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Stereoselective Reactions at the α-Carbon Atom in Organosulfur Compounds

Józef Drabowicz[a]; Piotr Kiełbasiński[a]; Piotr Łyzwa[a]
[a] Department of Organic Sulfur Compounds, Center of Molecular and Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza, Poland

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STEREOSELECTIVE REACTIONS AT THE α-CARBON ATOM IN ORGANOSULFUR COMPOUNDS

JÓZEF DRABOWICZ, PIOTR KIEŁBASIŃSKI and PIOTR ŁYŻWA
Center of Molecular and Macromolecular Studies, Polish Academy of Sciences, Department of Organic Sulfur Compounds, PL-90-363 Łódź, Sienkiewicza 112, Poland

(Received December 9, 1991)

The present state of knowledge concerning the formation of chiral carbon centers α to various sulfur substituents is reviewed. All the data are classified according to the valency of the sulfur in the sulfur-containing moiety. Thus, there are sections devoted to the formation of chiral carbon α to sulfenyl, sulfinyl and sulfonyl groups and to other, less common sulfur substituents. Within the sections appropriate subsections, concerning particular reactions, are included which allow the reader to find easily the proper subject.

Key words: Asymmetric induction; sulfenyl, sulfinyl and sulfonyl derivatives; cycloadditions; sulfur dienophiles; optically active sulfur compounds.

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CONTENTS

1. INTRODUCTION

The last two decades have witnessed the rapid development of investigations devoted to stereoselective syntheses of chiral carbon compounds in which the chiral carbon atom is directly linked to a heteroatom-containing substituent. This interest stems mainly from two facts. First of all, many such structures appear among natural products, often with very interesting biological activity. Secondly, these compounds, due to the presence of a heteroatom substituent can be easily and with high stereoselectivity converted to heteroatom-free compounds. The aim of the present report is to collect and discuss all synthetic procedures which can be considered as stereoselective functionalizations of a prochiral carbon atom linked directly to the sulfur-containing substituents. Due to the well known ability of sulfur atoms in various oxidation states to stabilize α-anionic or -cationic centers a very rich family of such conversions have already been reported. Accordingly, below we would like to describe comprehensively procedures leading to the formation of a chiral carbon atom functionalized by sulfenyl, sulfinyl, or sulfonyl substituents. The final chapter is devoted to procedures in which the newly created chiral center is linked to sulfur in a less common oxidation state.

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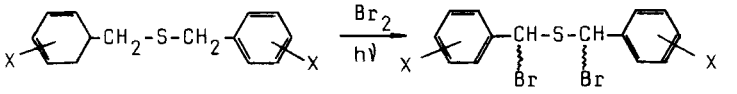
2. FORMATION OF CHIRAL CARBON α TO SULFENYL SULFUR

2.1. *Halogenation of sulfides*

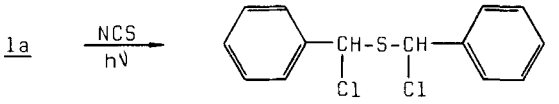
The radical bromination of dibenzyl sulfides **1** has been found to give the corresponding α,α′-dibromodibenzyl sulfides **2** as mixtures of the reacemic and the meso form.[1]



1 2

No	X	Yield [%]	Racemate -meso ratio
a	H	78.3	4:1
b	m-F	65	6:1
c	p-F	59	4:1

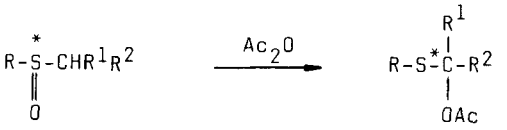
The analogous chlorination of the sulfide **1a** with NCS afforded the corresponding α,α′-dichlorodibenzyl sulfide **3**, also as a mixture of the racemic and the meso form, the ratio of which was not determined.[2]



3

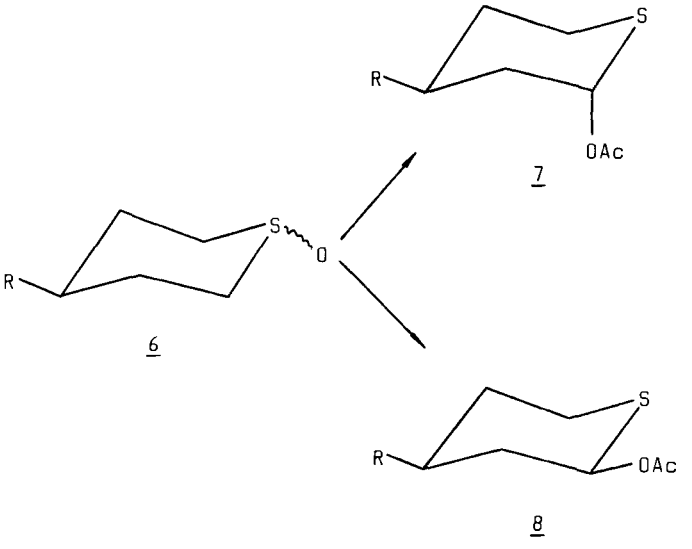
2.2. Pummerer-type rearrangement of sulfinyl derivatives

The Pummerer reaction depicted schematically below is a conversion in which chirality at sulfur is transferred to the α-carbon atom.[3]



4 5

Pummerer rearrangement of both the *cis*- and *trans*-sulfoxide **6** proceeds stereoselectively to give different products depending on the reaction conditions. Thus, the axial α-acetoxy sulfide **7** is formed upon heating of **6** with acetic anhydride alone, while the equatorial acetoxy sulfide **8** is obtained stereoselectively upon heating of **6** with acetic anhydride in the presence of excess DCC or of 2,6-lutidine as an acid scavenger.[4]



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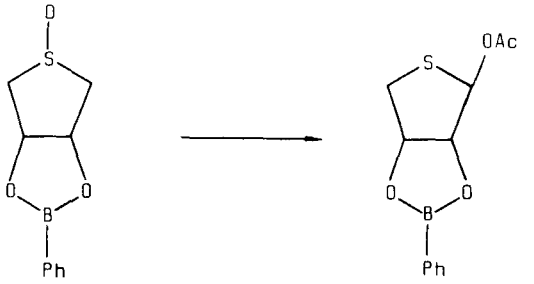
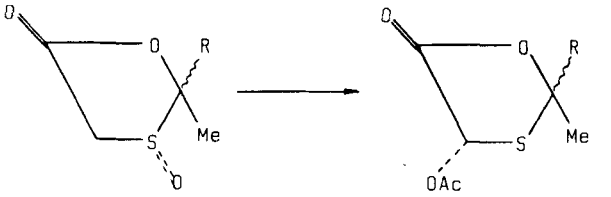
Also the sulfoxide derivative of a thiosugar **9** gives stereoselectively the corresponding rearrangement product **10** with a trans geometry.[5]



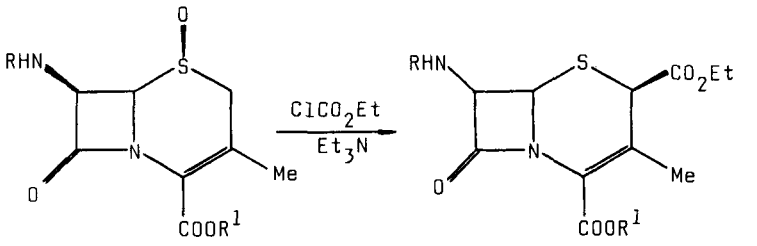
9 10

The earliest example of a stereoselective Pummerer rearrangement is the reaction of the five-membered cyclic sulfoxides **11** with acetic anhydride in the presence of an organic acid, which affords the corresponding acetates **12** with 85–90% stereoselectivity.[6]



11 12

In the reaction between (S)-3-cephem *S*-oxide **13** and ethyl chlorocarbonate in the presence of triethylamine the corresponding 2-carboxylate **14** is formed with full stereoselectivity. It is interesting to note that the (R)-sulfoxide does not react under the same conditions.[7]



13 14

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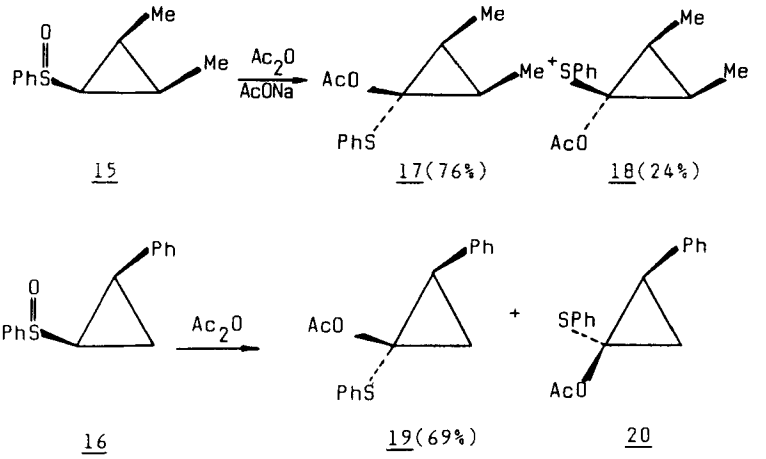
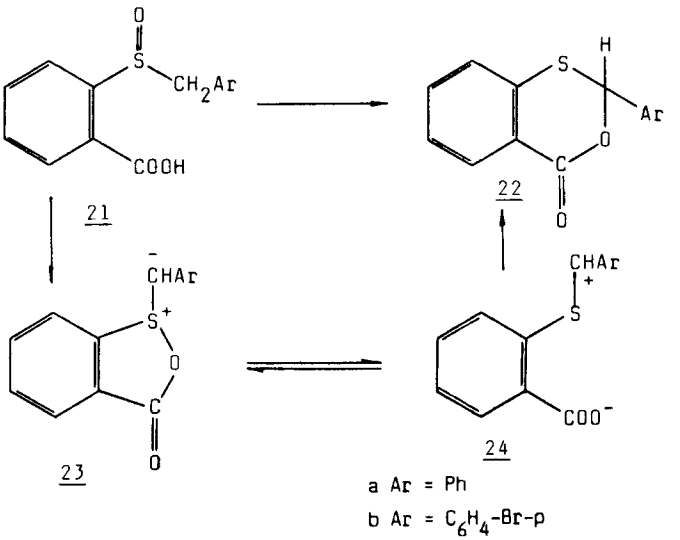
On the other hand, the Pummerer reaction of the phenyl cyclopropyl sulfoxides **15** and **16** with acetic anhydride proceeds with 69–76% stereoselectivity only.[8]



The first example of asymmetric induction in an intramolecular Pummerer reaction was observed when optically pure *o*-(benzylsulfinyl)benzoic acid **21a** was treated with acetic anhydride in the presence of dicyclohexylcarbodiimide (DCC).[9] The reaction product, the 3,1-benzoxathian-4-one **22a**, was found to be optically active. The optical rotation of **22a** (see Table 1) was dependent on the reaction conditions. In the mechanism proposed, the formation of a cyclic acyloxysulfonium ylide **23**, which yields optically active **22** via **24**, is the step responsible for the transfer of chirality from sulfur to carbon (Scheme 1).



Scheme 1.

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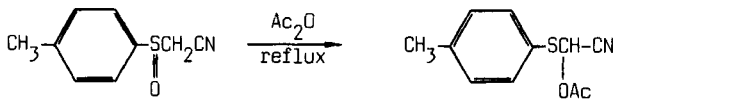
Table 1. Synthesis of optically active 2-phenyl-3,1-benzoxathian-4-ones **22**

Benzoic Acids				Benzoxathian-4-one **22**				
No.	Ar	$[\alpha]_D$	Condensation reagent/solvent	No.	Yield [%]	$[\alpha]_D$	e.e. [%]	Ref.
a	Ph	+451	DCC/CH_2Cl_2	**a**	91	−46.3	29.9	9
a	Ph	+451	$DCC/H_3PO_4/CH_2Cl_2$	**a**	73	−31.5	20.4	9
a	Ph	+451	$DCC/H_3PO_4/THF$	**a**	33	−7.5	4.9	9
a	Ph	+451	$DCC/H_3PO_4/Me_2CO$	**a**	64	+18.0	11.6	9
a	Ph	+451	Ac_2O/C_6H_6	**a**	91	−30.2	19.5	9
a	Ph	+451	$Ac_2O/MeCO_2H$	**a**	95	+17.3	11.2	9
b	C_6H_4Br-*p*	+406	Ac_2O	**b**		+7.0		10
c	C_6H_4Br-*o*	+286	Ac_2O	**c**		+9.0		10

A few other *o*-(benzylsulfinyl)benzoic acids **21** substituted in the aromatic ring of the benzyl group have also been converted to the corresponding 3,1-benzoxathian-4-one systems **22** by a modification of this procedure (see Table 1).[10]

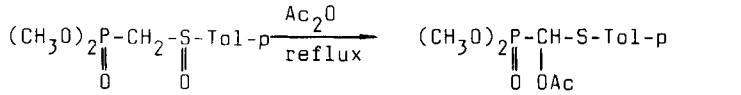
The optically active α-cyanomethyl *p*-tolyl sulfoxide **25** undergoes a Pummerer-type rearrangement upon heating with excess acetic anhydride at 120 °C to give the optically active α-acetoxy sulfide **26** with an optical purity with respect to the chiral α-carbon center equal to 29.8% (^{1}H NMR spectroscopy with a chiral shift reagent).[11]



25 **26**

$[\alpha]_D$ = +252.0 $[\alpha]_D$ = +26.8 (e.e.29.8%)

A similar extent of asymmetric induction is observed in the Pummerer reaction of the optically active α-phosphoryl sulfoxide **27**, which affords the corresponding optically active α-acetoxy-α-phosphorylmethyl sulfide **28**.[12]



27 **28**

$[\alpha]_D$ = 144.0 $[\alpha]_D$ = −4.0 (e.e.24%)

When this reaction was catalyzed by bromine or carried out in the presence of DCC the optical purity of the α-acetoxy sulfide **28** was much higher (up to 45%).[13] The same phenomenon was observed in the Pummerer reaction of the optically active sulfoxides **29**, bearing electron-withdrawing groups, with acetic anhydride.[14,15]

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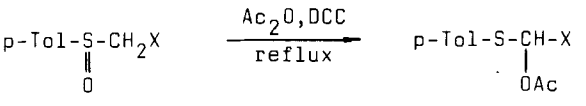

29 30

Sulfoxide **29**			α-Acetoxy sulfide **30**				
No.	X	DCC[a]	No.	Yield [%]	$[\alpha]_D$[b]	e.e. [%]	Ref.
a	$C(O)NMe_2$	–	**a**	51	−18.8	29	14
a	$C(O)NMe_2$	2	**a**	35	−44.0	65	14
b	C(O)OEt	–	**b**	26	−24.5	29	14
b	C(O)OEt	2	**b**	10	−52.5	70	14
b	C(O)OEt	4	**b**	43	−40.2	50	14
c	C(O)Ph	–	**c**	88	−0.5	0.5	14
c	C(O)Ph	2	**c**	58	−5.5	6.0	14
c	C(O)Ph	4	**c**	32	−35.9	38.0	14
d	C≡CH		**d**	83			15

a) number of equivalents b) in acetone

Scheme 2.

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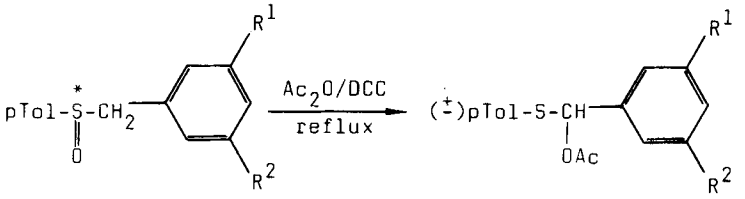
However, when the optically active substituted benzyl *p*-tolyl sulfoxides **31** were allowed to react with excess acetic anhydride in the presence of DCC under the same conditions, the corresponding α-acetoxy sulfides **32** exhibited no optical activity, while the sulfoxides recovered were found to have retained 90% of the original optical activity (Scheme 3).[16]



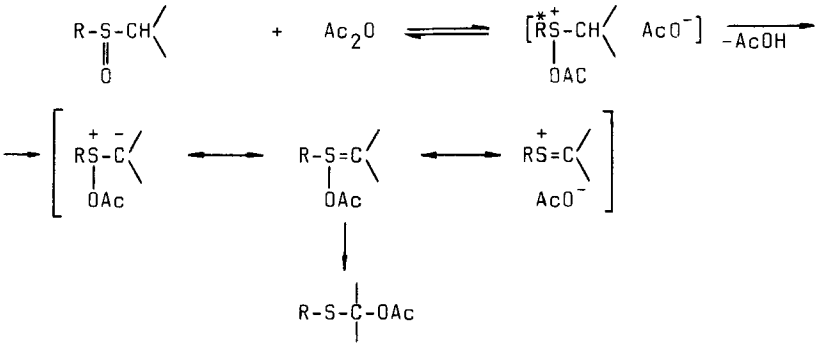
31 32

No.	R^1	R^2	**31**	$[\alpha]_D$	**32**
a	H	H	+251.0		0.0
b	Cl	H	+295		0.0
c	Cl	Cl	+288		0.0

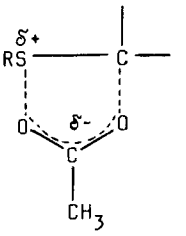
Scheme 3.

Detailed mechanistic studies of the Pummerer reaction[17] have shown that this conversion consists of three main steps (Scheme 4), the formation of the acyloxysulfonium salt, followed by proton abstraction, leading to the sulfonium ylide, which in the last step undergoes rearrangement to give the final reaction products.

Moreover, the substantial asymmetric induction strongly suggests that the migration of the acetoxy group from sulfur to carbon (1,2-shift) occurs to a large extent by an intramolecular process, presumably via the five-membered cyclic transition state shown as **33**. This seems to be responsible for the high stereoselectivity observed in some cases.

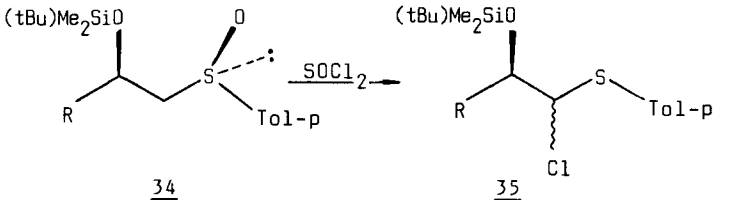


Scheme 4.



33

Pummerer-type rearrangements can also be induced by other electrophilic reagents. Thus, reaction of the optically active sulfoxide **34** with thionyl chloride in CH_2Cl_2 at 0 °C gave the α-chlorinated product **35** as a mixture of diastereoisomers.[18]



34 35

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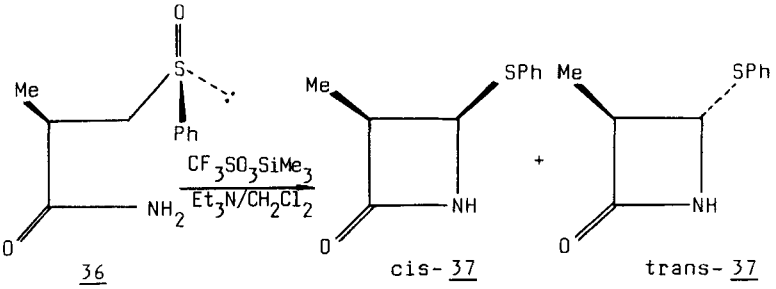
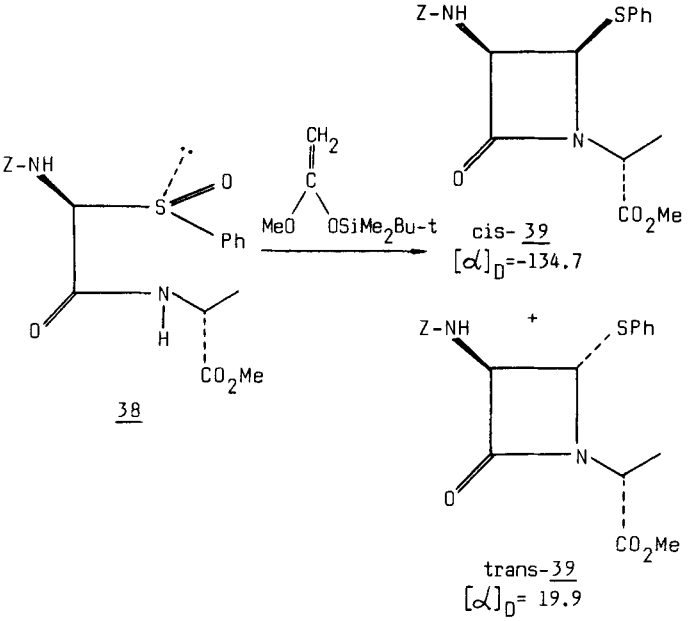
When a ca. 1:1 mixture of the diastereoisomeric sulfoxides **36** was treated with 5 equivalents of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and triethylamine at 20 °C, a mixture of the β-lactams *cis*-**37** and *trans*-**37** was obtained in 41% yield and the ratio of the *cis* and *trans* isomers was 2.7:1.[19]



A silicon-induced Pummerer-type rearrangement has been successfully applied for the conversion of the tripeptide sulfoxide **38** to the corresponding *cis*-β-lactam system.[20]

When **38** (a 37:63 mixture of diastereoisomers) was treated with 6 equivalents of ketene methyl *t*-butyldimethylsilyl acetal at room temperature in the presence of a catalytic amount of ZnI_2 in CH_2CN *cis*-**39** and *trans*-**39** were isolated in 40% and 15% yield, respectively.[20]



2.3. *Additive Pummerer rearrangement*

Cyclization of the alkenyl sulfoxides **40** with dichloroketene **41**, leading to the β-substituted α,α-dichloro-γ-arylthio-γ-butyrolactones **42**, is formally considered as an additive Pummerer rearrangement.[21]

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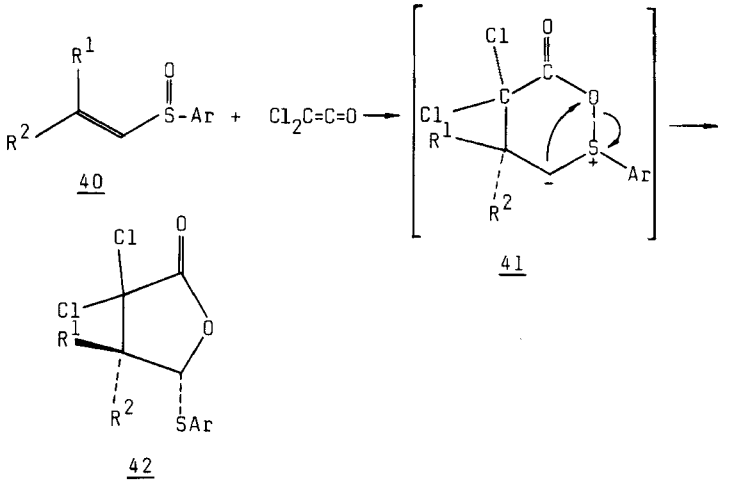
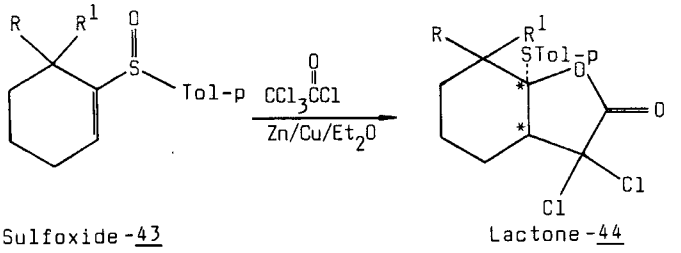
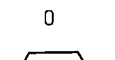
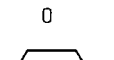


Scheme 5.

This reaction, when applied to enantiomerically pure *p*-tolyl alkenyl sulfoxides, leads to optically active γ-butyrolactones with complete enantioselectivity. Dichloroketene is generated *in situ* from trichloroacetyl chloride upon treatment with the zinc-copper couple in refluxing ether or activated zinc in the same solvent. Selected examples are shown in Schemes 6 and 7.[22-24]



R	R^1	abs.conf.	R	R^1	Yield[%]	$[\alpha]_D$
H	H	(+)-(R)	H	H	70	+68.5
H	H	(+)-(S)	H	H	68	-68.3
		(+)-(S)			60 25	-91.1 +13.9

Scheme 6.

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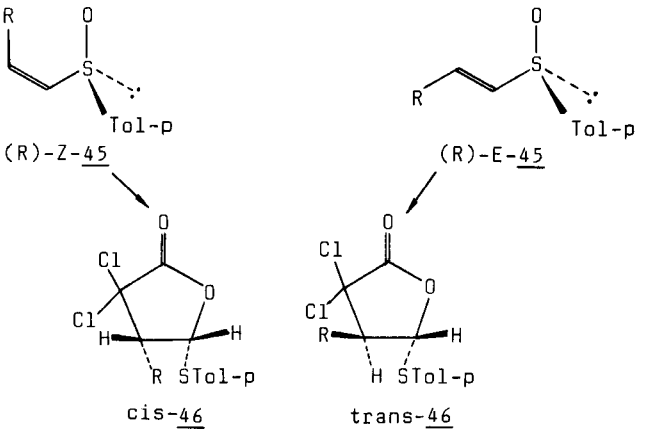
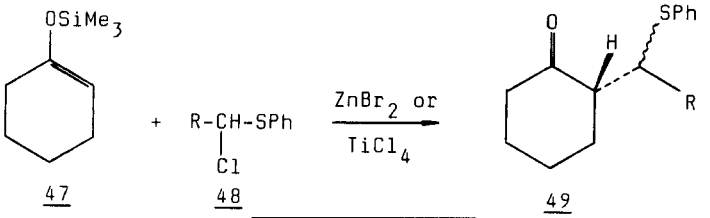


		Yield [%]	
No.	R	*cis*-**46**	*trans*-**46**
a	*n*-Pr	50	76
b	*n*-Bu	68	84
d	*n*-C_5H_{11}	49	84
e	*n*-C_6H_{13}	62	82

Scheme 7.

