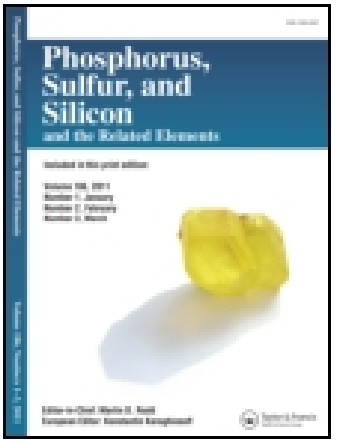


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Diastereoselective Reactions and Rearrangements of Chiral Allylic Sulfoximines

Stephen G. Pyne , Z. Dong , D. M. David & G. W. O'Meara
[a] Department of Chemistry , University of Wollongong , Wollongong, NSW 2522, Australia
[b] Department of Chemistry , University of Wollongong , Wollongong, NSW 2522, Australia
[c] Department of Chemistry , University of Wollongong , Wollongong, NSW 2522, Australia
[d] Department of Chemistry , University of Wollongong , Wollongong, NSW 2522, Australia
Published online: 17 Mar 2008.

To cite this article: Stephen G. Pyne , Z. Dong , D. M. David & G. W. O'Meara (1997) Diastereoselective Reactions and Rearrangements of Chiral Allylic Sulfoximines, Phosphorus, Sulfur, and Silicon and the Related Elements, 120:1, 275-289, DOI: 10.1080/10426509708545524

To link to this article: http://dx.doi.org/10.1080/10426509708545524

Phosphorus, Sulfur, and Silicon, 1997, Vol. 120 & 121, pp. 275–289
Reprints available directly from the publisher
Photocopying permitted by license only

DIASTEREOSELECTIVE REACTIONS AND REARRANGEMENTS OF CHIRAL ALLYLIC SULFOXIMINES

Stephen G. Pyne*, Z. Dong, D. M. David and G. W. O'Meara

Department of Chemistry, University of Wollongong, Wollongong, NSW 2522, Australia

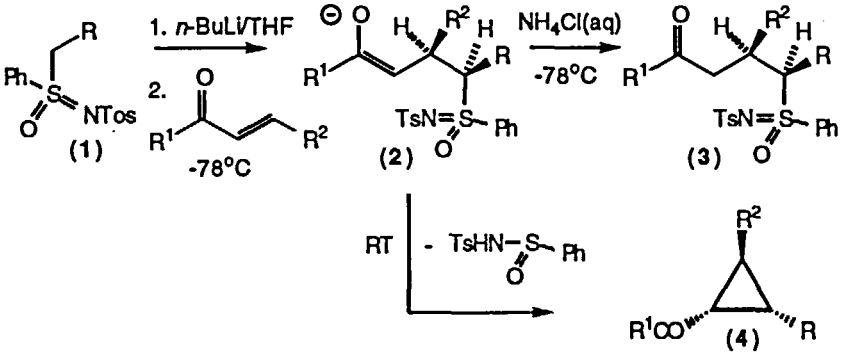
Abstract: The nucleophilic and electrophilic chemistry of chiral allylic sulfominines and their alkyl sulfoximine counterparts are described including the synthesis of highly functionalised cyclopropanes derivatives. The synthesis of primary and secondary *N*-tosyl allylic amines via the palladium(0) catalysed rearrangement of allylic sulfoximines to allylic sulfinamides is also described.

INTRODUCTION

Chiral allylic sulfoximines can act as nucleophiles in a basic medium or electrophiles in the presence of a Lewis acid. This paper highlights some of our recent results on the nucleophilic and electrophilic reactions of chiral allylic sulfoximines.

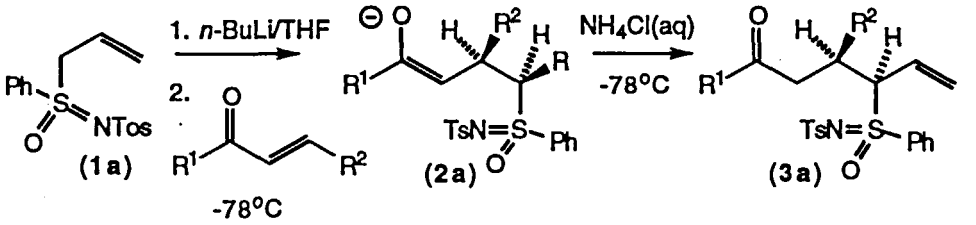
1. DIASTEREOSELECTIVE MICHAEL REACTIONS OF α–LITHIATED SULFOXIMINES AND THE SYNTHESIS OF CYCLOPROPANES.

Exploiting the nucleophilic nature of deprotonated sulfoximines we can prepare Michael addition adducts (**2**) from the reaction of α-lithiated derivatives of sulfoximines (**1**, R = $CH{=}CH_2$, Ph) with enones. Low temperature protonation of (**2**) gives Michael products (**3**) in a highly diastereoselective manner. However, upon warming the enolate adducts (**2**) to room temperature then the electrophilic nature of the sulfoximine moiety can be realised and this group can act as a leaving group to give the highly functionalised cyclopropanes derivatives (**4**) in high diastereoselectivities and enantiomeric purities.



