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Applications of Chiral Sulfoximines to Diastereoselective and Catalytic Asymmetric Synthesis

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APPLICATIONS OF CHIRAL SULFOXIMINES TO DIASTEREOSELECTIVE AND CATALYTIC ASYMMETRIC SYNTHESIS

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(Received 1 September 1998)

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This review deals with methods for the synthesis of chiral sulfoximines and their applications in diastereoselective and catalytic asymmetric synthesis. This review is an up-dated version of my 1992 review in this journal.

Keywords: Asymmetric synthesis; chiral ligands; diastereoselective synthesis; lithiated sulfoximines; palladium catalysis; sulfoximines

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1. INTRODUCTION

This is an up-dated version of my 1992 review on sulfoximines.[1] Sulfoximines continue to find many applications as both nucleophilic and electrophilic reagents in asymmetric and diastereoselective synthesis and as ligands in catalytic asymmetric synthesis.

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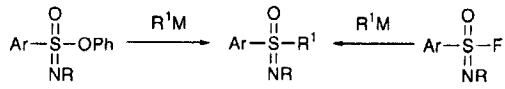
2. ALKYL SULFOXIMINES

2.1. Synthesis

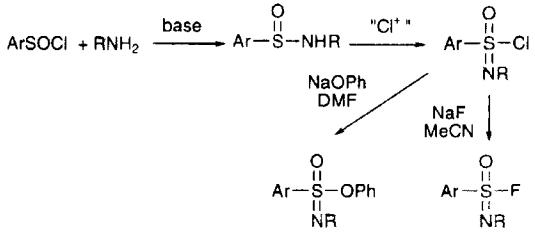
Methods for the resolution of (*S*)- and (*R*)-*S*-methyl-*S*-phenylsulfoximine and the synthesis of their *N*-substituted derivatives has been reported in my 1992 review.[1] The resolution of these former compounds using 0.6 molar equivalents of (+)- or (−)-camphorsulfonic acid was reported in 1997 by Gias.[2] This method is suitable for their large scale resolution.

The preparation of racemic sulfoximines from the reactions of phenyl sulfonimidates[3] or sulfonimidoyl fluorides[4] with organolithium and Grignard reagents was first reported by Johnson (Eq. (1)). The related sulfonimidoyl chlorides are not useful since they are generally reduced to the corresponding sulfinamide.[5]



(1)

Harmata,[6] however, found that treatment of sulfonimidoyl chlorides with ethylaluminium chloride gave *S*-ethylsulfoximines in good yields. Phenyl sulfonimidates[3] or sulfonimidoyl fluorides[4] are readily prepared from sulfonimidoyl chlorides which are available in two steps from arenesulfinyl chlorides (Eq. (2)). Treatment of the arenesulfinyl chloride with an amine and base (e.g. triethylamine) gives the corresponding sulfinamide which upon chlorination with chlorine,[3] *tert*-butyl hypochlorite[7] or *N*-chlorobenzotriazole[8,9] gives the corresponding sulfonimidoyl chloride (Eq. (2)).



(2)

Related methods have been more recently developed to prepare enantiomerically pure sulfoximines from optically active sulfonimidates. For

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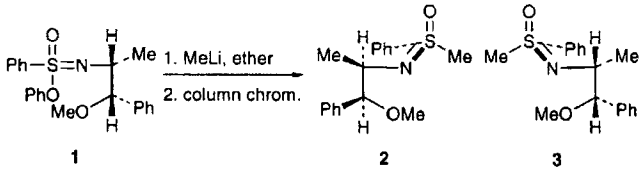
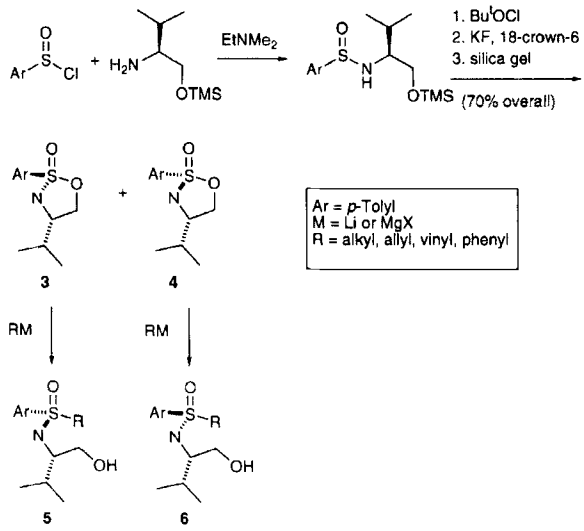
example, Pyne[9] prepared the optically active diastereomeric sulfoximines **2** and **3** from the reaction of the phenyl sulfonimidate **1** and methyllithium. Compound **1** was prepared from (+)-norephedrine as a 1.8 : 1 mixture of diastereoisomers that could not be separated chromatographically. The sulfoximines **2** and **3** were readily separated by column chromatography in isolated yields of 14% and 28%, respectively. A related method to prepare optically active *N*-(*S*)-1-phenylethyl-*S*-methyl-*S*-phenylsulfoximines has also been reported.[10]



1 **2** **3**

Regellin has reported that enantiomerically pure sulfoximines **5** and **6** can be prepared via the nucleophilic substitution of the cyclic sulfonimidates **3** and **4**, respectively, with 2 molar equivalents of an organolithium or Grignard reagent. Yields were excellent and ranged from 85–97%. These reactions were not successful with Bu^{t}MgBr. The diastereomeric sulfonimidates **3** and **4** were prepared from *O*-trimethylsilyl valinol and could be separated by column chromatography.[11]



3 **4** **5** **6**

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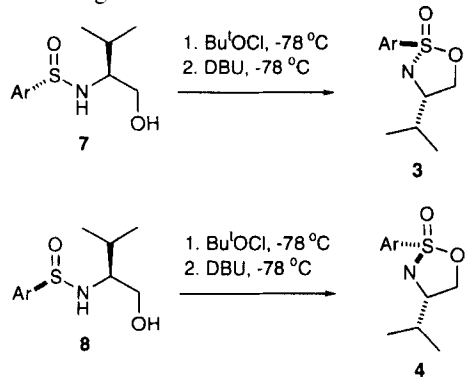
A more convenient synthesis of the diastereomerically pure cyclic sulfonimidates **3** and **4** has been developed. The diastereomeric sulfinamides **7** and **8** are more readily separated by crystallization than the cyclic sulfonimidates **3** and **4**. Treatment of these separated compounds with *tert*-butyl hypochlorite, a reaction that gives the corresponding sulfonimidoyl chlorides with retention of configuration, followed by base treatment at −78 °C gave the diastereomeric pure cyclic sulfonimidates **3** and **4**, respectively, with inversion of stereochemistry at the stereogenic sulfur.[12]



An alternative method for preparing sulfoximines is the imination of sulfoxides with hydrazoic acid[13] (prepared *in situ* from sodium azide and sulfuric acid in chloroform) or *O*-mesitylsulfonylhydroxylamine (MSH)[14,15] to afford *N*-unsubstituted sulfoximines. The former method, however, is not suitable for sulfoximines in which one or more *S*-alkyl substituents can readily undergo heterolysis of the C–S bond under the acidic conditions (e.g. benzyl, allyl, Bu^t or some secondary alkyl groups). The MSH method on optically active sulfoxides gives optically active sulfoximines with retention of configuration.[14] The copper(0) catalysed reactions of tosyl azide[16,17] or chloroamine-T[18] with sulfoxides gives *N*-tosyl sulfoximines (Eq. (3)). The *N*-tosyl group in these compounds can be cleaved by either acid hydrolysis,[19] photolysis[20] or reduction.[21,22] The most efficient method seems to be reduction with sodium anthracenide,[22] however, this method does not work for *N*-tosyl-*S*-methyl-*S*-phenylsulfoximine. The *N*-unsubstituted sulfoximines can be readily *N*-silylated,[23–25] methylated (HCOOH/HCHO[24,26,27] or Me_3OBF_4[28]), alkylated,[29] methoxcarbonylated,[30] tosylated,[15] trifluoromethylsulfonylated[31] or nitrosylated.[32]

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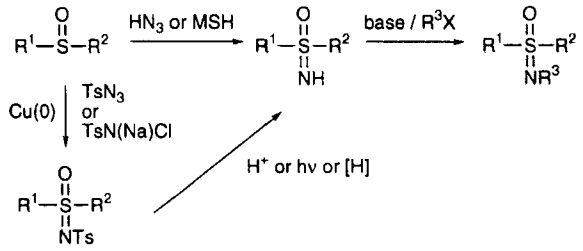
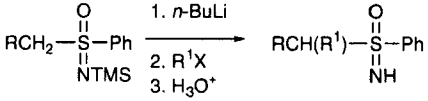


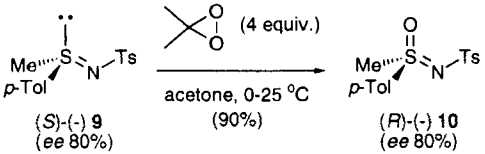
(3)

N-Trimethylsilyl *S*-alkylsulfoximines can be readily deprotonated with strong base (*n*-butyllithium or LDA) and alkylated with alkyl halides, aldehydes and epoxides to give, after mild acid hydrolysis, chain extended *N*-unsubstituted sulfoximines (Eq. (4)).[23]



(4)

Sulfoximines can also be prepared by oxidation of sulfilimines with sodium periodate/ruthenium dioxide,[33] alkaline hydrogen peroxide[34] or *m*-chloroperbenzoic acid anion.[35] *N*-(*p*-Tolylsulfonyl)sulfilimines have been oxidized to their corresponding sulfoximines in high yields using dimethyldioxirane in acetone.[36] Oxidation of (−)-(*S*)-*S*-(*p*-tolyl)-*S*-methyl-*N*-(*p*-tolylsulfonyl)sulfilimine **9** (ee 80%) gave the corresponding (−)-(*R*)-sulfoximine **10** with complete retention of configuration at the sulfur atom.



In 1998 Gais reported the synthesis of enantiomerically pure cyclic sulfoximines **16** and **17** from (+)-(*S*)-*S*-methyl-*S*-phenylsulfoximine **11** via *N*-alkylation with THP protected 2-bromoethanol and 3-chloropropanol, THP hydrolysis and then *O*-tosylation to give **14** and **15**, respectively. Base promoted cyclization of **14** and **15** gave the enantiomerically pure cyclic sulfoximines **16** and **17**, respectively.[37]

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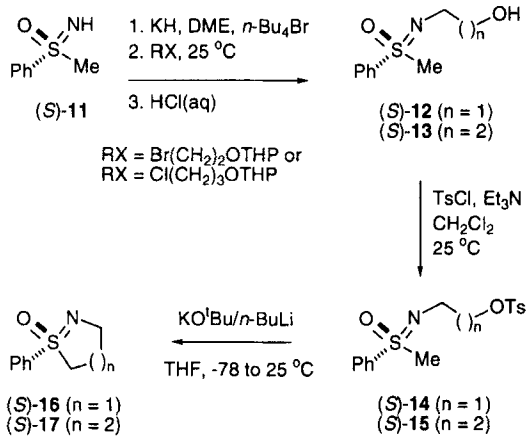

2.2. Lithiated Sulfoximines

2.2.1. Structural Studies

The X-ray crystal structures of lithiated sulfoximines were reported in 1986/87 by Gais. Lithiated (*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine crystallized as its tetramethylethylendiamine (tmeda) complex as a chiral tetramer of structure [(*S*)-*N*-methyl-*S*-phenylsulfonimidoyl)-methyllithium]$_4 \cdot$ 2(tmeda) with approximately C_2 symmetry.[38] Two of the lithium cations of the tetramer were coordinated to a tmeda molecule and the O atoms of two different carbanionic species. The other two lithium cations were found to be coordinated to the N atoms of three different sulfonimidoyl carbanionic species and to one C atom (the α-carbon) of each of these carbanionic species. These lithium cations were thus found to form four-membered chelate rings involving the atoms, Li–C_α–S–N. A latter study was successful in producing crystals in the absence of the tmeda donor ligand. In this study the X-ray crystal structure of lithiated racemic trimethyl[(*N*-(trimethylsilyl)-*S*-phenylsulfonimidoyl)methyl]silane [$(TMS)_2CHSO(NTMS)Ph$] showed a chiral tetramer structure with C_2 symmetry consisting of two (*R*),(*R*) and two (*S*),(*S*) diastereomers.[39] As was found above, the lithium cation formed four-membered chelate rings involving the atoms Li–C_α–S–N and Li–N S–O. In THF solution, however, ^{13}C NMR experiments suggest that the lithiated sulfonimidoyl carbanion forms a THF-solvated aggregate having little or no C_α–Li contact. Earlier solution ^{13}C NMR studies in THF concluded that C_α in lithiated

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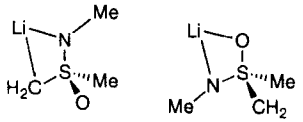
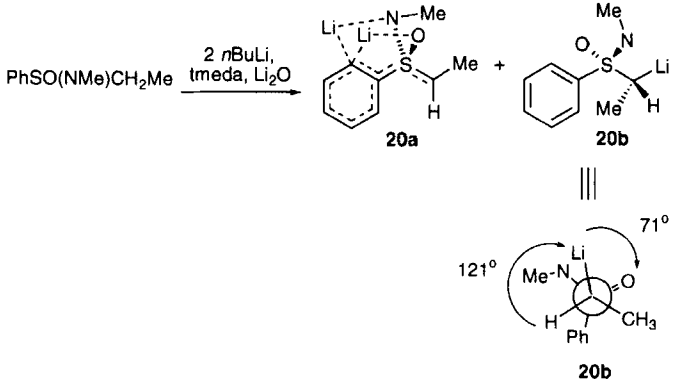
PhSO(NMe)Me was hybridized intermediate between pyramidal and planar.[40]

More recently, the gas phase structures of a lithiated *N*, *S*, *S*-trimethylsulfoximine have been calculated by *ab initio* methods.[41] It was found that a Li–C_α–S–N four-membered chelate **18** was the most stable isomer and the complex involving a Li–N–S–O four-membered chelate (**19**) was only 1.4 kcal/mol higher in energy. The alternative complex involving a Li–C_α–S–O four-membered chelate was 6.1 kcal/mol higher in energy.



