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DIASTEREOSELECTIVE REACTIONS OF SULFOXIMINES

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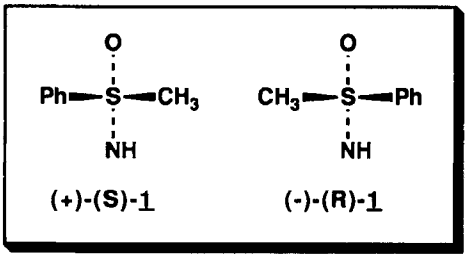
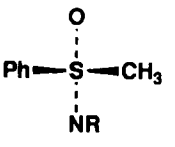
This review will deal exclusively with the diastereoselective reactions of chiral sulfoximine reagents that lead to the formation of new chiral C–C, C–N, and C–O bonds. The diastereoselective reactions of lithiated sulfoximines with electrophiles, including carbonyl compounds, imines, Michael acceptors and alkyl halides are discussed. The diastereoselective conjugate addition reactions of vinyl sulfoximines with various carbon, nitrogen and oxygen nucleophiles are also addressed. A number of studies reported here were performed on racemic substrates but only one enantiomer has been shown to assist the reader.

Key words: Sulfoximines, addition reactions, conjugate addition, Diels–Alder reaction, osmylation and reduction.

CONTENTS

Enantiomerically pure (+)-(S)- and (−)-(R)-*S*-methyl *S*-phenyl sulfoximine **1** are readily available via the resolution of racemic **1** with (+)- or (−)-10-camphorsulfonic acid.[1,2] The *N*-methyl,[2,3] *N*-tosyl[4] and *N*-silyl[5,6] derivatives **2a–f** are conveniently prepared from **1** and have been employed in diastereoselective synthesis.[7]



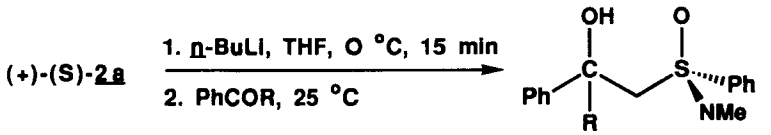


a. R = Me
b. R = Tos
c. R = TMS
d. R = Me_2Bu^tSi
e. R = Me_2Ph_2Si
f. R = Bu^tPh_2Si

1. DIASTEREOSELECTIVE 1,2-ADDITIONS OF LITHIATED SULFOXIMINES TO CARBONYL COMPOUNDS

1.1. Addition to Ketones

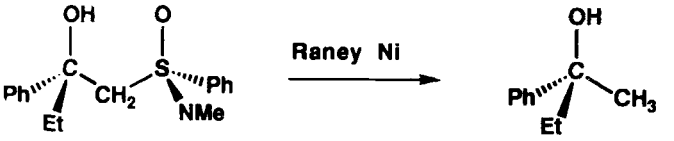
In 1982, Johnson[8] and co-workers reported the condensation reactions of (+)-(S)-*N*,*S*-dimethyl *S*-phenyl sulfoximine (**2a**) with various aldehydes and prochiral ketones. The reaction of lithiated **2a** with phenyl aryl ketones (PhCOR, R = Me, Et, *n*-Pr, *n*-Bu and *c*-C_6H_{11}) gave a mixture of two diastereomeric *β*-hydroxy sulfoximine adducts **3** with modest diastereoselectivity. Unfortunately the diastereoselectivities of all these reactions were not documented.



3

R	Diastereoselection	Yield(%)
Me	67:33	85
Et	60:40	88

While these diastereoselectivities were modest, the diastereomeric adducts **3** could be readily separated by column chromatography in good overall yields. The resulting diastereomerically pure adducts could be converted to chiral tertiary alcohols in high enantiomeric purity (87%–100%). For example, the higher R_f diastereoisomer **3** (R = Et) from the reaction of lithiated **2a** and ethyl phenyl ketone was converted to enantiomerically pure (+)-(S)-2-phenyl-2-butanol **4** by reductive desulfurization with Raney nickel.[8]



3 (2S,SS) (+)-(S)-4 (100% ee)

More recently Pyne and Dong have found that a much improved diastereoselection could be obtained with the more sterically demanding *N*-*t*-butyldiphenylsilyl *S*-methyl *S*-phenyl sulfoximine **2f**.[9] From an inspection of Table 1 it is evident, for the reaction of lithiated **2f** with ketones ($RCOCH_3$), that the diastereoselection increases as the steric bulk of the R group of the ketone increases. The relative stereochemistry of the major diastereomeric adducts in the case of R = *t*-Bu and Ph was determined by a single crystal X-ray structural analysis.[9]

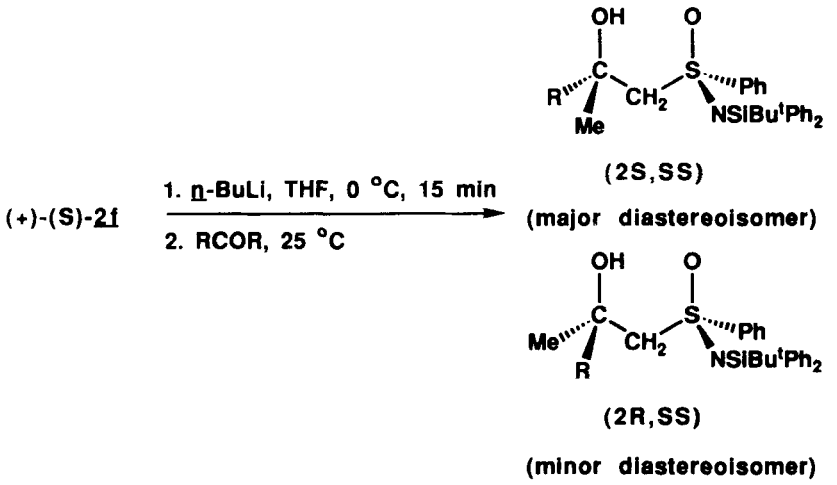
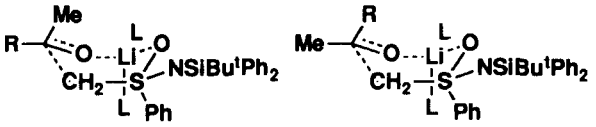


Table 1. Reaction of Lithiated **2f** with Ketones

R	Diastereoselection	Yield (%)
Et	80:20	69
i-Pr	79:21	43
Ph	91:9	65
t-Bu	98:2	63

The stereochemical outcome can be readily rationalized by invoking the two competing boat transition states **3A** and **3B** (refer to Scheme 1 for further details). The difference in free energy between **3A** and **3B** and hence the diastereoselectivity, would be expected to increase as the steric demand of the R group of the ketone increases due to an increasing flagpole interaction between R and the sulfoximine oxygen in **3B**.



3A **3B**

1.2. Addition to Aldehydes

The reaction of lithiated **2a** with aldehydes also proceeded with modest diastereoselectivity (Table 2).[8] In these cases the resolution of the diastereomeric adducts was difficult, however reductive cleavage of the diastereomeric product mixture gave secondary alcohols in 25–46% ee. For example, treatment of lithiated (+)-(S)-**2a** of 85% enantiomeric purity (e.e.) with benzaldehyde gave a mixture (3 : 1) of diastereomeric adducts. Reductive desulfurization of this mixture gave (+)-(R)-1-phenylethanol in 37% ee. The stereochemical outcome of these reactions can be rationalized as arising from a chelated boat conformation analogous to **8** in Scheme 1.

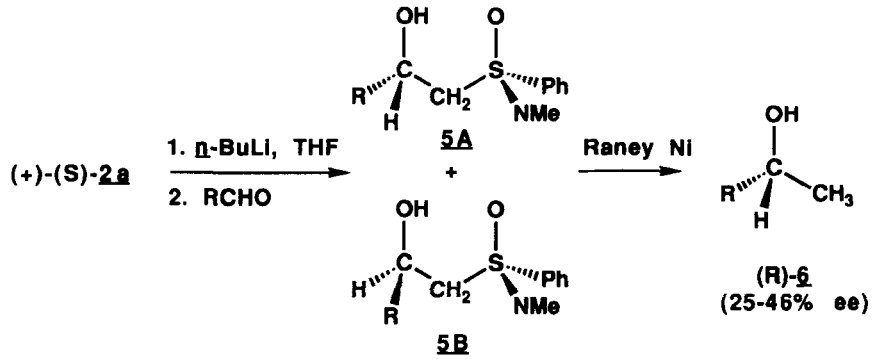


Table 2. Reaction of Lithiated **2b** with Aldehydes

Aldehyde	Optical Purity (%) of **2a**	Diastereoselection **5A:5B**	**6** (% ee)	Yield (%)
benzaldehyde	85	75:25	37	78
heptanal	85	60:40	25	70
3-methylbutanal	92	71:29	30	69
pivaldehyde	95	74:26	46	65

More recently Hwang[5] and Pyne[6] have reported much higher diastereoselectivities employing the *N*-silylated analogues of **2a**. While racemic *N*-trimethylsilyl *S*-methyl *S*-phenyl sulfoximine **2d** showed a similar diastereoselection to **2a** in its condensation reactions with aldehydes, the sterically more hindered *t*-butyldimethylsilyl, methyldiphenylsilyl and *t*-butyldiphenylsilyl derivatives **2d**, **2e** and **2f** exhibited much improved product diastereoselections. Table 3 clearly demonstrates the effect of the steric demand of the *N*-silyl group on the diastereoselectivity of the 1,2-addition reaction of the lithiated sulfoximines **2(a,c–f)** with pivaldehyde. Progressing from the least sterically demanding *N*-trimethylsilyl derivatives **2d** to the highly sterically demanding *N*-*t*-butyldiphenylsilyl derivative **2f** the product diastereoselection increased dramatically from 71 : 49 to 94 : 6. The *N*-methyl sulfoximine **2a** was slightly better than its *N*-trimethylsilyl counterpart.

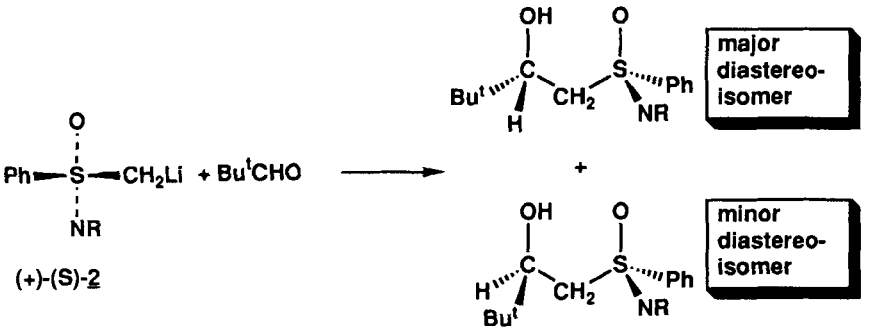


Table 3. Effect of the *N*-Substituent of **2** on the Diastereoselection for the Condensation of **2** with Pivaldehyde

Sulfoximine* R	Diastereoselection	Reference
Me	74:26	Johnson[8]
$SiMe_3$	71:29	Hwang[5]
$SiMe_2Bu^t$	89:11	Hwang[5]
$SiMePh_2$	89:11	Hwang[5]
$SiBu^tPh_2$	94:6	Pyne[6]

*In some cases racemic **2** was employed, in these cases the products were also racemic.