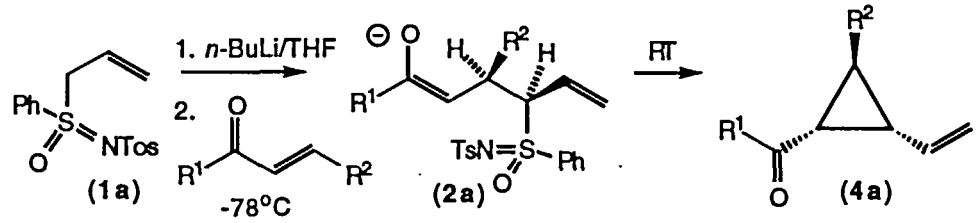
(i) *Allylic and Benzylic Sulfoximines*

α-Lithiated allylic sulfoximines (prepared from deprotonation of (**1a**)[1] undergo highly diastereoselective Michael addition reactions to acyclic enones to give, after quenching the reactions at -78°C, the 1,4-α-adducts (**3a**) and a minor 1,4-α-diastereoisomeric adduct in a diastereomeric ratio of 90-94 : 10-6. The relative stereochemistry of the major diastereomeric adducts (**3a**) has been determined by single crystal X-ray structural analysis.[1,2] In the case of cyclic enones mixtures of all four possible diastereomeric 1,4-α-adducts were obtained.[1]



R^1	R^2	yield (%)	d. r.
Ph	Ph	90	93 : 7
Ph	Me	61	94 : 6
Me	Ph	45	90 : 10

When solutions of the intial Michael adducts are warmed to room temperature for 1 h, prior to quenching with aqueous ammonium chloride solution, then the cyclopropanes (**4a**) could be isolated in good yields and with high diastereoselectivities.[3]

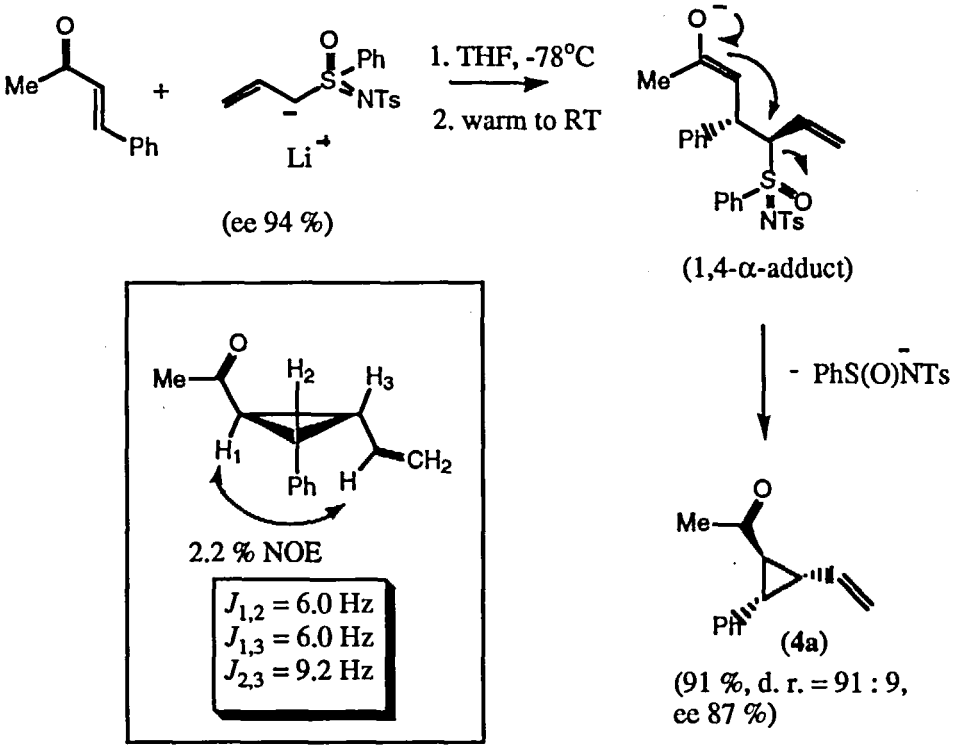


R^1	R^2	yield (%)	d. r.
Ph	Ph	83	79 : 21
Ph	Me	84	84 : 16
Me	Ph	91	91 : 9

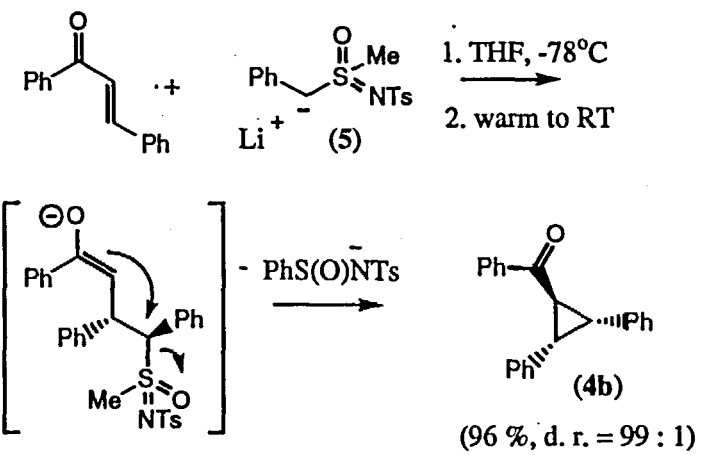
The relative stereochemistry of the cyclopropane adducts could be determined from NOE difference experiments and analysis of ^{1}H NMR coupling constants. These studies indicated that the sulfoximine group was being displaced via an intramolecular

S_N2 displacement reaction. When optically active sulfoximine (**1a**) was employed then the chiral cyclopropane (**4a**, R^1 = Me, R^2 = Ph) was obtained in 88% ee as acertained by chiral NMR shift studies (Scheme 1).

