Development and Synthetic Applications of

the

Asymmetric Anionic Amino-Cope Rearrangement

by

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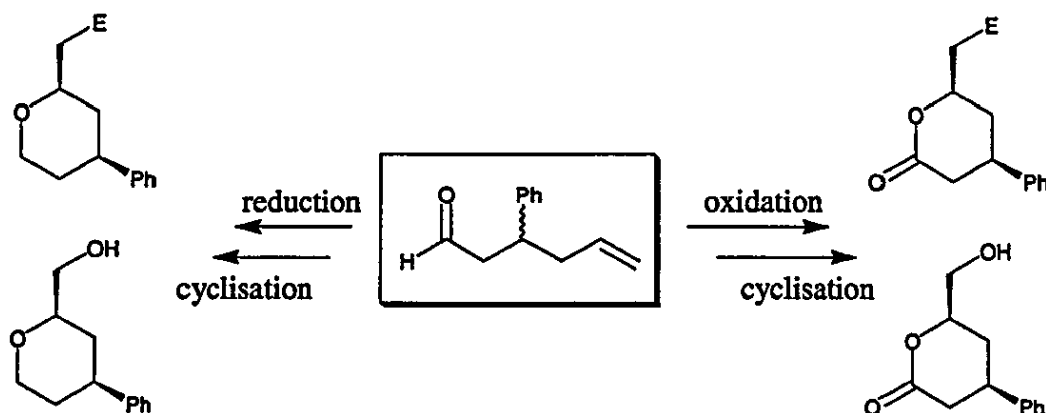
Thank you all so much!

Abstract

The thermal and anionic amino-Cope rearrangement of suitably functionalised 3-amino-1,5-hexadienes could potentially constitute a powerful tool for the stereoselective synthesis of highly functionalised acyclic or cyclic systems.
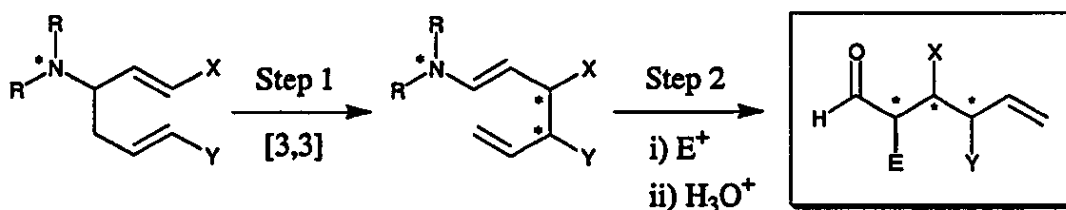
Incorporation of β-aminoalcohol auxiliaries into the diene enabled high diastereoselectivity to be obtained during the 1,2-addition of the allyl Grignard reagent to α,β-unsaturated imines. Asymmetric anionic amino-Cope rearrangement of the diastereoisomerically pure 3-amino-1,5-diene substrates furnished the target aldehyde in good yield and with high levels of asymmetric induction (up to 94% *e.e.*).

The aldehyde obtained was used as a non-racemic starting material to synthesise small heterocycles, with high levels of diastereoselectivity in some cases, providing a high yielding route to some important chiral building blocks. The successful formation of both tetrahydropyrans and lactones without any apparent loss of chirality was achieved and provided a background for investigation into the synthesis of piperidines, which could lead to a plausible route to biologically significant aza-sugars.

Contents

Development and Synthetic Applications of the Asymmetric

Anionic Amino-Cope Rearrangement

Contents   vii

A. (2*S*)-3-Phenyl-2-(((*S*)-1-styryl-but-3-enylamino)-propan-1-ol (**100f**)

   [^{1}H NMR, ^{13}C NMR and Single crystal X-ray with accompanying data]

B. (*S*)-3-Phenylhex-5-enal (**52**)

   [^{1}H NMR]

C. (2*S*, 4*S*, 5*R*)-3,4-Dimethyl-2-[(2*R*)-2-phenylpent-4-enyl]-1,3-oxazolidine

   [^{1}H NMR of aldehyde derivative demonstrating an *e.e.* of 84%]

D. (2*R*, 4*R*)-2-Iodomethyl-4-phenyltetrahydropyran-2-one (**164a**)

   [^{1}H NMR showing detailed coupling constants, ^{13}C NMR and HETCOR]

E. (2*S*, 4*R*)-2-Iodomethyl-4-phenyltetrahydropyran-2-one (**164b**)

   [^{1}H NMR with expansions showing coupling, ^{13}C NMR and COSY]