18 **19**

A single crystal X-ray structural analysis of dilithiated racemic *S*-ethyl-*N*-methyl-*S*-phenylsulfoximine/tmeda complex has been reported.[42] The unit cell contains two clusters, each composed of two sulfoximine dianions with the (*R*) configuration and two sulfoximine monoanions with the (*S*) configuration together with three tmeda molecules. The dianion shows two Li–C contacts with the *ortho*-C of the *S*-phenyl substituent, as shown in **20a** rather than the α-carbon. The monoanionic sulfoximine moiety shows Li–C_α contacts and the Li-substituent adopts a gauche conformation with respect to the *N*- and *O*-substituents of the sulfoximine group as shown in **20b**. This conformation is most likely favoured by a stabilizing n_C–σ^* interaction between the nonbonding orbital (n_C) on the α-carbon atom and the σ^* orbital of the S–Ph bond. Furthermore, the C_α methyl substituent is *anti* to the *N*-methyl substituent.



20a **20b**

20b

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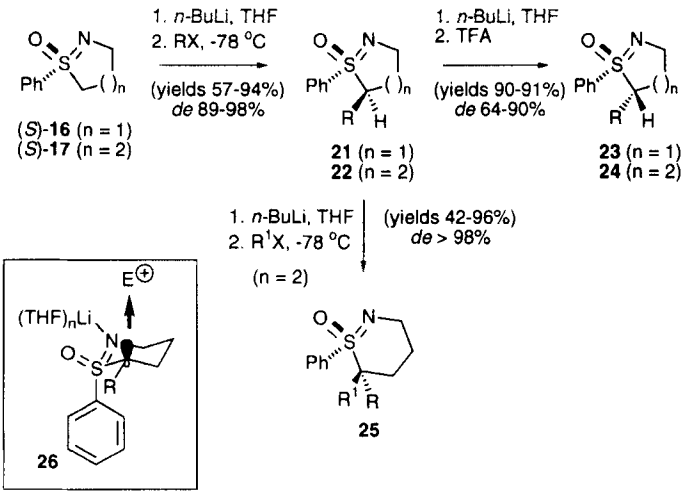
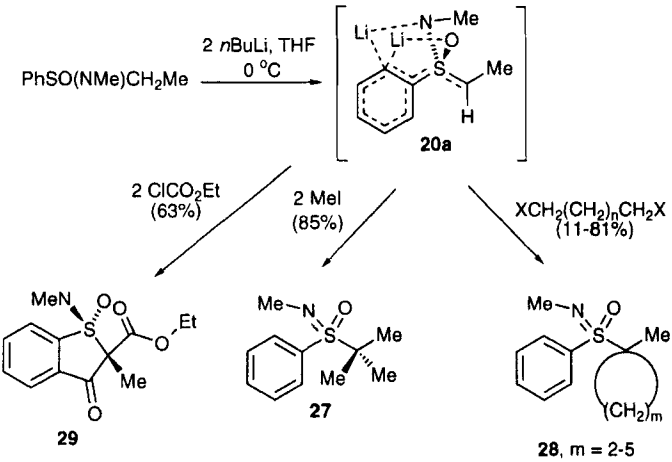
2.2.2. *Reactions with Alkylating Reagents*

Alkylation of the α-lithiated derivatives of the enantiomerically pure cyclic sulfoximines **16** and **17** with primary alkyl halides gave in high diastereomeric purities the corresponding alkylated products **21** and **22**.[37] Further treatment of these products with base and then trifluoroacetic acid (TFA) gave the corresponding epimeric products **23** and **24**, respectively. Treatment of lithiated **22** with a different alkylating agent (R^1X) gave the α,α-disubstituted adducts **25** in high diastereomeric purities. Thus all reactions are diastereoselective and electrophilic attack occurs from the side of the sulfoximine oxygen or *anti* to the *S*-phenyl substituent. The stereochemical outcome of these reactions was rationalized as arising from attack by the electrophile (RX or TFA) on the lithiated sulfoximine that would be expected to prefer the conformation **26**. This conformation was expected to be favoured because of a stabilizing n_C–σ^* interaction between the nonbonding orbital on the α-carbon atom and the σ^* orbital of the S–Ph bond. Consequently the S–Ph substituent is pseudo-axial. Attack on X would be expected from the top side of the molecule due to possible electrophilic assistance from the lithium cation and steric shielding of the bottom face by the S–Ph group.



Dilithiated racemic *S*-ethyl-*N*-methyl-*S*-phenylsulfoximine **20a** has been treated with electrophiles. For example, treatment with 2 molar equivalents of iodomethane gives the α,α-dimethylated product **27** in

85% yield.[32] Surprisingly, only traces (< 3%) of *ortho*-methylated products, that could arise from methylation of **20a**, could be detected by GC/MS. To explain this result it has been suggested that α-methylation occurs initially, followed by a translithiation from the *ortho*-position to the α-carbon. Similar reactions with bis-electrophiles gave cyclic sulfoximines **28**, including cyclopropane (11% yield) and cyclobutane derivatives (27% yield). Interestingly, treatment of the dianion with 2 equivalents of ethyl chloroformate gave the heterocycle **29** in which a bond has formed between the *ortho*-C and the electrophilic reagent.



Trost has reported a study on the alkylation reactions of different (*S*)-*N*-substituted sulfoximines **30**.[43] In contrast to our findings on the reactions of lithiated sulfoximines with aldehydes and imines,[1,44-46] the diastereoselectivity of the benzylation of lithiated **30** was not significantly dependent upon the steric demand of the *N*-substituent. The best diastereoselectivity (dr = 91 : 1) was found with the *N*-nitrosulfoximine derivative **30** (R = NO_2). Trost has suggested that the enhanced diastereoselectivity found using *N*-nitrosulfoximines is due to "its participation as a coordinating substituent for lithium".[43] The stereochemical outcomes of these alkylation reactions, for reasons that have been suggested above (see structure **26**) and published previously,[1,46] can be rationalized by evoking alkylation of the lithium chelated intermediate **32** from the less hindered face (*anti* to the *S*-phenyl substituent) with possible electrophilic assistance from the lithium cation.

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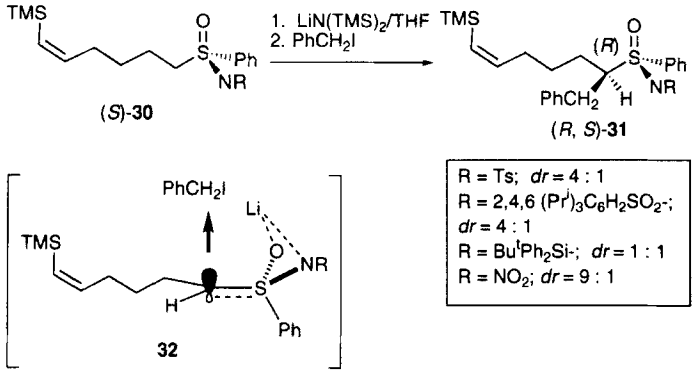
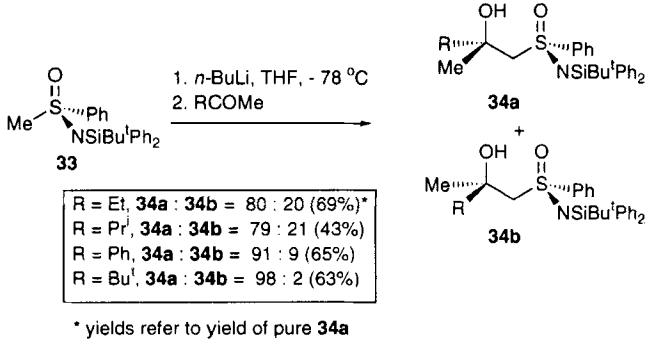


2.2.3. *Reactions with Aldehydes and Ketones: Synthesis of β-Hydroxy Sulfoximines and Oxiranes*

The diastereoselectivities and the stereochemistry of the products from the reactions of α-lithiated *N*-silylated-*S*-methyl-*S*-phenylsulfoximines with aldehydes have been summarized in the previous review.[1] The reaction of lithiated (+)-(*S*)-*N*-*tert*-butyldiphenylsilyl-*S*-methyl-*S*-phenylsulfoximine **33** with prochiral methyl ketones (RCOMe) gives a mixture of the diastereomeric β-hydroxy sulfoximine adducts **34a** and **34b**. The diastereoselectivity increased as the steric demand of the R group in RCOMe increased. In each case the major diastereomer could be isolated diastereomerically pure after purification of the crude reaction mixture by column chromatography or recrystallization. The relative (2*S*,S*S*) stereochemistry of the major adducts was determined by single crystal X-ray structural analysis.[47]



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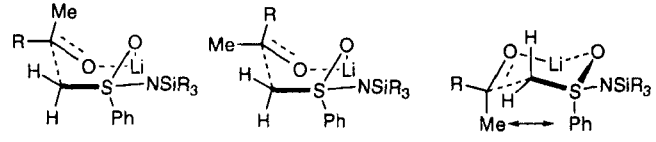
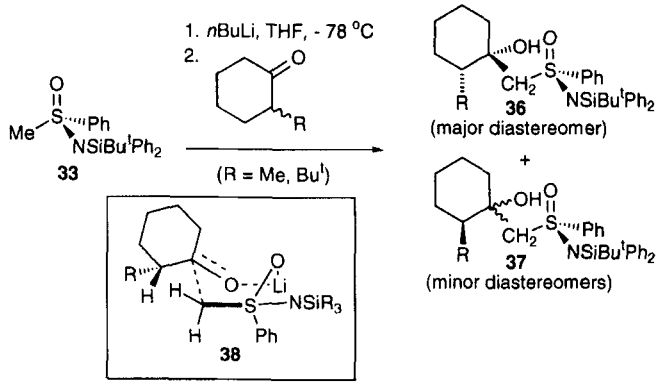
The stereochemical outcome of these reactions was rationalized as arising from the two competing boat transition states **35a** and **35b**. The difference in free energy between **35a** and **35b** and hence the diastereoselectivity, would be expected to increase as the steric demand of the R group of the ketone increases due to an increasing flagpole interaction between R and the sulfoximine oxygen in **35b**. Competing chair transition states (e.g. **35c**) were thought to be less favourable for steric reasons.[47]



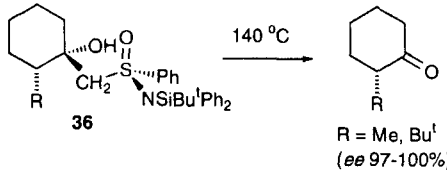
35a **35b** **35c**

The reaction of lithiated optically active **33** with racemic 2-alkylcyclohexanones gave three diastereomeric products, **36** and **37**; the latter product was obtained as a mixture of diastereoisomers. The preference for the formation of **36** was rationalized as occurring via the favoured boat transition state **38**.



33 **36** **37** **38**

Thermolysis of diastereomerically pure **36** gave (−)-(*R*)-2-methylcyclohexanone and (−)-(*S*)-2-*tert*-butylcyclohexanone, in 97% and 100% enantiomeric purities, respectively.[47]



36

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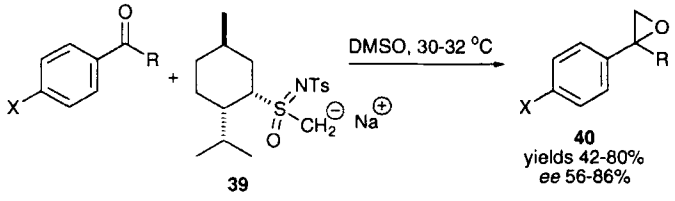
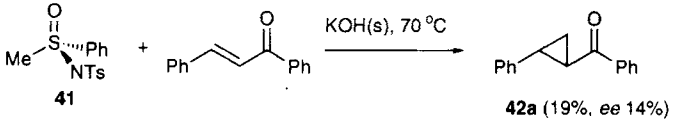
The formation of optically active oxiranes from the reaction of optically active sulfoximines and ketones by Johnson is reported in my earlier review.[1] The enantiomeric purities of the product oxiranes were not high (ee $< 40\%$). In an attempt to enhance the optical purities of these products the use of the ylide derived from (−)-*N*-tosyl-*S*-methyl-*S*-neomenthylsulfoximine **39** has been investigated. The enantiomeric purities of the oxirane products **40** ranged from 56% to 86%.[48] A related study using *S-exo*-2-bornylsulfoximines gave oxiranes in similar enantiomeric purities.[49]



2.2.4. *Reactions with Enones:* 1,2- *versus* 1,4-*Addition and the Synthesis of Cyclopropanes*

Johnson first described the cyclopropanation of chalcone using lithiated *N*-tosyl *S*-alkyl-*S*-phenylsulfoximines in 1973.[1,16] In one example, an optically active (ee 49%) cyclopropane [(1*S*,2*S*)-(2-phenylcyclopropyl) phenyl ketone] was prepared from the reaction of chalcone and lithiated (*R*)-*N*-tosyl-*S*-methyl-*S*-phenylsulfoximine (ee 84%) at room temperature (rt) for 12 h. More recently a solid-state version of this reaction was reported.[50] Treatment of a mixture of powdered chalcone, (+)-*N*-tosyl-*S*-methyl-*S*-phenylsulfoximine **41** and KOH in the solid state at 70 °C gave optically active phenylcyclopropyl phenyl ketone **42a** in poor yield (19%) and optical purity (14% ee). The yields could be enhanced to 94% using Bu^{t}OK at room temperature; however, the optical purity of **41** was still low (24% ee). The use of an optically active host molecule had an adverse affect on the optical purity of **42a**.



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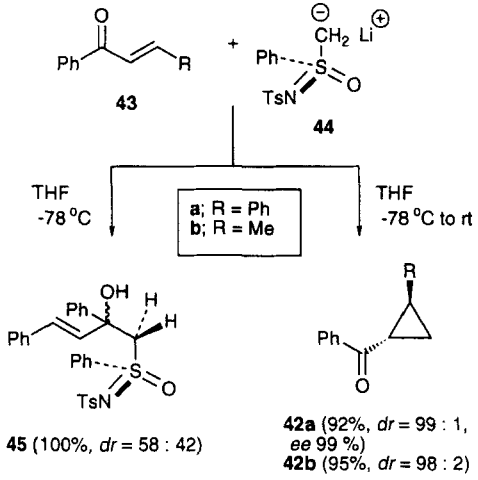
The reaction of optically active lithiated (*S*)-*N*-tosyl-*S*-methyl-*S*-phenylsulfoximine **44** (ee 99%) with enone **43a** at −78 °C gave exclusively the 1,2-adduct **45** as a 58 : 42 diastereomeric mixture in quantitative yield.[52] When this reaction was performed at rt the optically active and diastereomerically pure cyclopropane **42a** was isolated in 88% yield. The enantiomeric purity of **42a** ($[\alpha]_D^{27}$ −388° (c 0.05, acetone)) was judged to be 99% based on the reported specific rotation of enantiomerically pure **42a** (lit.[16] $[\alpha]_D^{25}$ +390.5° (c 1.0, acetone)).



