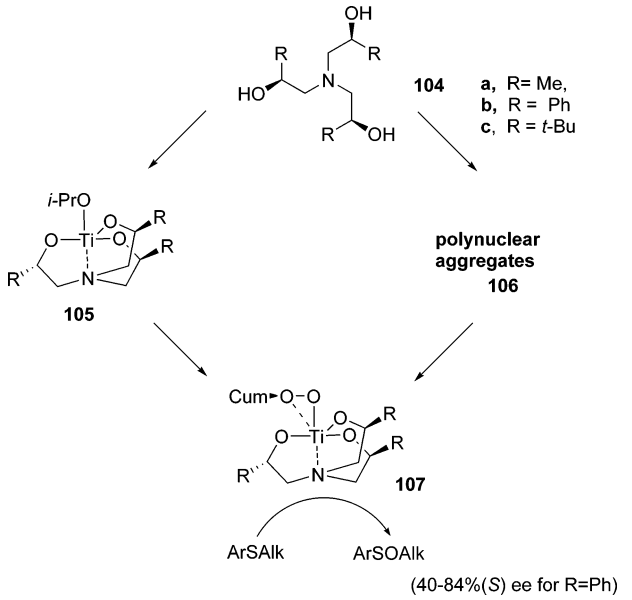
Bolm reported the synthesis of the BINOL-based ligand **102** from equilenine.[150] The ligand **102** was used in the Ti(O*i*-Pr)$_4$-mediated oxidation of aryl alkyl sulfides. In contrast to previous systems employing BINOL ligands, overoxidation to the sulfone does not occur, and hence, the high enantiomeric excesses observed (up to 92% ee, 76% yield for thioanisole) are not a result of kinetic resolution. F_8-BINOL-**103** is an interesting BINOL derivative, showing increased configurational stability and possessing significantly more acidic hydroxyl donor groups. Yudin recently found that enantiomerically pure F_8BINOL displays reversed selectivity in some titanium(IV)-mediated sulfoxidations when compared to analogous systems derived from BINOL.[151]

C. C_3-Symmetric Titanium-Catalyzed Sulfide Oxidation Systems

To overcome the small turnover obtained when using titanium peroxo catalyst bearing a C_2-symmetric diol, and to get better insight into the Ti-catalyzed sulfoxidation, Licini and Nugent use the C_3-symmetric chiral trialkanolamine **104** as ligand (Scheme 27).[152] When the oxidation of the aryl alkyl sulfide was performed with cumyl hydroperoxide (CHP) in the presence of catalyst **105** or **106**, high turnover number (TON) (1−2% catalyst loading) and enantiomeric excesses in the range of 40−84% were obtained.

The optical purities of the final sulfoxides were shown to be due in part to a kinetic resolution. Nevertheless, the kinetic resolution observed does not respond to the generally accepted mechanistic scheme involving two consecutive electrophilic oxygen-transfer steps to the sulfur atom. For example, the oxidation of methyl *p*-tolyl sulfide by $Ti^{IV}N(CH_2CHPhO)_3$(O*i*-Pr) **105** (R = Ph, Scheme 27) and CHP yields both the sulfoxide and the sulfone, with comparable reaction rates ($K_S/K_{SO} = 3.2$). However,

Scheme 27

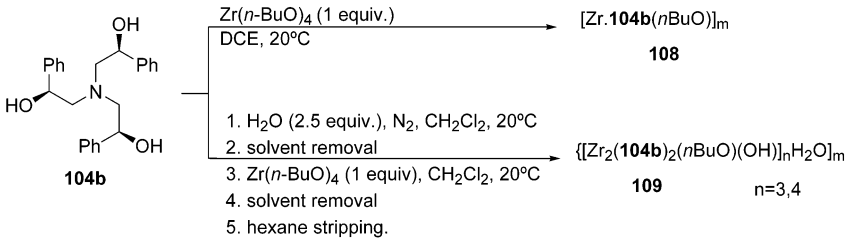


an inversion of selectivity ratio ($K_S/K_{SO} < 1$) was observed for electron-poor substrates. Kinetic studies and ab initio calculation at the RHF/3-21 G(*) level show that complex **107** has a biphilic nature, behaving as an electrophilic oxidant toward sulfides, while a nucleophilic pathway dominates the oxidation of sulfoxides.[153] The species formed when the catalyst was generated in situ were recently characterized by electron ionization mass spectroscopy (ESI-MS), in combination with low-temperature NMR techniques. It was shown that when a precise 1:1 ligand/Ti(IV) ratio is employed, catalyst **105** is obtained. In contrast, when a slight excess of trialkanolamine is used, a mixture of complexes consisting of a 2:1, 3:2, and 4:3 oligomers **106** is formed, in which the excess trialkanolamine bridges multiple titanate units. In the presence of excess *tert*-butyl hydroperoxide, all the precatalyst species are cleanly converted to a mononuclear titanium(IV) peroxo complex **107** (Scheme 27), which serves as the active sulfoxidation catalyst.[154]

The same group recently reported the first chiral zirconium(IV) catalyst for enatioselective sulfoxidation. It was found that the use of C_3-symmetric ligand **104b** afforded effective zirconium(IV) catalyst under precise conditions.[155] While the catalyst **108** (Scheme 28), prepared under anhydrous conditions, showed little catalytic activity, the preparation of the partially hydrolyzed Zr(IV) complex **109** afforded a very active catalyst (Scheme 28).

High enantioselectivities (80−90%) were obtained by using only 2 mol % of the catalyst, provided that [**109**] > 0.02 M. The reaction was shown to be fairly general for alkyl aryl sulfides, independent of their steric or electronic features. The high enantioselection was again the result of a kinetic resolution by overoxidation of the minor sulfoxide formed. An important characteristic of the new catalytic system is that it provided chiral sulfoxides in higher ee's and with opposite enantioselection as compared with the corresponding titanium-catalyzed oxidations.

Scheme 28



D. Metallo-(Salen)-Catalyzed Oxidation

Chiral oxatitanium(IV)−Schiff base complexes **110** (Figure 12) were developed in 1986 by Pasini and co-

Figure 12.

workers as catalyst for the oxidation of methyl phenyl sulfide.[156] While the catalytic activity of this system was excellent (catalyst/substrate ratio 1:1000 to 1:1500), the enantioselection was unfortunately low (<20% ee) (Figure 12). A more promising approach was later developed by Fujita using **111** (Figure 12), a binuclear Schiff base−titanium(IV) complex (4 mol % equiv), to catalyze the asymmetric oxidation of methyl phenyl sulfide by trityl hydroperoxides in methanol at 0 °C. The (*R*)-methyl phenyl sulfoxide was obtained with 60% ee.[157]

Jacobsen and Katsuki applied their system, developed for the asymmetric epoxidation of simple olefins, to the asymmetric oxidation of prochiral sulfides. In 1992, Jacobsen reported the use of 2 mol % of chiral (salen)−manganese complex **112a** (Figure 13) for the oxidation of sulfides with H_2O_2.[158] In contrast with the excellent results obtained with this system for the epoxidation of conjugated olefins, only moderate enantioselectivity (24% ee) was obtained for sulfoxidation of alkyl aryl sulfides. The enantioselectivity could be raised to 47% when a complex with a modified ligand having an electron-donating methoxy group **112b** was used. A new (salen)−manganese(III) complex **113** (Figure 13) was reported by Katsuki, which showed better catalytic asymmetric induction in the oxidation of sulfides (up to 90% ee) using PhIO instead of H_2O_2.[159,160] The asymmetric induction has been shown not to proceed via a kinetic resolution. The same group reported (Figure 13) the use of a (salen)−manganese complex with additional axial chirality, **114**. This complex showed improved enantioselectivities in the oxidation of prochiral sulfides with up to 84% ee.[161,162]

In 1986, Fujita reported the asymmetric oxidation of aryl methyl sulfide by hydroperoxides (TBHP, CHP) and an optically active catalyst formed by a Schiff base−oxovanadium(IV) complex **115**, giving (S_S)-sulfoxides in low ee (up to 40%) (Figure 14).[163]

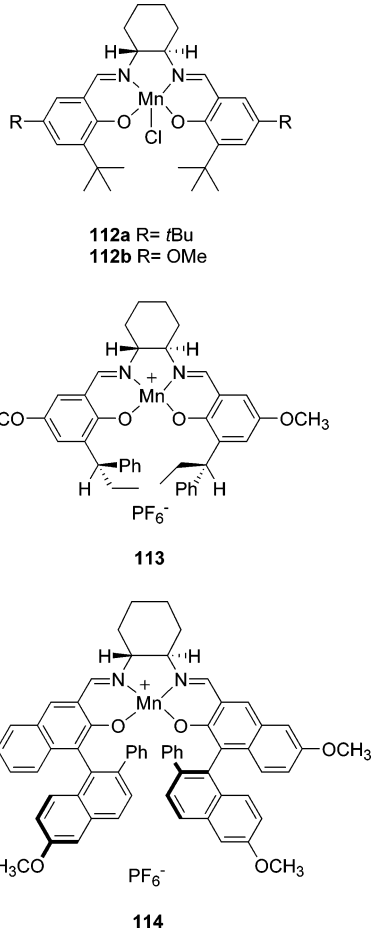


Figure 13.

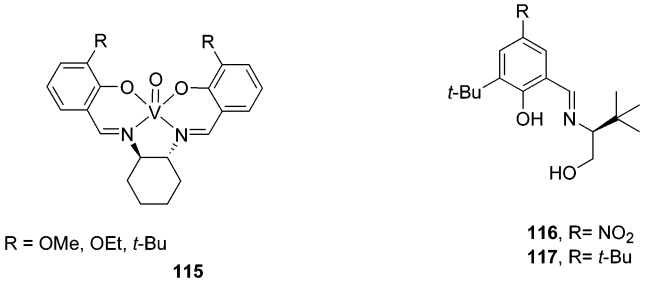


Figure 14.

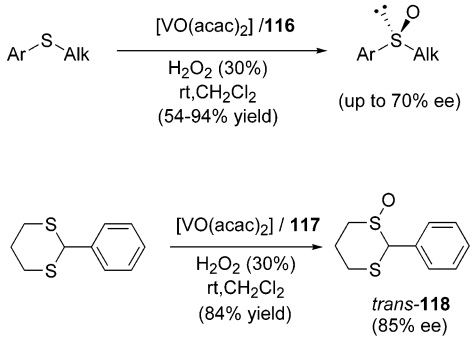
Recently, Bolm reported a very promising catalytic system formed in situ from $VO(acac)_2$ (acac = acetylacetonate) and ligand type **116** (Figure 14).[164] This system is able to catalyze sulfoxide formation in a concentration of 0.01 mol % and has the advantages of (i) proceeding under simple reaction conditions, (ii) using 30% aqueous H_2O_2 as the terminal oxidant, (iii) using simple ligands derived from (*S*)-*tert*-leucinol and salicylaldehydes, and (iv) effecting the ligand

Table 11. Catalytic Enantioselective Oxidation of Sulfides with H_2O_2, 1 mol % of [VO(acac)$_2$], and 1.5 mol % of Ligand 116 or 117 (Figure 14)

entry	ligand	sulfide	yield (%)	ee (%)	config
1	**116**	Ph-S-Me	94	70	(*S*)-(−)
2	**117**	Ph-S-Me	73	59	(*S*)-(−)
3	**116**	Ph-S-*i*-Pr	64	62	(*S*)-(−)
4	**116**	Ph-S-*n*$C_{10}H_{21}$	77	53	(*S*)-(−)
5	**116**	*p*-$NO_2C_6H_4$-S-Me	55	63	(*S*)-(−)

acceleration of catalysis. Though low catalyst loadings are possible, the reaction is usually conducted using the catalyst formed in situ from 1 mol % of VO(acac)$_2$ and 1.5 mol % of imine (Table 11). The best ligands were shown to be ligand **116** for the oxidation of aryl alkyl sulfides (up to 70% ee) and ligand **117**, with two *tert*-butyl groups, for the oxidation of thioacetals (Scheme 29). In the latter case, the

Scheme 29



oxidation of 2-phenyl-1,3-dithiane leads to trans-isomer **118** with 85% ee.[165]

Recently, Berkessel synthesized eight imines from the reaction of (*S*)-*tert*-leucinol with four chiral racemic salicylic aldehydes derivatives (Figure 15)

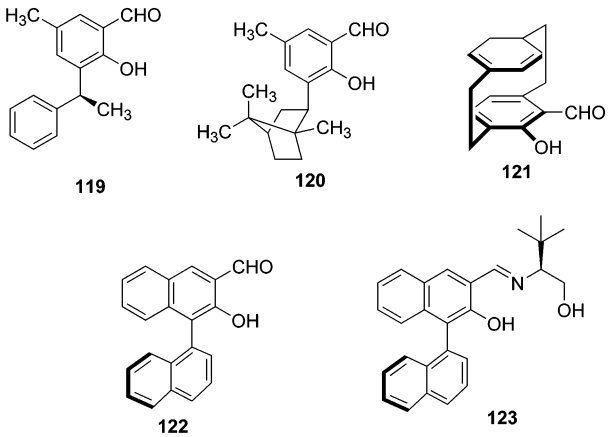


Figure 15.

having additional central (**119**, **120**), planar (**121**), and axial chirality (**122**). These imines were then separated into the corresponding pure diastereomers by preparative HPLC.[166] From the eight ligands prepared, it was shown that **123** gave the best results in the H_2O_2/VO(acac)$_2$-mediated oxidation of thioanisole (92% yield and 78% ee), improving those obtained with Bolm's system (73% yield and 59% ee). The method was also used for the oxidation of bis-thioethers, affording the corresponding sulfoxides in high ee's.[167]

The most practical application of Bolm's system has been done by Ellman in the enantioselective oxidation of *tert*-butyl disulfide en route to chiral *tert*-butyl sulfinyl compounds (vide infra).[168]

V. Enantioselective Sulfoxidation by Chiral Oxaziridines

In recent years, Davis and co-workers demonstrated that the stoichiometric asymmetric oxidation of prochiral sulfides with chiral oxaziridines is one of the best methods in the synthesis of optically active sulfoxides.[169] This research has yielded four types of chiral oxaziridines **124**−**127** (Figure 16) which, as a

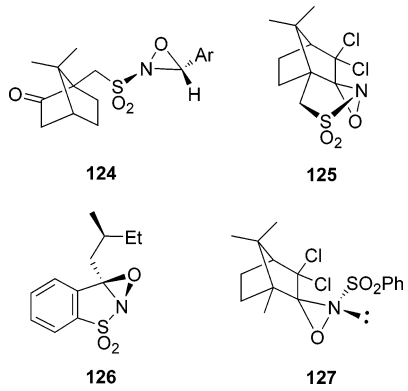


Figure 16.

result of their dissimilar active-site structures, give different stereoselectivities.[170−175]

(Camphorylsulfonyl)oxaziridine **127** (X = Cl), the most effective and general analogue, gives a large number of sulfoxides in high enantioselectivity and in a predictable manner. The oxidation of sulfides is generally conducted in CCl_4 or CH_2Cl_2 at 20 °C by treatment with 1 equiv of the oxaziridine (Table 12).

Table 12. Asymmetric Sulfoxidation of Sulfides, R_1SR_2, with Oxaziridine 127

R_1	R_2	yield (%)	config at S	ee (%)
p-tolyl	Me	95	*S*	>95
p-anisyl	Me	74	*S*	80
p-tolyl	$PhCH_2$	94	*S*	88
c-propyl	Ph	90	*S*	92
2-naphthyl	Me	84	*S*	94
9-anthranyl	Me	90	*S*	95
9-anthranyl	*i*-Pr	60	*S*	94
Me	*t*-Bu	84	*S*	94
$PhCH_2$	*t*-Bu	80	*S*	94
Me	*n*-octyl	60	*S*	45

The highest ee's (>90%) were observed for those sulfides in which the R_1 and R_2 groups were sterically very different.

Although the Davis and Kagan reagents give similar results for aryl alkyl sulfides, the former is generally better for the oxidation of dialkyl sulfides.[52] The high asymmetric oxidation of sulfides to sulfoxides has been explained by an active-site model that consists of three pockets, A, B, and C (Figure 17). For the oxaziridine **127**, the pocket B, defined by the

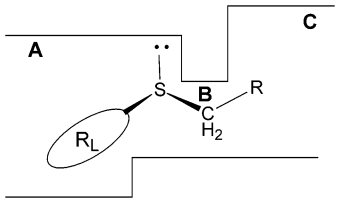


Figure 17. Top view of active-site model for (+)-**127**.

two chlorine atoms and the phenylsulfonyl group, is responsible for the high enantioselectivity exhibited for the oxidation of sulfides, and the absolute stereochemistry of the final sulfoxides is predicted in terms of a simple steric model.

In a related work, Page reported a method directed toward the in situ generation of a chiral oxaziridine. Various chiral nonracemic 3-substituted 1,2-benzisothiazole-1,1′-diooxide-type compounds **128** (Figure 18) were synthesized and used in the oxidation

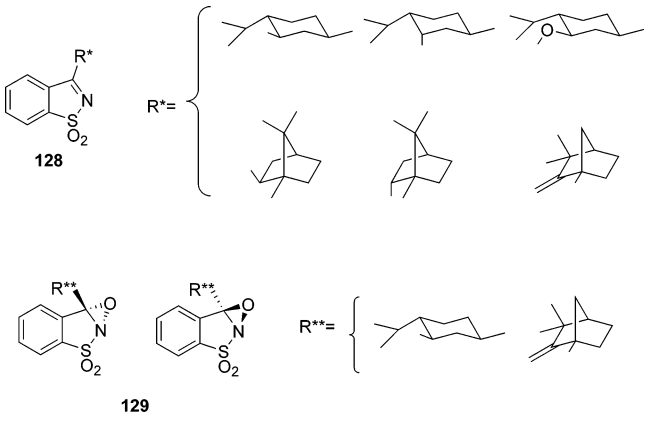


Figure 18.

of prochiral sulfides using hydrogen peroxide as the primary oxidant.[176] Using 1 equiv of sulfonylimines **128**, 4 equiv of H_2O_2, and 4 equiv of DBU per equivalent of sulfide, various prochiral sulfides were oxidized efficiently to the corresponding sulfoxides but with very low ee's (8−38%). To determine the mechanism of oxygen transfer in the reaction, the corresponding oxaziridines **129** were synthesized and used to oxidize the prochiral thioether. The result obtained shows that the sulfoxides are obtained in higher ee's with the oxaziridines than with the imines, and that the predominant enantiomer was the same as the one obtained using hydrogen peroxide and the corresponding imine mediator. These results show that the identity of the oxidizing species using imine **128**, hydrogen peroxide, and DBU remains uncertain.

VI. Enantioselective Sulfoxidation by Chiral Peroxides

In 1997, optically active hydroperoxides derived from sugars were used for the first time as enantioselective oxygen-transfer agents in the asymmetric oxidation of prochiral sulfides.[177] Hydroperoxides **130** and **131** (Figure 19) were obtained by oxidation of the corresponding α-methyl glycosides with hydrogen peroxide (in 65% and 75% yield, respectively) and were used in the asymmetric oxidation of methyl phenyl and methyl *p*-tolyl sulfides, giving the corresponding sulfoxides in a modest 25% ee.

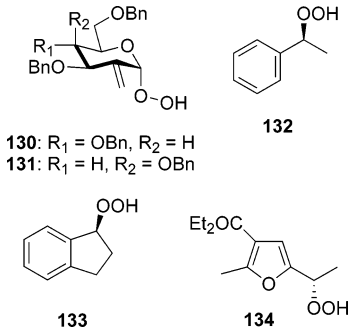


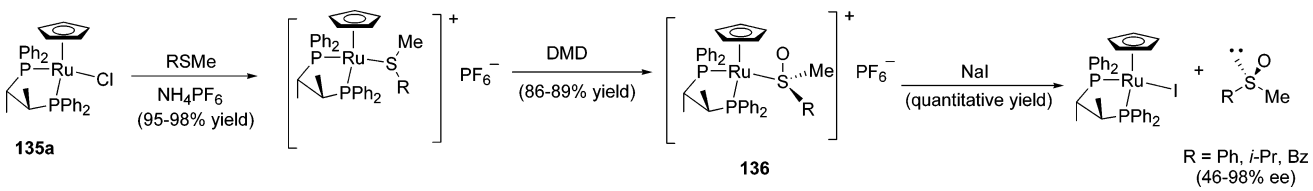
Figure 19.

Recently, Korb reported the use of enantiomerically pure hydroperoxides such as **132**−**134** (Figure 19), easily obtained by horseradish peroxidase-catalyzed kinetic resolution,[178] in the asymmetric oxidation of alkyl aryl sulfides.[179] The best results were obtained with (*S*)-(−)-phenylethyl hydroperoxide **132** at −20 °C in CCl_4, which afforded (*S*)-sulfoxides with low to modest enantioselectivity and low yield. A time profile of the oxidation of methyl *p*-tolyl sulfide with **132** showed that the asymmetric induction in the sulfoxidation was rather low (<20%), demonstrating that the enantioselectivity obtained is due to a concomitant kinetic resolution of the sulfoxide formed.

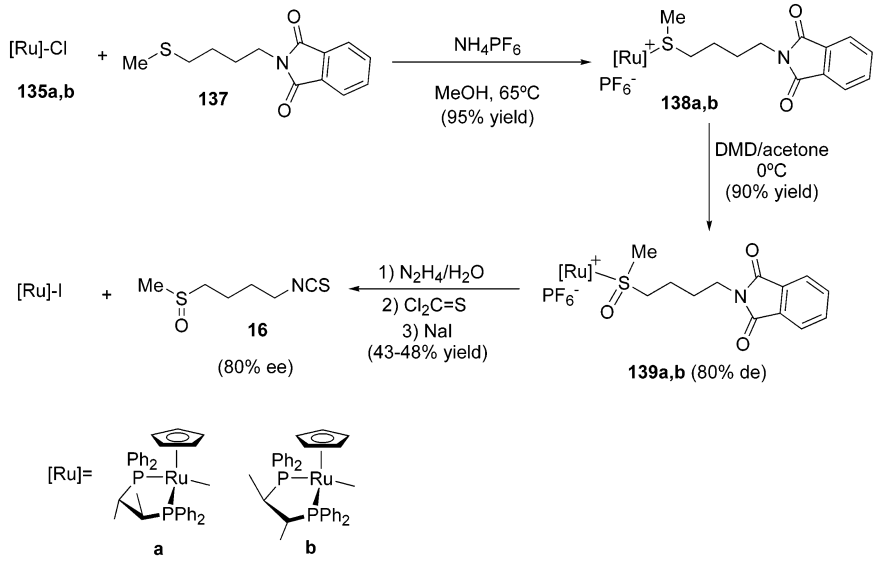
VII. Asymmetric Oxidation of Metal-Complexed Prochiral Thioethers

The main methodologies described thus far for enantioselective oxidation of sulfides are effective only in the oxidation of alkyl aryl sulfides, but dialkyl sulfides are generally oxidized with only poor selectivity. In an attempt to solve this problem, the Schenk group recently reported a stereoselective oxidation of metal-coordinated thioethers with dimethyldioxirane (DMD) (Scheme 30).[180] The prochiral thioether is first coordinated to a chiral ruthenium complex by reaction with the chloride complex [CpRu(*S*,*S*)-CHIRAPHOS]Cl] **135a** (Scheme 30). Diastereoselective oxygen transfer from DMD produces the corresponding sulfoxide in high yield and selectivity. The chiral sulfoxides are liberated from the complex **136** by treatment with sodium iodide. Several aryl methyl sulfoxides were obtained by this method in moderate to high ee (Scheme 30).[181] The authors recently applied this methodology to the synthesis of both isomers of sulforaphane (**16**), using either

Scheme 30



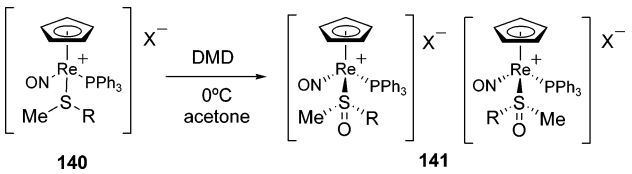
Scheme 31



[CpRu(*S*,*S*)-CHIRAPHOS]$^+$ or [CpRu(*R*,*R*)-CHIRAPHOS]$^+$ as chiral auxiliary.[182] The reaction between the ruthenium complex **135** (Scheme 31) and phthalimidobutyl methyl sulfide **137** in boiling methanol gave the complexed sulfide **138** in quantitative yield. Oxidation of this sulfide complex with 3-fold excess of DMD gave a nearly quantitative yield of the corresponding sulfoxides **139** (89:11 dr). The amino group of **139** was readily deprotected by hydrazolysis in methanol/water and transformed to an isothiocyanate group by treatment at 0 °C with thiophosgene and sodium hydroxide, and finally treatment with NaI afforded enantiomers of sulforaphane **16** in 43−48% yield and 80% ee (Scheme 31).

The same strategy was pursued by Gladysz for the oxidation of prochiral sulfides rhenium complexes **140** (Scheme 32). Among the oxidizing agents screened

Scheme 32[a]



[a] X = BF_4, TfO.

for the oxidation of these complexes, dimethyl dioxirane gave the best results. The DMD oxidation, conducted in an NMR tube, led to the sulfur-bound sulfoxides **141** in fair to good yields and diastereoselectivity (Scheme 32). However, except at low conversions, the oxidation gives a significant amount of phosphine oxide byproduct.[183]

VIII. Nucleophilic Substitution on Diastereomerically Pure Chiral Sulfur Derivatives

This is an indirect approach to enantiomerically pure sulfoxides which consists of the synthesis, in a preliminary step, of a sulfinylating agent with an electrophilic sulfur of known configuration, followed by nucleophilic addition of a metal organic reagent. Two approximations have been followed along these lines: (i) those using a chiral cyclic sulfinylating agent and (ii) those using a diastereomerically pure acyclic sulfinylating agent.

