

# ORGANOSULFUR CHEMISTRY

SYNTHETIC AND  
STEREOCHEMICAL ASPECTS

Edited by Philip Page



VOLUME 2

AP

# **Organosulfur Chemistry**

Volume 2

Synthetic and Stereochemical Aspects

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# **Organosulfur Chemistry**

## Volume 2

### Synthetic and Stereochemical Aspects

edited by

**Philip Page**  
Department of Chemistry  
Loughborough University  
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To my wife

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## Preface

The impact of organosulfur chemistry, especially in the areas of heterocyclic chemistry, stereocontrolled processes, and particularly asymmetric synthesis, has led to a resurgence of interest in the field and a rapidly growing number of related publications. This book is the second of a series intended to provide coverage of topics of current interest throughout the whole range of organosulfur chemistry. Each volume contains several articles, each consisting of an in-depth, self-contained review in a well-defined area.

This volume begins with a review by Henri Kagan and Patrick Diter of methods of asymmetric sulfur oxidation processes, and this is followed by a survey of the preparation of chiral sulfoxides by nucleophilic displacement at sulfur (the Andersen process and its derivatives) by Steven Allin and Stephen Shuttleworth. The conformational preferences of the sulfinyl group in the entire range of six-membered ring sulfur and sulfur–oxygen heterocycles are discussed by Eusebio Juaristi and Mario Ordoñez. Steven Allin, Stephen Shuttleworth and Philip Page describe applications of sulfoxides as stereocontrol elements in organic synthesis, and Andrew Westwell and Christopher Rayner report thoroughly on the preparation and chemistry of unsaturated sulfoxides, including their preparation and use in nonracemic form. The volume is completed by a discussion of the chemistry of sulfolenes by John Leonard, Andrew Hague and John Knight.

Offers of articles for consideration for inclusion in future volumes will be appreciated and should be sent to the editor, who would also welcome from readers any comments on the present volume.

*Philip Page*

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# ASYMMETRIC SULFOXIDATION – CHEMICAL AND ENZYMATIC

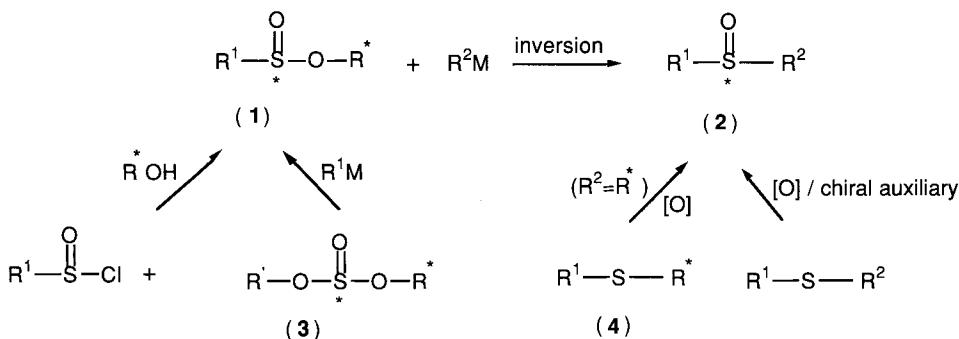
**Henri B. Kagan and Patrick Diter**

*Laboratoire de Synthèse Asymétrique, UA CNRS N° 1497,  
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## 1. INTRODUCTION

Sulfoxides are useful compounds for organic synthesis. The sulfinyl group is chiral if flanked by two different groups. This special feature explains why chiral sulfoxides are increasingly important as stereocontrol elements in asymmetric synthesis [1–6]. Moreover, there are various sulfoxides (both natural products and synthetic compounds) which exhibit biological activity related to the stereochemistry at sulfur [7,8]. As a consequence, it is quite important to have a set of methods for the generation of various types of chiral sulfoxides. *Resolution* of racemic mixtures has been used to prepare enantiomerically enriched sulfoxides, but this method is of limited use, owing to its lack of generality. *Asymmetric synthesis* provides a more successful approach to such materials (Scheme 1.1). The Andersen method is based on the use of sulfinate (1) derived from chiral alcohols [9,10]. It proceeds by preferential formation (or separation by crystallization) of one diastereoisomer of a sulfinate. This intermediate is then transformed stereospecifically into a sulfoxide (2) by nucleophilic substitution [11]. The most successful substrates are menthyl and various sugar sulfinate esters [12]. A chiral amidosulfite [13] or the chiral sulfite (3) [14], which can be submitted to two successive nucleophilic substitutions, are also useful precursors of sulfoxides.



**SCHEME 1.1** Various methods for preparing chiral sulfoxides by asymmetric synthesis

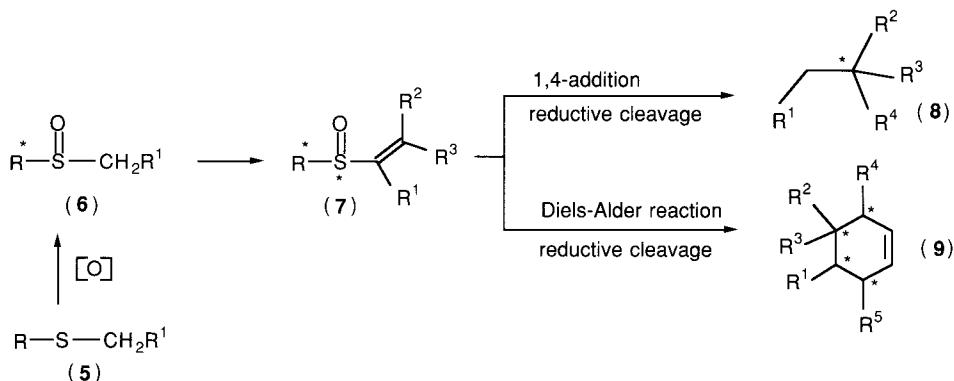
Another approach involves the stereoselective creation of the sulfinyl moiety by oxidative processes. One possibility is the use of a sulfide (4) bound to a chiral auxiliary  $\text{R}^*$ , with a structure or a functional group (usually a hydroxy) able to control the course of the transformation of sulfide (4) into sulfoxide (2). A second approach is the enantioselective oxidation of an achiral sulfide. In this case, the chiral auxiliary is connected to the oxidant, and the process is stoichiometric with respect to the chiral auxiliary. The most efficient production of chiral sulfoxides results where the chiral auxiliary is part of an oxidation catalyst, when, in principle, a large amount of enantiopure sulfoxide (2) is produced from a small amount of the chiral auxiliary.

This chapter does not consider the Andersen method: this is discussed by Allin in Chapter 2. Attention is focused on the *asymmetric oxidation* of sulfides to sulfoxides ('sulfoxidation'). Cases in which the chiral auxiliary is connected to the sulfide are detailed first, then stoichiometric and, finally, catalytic oxidations are discussed.

## 1.2 OXIDATION OF SULFIDES BEARING A REMOVABLE CHIRAL AUXILIARY

### 1.2.1 Introduction

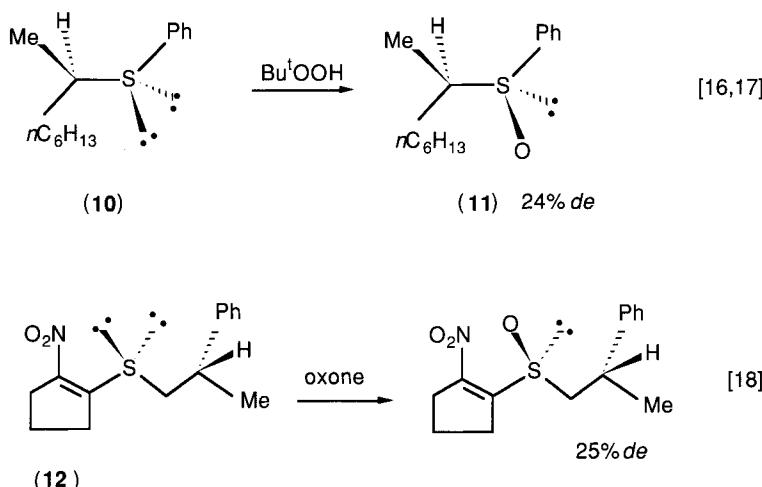
Chiral sulfoxides of type (6) (Scheme 1.2) are especially valuable in asymmetric synthesis if there are no vicinal hydrogens on the  $R^*$  group connected to  $S(O)$ . In this case vinylic sulfoxide (7) can be selectively generated. This compound can further react by 1,4-addition or by cycloaddition. It gives, for example, (8) or (9) after reductive cleavage (e.g. with  $Na/Hg$ ). In this manner the chiral fragment  $R^*$  is regenerated and can sometimes be transformed back into the sulfide (5). The difficulty with this approach is the stereoselective oxidation of (5) into (6), since the chiral moiety  $R^*$  must exercise a high level of stereocontrol.



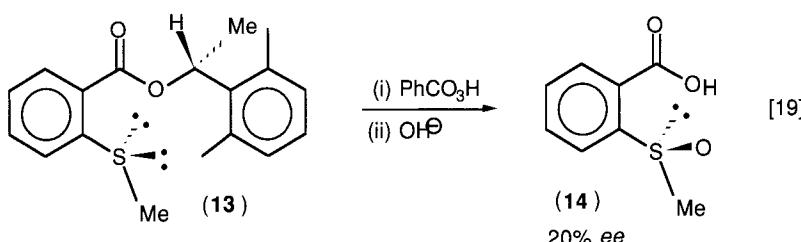
**SCHEME 1.2** Some examples of the use of a chiral sulfoxide in asymmetric synthesis

The first indication that some asymmetric induction is possible is found in the early literature (for a review see ref. [15]). For example, Cram *et al.* studied the oxidation of sulfide (10) (Scheme 1.3) and found that a sulfoxide is formed with 24% *de* [16]. Mislow *et al.* established that the major sulfoxide has the structure (11) [17]. 1,3-Asymmetric induction, however, is usually not very high. Thus, sulfide (12) was oxidized to give a mixture of diastereoisomeric sulfoxides (25%

*de*) which could be separated and were then used in Diels–Alder reactions [18]. Asymmetric oxidation of sulfoxide ester (13) (Scheme 1.4) was achieved with perbenzoic acid at  $-5^{\circ}\text{C}$  in chloroform [19]. The chiral alcohol was recovered by saponification, leaving the sulfoxide (14) with 20% *ee*. This is a case of 1,6-asymmetric induction during sulfide oxidation: unfortunately, the *ee* of the product is not high enough for this process to be of preparative interest.

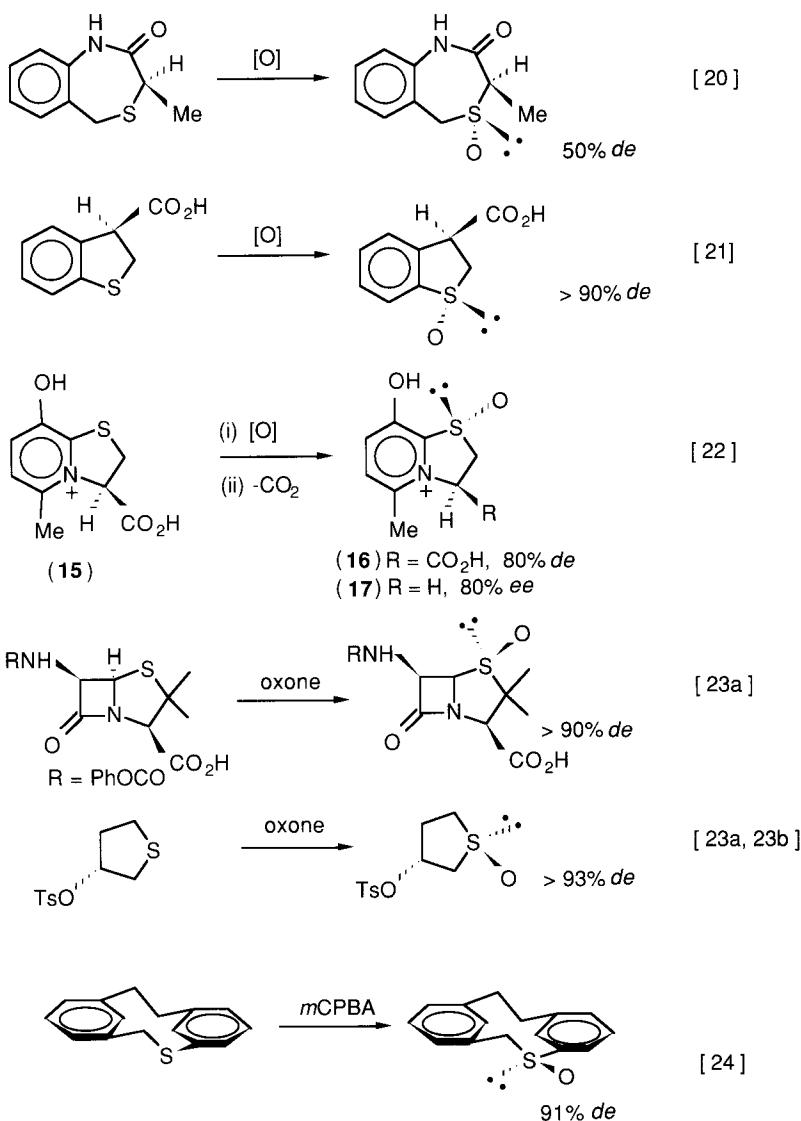


SCHEME 1.3 1,2-Asymmetric induction in sulfide oxidation



SCHEME 1.4 1,6-Asymmetric induction in sulfide oxidation

In this chapter we only consider sulfide oxidations which are directly relevant to asymmetric synthesis, e.g. providing chiral synthons or chiral auxiliaries. However, it is interesting that cyclic sulfides having an asymmetric centre in the ring often give highly diastereoselective oxidations. Some examples are indicated in Scheme 1.5. Of special interest is the oxidation of (15) into (16), since decarboxylating (16) removes the original asymmetric centre in (15) and provides an asymmetric synthesis of (17) [21].

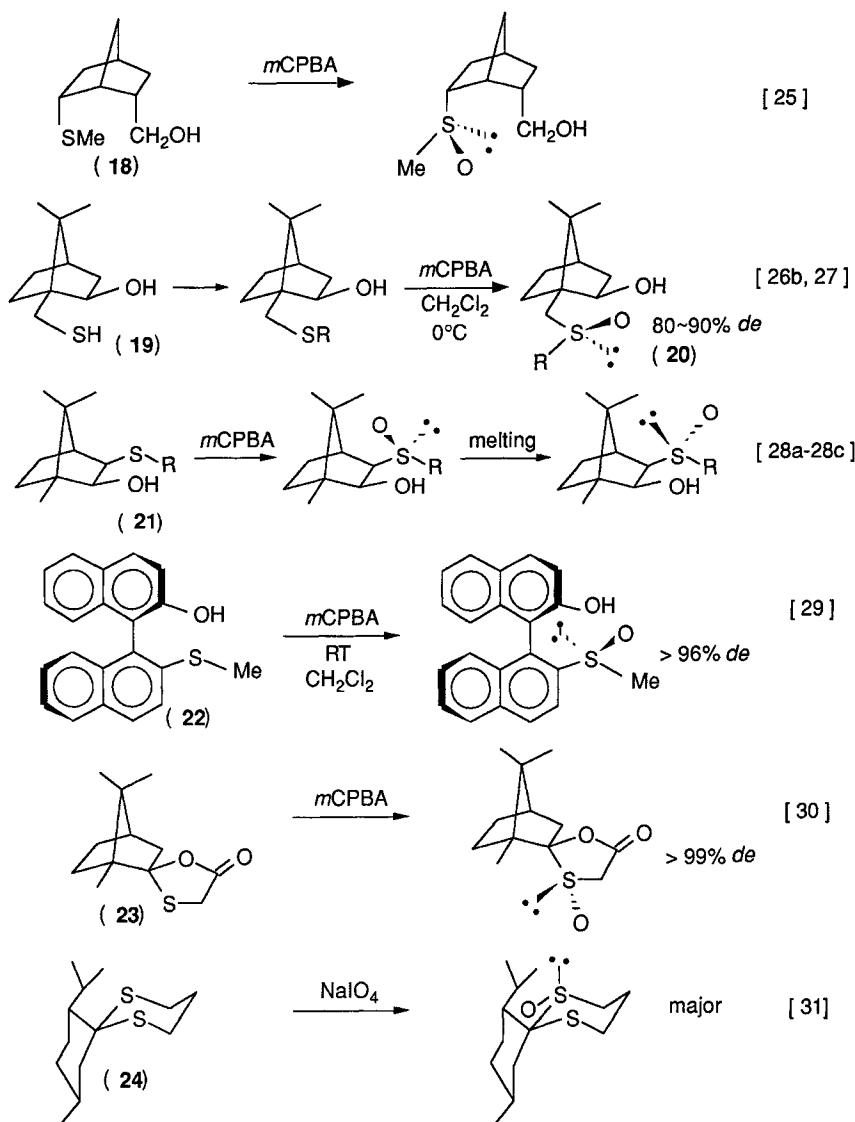


**SCHEME 1.5** Examples of stereoselective oxidations of cyclic sulfides

### 1.2.2 Examples of Diastereoselective Oxidations

Peracids are able to form a hydrogen bond with a hydroxyl group suitably located with respect to a reaction site. High stereoselectivity can often be expected under these circumstances. Glass *et al.* made a stereochemical study of oxidation of *endo* hydroxy thioether (**18**) (Scheme 1.6). The oxidation by *m*-chloroperbenzoic acid (*m*CPBA) is diastereoselective (92% *de*), while oxidation by *t*-butyl hypochlorite

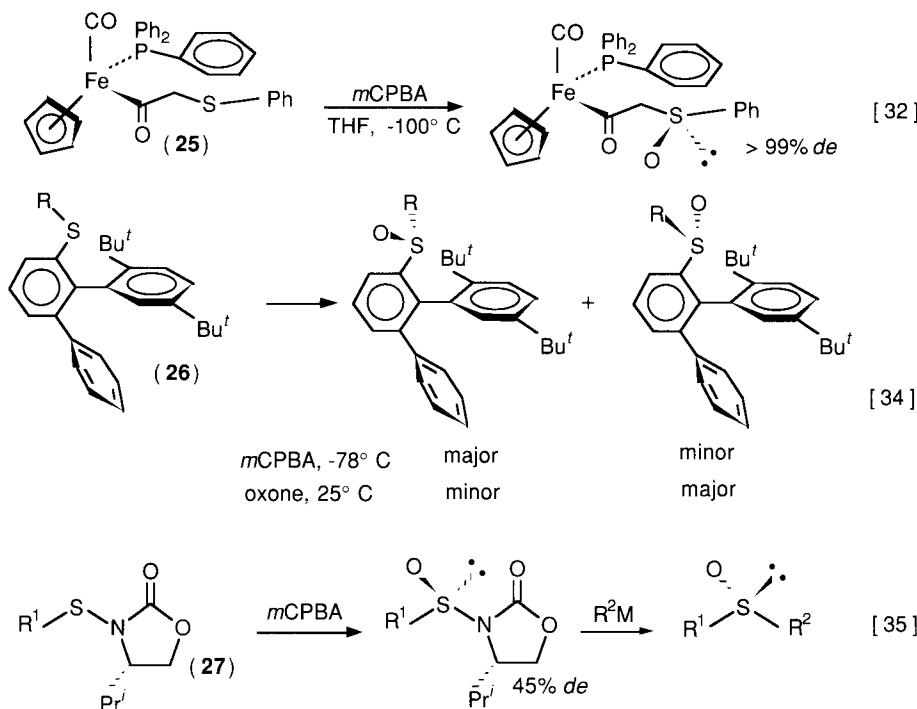
followed by hydrolysis of the intermediate alkoxysulfonium salt gives the epimeric sulfoxide (>95% *de*) with the opposite configuration at sulfur [25]. This approach has been successful using 10-mercaptopisoborneol (**19**) (easily available [26a]) as a chiral auxiliary. Alkylation provides a sulfide, whose peracid oxidation leads to sulfoxide (**20**) with high diastereoselectivity [26]. According to the nature of the group R, various stereoselective Diels–Alder reactions were performed [26b,27]. The isoborneol derivative (**21**) also undergoes a highly diastereoselective oxidation directed by the hydroxyl group. Interestingly, the diastereoisomeric sulfoxides are cleanly available by simply heating at the melting point [28a]. Reductive or oxidative cleavage of the carbon–sulfur bond in the functionalized molecules



allows the recovery of the chiral products as well as, in principle, the chiral auxiliary (**19**) or (**21**) ( $R = H$ ). Similarly, oxidation by *m*CPBA of sulfenimine (**21**) ( $R = N=CHPh$ ) is fully diastereoselective [28c].

The high degree of stereocontrol conferred by a hydroxy group has been also observed in the oxidation of 1,1'-binaphthyl thioether (**22**) [29].

Diastereoselective oxidations of sulfides sometimes occur in the absence of a hydroxy group, if the structure of the chiral molecule provides a significant differentiation of the possible directions of electrophilic attack at sulfur. For example, (**23**) (prepared from camphor) gives only the *endo* sulfoxide, which is a good starting material for asymmetric synthesis (with recovery of camphor) [30]. The 1,3-dithiane (**24**), derived from menthone, affords regioselectively and diastereoisomerically a sulfoxide that has subsequently been transformed into (*R*)- $\alpha$ -lipoic acid with recycling of menthone [31]. Oxidation of sulfide (**25**), where there are asymmetric iron and carbon atoms affords only one epimer of the corresponding sulfoxide. This can be transformed by treatment with alkylcuprates into various enantiopure phenyl alkyl sulfoxides with regeneration of the chiral iron auxiliary [32]. Some ferrocenyl sulfides with planar chirality and an asymmetric center are also oxidized stereoselectively by *m*CPBA [33]. Finally, compound (**26**), where a chiral auxiliary (with atropoisomerism) is connected to sulfur [34], undergoes oxidation by *m*CPBA (kinetic control) or by oxone (thermodynamic control) to provide different diastereoisomeric sulfoxides.



**SCHEME 1.6** Examples of sulfoxidations for asymmetric synthesis

Oxidation by mCPBA of sulfenamines (**27**) was investigated by Evans *et al.* [35]. Diastereoselectivity is moderate, and there is an inversion of the sense of asymmetric induction when oxidation is performed by *t*-butyl hypochlorite. The diastereoisomeric sulfinamides are easily separated by chromatography and could be transformed into sulfoxides in high yields.

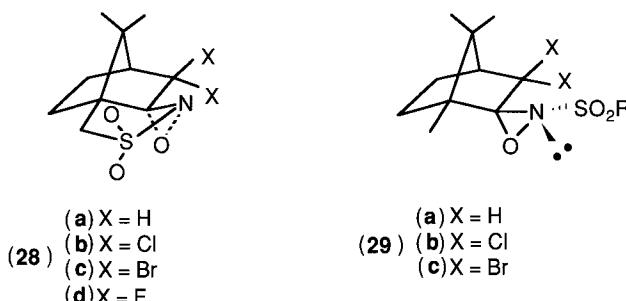
## 1.3 STOICHIOMETRIC ENANTIOSELECTIVE OXIDATION OF SULFIDES

### 1.3.1 Chiral Peracids

Oxidation of sulfides by chiral peracids was investigated very early by Montanari *et al.* [36,37] and Balenovic *et al.* [38], but enantiomeric excesses were disappointingly low (<10%). A detailed account of this area can be found in refs [15] and [39].

### 1.3.2 Chiral Oxaziridines

Davis *et al.* have developed a useful class of chiral oxidants based on *N*-sulfonyloxaziridines derived from camphor (for a review, see ref. [40]). Compounds (**28**) and (**29**) are the most efficient reagents [41,42]. Representative results are listed in Table 1.1.



As shown in Table 1.1, oxaziridine (**29b**) is a superior reagent for sulfide oxidation, compared to (**28b**). Values of *ee* up to 95% were obtained. The two chlorines of (**29b**) are crucial for the enantioselection (see entries 1, 2 and 5, 6 in Table 1.1). Chiral oxaziridines are now commercially available. A mechanism has been proposed for the electrophilic attack on sulfur. In the present case preferred transition states **I** and **II** were postulated.  $R_L$  and  $R_S$  are large and small groups, respectively. The steric influence seems to be of major importance, presumably because of a molecular cleft defined by a chlorine atom and the phenylsulfonyl

**TABLE 1.1** Oxidation of sulfides  $R^1-S-R^2$  into sulfoxides by chiral oxaziridines in  $CCl_4$  at 20°C

	$R^1$	$R^2$	Oxidant	ee (%)	Absolute Stereochem	Ref.
1	<i>p</i> -Tol	Me	<b>28a</b>	8	( <i>S</i> )	[41]
2	<i>p</i> -Tol	Me	<b>28b</b>	67	( <i>S</i> )	[41]
3	<i>p</i> -Tol	Me	<b>28c</b>	59	( <i>S</i> )	[41]
4	<i>p</i> -Tol	Me	<b>28d</b>	64	( <i>S</i> )	[41]
5	<i>p</i> -Tol	Me	<b>29a</b>	26	( <i>S</i> )	[42]
6	<i>p</i> -Tol	Me	<b>29b</b>	>95	( <i>S</i> )	[42]
7	<i>p</i> -Tol	Bu <sup>n</sup>	<b>28b</b>	74	( <i>S</i> )	[41]
8	<i>p</i> -Tol	Bu <sup>n</sup>	<b>29b</b>	91	( <i>S</i> )	[42]
9	9-Anthryl	Me	<b>28b</b>	30	( <i>S</i> )	[41]
10	9-Anthryl	Me	<b>29b</b>	94	( <i>S</i> )	[42]
11	PhCH <sub>2</sub>	Me	<b>28b</b>	20	( <i>S</i> )	[41]
12	PhCH <sub>2</sub>	Me	<b>29b</b>	13	( <i>S</i> )	[42]
13	PhCH <sub>2</sub>	Bu <sup>t</sup>	<b>29b</b>	91	( <i>S</i> )	[42]
14	Bu <sup>t</sup>	Me	<b>29b</b>	94	( <i>S</i> )	[42]

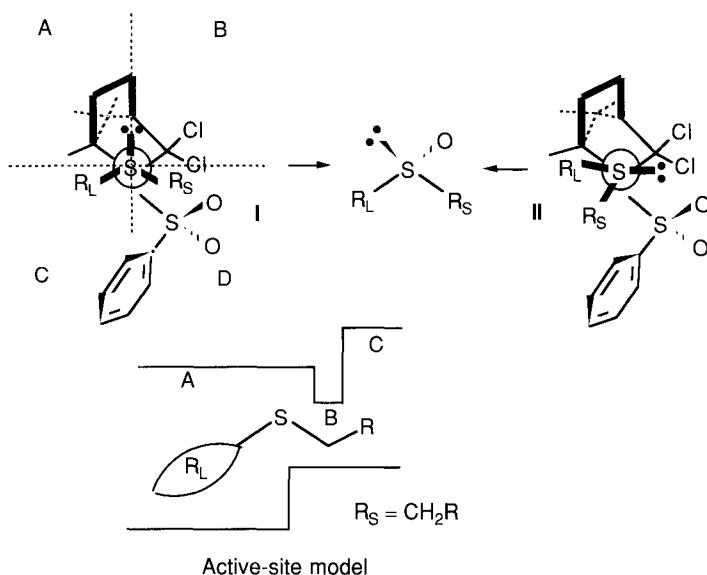


FIGURE 1.1 Preferred transition states and an active-site model for the oxidation of sulfides by oxaziridine (**29b**) [42].

group which can accommodate only small groups (Figure 1.1). The large group is preferentially pushed toward the vacant lower left quadrant.

Hermann *et al.* prepared several other classes of chiral oxaziridines, but these give lower ee's (up to 70%) in the asymmetric oxidation of sulfides [43,44]. Page *et al.* have shown that the dimethyl acetal corresponding to (**28**) ( $X = \text{OMe}$ ) is also

highly enantioselective for sulfide oxidation, particularly for non-aryl substrates, complementing other reagents [161] and can be used in a catalytic system with hydrogen peroxide as oxidant (see Section 1.4.7).

### 1.3.3 Chiral Titanium Complexes

The Sharpless epoxidation of allylic alcohols by hydroperoxides uses as mediator [45] or as catalyst [46] a chiral titanium complex obtained from the combination  $Ti(OPr^i)_4$ /diethyl tartrate (DET) in 1:1 ratio. Kinetic resolution of  $\beta$ -hydroxysulfides was also observed, but without diastereoselectivity for the product  $\beta$ -hydroxysulfoxides [47]. We found that the Sharpless reagent 'deactivated' by 1 equivalent of water allows the enantioselective oxidation of aryl methyl sulfides into sulfoxides to be performed with *ee*'s up to 90% [48–50]. The best reagent combination proved to be  $Ti(OPr^i)_4/DET/H_2O = 1:2:1$ . Independently, Modena *et al.* obtained similar enantioselectivities with the combination  $Ti(OPr^i)_4/DET$  in 1:4 ratio [51]. These two combinations are sometimes referred to as the Kagan reagent and the Modena reagent, respectively. They will be considered successively.

#### 1.3.3.1 Kagan reagent ( $Ti(OPr^i)_4/DET/H_2O = 1:2:1$ )

The combination has been studied with many classes of sulfides. In most of the early examples investigated, *t*-butyl hydroperoxide (TBHP) was the oxidant (1.1 equivalents), and 1 equivalent of the titanium combination was used. Reactions were performed in dichloromethane at  $-20^\circ C$ . Some representative examples are indicated in Table 1.2.

The highest *ee*'s (85–90%) were observed for TBHP oxidation of sulfides with general formula  $Me—S—(aryl)$ . There is generally a decrease in the *ee* when methyl group is replaced by a more sterically demanding one such as  $Pr^n$  or  $Bu^n$  (e.g. entry 2, Table 1.2). However, cyclopropyl—S—Ph is an excellent substrate for sulfoxidation (95% *ee*, entry 6). Dialkyl sulfides such as  $Me—S—Bu^t$  or  $Me—S—(n-octyl)$  gave *ee*'s in the range of 55% (entries 7, 8).

A significant improvement in enantioselectivity was obtained by replacing TBHP by cumene hydroperoxide (CHP) (e.g. compare entries 1, 4, 5, 7 with entries 10–13, respectively) [53,54].

A strong solvent effect has been detected when using TBHP as oxidant, studied in the specific case of methyl *p*-tolyl sulfide [55]. Thus, in the same experimental conditions, *ee*'s were 85% ( $CH_2Cl_2$ ), 86% ( $ClCH_2CH_2Cl$ ), 70% ( $CHCl_3$ ), 4.5% ( $CCl_4$ ), 26% (toluene), and 62% (acetone). With  $(R,R)$ -DET as a ligand, methyl *p*-tolyl sulfoxide has the *(R)* configuration, except when the reaction is run in  $CCl_4$ .

Ester moieties at the termini of alkyl chains do not perturb the *ee* (with respect to an unsubstituted chain): compare entries 7 and 14 for an example (Table 1.2). Finally, the oxidant system (with TBHP) has been found to oxidize  $R—S—XR'$  into  $R—S(O)—XR'$  when X is an heteroatom such as sulfur, nitrogen, or oxygen [56]. However, the enantioselectivities are modest. For example, isopropyl

**TABLE 1.2** Some representative examples of sulfoxidation in presence of the combination  $\text{Ti}(\text{OPr})_4/(R,R)\text{-DET}/\text{H}_2\text{O} = 1:2:1$  ('Kagan reagent')

	Sulfide <sup>a</sup>	Hydroperoxide <sup>b</sup>	Yield (%) <sup>c</sup>	ee (%) <sup>d</sup>	Ref.
1	Me—S—(p-Tol)	TBHP	90	89	[49]
2	Bu <sup>n</sup> —S—(p-Tol)	TBHP	75	75	[49]
3	Me—S—(1-Napht)	TBHP	98	89	[52]
4	Me—S—(o-Anisyl)	TBHP	70	84	[49]
5	Me—S—(p-Anisyl)	TBHP	72	86	[49]
6	Cycloprop—S—Ph	TBHP	73	95	[52]
7	Me—S—(n-Octyl)	TBHP	77	53	[52]
8	Me—S—(Bu <sup>t</sup> )	TBHP	72	53	[54]
9	Me—S—(p-Tol)	CHP	93	96	[54]
10	Me—S—(o-Anisyl)	CHP	97	93	[54]
11	Me—S—(p-ClC <sub>6</sub> H <sub>4</sub> )	CHP	85	91	[54]
12	Me—S—(n-Octyl)	CHP	71	80	[54]
13	Me—S—(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Me	TBHP	85	64	[54]
14	(Pr <sup>t</sup> )—S—S—(Pr <sup>t</sup> ) <sup>e</sup>	TBHP	43	52 <sup>d</sup>	[56]
15	(p-Tol)—S—OMe	TBHP	88	36	[56]

<sup>a</sup>Reaction performed at  $-20^\circ\text{C}$  in  $\text{CH}_2\text{Cl}_2$ , at 5 mmol scale.

<sup>b</sup>TBHP = *t*-butyl hydroperoxide; CHP = cumene hydroperoxide.

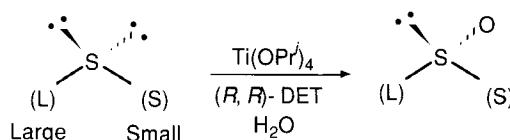
<sup>c</sup>Isolated yields after flash chromatography on silica gel.

<sup>d</sup>Measured by polarimetry or <sup>1</sup>H NMR in presence of a chiral reagent. All sulfoxides have (R) configuration except in entry 15.

<sup>e</sup>Isopropyl isopropylthiosulfinate.

isopropylthiosulfinate was obtained with 52% *ee* (entry 15, Table 1.2) while methyl *p*-tolylsulfinate was prepared with 36% *ee* (entry 12).

The absolute configurations of the sulfoxides resulting from the asymmetric oxidation of sulfides are safely predicted by the method shown in Scheme 1.7. In aryl methyl sulfides, one takes aryl as the 'large' (L) group. For methyl alkyl sulfides, it is the methyl group which is the smaller.  $\pi$ -Systems play a special role, as often encountered in asymmetric synthesis; thus in the oxidation of  $\text{Me—C}\equiv\text{C—Bu}^n$ , the triple bond has to be taken as the (L) group [54,55].



**SCHEME 1.7** Rule for the prediction of absolute configuration in asymmetric sulfoxidation by the Kagan reagent [54,55]

The mechanism of the reaction remains obscure. It has been found that the main species in solution has a molecular mass close to a dimeric complex; moreover,

infrared spectroscopy shows the presence of a free as well as a chelated ester [49]. The role of water has been ascribed to the formation of a Ti—O—Ti linkage. The model of asymmetric induction shown in Figure 1.2 was tentatively proposed [50,54]. It takes as an hypothesis that diethyl tartrate behaves as a trihapto ligand towards titanium, as it does in the Sharpless system [57].

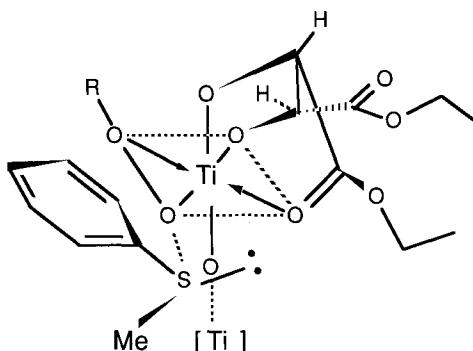
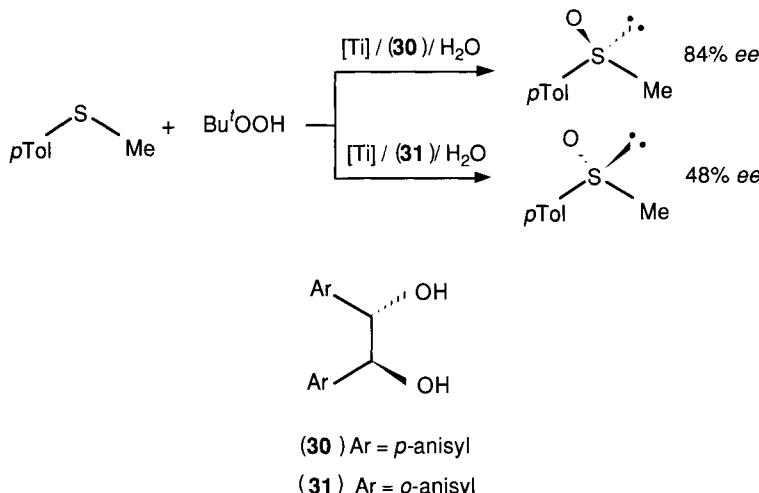


FIGURE 1.2 Tentative model of asymmetric induction [55].

This model assigns a role to the free ester function. Indeed, it was observed that dimethyl tartrate provides a low *ee* (62%) in the oxidation of methyl *p*-tolyl sulfide by TBHP [54]. The above mechanism is compatible with a *catalytic reaction* (with respect to titanium). This aspect is described and discussed in Section 1.4.

Diethyl tartrate (compared to various tartaric acid derivatives) still remains the best ligand for the enantioselective oxidation of sulfides, as exemplified by the oxidation of methyl *p*-tolyl sulfide [49]. Yamamoto *et al.* found that DET can be replaced by diols (**30**) or (**31**) in the Kagan reagent, giving sulfoxides of opposite



**SCHEME 1.8** Replacement of diethyl tartrate by some diols in the titanium complex [58]

absolute configuration (Scheme 1.8) [58]. 2,2'-Dihydroxy-1,1'-binaphthyl has also been used in combination with  $\text{Ti}(\text{OPr})_4$  and  $\text{H}_2\text{O}$  by Uemura *et al.*, giving a catalytic complex (see Section 1.4.1).

### 1.3.3.2 Modena reagent ( $\text{Ti}(\text{OPr})_4/(R,R)\text{-DET} = 1:4$ )

Oxidation of sulfides has been performed by TBHP in anhydrous conditions with an excess of diethyl tartarate (4 equivalents) [59]. Modena used 1,2-dichloroethane or toluene as solvent at  $-20^\circ\text{C}$ . Some examples are listed in Table 1.3. As with the Kagan reagent, a high *ee* (88%) is obtained for the sulfoxidation of methyl *p*-tolyl sulfide in 1,2-dichloroethane, but the *ee* drops to 64% in toluene.

Monooxidation of 1,3-dithiolanes gives both good diastereoselectivity (with oxygen introduced *trans* to the bulky group at C-2) and good enantioselectivity (entries 6, 7, Table 1.3).

**TABLE 1.3** Some representative examples of sulfoxidation by TBHP in presence of the combination  $\text{Ti}(\text{O}i\text{Pr})_4/(R,R)\text{-DET} = 1:4$  ('Modena reagent')<sup>a</sup>

	Sulfide	Yield (%)	ee (%)	Ref.
1	Me—S—( <i>p</i> -Tol)	46	64 ( <i>R</i> )	[51]
2	Me—S—( <i>p</i> -Tol)	60 <sup>b</sup>	88 ( <i>R</i> )	[51]
3	Bu <sup>—</sup> S—( <i>p</i> -Tol)	99	34 (+)	[51]
4	Me—S—CH <sub>2</sub> Ph	70 <sup>b</sup>	46 (+)	[51]
5	( <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> )—S—(CH <sub>2</sub> ) <sub>2</sub> OH	41	14 (—)	[51]
6		76 <sup>c,d</sup>	76	[59]
7		66 <sup>c,e</sup>	83	[59]

<sup>a</sup>Reaction performed with 1 equiv of Ti complex at  $-20^\circ\text{C}$ , in toluene, unless stated.

TBHP = *t*-butyl hydroperoxide.

<sup>b</sup>In dichloromethane at  $-77^\circ\text{C}$ .

<sup>c</sup>In 1,2-dichloroethane.

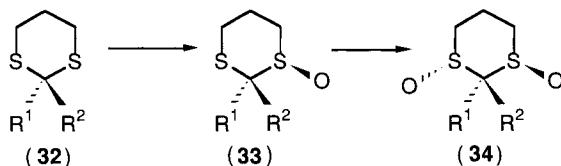
<sup>d</sup>S-monooxide: *trans/cis* = 94:6.

<sup>e</sup>S-monooxide: *trans/cis* = 97:3.

### 1.3.3.3 Some applications of the modified titanium reagents

The *Kagan reagent* has in a number of cases proved much more stereoselective than other systems. For example, Beckwith and Boate oxidized tetrahydrothiophene and 2-(2-bromophenyl)ethyl methyl thioether into the corresponding sulfoxides (>90% *ee*) [60]. Tanaka and coworkers used the method (with CHP as oxidant) to synthesize itomanindole A (80% *ee*) from an indolic disulfide precursor [61]. The monooxidation is fully regioselective. Both

enantiomers of enantiopure methyl *p*-anisyl sulfoxide have been prepared at Syntex (oxidation by CHP) for the synthesis of a chiral sulfone (for evaluation as a cardiovascular drug) [62]. Various aryl methyl sulfoxides have been prepared by Trost and Mallart in the same way [63]. Oxidation by TBHP of 2-aryl-1,3-dithiolanes and 2-aryl-1,3-oxathiolanes gave diastereoselectivities and enantioselectivities (up to 92%) comparable to some enzymatic oxidations of the same substrates [64]. A similar study was performed on 2-methyl-1,3-benzodithiole (*ee* up to 76%) [65]. The monooxidation of 1,3-dithianes (**32**) (Scheme 1.9) has been studied by Kagan *et al.* [66]. The maximum enantioselectivity was obtained at  $-40^{\circ}\text{C}$  (*ee*  $\leq 80\%$ ), with the oxygen introduced *trans* with respect to the more bulky group at C-3. For example, (**33**) ( $\text{R}^1 = \text{CO}_2\text{Et}$ ,  $\text{R}^2 = \text{Me}$ ) was prepared in 80% *ee*. The *ee* is very low (20%) for the unsubstituted 1,3-dithiane. Page *et al.* found that in the standard conditions (TBHP,  $-20^{\circ}\text{C}$ ), 2-acyl-2-substituted-1,3-dithianes give a mixture of *syn* and *anti* monosulfoxides (**33**) with high *ee* in many cases [67]. In a subsequent study, these authors described a basic deacylation process affording the *syn* monosubstituted sulfoxide (**33**) ( $\text{R}^1 = \text{H}$ ) without racemization [68]. For example, (**32**) ( $\text{R}^1 = \text{Ac}$ ,  $\text{R}^2 = \text{Ph}$ ) provided in 71% yield (**33**) (*anti/syn* = 30:1) which was deacylated into (**33**) ( $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{Ph}$ ) in 62% yield (*syn/anti* = 30:1, *syn*: 93% *ee*). The monosulfoxide is always the major product of the oxidation. In the specific case of (**32**) ( $\text{R}^1 = \text{Ac}$ ,  $\text{R}^2 = \text{Ph}$ ), the authors were alternatively able to obtain in 33% yield the corresponding disulfoxide, deacylated into (**34**) ( $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{Ph}$ , 96% *ee*).



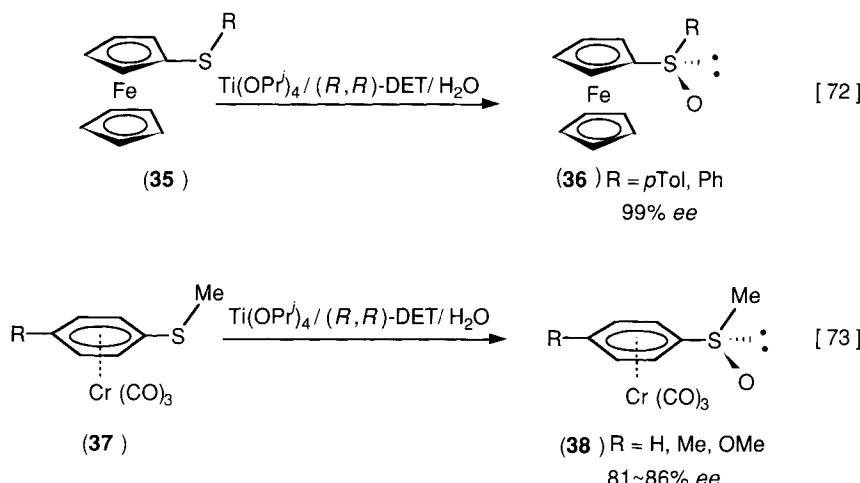
**SCHEME 1.9** Mono and bis *S*-oxidation of 1,3-dithianes

An enantioselective route to 1,3-dithiane 1-oxide (**33**) ( $\text{R}^1 = \text{R}^2 = \text{H}$ ) was subsequently developed [69]. It involves asymmetric oxidation of (**32**) ( $\text{R}^1 = \text{pivaloyl}$ ,  $\text{R}^2 = \text{H}$ ) by cumene hydroperoxide in presence of the chiral titanium complex. The *syn/anti* mixture (around 90% *ee* for each diastereoisomer) is recrystallized and then deacylated, giving the desired product in 80% yield. A recent application of this chemistry is the asymmetric synthesis of enantiopure (*R*)- $(-)$ -2,6-dimethylheptanoic acid in two steps from (**33**) ( $\text{R}^1 = \text{C}(\text{O})\text{Et}$ ,  $\text{R}^2 = \text{Et}$ ) [70]. The reaction involves a fully stereoselective methylation in the  $\alpha$ -position of the keto group, followed by basic deacylation, which also regenerates enantiopure 2-ethyl-1,3-dithiane 1-oxide (**33**) ( $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{Et}$ ). A range of  $\alpha$ -arylpropanoic acids have since been prepared by similar routes in high *ee*'s. [162]

Methyl vinyl sulfoxides of pharmaceutical interest, of general formula  $\text{Me}-\text{S}(\text{O})-\text{CH}=\text{C}(\text{Ar})(\text{R})$ , have been prepared by CHP oxidation in presence of the Kagan reagent. For example, 95% *ee* was obtained when  $\text{Ar} = m\text{-anisyl}$  and  $\text{R} =$

H, and 90% *ee* when Ar = Ph and R = H, while oxaziridine (**29b**) gave 40–42% *ee* [71]. In these cases, biooxidation provides up to 98% *ee* but in low yield.

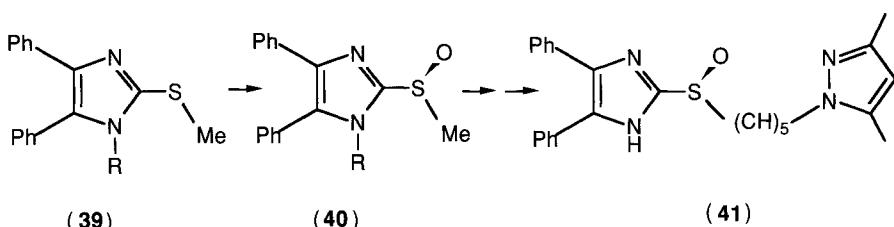
Various metallocene sulfoxides of quite high *ee*'s are now available through the asymmetric oxidation of the corresponding sulfides by the Kagan reagent (Scheme 1.10). Thus aryl ferrocenyl sulfoxides (**36**) ( $\geq 99\%$  *ee*) were prepared by CHP oxidation of (**35**), in presence of the titanium complex prepared under strictly defined conditions [72]. Similar oxidation was used by Gibson, née Thomas, *et al.* for the preparation of sulfinyl substituted tricarbonyl ( $\eta^6$ -arene) chromium(0) complexes (**38**), with *ee*'s of up to 86% [73]. It is remarkable that the conditions are mild enough to avoid overoxidation and destruction of the tricarbonylchromium moiety.



**SCHEME 1.10** Sulfoxidation of metallocenic precursors

The *Modena* reagent has been successful as a resolving reagent (see Section 1.5). A *comparison* between the *Kagan* and *Modena* reagents shows many similarities. The presence of molecular sieves decreases the enantioselectivity of the *Modena* reagent [54]. This effect could be related to the complete dryness during the whole course of the reaction or to a structural modification of the titanium complex induced by the sieves. Some differences in the influence of temperature have been noticed between the two reagents [59,74]. Aggarwal *et al.* recently made a detailed comparative study of the two reagents for the oxidation of 2-substituted-1,3-dithianes (**32**) [75]. Aggarwal found that it is difficult to prepare the disulfoxide (**34**) with the *Kagan* reagent, even in the presence of an excess of CHP. By contrast, the *Modena* reagent provides a faster reaction, giving (**34**) ( $R^1 = CO_2Et$ ,  $R^2 = H$ ) in 80% yield ( $\geq 97\% ee$ ). The very high *ee* comes in part during the separation of the meso disulfoxide (minor component); the actual enantioselectivity given by the *Modena* reagent can be estimated to be 85% *ee* in the formation of the parent monosulfoxide (**33**). Its saponification, followed by decarboxylation, gives enantiopure disulfoxide (**34**) ( $R^1 = R^2 = H$ ), a useful chiral auxiliary for asymmetric synthesis [76].

It has been reported that the Kagan reagent and CHP oxidized an *N*-protected 2-*S*-methylindole with moderate *ee* (50–70%), while the Modena procedure afforded the sulfoxide in 80% *ee* [77]. A related example was described by a team at Rhône-Poulenc-Rorer (Scheme 1.11) [18]. Asymmetric oxidation of sulfide (39) was the key step of the synthesis of the drug (41). A detailed investigation showed that the best procedure was neither the original Kagan or Modena reagents but a combination ( $\text{Ti}(\text{OPr})_4/\text{DET} = 1:2$ ), using cumyl hydroperoxide as oxidant. With the free NH ( $\text{R} = \text{H}$ ), the *ee* is only 65%, but it is in the range of 90–95% for various protecting groups ( $\text{R} \neq \text{H}$ ).



**SCHEME 1.11** Asymmetric sulfoxidation (cumene hydroperoxide,  $\text{Ti}(\text{OPr})_4/\text{DET} = 1:2$ ) in industry [78]

### 1.3.4 Achiral Oxidants in the Presence of Chiral Auxiliaries or Other Chiral Oxidants

There are many examples of limited asymmetric induction where an oxidant is used in the presence of a chiral additive. For example, sodium metaperiodate on alumina in the presence of (–)-menthol or (–)-2-methylbutan-1-ol provides methyl phenyl sulfoxide of 48% *ee* and 52% *ee*, respectively [79].

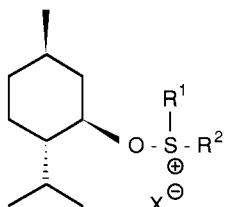
Various halogenating agents in the presence of a chiral additive have been used as oxidant systems to prepare sulfoxides (usually in low *ee*). Thus, the combinations iodine/water/(+)-2-methyl-2-phenylsuccinic acid [80] or *N*-chloroamides/chiral alcohols [81–83] gave sulfoxides with ~10% *ee* at best. Menthylloxysulfonium salts are prepared by oxidation of sulfides in presence of menthol. They can be isolated and recrystallized, with improvement of the diastereoisomeric excess. They are interesting intermediates for the synthesis of chiral sulfoxides, which are obtained by aqueous basic hydrolysis, with inversion of configuration at sulfur. Sulfoxide may also be obtained (in lower *ee*) by a one-pot reaction, without isolation of the sulfonium salt. Thus, 1-chlorobenzotriazole in the presence of (–)-menthol in methylenechloride oxidizes benzyl *p*-tolyl sulfide into the sulfonium salt (42a) (Figure 1.3). After crystallization and hydrolysis, (–)-benzyl *p*-tolyl sulfoxide is afforded in 87% *ee* [84]. A chiral derivative of *N*-chlorocaprolactam has been used to prepare some sulfoxides in low *ee* [85].

Imamoto and Koto prepared chiral hypervalent iodo reagents (43) by the reaction of tartaric anhydride derivatives with iodosylbenzene. Sulfoxides are formed in good yields with *ee*'s up to 50% [86]. A similar approach was developed

by Koser and Ray, by the preparation of iodinane (**44**) from menthol and  $\text{PhI}(\text{OMe})(\text{OTs})$ . This chiral reagent reacts with sulfides to give (menthyl)oxysulfonium tosylates (**42b**) ( $de \leq 57\%$ ) which are transformed by a basic hydrolysis into sulfoxides ( $ee \leq 57\%$ ) [87]. Sulfonium salt (**45**) has recently been prepared by bromine oxidation of the corresponding sulfide in the presence of (-)-menthol [88]. Its absolute configuration has been established by x-ray crystallography on a recrystallized sample (100%  $ee$ ). Hydrolysis provided a sulfoxide (73%  $ee$ ) with retention of stereochemistry, presumably a result of the bulkiness of the *ortho* substituent forcing the reaction to proceed by an elimination mechanism (and concomitant formation of menthene). The one-pot reaction (combination of sulfide oxidation followed by hydrolysis) afforded sulfoxide of 50%  $ee$ .

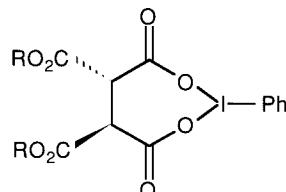
Treatment of sulfides by various oxidants in the presence of  $\beta$ -cyclodextrins (host for the sulfides) provided sulfoxides with moderate  $ee$ 's ( $\leq 40\% ee$ ) [89,90]. The alkyl aryl sulfides, in crystalline cyclodextrin suspended in a solvent, could be oxidized by various agents ( $\text{CH}_3\text{CO}_2\text{H}$ , TBHP,  $\text{H}_2\text{O}_2$ , or  $\text{NaOCl}$ ). The heterogeneous reaction gave up 80%  $ee$  [91].

Oxidation of sulfides in the presence of bovine serum albumin (BSA) gave sulfoxides with quite high  $ee$ 's (up to 90%) [92–94]. Moreover, the reaction could be carried out catalytically with respect to BSA. Ogura *et al.* used  $\text{NaIO}_4/\text{BSA}$  in a two-phase system for the oxidation of formaldehyde dithioacetals [95], while Colonna *et al.* took BSA (5% mol equiv) in buffer solution for oxidation of various sulfides [96–99].

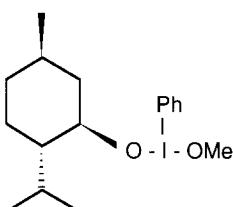


(42)

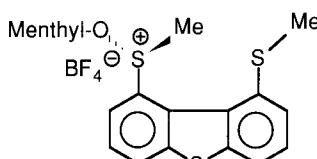
- (a) R<sup>1</sup> = Bn, R<sup>2</sup> = *p*Tol, X = BF<sub>4</sub><sup>-</sup>  
 (b) R<sup>1</sup> = Me, R<sup>2</sup> = *p*Tol, Bn or Bu<sup>t</sup>, X = OTs



(43)



(44)



(45)

FIGURE 1.3 Intermediates or reagents for asymmetric sulfoxidation.

## 1.4 CATALYTIC CHEMICAL ASYMMETRIC SULFOXIDATION

The *catalytic* asymmetric oxidation of prochiral sulfides by chemical means is a difficult task. While a number of workers have been active in this area during the past few years, few systems simultaneously show good induction of chirality and good catalytic activity. The most common catalysts involve transition-metal complexes (homogeneous or supported) as well as chiral electrodes. These approaches are described successively below.

### 1.4.1 Titanium Complexes

Methyl *p*-tolyl sulfide is oxidized to the corresponding sulfoxide in high enantiomeric excess (in the range of 80–96%) when the reagent developed by Kagan and colleagues is employed [50]. However, the standard conditions use a stoichiometric amount of the chiral titanium complex  $(\text{Ti}(\text{OPr}^i)_4/\text{DET}/\text{H}_2\text{O}$  in ratio 1:2:1). In the Kagan system, experimental conditions have been sought in order to decrease the amount of titanium complex without significant alteration of the enantiomeric excess achieved. Catalytic reactions using the Sharpless epoxidation have been achieved by the addition of molecular sieves [46] to suppress the formation of nonenantioselective complexes in the medium or those produced by the liberation of water during the reaction. For the catalytic asymmetric sulfoxidation, molecular sieves have been employed with the titanium complex [54] with an excess of diethyl tartrate  $(\text{Ti}(\text{OPr}^i)_4/\text{DET}$ , 1:4). The *ee* of the sulfoxides, for example methyl *p*-tolyl sulfoxide, remains quite good down to 20 mol% of catalyst (88% *ee*), but a significant decrease is found at 15 (76% *ee*) and 10 mol% of titanium complex (70% *ee*). Although the chemical yield is good, the sulfoxidation is then 200 times slower than the stoichiometric oxidation. This perhaps allows the effective catalyst to equilibrate with many other titanium species which can also perform the catalytic reaction, but which are less enantioselective.

The development of other efficient methods for the enantioselective oxidation of sulfides to sulfoxides has been pursued for many years. Various chiral additives and metal complexes have been investigated. However, most of these systems have disadvantages such as formation of sulfone, long reaction times, unsatisfactory yields and poor enantiomeric excesses. Diethyl tartrate remains the additive (combined with titanium alcoholates) which gives the best results in terms of enantioselectivity. Since 1989, it has been found that other chiral ligands can be efficient in asymmetric induction.

Pasini *et al.* [100] developed chiral oxotitanium(IV) complexes with Schiff bases (46) (Figure 1.4), which are highly efficient catalysts (0.1–0.07 mol%) for asymmetric oxidation of methyl phenyl sulfide by 35%  $\text{H}_2\text{O}_2$  in a mixture of aqueous ethanol and dichloromethane. However, these complexes are not very enantioselective: the *ee* remains below 20% and the corresponding sulfones are also formed.

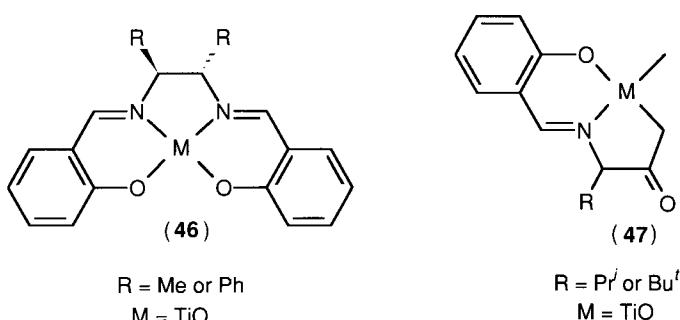


FIGURE 1.4 Chiral complexes of titanium [101,102].

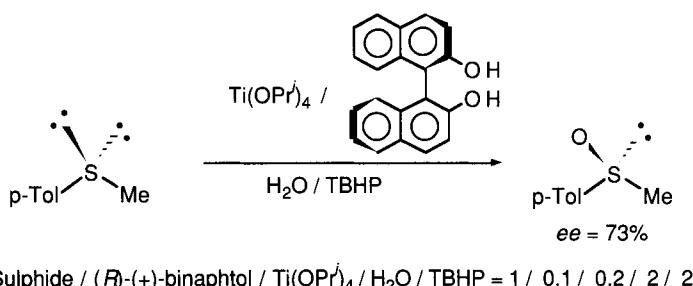
A similar methodology was applied by Colonna *et al.* [101] to the oxidation of aryl alkyl sulfides with  $\text{Bu}^i\text{OOH}$  as oxidizing agent and a catalytic amount of a titanium *N*-salicylidene-L-amino acid complex (47) (0.1 mol equiv) in benzene at room temperature. This catalyst is not very enantioselective, and often yields mixtures of sulfoxides and sulfones. The highest enantioselectivity was achieved in the oxidation of *t*-butyl (*p*-nitrophenylthio)acetate, which gave sulfoxide in 21% *ee* and 25% yield. Like the Kagan reagent, but to a lesser measure, the use of a stoichiometric amount of titanium complex substantially influences the enantioselectivity, which increases from 12% (catalytic) to 21% (stoichiometric) for the oxidation of methyl *p*-tolyl sulfide.

Another asymmetric sulfoxidation reported by Fujita *et al.* [102] used a chiral binuclear titanium(IV) complex (4 mol% equiv) in methanol with trityl hydroperoxide at 0°C, which gave methyl phenyl sulfoxide with an *ee* of 53% and a good yield (87%). The complex was prepared by treating  $\text{TiCl}_4$  in pyridine with *N,N'*-disalicylidene-(*R,R*)-1,2-cyclohexanediamine. The structure of the catalyst was determined by x-ray analysis. A binuclear titanium(IV) complex was present with an oxygen bridge between the two titanium atoms (Ti—O—Ti unit). This oxygen apparently comes from atmospheric or solvent moisture. Each titanium atom is octahedrally coordinated, and the planes of each titanium atom with its associated Schiff bases are almost parallel to each other.

Uemura *et al.* [103] developed an efficient catalytic and enantioselective oxidation of prochiral sulfides. As in the Kagan system, a titanium(IV) complex is produced *in situ* from a titanium alkoxide and two *R*-(+)-binaphthols (Scheme 1.12) as chiral auxiliaries (in place of diethyl tartrate), in the presence of a large amount of water (more than 1 equivalent). The oxidation of methyl *p*-tolyl sulfide gives the corresponding sulfoxide in 45 h in 90% yield and 73% *ee*.

In this procedure, the complex is formed in toluene and can be used over a range of temperatures (0 to  $-25^\circ\text{C}$ ), without any effect upon the enantioselectivity. The originality of this procedure is the amount of water utilized, more than 1 unusual feature of water per sulfide being essential to produce an effective catalyst, both for high enantioselectivity and to retain the catalytic activity of the titanium-binaphthol complex for an extended time.

More recently, Uemura *et al.* [104] have actively developed this sulfoxidation



**SCHEME 1.12** Asymmetric induction by binaphthol in sulfoxidation with titanium complexes [103].

and have attempted to define the scope and limitations of their approach. The different parameters that can increase the enantioselectivity have been studied. This procedure has allowed the preparation of methyl *p*-tolyl sulfoxide with 96% *ee* in 24% yield. A lesser amount of catalyst was used (2.5 in place of 10 mol% equiv), and a larger proportion of water (up to 20 mol equiv per sulfide). It was found that the high *ee* originates from the fact that the complex formed from  $\text{Ti}(\text{OPr})_4$  and binaphthol in toluene catalyses the kinetic resolution of the sulfoxide. In fact, the chiral (*R*)-methyl *p*-tolyl sulfoxide is initially formed with 50% *ee* (see Section 1.6.2). In spite of the good enantioselectivity of this method, the applicable sulfides were limited mainly to aryl alkyl sulfides. The selectivity is unsatisfactory with a dialkyl sulfide substrate.

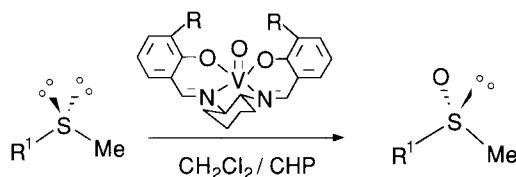
### 1.4.2 Vanadium Complexes

Fujita *et al.* used a catalytic amount of a binuclear titanium(IV) complex in an attempt to find an efficient system to oxidize sulfides with high enantioselectivity [102]. Prior to this study, they investigated other systems with several transition metals. A similar asymmetric sulfoxidation was discovered [105] using a catalytic amount of nonracemic Schiff base oxovanadium complex (Table 1.4) under atmospheric conditions at room temperature in dichloromethane. With 0.1 mol% of catalyst and cumene hydroperoxide as oxidant, oxidation produces sulfoxides in excellent yields. However, the reaction is limited to alkyl aryl sulfide substrates, and the best enantioselectivity obtained was 40% *ee*, for (*S*)-methyl *p*-methoxy phenyl sulfoxide.

### 1.4.3 Manganese Complexes

Oxometalloporphyrins are active intermediates in the catalytic oxygenation cycle of peroxidase and cytochrome P450. These catalysts have been adapted by several groups for enantioselective sulfoxidation using different transition metals and various oxygen sources. The first efficient catalytic oxidation of a sulfide was

**TABLE 1.4** Influence of substituent on the vanadium catalyst upon the asymmetric oxidation of methyl aryl sulfide



R <sup>a</sup>	R <sup>1</sup>	ee (%) <sup>b</sup>	Yield (%) <sup>c</sup>
H	Ph	21	77
OMe	Ph	40	96
OMe	<i>p</i> -Tol	35	71
OMe	2-Naphthyl	30	76
OEt	Ph	40	81
Bu <sup>t</sup>	Ph	10	70

<sup>a</sup>Substituent on the vanadium catalyst.

<sup>b</sup>Based on the optical rotation of the pure enantiomer.

Isolated yields.

developed by Ando *et al.* [106], who used an achiral metalloporphyrin of manganese or iron and iodosobenzene as oxidant. The catalyst is capable of transferring oxygen to form the corresponding sulfoxide highly selectively, with a turnover number as high as 100.

A  $D_4$  symmetric manganese tetraphenylporphyrin (48) (Figure 1.5) has been employed by Halterman *et al.* [107] for catalytic oxidation with iodosobenzene. The reaction proceeds with 0.025 mol% of catalyst at room temperature in dichloromethane to give the sulfoxide in less than 2 h. The yield is above 90% and the enantioselectivities range from 40% to 68%. With very reactive substrates, however, the reaction proceeded with low *ee*, and a large amount of the sulfone was obtained.

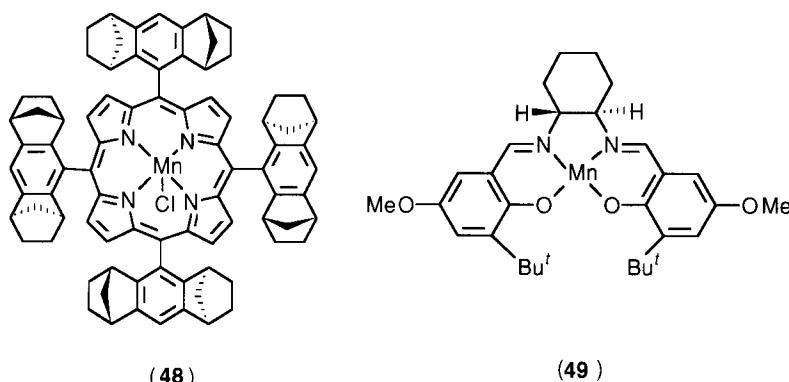


FIGURE 1.5 Manganese complexes in asymmetric sulfoxidation.

Another method, described by Jacobsen *et al.* [108], involves oxidizing the sulfide in the presence of an optically active Salen manganese(III) chloride complex (**49**). Alkyl aryl sulfides were oxidized at room temperature in 1 h with 2 mol% of catalyst using hydrogen peroxide as the stoichiometric oxidant. Sulfoxide yields are generally high (84–95%), with minimal overoxidation to sulfone. However, enantioselectivities are only moderate: 34% and 68% for 2-methoxyphenyl methyl sulfoxide and 2-bromophenyl methyl sulfoxide, respectively (Table 1.5).

Sulfoxidation with the above catalysts and hydrogen peroxide [108] or iodosobenzene [107], gave similar yields of sulfoxides, very small amounts of sulfone, and nearly identical enantioselectivities.

More recently, Katsuki *et al.* [109] prepared the Salen manganese complex (**50**) (Figure 1.6), which is efficient in the oxidation of alkyl aryl sulfide with iodosobenzene as oxidant. With 1 mol% of catalyst, they obtained the 2-nitrophenyl methyl sulfoxide in 1 h at  $-20^{\circ}\text{C}$  in acetonitrile solution with 90% *ee* and 88% yield. This is currently one of the best results for catalytic asymmetric sulfoxidation.

#### 1.4.4 Iron Complexes

The first examples of asymmetric oxidation of sulfides with significant *ee*'s using metalloporphyrins (**51**) (Figure 1.7) were published only fairly recently. Naruta *et*

**TABLE 1.5** Asymmetric oxidation of alkyl aryl sulfide using manganese catalyst

Entry	Ar	R	Sulfide		Catalyst ( <b>48</b> ) [107] <sup>a</sup>	Catalyst ( <b>49</b> ) [108] <sup>b</sup>
			ee (%) <sup>c</sup>	Yield (%) <sup>d</sup>	ee (%) <sup>e</sup>	Yield (%) <sup>f</sup>
1	Phenyl	Methyl	47	90	55	93
2	<i>o</i> -Bromophenyl	Methyl	68	80	68	99
3	<i>p</i> -Bromophenyl	Methyl	56	93	59	98
4	<i>p</i> -Tolyl	Methyl	42	95	—	—
5	<i>p</i> -Methoxyphenyl	Methyl	34	94	40	99
6	<i>o</i> -Iodophenyl	Methyl	65	95	—	—
7	Phenyl	Ethyl	—	—	42	82
8	2-Naphthyl	Methyl	46	84	—	—
9	<i>p</i> -Nitrophenyl	Methyl	66	86	—	—
10	<i>m</i> -Nitrophenyl	Methyl	63	84	—	—

<sup>a</sup>Condition: (**48**);  $\text{H}_2\text{O}_2$ ; substrate of 1:50:50 in  $\text{CH}_3\text{CN}$  at  $20^{\circ}\text{C}$ .

<sup>b</sup>Condition: (**49**); iodosobenzene; substrate of 1:200:400 in  $\text{CH}_2\text{Cl}_2$  at  $20^{\circ}\text{C}$ .

<sup>c</sup>Values of *ee* were determined by HPLC using a Chiralcel OD column except for entries 9 and 10, which were determined by  $^1\text{H}$  NMR in presence of (*R*)(*–*)-2,2,2-trifluoro-1-(9-anthryl) ethanol.

<sup>d</sup>The sulfoxides were isolated pure by flash chromatography.

<sup>e</sup>Values of *ee* were determined by  $\beta$ -cyclodextrin chiral capillary gas chromatography or by  $^1\text{H}$  NMR spectrometry in presence of  $\text{Eu}(\text{hfc})_3$  or (*R*)(*+*)-1,1'-binaphthyl-2,2'-diol.

<sup>f</sup>Yield determined by gas chromatography and  $^1\text{H}$  NMR spectrometry.

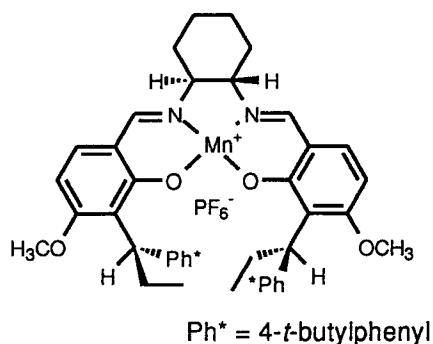
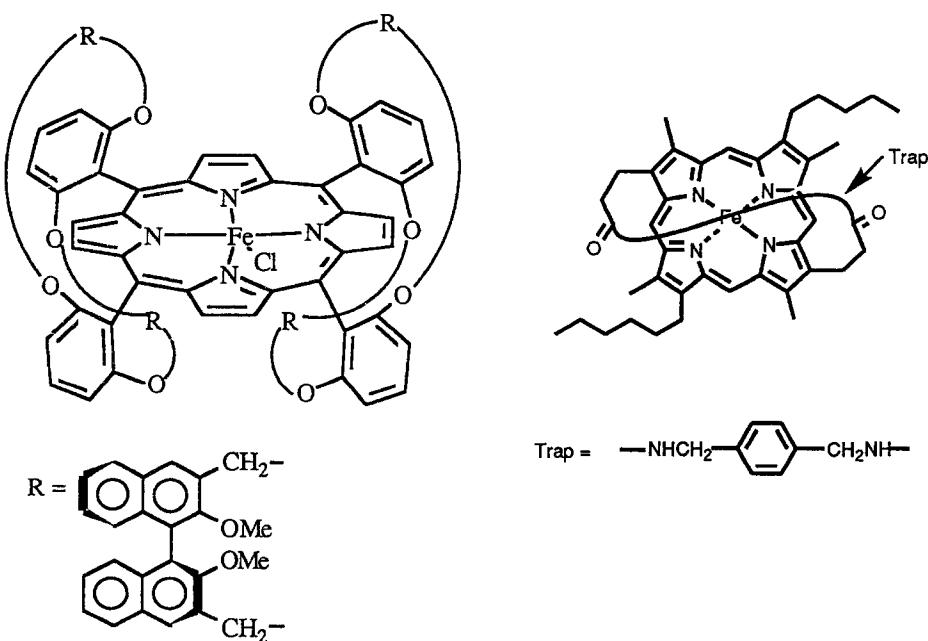


FIGURE 1.6 Chiral Salen manganese complex of Katsuki [110].

FIGURE 1.7 Iron porphyrins **51** [111,115].

al. [110] found that iron porphyrins modified by chiral binaphthalenes on both faces catalyse the oxidation of sulfides with good enantioselectivity.

This  $C_2$  symmetrical complex was used as a catalyst with iodosobenzene as oxidant in presence of 1-methylimidazole as an axial ligand. The turnover number is dependent on the substrates and fluctuates between 55 and 290. The enantiomeric excess is noticeably improved to 73% (31% without this reagent) for

methyl pentafluorophenyl sulfide. These results can be attributed to the steric action of imidazole around sulfur rather than to electronic effects. In 1991, the same authors [111] completed this work. Little improvement has been brought to the enantioselectivity, but a mechanistic model has been proposed to explain the asymmetric induction. This mechanism is based on steric control: the two binaphthyl moieties, facing each other over the macrocycles, form chiral cavities on the two faces which direct the approach of substrates and oxidant to the active metal centre.

Groves and colleagues reported similar results [112] with a binaphthyl iron(III) tetraphenylporphyrin as a catalyst (0.1 mol% equiv) and iodosobenzene as oxidant. Prochiral alkyl sulfide substrates gave sulfoxides in 14% to 48% *ee* with some overoxidation to sulfones (8%).

An iron porphyrin bearing (*S*)-naphthylpropionic amide groups has been synthesized by Zhou *et al.* [113]. With 10% of catalyst, methyl phenyl sulfide was oxidized in 94% yield, but with only 8% *ee*. The addition of imidazole increased the optical purity to 15%, but the yield of the reaction decreased to 79%.

In an analogous approach, the effect of imidazole was also observed by Inoue *et al.* [114]. When alkyl aryl sulfides were oxidized with a novel iron porphyrin catalyst (**52**) (0.2 mol% equiv), the reaction proceeded enantioselectively under appropriate conditions. Iodosobenzene was used as oxidant in dichloromethane at  $-43^{\circ}\text{C}$ . The turnover number increases to 142, and an *ee* of 73% was obtained in the presence of a 100 to 600 molar ratio of imidazole to catalyst for the synthesis of (*S*)-methoxymethyl phenyl sulfoxide. In the absence of imidazole, the enantioselectivity disappeared, giving the racemic sulfoxide.

As for the Naruta model [112], the mechanism is based on steric control, but chiral cavities are not present here. The catalyst has two chemically nonequivalent diastereotopic faces with different steric requirements for the access of substrates and/or oxidant. The unstrapped face of this catalyst is probably blocked by the

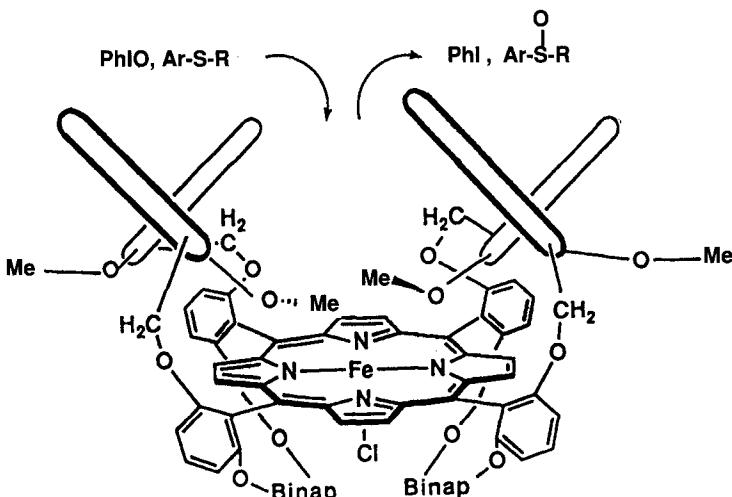


FIGURE 1.8 Conformation of iron porphyrins in asymmetric sulfoxidation.

coordination of imidazole, and the transfer of oxygen is considered to occur predominantly on the sterically hindered face.

### 1.4.5 Chiral Electrodes

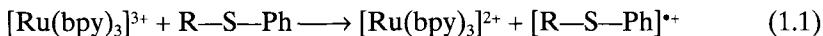
Among the less common methods of asymmetric oxidation of sulfides is electrochemical oxidation, which can be carried out by various modified electrodes. The first example was reported by Firht and Miller [115] in 1976. In spite of several improvements, the enantiomeric excess remained below 3% for the oxidation of aryl methyl sulfides.

The method was reinvestigated by Komori and Nonaka [116], who found high enantiomeric excesses for many alkyl aryl sulfides. Different kinds of electrodes effective for achieving chiral induction were prepared using poly(amino acid)s. The compounds were coated on the electrode simply by dipping a base electrode into poly(amino acid) solution; alternatively, the amino acid could be bound with a single or double coating of polypyrrole film. The asymmetric oxidations of sulfides were carried out by means of a controlled potential method in acetonitrile solution containing tetra-*n*-butylammonium tetrafluoroborate and water as supporting electrolyte and oxygen source. The chiral electrodes for electrosynthesis must be durable, otherwise the enantiomeric excess decreases. Several models have been tested in different oxidations, the best result being obtained with the more robust electrodes prepared by double-coating a platinum electrode with polypyrrole film and poly(L-valine). The covalently bound polymer layers were durable, but, when the electrode was reused, the asymmetric induction decreased slightly. Several sulfides were oxidized by this method; the enantioselectivities are greatly affected by the alkyl group. Methyl phenyl sulfide gives a low enantiomeric excess (below 2%). Higher enantioselectivities are obtained with isopropyl phenyl sulfide (77% *ee*) and *t*-butyl phenyl sulfide (93% *ee*). All the sulfoxides produced have the (*S*) configuration, but the detailed picture of the origin of asymmetric induction is unknown. This approach would be synthetically promising if there were not the delicate preparation of the coated electrodes to be considered.

### 1.4.6 Supported Complexes

The use of solid catalysts in liquid-phase reactions for selective organic oxidations affording significant enantioselectivity has been relatively unexplored. In 1989, it was shown that an ion-exchange adduct of a clay and a chiral metal complex can be useful in asymmetric synthesis [117]. In this process, the chiral auxiliary is adsorbed on the surface, leaving half of the active sites unoccupied. The prochiral substrate can be accommodated by these chiral sites. The photooxidation of the sulfide is performed in a mixture of methanol/water (1:4) by stirring the clay-chelate adduct (0.5 mol equiv) under bubbling oxygen gas with illumination by a 500 W tungsten lamp. In a first stage,  $\lambda$  or  $\Delta$ -(2,2'-bipy)<sub>3</sub>RuCl<sub>2</sub> (the photosensitive compounds) reacts with O<sub>2</sub> to provide O<sub>2</sub><sup>-</sup> and [Ru(bipy)<sub>3</sub>]<sup>3+</sup>. This

complex reacts with a sulfide, resulting in the one-electron oxidation of the sulfide (equation 1.1).

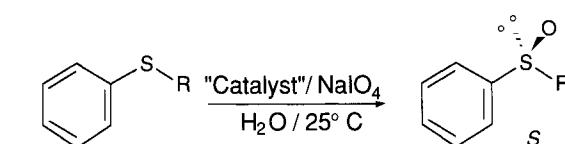


The attack of molecular oxygen on the one-electron oxidized sulfide forms a sulfoxide in less than 2 h without further overoxidation to the corresponding sulfone. However, the enantioselectivity is still unsatisfactory: the enantiomeric excess is always between 15% and 20% for a large variety of alkyl sulfides. The ruthenium complex itself, used under homogeneous conditions, led to racemic sulfoxides, in agreement with the hypothesis of asymmetric control during oxidation of absorbed sulfide. This is the first heterogeneous catalyst showing enantioselection in asymmetric sulfoxidation as well as selectivity for the sulfoxide formation.

In another system [118], a prochiral sulfide is chemically converted into an optically active sulfoxide with appreciable enantioselectivity ( $ee \leq 80\%$ ) upon reaction on the surface of a clay–chelate adduct,  $\Delta$ -tris-(1,10-Phenanthroline) nickel(II)–montmorillonite. The sulfide is added to a mixture of methanol/water (3:2) and is absorbed by the adduct. Under these conditions, the oxidation is effective with sodium periodate at room temperature in excellent yield (range of 80–90%) (Table 1.6).

In 1992, a montmorillonite catalyst was used by Choudary *et al.* in another catalytic system for selective oxidation in a liquid phase reaction [119]. A vanadium pillared clay (V-PILC), which was prepared by refluxing  $\text{VOCl}_3$  in benzene with H-montmorillonite, was used as the catalyst. The solid was filtered, and the resulting clay was found to have 14% of its weight of intercalated vanadium. X-Ray analysis showed an increase in dimensions of montmorillonite

**TABLE 1.6** Asymmetric oxidation of alkyl aryl sulfide by  $\Delta$ -tris(1,10 phenanthroline) nickel(II)–montmorillonite and  $\text{NaIO}_4$



R	ee (%) <sup>a</sup>	Yield (%) <sup>b</sup>
Me	0	95
Et	9	90
Bu <sup>s</sup>	65	90
Bu <sup>n</sup>	75	90
Bn	70	95
	78	90

<sup>a</sup>Based on the optical rotation of the pure enantiomer.

<sup>b</sup>Isolated yield.

due to the intercalation of the polymeric vanadium species. Many aryl methyl sulfides were investigated in asymmetric oxidation with this catalyst modified by (*R,R*)-(+)-diethyl tartrate (7 mol equivalents). The reaction was complete within 1.5 h using 1 mol% of this catalyst at  $-20^{\circ}\text{C}$  in dichloromethane solution. The substrate and the oxidant ( $\text{Bu}^{\prime}\text{OOH}$ ) were added to the mixture and the sulfoxide was obtained selectively in excellent yield (98%), even when the catalyst was reused following simple filtration. Unfortunately, the enantioselectivity was quite low, only 25% *ee* for the oxidation of methyl *p*-tolyl sulfide. Racemic material resulted from oxidation with recovered catalyst.

Various compounds containing  $\text{V}_2\text{O}_5$  and other supported phases such as alumina or silica have been compared with (V-PILC), but only poor performance has been found.

In summary, these catalytic systems can provide efficient methods for sulfoxidation with the advantages of high activity, selectivity, reusability, short reaction time, and enantioselectivities which are not negligible and which in principle can be improved with further research.

#### 1.4.7 Imines and Iminium Salts

Imines are oxidized by oxidants such as mCPBA into oxaziridines, which are good reagents for oxidation of sulfides [40]. It is possible, in principle, to use a catalytic amount of imine for sulfoxidation if the auxiliary oxidant reacts faster with imine than with sulfoxide. Unfortunately, there have been few successes in this area, which would open the route to catalytic asymmetric sulfoxidation. The enantiomeric excess observed by Lusinchi *et al.* [120a] in the oxidation of methyl *p*-tolyl sulfide by oxone was of 43% in presence of stoichiometric amount of chiral iminium salt. Achiral iminium salts were also used as catalysts in combination with oxone in sulfoxidations, with 60–70% yield [120b], and a BINAP-derived chiral iminium salt has been used in a derivative epoxidation process, providing high yields and *ee*'s [163]. Bulman Page has developed a catalytic system using chiral imines derived from camphor as enantioselective mediators and aqueous hydrogen peroxide as the stoichiometric oxidant, which has proved particularly effective for the oxidation of non-aryl sulfides, nicely complementing other systems in the literature [164].

### 1.5 Biosulfoxidations

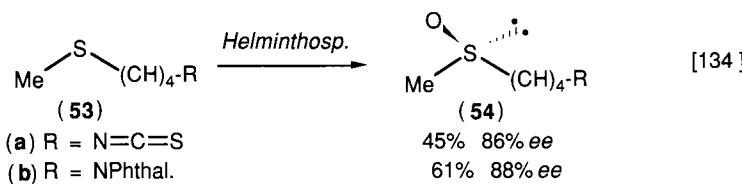
Biosulfoxidations were first studied in the late 1960s [121]. The area is now a very active field of interest both for biochemistry and for organic chemistry, and a few reviews on biosulfoxidations have appeared [39, 122–124]. Most of the studies involve microorganisms, but there is also the possibility of using an isolated enzyme and an oxidant. Both approaches have been described. Herein are presented the main trends of methods which, while perhaps not of general application, give excellent results in many cases.

### 1.5.1 Microorganisms

The use of intact cells is the easiest procedure. Henbest, in pioneering work, investigated sulfoxidations by *Aspergillus niger* [121]. (*R*)-Alkyl *p*-tolyl sulfoxides were prepared, sometimes with high *ee*'s: for example, *t*-butyl, isopropyl and methyl substrates gave *ee*'s of 98%, 70%, and 32%, respectively. Experiments were performed on small scale, with a low yield. Sih *et al.* found that oxidation of methyl *p*-tolyl sulfide by *Mortierella isabellina* NRRL 1757 and *Helminthosporium* sp. NRRL 4671 gave in good yields enantiopure (*R*) and (*S*) sulfoxides, respectively [125]. Later, the influence of the *para*-substitution in the oxidation of *para*-substituted methyl phenyl sulfides by *Mortierella isabellina* was investigated by Holland *et al.* [126]. Enantiomeric excesses ranged from 20% (*p*-nitrophenyl) to 100% (*p*-chlorophenyl). *Helminthosporium* NRRL 4671 has also been studied by the same authors in the oxidation of various aryl or benzyl alkyl sulfides [127]. *Mortierella isabellina*, *Helminthosporium* sp., and *Fusarium oxysporum* have been used for the oxidation of vinyl sulfides  $\text{Me}-\text{S}-\text{CH}=\text{C}(\text{Ar})(\text{R})$ , with *ee*'s up to 98% being obtained but with low chemical yields [70,128]. *Corynbacterium equi* IFO 3730 is highly enantioselective in the oxidation of aryl alkyl sulfides [129].

Thioacetals have been oxidized to their monosulfoxides by various fungal species with *ee*'s up to 70% [130,131]. This last result was obtained in the oxidation of 2-*t*-butyl-1,3-dithiane by *Helminthosporium* fungus into *trans*-2-*t*-butyl-1,3-dithiane 1-oxide.

Baker's yeast (*Saccharomyces cerevisiae*) contains a desaturase which is able to oxidize some almost symmetrical sulfides such as methyl thiostearate [132]. A less symmetrical sulfide,  $\text{Bn}-\text{S}-(\text{CH}_2)_7-\text{CO}_2\text{Me}$ , has been oxidized by *Saccharomyces cerevisiae* into an (*S*)-sulfoxide with 70% *ee*. The stereochemical course of the oxidation by *S. cerevisiae* of quasisymmetrical sulfides such as methyl 9-thiostearate has been established and found highly enantioselective (>95% *ee*) [133]. Recently, biosulfoxidation by the fungus *Helminthosporium* ARRL 4671 has been applied to the synthesis of (*R*)-(-)-sulforaphane (**54a**) (Scheme 1.13) [134]. This compound has interesting biological properties.



SCHEME 1.13 An example of biosulfoxidation [134]

### 1.5.2 Isolated Enzymes

Cytochrome P450 is a fundamental monooxygenase present in mammalian tissues. Oae *et al.* used rabbit liver microsomes for the oxidation of simple prochiral

sulfides (*ee* up to 54%) [135]. Walsh *et al.* studied the air oxidation of *p*-tolyl ethyl sulfide catalysed by two cytochrome P450 isoenzymes, which gave (*S*)-sulfoxide in ~80% *ee* [136]. Dopamine  $\beta$ -hydroxylase (DBH), a copper monooxygenase, catalysed the benzylic oxidation of dopamine to norepinephrine. Replacement of a benzylic carbon by a sulfur atom was investigated in a model system,  $\text{PhSCH}_2\text{CH}_2\text{NH}_2$ . May and Phillips found that the oxidation by oxygen in the presence of DBH produced the (*S*)-aminosulfoxide with a high *ee* and the same stereochemistry as in the dopamine oxidation [137]. Oxidation of *p*-tolyl methyl sulfide by a monooxygenase containing flavin-adenine dinucleotide (FAD) gave the (*R*)-sulfoxide (95% *ee*) [138]. Purified microsomal flavin-containing monooxygenase from hog liver, as well as cytochrome P450 from rat or mouse liver, was used by Cashman *et al.* in the oxidation of 2-(4-methoxyphenyl)-1,3-dithiolane and 2-(4-cyanophenyl)-1,3-oxathiolane. Very high *ee*'s (>90%) of the *trans*-sulfoxides were achieved [64,65].

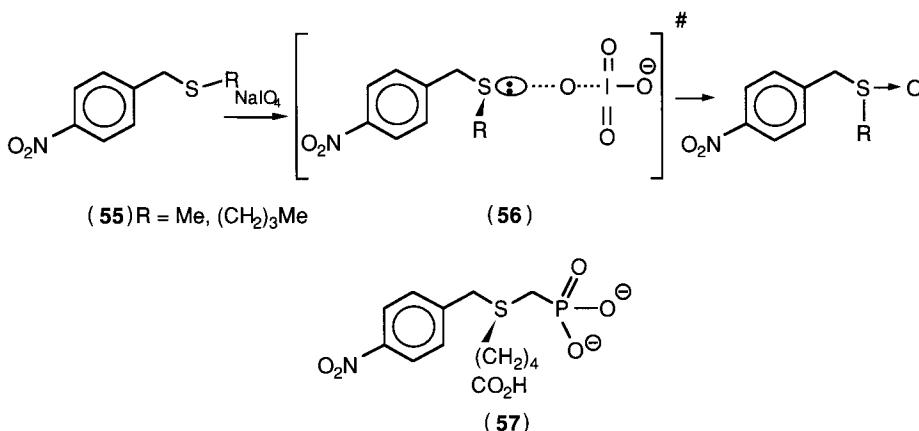
*Pseudomonas oliveorans* monooxygenase (POM) is an ' $\omega$ -hydroxylase', for hydroxylation of terminal methyl group of alkanes and epoxidation of terminal olefins. A reconstituted system in presence of NADH and oxygen oxidizes a large number of methyl alkyl sulfides with *ee*'s up to 80% [139]. Chloroperoxidase, isolated from *Caldariomyces fumago*, was found by Colonna *et al.* to catalyse the oxidation of sulfides by oxidants such as hydrogen peroxide, iodosobenzene or hydroperoxides. *t*-Butyl hydroperoxide gave the best results [140,141]. Reactions were performed in water at pH 5 with  $1.6 \times 10^{-5}$  mol equivalents of catalyst. For example, (*R*)-*p*-tolyl methyl sulfoxide and (*R*)-benzyl methyl sulfoxide were prepared in good yields and with 91% and 92% *ee*, respectively. 1,3-Dithiane 1-oxide is also produced with very high *ee* [165]. Chloroperoxidase has also been investigated by Wong *et al.* [142]. Excellent yields (66–92%) and enantiomeric excesses (97–100%) were observed with hydrogen peroxide as oxidant, under optimized experimental conditions (low substrate concentration). Racemic 1-phenylethyl hydroperoxides were also used in these oxidation reactions and are simultaneously kinetically resolved.

A systematic study of the sulfoxidation by cyclohexanone monooxygenase from *Acinetobacter* using as the substrates many alkyl aryl sulfides, dialkyl sulfides and dialkyl disulfides has been carried out by Carrea, Colonna, and colleagues in the presence of NADP and a NADPH-regenerating system [143,144]. Chemical yields are good (at 0.8 mmol scale), with wide variations of *ee*'s (from 0 to 98%) according to the structure of the sulfides.

Horseradish peroxidase catalyzes oxidation by hydrogen peroxide of several aryl methyl sulfides with moderate enantioselectivity (0–68%) [145]. Molecular engineering of horseradish peroxidase allowed the enantioselectivity of sulfoxidation to increase considerably. Ozaki and Ortiz de Montellano prepared a Phe-41 $\rightarrow$ Leu mutant (F41L HRP) which gave higher rates and *ee*'s than the native enzyme (e.g. for oxidation of ethyl phenyl sulfide: 35% *ee* and 94% *ee* for the native and the modified enzyme, respectively) [146]. The effect of replacement of Phe-41 by threonine or leucine was also explored. Molecular engineering of horseradish peroxidase is clearly a promising approach to devising enantioselective enzymes for sulfoxidation.

*Catalytic antibody* techniques were applied to sulfoxidation by Schultz

et al. [147]. The authors established that hapten (57) (Scheme 1.14), when conjugated to a protein, is able to generate a set of monoclonal antibodies which significantly accelerate ( $\times 10^5$ ) the oxidation of (55) by sodium periodate, presumably by complexation of transition state (56). This pioneering achievement provides great hope for the potential of artificial enzymes for enantioselective sulfoxidation.



SCHEME 1.14 Sulfoxidation by  $\text{NaIO}_4$  and a catalytic antibody [147]

## 1.6 KINETIC RESOLUTION

Kinetic resolution allows the preferential transformation of one of the components of a racemic mixture with formation of a product (achiral or chiral). [148] (Figure 1.9). The starting material is recovered with high *ee* if the selectivity factor  $s = k_R/k_S$  is high enough.