Treatment of **45** with LDA at −78 °C, followed by warming the reaction mixture to rt for 1 h gave the diastereomerically pure cyclopropane **42a** in 60% yield. Surprisingly, oxirane products, that could potentially arise from nucleophilic displacement of the sulfonimidoyl group by the alkoxide in **46**, could not be detected in the crude reaction mixture. This experiment indicated that at rt the kinetically favoured anionic 1,2-adduct **46** is in equilibrium with the anionic 1,4-adduct **47** and that the latter undergoes intramolecular displacement of the sulfonimidoyl group (to give **42a**) at a much faster rate than the former anion that could give rise to an oxirane. The reaction of racemic **44** with enone **43b** gave the cyclopropane **42b** in high diastereomeric purity (dr = 98 : 2 from GC analysis) in 95% yield.

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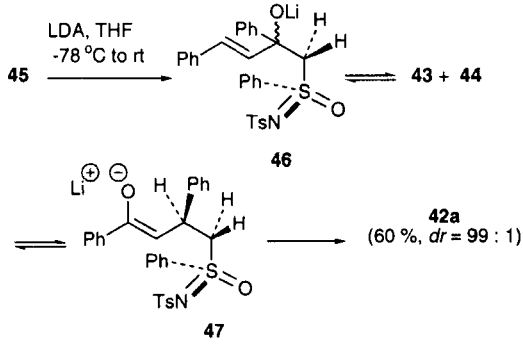
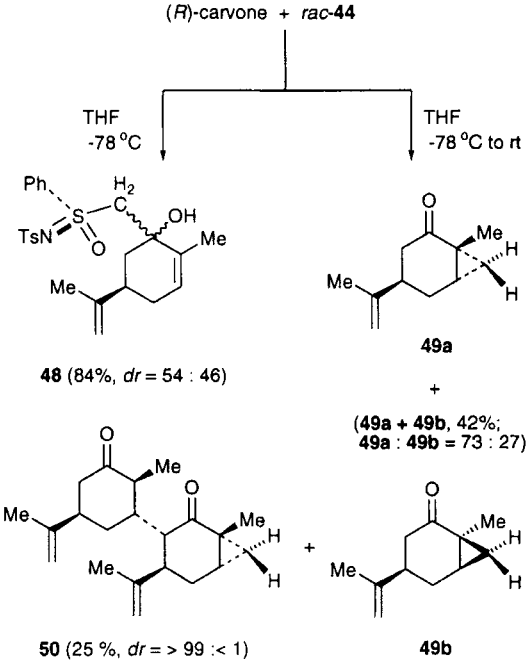


Treatment of (*R*)-carvone with racemic **44** gave a mixture of the diastereomeric 1,2-adducts **48** at −78 °C and the diastereomeric cyclopropanes **49a,b**, and the double addition product **50** as a single diastereoisomer at rt. The diastereoselectivity in the case of **49** was similar to that obtained when (*S*)-**44** was employed. Compound **49** has been prepared as a single diastereoisomer by Corey and Chaykovsky.[53]



Racemic and optically active (*S*)-*N*-tosyl-*S*-butyl-*S*-phenylsulfoximine have been prepared by alkylation of lithiated racemic **44** or

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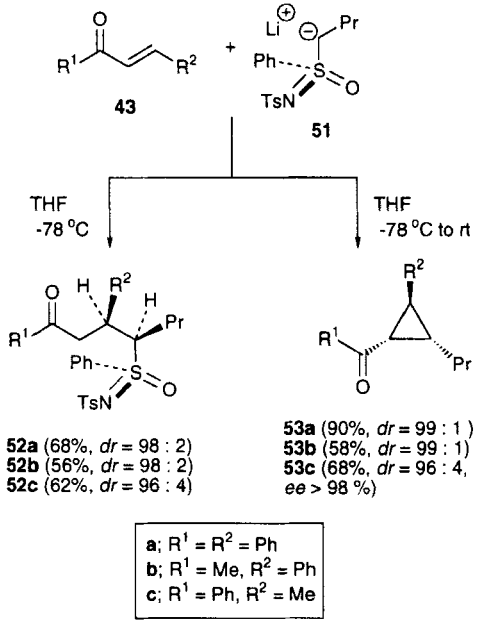
(*S*)-**44**[51,52] (ee 97%) with bromopropane, respectively. Treatment of lithiated racemic *N*-tosyl-*S*-butyl-*S*-phenylsulfoximine **51** with the acyclic enones **43a–c** at −78 °C gave mixtures of 1,2- and 1,4-adducts. The latter were formed in high diastereomeric purities (dr = 98-96 : 2-4) while the former were formed as diastereoisomeric mixtures. The relative stereochemistry of **52a** was determined by X-ray diffraction.[52] When these reactions were performed at rt, the cyclopropanes **53a–c** could be isolated in high diastereomeric purities. Optically active **53a** and **53c** were obtained from the reaction of (*S*)-**51** with **43a** and **43c**, respectively. The enantiomeric purity of **53c** was determined to be 98% from ^{1}H NMR studies using chiral shift reagents, while that of **53a** could not be determined in this manner. However the ee of **53a** was thought to be high, based upon its diastereomeric purity and the magnitude of its specific rotation when compared to that of **53c**.



2.3. Other Reactions

The resolution of racemic ketones based on the reversible addition of (*R*)- or (*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine to these compounds has been reviewed[1] and still remains a popular and useful method.[54,55]

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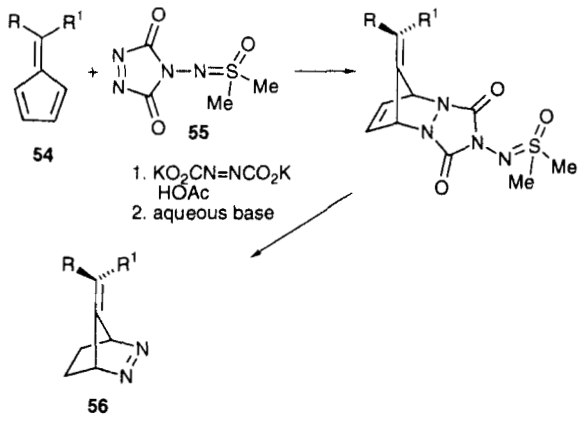
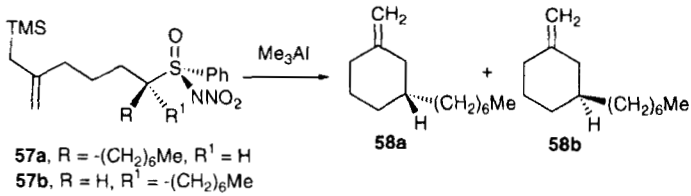
A new synthesis of diazenes (azoalkanes) has been developed using 4-(*S,S*-dimethylsulfoximino)-1,2,4-triazoline-3,5-dione **55**.[56] Treatment of fulvenes **54** with **55**, followed by diimide reduction of the carbon–carbon double of the resulting cycloadduct and then mild base treatment, gave the diazenes **56** in good overall yields.



Trost[43] has reported that *N*-nitrosulfoximines undergo Lewis acid promoted cyclizations to tethered allylsilanes, enol silyl ethers and activated aromatic rings. For example, the allyl silane **57** (3 : 1 mixture of **57a** and **57b**, respectively) underwent cyclization upon exposure to trimethylaluminium in refluxing dichloromethane to give a 3 : 1 mixture of the diastereomeric methylenecyclohexanes **58a** and **58b**, respectively. This reaction proceeded with inversion of stereochemistry at the stereogenic carbon bearing the sulfoximine leaving group.



57a, R = -$(CH_2)_6$Me, R^1 = H
57b, R = H, R^1 = -$(CH_2)_6$Me

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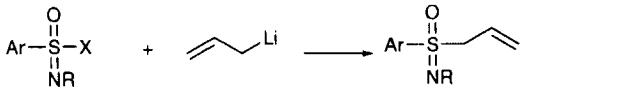
3. ALLYLIC SULFOXIMINES

3.1. Synthesis

Johnson disclosed the synthesis of the first reported allylic sulfoximine **60a** in 1979.[3] Treatment of racemic phenyl *N*-methylbenzenesulfonimidate **59** (X = OPh) with allyl lithium at 0–3 °C gave racemic *S*-allyl-*N*-methyl-*S*-phenylsulfoximine **60a** in 71% yield. Harmata[57] has used a method related to that developed by Johnson[4] to prepare the allylic sulfoximine **60b** from the reaction of allyllithium with the sulfonimidoyl fluoride **59** (X = F). The yield, however, was low (20%).



59 X = OPh, F

60a 71% X = OPh, Ar = Ph, R = Me
60b 20% X = F, Ar = *p*-Tol, R = Ph

In 1991 Gais reported a useful method for preparing allylic sulfoximines via base-catalysed (LiOMe, 3 equiv. THF/toluene/*n*-hexane) isomerization of vinyl sulfoximines.[58] The combination KOMe/THF was also found to be effective.[59] Vinyl sulfoximines can readily be obtained from the condensation of lithiated sulfoximines with aldehydes and ketones, followed by either dehydration of the resulting β-hydroxy sulfoximines by treatment with methanesulfonyl chloride/triethylamine and then elimination of the resulting mesylate with DBU[9,10] or triethylamine[60] or by trapping the intermediate lithium β-alkoxy sulfoximine with trimethylsilyl chloride[61] or methyl chloroformate,[31] followed by elimination of the β-oxygen substituent with *n*-butyllithium[61] or potassium *tert*-butoxide,[31] respectively. The former method, using DBU, gives mixtures of the vinyl sulfoximine **62** and the allylic sulfoximine **63**. Treatment of this mixture with KOMe/THF gives the allylic sulfoximines **63**.[62] The (*E*) isomer of **63** is usually the only or major isomer formed.[62]

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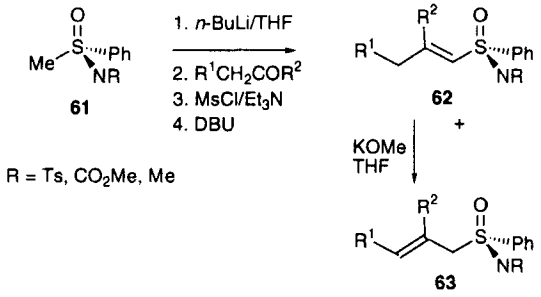
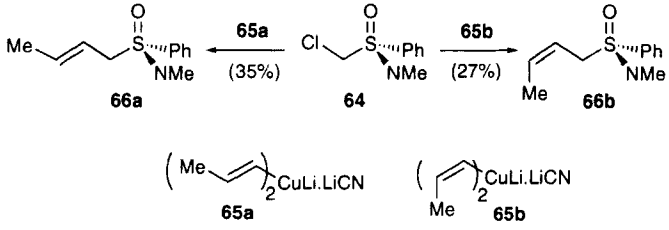


Recently Gais[63] disclosed a useful method for preparing enantiomerically and diastereomerically pure (*E*) or (*Z*) allylic sulfoximines from (+)-(*S*)-*S*-(chloromethyl)-*N*-methyl-*S*-phenylsulfoximine **64**. For example, treatment of **64** with the (*E*)- or (*Z*)-1-propenyl cuprates **65a** and **65b**, respectively, gave the corresponding (*E*)- and (*Z*)-allylic sulfoximines **66a** and **66b**. Unfortunately, the yields were not high for these reactions. This method is also successful for the preparation of the corresponding *S*-benzyl sulfoximine from the reaction of **64** with $Ph_2CuLi{\cdot}LiCN$.



Treatment of enantiomerically pure cyclic sulfonimidates **3** and **4** with allyllithium or allylmagnesium bromide gives the optically active allylic sulfoximines **5** and **6** (R = allyl) as described above in Section 2.1.[11] The reactions of *N*-phenyl-*S*-(methylphenyl)sulfoximidoyl chloride **67** with allyltrimethylsilane or allyltributylstannane in the presence of aluminium chloride gave mixtures of the benzothiazine **68** and the allyl sulfoximine **69**.[57] The organostannane gave better yields of the allylic sulfoximine **69**. This method was successfully used to prepare the *N*-*o*-methylphenyl, *N*-*o*-bromophenyl and *N*-benzyl analogues of **69**.

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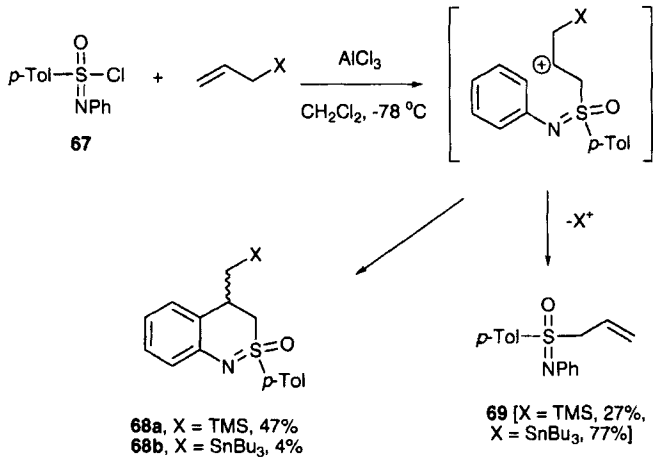
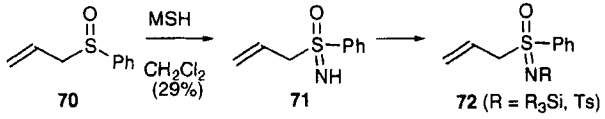
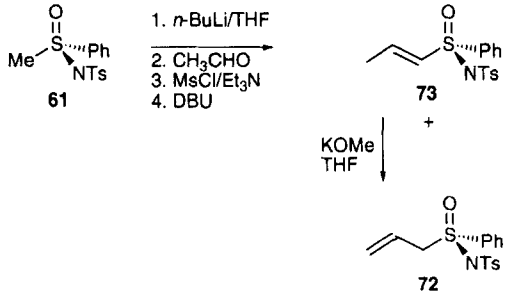


The imination of racemic allyl phenyl sulfoxide **70** with *O*-mesitylsulfonylhydroxylamine (MSH)[15] using a modification of the procedure described by Johnson,[14] gave the allylic sulfoximines **71** in poor yield (29%).[64] This compound was readily converted to the *N*-tosyl or *N*-silyl derivatives **72**.[62,64]



The optically active version of **72** (R = Ts) can be prepared from (*S*)-**61** (R = Ts) and acetaldehyde as shown below.[62]



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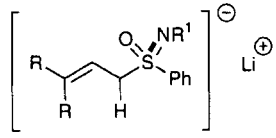
3.2. Lithiated Allylic Sulfoximines

3.2.1. Structural Studies

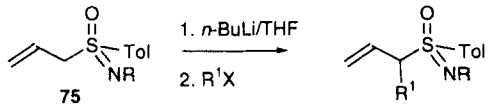
The crystal structures of three lithiated allylic sulfoximines have been reported.[41,65] The X-ray crystal structure of lithiated **73**/12-crown-4 complex showed solvent separated contact ion pairs of $[Li(12\text{-crown-}4)_2]^+$ and the allylic sulfonimidoyl anion.[65] The anion adopts a conformation in which the p-orbital at C_α is gauche to both the oxygen and nitrogen substituents of the sulfur atom. This conformation suggests a stabilizing $n_C-\sigma^*$ interaction between the nonbonding orbital on the α-carbon atom and the σ^* orbital of the S–Ph bond. A similar gauche conformation has been found in the solid state structure of racemic lithiated **74**.[41] Lithiated **74** forms a dimeric structure in which two allylic sulfonimidoyl anions with opposite chirality are linked by N–Li–O bridges to give an eight-membered ring with the atom sequence $(Li-N-S-O)_2$.