Abbreviations

*	=	denotes chiral centre
18-c-6	=	18-crown-6
Ac	=	acetyl
Ar	=	aryl
AIBN	=	azo-bis-*iso*-butyronitrile
br	=	broad
Bn	=	benzyl
Boc	=	*tert*-butoxycarbonyl
i-Bu	=	*iso*-butyl
n-Bu	=	*n*-butyl
cat.	=	catalytic
Cbz	=	benzyloxycarbonyl
COSY	=	Correlated Spectroscopy
CSA	=	camphorsulfonic acid
cyc- (cy- or c-)	=	cyclo-
d	=	doublet
(dba)	=	dibenzylideneacetone
DBU	=	1,8-diazobicyclo[5.4.0]undecane
o-DCB	=	*ortho*-dicyanobenzene
DCM	=	dichloromethane
DIBAL-H	=	di-*iso*-butylaluminium hydride
DMDO	=	dimethyldioxirane
DME	=	dimethoxyethane
DMF	=	dimethylformamide
DMPU	=	*N,N'*-dimethylpropyleneurea
DMSO	=	dimethylsulfoxide
d.e.	=	diastereomeric excess
e.e.	=	enantiomeric excess
E.I.	=	electron impact
Et	=	ethyl
F.A.B.	=	fast atom bombardment

(fod)	=	1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedianato
HETCOR	=	Heteronuclear Correlated Spectroscopy
(hfc)	=	heptafluoropropylhydroxymethylene
HMPA	=	hexamethylphosphoramide
HPLC	=	high performance liquid chromatography
hr	=	hour
ICl	=	iodine monochloride
I.R.	=	infra red
J	=	coupling constant
K_{eq}	=	equilibrium constant
KHMDS	=	potassium hexamethyldisilazide
LA	=	Lewis acid
LDA	=	lithium di-*iso*-propylamide
LDEA	=	lithium diethylamide
LHMDS	=	lithium hexamethyldisilazide
m	=	multiplet
*m*CPBA	=	3-chloroperbenzoic acid
Me	=	methyl
mp	=	melting point
MS	=	mass spectrum
NBS	=	*N*-bromosuccinimide
NHMDS	=	sodium hexamethyldisilazide
NIS	=	*N*-iodosuccinimide
NMR	=	nuclear magnetic resonance
NPSP	=	*N*-phenylselenylphthalimide
Ph	=	phenyl
Phth	=	phthalyl
PMB	=	*para*-methoxybenzyl
PPTS	=	pyridinium *para*-toluenesulfonic acid
i-Pr	=	*iso*-propyl
q	=	quartet (^{1}H NMR) or quaternary (^{13}C NMR)
Red-Al	=	sodium bis(2-methoxyethoxy)aluminium hydride
RMP	=	(*R*)-2-methoxymethylpyrrolidine

r.t.	=	room temperature
s	=	singlet
SMP	=	(*S*)-2-methoxymethylpyrrolidine
t	=	triplet
TBAF	=	tetrabutylammonium fluoride
TBCO	=	2,4,4,6-tetrabromo-2,5-cyclohexadienone
TBDMS	=	*tert*-butyldimethylsilyl
TBDPS	=	*tert*-butyldiphenylsilyl
TBS	=	tributylsilyl
Tf	=	trifluoromethanesulfonyl
TFA	=	trifluoroacetic acid
(tfc)	=	trifluoroacetylcamphorate
THF	=	tetrahydrofuran
TIPS	=	tri-*iso*-propylsilyl
tlc	=	thin layer chromatography
TMS	=	trimethylsilyl
Ts	=	tosyl
*p*TsOH	=	*para*-toluenesulfonic acid
Z	=	see Cbz