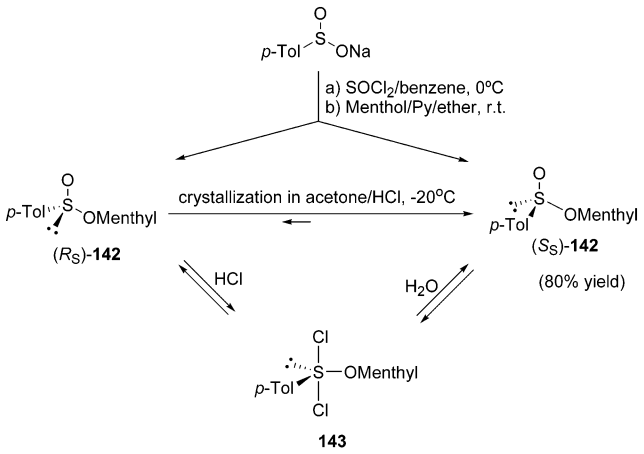
A. Historical Perspective

The latter approximation is undoubtedly the most widely used for the synthesis of optically pure sulfoxides. Its success relies on the fact that the sulfinylating agent can be obtained in 100% de thanks to either a good kinetic resolution or a high separation factor of the intermediate diastereoisomers formed. Until quite recently, the so-called Andersen method was the unique adaptation of this approximation. On the basis of the seminal work of Gilman,[184] Andersen proved at the beginning of the 1960s[185] that the nucleophilic substitution of diastereomerically pure (−)-(*S*)-menthyl sulfinates with Grignard reagents[186] leads to enantiopure sulfoxides with high yields. Mislow demonstrated later by means of chemical correlation[187] and optical rotatory dispersion studies[188,189] that this substitution occurs with complete inversion of configuration at the sulfinyl sulfur. Nevertheless, the synthesis of diastereomerically pure sulfinate esters by the Andersen method was experimentally tedious. The esterification reaction of (−)-menthol with *p*-toluenesulfinyl chloride, using pyridine as base, occurs without any stereoselectivity; thus, several fractional crystallizations were needed to obtain the sulfinylating agent in enantiopure form.

The work of Mioskowski and Solladié on the asymmetric transformation of **142** induced by crystallization constituted a real breakthrough in the synthesis of sulfoxides (Scheme 33). Epimerization of sulfinate esters (*R*)-**142** and (*S*)-**142** in acidic medium through **143** with an achiral sulfur atom[189] allowed the less soluble isomer (*S*)-**142** to be obtained in very high yield (80−90%).[190]

The Andersen methodology has allowed the synthesis of a wide variety of enantiomerically pure aryl sulfoxides,[191] but it suffers from the considerable drawback of not being general. Accordingly, dialkyl sulfoxides cannot be obtained by this method, as menthyl alkanesulfinates cannot be prepared dias-

Scheme 33



tereomerically pure (for instance, menthyl methanesulfinates are oils, and attempts to separate both epimers at sulfur have not succeeded). The lack of generality of this methodology, associated with an increasing need for diverse optically pure sulfoxides with tailored structures, promoted the development of different methodologies at the beginning of the 1990s. The scope, limitations, and applications of these methods will be discussed in detail in the following sections.

B. Nucleophilic Substitution on Chiral, Diastereomerically Pure Cyclic Sulfinylating Transfer Reagents

The basic idea behind these approaches is the utilization of a chiral bifunctional scaffold that is able to differentiate the two enantiotopic chlorine atoms of thionyl chloride, a low-cost sulfur compound. So far, two chiral scaffolds have been used, amino alcohols and diols. The overall scheme consists of three distinct steps: the formation of a chiral cyclic aminosulfite or a cyclic sulfite as a chiral sulfinylating transfer agent, followed by two consecutive reactions with organometallic reagents to afford a chiral sulfoxide.

1. Aminosulfite Methodologies

This concept was pioneered by Wudl and Lee in 1973, using ephedrine as chiral auxiliary.[192] The reaction with thionyl chloride at 0 °C, using NEt_3 as base, led to 1,2,3-oxathiazolidine-*S*-oxides (aminosulfite **144**, Scheme 34) in good yield and modest selectivity (44% de) after the diastereomers were separated by recrystallization. A first organometallic reagent reacts chemoselectively with the aminosulfite **144**, affording acyclic sulfinamide **145**, with some epimerization proposed to occur by a sulfinyl-transfer mechanism. The second carbon nucleophile substitution leading to chiral sulfoxide occurs in good yield only with organolithium reagents, due to the difficulty of breaking the S−N bond, and often results in significant racemization.

Table 13. Synthesis of Sulfoxides from Sulfinamides 145 (Scheme 34)

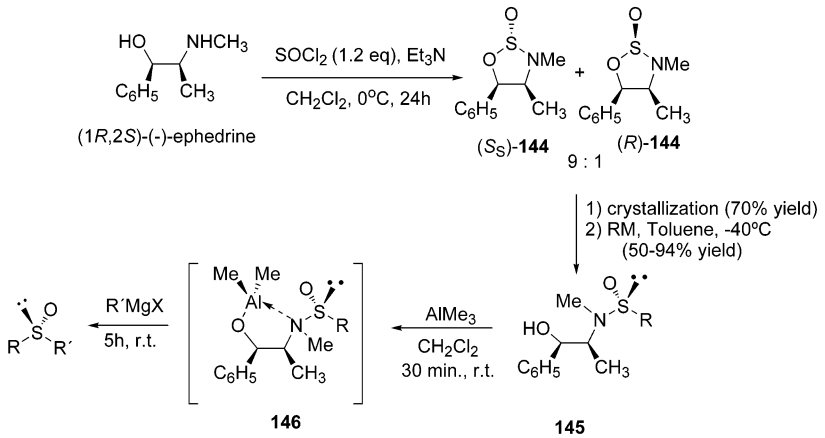
entry	sulfinamide **145** R	R'M	sulfoxide config	yield (%)	ee (%)
1	Me	PhMgBr	*S*	71	>99
2	Me	C_6F_5Li	*S*	30	60
3	Me	*n*-BuMgCl	*S*	76	>99
4	Me	*t*-BuMgCl	*S*	63	>99
5	CH_2=CH	PhMgBr	*S*	75	>99
6	CH_2CH=CH_2	PhMgBr	*S*	62	>99
7	*t*-Bu	PhMgBr	*a*		

[a] Only sulfinamide was recovered.

This procedure was modified in 1991 by Snyder and Benson, who obtained optically pure sulfoxides in high yield (Scheme 34).[193]

It was found that by storing the diastereomers (S_S)-**144** and (R_S)-**144** at 0 °C for 24 h in the presence of Et_3NHCl, the diastereoselectivity increased to 80%, and the diastereomer (S_S)-**144** could be isolated in 70% yield by crystallization. The addition of freshly prepared Grignard reagents to (S_S)-**144** in toluene led to the synthesis of sulfinamides **145** in good yield and diastereoselectivity. Nevertheless, no phenyl organometallic was able to give the corresponding intermediate phenyl sulfinamide **145** in good yield, this limitation being one of the considerable drawbacks of the method for the synthesis of diaryl sulfoxides. Additionally, to obtain the corresponding sulfoxides (Table 13) in good yields and enantioselectivities (>99% ee), the addition of $AlMe_3$ to the intermediate sulfinamide **145** is necessary prior to the addition of the Grignard reagent (Scheme 34). The *tert*-butyl sulfinamide **145** (R = *t*-Bu, entry 7 in Table 13) was

Scheme 34

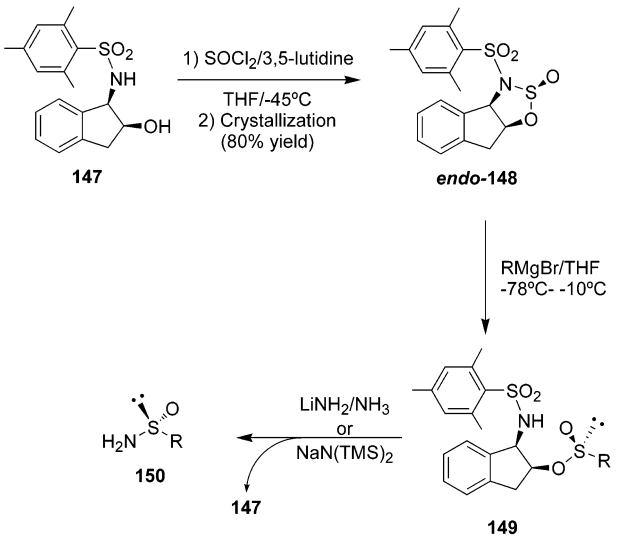


unreactive, and thus no *tert*-butyl sulfoxide could be produced under any conditions with any Grignard reagent.

The modified aminosulfite methodology is suitable for the synthesis of dialkyl and alkyl aryl sulfoxides in high ee. Both enantiomeric sulfoxides may be produced, either by reversing the order of organometallic displacement or by using the commercially available (1*S*,2*R*)-(+)-enantiomer of ephedrine. Compared with Kagan's sulfite (vide infra), the method has the advantage of regioselectivity but is limited by the inability to produce any *tert*-butyl or diaryl sulfoxides.[193]

Interestingly, Senanayake very recently found that the activation of the nitrogen atom in the aminosulfite intermediate with an electron-withdrawing group solves the latter problem by inverting the bond-cleaving order (S−N vs S−O).[194] The approximation uses *N*-sulfonyl (1*R*,2*S*)-aminoindanol as chiral auxiliary for the synthesis of activated 1,2,3-oxathiazolidine-2-oxide. It was found that the reaction of the *N*-sulfonyl amino alcohol **147** with thionyl chloride in the presence of 3,5-lutidine as base in THF afforded *endo*-**148** in 94% de on kilogram scale (Scheme 35). Interestingly, the activation of the

Scheme 35



nitrogen atom weakenes the S−N bond, reverting the reactivity of 1,2,3-oxathiazolidine-2-oxide toward nucleophile. Accordingly, the reaction of *endo*-**148** with hindered Grignard reagents occurs in a chemoselective manner, with complete inversion of configuration at the sulfinyl sulfur, affording diastereomerically sulfinate esters **149** instead of sulfinamide.

The usefulness of this method was demonstrated by the synthesis of various enantiopure aryl and alkyl sulfinamides **150a**−**f** (Figure 20), important building blocks (vide infra), by condensation of $LiNH_2/NH_3$ or $NaN(TMS)_2$ in THF at −78 °C. The accessibility of the intermediate, diastereomerically pure sulfinate esters bodes well for the future application of this approach for the synthesis of enantiopure sulfoxides by condensation of carbon nucleophile on the intermediate **149** in an Andersen-like manner.

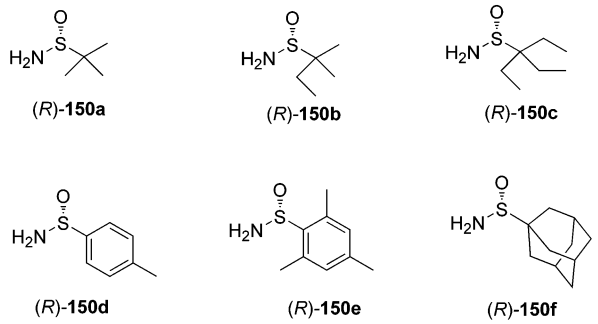


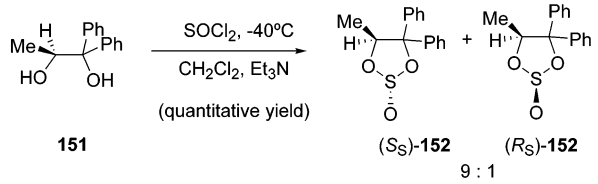
Figure 20.

2. The Sulfite Methodology

In 1991, Kagan reported a more general route using a cyclic sulfite[195] which solved some of the problems presented by the Wudl−Lee/Snider−Benson approaches.[196,197]

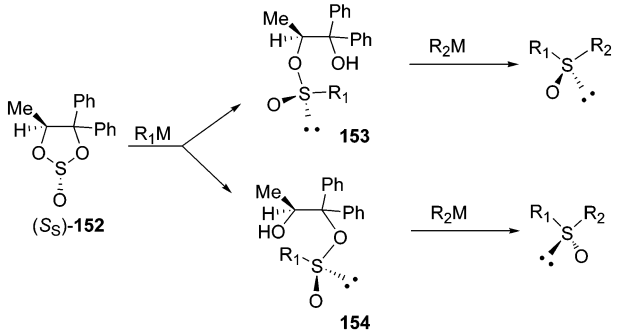
The intermediate five-membered ring cyclic sulfite was prepared by using the chiral diol **151** (Scheme 36), easily obtained from ethyl lactate in one step

Scheme 36



(75%).[198] The reaction of **151** with $SOCl_2$ gave a 1:1 mixture of *trans*- and *cis*-sulfite, (S_S)-**152** and (R_S)-**152**. It was found that the diastereoselectivity could be enhanced to 80% in favor of the *trans*-isomer (S_S)-**152** with a simple change in the experimental conditions. By adding NEt_3 slowly into a CH_2Cl_2 solution of diol **151** and thionyl chloride at −40 °C, sulfite (S_S)-**152** was obtained optically pure in 70% yield after crystallization from hexanes. In contrast to acyclic sulfites, which gave symmetric sulfoxides with small organometallics,[199] sulfite (S_S)-**152** was found to react cleanly with various organometallic reagents to give the corresponding intermediate sulfinate esters (Scheme 37). The *trans* structure of the starting

Scheme 37



sulfite (S_S)-**152** was originally determined by assuming a double inversion of configuration in both successive reactions with organometallics R_1M and R_2M. This is based on the transformation to sulfoxides with known absolute configuration. Recently,

this assignment has been confirmed by an X-ray analysis of the major sulfite (S_S)-**152**.

The regioselective ring-opening of the cyclic sulfite, with two potential leaving groups, is closely related to the steric volume of the organometallic. Accordingly, when R_1 is small, such as Et, *n*-octyl, or vinyl, the sulfinate **154** is the major product (>80%), whereas when R_1 is bulky, such as *t*-Bu or mesityl, sulfinate **153** is mainly obtained (80% and 76%, respectively). It was obtained with only moderate selectivity using MeMgI (60%) and with poor selectivity in the cases of benzyl and phenyl sulfinates (40 to 0%, see Table 14). Optically pure sulfinates were

Table 14. Synthesis of Chiral Sulfinates 153 and 154 from Sulfite (S_S)-152 (Scheme 37)

entry	R_1M	**154**:**153** ratio	isolated yield[a] of major sulfinate (%)
1	MeLi	75:25	55
2	MeMgI	80:20	70
3	EtMgBr	92:9	80
4	*n*-OctMgBr	95:5	60
5	*t*-BuMgBr	5:95	60
6	*t*-BuMgCl	10:90	70
7	*t*-BuLi	*b*	
8	BnMgCl	70:30	50
9	BnMgBr	55:45	*c*
10	HC=CHMgCl	95:5	50
11	MesitylMgBr	12:88	70
12	PhMgBr	50:50	*c*

[a] Purification by crystallization. [b] Only di-*tert*-butyl sulfoxide is obtained. [c] Separation of the two diastereomers by crystallization failed.

obtained via recrystallization, with an isolated product yield in the range of 60−80%.

The sulfinate esters, with a free hydroxyl group, were finally transformed to optically pure sulfoxides by treatment with 2 mol equiv of the Grignard or organolithium reagents (THF/room temperature). In this way, various dialkyl, alkyl aryl, and diaryl sulfoxides have been obtained in quantitative yield and in 100% ee (Table 15).

Table 15. Synthesis of Enantiomerically Pure Sulfoxides from Sulfinates 153 and 154 and an Organometallic R_2M (Scheme 37)

entry	sulfinate (R_1)	R_2	config of sulfoxide
1	**153** (*t*-Bu)	MeLi	*R*
2	**153** (*t*-Bu)	PhLi	*S*
3	**153** (*t*-Bu)	*n*-BuLi	*R*
4	**153** (*t*-Bu)	H_2C=CHMgCl	*R*
5	**153** (*t*-Bu)	1-[(2-CH_2)C_5H_4N]Li	*R*
6	**153** (*t*-Bu)	$PhCH_2MgBr$	*R*
7	**153** (*t*-Bu)	$Ph(CH_2)_2MgBr$	*R*
8	**153** (mesityl)	MeLi	*R*
9	**153** (mesityl)	PhMgBr	*R*
10	**154** (Me)	*n*-OctMgBr	*R*
11	**154** (Et)	PhLi	*R*
12	**154** (Et)	$PhCH_2MgBr$	*R*
13	**154** (*n*-octyl)	MeMgI	*S*
14	**154** ($PhCH_2$)	EtMgBr	*S*

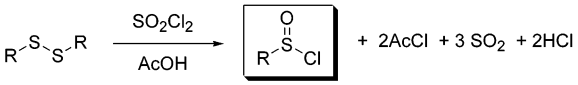
This method allows both isomers of a given sulfoxide to be synthesized by permutation of R_1 and R_2 in the organometallics involved in the two substitution steps and has been applied to the synthesis of optically pure (*R*)- and (*S*)-methyl octyl sulfoxide and benzyl ethyl sulfoxide. Thus, a single intermediate is used in an enantiodivergent approach to both sulfoxides. This can be applied only when both R_1 and R_2 are either small or bulky; when one of the groups is small and the other bulky, the permutation leads to the same sulfoxide. Nevertheless, the commercially available (*R*)-isobutyl lactate can be used for the synthesis of the other sulfite enantiomer. The sulfite method is a good diastereoselective route to optically pure sulfoxides, especially when group permutation is possible.

This method resolves some of the limitations of the traditional methodology in the synthesis of some dialkyl sulfoxides with high ee, and it is particularly suitable for the synthesis of *tert*-butyl sulfoxides. However, it suffers severely from the tedious experimental conditions leading to the sulfoxides from diol **151**. Several crystallizations are required—the first one to purify the *trans*-sulfite, a second one to purify the hydroxy sulfinate and, finally, column chromatography to purify the sulfoxide. This may be the reason this method has been scarcely reported in the literature.[200,201]

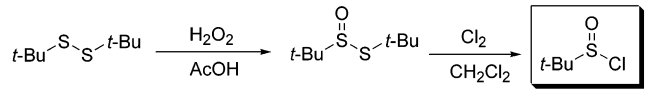
C. Nucleophilic Substitution on Chiral Acyclic Sulfinylating Transfer Reagents

To develop an effective Andersen-like strategy, various inducers of chirality were tried instead of the widely used menthol at the beginning of the 1990s. So far, various secondary carbinols, chiral amides, and sultam have been used to generate diastereomerically pure acyclic sulfinylating transfer reagents by either kinetic or dynamic transformation of sulfinyl chlorides. It is worth mentioning that actually a large number of methods permit the synthesis of diverse kind of alkyl, aryl, and functionalized sulfinyl chlorides (Scheme 38),[202] broadening the scope of these approaches.[203−205]

Scheme 38



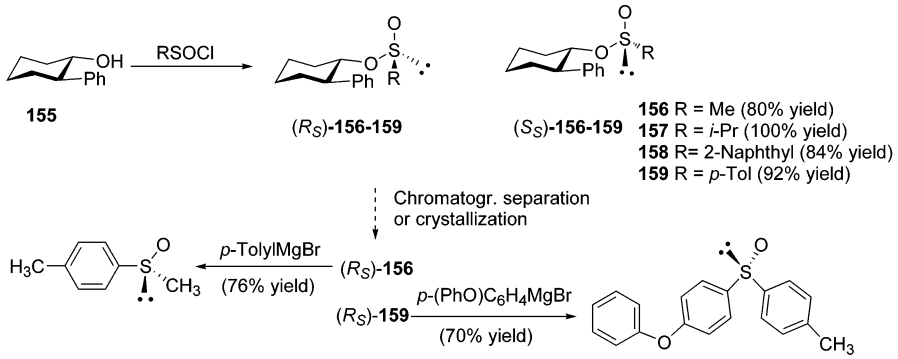
R= Me, Et, Pr, *i*-Pr, *p*-Tol, Bz, Ph, MeC(O)-CH_2-CH_2



1. Cyclohexyl-Based Methodology

The Whitesell group investigated the use of *trans*-2-phenylcyclohexanol **155** (Scheme 39), introduced by them in 1985,[206] as chiral auxiliary for the synthesis of chiral sulfoxides.[207] Sulfinate esters (R_S)-**156**−**159** and (S_S)-**156**−**159** were obtained in good yields and moderate selectivity (4: 1−10: 1) by the reaction of **155** with an excess of alkane- or arenesulfinyl chloride. The diastereomeric sulfinates obtained were separated either by crystallization or by column chromatography. In this way, two alkane- (**156** and **157**) and two arenesulfinates (**158** and **159**) were

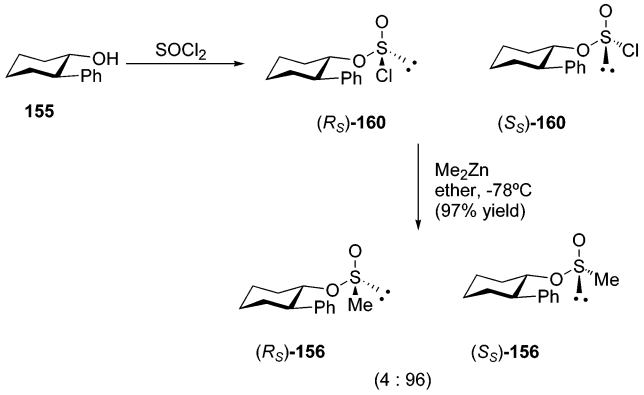
Scheme 39



prepared optically pure by this methodology (Scheme 39).[208] The reported method has permitted the synthesis of optically pure (*R*)-methyl *p*-tolyl sulfoxide and (*S*)-*p*-phenoxyphenyl *p*-tolyl sulfoxide in 76% and 70% yield, respectively.

The reaction of chlorosulfite esters of *trans*-2-phenylcyclohexanol with nucleophiles was later investigated, to improve the stereochemical control and to circumvent the use of sulfinyl chlorides in the synthesis of sulfinate esters (Scheme 40).[209] Thus, a

Scheme 40

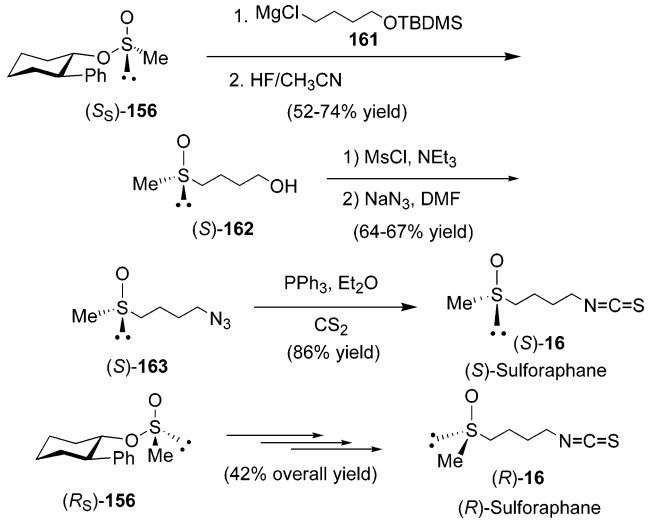


mixture of chlorosulfinates (S_S)-**160** and (R_S)-**160** in 1:1 and 2:1 ratios were obtained by reaction of **155** with thionyl chloride at room temperature and −78 °C, respectively. Reaction of the diastereomeric mixture of chlorosulfite esters (S_S)-**160** and (R_S)-**160** with different amounts of dialkylzinc reagent (Me, Et, *i*-Pr) afforded the corresponding sulfinate esters with high diastereoselection (>80%). Thus, in the reaction with Me_2Zn, the mixture of chlorosulfite (S_S)-**160** and (R_S)-**160** underwent a dynamic kinetic resolution, leading to methane sulfinate (S_S)-**156** and (R_S)-**156** in a 98:2 ratio (Scheme 40).

However, the reaction of chlorosulfite esters with alcohols and amines produced sulfinic acid derivatives in good yield but with low selectivity (<2:1). Additionally, this chlorosulfite method works only in the case of methanesulfinate, and the levels of control of diastereomeric excess with arylzinc and any arylmetal were in general very low.

The usefulness of the approach in producing methanesulfinates in high de was demonstrated by the synthesis of both isomers of the anticancer compound sulforaphane **16** (Figure 2).[208] Methanesulfinate **156** was reacted with the Grignard reagent **161**, followed by removal of the TBDMS group by HF in acetonitrile, affording the alcohols **(***S***)-162** and (*R*)-**162**. Mesylation, followed by treatment with sodium azide, afforded the azido sulfoxide (*S*)-**163** and (*R*)-**163** (Scheme 41). Staudinger reaction of the azido derivative with triphenylphosphine and subsequent aza Wittig-type condensation of the resulting iminophosphorane with carbon disulfide led to enantiomerically pure (*R*)- and (*S*)-sulforaphane in very high yield (Scheme 41).