Scheme 1



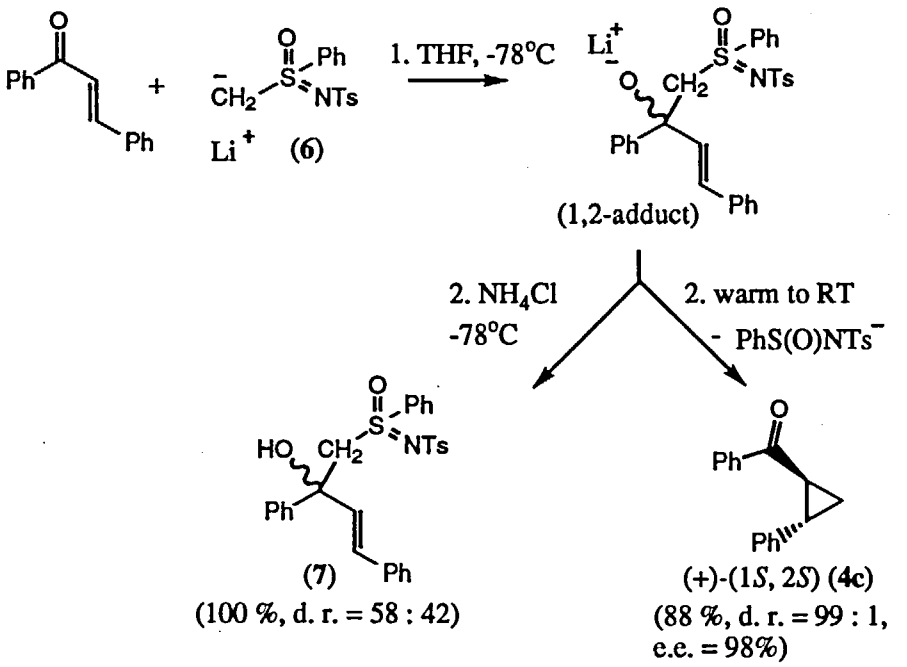
Under similar conditions to those descibe above, the reaction of chalcone with lithiated benzyl sulfoximine (**5**) gave the cyclopropane (**4b**) in good yield and high diasteeoselectivity. This reaction occured in the same stereochemical sence as those above.



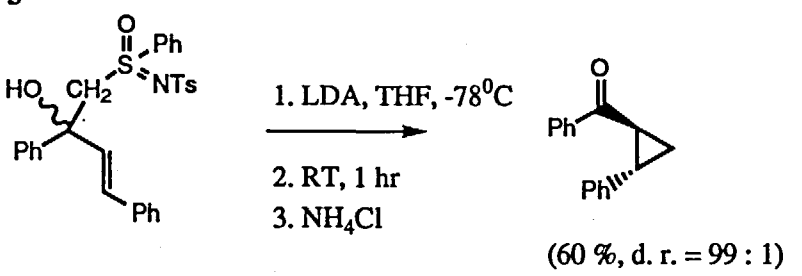
(ii) *Alkyl Sulfoximines*

The reaction of the lithited alkyl sulfoximines prepared from deprotonation of (1; R = H or $CH_2CH_2CH_3$) with acyclic enones gives mixtures of 1,2-and 1,4-adducts, after quenching the reactions at -78°C with an aqueous solution of ammonium chloride. For example, α-lithiated sulfoximine (**6**) reacted with chalcone at -78°C to give a 58 : 42 mixture of diastereomeric 1,2-adducts (**7**). However, when this reaction mixture was warmed to room temperature for 1 h then the cyclopropane product (**4c**) was isolated in good yield and with high diastereoselectivity (Scheme 2). When opticvally active (**6**) was employed then optically active (+)-(1*S*, 2*S*)-(**4c**) was obtained in 98 % ee. The cyclopropane (**4c**) could also be prepared from treatment of (**7**) with base (LDA) at -78°C followed by warming the reaction mixture to room temperature for 1 h (Scheme 3).

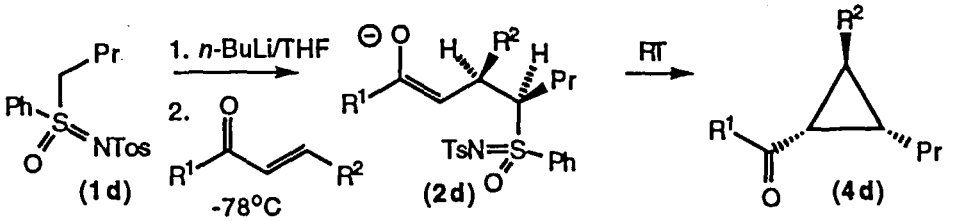
Scheme 2



Scheme 3



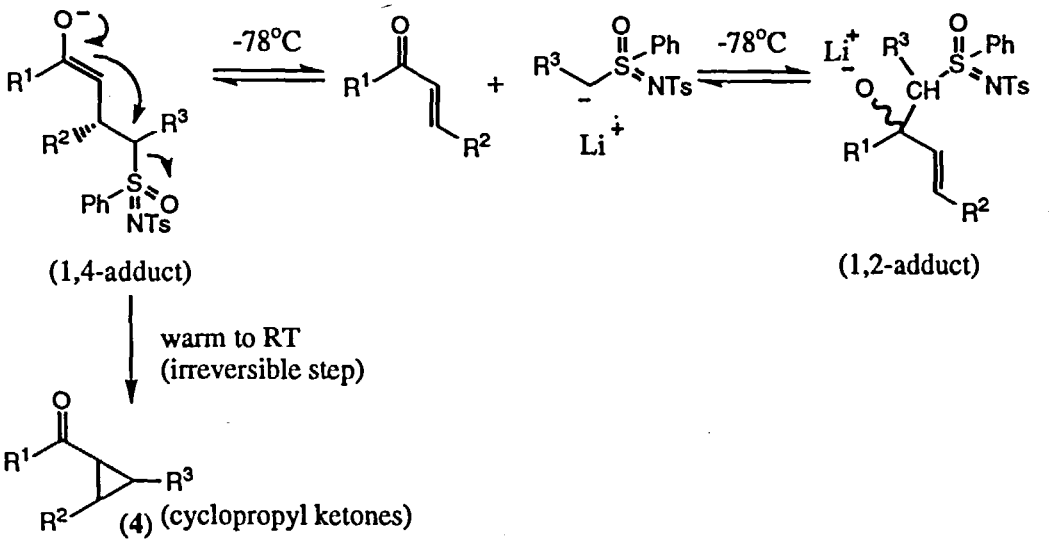
Similarly, the reactions of the lithited alkyl sulfoximines prepared from deprotonation of (1; R = $CH_2CH_2CH_3$) with acyclic enones gives mixtures of 1,2-and 1,4-adducts, after quenching the reactions at -78°C with an aqueous solution of ammonium chloride. When these reaction mixtures were first warmed to room temperature then the cyclopropanes (**4d**) were obtained in high yields and diastereoselectivities.