2.4. *Thioalkylation of carbonyl compounds*

Reaction of α-chloro sulfides with silyl enol ethers of carbonyl compounds in the presence of a Lewis acid is a useful method for the introduction of a thioalkyl group to the α-position of carbonyl compounds. Thus, reaction of the silyl enol ether **47** with the chloro sulfides **48** in CH_2Cl_2, either in the presence of one equivalent of $TiCl_4$ or a catalytic amount of $ZnBr_2$, gave the α-(phenylthio)cyclohexanones **49** as mixtures of diastereoisomers with no significant diastereoselectivity (Scheme 8).[25]



R	Yield [%]
Me	78
n-Pr	83
i-Pr	66
t-Bu	78
Me_3Si	84

Scheme 8.

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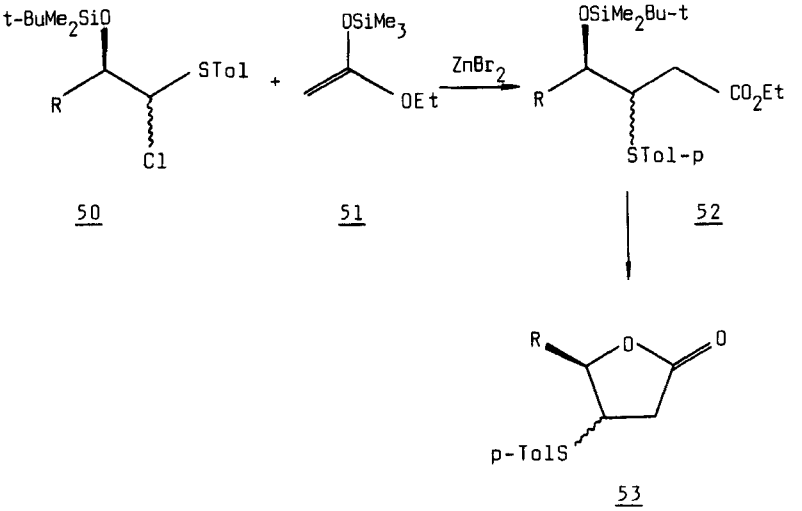
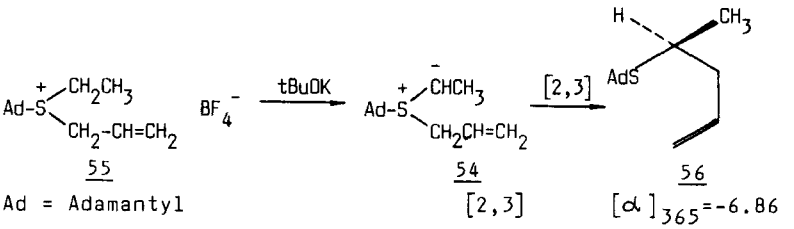
On the other hand, treatment of the α-chloro sulfide **50** with 1-ethoxy-1-(trimethylsilyloxy)ethene **51** in the presence of a catalytic amount of $ZnBr_2$ gave the α-silyloxy-α-(tolylthio) ester **52** in 97% yield, which after acid hydrolysis with aq. HF in CH_3CN furnished the α-(tolylthio)butyrolactone **53** as a 4:1 diastereoisomeric mixture in 92% yield.[18]



50 51 52 53

2.5. [2,3]-Sigmatropic rearrangement of sulfur ylides

The [2,3]-sigmatropic rearrangement of ylide **54**, derived from optically active 1-adamantylallylethylsulfonium tetrafluoroborate **55** by treatment with potassium *t*-butoxide, gives the optically active 1-adamantyl-2-pent-4-enyl sulfide **56** which has at least 94% optical purity.[26]



55 54 56

Ad = Adamantyl [2,3] $[\alpha]_{365}=-6.86$

The [2,3]-sigmatropic rearrangement of the chiral ylide **57**, generated *in situ* from the achiral sulfonium salt **58** by treatment with the lithium salt of optically active 2,2,2-trifluoro-1-phenylethanol, leads to the optically active sulfide **59** with 5% optical purity.[27]

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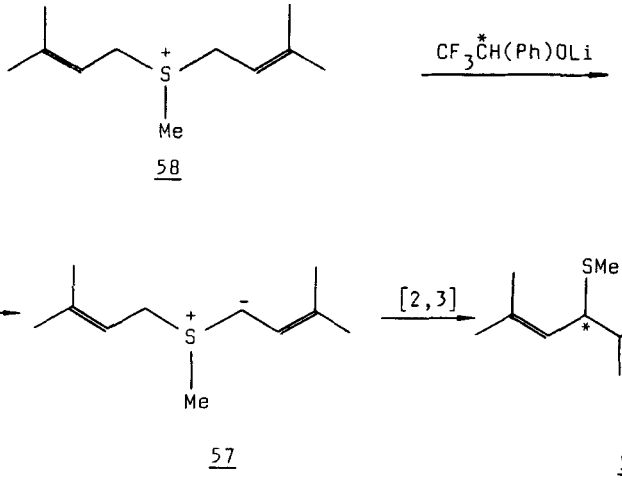
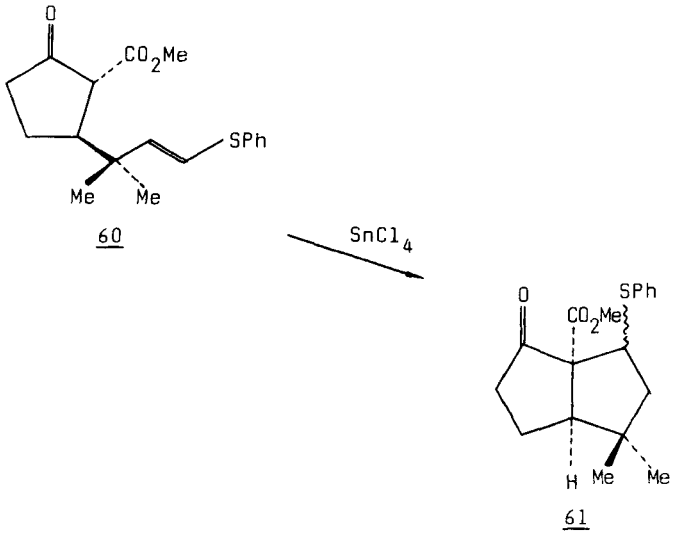


2.6. Intramolecular cyclization of enols containing vinyl sulfide moieties

Treatment of the unsaturated sulfide **60** with tin(IV) chloride in dichloromethane at 0 °C caused smooth intramolecular cyclization to the bicyclooctene **61** in 73% yield as a 4 : 1 mixture of isomers epimeric at the carbon carrying the phenylthio group.[28]



The analogous cyclization of a 9 : 1 mixture of the unsaturated sulfides **62** and **63** gave the bicyclooctanones **64**, **65**, and **66** in the ratio 73 : 18 : 9 (Scheme 9).[28]

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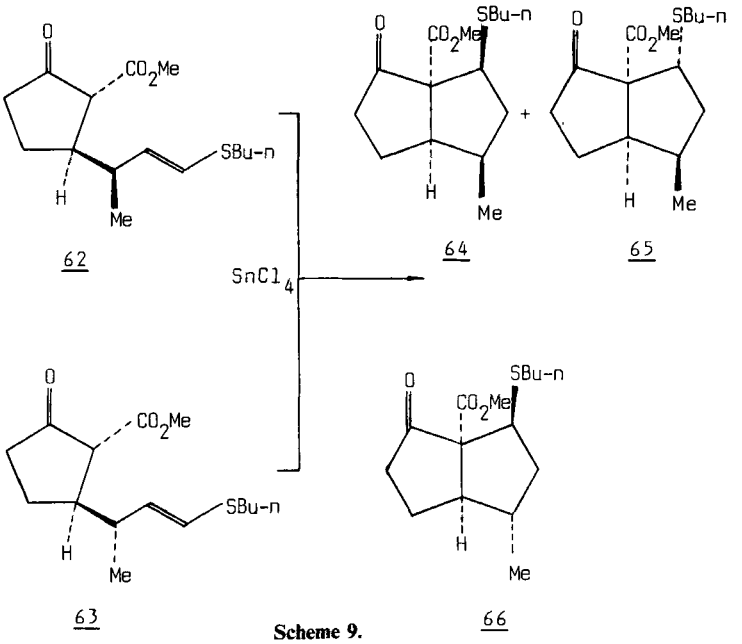
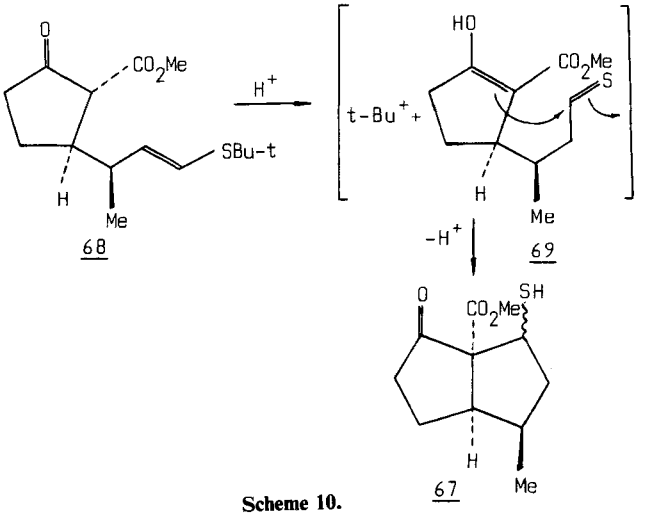


Scheme 9.

The diastereoisomeric bicyclooctanethiol **67** was isolated upon treatment of the unsaturated sulfide **68** with tin(IV) chloride in the presence of acetic acid. The loss of the *t*-butyl group presumably takes place from the intermediate carbocation formed by protonation of the double bond to generate the *t*-butyl cation and a thioaldehyde intermediate **69**. The thioaldehyde **69** then undergoes ring closure to form the final product **67** (Scheme 10).[28]



Scheme 10.

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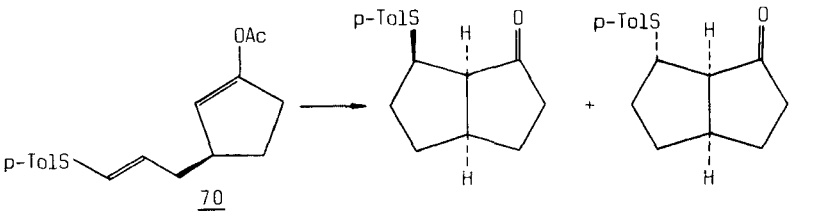
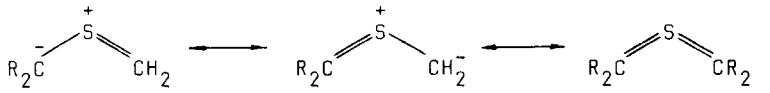
The intramolecular cyclization of the optically active enol acetate **70** taking place in the presence of one equivalent of $TiCl_4$ in acetic acid containing four equivalents of water was found to give the hexahydropentalenones **71** as a 1 : 4 mixture of diastereoisomers in 86% yield.[29]



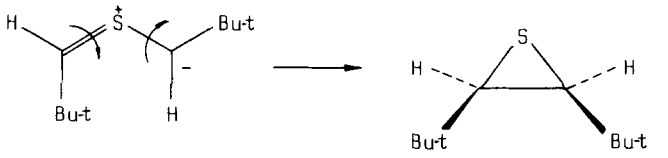
2.7. Reactions of thiocarbonyl ylides

Formal replacement of the central carbon atom of the allyl anion by a sulfonium sulfur gives rise to the thiocarbonyl ylides **72**. Usually, they are viewed as 1,3-dipoles, although contributions from other resonance structures are possible.



72a 72b 72c

Among many reactions of thiocarbonyl ylides the closure to the valence tautomeric thiiranes is very interesting because it occurs in a conrotatory manner giving *cis*-product exclusively.[30]



73 74

The thiocarbonyl ylide **73** also undergoes stereoselective cycloaddition to 1,3-dipolarophiles as shown in Scheme 11.[31]

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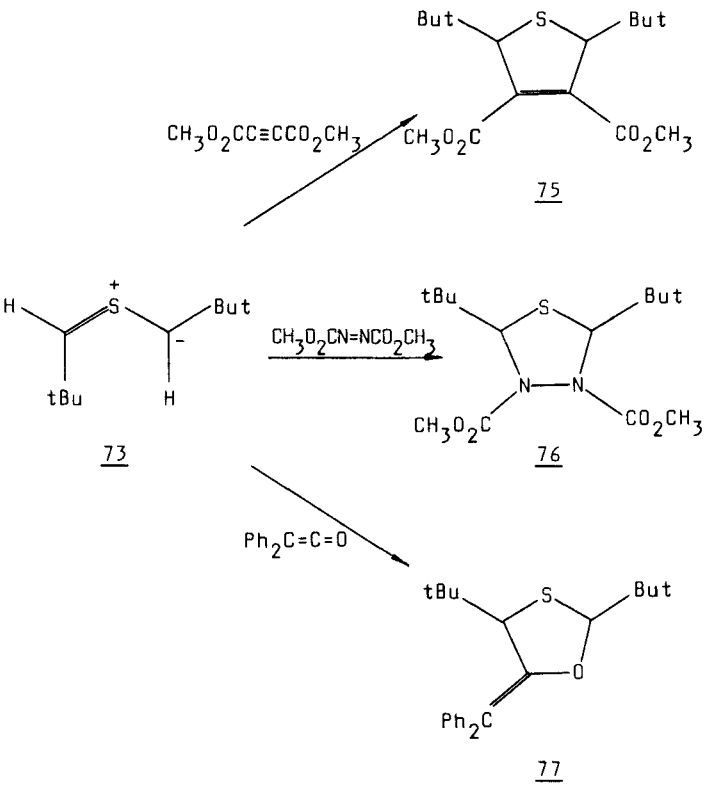
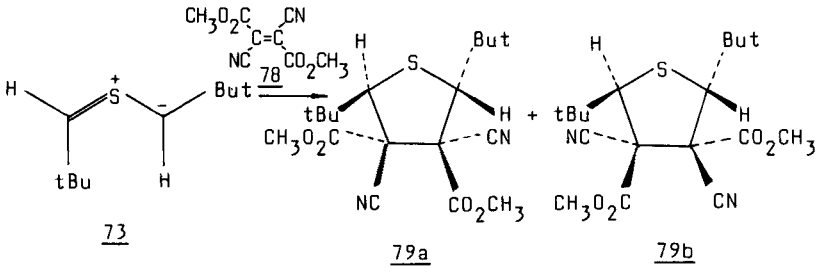


Scheme 11.

The reaction of the thiocarbonyl ylide **73** with dimethyl dicyanofumarate **78** is also stereoselective and gives two products where the *trans* relation of both the *t*-butyl groups and the ester functions is retained.[31]



Similarly, the addition of the above ylide to dimethyl fumarate **80** likewise proceeds with retention leading to a single product **82** with the *t*-butyl and ester substitutents *trans* to each other. Dimethyl maleate **81** reacts with the ylide **73** stereoselectively, too.

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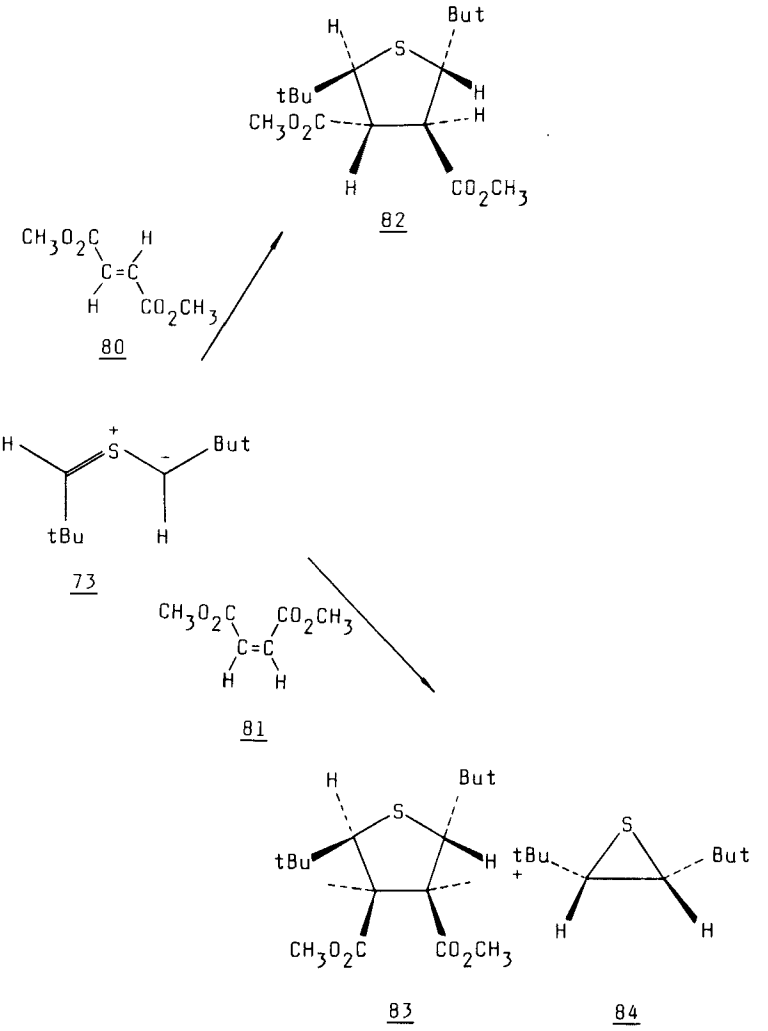
However, in addition to the expected cycloaddition product **83** comparable amounts of di-*t*-butylthiirane **84** are formed. (Scheme 12).[31]



Scheme 12.

Another thiocarbonyl ylide, 2,2,4,4-tetramethyl-l-oxocyclobutane-3-thione *S*-methylide **85**, behaves similarly towards dimethyl fumarate **80**, fumaronitrile **86**, and maleonitrile **87** affording in all cases stereochemically homogeneous products (Scheme 13).[32]

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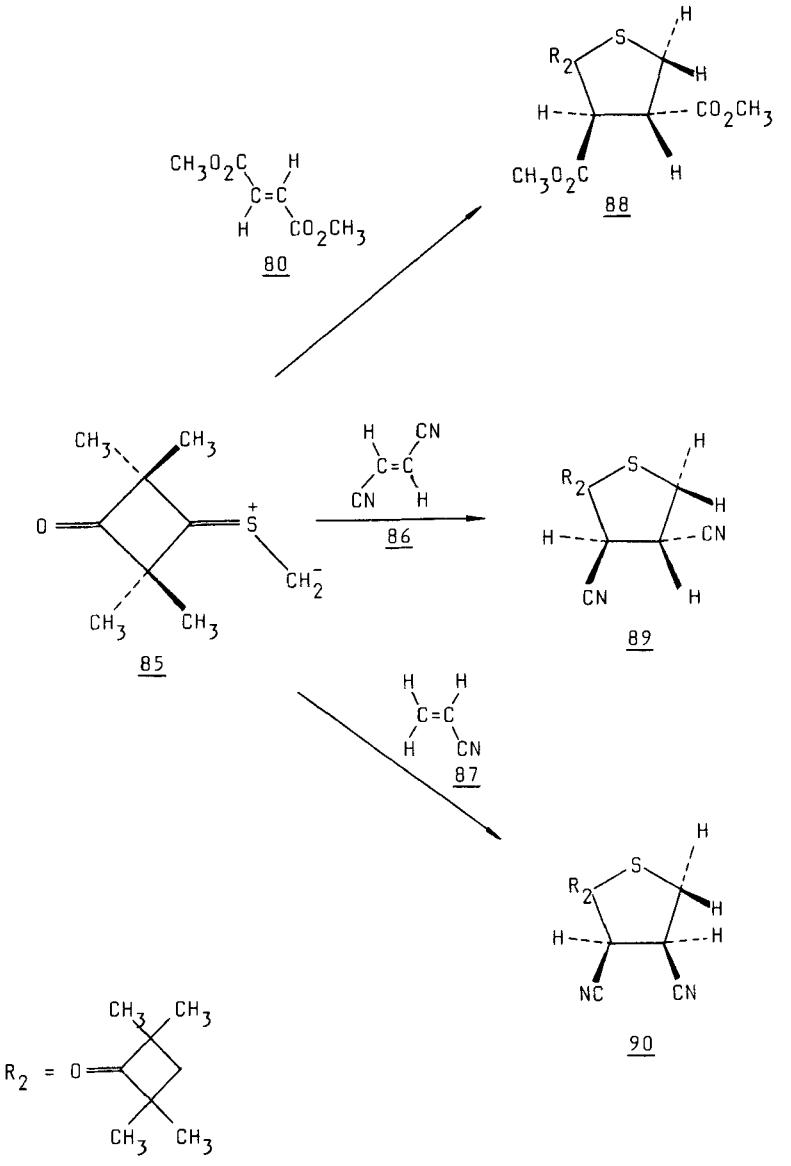

Scheme 13.

However, with dimethyl 2,3-dicyanofumarate **78** as a dipolarophile this ylide reacts nonstereoselectively giving a 52:48 mixture of the diastereomeric cycloadducts **89** and **90** in 94% yield. This is a consequence of the reaction mechanism involving formation of a zwitterionic intermediate which can rotate before ring closure (Scheme 14).[31,32]

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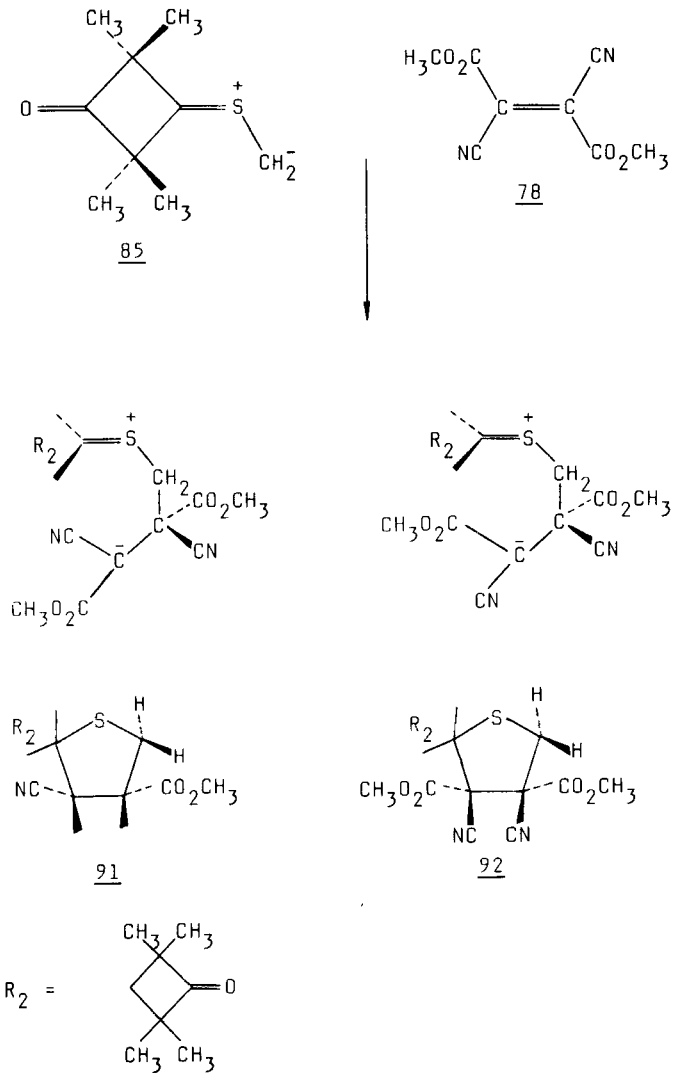

Scheme 14.

A lack of stereoselectivity is also observed in the additions of two other thiocarbonyl ylides to dimethyl dicyanofumarate **78**. Thus, 2,2,4,4-tetramethylcyclobutanethione *S*-methylide produces a 46 : 54 mixture of the corresponding *trans*-**93** and *cis*-**93** isomers of the cycloadduct, whereas the corresponding reaction of 2-adamantanethione *S*-methylide results in the formation of the corresponding *trans*- and *cis*-thiolanes in the ratio 59 : 41. A much higher content of the *trans*-adduct (93%) is observed with cyclopentanethione *S*-methylide indicating most probably that the zwitterionic inter-

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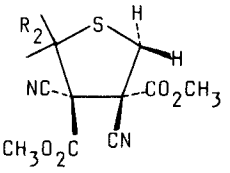
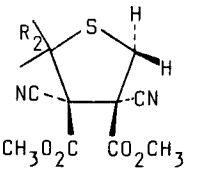
mediate cannot rotate freely. In this context, it should be noted that the diastereoisomeric ratios discussed above refer to kinetically and not to thermodynamically controlled reactions (Scheme 15).

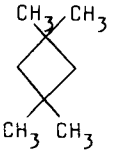


trans-93

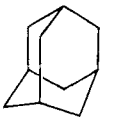


cis-93

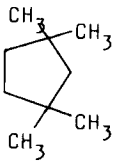
46 : 54 R_2 =



59 : 41 R_2 =



93 : 7 R_2 =



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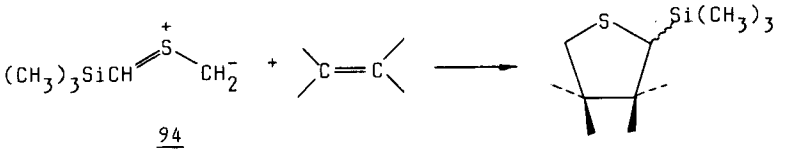
Scheme 15.