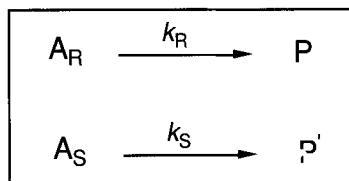
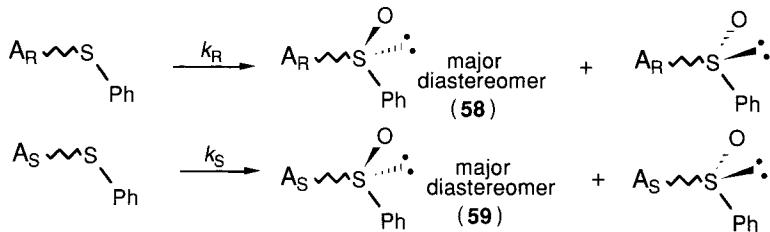


FIGURE 1.9 Kinetic resolution of a racemic mixture ( $\text{A}_R, \text{A}_S$ ),  $\text{P}$  and  $\text{P}'$  can be identical or different, according to the structure of  $\text{A}$ .  $k_R$  and  $k_S$  are pseudo first-order rate constants [148]

The selectivity factor  $s$  is calculated by equation (1.2) (if  $s > 1$ , then  $\text{ee} = (R-S)/(R+S) > 0$ ), as a function of the *ee* of recovered material and the conversion extent  $C$  [148,150]:

$$s = \frac{\ln[(1-ee)(1-C)]}{\ln[(1+ee)(1-C)]} \quad (1.2)$$

A resolution process, close to the classical resolutions by formation and separation of diastereoisomers, is the following (Scheme 1.15): a chiral reagent creates a new asymmetric centre in each of the enantiomers of a racemic mixture. This case has been analysed [151, 152]. If the reagent is able to give preferentially on both enantiomers the same absolute configuration at the new asymmetric centre (e.g. a sulfinyl moiety), it is then possible to separate the two major diastereoisomers (**58**) and (**59**), each being enantiomerically enriched. This process may be combined to provide a kinetic resolution in a partial conversion where the reagent is also able to react at different rates with the two enantiomers [151].



**Scheme 1.15** Asymmetric sulfoxidation of a racemic sulfide

The production of enantiomerically enriched sulfoxides by kinetic resolution can arise in three different situations:

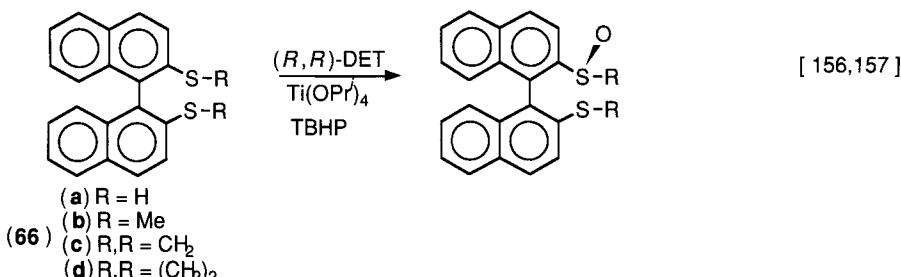
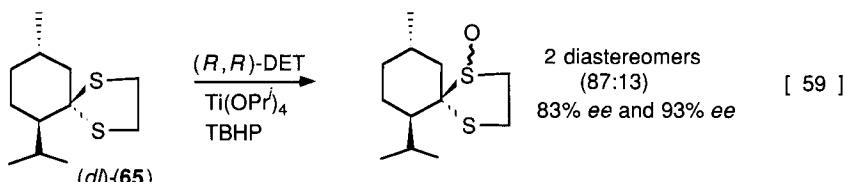
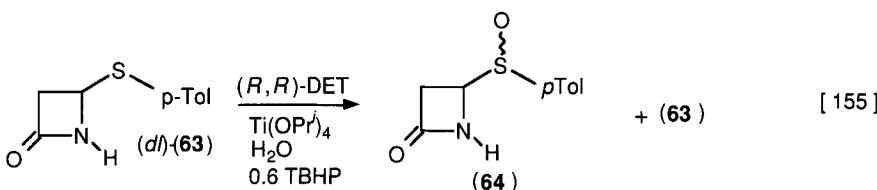
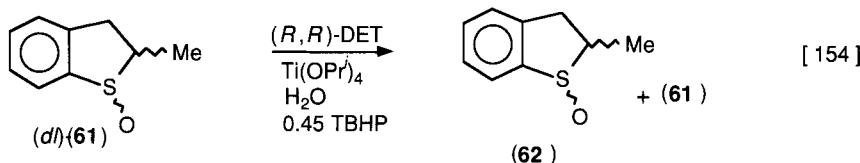
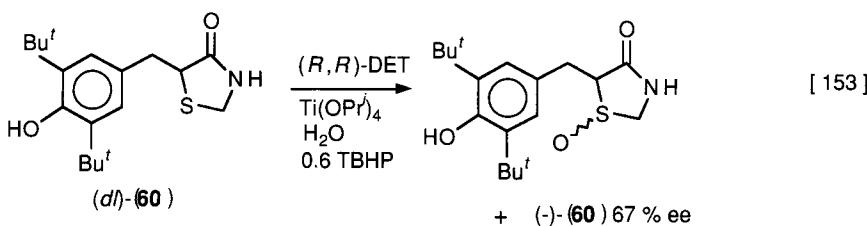
- Asymmetric oxidation of a racemic sulfide.
- Asymmetric oxidation of a racemic sulfoxide.
- Asymmetric reduction of a racemic sulfone.

In the following section cases (a) and (b) are detailed.

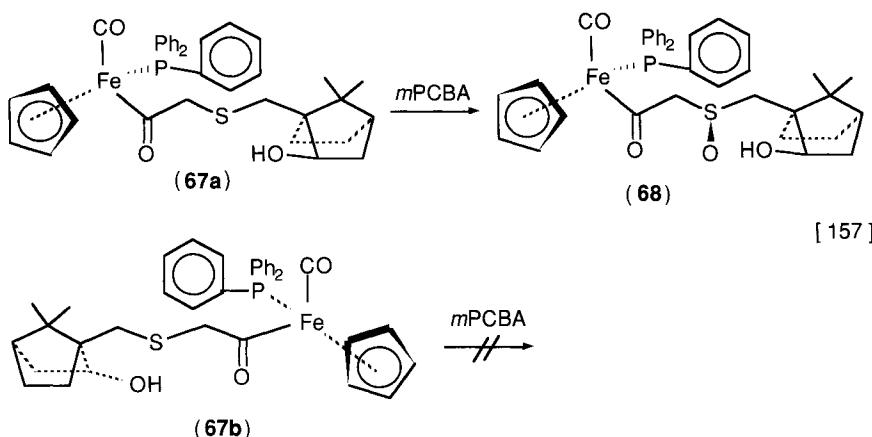
### 1.6.1 Oxidation of Racemic Sulfides

The Kagan reagent was used at Eli Lilly to resolve racemic thiazolidinone (**60**) (Scheme 1.16) [153]. At 60% and 80% completion, the *ee*'s of recovered (−)-(**60**) were 67% and 94%, respectively. The Modena procedure (i.e. no added water in the reagent system) gave a much slower reaction, but the *ee* shows only a small decrease.

The Kagan reagent allowed Ando *et al.* to prepare several nonracemic sulfoxides (**62**) by oxidation of (**61**) [154]. One calculates from *ee*'s and product distribution, using the formula for kinetic resolution [148–150], that the selectivity factor *s* is close to 12. A  $\beta$ -lactam (**63**) has been also resolved (*s* = 7) using the Kagan reagent [155].



The Modena reagent is the basis of a new method for the resolution of chiral ketones [59]. Thus,  $(\pm)$ -menthone was transformed into 1,3-dithiolane (65) and oxidized using TBHP. The two *S*-monooxides were separated, and the major one gave after cleavage  $(-)$ -menthone (93% ee). The Modena procedure is also very successful in the preparation of nonracemic 1,1'-binaphthyl-2,2'-dithiol (66a) [156,157]. Monooxidation of the dimethyl dithioether (66b) furnished an almost 1:1 mixture of diastereoisomeric sulfoxides (each with >98% ee). When the two sulfur atoms of (66) are connected by a carbon chain, such as in (66c) or (66d), the



**SCHEME 1.16** Examples of kinetic resolution of a racemic sulfide by asymmetric oxidation, or of resolution by combination with a chiral auxiliary and subsequent diastereoselective oxidation

diastereoselectivity is very high (>99% *de*), but the *ee*'s of the sulfoxides are only moderate (46% and 78%, respectively). Isolation of one diastereoisomer from oxidation of (66b) or (66c) affords by a set of transformations enantiomerically pure (66a). The recovered sulfide (66b) shows almost no enantiomerically enrichment. Thus there is no appreciable kinetic resolution in this oxidation, but enantioselective creation of an asymmetric sulfur atom allows the further diastereoisomeric separation.

The resolution of a racemic iron acetyl complex was achieved by Davies and Becker by its transformation into a 1:1 mixture of diastereoisomeric sulfides (67a) and (67b) [158]. Oxidation by mCPBA operates selectively on one diastereoisomer (because of a suitably located hydroxy group). The sulfoxide (68) was easily separated from sulfide (67b) and desulfurized to give the desired target. This a case of kinetic resolution of an equimolar mixture of diastereoisomers.

### 1.6.2 Oxidation of Sulfoxides to Sulfones

Oxidation of sulfides by an achiral oxidizing agent in the binding domain of BSA has been studied widely (see Section 1.3.4). Sugimoto *et al.* found that the *ee* of the sulfoxide thus produced increases with the amount of overoxidation to sulfone [93,94]. This is indicative of the combination of an asymmetric synthesis and a subsequent kinetic resolution (the minor enantiomer of sulfoxide being the faster to be oxidized to a sulfone). This was demonstrated by the partial oxidation of various racemic sulfoxides under the same conditions as above. For example, oxidation of racemic isobutyl *p*-tolyl sulfoxide by H<sub>2</sub>O<sub>2</sub>/BSA gave 33% *ee* and 69% *ee* at 50% and 75% conversions, respectively (*s* = 2.8). Isopropyl phenyl sulfoxide oxidized by the same system gave initially sulfoxide in 62% *ee*, but at 53%

conversion it reached 93% *ee*. For some sulfides, the combination of monooxidation and overoxidation decreases the *ee* of the sulfoxide because the minor sulfoxide is the slow-reacting species.

Uemura *et al.* found that the combination  $\text{Ti}(\text{OPr})_4/\text{binaphthol}/\text{water}$  in ratio  $1:2:10$  acts as a catalyst for oxidation of aryl methyl sulfides into the corresponding sulfoxides by  $\text{Bu}'\text{OOH}$  (see also Section 1.4.1) [159]. A mechanistic study showed that the titanium complex was a sulfoxidation catalyst (initial *ee* ~50%) as well as a catalyst for the overoxidation into sulfones, with an enhancement of the *ee* of the residual sulfoxides (because the minor sulfoxide enantiomer is preferentially oxidized). In a subsequent paper, the authors reported the kinetic resolution of racemic aryl methyl sulfoxides by the same catalyst [160]. A stereoselectivity factor *s* of 2.6 was calculated for the kinetic resolution of racemic methyl *p*-tolyl sulfoxide. For example, methyl *p*-tolyl sulfoxide (<99% *ee*) could be recovered from oxidation at about 75% conversion. Using partially resolved 1,1'-binaphthol, a positive nonlinear effect was established.

## 1.7 CONCLUSION

A wide range of *chiral reagents* or *chiral catalysts* is now available for asymmetric sulfoxidation. However, the most interesting situation, namely asymmetric catalysis, still needs much improvement because it is as yet only rarely possible to achieve a combination of high catalytic activity and high enantioselectivity. High enantioselectivity is also usually associated with suitable sulfide structure, where two very dissimilar groups are linked to the sulfur atom. The asymmetric oxidation of dialkyl sulfides remains difficult to realize with high *ee*.

*Biosulfoxidations* are also of interest. There are many cases where nearly enantiopure sulfoxides have been prepared by this route, using either entire cells or isolated enzymes. The yields, however, are often lower than in the chemical approach, and the enantioselectivity is correlated to a narrow range of substrates. Molecular engineering of enzymes could be a useful tool for acquiring enzymes better matched to substrate structure.

*Antibody-catalyzed* sulfoxidation is a very new area. One may expect in the near future that it will give rise to new generations of regio- and stereoselective catalytic antibodies for sulfoxidation.

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# THE SYNTHESIS OF CHIRAL SULFOXIDES THROUGH NUCLEOPHILIC DISPLACEMENT AT SULFUR

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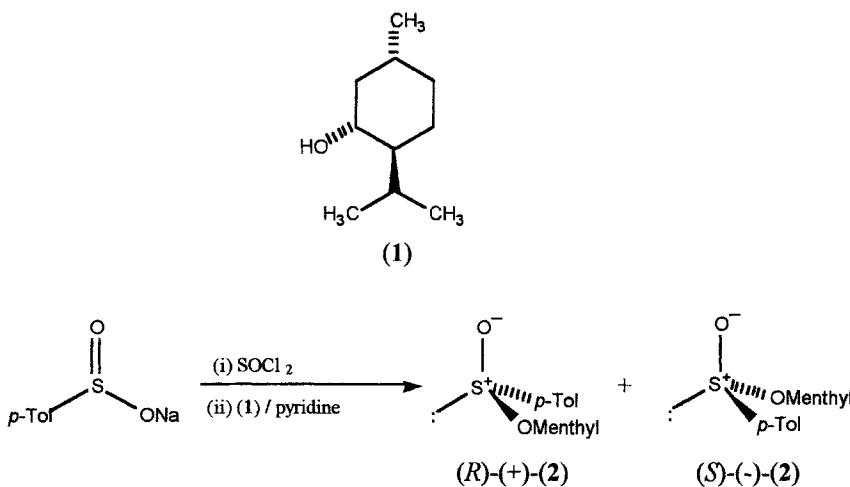
## 2.1 INTRODUCTION

The use of sulfoxides as chiral synthons has, over recent years, become a highly dependable protocol in synthetic organic chemistry. To some extent, however, the use of sulfoxides in asymmetric synthesis has been limited by the lack of a reliable and general method for their preparation in optically pure form. In this review we present the development of chiral sulfoxide synthesis via nucleophilic displacement at sulfur from the pioneering work of Andersen in 1962 to more recent methods. Sulfoxides have become associated with many diverse areas of synthetic chemistry; indeed, their ability to act as a handle for the stereoselective generation of chirality at proximate centres has attracted much research worldwide.

## 2.2 THE ANDERSEN PROCEDURE FOR THE SYNTHESIS OF ENANTIOMERICALLY ENRICHED, CHIRAL SULFOXIDES

Following the pioneering work of Gilman [1], Andersen, in 1962, reported the first synthesis of an optically active sulfoxide of high enantiomeric purity through nucleophilic displacement at sulfur [2]. The key step in Andersen's procedure

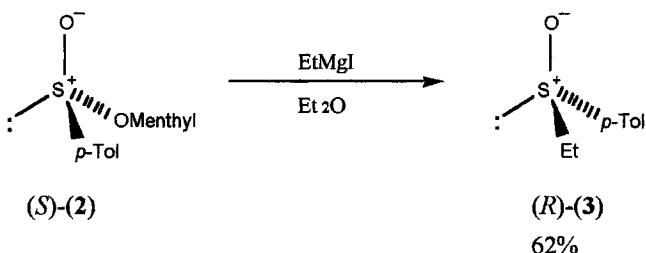
involves the preparation of a diastereoisomerically pure sulfinate ester, previously described by Phillips [3] as early as 1925 (Scheme 2.1).



SCHEME 2.1

Esterification of *p*-toluenesulfinic acid with  $(1R,2S,5R)$ - $(-)$ -menthol (**1**) is not stereoselective, producing a diastereoisomeric mixture of (*S*)- and (*R*)-menthyl *p*-toluene sulfinate esters (**2**), ( $(S):(R)$   $\sim$  2:1) (Scheme 2.1) [4]. Repeated recrystallization gave diastereoisomerically pure (*S*)- $(-)$ -menthyl *p*-toluene sulfinate in 30% yield.

Scheme 2.2 highlights Andersen's initial study, in which nucleophilic attack by ethylmagnesium iodide on enantiomerically pure (*S*)- $(-)$ -menthyl *p*-toluene sulfinate displaces the *O*-menthyl leaving group to yield 62% of (*R*)- $(+)$ -ethyl *p*-tolyl sulfoxide (**3**).

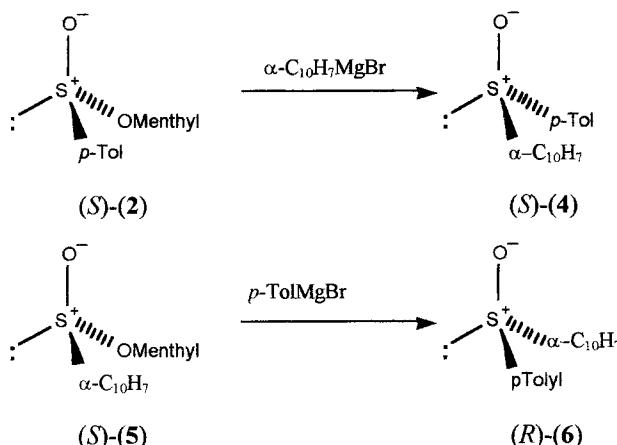


SCHEME 2.2

The reaction was found to have proceeded [3,5] with complete inversion of configuration at sulfur. The absolute configuration of the menthyl arenesulfinate

had been tentatively assigned by Hebrandson [5] and supported by others [6], but could be assigned with a much greater degree of certainty following Mislow's x-ray crystal structure determination of (−)-menthyl *p*-toluene sulfinate in 1964 [7].

Andersen later extended this work to include the synthesis of various chiral diaryl sulfoxides via the appropriate arylmagnesium bromide reagents and was also able to provide further evidence to support the proposed inversion of configuration at sulfur as highlighted in Scheme 2.3 [8].



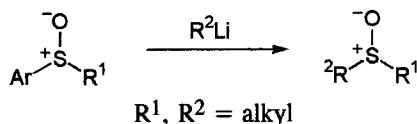
SCHEME 2.3

(*S*)-(−)-Menthyl *p*-toluene sulfinate (**2**) and 1-naphthylmagnesium bromide yielded (*S*)-(−)- $\alpha$ -naphthyl *p*-tolyl sulfoxide (**4**), while (*S*)-(−)-menthyl 1-naphthalene sulfinate (**5**) and *p*-tolylmagnesium bromide yielded (*R*)-(+) $\alpha$ -naphthyl *p*-tolyl sulfoxide (**6**). The enantiomers (**4**) and (**6**) gave optical rotations equal in magnitude but opposite in sign, indicating high enantiomeric purities and supporting the inversion theory [9].

To date, the main route for large-scale preparation of either enantiomer of non-racemic sulfoxides of type Ar—S(O)—R, where R can be introduced using organometallic chemistry, remains the Andersen procedure: both enantiomers of menthyl *p*-toluene sulfinate are commercially available [10]. However, the original procedure has limitations. As discussed above, multiple recrystallizations are necessary to achieve high diastereoisomeric purity during the preparation of (*S*)-(−)-menthyl *p*-toluene sulfinate (**2**); unfortunately, chromatographic separation is not a viable alternative owing to the similarity in *R*<sub>f</sub> values of the (*R*) and (*S*) sulfinate diastereoisomers [11]. Further, the Andersen procedure is also limited to the synthesis of alkyl aryl or diaryl sulfoxides. Dialkyl sulfoxides are not available via the classical procedure, since the required menthyl alkyl sulfinate esters could not readily be obtained in an enantiomerically pure form at sulfur [12].

## 2.3 ADAPTATIONS OF THE ANDERSEN PROCEDURE

Johnson was able to overcome the synthetic limitations of the Andersen procedure by inducing the displacement of aryl groups from diaryl or alkyl aryl sulfoxides with either alkylolithium or alkyl sodium reagents as a general approach to optically active, unsymmetrical dialkyl sulfoxides (Scheme 2.4, Table 2.1) [13].



SCHEME 2.4

Enantiomerically pure methyl phenyl sulfoxide and methyl *p*-tolyl sulfoxide in diethyl ether or dimethoxyethane were reacted with alkylolithium reagents. The exchange reactions were found to proceed with inversion of configuration at sulfur. The yields are somewhat variable, but Johnson's work did indicate that special procedures are necessary for the generation of lithium  $\alpha$ -sulfinyl carbanions for use in other synthetic purposes; for example, Johnson recommended the use of lithium dialkylamides as bases, since nucleophilic substitution can occur either on the neutral molecule or on the carbanion with alkylolithium reagents.

Andersen has described the synthesis of enantiomerically pure methyl alkyl and methyl aryl sulfoxides from cholesteryl methane sulfinate [12]. The reaction of cholesterol and menthanesulfinyl chloride provides the crystalline, epimeric cholesteryl methane sulfinate in quantitative yields (Scheme 2.5). Pure samples of the (*R*) or (*S*) epimers can be obtained in very low yield (0.7% and 3.5%, respectively) by crystallization.

TABLE 2.1 Asymmetric synthesis of unsymmetrical dialkyl sulfoxides

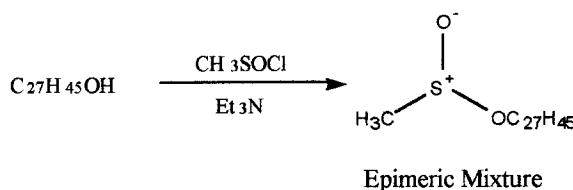
Ar	R <sup>1</sup>	R <sup>2</sup>	Conditions <sup>a</sup>	Yield (%)	Configuration
p-Tol	Me	Bu <sup>n</sup>	A	84	( <i>S</i> )
p-Tol	Me	Bu <sup>n</sup>	B	26	( <i>S</i> )
p-Tol	Bu <sup>n</sup>	Bu <sup>b</sup>	C	76	( <i>S</i> )
Phenyl	Me	Bu <sup>n</sup>	D	51	( <i>R</i> )
Phenyl	Me	Bu <sup>n</sup>	C	83	( <i>R</i> )

<sup>a</sup>A: (i) 4  $\times$  1 equivalent R<sup>2</sup>Li, Et<sub>2</sub>O,  $-78^\circ\text{C}$ , (ii) MeOH.

B: (i) 1 equivalent R<sup>2</sup>Li, DME,  $25^\circ\text{C}$ , 48 h.

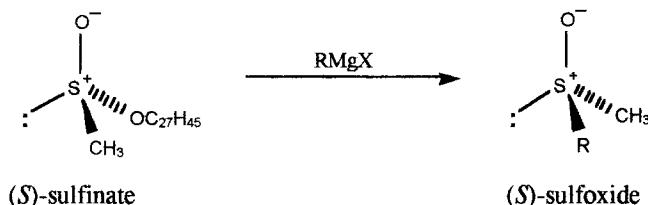
C: (i) 4  $\times$  1 equivalent R<sup>2</sup>Li, Et<sub>2</sub>O,  $-78^\circ\text{C}$ , 30 min.

D: (i) 1 equivalent R<sup>2</sup>Li, Et<sub>2</sub>O,  $-78^\circ\text{C}$ , 5 min.



### SCHEME 2.5

Upon treatment with alkyl or aryl Grignard reagents, the corresponding methyl alkyl or aryl sulfoxides are obtained with high enantiomeric purity (Scheme 2.6, Table 2.2), albeit in low yields.



### SCHEME 2.6

Another drawback of the classical Andersen procedure is that it allows for isolation of diastereoisomerically pure  $(S)$ - $(-)$ -menthyl *p*-toluene sulfinate in a poor 30% yield. An early improvement pioneered by Hebrandson employed the known racemization of sulfoxides by HCl in an epimerization/equilibration technique to increase the yield of  $(S)$ - $(-)$ -menthyl *p*-toluene sulfinate to 90% from the initial  $(R)$  and  $(S)$  diastereoisomeric mixture [14]. This adaptation has been described in detail by Solladié and the proposed epimerization/equilibration is

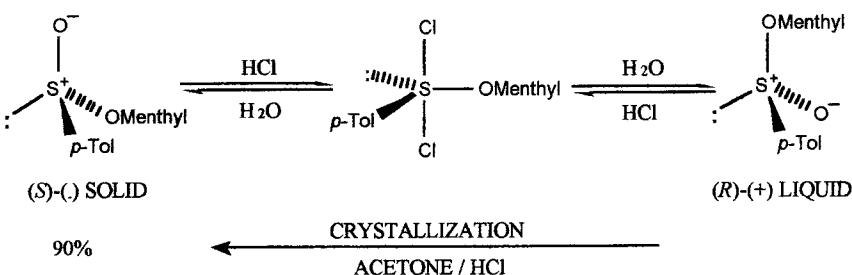
**TABLE 2.2** Synthesis of enantiomerically pure methyl alkyl and methyl aryl sulfoxides from cholesteryl methane sulfinate esters

R	Sulfoxide	Yield (%)	ee (%)
Pr <sup>n</sup>	(S)	32	> 95
Bu <sup>n</sup>	(S)	52	95
Bu <sup>i</sup>	(S)	50	— <sup>a</sup>
p-Tol	(R) <sup>b</sup>	35	95
PhCH <sub>2</sub>	(S)	36	100

<sup>a</sup>Not determined.

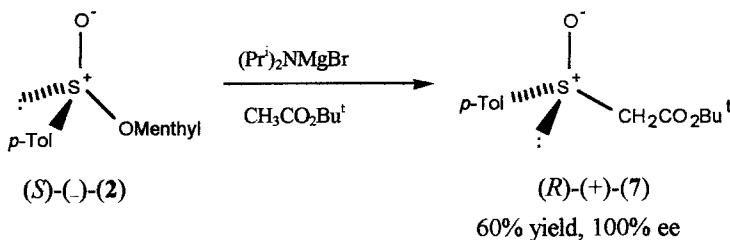
<sup>b</sup>From (R)-sulfinate.

illustrated in Scheme 2.7 [15]. In acidic media, the equilibrium is shifted toward the less soluble (*S*)-(−) diastereoisomer which is isolated by crystallization.



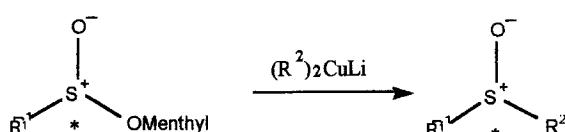
SCHEME 2.7

Solladié also reported a high-yielding, stereospecific synthesis of enantioselectively pure (*R*)-(+)α—sulfinylacetate (7), a synthetically useful chiral synthon, by nucleophilic displacement of the *O*-methyl group of (*S*)-(−)-(2) by the magnesium enolate of *t*-butyl acetate (Scheme 2.8) [16].



SCHEME 2.8

Harpp described the use of organolithium cuprate reagents in ether as alternatives to Grignard reagents (Scheme 2.9, Table 2.3) and observed high levels of optical purity in the chiral sulfoxide products. The yields are variable, however [17].

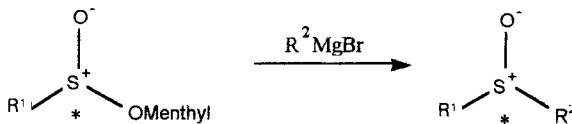


SCHEME 2.9

**TABLE 2.3** Use of organolithium cuprate reagents as alternatives to Grignard reagents in the Andersen procedure

R <sup>1</sup>	R <sup>2</sup>	Yield (%)	ee (%)
Ph	Me	16	96
p-Tol	Me	55	99
p-Tol	Ph	59	100

Mikolajczyk observed much increased yields, without loss of optical purity, in the Andersen procedure by simply changing the solvent from diethyl ether to benzene (Scheme 2.10, Table 2.4) [18].

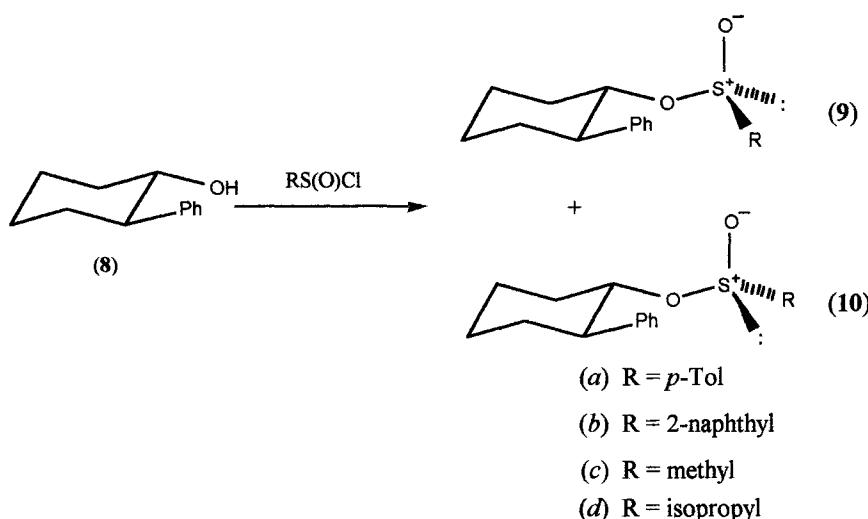


**SCHEME 2.10**

**TABLE 2.4** Effect of solvent variation on the Andersen procedure

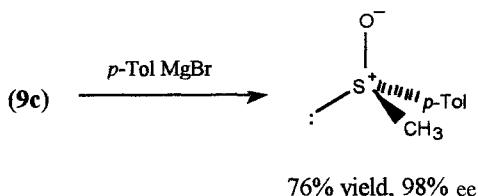
R <sup>1</sup>	R <sup>2</sup>	Solvent	Yield (%)	ee (%)
p-Tol	Me	Diethyl ether	61	85
p-Tol	Me	Benzene	82	89.6
p-Tol	Et	Diethyl ether	78	90.8
p-Tol	Et	Benzene	92	97.5
p-Tol	Ph	Diethyl ether	59	99.1
p-Tol	Ph	Benzene	88	91

More recently, Whitesell has recently reported an improved method for the preparation of enantiomerically pure sulfinate esters (Scheme 2.11) [19]. As previously described, the (S)-(-)-menthyl p-toluene sulfinate diastereoisomer only is readily available in a pure, crystalline form using the Andersen procedure. Whitesell discovered that reaction of the chiral auxiliary *trans*-2-phenylcyclohexanol (**8**) with an excess of alkyl or arene sulfinyl chloride afforded the appropriate sulfinate esters (**9**) and (**10**) in good yield and with better selectivities (up to 10:1) than those observed with (1*R*,2*S*,5*R*)-(-)-menthol (~2:1). These diastereoisomers can be readily separated (R = p-Tol; (**9a**) = 62% yield, 98% *de*) by either crystallization or by chromatography, in contrast to the Andersen procedure.



SCHEME 2.11

In all cases, the major diastereoisomer (9) is crystalline. The sulfinate esters (9a-d) undergo clean reaction with Grignard reagents to yield sulfoxides in good yield and with complete inversion of configuration at sulfur as highlighted in Scheme 2.12.



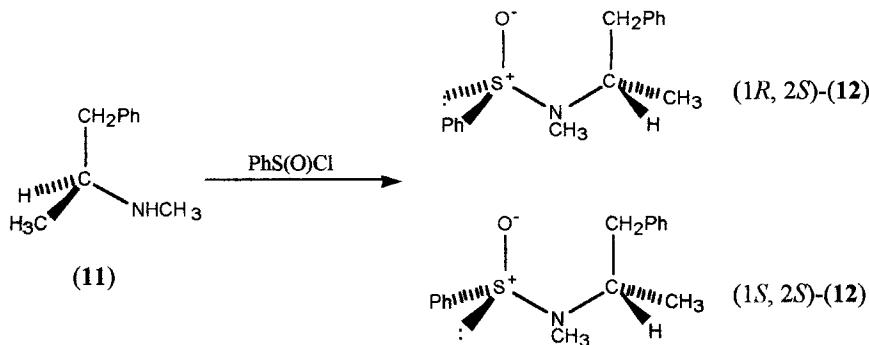
SCHEME 2.12

Both enantiomers of Whitesell's chiral auxiliary (8) are available by enzymatic resolution of commercially available racemic *trans*-2-phenylcyclohexanol [20,21], allowing ready and equal access to dialkyl, alkyl aryl and diaryl sulfoxides of high optical purity and with either absolute configuration.

## 2.4 APPLICATION OF CHIRAL SULFINAMIDES

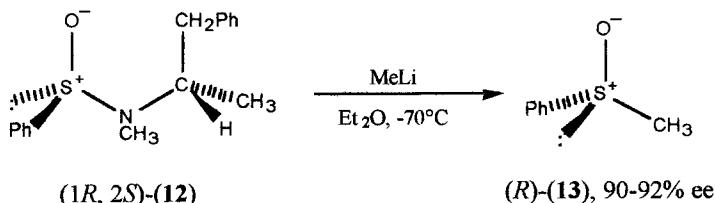
Jacobus and Mislow have investigated the development of chiral sulfinamides as precursors to optically pure sulfoxides [22]. The reaction of benzenesulfinyl chloride and (*S*)-(+)-deoxyephedrine proceeded at low temperature ( $0^\circ\text{C}$ ) to yield

a 3:1 mixture of sulfinamide diastereoisomers (*1R,2S*)-(12) and (*1S,2S*)-(12) respectively as shown in Scheme 2.13.



SCHEME 2.13

This reaction is more stereoselective than the corresponding synthesis of methyl sulfinate diastereoisomers in the Andersen procedure, allowing for easier fractional crystallization. Optically active (*R*)-(+)-methyl phenyl sulfoxide (13) is obtained on reaction of (*1R,2S*)-(12) with methylolithium (Scheme 2.14).

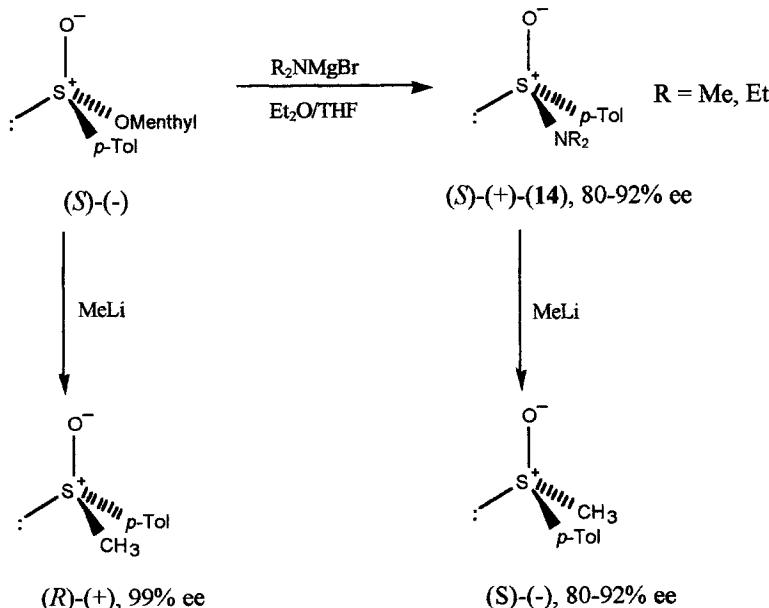


SCHEME 2.14

The (*S*)-(-) sulfoxide enantiomer is available from the other sulfinamide diastereoisomer (*1S,2S*)-(12). Methylolithium was the reagent of choice because no reaction was observed using methylmagnesium bromide as the nucleophile. It is, however, interesting to note that partial racemization of methyl aryl sulfoxides by methylolithium in DME solvent has been observed in other studies by this group [23]. This type of racemization has since been attributed to *S<sub>N</sub>2*-type attack at sulfur by organolithium reagents, resulting in displacement of a sulfoxide ligand. In the above case, methyl group exchange occurs with complete inversion of configuration at sulfur [24].

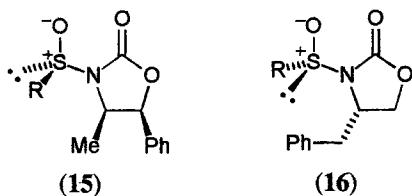
Montanari has also applied chiral sulfinamide methodology to the asymmetric synthesis of methyl aryl sulfoxides [25]. (*S*)-(-)-*p*-Toluene sulfinamides (14) were prepared from (*S*)-(-)-menthyl *p*-toluene sulfinate and the corresponding bromomagnesium dialkylamides in moderate yield and good enantioselectivity (Scheme 2.15).

Montanari's procedure allows access to both enantiomers of methyl *p*-tolyl sulfoxide. The sulfinamides (**14**) were, however, observed to racemize on exposure to light, but were reported to be optically stable in the dark.



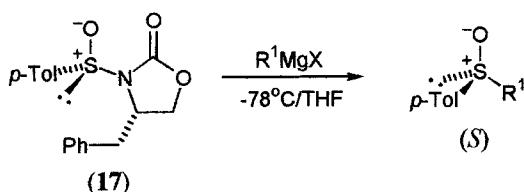
SCHEME 2.15

Recently, in a related approach by Evans, chiral oxazolidinones derived from (1*R*,2*S*)-norephedrine and (*S*)-phenylalanine were employed to prepare novel, chiral sulfinyl transfer reagents (**15**) and (**16**), respectively [26].



These *N*-sulfinyloxazolidinone reagents can be synthesized either by sulfinylation of the metallated oxazolidinone or by sulfoxidation of the *N*-sulfenimide. The crystalline reagents (**15**) and (**16**) are readily purified from their respective minor epimers to high diastereoisomeric purity by chromatography and their reactivity toward nucleophiles is reported to be ~100 times greater than that of methyl sulfinate esters.

The synthesis of a series of alkyl aryl sulfoxides using Grignard reagent nucleophiles was investigated by Evans and the results are summarized in Scheme 2.16 and Table 2.5 for the *N*-sulfinyloxazolidinone (**17**).



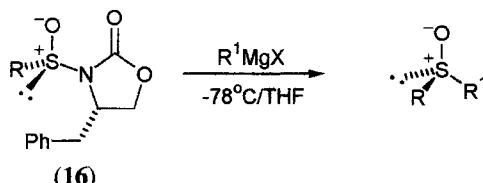
**SCHEME 2.16**

TABLE 2.5 Use of *N*-sulfinyloxazolidinone (17) in the asymmetric synthesis of sulfoxides

R <sup>1</sup>	Yield (%)	ee (%)
Me	90	99
Et	90	98
Pr <sup>i</sup>	91	97
Bu <sup>t</sup>	88	97
PhCH <sub>2</sub>	86	99 <sup>a</sup>

<sup>a</sup>After one recrystallization, initial ee = 94%.

The *N*-sulfinyloxazolidinones have also been demonstrated to be highly efficient reagents for the synthesis of dialkyl sulfoxides in high yields and with excellent enantioselectivities; as discussed, this class of sulfoxide has proved to be inaccessible through the Andersen procedure. Examples are highlighted in Scheme 2.17 and Table 2.6 for *N*-sulfinyloxazolidinone (**16**).

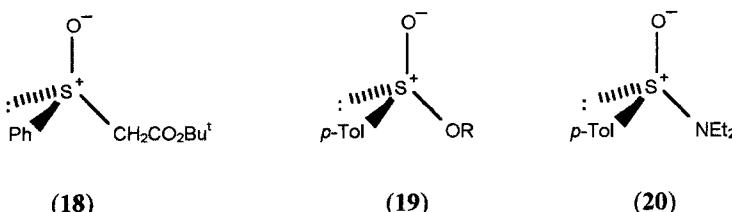


**SCHEME 2.17**

**Table 2.6** Use of *N*-sulfinyloxazolidinone (**16**) in the asymmetric synthesis of dialkyl sulfoxides

R	R <sup>1</sup>	Yield (%)	ee (%)	Configuration
Me	Bu <sup>t</sup>	78	93	(R)
Me	PhCH <sub>2</sub>	82	91	(R)
Me	Octyl	78	100	(R)
Bu <sup>t</sup>	Me	92	100	(S)
Bu <sup>t</sup>	Bu <sup>n</sup>	91	100	(S)

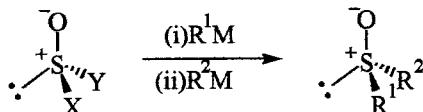
The *N*-sulfinyloxazolidinone reagents were found to be useful in the asymmetric synthesis of  $\alpha$ -sulfinyl acetate (**18**), sulfinate esters (**19**) and sulfinamides (**20**).



For brevity, only reactions of *N*-sulfinyloxazolidinone (**16**) and derivatives have been described; but it is necessary to point out that *N*-sulfinyloxazolidinone (**15**) was shown to be equally effective in all similar transformations. The *N*-sulfinyloxazolidinone reagents developed by Evans are among the most effective and efficient *N*-sulfinyl transfer reagents yet developed: these reactions proceed with high degrees of enantioselectivity and in excellent yields. The ready application to the synthesis of dialkyl sulfoxides must also be emphasized.

## 2.5 APPLICATION OF CHIRAL, CYCLIC SULFINAMIDES

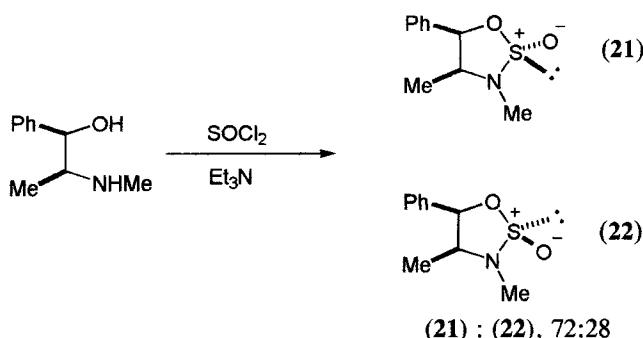
The possibility of employing a chiral sulfinyl group possessing two ligands with differing leaving group abilities in the synthesis of enantiomerically sulfoxides via consecutive nucleophilic attack has generated considerable interest within the synthetic community (Scheme 2.18).



**SCHEME 2,18**

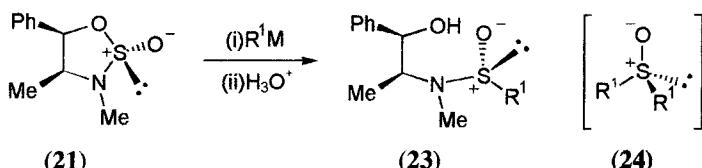
Wudl and Lee [27] developed this idea based on marked difficulty in cleaving the S—N bond of acyclic sulfinamides compared to the S—O bond of sulfonates [28]. (*1R,2S*)-(−)-Ephedrine was employed to obtain a diastereoisomeric mixture of cyclic 1,2,3-oxathiazolidine 2-oxides (**21**) and (**22**) on reaction with thionyl chloride (Scheme 2.19).

Diastereoisomers (**21**) and (**22**) were epimerized and equilibrated in acidic media as described above (in Scheme 2.7). The equilibrium is displaced toward the less soluble isomer (**21**), which precipitates from the reaction solution in 64% overall yield. Reaction of (**21**) with organometallic reagents in THF solvent under the conditions shown in Table 2.7 afforded the chiral hydroxysulfinamides (**23**).



SCHEME 2.19

(Scheme 2.20, Table 2.7). Under certain reaction conditions, formation of symmetrical sulfoxides (**24**) was observed in up to 35% yield.



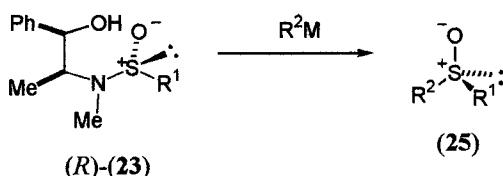
SCHEME 2.20

Table 2.7 Synthesis of chiral hydroxysulfinamides (**23**)

$\text{R}^1\text{M}$	Time (h)	Temperature (°C)	TMEDA <sup>a</sup> additive	ee (%)		Yield (%)	
				( <i>R</i> )-(23):( <i>S</i> )-(23)	( <i>R</i> )-(23)	(23)	(24)
<i>p</i> -TolMgBr	1	-18	-	100	0	7	11
<i>p</i> -TolMgBr	9	-27	-	100	0	18	35
<i>p</i> -TolMgBr	1	-25	+	88	12	47	26
PhLi	0.3	-78	-	70	30	89	Trace
PhLi	7	-78	+	72	28	87	Trace
PhLi	0.3	-78	+	76	24	84	Trace
PhLi	3	-100	+	75	25	90	Trace
MeMgBr	6	-25	+	72	28	41	0
MeLi	6	-25	+	74	26	61	0

<sup>a</sup>TMEDA = tetramethylethylene diamine (1,2-bis(dimethylamino)ethane).

The (*R*) and (*S*) epimers of (**23**) can be separated by crystallization when necessary. Representative conversions to methyl aryl sulfoxides (**25**) are highlighted in Scheme 2.21 and Table 2.8.

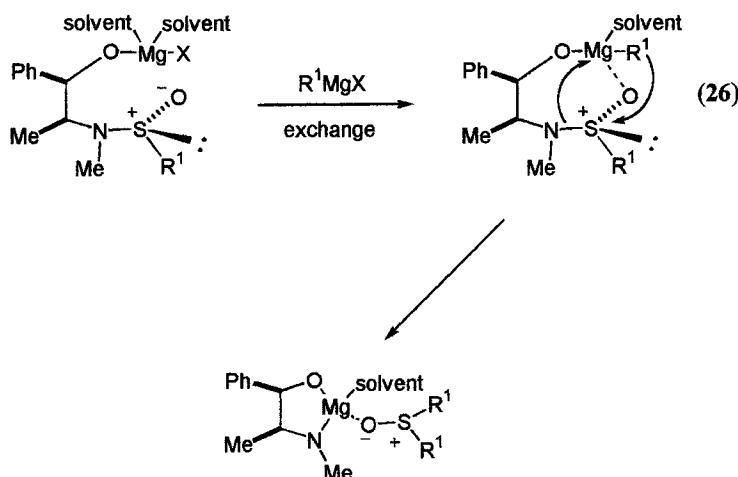


SCHEME 2.21

TABLE 2.8 Asymmetric synthesis of methyl aryl sulfoxides (25) from hydroxysulfinamides (23)

R <sup>1</sup>	R <sup>2</sup> M	Temperature (°C)	Yield (%)	ee (%)
p-Tol	MeMgBr	0	25	100
Ph	MeLi/TMEDA	-78	70	86
Me	PhLi	-78	75	85

The production of symmetrical sulfoxides (24) was suggested to proceed through an intramolecular process (Scheme 2.22) accelerated when the Grignard reagent was present in the reaction medium as an aggregate, and reduced if the Grignard reagent was monomeric in nature, since alkyl exchange in the Grignard reagent would be retarded. The use of THF containing tetramethyleneethylenediamine (TMEDA) as a cosolvent helped reduce the yield of symmetrical sulfoxide as expected; Grignard reagents are known to exist as monomers in the presence of TMEDA [29], and TMEDA is known to retard alkyl exchange in Grignard reagents [30].



SCHEME 2.22

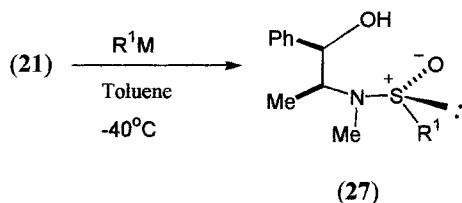
The reduced proportion of (**24**) observed when employing organolithium reagents can also be rationalized, since the lithium cation is monovalent and therefore cannot form species such as (**26**). Since, in this procedure, both nucleophilic groups add consecutively with inversion of configuration, the configuration of the final sulfoxide product (**25**) is dependent upon the order of addition of the attacking nucleophiles.

There are three main disadvantages with the method developed by Wudl and Lee:

1. Epimerization at sulfur, proposed to occur through sulfinyl transfer, reduces the diastereoselectivity of the initial displacement reaction.
2. Final displacement to yield the required sulfoxides occurs in good yield only with organolithium reagents, but is accompanied by significant racemization. The use of Grignard reagents eliminates racemization but results in lower yields.
3. Two equivalents of organometallic reagent are required for the final displacement reaction. One equivalent is consumed in deprotonation of the hydroxy group of the hydroxysulfonamide.

Snyder and Benson have recently overcome these drawbacks and reported a much improved synthesis of chiral sulfoxides based on the Wudl and Lee method [31]. Oxathiazolidine *S*-oxide (**21**) and its diastereoisomer (**22**) were prepared from (*1R,2S*)-*(−)*-ephedrine as reported by Wudl and Lee in a 4.4:1 ratio. It was found that storage of (**21**) and (**22**) at 0°C for 48 h in the presence of the triethylammonium chloride, formed in the reaction medium during their preparation, increased the ratio of (**21**):(**22**) to 34:1, enabling isolation of pure (**21**) in 70% yield.

The initial displacement (Scheme 2.23) was performed on (**21**) with freshly prepared Grignard reagent in toluene solvent. The chiral hydroxysulfonamides (**27**) were formed in good yield and with high levels of diastereoselectivity (Table 2.9). The use of toluene therefore overcomes the problem of racemization observed by Wudl and Lee.



SCHEME 2.23

The use of THF as solvent with organolithium nucleophiles, as described by Wudl and Lee, resulted in significant reduction in the levels of diastereoselectivity. Entries 7–9 of Table 2.9 highlight the limitations of this procedure for the synthesis of diaryl sulfoxides and therefore dictate that alkyl aryl sulfoxides are synthesized

**TABLE 2.9** Synthesis of chiral hydroxysulfinamides (27)

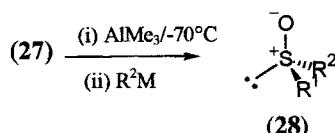
Entry	R'M	de (%) <sup>a</sup>	Yield (%)
1	MeMgBr	>99	64
2	VinylMgBr	96	94
3	AllylMgBr	97	84
4	ButMgBr	89	84
5	PrMgBr	98	91
6	EtMgBr	61	50
7	PhMgBr	0	0 <sup>b</sup>
8	Ph <sub>2</sub> CuLi	51	39
9	PhCeCl <sub>2</sub>	82	21
10	MeLi	0 <sup>c</sup>	49
11	MeMgBr	30 <sup>c</sup>	69

<sup>a</sup>Stereoisomers separable by crystallization.

<sup>b</sup>Diphenyl sulfoxide main product.

<sup>c</sup>THF solvent.

by prior addition of the alkyl organometallic reagent. The synthesis of sulfoxides from (27) was investigated as highlighted in Scheme 2.24.



**SCHEME 2.24**

Snyder and Benson modified the procedure of Wudl and Lee to include trimethylaluminium as an additive; the sulfoxides (**28**) were then isolated in good yield and with excellent enantioselectivity (Table 2.10). The notable exception to this procedure is the synthesis of *t*-butyl sulfoxides which cannot be produced from the corresponding *t*-butyl sulfinamides under *any* reaction conditions using *any* Grignard reagent. This anomalous result is thought to arise from steric factors; *t*-butyl sulfoxides can, however, be accessed in the reverse sense by using *t*-butyl Grignard reagents in the final displacement step. Addition of trimethylaluminium is proposed to form the intermediate dimethylaluminium alkoxide complex (**29**).

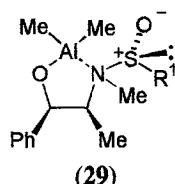


TABLE 2.10. Synthesis of enantiomerically pure sulfoxides (28)

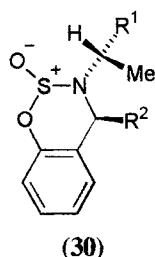
R <sup>1</sup>	R <sup>2</sup> M	Configuration (28)	Yield (%)	ee (%)
Me	PhMgBr	(S)	71	>99
Me	Bu <sup>n</sup> MgCl	(S)	76	>99
Me	Bu <sup>t</sup> MgBr	(S)	63	>99
Et	PhMgBr	(S)	44	>99
Vinyl	PhMgBr	(S)	75	>99
Allyl	PhMgBr	(S)	62	>99
Bu <sup>t</sup>	PhMgBr	—	0	—
Pr <sup>t</sup>	PhMgBr	(S)	82	>99

The effect of this complexation allows the drawbacks discussed previously to be circumvented by the following.

1. Acceleration of ephedrine displacement without racemization, since aluminium is chelated between the oxygen anion and the nitrogen leaving group.
2. Elimination of the need for two equivalents of organometallic reagent in the second displacement reaction.

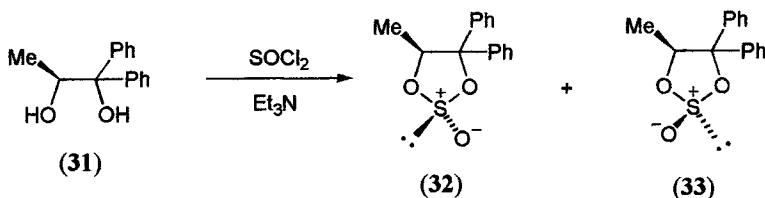
In conclusion, Snyder and Benson's approach allows the synthesis of enantiomerically pure dialkyl and alkyl aryl sulfoxides in good yields and with excellent enantioselectivities. Both enantiomers are accessible by reversing the order of organometallic displacement or by employing the (1*S*,2*R*)-(+)ephedrine enantiomer. The only limitations are observed in the synthesis of *t*-butyl phenyl and aryl phenyl sulfoxides. However aryl phenyl sulfoxides are accessible by the Andersen procedure, and *t*-butyl phenyl sulfoxides by an approach to chiral sulfoxides developed by Kagan, described below.

Hiroi applied the benzoxathiazine 2-oxide derivatives (**30**) to the asymmetric synthesis of chiral sulfoxides in a similar manner to that described above, but consistently observed lower yields (35–46%) and poorer levels of enantioselectivity (33–75% ee) [32].



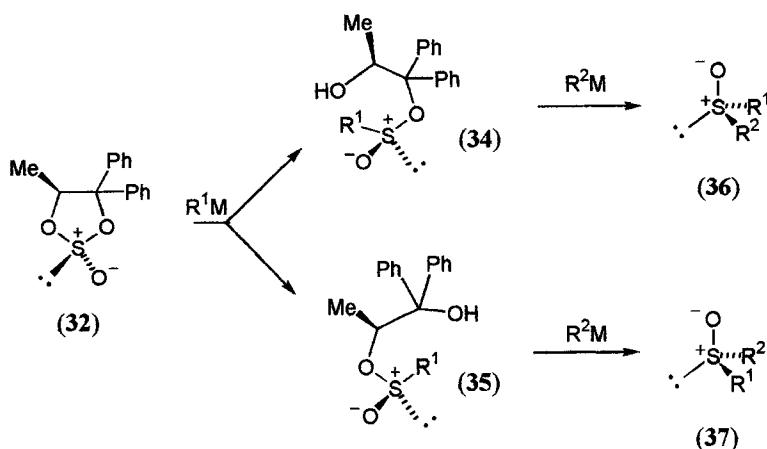
## 2.6 APPLICATION OF CHIRAL, CYCLIC SULFITES

Kagan has developed a useful asymmetric synthesis of chiral sulfoxides based on the derivatization of diol (31) with thionyl chloride (Scheme 2.25). Diol (31) is obtained in one step by reaction of readily available (S)-ethyl lactate with phenylmagnesium bromide.



SCHEME 2.25

The cyclic sulfite diastereoisomers (32) and (33) are formed in a 9:1 ratio. Pure (32) is obtained by crystallization in 60% overall yield. The reaction of (32) with suitable organometallic reagents could lead to two possible products, (34) and (35), as highlighted in Scheme 2.26.



SCHEME 2.26

Various organometallic species in THF were investigated (Table 2.11) in Kagan's initial study [33], and the range was later extended [34].

Enantiomerically pure *t*-butyl alkyl sulfoxides were isolated from (35) ( $\text{R}^1 = \text{Bu}^t$ ), as shown in Table 2.12. The displacement reactions were found to proceed with complete inversion of configuration at sulfur.

**TABLE 2.11** Reaction of organometallic reagents with cyclic sulfite (32)

$R^1M$	(34):(35)	Yield (%) (isomer)
MeMgI	80:20	56 (33)
MeLi	75:25	55 (33)
EtMgBr	92:8	57 (33)
Bu <sup>t</sup> MgBr	5:95	60 (34)
Bu <sup>t</sup> MgCl	10:90	70 (34)
VinylMgBr	95:5	50 (33)
PhCH <sub>2</sub> MgCl	70:30	50 (33)
<i>n</i> -OctylMgBr	95:5	60 (33)
MesitylMgBr	12:88	70 (34)

**TABLE 2.12** Synthesis of optically pure *t*-butyl alkyl sulfoxides from (35)

$R^1$	$R^2M$	(37) (%)	Configuration	ee (%)
Bu <sup>t</sup>	PhLi	99	( <i>S</i> )	100
Bu <sup>t</sup>	Bu <sup>t</sup> Li	99	( <i>R</i> )	100
Bu <sup>t</sup>	VinylMgBr	99	( <i>R</i> )	100

The stereoselective 1,4-addition reactions of *t*-butyl alkyl sulfoxides have been investigated, but prior to Kagan's work [35] (and more recently the work of Khiar and colleagues) [36], their preparation in an enantiomerically pure form had proved troublesome [36].

The results for the preparation of dialkyl or alkyl aryl sulfoxides are shown in Table 2.13.

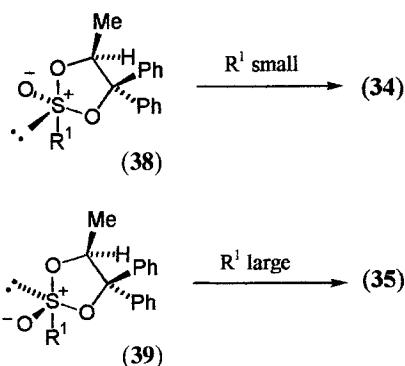
A general trend clearly emerges. When  $R^1$  is bulky, the regioselective cleavage gives mainly (35); however, when  $R^1$  is small, sulfinate (34) is the major product. No formation of symmetrical, achiral sulfoxides was observed using Grignard

**Table 2.13** Preparation of dialkyl and alkyl aryl sulfoxides from cyclic sulfite (34) or (35)

Sulfinate	$R^1$	$R^2M$	Temperature (°C)	Configuration	ee (%)
(34)	Me	<i>n</i> -OctylMgBr	0	( <i>R</i> )	100
(34)	Et	PhLi	0	( <i>R</i> )	100
(34)	Et	PhCH <sub>2</sub> MgBr	25	( <i>R</i> )	100
(34)	PhCH <sub>2</sub>	EtMgBr	0	( <i>S</i> )	100
(34)	<i>n</i> -Octyl	MeMgI	25	( <i>S</i> )	100
(35)	Mesityl	MeLi	0	( <i>R</i> )	100
(35)	Mesityl	PhMgBr	0	( <i>R</i> )	100

reagents; this is in contrast to the procedure of Wudl and Lee described above, in which up to 35% of symmetrical sulfoxide (**24**) was observed. Organolithium reagents are less regioselective on reaction with (**32**) and sometimes afford symmetrical sulfoxides (e.g.  $\text{Bu}^{\prime}\text{Li}$ ). The chiral auxiliary is recovered in quantitative yield on sulfoxide formation.

The regiochemistry of cleavage of the cyclic sulfite upon attack by small and large nucleophiles has been rationalized by invoking trigonal bipyramidal transition states or intermediates, as shown in transition states (**38**) and (**39**) (Scheme 2.27).



SCHEME 2.27

In these structures, the bulky  $-\text{[O—C(Ph)<sub>2</sub>]—}$  group prefers to occupy an equatorial position. On employing a small nucleophile ( $\text{R}^1$ ) in the displacement, as in (**38**), the incoming and leaving groups are both favourably accommodated in apical positions, and the ring cleavage occurs to give sulfinate (**34**). However, a bulky incoming nucleophile will severely interact with the  $-\text{[O—C(Ph)<sub>2</sub>]—}$  group in (**38**); hence for large  $\text{R}^1$ , the alternative transition state (**39**), in which the  $-\text{[O—C(Ph)<sub>2</sub>]—}$  group lies in an apical position, is favoured, producing sulfinate (**35**).

This procedure, developed by Kagan, allows access to various types of chiral sulfoxides, such as *t*-butyl alkyl or *t*-butyl aryl sulfoxides, neither of which are available in high enantiomeric excess from other methods.

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# Conformational Preference of the Sulfinyl Group in Six-Membered Heterocycles

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## 3.1 INTRODUCTION

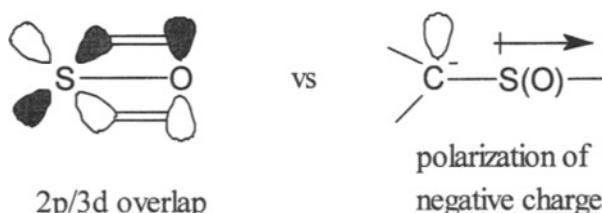
### 3.1.1 Scope of This Review

The lithiation-alkylation of organic sulfoxides represents a most useful strategy for the stereospecific introduction of a C–C bond into a molecule [1–3]. In these reactions, the relative kinetic acidity of the diastereotopic vicinal hydrogens, and the thermodynamic nonequivalence of the  $\alpha$ -metallated species, depend upon the orientation of the sulfinyl group. As a consequence, a substantial number of studies have been directed during the last 25 years towards the determination of the conformational behaviour of acyclic and cyclic sulfoxides. This review attempts to present an organized discussion of those efforts concerning six-membered heterocycles. It will become clear, nevertheless, that a proper understanding of the conformational preference of the sulfinyl group is not free from complications, which should provide stimulus for the development of additional experiments as well as further theoretical calculations.

### 3.1.2 Concerning the Nature of the Sulfinyl Bond

The nature of the S–O bond in sulfoxides and sulfones is still a matter of controversy [4]. Double bond character has been suggested from consideration of the rather short bond length (1.45 Å on average), and so these compounds are frequently represented as S=O double bonds with an expanded octet around sulfur. However, the sulfur–oxygen bond is not a double bond in the same sense as carbon–oxygen double bonds in which the second bond arises from  $\pi$ -overlap of atomic *p*-orbitals. Rather, it is proposed that sulfur–oxygen double bonds result from overlap of an oxygen *p*-orbital with a sulfur low-energy *d*-orbital [5] (Scheme 3.1).

Although quantum-mechanical calculations have challenged the possible involvement of 3*d* orbitals in sulfoxides and sulfones [5–8] this bonding model involving participation of 3*d* orbitals at sulfur is reviving again as the result of new basis sets for *ab initio* calculations [3,9]. It is noted, however, that the role of *d* functions in hypervalent molecules seems to be to provide additional flexibility for the orbitals to increase their overlap and thereby increase the stabilization of the system (*d*-orbitals polarization effect) [10], rather than to participate directly in bonding, as depicted in Scheme 3.1.



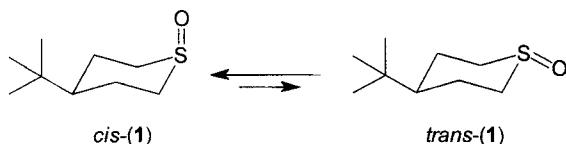
SCHEME 3.1

On the other hand, the highly polar nature of the S—O bond (2.8–4.5 D; 1 D =  $3.336 \times 10^{-30}$  C m), as well as the small force constants for this linkage in sulfoxides ( $6\text{--}8 \times 10^2$  N m $^{-1}$ ), which are similar to those of N—O linkages in pyridine *N*-oxides, have been taken to suggest a semipolar single S→O bond [4,11].

## 3.2 CONFORMATIONAL EQUILIBRIA OF THIANE-1-OXIDES

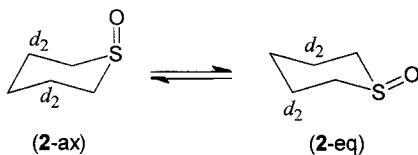
### 3.2.1 Thiane-1-oxide

Much of the sustained interest in the conformational analysis of sulfoxides was initiated by the discovery of the axial preference of the sulfinyl oxygen in thiane-1-oxide. Indeed, although Henbest and Khan [12] reported that the thermally-induced equilibrium of 4-*t*-butylthiane-1-oxides (**1**) afforded a *cis:trans* ratio of 20:80, a reexamination by Johnson and McCants established that the isomer bearing the axial oxygen is more stable [13] (Scheme 3.2).



SCHEME 3.2

While the value suggested by Johnson and McCants for the conformational free energy difference in Scheme 3.2 was a substantial  $\Delta G_{190^\circ\text{C}}^\circ = +1.3 \text{ kcal mol}^{-1}$  [13], a more precise determination was carried out by Lambert and Keske [14], who examined the slow-exchange nuclear magnetic resonance (NMR) spectra of the unsubstituted tetradeuteriated thiane-1-oxide (**2**) at  $-90^\circ\text{C}$  (Scheme 3.3).



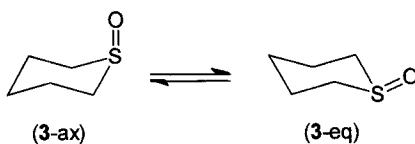
SCHEME 3.3

From integration of the resonances of the low-field  $\alpha$  protons, the equilibrium constant was calculated to be 0.62, corresponding to the well-accepted value of  $\Delta G_{-90^\circ\text{C}}^\circ = +0.175 \text{ kcal mol}^{-1}$ . Force-field calculations were found to be in agreement with the NMR data [15,16].

Barbarella and colleagues [17] described the conformational analysis of thiane-

1-oxide (**3**) (Table 3.1) in different solvents by low-temperature  $^{13}\text{C}$  NMR spectroscopy. The results are collected in Table 3.1, and show that in THF the proportion of the axial isomer is higher than in  $\text{CD}_2\text{Cl}_2$ . Surprisingly, in  $\text{CDCl}_3$  or  $\text{CHF}_2\text{Cl}$  the conformational preference is reversed: the equatorial conformer is slightly favoured. The higher stability of axial conformers in THF was tentatively explained [17] by assuming a specific association between the oxygen atom of the solvent and the positive end of the  $^+\text{S}\rightarrow\text{O}^-$  dipole. Solvation is then sterically more favourable in the axial than in the equatorial conformer. By contrast, should  $\text{CDCl}_3$  undergo hydrogen-bonding with the negative end of the  $^+\text{S}\rightarrow\text{O}^-$  dipole, then the equatorial conformer should be better solvated than the axial conformer, as experimentally observed. The authors point out, however, that an even higher proportion of the equatorial conformer would be expected in  $\text{CD}_3\text{OD}$  (a better hydrogen-bonding solvent), contrary to observation.

**TABLE 3.1** Percentage (%) of the axial and equatorial conformers of (**3**) at  $-75^\circ\text{C}$  [17]



	$\text{CD}_3\text{OD}$	$\text{CD}_3\text{COCD}_3$	$\text{CD}_2\text{Cl}_2$	$\text{THF-}d_8$	$\text{CDCl}_3$	$\text{CHF}_2\text{Cl}$
(3-ax)	73	75	50	80	45	45
(3-eq)	27	25	50	20	55	55

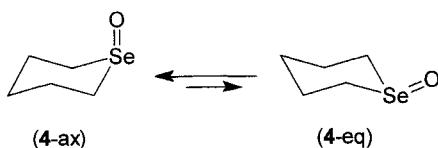
More recently, Abraham and coworkers [18] reexamined the conformational behaviour of thiane-1-oxide (**3**) by analysis of lanthanide-induced shifts (LIS) in the appropriate NMR spectra. Their results compare reasonably well with those obtained by Barbarella *et al.* [17], suggesting the applicability of the LIS method to sulfoxide conformational analysis.

The molecular structure of thiane-1-oxide has been determined by gas-phase electron diffraction [19]. The collected data indicate that the molecule adopts a chair conformation with an axial orientation of the oxygen atom, and there was no indication of any appreciable amount of equatorial form [20].

### 3.2.2 Rationalization of the Axial Preference of the Sulfinyl Oxygen in Thiane-1-oxide

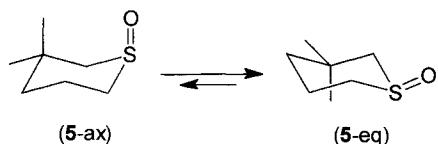
The predominance of *cis*-(**1**) in the equilibrium depicted in Scheme 3.2 has been attributed to a dominant attractive steric interaction between the axial oxygen and the *syn*-dialixial hydrogen atoms at the 3,5 positions. According to this

proposal, there should be an optimal distance that maximizes the  $\text{O}_{\text{ax}} \cdots \text{H}_{3,5\text{ax}}$  attractive interaction. In this regard, the observed increase in the proportion of the axial isomer in selenane-1-oxide ((**4**-ax), 84%) relative to that in the corresponding thiane system (62% (**2**-ax)) has been taken as an indication that lengthening the bonds ( $\text{C}=\text{Se} > \text{C}=\text{S}$ ) makes the interactions even more attractive by further descent into the Morse-like potential well [21] (Scheme 3.4).



**SCHEME 3.4**

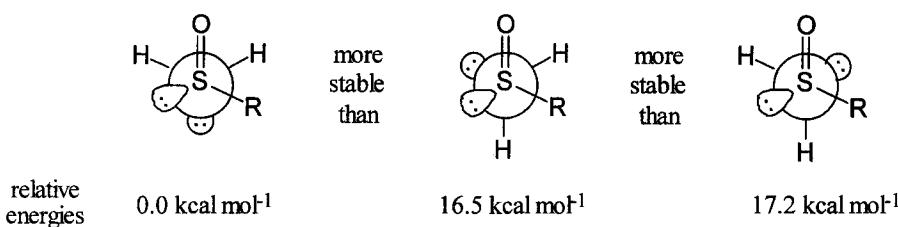
By contrast, substitution of an axial hydrogen with a methyl group, as in 3,3-dimethylthiane-1-oxide (**5**), gives rise to an equilibrium in which only the equatorial conformer was observed at low temperature in  $\text{CD}_2\text{Cl}_2$  [22–24] (Scheme 3.5). Apparently, the steric repulsion between the diaxial substituents in (**5**-ax) overwhelms the effect responsible for the axial preference in thiane-1-oxide, whatever its nature.



**SCHEME 3.5**

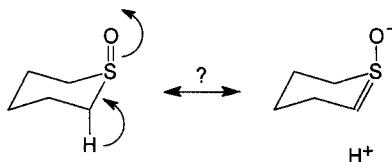
Interestingly, force-field calculations have been carried out on sulfoxides (**3**) and (**5**) [16,25]. The preference of thiane-1-oxide for the axial conformation was found to be due to a repulsion of the equatorial oxygen atom by its vicinal hydrogen atoms – not to an attraction of the axial oxygen atom by its *syn*-axial hydrogen atoms. The equatorial preference in 3,3-dimethylthiane-1-oxide is caused by van der Waals repulsion from the *syn*-axial methyl group.

On the other hand, the stereoelectronic interpretation of the anomeric effect [26] dictates the antiperiplanar orientation of an occupied, high-energy donor orbital and an empty, low-energy acceptor orbital. Such hyperconjugative stabilizing interaction is found in  $\alpha$ -sulfinyl carbanions, where the conformation allowing for  $n_c \rightarrow \sigma^*_{S-O}$  two-electron–two-orbital interaction corresponds to the energy minimum (Scheme 3.6).



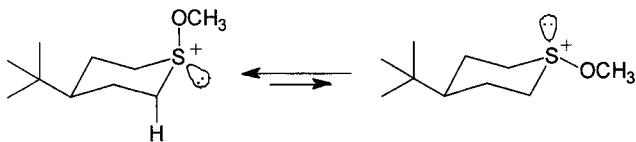
SCHEME 3.6

In view of this precedent, it is tempting to suggest the possibility that  $\sigma_{\text{C}-\text{H}} \rightarrow \sigma_{\text{S}-\text{O}}^*$  stereoelectronic interactions contribute to the stabilization of axial thiane-1-oxide (Scheme 3.7).



SCHEME 3.7

In apparent agreement with this hypothesis, Jalsovszky *et al.* [27] have determined a 4:1 axial over equatorial preference in the equilibrium shown in Scheme 3.8. This result was interpreted in terms of a stabilizing  $\sigma_{\text{C}-\text{H}} \rightarrow \sigma_{\text{S}-\text{OCH}_3}^*$  orbital interaction in the axial isomer. Inherent to this proposal is the assumption that a C—H sigma bond is a better donor orbital than a C—C sigma bond [28], which could stabilize the equatorial isomer.

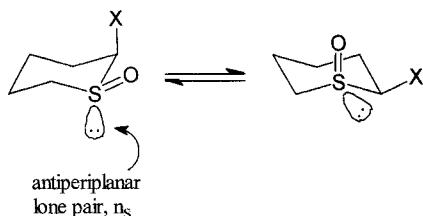


SCHEME 3.8

### 3.2.3 Conformational Equilibria in Substituted Thiane-1-oxides

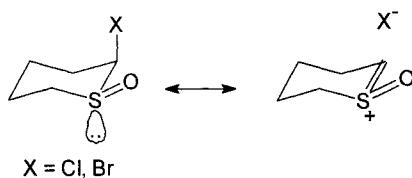
Recently, the conformational equilibria of several 2-polar-substituted tetrahydrothiopyran *S*-oxides was examined [29]. It was reasoned that the reduced capacity of sulfur in sulfoxides to act as lone electron pair donor should be reflected in a substantial reduction of the  $n_{\text{s}} \rightarrow \sigma_{\text{C}-\text{X}}^*$  hyperconjugative

interactions which would otherwise stabilize the conformer with axial C—X in the conformational equilibria of the *cis* diastereoisomers (Scheme 3.9).



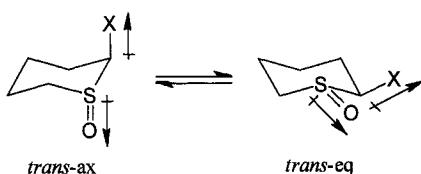
SCHEME 3.9

In the event, *cis*-2-bromo- and *cis*-2-chlorotetrahydrothiopyran *S*-oxide show a small but definite thermodynamic preference for the isomer with equatorial sulfinyl group and axial C—X bond:  $\Delta G_{167\text{K}}^{\circ} = +0.06$  and  $+0.02\text{ kcal mol}^{-1}$ , respectively (Scheme 3.9). This finding is not in line with expectation based on simple additivity of the conformational preferences of isolated systems. Indeed, for thiane oxide (**3**) the axial conformer is favoured by  $\sim 0.2\text{ kcal mol}^{-1}$  (see above), and equatorial bromo- and chlorocyclohexane are preferred by  $\sim 0.5\text{ kcal mol}^{-1}$ . Thus, simple additivity affords a calculated  $\Delta G^{\circ} = +0.7\text{ kcal mol}^{-1}$ , which by comparison with the observed  $\Delta G^{\circ} = 0.0\text{--}0.1\text{ kcal mol}^{-1}$  suggests the manifestation of a conformational effect stabilizing the isomer with axial C—X (and equatorial S=O) to the extent of  $0.7\text{--}0.8\text{ kcal mol}^{-1}$ . This is the isomer that presents an antiperiplanar (ap) arrangement between the sulfur lone pair,  $n_{\text{S(O)}}$ , and the carbon–halogen bond. The hypothesis that a  $n_{\text{S(O)}} \rightarrow \sigma_{\text{C-X}}^*$  hyperconjugative interaction is responsible for the observed stabilization (Scheme 3.10) seemed reasonable to Juaristi and Ordoñez [29].



SCHEME 3.10

By contrast, no suitable orientation of  $n_{\text{S}}$  and C—X is possible in the *trans* diastereoisomers (Scheme 3.11). Thus, it might be anticipated that the anomeric effect leading to the stabilization of axial C—X, will be less important in S(O)—C—X segments than in S—C—X segments, at least as far as stereoelectronic arguments are concerned.



SCHEME 3.11

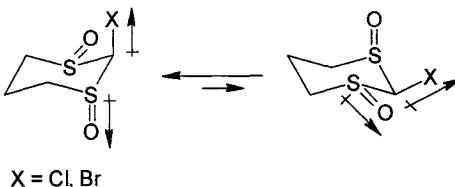
The experimentally observed preference for the diaxial conformation both in the chloro and bromo derivatives ( $\Delta G^\circ = +0.3 \text{ kcal mol}^{-1}$ ) shows the influence of a conformational effect that stabilizes *trans*-ax, or destabilizes *trans*-eq, in Scheme 3.11, and which probably originates from the favourable antiparallel orientation of the bond dipoles in the diaxial arrangement [30].

Finally, the finding of a preferred diequatorial conformation for 2c,6c-dichlorotetrahydrothiopyran-*r*-1-oxide (Scheme 3.12) was explained [29] in terms of a dominant 1,3-*syn* diaxial repulsive interaction between the chlorine atoms.



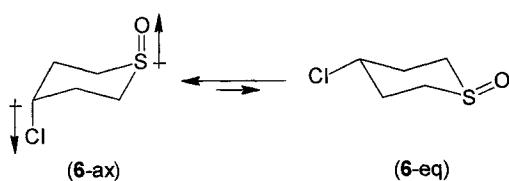
SCHEME 3.12

In a related study, Aggarwal, and colleagues [31] have observed that anomeric and dipole–dipole interactions result in a pronounced axial preference for the halogen substituent in 2-halo-1,3-dithiane-*trans*-1,3-dioxide (Scheme 3.13).



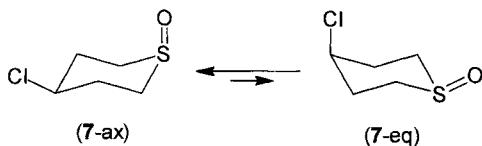
SCHEME 3.13

Interestingly, *trans*-4-chlorothiane-1-oxide (**6**) (Scheme 3.14) is at least 96% in the diaxial form (at  $-84^\circ\text{C}$  in  $\text{CD}_2\text{Cl}_2$ ) [32], which corresponds to a minimum value of  $1.2 \text{ kcal mol}^{-1}$  in conformational free energy difference for the equilibrium shown in Scheme 3.14. Clearly, there is no additivity of the conformational preferences of chlorine ( $\Delta G^\circ = -0.5 \text{ kcal mol}^{-1}$ ) [33] and the  $\text{S}=\text{O}$  group ( $\Delta G^\circ = +0.2 \text{ kcal mol}^{-1}$  [14]). The discrepancy was attributed to a 1,4-dipolar effect, although attempted calculations in terms of simple electrostatic interactions were unsuccessful [32].



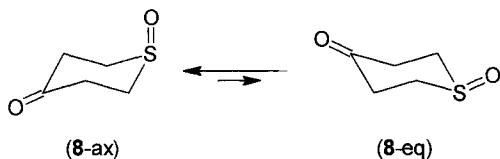
**SCHEME 3.14**

Wood and colleagues [32] reexamined the conformational behaviour of *cis*-4-chlorothiane-1-oxide (**7**) (Scheme 3.15). The approximate 1:1 ratio of (**7**-ax):(**7**-eq), which had been based on infrared studies [34], was corrected to a 74:26 ratio, as derived from low-temperature (below-coalescence)  $^1\text{H}$  NMR measurement of integrated intensities. The larger signal was assigned to (**7**-ax), and yielded a value  $\Delta G_{198\text{ K}}^{\circ} = +0.41 \text{ kcal mol}^{-1}$ . This result is reasonably close to the one anticipated assuming additivity.



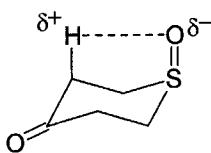
**SCHEME 3.15**

In a related study, the conformational equilibrium of 4-oxo-thiane-1-oxide (**8**) (Scheme 3.16) was determined by Anteunis and colleagues [35] as ~90% axial and 10% equatorial. The free energy difference ( $\Delta G_{298K}^{\circ} = +1.3 \text{ kcal mol}^{-1}$ ) is definitively larger than in thiane-1-oxide itself.

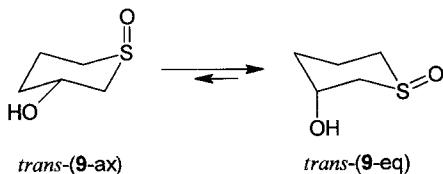


**SCHEME 3.16**

The high predominance of (8-ax) was explained in terms of a short-range attractive interaction between the negative sulfoxide oxygen and the positive *syn*-dixial hydrogens [35] as shown below. Quantum-mechanical calculations could be useful to support this argument.

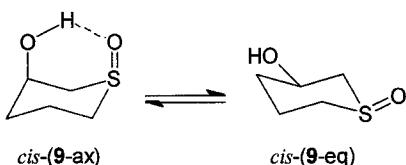


More recently, Brunet and Eliel [36] reported the conformational analysis of *cis*- and *trans*-3-hydroxythiane-1-oxides (*cis*-(9) and *trans*-(9)) at various dilutions. The low-temperature NMR examination of the *trans* isomer showed that the isomer with equatorial OH predominates under all conditions, as one might have expected from the tendency of OH to be predominantly equatorial [33] and from that of S=O to be predominantly axial [14]. A concentration dependence of  $\Delta G^\circ$  in  $\text{CD}_2\text{Cl}_2$  was observed: +0.60 kcal mol<sup>-1</sup> at high concentration and +1.05 kcal mol<sup>-1</sup> at the highest dilution. It was suggested that *intermolecular* hydrogen bonding is of the S=O⋯H-O type (rather than O—H⋯O—H), which is favoured when the molecule exists with equatorial S=O and axial OH. In dilute solution ( $3 \times 10^{-4}$  mol l<sup>-1</sup>),  $\Delta G^\circ$  agrees with the value of +1.1 kcal mol<sup>-1</sup> which would correspond to additivity between the equatorial preference of OH (0.9 kcal mol<sup>-1</sup>) [33] and the axial preference of S=O (0.2 kcal mol<sup>-1</sup>) [14] (Scheme 3.17).



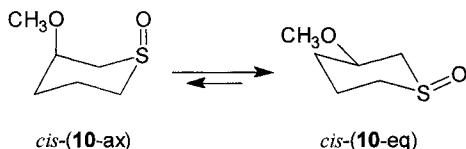
SCHEME 3.17

Much more significant changes were obtained with *cis*-(9) [36,37]. Here,  $\Delta G^\circ$  in  $\text{CD}_2\text{Cl}_2$  varied from +0.95 kcal mol<sup>-1</sup> at 2.8 mol l<sup>-1</sup> to less than -1.3 kcal mol<sup>-1</sup> at  $2.3 \times 10^{-3}$  mol l<sup>-1</sup>; i.e., there is a change in equilibrium from  $K \approx 12$  in favour of the diequatorial conformer to essentially total predominance of the axial one (Scheme 3.18). It was proposed that, in concentrated solution, hydrogen bonding is mostly *intermolecular* and of the S=O⋯H—O type, so that this stabilizing interaction forces both substituents to be equatorial. At high dilution, however, the molecule is stabilized by an *intramolecular* hydrogen bond which forces it into the diaxial conformation [36,37].



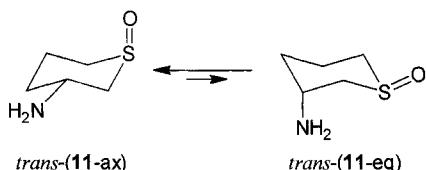
SCHEME 3.18

In contrast, the methyl ether derivative, *cis*-(**10**), exists entirely on the diequatorial side, showing that this conformational isomer is by far the predominant one in the absence of hydrogen bonding [36] (Scheme 3.19).



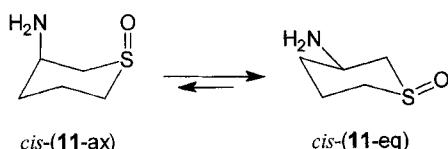
SCHEME 3.19

A related study by Brunet and Azpeitia [38] involved the conformational analysis of *cis*- and *trans*-3-aminothiane-1-oxide (*cis*-(**11**) and *trans*-(**11**)) (Scheme 3.20). In the *trans* isomer, in  $\text{CD}_2\text{Cl}_2$  as solvent, the fraction of the conformer with axial sulfinyl and equatorial nitrogen is higher than 95% ( $\Delta G_{170\text{K}}^\circ > +1.4 \text{ kcal mol}^{-1}$ ) and reflects the known tendencies of the  $-\text{NH}_2$  group to be equatorial ( $\Delta G^\circ = -1.4 \text{ kcal mol}^{-1}$ ) [33] and that of  $\text{S=O}$  to be axial ( $\Delta G^\circ = +0.2 \text{ kcal mol}^{-1}$ ) [14] (Scheme 3.20).



SCHEME 3.20

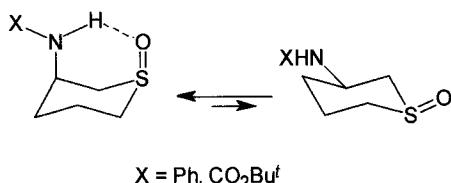
On the other hand, the population of the diaxial conformer in *cis*-3-aminothiane-1-oxide (*cis*-(**11**)) amounted to a mere 3% in  $\text{CD}_2\text{Cl}_2$  ( $\Delta G_{170\text{K}}^\circ = -1.27 \text{ kcal mol}^{-1}$ ). This equilibrium was unaffected by concentration, which suggests that, contrary to the situation in the 3-hydroxy analogue *cis*-(**9**), intramolecular  $\text{NH}_2 \cdots \text{O=S}$  attraction is not significant here (Scheme 3.21).



SCHEME 3.21

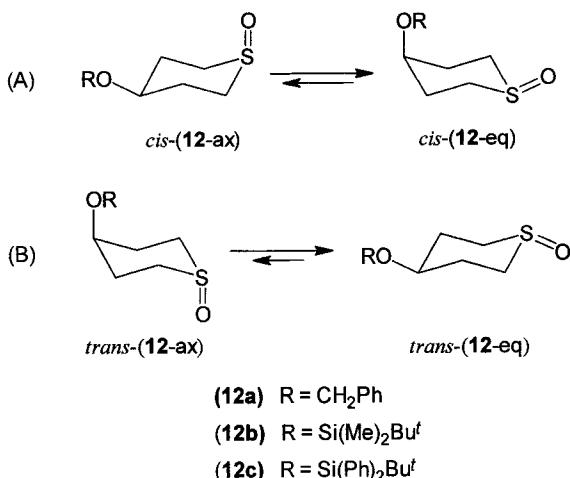
In this regard, introduction of electronegative substituents on nitrogen ( $\text{NH}_2 \rightarrow \text{NHPh} \rightarrow \text{NHCO}_2\text{Bu}^t$ ) increased the participation of the diaxial form to 67% and

>97%, respectively, strongly suggesting that hydrogen bonding forces the equilibrium towards the diaxial conformation [38,39] (Scheme 3.22).



SCHEME 3.22

More recently, Nagao and colleagues [40] described the conformational analysis of *cis*- and *trans*-4-benzyloxy- and 4-siloxy-substituted thiane-1-oxides (*cis*-(12) and *trans*-(12)) at  $-80^\circ\text{C}$  in  $\text{CD}_2\text{Cl}_2$ . The results are collected in Table 3.2, and show that in the cases of *cis*-4-RO-thiane-1-oxide (Scheme 3.23A), their RO-ax conformer preferences are 45% (**12a**), 66% (**12b**), and 67% (**12c**), respectively. In the cases of *trans*-4-RO-thiane-1-oxide (Scheme 3.23B), the preferences of RO for the axial position are higher.



SCHEME 3.23

In the conformational equilibria for *cis*-(12) and *trans*-(12), the  $\sigma_{\text{C}-\text{H}} \rightarrow \sigma_{\text{C}-\text{OR}}^*$  orbital overlap interaction may contribute to the stability of RO-ax conformers, while  $\sigma_{\text{C}-\text{C}} \rightarrow \sigma_{\text{C}-\text{OR}}^*$  orbital overlap may similarly stabilize their corresponding RO-eq conformers.

This model assumes that electron donation from an axial C—H bond toward a  $\sigma_{\text{C}-\text{OR}}^*$  orbital under antiperiplanar relation may be preferred over that from a C—C bond toward a  $\sigma^*$  orbital of the equatorial C—OR bond [28,41].

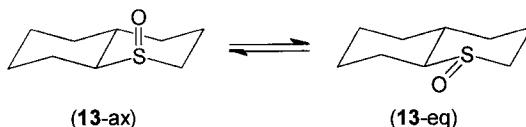
**TABLE 3.2** Conformer ratio in RO-substituted *cis*- and *trans*-thiane-1-oxide (**12**)<sup>a</sup>

Compd	R	Conformer ratio	Conformer ratio
		<i>cis</i> -( <b>12</b> -ax): <i>cis</i> -( <b>12</b> -eq)	<i>trans</i> -( <b>12</b> -ax): <i>trans</i> -( <b>12</b> -eq)
( <b>12a</b> )	CH <sub>2</sub> Ph	45:55	89:11
( <b>12b</b> )	Si(Me) <sub>2</sub> Bu <sup>t</sup>	66:34	96:04
( <b>12c</b> )	Si(Ph) <sub>2</sub> Bu <sup>t</sup>	67:33	98:02

<sup>a</sup>The conformer ratio was based on <sup>1</sup>H NMR (400 MHz) analysis in CD<sub>2</sub>Cl<sub>2</sub> at –80°C.

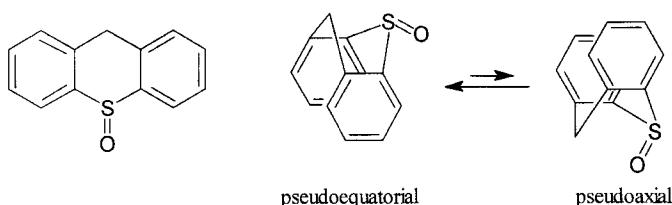
### 3.2.4 Conformational Analysis of *trans*-1-Thiadecalin-1-oxide

Evans and Rooney [42] determined the conformational energy of the (**13**-ax)  $\rightleftharpoons$  (**13**-eq) equilibrium (Scheme 3.24) by acid-catalysed equilibration. The axial isomer is favoured by a margin of 64:36 at 30°C, which corresponds to  $\Delta G_{303\text{K}}^\circ = +0.34\text{ kcal mol}^{-1}$ . This value is, of course, quite similar to that found in thiane-1-oxide itself ( $\Delta G_{183\text{K}}^\circ = +0.18\text{ kcal mol}^{-1}$ ) [44].

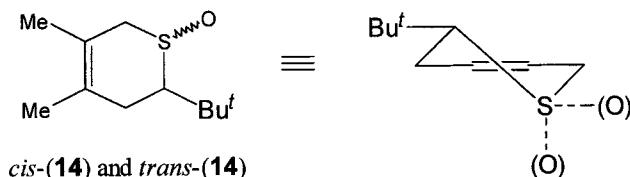
**SCHEME 3.24**

### 3.2.5 Conformation of Thioxanthene Sulfoxides

The sulfoxide of a thioxanthene has been shown to undergo rapid ring inversion, but to exist preferentially in the conformation with S=O pseudoequatorial (Scheme 3.25) [43]. A very recent study of a series of 2-substituted thioxanthene sulfoxides revealed that all of them have the same pseudoequatorial geometry [44].

**SCHEME 3.25**

A somewhat related system is that of 5,6-dihydro-2*H*-thiopyran-1-oxides. The literature on the conformational preferences of these compounds is scarce, but recent work by Tecklenburg and colleagues [45] shows that the preferred conformation in the thioether precursors is the half-chair. On the other hand, the preferred conformation of *cis*- and *trans*-3,4-dimethyl-6-*t*-butyl-5,6-dihydro-2*H*-thiopyran-1-oxides (*cis*-(14) and *trans*-(14)) has also been established as the half-chair, with the *t*-butyl group equatorial, and an axial or equatorial orientation of the oxygen substituent [46] (Scheme 3.26).



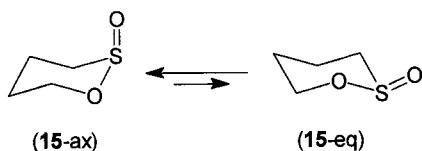
**SCHEME 3.26**

From the arguments presented by the authors (based on NMR measurements and molecular mechanics calculations), one could conclude that, for *cis*-(14), only the half-chair with the *t*-butyl equatorial and the S=O axial is populated. For the *trans* isomer, the most represented conformer has both the *t*-butyl and sulfinyl groups equatorial [46].

### 3.3 CONFORMATIONAL ANALYSIS OF OXATHIANE S-OXIDES

### 3.3.1 1,2-Oxathiane *S*-Oxide

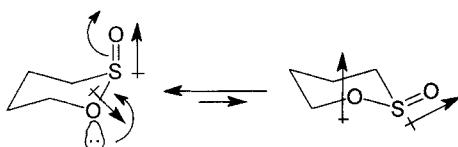
Substitution of an  $\alpha$ -methylene group in thiane-1-oxide by oxygen ((3)  $\rightarrow$  (15)) results in a greater predominance of the axial conformer [47] (Scheme 3.27). In fact, Harpp and Gleason interpreted the 100-MHz  $^1\text{H}$  NMR spectrum of 1,2-oxathiane-2-oxide (15) in terms of a single *axial* conformation.



**SCHEME 3.27**

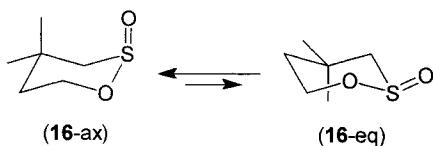
Since only one isomer was observed at ambient temperature for oxathiane (**15**), under conditions where less than 5% of the minor isomer would be detectable, the

authors [47] concluded that a conformational free energy difference in excess of  $\Delta G_{298\text{K}}^{\circ} > 2.0 \text{ kcal mol}^{-1}$  exists for the **(15-ax)**  $\rightleftharpoons$  **(15-eq)** equilibrium. It was suggested that this strong preference for the axial S=O conformation results from a dipolar interaction: the conformation in which the S=O bond is in an equatorial position possesses an unfavourable parallel arrangement of the net dipole resulting from the nonbonded lone-pair electrons of oxygen and the dipole of the S=O bond (Scheme 3.28). In addition, the high stability of **15-ax** relative to **15-eq** may be the result of stereoelectronic effects [48]. In particular, the anomeric effect [26,49–52] might be responsible for the antiperiplanar (diaxial) orientation of the S=O group and the lone pair of electrons at oxygen –  $n_{\text{O}} \rightarrow \sigma_{\text{S}-\text{O}}^*$  hyperconjugative interaction (Scheme 3.28).



