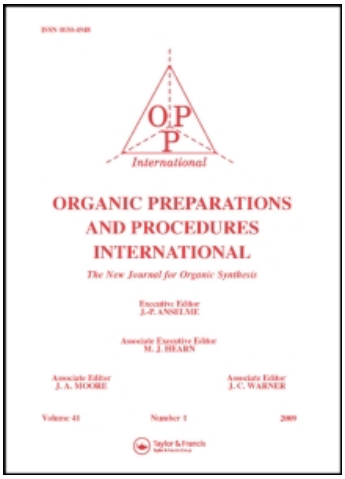

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NEW DEVELOPMENTS IN THE USE OF ENANTIOMERICALLY ENRICHED SULFOXIDES IN STEREOSELECTIVE SYNTHESES

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INTRODUCTION

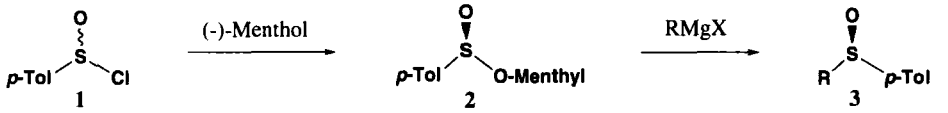
The use of chiral auxiliaries in enantioselective synthesis continues to be an important subject of research. The use of chiral, non-racemic sulfinyl auxiliaries in enantioselective synthesis has become increasingly more popular due to the recent advances and developments in the preparation of enantiomerically enriched sulfoxides. The stable pyramidal structure of a chiral sulfoxide allows for a diastereoselective reaction to occur at a nearby or distant reaction center. Complexation of the sulfoxide group with a suitable metal ion forms a rigid diastereomeric intermediate which can undergo subsequent reactions stereoselectively. Another key feature of the sulfoxide group is its electron-withdrawing nature which can stabilize an α-carbanion or activate an α,β-unsaturated bond for various stereoselective addition reactions.

This review focuses on the methodologies involving chiral, non-racemic sulfoxides that have been developed for asymmetric synthesis since 1991. Representative examples of these methodologies for the asymmetric syntheses of natural products or biologically important molecules are also provided. More detailed discussions of the application of enantiomerically enriched sulfoxides for the stereoselective synthesis of specific classes of molecules have been covered in other reviews.[1]

I. SYNTHESIS OF ENANTIOMERICALLY ENRICHED SULFOXIDES

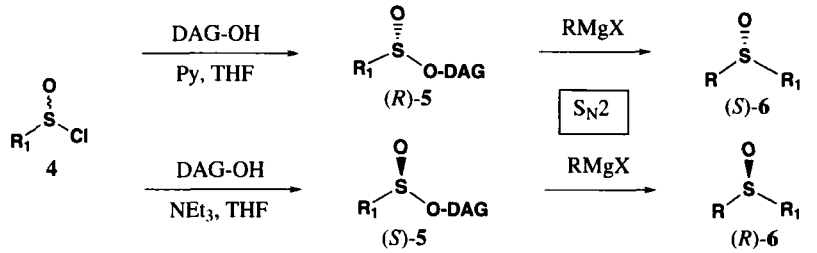
Synthetic methods for the preparation of enantiomerically enriched sulfoxides can be divided into the following categories: Anderson synthesis, asymmetric oxidation, and asymmetric biological oxidation. The Anderson procedure is the most important and generally used method for the synthesis of enantiomerically enriched sulfoxides. In this method, a sulfinyl chloride **1** is converted to the corresponding ester by reacting with a chiral alcohol such as (-)-menthol[2] (classical Anderson synthesis), DAG-OH[3] (diacetone D-glucose), or *trans*-2-phenylcyclohexanol.[4] In the classical Anderson synthesis (*Scheme 1*), the commercially available (*S*)-menthyl *p*-toluenesulfinate (**2**) is

treated with an appropriate organometallic reagent to give the (*R*)-sulfoxide **3** with complete inversion of configuration.



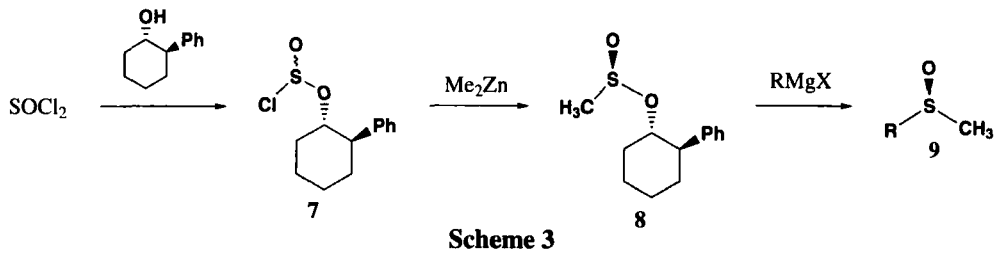
Scheme 1

Another commonly used alcohol for preparing enantiomerically enriched sulfinyl esters is DAG-OH. DAG-OH reacts with alkyl or aryl sulfinyl chlorides **4** in the presence of a base to give the corresponding sulfinyl esters **5** with excellent diastereoselectivities (*Scheme 2*). In the presence of pyridine, the (*R*)-isomer of **5** is formed in 90-92% diastereomeric excess (*de*) and 50-90% yield, while in the presence of triethylamine or *i*-Pr_2NEt the (*S*)-isomer is generated in 70-90% *de* and 55-90% yield. The subsequent nucleophilic substitution reaction of the chiral sulfinyl ester **5** with an appropriate Grignard reagent affords the chiral sulfoxide **6** with inversion of configuration.



Scheme 2

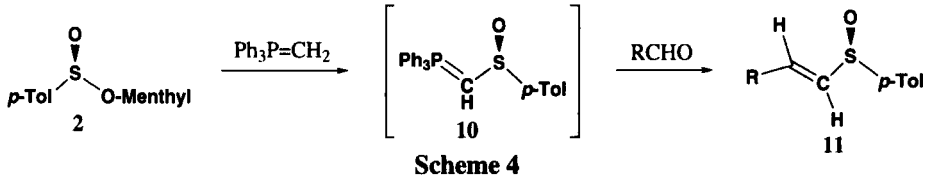
Another methodology for the preparation of enantiomerically enriched sulfoxides uses *trans*-2-phenylcyclohexanol for the formation of chlorosulfite ester **7** as a mixture of sulfur epimers (*Scheme 3*). The substitution reaction of **7** with dimethyl zinc gives **8** in very high yield and diastereoselectivity at –78°. The highly stereoselective formation of **8** can be attributed to the difference in the reaction rates of dimethyl zinc with the diastereomers of **7** and the equilibration of the diastereomers of **7** under the reaction conditions. Treatment of the sulfinyl ester **8** with a Grignard reagent affords the desired enantiomerically enriched sulfoxide **9**.



Scheme 3

In addition to the classical Anderson synthesis, enantiomerically enriched α,β-unsaturated sulfoxides can also be prepared in one pot *via* Wittig reactions of α-sulfinyl phosphonium ylides,[5]

prepared *in situ* from menthyl tolunesulfinate **2**. Mikolajczyk *et al.* reported a highly stereoselective synthesis of (*S*)-sulfinyl phosphonium ylides which subsequently react with aldehydes to give enantiomerically enriched vinyl and dienyl sulfoxides with very high *E*-stereoselectivity (*Scheme 4*).[6] The



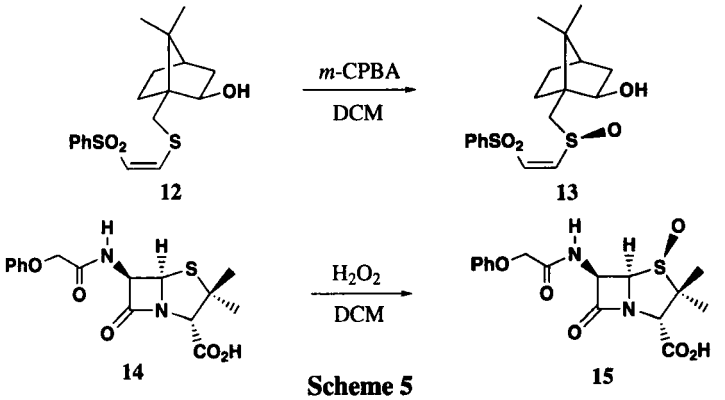
Scheme 4

enantiomerically enriched ylide **10** was prepared by reacting (*S*)-menthyl *p*-tolylsulfinate **2** with methyltriphenylphosphonium ylide. Reaction of **10** with benzaldehyde gave the (*E*)-phenyl vinyl sulfoxide of **11** (R = Ph) in 87% yield (*Table 1*); other aldehydes also afforded the (*E*)-isomers of **11**.

Table 1. Wittig Reactions of α-Sulfinyl Phosphonium Ylides **10**

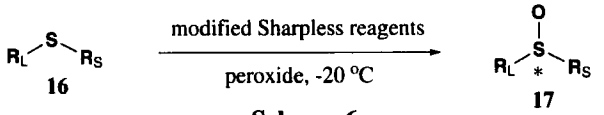
R	Yield (%)	*ee* (%)
Ph	87	100
p-MeOPh	82	96
(*E*)-MeCH=CH	61	100
H	40	94
CH2=CH	20	100

A sulfide may be oxidized to the corresponding sulfoxide in good enantiomeric excess (*ee*) *via* either diastereoselective or enantioselective oxidation. Diastereoselective oxidation often involves steric hindrance in the vicinity of the sulfur atom and/or participation of neighboring groups in the oxidation process (*Scheme 5*). In the oxidation of **12**, hydrogen bonding between *m*-CPBA and the hydroxy group directs the oxygen to transfer from the top face, leading to the formation of sulfoxide **13**.[7] The neighboring group effect is also seen in the oxidation of constrained ring systems such as **14** where an amide group directs the transfer of oxygen to afford the sulfoxide **15**.[8]



Scheme 5

Modified Sharpless reagents[9] and enantiomerically enriched oxaziridines[10] are frequently used for the enantioselective oxidation of a prochiral sulfide to the corresponding enantiomerically enriched sulfoxide. The Sharpless method is less costly than the oxaziridine method; however, oxaziridines are more general in scope. Recently the use of chiral transition metal (Ti, V, Mn, Fe, Ru) complexes with achiral oxidants has attracted much attention for the enantioselective oxidation of sulfides.[11] Kagan[9a] and Modena[9b] were first to report the use of a modified Sharpless procedure (*Scheme 6*) for enantioselective sulfide oxidation (*Table 2*). These modified methods give good to



16 17

Scheme 6

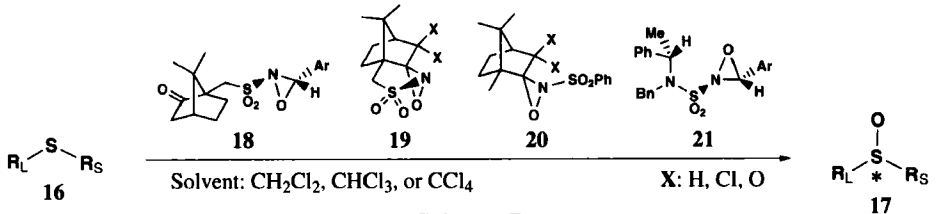
excellent enantioselectivities with aryl methyl sulfides **16** (R_L = Ar, R_S = Me). Uemura *et al.* further improved Kagan's procedure by using 2.0 equiv. of (+)-binaphthol instead of (+)-DET; chiral sulfoxides with (*R*) configurations in up to 96% *ee* were afforded.[12]

Table 2. Comparison of Enantioselective Oxidation of Sulfide to Sulfoxide **17**

Conditions	Peroxide*	Yield (%)	*ee* (%)
Kagan's	TBHP	60-90	20-90
Kagan's	CHP	60-90	> 95
Modena's	TBHP	60-90	30-90

Kagan's procedure: Ti(O*i-Pr*)$_4$: (+)-DET* : H_2O : TBHP = 1 : 2 : 1 : 1
Modena's procedure: Ti(O*i*-Pr)$_4$: (+)-DET : TBHP = 1 : 4 : 2
*TBHP: tert-butyl hydroperoxide, CHP: cumyl hydroperoxide; DET: diethyl tartrate

Enantiomerically enriched *N*-sulfonyloxaziridines **18-20** and *N*-sulfamyloxaziridine **21** are stoichiometric enantiomerically enriched oxidants (*Scheme 7*). They offer comparable enantioselectivities in the oxidation of aryl methyl sulfides to those of the modified Sharpless reagents, however, some oxaziridines are more efficient and enantioselective for the oxidation of *t*-butyl methyl, *t*-butyl benzyl, alkyl aryl, and other functionalized sulfides than modified Sharpless reagents. The outcome of using enantiomerically enriched oxaziridines for enantioselective sulfide oxidation largely depends on the difference in the size and nature of groups attached to sulfur; oxidation of sulfides with substituents of similar sizes and stereoelectronic nature is less enantioselective.



16 18 19 20 21 17

Scheme 7

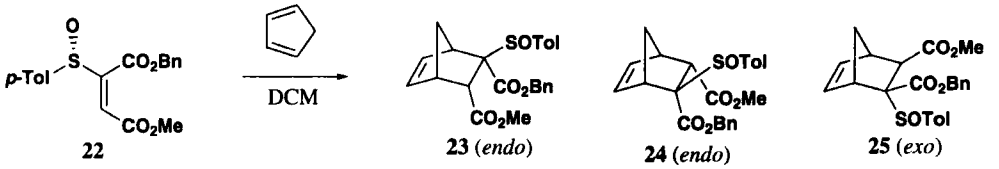
Asymmetric biological oxidation includes microbiological and enzymatic oxidations. Microbiological oxidation of sulfides has been employed in the enantioselective formation of chiral sulfoxides by using fungi such as *Helminthosporum*,[13] *Mortierella isabellina*,[14] *Corynebacterium equi*,[15] *Rhodococcus equi*,[16] *Saccharomyces cerevisiae*,[17] and *Pseudomonuas putida*.[18] Enzymatic oxidation involving monooxygenases and peroxidases has also been used to prepare enantiomerically enriched sulfoxides. Cyclohexanone monooxygenase effectively oxidizes 1,3-dithioacetals to the corresponding (*R*)-sulfoxides in 80-95% yield and > 98% *ee*.[19] Chloroperoxidase[20] and horseradish peroxidase[21] have been employed in the enantioselective oxidation where reduction of the substrate concentration is necessary to minimize the non-selective, spontaneous oxidation of sulfides.

II. CYCLOADDITION REACTIONS

1. Diels-Alder Reactions

Diels-Alder reactions of enantiomerically enriched sulfinyl dienes and dienophiles are highly stereoselective and efficient for the asymmetric construction of cyclic or bicyclic skeletons. Enantiomerically enriched α,β-unsaturated sulfoxides bearing one or more electron-withdrawing substituents are commonly used as dienophiles.[22] Enantiomerically enriched sulfinyl 1,3-butadienes are frequently used to react with a variety of dienophiles that undergo Diels-Alder cycloaddition.[23] The use of a Lewis acid to restrict the rotation around the C-S bond has been used to improve stereoselectivities.

Carretero *et al.* have reported the preparation of an enantiomerically enriched sulfinyl dienophile, 1-benzyl 4-methyl (*S*)-2-*p*-tolylsulfinyl maleate **22**, *via* the Anderson synthesis and Knoevenagel condensation.[24] This sulfinyl dienophile undergoes [4+2] cycloaddition reactions with cyclic and acyclic dienes in high yields and with excellent stereoselectivities. For example, the sulfinyl maleate **22** reacted with 6 equiv. of cyclopentadiene to afford the *endo*-isomers **23** and **24** and *exo*-isomer **25** in 84-100% yields (*Scheme 8* and *Table 3*). Without a Lewis acid the cycloaddition



22 **23** (*endo*) **24** (*endo*) **25** (*exo*)

Scheme 8

took place at room temperature to give the *endo*-isomer **23** as the major product (73%). In the presence of $Eu(fod)_3$ the cycloaddition afforded the *endo*-isomer **23** with higher π-facial selectivity but lower *endo* selectivity. In the presence of $TiCl_4$, the *endo*-isomer **23** was formed with the highest *endo* selectivity but with facial selectivity similar to that observed without a Lewis acid. The $ZnBr_2$-catalyzed cycloaddition reaction of **22** took place with inversion of facial selectivity to favor the formation of *endo*-isomer **24** with good facial and *endo* selectivities.