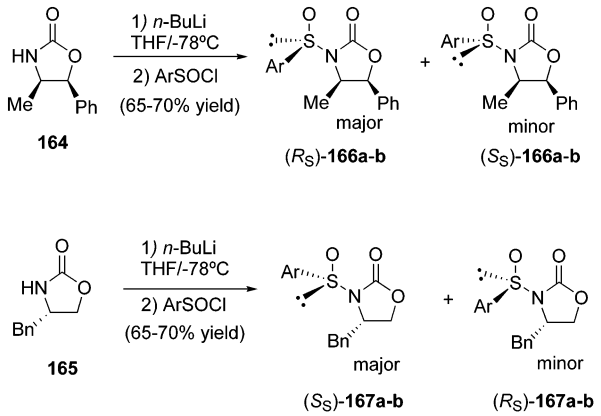
Scheme 41



2. N-Sulfinyloxazolidinones Methodology

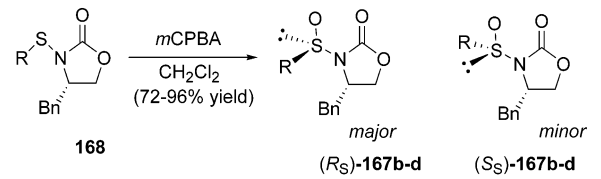
In 1992, Evans and co-workers described a new sulfinyl-transfer reagent, the *N*-sulfinyloxazolidinones **166** and **167**, derived from (4*R*,5*S*)-norephedrine and (4*S*)-phenylalanine, respectively.[210] Two different methods were used to prepare **166** and **167**, either by sulfinylation of the corresponding metalated oxazolidinone (Scheme 42)[211] or by oxidation of the corresponding *N*-sulfenamide **168** (Scheme 43). In both cases, the diastereoselective formation of *N*-sulfinyloxazolidinones was poor to modest (Table 16), but the mixtures of diastereomers were readily purified by chromatography. The sulfinylation diastereoselection of metalated oxazolidinone (Scheme 42) has been shown to be under thermodynamic control. Accordingly, treatment of diasteremerically pure **166a** (S_S) with either 1.0 or 0.1 equiv of lithiated oxazolidinone at −78 °C affords in less than 1 min a

Scheme 42[a]



[a] **a**: Ar = *p*-Tol. **b**: Ar = Ph.

Scheme 43[a]



[a] **b**: R = Ph. **c**: R = Me. **d**: R = *t*-Bu.

Table 16. Methods of Synthesis of *N*-Sulfinyloxazolidinones 166 and 167 (Schemes 42 and 43)

N-sulfinyl-oxazolidinone	method of synthesis	de (%)	isolated yield (% R_S)	isolated yield (% S_S)
166a	sulfinylation	32	69	1
166b	sulfinylation	54	61	4
167a	sulfinylation	46	9	61
167b	sulfinylation	44	20	50
167b	oxidation	42	68	28
167c	oxidation	16	a	33
167d	oxidation	16	35	49

[a] (R_S)-**167c** was unstable to chromatographic purification.

71:29 mixture of diastereomers. This same equilibrium ratio was also obtained from analogous experiments starting from diastereomer **166a** (R_S). The configurational assignment of **166** and **167** was achieved by X-ray crystallography and chemical correlation.

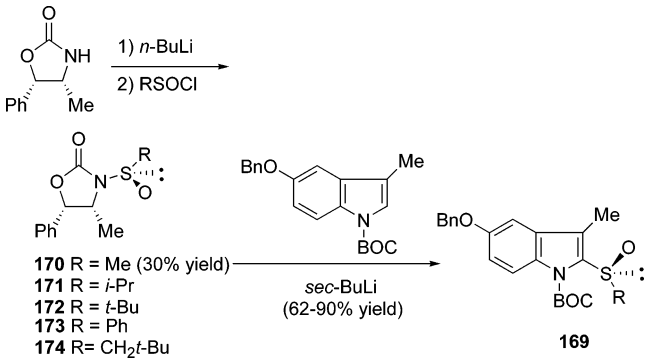
These compounds have been shown to be efficient sulfinylating agents. Various aryl alkyl and dialkyl sulfoxides have been obtained, in high yields (78−92%) and enantioselectivities (> 90%), by reaction of the *N*-sulfinyloxazolidinones with Grignard reagents (Table 17). The Evans group used this new sulfinyl-transfer reagent for the synthesis of (*S*)-*tert*-butyl (phenylsulfinyl)acetate in high yield using the Reformatsky reagent derived from *tert*-butyl bromoacetate and activated zinc.

It has been demonstrated that the nucleophilic displacement in *N*-sulfinyloxazolidinones occurs with inversion of configuration at the sulfur center, permitting the synthesis of chiral sulfinate esters, sulfinamides, and sulfoxides with high ee. Interestingly, the Evans group has shown that chiral *N*-sulfinyloxazolidinone is at least 2 orders of magnitude more reactive than Andersen's menthyl sulfinate ester.

Table 17. Synthesis of Sulfoxides, $R_1S(O)R_2$, from *N*-Sulfinyloxazolidinones 167 (Scheme 43)

entry	R_1	R_2	yield (%)	ee (%)	config at S
1	Me	*p*-Tol	90	99	*S*
2	Et	*p*-Tol	90	98	*S*
3	*i*-Pr	*p*-Tol	91	97	*S*
4	*t*-Bu	*p*-Tol	88	97	*S*
5	Bn	*p*-Tol	86	99	*S*
6	Me	Ph	87	90	*R*
7	Me	*t*-Bu	78	93	*R*
8	Me	Bn	82	91	*R*
9	Me	octyl	78	100	*R*
10	*t*-Bu	Me	92	100	*S*
11	*t*-Bu	*n*-Bu	91	100	*S*

Scheme 44

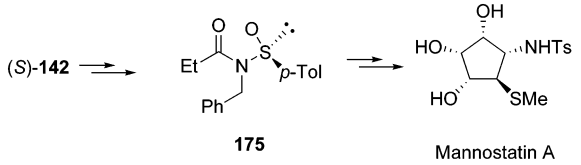


This result shows that the N−S bond with an electron-withdrawing group can be cleaved chemoselectively in the presence of an O−S bond, which constitutes an antecedent of the Senanayake approach (vide supra). Additionally, the *N*-sulfinyloxazolidinone method avoids some of the problems of the sulfinate ester approach, which is related to the nature of the alkoxide leaving group in the nucleophilic substitution.

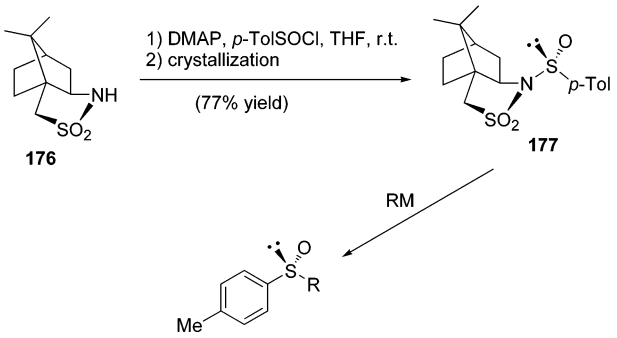
At the same time, Marino reported on the synthesis of sulfinyloxazolidinone (Scheme 44) as chiral intermediate in the total synthesis of optically pure (−)-physostigmine.[212] As the Andersen method fails in the preparation of alkyl indoyl sulfoxides of type **169** (R = CH_3), probably due to the poor electrophilic character of menthyl methanesulfinate, they thought of the utilization of a sulfinyloxazolidinone as a more electrophilic sulfinyl-delivering group. While full details are not given for the synthesis of the sulfinyloxazolidinone, they reported the synthesis and utilization of five optically pure sulfinyloxazolidinones **170**−**174**. In the case of *N*-(methyl or *tert*-butylsulfinyl)oxazolidinones **170** or **172**, reaction with a variety of Grignard reagents gave sulfoxides with optical yield ranging from 90 to 97%.

Recently, García Ruano and co-workers developed the *N*-acetylated sulfinamide **175** as a new, highly reactive sulfinylating agent (Scheme 45), obtained

Scheme 45



Scheme 46



from menthyl *p*-toluenesulfinate.[213] As in the case of the *N*-sulfinyloxazolidinones of Evans, the increase in reactivity is due to the amide anion as leaving group. They have applied this *N*-sulfinylated reagent in the synthesis of the glycosidase inhibitor mannostatin A.[214]

3. N-Sulfinylsultam Methodology

As part of a broad program on the use of the versatile bornane-10,2-sultam **176** (Scheme 46) in asymmetric synthesis,[215] the Oppolzer group recently reported on the synthesis and use of the *N*-sulfinylsultam **177** as a new sulfinylating agent. [216] The *N*-(*p*-tolylsulfinyl)bornane-10,2-sultam was obtained as a 6.2:1 diastereomeric mixture by condensation of *p*-toluenesulfinyl chloride with **176** in THF, in the presence of (dimethylamino)pyridine (DMAP) as catalyst. Optically pure *N*-sulfinylsultam **177** was obtained, in 77% yield, by crystallization of the mixture from Et_2O/hexane. X-ray analysis showed the absolute configuration at the sulfinyl sulfur to be R_S.[216] The reaction has been shown to be kinetically controlled, in contrast to the results obtained when *n*-BuLi was used instead of DMAP. In the case of *n*-BuLi, the reaction was under thermodynamic control, in accord with the result obtained by Evans with the *N*-sulfinyloxazolidinone.

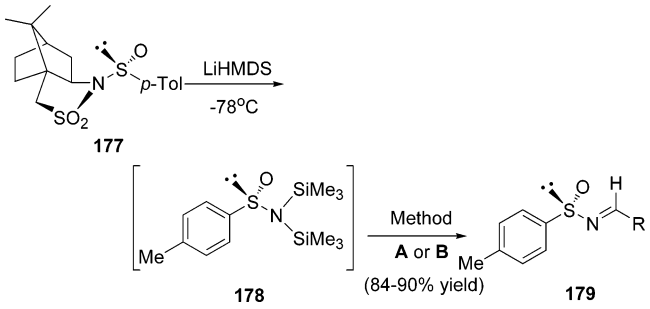
As a good sulfinylating agent, the *p*-toluenesulfinamide **177** reacts with various Grignard and Reformatsky reagents to give enantiomerically pure sulfoxides in high yield (Table 18), together with bornane-10,2-sultam **176**, which can be recovered (≥91% yield) and reused.

Table 18. Synthesis of Optically Active Alkyl (or Aryl) *p*-Tolyl Sulfoxides from *p*-Toluenesulfinamide 177 and Organometallic RM (Scheme 46)

RM	yield (%)	config	ee (%)
MeMgBr	93	*R*	99
i-PrMgCl	92	*R*	99
n-BuMgCl	97	*R*	97
BnMgCl	91	*R*	>99
vinylMgCl	95	*R*	96
(*Z*)-1-propenylMgBr	80	*R*	99
(*E*)-1-propenylMgBr	79	*R*	96
2-propenylMgBr	90	*R*	>99
allylMgCl	96	*R*	>99
2-thienylMgBr	89	*S*	99
3-furylMgBr	89	*S*	99
1-pentynylMgBr	85	*R*	>98
$BrZnCH_2COOt$-Bu	83	*R*	>99

The enantiopure *N*-sulfinylimines **179**, as precursors in the synthesis of enantiomerically pure amines and α- and *β*-amino acid derivatives, have also been prepared from the sulfinylsultam **177**.[217] In the case of enolizable aldehydes, the addition of 1 equiv of water to the sulfinylated HMDS **178**, prior to the addition of the aldehyde, was necessary to obtain the enantiomerically pure sulfinimines **179**, which could not be prepared by the original Davis procedure. Thus, both enolizable and nonenolizable aldehydes can afford enantiomerically pure aryl and alkyl sulfinilimine **179** in good yield (Scheme 47).

Scheme 47[a]



[a] Method A: (i) 1 equiv of H_2O in THF, −78 °C; (ii) 1.1 equiv of RCHO, −20 to 5 °C. Method B: (i) 1.1 equiv of RCHO, −20 °C; (ii) 2 equiv of CsF, −20 °C to room temperature.

4. The DAG (Diacetone-D-glucose) Methodology

Carbohydrates provide an ample body of hydroxylic functions in many configurations that can be easily manipulated and selectively protected in order to get a specific secondary alcohol. One such chiral carbinol is the pseudo-C_2-symmetric alcohol diacetone-D-glucose (DAG) **180**, obtained by a single ketalization step from glucose, the cheapest member of the chiral pool. At the beginning of the 1990s, we used alcohol **180** in the synthesis of chiral sulfinates. A general enantiodivergent approach for the synthesis of both enantiomers of a large number of dialkyl, diaryl, and alkyl aryl sulfoxides has resulted, which we named the "DAG methodology" (Scheme 48).[218]

The reaction of diacetone-D-glucose **180**[219] with various alkane (Me, Et, Pr, *i*-Pr, *t*-Bu) and *p*-toluenesulfinyl chlorides (Table 19) in THF at −78 °C, using pyridine as base, gave the corresponding sulfinate esters **181**−**186**, in high yield and selectivity in favor of the (R_S)-isomer (ranging from 86:14 to ≥98:≤2).[218,220−222] When Hunig's base (*i*-Pr_2NEt) was used as base, the diastereoselectivity of the reaction was improved (Table 19), and a single isomer was obtained in most of the cases. Surprisingly, this isomer *had the opposite configuration* (S_S) *at the sulfinyl sulfur* to the one obtained using pyridine as base (see Table 19, entries 1 and 2).

In addition to the high diastereoselection of the reaction, the DAG sulfinate ester diastereomers were easily separated by column chromatography or by crystallization. Another important feature of the DAG methodology is that the formation of the sulfinate esters intermediates takes place with *dynamic kinetic transformation* (DKR) of the starting sulfinyl chlorides.[223] Accordingly, condensation of 1.2 equiv of the racemic methane sulfinyl chloride with 1 equiv

Scheme 48

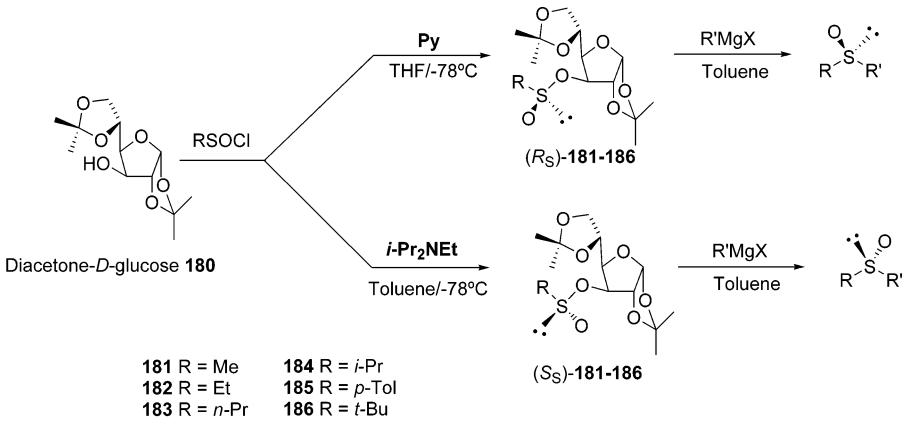
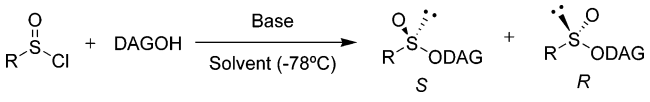


Table 19. Reaction of DAGOH with Different Sulfinyl Chlorides, RS(O)Cl (Scheme 48)



entry	R	base	solvent	*R*/*S*	yield[a] (%)
1	Me	pyridine	THF	93:7	87
2	Me	*i*-Pr_2NEt	toluene	<2:≥98	90
3	Et	pyridine	THF	86:14	85
4	Et	*i*-Pr_2NEt	toluene	<2:≥98	90
5	*n*-Pr	pyridine	THF	85:15	75
6	*n*-Pr	*i*-Pr_2NEt	toluene	4:96	80
7	*i*-Pr	pyridine	THF	≥98:≤2	56
8	*i*-Pr	*i*-Pr_2NEt	toluene	< 2:≥98	50
9	*p*-Tol	pyridine	THF	86:14	84
10	*p*-Tol	*i*-Pr_2NEt	toluene	6:94	87

[a] Diastereomerically pure compounds after purification of the major isomers by column chromatography or recrystallization.

of DAG **180**, using either pyridine or *i*-Pr_2NEt as base, allows the synthesis of diastereomerically pure (R_S)- or (S_S)-DAG methanesulfinate **181** in 86% and 90% isolated yield, respectively.

The reaction of a Grignard reagent with the intermediate sulfinate esters leads smoothly to the corresponding sulfoxides in high yield and selectivity. Both hindered and unhindered dialkyl, alkyl aryl, and diaryl sulfoxides have been obtained in both enantiomeric forms (Tables 20 and 21).[218,223] Most of these sulfoxides have been used to determine the absolute configuration of the intermediate sulfinates, by assuming that the substitution step occurs with complete inversion of configuration at the sulfur.

These results, which reveal the high capacity of the DAG methodology for the synthesis of optically pure sulfoxides, confirm the stereodirecting effect of the achiral tertiary amine used in the first step. This stereodirecting effect allows the utilization of a single inducer of chirality, DAG, for the synthesis of both (R_S)- and (S_S)-sulfinate esters, in an enantiodivergent manner by simply changing the base from Py to *i*-Pr_2-NEt. A study of the structure−activity relationship of tertiary amine has shown that neither the basicity nor the hybridization of the amine is important, and that the only meaningful parameter is its steric hindrance. Using different chiral carbinols, in the previously determined optimal conditions of base and

Table 20. Synthesis of Optically Active Sulfoxides, MeS(O)R, from DAGOH Methanesulfinates, (*R*)-181 and (*S*)-181, and R'MgX (Scheme 48)

			sulfoxide	
entry	methane-sulfinates	R'	yield (%)[a]	config[b]
1	(*R*)-**181**	*p*-Tol	84	*R*
2	(*R*)-**181**	Ph	78	*R*
3	(*R*)-**181**	$PhCH_2$	83	*R*
4	(*R*)-**181**	*n*-Pr	66	*R*
5	(*R*)-**181**	*t*-Bu	95	*R*
6	(*S*)-**181**	*p*-Tol	90	*S*
7	(*S*)-**181**	Ph	80	*S*
8	(*S*)-**181**	$PhCH_2$	83	*S*
9	(*S*)-**181**	*n*-Pr	69	*S*
10	(*S*)-**181**	*t*-Bu	95	*S*
11	(*S*)-**181**	vinyl	37	*S*

[a] Yield after flash chromatography. [b] ee = 100%.

Table 21. Synthesis of Optically Active Sulfoxides, RS(O)R', from DAG Alkane- or Arenesulfinates, RS(O)ODAG, and R'MgX (Scheme 48)

	RS(O)ODAG			sulfoxide	
entry	R	sulfinate	R'	yield (%)	config (% ee)
1	Et	(*S*)-**182**	*p*-Tol	96	*R* (99)
2	Et	(*R*)-**182**	*p*-Tol	90	*S* (99)
3	*n*-Pr	(*S*)-**183**	*p*-Tol	88	*R* (100)
4	*n*-Pr	(*R*)-**183**	*p*-Tol	89	*S* (100)
5	*i*-Pr	(*S*)-**184**	*p*-Tol	98	*R* (100)
6	*i*-Pr	(*R*)-**184**	*p*-Tol	89	*S* (100)
7	*p*-Tol	(*S*)-**185**	Et	87	*S* (70)[a]
8	*p*-Tol	(*R*)-**185**	Et	80	*R* (100)
9	*t*-Bu	(*S*)-**186**	Me	60	*S* (100)
10	*t*-Bu	(*R*)-**186**	Ph	85	*S* (90)
11	*t*-Bu	(*S*)-**186**	*p*-Tol	87	*R* (93)

[a] Obtained from a crude sulfinate with 70% de.

solvents, demonstrates unambiguously that the stereochemical outcome of sulfinate esters synthesis is highly dependent on the base used, which points to a general stereochemical behavior for the asymmetric synthesis of sulfinate esters.[224]

Accordingly, we recently found (Scheme 49) that the reaction of diacetone-D-glucose **180** or dicyclohexylidene-D-glucose (DCGOH) **187** with ethane 1,2-bis-sulfinyl chloride **188** in the presence of pyridine or Hunig's base afforded C_2-symmetric 1,2-bis-sulfinate esters (R_S,R_S)-**189**−**190** and (S_S,S_S)-**189**−**190**, respectively, in high yield and high diastereoselectivity.[225] The reaction occurs with dynamic kinetic resolution of the starting bis-sulfinyl chloride, with

Scheme 49

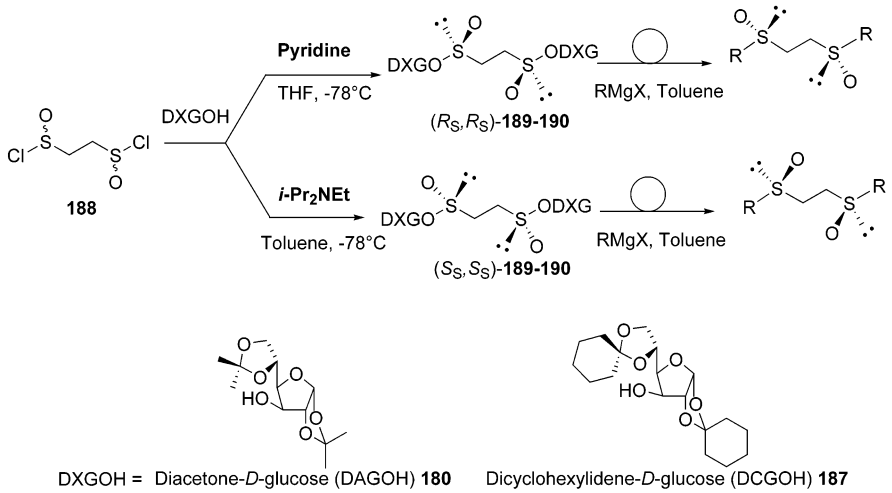
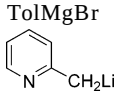
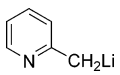


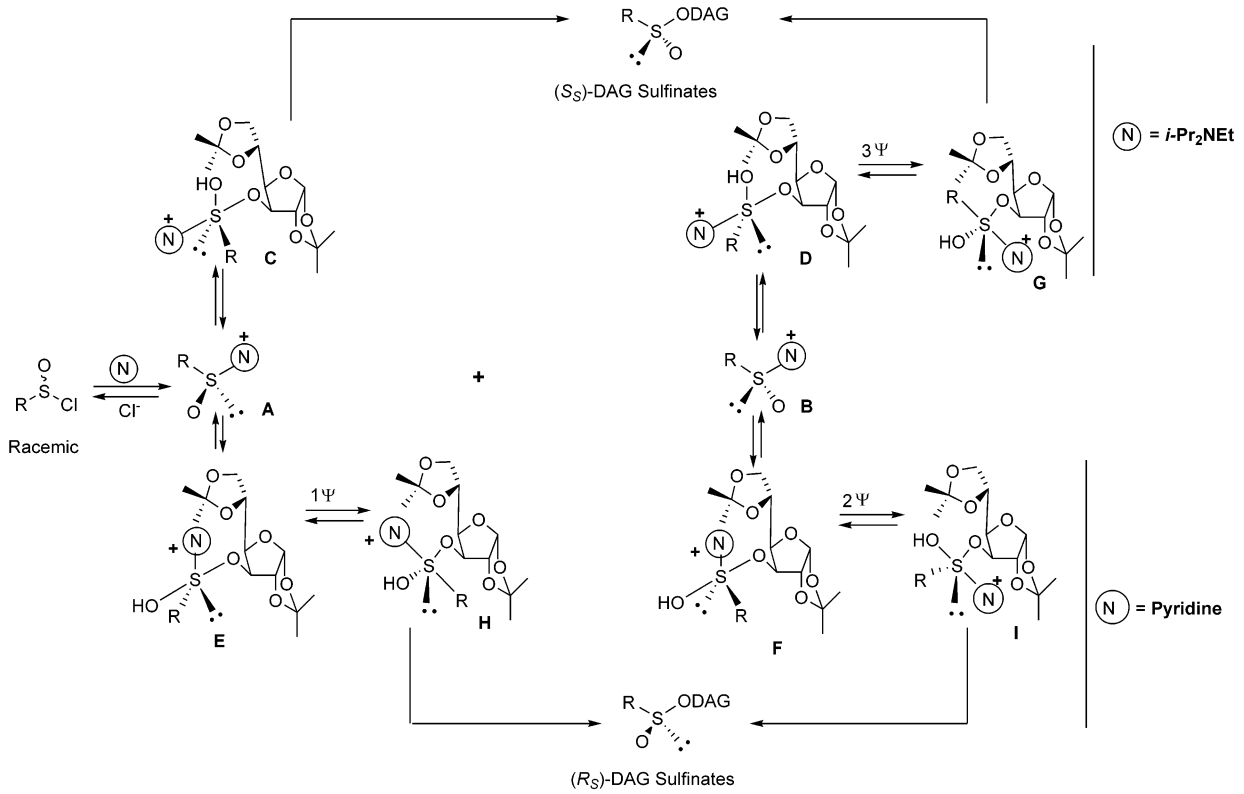
Table 22. Synthesis of Optically Active C_2-Symmetric 1,2-Bis-sulfinylethane, RS(O)CH$_2$Ch$_2$S(O)F, from Chiral Ethane-1,2-bis-sulfinate Esters, 183−190, and RM (Scheme 49)

	bis-sulfinate			bis-sulfoxide	
entry	compd	config at S	RM	yield (%)	config
1	**189**	(R_S,R_S)	MeMgl	40	(*S*,*S*)
2	**189**	(R_S,R_S)	^{t}BuMgCl	46	(*R*,*R*)
3	**189**	(R_S,R_S)	*o*-AnMgl	52	(*R*,*R*)
4	**189**	(S_S,S_S)	TolMgBr	54	(*S*,*S*)
5	**189**	(R_S,R_S)		60	(*S*,*S*)
6	**190**	(S_S,S_S)		50	(*R*,*R*)
7	**189**	(R_S,R_S)	^{t}BuO$_2$CCH$_2$Li	60	(*S*,*S*)
8	**190**	(S_S,S_S)	^{t}BuO$_2$CCH$_2$Li	70	(*R*,*R*)

higher diastereoselection than in the monosulfinate synthesis as a consequence of Horeau principle.[228] This principle, which has been used to describe the stereochemical outcome in the dimerization of a scalemic compound, applies also for the simultaneous diastereoselective bis-functionalization of a substrate.[228c] Considering that formation of monosulfinate ester gives a *x*:1 diastereomeric ratio, and as there is no double stereodifferenciation in the formation of bis-sulfinate esters (the formation of the second sulfinate is not influenced by the formation of the first one), the diastereomeric ratio of C_2-symmetric bis-sulfinate is x^2:1. The bis-functionalization process gives thus rise to C_2-symmetric bis-sulfinate esters in much higher diastereomeric ratio than the formation of monosulfinate and generates also a non-C_2-symmetric diastereoisomer in a 2*x* amount. Condensation of the Grignard reagent on the crude sulfinate esters mixture leads to the corresponding optically pure C_2-symmetric bis-sulfoxide, together with the *meso* compound, easily separable by column chromatography. Both isomers of various bis-alkyl, bis-aryl, as well as functionalized bis-sulfoxides have been obtained in optically pure form, in modest to good yields (Table 22).[225]