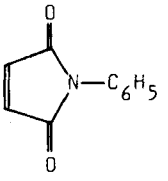
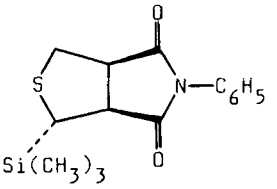
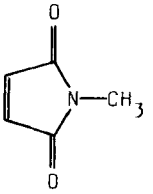
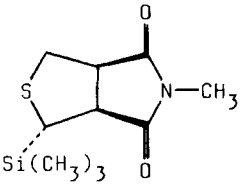
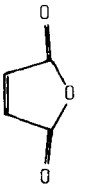
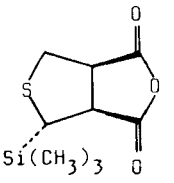
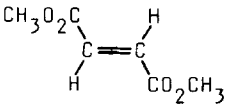
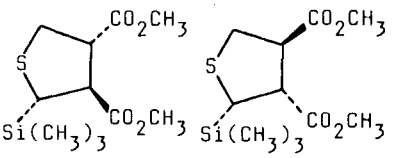
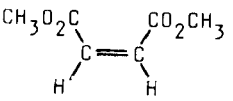
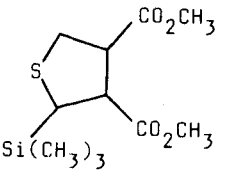
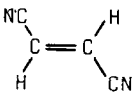
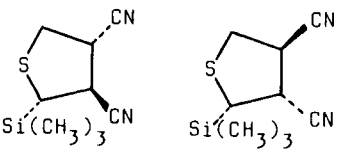
(Trimethylsilyl) methanethione *S*-methylide **94**, an interesting example of a thiocarbonyl ylide containing a heteroatom, undergoes clean 1,3-cycloadditions with activated olefins as dipolarophiles.[33]



94

95

Table 2. 1,3-Cycloaddition via (trimethylsilyl)methanethione *S*-methylide

Entry	Dipolarophile	Product[b]	Yield (%)
1			95
2			96
3			91
4			90
5			94
6			98

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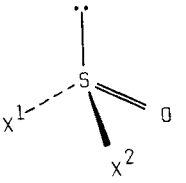
Its reaction with cyclic dipolarophiles gives rise to the corresponding substituted tetrahydrothiophenes with a 2-exo-trimethylsilyl group. Its reactions with acyclic olefins such as dimethyl fumarate and fumaronitrile result in the formation of two possible isomers, the major one has a *trans*-relationship of the 2,3-substituents. Dimethyl maleate gives a mixture of the four possible isomers (see Table 2).[33]

3. FORMATION OF CHIRAL CARBON α TO SULFINYL SULFUR

Sulfinyl compounds have a pyramidal structure **96** in which the sulfur occupies the vertex. The structure can be formally considered as a tetrahedron if the lone electron pair on sulfur is taken into account as the fourth substituent.

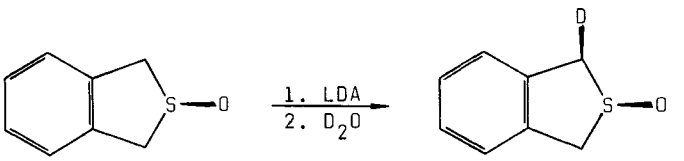


96

When X^1 is different from X^2 the sulfur atom becomes a chiral center and when X^1 is equal to X^2 the sulfur atom becomes a prochiral center. As a consequence, any functionalization of a chiral or prochiral sulfinyl drivative having diastereotopic hydrogen atoms will generate diastereoisomeric systems. Therefore, all conversions in which asymmetric carbon is generated lead to diastereoisomeric systems.

3.1. Metalation and alkylation of sulfoxides

Lithiation and deuteration of sulfoxide **97** led to **98** with the deuterium *cis* to the sulfoxide oxygen.[34] In this case the lithiation involves abstraction of the proton *cis* to the sulfoxide oxygen.



97 98

Lithiation and methylation of the equatorial sulfoxide **99a** led to a 10 : 90 mixture of methylated sulfoxides, the axial **100a** and the equatorial **100b**.[35] However, the axial sulfoxide **99b** afforded the axial methylated sulfoxide **101** exclusively (Scheme 16).[36]

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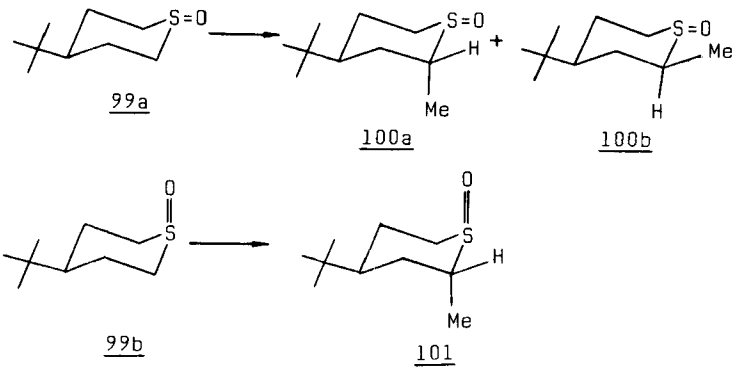
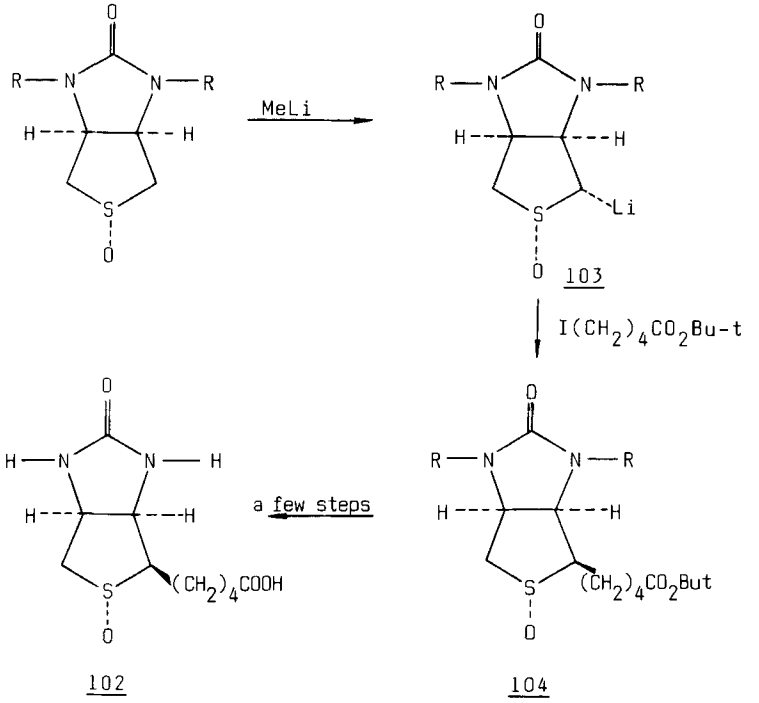


Scheme 16.

An interesting application of the alkylation of an α-sulfinyl carbanion in a cyclic system was reported in a total synthesis of biotin (Scheme 12). The carbanion **103**, generated with MeLi, was alkylated with *t*-butyl ω-iodovalerate. The reaction was highly stereoselective and a single isomer (**104**) with the side chain *trans* to the S–O bond was obtained (Scheme 17).[37]



Scheme 17.

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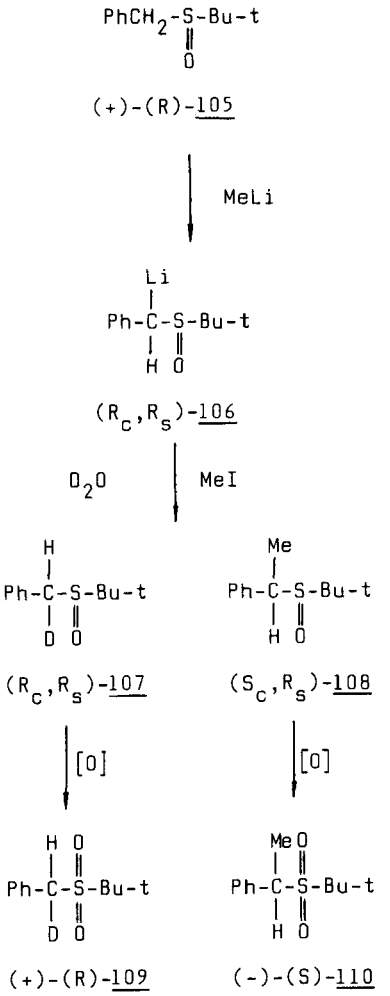
It has been reported[38] that the lithiation and the methylation of benzyl *t*-butyl sulfoxide (+)-(R)-**105**, proceed via different stereochemical pathways: retention of the configuration in the H-D exchange and inversion of the configuration in the methylation (Scheme 18).



Scheme 18.

The optical purities of the α-deutero sulfoxides **107** are unknown whereas that of the α-methyl sulfone **110** is 99%. This points to an almost complete asymmetric induction at the α-carbon atom in the generation of sulfoxide carbanions. The configurational assignments of the deuterated sulfoxides **107** were made by correlating them chemically

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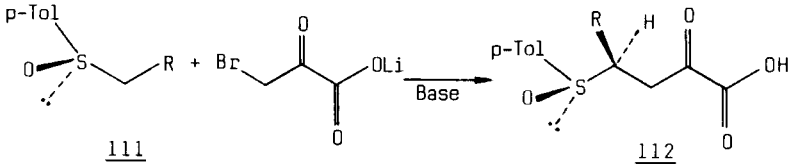
to optically active α-d alcohols, the configuration of which has been believed to be (+)-(S) and (−)-(R).[39] However, it was recently reported,[40] based on an X-ray analysis of a stereoselectively monodeuterated benzyl *t*-butyl sulfoxide **107**, that its relative configuration as assumed up to there should be reversed. In view of the revised configurational assignment of **107** it is also evident that the stereochemical pathways for the H-D exchange and the methylation of **106** are the same.

A high diastereoselection was observed in the alkylation of α-sulfinyl anions derived from optically active *p*-tolyl alkyl sulfoxides **110** with lithium α-bromopyruvate. It was found that the choice of the base has a decisive influence on the stereochemical outcome of the reaction. The highest asymmetric induction was found when the metallation of the sulfoxide was carried out in the presence of a highly hindered base, e.g. lithium tetramethylpiperidide (Scheme 19).[41]



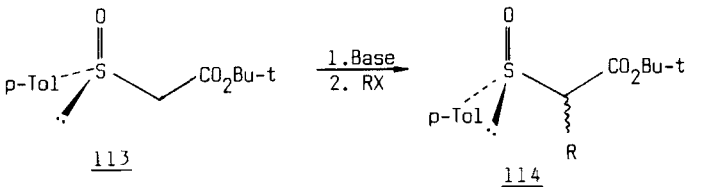
111 112

111			112		
No.	R	Base	Yield [%]	S : R ratio	$[\alpha]_D^{15a)}$
a	*n*-Pr	LDA	82	79 : 21	+ 102.0
a	*n*-Pr	LTMP	75	84 : 16	
b	*i*-Bu	LDA	85	78 : 22	+ 109.0
b	*i*-Bu	LTMP	73	82 : 18	
c	Ph	LDA	65	61 : 39	− 54.0
c	Ph	LTMP	55	64 : 36	

a) in chloroform

Scheme 19.

On the other hand, very poor diastereoselection was observed in the alkylation of the α-sulfinyl anion derived from (+)-*t*-butyl *p*-tolylsulfinylacetate **113** with alkyl halides (Scheme 20).[42] Moreover, the formation of **114** occurred only with bases such as *n*-butyllithium or *t*-butyllithium and only with alkyl halides as alkylating agents.



113 114

Scheme 20.

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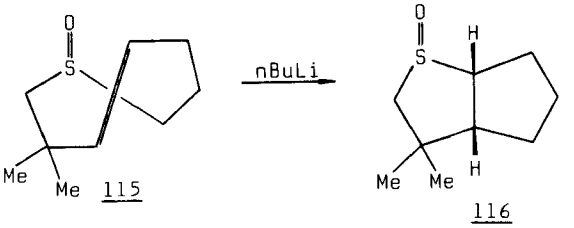
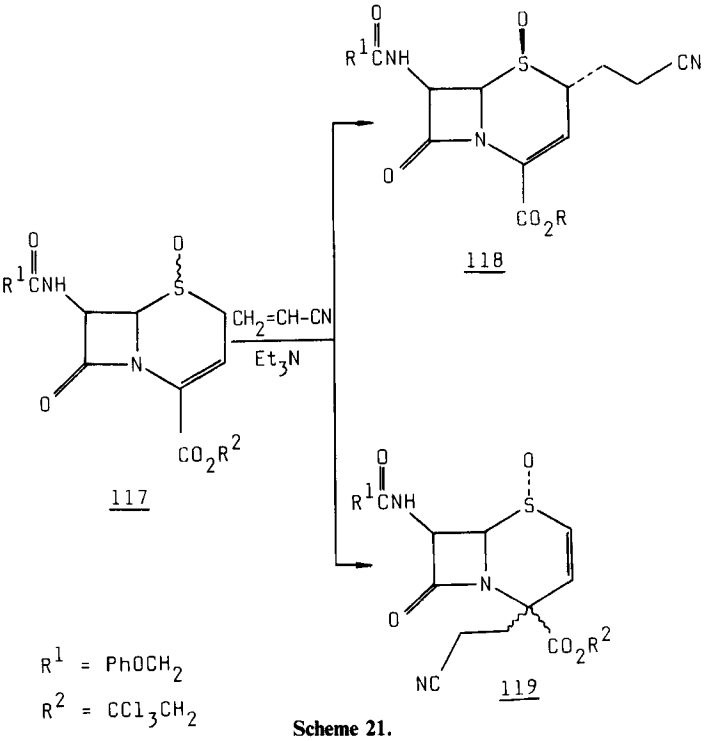
3.2. *Michael addition of α-sulfinyl carbanions*

The addition of a variety of α-sulfinyl carbanions to activated olefins can be easily achieved. Treatment of the (E)-homoallylic eight-membered ring sulfoxide **115** with *n*-BuLi in tetrahydrofuran results in transannular addition of the α-thio carbanion to the (*E*)-double bond with formation of a bicyclic product: *exo*-4,4-dimethyl-2-thiabicyclo-[3.3.0]octane 2-oxide **116**. Under the same conditions the corresponding (*Z*)-isomer is inert.[43]



Deacetoxycephalosporanate 1(*S*)-oxide **117** has been found to react slowly with acrylonitrile in the presence of triethylamine (other bases were less efficient) with formation of the *trans*-Michael adduct **118** in 24% yield (Scheme 21).[44] Under similar conditions the corresponding (R)-1-oxide underwent quantitative reaction at C-4 affording the Michael adduct **119**.



Scheme 21.

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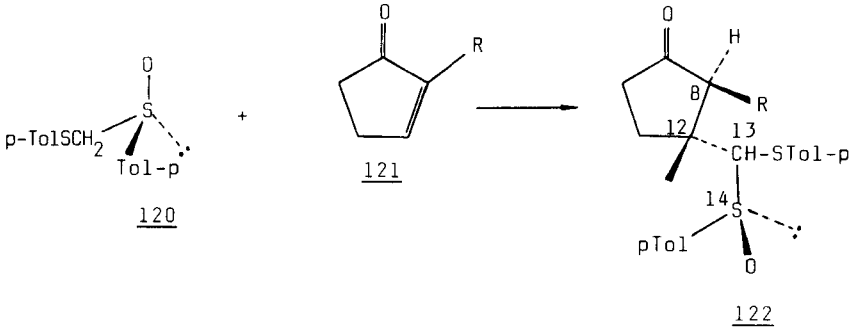
Michael addition[45] of the anion of optically active (+)-(S)-*p*-tolyl *p*-tolylthiomethyl sulfoxide **120** to the properly substituted cyclopentenone **121** led to the asymmetric synthesis of the optically active cyclopentanone **122** (Scheme 22). The reaction proceeds with a high *β*- and *γ*-asymmetric induction (92%) and with very poor *α*-stereoselection (52 : 48) (Scheme 22).



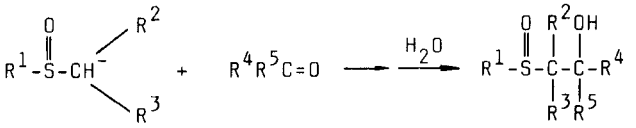
Relative ratio of the four diastereoisomers of 122

C-8	C-12	C-13	C-14	[%]
S	R	R or S	S	47.8
S	R	S or R	S	44.2
R	S	R or S	S	5.0
R	S	S or R	S	3.0

Scheme 22.

3.3. Condensation of α-sulfinyl carbanions with carbonyl compounds

α-Sulfinyl carbanions **123** undergo an aldol-type condensation with carbonyl compounds affording the *β*-hydroxyalkyl sulfoxides **124**.



123 124

Condensation of the phenyl sulfoxide anion **125** with benzaldehyde gave a mixture of four *α*-sulfinyl alcohols **126** (40% overall yield), the ratio of which after immediate work-up was 41 : 19 : 8 : 22.[46] When the reaction mixture was stirred for ca. 10 h before work-up, the isolated products were observed to be significantly richer in the *threo*-isomer **126** (Scheme 23).

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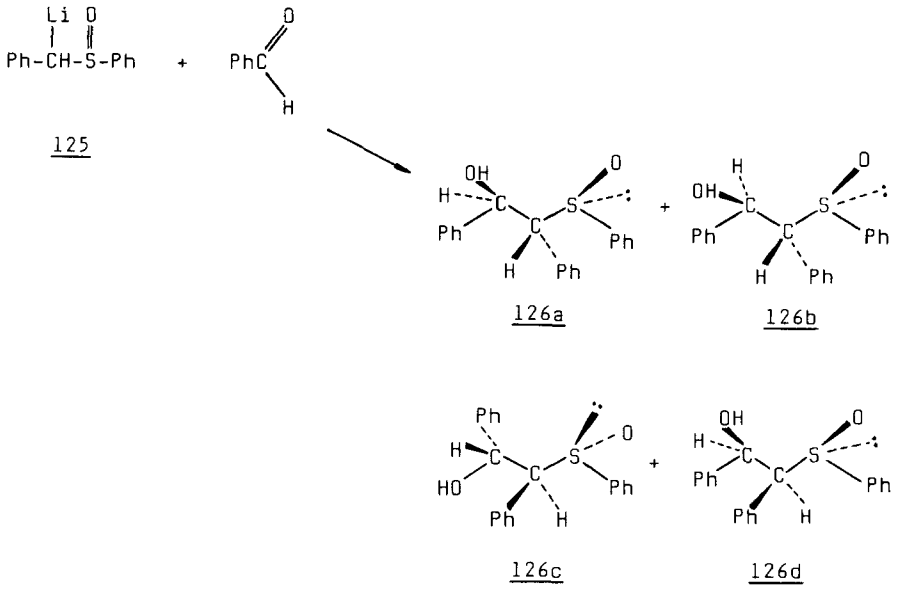
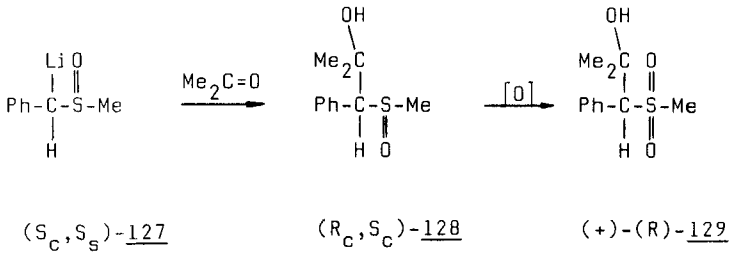


Scheme 23.

Reactions with several other aldehydes were similar, with low yields of the isomers analogous to **126b** and **126c**.

A highly efficient asymmetric induction was observed in the addition of the lithium salt of (+)-(S)-**126** to acetone. The addition product **128** (optical purity *ca.* 80%) was then oxidized to the corresponding homochiral sulfone **129** whose absolute configuration was established as R by chemical correlation.[47]



Condensation of the anions of the optically active alkyl *t*-butyl sulfoxides **130** with aldehydes gives the corresponding products **131** in a diastereoisomeric ratio of 3 : 2. The reaction has been used as a key step in the stereoselective synthesis of optically active oxiranes, among them the sex attractant (+)-disparlurene **132** (Scheme 24).[48]

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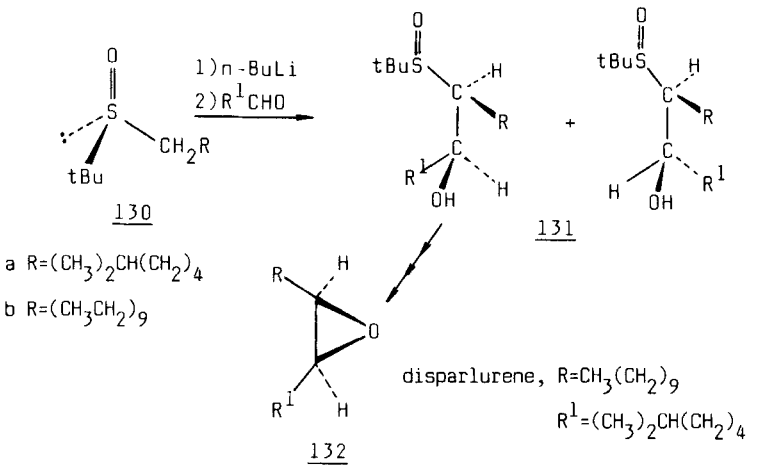
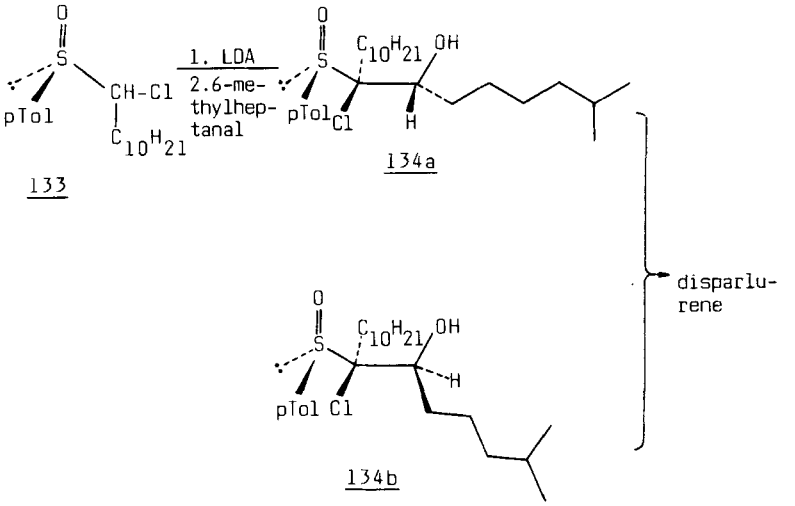


Scheme 24.

The reaction of the anion of α-chlorodecyl *p*-tolyl sulfoxide **133** with 6-methylheptanal afforded the chlorohydrins **134a** and **134b** in 90% yield as a 39 : 51 diastereoisomeric mixture. The isolated pure diastereoisomers **134a** and **134b** were also used in the stereoselective synthesis of disparlurene (Scheme 25).[49]



Scheme 25.

When chloromethyl methyl sulfoxide **135** was allowed to react with unsymmetrical ketones in the presence of potassium *t*-butoxide in *t*-butyl alcohol the methylsulfinyloxiranes **136** were directly formed as a mixture of diastereoisomers (Scheme 26).[50]

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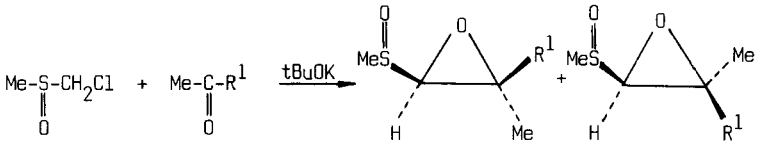
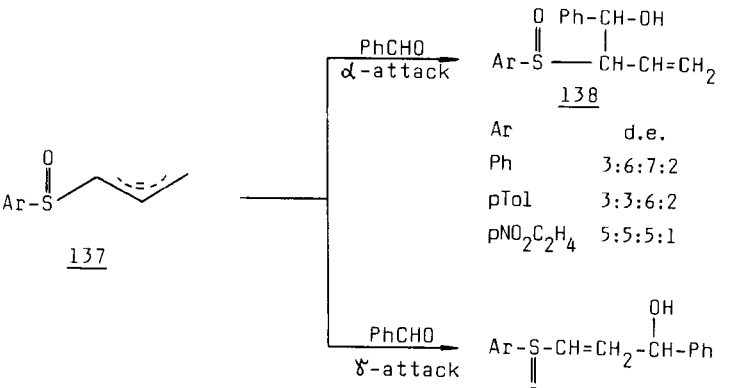


135 Z-136 E-136

	R^1	Z/E ratio
a	tBu	3:1
b	Ph	3:2

Scheme 26.

Addition of the anions of the aryl allyl sulfoxides **137** to benzaldehydes proceeds readily and gives a mixture of **138** and **139** resulting from both α- and γ-attack of the allyl anion[51] (Scheme 27). In the case of the α-attack a mixture of all four diastereoisomers is formed, while in the case of the γ-attack the diastereoisomeric ratio exceeds 2 : 1.



Ar	d.e.
Ph	3:6:7:2
pTol	3:3:6:2
$pNO_2C_2H_4$	5:5:5:1

Ar	d.e.
Ph	3:1
pTol	3:1
$pNO_2C_6H_4$	2:1

Scheme 27.