73, R = Me, R^1 = TMS
74, R = Ph, R^1 = Me

3.2.2. Reactions with Alkylating Agents

The alkylation of the lithiated allylic sulfoximine **75** (R = Ph or CH_2Ph) is completely regioselective and gives only α-alkylation products **76**.[57] The products were formed as mixtures of diastereoisomers; however, the diastereomeric ratios were not reported.



75
(R = Ph, CH_2Ph)
(54-81%)
76
(R^1 = Me, Et, allyl)

Lithiation and then methylation of the optically active allylic sulfoximine **77** gave the α-alkylation product **79** as a single diastereoisomer.[62]

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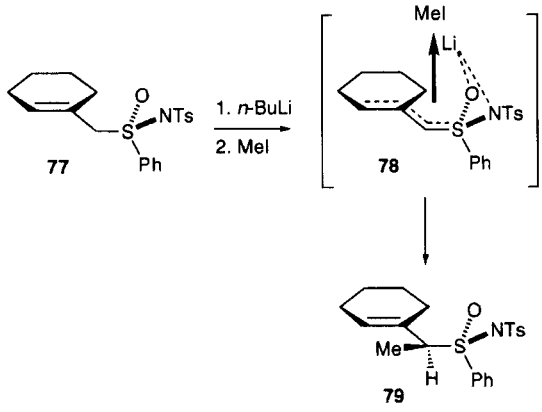
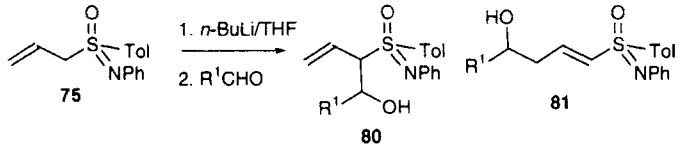
The stereochemistry of this compound was deduced by its transformation to a compound of known stereochemistry. The stereochemical outcome of this reaction was rationalized as arising from methylation of the lithiated species **78** in which the p-orbital at C_α is gauche to both the oxygen and nitrogen substituents of the sulfur atom. Methylation of **78** would be expected to occur *syn* to lithium and *anti* to the S–Ph group.



3.2.3. *Reactions with Aldehydes and Ketones: α- versus γ-regioselectivity*

The reaction of lithiated **75** with benzaldehyde gave a 5.3 : 1 mixture of the α-adduct **80** and the γ-adduct **81**, while a similar reaction with pivaldehyde produced only the α-adduct **80**.[57] These products were formed as mixtures of diastereoisomers, however, the diastereomeric ratios were not reported. In related examples, α-adducts were exclusively obtained from the reaction of lithiated *N*-tert-butyldiphenylsilyl[64] and *N*-methyl[66] allylic sulfoximines with aldehydes. Again these products were mixtures of diastereoisomers.



R^1 = Ph, 79%, **80** : **81** = 5.3 : 1
R^1 = Bu^t, 63%, **80** : **81** = 100 : 0

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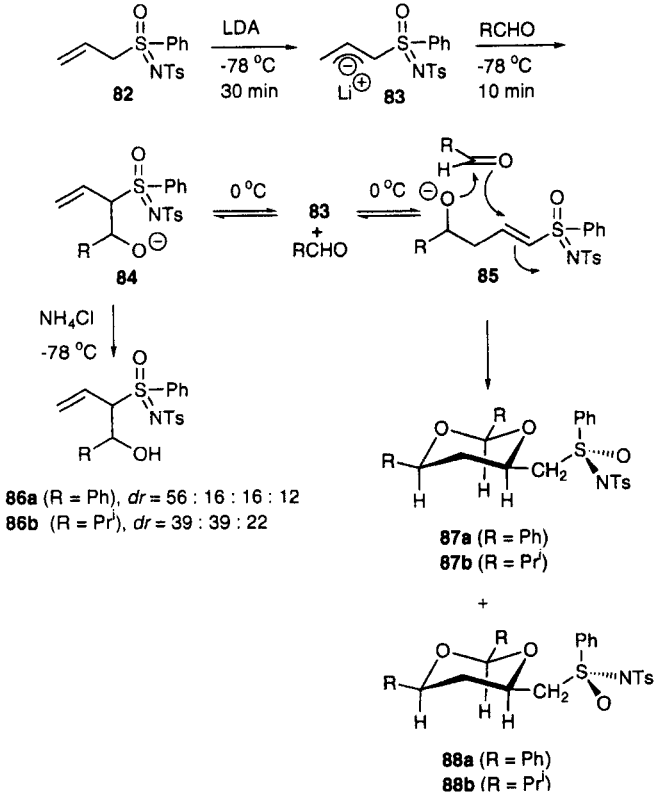
Lithiation of racemic *N*-tosyl allylic sulfoximine **82**, followed by quenching the reaction at −78 °C with benzaldehyde or isobutyraldehyde gave the α-adducts **86a** and **86b**, respectively, as mixtures of diastereoisomers.[67] Interestingly, when these reactions were performed with an excess of the aldehyde (2 molar equiv.) and warmed to room temperature the novel 1,3-dioxanes **87** and **88** were formed in good yields [81% (R = Ph) and 62% (R = Pr^i)] as 1 : 1 mixtures of diastereoisomers. The 1,3-dioxanes **87** and **88** were proposed to arise from the anionic γ-adduct **85** that must be formed from the kinetically favoured anionic α-adduct **84** via a reversible aldol-type reaction.[67]



In contrast, titanated allylic sulfoximines, which can be prepared from lithiated allylic sulfoximines by transmetallation with

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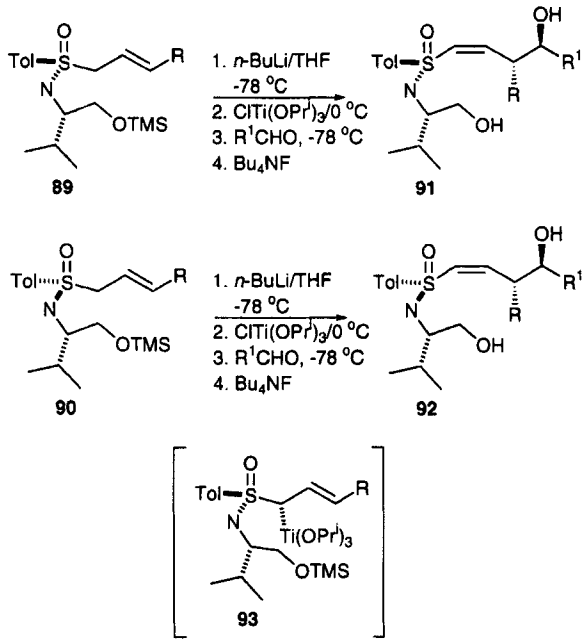
chlorotris(isopropoxy)titanium, react with aldehydes to give γ-adducts in a highly regioselective and diastereoselective manner.[68–71] For example, lithiation of the enantiomerically pure allylic sulfoximines **89** and **90** with *n*-butyllithium, followed by the addition of chlorotris(isopropoxy)titanium and then an aldehyde, gave exclusively the *anti*-(*Z*)-γ-adducts **91** and **92**, in high diastereomeric purity (> 97%). The stereochemical outcome of these reactions seems to be controlled predominantly by the configuration at the sulfur atom rather than that of the valine substituent. It has been suggested that transmetallation of lithiated **89** produces the configurationally stable titanium compound **93**.[68,69] These reactions are also highly regio- and diastereoselective with related cycloalkenyl sulfoximines.[69]



The reactions of titanated **89** and **90** with (*R*) and (*S*) TBDMS-protected lactaldehyde [MeCH(OTBDMS)CHO] are also highly diastereoselective. Very high levels of diastereoselectivity (> 98%) were observed when the facial selectivity of the allylic sulfoximine anion

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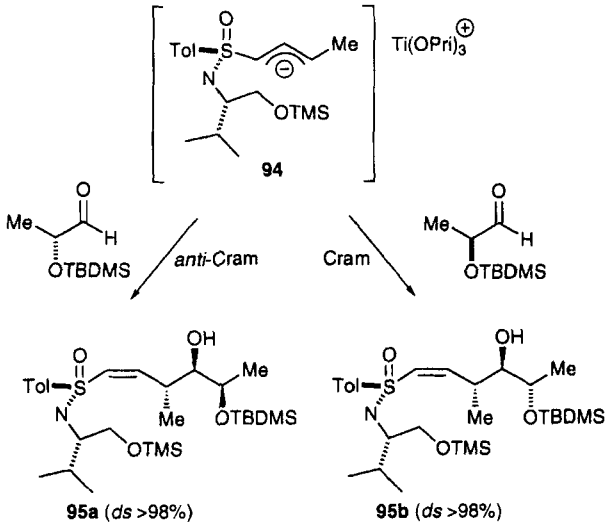
matched that of the chiral aldehyde (the matched case).[69,70] In the mismatched cases the diastereoselectivities were less but still relatively high (ds 80–98%). In the case of the titanated allylic sulfoximine anion **94** the asymmetric induction from the chiral aldehyde was overridden by that of the sulfoximine anion and high diastereoselectivities were observed in both the *anti*-Cram and Cram products **95a** and **95b**, respectively.



Optically active lithiated *N*-methyl allylic sulfoximines **96** which have undergone transmetallation with chlorotris(isopropoxy)titanium also react with aldehydes to give *anti*-(*Z*)-γ-adducts **97** in a highly regioselective and diastereoselective manner (de >95%).[71] The yields, however, are generally less than 50%, suggesting that a diorganotitanium compound is formed that only transfers one allyl sulfoximine ligand to the aldehyde.

In contrast, when the transmetallation is performed with chlorotris(diethylamino)titanium the resulting titanium species reacts with aldehydes to give (*E*)-*syn*-α-adducts **98** with very high regioselectivity (>95%) and diastereoselectivity (>95%).[72] The corresponding (*Z*) isomer of **96** ($R^1 = Pr^i$, $R^2 = H$) gives the corresponding (*Z*)-*syn*-α-adducts. In all cases the yields were good (70–76%).

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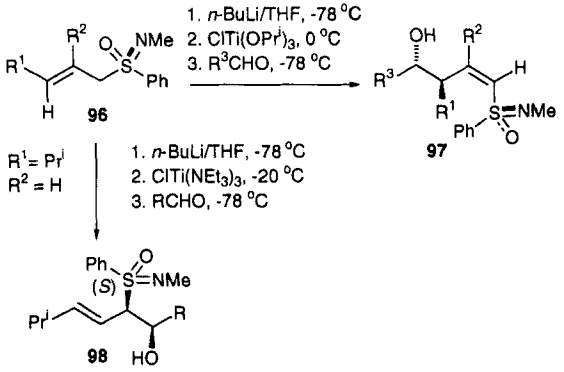
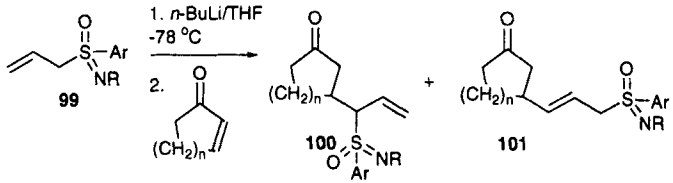


3.2.4. *Reactions with Enones:* 1,2- *versus* 1,4-*addition and the Synthesis of Cyclopropanes*

The reactions of lithiated sulfoximines **99** with cyclic enones give mixtures of regio- and diastereoisomers. The regioselectivity is dependent upon the nature of the *N*-substituent on sulfur.[52,57,64] *N*-Tosyl derivatives give exclusively α-1,4-addition products (**100**), while this type of adduct is only slightly favoured in the case of *N*-phenyl derivatives. *N-tert*-butyl-diphenylsilyl (TBDPS) derivatives, however, favour γ-1,4-adducts (**101**). In all cases the adducts were formed as mixtures of diastereoisomers except in the case of the γ-1,4-adduct **101** ($n = 1$, Ar = Tol, R = Ph) which was obtained in low yield as a single diastereoisomer.[57]



Ar	R	n	100 : 101	reference
Tol	Ph	1	58 : 42	[57]
Tol	Ph	2	60 : 40	[57]
Ph	TBDPS	1	15 : 85	[64]
Ph	TBDPS	2	16 : 84	[64]
Ph	Ts	1	100 : 0	[52]
Ph	Ts	2	100 : 0	[52]

Treatment of a solution of racemic lithiated *N*-tosyl-*S*-allyl-*S*-phenylsulfoximine **103** at −78 °C with the acyclic enones **102a–c** (1.2 equiv.)