Table 3. Stereoselective Cycloaddition Reaction of Sulfinyl Dienophile **22**

Lewis Acid	Temp (°C)	Yield (%)	**23** (%)	**24** (%)	**25** (%)
----	RT	93	73	8	19
$Eu(fod)_3$	-20	100	66	3	31
$TiCl_4$	-78	84	83	13	4
$ZnBr_2$	-20	95	7	88	5

The opposite facial selectivities obtained with $TiCl_4$ and $ZnBr_2$ have been rationalized (*Figure 1*). In the presence of either Lewis acid, the metal forms a tight complex with the sulfinyl and carbonyl oxygens. In the $TiCl_4$-dienophile complex (model **A**), the C_α-*si* face is more accessible to the approaching diene, leading to the formation of the *endo*-isomer **23**. On the other hand in the $ZnBr_2$-dienophile complex (model **B**), the C_α-*re* face is more accessible, thus favoring the formation of the *endo*-isomer **24**.

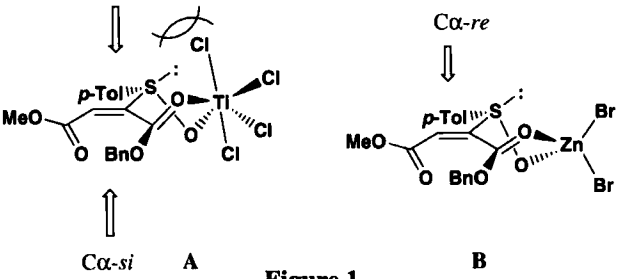


Figure 1

Other enantiomerically enriched sulfinyl dienophiles have also been used in stereoselective Diels-Alder reactions (*Figure 2*).[25] Sulfinyl furanone **26**,[25a] α-(bornyl)sulfinyl maleate **27**,[22g] and

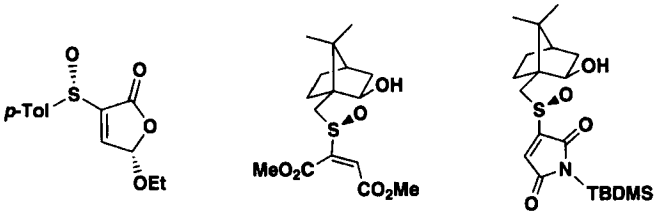
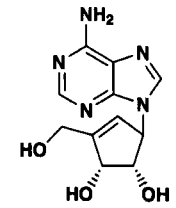
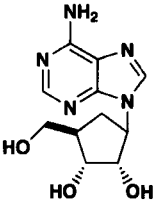
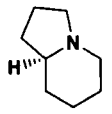


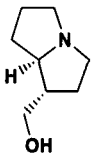
Figure 2

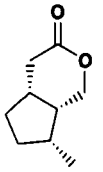
α-(bornyl)sulfinyl maleimide **28**[25c,d] all afforded cycloaddition products in greater than 99% *de*. These enantiomerically enriched sulfinyl dienophiles have been applied to the total synthesis of a number of natural products (*Figure 3*).


(-)-Neplanocin A[22c]


(-)-Aristeromycin[22c]


(+)-δ-Coniceine[26a]


(+)-Laburnine[26a]


(-)-Boschnialactone[26b]

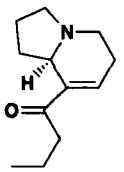
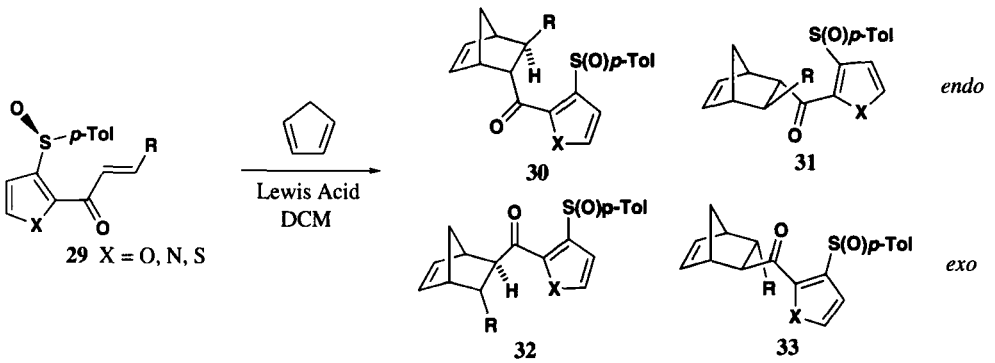

(+)-Elaeokanine A[25c]

Figure 3

Arai *et al.* synthesized a series of enantiomerically enriched α,β-unsaturated enones substituted with sulfinyl heterocycles **29** (furans,[27a,b] thiophenes[27b] and pyrroles[27a,c]). With the proper Lewis acid, the [4+2] cycloaddition reactions of these dienophiles with cyclopentadiene took place with good to high *endo* selectivities and diastereoselectivities (*Scheme 9*).[27b] However, without a Lewis



Scheme 9

acid the reaction of the sulfinyl furan **29** (X = O, R = Ph) afforded **30-33** in only 13% yield with no diastereoselectivity (*Table 4*). In the presence of $AlCl_3$, $Yb(OTf)_3$, or $Sm(OTf)_3$, **29** (X = O, R = Ph) gave products in quantitative yields and with good to high diastereoselectivities. Altering the R group from phenyl to methyl gave no improvement in the yield or selectivity of the reaction.

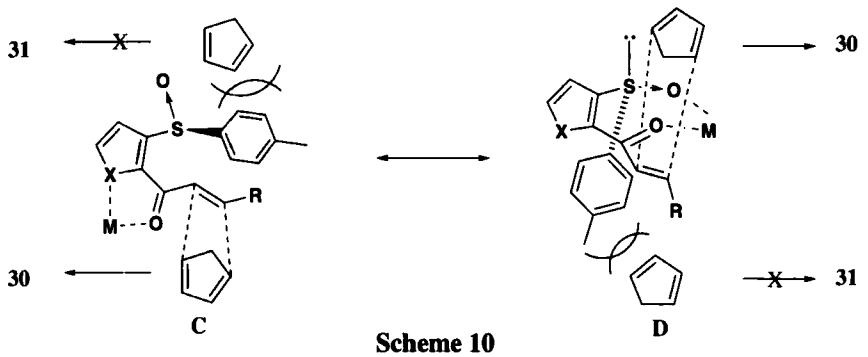
Table 4. Stereoselective Cycloaddition Reactions of Sulfinyl Furan **29** with Cyclopentadiene

X	R	Lewis Acid (eq)	Temp (°C), Time (h)	Yield (%)	***30: 31: 32: 33*** ***or 30: 31: (32+33)***	*de* (%) of *endo*	*endo* : *exo*
O	Ph	----	25, 20	13	37 : 37 : 13 : 13	0	74 : 26
O	Ph	$AlCl_3$, (1)	-20, 3	100	94 : 2 : 4 : 0	97	96 : 4
O	Ph	$Yb(OTf)_3$ (1)	25, 3	96	84 : 10 : 4 : 2	78	94 : 6

Table 4. Continued...

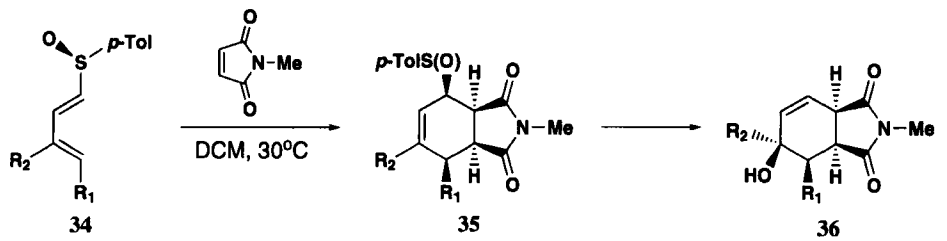
X	R	Lewis Acid (eq)	Temp (°C), Time (h)	Yield (%)	*30: 31: 32: 33* or *30: 31: (32+33)*	*de* (%) of *endo*	*endo* : *exo*
O	Ph	$Sm(OTf)_3$ (0.2)	25, 20	100	89 : 3 : 6 : 2	93	92 : 8
O	Me	$AlCl_3$ (1)	-20, 25	80	91 : 4 : 4 : 1	92	95 : 5
O	Me	$Yb(OTf)_3$ (0.2)	25, 20	94	87 : 4 : 7 : 2	91	91 : 9
S	Ph	$AlCl_3$ (1)	-20, 3	99	95 : 1 : (4)	98	96 : 4
S	Ph	$Sm(OTf)_3$ (0.2)	25, 22	99	89 : 2 : (9)	96	91 : 9

The diastereoselective formation of the *endo*-isomer **30** can be explained by chelated-reaction models **C** and **D** (*Scheme 10*). The metal can complex with the ring hetero-atom X and the carbonyl oxygen (model **C**) or with the sulfinyl and the carbonyl oxygens (model **D**). The cyclopentadiene reacts with the less hindered face of each intermediate avoiding steric interactions with the *p*-tolyl group and leads to the observed product **30**.



Scheme 10

Diels-Alder reactions of enantiomerically enriched sulfinyl dienes are less well documented in the literature presumably due to the synthetic difficulties in preparing such molecules. Nevertheless, these challenges have stimulated significant synthetic and mechanistic efforts toward the understanding and application of the cycloaddition of sulfinyl dienes in asymmetric synthesis. Carreno *et al.* reported the cycloaddition reactions of enantiomerically enriched sulfinyl diene **34** and *N*-methylmaleimide (NMM) (*Scheme 11*).[23a] Without a Lewis acid, the cycloaddition of **34** ($R_1 = CH_3$, $R_2 = H$)



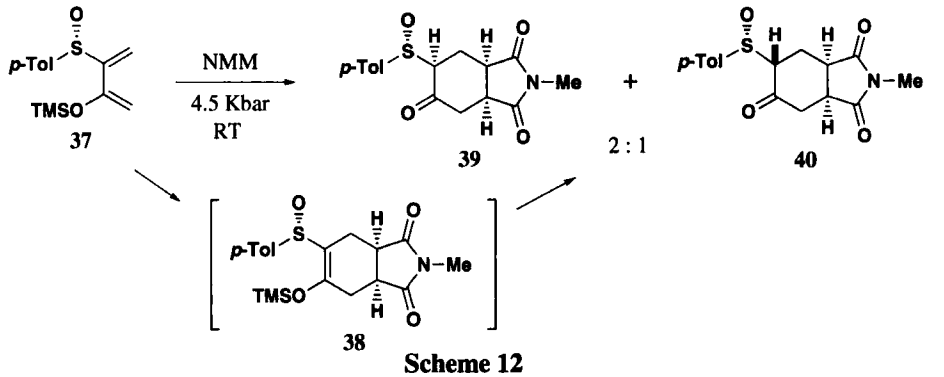
Scheme 11

with NMM after 34 days gave a 56 : 44 mixture of the corresponding *endo* product **35** and the cyclohexenol **36** in 66% yield (*Table 5*). The cyclohexenol **36** was a result of a [2,3] sigmatropic rearrangement of the cycloadduct **35**. The high diastereoselectivity observed can be explained by an endo transition state model in which the dienophile approaches the less hindered face of the diene in a s-*trans* configuration. In the presence of a Lewis acid, the reactions afforded **35** in 65-84% yield.

Table 5. Stereoselective Cycloaddition Reaction of Sulfinyl Butadienes **34** with *N*-Methylmaleimide

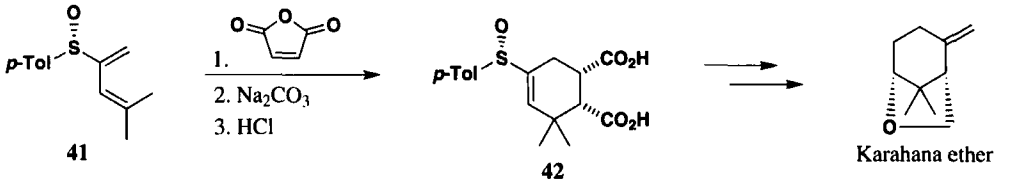
R_1	R_2	equiv. (NMM)	Lewis Acid	Temp (°C), T (days)	Yield (%)	**35 : 36**
Me	H	4	----	30, 34	66	56 : 44
Me	H	3	$ZnBr_2$	RT, 6	68	100 : 0
Me	H	3	$SnCl_4$	RT, 6	84	100 : 0
Ph	H	10	----	30, 40	72	0 : 100
Ph	H	3	$ZnBr_2$	RT, 18	65	100 : 0
Ph	H	3	$SnCl_4$	RT, 12	65	100 : 0
OEt	Me	5	----	RT, 27	66	0 : 100

Enantiomerically enriched 2-sulfinyl 1,3-butadienes undergo highly stereoselective Diels-Alder reactions to yield *endo* adducts. Cycloaddition of sulfinyl trimethylsilyloxy butadiene **37** with NMM afforded the *endo* cycloadduct intermediate **38** with high facial and diastereoselectivity (*Scheme 12*).[28] Spontaneous cleavage of the trimethylsilyl group during work-up gave a 2:1 mixture



Scheme 12

of diastereomers **39** and **40**. Maignan *et al.* used the stereoselective [4+2] cycloaddition of sulfinyl pentadiene **41** with maleic anhydride to prepare the intermediate **42** in the total synthesis of Karahana ether (*Scheme 13*).[23e]

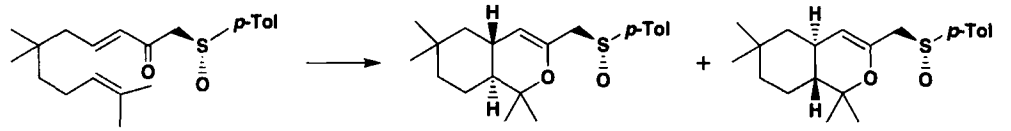


41 42

Scheme 13

2. Hetero Diels-Alder Reactions

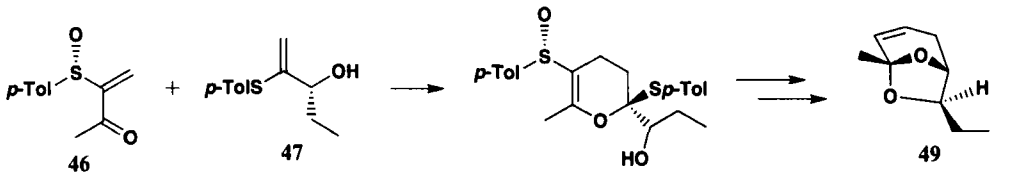
Both intermolecular and intramolecular hetero Diels-Alder reactions involving enantiomerically enriched sulfoxides have also been reported but few had high stereoselectivities. The Lewis acid-catalyzed intramolecular [4+2] cycloaddition reaction of the enantiomerically enriched α-sulfinyl α,β-unsaturated ketone **43** occurred in the presence of a Lewis acid to provide **44** in 3-61% *de* (*Scheme 14*).



43 44 45

Scheme 14

The highest selectivity was achieved using $SnCl_4$ as the catalyst at -78° (*Table 6*).[29] In another example, the intermolecular hetero Diels-Alder reaction of the enantiomerically enriched sulfinyl butenone **46** and enol thioether **47** took place without catalyst to afford the cycloadduct **48** in 40% *de* (*Scheme 15*).[30] Intermediate **48** was used in the total synthesis of the Mus musculus pheromone **49**.



