

1991

# Asymmetric synthesis of chiral amines and alcohols from chiral sulphur reagents

Branko Dikic

*University of Wollongong*

---

## Recommended Citation

Dikic, Branko, Asymmetric synthesis of chiral amines and alcohols from chiral sulphur reagents, Doctor of Philosophy thesis, Department of Chemistry, University of Wollongong, 1991. <http://ro.uow.edu.au/theses/1111>

## **NOTE**

This online version of the thesis may have different page formatting and pagination from the paper copy held in the University of Wollongong Library.

## **UNIVERSITY OF WOLLONGONG**

### **COPYRIGHT WARNING**

You may print or download ONE copy of this document for the purpose of your own research or study. The University does not authorise you to copy, communicate or otherwise make available electronically to any other person any copyright material contained on this site. You are reminded of the following:

Copyright owners are entitled to take legal action against persons who infringe their copyright. A reproduction of material that is protected by copyright may be a copyright infringement. A court may impose penalties and award damages in relation to offences and infringements relating to copyright material. Higher penalties may apply, and higher damages may be awarded, for offences and infringements involving the conversion of material into digital or electronic form.

**ASYMMETRIC SYNTHESIS OF  
CHIRAL AMINES AND ALCOHOLS  
FROM  
CHIRAL SULPHUR REAGENTS**

A thesis submitted in fulfilment of the  
requirements for the award of the degree

of

**DOCTOR OF PHILOSOPHY**

from

**THE UNIVERSITY OF WOLLONGONG**

by

**BRANKO DIKIC, B.Sc. (Hons)**

**DEPARTMENT OF CHEMISTRY  
MARCH 1991**

## **DECLARATION**

This is to certify that the work described in this thesis has not been submitted for a higher degree at any other University or institution.

B. Dikic

## ACKNOWLEDGMENTS

I would like to thank the following people and organisations for their help during the research and production of this thesis;

Dr Stephen G. Pyne, my supervisor.

Mrs. Barbara Pyne and Mrs Grace Benavente, for their help in the typing and compilation of this thesis.

## GENERAL PROCEDURES

### (a) Melting Points (mp)

Melting points were determined on a Reichert hot stage apparatus and are uncorrected.

### (b) Infrared (IR) Spectra

Infrared Spectra were recorded on a Perkin Elmer Infrared Spectrophotometer model 783 as mulls in nujol unless otherwise stated.

### (c) $^1\text{H}$ Nuclear Magnetic Resonance (NMR) Spectra

$^1\text{H}$  NMR spectra were recorded on a JEOL FX 90Q Fourier Transform NMR Spectrometer operating at 90 MHz, or a JEOL JNM-GX400 Fourier Transform NMR Spectrometer operating at 400 MHz. The spectra were measured in  $\text{CDCl}_3$  unless otherwise stated, relative to tetramethylsilane (0.00 ppm). Each signal is described in terms of chemical shifts in ppm from tetramethylsilane, multiplicity, intensity, coupling constant (Hz) and assignments in that order with the use of the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet.

### (d) $^{13}\text{C}$ Nuclear Magnetic Resonance (NMR) Spectra

$^{13}\text{C}$  NMR spectra were recorded on a JEOL FX 90Q Fourier Transform NMR Spectrometer or a JEOL JNM-GX400 Fourier Transform NMR Spectrometer. The spectra were measured in  $\text{CDCl}_3$  unless otherwise stated, relative to  $\text{CDCl}_3$  (77.0 pp).

**(e) Mass Spectra (MS)**

Low Resolution Mass Spectra were recorded on a Vacuum Generator VG 12-12 mass spectrometer.

High Resolution Mass Spectra were recorded on a AEI-MS-902 mass spectrometer using heptaperfluorotributylamine as reference.

**(f) Microanalysis**

Microanalysis were performed by the Australian National University Services Unit Canberra.

**(g) Column Chromatography**

The chromatography adsorbent used was silica gel (0.063-0.2 mm, Merck) unless otherwise indicated.

**(h)** X-ray structures were determined at the University of Western Australia by Professor Allan White.

**(i) Optical Rotation**

Optical rotations were recorded with a Perkin-Elmer 141 Polarimeter. All rotations were measured in water.

## ABSTRACT

This thesis investigates the application of chiral sulfoxides and sulfoximines to the asymmetric synthesis of chiral alcohols, amines and isoquinoline alkaloids. The results are presented in five chapters.

In chapter 1 the addition of the anions of methyl phenyl and methyl p-tolylsulfoxide to imines was shown to be highly diastereoselective process under kinetically controlled conditions. This method was extended to the asymmetric synthesis of R(+) tetrahydropalmatine.

Chapter 2 is an extension of this method to methyl phenylsulfoximines. The relative stereochemistry of major adduct between lithiated t-butyldiphenylsilyl sulfoximine and benzyldeneaniline was determined by x-ray crystallography.

In chapter 3 an attempt was made to extend this methodology to the synthesis of benzyl isoquinoline alkaloids. However, both the yields and diastereoselectivity were poor.

Chapter 4 deals with an attempt to solve the problems encountered with benzylmethylsulfoxide (in chapter 3). However the addition of the dianions of (R<sub>S</sub>)-10-methyl and (R<sub>S</sub>)-10-Benzyl-sulphinylbornan-2-Exo-ol to imines gave low yields and poor diastereoselectivity. Attempts to silylate these sulfoxides gave a number of novel Pummerer rearrangement products.

Chapter 5 deals with the successful application of benzyl methyl and benzylphenylsulfoximines to the synthesis of chiral amines, alcohols and 1-benzyl isoquinoline derivatives. The stereochemistry at these adducts was determined by x-ray crystallography.



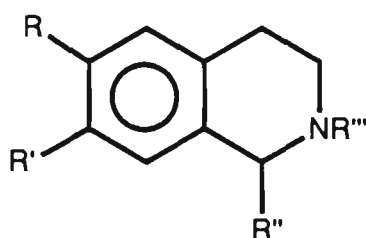
ABSTRACT	II
INTRODUCTION	1
CHAPTER 1	70
<p>DIASTEREOSELECTIVE ADDITION OF LITHIATED METHYL p-TOLYSULFOXIDE AND METHYL PHENYL SULFOXIDES TO IMINES.</p>	
CHAPTER 2	112
<p>DIASTEREOSELECTIVE ADDITIONS OF LITHIATED N-SUBSTITUTED S-METHYL-S-PHENYLSULFOXIMINE TO IMINES AND ALDEHYDES.</p>	
CHAPTER 3	151
<p>DIASTEREOSELECTIVE ADDITION OF BENZYL METHYL SULFOXIDE TO IMINES AND ALDEHYDES.</p>	
CHAPTER 4	184
<p>ADDITION OF THE ANIONS OF (R<sub>S</sub>)-10-METHYL-AND (R<sub>S</sub>)-10-BENZYL- SULPHINYLBORNAN-2-EXO-OL TO IMINES.</p>	
CHAPTER 5	215
<p>DIASTEREOSELECTIVE ADDITION OF ALDEHYDES AND IMINES TO N-SILYLATED BENZYL SULFOXIMINES.</p>	
REFERENCES	261

# INTRODUCTION

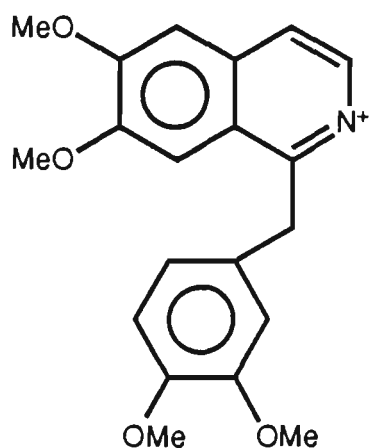
## INTRODUCTION

Alkaloids make the largest and most diverse of the groups of natural products. They include many compounds whose pharmaceutical activity has been known for centuries.<sup>1</sup> More specifically, isoquinolines comprise one of the most abundant groups of alkaloids.<sup>2</sup> Isoquinoline alkaloids, as the name implies, have the isoquinoline nucleus as their base structure (Figure1).

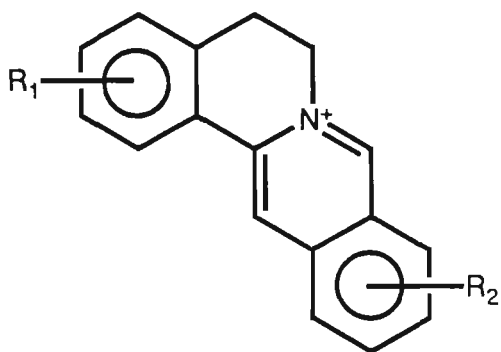
**Figure 1.**



**The Isoquinoline Alkaloids**



**Papaverine**

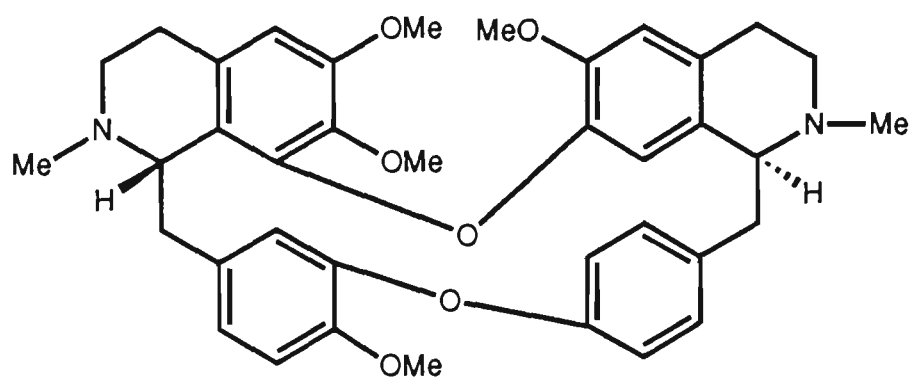


**Protoberberine**

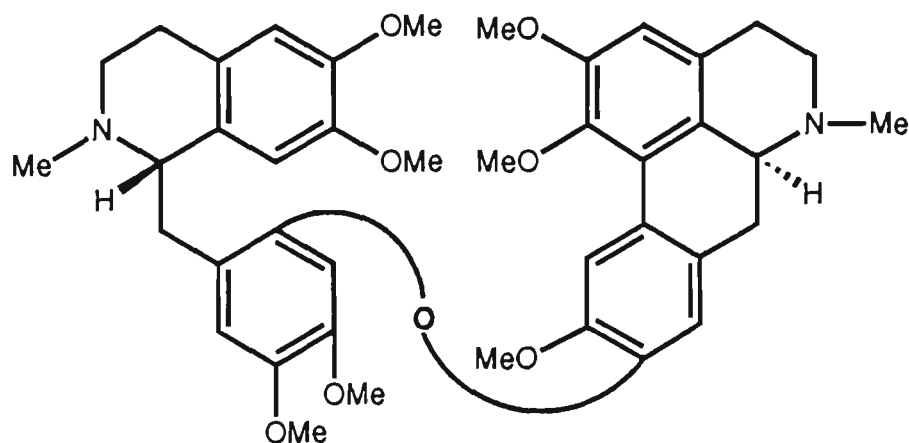
The interest in isoquinolines is due to their wide distribution among both the alkaloids<sup>2</sup> and biologically active compounds of synthetic origin<sup>3</sup>. The biological activities range from coronary vasodilation caused by papaverine to antibacterial activity caused by the protoberberines (Figure1). More recently,

by the protoberberines (Figure 1). More recently, since the discovery that apomorphine is useful in treating Parkinson's disease, there has been a good deal of interest taken in the apomorphine group in general<sup>4</sup>. On the other hand, the bisbenzylisoquinoline series and its analogues now form one of the largest single groups of alkaloids, and a lot of interest has been focused on them, particularly since the report of the antitumor properties associated with certain members, including tetrandrine and thalicarpine (Figure 2).<sup>5</sup>

**Figure 2.**



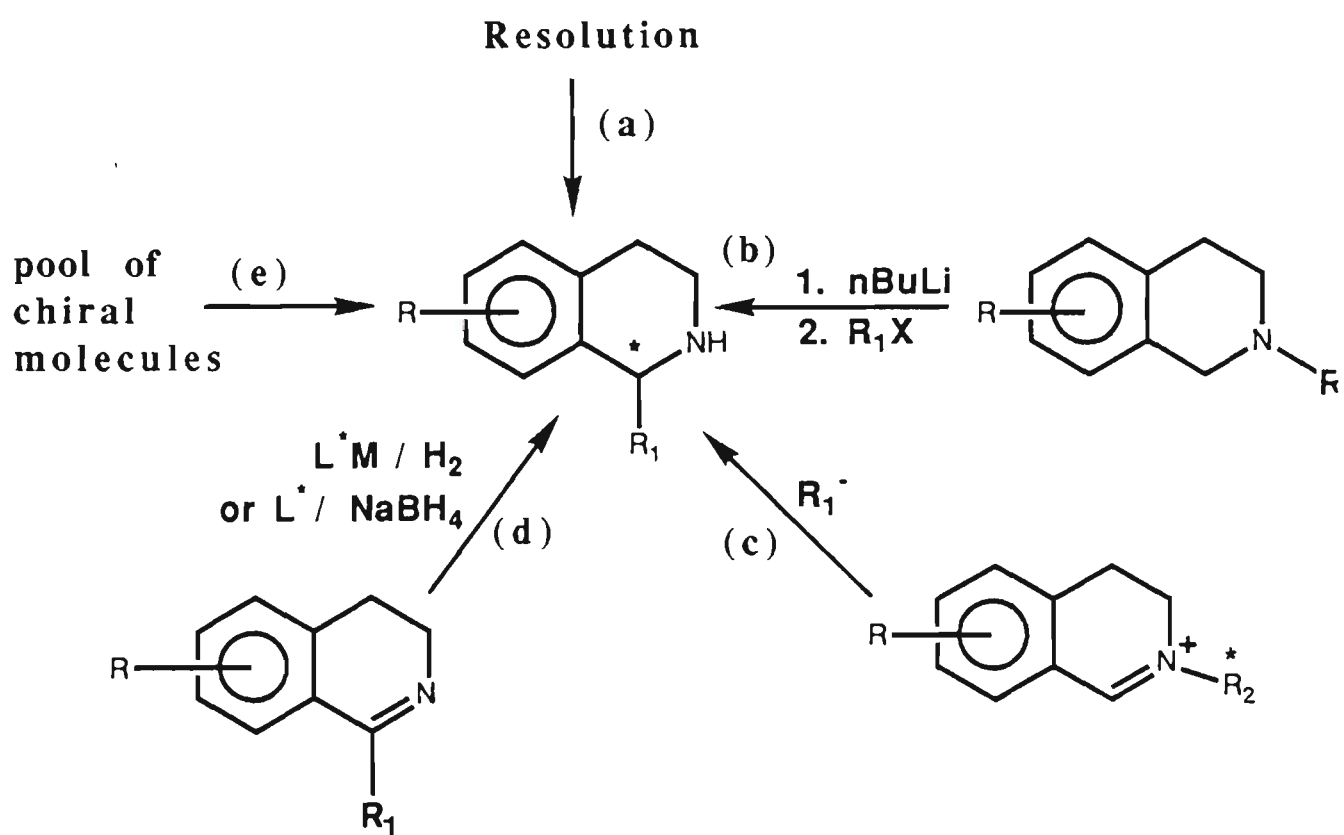
**Tetrandrine**



**Thalicarpine**

Increased interest focused on the development of suitable synthetic methodology to produce chiral isoquinoline alkaloids has resulted in a variety of methods being developed. Several methods for synthesizing enantiometrically pure compounds have been applied to obtain 1-substituted 1,2,3,4-tetrahydroisoquinolines (Scheme 1).

**Scheme 1.**



These include the use of:

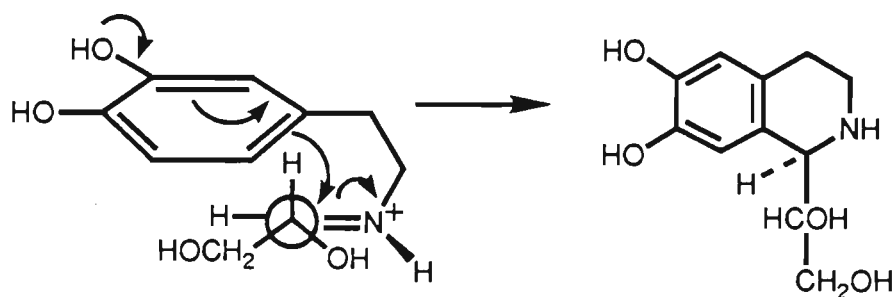
- (i) classical resolution techniques;<sup>6</sup>
- (ii) incorporation of compounds from the 'pool' of chiral building blocks;<sup>7-9</sup>
- (iii) chiral auxiliaries.<sup>10-20</sup>
- (iv) catalytic and stoichiometric asymmetric reductions.<sup>21-23</sup>

The latter three methods will be discussed in some detail.

## SYNTHESIS OF 1,2,3,4-TETRAHYDROISOQUINOLINES USING COMPOUNDS FROM THE POOL OF CHIRAL BUILDING BLOCKS

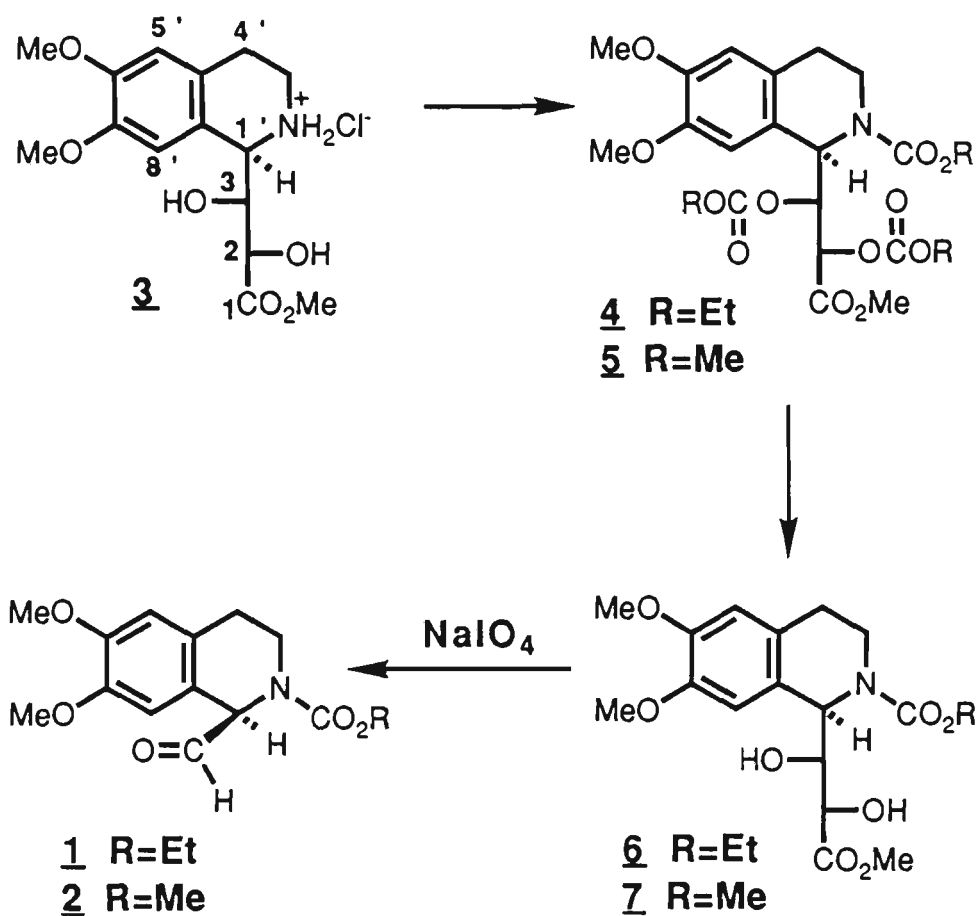
MacLean<sup>7</sup> reported a method of asymmetric synthesis which involves the reaction between dopamine and a variety of sugars and their derivatives (Figure 3).

**Figure 3. Orientation of iminium-salt intermediate for formation of the tetrahydroisoquinoline in the Pictet-Spengler condensation.**



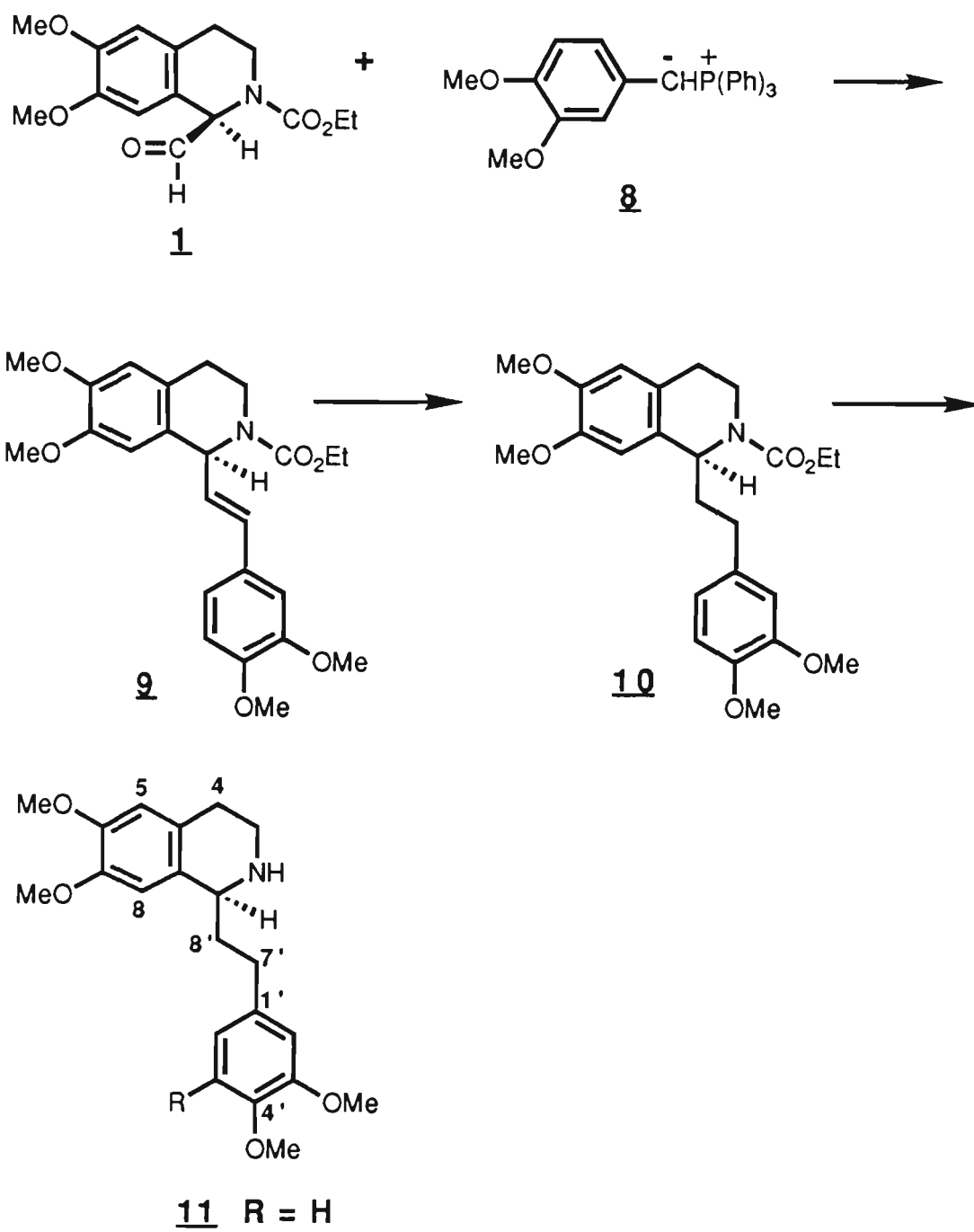
The reaction uses the Pictet-Spengler condensation, to yield a tetrahydroisoquinoline with a sugar moiety at the C-1 position. It is this step which secures the stereochemistry at C-1. This method yielded a variety of simple isoquinoline alkaloids but in low yield. MacLean<sup>8</sup> also reported an improved procedure for the formation of the (R)-aldehyde 1, which is based upon the use of D-(-)-tartaric acid as a means of inducing asymmetry at C-1 of the isoquinoline system (Scheme 2).

Scheme 2.

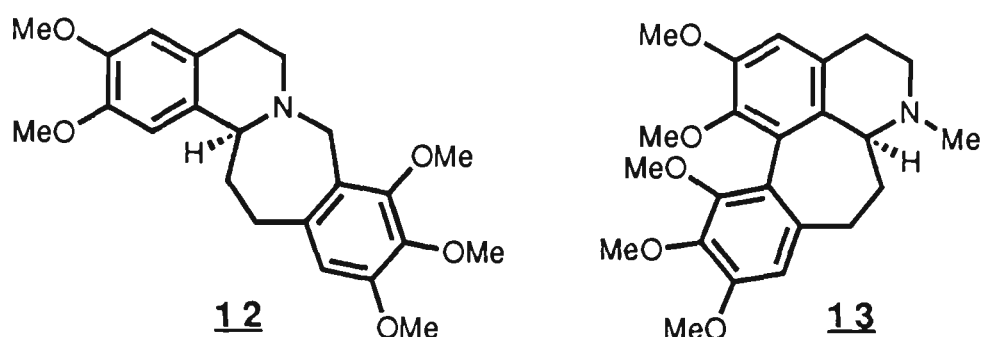


This method for the preparation of (R)-1 has several advantages over the previous method from glyceraldehyde, since it may be used to prepare 1-formylisoquinolines, with substituents other than O-methyl on the aromatic ring and the chemical yields are better. This method was used to synthesise (S)-homolaudanosine 11 and homoprotoberberine and homoapomorphine 12 and 13 (Scheme 3).

Scheme 3.

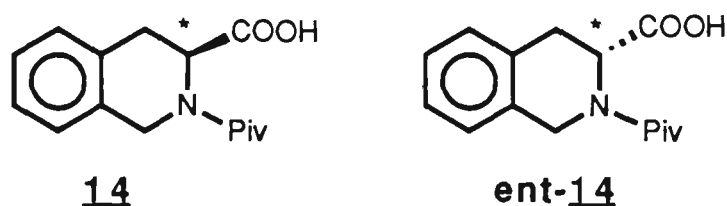






Seebach<sup>9</sup> has prepared the chiral N-pivoyl-tetrahydroisoquinoline-3-carboxylic acids (14) and (ent-14) from either (S) or (R)-phenylalanine (Figure 4).

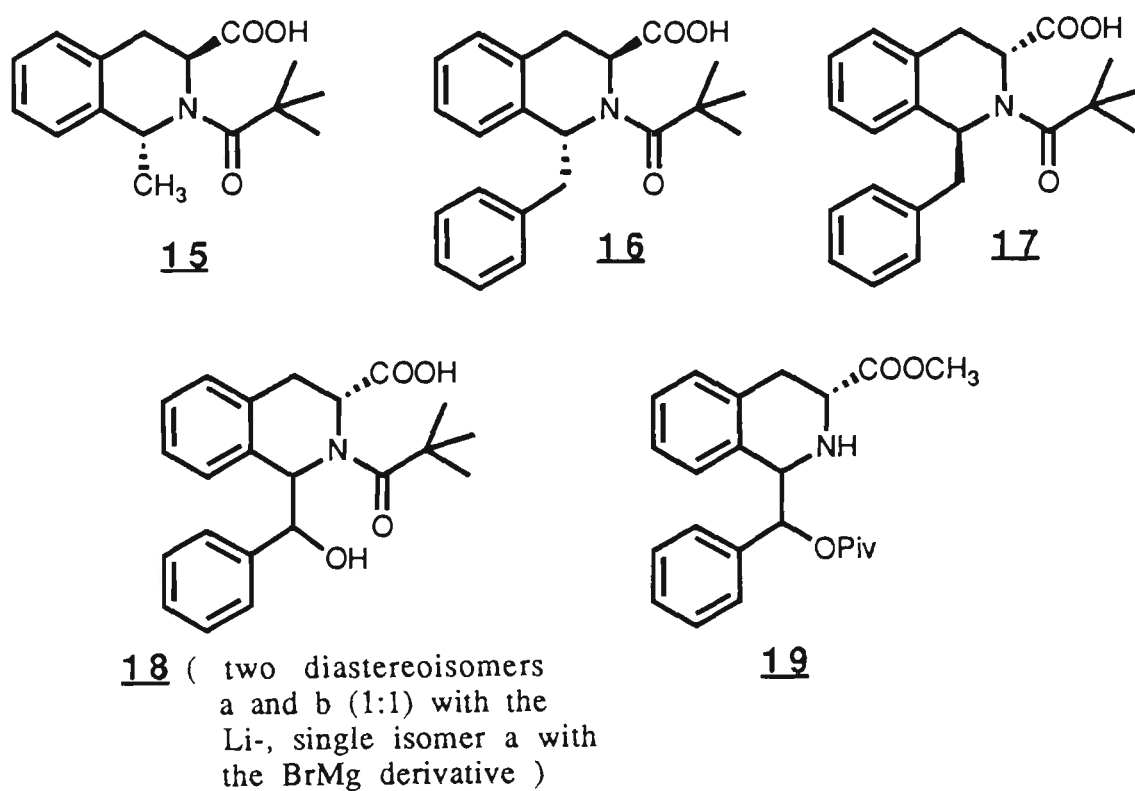
Figure 4.



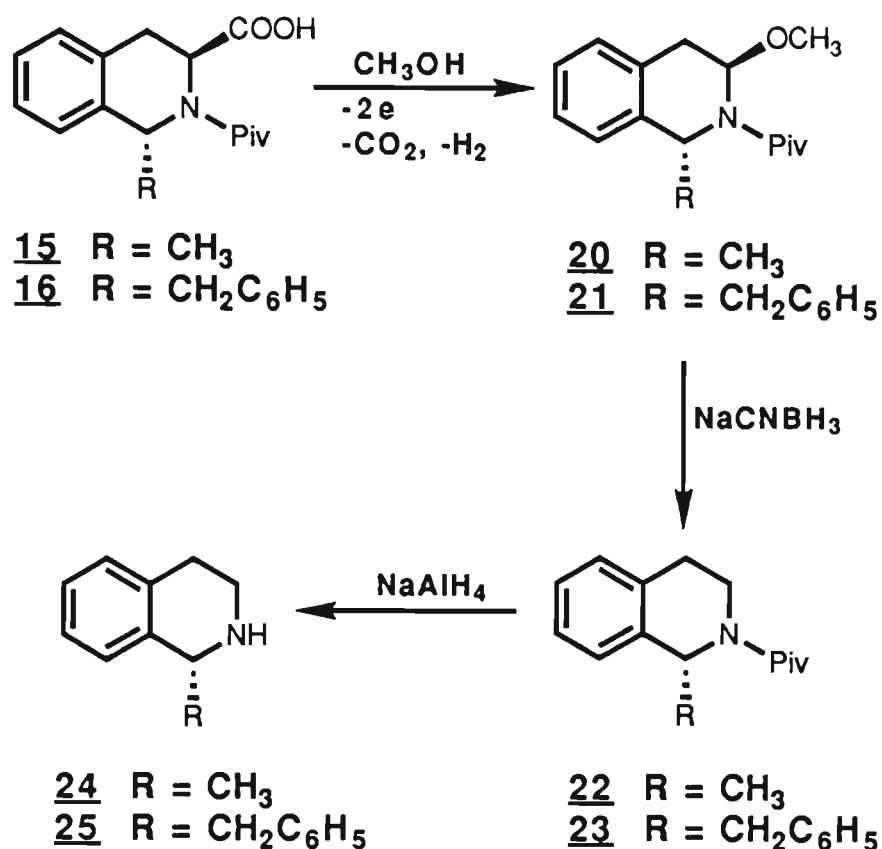
Treatment of the acids 14 and ent-14 with two equivalents of *tert*-butyllithium in tetrahydrofuran (THF) gave the corresponding dianions which were quenched with electrophiles. The derivatives 15 and 16 (Figure 5) were isolated as single diastereoisomers in good yield. The benzaldehyde adduct (18) consisted of a 1:1 mixture of diastereoisomers, if the lithium derivative was directly combined with the aldehyde, while a single diastereoisomer (18a) was isolated if transmetalation was carried out with magnesium bromide-etherate prior to aldehyde addition. Treatment with hydrochloric acid converted the hydroxy-amino acid 18 into amino diester 19. The configuration of the derivatives 15 and 16 was determined by chemical correlation to be *trans* and so Seebach<sup>9</sup> assumed that the major stereoisomers 18 and 19 have the same

trans-disposition of COOH and the newly introduced substituent at C-1. The correlation of the two alkylation products 15 and 16 with the parent (R)-1-methyl and (R)-1-benzyl tetrahydroisoquinolines 24 and 25, respectively is outlined in Scheme 4.

**Figure 5.**



Scheme 4.



## SYNTHESIS OF 1-SUBSTITUTED-1,2,3,4-TETRAHYDROISOQUINOLINES USING ENANTIOMERICALLY PURE CHIRAL AUXILIARIES.

Polniaszek and McKee<sup>10</sup>, have explored the conformational preference of iminium ions whose asymmetry originates from a chiral centre appended to the nitrogen atom of the iminium ion moiety. These iminium ions were prepared via a Bischler-Napieralski reaction as shown in Scheme 5. The chirality resident in the substrates was derived from (S)-(-)-1-phenylethylamine. Sodium borohydride ( $\text{NaBH}_4$ ) reduction of the iminium ions (29) gave the tetrahydroisoquinolines (30) in high diastereomeric purities (Table 1). Hydrogenolysis of 30a and 30d with hydrogen over palladium on carbon afforded (S)-(-)-salsolidine 31a and (S)-

(-)-norlaudanosine 31d respectively (Scheme 5). The configurations of 31b and 31c were assigned by analogy.

Scheme 5.

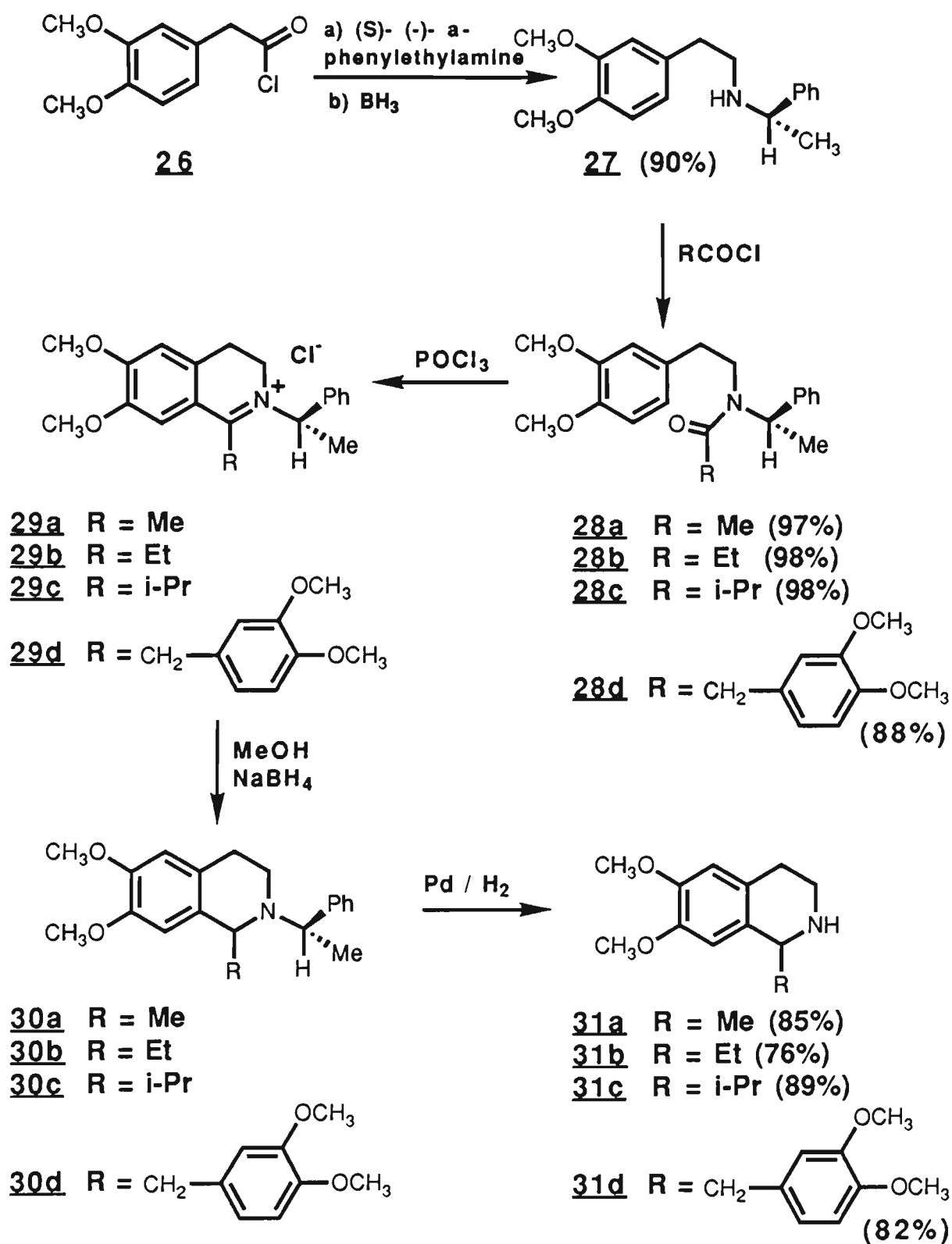
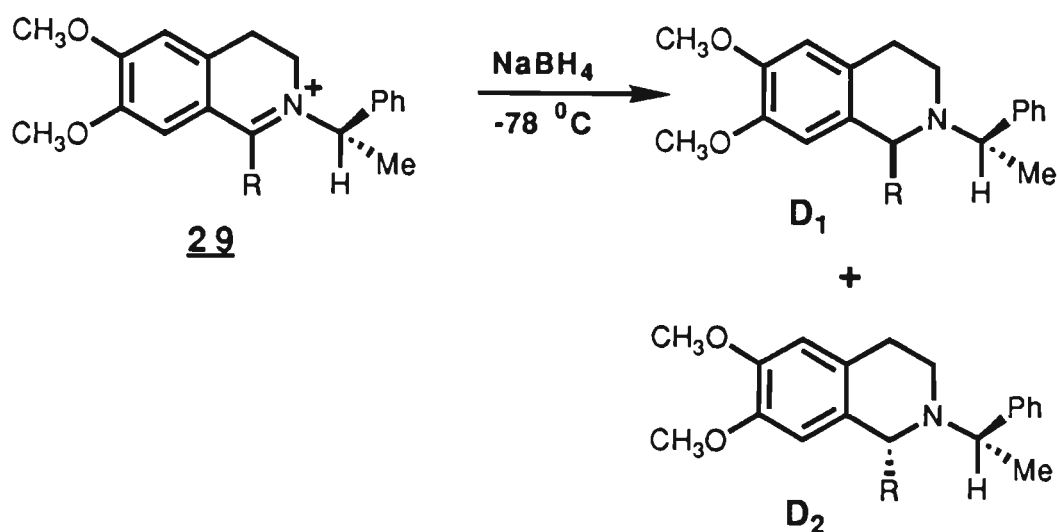


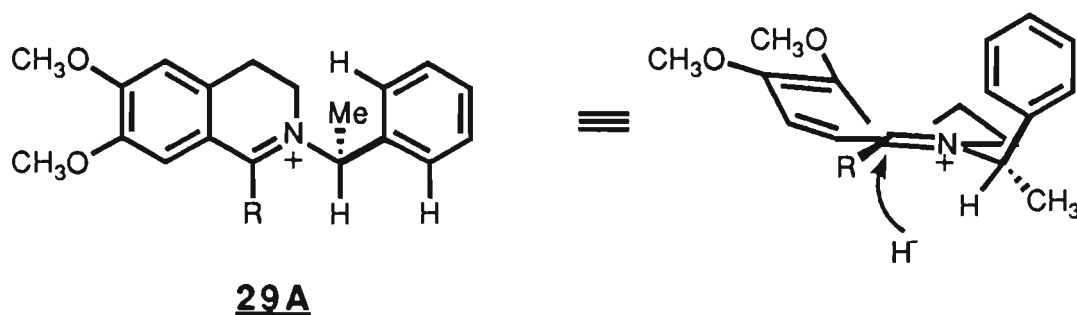
Table 1.



<u>Iminium Ion</u>	<u>R</u>	<u>D<sub>1</sub>:D<sub>2</sub></u>	<u>Yield</u>	<u>WWG<sup>‡</sup> (kcal/mol)</u>
<b>29a</b>	<b>Me</b>	<b>90.5 : 9.5</b>	<b>77%</b>	<b>0.87</b>
<b>29b</b>	<b>Et</b>	<b>92 : 8</b>	<b>75%</b>	<b>0.94</b>
<b>29c</b>	<b>iPr</b>	<b>88 : 12</b>	<b>61%</b>	<b>0.77</b>
<b>29d</b>		<b>94 : 6</b>	<b>72%</b>	<b>1.10</b>

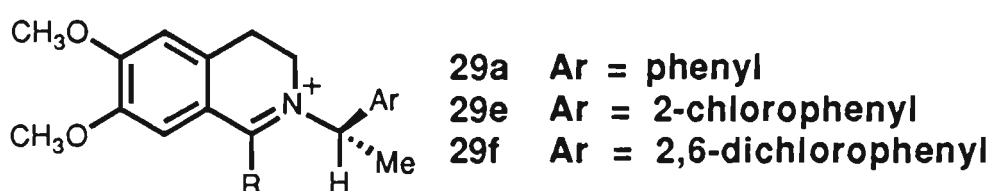
The diastereoselectivities shown in (Table 1) represent differences in free energies between competing diastereomeric transition states ( $\Delta\Delta G^\ddagger$ ) of .77 to 1.1 kcal/mol. Polniaszek<sup>10</sup> suggested that a model which accounts for the observed results is the selection of a ground state iminium ion conformation 29A which minimizes allylic A(1,3) interactions. Nucleophilic attack may then proceed by approach to the less sterically hindered diastereoface as shown in Figure 6.

Figure 6.



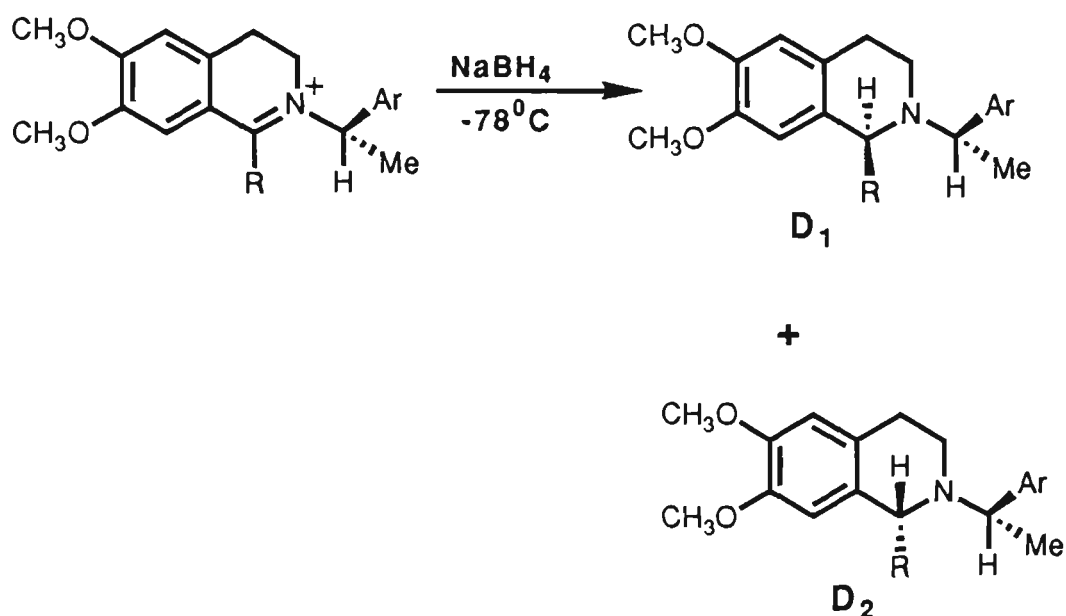
Furthermore Polniaszek and Kaufman<sup>11</sup> anticipated that increasing the relative size difference between the methyl and aryl groups in the iminium ions would selectively increase the steric crowding at one iminium ion diastereoface and enhance the hydride reduction diastereoselection in the series from 29a, to 29e to 29f (Figure 7). The data in Table 2, below, indicates that the iminium

Figure 7.



ions tend to prefer transition-state conformations in which the re diastereoface is more hindered to nucleophilic approach than the si diastereoface. Upon substitution of the phenyl moiety with chlorine, the net steric shielding of the iminium ion re diastereoface increases, and hence diastereoselection increases.

Table 2. Product ratios and differences in free energy for the reduction of iminium ions.



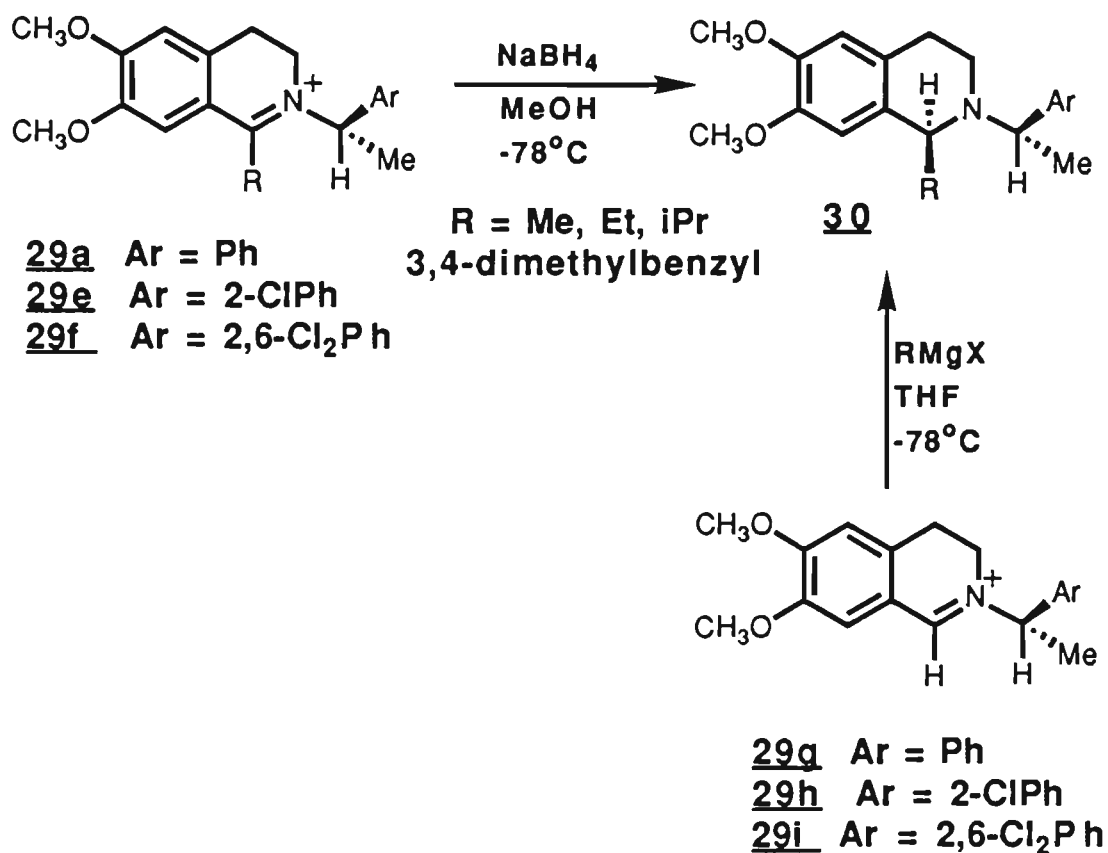
	Ar =				Ar =	
	Ar = phenyl		2-chlorophenyl		2,6-dichlorophenyl	
	D <sub>1</sub> :D <sub>2</sub>	WWG <sup>‡</sup>	D <sub>1</sub> :D <sub>2</sub>	WWG <sup>‡</sup>	D <sub>1</sub> :D <sub>2</sub>	WWG <sup>‡</sup>
R = Me	91:9	0.87	100:0	>1.8	98.4:1.6	1.6
R = Et	92:8	0.94	95:5	1.1	100:0	>1.8
R = iPr	88:12	0.77	98.6:1.4	1.7	98.6:1.4	1.7
R = 3,4-DMB <sup>a</sup>	94:6	1.1	87:13	0.73	99:1	1.8

<sup>a</sup> 3,4-DMB = 3,4-dimethoxybenzyl

Polniaszek<sup>12</sup> and colleagues have conducted complimentary experiments involving nucleophilic addition of organometallic reagents to iminium ions 29g, 29h and 29e (Scheme 6). The results of the Grignard reagent additions as presented in Table 3. An interesting observation emerging from these experiments is that the major diastereoisomer resulting from either hydride reduction of 29a-c or Grignard addition to 29g, 29h and 29i is D1. The diastereoselection of hydride reduction of iminium ions 29a, 29e and 29f is highest for substrate 29a while for the addition of

Grignard reagents to iminium ions 29g, 29h and 29i is high only for substrate 29i. Polnaiszek assumed that both sets of reactions proceed by a polar mechanism and states that his data can be explained by "the presumption that nucleophilic addition occurs

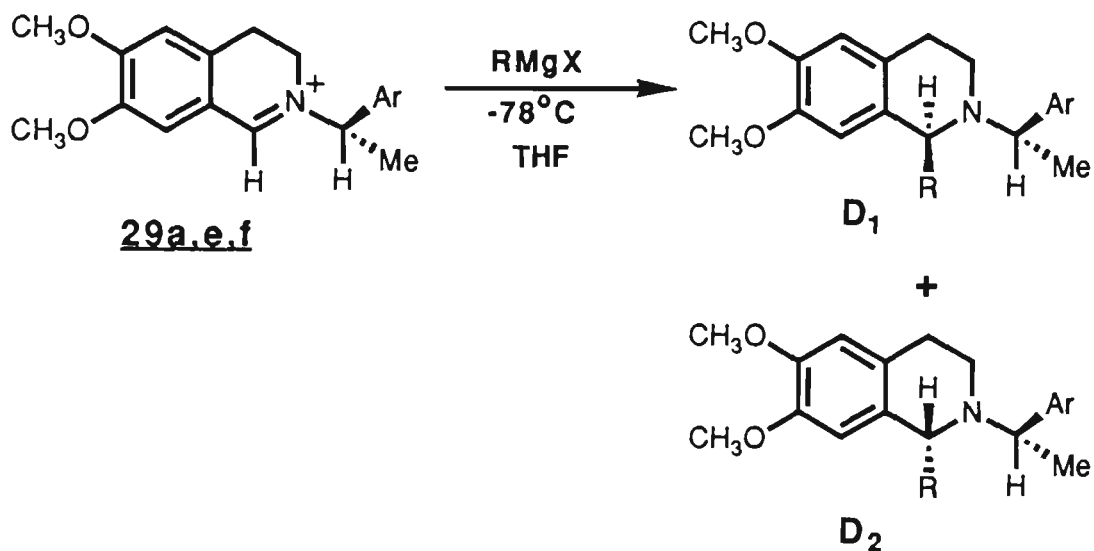
**Scheme 6.**



preferentially to certain select "reactive conformations" at each substrate. These "reactive conformations" provide maximum transition state stabilization by orbital overlap between the iminium ion  $\pi^*$  orbital and a suitably aligned  $\sigma^*$  orbital linking the stereogenic centre and the 2,6-dichlorophenyl moiety. Such conformers would be expected to react faster due to a stabilizing stereoelectronic effect in the transition state of the nucleophilic addition reaction."



Table 3.



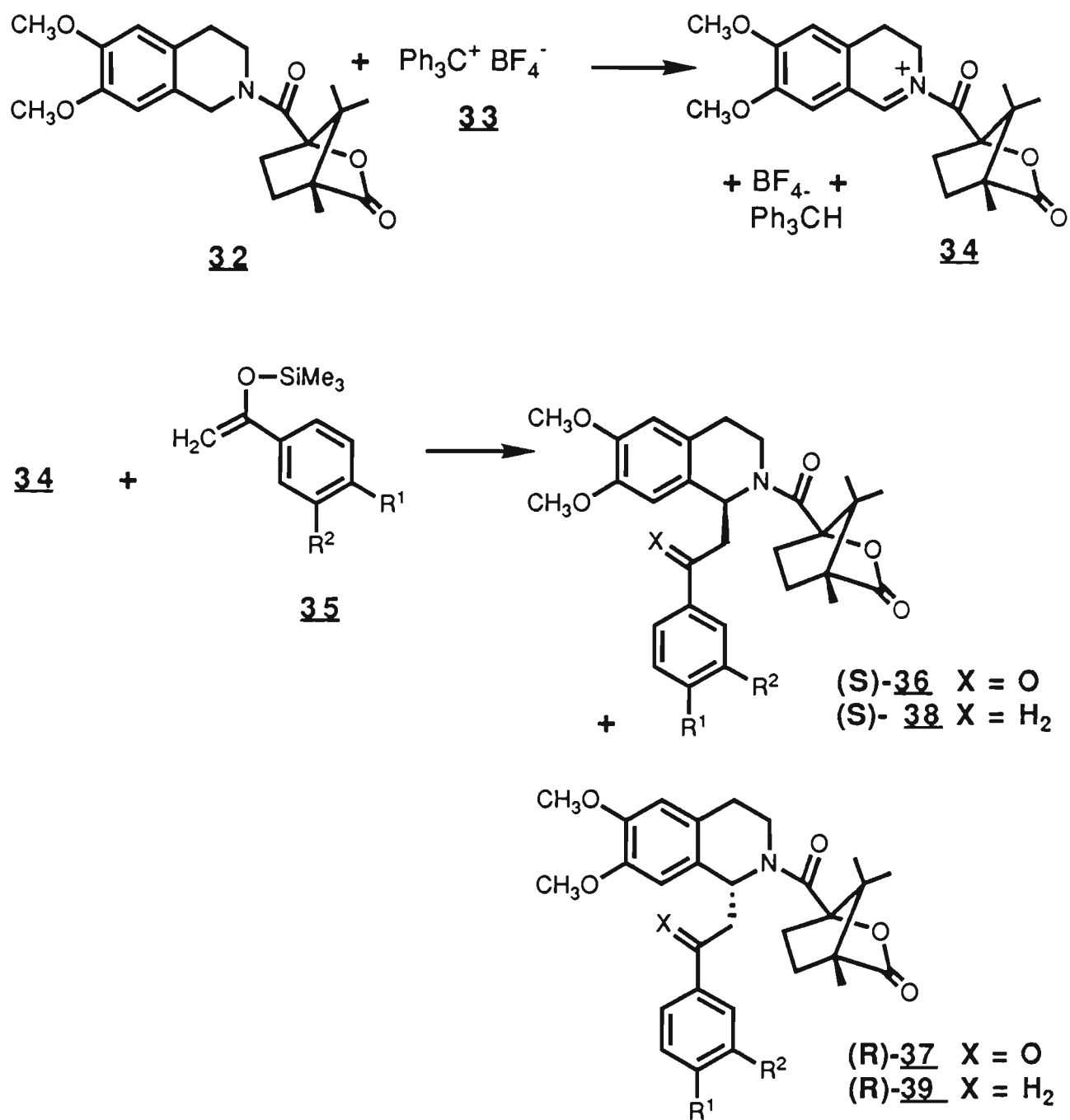
Ar	Substrate	RMgX	D1:D2	(%)
Ph	29a	MeMgBr	58:42	82
Ph	29a	EtMgBr	77:23	82
Ph	29a	i-PrMgBr	58:42	81
Ph	29a	i-BuMgBr	58:42	82
2-ClPh	29e	MeMgBr	54:46	84
2-ClPh	29e	EtMgBr	78:22	86
2-ClPh	29e	i-PrMgBr	74:26	78
2-ClPh	29e	i-BuMgBr	61:39	90
2,6-Cl <sub>2</sub> Ph	29f	MeMgBr	85:15	89
2,6-Cl <sub>2</sub> Ph	29f	EtMgBr	94:6	85
2,6-Cl <sub>2</sub> Ph	29f	i-PrMgBr	98:2	83
2,6-Cl <sub>2</sub> Ph	29f	i-BuMgBr	87:13	88

Two synthetic methods that have been extensively explored are the addition of nucleophiles to non-racemic chiral 3,4-dihydroisoquinolinium ions<sup>13</sup> and the alkylation of non-racemic chiral 1-lithio-1,2,3,4-tetrahydroisoquinolines in which a chiral auxiliary is attached to nitrogen<sup>14-19</sup>.

A paper by Prashak and Wenner<sup>13</sup> examines the former method as shown in Scheme 7. In this method the non-racemic chiral acyliminium ion 34 was combined with the enolsilyl ether

35, and after workup a mixture of diastereomeric ketones, (S)-36 and (R)-37 was obtained. The composition of the diastereomeric mixture was 20.3:79.7 (Table 4).

Scheme 7.



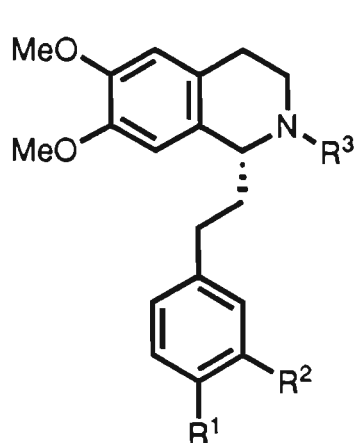
Interestingly the diastereoselection of the reaction could be improved by adding  $\text{TiCl}_4$  prior to the addition of enolsilyl ether 35, in which case diastereomeric ratios of 12.4:87.6 and 11.2:88.8 (Table 4 entries, 3 and 4 respectively) could be achieved.

**Table 4.**

en- try	<u>35</u>	$\text{R}^1$	$\text{R}^2$	Reaction cond.		Yield (%)		Ratio		(E Yield (%)
				Add.	Temp. ( $^{\circ}\text{C}$ )	(S)- <u>36</u>	+(R)- <u>37</u>	(S)- <u>36</u> /(R)- <u>37</u>	(S)- <u>38</u> /(R)- <u>39</u>	
1	a	H	H		-78	---		20.3/79.7	---	---
2	a	H	H		-90	97.2		17.6/82.4	16.7/83.3	59.1
3	a	H	H	1eq. $\text{TiCl}_4$	-78	---		12.4/87.6	---	---
4	a	H	H	1eq. $\text{TiCl}_4$	-93	---		11.2/88.8	---	---
5	b	H	Cl		-78	98.9		14.8/85.2	9.9/90.1	51.9
6	c	$\text{OCH}_3$	$\text{OCH}_3$		-78	96.8		17.6/82.4	18.5/81.5	37.8

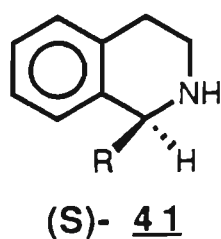
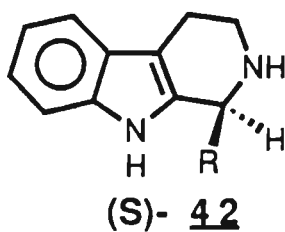
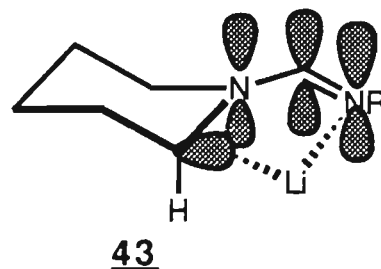
Enantiomerically pure amines could be obtained after the chromatographic separation of the diastereoisomers and then subsequent removal of the chiral auxiliary. The sense of the asymmetric induction was established by comparing the optical rotation of the synthetic compounds with that of the natural products. Compound (R)-37 has been employed in the synthesis of substituted tetrahydroisoquinolines ((R)-40) including the alkaloid (-)-homolaudanosine ((R)-40d) (Table 5).

Table 5.

(R)- 40(R) - 40

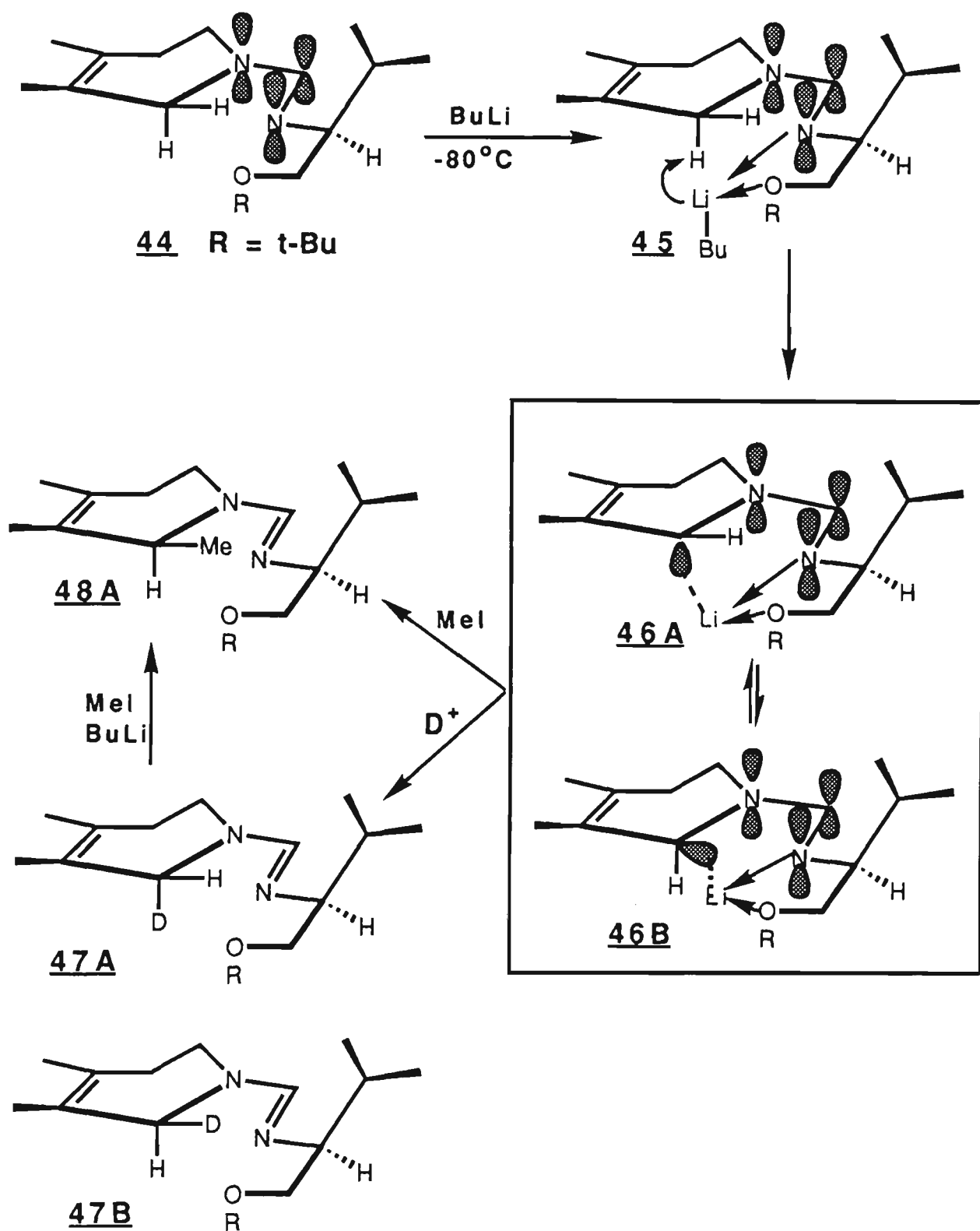
	R1	R2	R3	Yield (%)	[α] <sub>578</sub>
a	H	H	H	64.7	+25.5
b	Cl	H	H	16.1	+12.4
c	OMe	OMe	H	77.0	+15.1
d	OMe	OMe	Me	64.3	-13.5

Meyers<sup>14-16</sup> and his colleagues used a different method of asymmetric synthesis which involves the use of a chiral formamidine auxiliary attached to the nitrogen of the tetrahydroisoquinoline to direct substitution of the C-1 carbon. This highly efficient route to isoquinoline alkaloids, in their natural configuration, led him to probe for the underlying factors responsible for the observed stereochemical outcome. Meyers assumed that  $\alpha$ -amino carbanions are most stable when the carbanion orbital is orthogonal to the non-bonding orbitals of the formamidine auxiliary as shown in 43.

(S)- 41(S)- 4243

Experiments were first focused on the asymmetric synthesis of the ring systems, 41 and 42. When the chiral formamidine of 1,2,3,4-tetrahydroisoquinoline (depicted by partial structure 44, (Scheme 8) was metalated with *n*-butyllithium (*n*-BuLi) and treated with MeI the major product was 48A (>95% diastereomeric excess (de)). When the anion was quenched with D<sub>2</sub>O or MeOD, 47A and 47B were formed while quenching with DMSO-d<sub>6</sub>, produced only 47A. Meyers has rationalized the stereochemical outcome of these processes as depicted in Scheme 8. The kinetic acidity of the "axial" proton of 45, activated by the  $\pi$ -system, is greater than the "equatorial" proton and after coordination of *n*-BuLi from the bottomside, the "axial" proton is removed. Addition of MeI occurs with retention on 46B or via an S<sub>E</sub>2 mechanism from the back lobe of 46A to give 48A. Quenching 46A, B with D<sub>2</sub>O or MeOD gives 47A and 47B via a non-selective deuteration but DMSO-d<sub>6</sub> gives only 47A. This may be due to the coordination of DMSO to lithium cation from the underside followed by intramolecular D-transfer to 47A. Meyers has exploited these methods in the asymmetric synthesis of a variety of isoquinoline alkaloids in high enantiomeric purity<sup>15</sup>. Removal of formamidine moiety from 48A, gave the (S)-1-methyl product 41(R=Me).

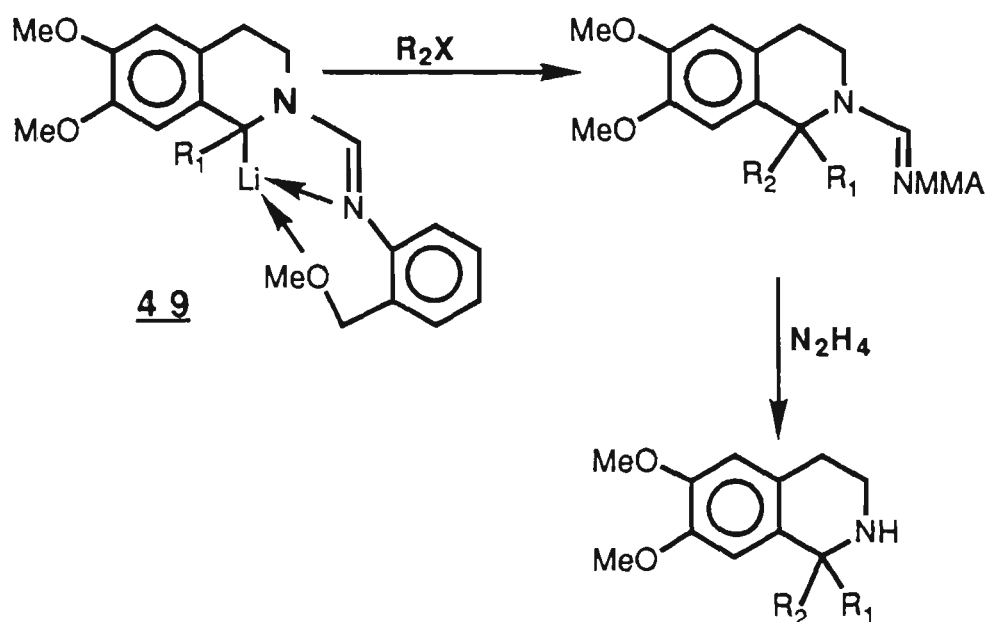
Scheme 8



Meyers<sup>16</sup> has also studied the use of the methoxymethylaniline (MMA) formamidine (**49**) for the  $\alpha$ -alkylation of 1-substituted tetrahydroisoquinolines. The products are important precursors

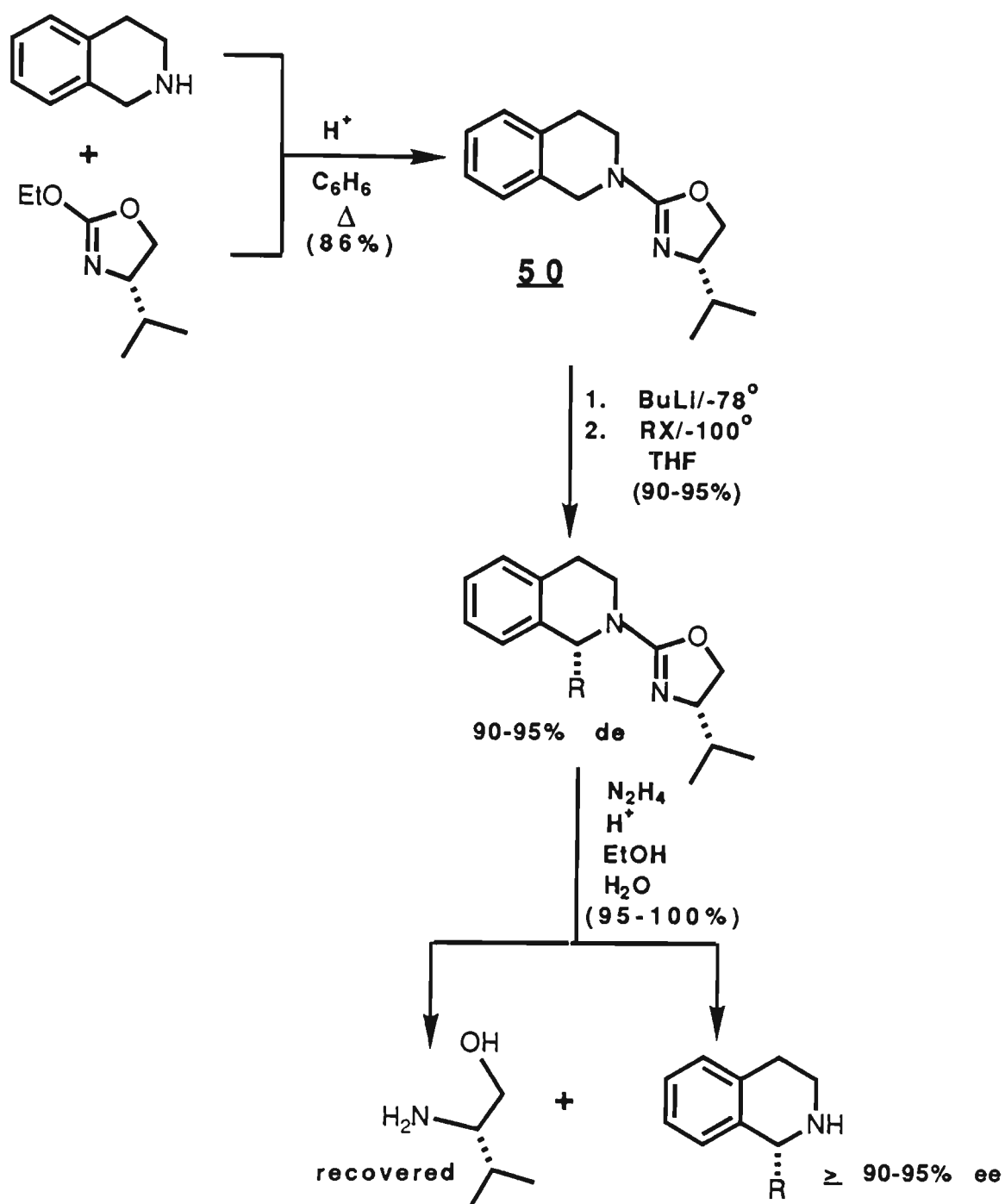
to a variety of isoquinoline alkaloids containing quaternary centres (Scheme 9). The chiral version of these reagents have not yet been reported.

Scheme 9.



Gawley<sup>17</sup> has extended the use of chiral auxiliaries via the condensation at tetrahydroisoquinolines with chiral oxazolines. The monodendate oxazoline auxiliary was designed to activate both allylic and nonallylic positions on a heterocycle<sup>18</sup>. This system allows the 100% diastereoselective deprotonation of piperidine and also allows the diastereoselective alkylation of tetrahydroisoquinolines (Scheme 10). The diastereomer ratios for the reactions are in the range of 15-40:1, with yields exceeding 90% for the alkylation step. The advantage of this auxiliary is that it is readily available, easily attached and removed and also recoverable. Gawley<sup>19</sup> reported its use in the synthesis of laudonosine and O-methylflavinantine in 94% enantiomeric excess.

Scheme 10.

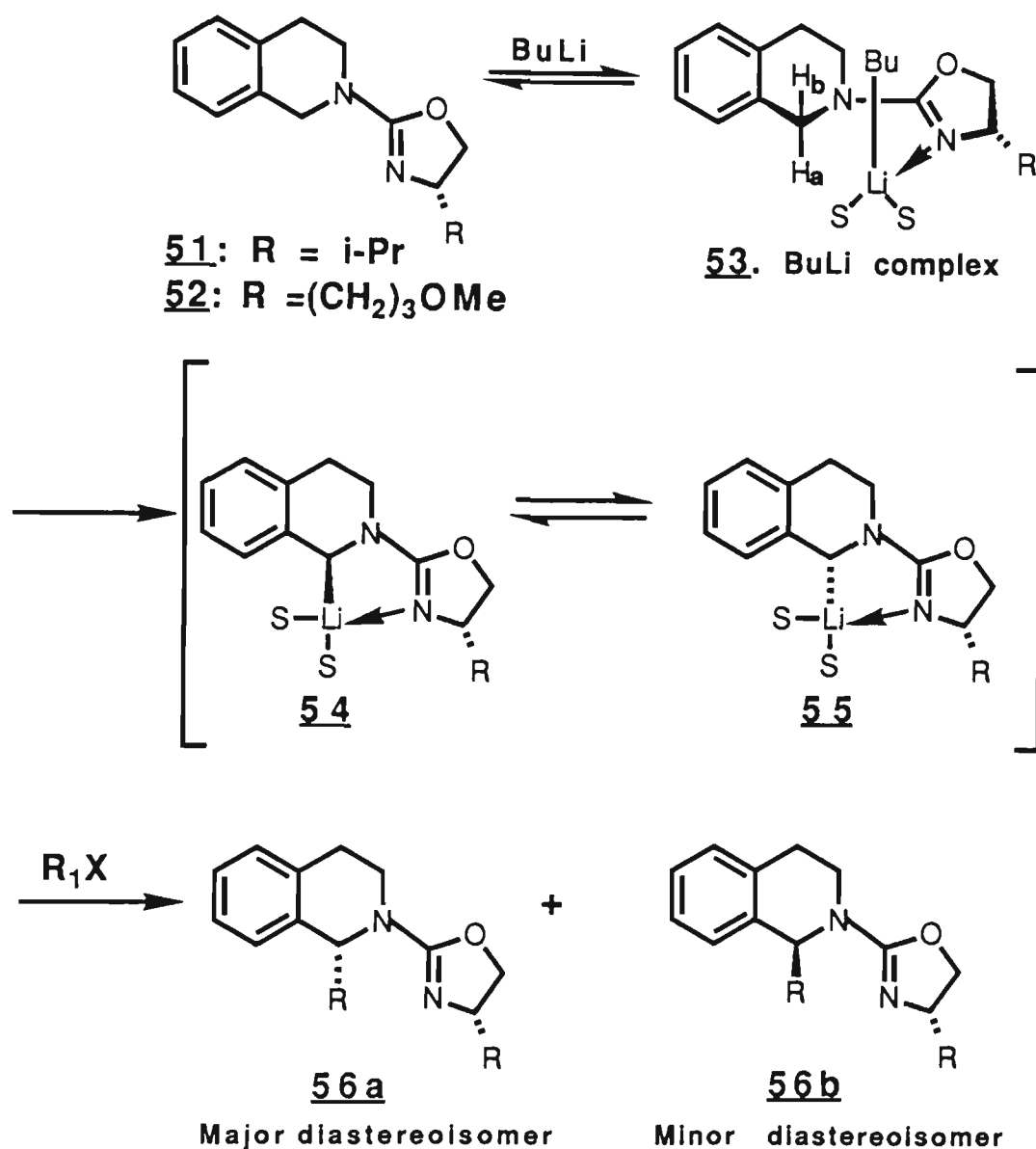


There are two potentially diastereoselective processes in the conversion of isoquinolyloxazoline 51 and 52 to 56, the deprotonation at C-1 and the alkylation of the intermediate organolithium reagent (Scheme 11). Interestingly, in the series



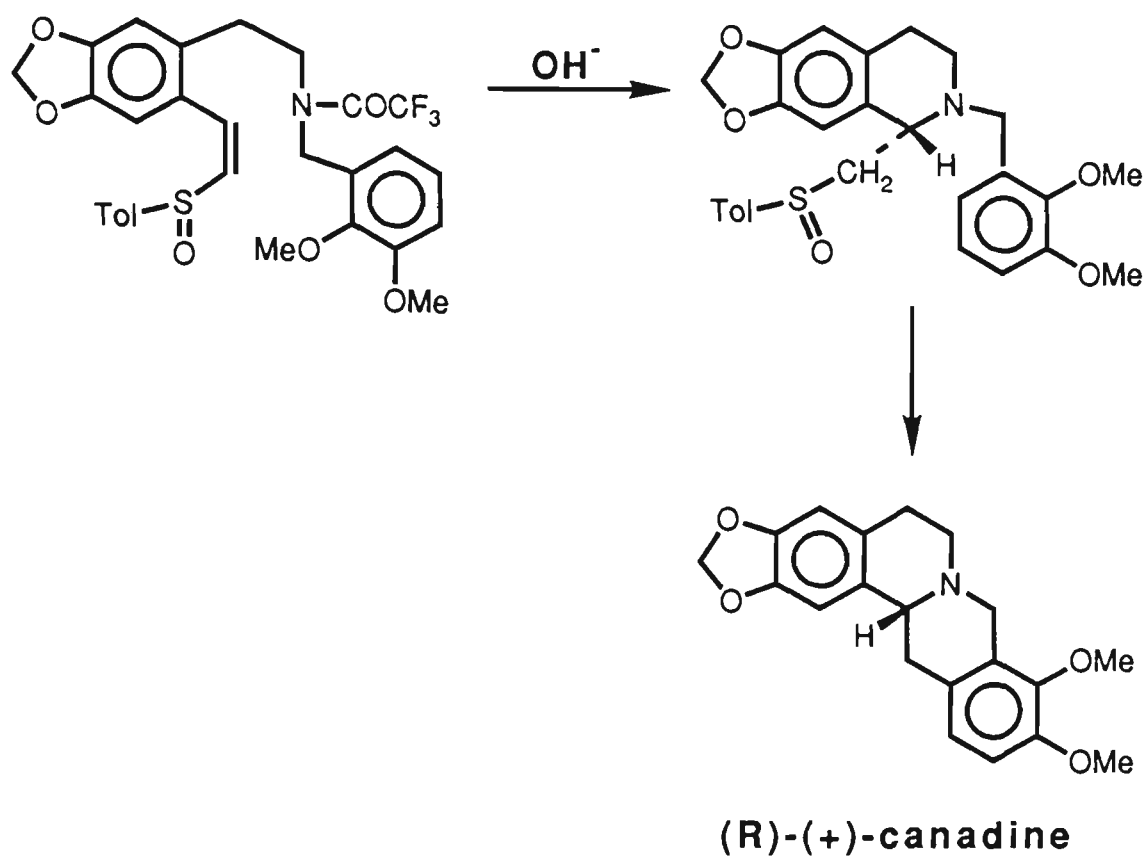
where the substituent on the alkylating agent,  $R_1$  = methyl, ethyl or iso-propyl there was only a slight increase in diastereoselectivity as the steric size of  $R_1$  increased, while for  $R_1$ =benzyl the diastereoselectivity diminished to 55%. The substituent R on the chiral auxiliary had little effect on the diastereoselectivity in the sense of the stereochemical outcome. The structure of the alkyllithium base also had no real effect: deprotonation with n-butyl-, sec-butyl, or tert-butyllithium and alkylation with n-propylbromide afforded 85+/-1% diastereoselectivity in each case. The diastereoselectivity was found to dependent upon both the reaction temperature and solvent. Low reaction temperatures (-100°C) and THF were essential for obtaining high product diastereoselection. The mechanism that Gawley postulated to account for his observations is shown in Scheme 11. The first step is the formation of a coordination complex, where the butyl group is oriented anti to the substituent on the oxazoline and is thus positioned for selective removal of the  $H_\beta$  proton. Proton loss then produces an equilibrating pair at organolithium diastereomers, 54 and 55. Upon addition of an electrophile the organolithium reagents are converted to a mixture of product diastereomers 56A,B in which 56A is favoured. However, the available evidence reveals neither the mechanism of the alkylation nor the structure of organolithium.

Scheme 11.



Pyne<sup>20</sup> devised another method of asymmetric synthesis, which involves nucleophilic addition of amines to chiral vinyl sulfoxides. This method involves control of the chirality at C-1 in a cyclization step. An outline of the synthesis of (R)-(+)-canadine is shown in Scheme 12. The diastereoselectivity in the key cyclization step however as only modest (80:20).

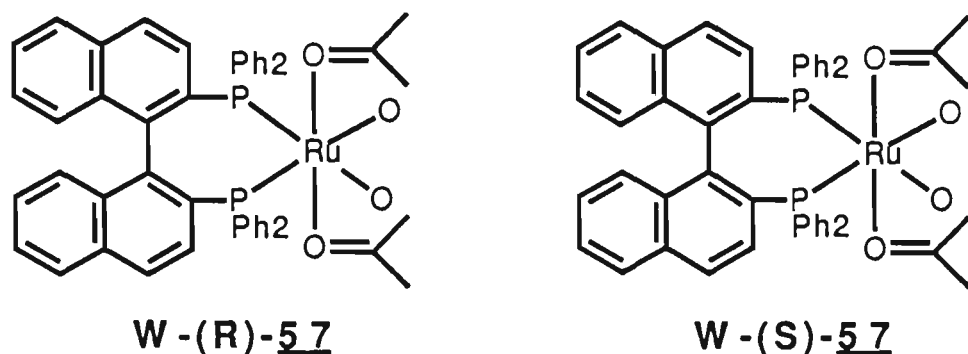
Scheme 12.



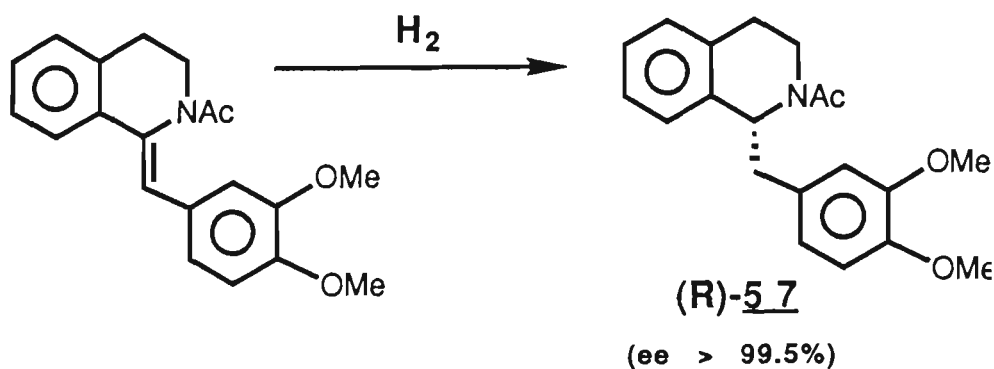
### SYNTHESIS OF 1,2,3,4 - TETRAHYDROISOQUINOLINES BY ASYMMETRIC REDUCTION

Chiral ruthenium complexes (Figure 8), have been shown to perform asymmetric catalytic hydrogenation of dehydro-1-substituted isoquinolines.<sup>21</sup>

**Figure 8. Ruthenium complexes used in isoquinoline synthesis.**



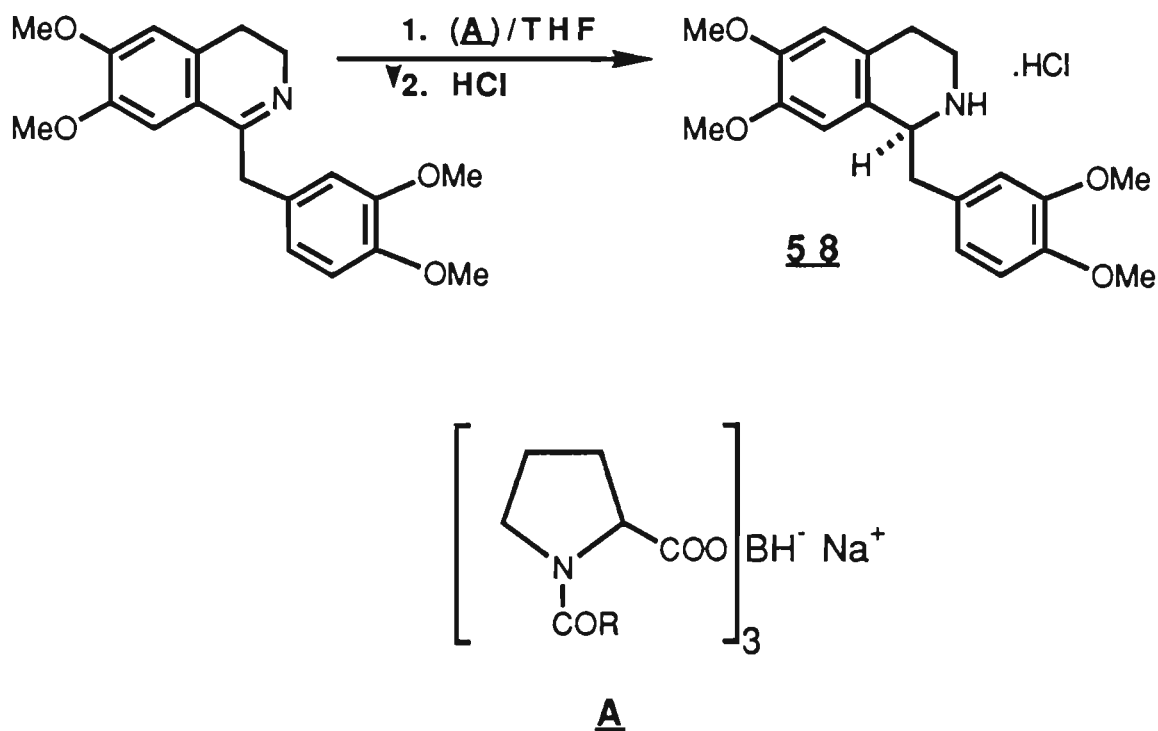
Here the enamine forms of isoquinolines are hydrogenated to produce such compounds as tetrahydropapaverine. These asymmetric hydrogenations result in the most extraordinary yields and optical purities (i.e. 92-100% yields and 96-100% enantiomeric excess), for a number of isoquinoline alkaloids. The advantage over many other methods of synthesis, is that both the (R) or (S) configurations of the isoquinoline can be obtained with no difficulty, simply by using one of the two optical isomers of the ruthenium complex.



Yamada<sup>22</sup> reported the asymmetric reduction of cyclic imines to optically active alkaloids by the use of chiral sodium trialkoxyborohydrides (Scheme 13). The reducing agent

prepared from the reaction of sodium borohydride and N-acyl proline was found to provide moderate optical yield (55-60% ee) of S-(+)-norlaudonosine.HCl(58). Reduction of 1-alkyl-3,4-dihydroisoquinolines gave products in up to 90% optical purity while methyl- $\beta$ -carboline gave the corresponding dihydro product in 79% optical purity.