R^1	R^2	yield (%)	d. r.
Ph	Ph	90	99 : 1
Ph	Me	68	96: 4
Me	Ph	58	99 : 1

We propose the following mechanism to explain the high yield of these cyclopropanation reactions (Scheme 4). At low temperatures (-78°C) a mixture of 1,2- and 1,4-adducts are obtained. However, at room temperature these adducts are interconvertable. The intramolecular displacement of the sulfoximine moiety from the 1,4-adduct is a reversible reaction and thus drives the equilibrium in favour of the cyclopropane products (**4**).

Scheme 4.



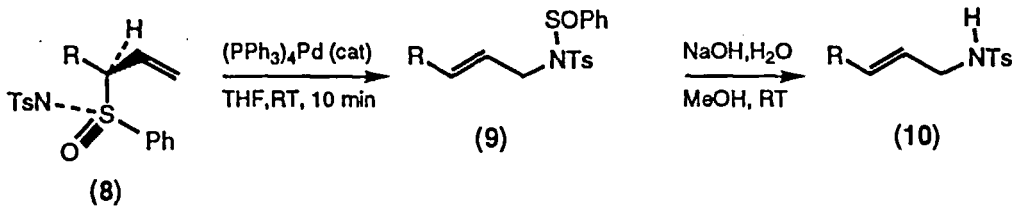
Thus a highly efficient and stereoselective method is available for the synthesis of 1,2,3-trisubstituted cyclopropanes from the reactions of α–lithiated sulfoximines and enones at room temperature. In these reactions both the nucleophilic and electrophilic nature of the sulfoximine group is clearly demonstrated.

2. PALLADIUM CATALYSED ALLYLIC SULFOXIMINE TO ALLYLIC SULFINAMIDE REARRANGEMENTS.

(i) *Palladium Catalysed Rearrangements of Secondary Allylic Sulfoximines*

We recently reported a novel method for the synthesis of primary *N*-tosyl allylic amines (**10**) via the palladium(0) catalysed rearrangement of α-substituted allylic sulfoximines (**8**) to allylic sulfinamides (**9**)[2,4] (eq 1). Thus treatment of a THF solution of the allylic sulfoximines (**8**) with 5 mol% of tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) at room temperature for 10 min resulted in a bright red solution. Evaporation of the THF *in vacuo* and exposure of the crude reaction mixture to 10% aqueous sodium hydroxide and MeOH (1 : 10) at room temperature for 2 h gave the primary *N*-tosyl allylic amines (**10**) (Table 1). In all cases the rearrangement reactions were completely regioselective and resulted in products that had undergone a 1,3-allylic rearrangement.

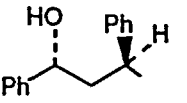
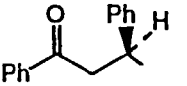
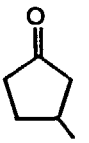
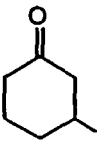
(eq 1)



(8) (9) (10)

This type of rearrangement reaction has been reported to occur under thermal induction but only in the case of γ-phenyl allylic sulfoximines.[5] In these compounds the phenyl substituent may facilitate the rearrangement process by providing stabilization of an ion-pair or other intermediate. These thermally induced rearrangements however, proceed with poor regioselectivity and poor yields of conversion.[5] Interestingly, semi-empirical[6] and *ab initio*[7] calculations indicate that allylic sulfinamides are thermodynamically much more stable than their isomeric allylic sulfoximines and that the free energy barrier, for conversion of allylic sulfoximines to their corresponding allylic sulfinamides, must be relatively large.

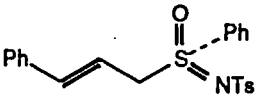
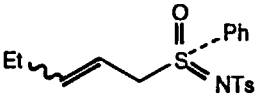
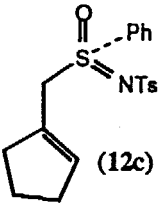
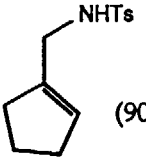
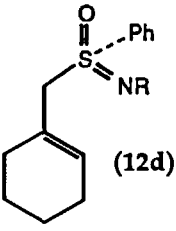
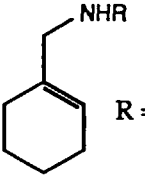
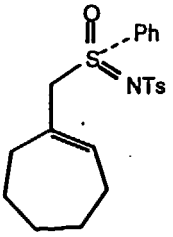
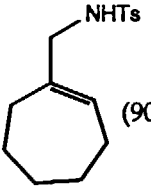
Table 1. Palladium Catalysed Reactions of Allylic Sulfoximines (**8**)

Sulfoximine (**8**)	R	Overall yield (%) of (**10**)
(8a)		81
(8b)		80
(8c)		81
(8d)		79
(8e)		90
(8f)	H	90

(ii) *Palladium Catalysed Rearrangements of Primary Allylic Sulfoximines*

Under similar reaction conditions to those described above a series of primary allylic sulfoximines (**12**) gave primary allylic sulfonamide products (**10**) without 1,3-allylic rearrangement (Scheme 5 and Table 2).[8] The regiochemistry of these reactions, and those in Table 1, can be understood in terms of the formation of the Pd-allylic cation complex (**11**) followed by addition of the sulfinamide anion to the least substituted terminus of the allylic cation moiety of (**11**) (Scheme 5). Formation of the more stable *syn* complex (**11**) (R = Et) would be expected from the initial mixture of *syn* and *anti* Pd-allylic cation complexes that could arise from the reaction of (*Z*)- and (*E*)- **12b** with $Pd(PPh_3)_4$ respectively.[9] The *N*-