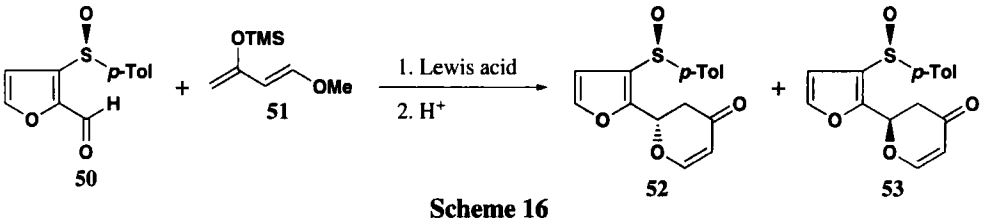
46 47 48 (40% *de*) 49

Scheme 15

Table 6. Lewis Acid-catalyzed Hetero Cycloaddition Reaction of **43**

Lewis Acid	Solvent	Temp (°C)	Yield (%)	*de* (%)
$ZnCl_2$	toluene	0	63	48.6
Et_2AlCl	CH_2Cl_2	-78	84	42.5
$AlCl_3$	toluene	-78	54	38
$FeCl_3$	CH_2Cl_2	0	42	44.8
$SnCl_4$	toluene	-78	81	60.6
$BF_3.Et_2O$	toluene	0	70	3.0

Intermolecular hetero Diels-Alder reactions of enantiomerically enriched furanyl aldehyde **50** with Danishefsky's diene (**51**) afforded the cycloadducts with high diastereoselectivities (up to 98% *de*) and in good yields (*Scheme 16*).[31] The zinc chloride-catalyzed cycloaddition reaction



50 51 52 53

Scheme 16

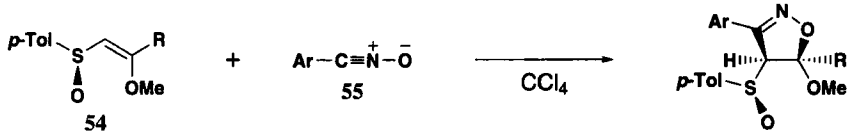
produced equal amounts of diastereomers **52** and **53**. In the presence of lanthanoid halides or triflates, the reaction afforded **52** in good yields and with high diastereoselectivities (*Table 7*).

Table 7. Lewis Acid-catalyzed Cycloaddition Reaction of Furanyl Aldehyde **50**

Lewis Acid	Solvent	Temp (°C)	Yield (%)	**52 : 53**
$ZnCl_2$	CH_2Cl_2	25	67	50 : 50
$CeCl_3$	CH_2Cl_2	25	58	90.5 : 9.5
$Yb(OTf)_3$	CH_2Cl_2	-20	29	96 : 4
$Yb(OTf)_3$	THF	-20	88	96.5 : 3.5
$Nd(OTf)_3$	THF	-20	68	99 : 1
$Sm(OTf)_3$	THF	-20	73	98.5 : 1.5

3. 1,3-Dipolar Cycloaddition Reactions

1,3-Dipolar cycloaddition involving a stereogenic center or a chiral auxiliary on the dipole or the dipolarophile moiety is a useful tool for the regio- and stereoselective construction of five-membered heterocycles. Bruché *et al.* demonstrated that the 1,3-dipolar cycloaddition of enantiomerically enriched vinyl sulfoxides **54** with nitrile oxides **55** was highly regio- and stereoselective (*Scheme 17*), leading to



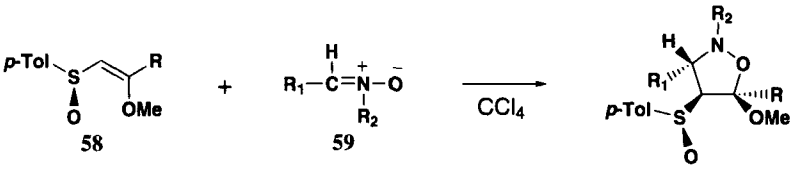
54 55 56

Scheme 17

the enantiomerically enriched (4*S*,5*R*,R_S)-4,5-dihydroisoxazoles **56** in 45-91% yields (*Table 8*).[32] Bruché also synthesized enantiomerically enriched (3*S*,4*S*,5*R*,R_S)-isoxazolidines **57** in 30-90% yields from the cycloaddition of chiral vinyl sulfoxides **58** with nitrones **59** (*Scheme 18*).[32b]

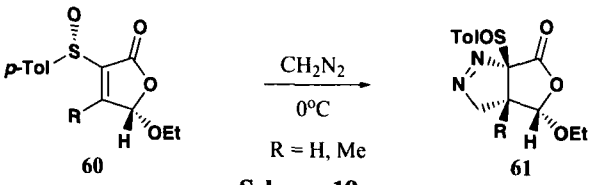
Table 8. 1,3-Dipolar Cycloaddition Reaction of Vinyl Sulfoxides **54**

R	Ar	Conversion (%)
CH_2F	2,-6-dichlorophenyl	72
CH_2F	3,5-dichloro-2,4,6-trimethylphenyl	71
CHF_2	3,5-dichloro-2,4,6-trimethylphenyl	57
CF_3	3,5-dichloro-2,4,6-trimethylphenyl	65
C_2F_5	2,-6-dichlorophenyl	45
C_2F_5	3,5-dichloro-2,4,6-trimethylphenyl	91



Scheme 18

1,3-Dipolar cycloaddition of enantiomerically enriched sulfinyl furanones **60** and diazomethane also occurs with high stereoselectivity to afford the enantiomerically enriched sulfinyl pyrazolines **61** in quantitative yields (*Scheme 19*).[33] The attack of diazomethane was suggested to take place from the less hindered face of the sulfinyl group.



Scheme 19

III. PUMMERER REACTIONS

Pummerer rearrangement reactions of enantiomerically enriched sulfoxides are of great importance for preparing enantiomerically enriched α-acetoxy, α-alkyl, α-aryl, α-halo, and α-siloxy substituted sulfides.[34] Intramolecular Pummerer cyclization is especially important for building enantiomerically enriched heterocycles.[35] Enantiomerically enriched lactones have been prepared from the additive Pummerer reactions of enantiomerically enriched vinyl sulfoxides with dichloroketene.[36] The reaction product of enantiomerically enriched vinyl sulfoxides with Grignard reagents undergoes Pummerer rearrangement to afford enantiomerically enriched vinyl sulfide adducts.[37] Chirality transfer from sulfur to the α-carbon *via* a Pummerer rearrangement has been exploited for the synthesis of many natural products and biologically important molecules (*Figure 4*).[38]

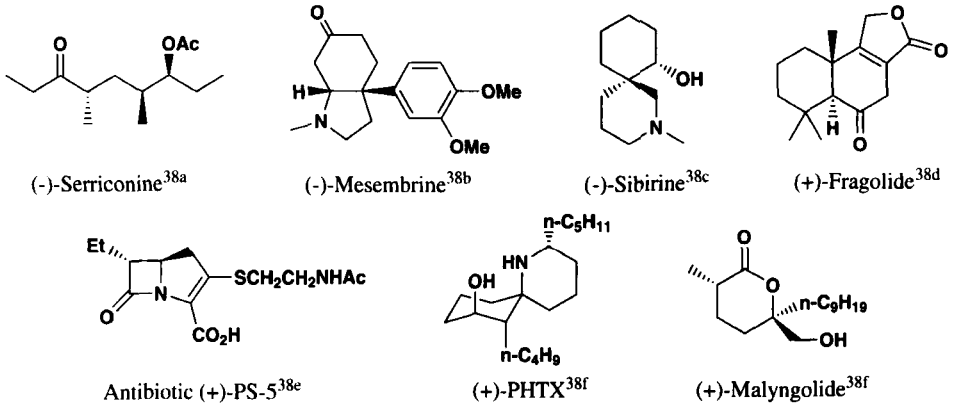
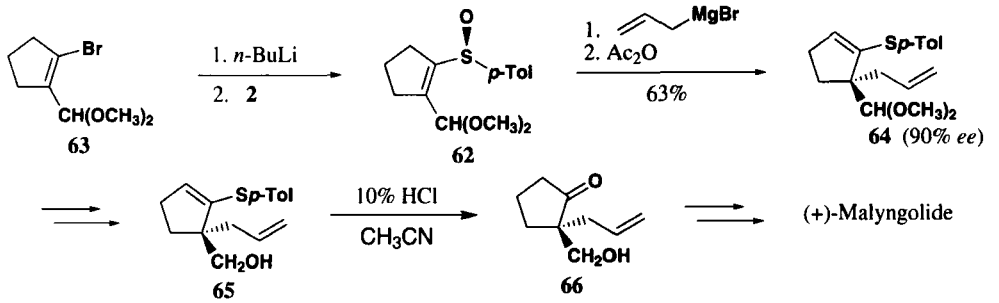


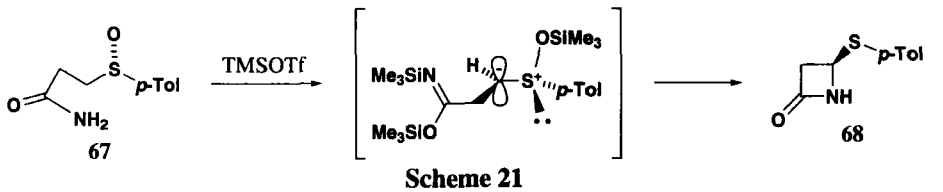
Figure 4

In the synthesis of a natural product (+)-malyngolide (*Scheme 20*), Maezaki *et al.* prepared the enantiomerically enriched sulfoxide **62** from the bromide **63** using Anderson's method. Pummerer rearrangement of the adduct formed from the reaction of **62** with allyl magnesium bromide in THF afforded the product **64** in 90% *ee* and 63% yield. The rearrangement product **64** was converted to the alcohol **65** and subsequently hydrolyzed to the cyclopentanone **66** which was used to synthesize (+)-malyngolide by a published procedure.[38f]



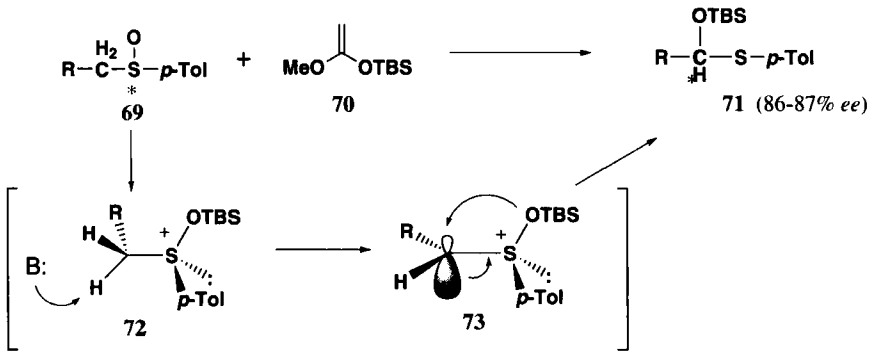
Scheme 20

Early investigations of the asymmetric Pummerer rearrangements of enantiomerically enriched sulfoxides with acetic anhydrides often gave unsatisfactory yields and selectivities due to the formation of sulfurane intermediates and racemization. Kaneko *et al.* successfully improved the Pummerer rearrangement of a β-amido sulfoxide **67** with trimethylsilyl triflate (TMSOTf) to furnish the sulfinyl lactam product **68** in 67% *ee* and 76% yield (*Scheme 21*).[39]



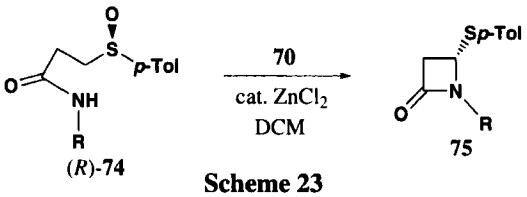
Scheme 21

Kita *et al.* reported the first highly enantioselective Pummerer rearrangement of enantiomerically enriched sulfoxides **69** with an silylated ketene acetal **70** to give α-siloxy sulfides **71** under mild conditions and without the formation of sulfuranes (*Scheme 22*).[40] The mechanism of this Pummerer



Scheme 22

rearrangement is proposed as follows: Silylation of sulfoxide **69** forms the intermediate **72**. Abstraction of the proton *anti*-periplanar to the sulfoxide oxygen of **72** gives the intermediate **73**, which undergoes a migration of the siloxy group to the α-carbon, possibly through an intimate ion pair dissociation-recombination. Kita also applied this silicon-induced Pummerer methodology to the intramolecular cyclization of enantiomerically enriched β-amidosulfoxides to the synthesis of α-sulfenyl lactams (*Scheme 23*).[41] Treatment of enantiomerically enriched (*R*)-sulfoxide **74** with the ketene acetal **70** and $ZnCl_2$ in dichloromethane afforded the α-sulfenyl lactams **75** in good *ee* (*Table 9*).

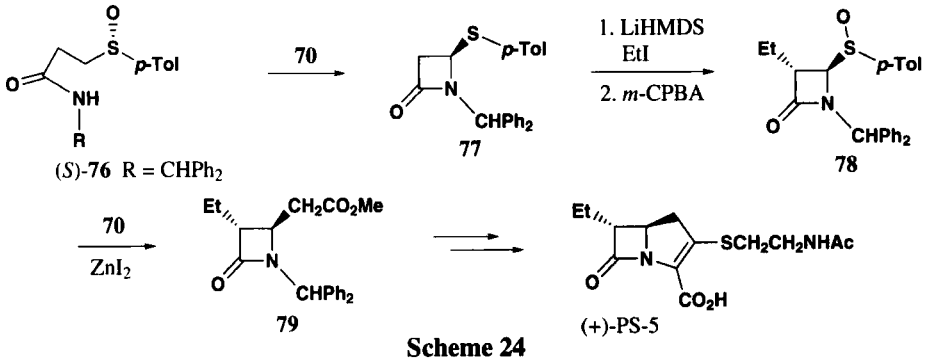


Scheme 23

Table 9. Preparation of α-Sulfenyl Lactams **75** *via* Pummerer Rearrangement

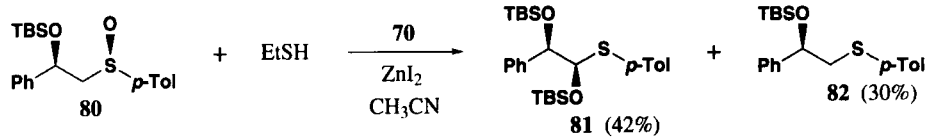
R	Conditions	Yield (%)	*ee* (%)
CH_2Ph	5°, 6 days	54	82
$CHPh_2$	15°, 2 days	90	83
(*S*)-CH(Me)Ph	0°, 3 days	89	85

The utility of this Pummerer methodology was further demonstrated by Kita in the total synthesis of enantiomerically enriched carbapenem antibiotic (+)-PS-5 (*Scheme 24*).[38e] Enantiomerically enriched β-amidosulfoxide **76** was cyclized to β-lactam **77** *via* this methodology, and the corresponding enolate of **77** was C-ethylated and oxidized to provide chiral sulfoxide **78**. Treatment of **78** with **70** in the presence of ZnI_2 gave a key ester intermediate **79** for the synthesis of (+)-PS-5.