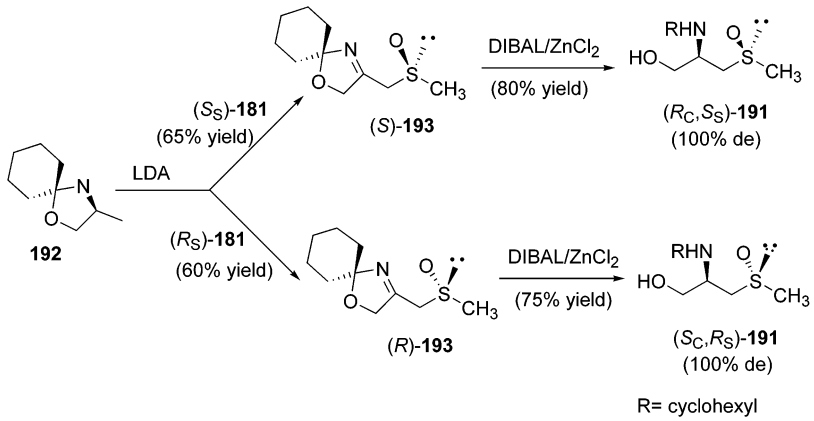
Taking into account all the results, we have proposed a model which explains both the opposite enantioselectivity introduced by the nature of the tertiary amine and the dynamic kinetic resolution observed. A plausible explanation is the formation of a pentavalent sulfurane intermediate that is able to undergo pseudorotation during the reaction (Scheme 50).[226] The stereodirecting base effect can be ascertained by assuming that sulfinamides **A** and **B**, formed from sulfinyl chlorides, are the *active sulfur* species which interact with the chiral alcohol along two different pathways.[227] In the case of the bulky and electronegative Hunig's base, there is a formation of two sulfurane intermediates **C** and **D**, with the chiral alcohol and the tertiary amine in the apical positions. In the case of reactions promoted by pyridine, sulfuranes **E** and **F** are formed, where the incoming alcohol is in the apical position and the less bulky aromatic base is in the equatorial position (Scheme 50).[228,229] The favored sulfurane **C** evolves directly to (S_S)-DAG sulfinate, and the dynamic kinetic resolution can thus be explained in two different manners: (a) Sulfurane **D**, less favored due a destabilizing interaction between the R group and the D-glyceraldehyde function, is not formed, allowing a classical type DKR by spontaneous equilibration of the sulfinamide via the sulfinyl chloride. (b) Alternatively, the formation of (S_S)-DAG sulfinate ester as the major isomer can be rationalized by the simultaneous formation of the two sulfuranes **C** and **D**. Accordingly, while sulfurane **C** leads directly to the desired (S_S)-sulfinate, sulfurane **D** gives sulfurane **G** by three consecutive pseudorotations, which evolves also into the (S_S)-sulfinate. When pyridine is used as base, the favored sulfurane **F** needs two pseudorotations in order to place the leaving amine in the apical position, leading to the sulfinate ester with the R_S absolute configuration at the sulfinyl sulfur. Likewise, the DKR can be explained in two ways (vide supra): the less favored sulfurane **E** either is not formed, allowing a classical DKR, or evolves to sulfurane **H** by a single Berry pseudorotation. Sulfurane **H** leads to the desired (R_S)-sulfinate ester by extrusion of the amine located in the apical position. The model presented in Scheme 50 may not be limited to sulfinate esters but should be general to those compounds with a chiral atom of the group IV−VI, such as the phosphinate esters, for

Scheme 50[a]



[a] Ψ: Simple pseudorotation of sulfurane.

Scheme 51



which a similar base effect has been observed.[230]

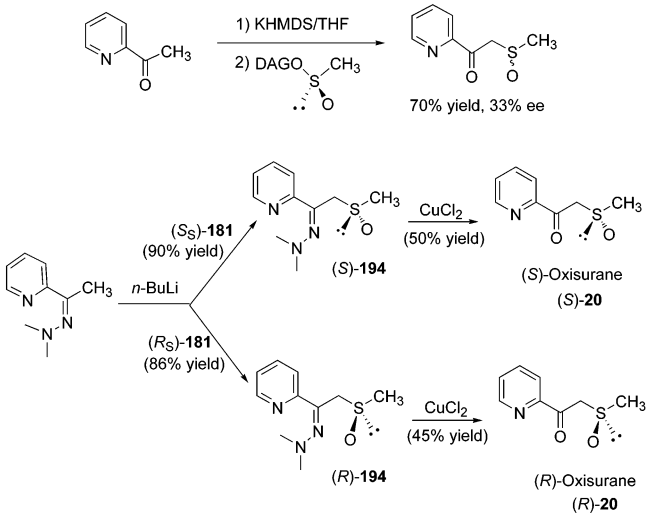
Some Applications. The DAG methodology has been widely used since its introduction by us, as well as by a large number of other groups.

The enantioselective synthesis of *N*-cyclohexyl analogues of β-amino-γ-hydroxysulfoxide **191** (Scheme 51), a chiral key intermediate in the asymmetric synthesis of the antibiotic sparsomycin **17** (Figure 2), using the DAG methodology was reported by us. Treatment of 1 equiv of the 3-oxazoline **192** with 2.2 equiv of LDA and (R_S)- or (S_S)-methanesulfinate of DAG gives optically pure methyl sulfoxides (R_S)-**193** and (S_S)-**193**, respectively. Reduction of the imine, using DIBAL in the presence of $ZnCl_2$ at −78 °C, afforded optically pure *N*-cyclohexyl derivatives (R_C-,S_S)-**191** and (S_C,R_S)-**191** as single isomers, in 80% and 75% yield, respectively.[231]

The only enantioselective synthesis of both isomers of oxisuran, (methylsulfinyl)methyl-2-pyridyl ketone **20** (Figure 2), has been achieved using the DAG method.[232] Oxisuran is a synthetic immunosuppressive drug used in organ and tissue transplants to suppress cell-mediated immunity, as well as to promote graft acceptance without inhibiting humoral antibody formation.[233] The direct condensation of the potassium enolate of methyl 2-pyridyl ketone with (S_S)-methanesulfinate, (S_S)-**181**, gave the desired β-ketosulfoxide in 70% yield and only 33% ee, due to the epimerization at the sulfinyl sulfur in the condensation step (Scheme 52).[232]

Fortunately, the reaction of 2 equiv of the α-lithio derivative of the corresponding *N*,*N*-dimethylhydrazone with (S_S)- or (R_S)-DAG methanesulfinates yielded optically pure sulfoxides (*S*)-**194** and (*R*)-**194**, respectively, in high yield. Reaction of these α-sulfinyl

Scheme 52



hydrazones, (*S*)-**194** and (*R*)-**194**, with copper chloride in aqueous THF led to the first synthesis of optically pure (*S*)- and (*R*)-oxisuran, respectively (Scheme 52).

Dithioacetal mono-*S*-oxides **195**, chiral formyl analogues, and the 3-ethylsulfinylmethyl-4,5-dihydro-4,5-diphenylisoxazoles **196** (Figure 21) were synthesized from DAG methane- and ethanesulfinates, **181** and **182**.[234]

In an interesting example of the first asymmetric Heck reaction using sulfoxides as chiral auxiliaries, Carretero et al. recently reported chiral sulfoxide **197** (Figure 21) obtained by the (S_S)-DAG methanesulfinate (S_S)-**181**.[235]

Both isomers of *N*-*tert*-butylsulfinimines **198** (Figure 21) were synthesized from (S_S)- and (R_S)-DAG *tert*-butanesulfinate esters **186** and used in the asymmetric synthesis of aziridines by García Ruano and Fernández et al.[236] Similarly, *tert*-butanesulfinamide **199** (Figure 21) was later synthesized from (R_S)-DAG *tert*-butanesulfinate ester (R_S)-**186** by Ellman.[237]

(*S*)-2-[(2,4,6-Triisopropylphenyl)sulfinyl]-2-cyclopentenone **201**, obtained from (S_S)-DAG 2,4,6-triisopropylbenzenesulfinate (S_S)-**200** (Scheme 53), was recently used by Toru et al. in a highly diastereoselective β-addition of tertiary, secondary, and even primary alkyl radicals.[238,239]

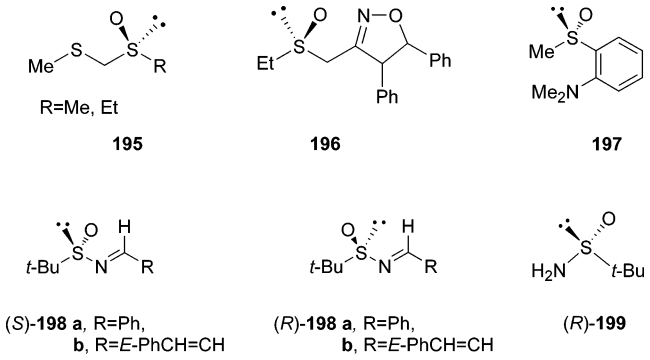


Figure 21.

Noiret et al. synthesized the two enantiomeric sulfoxides (*R*)-**203** and (*S*)-**203** in high yield and selectivity from the corresponding DAG butanesulfinates (R_S)-**202** and (S_S)-**202**, respectively (Scheme 54).[240]

Alayrac and Metzner reported on the synthesis of both enantiomers of ketene aminothioacetals of type **205** (Scheme 55), bearing the cyclohexylsulfinyl group from (S_S)- and (R_S)-DAG cyclohexanesulfinates **204**.[241]

Kusumi recently used the DAG methodology for the synthesis of various chiral sulfoxides. These sulfoxides were used to validate his sulfoximine model developed for the determination of the absolute configuration of chiral sulfoxides (vide infra).[242]

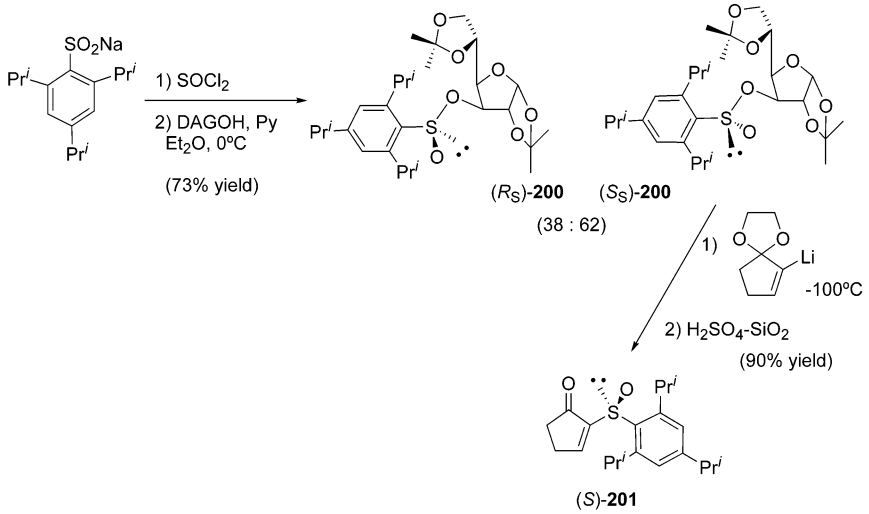
IX. Nucleophilic Substitution on Enantiomerically Pure Chiral Sulfur Derivatives

A. The Sulfinylmethyl Phosphonate Methodology

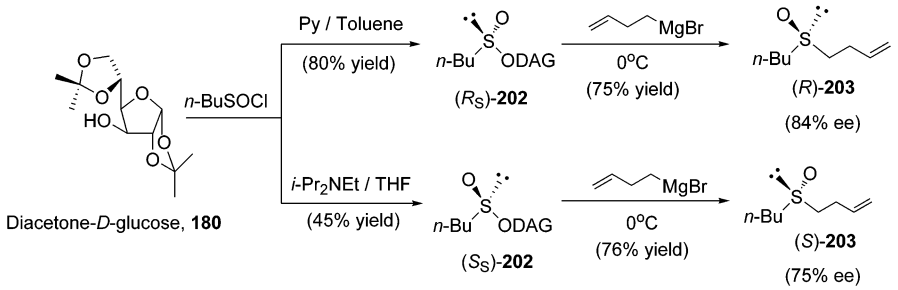
In a series of papers, Naso's group has been following a two-step strategy for the synthesis of chiral sulfoxides (Figure 22).[243−245] The idea behind this approach is the initial synthesis of chiral sulfinyl derivatives having a carbanionic leaving group. Upon reaction with an organometallic reagent in a second step, the desired sulfoxide is obtained.[245]

Thus, the method is a mixture of the two approaches for the synthesis of chiral sulfoxides dis-

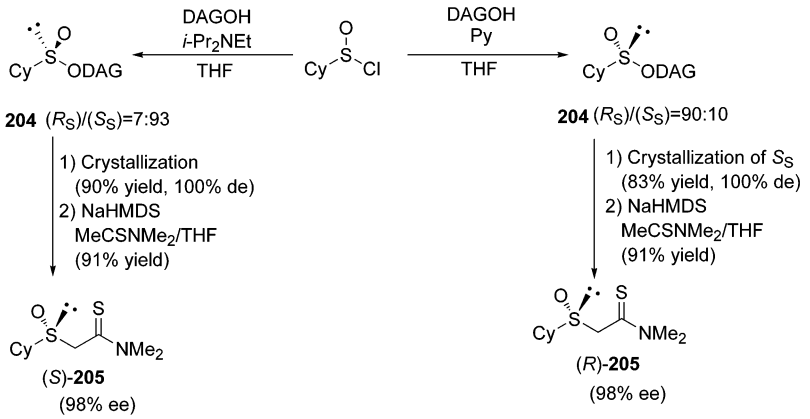
Scheme 53



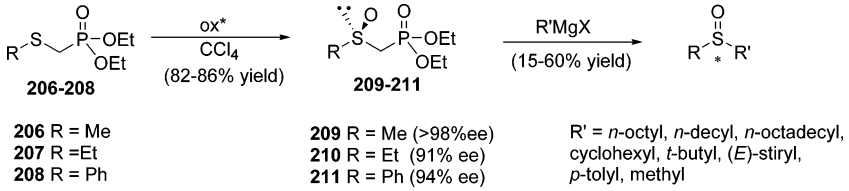
Scheme 54



Scheme 55



Scheme 56[a]



[a] ox* = TBHP/Ti(O-*i*-Pr)$_4$/(*R*)-BINOL/H_2O. Ratios: Ti(O-*i*-Pr)$_4$/BINOL/water/substrate = 1:2:20:40.

cussed before, first an enantioselective oxidation of a prochiral sulfide, and second the displacement of an electrophilic sulfur with predetermined chirality. It was primarily found that halovinyl and dialkyl methylphosphonate moieties bound to the sulfur atom behave as leaving groups in reaction with organometallic reagents.

Using diethylphosphonomethyl as leaving group (Scheme 56), these researchers recently reported a successful enantioselective oxidation of the commercially available diethyl (methylthio)methylphosphonate **206**, diethyl (ethylthio)methylphosphonate **207**, and diethyl (phenylthio)methylphosphonate **208**.[246] While the oxidation of **206** with cumene hydroperoxide using Kagan's conditions [Ti(O*i*-Pr)$_4$/(diethyl (*R*,*R*)-tartrate/water] allows the synthesis of the corresponding sulfoxide in acceptable ee (80%), the method suffers from the low chemical yield, due either to an overoxidation to the sulfone or to incomplete reaction.[167] These drawbacks have been solved using Uemura's conditions, that is, by using

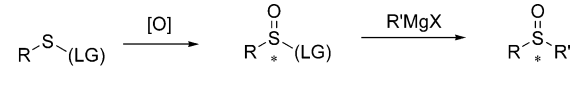


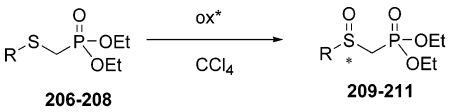
Figure 22.

hydroperoxides at room temperature in the presence of catalytic amounts of the complex formed in situ from Ti(O*i*-Pr)$_4$, (+)-1,1′-binaphthol (BINOL), and water. This allows the effective oxidation of prochiral sulfides **203**−**205**, with ee values typically >98% (Table 23).

As previously discussed, the high ee obtained by the Uemura approach was accounted for by assuming a kinetic resolution of the formed sulfoxide in the oxidation, but this is not the case for methylthiophosphonate, as a decrease of the oxidant amount reduced the proportion of the sulfone obtained without reducing the ee's. The sulfinylmethylphosphonates **209**−**211** were converted into sulfoxides, having the same ee values, by reaction with primary, secondary, and tertiary alkyl, vinyl, and aryl Grignard reagents to give dialkyl, alkyl aryl, and diaryl sulfoxides, albeit in low yield (Table 24). The low yield was accounted for by a competing metalation of the starting material by the organometallic compound. This drawback can be overcome in part by recovering the unreacted starting material.

Very recently, the same group applied their two-step approach (enantioselective oxidation followed by an aryl alkyl exchange) as a viable route to alkyl methyl sulfoxides. Haloaryl groups were found to be good leaving groups in the reaction with alkyl Grig-

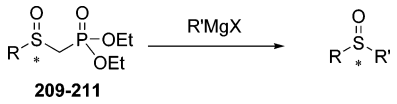
Table 23. Enantioselective Hydroperoxide Oxidation of Thiomethylphosphonates 206−208 Mediated by Chiral Titanium/BINOL Catalyst (Scheme 56)



ox* = TBHP or CHP, Ti(O-*i*-Pr)$_4$/BINOL/H$_2$O
Ratios: [Ti(O-*i*Pr)$_4$:BINOL:water:substrate]= [1:2:20:40]

entry	R	substrate	BINOL config	oxidant	substrate/ oxidant ratio	major product	yield (%)	ee (%)
1	Me	**206**	(*R*)	TBHP	1:2	(*S*)-**209**	39	>98
2	Me	**206**	(*R*)	TBHP	1:1.2	(*S*)-**209**	68	>98
3	Me	**206**	(*R*)	CHP	1:1.2	(*S*)-**209**		>98
4	Me	**206**	(*R*)	TBHP	1:1.1	(*S*)-**209**	85	>98
5	Me	**206**	(*R*)	TBHP	1:1	(*S*)-**209**		>98
6	Me	**206**	(*S*)	TBHP	1:1.1	(*R*)-**209**	86	>98
7	Et	**207**	(*R*)	TBHP	1:1.2	(*S*)-**210**	83	91
8	Ph	**208**	(*R*)	TBHP	1:1.1	(*S*)-**211**	82	94

Table 24. Enantiospecific Reactions of (Alkylsulfinyl)- or (Arylsulfinyl)methylphosphonates 209−211 with Grignard Reagents (Scheme 56)

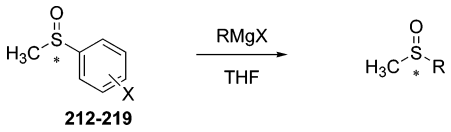


entry	R	substrate	R′	yield (%)	ee (%)
1	Me	(−)-**209**	*n*-octyl	54	>98
2	Me	(−)-**209**	*n*-decyl	46	>98
3	Me	(−)-**209**	*n*-octadecyl	49	>98
4	Me	(−)-**209**	cyclohexyl	50	>9
5	Me	(−)-**209**	*t*-butyl	15	>98
6	Me	(−)-**209**	(*E*)−2-stiryl	43	>98
7	Et	(−)-**210**	*n*-octyl	40	
8	Et	(−)-**210**	*p*-tolyl	36	91
9	Ph	(+)-**211**	methyl	60	94
10	Ph	(+)-**211**	*p*-tolyl	42	94

nards; thus, the next step was directed to the development of an effective enantioselective approach to haloaryl sulfoxides from the corresponding haloarylsulfides.[247] Surprisingly, Uemura's condition—TBHP in the presence of a Ti(O*i*-Pr)$_4$/(*R*)-BINOL complex, according to their previously reported procedure (vide supra)—gave products with low enantioselectivity (1−18% ee). On the other hand, use of CHP as the oxidant with Kagan's conditions—Ti(O-*i*-Pr)$_4$/diethyl (*R*,*R*)-tartrate/H$_2$O (1:2:0.5:1.1)—gave high %ee's in acceptable yield. The substituted enantiomerically enriched aryl methyl sulfoxides **212**−**219** (Table 25) were reacted with long-chain alkyl Grignard reagents, leading to the corresponding alkyl methyl sulfoxides in high enantiomeric purities and acceptable to good chemical yields. *p*-Bromophenyl methyl sulfoxide was shown to be the best starting material, as it is obtained in good chemical and optical yield in the first step. Primary and secondary Grignard reagents gave satisfactory yields of the corresponding sulfoxide, but as in the case of (alkylsulfinyl)methylphosphonates, only low conversion was observed for the synthesis of methyl *tert*-butyl sulfoxide.

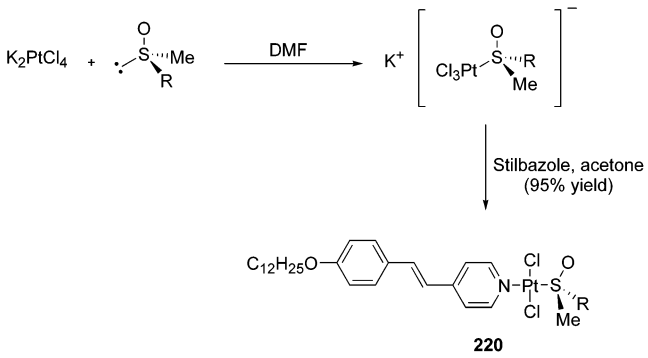
Naso's method was recently used to synthesize the sulfoxide utilized in the preparation of the first metallomesogen of type **220** (Scheme 57), containing a chiral center directly bonded to the metal.[248]

Table 25. Reaction of Chiral Substituted Aryl Methyl Sulfoxides with Grignard Reagents



substrate	X	ee of substrate (%)	R	yield (%)	ee of product (%)
212	2-OCH$_3$	88	*n*-decyl	40	86
213	3-OCH$_3$	93	*n*-decyl	56	91
214	4-OCH$_3$	92	*n*-decyl	24	92
215	2-Cl	80	*n*-octyl	65	81
216	4-Cl	91	*n*-decyl	73	89
217	2-Br	83	*n*-octyl	68	85
218	3-Br	96	*n*-decyl	81	96
219	4-Br	>98	*n*-octyl	84	>98
219	4-Br	>98	*n*-tridecyl	74	>98
219	4-Br	>98	*n*-tetradecyl	90	>98
219	4-Br	>98	*n*-hexadecyl	77	>98
219	4-Br	>98	cyclohexyl	72	>98

Scheme 57[a]

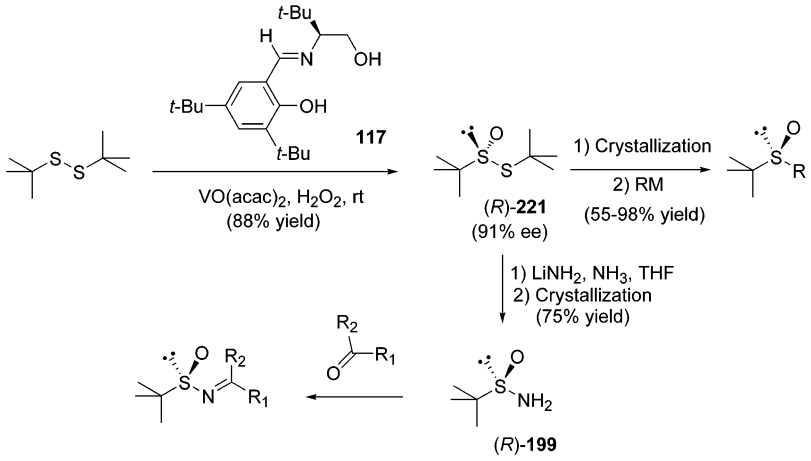


[a] R = $C_{14}H_{29}$, $C_{15}H_{31}$, $C_{16}H_{33}$.