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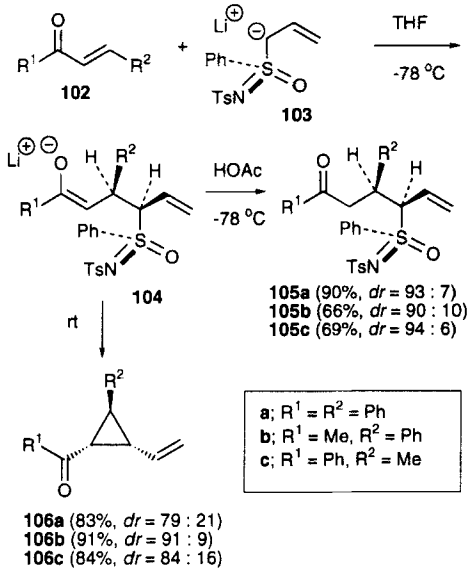
for 3 min gave, after quenching at −78 °C with acetic acid, the racemic 1,4-α adducts **105a–c** in modest to excellent yields. The product diastereoselection ranged from 90 : 10 to 94 : 6. The relative ($3R^*$,$4R^*$,SS^*) stereochemistry of **105a** was determined by X-ray structural analysis and has been rationalized as occurring via the transition state structure **A** in which the largest groups on the two reacting partners (R^2 and the sulfonimidoyl group) are *anti* in order to minimize steric interactions.[52,73]

Warming a solution of the anionic adducts **104a–c** to rt for 1 h gave the racemic vinylcyclopropanes **106a–c** in good yields (83–91% after column chromatography) and, in the case of the cyclopropyl phenyl ketones **106a** and **106c**, in lower diastereoselectivity than their respective Michael adducts **105a** and **105c**. In contrast, the diastereoselectivity observed for the cyclopropyl methyl ketone **106b** was essentially identical to that found with its related Michael product **105b**. Cyclopropane **106b** was easily obtained diastereomerically pure by column chromatography. Enantiomerically enriched (1*S*,2*R*,3*S*)-**106b** was prepared from the reaction of enantiomerically enriched (*S*)-**103** (ee 94%) and **102b** under identical reaction conditions and procedures as described above. ^{1}H NMR studies using the chiral shift agent europium tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] indicated that the enantiomeric purity of **106b** was 95% after correction for the enantiomeric purity of (*S*)-**103**.



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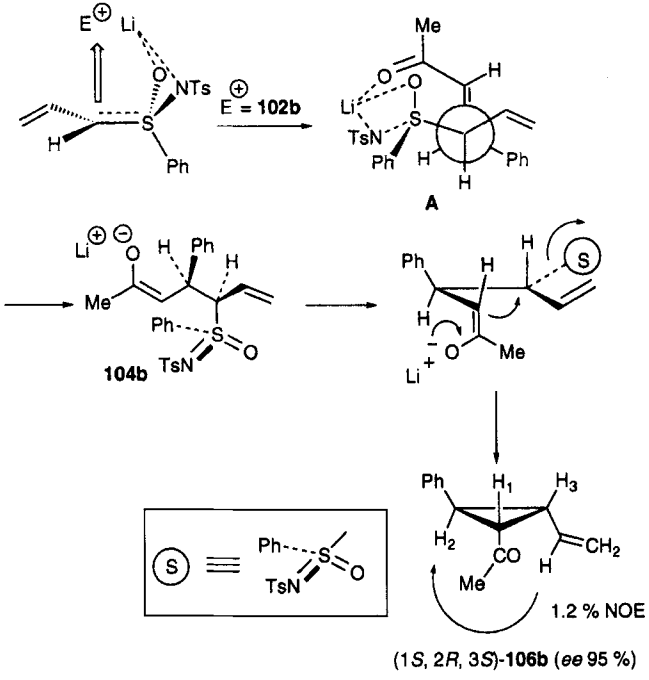
The stereochemistry of **106b** was established by NMR and NOE difference experiments. The stereochemistry of **106b** was that expected for an intramolecuar nucleophilic displacement reaction of the sulfoximidoyl group from the intermediate **104b**, with inversion of stereochemistry at the carbon bearing the sulfonimidoyl group.



(1*S*, 2*R*, 3*S*)-**106b** (*ee* 95 %)

The reaction of racemic **103** with (*R*)-carvone, initially at −78 °C, followed by warming to rt for 1 h, gave the vinylcyclopropane **107** in 72% yield and moderate diastereoselectivity (dr = 75 : 25). The stereochemistry of the major diastereoisomer is that shown in structure **107**. That was expected from ^{1}H NMR studies based upon the stereochemical outcome of the reaction of racemic **103** with the achiral cyclic enones **102** and consistent with our previously proposed chelated transition state[73] for cyclic enones (compare with the transition state **B**).

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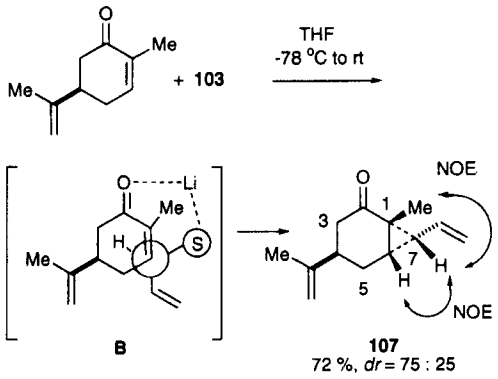
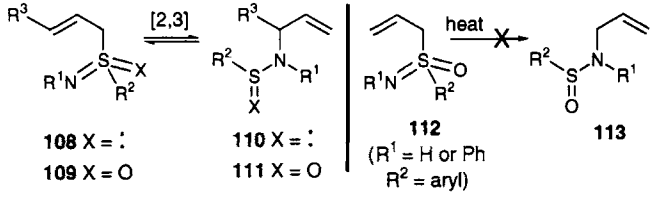


3.3. Rearrangements to Allylic Sulfinamides and Related Reactions

While the [2,3] sigmatropic rearrangement of allylic sulfilimines **108** to allylic sulfinamides **110** has been well documented[74] the related thermal rearrangement of allylic sulfoximines **109** to allylic sulfinamides **111** is not generally a kinetically favoured process. For example, Tamura,[75] Harmata,[57] and Pyne[64] have reported that the simple allylic sulfoximines **112** are thermally stable in refluxing toluene solution. These results were in contrast to MNDO[57,64] and *ab initio*[76] calculations which suggested that allylic sulfinamides should be thermodynamically more stable than their isomeric allylic sulfoximines. These calculations indicated that this rearrangement process was unfavourable due to a high kinetic energy barrier.



In 1994, Gais[77] reported that enantiomerically pure γ-phenyl substituted allylic sulfoximines undergo partial rearrangement to their isomeric sulfinamides with retention of configuration of the sulfur atom. For example, thermolysis of the enantiomerically pure allylic sulfoximine **114** at 85 °C for 112 h gave, after chromatography, recovered enantiomerically pure **114** and minor amounts of the two isomeric enantiomerically pure allylic sulfinamides **115** and **116** in almost equal

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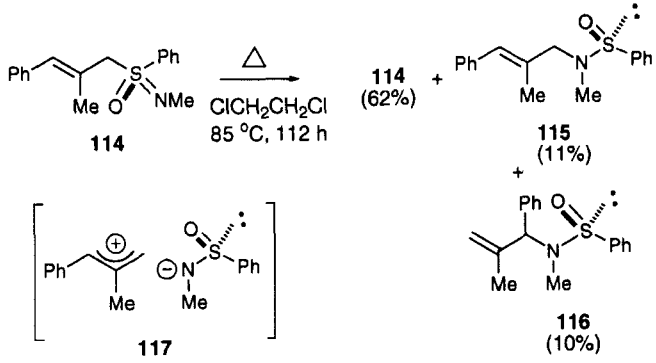
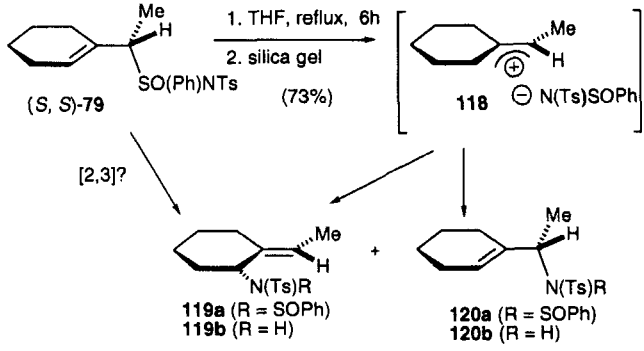
yields. This rearrangement was though to involve the ion pair intermediate **117** which is stabilized by the phenyl substituent.



In 1996, Pyne and Dong[62] reported that the thermolysis of (*S*,*S*)-**79** (ee 94%) in refluxing THF for 6 h gave a mixture of the rearranged allylic sulfinamides **119a** and **120a**. Exposure of this mixture to silica gel chromatography gave an inseparable 45 : 55 mixture of the sulfonamides **119b** and **120b** in 73% yield. These compounds were separated by HPLC and determined to be 87% and 88% enantiomerically pure, respectively. The absolute stereochemistry of **120b** was established by chemical correlation with a molecule of known absolute configuration. This thermal rearrangement was thought to occur via the intimate ion pair **118** with the anion being produced initially on the lower face of the cation for stereoelectronic reasons[62] or via a competing [2,3] sigmatropic rearrangement to give **119a**.



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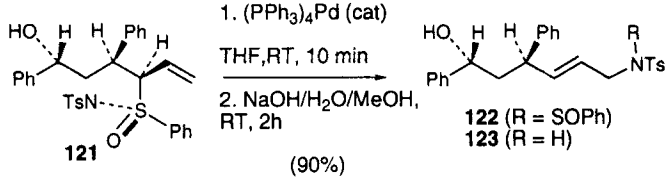
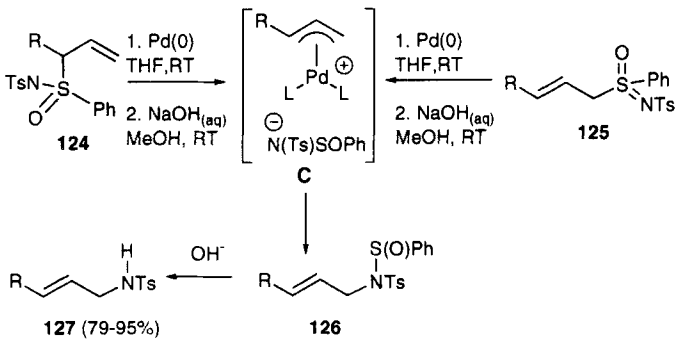
In 1995 Pyne and Dong[78] found that the allylic sulfoximine **121** underwent a facile and completely regioselective and efficient rearrangement to the allylic sulfinamide **122** in the presence of tetrakis(triphenylphosphine)palladium(0) ($(PPh_3)_4Pd$) catalyst (5 mol-%) at room temperature. Mild base hydrolysis of the reaction mixture (10% aqueous sodium hydroxide/methanol, 1 : 10, room temperature, 2 h) gave pure sulfonamide **123** after purification by column chromatography (silica gel) in 90% overall yield.



This mild rearrangement process was found to be general for both secondary **124**[79] and primary **125**[62] sulfoximines and in each case the reactions were completely regioselective and gave the primary allylic sulfonamide **127**. The overall yields ranged from 79% to 95% and the reactions were found to be compatible with other functional groups (e.g. hydroxyl and carbonyl groups).



It was assumed that the above palladium catalysed rearrangements occur via the allyl–palladium cation complex intermediate **C**, followed by attack of the ambident sulfinamide anion as a nitrogen nucleophile at the least hindered terminus of the allyl cation species, to give **126**. These palladium catalysed reactions also work well with cyclic allylic sulfoximines. For example, the cyclic sulfoximines **128** undergo palladium(0)

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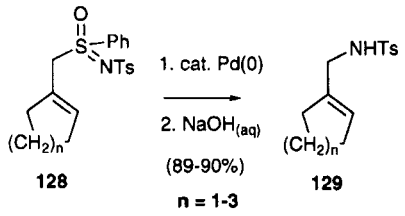
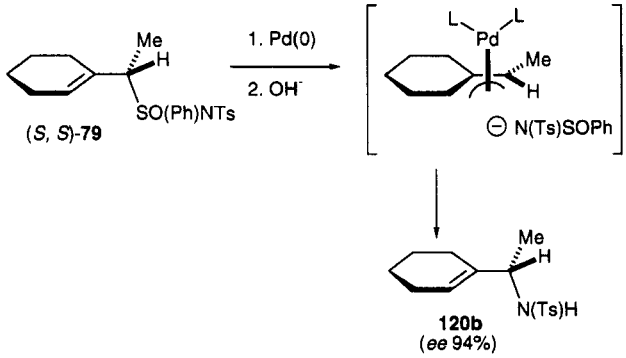
catalysed rearrangement to their corresponding allylic sulfinamides which upon mild base hydrolysis give exclusively the primary allylic sulfonamides **129** in excellent overall yields.[62]



128 **129**

Optically active (*S*,*S*)-**79** gave the optically active sulfonamide **120b** in 94% enantiomeric purity with overall retention of configuration at the allylic α-carbon.[62]



(*S*, *S*)-**79** **120b** (*ee* 94%)

Treatment of the (*E*) α-sulfonimidoyl β,γ-unsaturated ketones **130a** or **130b** or the ester **130c** with 10 mol-% of freshly prepared tetrakis(triphenylphosphine)palladium(0) ($(PPh_3)_4Pd$) in dry THF solution at rt for 1 h gave the unstable allylic sulfinamides **131a–c**. Mild methanolysis of the reaction mixtures with triethylamine/methanol at rt gave the pure (*E*)-sulfonamides **132a,c** (γ-amino α,β-unsaturated ketones) and the (*E*)-carbamate **132b** (γ-amino α,β-unsaturated ester) after purification of the crude reaction mixtures by column chromatography (silica gel) in overall yields of 32–68%.