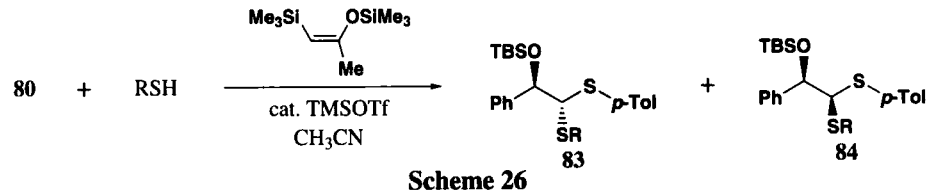
Scheme 24

Kita also examined the use of ketene acetal **70** for the synthesis of enantiomerically enriched thioacetals.[42] Reaction of the *syn*-(*R*)-sulfoxide **80** with the ketene acetal **70** and ethyl thiol in the presence of ZnI_2 gave a mixture of the normal Pummerer rearrangement product **81** and its reduction product **82** (*Scheme 25*). However, using *N,O-bis*trimethylsilylacetamide (BSA) and TMSOTf instead



Scheme 25

of Kita's ketene acetal **70** and ZnI_2 preferentially gave the *anti*-thioacetals **83** over the *syn*-thioacetals **84** (*Scheme 26*). The best diastereoselectivity was achieved when the sulfoxide **80** reacted with *i*-Pr mercaptan to give the *anti*-isomer **83** in 68% yield and 86% *de* (*Table 10*).[42]

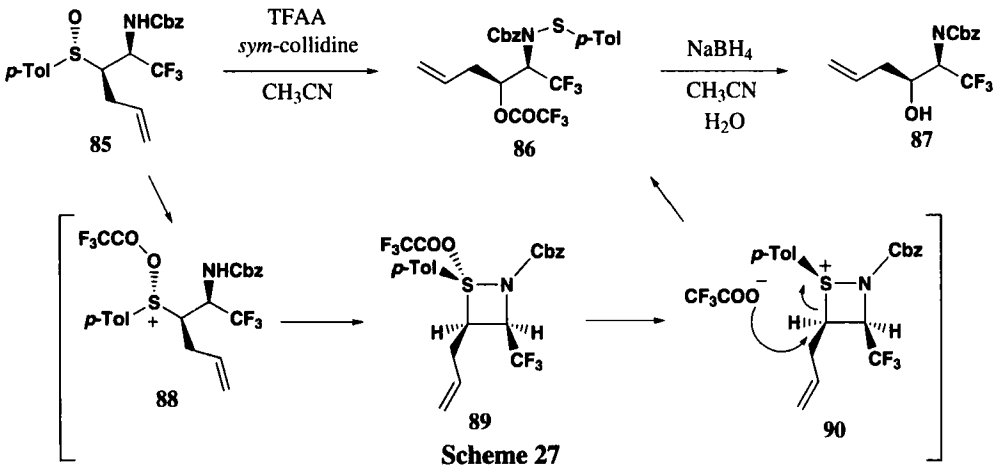


Scheme 26

Table 10. Stereoselective Pummerer Rearrangement of Sulfoxide **80** with Mercaptans

R	Yield (%)	*de* (%) of **83**
Et	82	83
Pr	75	81
i-Pr	68	86
t-Bu	62	71
Allyl	75	80
Bn	75	83

Zanda *et al.* discovered the non-oxidative Pummerer reaction during the investigation of the synthesis of a new statine dipeptide isostere.[43] When the enantiomerically enriched sulfoxide **85** was treated with 5 equiv. of trifluoroacetic anhydride and 3 equiv. of *sym*-collidine in acetonitrile, the normal Pummerer rearrangement did not take place (*Scheme 27*). Instead, the trifluoroacetoxy group

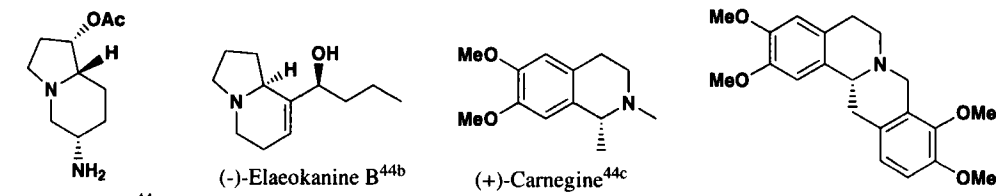


Scheme 27

displaced the sulfinyl group in the S_N2 manner to afford the sulfenamide intermediate **86**. Treatment of **86** with aqueous K_2CO_3 and an excess of $NaBH_4$ provided the β-amino alcohol **87** in high yield (94%) and with high diastereoselectivity (>96% *de*). Based on X-ray diffraction and ^1H NMR, Zanda proposed an explanation for this transformation that involves the formation of acylated sulfoxide **88**, followed by a cyclization to give σ-sulfurane **89**. The disassociation of the trifluoroacetoxy group and the subsequent S_N2 displacement gave sulfenamide **86** with inversion of configuration at the α-sulfinyl carbon.

IV. NUCLEOPHILIC ADDITION REACTIONS OF SULFINYL CARBANIONS

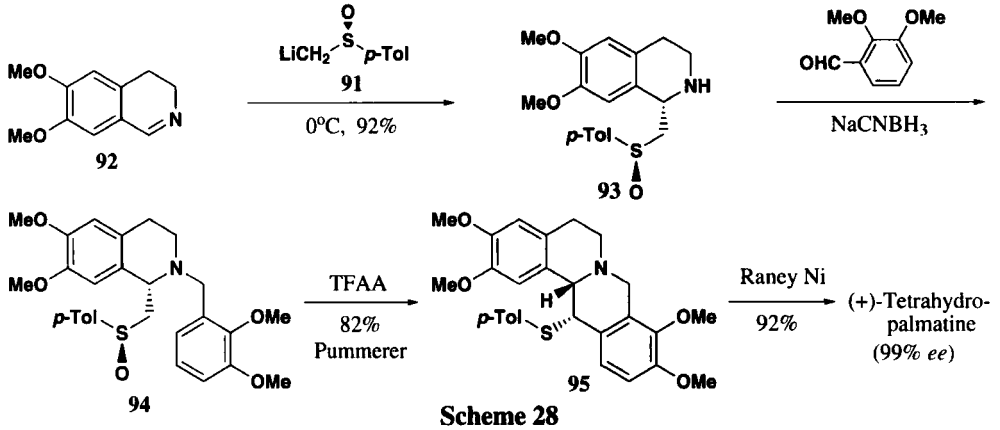
The diastereoselective addition of enantiomerically enriched sulfinyl carbanions to various electrophilic substrates has been extensively investigated and utilized for C-C bond formation in the synthesis of biologically important molecules (*Figure 5*).[44] Deprotonation of the α-carbon of the



(-)-Slaframine[44a] (-)-Elaeokanine B[44b] (+)-Carnegine[44c] (+)-Tetrahydropalmatine[44c]

Figure 5

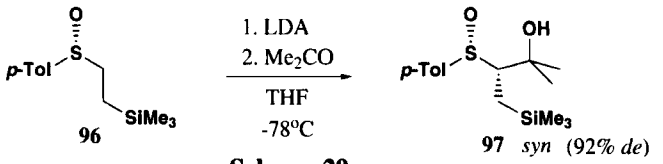
sulfoxide requires a strong base such as $LiNH_2$, LDA, *n*-BuLi, LiHMDS, or a Grignard reagent. High stereoselectivity usually requires steric hindrance in the vicinity of the α-carbon of the sulfoxide and the use of an electrophile with a bulky group. The stereochemical outcomes of the addition reactions are understood by examining the most favorable chelated transition state. Lithiated carbanions of enantiomerically enriched *p*-tolyl methyl[45] or vinyl[46] sulfoxides are valuable synthons for the introduction of a chiral sulfinyl group. These early stage enantiomerically enriched intermediates are useful in the asymmetric synthesis of complex molecules by directing subsequent stereoselective transformation. Pyne *et al.* has exploited this strategy in the total synthesis of (+)-tetrahydropalmatine by (*Scheme 28*).[44c]



Scheme 28

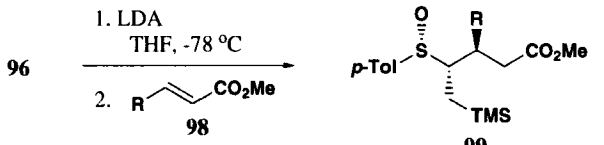
The addition of lithiated (*R*)-methyl *p*-tolyl sulfoxide **91** to 3,4-dihydro-6,7-dimethoxyisoquinoline (**92**) occurred at 0° to give the adduct **93** with high diastereoselectivity (84% *de*) (*Scheme 28*). Reductive alkylation of **93** with $NaCNBH_3$ and 2,3-dimethoxybenzaldehyde afforded the alkylation product **94** in 87% yield. The subsequent Pummerer rearrangement of **94** in the presence of trifluoroacetic anhydride took place with excellent diastereoselectivity to give the tetracyclic sulfide **95** as a single diastereomer in 82% yield. The final product (+)-tetrahydropalmatine was formed in 99% *ee* and 92% yield after desulfurization.

Michael addition of enantiomerically enriched sulfinyl carbanions to α,β-unsaturated carbonyl compounds is a very useful method for stereoselective C-C bond formation.[47] Both *p*-tolyl and *t*-butyl sulfinyl carbanions have been demonstrated to undergo stereoselective addition reactions with cyclic or acyclic α,β-unsaturated aldehydes, ketones, and esters. However, removal of the *t*-butylsulfinyl group sometimes results in a complex mixture of products.[48] During the development of a new enantiomerically enriched vinyl anion equivalent, Toru *et al.* discovered that the reaction of an enantiomerically enriched *p*-tolyl 2-(trimethylsilyl)ethyl sulfoxide (**96**) with LDA and acetone gave the *syn*-isomer **97** in 88% yield and 92% *de* (*Scheme 29*).[49] Toru postulated that a novel Si-O interaction between the trimethylsilyl and the carbonyl group, which stabilizes the transition state of the



Scheme 29

nucleophilic addition, accounts for *syn*-isomer formation. Conjugate addition reactions of the carbanion of enantiomerically enriched β-silylethyl sulfoxide **96** with α,β-unsaturated esters **98** affords the addition products **99** as single diastereomers in greater than 96% *de* (*Scheme 30* and *Table 11*).

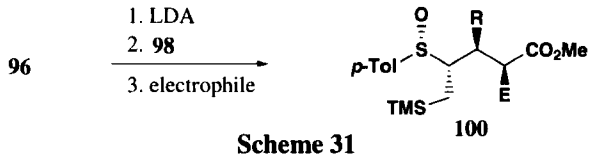


Scheme 30

Table 11. Stereoselective Conjugate Addition Reaction of Sulfoxide **96**

R	Yield (%)	*de* (%)
H	64	> 96
Me	95	> 96
Et	97	> 96
Ph	96	> 96

High diastereoselectivities were also observed for the Michael addition reactions of **96** with **98**, where the enolate intermediates were subsequently trapped with alkyl halides or aldehydes (*Scheme 31*). In general, trapping reactions took place in good to excellent yields to give **100**, except



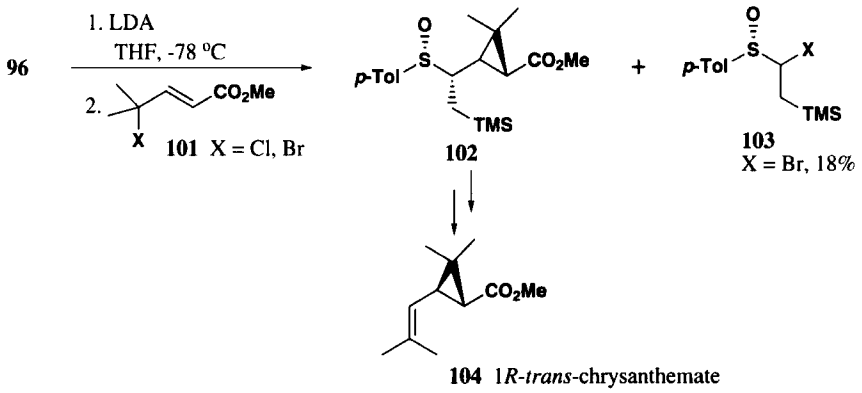
Scheme 31

for the reaction involving methyl acrylate (**98**, R = H) which was lower due to the polymerization (*Table 12*).[49d]

Table 12. Conjugate Addition and Subsequent Trapping Reactions of Sulfoxide **96**

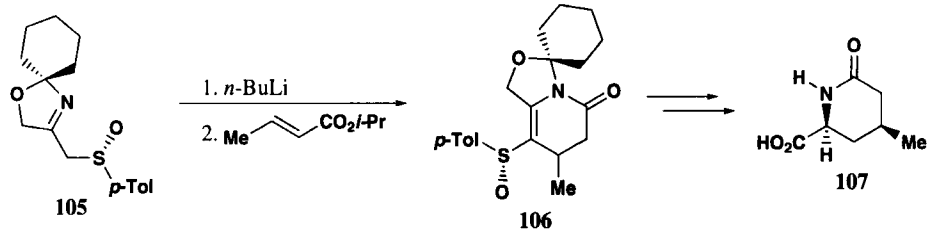
R	Electrophile	Yield (%)	*de (%)*
H	MeI	21	> 96
Me	MeI	59	> 96
Ph	MeI	75	> 96
Ph	BzBr	74	> 96
Ph	*i*-PrCHO	90	> 96
Ph	PhCHO	98	> 96

A highly stereoselective cyclopropanation was achieved when ethyl 4-chloro-4-methylpent-2-enoate (**101**, X = Cl) was reacted with the anion of **96**. A single diastereomer **102** was obtained in 84% yield without the formation of the chlorinated product **103** (*Scheme 32*).[50] The reaction with 4-bromo-4-methylpent-2-enoate (**101**, X = Br) under the same reaction conditions gave the anticipated cyclopropane **102** in 79% yield, along with an α-brominated product **103** (X = Br) in 18% yield. Ethyl cyclopropanecarboxylate **102** was converted to enantiomerically enriched chrysanthemate **104**.



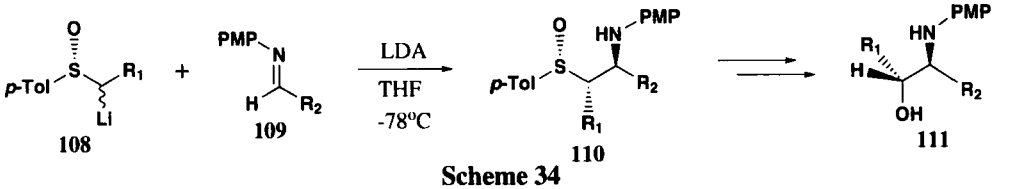
Scheme 32

Alvarez-Ibarra *et al.* successfully combined sulfoxide-mediated aza-enolate Michael addition and intramolecular cyclization in the stereoselective synthesis of pyroaminoadipic acids.[51] The lithium carbanion of enantiomerically enriched β-iminosulfoxide **105** reacted with isopropyl crotonate to give the sulfinyl piperidone **106** in 71% yield and 100% *de* (*Scheme 33*). The piperidone **106** was transformed to (2*S*,4*R*)-4-methyl pyroaminoadipic acid (**107**) in three additional steps.



Scheme 33

Stereoselective addition of α-lithiated alkyl *p*-tolyl sulfoxides to imines to generate enantiomerically enriched amines has been achieved.[52] The stereochemical outcome of this reaction depends on the reaction conditions and the nature of the electrophile. Aromatic imines were found to be more suitable than aliphatic imines for high diastereoselectivity. In the synthesis of chiral β-fluoroalkyl β-amino alcohol units, Zanda *et al.* reported that the addition reaction of α-lithium alkyl sulfoxides **108** with imines **109** afforded amines **110** in > 96% yield and 66-88% *de* (*Scheme 34*).[53]



Scheme 34

The highest selectivity (88% *de*) observed was for the reaction of **108** (R_1 = H) with the imine **109** (R_2 = CF_2CF_3). *Table 13* shows the diastereomeric ratios for the addition reaction of lithiated benzyl *p*-tolyl sulfoxide (**108**, R = Ph) to imines; this reaction forms two new stereogenic centers simultaneously. Zanda exploited this methodology in the synthesis of norephedrines (**111**, R_1 = Ph). The *Zimmerman-Traxler* chair-like transition state was proposed to rationalize the observed diastereoselectivities (*Figure 6*).