Lithiated **2f** showed high product diastereoselection with five representative aldehydes as shown in Table 4.[6] The diastereoselectivity was found to be independent upon the aldehyde (RCHO) substituent R. A similar trend was found with the related sulfoximines **2a** and **2c** (Table 5).

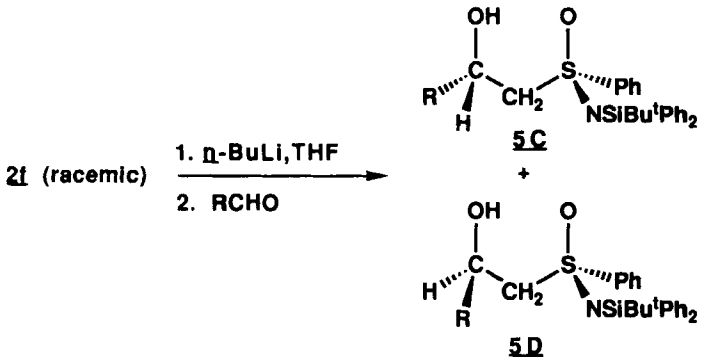


Table 4. Reaction of Lithiated **2f** with Aldehydes (RCHO)

Entry	R of Aldehyde	Yield (%)[a]	5C : 5D[b]
1	Et	82	92 : 8
2	*i*-Bu	79	96 : 4
3	*i*-Pr	74	93 : 7
4	Ph	89	91 : 9
5	*t*-Bu	86	94 : 6

[a] After purification by column chromatography.
[b] Determined by ^{1}H NMR spectroscopy (400 MHz) on the crude reaction mixture.

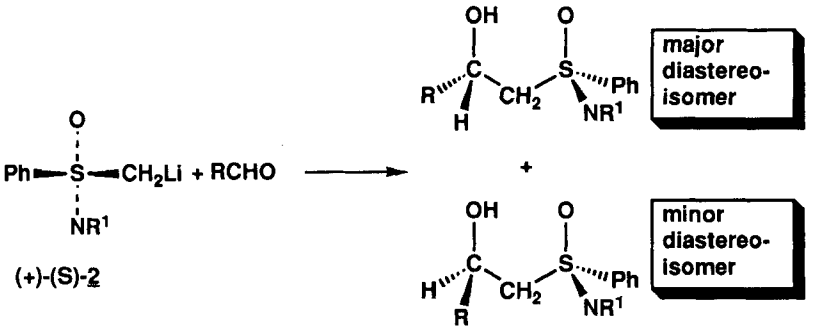


Table 5. Effect of the R Substituent of the Aldehyde upon Product Diastereoselection in the Condensation Reactions of **2**

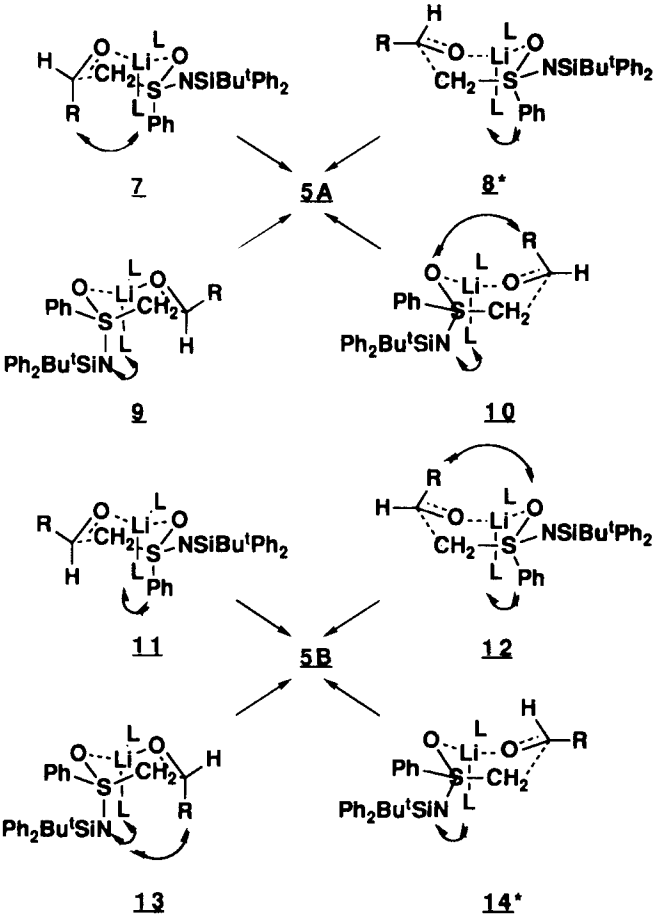
R^1*	R	Diastereoselection
Me	Ph	3:1
Me	*t*-Bu	2.8:1
$SiMe_3$	Ph	2.8:1
$SiMe_3$	*t*-Bu	2.5:1
$SiBu^tPh_2$	Ph	91:9
$SiBu^tPh_2$	*t*-Bu	94:6

* In some cases racemic **2** was employed, in these cases the products were also racemic.

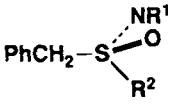
From X-ray structural analysis the major adduct between lithiated **2c** and acetaldehyde was determined to have the 2R*, SR* relative stereochemistry, identical to that found by Johnson for the reaction of **2a** with aldehydes.[8] Cyclic chair transition states for the reaction of **2c–e** with aldehydes, that involve chelation of both the aldehyde and sulfoximine oxygens or the aldehyde oxygen and the sulfoximine nitrogen by lithium cation, have been proposed by Hwang.[5] In the case of lithiated **2f**, chelation to the highly sterically hindered sulfoximine nitrogen would seem highly unlikely.

The four possible chair and four possible boat like transition states for the reaction of lithiated **2f** with aldehydes that involve chelation of both the aldehyde and sulfoximine oxygens by lithium cation are shown in Scheme 1. The chair transition states **7**, **9**, **11** and **13** suffer from severe 1,3-pseudo-diaxial like interactions and the boat like transition states **10** and **12** suffer from a flagpole interaction between the aldehyde substituent (R) and the sulfoximine oxygen and therefore these transition states would seem energetically unlikely. The preference for the diastereomeric adduct **5A** over **5B** can be readily accounted for by considering the competing boat transition states **8** and **14**. Transition state **14** would be expected to be energetically less favourable than **8** if one considers the steric interaction between the solvent ligand on the lithium cation and the sterically demanding $NSiBu^tPh_2$ group in **14** and that between the solvent ligand (L) on the lithium cation and the less sterically demanding SPh group in **8**. One would expect that as the steric demand of the *N*-substituent of the sulfoximine was increased, then transition state **14** would be destabilized relative to that of **8** and a higher production diastereoselection would result. This is indeed the case. Furthermore, the difference in free energy between transition states **8** and **14** would be expected to be largely independent of the steric demand of the aldehyde substituent (R) since in these two transition states R experiences little steric interaction with the large substituents (Ph, Bu^tPh_2SiN) on sulfur.

Scheme 1 (L = solvent ligand molecules)

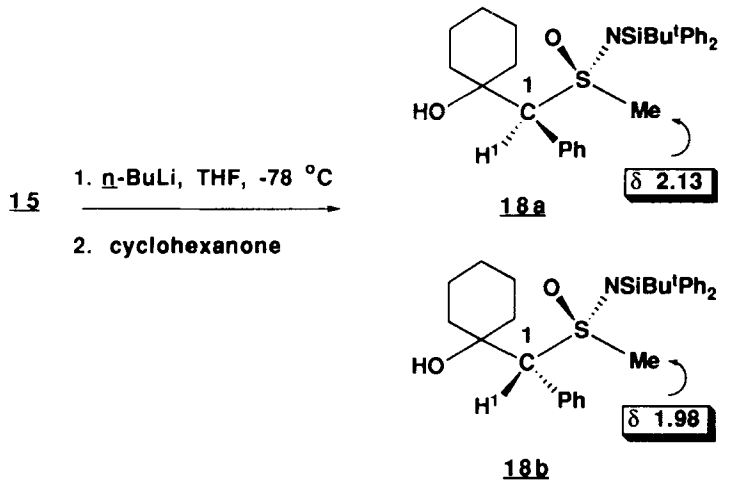


These studies have been extended to the reaction of lithiated racemic *N*-*t*-butyldiphenyl *S*-benzyl *S*-methyl sulfoximine **15** and its SPh analogue **17**.[10]



15 R^1 = $SiBu^tPh_2$, R^2 = Me
16 R^1 = $SiBu^tMe_2$, R^2 = Me
17 R^1 = $SiBu^tPh_2$, R^2 = Ph

The reaction of lithiated **15** with cyclohexanone proceeded with high diastereoselectivity (94:6) but the yield was low (60%) and starting materials were always recovered, probably as a result of a competing proton transfer reaction between the two reactants.



The stereochemical assignment of the major (**18a**) and minor diastereoisomers (**18b**) from this reaction was based upon their respective SMe chemical shifts and the X-ray structural analysis of the major diastereomeric adduct of lithiated **15** and propanal. In these two cases the major diastereoisomer showed an SMe resonance at lower field with respect to that of its minor diastereoisomer.[10]

The results of the reaction of lithiated **15** with various aldehydes are reported in Table 6. In each case studied all four possible racemic diastereomeric products were formed. In the case of benzaldehyde a much higher diastereoselectivity could be realized if the aldehyde was precomplexed with BF_3 etherate prior to addition to lithiated **15**. The major (**19s**) and the second most prominent diastereomeric products (**20a**) had the syn ($J_{1,2}$ = 1.8–2 Hz) and anti ($J_{1,2}$ = 9.3–10 Hz) relative stereochemistry, respectively,[11] while the former diastereoisomer showed a SMe resonance at lower field relative to the latter.