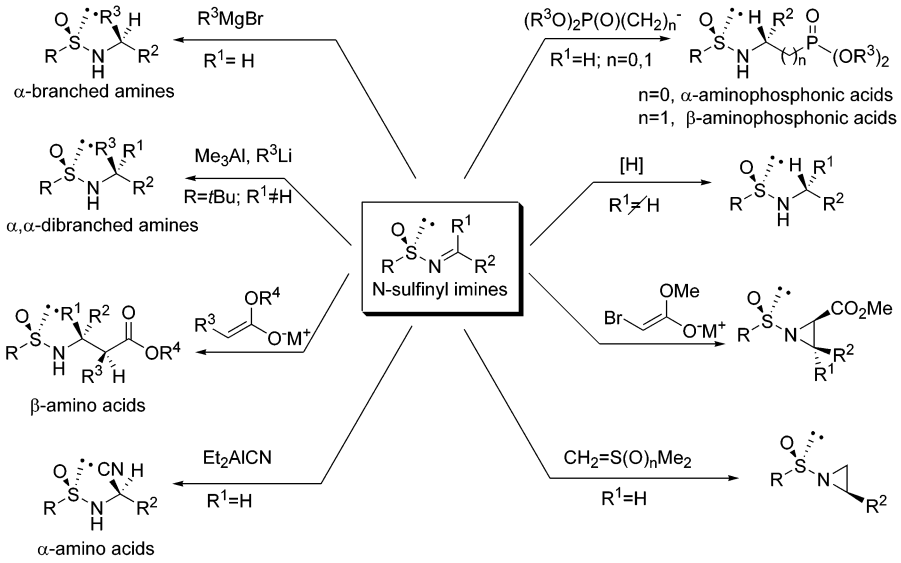
B. The Thiosulfinate Approach

In a project aimed toward diastereoselective alkylations of *N*-acylsulfinamide enolate, Ellman et al. found that the more sterically hindered *tert*-butanesulfinamide **199** (Scheme 58) provided a level of diastereoselection higher than that of *N*-acyl derivatives of arenesulfinamides.[249] The starting chiral *tert*-butanesulfinamide **199** was first prepared by Ellman's group using the DAG methodology.[237] Later,

Scheme 58



Scheme 59



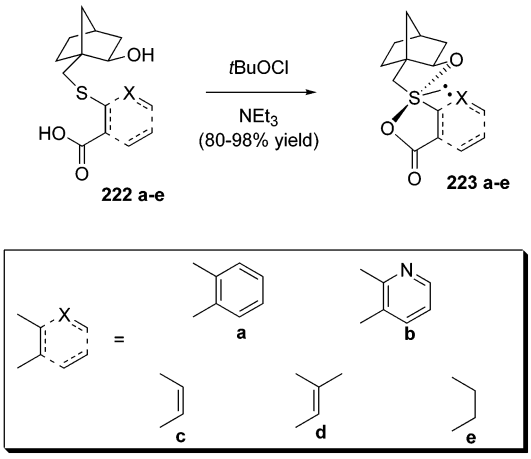
Ellman developed an efficient catalytic method of mono-oxidation of disulfide using the technology developed by Bolm et al., based on the use of chiral Schiff base−vanadium complexes.[164,237] A ligand screening achieved by varying the salicyaldehyde and the amino alcohol portions showed that Bolm's ligand **117** gave the best result for the conversion of *tert*-butyl disulfide into an enantioenriched thiosulfinate-and (Scheme 58). This was achieved by using H_2O_2 as oxidant in the presence of $VO(acac)_2$ (0.25 mol %) and ligand **117** (0.26 mol %); (*R*)-(+)-*tert*-butanethiosulfinate was prepared in 92% yield and 91% ee *on a 1 mol scale*. Two crystallizations from hexane led to optically pure (*R*)-**221** (52% yield, 99.8% ee). Thiosulfinate (*R*)-**221** was shown to react readily and totally stereoselectively with Grignard reagents, organolithium, lithium amides, and lithium imine salts to provide enantiomerically pure chiral sulfoxides, as well as sulfinamides and sulfinimines, in good yield. These results establish that the thiosulfinate route is the most effective one for the synthesis of *tert*-butyl sulfoxides. Addition of $LiNH_2$ in liquid ammonia and THF provides *tert*-butanesulfinamide (*R*)-**199** with 91% yield (Scheme 58). A single recrystallization provides the important enantiomerically pure chiral ammonia equivalent (*R*)-**199** in 71−75% overall yield from disulfide. *tert*-Butanesulfinamide **199** was shown to be an important chiral synthon for the synthesis of a wide range of important chiral molecules (Scheme 59).[250]

The mechanisms of Bolm's oxidation of prochiral sulfide and Ellman's oxidation of *tert*-butyl disulfide seem to be identical. In both cases there is a ligand acceleration, which eliminates the impact of vanadium species not complexed with the chiral ligand and precludes the need for excess ligand. No asymmetric amplification has been observed, and the oxidations performed with ligands of varying enantiopurity exhibited a linear dependence of product ee on ligand ee. These results prompted the authors to propose that the active catalyst is a vanadium species with just one ligand coordinated to the metal.[164,237]

X. Hydrolysis of Chiral Spiro-η⁴-sulfuranes

An interesting work on the enantiodivergent synthesis of chiral sulfoxides via the hydrolysis of chiral spiro-η^4-sulfuranes was recently reported by Koizumi's group.[251] The work is both synthetically and mechanistically of interest, as sulfuranes have been proposed as intermediates in various reactions of organosulfur compounds, including the synthesis of

Scheme 60



chiral sulfoxides from sulfinate esters. Various optically pure spirosulfuranes **223a**−**e** with 2-*exo*-hydroxy-10-bornyl group were synthesized (Scheme 60) from the corresponding sulfides **222a**−**e** in high yields (80−98%) by reaction with ^{t}BuOCl in CH_2Cl_2 at 0 °C, followed by treatment with NEt_3. X-ray crystallographic analysis of **223a** and **223b** indicated that the spirosulfuranes have a slightly distorted trigonal bipyramidal (TBP) structure. Compound **223a** was easily hydrolyzed under basic conditions (1 N NaOH) to give optically pure sulfoxide (R_S)-**224a** (Scheme 61) as a single diastereomer. In contrast, hydrolysis of the same spirosulfurane **223a** under acidic conditions (1 N HCl) gave sulfoxide (S_S)-**224a**, also as a single diastereoisomer, but *with the opposite absolute configuration at the sulfur atom*. The absolute configurations at the sulfur atom in sulfoxides (R_S)-**224** and (S_S)-**224** were determined by X-ray analysis. The mass spectra and ^{17}O NMR studies of sulfoxides prepared by hydrolysis under acidic and basic conditions with isotopically labeled water definitively revealed that the oxygen atom bound to the sulfur atom in these compounds is derived from water. On the basis of these results, they proposed a mechanism (Scheme 61) where the incoming hydroxide ion, or the water molecule, attacks the pentacoordinated sulfur atom at the same side in both conditions. The difference in the stereochemical outcome of the reaction depends on the first broken apical bound, the acyloxy one in basic conditions and the alkoxy one in acidic conditions, due to the previous protonation of the more basic ether oxygen atom.[252]

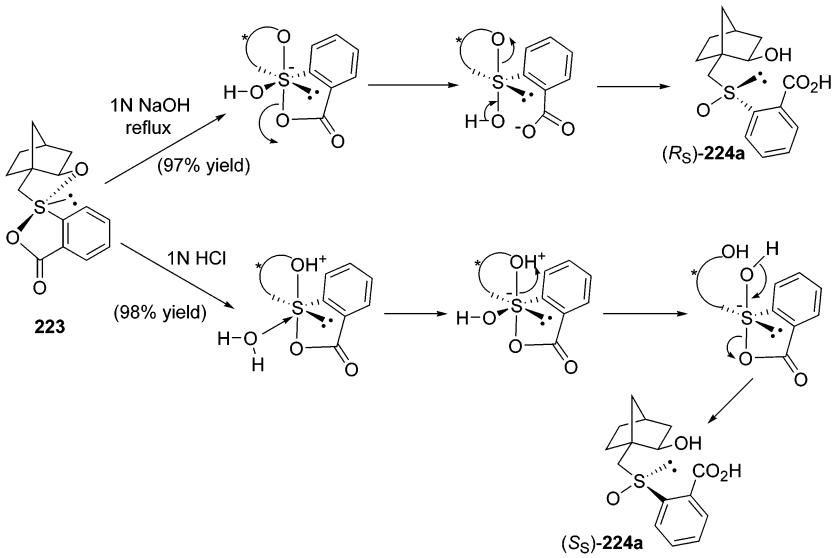
XI. Chiral Sulfoxides in Enantioselective Metal-Catalyzed Asymmetric Synthesis

The interest in using transition metal complexes with sulfoxides began in the early 1960s, when sulfoxides were recognized as useful ambidentate ligands for the synthesis of new organometallic and coordination compounds.[253] Additionally, the potential applications of ruthenium complexes both as antitumor agents[254] and as radiosentitizers[255] prompted their study in bioinorganic chemistry. Nevertheless, recent and more likely future interest in these complexes concerns their utilization in asymmetric synthesis. Two different approaches have been followed in this sense: first, the utilization of sulfoxide ligands in metal-catalyzed enantioselective catalysis, and, second, their more conventional utilization as chiral auxiliaries in various processes promoted by transition metals. Both approaches try to take advantage of the inherent chirality of the sulfur atom in sulfinyl compounds, which imprints a close discrimination around the metal center, thus allowing effective asymmetric inductions. The following section intends to survey the advances achieved in this context. As all these studies are related, in some way, to the strength and nature of the metal−sulfoxide bond, understanding the parameters affecting the bonding mode of sulfoxides in metal complexes is a fundamental aspect of their coordination chemistry.[256,257]

A. Metal−Sulfoxide Bonding

Before discussing the nature of metal−sulfoxide complexes, it is worthwhile to consider some struc-

Scheme 61



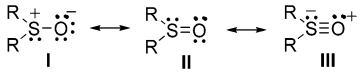


Figure 23.

tural characteristic of the free ligand. Many discussions in the literature have described the electronic structure of sulfoxides. Molecular orbital calculations and X-ray spectroscopy have shown that free sulfoxide molecules are polarized, with a net positive charge localized on the sulfur atom. These observations, together with the relatively short S−O bond distance, indicate that the sulfoxide structure is a resonance hybrid of three canonical forms (Figure 23), where the first two are largely predominant. The donor properties of sulfoxides seem to result mainly from structure **I** for either free or O-bonded complexes (sp^2 oxygen), while structure **II** contributes to S-bonding in complexes (sp^3 sulfur).

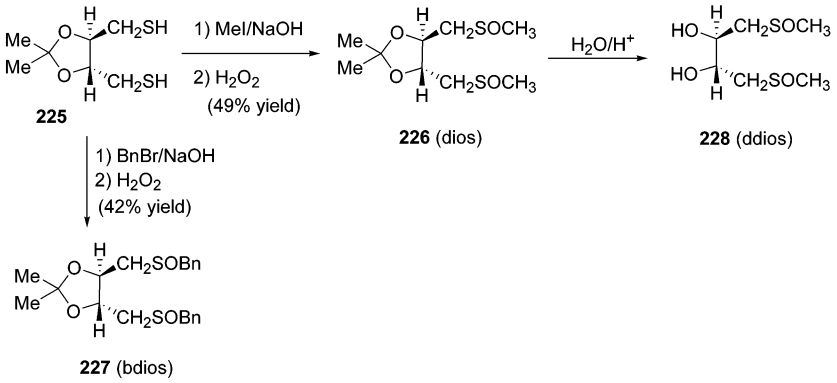
Initial indications of the nature of sulfoxide−metal bonding came from the observations that DMSO coordinated to "harder" metals via oxygen and to "softer" metals via the sulfur.[257] However, the "hardness" or "softness" of a metal ion can be affected by the nature of the coordinated ligands.[258−262] Accordingly, an interesting class of ligands in metal-catalyzed asymmetric synthesis are bidentate mixed ligands with a chiral sulfoxide and another heteroatom.[263] In mixed ligands, the preferred coordinating atom of sulfoxides is determined in part by the ability of another heteroatom at the metal center to compete for electron density. The presence of strong π-electron acceptors withdraws electron density from the metal and causes "softer" metals to become "harder". This reduction in electron density at the metal may be accompanied by a change in coordination mode of the sulfoxide ligand from a "soft" (sulfur) to a "hard" (oxygen) atom to optimize orbital overlap. Moreover, O-bonding may also be induced by the ligand bulkiness, as measured by the sulfoxide cone angle, and from entropic contributions, due to the increased number of degrees of freedom. In summary, the bonding mode of sulfoxide ligands is the result of a delicate balance between electronic and steric factors.

As reported by Calligaris and Carugo, in considering the whole Periodic Table (Figure 24), a prevalence of O-bonding is observed.[258] S-bonding seems to be favored in d^6 and d^8 transition metal ion complexes, probably through π back-bonding contributions. With regard to the coordination modes of sulfoxides to a metal, it is easily determined using ^{1}H NMR and IR spectroscopy.[262] Generally, O-bonding in sulfoxides results in small downfield chemical shifts of the α-protons (<0.5 ppm), while larger downfield chemical shifts (1 ppm) are seen for coordination through the S-atom. This trend is observed for the β- and γ-protons, although the extent of these effects decreases as the protons become further removed from the S-atom. Upon coordination of sulfoxide, a greater shift is observed in the sulfur−oxygen IR stretching frequency, ν_{SO}, in S-bonded than O-bonded sulfoxides, and the changes are useful indications of the bonding mode.

IA																0
H 4 O	IIB											IIIB	IVB	VB	VIB	VIIB	
Li 2 O												**B** 1 O					
Na 3 O		IIIA	IVA	VA	VIA	VIIA		VIII			IB	IIB					
K 2 O		**Sc**	**Ti**	**V** 3 O	**Cr** 1 S	**Mn** 3 O	**Fe** 2 S 5 O	**Co** 4 O	**Ni** 5 O	**Cu** 26 O	**Zn** 2 O						
	Sr 1 O	**Y** 1 O	**Zr** 3 O	**Nb**	**Mo** 13°	**Tc** 1 S	**Ru** 44 S 8S,O 4 O	**Rh** 26 S 3S,O 1 O	**Pd** 5 S 2S,O 1 O	**Ag** 1 O	**Cd** 13 O	**In** 4 O	**Sn** 18 O				
		La[a] 31 O	**Hf**	**Ta**		**Re** 1 S 2 O	**Os** 2 S 2 O	**Ir** 7 S	**Pt** 74 S 1S,O 1 O		**Hg** 8 O	**Tl** 1 O	**Pb** 4 O				
		Ac[b] 17 O															

Figure 24. Number of known X-ray molecular structures of sulfoxide complexes, containing only O-bonded (O), S-bonded (S), or both S- and O-bonded sulfoxides (S,O). [a]Lanthanides: La, Ce, Pr, Nd, Sm, Eu, Er, Yb, Lu. [b]Actinides: Th, U. (Reprinted with permission from ref 258. Copyright 1996 Elsevier Science.)

Scheme 62

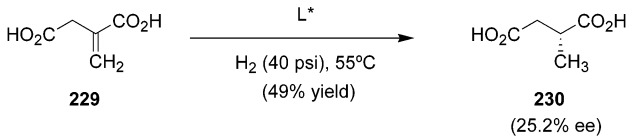


B. Catalytic Hydrogenations

As far as we know, the first work describing the utilization of chiral sulfoxides in asymmetric catalysis is from James and co-workers, in 1976, using (+)-methyl *p*-tolyl sulfoxide as ligand in Ru- and Rh-catalyzed hydrogenation of olefins with disappointing results.[264a] Inspired by the good results of rhodium and ruthenium complexed derived from the C_2-symmetric diphosphine diop developed by Kagan and Dang for catalytic hydrogenation,[265] James and McMillan synthesized three bis-sulfoxides which they named dios, bdios, and ddios (Scheme 62).[264b]

The synthesis of the ligands started from L-tartaric acid, used as key intermediate the already known dithiol **225**. C_2-symmetric dithioethers were obtained by quenching the dithiolate by methyl iodide or benzyl bromide. A nonstereoselective oxidation with H_2O_2 led to the bis-sulfinyl ligands **226** (dios) and **227** (bdios) as a mixture of diastereomers. Acid hydrolysis of the isopropylidene moiety of dios gave the third ligand **228** (ddios). Surprisingly, although the dios-type sulfoxide ligands are mixtures of up to three diastereoisomers, the corresponding Ru(II) catalysts do induce a moderate degree of asymmetry. Using 2.6 mol % of the catalyst $RuCl_2$(dios)(ddios) under 44 psi of H_2, up to 25% ee was obtained in the hydrogenation of itaconic acid **229** to methylsuccinic acid **230** (Scheme 63).[264b]

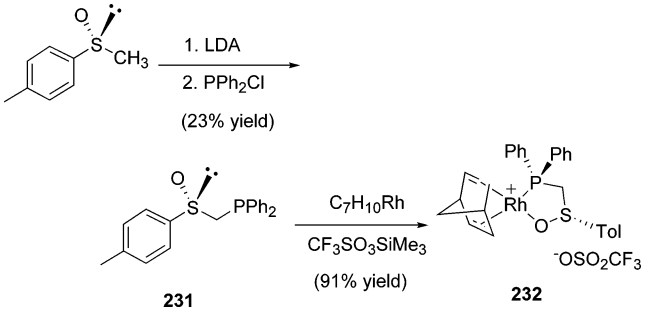
Scheme 63[a]



[a] L* = $RuCl_2$(dios)(ddios).

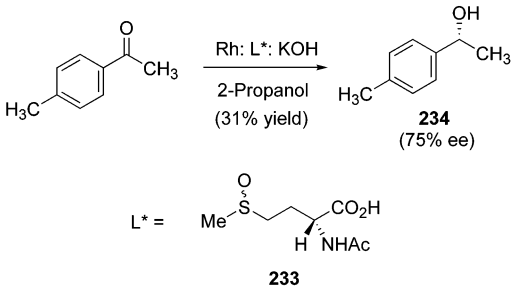
Alcock et al. reported on the synthesis of α-phosphinosulfoxides as ligands in Rh-catalyzed asymmetric hydrogenation.[266] An optically pure ligand, **231**, was synthesized by reacting α-lithio methyl *p*-tolyl sulfoxide with PPh_2Cl at −78 °C in 23% yield (Scheme 64). Ligands of type **231** proved to be stable when purified, as there was no internal oxygen transfer. The norboradiene cationic rhodium complex **232** was obtained by the reaction of **231** with C_7H_8-Rh and TMS triflate. While these complexes were active in hydrogenation of hex-1-ene and styrene, no application in asymmetric synthesis was reported.

Scheme 64



Promising results were obtained in rhodium-catalyzed asymmetric transfer hydrogenation of prochiral ketones using amino sulfoxide as a chiral ligand by Kvintovics, James, and Heil (Scheme 65).[267] The

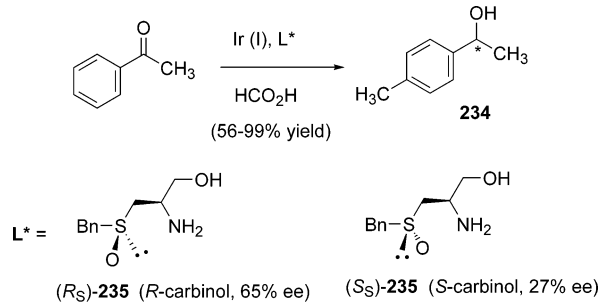
Scheme 65



ligand used was a mixture of sulfoxides, *N*-acetyl-(*S*)-methionine (*R* and *S*)-sulfoxide **233**, obtained from (*S*)-methionine by oxidation with H_2O_2 followed by standard acetylation. As the oxidation is not diastereoselective, both diastereoisomers **(**R_S**)-233** and (S_S)-**233** were obtained in a 1:1 ratio and used as such. The enantioselective catalytic hydrogen transfer to prochiral ketones, using *i*-PrOH as the hydrogen source, was achieved using an in situ-generated catalyst and operated optimally with a Rh/**233**/KOH ratio of 1:2:4−5. The in situ Rh(I) systems were shown to be effective catalysts for alkyl aryl ketones, while dialkyl ketones were not effectively hydrogenated under the same conditions. Surprisingly again, the use of the racemic ligand at sulfur gave high enantiomeric excess, affording carbinol **234** with 75% ee (Scheme 65). As in the case of dios-type ligands, no study had been done to evaluate the asymmetric induction of the two individual diastereomeric sulfoxides on the enantioselection.[268]

However, van Leewen's group recently used quite similar ligands in the same reaction process, except that formic acid was used as the hydrogen donor to avoid the problem of the reversibility of the reaction.[268] The aminosulfoxides used were obtained from (*R*)-cysteine or norephedrine. Oxidation of *S*-benzyl-(*R*)-cysteinol by hydrogen peroxide, followed by repeated crystallization, afforded diastereomerically pure (R_S)-**235** and (S_S)-**235** (Scheme 66). When a 1:1

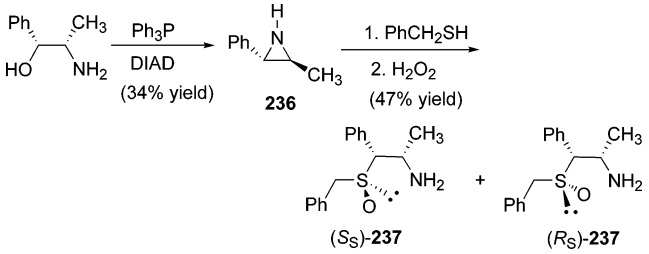
Scheme 66



diastereomeric mixture was used as such, carbinol (*R*)-**234** was obtained with 35% ee. Interestingly, a marked difference in stereoselection was observed when the two diastereoisomers were used separately. The diastereoisomer *S*-benzyl-(*R*)-cysteinol (S_S)-sulfoxide, (S_S)-**235**, in combination with $[IrCl(COD)]_2$, led to the *S*-carbinol with 27% ee, with the opposite absolute configuration compared to the 1:1 diastereomeric mixture. The use of the other diastereoisomer, (R_S)-**235**, induced an increase in the enantioselectivity of up to 65% of the (*R*)-carbinol, in 99% conversion after 1 h. These results clearly demonstrate a chiral cooperativity of the sulfoxide and the cysteine-derived stereogenic center in the catalytic transfer hydrogenation.

Two other aminosulfoxides **237,** obtained from the aziridine **236** derived from (1*R*,2*S*)-norephedrine, were used in this study. Oxidation of the thioether leads to a diastereomeric mixture of the amino sulfoxides (R_S)-**237** and (S_S)-**237**, which were separated by column chromatography (Scheme 67). As

Scheme 67



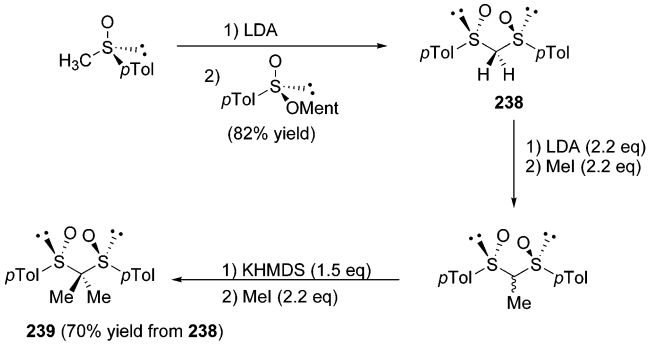
observed for (R_S)-**235** and (S_S)-**235**, a large difference in reaction rate (32% conversion vs 9%) and enantioselectivity (32% vs 2%) was observed for the two diastereoisomers (R_S)-**237** and (S_S)-**237** in the iridium(I)-catalyzed transfer hydrogenation of acetophenone, using formic acid as hydrogen donor. Catalyst optimization allows the (*S*)-carbinol (*S*)-**234** to be obtained (57% yield, 80% ee) using a substrate/$[IrCl(COD)]_2$/((R_S)-**237** ratio of 400:1:5.

C. Catalytic Cycloadditions

The Diels−Alder (D−A) reaction is one of the rare carbon−carbon bond-forming reactions that permit the rapid development of molecular complexity.[269] It allows the stereoselective formation of as many as four stereogenic centers and as many as three carbocyclic rings in the intramolecular and transannular variation. Although chiral auxiliary (including chiral sulfoxides)-based reactions retain a position of central importance, catalytic variants are developing rapidly.[270] Promotion of the D−A reaction by use of a substoichiometric amount of a chiral Lewis acid has developed to a relatively high level of sophistication as a result of the extensive research in this field.

The first application of chiral sulfoxide in a catalytic D−A reaction was done by us in 1993.[271] The ligands used were the C_2-symmetric bis-sulfinylmethanes **238** and **239**, obtained using the method developed by Kunieda (Scheme 68), by condensation

Scheme 68



of α-lithio (*R*)-methyl *p*-tolyl sulfoxide and (*S*)-menthyl *p*-toluenesulfinate followed by dimethylation.[272] An in situ catalyst (**238**·FeI_3) or (**239**·FeI_3) was used by mixing the bis-sulfoxides with the preformed precursor Fe and I_2. The bis(sulfoxide)−Fe(III) complexes were shown to be good chiral catalysts of the D−A reaction between 3-acryloyl-1,3-oxazolidin-2-one **240** and cyclopentadiene (Scheme 69). Both catalysts gave excellent diastereoselection (90−92%), and the enantioselection [(*S*)-**241**/(*R*)-**241**] depends on the substituent of the central methylenic carbon of the catalyst and goes from 36% to 56%.

