The Chemistry of C_2-Symmetric Bis(sulfoxides): A New Approach in Asymmetric Synthesis

Bénédicte Delouvrié,[a] Louis Fensterbank,*[a] Francisco Nájera,[a] and Max Malacria*[a]

Dedicated to Professor Marc Julia on the occasion of his 80th birthday[‡]

Keywords: Asymmetric synthesis / Chiral acyl anions / Ligand design / Bis(sulfoxides)

The preparation of various racemic or enantiopure C_2-symmetric bis(sulfoxides) has been developed over the last decades. Numerous applications in organic synthesis (anionic condensation, cycloadditions) as well as in coordination chemistry have been worked out.

Introduction

The first mentions of bis(sulfoxides) in organic chemistry date from the middle of the nineteenth century,[1] followed in the 1920s by the exploratory studies of Bell and Bennett on the stereoisomerism of these compounds.[2] After decades of sporadic reports, bis(sulfoxides) have enjoyed new interests from the synthetic community for the last ten years, especially C_2-symmetric derivatives for their intrinsic advantages in asymmetric synthesis.[3] New developments in asymmetric oxidation have largely contributed to this renaissance and spurred various preparations of enantiopure C_2-symmetric bis(sulfoxides). And even if a lot of issues concerning their synthesis, their physical properties and

Bénédicte Delouvrié (top, left) was born in Lille (France) in 1973. After graduating from the Ecole Nationale Supérieure de Chimie de Paris (ENSCP) in 1997, she joined the team of Professor Max Malacria at the Université Pierre & Marie Curie, and obtained her Ph.D. in 2000 for a work on new radical and anionic asymmetric reactions involving sulfoxides and bis(sulfoxides). She is currently a post-doctoral fellow in the group of Professor P. Andrew Evans at Indiana University, Bloomington.

Louis Fensterbank (top, right) was born in Poitiers in 1967 and raised in Tours. While graduating from the Ecole Supérieure de Chimie Industrielle de Lyon (ESCIL) in 1990, he joined the team of Professor Scott McN. Sieburth at the State University of New York at Stony Brook, worked on silicon-tethered reactions and obtained his Ph.D. degree in 1993. After a year of ATER (Attaché Temporaire d'Enseignement et de Recherche) at the Université Pierre & Marie Curie, working in Professor Max Malacria's laboratory, he was appointed by the CNRS in 1995 as a Chargé de Recherche in this team. His research interests concern the development of new radical reactions, organometallic catalysis and asymmetric synthesis.

Francisco Najera (bottom, left) was born in 1968 in Spain. He received his Ph.D. degree from the University of Malaga in 1997, under the direction of Professor R. Suau, for studies concerning the synthesis of new protoberberine alkaloids by a photochemical approach. In 1999, he obtained a post-doctoral position at the University of Bordeaux in the group of "Photochimie Supramoleculaire" and, in 2001, he obtained a CNRS "Poste Rouge" at the Université P. & M. Curie in the "Laboratoire de Chimie Organique de Synthèse" of Professor M. Malacira, working in asymmetric synthesis. He is now Assitant Professor at the University of Malaga.

Max Malacria (bottom, right) was born in Marseille in 1949. He received his Ph.D. degree in 1974 at the University of Aix-Marseille III under the supervision of Professor Marcel Bertrand. From September 1974 to August 1981, he served as an Assistant and Maître Assistant at the University of Lyon I and worked under the supervision of Professor Jacques Goré. From September 1981 to December 1982, he worked as a postdoctoral fellow with Professor K. Peter C. Vollhardt at the University of California, Berkeley. In 1983, he returned to the University of Lyon I as a Maître de Conférences. In 1988, he was appointed as Full Professor at the University Pierre & Marie Curie (Paris VI). In 1991, he was elected as a member of the "Institut Universitaire" de France. His current research interests include the development of new selective and efficient approaches to complex polycyclic molecules, transition metal catalyzed reactions, radical cyclizations and asymmetric synthesis of natural compounds of biological interests. In 1997, he received the award of the Organic Division of the French Chemical Society, in 2000 the prize Grammaticakis Neumann from the French Academy of Sciences and in 2001, the "Médaille d'Argent" from the CNRS. Since September 2001, he has been Editor of the European Journal of Organic Chemistry.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

---

[a] Université P. et M. Curie, UMR 7611,
Laboratoire de Chimie Organique de Synthèse,
4 place Jussieu, 75252 Paris Cedex 05, France
Fax: (internat.) + 33-1/44277360
E-mail: fensterb@ccr.jussieu.fr
malacria@ccr.jussieu.fr

[‡] and for his magnificent contribution to the art of organic synthesis with profound gratitude from the authors

their reactivity still have to be addressed, several important applications of these compounds have already been reported, mainly as ligands and as chiral acyl anions or, when unsaturated, as chiral ketene equivalents.

The interest of our group in C_2-symmetric bis(sulfoxides) stemmed from our initial work in the chemistry of enantiopure vinyl sulfoxides. We have shown over the last decade that the latter are versatile partners, generally resulting in high diastereoselectivities, for palladium-catalysed [3+2] cycloadditions,[4] radical Michael-type cyclizations,[5,6] radical *anti*-Michael cyclizations.[7,8] However, some cases of low diastereoselectivity also suggested that the presence of a second sulfinyl group could be helpful to rigidify the reacting system and thus enhance the diastereoselectivities. This led us naturally to the use of various alkylidene bis(sulfoxides), for which we have recently proposed a new synthesis.[9] This work is presented below (section II.5) and we are currently in the process of involving these promising compounds in a series of new applications. Thus, this microreview will primarily be devoted to past results from other groups and notably summarize the most significant advances in the preparation of C_2-symmetric bis(sulfoxides). The reactivity of these compounds will then be presented according to the following line: anionic reactivity including the condensation onto carbonyl derivatives, participation in cycloadditions, and coordination chemistry.

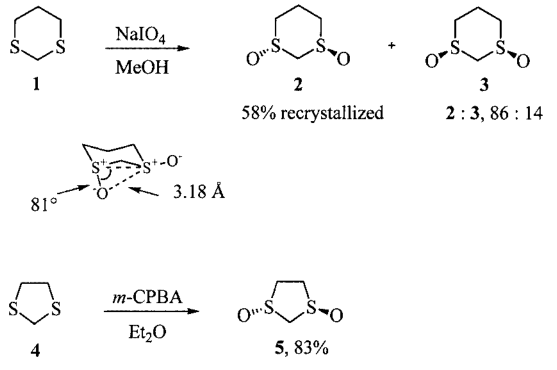
I. Preparation of C_2-Symmetric Bis(sulfoxides)

This section will not cover the synthesis of C_2-symmetric bis(sulfoxides) in an extensive manner. Rather, it will focus on more demonstrative examples in order to illustrate the different available methods.

I.1. Racemic C_2-Symmetric Bis(sulfoxides)

Most preparations have followed dioxidation approaches and though the adjective racemic could indicate easy chemistry, as pointed out by Aggarwal et al.,[10] "to limit the extent of oxidation to the sulfoxide level and to control the relative stereochemistry of the product to favour the (±) structure over the *meso* isomer" remains a challenge. A very pioneering work in that field was achieved by Montanari et al.[11] who showed that the dioxidation of diaryl vinylene disulfide (ArSCH=CHSAr) was electronically and sterically controlled in such a way that the second oxygenation is taking place in "the opposite direction to the first one with respect to the molecular plane". This results in the major formation of *meso* compounds in the *trans*-olefin series and C_2 derivatives in the *cis* one. More recently, studies by Skarzewski et al. showed that the oxoammonium salt catalysed oxidation of bis(phenylthio)alkanes with sodium hypochlorite was high-yielding but generally diastereoselective in favour of the *meso* diastereomer.[12] Other works have involved the DMSO/HCl oxidation of 1,*n*-bis(alkylsulfinyl)alkanes in good yield but no diastereoselectivity.[13,14]

Running the reaction in cyclic series generally renders the job easier and a lot of efforts have been oriented toward the oxidation of 1,3-dithiane (**1**) (Scheme 1).[15] On this substrate, best conditions for the reaction and the isolation were devised by Aggarwal et al. and of all the oxidants, sodium periodate in methanol was found to be the most selective in favour of **2**.[16] This stereoselectivity is governed by "product-development control",[17,18] suggesting that the *trans* isomer is the more stable one. This was confirmed by molecular mechanics calculations, indicating a bonus of stabilization of 0.8 kcal·mol^{-1} for the *trans* isomer.[16] This stabilization would originate from a favourable electrostatic interaction from the axial sulfoxide bent to the equatorial sulfoxide,[10] as confirmed by an X-ray structure determination. In his extensive studies, Aggarwal et al. also showed that the *cis* isomer **3** could be isomerized to **2** with N_2O_4 [19] and that for 5,5-dimethyldithiane, the *cis*-disulfoxide was always obtained as the major compound, except with ozone (*trans*/*cis* = 58:42).[16]



Scheme 1

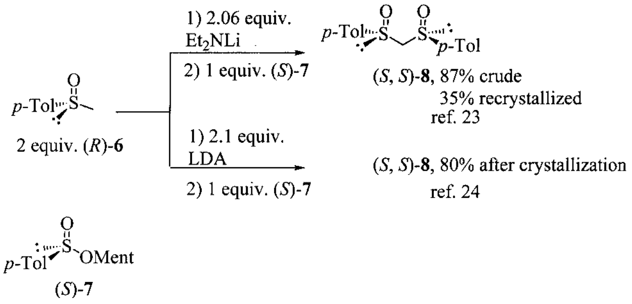
In contrast, racemic *trans*-1,3-dithiolane 1,3-dioxide (**5**) was prepared by an *m*-CPBA oxidation in good yield, and with a complete stereoselectivity.[20] An interesting total *trans* stereoselectivity has also been reported on 1,3-dithiolan-2-ylidenemalonate.[21]

I.2. Enantiopure C_2-Symmetric Bis(sulfoxides)

Several pathways have been investigated for the preparation of enantiopure C_2-symmetric bis(sulfoxides). They globally divide into two distinct chemistries: the Andersen sulfinate approach and the asymmetric oxidation.

I.2.a. The Andersen Approach

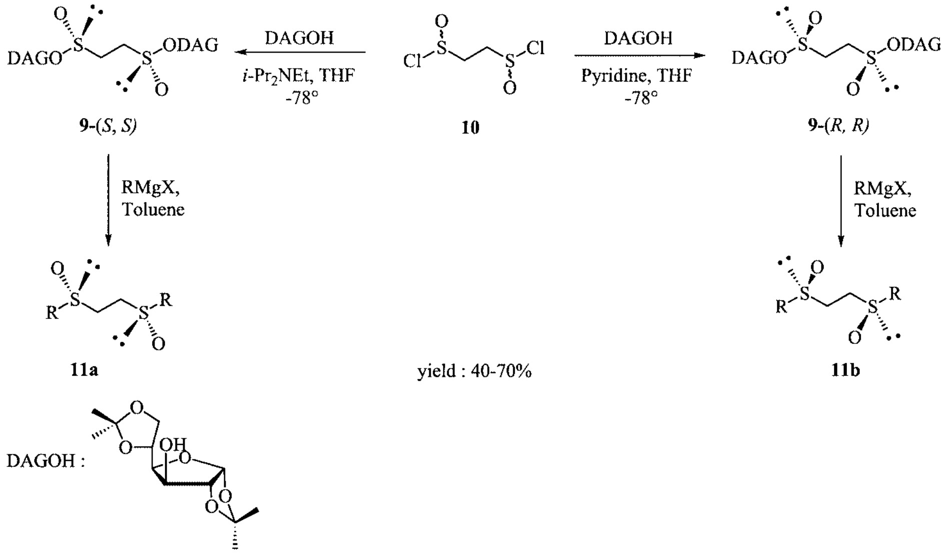
Early investigations were made by Louw et al. for γ-disulfoxides,[22] and by Kunieda et al.[23] on the simplest term, the (+)-(*S*,*S*)-1,1-bis(*p*-tolylsulfinyl)methane (**8**) (Scheme 2). The latter was prepared from the condensation of the lithium anion of the (*R*)-methyl sulfoxide **6** on the (*S*)-menthyl sulfinate **7**, in 35% recrystallised yield.[23] We have recently optimized this preparation on a large scale through a more efficient purification procedure.[24]



Scheme 2

This chemistry was recently studied in view of extending it to α-substituted sulfinyl anions. Thus, the monosubstituted (*S*,*S*)-1,1-bis(*p*-tolylsulfinyl)ethane could be obtained in good yield from the corresponding (*R*)-ethyl *p*-tolyl sulfoxide. However, in the case of the isopropyl *p*-tolyl sulfoxide, epimerization and elimination processes take place and complicate the reaction.[25]

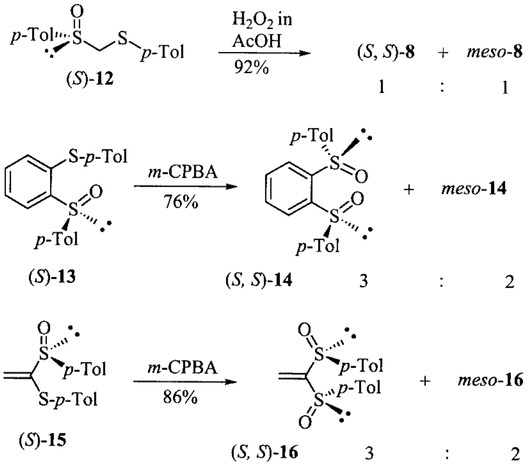
An interesting modern variation of this chemistry has been recently reported by Khiar et al.,[26] who devised a general enantiodivergent approach to both isomers of C_2-symmetric ethane-1,2-diyl bis(sulfoxides) **11a** and **11b** from the corresponding sulfinates esters (Scheme 3). Starting from the bis(sulfinyl chloride) **10**, the condensation of DAGOH gives, depending upon the nature of the tertiary amine used, the (*R*,*R*) or the (*S*,*S*) diastereomer **9** as the very major component, respectively, in mixture with the (*S*,*S*) or the (*R*,*R*) (< 1%) and the *meso* diastereomer (ca. 15%) of **9**. The authors claimed a dynamic kinetic resolution process for that transformation. Conveniently, the latter mixture can be treated with Grignard or lithium reagents to give the enantiopure bis(sulfoxides) **11a** and **11b** in satisfactory overall yields (40−70%), as well as the easily separated *meso* derivative as a minor component.