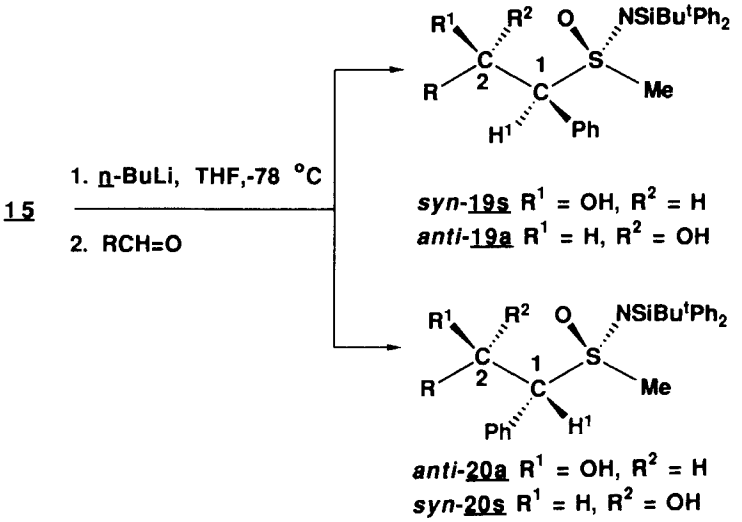
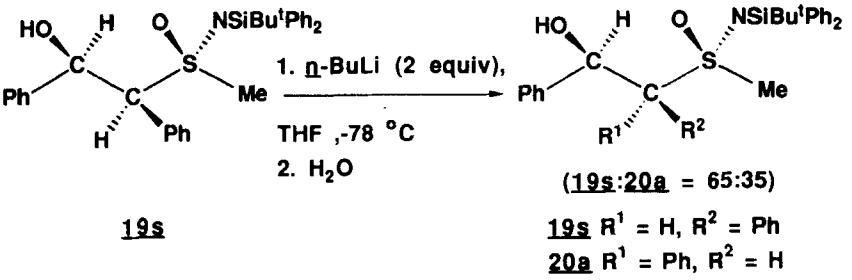


Table 6. Reactions of Lithiated **15** and Aldehydes.

Aldehyde	Yield (%)	Diastereoselection			
		19s:	**20a:**	**20s:**	**19a**
PhCHO	95	48:	26:	10:	16
PhCHO·BF_3	95	67:	28:	1:	4
EtCHO	96	77:	18:	4:	1
i-PrCHO	91	70:	16:	6:	8
t-BuCHO	90	75:	16:	1:	8

The relative 1S*,2R*,SS* stereochemistry of **19s** (R = Et) was unequivocally determined by single crystal X-ray analysis.[10] An estimate of the dihedral angle between C^1–H^1 and C^2–H^2 in **19s** (R = Et) from the structural analysis ($\phi_{1,2}$ *ca.* 60°) and the value of the H^1,H^2 coupling constant ($J_{1,2}$ = 1.8 Hz) in deuterochloroform suggest a similar conformation for this compound in the solid state and in solution.

The relative stereochemistry of **20a** (R = Ph) was determined from an experiment in which diastereomerically pure **19s** (R = Ph) was first treated with 2 equiv. of *n*-BuLi (−78 °C, 1 h) and the resulting dianion was then quenched with water. This reaction produced a 65 : 35 mixture of **19s** (R = Ph) and **20a** (R = Ph), respectively. This result clearly indicated that **19s** (R = Ph) and **20a** (R = Ph) differ only in relative stereochemistry at C^1. An analogous experiment with 1 equiv. of *n*-BuLi resulted in unchanged **19s** (R = Ph) and clearly indicated that interconversion of **19s** and **20a** via a retroaldol type process was not occurring at −78 °C. The relative stereochemistry of the two minor diastereoisomers **20s** and **19a** were based upon the chemical shift of their respective SMe groups and the magnitude of $J_{1,2}$.



19s

(**19s**:**20a** = 65:35)

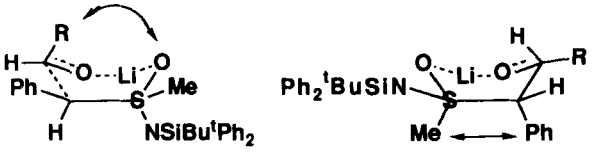
19s R^1 = H, R^2 = Ph

20a R^1 = Ph, R^2 = H

The reaction between lithiated *N*-*t*-butyldiphenyl *S*-benzyl *S*-phenyl sulfoximine **17** and benzaldehyde gave only three out of the possible four diastereomers in the ratio of 82 : 14 : 4 and in good yield. The major diastereoisomer had the syn relative stereochemistry ($J_{1,2}$ = 1.8 Hz).

While the stereochemistry of the major diastereomeric adducts from the reaction of lithiated **15** and carbonyl compounds can be rationalized as arising from cyclic boat transition states (**21a,b**), the transition state **21b**, which is analogous to the transition state **8** (Scheme 1) proposed for the reaction of **2f** with aldehydes, appears unlikely due to a number of severe 1,2-steric interactions, in particular the SMe group and the

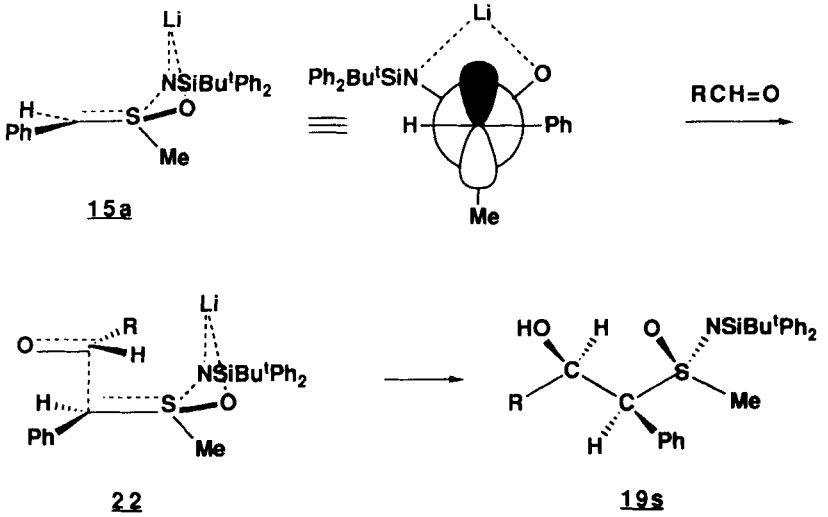
benzylic phenyl group are eclipsed in **21b**. Indeed when the aldehyde is precomplexed with BF_3 then a cyclic transition state cannot occur.



21a **21b**

We suggest that the structure of lithiated **15**, as shown by structure **15a** (only the monomeric species is considered) in Scheme 2, may be similar to that of lithiated benzyl phenyl sulfone.[12] One would expect the benzylic carbon of **15a** to be close to planar and the phenyl substituent to be anti to the bulky *N*-*t*-butyldiphenylsilyl moiety. The non-bonding orbital at the benzylic carbon would be approximately coplanar with the S–CH_3 σ bond due to a stabilizing $n_c \rightarrow \sigma^*$ s–c interaction. Electrophilic attack on **15a** should occur from the less hindered diastereoface, i.e. anti to the S–CH_3. An open transition state **22** in which R of the aldehyde and the phenyl substituent of **15a** are anti is consistent with the stereochemical outcome.

Scheme 2



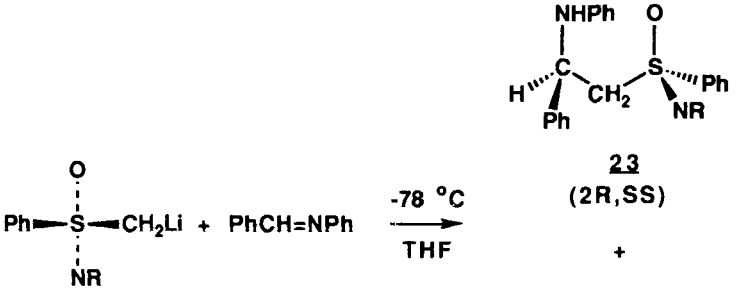
15a **22** **19s**

The major anti diastereoisomer **20a** most likely arises from an open transition state (involving attack of the aldehyde from the same diastereoface of **15a** as the SMe group) while the minor syn and anti diastereoisomers (**20s** and **19a**) most likely arise from a chelated chair transition state in which R of the aldehyde (RCHO) is pseudoequatorial. Consistent with this proposal is the observation that when PhCHO·BF_3 was employed

then the yield of **20a** was essentially unaffected while the combined yield of **19s** and **20a** decreased to about 5%.[10]

2. DIASTEREOSELECTIVE 1,2-ADDITIONS OF LITHIATED SULFOXIMINES TO IMINES

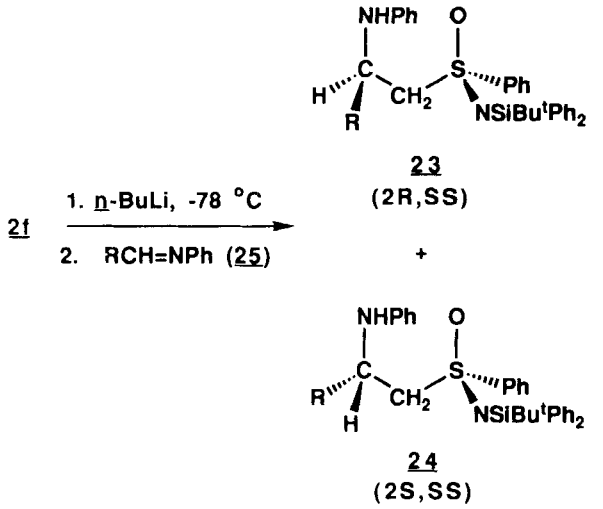
When a THF solution of lithated racemic **2a** was quenched with *N*-benzylideneaniline at −78 °C a 50 : 50 mixture of the two possible diastereoisomeric adducts **23** (R = Me) and **24** (R = Me) was obtained in 96% yield.[6] In contrast, the analogous reaction of the *N*-*t*-butyldiphenylsilylsulfoximine **2f** gave a 88 : 12 mixture of the diastereomeric products **23** (R = $SiBu^tPh_2$) and **24** (R = $SiBu^tPh_2$), respectively.[6]



2a R = Me
2f R = $SiBu^tPh_2$

Sulfoximine	Diastereoselection 23:24
2a	50:50
2f	88:12

It is again apparent that a highly sterically demanding substituent is required at the sulfoximine nitrogen to ensure high diastereoselectivity in these reactions. The diastereoselectivities for the reaction of lithiated **2f** with other imines of structure RCH=NPh is presented in Table 7. For these reactions the product diastereoselection progressively decreases as the steric demand of the substituent R increases. When R was relatively small (R = Et, *i*-Bu; entries 1–2) then high product diastereoselection (95 : 5) was observed, whereas when R was sterically demanding (R = *t*-Bu, entry 6) then the reaction proceeded with modest diastereoselectivity (79 : 21). When R was intermediate in size, that is *i*-Pr, phenyl or 2-furyl, then the product diastereoselection was consistently 90 : 10 (entries 3–5). The relative 2R*,SS* stereochemistry of **23** (R = Et) was unequivocally determined by a single crystal X-ray structure analysis.[13]



Since the imines must have the (*E*)-geometry, only four possible chelated cyclic transition states are available for the reaction of lithiated **2f** and imines, two chair (**26** and **28**) and two boat transition states (**27** and **29**).[11] The two possible chair transition states suffer from severe 1,3-pseudodiaxial like interactions and therefore would seem energetically unlikely. Clearly the preference for the diastereomeric adduct **23** over **24** suggests that the boat transiton state **27** is favoured over its boat counterpart **29**. This would seem likely when one considers the steric interaction between the solvent ligand on the lithium cation and the sterically demanding $NSiBu^tPh_2$ group in **29** and that between the solvent ligand (L) on the lithium cation and the less sterically demanding SPh group in **27**. One would expect that as the steric demand of the *N*-substituent of the sulfoximine was increased then transition states **27** and **29** would be destabilized (due to an increased flagpole interaction between R of the imine and the sulfoximine nitrogen)

Table 7. Reactions of Lithiated **2f** with Imines **25**

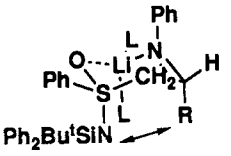
Entry	R of Imine **25**[a]		Yield (%)[b]	Diastereoselection **23**:**24**[c]
1	Et	(**25a**)	68	94:6
2	*i*-Bu	(**25b**)	76	95:5
3	2-furyl	(**25c**)	90	90:10
4	*i*-Pr	(**25d**)	70	90:10
5	Ph	(**25e**)	90	88:12
6	*t*-Bu	(**25f**)	24	79:21

[a] Reaction temp. −45 °C for a period of 2 h except for entries 3 and 5 (−78 °C, 1 h).