The most active chiral catalysts used to date employing a chiral sulfur atom as a unique source of chirality was reported very recently by Ellman's group.[273] The work, which was directed toward evaluating the usefulness of sulfinylimines as versatile donor ligands for asymmetric catalysis, started with the synthesis of C_2-symmetric ligands **242** and **243** (Figure 25), in a clear analogy to the highly successful bis-oxazoline.[274]

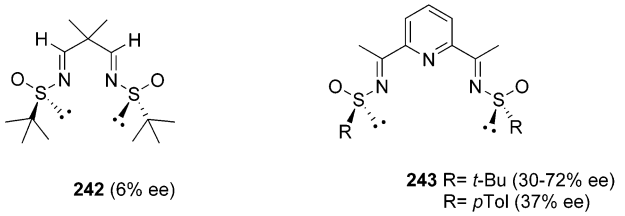
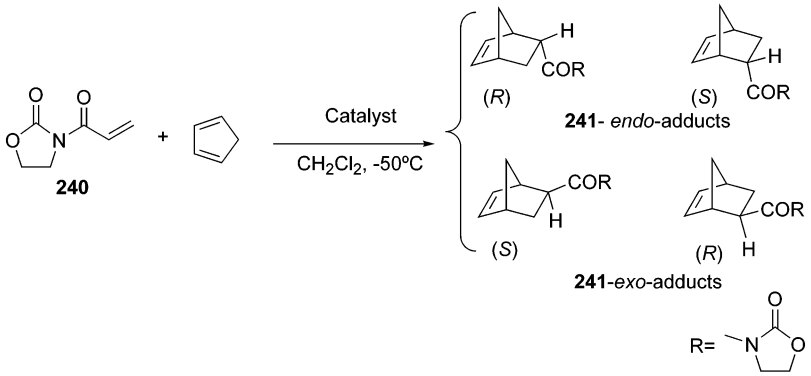


Figure 25.

Scheme 69[a]



[a] Catalyst **238**·FeI_3: 36% ee, 74% yield, 90% de. Catalyst **239**·FeI_3: 56% ee, 78% yield, 92% de.

Scheme 70

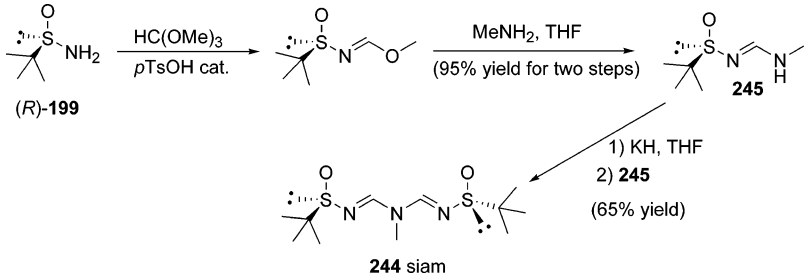
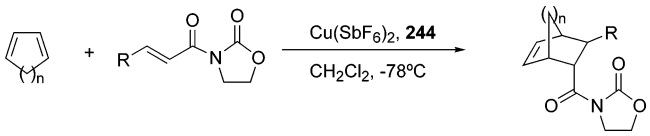


Table 26. Substrate Generality in the Diels−Alder Reaction Using Ligand 244 (siam) (Scheme 70)



entry	n	R	time (h)	temp (°C)	yield (%)	ee (%)	dr
1	1	H	0.1	−78	96	98	99:1
2	1	CH_3	8	−40	76	97	98:2
3	1	Ph	16	0	58	94	95:5
4	1	CO_2Et	2	−78	85	96	97:3
5	1	acrolein	2	−78	65	32	96:4
6	2	H	16	0	50	90	98:2

However, while the Cu(II) complex of ligand **242** displayed good catalytic activity for the asymmetric D−A reaction, the asymmetric induction was very low (6%). The Cu(II) complex of ligand **243** was less active but afforded the D−A adduct in moderate selectivity. Interestingly, bis(sulfinyl)imidoamine **244** (named siam), synthesized in three steps from the known *tert*-butylsulfinamide (*R*)-**199** (Scheme 70), was shown to be a valuable chiral ligand.

The use of siam **244**−$Cu(SbF_6)$ complex gave high catalytic activity (100%) with an exceptional level of enantioselectivity (98%). In a preliminary determination of substrate generality, **s**iam was shown to give the corresponding cycloadduct of a variety of dienophiles in high diastereo- and enantioselectivity (Table 26).

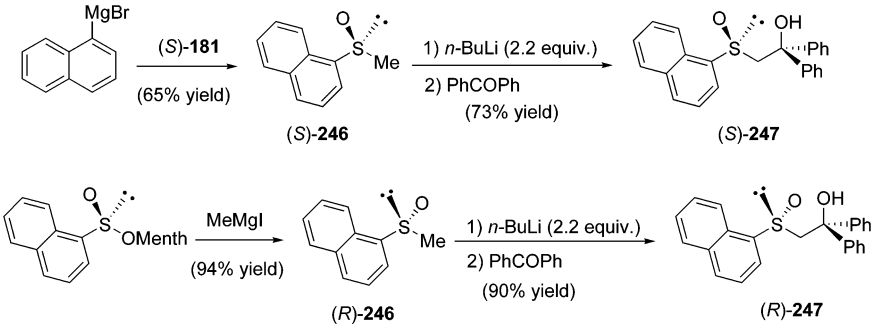
Furthermore, the Cu(II)−siam complex was shown by X-ray analysis to exhibit a unique mode of binding, self-assembling to form a rarely observed M_2L_4 quadruple-stranded helicate. Additionally, while **s**iam can coordinate to the metal through the N-, S-, and O-atoms, it was shown that both in the crystalline state and in CH_2Cl_2 solution, the ligand is O-coordinated to the Cu.

The use of magnesium complexes of non-C_2-symmetric β-hydroxyl sulfoxides in a metal-catalyzed D−A reaction was reported in 1996.[275] Following Johnson and Bolm's ligand design for the synthesis of β-hydroxysulfoximines (vide infra), β-hydroxysulfoxides (R_S)-**247** and (S_S)-**247** were synthesized via naphthyl methyl sulfoxide (*R*)-**246** and (*S*)-**246**, obtained either via the Andersen route or by the DAG methodology, respectively (Scheme 71)**.** Using 10 mol % of the complex **247**·MgI_2 led to the enantioselective synthesis of the *endo* adduct (*S*)-**241** (Scheme 69) in 88% ee.

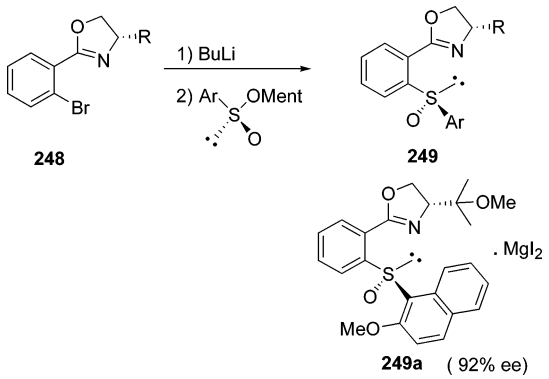
Rigid S,N-ligands formed by 1,3-oxazoline ring and a chiral sulfinyl function, bridged by a benzene ring, were recently evaluated in the same reaction.[276] It is worth noting that these S,N-ligands have been already used by Williams (vide infra) in palladium-catalyzed asymmetric allylic addition of diethyl malonate to 1,3-diphenyl-1-propenyl-3-acetate. The ligands of type **249** (Scheme 72) were prepared by the usual lithitation of known 2-(2-bromophenyl)-1,3-oxazoline **248** with *n*-butyllithium, followed by sulfinylation with either (−)-(S_S)-menthyl *p*-toluene-, 1-naphthalene-, or 2-methoxy-1-naphthalenesulfinate (Scheme 72).

A critical role of the Lewis acid catalyst has been observed in the D−A reaction using these ligands. Among the various Lewis acids used [$Cu(OTf)_2$, CuI_2, FeI_3, $MgCl_2$, $MgBr_2$, MgI_2·Et_2O, and $Mg(OTf)_2$], MgI_2 was revealed to be the most effective. As the chirality can be introduced on the sulfinyl sulfur as well as on the oxazoline ring, a study of the substituents has shown that the asymmetric induction was a consequence of a synergetic effect of the two chiral centers, since the loss of chirality on the oxazoline or on the

Scheme 71



Scheme 72[a]



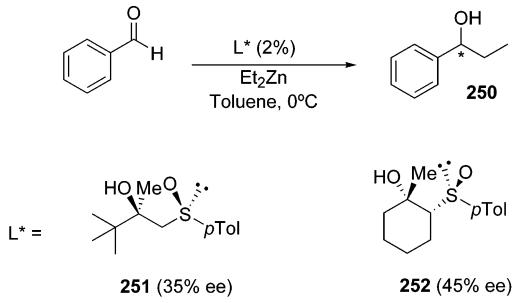
[a] Ar = *p*-Tol, 1-naphthyl, 2-methoxynaphthyl.

sulfoxide provided much lower enantioselectivity. The best ligand was shown to be **249a**, where the substituents were a 2-methoxyisopropyl group and a 2-methoxynaphthyl group on the oxazoline and sulfinyl sulfur, respectively. Use of **249a** and MgI_2 (10 mol %, Cl_2CH_2, −78 °C, 24 h) led to *endo*-(*S*)-**241** with high selectivity (90% de, 92% ee) (Scheme 69).

D. Addition of Diethylzinc to Benzaldehyde

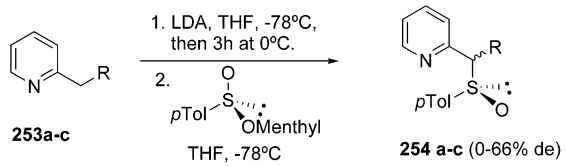
The enantioselective addition of diethylzinc to aldehydes (Scheme 73) mediated by chiral, nonracemic ligands is one of the most-studied examples of ligand-accelerated catalysis.[277]

Scheme 73



Several characteristics of the reaction, such as the very important nonlinear effects,[278,279] autocatalysis phenomena, and the derived amplification of enantiomeric excess, make it attractive from both intellectual and industrial perspectives, provided that sufficiently active catalytic ligands are developed. A large number of chiral ligands have been used in this reaction, including amino alcohols, diamines, and 1,2-diols. In 1993, Garcia Ruano's group reported on the first use of β-hydroxysulfoxides as chiral bidentate ligands in the enantioselective addition of diethylzinc to benzaldehyde.[280] The ligands used were cyclic and acyclic β-hydroxysulfoxides, with two or three stereocenters, having either a secondary or a tertiary carbinol (Scheme 73). The secondary carbinols were obtained by the reduction of β-ketosulfoxide with DIBAL or DIBAL/$ZnCl_2$, whereas for tertiary carbinols the method used was the stereoselective addition of $AlMe_3$ to the appropriate precursors in the presence of $ZnCl_2$. The catalytic reaction was done using 2% of the hydroxysulfoxide in toluene at 0 °C, and the enantiomeric excesses were determined by optical rotations. From these studies, it has been determined that tertiary carbinols give better enantioselectivity than the secondary ones, and that the cyclic hydroxysulfoxides are better ligands than the acyclic ones. The best ligands were hydroxysulfoxide **251** (35% ee) in the case of acyclic ligands and **252** in the case of cyclic ligands (45% ee).

Scheme 74[a]



[a] **a**: R = *i*-Pr. **b**: R = Ph. **c**: R = *t*-Bu.

S,N ligands **254a**−**c** (Scheme 74), using α-pyridiyl sulfoxides, used by Chelucci et al. in the palladium-catalyzed asymmetric alkylation (vide infra), were also tried in the addition of diethylzinc to benzaldehyde.[281] The ligands were obtained with low diastereomeric excess (0−66% de) by quenching the red solution of lithiated **253a**−**c** with Andersen's reagent at −78 °C. Whereas single diastereomers were obtained in pure form by column chromatography, the absolute configuration of the carbon stereocenter was not determined, and the problem of chiral cooperativity was not adressed. While these ligands made an active catalyst, the enantioselection was very low (up to 19% ee).

Quite recently, Carretero reported the synthesis and utilization of 2-sulfonamido 1-*tert*-butyl-sulfinylferrocene **255** (Figure 26) in the ethyl transfer from diethylzinc to aldehydes. The ligands were synthesized using Kagan's diastereoselective ortho-lithiation of sulfinyl ferrocene (vide infra), followed by amine derivatization. The utilization of 5 mol % of

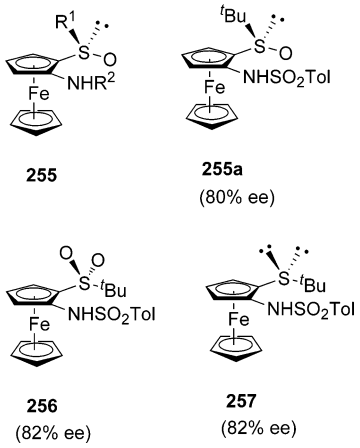
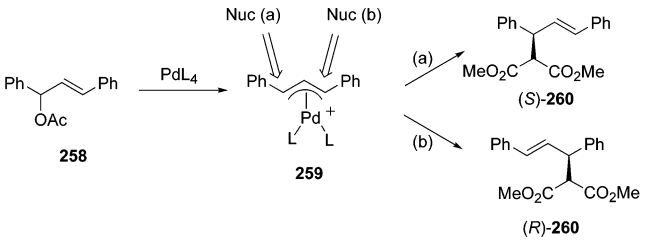


Figure 26.

Scheme 75



ligand **255** with a *tert*-butyl group on the sulfinyl sulfur gave the alcohol **250** with up to 88% ee.[282] Comparison of the ee obtained with **255a** (80% ee) with a chiral sulfinyl group, the corresponding sulfone **256** (82% ee), and the thioether **257** (82% ee) put forward the importance of the planar chirality of these ligands on the enantioselectivity observed.

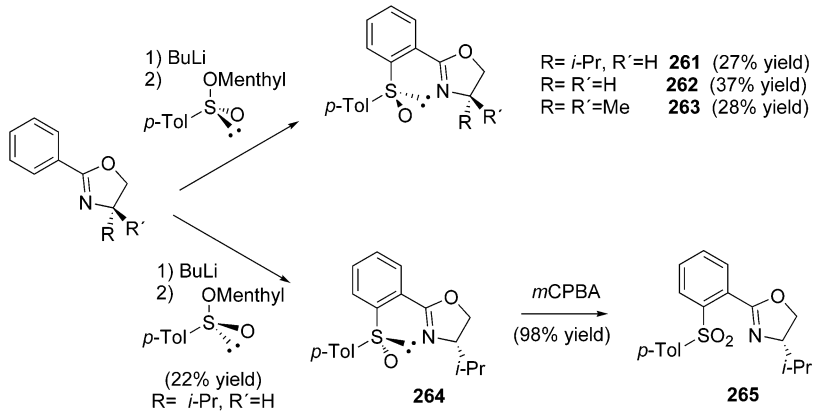
E. Catalytic Allylic Substitution

A particularly efficient way of carbon−carbon bond formation was opened up by the reaction of carbon nucleophiles with allylpalladium complexes, the generation of which is accomplished in situ and requires only a catalytic amount of the transition metal. After mechanistic studies had treated the problem of stereochemistry, considerable efforts were directed toward enantioselective variants.[283] One of the methods for generating an enantioselective variant of the palladium-catalyzed allylic substitution reaction has been to use substrate **258**, which proceeds via symmetrical complexes **259** (Scheme 75). The terminus of the allyl group which is attacked determines the enantiomer of substitution product, (*R*)-**260** or **(***S*)-**260**, that is obtained. While bidentate ligands with C_2 symmetry have been dominating the field of asymmetric catalysis, recent advances have shown that ligands with two different coordinating functionalities are highly effective, especially in the palladium-catalyzed allylic substitution. Ligands containing two different donor atoms are able to impart an electronic distortion upon the allyl moiety in the intermediate palladium allyl complex: nucleophilic addition to the complexed allyl is predicted to take place trans to the better π-acceptor. Williams, one of the pioneers of the concept of palladium allylic substitution, reported the first use of chiral sulfoxides tethered to an oxazoline ring in the reaction of 1,3-diphenylpropenyl acetate with dimethyl malonate.[284] The chiral ligands were prepared either by a diastereoselective oxidation of the parent sulfide[211] or by ortho-lithiation of the parent 2-phenyloxazoline with BuLi and addition of either (S_S)- or (R_S)-menthyl *p*-toluenesulfinate (Scheme 76).

The S,N ligands synthesized, **261**−**264**, were shown to be highly efficient in palladium-catalyzed asymmetric substitution, as they give the substitution product **260** in good yields and moderate to good enantioselectivities. Interestingly, ligand **261** provides much greater enantioselectivity (88% vs 55%) and also chemical yield (96% vs 42%) than does the diastereomeric ligand **264**. This result, associated with the reasonable level of enantioselectivity with ligands **262** and **263**, where the chirality is imparted solely by the sulfoxide group, indicates that the stereochemistry of the sulfur is important in determining the stereochemical outcome of the reaction. Additionally, the sulfone **265** did not provide a reactive Pd catalyst, suggesting that active catalysts are S-bonded.

A large number of chiral bidentate ligands with a chiral sulfoxide and other heteroatom were synthesized and evaluated by Hiroi's group, mainly from 1997 to date.[285−288] These ligands can be divided into two different groups depending on the nature of the heteroatom associated with the sulfinyl function in the chelation to the palladium. The first class of these

Scheme 76



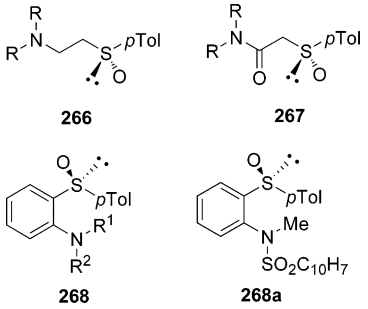


Figure 27.

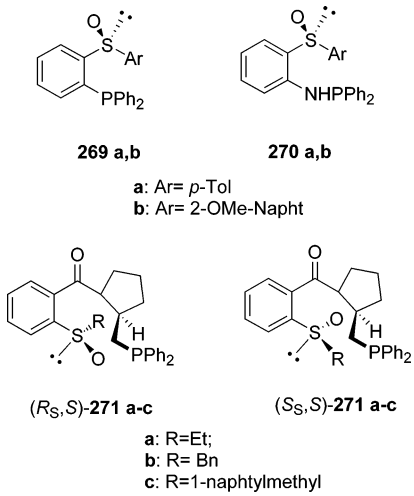


Figure 28.

ligands (Figure 27) are those having a nitrogen atom as an amine (**266**), an α-acetamide (**267**), or a sulfonamide (**268**).[285] The synthesis of these ligands has been achieved by Michael addition of a secondary amine to (*R*)-*p*-tolyl vinyl sulfoxide (for **266**), by an amidation of the known (*R*)-2-(*p*-toluenesulfinyl)-acetic acid (for **267**), or by *ortho*-sulfinylation of the preformed tertiary amine for rigid ligands **268** derived from *o*-bromoaniline. Among all these ligands, only **268a** shows some catalytic activity, leading to **260** (Scheme 75) with low yield (34%) and low ee (41%). The second class of ligands, **269**−**271** (Figure 28), are those possessing a phosphorus chelating atom, with the sulfoxide as the sole chiral center, **269** and **270**, or with an additional chiral center derived from proline **271**.[286−288]

Ligands **269** were prepared from 2-fluoroiodobenzene by sulfinylation, followed by an aromatic nucleophilic substitution with potassium diphenylphosphide. The reaction of 2-bromoaniline with chlorodiphenylphosphane, followed by ortho-sulfinylation, produced ligands **270** in good yields. Finally, the ligands of type **271**, derived from proline, were prepared starting from (*S*)-*N*-(2-bromobenzoyl)proline. A reduction of the amide group was followed by sulfinylation, or sulfenylation and oxidation with *m*-CPBA. Among the ligands prepared, those having a 2-naphthyl group were shown to be superior to those having a *p*-tolyl group. For instance, the catalyst formed by ligand **269b** and $PdCl(\pi\text{-allyl})_2$ (6% mol) gave the product of allylic alkylation (*S*)-**260** (Scheme 75) in 71% yield and 82% ee, while the ligand **270b** gave the same product in 97% ee, albeit in low yield (49%). Ligand **269b** has also been shown to be useful for palladium-catalyzed asymmetric amination. The use of the former catalytic system, using benzylamine as nucleophile, gave the aminated alkene in 85% ee and 51% yield.

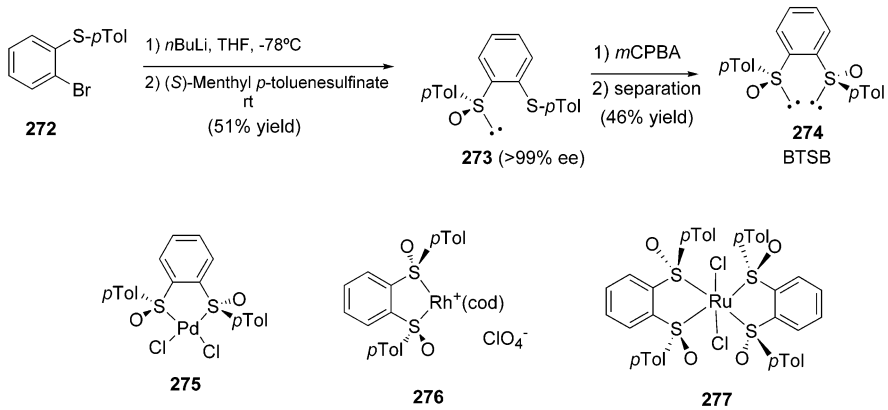
Rigid C_2-symmetric bis-sulfoxides were also used in the same reaction by Shibasaki's group in 1995.[289] The ligand was obtained in three steps from bromoaniline (Scheme 77) by introducing first the *p*-tolylthioether **272**, followed by ortho-lithiation and sulfinylation using Andersen's method. The final step was the diastereoselective oxidation of the thioether **273**, which was shown to be poorly diastereoselective, leading to the desired C_2-symmetric bis-sulfoxide **274** in 46% yield, together with the meso compound (30%) and the sulfoxide/sulfone (24%).

The ligand obtained, named BTSB by the authors, was shown to form stable palladium **275**, rhodium **276**, and ruthenium **277** complexes. All the complexes synthesized were shown to be S-coordinated, and the structure of $BTSBPdCl_2$ **275** was confirmed by X-ray analysis. Finally, the BTSB ligand (20% mol) was tried in the palladium-catalyzed asymmetric allylation using 5 mol % of $[Pd(\eta^3\text{-}C_3H_5Cl)]_2$, BSA, and acetate salt, leading to the (*S*)-**260** compound (Scheme 75) in modest to good yield (25−82%) and modest enantioselectivities (20−64%).

F. Miscellaneous

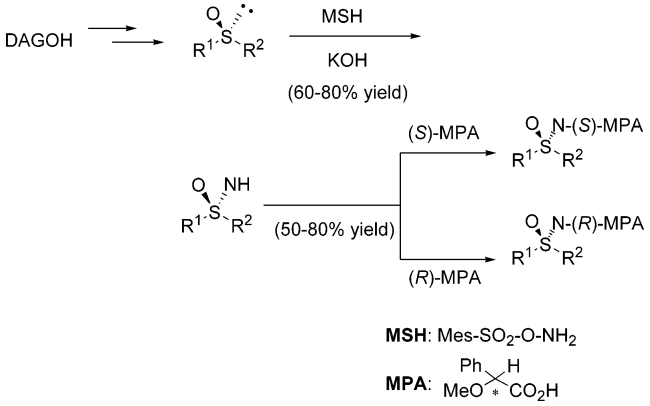
Sulfoximines with a chiral sulfur atom have emerged recently as valuable ligands for metal-

Scheme 77



catalyzed asymmetric synthesis.[290,291] Even though the sulfoximine behavior toward transition metals is very different from that of the sulfoxide group, we include in this section the most representative examples of sulfoximines used as chiral ligands in metal-catalyzed asymmetric synthesis. This is dictated by (i) the intrinsic stereochemical and synthetic pathways relationship between the two functions and (ii) the fact that chiral sulfoximines are by far the most successful chiral sulfur-based ligands used in asymmetric catalysis.While there are various methods for the synthesis of this interesting class of molecules, the most general one is by amination of the corresponding sulfoxide. Accordingly, the reaction of an optically pure sulfoxide with the nitrogen-transfer reagent *O*-mesityl sulfonylhydroxylamine (MSH) affords the corresponding sulfoximine with complete retention of configuration (Scheme 78).[292]

Scheme 78[a]



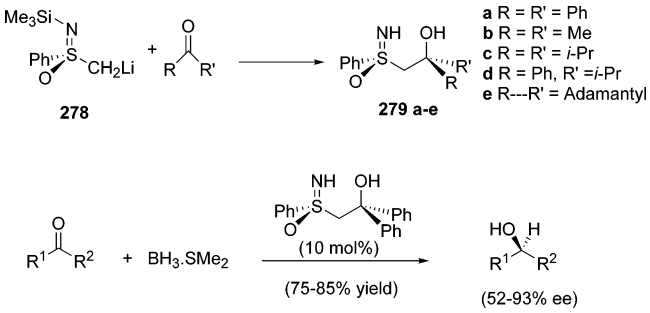
[a] R^1 = Et, Me, Bn. R^2 = *i*-Pr, Bu, $(CH_2)_2Ph$, hexyl, $(CH_2)_3Ph$, heptyl, $(CH_2)_4Ph$, *i*-Bu.

Thus, one anticipates that the advances in the asymmetric synthesis of chiral sulfoxides discussed so far will surely have a profound consequence on the asymmetric synthesis of chiral sulfoximines (vide infra). In this regard, it is interesting to mention the recent work of Kusumi, who reported the synthesis of a large number of sulfoximines from the corresponding sulfoxides obtained by the DAG methodology. These sulfoximines were used to validate his model for the determination of the absolute configuration of chiral sulfoxides by NMR spectroscopy (Scheme 78).[242]

Simple sulfoximines were shown to coordinate to transition metals such as copper and zinc through the nitrogen atom.[293] By far, bidentated β-hydroxysulfoximines were the most successful sulfoximine ligands in asymmetric catalysis. X-ray analysis of complexes of ethylzinc[294] and vanadium[295] coordinated to β-hydroxysulfoximines has shown that the metal is coordinated to the hydroxyl oxygen and the sulfoximine nitrogen.