Scheme 3

I.2.b. The Mixed Method

A tandem of Andersen condensation and asymmetric oxidation has also often been envisaged, the initially appended sulfinyl group serving as a chiral auxiliary during the oxidation step. The observed mediocre diastereoselectivities from **12**,[23] **13**[27] and **15**[28] (Scheme 4) illustrate the difficulty in obtaining a highly diastereoselective subsequent oxidation process on acyclic derivatives. Fortunately, the separation of the C_2 product from the *meso* one is generally possible.



Scheme 4

I.2.c. Asymmetric Oxidation

First mentions of the asymmetric oxidation of thioethers to sulfoxides date from the 1950s and involved biological oxidation.[29,30] A decade later, first chemical methods were devised, using for instance chiral peroxy acids. The strategy relying on chiral reagents culminated with Davis' oxaziridines.[31] Parallel to these developments, metal-catalysed processes rapidly imposed as very appealing methods. Landmarks in that domain include the works of Kagan et al.,[32] and Modena et al.[33] with modified Sharpless reagents, and more recently, for instance, the work of Bolm et al.[34] involving a vanadium catalyst under substoichiometric conditions.[35] We will not cover that highly productive field in this review. Rather, we will illustrate its impact on the asymmetric oxidation of bis(thioethers), which has rapidly become an important objective for the synthetic community.

Subsequent to the pioneering studies of Louw et al.,[22] who reported an *ee* of ca. 40% (estimated from their data) for the oxidation of 2,5-dithiahexane with monopercamphoric acid, three directions could be pursued: the chiral auxiliary (bound to the substrate or to the oxidant) method, the biocatalytic approach, and metal-catalysed processes. Following that order, we will discuss the scope and limitations of these approaches by giving the most representative examples.

The Chiral Auxiliary Approach

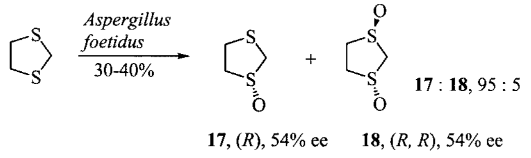
No breakthrough involving chiral oxidants has followed the work of Louw et al.[22] Chiral oxaziridines[36] or related reagents[37] have been used for the monosulfoxidation of dithiane derivatives; however, no mention of a possible diastereoselective dioxidation has been made.

Moreover, we have seen in the mixed method section, that a chiral auxiliary already present on the molecule such as a sulfoxide moiety, is not a good controlling element for the second oxidation. This was also confirmed by Tanaka et al.[38] on a benzodithiepan derivative, on which the first asymmetric oxidation was not controlled by a diethyl tartrate moiety, and the second one was little controlled by the newly introduced sulfinyl group (50% *de*). These contributions would intimate that the simultaneous diastereoselective dioxidation involving a chiral auxiliary on the substrate is probably not an easy task and this would be reflected by the fact that, to the best of our knowledge, there has been only one, though very particular, report of such a process.[39]

For all these reasons, catalytic reactions have appeared more promising, and have witnessed interesting developments.

Biocatalysis

The biocatalytic (enzymes and microorganisms) oxidation of dialkyl sulfides to monosulfoxides has yielded important reactions, and a lot of work has been devoted to the monooxidation of dithioacetals.[40−43] However, there has been no useful dioxidation to furnish a C_2-enantiopure disulfoxide. A notable result though stems from the work of Boyd, Drake et al.[44] with enzymes, who could obtain trace amounts of enantiopure disulfoxide **18** after recrystallization, this product remaining a side-product of the monooxidation of 1,3-dithiolane leading to **17** (Scheme 5).[45]

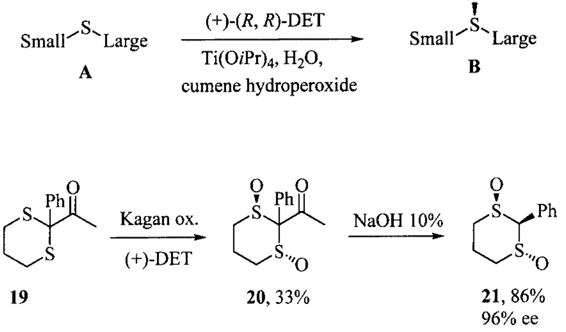


Scheme 5

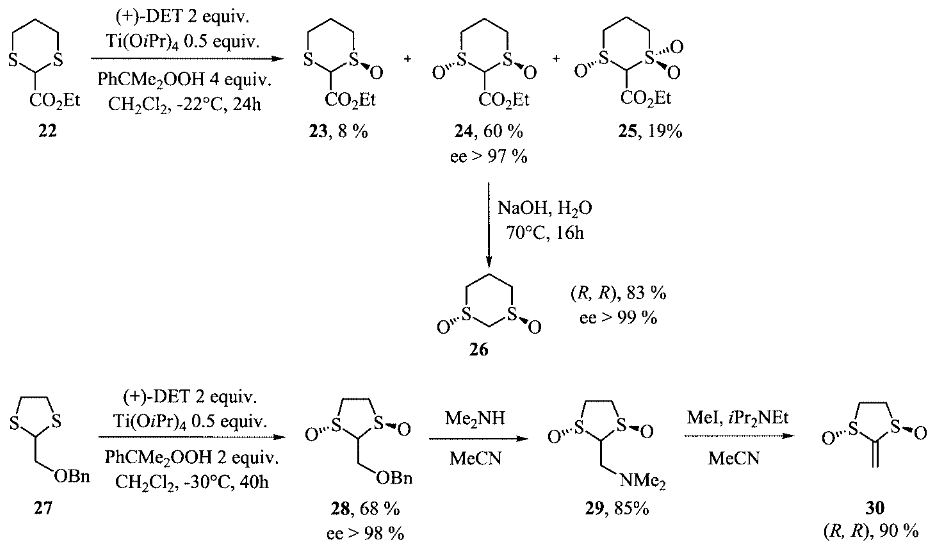
Metal-Catalyzed Oxidations

As for biocatalysis, the monosulfoxidation of 1,1-bis(sulfides) has been a major objective in metal-catalysed oxidations. This continued interest has resided in the quest for new chiral auxiliaries. At the end of the 1980s, Modena et al. and Kagan et al., both leaders, in the field of asymmetric oxidation disclosed their findings on the monooxidation of dithioacetals. Modena et al. showed that higher diastereo- and enantioselectivities were obtained on 1,3-dithiolane derivatives than on 1,3-dithiane and 1,3-oxathiolane.[46] Taking advantage of the optimization of his oxidation method, notably by replacing the *tert*-butyl hydroxyperoxide by the cumyl hydroperoxide, Kagan et al. reported the asymmetric oxidation of 2-substituted 1,3-dithianes with *ee*s up to 80%.[47,48] Kagan et al. also proposed a general model for predicting the absolute configuration: the (+)-tartrate gives birth to the sulfoxide **B** from **A** (Scheme 6). These seminal works paved the way for the preparation of various enantioenriched mono- and dioxides of dithioacetals. Using the Kagan system, Page et al. confirmed the beneficial role of a carbonyl moiety (acyl or ester) at the 2-position[47] in order to obtain high diastereo- and enantiomeric excesses (up to 99%) on 2-substituted 1,3-dithiane 1,3-dioxides.[49,50] In some cases, a small degree of over-oxidation furnished the C_2-symmetric disulfoxide. This could be adequately exploited as shown by the sequence in Scheme 6 which involves the titanium-catalysed asymmetric oxidation giving **20**, followed by a controlled deacylation to form **21**.[51]

The most elaborated developments in that domain were accomplished by Aggarwal et al. Starting from the commercially available ethoxycarbonyldithiane **22**, and using the Modena system (no water, DET/Ti = 4:1), which appears superior for that substrate, the C_2-1,3-dithiane-1,3-dioxide **24** was obtained with an excellent *ee*, accompanied by minor components **23** and **25** (Scheme 7).[52] Hydrolysis and



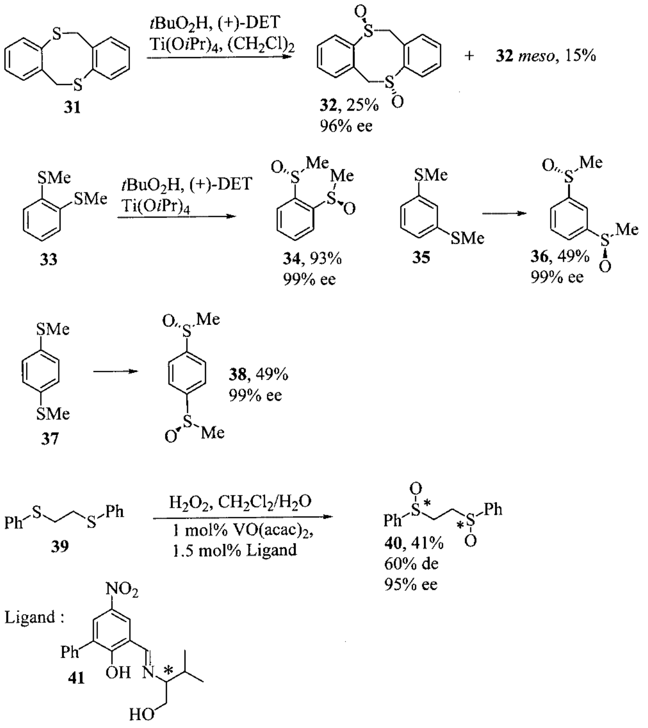
Scheme 6



Scheme 7

decarboxylation then provided the enantiopure (*R*,*R*)-dithiane dioxide **26**. This bis(oxidation) relies on the Horeau principle,[53] which, as summarized by Aggarwal et al., says: "If a reaction gives an x/y ratio of enantiomers in the first enantioselective operation, then, assuming there is no kinetic resolution ... or double stereo differentiation ..., the ratio of enantiomers for the bis(functionalized) product will be x^2/y^2".[54] Thus, the enantiomeric excess of the C_2-symmetric derivative is amplified compared to the monooxidized one. No synthesis of the enantiopure 1,3-dithiolane 1,3-dioxide has been proposed when using this method; however, it could be applied to the synthesis of the versatile (1*R*,3*R*)-2-methylene-1,3-dithiolane 1,3-dioxide (**30**).[55,56]

Other interesting examples involve the asymmetric oxidation of the dibenzodithiocin derivative **31** (Scheme 8). In addition to the C_2- and the *meso*-bis(sulfoxides) **32**, the monosulfoxide and the monosulfoxide sulfone products were formed.[39,57] This reaction could be run on a two-gram scale. In that case, the enantiomeric purity of **32** reached 96%. Very good results have been obtained by Licini, Modena et al. using their catalytic system on methylthiobenzenes such as **33**, **35** and **37**.[58] The authors noticed that the enantioselectivities experimentally agreed with those calculated according to the Horeau principle.[53] However, the observed diastereomeric excesses (C_2 vs. *meso*) were much higher than expected, suggesting that a certain degree of synergism takes place between the already present sulfinyl group and the asymmetric oxidant, the effect being reinforced by proximity effects. Finally, even on simple linear systems, very good selectivities have been recorded, as shown by Skarzewski et al. with the vanadium-catalysed enantioselective oxidation of bis(arylthio)alkanes such as **39**.[59] This method, inspired by the work of Bolm et al., uses a Schiff base **41** obtained from the easily accessible D- or L-valinol and 3-phenyl-5-nitrosalicylaldehyde. The authors checked that the stereoselectivity enhancement was consistent with statistical effects and they also noticed that the catalytic oxidizing species are electrophilic since the electron-richer systems were easier to oxidize and led to better stereoselectivities.