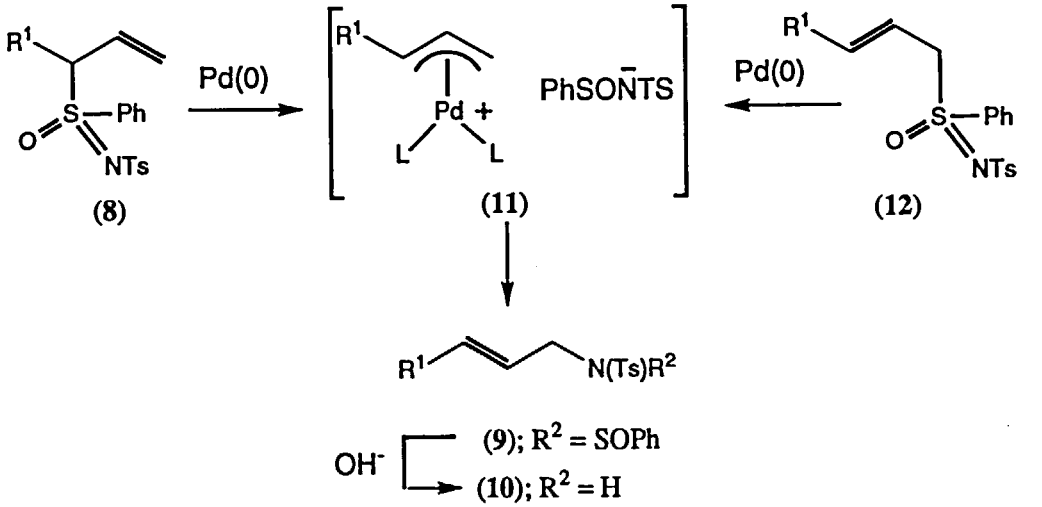
Table 2. Palladium Catalysed Rearrangements of Primary Allylic Sulfoximines (**12**) Followed by Base Treatment to give Primary Allylic Sulfonamides (**10**).

entry	substrate	time (min)	product (**10**) (yield (%))
1	 (**12a**)	10	 (87)
2	 (**12b**) ($E:Z = 58:42$)	10	 (95; $E:Z = 90:10$)
3	 (**12c**)	10	 (90)
4	 (**12d**) R = Ts	10	 R = Ts (89)
5	(**12e**) R = CO_2Me	30	R = CO_2Me (66)
6	(**12 f**) R = Me	60	R = Me (21) + PhSONHMe (68)
7		10	 (90)

methoxycarbonyl and *N*-methyl allylic sulfoximines, (**12e**) and (**12f**), also underwent rearrangement to their corresponding allylic sulfinamides with Pd (PPh3)4, however those reactions were much slower than that of the related *N*-tosyl analogue (**12d**). Qualitatively,

the relative rates of the reactions of (**12d**), (**12e**) and (**12f**) correlated closely with the electron withdrawing ability of the *N*-substituent of the sulfoximine. Thus while (**12d**) reacted in 10 min, (**12e**) required a reaction time of 30 min while the reaction of *N*-methyl compound (**12f**) was complete only after 1 h. In the later reaction the major product isolated was *N*-methyl phenylsulfinamide (68 %).

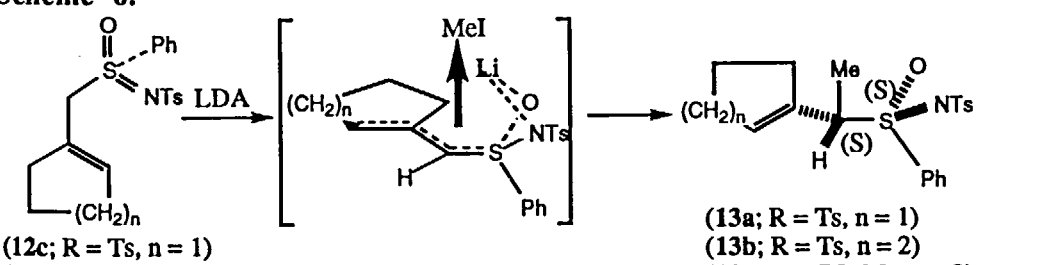
Scheme 5.



(iii) *Chiral α-substituted Allylic Sulfoximines*

In principle the palladium(0) catalysed rearrangement reaction of optically active α,γ-disubstituted allylic sulfoximines can give rise to optically active allylic amines. The success of this reaction depends upon the regioselectivity and diastereoselectivity of the rearrangement reaction. Methylation of the (*S*)-allylic sulfoximines (**12c**), (**12d**) and (**12e**) (ee = 96%) by first deprotonation with LDA at -78°C and then methylation with MeI gave the corresponding methylated allylic sulfoximines (**13a**), (**13b**) and (**13c**) respectively in 96-98% de (Scheme 6). These α-methylated sulfoximines were unstable and their attempted purification by chromatography gave complex mixtures that included rearranged allylic sulfinamides.

Scheme 6.