[b] After column chromatography.

[c] Determined by ^1H NMR spectroscopy (400 MHz) on the crude reaction mixture.

relative to alternative open transition states and that a lower product diastereoselection would result. This is indeed the case.



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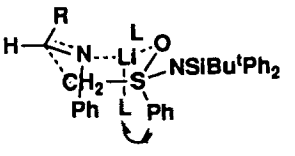

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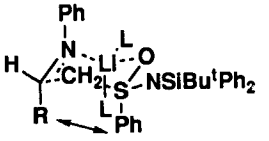

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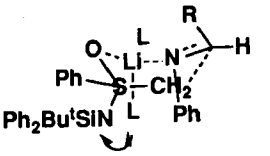
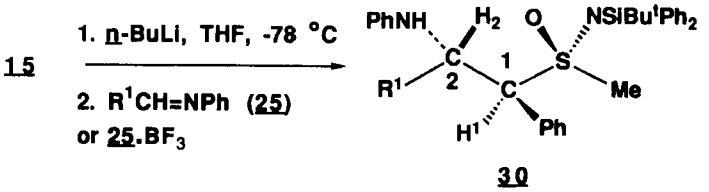


29

The results of the reaction of lithiated **15** with imines **25** or the imine·BF_3 complex is presented in Table 8.[14,15] In each case examined only two of the four possible racemic diastereoisomeric products were formed. While the reaction of lithiated **15** with imines (Table 8, entries 1, 4, 5 and 7) proceeded with moderate product diastereoselection the analogous reactions with imine·BF_3 complex gave the adducts **30** in consistently high diasteroselectivity (Table 8, entries 2, 3 and 6).[14] The relative 1S*, 2S*, SS* stereochemistry of **30** (R = Et) and **30** (R = *i*-Pr) were unequivocally determined by a single crystal X-ray structure analysis.[14,15] An estimate of the dihedral angle between C^1–H^1 and C^2–H^2 in **30** (R = Et) and **30** (R = *i*-Pr) from the structure analysis ($\phi_{1,2}$ *ca.* 77° and 175°, respectively) and the value of the H^1, H^2 coupling constant ($J_{1,2}$ = 3.2 Hz, 6.4 Hz, respectively), from the ^{1}H NMR analysis of **30** (R = Et, *i*-Pr) in deuterochloroform solution suggests that these compounds adopt a similar conformation in the solid state and in solution. The relative stereochemistry of the major diastereomeric adducts **30** (R = Ph, 2-furyl) were assigned by analogy with that of **30** (R = Et) and **30** (R = *i*-Pr).

The structural analysis clearly shows that the reaction of lithiated **15** with aldehydes and imines occurs in the same stereochemical sense with respect to the configuration at the stereogenic centre at C^1 but in the opposite stereochemical sense with respect to the configuration at the stereogenic centre at C^2.



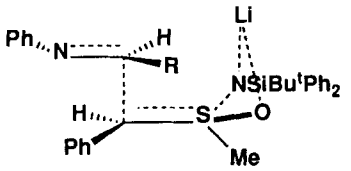
30

Table 8. Reactions of Lithiated **15** with Imines **25**

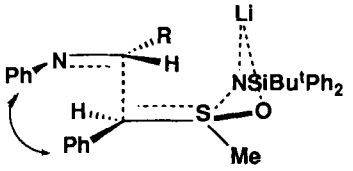
Entry	R^1 of imine (**25**)	Additive	Temp (°C)	Yield (%)	Diastereoselection[b]
1	Ph	–	−78	60	79:21
2	Ph	BF_3	−78	86	95:5
3	2-furyl	BF_3	−78	82	95:5
4	Et	–	−45	66	82:18
5	*i*-Bu	–	−45	51	82:18
6	*i*-Bu	BF_3	−78	70	96:4
7	*i*-Pr	–	−45	58	50:50
8	*i*-Pr	BF_3	−78	0[a]	–

[a] Complex mixtures of reaction products resulted.
[b] Determined by ^1H NMR (400 MHz) spectroscopy on the crude reaction mixture.

The open transition state **30a** is consistent with the stereochemical outcome. The alternative transition state **30b**, in which the *N*-phenyl substituent of the imine is anti to the benzyic phenyl group of the sulfoximine, suffers from severe steric interactions.



30a



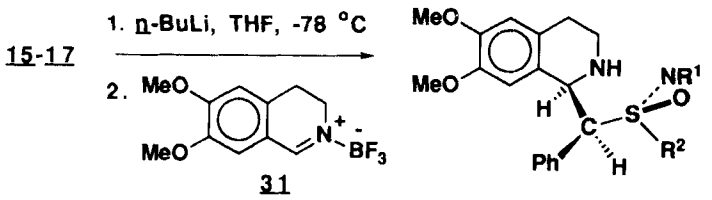
30b

Treatment of lithiated sulfoximines **16** and **17** with *N*-benzylideneaniline·BF_3 complex gave the desired adducts with only moderate to good diastereoselectivity (Table 9).[10] The lithiated sulfoximine **17** failed to give adducts with other acyclic imines even when the imines were precomplexed with BF_3 etherate. This is possibly a consequence of the increased steric demand and the resonance stabilizing effect of the *S*-phenyl group of **17**.

The reaction of lithiated **15** with the 3,4-dihydro-6,7-dimethoxyisoquinoline·BF_3 complex **31** gave the 1-benzyltetrahydroisoquinoline **32a** in a highly diastereoselective fashion (diastereoisomeric ratio 92:8). The relative stereochemistry of the major diastereomer of **32a** was tentatively assigned by analogy with **30**.[10]

Table 9. Reactions of Lithiated **15**, **16** and **17** with *N*-Benzylideneaniline·BF_3

Lithiated sulfoximine	Yield (%)	Diastereoselection
15	86	95:5
16	85	83:17
17	55	88:12



32a R^1 = $SiBu^tPh_2$, R^2 = Me
32b R^1 = $SiBu^tMe_2$, R^2 = Me
32c R^1 = $SiBu^tPh_2$, R^2 = Ph

In contrast, the reaction of lithiated **16** and 3,4-dihydro-6,7-dimethoxyisoquinoline·BF_3 complex **31** gave all four possible racemic diastereomeric products in a ratio of 40:30:16:14 (Table 10). The stereochemistry of the two major diasteromeric compounds could be tentatively assigned on the basis of their ^{1}H NMR spectra data, with the two major diastereoisomers assigned the 1S*,SS* relative stereochemistry on the basis of the downfield chemical shift of their SMe groups (δ 2.68 and 2.74, respectively). In contrast, the reaction of lithiated **17** with **31** proceeded in a highly diastereoselective fashion, the yield, however, was poor (40%, Table 10). The reactions of lithiated **15**, **16** and **17** with **31** appeared to have occurred in the same stereochemical sense as judged from their similar ^{1}H NMR spectra.[10]

Table 10. Diastereoselectivities for the Adducts from Lithiated **15**, **16** and **17** with **31**

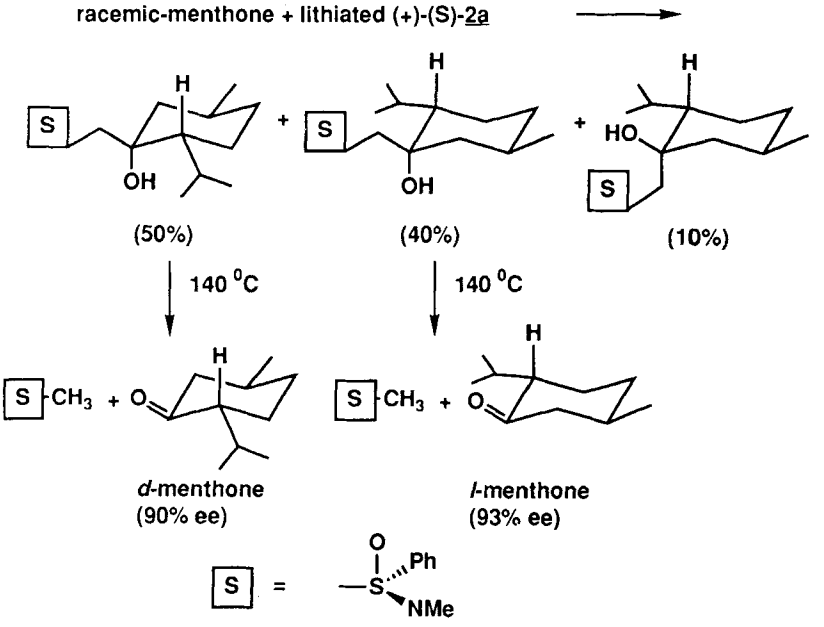
Lithiated sulfoximine	Yield (%)	Diastereoselection
15	43	92:8
16	55	40:30:16:14
17	40	92:8