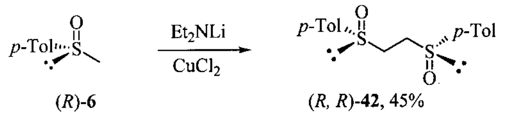


Scheme 8

I.2.d. Other Methods

A pioneering, but little exploited, method by Mislow et al.,[60] consists in the copper-promoted oxidative coupling of chiral sulfinyl anions. Thus, enantiomerically pure (+)-(*R*, *R*)-1,2-bis(*p*-tolylsulfinyl)ethane (**42**) was obtained from the coupling of the lithium anion of (+)-(*R*)-methyl *p*-tolyl sulfoxide (**6**) in the presence of copper(II) chloride

(Scheme 9). Interestingly, this method could also apply to bis(phosphane oxides).



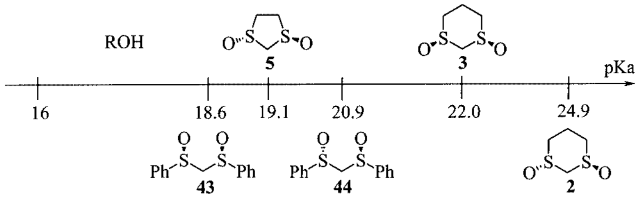
Scheme 9

II. Anionic Reactivity of C_2-Symmetric Bis(sulfoxides)

The anionic reactivity of bis(sulfoxides) has witnessed intense interest, the incentive being the development of versatile chiral acyl anion equivalents.[61–64]

II.1 Acidity of Geminal Bis(sulfoxides)

A few data dealing with the acidity of geminal bis(sulfoxides) have been published, and are summarized in Scheme 10. All these pK_a measurements were carried out in DMSO by Bordwell et al. and disclosed by Aggarwal et al. for **2**, **3**[10] and **5**[65] and, herein by us, for **43** and **44**.[66] It is interesting to observe that *cis* isomers **43** and **3** are more acidic than *trans* ones **44** and **2**. The latter example was rationalised by the reduced dipole moment of **2** compared to **3**, originating from the dipole stabilization displayed in Scheme 1. It is noteworthy that both C-2 protons of **2** underwent rapid deuterium exchange in D_2O with $t_{1/2}$ = 4 h at room temperature and neutral pH, which illustrates the great kinetic acidity of these compounds.[10] The structure of the bis(sulfinyl)methyl anions has been investigated and has revealed a trigonal structure.[67]

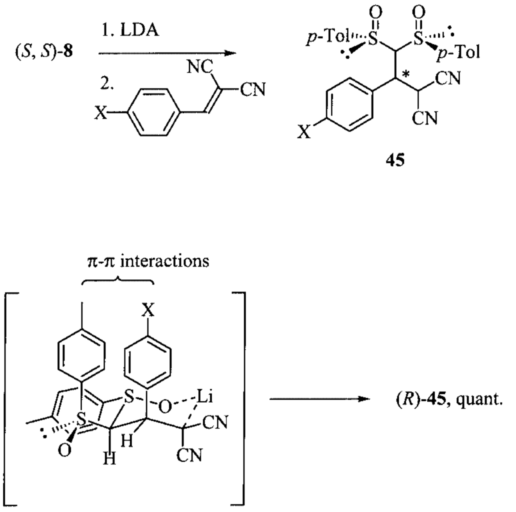


Scheme 10

II.2 Alkylation

The acidity of geminal bis(sulfoxides) has been early recognized and was initially applied in simple alkylation reactions with no consideration of potential stereochemical control. Thus, Trost et al.[68] proposed an alkylative elimination procedure to produce vinyl sulfoxides. The first step includes the alkylation of the sodium anion of **43** and **44** by a halide derivative, followed by thermolysis in the presence of trimethyl phosphite which serves as a scavenger of the phenylsulfenic acid that is eliminated. A related Michael addition, thermolysis, Evans–Mislow sequence has also been proposed.[69]

Recently, Khiar et al.[70] reported a highly diastereoselective example of Michael addition of the lithium salt of (*S*,*S*)-**8** (Scheme 11). While an equimolar mixture of Michael adducts with various benzylidenemalonitriles was produced at −78 °C, warming to room temperature yielded only one diastereomer of **45** in quantitative yield. The authors claimed thermodynamic control and proposed a Zimmerman–Traxler-type model which discloses a favourable π-π interaction between two aromatic rings, one belonging to the Michael acceptor, and the other one to the anion. However, no confirmation of the postulated (*R*) absolute configuration on **45** was given.

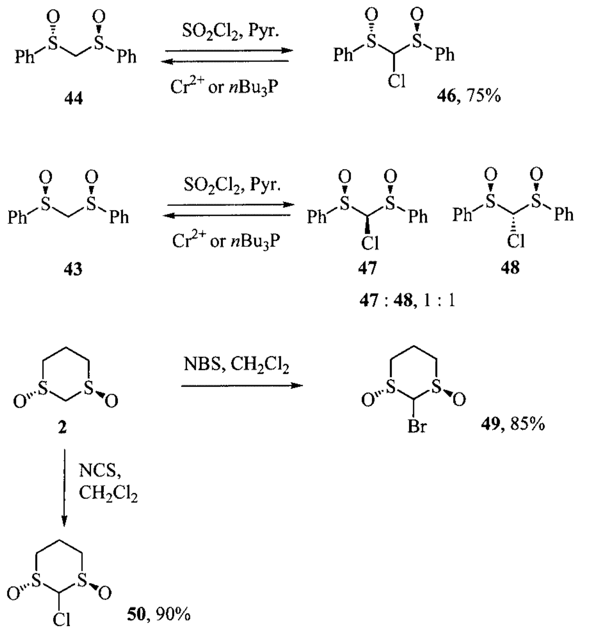


Scheme 11

Also worthy of note, an interesting example of completely diastereoselective bis(alkylation) on the non-geminal bis(sulfoxide) **32**, leading to a new C_2-symmetric derivative has been reported.[57]

II.3 Halogenation

Although the intervention of a bis(sulfinyl) anion in halogenation reactions has not been established, even sometimes discarded, these reactions will be covered in this section, since α-halo bis(sulfoxides) are interesting building blocks and have been used in various condensation reactions which will be detailed below. An early report by Jarvis et al.[71] mentioned that the best chlorinating agent for **43** and **44** was sulfuryl chloride in the presence of either pyridine or sodium bicarbonate (Scheme 12). Treating the corresponding chlorides **46**, **47** and **48** with chromium(II) chloride or tri-*n*-butylphosphane gave only the respective the starting materials **43** and **44**, demonstrating that no change in stereochemistry at the sulfur centres takes place during the chlorination step. Excess of reagent efficiently furnished the dichloride.



Scheme 12

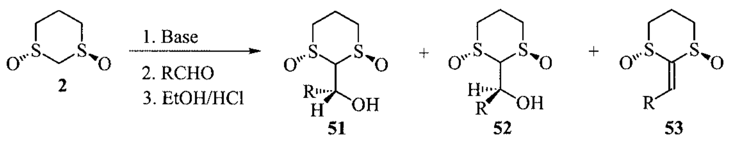
Halo derivatives **49** and **50**[72] could be obtained in good yields by simple treatment with NBS and NCS, respectively.[73] No isomerization of the sulfoxides was observed. Moreover, the chlorination reaction does not proceed in the dark, or in the presence of K_2CO_3, strongly suggesting a radical mechanism.

II.4 Condensation onto Carbonyl Derivatives

Oddly enough, the reverse reaction was described first. Thus, the alkaline treatment of β-hydroxy bis(sulfoxides), giving birth to an aldehyde and to a bis(sulfinyl) anion, was used to shorten sugar derivatives.[74,75] Nevertheless, the condensation of bis(sulfinyl) anions onto carbonyl derivatives has later witnessed much effort. The C_2-symmetric bis(sulfoxides) have appeared as candidates of choice for that task, since their intrinsic C_2-symmetry reduces the number of competing diastereomeric transition states and also results in the creation of only one new stereogenic centre in condensations with carbonyl derivatives. Major breakthroughs in that domain have been achieved on cyclic substrates by Aggarwal et al. and on acyclic substrates by Solladié et al. and us and are now summed up.

1,3-Dithiane 1,3-dioxide (**2**) has been engaged in a series of addition reactions.[76–78] For solubility reasons, a dual solvent system THF/pyridine has to be used. Several bases have been examined: *n*BuLi, LiHMDS and NaHMDS. On a general basis, the two diastereomeric alcohols **51**, **52** were obtained as well as minor amounts of dehydrated product **53** (Scheme 13). At −78 °C, the reaction was under kinetic control and a weak diastereoselectivity was observed in favour of **52**. In contrast, at 0 °C, the reaction was under thermodynamic control and alcohol **51** became the major adduct with a higher stereoselectivity (set 1). However, these ratios were sometimes complicated by an increased amount of compound **53**. Only aromatic aldehydes[79] gave high diastereoselectivities (*de* > 90%) and the best counterion for the base was sodium (set 2). The reactivity of ketones was also examined and proved to be limited to substrates with no α-branching.

The authors rationalised the observed diastereoselectivity under thermodynamic equilibrium by examining the alkoxides intermediates **54** and **55** (Scheme 14). As previously (Scheme 1), the crystallographic analysis of the alcohol **51** with R = Ph, shows that the axial oxygen atom of one of



set 1

Base	*T* (°C)	R	major alcohol	de (%)
n-BuLi/pyr.	-78	alkyl	**52**	0-28
	-78	Ph	**52**	32
	0	alkyl[a]	**51**	0-80
	0	Ph[a]	**51**	70

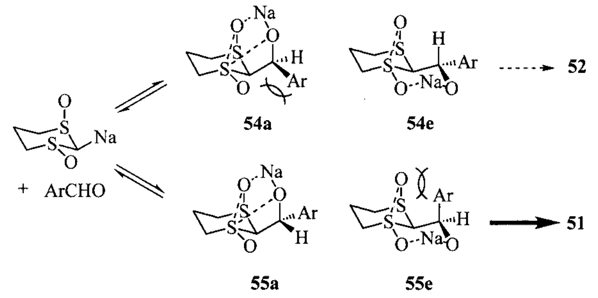
[a] Dehydrated product **53** was present in 0-36% of the crude product.

set 2

Base	*T* (°C)	R	major alcohol	yield	de (%)
NaHMDS	0	*n*Bu	**51**[a]	-	54
		*i*Pr	**51**[a]	-	20
		Ph	**51**	87	92
		Ar	**51**	34-91	> 90

[a] The use of KHMDS improved the diastereoselectivities to 60% and 40%.

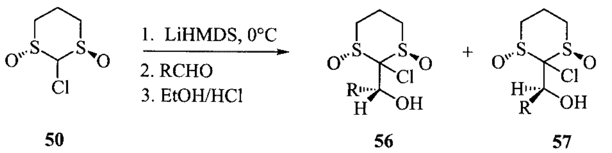
Scheme 13



Scheme 14

the sulfoxide groups is bent toward the sulfur atom of the other sulfoxide group due to a strong electrostatic interaction. By analogy, alkoxides **54** and **55** retain this electrostatic interaction, but conformers **54a** and **55a** benefit from an additional stabilizing interaction involving the axial alkoxide anion. However, **54a** displays electronic repulsions between the lone pairs of the sulfinyl oxygen atom and the π-system of the aromatic ring, so that diastereomer **55a** leading to **51** is favoured. With aliphatic aldehydes, the latter interaction disappears and **54a** and **55a** are too close in energy for discrimination.

The anionic chemistry of halo derivatives **49** and **50** in view of developing umpolung asymmetric Darzens-type reactions was also studied (Scheme 15).[73] Moreover, α-halo bis(sulfinyl) anions would be more stabilized and should favour equilibration. Although this phenomenon was confirmed with lithium bases, aliphatic aldehydes still gave low diastereoselectivities. The higher selectivities in favour of **56** observed with aromatic aldehydes originate from the same model of diastereoselection of Scheme 14. Use of sodium or potassium bases gave lower yields of chlorohydrins. Presumably, with these less strongly chelating metals (sodium or potassium), epoxides were formed but decomposed in the reaction medium. With chlorohydrins **56** in hands, conditions were sought for their clean conversion into epoxides. However, all attempts with R = Ph ended in a retroaldol process. The behaviour of **49** was also investigated with benzaldehyde and it was possible to obtain the phenyl bromohydrins with high selectivity (94% *de*) using the magnesium salt of **49**. Here also, no epoxide formation could be worked out.