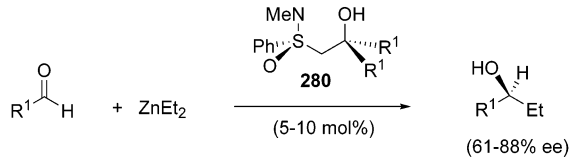
In 1993, Bolm reported the catalytic enantioselective borane reduction of prochiral ketones using β-hydroxysulfoximines as ligands,[296] pioneered by Johnson in 1979.[297] The ligands were obtained by condensation of the lithiated *N*-silyl-protected optically pure sulfoximine **278**[298] with ketones, followed by desilylation (Scheme 79). Using 10 mol % of ligand

Scheme 79



279, the secondary carbinols were obtained in high yield and good selectivities (up to 93% ee) (Scheme 79).[296,298] The same chemistry was extended to the catalytic asymmetric reduction of ketimines, *N*-SPh-substituted imines being the substrate of choice.[299] Related ligands were shown to be efficient catalysts for the ethyl transfer from diethylzinc to aldehydes. The use of 5−10 mol % of β-hydroxyl-*N*-methylsulfoximine **280** (Scheme 80) afforded the secondary carbinols in good yield and in high enantioselectivities (up to 88%).[300]

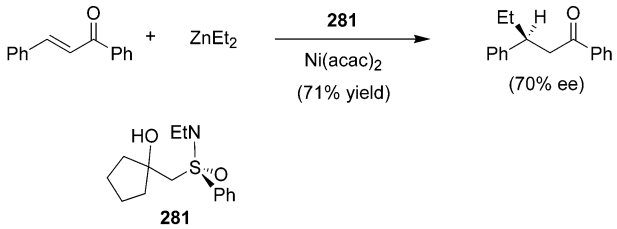
Scheme 80[a]



[a] R^1 = Me, $-(CH_2)_n-$ (n = 3 or 9).

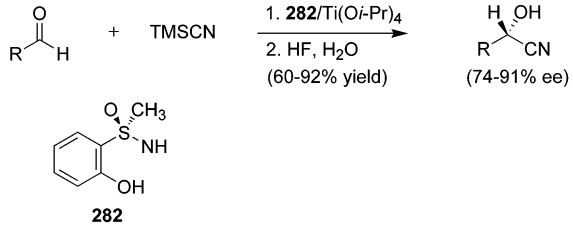
Additionally, β-hydroxysulfoximine **281** was shown to be an efficient ligand for Ni-promoted Michael addition of diethylzinc to chalcone (Scheme 81),[301]

Scheme 81



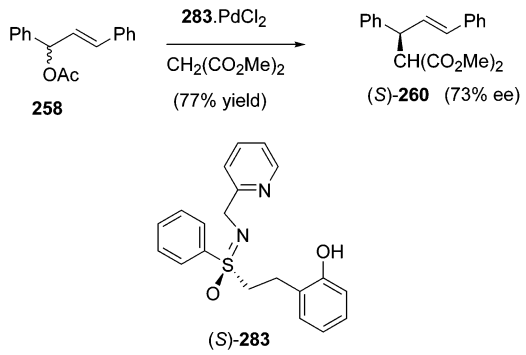
while β-hydroxysulfoximine **282** was efficient for Ti-promoted addition of TMSCN to aldehyde (Scheme 82).[302]

Scheme 82

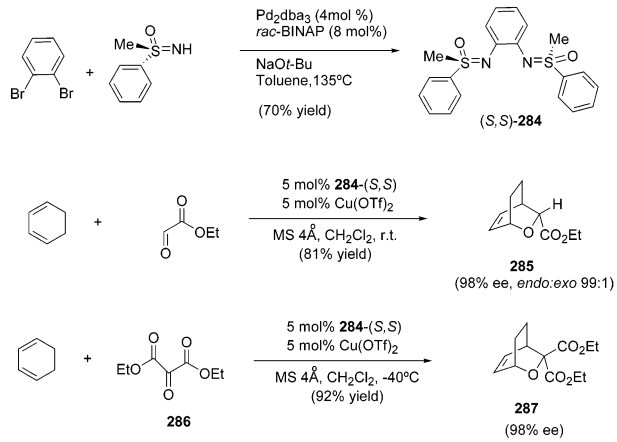


Sulfoximines embedded with a pyridine ring, such as **283** (Scheme 83), were shown to be good catalysts for palladium-catalyzed asymmetric substitution, affording (*S*)-**260** in good yield and modest selectivity (up to 73%).[303]

Scheme 83



Scheme 84



C_2-Symmetric bis-sulfoximine (*S*,*S*)-**284** (BISOX) (Scheme 84) was recently reported by Bolm as a highly efficient catalyst in copper-catalyzed asymmetric hetero-Diels−Alder reactions (HDA).[304]

The reaction of 1,3-cyclohexadiene and ethyl glyoxylate (Scheme 84), using the in situ-prepared Cu/MePh/BISOX catalyst (5%), afforded the HDA adduct **285** as a single diastereoisomer in 81% yield and high enantioselectivity (98%). Exceptionally enough, the catalyst loading can be reduced to up to 1 mol % without significant loss of enantioselectivity. BISOX/$Cu(OTf)_2$ was also an excellent catalyst in the reaction of cyclohexadiene and the activated ketone **286**. Up to 98% ee in 92% yield was achieved using 10 mol % of the catalyst at −20 °C, leading to the cycloadduct **287**.

XII. Sulfoxides as Chiral Auxiliaries in Metal-Promoted Asymmetric Synthesis

To combine the stereodirecting effect of the sulfinyl group with the chemistry of transition metals,[305] various groups started programs in the mid-1990s directed toward this end. The contributions in this specific area can be divided into two approaches: those using the transition metal as a part of the molecule, and those using the metal as a reagent in a key asymmetric bond event.

A. Sulfinyl Derivatives with Planar Chirality

An example of the first approach is the utilization of chiral sulfoxides to impart planar chirality, which is then used to diastereoselectively introduce new chiral centers. These include the synthesis of chiral ferrocenyl sulfoxides, η^6-sulfinyl arene−$Cr(CO_3)$ complexes, η^4-(3-sulfinyl enone)−$Fe(CO)_3$ complexes, and finally, η^4-sulfinyl diene−$Fe(CO)_3$. The groups of Paley and Fernández de la Pradilla reported on the stereoselective synthesis of η^4-sulfinyl diene−$Fe(CO)_3$ and their utilization in asymmetric synthesis.[306−309] As a first part of this work, various efficient strategies directed toward the synthesis of enantiopure sulfinyl dienes, either *E* or Z, **288** and **289** (Scheme 85), were developed.[217] This was achieved via Stille coupling of halovinyl sulfoxides and vinyl stannanes, hydrogenation of 1-sulfinyl-1-en-3-ynes, or vinylcupration of 1-sulfinyl alkynes.[306] Formation of the corresponding sulfinyl dienes−iron(0) tricarbonyl complexes **290** and **291** (Scheme 85) was accomplished by using $Fe(CO)_3$/NMO or (bda)$Fe(CO)_3$ as iron(0) tricarbonyl-transfer reagents, which led to an excellent diastereoselectivity in the case of 1-(*Z*)-sulfinyl dienes **288** (10:1 to 100:0), in favor of **290** with an α-position $Fe(CO)_3$ fragment on the diene, and low diastereoselectivity in the case of 1-(*E*)-sulfinyl dienes.[307] The selectivity observed was rationalized by allylic 1,3-strain, which forces the sulfoxide to adopt a conformation that places the *p*-tolyl group directly over the *β*-face of the diene system in the 1-(*Z*)-sulfinyl dienes. The complexes formed were later shown to be good substrates for the diastereoselective allylation of the corresponding aldehyde. Thus, the iron (0)−dienal complex **292** (Scheme 85) reacts predominantly through the *s-cis* conformer with allyl tri-*n*-butylstannane in the presence of $BF_3{\cdot}Et_2O$, affording the corresponding homoallylic alcohol **293** in modest to good selectivity (up to 95:5), depending on the substituent in the 3 position. For the 3-formyl-1-sulfinyl-1,3-butadiene iron complexes of type **294** (Scheme 86), the aldehyde predominantly reacts through the *s-trans* conformer, leading to the corresponding homoallylic alcohol **295** in a 89:11 diastereomeric ratio.[308]

Additionally, Paley recently exploited this finding by the elaboration of **295** to bis-olefin **296**, which is capable of undergoing ring-closing metathesis chemistry (Scheme 86).[309] Using Grubbs's ruthenium carbene catalyst,[310] a six-member carbocycle **297** (with one chiral center) was obtained in 93% yield. The generality of the method was shown by the preparation of seven-, eight-, and nine-membered carbocycles **298**, **299**, and **300** (Figure 29) with two chiral centers,

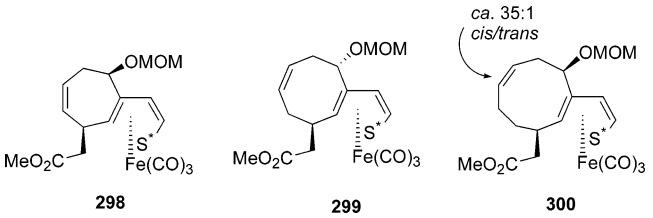
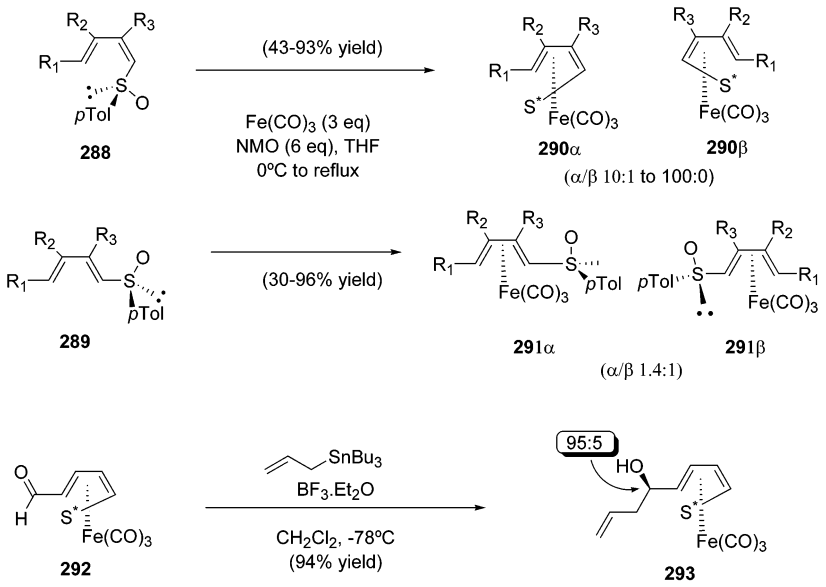


Figure 29.

with excellent yields (around 90%) using 8% of Grubbs's catalyst.

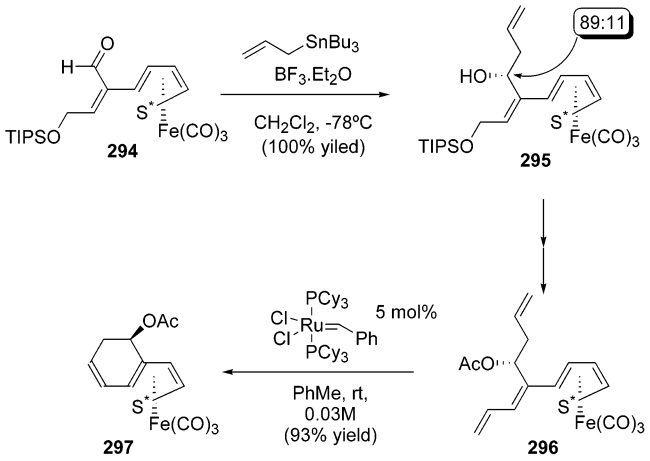
Ferrocene has played an important role in many areas of synthetic and material chemistry since its

Scheme 85[a]



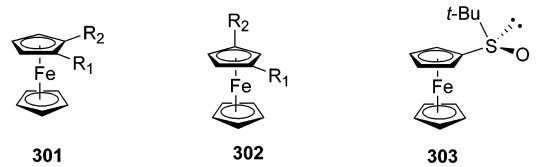
[a] S* = (*R*)-*p*-tolyl sulfoxide.

Scheme 86[a]



[a] S* = (*R*)-*p*-tolyl sulfoxide.

discovery 50 years ago.[311] From a stereochemical point of view, however, one of the most important attributes of 1,2- and 1,3-disubstituted ferrocene **301** and **302** (Figure 30) is that they are planar chiral



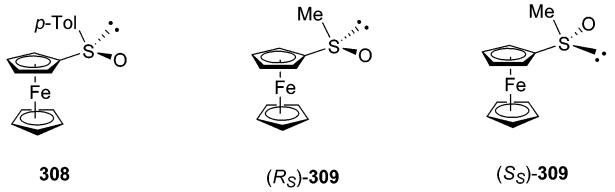
301 **302** **303**

Figure 30.

and thus potentially available in enantiomerically pure form.[311a] A number of methods are available for the preparation of optically pure ferrocenyl derivatives. Among the most effective strategies used to prepare these compounds are those based on the use of stereogenic ortho-directing group for a diastereoselective ortho-lithiation and subsequent reaction with an appropriate electrophile. The most prominent example of this methodology is based on the pioneering work of Ugi and co-workers, using chiral amine as the ortho-directing group.[312]

The use of chiral sulfoxides in this task was pioneered by Kagan in 1993.[200] The chiral sulfoxide **303** (Figure 30) resolve the problem of the additional resolution step of the Ugi approach and acts as an effective stereodirecting group. *tert*-Butylferrocenyl sulfoxide **303** (Scheme 87) was prepared in 100% ee and 75% yield from ferrocenyllithium **304** by the sulfite approach,[200] and in 90% ee and 55% yield by enantioselective oxidation of the corresponding prochiral thioether **305**, using cumene hydroperoxide in the presence of 1 equiv of the combination Ti(O-*i*-Pr)$_4$/(*S*,*S*)-DET/H$_2$O (1:2:1).

Surprisingly, the last approach was later described to occur with 100% ee and 61% yield.[313] The *tert*-butyl sulfoxide **303** was easily deprotonated by *n*-BuLi in THF at 0 °C to give the ortho-lithiated compound **306**. The absolute configuration of the sulfinyl sulfur was unambiguously determined by X-ray crystallography of **303**, which showed that the *tert*-butyl group prefers the anti orientation with respect to the iron atom, forcing the oxygen substituent to face the (*pro*-*S*) ortho position. The ortho-lithio compound **306** (Scheme 87) reacted with many electrophiles to give a large range of chiral ferrocenes type **307**, important intermediates for the preparation of chiral ligands with planar chirality. Two other chiral ferrocenyl compounds were prepared from ferrocenyllithium **304**. (*R*)-*p*-Tolylferrocenyl sulfoxide **308** (Figure 31)

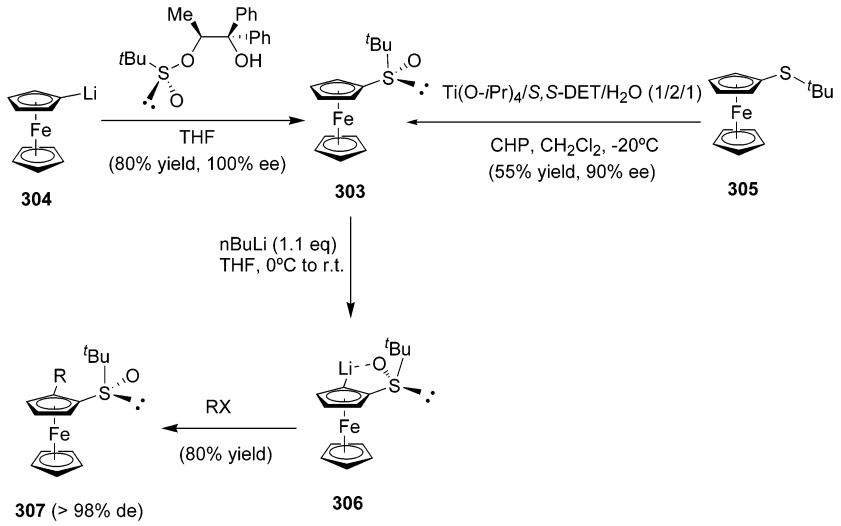


308 (R_S)-**309** (S_S)-**309**

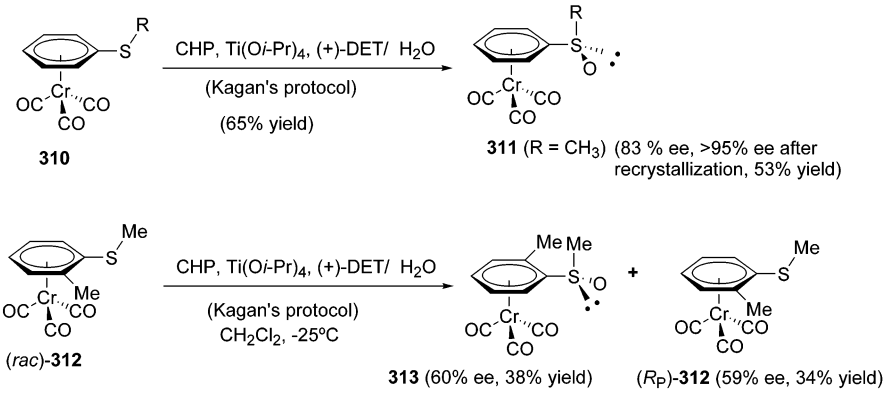
Figure 31.

was prepared either by using Andersen's reagent[314] or by enantioselective oxidation of the prochiral sulfide, and both enantiomers of (*R*)- and (*S*)-methylferrocenyl sulfoxide **309**, prepared by using the DAG method.[315]

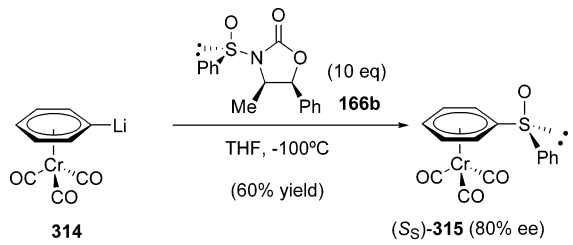
Scheme 87



Scheme 88



Scheme 89



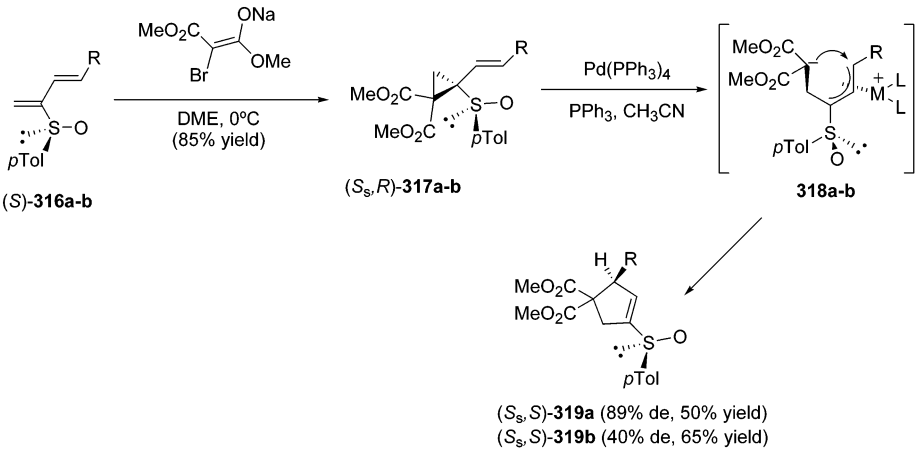
Other compounds with planar chirality are the 1,2-differentially substituted arene−chromium tricarbonyl complexes. Additionally, these complexes have been shown to undergo a variety of highly stereoselective reactions, making them interesting synthetic targets. Thomas reported the synthesis of chiral benchrotrenes using the Kagan protocol for the oxidation of tricarbonyl (η^6-thioanisole)chromium(0) **310** (Scheme 88) and two of its derivatives, obtaining **311** with up to 86% ee (Scheme 88). A kinetic resolution was observed in the oxidation of racemic **312** using 0.55 equiv of the oxidant. The sulfoxide **313** was obtained in 30% yield and 60% ee, while the unreacted sulfide **312** of opposite planar chirality was obtained in 34% yield and 59% ee.[316] **(**S_S)-Diphenyl sulfoxide−chromium tricarbonyl **315** (Scheme 89) was prepared by Davies's group in 80% ee and 60% yield, by reaction of phenyllithium−chromium tricarbonyl **314** with 10 equiv of (4*R*,5*S*)-4-methyl-5-phenyl-3-[(*R*)-phenylsulfinyl]-2-isoxazolidinone **166b** at −100 °C.[317] As in the case of ferrocenyl sulfoxides, sulfinyl−arene−chromium tricarbonyl complexes were recently shown to be good stereogenic ortho-directing groups. Additionally, these complexes have been shown to undergo a variety of highly stereoselective reactions, making them interesting synthetic targets.

B. Diastereoselective Processes of Sulfinyl Derivatives Promoted by Transition Metals

Hiroi demonstrated that 3-alkyl-1-sulfinylcyclopent-1-enes could be prepared with good diastereoselectivities by taking advantage of a Pd(0)-catalyzed 1-sulfinyl-1-vinylcyclopropane rearrangement.[318] The starting cyclopropane derivatives **317** (Scheme 90) were prepared in good diastereoselectivity (above 80% de) by Michael addition of dimethyl bromomalonate−sodium enolate to vinyl sulfoxide **316**, followed by intramolecular asymmetric alkylation. Treatment of (S_S,*R*)-**317a** with tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] (0.15 equiv) and triphenylphosphine (0.66 equiv) in acetonitrile gave the 3-alkyl-1-sulfinylcyclopent-1-enes **319a** in 50% yield and 89% de.

It should be noted that the origin of the stereoselectivity observed in this process was not a result of the influence of the sulfoxide on the presumed intermediate sulfinyl−π-allyl-Pd(0) complex **318**, but rather was due to a prior non-transition-metal-

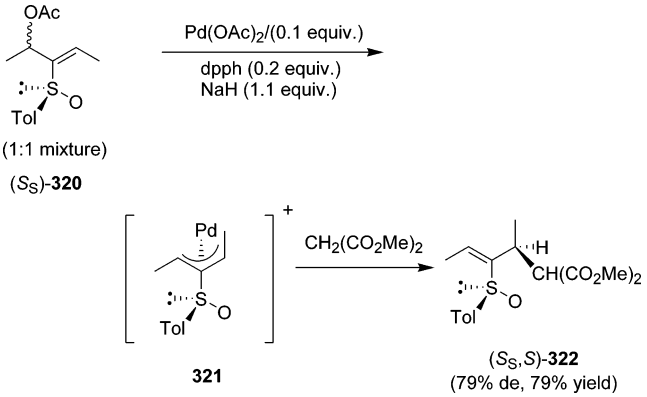
Scheme 90[a]



[a] **a**: R = Me. **b**: R = Et.

mediated diastereoselective vinyl cyclopropanation. In 1995, the same group reported the first asymmetric palladium-catalyzed nucleophilic substitution promoted by a chiral sulfinyl function. Addition of sodium enolate of dimethyl malonate on the vinylic sulfoxide (S_S)-**320** in the presence of 10 mol % of Pd(OAc)$_2$ and 20 mol % of phosphine ligand (dpph) afforded the allylic product (S_S,*S*)-**322** in good yield (79%) and diastereoselectivity (79% de). The stereoselectivity observed was rationalized by the influence of the sulfinyl group, which favors the formation of the presumed intermediate *s-trans*-sulfinyl−π-allyl-Pd(0) complex **321** (Scheme 91).[319]

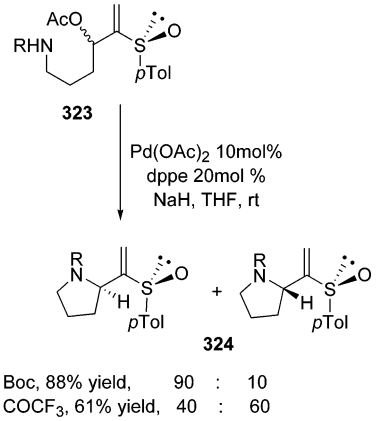
Scheme 91



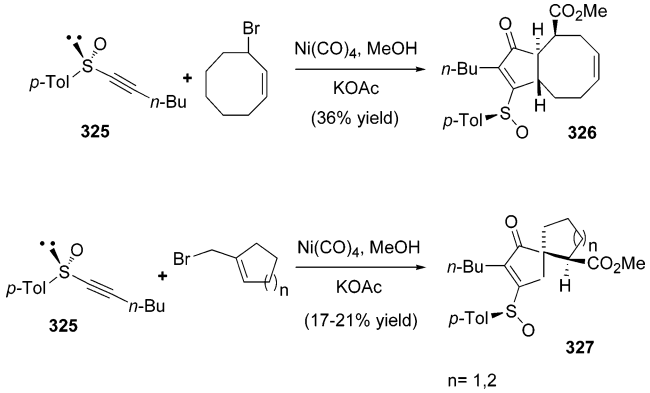
An intramolecular palladium-catalyzed asymmetric allylic amination directed by the sulfinyl group was recently reported by Llebaria et al. (Scheme 92).[320] The palladium-catalyzed cyclization of *N*-Boc- and *N*-trifluoroacetyl-substituted 4-acetoxy-5-(*p*-tolylsulfinyl)-hex-5-enylamines **323**, using either 10% Pd(OAc)$_2$ or 20% dppe, leads to the corresponding pyrrolidine **324** in good diastereoselectivity. Interestingly, the major adducts obtained in the trifluroacetamide and NHBoc series were epimeric at the α-nitrogen stereogenic carbon, indicating a stereochemical dependence on the nitrogen anionic nucleophile.