3. APPLICATIONS OF β-HYDROXY SULFOXIMINES TO ASYMMETRIC SYNTHESIS

3.1. Resolution of Racemic Chiral Cyclic Ketones

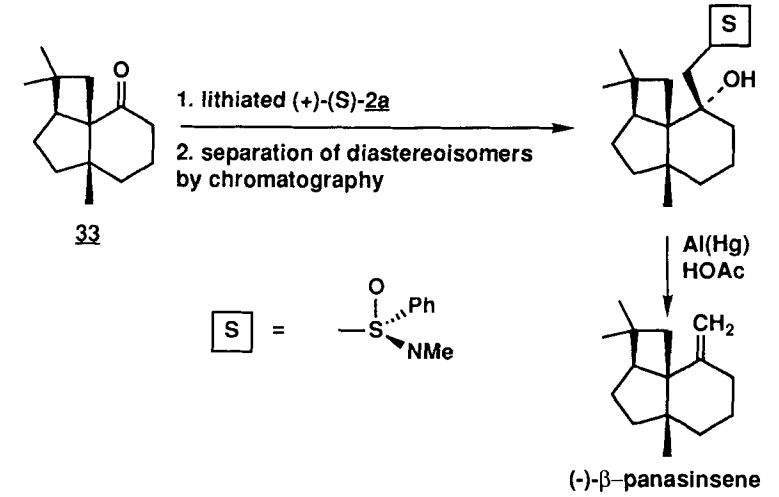
β-Hydroxy sulfoximines are thermally labile and revert to their starting carbonyl compound and sulfoximine upon mild thermolysis. This property has been exploited effectively as a method for the resolution of racemic chiral cyclic ketones.[16] For example, the addition of the lithium salt of (+)-(S)-**2a** (99% ee) under kinetically controlled conditions (−78 °C) to racemic menthone gave three of the four possible diastereomeric adducts. The major two adducts resulted from attack on the methone from the equatorial direction. These diastereomeric adducts could be readily separated by column chromatography. Thermolysis of the individual two major diastereomeric carbinols at 140 °C gave d- and l-menthone, respectively, in high enantiomeric purities (90–93% ee). This methodology has been successfully applied to the resolution of other 2-substituted

cyclohexanones as well as other chiral ketones that have served as advanced synthetic intermediates for the synthesis of natural products.[17,18]



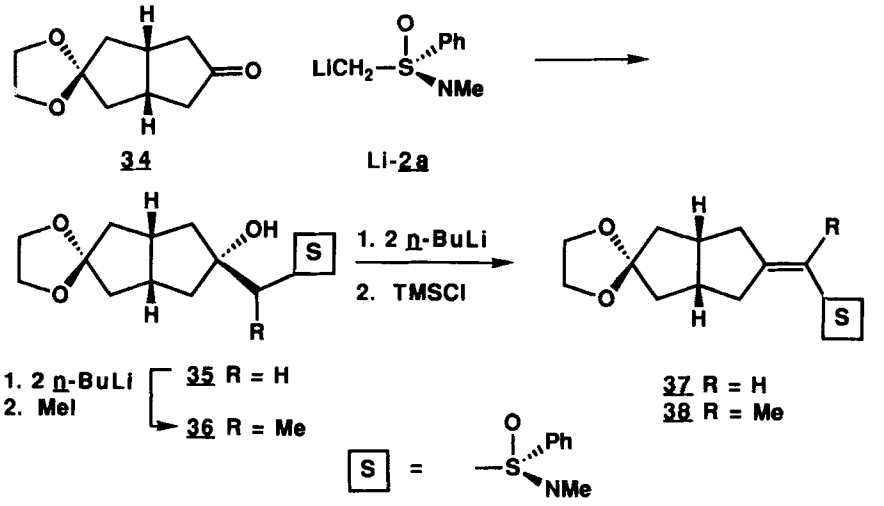
3.2. Synthesis of Alkenes via Reductive Elimination

Reductive elimination of β-hydroxy sulfoximines with aluminium amalgam in acetic acid gives alkenes in good yields.[19] In one study, the resolved carbinol adducts of the ketone **33** and (+)-(S)-**2a** were individually treated with aluminium amalgam in acetic acid to give natural (−)-β-panasinsene and its antipode in high enantiomeric purity.[20]

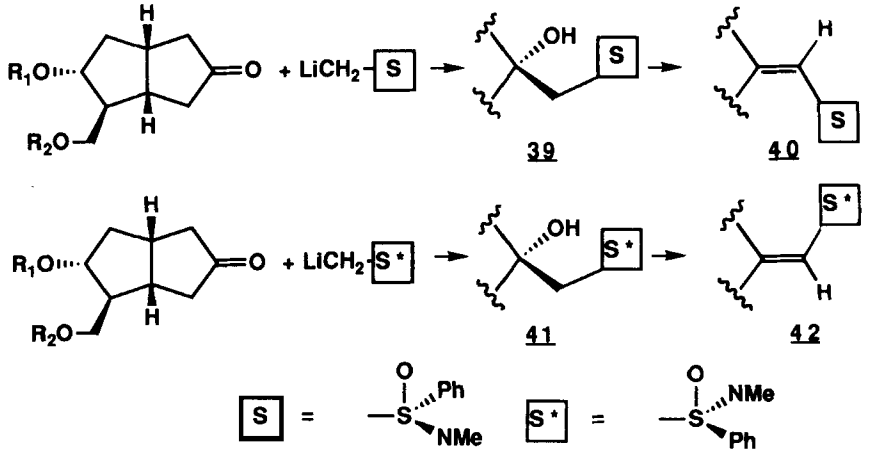


3.3. *Asymmetric Synthesis of Alkenes with Axial Chirality*

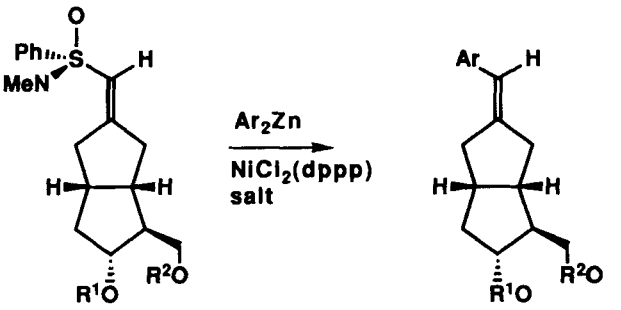
Axially chiral alkenyl sulfoximines have been prepared with high diastereoselectivity (> 99 : 1) by asymmetric elimination of $LiOSiMe_3$ from β-siloxy sulfoximines.[21] For example, addition of lithiated (+)-(S)-**2a** to ketone **34** gave the β-hydroxy sulfoximines **35** with a 99 : 1 diastereoselectivity. When the dianion of **35** was quenched at −78 °C with chlorotrimethylsilane the vinyl sulfoximine **37** was isolated in 69% yield with 99 : 1 diasteroselectivity. Similarly the dianion of the α-methyl sulfoximine analogue of **35** (**36**) gave the α-methylvinyl sulfoximine **38** in 73% yield with a high diastereoselection (99 : 1).



The geometry of the alkene is determined solely by the chirality at sulfur of the β-hydroxy sulfoximines, **39** and **41** were converted to the (*Z*)- and (*E*)-vinyl sulfoximines **40** and **42**, respectively, in high yield and with a high product diastereoselection (99 : 1).

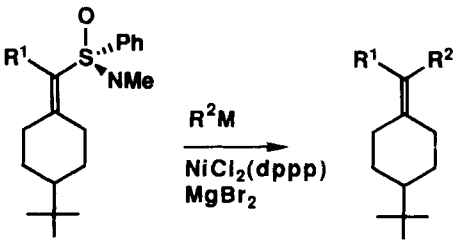


The nickel catalysed cross-coupling reaction of the vinyl sulfoximine **43** with diarylzinc reagents in the presence of a salt ($MgBr_2$, LiBr or $ZnCl_2$) gave exclusively the (*E*)-exocyclic alkenes **44** in high enantiomeric purity (> 98%).[22] Unfortunately this method could not be extended to the cross-coupling reaction with dialkylzinc reagents. In contrast, the nickel catalysed cross-coupling reaction of **45**, prepared from 4-*t*-butylcyclohexanone and (+)-(S)-**2a**, with dimethylzinc in the presence of $MgBr_2$ (2 equiv.) gave stereoselectively **46** in 74% yield and in high enantiomeric purity (> 98%). Vinyl sulfoximine **47** gave the optically active disubstituted exocyclic alkene **48** in good yield (80%) via a cross-coupling reaction with phenylmagnesium bromide.



43 **44**

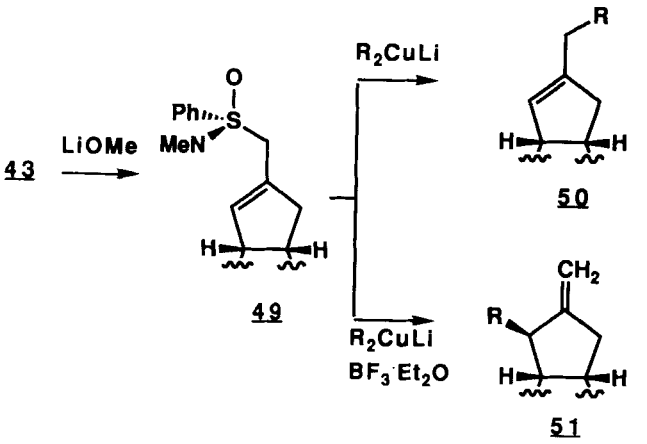
(dppp = $Ph_2P(CH_2)_3PPh_2$)



45 R^1 = H
47 R^1 = Me

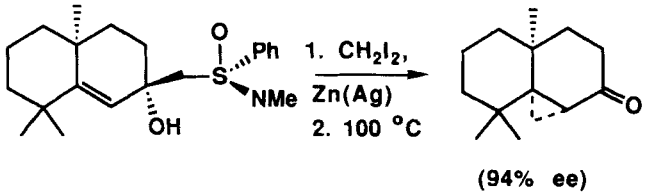
46 R^1 = H, R^2 = Me
48 R^1 = Me, R^2 = Ph

Regioselective isomerization of **43** with base (LiOMe) gave the allylic sulfoximine **49** which upon reaction with homocuprates (R_2CuLi, where R = alkyl) gave exclusively the endocyclic alkenes **50** via an "S_N2 like" displacement reaction. When these reactions were conducted in the presence of $BF_3 \cdot OEt_2$ (1 equiv.) then exocyclic alkenes **51** were formed (> 98% regioselectivity) via an "S_N2' like" displacement of sulfinamide.[23]



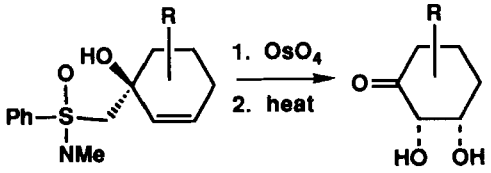
3.4. Directed Simmons-Smith Cyclopropanations

Resolved β-hydroxy sulfoximines derived from cyclic enones undergo diastereoselective Simmons–Smith cyclopropanation reactions to give, after thermolysis, cyclopropyl ketones in high enantiomeric purity (94–98%). Cyclopropanation occurs syn to the hydroxyl group of the β-hydroxy sulfoximine. This method is less diastereoselective for acyclic enones.[24]