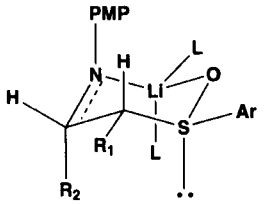


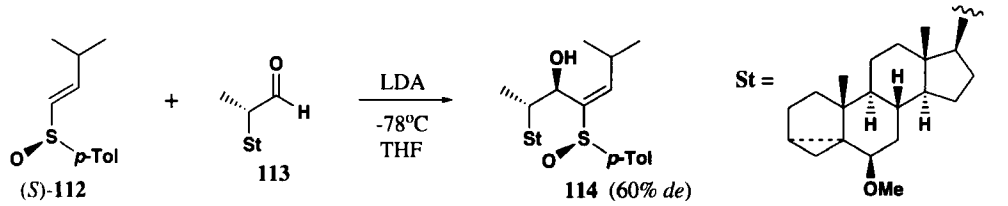
Figure 6

Table 13. Stereoselective Addition Reaction of Lithiated Sulfoxides **108** to Imine

R_1	R_2	Yield (%)	Diastereomeric Ratio
H	CF_3	> 98	92 : 8
H	CF_2CF_3	96	94 : 6
H	CF_2CF_2H	97	92 : 8
Ph	CF_3	98	85 : 15
Ph	CF_2CF_3	97	88 : 12
Ph	CF_2CF_2H	> 98	83 : 17

Nucleophilic addition of α-carbanions of enantiomerically enriched vinyl sulfoxides is also useful in the construction of new stereogenic centers. In the investigation of the synthesis of the plant growth regulator brassinolide, Marino *et al.* reported good diastereoselectivity in the addition of a

lithiated enantiomerically enriched vinyl sulfoxide to a steroidal aldehyde. (*E*)-(*S*)-3-Methyl-1-*p*-tolylsulfinyl-1-butene (*S*-**112**) was lithiated with LDA and condensed with the aldehyde **113** to give the desired product **114** in 60% *de* and 75% yield (*Scheme 35*).[54] A chelation-controlled transition state



Scheme 35

where the aldehyde adopts a Felkin-Anh rotational conformation was proposed to rationalize the stereoselectivity (*Figure 7*). Interestingly, poor selectivity was observed (20% *de*) for the other enantiomer (*R*)-**112**. Examination at the transition state of the (*R*)-sulfoxide with the aldehyde reveals unfavorable steric repulsion between methyl and isopropyl groups, thus accounting for the poor diastereoselectivity observed.

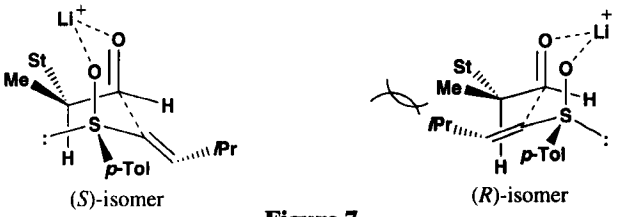
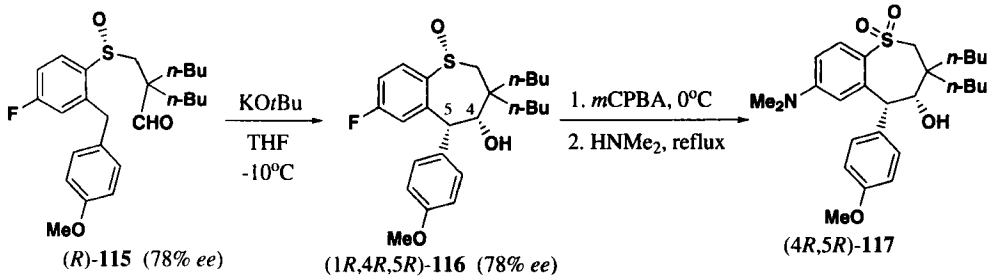


Figure 7

Wang *et al.* have reported a highly stereoselective intramolecular aldol condensation for the formation of benzothiepine ring where the chirality of the sulfoxide controls the configurations of two new stereogenic centers (*Scheme 36*).[55] This novel chemistry was used to prepare the apical sodium



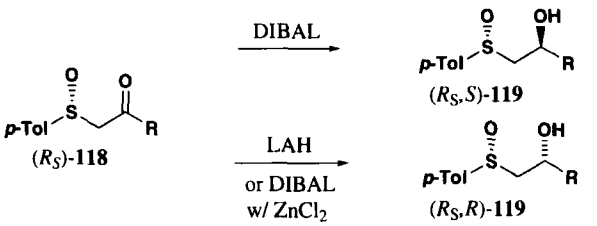
Scheme 36

co-dependent bile acid transporter (ASBT) inhibitor **117**. Treatment of the (*R*)-sulfoxide **115** (78% *ee*) with potassium *tert*-butoxide afforded the benzylic-carbanion of the sulfoxide. The intramolecular aldol condensation of this carbanion with the aldehyde group afforded the (1*R*,4*R*,5*R*)-benzothiepine

116 (78% *ee*) as a single diastereomer. The cyclization reaction was shown to be thermodynamically controlled. A metal chelate between the chiral sulfoxide oxygen and the alkoxide oxygen was proposed to rationalize the configuration of the newly formed stereogenic center at C4. The *cis* configuration is lower in energy due to unfavorable steric interactions between the C5-aryl and C3-butyl groups in the *trans* configuration. Thus, the configuration of the chiral sulfoxide determines the absolute configuration at both of the newly formed stereogenic centers.

V. REDUCTION REACTIONS

Since 1982 when Solladié *et al.* reported the highly stereoselective synthesis of enantiomerically enriched methyl carbinols, stereoselective reduction of enantiomerically enriched β-ketosulfoxides has been the most extensively investigated and utilized reactions involving asymmetric induction of chiral sulfoxides.[45b] The stereochemical outcome in the reduction of either isomer of the β-ketosulfoxide can be controlled by the configuration of the sulfoxide, the reducing reagent, and the absence or presence of a Lewis acid. The reduction of β-ketosulfoxide (R_S)-**118** by DIBAL gives (R_S,*S*)-carbinol **119** while the reduction by LAH or DIBAL with $ZnCl_2$ as the Lewis acid gives (R_S,*R*)-carbinol **119** (*Scheme 37*).[56] This methodology can be applied to the reduction of α-sulfinyl ketone



Scheme 37

118 with various α'-alkyl, alkenyl,[57] alkynyl,[58] and aryl[59] substituents. Increasing the size of R often results in the improvement of diastereoselectivity. In the absence of a Lewis acid, a chair-like transition state with a sulfoxide O-Al bridge is formed which undergoes an internal hydride transfer. In the presence of a chelating metal such as Li^+ or Zn^{+2}, an external hydride attack from the less hindered face of the carbonyl group is preferred.

Solladié *et al.* successfully applied this methodology to the total synthesis of many biologically important compounds such as (-)-tarchonanthuslactone,[60a] cladosolide A, [60b] solenopsins (A, B, and C), [60c] (+)-nonactic acid, [60d] (+)-gingerols, [60e] (+)-brefeldin A, [60f] and (*R*,*R*)-pyrenophorin[60g] (*Figure 8*). In the total synthesis of (-)-tarchonanthuslactone, two stereoselective reduction reactions induced by a chiral, non-racemic sulfoxide group were involved (*Scheme 38*). The β,δ-diketosulfoxide **120** was obtained from the commercially available dehydroacetic acid **121** in two steps. Stereoselective reduction of **120** with DIBAL at –78° gave the β-hydroxy δ-ketosulfoxide **122** in >95% *de* and 44% yield. The relatively low yield was attributed to decomposition during chromatographic purification. The $Et_2BOMe/NaBH_4$ reduction of **122** at –78° gave the *syn* diol **123** in >95% *de* and 90% yield.

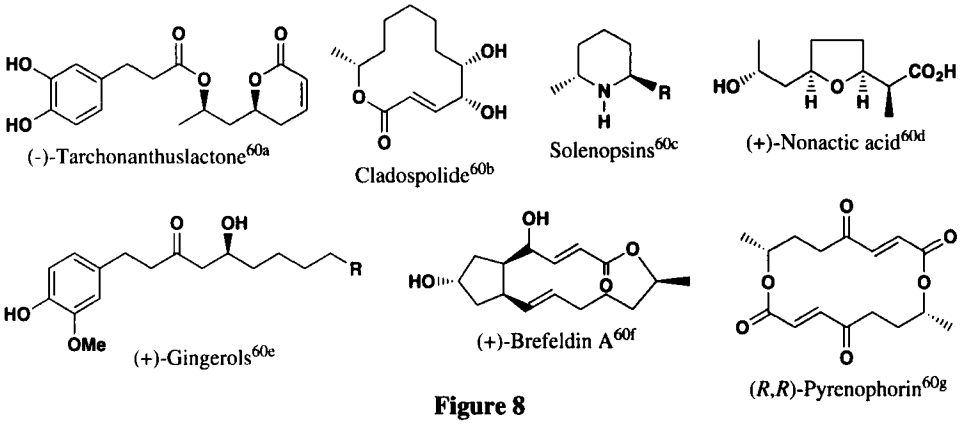
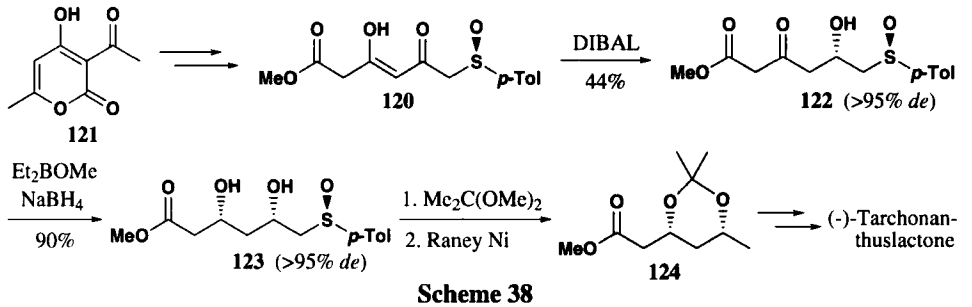


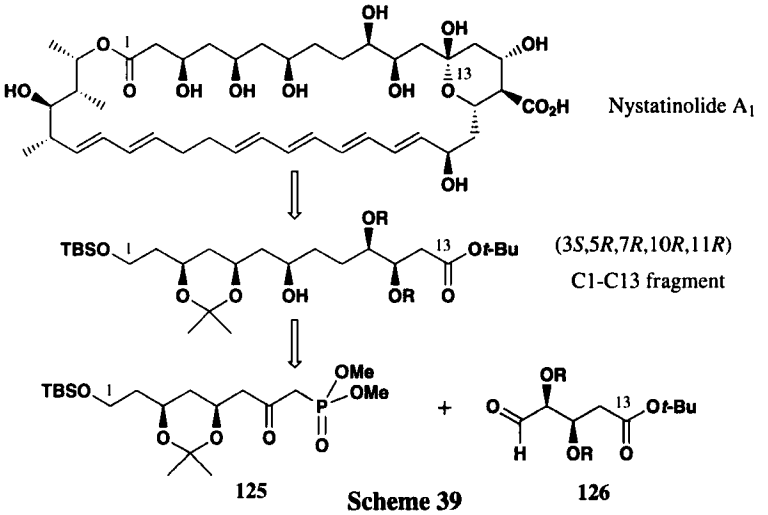
Figure 8

The diol was protected with 2,2-dimethoxypropane prior to reductive desulfurization with Raney nickel to afford the ester **124**, which was used to synthesize (-)-tarchonanthuslactone in six subsequent steps.



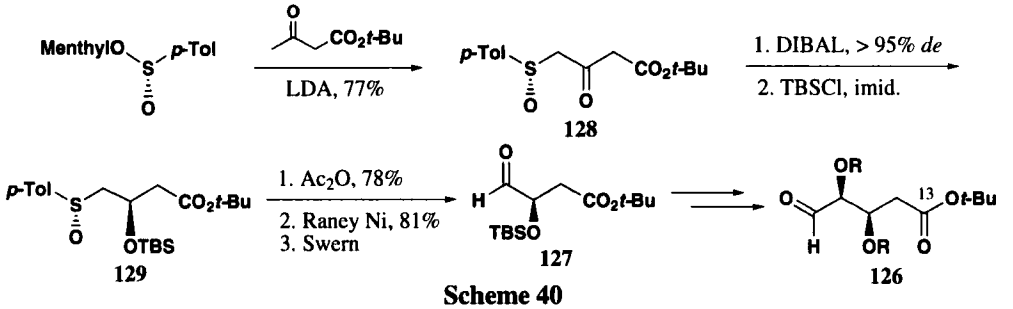
Scheme 38

Chiral sulfoxide directed reduction methodology was involved in the first convergent and stereoselective synthesis of the C1-C13 fragment of nystatin A_1, a macrolide antibiotic for antifungal therapy (*Scheme 39*).[61] The C1-C13 fragment was disconnected to two parts: enantiomerically



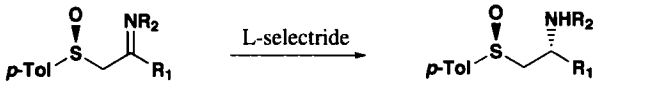
Scheme 39

enriched ketophosphonate **125** and aldehyde **126**. Aldehyde **126** could in turn be prepared from key intermediate **127** (*Scheme 40*). (+)-Menthyl-(*R*)-*p*-toluenesulfinate was treated with the dianion of *tert*-butyl acetoacetate to afford 77% of ketosulfoxide **128**. Subsequent stereoselective reduction and protection yielded sulfoxide **129**. Pummerer rearrangement of **129**, desulfurization of the rearrangement product and subsequent Swern oxidation of the resulting alcohol provided the key aldehyde intermediate **127**.



Scheme 40

Reduction of enantiomerically enriched β-iminosulfoxides to the corresponding β-aminosulfoxides can be achieved with high diastereoselectivity. Ogura *et al.* have demonstrated the L-selectride (lithium tri-*sec*-butylborohydride) reduction of enantiomerically enriched imine **130** to amine **131** with high diastereoselectivities (95-96% *de*) (*Scheme 41*).[62] The reduction was proposed to take



(*S*)-**130** (*S*S,*R*)-**131** (95-96% *de*)

Scheme 41

place *via* external hydride transfer to the less hindered bottom face of the C=N bond in a chelated chair-like transition state (*Figure 9*).[63] BH_3-THF complex has also been used to reduce the β-iminosulfoxides **130** in moderate diastereoselectivities (48-74% *de*).

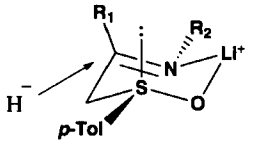
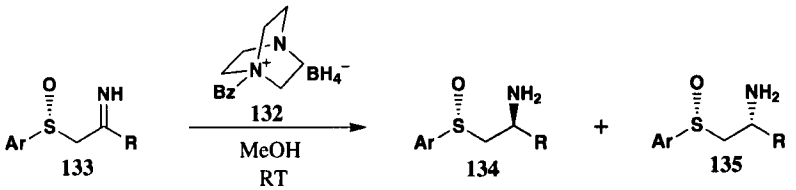


Figure 9

Hajipour reported the first use of 1-benzyl-1-azonia-4-azabicyclo[2,2,2]octane tetrahydroborate (BAAOTB) (**132**) in the hydride reduction of enantiomerically enriched β-iminosulfoxides **133** to the corresponding β-aminosulfoxides **134** and **135** (*Scheme 42*).[64] The BAAOTB reduction gave the



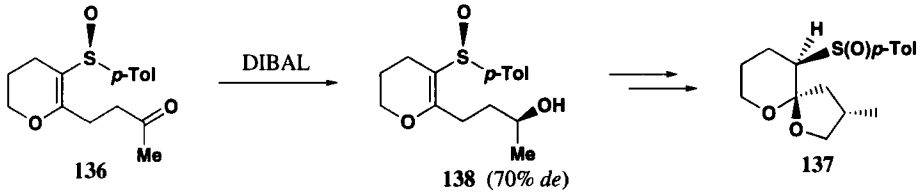
Scheme 42

(R_S, *S*)-isomer **133** with moderate to high diastereoselectivities (*Table 14*). Higher selectivities were achieved in the reduction of iminosulfoxides with a bulkier R group (R = *t*-Bu, Ph, Bn).