**Scheme 13.**

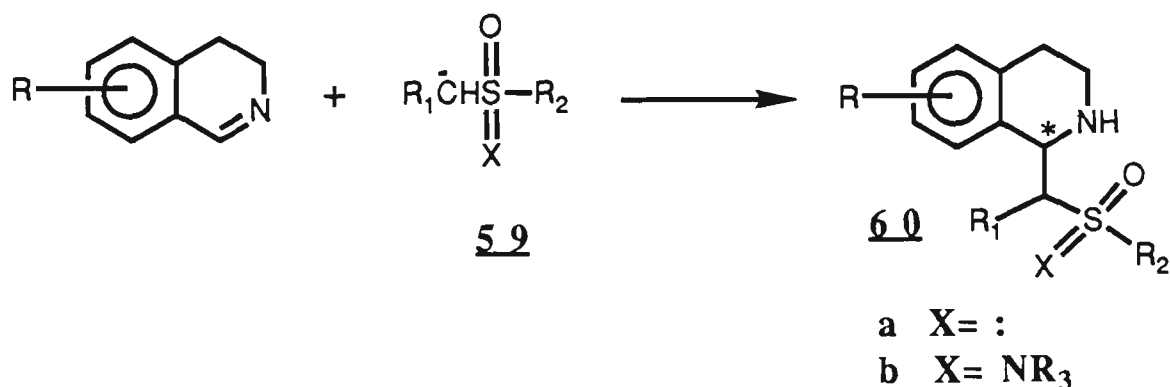


## ADDITION OF CARBANIONS TO 3,4-DIHYDROISOQUINOLINES

While several methods are available for the asymmetric synthesis of chiral 1-alkyl-1,2,3,4-tetrahydroisoquinolines the possibility of preparing these compounds by the addition of chiral nucleophiles to 3,4-dihydroisoquinolines has not been addressed. In particular the addition of the carbanions of chiral sulfoxides (59a) or sulfoximines (59b) to 3,4-dihydroisoquinolines may allow

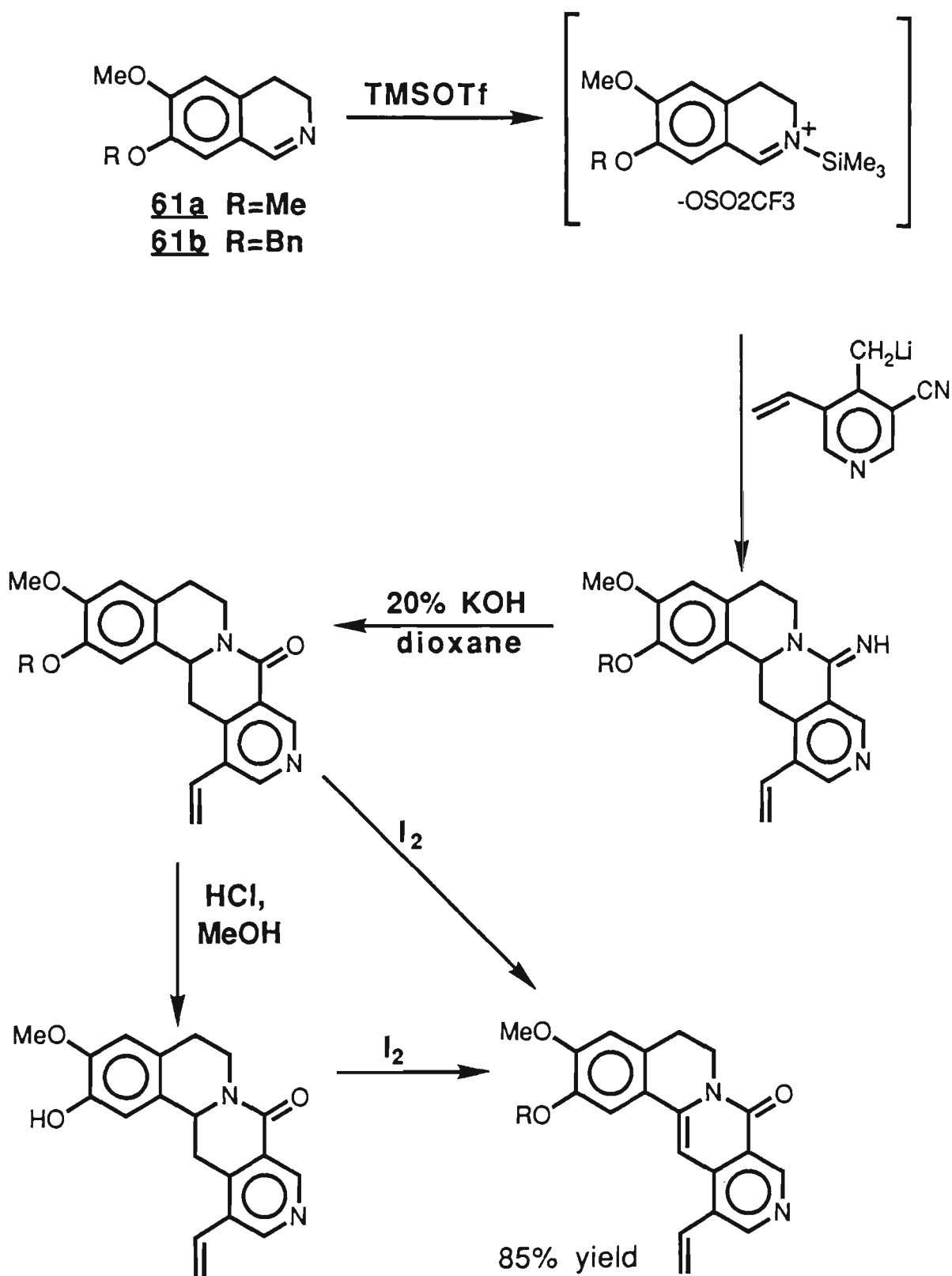
for a convergent and diastereoselective synthesis of 1-alkyl-1,2,3,4-tetrahydroisoquinolines. The chiral sulfur moiety in sulfoxides 60a or sulfoximines 60b would allow for the construction of further carbon-carbon bonds via alkylation and Pummerer reactions.<sup>20,23</sup> Compound 60 would appear an attractive intermediate for the synthesis of non-racemic chiral isoquinoline alkaloids (Scheme 14). The development of this type of approach to alkaloid synthesis is the subject of this thesis.

**Scheme 14.**



MacLean et al.<sup>24</sup> have used the imine 61 in the synthesis of racemic isoquinoline alkaloids by the addition of benzyl lithium reagents to 61 activated by trimethylsilyl triflate (Scheme 15).

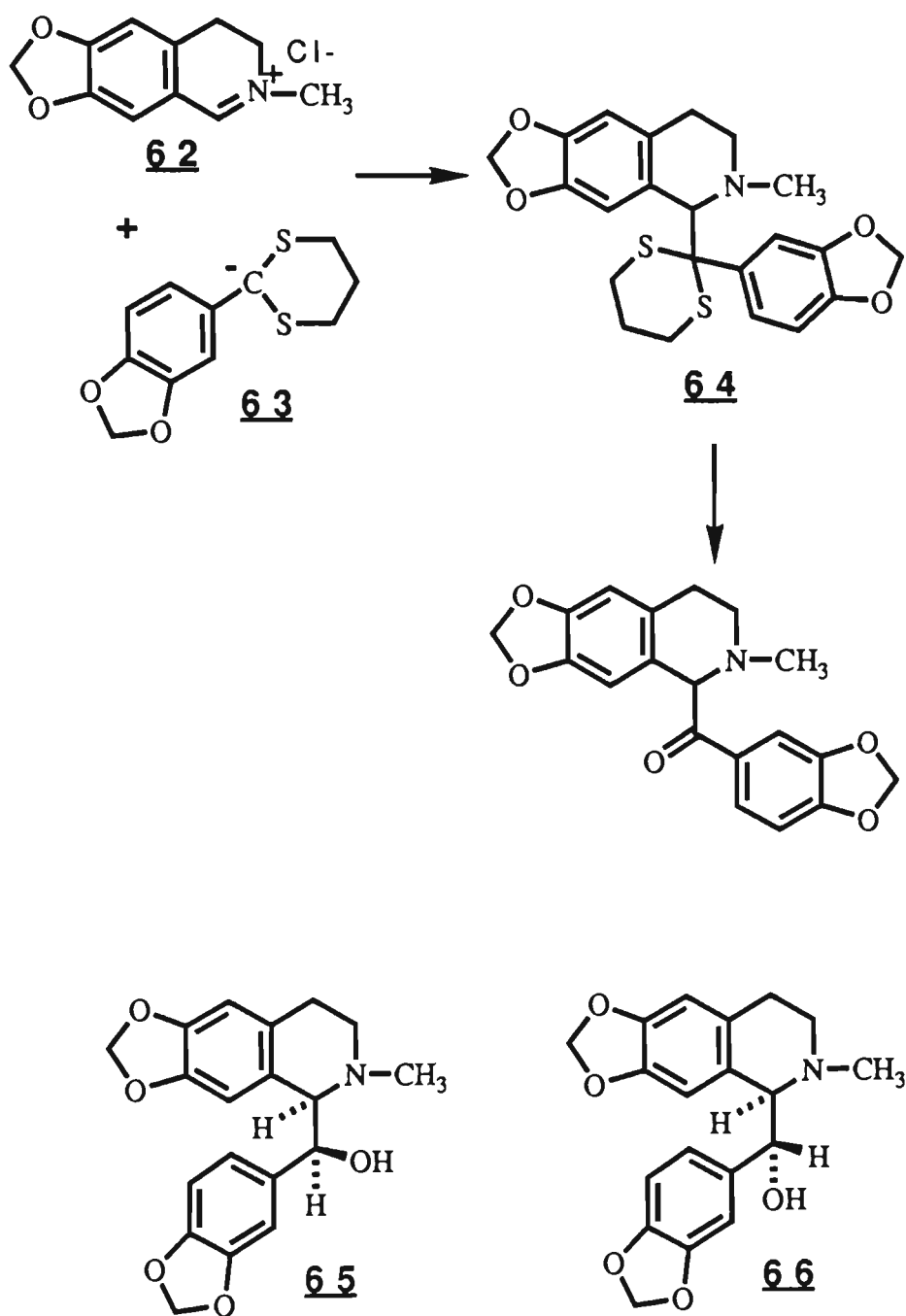
Scheme 15.



Rozwadowska<sup>25</sup> reacted iminium salt 62 with lithiated dithiane 63 (Scheme 16) to produce adduct 64 which upon

hydrolysis and then reduction with sodium borohydride yielded the diastereomeric alcohols 65 and 66 as racemates.

**Scheme 16.**





## THE STRUCTURE AND CHEMISTRY OF CHIRAL $\alpha$ -SULFINYL CARBANIONS

Before addressing the problem of alkaloid synthesis using chiral sulfoxide and sulfoximine reagents it seems appropriate to first survey the chemistry of these compounds to assist latter discussion in the results and discussion section of the thesis. Chiral  $\alpha$ -sulfinyl carbanions are well established as useful intermediates in asymmetric synthesis. In order to understand the factors determining the stereoselectivity of these compounds in asymmetric bond formation the knowledge of their structure is imperative. Wolfe and Buncl<sup>26,27</sup> observed selectivity in the base promoted H/D exchange of the diastereotopic methylene protons of benzyl methyl sulfoxide. This finding has been confirmed by several other studies and extended to other sulfoxides.<sup>28a,29</sup> It was also in agreement with the 3-21G\* calculations done by Wolfe et al.<sup>28b,28c,29</sup> as shown in Figure 9 and Table 6.

Figure 9. Newman projections of the energetically most favorable conformations of  $\text{H}_3\text{C-S(O)H}$  67 and its anion  $\text{H}_2\text{C}^-\text{-S(O)H}$  68 formed by reaction with  $\text{OH}^-$ .

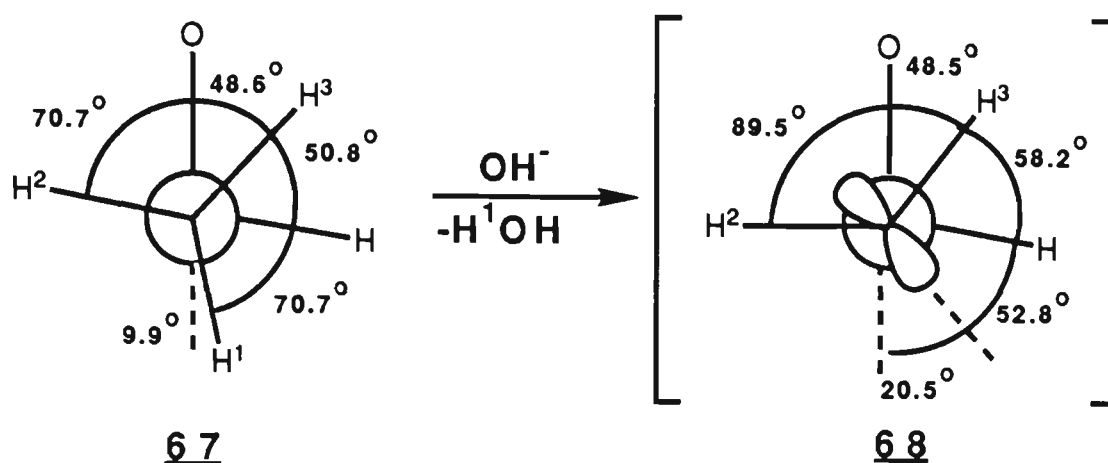


Table 6. 3-12G\* bond lengths [pm] for  $\text{CH}_3\text{SOCH}_3$  and  $\text{LiCH}_2\text{SOCH}_3$ ; experimental values in parentheses.

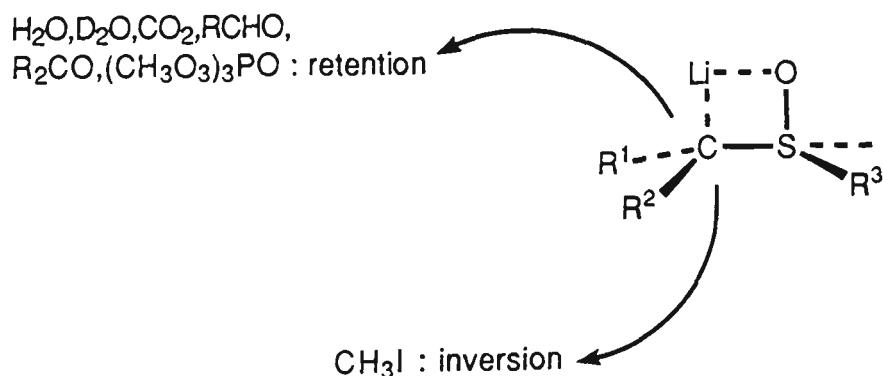
	$\text{H}_2\text{C}^-\text{-S}$	$\text{H}_3\text{C-S}$	$\text{S-O}$
$\text{CH}_3\text{SO CH}_3$	--	175.6 (177.1)	143.8 (143.5)
$\text{CH}_3\text{SO CH}_2^-$	161.8	179.7	146.2

"Proton H-1, which has a virtually antiplanar arrangement with respect to the S-O bond, is selectively removed by base from the sulfoxide  $\text{H}_3\text{C-S(O)H}$  (67), because the  $\alpha$ -sulfinyl carbanion which is thus formed most closely resembles the optimum structure of  $\text{H}_2\text{C}^-\text{-S(O)H}$  (68). The conformation about the C-S axis in (68), in which the lone pair of electrons on the  $\alpha$ -C atom is rotated  $20.5^\circ$  away from the position antiplanar to the S-O bond,

represents a compromise between maximisation of the  $n_{\text{C}}-\sigma^*_{\text{S-O}}$  and  $n_{\text{C}}-\sigma^*_{\text{S-H}}$  stabilization as well as minimisation of the lone pair repulsion<sup>27</sup>. The configuration of the "anionic" C atom is strongly pyramidalized, with the substituents (H-2 and H-3) bent toward the O atom."

Electrophiles containing oxygen react with  $\alpha$ -lithiosulfoxides in THF with retention of configuration, while  $\text{CH}_3\text{I}$ , except for *t*-butyl benzyl sulfoxide<sup>29</sup>, reacts with inversion. On the basis of this finding, Biellman et al.<sup>30</sup>, Durst et al.<sup>31</sup>, and Chassaing and Marquet<sup>32,33</sup> concluded that the Li atom in the  $\alpha$ -lithiosulfoxide is bound to the sulfoxide O and to the  $\alpha$ -C atom, and that the stereoselectivity is connected with the ability of the electrophile to form a complex with lithium as shown in Figure 10.

**Figure 10. "Ion-pair" model of " $\alpha$ "-lithiosulfoxides, and diastereofacial differentiation.**



On the basis of C-H coupling constants in 69, 70 and 71, Chassaing and Marquet<sup>32-35</sup> concluded that the  $\alpha$ -C atoms in the

benzylic anions 69 and 70 are largely planar, while the  $\alpha$ -C atom in 71 is hybridized "between  $sp^2$  and  $sp^3$ "(Table 7).

Table 7. C-H coupling constants( $J_{C,H}$ ) for the  $\alpha$ -C atom of 69, 70 and 71.

	$^1J_{C,H}$	$W^1J$ ("anion"-sulfoxide)
$CH_3SOCHPhLi$ <u>69</u>	160	+23
$tBuSOCHPhLi$ <u>70</u>	161	+23
$tBuSOCH_2Li$ <u>71</u>	147.5	+10

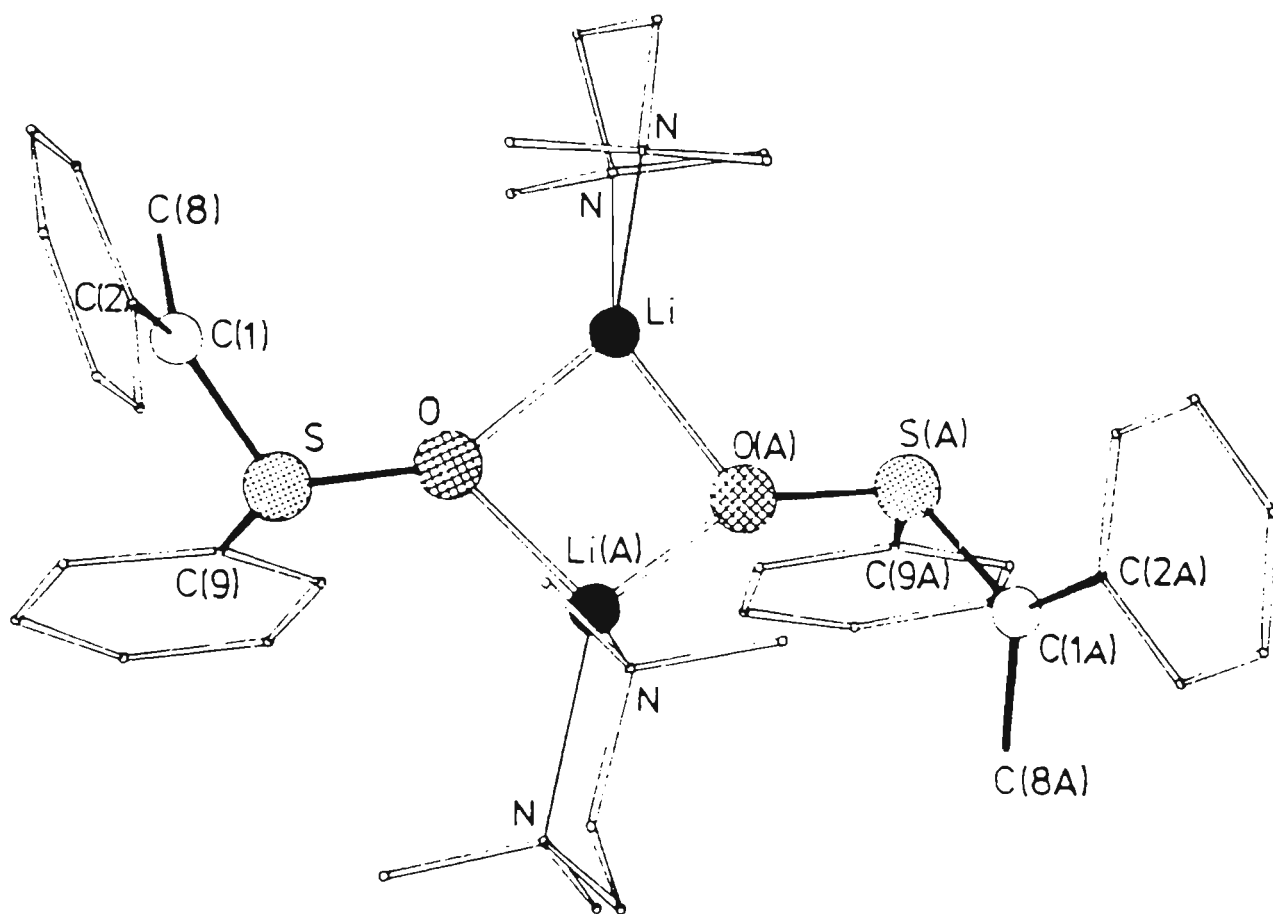
Table 8. Coalescence temperature of the signals of the two H atoms on  $C_\alpha$ , and  $\Delta G^\ddagger$  values for the topomerization, for 72a-c.

	$T_{coal.}(^\circ C)$	$W G^\ddagger(T_{coal.})$ (Kcal mol $^{-1}$ )
$PhSOCH_2Li$ <u>72a</u>	- 5	13.6
$PhSOCH_2K$ <u>72b</u>	-47.5	10.7
$PhSOCH_2K + [2.2.2]Cryptand$ <u>72c</u>	- 66	10.7

As seen from Table 8<sup>35</sup> the  $\alpha$ -H atoms in 72a-c are configurationally stable at low temperature, and the counter ion has an influence on the rate of topomerisation.

Boche et al.<sup>36</sup> published an x-ray crystal structure of the  $\alpha$ -sulfinyl "carbanion" of 1-phenylethyl phenyl sulfoxide(73) which crystallized as the dimeric species (74b)<sub>2</sub>•2tetramethylethylenediamine(TMEDA). The dimer was linked together through a (Li-O-Li-O) four membered ring (Figure11).

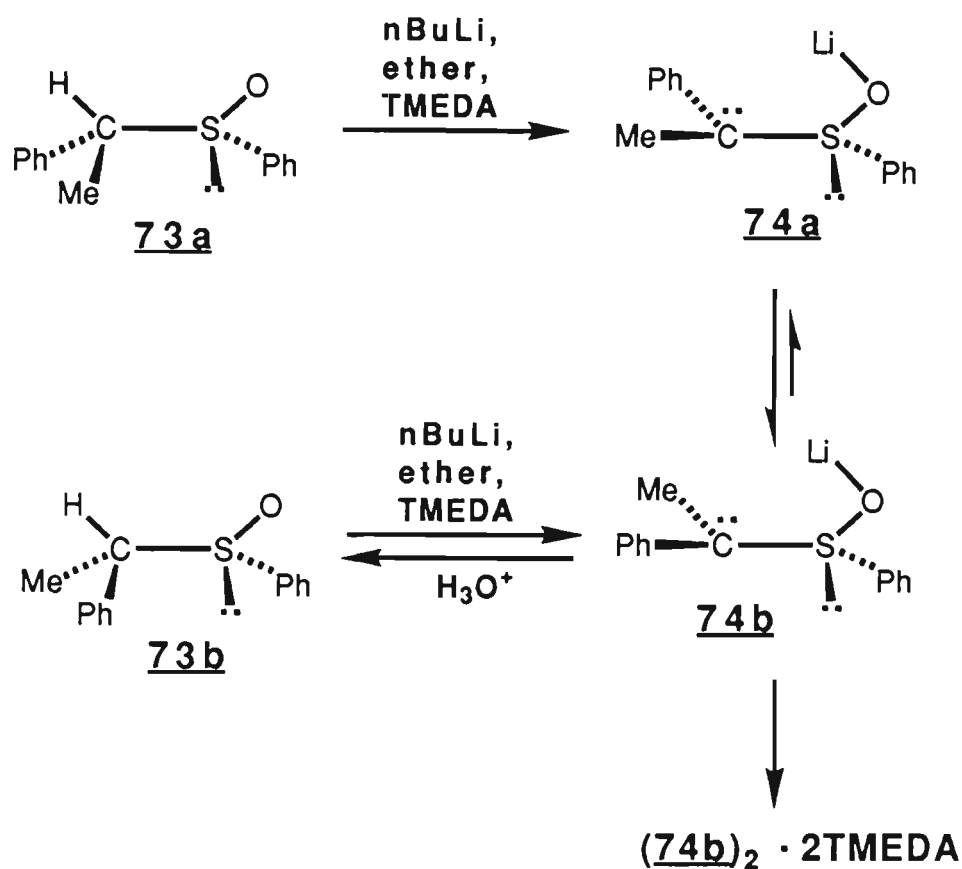
Figure 11. Crystal structure of dimeric (74b)<sub>2</sub>•2TMEDA.



The diastereomer (74b)<sub>2</sub> •2TMEDA is produced from approximately a 1:1 mixture of the two diastereomeric sulfoxides 73a,b. The diastereoisomer 74b would be expected to be more stable since the phenyl rings at C-1 and S are oriented trans to one another. Since protonation of 74 in ether solution yields only 73b, and since protonation of  $\alpha$ -sulfinyl "carbanion" proceeds

stereoselectively, then it is expected that only one diastereomer is present in solution, that is the one observed in the crystalline state (74b, Scheme 17).

**Scheme 17.**



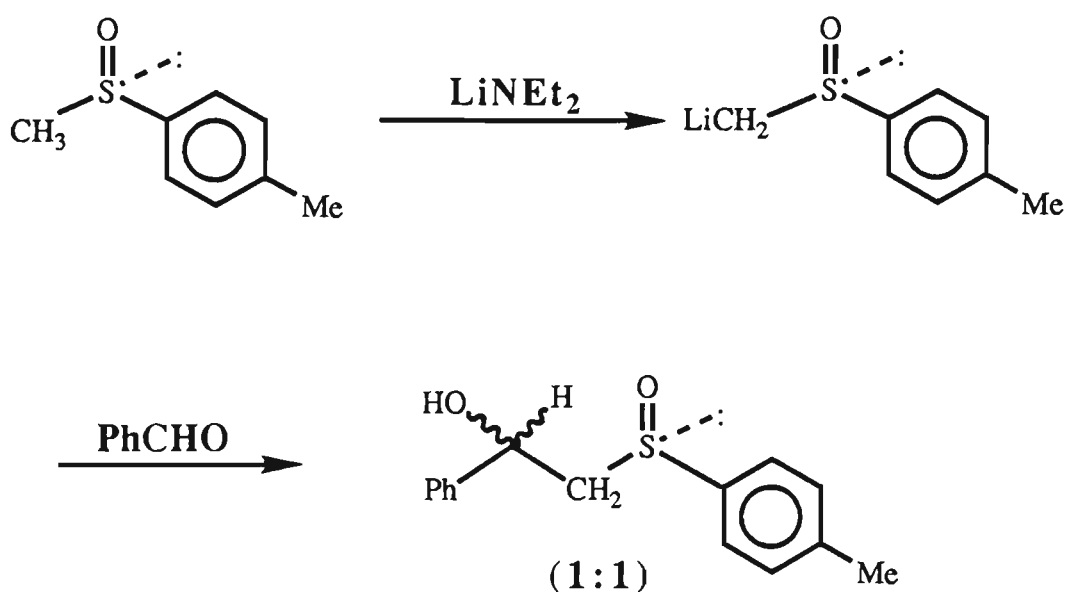
From the stereoselectivity of sulfoxide deprotonations with  $n\text{-BuLi}$ /ether one would expect formation of isomeric lithio sulfoxide 74a from deprotonation of 73a, however topomerisation data (see Table 8) shows that in solution at room temperature, 74a will be rapidly converted into the more thermodynamically stable 74b. The C-1-S distance (163pm) in  $(\text{74b})_4$  TMEDA is shorter, and the S-O distance (158 pm) is slightly larger than the corresponding bonds in sulfoxides (dimethyl sulfoxide (80pm and 147 pm, respectively))<sup>38</sup>, which is in agreement with the vibrational spectral

data<sup>35</sup>. Since the C-l-Li distance is so large (400pm), one cannot speak of C-Li bonds (C-Li bonds are shorter than ca.250pm)<sup>39</sup> and therefore (74b)<sub>2</sub> •2TMEDA cannot be called an  $\alpha$ -lithiosulfoxide.

## REACTIONS OF SULFINYL ANIONS WITH CARBONYL COMPOUNDS

Tsuchihashi<sup>40</sup> found that the carbanion of (R)-(+)-methyl p-tolyl sulfoxide is quantitatively generated from (R)-(+)-methyl p-tolyl sulfoxide by the action of lithium diethylamide. This carbanion reacts with aldehydes and ketones (Scheme 14) to produce a diastereomeric mixture of  $\beta$ -hydroxysulfoxides, however, these reactions proceeded with very poor diastereoselectivity (1:1).

Scheme 18.



Kunieda<sup>41</sup> studied the asymmetric addition of (R)-(+)-methyl p-tolyl sulfoxide to ketones but reported poor diastereoselectivities (Table 9). Despite this poor diastereoselectivity, this method was applied to the asymmetric synthesis of gypsy moth sex pheromone disparlure. Better diastereoselectivities have been reported using the more hindered methyl 1-naphthyl sulfoxide.<sup>42</sup>

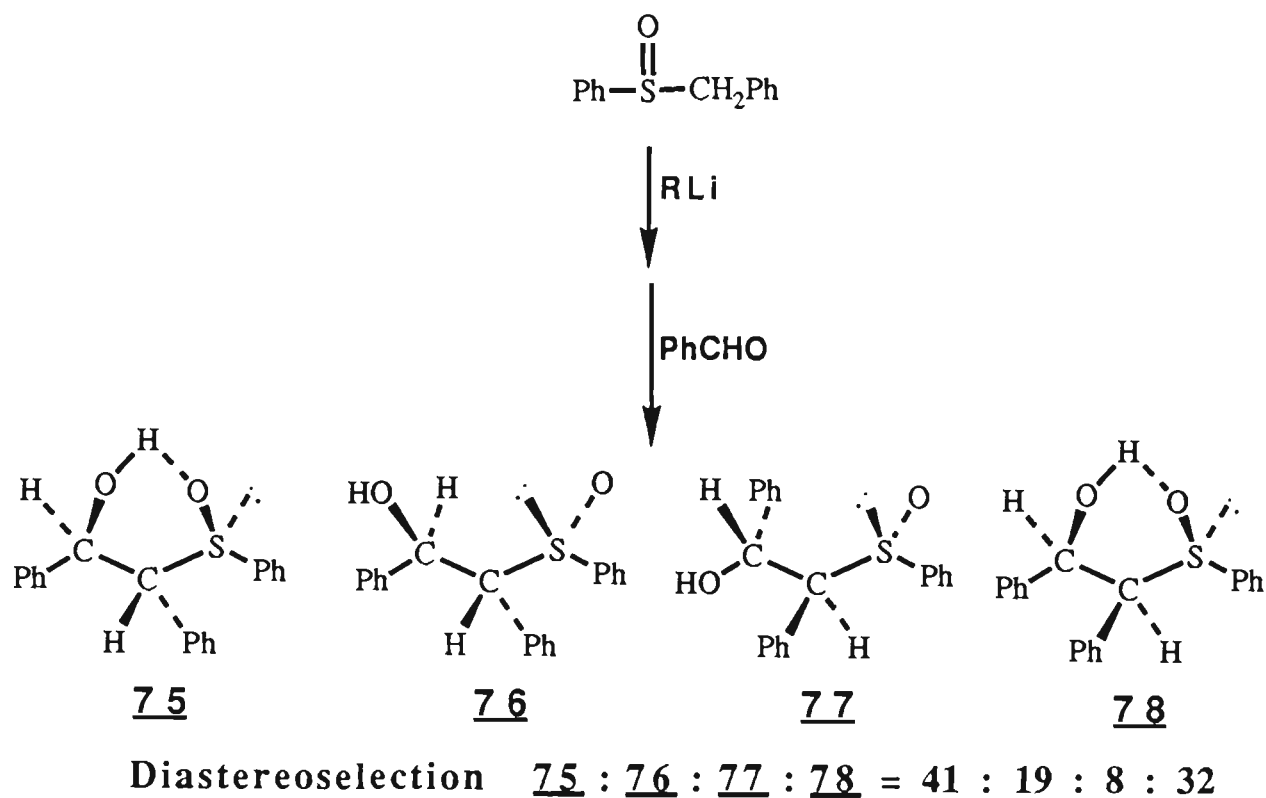


Table 9. Addition of (R)-(+)-methyl p-tolyl sulfoxide to ketones.

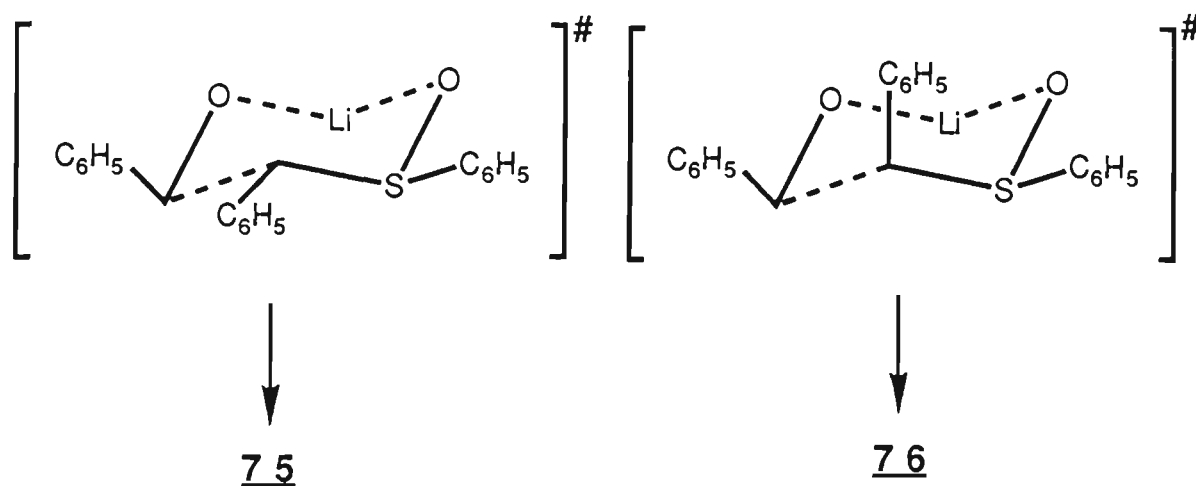
R <sup>1</sup>	R <sup>2</sup>	Diastereoisomeric
		ratio
Me	Et	50 : 50
Me	iPr	51 : 49
Me	tBu	53 : 47
Ph	Me	67 : 33
Ph	Et	58 : 42
Ph	iPr	60 : 40
Ph	c-C <sub>6</sub> H <sub>11</sub>	59 : 41
Ph	tBu	70 : 30

Kingsbury<sup>43</sup> reported the condensation of aldehydes with the carbanion of benzyl phenyl sulfoxide (Scheme 19). These reactions occurred with poor diastereoselectivity. The transition state for the formation of the major diastereomeric products 75 and 76, according to Kingsbury<sup>43</sup>, are likely to involve a six-membered chair transition state in which a lithium cation is chelated to the oxygen groups of the aldehyde and sulfoxide carbanion (Scheme20).

Scheme 19.

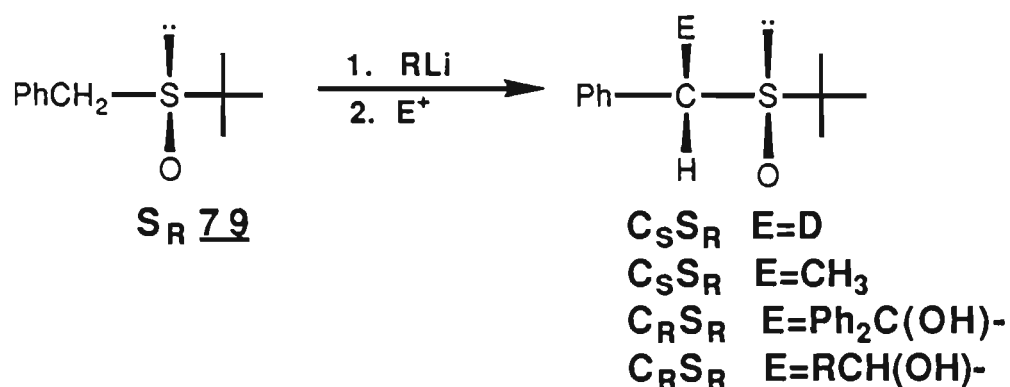


Scheme 20.



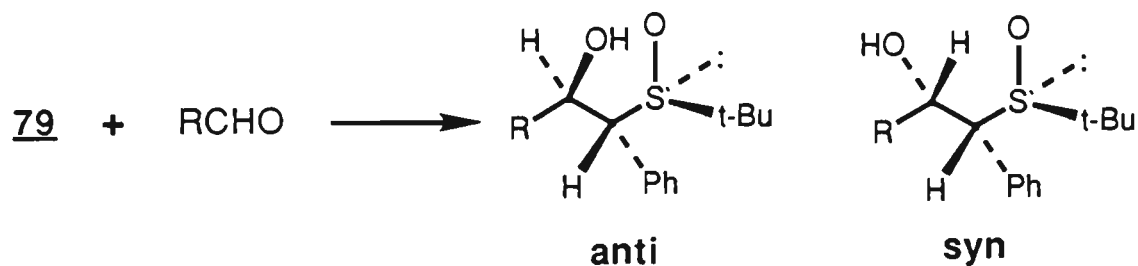
Pyne<sup>44</sup> showed that addition of the lithium salt of benzyl *tert*-butyl sulfoxide carbanion (79) to benzophenone, (Scheme 21) occurred in the same stereochemical sense as deuteration and methylation on the basis of single-crystal x-ray analysis .

Scheme 21.



Pyne<sup>44</sup> also conducted a survey of the effect of the aldehyde substituent and zinc cation on the reaction of the above carbanion with various aldehydes as shown in Table 10.

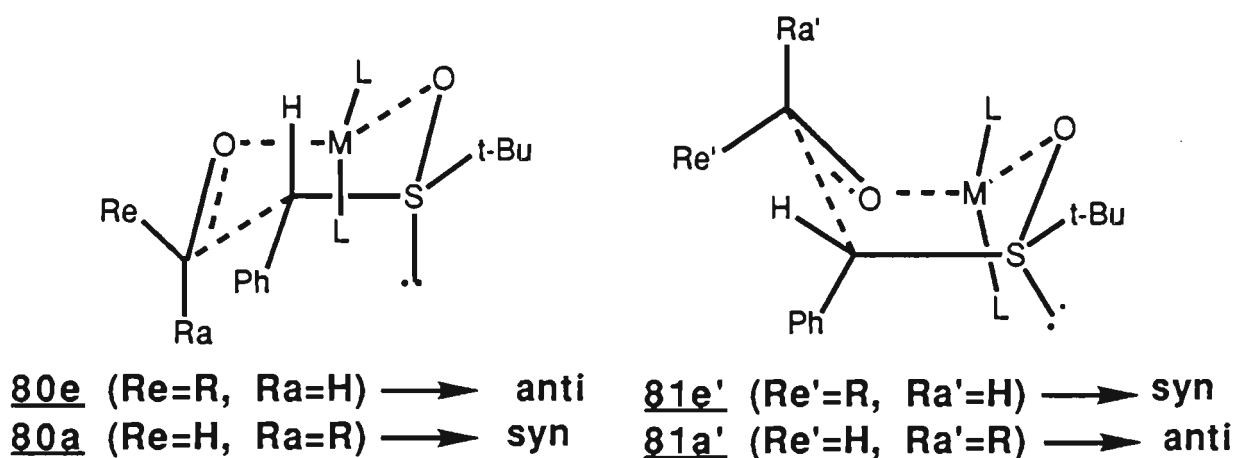
Table 10. Reaction of lithium and zinc **79** with aldehydes RCHO.



entry	R of RCHO	counterion	yield(%)	diastereoselection anti:syn
1	(E)-PhCH=CH	Li <sup>+</sup>	100	49:51
2	(E)-PhCH=CH	Zn <sup>2+</sup>	82	57:43
3	CH <sub>3</sub> CH <sub>2</sub>	Li <sup>+</sup>	85	65:35
4	CH <sub>3</sub> CH <sub>2</sub>	Zn <sup>2+</sup>	85	80:20
5	Ph	Li <sup>+</sup>	81	63:37
6	Ph	Zn <sup>2+</sup>	98	84:16
7	i-Pr	Li <sup>+</sup>	90	78:22
8	i-Pr	Zn <sup>2+</sup>	72	91:9
9	t-Bu	Li <sup>+</sup>	87	57:43
10	t-Bu	Zn <sup>2+</sup>	85	61:39

There are four possible diastereomeric chelated cyclic transition states possible for the reaction of lithium salt of benzyl *tert*-butyl sulfoxide carbanion with aldehydes. Scheme 22 shows the two possible chair and boat transition states. The preference for anti-diastereoselection suggests that chair or boat transition states 80e or 81a' are favoured.

Scheme 22.



The anomalous result with pivaldehyde suggest that a boat-like transition state would be more likely. In the boat transition state 81e', the aldehyde substituent R experiences a gauche interaction with the Ph group of the sulfoxide, while in the boat form it would experience a flagpole interaction with the sulfoxide oxygen. In the case when R is small the flagpole interaction would not be important resulting in transition state 81a', the anti diastereoselection increases with the increasing steric bulk at the aldehyde substituent as transition state 81e' becomes energetically less favourable. When R becomes sterically demanding (i.e. when

R = *t*-Bu) the flagpole interaction in 81a' becomes significant and poor product diastereoselection results.

### RESONANCE STABILISED $\alpha$ -SULFINYL-CARBANIONS

Chiral  $\alpha$ -sulfinyl carbanions stabilized with electron withdrawing groups react with aldehydes to give the corresponding  $\beta$ -hydroxy sulfoxides with moderate to high diastereoselectivity.

Annunzioto et al.<sup>45</sup> devised a highly diastereoselective method of asymmetric synthesis (up to 99%ee) of  $\beta$ -hydroxy-N,N-dimethylacetamides from aldehydes and optically active sulfoxides Scheme 23. The results obtained are shown in the Table 11. Best results were obtained when magnesium rather than lithium salts were employed. A chelated transition state was postulated.

Scheme 23.

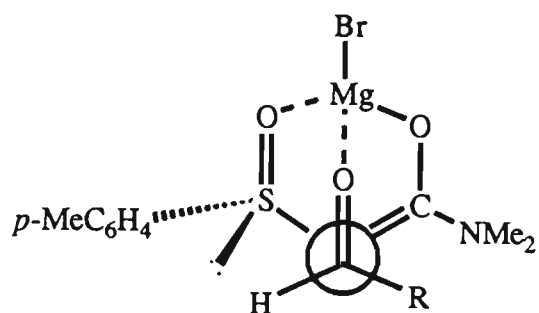
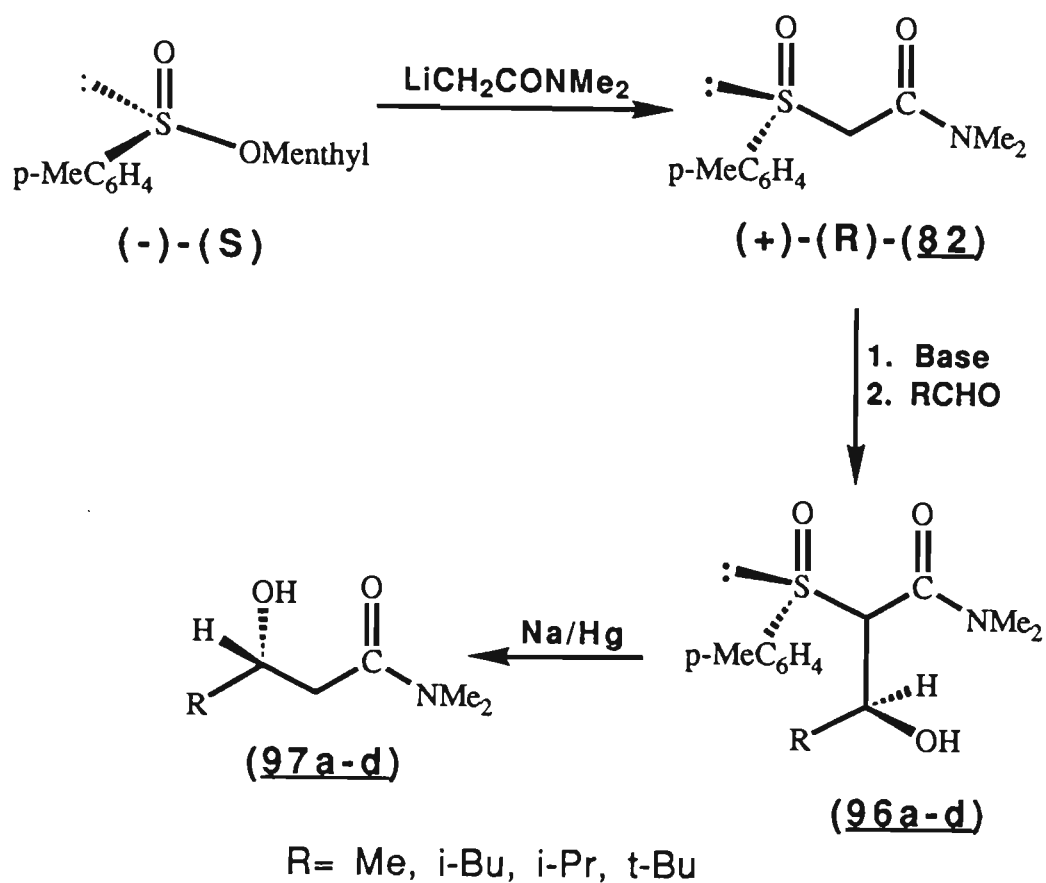


Table 11. Results of the enantioselective condensation of (+)-(R)-82 with aldehydes RCHO.

R	Base	(%)	$[\alpha]_D^{22}$	Enantiomeric excess (%)
Me	n-BuLi	65	+30.3	47
i-Bu	n-BuLi	77	+14.3	45
i-Pr	n-BuLi	77	+21.6	34
i-Pr	n-BuLi	78	+19.4	31
i-Pr	n-BuLi	40	+10.6	17
t-Bu	n-BuLi	20	+ 6.6	8
i-Pr	n-BuLi	78	-11.9	19
Me	t-BuMgBr	68	-65.0	$\geq 99$
i-Bu	t-BuMgBr	71	-31.3	98
i-Bu	t-BuMgBr	73	-28.4	89
i-Pr	t-BuMgBr	62	-53.5	85
i-Pr	t-BuMgBr	66	-59.7	95
i-Pr	t-BuMgBr	63	-43.3	69
t-Bu	t-BuMgBr	56	-70.9	90

Scolastico<sup>46</sup> on the other hand, improved the stereoselectivity of such reactions by introducing a sulfide group  $\alpha$  to the carbanion. The carbanion of (S)-(-)-p-tolyl p-tolylthiomethyl sulfoxide was added to benzaldehyde and phenylacetaldehyde and the adducts were transformed into  $\alpha$ -methoxyaldehydes with up to 70%ee (Scheme 24). The observed stereoselectivity may be explained by a cyclic chair transition state, that is stabilized by chelation of both reaction partners to the lithium cation (Figure 12).

Scheme 24.

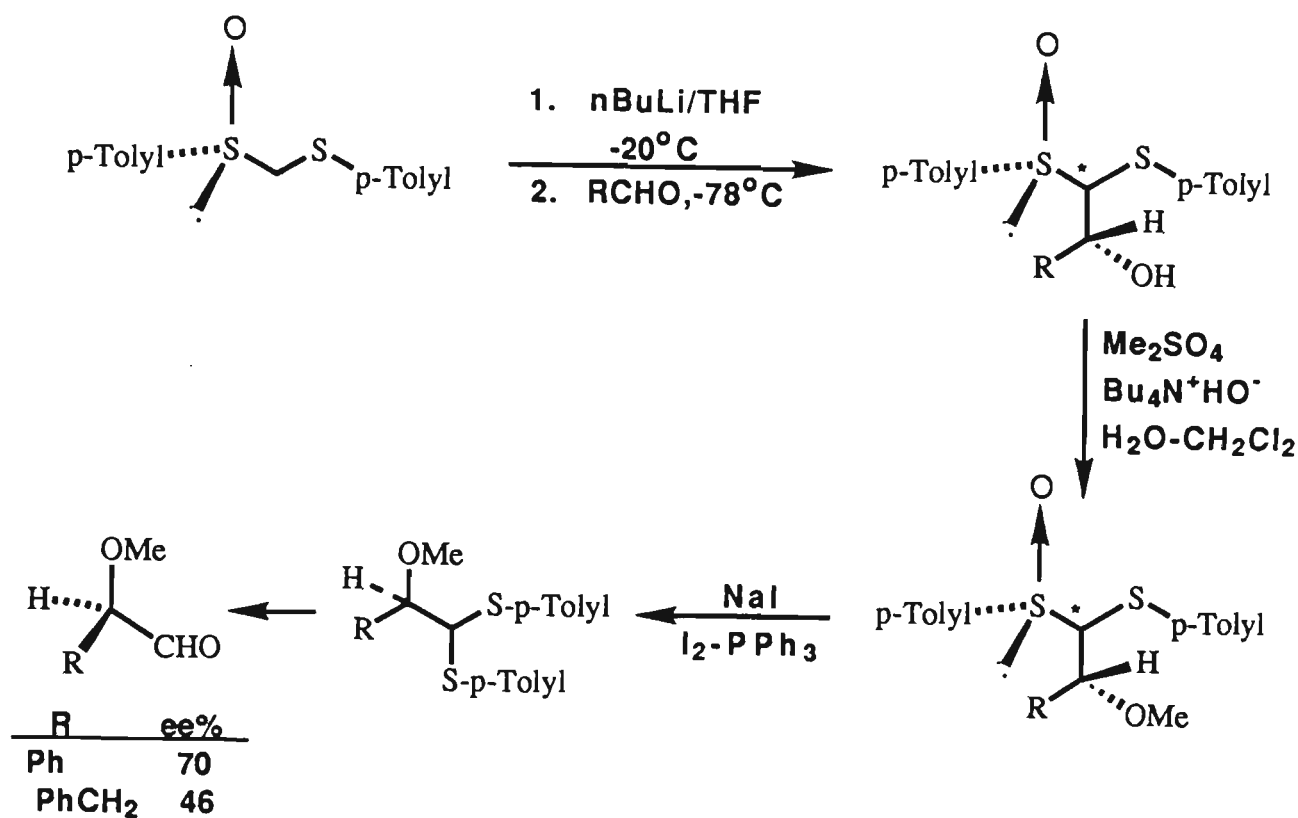
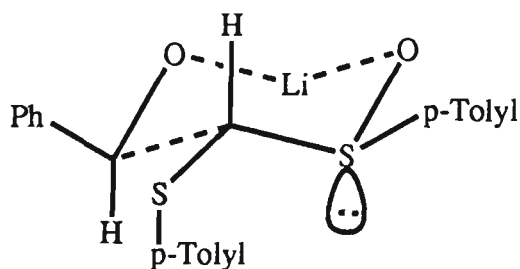


Figure 12.

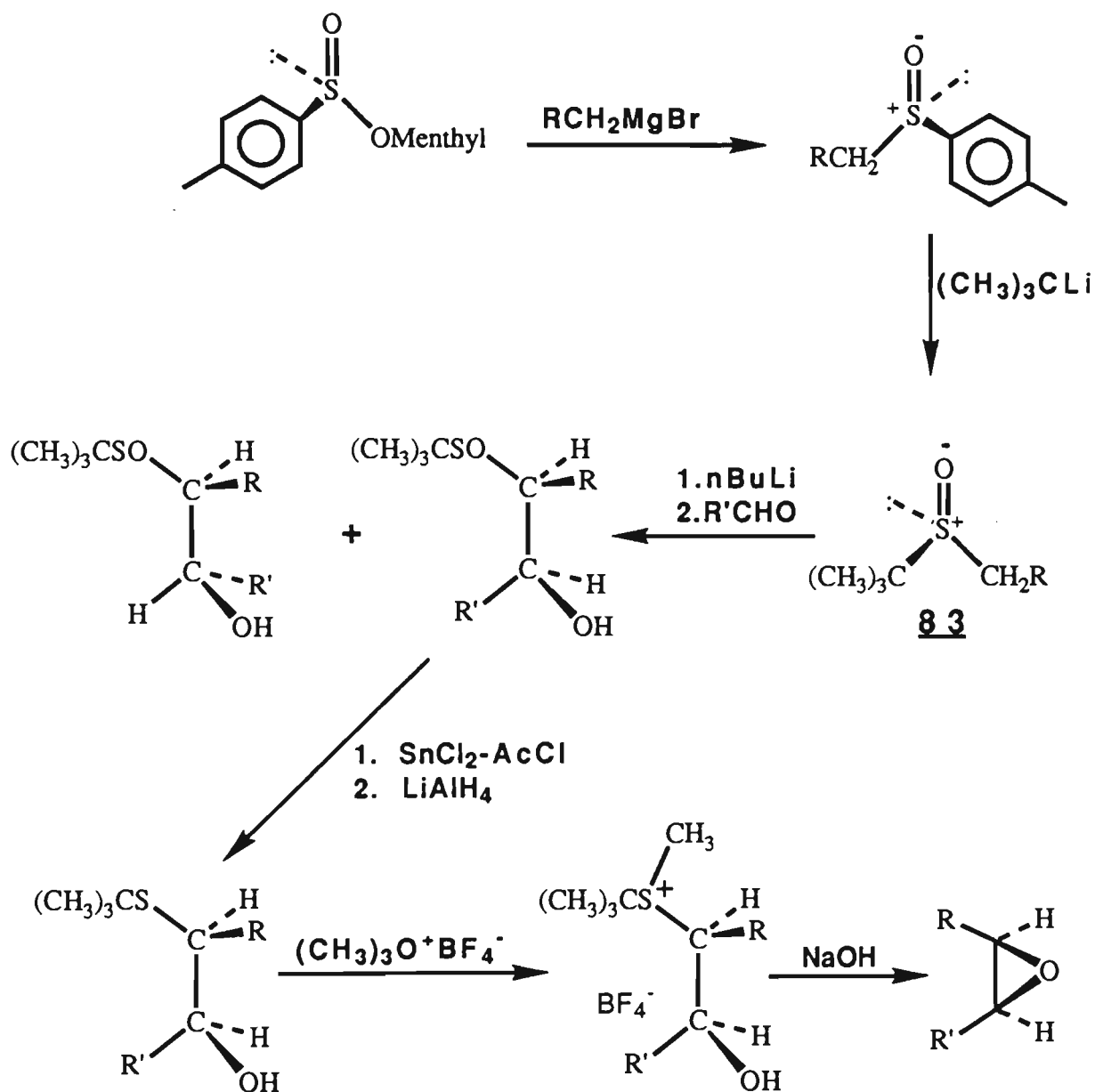


Farnum et al.<sup>47</sup> described a synthesis of the pheromone (7R,8S)-epoxy-2-methyloctadecane in 15% yield in six steps from menthyl p-toluenesulfinate (Scheme 25). The reaction of the carbanion of the alkyl tert-butyl sulfoxide 83 with undecanal gave a mixture (45:55) of two diastereomeric carbinols that differed in configuration at the carbinol stereogenic centre. These could be



separated and then converted to the target molecule as outlined in Scheme 25.

Scheme 25.



## REACTIONS OF $\beta$ AND $\alpha$ -HYDROXYSULFOXIDE DIANIONS.

Fujisawa et al.<sup>48</sup> described the diastereoselective  $\alpha$ -alkylation of the dianions of  $\beta$ -hydroxy sulfoxides which gave the

anti  $\alpha$ -alkyl- $\beta$ -hydroxy sulfoxides as the major diastereomeric products (Scheme 26). The results obtained are shown in Table 12.

Scheme 26.

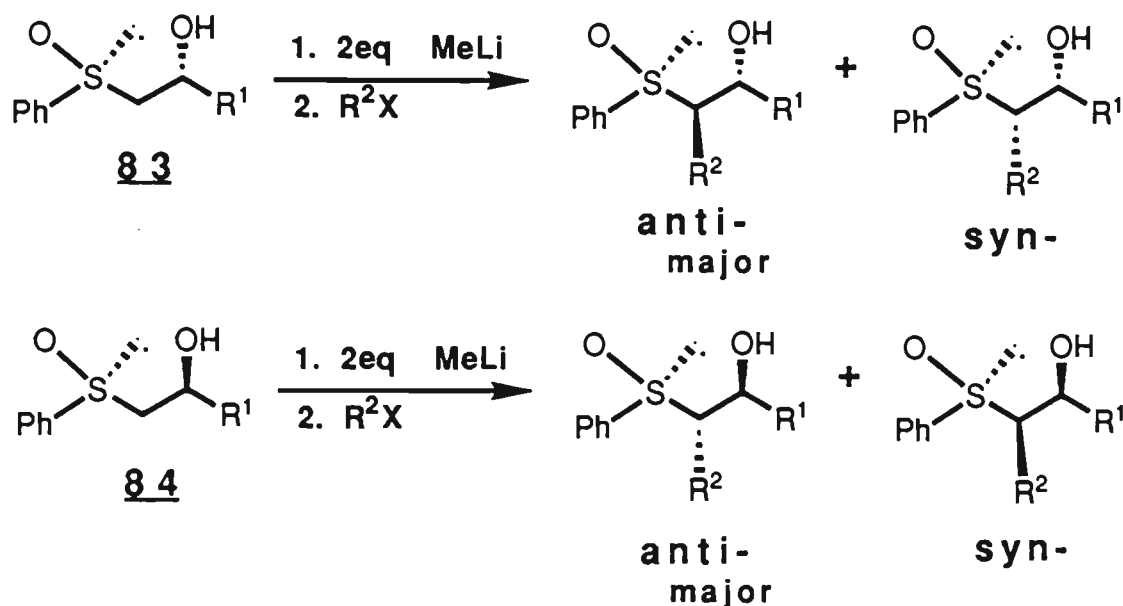
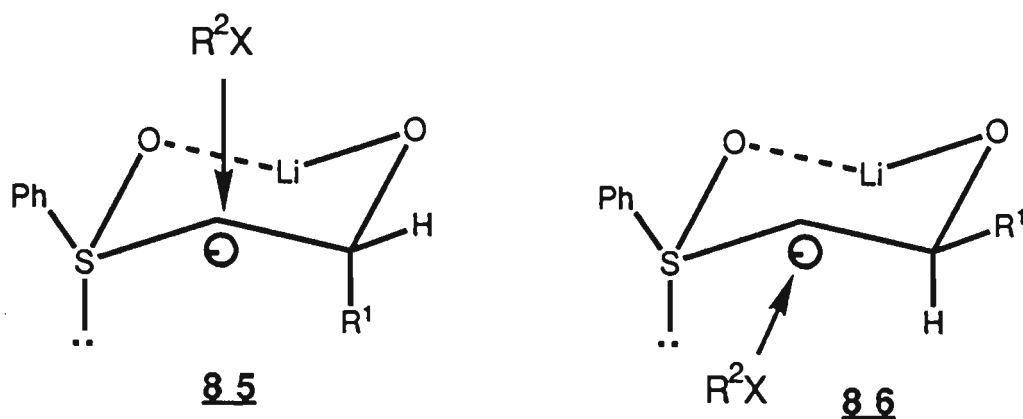


Table 12.  $\alpha$ -Alkylation of  $\beta$ -hydroxy sulfoxide **83** and **84**.

Entry	b-hydroxy sulfoxide		$R^2X$	Yield (%)	Ratio anti: syn
	<b>83</b>	or <b>84</b>			
1	$R^1 = \text{CH}_3$		$\text{CH}_3\text{I}$	87	16:1
2	$R^1 = i\text{-C}_7\text{H}_{15}$		$n\text{-C}_{10}\text{H}_{21}\text{I}$	58	4:1 <sup>b</sup>
3	$R^1 = \text{CH}_3$		$\text{CH}_3\text{I}$	76	11:1
4	$R^1 = \text{CH}_3$		$\text{CH}_3\text{I}$	62	11:1
5	$R^1 = \text{CH}_3$		$(\text{CH}_3\text{O})_3\text{P=O}$	50	10:1
6	$R^1 = i\text{-C}_7\text{H}_{15}$		$n\text{-C}_{10}\text{H}_{21}\text{I}$	75	20:1 <sup>b</sup>

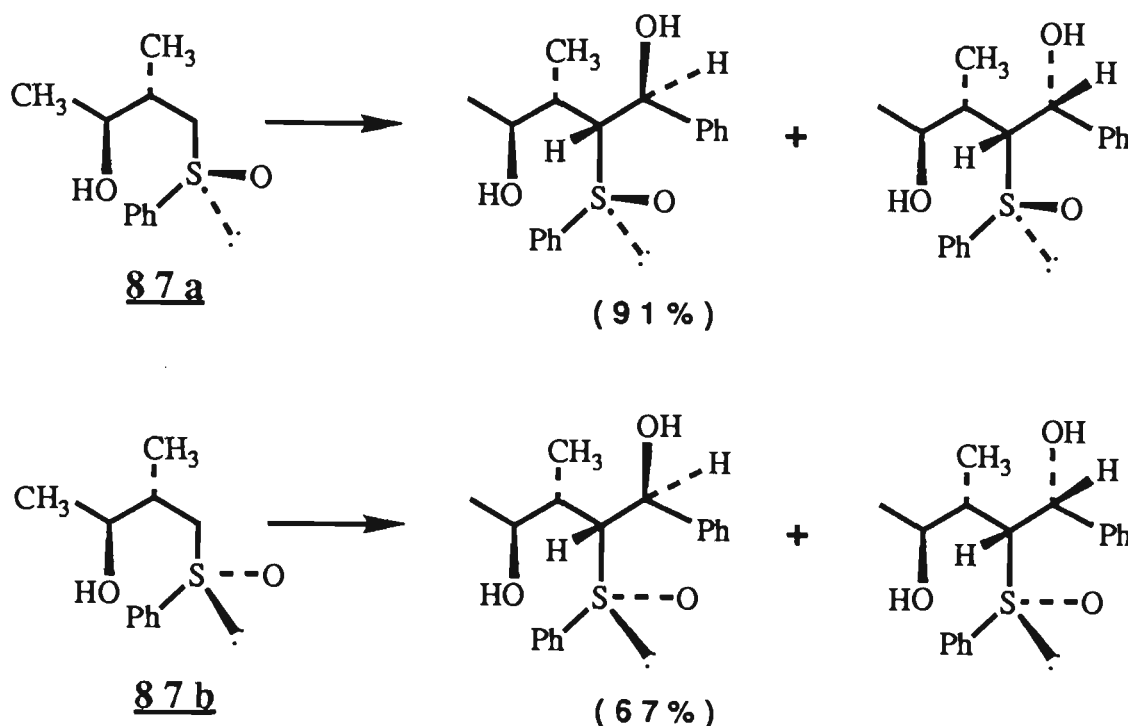
These results indicate that the stereoselectivity of the alkylation reaction is controlled by the stereochemistry at the carbinol carbon and not by that of the sulfinyl group. The stereochemical outcome could be explained by the chair transition states **85** and **86** produced by the chelation of both oxygens of the hydroxyl and

sulfinyl groups to the lithium cation. Alkylation occurred opposite to the carbinol substituent  $R_1$ . A similar study was reported by Tannikaga.<sup>49</sup>



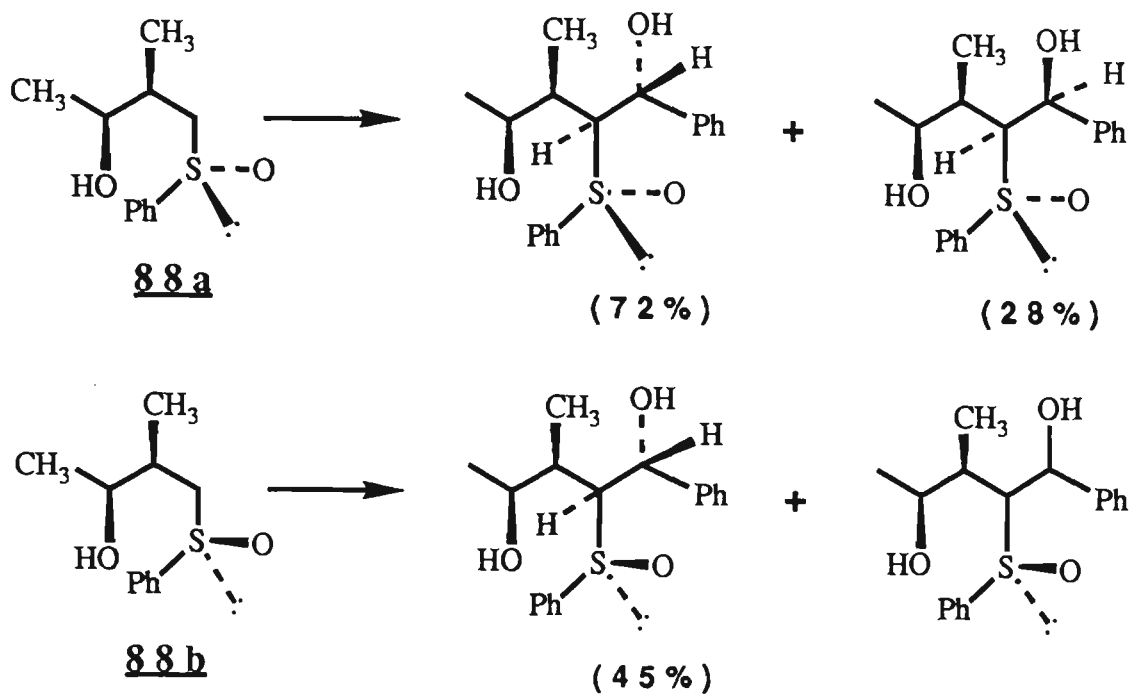
Williams<sup>50</sup> and colleagues conducted a set of experiments between racemic  $\gamma$ -hydroxy-sulfoxides **87a,b** and benzaldehyde. Quenching the dianion of **87a,b** with benzaldehyde gave the carbinol adducts shown in Scheme 27.

Scheme 27.



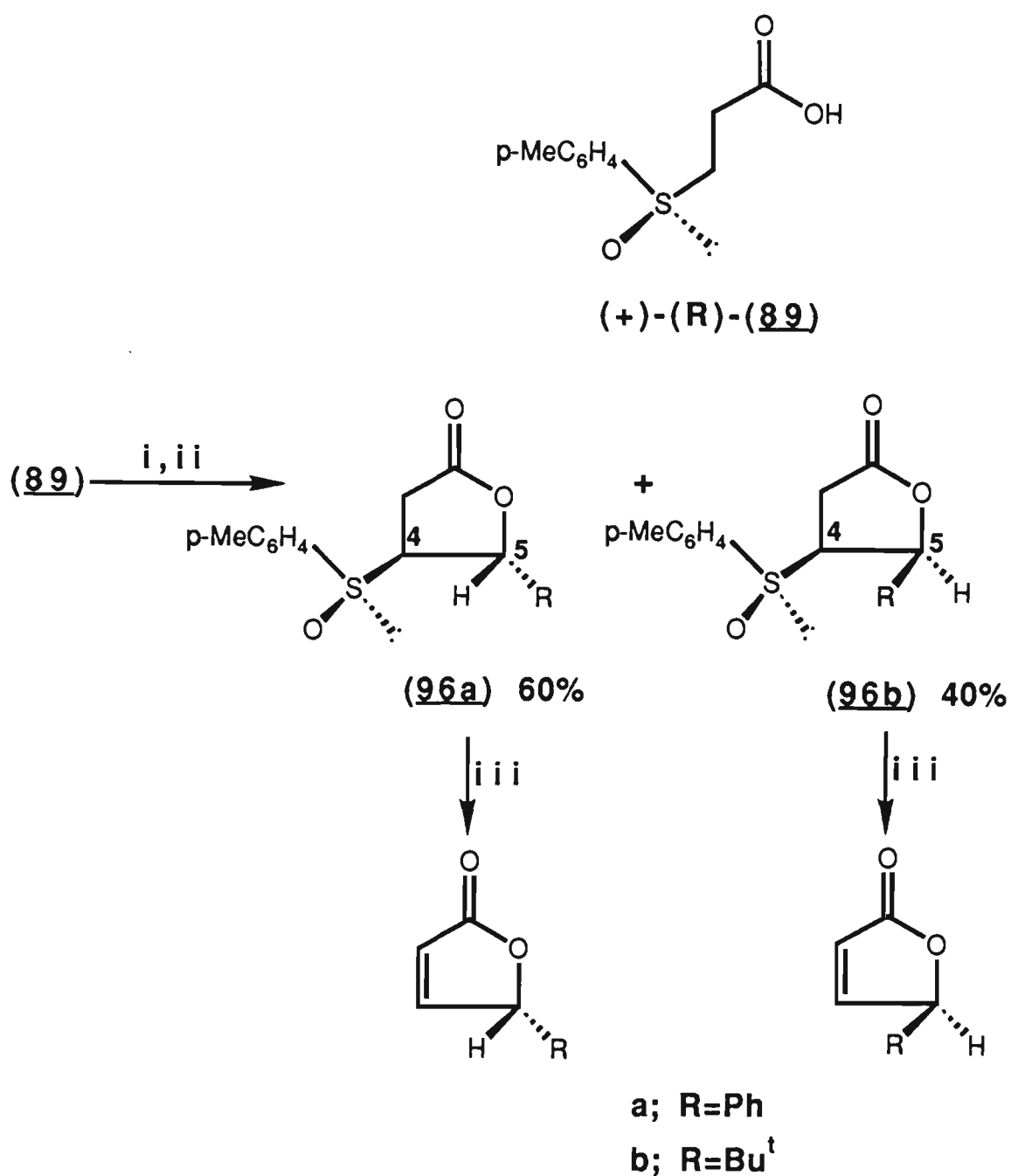
In a similar fashion, condensation of the carbanion of the racemic sulfoxides 88a,b (Scheme 24) which have inverted configuration of the  $\beta$ -methyl substituent afforded the carbinol products shown in Scheme 28. Interestingly the major products from both of these studies show the same relative stereochemistry at the two newly created stereogenic centres despite the inversion of sulfoxide configuration. Williams however was not able to rationalise this result.

Scheme 28.



Bravo et al.<sup>51</sup>, studied the addition of the dianion of 3-(p-tolylsulfinyl)propanoic acid (**89**) to aldehydes to achieve the synthesis of two diastereomeric lactones **96a** and **96b** (Scheme 29). The diastereoselection however was poor (60:40).

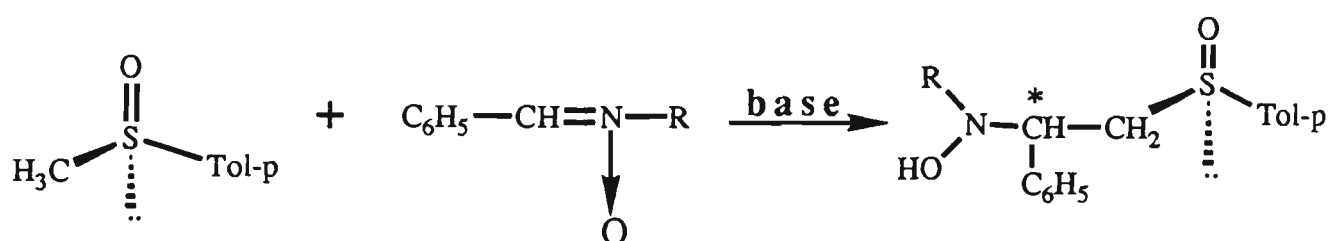
Scheme 29.



## ADDITION OF SULFOXIDE ANIONS TO IMINES

Annunziato <sup>52</sup> formed optically active  $\beta$ -oximino sulfoxides from the addition of methyl p-tolyl sulfoxide to nitrones (Scheme 30). The diastereomeric ratio was determined by <sup>1</sup>H NMR to be 75:25, 82:18 and 100:0 in the case where R was Me, Ph and tert-Bu respectively. The stereochemistry of the adducts was not determined.

Scheme 30.

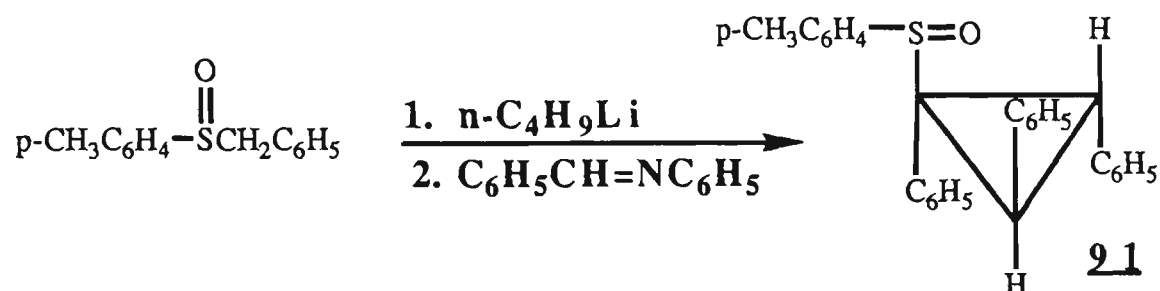


(+)-(R)

R= CH<sub>3</sub>, Ph, t-Bu

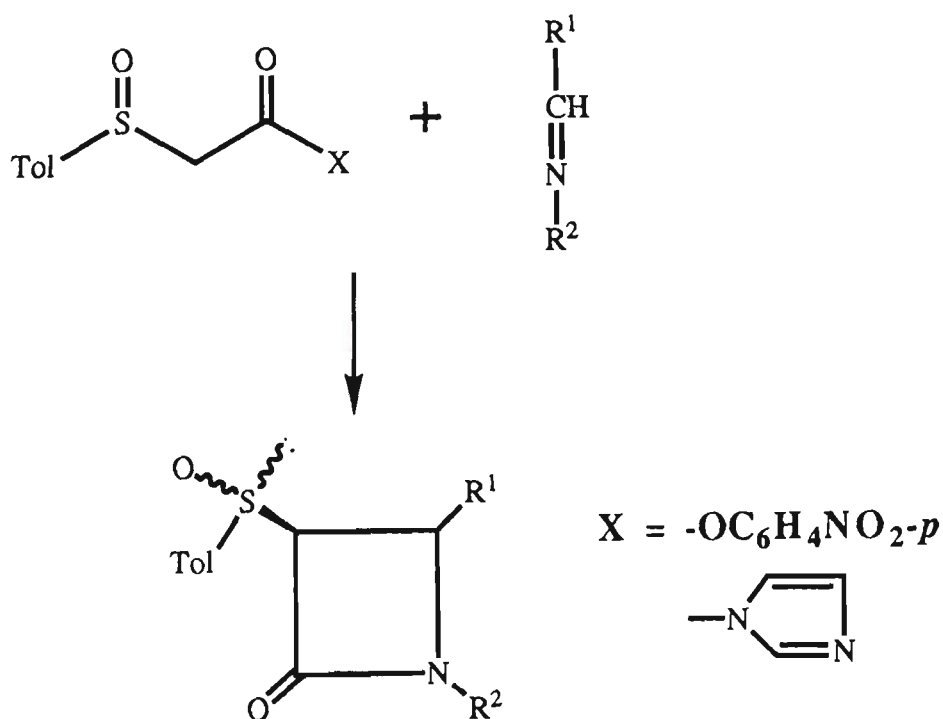
Cram<sup>53</sup> found that when reacting lithiated benzyl p-tolyl sulfoxide with N-benzylideneaniline, instead of the anticipated 1,2 addition adduct a single racemate of the cyclopropane derivative(91) was produced (Scheme 31). The reaction however was carried out at reflux.

Scheme 31.



Guanti et al.<sup>54</sup> in the course of his studies, on sulfoxide-mediated asymmetric synthesis, exposed the feasibility of synthesis of  $\beta$ -lactams, based on the condensation between an imine and derivatives of racemic 2-(p-tolylsulphonyl)acetic acid (Scheme 32). The diastereoselectivities however were modest (53-87 : 47-13).

Scheme 32.





Pyne<sup>29</sup> conducted a study of the addition of the carbanion of benzyl tert-butyl sulfoxide to imines (Scheme 33). High anti selectivity was observed when aromatic imines were employed (Table 12). Alkyl imines were less reactive and less diastereoselective.

Scheme 33.

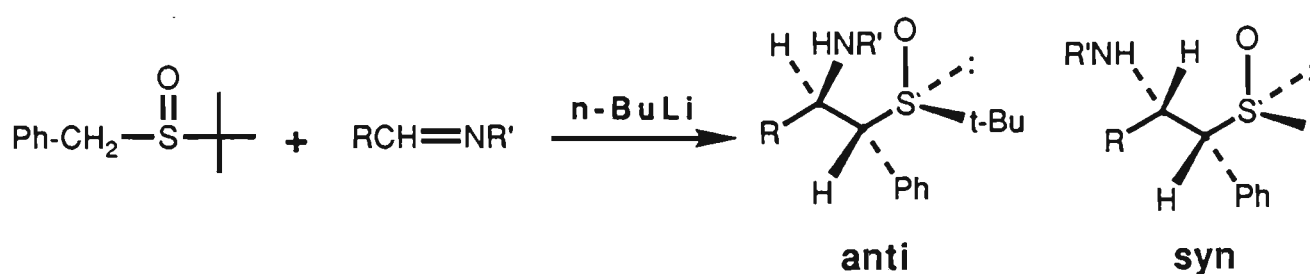
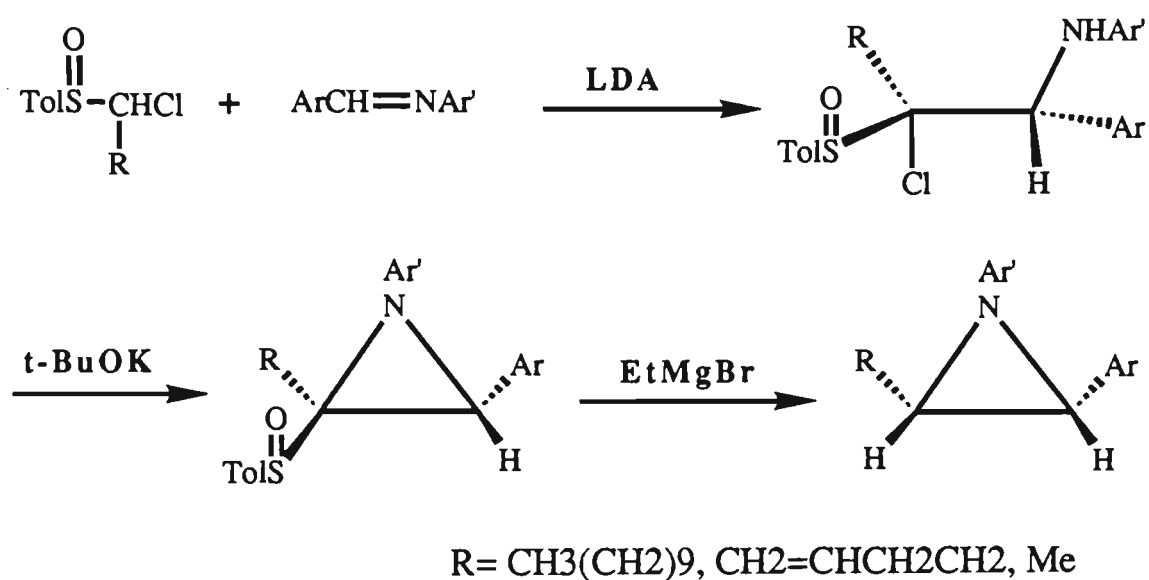


Table 12. Reactions of lithium and zinc benzyl *t*-butyl sulfoxide with imines.

entry	imine (RCH=NR')		counterion		yield (%)	diastereo-selection anti:syn
	R	R'	(temp, °C;	time, h)		
1	Ph	Ph	Li <sup>+</sup>	(-78; 2)	94	>97:<3
2	(E)-PhCH=CH	Ph	Li <sup>+</sup>	(-78; 2)	52	>97:<3
3	(E)-PhCH=CH	Ph	Zn <sup>2+</sup>	(-78; 5)	82	>97:<3
4	2-furyl	Ph	Li <sup>+</sup>	(-78; 2)	100	97:3
5	Ph	CH <sub>3</sub>	Zn <sup>2+</sup>	(-78->0; 2)	28	42:58
6	Ph	CH <sub>3</sub>	Zn <sup>2+</sup>	(-78->0; 2)	85	58:42
7	(BF <sub>3</sub> complex) CH <sub>3</sub> CH <sub>2</sub>		Zn <sup>2+</sup>	(-78->0; 2)	57	67:33

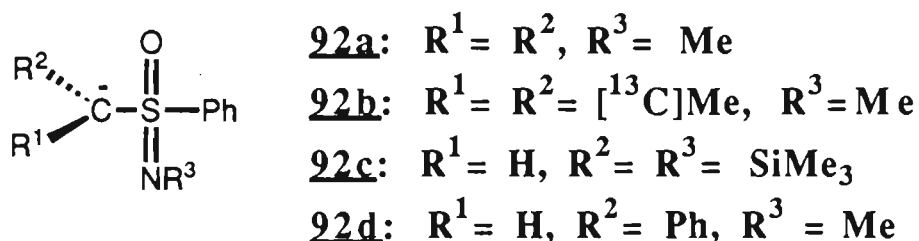
Yamakawa et al.<sup>55</sup> synthesised (Z)-N-arylaziridines from the addition reaction of 1-chloroalkyl p-tolyl sulfoxides and N-arylimines through sulfinylaziridines according to the Scheme 34 in good to excellent yield (85-95%).

Scheme 34.



## THE STRUCTURE AND CHEMISTRY OF LITHIUM COMPOUNDS OF CHIRAL SULFOXIMINES.

Despite the importance of sulfoximines in asymmetric synthesis<sup>56</sup>, on account of the chiral centre at sulfur, far less information is available on the structures of lithium derivatives of sulfoximines than for the related lithiosulfones and sulfoxides.

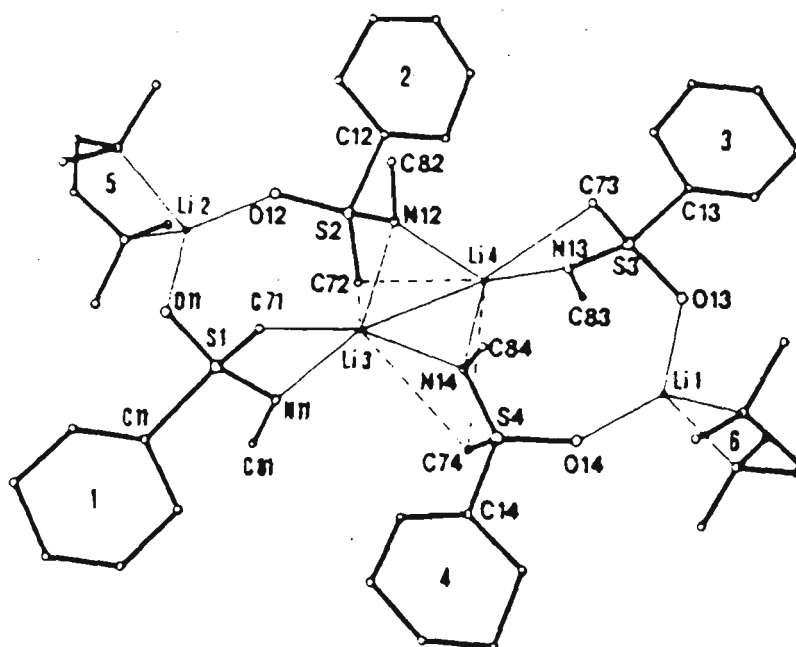


From a study of the  $^{13}\text{C}$  NMR coupling constants ( $^1J_{\text{CH}}$ ) of lithiated N-methyl-S-methyl,S-phenyl-sulfoximine (92a) in THF, Chassaing and Marquet<sup>57</sup> concluded that the configuration of the  $\alpha$ -C atom is pyramidal.

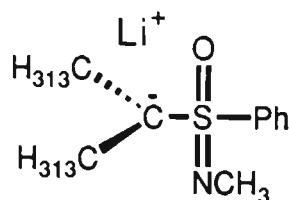
Gais et al.<sup>58</sup> published a detailed structural information provided by the x-ray structure analysis of lithiated (S) N-methyl-S-benzyl-S-phenyl-sulfoximine(92d).TMEDA complex (Figure 13). The single-crystal x-ray structure analysis revealed a tetramer structure ((92d)<sub>4</sub>. 2TMEDA) with the Li atom and the sulfoximine anion moiety each occurring in two different co-ordination environments. Li-1 and Li-2 are each co-ordinated to TMEDA and to the O atoms of two different "carbanions" (O-13, O-14 and O-11, O-12). Each of the other two Li atoms are coordinated to the three N atoms of a sulfoximine group (N-11, N-12, N-14, and N-12, N-13, N-14) and to an "anionic" C atom (C-71 or C-73). The author notices

a contact between the other two "anionic" C atoms (C-72 and C-74) and Li-3 and Li-4, respectively, but with a Li-C distance of 323 pm this too large to represent a bonding interaction.

**Figure 13. Crystal structure of ((S)-92)<sub>4</sub>.2TMEDA.**



Further information concerning the structure in solution was obtained from  $^{13}\text{C}$  NMR (THF- $d_8$ ) using the  $^{13}\text{C}$ -labeled compound 92b.<sup>59</sup> A diastereotopomerisation of the two  $^{13}\text{CH}_3$  groups was observed, caused either by rotation around the C-S bond, if the configuration of the "anionic" C atom is planar, or by rotation and inversion if it is pyramidal. It was, however, not possible to determine which mechanism is responsible for the topomerisation.

**92b**

$[(\text{Me}_3\text{Si})\text{CH}\{\text{S}(\text{O})(\text{NSiMe}_3)\}\text{Li}]_4 \cdot 2\text{C}_6\text{H}_{12}$  (92c) $\cdot 4.2\text{C}_6\text{H}_{12}$ ) could be crystallized without donor solvent molecules. The x-ray structure analysis shows a chiral tetramer<sup>59</sup> (Figure 14 and Figure 15) composed of two R, R- and two S, S- 89c diastereomers. A  $\text{Li}_4\text{O}_4$  cube forms its centre. Each Li atom is pentacoordinated to the O and C atoms of one sulfoximine anion, to the N and O atom of a second, and to the O atom of a third. C-1 projects 17 pm out of the plane defined by its substituents S, Si-1 and H-1, so that C-1 is markedly pyramidalized, in accordance with the results of the  $^{13}\text{C}$  NMR studies<sup>57</sup>. The author<sup>60</sup> contests that the stabilizing  $n_{\text{C}}-\sigma^*_{\text{S-C}}$  interaction is responsible for the observed configuration and conformation.

Figure 14. Crystal structure of  $(\underline{92c})_{4.2}C_6H_{12}$ .

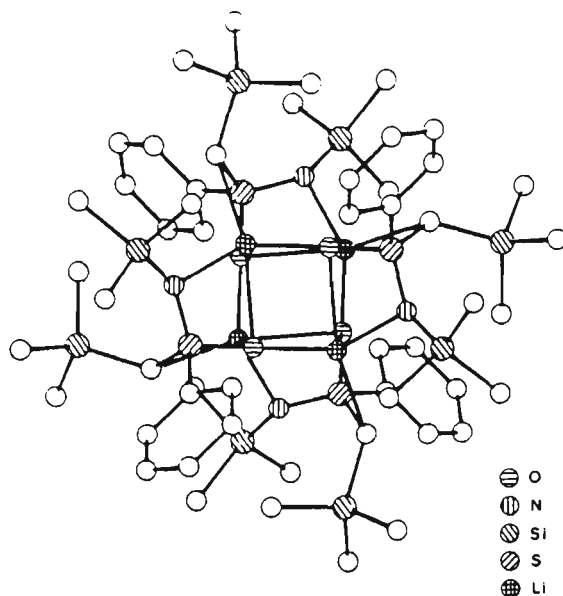
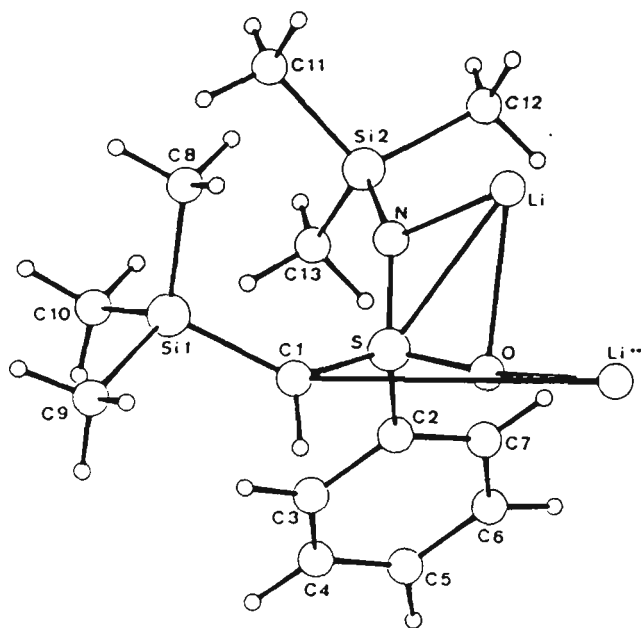


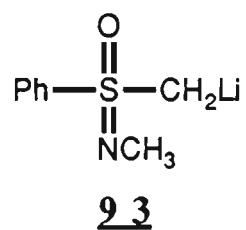
Figure 15. Partial structure of  $(\underline{92c})_{4.2}C_6H_{12}$  with numbering scheme.