R	major alcohol	yield (%)	de (%)
*n*Bu	57	-	2
*i*Pr	56	8	6
Ph	56	64	84
2-naphthyl	56	61	96

Scheme 15

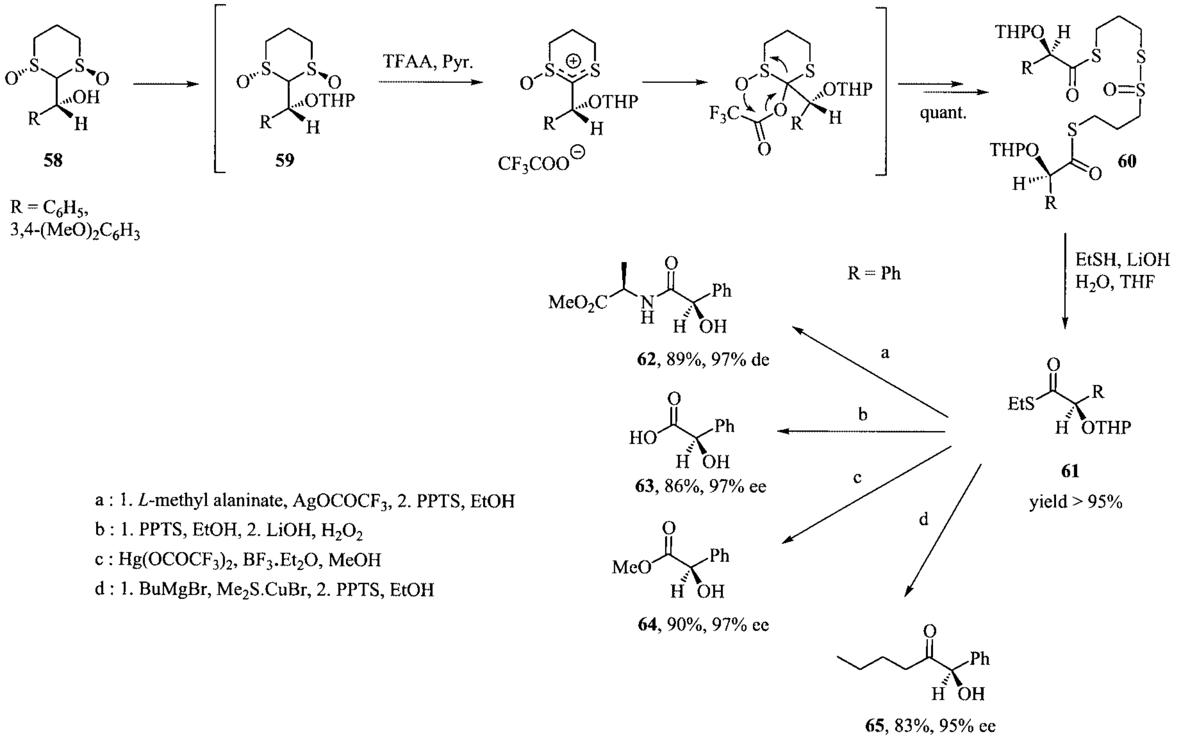
Taking advantage of the high diastereoselectivity observed with aromatic aldehydes in all these reactions, Aggarwal et al. used (*R*,*R*)-(+)-1,3-dithiane 1,3-dioxide (**26**) as starting material in view of preparing enantiopure materials.[80,81]Based on an initial Pummerer reaction, several enantioenriched derivatives of α-hydroxy acids were readily obtained, as illustrated in Scheme 16. The aldol adducts **58** had first to be protected as THP ethers **59** before submission to trifluoroacetic anhydride (TFAA). This gave birth to the mixture of thiosulfinates **60** in nearly quantitative yield. These intermediates were not suitable for any further synthetic transformation and were carefully transthioesterified to **61** with LiSEt to avoid any racemization. Thioesters **61** proved then to be versatile intermediates as demonstrated by their clean transformations to α-hydroxy carbonyl derivatives **62**, **63**, **64** and **65**.

The anionic chemistry of dithiolane derivative **5** also provided distinct but interesting results.[20] These were evidenced through variations in the metal counterion, reaction temperature and aldehydes. The authors first showed that the anion of **5** was much more stable than the monosulfoxide one or the parent dithiolane one, and could give birth to satisfactory yields of alcohols **66** and **67** (Scheme 17). However, in contrast to the dithiane dioxide **2** (see Scheme 13), best diastereoselectivities were obtained at low temperature (−78 °C). At that temperature, as demonstrated by scrambling experiments with aldehydes, equilibration begins to occur with a slow reverse reaction. Upon heating, the equilibration erodes the good initial kinetic ratio and diminishes the yield. To circumvent this, the authors used 2.4 equiv. of LiHMDS. This results in the formation of a bis(sulfinyl) alkoxide dianion and renders the reaction irreversible. Under these optimal conditions, the best diastereoselectivities were still observed with aromatic and α, β-unsaturated aldehydes. The authors attributed the greater propensity of Li-**5** to undergo reversible reaction to its higher stability (pK_a = 19.1 for **5** vs. pK_a = 24.9 for **2**).

The stereoselectivity was rationalised by considering Zimmerman−Traxler transition states **68** and **69**, giving **66** and **67**, respectively, on which the R group occupies an equatorial position. Transition state **69** would suffer from two non-bonding interactions between the axial dithiolane methylene groups and both the ligand on the metal ion and the C−H bond of the aldehyde (Scheme 18).

Under thermodynamic control, possible models for the chelated alkoxides **70** and **71** are presented in Scheme 19. In five-membered rings, electrostatic interactions are reduced compared to the one present in alkoxides **54** and **55** (Scheme 14). Notably, the alkoxide anion cannot interact with the sulfur atoms. The principal nonbonding factor remains the electronic repulsion between the aryl group and the oxygen atom of the sulfinyl group and disfavours **70a** and **71b**. There is no real bias between intermediates **70b** and **71a** and this leads to a close ratio of **66** and **67**.

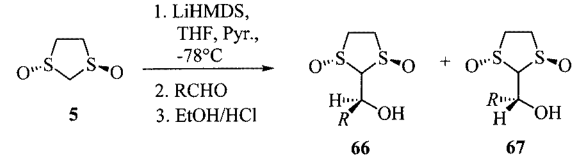
In acyclic series with (*S*,*S*)-**8**, Solladié et al.[82] and we[9] have found good yields and diastereoselectivities with aro-



R = C_6H_5,
3,4-$(MeO)_2C_6H_3$

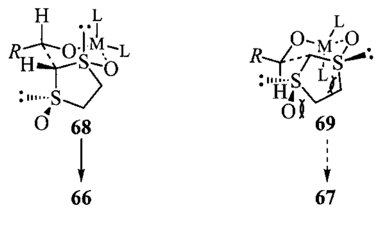
a : 1. *L*-methyl alaninate, $AgOCOCF_3$, 2. PPTS, EtOH
b : 1. PPTS, EtOH, 2. LiOH, H_2O_2
c : $Hg(OCOCF_3)_2$, $BF_3.Et_2O$, MeOH
d : 1. BuMgBr, $Me_2S.CuBr$, 2. PPTS, EtOH

Scheme 16

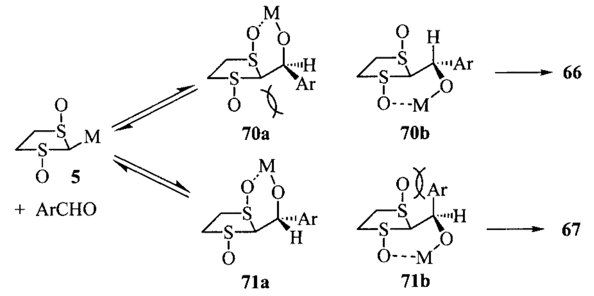


R	66+67 (%)	major alcohol	de (%)
Ph	90	**66**	92
crotyl	67	"	90
cyclohexyl	92	"	52
*t*Bu	53	"	62

Scheme 17



Scheme 18



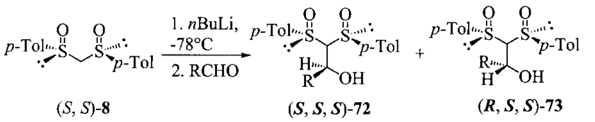
Scheme 19

matic and alkyl aldehydes. Based on the work of Solladié et al. describing the condensation of the anion of the (*R*)-*tert*-butyl (*p*-tolylsulfinyl)acetate with carbonyl derivatives,[83] we have proposed the model displayed in Scheme 20. The most favourable approach involves chelated transition state **74** in which nonbonding interactions between the *p*-tolyl group of the anion of **8**, and the R group of the aldehyde are minimised (compared to **75**). With α,β-unsaturated aldehydes, the reaction led directly to the bis(sulfinyl)dienes **76**.

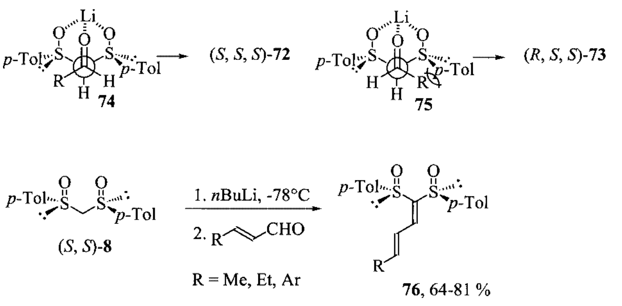
Interestingly, when this Knoevenagel condensation was run in piperidine, a Sulfoxide Piperidine Aldehyde Condensation (SPAC[84]) took place, furnishing good yields of (*E*)-γ-hydroxy-α,β-unsaturated sulfoxides **77** with no diastereoselectivity.[85] After the initial condensation, the basic reaction medium led to the isomerization of the adduct **78** into allyl sulfoxides **79**. This is followed by a [2,3]-sigmatropic allyl sulfoxide−sulfenate (Evans−Mislow) rearrangement providing **80**. The piperidine now serves as a thiophile and cleaves the sulfenate ester to give final product **77**. The authors rationalised the lack of stereoselectivity by the fact that both sulfinyl moieties are able to migrate during the Evans−Mislow rearrangement.

II.5. Preparation of Alkylidenebis(sulfinyl) Derivatives

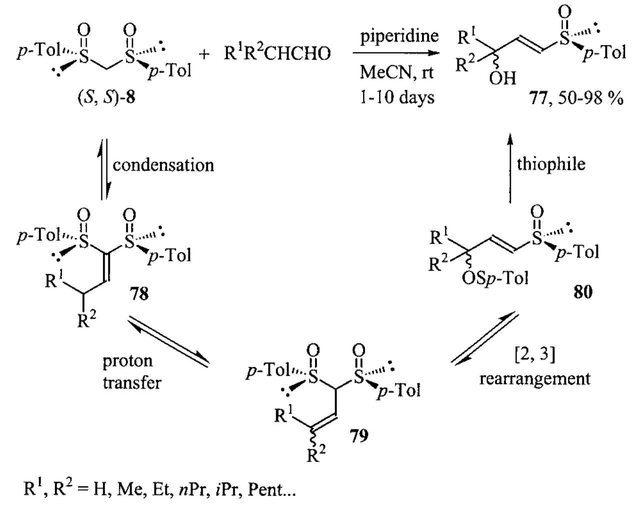
Dehydration of the alcohols originating from the condensation of the bis(sulfoxides) with carbonyl derivatives



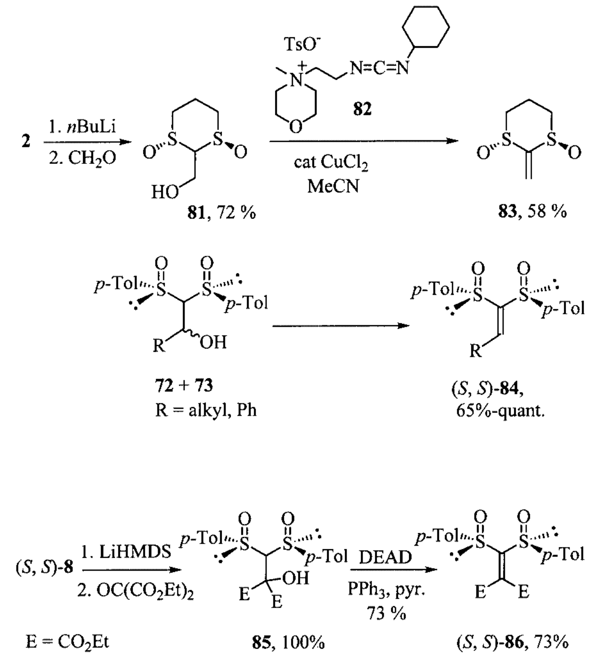
R	72+73 (%)	major alcohol	de (%)
alkyl	77-89	**72**	62-98
aryl	37-93	**72**	48-90



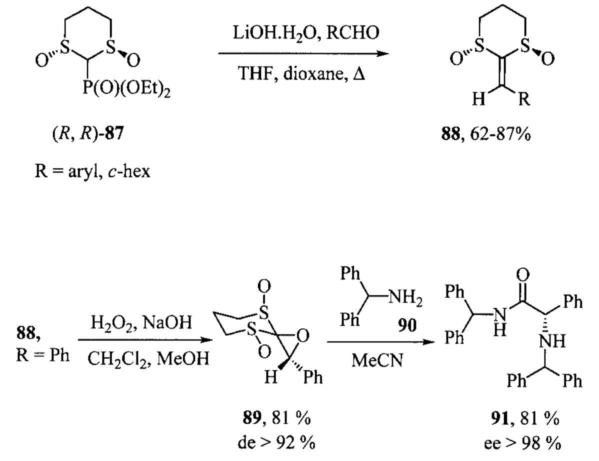
Scheme 20



Scheme 21



Scheme 22



Scheme 23

gives birth to versatile methylene- and alkylidenebis(sulfinyl) derivatives. This was first accomplished by Aggarwal et al. using a water-soluble DCC variant reagent (morpho CDI **82**) to transform the formaldehyde-alkylated bis(sulfoxide) **81** into methylenebis(sulfoxide) **83** (Scheme 22).[86] This reaction proved also adequate for the preparation of acyclic derivatives **84** from the alcohol mixture of **72** + **73**.[9] Another report by Carretero et al.[87] mentions the synthesis of the (*S*,*S*)-1,1-bis(ethoxycarbonyl)-2,2-bis(*p*-tolylsulfinyl)ethene (**86**), in a two-step sequence involving first a quantitative condensation with oxomalonate, followed by a dehydration of **85** with DEAD.