SCHEME 3.28

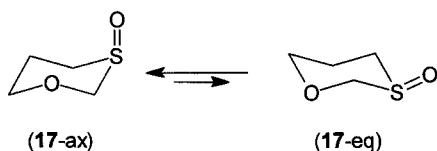
The proton NMR studies described above were expanded to  $^{13}\text{C}$  NMR spectroscopy [53] in order to take advantage of the greater chemical shift differences in carbon spectra. The high predominance of 1,2-oxathiane S-oxide (**15**) in the conformation with axial S=O was confirmed. Furthermore, even sterically bulky groups, such as methyl and phenyl, *syn*-diaxial to the sulfinyl group, are incapable of overcoming such preference [53] (Scheme 3.29).



SCHEME 3.29

### 3.3.2 1,3-Oxathiane S-Oxide

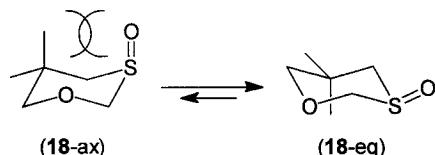
Two independent studies in 1974 described the NMR spectra of the title sulfoxide [54,55]. From these data, Bergesen *et al.* [54] suggested an equilibrium constant for **(17-ax)**  $\rightleftharpoons$  **(17-eq)** (Scheme 3.30) close to unity, in  $\text{CDCl}_3$  and at  $38^\circ\text{C}$ . In contrast, the low-temperature spectrum ( $-95^\circ\text{C}$ , in acetone- $d_6$ ) was interpreted by these researchers as containing at least 90% of the axial isomer.



**SCHEME 3.30**

Although not discussed in detail by the authors, the dramatic difference in conformational behaviour at  $T = 38^\circ\text{C}$  ( $\Delta G^\circ \approx 0.0 \text{ kcal mol}^{-1}$ , in  $\text{CDCl}_3$ ) and  $T = -95^\circ\text{C}$  ( $\Delta G^\circ \geq 0.8 \text{ kcal mol}^{-1}$ , in acetone- $d_6$ ), if real, reflects a rather substantial solvent effect – the axial conformer being stabilized by the more polar solvent. Alternatively, solvation of (17-ax) could give place to a loss of entropy, whose effect ( $T \Delta S^\circ$  contribution) on  $\Delta G^\circ$  is not as important at low temperature.

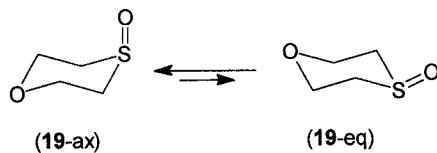
In their independent study, Van Acker and Anteunis established an 84:16 ratio of **(17-ax)** to **(17-eq)** ( $-98^{\circ}\text{C}$  in freon 21;  $\Delta G^{\circ} = +0.57 \text{ kcal mol}^{-1}$  in Scheme 3.30) [55]. A *gem*-dimethyl group at C-5 decreased the proportion of the axial isomer to only 10% at  $-102^{\circ}\text{C}$  ( $\Delta G^{\circ} = -0.73 \text{ kcal mol}^{-1}$ ) [55], and suggests a value of  $1.3 \text{ kcal mol}^{-1}$  for the  $\text{S=O/CH}_3$  *syn*-dixial steric interaction in **(18-ax)** (Scheme 3.31).



**SCHEME 3.31**

### 3.3.3 1,4-Oxathiane S-Oxide

The proton and carbon NMR spectra of the title heterocycle (**19**) were first reported by Szarek and colleagues in 1974 [56] and were found to be consistent with a predominantly axial conformer (Scheme 3.32).

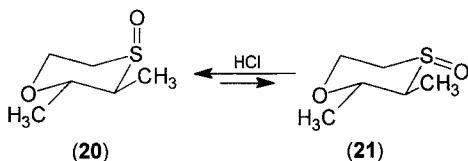


**SCHEME 3.32**

A quantitative determination of this equilibrium (Scheme 3.32) was reported a year later by Frieze and Evans [57], who found  $\Delta G_{193\text{K}}^{\circ} = +0.68 \text{ kcal mol}^{-1}$ ; i.e.,

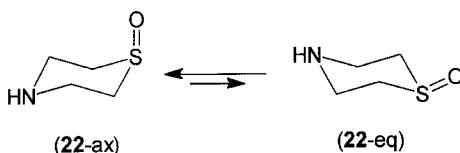
three times greater axial preference relative to that displayed by thiane-1-oxide (see Section 3.2.1).

More recently, Carretero and colleagues [58] described the acid-catalysed equilibration of diastereoisomeric sulfoxides (**20**) and (**21**) (Scheme 3.33). The axial-equatorial ratio was 4:1, which indicates  $\Delta G_{313\text{K}}^\circ = +0.86\text{ kcal mol}^{-1}$ , very similar to the value obtained in the unsubstituted system.



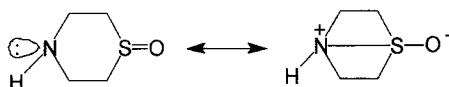
SCHEME 3.33

A related study by Nachtergael and Anteunis [59] concerns the conformational preference of 1,4-thiazane-1-oxide (**22**). Although an attempt to determine the conformational equilibrium (**22-ax**)  $\rightleftharpoons$  (**22-eq**) (Scheme 3.34) by slow-exchange <sup>1</sup>H NMR spectroscopy was unsuccessful, both conformers could be quantified in the low-temperature <sup>13</sup>C NMR spectra. An average value,  $\Delta G_{220\text{K}}^\circ = +0.12\text{ kcal mol}^{-1}$ , indicates a slight predominance of the axial isomer.



SCHEME 3.34

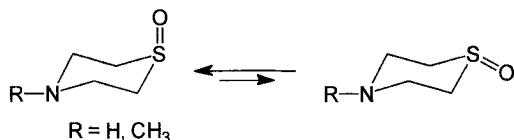
The spectrum of the hydrochloride salt of (**22**) in CD<sub>3</sub>OD was interpreted as suggesting an even higher population of the axial sulfoxide [59]. The suggestion by Zefirov [60] that the equatorial sulfoxide could, in the unprotonated form, be stabilized by electron donation from nitrogen (Scheme 3.35) could accommodate the experimental results.



SCHEME 3.35

In this context, Gallego and colleagues [61] measured the  $\Delta G^\circ$  value in the conformational equilibrium of *N*-methyl-1,4-thiazane S-oxide (Scheme 3.36),

which turned out to be 0.84 kcal mol<sup>-1</sup> in CD<sub>2</sub>Cl<sub>2</sub>. This value shows that the axial S=O is considerably more favoured than in the NH analogue, and this behaviour was explained on dipolar grounds.

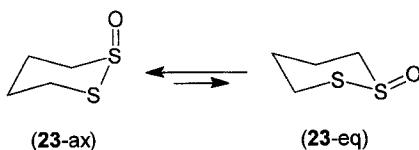


**SCHEME 3.36**

### 3.4. CONFORMATIONAL ANALYSIS OF DITHIANE S-OXIDES

### 3.4.1 1,2-Dithiane S-Oxide

That the substitution of an  $\alpha$ -methylene group by sulfur in thiane-1-oxide (**3**) to give the cyclic thiosulfinate (**23**) results in a greater predominance of the axial conformer (Scheme 3.37) was first proposed by Harpp and Gleason in 1971 [47] and was confirmed by several groups in the early 1980s [62–64].

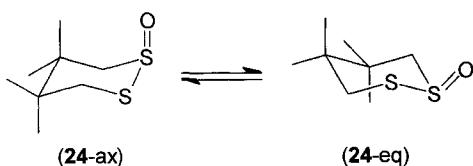


**SCHEME 3.37**

In fact, the equilibrium (23-ax)  $\rightleftharpoons$  (23-eq) is so much tilted to the left that the participation of the equatorial isomer is too small to permit a quantitative measurement of the equilibrium constant.

Nevertheless, it has been demonstrated by Lambert *et al.* [22] that the introduction of a *gem*-dimethyl group at C-3 in thiane-1-oxide to afford (**5**) strongly disfavours the axial conformer (see Section 3.2.2). For example, comparison of the conformational equilibria in 1,3-oxathiane *S*-oxide (**17**) and 5,5-dimethyl-1,3-oxathiane *S*-oxide (**18**) suggests that the magnitude of the *syn*-diaxial  $\text{CH}_3/\text{S}=\text{O}$  interaction amounts to  $\sim 1.3 \text{ kcal mol}^{-1}$  [55] (see Section 3.3.2).

With this information at hand, Juaristi and Cruz-Sánchez [65] prepared 4,4,5,5-tetramethyl-1,2-dithiane mono-*S*-oxide (**24**), the rationale being that the *syn*-dixial  $\text{CH}_3/\text{S}=\text{O}$  interaction in (**24**-ax) would produce an equilibrium closer to unity in Scheme 3.38, therefore allowing a more precise determination of the conformational preference of the  $\text{S}=\text{O}$  group in (**24**) and, indirectly, in (**3**).

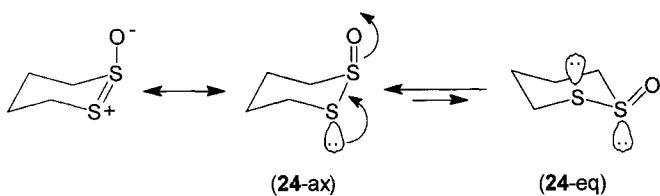


**SCHEME 3.38**

The very large difference in chemical shifts for the hydrogen atoms at C-3 ( $\Delta\delta = 1.45$  ppm) [66] was attributed to a *predominantly axial conformation* in (24), in which H-3ax experiences a strong deshielding effect by the *syn*-diaxial sulfinyl group.

In an attempt to observe different signals for the individual conformers in the **(24-ax)  $\rightleftharpoons$  (24-eq)** equilibrium, the spectrum was recorded at  $-80^{\circ}\text{C}$  in  $\text{CD}_2\text{Cl}_2$ . The proton NMR spectrum was similar to that recorded at ambient temperature ( $\Delta\delta$  for all hydrogens  $\leq 0.1$  ppm) [66], indicating that the participation of **(24-eq)** is not significant:  $K$  in Scheme 3.38 should be greater than 19; i.e.,  $\Delta G^{\circ} > 1.7 \text{ kcal mol}^{-1}$ . Because the  $\text{CH}_3/\text{S}=\text{O}$  *syn*-dixial interaction present in **(24-ax)** amounts to approximately  $1.3 \text{ kcal mol}^{-1}$  (see above), the conformational free energy difference in the **(3-ax)  $\rightleftharpoons$  (3-eq)** equilibrium was estimated as  $\Delta G^{\circ} > 3.0 \text{ kcal mol}^{-1}$  [65,66].

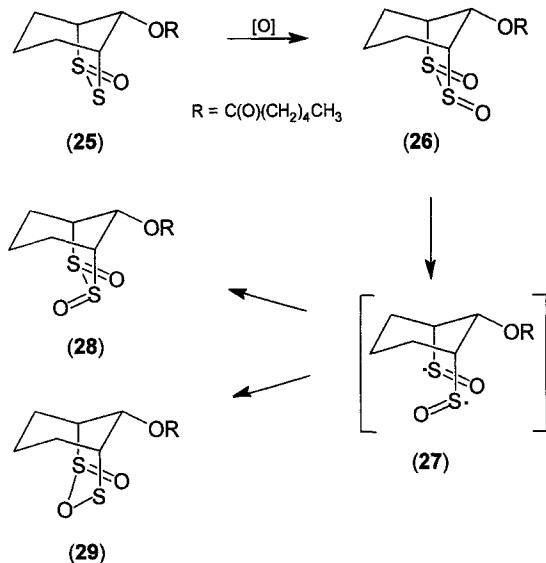
The remarkably high stability of **(24-ax)** (and **(3-ax)**) relative to **(24-eq)** (and **(3-eq)**) is probably the result of stereoelectronic effects. In particular,  $n_s \rightarrow \sigma_{S-O}^*$  hyperconjugative interaction [3] might be responsible for the preferred antiperiplanar (diaxial) orientation of the S=O group and one of the lone pairs of electrons at sulfur (Scheme 3.39). In addition, the destabilizing antiperiplanar arrangement of lone pairs in **(24-eq)** (and **(3-eq)**), as illustrated in Scheme 3.39, is also expected to be an important factor [67].



**SCHEME 3.39**

Of related interest is the recently disclosed preparation of symmetric  $\alpha$ -disulfoxide (**26**) (Scheme 3.40) by oxidation of bridged bicyclic thiosulfinate (**25**) [68,69]. The mutual dipolar repulsion of the adjacent sulfur–oxygen bonds was apparently not strong enough to inhibit the parallel attack of oxygen; clearly, the *endo* face is highly hindered (Scheme 3.40). However, the appearance of (**28**) as

the second intermediate in the oxidation of (25) was explained as occurring via diradical (27). The final product of the oxidation was thiosulfonate (29) [68].



SCHEME 3.40

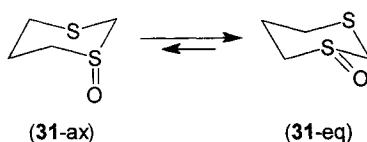
### 3.4.2 1,3-Dithiane S-Oxide

That the ‘normal’ axial preference of the sulfinyl oxygen is reversed in 1,3-dithiane S-oxides was first observed by Cook and Tonge [70], who examined the diastereoisomeric equilibrium (30-ax)  $\rightleftharpoons$  (30-eq) under basic conditions (Scheme 3.41).



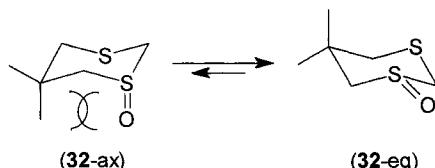
SCHEME 3.41

The diastereoisomeric ratio at equilibrium afforded  $\Delta G^\circ = -0.5 \text{ kcal mol}^{-1}$  in favour of the isomer with lower dipole moment (30-eq). This result was confirmed, qualitatively, by examination (NMR and dipole moments) of the parent sulfoxide (31) and its anancomeric models [71] (Scheme 3.42).



**SCHEME 3.42**

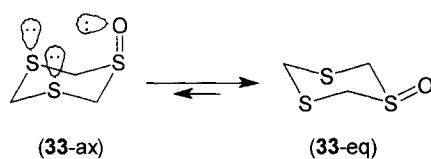
Quantitative data for the equilibrium depicted in Scheme 3.42 was obtained by Van Acker and Anteunis [55] by low-temperature  $^1\text{H}$  NMR spectroscopy in freon 21. The 84.6:15.4 ratio determined for **(30-eq):(30-ax)** afforded a  $\Delta G_{181\text{K}}^\circ = -0.63\text{ kcal mol}^{-1}$ , in good agreement with the value obtained by chemical equilibration [70] (Scheme 3.41). Only the equatorial isomer was observed in the 5,5-dimethyl analogue **(32)**, as expected from the additional steric destabilization in **(32-ax)** [55] (Scheme 3.43).



**SCHEME 3.43**

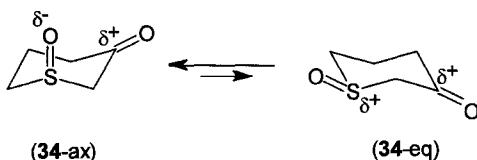
Quantitative data for the conformational equilibrium of 1,3-dithiane *S*-oxide (**31**) were also collected by Khan *et al.* [72] ( $\Delta C_{192\text{K}}^\circ = -0.63 \text{ kcal mol}^{-1}$ , in  $\text{CHClF}_2$ ) and by Juaristi *et al.* [64] ( $\Delta G_{193\text{K}}^\circ = -0.64 \text{ kcal mol}^{-1}$ ). The lack of a solvent effect appears to indicate that dipole–dipole interactions do not control the (**31**–ax)  $\rightleftharpoons$  (**31**–eq) equilibrium (Scheme 3.42).

A tentative assignment of the 270 MHz  $^1\text{H}$  NMR spectrum of 1,3,5-trithiane S-oxide (33) (Scheme 3.44) suggested [72] that (33-eq) predominates by more than 95%. The apparent trend of increasing amounts of the equatorial isomer in going from thiane S-oxide (38%) to 1,3-dithiane S-oxide (84%) to 1,3,5-trithiane S-oxide (>95%) could reflect the participation of a *gauche* repulsive effect [73], that is, electron–electron repulsion between the two *gauche* substituents, O and S, may overwhelm the normal tendency of the S=O group to be axial. On the other hand, the increased axial preference in the oxathiane analogue (see Section 3.3.2) could be the result of an O/O attractive *gauche* effect [73].



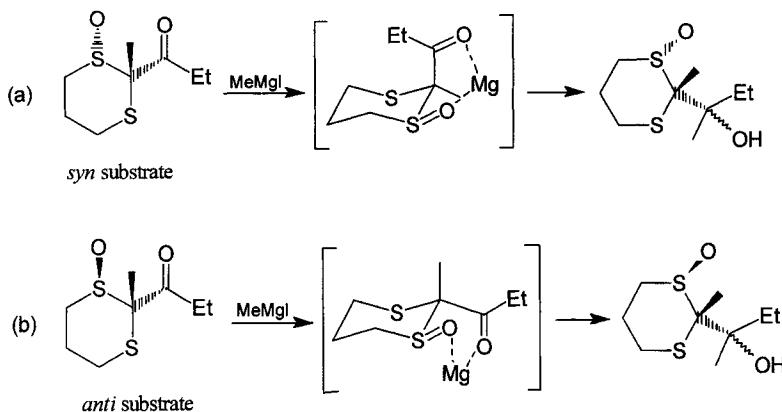
**SCHEME 3.44**

In this regard, sulfoxide (34) (Scheme 3.45) which contains an electron-deficient group at the  $\beta$ -position, adopts a predominantly axial conformation [74] ( $\Delta G_{253\text{K}}^\circ = +1.1 \pm 0.2 \text{ kcal mol}^{-1}$ ). The authors [74] suggest that, on the assumption that the  $\Delta G^\circ$  value for (34) is dominated by  $\Delta H^\circ$  rather than  $\Delta S^\circ$ , it may be concluded that replacement of a  $\beta\text{-CH}_2$  unit by  $\text{C=O}$  enhances the axial preference. Indeed, in terms of steric factors, replacement of  $\text{CH}_2$  by an  $\text{sp}^2$  carbon atom should lead to a reduction in 1,3-steric repulsion. On the other hand, electrostatic interactions should be repulsive in (34-eq), but could be attractive in (34-ax).



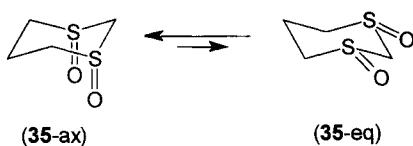
SCHEME 3.45

Of related interest is the diastereoselective addition of Grignard reagents to 2-acyl-1,3-dithiane *S*-oxides [75], which gave results in accordance with chelated Cram-type transition states [76] involving *equatorial* sulfoxides (Scheme 3.46).



SCHEME 3.46

Very recently, the two configurational isomers of 1,3-dithiane-1,3-dioxide were prepared by Bien and colleagues [77] and the information obtained from  $^{13}\text{C}$  NMR spectroscopy suggested a predominant diaxial conformation for the *cis* isomer (35) (Scheme 3.47).

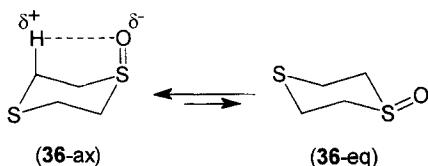


**SCHEME 3.47**

x-Ray crystallographic analysis of (35) confirmed a *syn*-dixial conformation in a distorted chair. The strain introduced by the repulsive interactions between the polarized S—O bonds is partially relieved by an elongated S-1…S-2 distance of 3.14 Å across the ring as compared with the normal value of 3.01 Å in the unstrained isomer *trans*-(35) [77,78]. No explanation is advanced by the authors regarding the surprising finding of diaxial *cis*-(35). In fact, they caution [77] that the x-ray results should not be extrapolated to solution, and that even the  $^{13}\text{C}$  NMR data (unusually upfield chemical shift for C-5) could be misleading.

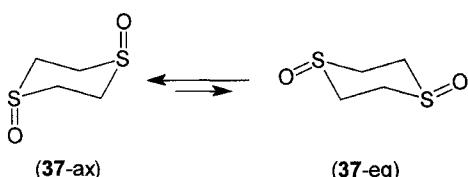
### 3.4.3 1,4-Dithiane *S*-Oxide

It has been established that the axial conformer of the title sulfoxide (**36**) is the more stable by 0.77 kcal mol<sup>-1</sup> at -80°C [79] (Scheme 3.48).



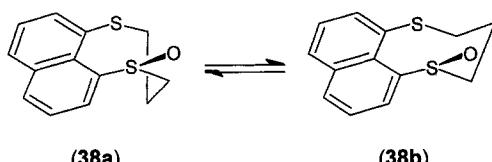
**SCHEME 3.48**

The increased axial preference relative to that observed in thiane-1-oxide, but comparable to that observed in the oxathiane analogue (see Section 3.3.3), could support the influence of an electrostatic attraction between the sulfinyl oxygen atom and the *syn*-dialixial hydrogen atoms (Scheme 3.48). Interestingly, *trans*-1,4-dithiane-1,4-dioxide (37) possesses a dialixial oxygen conformation in the solid state [80] and appears to exist preferentially in the same conformation in solution [81] (Scheme 3.49).



**SCHEME 3.49**

Of related interest is the recent conformational study of naphtho[1,8-*bc*]-1,5-dithiocin-1-oxide (**38**) (Scheme 3.50) by Glass and coworkers [82]. The conformation of sulfoxide (**38**) was established (by x-ray crystallographic analysis) to be boat (**38a**) with equatorial sulfinyl oxygen. In solution, however, <sup>1</sup>H NMR spectroscopic analysis revealed that (**38**) is predominantly in chair conformation (**38b**) with equatorial sulfoxide (Scheme 3.50).



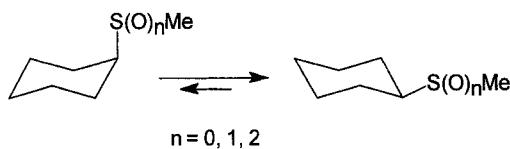
**SCHEME 3.50**

The experimental [82] and theoretical [83] evidence indicates that the equatorial sulfoxide oxygen is at least 3 kcal mol<sup>-1</sup> lower in energy than the axial counterpart in (38). An axial orientation of the sulfinyl oxygen is also unstable in the corresponding 1,5-dioxide, where the sulfinyl oxygens in the diaxial isomer repel each other sterically and electrostatically [84].

### 3.5 CONFORMATIONAL ANALYSIS OF 5-SULFINYL-1,3-DIOXANES

### 3.5.1 Eclipsed Conformation in *cis*-2-*t*-Butyl-5-(*t*-butylsulfonyl)-1,3-dioxane

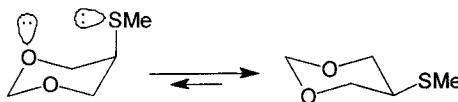
Several years ago, Eliel and Kandasamy described the conformational free energies ( $\Delta G^\circ$  values) for the methyl sulfide, methyl sulfoxide, and methyl sulfone groups in the cyclohexane ring [85]. The reported values,  $-1.00$ ,  $-1.20$ , and  $-2.50$  kcal mol $^{-1}$ , respectively, clearly reflect the steric requirements of the sulfur functions (Scheme 3.51).



### SCHEME 3.51

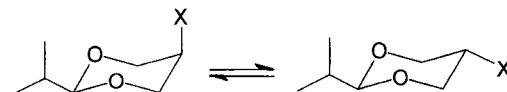
Eliel and colleagues [86] discovered also that the  $\text{CH}_3\text{S}$  group attached to C-5 in a 1,3-dioxane has a stronger preference for the equatorial conformation

( $\Delta G^\circ = -1.82 \text{ kcal mol}^{-1}$  in solvent cyclohexane) than that measured for (methylthio)cyclohexane, this being the result of a repulsive interaction of the unshared electrons of sulfur with the unshared electrons of the ring oxygens (the so-called 'repulsive gauche effect' [73]) (Scheme 3.52).



SCHEME 3.52

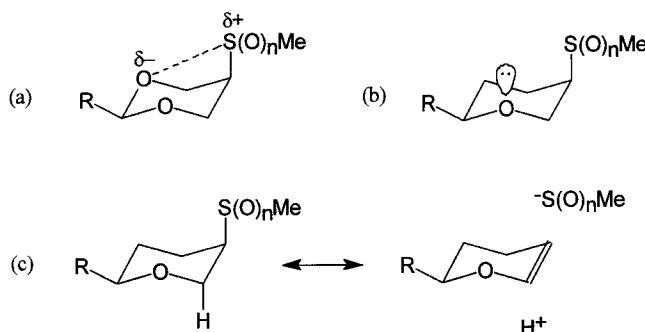
TABLE 3.3 Conformational equilibria in 5-substituted 1,3-dioxanes [90,91]



Compound	X	$\Delta G^\circ (\text{kcal mol}^{-1})$
(39)	$\text{CH}_3\text{S}$	$-1.82 \pm 0.01$
(40)	$\text{CH}_3\text{SO}$	$+0.82 \pm 0.11$
(41)	$\text{CH}_3\text{SO}_2$	$+1.19 \pm 0.10$
(42)	$\text{Bu}'\text{S}$	$-1.90 \pm 0.11$
(43)	$\text{Bu}'\text{SO}$	$+0.10 \pm 0.01$
(44)	$\text{Bu}'\text{SO}_2$	$-1.14 \pm 0.01$

In strong contrast, similarly placed methylsulfinyl ( $\text{CH}_3\text{SO}$ ) and methylsulfonyl ( $\text{CH}_3\text{SO}_2$ ) groups prefer the axial conformation [86] (Table 3.3). This unusual behaviour was rationalized in terms of an attractive, electrostatic interaction between the (negative) endocyclic oxygen atoms and the (positive) sulfinyl or sulfonyl sulfur (Scheme 53a). Nevertheless, the axial predominance of a methylsulfinyl group in analogous oxane rings has been explained in terms of (1) a donor-acceptor ( $n_{\text{O}} \rightarrow d_{\text{S}}$ ) stabilizing interaction (Scheme 53b) [87,88] and (2) a stereoelectronic orbital interaction between the axial, occupied  $\sigma_{\text{C}-\text{H}}$  bonds at C-2 and the antiperiplanar, empty  $\sigma_{\text{C}-\text{S}}^*$  orbital [89] (Scheme 53c).

In this context, the positions of equilibrium between diastereoisomeric *cis*- and *trans*-5-(*t*-butylthio)-, 5-(*t*-butylsulfinyl)-, and 5-(*t*-butylsulfonyl)-2-isopropyl-1,3-dioxanes were reported recently [90,91] (Table 3.3). Although  $\Delta G^\circ$  values for the sulfides are very similar, the difference in conformational behaviour for the sulfoxides is significant, and the effect of changing from methyl to *t*-butyl in the sulfones is quite dramatic: the large preference of the methyl analogue for the axial position (1.19 kcal mol<sup>-1</sup>, Table 3.3) is reversed in the *t*-butyl derivative, where the equatorial isomer is more stable by 1.14 kcal mol<sup>-1</sup>. Thus, the *t*-butyl ligand on

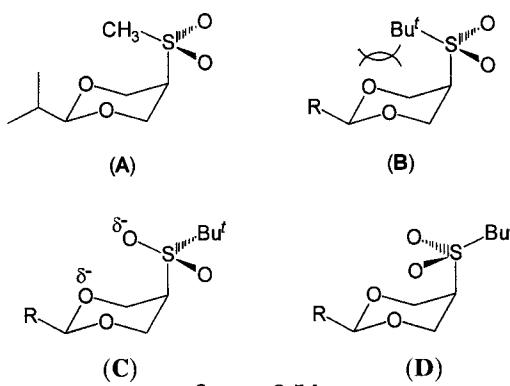


SCHEME 3.53

sulfur shifts the equilibrium toward the equatorial conformation by 2.33 kcal mol<sup>-1</sup>.

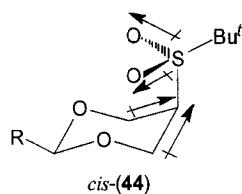
The axial preference of the methylsulfonyl group in (41) has also been explained in terms of an attractive, electrostatic interaction between the positive end of the S<sup>+</sup>—O<sup>-</sup> dipole and the negative ring oxygen atoms [86]. A large long-range (*W*) coupling constant of 1.14 Hz between the sulfonyl methyl and the hydrogen at C-5 of the dioxane indicates that *cis*-(41) exists with the methyl group pointing into the ring (structure (A), Scheme 3.54) [86]. Two explanations are suggested to account for the contrasting behaviour of (41) and (44) [90]: (1) An axial sulfonyl group with the alkyl ligand still inside the ring (structure (B)) would lead to significant steric congestion, causing the axial isomer to be destabilized. (2) A conformation with the *t*-butyl group turned outward (structure), places the negative ring oxygen atoms close to the negative sulfonyl oxygen, leading to an unfavourable electrostatic interaction.

However, that the structure of (44) in the solid state actually corresponds to (D) was established by x-ray diffraction analysis [90,91]. The sulfonyl *t*-butyl group is outside the ring, suggesting that the steric congestion that would be present if the alkyl group were inside the ring is more severe than the electrostatic repulsion between the negative oxygen atoms.



SCHEME 3.54

The most interesting feature of the crystallographic data, however, is that the average torsional angles  $O—S—C—C$  are  $8.25 \pm 2.35^\circ$ , indicating the nearly eclipsed nature of structure (**D**). This structure was compared with the most stable conformation predicted by molecular mechanics calculations [92]. From the results of this study, both steric and stereoelectronic interactions appear to be responsible for the  $S—O/C—C$  bond eclipsing. In particular, the eclipsing of bonds is a necessary evil to mitigate  $Bu^t/CH_2$  steric interactions present in (**C**) [93]. In addition, dipole-induced dipole interactions seem to be important in lowering the energy of the eclipsed sulfone [90,91,94] (Scheme 3.55).



SCHEME 3.55

### 3.5.2 Precise Structural Information on *cis*-5-(*t*-Butylsulfinyl)-2-*t*-butyl-1,3-dioxane

As for the axial sulfoxides, a single-crystal x-ray structure determination of *cis*-(43) (see Table 3.3) was carried out [95] and compared with data for the corresponding sulfone (*cis*-(44)). Whereas the latter adopts an eclipsed conformation (see above), both the *t*-butyl and the  $S=O$  group in the sulfinyl function of (**43**) point outside the ring in an approximately staggered rotamer.

A most interesting finding is the substantial difference in bond lengths between the two endocyclic  $C—C$  bonds of (**43**): while  $C-4—C-5$ , which is *syn* to the  $S=O$  group, seems shorter than normal ( $1.493 \text{ \AA}$ ),  $C-5—C-6$ , which is *syn* to the sulfur lone pair ( $n_S$ ), is unusually long ( $1.571 \text{ \AA}$ ). A theoretical model that explains this structural effect is the following: the through-space  $\sigma_{C-C} / \sigma_{S-O}^*$  interaction (two orbitals, two electrons) is stabilizing, and leads to a shortening in the  $C-4—C-5$   $\sigma$  bond, but the through-space  $\sigma_{C-C} / n_S$  interaction is destabilizing and causes a length increase in the  $\sigma$  bond [95].

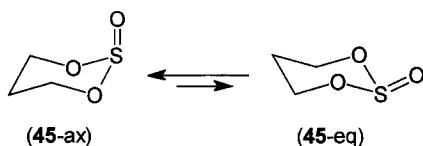
In this context, the short  $C-4—C-5$  bond, together with the finding of a longer than normal  $C-5—S$  bond ( $1.844 \text{ \AA}$ ), could be accounted for in terms of a hyperconjugative interaction between the (antiperiplanar) axial  $C-4—H$  bond and the  $C-5—S$  antibonding orbital,  $\sigma_{C-H} \rightarrow \sigma_{C-S}^*$  [96].

Interestingly, the *t*-butylsulfonyl group in (**44**) adopts an eclipsed conformation (two  $S=O/C—C$  pairs and one  $S—C/C—H$  pair of eclipsing bonds), whereas the *t*-butylsulfinyl group adopts a staggered conformation, even when only two pairs of bonds would become eclipsed. This observation might suggest the existence of a stabilizing interaction in the eclipsed bonds.

### 3.6. CONFORMATIONAL ANALYSIS OF 2-Oxo-1,3,2-DIOXATHIANES

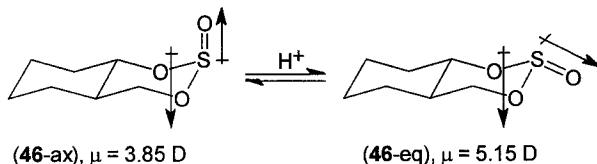
#### 3.6.1 Trimethylene Sulfite

It is now well established that the most stable conformation of the title compound (**45**) is a chair form containing an axially oriented S=O bond [97] (Scheme 3.56).



SCHEME 3.56

Chemical equilibration of the anancomeric models (**46-ax**)  $\rightleftharpoons$  (**46-eq**) (Scheme 3.57) indicated that the conformational preference for the equatorial orientation amounts to about 2 kcal mol<sup>-1</sup> in CCl<sub>4</sub> [98]. Interestingly, the differences in free energies ( $\Delta G^\circ$  values,) decrease with increasing solvent polarity (Table 3.4) suggesting that the more polar diastereoisomer (**46-eq**) is stabilized in more polar media.



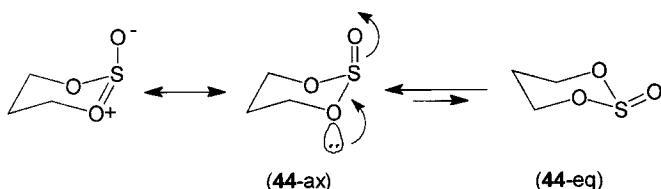
SCHEME 3.57

In addition to dipole–dipole interactions, a stereoelectronic effect is likely to stabilize the axial orientation of the S=O bond in trimethylene sulfite. In

TABLE 3.4 Chemical equilibration (BF<sub>3</sub>) of diastereoisomeric *trans*-1,3,2-dioxathiadecalin-2-oxides, at 40°C [98]

Solvent	$K [(\mathbf{46-ax}) / (\mathbf{46-eq})]$	$\Delta G^\circ$ (kcal mol <sup>-1</sup> )
CCl <sub>4</sub>	25.0	1.95
C <sub>6</sub> H <sub>6</sub>	18.7	1.80
CHCl <sub>3</sub>	13.9	1.61
CH <sub>3</sub> CN	12.9	1.57

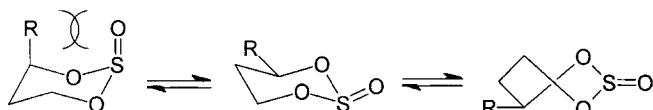
particular, stabilization results from electronic donation of the antiperiplanar lone pairs on the adjacent oxygen atoms into the  $\sigma^*$  antibonding orbital of the S—O bond (i.e.,  $n_O \rightarrow \sigma_{S-O}^*$  hyperconjugation) [49–52,99]. Because no antiperiplanar lone pairs to the S=O are found in (45-eq) (or (46-eq)), whereas (45-ax) contains two, the equatorial conformation is not stabilized by this stereoelectronic interaction (Scheme 3.58).



**SCHEME 3.58**

### 3.6.2 C(4,6)-Substituted Trimethylene Sulfites

For compounds incorporating a *syn*-dialixial, sterically demanding substituent, the question arises whether the ring will change its geometry. If so, it may invert to a chair with equatorial S=O, or adopt a twist conformation (Scheme 3.59).



**SCHEME 3.59**

On the basis of dipole moment measurements [100] and IR [101] and NMR [102] studies it has been suggested that twist forms are populated appreciably when a *syn*-dixial interaction occurs between the S=O and a methyl group at C-4 or C-6. However, these interpretations have been questioned by Pihlaja and coworkers [103,104], who examined NMR data on 2-oxo-1,3,2-dioxathiane and 39 methyl derivatives and preclude significant contributions from twist forms.

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# APPLICATIONS OF CHIRAL SULFOXIDES AS STEREOCONTROL ELEMENTS IN ORGANIC SYNTHESIS

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In the following discussion we highlight the relative ease of introduction of the sulfoxide moiety into the desired substrate, the ability of the sulfoxide group to control – predictably – the stereochemical outcome of a wide range of reaction types, and the facile removal of the sulfoxide moiety to yield the desired chiral products without loss of stereochemical integrity. Such properties are prerequisites of the model chiral auxiliary.

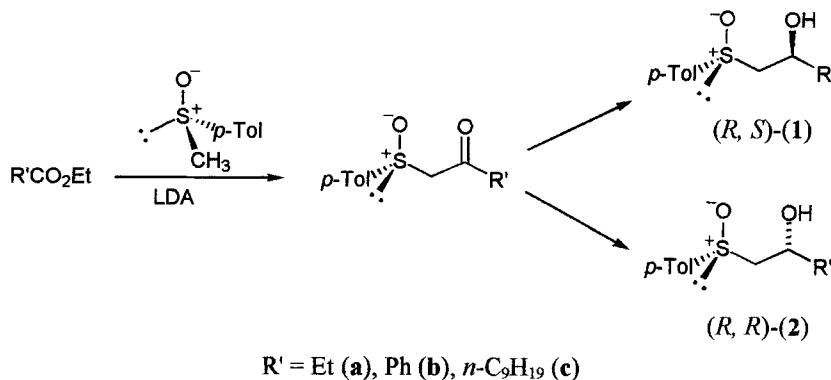
The stereocontrolled introduction of chirality into organic molecules remains an important challenge to the synthetic organic chemist. To produce, at will, only one of two possible enantiomeric compounds is more cost-effective than traditional resolution procedures, and considerably more elegant.

Over the past decade, the stereocontrolled reduction of enantiomerically pure  $\beta$ -ketosulfoxides by hydride reagents, particularly within the Solladié research group, has sparked considerable interest, as an approach to many synthetically important intermediates and biologically active molecules of defined chirality. The applications described below outline the effectiveness of the chiral sulfoxide moiety as a stereocontrol element, and highlight the ready removal of the sulfoxide group after its contribution to the synthetic scheme. In all cases, the sense of stereochemical induction can be rationalized and predicted on the basis of steric, stereoelectronic and/or chelation control factors.

## 4.1 STEREOSELECTIVE REDUCTION OF $\beta$ -KETOSULFOXIDES: SOME APPLICATIONS IN ORGANIC SYNTHESIS

### 4.1.1 The Synthesis of Non-racemic Alcohols

In 1982, Solladié reported a highly efficient, asymmetric synthesis of both enantiomers of methyl carbinols based on the stereoselective reduction of an enantiomerically pure  $\beta$ -ketosulfoxide [1]. Prior to this work, only low to moderate levels of enantiomeric purity had been observed by Cinquini [2] and Johnson [3] in similar studies. The  $\beta$ -ketosulfoxides used in Solladié's study were prepared by condensation of the  $\alpha$ -sulfinyl carbanion of (*R*)-methyl *p*-tolyl sulfoxide with esters (Scheme 4.1).



SCHEME 4.1

At low temperature ( $-100^\circ\text{C}$ ), high levels of diastereoselectivity were observed using hydride reagents. Products of opposite stereochemistry are available, depending upon the reducing agent employed (Scheme 4.1, Table 4.1).

The absolute configuration of the major diastereoisomer of either (**1a**) or (**2a**) was assigned by conversion to, and chemical correlation with, the known benzoate

TABLE 4.1 Reduction of  $\beta$ -ketosulfoxides (Scheme 4.1)

Reducing agent	Temperature ( $^\circ\text{C}$ )	$(\text{R}, \text{R})-(2):(\text{R}, \text{S})-(2)$		
		(a)	(b)	(c)
LAH/Et <sub>2</sub> O/THF	-100	93:7	90:10	90:10
DIBAL/THF	-100	12:88	18:82	0:100

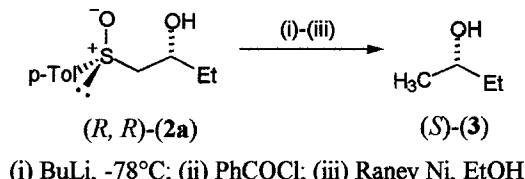
LAH = lithium aluminium hydride

THF = tetrahydrofuran

DIBAL = diisobutylaluminium hydride

of *(S)*-*(+)*-butan-2-ol (**3**), demonstrating the potential for the synthesis of enantiomerically enriched alcohols (Scheme 4.2).

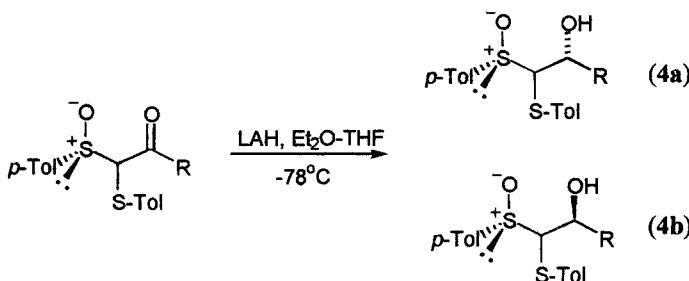
The stereochemical outcome of these reactions can be rationalized as discussed below (Section 4.1.3).



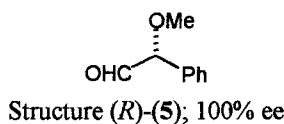
**SCHEME 4.2**

#### 4.1.2 The Synthesis of Enantiomerically Pure $\alpha$ -Hydroxy Aldehydes

Guanti established [4] that the LAH reduction of  $\alpha$ -tolylthio- $\beta$ -ketosulfoxides, prepared by direct acylation of the lithio-anion of optically pure (*S*)-(+) -*p*-tolyl *p*-tolylthiomethyl sulfoxide was highly diastereoselective, yielding diastereoisomeric product alcohols in ratios up to >99:1 (**4a**:**4b**) (Scheme 4.3) [5]. The  $\beta$ -hydroxysulfoxide products (**4a**) and (**4b**) can be considered as protected  $\alpha$ -hydroxyaldehydes; indeed, the synthesis of enantiomerically pure (*R*)-(−)- $\alpha$ -methoxyphenylacetaldehyde (**5**) (and its (*S*)-(+) antipode) was demonstrated through application of a previously established procedure [6].



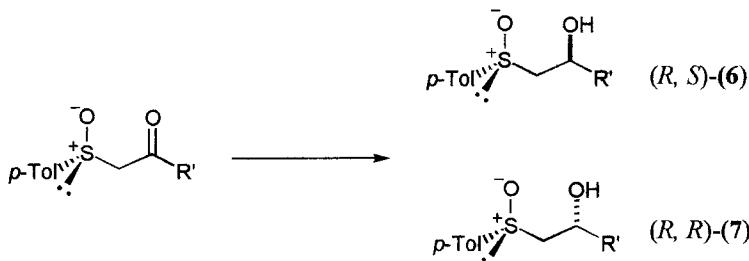
### SCHEME 4.3



#### 4.1.3 The Synthesis of Nonracemic Epoxides

Solladié later refined the reduction procedure, and applied the methodology to the synthesis of nonracemic epoxides [7]. Interestingly, he discovered that the addition of an equimolar amount of anhydrous zinc chloride to the ketone substrate in

solution prior to DIBAL reduction at  $-78^{\circ}\text{C}$  gave the opposite major product diastereoisomer to that produced on employing DIBAL alone; further, in the Lewis acid-assisted reduction, the major product diastereoisomer was found to be identical to that produced when using LAH as the reducing agent (Scheme 4.4, Table 4.2).



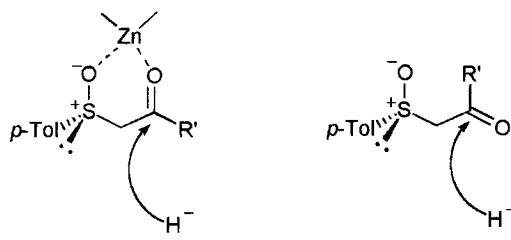
SCHEME 4.4

TABLE 4.2. Reduction of  $\beta$ -ketosulfoxides (Scheme 4.4)

$\text{R}'$	Reducing agent	$(R,S)$ - <b>(46)</b> : $(R,R)$ - <b>(47)</b>	Yield (%)
Ph	DIBAL	95:5	95
Ph	LAH	20:80	80
Ph	$\text{ZnCl}_2$ /DIBAL	5:95	90

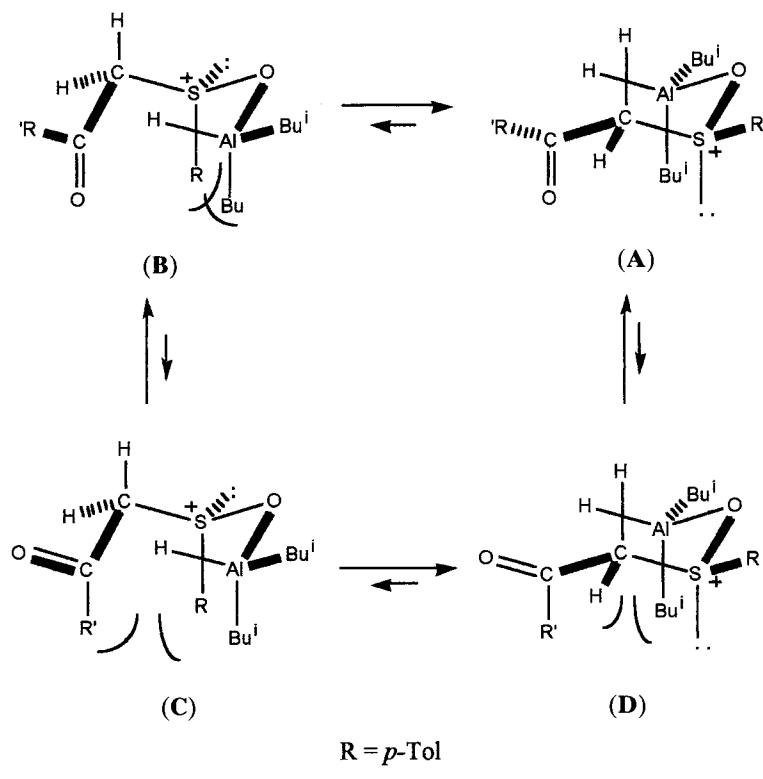
In the presence of a metal cation capable of chelation, transition state **(8)** was proposed to be favoured; the high levels of diastereoselectivity observed in the  $\text{ZnCl}_2$ /DIBAL reduction can therefore be rationalized on the basis of intermolecular hydride transfer from the least hindered face of the chelated, prochiral carbonyl system.

It was originally proposed that in the absence of a chelating metal counterion, conformation **(9)** would be favoured owing to the electronic repulsion of the oxygen atoms [7]. Intermolecular hydride delivery would then be favoured from the least sterically hindered face of the prochiral carbonyl group.

Structure **(8)**Structure **(9)**

Solladié later proposed the now favoured explanation of intramolecular hydride transfer from the DIBAL reducing agent in the absence of a chelating metal

counterion [8]. The Lewis acidic character of DIBAL allows formation of an O—Al bond with the more basic sulfinyl oxygen atom. Intramolecular hydride transfer can now take place through a nonchelated, chair-like transition state intermediate. Scheme 4.5 highlights the four chair-like transition states (**A–D**) for acyclic  $\beta$ -ketosulfoxide substrates.



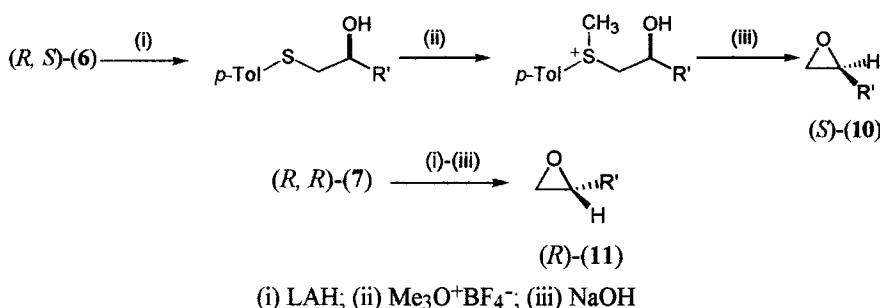
**SCHEME 4.5**

Transition state **(A)** is favoured since both **(C)** and **(D)** suffer from unfavourable  $R'/Bu^i$  1,3-diaxial interactions. **(B)** IS also disfavoured owing to  $R/Bu^i$  1,3-diaxial interactions.

Epoxide enantiomers (**10**) and (**11**) were prepared in good yields (60–70%) and excellent enantioselectivity (>90% *ee*) from the  $\beta$ -hydroxysulfoxides (**6**) and (**7**), respectively (Scheme 4.6).

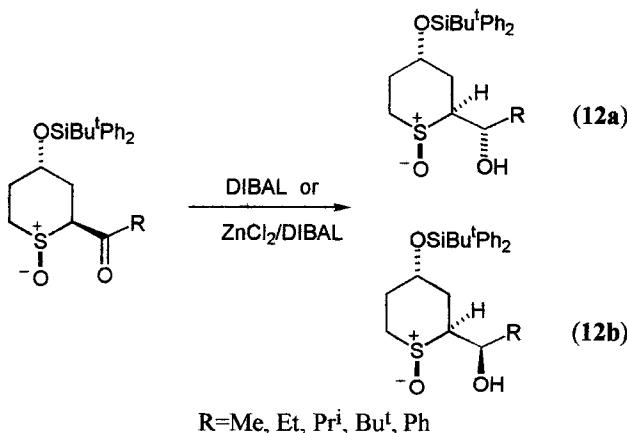
Later work by Solladié-Cavallo demonstrated the use of catalytic quantities of zinc chloride in the reduction procedure. Diastereoselectivities of up to 97:3 were observed [9].

More recently, Simpkins has described a route to functionalized epoxides by diastereoselective reduction of racemic cyclic  $\beta$ -ketosulfoxides (Scheme 4.7) [10]. Exclusive formation of (**12a**), (R = Bu<sup>t</sup>, Pr<sup>i</sup>; DIBAL), or (**12b**) (R = Me, Et, Bu<sup>t</sup>, Pr<sup>i</sup>, Ph; ZnCl<sub>2</sub>/DIBAL), could be realised by appropriate selection of reaction conditions. Preference for (**12a**) was rationalized by intramolecular hydride delivery from

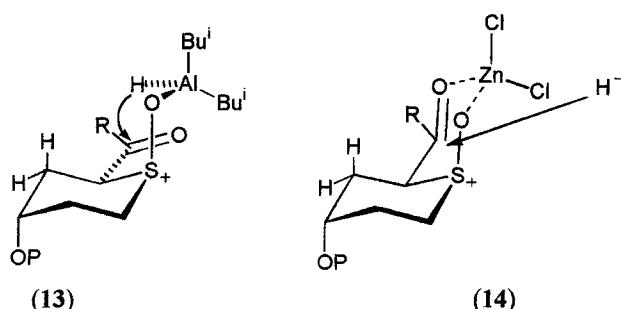


SCHEME 4.6

DIBAL as shown in transition state (13), and formation of (12b) occurred through intermolecular hydride attack on the chelated transition state intermediate (14).

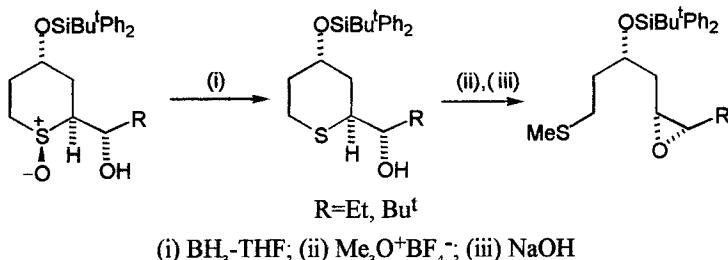


SCHEME 4.7



Interestingly, functionalized epoxides were readily obtained through functional group interconversion (Scheme 4.8). Although it was initially performed on a

racemic series of ketosulfoxides, Simpkins has demonstrated the utility of the above methodology in the synthesis of an enantiomerically pure epoxide [10] ( $R = Bu^t$ ) from a nonracemic ketosulfoxide substrate [11].

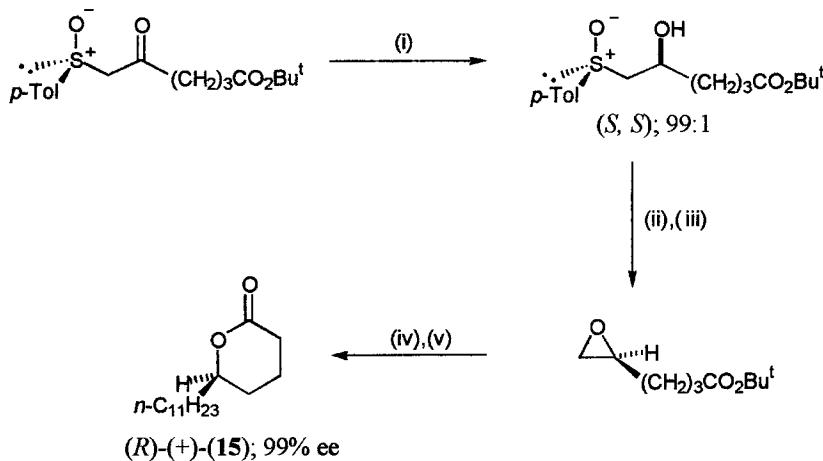


SCHEME 4.8

#### 4.1.4 The Synthesis of Enantiomerically Pure Lactones

Kosugi has applied the  $ZnCl_2$ /DIBAL methodology to the synthesis of enantiomerically pure lactones [12].

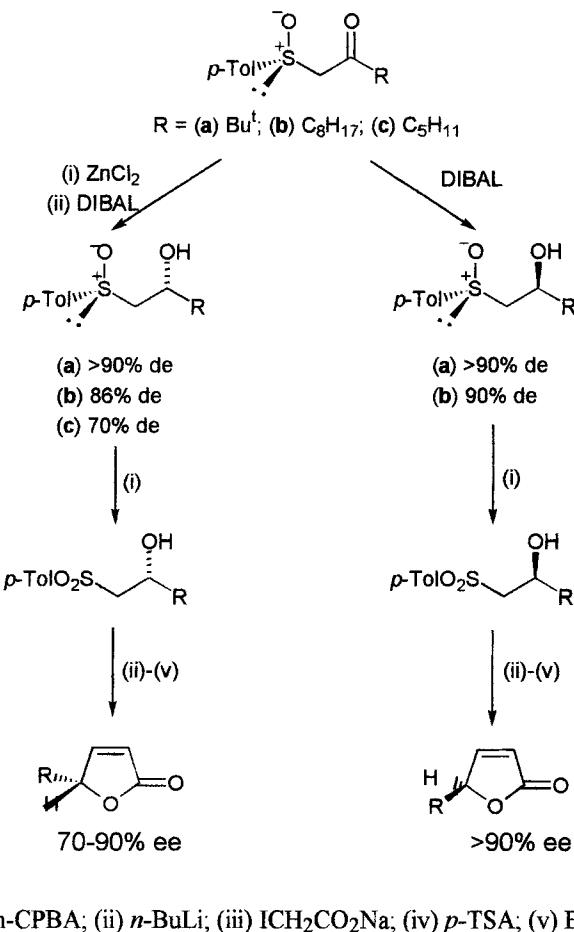
(*R*)-(+)-Hexadecanolactone (**15**), a pheromone responsible for social behaviour of the oriental hornet *Vespa orientalis*, was prepared as illustrated in Scheme 4.9. The natural product was obtained in 64% yield with an *ee* of 99%.



SCHEME 4.9

#### 4.1.5 The Synthesis of Non-racemic Butenolides

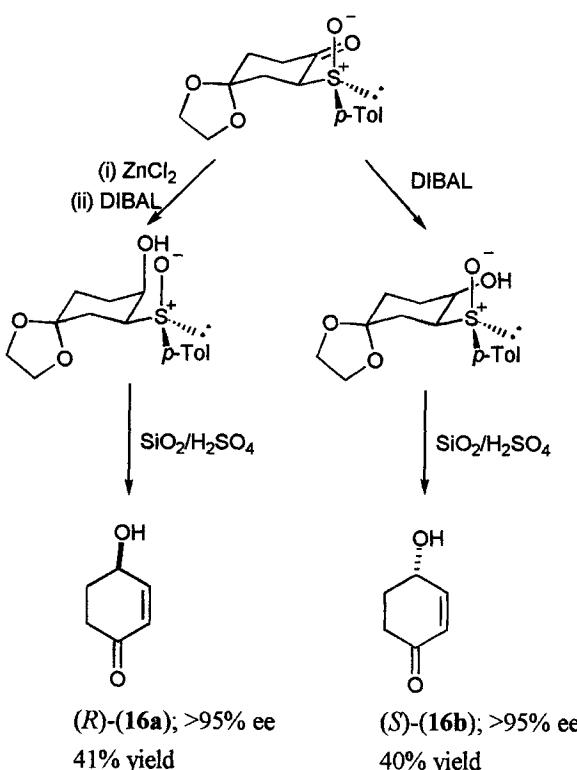
The asymmetric synthesis of both enantiomers of various butenolides was reported by Solladié in 1986, based upon his diastereoselective  $\beta$ -ketosulfoxide reduction chemistry (Scheme 4.10) [13]. Butenolides are widely found as subunits in many naturally occurring compounds [14–17].



SCHEME 4.10

#### 4.1.6 The Synthesis of Enantiomerically Pure Hydroxycyclohexanones

Both enantiomers of 4-hydroxy-cyclohex-2-enone (**16a**) and (**16b**) are useful synthetic intermediates in the synthesis of compactin [18]; a stereoselective synthesis of this class of compound has been reported by Solladié using  $\beta$ -ketosulfoxide chemistry, and is highlighted in Scheme 4.11 [19].



SCHEME 4.11

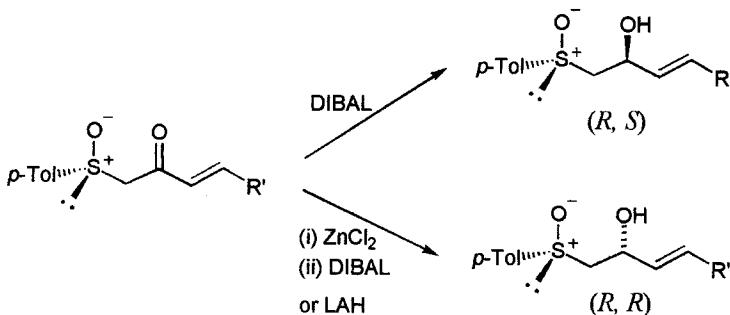
#### 4.1.7 The Synthesis of Non-racemic Allylic Alcohols

The  $\beta$ -ketosulfoxide reduction methodology is also successful with  $\alpha,\beta$ -unsaturated substrates. The asymmetric synthesis of both enantiomers of a range of allylic alcohols was achieved by Solladié from the corresponding  $\alpha,\beta$ -unsaturated  $\beta$ -ketosulfoxides [20, 21]. The reactions were found to be

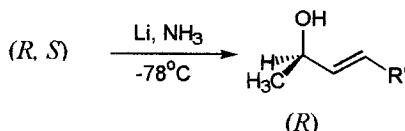
TABLE 4.3 Reduction of  $\alpha,\beta$ -unsaturated  $\beta$ -ketosulfoxides  
(Scheme 4.12)

$\text{R}'$	LAH	$(R:R):(R,S)$	
		$\text{ZnCl}_2/\text{DIBAL}$	DIBAL
$\text{CH}_3$	81:19	>95:5	6:94
<i>n</i> -Pentyl	—	>95:5	7:93
Ph	80:20	>95:5	5:95
<i>n</i> -Heptyl	95:5	—	5:95

highly efficient and stereoselective (Scheme 4.12, Table 4.3) using LAH or  $ZnCl_2$ /DIBAL to obtain the  $(R,R)$ -diastereoisomer, or DIBAL alone to produce the  $(R,S)$ -diastereoisomer. Desulfurization using lithium in ethylamine solvent at low temperature afforded the enantiomerically pure allylic alcohols (Scheme 4.13).



SCHEME 4.12

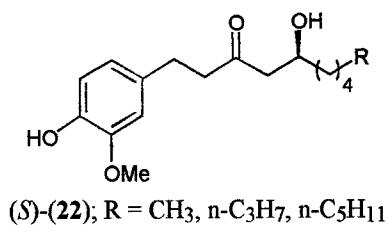
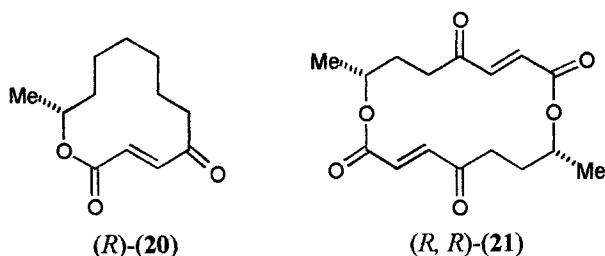
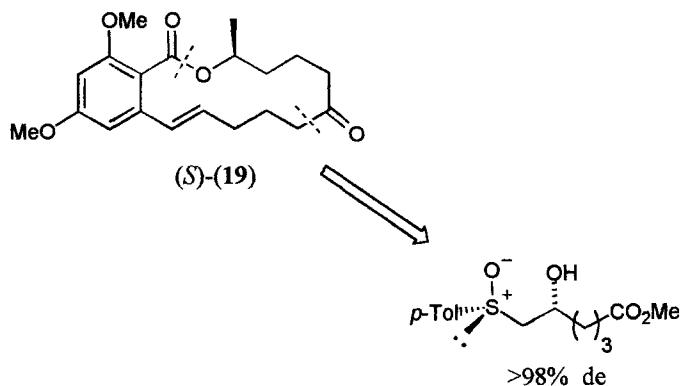
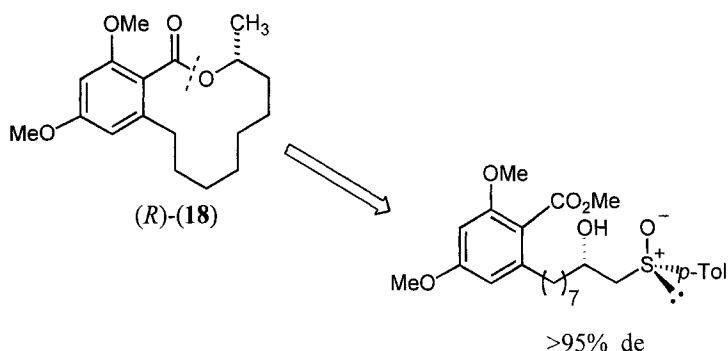


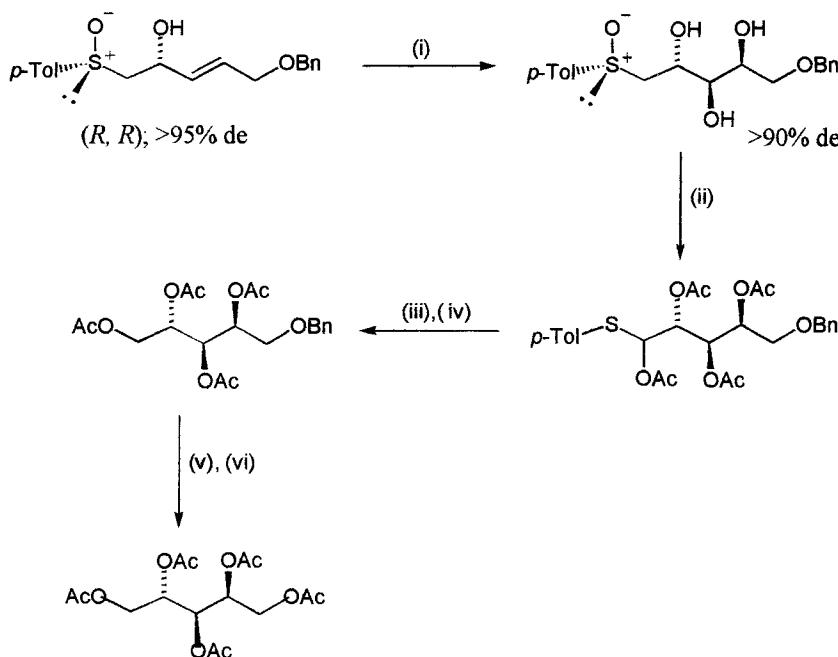
SCHEME 4.13

This methodology, in association with a highly diastereoselective hydroxylation procedure, was exploited to great effect by Solladié in the asymmetric synthesis of protected L-arabinitol (**17**), (Scheme 4.14) [21].

#### 4.1.8 The Total Synthesis of Enantiomerically Pure Natural Products

A range of natural products has been prepared by Solladié in enantiomerically pure form through application of the  $\beta$ -ketosulfoxide reduction methodology, including  $(R)$ - and  $(S)$ -lapsidiplodin (macrolide) (**18**) [22],  $(S)$ -zearolenone dimethyl ether (macrolide) (**19**) [23],  $(R)$ -patulide (antifungal and antibacterial) (**20**),  $(R,R)$ -pyrenophorin (antifungal) (**21**) [24], and gingerols (spices, cardiotonic) (**22**) [25]. Representative retrosynthetic disconnections of  $(R)$ -(**18**) and  $(S)$ -(**19**) are shown below to highlight the introduction of chirality through application of the stereoselective  $\beta$ -ketosulfoxide reduction methodology.





- (i)  $\text{OsO}_4$  (5%), NMO (1 eq), THF,  $\text{H}_2\text{O}$ ; (ii)  $\text{Ac}_2\text{O}/\text{AcONa}$ ;  
 (iii) DIBAL; (iv)  $\text{Ac}_2\text{O}$ ; (v)  $\text{Pd/C}/\text{cyclohexene}$ ; (vi)  $\text{Ac}_2\text{O}$ , pyridine

SCHEME 4.14

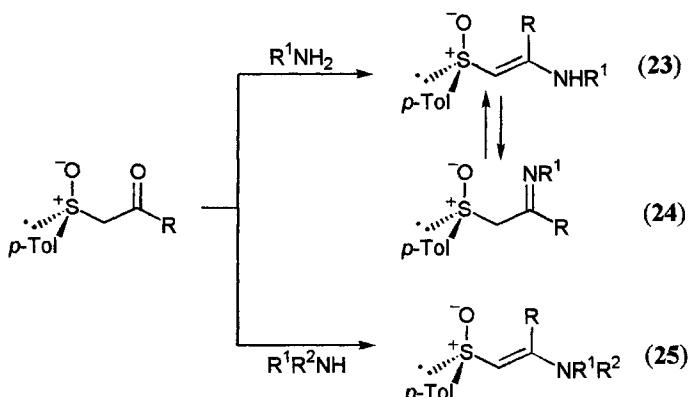
## 4.2 STEREOCONTROLLED REACTIONS OF IMINOSULFOXIDES

### 4.2.1 Stereoselective Reduction of $\beta$ -Iminosulfoxides: Application to the Synthesis of Nonracemic Amines

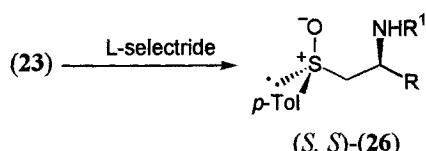
While much effort has been concentrated on the stereoselective reduction of  $\beta$ -ketosulfoxides (Section 4.1), relatively little attention has been paid to the analogous reactions of  $\beta$ -iminosulfoxides or the corresponding enamine tautomers as an approach to chiral  $\beta$ -aminosulfoxides.

Ogura prepared  $\beta$ -enaminosulfoxides of types (**23**) and (**25**) by condensation of primary and secondary amines, respectively, with  $\beta$ -ketosulfoxide substrates (Scheme 4.15) [26].

Reduction of (**23**) with L-selectride was found to be highly diastereoselective (Scheme 4.16, Table 4.4).



SCHEME 4.15

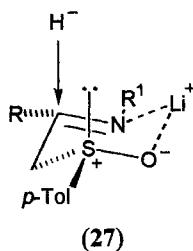


SCHEME 4.16

TABLE 4.4 Reduction of  $\beta$ -enaminosulfoxides (23) using L-selectride

R	R <sup>1</sup>	Temperature (°C)	Yield (%)	(S,S):(S,R)
Me	PhCH <sub>2</sub>	-20	57	97:3
Me	PhCH <sub>2</sub>	-78	14	98:2
Me	(CH <sub>2</sub> ) <sub>3</sub> OH	-20	41	98:2

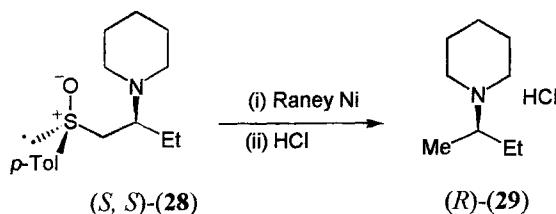
The reduction of (23) is believed to proceed *via* imine tautomer (24) since enamines (25) are not reduced under identical reaction conditions. The high levels of diastereoselectivity were rationalized by postulation of a chelated transition state (27), which is similar in structure to those used to rationalize the diastereoselective reduction of  $\beta$ -ketosulfoxides described in Section 4.1.



The reduction of  $\beta$ -enaminosulfoxides (**25**) with borane-THF complex was also investigated. These reactions clearly involve direct hydroboration of the carbon-carbon double bond and are only moderately diastereoselective (Table 4.5). The potential application of this methodology to the synthesis of non-racemic amines was demonstrated (Scheme 4.17) by Raney nickel desulfinylation of  $\beta$ -enaminosulfoxide (**28**) to furnish (**29**) in 86% yield.

**TABLE 4.5** Reduction of  $\beta$ -enaminosulfoxides (**25**) using borane-THF complex

R	R <sup>1</sup>	R <sup>2</sup>	Temperature (°C)	Yield (%)	(S,S):(S,R)
Me	—(CH <sub>2</sub> ) <sub>4</sub> —		−78	95	87:13
Et	—(CH <sub>2</sub> ) <sub>5</sub> —		−78	73	73:27
Pr <sup>n</sup>	Me	PhCH <sub>2</sub>	−78	82	85:15

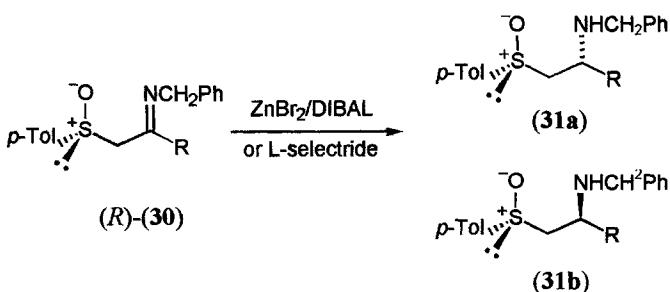


**SCHEME 4,17**

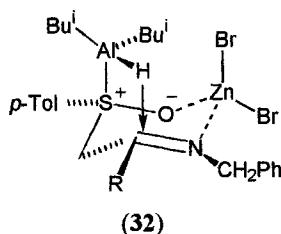
In direct analogy to Solladié's work with  $\beta$ -ketosulfoxides, Ruano has investigated the DIBAL reduction of *N*-benzyl- $\beta$ -iminosulfoxides (**30**) [27]. DIBAL alone was found to be inactive toward (**30**); however in the presence of  $ZnBr_2$  as Lewis acid, the reduction was observed to be highly diastereoselective (Scheme 4.18, Table 4.6). This behaviour can be explained by assuming that the Lewis acid stabilizes the (*E*) regioisomer of the  $\beta$ -iminosulfoxide tautomer by formation of a chelate which shifts the enamine-imine equilibrium toward the latter. This chelated tautomer is now readily reduced by DIBAL. To verify this proposal, the influence of the Lewis acid on the enamine-imine equilibrium was studied by NMR spectroscopy ( $R = Ph$ ). It was observed that the initially formed enaminic tautomer was converted completely into the iminic form by addition of the  $ZnBr_2$ .

Examination of these results (Table 4.6) reveals that opposite diastereoselectivities are available by variation of the reducing agent. On employing L-selectride, diastereoisomer (**31b**) is preferred, while the  $ZnBr_2/DIBAL$  reducing system selectively produces (**31a**).

Transition states, similar in structure to those previously described above, have been proposed to explain the stereochemical outcome of these reductions. Transition state (32) shows the chelated intermediate giving rise to (31a).



SCHEME 4.18

TABLE 4.6 Reduction of  $\beta$ -iminosulfoxides (30)

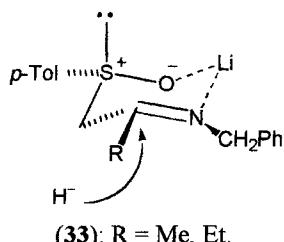
R	$\text{ZnBr}_2/\text{DIBAL}$ (31a):(31b)	Yield (%)	<i>L</i> -selectride (31a):(31b)	Yield (%)
Me	>97:3	80	<9.91	50
Pr <sup>n</sup>	>97:3	72	<9.91	10
Pr <sup>i</sup>	>97:3	82	—	—
Bu <sup>t</sup>	>97:3	15	—	—
Ph	>97:3	75	—	0

In addition to approaching the chelated system from the least sterically hindered direction, the DIBAL reducing agent has electrophilic character which encourages an attractive interaction with the lone pair of electrons on sulfur as indicated. Both effects, if present, could explain the high levels of diastereoselectivity and preference for isomer (31a) on employing the  $\text{ZnBr}_2/\text{DIBAL}$  reducing system.

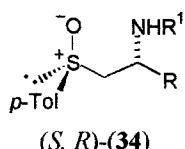
Ruano's study leads one to question Ogura's rationale: if the chelated transition state (27) proposed by Ogura is correct, one would expect Ruano to obtain diastereoisomer (31a) preferentially when employing *L*-selectride, as with the  $\text{ZnBr}_2/\text{DIBAL}$  system. This is *not* observed by Ruano; instead opposite diastereoselectivities for both reducing systems are obtained.

Ruano does not comment on the reason for reversal in selectivities observed on changing reducing systems, but the explanation may lie in a transition state such as

(33). The least sterically demanding approach of the reducing agent would indeed involve attack by the reducing agent from the same face of the prochiral imine double bond as the sulfur lone pair, as in transition state (32). The nucleophilic nature of the L-selectride reducing species would however encounter notable stereoelectronic repulsion from the sulfur lone pair. This factor may override the steric bias and encourage hydride delivery from the opposite face of the imine double bond to that shown in (32), as indicated below in (33). The above rationalization would explain the change in stereochemistry upon change of reagent.



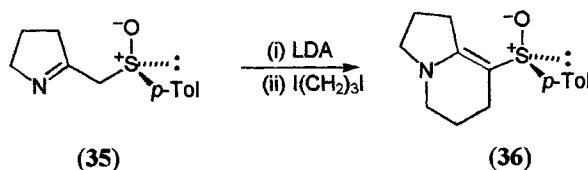
Ruano's results could therefore suggest that the major isomer produced in Ogura's study employing L-selectride is *actually* the (*S,R*) diastereoisomer (34), *not* (*S,S*)-(26) as claimed by Ogura, and could be rationalized by invoking the above rationale.



It is interesting to note that Ogura assigned the same relative stereochemistry to the major product isomers obtained by L-selectride reduction of (23) as to the major product isomers obtained by borane-THF reduction of (25). This assumption was based on similar spectroscopic behaviour in the products. Although the absolute stereochemistry of the major isomer obtained from borane-THF reduction of enamine (25) was determined (Scheme 4.17), *no* similar absolute structural determination was carried out for aminosulfoxides (26), obtained from L-selectride reduction of compounds (23). This omission may explain the difference in observations reported by Ogura and Ruano.

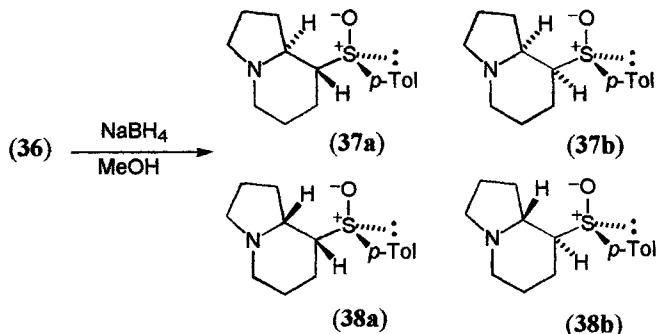
#### 4.2.2 The Synthesis of Non-racemic Natural Products

An application of the methodology described above to the synthesis of naturally occurring elaeokanine alkaloids was reported by Hua [28]. The chiral, cyclic  $\beta$ -sulfinylenamine (36) was prepared by alkylation-annelation of the  $\alpha$ -sulfinylketimine anion of (35) (Scheme 4.19).

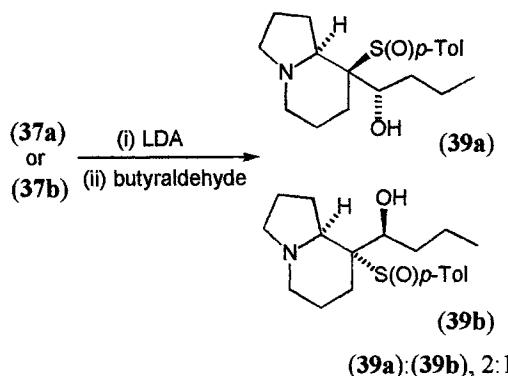


**SCHEME 4.19**

Sulfinylenamine (**36**) was reduced in a diastereoselective fashion to yield 81% of diastereoisomers (**37a**), (**37b**), (**38a**) and (**38b**) in 4:4:1:1 ratio, as indicated in Scheme 4.20. The diastereoisomers were separable by flash column chromatography. As in previous transition state models, approach of the hydride nucleophile from the least hindered face of the enamine is preferred. Since the stereochemistry of the  $\beta$ -position chiral centre is controlled by hydride addition, both (**37a**) and (**37b**) are equally useful in later synthetic steps. Aldol-type butyrylation of (**37a**) or (**37b**) was found to be stereoselective, yielding 76% of a 2:1 mixture of alcohols (**39a**) and (**39b**), irrespective of the isomer of (**37**) used (Scheme 4.21).



**SCHEME 4.20**



**SCHEME 4.21**

Although such stereoselective aldol-type addition of  $\alpha$ -sulfinyl carbanions to aldehydes will not be dealt with in this review, this topic has received considerable attention elsewhere [29, 30]. The structure of  $\alpha$ -sulfinyl carbanions has provoked considerable discussion, some research groups having rationalized their observed results by proposing a planar configuration about the metalated carbon atom [31], and others a tetrahedral structure [32]. Williams has investigated stereoselectivity in the reaction of  $\alpha$ -lithio sulfinyl carbanions with aldehydes [33]. Williams has proposed that generation of  $\alpha$ -lithio sulfinyl carbanions by an initial kinetic deprotonation affords an unequal pair of diastereoisomeric, tetrahedral anions (Scheme 4.22), in which the lithium atom is intramolecularly coordinated with the sulfinyl group oxygen atom.



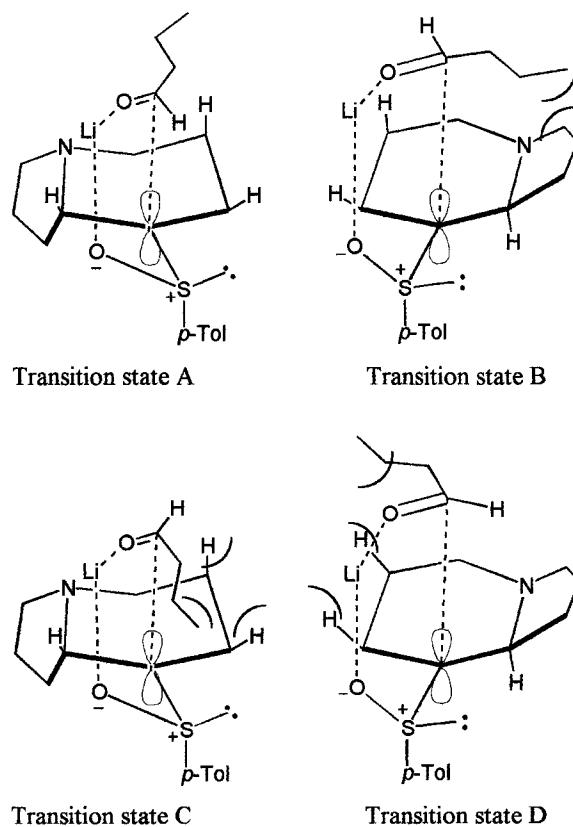
SCHEME 4.22

These tetrahedral structures are capable of interconversion by pyramidal inversion and C—S bond rotation. Williams suggests that the relative reactivity of the above  $\alpha$ -lithio sulfinyl carbanion diastereoisomers with aldehydes (and therefore the stereoselectivity of the reaction) is governed by the steric environment of the process.

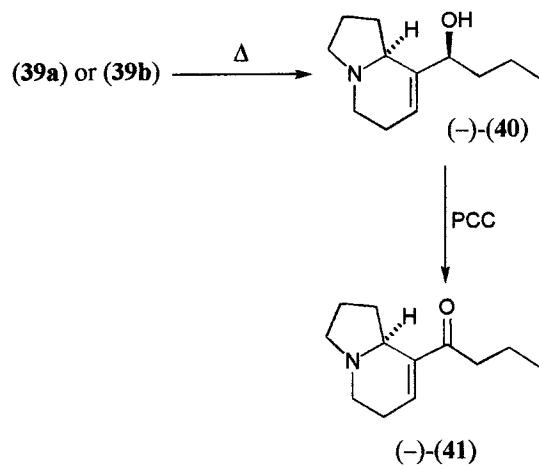
Hua rationalizes the stereoselectivity observed in Scheme 4.21 by reference to a planar species. Hua proposes that (37a) and (37b) both generate the same  $sp^2$ -p hybridized  $\alpha$ -sulfinyl carbanion on deprotonation. Scheme 4.23 illustrates the suggested transition states for addition of conformeric anions to butyraldehyde. Transition state A appears to be the most favourable and leads to the major product isomer (39a). Transition state B (related to A simply by attack of the aldehyde from the opposite apex of the p-orbital) shows slightly more steric hindrance between the five-membered ring and the butyryl chain and leads to (39b). Both transition states A and B give rise to the (S) configuration at the new alcohol chiral centre.

The absence of the (R) alcohol product can be explained from the greater steric hindrance observed in transition states C and D, which would lead to the formation of the (R) product. Transition states C and D are again related to each other through attack of the aldehyde from the opposite apex of the p-orbital. Transition state C is related to A by attack at the opposite face of the prochiral carbonyl moiety (as B is to D).

Desulfinylation of (39a) and (39b) separately furnished non-racemic (−)-elaeokanine B (40), in 90% and 92% yield, respectively. Oxidation of (40) yielded the unnatural (−)-elaeokanine A (41) in 89% yield, as shown in Scheme 4.24.

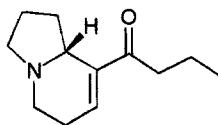


SCHEME 4.23



SCHEME 4.24

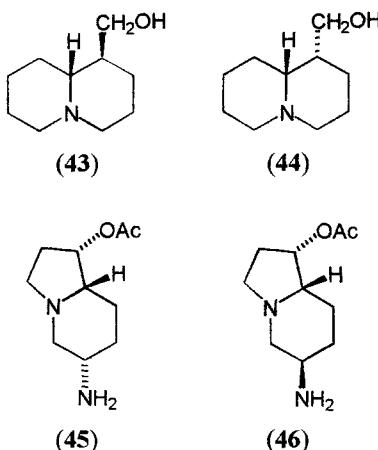
Natural (+)-elaeokanine A (**42**) was obtained in 93% yield through similar manipulation of (**38a**) or (**38b**).



(+)-(42)

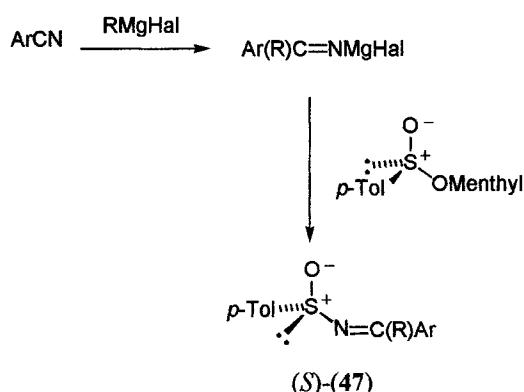
The above synthetic schemes represent the first asymmetric synthesis of these alkaloids; as a result, Hua was able to establish the absolute configurations of the natural elaeokanine alkaloids.

Hua has recently extended this methodology as a route toward the asymmetric total synthesis of alkaloids including: (+)-epilupinine (**43**) and (-)-lupinine (**44**) [34], and (-)-slaframine (**45**) and (-)-6-epislaframine (**46**), in enantiomerically pure form [35].



#### 4.2.3 The Synthesis of Non-racemic Amines by Reduction of *N*-Alkylidene Sulfinamides

Around the time of Solladié's initial work on  $\beta$ -ketosulfoxide reduction, Cinquini reported an enantioselective route to chiral amines by reduction of non-racemic *N*-alkylidene sulfinamides [36]. The *N*-alkylidene sulfinamide substrates were readily prepared in one pot by addition of alkyl or aryl Grignard reagents to a nonenolizable aromatic nitrile to yield an imino-Grignard intermediate which was allowed to react with *(S)*- $(-)$ -menthyl *p*-toluene sulfinate (Scheme 4.25). The resulting *N*-alkylidene sulfinamides were found to be enantiomerically pure and of *(S)* configuration.



SCHEME 4.25

Reduction of (S)-(47) with sodium borohydride or LAH (or derivatives) was found to be diastereoselective (Table 4.7).

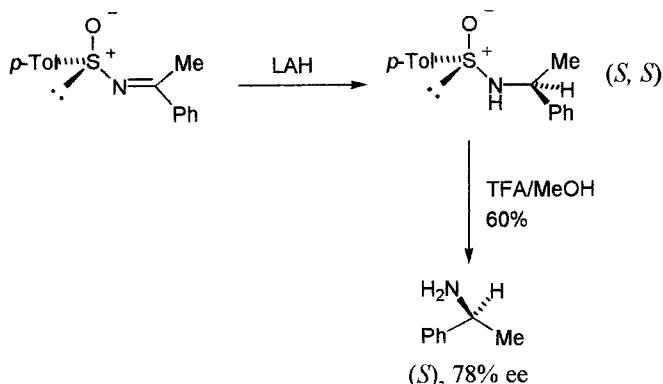
Diastereoselectivities of up to 93:7 were observed on employing the more sterically demanding alkoxy-lithium aluminium hydride reagents. Complexation of the reducing species at the sulfoxide oxygen followed by hydride delivery from the least sterically demanding face of the prochiral imine bond was invoked to explain the high levels of diastereoselectivity observed in the sulfinamide products. A similar approach employing DIBAL in THF at low temperature was reported by Hua in which diastereoselectivities of (up to) 94:6 were observed [37].

Determination of the absolute configuration of the sulfinamide major isomers was achieved by conversion to non-racemic amines (Scheme 4.26) and comparison of the optical rotations observed with literature values.

TABLE 4.7 Reduction of *N*-alkylidene sulfinamides (47)

Reducing agent	R	Yield (%)	Diastereoselectivity
NaBH <sub>4</sub>	Me	— <sup>a</sup>	3:2
	Et	— <sup>a</sup>	13:7
	Pr <sup>i</sup>	— <sup>a</sup>	13:7
	Naphthyl	— <sup>a</sup>	4:1
	Me	— <sup>b</sup>	9:1
LAH	Et	— <sup>b</sup>	4:1
	Pr <sup>i</sup>	— <sup>b</sup>	4:1
	Naphthyl	— <sup>b</sup>	9:1
	Me	81	93:7
LiAlH <sub>3</sub> -A <sup>c</sup>	Naphthyl	75	47:3
	Naphthyl	57	19:1

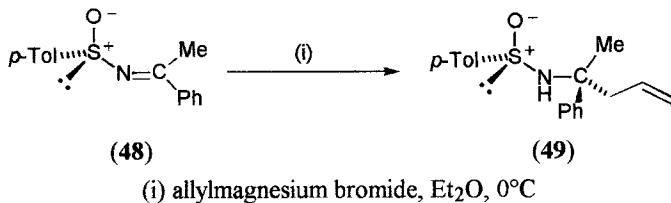
<sup>a</sup>Yields 90–100%. <sup>b</sup>Yields 80–90%. <sup>c</sup>A = menthyl, B = bornyloxy, C = ephedrinyl.



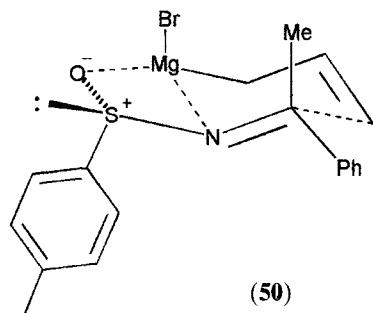
**SCHEME 4.26**

#### 4.2.4 The Synthesis of Enantiomerically Pure $\beta$ - and $\gamma$ -Amino Acids by Nucleophilic Addition to *N*-Alkylidene Sulfinamides

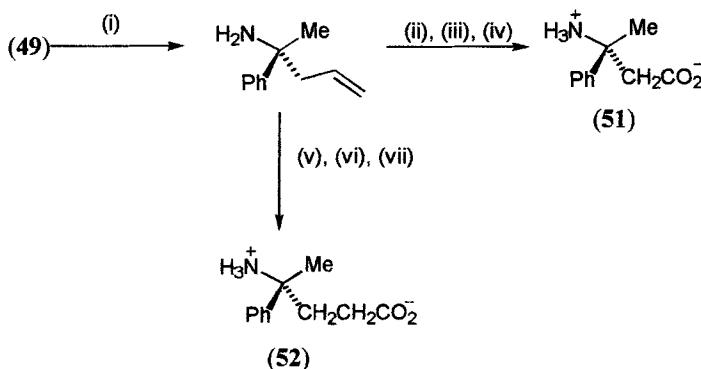
Hua has also investigated the addition of carbon nucleophiles to chiral *N*-benzylidene *p*-toluene sulfinamide substrates as an approach to enantiomerically pure  $\beta$ - and  $\gamma$ -amino acids, important intermediates in organic synthesis and biological studies [37]. Addition of allyl magnesium bromide to (48) produced a 98% yield of (49) as a single diastereoisomer (Scheme 4.27). This highly selective addition reaction was rationalized by invoking transition state (50). The authors propose that the magnesium ion is chelated to both the N-atom and the sulfoxide oxygen atom; approach of the allyl Grignard reagent then occurs from the *re* face of the prochiral imine bond.



**SCHEME 4.27**



Representative conversions of (**49**) to  $\beta$ -amino acid (**51**) and  $\gamma$ -amino acid (**52**) appear in Scheme 4.28.



(i) 2 eq.  $\text{CF}_3\text{CO}_2\text{H}$ ,  $\text{MeOH}$ ,  $25^\circ\text{C}$ , 3 hrs; 97%

(ii)  $\text{Ac}_2\text{O}$ ,  $\text{Et}_3\text{N}$ ,  $\text{Et}_2\text{O}$ ,  $0^\circ\text{C}$ , 1 hr, 95%

(iii)  $\text{O}_3$ ,  $\text{DCM}$ ,  $-78^\circ\text{C}$ ;  $\text{AgNO}_3$ ,  $\text{KOH}$ ,  $\text{EtOH}$ ,  $0^\circ\text{C}$ ; 70%

(iv) 1 mol. l<sup>-1</sup>  $\text{HCl}$ ,  $\text{H}_2\text{O}$ ,  $100^\circ\text{C}$ , 12 hrs;  $\text{NH}_4\text{OH}$  (aq.); Rexyn-101 ( $\text{H}^+$ ); 80%

(v)  $\text{BH}_3\text{-THF}$ ,  $0^\circ\text{C}$ , 3 hrs;  $\text{NaOH}$ , 30%  $\text{H}_2\text{O}_2$ ; 55%

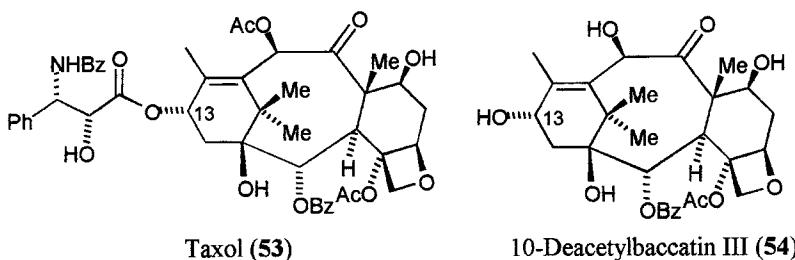
(vi) PCC,  $\text{DCM}$ ,  $25^\circ\text{C}$ ;  $\text{AgNO}_3$ ,  $\text{KOH}$ ,  $\text{EtOH}$ ,  $0^\circ\text{C}$ ; 65%

(vii) 1 mol. l<sup>-1</sup>  $\text{HCl}$ ,  $\text{H}_2\text{O}$ ,  $100^\circ\text{C}$ , 12 hrs;  $\text{NH}_4\text{OH}$  (aq.); Rexyn-101 ( $\text{H}^+$ ); 81%

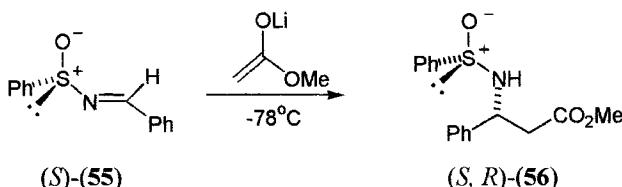
SCHEME 4.28

#### 4.2.5 The Synthesis of Enantiomerically Pure $\alpha$ -Hydroxyl- $\beta$ -amino Acids, Including the Taxol Side Chain, by Enolate Addition to $N$ -Alkylidene Sulfinamides

Taxol (**53**) is currently receiving enormous attention from synthetic organic chemists owing to its remarkable antitumour activity [38]. To date, the main source of taxol stems from derivatization of naturally occurring 10-deacetylbaconin III (**54**). This compound lacks the  $\text{C}_{13}$  side-chain of taxol, a structural unit essential for biological activity [38].