Reaction of the optically active α-sulfinyl acetate **113** with prochiral carbonyl compounds proceeds with a high β-asymmetric induction, the degree of which depends on the nature of the substituents at the carbonyl group, and with an unknown degree of α-induction (Scheme 28).[52]

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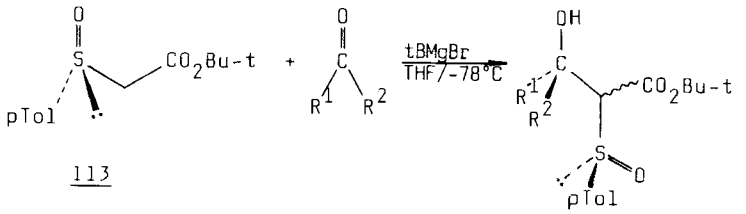

113 140

R^1	R^2	Yield of **140**	β-asymmetric induction [%]
H	Ph	85	91
Me	Ph	75	68
Ph	CF_3	75	20
H	n-C_7H_{15}	80	86
M	c-Hex	88	95

Scheme 28.

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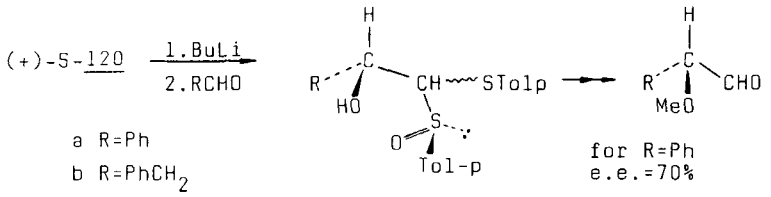
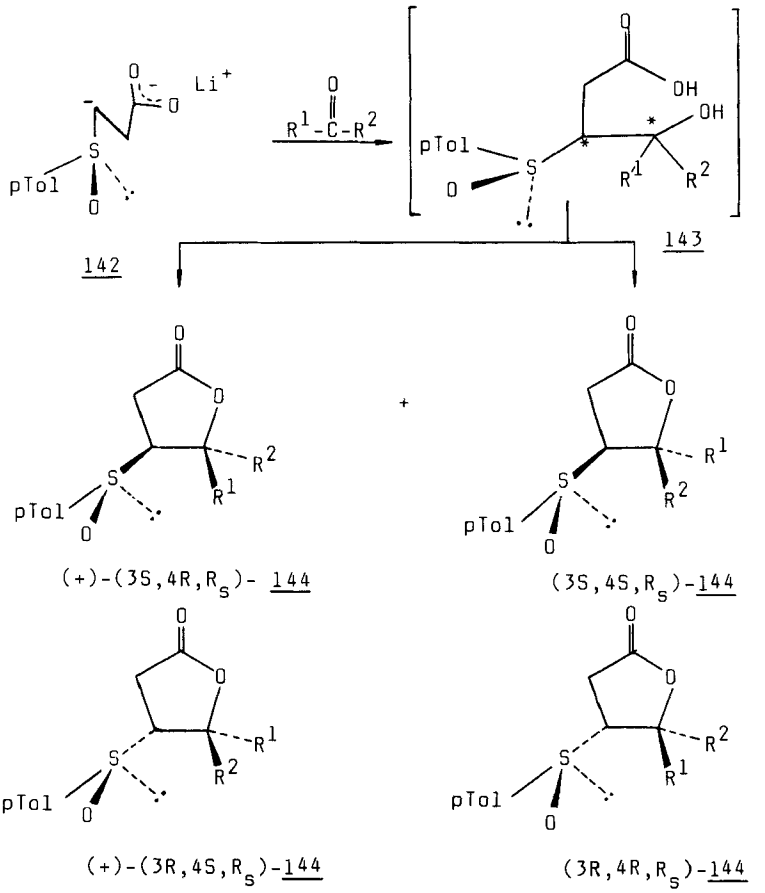
A high degree of β-asymmetric induction (46–70%) and a low percentage of α-asymmetric induction (below 15%) was also observed in the condensation of the anion of the optically active *p*-tolyl *p*-tolylthiomethyl sulfoxide **120** with benzaldehyde and phenylacetaldehyde.[53,54]



141

Addition of the dianions of β-sulfinylcarboxylic acids to carbonyl compounds leads to the formation of the corresponding hydroxy derivatives which undergo spontaneous cyclization to give γ-lactones.[55]

Thus, condensation of the dianion of optically active (+)-(R)-β-(*p*-toluenesulfinyl)-propionic acid **142** with aldehydes and ketones furnished the β-sulfinyl-γ-hydroxy carboxylic acids **143** which cyclized spontaneously to the corresponding diastereoisomeric γ-lactones **144** (Scheme 29).



Scheme 29.

Table 3. Yields and physical data of compounds **144**

Compound	R^1	R^2	Yield [%]	m.p. [°C]	$[\alpha]_D$ ($CHCl_3$)
(3S,4R,R_s)-**117a**	H	*t*-Bu	35	95–97	+202.0
(3S,4R,R_s)-**117a**	*t*-Bu	H	31	98–100	+211.0
(3S,4R,R_s)-**117b**	H	Ph	33	liq	+78.6
(3S,4R,R_s)-**117b**	Ph	H	28	liq	+65.0
(3S,4R,R_s)-**117c**	Me	*t*-Bu	8.8	87–89	+147.0
(3S,4R,R_s)-**117c**	*t*-Bu	Me	38	102–104	+107.0
(3S,4R,R_s)-**117d**	Me	Ph	8.0	liq	+54.4
(3S,4R,R_s)-**117d**	Ph	Me	25.0	140–141	+187.0
(3S,4R,R_s)-**117d**	Me	Ph	18.0	130–131	+9.9
(3S,4R,R_s)-**117e**	Me	Cyclohex-1-enyl	10.4	80–81	+150.0
(3S,4R,R_s)-**117e**	Cyclohex-1-enyl	Me	16.7	110–112	+138.0
(3S,4R,R_s)-**117e**	Me	Cyclohex-1-enyl	9.0	132–134	+81.0
(3S,4R,R_s)-**117f**	Me	Et	14.0	85–87	+251.0

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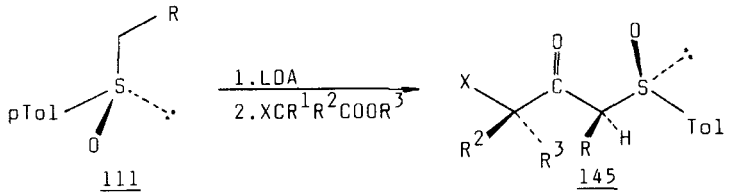
Two isomers, (+)-(3S,4R,R_s)-**144** and (+)-(3R,4S,R_s)-**144**, were formed exclusively when there was a great steric difference between the two substituents attached to the carbonyl group (R^1 = H; R^2 = *t*-Bu or Ph).

When this difference became smaller the (3R,4R,R_s)-isomer also appeared (R^1 = Me, R^2 = Ph and 2-acetylcyclohexenyl). Starting from 2-butanone all four possible diastereoisomers of **144** were obtained. Single diastereoisomers of the sulfinyl lactones **144** could be obtained in enantiomerically pure form through flash chromatography of the product mixture formed in the condensation reaction [56] (Table 3).

3.4. Acylation of α-sulfinyl carbanions

It has been shown that the α-lithiosulfinyl carbanions derived from the optically active *p*-tolyl alkyl (benzyl) sulfoxides **111** react at the ester site of α-bromo or α-chloro carboxylates to give diastereoisomeric α-sulfinyl ketones (Scheme 30).[57]



111

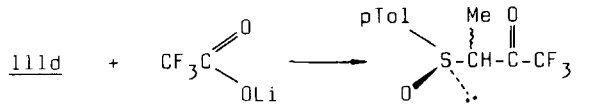
c R=Ph
d R=Me

145

X	R	R^1	R^2	$[\alpha]_D$	d.e.
Cl	Ph	H	H	+321	not given
Br	Ph	H	H	+189	75:25
Cl	Me	H	H	+104	55:45

Scheme 30.

The same α-lithiosulfinyl derivative **111d** reacts cleanly with lithium trifluoroacetate to give the C-acylation product **146** in 80% yield.[58]



146

In compound **146** the asymmetric atom C-1 is stereochemically highly unstable. Hence, a single diastereoisomer is present in dimethyl sulfoxide solution at room temperature, whereas a 68 : 32 ratio of the two C-1 epimers is observed when a crystallized sample of **146** is dissolved in chloroform.

When the lithium salt of (+)-(R)-*n*-hexyl *p*-tolyl sulfoxide **111f** was treated with the succinate **147** a regioselective attack on the less hindered ester group led to the formation of (R_s)-*t*-butyl 4-oxo-5-(*p*-toluenesulfinyl)decanoate **148** in 80% chemical yield and as a 6 : 4 mixture of the two diastereoisomers.[59]

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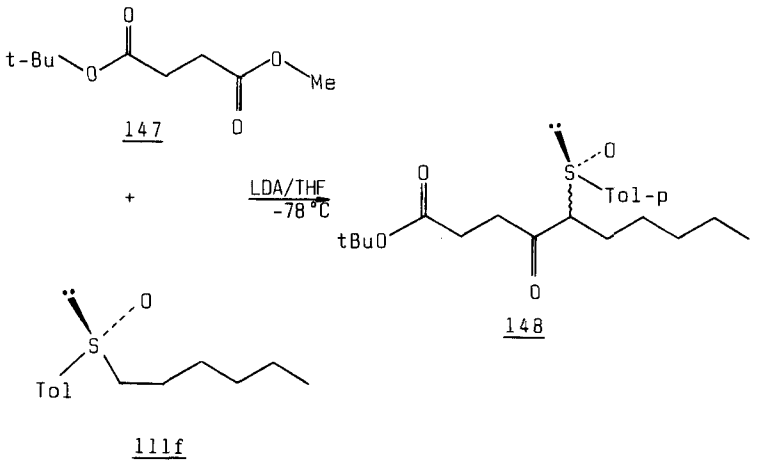
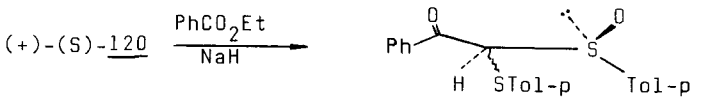


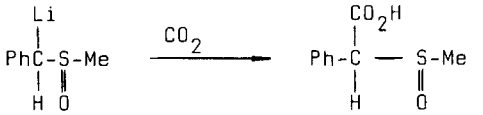
147 148 111f

Treatment of the optically active dithioacetal monoxide **120** with ethyl benzoate in the presence of sodium hydride gives the benzoylated product **149** as a diastereoisomeric mixture, in the thermodynamically controlled (65 : 35) ratio.[56]



149

It has been reported[61] that the carbonation of the α-sulfinyl carbanion (S_s,S_c)-**150** proceeds under kinetic control with retention of configuration at the metallated carbon atom and gives diastereoisomerically pure α-(methylsulfinyl)phenylacetic acid **151** after crystallization of the crude reaction product.[61]



(S_s,S_c)-150 151

$[\alpha]_D$ = +182.0 (acetone)

Later on it was found that carbonation of the α-sulfinyl anions derived from the optically active trans-(+)-(R)-(4-substituted cyclohexyl)methyl *p*-tolyl sulfoxides **152** also proceeds under kinetic control with retention of configuration. However, it was found that the stereochemical outcome of this reaction depends on other factors as well and that the highest asymmetric induction (up to 90% can be achieved under kinetic

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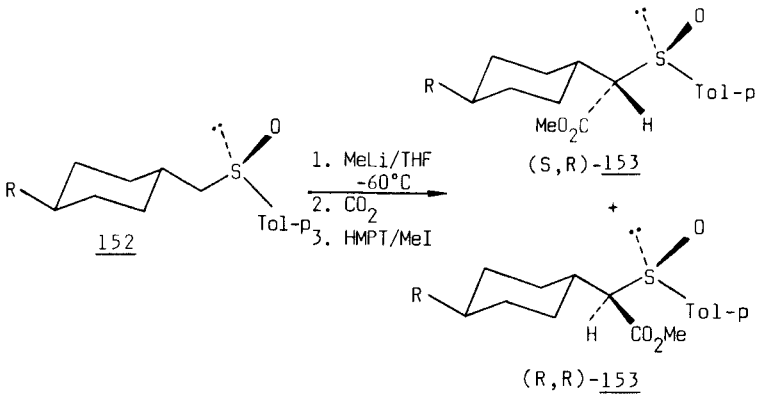
control (reaction time 0.5 min) by using a base with a low content of lithium salt, a result consistent with electrophilic assistance by the lithium cation.[62]



No.	R	Solvent	Time [min]	Lithium salt eq.	153 Yield [%]	153 (S,R/R,R) ratio
a	Me	THF	0.5	1	70	70:30
a	Me	THF	5	1	90	36:64
b	CH_2OMe	THF	0.5	1	89	75:25
b	CH_2OMe	THF	0.5	7.10^{-2}	79	95:5
b	CH_2OMe	THF	1	1	90	65:35
b	CH_2OMe	THF	2	1	88	56:44
b	CH_2OMe	THF	15	1	87	25:75
c	CH_2Cl	THF	0·5	1	70	80:20

Scheme 31.

Table 4. Methyl α-(4-methylphenylsulfinyl)cyclohexaneacetates **153a–e**[b,c]

Product	Performance of Reaction	(S,R)/(R,R)	Yield [%]	m.p. [°C]	$[\alpha]_D$ (acetone)
(+)-(S,R)-**153a**	T	30:70	80	80–82	+59.0
(+)-(R,R)-**153a**				134–136 (dec)	+258.0
(+)-(S,R)-**153b**	K	75/25	89	62–65	+50.0
(+)-(R,R)-**153b**				82 (dec)	+222.0
(+)-(S,R)-**153c**	K	80/20	70	78 (dec)	+43.0
(+)-(R,R)-**153c**				138 (dec)	+180.0
(+)-(S,R)-**153d**	T	30/70	98	oil	+44.0
(+)-(R,R)-**153d**				93 (dec)	+182.0
(+)-(S,R)-**153e**	T	31/69	98	67 (dec)	+55.0
(+)-(R,R)-**153e**				90 (dec)	+198.0

[a] K = kinetic control; T = thermodynamic control.
[b] **a** R = Me; **b** R = CH_2OMe; **c** R = $ClCH_2$; **d** R = n-C_5H_{11}; **e** R = t-Bu.
[c] Taken from reference 63.

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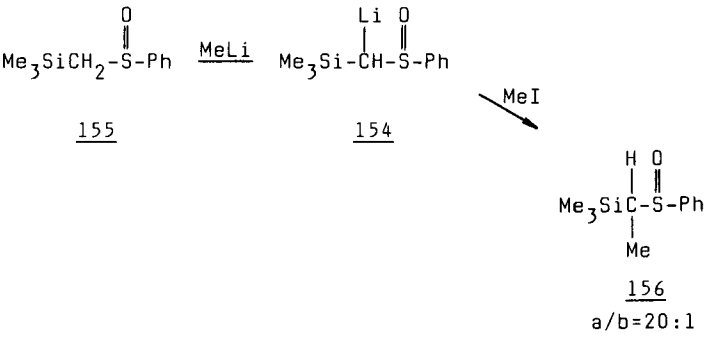
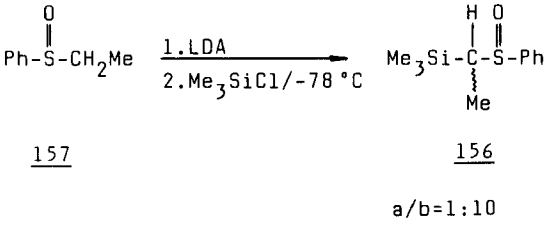
The diastereomeric methyl α-(4-methylphenylsulfinyl)cyclohexaneacetates **153a–e** prepared according to this procedure are listed in Table 4.[63]

3.5. *Other reactions of α-sulfinyl carbanions*

1-Trimethylsilyl-1-(phenylsulfinyl)methyllithium **154**, prepared by metalation of (trimethylsilyl)methyl phenyl sulfoxide **155**, was found to be easily alkylated by methyl iodide to produce 1-trimethylsilyl-1-(phenylsulfinyl)ethane **156** in 92% yield, apparently as a single diastereomer.[64] It was later reported[65] that, in fact, this reaction affords both diastereoisomers of **156** in a ratio of approximately 20 : 1.



It was also found[65] that the minor diastereoisomer of **156** is formed almost exclusively by dropwise addition of the anion formed from phenyl ethyl sulfoxide **157** to excess chlorotrimethylsilane at −78 °C.



Silylation of benzyl *t*-butyl sulfoxide anion **106** also affords a mixture of diastereoisomeric sulfoxides **158** which exhibit dramatic stability differences.

Thus, the major diastereoisomer **158a** cannot be isolated at room temperature due to its facile rearrangement to **159**. In contrast, the minor isomer **158b** is quite stable at room temperature and can be purified by chromatography. Taking into account these observations an assignment of the relative configurations of both diastereoisomers of **158** has been proposed.[65]

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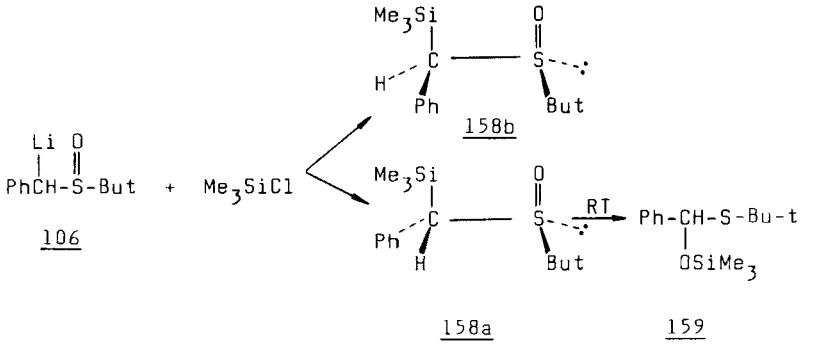
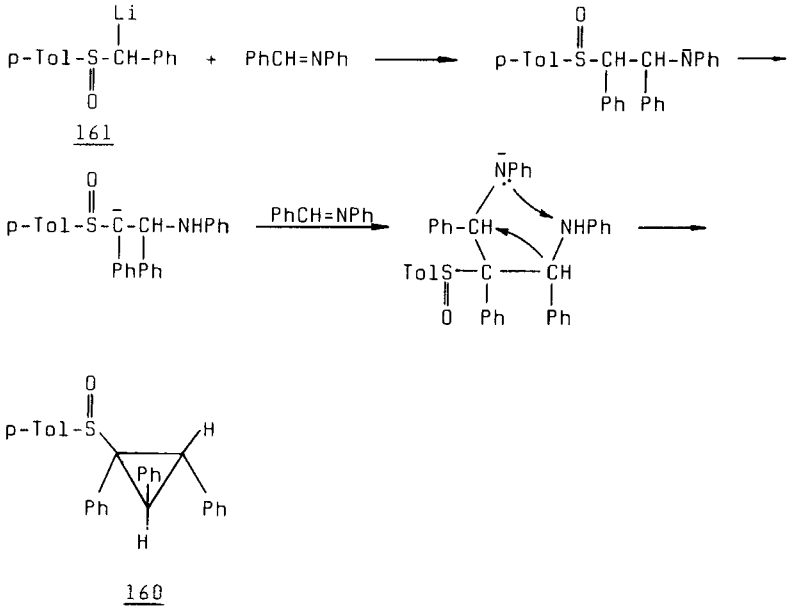


Scheme 32.

A single racemate of 1,2,3-triphenylcyclopropyl *p*-tolyl sulfoxide **160** was produced in 56% yield when the carboanion of benzyl *p*-tolyl sulfoxide **161** was treated with benzalaniline. To explain the formation of **160** the following mechanistic sequence was proposed[66] (Scheme 33).



Scheme 33.

It has been reported that the anions derived from the *t*-butyl alkyl (benzyl) sulfoxides **162** can be added to the α,β-unsaturated esters **163** to give the conjugate products **164** with high stereoselectivity, one diastereoisomer being formed almost exclusively (10 : 1) (Scheme 34).[67]

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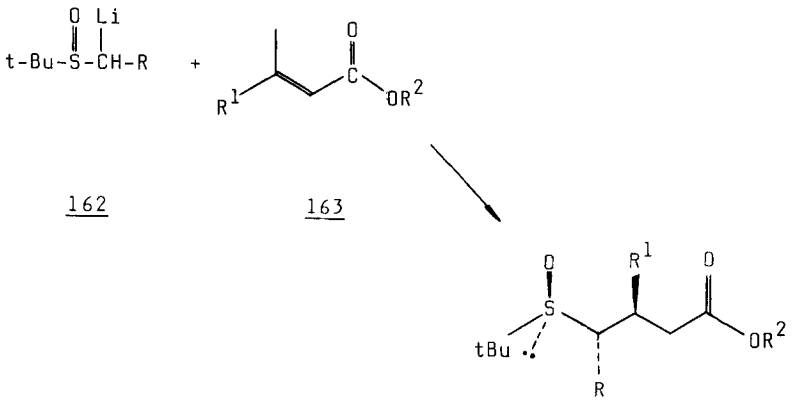

162 163 164

R	R^1	R^2	Yield [%]
Ph	H	Me	78
Ph	Me	Me	74
Ph	Ph	Me	86
p-ClC_6H_4	Me	Me	95
p-$MeOC_6H_4$	Me	Me	91
$PhCH_2$	H	Me	64
$PhCH_2$	Me	Me	68
$PhCH_2$	Ph	Me	63
n-Pr	Me	Me	64
i-Pr	Me	Me	63
Et	Me	Me	53

Scheme 34.

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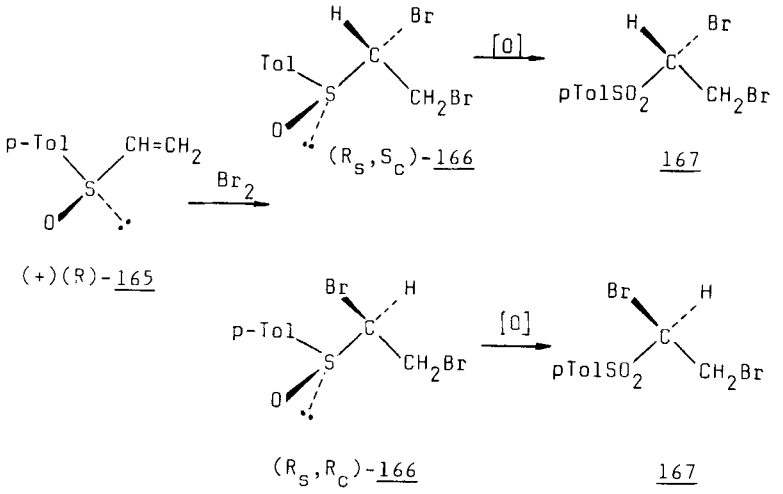
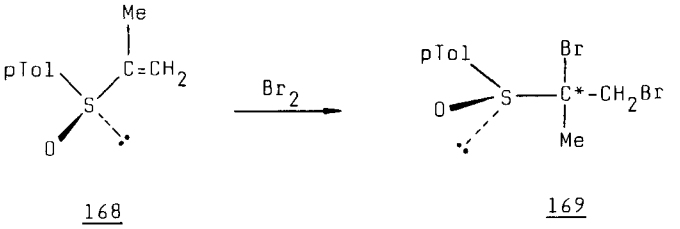
3.6. Addition of electrophilic and nucleophilic reagents to α,β-unsaturated sulfoxides

The addition of electrophilic or nucleophilic reagents to suitable chiral α,β-unsaturated sulfoxides creates a new chiral center at the α-carbon atom. It was found[68] that the addition of bromine to the optically active (R)-vinyl *p*-tolyl sulfoxide **165** yields a mixture of diastereoisomeric α,β-dibromo sulfoxides **166**. The degree of asymmetric induction was determined by oxidation of the mixture of diastereoisomers and comparison of the rotation of the dibromo sulfone mixture **167** obtained with that of the sulfone obtained by oxidation of the pure major diastereoisomer (R_S,C_s)-**167** (Scheme 35).



Scheme 35.

The reaction of bromine with optically active (R)-α-methylvinyl *p*-tolyl sulfoxide **168** also affords a 71.5 : 28.5 mixture of the diastereoisomeric sulfoxides **169**.[69]



A very high degree of asymmetric induction was observed in the addition of hypobromous acid and methyl hypobromite to the optically active styryl sulfoxide (R)-**170**. The ratio of diastereoisomeric β-hydroxy sulfoxides **171** formed in the first reaction was 9 : 1, whereas the diastereoisomeric β-methoxy sulfoxides **171b** were obtained in the second reaction in a 95 : 5 ratio. Such an almost complete asymmetric inductions is due to the reaction mechanism involved. In the first step of the reaction a bromonium ion Br^+ attacks the carbon–carbon double bond to form a cyclic bromonium structure **172**, which subsequently reacts with the nucleophile ^-OR at the β-carbon atom, leading to the final product **171**. The formation of **172a** is strongly preferred over **172b** for steric reasons (Scheme 36)[69]

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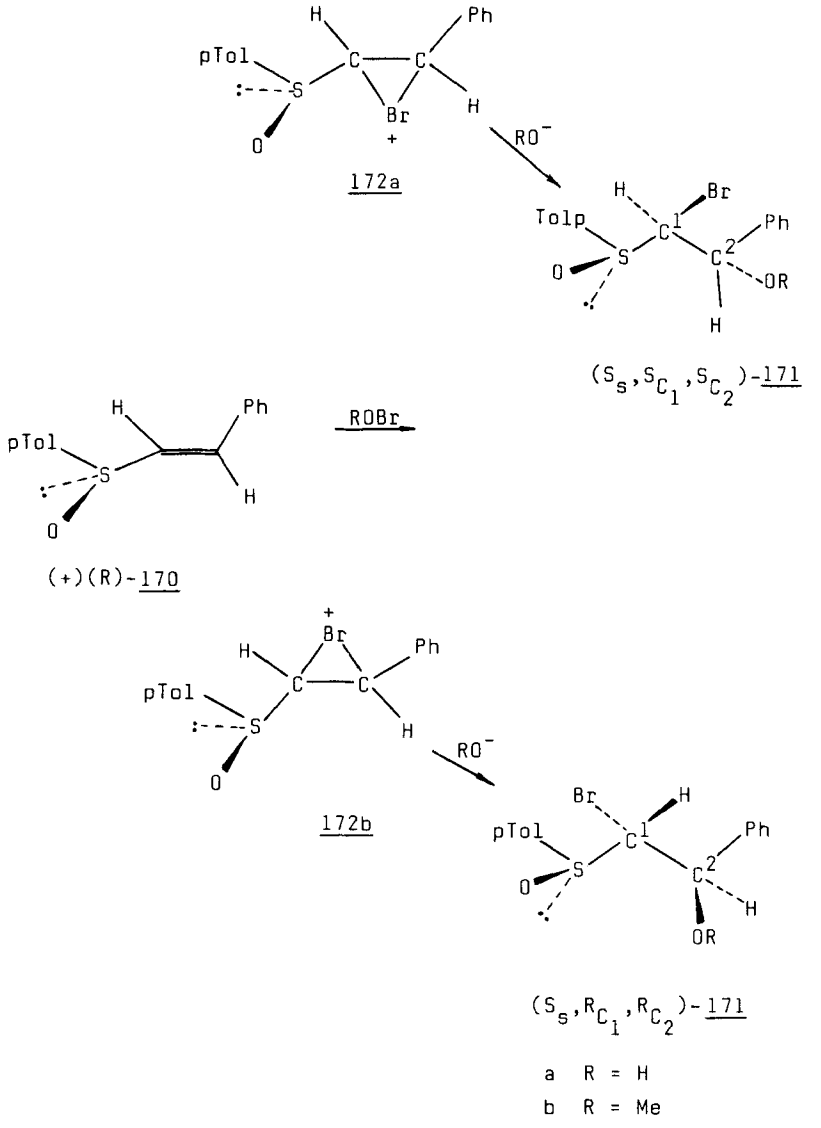

Scheme 36.