3.5. Directed Osmylations

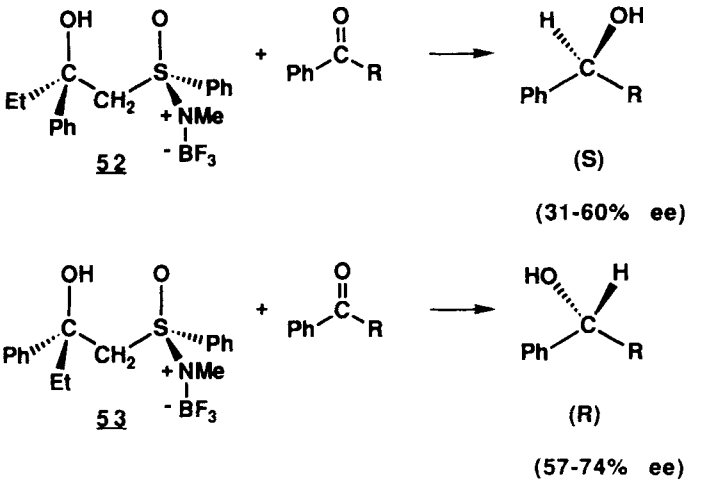
Osmylation of diastereomerically pure β-hydroxy sulfoximines, derived from **2a** and cyclic enones, with a catalytic amount of osmium tetroxide (5 mol %) and trimethylamine *N*-oxide (1.5 equiv.) gives diastereomerically pure triols which upon thermolysis yield 2,3-dihydroxy cyclic ketones in high enantiomeric purity ("100%" ee). Osmylation occurs syn to the sulfoximine group.[25]



3.6. Enantioselective Reductions

Prochiral alkyl phenyl ketones (RCOPh) undergo enantioselective reduction with

enantiomerically pure β-hydroxy sulfoximine borane complexes (**52** and **53**). These complexes are prepared by reaction of the corresponding β-hydroxy sulfoximine with borane at −78 °C. The structures **52** and **53** have been suggested for these complexes. In the case of the borane complex **52**, the enantioselectivity increased as the steric bulk of the R substituent of the ketone (RCOPh) was decreased from *i*-Pr to Me. The analogous reductions of methyl alkyl ketones (MeCOR) with these borane complexes were less enantioselective (3–27% ee).[26]



4. REDUCTION OF β-KETO SULFOXIMINES

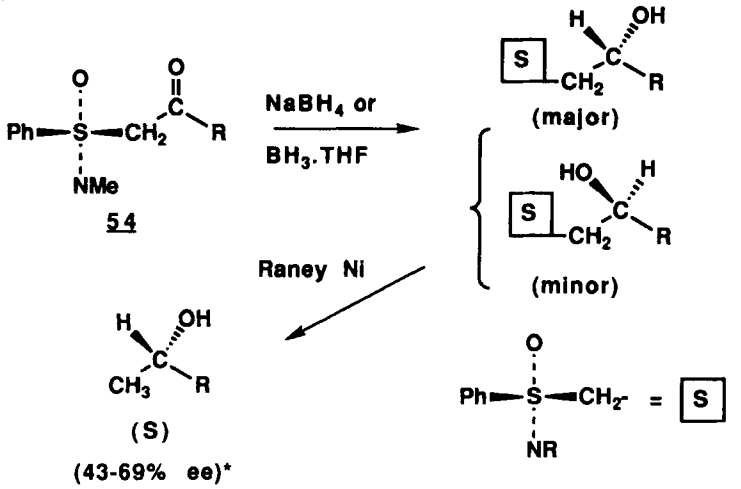
β-Keto sulfoximines **54** are readily prepared by condensation of (+)-(S)-**2a** with nitriles[27] or esters.[28] These compounds undergo diastereoselective reductions at −78 °C with sodium borohydride or diborane to give mixtures of diastereomeric β-hydroxy sulfoximines. The product diastereoselection increases as the steric demand of the

Table 11. Diasteroselective Reductions of **54**

β-Keto sulfoximine (**54**) (R)	Reducing Agent	Yield (%)	Diastereoselection
Me	$NaBH_4$	q*	50:50
Et	$NaBH_4$	q	56:44
i-Pr	$NaBH_4$	q	60:40
Ph	$NaBH_4$	q	70:30
t-Bu	$NaBH_4$	q	75:25
n-hexyl	BH_3	75	75:25
Ph	BH_3	90	80:20
i-Bu	BH_3	83	83:17
t-Bu	BH_3	91	90:10

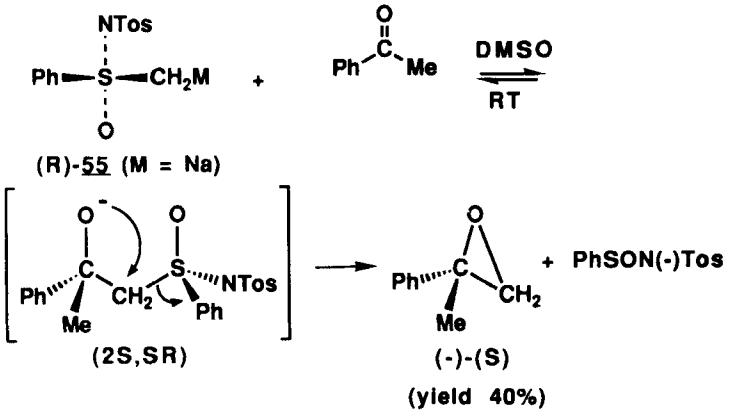
*q = quantitative yield.

substituent R of **54** increases (Table 11). Reductive removal of the β-sulfoximine group of the diastereomeric mixture of β-hydroxy sulfoximines gives secondary alcohols with the (S)-configuration.

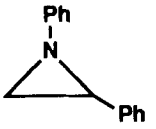


5. ASYMMETRIC SYNTHESIS OF CHIRAL OXIRANES, OXETANES, CYCLOPROPANES AND AZIRIDINES

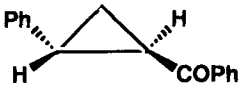
Reaction of the sodium salt of (R)-*N*-(*p*-tolylsulfonyl) *S*-methyl *S*-phenyl sulfoximine **2b** (84% ee) with acetophenone at room temperature gave (−)-(S)-2-methyl-2-phenyloxirane.[4] The (S)-oxirane product must arise from the collapse of the (2S,SR)-β-oxy sulfoximine intermediate shown below. Under kinetically controlled conditions one would expect that the (2R,SR)-β-oxy sulfoximine intermediate would predominate. It has been demonstrated that under these reaction conditions the 1,2-addition of **2b** to ketones is reversible.[29] It is apparent that in this case the rate of formation of the (S)-oxirane product from the (2S,SR)-β-oxy sulfoximine intermediate is faster than that of the (R)-oxirane product from the diastereomeric (2R,SR)-β-oxy sulfoximine intermediate.



The reaction of the above sulfoximine anion with *N*-benzylideneaniline gave (−)-1,2-diphenylaziridine ($[\alpha]_D$-12.9°), whereas the lithium salt of this sulfoximine, upon reaction with the enone, (*E*)-benzalacetophenone, gave (1R,2R)-1-benzyl-2-phenylcyclopropane ($[\alpha]_D$-190°) in 49% enantiomeric purity.[4]

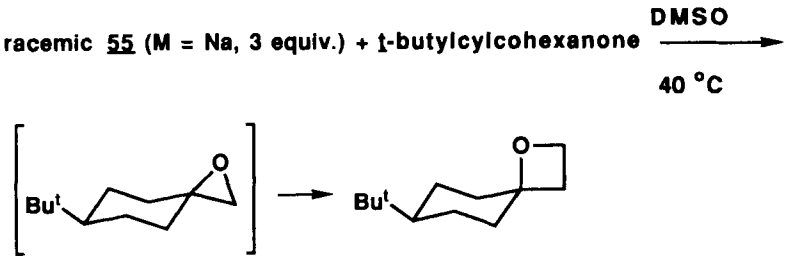


(-)



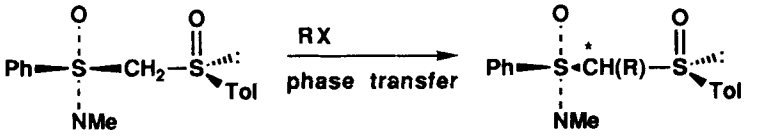
(-)-(1R,2R)

The reaction of ketones with excess of the sulfoximine salt **55** (M = Na) gives oxetanes formed by ring opening of the initially formed oxirane and subsequent ring closure. These reactions are highly diastereoselective and generally the thermodynamically more stable oxetane, in which the C–O bond is "axial", is formed from cyclic ketones since the intermediate oxirane is formed under thermodynamically controlled conditions.[29]



6. DIASTEREOSELECTIVE ALKYLATIONS

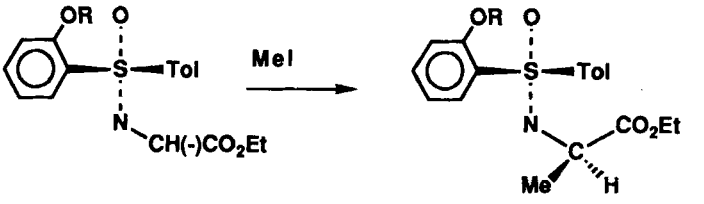
Alkylation of (+)-(S,S)-*N*-methyl *S*-phenyl *S*-(*p*-tolylsulfinylmethyl) sulfoximine **56** under phase-transfer conditions (50% aqueous NaOH/CH_2Cl_2/benzyltriethylammonium chloride) gave monoalkylated products with extremely high diastereoselectivity (100%). Its (S,R)-diastereomer, however, is much less diastereoselective (diastereoselection *ca.* 80 : 20). In contrast, ethylation of the corresponding sulfone analogue of **56**, [*N*-methyl *S*-phenyl *S*-(*p*-tolylsulfonylmethyl) sulfoximine] resulted in a 50 : 50 mixture of diastereomeric products; clearly the diastereoselectivity in these reactions is primarily determined by the sulfinyl moiety rather than by the sulfoximine group.[30]



56

(100% diastereoselection)

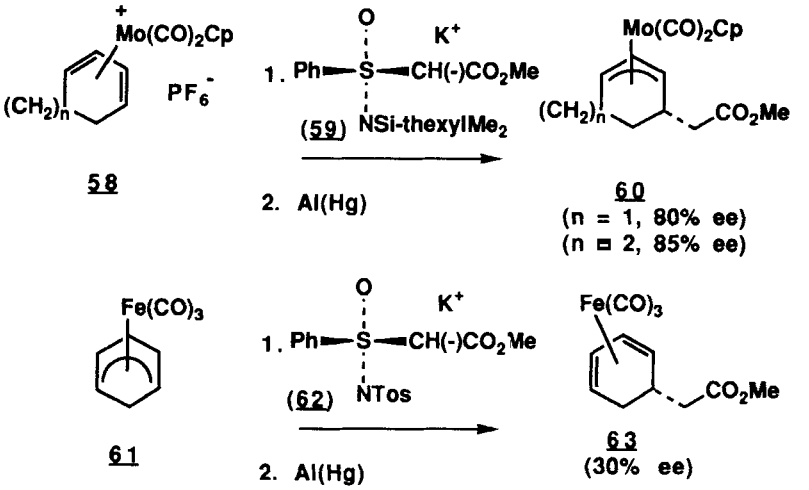
Methylation of the lithium salts of (S)-(+)-*N*-ethoxycarbonylmethyl *S*-aryl *S*-*p*-tolyl sulfoximines (**57**) is 100% diastereoselective when the *S*-aryl group is capable of coordination to the lithium cation.[31]