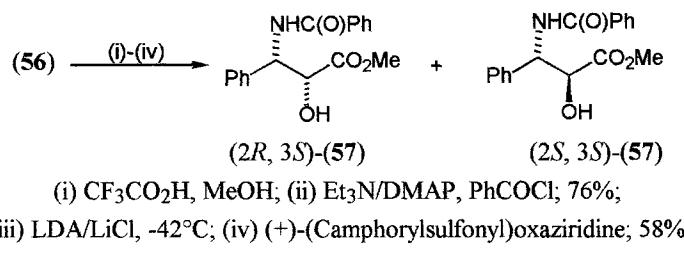


The stereoselective synthesis of  $\alpha$ -hydroxyl- $\beta$ -amino acids such as *N*-benzoyl-(2*R*,3*S*)-(-)-3-phenylisoserine, the C<sub>13</sub> side-chain (**57**) of taxol, has been described by Davis [39]. The pivotal step in the synthetic procedure involves addition of an ester enolate to the chiral *N*-alkylidene sulfinamide (**55**) (Scheme 4.29).



SCHEME 4.29

The major sulfinamide diastereoisomer (**56**) was obtained diastereoisomerically pure in 74% yield after crystallization (initial diastereoisomer ratio  $\sim$  90:10). Subsequent desulfurization, benzoylation, and stereoselective enolate hydroxylation (Scheme 4.30) gave an 86:14, *syn:anti* mixture of the target diastereoisomers. Chromatographic separation of the product diastereoisomers afforded (2*R*,3*S*)-(-)-(**57**), the methyl ester of the taxol C<sub>13</sub> side chain, in 49% yield and  $> 93\%$  *ee*.



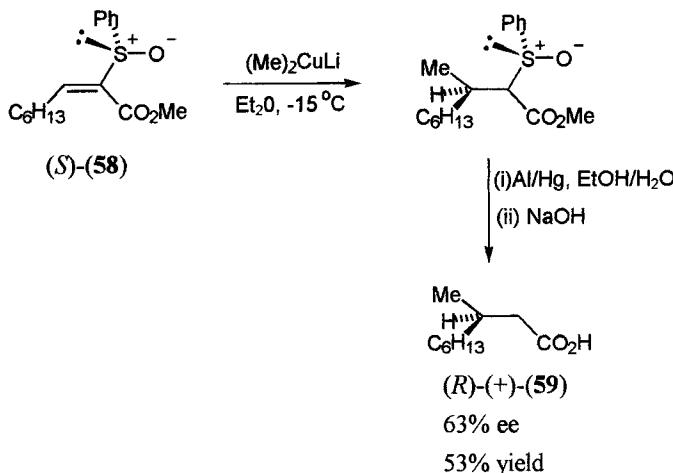
SCHEME 4.30

### 4.3 THE STEREOCONTROLLED ADDITION OF NUCLEOPHILES TO CHIRAL VINYLIC SULFOXIDES

The transfer of chirality from a sulfoxide moiety to the  $\beta$ -carbon atom of enantiomerically pure  $\alpha$ -carbonyl  $\alpha,\beta$ -unsaturated sulfoxides through organometallic addition has attracted considerable attention [40]. A wide variety of synthetically useful compounds are available by application of this methodology, as discussed below.

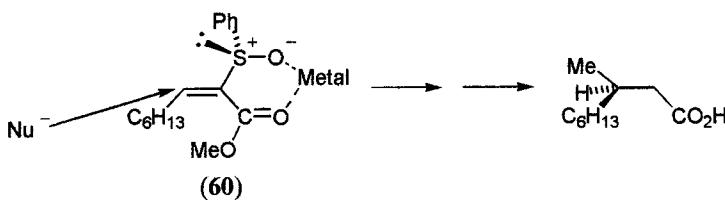
### 4.3.1 The Asymmetric Synthesis of Nonracemic $\beta$ -Alkyl Carboxylic Acids and $\beta$ -Substituted Cyclopentanones

Following initial investigations [41], Posner reported the stereoselective synthesis of  $(R)$ - $(+)$ -3-methylnonanoic acid (**59**) with an *ee* of 65% through Michael addition of dimethylcopper lithium to enantiomerically pure  $(S)$ - $(E)$ -1-octenyl sulfoxide (**58**), as shown in Scheme 4.31 [42].



SCHEME 4.31

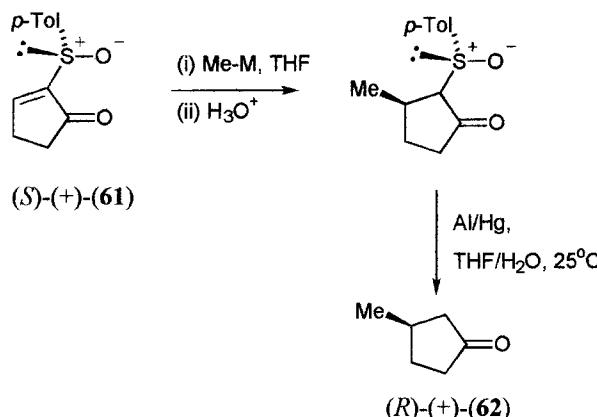
Reversing the order of introduction of the alkyl groups at the  $\beta$ -position afforded, as expected, major diastereoisomers of opposite absolute configuration; for example, the  $(S)$ - $(-)$  antipode of (**59**) is available by employing the appropriate substrate and *n*-hexyl organometallic reagent. The results are rationalized by reference to chelated transition state model (**60**), attack of the nucleophile being favoured from the least hindered face of the prochiral  $\beta$ -carbon atom (i.e. from the same side as sulfoxide lone pair) (Scheme 4.32).



SCHEME 4.32

Posner determined that reactions of various methyl metallic species with enantiomerically pure cyclopentenone *p*-tolyl sulfoxide, (*S*)-**61**, allowed the

synthesis of *(R)*-*(+)*-3-methylcyclopentanone (**62**) in good yields and with good to excellent levels of enantiomeric purity (Scheme 4.33, Table 4.9) [41].

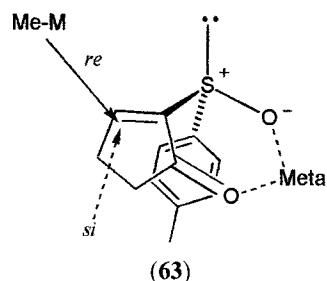


SCHEME 4.33

**TABLE 4.8** Nucleophilic addition of methyl organometallic reagents to enantiomerically pure cyclopentenone *p*-tolyl sulfoxide, *(S)*-**(61)**

Entry	Me-M	Yield ( <b>62</b> ) (%)	ee ( <b>62</b> ) (%)	Configuration
1	MeMgBr	86	84	( <i>R</i> )
2	MeMgCl	91	95–100	( <i>R</i> )
3	Me <sub>2</sub> CuLi	100	80	( <i>R</i> )
4	Me <sub>2</sub> CuMgBr	96	60	( <i>R</i> )
5	MeMgI	76	72	( <i>S</i> )
6	ZnBr <sub>2</sub> /MeMgI	100	87	( <i>R</i> )
7	MeTi(iPrO) <sub>3</sub>	44	90	( <i>R</i> )
8	LiAl(Me) <sub>4</sub>	68	88	( <i>R</i> )

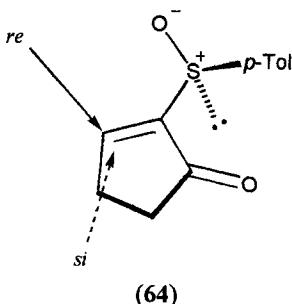
A chelated transition state model, (**63**), was proposed to rationalize the high levels of enantioselectivity and the observed preference for the (*R*) product on reaction of the substrate with strongly complexing reagents, or in the presence of strongly complexing metals. The bulky *p*-tolyl group shields one prochiral face (the *si* face) of the enone system and thus encourages nucleophilic attack from the less hindered *re* face.



It is interesting to note the difference in enantiomeric purity and reversal of enantioselection observed for entries 5 and 6 in Table 4.8. Upon employing methylmagnesium iodide alone in the Michael addition reaction (entry 5), *(S)*-(-)-3-methylcyclopentanone was produced in 76% yield and 72% *ee* [43], while with prior addition of ZnBr<sub>2</sub>, *(R)*-(-)-3-methylcyclopentanone was produced in 100% yield and 87% *ee* [41].

Posner's explanation of these results invokes both chelated and nonchelated transition state models. In the presence of chelating agents such as ZnCl<sub>2</sub>, chelated transition state (63) is favoured, with delivery of the nucleophile from the less hindered *re* face to yield the *(R)* product.

Posner suggests that upon employing methylmagnesium iodide alone (Table 4.8, entry 5) an alternative transition state model (64), having the sulfoxide and carbonyl group oxygen atoms oriented remotely, is favoured. Delivery of the nucleophile then occurs preferentially from the sterically more favourable *si* face of the enone system to yield the *(S)* product. However, Posner does *not* provide a reasonable explanation for why both methyl magnesium bromide (Table 4.8, entry 1) and chloride (entry 2) reagents, when employed in the absence of ZnCl<sub>2</sub>, give the product of *(R)* configuration while methyl magnesium iodide gives the *(S)* product.

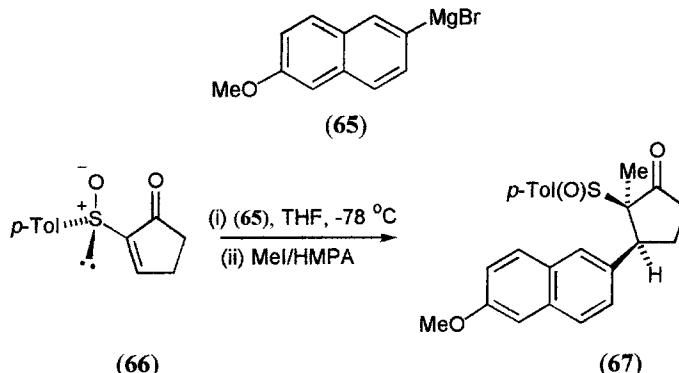


It appears to this author that, of the alkyl magnesium halides used, methylmagnesium iodide should be least Lewis acidic (least electropositive metal centre) owing to the lower electronegativity of the iodide halogen atom. In this case, therefore, the methylmagnesium iodide is less able to chelate to the sulfinyl and carbonyl group oxygen atoms and thus, in the absence of chelating metals, the weakly complexing methylmagnesium iodide reagent would favour transition state (64). As the electronegativity of the halogen counterion of the Grignard reagent increases (Cl > Br > I), the reagent becomes more Lewis acidic (more electropositive metal atom) and is able to form a chelated species such as (63). Of the alkyl magnesium halides, the chlorides are known to form the strongest complexes and largest aggregates [44] and hence lead to the highest levels of enantioselectivity in these reactions.

Other 3-substituted cyclopentanone derivatives are available (80% >98% *ee*) by variation of the organometallic reagent used in the initial conjugate addition reaction [45].

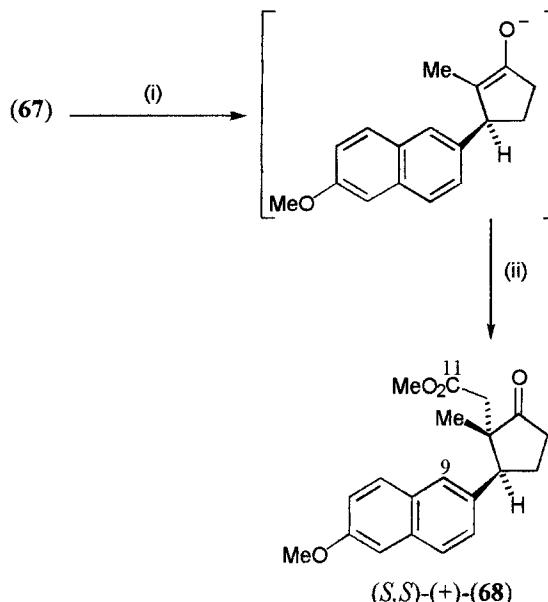
### 4.3.2 The Asymmetric Synthesis of Steroidal Intermediates

Posner investigated the addition of the larger naphthyl Grignard reagent (**65**) to enantiomerically pure cyclopentanone sulfoxide (**66**). The reaction proceeded with excellent enantioselectivity to provide  $\beta$ -naphthyl- $\alpha$ -methylcyclopentanone sulfoxide (**67**) in 42% yield and  $>98\%$  *de* after *in situ* methylation of the intermediate enolate anion (Scheme 4.34) [42].



SCHEME 4.34

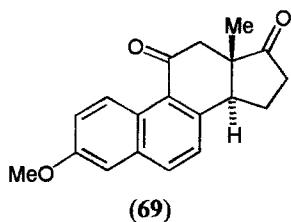
Desulfinylation of (**67**) using dimethylcopper lithium allowed regiospecific and stereospecific alkylation of the enolate system to yield exclusively enantiomerically pure 2,2,3-trisubstituted cyclopentanone (*S,S*)-(+)-(**68**) in 89% yield (Scheme 4.35).



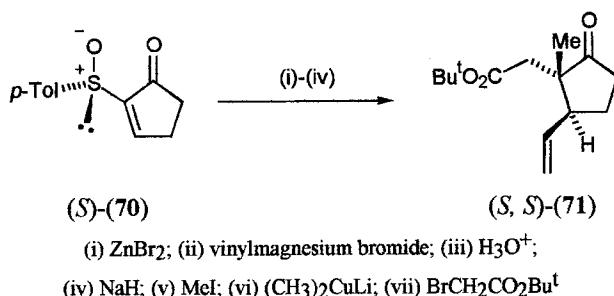
(i)  $(\text{CH}_3)_2\text{CuLi}$ ; (ii)  $\text{BrCH}_2\text{CO}_2\text{Me}$

SCHEME 4.35

The 9,11-seco steroid (**68**) was formed with the desired natural (13*S*,14*S*) absolute stereochemistry. Conversion of a racemic sample of (**68**) into racemic steroidal equilenin (**69**) was used to demonstrate the potential of this methodology for the total synthesis of enantiomerically pure steroidal material of natural configuration, although an enantiomerically pure synthesis was not performed [46].



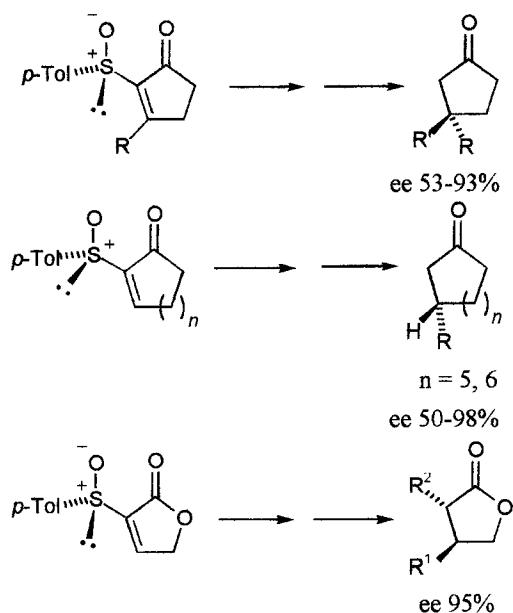
Posner has also described the stereocontrolled addition of vinyl Grignard reagents to enantiomerically pure cyclopentanone sulfoxides [43,47]. The addition of vinylmagnesium bromide to (**70**) pre-complexed with zinc bromide, and further reaction as described in Scheme in 4.36, yielded exclusively (*S,S*)-3-vinylcyclopentanone (**71**) in 30% overall yield.



**SCHEME 4.36**

\* The synthetically important intermediate (**71**) has been used by Saegusa to prepare oestrone [48] stereoselectively by an intramolecular Diels–Alder route; and also employed in a non-racemic synthesis of oestradiol by Oppolzer [49].

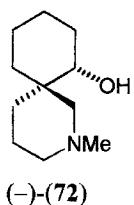
Scheme 4.37 highlights other applications of the above methodology; enantiocontrolled syntheses of quaternary carbon centres [50], 3-substituted cycloalkanones [51], and substituted butenolides [52] are shown.

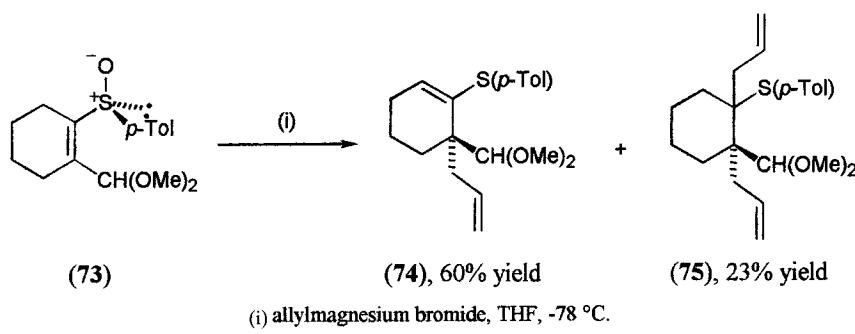


SCHEME 4.37

#### 4.3.3 The Asymmetric Synthesis of Natural Products by Intermolecular Conjugate Addition to Enantiomerically Pure Vinylic Sulfoxides

The synthesis of the natural product  $(-)$ -sibirine (**72**), a compound containing an unusual 2-azaspiro[5.5]undecane skeleton, was described by Iwata [53]. The method involved initial attack of allylmagnesium bromide on the non-racemic vinylic sulfoxide (**73**) (Scheme 4.38), followed by a Pummerer-type reaction (or isomerization) of the double bond as illustrated in Scheme 4.39 [54].

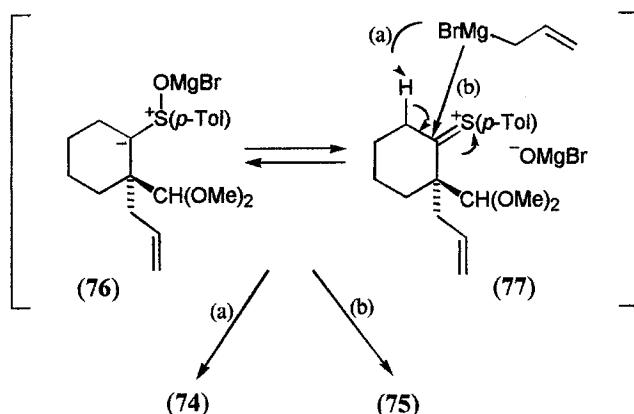




**SCHEME 4.38**

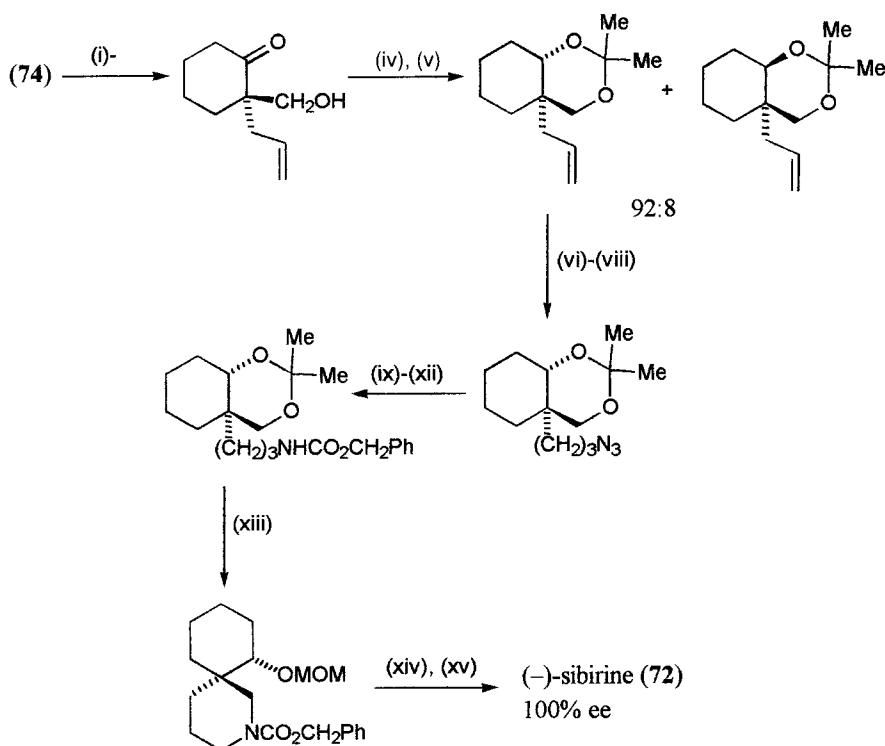
The enantiomeric excess of vinylic sulfide (**74**) was determined to be 96%. The mechanism is believed to involve coordination of the allylmagnesium bromide to both sulfoxide and acetal oxygen atoms with *si* face attack on the prochiral  $\beta$ -carbon.

Following nucleophilic addition to **(73)**, the initially formed ylide **(76)** gives the sulfonium cation **(77)** by cleavage of the sulfoxide bond (Scheme 4.39). Further deprotonation by Grignard reagent [pathway (a)] at the  $\beta$ -position completes conversion to **(74)**. The isolation of significant amounts of the diallyl compound **(75)** is readily explained through further attack by the Grignard reagent as a nucleophile at the  $\alpha$ -position of intermediate **(77)** [pathway (b)].



**SCHEME 4.39**

Conversion of vinyl sulfide (**74**) to the target natural product is outlined in Scheme 4.40.



- (i) *p*-TSA, acetone, 25°C (92%); (ii) NaBH<sub>4</sub>, MeOH, 0°C (83%); (iii) 10% HCl, MeCN, Δ (62%); (iv) Zn(BH<sub>4</sub>)<sub>2</sub>, Et<sub>2</sub>O/THF, -78°C; (v) dimethoxypropane, *p*-TSA, 25°C (95%); (vi) BH<sub>3</sub>-DMS, 0°C then H<sub>2</sub>O<sub>2</sub>, NaOH (75%); (vii) MeSO<sub>2</sub>Cl, pyridine, 0°C (87%); (viii) NaN<sub>3</sub>, Bu<sub>4</sub>N<sup>+</sup>, C<sub>6</sub>H<sub>6</sub>, Δ (90%); (ix) H<sub>2</sub>, Pd-C; (x) ClCO<sub>2</sub>CH<sub>2</sub>Ph, K<sub>2</sub>CO<sub>3</sub> (aq.), DCM, 0°C; (xi) MeSO<sub>2</sub>Cl, pyridine, 0°C; (xii) MOMCl, DIPEA, DCM, 25°C (62%); (xiii) KH, THF, 0°C (92%); (xiv) LAH, THF, 0°C; (xv) 10% HCl, 25°C (70%)

SCHEME 4.40

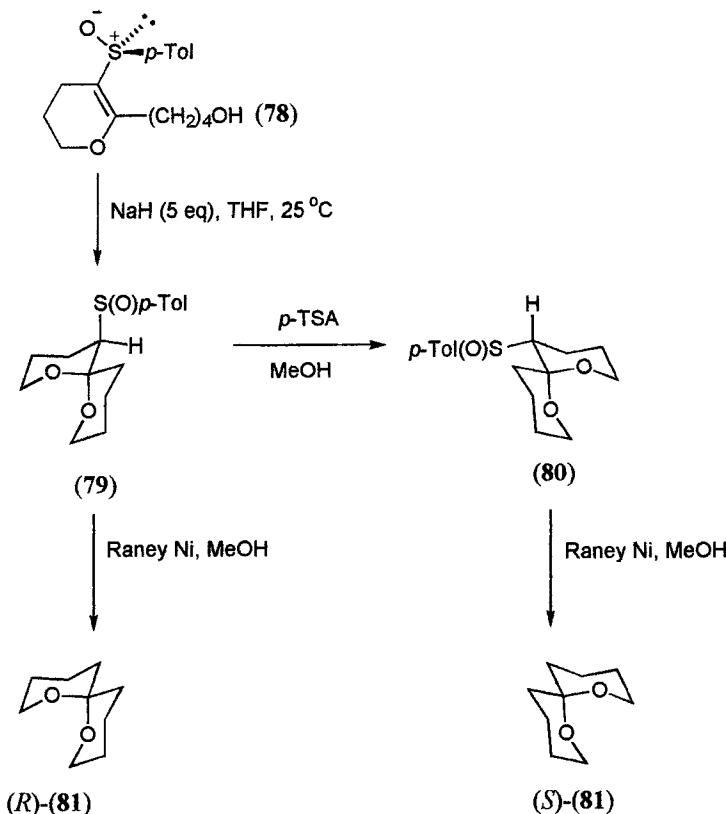
#### 4.3.4 The Asymmetric Synthesis of Natural Products by Intramolecular Conjugate Addition to Enantiomerically Pure Vinylic Sulfoxides

The intramolecular conjugate addition of nucleophiles to chiral vinylic sulfoxides has proved particularly useful in the asymmetric synthesis of a variety of natural products.

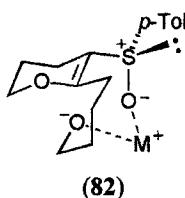
The spiroketal moiety is a common structural unit in a variety of biologically active products such as milbemycins (insecticides) [55], avermectins (anthelmintic activity) [56], and phyllanthosides (antileukemic) [57]. Iwata has described the

enantioselective synthesis of both enantiomers of the naturally occurring spiroketal 1,7-dioxaspiro[5,5]undecane, (*R*)- and (*S*)-(81), a sex pheromone of the olive fly (*Dacus oleae*) [58]. The pivotal step in this novel, stereoselective route to spiroketal systems involves the intramolecular Michael addition of hydroxybutylated chiral vinylic sulfoxides (Scheme 4.41).

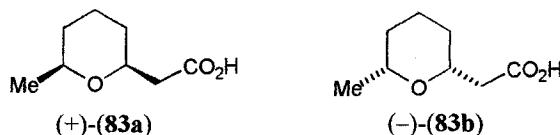
Initial cyclization of (78) yielded exclusively the kinetically favoured (79) in 77% yield. Compound (79) could be quantitatively isomerized to the more stable (80) upon treatment with acid. Raney nickel desulfurization of (79) and (80) yielded the desired enantiomers, (*R*)- and (*S*)-(81), respectively. Chelated transition state (82) was proposed to explain the high levels of stereoselectivity.



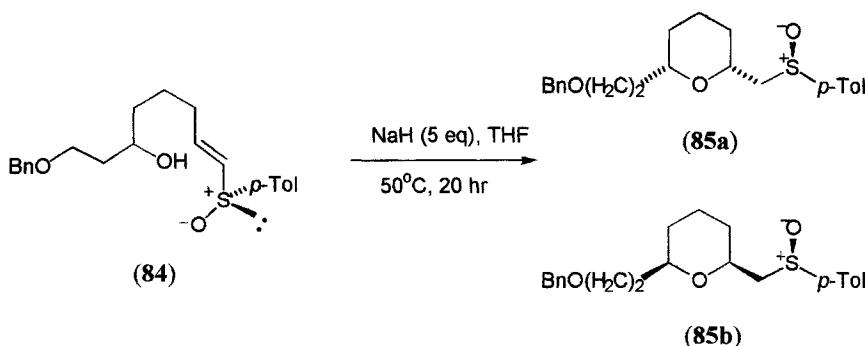
SCHEME 4.41



Intramolecular oxyanion conjugate addition has also been applied to the stereoselective synthesis of *cis*-2,6-disubstituted tetrahydropyrans by Mandai [59]. Of particular interest was an application to the enantioselective synthesis of (*cis*-6-methyltetrahydropyran-2-yl) acetic acids such as (+)-(83a) and (−)-(83b). These naturally occurring compounds have been isolated from the glandular secretions of the civet cat (*Viverra civetta*).



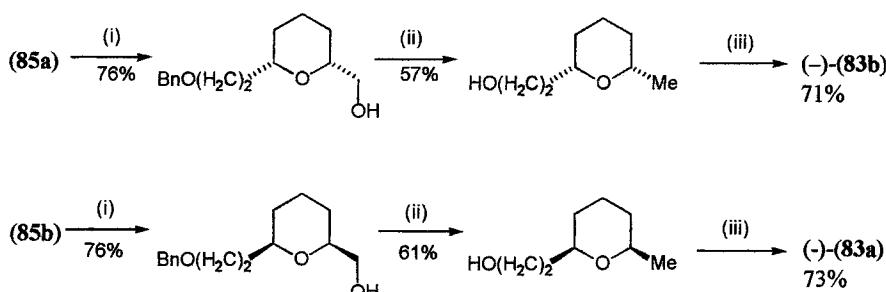
Under thermodynamically controlled conditions, enantiomerically pure (*E*)-vinyl sulfoxide (84) (as a mixture of epimers at the hydroxy centre), underwent intramolecular Michael addition to produce a mixture of the *cis* diastereoisomers (85a and 85b) in 88% combined yield (the two *trans* isomers were isolated in only 2.3% combined yield), as shown in Scheme 4.42.



SCHEME 4.42

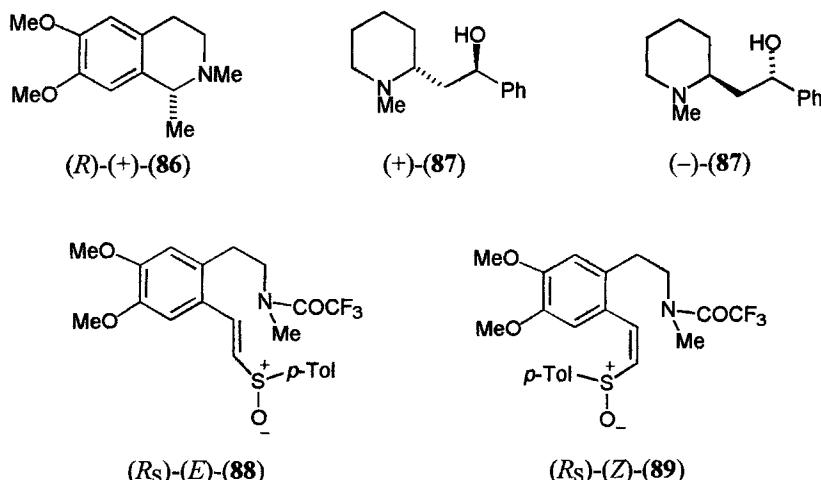
Diastereoisomers (85a) and (85b) were separated by flash column chromatography. Functional group interconversions enabled isolation of the desired product enantiomers in enantiomerically pure form (Scheme 4.43).

The intramolecular addition of amines to chiral vinylic sulfoxides has been investigated by Pyne and coworkers as an approach to various chiral natural products such as (*R*)-(+)-carnegine (86) [60, 61] and (+) and (−)-sedamine (87) [61]. As an outline of this methodology, Pyne's approach to the chiral isoquinoline, (*R*)-(+)-carnegine (86), is described below.

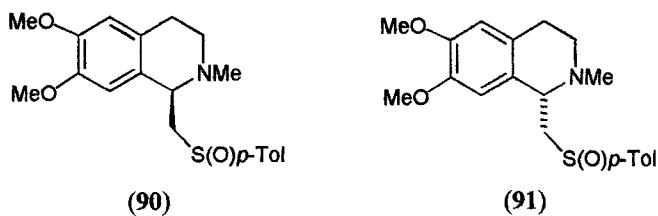


(i)  $\text{Ac}_2\text{O}/\text{NaOAc}$ , LAH, THF; (ii)  $\text{MsCl}/\text{Et}_3\text{N}$ , LAH, THF,  $\text{H}_2/\text{Pd-C}$ ; (iii)  $\text{CrO}_3$ , acetone.

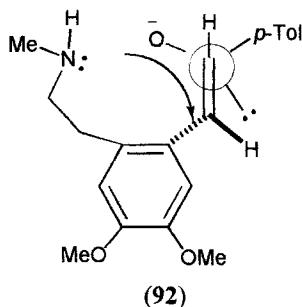
SCHEME 4.43



Chiral, isomeric vinyl sulfoxides (88) and (89) were treated separately with benzyltrimethylammonium hydroxide. On cyclization of the proposed incipient amino-anion, (*R*<sub>S</sub>)-(E)-(88) gave a 63:37 mixture of the diastereoisomeric isoquinolines (90) and (91). An enhancement and reversal of diastereoselectivity was observed on base hydrolysis of (*R*<sub>S</sub>)-(Z)-(89). This reaction gave a 16:84 ratio of (90):(91) in 96% yield from which diastereoisomerically pure (91) was obtained in 78% yield after column chromatography.

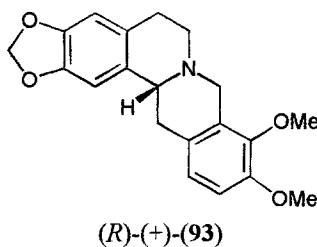


The stereochemical outcomes of these base-induced cyclizations were rationalized on the basis of nucleophilic attack by the amino group from the least hindered face of the vinylic system; transition state model (92) was proposed for the cyclization of (88).



Reductive desulfinylation of (91) with Raney nickel gave the target *(R)*-*(+)*-carnegine (86) in 51% yield.

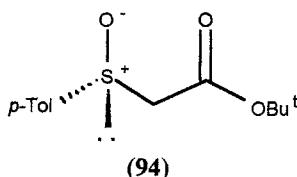
Pyne has recently extended this methodology to the synthesis of the tetrahydroprotoberberine alkaloid *(R)*-*(+)*-canadine (93) [62].



#### 4.4 MISCELLANEOUS REACTION TYPES AMENABLE TO STEREOCONTROL BY ACYCLIC CHIRAL SULFOXIDES

An important area of sulfoxide chemistry not covered elsewhere in this review involves the synthetic utility that arises as a result of the capacity of sulfur to stabilize a negative charge on an adjacent carbon atom. This property has been studied extensively in the area of carbon–carbon bond formation [63].

Compounds such as *(R)*-*(+)*-*t*-butyl(*p*-tolylsulfinyl) acetate (94) have proved to be powerful chiral synthons in asymmetric aldol-type condensation reactions [64]. Applications have included the asymmetric synthesis of  $\beta$ -hydroxy acids and esters [65] and naturally occurring five- and six-membered lactones [66].



Reactions of  $\alpha$ -sulfinyl carbanions that involve 1,2 asymmetric induction include alkylation [67], carbonylation [68,69], halogenation [70,71] and acylation [72].

Sulfoxide-stabilized carbanions also undergo stereoselective conjugate addition to  $\alpha,\beta$ -unsaturated esters [73,74]. One application has described the asymmetric synthesis of chiral indolizine and yohimboid alkaloids [75].

The addition of  $\alpha$ -sulfinyl carbanions to carbonyl compounds followed by further functional group modification has proved to be an efficient and highly stereoselective approach to epoxides,  $\alpha$ -aminoketones,  $\alpha$ -aminoaldehydes,  $\alpha$ -hydroxy esters, and allylic and propargylic alcohols [76–80].

The analogous additions of  $\alpha$ -sulfinyl carbanions to imines have provided asymmetric access to *N*-aryleziridines [81] and have been applied to natural product synthesis [82].

## 4.5 CYCLIC SULFOXIDES IN ORGANIC SYNTHESIS

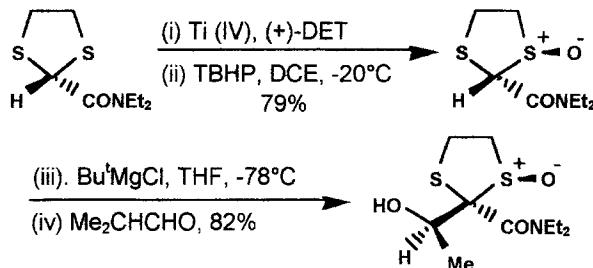
While many enantioselective processes utilizing enantiomerically pure acyclic sulfoxide derivatives have been studied extensively by the synthetic community [83], their cyclic counterparts have, by comparison, received little attention. This is somewhat surprising, since the most effective transfer of chirality occurs in saturated cyclic sulfoxides, where it has been shown that alkylation and halogenation reactions proceed in an extremely highly stereoselective manner [84–86]. Cyclic sulfoxide systems which have received the most attention are five- and six-membered ring derivatives, and the chemistry of such compounds forms the subject of this discussion.

### 4.5.1 Five-membered Rings

#### 4.5.1.1 *(–)-trans-2-N,N-Diethylacetamide-1,3-dithiolane-1-oxide*

The aldol addition of certain non-racemic  $\alpha$ -sulfinyl enolates to carbonyl compounds affords the corresponding adducts in up to 98% enantiomeric excess and in good chemical yields [87a,b, 88]. DiFuria has shown that the magnesium enolate derived from *(–)-trans-2-N,N-diethylacetamide-1,3-dithiolane-1-oxide*, which is obtained in high *ee* using the enantioselective oxidation pioneered by himself and Modena [89], undergoes aldol-type addition with isobutanal to furnish the alcohol as a single diastereoisomer [90]. The relative stereochemistry of the

product, determined to be (1*R*,2*R*,1*'R*) from x-ray diffraction studies, is presumed to originate from the rigid transition state in which both the enolate and aldehyde oxygen atoms are coordinated to the magnesium atom (Scheme 4.44).

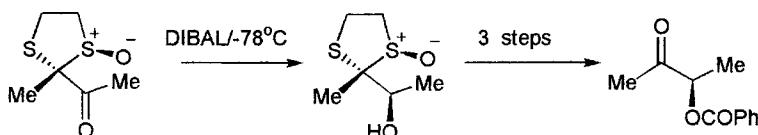


SCHEME 4.44

#### 4.5.1.2 2-Alkyl-2-acyl-1,3-dithiolane 1-oxides

Maycock has recently reported the use of an enantiomerically pure 2-alkyl-2-acyl-1,3-dithiolane 1-oxide to synthesize non-racemic active  $\alpha$ -hydroxyketone derivatives [91]. The acyldithiolane 1-oxide was prepared by an enantioselective sulfoxidation procedures [91].

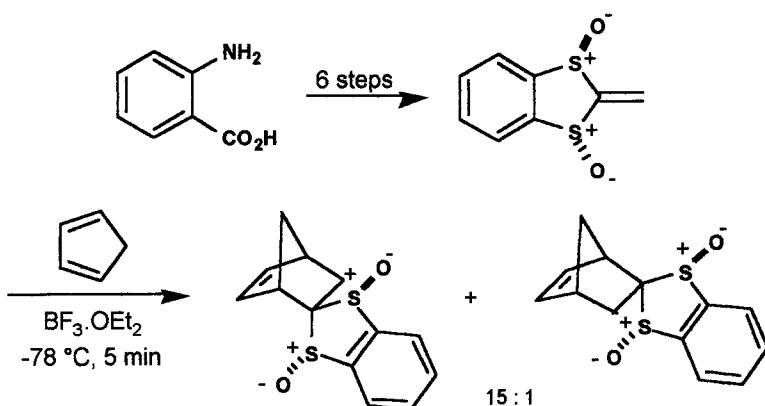
Reduction of the carbonyl group using DIBAL at low temperatures afforded the desired alcohol with complete diastereoselectivity. Deprotection yielded the protected  $\alpha$ -hydroxyketone in good yield and with  $>98\% ee$  (Scheme 4.45).



SCHEME 4.45

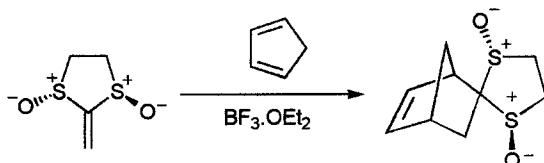
#### 4.5.1.3 Cycloaddition reaction of trans-2-methylene-1,3-dithiolane 1,3-dioxide

Aggarwal has shown that the *trans*-2-methylene-1,3-dithiolane 1,3-dioxide, which is prepared in six steps from anthranilic acid, reacts well with cyclopentadiene under Lewis acid conditions and in highly diastereoselective fashion to furnish a [4+2] cycloadduct (Scheme 4.46) [93]. Aggarwal has suggested that these cyclic alkenyl sulfoxides have potential chiral ketene equivalents, offering several advantages over other ketene equivalents such as  $\alpha$ -acetoxyacrylonitrile [94] and nitroethane [95]: Aggarwal's species offer low steric bulk with two activating groups present at the same carbon atoms.



SCHEME 4.46

This methodology has been extended to include a simpler dithiolane 1,3-dioxide derivative which undergoes highly stereoselective Diels–Alder reactions giving adducts as single diastereoisomers (Scheme 4.47) [96].



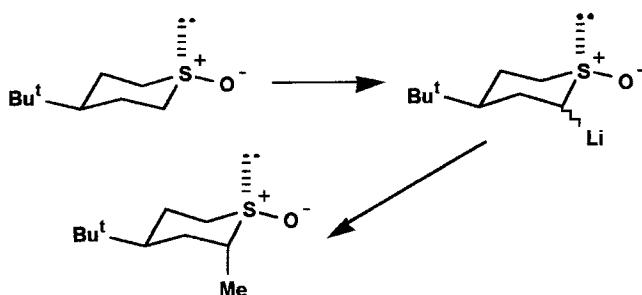
SCHEME 4.47

## 4.5.2 Six-membered Rings

### 4.5.2.1 Thiane oxides

Perhaps the first intensive study undertaken on reaction of cyclic sulfoxides was by Marquet and coworkers in the early 1970s. Of particular significance was Marquet's study of the stereochemistry of simple methylations of 4-*t*-butylthiane 1-oxides (Scheme 4.48) [84,85,97].

The stereochemistry of electrophilic substitutions of  $\alpha$ -lithio sulfoxides had previously been studied by a number of groups, albeit using only acyclic sulfoxides, and it was thought that the electrophiles used in these studies ( $\text{D}_2\text{O}$ ,  $\text{MeI}$ ,  $\text{CO}_2$ ,  $\text{Me}_2\text{CO}$ ) quenched the equilibrium between diastereoisomeric lithiated intermediates, and hence reflected the stabilities of the corresponding carbanions [84]. However, such interpretations do not account for many experimental discoveries when  $\text{MeI}$  and  $\text{D}_2\text{O}$  were used, and consequently Marquet proposed



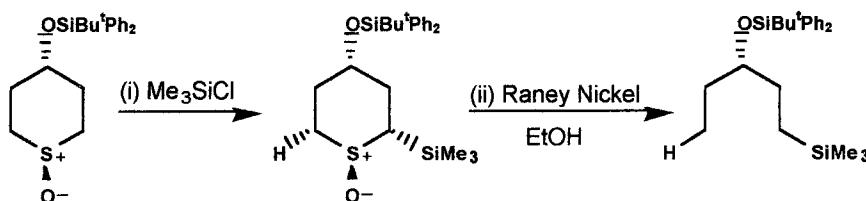
SCHEME 4.48

that the course of the reactions could depend upon an anion–cation interaction [85]. Further work from Durst [86,98] and Biellmann [99] demonstrated the influence of both added lithium salts and strong solvating agents upon the stereoselectivity of deuteration and methylation of  $\alpha$ -lithio benzylmethyl sulfoxide, for which Biellmann proposed a chelated intermediate. Indeed, in a later report, Marquet confirmed the contribution of the cation to the stereochemistry observed in the methylation reactions of 4-*t*-butylthiane 1-oxides; his judgement, based upon a chelated  $\alpha$ -lithiosulfoxide with a planar metallated carbon, was made from NMR studies [100].

The methylation reactions always proceed *trans* to the sulfoxide, with a high degree of stereocontrol (90%), even in highly crowded substrates [85]. The directing effect of the sulfoxide upon alkylation of these planar carbanions could arise as a consequence of either: (a) repulsive effects which exist between the sulfoxide dipole and the developing negative charge on the leaving group ( $\text{I}^-$ ), or (b) the large steric hindrance exerted by the sulfoxide coordinated to  $\text{Li}^+$  externally solvated, which is highly likely in a stable, chelated structure. Indeed, at a given temperature, no (or negligible) variations of the stereochemistry of methylation by  $\text{MeI}$ , and no important kinetic activation of the reaction, are observed if HMPA, DABCO, or lithium salts are added. Such results are consistent with a chelated species as the reacting entity and support the theory that the same lithio species is always involved.

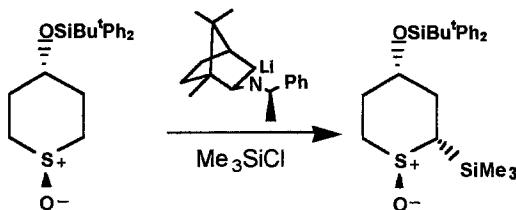
#### 4.5.2.2 *The chemistry of trans-4-*t*-butyl(diphenyl)silyloxythiane oxide*

The chemistry of *trans*-4-*t*-butyl(diphenyl)silyloxythiane oxide has been investigated by Simpkins in the synthesis of protected, substituted secondary alcohols. Simpkins has found that the anion of *trans*-4-*t*-butyl(diphenyl)silyloxythiane oxide, when treated with trimethylsilyl chloride, can form a 2,4-disubstituted thiane; in turn, this product may be easily desulfurized with Raney nickel to liberate (S)-3-*t*-butyl(diphenyl)silyloxy-1-trimethylsilylpentane in good yield (Scheme 4.49) [101].



SCHEME 4.49

Simpkins has also applied the well-documented homochiral lithium amide (HCLA) base chemistry [102] to these substrates, and has found that upon treating *trans*-4-*t*-butyl(diphenyl)silyloxythiane oxide with an optically active, camphor-derived base followed by quenching with trimethylsilyl chloride, non-racemic products are isolable in up to 69% enantiomeric excess (Scheme 4.50) [102].



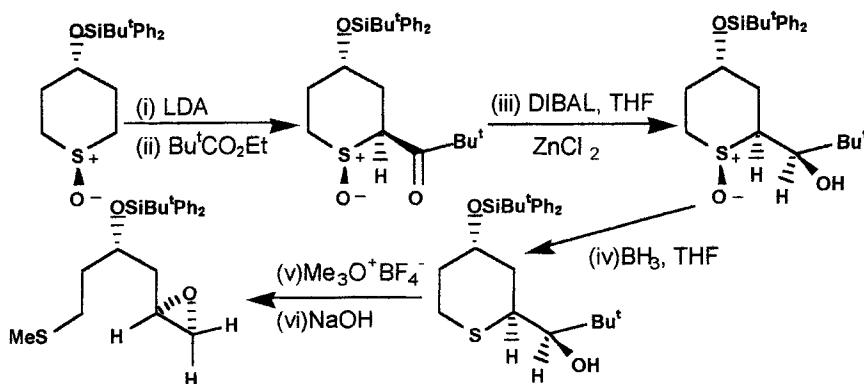
SCHEME 4.50

Finally, and perhaps most interestingly, Simpkins has shown that *trans*-4-*t*-butyl(diphenyl)silyloxythiane oxide may undergo stereoselective acylation to furnish a range of  $\beta$ -keto sulfoxides which may be reduced in stereoselective fashion to liberate either of the corresponding hydroxysulfoxides [103]. Subsequent manipulation of these products, involving initial sulfoxide reduction to the sulfide as reported by Williams and Phillips [104] and thiane ring opening using Meerwein's reagent, ultimately leads to functionalized epoxides with a high degree of stereocontrol (Scheme 4.51).

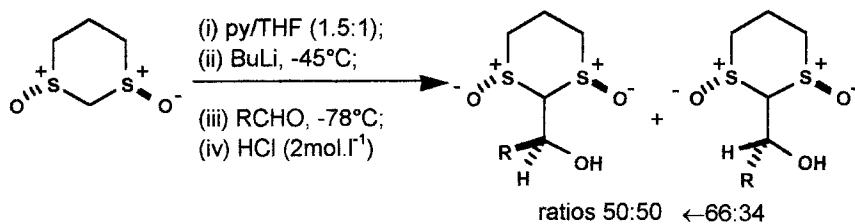
#### 4.5.2.3 1,3-Dithiane dioxides

Aggarwal has demonstrated the success of a variety of electrophilic reactions involving the  $C_2$  symmetric species 1,3-dithiane dioxide [105a–c]. This substrate is easily prepared in 60% yield from oxidation of 1,3-dithiane with sodium metaperiodate, and is isolated as a mixture of diastereoisomers in a ratio of 95:5 in favour of the *trans*-1,3-dithiane-1,3-dioxide product.

Aggarwal has discovered that the anion derived from 1,3-dithiane dioxide undergoes rapid reaction with a range of aldehydes, leading to the formation of diastereoisomeric mixtures in good yield (Scheme 4.52) [105b].

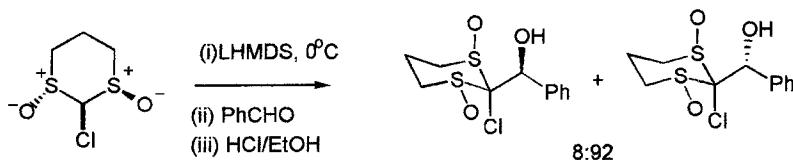


SCHEME 4.51



SCHEME 4.52

Lithiated 2-chloro-1,3-dithiane 1,3-dioxide undergoes an analogous addition reaction with aldehydes to give product mixtures displaying high diastereoselectivities (Scheme 4.53) [106].



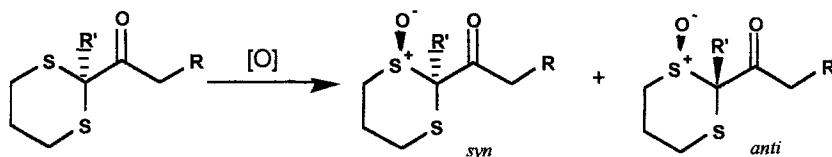
SCHEME 4.53

#### 4.5.2.4 1,3-Dithiane 1-oxide (DiTOX)

Over the last two decades, 1,3-dithianes have become ubiquitous as acyl anion equivalents in organic synthesis, with thioacetal chemistry having already been well established [107]. It is therefore somewhat surprising to find that 2-acyl-1,3-dithianes, which may easily be prepared in excellent yield from dithiane 2-anions, have received relatively little attention [108]. The development of 2-acyl-1,3-

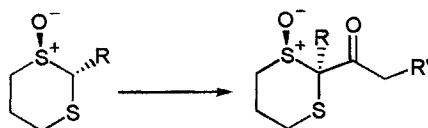
dithiane 1-oxides and their application to a number of stereoselective transformations has been accomplished by Page.

Acyldithianes may be oxidized at sulfur using mCPBA, sodium metaperiodate, oxone or *t*-butyl hydroperoxide to furnish the *syn* and *anti* derivatives, which may easily be separated by chromatography (Scheme 4.54). Alternatively, sulfoxidation by an asymmetric procedure, for example using the Kagan or Modena procedures [92, 109] or catalytic processes involving duiral sulfonylimines and hydrogen peroxide [110] has been developed which allows access to optically pure 2-acyldithiane 1-oxides after crystallization [110]. It is the stereoselective reactions of these substrates that have formed the basis of many of Page's studies over recent years.



SCHEME 4.54

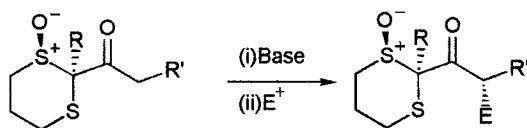
Alkylation and acylation of dithiane oxides are highly stereoselective processes. In such transformations, it is noticed that the *anti* substrate leads to the *syn* acyldithiane oxide (Scheme 4.55), with the choice of base being pivotal in the process. The use of butyllithium for acylation and sodium *t*-butoxide/butyllithium mixtures for alkylation with aldehydes tends to give the cleanest and most efficient reactions. Of late, simple 2-substituted dithiane oxides have been prepared with very high enantioselectivity, and such compounds have become the preferred starting materials for the various systems under scrutiny.



SCHEME 4.55

#### *Enolate alkylation of acyldithiane oxides*

Enolates of acyldithiane oxides may be prepared by treatment with a single equivalent of base, the most efficient being lithium hexamethyldisilazide (LHMDS), followed by quenching with an alkyl halide (Scheme 4.56) [111]. The reactions proceed in good yields (~70–80%) and with very high stereoselectivity; the presence of a single enolate geometry at –78°C has been proven, with ratios decreasing to approximately 10:1 at room temperature. Stereoselectivities have been obtained for both the *syn* and *anti* systems that are so high that the minor isomers are not detectable either by 400 MHz <sup>1</sup>H NMR spectroscopy or HPLC techniques.

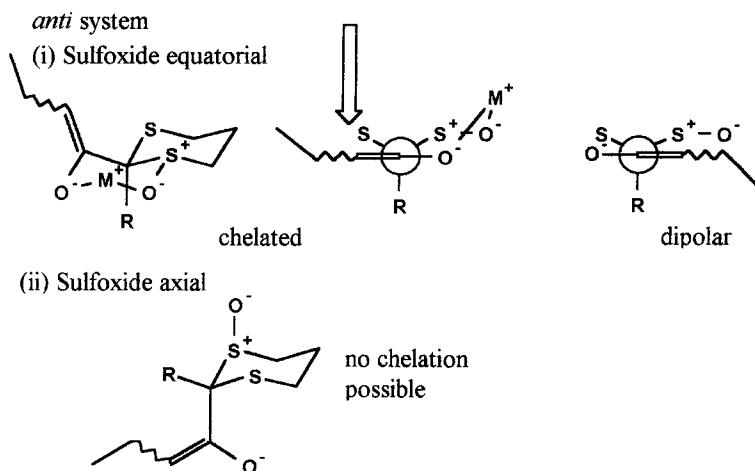


SCHEME 4.56

The reaction has been used to prepare a range of  $\alpha$ -methyl carboxylic acids with very high *ee* [129, 138].

Chelated transition state models have been proposed to account for the high stereoselectivities induced by the DiTOX system in many synthetic transformations. These are highlighted below for the case of enolate alkylation.

In general, for the *anti* series, as the size of the group at carbon atom 2 (C-2) increases so does the selectivity for the alkylation step. This is in accord with a chelated transition state containing an equatorial sulfoxide; the approach of the electrophile toward the (*Z*) enolate at the face of the enolate furthest from the C-2 group, the less hindered face, is shown in Scheme 4.57.

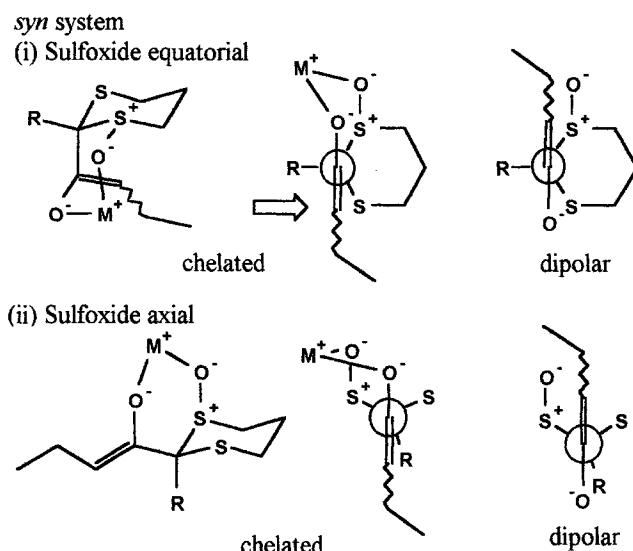


SCHEME 4.57

In contrast, the selectivity obtained for reactions involving the *syn* substrates decreases as the size of the C-2 substituent increases; this discovery may once again be explained in terms of a chelated transition state. The model generally depicts an equatorial sulfoxide moiety, and here the approach of the electrophile toward the (*Z*) enolate at the face of the enolate nearest to the C-2 substituent occurs, since this face is now the least hindered (Scheme 4.58).

Little or no selectivity would be expected from transition state conformations containing axial sulfoxide units, although chelated transition states containing axial sulfoxides are possible in *syn* systems.

The above predictions of stereochemical induction have been borne out during Page's studies of enolate reactivity and the relative sense of induction resulting from the application of the above models is as shown in Scheme 4.56. Interestingly,

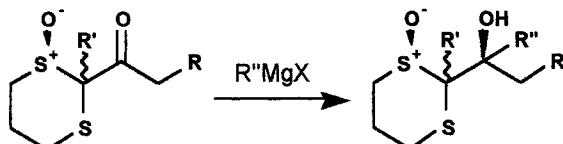


**SCHEME 4.58**

the same absolute sense of induction is expected alkylation of enolates derived from both *syn* and *anti* acyldithiane oxide enolates having the same absolute configuration at the sulfinyl sulfur atom. Separation of the **syn** and **anti** isomers of the acyl dithiane oxide is therefore unnecessary if the thioacetal unit is subsequently to be removed.

### Additions of Grignard reagents to acyldithiane oxides

Grignard reagents add efficiently to acyldithiane oxides to furnish tertiary alcohols in excellent yields and without loss of the dithiane oxide unit by nucleophilic displacement (Scheme 4.59) [112].



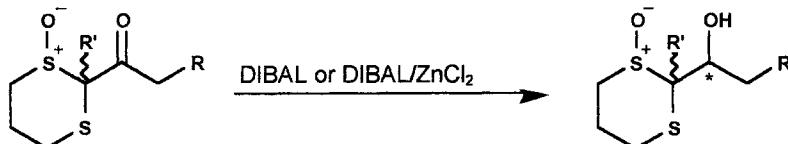
**SCHEME 4.59**

Several factors have a profound effect upon the stereoselectivity of these additions, including (a) *solvent conditions*, reactions performed in THF proving more selective than those carried out in diethyl ether; (b) *temperature*, lower temperatures leading to increased selectivity; and (c) *dithiane ring opening* by nucleophilic attack at the sulfoxide sulfur atom occurring preferentially in substrates possessing large R' groups.

### *Hydride reduction of acyldithiane oxides*

High levels of asymmetric induction have been obtained in the reduction of the

carbonyl groups of acyldithiane oxides to furnish secondary alcohols using DIBAL (Scheme 4.60) [113]. The reversed sense of selectivity is obtained when zinc chloride is present in the reaction mixture.

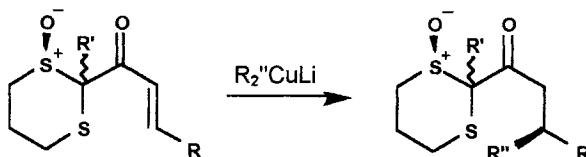


SCHEME 4.60

The DIBAL/ZnCl<sub>2</sub> reductions proceed via chelated transition states in which the Lewis acid introduces rigidity through chelation, and thus allows delivery of hydride to occur at the less hindered face of the prochiral carbonyl moiety. The reaction has been used to prepare  $\alpha$ -hydroxyketones in good to high *ee* [132].

#### *Conjugate addition to $\alpha,\beta$ -unsaturated acyldithiane oxides*

Reactions of organocuprates with  $\alpha,\beta$ -unsaturated 2-acyl-1,3-dithiane 1-oxides have also been studied (Scheme 4.61) [114].

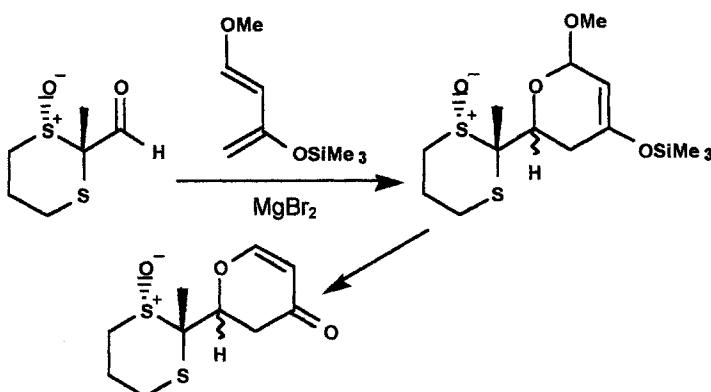


SCHEME 4.61

These reactions are rather difficult to control owing to the range of reactive substrate conformations available, and perhaps also because of the complex reaction mechanism involved. Nevertheless, stereoselectivities as high as 10:1 have been obtained in the 2-but-2-enoyl series. The most selective reagents are the simple dialkyl lithium cuprates; despite being slightly solvent-sensitive, they react in excellent yields, whereas organocupper reagents are too unreactive and higher order cuprates tend to give inconsistent results.

#### *Heterocycloaddition reactions of 2-formyl-1,3-dithiane oxides*

2-Formyl-2-methyl-1,3-dithiane 1-oxide undergoes a highly diastereoselective heterocycloaddition reaction with Danzig's diene [115]; the reaction is mediated by magnesium bromide (Scheme 4.62). The cycloaddition reactions may be performed using a range of Lewis acids and different solvent conditions.

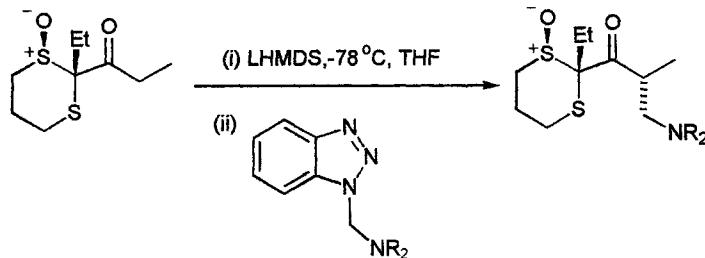


SCHEME 4.62

As in previous cases, the chelated transition state rationale is applicable here. Initially, coordination of the sulfoxide and carbonyl group oxygen atoms to the Lewis acid is believed to occur, allowing the diene to approach the carbonyl function from the least sterically hindered face, leading to the observed cycloadduct. Interestingly, both Danishefsky [116] and Midland [117] have proposed chelated transition states for stereoselective additions of Danishefsky's diene to chiral  $\alpha$ -alkoxy aldehydes.

*Introduction of nitrogen into acyldithiane oxide systems: the Mannich reaction*

High diastereofacial selectivity has been observed in asymmetric Mannich reactions of 2-acyl-2-alkyl-1,3-dithiane 1-oxides, leading to  $\beta$ -amino ketones in good yield [118]. This study is of particular significance since stereoselectivity in the Mannich reaction has received relatively little attention [119].



$\text{NR}_2 = \text{NHPh, NHCOPh, NMe}_2$

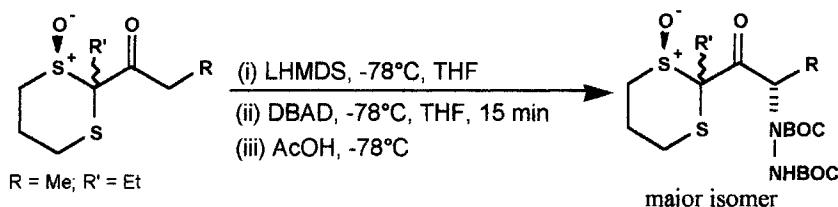
SCHEME 4.63

For the DiTOX series, Mannich reactions were initially performed using commercially available Eschenmoser's salt over a range of reaction conditions and with a variety of metal counterions, although the most promising results were

obtained when the benzotriazole-based aminoalkylating agents, pioneered by Katritzky [120], were used (Scheme 4.63). Reactions of lithium enolates derived from *syn*- and *anti*-2-propanoyl-2-ethyl-1,3-dithiane 1-oxide with benzotriazole derivatives provided the desired aminoalkylated products in good yield and with excellent diastereoselectivity.

*Electrophilic amination of DiTOX ketone enolates*

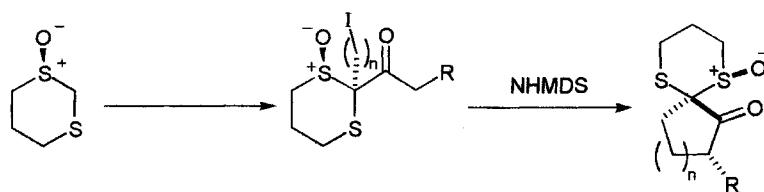
Enolate anions derived from *syn* and *anti* 2-substituted 2-acyl-1,3-dithiane 1-oxides react readily with the nitrogen electrophile di-*t*-butyl azodicarboxylate (DBAD) to give  $\alpha$ -aminoketones with good diastereoselectivity and in moderate yields (Scheme 4.64) [121]. A low-temperature acetic acid quench is necessary and is believed to prevent loss of stereochemical integrity at the new asymmetric centre which can otherwise occur.



SCHEME 4.64

*One-pot stereocontrolled cycloalkanone synthesis using dithiane oxides*

Sequential treatment of 1,3-dithiane 1-oxide with NHMDS, butyllithium, propionyl or butyryl imidazole, and a diiodoalkane led to the corresponding haloalkylated materials in  $\sim$ 70% yield and with exclusive *syn* stereochemistry. Further treatment with NHMDS led to carbocyclic products with sufficiently high diastereoselectivity that the minor isomer could not be detected by 400 MHz  $^1\text{H}$  NMR spectroscopy (Scheme 4.65) [122].

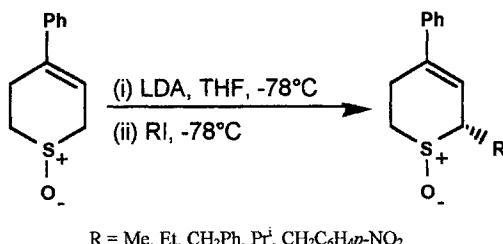


SCHEME 4.65

#### 4.5.2.5 4-Phenyl-5,6-dihydro-2*H*-thiopyran 1-oxide

Crumbie has found that treatment of the anion of the allylic sulfoxide 4-phenyl-5,6-dihydro-2*H*-thiopyran 1-oxide with primary alkyl halides at  $-78^\circ\text{C}$  affords exclusively

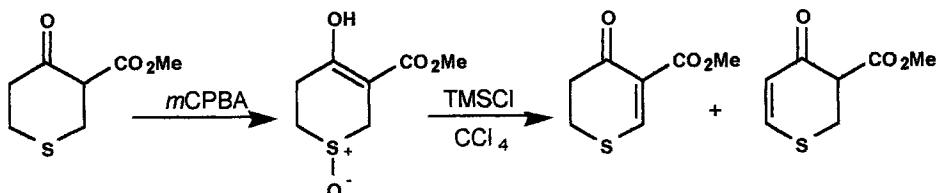
the *trans*-2-alkyl-4-phenyl-5,6-dihydro-2*H*-thiopyran 1-oxide derivatives as crystalline solids [123]. The reaction is thus both regio- and stereospecific (Scheme 4.66).



SCHEME 4.66

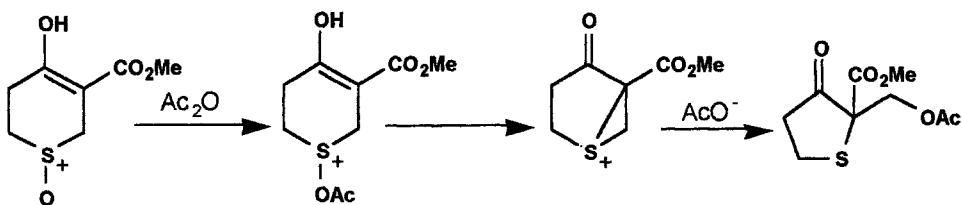
#### 4.5.2.6 3-Methoxycarbonylthian-4-one 1-oxide

Taylor has demonstrated that conversion of the title sulfoxide, prepared by oxidation of the known sulfide, shown in Scheme 4.67 [124], into two desired enones which were required as starting materials for the synthesis of thiathromboxane analogues, could be carried out using trimethylsilyl chloride (TMSCl) in refluxing tetrachloromethane. At the time, this was the first occasion on which TMSCl had been used in order to effect a Pummerer rearrangement for such species (Scheme 4.67) [125a,b].



SCHEME 4.67

Taylor has also shown that treatment of 3-methoxycarbonylthian-4-one 1-oxide with acetic anhydride under reflux furnishes a product in which  $\beta$ -carbon oxidation and ring contraction have taken place (Scheme 4.68).



SCHEME 4.68

Both of these rearrangements may be rationalized in terms of a common intermediate thiiranium ion (Scheme 4.68).

## 4.6 APPLICATION OF CHIRAL CYCLIC SULFOXIDES TO THE SYNTHESIS OF NATURAL PRODUCTS

### 4.6.1 Total Synthesis of *dl*-Biotin

The first example, reported in 1975 by Marquet, concerns a novel total synthesis of biotin, based on stereoselective alkylation of a bicyclic, *cis*-fused, five-membered ring sulfoxide [126,127].

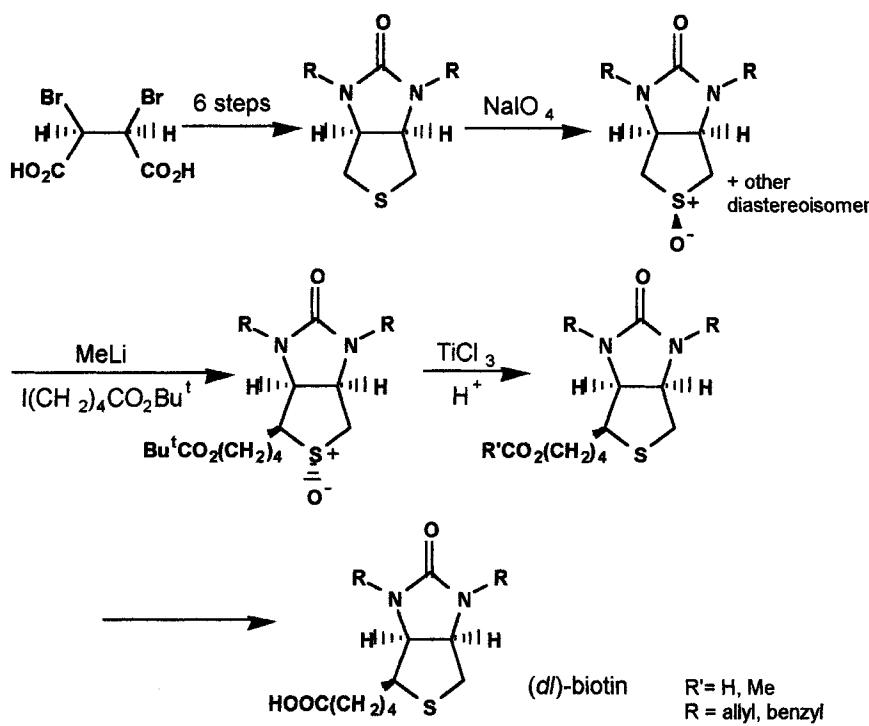
The total synthesis of biotin has been achieved by a number of groups, each employing a very different synthetic strategy [128]. An intermediate sulfide bearing the biotin moiety was initially prepared and was then oxidized with sodium metaperiodate to furnish a mixture of sulfoxides in a 10:90 ratio. The  $\alpha$ -carbanion was generated by treatment with MeLi in a HMPA-THF or HMPA-diglyme solution at  $-78^{\circ}\text{C}$ , and was subsequently alkylated with *t*-butyl  $\omega$ -iodovalerate at  $-30^{\circ}\text{C}$ ; it was found that the use of a *t*-butyl ester was absolutely necessary in order to prevent addition at the ester by the lithiated sulfoxide. The reaction proceeds in a highly stereoselective fashion and a single isomer, possessing the side-chain *trans* to the sulfoxide, may be isolated. After reduction of the sulfoxide and removal of the nitrogen protecting groups, *dl*-biotin is obtained (Scheme 4.69). The synthesis proved highly versatile for the preparation of several biotin analogues, since different substituents can be introduced by alkylating the same key intermediate sulfoxide, and the versatility has been illustrated in the preparation of the two isomeric 5-methylbiotins.

The yield of the alkylated material depends largely on the choice of both base and solvent. It was discovered that the use of butyllithium leads to reaction at sulfur, resulting in formation of a carbamate (Scheme 4.70), while in the absence of HMPA reprotonation of the intermediate carbanion competes strongly with alkylation.

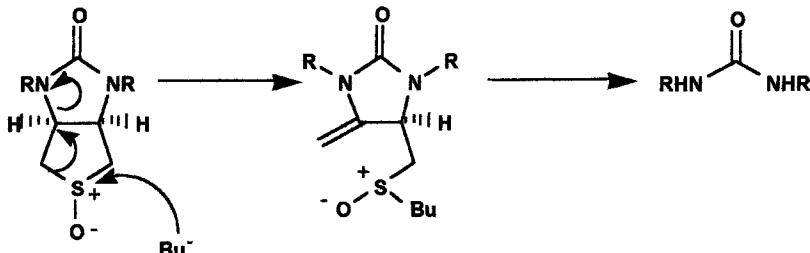
### 4.6.2 Enantioselective Synthesis of $\alpha$ -Methyl Carboxylic Acids

Studies within the Page group geared toward the synthesis of (*R*)- $(-)$ -2,6-dimethylheptanoic acid [129], a simple natural product derived from citronellal, have proved effective. This species contains a carboxylic acid function substituted at the  $\alpha$ -carbon atom, a feature common to many analgesic compounds. This synthesis promises the first application of DiTOX as a chiral building block in organic synthesis.

(1*R*,2*R*)- $(+)$ -*anti*-2-Ethyl-2-propanoyl-1,3-dithiane 1-oxide was prepared by enantioselective sulfur oxidation of *anti*-2-ethyl-2-propanoyl-1,3-dithiane, followed

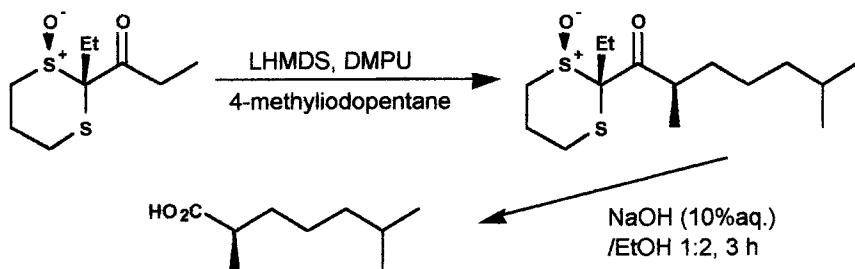


SCHEME 4.69



SCHEME 4.70

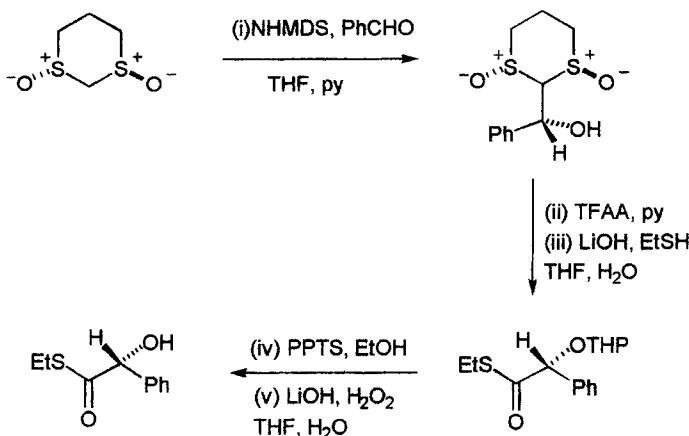
by crystallization to optical purity [110]. Enolate alkylation with 4-methyliodopentane leads to the enantiomerically pure intermediate in moderate yield and, once again, with a high degree of stereocontrol. The minor diastereoisomer could not be detected in the 400 MHz  $^1H$  NMR spectrum. Simple base-mediated deacylation of this species, a technique previously used by Aggarwal [130] to prepare nonracemic dithiane derivatives, leads directly to the desired target without loss of stereochemical integrity in 39% yield (Scheme 4.71). Further, the 2-ethyl-1,3-dithiane 1-oxide auxiliary is recoverable in optically pure form. Similar chemistry has recently been used to prepare a series of biologically active  $\alpha$ -aryl propanoic acids in very high *ee* and good overall yields [138].



SCHEME 4.71

#### 4.6.3 Enantioselective Synthesis of $\alpha$ -Hydroxy Acid Derivatives

Aggarwal has reported an enantioselective approach to the synthesis of  $\alpha$ -hydroxy acid derivatives using *trans*-1,3-dithiane 1,3-dioxide. For example, reaction of *trans*-1,3-dithiane 1,3-dioxide with an aromatic aldehyde liberates the alcohol which is protected as the tetrahydropyranyl (THP) ether; the resulting product may then be subjected to a Pummerer reaction, using trifluoroacetic anhydride, to give a thiolester. Transthiolesterification of this product using LiSEt gives the ethylthioester as shown in Scheme 4.72. Subsequent hydrolysis furnishes the corresponding  $\alpha$ -hydroxy acid in 86% yield and 97% enantiomeric excess (Scheme 4.72) [131].



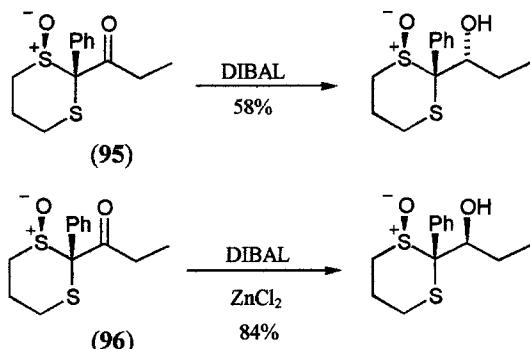
SCHEME 4.72

#### 4.6.4 Enantioselective Synthesis of $\alpha$ -Hydroxy Ketones

$\alpha$ -Hydroxy ketones are an important structural feature of many biologically active molecules [133]. Compounds containing this functionality have also been

reported to control the stereochemistry for several different transformations [134–137].

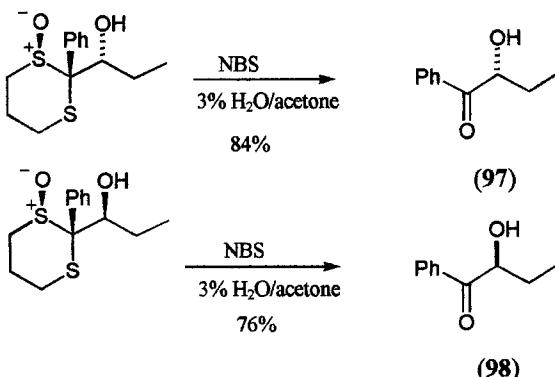
Enantiomerically pure DiTOX systems (**95**) and (**96**) were used to prepare  $\alpha$ -hydroxy acids [132]. Page had previously described the stereoselective reduction of 2-acyl-2-alkyl-1,3-dithiane 1-oxides with DIBAL [113], and normally observed [132] a reversal of selectivity upon addition of zinc chloride. In this case (Scheme 4.73), THF solutions of the substrates were treated at  $-78^{\circ}\text{C}$  with either DIBAL or DIBAL/ZnCl<sub>2</sub> reducing systems. As expected, the DIBAL and DIBAL/ZnCl<sub>2</sub> reducing systems gave products of opposite stereoselectivity; in most cases only one product diastereoisomer was observed.



SCHEME 4.73

Hydrolysis of the 1,3-dithiane 1-oxide moieties of the product alcohols under standard conditions using NBS/acetone/water gave the corresponding  $\alpha$ -hydroxyketones (**97**) and (**98**) in excellent yields (Scheme 4.74).

An enantioselectivity of 93% was observed for products (**97**) and (**98**); in the case of 2-methyl analogues, a degree of racemization was observed.



SCHEME 4.74

## 4.7 CONCLUDING REMARKS

As can perhaps be appreciated from this account, the sulfoxide moiety can be an efficient and highly selective stereocontrol element for a wide variety of synthetic transformations. The sulfoxide group is readily incorporated into the substrate structure, using established methods. In most cases, the sulfinyl group can be removed after its contribution to the synthetic scheme without loss of enantiomeric purity in the desired product. In most cases the sense of stereoselection observed can be predicted and rationalized on the basis of steric, stereochemical and/or chelation control mechanisms.

The versatility of the sulfoxide group as a stereocontrol element ensures a constant supply of new applications to add to its already impressive portfolio.

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# THE CHEMISTRY OF $\alpha,\beta$ -UNSATURATED SULFOXIDES

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## 5.1 INTRODUCTION

The synthetic utility of the sulfoxide functionality is well established in organic chemistry and has been known for many years [1]. More specifically, the use of nonracemic sulfoxides in asymmetric synthesis has assumed growing importance in recent years since the chiral sulfoxide group is often able to exert significant stereochemical control in bond-forming reactions. Such advances in asymmetric synthesis have been made possible by the development of new methodology for the preparation of nonracemic sulfoxides.

This review is concerned with the use of  $\alpha,\beta$ -unsaturated sulfoxides in organic synthesis and covers the chemistry of vinyl (alkenyl) and dienyl sulfoxides. Other types of  $\alpha,\beta$ -unsaturated sulfoxides such as allenyl and propargyl (alkynyl) sulfoxides are beyond the scope of this review. Particular emphasis is given to the use of nonracemic  $\alpha,\beta$ -unsaturated sulfoxides throughout, reflecting recent developments in this field.

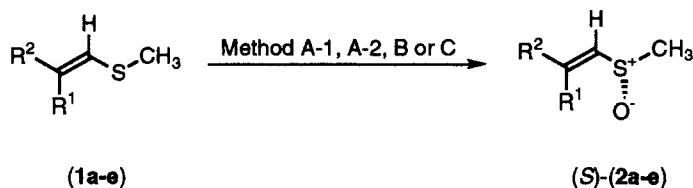
## 5.2 PREPARATION OF OPTICALLY ACTIVE $\alpha,\beta$ -UNSATURATED SULFOXIDES

The methods available for the preparation of optically active  $\alpha,\beta$ -unsaturated sulfoxides are discussed, including the asymmetric synthesis of dienyl sulfoxides, as most of the subsequent work discussed in this chapter is concerned with the use of the sulfoxide group as a stereocontrolling element in synthesis.

### 5.2.1 Asymmetric Oxidation of $\alpha,\beta$ -Unsaturated Sulfides

There are many methods available for the nonstereoselective oxidation of sulfides to the corresponding sulfoxides, and this transformation can now be considered in most cases to be trivial [2]. More recently, the development of methodology for the asymmetric oxidation of sulfides to sulfoxides has been the subject of considerable effort by many research groups around the world as the use of nonracemic sulfoxides in asymmetric synthesis has assumed growing importance. The

application of this methodology to the synthesis of nonracemic  $\alpha,\beta$ -unsaturated sulfoxides has been the subject of recent studies [3–5]. Fauve and coworkers [3] made use of two of the most successful and widely used chemical methods for the enantioselective oxidation of sulfides, namely the Kagan [6] and Davis [7,8] techniques, and also microbiological oxidation methods, in a comparative study for the preparation of (*S*)- $\alpha,\beta$ -unsaturated sulfoxides. Oxidation of sulfides (**1a–e**) (Table 5.1) was carried out under the conditions described (Scheme 5.1), and all three methods were found to be substrate dependent in terms of their enantioselectivity. The highest optical purities were obtained by microbiological oxidation, or using the Kagan method (90–95% *ee*), to give (*S*)- $\alpha,\beta$ -unsaturated sulfoxides (**2a**), (**2b**) and (**2e**). High enantiomeric excesses were not obtained for the 1,1-disubstituted sulfoxide (**2c**), whichever method was used. The sulfoxide (**2d**) was prepared with moderate enantioselectivity using the three methods (58–66% *ee*). Tentative explanations for the substrate dependence of enantiomeric excess were proposed by the authors.



#### Method A-1: *Helminthosporium* sp., for (1a) and (1b)

#### Method A-2: *Oxysporum* for (1c), (1d) and (1e)

Method B:  $\text{Ti}(\text{OPr})_4$ , (-)-diethyl tartrate,  $\text{H}_2\text{O}$ ,  $\text{PhCMe}_2\text{OOH}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-20^\circ\text{C}$

Method C: (–)- $\alpha,\alpha$ -dichlorocamphorbenzenesulphonyloxaziridine,  $\text{CCl}_4$

### SCHEME 5.1

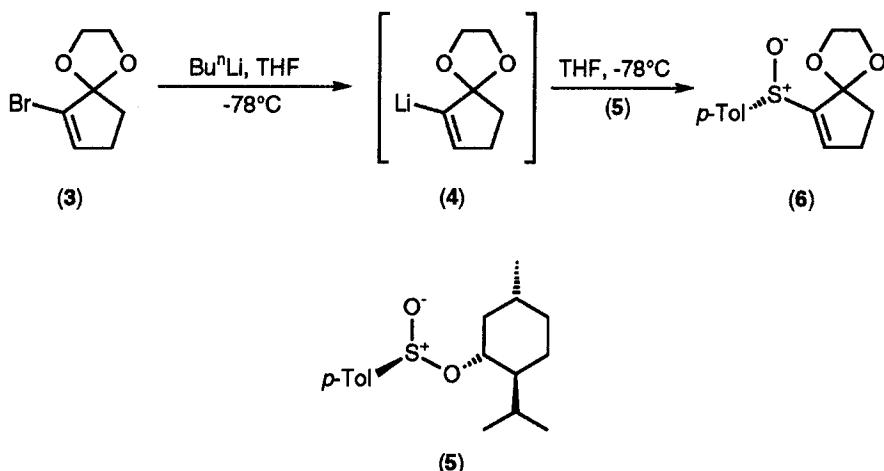
TABLE 5.1

Substrate	Stereoisomer	R <sup>1</sup>	R <sup>2</sup>
<b>(1a)</b>	(E)	H	Ph
<b>(1b)</b>	(E)	H	3-MeO-C <sub>6</sub> H <sub>4</sub>
<b>(1c)</b>	–	Ph	Ph
<b>(1d)</b>	(Z)	Ph	3-Pyridyl
<b>(1e)</b>	(Z)	Ph	4-Pyridyl

### 5.2.2 The Andersen Method

The highly stereoselective synthesis of optically active sulfoxides using the methodology first developed by Andersen in 1962 is still the most important and widespread approach used today [9,10]. The method is based on the reaction of

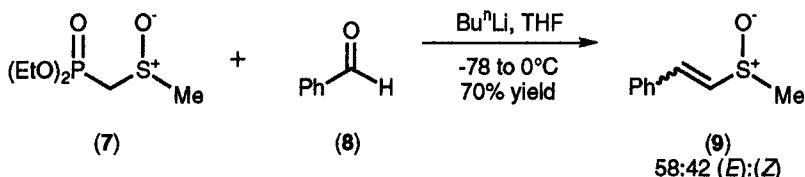
diastereoisomerically pure menthyl arenesulfinates with Grignard reagents, and was first applied to the synthesis of optically active  $\alpha,\beta$ -unsaturated sulfoxides by Stirling and coworkers [11,12]. Posner and coworkers have used this method for the preparation of enantiomerically pure enone sulfoxides [13,14], widely used as Michael acceptors in asymmetric synthesis (see Section 5.4). For example, treatment of the protected 2-bromo-2-cyclopentenone (**3**) with *n*-butyllithium in THF at  $-78^{\circ}\text{C}$  gives the lithiated intermediate (**4**), which, on reaction with (*S*)-(*-*)-menthyl *p*-toluenesulfinate (**5**), gives the protected (*S*)-(+)-2-(*p*-toluenesulfinyl)-2-cyclopentenone (**6**) in 67% yield (Scheme 5.2).



SCHEME 5.2

### 5.2.3 The Horner–Wittig Procedure

The synthesis of racemic  $\alpha,\beta$ -unsaturated sulfoxides by the Horner–Wittig olefination of aldehydes is a well-established process [15]. In this procedure, deprotonation of a dialkyl arenesulfinylmethanephosphonate and reaction of the resulting anionic species with an aldehyde gives  $\alpha,\beta$ -unsaturated sulfoxides in high yield, but with variable (*E*):(*Z*) ratios according to the nature of the aldehyde. For example, reaction of  $\alpha$ -phosphoryl sulfoxide (**7**) with benzaldehyde (**8**) gives the  $\alpha,\beta$ -unsaturated sulfoxide (**9**) in 70% yield with an (*E*):(*Z*) ratio of 58:42 (Scheme 5.3) [16].

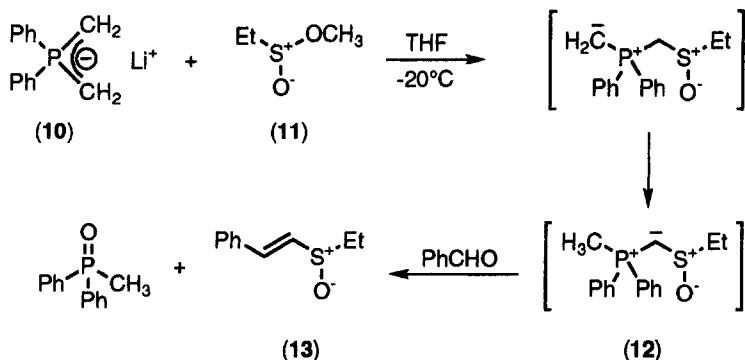


SCHEME 5.3

Dialkyl arenesulfinylmethanephosphonates are available by *S*-oxidation of the corresponding dialkyl arenesulfonylmethanephosphonates or by reaction of anions derived from dialkyl methanephosphonates with sulfinic esters. With regard to the synthesis of optically active  $\alpha,\beta$ -unsaturated sulfoxides, the former method may not be applied in the absence of a reliable, highly enantioselective *S*-oxidation procedure without recourse to resolution methods, while the latter method suffers from the relatively polar nature of dialkyl arenesulfinylmethanephosphonates, which renders their chromatographic separation tedious and costly.

Craig and coworkers have recently published an improved method for the preparation of both racemic and enantiomerically pure  $\alpha,\beta$ -unsaturated sulfoxides [17], in which addition of a solution of either isopropyl benzenesulfinic ester or menthyl *p*-toluenesulfinic ester to a cold solution of lithiated dimethyl methanephosphonate cleanly generates the lithiated dimethyl arenesulfinylmethanephosphonate, with regeneration of dimethyl methanephosphonate. Addition of this solution to various aldehydes gives the corresponding  $\alpha,\beta$ -unsaturated sulfoxides in high yield, but often with poor (*E*):(*Z*) ratios. The volatility of the regenerated phosphonate allows its easy removal *in vacuo* at ambient temperature.

The issue of the variable (*E*):(*Z*) ratios synthesized using this method has recently been addressed by Mikolajczyk and coworkers [18], who have reported a new one-pot (*E*)-stereoselective synthesis of both racemic and optically active  $\alpha,\beta$ -unsaturated sulfoxides. In this procedure, (*E*)- $\alpha,\beta$ -unsaturated sulfoxides were prepared by the reaction of lithium dimethyldiphenylphosphonium diylide (**10**) with sulfinates such as (**11**), followed by treatment of the  $\alpha$ -sulfinylmethyldiphenylphosphonium ylide (**12**), formed with benzaldehyde to give the (*E*)-styryl sulfoxide (**13**) in 70% yield (Scheme 5.4).



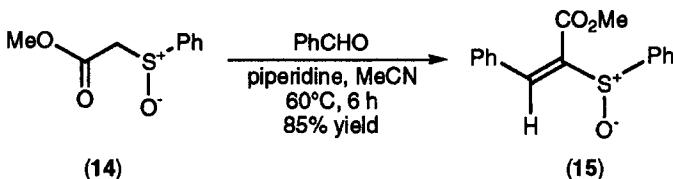
SCHEME 5.4

### 5.2.4 The Knoevenagel-type Condensation and Related Routes

The first examples of the use of the Knoevenagel-type condensation for the synthesis of  $\alpha,\beta$ -unsaturated sulfoxides were made by Ogura and Tsuchihashi, who prepared racemic ketene thioacetal monoxides by the condensation of methyl

thiomethyl sulfoxide with carbonyl compounds and nitriles [19–22]. The use of ketene thioacetal monoxides as Michael acceptors is described in Section 5.4.

Sammes and coworkers have reported that the treatment of the zinc enolate of methyl phenylsulfinylacetate (**14**) with aldehydes gives the corresponding (*E*)-sulfinyl- $\alpha,\beta$ -unsaturated esters in moderate yields [23,24]. A similar observation was made by Tanikaga and coworkers [25–27], who found that treatment of  $\beta$ -keto sulfoxides such as (**14**) with aldehydes in the presence of piperidine gives the (*E*)- $\alpha$ -sulfinyl- $\alpha,\beta$ -unsaturated esters (**15**) (Scheme 5.5) [25].