The  $J_{CH}$  coupling constant for the anionic C atom in  $(\underline{92c})_{4.2}C_6H_2$  (in cyclohexane- $d_{12}$ ) is 5 Hz larger than for the corresponding non-lithiated sulfoximine. This points to a hybridization between  $sp^2$  and  $sp^3$  in the solution, a finding which is agreement with the crystal structure of  $(\underline{89c})_{4.2}C_6H_{12}$ .

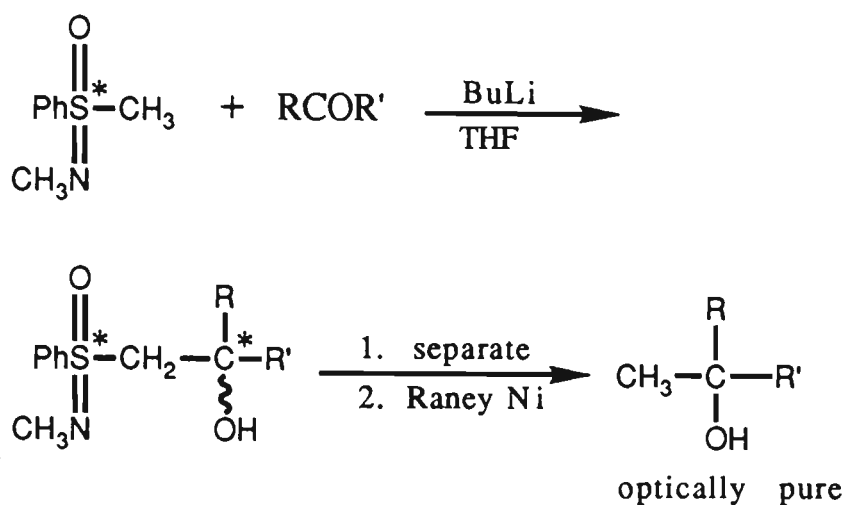
## REACTIONS OF LITHIUM COMPOUNDS OF SULFOXIMINES WITH ELECTROPHILES.

Compared with sulfoxides and sulfones much less work has been devoted to the study of the lithium compounds of sulfoximines with electrophiles. Johnson and colleagues<sup>61</sup> found that the anion of N,S-dimethyl-S-phenylsulfoximine (93) adds to aldehydes and ketones to yield  $\beta$ -hydroxysulfoximines. Reductive elimination of these adducts with aluminium amalgam under acidic conditions was developed as a useful method for alkene synthesis.



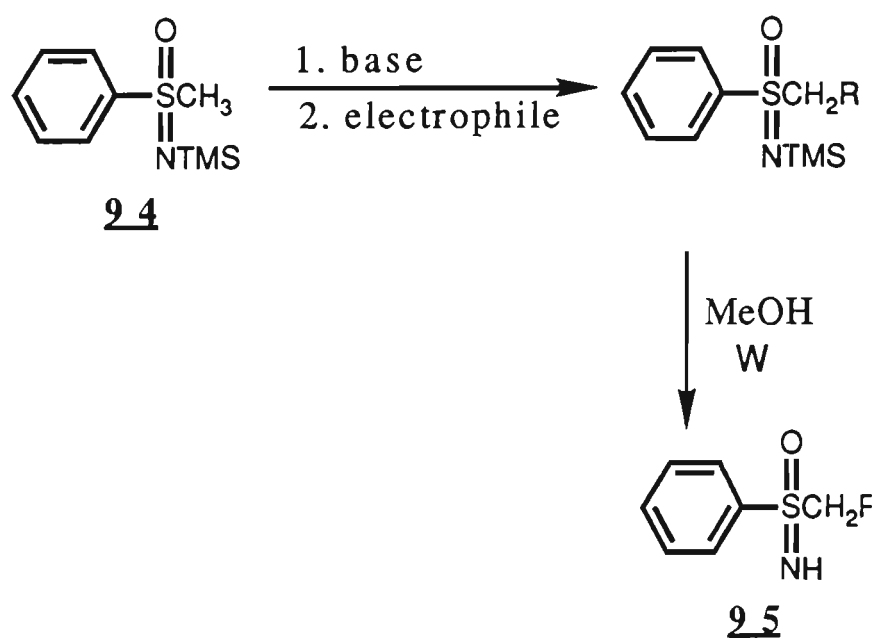
Johnson<sup>62</sup> extended his study to the synthesis of optically active secondary and tertiary alcohols. The asymmetry in this case was generated by employing enantiomerically pure (S) (-)- N,S-dimethyl-S-phenylsulfoximine. Reaction of this compound as the lithium derivative with aldehydes (Scheme 35) or ketones produced  $\beta$ -hydroxy sulfoximines as a mixture of diastereoisomers. The diastereoselectivities in each case were only modest (60-70 : 40-30). These adducts could be separated and then desulfurization of the diastereomerically pure  $\beta$ -hydroxysulfoximines with aluminium amalgam gave optically active secondary alcohols.

Scheme 35.



Hwang<sup>63</sup> treated the anion of N-trimethylsilyl-S-methyl-S-phenyl sulfoximine 94 (Scheme 36) with alkyl halides, esters, methyl chloroformate, and epoxides to give corresponding products 95 in good yield.

Scheme 36.

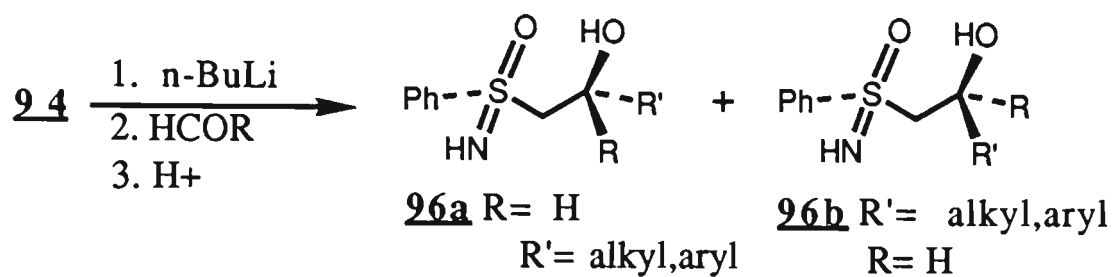


Hwang<sup>64</sup> also found that treatment of anion of racemic N-trimethylsilyl-S-methyl-S-phenylsulfoximine with aldehydes or ketones furnished  $\beta$ -hydroxy sulfoximines 96a and



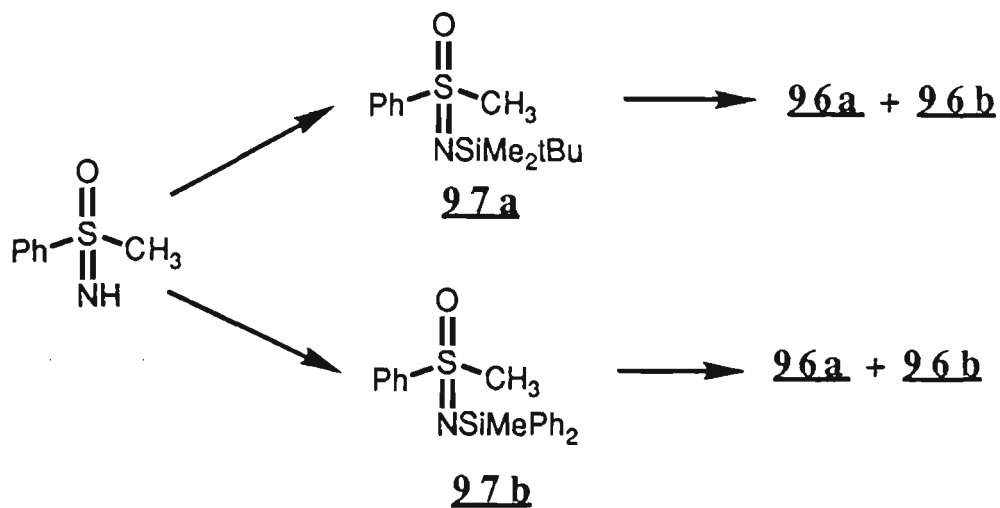
ketones furnished  $\beta$ -hydroxy sulfoximines 96a and 96b in good yield. Product ratios were insensitive to reaction temperature in the range  $-78^{\circ}\text{C}$  to  $10^{\circ}\text{C}$ , as well as to the steric bulk of the reacting aldehyde (Table 15). He found, however, that the diastereomeric ratio was sensitive to the size of the N-silyl group. As shown in the Table 14 the use of larger N-silyl groups enhanced the diastereoselectivity of the 1,2-addition, especially when a sterically bulky aldehyde was used.

Table 13. Condensation of  
N-(Trimethylsilyl)methylphenylsulfoximine (94) with  
aldehydes and ketones.



entry	R,R'	yield (%)	ratio <u>96a</u> / <u>96b</u>
1	H, CH <sub>3</sub>	69	2:1
2	H, CH(CH <sub>3</sub> ) <sub>2</sub>	80	2:1
3	H, CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	79	2:1
4	H, C(CH <sub>3</sub> ) <sub>3</sub>	91	2.5:1
5	H, Ph	81	2.8:1
6	H, 2-thienyl	94	2.3:1
7	H, H	41	n.a.
8	CH <sub>3</sub> CH <sub>2</sub> , Ph	70	n.a.
9	CH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub>	83	n.a.
10	CH <sub>2</sub> (CH <sub>2</sub> ) <sub>3</sub> CH <sub>2</sub>	97	n.a.

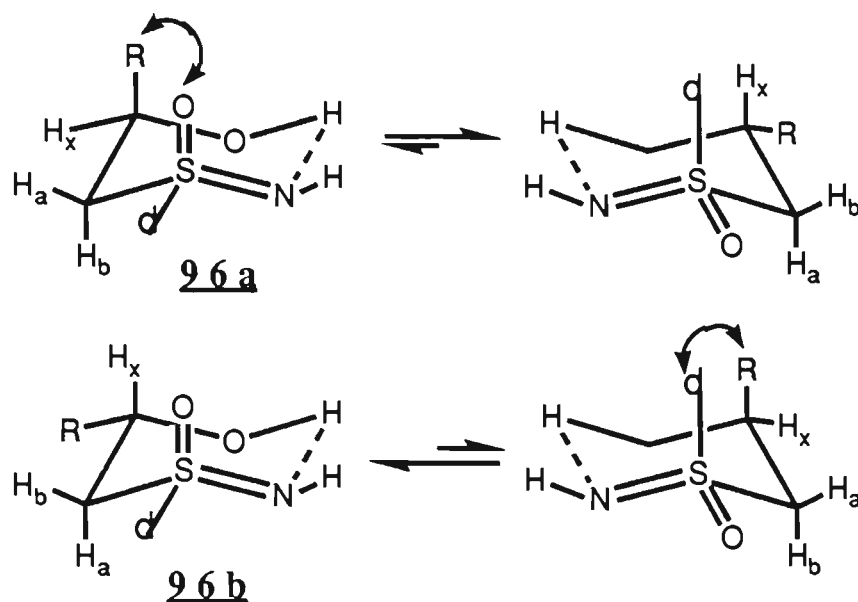
Table 14. Effect of N-trialkylsilyl group on diastereoselectivity of aldehydes 1,2-additions.



entry	R, R'	diastereomer ratio $\underline{96a}/\underline{96b}$		
		$\underline{91}$	$\underline{96a}$	$\underline{96b}$
1	H, $\text{CH}_3$	2:1	4:1	6:1
2	H, $\text{C}(\text{CH}_3)_3$	2.2:1	8:1	8:1

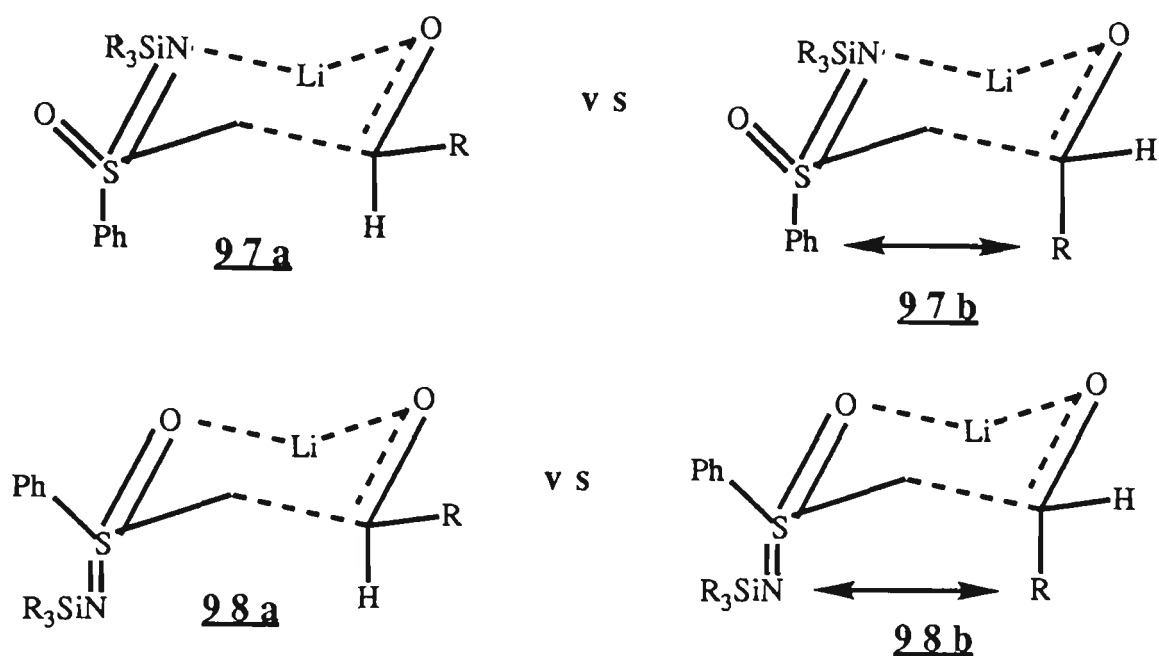
The coupling constants for the ABX spin system in  $\underline{96a}$  and  $\underline{96b}$  suggest that internally hydrogen-bonded conformations maintain similar bond angles for protons  $\text{H}_A$ ,  $\text{H}_B$  and  $\text{H}_X$  in both diastereoisomers as shown in Scheme 37.

Scheme 37.



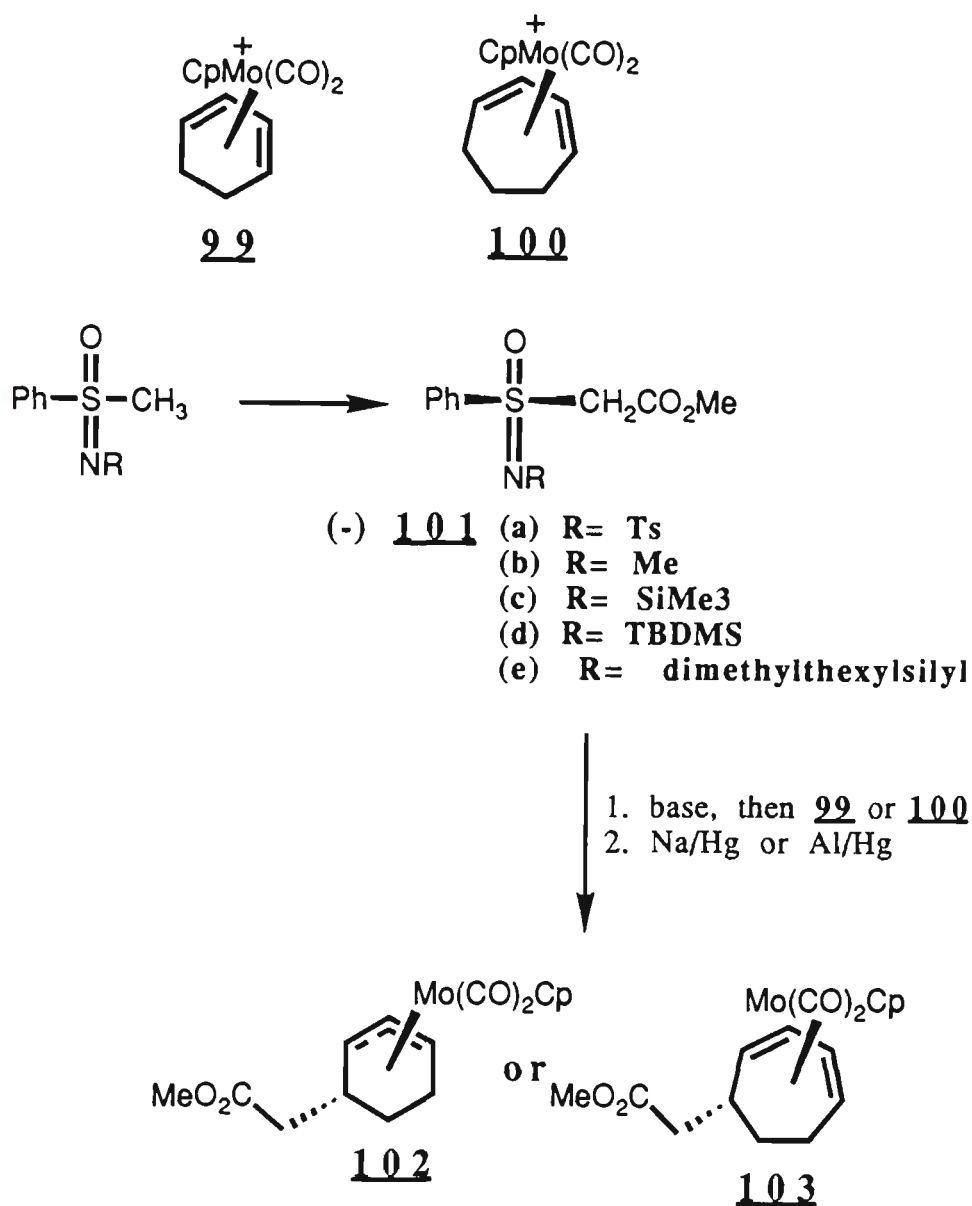
The 1,3 diaxial relationship between the sulfoximine phenyl ring and H<sub>x</sub> in **96a** would cause shielding and therefore an upfield shift at H<sub>x</sub>. Consequently **96a** was assigned as the major diastereomer for all the diastereomeric β-hydroxyalkylsulfoximines pairs examined since the major diastereomer exhibited an upfield shift for H<sub>x</sub> of approximately 0.6 ppm relative to that of the minor diastereomer. However Hwang was not able to obtain x-ray crystal structure. Hwang tentatively suggested two possible transition states **97a,b** and **98a,b** (Scheme 38). The cyclic transition states **97a,b**, involving nitrogen-lithium chelation, cannot explain the diastereoselective enhancement observed for the bulky silyl group (as the orientation at N-trialkylsilyl group is away from the aldehyde). The oxygen-coordinated transition states **98a,b** allows for interaction of the silylated sulfoximine nitrogen with the R group of the aldehyde. Clearly the chair transition state **98a** would be expected to be favoured and would lead to the observed major diastereomeric adduct.

Scheme 38.



Pearson<sup>65</sup> devised a different method of asymmetric synthesis by the use of organometallic diene- $\text{Mo}(\text{CO})_2$  Cp hexafluoro phosphates (99 and 100, Scheme 39). Optically active S-methyl-S-phenyl-sulfoximines were converted to sulfoximinyl ester derivatives (101), which were then reacted with 99 or 100, and resulting adducts were desulfonylated to give the optically active monoester derivatives 102 and 103. The best diastereoselectivities (95 : 5) were obtained when the sterically bulky N-dimethylhexylsilyl reagent (101e) was employed. These methods allowed the synthesis of enantiomerically enriched six and seven ring compounds that were useful for natural product synthesis.

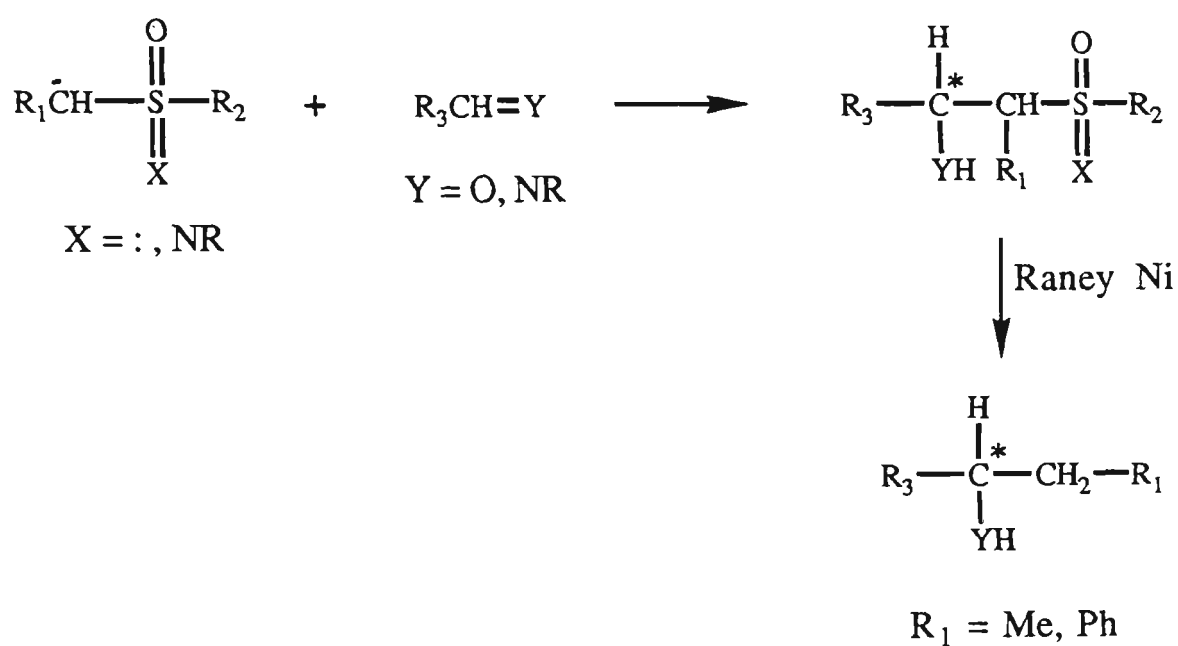
Scheme 39.



It appears that the structural features of sulfoximines afforded unique opportunities to tailor compounds for specific functions. It is the purpose of this thesis to investigate the diastereoselectivity, stereochemistry and reactions of various sulfoxides and sulfoximines with imines and aldehydes and then

apply this methodology to the asymmetric synthesis of chiral amines, alcohols and alkaloids according to the general scheme outlined below (Scheme 40). The possibility of preparing chiral isoquinoline alkaloids has been already discussed earlier in Scheme 14.

**Scheme 40.**



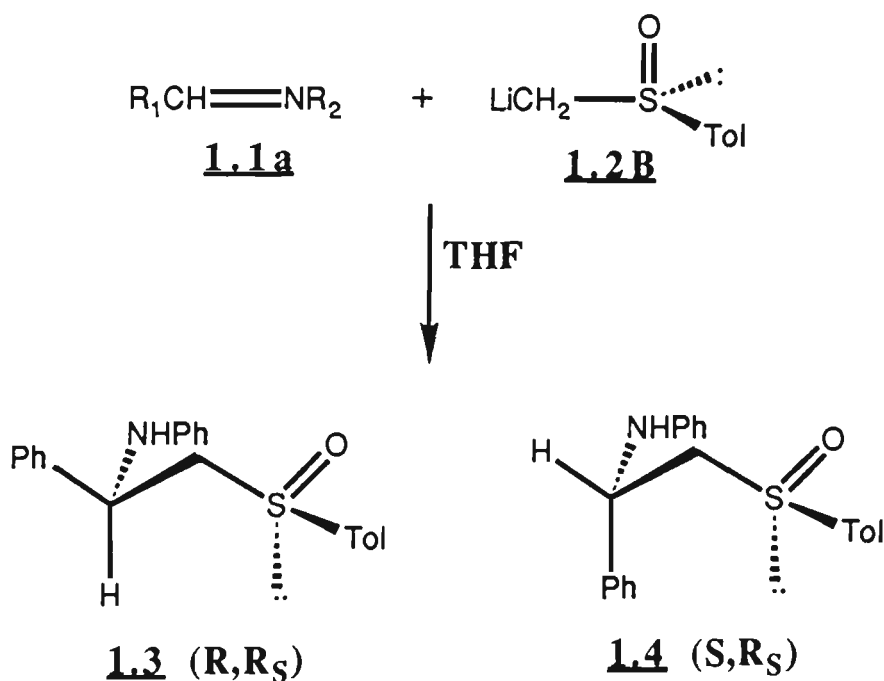
# CHAPTER 1



## DIASTEREOSELECTIVE ADDITION OF LITHIATED METHYL p-TOLYLSULFOXIDE AND METHYL PHENYL SULFOXIDES TO IMINES.

In 1973, Tsuchihashi<sup>40</sup> reported that the addition of lithiated (R)-(+)-methyl p-tolyl sulfoxide **1.2B** to N-benzylideneaniline **1.1A** at -10 to -20°C in tetrahydrofuran solution was a highly diastereoselective process and proceeded in a good yield (70%) Scheme (1.1).

Scheme 1.1



Tsuchihashi claimed that in this reaction only one of the two possible diastereoisomers was produced by asymmetric induction of the chiral tricoordinate sulfur and easily isolated by recrystallization. The generality of this process however, was not demonstrated. It was our initial intention to repeat Tsuchihashi's work and examine the generality of this type of reaction. After an

initial communication of our work in this area had been accepted for publication, a communication by Kagan appeared in the literature. Kagan<sup>66</sup> and co-workers repeated Tsuchihashi's work and found two diastereomers were formed. They attempted to improve the diastereoselectivity of this reaction by the proper choice of experimental conditions. Kagan<sup>66</sup> found that diastereomer ratio was dependant on two temperatures: that used during carbanion formation(T1) and that maintained during the condensation of the carbanion with the imine (T2). From Table 1.1 it is obvious that Kagan obtained two diastereoisomers contrary to claims made by Tsuchihashi.

**Table 1.1. Condensation of lithiated (R)-(+)-methyl p-tolyl sulfoxide with N-benzylideneaniline.**

Entry	T <sub>1</sub> °C <sup>a</sup>	T <sub>2</sub> °C <sup>b</sup>	Reaction time	Diastereo- meric ratio	Yield (%) <sup>d</sup>
1	-15	-15	10 min	75:25	98
2	-40	-78	1.5 h	77:23	88
3	-15	-78	1.5 h	81:19	98
4	0	-78	10 min	92:8	99
5	0	-110	10 min	87:13	73
6	+10	-78	10 min	84:16	93

*a: Temperature during deprotonation of (R)-methyl-tolyl sulfoxide by one molar equivalent of lithium diisopropylamide (LDA) in tetrahydrofuran (THF).*

*b: Reaction temperature, reaction performed in THF.*

*c:* Measured by  $^1\text{H}$  NMR on  $\text{CH}_2$  to a sulfinyl group.

*d:* Isolated yield.

The importance of the temperature during deprotonation, for high diastereoselectivity could be related to a reorganization of the organolithium species occurring at higher temperatures. At  $-40^\circ\text{C}$ , the diisopropylamine remains tightly bound to the lithium cation, while at  $0^\circ\text{C}$  the sulfinyl group is able to displace this amine, giving a chelated anion.

Using the optimized conditions of Table 1.1, Kagan extended this reaction to various imines of the type  $\text{ArCH}=\text{NR}$  as shown in Table 1.2.

**Table 1.2. Condensation of the (R)-(+)-methyl p-tolyl sulfoxide<sup>66</sup> anion with  $\text{ArCH}=\text{NR}^{\text{a, b}}$**

Entry	Ar	R	Diastereomer ratio <sup>c</sup>	Yield (%) <sup>d</sup>
1	Ph	Ph	92:8	99
2	Ph	p-OMeC <sub>6</sub> H <sub>4</sub>	86:14	32
3	p-OMeC <sub>6</sub> H <sub>4</sub>	Ph	86:14	30
4	p-OMeC <sub>6</sub> H <sub>4</sub>	p-OMeC <sub>6</sub> H <sub>4</sub>	95:5	74
5	p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	p-OMeC <sub>6</sub> H <sub>4</sub>	76:24	95
6	Ph	Me	82:18	84
7	Ph	<i>n</i> - Pr	90:10	76
8	Ph	<i>i</i> - Pr	88:12	27
9	Ph	Cyclopropyl	84:16	21

10	Ph	$n - C_5H_{11}$	87:13	52
----	----	-----------------	-------	----

- a: Entries 1-5: Experimental conditions as in Table 1.1 entry 4. Reaction time is 10 min (entries 1, 5), 15 min (entry 2), 20 min (entry 3) or 40 min (entry 4). Hydrolysis at  $-78^{\circ}\text{C}$  by dilute HCl.
- b: Entries 6-10: reaction temperature (deprotonation and condensation):  $-20^{\circ}\text{C}$ . Hydrolysis at  $-20^{\circ}\text{C}$  by dilute HCl.
- c: Measured by  $^1\text{H}$  NMR.
- d: Isolated yield after flash chromatography.

The major diastereomer was assigned by Kagan the configuration  $R_S S_C$ , by analogy to the already determined stereochemistry of the N-benzylideneaniline adduct 1.4 (Scheme 1.1) by Tsuchihashi. Kagan's results (Table 1.2) indicate moderate to good stereoselectivity with poor to excellent yield.

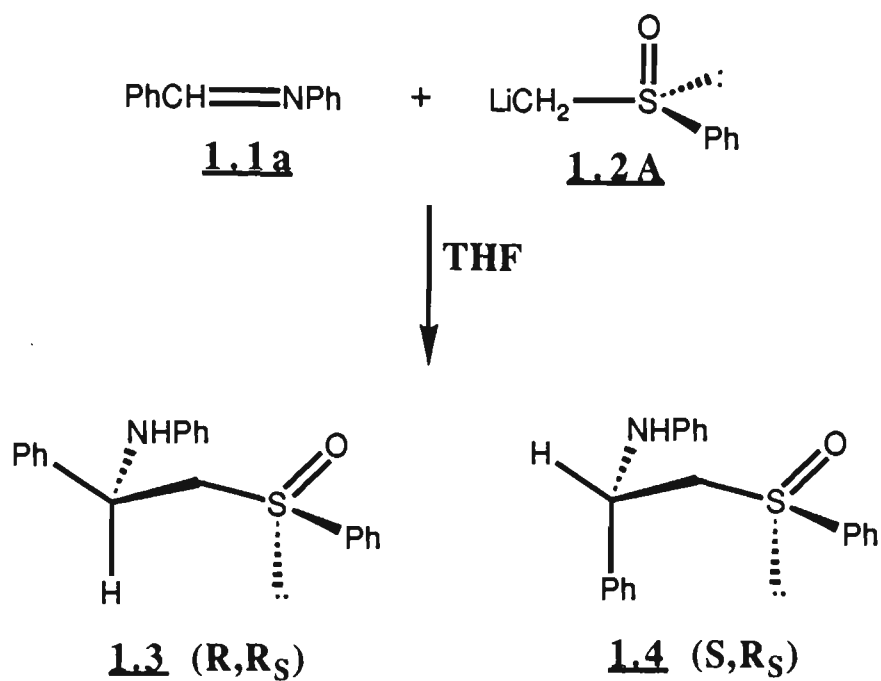
Our initial studies focused on racemic methyl phenyl sulfoxide and later on (R)-(+)-methyl p-tolyl sulfoxide  $[\alpha]_D^{20} +166^{\circ}$  (c 1.8, acetone) (Scheme 1.2). Methyl phenyl sulfoxide was prepared by oxidation of thioanisole with sodium periodate in methanol<sup>67</sup>, while (R)-(+)-methyl p-tolylsulfoxide was prepared from (-)-(S)-menthyl p-toluenesulfinate (Aldrich Chemical Company) and methylmagnesium iodide in 90% by the method of Solladie<sup>68</sup>. The imines were prepared, in all cases, from the reaction of the appropriate aldehyde and amine in the presence of anhydrous potassium carbonate and purified by vacuum distillation or recrystallization<sup>69</sup>. Methyl phenyl sulfoxide or (R)-(+)-methyl p-tolylsulfoxide was treated with lithium diisopropylamide (LDA, 1.1 equiv. from 1 equiv. n-butyllithium and 1 equiv. of

diisopropylamine at 0°C for 15 min) in tetrahydrofuran at -78°C for 1 hr. The solution was then treated with the imine (1.5 equivalents in tetrahydrofuran) for the appropriate amount of time at a specific temperature (Table 1.3 and Table 1.4). The resulting adducts were in all cases purified by column chromatography on silica gel.

Our own study<sup>23,70</sup> agrees with Kagan's findings and contrasts that of Tsuchihashi as presented in Table 1.3. The diastereoselectivity of our reactions with either lithiated methyl phenyl sulfoxide or (R)-(+)-methyl p-tolyl sulfoxide with various imines was determined from <sup>1</sup>H NMR (400 MHz) analysis of the crude reaction product. Although Kagan<sup>66</sup> chose to study the addition of different imines to our own, the two cases which are in common show similar results. The diastereoselectivity for the addition of lithiated (R)-(+)-methyl p-tolyl sulfoxide to N-benzylideneaniline by Kagan was similar to our study (Table 1.3), on the addition of racemic lithiated methyl phenyl sulfoxide to N-benzylideneaniline. Kagan et al.<sup>66</sup> achieved a 92:8 diastereomeric ratio at -78°C for 10 min., while our own study produced a 86:14 diastereomeric ratio at -78°C for 5 hrs. The slight difference in diastereoselectivity can be attributed to different reaction conditions (reaction time, temperature and concentration) and the use of methyl phenyl sulfoxide in the place of (R)-(+)-methyl p-tolyl sulfoxide. While for N-benzylidenemethylamine, Kagan achieved a diastereoselectivity of 82:18 at -20°C, our own results show a 91:9 diastereomeric ratio at 0°C for 10 min. (Table 1.4). This slight discrepancy can also be fully accounted for by differences in reaction conditions, namely the duration of the

reaction and the reaction temperature. This point becomes even more clear when we observed the diastereoselectivity was 57:43 after a reaction time of 12 hrs at 0°C, for the same reaction.

From the Table 1.3 it is clear that both the temperature and the duration of reaction affected the diastereomeric ratios leaving the yield unaffected. When the reaction was conducted at -78°C for 5 hrs the ratio of diastereomers was 86:14. This did not change when the reaction was warmed to -45°C for 2 hrs, or even when the temperature was elevated to 0°C for 5 mins before quenching with 10% aqueous potassium carbonate. However, when the duration of time was increased to 12 hrs at 0°C the diastereoselectivity diminished, and gave essentially an equal mixture of 1.3 and 1.4.

Table 1.3. Reaction of 1.1a with 1.2A.

Temp./ °C	Time	Yield/ %	<u>1.3</u> : <u>1.4</u>
-78	5 h	96	14 : 86
-45	2 h	95	14 : 86
0	5 min	95	14 : 86
0	0.5 h	95	30 : 70
0	1 h	95	42 : 58
0	12 h	95	43 : 57

Figure 1.1  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) of the crude reaction mixture from the reaction of 1.2B and 1.1a

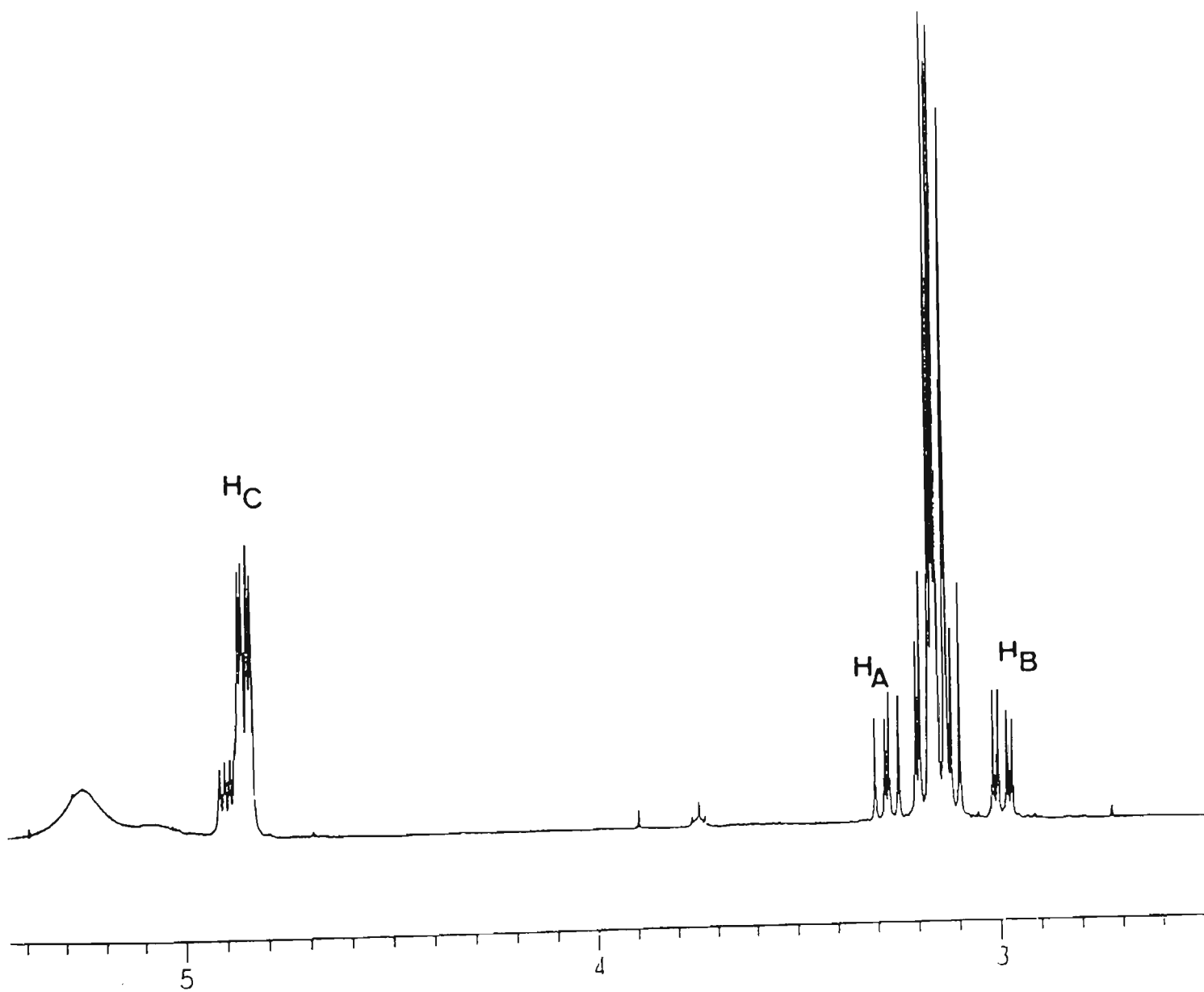
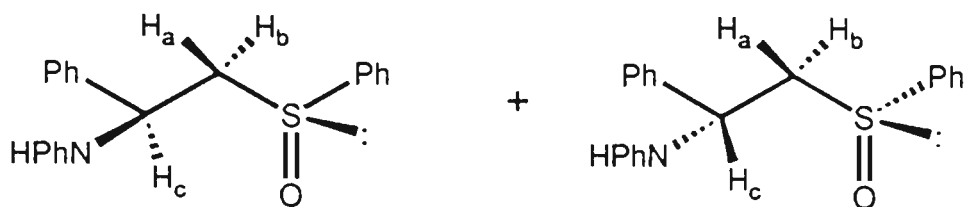
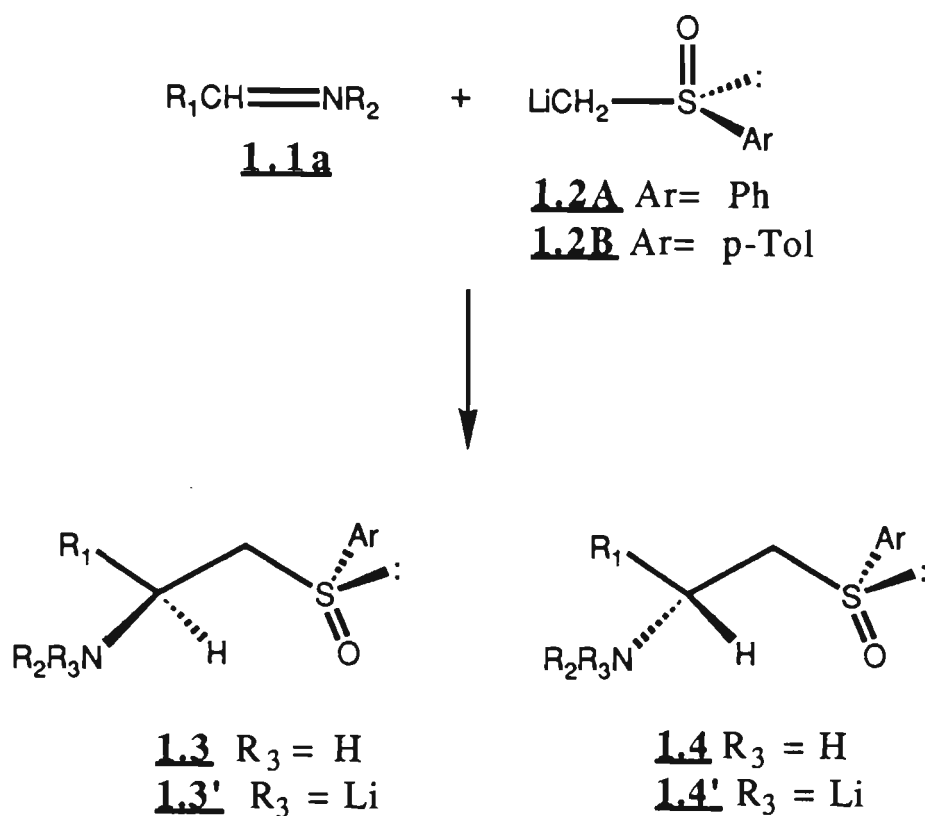




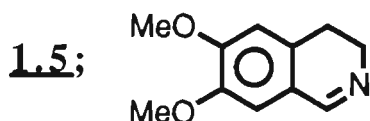
Figure 1.1 shows the copy of the  $^1\text{H}$  NMR of the crude reaction mixture when the reaction of 1.1a and 1.2B was warmed to  $0^\circ\text{C}$  and then quenched after 5 min at that temperature. The protons  $\text{H}_\text{C}$  of both diastereomers (1.3a and 1.4a) are clearly shown as a doublet of doublets at 4.85 and 4.90 ppm and their coupling constants are 3.7 and 8.7Hz and 9.8 and 4.9Hz respectively. For the protons  $\text{H}_\text{A}$  and  $\text{H}_\text{B}$  of the major diastereomer the chemical shifts are 3.18 and 3.12 ppm ( $J_{\text{AB}} = 13.7\text{Hz}$ ) respectively, while for the minor diastereomer the chemical shifts are 3.28 and 2.98 ppm ( $J_{\text{AB}} = 13.6\text{Hz}$ ) respectively.

Scheme 1.2.



a; R1 = Ph, R2 = Ph

b; R1 = 2-furyl, R2 = Ph

c; R1 = Ph, R2 = CH<sub>3</sub>d; R1 = CH<sub>3</sub>CH<sub>2</sub>, R2 = Phe; R1 = (CH<sub>3</sub>)<sub>2</sub>CH, R2 = Phf; R1 = (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>, R2 = Ph

From Tables 1.3 and 1.4 it is clear that the diastereoselection was better under kinetically controlled conditions (short reaction times and low reaction temperature) and that in general diastereoselection was poor under equilibrium control. The reactions which were conducted under kinetic control and then warmed up before quenching showed poor stereoselectivity showing that the initially formed diastereomeric adducts interconvert after an extended period of time under

interconvert after an extended period of time under elevated temperatures (Scheme 1.3).

**Scheme 1.3.**

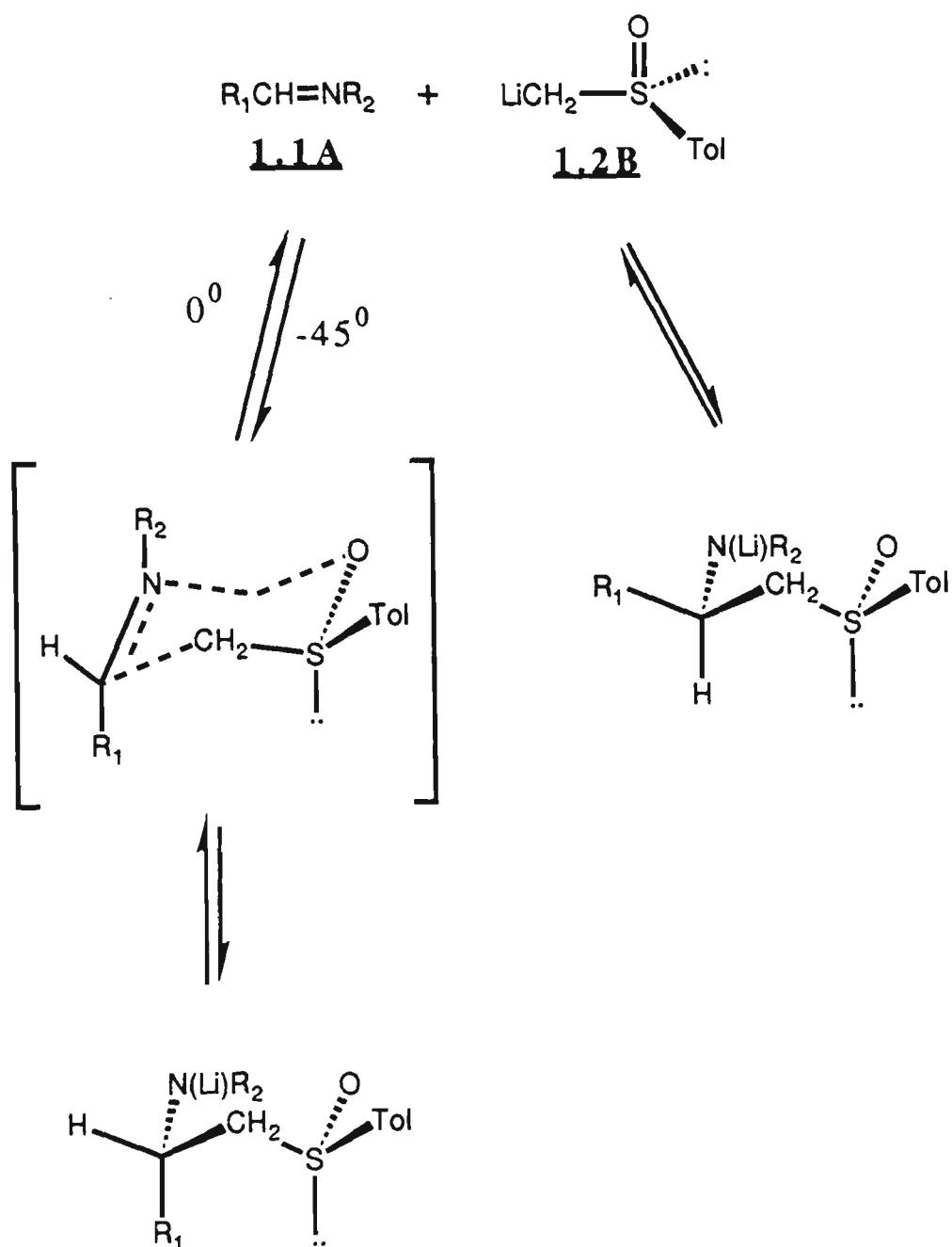
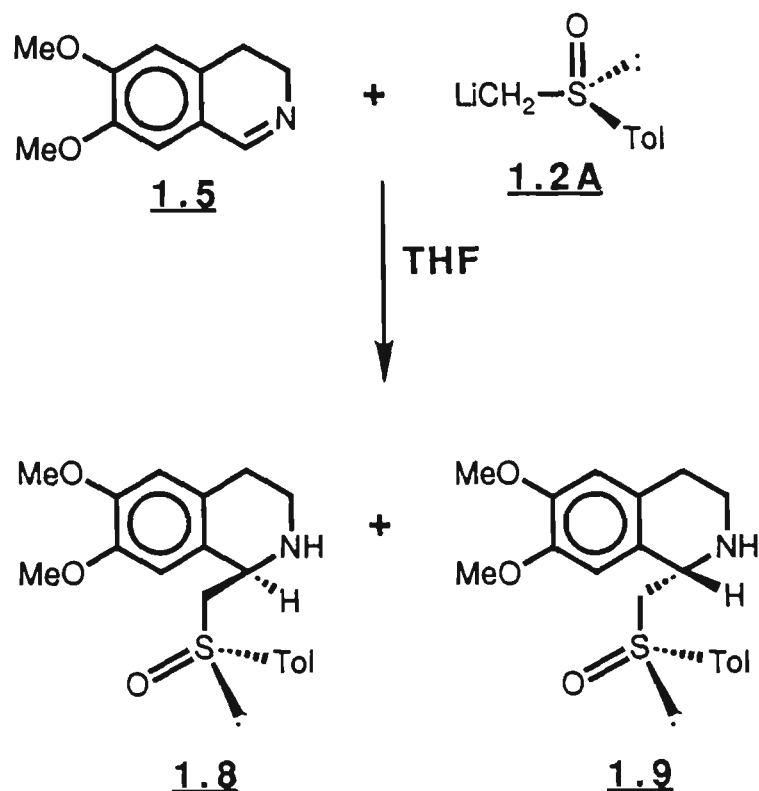


Table 1.4. Reactions of 1.2A and 1.2B with Imines 1.1 or 1.5

Entry	Imine <u>1.1</u> or <u>1.5</u>	anion	Temp, °C; <sup>a</sup> time, hr	yield, % <sup>b</sup>	diastereo selectn 1.3:1.4 (1.8:1.9) <sup>c</sup>
1	1.1a	1.2A	-78;5	96	82:18
2	1.1a	1.2A	-45;2	95 <sup>a</sup>	82:18
3	1.1a	1.2A	0;5 min	95 <sup>a</sup>	82:18
4	1.1a	1.2A	0;1	95	58:42
5	1.1a	1.2B	0;5 min	95	86:14
6	1.1b	1.2A	-45;2	86	88:12
7	1.1b	1.2A	0;2	94	76:24
8	1.1b	1.2B	0;10 min	96	91:9
9	1.1c	1.2A	0;2	86	88:12
10	1.1c	1.2B	0;10 min	89	91:9
11	1.1c	1.2B	0;12	89	51:49
12	1.1d	1.2A	-45;2	85	79:21
13	1.1d	1.2A	0;2	81	63:37
14	1.1d	1.2B	-45;2	90	80:20
15	1.1e	1.2B	-45;2	72	81:19
16	1.1e	1.2B	0;2	62	66:44
17	1.1f	1.2B	-45;2	78	81:19
18	1.1f	1.2B	0;2	84	71:29
19	1.5	1.2A	-45;2	64	(23:77)
20	1.5	1.2A	0;12	85	(89:11)
21	1.5	1.2B	0;12	92	(92:8)

- a All reactions were initiated at -78°C and then warmed to the temperature designated for the period of time designated and then quenched with water.*
- b After purification by column chromatography.*
- c Determined by  $^1\text{H}$  NMR spectral analysis on the crude reaction mixture*

In contrast the reaction of 1.2A and 3,4-dihydro-6,7-dimethoxyisoquinoline (1.5) gave the highest diastereoselection (92:8) under equilibrium controlled conditions (Table 1.5). When the reaction was conducted at -45°C, 1.8, and 1.9 were obtained with a diastereoselectivity of 23:77 with 1.8 being major isomer; while when reaction was conducted at 0°C for 12 hrs the diastereoselectivity observed was 92:8, with 1.9 being favoured. Identical diastereoselection was observed when the mixture of 1.5 and 1.2B was initially held at -45°C for 2 hours and then warmed to 0°C for 12 hrs. The reaction of 1.5 and 1.2 conducted at 0°C for 2 hrs resulted in diastereoselectivity of 25:75. The Figures 1.3-1.5 show the  $^1\text{H}$  NMR of the crude reaction mixture for the reaction of 1.2B and 1.5 under various conditions and the relative abundance of diastereomers 1.8 and 1.9.

Table 1.5. Preparation of 1.8 and 1.9.

Temp./ °C	Time	Yield/%	<u>1.8</u> : <u>1.9</u>
-45	2 hr	64	77 : 23
0	2 hr	72	25 : 75
0	12 hr	92	8 : 92

The remainder of our study concentrated on a variety of imines that were fortunately not studied by Kagan. Analogous results were obtained to those of N-benzylideneaniline in most cases. An increase in the duration or the temperature of the reaction generally favoured poor diastereoselectivity. For example, reaction of 1.1 with 1.2A at -45°C for 2 hrs resulted in a diastereoselectivity of 79:21 while at 0°C for 2 hrs the diastereomeric ratio was 63:37. Our initial study which focused on the addition of the anion of racemic methyl phenyl sulfoxide 1.2A

Figure 1.2  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) of the crude reaction mixture from the reaction of 1.2B and 1.5 at  $-45^\circ\text{C}$ , 2hrs.

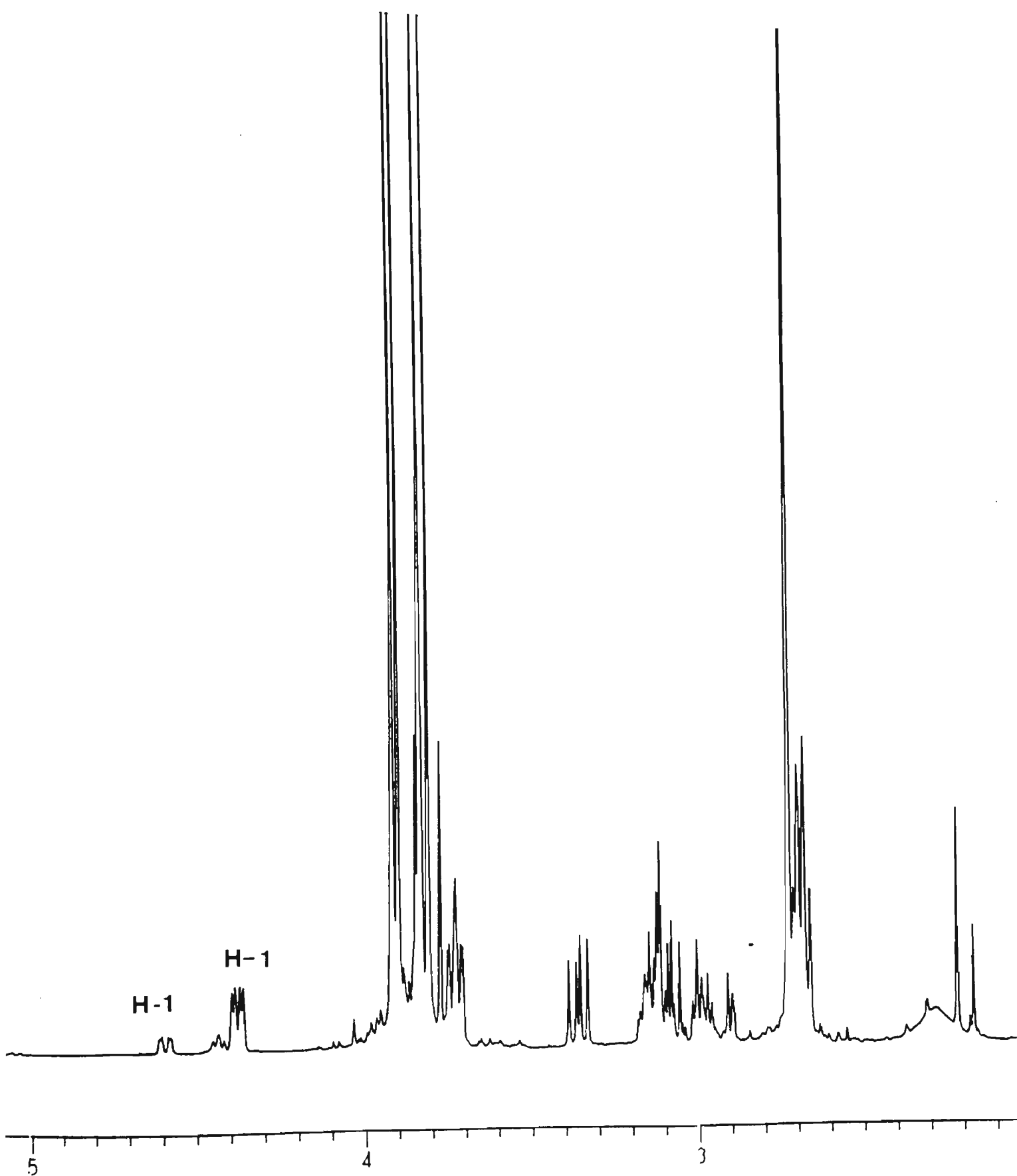
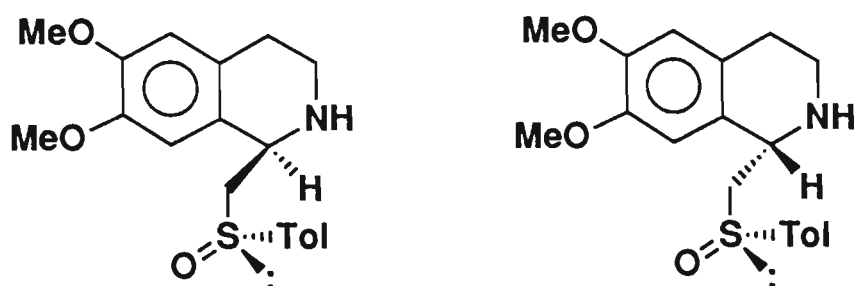


Figure 1.3  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) of the crude reaction mixture from the reaction of 1.2B and 1.5 at  $0^\circ\text{C}$ , 2hrs.

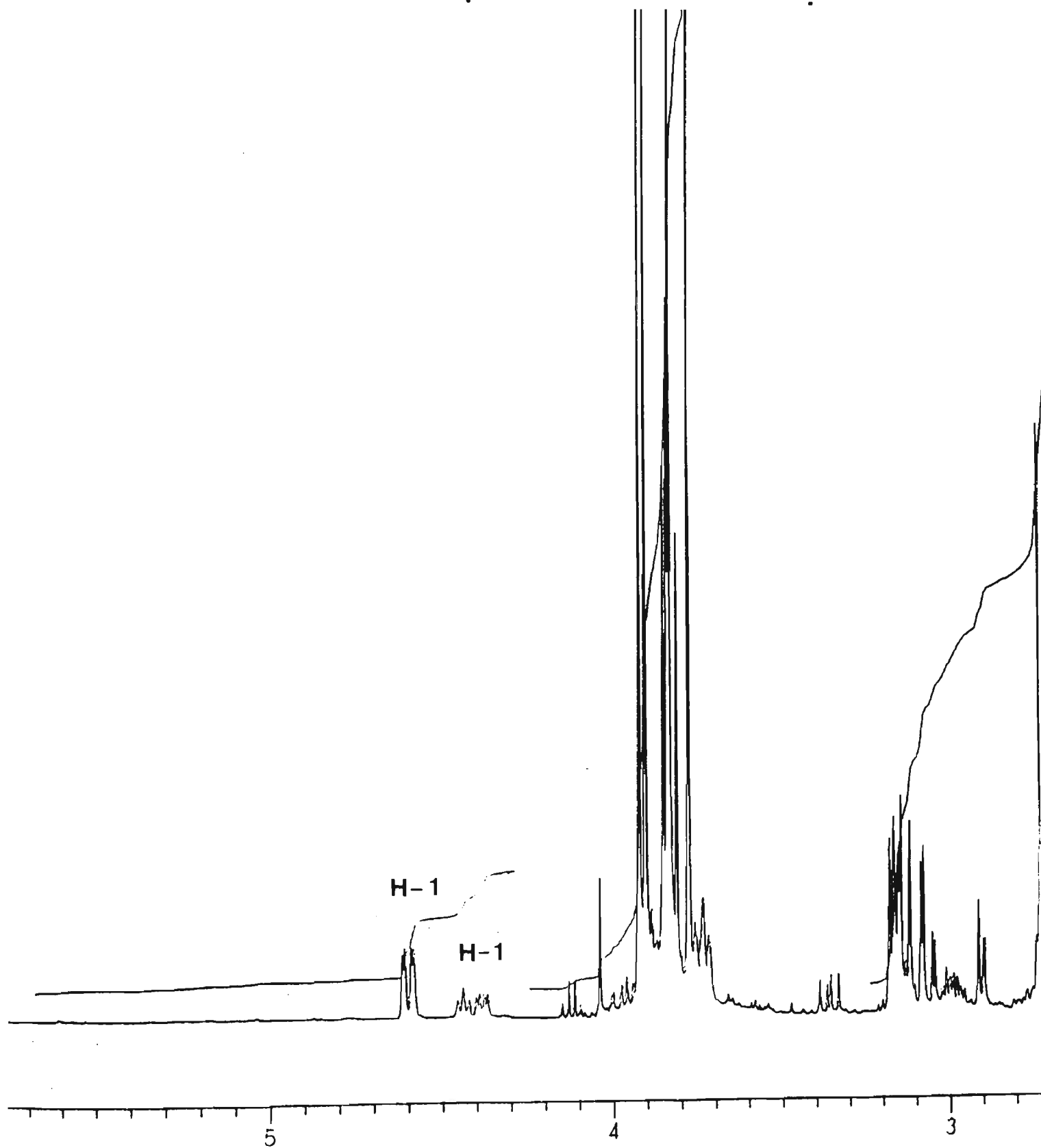
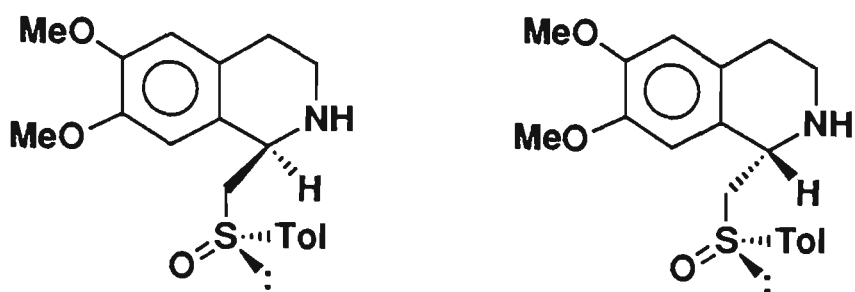
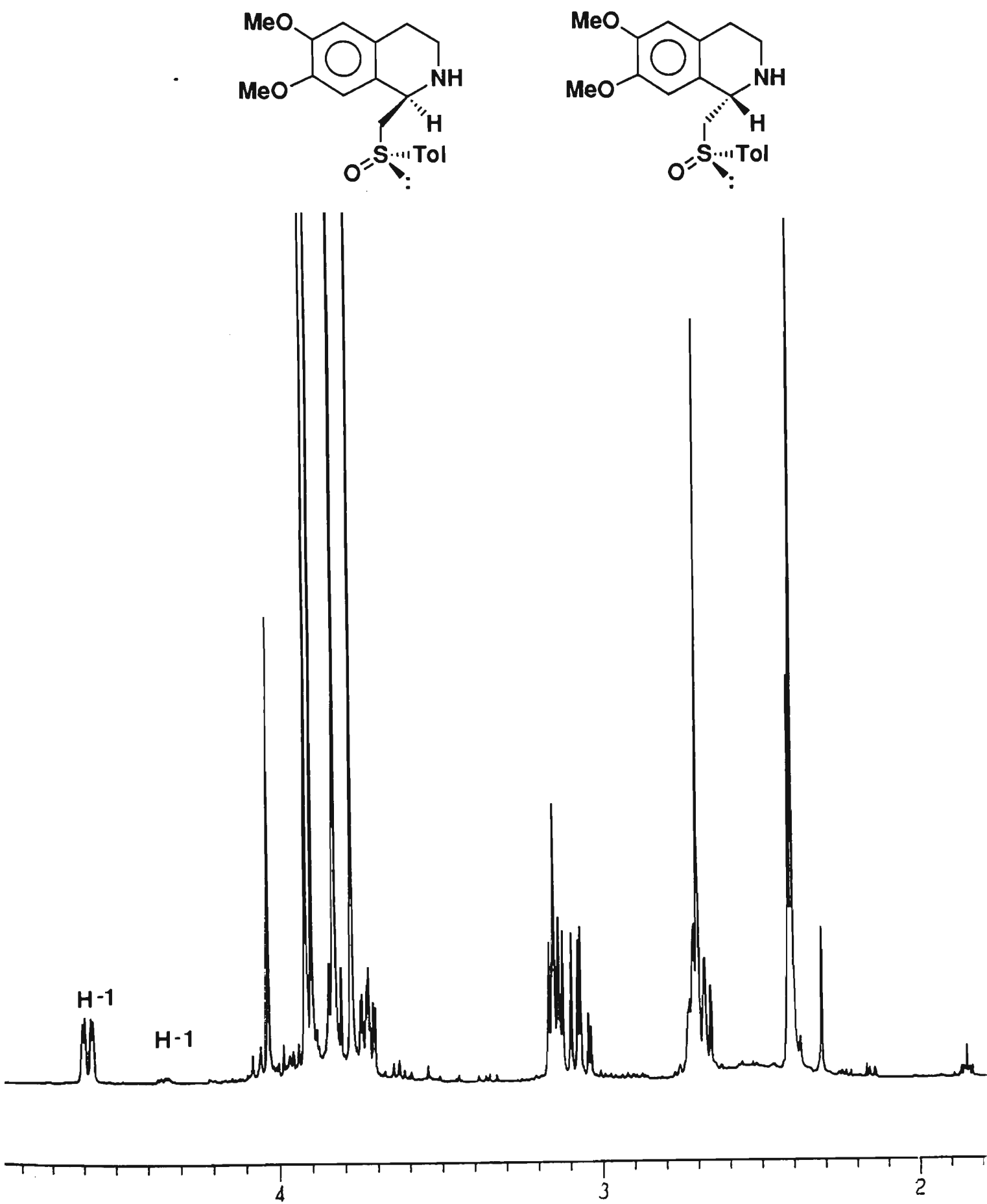




Figure 1.4  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) of the crude reaction mixture from the reaction of 1.2B and 1.5 at  $0^\circ\text{C}$ , 12hrs.



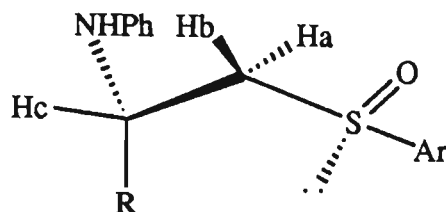
to imines was then extended to (R)-(+)-methyl p-tolyl sulfoxide (Scheme 1.2) and these results are summarised in Table 1.4.

With this method it was possible to obtain adducts from di and mono aryl substituted imines ( $\text{ArCH=NR}$  or  $\text{RCH=NAr}$ ) only. Attempts to obtain adducts from dialkyl substituted imines were unsuccessful. For example, reaction of the anion of methyl phenyl sulfoxide with N-pentylidenepentylamine or N-tert-butylidenepentylamine yielded a mixture of intractable products.

It is therefore clear that an aryl group substituted on the imine is necessary in order to stabilise the incipient charge in the transition state and this ensures good reactivity. It is possible that when purely aliphatic imines are employed then the sulfoxide anion acts as a base rather than a nucleophile towards the imine. The imine undergoes deprotonation at the carbon  $\alpha$  to the imine function to give a resonance stabilized carbanion ( $\text{RCH}(-)\text{CH=NR}_1$ ) which undergoes polymerisation with other imine molecules.

The relative stereochemistry of the adducts 1.3a-f and 1.4a-f was established by  $^1\text{H}$  NMR (400 MHz) spectroscopic analysis using 1.3a and 1.4a of known absolute stereochemistry. In general, the diastereotopic methylene protons  $\text{H}_\text{A}$ ,  $\text{H}_\text{B}$  in the compounds 3a, b, d, e, f (Table 1.6) have the  $1\text{S}, \text{R}_\text{S}$  absolute stereochemistry and show chemical shifts which are intermediate between the individual signals for the same protons in 1.4a, b, d, e & f. ( $1\text{R}, \text{R}_\text{S}$ ) series.

Table 1.6.  $^1\text{H}$  NMR chemical shifts and coupling constants for the reaction of 1.2A and 1.2B to imines 1.1 or 1.5.



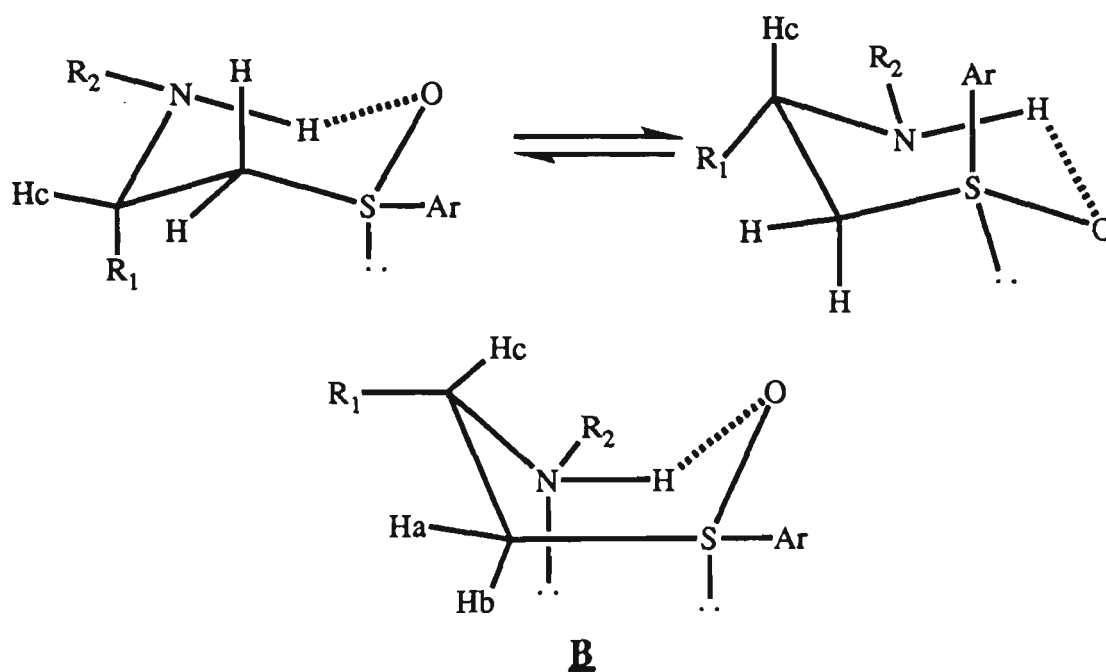
Compound		Chemical	Shift	(ppm)	J <sub>ac</sub>	J <sub>bc</sub>	J <sub>ab</sub>	
		H <sub>a</sub>	H <sub>b</sub>	H <sub>c</sub>				
1.3a	(Ar = p-tolyl)	3.16	3.06	4.84	3.6	8.8	13.7	
1.3a	(Ar = Ph)	3.18	3.12	4.85	3.7	8.7	13.7	
1.4a	(Ar = p-tolyl)	3.26	2.94	4.90	9.8	4.7	13.5	
1.4a	(Ar = Ph)	3.28	2.98	4.90	9.8	4.9	13.6	
1.3b	(Ar = p-tolyl)	3.26	3.20	4.80	4.0	8.2	13.3	
1.3b	(Ar = Ph)	3.28	3.22	4.70	4.1	8.2	13.4	
1.4b	(Ar = Ph)	3.38	3.19	4.47	7.3	7.2	13.3	
1.3c	(Ar = p-tolyl)	3.00	2.93	4.06	10.2	3.4	13.4	
1.3c	(Ar = Ph)	3.01	2.95	4.07	10.1	3.5	13.4	
1.4c	(Ar = p-tolyl)	3.22	2.81		8.4	5.5	13.1	
1.3d	(Ar = p-tolyl)	2.98	2.79	3.89	3.7	7.8	13.3	
1.4d	(Ar = p-tolyl)			3.13			13.4	
1.3d	(Ar = Ph)	2.99	2.81	3.88	3.5	7.9	13.2	
1.3e	(Ar = p-tolyl)	2.99	2.78	3.99	4.6	8.2	13.3	
1.4e	(Ar = p-tolyl)	3.08	2.76	3.87	4.3	8.0	13.2	
1.3f	(Ar = p-tolyl)	2.46	2.71	3.60	3.0	9.9	13.3	
1.4f	(Ar = p-tolyl)	3.09	2.88	3.89	7.7	5.8	13.3	
1.8	(Ar = p-tolyl)	major minor	3.15 3.10	4.59	2.9	3.1	10.7	
				4.38	3.8		9.2	
1.9	(Ar = Ph)	major	3.15	3.06	4.60	2.9	3.1	10.7

The compound 1.3c showed different coupling constant for  $H_A$ ,  $H_B$  and  $H_C$  in the  $^1\text{H}$  NMR (Table 1.6) and a different chemical shift for  $C_2$  in  $^{13}\text{C}$  NMR (Table 1.7) suggesting it had a different conformation than 3a-b and 3d-f.

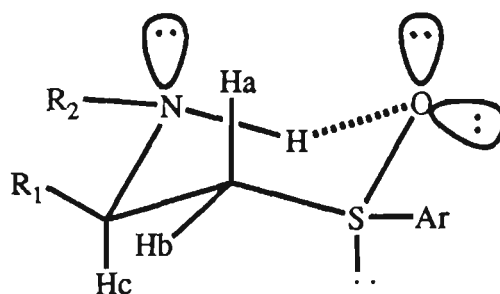
In all cases a large geminal coupling (13.2-13.7Hz) was observed for the diastereomeric protons  $H_A$  and  $H_B$ . The major diastereomers showed coupling constants  $J_{AC} \sim 4\text{Hz}$  and  $J_{BC} \sim 9\text{Hz}$

while the minor diastereomer in contrast showed  $J_{AC} \sim 10\text{Hz}$  and  $J_{BC} \sim 4\text{-}5\text{Hz}$ . In all cases the proton  $H_A$  occurred downfield from proton  $H_B$ .

The major diastereomer 1.3 probably exists as the intermolecular H-bonded boat conformation (B), the two possible chair conformations would appear less likely since R, or Ar is axial.

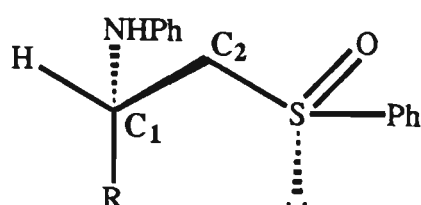


In case of minor isomer, a H-bonded chair conformation (in which the dihedral angles  $\phi_{AC}$  and  $\phi_{BC}$  are about  $180^\circ$  and  $60^\circ$  respectively) would be expected. In this conformation  $H_A$  would be deshielded by the 'axial' electron pairs at N and O<sup>71</sup>.



As the compounds were extensively purified it made observation of the minor isomer by  $^{13}\text{C}$  NMR almost impossible, however, when minor isomer was observed it always showed upfield shifts for both  $\text{C}_1$  and  $\text{C}_2$  relative to the major isomer (Table 1.7 and Figure 1.5).

**Table 1.7.  $^{13}\text{C}$  NMR chemical shifts for the aliphatic section of the adducts 1.3a-1.3f.**



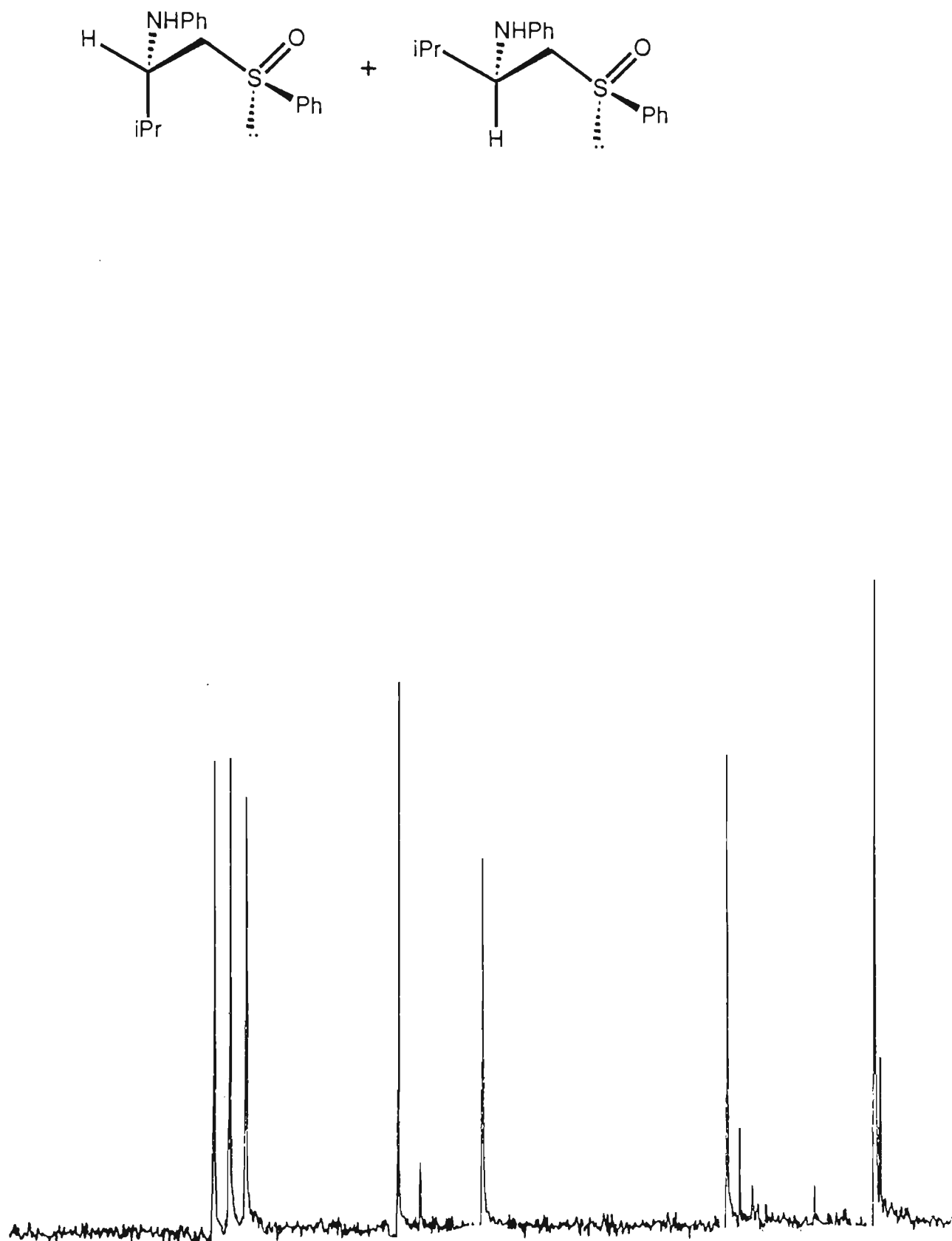
	$\text{R}_1$	$\text{R}_2$	$\text{R}_3$	$\text{C}_1$	$\text{C}_2$	$\text{R}_2$	$\text{R}_3$
	Ph	Ph	H	64.13	54.66		
	Et	Ph	Me	63.20	51.11		21.32
major	i-Pr	Ph	H	61.84	54.23		
minor				59.84	54.38		
major	i-Bu	Ph	Me	63.88	48.04		21.27
minor				62.67	47.73		
	Fur	Ph	H	61.55	48.62		
	Fur	Ph	Me	61.64	48.96		21.37
	Ph	Me	Me	64.96	59.06	33.75	20.93
	Ph	Ph	Me	64.13	54.82		21.35

The Figure 1.5 shows the aliphatic section of  $^{13}\text{C}$  NMR of the adducts 1.3e and 1.4e with both isomers clearly shown.

The stereochemistry of the major diastereomeric product can be rationalized by assuming a chelated cyclic chair transition state as shown in Scheme 1.4. Since imines 1.4a-f must have the (E) geometry<sup>29</sup>, only two chelated cyclic transition states are available

for the reaction of 1.2A and 1.2B with imines, the chair and boat transition state. Clearly the high diastereoselection (Table 1.4) suggests that if a cyclic transition state is involved, then chair transition state 1.10A is favoured over its boat counterpart 1.11A.

Figure 1.5  $^{13}\text{C}$  NMR( $\text{CDCl}_3$ , aliphatic section) of the adducts 1.3e and 1.4e.





Scheme 1.4.

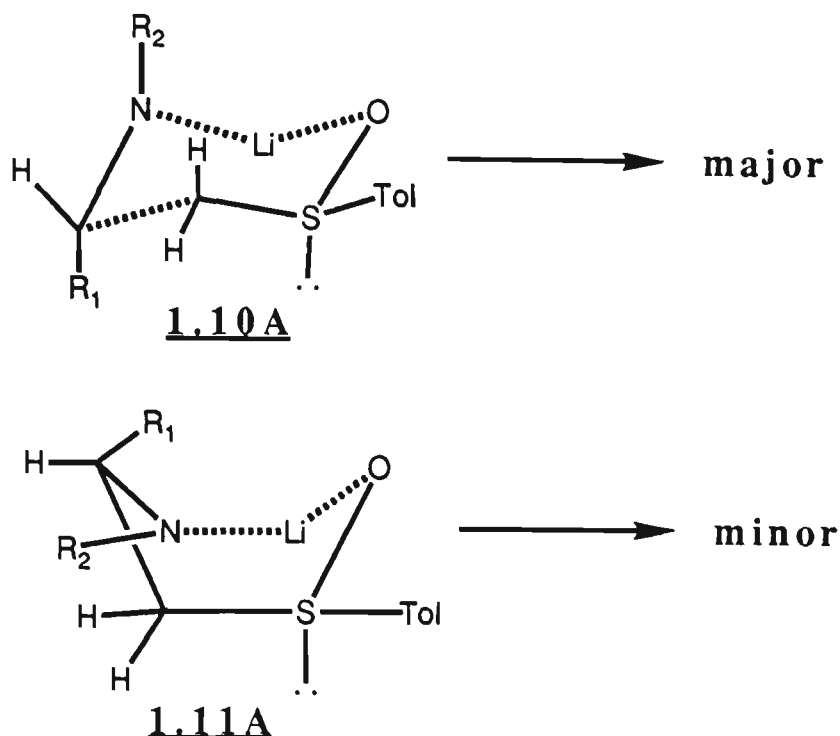
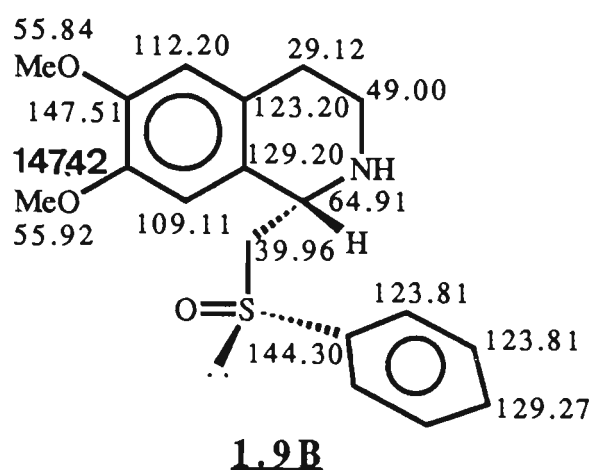
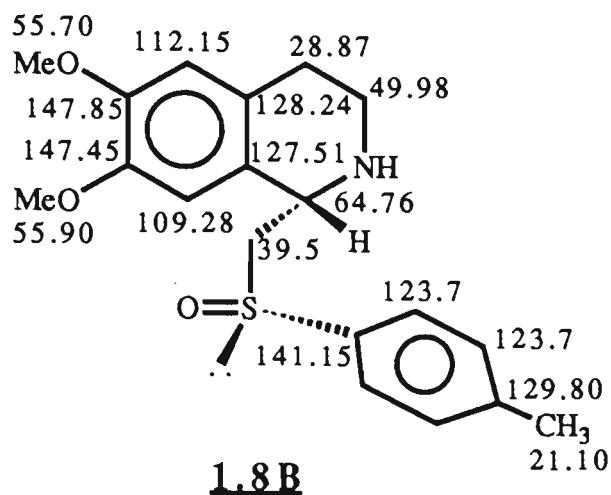


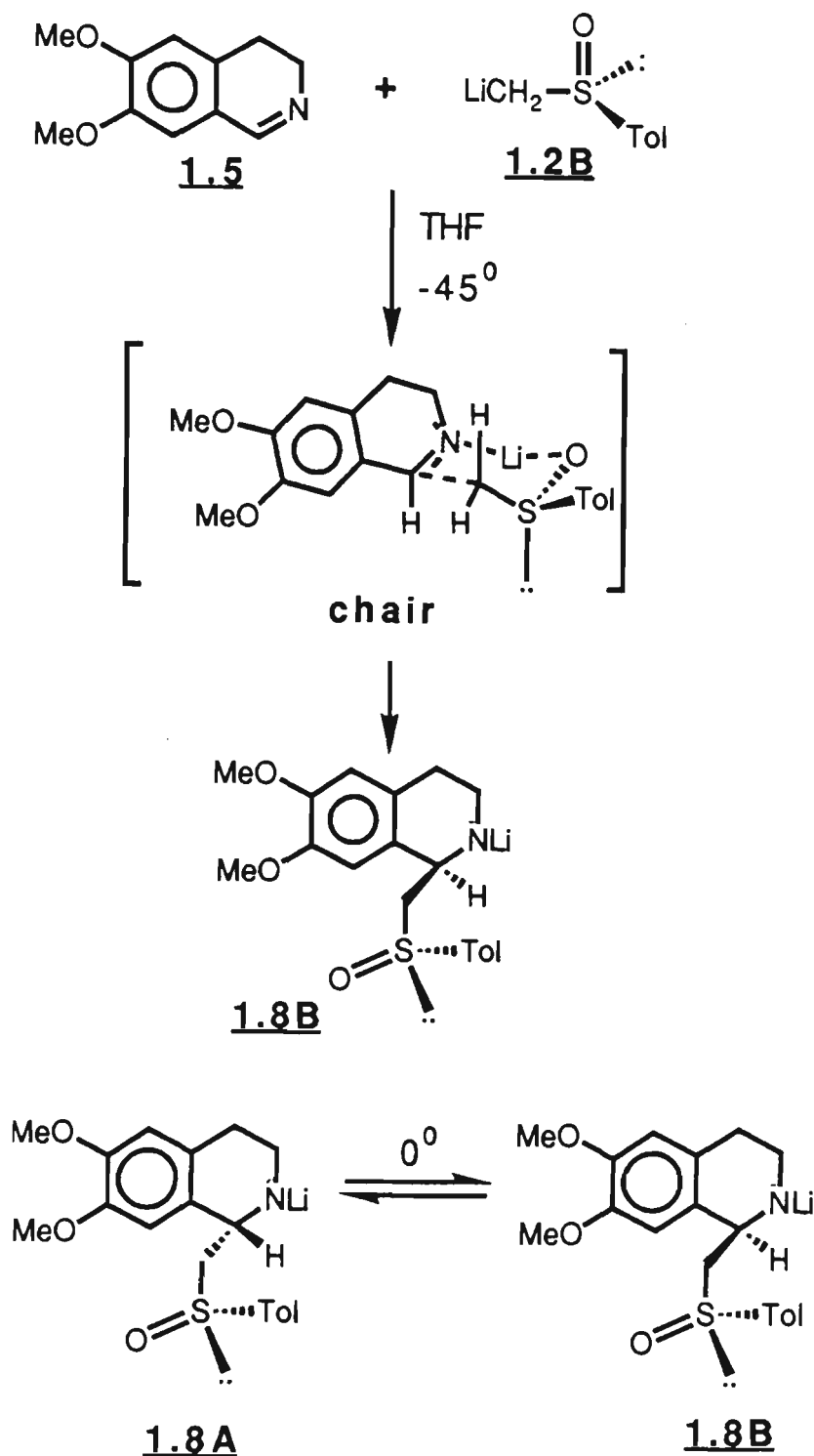
Table 1.8 shows  $^{13}\text{C}$  assignments for the two isoquinoline adducts 1.9A and 1.9B. Adduct 1.9A shows the two methoxy carbons at 55.84 and 55.82ppm while in adduct 1.9B these occur at 55.7 and 55.90ppm. Both adducts show similar chemical shifts for the methylene carbon next to sulfoxide group at 39.96 ppm for adduct 1.9A and 39.50ppm for adduct 1.9B. The only substantial difference between the carbon spectra of the two adducts is the existence of the methyl carbon at 21.10 ppm in adduct 1.9B which does not exist in the case of adduct 1.9A. The assignment of  $^{13}\text{C}$  NMR of the adducts 1.9A and 1.9B is based upon a literature precedent by MacLean et al.<sup>72</sup>

Table 1.8.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) assignments of the adducts **1.8A** and **1.9B**.