57a R = Me
57b R = CH_2CH_2OMe

diastereoselection
R = Me, 76:22
R = CH_2CH_2OMe, 100:0

The addition of the potassium salts of the sulfoximinyl esters **59** and **62** to the dienemolybdenum complex (**58**) and dienyliron complex (**61**) gave adducts which, after desulfonylation, yielded the enantiomerically enriched organometallic complexes **60** and **63**. The potassium salts gave the highest diastereoselectivities and the more sterically demanding *N*-(dimethylthexysilyl) derivative **59** gave products with the highest enantiomeric purity.[32]



7. CHIRAL VINYL SULFOXIMINES

7.1. Addition of Nucleophiles

7.1.1. Addition of organometallic reagents Enantiomerically pure chiral vinyl sulfoximines having a chiral auxiliary at nitrogen undergo conjugate addition of alkyllithium and organocopper reagents with high asymmetric induction at the β-position (Tables 12

and 13).[33] The stereochemical outcome of these reactions seemed to be chiefly governed by the chirality at sulfur of the sulfoximine group rather than the chiral norephedrine derived auxiliary. For example, vinyl sulfoximines **64** and **67** underwent conjugate addition of alkyllithium with opposite π-face diastereoselectivity (cf. entry 1, Table 12 and entries 1 and 2, Table 13).

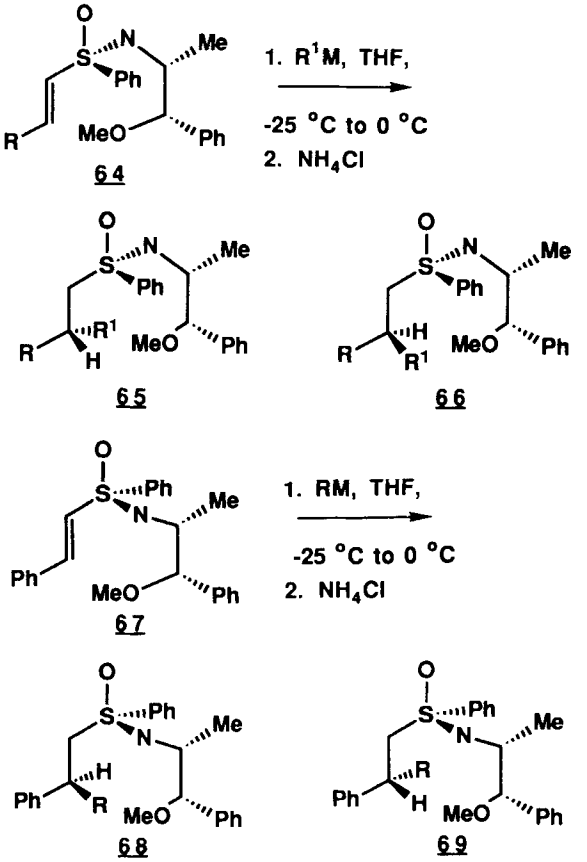


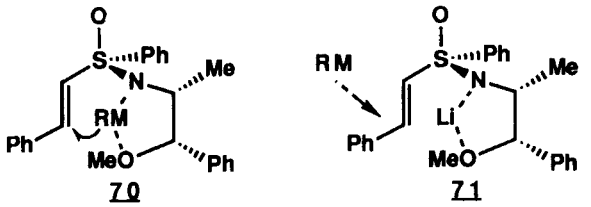
Table 12. Addition of Organometallics (R^1M) to Vinyl Sulfoximines **64**

Entry	R	R^1M	Yield (%)	Diastereoselection (**65**:**66**)
1	Ph	*n*-BuLi	69	73:27
2	Ph	*n*-Bu_2CuLi	76	86:14
3	Ph	*n*-BuCu	71	5:95
4	Me	*n*-Bu_2CuLi	77	81:19
5	Me	*n*-BuCu	81	5:95
6	Me	*n*-BuCu(LiI "free")	68	33:67
7	*n*-Bu	MeCu	72	4:96
8	$PhCH_2CH_2$	MeCu	75	5:95

Table 13. Addition of Organometallics (RM) to Vinyl Sulfoximine **67**

Entry	RM	Yield (%)	Diastereoselection (**68**:**69**)
1	MeLi	85	96:4
2	*n*-BuLi	82	95:5

The stereochemical outcome of these reactions was rationalised by invoking the initial formation of the complex **70** between the organometallic reagent and the sulfoximine via coordination at the sulfoximine nitrogen. The organometallic reagent may then be directed preferentially to one of the diastereotopic faces of the vinyl group. It was discovered that alkylcopper reagents (RCu) underwent conjugate addition in the opposite diastereofacial sense to alkyllithium and dialkylorganocopper reagents (R_2CuLi) and with a very high diastereofacial selectivity (Table 1, entries 3, 5–7). By the nature of their preparation [RLi + CuI (0.5 or 1.0 equiv.)], both R_2CuLi and RCu contain 1 equiv. of soluble LiI which can compete with the organometallic reagents for chelation at the sulfoximine nitrogen. The reversal of π-facial diastereoselectivity with RCu was explained by the attack on RCu on the Li^+-chelated species **71** from the least sterically demanding π-face. Consistent with this proposal was the reduction in diastereoselectivity in favour of **66** when LiI "free" *n*-BuCu was employed (Table 12, entry 6).

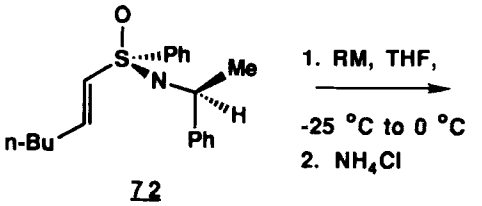


Further experiments, in which the stereochemical outcomes could be rationalized as arising from coordinated intermediates analogous to **70** and **71**, were performed on the enantiomerically pure vinyl sulfoximines **72** and **75**.[34] Vinyl sulfoximine **72** underwent conjugate addition of R_2CuLi in the expected stereochemical sense, presumably via a coordinated intermediate analogous to **70** (Table 14, entry 1). In the absence of LiI,

Table 14. Addition of Organometallics (RM) to Vinyl Sulfoximine **72**

Entry	RM	Yield (%)	Diasteroselection (**73**:**74**)
1	Me_2CuLi	60	88:12
2	Me_2CuLi (LiI ("free")	72	94:6
3	Me_2CuLi $ZnBr_2$(1.1 equiv.)	64	12:88
4	MeCu	83	15:85
5	MeCu (LiI "free")	74	20:80

which could also complex to the sulfoximine nitrogen, the diastereoselection, in favour of diastereoisomer **73**, was enhanced (Table 3, entry 2). When **72** was precomplexed with $ZnBr_2$ prior to the addition of Me_2CuLi, the reaction proceeded in the opposite stereochemical sense and favoured the diastereoisomer **74** (Table 14, entry 3). This result was clearly consistent with attack of Me_2CuLi on a zinc coordinated intermediate analogous to **71**. The reactions of **72** with MeCu (Table 14, entries 4 and 5) occurred in the same stereochemical sense as the reaction of **64** and RCu described above.



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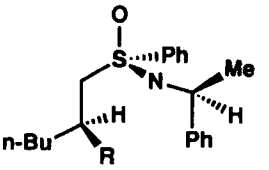

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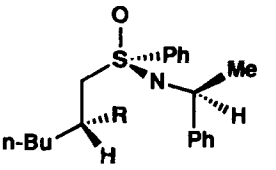

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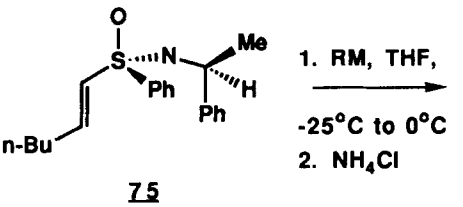
The stereochemical outcome of the reaction of the vinyl sulfoximine **75** with Me_2CuLi (Table 15, entry 1) appears anomalous, whereas that from the reaction of this substrate with the other organometallic reagents reported in Table 15 (entries 2–5) is consistent with those in Tables 12–14 above.



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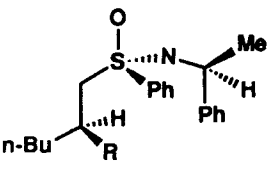

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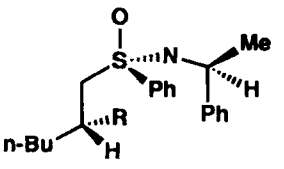

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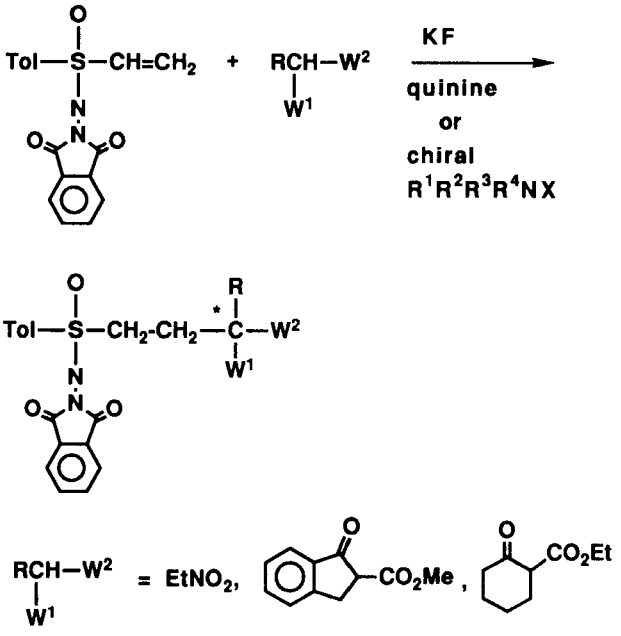
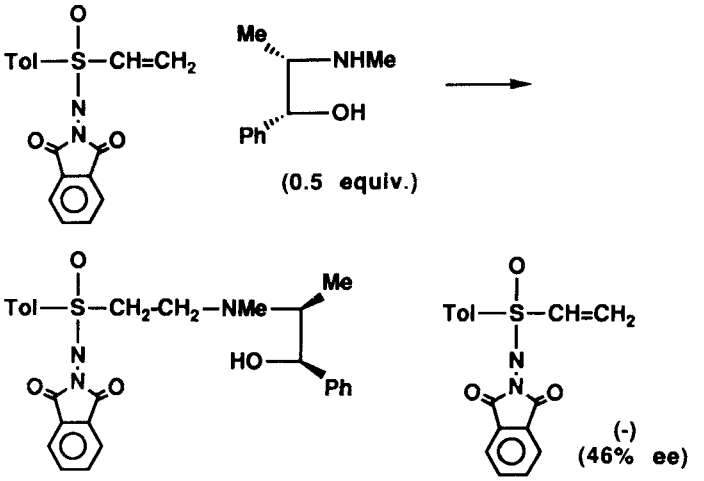
Table 15. Addition of Organometallics (RM) to Vinyl Sulfoximine **75**