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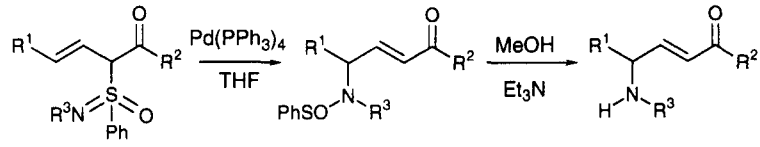

130a
130b
130c

131a
131b
131c

132a
132b
132c

a; R^2 = Ph, R^3 = Ts
b; R^2 = Ph, R^3 = CO_2Me
c; R^2 = OMe, R^3 = Ts

starting compound	product	yield(%)[a]
130a; R^1 = *n*-Bu	**132a**; R^1 = *n*-Bu	32
130b; R^1 = *n*-Bu	**132b**; R^1 = *n*-Bu	64
130a; R^1 = *n*-pent	**132a**; R^1 = *n*-pent	60
130b; R^1 = *n*-pent	**132b**; R^1 = *n*-pent	49
130a; R^1 = *n*-hexyl	**132a**; R^1 = *n*-hexyl	68
130c; R^1 = Et	**132c**; R^1 = Et	57

[a] after chromatography

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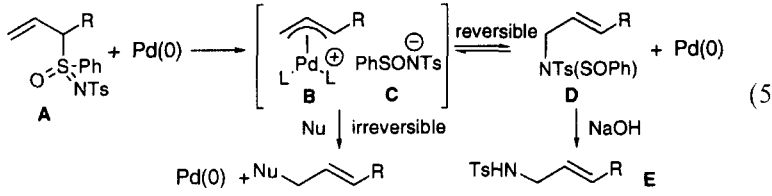
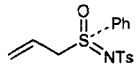
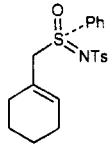
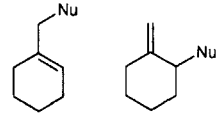
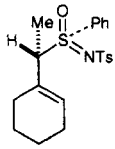
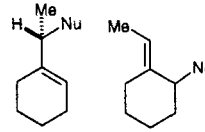
In principle, allylic sulfoximines can be used as substrates for the allylation of an external nucleophile (Nu) if that nucleophile can compete with the sulfinamide anion **C** for the palladium(0) complex **B** or if the formation of **D** is reversible. In 1997 Pyne and co-workers[81] reported that stabilised carbon and nitrogen nucleophiles can be efficiently allylated in a regioselective manner using allylic sulfoximines and palladium(0) catalysis (Eq. (5)).



A **B** **C** **D** **E** (5)

Treatment of the racemic allylic sulfoximines **133–135** with 5 mol-% of tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) in THF at rt for 10–30 min, in the presence of the nucleophiles dibenzylamine, sodium diethyl malonate or the lithium salt of *tert*-butyl *N*-(diphenylmethylene)glycinate (BDMG) (1.2 molar equivalents), gave the allylated products **136–140** in generally good yields with a good to high

TABLE I Allylation of nucleophiles by the allylic sulfoximines **133**–**135**

Entry	*Substrate*[a]	*Nucleophile*[b]	*Products* (*yield*[c] (%))
1	 **133**	A	 **136** (67)
2	 **134**	A	 **137** **138** Nu = Bn_2N (73); **137** : **138** = > 98 : < 2
3	**134**	B	Nu = $CH(CO_2Et)_2$ (77); **137** : **138** = 89 : 11
4	**134**	C	Nu = $CH(N{=}CPh_2)CO_2Bu^t$ (80); **137** : **138** = 94 : 6
5	 *rac*-**135**	C	 **139** **140** Nu = $CH(N{=}CPh_2)CO_2Bu^t$ (66); **139** : **140** = 90 : 10 (**139**; *dr* = 74 : 26)

[a]Unless indicated all compounds are racemic.
[b]Nucleophiles: A, dibenzylamine; B, sodium diethyl malonate and C, lithium salt of *tert*-butyl *N*-(dipbenylmethyne)glycinate.
[c]After purification by column chromatography on silica gel.

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regioselectivity (Table I). In general, the nucleophile added to the least substituted and/or sterically least demanding position of the allylic moiety. In the case of the allylic sulfoximine **133** it was found that compound **136** could also be obtained in a similar yield by first converting **133** *in situ* to its isomeric allylic sulfinamide **D** (R = H, Eq. (5)) by initial treatment of **133** with $Pd(PPh_3)_4$ in THF at rt for 15 min, followed by the addition of dibenzylamine. Thus, the allylic sulfinamide **D** (R = H, Eq. (5)) is readily converted to its allylic cation **A** (R = H, Eq. (5)) in the presence of Pd(0). The cyclic substrates **134** and **135** gave a mixture of regioisomers, **137** and **138** and **139** and **140**, respectively. The reaction of the secondary allylic sulfoxirnines **134** with dibenzylamine was completely regioselective and gave exclusively **137**.

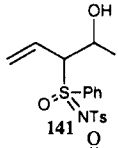
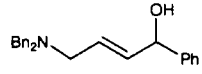
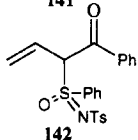
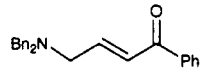
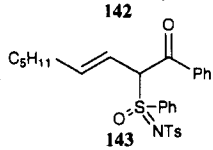
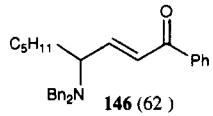
In the case of the reaction of the racemic allylic sulfoximine *rac*-**135** with the lithium salt of BDMG (Table I, entry 5, Nu = CH(N=CPh_2)CO_2Bu^t)) a 90 : 10 mixture of the regioisomeric adducts **139** and **140** resulted. The major regioisomeric product **139** (Nu = CH(N=CPh_2)CO_2Bu^t) was a 74 : 26 mixture of diastereoisomers.

The reactions of the secondary allylic sulfoximines **141**–**143** with dibenzylamine were completely regioselective and afforded the 4-amino alcohol **144** and the γ-amino enones **145** and **146**, respectively (Table II, entries 1–3).

Treatment of enantiomerically pure (*S*,*S*)-**79** with dibenzylamine or sodium diethyl malonate in the presence of palladium(0) gave the essentially enantiomerically pure (ee > 98%) products (*S*)-**147** (Nu = Bn_2N) and (*S*)-**147** (Nu = $CH(CO_2Et)_2$), respectively (Table III).

Based on the sign of the specific rotation of **147** (Nu = Bn_2N) the reaction of (*S*,*S*)-**79** with $Pd(PPh_3)4$/dibenzylamine was shown to have occurred with overall retention of configuration at the stereogenic carbon, consistent with attack of the nucleophile on the palladium allyl cation complex **F**, *anti* to the sterically demanding palladium(II) moiety (Eq. (6)). The stereochemistry assigned to **147** (Nu = $CH(CO_2Et)_2$) was made by analogy to that of **147** (Nu = Bn_2N) and the known tendency of

TABLE II Allylation of dibenzylamine by the allylic sulfoximines **141**–**143**

Entry	*Substrate*[a]	*Nucleophile*	*Products* (*yield*[b] (%))
1	 **141**	Bu_2NH	 **144** (66)
2	 **142**	Bu_2NH	 **145** (43)
3	 **143**	Bu_2NH	 **146** (62)

[a]Unless indicated all compounds are racemic.
[b]After purification by column chromatography on silica gel.

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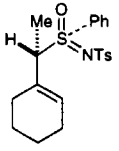
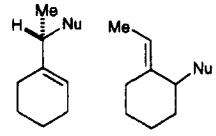
TABLE III Allylation of nucleophiles by the optically active allylic sulfoximine (*S,S*)-**79**

Entry	*Substrate*	*Nucleophile*[a]	*Products (yield*[b] *(%))*
1	 (*S,S*)-**79**	A	 **147** **148** Nu = Bn_2N (60); **147** : **148** = > 98 : < 2 (**147**; *ee* > 98%)
2	(*S,S*)-**79**	B	Nu = $CH(CO_2Et)_2$ (62); **147** : **148** = 92 : 8 (**147**; *ee* > 98%)

[a]Nucleophiles: A, dibenzylamine; B, sodium diethyl malonate.
[b]After purification by column chromatography on silica gel.

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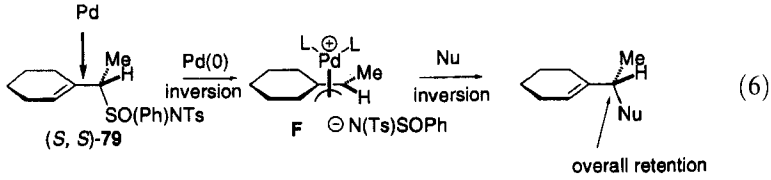
malonate nucleophiles to add *anti* to the palladium moiety in cations such as **F** (Eq. (6)).

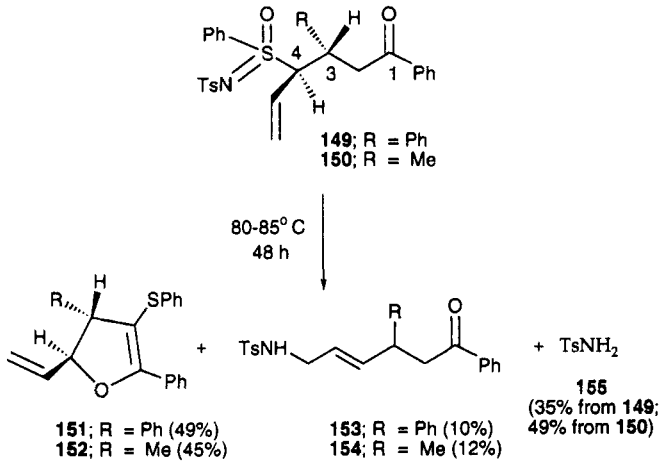


(6)

Thermolysis of the racemic γ-sulfonimidoyl ketones **149** and **150** gave the 2,3-dihydrofurans **151** and **152**, respectively.[82] When a sample of **149** was being dried for combustion analysis at 50–60 °C it was noticed that the sample rapidly turned black. ^{1}H NMR analysis of the black solid indicated the formation of a novel product. When this thermal process was repeated on a preparative scale at 80–85 °C for 48 h then the novel 2,3-dihydrofuran **151** could be isolated, as a single diastereoisomer, in 49% yield after purification by column chromatography. In addition, the known sulfonamide **153** and 4-methylbenzenesulfonamide **155** were also isolated in yields of 10% and 35%, respectively. The structure of compound **151** was unequivocally determined by a single-crystal X-ray structural analysis which showed that the allylic carbon

(C-4) in **149** had undergone inversion of stereochemistry upon cyclization to **151**. When a solution of **149** was heated to reflux in toluene for 2 h then the same three products **151**, **152** and **155** were isolated in yields of 42%, 18% and 32%, respectively.

Heating the racemic γ-sulfonimidoyl ketone **150** in the solid state under similar conditions afforded the analogous dihydrofuran **152** in 45% yield plus the sulfonamides **154** (12%) and **155** (49%) after purification by column chromatography. The dihydrofuran **152** however, was a 87 : 13 mixture of *trans* and *cis* isomers, respectively, which could not be separated. A tentative mechanistic scheme, involving cyclization of the enol form of the ketone and nucleophilic displacement of the sulfoximine group, was proposed to account for this chemistry.[82]



3.4. Allylic Substitution Reactions with Organometallic Reagents

In the earlier review[1] the work by Gais on the substitution reactions of optically active endocyclic allylic sulfoximines with organocopper reagents was reported. Since then a full account of this study has been published.[83] The reactions of primary endocyclic allylic *N*-methyl-*S*-phenylsulfoximines with organocuprate. LiI reagents give products of α-substitution while the addition of boron trifluoride results in the formation of γ-substitution products.

Enantiomerically pure (*E*)-acyclic sulfoximines **156** react with *n*-BuCuLi·LiI in the presence of boron trifluoride to give almost exclusively the γ-substitution products **157**.[84] The enantiomeric purities of

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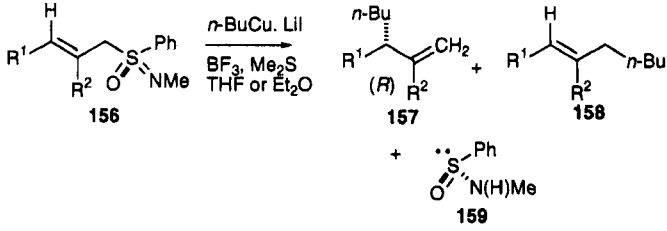
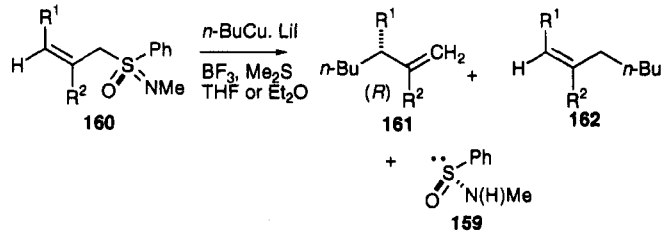
the γ-substitution products ranged from 2–72% depending upon the nature of the solvent and the substituents R^1 and R^2 in **156**. (*S*)-*N*-methyl-*S*-phenylsulfinamide **159** was isolated in high yield (> 80%) and enantiomeric purity (> 95%).



The corresponding (*Z*)-acyclic sulfoximines **160** react with *n*-BuCuLi·LiI in the presence of boron trifluoride to give almost exclusively γ-substitution products **161**.[84] The enantiomeric purities of the γ-substitution products ranged from 12% to 92%, depending upon the nature of the solvent and the substituents R^1 and R^2 in **160**. (*S*)-*N*-Methyl-*S*-phenylsulfinamide **159** was again isolated in high yield (> 80%) and enantiomeric purity (> 95%). Further studies revealed that the nature of the *N*-substituent had little influence on the regio- or enantioselectivities of these reactions.



4. VINYL SULFOXIMINES

4.1. Synthesis

The synthesis of vinyl sulfoximines via the elimination reactions of β-hydroxy sulfoximines[9,10,31,60,61] has been discussed in Section 2.1. The method of Craig[31] is particularly useful for the preparation of *N*-unsubstituted vinyl sulfoximines **163** which can be readily substituted at nitrogen by reactions with a number of reagents (see Section 2.1) including trifluoromethanesulfonic anhydride (triflic anhydride).[31]

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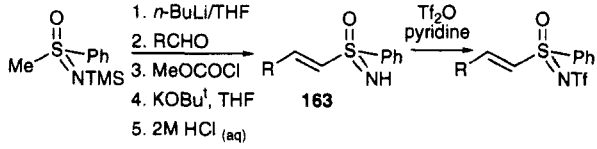
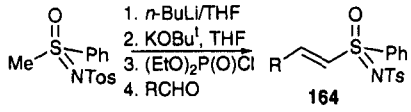
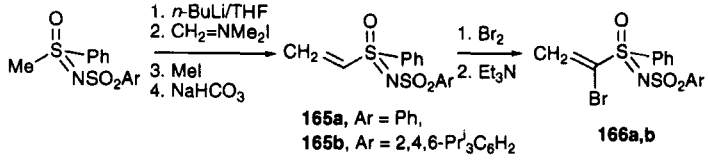


N-Tosyl vinyl sulfoximines **164** can be prepared in a one-pot reaction via an *in situ* Wadsworth–Emmons procedure from *S*-methyl-*S*-phenyl-*N*-tosylsulfoximine by sequential treatment at −78 °C with *n*-BuLi, potassium *tert*-butoxide and diethyl chlorophosphate, followed by addition of an aldehyde and warming to 0 °C.[85] The resulting *N*-tosyl vinyl sulfoximines **164** are formed almost exclusively as the (*E*)-isomers in good overall yields (60–91%).