Reaction of the optically active sulfoxide **168** with piperidine at 80 °C gave after 1 week the diastereoisomeric adduct **173** which according to the ^{1}H NMR spectrum was a mixture of diastereoisomers present in the ration 1.8 : 1. This corresponds to an optical purity of 29%. The diastereoisomers were readily separated by chromatography and the major diastereoisomer was a solid which could be crystallized to constant rotation (Scheme 37).[68b]

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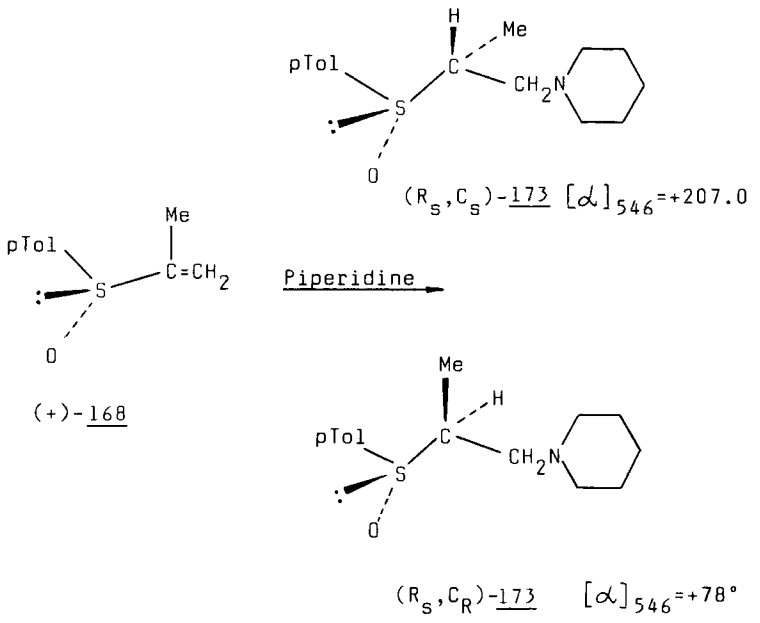

Scheme 37.

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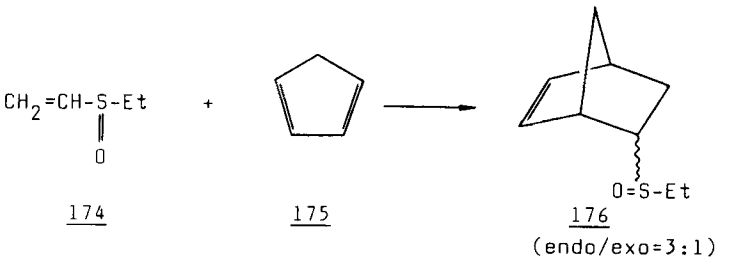
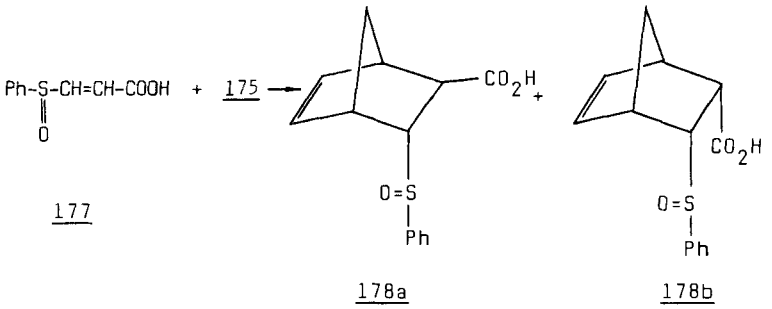
3.7. Diels-Alder reactions of sulfinyl dienophiles

The sulfinyl group has long been known to be a moderately activating functionality in Diels-Alder cycloadditon reactions.[70] The pioneering work in this field showed, however, that the chiral sulfoxide group is a poor diastereofacially selective agent, as racemic sulfinyl dienophiles add almost indistinctly from the oxygen as well as from the electron pair side and with a moderate endo selectivity.[71] Recently, a good endo selectivity has been achieved with the introduction of an additional activating electron-withdrawing group.

In the reaction of vinyl ethyl sulfoxide **174** with cyclopentadiene **175** the corresponding diastereoisomeric mixture of bicyclo[2.2.1]hept-5-yl sulfoxides **176** is formed.[72]

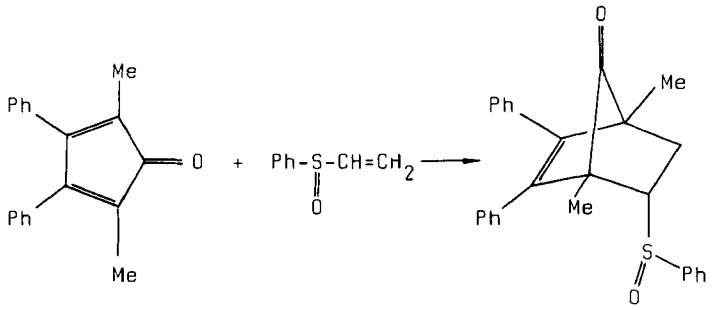


In the reaction between cyclopentadiene and β-phenylsulfinylacrylic acid **177** the endo-syn products **178a,b** are favored (~80%) over the endo-anti forms.[73]



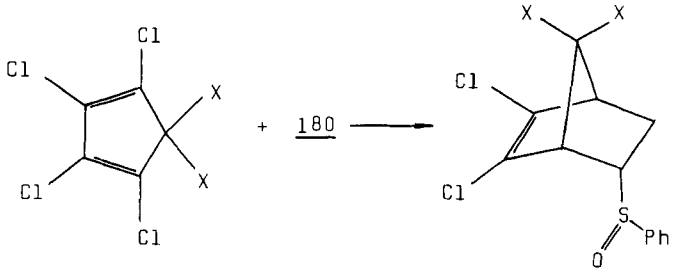
177 178a 178b

Heating 2,5-dimethyl-3,4-diphenylcyclopentadienone **179** with phenyl vinyl sulfoxide **180** in toluene for 24 h affords also the endo isomer **181** in 73% yield.[70]



179 180 181

Both hexachlorocyclopentadiene and 5,5-dimethoxytetrachlorocyclopentadiene **182b** react readily with **180** as neat mixtures, at 100 °C and 60 °C, respectively, to form the spectroscopically identifiable endo cycloadducts **183a** and **183b**.[70]



182

a X = Cl

b X = OMe

183

a X = Cl

b X = OMe

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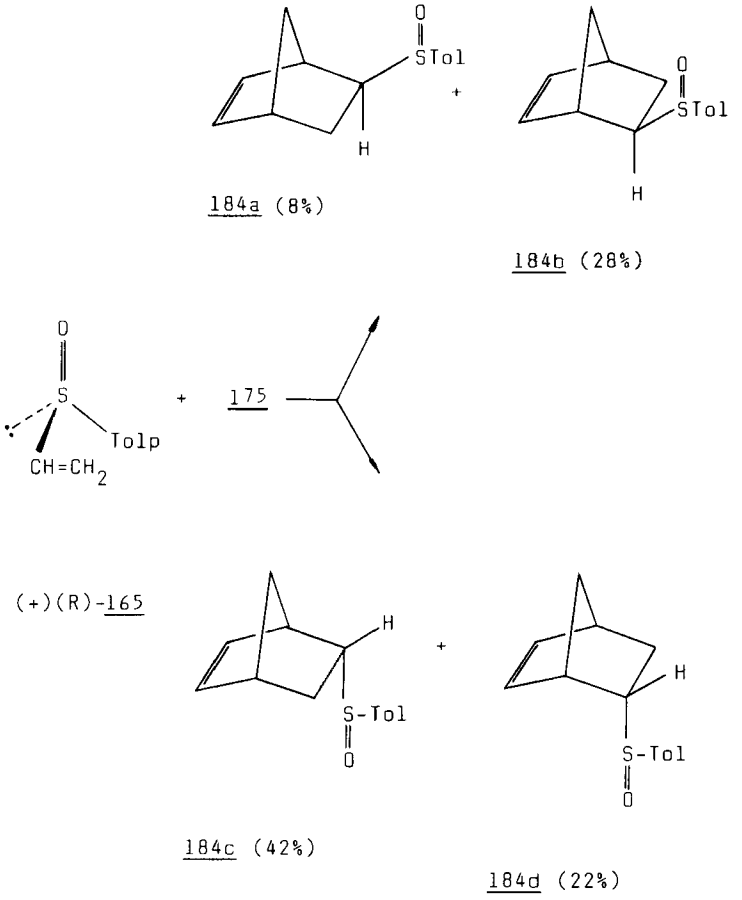
The reaction of cyclopentadiene with optically active (+)-(R)-*p*-tolyl vinyl sulfoxide **165** gave an adduct mixture from which four diastereoisomers of the bicyclic sulfoxide **184** were isolated (Scheme 38).[74]



Scheme 38.

When this reaction was promoted by trimethylsilyl trifluoromethanesulfonate (TMSOTf), the endo product was predominantly formed with a high d.e. (Scheme 39).[75]

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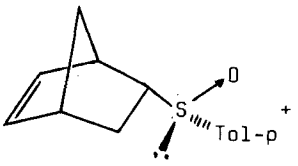
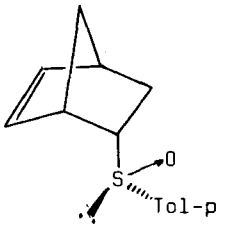
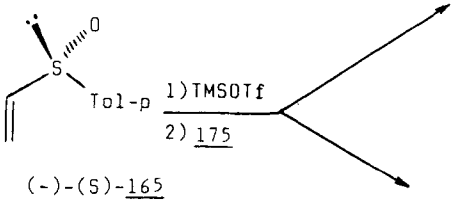


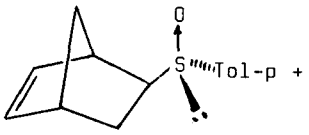
184e endo (major)



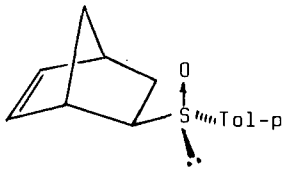
184f endo (minor)



(-)-(S)-165



184g exo (minor)



184h exo (major)

Mol. equiv. TMSOTf	Time [h]	Yield (total) [%]	Endo d.e.	Exo d.e.	Endo/Exo
0.05	15	20	57	–	99:1
0.20	15	60	96	63	92:8
1.00	3	61	92	99	89:11

Scheme 39.

Optically active bis-sulfoxide (+)-(S,S)-**185** was found to be a good chiral dienophile for cycloaddition to cyclopentadiene. Its reaction with cyclopentadiene (20 equivalents) in a sealed tube at 60–70 °C gave **186** as an unseparable diastereoisomeric mixture in a ratio of 4:1.[76]

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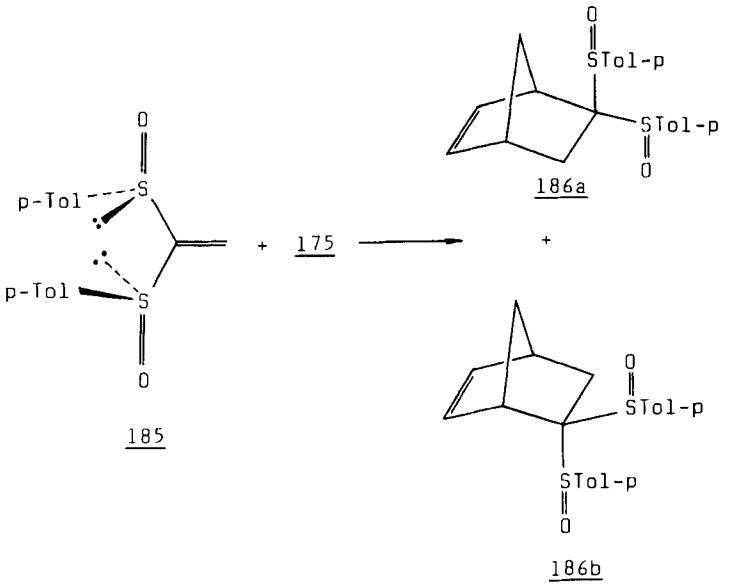
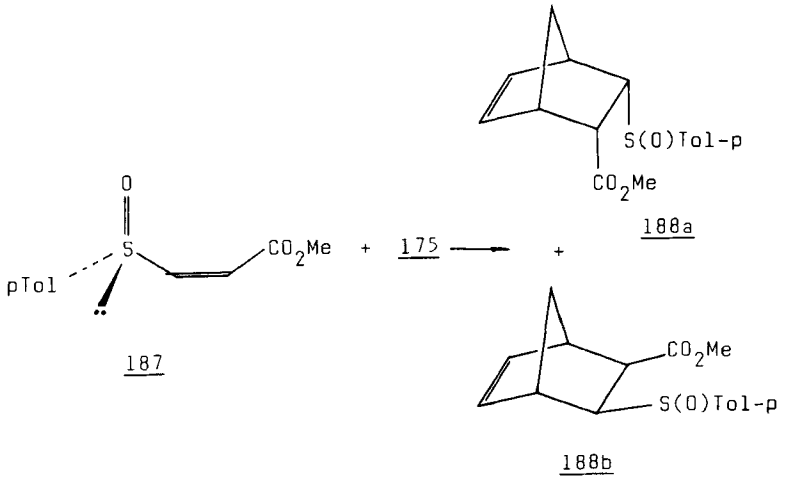


On the other hand, methyl (*Z*)-(R)-3-(*p*-toluenesulfinyl)propenoate **187** reacts with cyclopentadiene giving only the two diastereoisomeric sulfoxides **188a** and **188b** in a 93 : 6 ratio.[77]



The reaction of ethyl (*E*)-(R_s)-(*p*-tolylsulfinyl)methylenepropionate **189** with cyclopentadiene was found to give the endo sulfoxides **190a** and **190b** and exo sulfoxide **191a** in 63, 15, and 22% yields, respectively. The diastereoisomeric exo sulfoxide **191b** could not be detected in the crude reaction mixture.[78]

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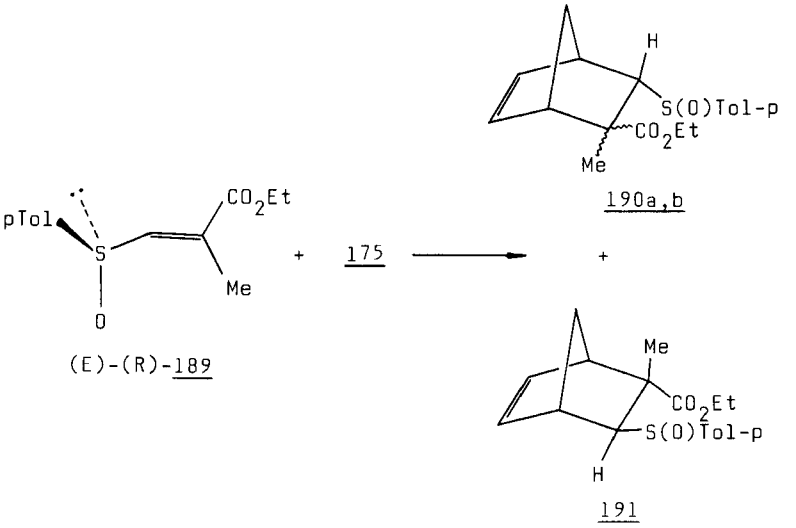
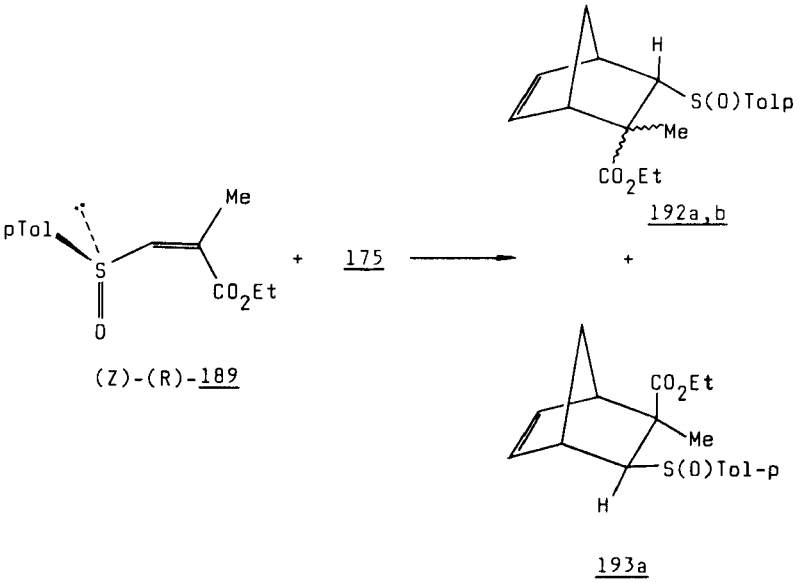


Similarly, (*Z*)-(R_s)-**189** afforded the endo sulfoxides **192a** and **192b** and the exo sulfoxide **193a** in 63, 2, and 35% yield, respectively, and again, the diastereoisomeric exo sulfoxide **193b** could not be detected.[78]



The Diels-Alder cycloaddition of the optically active dienophiles with (*Z*)-geometry **194a** and **194b** to cyclopentadiene leads with almost full stereoselectivity to the single diastereoisomers **195a** and **195b**, respectively. When the corresponding (*E*)-isomers were used in this reaction, mixtures of diastereoisomers were produced[79] (Scheme 40).

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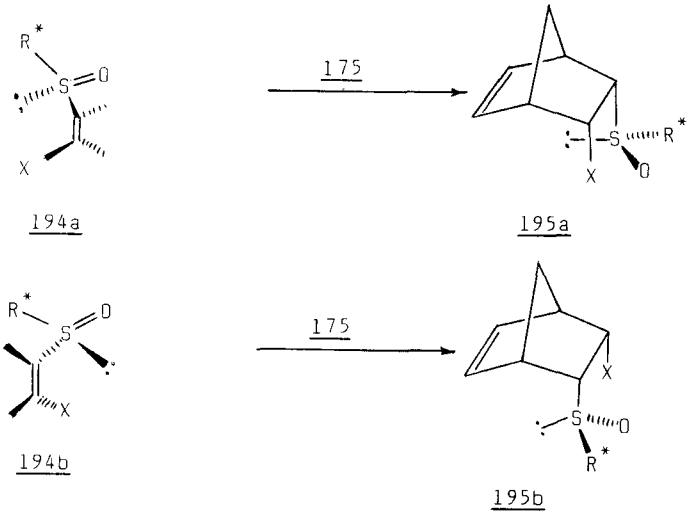
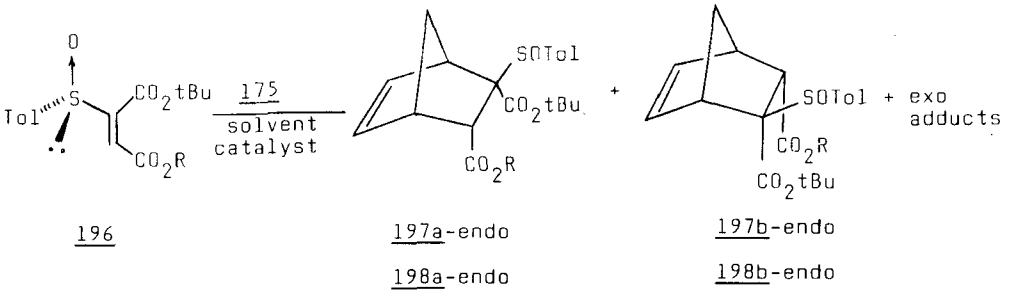


Scheme 40.

A high reactivity towards cyclopentadiene (but not towards furan) was also observed when the sulfinylmaleates **196** were used as dienophiles. The corresponding products **197a** and **198a** were usually obtained in almost quantitative yields.[80,81] The endo/exo and facial selectivities depend on the solvent and catalyst used[81] (see Table 5A) (Scheme 41).



Scheme 41.

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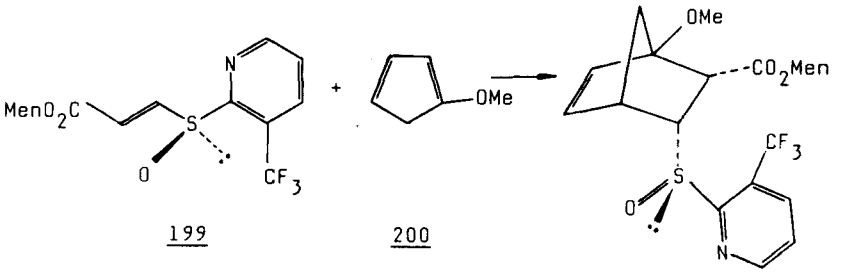
Table 5A. Cycloaddition of sulfinylmaleates to cyclopentadiene[81]

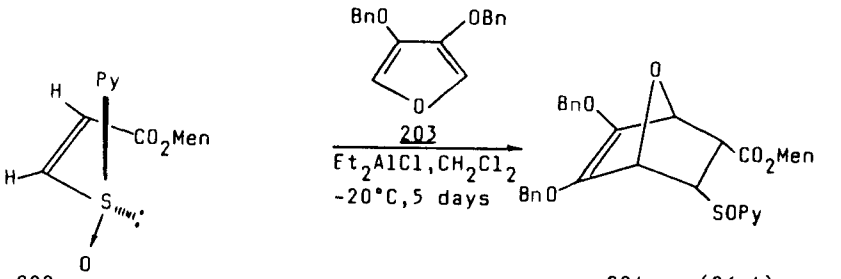
Dienophile (equiv.)	Catalyst 1.2 eq.	*T* [°C]	Reaction Time [h]	Products		
				197a-*endo*	**197b**-*endo*	*exo*
196a (3)	–	0	3	88	7	5
196a (10)	–	−20	12	91	5	3
196a (3)	$ZnBr_2$	−20	2	complex mixture		
196a (10)	$BH_3 \cdot THF$	−10	20	84	9	7
196a (10)	$H_2O/NaHCO_3$	r.t.	28	30	47	–
				198a-*endo*	**198b**-*endo*	*exo*
196b (10)	–	r.t.	41	58	17	25
196b (6)	$ZnBr_2$/	0	2	9	82	9
196b (6)	$ZnBr_2$	−20	7	6	89	5
196b (5)	$LiClO_4$/ether	r.t.	4	31	48	21
196b	$BF_3 \cdot Et_2O$	−20	7	43	37	20

Diastereoisomerically pure (S_s)-menthyl β-[3-(trifluoromethyl)pyrid-2-ylsulfinyl]acrylate **199** was found to react smoothly with 2-methoxyfuran **100** to give the cycloadduct **201** with 96% stereoselectivity.[82]



199 200 201

As a first step in the toal synthesis of optically active (+)-methyl 5-epishikimate, the Diels-Alder reaction of **202** with 3,4-dibenzyloxyfuran **203** was carried out and gave the cycloadduct **204** in 50% yield.[80,83,84]



202 204 (96:4)

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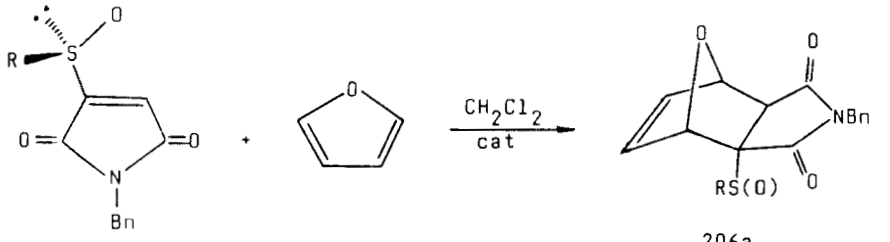
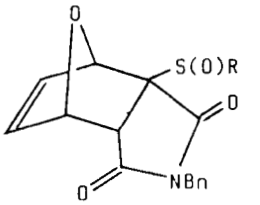
α-Sulfinyl *N*-benzylmaleimides **205** exhibit high dienophilic reactivity. In contrast to sulfinyl maleates, however, they react with furan quite smoothly.[80]