Besides Mannich and substitution reactions (see Scheme 7),[56] a direct method, relying on the phosphorylated bis(sulfoxide) precursor **87** has been examined (Scheme 23).[88] This compound was produced in 43% yield and > 98% *ee* through asymmetric oxidation of the corresponding dithiane. Wadsworth−Emmons-type olefination of a series of aldehydes using lithium hydroxide as a base furnished good yields of alkylidene derivatives **88**. Interestingly, the phenyl derivative of **88** could be oxidized to epoxide **89** with a high diastereoselectivity. Ring-opening with nitrogen nucleophiles like **90** gave birth to enantiopure amino amides such as **91**.

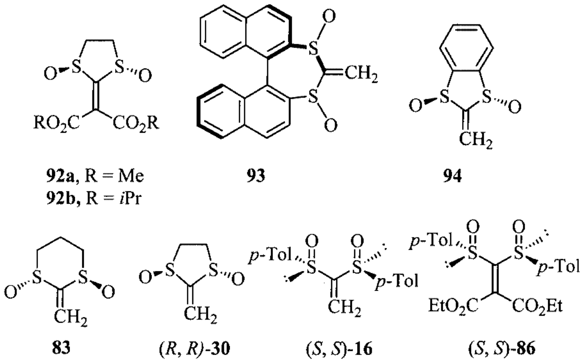
III. Synthetic Applications of C_2-Symmetric Bis(sulfoxides)

III.1. Cycloadditions

Ketene equivalents have found wide use in synthesis because they readily undergo [4+2] cycloadditions with dienes, whereas ketenes themselves give [2+2] cycloadducts.[89] For the purpose of asymmetric reactions, the use of ketene equivalents based on vinyl bis(sulfoxides) should present several advantages like reducing the number of different approaches of the diene, eliminating the *endo*/*exo* problem and enhancing the selectivity.

Diels−Alder Reactions

Ketene equivalents based on simple vinyl sulfoxides are poor dienophiles and show low levels of diastereocontrol,[90] except when activated as a sulfonium salt by alkylation of the sulfinyl oxygen atom.[91] Several authors have proposed the chiral dienophiles shown in Scheme 24 and studied their behaviour in Diels−Alder (DA) reactions with various dienes. Dienophiles **92a**,**b**,[21] **93**,[92] **94**,[86] **83**,[86] and (±)-**30**[93] have been employed as racemics and there are only three cases with enantiopure substrates: (*S*,*S*)-**16**,[28] (*S*,*S*)-**86**,[87] and (*R*,*R*)-**30**.[55,56]



Scheme 24

In 1990, Katagiri et al.[21] proposed dienophiles **92a** and **92b** as bis(alkoxycarbonyl)ketene equivalents. These two compounds proved much more reactive than the monosulfoxide or the plain dithiolane analogs and when treated with cyclopentadiene gave DA adducts **95Ma**,**b** and **95ma**,**b** with fair diastereoselectivity (Table 1, Entries 1 and 2). These adducts could then be easily transformed into 3-oxobicyclo[2.2.1]heptane-2,2-dicarboxylate derivatives. Entry 3 shows a unique example of a C_2 dienophile (**93**) based on a 1,1′-binaphthalene-2,2′-dithioacetal dioxide system.[92] A similar level of diastereoselection was observed with cyclopentadiene, providing diastereomers **96M** and **96m**.

With dienophiles **94** and **83**,[86] and upon $BF_3{\cdot}OEt_2$ catalysis, Aggarwal et al. were able to improve the diastereoselectivity of the reaction with cyclopentadiene (Entries 1 and 5 of Table 2, adducts **97M**,**m** and **101M**,**m**). Acyclic dienes reacted also very selectively with **94**, even in the absence of a Lewis acid (Entries 3 and 4). The failure of **83** to react with 1-methoxybutadiene (Entry 7) was attributed to unfavourable steric interactions between the diene substituent and axials groups of the dithiane moiety.

Then dithiolane dioxide **30**, used as a racemate or as the (*R*,*R*) enantiomer, was shown to be a more reactive and selective chiral ketene equivalent than **83** and **94** (Table 3).[55,56] Optimal results with reference dienes like cyclopentadiene (Entry 1), furan (Entry 2), 1-methoxybutadiene (Entry 3), Danishefsky's diene (Entry 4) were obtained in propionitrile as a solvent.

Dienophile (±)-**30** could also react with less reactive dienes like 1-(phenoxycarbonyl)-1,2-dihydropyridine **107** (Table 4, Entries 1 and 2).[56] In that case, yields and selectivities are more moderate. With cyclohexa-1,3-diene (Entries 3 and 4), Lewis acid catalysis was required to guarantee some reactivity. Bicycloadducts **109M**,**m** could be obtained with *de*s up to 90%, albeit in low yield (26%). Diethylaluminium chloride proved to be the Lewis acid of choice in terms of diastereoselectivity for the reaction of (±)-**30** with 1-methoxycyclohexa-1,3-diene (Entry 7). Even the notoriously unreactive diene 2*H*-pyran-2-one could be involved in

Table 1. DA reactions with cyclic bis(sulfoxide) dienophiles

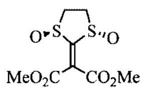
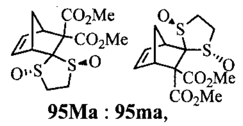
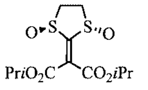
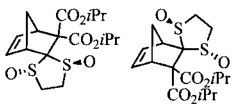
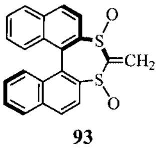
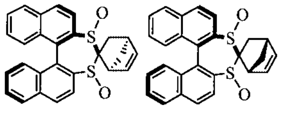
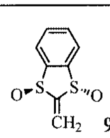
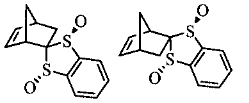
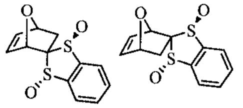
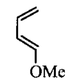
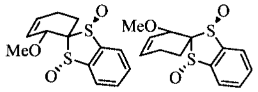
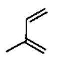
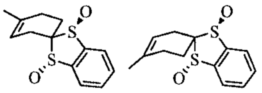
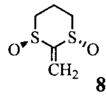
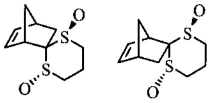
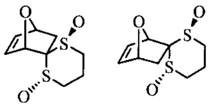
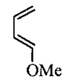
Entry	Dienophile	Diene	Solvent/ L. A.	Time/ T °C	Yield (%)	Diastereomers
1	 **92a**		CH_2Cl_2	7 h, rt	98	 **95Ma** : **95ma**, 78 : 22
2	 **92b**		CH_2Cl_2	12 h, rt	82	 **95Mb** : **95mb**, 88 : 12
3	 **93**		$CDCl_3$	12 h, rt	92	 **96M** : **96m**, 75 : 25

Table 2. Compared DA reactions of dienophiles **94** and **83**

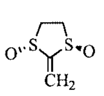
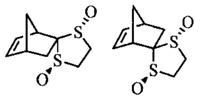
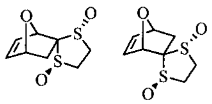
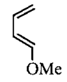
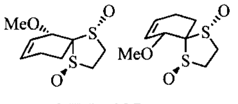
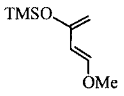
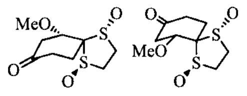
Entry	Dienophile	Diene	Solvent/ L. A.	Time/ T °C	Yield (%)	Diastereomers
1	 **94**		$BF_3.OEt_2$	5 min, -78	75	 **97M** : **97m**, 94 : 6
2	**94**		$SnCl_4$	30 min, -78	98	 **98M** : **98m**, 83 : 17
3	**94**		----	24 h, rt	78	 **99M** : **99m**, 96 : 4
4	**94**		CF_3CH_2OH	6 h, rt	70	 **100M** : **100m**, 92 : 8
5	 **83**		$BF_3.OEt_2$	10 min, -78	80	 **101M** : **101m**, > 96 : 4
6	**83**		$BF_3.OEt_2$	1 h, -78	95	 **102M** : **102m**, 64 : 36
7	**83**		----	rt	no reaction	-----

these cycloadditions. The best selectivity (**111M**/**111m** = 94:6) was obtained in refluxing toluene in 5 d (Entry 9).

The stereochemical outcome of these [4+2] cycloadditions may be rationalised, as proposed by Katagiri et al.[21] and Aggarwal et al.,[55,56] by considering the two transition states **TS1** and **TS2** involved in the [4+2] reaction of (*R*,*R*)-**30** and cyclopentadiene (Scheme 25). **TS2** suffers from greater nonbonding interactions between the sulfinyl oxygen atom and the diene substituent than **TS1**, promoting the major formation of diastereomer **103M**. Other examples of selective DA reactions resulting from the difference in size between the sulfinyl oxygen atom and the lone pair have been reported in the literature.[94−96] Electronic factors consisting of the repulsive interaction between the lone pairs of the sulfinyl oxygen atoms with π systems were also invoked.[97] Moreover, by binding to the sulfinyl oxygen atom, Lewis acids would increase not only the reactivity of the dienophile, but also its effective size and amplify the steric interaction in **TS2**. Finally, the enhanced reactivity of dithiolane systems compared to dithiane has been ascribed to the ring strain in five-membered rings, and the higher selectivity to conformational effects.

Acyclic enantiopure dienophiles have also been examined. The first example was reported by Koizumi et al. in 1986 with (*S*,*S*)-**16**.[28] A moderate diastereoselectivity (60%) was observed with cyclopentadiene (adducts **112M,m**, Table 5, Entry 1). Over the last decade, Carretero et al. have pursued the development of mono-, di- and triactivated vinyl sulfoxides, the activation consisting in a carbonyl moiety.[98] However, the cycloadditions generally

Table 3. DA reactions of enantiopure dienophile **30**

Entry	Dienophile	Diene	Solvent/ L. A.	Time/ T °C	Yield (%)	Diastereomers
1	 (1*R*, 3*R*)-**30**		EtCN/ $BF_3.OEt_2$	20 min, -78	74	 **103M** : **103m**, > 97 : 3
2	(1*R*, 3*R*)-**30**		EtCN/ $SnCl_4$	-78	65	 **104M** : **104m**, > 97 : 3
3	(1*R*, 3*R*)-**30**		EtCN	18 h, rt	83	 **105M** : **105m**, > 97 : 3
4	(1*R*, 3*R*)-**30**		EtCN	2 h, rt	90	 **106M** : **106m**, > 97 : 3

took place with moderate or even low *endo* selectivity. Encouraged by the work of Katagiri et al. with cyclic dienophiles **92a**,**b**,[21] he proposed the acyclic enantiopure analogue (*S*,*S*)-**86**, whose synthesis was described above (Scheme 22).[87] Surprisingly, this compound did not react with cyclopentadiene either in the absence or in the presence of Lewis acids. Only at high pressure (13 kbar) were the adducts **113M**,**m** obtained (Table 5, Entry 2). Under these conditions, and with 1.2 equiv. of $ZnBr_2$, the reaction can work with different kinds of dienes with complete conversions (Entries 3−5). The cycloaddition adducts were found to be unstable at room temp., evolving by spontaneous elimination of sulfenic acid to give the corresponding 1,3-cyclohexadienes **114**−**116**. In almost all the cases, a single adduct was obtained showing that the cycloaddition proceeded with complete regioselectivity (controlled by the olefinic carbon atom bearing the ester functions) and π-facial selectivity. The authors proposed the two conformers (*S*,*S*)-**86A** and (*S*,*S*)-**86B** as the two most stable ones, because both minimize the electrostatic repulsion between the sulfinyl oxygen atoms and the ester groups (Scheme 26). However, conformer (*S*,*S*)-**86A** would suffer from a strong repulsion between the two sulfinyl oxygen atoms so that conformer (*S*,*S*)-**86B**, displaying both sulfinyl groups in *s*-*cis*,*s*-*trans* arrangements respectively, and the out-of-plane ester group, *cis* to the *s*-*cis*-sulfinyl group, appears as the most stable. Stereoselectivity was then ascribed to the preferential cycloaddition of this most populated conformer (*S*,*S*)-**86B**. Because both aryl groups are placed towards the same face in this conformer, the approach of the diene would take place from the less hindered face and *endo* to the conjugated ester as in **TS3**, resulting in the formation of the major adduct.