The formation of **1.8B** as the major diastereomeric product under kinetically controlled conditions ( $-45^\circ\text{C}$ ) can be readily rationalized as occurring through a chair like transition state (Scheme 1.5).

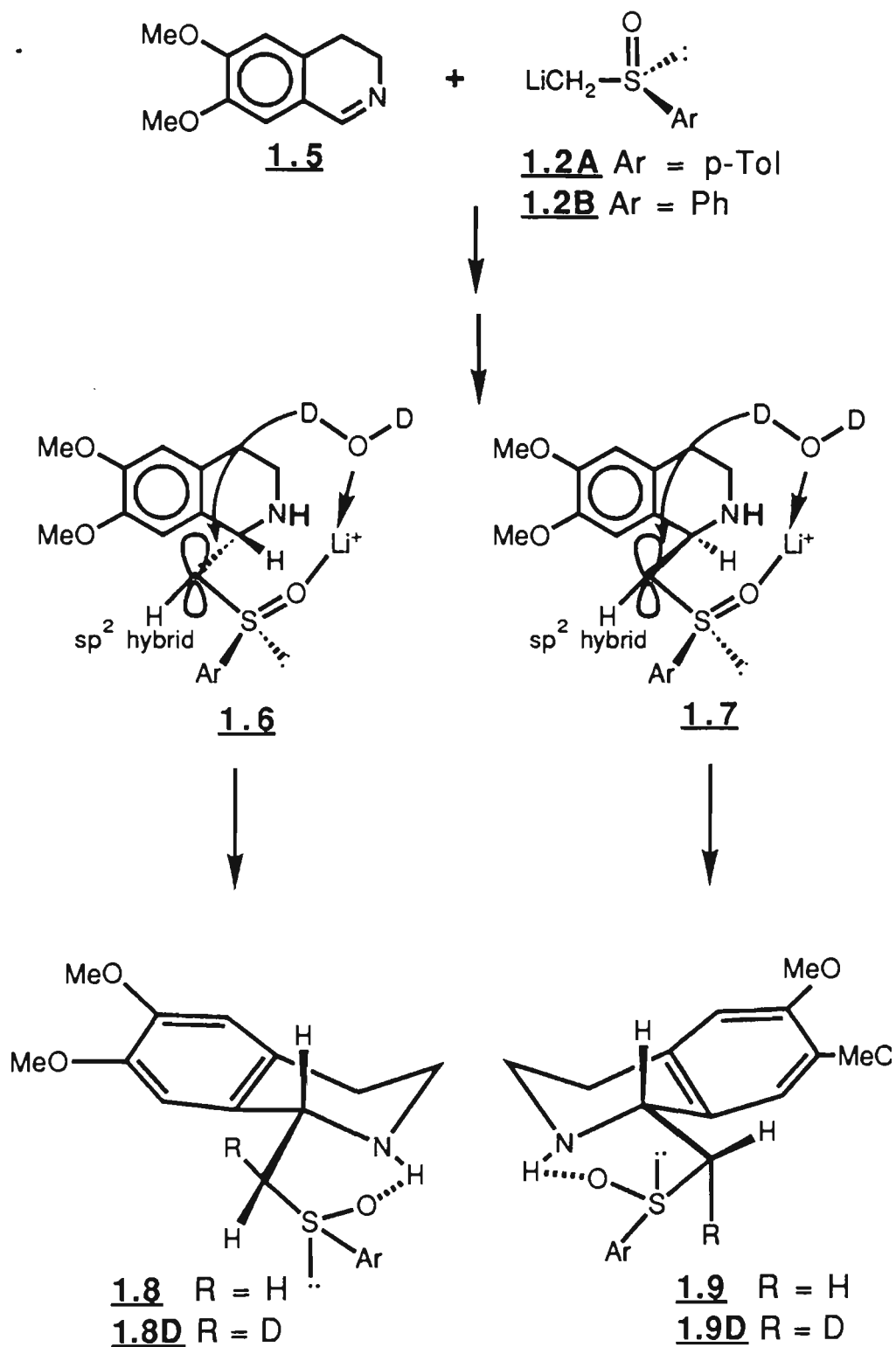
Scheme 1.5.



When the reaction mixture resulting from the reaction of **1.5** and **1.2B** (Scheme 1.6) at  $-45^\circ\text{C}$  for 2 hrs was quenched with  $\text{D}_2\text{O}$ , a mixture of deuterated adducts **1.8D** and **1.9D** resulted. The deuteration was quantitative and stereospecific ( $>95\%$ ) from  $^1\text{H}$  NMR analysis.

These compounds must result from deuteration of the  $\alpha$  sulfinyl carbanions 1.6 and 1.7 respectively (Scheme 1.6), which most likely arise via a proton transfer mechanism from the initially formed adducts 1.6 and 1.7. The stereochemistry of 1.8D and 1.9D is based on  $^1\text{H}$  NMR analysis ( $^1\text{H}$  NMR:1.8D)  $\delta$ 4.59 (d,  $J = 3.1$  Hz, H-1);1.9D ( $\delta$ 4.38 (d,  $J = 3.8$  Hz, H-1), compared with 1.8 ( $\delta$  4.59(dd,  $J=2.9, 10.7\text{Hz}$ ) and 1.9 ( $\delta$  4.38(dd,  $J=3.8, 9.2\text{Hz}$ ), assuming that the intramolecular hydrogen bonded forms of 1.8D and 1.9D are major conformational isomers then the stereochemistry of deuteration is that which is expected from Biellmans<sup>72</sup> work, who suggested that the deuterium oxide first coordinated to lithium cation before deuteration (see Introduction for details).<sup>30</sup> The coupling constant of 1.8D and 1.9D indicate that the dihedral angle between the vicinal protons that are  $\alpha$  and  $\beta$  to the sulfinyl group are approximately  $90^\circ$ .

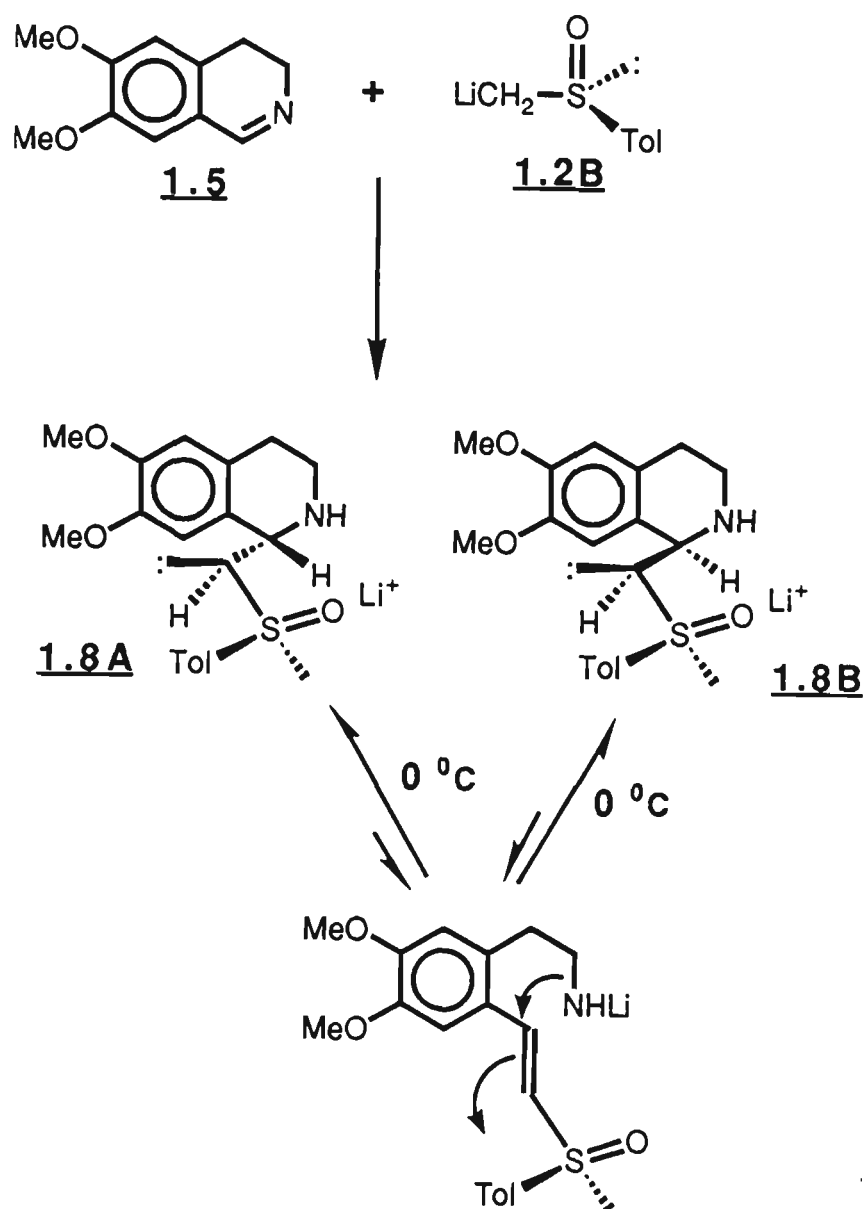
Scheme 1.6.



### Mechanism

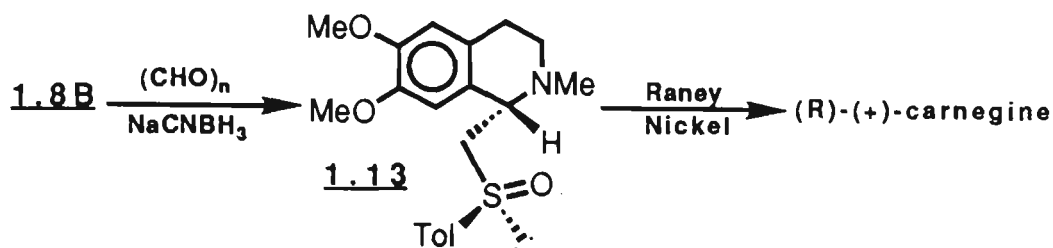
The interconversion of **1.8A** and **1.8B** at  $0^\circ$  probably occurs via a retro-Michael addition sequence shown in Scheme 1.7.

Scheme 1.7.



The absolute stereochemistry of **1.8B** was determined by its conversion to (S, R<sub>S</sub>)-(+)-**1.13** by reductive methylation.<sup>73</sup> The adduct **1.8B** was reductively methylated with formaldehyde and sodium cyanoborohydride in acetonitrile giving the known N-methylated product **1.13** which has been converted previously to (R)-(+)-carnegine  $[\alpha]_{\text{D}}^{23} +206^\circ$  (c 1.1,  $\text{CHCl}_3$ ) by reductive desulfurization (Scheme 1.8).<sup>74</sup>

Scheme 1.8.

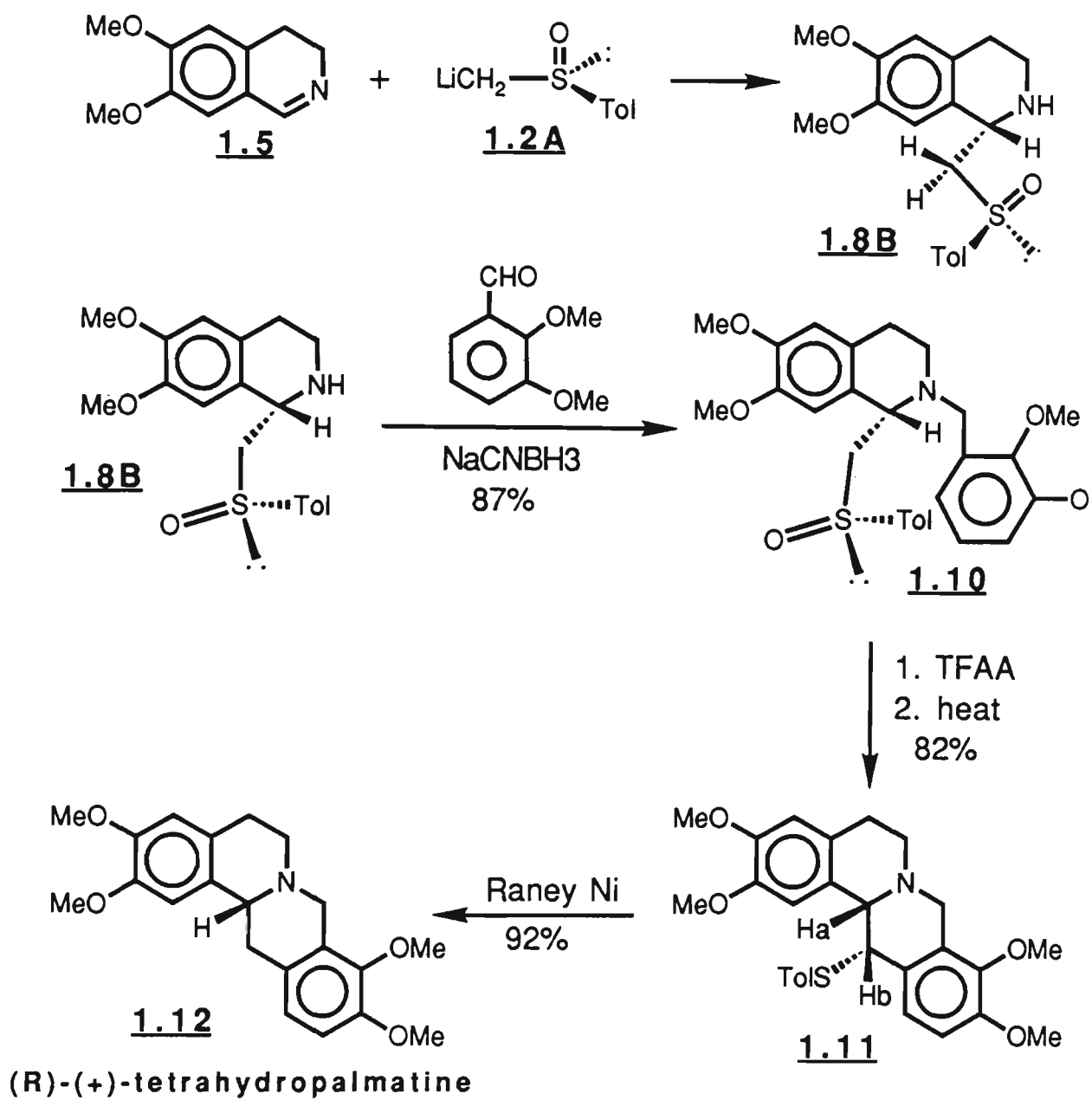


In order to extend the above developed methodology synthesis of natural product (R)-(+)-tetrahydropalmatine was carried out (Scheme 1.9). The initially formed adduct 1.8B was subjected to reductive alkylation with 2,3-dimethoxybenzaldehyde and sodium cyanoborohydride<sup>73</sup> in acetonitrile to yield the N-substituted product 1.10 in 87% yield. Upon heating of 1.10 with trifluoroacetic anhydride in toluene, cyclization to the sulfide 1.11 was achieved in 82% yield. The <sup>1</sup>H NMR spectrum of this compound ( $\delta$  4.43, d,  $J = 2\text{Hz}$ , H-13a) is consistent with Ha and Hb having a cis relationship<sup>75</sup>.

When 1.12 was subjected to desulfurization with Raney Ni in ethanol (R)-(+)-tetrahydropalmatine was obtained. This compound had m.p. 138-139°C,  $[\alpha]_{\text{D}}^{20} + 288.5$  (c 2.0, EtOH), lit.<sup>75a</sup> m.p. 142°C,  $[\alpha]_{\text{D}} + 292^\circ$  (EtOH) and identical spectral properties (<sup>1</sup>H NMR, <sup>13</sup>C NMR, MS)<sup>75b</sup> with those reported for the authentic material.

In conclusion, the methodology developed in this Chapter allows for the construction of usefully functionalized enantiometrically pure isoquinolines that have potential for the asymmetric synthesis of a variety of alkaloids.

Scheme 1.9.





## EXPERIMENTAL

### **Procedure 1: Methyl phenyl sulfoxide<sup>1,2 A</sup>**

To a solution of thioanisole (6.4g, 52mmol) in 300ml dichloromethane (DCM) at 0°C was added dropwise a solution of m-CPBA<sup>68</sup> (10.6g, 52mmol) in 50ml dichloromethane. The resulting mixture was stirred at 0°C for 2hrs and then at room temperature overnight following which it was neutralised by the addition of saturated Na<sub>2</sub>CO<sub>3</sub>, washed with water and then dried with MgSO<sub>4</sub>. Upon evaporation of the dichloromethane, the resulting solid was subjected to column chromatography on silica gel using ethyl acetate as eluent to yield 6.86g (94%) of pure methyl phenyl sulfoxide, m.p. 28-29°C, lit.<sup>68</sup> m.p. 29-30°C.

### **Procedure 2: Methyl phenyl sulfoxide<sup>67 1,2 A</sup>**

A solution of sodium periodate (19.26g, .09mol) in 200 ml of water was added at 0°C to thioanisole (11.16g, .09mol) in 180ml at methanol and the resulting solution was stirred at room temperature overnight. The resulting mixture was filtered, extracted with dichloromethane and the extracts were washed with water. The organic layer was then dried (MgSO<sub>4</sub>), evaporated and the resulting solid was subjected to column chromatography on silica gel using ethyl acetate as eluent to yield (7g, 85%) of pure methyl phenyl sulfoxide, m.p. 28-29°C, lit.<sup>68</sup> m.p. 29-30°C.

### General procedure for synthesis of imines 1.1

To a solution of amine (.1 mmol) in 50 ml ether at 0°C was added potassium carbonate (50g) followed by the addition of the aldehyde (.1 mmol). The solution was stirred at room temperature overnight, filtered, the solvent evaporated and the resulting imine was vacuum distilled at reduced pressure or recrystallized.

### (R)-(+) - Methyl p-Tolyl Sulfoxide<sup>68</sup> 1.2 B

To a solution of (-)-(S)-menthyl p-toluenesulfinate (10g, 30 mmol) ether (50ml) and THF (20ml) at 0°C under nitrogen was added MeMgI [from Mg(2g) and CH<sub>3</sub>I(6.2ml) in ether (70ml) dropwise over 30 min. The solution was stirred at room temperature for 2 hr and then decomposed with sat. NH<sub>4</sub>Cl (30ml), the organic layer was dried (MgSO<sub>4</sub>) and evaporated and the resulting solid recrystallized from ether/hexane (1:1) to yield 10.1g (90%), m.p. 74°C, lit.<sup>68</sup> m.p. 74°C.

### 3,4-dihydro-6,7-dimethoxyisoquinoline 1.5<sup>75b</sup>

A mixture of 3,4- dimethoxy phenylethylamine (15g, .083mol) and ethyl formate (31g) was refluxed for 12 hrs and then the ethyl formate was evaporated. Benzene (400 ml) and phosphoryl chloride (150 ml) were added and the resulting mixture was stirred for 4 hrs at room temperature following which time the benzene and phosphoryl chloride were then evaporated. The

resulting mixture was cooled to 0°C and water (10ml) and DCM (200 ml) were added and then the solution was made strongly basic with  $\text{NH}_4\text{OH}$ . The DCM layer was separated then dried ( $\text{MgSO}_4$ ) and evaporated. Column chromatography on silica gel gave pure 1.5, 11.15g (70%) as a thick oil.  $^1\text{H}$  NMR 6.81(s, 1H), 6.68(s, 1H), 3.91(s, 3H), 3.89(s, 3H), 3.73(m, 2H), 3.20(m, 2H).

**Reaction of 1.2A or 1.2B with Imines: A General Procedure.**

To a solution of diisopropylamine (121 mg, 1.2 mmol) in dry THF (3 mL) at 0°C was added n-BuLi in hexane (1.1 mmol). After 10 min the solution was cooled to -78°C and then a solution of (R)-(+)-methyl p-tolyl sulfoxide (1.0 mmol) in THF (2 mL) was added dropwise. After 1hr at -78°C a solution of the imine (1.3 mmol) in THF (2 mL) was added. After 1hr, the solution was warmed slowly to the temperature specified in Tables 1.3 and 1.4, for the designated period of time. The reaction then quenched rapidly by the addition of 10%  $\text{K}_2\text{CO}_3$  (10 mL) and then extracted with  $\text{CHCl}_3$  (2x). The combined extracts were dried ( $\text{MgSO}_4$ ) and evaporated. The diastereoselection of these reactions was determined from  $^1\text{H}$  NMR (400 MHz) analysis of the crude reaction product. Purification of the crude product on silica gel using ethyl acetate/hexane as eluent gave the pure product. Yields are reported in Tables 1.3 and 1.4.

m.p. 200°C (lit.<sup>40</sup> 216-217°C); IR (nujol) 3310, 1030 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.49 (d, J = 8.2 Hz, 2H), 7.3 (m, 6H), 7.07 (m, 3H), 6.67, (t, J = 7.3 Hz, 1H), 6.53 (d, J = 7.6 Hz, 2H), 5.28 (d, 1H), 4.84 (t, 1H), 3.16, (dd, J = 3.6, 13.7 Hz, 1H), 3.06 (dd, J = 8.8, 13.7 Hz, 1H), 2.39 (s, 3H); <sup>13</sup>C NMR 146.6, 141.7, 141.4, 130.1, 129.0, 127.66, 127.65, 124.1, 118.0, 114.0, 64.1, 54.8, 21.4; MS 336 (51, M+H<sup>+</sup>), 196 (100), 180 (22), 139 (22), 91 (22).

Anal. Calcd for C<sub>21</sub>H<sub>21</sub>NOS: C, 75.19; H, 6.31; N, 4.18. Found: C, 75.23; H, 6.43; N, 4.37.

**(R<sub>s</sub>,1R) N-Phenyl-N-(1-phenyl-2-(p-tolylsulfinyl))-ethylamine 1.4a** (Ar = p-tolyl):

<sup>1</sup>H NMR (in part)  $\delta$  5.12 (br. s, 1H), 4.90 (dd, J=4.7, 9.8 Hz, 1H), 3.26 (dd, J = 9.8, 13.5 Hz, 1H), 2.94 (dd, J = 4.7, 13.5 Hz, 1H), 2.38 (s, 3H).

**(R<sup>\*</sup><sub>s</sub>,1S<sup>\*</sup>) N-Phenyl-N-(1-phenyl-2-(phenylsulfinyl))-ethylamine 1.3a** (Ar = Ph):

m.p. 177-178°C ; IR (nujol) 3320, 1030 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.68-7.05 (m, 12H), 6.7-6.5 (m, 3H), 5.28 (br. s, 1H), 4.85 (m, 1H), 3.18 (dd, J = 3.7, 13.7 Hz, 1H), 3.12 (dd, J = 8.7, 13.7 Hz, 1H), ; <sup>13</sup>C NMR 131.1, 129.3, 129.0, 127.7, 126.3, 124.0, 118.0, 113.9, 64.1, 54.7; MS 322 (100, M+H<sup>+</sup>), 196 (100), 182 (57), 104 (67), 93 (100).

Anal. Calcd for C<sub>20</sub>H<sub>19</sub>NOS: C, 74.36; H, 5.96; N, 4.36. Found: C, 73.15; H, 6.00; N, 4.36.

(R<sup>\*</sup><sub>s</sub>,1R<sup>\*</sup>) N-Phenyl-1-phenyl-2-(p-phenylsulfinyl)-ethylamine 1.4a (Ar = Ph):

<sup>1</sup>H NMR (in part) δ 3.28 (dd, J = 9.8, 13.6 Hz, 1H), 2.98 (dd, J = 4.9, 13.6 Hz, 1H).

(R<sub>s</sub>,1S) N-Phenyl-N-(1-(2'-furyl)-2-(p-tolylsulfinyl))-ethylamine 1.3b (Ar = p-tolyl):

m.p. 181° C; <sup>1</sup>H NMR δ 7.52 (d, J = 8.1 Hz, 2H), 7.32 (m, 3H), 7.16 (t, J = 7.4 Hz, 2H), 6.75 (t, J = 9.32 Hz, 1H), 6.66 (d, J = 7.78 Hz, 2H), 6.28 (m, 1H), 5.05 (m, 1H), 4.80 (m, 1H), 3.26 (dd, J = 4.0, 13.3 Hz, 1H), 3.20 (dd, J = 8.2, 13.3 Hz, 1H), 2.41 (s, 3H); <sup>13</sup>C NMR 153.2, 152.7, 146.8, 141.9, 130.1, 129.2, 124.1, 118.7, 114.2, 110.5, 107.4, 61.6, 49.0, 21.4; MS 186 (48, M-p-TolSO), 139 (41), 125 (72), 94 (100).

Anal. Calcd for C<sub>19</sub>H<sub>19</sub>NO<sub>2</sub>S: C, 70.13; H, 5.88; N, 4.30. Found: C, 70.10; H, 5.94; N, 4.65.

(R<sup>\*</sup><sub>s</sub>,1S<sup>\*</sup>) N-Phenyl-N-(1-(2'-furyl)-2-(phenylsulfinyl))-ethylamine 1.3b (Ar = Ph):

m.p. 176-177° C; IR (nujol) 3295, 1600, 1460, 1030; <sup>1</sup>H NMR δ 7.73-7.15 (m, 8H), 6.82-6.25 (m, 5H), 5.07 (m, 1H), 4.70 (br. s, 1H), 3.28 (dd, J = 4.1, 13.3 Hz, 1H), 3.22 (dd, J = 8.2, 13.4 Hz, 1H), 2.41 (s, 3H); <sup>13</sup>C NMR 153.3, 146.2, 143.6, 142.1, 131.1, 129.4, 129.3, 123.85, 118.6, 114.1, 110.5, 107.4, 61.6, 48.6; MS 312 (8, M+H<sup>+</sup>), 219 (57), 185 (100), 125 (94), 93 (90).

Anal. Calcd for  $C_{18}H_{17}NO_2S$ : C, 69.43; H, 5.50; N, 4.50. Found: C, 69.93; H, 5.71; N, 4.63.

**(R<sup>\*</sup><sub>S</sub>,1R<sup>\*</sup>) N-Phenyl-N-(1-(2'-furyl)-2-(phenylsulfinyl))-ethylamine 1.4b** (Ar = Ph):

$^1H$  NMR (in part)  $\delta$  5.03 (t,  $J$  = 7.41 Hz, 1H), 4.47 (br. s, 1H), 3.38 (dd,  $J$  = 7.3, 13.3 Hz, 1H), 3.19 (dd,  $J$  = 7.2, 13.3 Hz, 1H).

**(R<sub>S</sub>,1S) N-Methyl-N-(1-phenyl-2-(p-tolylsulfinyl))-ethylamine 1.3c** (Ar = p-tolyl):

oil; IR (film) 3600-3200 (br.) 3300 (sharp), 1035  $cm^{-1}$ ;  $^1H$  NMR  $\delta$  7.52 (d,  $J$  = 8.2 Hz, 2H), 7.27 (m, 7H), 4.06 (dd,  $J$  = 3.4, 10.2 Hz, 1H), 3.00 (dd,  $J$  = 10.2, 13.4 Hz, 1H), 2.93 (dd,  $J$  = 3.4, 13.4 Hz, 1H), 2.39 (s, 3H) 2.31 (s, 3H);  $^{13}C$  NMR 141.2, 140.9, 140.6, 129.6, 128.3, 127.2, 126.6, 123.6, 65.0, 59.1, 33.8, 20.9; MS 274 (100,  $M+H^+$ ), 148 (100), 134 (95), 118 (93), 106 (100).

HRMS calcd for  $C_{16}H_{20}NOS$  274.1264, found 274.126.

**(R<sub>S</sub>,1R) N-Methyl-N-(1-phenyl-2-(p-tolylsulfinyl))-ethylamine 1.3c** (Ar = p-tolyl):

$^1H$  NMR (in part)  $\delta$  3.22 (dd,  $J$  = 8.4, 13.1 Hz, 1H), 2.81 (dd,  $J$  = 5.5, 13.1 Hz, 1H), 2.39 (s, 3H), 2.25 (s, 3H).

**(R<sub>S</sub>,1S) N-Methyl-N-(1-phenyl-2-(p-tolylsulfinyl))-ethylamine 1.3c** (Ar = Ph):

oil; IR (nujol) 3700-3000 (br.), 1650, 1050  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  7.63 (dd,  $J = 2.0, 7.3$  Hz, 2H), 7.50 (m, 3H), 7.3 (m, 2H), 7.26 (m, 2H), 4.07 (dd,  $J = 3.4, 10.1$  Hz, 1H), 3.01 (dd,  $J = 10.1, 13.4$  Hz, 1H), 2.95 (dd,  $J = 3.5, 13.4$  Hz, 1H), 2.33 (s, 3H);  $^{13}\text{C}$  NMR 144.2, 141.4, 140.0, 129.3, 128.8, 127.8, 126.9, 123.9, 65.4, 59.3, 34.2; MS 260 (95,  $\text{M}+\text{H}^+$ ), 134 (100), 125 (85), 120 (89), 91 (24).

**(R<sub>S</sub>,1S) N-Phenyl-N-(1-ethyl-2-(p-tolylsulfinyl))-ethylamine 1.3d** (Ar = p-tolyl):

m.p. 167° C ; IR (nujol) 3330, 1030  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  7.52(d,  $J = 8.1$  Hz, 2H), 7.31 (d,  $J = 8.2$  Hz, 2H), 7.16 (t,  $J = 7.5$  Hz, 2H), 6.70(t,  $J = 7.3$  Hz, 1H), 6.64 (d,  $J = 7.8$  Hz, 2H), 3.89 (br. s, 2H), 2.98 (dd,  $J = 3.7, 13.3$  Hz, 1H), 2.79 (dd,  $J = 7.8, 13.3$  Hz, 1H), 2.41 (s, 3H), 1.92-1.65 (m, 3H), 0.96 (t,  $J = 7.5$  Hz, 3H);  $^{13}\text{C}$  NMR 147.0, 141.5(2 carbons), , 130.0, 129.2, 123.9, 117.9, 113.8, 63.7, 51.1, 28.0, 21.3, 10.2; MS 288 (20,  $\text{M}+\text{H}^+$ ), 148 (100), 134 (55), 125 (27), 118 (20), 91 (45), 77 (23).

HRMS calcd for  $\text{C}_{17}\text{H}_{22}\text{NOS}$  288.1420, found 288.140.

Anal. calcd for  $\text{C}_{17}\text{H}_{21}\text{NOS}$  : C, 71.04; H, 7.36; N, 4.87. Found: C, 71.53; H, 7.49; N, 4.92.

**(R<sub>S</sub>,1R) N-Phenyl-N-(1-ethyl-2-(p-tolylsulfinyl))-ethylamine 1.4d** (Ar = p-tolyl):

$^1\text{H}$  NMR (in part)  $\delta$  3.13 (dd,  $J = 5.2, 13.4$  Hz, 1H).

**(R<sub>S</sub>,1S) N-Phenyl-N-(1-ethyl-2-(phenylsulfinyl))-ethylamine 1.3d** (Ar = Ph):

m.p. 119-120° C ; IR (nujol) 3330, 1030 cm<sup>-1</sup>; <sup>1</sup>H NMR δ 7.63 (dd, J = 2.2 7.6 Hz, 2H), 7.51 (m, 3H), 7.17 (t, J = 7.6 Hz, 2H), 6.72 (t, J = 7.3 Hz, 1H), 6.66 (d, J = 8.2 Hz, 2H), 3.92 (br. s, 1H), 3.88 (br. s, 1H), 2.99 (dd, J = 3.5, 13.2 Hz, 1H), 2.81 (dd, J = 7.9, 13.2 Hz, 1H), 1.81-1.68 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H); <sup>13</sup>C NMR 147.1, 131.0, 129.3, 123.9, 118.0, 113.8, 63.2, 51.2, 28.1, 10.3; MS 274 (21, M+H<sup>+</sup>), 148 (100), 134 (37), 99 (90).

**(R<sub>S</sub>,1S) N-Phenyl-N-(3-methyl-2-(p-tolylsulfinyl))-2-butylamine 1.3f** (Ar = p-tolyl):

oil ; <sup>1</sup>H NMR δ 7.55-6.5 (m, 9H), 3.99 (m, 1H), 2.99 (dd, J = 4.6, 13.3 Hz, 1H), 2.78 (dd, J = 8.2, 13.3 Hz, 1H), 2.40 (s, 3H), 1.75 (m, 1H), 1.6 (m, 2H), 0.94 (d, J = 6.5 Hz, 3H) 0.89 (d, J = 6.6 Hz, 3H); <sup>13</sup>C NMR 147.0, 146.3, 141.4, 129.9, 129.3, 124.0, 117.7, 113.5, 113.1, 63.9, 48.0, 44.8, 24.9, 22.7, 22.3, 21.3, ; MS 316 (80, M+H<sup>+</sup>), 176 (100), 162 (75), 133 (80) 119 (55), 106 (77).

HRMS calcd for C<sub>19</sub>H<sub>26</sub>NOS 316.1733, found 316.174.

**(R<sub>S</sub>,1R) N-Phenyl-N-(3-methyl-2-(p-tolylsulfinyl))-2-butylamine 1.4e** (Ar = p-tolyl):

<sup>1</sup>H NMR (in part) δ 3.87 (m, 1H), 3.08 (dd, J = 4.3, 13.2 Hz, 1H), 2.76 (dd, J ca 8, 13.2 Hz, 1H); <sup>13</sup>C NMR (in part) 62.7, 47.3, 44.5.



**(R<sub>S</sub>,1S)-N-Phenyl-N-(4-methyl-2-(p-tolylsulfinyl))-2-pentylamine 1.3f** (Ar = p-tolyl):

oil ; <sup>1</sup>H NMR δ 7.60-7.05 (m, 6H), 6.75-6.50 (m, 3H), 3.60 (m, 1H), 2.96 (dd, J = 3.0, 13.3 Hz, 1H), 2.71 (dd, J = 9.9, 13.3 Hz, 1H), 2.41 (s, 3H), 2.05 (m, 1H), 0.97 (d, J = 6.9 Hz, 3H) 0.92 (d, J = 6.7 Hz, 3H); <sup>13</sup>C NMR (in part) 61.9, 54.1, 32.0, 21.3, 18.5, 18.3. MS 302 (100, M+H<sup>+</sup>), 162 (65), 139 (18), 119 (20), 106 (18).

HRMS calcd for C<sub>18</sub>H<sub>24</sub>NOS 302.1577, found 302.155.

**(R<sub>S</sub>,1R)-N-Phenyl-N-(4-methyl-2-(p-tolylsulfinyl))-2-pentylamine 1.4f** (Ar = p-tolyl):

<sup>1</sup>H NMR (in part) δ 3.89 (m, 1H), 3.09 (dd, J = 7.7, 13.3 Hz, 1H), 2.88 (dd, J = 5.8, 13.3 Hz, 1H), 2.41 (s,3H), 2.15 (m, 1H), 0.95 (d,J = 6.7 Hz, 3H) 0.90 (d, J = 6.9 Hz, 3H); <sup>13</sup>C NMR (in part) 59.8, 54.4, 30.7, 17.8.

**(1S,R<sub>S</sub>)1,2,3,4-Tetrahydro-6,7-dimethoxy-1(p-tolylsulfinyl)-methyloquinoline 1.9 and (1R, R<sub>S</sub>) 1.8**

**1.9** (Ar = p-tolyl): m.p. 124-125° C ; IR (nujol) 3650-3310, 3265 (sharp), 1110, 1035 cm<sup>-1</sup>; <sup>1</sup>H NMR δ 7.57 (d, J = 8 Hz, 2H), 7.32 (d, J = 8 Hz, 2H), 6.56 (s, 1H), 6.45 (s, 1H) 4.59 (dd, J = 2.9, 10.7 Hz, 1H), 3.91 (s, 3H), 3.77 (s, 3H), 3.15 (m, 3H), 3.10 (dd, J = 3.1, 13.4 Hz, 1H), 2.7 (m, 2H), 2.40 (s, 3H); <sup>13</sup>C NMR 147.8, 147.5, 141.1, 129.8, 128.2, 127.51, 123.7,112.2, 109.3, 64.8, 55.9, 54.7, 49.8, 39.5, 28.8, 21.1; MS 346 (24, M+H<sup>+</sup>), 205 (15), 192 (29), 154 (100), 136 (100).

**1.8** (Ar = p-tolyl):  $^1\text{H}$  NMR (in part)  $\delta$  6.57 (s, 1H), 6.49 (s, 1H) 4.38 (dd,  $J$  = 3.8, 9.2 Hz, 1H),

**(1S\*,R<sub>S</sub>\*),2,3,4-Tetrahydro-6,7-dimethoxy-1(phenylsulfinyl)-methylisoquinoline 1.9 and (1R\*,R<sub>S</sub>\*) 1.8**

**1.9** (Ar = Ph): m.p. 170° C ; IR (nujol) 3650-3100, 3380 (sharp), 1110, 1030  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  7.68 (dd,  $J$  = 1.5, 8.2 Hz, 2H), 7.52 (m, 3H), 6.56 (s, 1H), 6.44 (s, 1H) 4.60 (dd,  $J$  = 2.9, 10.7 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.15 (m, 3H), 3.06 (dd,  $J$  = 3.1, 13.4 Hz, 1H), 2.71(m, 2H);  $^{13}\text{C}$  NMR 147.8, 147.5, 144.3, 130.8, 129.3, 128.1, 127.5, 123.8, 112.1, 109.1, 64.9, 55.9, 55.8, 50.0, 39.5, 28.9; MS 322 (24,  $\text{M}+\text{H}^+$ ), 205 (15), 192 (29), 154 (100), 136 (100).

Anal. calcd for  $\text{C}_{18}\text{H}_{21}\text{NO}_3\text{S}$ : C, 65.23; H, 6.39; N, 4.23. Found: C, 65.15; H, 6.65; N, 4.57.

**(+)-(1S,R<sub>S</sub>) 2-Methyl-.2,3,4-tetrahydro-6,7-dimethoxy-1(p-tolylsulfinyl)-methylisoquinoline 1.13**

To a solution of **1.9** (Ar = p-Tol, 198 mg, 0.6 mmol) in acetonitrile (2 mL) and aqueous formaldehyde (37%, 0.5 mL) was added sodium cyanoborohydride (50 mg, 0.8 mmol). After 20 min the pH of the solution was adjusted to neutral on wet pH paper by the addition of glacial acetic acid. After 6 hr the mixture was concentrated by evaporated, treated with 2M KOH (2 mL) and then extracted with chloroform. The combined extracts were dried ( $\text{MgSO}_4$ ) and evaporated. The crude product was purified by column chromatography on silica gel using ethyl acetate as eluent. The pure product (190 mg, 92%) had mp 71 °C ,  $[\alpha]_{\text{D}}^{23} +206^\circ$

(c 1.1 (CHCl<sub>3</sub>)) (lit.<sup>74</sup> mp 70-72°C,  $[\alpha]_D^{23}$  +206° (c 1.1 (CHCl<sub>3</sub>)) and spectral properties identical with an authentic sample.

**(1S,R<sub>S</sub>) 2-(2',3'-dimethoxyphenylmethyl)-3,4-dihydro-6,7-dimethoxy-1(p-tolylsulfinyl)-methylisoquinoline 1.10.**

The titled compound was prepared from 19B (0.91 mmol) as described above for the preparation of 1.13 except that 2,3-dimethoxybenzaldehyde (1.5 mmol) was used in place of formaldehyde. Purification of the crude product by column chromatography on silica gel gave 1.10 (392 mg, 87%). oil; IR (film) 1520, 1460, 1260, 1040 cm<sup>-1</sup>; <sup>1</sup>H NMR δ 7.52 (d, J = 8.1 Hz, 2H), 7.28 (m, 3H), 7.11 (t, J = 8.3 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.58 (s, 1H), 6.57 (s, 1H) 4.39 (dd, 1H), 4.12 (d, J = 13.9 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.76 (d, J = 13.9 Hz, 1H), 3.2-2.9 (m, 5H), 2.40 (s, 3H); <sup>13</sup>C NMR 152.6, 147.8, 147.7, 142.3, 140.9, 132.6, 129.8, , 127.27, 126.7, 124.0, 123.8, 122.9, 112.0, 111.2, 110.5, 66.5, 61.0, 56.7, 56.0, 55.9, 55.7, 50.8, 41.3, 22.4, 21.3; MS 496 (88, M+H<sup>+</sup>), 480 (75), 356 (100), 342 (60), 324 (60).

HRMS calcd for C<sub>28</sub>H<sub>34</sub>NO<sub>5</sub>S 496.2154, found 496.212.

**(+)-(13S,13aS)5,8,13,13a-Tetrahydro-2,3,9,10-tetramethoxy-13-(4-methylphenyl)thio-6H-dibenzo[a,g]quinolizine 1.11.**

A solution of 1.10 (100 mg, 0.2 mmol) in chloroform (2.5 mL) at 0°C was treated dropwise with trifluoroacetic anhydride (0.4 mmol). The mixture was heated at 95°C in a sealed tube for 4 h. The mixture was then cooled, diluted with saturated sodium

carbonate solution and then extracted with ether (3x). The combined extracts were dried ( $\text{MgSO}_4$ ) and evaporated. The crude product was purified by column chromatography on alumina using ethyl acetate/hexane (1:1) and then ethanol as eluent. The desired product (81 mg, 82%) was obtained as an oil.  $[\alpha]_{\text{D}}^{20} +148.3^\circ$  (c 3.6 ( $\text{CHCl}_3$ )); IR (nujol) 1600, 1515, 1490, 1460, 1375  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  7.07 (d,  $J = 8.1$  Hz, 2H), 6.98 (d,  $J = 7.9$  Hz, 2H), 6.73 (d,  $J = 8.4$  Hz, 2H), 6.68 (d,  $J = 7.9$  Hz, 1H), 6.67 (s, 1H), 6.52 (s, 1H) 4.43 (d,  $J = 2$  Hz, 1H), 4.30 (d,  $J = 16.2$  Hz, 1H), 3.99 (br. s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.71 (s, 3H), 3.58 (d,  $J = 16.2$  Hz, 1H), 3.25 (m, 2H), 2.65 (m, 2H), 2.29 (s, 3H);  $^{13}\text{C}$  NMR (in part) 63.8, 60.0, 58.0, 55.8, 54.1, 51.1, 29.3, 21.0; MS 478 (25,  $\text{M}+\text{H}^+$ ), 354 (100), 286 (14), 195 (50), 151 (39), 125 (89), 91 (47).

**(R)-(+)-Tetrahydropalmatine 1.12**

To a solution of 1.11 (70 mg) in ethanol (0.5 mL) was added Raney nickel (W2, ca 200mg) and the reaction mixture was stirred rapidly for 10 h. The mixture was then filtered through a pad of celite and the ethanol was evaporated giving a pale yellow solid (46 mg). Recrystallization from ethanol gave pure (R)-(+)-tetrahydropalmatine, mp 138-139°C,  $[\alpha]_{\text{D}}^{20} +288.5^\circ$  (c 2 (EtOH)) (lit.<sup>75</sup> mp 142°C,  $[\alpha]_{\text{D}}^{20} +292.5^\circ$  (EtOH)).  $^1\text{H}$  NMR  $\delta$  6.89 (dd,  $J = 8.4$  Hz, 1H), 6.80 (dd,  $J = 8.4$  Hz, 1H), 6.73 (s, 1H), 6.63 (s, 1H), 4.29 (d,  $J = 15.8$  Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.86 (s, 6H), 3.61 (d,  $J = 15.8\text{Hz}$ , 1H);  $^{13}\text{C}$  NMR 150.0, 147.8, 145.0, 129.5, 128.3, 127.7, 126.8, 123.8, 111.7, 111.4, 109.1, 60.2, 59.4, 56.2, 56.0, 53.9, 51.5, 36.1, 29.0; MS 356 (58,  $\text{M}+\text{H}^+$ ), 190 (33), 164 (77), 144 (100), 121 (36).

## CHAPTER 2

## DIASTEREOSELECTIVE ADDITIONS OF LITHIATED N-SUBSTITUTED S-METHYL-S-PHENYLSULFOXIMINE TO IMINES AND ALDEHYDES.

While considerable effort has been directed at the studies of the stereochemistry of reactions involving sulfoxides, the stereochemistry of reactions involving the related sulfoximines has received relatively little attention.

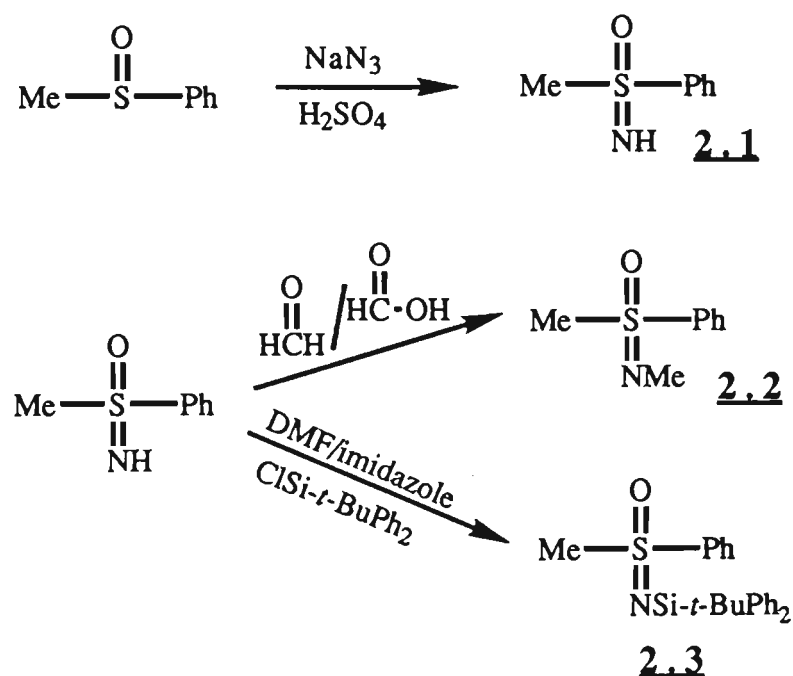
During the course of our sulfoxide study (Chapter 1) it was seen that  $\beta$ -aminosulfoxides were produced in modest to good diastereoselectivity. Unfortunately, these studies could not be extended to N-alkylidenealkylamines (alkylCH=Nalkyl). In order to overcome the above problems we next examined the reactions of lithiated sulfoximines ( $\text{LiCH}_2\text{S}(\text{O})(\text{Ph})\text{NR}$ ) with aldehydes and imines.

From previous studies on the addition of lithiated N-methyl-S-methyl-S-phenylsulfoximine ( $\text{LiCH}_2\text{S}(\text{O})(\text{Ph})\text{NCH}_3$ ) to aldehydes and ketones it was apparent that the oxygen and the N-methyl group at sulfur of the sulfoximine have similar electronic and/or steric requirements and that little chiral induction results.<sup>61</sup> Modest chiral induction also results in similar reaction involving the N-tosyl analogues.<sup>76</sup>

Racemic S-methyl-S-phenylsulfoximine (2.1) was synthesised from the corresponding methyl phenyl sulfoxide by the use of sodium azide and concentrated sulfuric acid<sup>77a,b</sup> (Scheme 2.1). The enantiomeric pure version of this reagent is readily available via resolution of the racemic S-methyl-S-phenylsulfoximine with commercially available (-)-10-camphorsulfonic acid.<sup>78</sup> The sulfoximine was then subjected to Eschweiler-Clarke N-methylation

by refluxing a solution of sulfoximine in formaldehyde and formic acid<sup>77c</sup> to give S,N-dimethyl-S-phenylsulfoximine in excellent yield (Scheme 2.1) or N-silylation with tert-butylchlorodiphenylsilane and imidazole in dimethylformamide (DMF)<sup>79</sup> to give N-tert-butyldiphenylsilyl-S-methyl-S-phenylsulfoximine (2.3).

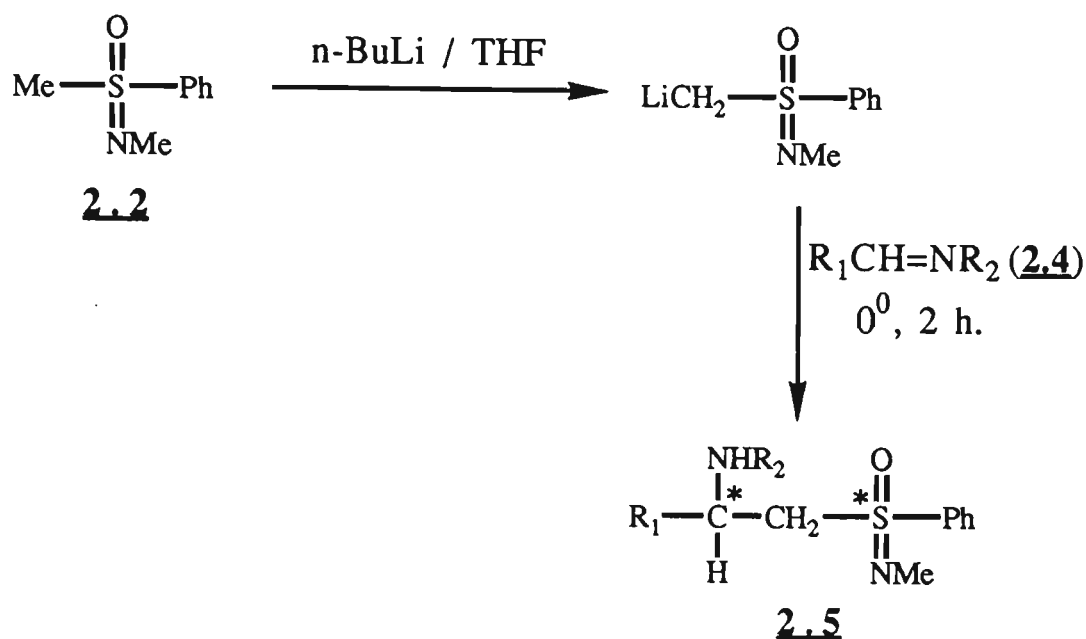
**Scheme 2.1.**



We firstly examined the reaction of lithiated N,S-dimethyl-S-phenylsulfoximine to N-benzylideneaniline (2.4e) (Scheme 2.2).



Scheme 2.2.



N,S-dimethyl-S-phenylsulfoximine was first treated with n-butyllithium (1.1 equiv.) in tetrahydrofuran at 0°C for 15 min. The solution was then cooled to -78°C and then treated with a solution of the imine for a period of 1 hr. The reaction was then quenched at -78°C with 10% aqueous potassium carbonate. The yield after purification by column chromatography was 95% (Table 2.1). The diastereoselectivity of this reaction was found to be approximately 60:40 as measured by integration of the <sup>1</sup>H NMR spectrum (400 MHz) of crude reaction mixture (Figure 2.1). Figure 2.2 is a copy of the accompanying <sup>13</sup>C NMR spectrum (90MHz) also showing both diastereomers in approximately equal abundance. Two more imines, N-pentylidenepentylamine (CH<sub>3</sub>(CH<sub>2</sub>)<sub>3</sub>CH=N(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub> Table 2.1 entry 3) and N-pentylidene-*tert*-butylamine (CH<sub>3</sub>(CH<sub>2</sub>)<sub>3</sub>CH=N *t*- Bu, entry 4, Table 2.1), were reacted with lithiated N,S-dimethyl-S-phenylsulfoximine at 0°C for a period of 2 hrs. Little reaction occurred below this temperature. After work up, it was found that the mixture of diastereomers was

the mixture of diastereomers was approximately equal for entries 3 and 4 (Table 2.1) as measured by integration of the  $^1\text{H}$  NMR spectrum (400MHz) of the crude reaction mixture. The yields after chromatography were poor, being 15% and 18% respectively (Table 2.1 entries 3 and 4).



Figure 2.2.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , aliphatic region) for the adducts 2.5

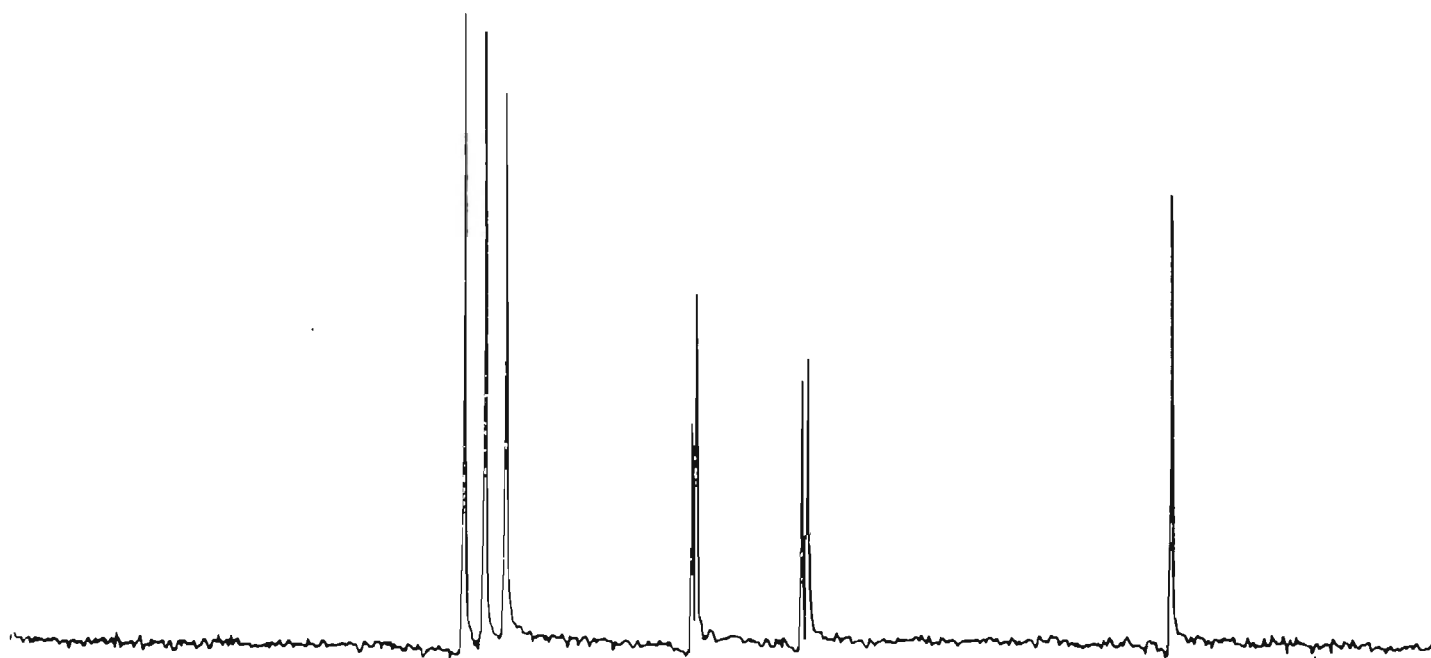
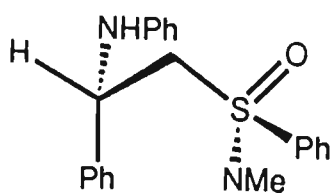
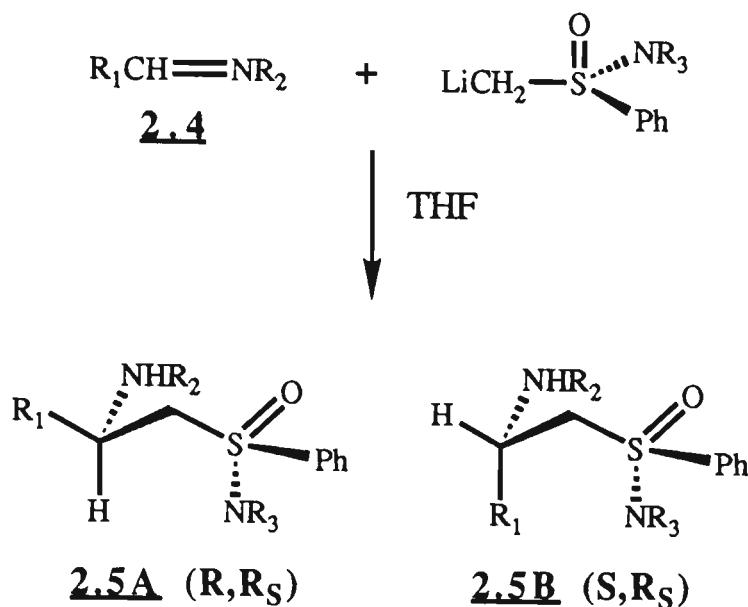


Table 2.1.

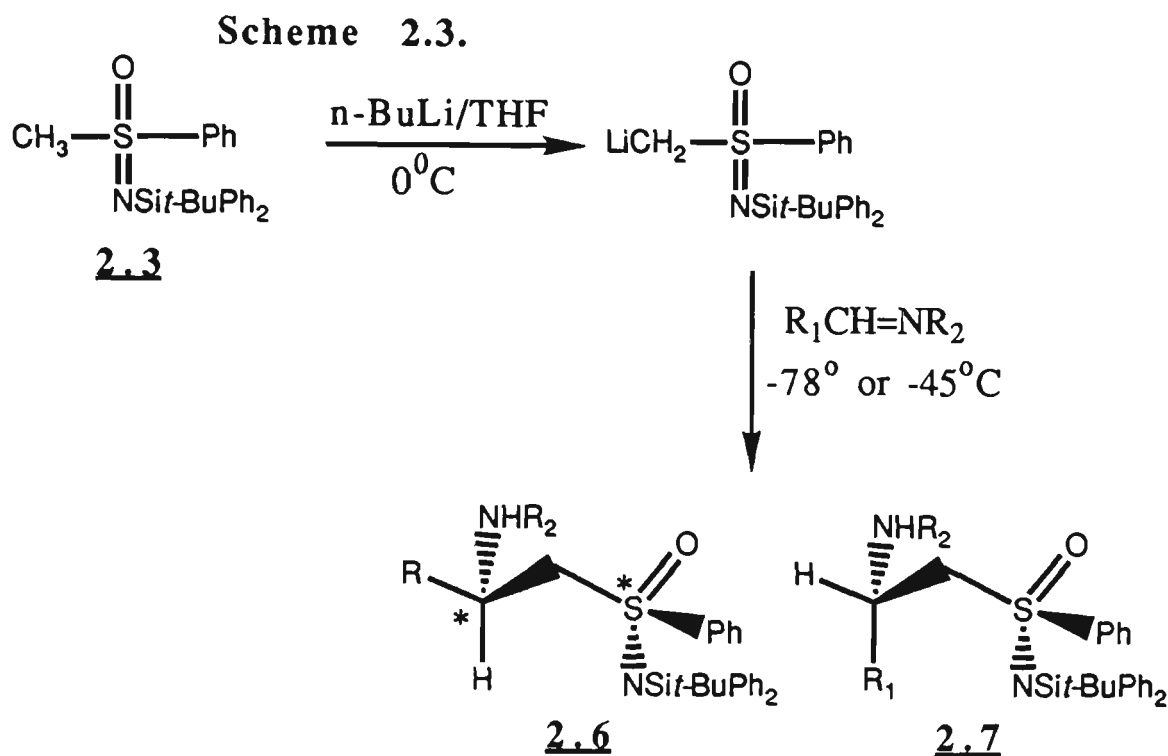


Entry	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Temp/°C	Time	Yield/%	<u>2.5A</u> : <u>2.5B</u>
1	Ph	Ph	Me	-78	1 hr	95	50 : 50
2	Ph	Ph	<i>Sit</i> -BuPh <sub>2</sub>	-78	1 hr	90	88 : 12
3	Bu	Pent	Me	0	2 hr	15	
4	Bu	<i>t</i> -Bu	Me	0	2 hr	18	

As these reactions proceeded with poor diastereoselection and result in a multitude of side reactions it was decided to terminate the use of N,S-dimethyl-S-phenylsulfoximine.

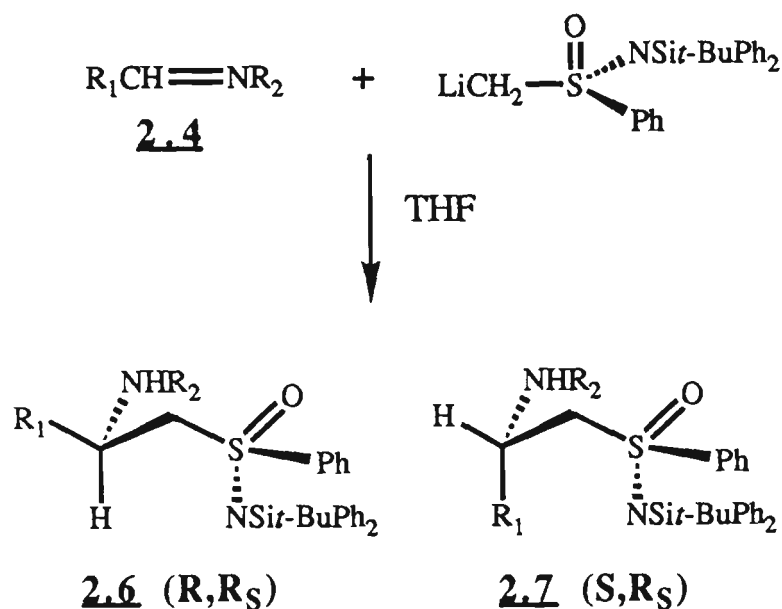
In order to gain a better stereoselectivity the reaction of the N-tert-butyldiphenylsilyl analogue (2.3) with imines was studied. When lithiated N-tert-butyldiphenylsilyl-S-methyl-S-phenylsulfoximine (2.3) was reacted with N-benzylideneaniline (Scheme 2.3) at -78° for 1 hr the diastereoselection was dramatically increased to give a 88:12 ratio of the diastereoisomers 2.5A and 2.5B (Table 2.1). It was possible to isolate the product in 90% yield after two recrystallisations from ethanol. The <sup>1</sup>H NMR of this purified adduct (Figure 2.3) shows only the diastereomer with a doublet of doublets for the proton next to nitrogen at 4.5ppm and

a doublet of doublets for the two diastereomeric methylene protons next to sulfur at 3.43 and 3.25ppm. Figure 2.4 shows the  $^{13}\text{C}$  NMR spectrum of the adduct 2.6e, which indicates essentially one diastereoisomer.



Unlike methyl phenyl sulfoxide or methyl p-tolyl sulfoxide, *N-tert*-butyldiphenylsilyl-*S*-methyl-*S*-phenylsulfoximine reacted with imines of the kind  $\text{R}_1\text{CH}=\text{NR}_2$  where both  $\text{R}_1$  and  $\text{R}_2$  were alkyl substituents. From an inspection of Table 2.2 it is clear that when  $\text{R}_2 = \text{Ph}$ , the diastereoselection was good when  $\text{R}_1$  was small, as is the case for entry 1 and 2 ( $\text{R}_1 = \text{Et}$ , *i*-Bu) but steadily decreased as

Table 2.2. Diastereoselective addition of **2.3** to imines **2.4**.



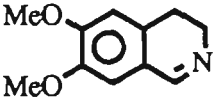
Entry	Imine ( <b>2.4</b> )		Yield/%	Temp./°C	<b>2.6</b> : <b>2.7</b>	Adduct
	R <sub>1</sub>	R <sub>2</sub>				
1	Et	Ph (2.4a)	68	-45	94 : 6	2.6a
2	i-Bu	Ph (2.4b)	76	-45	95 : 5	2.6b
3	i-Pr	Ph (2.4c)	70	-45	90 : 10	2.6c
4	2-furyl	Ph (2.4d)	90	-78	90 : 10	2.6d
5	Ph	Ph (2.4e)	90	-78	88 : 12	2.6e
6	t-Bu	Ph (2.4f)	40	-45	79 : 12	2.6f
7	 (2.4g)		82	-78	80 : 20	2.6g
8	Ph	t-Bu (2.4h)	40	-45	96 : 4	2.6h
9	Ph	Me (2.4i)	72	-45	89 : 11	2.6i
10	Bu	t-Bu (2.4j)	35	10	85 : 15	2.6j
11	Bu	Pent (2.4k)		10	73 : 27	2.6k

Figure 2.3  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , aliphatic region) for the adduct 2.5

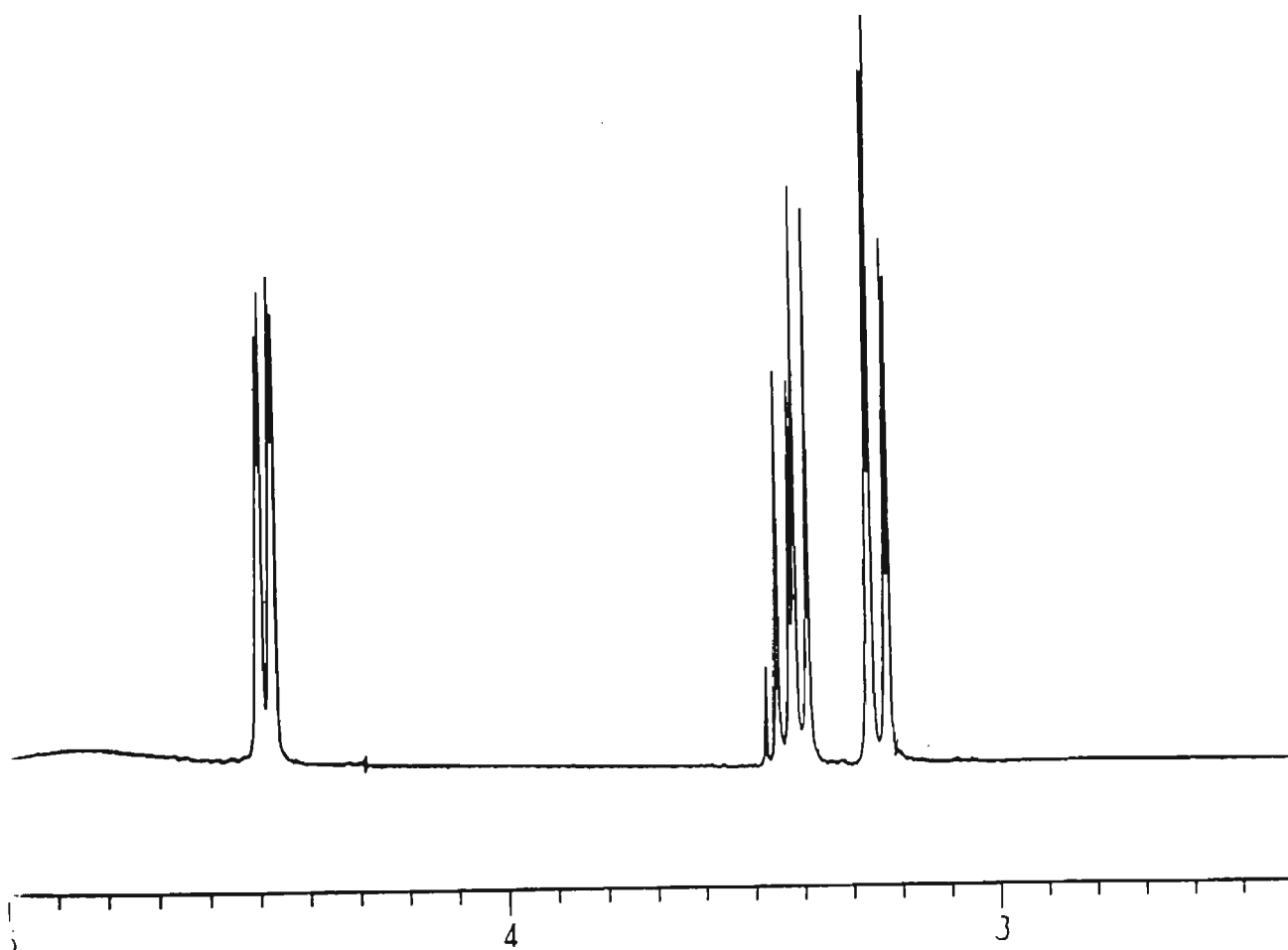
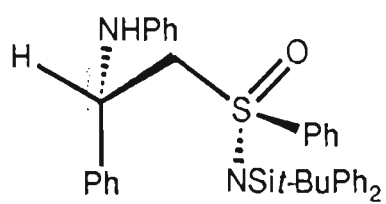
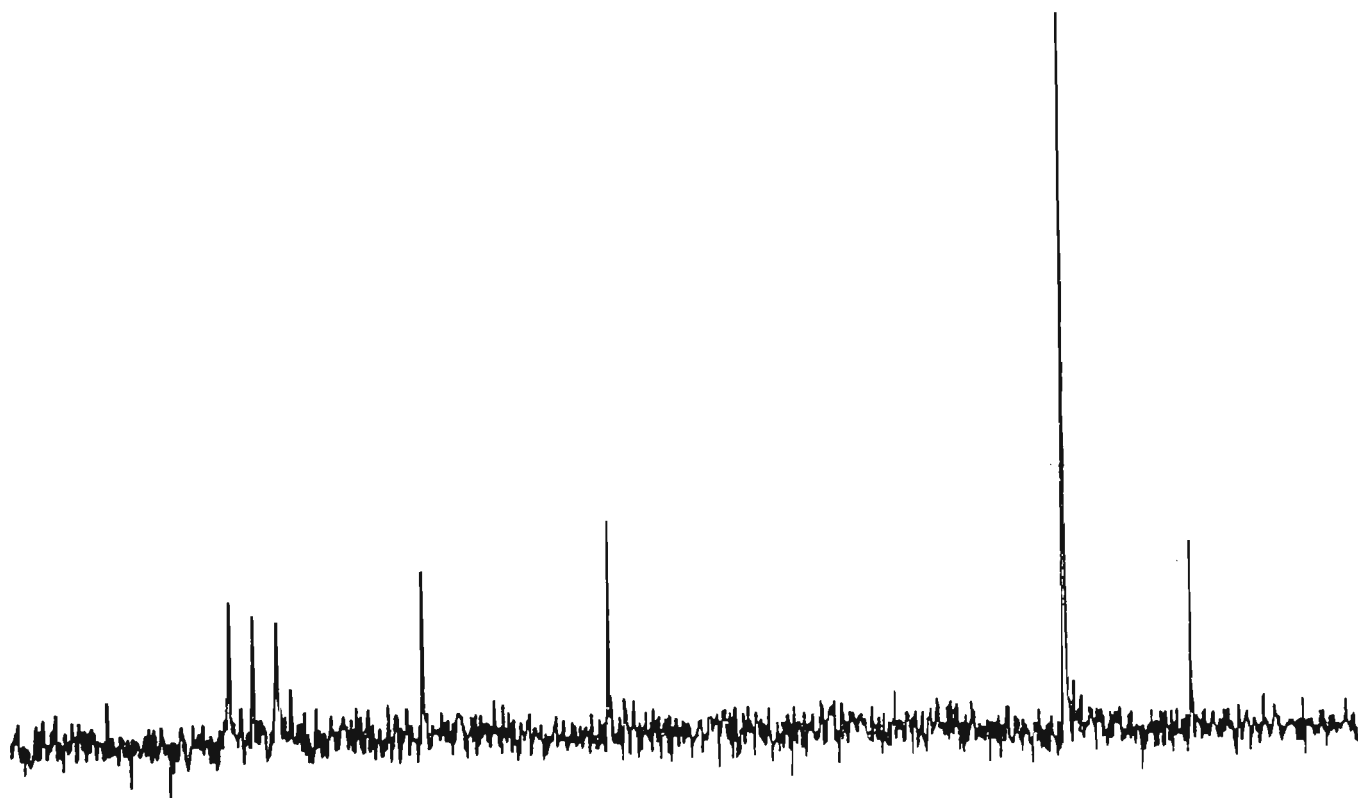
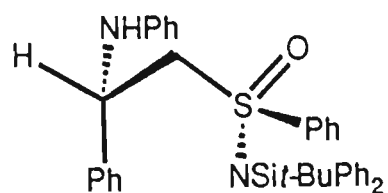




Figure 2.4  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , aliphatic region) for the adduct 2.6e.



the size of R<sub>1</sub> increased from *i*-Pr through to *t*-Bu (entries 3,4,5 and 6, R<sub>1</sub> = *i*-Pr, 2-furyl, Ph, *t*-Bu). It is interesting to note that the yields followed an opposite trend with the lowest yield being observed when R<sub>1</sub> = Et and the highest when R<sub>1</sub> = 2-furyl or Ph. Opposite trends in diastereoselectivity were observed when the size of R<sub>2</sub> was increased but keeping R<sub>1</sub> constant. For example when R<sub>1</sub> = Ph and R<sub>2</sub> = Me the diastereoselectivity was 89:11 and the yield was 72%, however when R<sub>1</sub> = Ph and R<sub>2</sub> = *t*-Bu the diastereoselectivity was high (96:4) but the yields were poor (40%). When R<sub>1</sub> was *n*-butyl an increase in the size of R<sub>2</sub> resulted in an increase in the diastereoselectivity (Table 2.2, entry 10 and 11). For example, when R<sub>2</sub> = pentyl (Table 2.2, entry 11) the diastereoselectivity was 73:23 and the yield was 20%, while when R<sub>2</sub> = *t*-Bu (Table 2.2, entry 10) the diastereoselectivity was 85:15 with a somewhat better yield of 35%. In general, the starting *N*-tert-butyldiphenylsilyl-*S*-methyl-*S*-phenylsulfoximine was the major component of the crude reaction mixture for reactions that proceeded with poor yield. A major problem encountered in the purification of these poor yielding reactions was the separation of the starting sulfoximine from the imine adducts, which had very similar polarities on silica gel, thus rendering column chromatography difficult and tedious.

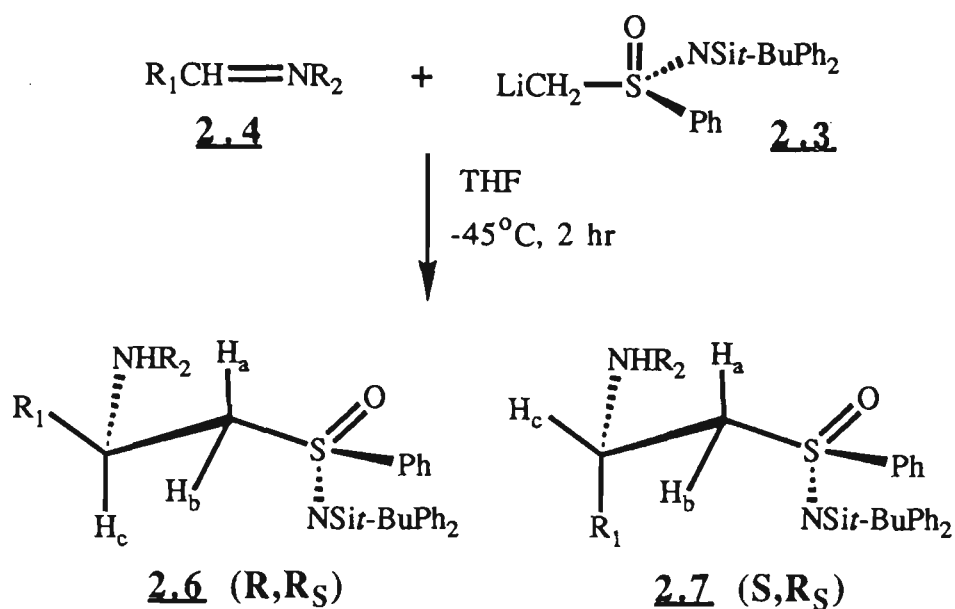
The reaction between *N*-tert-butyldiphenylsilyl-*S*-methyl-*S*-phenylsulfoximine and highly reactive imines (Table 2.2, entries 4 and 5, where R<sub>1</sub> and R<sub>2</sub> are both aromatic) were carried out at -78°

C for 1 hr, while reactions with less reactive imines (Table 2.2, entries 1-3, 6, 7, and 8, where R<sub>1</sub> or R<sub>2</sub> is aromatic) were conducted at -45°C for a period of 2 hrs. In the case of unreactive imines (Table 2.2, entries 8, 10 and 11 where R<sub>1</sub> and R<sub>2</sub> are both alkyl or the imine is sterically hindered (PhCH=N<sub>t</sub>-Bu) it was necessary to increase the reaction temperature to 0°C for a period of 2 hrs.

In the case of 6,7-dimethoxy-3,4-dihydroisoquinoline (Table 2.2, entry 7 ) essentially no difference in diastereoselectivity was observed when the temperature was increased from -45°C to 0°C and yields were also unaffected, in contrast to lithiated methyl p-tolyl sulfoxide (Chapter 1). The addition reaction proved to be insensitive to the metal cation used and substitution of potassium (by using potassium diisopropylamide<sup>80</sup> as base instead of n-BuLi) for lithium had no effect on diastereoselectivity or yield in the reactions. However when transmetalation was attempted by treating the lithium sulfoximine anion with TiCl<sub>4</sub>, Ti(iPrO)<sub>4</sub>, ZnCl<sub>2</sub>, ZrCl<sub>4</sub> or ZnBr<sub>2</sub> the reactions either failed to occur or produced a variety of intractable materials.

Table 2.3 shows the <sup>1</sup>H NMR chemical shifts and coupling constants of H<sub>A</sub>, H<sub>B</sub> and H<sub>C</sub> for the major diastereomeric adducts (2.6) while Table 2.4 shows <sup>13</sup>C chemical shifts of C-1 and C-2 for the adducts 2.6 and 2.7.

Table 2.3.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) data for the addition of 2.3 to imines 2.4.



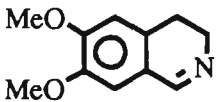
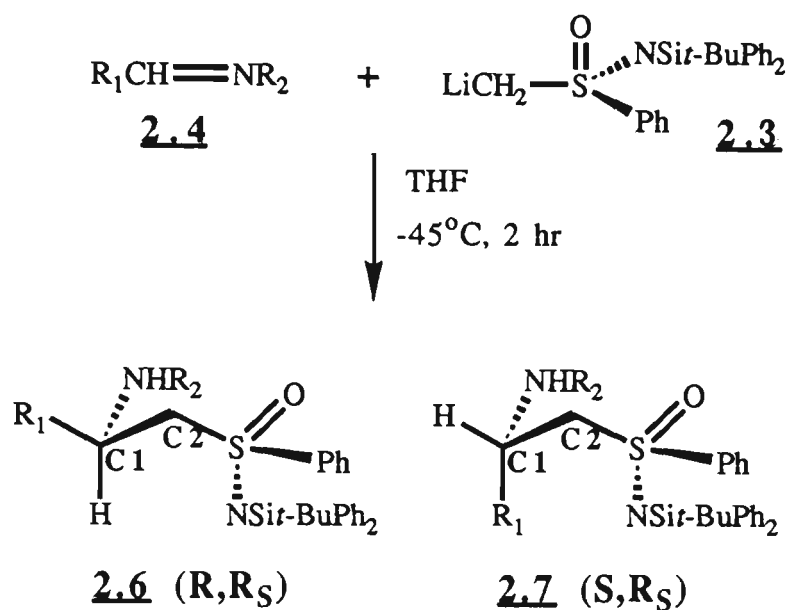
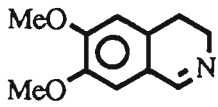
Entry	Adduct <u>2.6</u>			H <sub>a</sub>	H <sub>b</sub>	H <sub>c</sub>	J <sub>ac</sub>	J <sub>bc</sub>	J <sub>ab</sub>
	R <sub>1</sub>	R <sub>2</sub>							
1	Et	Ph	(a)	3.31	2.94	3.83	5.03	6.68	13.88
2	i-Bu	Ph	(b)	3.38	2.89	4.08	3.67	7.63	13.58
3	i-Pr	Ph	(c)	3.13	3.03	3.77	7.33	5.19	14.10
4	2-furyl	Ph	(d)	3.55	3.47	4.80	8.39	4.57	14.34
5	Ph	Ph	(e)	3.42	3.24	4.48	10.53	2.75	14.53
6	t-Bu	Ph	(f)	3.32	2.95	3.38	5.40	7.20	14.40
7			(g)	3.51	3.31	4.53	9.31	1.52	14.00
8	Ph	t-Bu	(h)	3.35	3.22	5.05	10.22	1.68	13.88
9	Ph	Me	(i)	3.45	3.10	3.95	10.70	1.68	14.40
10	Bu	t-Bu	(j)	3.38	2.89	4.08	8.22	2.74	13.70
11	Bu	Pent	(k)	2.95	2.40	3.19	8.70	2.20	14.80

Table 2.4.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) data for the addition of 2.3 to imines 2.4.

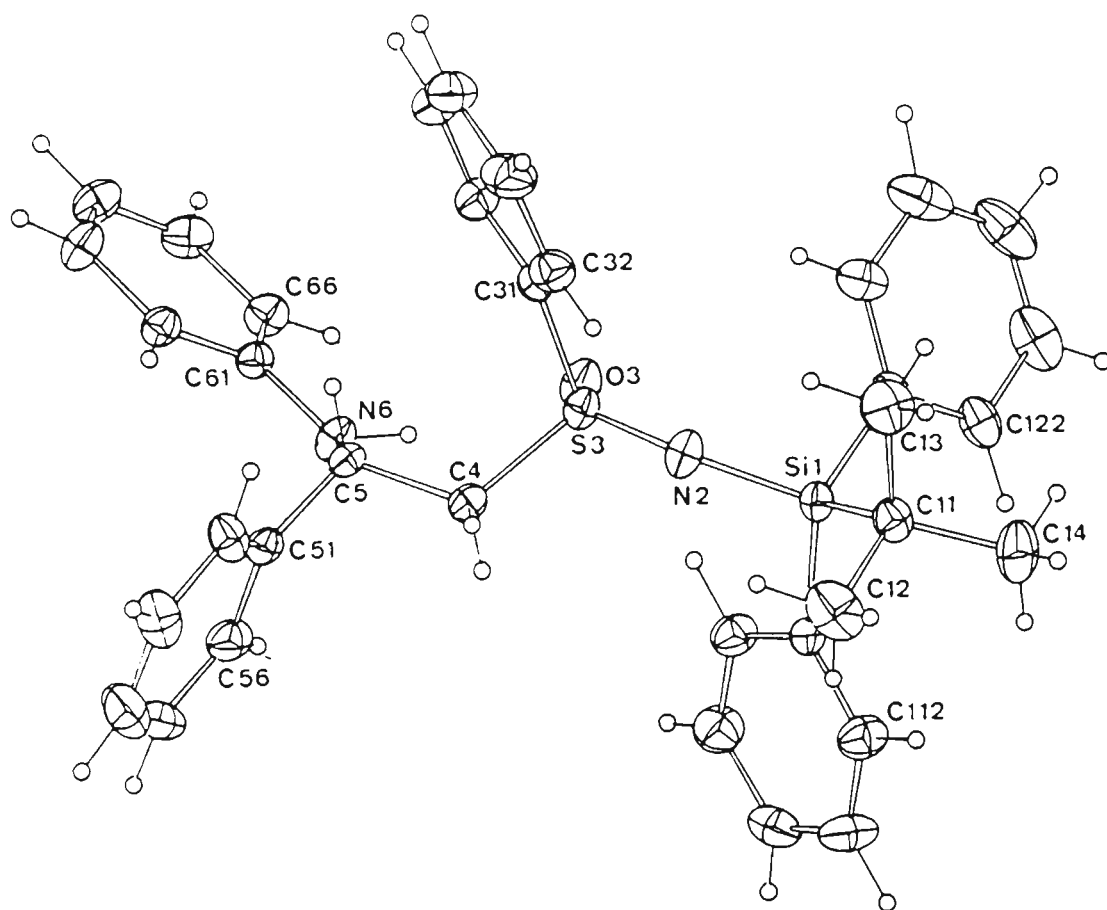


Adduct		C <sub>1</sub>	C <sub>2</sub>
R <sub>1</sub>	R <sub>2</sub>		
2-furyl	Ph	62.96	48.83
Et	Ph	63.39	59.14
i-Pr	Ph	59.71	52.36
i-Bu	Ph		
Bu	t-Bu		
		65.60	50.91
t-Bu	Ph		
Ph	t-Bu		
Ph	Me	65.52	59.06
Ph	Ph	66.73	55.29

Compound 2.6e gave suitable crystals for x-ray structure analysis. The x-ray structure (Figure 2.5) of 2.6e shows this compound has the S\*, R<sub>s</sub>\* relative stereochemistry and adopts an

intermolecularly H-bonded boat conformation in the crystalline state. The H-bonding occurs between the NH of the amino group and the oxygen of the sulfoximine moiety. The dihedral angles between protons  $H_a$  and  $H_c$  and  $H_b$  and  $H_c$  were approximately  $173^\circ$  and  $71^\circ$ .

Figure 2.5. ORTEP drawing of the x-ray structure of 2.6e.

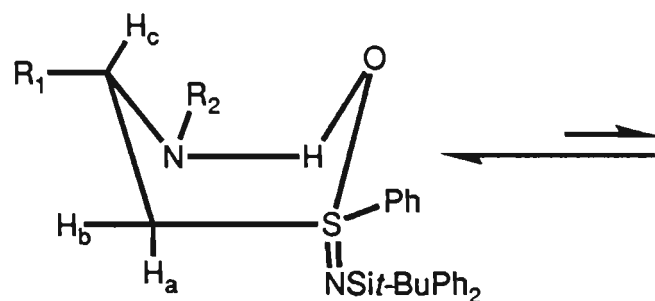


The two possible intramolecularly H-bonded conformations for adducts with the  $S^*$ ,  $R_S^*$  relative stereochemistry, the chair and

boat conformation A and B are shown in Scheme 2.5. The  $^1\text{H}$  NMR coupling constants of the diastereotopic methylene protons in 2.6e ( $J_{ac} = 10.52\text{Hz}$ ,  $J_{bc} = 2.25\text{Hz}$ ) are consistent with the boat conformation in solution; similar to that found in the solid state (Figure 2.5) rather than the chair conformation B in which  $J_{ac}$  and  $J_{bc}$  would be expected to be 2-5 Hz (Scheme 2.5 ). The chair conformation B would be expected to be energetically less favourable because of severe 1,3-diaxial like steric interaction between  $R_1$  (Ph) and the N-tert-butyldiphenylsilyl moiety. It is highly likely that 2.6e exists as an equilibrium mixture of the boat and chair conformations A and B in solution and one observes a time average  $^1\text{H}$  NMR spectrum of these two forms. Clearly, in the case of 2.6e this equilibrium must favour the boat conformation A.