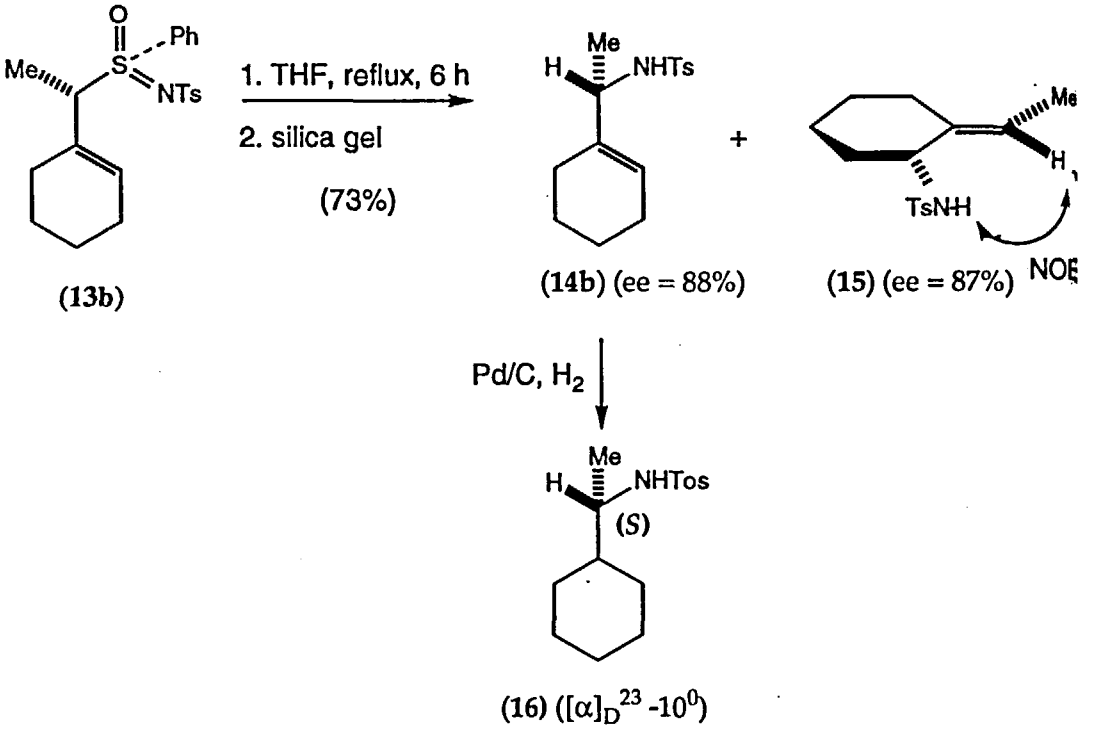
(**12c**; R = Ts, n = 1)
(**12d**; R = Ts, n = 2)
(**12e**; R = CO_2Me, n = 2)

(**13a**; R = Ts, n = 1)
(**13b**; R = Ts, n = 2)
(**13c**; R = CO_2Me, n = 2)

Heating a THF solution of (**13b**) at reflux for 6 h, followed by purification on silica gel gave an inseparable 45 : 55 mixture of the rearranged *N*-tosyl allylic amines (**14b**) and (**15**), respectively, in a combined yield of 73% (Scheme 7). These compounds could be separated by preparative HPLC. The absolute (*S*) stereochemistry of (**14b**) was determined by a comparison of the specific rotation of its *N*-tosyl-1-cyclohexylethylamine derivative (**16**) ($[\alpha]_D^{23}$ -10^0 (c 0.4, $CHCl_3$) with that prepared from tosylation of commercially available (*R*)-1-cyclohexylethylamine ((*R*)-*N*-tosyl-1-cyclohexylethylamine had a specific rotation of $[\alpha]_D^{23}$ $+24.0^0$ (c 0.5, $CHCl_3$)).

The absolute stereochemistry assigned to (**15**) is more tenuous and is based on mechanistic considerations (Scheme 8). The (*E*) stereochemistry of (**15**) was established by a NOESY experiment that showed a cross peak between the alkene proton and the NH group. The enantiomeric purities of (**14b**) and (**15**) were determined to be 88% and 87% respectively (92% and 91% ee corrected for the ee of **12d**), by ^1H NMR studies using the chiral shift agent europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate].

Scheme 7.



(**13b**)

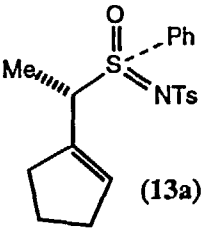
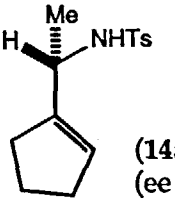
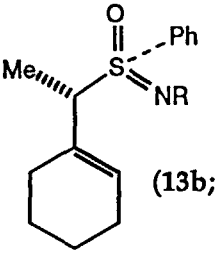
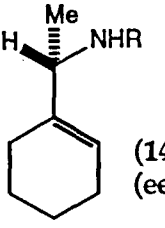
(**14b**) (ee = 88%)

(**15**) (ee = 87%)

(**16**) ($[\alpha]_D^{23}$ -10^0)

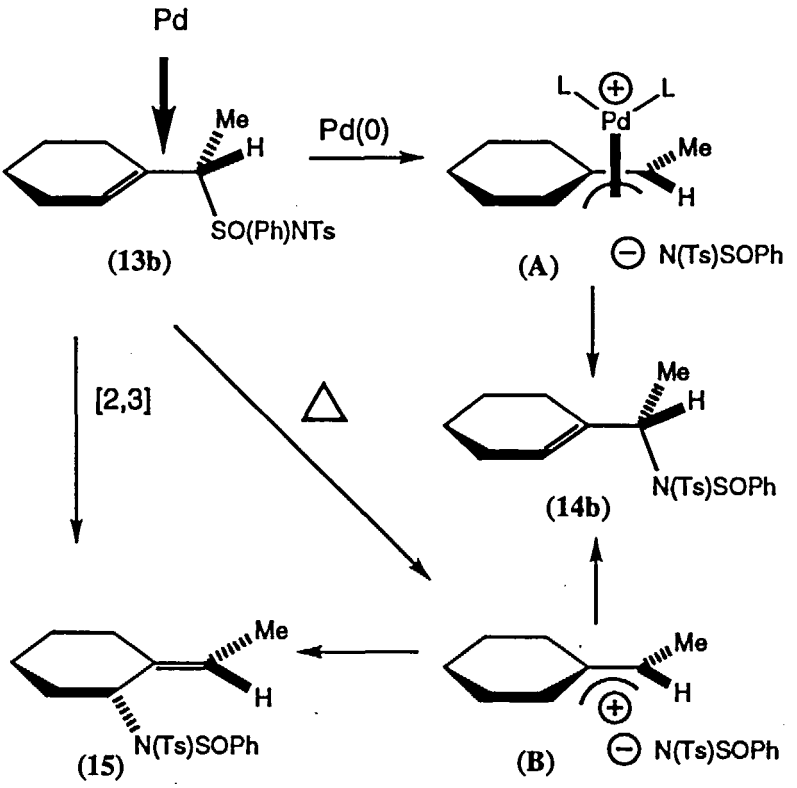
Treatment of the crude methylation products (**13a-c**) with 5% mol $Pd(PPh_3)_4$ n THF, followed by base hydrolysis, gave the related *N*-protected allylic amines (**14a-c**) Table 3).[8] These reactions were completely regioselective and gave none of the 1,3-allylic earrangement products (e.g. (**15**)). The stereochemical sense of all these reactions were dentical and like (**14b**), that was obtained from the thermal rearrangement of (**13b**), these :ompounds had the (*S*) absolute stereochemistry. While the enantiomeric purities of (**14a**) ınd (**14b**) were high (both had an ee of 88% (92% corrected)) that of (**14c**) was only noderate (ee 34 % from analysis by chiral HPLC).