1,2-bis(ketene) equivalents have also been reported. Montanari et al. showed that (±)-*cis*-**117** yielded only the *endo* stereoadduct **118** in good yield (Scheme 27),[99] in contrast to the *trans*-C_2 analogue that gave two diastereomeric norbornenebis(sulfoxides).[100] Licini et al. recently pursued this approach and focused on (−)-*trans*-benzo[*d*]dithiine *S*,*S*′-dioxide (**119**).[101] An enhanced reactivity compared to **117** was observed with cyclopentadiene. The reaction with cyclopentadiene and cyclohexadiene afforded only the *endo* products **120** in good yield. Thermal reaction with furan resulted in a reverse stereoselectivity (*exo* adduct **121**), and addition of a Lewis acid restored the *endo* selectivity.

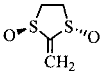
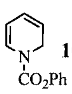
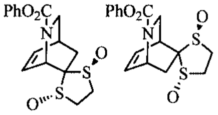
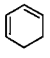
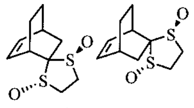
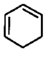
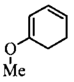
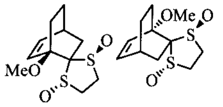
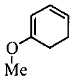
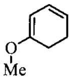
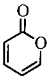
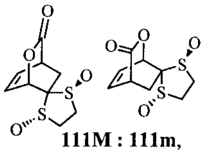
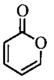
1,3-Dipolar Cycloadditions

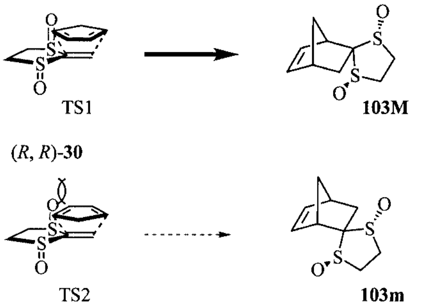
Preliminary findings have focussed on the reaction of (*R*,*R*)-**30** with aromatic betaines.[102] This study has been pursued with nitrones.[103] The reaction proceeded smoothly at room temp. with an excess of nitrones **122** and gave in each case a single diastereomeric adduct **123** (Scheme 28). This diastereoselectivity was rationalised by the preferred transition state **TS6**, compared to **TS5** which suffers from steric and/or electronic repulsions between the phenyl ring of the nitrone and the sulfinyl oxygen atom. Higher reactivity with comparable diastereoselectivity was observed with cyclic nitrones.

III.2. Coordination and Catalysis

Most of the applications in this part involve the coordination properties of the sulfoxide moiety, and obviously

Table 4. DA reactions of (±)-**30** with less reactive dienes

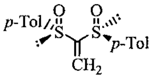
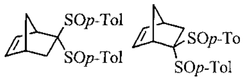
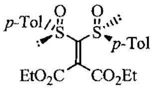
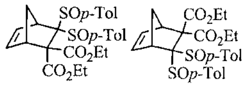
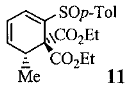
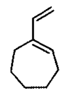
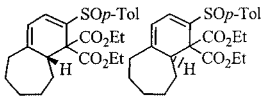
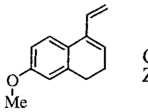
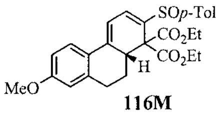
Entry	Dienophile	Diene	Solvent/ L. A.	Time/ T °C	Yield (%)	Diastereomers
1	 (±)-**30**	 **107**	CH_2Cl_2	8 days, 40	60	 **108M** : **108m**, 73 : 27
2	(±)-**30**	**107**	CH_2Cl_2/ $BF_3.OEt_2$	2 h, -78	96	68 : 32
3	(±)-**30**		CH_2Cl_2/ $BF_3.OEt_2$	6 h, -78	26	 **109M** : **109m**, 95 : 5
4	(±)-**30**		CH_2Cl_2/ $BF_3.OEt_2$	24 h, -35	60	90 : 10
5	(±)-**30**		EtCN	24 h, 97	77	 **110M** : **110m**, 59 : 41
6	(±)-**30**		CH_2Cl_2/ $BF_3.OEt_2$	2 h, -78	21	80 : 20
7	(±)-**30**		hexane/ Et_2AlCl	1 h, -78	50	> 97 : 3
8	(±)-**30**		CH_2Cl_2	18 days, 40	29	 **111M** : **111m**, 54 : 46
9	(±)-**30**		Toluene	5 days, 111	33	94 : 6

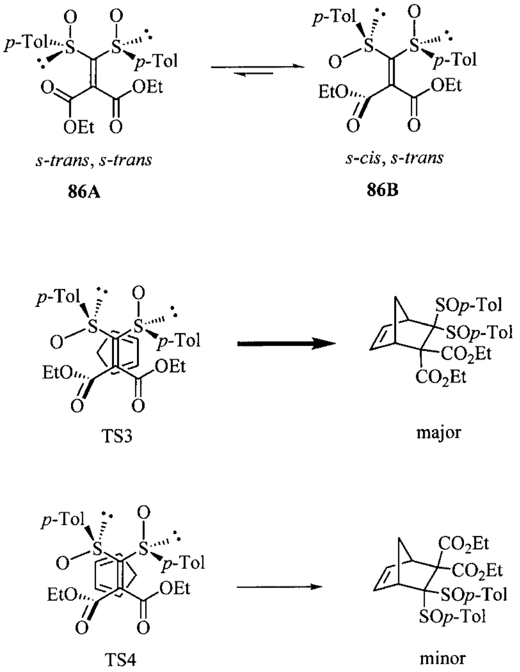


Scheme 25

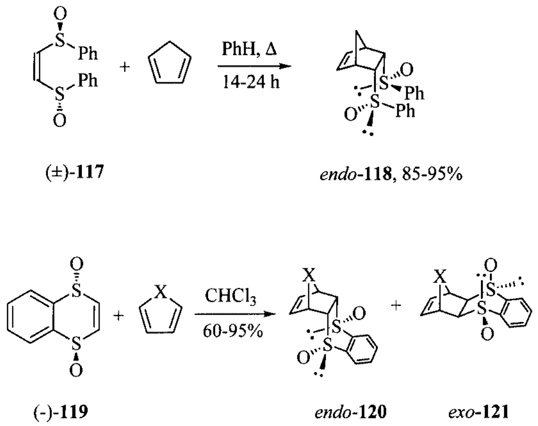
the development of new ligands for metal-catalysed asymmetric processes has attracted interest. This stems from the now mature coordination chemistry of sulfur ligands which has shown a unique variety of structures with most transition metals in different transition states and promising results in catalysis.[104,105] In that context, an initial study revealed the high complexation ability of 2,5-dithiahexane 2,5-dioxide ($DTHO_2$) with transition metal salts. Thus, coordination compounds of the formulas $[M(DTHO_2)_3](ClO_4)_2$ ($M = Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}$) and $[M(DTHO_2)Cl_2]$ ($M = Pd^{2+}, Pt^{2+}$) have been synthesised and analysed by a variety of analytical techniques (IR, X-ray, magnetic susceptibility, ...).[106] It was concluded from IR data (S−O shifts) that in all these complexes, with the exception of the Pd^{2+} and Pt^{2+} ones, coordination occurs through the oxygen atoms of $DTHO_2$. Five-membered ring chelates of platinum(II) salts involving 1,2-bis(sulfoxides) have also been well characterised and showed square-planar structures with *S*-coordination.[107,108] Recently, enantiopure C_2-3,4-bis(*p*-tolylsulfinyl)hexanes have been synthesised by the copper(II) oxidative anionic coupling method[60] (cf. section I.2.d.). Palladium(II) and rhodium(I) complexes with these ligands have been formed and featured a homocoordination between the two sulfur atoms and the metal atoms in solution as well as in the solid state.[109] Finally, before dealing with synthetic applications in catalysis, it should also be noted that some ruthenium(II)

Table 5. DA reactions with acyclic bis(sulfoxide)dienophiles

Entry	Dienophile	Diene	Solvent/ L. A.	Time/ T °C	P	Yield (%)	Diastereomers
1	 (*S*, *S*)-**16**		---	4 h, 60-70	sealed tube	98	 **112M** : **112m**, 80 : 20
2	 (*S*, *S*)-**86**		CH_2Cl_2	24 h, rt	13 kbar	76	 **113M** : **113m**, 87 : 13
3	(*S*, *S*)-**86**		CH_2Cl_2/ $ZnBr_2$	68 h, rt	13 kbar	82	 **114M**
4	(*S*, *S*)-**86**		CH_2Cl_2/ $ZnBr_2$	48 h, rt	13 kbar	58	 **115M** : **115m**, 88 : 12
5	(*S*, *S*)-**86**		CH_2Cl_2/ $ZnBr_2$	46 h, rt	13 kbar	74	 **116M**

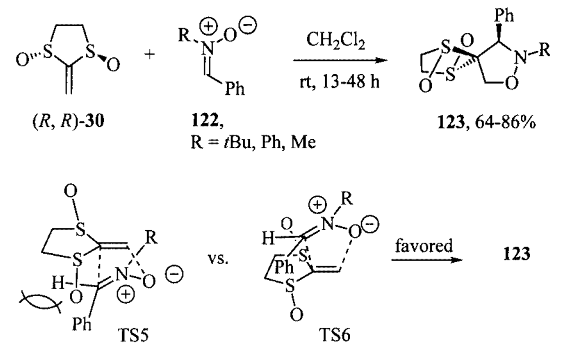


Scheme 26

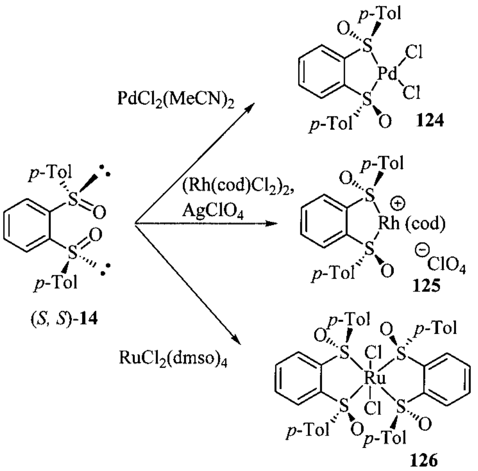


	endo-**120**		*exo*-**121**
X = CH_2, CH_2CH_2	> 99	:	1
X = O	28	:	72
with 0.5 equiv. Et_2AlCl	71	:	29

Scheme 27



Scheme 28

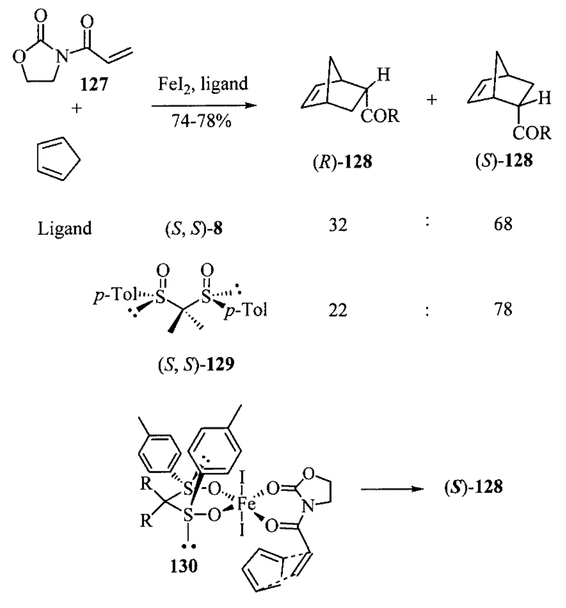


Scheme 29

complexes of 1,2-bis(alkylsulfinyl)alkanes that are solely *S*-bonded have been evaluated for their biological activity.[14]

In a pioneering work, James et al. reported the first sulfoxide analogs of the diop ligand and named them dios.[110] Their complexes with Ru^{II} were synthesised and tested as catalysts for asymmetric hydrogenation. Although the dios-type sulfoxide ligands were prepared as mixtures of diastereomers, the corresponding catalysts induced some degree of asymmetry (up to 25%). Shibasaki[27] designed (*S*,*S*)-1,2-bis(*p*-tolylsulfinyl)benzene (**14**) in order to coordinate to various transition metal species (palladium, rhodium and ruthenium) only via sulfur atoms. Complexes **124**, **125** and **126** were fully characterised (Scheme 29). Moderate enantioselectivity (up to 64%) was observed in palladium-catalysed allylic substitution reactions using **14** as a ligand.