N-Arylsulfonyl-*S*-ethenyl-*S*-phenylsulfoximines have been prepared from *N*-arylsulfonyl-*S*-methyl-*S*-phenylsulfoximines by deprotonation and then treatment with Eschenmoser's salt. Treatment of the resulting tertiary amine with excess methyl iodide, followed by base treatment, gave **165a,b** in 26–42% overall yields.[86,87] Bromination of **165a,b** and then elimination with triethylamine gave the α-bromo derivatives **166a,b** in 26–32% yield.[86]



Paley[88] has reported a method for preparing *N*-*tert*-butyldimethylsilyl (*E*)-vinyl, dienyl and enynyl sulfoximines from the reactions of the *N*-*tert*-butyldimethylsilyl β-*O*-tosyl vinyl sulfoximine **167**. Compound **167** was prepared in 60–65% yield in a one-pot reaction from its corresponding *S*-methyl sulfoximine via a deprotonation (with lithium tertamethylpiperidine), formylation and tosylation sequence. Treatment of **167** with "higher-order" cuprates ($R_2CuCNLi_2$, R = Me, Et, Bu, Pr^i, Ph) in diethyl ether solution gave the (*E*)-vinyl sulfoximines **170** in fair to good yields (50–74%). The yield of **170** (R = Me) could be enhanced from 50% using organocopper chemistry to 87% by employing trimethylaluminium and palladium(0) catalysis. Treatment

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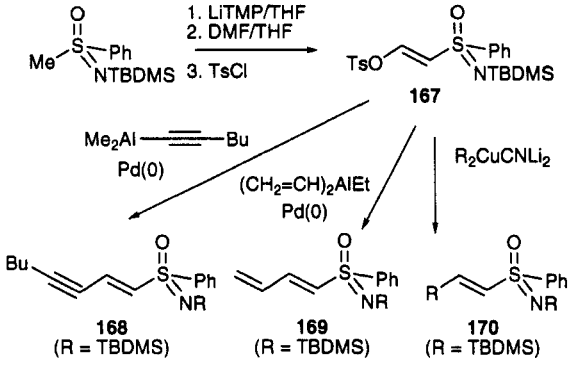
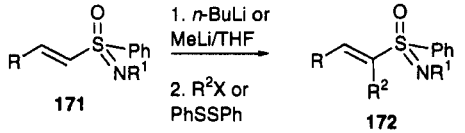
of **167** with 1-hexenyldimethylalane or divinylethylalane using palladium(0) catalysis gave the corresponding (*E*)-enynyl and dienyl sulfoximines **168** and **169**, respectively.



Both Gais and Jackson have reported the preparation of α-alkyl and α-trimethylsilyl vinyl sulfoximines **172** by α-lithiation of vinyl sulfoximines **171** with butyllithium or methyllithium, followed by treatment with alkyl halides, chlorotrimethylsilane[60,71,89,90] or diphenyl disulfide.[91]



4.2. Conjugate Addition (Michael) Reactions

The conjugate addition reactions (Michael reactions) of vinyl sulfoximines with organometallic reagents and oxygen, nitrogen and carbon centred nucleophiles was reported in the earlier review.[1]

In 1996, Jackson[90] reported the stereoselective addition of organometallic reagents to *N*-tosyl α-trimethylsilyl vinyl sulfoximines. Treatment of these compounds with either alkyl- or phenyllithium, dialkylcopperlithium or alkyl Grignard reagents (R^1M), followed by quenching with mild acid and then desilylation with tetrabutylammonium fluoride, gave β-substituted sulfoximines in moderate to good overall yields. The diastereoselection varied from 1 : 1 to 25 : 1 and was dependent upon the nature of the groups R and R^1 and the metal M. Organolithium reagents gave the best overall yields and levels of diastereoselectivity. Two examples that worked well include the

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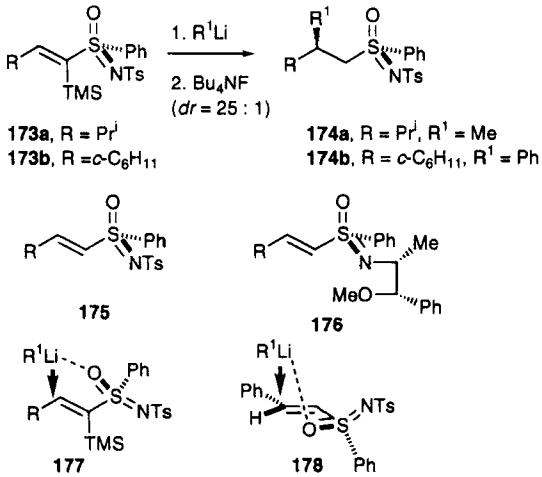
N-tosyl α-trimethylsilyl vinyl sulfoximines **173a,b**. In both cases the diastereomeric ratio of the products **174a,b** was 25 : 1 and the overall yields were greater than 65%. The relative stereochemistry of **174a** and **174b** was determined by X-ray crystal structure analysis. The α-unsubstituted vinyl sulfoximines **175** underwent α-deprotonation with organolithium reagents in contrast to the vinyl sulfoximines **176** which undergoes conjugate addition reaction with alkyllithiums, perhaps due to the formation of a strong chelate between the sulfoximine nitrogen and the methoxy oxygen atom.[9,10] The stereochemical outcome of the reactions of **173** with organolithium reagents was rationalized as occurring via attack on the conformation **177** with possible assistance from the sulfoximine oxygen atom.[90]

4.3. Structural studies

X-ray structural analysis on **175** (R = Ph) suggested that attack would occur on the conformation **178** in which the S=O and C=C bonds are approximately *syn* coplanar and approach of the nucleophile would occur *anti* to the large *S*-phenyl substituent.[92a] A later and more comprehensive study of the solid state structures of vinyl sulfoximines has been reported by Jackson.[92b] In this latter study vinyl sulfoximines **175** (R = H, Me) were found to have a conformation in which the S=O and C=C bonds are approximately *syn* coplanar while vinyl sulfoximines **175** (R = *c*-C_6H_{11}, $PhCH_2CH_2$, Pr^i) have a conformation in which the S=N and C=C bonds are approximately *syn* coplanar.[92b]



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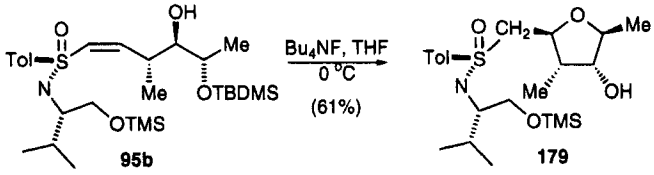
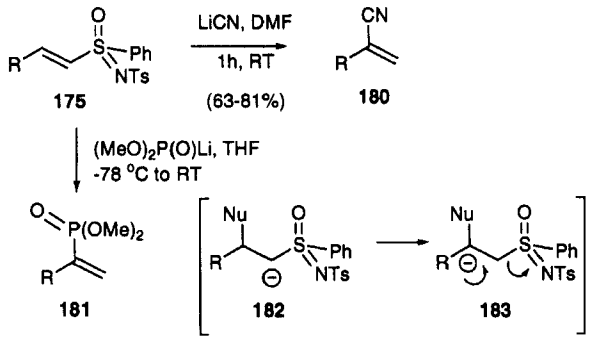
Treatment of the *tert*-butyldimethylsilyloxy vinyl sulfoximine **95b** with tetrabutylammonium fluoride in THF at 0 °C afforded the 2,3,4,5-tetrasubstituted dihydrofuran **179** in greater than 97% diastereoselectivity.[69,70] This method works equally well with the other diastereoisomers of **95b**.



Reaction of the *N*-tosyl vinyl sulfoximines **175** with lithium cyanide in DMF at room temperature for 1 h gave the vinyl nitriles **180** in good yields.[93] Treatment of **175** with lithium dimethylphosphonate in THF at −78 °C to room temperature gave moderate yields of the vinyl phosphonates **181**.[93] These yields could be improved to 54–64% by isolation of the initial Michael adducts by quenching these reactions at −20 °C and then treatment of these products with sodium methoxide in methanol at reflux. These reactions proceed via the intermediates **182** and **183**.



The reaction of the α-phenylthio vinyl sulfoximine **184** with lithiated phenyl phenylthiomethyl sulfone **185** gave a 3 : 1 mixture of the cyclopropanes **186a** and **186b**, respectively.[91] In contrast, the α-unsubstituted vinyl sulfoximine **187** gave a mixture of the cyclopropyl sulfone **188**, isolated as a single diastereoisomer in 49% yield, and the cyclopropylsulfoximine **189** which was difficult to characterize.[91]

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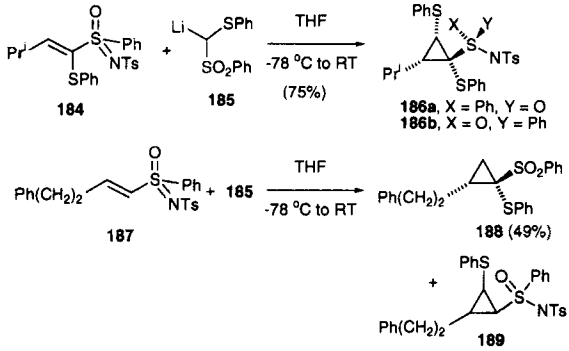
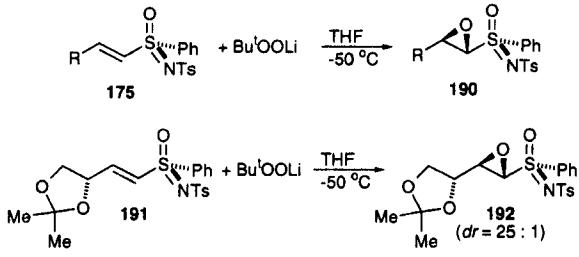


Racemic *N*-tosyl vinyl sulfoximines **175** undergo nucleophilic epoxidation with lithium *tert*-butyl peroxide in THF at −50 °C for 5 min gave the sulfoximinooxiranes **190** as single diastereoisomers in excellent yields (72–97%).[60] The relative stereochemistry of **190** (R = Pr^i) was established by X-ray crystal structure analysis. The epoxidation process occurred from the same diastereoface of the C=C of **175** as the addition of organolithium reagents to **175** (see structures **174a,b** above). In contrast, the reaction of **175** (R = Pr^i) with alkaline hydrogen peroxide gave a 1.7 : 1 mixture of diastereomeric sulfoximinooxiranes. The nucleophilic expoxidation of **175** (R = Pr^i) was also highly diastereoselective with lithium triphenylmethyl peroxide whereas the analogous potassium reagents were poorly diastereoselective.[94] It was suggested that coordination of the lithium cation to the sulfoximine oxygen was essential to obtain a high level of diastereoselectivity in these reactions.[94] When the R substituent in **175** contains additional stereogenic centres these expoxidation reactions give variable ratios of diastereoisomers. Matched situations usually, depending upon the nature of the epoxidation reagent, result in a very high diastereoselectivity (25 : 1) (e.g. **191**–**192**) whereas in the unmatched situations the diastereoselectivity was generally poorer.



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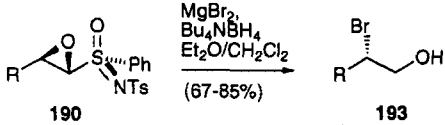
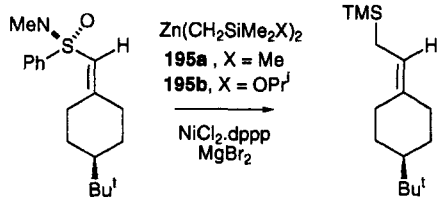
Treatment of enantiomerically pure sulfoximinooxiranes **190** with magnesium bromide in the presence of tetrabutylammonium borohydride gave the enantiomerically enriched bromohydrins **193** in good yields and with enantiomeric purities ranging from 70% to 91%.[95]



190 **193** (*ee* 70-91%)

4.4. Cross-coupling Reactions

The nickel-catalysed cross-coupling reactions of vinyl sulfoximines with organozinc reagents developed by Gais[89] was reported in the previous review.[1] Since then two further papers have appeared.[96,97] Nickel- and magnesium-catalysed coupling of the optically active vinylsulfoximine **194** and the organozinc reagents **195a,b** gave the optically active allyl silanes **196a,b** (ee > 95%) in excellent yields (91–95%).[96] This method also worked efficiently on an optically active 3-oxacarbacyclin intermediate.[97]



194 **196a,b**

α-Metallated (metal = Li or BrMg) vinyl sulfoximines undergo nickel-catalysed substitution with organometallic reagents to give vinyl organometallic compounds.[71,89] For example, the α-lithiated (*Z*)-vinyl sulfoxirnine **198**, which is stable to isomerization to (*E*)-**200** at −78 °C, when treated with phenyllithium in the presence of 5 mol-% $NiCl_2(PPh_3)_2$ gave the (*Z*)-vinylsilane **199** as a single diastereoisomer in 72% yield. The same (*Z*)-isomer of **199** was obtained starting from (*E*)-**200** which is formed at −30 °C from (*Z*)-**198**. It was asumed that **199** arises from a 1,5-*O*,*C*-silyl migration from the vinyllithium intermediate **201**.[71]

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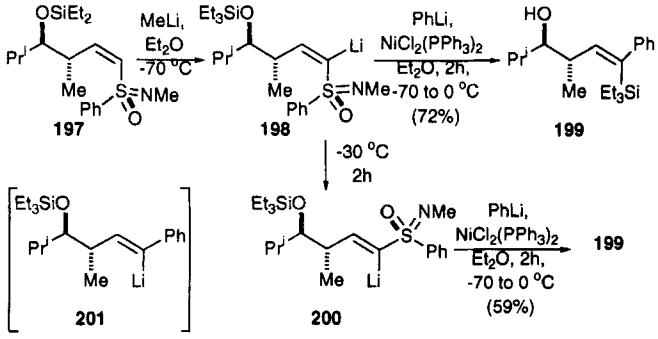
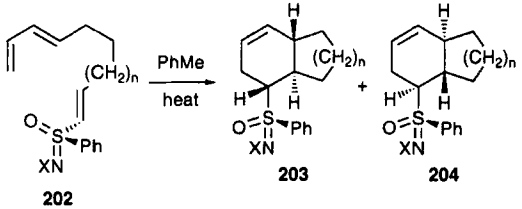


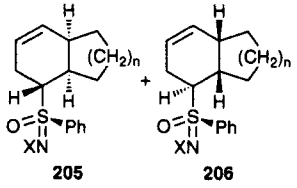
4.5. Cycloaddition Reactions

The intramolecular Diels–Alder reactions of vinyl sulfoximines **202** ($n = 1, 2$) have been studied by Craig.[98,99] In all cases mixtures of four diastereomeric cycloadducts were formed. When $n = 1$ the major diastereoisomer was the *trans*-fused compound **203** ($n = 1$) while when $n = 2$ the major diastereoisomer was the *cis*-fused compound **205** ($n = 2$). The diastereoselectivity of these reactions where $n = 1$ was essentially independent of the nature of the *N*-substituent in **202**, while when $n = 2$ the *N*-2,4,6-triisopropylphenylsulfonyl (Tris) derivative gave the highest selectivity for **205**.