Table 3. Palladium Catalysed Rearrangements of the α-Methyl Allylic Sulfoximines (**13a-c**) to give (**14a-c**) after base hydrolysis.

entry	substrate	time (min)	product (yield (%))
1	 (**13a**)	10	 (**14a**) (36) (ee = 88%)
2	 (**13b**; R = Ts)	10	 (**14b**; R = Ts (59)) (ee = 88%)
3	(**13c**; R = CO_2Me)	30	(**14c**; R = CO_2Me (40)) (ee = 34%)

The α-methylated allylic sulfoximines (**13a-c**) were too unstable to prepare crystals for X-ray crystallographic analysis. However, based on our previous work,[1] we would predict that these compounds had the (*S*) stereochemistry at the α–carbon (Scheme 6). If this stereochemical assignment is correct then the thermal and palladium(0) induced rearrangement reactions on (**13b**) can be rationalised as depicted in Scheme 8.

Scheme 8.



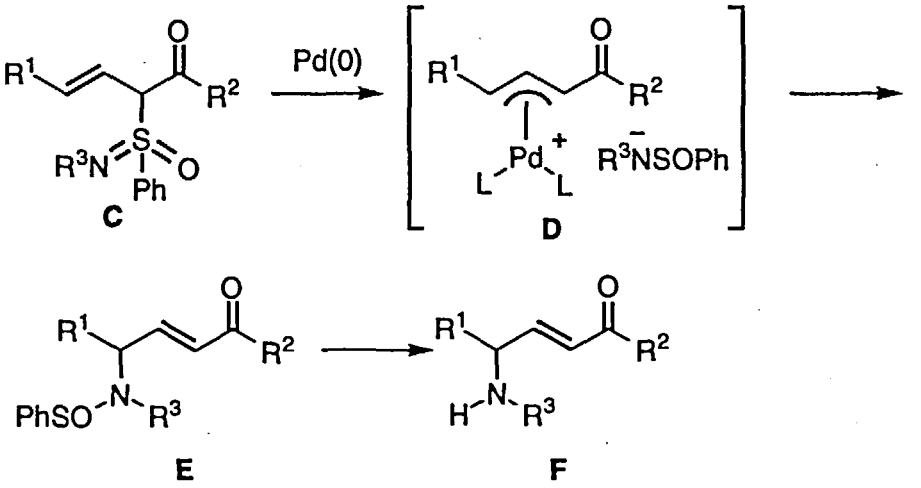
The reactive conformation of **(13b)** would be expected to be that shown in Scheme 8 from stereoelectronic considerations[9,10] and in order to minimise allylic $A^{1,3}$ strain.[10] Attack of palladium(0) on the conformation **(13b)** would be expected to occur *anti* to the sulfoximine leaving group for stereoelectronic reasons to give the Pd-allylic cation complex **(A)** with the planar chirality shown. Addition of the sulfinamide anion to the allylic cation moiety would be expected to occur *anti* to palladium[9] to give sulfinamide **(14b)** with the (*S*)-stereochemistry at the carbon of the newly created C-N bond. The thermal rearrangement of **(13b)** may proceed via the intimate ion pair **(B)**, followed by collapse of this intermediate to give **(14b)** or **(15)**. Alternatively, some or all of **(15)** may arise from a [2,3]-sigmatropic rearrangement. In the later scenario, collapse of the ion pair intermediate **(B)** would necessarily be regioselective and give only **(14b)**. From this study, however, it is not possible to distinguish between the different possible reaction pathways.

(iv) Synthesis Of γ-Amino α,β-Unsaturated Ketones and Esters

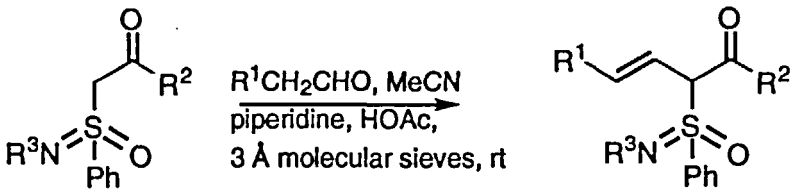
γ-Amino α,β-unsaturated ketones and esters are useful substrates for natural product and bioactive molecule synthesis.[11] The latter amino compounds have often been found as

important structural elements of peptide-like protease inhibitors.[11] γ-Amino α,β-unsaturated esters are readily prepared from the Wittig-Horner reaction of *N*-protected α-amino aldehydes that are available in a few synthetic steps from naturally occurring α-amino acids.[11] This methodology however, is clearly only convenient for the preparation of γ-amino α,β-unsaturated esters from naturally occurring α-amino acids.[11] As part of a synthetic project we required a general method for the preparation of γ-amino α,β-unsaturated ketones and esters that could not be prepared from "the pool" of naturally occurring α-amino acids. Based on our previous success on the synthesis of chiral allylic amines from the palladium(0) catalysed rearrangement of allylic sulfoximines to allylic sulfinamides we reasoned that the analogous palladium(0) catalysed rearrangement of α–sulfonimidoyl β,γ-unsaturated ketones **C** (R^2 = alkyl, aryl) and esters **C** (R^2 = OR) to the allylic sulfinamides **D** would give a route to the desired γ-amino α,β-unsaturated ketones and esters **E** (Scheme 9).