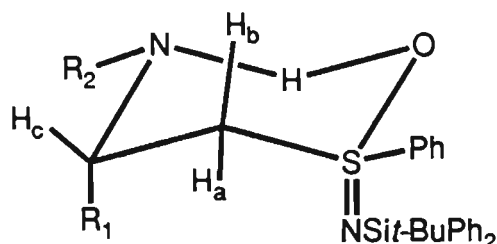
**Scheme 2.5. Possible chair and boat conformations for the adducts 2.6 and 2.7.**



$(S^*, R_S^*)$  boat conformation A

Expected  $J_{ac}$  Z 8-13 Hz

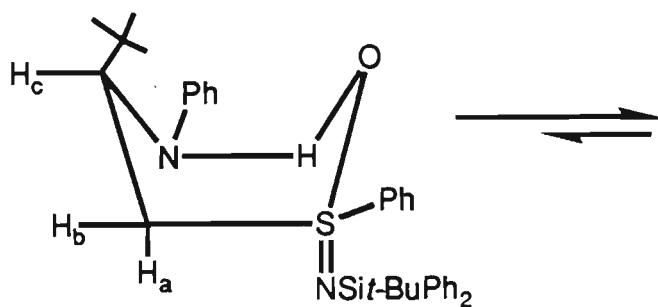
Expected  $J_{bc}$  Z 2-5 Hz



$(S^*, R_S^*)$  chair conformation B

$J_{ac}$  Z 2-5 Hz

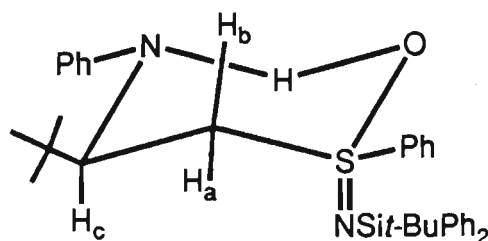
$J_{bc}$  Z 2-5 Hz



$(R^*, R_S^*)$  boat conformation C

Expected  $J_{ac}$  Z 2-5 Hz

Expected  $J_{bc}$  Z 2-5 Hz



$(R^*, R_S^*)$  chair conformation D

$J_{ac}$  Z 2-5 Hz

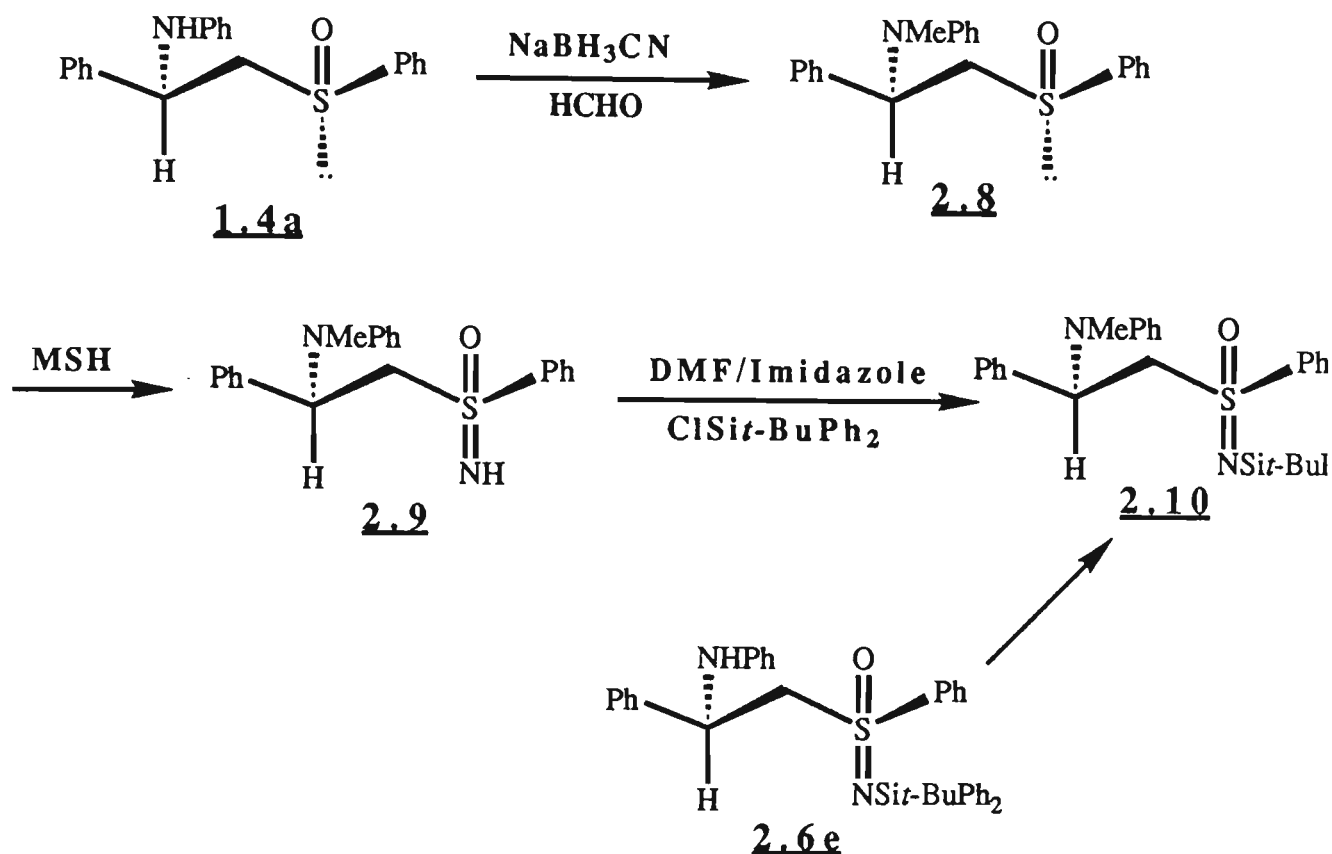
$J_{bc}$  Z 8-13 Hz

Similar coupling constants for  $J_{ac}$  and  $J_{bc}$  are observed for compounds 2.6c, 2.6d and 2.6g-2.6k (Table 2.3) in which  $J_{ac}$  ranges from 7.3 - 10.7 Hz and  $J_{bc}$  ranges from 1.5-5.2Hz. The  $^1\text{H}$  NMR spectra of these compounds is consistent with the  $S^* R_S^*$  relative stereochemistry and an internal H-bonded boat conformation. The  $^1\text{H}$  NMR spectra of 2.6a-2.6d appear anomalous ( $J_{ac}$  = 3.7 - 5.0 Hz,  $J_{bc}$  = 6.7-7.6 Hz), however when  $R_1$  is relatively small the chair-boat conformation equilibrium may favour more of the chair form

in which  $R_1$  is pseudo-axial, thus  $J_{ac}$  and  $J_{bc}$  are approximately the same magnitude. On the basis of the above arguments one would expect 2.6f ( $R_1 = t\text{-Bu}$ ,  $R_2 = \text{Ph}$ ) to highly favour the boat conformation. The  $^1\text{H}$  NMR coupling constants for this compound  $J_{ac} = 5.4$  Hz and  $J_{bc} = 7.2$  Hz are clearly not consistent with this conformation. Compound 2.6f may prefer a non-hydrogen bonded conformation or have the  $R^*$ ,  $R_s^*$  relative configuration.

Prior to obtaining suitable crystals for x-ray crystallographical analysis of the relative stereochemistry of the major adduct 2.6e was established by means of a chemical correlation between 2.6e and the major diastereomeric adduct from the addition of lithiated methyl phenyl sulfoxide and N-benzylideneaniline (Chapter 1).

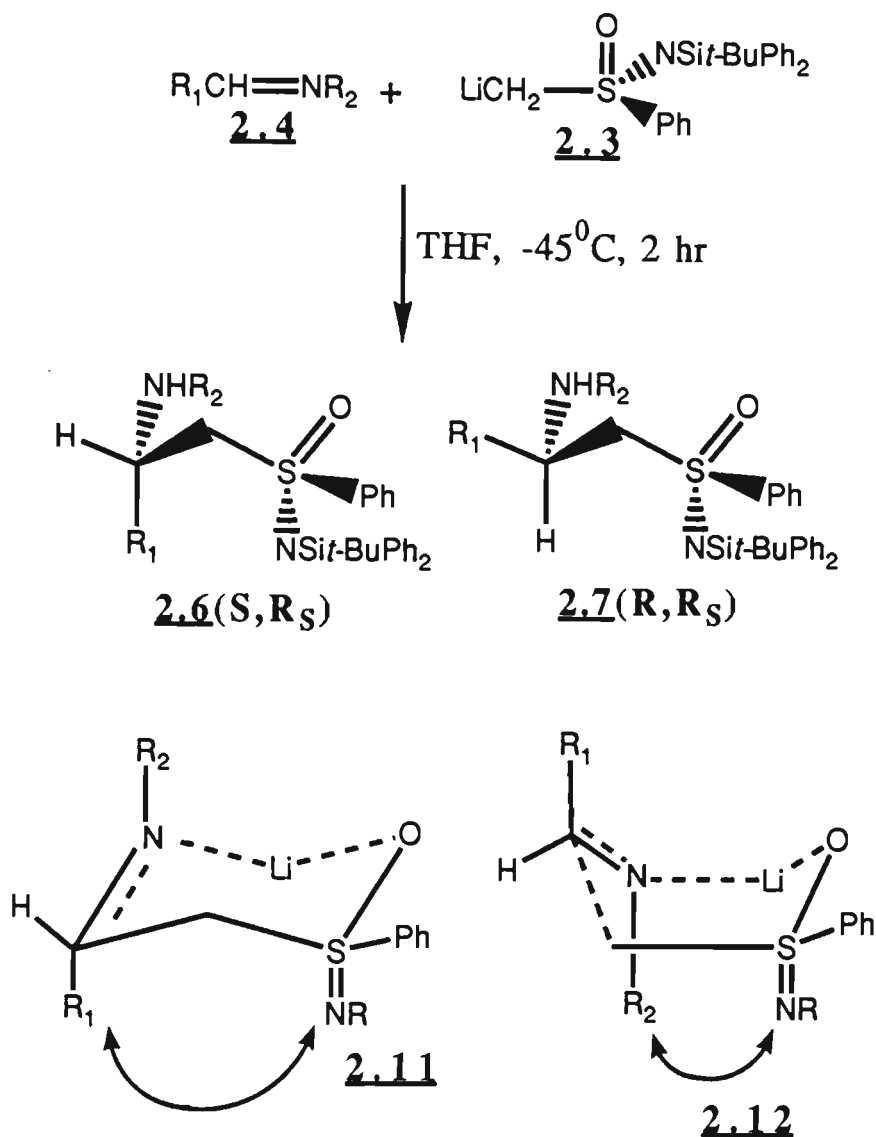
The adduct 1.4a (Scheme 2.6) which was generated from N-benzylideneaniline and lithiated methyl phenyl sulfoxide (Chapter 1) was N-methylated quantitatively using sodium cyanoborohydride and formaldehyde as described by Borch<sup>73</sup>. The resulting N-methylated compound 2.8 was treated with mesitylenesulfonylhydroxylamine<sup>81</sup> (MSH) to generate the sulfoximine<sup>83</sup> 2.9 in 30% yield. It was considered necessary to methylate the  $\beta$ -nitrogen substituted first due to the documented reactivity of MSH (mesitylene sulfonylhydroxylamine) towards secondary amines.<sup>82</sup>

Scheme 2.6. Chemical correlation of 1.4a and 2.6e.

The sulfoximine was then silylated with *t*-butylchlorodiphenylsilane in 95% yield<sup>79</sup>. The sulfoximine adduct 2.2e (entry 5, Table 2.2) was also N-methylated as described above. The  $^1\text{H}$  NMR of 2.10 prepared from either 1.4a or 2.6e were identical. Although the stereochemistry of 2.6e has been unequivocally determined by x-ray structural analysis, this correlation confirms the initial structural assignment made by Tsushihashi for  $\beta$ -amino sulfoxide 1.4. Since 2.10 is a tertiary amine and therefore can not form internally bonded structure, it must have different conformation to 2.6e. This is evident in the difference in their  $^1\text{H}$  NMR. The  $^1\text{H}$  NMR of 2.10 showed  $\text{H}_\text{C}$  at 3.95ppm with coupling constants  $J=1.52, 10.07$  Hz while 2.6e showed  $\text{H}_\text{C}$  at 4.48ppm with coupling constants  $J=2.92, 10.53$  Hz.

Since imines must have E geometry, only two possible chelated cyclic transition states are available for the reaction of lithiated N-tert-butyldimethylsilyl-S-methyl-S-phenylsulfoximine and imines, that is the chair and boat transition states 2.12 and 2.11 (Scheme 2.7). The preference for diastereomeric adduct 2.6 over 2.7 suggests that chair transition state 2.11 is favoured over the boat transition state 2.12. It would be expected that the pseudo 1,3-diaxial like interaction between R<sub>1</sub> and the large N-tert-butyldiphenylsilyl moiety in 2.11 would become more severe as the size of R<sub>1</sub> increases and therefore destabilizing transition state 2.11 over 2.12. In agreement with this we see that for the reaction of lithiated 2.3 with imines (RCH=NPh, where R<sub>1</sub> = alkyl) the product diastereoselection decreases as the size of substituent R<sub>1</sub> increases (Table 2.2, entries 1-6). When R<sub>1</sub> is relatively small (R<sub>1</sub> = Et, i-Bu, entries 1 and 2) high product diastereoselection (95:5) is observed in agreement with proposed mechanism. When R<sub>1</sub> becomes sterically demanding (R<sub>1</sub> = i-Pr, t-Bu, Table 2.2, entries 3 and 6) the reaction proceeds with lower diastereoselectivity (90:10 and 79:21 respectively). Interestingly, when R<sub>1</sub> is phenyl, we observe an increase in diastereoselectivity as R<sub>2</sub> becomes more

Scheme 2.7.



sterically demanding ( $\text{R}_2 = \text{Me}, \text{Ph}, t\text{-Bu}$  entries 5, 8 and 9 respectively). As we increase the steric demand of  $\text{R}_2$  from  $\text{R}_2=\text{Me}$  to  $\text{R}_2=t\text{-Bu}$  the diastereoselection increases from 89:11 to 96:4, this would suggest that boat transition state **2.12** is destabilised relative to **2.11** as the steric interaction between  $\text{R}_2$  and large *N-tert*-butyldimethylsilyl moiety increases.

## THE REACTIONS OF N-SUBSTITUTED-S-METHYL-S-PHENYLSULFOXIMINES TO ALDEHYDES.

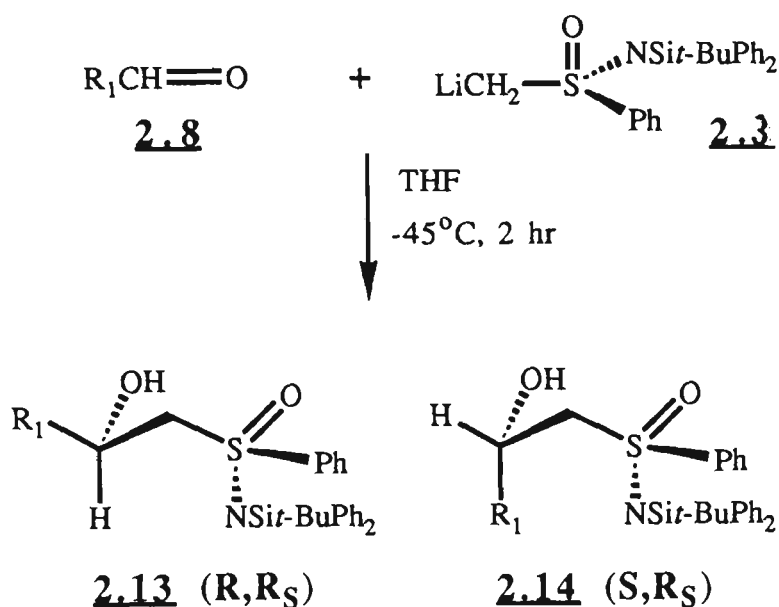
Like imines, very little work has been done on the reaction between lithiated sulfoximines and aldehydes and only several examples are found in literature.<sup>61,62,64</sup> In contrast to our work with imines, Hwang<sup>64</sup> reported that the 1,2 addition of lithiated N-trimethylsilyl-S-methyl-S-phenylsulfoximine to aldehydes was insensitive to the steric bulk of the aldehyde substituent (R) (Table 13 in the introduction). However, the variation in the size of the N-trialkylsilyl group had a considerable influence on the diastereoselection<sup>64</sup> (Table 14 in the Introduction). The relative stereochemistry of the major diastereomeric adduct formed from acetaldehyde and lithiated N-trimethylsilyl-S-methyl-S-phenylsulfoximine was determined by a single crystal x-ray structure analysis.

Johnson<sup>61</sup> found that lithiated N,S-dimethyl-S-phenylsulfoximine underwent reaction with benzaldehyde with a diastereoselectivity of 3:1, while reaction with heptanal and 3-methylbutanal gave a 3:2 and 5:2 mixture of diastereomers respectively.

In our study of the reactions of lithiated N-tert-butyldiphenylsilyl-S-methyl-S-phenylsulfoximine with aldehydes were conducted at -78°C for a period of 15 mins (Table 2.5, entries 1-5) except for pivaldehyde (entry 6) which was allowed to react for 5 hrs in order to optimise the yield. The crude reaction mixture was analysed by <sup>1</sup>H NMR (400 MHz). This analysis showed a good diastereoselectivity for all the aldehydes studied (Table 2.5). The yields were found to be good to excellent after purification of the

crude product by column chromatography on silica gel, ranging from 74% (entry 2) to 98% (entry 6, Table 2.5).

**Table 2.5. Diastereoselective addition of lithiated 2.3 to aldehydes 2.8**

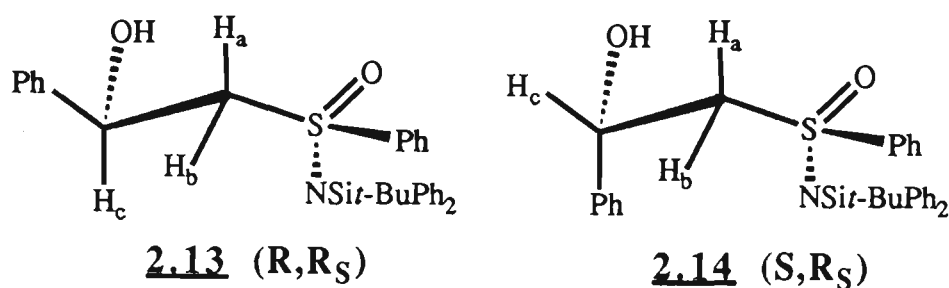


Entry	Aldehyde R <sub>1</sub>	Time	Yield/%	<u>2.13</u> : <u>2.14</u>
1	(a) Et	15 min	82	92 : 8
2	(b) i-Pr	15 min	74	93 : 7
3	(c) i-Bu	15 min	79	96 : 4
4	(d) t-Bu	15 min	86	91 : 9
5	(e) Ph	15 min	89	91 : 9

The assignment of the major diastereomeric product was made by analogy with the work of Hwang.<sup>64</sup> Table 2.6 shows the chemical shifts and coupling constants for the aldehyde adducts from which it is clear that compounds 2.13a-c and 2.13e must have the same relative stereochemistry and adopt the same conformation. The magnitude of the coupling constant is consistent with a H-bonded chair conformation (Figure 2.9) in which  $J_{ac}$  would be expected to be 8-13 Hz ( $\phi_{ac\text{ca}}$  180°) and  $J_{bc}$  to be 2-3Hz ( $\phi_{ac\text{ca}}$

90°). Table 2.7 shows the  $^{13}\text{C}$  NMR chemical shift assignments for the adducts 2.13.

Table 2.6.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) data of adducts 2.13.

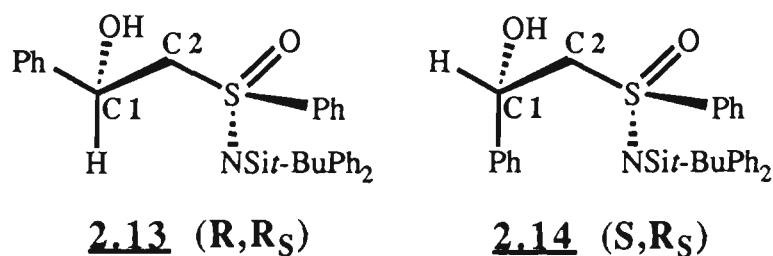


Entry	<u>2.13</u> R <sub>1</sub>	H <sub>a</sub> <sup>*</sup>	H <sub>b</sub> <sup>*</sup>	H <sub>c</sub> <sup>*</sup>	J <sub>ac</sub> <sup>+</sup>	J <sub>bc</sub> <sup>+</sup>	J <sub>ab</sub> <sup>+</sup>
1	(a) Et	3.08	3.06	3.76	8.24	1.98	13.58
2	(b) i-Pr	3.08	3.08	3.59			
3	(c) i-Bu	3.10	3.06	4.09	8.85	2.29	13.73
4	(d) t-Bu	3.16	3.01	3.59	< 1	10.08	13.58
5	(e) Ph	3.35	3.22	5.07	10.23	1.67	13.89

\* Chemical shifts in ppm from TMS.

+ Coupling constants in Hz.

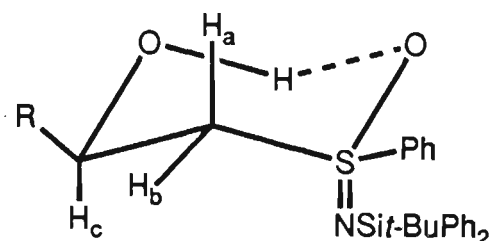
Table 2.7.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) data of the adducts 2.13.



Entry	<u>2.13</u> R <sub>1</sub>	C <sub>1</sub> p p m	C <sub>2</sub> p p m
1	(a) Et	65.78	63.74
2	(b) i-Pr	70.37	63.43
3	(c) i-Bu	65.90	64.22
4	(d) t-Bu	73.27	62.52
5	(e) Ph	66.99	65.78



Figure 2.9.

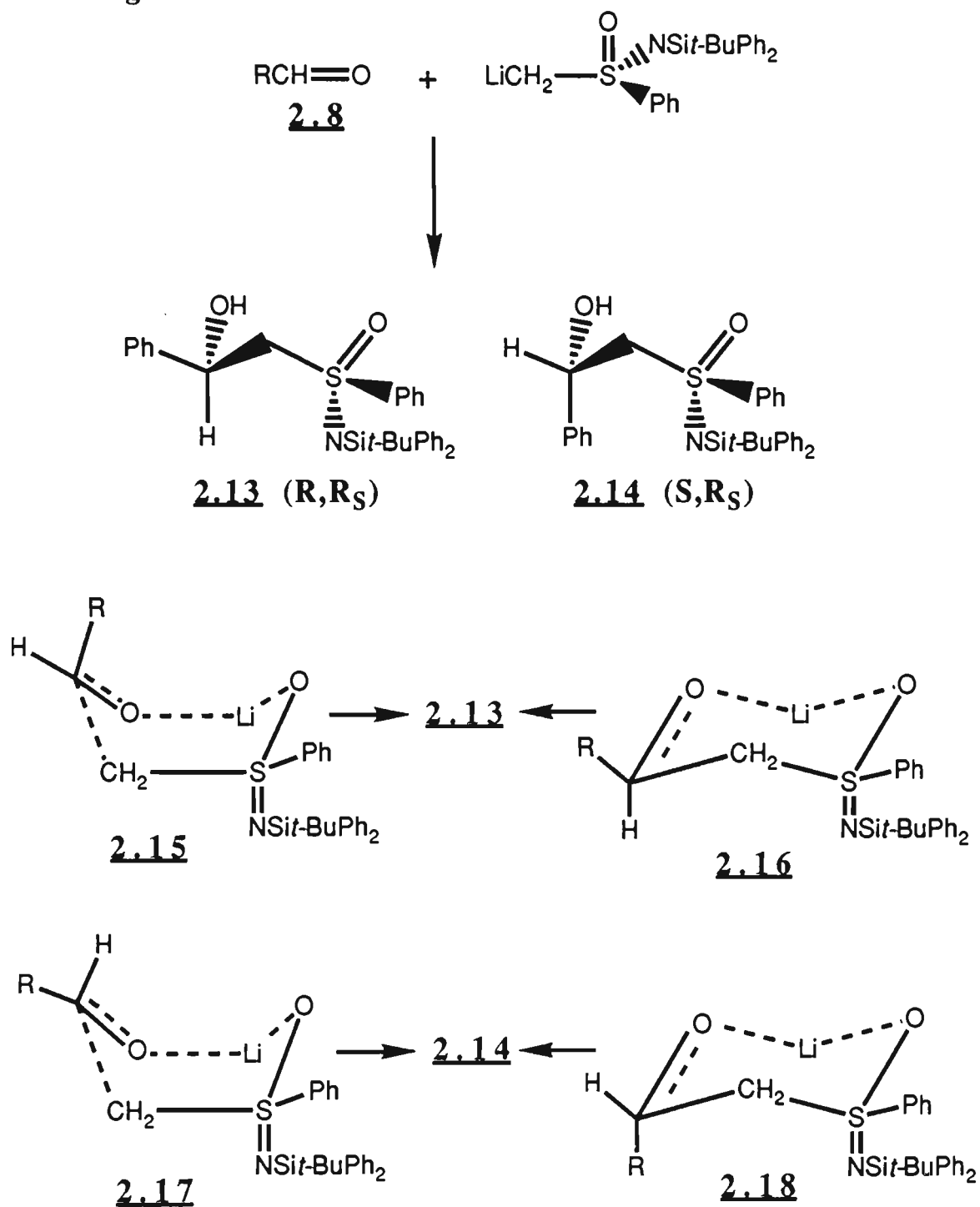


The  $^1\text{H}$  NMR of the pivaldehyde adduct (2.13d) shows similar vicinal coupling constants for the diastereotopic protons  $\text{H}_a$  and  $\text{H}_b$ , however the relative chemical shifts of these protons are reversed. However since the difference in chemical shifts between  $\text{H}_a$  and  $\text{H}_b$  in the other adducts is very small the pivaldehyde adduct probably also adopts an analogous H-bonded chair conformation and has the same relative stereochemistry.

The preference for the diastereomeric adduct 2.13 over 2.14 can be accounted for by the chair transition state 2.16 in which the aldehyde substituent R is pseudo-equatorial. The boat transition state 2.15 would be expected to be less energetically less favoured due to a steric interaction between the oxygen substituent of the sulfoximine and the R substituent of the aldehyde. The chair transition state 2.18 in which R is pseudo-axial would be expected to be energetically less favoured than the other chair and boat transition states due to a severe 1,3-diaxial like steric interaction between R and the  $t\text{-BuPh}_2\text{SiN}$  group on sulfur. This is what both Hwang's and our own study confirm. Since the diastereoselectivity is largely independent of the size the aldehyde substituent (R), it is likely that the reaction occurs via the transition states 2.16 and 2.17 in which there is little steric interaction between (R) of the

aldehyde and the large substituent ( $t\text{-BuPh}_2\text{SiN}$ ) on sulfur. The mechanism for this reaction, however, remains speculative.

**Figure 2.10.**



## **EXPERIMENTAL**

### **Ethyl o-(mesitylenesulfonyl)-acetohydroxamate<sup>81</sup>**

To a solution ethyl acetoxhydroxamate (3.4g, .033 mol) and triethylamine (3.3g, .033 mol) in DMF (90 ml) at 0°C was slowly added mesitylbenesulfonyl chloride (7.2g, .033 mol) and the solution was stirred for 40 min and then poured on ice water. The crystals were collected, dissolved in ether and washed with water. The ether layer was dried (MgSO<sub>4</sub>) and evaporated and the resulting solid recrystallized from hexane to yield 6.8g (74%).

### **O-mesitylenesulfonylhydroxylamine (MSH)<sup>81</sup>**

To a solution of ethyl O-(mesitylenesulfonyl)-acetoxhydroxamate (7.5g) in dioxane (5ml) at 0°C was added 70% perchloric acid (3 ml) dropwise over 10 min and stirring continued for further 10 min. The resulting mixture was then poured on ice water, the crystals were collected, crushed with water and dissolved in minimum volume of diethyl ether and organic layer washed with water and poured onto cold hexane. The resulting MSH crystals were collected subjected to drying under low pressure (2 mm) for 5 min and stored in a plastic container at -25 °C. The yield was 6.98g (50%).

### **S-Methyl-S-phenylsulfoximine(2.1)<sup>77</sup>**

To a solution of methyl phenyl sulfoxide (10g, .071 mol) and sodium azide (5.54g, .085 mol) in chloroform (78ml) at 0°C was added slowly conc. sulfuric acid (19.5ml) and the solution was warmed to 40-45°C and stirred over night. The reaction mixture was then cooled and ice water (200ml) was added to dissolve the salts and then extracted with DCM. The organic layer was dried

(MgSO<sub>4</sub>), evaporated and the resulting solid recrystallized from ethanol to yield 10g (91%) of 2.1 as a white solid m.p. 180-181°C (lit.<sup>77</sup> m.p. 182°).

### **N,S-Dimethyl-S-phenylsulfoximine<sup>77c</sup> 2.2**

A mixture of S-methyl-S-phenylsulfoximine (2.1, .93g), 40% formaldehyde (9.3ml) and formic acid (4.65ml) was refluxed for 8hr. The cooled mixture was basified with solid Na<sub>2</sub>CO<sub>3</sub> and extracted with DCM. The organic layer was dried (MgSO<sub>4</sub>) and evaporated to yield N,S-Dimethyl-S-phenylsulfoximine 0.96g, 95%. M.p. 30-31°C, lit.<sup>77c</sup> m.p. 32-34°C. <sup>1</sup>H NMR 7.9-7.1 (m, 5H), 3.08 (s, 3H), 2.56 (s, 3H).

### **N-(tert-Butyldiphenylsilyl)-S-methyl-S-phenylsulfoximine (2.3). (Procedure 1)**

To a methyl phenyl sulfoximine 2.1 (3.3g, .0213 mol) in dry pyridine (30ml) at 0° was added tert-Butylchlorodiphenylsilane (6.41g, .0234 mol) and the solution was stirred at room temperature for 12 hrs. Water (5ml) was then added and stirring continued for 30 min following which the solution was extracted with ether, the ether layers were washed with water (6X) and dried (MgSO<sub>4</sub>). Column chromatography on silica gel in 2% ethyl acetate in hexane gave pure 2.3 (4.2g, 83%) m.p. 54-55°C. <sup>1</sup>H NMR 7.93(d, 2H, J=7.02Hz), 7.76 (d, 2H, J=7.78Hz), 7.71(d, 2H, J=6.41), 7.55-7.2(m, 9H), 2.85(s, 3H), 1.09(s, 9H), <sup>13</sup>C NMR 135.51, 132.04,

128.92, 128.75, 127.32, 126.84, 48.96, 27.12, 19.31. MS (CI +ve), 393(M+H<sup>+</sup>, 16%), 339 (100%), 316 (100%), 276 (26%), 256 (20%), 238 (26%), 212 (38%), 199 (37%), 165 (15%), 135 (18%), 123 (20%). Anal. calcd for C<sub>23</sub>H<sub>27</sub>NOSSi: C, 70.18; H, 6.91; N, 3.56 found C, 69.74; H 7.37; N, 3.62.

**N-(tert-Butyldiphenylsilyl)-S-methyl-S-phenylsulfoximine (2.3) (Procedure 2).**

To a solution of sulfoximine 2.1 (.0183 mol) and imidazole (3.1g) in 10ml DMF<sup>79</sup> at 0°C was added a solution of tert-butylchlorodiphenylsilane in 10ml DMF and resulting mixture stirred at room temperature for 15 hrs. Water (5 ml) was added and stirring continued for 30 min following which the solution was extracted with DCM. The DCM was dried (MgSO<sub>4</sub>) and evaporated. The crude product was subjected to column chromatography to yield a pure 2.3 (6.88g, 94%).

**Reaction of 2.2 or 2.3 with imines: A general procedure.**

To a solution of the appropriate sulfoximine (1 mmol) in dry THF (3 ml) at 0° was added n-BuLi in hexane (1.1 mmol). After 15 min the solution was cooled to -78°C and a solution of the appropriate imine (1.2 mmol) in THF (3ml) was added. The resulting mixture was stirred for 2 hrs at a designated temperature (Table 2.1, Table 2.2). The reaction was then quenched by the addition of 10% K<sub>2</sub>CO<sub>3</sub> (5ml) and then extracted with DCM. The combined extracts were dried (MgSO<sub>4</sub>) and evaporated. The diastereoselection of these reactions was determined from <sup>1</sup>H NMR

analysis of the crude reaction product. The crude product was purified by column chromatography on silica gel employing ethyl acetate/hexane as eluent. Yields are reported in Table 2.1 and 2.2.

**N-Methyl-N-(2-(N'-methyl)-S-phenylsulfonimidoyl)-1-phenyl) ethylamine (2.5A(e)).**

oil;  $^1\text{H}$  NMR 7.85-7.03m (m, 12H), 6.68(t,  $J=7.33$  Hz, 1H), 6.50(d,  $J=7.71$  Hz, 1H), 6.43(d,  $J=7.4$  Hz, 1H), 6.1(s, 1H, NH), 4.89\*(dd,  $J=8.24$ ,  $J<1$  Hz, 1H), 4.51(dd,  $J=10.38$ ,  $J<1$  Hz, 1H), 3.62\*(dd,  $J=10.99$ , 14.19 Hz, 1H), 3.50(dd,  $J=10.83$ , 14.49 Hz, 1H), 3.35(dd,  $J=2.45$ , 10.50 Hz, 1H), 3.20\*(dd,  $J=2.74$ , 10.03 Hz, 1H), 2.77\*(s, 3H), 2.72(s, 3H).  $^{13}\text{C}$  NMR (on diastereomeric mixture) 147.31, 141.70, 141.31, 128.24, 133.17, 133.02, 129.51, 129.07, 128.98, 127.76, 126.24, 114.44\*, 114.01, 62.71, 62.42\*, 55.11, 54.67\*, 29.37. MS (CI +ve), ( $\text{M}+\text{H}^+$ ) 351 (3%), 258 (85%), 196 (81%), 170 (100%), 156 (39%), 132 (37%), 125 (30%), 104 (40%), 91 (48%). (\* major diastereoisomer).

**N-Phenyl-N-(2-(N'-tert-butyldiphenylsilyl-S-phenylsulfonimidoyl))2-butylamine (2.6a)**

oil;  $^1\text{H}$  NMR 7.98-7.20 (m, 17H), 6.46 (d, 1H,  $J=7.4\text{Hz}$ ), 6.4 (t, 1H,  $J=7.25$ ), 3.83 (m, 1H), 3.31 (dd, 1H,  $J=5.03$ ; 13.88 Hz), 2.94 (dd, 1H,  $J=6.68$ , 13.88 Hz), 1.94 (m, 1H), 1.45 (m, 2H), 1.09 (s, 9H);  $^{13}\text{C}$  NMR 143.79, 135.68, 132.04, 129.27, 128.96, 128.88, 128.66, 127.53, 127.36, 127.27, 117.56, 113.10, 63.39, 59.14, 50.35, 27.89, 27.29, 19.44; MS (CI +ve), 527( $\text{M}+\text{H}^+$ , 5.7%), 483 (5.7%), 469 (5%), 394 (10%), 380 (20%), 316 (40%), 162 (57%), 148 (71%), 94 (100%). IR (neat) 330(br), 1400-1250(br), 1150(s), 1110(s).

**N-Phenyl-N-(2-(N'-tert-butyldiphenylsilyl-S-phenylsulfonimidoyl)4-methyl)2-pentylamine (2.6b)**

oil;  $^1\text{H}$  NMR 7.79-6.95 (m, 20H), 4.08 (m, 1H), 3.38 (dd, 1H,  $J=3.67$ , 13.58 Hz), 2.89 (dd, 1H,  $J=7.63$ , 13.58 Hz), 1.86 (m, 1H), 1.7 (m, 1H), 1.4 (m, 1H), 1.09 (s, 9H), .858 (t, 6H,  $J=9$  Hz);  $^{13}\text{C}$  NMR 145.99, 143.44, 135.42, 131.74, 129.05, 128.66, 128.31, 127.14, 127.06, 126.93, 117.26, 112.71, 27.07, 24.52, 22.96, 21.53, 19.14; MS (CI+ve ) 555 ( $\text{M} + \text{H}^+$ , 23%), 497 (100%), 336 (14.3%), 322 (23%), 288 (74%), 244 (86%), 176 (63%), 118 (51%), 106 (34%), 77 (40%); IR (neat) 3375(s), 1700(s), 1600(s), 1400-1250(br), 1150, 1110.

**N-Phenyl-N-(2-(N'-tert-butyldiphenylsilyl-S-phenylsulfonimidoyl)3-methyl)2-butylamine (2.6c)**

oil;  $^1\text{H}$  NMR 7.96-7.20 (m, 16H), 7.05 (t, 2H,  $J=3.2$  Hz), 3.77 (m, 1H), 3.41 (d, 1H,  $J=10.6$ ), 3.13 (dd, 1H,  $J=7.33$ , 14.10 Hz), 3.03 (dd, 1H,  $J=5.19$ , 14.19 Hz), 2.1 (m, 1H), 1.09 (s, 9H), .78 (d, 3H,  $J=2$  Hz), .071 (d, 3H, 2 Hz);  $^{13}\text{C}$  NMR 134.21, 130.65, 130.52, 127.66, 127.53, 127.36, 127.10, 126.10, 125.93, 125.45, 115.88, 111.63, 59.71, 52.56, 47.53, 25.82, 25.73, 16.67, 15.38; MS (CI +ve), 541 ( $\text{M} + \text{H}^+$ , 5.7%), 497 (5.6%), 483 (43%), 244 (26%), 199 (28%), 167 (100%), 148 (34%), 118 (71%), 106 (43%), 93 (63%), 78 (100%). IR (neat) 3390 (br), 1400-1250 (br), 1150 (s), 1110 (s).

**N-Phenyl-N-(2-(N'-tert-butyldiphenylsilyl-S-phenylsulfonimidoyl)-1-(2'-furyl))ethylamine (2.6d).**

oil;  $^1\text{H}$  NMR 7.8-6.01 (m, 23H), 4.78 (m, 1H), 4.76 (d, 1H, NH), 3.55 (dd, 1H,  $J=8.39$ , 14.34 Hz) 3.47 (dd, 1H,  $J=4.57$ , 14.34 Hz)), 1.09 (s, 9H);  $^{13}\text{C}$  NMR 174.99, 141.75, 135.51, 132.08, 128.92, 128.57, 127.58, 127.32, 127.23, 118.26, 113.88, 113.62, 110.28, 106.99, 91.65, 62.46, 48.83, 27.16, 19.27; MS (CI +ve), 565 ( $\text{M} + \text{H}^+$ , 2.8%), 507 (5%), 413 (10%), 378 (18%), 288 (86%), 244 (14%), 185 (100%),

94 (43%), 77 (34%)); IR (neat) 3360(s), 1400-1250 (br), 1150 (s), 1110 (s); HRMS calcd for  $C_{30}H_{27}N_2O_2SSi$ ; 507.1563, found 507.1563.

**N-Phenyl-N-(2-(N'-tert-butyldiphenylsilyl-S-phenylsulfonimidoyl)-1-phenyl)ethylamine (2.6e).**

oil;  $^1H$  NMR 7.59-6.97 (m, 2.24), 6.67 (t, 1H),  $J=6.81$ ), 6.25 (d, 7.69, 2H), 4.48 (dd, 9H,  $J=2.92$ , 10.53 Hz), 3.42 (dd, 4H,  $J=10.53$ , 14.5 Hz), 3.24 (dd, 4H,  $J=2.75$ , 14.5), 1.06 (s, 9H);  $^{13}C$  NMR 46.60, 141.53, 137.34, 135.59, 132.38, 132.08, 129.05, 128.96, 128.83, 127.53, 127.36, 126.93, 126.06, 117.95, 119.01, 66.73, 55.29, 27.25, 19.36; MS (CI +ve), 518, ( $M + H^+$ , 2.9%), 288 (80%), 195 (100%), 104 (86%), 93 (31%), 77 (51%); IR 3365 (s), 1600 (b), 1500 (s), 1900-1250 (b), 1150 (s), 1110 (s); HRMS calcd for  $C_{32}H_{29}N_2OSSi$ , 517.1770, found 517.1768.

**N-Phenyl-N-(2-(N'-tert-butyldiphenylsilyl-S-phenylsulfonimidoyl)-3,3-dimethyl)2-butylamine (2.6f).**

oil;  $^1H$  NMR 7.8-7.05 (m, 20H), 3.38 (m, 1H), 3.32 (dd,  $J=5.6$ , 12.59 Hz, 1H), 2.95 (dd,  $J=5.6$ , 12.50 Hz, 1H); 1.10 (s, 9H), 1.08 (s, 9H).

**1,2,3,4-tetrahydro-6,7-dimethoxy-1-(N-tert-butyldiphenylsilyl-S-phenyl-S-methylsulfoximidoyl]isoquinoline(2.6g).**

oil;  $^1H$  NMR 7.98-7.22 (m, 15H),  $^1H$  NMR (major):  $\delta$  6.99 9s, 1H), 6.04 (s, 1H), 4.53 (dd,  $J=8.85$ ,  $l < 3$ ), 3.39 (s, 3H), 3.66 (s, 3H), 3.51 (dd, 1H,  $J=9.31$ , 14.01), 3.31 (dd, 2.86 (m, 2H), 2.75 (m, 2H); minor 6.49 (s, 1H), 6.15 (s, 1H), 4.40 (dd, 1H,  $J=9.16$ ,  $J < 1$  Hz), 3.59 (dd,  $J=9.51$ , 12.49) 3.22 (dd,  $J=12.97$ ,  $J < 1$  Hz);  $^{13}C$  NMR 197.82, 147.34, 1433.35, 135.89, 135.38, 132.08, 128.83, 128.66, 127.75, 127.32,



127.19, 111.93, 109.33, 65.60, 55.80, 55.68, 50.91, 39.16, 28.68, 27.67, 19.27; MS (CI +ve), 585 (M +H<sup>+</sup>, 5.7%), 394 (5.7%), 322 (5.7%), 302 (8.6%), 205 (100%), 192 (74%); IR (neat) 3340 (s), 1400-1300 (br), 1250 (s), 1150 (s), 1110 (s), 1050 (s); HRMS calcd for C<sub>30</sub>H<sub>31</sub>N<sub>2</sub>O<sub>3</sub>SSi, 527.1825, found 527.1824.

**N-tert-Butyl-N-(2-(N'-tert-butyldiphenylsilyl-S-phenylsulfonimidoyl)-1-phenyl)ethylamine (2.6h)**

oil; <sup>1</sup>H NMR 7.97-7.10 (m, 20H), 5.05 (dd, J=9.01, J<1Hz), 3.35 (dd, J=10.22, 13.88, 1H), 3.22 (dd, J=1.68, 13.89, 1H), 1.13 (s, 9H), 1.09 (s, 9H); MS (CI +ve), 555(14%, M+H<sup>+</sup>), 500 (100%), 482 (50%), 378 (56%), 200 (39%); IR 3480 (br), 1400-1220 (br), 1140 (s), 1100 (s).

**N-Methyl-N-(2-(N'-tert-butyldiphenylsilyl-S-phenylsulfonimidoyl)1-phenyl)ethylamine(2.6i).**

oil; <sup>1</sup>H NMR 7.85-7.15 (m, 20H), 4.29 (s, 1H, NH), 3.95 (dd, 1H, J=1.52, 10.07 Hz), 3.45 (dd, 1H, J=10.7, 19.4 Hz), 3.10 (dd, 1H, J=1.68, 14.4 Hz), 2.11 (s, 3H), 1.07 (s, 9H); <sup>13</sup>C NMR 134.69, 134.47, 134.34, 134.16, 130.74, 128.75, 127.53, 127.27, 127.14, 126.49, 126.15, 126.02, 125.93, 125.80, 125.71, 123.286, 65.52, 59.06, 32.71, 25.77, 25.7; MS (CI +ve), 513 (M +H<sup>+</sup>, 8.6%), 455 (11%), 394 (8.6%), 322 (17%), 199 (37%), 134 (100%), 120 (63%), 91 (50%), 77 (50%).

**N-tert-Butyl-N-(2-(N'-tert-butyldiphenylsilyl-S-phenylsulfonimidoyl))-2-hexylamine (2.6j)**

oil; <sup>1</sup>H NMR 7.85-6.19 (m, 15H), 4.08 (m, 1H), 3.47 (dd, J=8.22, 13.7 Hz, 1H), 3.38 (dd, J=2.79, 13.7 Hz, 1H), 1.13 (m, 6H), 1.07 (s, 9H), .99

(s, 9H), .97 (s, 3H); IR 3480 (br), 1400-1200 (br), 1110 (s), 1090 (s).

**N-Pentyl-N-(2-(N'-tert-butyldiphenylsilyl-S-phenylsulfonimidoyl))2-hexylamine (2.6k)**

oil;  $^1\text{H}$  NMR 7.80-7.20 (m, 15H), 3.19 (dd, 1H,  $J=8.7, 14.8$  Hz), 2.95 (dd, 1H,  $J=2.2, 14.9$  Hz), 2.4 (m, 1H), 2.25 (m, 2H), 1.5-1.2 (m, 16H), 1.05 (s, 9H), .95-.75 (m, 6H);  $^{13}\text{C}$  NMR 143.35, 136.16, 135.99, 135.51, 131.91, 128.79, 128.57, 127.36, 127.19, 127.10, 64.04, 53.47, 46.32, 33.44, 29.76, 29.46, 27.16, 22.34, 19.23, 13.86; MS (CI +ve), 549 (M +H<sup>+</sup>, 100%), 491 (80%), 433 (8.6%), 322 (11%), 199 (14%), 170 (91%), 156 (20%), 127 (34%), 112 (63%), 77 (31%); IR (neat) 3320 (s), 1400-1250 (br), 1150 (s), 1110 (s); HRMS calcd for C<sub>29</sub>H<sub>39</sub>N<sub>2</sub>OSSi, 491.2552, found 491.2552.

**2-(N-methyl-N-phenylamino)-2-phenylethyl phenyl sulfoxide (2.8)**

Prepared by an identical procedure as 1.13 (Chapter 1). oil;  $^1\text{H}$  NMR 7.7-6.7 (m, 15H), 5.55 (dd,  $J=5.95, J=9.61$ , 1H), 2.68 (s, 3H);  $^{13}\text{C}$  NMR 149.90, 137.60, 131.17, 129.32, 129.12, 129.02, 128.44, 127.61, 126.88, 123.86, 118.44, 114.98, 60.81, 57.94, 32.44; MS (CI+ve), 336(M+H<sup>+</sup>, 100%), 317 (48%), 196 (100%), 118 (100%).

**N-Phenyl-N-(2-(S-phenylsulfonimidoyl)1-phenyl)ethylamine (2.9)**

Prepared by an identical procedure as 2.1 (Chapter 2). oil;  $^1\text{H}$  NMR 8.1-6.8 (m, 15H), 5.8 (dd,  $J=4.58, J=9.31$ , 1H), 3.91 (dd, 9.31, 14.35, 1H), 3.78 (dd,  $J=4.58, J=14.34$ , 1H), 2.3 (s, 3H);  $^{13}\text{C}$  NMR (in part)

59.06, 32.06, 29.63; MS (CI+ve), 244 (M-PhCHNMe, 53%), 209 (42%), 118 (100%), 91 (75%), 77 (83%).

**N-Phenyl-N-methyl-N-(2-(N'-tert-butyldiphenylsilyl)-S-phenylsulfonimidoyl)1-phenyl)ethylamine (2.10)**

Prepared by an identical procedure as 2.3 (Chapter 2). oil;  $^1\text{H}$  NMR 7.9-6.45 (m, 25H), 5.56 (dd, 1H,  $J=4.57, 8.24$  Hz), 3.80 (dd, 1H,  $J=8.24, 14.65$  Hz) 3.52 (dd, 1H,  $J=4.58, 14.65$  Hz), 3.38 (s, 3H), 1.05 (s, 9H);  $^{13}\text{C}$  NMR (in part) 61.84, 58.13, 32.44, 27.27, 19.37; MS (CI+ve), 427 (M-t-Bu-PhNMe, 54%), 378 (5.4%), 322 (6%), 302 (27%), 209 (86%), 199 (50%), 118 (100%).

**1-[N-(tert-Butyldiphenylsilyl)-S-phenylsulfonimidoyl]-2-butanol (2.13a)**

oil;  $^1\text{H}$  NMR 7.8-7.2 (m, 15H), 4.54 (br.s, 1H, OH), 3.88 (m, 1H, CH(OH)), 3.08 (dd, 1H,  $J=8.24, 13.89$  Hz), 3.06 (dd, 1H,  $J=8.24, 13.89$  Hz), 1.54-1.23 (m, 2H), 1.11 (s, 9H), 0.80 (t,  $J=7.03$  Hz, 3H);  $^{13}\text{C}$  NMR 141.32, 134.08, 130.91, 127.53, 127.27, 125.93, 125.76, 65.78, 63.74, 27.81, 25.73 ((CH<sub>3</sub>)<sub>3</sub>C), 17.80, 7.62; MS (CI+ve), 452 ( $\text{M}+\text{H}^+$ , 2.7%), 338 (19%), 316 (100%), 244 (8%), 199 (50%), 167 (8%); IR (neat) 3600-3200 (br), 1400-1240 (br), 1150 (s), 1100 (s); HRMS calcd for  $\text{C}_{27}\text{H}_{36}\text{NO}_2\text{Si}$ , 466.2235, found 4.66.222.

**2-Methyl-1-[N-tert-butyldiphenylsilyl)-S-phenylsulfonimidoyl]-2-butanol (2.13b)**

oil;  $^1\text{H}$  NMR 7.87, 7.2 (m, 15H), 4.29 (d,  $J=1.32$  Hz, 1H, OH), 3.74 (m, 1H, CH(OH));  $^{13}\text{C}$  NMR 135.46, 132.34, 128.96, 128.70, 127.36, 127.27, 127.19, 70.37, 63.43, 33.10, 27.16, 19.23, 17.71, 17.02; MS (CI+ve) 480 (100%,  $\text{M}+\text{H}^+$ ), 394 (17%,), 330 (37%,), 200 (46%,), 127

(100%,); IR (neat) 3600-3200 (br), 1400-1250 (br), 1150 (s), 1085 (w); HRMS calcd for C<sub>28</sub>H<sub>38</sub>NO<sub>2</sub>SiS, 480.2391, found 480.235.

**5-Methyl-1-[N-(tert-Butyldiphenylsilyl)-S-phenylsulfonimidoyl]-2-hexanol (2.13c)**

oil; <sup>1</sup>H NMR 7.8-7.2 (m, 15H), 4.09 (m, 1H, CH(OH)), 3.10 (dd, J=8.85, 13.73 Hz, 1H), 3.06 (dd, J=2.29, 13.73 Hz, 1H), 1.71-1.38 (m, 3H), 1.10 (s, 9H), 0.84 (d, J=7.03 Hz, 3H), 0.76 (d, J=6.16 Hz, 3H); <sup>13</sup>C NMR 135.29, 134.60, 132.21, 129.09, 128.83, 128.57, 127.27, 127.18, 127.06, 65.90, 64.22, 45.10, 30.41, 26.99, 23.82, 22.65, 21.61; MS(CI+ve) 494 (M+H<sup>+</sup>, 11.1%), 394 (1.1%), 241 (100%), 199 (30.66%), 155 (100%), 137 (69.4%); IR (neat) 3600-3200 (br), 1400-1250 (br), 1150 (s), 1110 (s), 1080 (s). HRMS calcd for C<sub>29</sub>H<sub>40</sub>NO<sub>2</sub>SiS, 494.2548, found 494.255.

**3,3-Dimethyl-1-[N-(tert-Butyldiphenylsilyl)-S-phenylsulfonimidoyl]-2-butanol (2.13d)**

oil; <sup>1</sup>H NMR 8.00-7.20 (m, 10H), 4.2 (s, 1H, OH), 3.69 (dd, 1H, J=9, J<1 Hz), 3.16 (dd, 1H, J=13.58, J<1 Hz), 3.01 (dd, 1H, J=13.58, 10.81, 2.85, (s, 3H), 1.12 (s, 9H), .76 (s, 9H); <sup>13</sup>C NMR 135.33, 132.17, 128.83, 128.57, 127.19, 127.06, 126.62, 73.27, 62.52, 48.90, 34.60, 27.25, 25.34; MS(CI+ve) 422 (M-t-Bu, 2.9%), 338 (91%), 199 (100%), 77 (77%). IR 3600-3200 (br), 1400-1250 (br), 1145 (s), 1110 (s), 1090 (w).

**2-Phenyl-1-[N-(tert-butyldiphenylsilyl)-S-phenylsulfoximinidoyl]-ethanol (2.13e)**

m.p. °C; <sup>1</sup>H NMR 5.07 (dd, J=1.67, 10.23 Hz, PhCH(OH), 1H), 3.35 (dd, J=10.23, 13.89 Hz, 1H), 3.22 (dd, J=1.67, 13.88 Hz, 1H), 1.16 (s,

9H);  $^{13}\text{C}$  NMR 141.10, 139.63, 133.99, 130.96, 127.53, 127.27, 126.48, 126.23, 125.89, 125.76, 124.02, 66.99, 65.78, 25.69 ((CH<sub>3</sub>)<sub>3</sub>C), 17.76 ((CH<sub>3</sub>)<sub>3</sub>C); MS(CI+ve) 500 (42%, M+H<sup>+</sup>), 378 (100%), 338 (44%), 200 (83%); IR (neat) 3600-3200 (br), 1400-1250 (br), 1140 (s), 1110 (s), 1090 (s); Anal. calcd for C<sub>30</sub>H<sub>33</sub>NO<sub>2</sub>SSi; C, 72.10; H, 6.66; N, 2.80 found C, 71.78; H, 7.08.

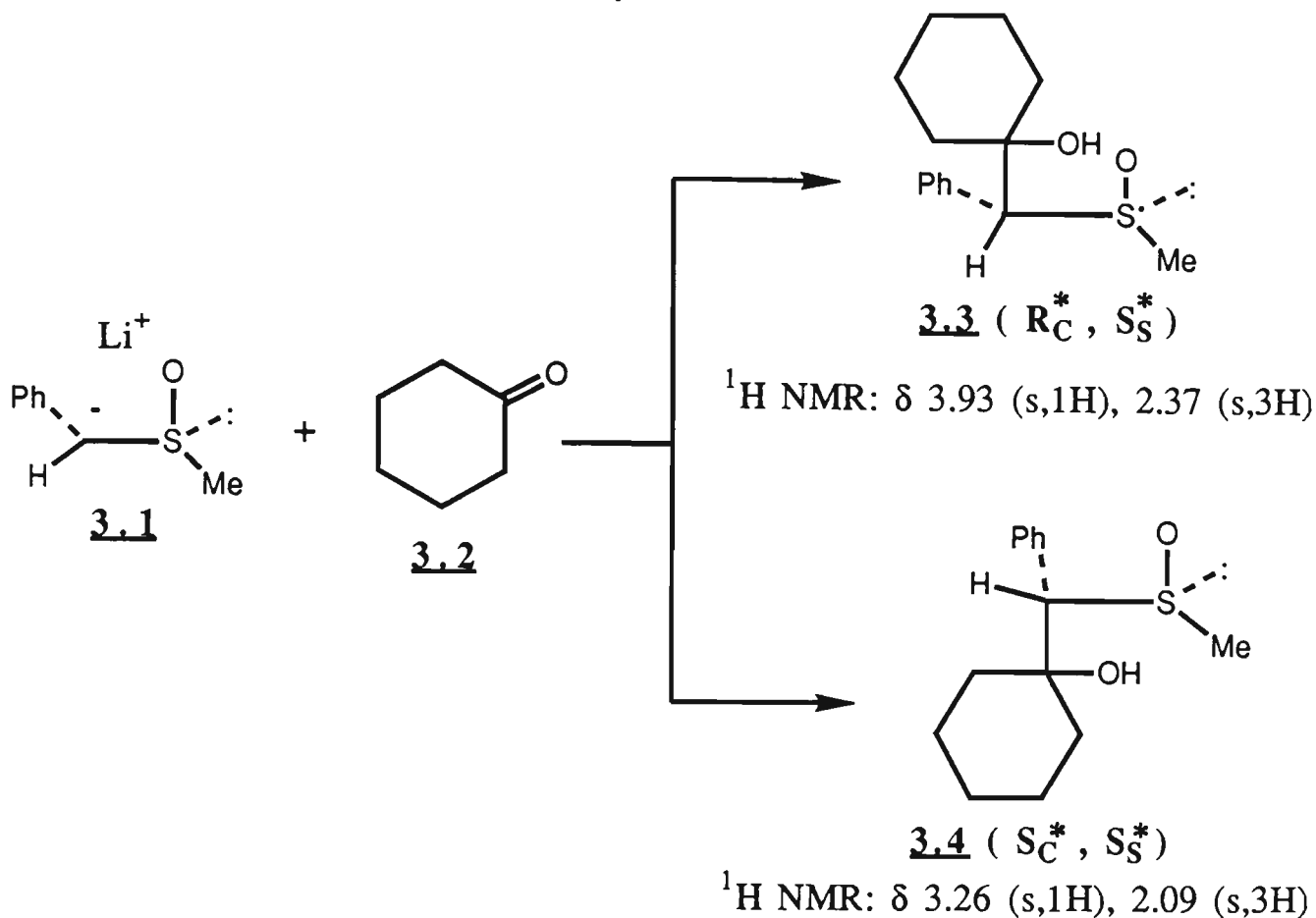
## CHAPTER 3

## DIASTEREOSELECTIVE ADDITION OF BENZYL METHYL SULFOXIDE TO IMINES AND ALDEHYDES.

Having developed the method for preparing 1-methylisoquinoline alkaloids in high enantiomeric purity <sup>70a,b,84</sup> we turned our attention to the development of the methods for preparing 1-benzylisoquinoline alkaloids by addition of the anions of benzyl sulfoxides to imines. The racemic methyl benzyl sulfoxide (3.1) was synthesized in 95% yield from methyl phenyl sulfide by oxidation with sodium periodate, while benzyl phenyl sulfoxides (3.9) was synthesized in 87% yield by oxidation of phenyl benzyl sulfide which was generated by reacting thiophenol with benzyl chloride in 0.5M potassium hydroxide ethanolic solution.

In 1970, Durst<sup>83</sup> reported that the addition of lithiated benzyl methyl sulfoxide 3.1 to cyclohexanone 3.2 gave the  $\beta$ -hydroxysulfoxide adduct with high product diastereoselection (15:1). The major diastereomeric product 3.3 had the R<sup>\*</sup>c, S<sup>\*</sup>s stereochemistry (Scheme 3.1). We have repeated this reaction and have found the two diastereomeric product 3.3 and 3.4 were formed in a ratio of 75:25 from <sup>1</sup>H NMR analysis.

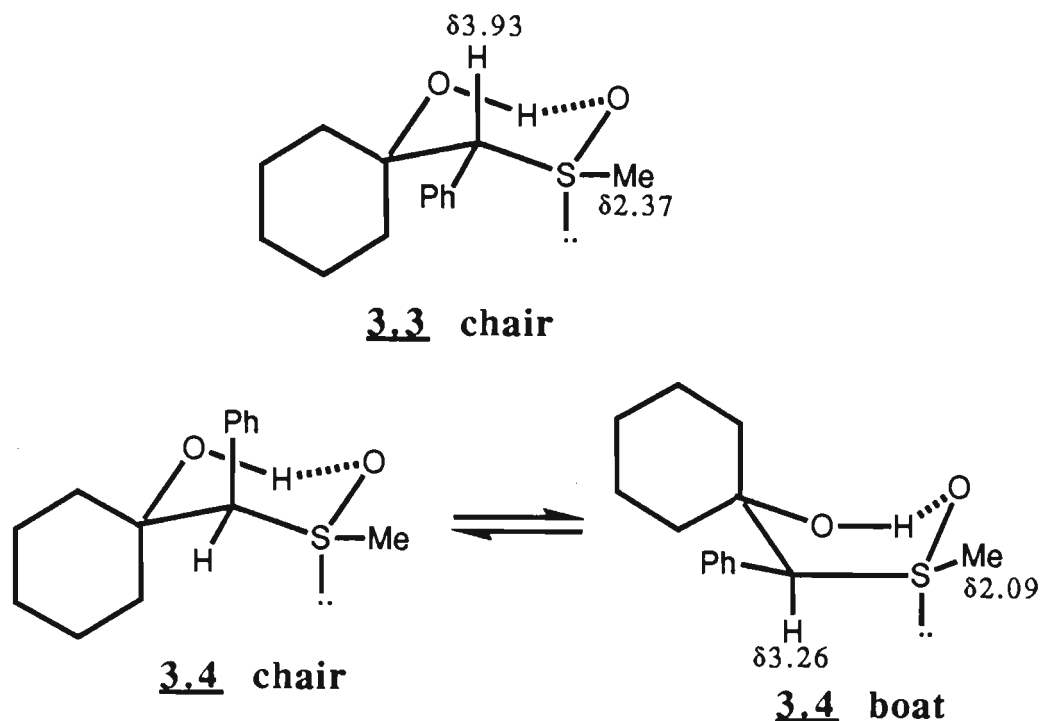
**Scheme 3.1. Diastereoselective addition of benzyl methyl sulfoxide to cyclohexanone.**



The  $^1\text{H NMR}$  of the major isomer (**3.3**) shows a signal for the SMe group at the expected chemical shift (2.37ppm) while that for **3.4** was found to be highly shielded (2.09 ppm). In benzyl methyl sulfoxide (**3.1**) itself the SMe group occurs at 2.45 ppm in the  $^1\text{H NMR}$ . The possible intramolecular hydrogen-bonded conformations for **3.3** and **3.4** are shown in Scheme 3.2.



Scheme 3.2.



Diastereomer **3.4** probably exists in the boat conformation because of the axial disposition of two substituents ( $\text{CH}_2$ , Ph) in the chair conformation. It is evident that in this conformation the SMe group in **3.4** is in the shielding region of the phenyl substituent at the stereogenic carbon. The benzylic proton in **3.3** probably resonates at lower field compared to that in **3.4** due to the deshielding effect of the two "axial" lone pairs on the carbinol and sulfoxide oxygens<sup>71</sup>. Thus the stereochemistry at the benzylic carbon can readily be determined from the chemical shift of the SMe group of these and related adducts.

Figure 3.1 is a copy of the  $^1\text{H}$  NMR of the  $\beta$ -hydroxysulfoxides in 3.3 and 3.4. We see that H-1 occurs at 3.93 and 3.26ppm. While upon addition of  $\text{D}_2\text{O}$  to the NMR sample the two hydroxy peaks disappeared. Figure 3.2 is a copy of the  $^{13}\text{C}$  NMR (aliphatic section) of the  $\beta$ -hydroxysulfoxides A and B with both diastereomers clearly visible.

Lithium sulfoxides 3.1 and 3.9 were prepared by treating the appropriate sulfoxide with n-butyllithium (1.1 equiv) in THF at  $-78^\circ\text{C}$  for 1 hr and were then quenched with either a solution of imine or suspension of imine  $\text{BF}_3$  complex for 1 hr at the temperature indicated in Table 3.1. The imine  $\cdot\text{BF}_3$  complex was prepared by stirring the imine and  $\text{BF}_3\cdot\text{etherate}$  at  $-78^\circ\text{C}$  for 15 mins. The diastereomeric ratio was determined by integration of the SMe region of the  $^1\text{H}$  NMR spectrum on the crude reaction mixture.

The  $\beta$ -amino sulfoxide adducts (3.6) were obtained after a standard aqueous work up followed by extraction into dichloromethane and column chromatography on silica gel.

Figure 3.1  $^1\text{H}$  NMR of the crude reaction mixture for the reaction of 3.1 and 3.2.

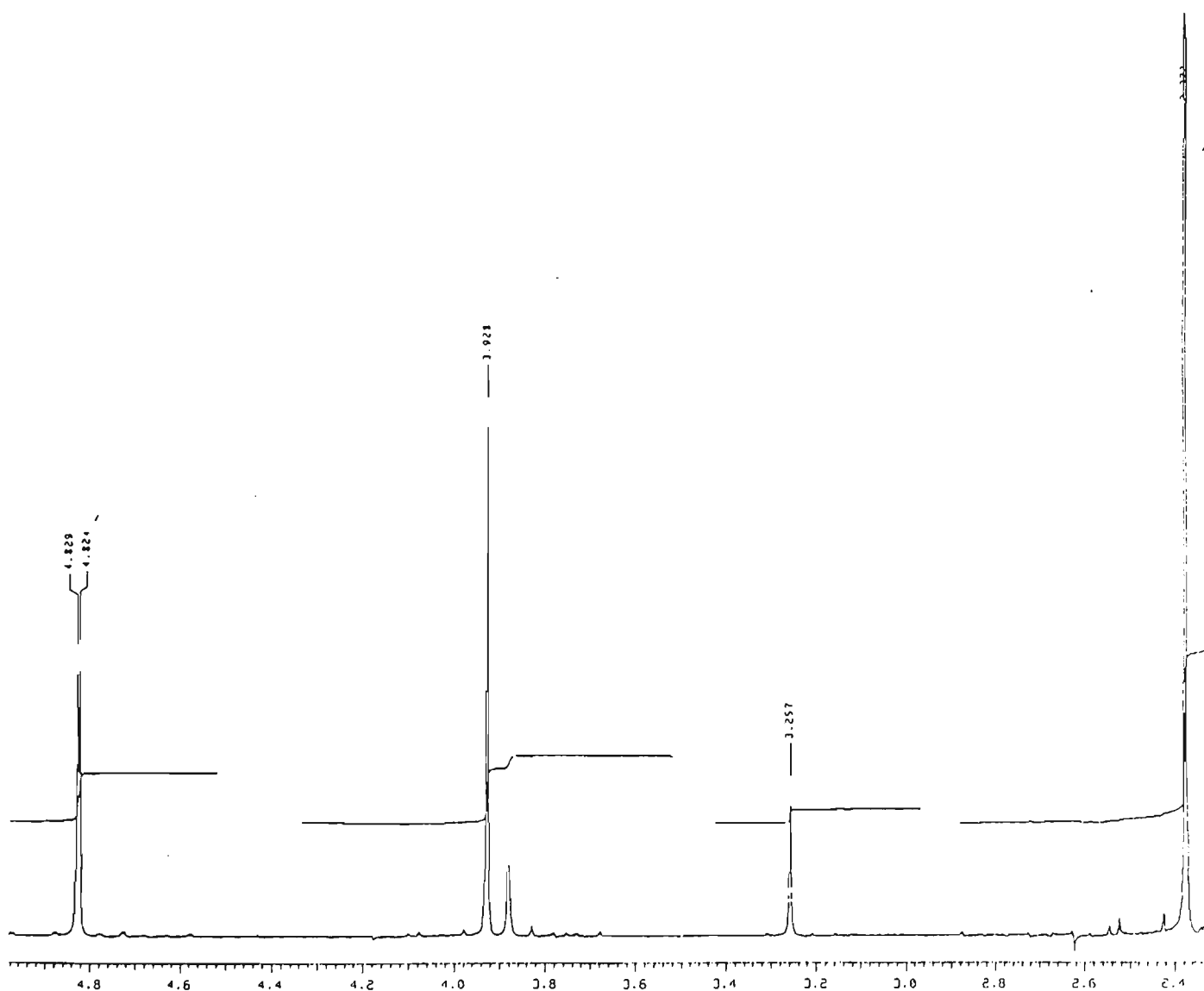
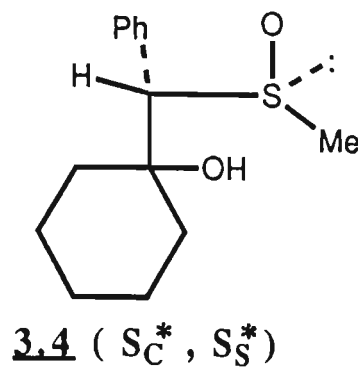
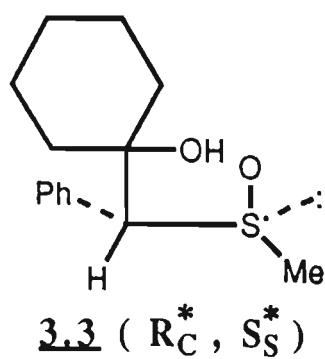
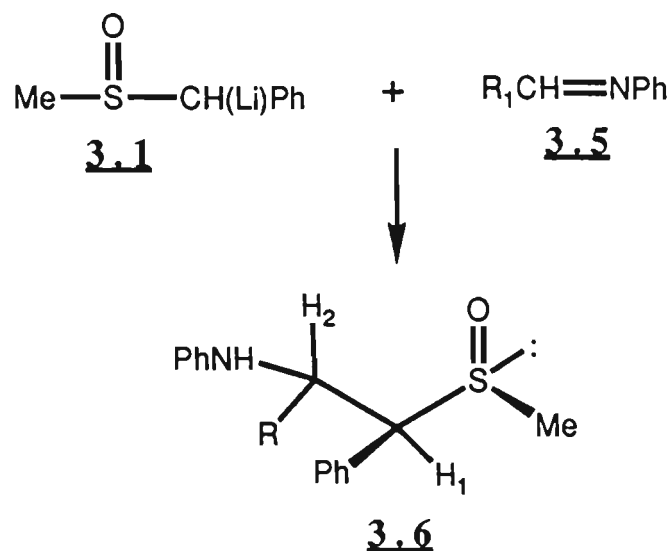


Table 3.1. Diastereoselective addition of 3.1 to imines 3.5.



R <sub>1</sub>	yield %	Temp °C
(a) 2-furyl	50	-78
(b) Ph	45	-78
(c) <i>i</i> -Pr	0	-45
(d) <i>i</i> -Pr (BF <sub>3</sub> complex)	30	-78
(e) <i>i</i> -Pent	20	-45

The yield of adducts 3.6 were in general poor ranging from minimum of 20% when 3.5 (R=*i*-Bu) to a maximum of 50% for the imine 3.5 (R=2-furyl). The reaction of lithiated benzyl methyl sulfoxide with imine 3.5 (R=*i*-Pr) gave intractable material which could not be purified. It was found necessary to complex the imine 3.5 (R=*i*-Pr) with BF<sub>3</sub>· etherate in order to effect the reaction with 3.1 as the uncomplexed imine failed to react. In each case all four possible racemic diastereomeric products were obtained. The reaction of lithiated methyl benzyl sulfoxide 3.1 with N-

benzylideneaniline 3.5 (R=Ph) proceeded in 45% yield and a product diastereoselection of 27:22:24:27. It was possible to isolate one major diastereomeric product in pure form after extensive column chromatography as a single diastereomer. The reaction of 3.1 and 3.5 (R=2-furyl) also proceeded in poor yield with a diastereoselectivity of 52:14:22:12.

Inspection of Table 3.2 shows that in one pair of diastereomers the SMe group resonates at the 'normal' chemical shift (2.3-2.4 ppm) while in the other pair the SMe is shielded (2.0-2.1 ppm). By analogy with the adducts 3.3 and 3.4 from the reaction of lithiated 3.1 and cyclohexanone, we can tentatively assign the R\*c and S\*c relative stereochemistry at the benzylic stereogenic centre to these two diastereomeric pairs respectively.

Table 3.2. Preparation and  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) data for 3.6.

$  \begin{array}{c}  \text{O} \\  \parallel \\  \text{Me}-\text{S}-\text{CH}(\text{Li})\text{Ph} \quad + \quad \text{RCH}=\text{NPh} \\  \text{3.1} \qquad \qquad \qquad \text{3.5} \\  \downarrow \\  \text{3.6}  \end{array}  $				
	<b>anti</b>	<b>syn</b>	<b>syn</b>	<b>anti</b>
<b>R= 2-furyl</b>				
Diastereomeric ratio (%)	52	12	22	14
$\delta\text{H}_1$ (ppm)	3.88	3.83	4.25	4.41
$\delta\text{H}_2$ (ppm)	5.27		5.50	
$J_{1,2}$ (Hz)	11.0	7.40	2.96	11.12
$\delta\text{SMe}$ (ppm)	2.02	2.07	2.34	2.41
<b>R= Ph</b>				
Diastereomeric ratio (%)	27	24	27	22
$\delta\text{H}_1$ (ppm)	3.50	3.92	3.71	3.33
$\delta\text{H}_2$ (ppm)	4.93	4.76	5.39	5.05
$J_{1,2}$ (Hz)	10.8	2.50	1.60	11.9
$\delta\text{SMe}$ (ppm)	1.97	2.14	2.43	2.33
<b>R= i-Pr BF<sub>3</sub></b>				
Diastereomeric ratio (%)	68	20	9	3
$\delta\text{H}_1$ (ppm)	3.30			
$\delta\text{H}_2$ (ppm)	4.25			
$J_{1,2}$ (Hz)	11.3			
$\delta\text{SMe}$ (ppm)	2.00			

As expected, each of these diastereomeric pairs was a mixture of syn and anti-isomers based upon the vicinal coupling constant  $J_{1,2}$  between the methine protons on the two stereogenic carbon atoms. Typically the syn isomer has a  $J_{1,2}$  value of around 1.6-7.4 Hz while the value for the anti isomer is typically around 11 Hz<sup>43,29</sup>.

The relative stereochemistry for these adducts is shown in Table 3.2 and is based upon the chemical shifts of the SMe group and the value of  $J_{1,2}$ . The major diastereoisomer had the (S\*,S\*,S\*) relative stereochemistry. It appears that the diastereofacial selectivity for attack at the  $\alpha$ -sulfinyl carbon occurs in the reverse sense to that for cyclohexanone and aldehydes (see later). Figures 3.3-3.7 are copies of  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra at the purified major anti adducts 3.6 (R=Ph), 3.6 (R=2-furyl) and 3.8 (R=3,4-dihydro-6,7-dimethoxyisoquinoline). The  $^1\text{H}$  NMR of adduct 3.6 (R=Ph; Figure 3.3) shows a doublet at 5.10ppm for the proton at the stereogenic carbon atom with  $J_{1,2}=11.1\text{Hz}$ . Figure 3.7 shows the adduct 3.8 with a doublet at 4.64ppm and  $J_{1,2}=10.53\text{Hz}$ .

The  $^{13}\text{C}$  NMR chemical shifts for the adducts 3.6 (R<sub>1</sub>=Ph, 2-furyl and *i*-Pr) are also very similar (Table 3.3). The SMe group for the adduct 3.6 (R<sub>1</sub>=Ph) occurs at 36.22 ppm while that of 3.6 (R=2-furyl) occurs at 36.16ppm and for 3.6 (R=*i*-Pr) occurs at 35.05ppm. In the case of 3.6(R=Ph) C-1 occurs at 54.15 ppm and C-2 at 73.23 ppm while for 3.6(R=2-furyl) C-1 occurs at 53.00 ppm and C-2 at 70.02 ppm. The Figures 3.4 and 3.6 are copies of  $^{13}\text{C}$  NMR for these two compounds.

Figure 3.3  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) for **3.6b**.

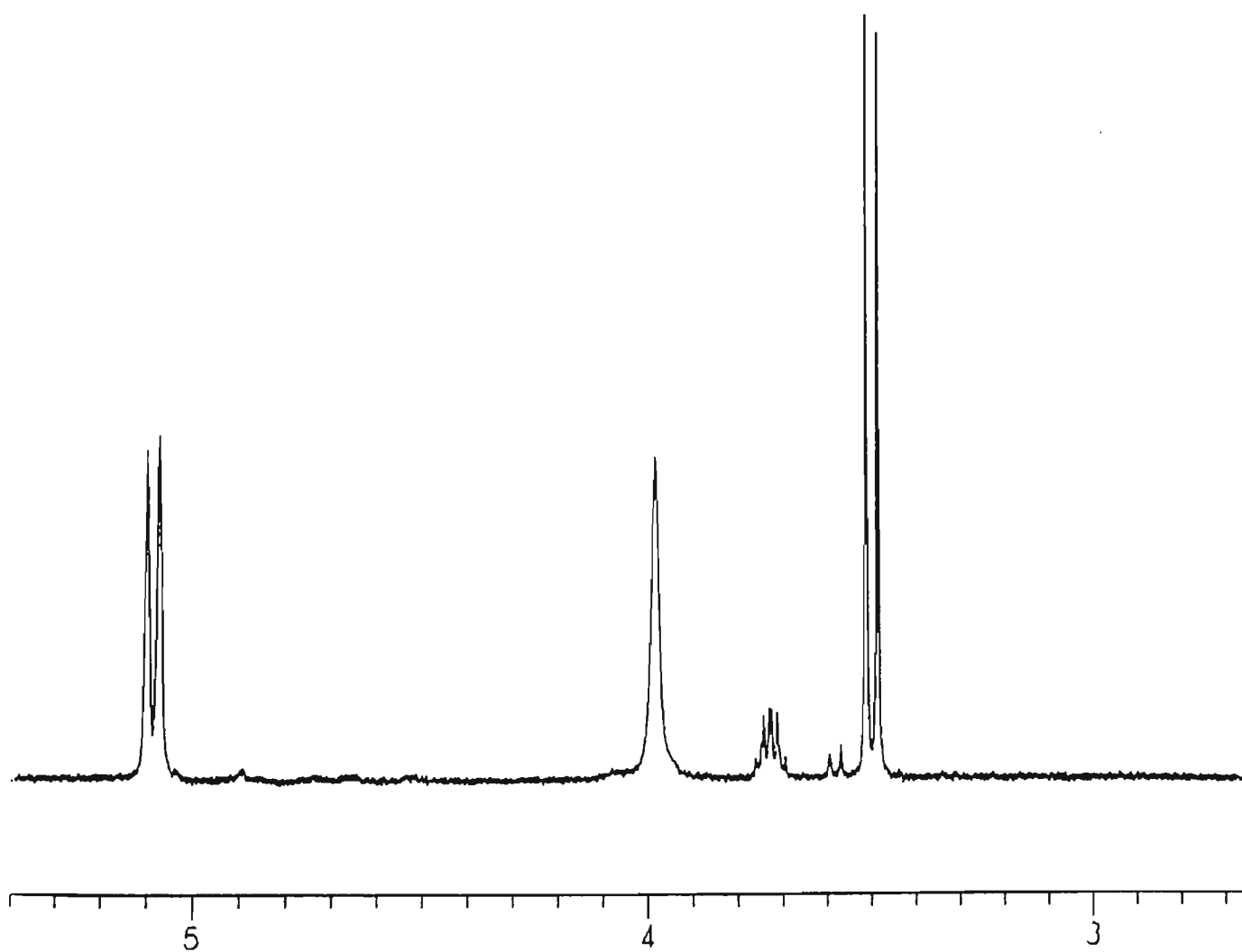
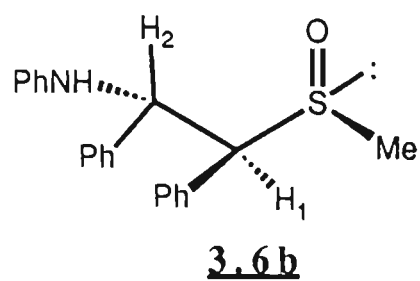




Figure 3.4  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) for 3.6b.

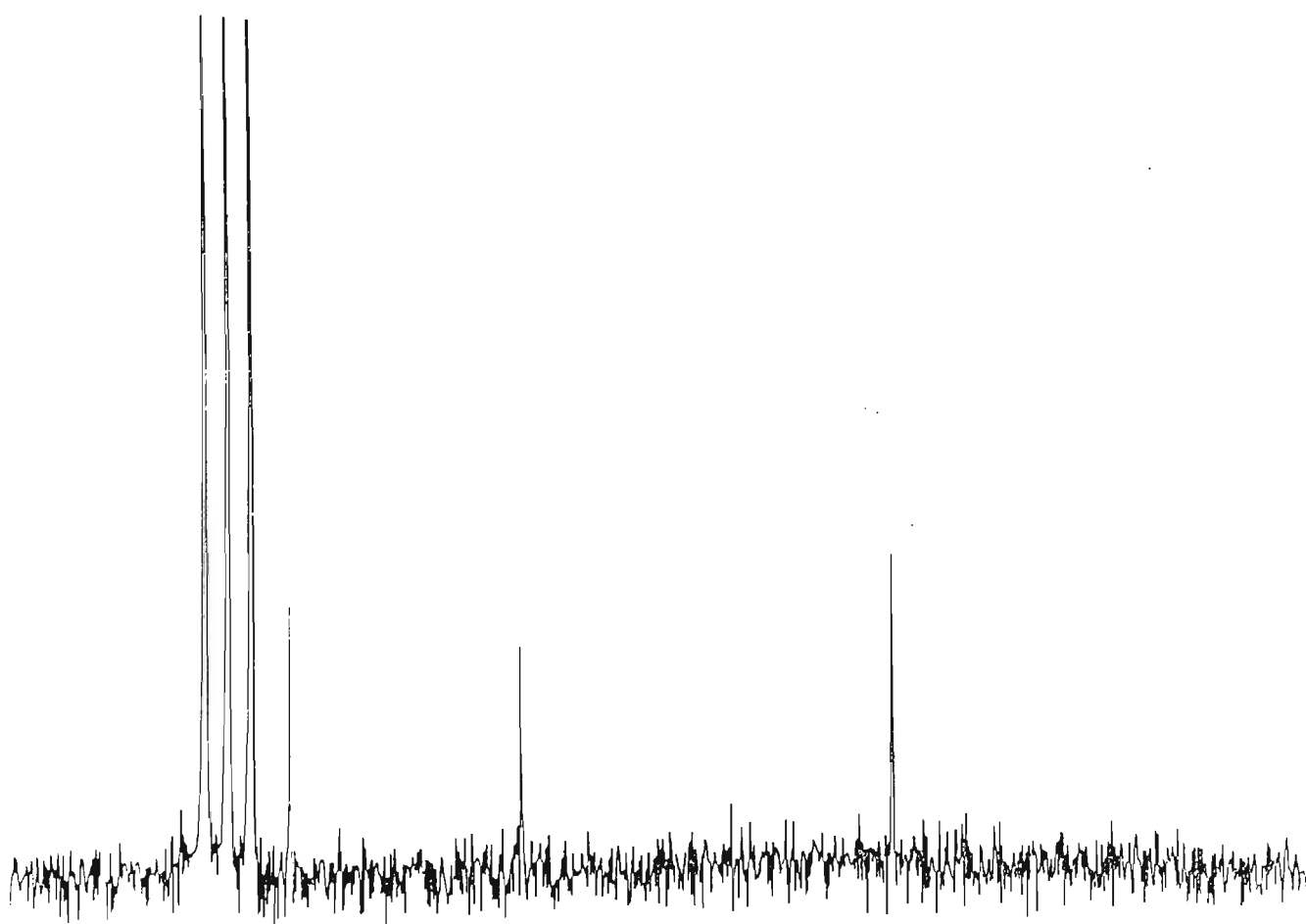
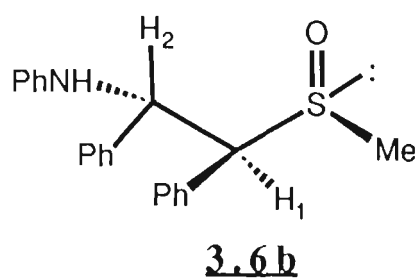


Figure 3.5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) for 3.6a.

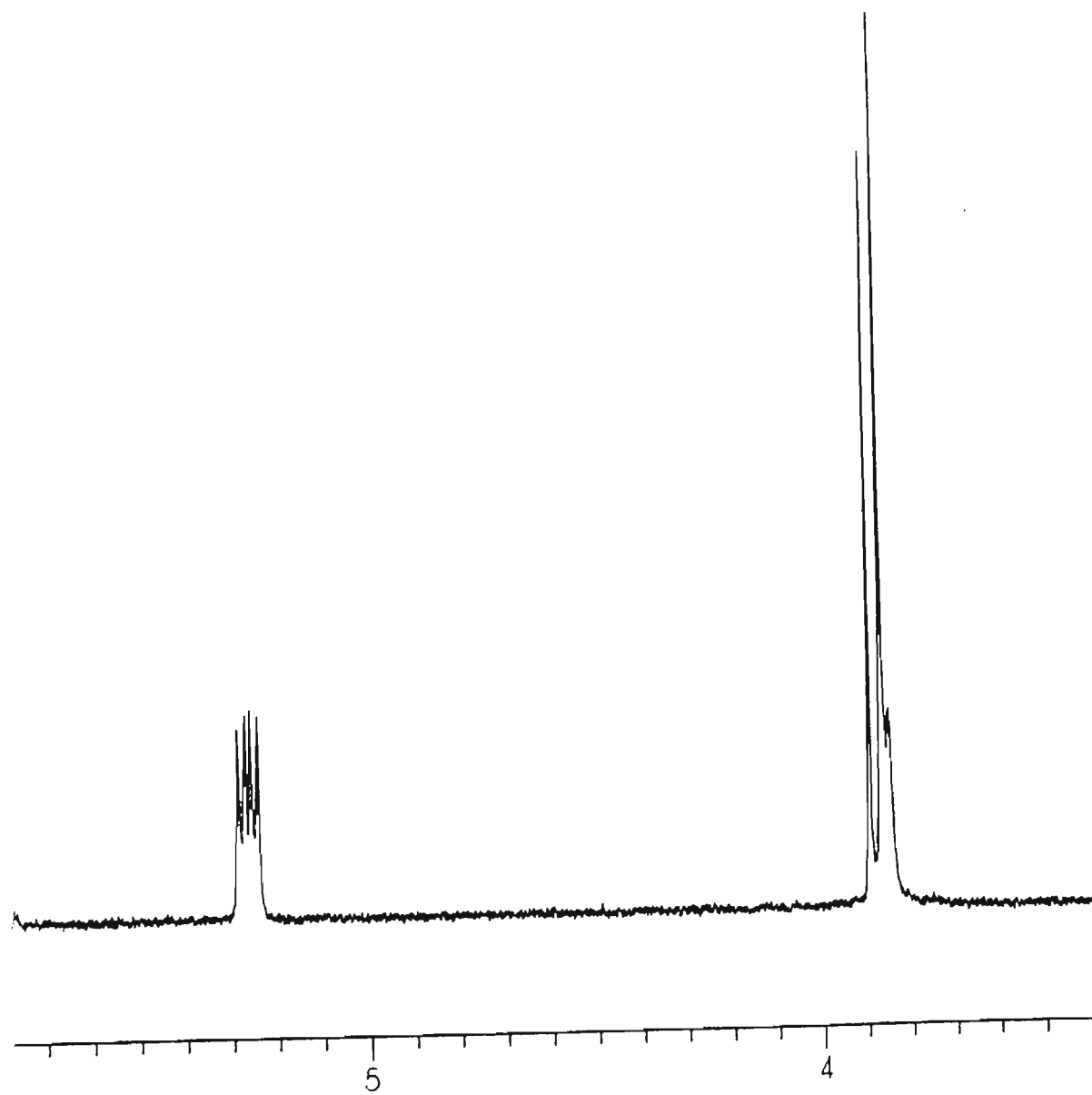
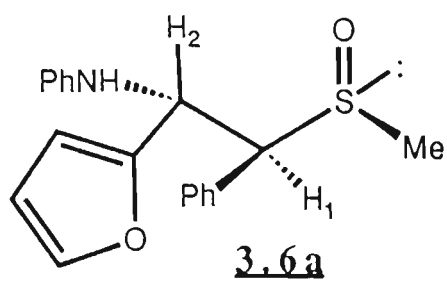


Figure 3.6  $^{13}\text{C}$  NMR for 3.6a.

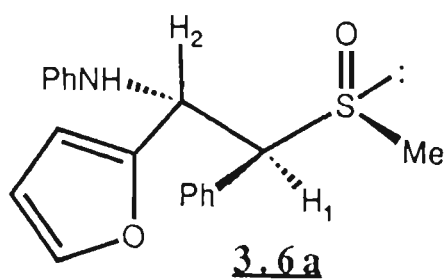
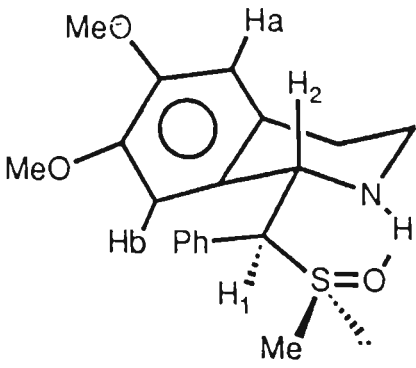


Figure 3.7  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) for 3.8B.