205a

206a

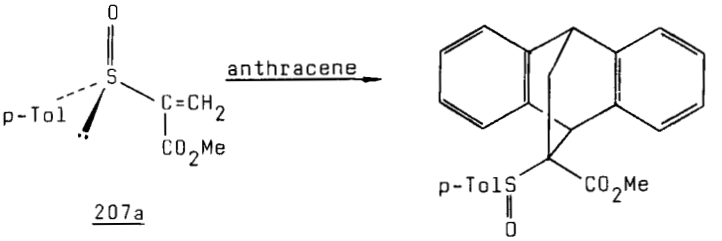
+



206b

	206a :	206b
$ZnCl_2$, 0°C, 0.5 h	51% (100:0)	15% (100:0)
—— 25°C, 5 h	25% (49:51)	29% (61:39)

The Diels-Alder reaction of methyl α-(*p*-toluenesulfinyl) acrylate **207a** with anthracene in the presence of zinc chloride gave the single diastereoisomeric adduct **208**.[85]



207a

208

On the other hand, reaction of the ethyl ester **207b** with cyclopentadiene afforded the cycloadducts **209** and **210** as mixtures of diastereoisomers (Scheme 42) the ratio of which is strongly influenced by the presence of Lewis acids.[85]

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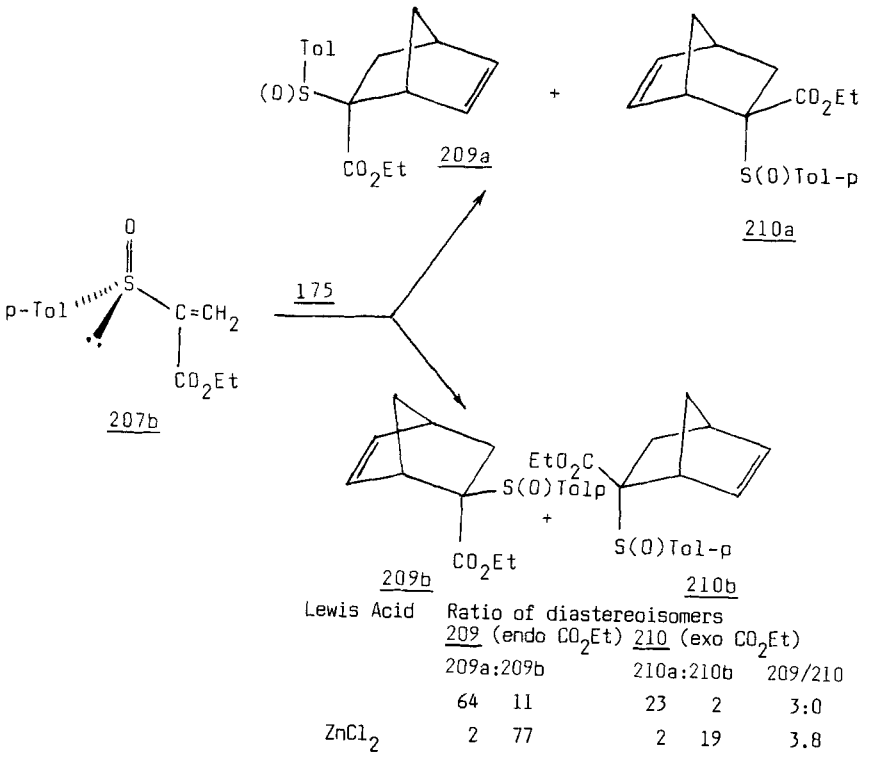
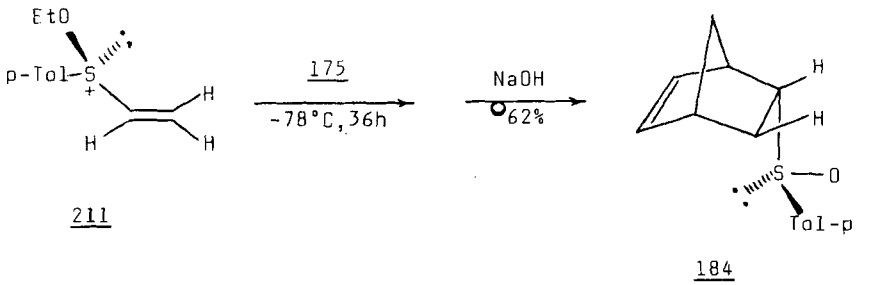


Lewis Acid	Ratio of diastereoisomers 209 (endo CO_2Et)		210 (exo CO_2Et)		
	209a:209b		210a:210b		209/210
	64	11	23	2	3:0
$ZnCl_2$	2	77	2	19	3.8

Scheme 42.

The unsaturated sulfonium salts **211** undergo Diels-Alder cycloaddition with cyclopentadiene to give, after hydrolysis with NaOH, the corresponding sulfoxides **184** with almost 100% diastereoselectivity and an endo/exo ratio of over 99 : 1.[83]



3.8. Other cycloadditions of sulfinyl dienophiles

1,3-Dipolar cycloadditions of nitrile oxides to vinyl sulfoxides usually afford mixtures of regio- and diastereoisomers. Thus, in the cycloaddition of benzo- and mesitonitrile oxide

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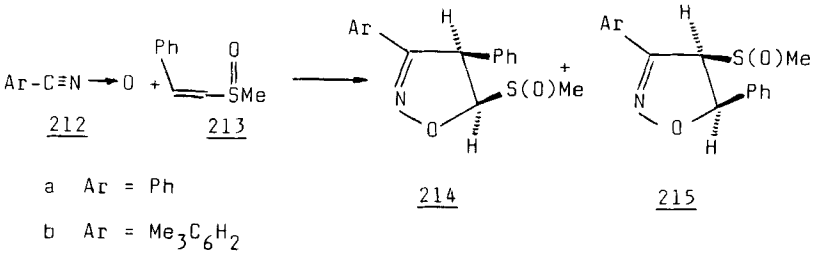
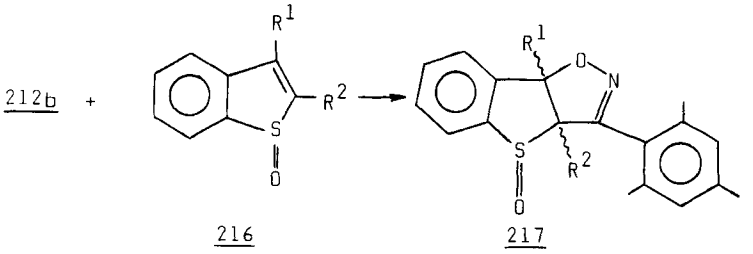
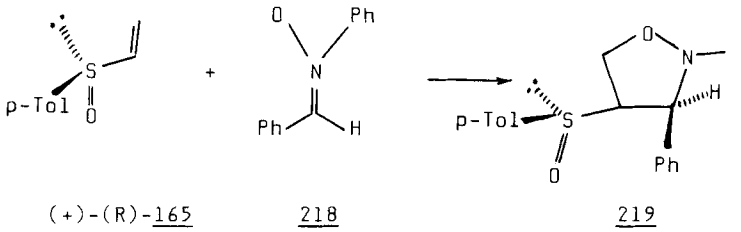
212a,b to (*Z*)-*β*-phenylvinyl methyl sulfoxide **213** only two of the four possible diastereoisomeric and regioisomeric cycloadducts **214** and **215** are discernible in the ^{1}H NMR spectra of the reaction mixtures in 9:1 and 7:3 ratio, respectively.[86]



The 1,3-dipolar cycloaddition of mesitonitrile **212b** to the benzo[*b*]thiophene *S*-oxides **216** is non-stereoselective and both syn and anti adducts **217** are formed.[87]



On the other hand, very high asymmetric induction was observed in the 1,3-dipolar cycloaddition of (+)-(R)-*p*-tolyl vinyl sulfoxide **165** to the acyclic nitrone **218**. This reaction affords the cycloadduct **219** in 57% yield and with 90% e.e.[88]



The palladium catalyzed [3+2]-cycloaddition of trimethylenemethane generated *in situ* from (2-acetoxymethyl)allyltrimethylsilane **220** with a variety of optically active vinyl sulfoxides **221** led to a mixture of only two diastereoisomers of the 3,4-disubstituted methylenecyclopentane derivatives **222** in good chemical yields (Scheme 43).[89]

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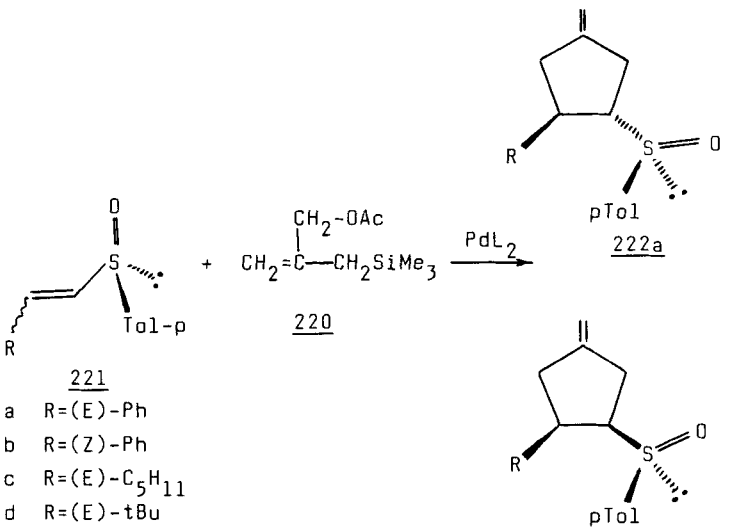


221

a R=(E)-Ph
b R=(Z)-Ph
c R=(E)-C_5H_{11}
d R=(E)-tBu

220

222a

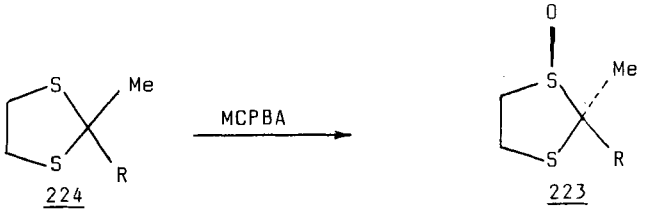
222b

a/b = 9:10
a/b = 25:75
a/b = 23:77
a/b = 18:82

Scheme 43.

3.9. Oxidation of prochiral sulfenyl derivatives

The *S*-monoxidation of prochiral sulfenyl derivatives such as 1,3-dithiolanes and 1,3-dithianes leads to the formation of two diastereoisomeric pairs of enantiomers because of the presence of two chiral centers, i.e. the carbon in position 2 of the ring and the sulfinyl sulfur atom. The *cis*-monosulfoxides of the 1,3-dithiolanes **223** have been prepared by selective oxidation of the ethylene dithioketals of the corresponding ketones **224a–c** with *m*-chloroperbenzoic acid in cold dichloromethane (Scheme 44).[90]



224

a R = Anisyl
b R = pNO_2-C_6H_4
c R = tBu
d R = Ph

223

Scheme 44.

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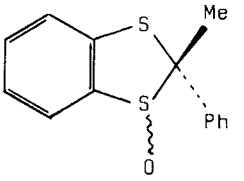
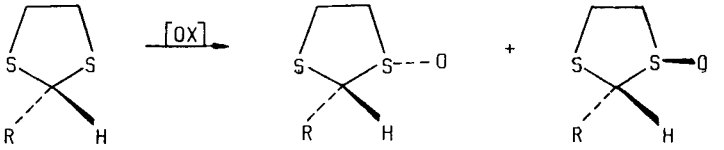
Oxidation of **224d** under the same conditions gave, however, both diastereoisomers of **223d**. Also, oxidation of 1,3-benzodithiolane with MCPBA is not stereoselective and both diastereoisomers of the corresponding sulfoxide **225** are formed.[91]



225

In the oxidation of the 2-substituted 1,3-dithiolanes **226** the relative amounts of the two diastereoisomers were found to be determined mainly by the relative steric congestion around the sulfur atom and the nature of the oxygen transfer reagent (Scheme 45).[92]



226 Z-227 E-227

No.	R	Oxidant	E/Z ratio
a	Ph	t-BuO_2H/Ti(O-i-Pr)$_4$	16
a	Ph	VO(acac)$_2$/DCE	32
a	Ph	VO(acac)$_2$/EtOH	99
a	Ph	Mo(acac)$_2$	32
a	Ph	MCPBA	2.3
a	Ph	$NaIO_4$	7.3
b	Me	MCPBA	2.3
b	Me	$NaIO_4$	1.5
c	t-Bu	MCPBA	100
c	t-Bu	$NaIO_4$	100
c	t-Bu	H_2O_2	100

Scheme 45.

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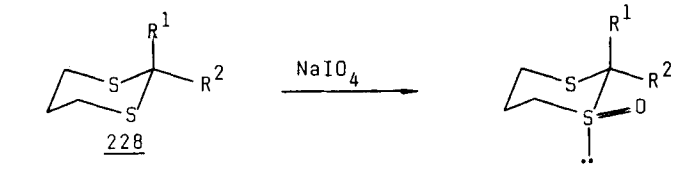
Similarly, sodium metaperiodate differentiates between the diastereotopic lone pairs of the sulfur atom in the 2-substituted 1,3-dithianes **228** affording the corresponding *trans*-monosulfoxides **229** as the major product (90–100%), (Scheme 46).[93]



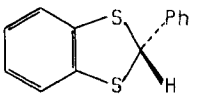
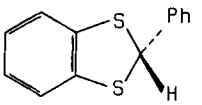
228 229

a R^1 = H, R^2 = Me
b R^1 = H, R^2 = Bu-t
c R^1 = Me, R^2 = Bu-t

Scheme 46.

The enantioselective oxidation of a series of dithioacetals and dithioketals **230** to their corresponding monosulfoxides **231** and **232** with a modified Sharpless reagent has been reported (Table 5B).[92] It was found that the 1,3-dithiolanes **230a–d** are the best substrates since the enantioselectivity is high (> 80%) and also the diastereoisomeric ratio is very favorable (> 6 : 1).

Table 5B. Enantioselective oxidation of substituted 1,3-dithiolanes and 1,3-dithianes[a] with the [Ti(O-*i*-PR)$_4$-*t*-Bu-O$_2$H-diethyl tartrate] system[a]

Substrate **230**				Yield [%]	E/Z	e.e. [%]
No.	R^1	R^2	n			
a	*t*-Bu	H	2	82	99 : 1	70
b	*t*-Bu	Me	2	61	99 : 1	68
c	EtO_2C	H	2	64	7 : 1	85
d	$PhCH_2O_2C$	H	2	79	6 : 1	98
e	Ph	Me	2	66	97 : 3	81
f	Ph	H	3	79	9 : 1	14
g	Ph	Me	3	87	85 : 15	39
h				92	100 : 0	24
i				85	(55 + 44) : 0[b]	39

[a] Taken from reference.[92]

[b] The data refer to the oxidation of the *trans*-isomer where, due to the chirality of the cyclohexane carbon, the number of stereoisomers formed doubles (2 Z + 2 E diastereoisomeric pairs). Only the E isomers were found in the ratio reported.

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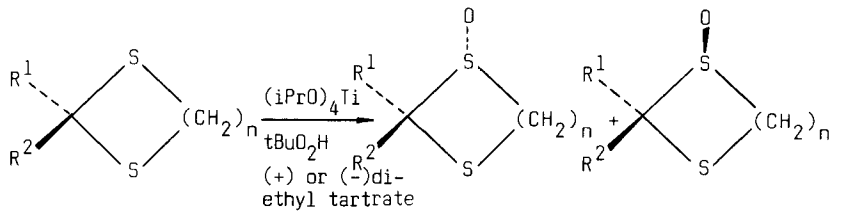
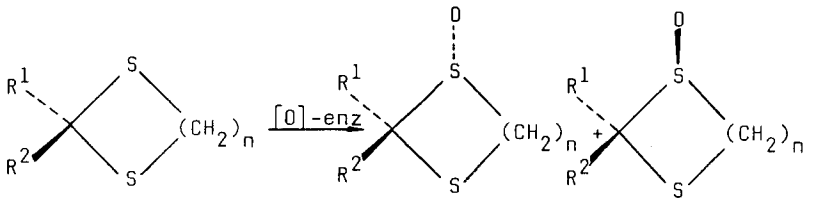


230 231 232

It has also been reported[94,95] that the monoxygenase enzymes present in fungi are able to discriminate between prochiral thioalkyl substituents on a carbon atom of the substituted 1,3-dithiolanes and 1,3-dithianes **230** during the formation of the monosulfoxides **231** and **232** (Scheme 47).



230 231 232

n	R^1	R^2	Fungus[a]	Z (yield %; $[\alpha]_D$; e.e. [%])			E (yield %; $[\alpha]_D$ e.e.)		
1	H	Me	A	75	+18	28	25	0	0
1	H	Me	H	75	−3	4	25	0	0
1	H	Me	M	75	+9	15	25	0	0
1	H	*t*-Bu	M				7 − 20	+6 ÷ +13	14 ÷ 32
2	H	Me	A	23	0	0	30	35	27
2	H	Me	H	2	−71.5	33.5	28	−71.1	27
2	H	Me	M	9	−11.2	19	1	−39.0	21
2	H	*t*-Bu	H	4	+80.3	65	22	−5.4	14
2	H	*t*-Bu	M	7	0.0	0	29	+5.8	10
2	Me	*t*-Bu	A				30	+6.4	8
2	Me	*t*-Bu	H				24	0	0

[a]A = Aspergillus fetidus, H = Helminthosporium, M = Mortierella isabellina

Scheme 47.

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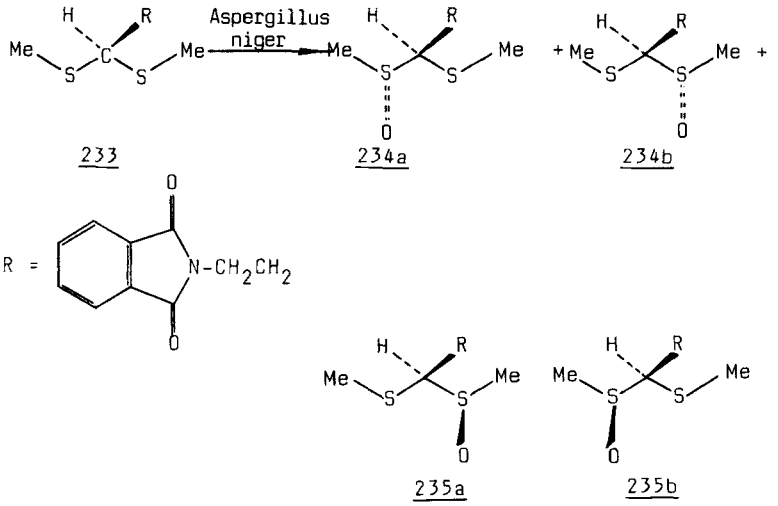
Fermentation of the prochiral dithioacetals **233** with Aspergillus niger NRRL 337 produced a diastereoisomeric mixture of the 1-methylsulfinyl-1-methylthio-3-phthalimidopropanes **234** and **235** in a ratio of 2:3. The enantiomeric composition of this mixture [**234a/234b** = 2.75 and **235a/235b** = 29] was determined by NMR spectroscopy with a chiral solvent.[96]



233 234a 234b 235a 235b

Scheme 48.

3.10. Halogenation of sulfoxides

Sulfoxides have been found to undergo very ready halogenation at the α-carbon with a number of electrophilic halogenating agents. For the preparation of α-chloro sulfoxides the following chlorinating reagents have been used: chlorine in the presence of pyridine, *N*-chlorosuccinimide, sulfuryl chloride, dichloroiodobenzene, *t*-butyl hypochlorite, *N*-chlorobenzotriazole and *N*-chlorosulfoximine.[97,98] α-Bromo sulfoxides have been prepared by bromination of sulfoxides with *N*-bromosuccinimide in the presence of pyridine. The stereochemistry of the α-halogenation of sulfoxides has been reviewed.[99]

Chlorination of the six-membered thiane 1-oxide **236** with *t*-butyl hypochlorite in the presence of anhydrous potassium acetate produced *cis*-2-chlorothiane 1-oxide **237** with full stereoselectivity.[100]

236 237

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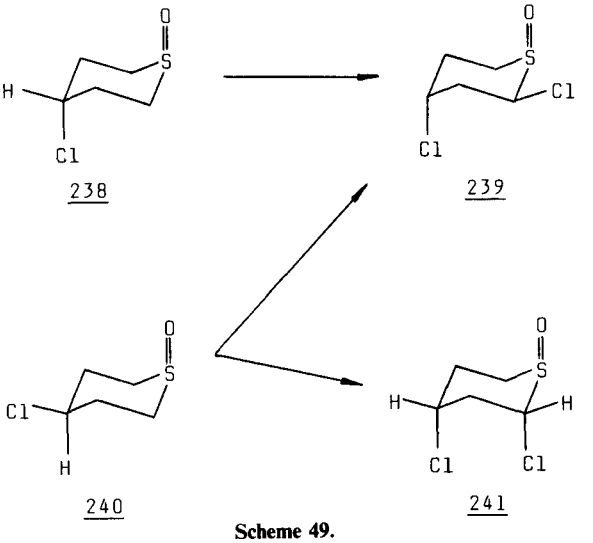
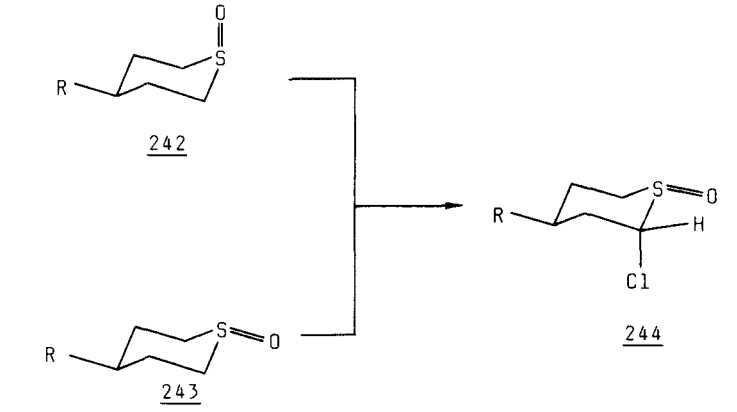
Chlorination of *trans*-4-chlorothiane 1-oxide **238** with the same reagent gave, fully stereoselectively, 2e,4a-dichlorothiane 1-oxide **239** while *cis*-4-chlorothiane 1-oxide **240** furnished a 67 : 33 mixture of **239** and 2e,4a-dichlorothiane 1a-oxide **241** (Scheme 49).[100]



Scheme 49.

Chlorination of the conformationally biased *trans*-4R-thiane 1-oxides **242** and *cis*-3R-thiane 1-oxides **243** with different chlorinating agents gave always the same single product, the 2a-chloro-4e-R-thiane 1-oxide **244** (Scheme 50).[100,101]



Scheme 50.

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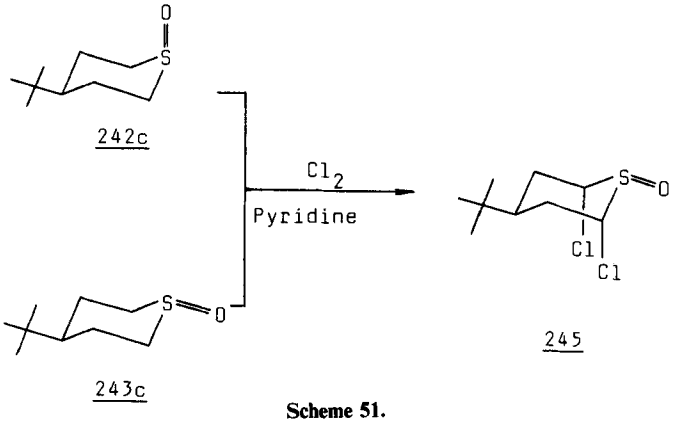
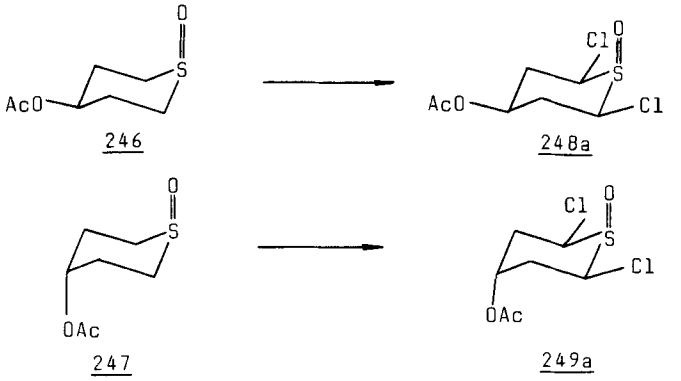
Chlorination of both *cis*-**242c** and *trans*-4-*t*-butylthiane 1-oxide **243c** with chlorine in pyridine yielded the same dichloro compounds (Scheme 51).[102]

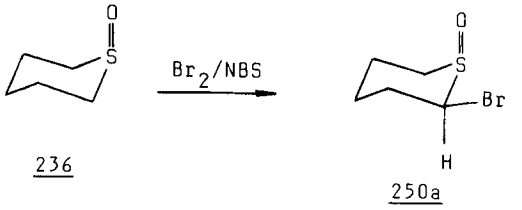


Scheme 51.