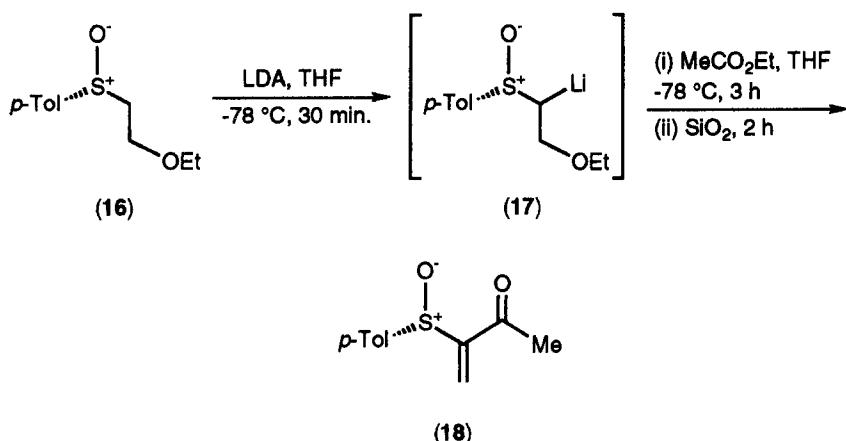
SCHEME 5.5

The synthesis of nonracemic  $\alpha,\beta$ -unsaturated sulfoxides bearing an electron-withdrawing group at the  $\alpha$ -position has received attention [28–30] because these types of substrates have proved useful as chiral dienophiles (see Section 5.5) [28,29]. These methods suffered from the disadvantage that several steps were involved. Maignan and coworkers [31] have recently described a one-pot synthesis of nonracemic  $\alpha$ -acyl- and  $\alpha$ -hydroxyalkyl- $\alpha,\beta$ -unsaturated sulfoxides from 2-ethoxyethyl *p*-tolyl sulfoxide (**16**), readily prepared from (*R*)-*p*-tolyl vinyl sulfoxide by addition of sodium ethoxide in ethanol. Thus, treatment of (**16**) with LDA in THF, followed by the addition of ethyl acetate, gave enantiomerically pure  $\alpha$ -acyl- $\alpha,\beta$ -unsaturated sulfoxide (**18**) in 69% yield via the intermediate (**17**) (Scheme 5.6).

### 5.2.5 Routes to Enantiomerically Pure Dienyl Sulfoxides

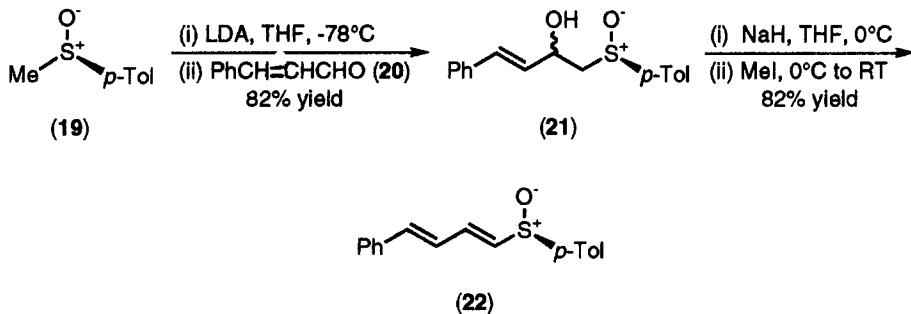
The first report concerning the synthesis of enantiomerically pure dienyl sulfoxides was made by Hoffmann and coworkers [32], who made use of the Horner–Wittig reaction between an  $\alpha$ -phosphoryl sulfoxide and acrolein to give the corresponding dienyl sulfoxides as a mixture of geometric isomers. Recently, there has been considerable interest in the synthesis of 1-sulfinyl and 2-sulfinyl-1,3-butadienes, as these types of substrates have considerable potential as diene components in asymmetric Diels–Alder cycloadditions.

Solladié and colleagues have reported the synthesis of enantiomerically pure 4-substituted (*1E,3E*)-1-[*(R*)-*p*-tolylsulfinyl]-1,3-butadienes such as (**22**) in two steps through the condensation of (+)-*(R*)-methyl *p*-tolyl sulfoxide (**19**) with  $\alpha,\beta$ -unsaturated aldehydes followed by one-pot dehydration of the resulting  $\beta$ -hydroxy sulfoxide (**21**) to give (**22**) in enantiomerically pure form (Scheme 5.7) [33]. The



SCHEME 5.6

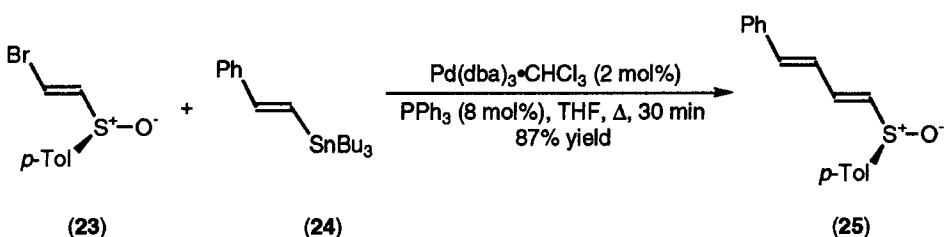
corresponding 4-substituted-(1*E,3E*)-(S,S)-1,1-bis-(*p*-tolylsulfinyl)-1,3-butadiene was prepared by the reaction between (S,S)-bis-(*p*-tolylsulfinyl) methane and  $\alpha,\beta$ -unsaturated aldehydes [34].



SCHEME 5.7

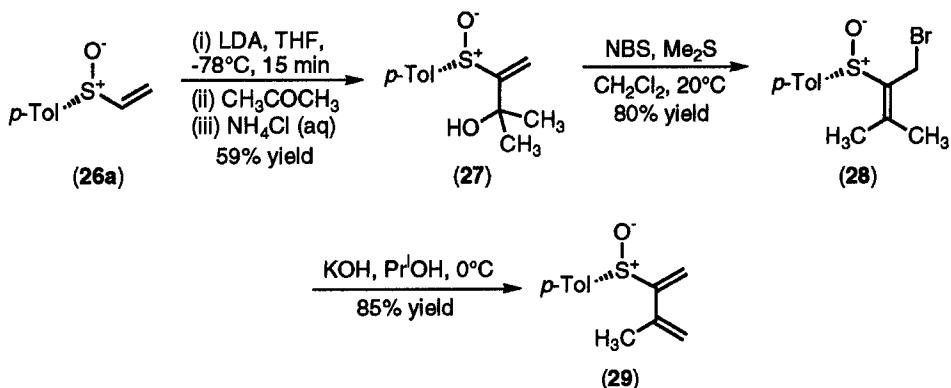
Similar methodology has been employed by the same group in the synthesis of enantiomerically pure 4-substituted-(1*Z,3E*)-1-[(*R*)-*p*-tolylsulfinyl]-2-*t*-butyldimethylsilyloxy-1,3-butadienes [35].

The synthesis of enantiomerically pure dienyl sulfoxides through palladium-catalysed coupling reactions has been reported [36,37]. An efficient Stille coupling process was used to synthesize both (1*E,3E*)- and (1*Z,3E*)-1-sulfinyl-1,3-butadienes through the use of stereodefined vinyl stannanes [36]. For example, coupling of the  $\beta$ -bromo- $\alpha,\beta$ -unsaturated sulfoxide (23) with vinylstannane (24) under palladium catalysis leads to the enantiomerically pure (1*E,3E*)-1-sulfinyl-1,3-butadiene (25) (Scheme 5.8) [36].



SCHEME 5.8

The synthesis of enantiomerically pure 2-sulfinyl-1,3-alkadienes has recently been described [38–40]. Maignan and coworkers [39] have reported that condensation of (*R*)-(–)-vinyl-*p*-tolylsulfoxide (**26a**) with a carbonyl compound such as acetone gave the allylic sulfinylalcohol (**27**), which, on treatment with *N*-bromosuccinimide (NBS) in dimethyl sulfide, was converted to the rearranged primary allylic bromide (**28**) by  $S_N2'$  displacement. The action of potassium hydroxide in methanol or isopropanol then yielded optically pure 2-*p*-tolylsulfinyl-1,3-alkadiene (**29**) by E2' elimination (Scheme 5.9).



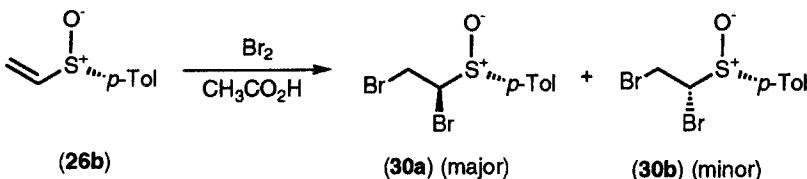
SCHEME 5.9

Nonracemic 1-methoxy-3-sulfinyl-1,3-butadienes derived from 10-mercaptopisoborneol have been prepared by the cycloaddition of (*1S*)-isobornyl-10-sulfenic acid to (*Z*)- and (*E*)-1-methoxybut-1-en-3-yne. High levels of asymmetric induction were observed for the cycloaddition in some cases [40].

### 5.3 ELECTROPHILIC ADDITIONS TO $\alpha,\beta$ -UNSATURATED SULFOXIDALS

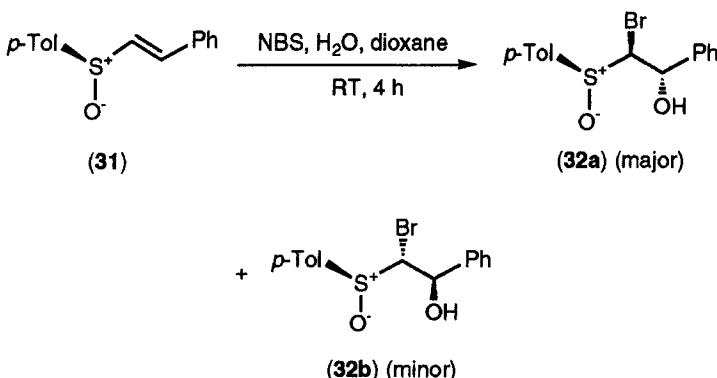
The first report of asymmetric induction in the electrophilic addition to  $\alpha,\beta$ -unsaturated sulfoxides was made by Abbott and Stirling [12,41] who found that treatment of nonracemic (*S*)-(+)-*p*-tolyl vinyl sulfoxide (**26b**) with bromine in acetic acid gave the dibromide (**30**) with *ee* ( $\alpha$ -induction) of 32% and 92% overall chemical yield (Scheme 5.10). (+)- $\alpha,\beta$ -Methylvinyl *p*-tolyl sulfoxide gave a higher

degree of asymmetric induction (43%) but a lower yield of dibromide (50%) under identical conditions. The stereochemical outcome of the reaction was accounted for by consideration of the most stable conformer of the bromonium ion intermediate.



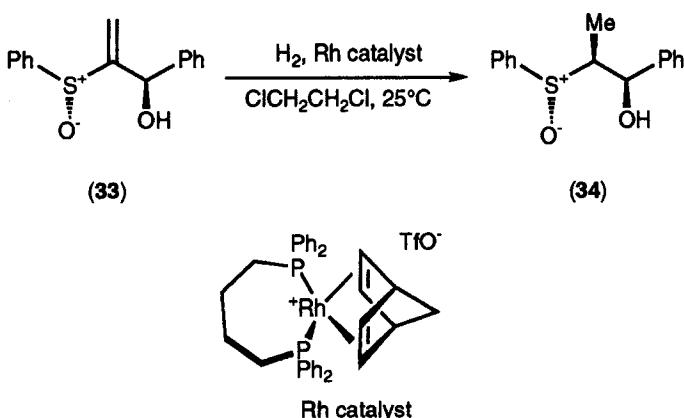
SCHEME 5.10

The reaction between *N*-bromosuccinimide and (+)-(E)-*p*-tolyl-2-styryl sulfoxide (**31**) in water was observed to be highly diastereoselective [42], giving the  $\alpha$ -bromo- $\beta$ -hydroxy sulfoxides (**32a**) and (**32b**) in a 9:1 ratio (Scheme 5.11). The corresponding reaction in methanol also proceeded with high diastereoselectivity (95% *de*), giving the analogous  $\alpha$ -bromo- $\beta$ -methoxy sulfoxides.



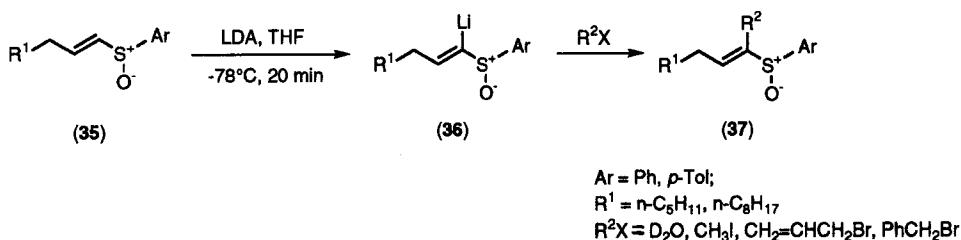
SCHEME 5.11

Recently, the directed homogenous hydrogenation of enantiomerically pure ( $\alpha$ -hydroxyalkyl)- $\alpha,\beta$ -unsaturated sulfoxides has been reported [43]. Thus, the rhodium-catalysed hydrogenation of (**33**) was directed by S=O coordination which was found to override OH-participation (the dominant factor in the directed hydrogenation of the corresponding sulfones), leading to product (**34**) with 97% diastereoisomeric excess (see Scheme 5.12). The highly stereoselective reduction of acyclic enamino sulfoxides using boranes (Scheme 5.20) [44] and of cyclic enamino sulfoxides with moderate to high stereoselectivity [45,46] has also been reported.



### SCHEME 5.12

The generation of  $\alpha$ -lithiated- $\alpha,\beta$ -unsaturated sulfoxides, their configurational stability, and their subsequent reactions with electrophiles have been the subject of considerable attention. Posner and coworkers [47] reported that racemic  $\alpha,\beta$ -unsaturated sulfoxides of type (35) can be effectively  $\alpha$ -lithiated to give (36) by treatment with LDA in THF at  $-78^\circ\text{C}$ , and that the anions so generated react cleanly and rapidly with a variety of electrophiles in 76–94% overall yields, to give products of the type (37) (Scheme 5.13). The authors also noted the configurational instability of  $\alpha$ -lithiated- $\alpha,\beta$ -unsaturated sulfoxides, both (*Z*)- and (*E*)-sulfoxides undergoing  $\alpha$ -lithiation followed by methylation to give almost entirely the corresponding (*E*)- $\alpha$ -methyl- $\alpha,\beta$ -unsaturated sulfoxides.

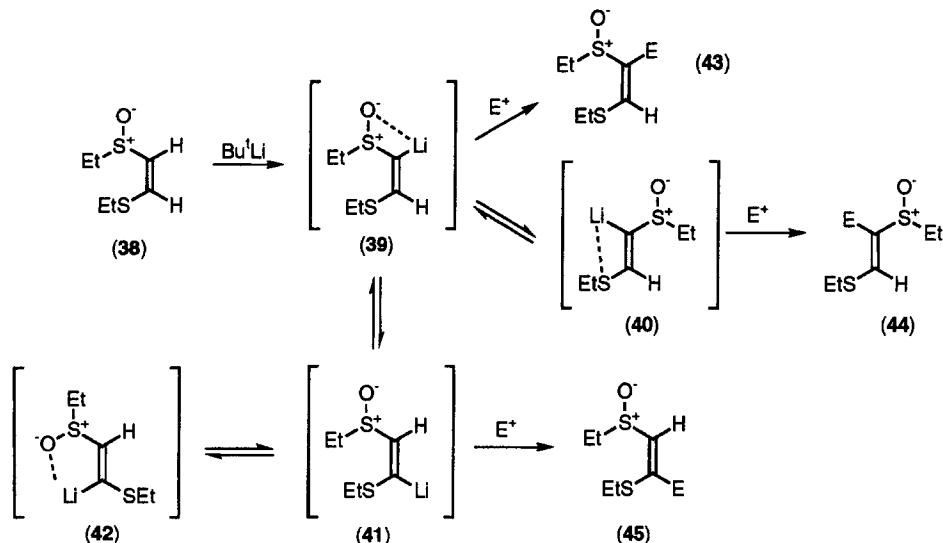


**SCHEME 5.13**

Independently, Okamura and colleagues generated racemic  $\alpha$ -lithiated- $\alpha,\beta$ -unsaturated sulfoxides in the same way as Posner's group and reported their reactions with methyl iodide, carbonyl compounds, and epoxides [48,49]. They also noted the configurational instability of such intermediates. Alkylation of the intermediates using butyl iodide or benzyl bromide gave low yields of products.

It has been demonstrated that the monosulfoxide of *cis*-diethylmercaptoethylene (38) yields almost exclusively  $\alpha$ -deprotonated species (39) on treatment with *t*-butyllithium [50] (Scheme 5.14). The reaction with electrophiles at various

temperatures shows that these functionally substituted vinylolithium derivatives are configurationally labile, as seen by the increasing amounts of isomerized product (**44**) formed with increasing reaction temperature (Table 5.2).

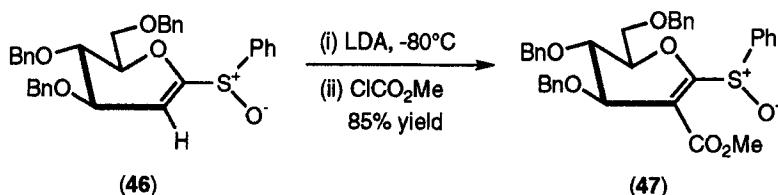


SCHEME 5.14

TABLE 5.2

Electrophile	Temperature (°C)	Yield (%)	Product ratios (%)	(44)	(43)	(45)
CH <sub>3</sub> OD	-120	100	-	95	5	
	-100	100		31	59	10
	-80	100		73	17	10
CH <sub>3</sub> -I	-120	89	-	95	5	
CH <sub>3</sub> S-SCH <sub>3</sub>	-120	100	-	85		15

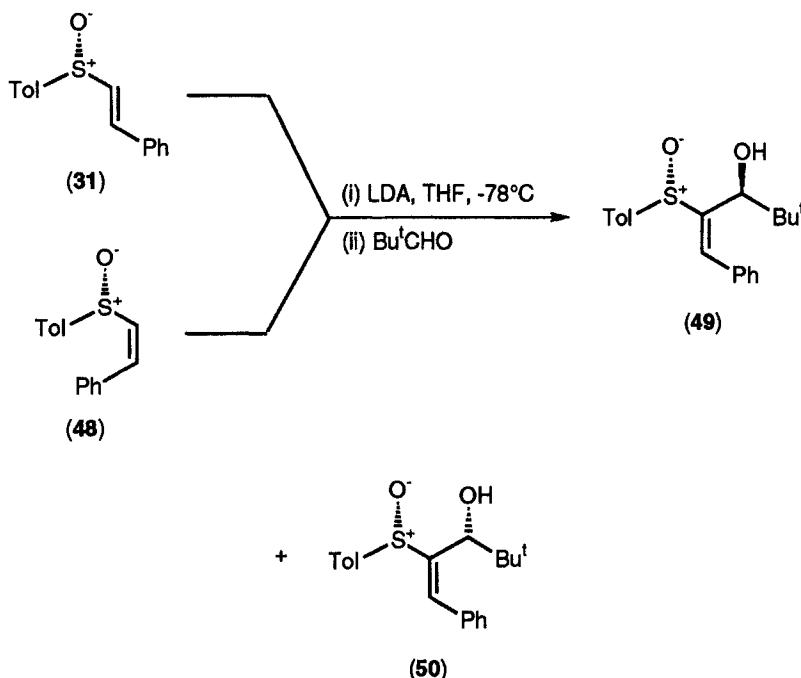
Schmidt and coworkers have described the direct lithiation at the C-2 atom of the 1-phenylsulfinyl substituted glycal (**46**) using LDA followed by reaction with C-electrophiles to give products such as (**47**) (Scheme 5.15) [51].



SCHEME 5.15

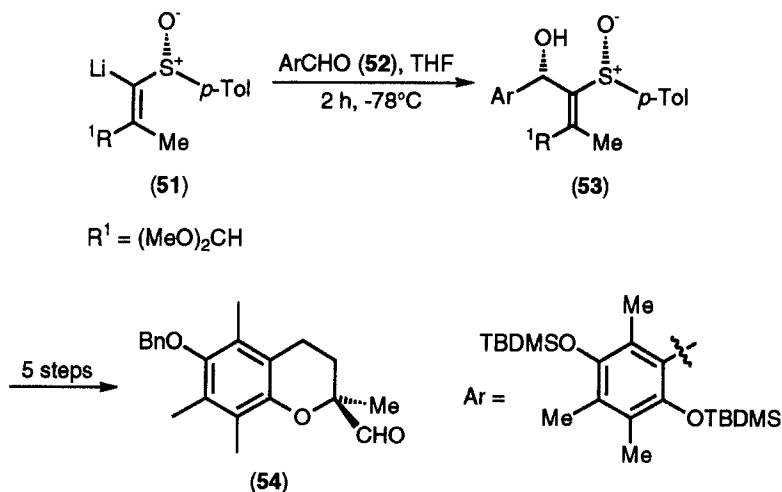
The treatment of nonracemic  $\alpha$ -lithiated- $\alpha,\beta$ -unsaturated sulfoxides with aldehydes has received attention because of the possibility of high diastereoselection on creation of the new asymmetric centre. Posner added these nonracemic vinylolithium species to various aldehydes under different conditions of solvent, reaction temperature, base used for deprotonation, structure of aldehyde, and various metal additives, but obtained no more than 25% asymmetric induction [52].

Jenkins and colleagues have achieved greater levels of asymmetric induction in the reaction between nonracemic (*E*)- and (*Z*)-lithiated vinyl sulfoxides (**31**) and (**48**) and the bulky aldehyde trimethylacetaldehyde [53,54]. In both cases, the major diastereoisomer (**49**) was isolated in 59% yield from (**31**) (85% *de*) and 71% yield from (**48**) (86% *de*) (Scheme 5.16). Other less hindered aldehydes gave poor levels of asymmetric induction.



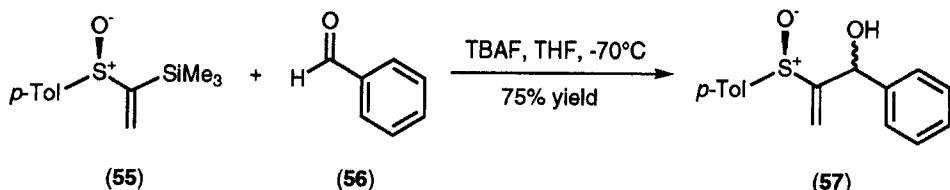
SCHEME 5.16

Solladié and Moine have reported the highly diastereoselective reaction between the  $\alpha$ -lithiated- $\alpha,\beta$ -unsaturated sulfoxide (**51**) and the aromatic aldehyde (**52**), giving (**53**) as the predicted product diastereoisomer as part of the enantioselective synthesis of the (*S*)-chroman-2-carboxaldehyde (**54**) (Scheme 5.17) [55,56]. The high diastereoselectivity is particularly notable in view of the much smaller effects observed using similar systems [52].



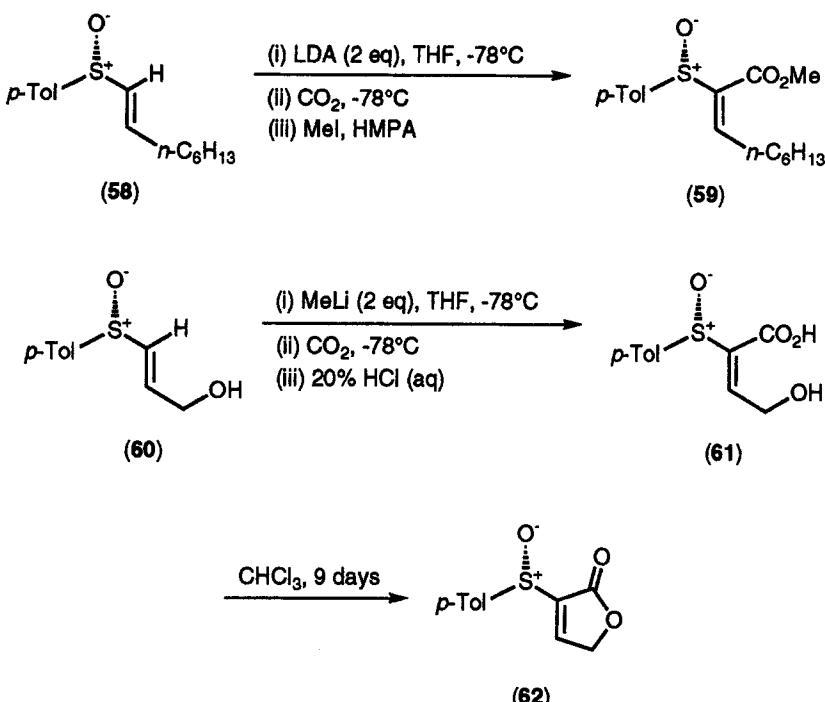
**SCHEME 5.17**

Recently, the fluoride ion-catalysed desilylation of *p*-tolyl 1-(trimethylsilyl)vinyl sulfoxide (**55**) and reaction with aldehydes such as benzaldehyde (**56**) to give the corresponding allylic alcohol (**57**) has been studied (Scheme 5.18) [57]. The diastereoselectivity of the reaction was not evaluated and the products were obtained in moderate to good yields. The authors suggested possible mechanistic pathways for the reaction.



**SCHEME 5.18**

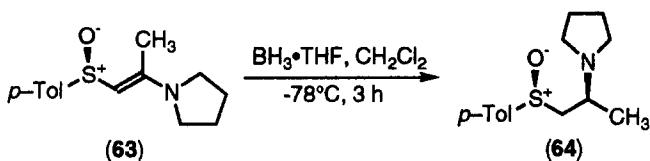
The carboxylation of optically active  $\alpha$ -lithiated- $\alpha,\beta$ -unsaturated sulfoxides has been reported. For example, Posner and coworkers have performed a one-pot  $\alpha$ -lithiation followed by carboxylation and esterification of the  $\alpha,\beta$ -unsaturated sulfoxide (**58**) to give enantiomerically pure  $\alpha$ -methoxycarbonyl- $\alpha,\beta$ -unsaturated sulfoxide (**59**) in 80% yield (Scheme 5.19) [52,58]. Protonation rather than methylation leads to the corresponding carboxylic acid in >95% yield. This methodology has been utilized in the synthesis of enantiomerically pure (*S*)-(+)-2-(*p*-tolylsulfinyl)-2-buten-4-oxide (**62**) from the  $\alpha,\beta$ -unsaturated sulfoxide (**60**) via the carboxylic acid derivative (**61**) (Scheme 5.19) [59]. An efficient route to nonracemic 2-(*p*-tolylsulfinyl)-2-buten-4-olides employing carboxylation of an  $\alpha$ -lithio- $\alpha,\beta$ -unsaturated sulfoxide has also been developed by Holton and Kim [60].



SCHEME 5.19

A recent publication describes the  $\pi$ -facial stereoselectivity observed in electrophilic addition reactions to  $\alpha,\beta$ -unsaturated sulfoxides in terms of an electronic model (Figure 5.1), showing the preferred orientation of attack by an electrophile,  $E^+$  [61]. In this transition state model, the lone-pair electrons and the oxygen atom are orientated at the *anti* and *inside* positions, respectively, to the incipient bond, for the following reasons: the most electron-donating group (lone-pair electrons) is orientated at the *anti* position to maximize  $\sigma$ - $\pi$  overlap, which increases the energy level of the alkene HOMO, while the most electron-withdrawing group (oxygen atom) is thought to occupy the *inside* position to minimize  $\sigma^*$ - $\pi$  orbital overlap, which decreases the HOMO energy level.

Evidence for this model was provided by quantum-mechanical calculations on the transition state structures for addition of a proton to methyl vinyl sulfoxide, and by experimental observations, both by the authors and other groups [42,44]. For example, reduction of the enamino sulfoxide (63) using BH<sub>3</sub>·THF complex gave (64) as the major product [44] with 87% *de* and in 95% yield (Scheme 5.20). The stereochemical outcome of this reaction can be explained satisfactorily using this model, where the lone-pair electrons occupy the *anti* position and the sulfinyl oxygen the *inside* position, and hydrogen delivery occurs at the least electron-rich face of the double bond, i.e. the outside position in Figure 5.1. Results from the authors' own work on the alkylation of enolates bearing a sulfinyl group on the enolate carbon [61] were also consistent with a transition-state model as in Figure 5.1.



SCHEME 5.20

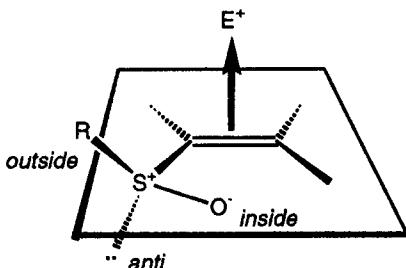


FIGURE 1

## 5.4 NUCLEOPHILIC ADDITIONS TO $\alpha,\beta$ -UNSATURATED SULFOXIDES

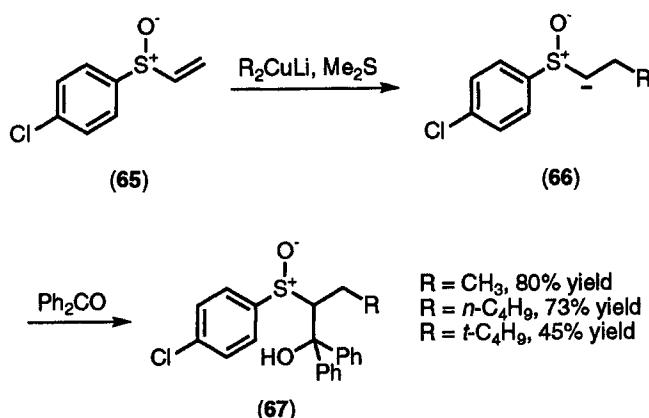
Nucleophilic addition to the  $\beta$ -position of satisfactorily unsaturated sulfoxides has been known for many years [62–64]. Both carbon- and hetero-nucleophiles have been successfully added in such a manner, often followed by sulfoxide pyrolysis, the synthetic equivalent of addition of a vinyl group to a nucleophile.

Much recent work in this area has been devoted to stereochemical control at the  $\beta$ -position during addition [11,65] and this is the main focus of this review. Comparatively little work has been devoted to control of stereochemistry at the  $\alpha$ -position during the reaction. In many cases, however, this stereochemical control becomes unnecessary since the required product is achiral at the  $\alpha$ -position (often after removal of the sulfoxide functionality).

### 5.4.1 Conjugate Addition of Carbon Nucleophiles to $\alpha,\beta$ -Unsaturated Sulfoxides

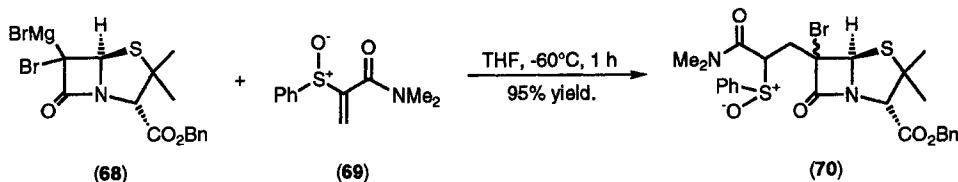
#### 5.4.1.1 Nonstereoselective additions

There are numerous reports of the  $\beta$ -addition of organometallic reagents to racemic  $\alpha,\beta$ -unsaturated sulfoxides [62,63]. For example, the Michael-type reaction of dialkylcuprates with *p*-chlorophenyl vinyl sulfoxide (65), followed by reaction of the initially formed  $\alpha$ -sulfinyl carbanion (66) with electrophiles such as benzophenone, gave the products (67) (Scheme 5.21) [66].



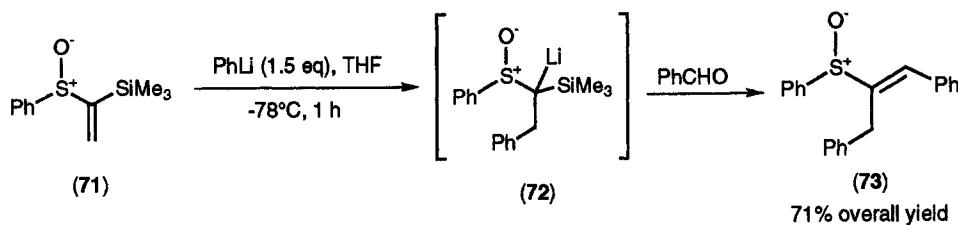
**SCHEME 5.21**

Sammes and coworkers have described the nonstereoselective conjugate addition of Grignard reagents, derived from 6,6-dibromopenicillanates, e.g. (68), to racemic  $\alpha$ -sulfinyl acrylates and acrylamides such as (69) as part of a route to 6 $\beta$ -vinylpenicillanic acids (70) (Scheme 5.22) [67], which were potential antibiotics. Unfortunately, they possessed only weak antibiotic activity.



**SCHEME 5.22**

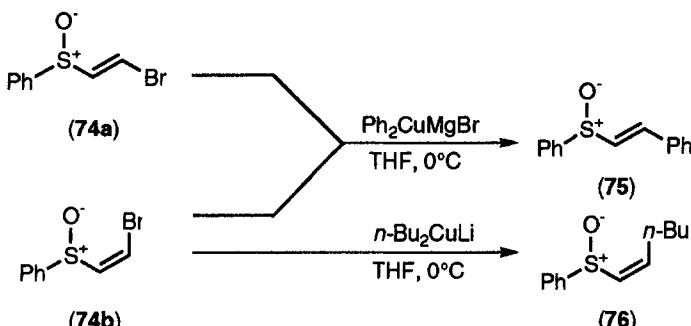
A Michael addition–Peterson olefination sequence using  $\alpha$ -silyl- $\alpha,\beta$ -unsaturated sulfoxides has been reported [68]. The addition of organolithiums such as phenyllithium to the substrate (71) gave the intermediates (72), which were quenched with various aldehydes, such as benzaldehyde, to give the products (73) in good overall yields (Scheme 5.23). The product from the stereospecific Peterson olefination was the (*E*)-isomer in most cases tested. The use of Grignard and cuprate reagents in place of some organolithiums gave good results.



**SCHEME 5.23**

The reactions of organometallic reagents (copper, magnesium, and lithium species) with racemic (*E*)- and (*Z*)- $\beta$ -halo- $\alpha,\beta$ -unsaturated sulfoxides has been studied recently [69]. The various organometallic species undergo different modes of addition: diorganocuprates led to carbon–carbon bond formation through a cross-coupling process, whereas reaction with organomagnesium and organolithium species led to carbon–sulfur bond formation and production of diaryl or aryl alkyl species.

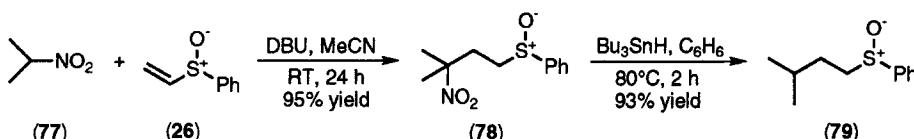
The stereochemical outcome for the addition of organocuprates was variable (Scheme 5.24). For example, reaction of (*E*)- or (*Z*)- $\beta$ -halo- $\alpha,\beta$ -unsaturated sulfoxides (**74a**) or (**74b**) with  $\text{Ph}_2\text{CuMgBr}$  gave only the product (**75**) in the (*E*)-configuration, in both cases in moderate yield, whereas reaction of (**74b**) with  $\text{Bu}^n\text{CuLi}$  gave the (*Z*)-product (**76**) predominantly (10:90, *E*:*Z*) in 64% yield.



**SCHEME 5.24**

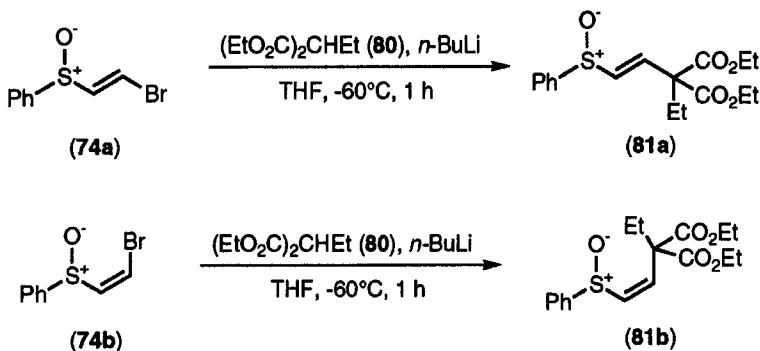
Spry has reported that *cis*- $\beta$ -halo- $\alpha,\beta$ -unsaturated sulfoxides, on treatment with Grignard reagents, react to form carbon-sulfur bonds, and has used this methodology as part of the preparation of *S*(1)-*C*(2)-secocephems [70], while Posner found that  $\alpha,\beta$ -unsaturated aryl sulfoxides were easily reduced to the corresponding sulfides upon treatment with ethylmagnesium bromide/10% cuprous iodide with retention of double bond stereochemistry [71].

Tanikaga and coworkers have reported the addition of nitroalkane anions to  $\alpha$ -halo- $\alpha, \beta$ -unsaturated sulfoxides [72]. Further development of this work led to the use of nitroalkanes as alkyl group equivalents in conjugate addition to  $\alpha, \beta$ -unsaturated sulfoxides [73–75]. Primary or secondary nitroalkanes such as 2-nitropropane (77), with DBU as a non-nucleophilic base, add to  $\alpha, \beta$ -unsaturated sulfoxides including phenyl vinyl sulfoxide (26) to give products such as (78), which can be denitrated to yield (79) (Scheme 5.25). The Michael addition of nitroalkanes, and of diethyl *N*-acetylaminomalonate, to racemic phenyl vinyl sulfoxide using solid–liquid phase-transfer catalysis in the absence of solvent has also been accomplished [76].



**SCHEME 5.25**

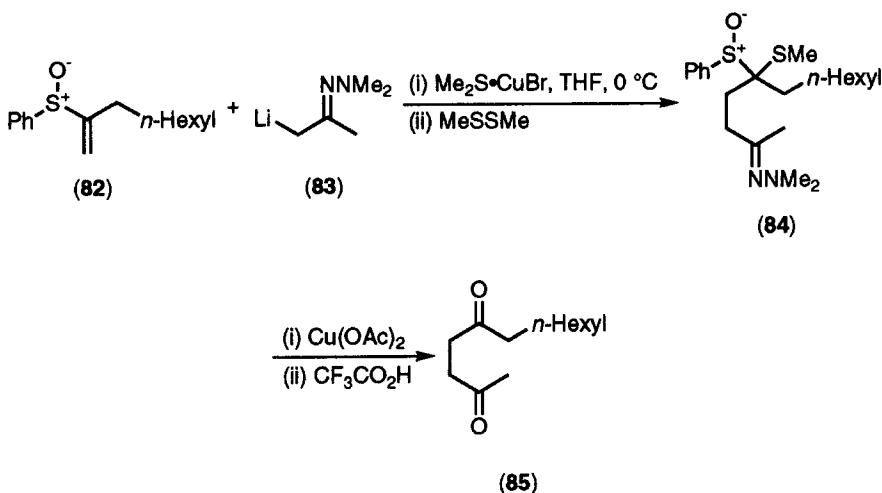
The addition of the anions generated from  $\beta$ -dicarbonyl species to  $\alpha,\beta$ -unsaturated sulfoxides is known [72,77–79]. For example, diethyl ethylmalonate (80), has been added to the racemic  $\beta$ -bromo- $\alpha,\beta$ -unsaturated sulfoxides (74a) and (74b) (*trans* and *cis* forms, respectively) to give the *trans* and *cis* products (81a) and (81b) in quantitative yields with retention of double bond stereochemistry in each case (Scheme 5.26) [79].



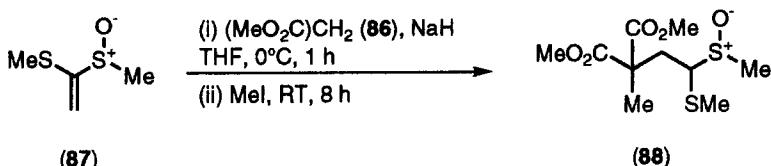
SCHEME 5.26

Jones and colleagues have prepared 1,4-dicarbonyl compounds by conjugate additions of enolate and related anions to  $\alpha,\beta$ -unsaturated sulfoxides [80,81]. For example, the lithium enolate of acetone dimethylhydrazone (83), in the presence of dimethyl sulfide–copper(I) bromide complex, underwent conjugate addition to 2-phenylsulfinyl-1-ene (82). Quenching the reaction mixture with dimethyl disulfide gave the doubly protected 1,4-diketone derivative (84), which, on sequential hydrolysis with copper(II) acetate and trifluoroacetic acid gave the dodecane-2,5-dione (85) as the product in 54% yield from (82) (Scheme 5.27). Other examples of the addition of enolate-type species to  $\alpha,\beta$ -unsaturated sulfoxides have also been reported [82,83].

Nucleophilic additions to the carbon–carbon double bond of ketene dithioacetal monoxides have been reported [84–86]. These substrates are efficient Michael acceptors in the reaction with enamines, sodium enolates derived from  $\beta$ -dicarbonyl compounds, and lithium enolates from simple ester systems. Hydrolysis of the initial products then led to substituted 1,4-dicarbonyl systems [84]. Alternatively, the initial product carbanion could be quenched with electrophiles [85]. For example, the anion derived from dimethyl malonate (86) was added to the ketene dithioacetal monoxide (87). Regioselective electrophilic addition led to the product (88) in 97% overall yield (Scheme 5.28). The application of this methodology to the synthesis of rethrolones [87] and prostaglandin precursors [88] has been demonstrated. Recently, Walkup and Boatman noted the resistance of endocyclic ketene dithioacetals to nucleophilic attack [89].



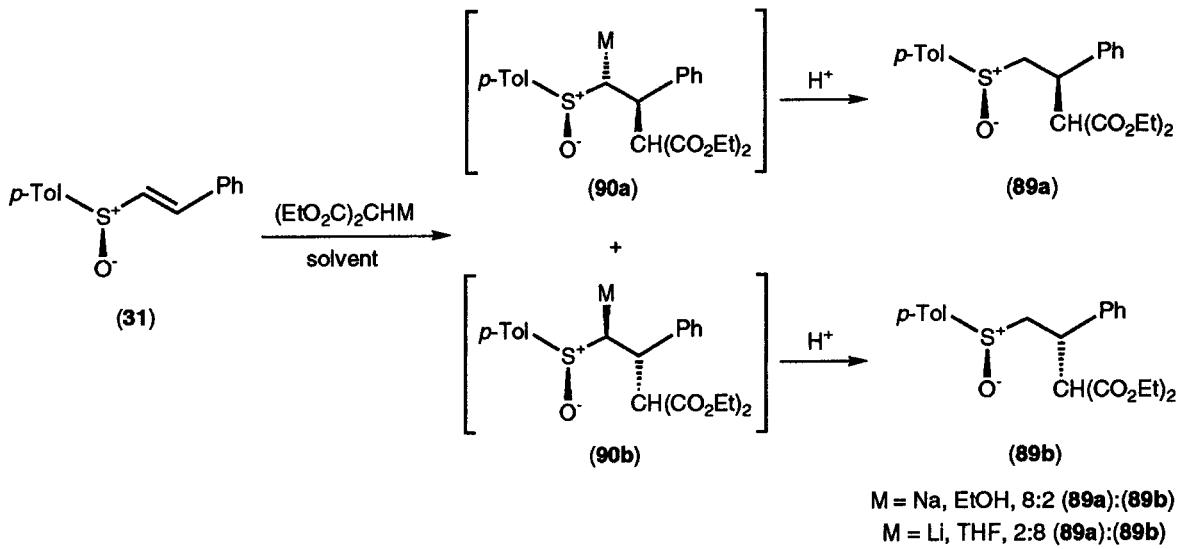
**SCHEME 5.27**



**SCHEME 5.28**

### 5.4.1.2 Stereoselective additions

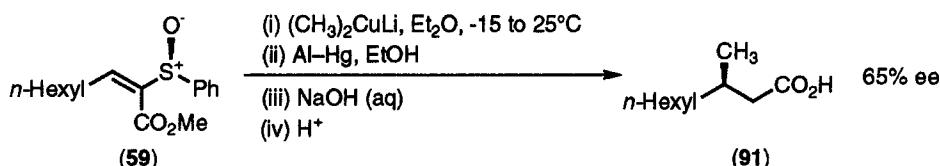
The first report on the stereochemical outcome of C–C bond formation by Michael addition to  $\alpha,\beta$ -unsaturated sulfoxides was made by Tsuchihashi and coworkers in 1973 [90], who observed that the addition of diethyl malonate to (+)-(*R*)-*trans*- $\beta$ -styryl *p*-tolyl sulfoxide (**31**) using sodium ethoxide as base in ethanol (a polar protic solvent) gave the addition products (**89a**) and (**89b**) in the ratio 8:2 and in 87% overall yield. The authors later found [91] that conducting the same reaction using *n*-butyllithium in THF (a nonprotic solvent) led to a complete reversal of diastereoselectivity in 60% overall yield (Scheme 5.29). The reasons for the stereochemical observations were discussed by the authors, who assumed that the reaction was kinetically controlled and that the rate-determining step was the formation of the anion (**90a**) or (**90b**), the stability of which determined the stereochemical course of the reaction. In polar protic solvents such as ethanol, previous observations had shown that maximum stability is attained when the carbanion is *trans* to the sulfinyl oxygen (**90a**), while in the THF-Li<sup>+</sup> system, the conformer in which it is *gauche* to the sulfinyl oxygen is preferred (**90b**). The experimental observations were in agreement with this proposal.



SCHEME 5.29

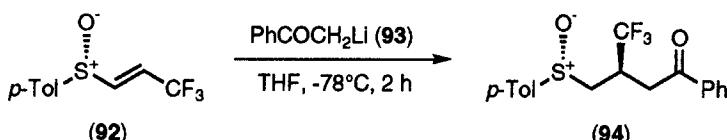
Few further examples of asymmetric Michael addition to acyclic  $\alpha,\beta$ -unsaturated sulfoxides have appeared compared with the corresponding additions to the cyclic sulfoxides.

Posner and colleagues have observed high asymmetric induction in the addition of organocuprate reagents to  $\alpha$ -methoxycarbonyl- $\alpha,\beta$ -unsaturated sulfoxides such as (59) [52,58] (Scheme 5.30). Subsequent reduction using aluminium amalgam in ethanol and saponification gave (*R*)-(+)3-methylnonanoic acid (91) in 53% overall yield and 65% *ee*. The results were tentatively rationalized by assuming a planar metal chelate between the carbonyl and sulfinyl groups, and nucleophilic attack from the side of that plane containing the nonbonding electron pair on sulfur.



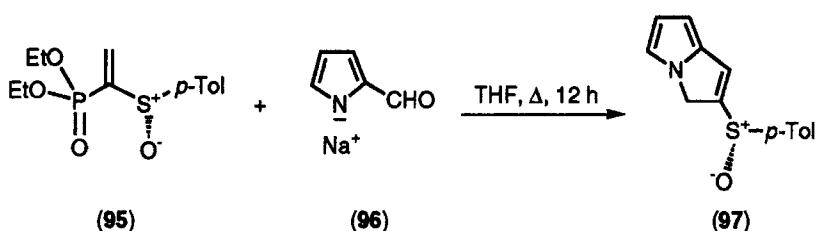
SCHEME 5.30

Ishikawa and colleagues observed a high degree of diastereoselectivity in the addition of enolate anions to (*R*)-(*E*)-3,3,3-trifluoroprop-1-enyl *p*-tolyl sulfoxide (92) [92,93]. For example, reaction with the enolate anion of acetophenone (93) gave product (94) as the major diastereoisomer with 94% *de* (Scheme 5.31).



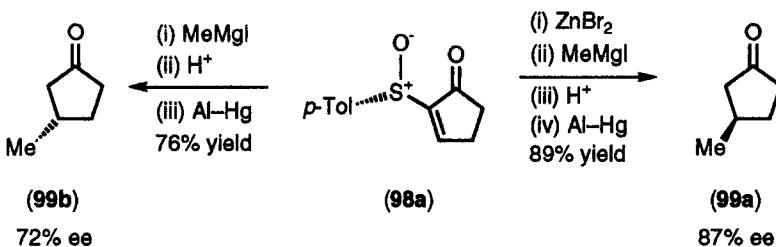
SCHEME 5.31

Recently, a new enantiomerically pure Michael acceptor, (+)-(S)- $\alpha$ -diethoxyphosphorylvinyl *p*-tolyl sulfoxide (95), has been reported [94]. In this new type of substrate, the phosphoryl group not only functions as a double bond-activating substituent, but also allows the Horner-Wittig reaction to be carried out following the Michael addition. Furthermore, the phosphoryl group may be chiral, thus allowing double asymmetric induction in the Michael and Diels-Alder reactions (see Section 5.5) to be studied. The tandem Michael addition/intramolecular Horner-Wittig reaction of (95) with the sodium salt of 2-formylpyrrole (96) gives the *p*-tolyl 3H-pyrrolizine-2-sulfoxide (97) in 76% yield (Scheme 5.32).



SCHEME 5.32

The corresponding Michael additions to cyclic  $\alpha,\beta$ -unsaturated sulfoxides has received considerable attention, especially in the work of Posner and coworkers [13]. The majority of this work has focused on the nucleophilic conjugate addition of alkyl and aryl groups and of enolate ions to 2-sulfinyl-2-cycloalkenones and to 2-sulfinyl-2-alkenolides. The authors have achieved virtually complete asymmetric induction during methyl-, vinyl-, and naphthylmetallic conjugate addition to (*S*)-(+)-2-(*p*-tolylsulfinyl)-2-cyclopentenone (**98a**) [95,96]. (*R*)-3-Methylcyclopentanone (**99a**) was obtained in high optical purity when the enone sulfoxide (**98a**) was first allowed to form a complex with divalent zinc and then was methylmagnesium iodide added, whereas (*S*)-3-methylcyclopentanone (**99b**) was obtained as the major product with somewhat lower *ee* when methylmagnesium iodide was added to the same uncomplexed enone sulfoxide (**98a**) (Scheme 5.33).



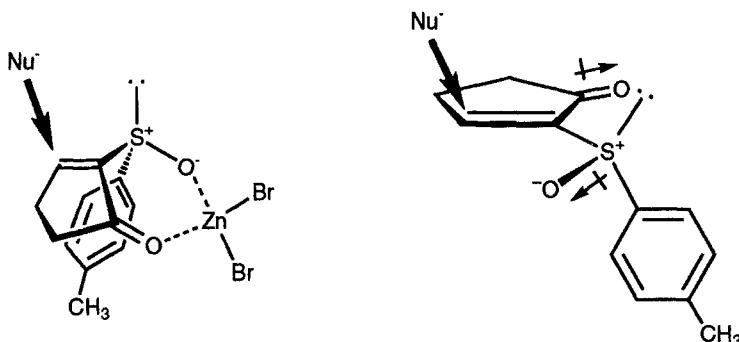
SCHEME 5.33

The stereochemical outcome observed for the conjugate addition in the presence of zinc bromide was explained on the basis of the previously proposed [52,58] chelate model (Figure 5.2), where the zinc atom is associated with both the sulfinyl and carbonyl groups as shown, giving a rigid intermediate. Nucleophilic delivery would then be from the *re*-face of the reactive double bond, i.e. the face from which the lone-pair electrons protrude (the top face in Figure 5.2).

In the absence of divalent metals, the enone sulfoxide was thought to exist mainly in the conformation shown in Figure 5.3, having the sulfoxide and carbonyl dipoles oriented in opposite directions. Conjugate addition then occurs at the face not shielded by the *p*-tolyl group, i.e. that containing the sulfur lone pair (*si*-face). The zinc bromide-mediated addition of vinylmagnesium bromide to (**98a**) has led

to the development of a convenient synthesis of enantiomerically pure steroid intermediates [95].

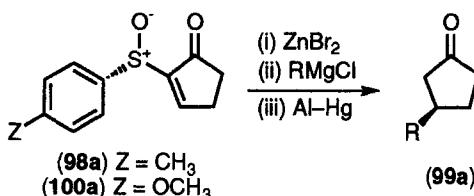
Improvements in the diastereoselectivity of conjugate addition of organometallic reagents to optically pure 2-sulfinyl-2-cycloalkenones (pentenones and hexenones)



FIGURES 5.2 AND 5.3

have been reported by the same authors [97,98]. For example, conjugate additions to 2-(*p*-anisylsulfinyl)-2-cycloalkenones [97] such as (100a) in THF proceed with much greater diastereoselectivity in the presence of zinc bromide than do corresponding additions to 2-(*p*-tolylsulfinyl)-2-cycloalkenones such as (98a) (Scheme 5.34 and Table 5.3). It was reasoned that a stronger electron-donating group on the aromatic ring increased the Lewis basicity of the sulfinyl oxygen, leading to a more rigid and conformationally stable complex of the type shown in Figure 5.2. This increased stability would then account for the increase in the diastereoselectivity observed during organometallic conjugate addition to the enone sulfoxide.

Dramatic increases in diastereoselectivity were also observed by replacing THF by the less coordinating solvent, 2,5-dimethyltetrahydrofuran (DMTHF) for the conjugate addition of organometallic reagents to 2-(*p*-tolylsulfinyl)-2-cycloalkenones [98]. Unfortunately, for the cases studied, the *p*-anisyl sulfoxides such as (100a) were not soluble in DMTHF, and therefore the combined benefit of the anisyl group and the less polar solvent in increasing asymmetric induction could not be realized.

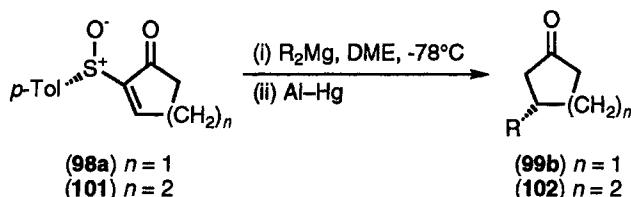


SCHEME 5.34

TABLE 5.3

RMgCl	(98a) Z = CH <sub>3</sub>		(100a) Z = OCH <sub>3</sub>	
	Yield (%)	ee (%)	Yield (%)	ee (%)
CH <sub>3</sub> CH <sub>2</sub> MgCl	90	81	83	89
(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> MgCl	67	87	74	90
(CH <sub>3</sub> ) <sub>3</sub> CCH <sub>2</sub> MgCl	32	58	69	94
CH <sub>2</sub> =CHCH <sub>2</sub> MgCl	80	78	60	84

The diastereoselectivity observed for the conjugate addition to the nonchelated enone sulfoxide (98a) was improved by the use of diorganomagnesium reagents with DME as solvent. Under the same reaction conditions, nucleophilic additions to the corresponding cyclohexenone (101) proceeded with moderate stereoselectivity, giving cyclohexanones (102) as products with somewhat lower enantiomeric excesses than for cyclopentanones (99b) (Scheme 5.35 and Table 5.4) [99]. It should also be noted that in several cases the addition of a highly complexing additive such as 18-crown-6 served to raise the amount of asymmetric induction by about 20% (Table 5.4).



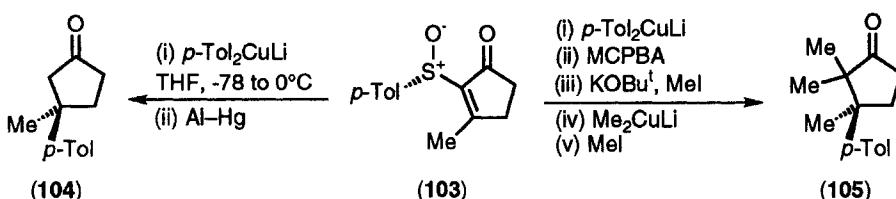
SCHEME 5.35

TABLE 5.4

Substrate	R	Yield (%)	ee (%)
(98a)	Methyl	69 <sup>a,b</sup>	97
(98a)	Ethyl	88	81
(98a)	Neopentyl	77 <sup>a</sup>	91
(98a)	Vinyl	74 <sup>a</sup>	57
(98a)	Phenyl	72 <sup>b</sup>	>98
(101)	Methyl	67 <sup>a</sup>	79
(101)	Pr <sup>i</sup>	53 <sup>a</sup>	50
(101)	Bu <sup>s</sup>	67 <sup>a</sup>	62

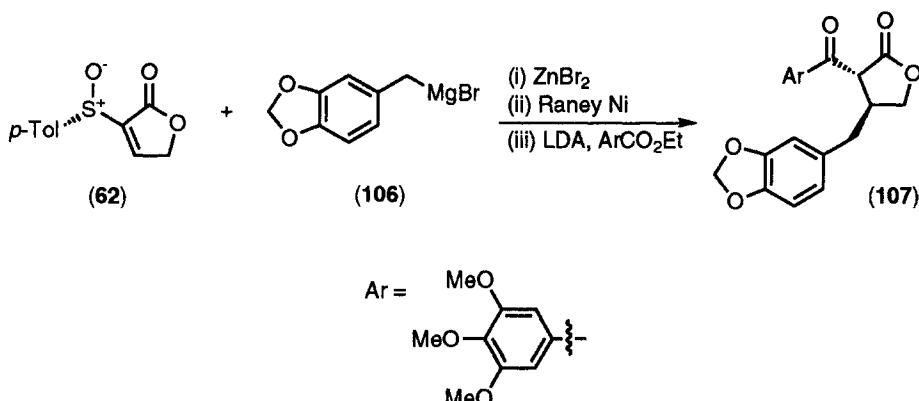
<sup>a</sup>18-crown-6 (1 eq) added. <sup>b</sup>Reaction in THF.

This methodology has been extended to the enantiocontrolled synthesis of quaternary carbon centres, through the preparation of a series of 3,3-disubstituted cyclopentanones in 78–93% enantiomeric purity by asymmetric conjugate addition of organocuprate reagents to enantiomerically pure 3-methyl- and 3-tolyl-2-(*p*-tolylsulfinyl)cyclopentenones [100]. For example, the enone sulfoxide (**103**) reacts with di(*p*-tolyl)copper lithium to give the product (**104**) in 93% *ee* and 53% chemical yield after removal of the sulfinyl group (Scheme 5.36). This methodology has been applied to the synthesis of natural (+)- $\alpha$ -cuparenone (**105**), which contains two vicinal quaternary carbon centres.

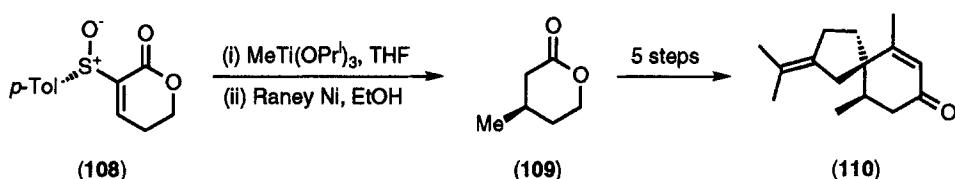


SCHEME 5.36

The conjugate addition to enantiomerically pure 2-sulfinylbutenolides has also been reported [59]. Thus, the zinc-promoted conjugate addition of a functionalized benzylic Grignard reagent (**106**) to the optically pure lactone sulfoxide (**62**), prepared as described previously (Scheme 5.19), leads ultimately to (–)-podorhizon (**107**), a member of the anticancer podophyllotoxin family, in 95% *ee* (Scheme 5.37). Similarly, the conjugate addition of methyltitanium triisopropoxide to enantiomerically pure *p*-anisylpentenolide sulfoxide (**108**) gives the product lactone (**109**) in 93% *ee* after reductive desulfinylation; (**109**) was subsequently converted into the fragrant spiro[4.5]decane sesquiterpene (–)- $\beta$ -vetivone (**110**) in five further steps (Scheme 5.38) [101].

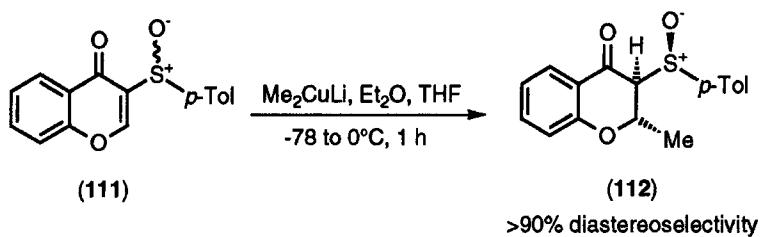


SCHEME 5.37



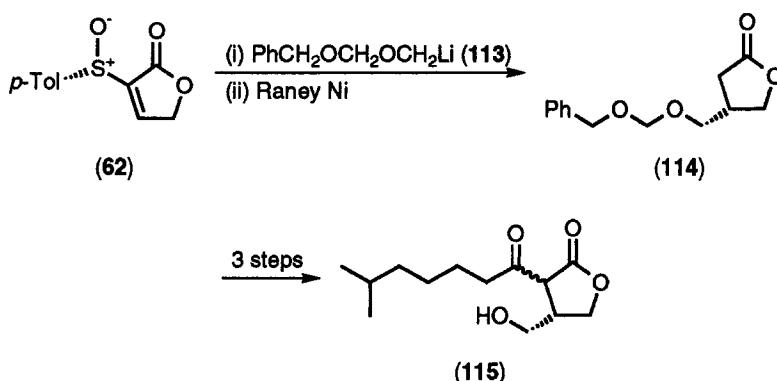
SCHEME 5.38

Wallace and Saengchantara have reported that the conjugate addition of lithium dimethylcuprate to racemic 3-(*p*-tolylsulfinyl)chromanone (**111**) proceeds with at least 90% diastereoselectivity to yield (**112**) as the major product (Scheme 5.39) [102].



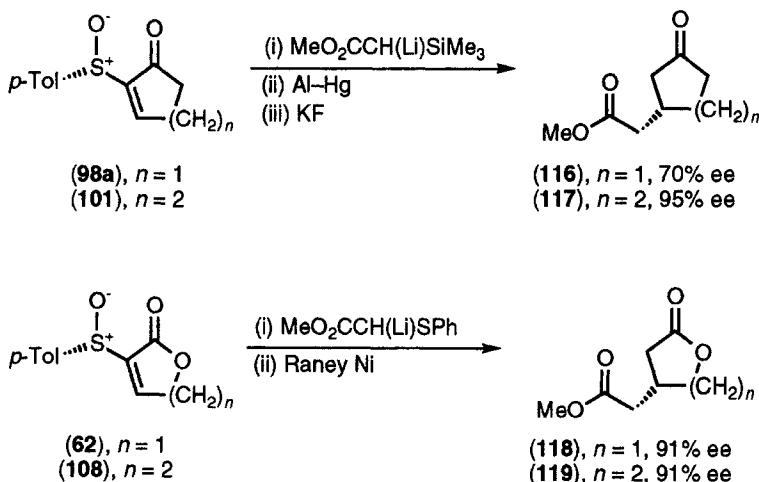
SCHEME 5.39

The lactone sulfoxide (**62**) has been used in the synthesis of (+)-A factor (**115**), a potent autoregulating factor essential for streptomycin production [103]. Conjugate addition of the hydroxymethyl carbanion equivalent (**113**) to the nonchelated conformer (see Figure 5.3) of (**62**) gave, after reductive desulfinylation, *O*-protected 3-hydroxymethyl-4-butanolide (**114**) in 87% *ee*, which was subsequently converted to the A-factor (**115**) (Scheme 5.40).



SCHEME 5.40

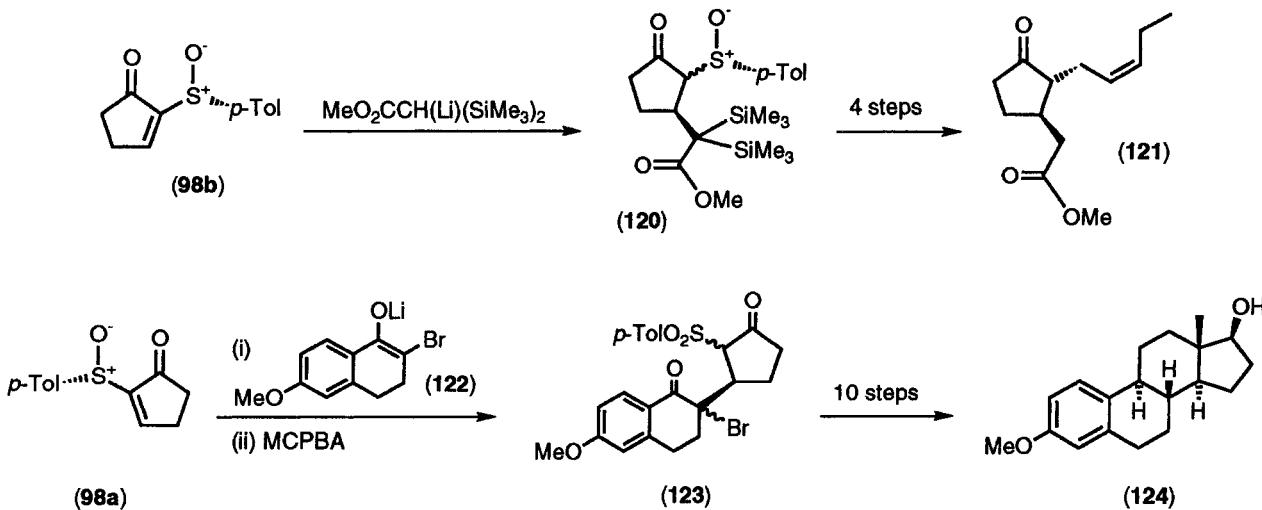
The addition of ester enolate anions to the enantiomerically pure Michael acceptor cycloalkenone sulfoxides (**98a**) and (**101**) and the unsaturated lactone sulfoxides (**62**) and (**108**) has been studied by Posner and coworkers [104]. Asymmetric induction to the extent of 70% was achieved in the addition of  $\alpha$ -trimethylsilyl- $\alpha$ -lithioacetate at  $-78^{\circ}\text{C}$  in THF to cyclopentenone sulfoxide (**98a**) to give (**116**) after reductive desulfinylation and desilylation. Extremely high levels of asymmetric induction were achieved in  $\alpha$ -trimethylsilyl- $\alpha$ -lithioacetate addition to the corresponding cyclohexenone sulfoxide (**101**) (95% *ee*) to give (**117**). Asymmetric Michael addition of various ester enolates to lactone sulfoxides (**62**) and (**108**) proceeded smoothly to give 1,5-dicarbonyl adducts (**118**) and (**119**) in good to excellent enantiomeric excesses. The best results were obtained using  $\alpha$ -lithio- $\alpha$ -phenylthioacetates as Michael donors. The above findings are summarized in Scheme 5.41. The stereochemical outcome of these Michael additions can be explained by assuming the enone sulfoxides react from a nonchelated conformer where the  $\text{S}=\text{O}$  and  $\text{C}=\text{O}$  dipoles are oriented in opposite directions (Figure 5.3).



SCHEME 5.41

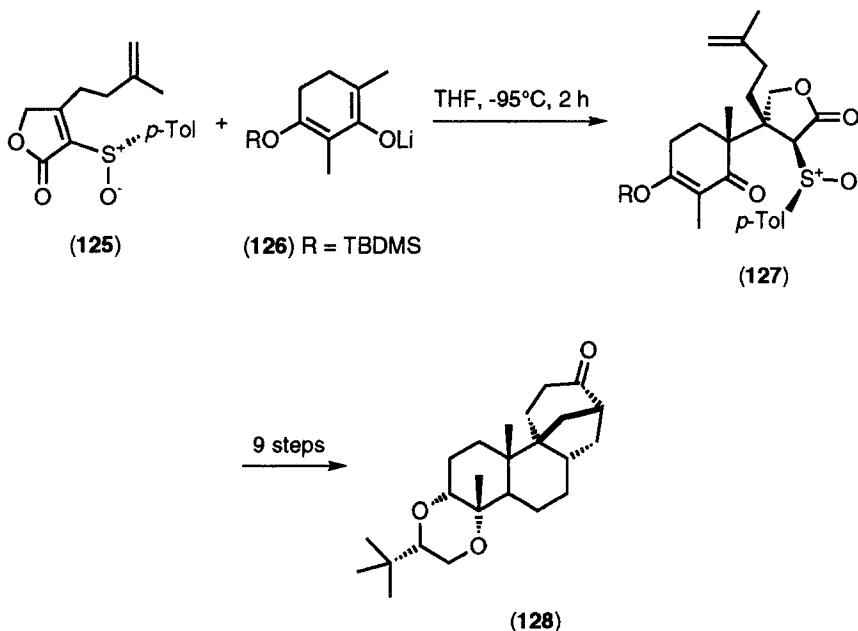
In contrast, Michael additions of  $\alpha,\alpha$ -disubstituted lithium enolates proceed, apparently via the chelated form of enone sulfoxides (Figure 5.2), with almost complete  $\pi$ -facial diastereoselectivity [104]. This methodology has been used in the asymmetric synthesis of the pheromone, (−)-methyl jasmonate (**121**), from cyclopentenone sulfoxide (**98b**) [105] via the intermediate (**120**), which was formed in at least 98% enantiomeric purity upon asymmetric Michael addition of bis  $\alpha$ -silylated  $\alpha$ -lithioacetate to (**98b**). Addition of the  $\alpha$ -bromo enolate (**122**) to enantiomerically pure (**98a**) and oxidation gives the product sulfone (**123**), with almost complete asymmetric  $\beta$ -induction with respect to the sulfoxide. Sulfone (**123**) was then converted into the steroid sex hormone, (+)-oestradiol (**124**) (Scheme 5.42) [106].

Holton and coworkers have used the asymmetric conjugate addition of an  $\alpha,\alpha$ -



SCHEME 5.42

disubstituted lithium enolate to a lactone sulfoxide in the enantioselective total synthesis of pivalyl aphidicolinone (**128**) [107]. Michael addition of lithium enolate (**126**) to enone sulfoxide (**125**) in THF at  $-95^{\circ}\text{C}$  afforded the product (**127**) with 88% *de* and 75% overall yield. Product (**127**) was then converted to (**128**) in nine further steps (Scheme 5.43).

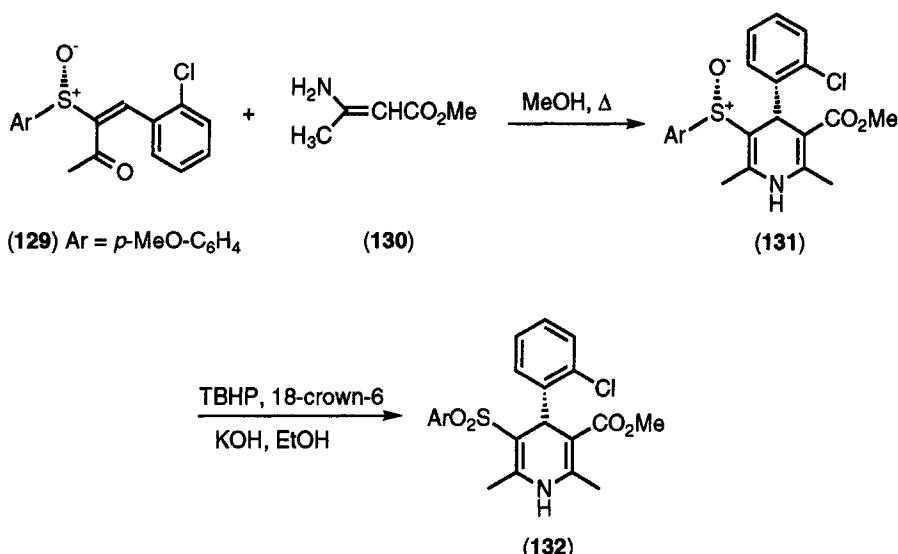


SCHEME 5.43

Davis and coworkers have used an intramolecular asymmetric Michael addition to an optically pure  $\alpha,\beta$ -unsaturated sulfoxide as part of the synthesis of the dihydropyridine sulfone (**132**), a potent antihypertensive agent [108]. The Hantzsch reaction (treatment with 3-aminocrotonate (**130**) in MeOH under reflux) of the  $\alpha$ -acyl- $\alpha,\beta$ -unsaturated sulfoxide (**129**) gave the product (**131**) as a single diastereoisomer in 48% yield, resulting from an asymmetric Michael addition followed by dehydrative cyclization. The sulfoxide was then oxidized to the corresponding sulfone (**132**) (Scheme 5.44).

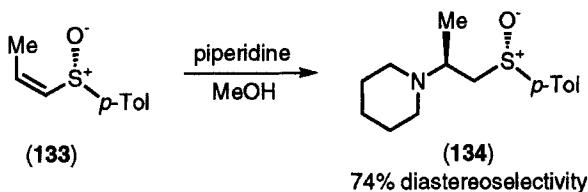
#### 5.4.2 Conjugate Addition of Heteroatom Nucleophiles to $\alpha,\beta$ -Unsaturated Sulfoxides

The first report of asymmetric heteroatom conjugate addition to  $\alpha,\beta$ -unsaturated sulfoxides was made in 1971 [11,12], and has been followed by few studies in this area relative to the analogous asymmetric reactions with carbon nucleophiles. The addition of piperidine in methanol to  $(-)$ -(*S*)-*cis*-propenyl *p*-tolyl sulfoxide (**133**)



SCHEME 5.44

gave (134) as the major diastereoisomer. On reduction, the corresponding sulfide was obtained with an optical yield of 74% (Scheme 5.45). Tanikaga and colleagues have added piperidine to racemic phenyl and *p*-chlorophenyl vinyl sulfoxide, but no mention of the stereochemical outcome of the reaction was made [72].

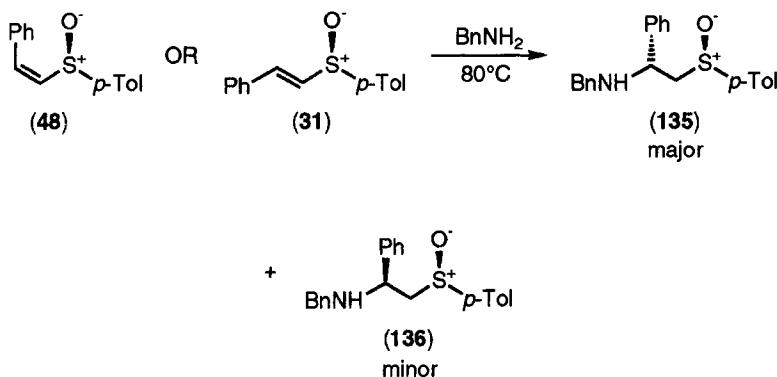


SCHEME 5.45

Pyne and coworkers have studied both the inter- and intramolecular reaction between amines and optically active  $\alpha,\beta$ -unsaturated sulfoxides, and have applied this methodology to synthesis of natural products [109,110,112–114].

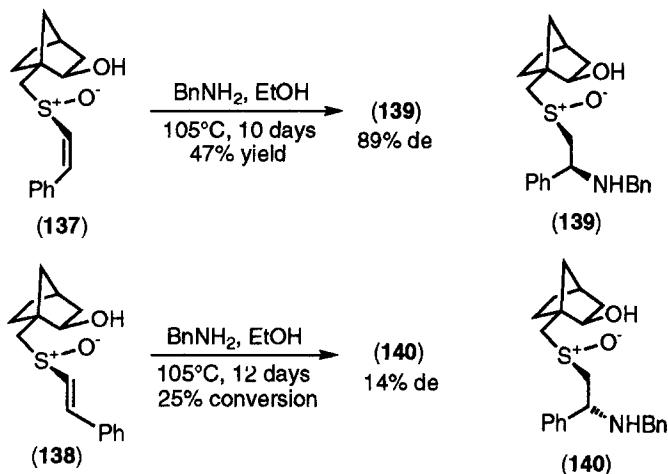
The kinetically controlled intermolecular conjugate addition of benzylamine to isomeric (*E*) or (*Z*) chiral  $\alpha,\beta$ -unsaturated sulfoxides such as (48) and (31) afforded the same major diastereoisomeric adduct (135) in each case in 72% and 76% *de*, respectively (Scheme 5.46) [109]. A tentative explanation for this stereochemical outcome was proposed.

The intermolecular conjugate addition of benzylamine to (*R*<sub>S</sub>)-10-isobornyl  $\alpha,\beta$ -unsaturated sulfoxides has been studied [110]. The (*Z*)-isomer (137) underwent highly diastereoselective conjugate addition to give (139) as the major product



SCHEME 5.46

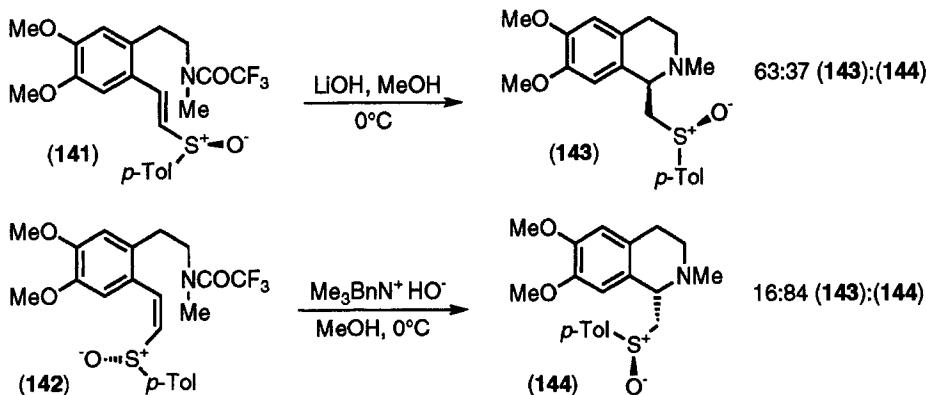
with 89% *de*, whereas the corresponding (*E*)-isomer (**138**) underwent conjugate addition with poor diastereoselectivity (14% *de* for the major product (**140**)) and was less reactive (Scheme 5.47).



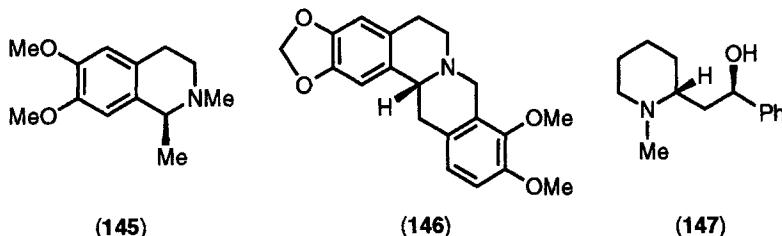
SCHEME 5.47

The asymmetric intramolecular conjugate addition of amines to optically active  $\alpha,\beta$ -unsaturated sulfoxides has been studied [111–115]. For example, the (*R*<sub>S</sub>)-(E)- $\alpha,\beta$ -unsaturated sulfoxide (**141**), upon basic hydrolysis with lithium hydroxide, gave a mixture of the diastereoisomeric isoquinolines (**143**) and (**144**) in the ratio 63:37. An enhanced diastereoselectivity was observed upon basic hydrolysis of the (*R*<sub>S</sub>)-(Z)- $\alpha,\beta$ -unsaturated sulfoxide (**142**) with benzyltriethylammonium hydroxide, giving (**143**) and (**144**) in the ratio 16:84 (note that the major product

diastereoisomers were different in the two cases) [112]. These results are summarized in Scheme 5.48. This methodology has been applied to the total synthesis of (*R*)-(+)-carnegine (**145**) [112,114], (*R*)-(+)-canadine (**146**) [113], and the two enantiomeric forms of sedamine (**147**) [114].

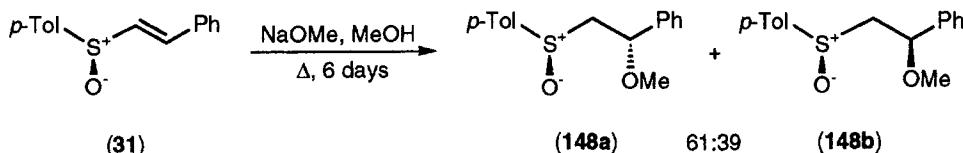


SCHEME 5.48



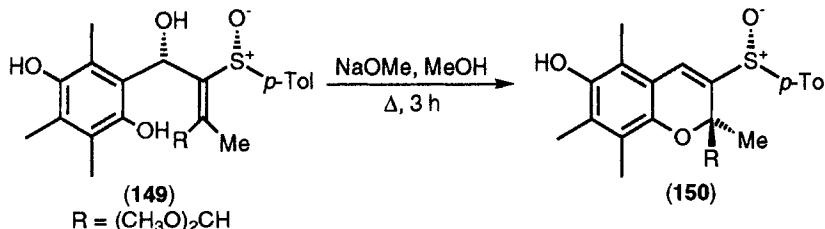
$\beta$ -Nitro- $\alpha,\beta$ -unsaturated sulfoxides have been shown to react with pyrrolidine to give the corresponding nitroenamine with loss of the sulfoxide functionality [116].

The first report concerning the stereoselective addition of oxygen nucleophiles to  $\alpha,\beta$ -unsaturated sulfoxides made by Tsuchihashi [117], who found that addition of methoxide anion to *trans*- $\beta$ -styryl *p*-tolyl sulfoxide (**31**) gave a 61:39 ratio of diastereoisomers (**148a**) and (**148b**) in 93% overall yield (Scheme 5.49). It should be noted that the major diastereoisomer (**148a**) has the opposite configuration at the  $\beta$ -sulfinyl carbon atom to that in (**89a**), the major product resulting from the addition of malonate anion to (**31**) (Scheme 5.29). This finding was experimentally associated with the reversible (thermodynamically controlled) addition of the alkoxide in contrast to the kinetically controlled addition of diethyl malonate, and it was concluded that the ratio of (**148a**) to (**148b**) reflects the thermodynamic stabilities of the products.



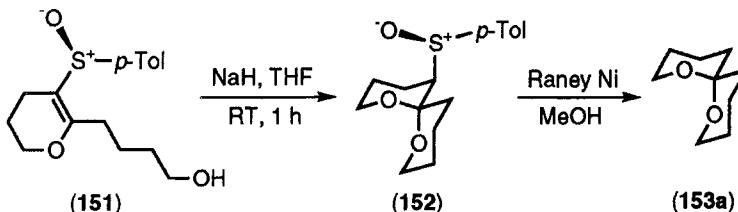
SCHEME 5.49

Few further examples exist concerning the intermolecular addition of oxygen nucleophiles to  $\alpha,\beta$ -unsaturated sulfoxides [72,118,119]; however, several reports have been made concerning the stereoselective intramolecular conjugate addition of oxygen nucleophiles to  $\alpha,\beta$ -unsaturated sulfoxides [55,56,120–122]. Solladié and Moine [55] reported the highly stereoselective formation of the chromene (150) in 96% yield from the hydroquinone (149) on treatment with sodium methoxide in refluxing methanol (Scheme 5.50).

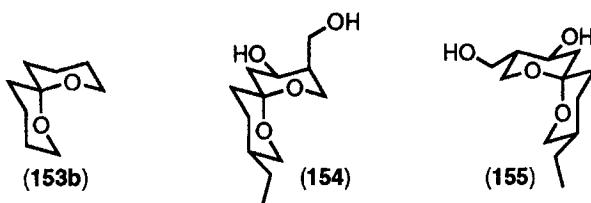


SCHEME 5.50

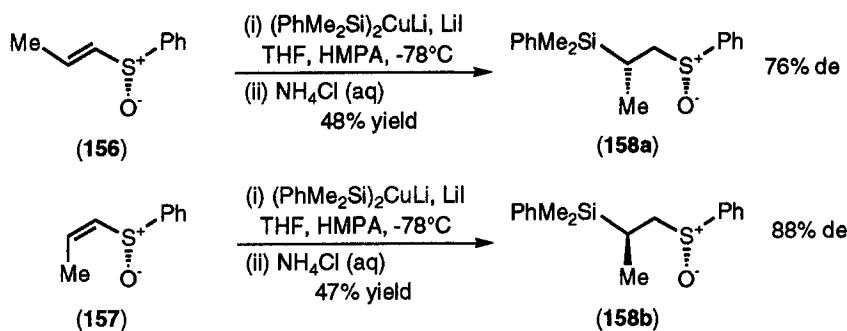
Iwata and coworkers have reported a facile route for formation of the optically pure spiroketal skeleton through stereoselective intramolecular addition of oxygen nucleophiles to  $\alpha,\beta$ -unsaturated sulfoxides [120–122]. For example, the hydroxybutylated  $\alpha,\beta$ -unsaturated sulfoxide (151), on treatment with sodium hydride in THF, gave a single kinetically controlled product (152), which on desulfurization afforded (*R*)-1,7-dioxaspiro[5.5]undecane (153a), a sex pheromone of an olive fly (Scheme 5.51) [121]. The stereochemical control exerted by the sulfoxide group in the cyclization step can be interpreted in terms of chelation of the side-chain oxido anion and the sulfoxide oxygen of the sodium cation. This methodology has been applied by the same authors to the synthesis of (*R*)- and (*S*)-1,7-dioxaspiro[5.5]undecane (153a) and (153b) [121], (+)-talaromycin A (154), and (–)-talaromycin B (155) (Scheme 5.51) [122].



SCHEME 5.51



Takaki and colleagues have studied the stereochemistry of the conjugate addition of silylcuprates to optically active sulfoxides, and found that lithium bis(dimethylphenylsilyl)cuprate, in contrast to dialkylcuprates, reacts with (*E*)- and (*Z*)- $\alpha,\beta$ -unsaturated sulfoxides such as (156) and (157) to give the Michael adducts (158a) and (158b) with high diastereoselectivity (Scheme 5.52) [123]. Thus reaction of (*E*)- $\alpha,\beta$ -unsaturated sulfoxide (156) under the conditions described gives (158a) as the major diastereoisomer in 76% *de*, while the corresponding (*Z*)- $\alpha,\beta$ -unsaturated sulfoxide (157) yields (158b) as the major product with 88% *de*.



SCHEME 5.52

The addition of sulfur nucleophiles to  $\alpha,\beta$ -unsaturated sulfoxides is known, although the stereochemical outcome of such additions has not been studied extensively [12,72,94].

### 5.4.3 Theoretical Considerations

Hehre and Kahn have developed a model for the reaction of nucleophiles with  $\alpha,\beta$ -unsaturated sulfoxides [64,124,125], that suggests that the product stereochemistries of many of these reactions are determined along the reaction coordinate on the basis of electrostatic interactions. They argue that the  $\alpha,\beta$ -

unsaturated sulfoxide concerned reacts from an *s-cis* conformer where the sulfur–oxygen and carbon–carbon bonds are *syn*-coplanar (Figure 5.4). Evidence for this particular reactive conformer comes from theoretical calculations carried out on methyl vinyl sulfoxide.

In this approach, the nucleophiles are categorized according to whether or not they incorporate an electropositive metal, and those that do are further divided according to whether or not they have an accessible or inaccessible coordination site. Nucleophiles that do not have an accessible coordination site (e.g.  $(\text{Pr}^{\text{i}}\text{O})_3\text{TiMe}$  or ‘metal-free’ nucleophiles such as amines) approach the  $\alpha,\beta$ -unsaturated sulfoxide from the ‘electron-poor alkene face’, i.e. the face of the double bond that is remote from the sulfur lone pair. ‘Coordinating nucleophiles’, i.e. those nucleophiles whose metal counterion is able to coordinate to the sulfur lone pair, however, will attack from the same face as the sulfur lone pair. The argument is proposed on purely electrostatic grounds without reference to steric effects and is borne out by the stereoselectivities of several conjugate additions, although in many cases the stereochemical outcome can also be explained on steric grounds as a consequence of chelation effects (Figure 5.2) [13].

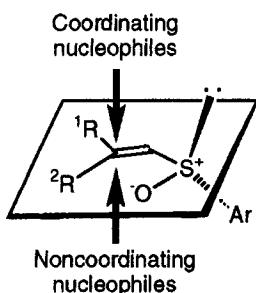


FIGURE 5.4

## 5.5 PERICYCLIC REACTIONS OF $\alpha,\beta$ -UNSATURATED SULFOXIDES

$\alpha,\beta$ -Unsaturated sulfoxides have been used widely as dienophiles in [4+2] cycloaddition reactions and less frequently as dipolarophiles in 1,3-dipolar cycloadditions, and are the subject of several reviews [126–136].

Recent work in this area has concentrated on the use of chiral  $\alpha,\beta$ -unsaturated sulfoxides to control facial selectivity in asymmetric cycloaddition processes, and is the main focus of this section. These substrates are an attractive proposition for use in asymmetric Diels–Alder reactions since the sulfoxides can be prepared enantiomerically pure in many cases, and also because the sulfoxide group is close to the dienophilic double bond and can exert a significant effect on the stereochemical outcome of the cycloaddition.

There is also considerable current interest in the use of dienyl sulfoxides as  $4\pi$  components in asymmetric Diels–Alder cycloadditions and as enophiles, and work

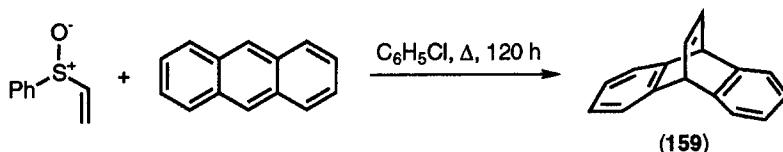
in this area is discussed below (recent publications concerning the preparation of optically active dienyl sulfoxides are described in Section 5.2.5).

### 5.5.1 [4+2] Cycloadditions Using $\alpha,\beta$ -Unsaturated Sulfoxides

#### 5.5.1.1 As dienophiles

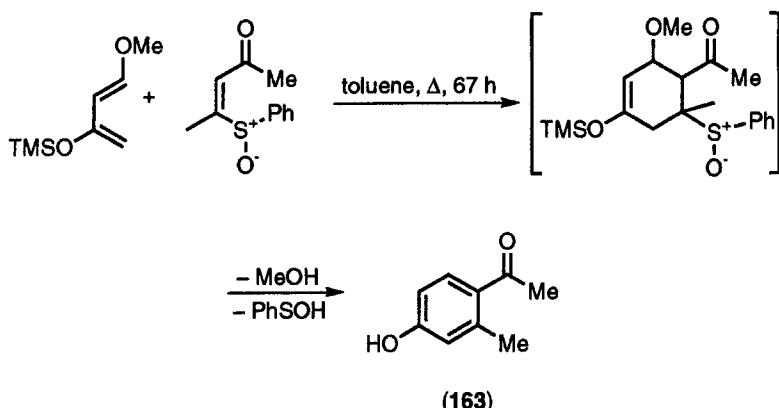
##### Racemic $\alpha,\beta$ -unsaturated sulfoxides

Early reports on the use of racemic vinyl sulfoxides as dienophiles were chiefly concerned with their use as acetylene equivalents, since the primary cycloadducts may extrude sulfenic acid [137–139]. For example, heating phenyl vinyl sulfoxide and anthracene in chlorobenzene afforded dibenzobarrelene (**159**) in 83% yield (Scheme 5.53) [137].



SCHEME 5.53

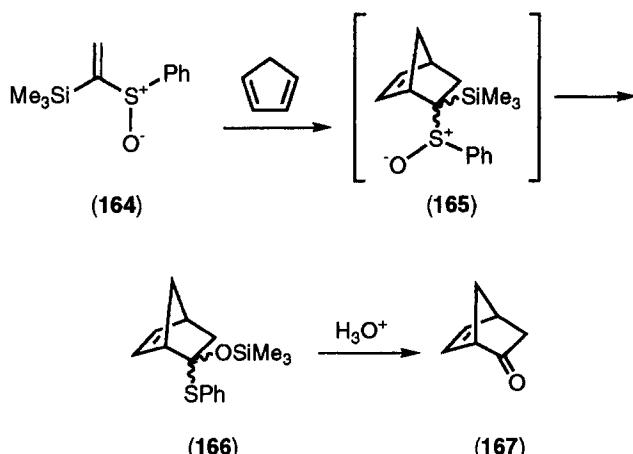
Danishefsky and coworkers have used the racemic  $\beta$ -phenylsulfinyl- $\alpha,\beta$ -unsaturated ketone (**160**) as an  $\alpha,\beta$ -ethynyl carbonyl synthetic equivalent and found that the phenylsulfinyl group did not compete with the carbonyl group in determining the regioselectivity of cycloaddition with the 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**161**), now known as Danishefsky's diene [140] (Scheme 5.54). Loss of methanol and phenyl sulfenic acid from the initial cycloadduct (**162**) gave the aromatic product (**163**).



SCHEME 5.54

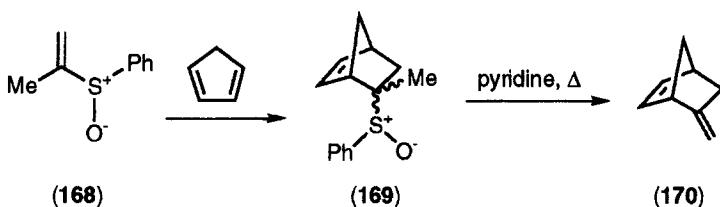
Racemic vinyl sulfoxides have also been used as synthetic equivalents of nitroacetylene [116] and naphthynoquinone [141], their synthetic utility again depending on the ability of the primary cycloadducts to extrude sulfenic acid.