3.8B (threo)

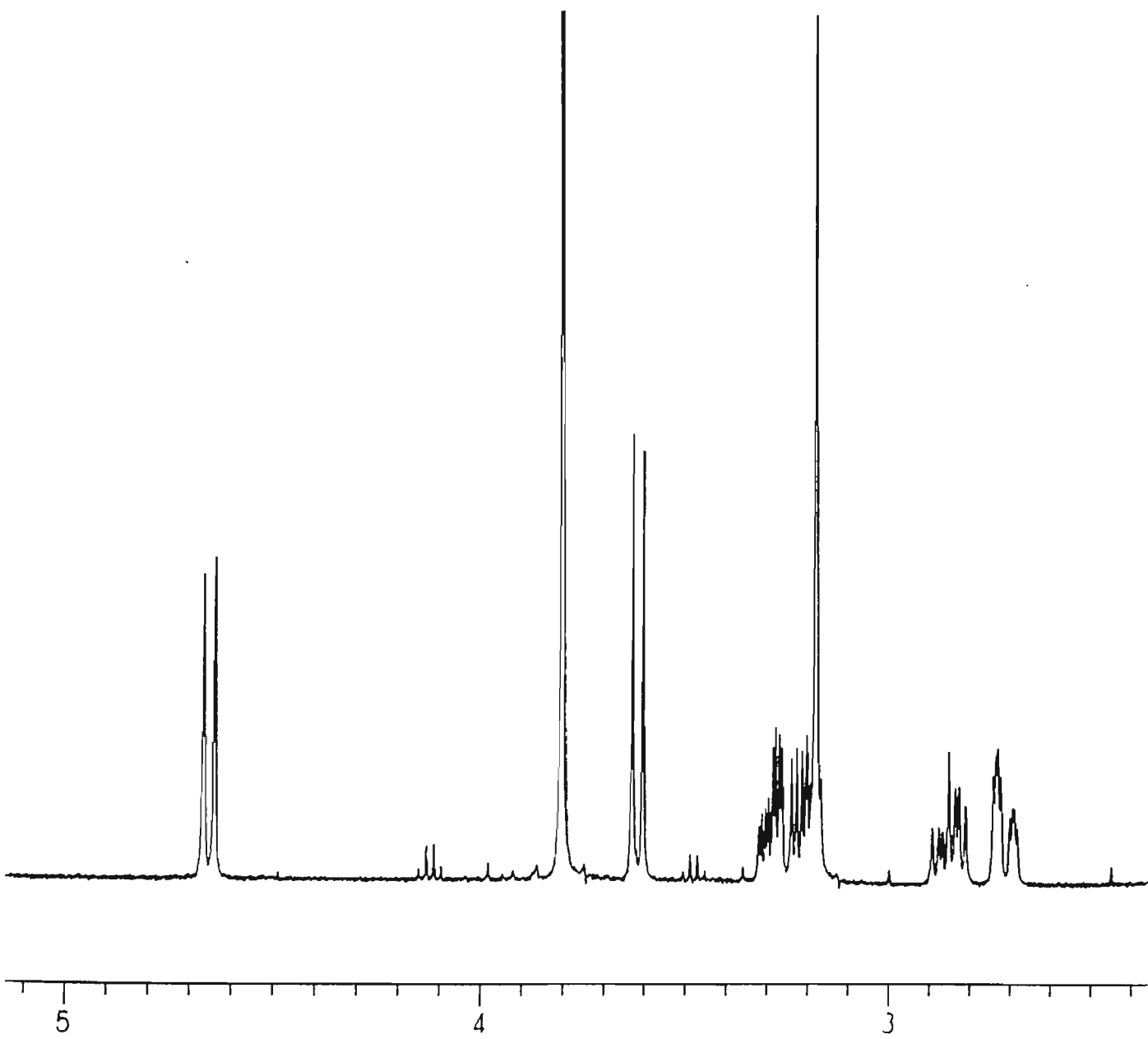
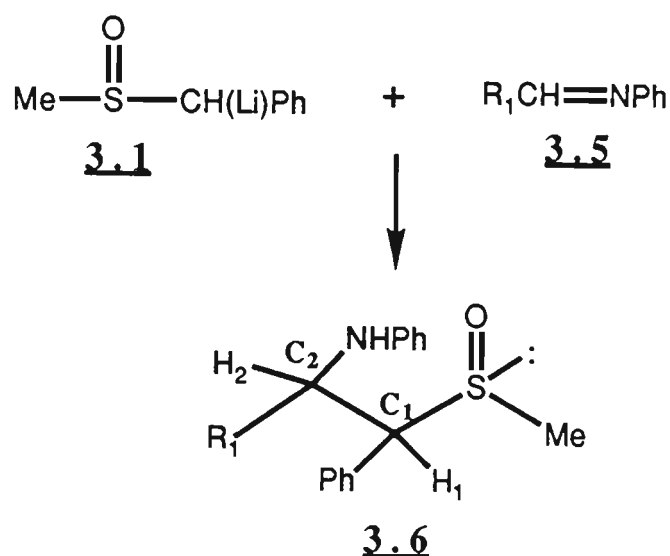


Table 3.3  $^{13}\text{C}$  NMR data for the addition of 3.1 to imines 3.5.



Entry		R <sub>1</sub>	C <sub>1</sub>	C <sub>2</sub>	SMe
1	a	2-Fur	53.00	70.02	36.16
2	b	Ph	59.15	73.23	36.22
3	c	i-Pr	57.02	71.15	35.05

It is important to note that 3.7 (3-4-dihydro-6,7-dimethoxyisoquinoline) was the only imine which when reacted with 3.1 gave only two out of the four possible diastereomers (Table 3.4). Interestingly this imine failed to react with lithiated benzyl methyl sulfoxide 3.1 without the prior complexation of 3.7 with  $\text{BF}_3 \cdot \text{etherate}$ , while precomplexed imine 3.7 gave the adduct 3.8 at  $-78^\circ\text{C}$  for 1 hr and the adduct 3.8 in 55% yield. When this reaction was carried at  $0^\circ\text{C}$  for 2 hrs or at  $0^\circ\text{C}$  for 12 hrs an untractable material was obtained which could not be successfully purified by column chromatography.

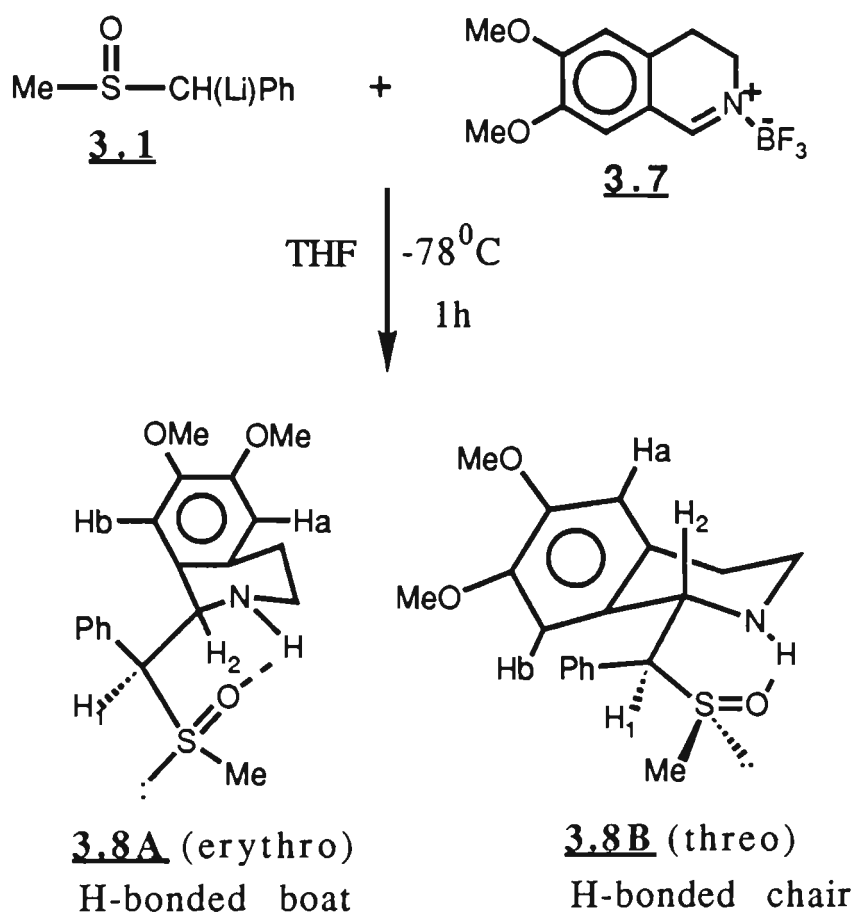
Analysis of  $^1\text{H}$  NMR of 3.8 indicates that a mixture of two diastereomers were produced ( $J_{1,2} > 10\text{Hz}$ ) in a ratio of 58:42. The

chemical shift of the SMe group of both of these diastereomers was highly shielded (2.01 and 2.05 ppm) suggesting they both have the S\* relative stereochemistry at the benzylic carbon.

The  $^1\text{H}$  NMR spectrum of the major diastereomer (3.8B) indicate a highly shielded aromatic proton (5.59 ppm, s, 1H) and methoxy group (3.19 ppm, s, 3H). Of the two possible diastereomers with the S\* configuration at the benzylic stereogenic centre  $\alpha$  to sulfur (3.8a and 3.8b) shielding at these two sets of protons would be most likely in 3.8b, since in the H-bonded chair like conformation the substituents Ph and CH<sub>3</sub> are both equatorial. In this conformation one aromatic proton and one methoxy group are in the shielding cone of the Ph group. Inspection of molecular models suggests that shielding of these protons in the other three possible racemic diastereoisomers is unlikely since they involve H-bonded boat conformations.

The  $^{13}\text{C}$  NMR of adducts 3.8 showed similar chemical shifts for SMe, at 35.18 and C-1, at 53.33 and for C-2, at 70.46 ppm .

Table 3.4. Preparation and  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) data for the addition of 3.1 to 3.7.



Diastereomeric

ratio %	42	58
$\delta\text{H}_1$ (ppm)	3.73	3.62
$\delta\text{H}_2$ (ppm)	4.68	4.64
$J_{1,2}$ (Hz)	10.07	10.53
$\delta\text{SMe}$	2.05	2.01
$\delta\text{Ha}$	6.33	5.59
$\delta\text{Hb}$	7.20	6.54
$\delta\text{OMe}$	3.86, 3.94	3.19, 3.80

## ADDITION OF BENZYL PHENYL SULFOXIDE TO 3-4-DIHYDRO-6,7-DIMETHOXYISOQUINOLINE

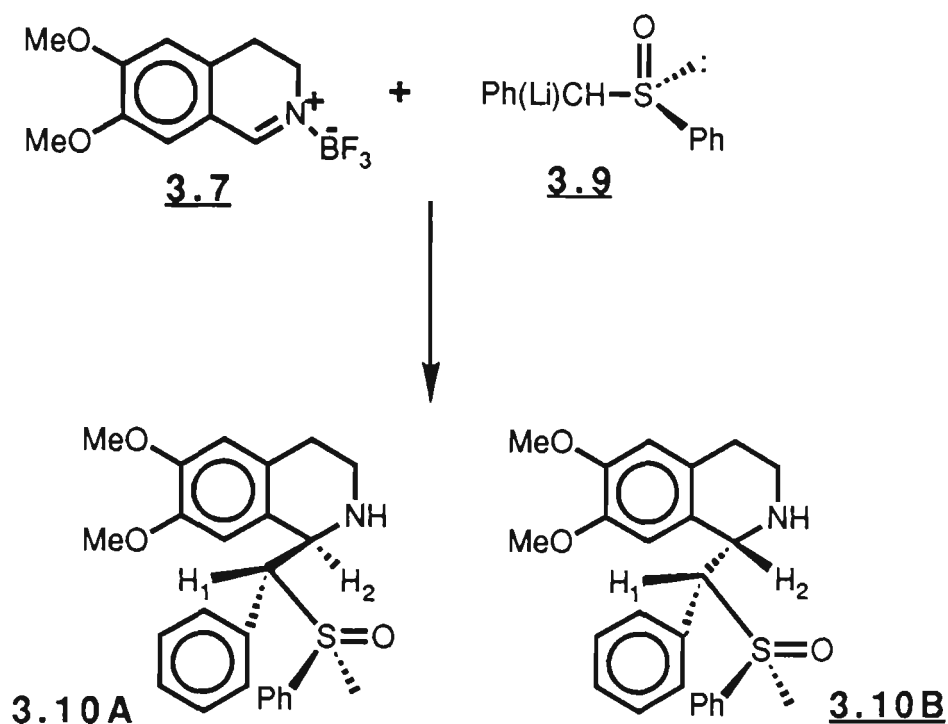
The reaction between lithiated benzyl phenyl sulfoxide 3.9 and 4,5-dihydro-6,7-dimethoxyisoquinoline. $\text{BF}_3$  complex (3.7) at

-78°C for 1 hr gave a low yield (45%) of adduct 3.10 with a diastereoselection of 33:33:33. An increase in reaction temperature gave unidentifiable products with none of the desirable adduct being obtained, in this, benzyl phenyl sulfoxide parallels the reaction of benzyl methyl sulfoxide with imines 3.5 (R=i-Pr and i-Bu).

Table 3.5 shows  $^1\text{H}$  NMR chemical shifts as well as the coupling constant  $J_{1,2}$  for the protons H-1 and H-2 situated on the stereogenic carbon atoms. The syn and anti stereochemistry of the adducts 3.8 were assigned on the bases of analogy to the literature precedent<sup>85a</sup>.



Table 3.5.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) data for the addition of 3.9 to 3.7.



	syn	anti	anti
Diastereomeric ratio %	33	33	33
$\delta \text{H}_1$	4.08	3.61	3.64
$\delta \text{H}_2$	5.19	4.89	4.86
$J_{1,2}$ (Hz)	3.70	10.10	10.77

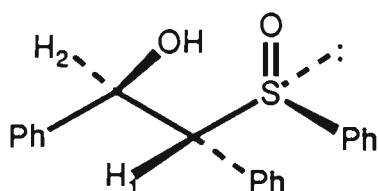
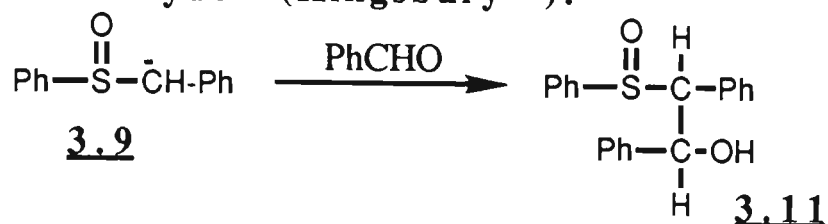
The lithiated benzyl phenyl sulfoxide however, did not react with other imines even when these imines were precomplexed with  $\text{BF}_3$ . This lack of reactivity could be due to the increased steric bulk on the sulfoxide. In conclusion it can be said that the addition of that alkyl benzyl sulfoxide anion to imines occurs in low yield with poor diastereoselectivity. The reactions are accompanied with competing side reactions that gave a multitude of intractable and unidentified products. The reaction yields and diastereoselectivity could not be improved substantially even when imines were complexed with  $\text{BF}_3$ .

## DIASTEREOSELECTIVE ADDITION OF ALDEHYDES TO BENZYL METHYL SULFOXIDE.

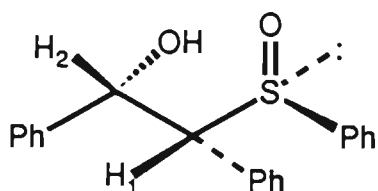
In 1972, Kingsbury<sup>43</sup> condensed lithiated benzyl phenyl sulfoxide with benzaldehyde and found that the reaction resulted in a mixture of four  $\beta$ -hydroxysulfoxides (3.11) in a 40% yield. Kingsbury found that product ratio was richer in the two  $\beta$ -hydroxysulfoxides which exhibit substantial intramolecular hydrogen bonding through a six member ring. Kingsbury's findings are shown in Table 3.6 (all products were racemic, however only one enantiomer is shown).

In our study we initially quenched  $\alpha$ -lithiated benzyl methyl sulfoxide with benzaldehyde for 10 min at  $-78^{\circ}\text{C}$ . We found all four possible isomers diastereomeric ratio of 55:26:11:8 which was in general agreement with Kingsbury's finding for the reaction of  $\alpha$ -lithiated benzyl phenyl sulfoxide. Furthermore the yield after column chromatography was 40%, again in agreement with Kingsbury's findings. In further studies, a solution of lithiated benzyl methyl sulfoxide in THF was quenched with freshly distilled aldehyde for 10 min at  $-78^{\circ}\text{C}$ . The pure  $\beta$ -hydroxy sulfoxide alcohols were obtained after a standard aqueous work up followed by extraction into dichloromethane and extensive column chromatography on silica gel (Table 3.7).

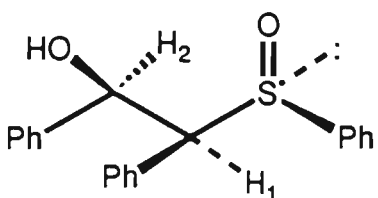
Table 3.6.  $^1\text{H}$  NMR data for the addition of 3.4 to benzaldehyde (Kingsbury<sup>43</sup>).



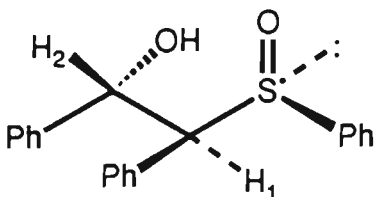
	$\text{H}_1$ (ppm)	$\text{H}_2$ (ppm)	$\text{J}_{1,2}$ (Hz)	Diastereomeric ratio %
anti	3.94	5.64	9.5	47
				(H- bonded)



	$\text{H}_1$ (ppm)	$\text{H}_2$ (ppm)	$\text{J}_{1,2}$ (Hz)	Diastereomeric ratio %
syn	3.66	5.55	8.3	8



	$\text{H}_1$ (ppm)	$\text{H}_2$ (ppm)	$\text{J}_{1,2}$ (Hz)	Diastereomeric ratio %
syn	3.68	5.87	2.9	32
				(H- bonded)

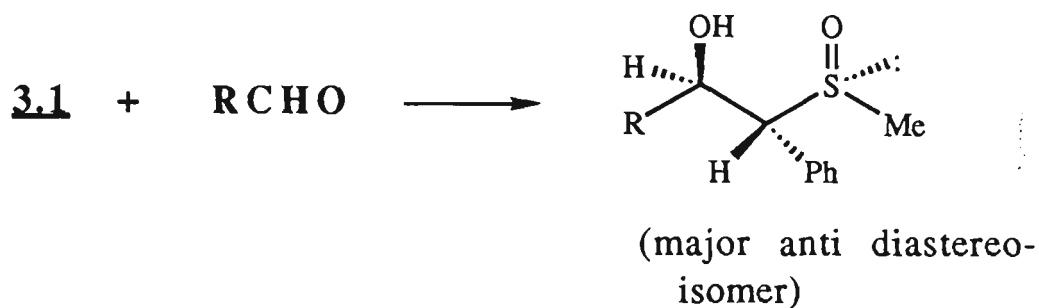


	$\text{H}_1$ (ppm)	$\text{H}_2$ (ppm)	$\text{J}_{1,2}$ (Hz)	Diastereomeric ratio %
anti	3.95	5.91	10.2	19

The diastereoselectivity appears to be insensitive to the steric demand of the aldehyde and was approximately equal for all aldehydes, so much so that even highly sterically demanding pivaldehyde ( $R=t\text{-Bu}$ ) showed little diastereoselection. The assignment of the four diastereomeric products was made by analogy with the literature precedent (Kingsbury et al.<sup>85</sup>) and was determined from the  $^1\text{H}$  NMR coupling constants  $J_{1,2}$  and the chemical shift of the SMe group. Large values of  $J_{1,2}$  (10-13 Hz) are indicative of predominantly trans(anti) protons, while intermediate values are indicative of syn protons. The chemical shift of the SMe group of the major diastereoisomer suggested it had the  $R^*_C$ ,  $S^*_S$  relative stereochemistry as found in the major adduct from the reaction of 3.1 with cyclohexanone.

Table 3.7 shows chemical shifts of H-1, H-2 and SMe as well as coupling constants for the aldehyde adducts ( $R=\text{Ph}$ ,  $t\text{-Bu}$ , Et,  $i\text{-Bu}$  and  $i\text{-Pr}$ ).

Table 3.7.  $^1\text{H}$  NMR( $\text{CDCl}_3$ ) data for the addition of **3.1** to aldehydes.



3.11	anti-	syn	syn	anti
$\text{R}=\text{Ph}$ (a)				
Diastereomeric				
Ratio %	55	26	11	8
$\text{H}_1(\text{ppm})$	3.92	3.75		
$\text{H}_2(\text{ppm})$	5.50	5.70		
$\text{J}_{1,2}(\text{Hz})$	9.20	2.80		
$\text{SMe}(\text{ppm})$	2.44	2.24	2.03	1.99
$\text{R}=\text{t-Bu}$ (b)				
Diastereomeric				
Ratio %	49	26	12	13
$\text{H}_1(\text{ppm})$	3.88	3.82		
$\text{H}_2(\text{ppm})$	4.22	4.27		
$\text{J}_{1,2}(\text{Hz})$	8.82	2.3		
$\text{SMe}(\text{ppm})$	2.3	2.28	2.15	1.96
yield 35%				

R=Et (c)				
Diastereomeric				
Ratio %	63	20	10	7
H <sub>1</sub> (ppm)	3.78	3.66		
H <sub>2</sub> (ppm)	4.55			
J <sub>1,2</sub> (Hz)	9.86	1.2		
SMe(ppm)	2.45	2.37	2.21	2.10
yield 35%				
R=i-Bu (d)				
Diastereomeric				
Ratio %	51	26	17	6
H <sub>1</sub> (ppm)	3.75	3.62	3.70	3.38
H <sub>2</sub> (ppm)	4.72			
J <sub>1,2</sub> (Hz)	8.85	3.20	3.20	10.53
SMe(ppm)	2.45	2.32	2.25	2.05
yield 40%				
R=i-Pr (e)				
Diastereomeric				
Ratio %	43	24	17	16
H <sub>1</sub> (ppm)	3.80			
H <sub>2</sub> (ppm)	4.50	4.76		
J <sub>1,2</sub> (Hz)	11	3		
SMe(ppm)	2.45	2.35	2.20	2.05
yield 37%				
	H-bonded		H-bonded	

From the Table 3.7 it is clear that the diastereoselection was poorest when R of the aldehyde was i-Pr (43:24:17:6) and the best when R was Et (63:20:10:7), however, it is also evident that the diastereoselection was essentially similar in all cases. The chemical shift for the SMe group of the major diastereomer consistently appeared at 2.40-2.44 ppm except in 3.11 (R=t-Bu).

Furthermore the chemical shifts for the SMe group of other related diastereomers were consistent with each other as can be seen from the Table 3.7, as were the chemical shifts for the diastereomeric protons H-1 and H-2. In some cases it was impossible to assign the chemical shifts of H-1, H-2 or J<sub>1,2</sub> for the minor isomers with certainty as these were obscured by other protons.

Figure 3.8 is a copy of <sup>1</sup>H NMR for β-hydroxysulfoxide 3.11 (R=t-Bu) showing both of the major diastereomers, while Figure 3.9 is a copy of the accompanying <sup>13</sup>C NMR.

In conclusion it can be said that the addition of benzyl methyl sulfoxide anions to aldehydes occurs in low yield and with a poor diastereoselection. The diastereoselectivity appears to be essentially independent on the kind of alkyl group R on the aldehyde.

Figure 3.8.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) for the 3.8b.

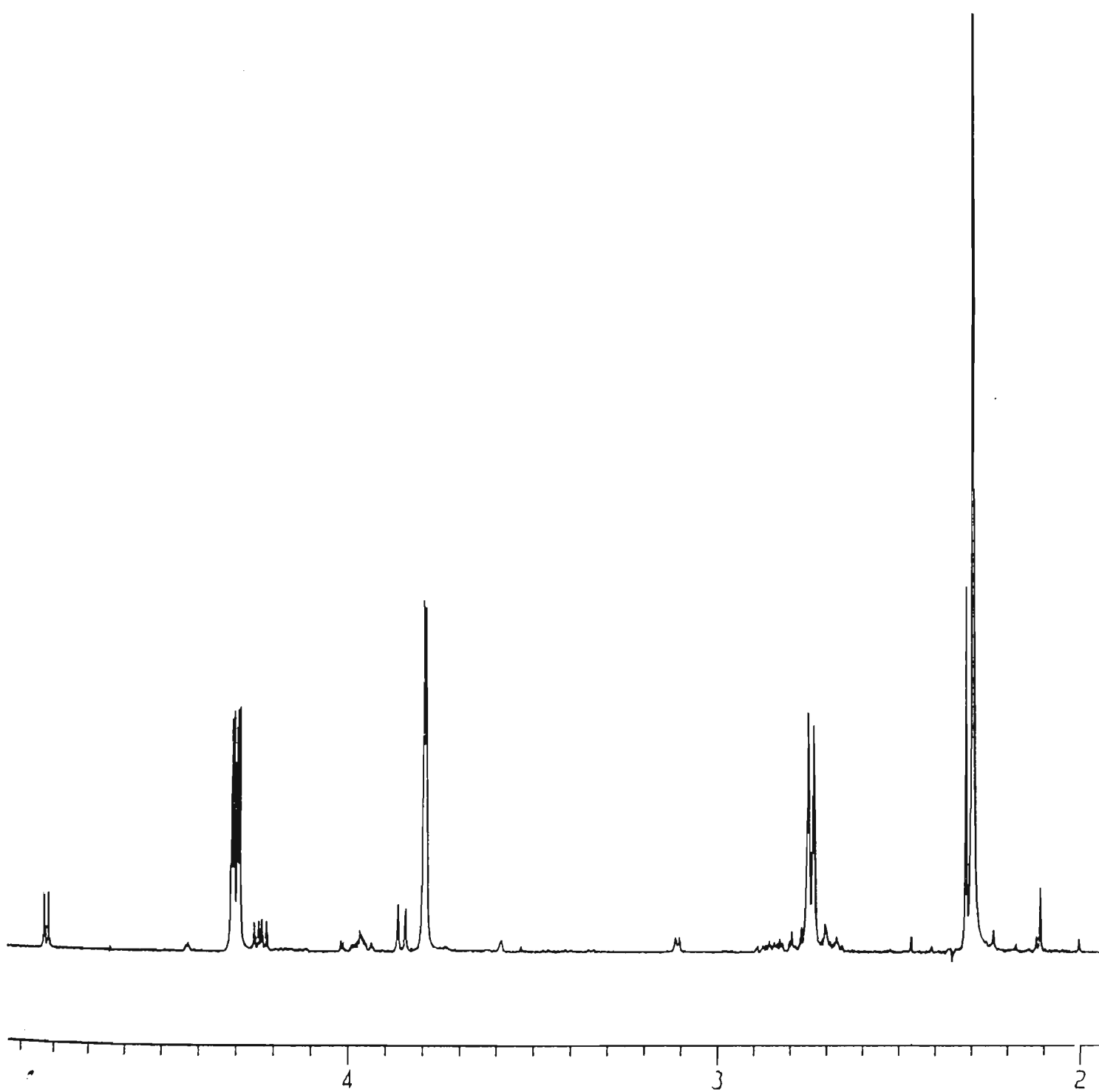
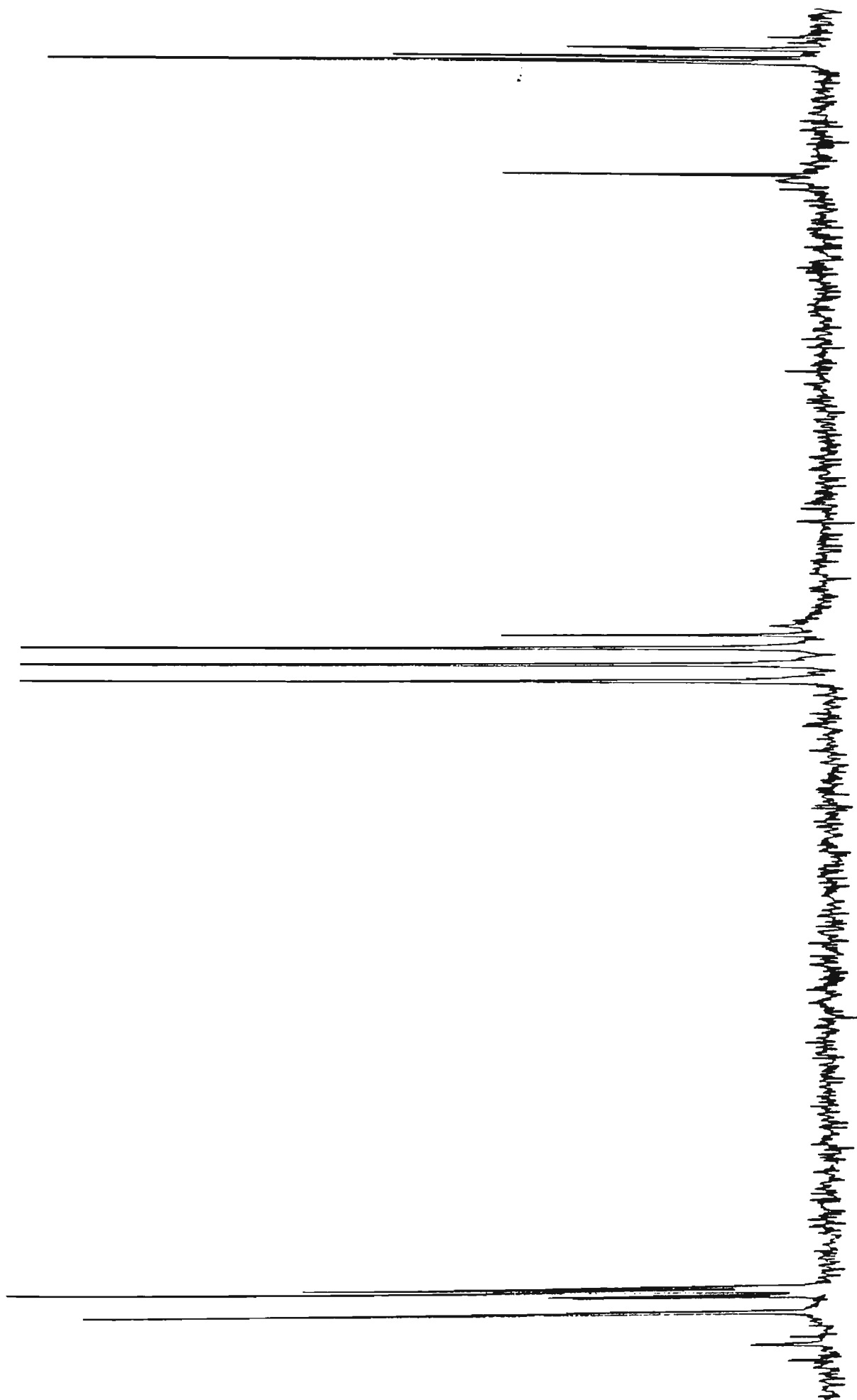




Figure 3.9.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) for the 3.8b.



## **EXPERIMENTAL**

### **Benzyl methyl sulfoxide 3.1<sup>67b</sup>**

To a solution of benzyl methyl sulfide (0.161mol, 20g) in methanol (320ml) at 0°C was added a solution of NaIO<sub>4</sub> (0.161mol, 34.44g) in water (360ml) dropwise and the resulting mixture stirred overnight at room temperature. The white precipitate was filtered and the methanol was evaporated and the mixture was then extracted with DCM. The DCM extracts were dried (MgSO<sub>4</sub>) and evaporated. The resulting solid was recrystallized from 6:4 toluene/hexane to yield pure methyl phenyl sulfoxide 21g (84%). M.p. 51-53°C, lit.<sup>67b</sup> m.p. 54°C.

### **Benzyl phenyl sulfide**

To a solution at benzyl chloride (25.2g, 0.2mol) in 0.5 molar ethanolic KOH (400ml) at 0°C was added thioanisole (22g, 0.2mol) and the solution warmed to room temperature and stirred for 10-12hrs. The ethanol was evaporated, water was added (50ml) and the mixture was extracted with DCM. The DCM was dried (MgSO<sub>4</sub>) and evaporated to yield a solid which was recrystallized from ethylacetate to yield 348g (87%) of benzyl phenyl sulfide., m.p. 96°C

### **Benzyl phenyl sulfoxide 3.2<sup>67b</sup>**

A solution of benzyl phenyl sulfide (32.2g, 0.162mol) in methanol (390ml) was cooled in an ice bath and a solution of sodium periodate (34.44g, 0.162mol) in water 360ml was added dropwise. The resulting solution was warmed to 60°C for 4 hrs. The mixture was evaporated to dryness and the resulting solid

extracted with DCM (3x100ml) to yield 30g (86%) after recrystallization from ethanol or ethyl acetate. M.p. 128-129°C, lit.<sup>67b</sup> m.p. 127°C.

### Reaction at 3.1 or 3.9 with imines: A General Procedure

To a solution of (1 mmol) of 3.1 or 3.9 in THF (3ml) at -78°C was added n-BuLi in hexane (1.1mmol). After 1hr a solution of imine 3.5 or 3.7 (1mmol) in THF (2ml) was added. The solution was warmed and kept at the temperature specified in Table 3.1, 3.4 or 3.5 for 1 hr. The reaction was quenched by the addition of 10% K<sub>2</sub>CO<sub>3</sub> (5 ml) and extracted with DCM (2x). The combined extracts were dried (MgSO<sub>4</sub>) and evaporated. The diastereoselection of these reactions was determined from <sup>1</sup>H NMR (400MHz) analysis of crude product.

### Reaction of 3.1 and 3.12 with aldehydes: A General Procedure

To a solution of methyl benzyl sulfoxide (154mg, 1.0 mmol) in THF (3ml) at -78°C was added n-BuLi(1.1mmol) in hexane. After 1 hr the neat aldehyde (1.1mmol) was then added. After 5 min, a solution of 10% K<sub>2</sub>CO<sub>3</sub> (5ml) was added and the mixture was extracted with DCM (2x). The combined extracts were dried (MgSO<sub>4</sub>) and evaporated. The diastereoselection of these reactions was determined from <sup>1</sup>H NMR (400MHz) analysis on crude product.

### N-Phenyl-N-(1-(2'-furyl-2-(methylsulfinyl)-2-phenyl)ethylamine 3.6a.

Oil; <sup>1</sup>H NMR 7.5-6.35(m,13H), 5.26 (dd, 1H, J=8.7, 1<Hz) 3.88(d, J=10.99), 3.86(s,1H), 2.05(s, 3H); <sup>13</sup>C NMR 146.47, 142.44, 130.22,

129.87, 128.96, 128.70, 118.82, 114.82, 114.32, 110.50, 109.76, 70.02, 52.99, 36.18; MS (CI +ve), 326(M+H<sup>+</sup>, 1%), 262(100%), 217(23%), 172(100%), 141(30%), 115(30%), 94(73%); IR (neat) 3300(s), 1030(s); HRMS calcd for C<sub>11</sub>H<sub>20</sub>NO<sub>2</sub>S, 326.1213, found 326.118.

**N-Phenyl-N-(2-methylsulfinyl-1,2-diphenyl)ethylamine**  
**(3.6b)**

Oil; <sup>1</sup>H NMR δ 7.61-6.35 (m, 15H), 5.08(d, 1H, J=10.68Hz), 3.49 (d, 1H, J=1.53Hz), 1.99 (s, 3H); <sup>13</sup>C NMR δ 130.18, 129.53, 129.18, 128.92, 128.23, 127.84, 118.48, 114.32, 73.23, 59.15, 36.22; IR (nujol) 3350(s), 1030(s); MS (CI +ve) 320(M-Me, 1%), 272 (33%), 227 (46%), 182 (100%), 107 (60%), 91 (36%), 77 (45%); HRMS calcd for C<sub>21</sub>H<sub>22</sub>NOS, 336.1420, found 336.146.

**N-Phenyl-N-(3-methyl-1-(methylsulfinyl)-1-phenyl)**  
**butylamine 3.6e**

Oil; MS (CI+ve), 316(6%), 237(51%), 204(23%), 135(26%), 122(100%).

**1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(methylsulfinyl)**  
**phenylmethyl)isoquinoline 3.8.**

<sup>1</sup>H NMR δ 7.29(5,5H), 6.54(s, 1H), 5.59(s, 1H), 4.65(d, 1H, J=10.55 Hz), 3.8 (s, 3H), 3.61(d, 1H, J=10.33 Hz), 3.19 (s, 3H), 3.22 (m, 2H), 2.85(m, 2H), 2.01(s, 3H); <sup>13</sup>C NMR δ 133.69, 130.48, 128.57, 128.36, 127.67, 126.75, 111.85, 110.80, 75.57, 70.46, 55.68, 55.33, 55.03, 38.69, 35.18, 28.59, 15.16; MS (CI +ve), 346 (M+H<sup>+</sup>, 1%), 281(39%), 266(16%), 192(98%), 176(33%), 137(29%), 91(100%), 77(43%); IR (neat), 3290(w), 1265(s), 1110(s), 1030(s).

**1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[1'-(phenylsulfinyl)phenyl]methylisoquinoline 3.10.**

M.p. 61°C;  $^1\text{H}$  NMR 7.29-7.02(m, 10H), 6.6(s,1H), 6.39(s,1H), 5.21(d, 1H,  $J=3.52\text{Hz}$ ), 4.01(d, 1H,  $J=3.52\text{Hz}$ ), 3.79(s,3H), 3.74(s, 3H), 3.53(m, 2H), 3.09(m, 2H); IR 3340(w), 1035(sh); MS (CI +ve), 390(43%), 363(9%), 282(43%), 205(29%), 192(100%), 176(51%), 91(92%); Anal. calcd for  $\text{C}_{24}\text{H}_{25}\text{NO}_3\text{S}$ : C, 70.74; H, 6.18; N, 3.44: found: C, 72.84; H, 6.41; N, 3.20.

**2-Phenylsulfinyl-1,2-diphenyl-1-ethanol 3.11a.**

$^1\text{H}$  NMR 7.49-7.11(m, 10H), 5.75(d, 1H,  $J=2.66\text{Hz}$  minor), 5.5 (d, 1H,  $J=9.15$ ), 3.93(d,1H,  $J=9.15$ ), 3.75(d, 1H,  $J=2.6\text{Hz}$ ), 2.33(s, 3H);  $^{13}\text{C}$  NMR 150.29, 128.83, 127.23, 127.01, 126.54, 125.97, 124.89, 75.96, 69.07, 35.86; MS 241(7.2%), 227(9%), 210(48%), 195(100%), 167(15%), 135(10%) IR(neat) 3700-3100(br), 1050(s), 1120(s).

**(3,3-Dimethyl)-1-phenylsulfinyl-1-phenyl-2-butanols 3.11b.**

$^1\text{H}$  NMR 7.5-7.2(m, 5H), 4.22(d, 2H,  $J= 8.24$ ,major), 3.88(d, 2H,  $J= 8.24$  major), 2.29(s, 3H), .81(s, 9H);  $^{13}\text{C}$  NMR 130.61, 129.31, 129.18, 128.83, 128.66, 128.53, 74.49, 36.00, 26.73, 26.29, 25.51; IR 3600-3100(br), 1085(s), 1040(s); MS (CI +ve), 241( $\text{M}+\text{H}^+$ , 52%), 207(19%), 177(100%), 159(52%), 137(22%), 12(40%), 107(47%), 91(100%), 87(52%); HRMS calcd for  $\text{C}_{13}\text{H}_{20}\text{SO}_2$ , 241.1262, found 241.1261.

**1-Phenylsulfinyl-1-phenyl-2-butanol    3.11c**

IR(neat) 3700-3100(br), 1110(s), 1150(s), MS (CI +ve), 213(100%), 149(98%), 139(66%), 91(72%).

**S-Methyl-(1-phenylsulfinyl)-1-phenyl-2-pentanol    3.11d.**

<sup>1</sup>H NMR 7.44-7.05 (m, 5H), 4.63(m, 1H), 3.74(d, 1H, J=8.85), 2.45(s, 3H), .78(d, 3H, J=3.08); <sup>13</sup>C NMR 132.43, 129.14, 128.70, 128.57, 74.88, 71.89, 43.93, 37.43, 23.48, 20.92; MS (CI +ve), 241(M+H<sup>+</sup>,6%), 207(10%), 177(52%), 117(52%), 107(50%), 91(100%).

**3-Methyl-(1-phenylsulfinyl)-1-phenyl-2-butanol    3.11e.**

<sup>1</sup>H NMR 7.41-7.03(m, 5H), 4.50(dd, 1H, J=2.13, 9.61Hz) 3.79(d, 1H, J=9.61Hz), 2.45(s, 3H), 1.00(d, 3H, J=6.59Hz), .82(d, 3H, J=6.37Hz); <sup>13</sup>C NMR 129.18, 128.79, 128.57, 77.39, 72.97, 37.39, 30.24, 19.75, 13.77; IR (neat) 3700-3100(br), 1010(s); MS (CI +ve), 227 (M+H<sup>+</sup>,100%), 209(30%), 193(100%), 163(100%), 145(70%), 119(100%), 105(60%), 91(100%), 73(100%).

# CHAPTER 4

## ADDITION OF THE ANIONS OF (R<sub>S</sub>)-10-METHYL- AND (R<sub>S</sub>)-10-BENZYL-SULPHINYLBORNAN-2-EXO-OL TO IMINES.

Our attempt to generate chiral amines from the addition of lithiated methyl and phenyl benzyl sulfoxide to imines produced adducts in poor yield and low diastereoselectivity, we next turned our attention to the addition of carbanions of (R<sub>S</sub>)-10-alkyl sulfinylbornan-2-exo-ols to imines.

10-Camphorsulfonyl chloride 4.1 was reduced with lithium aluminium hydride in ether to give 10-thio-bornan-2-exo-ol 4.2 in 69% yield<sup>86</sup>. The 10-thio-bornan-2-exo-ol was treated with either methyl iodide or benzyl chloride in 1 molar ethanolic potassium hydroxide to yield 10-methylthio-bornan-2-exo-ol 4.3 and 10-benzylthio-bornan-2-exo-ol<sup>87</sup> 4.4 in 86% and 93% yield respectively. The 10-methyl and 10-benzylthio-bornan-2-exo-ol 4.3 and 4.4 were then oxidised with meta-chloroperoxybenzoic acid (m-CPBA)<sup>88</sup> in dichloromethane (DCM) to yield (R<sub>S</sub>)-10-methylsulfinylbornan-2-exo-ol 4.5 and (R<sub>S</sub>)-10-benzylsulfinylbornan-2-exo-ol 4.6 in 83% and 69% yield (Scheme 4.1).

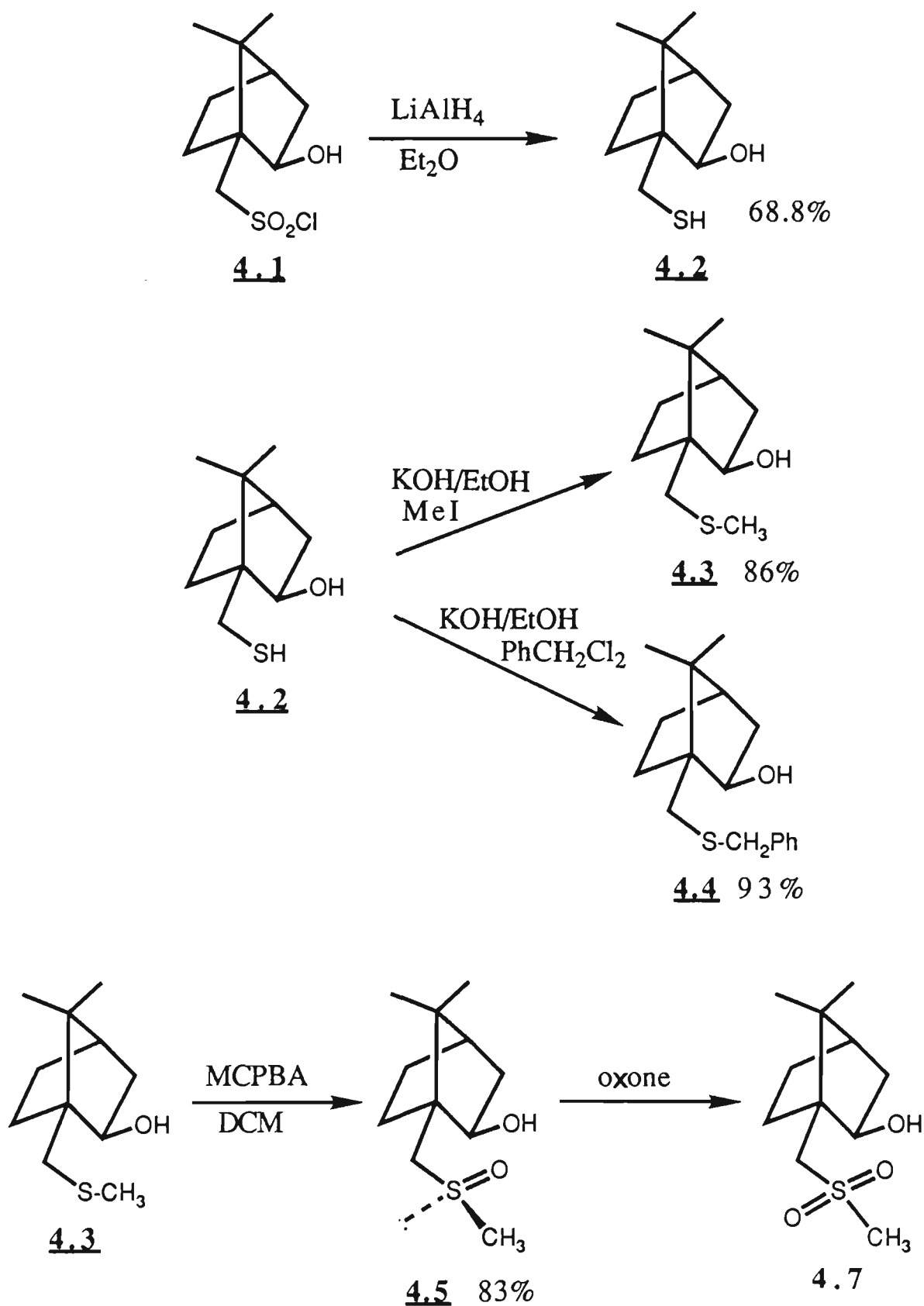
As previously noted by other workers<sup>88</sup> in the oxidation of related sulfides these oxidations were highly diastereoselective (de >95:<5) due primarily to the hydroxy group which can H-bond the m-CPBA and this directs the oxidant specifically to one of the diastereotopic lone pairs on the sulfur atom of the sulfide.

The 10-methylsulfonylbornan-2-exo-ol 4.7 was synthesized by oxidation of (R<sub>S</sub>)-10-methylsulfinylbornan-2-exo-ol 4.5 with  $\text{SO}_3$ .

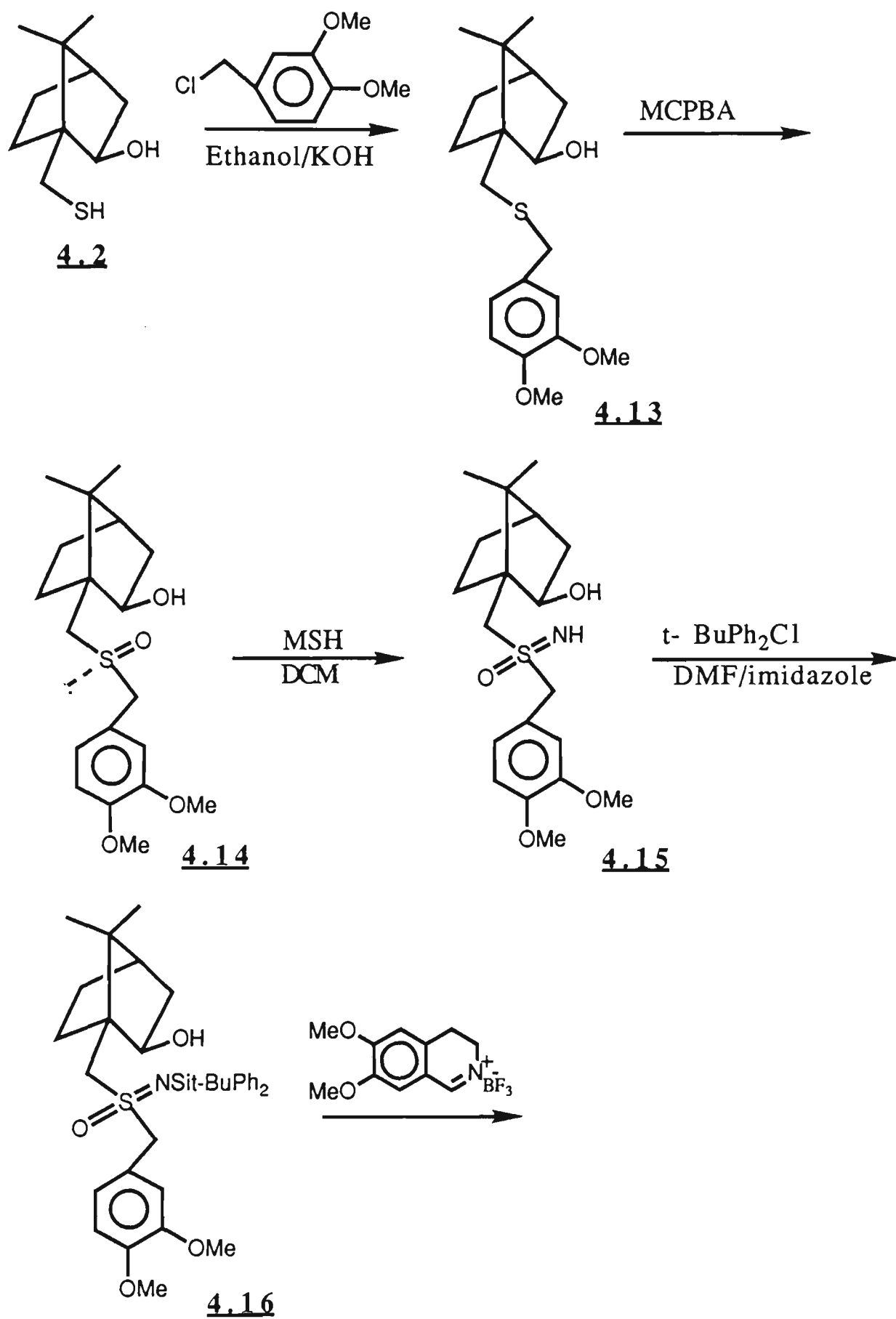


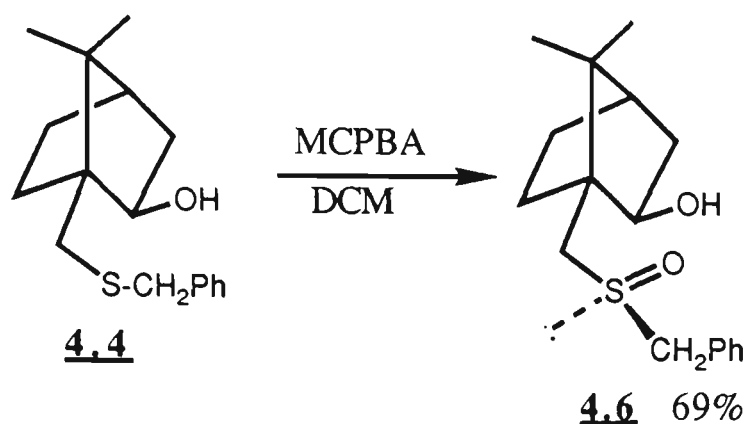
potassium hydrogenpersulfate (oxone) in aqueous methanol according to the method reported by Trost.<sup>89</sup>

**Scheme 4.1.**



Scheme 4.2.



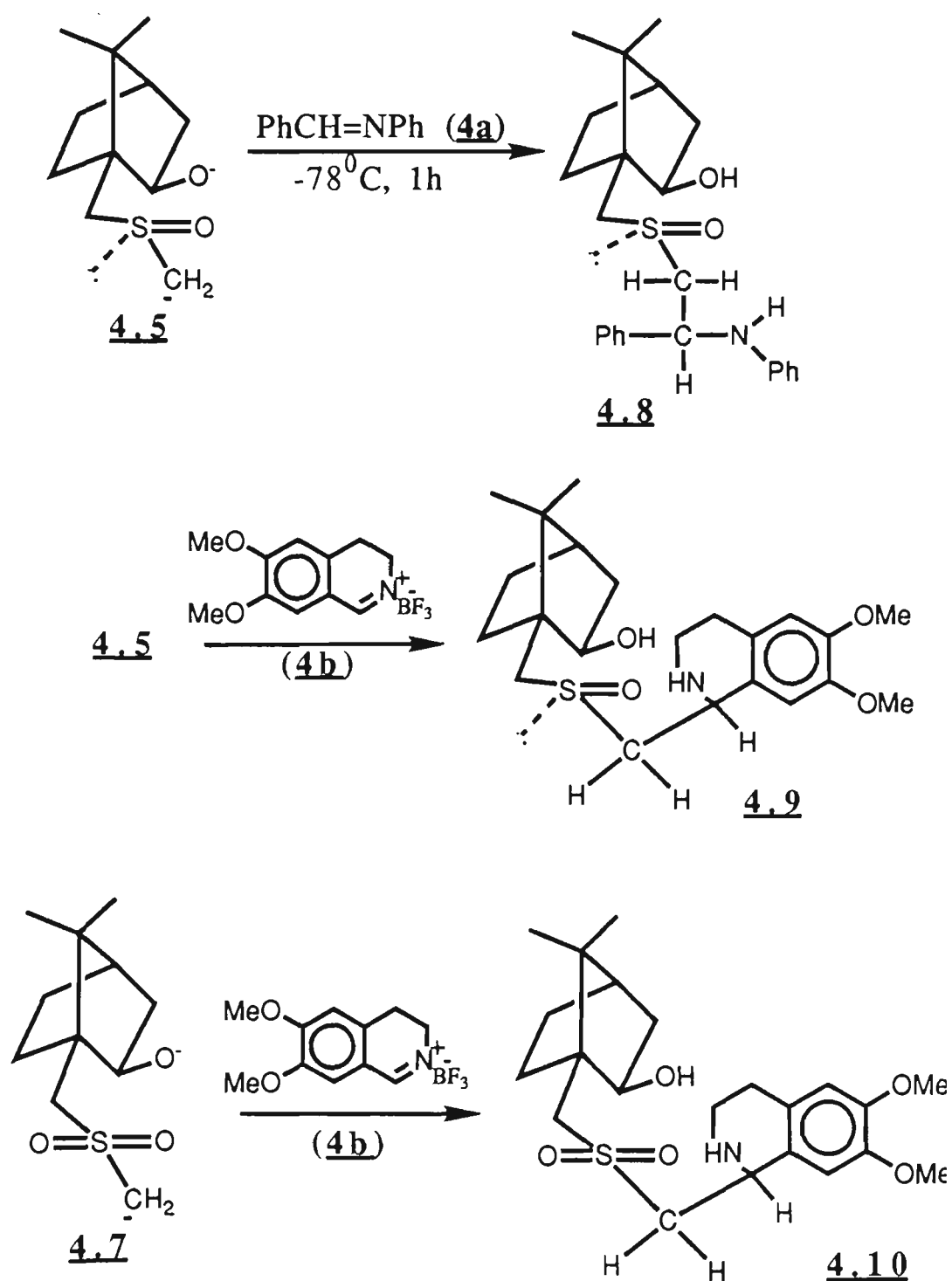


The 10-thio-bornan-2-exo-ol 4.2 when treated with 3,4-dimethoxybenzyl chloride in 1 molar ethanolic potassium hydroxide gave 10-(3,4-dimethoxyphenyl)methylthio-bornan-2-exo-ol (4.13) which upon oxidation with m-CPBA in methylene chloride gave ( $R_S$ )-10-(3,4-dimethoxyphenylmethyl)sulfinylbornan-2-exo-ol 4.14. Upon treatment of 4.14 with mesitylenedihydroxylamine (MSH)<sup>81,82</sup> in dichloromethane the sulfoximine 4.15 was produced in low yield (18%). Silylation of 4.15 with *tert*-butylchlorodiphenylsilane in dimethylformamide and imidazole<sup>79</sup> produced the N-silylated sulfoximine 4.16 (Scheme 4.2). Unfortunately the dilithiated 4.16 when reacted with 3,4-dihydro-6,7-dimethoxyisoquinoline. $\text{BF}_3$  complex did not produce any of the desired adduct.

Dilithiated sulfoxides 4.5, 4.6 and dilithiated sulfone 4.7 were prepared by treating the appropriate sulfoxide or sulfone in tetrahydrofuran (THF) with *n*-butyllithium (2.1 equiv.) for 1 hr. The resulting dianions were then quenched with a solution of *N*-benzylideneaniline or 3,4-dihydro-6,7-dimethoxyisoquinoline. $\text{BF}_3$  complex for 1 hr at  $-78^\circ\text{C}$  (Scheme 4.3). The  $\beta$ -amino sulfoxides or sulfone adducts 4.8, 4.9, 4.10, 4.11 and 4.12 were obtained after a standard aqueous work up followed by extraction into dichloromethane and extensive chromatography on silica gel.

The diastereomeric ratio of the adducts was in all cases determined by  $^1\text{H}$  NMR (400 MHz) spectroscopy on the crude reaction mixture. As the sulfone 4.7 gave 1:1 mixture of diastereoisomers when reacted with imines further experiments on this compound were terminated.

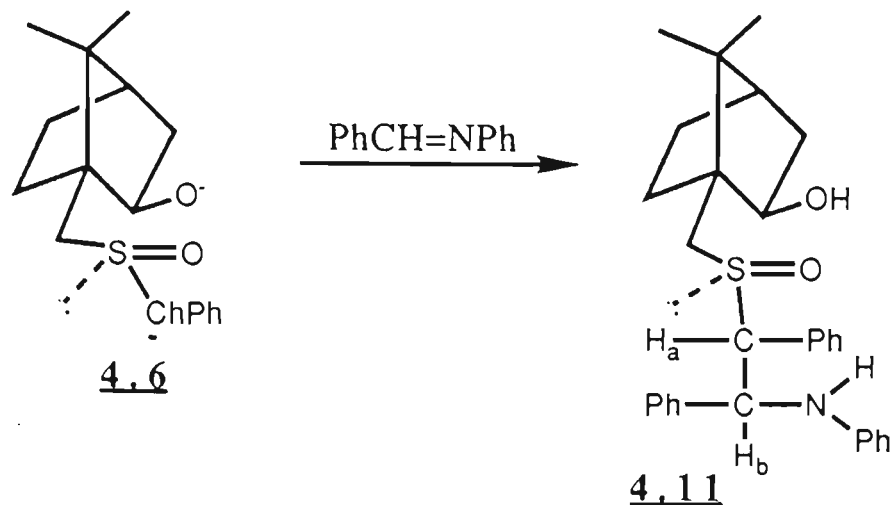
Scheme 4.3.



The yield of adducts 4.8 and 4.9 was poor, 47% and 30% respectively, even though the crude  $^1\text{H}$  NMR showed little starting material. NMR analysis showed the desired products were accompanied with several other products and extensive column chromatography had to be undertaken resulting in lower yields. In each case both of two possible diastereomeric products were obtained. In the case of the adduct 4.8 the diastereomeric ratio was 66:34 while for the adduct 4.9 the diastereomeric ratio was found to be 63:37 (Table 4.1) It was found necessary to complex 3,4-dihydro-6,7-dimethoxyisoquinoline with  $\text{BF}_3 \cdot \text{etherate}$  in order to effect the reaction with 4.5 as the uncomplexed imine failed to react.

Table 4.1 shows the  $^1\text{H}$  NMR chemical shifts of the diastereomeric protons  $\text{H}_a$  and  $\text{H}_b$  as well as the coupling constants  $J_{ab}$ ,  $J_{bc}$  and  $J_{ac}$ . The proton  $\text{H}_b$  could not be assigned with certainty as it was obscured by other protons. Figure 4.1 is a copy of  $^{13}\text{C}$  NMR of the adduct 4.8.

Figure 4.2. Preparation and  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) data for 4.11, and 4.12.



Diastereomeric

ratio (%)

46      21      23      8

$\delta\text{H}_a$  (ppm)

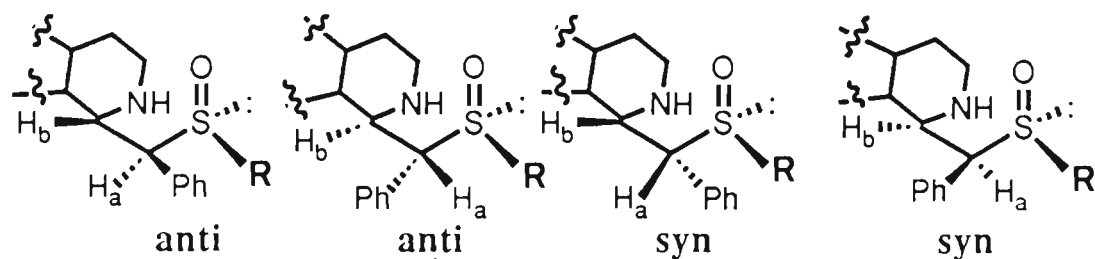
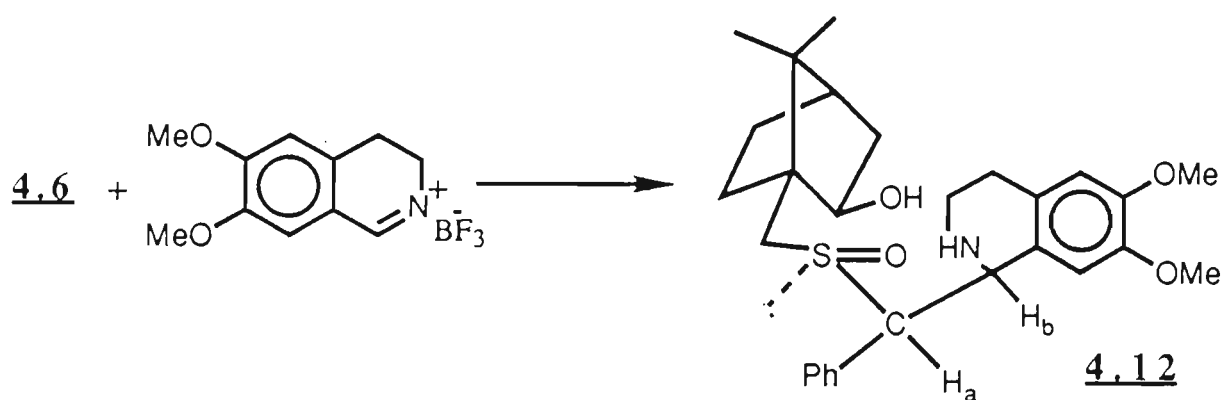
$\delta\text{H}_b$  (ppm)

5.48    4.92    4.85    5.35

$J_{a,b}$  (Hz)

8.1    6.5    3.3

yield 27%



Diastereomeric

ratio (%)

51      35      8      6

$\delta\text{H}_a$  (ppm)

4.64    4.69    4.84    5.01

$\delta\text{H}_b$  (ppm)

3.83    3.82    4.27    4.23

$J_{a,b}$  (Hz)

10.38    9.77    3.05    7.93

yield 40%

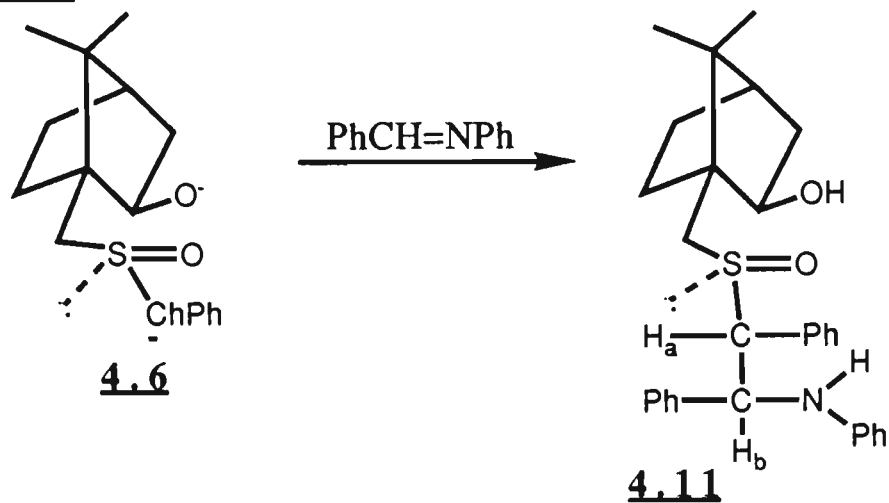
The addition of the dianion (R<sub>S</sub>)-10-benzylsulfinyl-bornan-2-exo-ol 4.6 to benzylideneaniline or 3-4-dihydro-6,7-dimethoxyisoquinoline·BF<sub>3</sub> produced all four possible diastereomers Table 4.2. From Table 4.2 we see that adduct 4.11 was produced in diastereomeric ratio of 46:23:23:8 with H<sub>b</sub> showing as a doublet with H<sub>b</sub> at 5.48, 4.82, 4.85 and 5.35 ppm, for the four diastereomers respectively. The chemical shifts for the proton H<sub>a</sub> situated on the stereogenic benzylic carbon as well as J<sub>ab</sub> would not be assigned with certainty as they were obscured with other protons.

The yield of the adduct 4.11 was 27% as the reaction was accompanied by multitude of side reaction and extensive column chromatography had to be done on the product which resulted in low yield. The adduct 4.12 which resulted from the addition of the dianion of (R<sub>S</sub>)-10-benzylsulfinylbornan-2-exo-ol 4.6 to 3,4-dihydro-6,7-dimethoxyisoquinoline·BF<sub>3</sub> complex gave 40% yield of four diastereomers in a ratio of 51:35:8:6. Figure 4.2 shows the major diastereomer of 4.12 with two aromatic protons each showing as a singlet at 6.56 and 5.58ppm while H<sub>a</sub> appears a doublet at 4.64 ppm. Figures 4.3 and 4.4 are copies of the <sup>13</sup>C NMR of the two major diastereomers of the adduct 4.12. <sup>1</sup>H NMR analysis showed that the two major diastereoisomers (J<sub>ab</sub>=10.38, 9.77 Hz) had the anti-relative stereochemistry at the two stereogenic benzylic carbons while the two minor isomers (J<sub>ab</sub>=3.05 and 7.93 Hz) had the syn relative stereochemistry. As previously noted in Chapter 3 the major diastereoisomer showed a highly shielded aromatic proton (5.59 ppm) and methoxy group (3.19 ppm) in the <sup>1</sup>H NMR spectrum. On the basis of this data the

absolute stereochemistry for the two major diastereomeric adducts is as shown in Table 4.2.



Figure 4.2. Preparation and  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) data for 4.11 and 4.12.



Diastereomeric

ratio (%)

46

21

23

8

$\delta H_a$  (ppm)

$\delta H_b$  (ppm)

5.48

4.92

4.85

5.35

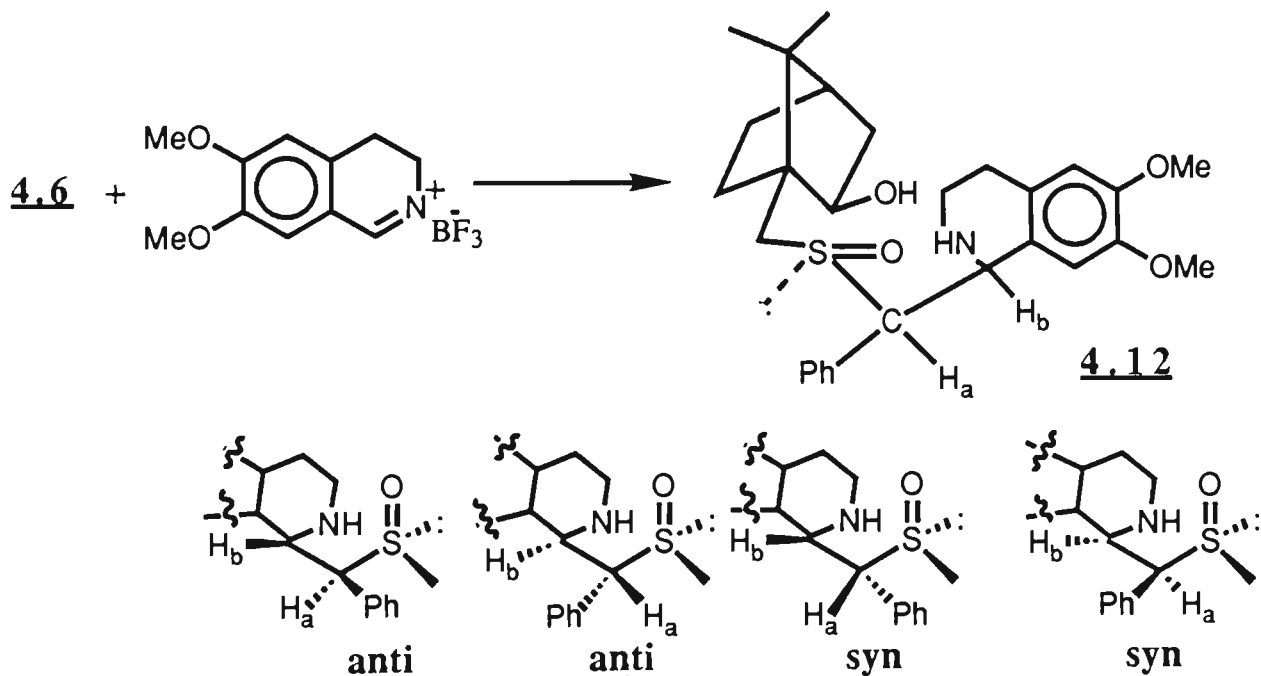
$J_{a,b}$  (Hz)

8.1

6.5

3.3

yield 27%



Diastereomeric

ratio (%)

51

35

8

6

$\delta H_a$  (ppm)

4.64

4.69

4.84

5.01

$\delta H_b$  (ppm)

3.83

3.82

4.27

4.23

$J_{a,b}$  (Hz)

10.38

9.77

3.05

7.93

yield 40%

Figure 4.1  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) of the crude reaction mixture for the reaction of 4.5 and 4a.

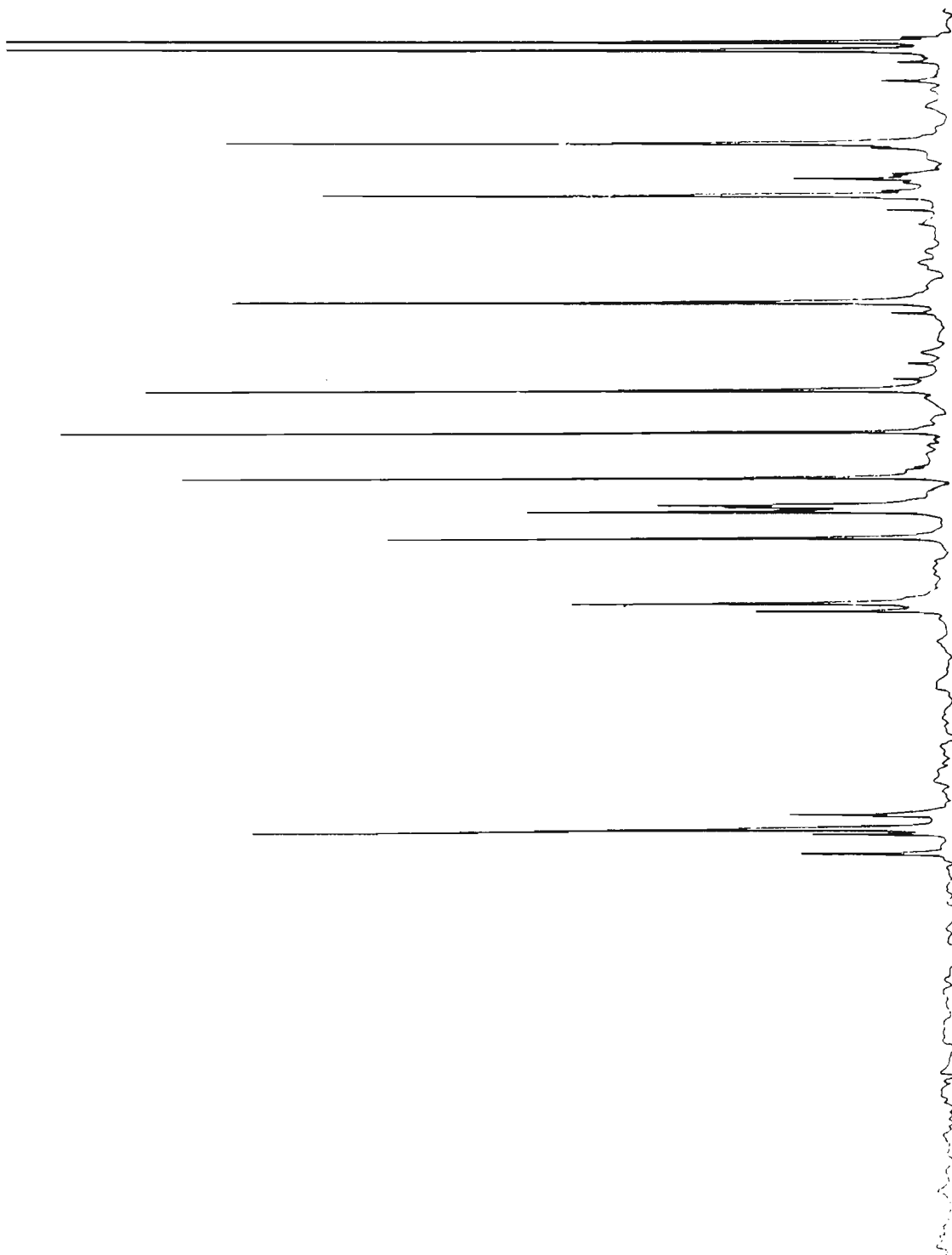
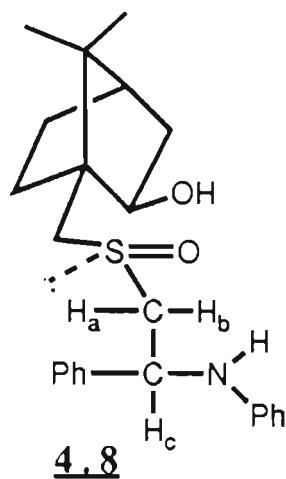


Figure 4.2  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) of 4.12.

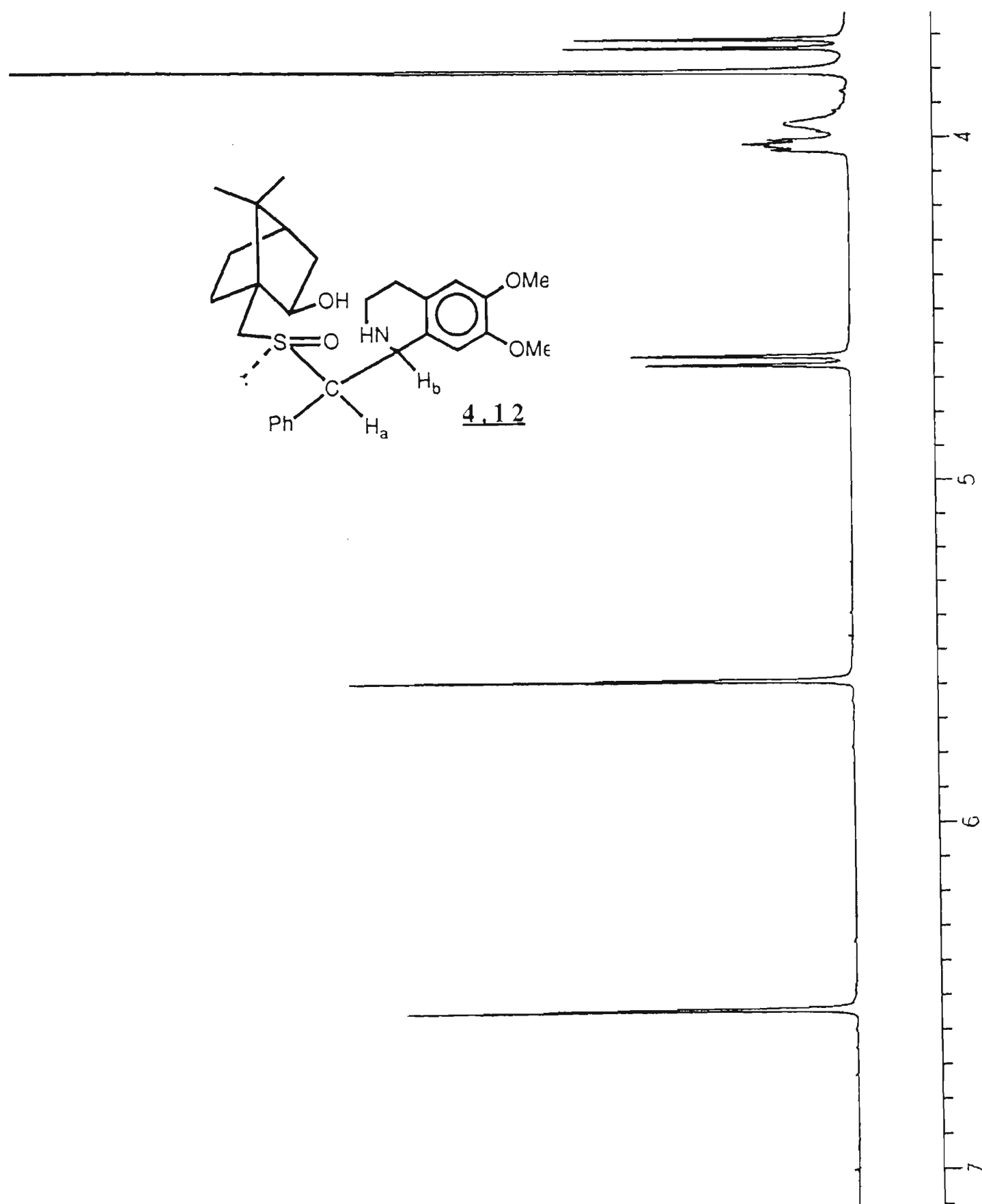


Figure 4.3  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) for the 4.12 (major anti diastereoisomer)

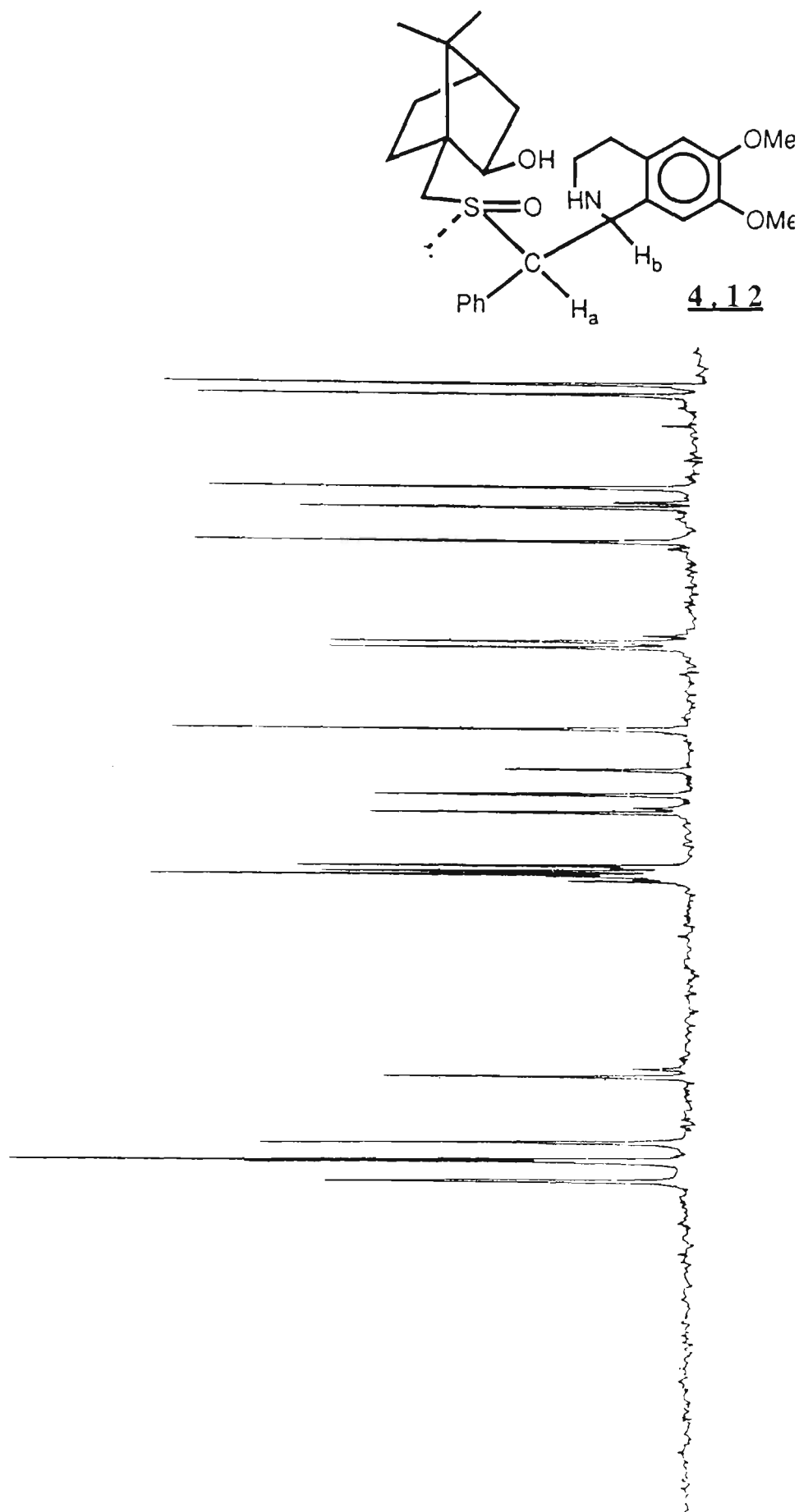
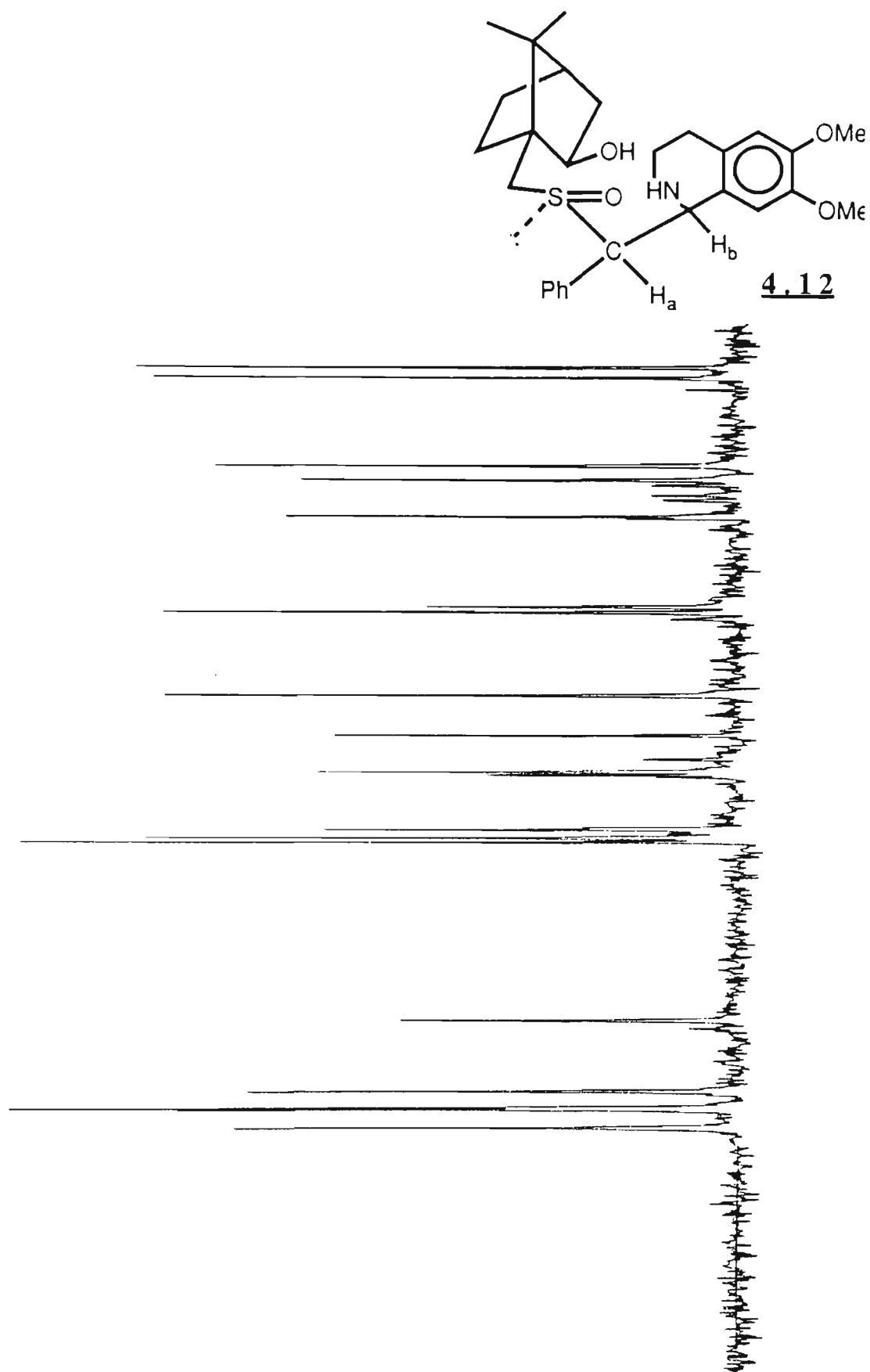


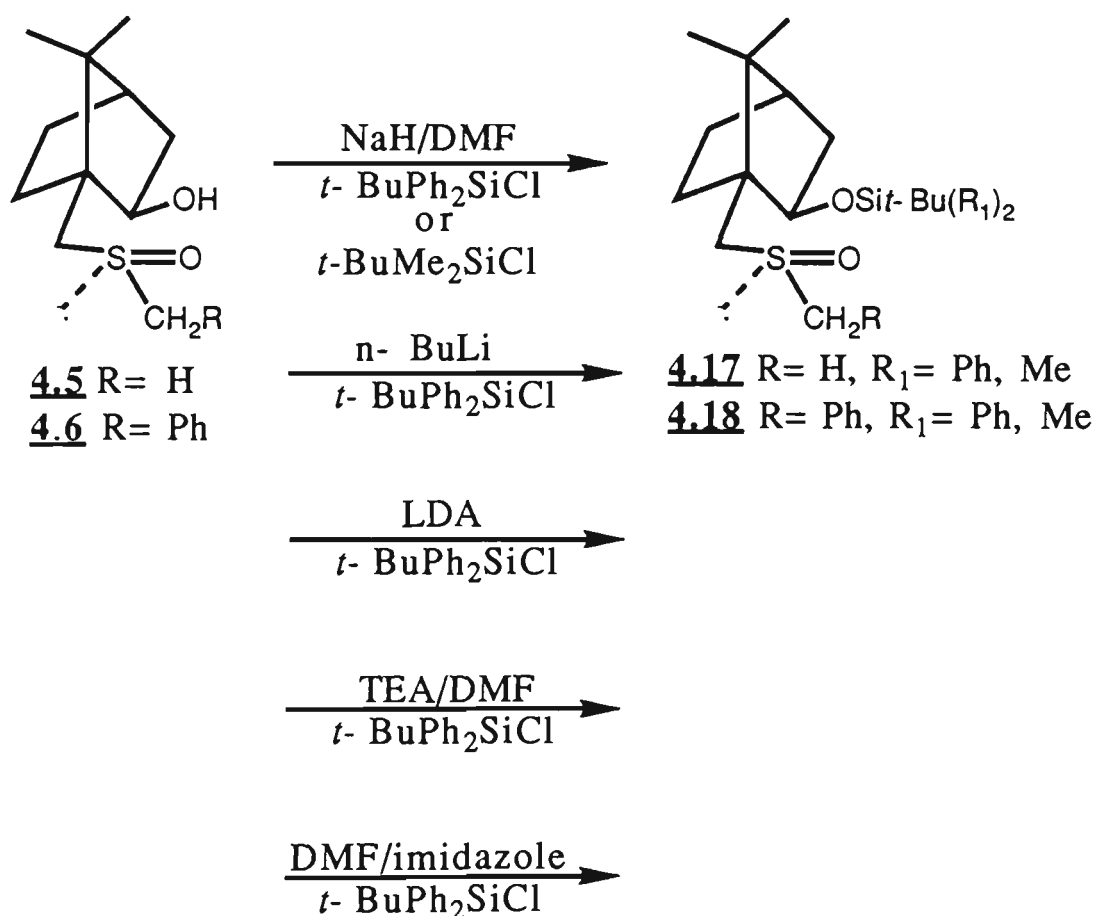
Figure 4.4  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) for the 4.12 (minor anti diastereoisomer)



**Tert-Butylchlorodimethylsilane-mediated Pummerer reactions of (R<sub>S</sub>)-10-Alkylsulfinylbornan-2-exo-ols**

As the above additions to N-benzylideneaniline or 3,4-dihydro-6,7-dimethoxyisoquinoline·BF<sub>3</sub> proceeded in low stereoselectivity and were accompanied with side reactions we attempted to protect the hydroxyl group of the borneol moiety of sulfoxides 4.5 and 4.6 in order to examine its effect on the diastereoselectivity of these reactions. A variety of literature methods were tried as shown in Scheme 4.4.