Table 14. Stereoselective Reduction of β-Iminosulfoxides **133**

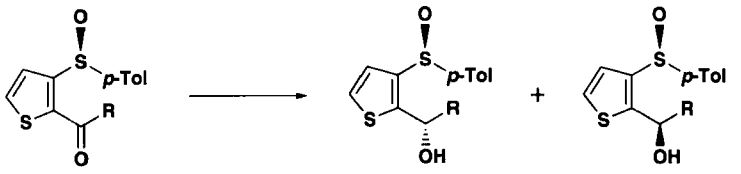
Ar	R	Time (min)	Yield (%)	**134 : 135**
Ph	Me	120	93	80 : 20
Ph	Ph	100	93	90 : 10
Ph	*t*-Bu	150	80	95 : 5
p-Tol	Bn	120	90	93 : 7
p-Tol	*t*-Bu	150	80	98 : 2

1,3-Asymmetric induction of chiral sulfoxides in β-carbonyl reduction is the most well-known and utilized method for the preparation of enantiomerically enriched alcohols, but other more remote asymmetric inductions have also been investigated. Iwata *et al.* reported a 1,6-asymmetric induction involving a sulfinyl group in an enantiomerically enriched ε-ketosulfoxide **136** that was used in the stereoselective synthesis of the dioxaspiro **137** (*Scheme 43*).[65] The DIBAL reduction of this ε-ketosulfoxide **136** gave the (*S*)-OH isomer **138** in 70% *de*. In the presence of $ZnCl_2$ the diastereoselectivity was reversed to favor the formation of the (*R*)-OH isomer in 56% *de*. Chiral discrimination is presumably less effective as a result of the large ring size of the metal complex.



Scheme 43

Arai *et al.* have reported a 1,4-asymmetric induction in the stereoselective reduction of enantiomerically enriched γ-ketosulfoxides **139** where the sulfinyl and carbonyl groups are separated by a thiophene ring (*Scheme 44*).[66] The thienyl methyl ketone **139** (R = Me) underwent DIBAL reduction to give a 3.3 : 1 mixture of **140** and **141**, respectively, in 90% yield (*Table 15*). In the presence of a Lewis acid the selectivity of the DIBAL reduction was reversed and **141** was formed predominantly. With $Yb(OTf)_3$ the reaction gave the highest diastereoselectivity (1 : 8.3). For L-selectride, the methyl



139 140 141

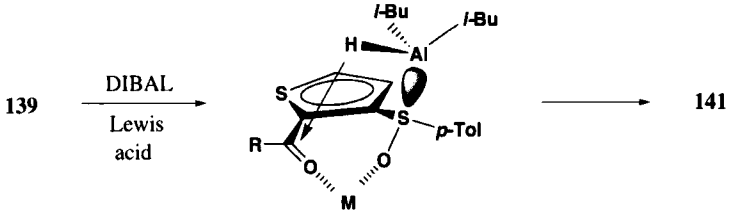
Scheme 44

ketone gave the isomer **141** in 85% yield and very good diastereoselectivity (1 : 17). Interestingly, the presence of a Lewis acid in the L-selectride reduction did not reverse the selectivity, and the highest diastereoselectivity (1 : 42) observed was for $Yb(OTf)_3$.

Table 15. Stereoselective Reduction of γ-Ketosulfoxides **139**

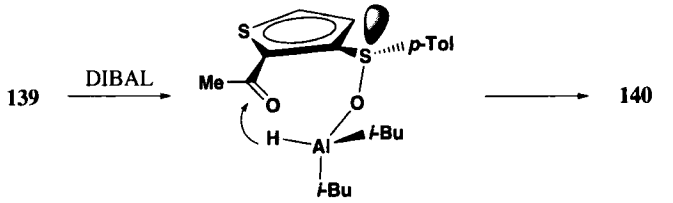
R	Reagent	Lewis Acid	Conditions	Yield (%)	**140 : 141**
Me	DIBAL	----	-78° 2h	90	3.3 : 1
Ph	DIBAL	----	-78° 3h	61	8.9 : 1
Me	DIBAL	$Yb(OTf)_3$	-30° 2h	88	1 : 8.3
Me	DIBAL	$ZnCl_2$	-78° 1h	35	1 : 5.2
Me	DIBAL	LiBr	-30° 2h	89	1 : 5.4
Me	L-selectride	----	-78° 2h	85	1 : 17.1
Me	L-selectride	$Yb(OTf)_3$	-30° 2h	99	1 : 41.6
Ph	L-selectride	----	-78° 3h	85	1 : 3.6
Ph	L-selectride	$ZnCl_2$	-78° 1h	93	1 : 3.2
Pen	L-selectride	----	-78° 3h	99	1 : 7.2
Pen	L-selectride	$ZnCl_2$	-30° 2h	99	1 : 7.5
i-Pr	L-selectride	----	-78° 3h	92	1 : 3.2
i-Pr	L-selectride	$ZnCl_2$	-78° 2h	89	1 : 2.5

DIBAL reductions of **139** involving a Lewis acid proceed *via* a seven-membered metal chelate. Top-face hydride delivery from DIBAL gives **141** (*Scheme 45*). The highest diastereoselectivity observed for $Yb(OTf)_3$ is probably due to the large size of ytterbium which forms a more stable



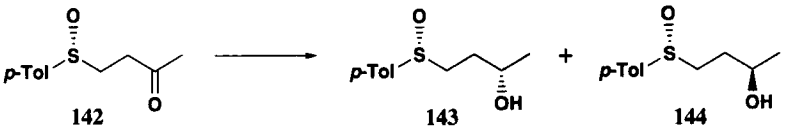
Scheme 45

complex with C=O and S-O in the seven-membered chelate. DIBAL reductions in the absence of a Lewis acid favor a transition state where the intramolecular dipole-dipole interactions are minimized (*Scheme 46*). The hydride is delivered to the carbonyl carbon from the bottom face to give **140**.



Scheme 46

Solladié *et al.* prepared a γ-ketosulfoxide **142** to investigate the 1,4-asymmetric induction effect of the sulfinyl group in reduction (*Scheme 47*).[67] $NaBH_4$ reduction at -78° gave a 50 : 50



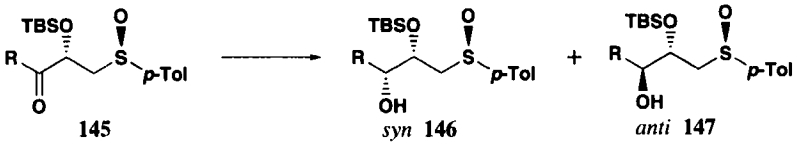
Scheme 47

mixtures of isomers **143** and **144**, while DIBAL reduction at -78° showed a preference for **143** (60% *de*); lowering the reaction temperature to −105° increased the selectivity to 70% *de* (*Table 16*). Diastereoselectivity was lowered (38% *de*) but not reversed in the presence of ZnI_2, which is the opposite of what was observed for the reduction of β-ketosulfoxides. DIBAL reduction in the presence of lanthanide triflate or cerium chloride favored the formation of diastereomer **144** with moderate diastereoselectivities.

Table 16. Stereoselective Reduction of γ-Ketosulfoxide **142**

Reagent, Lewis Acid	Solvent/Temp/Time	Yield (%)	**143 : 144**
$NaBH_4$ (1eq)	EtOH/-78°/4 h	75	50 : 50
DIBAL (1.1 eq)	THF/-78°/1.5 h	85	80 : 20
DIBAL (1.1 eq)	THF/-105°/1.5 h	85	85 : 15
DIBAL (1.5 eq), ZnI_2 (1.1 eq)	THF/-78°/3 h	84	69 : 31
DIBAL (2.5 eq), $Yb(OTf)_3$ (1.1 eq)	THF/-78°/5 h	40	20 : 80
DIBAL (3 eq), $Yb(OTf)_3$ (0.5 eq)	THF/-78°/5 h	56	30 : 70
DIBAL (3 eq), $CeCl_3$ (1.1 eq)	THF/-78°/4 h	66	25 : 75

The presence of Lewis acids had varying effects on the reduction of enantiomerically enriched β-siloxy-γ-ketosulfoxides with DIBAL (*Scheme 48*).[68] DIBAL reduction of the keto ester **145** (R = CH_2CO_2t-Bu) gave a 2 : 98 mixture of **146** : **147** in 55% yield with the *anti*-isomer **147** as the major product (96% *de*) (*Table 17*). The presence of ZnI_2 in the reduction decreased the selectivity



Scheme 48

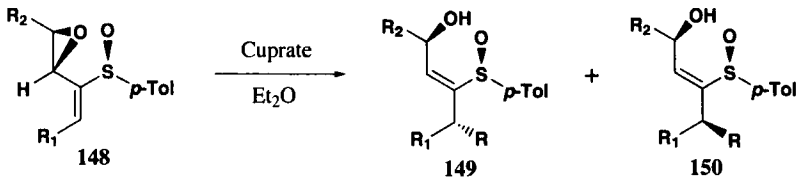
(56% *de*), but still favored the *anti*-isomer. Reduction of the keto nitrile **145** (R = CH_2CN) gave a 2 : 98 mixture of **146** : **147** in 94% yield. The selectivity was substantially lower (20% *de*) in the presence of ZnI_2. Reduction of ketone **145** (R = (*E*)-CH=CH$C_{10}H_{21}$) provided **147** in 80% *de*; addition of $Yb(OTf)_3$ improved the selectivity to 96% *de*, while ZnI_2 reversed the selectivity in favor of **146** (94% *de*).

Table 17. Stereoselective Reduction of β-Siloxy-γ-Ketosulfoxides **145**

R	Reagent, Lewis Acid	Time (min)	Yield (%)	**146 : 147**
CH_2CO_2t-Bu	DIBAL	60	55	2 : 98
CH_2CO_2t-Bu	DIBAL, ZnI_2 (1.1 eq)	420	45	22 : 78
CH_2CN	DIBAL	120	94	2 : 98
CH_2CN	DIBAL, ZnI_2 (1.1 eq)	120	92	60 : 40
(*E*)-CH=CH$C_{10}H_{21}$	DIBAL	60	84	10 : 90
(*E*)-CH=CH$C_{10}H_{21}$	DIBAL, $Yb(OTf)_3$ (1.1 eq)	30	93	2 : 98
(*E*)-CH=CH$C_{10}H_{21}$	DIBAL, ZnI_2 (1.1 eq)	45	92	97 : 3

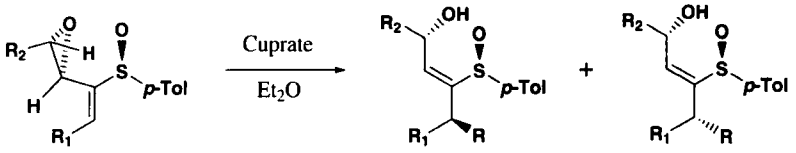
VI. NUCLEOPHILIC SUBSTITUTION REACTIONS

Enantiomerically enriched sulfinyl auxiliaries are able to induce asymmetry in nucleophilic substitution reactions. Marino *et al.* demonstrated highly regio- and stereoselective S_N2' reactions of enantiomerically enriched epoxy vinyl sulfoxides with alkyl cyanocuprates.[69] Epoxy vinyl sulfoxide **148** (R_1 = R_2 = *n*-Bu) reacted with MeCuCNLi in ether to give a 96 : 4 mixture of *anti*- and *syn*-isomers **149** and **150**, respectively, in 91% yield (*Scheme 49*). Epoxy vinyl sulfoxide **148** (R_1 = Ph, R_2 = *n*-Bu) reacted with *n*-BuCuCNLi to give exclusively the *anti*-isomer **149** in 87% yield (*Table 18*).



Scheme 49

Nucleophilic substitution of **151** (R_1 = R_2 = *n*-Bu) with MeCuCNLi produced the *syn*-isomer **153** in 68% yield and 70% *de* (*Scheme 50*); EtCuCNLi in this reaction gave the *anti*-isomer **152** exclusively (100% *de*) (*Table 19*).



Scheme 50

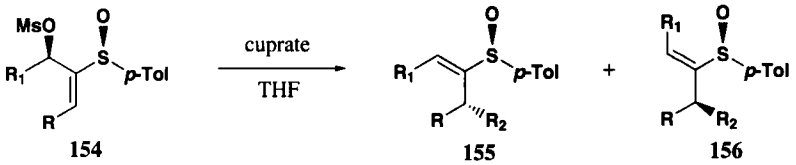
Table 18. Stereoselective S_N2' Reactions of Epoxy Vinyl Sulfoxides **148**

R_1	R_2	Cuprate	Yield (%)	**149 : 150**
n-Bu	*n*-Bu	MeCuCNLi	91	96 : 4
Ph	*n*-Bu	*n*-BuCuCNLi	87	100 : 0

Table 19. S_N2' Reactions of Epoxy Vinyl Sulfoxides **151**

R_1	R_2	Cuprate	Yield (%)	**152 : 153**
n-Bu	*n*-Bu	MeCuCNLi	68	15 : 85
n-Bu	*n*-Bu	EtCuCNLi	70	0 : 100
Ph	*n*-Bu	*n*-BuCuCNLi	78	9 : 91

Marino *et al.* have developed another methodology for conducting highly stereoselective S_N2' reactions involving allylic mesyloxy vinyl sulfoxides and alkyl cuprates.[70] Treatment of phenyl substituted vinyl sulfoxide **154** (R = Ph, R_1 = Et) with MeCuCNLi in THF at –78° to room temperature provided a 6 : 94 mixture of **155** and **156**, respectively, in 81% yield (*Scheme 51*). Comparable

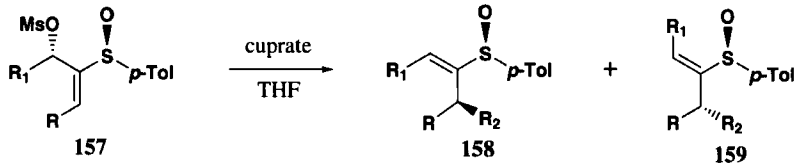


Scheme 51

results were obtained for the bulkier alkyl cuprate, *t*-BuCuCNLi (*Table 20*). Grignard-derived $Me_2CuMgBr$ gave the highest selectivity when reacted with **157** for the formation of isomer **159** (100% *de*). Interestingly, the *n*-butyl substituted vinyl sulfoxide of **157** (*Scheme 52*, R= *n*-Bu, R_1 = Et) reacted with Me_2CuLi to give isomer **158** in 80% *de* (*Table 21*).

Table 20. Stereoselective S_N2' Reactions of Allylic Mesyloxy Vinyl Sulfoxides **154**

R	R_1	R_2 Cuprate	Yield (%)	**155 : 156**
Ph	Et	MeCuCNLi	81	6 : 94
Ph	Et	*t*-BuCuCNLi	69	9 : 91
n-Bu	Et	MeCuCNLi	80	12 : 88



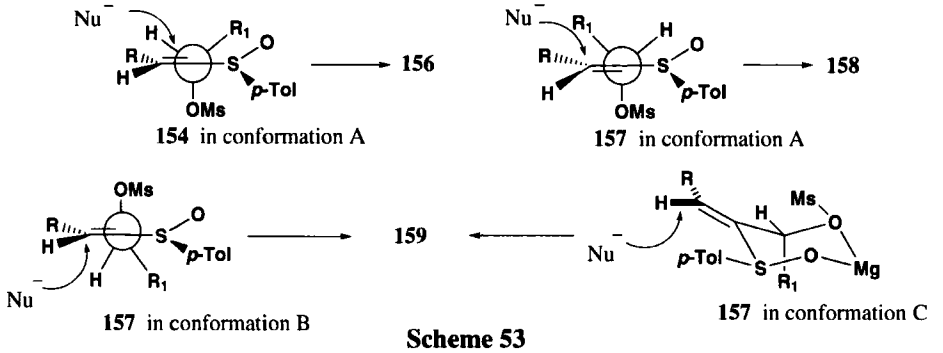
157 158 159

Scheme 52

Table 21. Stereoselective S_N2' Reactions of Allylic Mesyloxy Vinyl Sulfoxides **157**

R	R_1	R_2Cuprate	Yield (%)	**158 : 159**
n-Bu	Et	$Me_2CuMgBr$	50	0 : 100
n-Bu	Et	Me_2CuLi	80	90 : 10
Ph	Et	MeCuCNMgBr	80	6 : 94
Ph	Et	*t*-BuCuCNMgCl	71	6 : 94

The stereochemical consequences of Marino's cuprate reactions with mesyloxy sulfoxides **154** and **157** can be rationalized by an *anti* S_N2' process (*Scheme 53*). Nucleophilic attacks of the vinyl group from the face *anti* to the mesylate and away from the *p*-tolyl group in **154** and **157**, as shown in conformation A, gives **156** and **158**, respectively.[70] For bulky cuprate reagents, addition of nucleophiles to **157** in conformation A is higher in energy due to its steric interactions with R and R_1 groups, a non-chelated (conformation B) or chelated (conformation C) transition state is favored to give product **159**.