Williams has demonstrated the use of 1-phenylsulfinyl-1-trimethylsilyl ethene (**164**) and phenyl vinyl sulfoxide as effective ketene equivalents for the Diels–Alder reaction [142,143], important as it is known that ketenes do not undergo satisfactory [4+2] cycloadditions. The initial cycloadduct (**165**), derived from the Diels–Alder reaction between 1-phenylsulfinyl-1-trimethylsilyl ethene (**164**) and cyclopentadiene, undergoes a facile sila-Pummerer rearrangement to give the thioacetal (**166**), which yields the product (**167**) upon hydrolysis (Scheme 5.55) [142].



SCHEME 5.55

Using similar methodology to that employed in the use of vinyl sulfoxides as acetylene equivalents, 2-phenylsulfinylpropene (**168**) has recently been shown to be an effective allene equivalent for the Diels–Alder reaction [144] (Scheme 5.56), valuable since allene, as well as being difficult to handle, undergoes [2+2] cycloaddition, in addition to the desired [4+2] process.

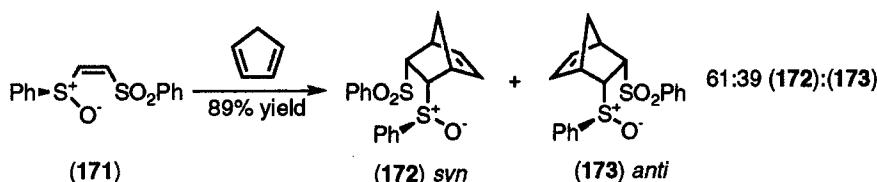


SCHEME 5.56

The stereochemical outcome of the Diels–Alder reaction between racemic vinyl sulfoxides and dienes (usually cyclopentadiene) has been studied since the late

1950s [145–152]. In the majority of cases, the preferred orientation of attack of the diene to the vinyl sulfoxide has been shown to be *endo*–*syn*, as shown in Scheme 5.57 [147].

The *endo*–*exo* terminology was explained by considering the orientation of the S=O bond in the cycloadduct; when the S=O bond was ‘below’ the norbornenyl skeleton with the S–Ph bond positioned parallel to the bridgehead proton, the cycloadduct was termed *syn* (172); when the S=O bond was outside the norbornenyl skeleton, this was termed the *anti* cycloadduct (173).



SCHEME 5.57

#### *Optically active $\alpha,\beta$ -unsaturated sulfoxides – theoretical considerations*

The diastereofacial selectivity observed in the cycloaddition of chiral  $\alpha,\beta$ -unsaturated sulfoxides with various dienes has received considerable attention from a synthetic viewpoint and is discussed extensively in the following sections. In the majority of cases, the diastereofacial selectivity of the cycloaddition is explained in terms of steric factors. The diastereofacial differentiation is accounted for by the preferred addition of the dienes to the energetically favoured *s-trans* or *s-cis* conformer of  $\alpha,\beta$ -unsaturated sulfoxides from the less sterically crowded side of the double bond, i.e. *syn* to the lone-pair electrons on sulfur. The *s-trans* and *s-cis* conformations for two different  $\alpha,\beta$ -unsaturated sulfoxides (lowest energy conformers) are shown in Figure 5.5, together with the preferred orientation of attack of the diene on steric grounds alone. In Figure 5.5, the mode of addition of cyclopentadiene shown leads to the *endo* cycloadduct with respect to the sulfoxide; this is not always the case, and often *endo*/*exo* mixtures are obtained with other  $\alpha,\beta$ -unsaturated sulfoxide dienophiles and dienes.

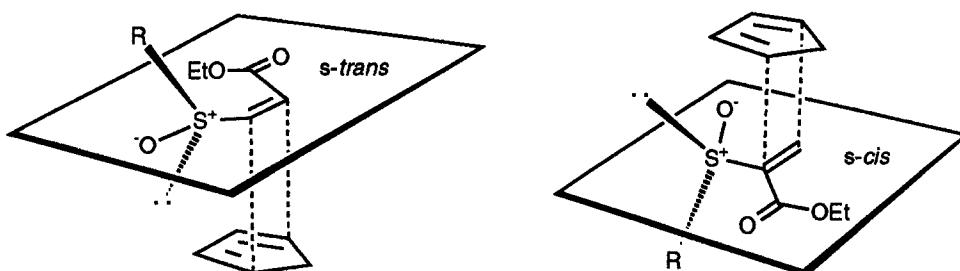


FIGURE 5.5

The position of the conformational equilibrium (*s-trans* or *s-cis*) is thought to be influenced mainly by the substituents at the  $\alpha$ - or  $\beta$ -position owing to dipole–dipole repulsion and/or steric hindrance, an idea validated by x-ray analysis and CD spectra of some optically active  $\alpha,\beta$ -unsaturated sulfoxides [153]. Several results in this area are summarized in Table 5.5 and are discussed further later in this section.

The  $\alpha,\beta$ -unsaturated sulfoxides (174a), (174b), and (174c) (Table 5.5), in which the *s-trans* conformers are the most stable owing to dipole–dipole repulsion between the S=O and C=O bonds and to steric repulsion, exhibited high diastereoselectivities, and the relative configurations of the cycloadducts could be explained by the addition of diene to the less hindered face of the dienophilic double bond, containing the lone-pair electrons on sulfur.

The dienophile (175) was considered to exist mainly in the *s-cis* conformation owing to dipole–dipole repulsion between the S=O and C=O bonds and also exhibited high diastereoselectivities in the Diels–Alder reaction, the major cycloadducts arising by attack of the diene from the sulfur lone-pair side of the double bond. On the other hand, dienophiles (176a) and (176b), which could exist in both *s-trans* and *s-cis* conformations because of the absence of  $\alpha$ - or (*Z*)- $\beta$  substituents, exhibited low diastereoselectivities upon cycloaddition.

An alternative explanation for the steric course of Diels–Alder cycloadditions involving  $\alpha,\beta$ -unsaturated sulfoxides has been proposed by Kahn and Hehre [154,155], who rationalized diastereofacial selectivities in terms of electrostatic effects. They assume that  $\alpha,\beta$ -unsaturated sulfoxides react from an *s-cis* conformer,

TABLE 5.5

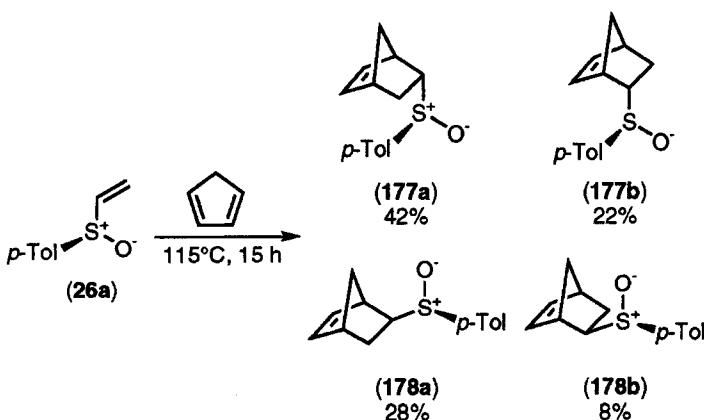
Most stable conformations	Dienophiles
<i>s-trans</i> High diastereoselectivity	  
<i>s-trans</i> and <i>s-cis</i> Low diastereoselectivity	 
<i>s-cis</i> High diastereoselectivity	

an assumption arising from previous theoretical work on methyl vinyl sulfoxide [124].

In terms of their electrostatic model [155], the more electron-rich face of the diene, which acts as a nucleophile, is paired with the more electron-poor face of the dienophile, which acts as an electrophile. Therefore, one face of the double bond in  $\alpha,\beta$ -unsaturated sulfoxides is rendered relatively electron-rich owing to the lone-pair electrons on sulfur, while the remaining face is left relatively electron-poor. Thus, the electrostatic bias is for diene addition to the face opposite to the sulfur lone pair in the *s-cis* conformation, i.e. toward the more sterically encumbered face. The authors then argued that electrostatic factors override steric arguments, and were able to explain the diastereofacial selectivity of several cycloadditions in this way. Koizumi and coworkers have since offered a disproof of the Kahn–Hehre proposal [153].

#### Nonracemic unsubstituted $\alpha,\beta$ -unsaturated sulfoxides

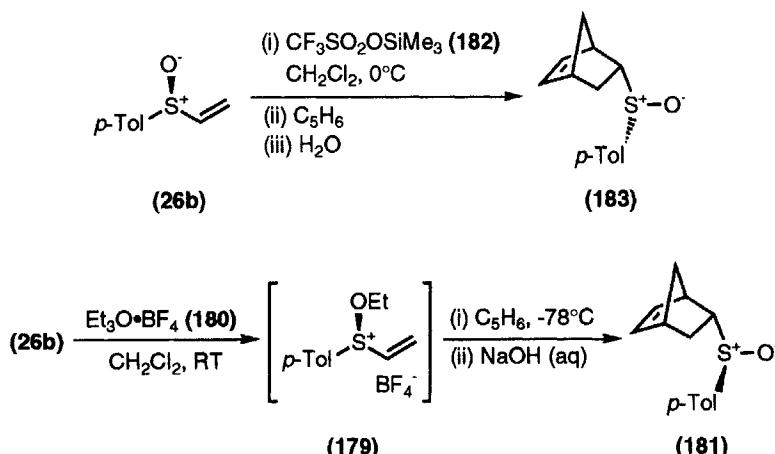
The first report on the use of enantiomerically pure sulfinyl dienophiles in Diels–Alder cycloadditions was by Maignan and Raphael [156], who utilized (+)-(*R*)-*p*-tolyl vinyl sulfoxide (**26a**) as an optically active dienophile (Scheme 5.58). A mixture of *endo* (**177a**) and (**177b**) and *exo* (**178a**) and (**178b**) diastereoisomers were formed as a result of poor selectivity.



SCHEME 5.58

Subsequent work has shown that simple, unactivated enantiomerically pure vinyl sulfoxides such as *p*-tolyl vinyl sulfoxide, without further substitution on the double bond, are not effective dienophiles for inducing diastereoselectivity in asymmetric Diels–Alder reactions. In the majority of cases, further substitution of the double bond by electron-withdrawing groups is necessary to achieve high stereoselectivity under mild conditions. However, a recent report by Ronan and Kagan [157,158] has shown that (*S*)-*p*-tolyl vinyl sulfoxide (**26b**) can be efficiently activated toward Diels–Alder cycloaddition by transformation into a sulfoxonium

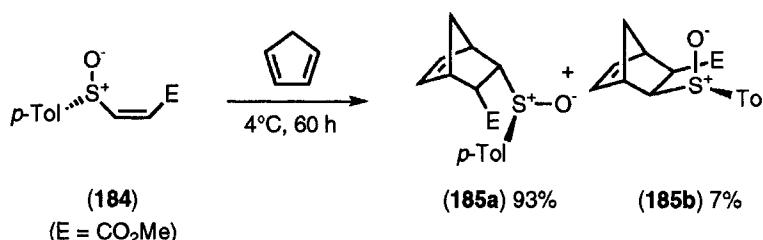
salt (**179**) using Meerwein's reagent (**180**) or by the addition of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (**182**). Using the activated dienophilic salt (**179**), very high diastereoselectivities were achieved in the Diels–Alder cycloaddition, particularly with cyclopentadiene to give the major cycloadduct (**181**) (with inversion of configuration at sulfur after workup with aqueous sodium hydroxide), although the reaction was poor with other dienes. Activation of (**26b**) using TMSOTf led to the cycloadduct (**183**) (epimeric at sulfur relative to (**181**)) with very high diastereoselectivity. The results are summarized in Scheme 5.59 [157].



SCHEME 5.59

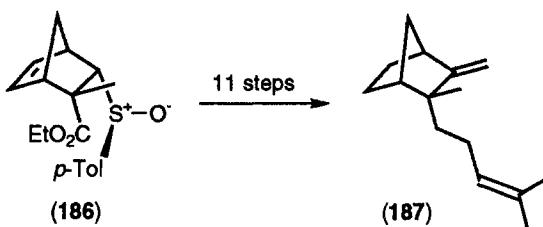
#### Nonracemic substituted $\alpha,\beta$ -unsaturated sulfoxides

Vinyl sulfoxides substituted at the  $\beta$ -position by electron-withdrawing groups have been used extensively as enantiomerically pure dienophiles in asymmetric Diels–Alder cycloadditions. Maignan and colleagues utilized methyl (*Z*)-(R)-3-*p*-tolylsulfinyl propenoate (**184**), which reacted with cyclopentadiene under mild conditions; high stereoselectivity and diastereoselectivity were observed [159] in formation of the *endo* and *exo* cycloadducts (**185a**) and (**185b**) (Scheme 5.60).



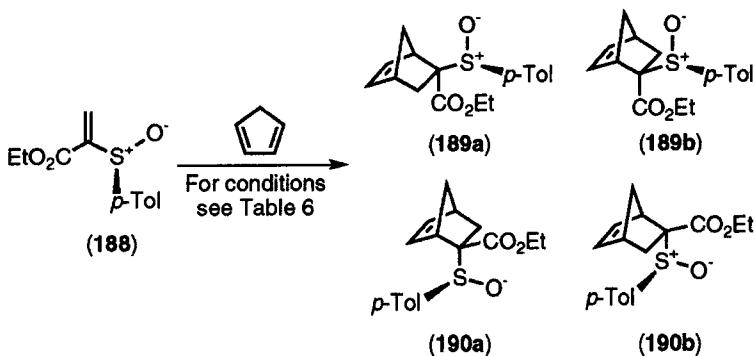
SCHEME 5.60

Independently, Koizumi *et al.* also reported [160] the use of nonracemic 3-*p*-tolylsulfinylacrylates as dienophiles in highly diastereoselective Diels–Alder reactions. The functionalized bicyclo[2.2.1]heptane derivatives such as (186), obtained by asymmetric Diels–Alder cycloaddition of ethyl *p*-tolylsulfinylmethylenepropionate with cyclopentadiene, have been used as intermediates for the synthesis of bicyclic sesquiterpenes such as (+)-epi- $\beta$ -santalene (187) [161,162] (Scheme 5.61).



SCHEME 5.61

Nonracemic  $\alpha,\beta$ -unsaturated *p*-tolylsulfoxide dienophiles bearing an electron-withdrawing group in the  $\alpha$ -position have been employed successfully in Diels–Alder cycloadditions [28,29,94,133], although less frequently than their  $\beta$ -substituted counterparts. Koizumi and coworkers have reported the use of optically active 2-*p*-tolylsulfinylacrylate (188) as a chiral dienophile which exhibits high reactivity and diastereoselectivity in cycloaddition reactions with anthracene and cyclopentadiene (Scheme 5.62), affording cycloadducts (189) and (190),



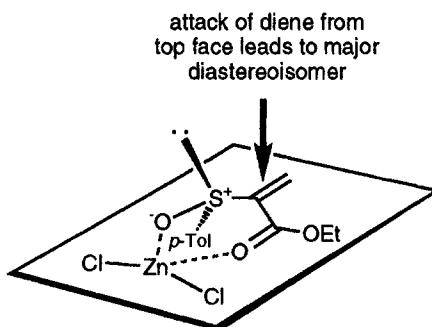
SCHEME 5.62

although *endo*–*exo* stereoselectivity was low (Table 5.6) [28]. Indeed, the dienophile (188) was reported to have a much higher dienophilic reactivity than the corresponding 3-*p*-tolylsulfinylacrylate. In the reaction with cyclopentadiene, the diastereoselectivity could be reversed by the addition of a Lewis acid (zinc(II))

chloride) to the reaction mixture (Table 5.6). This effect arises because of the conformational change in the dienophile on the addition of Lewis acid (chelation control as shown in Figure 5.6).

TABLE 5.6

Lewis acid	Solvent	Ratio of diastereomeric cycloadducts		
		(189) ( <i>endo</i> CO <sub>2</sub> Et) (189a) : (189b)	(190) ( <i>exo</i> CO <sub>2</sub> Et) (190a) : (190b)	(189) : (190)
None	PhH	64 : 11	23 : 2	3.0 : 1
ZnCl <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	2 : 77	2 : 19	3.8 : 1

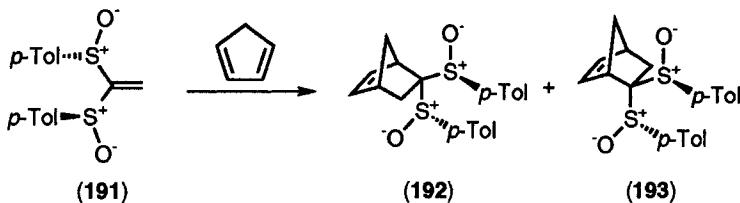
FIGURE 5.6 Stereochemical outcome of cycloaddition after addition of ZnCl<sub>2</sub>

Maignan and coworkers have reported the preparation and Diels–Alder reaction of  $\alpha$ -keto- $\alpha,\beta$ -unsaturated sulfoxides and have observed exclusive formation of *exo*-sulfinyl cycloadducts albeit with poor diastereoselectivity [29].

The use of (+)-(*S*)- $\alpha$ -diethoxyphosphorylvinyl *p*-tolyl sulfoxide as a new optically active dienophile has been described recently by Mikolajczyk and Midura. This new type of dienophile underwent a diastereoselective reaction with cyclopentadiene but with poor *endo/exo* selectivity [94].

The effect of an amide group in the  $\alpha$ -position of an  $\alpha,\beta$ -unsaturated dienophile has also been reported, although reaction with cyclopentadiene proceeds with poor stereoselectivity [133].

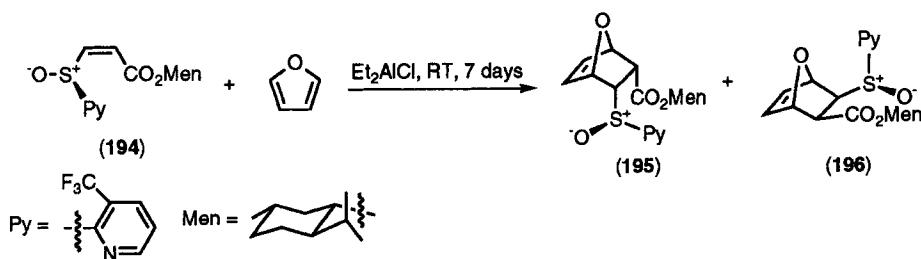
(+)-(*S,S*)-1,1-Bis(*p*-tolylsulfinyl)ethene (191), an  $\alpha,\beta$ -unsaturated sulfoxide dienophile bearing a second chiral sulfoxide group in the  $\alpha$ -position, has been used as a latent chiral ketene equivalent in the Diels–Alder reaction [163]. The cycloadducts (192) and (193) are formed as a 4:1 mixture upon cycloaddition with cyclopentadiene (Scheme 5.63).



SCHEME 5.63

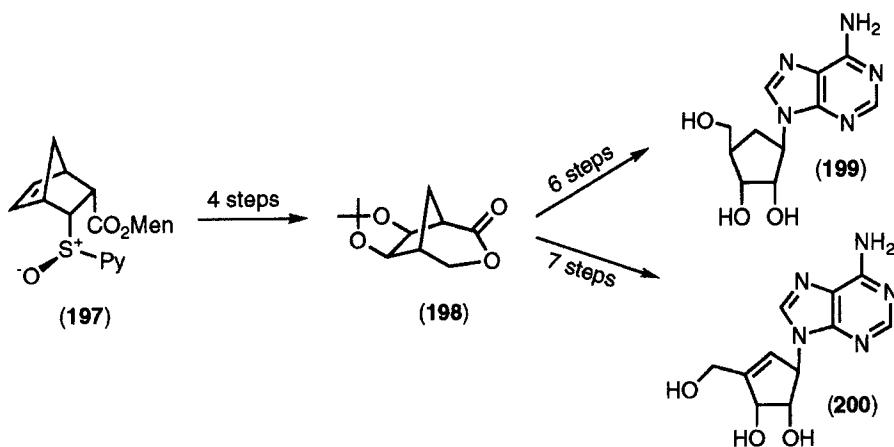
Carretero and colleagues have recently reported a systematic study on the use of enantiomerically pure 2-*p*-tolylsulfinylmaleates as dienophiles in asymmetric Diels–Alder cycloadditions with cyclopentadiene over a wide range of catalysed and uncatalysed conditions [164]. High diastereofacial selectivities were observed in some cases, and the stereochemical results have been interpreted using a sterically controlled approach.

Koizumi and colleagues [165] have developed nonracemic 3-(2-pyridylsulfinyl) acrylates, which show enhanced reactivity as dienophiles compared to 3-(2-*p*-tolylsulfinyl)acrylates such as (184) owing to the stronger inductive electron-withdrawing effect of the pyridyl group over the tolyl group. For example, the enantiomerically pure (*S*)-3-(2-pyridylsulfinyl)acrylate (194) undergoes a highly diastereoselective Diels–Alder cycloaddition with furan, well known as a diene of low reactivity, in the presence of diethylaluminium chloride, to give the corresponding cycloadducts as a mixture of *endo* (195) and *exo* (196) isomers (Scheme 5.64).



SCHEME 5.64

The *endo* cycloadducts resulting from the cycloaddition of optically active 3-(2-pyridylsulfinyl)acrylates and simple dienes such as cyclopentadiene and furan have been utilized successfully in the asymmetric synthesis of several natural products [166–170]. For example, cycloadduct (197), synthesized as a single diastereoisomer from the reaction of (*S*)-3-(2-pyridylsulfinyl)acrylate with cyclopentadiene, was converted to the lactone (198) [166], a key intermediate in the synthesis of the carbocyclic nucleosides (–)-aristeromycin (199) and (–)-neplanocin A (200) (Scheme 5.65) [167].



SCHEME 5.65

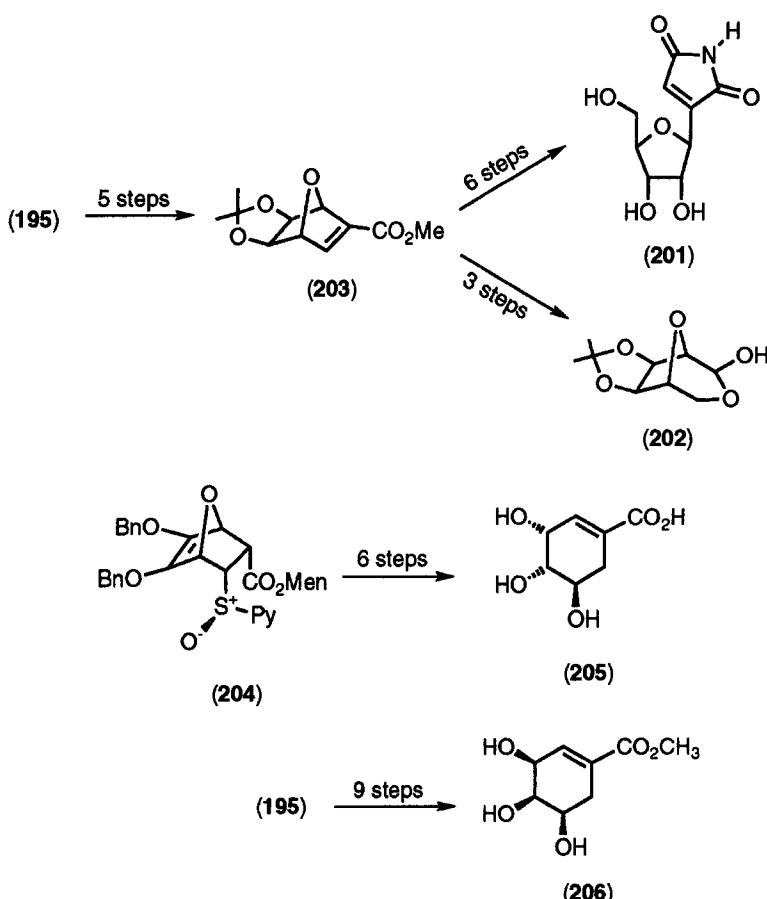
Cycloadduct (195) has been used in the synthesis of the C-nucleosides D-showdomycin (201) and D-3,4-*O*-isopropylidene-2,5-anhydroallose (202) via the common intermediate (203) (Scheme 5.66) [168]. The Diels–Alder *endo* cycloadduct (204), prepared in 50% yield and 92% diastereomeric excess by the reaction of (*S*)-3-(2-pyridylsulfinyl)acrylate (194) with 3,4-dibenzoyloxyfuran, was converted into the secondary metabolite (−)-shikimic acid (205) in six steps [169]. Cycloadduct (195), prepared as shown in Scheme 5.64, has also been transformed into (+)-methyl 5-epi-shikimate (206) [170] (Scheme 5.66).

The introduction of a nitro or trifluoromethyl group at the C-3 position on the pyridine ring in 3-(2-pyridylsulfinyl)acrylates has been shown to enhance the reactivity and diastereoselectivity of the dienophile in the Diels–Alder reaction with furan and its derivatives [171]. Such a modification of the dienophile renders the addition of diethylaluminium chloride unnecessary in order to achieve the desired asymmetric cycloaddition. The cycloadduct (207), prepared with high stereoselectivity from the asymmetric Diels–Alder reaction between (*S*)-menthyl 3-(3-trifluoromethylpyrid-2-ylsulfinyl)acrylate (194) and 2-methoxyfuran (208), was converted in seven steps to the glyoxalase I inhibitor (209) [171] (Scheme 5.67).

The use of 3-(2-pyridylsulfinyl)acrylates as enantiomerically pure dienophiles of enhanced reactivity in Diels–Alder reactions with dienes of low reactivity such as furan suffer from the following disadvantages:

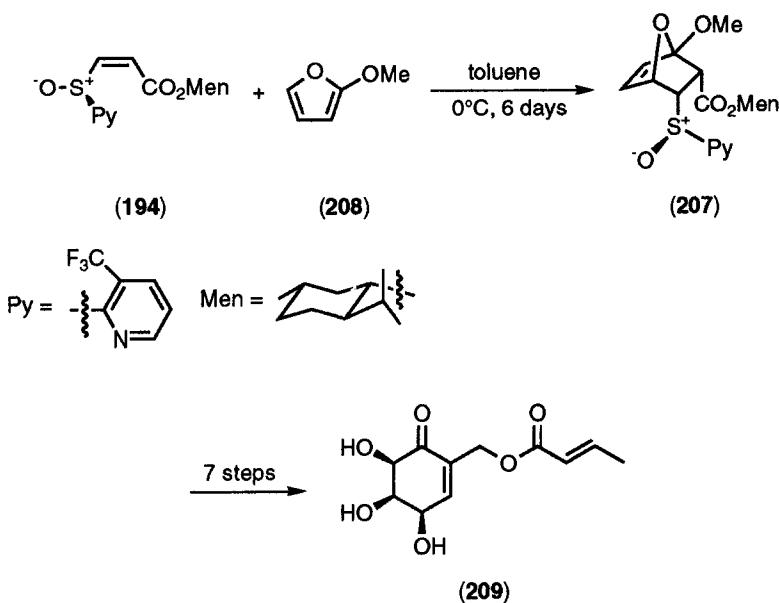
1. Long reaction times (about a week) were required for highly diastereoselective reactions with furan.
2. Enantiomerically pure 3-(2-pyridylsulfinyl)acrylates were obtained by fractional recrystallization of a mixture of diastereoisomers.
3. The Diels–Alder reaction of the dienophile did not proceed stereoselectively, a mixture of *endo* and *exo* cycloadducts being obtained in all cases.

To overcome some of these problems,  $\alpha,\beta$ -unsaturated sulfoxide dienophiles employing 10-mercaptopisoborneol (210) as a chiral auxiliary have been developed

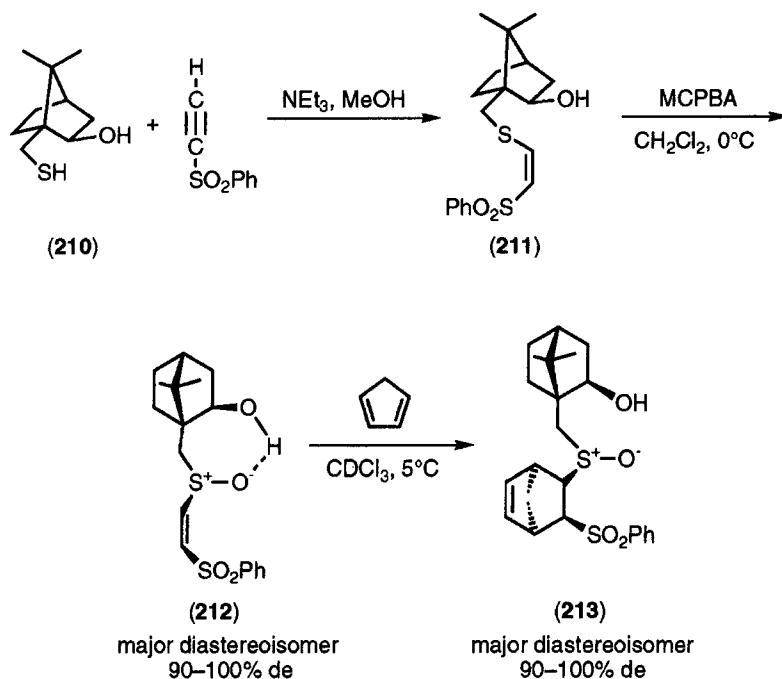


SCHEME 5.66

[126–130,133–135]. This strategy, first used by De Lucchi *et al.* [172,173], allows the highly stereoselective synthesis of enantiomerically pure  $\alpha,\beta$ -unsaturated sulfoxide dienophiles in two steps (Michael addition and diastereoselective oxidation) from cheap and readily available starting materials. Michael addition of 10-mercaptopisoborneol (210) to phenylsulfonyl acetylene gave the (*Z*)-alkene (211) stereoselectively. The formation of the (*Z*)-adduct was desirable as the corresponding (*E*)-alkene had been shown to give a mixture of *endo* and *exo* isomers on reaction with cyclopentadiene. The presence of the hydroxy group in the chiral auxiliary controls the diastereoselectivity of the sulfide oxidation, and helps to give conformational rigidity to sulfinyl dienophile (212) through hydrogen-bonding with the sulfoxide oxygen atom. Most importantly, this type of dienophile shows high asymmetric induction in the Diels–Alder reaction, the rotational preference of the dienophile driving efficiently and selectively the cyclopentadiene addition to the ene face pointing toward the sulfoxide lone pair (Scheme 5.68), giving cycloadduct (213) with almost compete diastereofacial control.

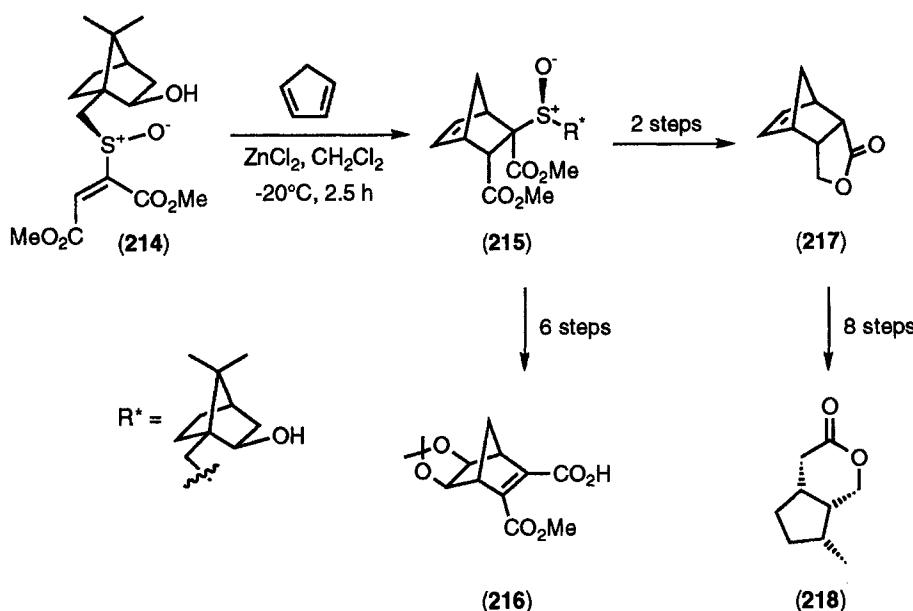


**SCHEME 5.67**



**SCHEME 5.68**

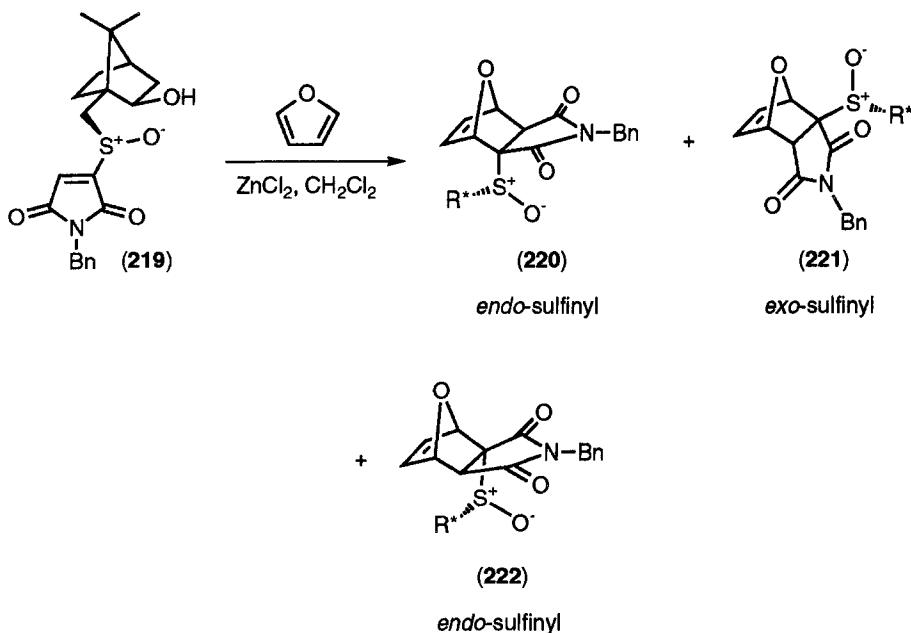
Koizumi and coworkers have developed a new enantiomerically pure  $\alpha,\beta$ -unsaturated sulfoxide dienophile bearing the isoborneol group as a chiral auxiliary, dimethyl (*R*)-2-(10-isoborneolsulfinyl)maleate (**214**), which has been successfully employed as a chiral synthetic equivalent of dimethyl acetylenedicarboxylate [174]. The dienophile (**214**) underwent cycloaddition with cyclopentadiene, in the presence of zinc chloride, with high stereo- and diastereoselectivity (92% single *endo* diastereoisomer, 6% single *exo* diastereoisomer) to yield the major cycloadduct (**215**), which was subsequently transformed into the half-ester (**216**), an intermediate in the syntheses of (–)-aristeromycin (**199**) and (–)-neplanocin A (**200**). Cycloadduct (**215**) has also recently been used for the synthesis of bicyclo[2.2.1]heptane lactone (**217**) [175,177], which itself is an intermediate in the synthesis of the iridoid (–)-boschnialactone [176] (**218**) (Scheme 5.69), and also in the formal synthesis of (–)-aristeromycin (**199**) and (–)-neplanocin (**200**) [177].



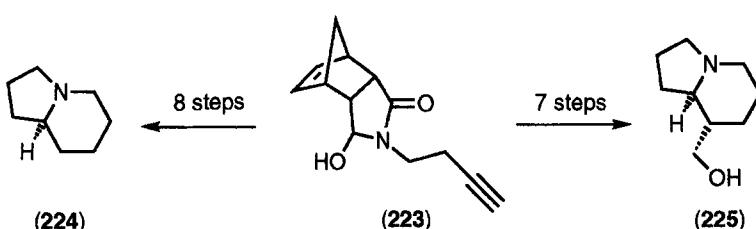
SCHEME 5.69

The enantiomerically pure dienophile (**214**) was completely unreactive towards furan. To overcome this difficulty, Koizumi and coworkers designed a new, highly reactive, enantiomerically pure  $\alpha,\beta$ -unsaturated sulfoxide dienophile bearing the isoborneol chiral auxiliary,  $\alpha$ -(2-*exo*-hydroxy-10-bornylsulfinyl)maleimide (**219**) [178] (Scheme 5.70). This dienophile has been shown to react with furan with high diastereoselectivity under mild conditions. Another advantage of using this particular dienophile for cycloaddition reactions with furan is that the reaction times are short, compared to the long reaction times required for cycloaddition

using (2-pyridylsulfinyl)acrylates such as (194), described above. Dienophile (219) underwent cycloaddition with furan in the presence of zinc chloride; however, the product ratios were entirely dependent upon reaction temperature. At 0°C, the diastereofacial selectivities for *endo*- and *exo*-sulfinyl additions were 100%, while the *endo/exo* (220)/(221) selectivity was low (71:29). In contrast, at room temperature, *endo*-sulfinyl cycloadducts were produced exclusively, although the diastereoselectivity (220)/(222) was low (55:45) (Scheme 5.70). The cycloadduct (223), synthesized by Diels–Alder cycloaddition between an  $\alpha$ -(2-*exo*-hydroxy-10-bornylsulfinyl)maleimide and cyclopentadiene, has recently been used in the asymmetric synthesis of the bicyclic alkaloids (+)-indolizidine (224) and (+)-laburnine (225) (Scheme 5.71) [179].

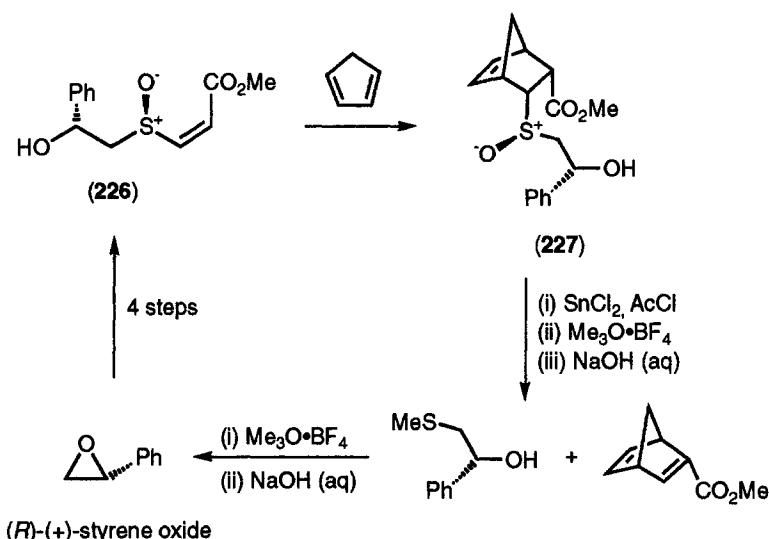


SCHEME 5.70



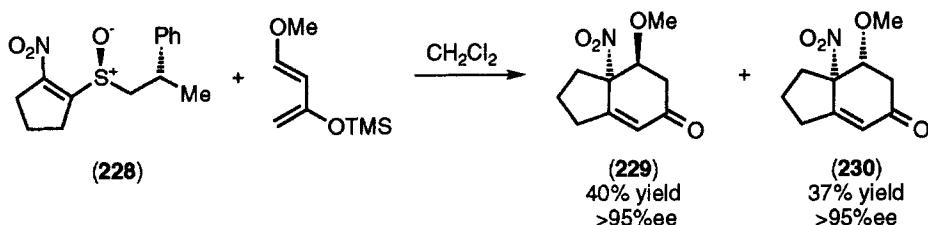
SCHEME 5.71

The use of isoborneol as a chiral auxiliary, although successful in terms of simplicity of operation and diastereofacial selectivity, suffered from a poor recovery of the auxiliary after cycloaddition, thus hampering its synthetic value. De Lucchi [180] has designed an enantiomerically pure  $\alpha,\beta$ -unsaturated sulfoxide dienophile containing a chiral auxiliary (226) derived from (*R*)-styrene oxide, which undergoes a highly diastereoselective cycloaddition with cyclopentadiene to give cycloadduct (227) which in turn, on further manipulation, allows good recovery of (*R*)-styrene oxide with no loss of *ee* from the starting epoxide (Scheme 5.72).



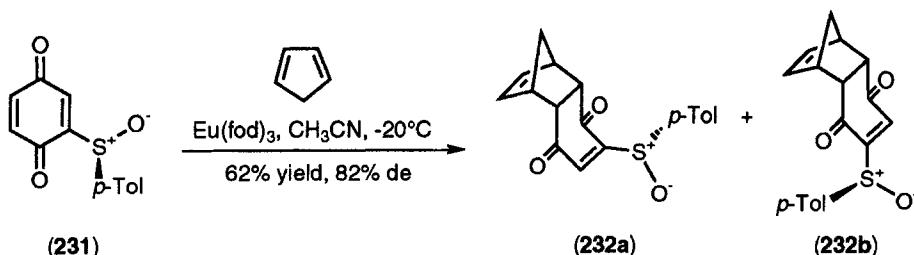
SCHEME 5.72

Recently, Fuji and coworkers have reported the enantioselective construction of a highly functionalized bicyclo[4.3.0] system through the Diels–Alder cycloaddition between Danishefsky’s diene and an enantiomerically pure  $\alpha,\beta$ -unsaturated sulfoxide substituted at the  $\beta$ -position by an electron-withdrawing nitro group [181,182]. Despite the numerous examples of diastereoselective Diels–Alder cycloadditions described above for enantiomerically pure  $\beta$ -substituted- $\alpha,\beta$ -unsaturated sulfoxide dienophiles, this is the first report of an enantioselective version of the reaction, where the chiral auxiliary is eliminated under the reaction conditions or during the workup procedure. Thus, the Diels–Alder reaction between optically active 2-alkylsulfinyl-1-nitroalkene (228) and Danishefsky’s diene afforded *endo* and *exo* cycloadducts (229) and (230) in good yields with high enantiomeric excesses (Scheme 5.73).



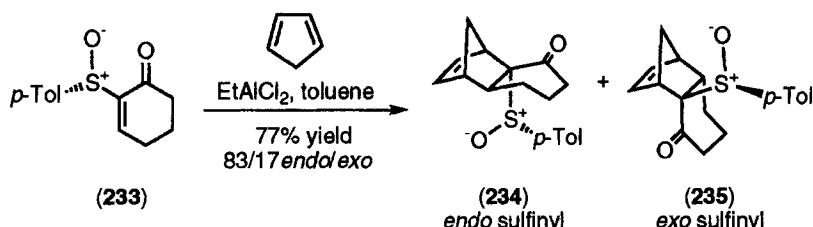
SCHEME 5.73

Carreño and colleagues [133,183] have synthesized enantiomerically pure (*S*)-2-*p*-tolylsulfinyl-1,4-benzoquinone (231), which, on cycloaddition with cyclopentadiene in the presence of a Lewis acid, gave cycloadducts (232a) and (232b) with good diastereofacial control (up to 82% *de*). The diastereoselectivity could be inverted by changing the Lewis acid used (e.g. chelation control in the case of  $\text{Eu}(\text{fod})_3$  but not in the case of  $\text{BF}_3 \cdot \text{OEt}_2$ ). In all cases, exclusive *endo* selectivity was observed (Scheme 5.74).



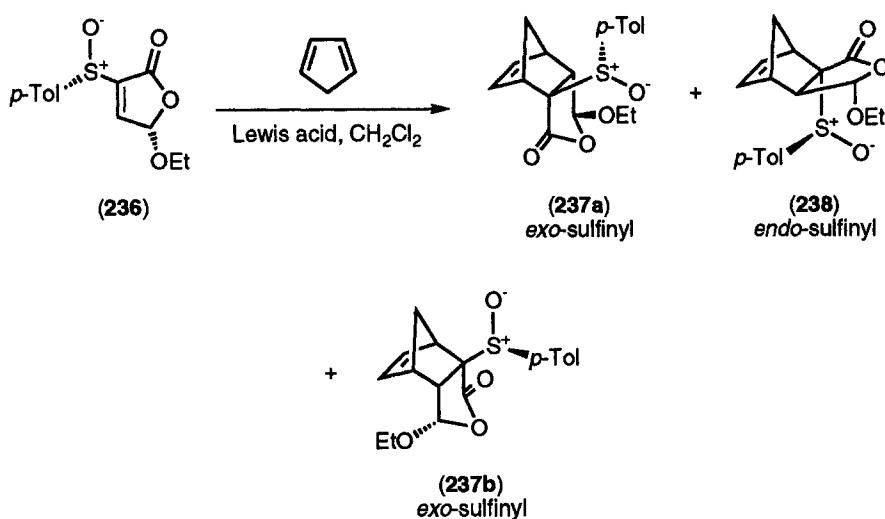
SCHEME 5.74

(*S*)-2-*p*-Tolylsulfinyl-2-cycloalkenones, such as (233), have been reported [133,184] to undergo cycloaddition with cyclopentadiene, catalysed by Lewis acids, at room temperature and with complete diastereoselectivity, but with moderate *endo/exo* selectivity, to give *endo* and *exo*-sulfinyl cycloadducts (234) and (235) in good overall yield (Scheme 5.75). As described previously, a chelation control model was used to account for the observed diastereofacial selectivity.



SCHEME 5.75

Recently, the use of enantiomerically pure  $\gamma$ -ethoxy- $\alpha$ -sulfinylbutenolides such as (236) as dienophiles in asymmetric Diels–Alder reactions with cyclopentadiene has been reported [185], giving *exo*-sulfinyl cycloadducts (237a) and (237b) and the *endo* sulfinyl adduct (238) in various proportions depending upon the reaction conditions (Scheme 5.76). In the absence of Lewis acids, the diastereofacial selectivity was thought to be controlled by the configuration at C-5 (bearing the ethoxy group), the *s-cis* conformation being the most reactive. However, the formation of the chelated species in the presence of  $ZnBr_2$  suggests that there is a significant increase in the steric hindrance to the approach of the diene towards the face supporting the *p*-tolyl group. In these circumstances, the steric effect exerted by the sulfoxide group is now greater than that of the ethoxy group. This explanation is supported by the experimental results (Table 5.7).



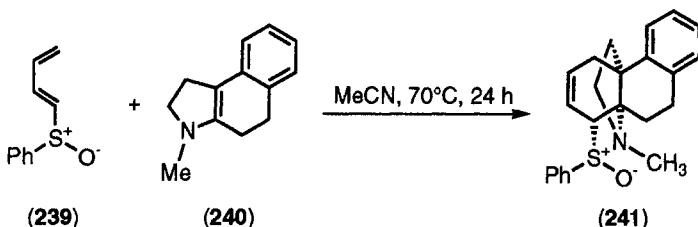
SCHEME 5.76

TABLE 5.7

Lewis acid	Temperature	Cycloadduct ratio			Yield (%)
		(237a)	(238)	(237b)	
None	RT	79	19	11	87
$ZnBr_2$	0°C	83	17	0	84
$Eu(fod)_3$	0°C	75	19	6	88

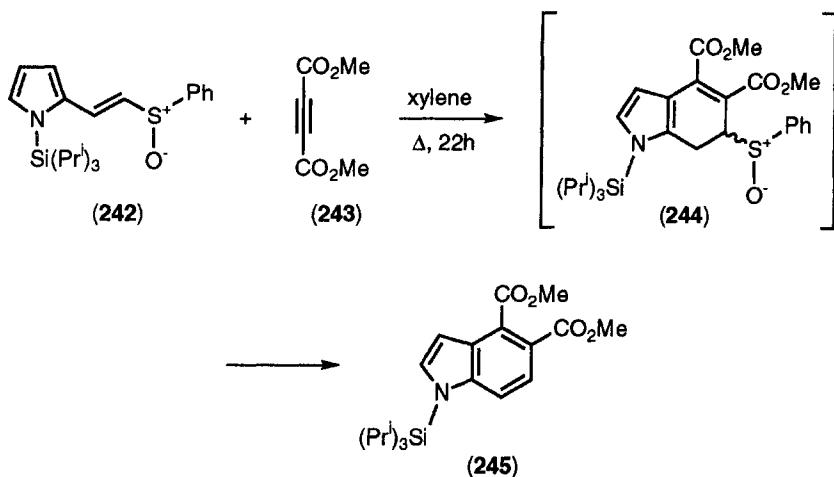
### 5.5.1.2 Dienyl sulfoxides

The earliest report of the use of  $\alpha,\beta$ -unsaturated sulfoxides as racemic diene components in Diels–Alder cycloadditions was by Evans and coworkers [186], who heated the previously unknown 1-butadienyl phenyl sulfoxide (**239**) with the tetrahydrobenzindole (**240**) to obtain cycloadduct (**241**) as a mixture of two diastereoisomers (epimeric at sulfur) (Scheme 5.77).



SCHEME 5.77

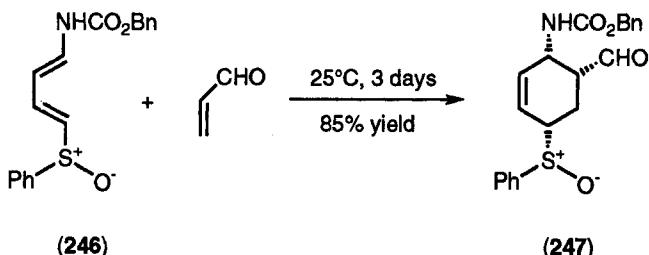
The synthesis of 4-acylindole derivatives, including (**245**), by the Diels–Alder cycloaddition between the 2-(2-phenylsulfinylvinyl)pyrrole (**242**) and electron-deficient alkynes such as (**243**), has been reported [187]. The initial cycloadduct (**244**) spontaneously aromatized under the reaction conditions to give (**245**) (Scheme 5.78).



SCHEME 5.78

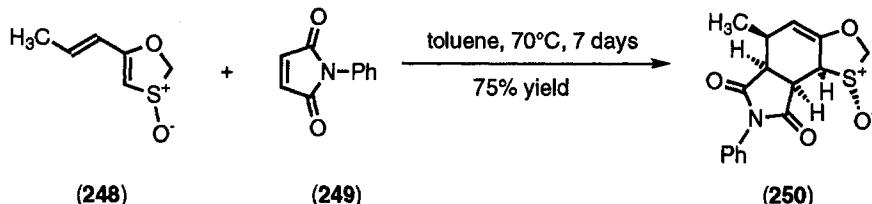
The preparation and Diels–Alder reactions of 1,3-dienes containing both sulfur and nitrogen substituents, such as (*1E,3E*)-4-(phenylsulfinyl)-1,3-butadiene-1-carbamate (**246**), have been reported [188]. Thus, the 1,3-diene (**246**) reacted with

acrolein to give exclusively the *endo* cycloadduct (**247**) as a mixture of two diastereoisomers (epimeric at sulfur) (Scheme 5.79). It should be noted that the acylamino substituent had a stronger influence on the regioselectivity of the reaction than did the phenylsulfinyl group.



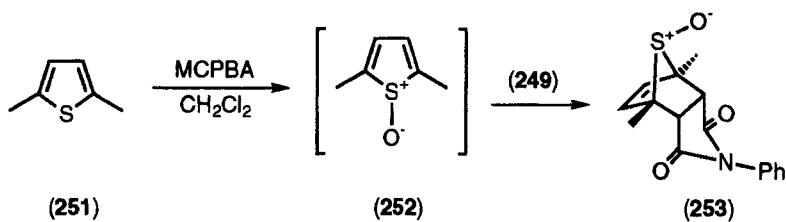
SCHEME 5.79

Overman and coworkers have reported the synthesis and Diels–Alder reactions of 5-alkenyl-1,3-oxathiole-3-oxides such as (**248**), a new class of diheterosubstituted 1,3-dienes [189]. The Diels–Alder reactivity of these substrates proved disappointing. For example, diene (**248**) failed to give a cycloadduct when heated with neat acrolein at 80°C, but reacted smoothly when heated with the more electron-deficient dienophile *N*-phenylmaleimide (**249**) to give exclusively the *endo* cycloadduct (**250**), diastereoisomerically pure (Scheme 5.80). The Diels–Alder reaction between 3-(*p*-tolylsulfinyl)-2-(trimethylsilyloxy)-1,3-butadiene and methyl acrylate has been reported to give the corresponding cycloadducts as a mixture of regioisomers, although no discussion of the stereochemical outcome of the reaction was given [190].



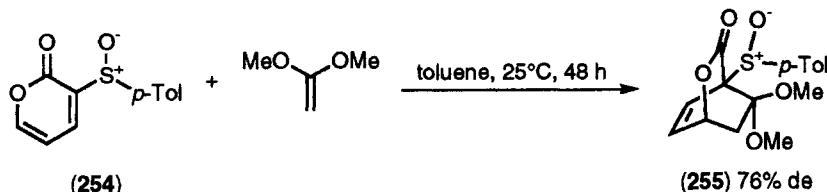
SCHEME 5.80

Fallis and coworkers have used 2,5-dimethylthiophene oxide (**252**), generated *in situ* by peracid oxidation of 2,5-dimethylthiophene (**251**), as a diene in the Diels–Alder reaction with various dienophiles including *N*-phenylmaleimide (**249**) [191]. In all cases, the *syn* cycloadduct (with respect to the sulfoxide oxygen) was formed exclusively (Scheme 5.81).

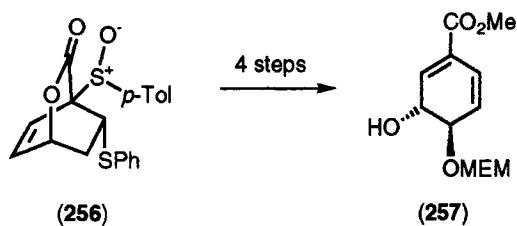


**SCHEME 5.81**

Racemic pyrone sulfoxide (**254**), an electrophilic diene, has been reported [13,192,193] to undergo an inverse electron demand Diels–Alder cycloaddition with 1,1-dimethoxyethylene to give the major cycloadduct (**255**) in high yield under mild conditions, and with good stereoselectivity (Scheme 5.82). The cycloadduct (**256**), prepared by the reaction between pyrone sulfoxide (**254**) and phenyl vinyl thioether, has been used in the stereocontrolled synthesis of the cyclohexadiene (**257**), a key intermediate in the synthesis of chorismic acid (Scheme 5.83) [194].



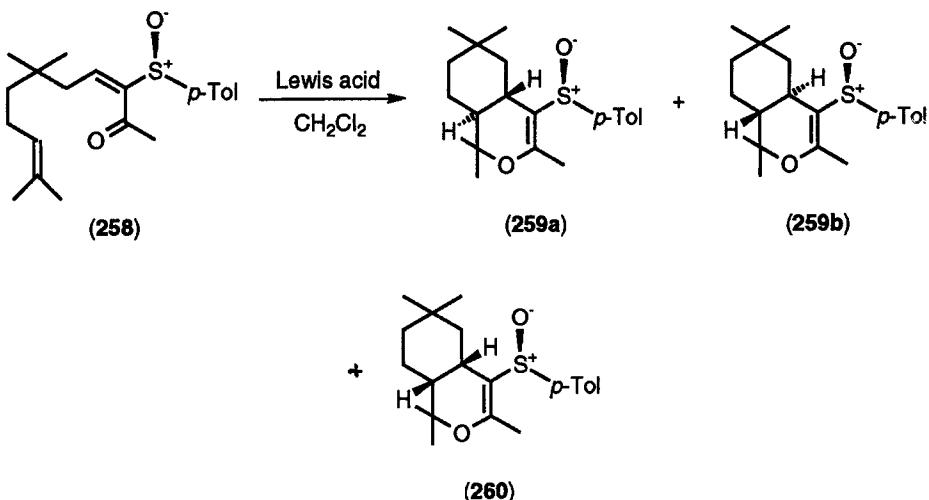
**SCHEME 5.82**



**SCHEME 5.83**

The first example of an intramolecular asymmetric Diels–Alder reaction of a diene bearing an optically active sulfinyl group has recently been reported [195]. The reaction of the  $\alpha$ -keto- $\alpha,\beta$ -unsaturated sulfoxide (**258**) in the presence of various monodentate Lewis acids (see Table 5.8) gave the nonracemic hetero-

Diels–Alder cycloadducts (**259a**) and (**259b**) (*trans*-fused adducts) with moderate to high diastereoisomeric excess, plus a small amount of the *cis*-fused adduct (**260**) (Scheme 5.84).



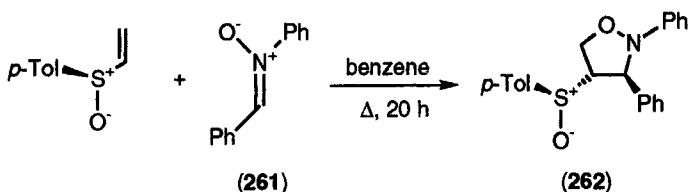
SCHEME 5.84

TABLE 5.8

Lewis acid	Reaction conditions		Yield (%) of ( <b>259</b> ) and ( <b>260</b> ) (Ratio of ( <b>259</b> ) : ( <b>260</b> ))	de (%) of ( <b>259</b> )
	$T$ (°C)	Time (h)		
$\text{Et}_2\text{AlCl}$	−78	1	99 (96:4)	81.7
$\text{EtAlCl}_2$	−78	1	96 (84:16)	83.8
$\text{BF}_3 \cdot \text{OEt}_2$	0	2	89 (74:26)	75.3
$\text{FeCl}_3$	0	2	45 (89:11)	39.4

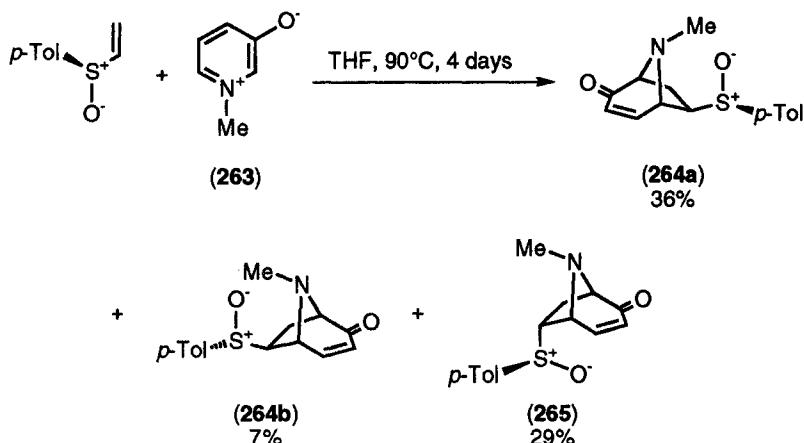
### 5.5.2 [3+2] Cycloadditions of $\alpha,\beta$ -Unsaturated Sulfoxides

The first report of the use of optically active  $\alpha,\beta$ -unsaturated sulfoxides as dipolarophiles was by Koizumi *et al.* in 1982 [196] and preceded the first report of their use as optically active dienophiles, despite the fact that the vast majority of subsequent work in this area has been in the use of dienophiles in asymmetric Diels–Alder reactions. The 1,3-dipolar cycloaddition between (*R*)-(+)–*p*-tolyl vinyl sulfoxide and acyclic nitrones such as (**261**) gave the major cycloadducts such as (**262**) (90% *de*) in 57% overall yield (Scheme 5.85).



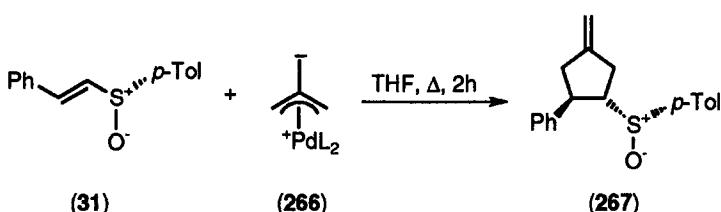
SCHEME 5.85

Koizumi and coworkers have recently reported an asymmetric 1,3-dipolar cycloaddition between (*R*)-(+)-*p*-tolyl vinyl sulfoxide and cyclic dipoles such as 1-methyl-3-oxidopyridinium salt (263) to give the cycloadducts (264a), (264b), and (265) in the ratios shown (Scheme 5.86) [197]. The major cycloadduct results from addition of the dipolar species from the face of the sulfoxide containing the lone pair, assuming that the dipolarophile reacts from an *s-trans* conformation.



SCHEME 5.86

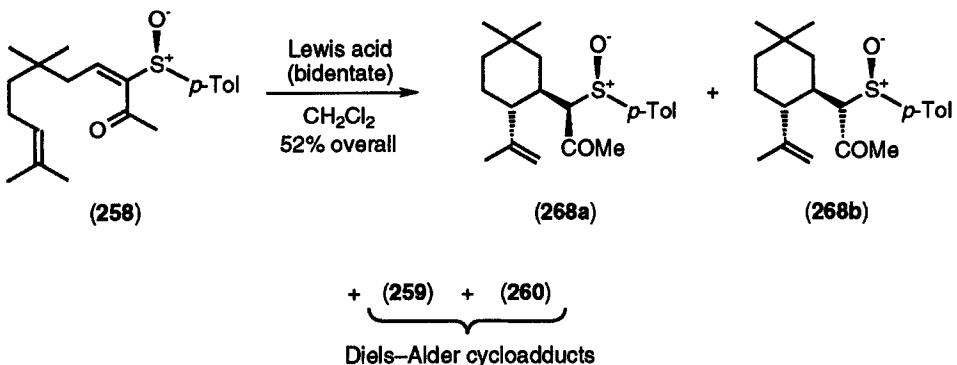
The palladium-catalyzed [3+2] cycloaddition reaction between enantiomerically pure  $\alpha,\beta$ -unsaturated sulfoxides and trimethylenemethane (266), using the methodology developed by Trost [198], has been reported [199]. Thus, reaction of the sulfoxide (31), 2-acetoxymethyl-3-allyltrimethylsilane (2 eq), palladium acetate (5 mol%), and triisopropylphosphite (20 eq) in THF under reflux gave the major cycloadduct (267) in 80% yield and 80% *de* (Scheme 5.87). Moderate to good levels of asymmetric induction were observed for various  $\alpha,\beta$ -unsaturated sulfoxides.



**SCHEME 5.87**

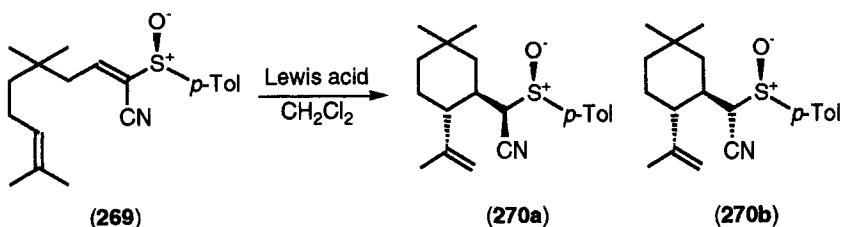
### 5.5.3 Ene Reactions of $\alpha,\beta$ -Unsaturated Sulfoxides

Recently, Hiroi and coworkers published the first examples of asymmetric ene reactions using chiral  $\alpha,\beta$ -unsaturated sulfoxides.  $\alpha$ -Keto- $\alpha,\beta$ -unsaturated sulfoxide (**258**), in dichloromethane in the presence of bidentate Lewis acids, undergoes an asymmetric ene reaction in addition to the intramolecular Diels–Alder reaction discussed above (Scheme 5.84) [195]. Thus, in the presence of zinc bromide, (**258**) reacts to give the ene products (**268a**) and (**268b**) in the ratio 73:27 and 52% yield in addition to a 42% yield of Diels–Alder cycloadducts (Scheme 5.88). It should be noted that, in the presence of monodentate Lewis acids, the reaction of (**258**) produces no ene products.



**SCHEME 5.88**

The chiral  $\alpha$ -cyano- $\alpha,\beta$ -unsaturated sulfoxide (**269**) has been shown to be an efficient enophile in a Lewis acid-catalysed intramolecular ene reaction [200,201]. Of the Lewis acids tested, the use of diethylaluminium chloride in dichloromethane gave particularly high diastereoselectivities (97% *de*) (Scheme 5.89). The results obtained using various Lewis acids are summarized in Table 5.9, in each case the major product being diastereoisomer (**270a**).



**SCHEME 5.89**

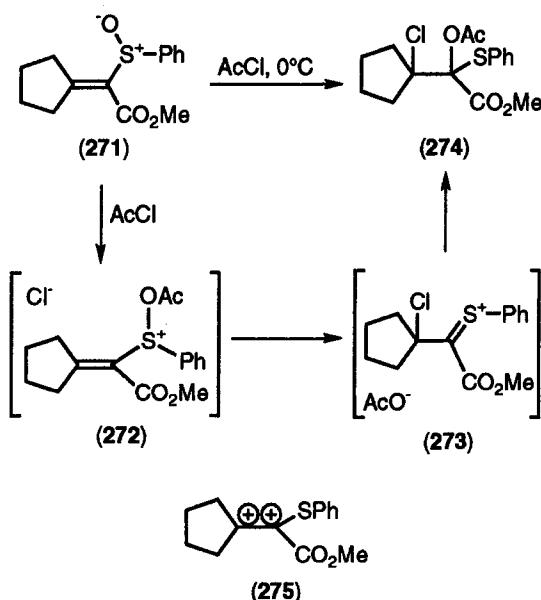
TABLE 5.9

Lewis acid	Temperature	Time (h)	(270) Yield (%)	de (%)
ZnCl <sub>2</sub>	RT	12	61	78
ZnBr <sub>2</sub>	RT	18	82	77
ZnI <sub>2</sub>	RT	17	70	66
Et <sub>2</sub> AlCl	-20°C	2	62	97
EtAlCl <sub>2</sub>	-78°C	12	34	95
Me <sub>3</sub> Al	0°C	4	22	20
Bu <sup>i</sup> <sub>3</sub> Al	0°C	4	26	31
BF <sub>3</sub> .OEt <sub>2</sub>	RT	22	27	57

## 5.6 REARRANGEMENTS INVOLVING $\alpha,\beta$ -UNSATURATED SULFOXIDES

### 5.6.1 The Additive Pummerer Rearrangement

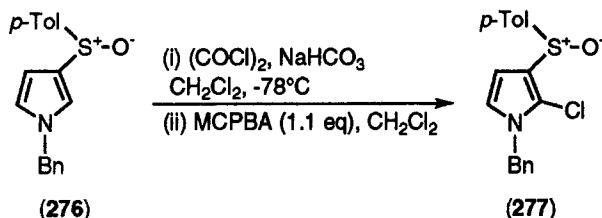
The Pummerer reaction is a well-established procedure in organic synthesis [202]. The related additive Pummerer reaction of  $\alpha,\beta$ -unsaturated sulfoxides has been known for many years, and the reaction mechanism can be illustrated by the following example [203,204]. Reaction at the sulfinyl oxygen atom of racemic (271) with an electrophile (AcCl) gives a highly reactive intermediate (272) in which the  $\beta$ -position is activated by the positively charged sulfur atom. Addition of a nucleophile ( $\text{Cl}^-$ ) at the  $\beta$ -position results in cleavage of the  $\text{S}=\text{O}$  bond to yield a sulfenium intermediate (273). Attack by a second nucleophile ( $\text{AcO}^-$ ) gives an  $\alpha,\beta$ -disubstituted thioether (274). In this reaction, the  $\alpha,\beta$ -unsaturated sulfoxide is thus synthetically equivalent to a thioether  $\alpha,\beta$ -dication (275) (Scheme 5.90). An analogous type of reaction can also be accomplished using thionyl chloride or trifluoroacetic anhydride as the electrophilic species [204].



SCHEME 5.90

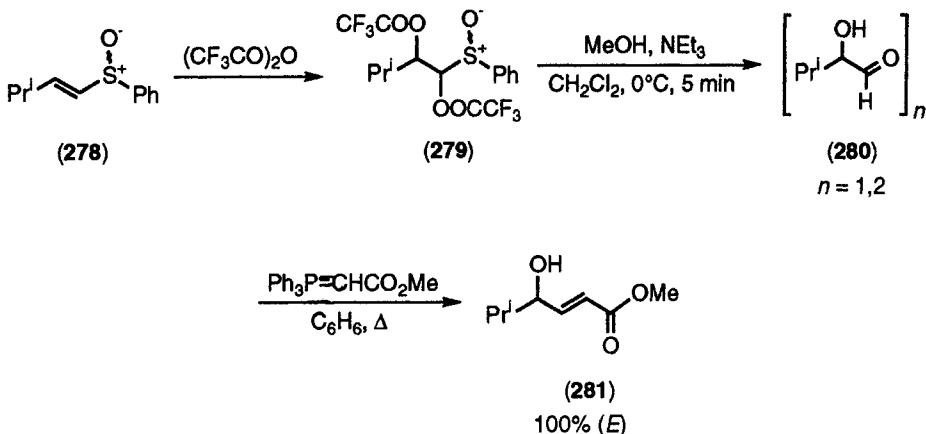
Additive Pummerer reactions of the type described above using racemic  $\alpha,\beta$ -unsaturated sulfoxides can be accomplished using the following electrophiles: acyl chlorides [205,206], dithioacetic acid [207], acetic anhydride [208], mineral acids/alcohols [209], phosphorus pentachloride [210], silyl ketene acetals/zinc iodide [211], thionyl chloride [212], oxalyl chloride [213], trifluoroacetic acid and its anhydride [214–218], triflic anhydride/sodium acetate [219], and dichloroketene (see below). Selected recent examples of work in this area are presented here.

Greenhouse and colleagues have reported the regiospecific introduction of chlorine atoms into the 2-position of pyrrol-3-yl and indol-3-yl sulfoxides using oxalyl chloride [213]. For example, the pyrrol-3-yl sulfoxide (276), on treatment with oxalyl chloride followed by *m*-chloroperbenzoic acid oxidation (1.1 eq), gives the 2-chloro-substituted product (277) in 83% yield (Scheme 5.91).



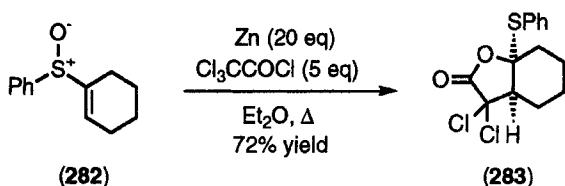
SCHEME 5.91

The products resulting from the additive Pummerer reaction of  $\alpha,\beta$ -unsaturated sulfoxides with trifluoroacetic anhydride have been converted into  $\gamma$ -hydroxy- $\alpha,\beta$ -unsaturated esters and  $\alpha$ -hydroxyketones in high yields [216]. For instance,  $\alpha,\beta$ -unsaturated sulfoxide (278) undergoes an additive Pummerer rearrangement to give the corresponding  $\alpha,\beta$ -bis(trifluoroacetoxy)thioether (279) in 95% yield, which was then treated with triethylamine in methanol, yielding a mixture of  $\alpha$ -hydroxy aldehyde monomer (280) and dimer. Reaction of (280) with methoxycarbonylmethylenetriphenylphosphorane in boiling benzene gave the  $\gamma$ -hydroxy- $\alpha,\beta$ -unsaturated ester (281) in 95% yield from (279) (Scheme 5.92). Treatment of the substrates of type (278) with sodium acetate and triflic anhydride leads to rearrangement of the sulfenium intermediate, yielding 2-(phenylsulfenyl)acylals [219].



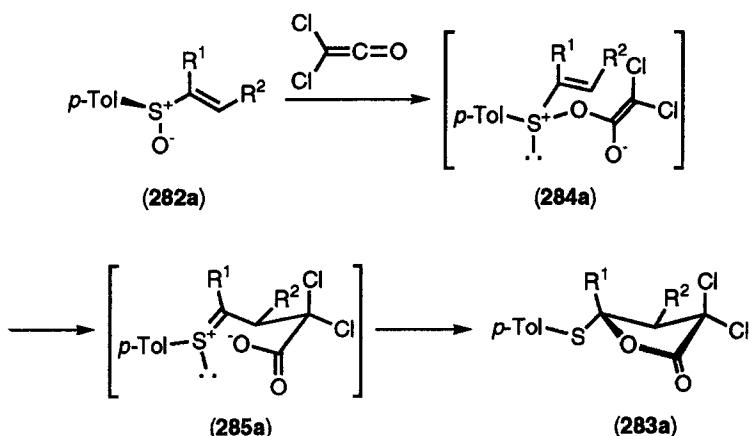
**SCHEME 5.92**

The first report concerning the additive Pummerer reaction of  $\alpha,\beta$ -unsaturated sulfoxides with dichloroketene appeared in 1981 [220], and work in this area has recently been reviewed [221]. Simple  $\alpha,\beta$ -unsaturated sulfoxides such as (282) react with dichloroketene (generated from the addition of trichloroacetyl chloride to zinc) to produce diastereoisomerically pure *cis*- $\gamma$ -butyrolactones such as (283) (Scheme 5.93) [220].



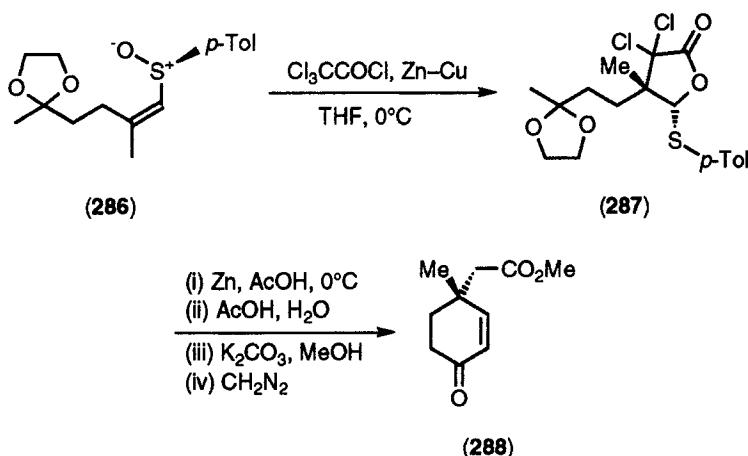
**SCHEME 5.93**

Subsequent work by the same group [222,223] demonstrated that the reaction was very highly enantioselective for optically pure cyclic or acyclic trisubstituted  $\alpha,\beta$ -unsaturated sulfoxides where the  $\alpha$ - and  $\beta$ -substituents were carbon-containing groups. For example, reaction of *(R)*- $(+)$ -1-(*p*-tolylsulfinyl)cyclohexene (**282a**) with dichloroketene gave a single enantiomer of product (**283a**) in 70% yield [222]. Conformational analysis [223] of the reaction pathway points to the intermediacy of a pseudochair conformation for the oxysulfonium species (**284a**), with the *p*-tolyl group preferring a pseudoequatorial position. This then undergoes [3,3]-sigmatropic rearrangement to give the Pummerer-type intermediate sulfenium species (**285a**). Intramolecular attack by the carboxylate anion gives the product (**283a**) with complete enantioselectivity (Scheme 5.94).



SCHEME 5.94

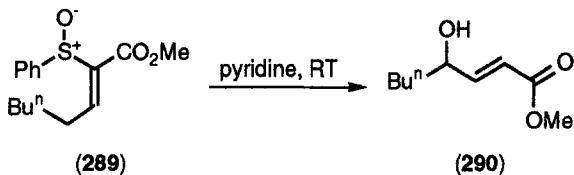
The synthetic utility of the additive Pummerer rearrangement reaction of enantiomerically pure trisubstituted  $\alpha,\beta$ -unsaturated sulfoxides has been illustrated by the asymmetric synthesis of several natural products or their key intermediates utilizing this reaction as an important step [224–228]. The use of indole sulfoxides in this context has also been demonstrated, with application to the enantioselective synthesis of *(-)*-physostigmine by Marino and coworkers [222,228]. Recently, Kosugi *et al.* have reported the synthesis of enantiomerically pure  $\beta,\beta$ -disubstituted  $\gamma$ -lactones such as (**287**) through the reaction of  $\beta,\beta$ -disubstituted  $\alpha,\beta$ -unsaturated sulfoxide (**286**) with dichloroketene [229]. The initial product (**287**) was then transformed into the corresponding 4,4-disubstituted cyclohex-2-enone (**288**) in enantiomerically pure form in three steps (Scheme 5.95). The highly enantioselective reaction of an optically active dienyl sulfoxide with dichloroketene has also been reported as part of the synthesis of the drimane sesquiterpenes, *(+)*-fragolide and *(-)*-pereniporin B [230].



**SCHEME 5,95**

## 5.6.2 [2,3]-Sigmatropic Rearrangements

Sammes and coworkers [23,24] observed that treatment of  $\alpha,\beta$ -unsaturated sulfoxides such as (289) with tertiary amine bases causes  $\alpha,\beta$ - to  $\beta,\gamma$ -isomerization of the double bond followed by the well-known [2,3]-sigmatropic rearrangement of the allylic sulfoxide [231] and collapse of the sulfenate species to the product alcohol (290) (Scheme 5.96).



**SCHEME 5.96**

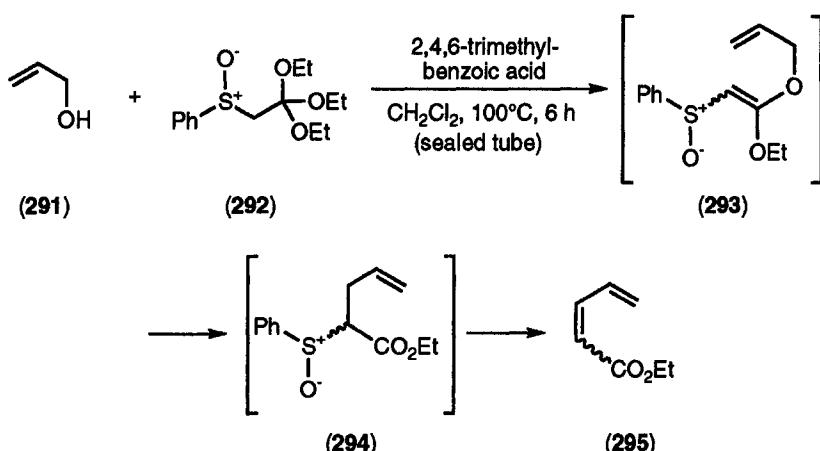
### 5.6.3 [3,3]-Sigmatropic Rearrangements

[3,3]-Sigmatropic rearrangements have been described above as part of the proposed mechanism of additive Pummerer rearrangements such as the reaction between  $\alpha,\beta$ -unsaturated sulfoxides and dichloroketene [220]. De Lucchi *et al.* have observed a similar type of rearrangement with isopropenyl acetate under acidic conditions [232].

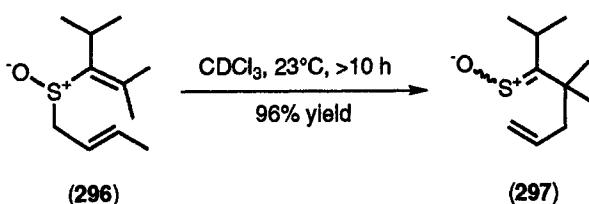
Posner and colleagues have recently made use of a [3,3]-sigmatropic rearrangement of an  $\alpha,\beta$ -unsaturated sulfoxide as part of a regiospecific conversion of allylic alcohols into two-carbon-extended conjugated dienoate esters [233]. For example, reaction of allyl alcohol (**291**) with the sulfinyl orthoester (**292**) and a catalytic amount of 2,4,6-trimethylbenzoic acid in dichloromethane at 100°C produced ethyl pentadienoate (**295**) in 75% yield. The reaction is believed to

proceed via the intermediate (293), which undergoes [3,3]-sigmatropic rearrangement to (294), which in turn gives the product (295) as a 1:4 mixture of (*Z*) and (*E*) geometric isomers (Scheme 5.97).

The [3,3]-sigmatropic rearrangement of allyl vinyl sulfoxides (thio-Claisen rearrangement) is known to proceed under mild conditions compared to the analogous rearrangements using allyl vinyl sulfides and sulfones, which require elevated temperatures [234–237]. The increase in rate of rearrangement is accounted for by the zwitterionic character of the sulfoxide group and was thought to accelerate rearrangement in a similar way as for cation- or anion-accelerated rearrangements. Thus, the racemic allyl vinyl sulfoxide (296), prepared by mCPBA oxidation of the corresponding sulfide, undergoes [3,3]-sigmatropic rearrangement to the thione *S*-oxide (297) under neutral conditions at 23°C (Scheme 5.98) [236,237].



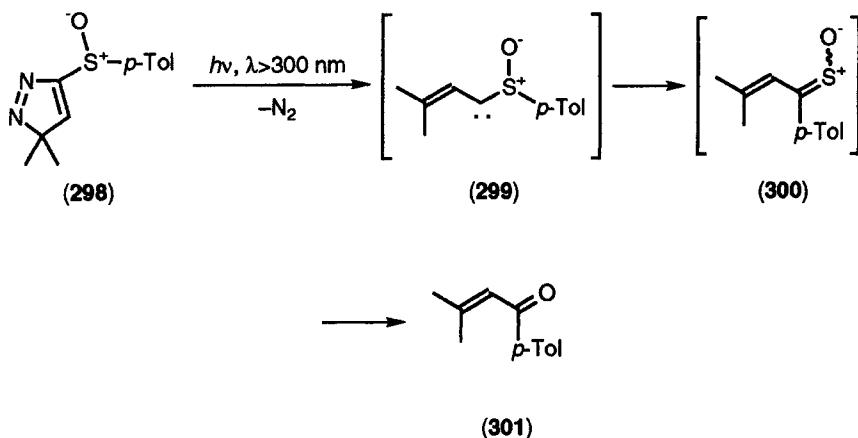
SCHEME 5.97



SCHEME 5.98

### 5.6.4 Miscellaneous Rearrangements

Franck-Neumann and Lohmann have reported [238] that photolysis of the sulfinylpyrazolenine (298) generates the sulfinylcarbene (299), which undergoes a novel rearrangement leading to the sulfine (300), followed by the product (301) in 96% overall yield (Scheme 5.99).



SCHEME 5.99

## 5.7 CONCLUSION

It is evident from this review that  $\alpha,\beta$ -unsaturated sulfoxides are powerful and versatile synthetic intermediates. The methods now available for the synthesis of enantiomerically pure sulfoxides will result in their increasing importance in asymmetric synthesis as a result of the unique character of the sulfoxide functional group and its ability to exert a strong stereocontrolling influence. We hope this review will help to stimulate further research in this important, rapidly developing area.

## ACKNOWLEDGEMENTS

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# PREPARATION OF SUBSTITUTED 3-SULFOLENES AND THEIR USE AS PRECURSORS FOR DIELS–ALDER DIENES

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## 6.1 INTRODUCTION

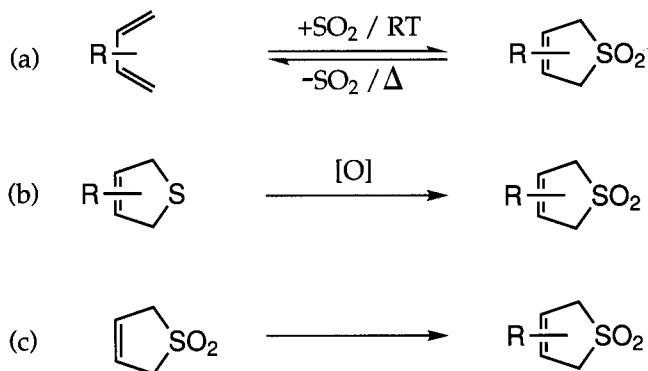
Over recent years substituted 3-sulfolenes have attracted great interest as intermediates in organic synthesis. This is largely because they are easily converted to dienes by cheletropic extrusion of  $\text{SO}_2$ . Such pericyclic processes are

stereospecific (disrotatory) and it is useful that dienes are normally formed as a single isomer of predictable geometry. The sulfolene ring can therefore have two functions: it can simply act as a masking group to allow a potential diene to be carried through a number of otherwise incompatible synthetic steps; or the sulfolene nucleus can act as a template for assembling functionality around a potential diene in a predictable manner. In either case,  $\text{SO}_2$  extrusion from the sulfolene leads to a diene, which is most commonly utilized in a Diels–Alder reaction. Both cheletropic  $\text{SO}_2$  extrusions and Diels–Alder reactions are normally induced by heating, and it is often possible to carry out the two steps consecutively, without isolation of the intermediate diene.

The main part of this chapter is split into four sections, each of which highlights a particular aspect of the chemistry of sulfolenes which is important to those contemplating the use of sulfolene intermediates in organic synthesis. In the first section we describe some important methods for construction of particular sulfolene nuclei; in the second section we review methods for installing substituents selectively into various sulfolene rings; in the third section we consider the selective formation of dienes from sulfolenes; and finally we use examples to illustrate how dienes generated from sulfolene intermediates have been incorporated in Diels–Alder based synthetic routes.

## 6.2 PREPARATION OF SUBSTITUTED 3-SULFOLENES

There are three general approaches to the synthesis of substituted sulfolenes, as represented in Scheme 6.1:



SCHEME 6.1

- (a) The classic way to prepare sulfolenes is by treating a presubstituted diene directly with liquid  $\text{SO}_2$ . The yields for such processes are generally favourable, particularly for simple dienes, and early work in this field has been reviewed [113].

- (b) Substituted 3-sulfolenes are commonly prepared via substituted 2,5-dihydrothiophene intermediates, which are easily oxidized to give the 1,1-dioxide (sulfolene).
- (c) 3-Sulfolene and other simple analogues are readily available from dienes (as above) and many are commercially available. There are various ways in which these can be selectively substituted to provide more highly functionalized sulfolenes as diene precursors. Section 6.3 concentrates on such processes.

This review will concentrate on ways in which functionality can be assembled around the sulfolene nucleus, to provide useful masked diene precursors for Diels–Alder reactions. We therefore make only brief mention of ways in which  $\text{SO}_2$  has been added to dienes. Such reactions are used mainly to prepare simple sulfolenes, or to mask existing dienes [113].

### 6.2.1 The Synthesis of Simple Substituted 3-Sulfolenes via 2,5-Dihydrothiophenes

Dihydrothiophenes are very easily oxidized to sulfolenes by a variety of oxidizing agents. Accordingly, a common approach to sulfolenes is to construct a substituted dihydrothiophene first, then oxidize it. The synthesis of dihydrothiophenes has been reviewed [11]. As the approaches to sulfolenes are very wide ranging, we illustrate general strategies which are frequently employed to provide common basic types of sulfolene unit. We also exemplify the preparation of commonly used sulfolene ring systems.

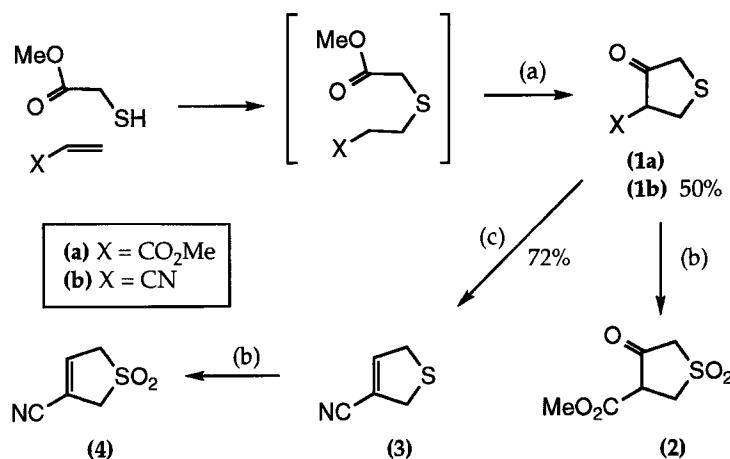
#### 6.2.1.1 *Michael–Diekmann approaches to sulfolenes*

Michael additions of  $\alpha$ -mercaptopacetates to  $\alpha,\beta$ -unsaturated systems, followed by Diekmann or aldol-type cyclization, provide access to hydrothiophenes, such as (1), which are useful precursors for a variety of sulfolenes, Scheme 6.2 [27,115]. The ester group of ketoester (1a) can be manipulated to provide a range of substituents. The ketone group can then be reduced to an alcohol, and after this has been eliminated, the resultant dihydropyran can be oxidized to a 3-sulfolene. 3-Cyano-3-sulfolene (4) is of general utility and can be efficiently prepared by this strategy from intermediate cyanoketone (1b) [9,10]. Other sulfolenes can be prepared by analogous methods.

#### 6.2.1.2 *The McIntosh and Sieler approach to 3-substituted sulfolenes*

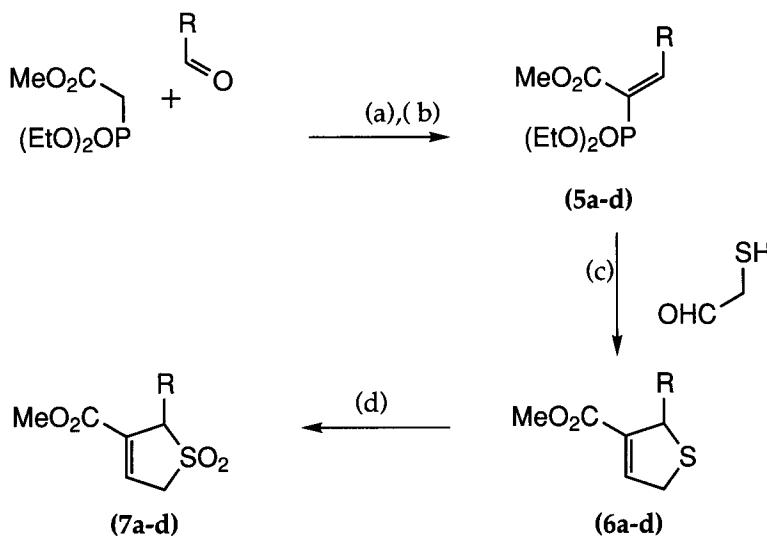
Dienes with a mesomerically electron withdrawing group in the 2-position are often unstable and are prone to dimerization. 3-Sulfolenes bearing a mesomerically electron withdrawing group at the 3-position have therefore become established as useful stable precursors for their equivalent dienes.

Perhaps the most commonly employed route to 3-carbomethoxy-3-sulfolenes is the elegant method reported by McIntosh and Sieler [83,84]. In the first step of the



**SCHEME 6.2** (a)  $\text{NaOMe}/\text{MeOH}$ ; (b)  $m\text{CPBA}$ ; (c) (i)  $\text{NaBH}_4$ , (ii)  $\text{MsCl}/\text{Et}_3\text{N}$

preparation, methyl diethylphosphonoacetate is condensed with an aldehyde, to provide vinylphosphonates (**5a-d**). When  $\alpha$ -mercaptopropanaldehyde is added to the vinylphosphonate it undergoes a Michael addition followed by subsequent ring closure, to provide the substituted dihydrothiophene (**6a-d**). Finally, oxidation with *m*-chloroperoxybenzoic acid (*m*CPBA) gives the sulfolene (**7a-d**) (Scheme 6.3, Table 6.1).



**SCHEME 6.3** (a) Morpholine (cat.)  $\text{MeOH}/\text{reflux}$ ; (b)  $p\text{-TsOH}/\text{toluene}/\text{reflux}$ ; (c)  $\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2/\text{reflux}$ ; (d)  $m\text{CPBA}/\text{CH}_2\text{Cl}_2/0^\circ\text{C}$

TABLE 6.1

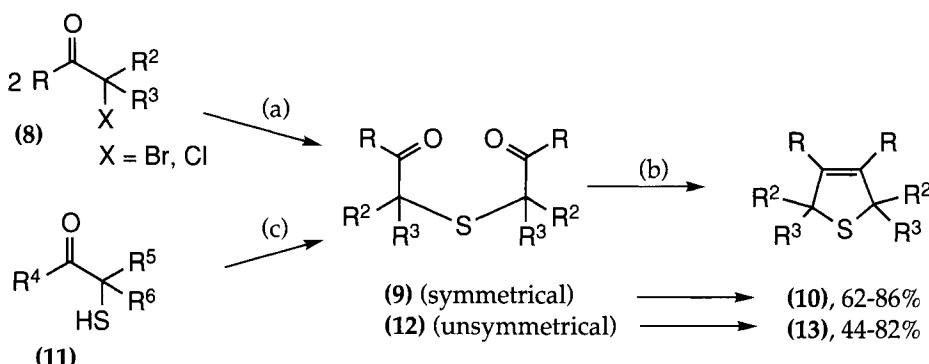
R	Entry (6)	Yield (5) (%)	Yield (6) (%)	Yield (7) (%)
H	(a)	76	68	90
Ph	(b)	55	91	50
c-C <sub>6</sub> H <sub>11</sub>	(c)	74	88	87
Pr <sup>n</sup>	(d)	87	75	86

Analogues of  $\alpha$ -mercaptopropanaldehyde were also used in this route to incorporate substituents at C-5. This approach to sulfolenes has been adapted by several other workers to provide useful diene precursors. In our laboratory we have recently developed a modification of the synthetic procedure to provide 3-carbomethoxy-3-sulfolene on a large scale, in one pot, and using cheaper reagents than the original method [74].

### 6.2.1.3 Approaches involving nucleophilic displacement by sulfur

Many approaches to dihydrothiophenes rely on an intramolecular nucleophilic displacement by a thiol group to bring about cyclization. Some examples of such procedures are given below, but we will not give a comprehensive review here.

An interesting strategy for the construction of 2,5-dihydrothiophenes employed nucleophilic displacement to introduce the sulfur atom into a diketone intermediate (**9**) or (**12**). This was followed by an intramolecular reductive coupling of the diketosulfide, using a low-valent titanium reagent generated *in situ* [88] (Scheme 6.4). Either symmetrical or unsymmetrical compounds could be prepared and converted to sulfolenes by treatment with mCPBA.