In contrast to the pair **242c** and **243c** chlorination of the isomeric 4-acetoxythiane 1-oxides **246** and **247** gave different dichloro derivatives, i.e. **248a** and **249a**.[102]



Bromination of the thiane 1-oxide **236** with a mixture of 0.5 equivalents of bromine and 1 equivalent of *N*-bromosuccinimide in the presence of pyridine produced, with full stereoselectivity, *cis*-2-bromothiane 1-oxide **214a**.[103]



Bromination of *trans*-4-chlorothiane 1-oxide **238** with the same reagent afforded stereoselectively the corresponding 2e-bromo-4a-chlorothiane 1-oxide **251**, while in the

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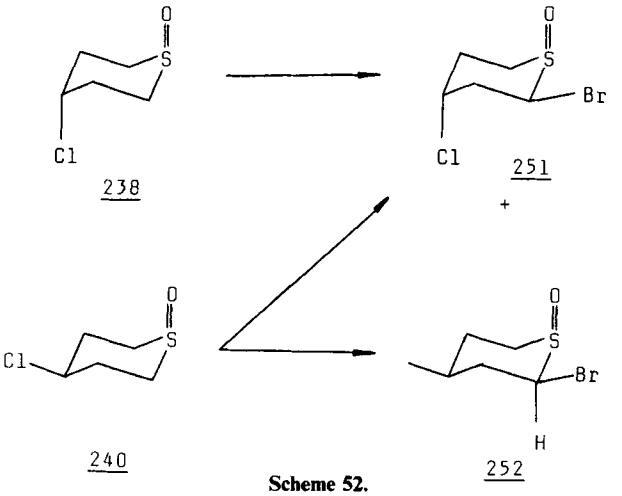
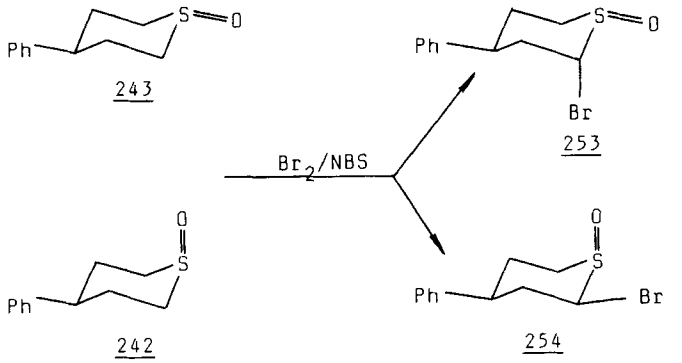
corresponding reaction of *cis*-4-chlorothiane 1-oxide **240** a 20:80 mixture of **251** and 2e-bromo-4e-chlorothiane **252** was formed (Scheme 52).[103]

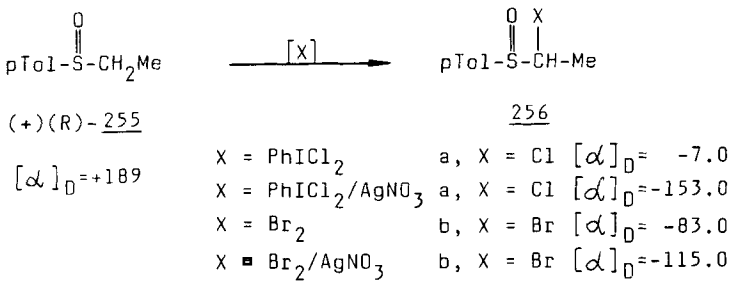


Scheme 52.

Similarly, bromination of the 4-phenylthio 1-oxides **243** and **242** is not stereoselective. Thus, the *trans*-oxide **243a** under the same conditions gives a 63:37 mixture of 2a-bromo-4e-phenylthiane 1-oxide **253** and 2e-bromo-4e-phenylthiane 1-oxide **254**, while the *cis* isomer **242** afforded a 18:19 mixture of **253** and **254** (Scheme 53).[103]



Scheme 53.



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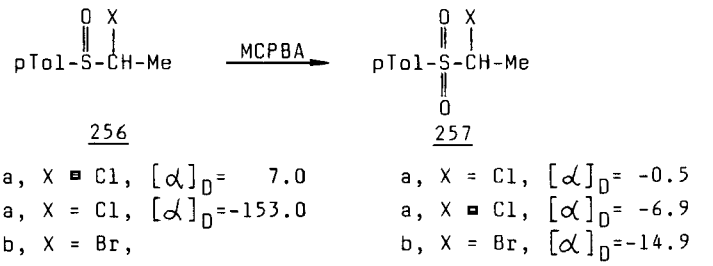
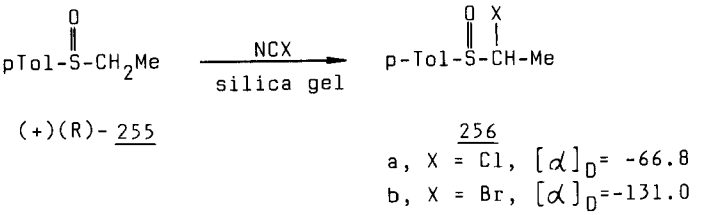
For the first time asymmetric induction in the α-halogenation of acyclic sulfoxides was observed when optically active (+)-(R)-*p*-tolyl ethyl sulfoxide **255** was converted to the corresponding α-halo derivatives **256** by treatment with dichloroiodobenzene or bromine, respectively.[104] It was found that these conversions are accompanied by asymmetric induction at the α-carbon atom, since the sulfones **257** obtained from the α-halo sulfoxides **256** were in all cases optically active. It was observed that the extent of asymmetric induction is strongly influenced by the nature of the halogenation agent and that chlorination of **255** with $PhICl_2$ in the presence and absence of $AgNO_3$ leads to the same structure of **256**. The differences in optical activity are due to the formation of different ratios of enantiomers, not to different ratios of diastereoisomers (the chirality of the sulfinyl sulfur atom is not preserved) (Scheme 54).



Scheme 54.

Later on it was reported[105] that halogenations of optically active (+)-(R)-**255** with *N*-halosuccinimides can be carried out with much higher stereselectivity in the solid phase with silica gel as support.



Very recently it was found that the chlorination of the sulfoxides **255** with *N*-chlorosuccinimide in dichloromethane in the presence of potassium carbonate affords the optically active chloro sulfoxide **256**, having a much higher specific rotation ($[\alpha]_D$ = −207.9°), as a 3:1 diastereoisomeric mixture. Application of this procedure to the chlorination of the optically active *p*-tolyl 2-phenylethyl sulfoxide **258** gave the corresponding α-chloro sulfoxide **259** as a 6.6:1 diastereoisomeric mixture.[45]

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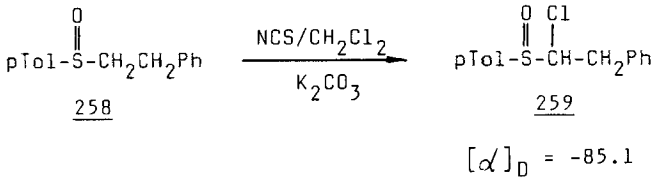
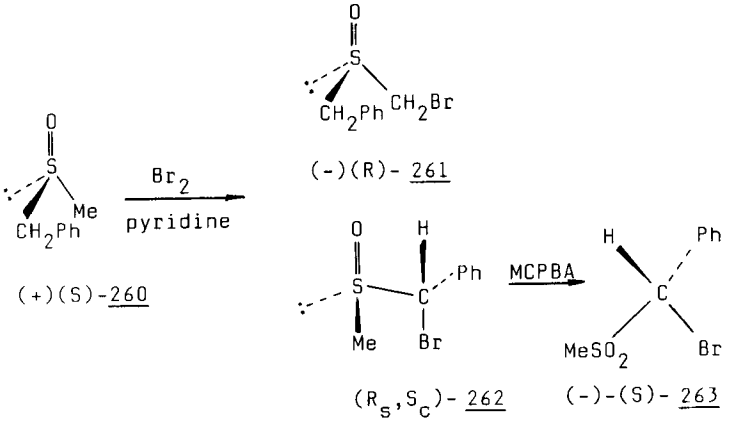
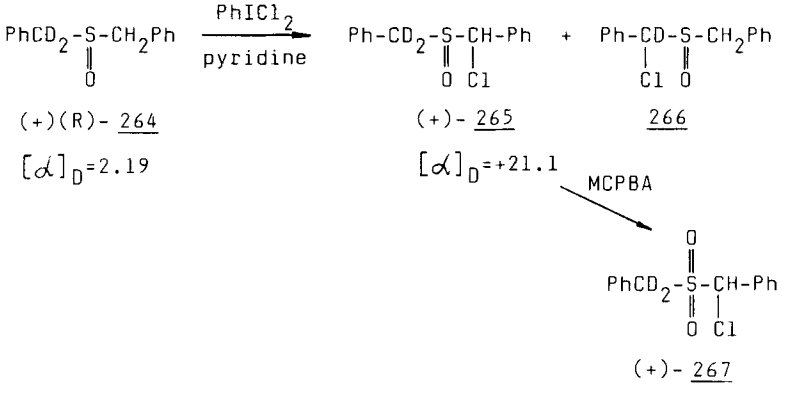


Bromination of (+)-(S)-benzyl methyl sulfoxide **260** with bromine in pyridine afforded a mixture of two regioisomers: α-bromomethyl benzyl sulfoxide **261** and α-bromobenzyl methyl sulfoxide **262** as a single diastereoisomer in a molar ratio of 3:2. Oxidation of the latter gave the corresponding sulfone (−)-(S)-**263**.[106]



An interesting case of asymmetric induction caused by isotopic substitution was observed when the optically active (+ 1)-(R)-α,α-dideuteriobenzyl sulfoxide **264** was chlorinated with dichloroiodobenzene in pyridine. α,α-Dideuteriobenzyl α'-chlorobenzyl sulfoxide **265**, obtained as the major regioisomer with at least 78% isotopic purity, was found to be a single diastereoisomer. Oxidation of **265** afforded the sulfone **267** (Scheme 55).[107]



Scheme 55.

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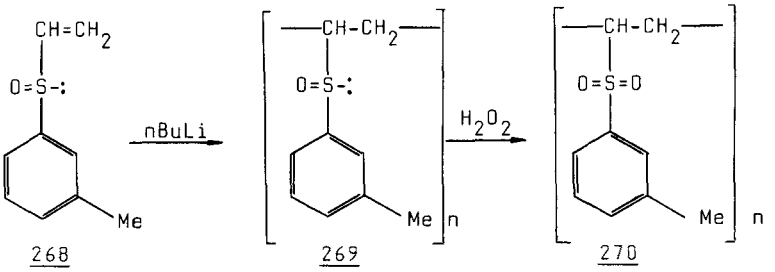
Polymerization of optically active *m*-tolyl vinyl sulfoxide **268** by treatment with *n*-butyllithium in the presence of sparteine afforded the optically active polymer **269** in 90% yield. This polymer was converted into the optically active polysulfone **270** by treatment with H_2O_2 (Scheme 56).[108]



268 269 270

$[\alpha]_D$ = +486.0 (-486.0)

Molar ratio of nBuLi-sparteine	269	270
1:0	+274 (-272)	+19 (-16)
1:1	+310 (-307)	+42 (-40)
1:10	+311 (-310)	+42 (-41)

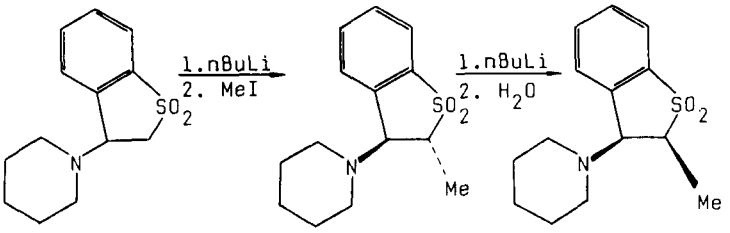
Scheme 56.

The $[\alpha]_D$ value of **270** was attributed to the induced asymmetry of the polysulfone since it was not changed on further oxidation, nor did the polysulfone show any sulfoxide absorption in the IR spectrum. It is not clear, however, whether the $[\alpha]_D$ value of the optically active polysulfone is due to its asymmetric carbons or to its helicity.[108]

4. FORMATION OF CHIRAL CARBON α TO SULFONYL GROUP

4.1. Alkylation of α-sulfonyl carbanions

Treatment of the cyclic sulfone **271** with *n*-butyllithium and then with methyl iodide gave the trans-alkylation product **272a** exclusively. It could be isomerized to the *cis*-isomer **272b** by deprotonation with *n*-butyllithium and *in situ* quenching of the resulting anion with water.[109]



271 272a 272b

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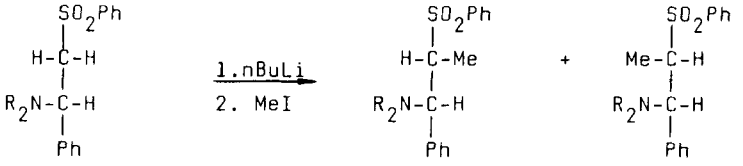
A highly diastereoselective, direct methylation of the acyclic β-aminoalkyl sulfones **273** has been shown capable of producing either of the diastereoisomeric derivatives **274** and **275** with a selectivity higher than 90%, depending upon the nature of the amino group (Scheme 57).[110]



273 274 275

No	R	R	274/275 ratio
a	Me	Me	84:16
b	Morpholine		94:16
c	H	H	13:87
d	Me	H	0:100

Scheme 57.

Alkylation of the dianions of the 1-sulfonylpropanols **276** with alkenyl bromides **277** at −78 °C produces a diastereoisomeric mixture of the alkylated products **278** and **279** the ratio of which increases with the bulk of the group R^1 (Table 6).[111]

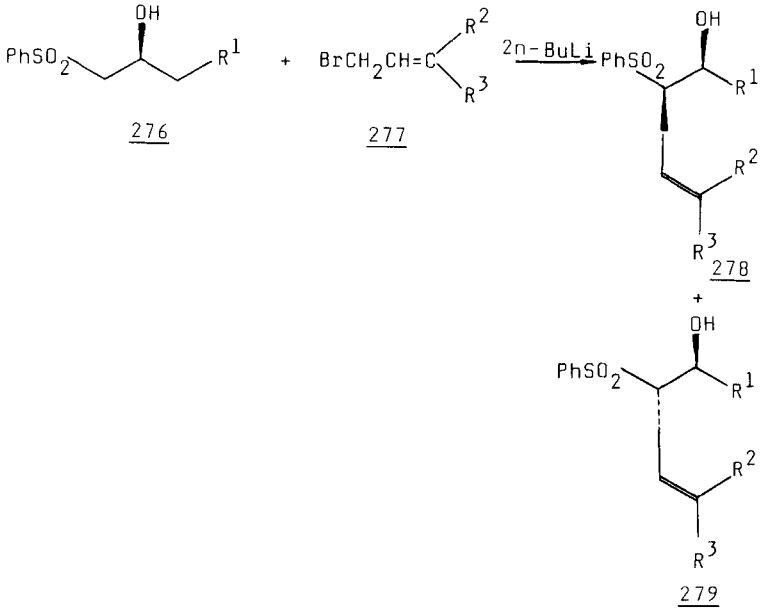


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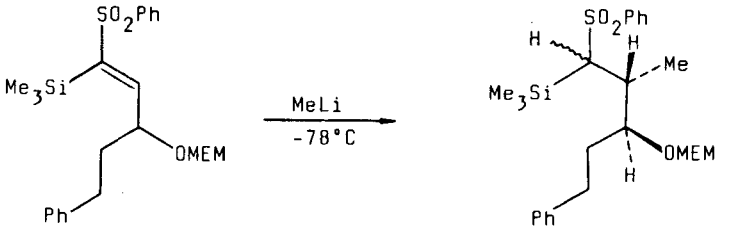
Table 6. Preparation of compounds **278** and **279**

No	R^1	R^2	R^3	Yield [%]	**278/279** ratio
a	H	Me	H	74	73:27
b	Et	Me	H	82	87:13
c	*i*-Pr	Me	H	74	79:21
d	*c*-$C_6H_{11}CH_2$	Me	H	72	100:0
e	*n*-C_8H_{17}	H	H	79	87:13
f	*n*-C_8H_{17}	Me	H	80	88:12
g	*n*-C_8H_{17}	Me	Me	76	90:10
h	*n*-$C_{12}H_{25}$	Me	H	81	90:10
i	Ph	H	H	69	100:0
j	Ph	Me	H	75	100:0
k	Ph	Me	Me	66	100:0

4.2. Nucleophilic addition to α,β-unsaturated sulfones

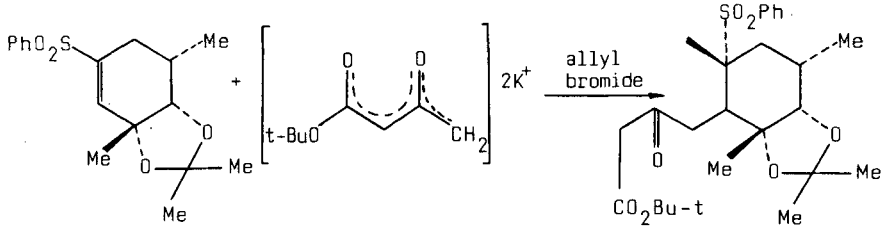
Heteroconjugate addition of methyllithium to **280** was found to give the diastereoisomeric product **281** resulting only from the one-sided attack of the methyl anion on the olefinic β-carbon atom.[112]



MEM = $CH_2O(CH_2)_2OMe$

280 **281**

Conjugate addition of the dipotassium β-keto ester **282** to the vinyl sulfone **283**, followed by *in situ* quenching with allyl bromide, gave the chiral β-keto ester **284**.[113]



283 **282** **284**

A fully stereoselective alkylation of the sulfone-stabilized carbanion formed by conjugate addition of the optically active vinyllithium reagent **285** to the chiral sulfone **286** gave the chiral prostaglandin precursor **287** in 67% yield.[114]

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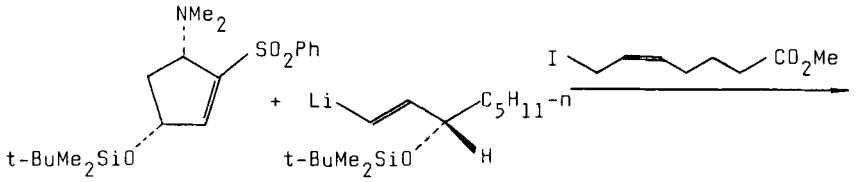
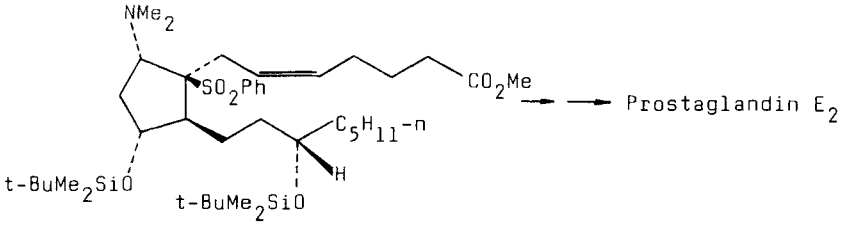
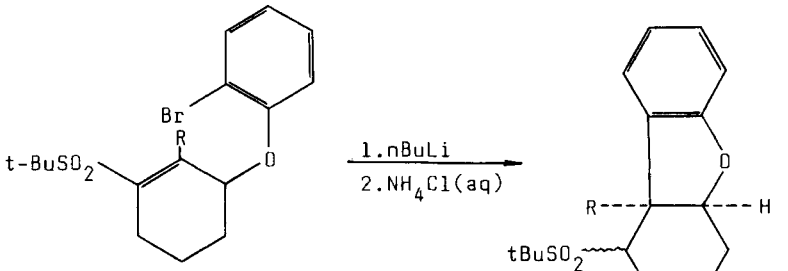


286 285



287

When a series of appropriately brominated vinyl sulfones **288** were subjected to metalation with *n*-butyllithium in THF at −78 °C, an intramolecular Michael addition efficiently produced the tricyclic adducts **289** as a diastereoisomeric mixture at the carbon α to the sulfonyl group.[115]



288 289

a	R = H	a	(99%)
b	R = Ph	b	(83%)
c	R = CH = CH_2	c	(62%)

Reaction of the γ-bromo sulfone **290** with the Grignard reagents **291** gave in each case a single stereoisomer of the 2-substituted cyclopropyl phenyl sulfone **292** in good to excellent isolated yields (Scheme 58).[116]

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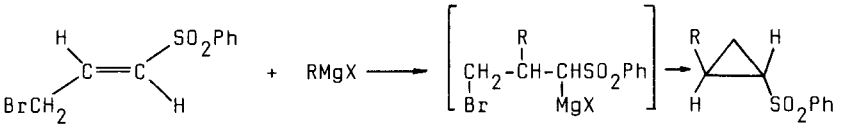


290 291 292

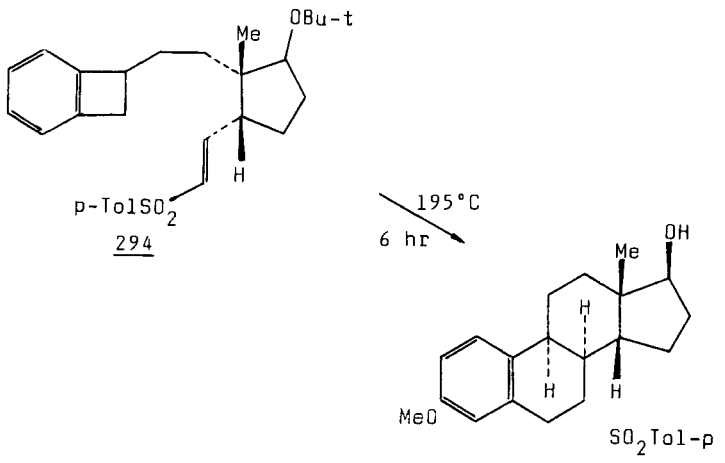
a	$CH_2 = CH - CH_2$	**a**	(76%)
b	$HC = CCH_2$	**b**	(50%)
c	$CH_2 = CH - CMe_2 -$	**c**	(55%)
d	Ph	**d**	(40%)
e	$PhCH_2$	**e**	(54%)

Scheme 58.

4.3. Cycloadditions to unsaturated sulfones

4.3.1. [4+2]-Cycloadditions with dienes The first cycloadditions of α,β-unsaturated sulfones were reported as early as 1938.[117] Since that time a variety of α,β-unsaturated sulfones and sulfonates have been prepared and used as dienphiles. Selected examples of such cycloaddition reactions are collected in Table 7.

An efficient construction of the steroidal skeleton **293** is based on an intramolecular Diels-Alder reaction of the α,β-unsaturated sulfone **294**.[122]



294 293

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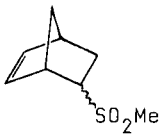
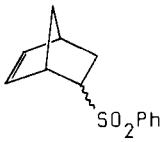
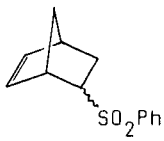
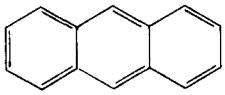
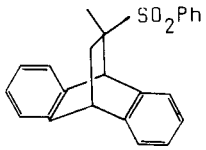
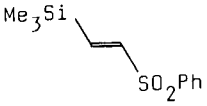
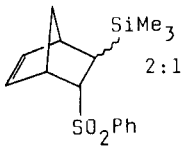
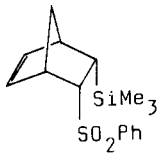
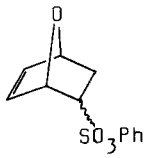
Table 7. Cycloaddition of α, β-unsaturated sulfones and sulfonates to dienes

Dienophile	Diene	Conditions	Product	exo endo ratio	Ref.
$MeSO_2$-CH=CH_2		r.t. 4 days		28:72	118
$PhSO_2$-CH=CH_2		r.t. 40 hr		22:78	119
$PhSO_2$-CH=CH_2		125°C 17 hr		19:81	119
$PhSO_2$-CH=CH_2		155°C 100 hr			119
		r.t. 3 days		2:1	119
		r.t. 2.5 weeks			119
$PhOSO_2$-CH=CH_2		r.t. 20 days		1:2.6	120

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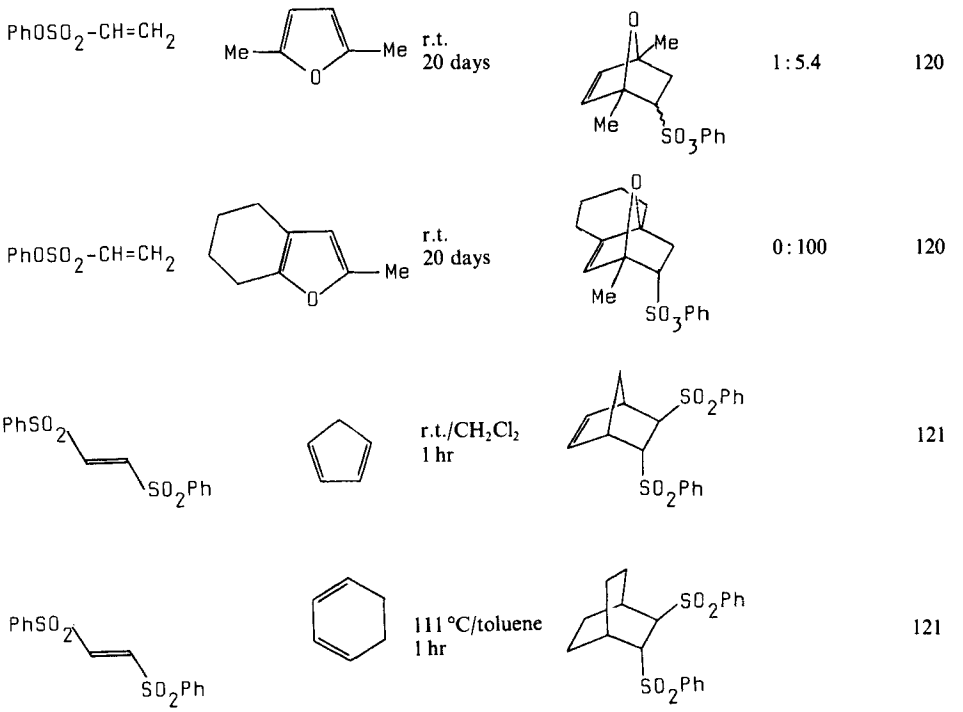
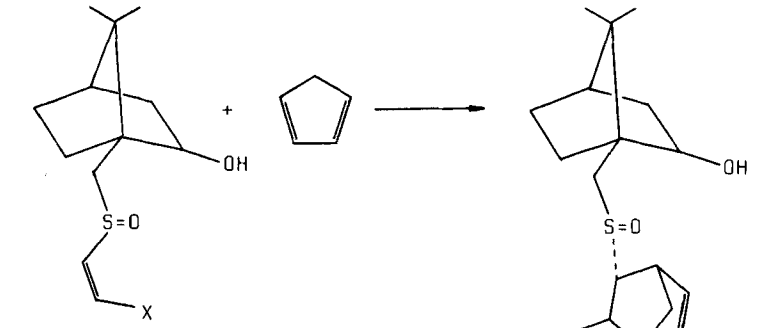