Scheme 9.



The α–sulfonimidoyl β,γ-unsaturated ketones **17a,b** and ester **17c** were prepared by a Knoevenagel type condensation of the α-sulfonimidoyl ketones **16a** or **16b** or the α-sulfonimidoyl ester **16c** with aldehydes as shown in equation 2. These condensation reactions proceeded in modest to good yields (46-87 %) and gave the desired (*E*) α–sulfonimidoyl β,γ-unsaturated ketones **17a** and **17b** and the (*E*) α–sulfonimidoyl β,γ-unsaturated ester **3c** as mixtures of two diastereomeric compounds (Table 4).[11]



(eq 2)

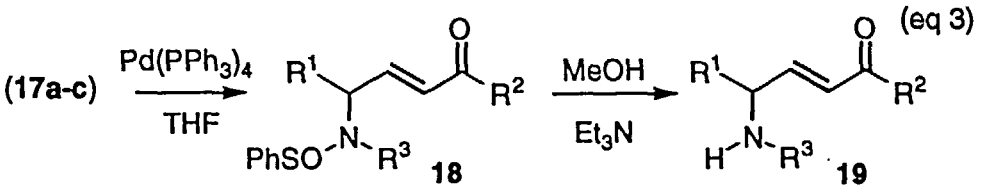
16a; R^2 = Ph, R^3 = Ts
16b; R^2 = Ph, R^3 = CO_2Me
16c; R^2 = OMe, R^3 = Ts

17a; R^2 = Ph, R^3 = Ts
17b; R^2 = Ph, R^3 = CO_2Me
17c; R^2 = OMe, R^3 = Ts

Table 4. Synthesis of **17a-c**

aldehyde (R^1)	product	reaction time (h)[a]	yield(%)[b]	d. r.[c]
n-Bu	**17a**; R^1 = n-Bu	4.5	47	74 : 26
n-Bu	**17b**; R^1 = n-Bu	24	46	76 : 24
n-pent	**17a**; R^1 = n-pent	6	53	76 : 24
n-pent	**17b**; R^1 = n-pent	24	65	69 : 31
n-hexyl	**17a**; R^1 = n-hexyl	5	53	88 : 12
Et	**17c**; R^1 = Et	5	87	58 : 42

Treatment of the individual (*E*) α–sulfonimidoyl β,γ-unsaturated ketones **17a** or **17b** or the ester **17c** with 10 mol % of freshly prepared tetrakis(triphenylphosphine)palladium(0) ($(PPh_3)_4Pd$) in dry THF solution at room temperature gave a red or orange coloured solution. TLC analysis of the reaction mixtures after 1h indicated complete consumption of the starting allylic sulfoximines. ^1H NMR analysis of the crude reaction mixtures showed the formation of the often unstable allylic sulfinamides **18a-c.** In the case of the *N*-Ts allylic sulfinamides **18a** and **18c** (R^3 = Ts) these appeared as single diastereomeric products while in the case of **18b** (R^3 = CO_2Me) mixtures (75-85 : 25-15) of diastereomeric products were evident. Mild methanolysis of the reaction mixtures with triethylamine / methanol at rt gave pure (*E*)-sulfonamides **19a,c** and the (*E*)-carbamate **19b** after purification of the crude reaction mixtures by column chromatography (silica gel) in overall yields of 32-68 % as shown in Table 5.[16] We have briefly examined the thermal rearrangement of **17a** and **17b** in acetonitrile at 70-75°C. While the former substrates do undergo rearrangement to **18a** the latter compounds give a complex mixture of products.



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

Table 5. Synthesis of **19a-c** from **17a-c.**

starting compound	product	yield(%)[a]	mp (^{0}C)
17a; R^1 = n-Bu	**19a**; R^1 = n-Bu	32	103-104
17b; R^1 = n-Bu	**19b**; R^1 = n-Bu	64	oil
17a; R^1 = n-pent	**19a**; R^1 = n-pent	60	99
17b; R^1 = n-pent	**19b**; R^1 = n-pent	49	oil
17a; R^1 = n-hexyl	**19a**; R^1 = n-hexyl	68	ND
17c; R^1 = Et	**19c**; R^1 = Et	57	oil

In conclusion, the palladium(0) catalysed rearrangement of certain primary and secondary allylic sulfoximines to give *N*-protected allylic amines has been shown to be highly regioselective and in the case of the later compounds highly enantioselective. Further extensions and applications of this methodology for asymmetric synthesis are under active investigation.

Acknowledgment: We thank the Australian Research Council for financial support.

References

1. Pyne, S.G.; Dong, Z.; Skelton, B.W.; White, A.H. *Chem. Commun.* **1994**, 751.
2. Pyne, S.G.; Dong, Z.; Skelton, B.W.; White, A.H. *Chem. Commun.* **1995**, 445.
3. Pyne, S.G.; Dong, Z., unpublished results.
4. Pyne, S.G.; Dong, Z. *Tetrahedron Lett.* **1995**, *36*, 3029.
5. Gais, H.-J.; Scommoda, M.; Lenz, D. *Tetrahedron Lett.* **1994**, *35*, 7361.
6. Harmata, M.; Claassen II, R.J. *ibid.* **1991**,*32*, 6497; Pyne, S.G.; Boche, G. *Tetrahedron* **1993**, *49*, 8449.
7. Harmata, M.; Glaser, R.; Chen, G.S. *Tetrahedron Lett.* **1995**, *36*, 9145.
8. Pyne, S.G.; Dong, Z. *J. Org. Chem.* **1996**, *61*, in press.
9. Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedon: Asymmetry* **1992**, *3*, 1089.
10. Hoffman, *R.W. Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 563.
11. David, D. M.; O'Meara. G. W.; Pyne, S. G.*Tetrahedron Lett.* **1996**, *37*, in press and references cited therein.