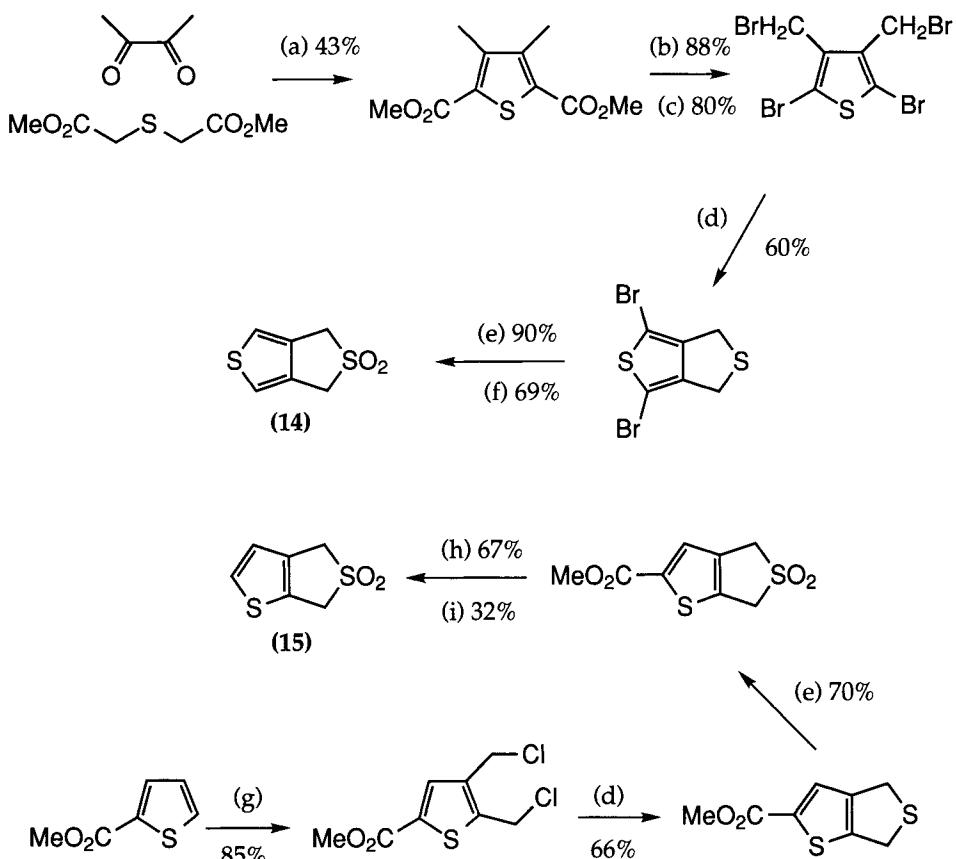
SCHEME 6.4 (a) Na<sub>2</sub>S; (b) TiCl<sub>4</sub>-Zn; (c) **(8)** + **(11)** /base

### 6.2.1.4 Preparation of sulfolenes fused to heteroaromatic rings

The preparation of 2,3-dimethylene heteroaromatics (DMHAs), as analogues of orthoquinonodimethanes, has attracted a good deal of attention in recent years. Such systems are often quite labile, and one of the most commonly employed synthetic strategies to them has been to build the required heteroaromatic ring fused to a sulfolene, as a direct precursor to the DMHA [79]. Some interesting work has been done on Diels–Alder reactions from DMHAs derived from fused sulfolenes, and these are covered in more detail in Section 6.5.

### 6.2.1.5 Preparations of DMHA precursors starting from the parent heterocycle

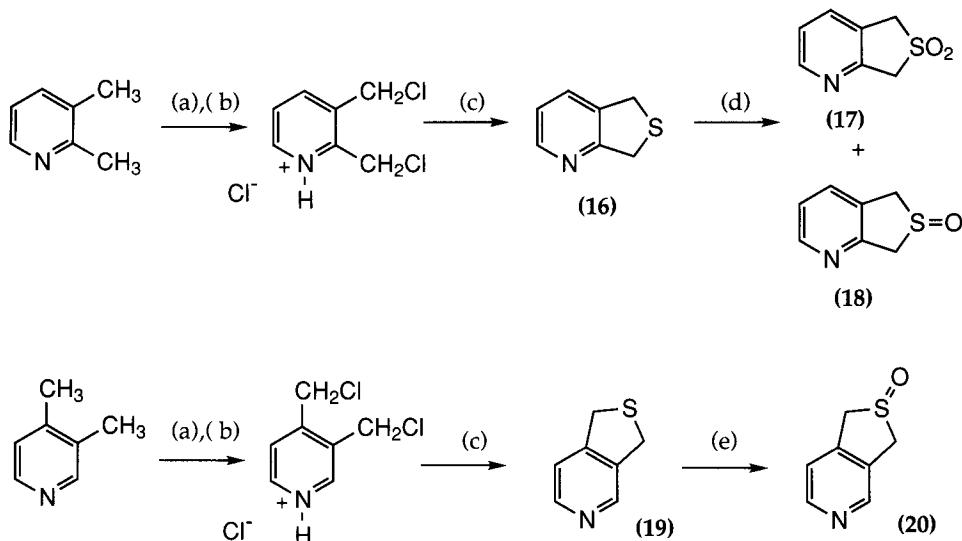
Several approaches to DMHAs start from a parent heterocyclic precursor to which a fused sulfolene ring is added, prior to  $\text{SO}_2$  extrusion.



**SCHEME 6.5** (a)  $\text{NaH}/\text{DMSO}$ ; (b)  $\text{NaOH}/\text{H}_2\text{O}$  followed by  $\text{Br}_2$ ; (c)  $\text{NBS}/\text{dibenzoyl peroxide}$ ; (d)  $\text{Na}_2\text{S}/\text{MeOH}$ ; (e)  $\text{H}_2\text{O}_2/\text{AcOH}/\text{Zn}/\text{dioxane}/\text{AcOH}$ ; (g)  $\text{ClCH}_2\text{OCH}_3/\text{ZnCl}_2$ ; (h)  $\text{KOH}/\text{H}_2\text{O}$  followed by  $\text{Br}_2$ ; (i)  $\text{Pd/C}/\text{MeOH}$

Thiophene-fused sulfolenes (**14**) and (**15**) were first synthesized some time ago [119,120] as outlined in Scheme 6.5, but their chemistry was not investigated at that time.

The pyridinosulfolenes were synthesized later using similar chemistry [64]. These workers were mainly interested in preparing the sulfoxides (**18**) and (**20**), but the sulfolenes could also be prepared from the unstable dihydrothiophenes (**16**) and (**19**), by treatment with mCPBA (Scheme 6.6).

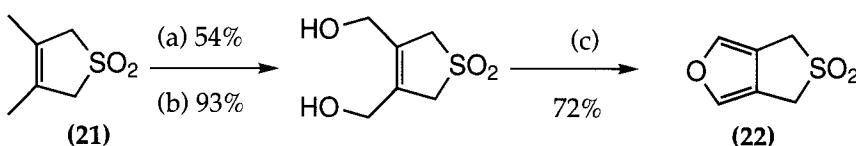


**SCHMЕE 6.6** (a) NCS/Δ/hv/CCl<sub>4</sub>; (b) HCl; (c) Na<sub>2</sub>S; (d) mCPBA; (e) C<sub>6</sub>H<sub>5</sub>ICl<sub>2</sub>/H<sub>2</sub>O

### 6.2.1.6 Preparations of DMHA precursors starting from sulfolenes

An obvious and common approach is to build a heteroaromatic ring onto a sulfolene.

The group of Takayama has carried out a considerable amount of work in this area and this has been reviewed [2]. They prepared the previously unknown furan annelated 3-sulfolene (**22**) in a facile three-step procedure, from 3,4-dimethyl-3-sulfolene (**21**) (Scheme 6.7) [103]. Intermediates used in this sequence had been described previously [15,91].

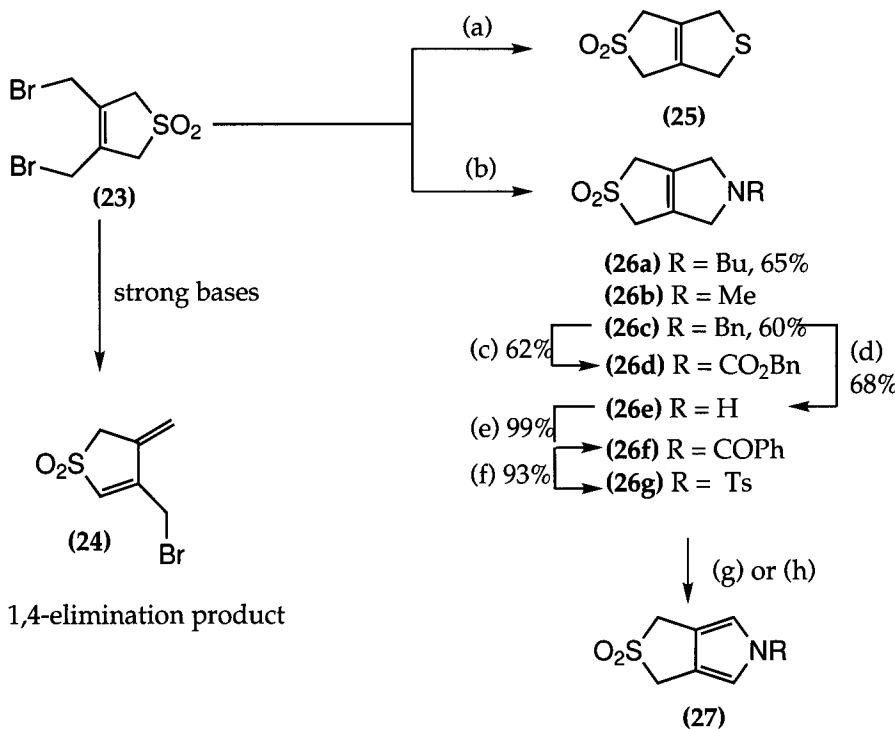


**SCHMЕE 6.7** (a) NBS/CHCl<sub>3</sub>/reflux; (b) CF<sub>3</sub>CO<sub>2</sub>Ag/H<sub>2</sub>O/RT; (c) PCC/CF<sub>3</sub>CO<sub>2</sub>H/CH<sub>2</sub>Cl<sub>2</sub>/RT

When dibromide (23) was reacted with nucleophiles, the formation of (24) was problematic, particularly with strongly basic reagents. However, sodium sulfide and primary amines were found to give satisfactory yields of heterocycles (25) and (26a–c), respectively [7,33]. The benzylamine 26c was subsequently converted into various other derivatives (Scheme 6.8).

Finally, oxidation of the dihydropyrroles gave pyrroles (27). DDQ (dichlorodicyanobenzoquinone) oxidation was successful for amines (26b), (26c), and (26e), but was not suitable for those bearing electron withdrawing substituents. Compounds (26d), (26f), and (26g) could be oxidized using manganese dioxide, in yields of 50–59%.

A number of approaches to sulfolene fused heterocycles have begun from 3-chloro-4-bromo-2-sulfolene (28) [69]. The C–Br bond was zinctated in the presence of boron trifluoride with ultrasound, and various aldehydes (29) were then reacted to give (30a–c). Benzoyloxyacetaldehyde gave (30a) ( $X = \text{BzO}$ ) in moderate yield [35] and the sulfur analogue ( $\text{MeCOSCH}_2\text{CHO}$ ) reacted in a similar manner [34], to give (30b). However, simple protected aminoaldehydes did not react successfully and phthalimide protection (30d) was required [37]. Once the protecting groups were hydrolysed from intermediates (30a–d) cyclization took place to give (31), which were subsequently dehydrated via their mesylates,



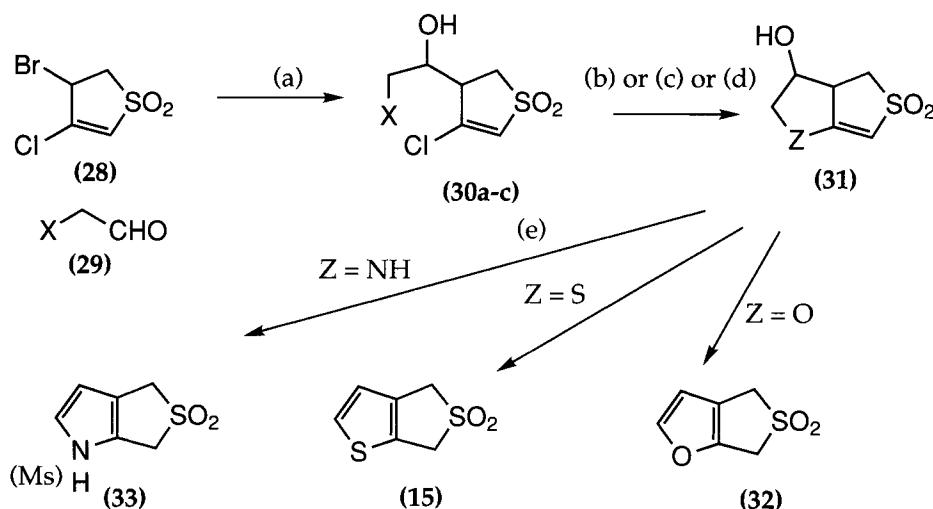
**SCHEME 6.8** (a)  $\text{Na}_2\text{S}$ ; (b)  $\text{RNH}_2$ ; (c)  $\text{ClCO}_2\text{CH}_2\text{Ph}/\text{benzene}$ ; (d) (i)  $\text{ClCO}_2\text{CHClMe}/(\text{CH}_2)_2\text{Cl}_2$ , (ii)  $\text{MeOH}$  at  $50^\circ\text{C}$ ; (e)  $\text{PhCOCl}/\text{K}_2\text{CO}_3$ ; (f)  $p\text{-TsCl}/\text{pyr}$ ; (g) DDQ/dioxane; (h) manganese dioxide

providing compounds (32), (15), and (33) (Scheme 6.9, Table 6.2).

3-Sulfolene (35) (Scheme 6.10) has been used in some simple approaches to sulfolene-fused heterocycles.

The conversion of 3-sulfolene to the useful sulfone (36) is itself an important procedure. A 1,3-dipolar cycloaddition of diazomethane to (36) was based on literature precedent for the formation of pyrazoles from sulfonyl alkenes and provided (37), from which benzene sulfonic acid was eliminated to give diazole (38) [17]. A mixture of products was obtained upon subsequent *N*-substitution (Scheme 6.10).

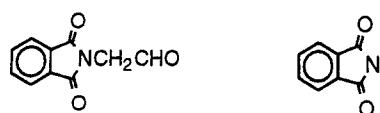
Thiazole-fused 3-sulfolenes have been built using a short and straightforward



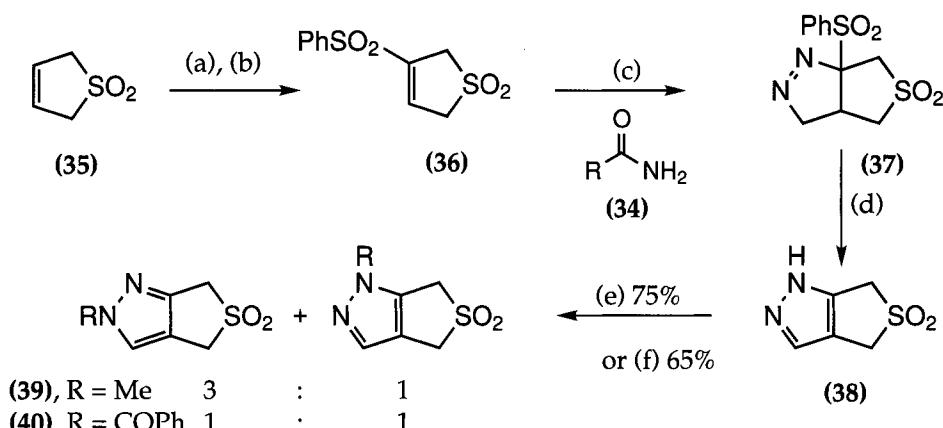
**SCHEME 6.9** (a)  $Zn(Ag)$  zincation/ $BF_3 \cdot Et_2O$ ; (b) (for  $Z = O$ )  $KCN/MeOH$ ; (c) (for  $Z = S$ )  $HCN/NaHCO_3$ ; (d) (for  $Z = NH$ ) aq  $HCl$ /reflux; (e)  $MsCl/Et_3N$

**TABLE 6.2**

Aldehyde	X	(30) (%)	Z	Product	Yield (%)
$PhCO_2CH_2CHO$	BzO	(a) (50)	O	32	31%
$MeCOSCH_2CHO$	MeCOS	(b) (43)	S	15	49%
$BocNHCH_2CHO$	BocNH	(c) (0)			
		(d) (79)	NH	33	<sup>a</sup>

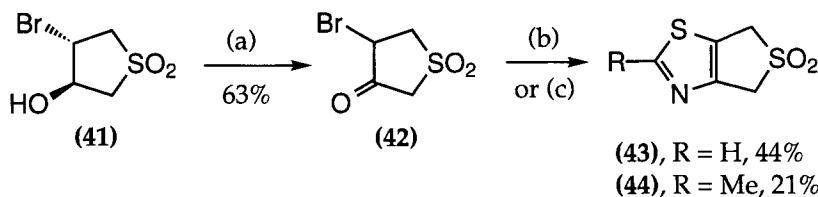


<sup>a</sup>Product always contains some NMs compound and yield depends on conditions.



**SCHEME 6.10** (a) phenylsulfonyl chloride; (b) mCPBA; (c)  $\text{CH}_2\text{NH}_2$ ; (d)  $\text{KOH}/\text{MeOH}$ ; (e)  $\text{Me}_2\text{SO}_4/\text{NaOMe}/\text{MeOH}$ ; (f)  $\text{PhCOCl}/\text{pyridine}$

route originating from 3-sulfolene [36]). 3-Bromo-4-hydroxysulfolane (41) is readily available from 3-sulfolene [98], and was oxidized to give the  $\alpha$ -bromoketone (42). Treatment of (42) with formamide and phosphorus pentasulfide afforded the thiazole sulfolene (43). Using similar reaction conditions, the 2-methyl analogue (44) was obtained, albeit in a lower yield (Scheme 6.11).

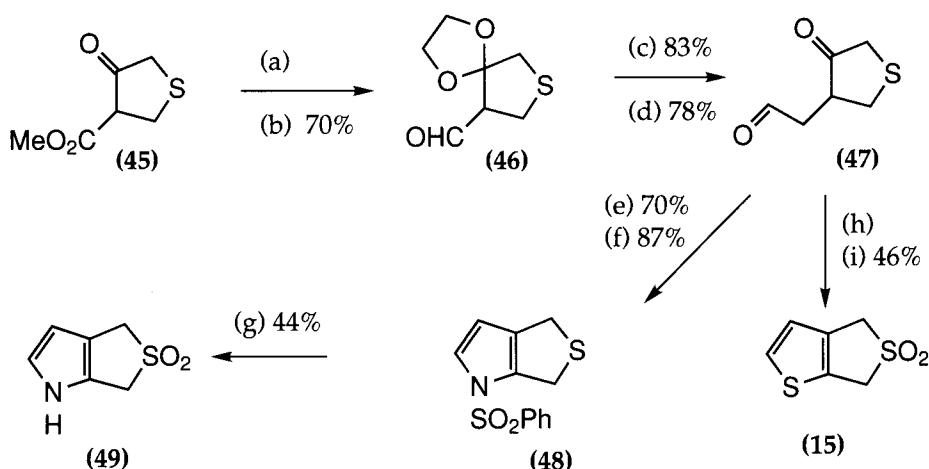


**SCHEME 6.11** (a) Jones' reagent; (b)  $\text{P}_2\text{S}_5/\text{dioxane}/\text{HCONH}_2/\text{reflux}$ ; (c)  $\text{MeCSNH}_2/\text{dioxane}/\text{reflux}$

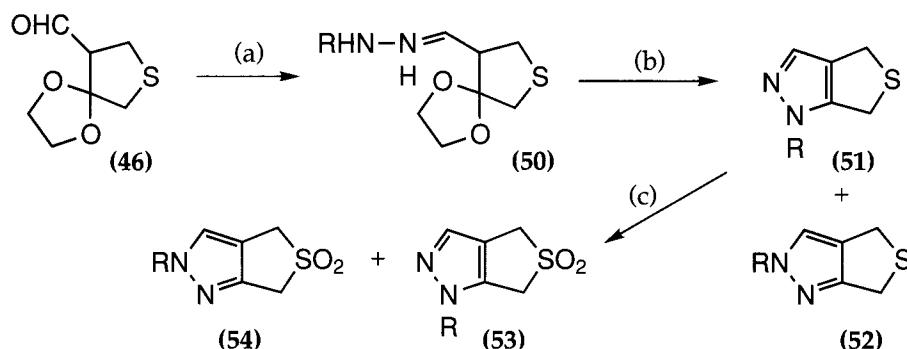
### 6.2.1.7 *Preparations of DMHA precursors starting from the tetrahydrothiophenes*

Ketoester (45) has been used to synthesize a number of sulfolene-fused heterocycles. In a straightforward series of steps, (45) was converted to ketoaldehyde (47), and this was readily converted to either thiazole-3-sulfolene (15) or pyrrole-3-sulfolene (49) [26,34] (Scheme 6.12).

Aldehyde (46) has also been converted into diazole-fused thiophenes. Reaction with hydrazine derivatives gave hydrazones (50), which on treatment with acid were converted to diazoles (51). Unfortunately, the nitrogen substituent was sometimes scrambled, leading to mixtures of (51) and (52). The final sulfur oxidation was uniformly high yielding [28,29] (Scheme 6.13, Table 6.3).



**SCHEME 6.12** (a)  $(\text{CH}_2\text{OH})_2 / \text{H}^+$ ; (b) DIBALH/CH<sub>2</sub>Cl<sub>2</sub>/−78°C; (c) Ph<sub>3</sub>PCH<sub>2</sub>(OMe)Cl/LDA/THF/0°C; (d) 20% H<sub>2</sub>SO<sub>4</sub>/Et<sub>2</sub>O/RT; (e) PhSO<sub>2</sub>NH<sub>2</sub>/p-TsOH/toluene/reflux; (f) mCPBA/CH<sub>2</sub>Cl<sub>2</sub>/RT; (g) LiOMe/MeOH-THF/RT; (h) Lawesson's reagent/toluene/reflux; (i) MeCO<sub>3</sub>H/RT

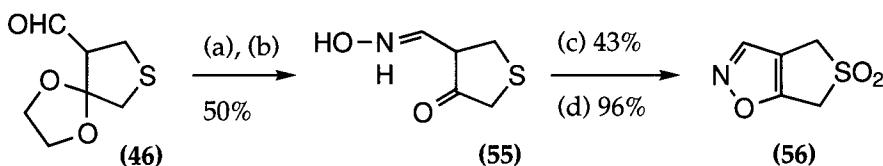


**SCHEME 6.13** (a) RNHNH<sub>2</sub>; (b) H<sub>2</sub>SO<sub>4</sub>-THF; (c) mCPBA

**TABLE 6.3**

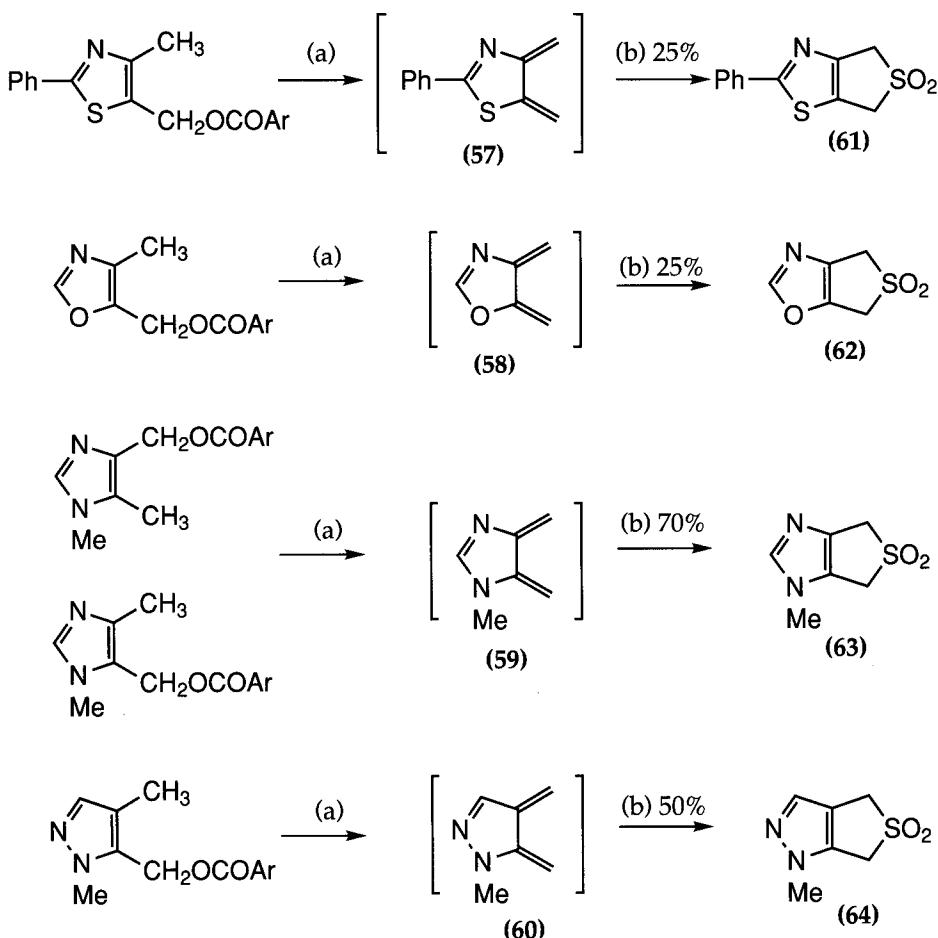
R	% (51)/(52)	Ratio (51)/(52)	% (53)
H	61	—	100
Boc	78 (R=H)	—	100
Ph	55	10:1	97
2,4-DNB	60	100:0	60 (overall)
Ts	Depends on conditions	Depends on conditions	98
CONHPh	51	9:1	98 (% (58))

A very similar sequence to that above was used to prepare isoxazolene fused sulfolene (**56**) [27] (Scheme 6.14).



**SCHEME 6.14** (a) 20%  $\text{H}_2\text{SO}_4$ (aq); (b)  $\text{NH}_2\text{OH} \cdot \text{HCl}$ ; (c)  $\text{PPA}/\text{N}_2$ ; (d)  $\text{mCPBA}$

The group of Storr have synthesized a variety of heterocyclic *o*-quindomethane analogues, e.g., (57)–(60). These are often quite unstable and have therefore been trapped with  $\text{SO}_2$ , to provide the equivalent sulfolenes (61)–(64) [16–18,53] (Scheme 6.15).



**SCHEME 6.15** (a) Flash vacuum pyrolysis; (b)  $\text{SO}_2$

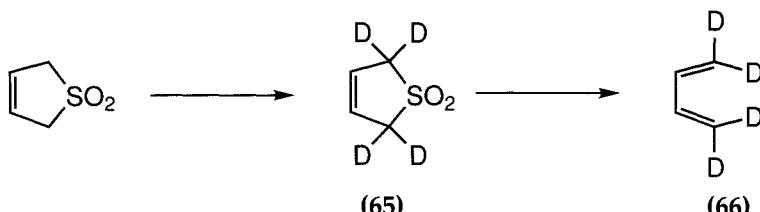
## 6.3 SUBSTITUTION REACTIONS OF SULFOLENES

### 6.3.1 Introduction

Simple sulfolenes can be prepared by addition of sulfur dioxide to a diene, but it is often useful to prepare substituted sulfolenes indirectly. A good deal of research effort has been expended in finding regioselective methods for substituting those sulfolenes that are readily available. Since the sulfone functionality is a powerfully electron withdrawing group, the sulfolene nucleus is readily deprotonated and many substitution methods involve reacting a sulpholene anion with an electrophile. In this section we review methods that have been employed to substitute sulfolenes via their anions, and highlight selectivity patterns. We also look briefly at other effective substitution methods.

### 6.3.2 Sulfolene substitution via anion formation

The ease of hydrogen exchange in 3-sulfolene is illustrated by rapid and complete exchange of the 2- and 5-protons, under basic conditions, to give tetradeuteriated 3-sulfolene (**65**) [52]. This delivers 1,1,4,4-tetradeutero-1,3-butadiene (**66**) on thermolysis (Scheme 6.16).

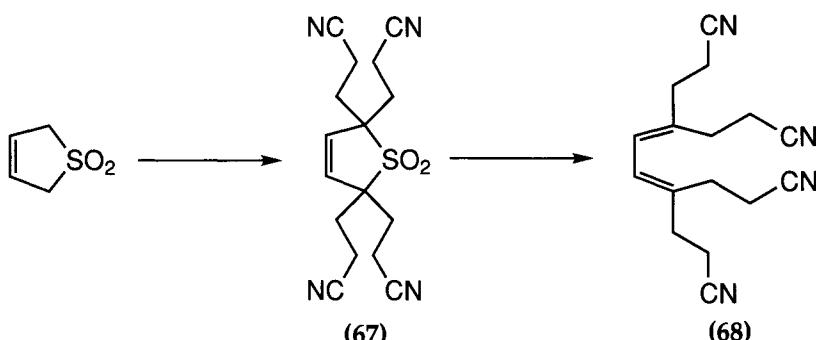


**Scheme 6.16** (a)  $\text{K}_2\text{CO}_3/\text{D}_2\text{O}$ ; (b) heat/160°C

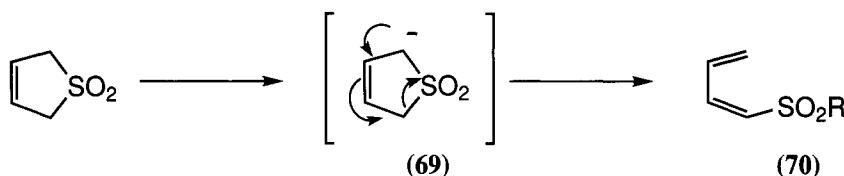
3-Sulfolene readily undergoes Michael additions with acrylonitrile, at the 2- and 5-positions, in the presence of a catalytic amount of trimethylbenzyl ammonium hydroxide to give tetrakis(cyanomethyl)-3-sulfolene (**67**). This gives the corresponding tetrasubstituted 1,3-butadiene (**68**) upon thermolysis at reduced pressure [114] (Scheme 6.17).

Despite early successes in substitution of sulfolenes, initial attempts to develop methods for the deprotonation/substitution of 3-sulfolenes using stronger bases such as  $\text{NaH}$ ,  $\text{BuLi}$ ,  $\text{LDA}$ , and Grignard reagents were unsuccessful. This is caused by cycloreversion of the labile  $\alpha$ -carbanion (**69**) to the more thermodynamically stable butadienyl sulfinate (**70**) (Scheme 6.18).

Takayama and colleagues found that cycloreversion can be prevented if the  $\alpha$ -carbanion is trapped by formation in the presence of an alkylating agent [116,117]. The solvent and base were also found to be important. Hence, addition of lithium

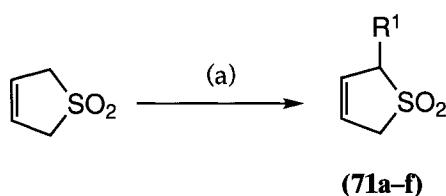


**SCHEME 6.17** (a)  $\text{H}_2\text{C}=\text{CHCN}/\text{BnMe}_3\text{NOH}$ ; (b) heat/ $200^\circ\text{C}/0.1$  torr



**SCHEME 6.18** (a) Strong base; (b)  $\text{R}-\text{X}$

hexamethyldisilazide to a mixture of 3-sulfolene and an alkyl halide in HMPA/THF at low temperature delivered 2-alkyl-3-sulfolenes (**71a-f**) in moderate yield. Alkylation did not occur when HMPA was omitted from the reaction mixture and dialkylation was kept to a minimum by using 3-sulfolene in excess. A selection of the results are shown in Scheme 6.19, Table 6.4.



**SCHEME 6.19** (a)  $\text{LiHMDS}/\text{R}^1-\text{I}/\text{HMPA}$  (4 eq)

On further alkylation, 2-substituted-3-sulfolenes delivered *trans*-2,5-disubstituted 3-sulfolenes (**72**) in moderate to high yield with ~90% stereoselectivity and 100% regioselectivity. A selection of the results is shown in Scheme 6.20, Table 6.5.

T-S. Chou and colleagues carried out similar deprotonation/alkylation studies, but using sodium hydride as the base [48]. DMF was found to be the solvent of choice and it was necessary to form the anion in the presence of the alkylating agent to obviate sulfolene ring opening. A mixture of 2-alkyl-3-sulfolenes (**74**) and the 2-alkyl-2-sulfolenes (**75**) was usually obtained, as shown by representative

TABLE 6.4

Component (71)	R <sup>1</sup>	Yield (%)
(a)	Me	46
(b)	Bu <sup>n</sup>	65
(c)	Isoamyl	61
(d)	(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> Bu <sup>t</sup>	40
(e)	(CH <sub>2</sub> ) <sub>7</sub> OTHP	58
(f)	PhCH <sub>2</sub>	55

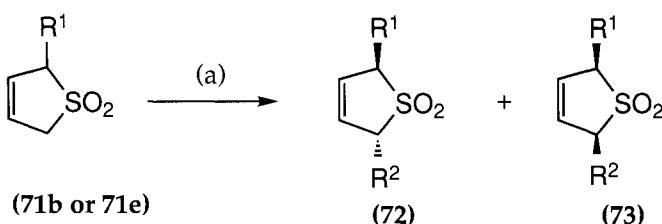
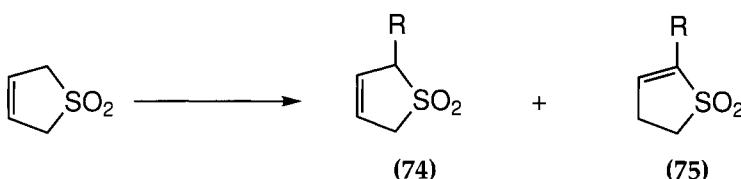
SCHEME 6.20 (a) LiHMDS/R<sup>2</sup>—I/HMPA (4 eq)

TABLE 6.5

Starting compound	R <sup>1</sup>	R <sup>2</sup>	(72) %	(73) %
(71b)	Bu <sup>n</sup>	Bu <sup>n</sup>	58	1
(71b)	Bu <sup>n</sup>	n-C <sub>7</sub> H <sub>15</sub>	56	4
(71e)	(CH <sub>2</sub> ) <sub>7</sub> OTHP	Me	55	6

examples in Scheme 6.21, Table 6.6. Similar treatment using the alkyl tosylates was unsuccessful.



SCHEME 6.21 (a) NaH/R—I/DMF

The formation of the 2-sulfolene products was investigated further. It was found that, with the exception of 3-sulfolene itself, double-bond migration to the more thermodynamically stable 2-sulfolene occurred under the basic reaction conditions (Scheme 6.22, Table 6.7).

TABLE 6.6

R	(74) %	(75) %
Me	69	20
Et	43	33
Pr <sup>n</sup>	41	40
Bu <sup>n</sup>	40	28
Allyl	65	0

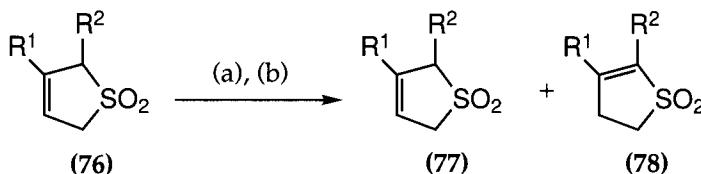
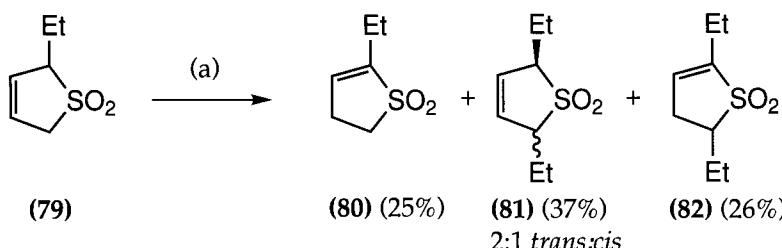
SCHEME 6.22 (a) NaH/DMF; (b) H<sub>2</sub>O

TABLE 6.7

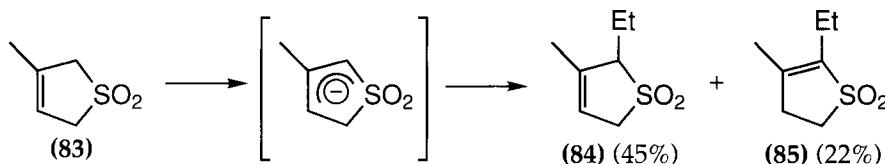
Starting compound	R <sup>1</sup>	R <sup>2</sup>	(77) %	(78) %
(76a)	H	H	50	50
(76b)	H	Me	0	100
(76c)	H	Et	0	100
(76d)	Me	H	17	83
(76e)	Me	Me	0	100

When the reaction product from the ethylation of 3-sulfolene was analysed carefully, small amounts (~10% yield) of 2,5-diethylated sulfolenes were also identified, but no 2,2-diethylated material was detected. The regioselectivity of direct alkylation of 2- and 3-substituted 3-sulfolenes was therefore investigated. Under the conditions already outlined, 2-ethyl-3-sulfolene (79) was ethylated in the 5-position with high regioselectivity. The *trans* stereoisomer was the major product, but the selectivity was low, and 2-sulfolene products were again also produced as the result of double-bond isomerization (Scheme 6.23).



SCHEME 6.23 (a) NaH/EtI/DMF

Under similar conditions, ethylation of 3-methyl-3-sulfolene (**83**) gave 2-substituted products (**84**) and (**85**) only, together with some starting material (13%) and isomerized starting material (20%) (Scheme 6.24). It was suggested that deprotonation occurred solely at the 2-position of 3-methyl-3-sulfolene (**83**) because of the stability of the more substituted C-2 anion.



SCHEME 6.24 (a) NaH/EtI/DMF

In further studies, Chou and colleagues found that the sulfolene nucleus could be regioselectively substituted with alkyl chains incorporating an alkene bond. Alkylations with allylic halides were particularly effective (Scheme 6.25, Table 6.8). They utilized this chemistry in neat syntheses of simple terpenes (see Section 6.4). In some cases the alkene bond of the side-chain was utilized as a dienophile in an intramolecular Diels–Alder reaction [43,46,69,109].

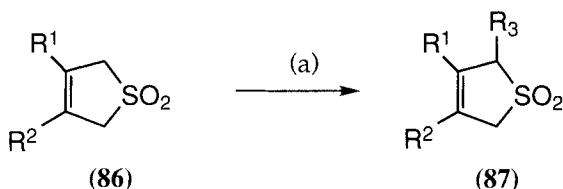
SCHEME 6.25 (a) LiHMDS/HMPA/THF; R<sup>3</sup>I

TABLE 6.8

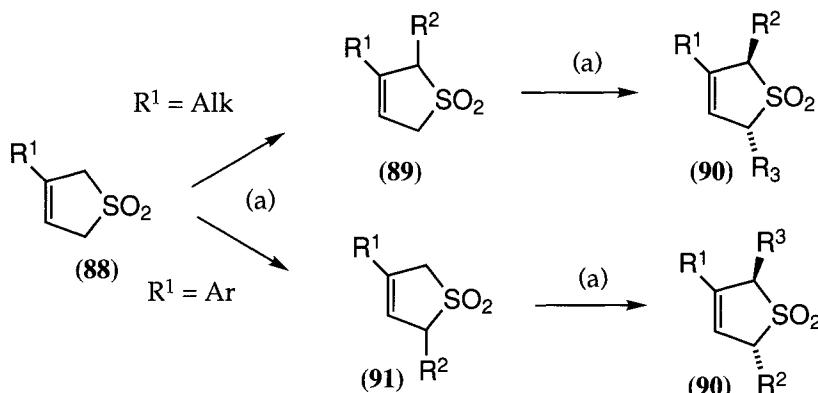
R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield (%)
H	H	~	65
H	H	~	57
Me	H	~	7
Me	H	~	75
Me	H	~	68
Me	H	~	68
Me	H	~	62
Me	Me	~	67
Me	Me	~	66

Using the LiHMDS/in situ alkylating agent conditions for alkylation, the directing effect of different substituents on the double bond of 3-sulfolene was

examined [90,104,118]. Very selective 2-alkylation always occurred when there was an alkyl substituent on the 3-position, and it was argued that the substituent had a stabilizing effect on the C-2 anion. This selectivity was exploited in a synthesis of epilupinine. Once the C-2 position had been alkylated, a second alkylation occurred in the 5-position to provide 2,3,5-trisubstituted 3-sulfolenes (**90**) selectively (Scheme 6.26, Table 6.9).

The presence of a phenyl group at the 3-position of the sulfolene nucleus stabilizes an anion at C-5, and thus alkylation occurs selectively in that position. The selectivity is slightly reduced when the phenyl ring carries an electron donating methoxy substituent. The disubstituted compounds (**91**), obtained after alkylation, could then be selectively alkylated in the 2-position.

3-Benzyl-3-sulfolene was found to be inert to alkylation, even at elevated temperatures, probably as a result of steric hindrance of the carbanion generated in the 2-position. Attempts at alkylation of 3-trifluoromethyl-3-sulfolene resulted in decomposition of starting material, most likely due to elimination of a fluorine atom situated  $\gamma$  to the carbanion.



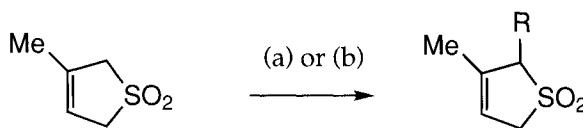
**SCHEME 6.26** (a) LiHMDS/HMPA/THF/RI

**TABLE 6.9**

Starting compound	Alkylating agent	Products (yield %)	
( <b>88</b> ) (R <sub>1</sub> =Me)	BuLi	( <b>89</b> ) (71)	( <b>91</b> ) (0)
( <b>88</b> ) (R <sub>1</sub> =Ph)	BuLi	( <b>89</b> ) (0)	( <b>91</b> ) (72)
( <b>88</b> ) (R <sub>1</sub> =p-OMeC <sub>6</sub> H <sub>4</sub> )	BuLi	( <b>89</b> ) (12)	( <b>91</b> ) (49)
( <b>89</b> ) (R <sub>1</sub> =Me, R <sub>2</sub> =Bu)	EtLi	( <b>90</b> ) (73)	
( <b>91</b> ) (R <sub>1</sub> =Ph, R <sub>2</sub> =Bu)	EtLi	( <b>90</b> ) (14)	

In later studies further regioselective alkylations on 3-methyl-3-sulfolene were carried out, extending further the range of side-chain substituents [54,55]. It was found that alkylations with reactive alkylating agents could be carried out without

HMPA. Representative examples of their studies are shown in Scheme 6.27, Table 6.10.

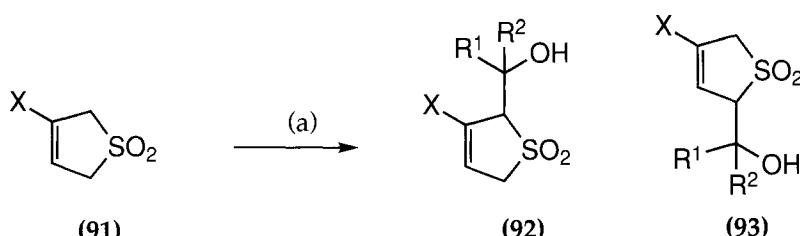


**SCHMЕ 6.27** (a) LiHMDS/THF/R<sup>3</sup>I or R<sup>3</sup>Br; or (b) LiHMDS/HMPA/THF/R<sup>3</sup>I or R<sup>3</sup>Br

**TABLE 6.10**

R	Conditions	Yield (%)
MeOCH <sub>2</sub>	(a)	88
PhCH <sub>2</sub>	(a)	27
PhCH <sub>2</sub>	(a)	82
MeI	(a)	85
Me <sub>2</sub> C=CHCH <sub>2</sub>	(a)	77
Geranyl	(a)	97
MeO(CH <sub>2</sub> ) <sub>2</sub>	(b)	89
	(b)	85
	(b)	80

Aldehydes and ketones also reacted with sulfolene anions to provide secondary alcohols. Substituents in the 3-position were again found to be influential, with alkyl groups directing substitution to the 2-position, while 3-phenylsulfolene reacted at the 5-position [118]. These authors found that conjugated carbonyl compounds gave a mixture of 1,2- and 1,4-addition products favouring the conjugate addition product. However, in later studies [55,92] a wider range of aldehydes was used and it was found that 1,2-addition to unsaturated aldehydes predominated at  $-105^{\circ}\text{C}$  (Scheme 6.28, Table 6.11).



**SCHMЕ 6.28** (a) LiHMDS/HMPA/THF/RCHO

TABLE 6.11

X	Carbonyl	R <sup>1</sup>	R <sup>2</sup>	Product	Yield (%)
Me	Me <sub>2</sub> CO	Me	Me	(92)	75
Ph	Me <sub>2</sub> CO	Me	Me	(93)	60
Ph	Me <sub>2</sub> CHCH <sub>2</sub> CH <sub>O</sub>	Me <sub>2</sub> CHCH <sub>2</sub>	H	(93)	44
Me	Ph-CH <sub>2</sub> CHO	Ph-CH <sub>2</sub>	H	(92)	80
Me	CH <sub>2</sub> OC(=O)CHO	CH <sub>2</sub> OC(=O)	H	(92)	56
Me	CH <sub>2</sub> CH(=O)CHO	CH <sub>2</sub> CH(=O)	H	(92)	80
Me	CH <sub>2</sub> CH(=O)C(=O)O	CH <sub>2</sub> CH(=O)	Me	(92)	60

It was discovered that sequential deprotonation of sulfolenes using butyllithium, followed by alkylation, could occur without ring fragmentation, provided the temperature was kept at  $-105^{\circ}\text{C}$  [40,49,50]. Simple methylation of 3-sulfolene or 3-methyl-3-sulfolene occurred smoothly and in high yield. When acylation of (94) was attempted, the initial acyl product was further *O*-acylated via sulfolene anion (98). This intermediate anion could, however, be utilized for alkylation, providing access to 2-acyl-2-alkyl-3-sulfolenes (100). Representative examples are shown in Scheme 6.29, Table 6.12.

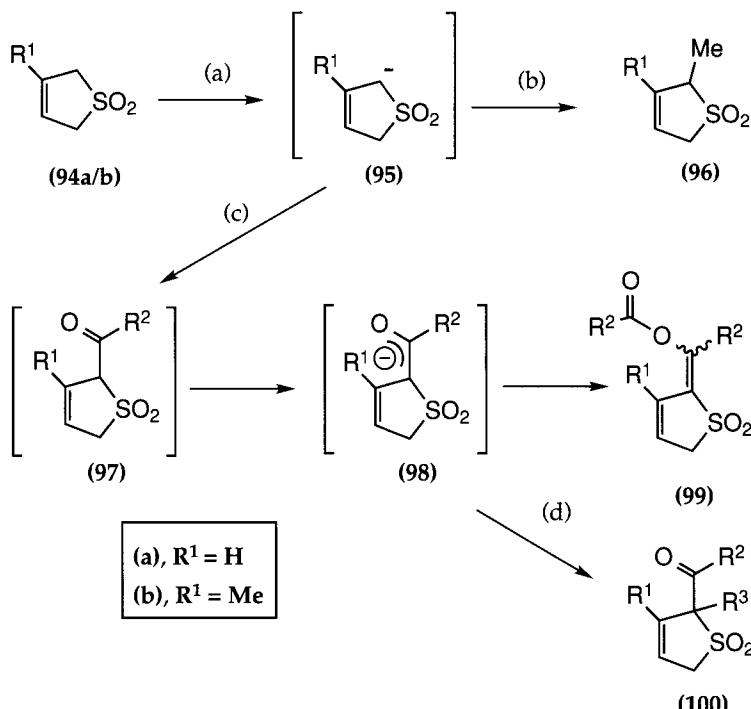
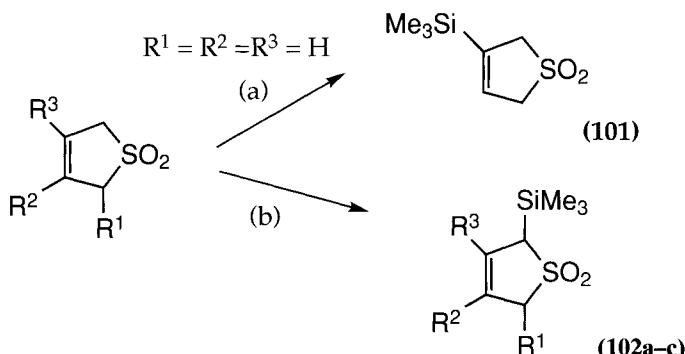
SCHEME 6.29 (a) BuLi/HMPA/THF/ $-105^{\circ}\text{C}$ ; (b) MeI; (c)  $\text{R}_2\text{COCl}$ ; (d)  $\text{R}_3\text{X}$

TABLE 6.12

Starting compound	R <sub>c</sub> COCl	R <sup>3</sup>	Product	Yield (%)
(94a)	MeCOCl	—	(99a)	91
(94a)	PhCOCl	—	(99a)	55
(94a)	MeCOCl	—	(99a)	85
(94a)	MeCOCl	Me	(100a)	51
(94a)	MeCOCl	Bn	(100b)	60
(94a)	Bu <sup>i</sup> COCl	Bn	(100c)	43
(94a)	MeCOCl	Me	(100d)	56
(94a)	Bu <sup>i</sup> COCl	H <sub>2</sub> C=CHCH <sub>2</sub>	(100e)	92

In a later study [50], the regioselectivity of silylation was found to be dependent on reaction conditions. When the anion of 3-sulfolene was generated at  $-105^{\circ}\text{C}$  then treated with slightly less than 1 equivalent of TMS-Cl, 3-trimethylsilyl-3-sulfolene (**101**) was the major product. However, when NaI was added to the reaction, substitution occurred at the 2-position. Under these conditions, other substituted sulfolenes also reacted in the  $\alpha$ -position (Scheme 6.30, Table 6.13).



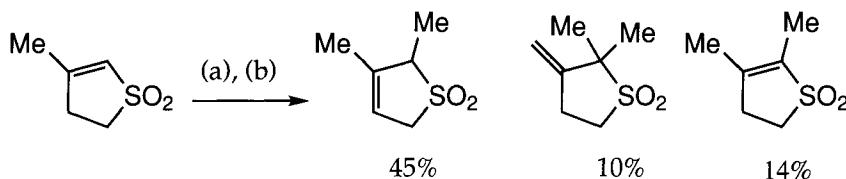
**SCHEME 6.30** (a) (i) BuLi/THF/ $-105^{\circ}\text{C}$ , (ii) TMS-Cl; (b) (i) BuLi/NaI/THF/ $-105^{\circ}\text{C}$ , (ii) TMS-Cl

TABLE 6.13

R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Conditions	Product	Yield (%)
H	H	H	(a)	(101)	25
H	H	H	(b)	(102a)	43
Me	H	H	(b)	(102b)	11
H	H	Me	(b)	(102c)	70
H	Me	Me	(b)	(102d)	81

The alkylation reactions of 2- and 3-sulfolenes were also compared [40]. It was found that a certain amount of 3-sulfolene product could be isolated when

3-substituted-2-sulfolenes were alkylated, but none of the reaction products was produced cleanly. An example is given in Scheme 6.31.

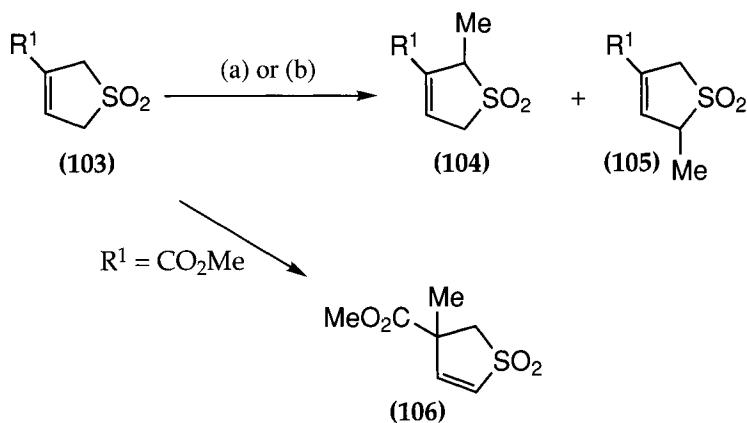


SCHEME 6.31 (a) BuLi/HMPA/THF/−105°C; (b) MeI

A comparison of the effect of different substituents in the 3-position of 3-sulfolenes upon deprotonation/alkylation was carried out [107]. The in situ alkylation conditions (LiHMDS/THF/HMPA) were also compared with the 2-step (BuLi/THF/HMPA) procedure. When the 3-substituent was an alkyl group, the reactions were generally high-yielding, with high selectivity for 2-substitution, and the 2-step procedure was generally more efficient. Considerable polymerization of the 3-halogenated sulfolenes always occurred and this was ascribed to destabilization of the adjacent carbanion. However, 2-alkylated sulfolenes were isolated in low yield, as the only products, and the in situ procedure was more efficient in these cases.

Phenyl, *S*-phenyl or  $\text{SiMe}_3$  groups at the 3-position all caused a complete reversal of regioselectivity, with 5-substitution products being formed exclusively under either conditions.

It was no surprise that deprotonation of 3-carbomethoxy-3-sulfolene (**103g**) occurred at the 5-position, since the anion formed at this position can be stabilized by the ester group, but it is interesting that alkylation occurred at the 3-position. A selection of the results is presented in Scheme 6.32, Table 6.14.

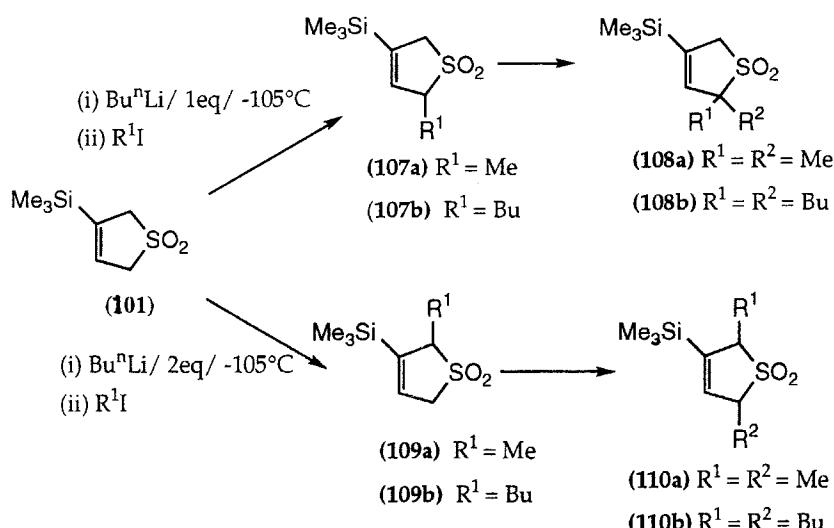


**SCHEME 6.32** (a) (i) BuLi/HMPA/THF/-105°C, 10 min, (ii) MeI; (b) LiHMDS/THF/HMPA/MeI/-78°C

TABLE 6.14

S.M.	R <sup>1</sup>	Conditions	Product(s) (%)		
			(104)	(105)	(106)
(103a)	Me	(a)	91	0	0
(103a)	Me	(b)	78	0	0
(103b)	Pr <sup>i</sup>	(a)	92	0	0
(103b)	Pr <sup>i</sup>	(b)	76	8	0
(103c)	Cl	(a)	10	0	0
(103c)	Cl	(b)	32	0	0
(103d)	Ph	(a)	0	95	0
(103d)	Ph	(b)	0	21	0
(103e)	SPh	(a)	0	67	0
(103f)	SiMe <sub>3</sub>	(a)	0	90	0
(103g)	CO <sub>2</sub> Me	(a)	0	0	60

In a follow-up study [106] alkylation of 3-trimethylsilyl-3-sulfolene (101) was studied in more detail and some interesting results were obtained [106]. The monoanion, formed by reaction with 1 equivalent of Bu<sup>n</sup>Li, was cleanly alkylated in the 5-position. This position was also favoured for a second alkylation even though sterically hindered. On the other hand, when the dianion was formed it gave a mixture of products, but alkylation at the 2-position was favoured. Subsequent alkylation of the 2-alkylated compounds (109) was again directed to the 5-position to provide (110) (Scheme 6.33, Table 6.15).

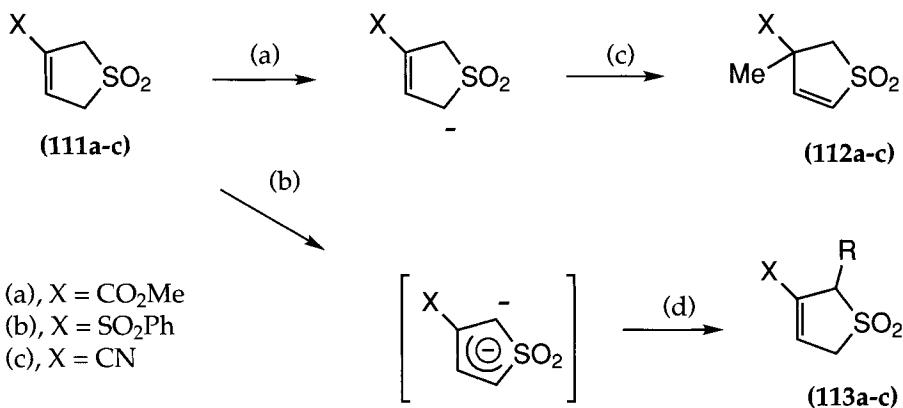


SCHEME 6.33 (a) (i) BuLi (1 eq)/THF/−105°C, (ii) RI; (b) (i) BuLi/2eq/THF/−105°C, (ii) RI

TABLE 6.15

S.M.	R <sup>1</sup>	R <sup>2</sup>	Conditions	Product(s) %	
				(107/108)	(109/110)
(101)	Me	—	(a)	90	—
(101)	Bu	—	(a)	85	—
(107a)	Me	C <sub>6</sub> H <sub>11</sub>	(a)	78	—
(101)	Me	—	(b)	60	—
(101)	Bu	—	(b)	—	70 <sup>a</sup>
(101)	Pri	—	(b)	—	60
(109a)	Me	Me	(b)	—	55
(109b)	Bu	Bu	(b)	—	50

<sup>a</sup>Includes other regioisomers (~25%).



**SCHEME 6.34** (a) 1 eq BuLi/THF/-78°C; (b) 2 eq BuLi/THF/-78°C; (c) MeI (2 eq); (d) AcCl

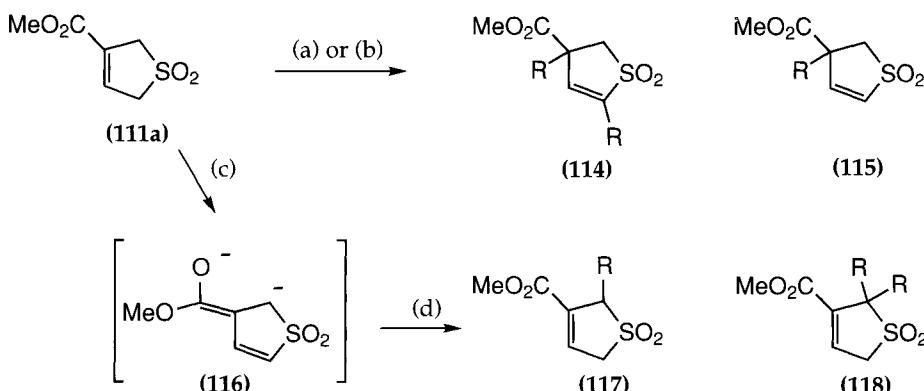
TABLE 6.16

Starting compound	Conditions	E <sup>+</sup>	Product	Yield (%)
(111a)	(a) BuLi/1eq	MeI	(112a)	67
(111a)	(a) BuLi/1eq	MeI	(112b)	71
(111b)	(a) BuLi/1eq	MeI	(112c)	13 <sup>a</sup>
(111a)	(b) BuLi/2eq	MeI	(113a)	75
(111b)	(b) BuLi/2eq	MeI	(113b)	76 <sup>b</sup>
(111c)	(b) BuLi/2eq	MeI	(113c)	75
(111c)	(b) BuLi/2eq	AcCl	(113a) (R=Ac)	72 <sup>c</sup>

<sup>a</sup>Other isomers also isolated. <sup>b</sup>Including 2-sulfolene isomer. <sup>c</sup>Based on recovered starting material.

Methods for regioselective alkylation of 3-sulfolenes with a mesomerically electron withdrawing substituent at C-3 were independently investigated by two groups [45,71]. The Chou group found that compounds (111a–c) were methylated selectively at position C-3 on treatment with 1 equivalent of BuLi, followed by methyl iodide, to give (112a–c). However, treatment with 2 equivalents of BuLi, followed by either methyl iodide or acetyl chloride gave the 2-substituted product (113a–c) predominantly (Scheme 6.34, Table 6.16).

The Leonard group explored regioselective substitution of (111a) in order to prepare diene precursors for syntheses of yohimbine and manzamine alkaloids [70–72]. They found that the position of substitution was highly dependent on the base used, on reaction conditions and on the nature of the electrophile. When the anion was formed using 1 equivalent of BuLi or using 1–3 equivalents of a lithium amide base, a mixture containing only 3- and 3,5-disubstituted products (114) and (115) was obtained upon alkylation with reactive alkylating agents, such as allyl bromide. When the dianion (116) was formed with 2 equivalents of BuLi, alkylation occurred at the 2-position only with no trace of 3- or 5- substitution. The only other detectable products were small amounts of 2,2-disubstituted products (118). Alkylation, acylation and aldol reactions were all successful, but  $\alpha,\beta$ -unsaturated electrophiles gave mixtures of 1,2 and 1,4-addition products (Scheme 6.35, Table 6.17).



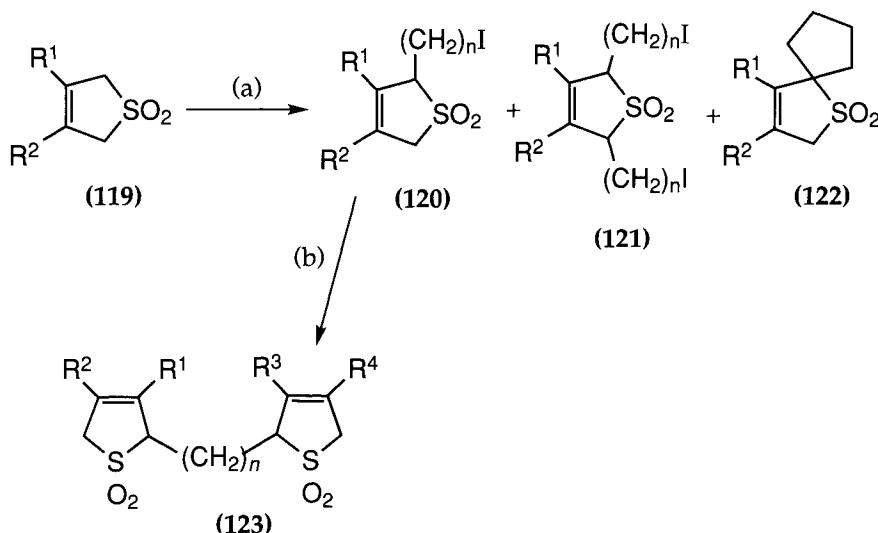
**SCHEME 6.35** (a) 1 eq BuLi/THF/−78°C; (b) R<sub>2</sub>NLi (1–3 eq)/THF/−78°C; (c) 2 eq BuLi/THF/−78°C; (d) electrophile (1.3 eq)

Bis-sulfolenes have been prepared by the addition of two 3-sulfolene molecules to a dihaloalkane [42]. The one-step formation of symmetrical bis-sulfolenes was found to be impractical, as the numerous possible side-reactions resulted in a very low yield of required product. However, stepwise connection of 3-sulfolenes with a single mole of diiodoalkane enabled preparation of both symmetrical and unsymmetrical bis-sulfolenes in modest yields. Intermediates (120) were isolated in 5–53% yield depending on substituents. The main by-products were usually 2,5-dialkylated compounds (121) except in the case of halide or sulfide substituents where spiro compound (122) was formed. Provided the sulfolene to be added was less acidic than intermediate (120), its anion could be added to (120) to give the bissulfolene (123) (12–56% yield) (Scheme 6.36).

TABLE 6.17

Base	Electrophile	R	Products (yield%)	
(b)	$\text{H}_2\text{C}=\text{CHCH}_2\text{Br}$	$\text{H}_2\text{C}=\text{CHCH}_2$	(115a) (29)	(114a) (17)
(c)	$\text{H}_2\text{C}=\text{CHCH}_2\text{Br}$	$\text{H}_2\text{C}=\text{CHCH}_2$	(117a) (75)	(118a) (6)
(c)	$\text{Me}_2\text{C}=\text{CHCH}_2\text{Br}$	$\text{Me}_2\text{C}=\text{CHCH}_2$	(117b) (84)	(118b) (5)
(c)	$\text{PhCH}_2\text{Br}$	$\text{PhCH}_2$	(117c) (71) <sup>a</sup>	
(c)	$\text{EtOCOCN}$	$\text{CO}_2\text{Et}$	(117d) (48) <sup>a</sup>	
(c)	$\text{Me}_2\text{CHCHO}$	$\text{Me}_2\text{CHC(OH)}$	(117e) (73)	(118e) (16) <sup>b</sup>
(c)	$\text{H}_2\text{C}=\text{CHCOMe}$	$\text{H}_2\text{CCH}_2\text{COMe}$	(117f) (20)	
(c)	$\text{C}_6\text{H}_{13}\text{Br}$	$\text{C}_6\text{H}_{13}$	(117g) (36)	(118g) (35)
(c)	$\text{CH}_3\text{COCl}$	$\text{CH}_3\text{CO}$	(117h) (55) <sup>a</sup>	

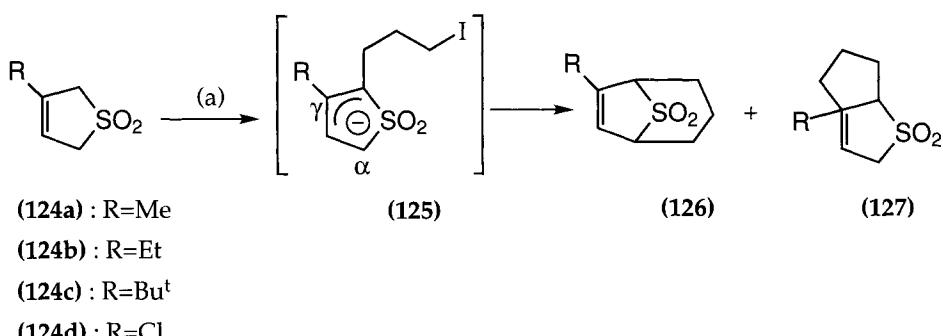
<sup>a</sup>Starting material also isolated. <sup>b</sup>13% 1,2-addition products also isolated.



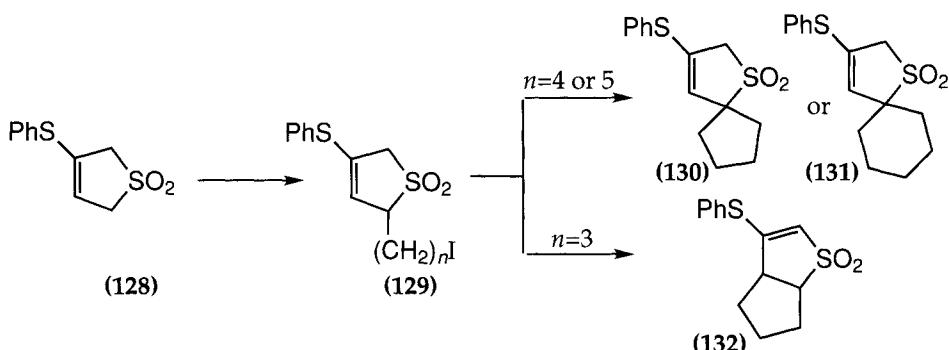
**SCHEME 6.36**  $\text{R}^1 = \text{H, Me, Cl}; \text{R}^2 = \text{H, Me, PhS, TMS}$ . (a)  $\text{LiHMDS/THF/I}(\text{CH}_2)_n\text{I}/-78^\circ\text{C}$ ; (b)  $\text{LiHMDS/THF/sulfolene}/-78^\circ\text{C}$

Dialkylative cyclization reactions have been used to prepare bridged, spiro, and fused bicyclic sulfolenes. Reaction of 3-alkyl- and 3-chloro-3-sulfolenes (**124a-d**) with 1,3-diiodopropane, in the presence of 2 equivalents of base, initially furnishes intermediate anion (**125**). Intramolecular alkylation then takes place either at the  $\alpha$ -position to deliver the bridged product (**126**) or at the  $\gamma$ -position for the fused bicycle (**127**) [25] (Scheme 6.37).

Spirobicyclic 3-sulfolenes (**130**) and (**131**) were obtained from 3-thiophenyl-3-sulfolene (**128**), by reaction with 1,4-diiodobutane and 1,5-diiodopentane, respectively, utilizing the ability of the thiophenyl group to direct dialkylation at the C-5 position. However, dialkylation with 1,3-diiodopropane gave fused bicyclic 2-sulfolene (**132**) [21] (Scheme 6.38).



**SCHEME 6.37** (a) LiHMDS (2 eq)/THF/I(CH<sub>3</sub>)<sub>2</sub>I/-78°C



**SCHEME 6.38** (a) LiHMDS (2 eq)/THF/I(CH<sub>2</sub>)<sub>n</sub>I/-78°C

### 6.3.3 Other substitution methods using electrophiles

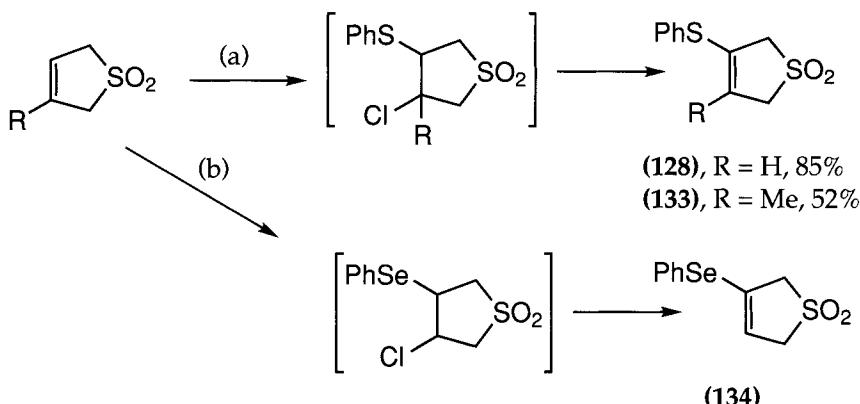
The alkene bond of 3-sulfolene (and some derivatives) is quite reactive to electrophiles and this allows access to 3-substituted sulfolenes through addition-elimination reactions.

A large-scale ‘one-pot’ preparation of 3-thiophenyl-3-sulfolene (**128**) was achieved by addition of phenylsulfenyl chloride, followed by triethylamine [61] (Scheme 6.39). In a later study 3-methyl-3-sulfolene was reacted in a similar manner to give a 52% yield of the 3,4-disubstituted sulfolene (**133**) [93]. The route was also adapted for the synthesis of 3-phenylselenyl-3-sulfolene (**134**) [77].

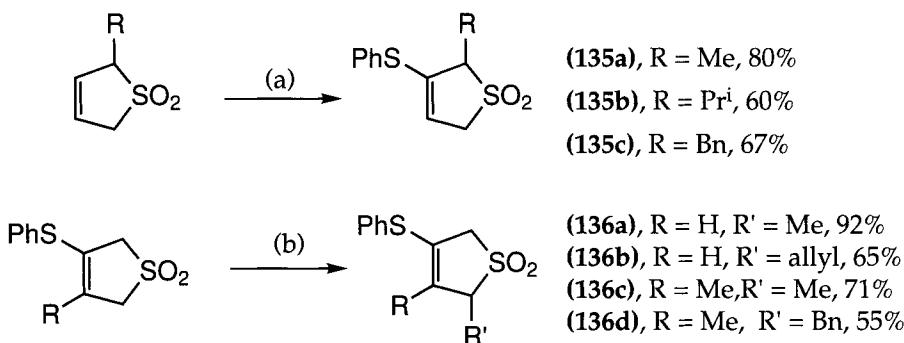
Other methods for the selective preparation of thiophenyl derivatives have also been described [20]. 2-Alkyl-3-sulfolenes were converted to 3-thiophenyl derivatives (**135**) by treatment with phenylsulphenyl chloride in the presence of  $\text{Et}_3\text{N}$ , and 3-thiophenylsulfolenes were alkylated selectively via their lithium anions, providing (**136a-d**) (Scheme 6.40).

The alkene of 3-thiophenyl-3-sulfolene is electron-rich and can be acylated under Friedel-Crafts conditions [23] (Scheme 6.41).

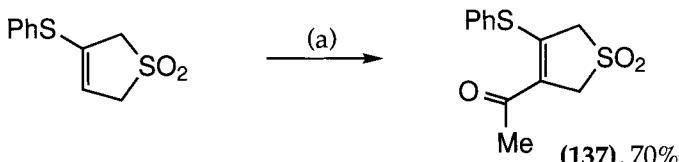
Bromination of 3-sulfolenes, followed by debromination, provides a useful means for adding extra functionality to the ring, and examples are given in Scheme 6.42 [8,44,56]. Both nucleophilic and electrophilic methods have been devised for substituting the



**SCHEME 6.39** (a) (i) PhSCl/0°C, (ii) Et<sub>3</sub>N 0°C – RT; (b) (i) PhSeCl/CH<sub>2</sub>Cl<sub>2</sub>; (ii) pyridine, (iii) DBU



**SCHEME 6.40** (a) (i) PhSCl, (ii) Et<sub>3</sub>N; (b) (i) BuLi/HMPA/THF, (ii) R'I or R'Br



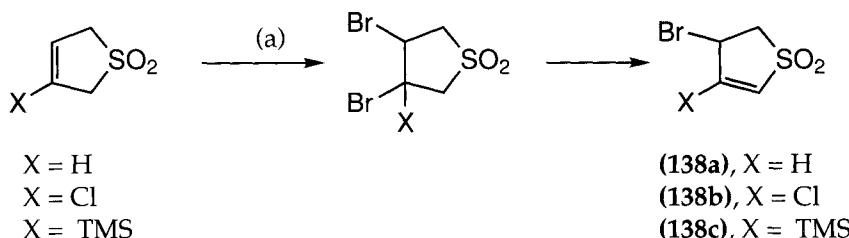
**SCHEME 6.41** (a) CH<sub>3</sub>COCl/AlCl<sub>3</sub>/CS<sub>2</sub>

halide atoms in (138a–c) and isomerizing the alkene bond to the 3-position.

Hydrobromination of 3-sulfolene is also a useful method for adding functionality to the ring (see Section 6.2).

Several methods for sulfolene substitution have been devised which utilize bromo groups to introduce other substituents into the sulfolene ring.

It was found that 4-bromo-2-sulfolenes can also be reacted with electrophilic carbonyl reagents in the presence of Zn–Ag with sonication, providing alcohols (139) in very good yields [110,111]. The alcohols could be converted to ketones (140). Alternatively, the alcohol could be displaced by thiophenol via the mesylate,

SCHEME 6.42 (a)  $\text{Br}_2$ 

to provide (141). These compounds have a variety of uses, one of which is reduction to an alkyl chain, providing compounds (142) (Scheme 6.43, Table 6.18).

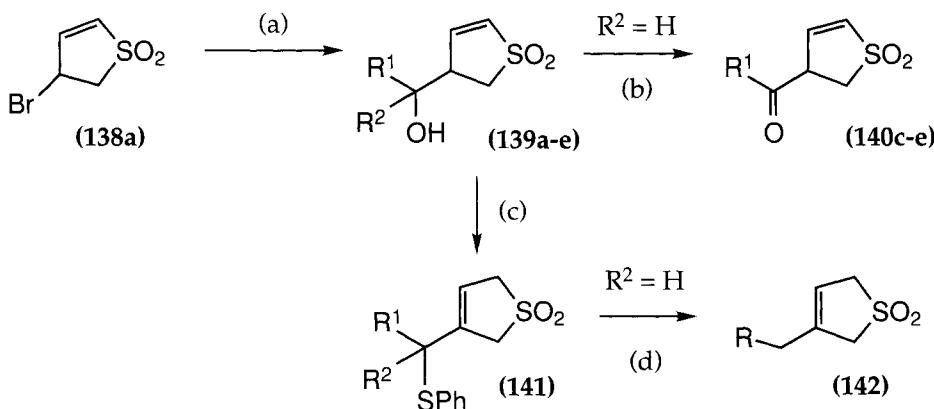
SCHEME 6.43 (a)  $\text{Zn-Ag/R}^1\text{R}^2\text{CO/THF/ultrasound}$ ; (b)  $\text{PCC/molecular. sieves}$ ; (c) (i)  $\text{MsCl/Et}_3\text{N}$ , (ii)  $\text{LiOH}$ , (iii)  $\text{NaSPh}$ ; (d)  $\text{Bu}_3\text{SnH}$ 

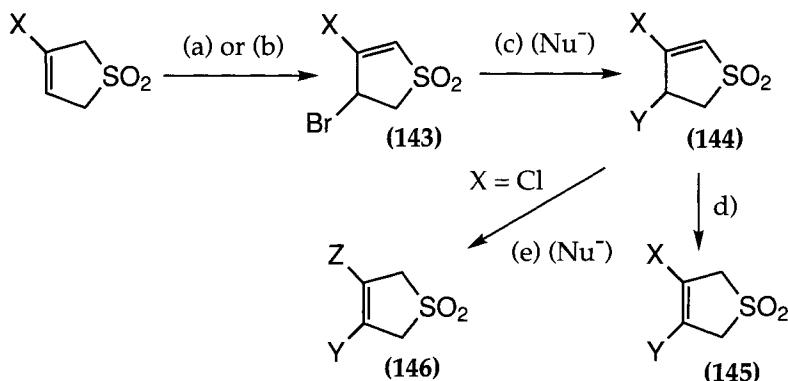
TABLE 6.18

Carbonyl compound	$\text{R}^1$	$\text{R}^2$	Products (yield%)	
			(139)	(140)
$\text{Me}_2\text{CO}$	Me	Me	89	–
$\text{PhMeCO}$	Ph	Me	78	–
$\text{EtCHO}$	Et	H	85	48
$\text{PhCHO}$	Ph	H	87	50
$\text{H}_2\text{C}=\text{CH}(\text{CH}_2)_3\text{CHO}$	$\text{H}_2\text{C}=\text{CH}(\text{CH}_2)_3$	H	92	45

### 6.3.4 Substitution via Nucleophilic Reagents

3,4-Diheterosulfolenes have been prepared from 3-substituted 3-sulfolenes utilizing 4-bromo-2-sulfolenes as butadienyl cation equivalents [44]. These compounds are of considerable interest, in terms of the influence of the

heteroatoms on the reactivity and regioselectivity of the corresponding dienes. 3-Substituted-3-sulfolenes were readily converted to the equivalent 4-bromo-2-sulfolenes (**143**). Subsequent treatment of these compounds with the sodium salts of various nucleophiles gave isomers (**144**) and (**145**) of the 3,4-diheterosubstituted sulfolenes. In most cases, treatment of the mixture with base caused equilibration which favoured the 3-sulfolene (**145**) (Scheme 6.44, Table 6.19). 3-Chloro-2-sulpholenes (**144**) could also be reacted with a further nucleophile to undergo conjugate addition–elimination reactions.



**SCHEME 6.44** (a)  $\text{Br}_2$  then pyridine; (b) NBS; (c)  $\text{Nu}^-$ (1); (d)  $\text{Et}_3\text{N}$  or DBN; (e)  $\text{Nu}^-$ (2)

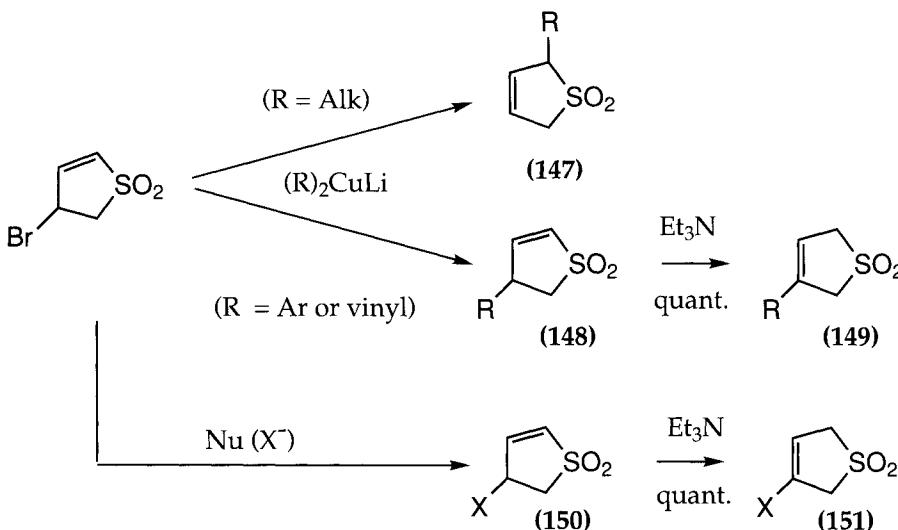
**TABLE 6.19**

X	Nucleophile	Y	Products (yield %)	
			( <b>144</b> <b>145</b> )	( <b>145</b> )
Cl	NaSPh	SPh	68 (17)	100
Cl	$\text{NaSO}_2\text{Ph}$	$\text{SO}_2\text{Ph}$	22 (45)	
Cl	$\text{NaN}_3$	$\text{N}_3$	61	82
TMS	NaSPh	SPh	87	81
TMS	$\text{NaN}_3$	$\text{N}_3$	86	7 <sup>a</sup>
SPh	NaSPh	SPh	1 (93)	100
SPh	$\text{NaSO}_2\text{Ph}$	$\text{SO}_2\text{Ph}$	66 (33)	
SPh	$\text{NaN}_3$	$\text{N}_3$	91	73
SPh	NaOMe	OMe	98	

<sup>a</sup> Significant desilylation to 3-azido-3-sulfolene was found to occur.

Useful yields of substituted 3-sulfolenes were produced by nucleophilic reactions with 4-bromo-2-sulfolenes [41,50]. Treatment with alkyl cuprates led to conjugate displacement, providing 2-substituted-3-sulpholenes (**147**), whereas aryl or vinyl cuprates gave direct displacement products (**148**), which were easily isomerized to

the 3-sulpholenes (**149**). A range of heteronucleophiles also reacted by direct displacement. Sulfide and sulfone products (**150**) and were again easily isomerized to 3-sulfolenes (**151**). Not all nucleophiles gave substitution products; in some cases anion exchange occurred and in other cases elimination occurred followed by dimerization (Scheme 6.45, Table 6.20).



SCHEME 6.45

TABLE 6.20

Nucleophile	R/X	Product	Yield (%)
Me <sub>2</sub> CuLi	Me	( <b>147a</b> )	87
Bu <sub>2</sub> CuLi	Bu	( <b>147b</b> )	70
(H <sub>2</sub> C=CH) <sub>2</sub> CuLi	H <sub>2</sub> C=CH	( <b>148a</b> )	41
Ph <sub>2</sub> CuLi	Ph	( <b>148b</b> )	64
NaSPh	SPh	( <b>150a</b> )	86
NaSO <sub>2</sub> Ph	SO <sub>2</sub> Ph	( <b>151b</b> )	86

Malonate anions were found to undergo conjugate addition to 2-sulfolenes bearing a 4-phenylsulfone group (**152**). This led to a useful method for preparing 3,4-disubstituted sulfolenes (**154a–d**) through an interesting addition–elimination process starting from (**152a–d**) [51]. 2-Sulfolenes (**153**) were initially formed, but were readily isomerized to 3-sulfolenes (Scheme 6.46, Table 6.21).

### 6.3.4.1 Substitution via palladium catalysed coupling

3-Sulfolene has been converted to a variety of 3-aryl-3-sulfolenes via a Pd(0)-catalysed coupling method. A representative range of aryl iodides were coupled with 3-sulpholene using a catalytic amount of Pd(OAc)<sub>2</sub> [59] (Scheme 6.47).

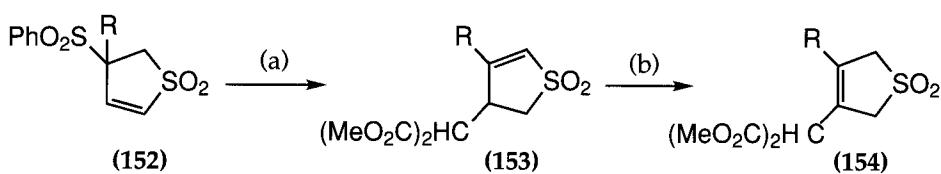
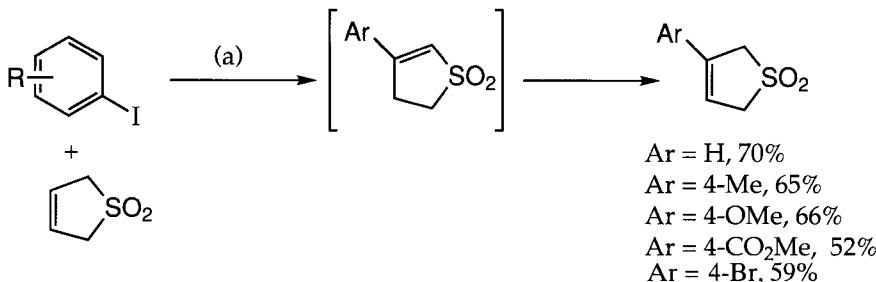
SCHEME 6.46 (a)  $\text{NaCH}(\text{CO}_2\text{Me})_2$ /THF/reflux; (b)  $\text{NaOMe}/\text{MeOH}/\text{reflux}$ 

TABLE 6.21

Substituent (R)	Compound	Products (yield %)	
		(153)	(154)
Me	(a)	73	81
Et	(b)	88	91
$\text{CH}_2\text{CH}=\text{CH}_2$	(c)	79	12
$\text{CH}_2\text{Ph}$	(d)	71	75

SCHEME 6.47  $\text{Et}_3\text{N}/\text{Bu}_4\text{NBr}/\text{Pd}(\text{OAc})_2$  (5 mol%)/benzene

## 6.4 FORMATION OF DIENES FROM SULFOLENES

Sulfolenes are powerful tools for synthetic organic chemistry, mainly because of their ability to act as masked dienes. Cheletropic extrusion of  $\text{SO}_2$  releases the diene and this is commonly utilized to participate in an *in situ* Diels–Alder reaction.

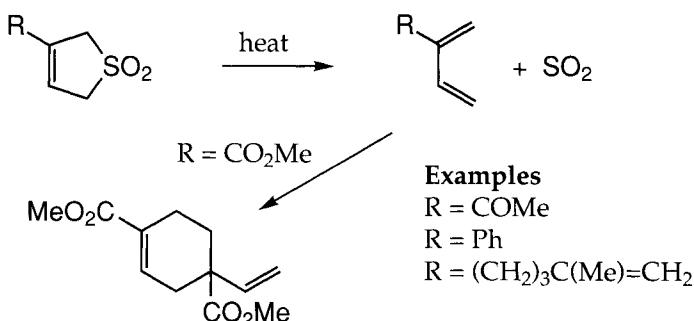
The  $\text{SO}_2$  extrusion is normally induced by heating the sulfolene. The temperature required to bring about extrusion is somewhat dependent on the substituents, but 110–130°C is normally sufficient and heating to reflux in a solvent such as toluene is a convenient way to bring about the reaction. Higher boiling solvents, or a sealed tube, can be used if required for the extrusion or for a subsequent *in situ* Diels–Alder reaction. Alternatives to thermal

methods have also been reported, and these include treatment with lithium aluminium hydride [57] or ultrasonically dispersed potassium (USP) [32]. It has been reported that the USP method is useful for bringing about  $\text{SO}_2$  extrusion from 2,2,5,5-tetrasubstituted sulfolenes, which are stable to thermal conditions [30].

## 6.4.1 Sulfur Dioxide Extrusion from Monosubstituted Sulfolenes

### 6.4.1.1 Dienes from 3-substituted sulfolenes

The elimination of  $\text{SO}_2$  from simple 3-substituted 3-sulfolenes is normally straightforward under thermal conditions, and there are no geometrical considerations. However, some dienes, such as 2-carbomethoxy butadiene, are unstable because of spontaneous Diels–Alder dimerization [83,84] (Scheme 6.48).

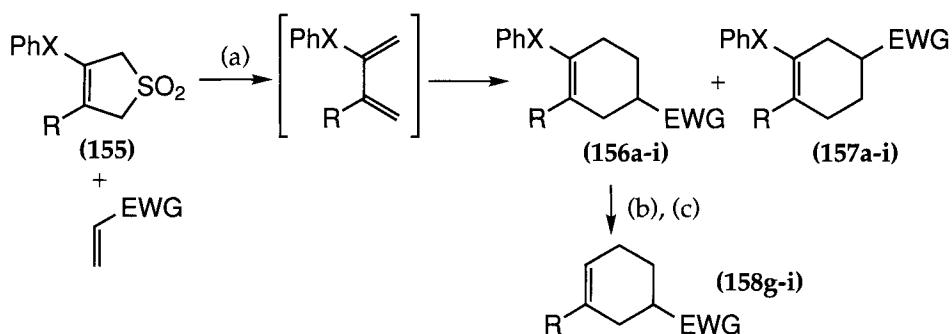


SCHEME 6.48

Simple 3-substituted dienes are therefore often generated with a dienophile present in order to bring about an *in situ* Diels–Alder reaction. This has led to some useful regiochemical studies; for example, dienes with sulfur or selenium substituents in the 3-position gave high regioselectivity for 1,4-substituted products with electron-deficient dienophiles [77,93] (Scheme 6.49, Table 6.20). It was useful that the thiophenyl group could be reductively removed from (**156g–i**) to provide (**158g–i**) regioselectively.

### 6.4.1.2 Dienes from 2-substituted sulfolenes

A variety of methods are available for preparing 2-substituted sulfolenes, as described in Section 6.3. The extrusion of sulfur dioxide is a concerted stereospecific process, and has been shown to follow a disrotatory pathway. Sulfur dioxide extrusion from mono-2-substituted sulfolenes could in principle lead to (*E*)- or (*Z*)-diene formation through alternative disrotatory modes of reaction.

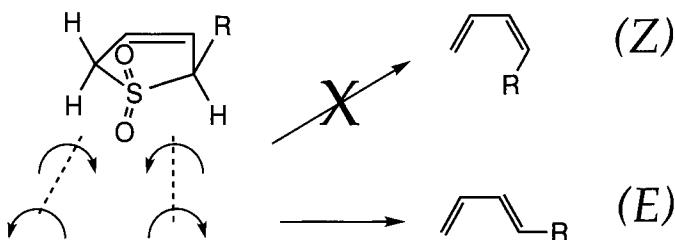


SCHEME 6.49 (a) 110°C/toluene; (b) mCPBA; (c) Na(Hg)

TABLE 6.22

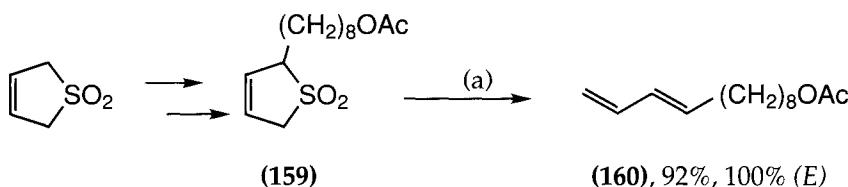
Reference	X	R	EWG	Yield (%)	(156) : (157)
(a)	S	H	COMe	97	91 : 9
(b)	S	H	CO <sub>2</sub> Et	95	91 : 9
(c)	S	H	C≡N	90	>95 : <5
(d)	Se	H	COMe	96	82 : 18
(e)	Se	H	CO <sub>2</sub> Et	94	83 : 17
(f)	Se	H	C≡N	81	>95 : <5
(g)	S	Me	COMe	77	95 : 5
(h)	S	Me	CO <sub>2</sub> Me	68	93 : 7
(i)	S	Me	C≡N	77	96 : 4

However, (*E*)-dienes are normally produced in a highly selective manner, because there is less steric crowding in the transition state leading to that isomer [62,63] (Scheme 6.50).