Reaction of the chiral dienophiles **295** with cyclopentadiene was found to give predominantly the endo adducts **296** in a diastereoisomeric ratio higher than 90 : 10.[123]



A high endo selectivity was observed in the Diels-Alder cycloaddition of phenylsulfonylallene **297a** with cyclopentadiene.[124]

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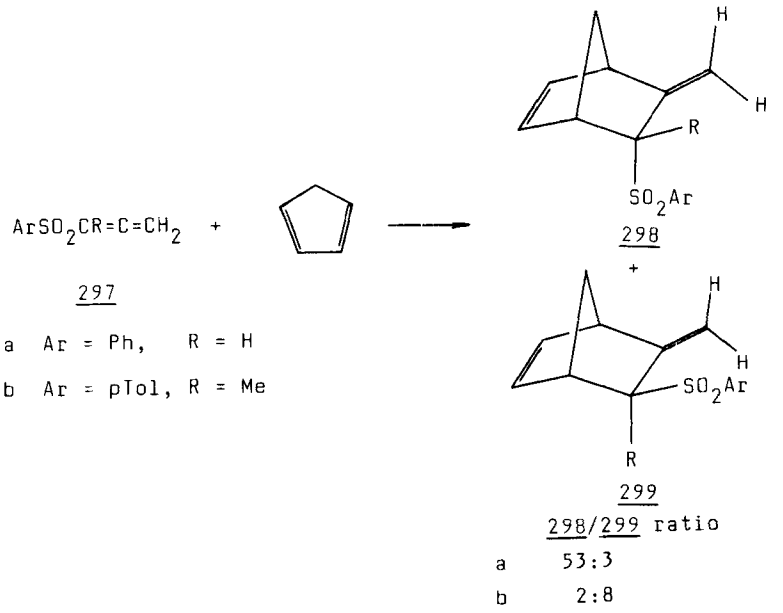
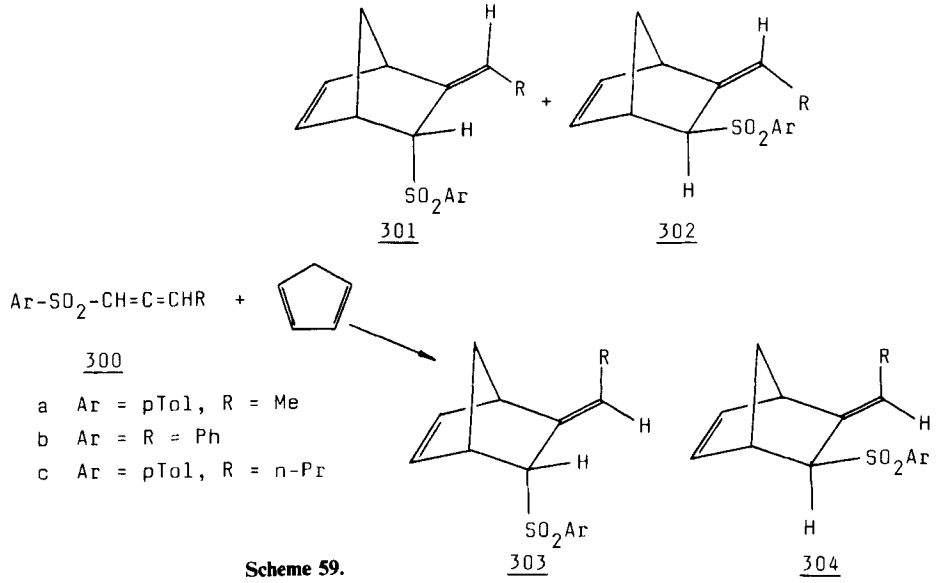
On the other hand, the allene **297b** gave *endo*-**298b** and the *exo*-adducts **299b** in a ratio of 2 : 8.[125]



A chirality transfer from the allenic moiety to the Diels-Alder adduct was observed in the reaction of the chiral sulfonylallenes **300** with cyclopentadiene. This reaction should in principle produce four diastereoisomeric adducts (Scheme 59).[125]



Scheme 59.

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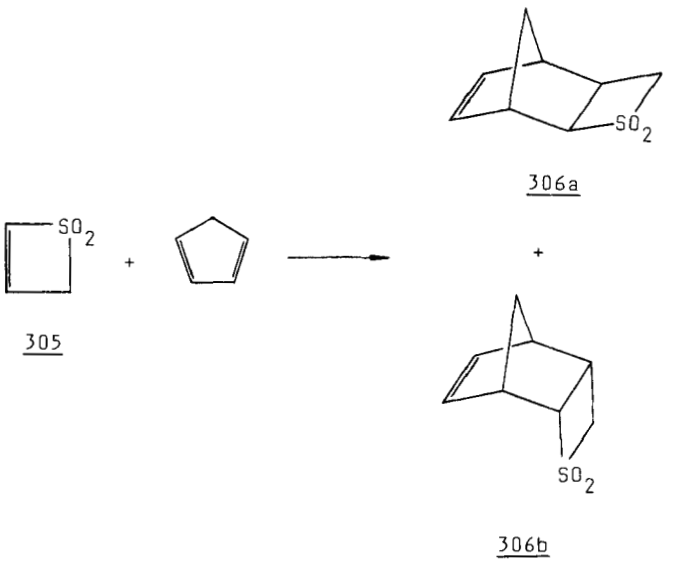
This was the case with 1-(*p*-toluenesulfonyl)-buta-1,2-diene **300a** and 3-phenyl-1-(phenylsulfonyl)propadiene **300b**, whereas from 1-(*p*-toluenesulfonyl)-hexa-1,2-diene **300c** only three isomers were formed. At any rate, the process was found to be highly stereoselective: e.g., when **300a–c** were used as substrates, the predominant diastereoisomers **301** and **302** constituted 94, 80, and 96% of the reaction products, respectively. Reaction of optically active (+)-(S)-**300c** with cyclopentadiene afforded the optically active adducts **301–304**. The predominant diastereoisomers **301** $[\alpha]_D = +35.9$ ($CDCl_3$) and **302** $[\alpha]_D = +25.6$ ($CHCl_3$) were isolated by column chromatography.[125]

The cycloaddition of thietene dioxide **305** to cyclopentadiene gave 3-thiatricyclo[4.2.1.$0^{2,5}$]non-7-ene 3,3-dioxide **306a,b** as a 1:4 exo-endo isomeric mixture.[126]



4.3.2. Cycloadditions of β,γ-unsaturated sulfones to olefins One of the most efficient methods for the synthesis of functionalized methylenecyclopentane systems such as **307** is the palladium catalyzed [3+2]-cycloaddition of allyl acetates **308** to the electron-deficient olefins **309**. This reaction has been proposed to proceed via the trimethylenemethane-palladium complex **310**.[127]

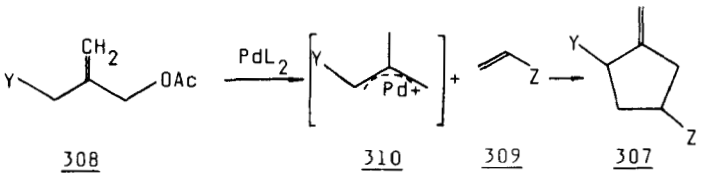


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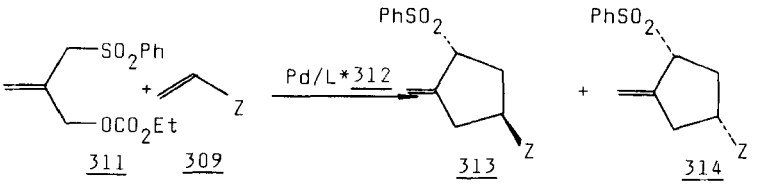
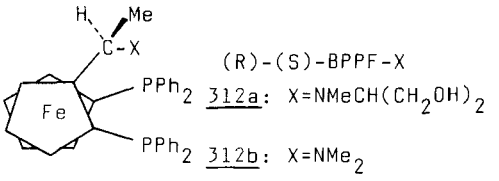
Table 8. Asymmetric [3+2]-cycloaddition of 2-(sulfonylmethyl)-2-propenoates **311** catalyzed by the palladium complex **312**[a]

			% ee (configuration)	
311	**309**	**313/314** ratio	**313**	**314**
a	**a**	82/18	73 (1R,3S)	58 (1R,3R)
b	**a**	77/23	66 (1R,3S)	64 (1R,3R)
c	**a**	73/27	46 (1R,3S)	21 (1R,3S)
d	**a**	78/22	19 (1R,3S)	4 (1R,3R)
a	**b**	66/34	75 (1R,3S)	78 (1R,3R)
b	**b**	72/28	54 (1R,3S)	61 (1R,3R)

[a] Taken from reference 115.

Recently, this approach has been applied in the first asymmetric synthesis of optically active methylenecyclopentanes functionalized at the α-carbon with a sulfonyl substituent. It was found that the reaction of ethyl 2-(benzenesulfonylmethyl)-2-propenoate **311** with methyl acrylate **309** or methyl vinyl ketone **309b** in the presence of the chiral ferrocenylphosphine-palladium catalyst **312** gave the optically active methylenecyclopentane derivatives **313** and **314** with an optical purity of up to 78%.[128]





(S,S) chiraphos: 312c

5. FORMATION OF CHIRAL CARBON α TO SULFUR SUBSTITUENTS STARTING FROM LESS COMMON ORGANOSULFUR SUBSTRATES

α-Sulfinylmethyl sulfoximines, like simple sulfoxides and α-sulfonylmethyl sulfoxides, undergo facile alkylation. The reaction of diastereoisomerically pure *p*-tolylsulfinyl-

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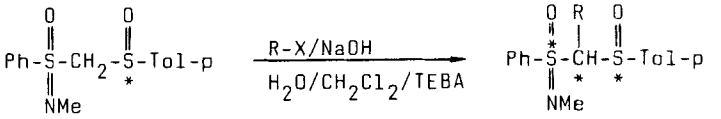
Table 9. Alkylation of (+)-(S,S)-**315** and (−)-(S,R)-**315** with alkyl halides under phase transfer conditions

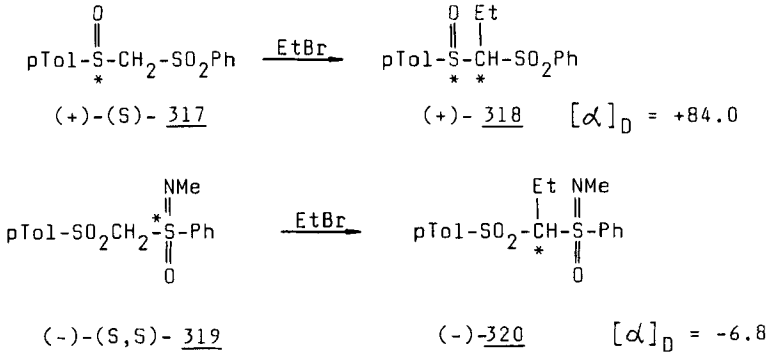
Substrate **315**	Alkyl halide	Yield of alkylated product [%]	$[\alpha]_D$	Diastereoisomeric ratio
(+)-(S,S)	CH_2=CH-CH_2Br	93	+97.7	100:0
(−)-(S,R)	CH_2=CH-CH_2Br	87	−49.0	83:17
(+)-(S,S)	$PhCh_2Br$	77	+86.3	100:0
(−)-(S,R)	$PhCH_2Br$	79	−34.4	80:20
(+)-(S,S)	H_2C=CH-CH_2Br	91	+80.0	100:0
(−)-(S,R)	H_2C=CH-CH_2Br	73	−28.5	100:0
(+)-(S,S)	EtBr	80	+103.0	100:0
(−)-(S,R)	EtBr	82	−18.2	80:20
(+)-(S,S)	EtI	70	+103.0	100:0
(+)-(S,S)	*n*-BuBr	30	+84.6	100:0

methyl phenyl sulfoximine **315** with two chiral moieties, both able to induce optical activity at the α-carbon atom, with alkyl halides was performed under phase-transfer conditions and resulted in a high asymmetric induction on the α-carbon atom (Table 9).[129]



315 316

It is interesting to note that the ethylation of the optically active α-sulfinyl sulfone (+)-(S)-**317** afforded a mixture of two diastereoisomers **318**, $[\alpha]_D = +84.0$ in a 95:5 ratio while the ethylation of (−)-(S)-**319** gave a mixture of the two diastereoisomers **320** in a 1:1 ratio. These results seem to indicate that in the case of the *S*-(sulfinylmethyl) sulfoximines the sulfinyl group exerts the stronger effect in asymmetric induction.[129]



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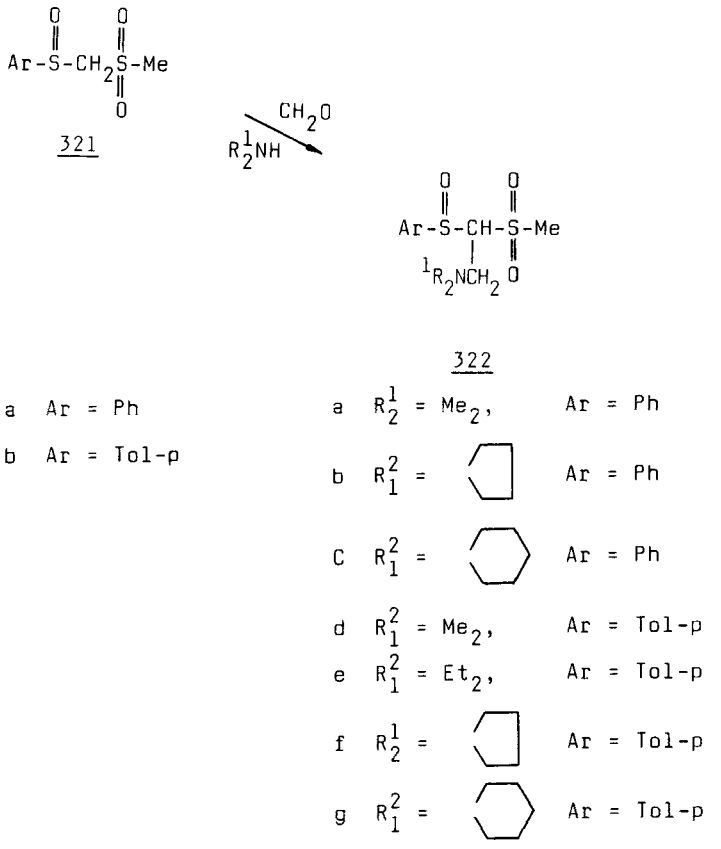
Alkylation of racemic sulfinylmethyl sulfones with sodium hydride or butyllithium as a base has also been reported to give, after crystallization, a 3:2 mixture of diastereoisomers.[130]

The Mannich-type condensation of the racemic sulfinyl sulfone **321** has also been found to afford a 3:2 mixture of the diastereoisomeric amino sulfones **322**[130] (Scheme 60).



Scheme 60.

The Diels-Alder reaction of the optically active sulfoximine **323a** with cyclopentadiene produced a mixture of the four cycloadducts **324a–327a** in 95% yield. The ratio of the products **324a**:(**325a** + **326a**):**327a** was approximately 1:4:4. The analogous reaction with the sulfoximine **323b** gave the cycloadducts **324b–327b** in a ratio of 1:1:4:5. Reaction of the vinyl sulfoximine **323a** with cyclohexadiene afforded the cycloadducts **324c–327c** in which the first two (exo isomers) constitute less than 5% of the mixture; the ratio **326c**:**327c** was 4:5 (Scheme 61).[131]

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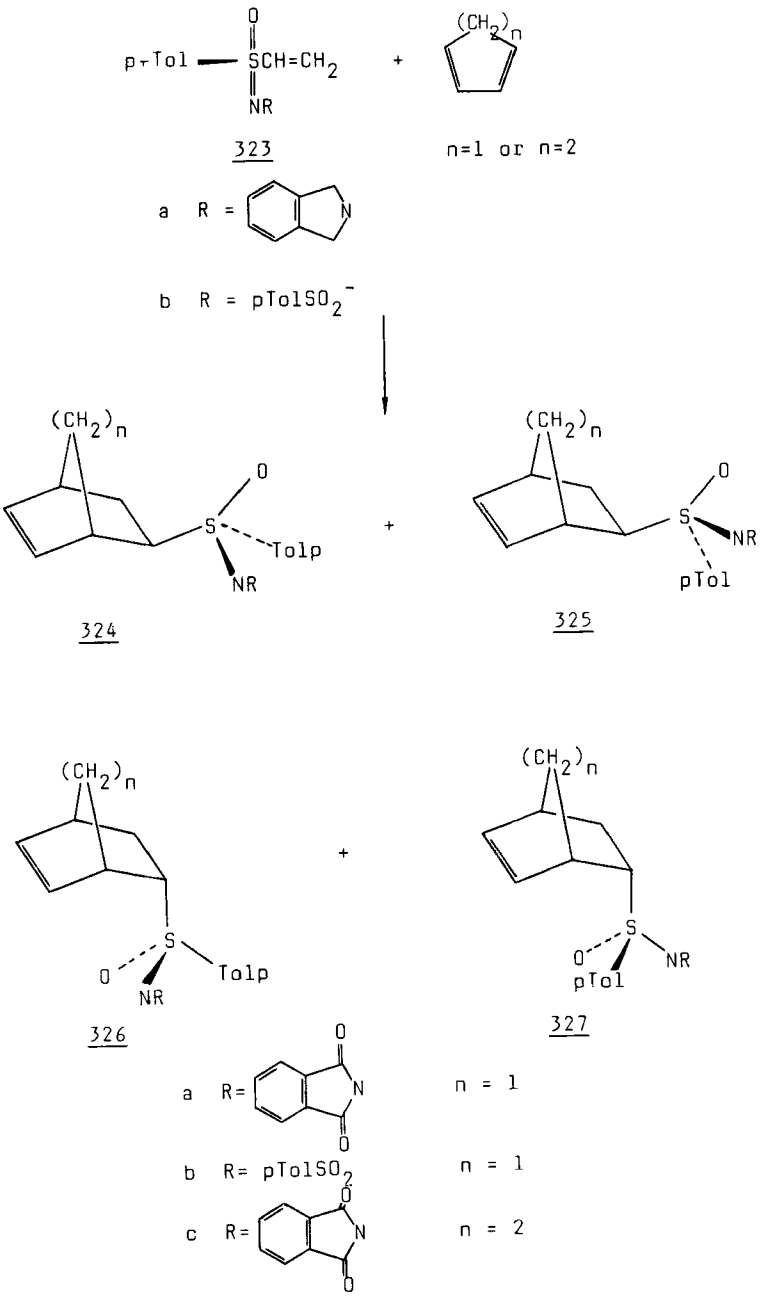

Scheme 61.

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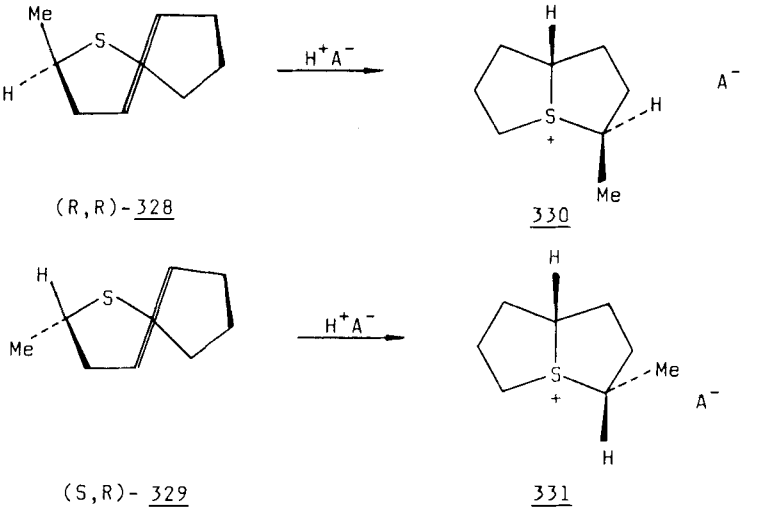
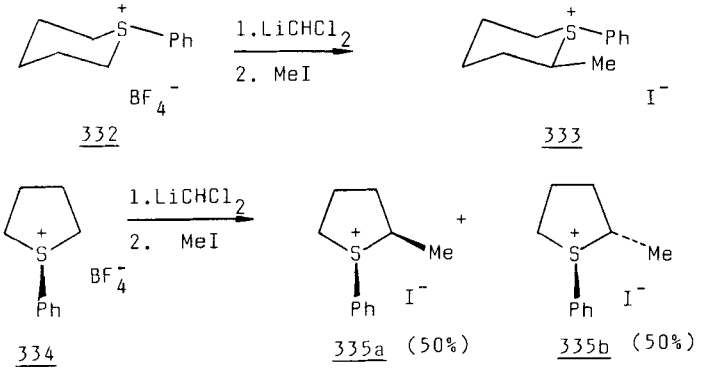
A fully stereoselective transannular cyclization of the (*E*)-thiacyclooct-4-enes **328** and **329** by acid was found to give the *exo*- and *endo*-2-methyl-*cis*-1-thianiobicyclo[3.3.0]-octane salts **330** and **331**, respectively.[132]



The methylation of the sulfonium ylide derived from the six-membered sulfonium salt **332** was found to be highly stereoselective. On the other hand, no appreciable stereoselectivity was observed with the five-membered analog **334**.[133]



Alkylation of a 1 : 1 mixture of the ylides **336** and **337** with methyl iodide at −72 °C gave the corresponding methylation products **338** and **339** in nearly equal amounts. When this mixture was heated at 110 °C in chloroform the amount of the isomer **339** increased, while that of the isomer **338** decreased. The pure isomer **339** (X = picrate) was isolated by recrystallization of the picrates. When the ylide mixture was equilibrated at −23 °C for 2 h and then methylated at −72 °C, the alkylation product consisted of isomer **338** and a new isomer **340** in a ratio of 23 : 2. Thermal equilibration of this mixture afforded a 3 : 2 mixture of the isomers **339** and **340** (Scheme 62).[134]

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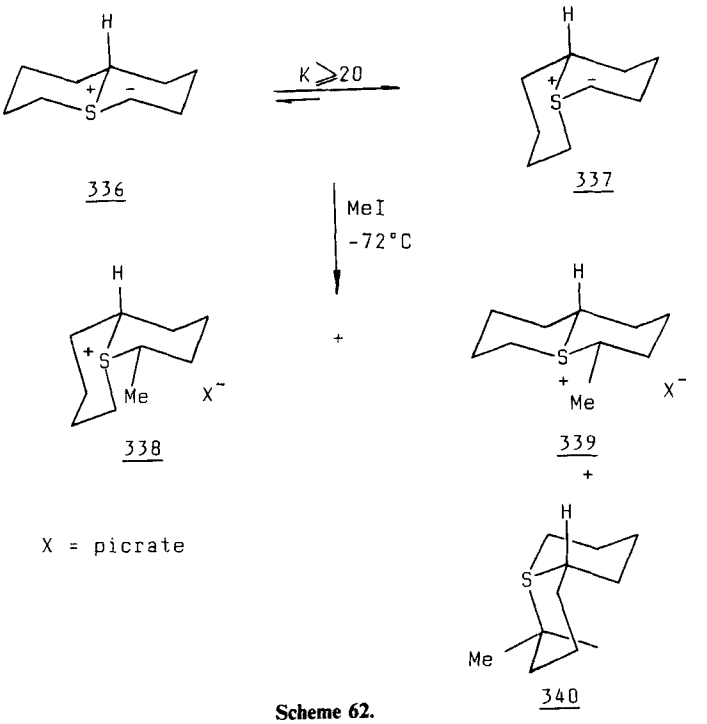
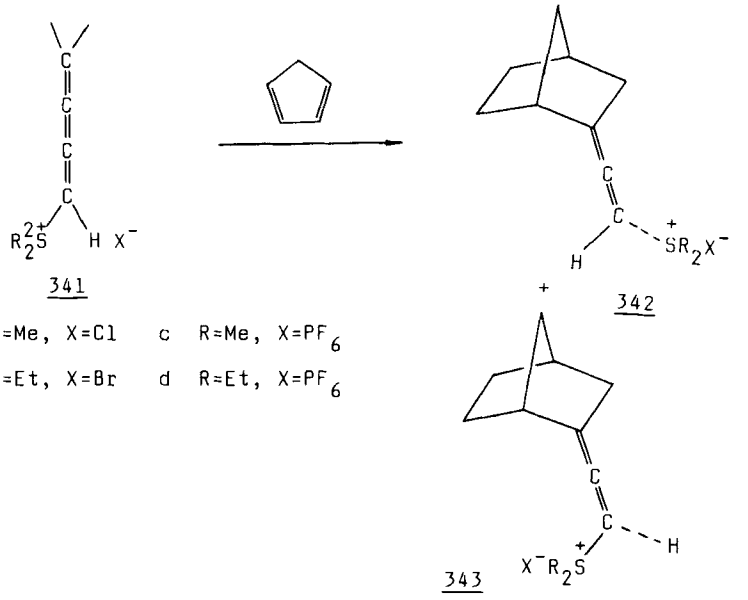


336 337 338 339 340

Scheme 62.

[4+2]-Cycloaddition of cyclopentadiene and the butatrienylsulfonium salts **341** afforded a mixture of the crystaline salts **307** and **308** in a ratio of 1 : 1.[135]



341 342 343

a R=Me, X=Cl c R=Me, X=PF_6

b R=Et, X=Br d R=Et, X=PF_6

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