Moretó reported a Ni(CO)$_4$-mediated approach to enantiomerically pure fused and spiro cyclopentanones **326** and **327** (Scheme 93), using alkynyl

Scheme 92



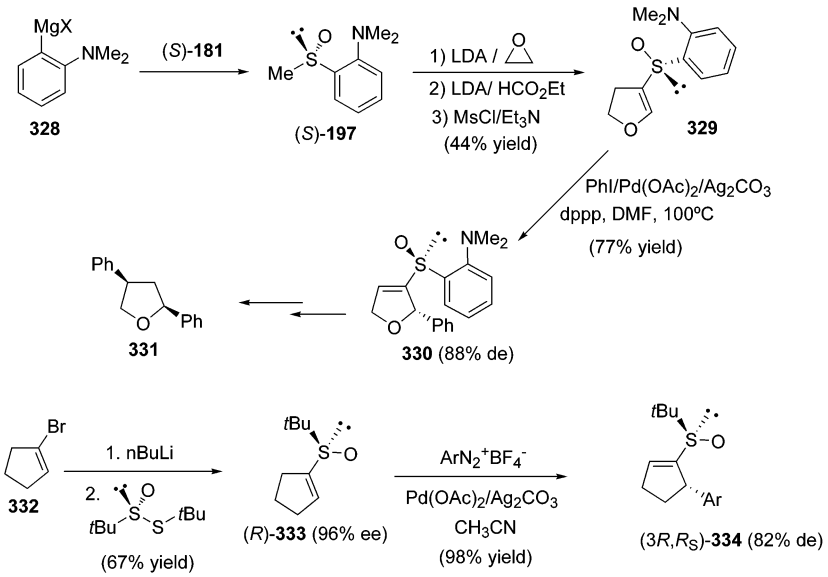
Scheme 93



sulfoxides **325** and allylic bromides, but the diastereoselectivity of this process was modest.[321]

Carretero and co-workers demonstrated that the stereochemical outcome of the palladium-catalyzed arylations (Heck reaction)[322] of 4-arylsulfinyl-2,3-dihydrofurans **329** (Scheme 94) is highly dependent on the substitution of the sulfoxide.[235] The starting (*S*)-*o*-(*N*,*N*-dimethylamino)phenyl methyl sulfoxide (*S*)-**197** was obtained using the DAG methodology by condensation of *o*-(*N*,*N*-dimethylamino)phenyl Grignard **328** on the (S_S)-methanesulfinate (S_S)-**181**. Palladium-catalyzed arylation of **329** affords Heck adduct **330** with high stereocontrol (70−88% de). The method is also useful for the synthesis of 3,5-diaryl-

Scheme 94[a]



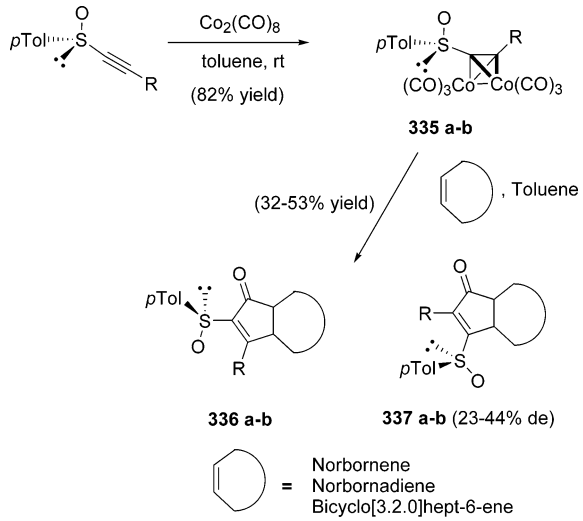
[a] dppp = 1,3-bis(diphenylphosphino)propane.

2,3-dihydrofuran **331**, as the 2-phenyl-3-(arylsulfinyl)-2,5-dihydrofuran obtained, **330**, which is also a vinyl sulfoxide, can undergo a second Heck reaction. Surprisingly, the use of the more hindered *tert*-butylsulfinyl group in the same process not only did not improve the diastereoselectivity but also led to a complex mixture.[323]

The desired (*R*)-1-*tert*-butylsulfinyl-1-cyclopentene **333** (Scheme 94) was readily obtained, in 67% yield and 96% ee, by sulfinylation of cyclopentene lithium (obtained from 1-bromocyclopentene **332**) with Ellman's (*R*)-*tert*-butyl *tert*-butanethiosulfinate. Cyclopentene **333** was found to be a good substrate for the Heck reaction using the more reactive arenediazonium salt Ag_2CO_3 (2 equiv) as base and acetonitrile as solvent. Using these conditions, the Heck adducts (3*R*,R_S)-**334** were obtained in both good yields (55% to quantitative) and high diastereoselectivities (91:9 to 96: 4).[324]

The cobalt-mediated carbonylative co-cyclization of an alkyne and an alkene, known as the Pauson–Khand (PK) reaction,[325] is one of the most powerful established methodologies for the construction of five-membered rings in general, and cyclopentanone in particular. One of the best approaches for an asymmetric PK (APK) reaction is the use of a chiral auxiliary attached to the alkyne or to the alkene counterpart. Pericàs and co-workers were the first to use a chiral alkynyl sulfoxide in an APK reaction with strained alkene.[326] Various alkynyl sulfoxides were synthesized and transformed into the corresponding hexacarbonyl dicobalt complexes **335a–d** (Scheme 95) in high yield by stirring with octacarbonyl dicobalt in toluene at room temperature. The APK reaction of these complexes with strained alkenes (norbornene, norbornadiene, and bicyclo[3,2,0]-hept-6-ene) led to the regioisomeric bicyclic enones **336** and **337**, in modest yield and low selectivity. Interestingly, it was found that the decreased enantiomeric excess of the final products was a consequence of an unprecedented low-temperature racemization of the hexacarbonyl dicobalt complexes of

Scheme 95[a]

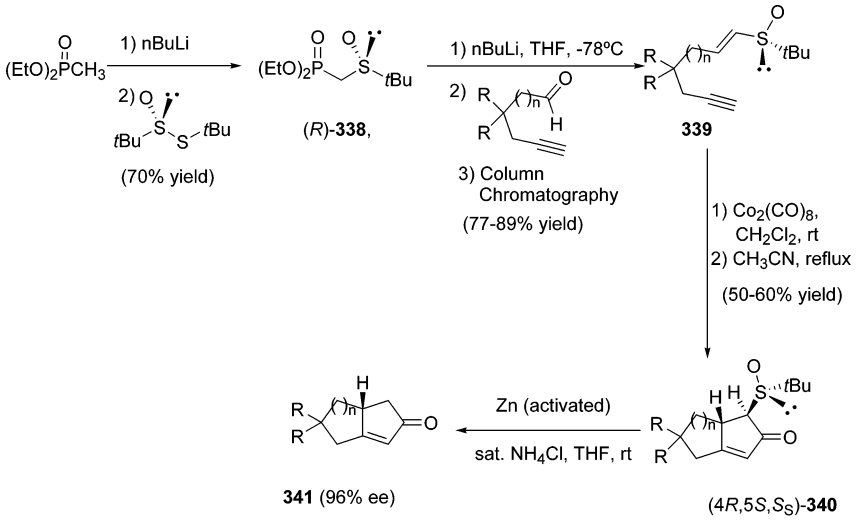


[a] **a**: R = *n*-C_4H_9. **b**: R = Ph.

the alkynyl sulfoxides. The epimerization process has been shown to take place by means of a first-order kinetics with a rate constant of 2.8×10^{-6} at 25 °C. Three possible causes of the racemization have been envisaged: (a) homolytic cleavage of the sulfur–cabon bond, (b) pyramidal inversion, and (c) formation of a pentavalent sulfur intermediate followed by Berry pseudorotations.

Shortly after, Carretero et al. found that the use of a *tert*-butylsulfinyl group attached to the alkene moiety allows a high selectivity in the intramolecular APK reaction.[327] A variety of (*S*)-*tert*-butylsulfinylated enynes were prepared by olefination of the corresponding alkynyl aldehyde with (*R*)-diethyl *tert*-butylsulfinylmethylphosphonate **338**. The major *trans*-isomer obtained, **339**, was submitted to a thermal APK reaction (Scheme 96). In all the studied cases, a single isomer **340** was obtained (de > 98%) as a single reaction product. Interestingly, it was found that both *cis*- and *trans*-1-alkenyl sulfoxides **339** led to PK adducts with high selectivity. The desulfiny-

Scheme 96[a]



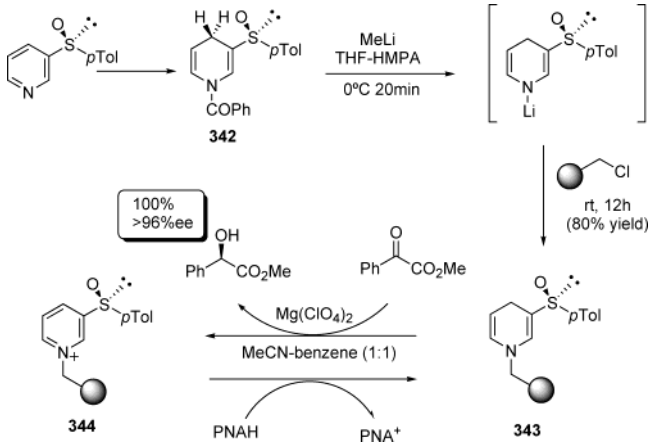
[a] R = H, Me, CO_2Et.

lation of PK adducts was simply performed with activated zinc (saturated NH_4Cl, THF, room temperature), leading to the bicylic enones **341** in high yields (92−96%).

XIII. Chiral Sulfoxides on Solid Support

Some work directed toward the utilization of chiral sulfoxides as components in solid-phase and combinatorial synthesis has recently appeared.[328,329] These approaches are directed toward the preparation of libraries of chiral and biologically significant small molecules bearing (or not bearing) a chiral sulfinyl group. The first use of chiral sulfoxides on solid support was achieved by Imanishi in 1998 in a project directed toward the development of a catalytic chiral NADH model. (*S*)-3-(*p*-Tolylsulfinyl)-1,4-dihydropyridine was grafted at the N-1 position on Merrifield resin via (*S*)-1-lithio-3-(*p*-tolylsulfinyl)-1,4-dihydropyridine, obtained from chiral sulfinyl dihydropyridine **342** (Scheme 97).[330] The polymer-supported

Scheme 97[a]



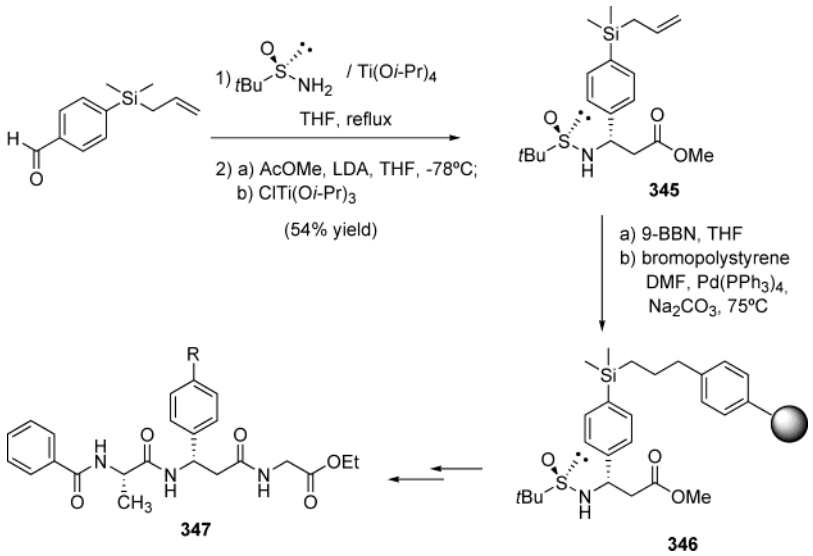
[a] PNAH = 1-propyl-1,4-dihydronicotinamide.

NADH model **343** was shown to reduce methyl benzoylformate to (*R*)-methyl mandelate in quantitative yield and with excellent enantioselectivity. Additionally, the NADH model could be regenerated from the corresponding pyridine analogue **344** by treatment with 1-propyl-1,4-dihydronicotinamide and reused without loss of its enantioselective capacity.

Silvermann used (*R*)-*tert*-butanesulfinamide as an efficient chiral ammonia equivalent for the synthesis of *β*-amino acid analogous **345** with an aromatic side chain substituted with a silyl group. Hydroboration of the terminal olefin of **345**, followed by Suzuki coupling of the borane complex with bromopolystyrene resin, afforded the polymer-bound *β*-amino acid derivative **346** (Scheme 98).[331] The side-chain-linked *β*-amino acid **346**, with a *tert*-butanesulfinyl group acting as a Boc surrogate, permitted the elongation in both directions, thus allowing the preparation of more diverse libraries of peptides than with conventional methods. The usefulness of the building block **346** was demonstrated by solid-phase synthesis of the *β*-amino acid-containing tripeptide **347**, with the aromatic ring either unsubstituted or halogenated at the position of the silyl group.

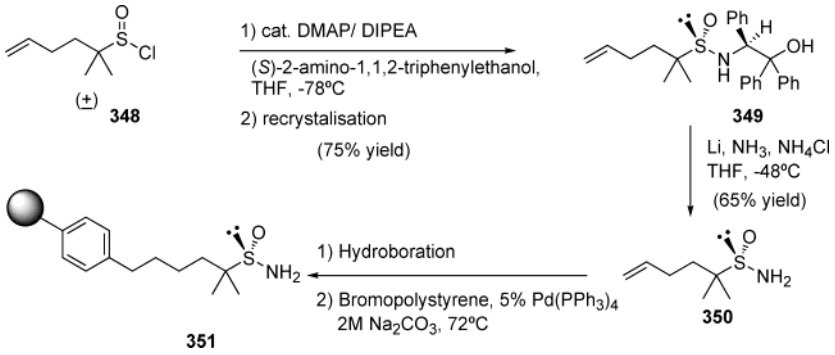
Ellmann recently reported the first synthesis of a support-bound chiral sulfinamide directed toward the asymmetric solid-phase synthesis of amine containing compounds. A new strategy for the synthesis of the *tert*-butanesulfinamide intermediate **349** using (*S*)-2-amino-1,1,2-triphenylethanol as chiral auxiliary was developed. Interestingly, it was found that the use of DMAP as catalyst allowed a dynamic transformation of sulfinyl chloride **348**, affording a 16:1 diastereomeric sulfinamide mixture.[332] A single diastereoisomer **349** was isolated in 75% yield by recrystallization (Scheme 99), which was converted in 65% yield to the enantiomerically pure sulfinamide **350** by dissolving metal reduction. Hydroboration of **350**, followed by Suzuki coupling of the borane intermediate with bromopolystyrene, provided the support-bound *tert*-butanesulfinamide derivative **351** (SBS linker). The usefulness of the SBS linker **351** for the asymmetric synthesis of amine compounds was demonstrated by the preparation of various secondary amines in nearly quantitative yields and high ee's. Moreover, the ee's of the final amines were only slightly lower than those observed for the

Scheme 98[a]

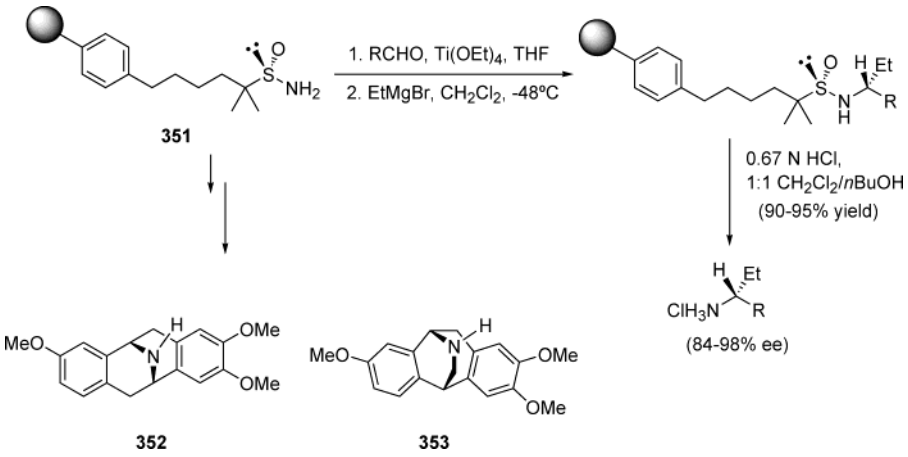


[a] R = H, Br, I.

Scheme 99



Scheme 100[a]

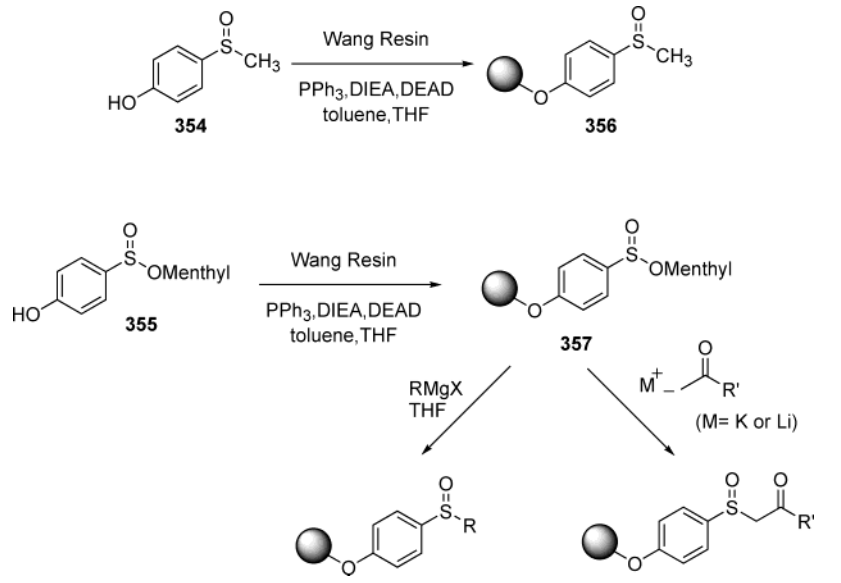


[a] R = *i*-Pr, Ph, Bn, *p*-MeOPh.

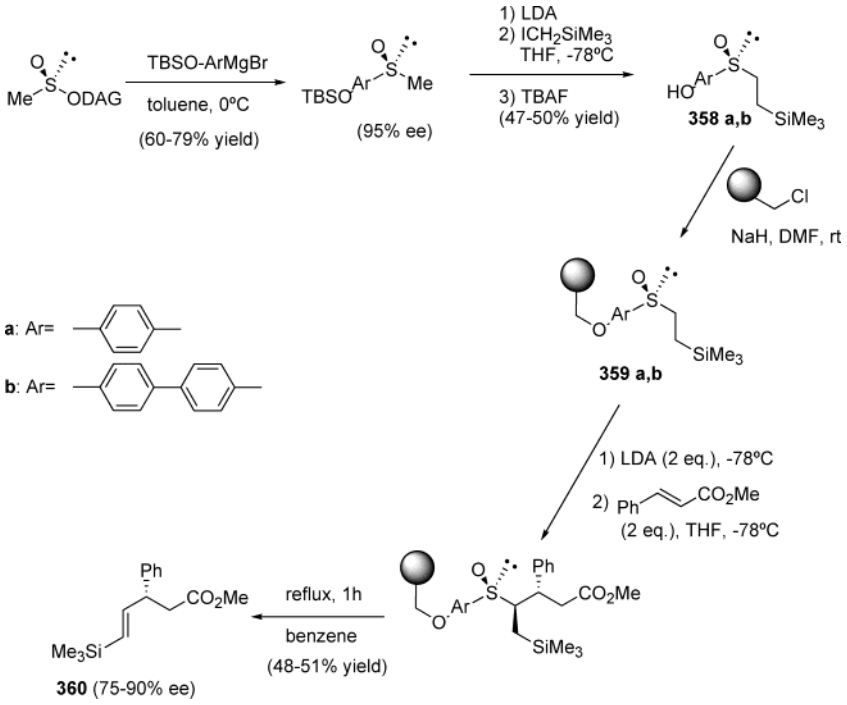
corresponding solution-phase synthesis. On the other hand, the total synthesis of pavine (**352**) and isopavine (**353**) alkaloids established the SBS linker as a valuable tool for the solid-phase multistep synthesis of natural products (Scheme 100).

Hanquet and Solladié recently reported the support-bound menthyl sulfinate and sulfoxides as a first step toward applying their well-established sulfoxide chemistry to solid-phase synthesis.[333,334] Racemic *p*-hydroxyphenyl sulfoxide **354** and the diastereomeric mixture of menthyl sulfinate esters **355** were attached to the Wang resin via a Mitsonubu reaction, affording methyl sulfoxide and menthyl sulfinate linkers **356** and **357** (Scheme 101). Condensation of Grignard reagents on **357** afforded polymer-supported aryl sulfoxides, while the condensation of potassium or lithium enolates afforded β-keto sulfoxides in moderate yields. No conclusion regarding the diastereochemical outcome of these tranformations can be drawn yet, as all the transformations

Scheme 101



Scheme 102



have been conducted on diastereomeric sulfinate ester mixtures, even though a stereoselective synthesis of menthyl *p*-hydroxyphenylsulfinate has been developed.

Toru recently reported on polymer-bound chiral *β*-(trimethysilyl) ethyl sulfoxides, directed toward the synthesis of optically active pentenoates using an approach that they recently developed on the solution phase.[335] The starting aryl methyl sulfoxides were obtained in high yield and ee using the DAG methodology (Scheme 102). Treatment of the hydroxyphenyl sulfoxides with NaH followed by Merrifield resin in DMF afforded polymer-bound *β*-silylethyl sulfoxides **359a** and **359b**. Conjugate addition to methyl cinnamate using LDA as base, followed by thermal *syn* elimination, afforded methyl 3-phenyl-5-trimethylsilylpent-4-enoate (*R*)-**360** in moderate yield. Interestingly, it was found that the stereoselectivity of the Michael addition depended on the spacer and ranged from 75% for **359a** to 90% for **359b**.

Finally, a recent development of combinatorial methods for the discovery of new asymmetric catalysts may offer a potential solution for finding an efficient system for the oxidation of prochiral sulfides which combine high catalytic efficiency and high enantiomeric excess.[336] Accordingly, Jackson recently applied Hoveyda and Snapper's approach (for the discovery of new catalysts for various C−C bond processes) for the optimization of Bolm system.[337] The approach consists of the parallel synthesis of peptide Schiff base libraries of structure **361** having four diversity points: the amino acid AA_1, the hydroxyl amino acid AA_2, salicylaldehyde, and the metal. A first library of 72 ligands, followed by a second with

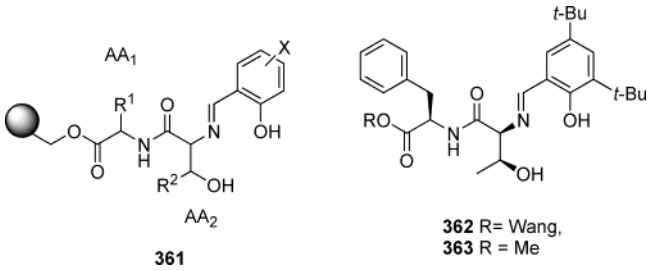


Figure 32.

18 ligands, and a final one with 19 ligands allowed determination of the optimal ligand combination as Wang-D-Phe-Thr-DtBS **362** (Figure 32). Finally, an optimization of the metal shows that the combination of **362** and Ti(O-*i*-Pr)$_4$ gives the best catalyst for the oxidation of methyl phenyl sulfide, giving the (*R*)-isomer in 64% ee. Exceptionally enough, the solid-supported ligand **362** gave the same level of enantioselectivity in the oxidation of methyl phenyl sulfide as the corresponding solution-phase ligand **363**.

XIV. Concluding Remarks and Future Directions

The previous sections demonstrate, without any doubt, that the synthesis of chiral sulfoxides has experienced an enormous expansion in the past decade both from quantitative and qualitative points of view. Today it is possible to access a large number of optically pure sulfoxides with tailored structural properties employing relatively simple and very efficient synthetic procedures. The ease and generality of the new methods have opened the way for the utilization of chiral sulfoxides in new chiral transformations. In addition to the classical uses of sulfoxides as chiral controllers in a few chemical transformations, there are new applications on record concerning virtually every aspect of asymmetric synthesis. The wide range of structures reported to date demonstrates that the basis for the synthesis of this interesting class of molecules is now established, and further challenges are ready to be undertaken soon. As we have seen, the use of sulfoxides as efficient chelators of transition metals remains almost unexplored. This area will surely benefit from recent developments, as the methods described so far allow modular design of sulfinyl-containing ligands in connection with transition-metal-catalyzed enantioselective transformations. The excellent results achieved in the asymmetric synthesis of non-natural amino acids, radical addition, aziridination, and Heck reactions demonstrate the benefit of using sterically and stereoelectronically different sulfinyl derivatives distinct from the widely used *p*-tolyl sulfoxide. The effectiveness of the recent synthetic methodologies anticipates the future utilization of chiral sulfoxides in solid-phase and combinatorial chemistry for the preparation of libraries of chiral small molecules bearing (or not bearing) a chiral sulfinyl group.

Surprisingly, little attention has been given to chiral sulfoxides in the area of supramolecular chemistry and molecular recognition, even though the chelating and hydrogen-bonding capabilities of sulfoxides in combination with the chirality of the sulfinyl group suggest interesting results in this regard.[338]

XV. Acknowledgments

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XVI. References

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