Scheme 4.4.



Treatment on the sulfoxides 4.5 or 4.6 with sodium hydride in dimethylformamide (DMF) followed by addition of either tert-butylchlorodimethylsilane (TBMSCl) or tert-

butylchlorodiphenylsilane (TBPSCl) resulted in none of the desired silylethers 4.17 or 4.18 and only starting material was obtained. Treatment of sulfoxide 4.5 or 4.6 with first n-butyllithium or lithium diisopropylamide (LDA) followed by the addition of TBMSCl or (TBPSCl) also resulted in the recovery of the starting materials.

Treatment of sulfoxide 4.5 with (TBMSCl) and imidazole in dimethylformamide (DMF)<sup>79</sup> at room temperature for 18 hrs gave none of the desired silylether 4.17, however the imidazole derivative 4.19 (Figure 4.5) was isolated in 70% yield after purification by column chromatography on silica gel. The <sup>1</sup>H NMR showed a broad singlet at 7.6 ppm integrating for 1 proton and a broad singlet at 7.29 ppm integrating for 2 protons (1-methylimidazole<sup>80a,b</sup> has the following spectral data: <sup>1</sup>H NMR (d<sup>6</sup>-DMSO), 6.9, 7.2, 7.4 ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>) 138.7, 130.2, 121.05 ppm and <sup>13</sup>C NMR (136.7, 128.8, 118.4 ppm), while a mass spectra (CI) showed M/Z (relative intensity) 267 (100, M+H<sup>+</sup>), 249 (22, M+H-H<sub>2</sub>O), 69(40). This spectral data is consistent with the product 4.19 (Figure 5). The <sup>1</sup>H NMR chemical shifts and proton assignments for the compound 4.19 are tabulated in Table 4.3.

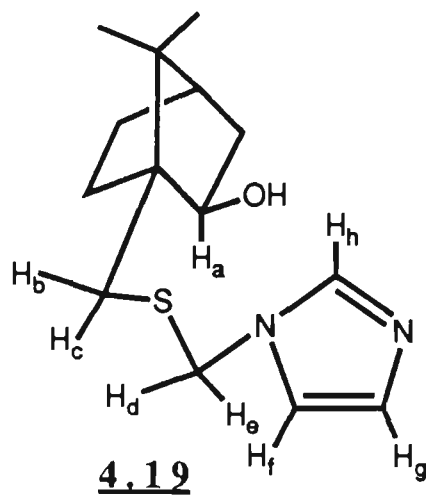
In contrast to sulfoxide 4.5, the analogous benzyl sulfoxide 4.6, when treated under similar conditions, gave a mixture of the imidazole derivative 4.21 (as a mixture of diastereomers in 57:43 ratio and 47% yield) and monothioketal 4.22 (as a mixture of diastereomers in 72:28 ratio and 24% yield). Interestingly pure imidazole derivative 4.21 did not undergo cyclization to monothioketal the 4.22 in dimethylformamide (DMF) at room temperature over 48 hrs or upon exposure to the original reaction conditions. The structures of 4.21 and 4.22 were consistent with

spectral data ( $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, MS, IR). The  $^1\text{H}$  NMR chemical shifts and proton assignments for the major diastereomer of 4.21 and 4.22 are shown in Table 4.4.

Upon the treatment with (TBMSCl), 4-dimethylaminopyridine (DMAP) and triethylamine (TEA) in dimethylformamide (DMF)<sup>89</sup> at room temperature for 18 hrs, sulfoxide 4.6 was cleanly converted to the monothioketal 4.22 as a 62:38 mixture of diastereoisomers in 74% yield with 5% of the disulphide 4.20 also formed.

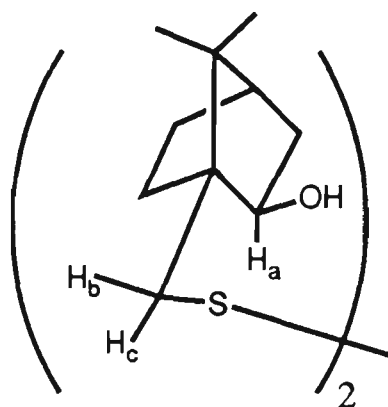


**Table 4.3.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) data and assignments of 4.19 and 4.20.**



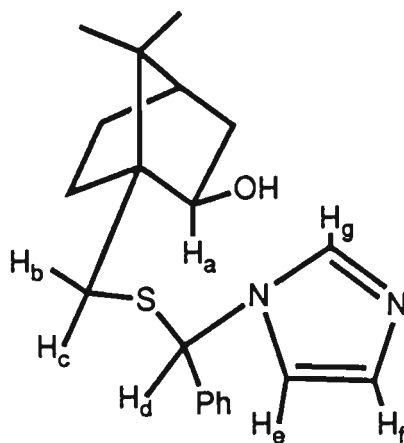
$\text{H}_a$	$\text{H}_b$	$\text{H}_c$	$\text{H}_d$
dd 3.84 ppm	d 2.43 ppm	d 2.80 ppm	d 4.97 ppm
$J = 6.18 \text{ Hz}$	$J_{b,c} = 10.45 \text{ Hz}$		$J_{d,e} = 14.04 \text{ Hz}$

$\text{H}_e$	$\text{H}_f/\text{H}_g$	$\text{H}_h$
d 5.13 ppm	s 7.29 ppm	s 7.60 ppm



$\text{H}_a$	$\text{H}_b$	$\text{H}_c$
dd 3.94 ppm	d 3.19 ppm	d 2.79 ppm
$J = 7.80 \text{ Hz}$	$J_{b,c} = 12.80 \text{ Hz}$	

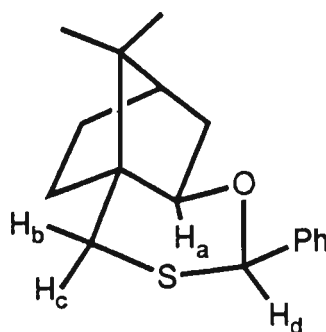
Table 4.4.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) data and assignment of 4.21 and 4.22.



4.21 major isomer

$\text{H}_a$	$\text{H}_b$	$\text{H}_c$
dd 3.91ppm	d 2.93ppm	d 2.35ppm
$J = 7.3 \text{ Hz}$	$J_{b,c} = 11.3 \text{ Hz}$	

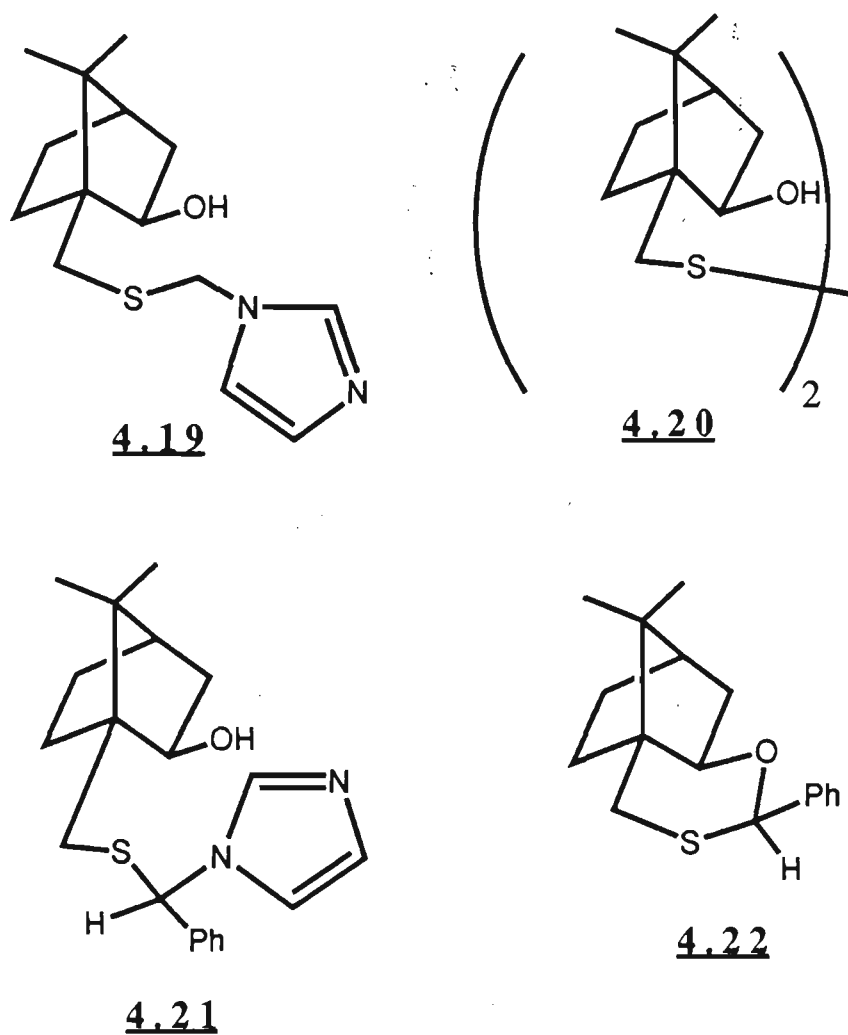
$\text{H}_d$	$\text{H}_{e/f}$	$\text{H}_g$
	s 6.43ppm	



4.22 major isomer

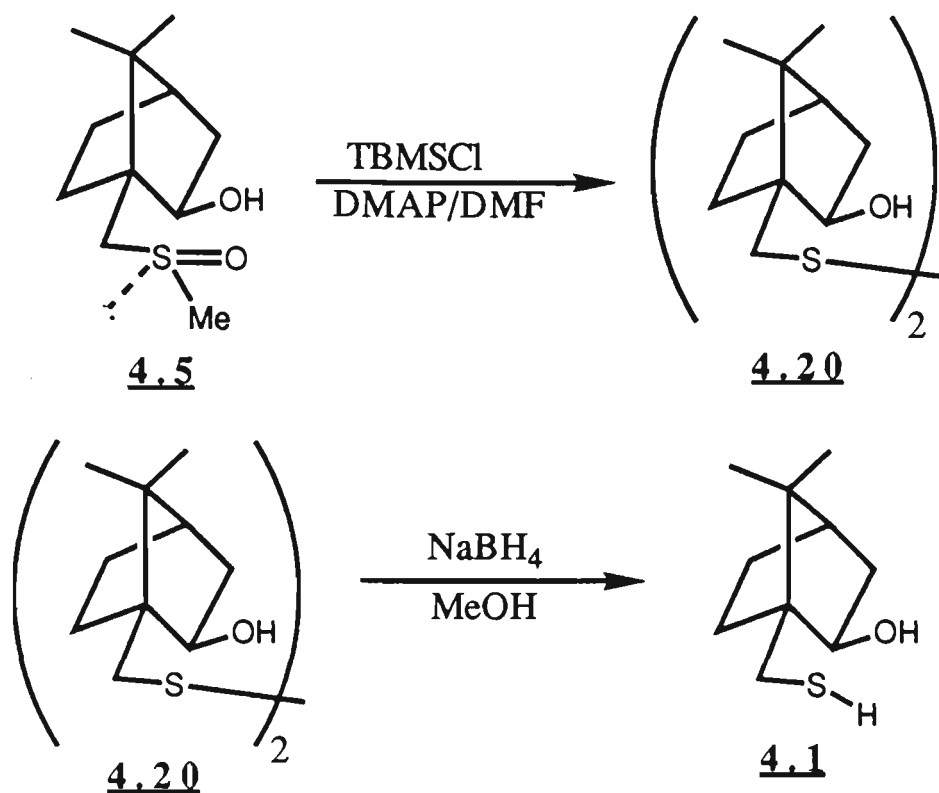
$\text{H}_a$	$\text{H}_b$	$\text{H}_c$	$\text{H}_d$
dd 3.79ppm	d 3.29ppm	d 2.81ppm	s 5.69ppm
$J = 7.5 \text{ Hz}$	$J_{b,c} = 14.2 \text{ Hz}$		

Figure 4.5.



When the sulfoxide 4.5 was treated with TBMSCl, 4-dimethylaminopyridine (DMF) at 25°C for 18 hrs then disulfide 4.20 was the only isolated product in 43% yield. The structure of 4.20 was consistent with spectral data (Table 4.3) and was verified by conversion to 10-thioisoborneol upon reduction with sodium borohydride in methanol (Scheme 4.5).

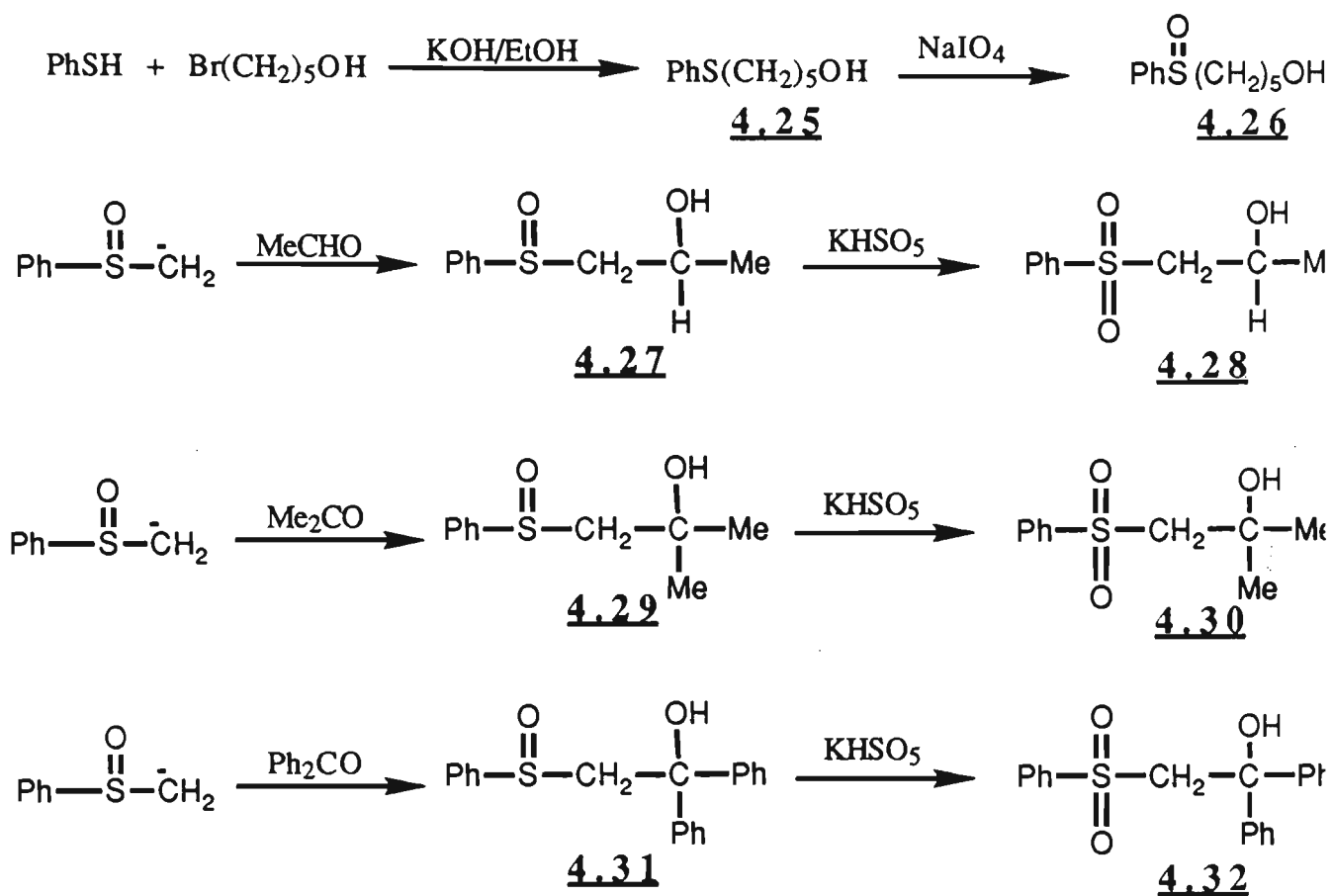
Scheme 4.5.



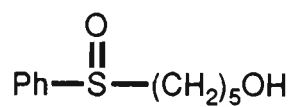
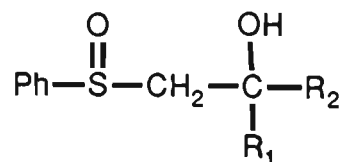
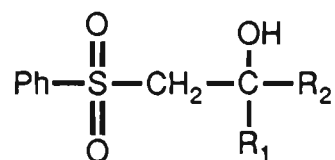
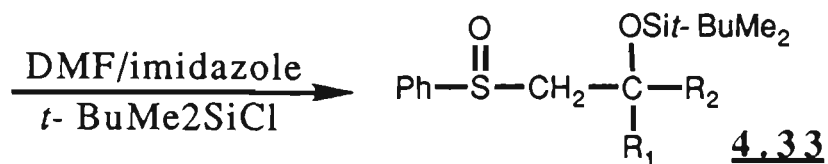
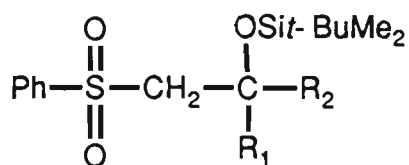
In the attempt to ascertain if this type of reaction can be extended to other sulfoxides we prepared the  $\beta$ -hydroxy sulfoxides and  $\beta$ -hydroxy sulfones shown in Scheme 4.6. The sulfide 4.25 was prepared from thiophenol and 5-bromopentanol in 1M ethanolic potassium hydroxide and then oxidised with sodium periodate to give the sulfoxide 4.26. Sulfoxides 4.27, 4.29 and 4.31 were synthesized from lithiated methylphenylsulfoxide and acetaldehyde, acetone and benzophenone respectively, at  $-78^{\circ}\text{C}$  for 1 hr. The sulfones 4.28, 4.30 and 4.32 were made from oxidation of the corresponding sulfoxides 4.27, 4.29 and 4.31 with oxone. When these sulfoxides and sulfones were treated with TBDMSCl and imidazole in DMF (Scheme 4.7) the only products observed however were the corresponding silylethers 4.33 and 4.34.

The products 4.19-4.22 most likely arise from the silyloxysulfonium intermediate 4.35 which can undergo a Pummerer type rearrangement to the sulfenium ion 4.37 via  $\beta$ -elimination of tert-butyldimethylsilanol (Scheme 4.8). Intramolecular addition of hydroxyl or intermolecular addition of imidazole to 4.37 then gives 4.24 or 4.23 respectively. Pummerer-type rearrangement of sulfoxides by trimethylsilylhalides have been reported<sup>91a,b,c,d</sup>, however there has been little application of TBMSCl/imidazole or TBMSCl/DMAP to these type of reactions. The disulfide possibly arises from 4.36 formed by nucleophilic carbon-sulfur bond cleavage of intermediate 4.35. Disulfides have been reported from the reduction of sulfonylhalides with iodotrimethylsilane<sup>92</sup>. TBMSCl is an effective and efficient reagent for chemoselective O-silylation of the sulfoxide moiety of 10-alkylsulfinylbornan-2-oxo-ols. We suggest the reason for this high chemoselectivity is purely steric in nature since the 2-hydroxy function resides in a highly sterically hindered environment. Consistent with this suggestion was the observation that the corresponding sulfones of 4.5 and 4.6 could be recovered completely unchanged after exposure to the above silylation conditions.

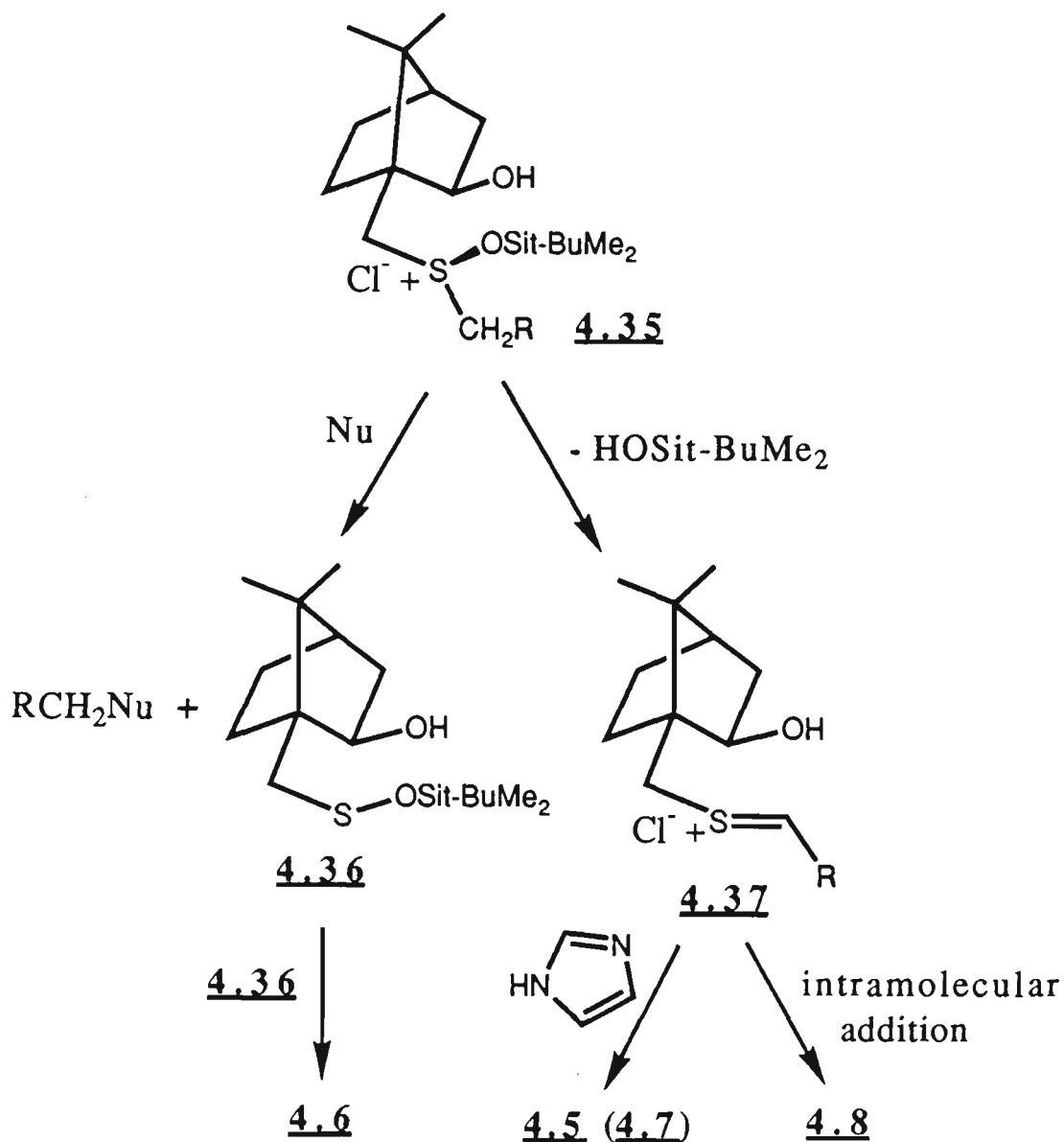
Scheme 4.6.



Scheme 4.7.

**4.26****4.27**  $\text{R}_1 = \text{H}, \text{R}_2 = \text{Me}$ **4.29**  $\text{R}_1 = \text{Me}, \text{R}_2 = \text{Me}$ **4.29**  $\text{R}_1 = \text{Ph}, \text{R}_2 = \text{Ph}$ **4.28**  $\text{R}_1 = \text{H}, \text{R}_2 = \text{Me}$ **4.30**  $\text{R}_1 = \text{Me}, \text{R}_2 = \text{Me}$ **4.32**  $\text{R}_1 = \text{Ph}, \text{R}_2 = \text{Ph}$ **4.33** $\text{R}_1 = \text{H} \quad \text{R}_2 = \text{Me}$ **4.34**

Scheme 4.8.



## EXPERIMENTAL

### 10-Thio-bornan-2-exo-ol<sup>86</sup> 4.2

To a solution of  $\text{LiAlH}_4$  (7.6g, 0.2mol) in 186ml of dry ether at  $-78^\circ\text{C}$  was added camphorsulfonyl chloride (25.3g, 0.1mol) and the resulting mixture was warmed to room temperature and then refluxed overnight. The solution was then quenched with ethyl acetate (50ml) and 1%  $\text{HCl}$  (50ml). The organic layer was then separated and washed with brine, dried ( $\text{MgSO}_4$ ) and evaporated. Column chromatography on silica gel eluting with 5% ethyl



acetate/hexane gave the pure sulfide, 18.6g (68.8%). mp 72-76°C, lit<sup>88</sup>. mp 86-70°C.

**10-Benzylthio-bornan-2-exo-ol 4.4 and 10-methylthio-bornan-2-exo-ol 4.3.**

The 10-thio-bornan-2-exo-ol 4.2 (6.3g, .0339mol) was dissolved in 68ml at .5 molar KOH in ethanol and cooled to 0°C. Either benzyl chloride or methyl iodide (.0339mol) was then added dropwise and stirring was continued overnight at room temperature. The ethanol was then evaporated, water was added (20ml) and the solution was extracted with ether. The ether layers were dried (MgSO<sub>4</sub>) and evaporated to yield 8.72g (93%) of 10-benzylthio-bornan-2-exo-ol 4.4 or as a semisolid 6g (86%) of 10-methylthio-bornan-2-exo-ol 4.3 as a semisolid.

4.3: <sup>1</sup>H NMR 3.8 (m, 1H), 2.81(d, 1H), 2.51(d, J=11.4 Hz, 1H), 2.07(s, 3H), 1.64(m, 7H), 0.99(s, 3H), 0.77(s, 3H); <sup>13</sup>C NMR 76.57, 52.16, 47.26, 44.93, 39.12, 343.18, 30.98, 26.94, 20.40, 19.71, 16.80.

4.4: <sup>1</sup>H NMR 7.32(s, 5H), 3.75(m, 1H), 3.71(s, 1H), 2.70(s, J=9.7 Hz, 1H), 2.47(d, J=9.1 Hz, 1H), 0.98 (s, 3H), 0.77(s, 3H).

**(R<sub>S</sub>)-10-Methylsulfinylbornan-2-exo-ol 4.5 and (R<sub>S</sub>)-1-benzylsulfinylbornan-2-exo-ol 4.6**

4.3 or 4.4 (0.0316mol) was dissolved in DCM (200ml) and cooled to 0°C then a solution of m-CPBA (0.0316mol, 6.4g) in DCM (100ml) was added dropwise and stirring continued at room temperature over night. A saturated solution of NaHCO<sub>3</sub> (100ml) was added and stirring continued for 1 hr. The organic layer was then separated, dried (MgSO<sub>4</sub>) and evaporated. Column chromatography on silica gel in 1:1 ethyl acetate / hexane provided the pure

product. (R<sub>S</sub>)-10-methylsulfinylbornan-2-exo-ol (4.5) was obtained in 64% yield, m.p. 75-76°C.

(R<sub>S</sub>)-10-methylsulfinylbornan-2-exo-ol 4.6 was obtained in 83% yield, m.p. 84-85°C.

4.5: <sup>1</sup>H NMR 4.04 (m, 1H), 3.38 (d, J=13.12 Hz, 1H), 2.65 (s, 3H), 3.41(d, J=13.12 Hz, 1H), 1.29(m, 7H), 1.12(s, 3H); <sup>13</sup>C NMR 76.43, 55.02, 51.04, 47.57, 46.63, 39.56, 38.12, 30.50, 26.73, 20.05, 19.49; IR (nujol) 3340 (br), 1080 (s).

4.6: <sup>1</sup>H NMR 7.40-7.24 (m, 5H), 4.00 (m, 4H), 3.12 (d, J=13.93, 1H), 2.40 (d, J=13.93, 1H), 1.80-1.60 (m, 7H), 1.07 (s, 3H), 0.76 (s, 3H); <sup>13</sup>C NMR 129.60, 128.39, 127.90, 76.41, 59.11, 51.45, 50.67, 47.55, 44.53, 38.09, 30.39, 26.63, 20.00, 19.47.

#### General Procedure for the addition of 4.5 and 4.6 to imines.

To a solution of 4.5 or 4.6 (1mmol) in THF (3 ml) at 0°C was added n-butyllithium (2.1 equiv.) and stirring was continued for 1 hr. The reaction was cooled to -78°C and the imine 4a and 4b was added. The reaction was worked up after 1 hr. by the addition of 10% aqueous K<sub>2</sub>CO<sub>3</sub> (1 ml). The crude reaction mixture was extracted with DCM and dried with MgSO<sub>4</sub>. Yields are recorded in Table 4.1 and 4.2.

#### (R<sub>S</sub>)-10-(2'-phenyl-2'-phenylamino)-ethylsulfinylbornan-2-exo-ol 4.8

<sup>1</sup>H NMR 7.45-6.50(m, 10H), 4.91(dd, 1H, J=5.49, 14.5Hz), 4.03(dd, 1H, J=4.12, 8.08Hz), 3.91(d, 1H, OH), 3.33(d, 1H, J=5.95Hz); <sup>13</sup>C NMR 146.30, 146.13, 141.40, 140.80, 128.79, 127.66, 127.40, 126.02, 117.78, 113.71, 76.57, 60.27, 55.46, 53.51, 51.04, 47.79, 44.71,

38.26, 30.45, 26.81, 20.18, 19.62; IR(film) 3600-3200 (br), 1080(s), 1000(s); MS (CI+ve), 398 (M+H<sup>+</sup>, 100%), 196 (100%), 182(34%), 135(14%), 104(14%), 77(11%); HRMS calcd for C<sub>24</sub>H<sub>31</sub>NO<sub>2</sub>S, 397.2075, found 397.2065.

**1,2,3,4-Tetrahydro-6,7,dimethoxy-1-(exo-2'-hydroxybornan 10'-sulfinyl) methyl] isoquinoline 4.9**

<sup>1</sup>H NMR (major isomer, in part) δ6.61 (s,1H), 6.62(s,1H), 4.56 (m,1H), 4.08(br, 1H, CH(OH)), 3.35 (d, 1H, J=13.1Hz), 2.43 (d,1H, J=13.1Hz); (minor isomer in part) 4.53 (m,1H), 3.45(d,1H), 12.97Hz), 2.52(d,1H, J=12.07 Hz); <sup>13</sup>C NMR (major isomer) 147.51, 147.17, 111.76,109.11, 76.22, 59.62, 55.50, 52.68, 50.73, 47.70; MS (CI+ve) 408(M+H<sup>+</sup>,94%), 390(39%), 205(100%), 192(100%), 176(83%), 135(57%), 107(66%), 91(100%), 77(100%).

**1,2,3,4-Tetrahydro-6,7,dimethoxy-1(exo-2[hydroxybornan-10-sulfinyl)2-phenylmethyl]isoquinoline 4.12**

M.p. 83-84°C; <sup>1</sup>H NMR 7.43-7.16 (s, 5H), 6.54 (s, 1H), 5.59 (s, 1H), 4.64 (d, 1H), ( J=10.33 Hz), 3.78 (s, 3H), 3.18 (s, 3H); <sup>13</sup>C NMR 134.08, 130.44, 128.92, 128.79, 128.70, 127.88, 126.93, 112.06, 110.98, 77.17, 10.80, 55.89, 55.63, 55.24, 51.21, 49.91, 48.05, 45.06, 78.99, 38.56, 31.19, 28.72, 27.29, 20.49, 19.71; IR 3600-3200 (br), 1510 (s), 1460 (s), 1265 (s), 1225 (s), 1115 (s), 1030 (s), MS (CI+ve) 296 (23%), 282 (74%), 192 (100%), 182 (74%), 135 (100%), 107 (100%), 91 (74%); HRMS calcd for C<sub>28</sub>H<sub>38</sub>NO<sub>4</sub>S 484.2522, found 484.2494.

**A General Procedure for the TBMSCl/imidazole Reaction:**

To a solution of the sulfoxide 4.5 or 4.6 (2 mmol) and TBMSCl

(330 mg, 2.2 mmol) in dry DMF (3ml) and was added imidazole (340 mg, 5 mmol) and the solution was stirred at room temperature for 18 h. Water (10ml) was added and the solution was extracted with dichloromethane (3 x 10ml). The combined extracts were washed with water (5 x 15ml), dried (MgSO<sub>4</sub>) and then evaporated. The crude product was purified by column chromatography on silica gel using ethyl acetate and then methanol/ethyl acetate (5:95) as eluent. Sulfoxide 4.5 gave 4.19 (370 mg, 70%) as a colourless oil. Sulfoxide 4.6 gave 4.21 (320 mg, 47% yield) and 4.22 (130 mg, 24%) as colorless oils and as a mixture of diastereoisomers.

**(1S,2R,4R)1-(1-(2-hydroxy-7,7-dimethyl)-bicyclo-[2.2.1] heptyl methylthiomethyl imidazole 4.19.**

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.60 (br. s, 1H), 7.29 (br. s, 2H), 5.09 (d, J = 14 Hz, 1H), 4.95 (d, J = 14 Hz, 1H), 3.84 (dd, J = 4, 7.5 Hz, 1H), 3.28 (br. s, 1H, OH), 2.81 (d, J = 11.5 Hz, 1H), 2.44 (d, J = 11.5 Hz, 1H), 1.75 (m, 4H), 1.44 (sex, 1H), 1.19 (sex, 1H), 1.03 (m, 1H), 1.02 (s, 3H), 0.79 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 136.7, 128.8, 118.4, 75.1, 51.7, 48.3, 47.0, 45.0, 40.2, 30.5, 29.9, 25.3, 20.1, 17.6; IR (film) 3600-2940 (br. s), 3010 (shoulder), 1455 (m), 1340 (m), 1321 (m), 1178 (m), 1024 (s), 980 (m), 868 (m), 789 (m), 663 (m), 611 (m) cm<sup>-1</sup>; MS(CI +ve) 267 (100, M + H<sup>+</sup>), 249 (22, M + H<sup>+</sup> - H<sub>2</sub>O), 69 (40), ; HRMS calcd for C<sub>14</sub>H<sub>23</sub>N<sub>2</sub>OS 267.1530, obsd 267.152.

**4a,5,6,7,8,8a-hexahydro-2-phenyl-4a,7(1-1-dimethyl) methano-2H,4H-1-oxa-3-thianaphthalene 4.22.**

IR (film) 1452 (m), 1389 (m), 1261 (m), 1180 (m), 1072 (s), 1060 (m), 1044 (m), 710 (s), 697 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): (in part) major isomer  $\delta$  7.45 - 7.25 (m, 5H), 5.69 (s, 1H), 3.79 (dd,  $J$  = 3.3, 7.5 Hz, 1H), 3.29(d,  $J$  = 14.2 Hz, 1H), 2.81 (d,  $J$  = 14.2 Hz, 1H), 1.49 (s, 3H), 0.96 (s, 3H); minor isomer (in part)  $\delta$  6.08 (s, 1H), 3.87 (dd,  $J$  = 3.7, 7.7 Hz, 1H), 1.25 (s, 3H), 0.93 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): major isomer (in part)  $\delta$  85.7, 78.0, 45.6, 38.0, 29.9, 27.3, 23.4, 20.4; minor isomer 83.1, 79.6, 44.8, 37.2, 26.9; MS(CI +ve) 275 (95,  $\text{M} + \text{H}^+$ ), 169 (100), 157 (80); HRMS calcd for  $\text{C}_{17}\text{H}_{22}\text{SO}$ , 274.1390, obsd 274.139.

**(1S,2R,4R)1-(1-(2-hydroxy-7,7-dimethyl)-bicyclo-[2.2.1]heptyl)methylthio(phenyl)methylimidazole 4.21.**

IR (film) 3650-3020 (br. s), 3110 (shoulder), 1457 (m), 1390 (m), 1372 (m), 1222 (m), 1110 (m), 1073 (s), 1030 (m), 918 (m), 879 (m), 821 (m), 732 (m), 661 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): major isomer (in part),  $\delta$  8.85 (s, 1H), 7.6 - 7.1 (m, 7H), 6.43 (s, 1H), 3.91 (dd,  $J$  = 3.9, 7.3 Hz, 1H), 2.93 (d,  $J$  = 11.3 Hz, 1H), 2.35 (d,  $J$  = 11.3 Hz, 1H), 1.03 (s, 3H), 0.74 (s, 3H), minor isomer (in part)  $\delta$  8.82 (s, 1H), 6.30 (s, 1H), 3.84 (dd,  $J$  = 3.7, 7.5 Hz, 1H), 2.74 (d,  $J$  = 11.5 Hz, 1H), 2.55 (d,  $J$  = 11.5 Hz, 1H), 0.99 (s, 3H), 0.80 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): major isomer,  $\delta$  138.2, 136.7, 129.1, 128.4, 128.2, 126.0, 118.0, 75.6, 65.1, 52.0, 47.4, 45.2, 40.5, 30.8, 26.7, 20.3, 19.8, minor isomer (in part)  $\delta$  138.0, 129.4, 128.4, 118.0, 75.8, 45.0, 40.2, 31.1, 26.8, 20.4, 19.8; MS(CI +ve) 343 (12,  $\text{M} + \text{H}^+$ ), 275 (100), 169 (51); HRMS calcd for  $\text{C}_{20}\text{H}_{27}\text{N}_2\text{OS}$  343.1843, obsd 343.184.

**A General Procedure for the TBMSCl/DMAP Reaction.**

To a solution of the sulfoxide 4.5 or 4.6 (1 mmol), 4-dimethylaminopyridine (40 mg, 0.33 mmol) and dry triethylamine (1 mmol) in dry DMF (3ml) was added TBMSCl (150 mg, 1 mmol). The solution was stirred at room temperature for 18 h. The crude product was isolated as described above and then purified by column chromatography on silica gel 60. Elution with ethyl acetate/hexane (1:1) gave the disulfide 4.20 and then 4.22 upon elution with methanol/ethyl acetate (5:95). Sulfoxide 4.5 gave 4.20 (160 mg, 43%) as a colorless oil. Sulfoxide 4.6 gave 4.21 (202 mg, 74%) and 4.22 (18 mg, 5%) as colorless oils.

**(1S,2R,4R)Di(1-(2-hydroxy-7,7-dimethyl)-bicyclo[2.2.1]heptyl) methyl) disulfide 4.20.**

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.95 (dd, J=3, 7.8 Hz, 1H), 3.19 (d, J = 12.8 Hz, 1H), 2.79 (d, J = 12.8 Hz, 1H), 2.63 (br. s, 1H, OH), 1.84 - 1.6 (m, 4H), 1.49 (sex, 1H), 1.29 (sex, 1H), 1.09 (sex, 1H), 1.08 (s, 3H), 0.84 (s, 3H); EIMS m/z (relative intensity) 370 (8, M<sup>+</sup>), 352 (2, M - H<sub>2</sub>O), 336 (20); HRMS calcd for C<sub>20</sub>H<sub>34</sub>O<sub>2</sub>S<sub>2</sub> 370.1997, obsd 370.200.

## CHAPTER 5

## DIASTEREOSELECTIVE ADDITION OF ALDEHYDES AND IMINES TO N-SILYLATED BENZYL SULFOXIMINES.

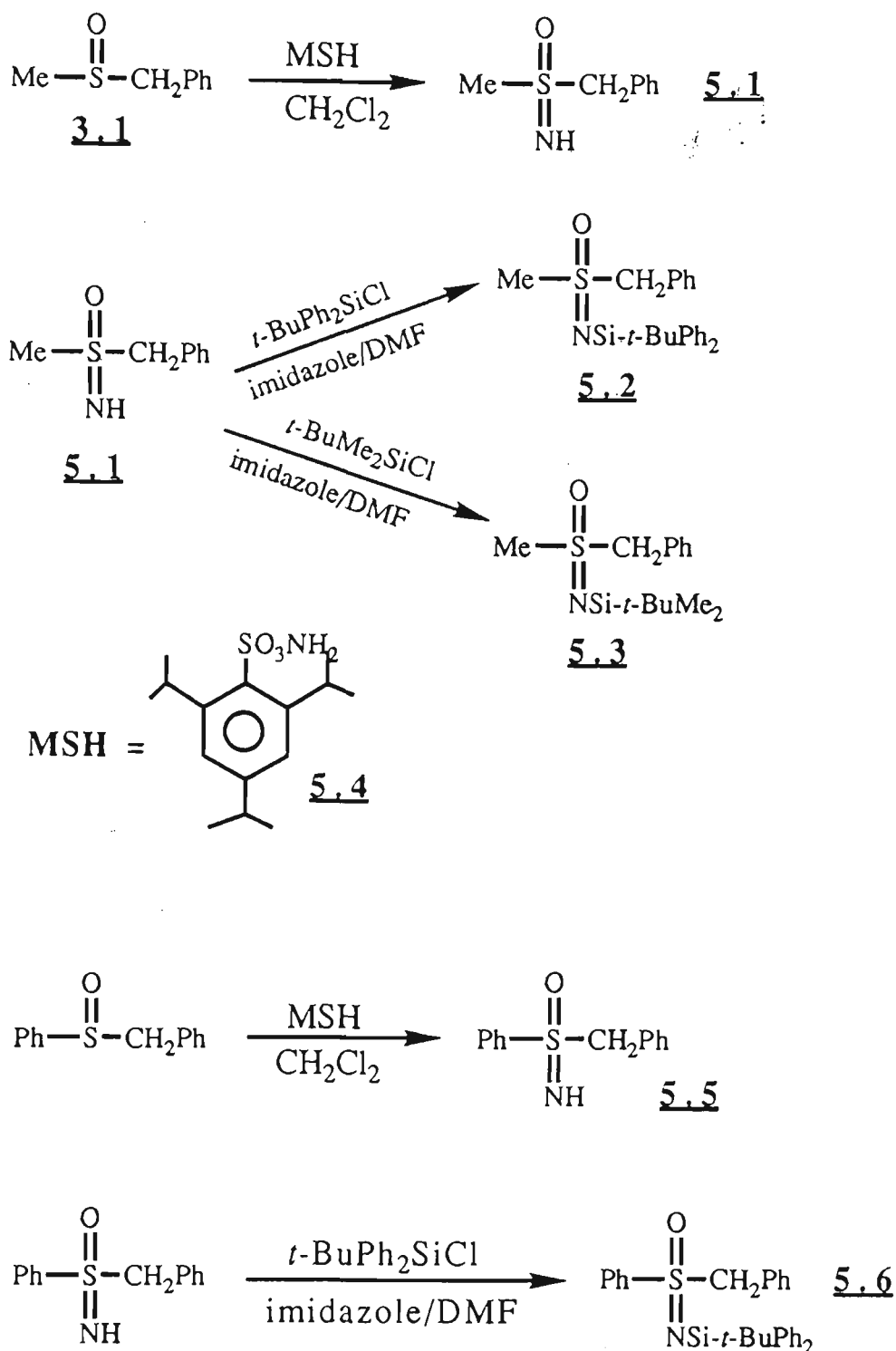
In order to develop methods for preparing 1-benzylisoquinoline alkaloids in high enantiomeric purity we have investigated the addition of benzyl carbanions that are stabilized by an alpha stereogenic sulfur group, to prochiral imines.

Since the addition of the lithium salts of S-benzyl-S-alkylsulfoxides to imines proceeded either with poor chemical yield or modest diastereoselectivity (refer to Chapter 3), we turned our attention to S-benzyl sulfoximines in order to circumvent these problems.

The racemic N-tert-butyldiphenylsilyl-S-benzyl-S-methylsulfoximine 5.2 and N-tert-butyldimethyl-S-benzyl-S-methylsulfoximine 5.3 were synthesized from benzyl methyl sulfoxide 3.1. Sulfoxide 3.1 was reacted with mesitylenesulfonylhydroxylamine<sup>81,82</sup> (MSH) in dichloromethane (Scheme 5.1) to yield S-benzyl-S-methyl sulfoximine in 42% yield, which was then subjected to N-silylation with either tert-butylchlorodiphenylsilane (t-BuPh<sub>2</sub>SiCl) or tert-butylchlorodimethylsilane (t-BuMe<sub>2</sub>SiCl) and imidazole in dimethylformamide to yield racemic 5.2 or 5.3 in excellent yield (96%). Similarly benzyl phenyl sulfoxide was firstly treated with mesitylenesulfonylhydroxylamine 5.4 to form S-benzyl-S-phenyl sulfoximine<sup>67c</sup> 5.5 in 30% yield which was then N-silylated with t-BuPh<sub>2</sub>SiCl and imidazole in dimethylformamide to give N-tert-butyldiphenylsilyl-S-benzyl-S-phenylsulfoximine (5.6) in 95% yield (Scheme 5.1).



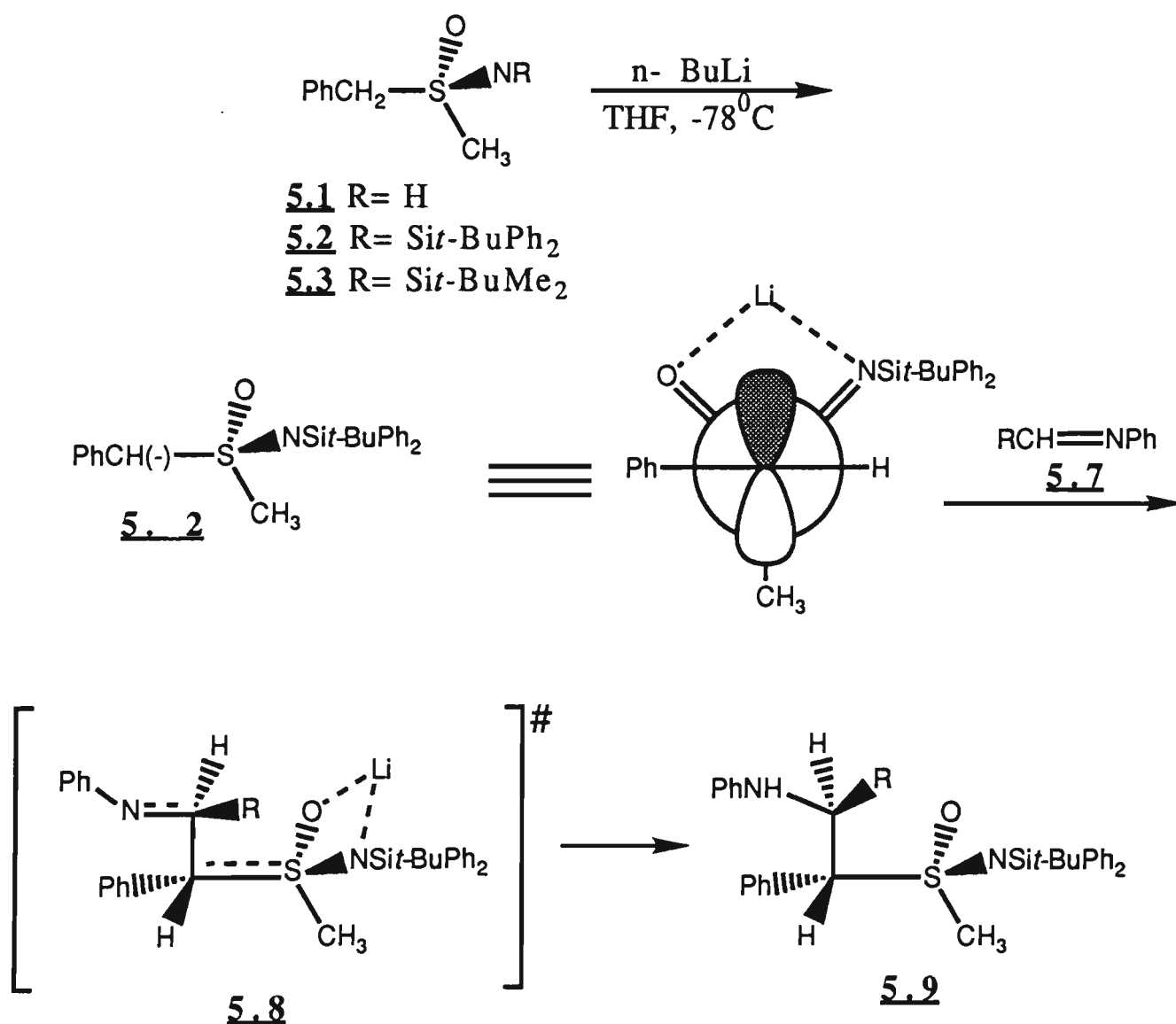
Scheme 5.1.



Sulfoximines 5.2, 5.3 and 5.6 were treated with *n*-butyllithium (1.1 equiv) in tetrahydrofuran at  $-78^\circ\text{C}$  for 1 hr and then treated with either a solution of an imine or a suspension or solution of the imine  $\cdot\text{BF}_3$  complex for 1 hr (Scheme 5.2) at the temperature indicated in Table 5.1. The imine  $\cdot\text{BF}_3$  complex was

prepared by adding  $\text{BF}_3$  etherate (1 equiv.) to a solution of the imine in tetrahydrofuran at  $-78^\circ\text{C}$  for 15 minutes. The pure  $\beta$ -amino sulfoximine adducts (5.9) were obtained after a standard aqueous work up followed by extraction into dichloromethane and column chromatography on silica gel.

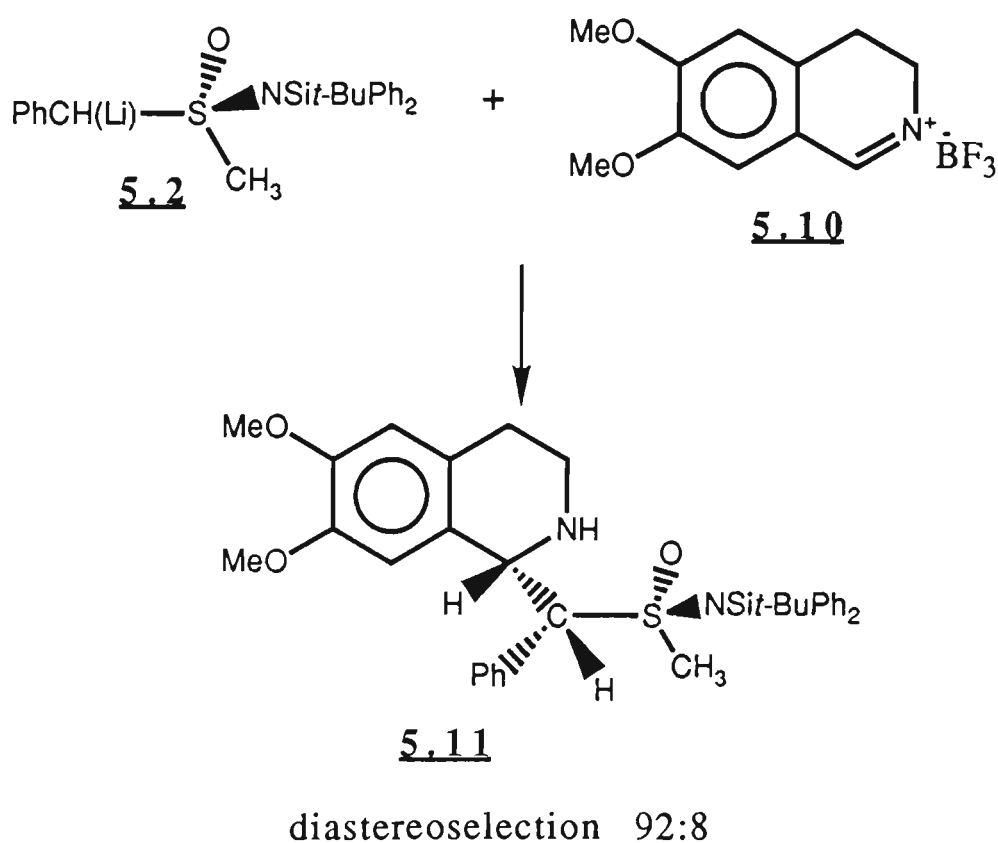
**Scheme 5.2** Diastereoselective addition of 5.1, 5.2 and 5.3 to imines 5.7.



When lithiated 5.2 was treated with N-benzylideneaniline (entry 1, Table 5.1), the yield was 60% and the diastereomeric ratio was 79:21, but when lithiated 5.2 was reacted with N-

benzylideneaniline  $\cdot \text{BF}_3$  complex, the yield improved to 86% and the diastereomeric ratio improved to 95:5. It is also interesting to note that 3,4-dihydro-6,7-dimethoxyisoquinoline would not react at all with 5.2. However when 5.2 was treated with 3,4-dihydro-6,7-dimethoxyisoquinoline. $\text{BF}_3$  complex (5.10) a yield of 45% of the adduct 5.11 and diastereoselection of 92:8 was obtained (Scheme 5.3).

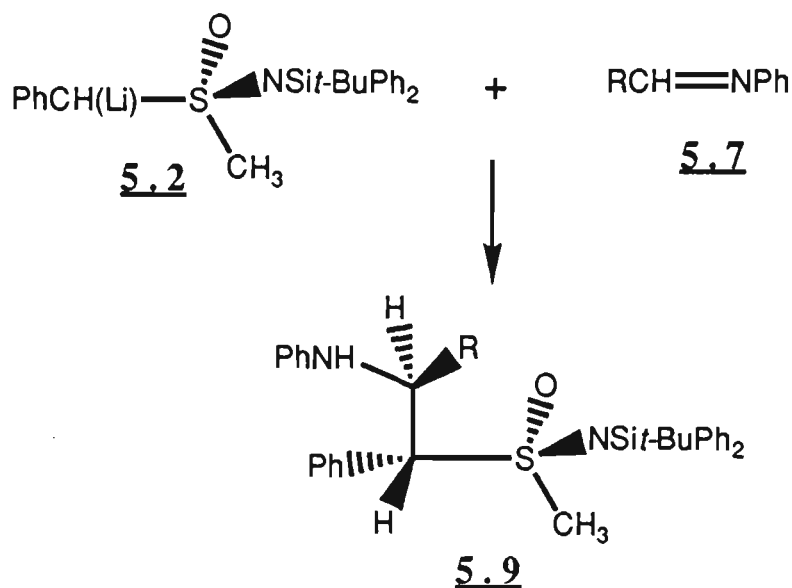
**Scheme 5.3. Diastereoselective addition of 5.2 to 5.10.**



The temperature during addition was always  $-78^\circ\text{C}$  when imines were precomplexed with  $\text{BF}_3$  or when imines were highly reactive (entry 1 and 3), and  $-45^\circ\text{C}$  when imines were less reactive (entries 4 and 6, Table 5.1). The diastereomeric ratio was in all

cases determined by  $^1\text{H}$  NMR (400MHz) spectroscopy on the crude reaction mixture.

It was noteworthy that in each case examined only two of the four possible racemic diastereomeric products were formed. While the reaction of lithiated N-tert-butyldiphenylsilyl-S-benzyl-S-methylsulfoximine with imines 5.7 (entries 1,4 and 5) proceeded with moderate yields (60%, 66% and 58% respectively) and moderate product diastereoselection (79:21, 82:18 and 82:18 respectively) the analogous reaction with 5.7·BF<sub>3</sub> complex gave product 5.9 in considerable better yield and with consistently high diastereoselectivity (entries 2,3,5 and 6, Table 5.1). This point can be clearly illustrated by considering the reaction between lithiated 5.2 and N-benzylideneaniline (entries 1 and 2, Table 5.1). When R of imine 5.7 was i-Pr (entry 7, Table 5.1) the diastereoselectivity was 50:50, unfortunately when this reaction was repeated on the BF<sub>3</sub> complexed the imine numerous unidentifiable products resulted.

Table 5.1. Reaction of lithiated 5.2 with imines 5.7.

entry	R of additive <sup>a</sup> imine <u>5.7</u>		Yield, % <sup>b</sup>	Temp., °C	Diastereo- selection <sup>c</sup>
1	Ph	---	60	-78	79 : 21
2	Ph	BF <sub>3</sub>	86	-78	95 : 5
3	2-Furyl	BF <sub>3</sub>	82	-78	95 : 5
4	Et	---	66	-45	82 : 18
5	i-Bu	---	51	-45	82 : 18
6	i-Bu	BF <sub>3</sub>	70	-78	96 : 4
7	i-Pr	---	58	-45	50 : 50
8	i-Pr	BF <sub>3</sub>	0	-78	---

<sup>a</sup> Imine 5.7 was pre-complexed with BF<sub>3</sub>.Et<sub>2</sub>O (1 equiv) at -78°C in the THF prior to addition to lithiated 5.2. <sup>b</sup> Yield of diastereomerically pure product after column chromatography. <sup>c</sup> Determined by <sup>1</sup>H NMR (400 MHz) spectroscopy on the crude reaction mixture.

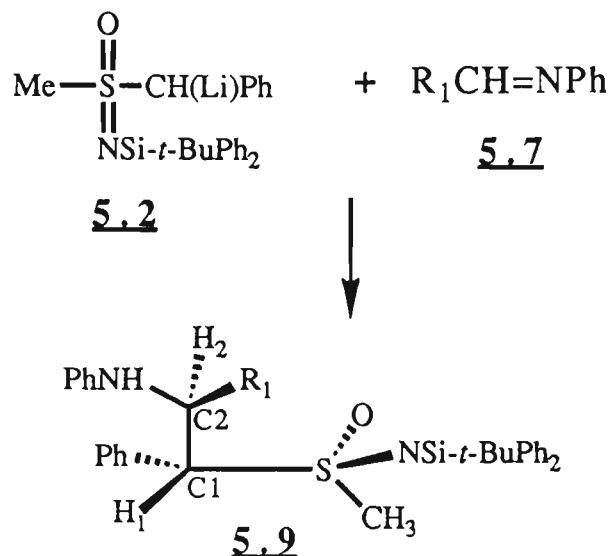
Table 5.2 shows the <sup>1</sup>H NMR chemical shifts for the S-methyl group and the diastereomeric protons H-1 and H-2 as well as the coupling constant J<sub>1,2</sub> of the adducts 5.9. The <sup>13</sup>C NMR chemical

shifts of C-1 and C-2 and the S-methyl group of these adducts is shown in Table 5.3.

In each case investigated the  $^1\text{H}$  NMR spectrum of the major diastereomer 5.9 revealed a one proton doublet at 3.84-4.58ppm with  $J_{1,2}=2.9-6.1$  Hz for the proton H-1 at the stereogenic benzylic carbon, while H-2 occurred between 4.45-5.78ppm. The methyl group attached to sulfur occurred in the range 2.14-2.41ppm.

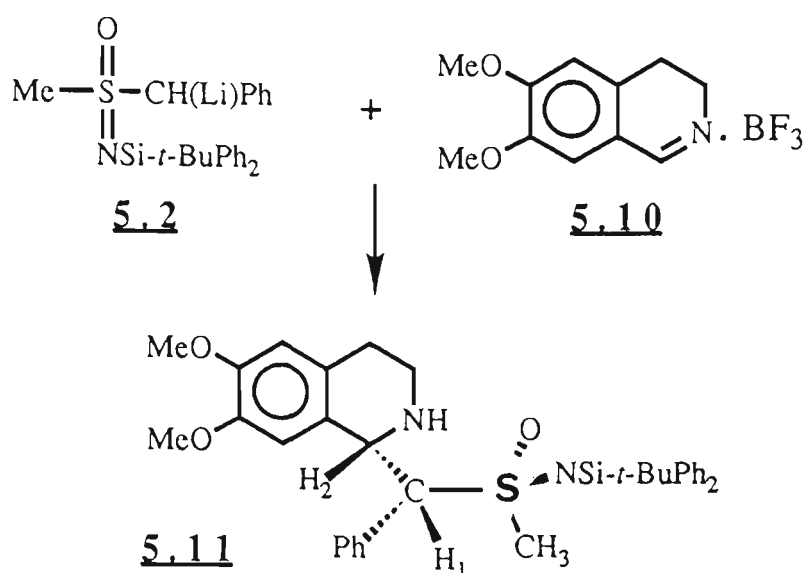
In the case of the minor diastereomer 5.9  $^1\text{H}$  NMR revealed a one proton doublet for the proton  $^1\text{H}$  between 4.14-4.43ppm with  $J_{1,2}=3.58-6.07\text{Hz}$  while H-2 occurred between 4.41-5.82ppm. The methyl group attached to sulfur occurred in the range of 2.02-2.23ppm. For each diastereomeric pair the S-methyl group and H-1 occurs at higher field in the minor diastereoisomer. Whereas H-2 occurs at lower field in the minor diastereoisomer, except for the case when  $\text{R}=\text{i-Bu}$ .

Table 5.2  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) data and assignments for 5.9 and 5.11.



Entry	5.9		R	SMe	H <sub>2</sub>	H <sub>1</sub>	J <sub>1,2</sub> (Hz)	J <sub>NH<sub>2</sub></sub> (Hz)
1	a	major	2-Fur	2.31	5.56	4.58	6.10	---
1 A		minor		2.12	5.82	4.55	5.07	---
2	b	major	Pur	2.30	5.61	4.26	4.01	---
2 A		minor		2.07	5.78	4.22	3.30	---
3	c	major	Et	2.26	4.78	4.43	3.16	10.53
3 A		minor		2.22	5.09	4.27	6.97	---
4	d	X-ray	i-Pr	2.41	4.41	4.13	6.41	10.30
4 A		material		2.26	4.59	a	a	---
5	e	major	i-Bu	2.14	5.09	4.47	2.79	10.50
5 A		minor		2.05	4.80	4.29	3.87	---

a Obscured by signal from the other diastereomeric product.

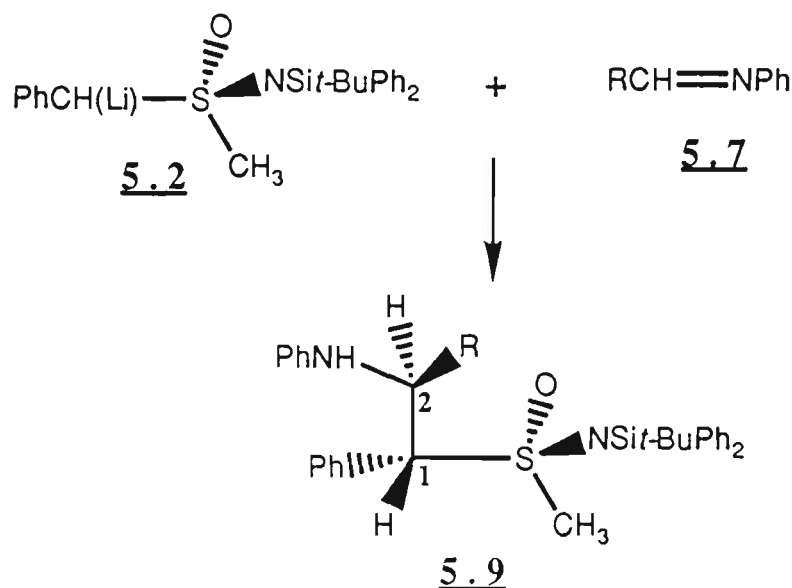


	SMe	H <sub>1</sub>	H <sub>2</sub>	J <sub>1,2</sub> (Hz)
major	2.53	5.38	4.37	2.90
minor	2.47	5.05	4.60	9.94

From the Table 5.3 it is clear that the  $^{13}\text{C}$  NMR resonances for the S-methyl group occur in a narrow range between 43.9-45.8ppm, while C-2 occurs in the range 72.19-77.61 ppm, and C-1 in the range 52.08-58.20ppm Entry 3 is anomalous since C-1 resonates at 48.79ppm.



Table 5.3  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) data and assignments for 5.9.



entry	R	C <sub>1</sub>	C <sub>2</sub>	SMe
1	Et	54.20	73.20	45.80
2	i-Pr	58.49	75.66	44.25
3	i-Bu	48.79	72.19	43.90
4	Ph	57.24	77.61	44.20
5	2-Furyl	52.08	75.05	44.40

The relative  $1\text{S}^*$ ,  $2\text{S}^*$ ,  $\text{Ss}^*$  of 5.9 (R=Et and i-Pr entries 1 and 3) was unequivocally determined by a single-crystal x-ray crystal structure analysis (Figures 5.1 and 5.2).

It is of interest to note that the estimate of the dihedral angle between bond C-1-H-1 and C-2-H-2 in (R=Et) from the structure analysis ( $\angle 1,2 \text{ ca } 77^\circ\text{C}$ ) and the value of the H-1, H-2 coupling constant ( $J_{1,2} = 3.2\text{Hz}$ ) from the  $^1\text{H}$  NMR analysis of 5.9 (R-Et) in deuteriochloroform solution suggest that this compound adopts a similar conformation in the solid state and in solution, Figure 5.1.

When  $R=(i\text{-Pr})$  the estimate of the dihedral angle between bond C-1-H1 and C-2-H-2 is ca  $175^\circ\text{C}$  and the value of the H-1, H-2 coupling constant ( $J_{1,2}=6.41\text{Hz}$ ) from the  $^1\text{H}$  NMR analysis in deuteriochloroform solution, also suggesting that this compound adopts a similar conformation in the solid state and in solution and a different conformation from adduct 5.9 ( $R=\text{Et}$ ) (Figure 5.2).

Figure 5.1 ORTEP drawing of the X-ray structure of the compound 5.9c.

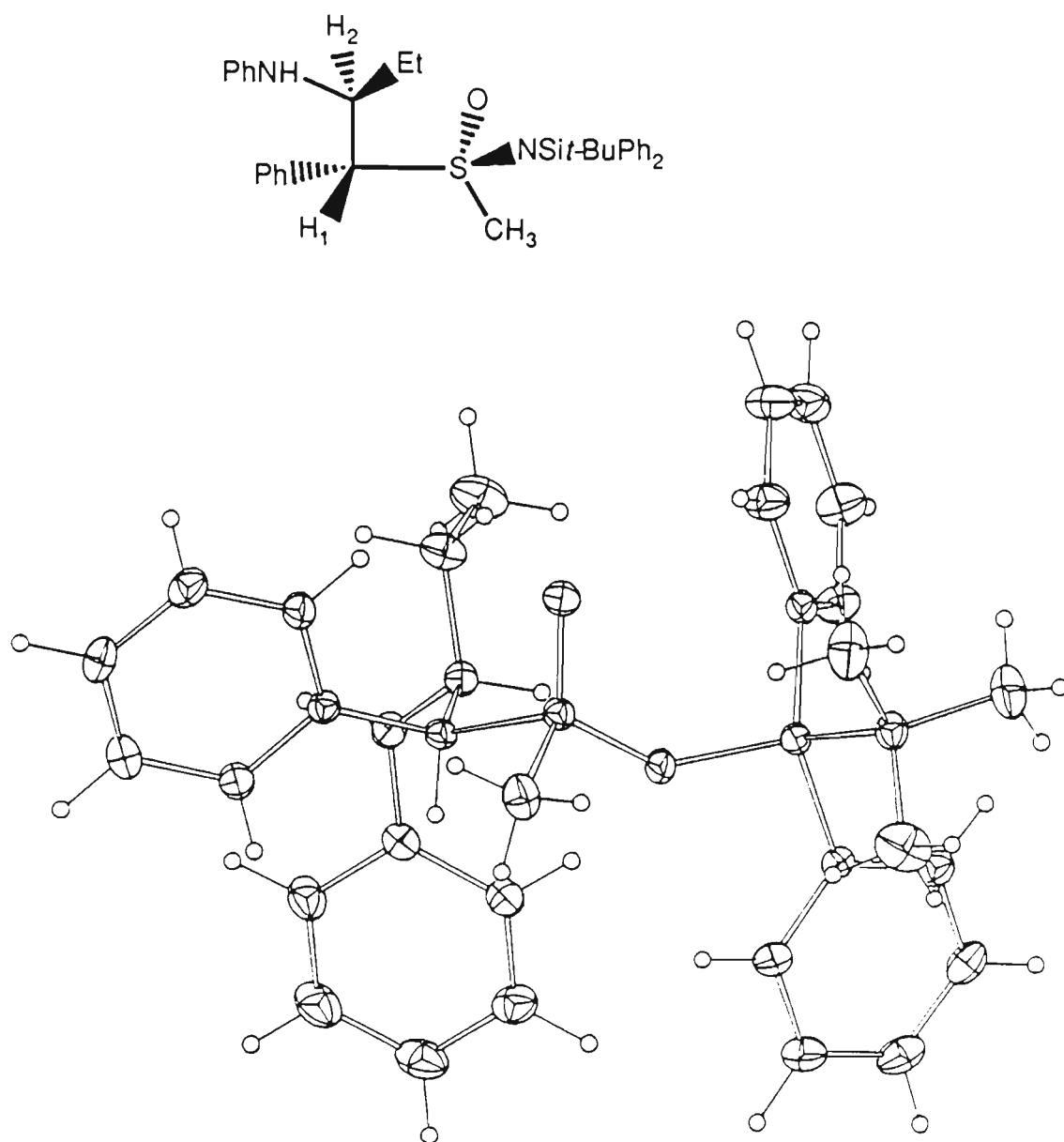
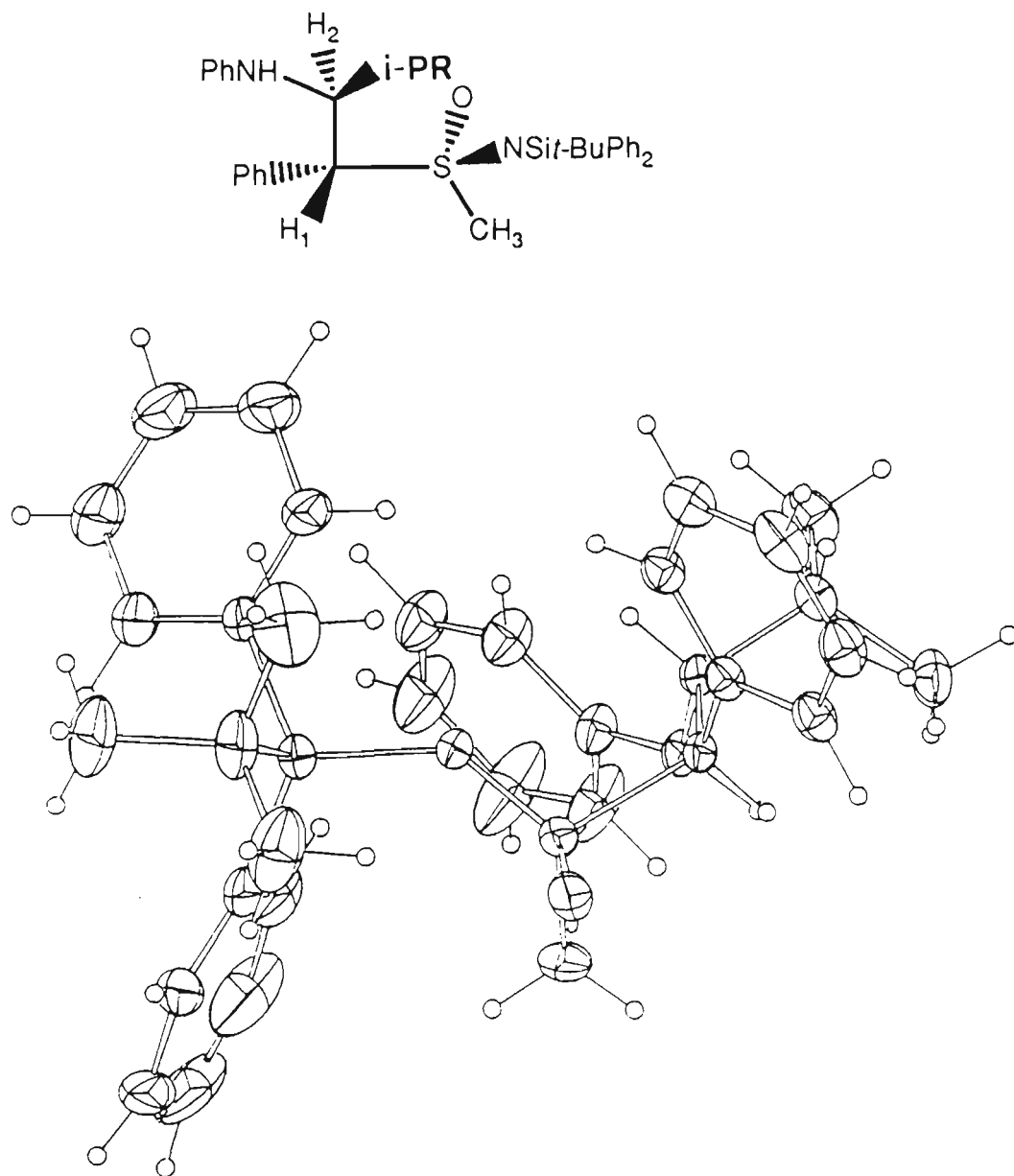


Figure 5.2 ORTEP drawing of the X-ray structure of the compound 5.9d.



The relative  $1S^*$ ,  $2S^*$ ,  $Ss^*$  stereochemistry of adducts 5.9 (entries 1,2,4-6) were assigned by analogy to entries 3 and 4, on the bases of the  $^1H$  NMR and  $^{13}C$  NMR spectra. From the magnitude of their coupling constants  $J_{1,2}=3.16\text{Hz}$  and  $J_{1,2}=6.41\text{Hz}$  respectively it is clear that compound 5.9 ( $R=\text{Et}$ ) and 5.9 ( $R=i\text{-Pr}$ ) must assume different conformations. Similarly compounds 5.9 ( $R=2\text{-furyl}$ ) and 5.9 ( $R=i\text{-Pr}$ ) have a similar conformation ( $J_{1,2}=6.10\text{Hz}$  and  $J_{1,2}=6.41$  respectively) and compounds 5.9 ( $R=\text{Et}$ ), 5.9 ( $R=i\text{-Pr}$ ), and 5.11 have a similar conformation ( $3.16\text{Hz}$ ,  $2.79\text{Hz}$  and  $2.90\text{Hz}$  respectively). While compound 5.9 ( $R=\text{Ph}$ ) may have a conformation intermediate between that of 5.9 ( $R=\text{Et}$ ) and 5.9 ( $R=i\text{-Pr}$ ) since  $J_{1,2}=4.01\text{Hz}$ . Figures 5.3-5.6 are copies of the  $^1H$  NMR and  $^{13}C$  NMR spectra of the compounds 5.9 ( $R=i\text{-Pr}$ ) and 5.9 ( $R=\text{CH}_3\text{CH}_2$ ) whose structure and relative stereochemistry have been determined by x-ray analysis.

The  $^{13}C$  chemical shifts for these two compounds are similar. The S-methyl for 5.9 ( $R=\text{Et}$ ) occurs at  $44.25\text{ ppm}$  while for 5.9 ( $R=i\text{-Pr}$ ) S-methyl occurs at  $44.54\text{ ppm}$ . In the case of 5.9 ( $R=\text{Et}$ ) C-1 occurs at  $54.20\text{ ppm}$  and C-2 at  $73.84\text{ppm}$  while for 5.9 ( $R=i\text{-Pr}$ ), C-1 occurs at  $58.49\text{ ppm}$  and C-2 at  $73.84\text{ppm}$ .

The structure of lithiated 5.2, as shown by structure 5.12 (only the monomeric species is considered) in Scheme 5.2, may be similar to that of lithiated benzylphenylsulfone<sup>36</sup>. One would expect the benzylic carbon of 5.12 to be close to planar and the phenyl substituent to be anti to the bulky N-tert-butyldiphenylsilyl moiety. The non-bonding orbital at the benzylic carbon would be approximately coplanar with the S- $\text{CH}_3$  sigma

bond due to a stabilizing  $n_c \sigma^*_{s-c}$  interaction. Electrophilic attack on 5.12 should occur from the less hindered diastereoface, that is, anti to the S-CH<sub>3</sub>. An open transition state (5.8) in which R<sub>1</sub> of the imine 5.7 and the phenyl substituent of 5.12 are anti is consistent with the stereochemical outcome. Inspection of molecular models suggests a cyclic transition state may be too sterically congested. Indeed in the case where the imine was pre-complexed with BF<sub>3</sub> then a cyclic chelated transition state could not occur. The enhanced diastereoselectivity found in these cases may suggest that the minor isomer using the free imine arises from a cyclic chelated transition state. Figure 5.3 in <sup>1</sup>H NMR of 5.9d and Figure 5.4 is its accompanying <sup>13</sup>C NMR, while Figures 4.5 and 4.6 are <sup>1</sup>H NMR and <sup>13</sup>C NMR of 5.9c respectively.

Figure 5.3  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) data of the crude reaction mixture for the reaction of 5.2 and imine 5.7.

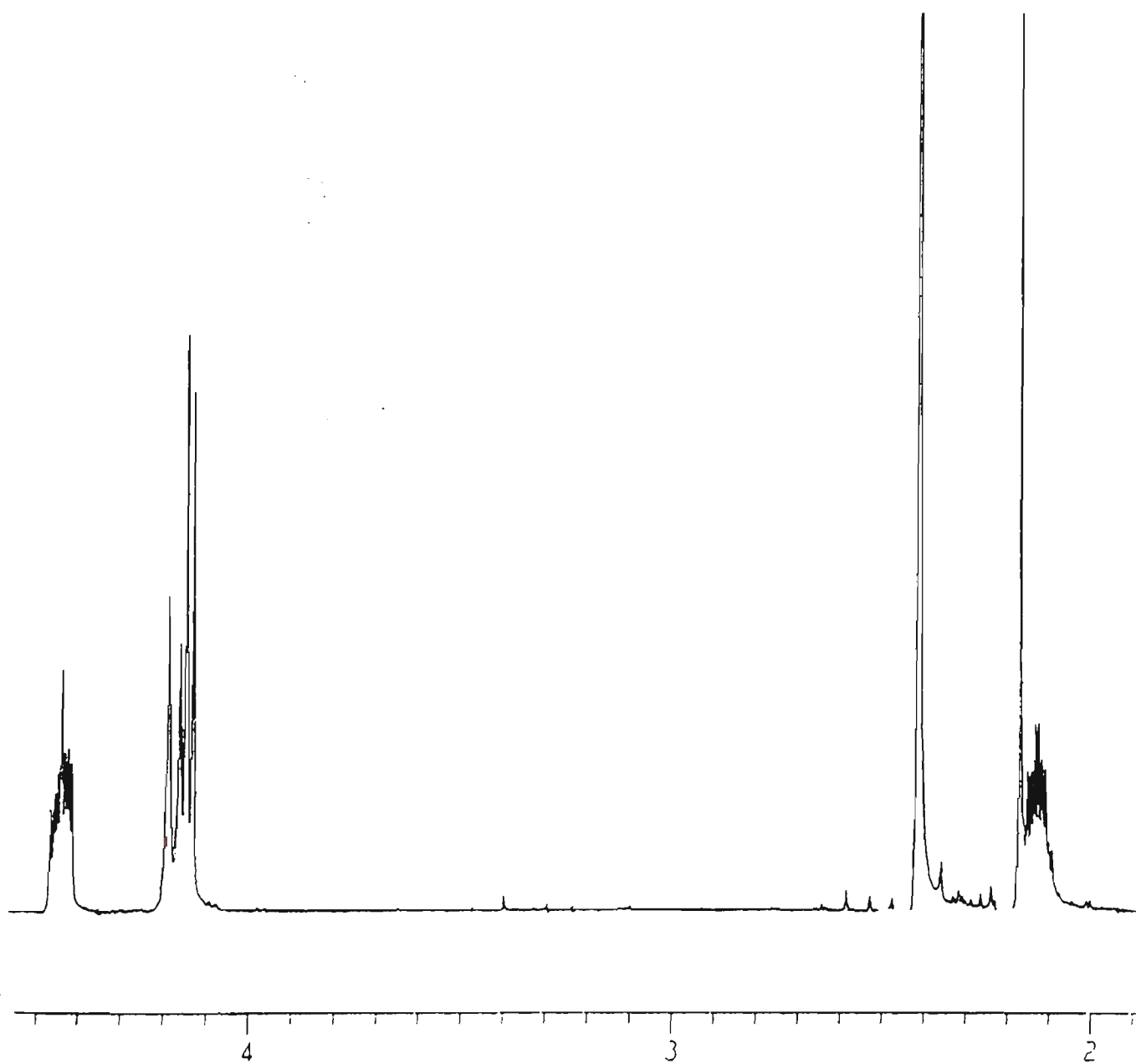
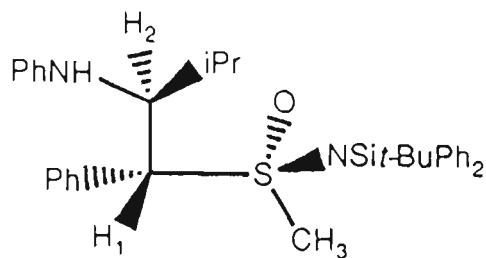


Figure 5.4  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) data for 5.9d (aliphatic section).

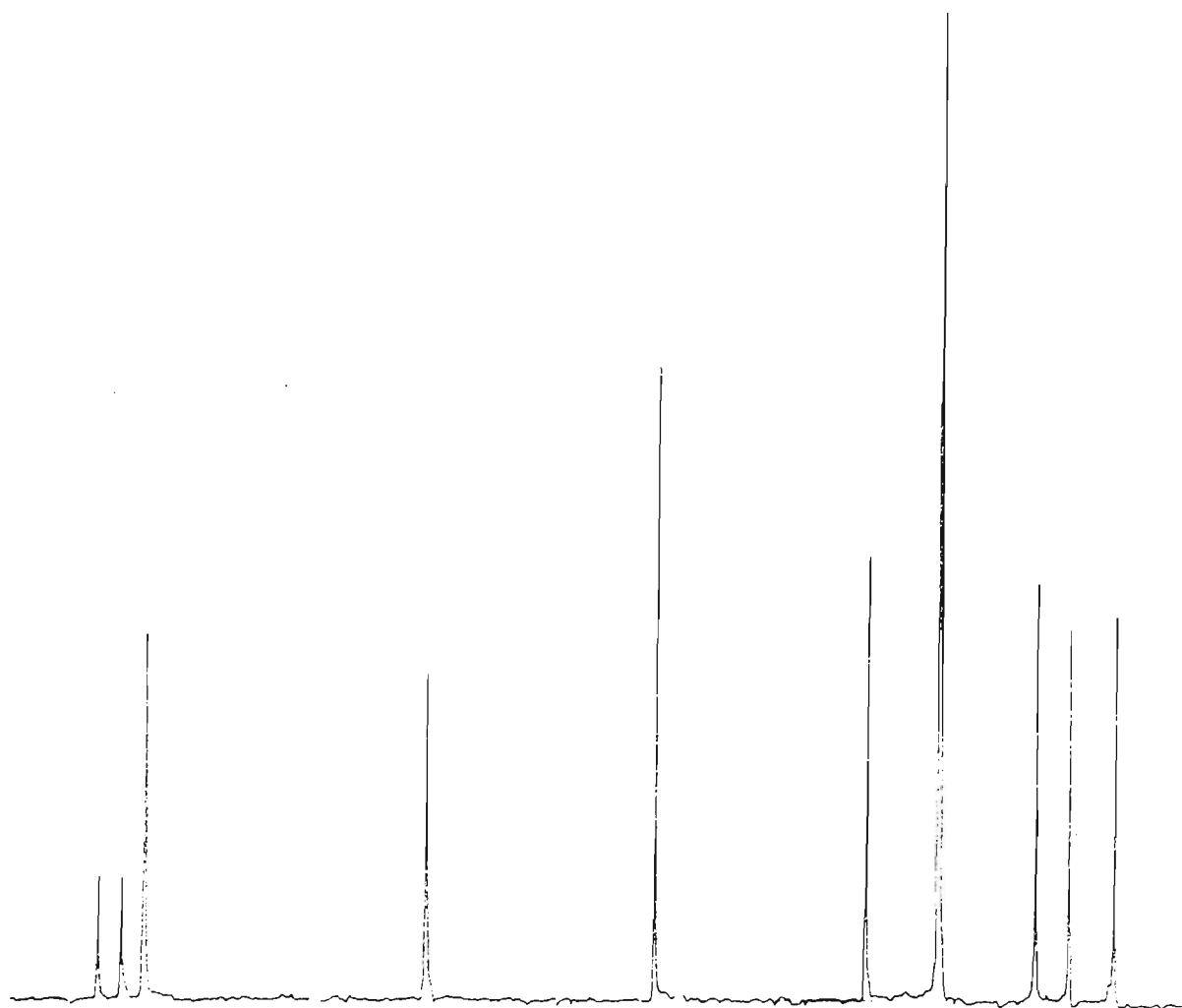
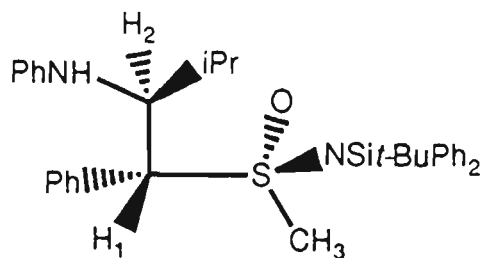




Figure 5.5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) data for 5.9c.