(+)-(*S*,*S*)-1,1-Bis(*p*-tolylsulfinyl)methane (**8**) and its dimethylated adduct **129** have also been tested as ligands in the iron-catalysed Diels−Alder reaction of cyclopentadiene with 3-acryloyl-1,3-oxazolidin-2-one (**127**) (Scheme 30).[111] Good *endo* diastereoselectivity (*de* > 90%) was observed. The best enantioselectivity on *endo*-cycloadduct (*S*)-**128** was obtained with ligand **129** and was rationalised by the formation of the octahedral complex **130**, on which the cyclopentadiene approaches from the less hindered face.

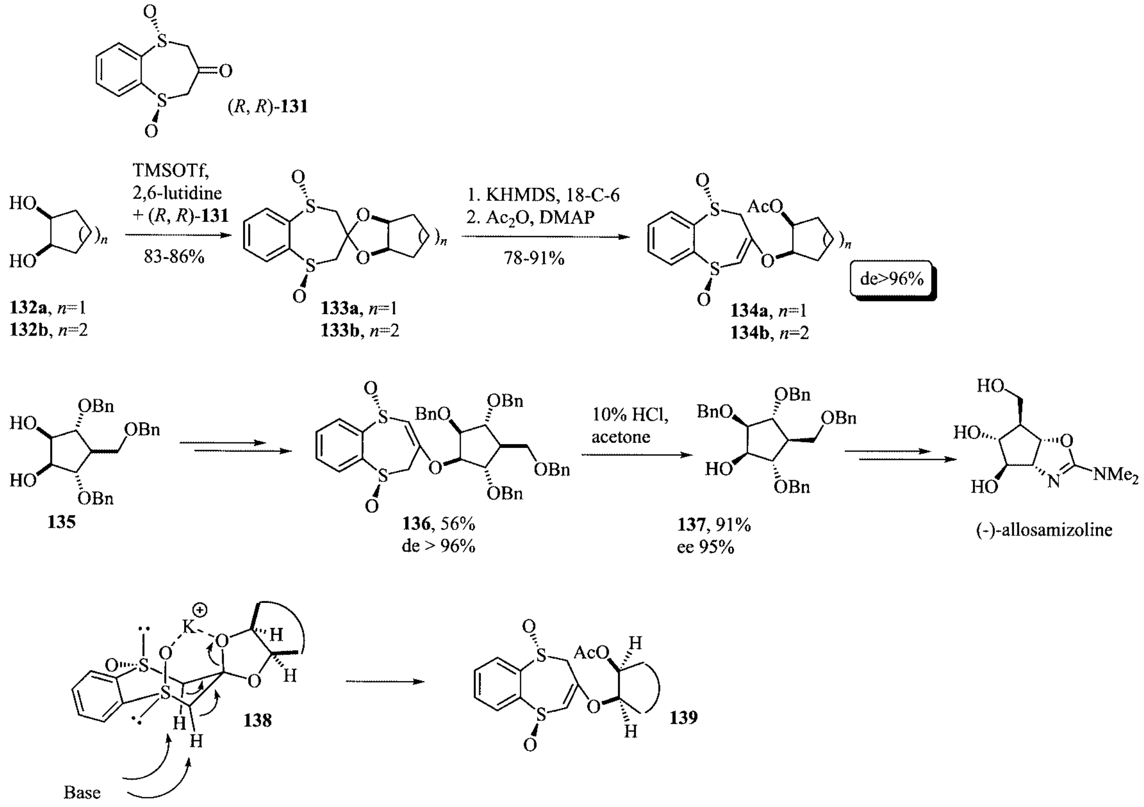


Scheme 30

Recently, Hiroi et al. have invoked a magnesium chelate between (*S*,*S*)-**8** and a prochiral *N*-arylsulfonyl-α-carboxamide radical, leading to a fairly enantioselective allylation reaction.[112]

III.3. Desymmetrization

A unique but quite intriguing application of bis(sulfoxides) has been proposed by Tanaka, Iwata et al. with compound (*R*,*R*)-**131** for the desymmetrization of *meso*-1,2-diols.[38,113] Thus, diols **132a** and **132b** were acetalized with **131** in the presence of TMSOTf and 2,6-lutidine in good yields to provide **133a** and **133b** (Scheme 31). Upon treatment with KHMDS, followed by acetylation, enol ethers **134a** and **134b** could be obtained in good yield and with a high diastereoselectivity (> 96%). This strategy has proved quite useful for the total synthesis of several relevant natural compounds such as (−)-allosamizoline[114] (**135** → **137**), (−)-galaquercitol,[115] (+)-aspicillin,[116] mosin B.[117] Mechanistic insights of this reaction have been given and the authors have proposed the intermediate **138**, displaying minimised steric interactions and leading to the major desymmetrized adduct **139**.[38] The coordination of the sodium or potassium cation would stabilize this preferred conformation in a better fashion than the lithium cation, which was justified experimentally since almost no diastereoselectivity was observed with lithium bases. A stereoelectronically controlled *anti* elimination then opens up the ketal ring to provide **139**. It should also be noted that the mild acidic hydrolysis which delivers the enantioenriched alcohol from **139** allows the recovery of the chiral auxiliary **131** in good yield and in high *ee* (> 98%).



Scheme 31

Conclusion

In summary, the interest in the chemistry of C_2-symmetric bis(sulfoxides) has grown steadily over the last three decades, mixing advances in their syntheses and their applications. Several of these compounds are now easily available, even in enantiopure form, and their uses in organic synthesis already span anionic condensation to cycloadditions giving birth to highly versatile α-hydroxy carboxylic acid derivatives, carbocycles and heterocycles. C_2-symmetric bis(sulfoxides) have also been involved in more specific applications like desymmetrization which proved useful for the total synthesis of natural products, and coordination to transition metals for catalysis and biological assays. Highly tailored preparations have been developed to obey the design of the required structures. This evolution in the chemistry of C_2-symmetric bis(sulfoxides) might be a trend and augurs well for the development of very refined utilizations.

---

[1] J. M. Crafts, *Justus Liebigs Ann Chem.* **1862**, *124*, 110−114.

[2] E. V. Bell, G. M. Bennett, *J. Chem. Soc.* **1927**, 1798−1803 and 3189−3192.

[3] For a review on the advantages of C_2-symmetric auxiliaries, see: J. K. Whitesell, *Chem. Rev.* **1989**, *89*, 1581−1590.

[4] F. Chaigne, J.-P. Gotteland, M. Malacria, *Tetrahedron Lett.* **1989**, *30*, 1803−1806.

[5] M. Zahouily, M. Journet, M. Malacria, *Synlett* **1994**, 366−368.

[6] E. Lacôte, M. Malacria, *C. R. Acad. Sci. Fr., Ser. IIc* **1998**, 191−194.

[7] E. Lacôte, B. Delouvrié, L. Fensterbank, M. Malacria, *Angew. Chem. Int. Ed.* **1998**, *37*, 2116−2218.

[8] B. Delouvrié, L. Fensterbank, E. Lacôte, M. Malacria, *J. Am. Chem. Soc.* **1999**, *121*, 11395−11401.

[9] B. Delouvrié, F. Nájera, L. Fensterbank, M. Malacria, *J. Organomet. Chem.* **2002**, *643−644*, 130−135.

[10] V. K. Aggarwal, I. W. Davies, R. Franklin, J. Maddock, M. F. Mahon, K. C. Molloy, *J. Chem. Soc., Perkin Trans. 1* **1994**, 2363−2368.

[11] G. Farina, F. Montanari, A. Negrini, *Gazz. Chim. Ital.* **1959**, *89*, 1548−1563.

[12] R. Siedlecka, J. Skarzewski, *Synthesis* **1994**, 401−404.

[13] C. M. Hull, T. W. Bargar, *J. Org. Chem.* **1975**, *40*, 3152−3154.

[14] D. T. T. Yapp, S. J. Rettig, B. R. James, K. A. Skov, *Inorg. Chem.* **1997**, *36*, 5635−5641.

[15] S. Bien, S. K. Celebi, M. Kapon, *J. Chem. Soc., Perkin Trans. 2* **1990**, 1987−1990 and references therein.

[16] V. K. Aggarwal, I. W. Davies, R. J. Franklin, J. Maddock, M. F. Mahon, K. C. Molloy, *J. Chem. Soc., Perkin Trans. 1* **1991**, 662−664.

[17] C. R. Johnson, D. McCants Jr., *J. Am. Chem. Soc.* **1965**, *87*, 1109−1114.

[18] L. Van Acker, M. J. O. Anteunis, *Bull. Soc. Chim. Belg.* **1977**, *86*, 299−308.

[19] For pioneering work with N_2O_4, see: C. R. Johnson, D. McCants, Jr., *J. Am. Chem. Soc.* **1964**, *86*, 2935−2936.

[20] V. K. Aggarwal, S. Schade, H. Adams, *J. Org. Chem.* **1997**, *62*, 1139−1145.

[21] N. Katagiri, S. Ise, N. Watanabe, C. Kaneko, *Chem. Pharm. Bull.* **1990**, *38*, 3242−3248.

[22] H. Nieuwenhuyse, R. Louw, *J. Chem. Soc., Perkin Trans. 1* **1973**, 839−841.

[23] N. Kunieda, J. Nokami, M. Kinoshita, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 256−259.

[24] B. Delouvrié, F. Nájera, L. Fensterbank, F. Brebion, M. Malacria, to be published.

[25] G. Asensio, P. A. Alemán, M. Medio-Simón, *Tetrahedron: Asymmetry* **1997**, *8*, 3647−3650.

[26] N. Khiar, F. Alcudia, J.-L. Espartero, L. Rodríguez, I. Fernández, *J. Am. Chem. Soc.* **2000**, *122*, 7598−7599.

[27] R. Tokunoh, M. Sodeoka, K.-i. Aoe, M. Shibasaki, *Tetrahedron Lett.* **1995**, *36*, 8035−8038.

[28] Y. Arai, S. Kuwayama, Y. Takeuchi, T. Koizumi, *Synth. Commun.* **1986**, *16*, 233−244.

[29] S. Uemura, in *Comprehensive Organic Synthesis*, vol. 7 (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, p. 757−787.

[30] M. Madesclaire, *Tetrahedron* **1986**, *42*, 5459−5495.

[31] F. A. Davis, R. T. Reddy, M. C. Weismiller, *J. Am. Chem. Soc.* **1989**, *111*, 5964−5965.

[32] P. Pitchen, E. Duñach, M. N. Deshmukh, H. B. Kagan, *J. Am. Chem. Soc.* **1984**, *106*, 8188−8193.

[33] F. Di Furia, G. Modena, R. Seraglia, *Synthesis* **1984**, 325−326.

[34] C. Bolm, F. Bienewald, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2640−2642.

[35] For an interesting application of the Bolm process, see: D. A. Cogan, G. Liu, K. Kim, B. J. Backes, J. A. Ellman, *J. Am. Chem. Soc.* **1998**, *120*, 8011−8019.

[36] P. C. B. Page, J. P. Heer, D. Bethell, E. W. Collington, D. M. Andrews, *Tetrahedron: Asymmetry* **1995**, *6*, 2911−2914.

[37] P. C. B. Page, J. P. Heer, D. Bethell, E. W. Collington, D. M. Andrews, *Synlett* **1995**, 773−775.

[38] N. Maezaki, A. Sakamoto, N. Nagahashi, M. Soejima, Y.-X. Li, T. Imamura, N. Kojima, H. Ohishi, K.-i. Sakaguchi, C. Iwata, T. Tanaka, *J. Org. Chem.* **2000**, *65*, 3284−3291.

[39] A total C_2 diastereoselectivity, in racemic series though, has been observed on a dinaphthodithiepine derivative, see: O. De Lucchi, *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *74*, 195−213.