The trienes **207** and **210** underwent cyclization to give only two cycloadducts. The major adduct from **207** was the *trans*-fused adduct **208**, while that from **210** was the *cis*-fused product **212**.[99]



X	n	yield (%)	203 : 204 : 205 : 206
Ts	1	72	39 : 31 : 25 : 5
Ts	2	70	20 : 14 : 40 26
Tris	1	79	35 : 30 : 30 : 5
Tris	2	75	15 : 5 : 65 : 15
Tf	1	89	38 : 32 : 22 : 8
Tf	2	68	24 : 21 : 35 : 20



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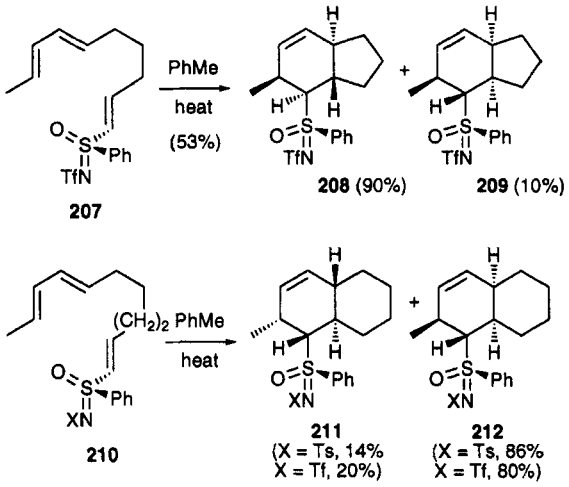

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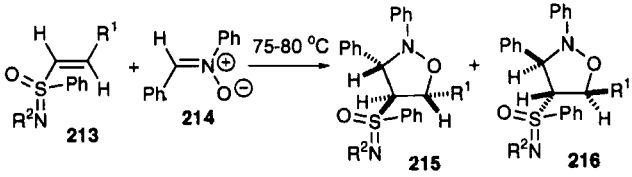
The reactions of the vinyl sulfoximines **213** with *C*,*N*-diphenylnitrone **214** are highly regioselective and give only the 4-sulfonimidoyl-isoxazolidine cycloadducts **215** and **216**.[86] These reactions proceed with modest π-facial selectivity with respect to the dipolarophiles **213**. The stereochemical outcomes of these reactions are consistent with attack on the ground state conformation **178** of the sulfoximine through an '*endo*'-like transition state.

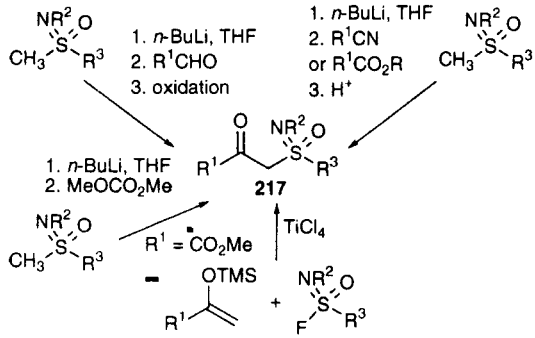


R^1	R^2	Yield (%)	215 : 216
H	Ts	46	65 : 35
Me	Ts	55	64 : 36
Ph	Ts	67	67 : 33
Ph	Tris	66	75 : 25
Ph	Me	43	47 : 53

5. α-SULFONIMIDOYL KETONES AND ESTERS

5.1. Synthesis

α-Sulfonimidoyl ketones **217** have been prepared from *S*-methyl sulfoximines via three different methods: (1) by deprotonation with *n*-butyllithium, followed by reaction with aldehydes and then oxidation of the resulting β-hydroxy sulfoximines;[80] (2) by deprotonation with *n*-butyllithium, followed by reaction with nitriles and then acid hydrolysis[100,101] and (3) by deprotonation with lithiumdiisopropylamide (LDA), followed by reaction with esters.[102] The titanium tetrachloride catalysed reaction of silyl enol ethers with *N*-methylbenzenesulfonimidoyl fluoride also gives α-sulfonimidoyl ketones.[4] α-Sulfonimidoyl esters **217** ($R^1 = OR$) can be readily prepared from *S*-methyl sulfoximines by deprotonation with *n*-butyllithium, followed by reaction with dimethyl carbonate.[101]



5.2. Reactions

The diastereoselective reductions of α-sulfonimidoyl ketones with hydride reducing agents has been reviewed.[1] The Knoevenagel type condensation of the α-sulfonimidoyl ketones **218a** or **218b** or the α-sulfonimidoyl ester **218c** with aldehydes proceeded in modest to good yields (46–87%) and gave the (*E*)-α-sulfonimidoyl β,γ-enones **219a** and **219b** and the (*E*) α-sulfonimidoyl β,γ-unsaturated ester **219c** as mixtures of two diastereomeric compounds.[80]

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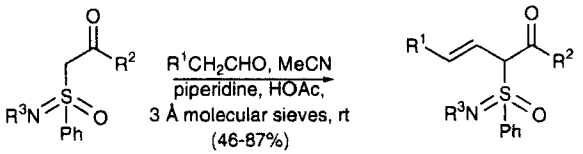
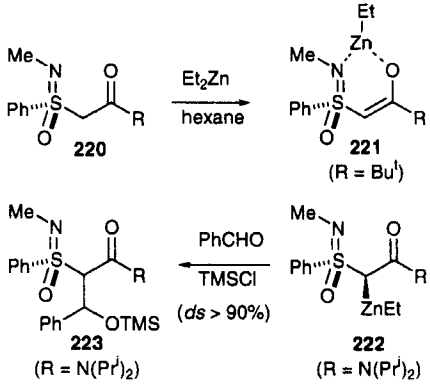


218a; R^2 = Ph, R^3 = Ts
218b; R^2 = Ph, R^3 = CO_2Me
218c; R^2 = OMe, R^3 = Ts

219a; R^2 = Ph, R^3 = Ts
219b; R^2 = Ph, R^3 = CO_2Me
219c; R^2 = OMe, R^3 = Ts

[R^1 = Bu, pent, hexyl, Et]

Treatment of β-carbonyl sulfoximines **220** (R = Bu^t, CO_2Me, $N(Pr^i)_2$) with diethylzinc gave the corresponding ethyl zinc derivatives.[101] The X-ray crystal structure of the ethyl zinc derivative (R = Bu^t) showed a dimeric *O*-metallated enolate form (**221**) in which two enolates of opposite chirality were connected to form an eight-membered $(Zn-O-S-N)_2$ ring. In contrast, the organometallic compound formed from the reaction of **220** (R = $N(Pr^i)_2$) formed a dimeric C-metallated carbonyl species (**222**) that involved an eight-membered $(Zn-C-C-O)_2$ ring structure. Solution NMR studies suggested that **222** (R = $N(Pr^i)_2$) had a much higher electron density at the sulfur carbon than **221** (R = Bu^t) consistent with the observation that **222** (R = $N(Pr^i)_2$) was more reactive towards electrophiles. For example, while **221** (R = Bu^t) did not react with methyl iodide or benzaldehyde, compound **222** (R = $N(Pr^i)_2$) reacted with benzaldehyde in the presence of chlorotrimethylsilane to give **223** in greater than 90% diastereoselectivity.



220
221 (R = Bu^t)
223 (R = $N(Pr^i)_2$)
222 (R = $N(Pr^i)_2$)

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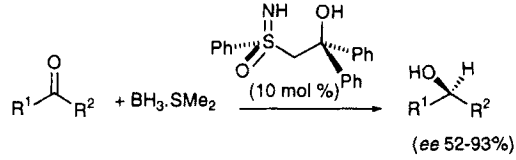
6. SULFOXIMINES AS LIGANDS FOR ASYMMETRIC SYNTHESIS

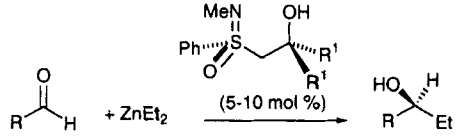
The X-ray crystal structures of β-hydroxy sulfoximines coordinated to metals are known, including complexes to ethylzinc[103] and vanadium.[104] These complexes involve coordination of the metal to the hydroxyl oxygen and the sulfoximine nitrogen. A palladium(II) bidentate pyridine–sulfoximine complex[105] and simple sulfoximine–copper(II) and zinc complexes are also known.[106] These latter complexes involve coordination of the metal to the sulfoximine nitrogen.

In 1979, Johnson reported the enantioselective reduction of ketones with stoichiometric amounts of optically active β-hydroxy sulfoximine–borane complexes.[1,107] In 1993, Bolm reported that these reactions could be performed using catalytic quantities (10 mol-%) of the chiral β-hydroxy sulfoximine.[108] The enantiomeric purities of the product alcohols ranged from 52% (1-indanone) to 93% ($PhCOCH_2OSiR_3$). In many cases the enantiomeric purities were enhanced when sodium borohydride was used as reductant in the presence of chlorotrimethylsilane.[109] These methods have been extended to the asymmetric reductions of imines.[110] *N*-SPh substituted imines gave the highest enantioselectivities and these reductions proceeded in the same stereochemical sense as the reductions of ketones.



(*ee* 52-93%)

Optically active β-hydroxy *N*-methyl sulfoximines have been used as catalysts for the enantioselective transfer of an ethyl group from diethylzinc to aldehydes to give secondary alcohols in enantiomeric excesses of 61–88%.[103,111] Related chiral ligands have been used with nickel acetylacetone to promote the enantioselective Michael addition of diethylzinc to chalcones.[112]



R^1 = Me, $-(CH_2)_n-$ (n = 3 or 9) (*ee* 61-88%)

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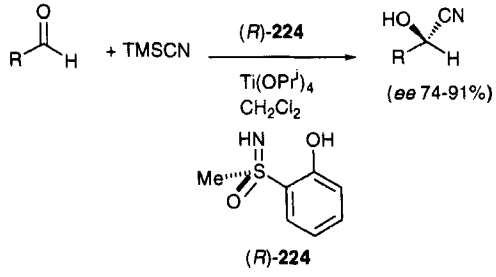
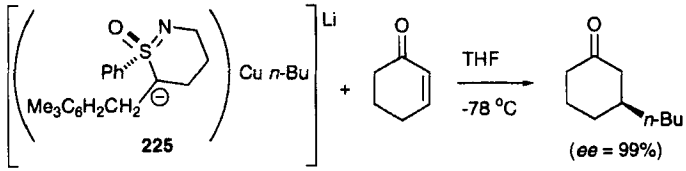
Chiral titanium reagents derived from optically active β-hydroxy sulfoximines and $Ti(OPr^i)_4$ promote the asymmetric addition of trimethylsilyl cyanide to aldehydes.[113] The resulting cyanohydrins are generally formed in 74–91% enantiomeric excess. The (*R*)-β-hydroxy sulfoximine **224** was found to be particularly effective. When substoichiometric amounts of **224** and $Ti(OPr^i)_4$ were used (20 mol-%) the enantioselectivities and yields dropped dramatically. For example, with benzaldehyde the stoichiometric reaction gave the corresponding cyanohydrin in 91% ee (yield 72%) while when catalytic conditions were employed the ee was 43% (yield 29%).



Gais used chiral cyclic α-sulfonimidoyl carbanions as non-transferable ligands in copper-mediated enantioselective Michael additions to cyclic enones.[37] For example, the organocopper reagent **225** underwent conjugate addition to cyclohexenone to give (*S*)-3-butylcyclohexanone in 99% enantiomeric excess.



Bolm has discovered that chiral sulfoximine/palladium complexes formed between pyridine and sulfoximine ligands and palladium(0) catalyse the enantioselective allylation of dimethyl malonate with the racemic allyl acetate **226**.[105] The best enantiomeric purity of the product **228** was obtained using the chiral ligand **227**.

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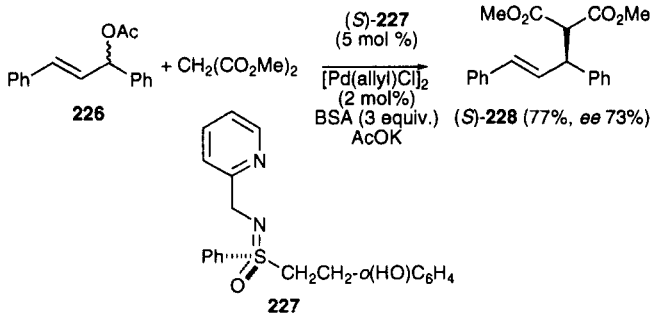

7. CONCLUSIONS

Sulfoximines are versatile reagents for diastereoselective and asymmetric synthesis. They continue to find many synthetic applications as both nucleophilic and electrophilic reagents. While the nucleophilic character of sulfoximine reagents has been well exploited[1] the use of the sulfoximine group as a nucleofuge is more recent and adds to the synthetic use of these compounds. The palladium(0) catalysed chemistry of allylic sulfoximines and the use of chiral sulfoximines as ligands in catalytic asymmetric synthesis are areas of recent development that have potentially useful applications. Further work is required to understand the factors that determine the diastereoselection and the stereochemical outcomes of these reactions. These studies will result in enhanced product diastereo- and enantioselectivities and make these reagents more attractive to the wider synthetic chemistry community.

Note Added in Proof

A method for preparing *N*-Boc sulfoximines from sulfoxides using *tert*-butyloxycarbonyl azide (CAUTION: potentially explosive) and iron(II) chloride has been reported (Bach, T. and Korber, C. (1998), *Tetrahedron Lett.*, **39**, 5015).

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