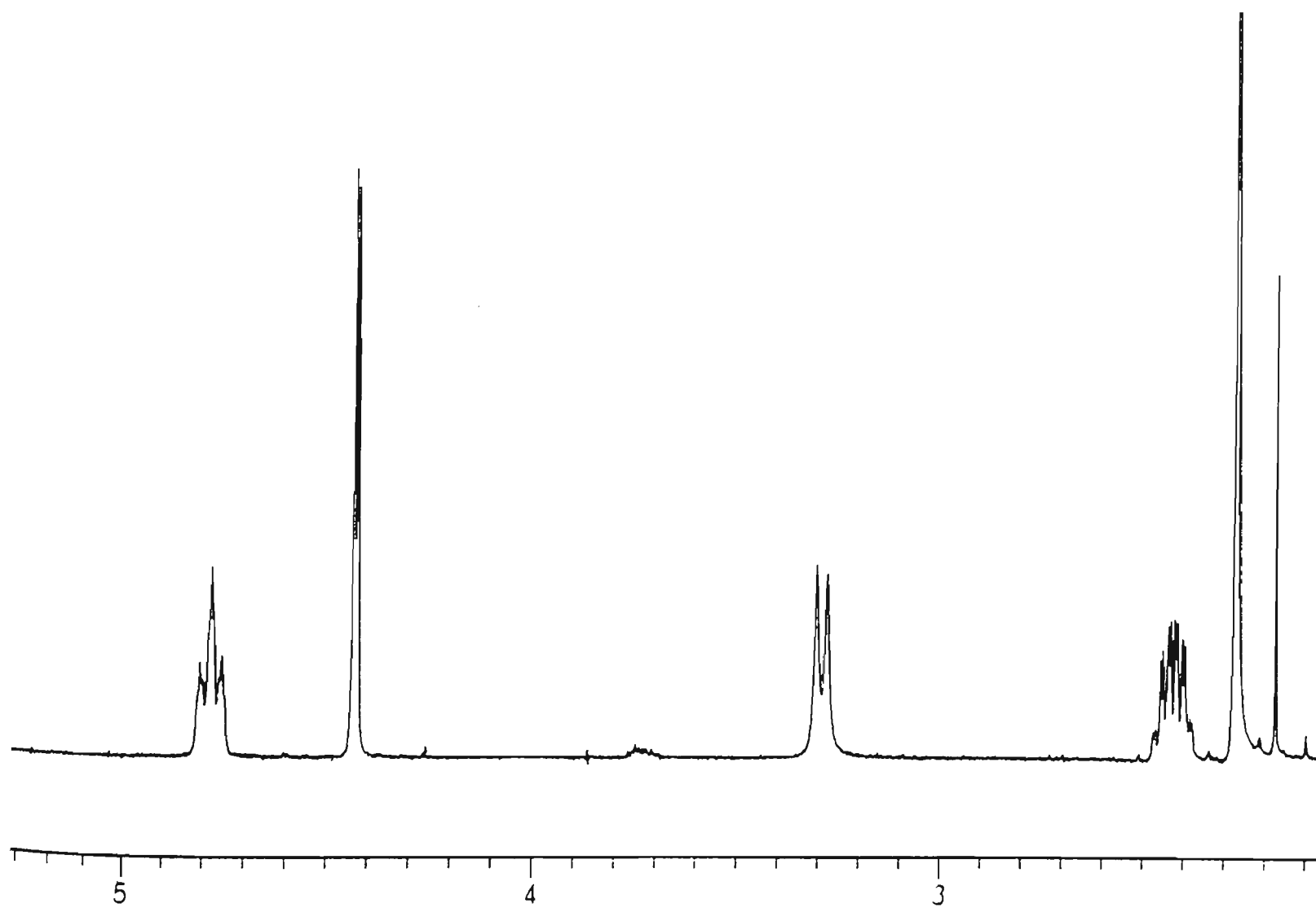
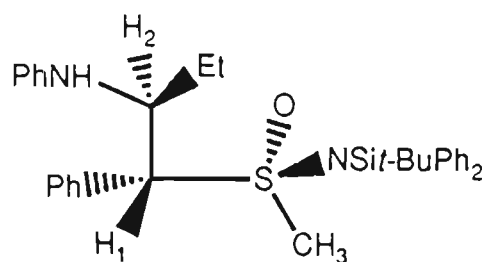
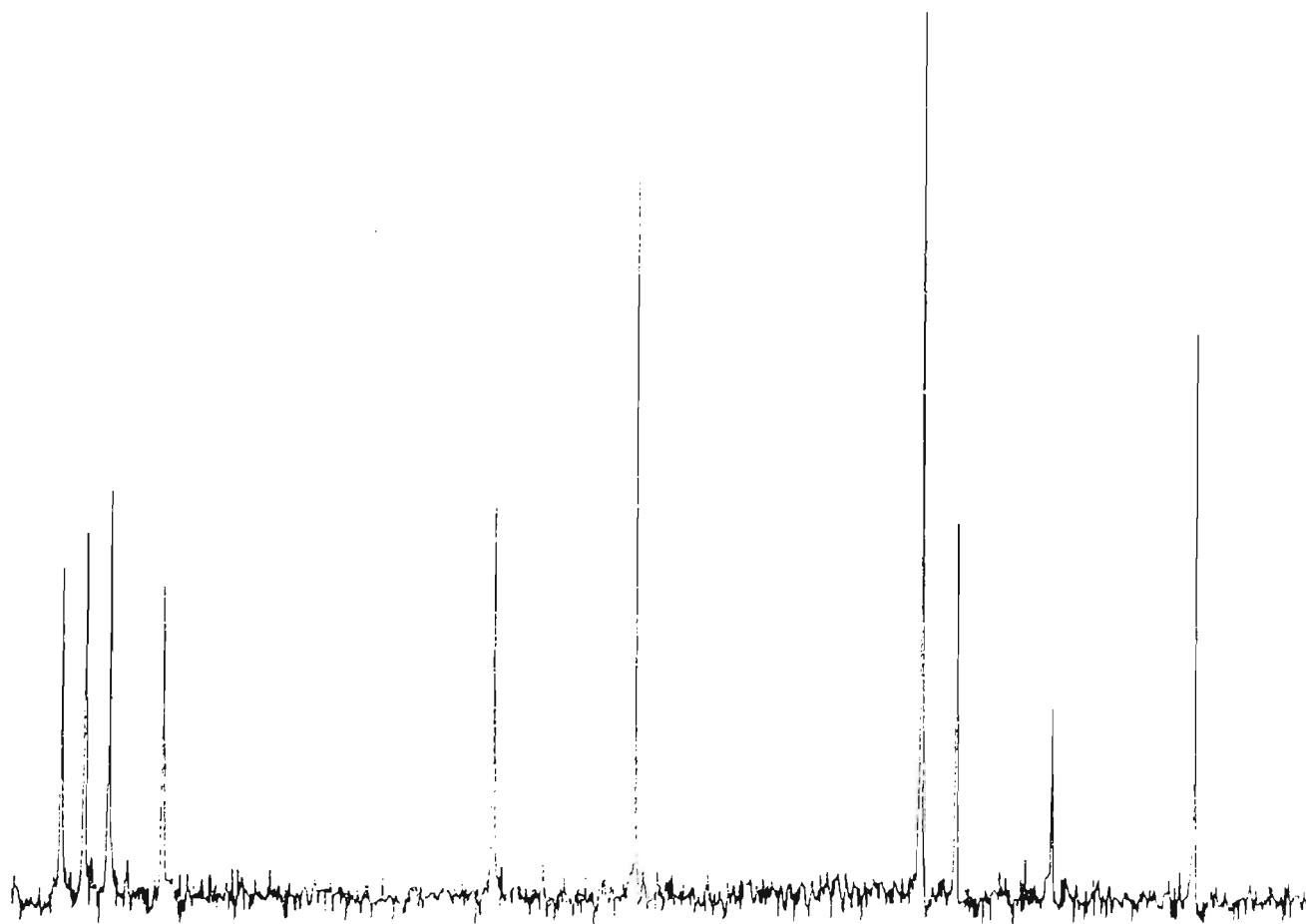
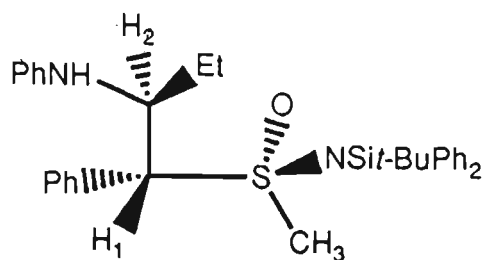


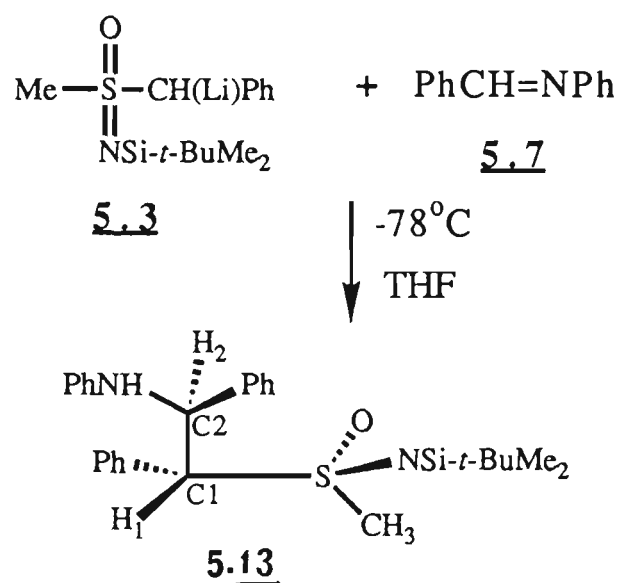
Figure 5.6  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) data for 5.9c (aliphatic section).



## ADDITION OF LITHIATED N-TERT-BUTYLDIMETHYLSILYLS-BENZYL-S-METHYL SULFOXIMINE TO IMINES

When lithiated N-tert-butyldimethylsilyl-S-benzyl-S-methyl sulfoximine 5.3 was treated with N-benzylideneaniline  $\cdot\text{BF}_3$  complex (5.6) for 1 hr at  $-78^\circ\text{C}$  in tetrahydrofuran the reaction proceeded with good yield (85%) and moderate product diastereoselection (83:13, Table 5.4). This is in clear contrast to the reaction between 5.2 and N-benzylideneaniline $\cdot\text{BF}_3$  complex (5.7) where a yield of 86% was obtained and the diastereomeric ratio was 95:5 under the same reaction conditions.

Table 5.4  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) data and assignments for 5.13.

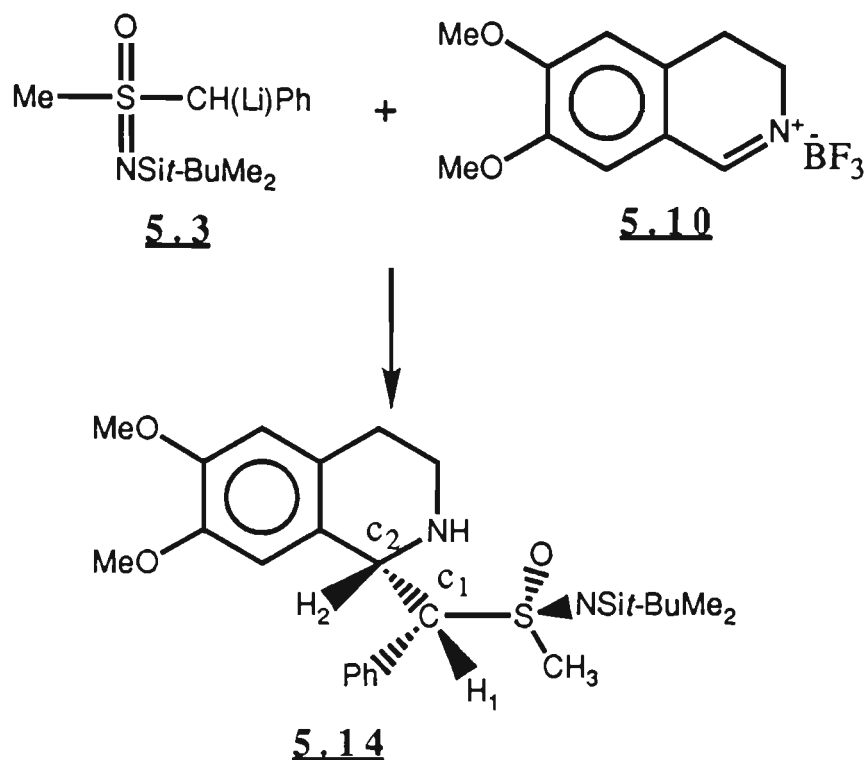


	SMe	H <sub>1</sub>	H <sub>2</sub>	J <sub>1,2</sub> (Hz)	Diastereomeric Ratio
major	2.73	4.22	5.49	3.82	83 : 17
minor	2.63	4.12	5.40	4.12	

The reaction of lithiated 5.3 and 3,4-dihydro-6,7-dimethoxyisoquinoline  $\cdot\text{BF}_3$  complex 5.10 gave all four possible

racemic diastereomeric products (Table 5.5) in a ratio of 40:39:16:14 and in 50% yield. This is in clear contrast to the analogous reaction of the N-tert-butyldiphenylsilylsufoximine with 3,4-dihydro-6,7-dimethoxyisoquinoline·BF<sub>3</sub> complex 5.10 which yielded only two of the four possible diastereomeric products with high product diastereoselection (92:8). The stereochemistry of these diastereomeric compounds could be tentatively assigned on the bases of the <sup>1</sup>H NMR spectra, with the two major isomers assigned the 1R\*, 2S\*, Ss\* and on the basis of the downfield chemical shift of their S methyl groups (2.68ppm and 2.74ppm respectively).

Table 5.5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) data and assignments for 5.14.



<b>entry</b>	1	2	3	4
<b>H<sub>a</sub></b>	4.46	4.57	4.50	4.46
<b>H<sub>b</sub></b>	5.38	4.87	4.94	5.26
<b>J<sub>a,b</sub>(Hz)</b>	2.50	10.12	9.60	3.80
<b>SMe</b>	2.68	2.74	2.48	2.66
<b>Diastereomeric ratio %</b>	40	30	16	14
<b>Yield 50%</b>				

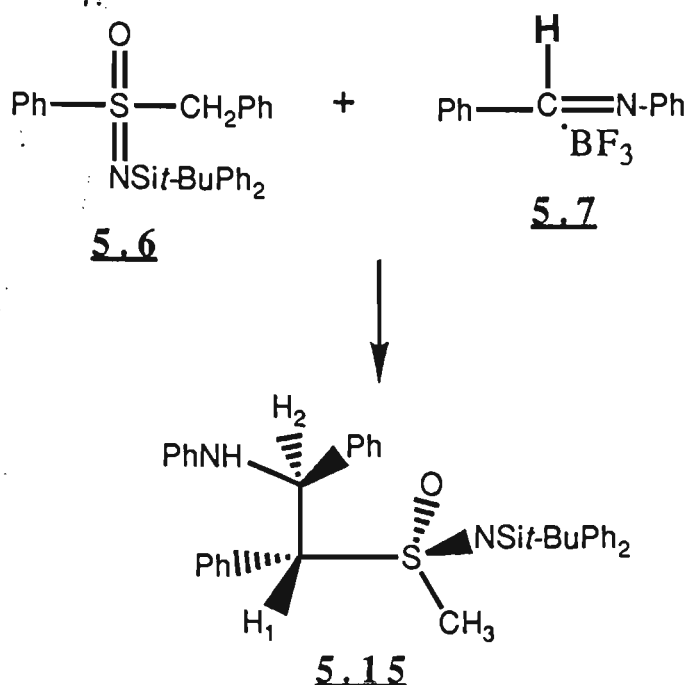
In the case of entry 2 (Table 5.1) this compound must have the anti stereochemistry and differs from entry 1 in the configuration at C-2. In the case of entry 3 and entry 4 with

( $J=9.60\text{Hz}$  and  $J=3.80\text{Hz}$  respectively) they are anti and syn isomers respectively and differ in configuration at C-2. These stereochemical assignments of the entry 3 (Table 5.5) must remain tentative. As the polarity of the tert-butyldimethyl-S-methyl-S-benzyl sulfoximine 5.3 on silica gel was extremely close to the polarity of the resulting adduct 5.14 it was impossible to obtain analytically pure sample. It again appears that the highly sterically demanding substituents are required at the sulfoximine nitrogen to ensure high diastereoselectivity in these and analogous reactions (see Chapter 3).

#### ADDITION OF LITHIATED TO N-TERT-BUTYLDIPHENYLSILYL-S-BENZYL-S-PHENYL SULFOXIMINE TO IMINES.

The lithiated tert-butyldiphenyl-S-phenyl-benzyl sulfoximine 5.6 when treated with N-benzylideneaniline  $\cdot\text{BF}_3$  complex resulted in modest yield of the desired adduct (55%) in moderate to good diastereoselectivity (88:12) Table 5.6. This lithiated sulfoximine (5.6) would not react with other imines (except for 5.10) even when the imines were precomplexed with  $\text{BF}_3$  etherate. This decrease in chemical reactivity probably arises from the extra steric demand and the resonance stabilizing effect of the S-phenyl group of 5.6. The analogous reaction of the highly hindered lithiated benzyl tert-butyl sulfoxide with 5.7  $\cdot\text{BF}_3$  also failed to give any adduct.

Table 5.6  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) data and assignments for 5.15.

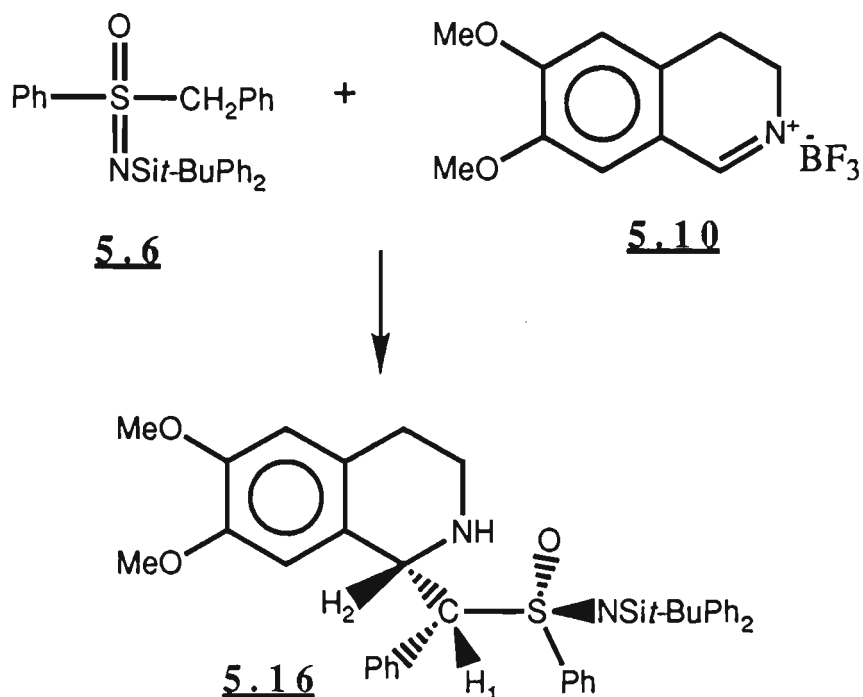


$\text{H}_2$	$\text{H}_1$	$J_{1,2}$ (Hz)	Diastereomeric ratio	88:12
4.90	4.31	3.40	major	
5.02	4.42	10.36	minor	

Yield 55%

The reaction of lithiated 5.6 with 3,4-dihydroxy-6,7-dimethoxyisoquinoline  $\cdot \text{BF}_3$  complex gave the 1-benzyltetrahydroisoquinoline 5.16 in poor yield (40%) but proceeded in a highly diastereoselective fashion (d.r.92:8) Table 5.7.

Table 5.7  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) data and assignments for 5.10.



$\text{H}_2$	$\text{H}_1$	$J_{1,2}$ (Hz)	
5.35	4.43	2.44	major
5.04	4.50	9.60	minor
Yield 40%			
Diastereomeric ratio 92:8			

The relative  $1S^*$ ,  $2S^*$ ,  $Ss^*$  stereochemistry of the major isomer of these compounds 5.15 and 5.16 ( $J_{1,2}=3.40\text{Hz}$  and  $J_{1,2}=2.44\text{ Hz}$ ) was made by analogy with 5.8.

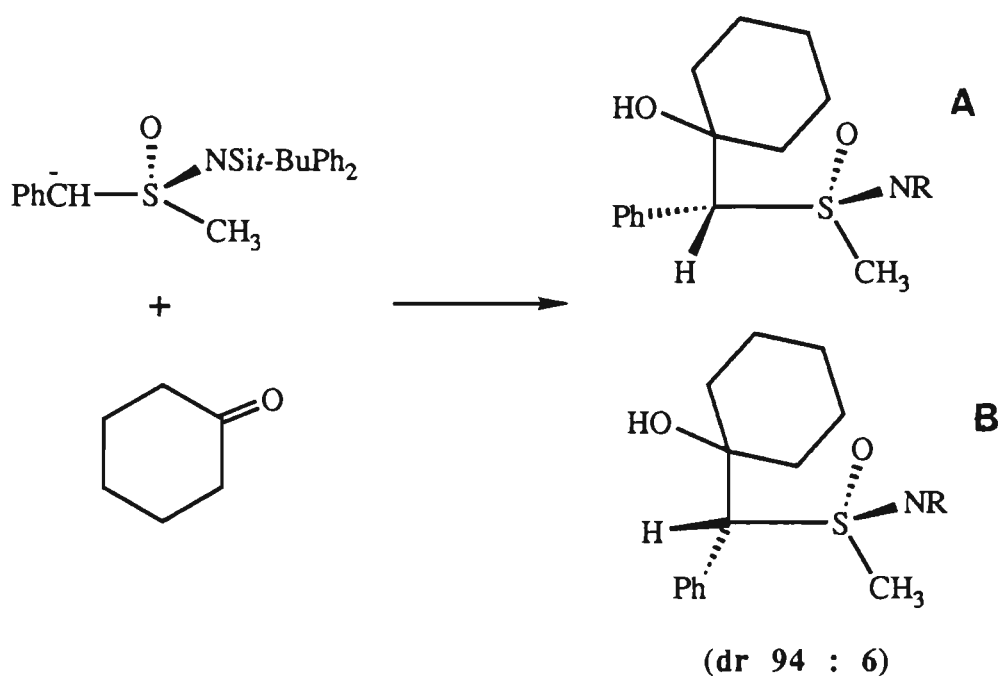
In conclusion, a highly diastereoselective method for delivering a benzyl substituent to prochiral imines has been developed. In principle the sulfoximine 5.1 can be readily resolved into its pure enantiomers<sup>78</sup> from which enantiomerically pure 5.2 can be obtained.



# REACTION OF LITHIATED N-TERT-BUTYLDIPHENYLSILYL-S-METHYL-S-BENZYLSULFOXIMINE WITH CARBONYL COMPOUNDS

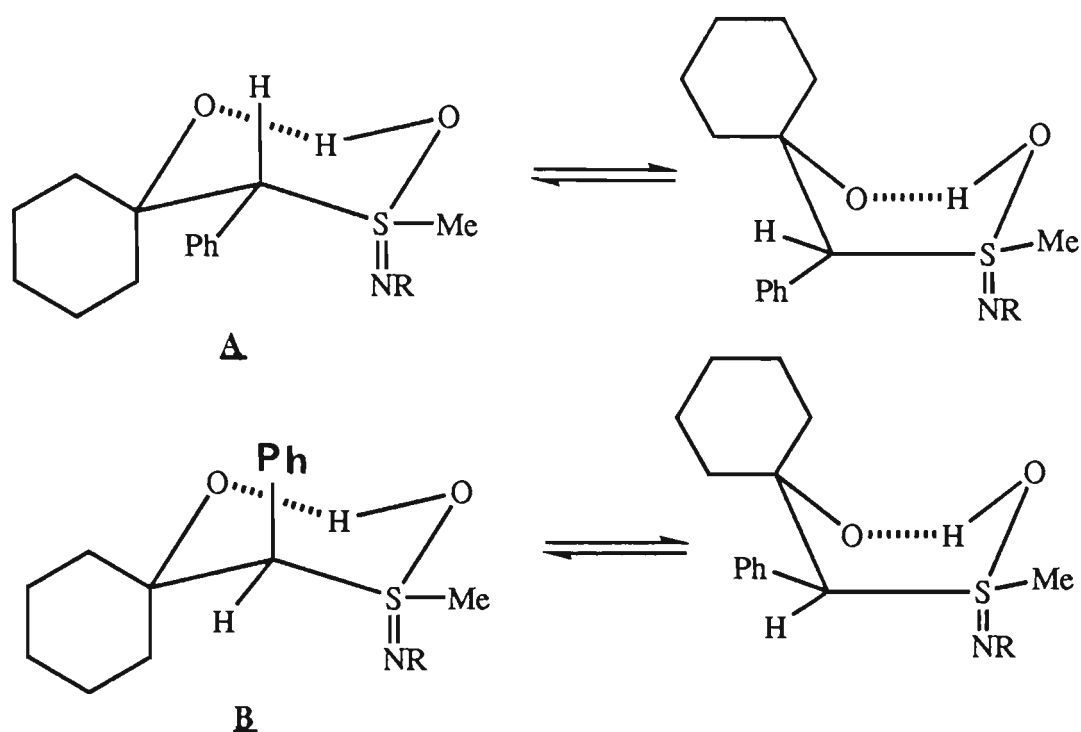
In our study we initially reacted lithiated N-tert-butyldiphenylsilyl-S-methyl-S-benzylsulfoximine with cyclohexanone at  $-78^{\circ}\text{C}$  for 10 min (Scheme 5.4).

Scheme 5.4



We found that the diastereomeric ratio was 94:6 but the yield was low (60%). The  $^1\text{H}$  NMR of the major diastereomer A shows the SMe at the 2.13 ppm while that of B shows more shielded SMe at 1.98ppm (Scheme 5.5). The possible intramolecular hydrogen-bonded conformations for A and B are shown in Scheme 5.5.

Scheme 5.5.

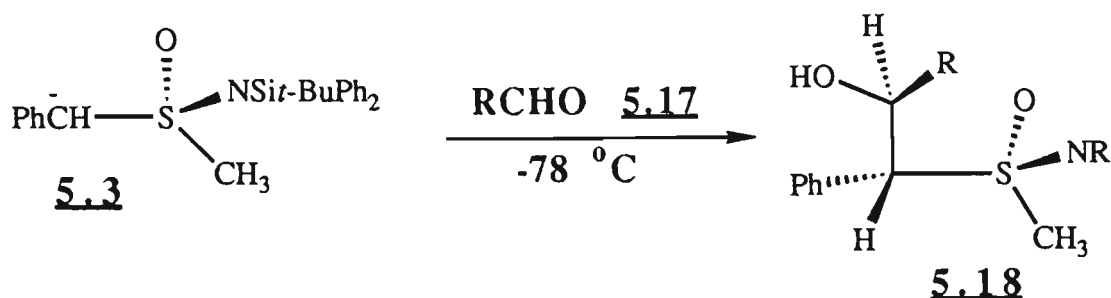


Diastereomers **A** and **B** most likely favour the boat conformation because of the axial disposition of the  $\text{CH}_2$  and the  $\text{NSi t-BuPh}_2$  substituents in the chair conformation. It is clear that the  $\text{SMe}$  group in **B** is in the shielding region of the phenyl substituent at the stereogenic carbon. The benzylic proton in **A** possibly resonates at the lower field compared to that in **B** due to the deshielding effect of the axial lone pairs on the sulfoximine oxygen and hydroxyl group in the chair conformation.<sup>71</sup>

The lithiated *N-tert*-butyldiphenylsilyl-*S*-methyl-*S*-benzyl sulfoximine in tetrahydrofuran at  $-78^\circ\text{C}$  were quenched with aldehydes or in the case of benzaldehyde the aldehyde  $\cdot\text{BF}_3$  complex for 10 min (Scheme 5.6). The later was formed by stirring a tetrahydrofuran solution of benzaldehyde with  $\text{BF}_3$  etherate at  $-78^\circ\text{C}$  for 15 minutes. After the usual aqueous workup the reaction mixture was extracted in dichloromethane, dried and subjected to column chromatography on silica gel. The pure  $\beta$ -hydroxy-sulfoximines were obtained in good yield. The

diastereomeric ratio was in all cases determined by  $^1\text{H}$  NMR (400MHz) spectroscopy on the crude reaction mixture.

Scheme 5.6.



In each case studied all four out of four possible racemic diastereomeric products were formed, paralleling our finding for the reaction of aldehydes and methyl benzyl sulfoxide. In contrast to methyl phenyl sulfoxide (refer to Chapter 3), where low product yields and diastereoselectivity was observed, reaction of *N*-tert-butyldiphenylsilyl-*S*-methyl-*S*-benzylsulfoximine with aldehydes gave good yields of over 90% in all cases and in good diastereoselectivity.

The results of the reaction of **5.3** with various aldehydes **5.17** are tabulated in Table 5.8 while Table 5.9 shows the  $^{13}\text{C}$  NMR chemical shifts for C-1, C-2 and SMe for the aldehyde adducts. Figure 5.7 is a copy of  $^1\text{H}$  NMR of **5.18** (R=Et) while Figure 5.8 is a copy of  $^{13}\text{C}$  NMR for this compound. The relative  $R_C^*$ ,  $R_S^*$  stereochemistry of the major syn diastereoisomer of **5.18** (R=Et) was unequivocally determined by a single crystal x-ray crystal analysis (Figure 5.9).

Figure 5.9 ORTEP drawing of the x-ray structure of 5.18 (R=Et)

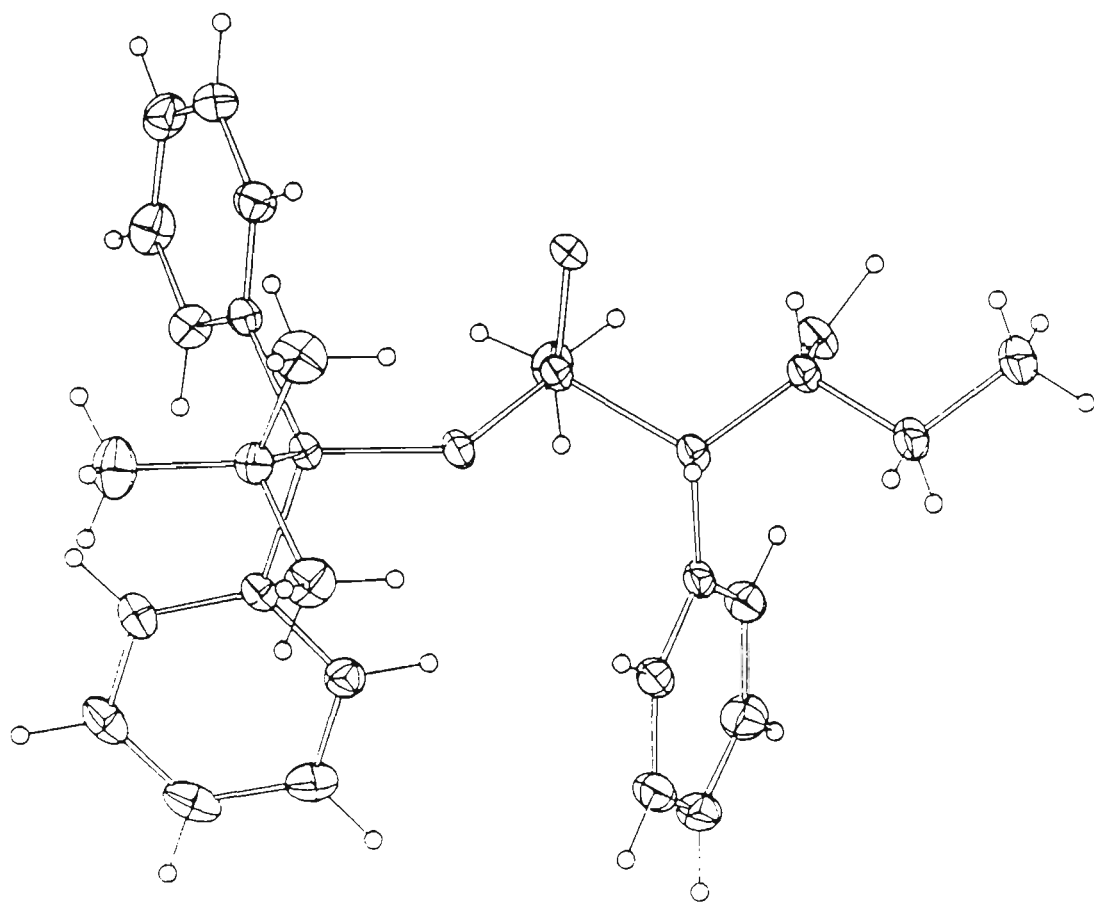


Figure 5.7  $^1\text{H}$  NMR( $\text{CDCl}_3$ ) of 5.18( $\text{R}=\text{Et}$ )

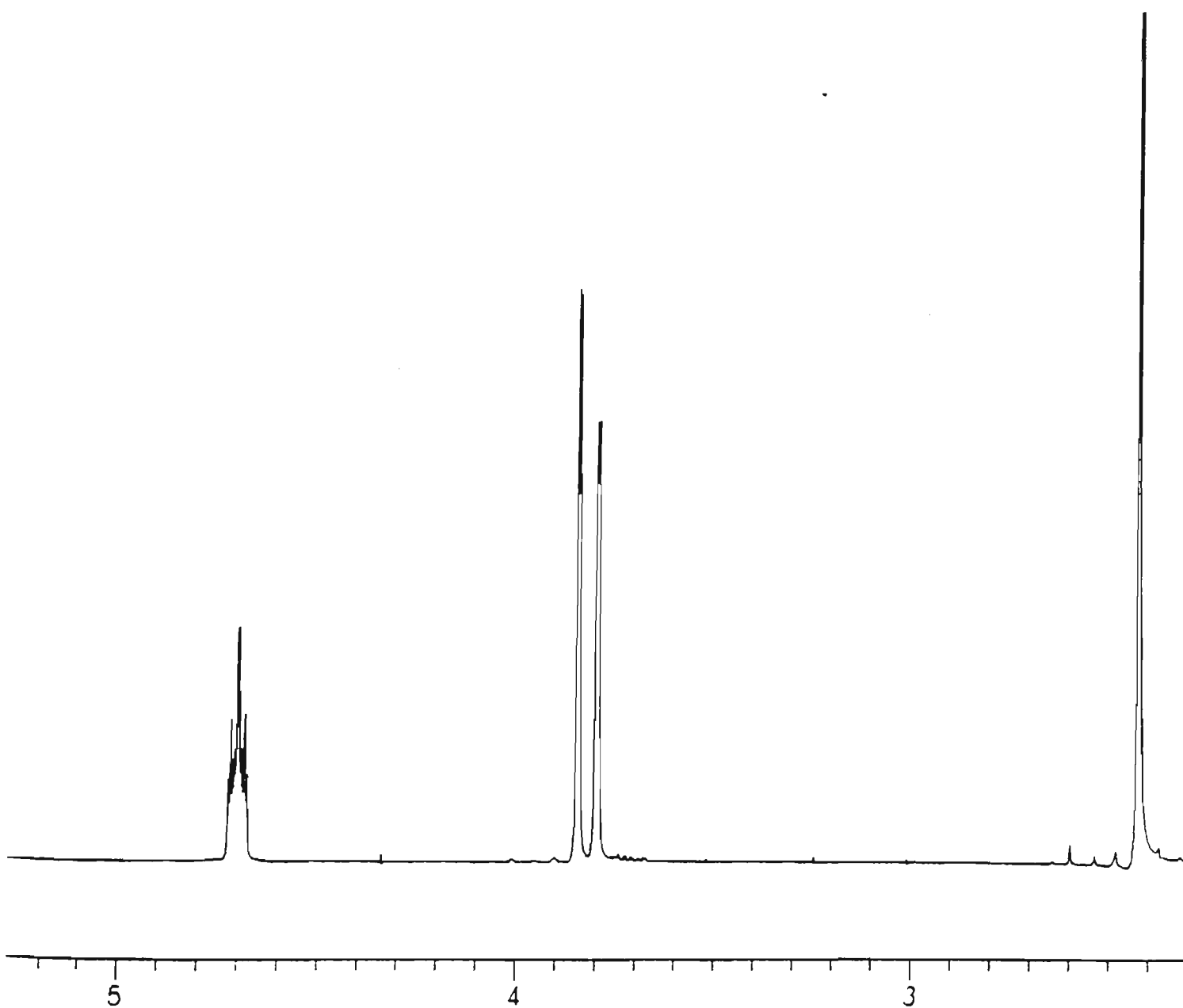
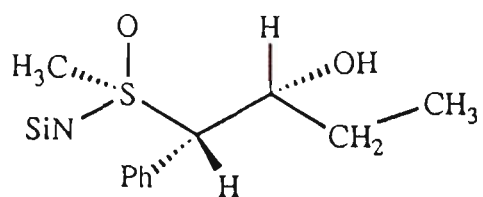
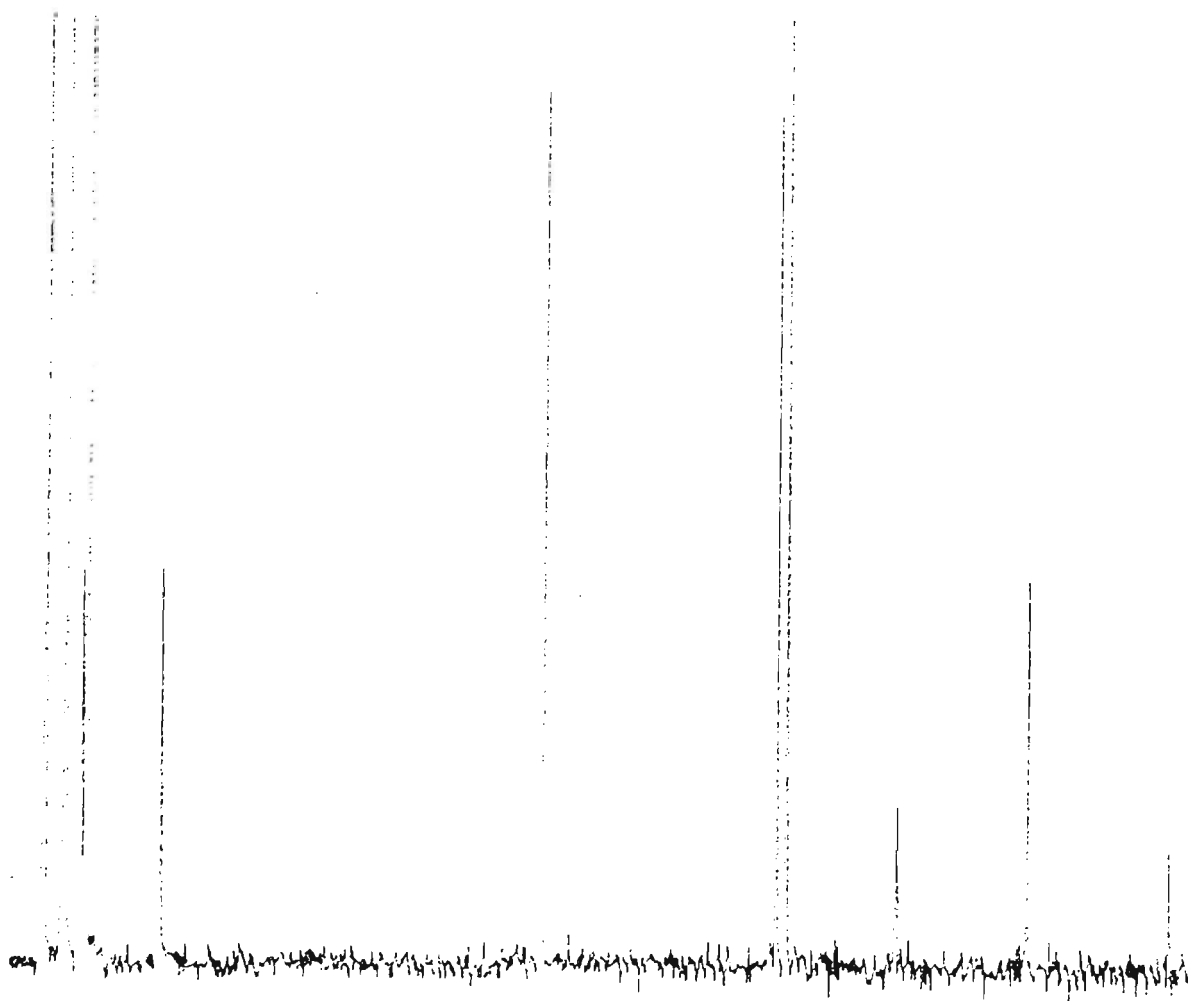
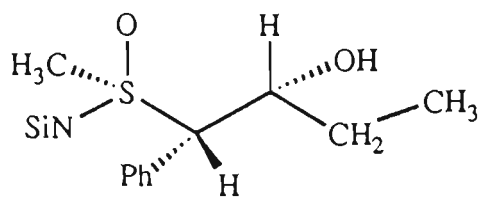
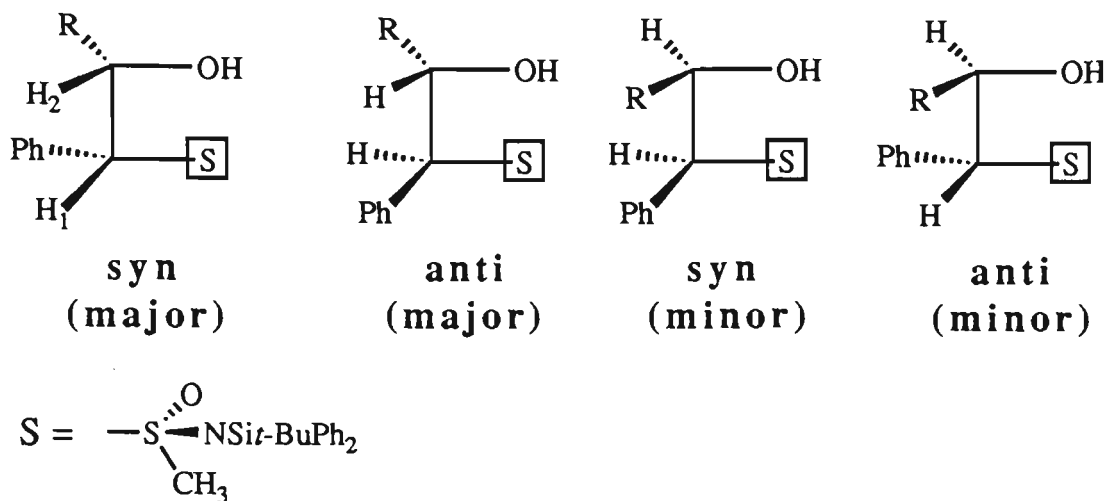


Figure 5.8  $^{13}\text{C}$  NMR( $\text{CDCl}_3$ , aliphatic section) of 5.18( $\text{R}=\text{Et}$ )



The stereochemistry of the aldehyde adducts 5.18 were assigned (see Table 5.8) as syn or anti on the basis of the value of  $J_{1,2}$  and the literature precedent (Kingsbury<sup>85a</sup>) and the relative stereochemistry at sulfur and the  $\alpha$  carbon from a comparison of chemical shifts for SMe group of the adducts to that of the values of cyclohexanone adduct. Coupling constant of 10-13Hz are taken as indicative of a strong preference for a diastereomer with trans (anti) vicinal hydrogen, and values in the 1-3Hz range are taken to indicate gauche hydrogen, and intermediate values are taken as indicative of weighted means of the above conformations. From the table 8 it is clear that the chemical shifts for the SMe group of the major syn diastereoisomer occur in the range of 2.35-2.45ppm. The values for the chemical shifts of  $H_1$  and  $H_2$  as well as  $J_{1,2}$  are tabulated in the Table 5.8.

**Table 5.8. Preparation and  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) assignments for 5.18.**



R=Ph	Syn	Anti	Syn	Anti
Diastereomeric				
ratio %	48	26	10	16
R=Ph·BF <sub>3</sub>	67	28	1	4
H <sub>1</sub> (ppm)	4.01	4.40	4.04	4.39
H <sub>2</sub> (ppm)	6.07	5.78	6.17	5.63
J <sub>1,2</sub> (Hz)	1.8	9.5	2.0	9.76
SMe(ppm)	2.45	2.30	2.25	2.49
yield	95%			
R=Et	<u>5.18</u>			
Diastereomeric				
ratio %	77	18	4	1
H <sub>1</sub> (ppm)	3.86	4.11	a	a
H <sub>2</sub> (ppm)	4.69	4.79		
J <sub>1,2</sub> (Hz)	1.84	9.31		
SMe(ppm)	2.42	2.28	2.20	2.39
yield	96%			



R=iPr 5.18C

Diastereomeric

ratio %	70	16	6	8
H1(ppm)	4.00	a	a	a
H2(ppm)	4.34	4.69	4.56	4.52
J <sub>1,2</sub> (Hz)	2.0	(H <sub>2</sub> ,dd, J <u>ca</u> , 10 Hz)		
SMe(ppm)	2.44	2.18	2.16	2.42
yield	91%			

R=t-Bu 5.18d

Diastereomeric

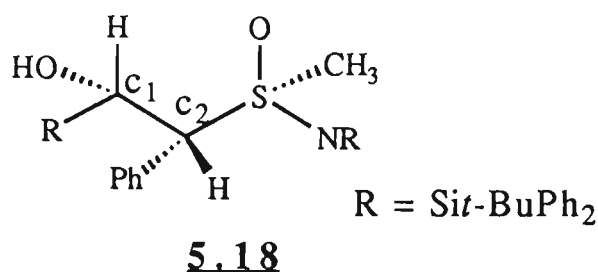
ratio %	75	16	1	8
H1(ppm)	4.09	4.22	4.01	a
H2(ppm)	4.60	4.94	4.61	a
J <sub>1,2</sub> (Hz)	<1	5.3	2.4	
SMe(ppm)	2.35	2.52	2.49	2.56
yield	91%			

R=i-Bu 5.18e

Diastereomeric

ratio %	29	21.8	26.5	22.5
H1(ppm)	3.74	4.08	3.82	4.06
H2	4.97	5.09	5.09	4.97
J <sub>1,2</sub> (Hz)	2.23	9.1	2.23	9.1
SCH <sub>3</sub> (ppm)	2.38	2.17	2.20	2.40

a Diifcult to assign with any certainty because of overlapping peaks.

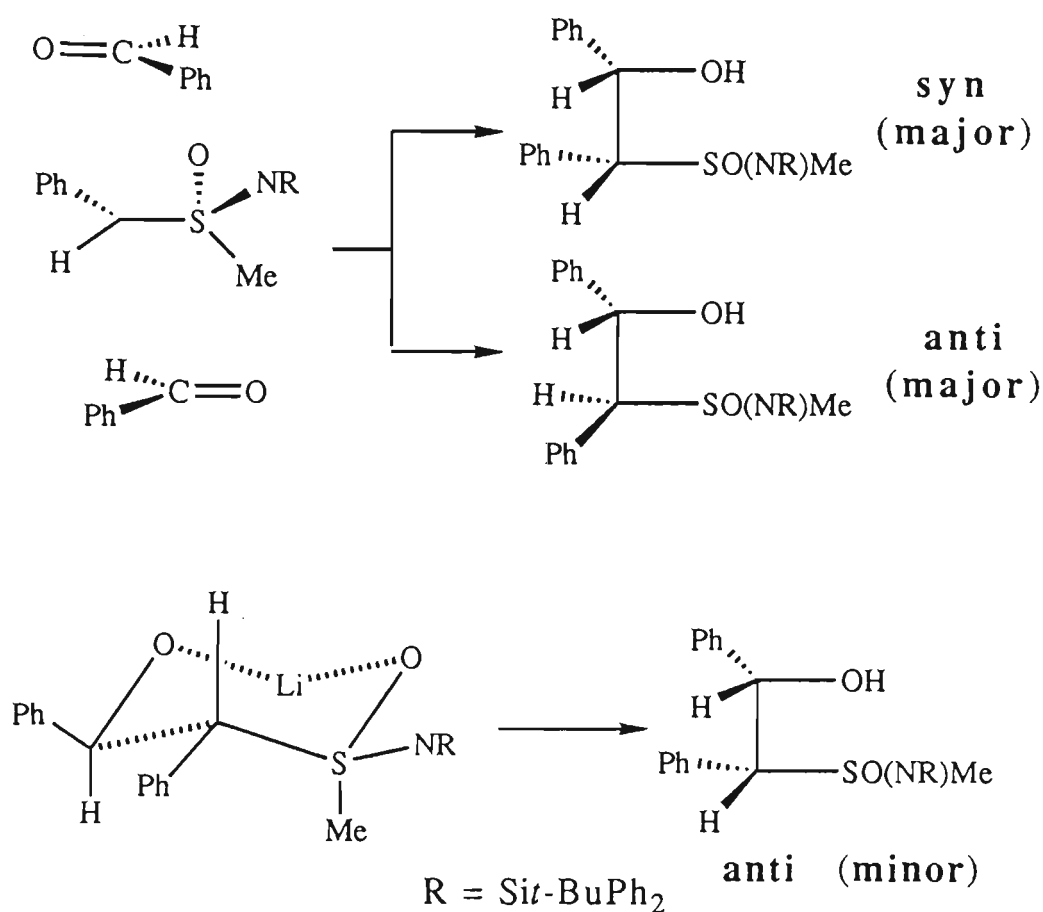
Table 5.9  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) assignments for 5.18.

entry	5.18	R	C <sub>1</sub>	C <sub>2</sub>	SMe
1	a	Ph	72.2	80.0	45.2
2	b	Et	70.5	75.9	44.0
3	c	i Bu	66.64	76.65	43.7
4	d	t-Bu	74.3	75.0	45.9

Quenching of the lithiated sulfoximine 5.2 with benzaldehyde resulted in a product diastereoselectivity of 48:26:10:16, however conducting the same reaction using benzaldehyde that has been precomplexed with  $\text{BF}_3$  etherate resulted in a 67:28:1:4 ratio of the diastereomers. Treatment of the solution of pure major syn sulfoximine adduct 5.18 ( $\text{R}=\text{Ph}$ ) in tetrahydrofuran (THF) with *n*-butyllithium (2 equivalents) and subsequent quenching of the resulting dianion ( $\text{PhCH}(\text{OLi})\text{C}(\text{Li})\text{PhSO}(\text{NR})\text{Me}$ ) with water produced a 65:35 mixture of the major syn and anti-diastereomers obtained from the reaction of the sulfoximine anion and benzaldehyde. While the addition of 1 equivalent of *n*-butyllithium to this adduct and subsequent quenching with water resulted in no change in stereochemistry (Figure 5.10). This result unequivocally demonstrated that these adducts must have opposite configuration

The stereochemistry of the major diastereomer from the reaction of sulfoximine 5.2 with aldehydes can be rationalized as resulting from electrophilic attack on lithiated 5.2 from the less hindered diastereoface (Scheme 5.10). In this transition state the aldehyde substituent (R) and the benzylic phenyl group are anti.

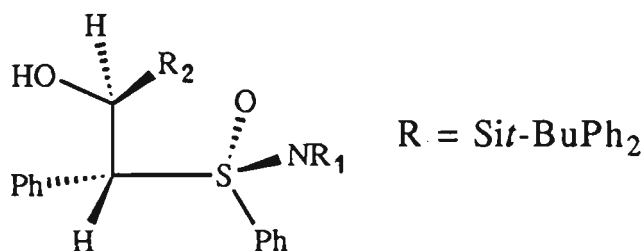
**Scheme 5.10.**



The reaction between N-tert-butyldiphenylsilyl-S-benzyl-S-phenyl-sulfoximine 5.2 with benzaldehyde gave only three out of the possible four diastereomers in the ratio of 82:14:4 and in good yield at 98% Table 5.8. The chemical shift for diastereomeric proton H-1 could be assigned only for two of the major isomers and were 4.08 and 4.45 respectively. The chemical shifts for the diastereomeric proton H-2 were 5.14, 5.78 and 5.44ppm respectively with  $J_{1,2}=1.83\text{Hz}$ ,  $J_{1,2}=9.16$

The reaction between N-tert-butyldiphenylsilyl-S-benzyl-S-phenyl-sulfoximine 5.2 with benzaldehyde gave only three out of the possible four diastereomers in the ratio of 82:14:4 and in good yield at 98% Table 5.10 The chemical shift for diastereomeric proton H-1 could be assigned only for two of the major isomers and were 4.08 and 4.45 respectively. The chemical shifts for the diastereomeric proton H-2 were 5.14, 5.78 and 5.44ppm respectively with  $J_{1,2}=1.83\text{Hz}$ ,  $J_{1,2}=9.16$  and  $J_{1,2}=9.09$  Hz. The stereochemistry was assigned on the basis of literature precedent (Kingsbury<sup>86</sup>) and are shown in Table 5.10.

Table 5.10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) spectral data of 5.19



Diastereomeric	syn	anti	anti
ratio %	82	14	4
H <sub>1</sub>	4.08	4.45	
H <sub>2</sub>	5.14	5.78	5.44
$J_{1,2}(\text{Hz})$	1.83	9.16	9.09
yield	98%		

## EXPERIMENTAL

### S-Benzyl-S-methylsulfoximine<sup>81,82</sup> 5.1

To a solution of benzyl methyl sulfoxide (0.02 mol) and MSH (6.02g, 0.03mol) in 40ml DCM was stirred for 2 hours at room temperature and poured in a cold 10% NaOH (40ml) and stirring continued for 10min. The resulting mixture was extracted with DCM, DCM was washed with 10% HCL (2x40ml) and acid layer was made basic with solid Na<sub>2</sub>CO<sub>3</sub> the aqueous layer was then extracted with DCM, DCM evaporated and the resulting solid recrystallised from hexane to yield 42% of S-benzyl-S-methylsulfoximine. M.p.=54°-55°C lit<sup>67c</sup> m.p. 54°C. <sup>1</sup>H NMR 7.9-7.6 (m, 5H), 4.1(s, 2H), 2.51(s, 3H); <sup>13</sup>C NMR 130.70, 128.88, 64.04, 41.46; IR 3300(s), 1220 (s), 1040(s); MS (CI+VE) 170(M+H<sup>+</sup>, 100%), 106 (53%), 91(100%); Anal. calcd for C<sub>8</sub>H<sub>11</sub>NOS: C, 56.78; 6.55; N, 8.28. Found: C, 56.64; H, 6.83; N, 8.16.

### S-Benzyl-S-phenylsulfoximines<sup>67c</sup> 5.5

Synthesized by the same procedures as the compound 5.1 in 30% yield. <sup>1</sup>H NMR 8.0-6.9 (m, 1OH), 4.34 (s, 2H), 2.80 (s, 1H); <sup>13</sup>C NMR 130.91, 128.70, 128.57, 128.31, 64.45; IR (nujol) 3320(s), 1220 (s), 1110 (s), 1085 (s); MS (CI+ve), 232 (M+H<sup>+</sup>, 100%), 196 (60%), 183 (14), 125 (51), 106 (86%), 91 (100%), 77 (29); Anal. calcd. for C<sub>12</sub>H<sub>11</sub>NOS: C, 66.33; H, 5.10; N, 6.45. m.p. 107-108°C, lit<sup>67c</sup> m.p.109-112°C.;

Compounds 5.2 to 5.6 were synthesized by the same general procedure as the compound 2.5 (Chapter 2):

### N-tert-Butyldiphenylsilyl-S-benzyl-S-methylsulfoximine 5.2

Yield 96%. m.p. 78-80°C;  $^1\text{H}$  NMR 7.2-7.6(m, 15H), 4.1(s, 2H), 2.51 (s, 3H), 1.05 (s, 9H);  $^{13}\text{C}$  NMR 136.38, 135.51, 130.78, 130.13, 128.96, 128.53, 128.44, 127.32, 65.52, 43.02, 27.03, 19.14; IR 1400(s), 1390(s), 1275(s), 1190(s), 1100(s).; MS (CI+ve), 409 ( (M+H<sup>+</sup>, 6%), 351 (8%), 331 (8%), 224 (11%), 199 (54%), 91 (100%); Anal. calcd. for C<sub>24</sub>H<sub>29</sub>NOSSi; C, 70.71; H, 7.71; N, 3.34: Found: C, 70.56; H, 7.46; N, 3.33.

### **N-tert-Butyldimethylsilyl-S-benzyl-S-methylsulfoximine 5.3**

Yield 95%; m.p. 70°C;  $^1\text{H}$  NMR 7.36 (s, 5H), 4.14(s, 2H), 2.71 (s, 3H), .84 (s,15H);  $^{13}\text{C}$  NMR 130.74, 130.13, 128.49, 65.60, 44.11, 25.90, 117.84; IR 1450-1350 (b), 1325 (s), 1225 (s), 1090 (s); MS (CI+ve), 284 ( (M+H<sup>+</sup>, 3%), 252 (14%), 226 (14%), 226 (14%), 199 (23%), 91 (100%). Anal. calcd. for C<sub>14</sub>H<sub>25</sub>NOSSi; C, 59.31; H, 8.89; N, 4.49: Found: C, 59.08; H, 9.16;N, 4.97

### **N-tert-Butyldiphenylsilyl-S-benzyl-S-phenylsulfoximine 5.6**

Yield 95%; m.p. 84-85°C;  $^1\text{H}$  NMR 7.73-7.11 (m, 2H), 9.13(s, 2H),1.04 (s, 9H);  $^{13}\text{C}$  NMR 135.64, 132.13, 131.09, 129.83, 128.83, 128.31, 128.01, 127.19, 67.29, 27.16, 19.40; IR (nujol) 1290 (s), 1170 (s), 1140 (s); MS (CI+ve), 471( (M+H<sup>+</sup>, 3%), 413(17%), 393(6%), 3936(6%), 314(6%), 244(9%), 199(26%), 91(100%). Anal. calcd. for C<sub>28</sub>H<sub>29</sub>NSOSSi: C, 73.80; H, 6.41; N, 3.07: Found: C, 73.82; H, 6.72; N, 2.88.

### **Reaction of 5.2, 5.3 and 5.6 with imines or aldehydes: A General Procedure**

To a solution of appropriate sulfoximine (1.0 mmol) in dry THF (3ml) at -78°C was added n-BuLi in hexane (1.1 mmol). After 1 hr a solution of the appropriate imine (1.2 mmol) or aldehyde (1.2 mmol) in THF (3ml) was added. The resulting mixture was stirred for 1 hr in

case of imines or 5 min., in case of aldehydes. The reaction was then quenched by the addition of 10%  $K_2CO_3$  (5ml) and then extracted with  $CH_2Cl_2$ . The combined extracts were dried ( $MgSO_4$ ) and evaporated. The diastereoselection of these reaction was determined from  $^1H$  NMR analysis of the crude reaction products. The crude product was purified by column chromatography on silica gel employing ethyl acetate/hexane as eluent. The yields are reported in Tables 5.1, 5.5, 5.6, 5.7, 5.8 and 5.10.

**N-tert-Butyldiphenylsilyl-S-[2-(2-furyl)-2-phenylamino-1-phenyl)ethyl-S-methylsulfoximine 5.9a**

$^1H$  NMR 7.70-6.1 (m, 18H), 5.56(br.d, 1H), 4.58 (d, 1H,  $J=6.01Hz$ ), 4.44 (br.s, 1H,  $NH$ );  $^{13}C$  NMR 152.71, 146.34, 141.62, 135.64, 131.69, 130.71, 129.14, 127.96, 128.79, 128.40 127.27, 118.74, 119.15, 113.93, 110.46, 108.28, 756.94, 52.08, 44.37, 27.03, 19.19; IR (nujol) 3360 (s), 1720 (s), 1610 (s), 1500 (s), 1400-1250 (br), 1150 (s), 1200 (s), 1140 (s), 1040 (s).

**N-tert-Butyldiphenylsilyl-S-(1,2-diphenyl-1-phenylamino)ethyl-S-methylsulfoximine 5.9b**

$^1H$  NMR 7.65-6.93 (m, 18H), 6.68(t, 3H,  $J=6.37$ ), 6.50 (d, 1H,  $J=8.35Hz$ ), 5.61( brs. 1H), 5.38 (br, s, 1H,  $NH$ ), 4.26 (d,  $J=4.01Hz$ , 1H), 2.30 (s, 3H), 1.05 (s, 9m);  $^{13}C$  NMR 146.65, 140.71, 136.12, 135.68, 135.68, 131.26, 130.29, 120.00, 129.05, 128.83, 128.4, 128.27, 128.05, 127.75, 127.36, 127.14, 118.30, 114.79. 77.61, 57.24, 44.19, 27.16, 19.23; IR (neat) 3390(s), 1610(s), 1510(s), 1400-1260, 1180(s), 1120(s); MS (CI+ve), 584 ( $M+H^+$ , 2.9%), 531(11%), 408(3%), 314(17%), 288(14%), 271(100%), 240 (26%), 182 (43%), 104 (20%), 94 (23%).

**N-tert-Butyldiphenylsilyl-S-(1-phenyl-2-phenylamino) butyl-S-methylsulfoximine 5.9c**

M.p. 138-140°C;  $^1\text{H}$  NMR 7.85-7.30 (m, 18H), 7.20 (t, 1H,  $J=6.81\text{Hz}$ ), 6.80 (d, 1H,  $J=4.18\text{Hz}$ ), 4.76(m, 1H), 4.43(d,  $J=3.16\text{Hz}$ ), 3.39(d, 1H,  $J=10.33\text{Hz}$ , NH), 2.43(s, 3H), 2.41(m, 1H), 1.20(m, 2H), 1.16(s, 9H), 1.02(t, 3H,  $J=2.86\text{Hz}$ );  $^{13}\text{C}$  NMR 147.99, 137.68, 137.20, 137.11, 133.30, 132.17, 131.04, 130.57, 130.14, 129.07, 128.92, 119.39, 115.09, 72.84, 54.20, 45.75, 28.70, 26.55, 20.83, 12.21; MS (CI+ve), 541( $\text{M}+\text{H}^+$  2.9%), 482(11%), 462(2.9%), 260(11%), 240(24%), 224(100%), 134(32%), 94(63%).

**N-tert-Butyldiphenylsilyl-S-methyl-S-(1-phenyl-2-phenylamino-3-methyl)butylsulfoximine 5.9d**

M.p. 145-146°C;  $^1\text{H}$  NMR 7.65-6.65 (m, 25H), 4.42(m, 1H), 4.18(d,  $J=10.3\text{ Hz}$ , 1H, NH), 4.14(d,  $J=6.41\text{Hz}$ , 1H), 2.41(s, 3H), 2.13(m, 1H), 1.06(s, 9H), 1.00(d,  $J=8.01\text{Hz}$ , 3H), .65(d,  $J=6.8\text{Hz}$ , 3H);  $^{13}\text{C}$  NMR 147.56, 135.68, 135.55, 135.41, 130.74, 130.13, 129.31, 128.88, 128.44, 128.36, 127.23, 117.52, 113.40, 50.39, 44.54, 31.54, 27.12, 26.99, 22.22, 19.19, 16.33; IR (nujol) 3325(s), 1440(s), 1560(s), 1340(s), 1280(s); MS (CI+ve), 555( $\text{M}+\text{H}^+$  26%), 477(2.9%), 409(6%), 238(100%), 194(11%), 148(20%), 93(14%); HRMS calcd. for  $\text{C}_{30}\text{H}_{33}\text{N}_2\text{OSSi}$ , 497.2083, found 497.2083.

**N-tert-Butyldiphenylsilyl-S-methyl-S-(1-phenyl-2-phenylamino-4-methyl)pentylsulfoximine 5.9e**

$^1\text{H}$  NMR 7.88-6.70(m, 20H), 5.08(m, 1H), 4.45(d, 1H,  $J=2.79\text{ Hz}$ ), 3.24 (d, 1H,  $J=10.5\text{Hz}$ , NH), 1.8(m, 1H), 1.17(m, 1H), 1.08(m, 9H), .90(d, 3H,  $J=6.5\text{Hz}$ ), 0.8(d, 3H,  $J=6.15\text{Hz}$ ); IR(film) 3395(s), 1520(s), 1410(s),



1285(s), 1150(s), 110(s); MS (CI+ve), 569(M+H<sup>+</sup>, 3%), 294(9%), 552(100%), 240(20%), 199(16%), 162 (33%), 117(23%), 104(23%), 91(29%).

**1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(N-tert-butyldiphenylsilyl-S-methylsulfoximidoyl)phenylmethylisoquinoline 5.11**

<sup>1</sup>H NMR 7.82-7.05 (m, 10H), 6.47(s, 1H), 6.36(s,1H), 5.35(br.d, 1H), 4.37 (d, 1H, J=2.9Hz), 3.73(s, 6H), 3.10(m, 2H), 2.9(m, 2H), 2.5(s, 3H), 1.12(s, 9H); <sup>13</sup>C NMR 134.08, 133.95, 129.96, 128.23, 127.49, 126.49,126.02, 125.37, 110.41, 108.03, 76.65, 54.64, 53.99, 52.73, 42.72, 40.21, 27.72, 25.60, 17.76; IR 3340(s), 1520(s), 1400-1200(s), 1140(s), 1090(s), 1020(s); MS (CI+ve), 599( (M+H<sup>+</sup>,11%), 540(11%), 521(14%), 408(57%), 350(14%), 330(14%), 234(57%), 204(100%), 191(100%), 146(40%), 105 (29%), 91(100%).

**N-tert-Butyldimethylsilyl-S-(1-phenyl-2-phenylamino)ethyl-S-methylsulfoximine 5.13**

<sup>1</sup>H NMR 7.80-6.60 (m, 15H), 6.69(s, 1H), 6.45(s,1H), 5.49(d, 1H, J=3.97Hz), 4.22(d, 1H, J=3.82Hz), 4.16(s, 6H), 2.65(s, 3H), .895(s, 9H), .13(d, 6H, J=5.03); IR (nujol) 3380(s), 1400-1200(br), 1160(s); MS (CI+ve), 465 (M+H<sup>+</sup>,17%), 407(8%), 375(100%), 358(77%), 271(100%), 165(100%), 180(100%), 165(29%), 118(34%), 104(86%), 93(100%), 77 (80%); HRMS calcd. for C<sub>23</sub>H<sub>27</sub>N<sub>2</sub>OSSi, 407.1613, found 407.1609.

**1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(N-tert-butyldiphenylsilyl-S-methylsulfoximidoyl)phenylmethylisoquinoline 5.14**

<sup>1</sup>H NMR 7.55-7.20(m, 5H), 6.67(s, 1H), 6.40(s, 1H), 4.40(d,1H, 2.63), 3.86(s, 3H), 3.77(s, 3H), 2.99(m, 2H), 2.67(s, 3H), 2.s(m, 2H), .95(s,

9H), .16 (s, 6H); IR (neat) 3400(h), 1400-1200(br), 1100(s), 1130(s), 1070(sh); MS (CI+ve), 475(M+H<sup>+</sup>, 6%), 473(9%), 417(17%), 296(69%), 281(100%), 266 (57%), 226 (87%), 191(100%), 176(100%), 170(100%), 105 (100%), 91(100%), 77(100%).

**N-tert-Butyldimethylsilyl-S-(1-phenyl-2-phenylamino)ethyl-S-methylsulfoximine 5.13**

<sup>1</sup>H NMR 7.69-6.35(m,18H), 6.44(d, 2H, J=7.47Hz), 4.90(d,1H, J=3.36Hz), 4.32(d, 1H, J=3.51Hz), 1.05(s, 9H); <sup>13</sup>C NMR 146.99, 140.32, 135.42, 132.08, 131.87, 130.09, 129.61, 128.66, 128.57, 128.4, 128.23, 128.10, 127.67, 127.88, 127.71, 127.10, 126.97, 126.88, 126.58, 117.96, 114.36, 58.23, 26.99, 19.19; IR(film) 3375(s), 1400-1230(br), 1150(s), 1110(s); MS (CI+ve), 593(23%), 378(14%), 362(11%), 335(14%), 332(26%), 302 (51%), 288(100%), 272(100%), 212(17%), 194(34%), 182(100%), 167 (77%), 104(60%), 91(67%), 77(100%); HRMS calcd. for C<sub>42</sub>H<sub>43</sub>N<sub>2</sub>OSSi, 651.2863, found 651.290.

**3,4-Dihydro-6,7-dimethoxy-1-(N-tert-butyldiphenylsilyl-S-phenylsulfoximidoyl)-1-phenylmethylisoquinoline 5.16**

<sup>1</sup>H NMR 7.8-6.85(m, 20H), 6.16(s, 1H), 6.32(s,1H), 5.35(d, 1H, J<1Hz), 4.43(d, 1H, J=2.44Hz), 3.76(s, 3H), 3.69(s, 3H), 2.8(m, 2H), 2.5(m, 2H), 1.09(s, 9H); <sup>13</sup>C NMR 147.17, 146.86, 141.79, 136.12, 135.94, 135.42, 132.08, 131.61, 131.26, 129.83, 128.79, 128.05, 127.79, 127.45, 147.14, 126.80, 111.89, 109.42, 78.91, 56.20, 55.37, 54.33, 41.90, 29.20, 27.16, 19.45; IR 3460(s), 1450-1300(br), 1210(s), 1160(s), 1140(s); MS (CI+ve), 471(3%), 413(11%), 393(3%), 283(9%), 192(100%), 91(86%); HRMS(EI) calcd. for C<sub>40</sub>H<sub>45</sub>N<sub>2</sub>O<sub>3</sub>SSi, 661.2917, found 661.284.

**(N-tert-Butyldiphenylsilyl)-S-methyl-S-(1-phenyl-2-hydroxy-2-phenyl)ethylsulfoximine 5.18a**

$^1\text{H}$  NMR 7.9-6.89(m, 20H), 6.07(d, 2H,  $J=1.83\text{Hz}$ ), 5.78(d, 1H,  $J=9.64\text{Hz}$ ), 5.63(d, 1H,  $J=9.76\text{Hz}$ ), 4.39(d, 1H,  $J=9.77$ ), 4.04(d, 1H,  $J=1.99$ ), 4.01(d, 1H,  $J=1.98$ ), 2.45(s, 3H), 1.14(s, 9H);  $^{13}\text{C}$  NMR (a) 141.75, 137.42, 136.94, 136.35, 132.65, 131.78, 130.52, 129.87, 129.70, 129.57, 129.35, 129.18, 128.83, 128.62, 127.23, 79.99, 72.19, 45.19, 28.50, 20.66, (b)141.62, 139.24, 137.11, 136.89, 131.69, 131.61, 130.69, 130.44, 129.79, 129.66, 129.567, 129.44, 129.35, 129.22, 128.88, 128.70, 29.43, 75.79, 45.28, 28.50, 20.53; IR 3420(s), 1400-1240(b), 1130(s), 1110(s), 1060(s); MS (CI+ve), 514 ( $\text{M}+\text{H}^+$ , 20%), 496(14%), 456(49%), 408(14%), 316(57%), 271(40%), 240(49%), 161(32%), 138(100%), 105(51%), 91(80%); HRMS calcd. for  $\text{C}_{31}\text{H}_{36}\text{NO}_2\text{SSi}$ , 514.2234, found 514.221.

**(N-tert-Butyldiphenylsilyl)-S-methyl-S-(1-phenyl-2-hydroxy)butyl sulfoximine 5.18b**

M.p.133-134°C.  $^1\text{H}$  NMR 7.72-7.3(m, 13H), 4.69(m, 1H), 3.84(d, 1H,  $J=1.84\text{Hz}$ ), 3.79(d, 1H,  $J=2.14\text{Hz}$ , OH), 2.42(s, 3H), 1.39(m, 1H), 1.17(m, 2H), 1.09(s, 9H), .85(t, 3H,  $J=7\text{Hz}$ );  $^{13}\text{C}$  NMR 135.64, 135.51, 135.38, 131.17, 129.18, 129.05, 128.53, 128.4, 128.27, 127.49, 127.32, 127.23, 76.00, 75.57, 70.37, 47.67, 27.77, 27.03, 9.91; IR (neat) 3600-3300(s), 1290(s), 1135(s), 1135(s), 1110(s); MS (CI+ve), 480( $\text{M}+\text{H}^+$ , 14%), 408(14%), 390(26%), 350(34%), 330(51%), 318(32%), 940(100%), 138(20%), 107(49%), 91(100%).

**(N-tert-Butyldiphenylsilyl)-S-methyl-S-(1-phenyl-2-hydroxy-3-methyl)pentylsulfoximine 5.18c**

$^1\text{H}$  NMR 7.76-7.26(m, 15H), 4.34(dd, 1H,  $J=1.83$ , 4.3Hz), 4.00(d, 1H,  $J=1.99\text{Hz}$ ), 2.44(s, 3H), 2.44(s, 3H), 1.00(s, 9H), .96(d, 3H,  $J=6.7\text{Hz}$ ), .82(d, 3H,  $J=6.7\text{Hz}$ ); IR (neat) 3700-3200(br), 1900-1230(br), 1200(s), 1110(s); MS (CI+ve), 480 (83%), 408(26%), 388(17%), 330(43%), 318(34%), 260(26%), 240(100%), 199(20%), 149(23%), 138(37%), 131(32%), 91(69%).

**(N-tert-Butyldiphenylsilyl)-S-methyl-S-(1-phenyl-2-hydroxy-3,3-dimethyl)butylsulfoximine 5.18d**

$^1\text{H}$  NMR 7.70-7.25(m, 15H), 4.93(d, 1H,  $J=5.35\text{Hz}$ ), 4.59(d, 1H,  $J<1\text{Hz}$ ), 4.25(d, 1H,  $J=4.90\text{Hz}$ ), 4.09(d, 1H,  $J<1\text{Hz}$ ), 2.36(s, 3H), 1.14(s, 9H), .74(s, 9H);  $^{13}\text{C}$  NMR 138.99, 138.41, 138.33, 138.19, 134.73, 134.38, 132.04, 131.82, 131.26, 131.04, 130.96, 130.26, 130.13, 45.88, 38.56, 29.98, 29.85, 29.28, 27.81, 22.00; IR (neat) 3700-3200(br), 1400-1200(br), 11400(s), 1010(s); MS (CI+ve), 494 ( $\text{M}+\text{H}^+$ , 100%), (83%), 408(57%), 318(32%), 138(14%), 91(32%).

**(N-tert-Butyldiphenylsilyl)-S-methyl-S-(1-phenyl-2-hydroxy-4-methyl)pentylsulfoximine 5.18e**

$^1\text{H}$  NMR 7.8-7.24(m, 15H), 5.08(m, 1H), 4.97(m, 1H), 4.89(m, 1H), 4.87(m, 1H), 4.07(d, 1H,  $J<1\text{Hz}$ ), 4.05(d, 1H,  $J<1\text{Hz}$ ), 3.8(d, 1H,  $J<1\text{Hz}$ ), 3.74(d, 1H,  $J<1\text{Hz}$ ), 2.39(s, 3H), 1.90(m, 1H), 1.10(s, 9H), .85(d, 3H,  $J=7\text{Hz}$ ), .79(d, 3H,  $J=7\text{Hz}$ );  $^{13}\text{C}$  NMR 135.68, 135.59, 135.46, 130.13, 129.22, 129.05, 128.62, 128.53, 127.49, 127.32, 78.39, 68.55, 44.41, 43.76, 27.07, 23.82, 23.74, 23.65, 20.49, in part 76.94, 65.18; IR(film) 3700-3200(br), 1400-1330(br), 1180(s), 1110(s), 1075(s); MS (CI+ve), 494 ( $\text{M}+\text{H}^+$ , 44%), 408(23%), 358(63%), 318(37%), 240(100%), 212(43%), 199(51%), 159(57%), 138(100%), 117(60%), 91(100%), 77(37%).

**(N-tert-Butyldiphenylsilyl)-S-phenyl-S-(1-phenyl-2-hydroxy-2-phenyl)ethylsulfoximine 5.19**

$^1\text{H}$  NMR 7.9-6.83(m, 25H), 5.96(d, 1H,  $J < 1\text{Hz}$ , OH), 5.14(dd, 1H,  $J = 2.36, 9.16\text{Hz}$ ), 4.44(d, 1H,  $J = 9.76\text{Hz}$ ), 1.14(s, 9H);  $^{13}\text{C}$  NMR 141.19, 140.19, 135.81, 135.51, 134.69, 131.99, 131.69, 129.61, 129.05, 128.96, 128.44, 128.14, 128.05, 127.75, 127.49, 127.40, 127.23, 127.06, 125.84, 79.17, 70.72, 27.25, 19.49; IR(film)3600-3200(br), 1900-1200(br), 1150(s), 1110(s); MS (CI+ve), 576 ( $\text{M} + \text{H}^+$ , 11%), 560(17%), 518(21%), 500(24%), 378(100%), 362(34%), 338(66%), 302(77%), 200(100%), 167(74%), 105(100%), 91(100%), 77(100%), 77(100%); HRMS calcd for  $\text{C}_{36}\text{H}_{38}\text{NO}_2\text{SSi}$ , 576.2389, found 576.238.

1. G.A. Cordell, 'Introduction to Alkaloids', 1981, Wiley Interscience, New York.
2. R.H.F. Manske, in 'Alkaloids' (Manske, ed.) Academic Press, London, 1960, Vol. 7, 423; J. Lundstrom, in 'Alkaloids' (Brossi, ed.) Academic Press, London, 1983, vol.21, 255.
3. A. Brassi, H. Besendorf, L.A. Pirk, and A. Rheiner, in 'Analgetics, Medicinal Chemistry' (G. de Stevens, ed.), Academic Press, London, 1965, vol. 5, 281.
4. S.M. Kapchan and C.-K. Kim, J. Amer. Chem. Soc., 97, 5623 (1975).
5. D.R. Dalton, 'The Alkaloids A Biogenetic Approach' 1979, New York
6. K.C. Rice, Chem. and Eng. News 1982, April 19, p.41; B. Schnenberger and A. Brossi, Helv. Chim. Acta, 69, 1486 (1986).
7. Z. Czarnocki, D.B. MacLean and W.J. Szarek, J. Chem. Soc. Chem. Commun. (1985), 1318.
8. Z. Czarnocki and D.B. MacLean. Can. J. Chem., 65, 2356 (1987).
9. I.M.P. Hubber and D. Seebach, Hel. Chim. Acta, 70, 1944 (1987)
10. R.P. Polniaszek and J.A. McKee, Tetrahedron Lett., 28, 4511 (1987)
11. R.P. Polniaszek and C.R. Kaufman, J. Am. Chem. Soc., 111, 4859 (1989)
12. R.P. Polniaszek and L.W. Dillard, Tetrahedron Lett., 31, 797 (1990)
13. K.T. Wenner and I. Prashak, Heterocycles, 29, 29 (1989)
14. M.F. Loewe, M. Boes, and A.I. Meyers, Tetrahedron Lett., 26, 3295 (1985).

15. A.I. Meyers, T. Sohda and M.F. Loewe, J. Org. Chem., 51, 3108 (1986)
16. M.A. Gonzalez and A.I. Meyers, Tetrahedron Lett., 30, 47 (1989)
17. K. Rein, M. Goicoechea-Pappas, T.V. Ankleker, G.C. Hart, G.A. Smith and R.E. Gawley, J. Am.Chem. Soc., 111, 2211 (1989)
18. R.E. Gawley, G.C. Hart and L.J. Bortolotti, J. Org. Chem., 54, 175 (1989)
19. R.E. Gawley and G.A.Smith, Tetrahedron Lett., 29, 301 (1988)
20. S.G. Pyne, Tetrahedron Lett., 28, 4737 (1987)
21. R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, T. Ohta and H. Takaya, J. Am. Chem. Soc., 108, 7117(1986)
22. K. Yamada, M. Takeda and T. Iwakuma, Tetrahedron Lett., 22, 3869 (1981)
23. S.G. Pyne and B. Dikic, J. Org. Chem., 55, 1932 (1990)
24. Jahangir, M. A. Brook and D.B. MacLean, Can. J. Chem., 65, (1987).
25. M.D. Rozwadowska, D. Matecka and D. Brozda, Tetrahedron Lett., 30, 6215 (1989)
26. A. Rank, E. Buncel, R.Y. Moir and S. Wolfe, J. Org. Chem. Soc., 87, 1498 (1965)
27. S. Wolfe, Acc. Chem. Res., 5, 102 (1972)
28. (a) S. Wolfe, A. Stolow and L.A.laJohn, Can. J. Chem., 62, 1470 (1984); (b) S. Wolfe and L.A. la John, Tetrahedron Lett., 24, 4071 (1983); (c) H. Hargittai and I. Hargittai, J. Mol. Struct., 20, 283 (1974).
29. K. Nakamura, M. Higaki, S. Adachi, S. Oka and A. Ohno, J. Org. Chem., 52, 1414 (1987).
30. J.F. Biellmann and J.J. Vicens, Tetrahedron Lett., 2915 (1974)

31. T. Durst and M. Molin, Tetrahedron Lett., 63, (1975)
32. G. Chassaing, R. Lett and A. Marquet, Tetrahedron Lett., 471 (1978)
33. R. Lett, G. Chassaing and A. Marquet, J. Organomet. Chem., C17, 111 (1976)
34. a) G. Chassaing and A. Marquet, Tetrahedron Lett., 1399 (1978); b) W.Zorges, Diplomarbeit, Universitat Marburg, 1987
35. G. Chassaing, A. Marquet, J. Corset and F.Froment, J. Organomet. Chem., 232, 293 (1982)
36. M. Marsch, W. Massa, K. Harms, G. Baun and G. Boche, Angew. Chem. Int. Ed. Engl., 25, 1011 (1983)
37. M. Marsch, W. Massa, K. Harms, G. Baun and G.Boche, Angew. Chem. Int. Ed. Engl., 25, 1011 (1986)
38. M.A. Visioamitra and K.K. Kennam, Nature (London), 209, 2016 (1966)
39. W. Setzer and P.vonR. Schleyer, Adv. Organomet. Chem, 24, 353 (1985)
40. G. Tsuchihashi, S. Iriuchijama and K. Maniwa, Tetrahedron Lett., 3389 (1973)
41. N. Kunieola, M. Kinoshita and Nokenni, Chem. Lett., 289 (1977)
42. G. Damailly, C. Greek and G. Solladie, Tetrahedron Lett., 25, 4113 (1984); H. Sakuraba and S. Usiki, Tetrahedron Lett., 31, 5349 (1990)
43. C. Kingsbury, J Org. Chem., 37,102 (1972)
44. S.G. Pyne and G. Boche, J. Org. Chem. 54, 2663 (1989)
45. R. Annunziola, M. Cinquini, F. Cozzi, F. Montonori and A. Restelli, J.Chem. Soc. Chem. Commun., 1138 (1983)



46. L. Colombo, C. Gennari and C. Scollostico, J.Chem.Soc.Perkin  
I,1279 (1981)
47. D.G. Farnum, T. Veysogly and A.M.Carole, Tetrahedron Lett.,  
4009 (1977)
48. T. Seto, T. Itoh and T. Fujisawa, Tetrahedron Lett., 28, 5677  
(1987)
49. R. Tannikaga, K. Hosoya, K. Hannamura and A. Kaji,  
Tetrahedron Lett., 22, 4103 (1981)
50. D.R. Williams and J.G. Phillips, J. Org. Chem., 46, 4103 (1981)
51. P. Bravo, P. Carrera, G. Resnati and C. Ticozzi, J. Chem. Soc.  
Chem. Commun., 19 (1984)
52. J. Annunziata and M. Cinquini, Synthesis, 929 (1982)
53. A. Nudelman and D.J. Cram, J. Org. Chem., 34,3659 (1969)
54. G. Guanti, L. Banli, E. Nariseno and S. Thea, J. Chem. Soc.  
Chem. Commun., 861 (1984)
55. T. Satoh, T. Oohara and K. Yamakawo, Tetrahedron Lett., 29  
4093 (1988)
56. (a) C.R. Johnson and J.R.Zeller, Tetrahedron Lett., 25, 1225  
(1984); (b) C.R. Johnson, Aldrichim. Acta, 18, 3 (1985) (c)  
I. Erdelmeier, H.J. Gais and H.J. Linder, Angew. Chim. Int. Ed.  
Engl., 25, 935 (1986)
57. G. Chassaing and A. Marquet, Tetrahedron Lett., 1399  
(1978)
58. H.J. Gais, I. Erdelmeir and H.J.Lindner and J. Vollhardt  
Angew. Chem. Int. Ed. Engl., 25, 938 (1986)
59. H.J. Gais, V. Dingerdissen, C. Kruger and K. Angermund, J. Am.  
Chem. Soc., 109, 3775 (1987)
60. G. Boche, Angew. Chem. Int. Ed. Engl., 28, 277 (1989)
61. C.R. Johnson and C.J. Stark, Jr., J. Org. Chem., 47, 1193 (1982)

62. C.R. Johnson and C.J. Stark, Jr., J. Org. Chem., 47, 1196 (1982)
63. K.J. Hwang, J. Org. Chem., 51, 99 (1986)
64. K.J. Hwang, E.W. Logoursch and L.H. Brannigan, J. Org. Chem., 52, 3435 (1987)
65. A.J. Pearson, C.L. Blystone and B.A. Roden, Tetrahedron Lett., 28, 2459 (1987)
66. S. Ronan, S. Marchalin, O. Samuel and H.B. Kagan, Tetrahedron Lett., 29, 6104 (1988).
67. (a) N.J. Leonard and C.R. Johnson, J.Org.Chem., 27, 282 (1962).  
 (b) S. Hunig, Ann. Chem. 23, 579 (1953).  
 (c) T. Yoshida, S. Noruta, H. Uno and H. Nishimura, Chem. Pharm. Bull. 30, 4346 (1984)
68. G. Solladie, Synthesis, 187 (1981).
69. Tiollais, R. Bull. Soc. Chim. Fr., 708 (1947).
70. a) S.G. Pyne and B. Dikic, J. Chem. Soc., Chem. Commun., 826, (1989).  
 b) S.G. Pyne and B. Dikic, J. Org. Chem., 55, 1932 (1990).
71. H. Booth and R.V. Lemieuse, Can. J. Chem., 49, 777 (1971).
72. D.W. Hughes, H.L. Holland and D.B. MacLean, Can. J. Chem., 54, 2254 (1976).
73. R.F. Borch and A.I. Hassid, J. Org. Chem., 37, 1673 (1972).
74. S.G. Pyne and S. Chapman, J. Chem. Soc., Chem. Commun., 1688 (1986).
75. a) E. Spoth, E. Mosettig and O. Trothondl, Chem. Ber., 1932, 56B, 875-879.  
 b) Johangir, D.B. MacLean and H.L. Holland, Can. J. Chem., 64, 1031 (1986).
76. T.W. Mumbley, B. Raguse and D.D. Ridley, Aust. J. Chem., 39, 1833 (1986).

- 77 a) C.R. Johnson, R.A. Kirchhoff, R.J. and G.F. Katekor, J. Am. Chem. Soc., 95, 4287 (1973).  
b) R.W. Heitzelman, D. Swern, Synthesis, 1976, 731.  
c) C.R. Johnson and C.W. Schroeck, J. Am. Chem. Soc., 95, 7418 (1973).
78. C.S. Shiner and A.H. Berks, J. Org. Chem., 53, 5542 (1988).
79. E.J. Corey and A. Vonkateswarlu, J. Am. Chem. Soc., 94, 6190 (1972).
80. (a) 'Atlas of Spectral Data and Physical Constants for Organic Compounds', J.G. Grasselli and W.M. Ritchey, Eds. CRC Press, Cleveland, Ohio, 2nd Ed., Vol. III, 1975, p. 486.  
(b) J. Elguero, C. Marzin and J.D. Roberts, J. Org. Chem., 39, 357 (1974)
81. S. Raucher and G.A. Koope, J. Org. Chem., 43, 3794 (1978).
82. Y. Tamura, J. Minamikawa, K. Sumoto, S. Fujii and M. Ikeda, J. Org. Chem., 38, 1239 (1973).
83. C.R. Johnson, R.A. Kirchhoff and H.G. Conkins, J. Org. Chem., 39, 2458 (1974).
84. T. Durst and R. Viau, J. Amer. Chem. Soc., 93, 3077 (1971).
85. S.G. Pyne and B. Dikic, Tetrahedron Lett., 31, 5231 (1990).
86. C.A. Kingsbury, V.W. Day and R.O. Day, J. Org. Chem., 45, 5255 (1980).
87. E.L. Eliel and W.J. Frazee, J. Org. Chem., 44, 3598 (1979).
88. O. De Lucchi, V. Luccihini, C. Marchioro, G. Valle and G. Modena, J. Org. Chem., 51, 1457 (1986).
89. B.M. Trost and D.P. Curran, Tetrahedron Lett., 22, 1287 (1981).
90. S.K. Chaudhary and O. Hernandez, Tetrahedron Lett., 30, 99 (1979).

91. a) R.D. Miller and D.R. McKean, Tetrahedron Lett., 24, 2619 (1983).  
b) S. Lane, S.J. Quick and R.J. Taylor, Tetrahedron Lett., 25, 1039 (1984).  
c) J. Chem. Soc., Perkin Trans 1, 2599 (1984).  
d) G.A. Olah and S.C. Narang, Tetrahedron, 38, 2225 (1982).
92. G.A. Olah, S.C. Narang, L.D. Field and G.F. Salem, J. Org. Chem., 45, 4792 (1980).

## GENERAL PROCEDURES

### (a) Melting Points (mp)

Melting points were determined on a Reichert hot stage apparatus and are uncorrected.

### (b) Infrared (IR) Spectra

Infrared Spectra were recorded on a Perkin Elmer Infrared Spectrophotometer model 783 as mulls in nujol unless otherwise stated.

### (c) $^1\text{H}$ Nuclear Magnetic Resonance (NMR) Spectra

$^1\text{H}$  NMR spectra were recorded on a JEOL FX 90Q Fourier Transform NMR Spectrometer operating at 90 MHz, or a JEOL JNM-GX400 Fourier Transform NMR Spectrometer operating at 400 MHz. The spectra were measured in  $\text{CDCl}_3$  unless otherwise stated, relative to tetramethylsilane (0.00 ppm). Each signal is described in terms of chemical shifts in ppm from tetramethylsilane, multiplicity, intensity, coupling constant (Hz) and assignments in that order with the use of the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet.

### (d) $^{13}\text{C}$ Nuclear Magnetic Resonance (NMR) Spectra

$^{13}\text{C}$  NMR spectra were recorded on a JEOL FX 90Q Fourier Transform NMR Spectrometer or a JEOL JNM-GX400 Fourier Transform NMR Spectrometer. The spectra were measured in  $\text{CDCl}_3$  unless otherwise stated, relative to  $\text{CDCl}_3$  (77.0 pp).

(e) Mass Spectra (MS)

Low Resolution Mass Spectra were recorded on a Vacuum Generator VG 12-12 mass spectrometer.

High Resolution Mass Spectra were recorded on a AEI-MS-902 mass spectrometer using heptaperfluorotributylamine as reference.

(f) Microanalysis

Microanalysis were performed by the Australian National University Services Unit Canberra.

(g) Column Chromatography

The chromatography adsorbent used was silica gel (0.063-0.2 mm, Merck) unless otherwise indicated.

(h) X-ray structures were determined at the University of Western Australia by Professor Allan White.

(i) Optical Rotation

Optical rotations were recorded with a Perkin-Elmer 141 Polarimeter. All rotations were measured in water.