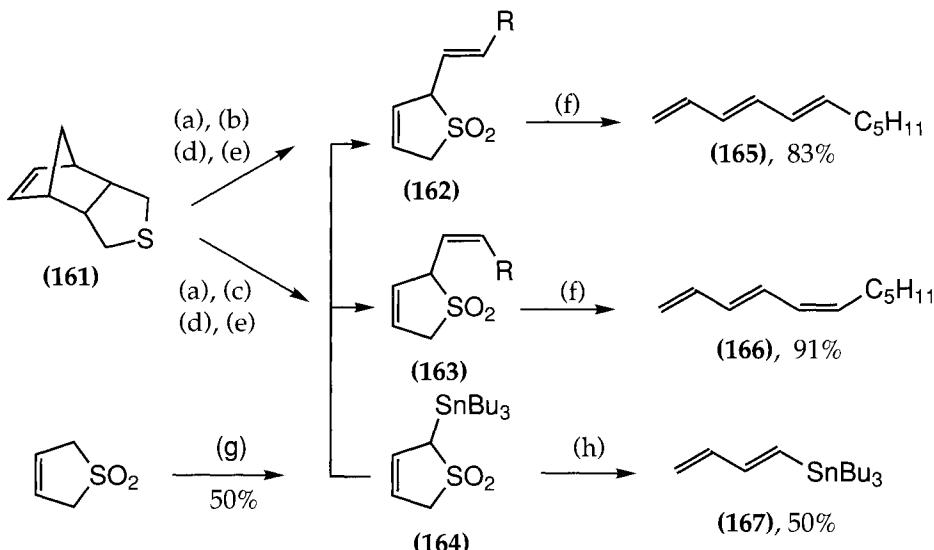
SCHEME 6.50

An example of the stereoselective formation of (*E*)-dienes was the synthesis of a red bullworm moth pheromone (**160**). Sulfolene (**159**) was available from 3-sulfolene by selective alkylation, and on heating gave diene (**160**) as a single isomer [116,117] (Scheme 6.51).

SCHEME 6.51 (a)  $125^{\circ}\text{C}/\text{EtOH}/\text{NaHCO}_3$ 

(*E*)- and (*Z*)-sulfolenes (**162**) and (**163**) were prepared from (**161**) by an interesting route involving a retro-Diels–Alder reaction [14]. They were also prepared by a palladium-catalysed coupling of stannane (**164**) with the appropriate vinyl iodides [105] (Scheme 6.52). The presence of the alkene bond adjacent to the sulfolene ring lowered the transition state energy for  $\text{SO}_2$  extrusion, which took place at  $40\text{--}50^{\circ}\text{C}$ . The products were natural trienes (**165**) and (**166**), formed with complete stereoselectivity with respect to the central alkene bond.

Stannane (**164**) was prepared by reaction of the anion of 3-sulfolene with  $\text{Bu}_3\text{SnI}$ , and was also converted to the useful (*E*)-stannylbutadiene (**167**) [58].

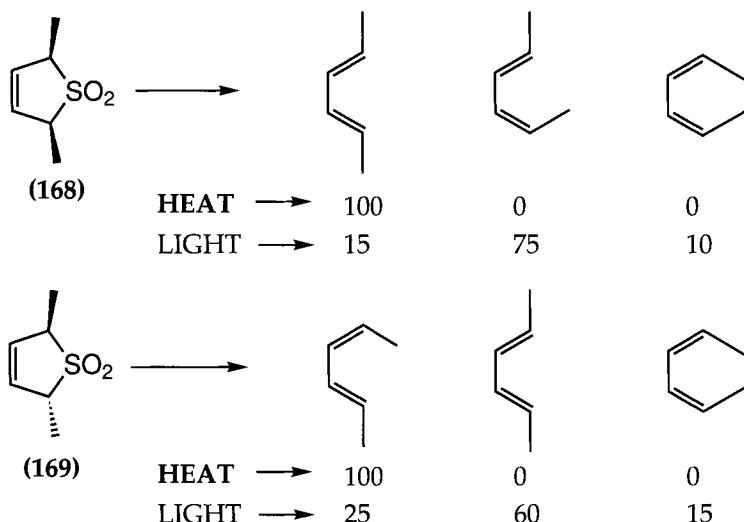
SCHEME 6.52 (a)  $\text{NCS}/\text{toluene}/20^{\circ}\text{C}$ ; (b) unsaturated (*E*)- $\text{CH}=\text{CHC}_5\text{H}_{11}/\text{THF}/0^{\circ}\text{C}$ ; (c) unsaturated (*Z*)- $\text{CH}=\text{CHC}_5\text{H}_{11}/\text{THF}/0^{\circ}\text{C}$ ; (d)  $600^{\circ}\text{C}$ ; (e)  $\text{KHSO}_5/\text{MeOH}/\text{H}_2\text{O}$ ; (f)  $40\text{--}50^{\circ}\text{C}/0.05$  torr and trapping at  $-78^{\circ}\text{C}$ ; (g)  $\text{LHMDS}/\text{Bu}_3\text{SnI}/\text{THF}$ ; (h)  $\text{Xylene}/\text{pyridine}/\text{reflux}$ 

#### 6.4.2 Sulfur Dioxide Extrusion from 2,5-Disubstituted Sulfolenes

Orbital symmetry arguments imply that thermal sulfolene opening reactions should follow a disrotatory mode of reaction, and this prediction was confirmed experimentally [82,85–87]. When heated, *cis*-2,5-dimethyl-3-sulfolene (**168**) was

converted to *(E,E)*-2,4-hexadiene stereospecifically, whereas the *trans* isomer (**169**) was converted to *(E,Z)*-2,4-hexadiene.

When the same reactions were carried out under photochemical conditions, mixtures of diene isomers were formed in which the conrotatory extrusion products predominate, in accordance with orbital symmetry predictions [95] (Scheme 6.53).



SCHEME 6.53

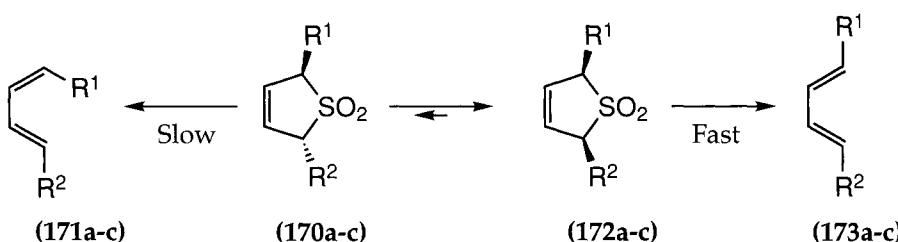
From a practical point of view, disrotatory extrusion of  $\text{SO}_2$  can be assumed for thermal reactions, and the geometry of the diene formed is therefore dictated by the stereochemistry of the sulfolene precursor.

*Trans*-2,5-disubstituted sulfolenes (e.g., (**170a/b**)) can be prepared by alkylation procedures as described in Section 6.3. Under thermal (neutral) or reductive conditions these extrude  $\text{SO}_2$  to give the predicted *(E,Z)*-dienes (**171**). However, a dramatic reversal of stereoselectivity was observed when the reactions were carried out under basic conditions [116,117] (Scheme 6.54, Table 6.23). This appears to be because the rate of  $\text{SO}_2$  extrusion to the *(Z)*-alkene is relatively low. Thus, under basic conditions, epimerization to the *cis*-sulfolene (**172**) can occur and this will extrude  $\text{SO}_2$  at a much higher rate than (**170**). This principle has been used in the synthesis of (**173b**), a sex pheromone of the coding moth, and *(E,E)*-11,12-hexadecadienal, a cabbage webworm sex pheromone.

An alternative approach to 2,5-*cis* disubstituted sulfolenes (**172**) and their *(E,E)*-diene derivatives (**173**) involves the sequential *exo*-alkylation of (**174**), followed by tandem retro-Diels–Alder– $\text{SO}_2$  extrusion [12,13] (Scheme 6.55).

Ultrasonically dispersed potassium (UDP) has been utilized to promote the rapid, stereoselective extrusion of  $\text{SO}_2$  from di-, tri-, and tetrasubstituted 3-sulfolenes [39] (Scheme 6.56).

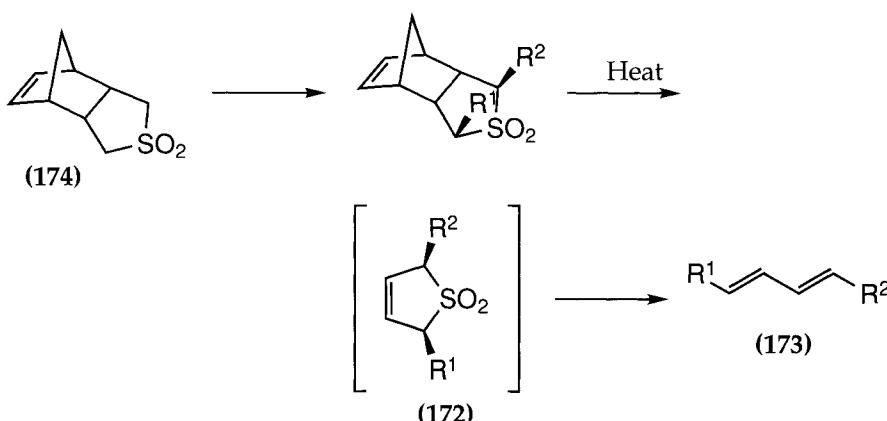
The reactions are instantaneous with the *trans*-dialkylated 3-sulfolenes giving 8:1



SCHEME 6.54

TABLE 6.23

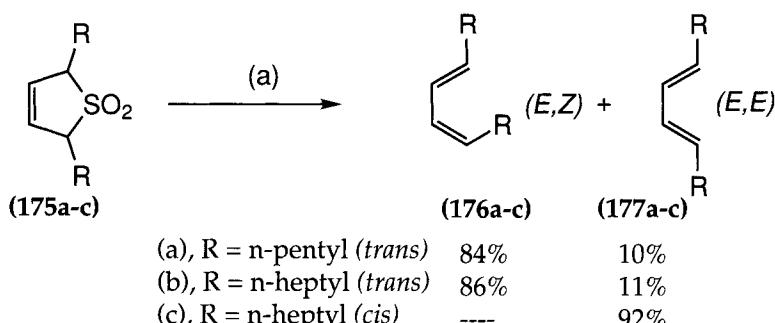
Substrate	R <sup>1</sup>	R <sup>2</sup>	Conditions	(171) : (173)	Yield (%)
(170a)	Bu <sup>n</sup>	Bu <sup>n</sup>	Octane/125°C	97:3	92
(170a)	Bu <sup>n</sup>	Bu <sup>n</sup>	KOH/EtOH/125°C	0:100	90
(170a)	Bu <sup>n</sup>	Bu <sup>n</sup>	LiAlH <sub>4</sub> /Et <sub>2</sub> O/36°C	100:0	91
(170b)	(CH <sub>2</sub> ) <sub>2</sub> OH	Me	K <sub>2</sub> CO <sub>3</sub> /EtOH/125°C	0:100	100
(170c)	(CH <sub>2</sub> ) <sub>10</sub> OH	Et	K <sub>2</sub> CO <sub>3</sub> /EtOH/125°C	0:100	94



SCHEME 6.55

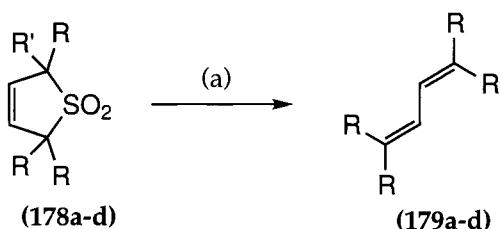
mixtures of (*E,Z*:*E,E*)-dienes (**176/177**) and the *cis*-dialkylated 3-sulfolenes, giving (*E,E*)-dienes (**177**) exclusively. If the reactions were conducted in an inert atmosphere, the stereoselectivity was improved to around 20:1 ratio, but longer reaction times were required, giving poor overall yields. The small quantities of (*E,E*)-dienes from *trans* sulfolenes were apparently formed by isomerization after SO<sub>2</sub> extrusion.

Trisubstituted 3-sulfolenes (**178a–b**) behaved similarly, affording high yields of (*E*)-trisubstituted dienes. Although tetrasubstituted 3-sulfolenes (**178c–e**) did not



SCHEME 6.56 (a) (i) UDP/1 min/toluene/reflux

react under these conditions, the introduction of a proton source facilitated the reaction [30] (Scheme 6.57, Table 6.24).



SCHEME 6.57 (a) (i) UDP/1 min/toluene

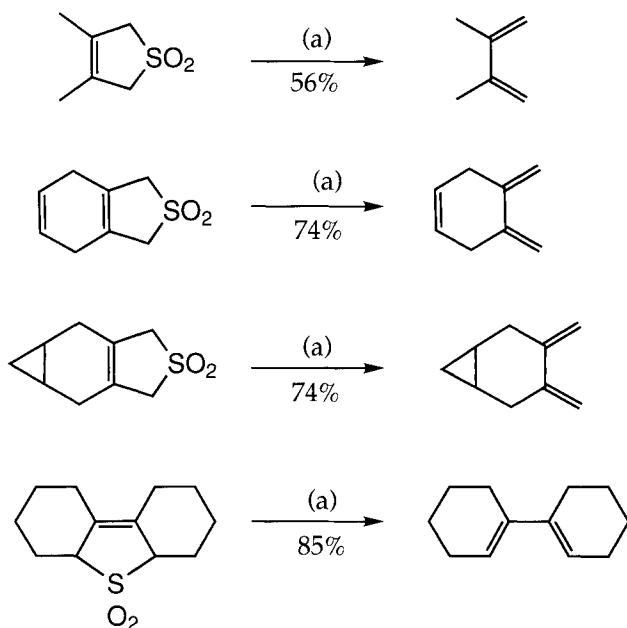
TABLE 6.24

Reference	R	R'	Proton source	Yield (%)
(a)	Et	H	—	90
(b)	Pr	H	—	91
(c)	Et	Et	None	—
(c)	Et	Et	$\text{H}_2\text{O}$	64
(c)	Et	Et	$\text{Bu}'\text{OH}$	92
(d)	Bu	Bu	$\text{Bu}'\text{OH}$	70

### 6.4.3 Sulfur Dioxide Extrusion from 3,4-Disubstituted Sulfolenes

In general,  $\text{SO}_2$  extrusion from 3,4-disubstituted sulfolenes is straightforward and there are no stereochemical implications. Alternative methods for  $\text{SO}_2$  extrusion have been reported. Examples of some sulfolenes which underwent reductive desulfonylation in  $\text{LiAlH}_4$  are shown in Scheme 6.58 [57]. It was postulated that the cheletropic elimination of  $\text{SO}_2$  proceeds via thermal cleavage, with  $\text{LiAlH}_4$

acting as a catalyst by lowering the transition state energy and binding to the liberated  $\text{SO}_2$ .



**SCHEME 6.58** (a) solid sulfolene added to  $\text{LiAlH}_4$  in ether at reflux

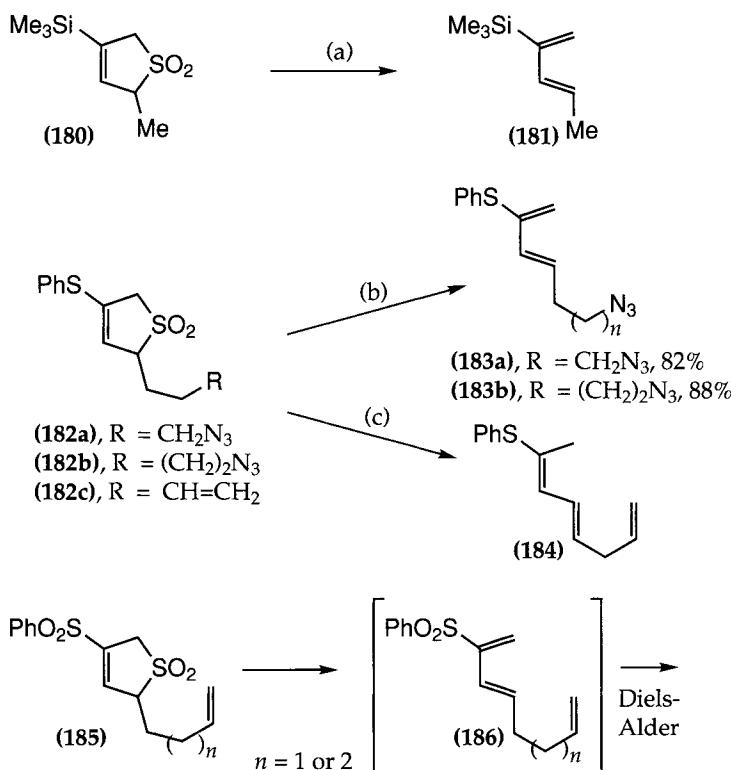
#### 6.4.4 Sulfur Dioxide Extrusion from 3,5-Disubstituted Sulfolenes

The geometrical preferences during  $\text{SO}_2$  extrusion from 3,5-disubstituted sulfolenes are similar to those for mono-2-substituted compounds, and dienes with (*E*)-geometry are generated. For example, sulfolene (**180**) opened to give diene (**181**) exclusively and the geometry was easily established by NMR coupling-constant data [50].

For extrusion of  $\text{SO}_2$  from the thiophenyl sulfolenes (**182a–c**) the course of the reaction appeared to depend on the nature of the 5-substituent. Azides (**182a/b**) gave dienes (**183a/b**) cleanly [22], whereas thermolysis of (**182c**) gave only the rearranged diene (**184**), said to be ‘as a result of a 1,5-hydrogen shift from the expected triene.’ However, the derived sulfone (**185**) extruded  $\text{SO}_2$  smoothly and the diene (**186**) underwent a spontaneous Diels–Alder cyclization (see Section 6.5 for details) [24] (Scheme 6.59).

#### 6.4.5 Sulfur Dioxide Extrusion from 2,3-Disubstituted Sulfolenes

2,3-Substituted sulfolenes can again undergo one of two disrotatory ring-opening pathways, leading to different geometrical diene isomers. However, it is not easy to

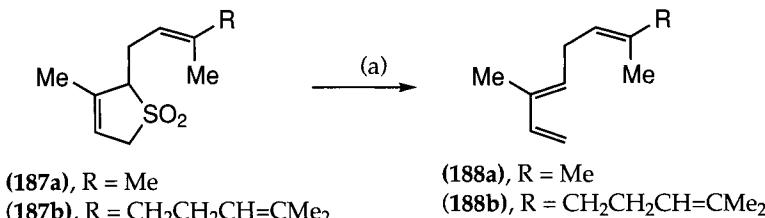


**SCHEME 6.59** (a) Preparative GC/240°C; (b)  $\text{CHCl}_3$ /reflux; (c) toluene/reflux

predict which diene isomer will be preferred and, because the alkene in question is trisubstituted, it is not possible to distinguish between them by simple coupling-constant data. For this reason, particular diene geometries have often been suggested in the literature without conclusive experimental evidence.

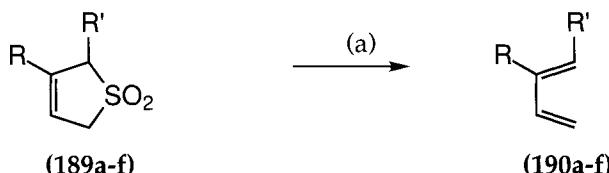
The terpenes *trans*- $\beta$ -ocimene (**188a**) and  $\alpha$ -farnesene (**188b**) were prepared by preparative GC treatment of sulfolenes (**187a**) and (**187b**), respectively (Scheme 6.60). The geometry of the dienes was deduced by comparing the data of the products with that from the natural compounds [46,109]. Sulfolenes with terminal alkenyl chains in the 2-position and a methyl group in the 3-position were also prepared and were assumed to also give (*E*)-dienes. These cyclized spontaneously to hydroindans or hydronaphthalene compounds [43,47,68,109].

A range of 2-alkyl-3-methyl sulfolenes (**189a,b**) [104] were prepared by



**SCHEME 6.60**

alkylation of sulfolene anions, and a range of 2-alkenyl-3-sulfolenes (**189c–e**) [105] were prepared by palladium-catalysed coupling reactions. In all cases extrusion of  $\text{SO}_2$  was said to give the (*E*)-diene with very high selectivity (Scheme 6.61, Table 6.25). Replacing the 3-methyl group with  $\text{CH}_2\text{NMe}_2$  did not appear to alter the stereoselectivity and this methodology was utilized for the synthesis of quinolizidine alkaloids [90] (see Section 6.5 for more detail).



SCHEME 6.61 (a) Heat

TABLE 6.25

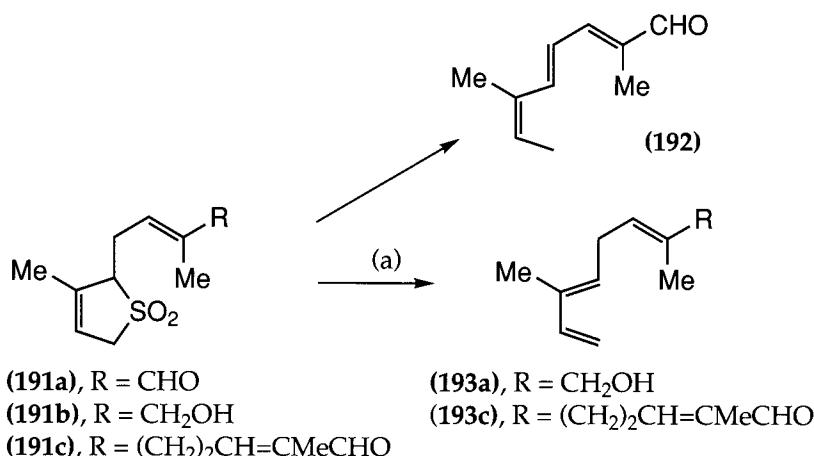
Reference	R	R'	Geometry	Yield (%)
(a)	Me	Et	( <i>E</i> ) (100%)	100
(b)	Me	Bu	( <i>E</i> ) (100%)	100
(c)	Me	( <i>E</i> )- $\text{CH}=\text{CHBu}$	( <i>E</i> ) (>95%)	95
(d)	Me	( <i>Z</i> )- $\text{CH}=\text{CHBu}$	( <i>E</i> ) (>95%)	92
(e)	Me	cyclohexenyl	( <i>E</i> ) (>95%)	84
(f)	$\text{CH}_2\text{NMe}_2$	$(\text{CH}_2)_3\text{CO}_2\text{Bu}^t$	( <i>E</i> )	?

Chou's synthetic strategy for terpenes was developed further, to give access to terpinals. Alkylation of 3-sulfolene with allylic reagents was found to occur efficiently, without the need for HMPA, and the terminal allylic methyl groups could be oxidized selectively to provide aldehydes (**191a**) and (**191c**). Thermal desulfonation of (**191a**) gave only the rearranged triene (**192**), said to be caused by [1,5]-prototropic shift. However, the alcohol (**191b**) was desulfurized without rearrangement, as was the aldehyde (**191c**), which provided  $\alpha$ -sinensal (**193c**) [54] (Scheme 6.62).

Sulfur dioxide extrusion from  $\alpha$ -hydroxy sulfolenes (**194a–f**) also appears to give (*E*)-dienes [55,118] (Scheme 6.63, Table 6.26). Rearrangement of dienes such as (**195f**) was found to occur, but this could be avoided by protecting the alcohol as a silyl ether [92].

From the examples above, it appears that 2,3-substituted sulfolenes with a methyl group as the 3-substituent open in a highly selective manner to provide the diene with the two substituents *cis* to one another, but this is not always the case with other 3-substituents.

2-Alkyl-3-thiophenyl sulfolenes gave (*Z:E*)-dienes (**197**) in a ratio of about 9:1 [20]. The geometry of the dienes was determined by nuclear Overhauser enhancement ( ${}_{\text{n}}\text{O}_e$ ) measurements (Scheme 6.64, Table 6.27, entries **a–d**). A trimethylsilyl group in the 3-position appeared to have a similar effect [106] (Table 6.27, entry **e**).



SCHEME 6.62 (a) Pyridine/reflux

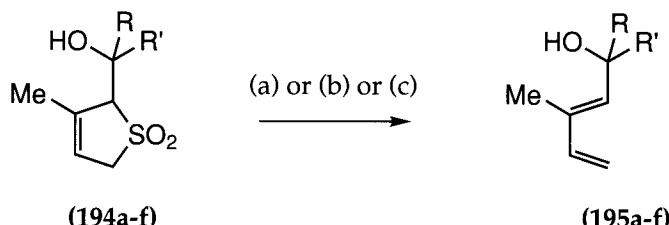
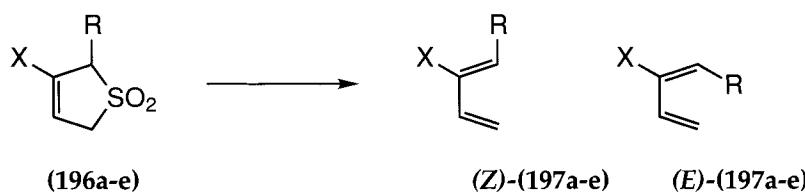
SCHEME 6.63 (a) EtOH/NaHCO<sub>3</sub>/125°C; (b) pyridine/reflux; (c) (i) TMS-Cl/pyridine, (ii) Pyridine/reflux

TABLE 6.26

Entry (194, 195)	Method	R	R'	Yield (%)
(a)	(a)	Me	Me	84
(b)	(a)	Ph	H	70
(c)	(a)	CH=CM <sub>2</sub>	Me	96
(d)	(b)	CH <sub>2</sub> CM <sub>2</sub> (OCH <sub>2</sub> ) <sub>2</sub>	H	68
(e)	(b)	CH <sub>2</sub> CH <sub>2</sub> Ph	H	74
(f)	(c)	CH=CM <sub>2</sub>	H	72

In our laboratories, problems have been encountered in predicting the stereoselectivity of intramolecular Diels–Alder reactions from 2,3-disubstituted sulfolenes bearing a methyl ester or dimethylamide in the 3-position, intermediate dienes of differing geometries perhaps being responsible [70,72,75]. Model sulfolenes we therefore constructed to find out the effect of changing substituents

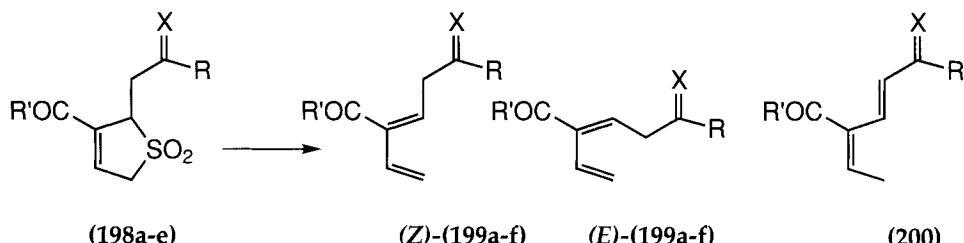


**SCHEME 6.64**

TABLE 6.27

Entry	X	R	Z : E ratio	Yield (%)
(a)	SPh	Me	86 : 14	99
(b)	SPh	Et	90 : 10	85
(c)	SPh	Pr <sup>i</sup>	100 : 0	99
(d)	SPh	CH <sub>2</sub> Ph	96 : 4	99
(e)	SiMe <sub>3</sub>	Bu <sup>n</sup>	90 : 10	

on the diene geometry generated during  $\text{SO}_2$  extrusion (Scheme 6.65, Table 6.28). The geometries of all the diene products were determined by  $^n\text{O}_e$  experiments. In



**SCHEME 6.65**

TABLE 6.28

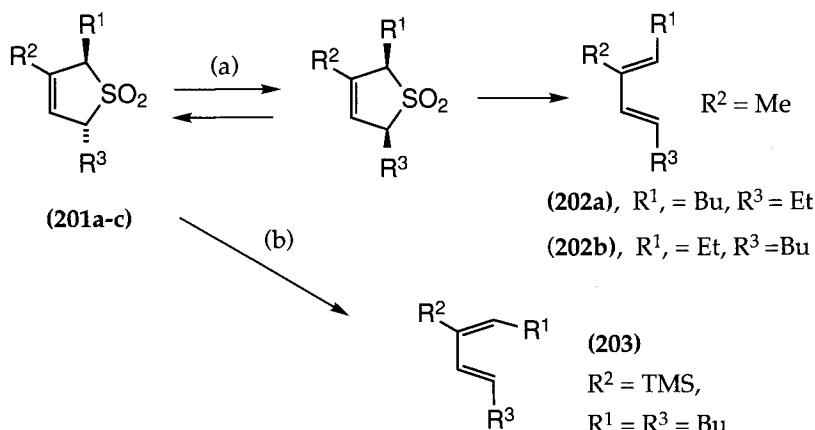
Entry	X	R	R'	(E)-(199)	(E)-(199)	(200)
<b>(a)</b>	(OMe) <sub>2</sub>	H	NMe <sub>2</sub>	1	0	0
<b>(b)</b>	(OMe) <sub>2</sub>	H	N(Me)OMe	1	0	0
<b>(c)</b>	=CMe <sub>2</sub>	H	NMe <sub>2</sub>	1	0	0
<b>(d)</b>	O	OMe	NMe <sub>2</sub>	1	0	0
<b>(e)</b>	O	NMe <sub>2</sub>	NMe <sub>2</sub>	>96	<2	<2
<b>(f)</b>	H <sub>2</sub>	NMeBn	OMe	>98	<2	0
<b>(g)</b>	=CH <sub>2</sub>	H	OMe	>96	<2	<2
<b>(h)</b>	O	NMe <sub>2</sub>	OMe	1	1	3 <sup>a</sup>
<b>(i)</b>	(OMe) <sub>2</sub>	H	OMe	Mixture containing (200)		

<sup>a</sup>After 6 h.

all cases, sulfolenes with an amide in the 3-position opened to give a (*Z*)-diene almost exclusively, as did methyl ester, entry (**f**). However, other methyl esters gave mixtures containing each diene isomer as well as rearranged diene (**200**). It is possible that the diene (**200**) is derived from the (*E*)-(**199**) by a sigmatropic [1,5]-hydrogen shift. 2,3-Dicarbomethoxy-3-sulfolene opens to give a 1:1 mixture of (*E*)- and (*Z*)-dienes [99].

## 6.4.6 Sulfur Dioxide Extrusion from 2,3,5-Trisubstituted Sulfolenes

2,3,5-Trisubstituted trienes open to give as the major product the geometrical isomers which would be predicted given the results for disubstituted compounds. Under basic conditions, **(201a,b)** with a 3-methyl substituent open to give *(E,E)*-dienes **(202)**, but the extrusion presumably occurs via the *cis*-sulfolene isomer [104]. Without base present (GC injection port 220°C), **(201c)** ( $R^2 = \text{TMS}$ ,  $R^1 = R^3 = \text{Bu}$ ) opens to give diene **(203)** (Scheme 6.66). No definitive proof of the assignment of above geometrical isomers was however presented.



**SCHEME 6.66** (a)  $\text{K}_2\text{CO}_3/\text{EtOH}/\text{heat}$ ; (b)  $220^\circ\text{C}/\text{GC injection port}$

Further studies should provide a better rationale for the opening of di- and trisubstituted sulfolenes to give particular diene geometrical isomers.

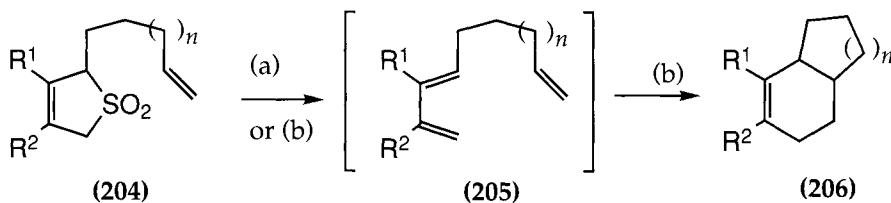
## 6.5 APPLICATIONS OF SUBSTITUTED SULFOLENES IN DIELS–ALDER BASED SYNTHESSES

As illustrated in the previous sections, a variety of methods has been developed for selective functionalization of the sulfolene nucleus. Sulfolenes are also readily

converted to dienes under thermal conditions. Thus, with careful utilization of the substitution methodology, they can be exploited for the construction of the central intermediates required in Diels–Alder-based synthetic strategies.

Sulfolenes have found particular favour for constructing precursors for intramolecular Diels–Alder reactions, since the extrusion of  $\text{SO}_2$  and the Diels–Alder cyclization require similar conditions, and normally occur in tandem in a single synthetic step. The value of sulfolene intermediates in intramolecular Diels–Alder strategies has been recognized and put to good effect since the early 1980s. In recent years more systematic studies have been carried out, methods for introducing different substituents have been developed, and stereochemical preferences have been explored.

Several studies have been carried out on the transformation of sulfolenes bearing a 2-alkenyl chain into hydroindenes and hydronaphthalenes. The 2-substituents of sulfolenes (**204a–f**) were introduced by selective alkylation methods, and thermolysis provided bicyclic compounds (**206a–f**) [43,47,109]. The intermediate dienes (**205a–f**) could be isolated and were found to be single isomers, presumed to be of (*E*)-geometry, but this was not confirmed experimentally. It was interesting that monosubstituted dienes cyclized with low selectivity, whereas the presence of a 2- or 3-methyl substituent led to almost complete stereoselectivity. In some of the cases, the sense of the stereoselectivity was not confirmed, but the major isomer was tentatively assigned as *trans* (Scheme 6.67, Table 6.29).



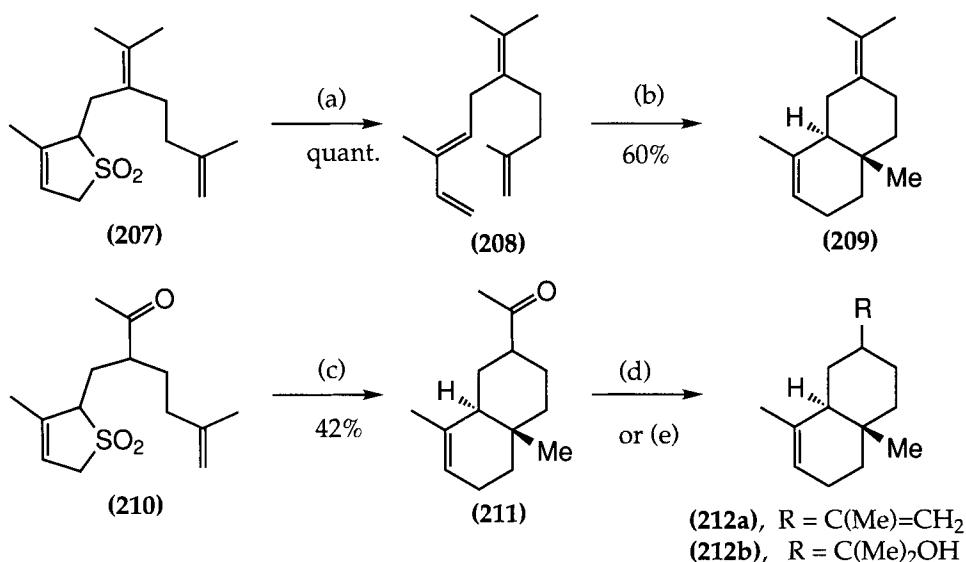
**SCHEME 6.67** (a) Preparative GC/injection temperature 240°C/oven temperature 150°C; (b) 580°C

**TABLE 6.29**

Entry	$\text{R}^1$	$\text{R}^2$	$n$	<i>cis:trans</i>	Yield (%)
(a)	H	H	1	3:1	67
(b)	H	H	2	1:1	73
(c)	Me	H	1	<sup>a</sup>	75
(d)	Me	H	2	<5:>95	76
(e)	Me	Me	1	<sup>a</sup>	58
(f)	Me	Me	2	<sup>a</sup>	51

<sup>a</sup>Only one product isolated (>95%), stereochemistry not determined, but tentatively assigned as *trans*.

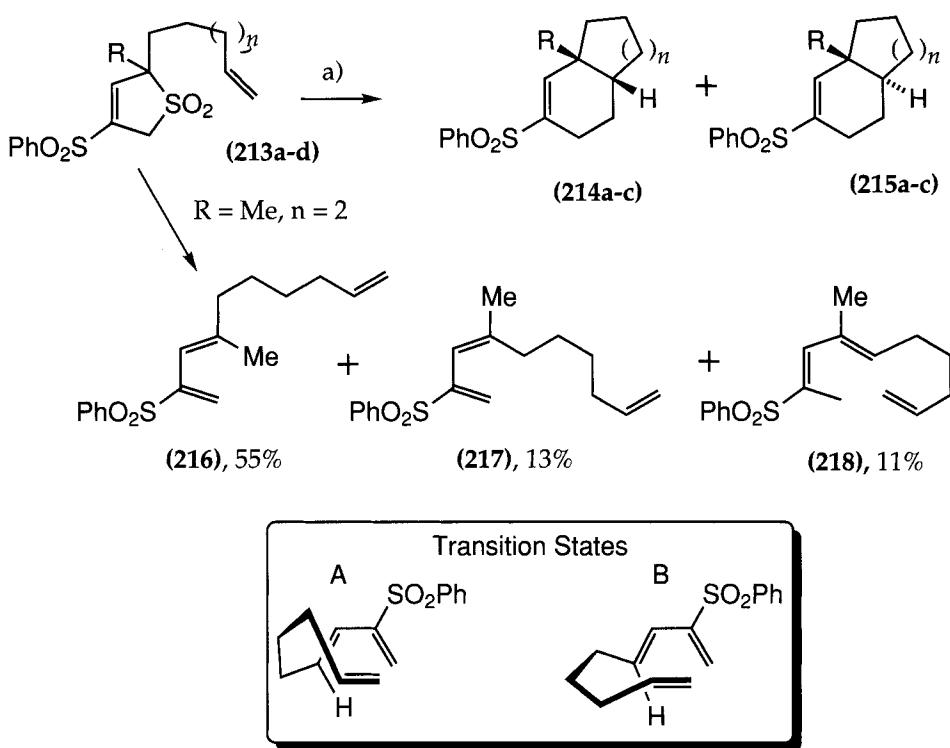
The methodology was extended to provide synthetic routes to the sesquiterpenes eudesmane (209),  $\alpha$ -selinene (212a), and  $\alpha$ -eudesmol (212b) [43,68] (Scheme 6.68). The intermediate diene (208) was found to be a single isomer, presumed to have (*E*)-geometry.



**Scheme 6.68** (a) Hot tube/180°C; (b) toluene/sealed tube/190°C; (c) toluene/sealed tube/170°C; (d) Ph<sub>3</sub>P=CH<sub>2</sub>; (e) MeMgBr

When hydroindenes and hydronaphthalenes were prepared by reaction of 2-alkenyl-3-sulfolenes bearing a sulfur substituent at C-4, the oxidation state of the sulfur, the alkenyl chain length, and the nature of the other sulfolene substituents were all found to have important contributions in controlling the reactivity and stereoselectivity of the reactions. Only rearranged dienes were formed from sulfolenes with a 4-thiophenyl substituent (see Section 6.4), but dienes were formed, without rearrangement, from the equivalent sulfones. Sulfolenes (213a) and (213b) reacted smoothly to give bicyclic compounds, but the stereoselectivity was low. Inserting an angular methyl group led to high *cis*-stereoselectivity in the hydroindene series, but sulfolene (213d) gave only a mixture of dienes (216)–(218) on heating. Transition states A and B were proposed for the formation of the isomeric bicycles and it was suggested that either transition state for cyclization of (216) would be too strained because of steric interactions [24] (Scheme 6.69, Table 6.30).

More recently, the formation of hydroindenes and hydronaphthalenes from sulfolenes bearing a 3-sulfone substituent has been investigated [19] (Scheme 6.70, Table 6.31). A substituent at C-4 had little effect on the stereoselectivity of the cyclization, but did affect the diene reactivity. Indeed, the strongly electron-donating thiophenyl group prevented cyclization taking place. Instead, dienes (222e) and (222f) were isolated and shown to have (*E*)-configurations. However,

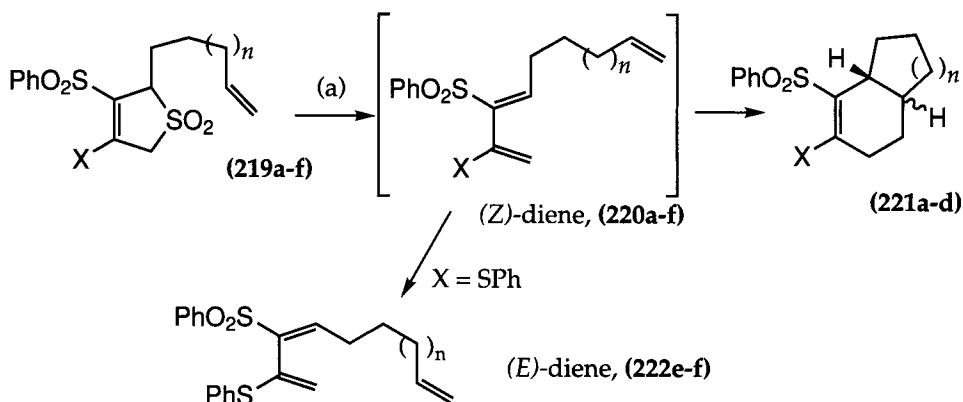


SCHEME 6.69 (a) Toluene/pyridine/165–250°C

dienes isolated after partial reaction of the other sulfolenes had (*Z*)-configurations, and it was suggested that it was the (*Z*)-isomers (220a–d) that were involved in the Diels–Alder cyclizations, and that the unreactive (*Z*)-dienes (220e,f) preferentially isomerize to the more stable (*E*)-arrangements.

Benzene-fused sulfolenes were found to be readily alkylated with alkenyl side-chains and the alkylated products, when heated, were converted to *o*-quinonodimethanes by SO<sub>2</sub> extrusion. These spontaneously reacted in an intramolecular Diels–Alder fashion, to produce tricyclic systems with good stereochemical control. The methodology was exploited in a short and efficient synthesis of ( $\pm$ )-estra-1,3,5(10)-triene-17-one (228) [89] (Scheme 6.71). Sulfolene (223) was first alkylated with tosylate (224) to provide (225) in good yield. After ketal removal, (226) was thermolysed to provide estratriene (228) in 85% yield, via *o*-quinonodimethane (227). The compound was contaminated by 5–7% of the C-9 epimer, which was easily removed by recrystallization.

In a later study, a tetracyclic quassinoid skeleton was synthesized in optically active form, starting from (+)-methylcarvone. The sulfolene aldehyde (229) was prepared by regioselective allylation of 3-methyl-3-sulfolene, followed by oxidative cleavage of the alkene bond. Reaction of (229) with the enolate formed from methylcarvone (230) provided alcohol (231), which was acetylated to give (232). Heating (232) provided the tricycle (233) as a single diastereoisomer, and this was



SCHEME 6.70 (a) Heat/130–310°C

TABLE 6.30

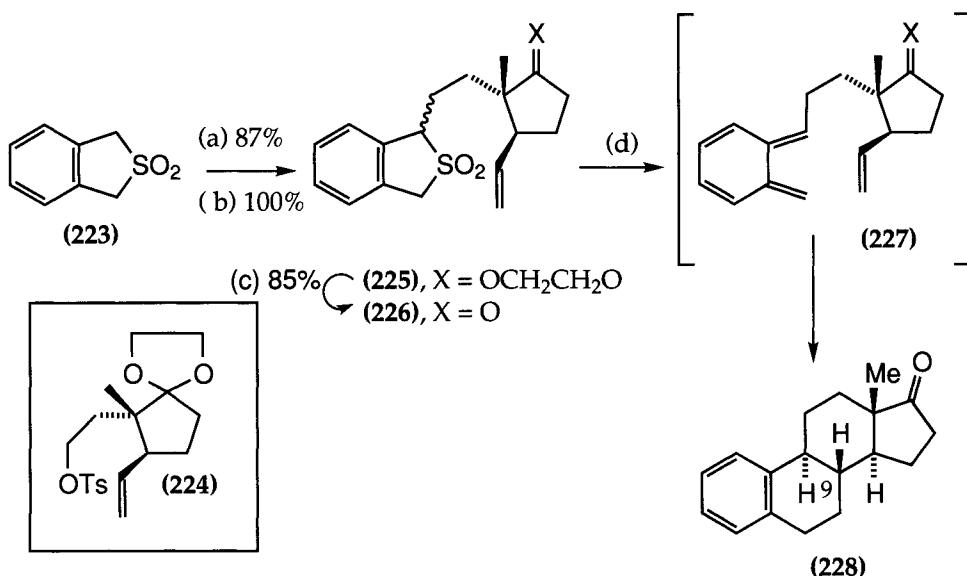
Entry	R	n	Yield (214) (%)	Yield (215) (%)
(a)	H	1	53	12
(b)	H	2	27	26
(c)	Me	1	88	0
(d)	Me	2	–	–

TABLE 6.31

Entry	X	n	trans:cis	Yield (221) (%)
(a)	H	1	3:1	75
(b)	H	2	100:0	98
(c)	Me <sub>3</sub> Si	1	2.3:1	88
(d)	Me <sub>3</sub> Si	2	100:0	83
(e)	SPh	1	–	–
(f)	SPh	2	–	–

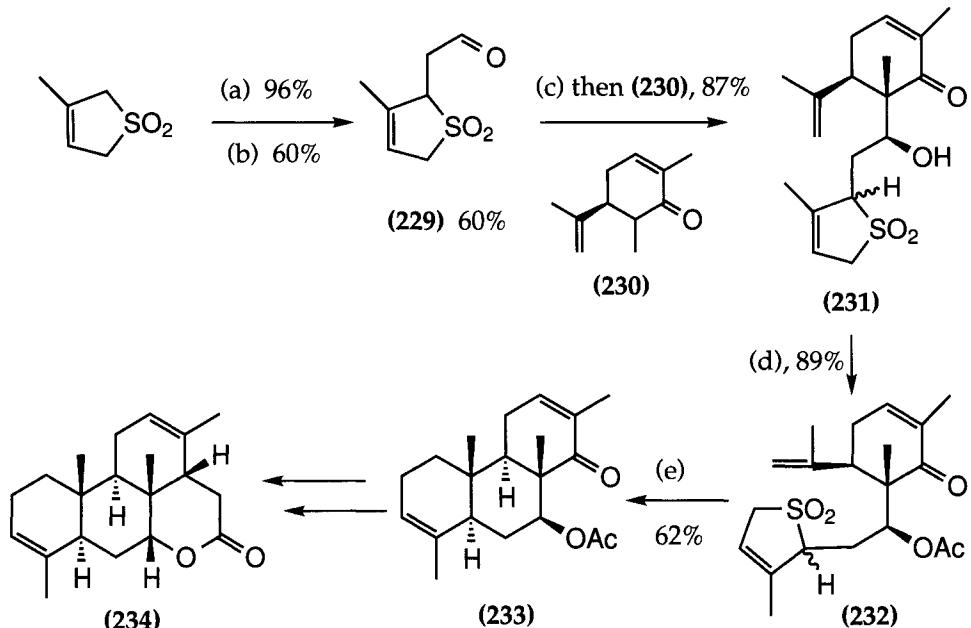
converted, in a number of steps, to the quassinoid skeleton (234) [97] (Scheme 6.72).

In early studies involving sulfolene-based synthetic approaches to alkaloids, intramolecular Diels–Alder cyclizations were carried out between dienes derived from monosubstituted sulfolenes and enamide dienophiles [80,81]. For example, acid chloride (233) reacted with imine (234) to provide enamide (235). Upon heating, this extruded sulfur dioxide and the intermediate diene cyclized to provide tricycle (236) stereoselectively. A straightforward sequence of steps was used to convert the Diels–Alder product into ketone (237), which had been used previously as a precursor to aspidospermine (238) (Scheme 6.73).

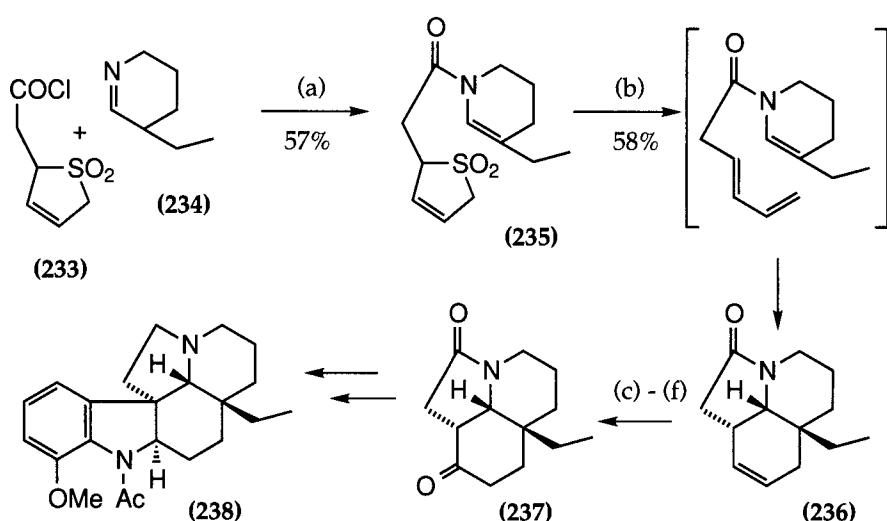


**SCHEME 6.71** (a) (i) 2 eq KH/DME/0–25°C/15 h, (ii) 1 eq (224)/87%; (b) AcOH–THF–H<sub>2</sub>O 3:2:2/45°C/24h/100%; (c) di-*n*-butyl phthalate/210°C/8 h/85%

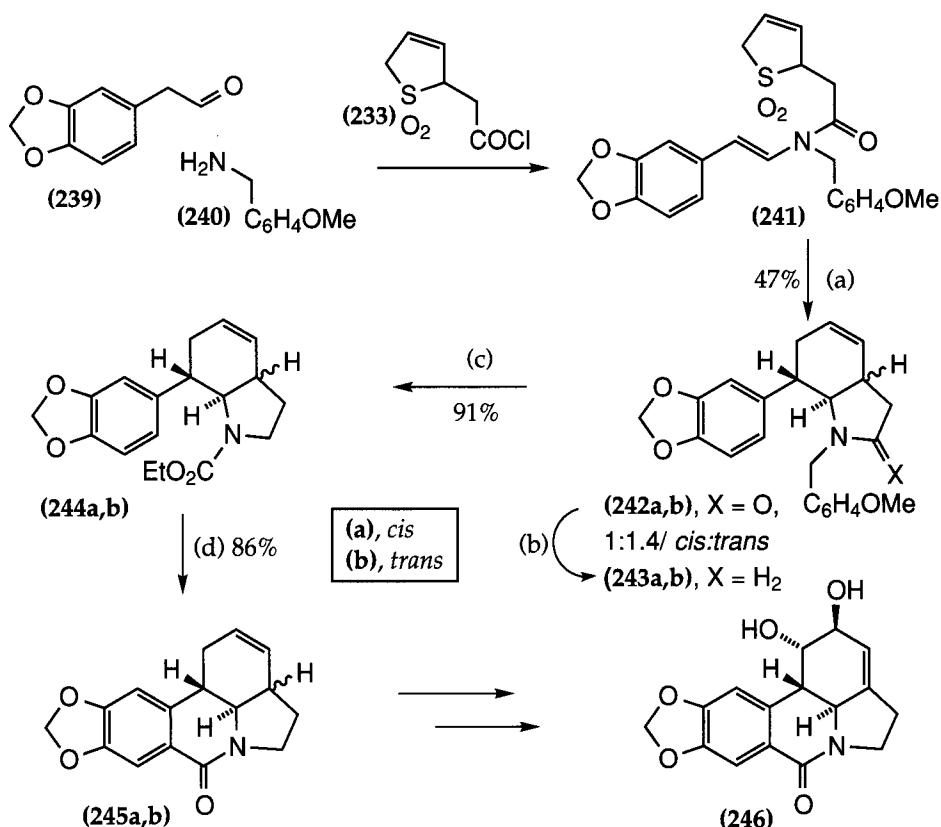
The Amaryllidaceae alkaloid lycorine (246) was also synthesized by a similar strategy [81]. Condensation of homopiperonal (239) with methoxybenzylamine



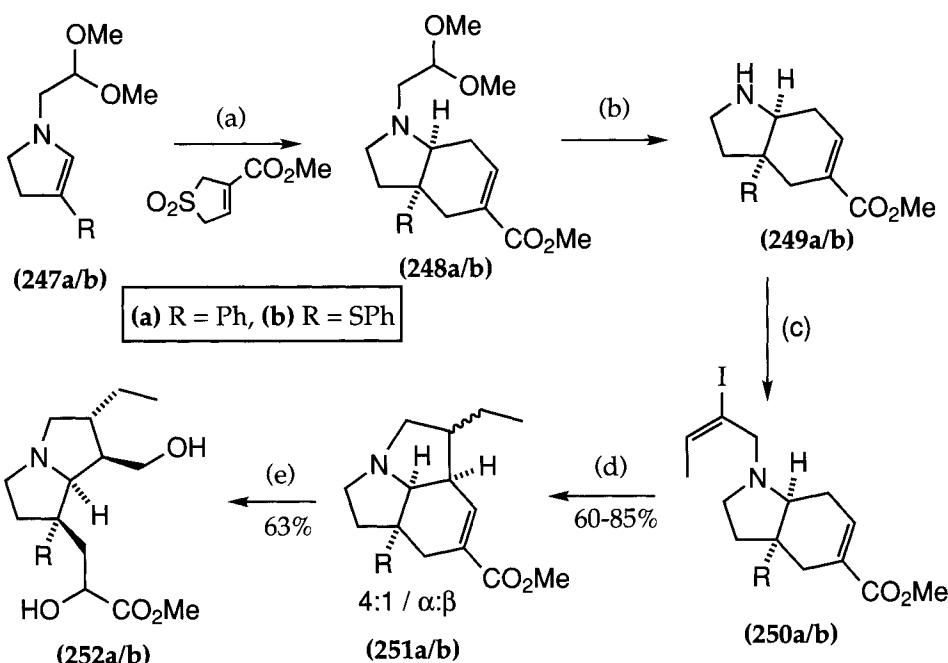
**SCHEME 6.72** (a) NaHMDS (2 eq)/THF/–105°C, allyl bromide; (b) (i) OsO<sub>4</sub>/MNO aq 1,4-dioxane, (ii) NaIO<sub>4</sub>, aq MeOH; (c) LDA/THF/DMPU/–78°C; (d) Ac<sub>2</sub>O/pyridine/DMAP, CH<sub>2</sub>Cl<sub>2</sub>/RT; (e) PhCN/190°C/110 h.



**SCHEME 6.73** (a)  $\text{DMF}/\text{Et}_3\text{N}$ ; (b) heated column/600°C; (c)  $\text{SeO}_2/\text{AcOH}$ ; (d)  $\text{KOH}/\text{EtOH}$ ; (e)  $\text{H}_2\text{CrO}_4/\text{pyridine}/\text{CH}_2\text{Cl}_2$ ; (f)  $\text{Pd/C}/\text{H}_2$



**SCHEME 6.74** (a) Xylene/reflux (+ additives); (b)  $\text{LiAlH}_4$ ; (c)  $\text{EtOCOCl/benzene/NaHCO}_3/\text{reflux}$ ; (d)  $\text{POCl}_3$



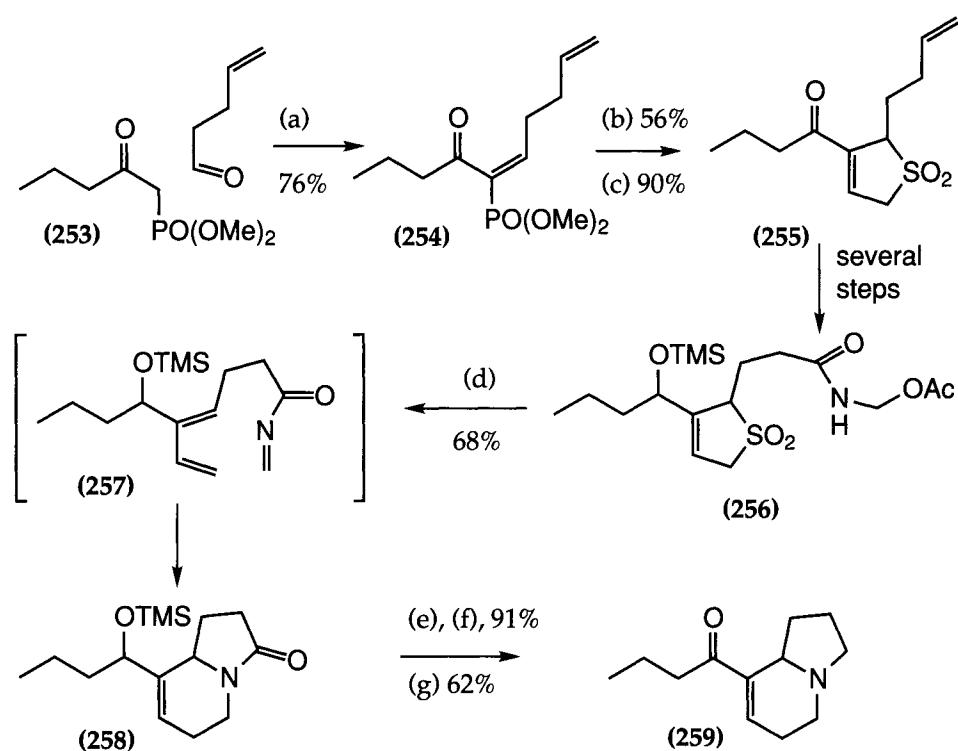
**SCHEME 6.75** (a) 110°C/PhMe; (b)  $(CO_2H_2)_2$  then aq PhNHOH.HCl in aq  $Na_2CO_3$ ; (c)  $trans$ -MeCH=ClCH<sub>2</sub>Br/K<sub>2</sub>CO<sub>3</sub>; (d) Bu<sup>n</sup><sub>3</sub>SnH/benzene/ $h\nu$ ; (e)  $O_3$ , then NaBH<sub>4</sub>/MeOH

(240), followed by reaction with acid chloride (233) provided enamide (241). This was thermolysed under carefully developed conditions to give Diels–Alder product (242) as a mixture of *cis* and *trans* isomers. A short sequence of steps was used to convert the *cis* isomer into (245a), from which lycorine had previously been synthesized (Scheme 6.74).

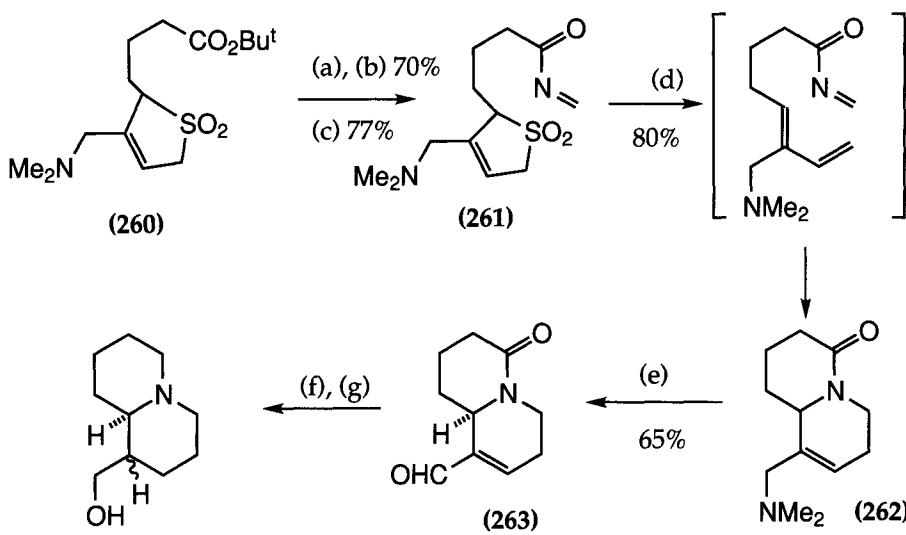
In a novel approach to the pyrrolizidine ring system, enamines (247a) and (247b) were heated with 3-carbomethoxy-3-sulfolene to give Diels–Alder adducts (248a/b) [67]. Following removal of the *N*-protecting group, vinyl iodides (250a/b) were formed and subjected to radical cyclizations to provide tricycles (251a/b). Finally ozonolysis gave the pyrrolizidines (252a/b) (Scheme 6.75).

The methodology of McIntosh and Sieler for construction of sulfolenes [83,84] was neatly modified and incorporated in a synthesis of the alkaloid elaeokanine (259) [96]. Ketophosphonate (253) was first condensed with 4-pentenal to give phosphonate (254), which was converted to sulfolene (255). This was transformed into amide (256), which expelled  $SO_2$  and AcOH upon heating; intermediate (257) cyclized spontaneously to bicycle (258), which was easily converted to elaeokanine (259) (Scheme 6.76).

A similar approach was later taken to the alkaloids lupinine and epilupinine [90]. Ester (260) was obtained by sulfolene alkylation and easily converted to enamide (261). Thermolysis of this gave Diels–Alder cyclization product (262), from which aldehyde (263) was obtained. Hydrogenation produced a mixture of



**SCHEME 6.76** (a) Piperidine/AcOH/benzene; (b)  $\alpha$ -mercaptopropanal/Et<sub>3</sub>N; (c) mCPBA; (d) 370°C; (e) MeOH/H<sup>+</sup>; (f) DIBAL/THF; (g) DMSO/TFAA/CH<sub>2</sub>Cl<sub>2</sub>

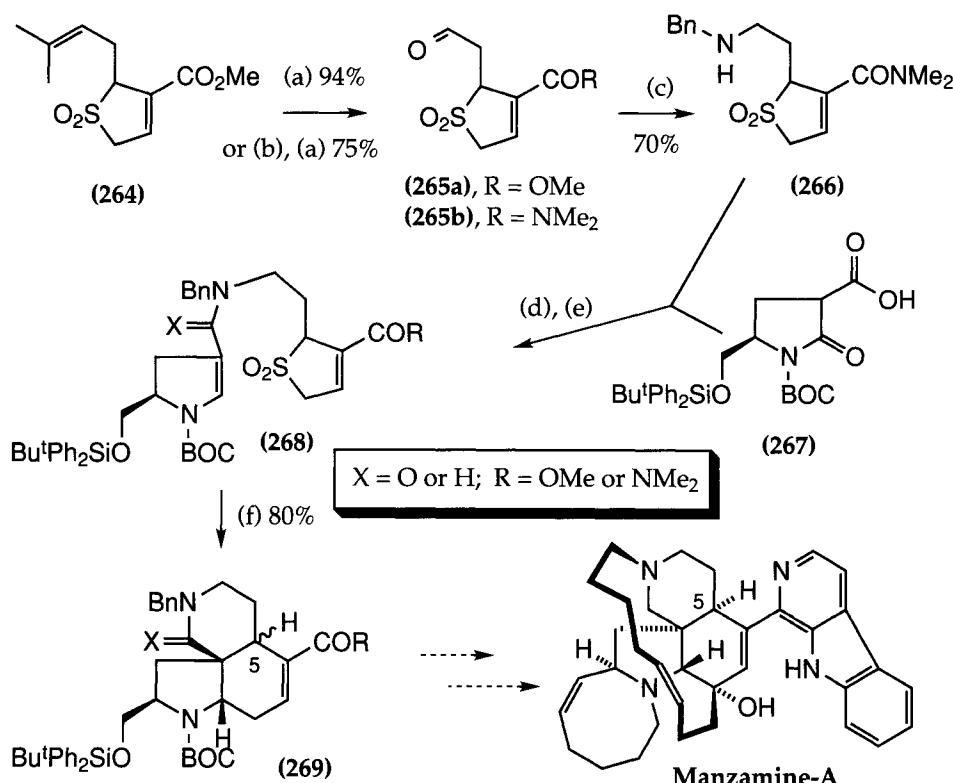


**SCHEME 6.77** (a) TFA/CH<sub>2</sub>Cl<sub>2</sub>; (b) EtOCOCl/Et<sub>3</sub>N/CH<sub>2</sub>Cl<sub>2</sub>, then NH<sub>2</sub>OH; (c) Ac<sub>2</sub>O/pyridine; (d) toluene/200°C; (e) mCPBA/CH<sub>2</sub>Cl<sub>2</sub>, then Ac<sub>2</sub>O; (f) H<sub>2</sub>/cat; (g) LiAlH<sub>4</sub>

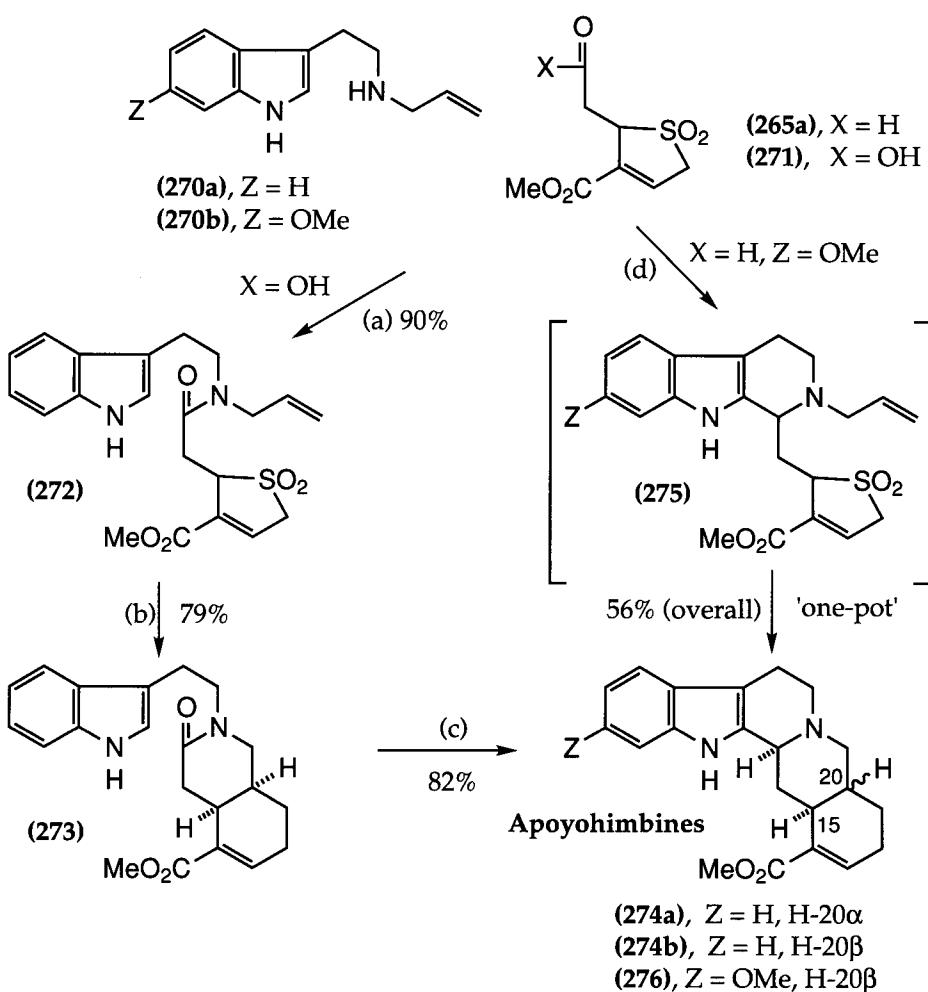
diastereoisomers, which led to a mixture of lupine and epilupine after  $\text{LiAlH}_4$  reduction (Scheme 6.77).

Our group began working with functionalized sulfolenes as part of an approach to the synthesis of manzamine-type alkaloids. Sulfolene (264) was prepared in good yield and excellent selectivity by prenylation of the dianion of 3-carbomethoxy-3-sulfolene [41]. Ozonolysis of (264) or its dimethylamide derivative provided aldehydes (265a) and (265b). These aldehydes have been useful intermediates in approaches to a variety of alkaloids. In the original manzamine approach, (265b) was reductively aminated to give amine (266), which was coupled to acid (267) to give an amide. The pyrrolidone carbonyl group was reduced, leading to Diels–Alder precursor (268) ( $X = \text{O}$ ). Desulfurization and cyclization led smoothly to tricycle (269) with one major stereoisomer predominating (~5:1). Unfortunately, the major stereoisomer had the wrong H-5 $\beta$  stereochemistry [72]. Recently we have been able to construct (268) ( $X = \text{H, H}$ ) in both the ester and amide forms, and are exploring their Diels–Alder cyclizations to determine if the stereochemical outcome is the same as in the series where  $X = \text{O}$  (Scheme 6.78).

The substituted sulfolene (265a) was also utilized in two complementary



**SCHEME 6.78** (a)  $\text{O}_3/\text{CH}_2\text{Cl}_2$ ; (b) (i)  $\text{LiOH}/\text{THF}/\text{H}_2\text{O}$ , (ii)  $\text{DCC}/\text{NHMe}_2$ ; (c)  $\text{PhCH}_2\text{NH}_2/\text{NaBH}_3\text{CN}/\text{MeOH}$ ; (d)  $\text{imidazole}_2\text{CO}$ ; (e) (i) superhydride, (ii)  $\text{MsCl}/\text{Et}_3\text{N}$ ; (f) toluene/reflux



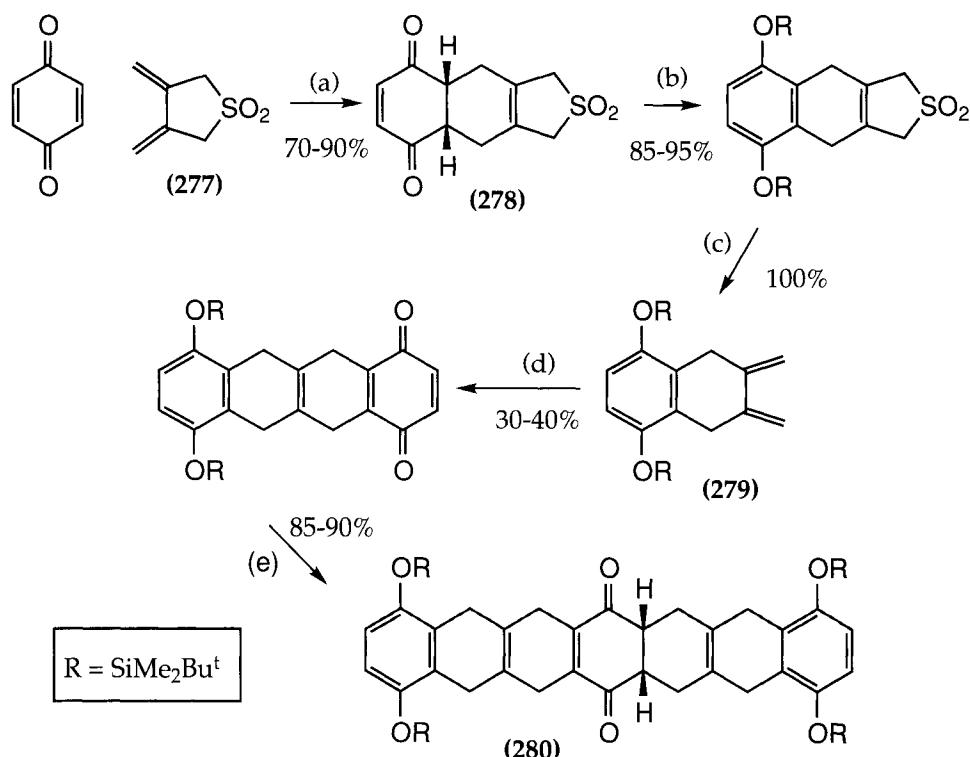
**SCHEME 6.79** (a) DCC/CH<sub>2</sub>Cl<sub>2</sub>; (b) toluene/reflux/3 h; (c) (i) POCl<sub>3</sub>/toluene, then (ii) NaBH<sub>4</sub>; (d) (i) AcOH/RT, then (ii) toluene/reflux

synthetic routes to *cis*- and *trans*-yohimbine alkaloids. The first route started from acid (271), which was first coupled to allyltryptamine to provide amide (272) in almost quantitative yield. Thermolysis of this gave 6,6-Diels–Alder products in 79% yield, with the *cis* isomer (273) predominating (4:1). Cyclization of the inseparable mixture provided apoyohimbines (274a/b) in a 4:1 ratio [70]. A more exciting prospect was a ‘one pot’ route from aldehyde (265a) to apoyohimbines, through tandem Pictet–Spengler (intermediate (275)) and Diels–Alder cyclizations. We have now devised a successful procedure for carrying this out. The ‘one-pot’ sequence is more efficient for tryptamine units substituted with an alkoxy group in the 6-position. For example, 11-methoxyapoyohimbine (276) was formed in 56% yield via (275), and the product was a single diastereoisomer [76] (Scheme 6.79).

Sulfone diene (277) was employed in an interesting approach towards linear chains of 1,2:4,5-fused cyclohexa-1,4-diene rings, both linear and cyclic (beltenes) [1]. A Diels–Alder reaction between sulfone (277) and benzoquinone provided sulfolene (278), which is potentially poised for addition of another sulfone diene, followed by desulfurization to reveal a bifunctional diene. Unfortunately, the bifunctional approach has not proved fruitful so far, but (278) has been extended by an iterative, linear procedure to provide linear fused systems such as (280) (Scheme 6.80).

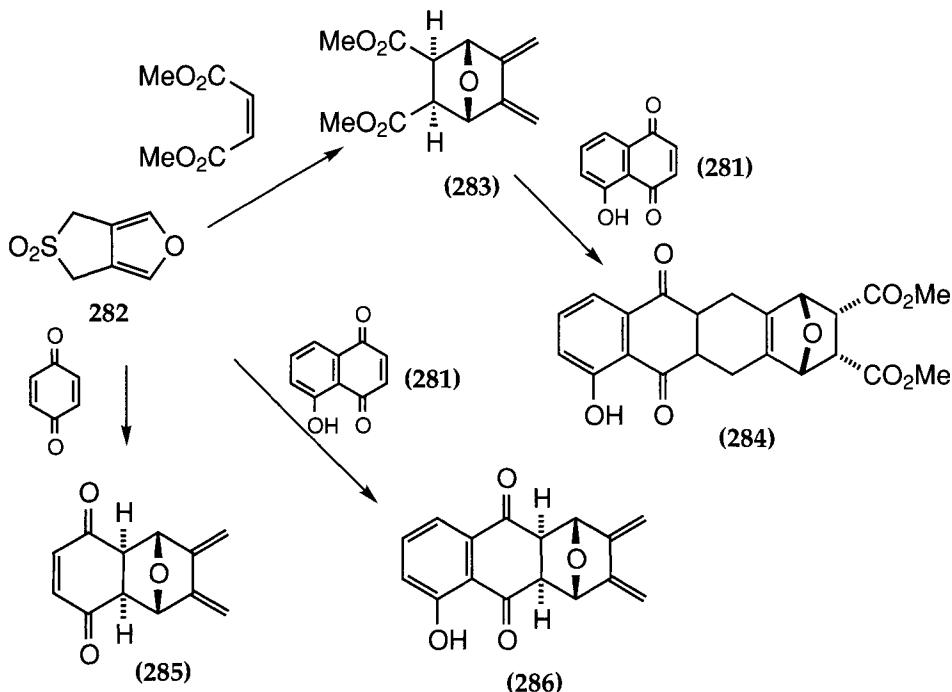
The chemistry of sulfolene-fused heterocycles has attracted a good deal of attention in recent years, particularly by the group of Takayama, and their work has been reviewed [2]. An interesting feature of the sulfolenes fused to five-membered ring heterocycles is that they can often be utilized as bifunctional dienes for consecutive Diels–Alder reactions.

Representative examples of the reactions of furan (282) are shown in Scheme 6.81 [102]. The furan system can be reacted as a diene initially with *in situ* desulfurization to release the diene from the sulfolene. This diene can then be reacted in a subsequent Diels–Alder reaction. For example, (283) reacts with juglone to give (284).

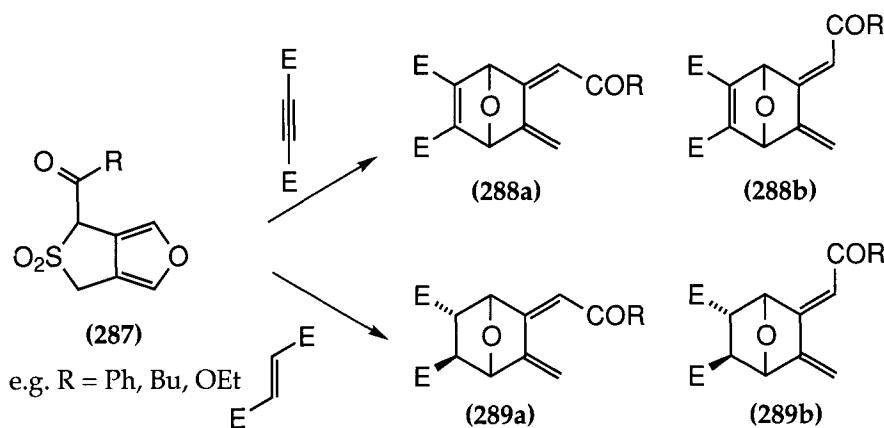


**SCHEME 6.80** (a) *p*-Benzoquinone/ $\text{CH}_2\text{Cl}_2$ /70–90%; (b)  $\text{Bu}^t\text{Me}_2\text{SiCl}$ /imidazole/DMF/85–95%; (c)  $\text{LiAlH}_4$ / $\text{Et}_2\text{O}$ /100%; (d) 2 eq *p*-benzoquinone/30–40%; (e) (279)/ $\text{EtOAc}$ /reflux/85–95%

Tandem Diels–Alder/desulfurization reactions of acylated derivatives (**287**) were interesting. The less stable dienes (**288a**) and (**289a**) were formed selectively, but molecular modelling studies were used to explain this behaviour [4] (Scheme 6.82).



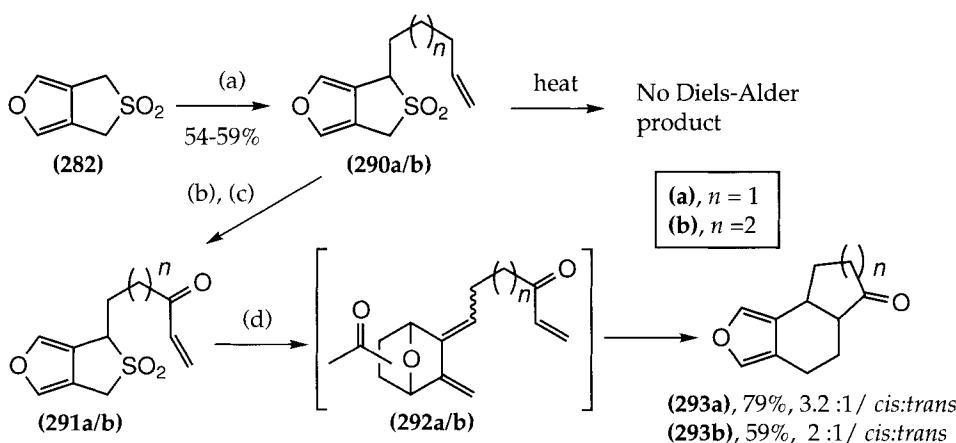
SCHEME 6.81



SCHEME 6.82

Substitution on the furan ring generally leads to mixtures of Diels–Alder products from intermolecular reactions [101], but intramolecular Diels–Alder reactions are easier to control.

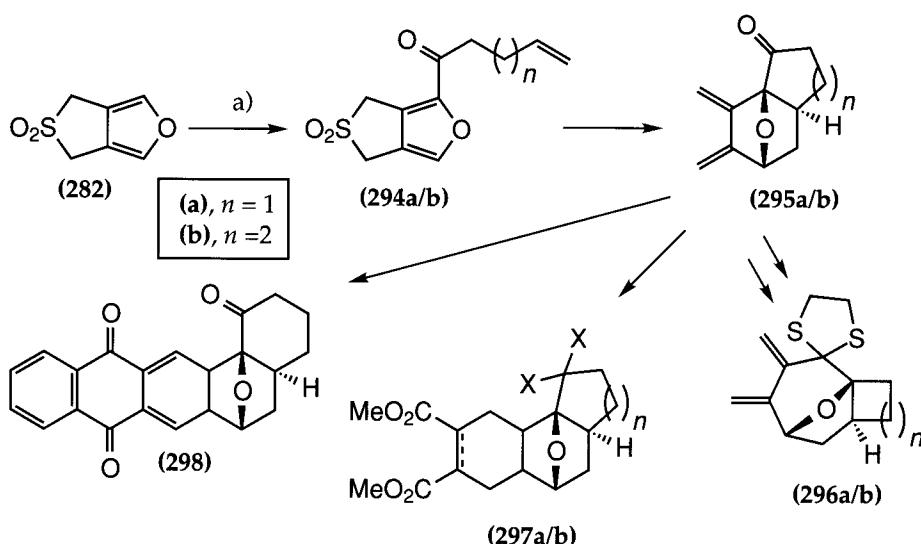
Furan (282) can be alkylated  $\alpha$  to the  $\text{SO}_2$  group, but a mixture of mono- and bis-alkylation products is always obtained. Alkene (290b) did not cyclize on heating and the sulfolene-derived diene moiety was unreactive towards intramolecular Diels–Alder cyclization, even following reaction of the furan moiety with dienophiles. However, dienophiles (291a/b) were more reactive and cyclized via (292a/b), which were formed *in situ* by reversible reaction of the furan with methylvinyl ketone [3] (Scheme 6.83).



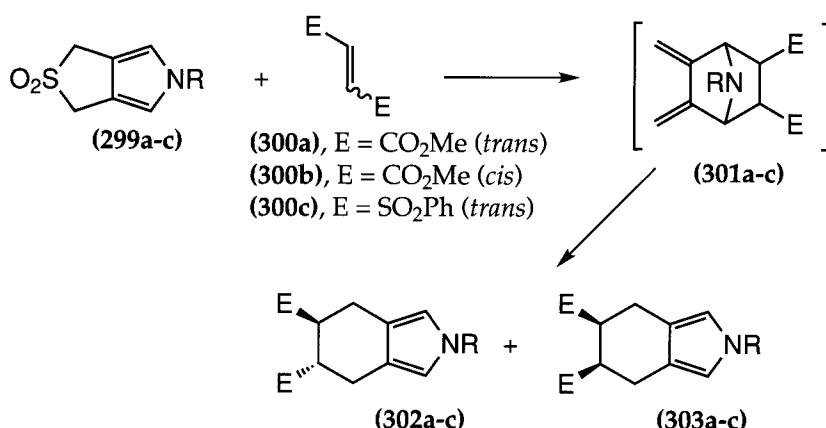
**SCHEME 6.83** (a) LiHMDS/THF/HMPA/ $\text{H}_2\text{C}=\text{CHCH}_2\text{CH}_2(\text{CH}_2)_n\text{Br}$ /54–59%; (b)  $\text{SeO}_2/\text{Bu}^{\prime}\text{OOH}$ ; (c) Swern oxidation; (d) (i) methyl vinyl ketone/RT, (ii) toluene/180°C/8 h

Acylated derivatives of (282), (294a/b), cyclized and expelled  $\text{SO}_2$  upon heating to afford dienes (295a/b) selectively. Intermolecular Diels–Alder reactions of the dienes were subsequently carried out. For example, tetracycles (297a/b) were formed from simple diester dienophiles, and hexacyclic system (298) was formed when juglone was the dienophile [60,66]. 1,3-Dithiane derivatives of (295a/b) underwent interesting rearrangements when treated with Lewis acids, leading to cyclobutane (296a) and cyclopentane (296b) [65] (Scheme 6.84).

*N*-Substituted pyrrole-fused sulfolenes (299a–c) also underwent Diels–Alder reactions in the heterocyclic ring, although the reactivity was somewhat lower than the furan analogue. The results of the reactions are complex and depend on reaction conditions and the nitrogen substituent, but some examples are presented below which illustrate the general trends. Electron-deficient alkenyl dienophiles react reversibly with the pyrrole moiety with concomitant extrusion of  $\text{SO}_2$ , and diene intermediates react further to afford adducts (302a–c) and (303a–c) [4,6] (Scheme 6.85, Table 6.32). With *N*-alkyl substituents, dimethyl maleate (*cis*) gave a



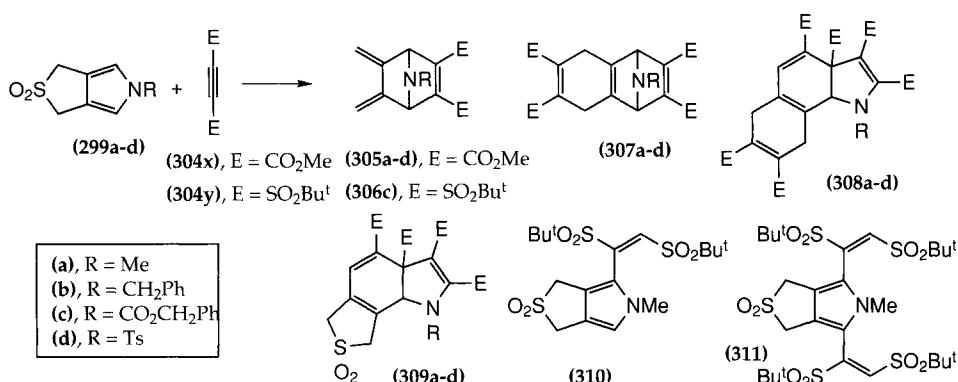
SCHEME 6.84



SCHEME 6.85

TABLE 6.32

Pyrrole (299)	R	Dienophile	E	(302) %	(303) %
(a)	Bn	(300a)	$\text{CO}_2\text{Me}$	91	—
(b)	$\text{CO}_2\text{CH}_2\text{Ph}$	(300a)	$\text{CO}_2\text{Me}$	88	—
(c)	Ts	(300a)	$\text{CO}_2\text{Me}$	0(NR)	0(NR)
(a)	Bn	(300b)	$\text{CO}_2\text{Me}$	23	47
(b)	$\text{CO}_2\text{CH}_2\text{Ph}$	(300b)	$\text{CO}_2\text{Me}$	0	97
(c)	Ts	(300b)	$\text{CO}_2\text{Me}$	0(NR)	0(NR)
		(300c)	$\text{SO}_2\text{Ph}$	71	0



SCHEME 6.86

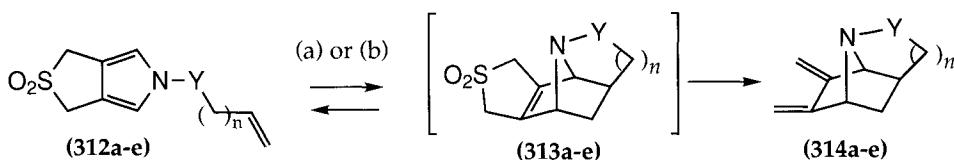
SCHEME 6.87 (a) Benzene/sealed tube/150°C; (b) 12 kbar/ $\text{CH}_2\text{Cl}_2$ 

TABLE 6.33

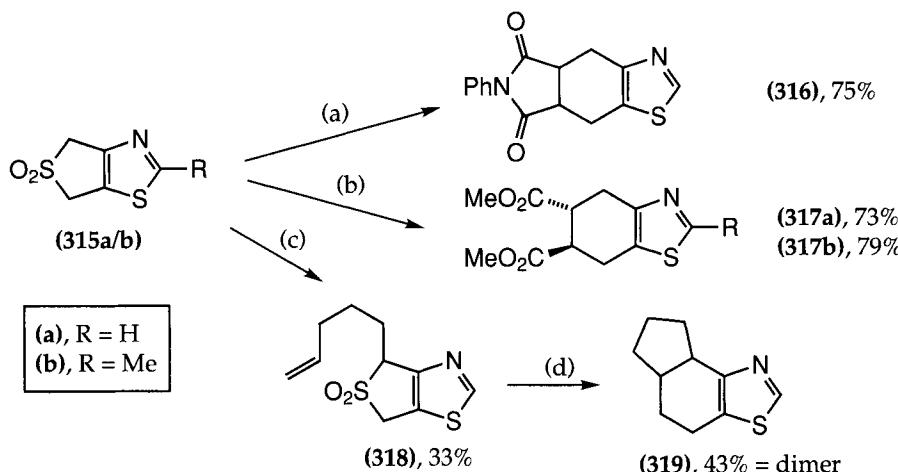
Entry	Y	n	Yield (%)	
			Thermal	High pressure
(a)	$\text{CO}_2$	1	46	66
(b)	CO	2	45	69
(c)	CO	1	48	54
(d)	$\text{SO}_2$	2	49	54
(e)	$\text{SO}_2$	1	43	52

mixture of *cis* and *trans* products, but when an electron withdrawing group was attached to nitrogen, the reactivity of the diene was increased, and only *cis* product was obtained. *N*-Tosyl derivatives did not react.

Electron-deficient acetylenes reacted irreversibly with (299a-c), and the products obtained were dependent upon the nitrogen substituent, the acetylene substituent, and reaction conditions. For reactions of dimethyl acetylene dicarboxylate, electron withdrawing groups on nitrogen led to a preference for the bis-adduct (307c/d), but rearranged products (308a/b) and (309a/b) (mainly (308a/b)) were produced for *N*-alkyl derivatives, with a small amount of diene (305a) produced under certain conditions. A different pattern was obtained when bis-*t*-butylsulfonyl acetylene was reacted with (299a) and (299c). Michael addition adducts (310) and (311) were formed from (299a), whereas diene (306c) was formed from (299c) (Scheme 6.86).

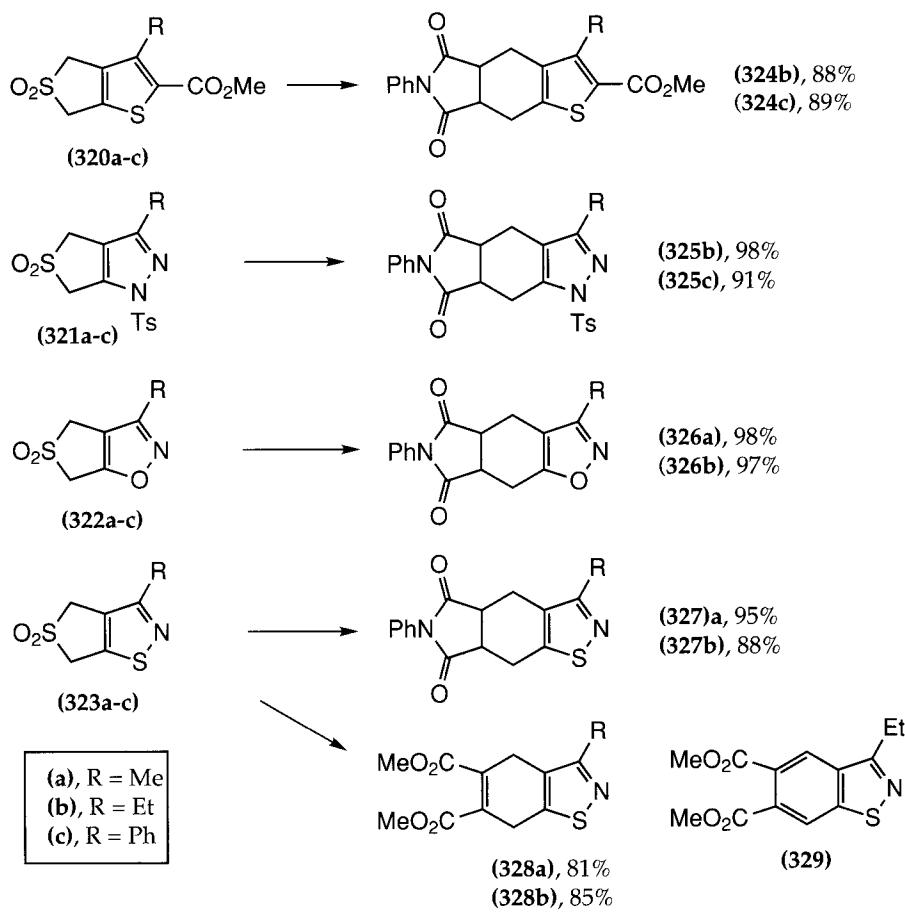
An interesting observation was that unactivated alkenes reacted as dienophiles in intramolecular Diels–Alder reactions of *N*-substituted pyrrole-fused sulfolenes. Compounds (312a–e) cyclized under thermal or high-pressure conditions, providing dienes (314a–e) in good yield. In contrast, the analogous pyrroles, lacking the fused sulfolene (281), did not cyclize under the same conditions. To explain this, it was suggested that the initial cyclizations were reversible but, following extrusion of  $\text{SO}_2$  from intermediates (313a–e), cycloreversion of dienes (314a–e) does not occur [100] (Scheme 6.87, Table 6.33).

Some interesting heterocyclic analogues of *o*-quinodimethylenes, which are known to be very unstable, have been prepared and trapped with dienophiles. Thiazole-fused sulfolenes (315a/b) provided intermolecular Diels–Alder products, derived from the intermediate *o*-quinodimethylene dienes when heated in the presence of suitable dienophiles. Thus (316) and (317a/b) were prepared by trapping with *N*-phenylmaleimide and dimethyl fumarate, respectively. Sulfolene (315a) was also alkylated, giving (318) which was converted to (319) on heating through an intramolecular Diels–Alder reaction [36] (Scheme 6.88).



**SCHEME 6.88** (a) Toluene/sealed tube/heat/*N*-phenylmaleimide; (b) sealed tube/heat/dimethyl fumarate; (c) (i) BuLi/HMPA, (ii) 5-iodo-1-pentene; (d) toluene/sealed tube/180–190°C

In later studies, dienes generated from sulfolenes (320–323) were trapped in situ, to provide Diels–Alder adducts of the *o*-quinodimethylene diene intermediates in good yields. Some examples of such reactions are shown in Scheme 6.89 [108,112].

SCHEME 6.89 Toluene/sealed tube/heat/*N*-phenylmaleimide or DMAD

## 6.6 CONCLUSION

Over recent years a diverse range of methods has been developed for preparing selectively functionalized 3-sulfolenes. The use of such compounds as diene precursors for intermolecular and intramolecular Diels–Alder reactions has also been explored extensively. Thus, it is now possible to prepare and utilize substituted sulfolene intermediates in efficient strategies for the synthesis of complex organic molecules. There is, however, scope for more research into the basic principles underlying the preparation and reactions of substituted sulfolenes.

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