[40] For an effective enantioselective monooxidation with whole-cell cultures of bacteria of 1,3-dithiane, see: V. Alphand, N. Gaggero, S. Colonna, R. Furstoss, *Tetrahedron Lett.* **1996**, *37*, 6117−6120.

[41] For an account on enantioselective sulfoxidation with monooxygenases, see: S. Colonna, N. Gaggero, P. Pasta, G. Ottolina, *Chem. Commun.* **1996**, 2303−2307.

[42] For an oxidation leading to an enantiopure sulfone sulfoxide, see: Y. Okamoto, H. Ohta, G.-i. Tsuchihashi, *Chem. Lett.* **1986**, 2049−2052.

[43] For an interesting case of formation of a *meso*-disulfoxide from a 1,1-bis(methylthio) derivative, see: M. Poje, O. Nota, K. Balenovic, *Tetrahedron* **1980**, *36*, 1895−1897.

[44] B. J. Auret, D. R. Boyd, R. Dunlop, A. F. Drake, *J. Chem. Soc., Perkin Trans. 1* **1988**, 2827−2829.

[45] See also for their work on 2-alkyl-1,3-dithianes: B. J. Auret, D. R. Boyd, E. S. Cassidy, R. Hamilton, F. Turley, A. F. Drake, *J. Chem. Soc., Perkin Trans. 1* **1985**, 1547−1552.

[46] O. Bortolini, F. Di Furia, G. Licini, G. Modena, M. Rossi, *Tetrahedron Lett.* **1986**, *27*, 6257−6260.

[47] O. Samuel, B. Ronan, H. B. Kagan, *J. Organomet. Chem.* **1989**, *370*, 43−50.

[48] For preliminary work on the naked 1,3-dithiane, see: E. Duñach, H. B. Kagan, *New J. Chem.* **1985**, *9*, 1−3.

[49] P. C. B. Page, E. S. Namwindwa, S. S. Klair, D. Westwood, *Synlett* **1990**, 457−459.

[50] See also: P. C. B. Page, R. D. Wilkes, E. S. Namwindwa, M. J. Witty, *Tetrahedron* **1986**, *52*, 2125−2154.

[51] P. C. B. Page, E. S. Namwindwa, *Synlett* **1991**, 80−83.

[52] V. K. Aggarwal, B. N. Esquivel-Zamora, G. R. Evans, E. Jones, *J. Org. Chem.* **1998**, *63*, 7306−7310.

[53] For a review on this principle, see: V. Rautenstrauch, *Bull. Soc. Chim. Fr.* **1994**, *131*, 515−524.

[54] For an application of this principle in enolate alkylation chemistry, see: S. G. Davies, A. A. Mortlock, *Tetrahedron Lett.* **1992**, *33*, 1117−1120.

[55] V. K. Aggarwal, J. Drabowicz, R. S. Grainger, Z. Gültekin, M. Lightowler, P. L. Spargo, *J. Org. Chem.* **1995**, *60*, 4962−4963.

[56] V. K. Aggarwal, Z. Gültekin, R. S. Grainger, H. Adams, P. L. Spargo, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2771−2781.

[57] S. Cossu, O. De Lucchi, E. Piga, G. Licini, *Tetrahedron Lett.* **1992**, *33*, 2053−2054.

[58] P. Bendazzoli, F. Di Furia, G. Licini, G. Modena, *Tetrahedron Lett.* **1993**, *34*, 2975−2978.

[59] J. Skarzewski, E. Ostrycharz, R. Siedlecka, *Tetrahedron: Asymmetry* **1999**, *10*, 3457−3461.

[60] C. A. Maryanoff, B. E. Maryanoff, R. Tang, K. Mislow, *J. Am. Chem. Soc.* **1973**, *95*, 5839−5840.

[61] For first reports of chiral acyl anions, see: L. Colombo, C. Gennari, E. Narisano, *Tetrahedron Lett.* **1978**, *19*, 3861−3862.

[62] L. Colombo, C. Gennari, C. Scolastico, G. Guanti, E. Narisano, *J. Chem. Soc., Chem. Commun.* **1979**, 591−592.

[63] R. F. Bryan, F. A. Carey, O. D. Dailey, Jr., R. J. Maher, R. W. Miller, *J. Org. Chem.* **1978**, *43*, 90−96.

[64] C. Gaul, K. Schärer, D. Seebach, *J. Org. Chem.* **2001**, *66*, 3059−3073 and references therein.

[65] V. K. Aggarwal, S. Schade, H. Adams, *J. Org. Chem.* **1997**, *62*, 1139−1145.

[66] F. G. Bordwell, J. E. Bartmess, personal communication.

[67] E. Barchiesi, S. Bradamante, R. Ferraccioli, G. A. Pagani, *J. Chem. Soc., Perkin Trans. 2* **1990**, 375−383.

[68] B. M. Trost, A. J. Bridges, *J. Org. Chem.* **1975**, *40*, 2014−2016.

[69] J. Boivin, C. Chauvet, S. Z. Zard, *Tetrahedron Lett.* **1992**, *33*, 4913−4916.

[70] I. Fernández, C. S. Araújo, M. J. Romero, F. Alcudia, N. Khiar, *Tetrahedron* **2000**, *56*, 3749−3753.

[71] B. B. Jarvis, H. E. Fried, *J. Org. Chem.* **1975**, *40*, 1278−1280.

[72] For X-ray crystal structures and conformational analysis, see: V. K. Aggarwal, J. M. Worrall, H. Adams, R. Alexander, B. F. Taylor, *J. Chem. Soc., Perkin Trans. 1* **1997**, 21−24.

[73] V. K. Aggarwal, G. Boccardo, J. M. Worrall, H. Adams, R. Alexander, *J. Chem. Soc., Perkin Trans. 1* **1997**, 11−19.

[74] R. Kuhn, W. Baschang-Bister, W. Dafeldecker, *Justus Liebigs Ann. Chem.* **1961**, *641*, 160−176.

[75] See also: G. Delogu, O. De Lucchi, P. Maglioli, G. Valle, *J. Org. Chem.* **1991**, *56*, 4467−4473.

[76] V. K. Aggarwal, I. W. Davies, J. Maddock, M. F. Mahon, K. C. Molloy, *Tetrahedron Lett.* **1990**, *31*, 135−138.

[77] V. K. Aggarwal, R. J. Franklin, M. J. Rice, *Tetrahedron Lett.* **1991**, *32*, 7743−7746.

[78] V. K. Aggarwal, R. J. Franklin, J. Maddock, G. R. Evans, A. Thomas, M. F. Mahon, K. C. Molloy, M. J. Rice, *J. Org. Chem.* **1995**, *60*, 2174−2182.

[79] This is a rather general trend in the alkylation of α-sulfoxide anion, see ref.[61]; see also: H. Sakuraba, S. Ushiki, *Tetrahedron Lett.* **1990**, *31*, 5349−5352.

[80] V. K. Aggarwal, A. Thomas, R. J. Franklin, *J. Chem. Soc., Chem. Commun.* **1994**, 1653−1654.

[81] V. K. Aggarwal, A. Thomas, S. Schade, *Tetrahedron* **1997**, *53*, 16213−16228.

[82] G. Solladié, F. Colobert, P. Ruiz, C. Hamdouchi, M. Carmen Carreño, J. L. García Ruano, *Tetrahedron Lett.* **1991**, *32*, 3695−3698.

[83] C. Mioskowski, G. Solladié, *Tetrahedron* **1980**, *36*, 227−236.

[84] K. Burgess, J. Cassidy, I. Henderson, *J. Org. Chem.* **1991**, *56*, 2050−2058.

[85] V. Guerrero-de la Rosa, M. Ordoñez, F. Alcudia, J. M. Llera, *Tetrahedron Lett.* **1995**, *36*, 4889−4892. For the use in palladium chemistry of these derivatives, see: V. Guerrero de la Rosa, M. Ordóñez, J. M. Llera, *Tetrahedron: Asymmetry* **2001**, *12*, 1089−1094.

[86] V. K. Aggarwal, M. Lightowler, S. D. Lindell, *Synlett* **1992**, 730−732.

[87] J. C. Carretero, J. L. García Ruano, L. M. Martín Cabrejas, *Tetrahedron: Asymmetry* **1997**, *8*, 409−416.

[88] V. K. Aggarwal, J. K. Barrell, J. M. Worrall, R. Alexander, *J. Org. Chem.* **1998**, *63*, 7128−7129.

[89] S. Ranganathan, D. Ranganathan, A. K. Mehrotra, *Synthesis* **1977**, 289−296.

[90] C. Maignan, R. A. Raphael, *Tetrahedron* **1983**, *39*, 3245−3249.

[91] B. Ronan, H. B. Kagan, *Tetrahedron: Asymmetry* **1991**, *2*, 75−90.

[92] O. De Lucci, D. Fabbri, V. Lucchini, *Synlett* **1991**, 565−568.

[93] V. K. Aggarwal, M. Lightowler, *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *74*, 407−408.

[94] A. Waldner, *Tetrahedron Lett.* **1989**, *30*, 3061−3064.

[95] J. Martynow, M. Dimitroff, A. G. Fallis, *Tetrahedron Lett.* **1993**, *34*, 8201−8204.

[96] M. J. Fisher, W. J. Hehre, S. D. Kahn, L. E. Overmann, *J. Am. Chem. Soc.* **1988**, *110*, 4625−4633.

[97] M. A. McCarrick, Y.-D. Wu, K. N. Houk, *J. Am. Chem. Soc.* **1992**, *114*, 1499−1500.

[98] J. C. Carretero, J. L. García Ruano, L. M. Martín Cabrejas, *Tetrahedron* **1995**, *51*, 8323−8332.

[99] E. Bertotti, G. Luciani, F. Montanari, *Gazz. Chim. Ital.* **1959**, *89*, 1564−1578.

[100] For further manipulations of the norbornene bis(sulfoxides), see: M. Cinquini, S. Colonna, F. Montanari, *J. Chem. Soc. C* **1970**, 572−576.

[101] E. Cecchet, F. Di Furia, G. Licini, G. Modena, *Tetrahedron: Asymmetry* **1996**, *7*, 369−372.

[102] V. K. Aggarwal, R. S. Grainger, P. L. Spargo, *Phosphorus, Sulfur Silicon Relat. Elem.* **1994**, *95−96*, 337−338.

[103] V. K. Aggarwal, R. S. Grainger, H. Adams, P. L. Spargo, *J. Org. Chem.* **1998**, *63*, 3481−3485.

[104] J. Carles Bayón, C. Claver, A. M. Masdeu-Bultó, *Coord. Chem. Rev.* **1999**, *193−195*, 73−145.

[105] W. Weigand, R. Wünsch, *Chem. Ber.* **1996**, *129*, 1409−1419.

[106] S. K. Madan, C. M. Hull, L. J. Herman, *Inorg. Chem.* **1968**, *7*, 491−495.

[107] L. Cattalini, G. Michelon, G. Marangoni, G. Pelizzi, *J. Chem. Soc., Dalton Trans.* **1979**, 96−101.

[108] W. De Azevedo Filgueira, Jr., Y. Primerano Mascarenhas, *Acta Crystallogr., Sect. C* **1995**, *51*, 619−621.

[109] C. Pettinari, M. Pellei, G. Cavicchio, M. Crucianelli, W. Panzeri, M. Colapietro, A. Cassetta, *Organometallics* **1999**, *18*, 555−563.

[110] B. R. James, R. S. McMillan, *Can. J. Chem.* **1977**, *55*, 3927−3932.

[111] N. Khiar, I. Fernandez, F. Alcudia, *Tetrahedron Lett.* **1993**, *34*, 123−126.

[112] K. Hiroi, M. Ishii, *Tetrahedron Lett.* **2000**, *41*, 7071−7074.

[113] N. Maezaki, A. Sakamoto, M. Soejima, I. Sakamoto, L. Y. Xia, T. Tanaka, H. Ohishi, K.-i. Sakaguchi, C. Iwata, *Tetrahedron: Asymmetry* **1996**, *7*, 2787−2790.

[114] N. Maezaki, A. Sakamoto, T. Tanaka, C. Iwata, *Tetrahedron: Asymmetry* **1998**, *9*, 179−182.

[115] N. Maezaki, N. Nagahashi, R. Yoshigami, C. Iwata, T. Tanaka, *Tetrahedron Lett.* **1999**, *40*, 3781−3784.

[116] N. Maezaki, Y.-X. Li, K. Ohkubo, S. Goda, C. Iwata, T. Tanaka, *Tetrahedron* **2000**, *56*, 4405−4413.

[117] N. Maezaki, N. Kojima, A. Sakamoto, C. Iwata, T. Tanaka, *Org. Lett.* **2001**, *3*, 429−432.

Received February 26, 2002
[O02104]