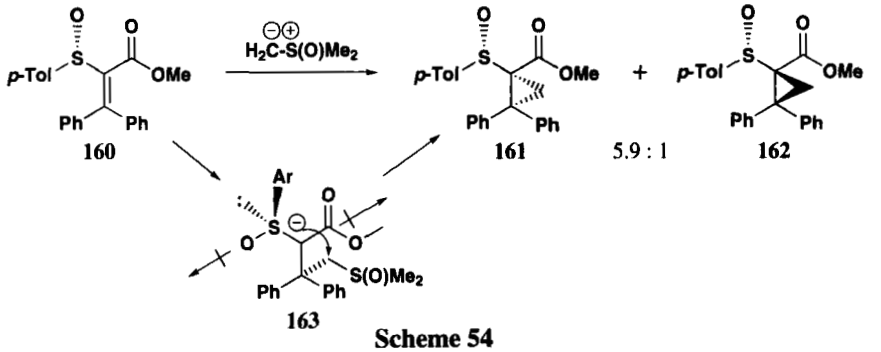


Scheme 53

VII. CYCLOPROPANATION REACTIONS

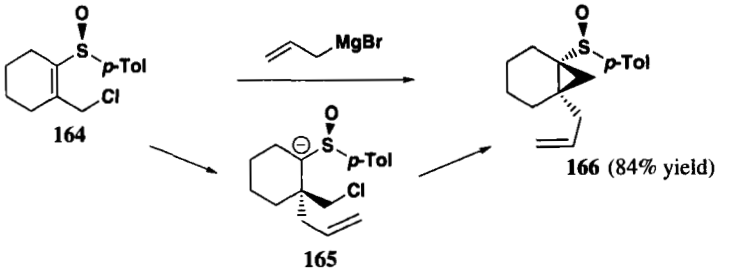
Enantiomerically enriched cyclopropanes are widely used as building blocks for the synthesis of complex molecules. Based on a stereoselective Michael addition of nucleophiles to enantiomerically enriched vinyl sulfoxides, Hamdouchi was first to develop this methodology for the stereoselective construction of a functionalized cyclopropane ring bearing a chiral sulfoxide.[71] Reaction of (*S*)-sulfinyl acrylate **160** with an excess of dimethyl sulfoxonium methylide in DMSO gave a 5.9 : 1 mixture of diastereomers **161** and **162** in 96% yield (*Scheme 54*). Michael addition of methylide to

sulfinyl acrylate leads to adduct **163**, which minimizes the dipole moments of the sulfinyl and carbonyl groups. Backside displacement of dimethyl sulfoxide forms the cyclopropane ring of **161**.



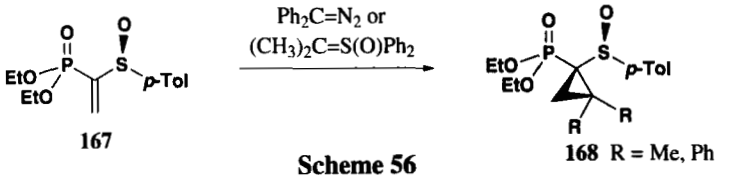
Scheme 54

Iwata *et al.* also have developed methodology for stereoselective cyclopropanation involving a enantiomerically enriched cyclic vinyl sulfoxide with a γ–leaving group.[72] Michael addition of the allyl Grignard reagent to the vinyl sulfoxide **164** produces the α-carbanion **165**. Backside displacement of chloride forms the cyclopropane ring of **166** as the only diastereomer in 84% yield (*Scheme 55*).



Scheme 55

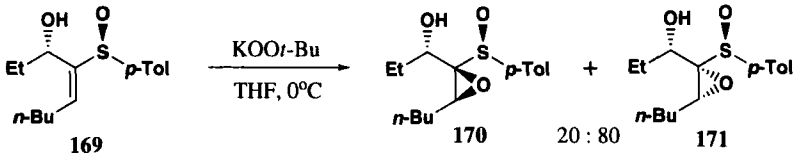
Mikolajczyk *et al.* have developed a diastereoselective cyclopropanation reaction[73] that is similar to Hamdouchi's method. Reactions of (*S*)-α-(diethoxyphosphoryl)vinyl *p*-tolyl sulfoxide (**167**) with diphenylsulfonium isopropylide or diphenyldiazomethane in DMSO afforded the corresponding cyclopropanes **168** in 100% *de* (*Scheme 56*). Ring closure from the less hindered diastereotopic face occupied by the lone pair electrons of sulfur of the initial Michael adduct was proposed as the source of asymmetric induction.



Scheme 56

VIII. EPOXIDATION REACTIONS

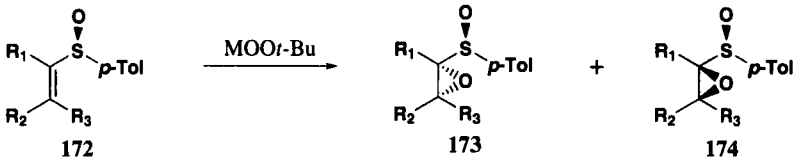
Diastereoselective nucleophilic epoxidation takes place when enantiomerically enriched vinyl sulfoxides are treated with MOO*t*-Bu (M: Li, Na, K) in ether or THF at 0° to afford α,β-epoxy sulfoxides in good yield. Jackson *et al.* reported the asymmetric nucleophilic epoxidation of enantiomerically enriched vinyl sulfones by LiOO*t*-Bu to give sulfonyl oxiranes in high yields and with good stereoselectivities.[74] Fernandez de la Pradilla *et al.* used Jackson's methodology for the epoxidation of enantiomerically enriched (S,R_S)-hydroxy vinyl sulfoxide **169** with KOO*t*-Bu. The reaction in THF at 0° gave a 20 : 80 mixture of sulfinyl epoxides **170** and **171** in 60% yield (*Scheme 57*).[75]



169 **170** **171**

Scheme 57

Fernandez de la Pradilla also used Jackson's epoxidation methodology on other enantiomerically enriched vinyl and dienyl sulfoxides in the preparation of enantiomerically enriched sulfinyl oxiranes (*Scheme 58*).[76] (*E*)-*n*-Butyl vinyl *p*-tolyl sulfoxide **172** (R_1 = H, R_2 = *n*-Bu, R_3 = H) was



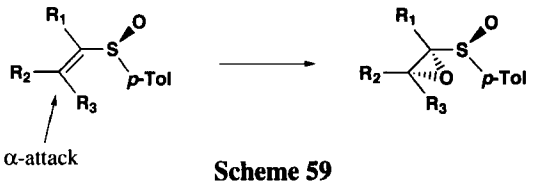
172 **173** **174**

Scheme 58

oxidized by KOO*t*-Bu in THF at 0° to give a 94 : 6 mixture of **173** and **174** (*Table 22*). The selectivity was reversed to favor the formation of **174** in the epoxidation of **172** (R_1 = CH_2=CH, R_2 = *n*-Bu, R_3 = H) with LiOO*t*-Bu. In most cases the epoxidation reactions favored nucleophilic attack of the peroxide to the less hindered face of the C=C which is in *s-trans* coplanar arrangement with respect to the S-O bond (*Scheme 59*).

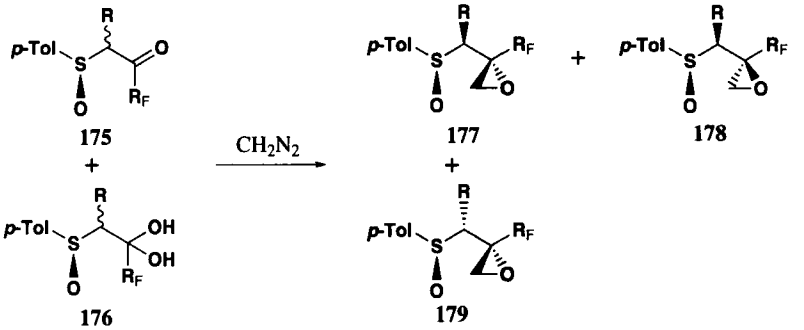
Table 22. Epoxidation of Vinyl Sulfoxides **172**

R_1	R_2	R_3	M	**173 : 174**
H	*n*-Bu	H	K	94 : 6
Ph	H	*n*-Bu	Na	91 : 9
CH_2=CH	*n*-Bu	H	Li	20 : 80
CH_2=CH	*n*-Bu	H	Na	90 : 10
CH_2=CH	H	*n*-Bu	Li	77 : 23
CH_2=CH	H	*n*-Bu	Na	95 : 5
CH_2=CH	Me	*n*-Bu	Na	95 : 5



Scheme 59

Enantiomerically enriched sulfinyl oxiranes can be prepared *via* diastereoselective methylene transfer from diazomethane to the carbonyl group of enantiomerically enriched β-ketosulfoxides. Bravo and Soloshonok *et al.* reported the reactions of diazomethane with α-alkyl and α-phenyl-substituted fluorinated (R_S)-β-ketosulfoxides to afford the corresponding diastereomerically and enantiomerically enriched epoxides (*Scheme 60*).[77] A keto/hydrate mixture of the sulfoxides **175** and



Scheme 60

176 was used to investigate methylene transfer reactions. The diastereomeric mixture of the products **177-179** was formed in good to high yields (75-94%) and with good to high diastereoselectivities (50-96% *de*), regardless of the configuration of the α carbons (*Table 23*).

Table 23. Stereoselective Methylene Transfer from CH_2N_2 to β-Ketosulfoxides **175**

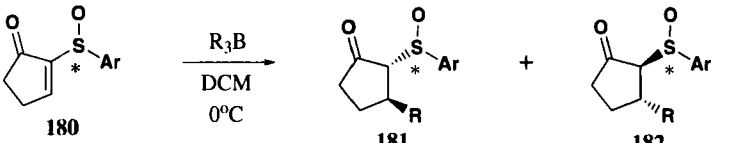
R	R_F	Solvent	Yield (%)	**177** (1'*S*,2*S*)	**179** (1'*R*,2*S*)	**178** (1'*S*,2*R*)	2*S* : 2*R*
Me	CF_3	MeOH	83	68	23	9	91 : 9
n-Pr	CHF_2	Et_2O	80	65	20	15	85 : 15
Allyl	$CClF_2$	MeOH	86	82	13	5	95 : 5
Ph	CH_2F	MeOH	91	17	78	5	95 : 5
Ph	CF_3	MeOH	88	25	75	-	> 98 : 2
Ph	CHF_2	MeOH	80	10	90	-	> 98 : 2

IX. RADICAL REACTIONS

1. Addition Reactions

Enantiomerically enriched sulfoxides have been used to control the configuration of newly formed stereogenic centers in free radical reactions. Toru *et al.* reported good to high diastereoselec-

tivities in the β-addition of alkyl radicals to enantiomerically enriched sulfinyl cyclopentenones **180** to give sulfinyl cyclopentanones with or without a Lewis acid (*Scheme 61*).[78] Reaction of **180a**, a



180 **181** **182**

a: Ar = (S)-p-Tol
b: Ar = (R)-3,5-di-tert-butyl-4-methoxyphenyl
c: Ar = (S)-2,4,6-triisopropylphenyl
d: Ar = (S)-2,4,6-trimethylphenyl

Scheme 61

cyclopentenone bearing a (*S*)-*p*-tolyl sulfinyl group, with tri-*tert*-butylborane and $TiCl_2(Oi\text{-}Pr)_2$ gave a 28 : 72 mixture of **181a** : **182a**, respectively, in moderate yield (60%). Reaction of **180b**, a cyclopentenone bearing a (*R*)-3,5-di-*tert*-butyl-4-methoxyphenyl sulfinyl group, with $(t\text{-}Bu)_3B$ in the absence of a titanium Lewis acid afforded a 38 : 62 mixture of **181b** : **182b**, resepectively, in higher yield (91%). With a titanium catalyst the diastereoselectivity of the same reaction was significantly improved (96% *de*) and reversed to give isomer **181b** as the major product (*Table 24*).

Table 24. Stereoselective Addition of Alkyl Radicals to Sulfinyl Enones **180**

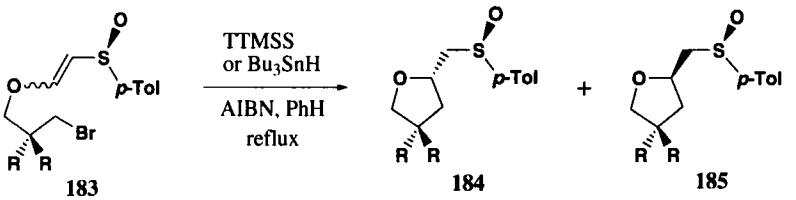
Enones	R	Lewis Acid	Time (h)	Yield (%)	**181** : **182**
180a	*t*-Bu	$TiCl_2(Oi\text{-}Pr)_2$	8	60	28 : 72
180b	*t*-Bu	----	8	91	38 : 62
180b	*t*-Bu	$TiCl_2(Oi\text{-}Pr)_2$	8	94	98 : 2
180b	*c*-C_6H_{11}	$TiCl_2(Oi\text{-}Pr)_2$	3	90	89 : 11
180b	*i*-Pr	$TiCl_2(Oi\text{-}Pr)_2$	10	61	84 : 16
180b	Et	$TiCl_2(Oi\text{-}Pr)_2$	12	72	77 : 23
180c	*i*-Pr	----	1	99	> 98 : 2
180c	Et	----	1	94	94 : 6
180d	*t*-Bu	----	8	66	> 98 : 2
180d	*c*-C_6H_{11}	----	3	71	> 98 :2
180d	*i*-Pr	----	2	94	> 98 :2
180d	Et	----	6	95	> 98 : 2

Reaction of **180** with various trialkylboranes in the presence of a Lewis acid favored the formation of isomer **181** with moderate to good diastereoselectivities (54-78% *de*). Reactions of sulfinyl cyclopentenones bearing a (*S*)-2,4,6-triisopropylphenyl (**180c**) or a (*S*)-2,4,6-trimethylphenyl (**180d**) group with trialkylboranes in the absence of the Lewis acid gave very high diastereoselectivities (88 to 96% *de*). The stereochemical outcomes were rationalized by invoking a transition state

where the S-O and C=O bonds are antiperiplanar to each other. Toru *et al.* found that free radical addition to enantiomerically enriched acyclic sulfinyl enones were not selective and that Pummerer rearrangement products were formed. [78]

2. Cyclization Reactions

Malacria *et al.* have demonstrated that a sulfinyl group of an enantiomerically enriched α,β-unsaturated sulfoxide is capable of controlling the configuration of the products in a free radical intramolecular cyclization.[79] Enantiomerically enriched β-alkoxy vinyl sulfoxides **183** reacted with either tris(trimethylsilyl)silane (TTMSS) or tributyltin hydride in benzene at reflux to give tetrahydrofurans in high yields and with good to excellent diastereoselectivities (*Scheme 62*). The (*E*)-vinyl



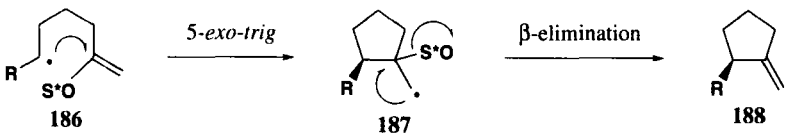
Scheme 62

sulfoxide of **183** (R = H) reacted with TTMSS and AIBN to generate a 70 : 30 mixture of diastereomers **184** (R = H) : **185** (R = H), respectively, in 89% yield while the (*Z*)-vinyl sulfoxide of **183** (R = Me) gave a 12 : 88 mixture of **184** (R = Me) : **185** (R = Me), resepectively, in 94% yield (*Table 25*). Isomer **184** (R = Me) was also formed in the cyclization of the (*E*)-vinyl sulfoxide **183** (R = Me) in 93% yield and in 64% *de*, while **184** (R = Me) was formed in the cyclization of the (*Z*)-vinyl sulfoxide **183** (R = Me) in 90% yield and ≥ 96% *de*. Malacria proposed a transition state model in which the vinyl sulfoxide moiety adopts a *s-trans* conformation to avoid the repulsive interaction between the S-O bond and the β-substituent to explain the stereochemical outcomes.