Entry	RM	Yield (%)	Diasteroselection (**76**:**77**)
1	Me_2CuLi	60	23:77
2	Me_2CuLi (LiI "free")	69	90:10
3	Me_2CuLi $ZnBr_2$(1.1 equiv.)	65	12:88
4	MeCu	79	21:79
5	MeCu (LiI "free")	80	13:87

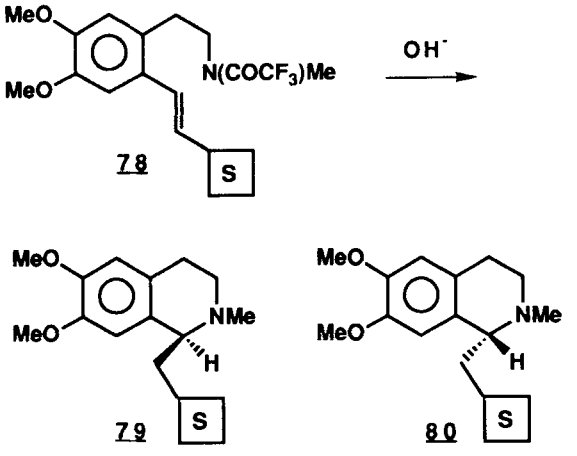
7.1.2. Resonance stabilized carbanions Base catalysed addition of nitroethane and cyclic β-keto esters to racemic *N*-phthalimido *S*-*p*-tolyl *S*-vinyl sulfoximine with either an enantiomerically pure chiral amine (quinine) or under phase-transfer conditions in the presence of an enantiomerically pure phase transfer catalyst (*N*-benzylquininium chloride or *N*-dodecyl-*N*-methylephedrinium bromide), proceeded with little or no asymmetric induction at the newly created stereogenic carbon centre.[35] It is not clear from this report whether these reactions were terminated at 50% conversion or less, a condition necessary to observe kinetic resolution of the vinyl sulfoximine. Only in the case of the reaction of the vinyl sulfoximine with nitroethane was the product obtained with a measurable optical rotation [$[\alpha]_D^{25}$ + 5.4° ($CHCl_3$)], however, the enantiomeric purity was not determined. The unreacted vinyl sulfoximine was recovered and found to have an enantiomeric purity of 7%.



7.1.3. Nitrogen nucleophiles The reaction of racemic *N*-phthalimido *S*-*p*-tolyl *S*-vinyl sulfoximine with a deficiency (0.5 molar equiv.) of enantiomerically pure (−)-ephedrine resulted in a kinetic resolution of the vinyl sulfoximine.[36] When the reaction was conducted at −30 °C the unreacted vinyl sulfoximine could be recovered with an enantiomeric purity of 46%. (−)-Amphetamine and (+)-1-phenylethylamine were not effective for kinetic resolution. The analogous (*Z*)-propenyl sulfoximine also underwent kinetic resolution with (−)-ephedrine; however, the extent of kinetic resolution was not determined.



The enantiomerically pure vinyl sulfoximines **78a** and **78b**, upon treatment with hydroxide, undergo cyclization to give chiral isoquinolines with a modest diastereoselectivity. Reductive desulfurization of the major diastereomeric products from these cyclization reactions (**80a** and **79b**) with Raney nickel gave the chiral isoquinoline alkaloids, (S)-(−)-carnegine and (R)-(+)-carnegine, respectively, in high enantiomeric purity (95% ee).[37]



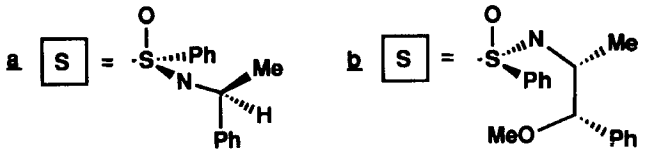
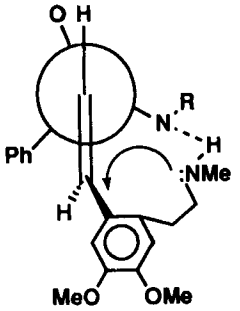


Table 16. Base Induced Cylization of **78a** and **78b**

Sulfoximine	Base	Solvent	T (°C)	Diastereoisomeric ratio **79**:**80**
78a	$[PhCH_2NMe_3]^+[OH]^-$	CH_2Cl_2	0	26:74
78a	$[PhCH_2NMe_3]^+[OH]^-$	CH_2Cl_2	−40	28:72
78a	$[PhCH_2NMe_3]^+[OH]^-$	MeOH	0	58:42
78a	Li^+OH^-	MeOH–H_2O (2:1)	0	65:35
78b	$[PhCH_2NMe_3]^+[OH]^-$	CH_2Cl_2	0	71:29
78b	$[PhCH_2NMe_3]^+[OH]^-$	CH_2Cl_2	−40	68:32
78b	$[PhCH_2NMe_3]^+[OH]^-$	MeOH	0	54:46
78b	Li^+OH^-	MeOH–H_2O (2:1)	0	65:35

The stereochemical outcome of these cyclizations seems largely governed by the chirality at sulfur of (**78**) and not by the chiral auxiliary ligand. Changing the reaction solvent of methylene chloride (CH_2Cl_2) to methanol (MeOH) in the reaction of (**78a**) with benzyltrimethylammonium hydroxide ($[PhCH_2NMe_3]^+[OH]^-$) dramatically affects the diastereoselectivity (from 48% to 16%). Surprisingly, the reaction temperature had little effect on the diastereoselectivity. It was proposed that in a nonpolar aprotic solvent (CH_2Cl_2) the reaction proceeds via the intermediate (**81**) in which there is H-bonding between the NH of the amino group and the nitrogen of the sulfoximine moiety.



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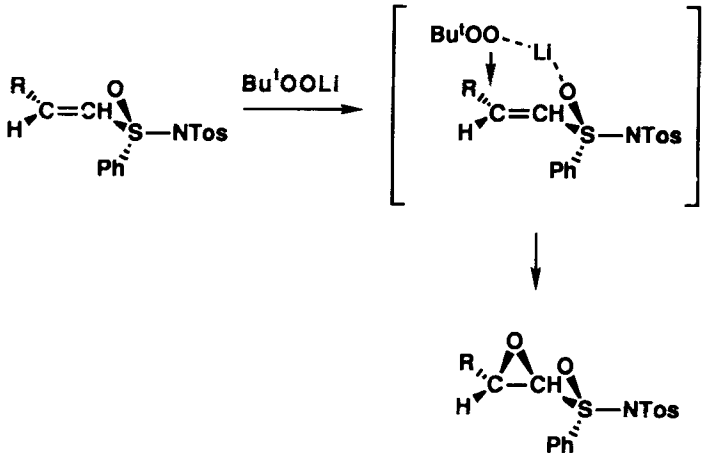
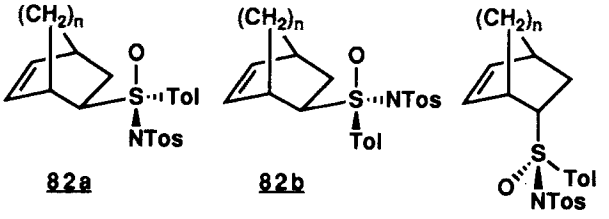
7.1.4. Oxygen nucleophiles Nucleophilic epoxidation of racemic *N*-(*p*-tolylsulfonyl) S-vinyl sulfoximines with lithium *t*-butylhydroperoxide proceeds in high yield and with a very high diastereofacial selectivity. The relative stereochemistry of the α,β-epoxy

sulfoximines has been unequivocally determined by a single crystal X-ray structural analysis. A reactive ground state conformation in which the bulky *N*-(*p*-tolylsulfonyl) group is anti-coplanar with the vinyl group has been suggested to account for the stereochemical outcome of these reactions.[38]

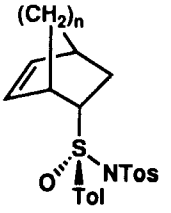


7.2. Diels-Alder Reactions

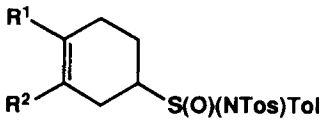
The Diels-Alder reactions of racemic *N*-(*p*-tolyl) *S*-*p*-tolyl *S*-vinyl sulfoximine with dienes gives mixtures of diastereomeric cycloadducts in good yield (Table 17). When cyclopentadiene and 1,3-cyclohexadiene were employed as dienophiles the endo diastereomeric products **82c** and **82d** (n = 1, 2) predominated.[39]



82a **82b** **82c**



82d



83a, R^1 = Me, R^2 = H
83b, R^1 = H, R^2 = Me

Table 17. Diels-Alder Reactions of Racemic *N*-(*p*-Tolyl) *S*-*p*-Tolyl *S*-Vinyl Sulfoximine with Dienes

Diene	Yield (%)	Cycloadducts (Diastereoselection)
cyclopentadiene	81	**82a** + **82b** + **82c** + **82d** (1 : 1 : 4 : 5)
1,3-cyclohexadiene	95	[**82a** + **82b**] + **82c** + **82d** (7 : 41 : 52)
2,3-dimethyl-1,3-butadiene	95	**83a** + **83b** (4 : 1)

8. CONCLUSION

Sulfoximines are versatile reagents for diastereoselective and asymmetric synthesis. Highly diastereoselective 1,2-additions of sterically hindered lithiated sulfoximines to carbonyl compounds can now be achieved. The resulting β-hydroxy sulfoximine adducts can be exploited for the resolution of chiral racemic ketones and in the asymmetric synthesis of chiral alcohols, alkenes and oxiranes. β-Hydroxy sulfoximines can be used to direct osmylations and cyclopropanations and to give chiral borane complexes with borane·THF to give enantioselective reducing agents. In contrast, vinyl sulfoximines have been less widely utilized in asymmetric synthesis. The additions of nucleophiles to these substrates vary greatly in their diastereoselectivities. Further work is required in this area to understand the factors that determine the diastereoselection and the stereochemical outcome in these reactions.

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15. Entry 7 in Table 1 was incorrectly reported in the initial communication as was the stereochemistry at C^2 in structure 7.[14] The figure caption therein also requires amendment, thus: 0(3)-S(3)-C(31,4), 109.9 (1); C(4)-S(3)-C(31), 102.3(2)°.
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