Table 25. Stereoselctive Free Radical Cyclization of α,β-Unsaturated Sulfoxide **183**

R	C=C	Yield (%) (TTMSS)	**184** : **185**
H	*E*	89	70 : 30
H	*Z*	94	12 : 88
Me	*E*	93	82 : 18
Me	*Z*	90	≥ 2 : 98

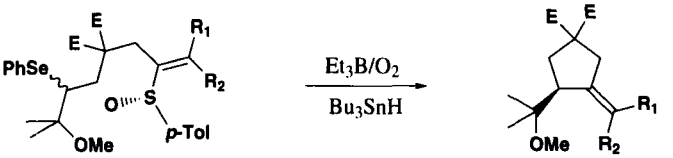
Malacria *et al.* reported a methodology that allows for spontaneous removal of the chiral sulfinyl auxiliary after the formation of the enantiomerically enriched five-membered rings.[80] This one-pot method combines the free radical cyclization of **186** to form the ring in **187** and a subsequent β-elimination to remove the chiral auxiliary to afford the product **188** (*Scheme 63*).



S*O = homochiral sulfoxide auxilliary

Scheme 63

This methodology gives more satisfactory results on terminally substituted vinyl sulfoxides. For example, the vinyl sulfoxide **189** (R_1 = $CH(CH_3)_2$, R_2 = H) underwent *anti*-Michael 5-*exo-trig* radical cyclization and β-elimination at –78° to afford the (*S*)-cyclopentyl derivative **190** (R_1 = $CH(CH_3)_2$, R_2 = H) in 60% yield and 54% *ee* (*Scheme 64*). Cyclization of the *gem*-dimethyl vinyl sulfoxide **189** (R_1 = R_2 = Me) gave the (*S*)-isomer **190** (R_1 = R_2 = Me) in 72% yield and in >96% *ee*. The yield was improved to 93% without the loss of diastereoselectivity when the reaction was conducted at 0°. Inversion of configuration of the product took place when the very bulky Lewis acid methylaluminum *bis*(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) was used in the cyclization of the *gem*-dimethyl vinyl sulfoxide **189** (R_1 = R_2 = Me) to afford the (*R*)-isomer **190** (R_1 = R_2 = Me) in 52% yield and 92% *ee*.

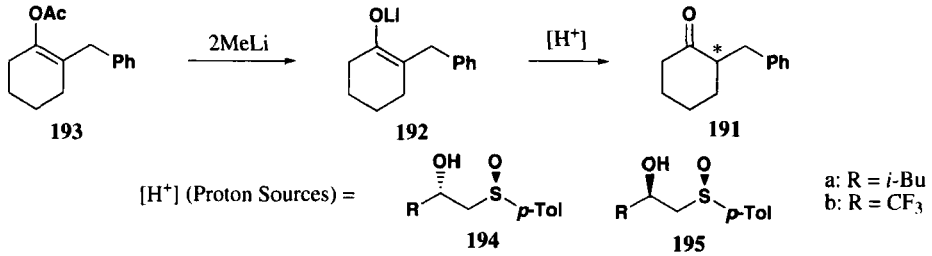


189 (E = CO_2Et) (*S*)-**190**

Scheme 64

X. PROTONATION REACTIONS

Enantiomerically enriched β-hydroxy sulfoxides, readily prepared by the diastereoselective reduction of β-ketosulfoxides (Section V), are efficient chiral proton sources for the enantioselective synthesis of cyclic carbonyl compounds **191** from the prochiral lithium enolate precursors. Kosugi *et al.* investigated the enantioselective protonation of the regiochemically pure lithium enolate **192**, generated from 1-acetoxy-2-benzyl-1-cyclohexane **193**, with enantiomerically enriched β-hydroxy sulfoxides **194** and **195** (*Scheme 65*).[81] In general, higher diastereoselectivities were achieved for β-hydroxy sulfoxides **194** than **195** in enantioselective protonations. Treatment of lithium enolate **192**



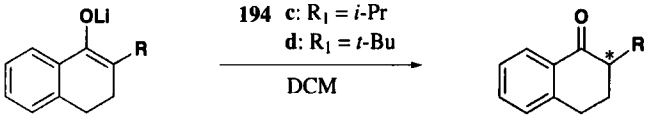
Scheme 65

with β-hydroxy ketone **195a** (R = *i*-Bu) in ether gave the (*R*)-isomer of cyclohexanone **191** in 77% yield and 43% *ee*; changing the solvent from ether to ether-dichloromethane afforded the opposite (*S*)-isomer of **191** in 87% yield and 26% *ee*. The highest enantioselectivity (97% *ee*) was observed when β-hydroxy sulfoxide **194b** (R = CF_3) was used as the chiral proton source for the protonation of **192** in Et_2O-DCM at –100 to –50°; the (*S*)-isomer of **191** was provided in 93% yield (*Table 26*). The (*R*)-isomer was afforded in 84% yield and 79% *ee* when the sulfoxide **195b** (R = CF_3) was used under the same conditions.

Table 26. Enantioselective Protonation of Enolate **192** with β-Hydroxy Sulfoxides

H^+ Source	Conditions	Yield (%)	*ee* (%)	Configuration
194a	Et_2O-DCM (-100 to 0°)	81	90	(*S*)
194b	Et_2O-DCM (-100 to 0°)	94	92	(*S*)
194b	Et_2O-DCM (-100 to -50°)	93	97	(*S*)
194b	Et_2O (-100 to -50°)	81	87	(*S*)
195a	Et_2O (-100 to 0°)	77	43	(*R*)
195a	Et_2O-DCM (-100 to 0°)	87	26	(*S*)
195b	Et_2O-DCM (-100 to -50°)	84	79	(*R*)

Asensio extended the use of (S,R_S)-sulfoxides **194c** (R_1 = *i*-Pr) and **194d** (R_1 = *t*-Bu) as a chiral proton source to the enantioselective protonation of the lithium enolates **196**, in the presence of lithium bromide or lithium chloride (*Scheme 66*).[82] In the presence of LiBr, the sulfoxide **194c** enantioselectively protonated the enolate **196a** at –100° to give the corresponding (*R*)-isomer of **197** in



196 a: R = Me
b: R = Bn

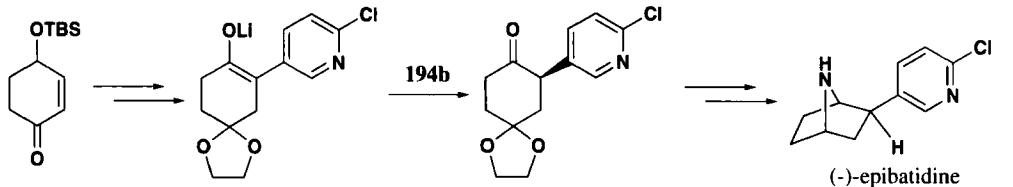
197

Scheme 66

83% *ee* (*Table 27*). Surprisingly, the enantioselectivity was slightly higher (90%) when the reaction took place at –50°. In the presence of LiCl, the protonation of **194a** gave the (*R*)-isomer of **197a** in lower *ee* (54%). Protonation of enolate **196a** with sulfoxide **194d** in the presence of LiBr and at a somewhat higher temperature (–100 to –50°) gave the (*R*)-isomer of **197a** in 65% *ee*. Protonation of enolate **196b** with sulfoxide **194c** in the presence of LiBr at –100° gave the corresponding (*S*)-isomer of **197b** in 76% *ee*. Selectivity was dramatically reduced when the same reaction was carried out at –25°. Kosugi *et al.* successfully applied this methodology to the asymmetric synthesis of (-)-epibatidine (Scheme 67).[83] Their synthesis involved the enantioselective protonation of **198** to give the cyclohexanone product **199** in 82% *ee* (Scheme 67).

Table 27. Enantioselective Protonation of Enolate with β-Hydroxy Sulfoxides **194**

Enolate	H^+-Source	Temp (°C)	Additive	*ee* (%)	Configuration of **197**
196a	194c	-100	LiBr	83	(*R*)
196a	194c	-50	LiBr	90	(*R*)
196a	194c	-50	LiCl	54	(*R*)
196a	194d	-100	LiBr	82	(*R*)
196a	194d	-50	LiBr	65	(*R*)
196b	194c	-100	LiBr	76	(*S*)
196b	194c	-50	LiBr	84	(*S*)
196b	194c	-25	LiBr	3	(*S*)



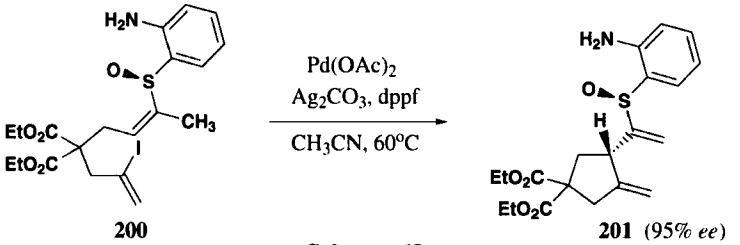
198 **199** (82% *ee*)

Scheme 67

XI. MISCELLANEOUS REACTIONS

1. Intermolecular Heck Reactions

The Heck reaction is widely used for C-C bond formation that couples a vinyl or aryl halide (or anhydride) with an alkene in the presence of an appropriate palladium catalyst. Stereoselective Heck reactions usually involve the use of palladium complexes with chiral ligands. Carretero *et al.* successfully used chiral 2-(*N,N*-dimethylamino)phenyl sulfinyl group as a chiral auxiliary in an intramolecular Heck reaction to construct a five-membered ring.[84] Sulfoxide **201** was formed in 81% yield and 95% *ee* from the cyclization of the (*Z*)-vinyl sulfoxide **200** (*Scheme 68*). Chiral *tert*-butylsulfinyl (66% *de*) and *p*-tolylsulfinyl (8% *de*) groups were shown to be less effective for asymmetric induction in this intramolecular cyclization. Cyclization of the (*E*)-vinyl sulfoxide of **200** was found to give **201** in 60% *de*.

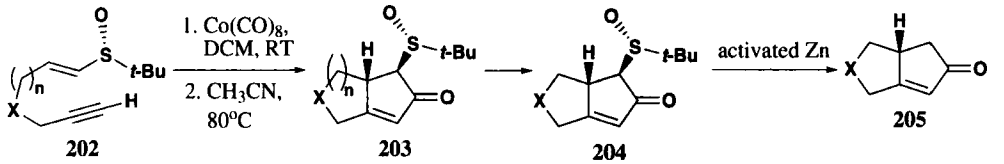


200 **201** (95% *ee*)

Scheme 68

2. Intramolecular Pauson-Khand Reactions

The Pauson-Khand reaction involves the $Co(CO)_8$-catalyzed coupling of an alkene and an alkyne. The intramolecular version is useful for the synthesis of cyclopentenones. Introduction of a chiral auxiliary that is attached to either the alkene or the alkyne in the Pauson-Khand reaction leads to enantiomerically enriched cyclopentenones. Carretero *et al.* investigated the intramolecular Pauson-Khand reactions of enantiomerically enriched sulfinyl enynes **202** and the cyclization was found to be highly stereoselective, leading to **203** in greater than 96% *ee* (*Scheme 69*).[85] The (*E*)-enyne **202** (n = 1, X = CH_2, R = H) underwent cyclization to give the corresponding cyclopentenone product **203** (n = 1, X = CH_2, R = H) in 50% yield and 96% *ee*. When the terminal alkyne was substituted, the intramolecular Pauson-Khand reaction did not take place. Desulfinylation of the cyclization products **204** afforded the enone **205** in high yields (92-96%) and without loss of enantiomeric purity.



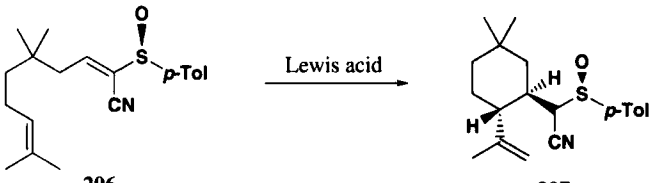
202 **203** **204** **205**

n = 1, 2
X = CH_2, CMe_2, $C(CO_2Et)_2$, *N*-Boc

Scheme 69

3. Intramolecular Ene Reactions

Intramolecular ene reactions are useful in the synthesis of enantiomerically enriched cyclic molecules. Hiroi *et al.* developed a novel method for asymmetric cyclization *via* an intramolecular ene reaction using a (*S*)-*p*-tolylsulfinyl group to control the stereochemistry of the cyclization product.[84] The enantiomerically enriched α-cyanovinyl sulfoxide **206** underwent Lewis acid-catalyzed intramolecular asymmetric ene reaction to afford the product **207** with high diastereoselectivity (62.9-97.3% *de*). The highest selectivity was achieved when the ene reaction took place in the presence of Et_2AlCl in methylene chloride at -20° (*Scheme 70*). A transition state model where the Lewis acid metal



206 **207**

Scheme 70

chelates with the sulfinyl oxygen and the cyano nitrogen to form a chair-like six-membered ring was proposed to explain the observed stereochemical outcomes (*Figure 10*).

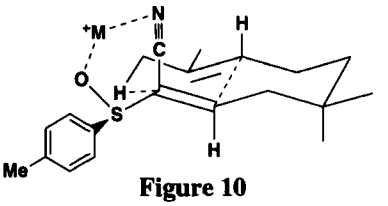
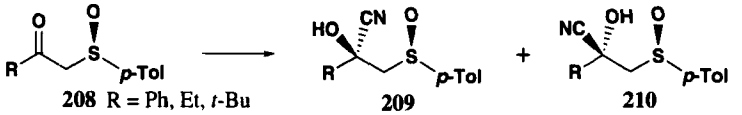


Figure 10

4. Hydrocyanation Reactions

The presence of a sulfinyl auxiliary can also have a significant impact on the diastereoselectivities of hydrocyanation reactions of β-ketosulfoxides. Ruano and Rodriguez *et al.* studied the hydrocyanation of enantiomerically enriched β-ketosulfoxides with Et_2AlCN to form sulfinyl cyanohydrins in 85-96% yields and > 96% diastereoselectivities (*Scheme 71*).[87] The phenyl β-ketosulfoxide of **208** (R = Ph) reacted with Et_2AlCN to give predominantly the (*S*)-isomer **209** (R = Ph) with very little (*R*)-isomer **210** in 87% yield; the addition of zinc halide had no effect on the reaction. However, the yield of **209** was improved slightly (90%) in the presence of a magnesium halide. Under the same conditions, with or without a Lewis acid, other β-ketosulfoxides of **208** (R = Et, *t*-Bu) also gave **209** in very good yields. These enantiomerically enriched cyanohydrins can be easily transformed to α-hydroxy acids, vicinal diols, α-hydroxy ketones, ethanolamines, amino acids, etc. The stereochemical outcomes in the hydrocyanation were consistent with those in the hydride reduction. However, the presence of a Lewis acid in hydrocyanation did not reverse the diastereoselectivities.



Scheme 71

XII. CONCLUSIONS

The utility of enantiomerically enriched sulfoxides as asymmetric induction agents in stereoselective syntheses has been documented in this review. Chiral sulfinyl auxiliaries can be readily introduced to effect diastereomeric induction and subsequently removed to afford the molecule of interest. The stereochemical course can be successfully navigated by the configuration of the sulfoxide and the reaction conditions. New examples and methodologies using enantiomerically enriched sulfoxides for asymmetric syntheses continue to emerge in the literature. The successful use of enantiomerically enriched sulfoxides for the total synthesis of natural products will undoubtedly stimulate the investigation of the new methodologies.

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