Chapter 1

Introduction
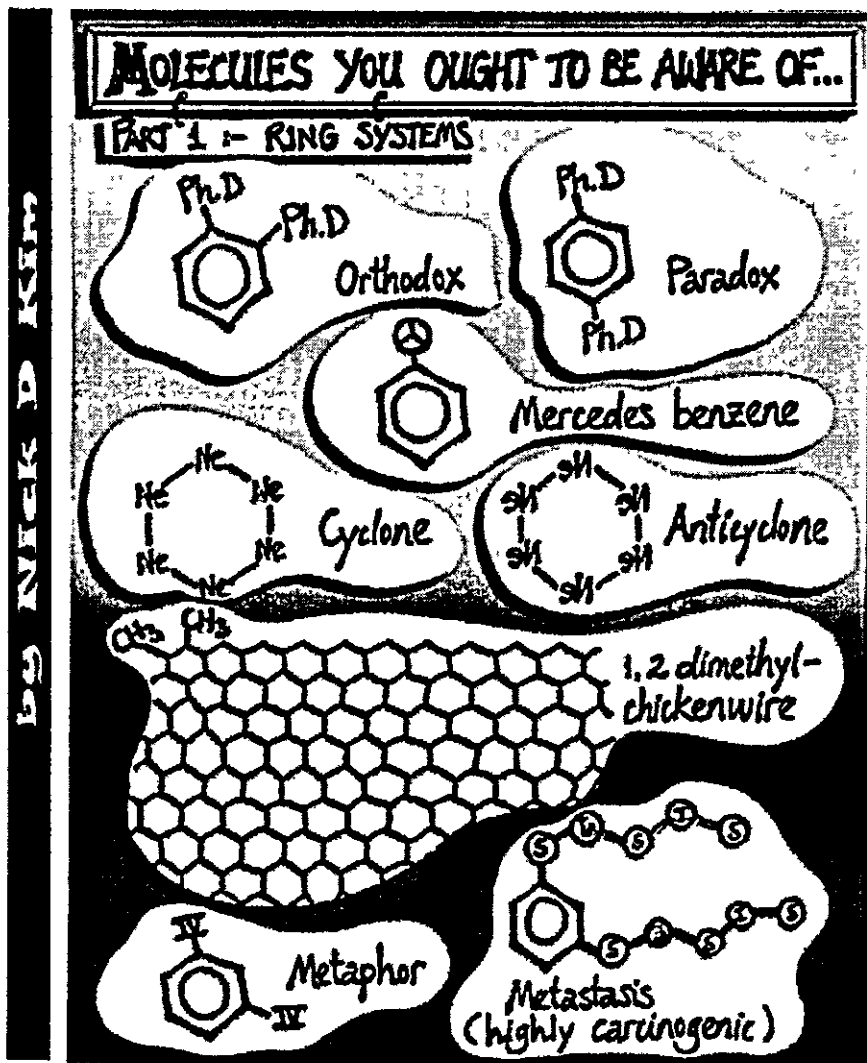
1. Introduction

1.1. [3,3] Sigmatropic Rearrangements

In the mid 1960's Woodward and Hoffman[1] derived a simple classification system for the branch of pericyclic reactions now known as sigmatropic rearrangements. A pericyclic reaction is one that commonly involves the concerted reorganisation of π-electrons through a cyclic transition state to give a product containing one or more new σ-bonds.[2] The term 'sigmatropic' is used when the reorganisation involves the movement of a σ-bond across one or two conducting π-electron systems whose double bonds are reorganised in the process.

The Woodward-Hoffman classification employs two numbers set in brackets [i, j] indicating atoms along the conducting chains to which each end of the migrating σ-bond becomes attached. Migration across one chain therefore is classified as [1, j] whilst if two chains are involved the classification uses two numbers other than 1. **Scheme 1** shows an example of a [3,3] sigmatropic rearrangement which results in a six π-electron reorganisation, leading to the formation of a product containing a new σ-bond.
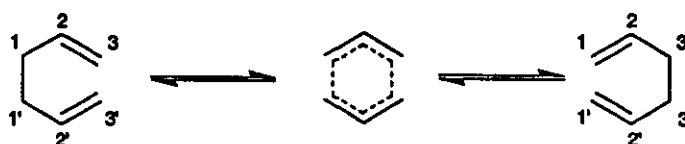
Scheme 1. [3,3] Sigmatropic Rearrangement

This is known as the Cope Rearrangement[3] and today is recognised as the prototype all-carbon [3,3] sigmatropic rearrangement.

1.2. Cope Rearrangement

As indicated in **Scheme 1** the Cope rearrangement is reversible and the starting and product dienes exist at equilibrium at rearrangement temperature through a cyclic transition state. The position of equilibrium can depend on a number of factors outlined below. Alkyl

substitution, in the absence of any conjugating substituents, generally causes the reaction to favour the side containing more-substituted double bonds. For example a substituent at C-1 or C-1' would tend to force the equilibrium more to the right hand side.

Conjugation of one or both of the double bonds with π-substituents such as ketone, ester, cyano or phenyl causes the conjugated isomer to predominate at equilibrium.[4] Incorporation of one of the double bonds into an aromatic system is also highly favoured and drives the reaction to completion in most cases.[5] The removal of ring strain in three- and four-membered ring dienes can also force the equilibrium in favour of the formation of less strained products.[6]

The synthetic value of the Cope rearrangement and its remarkable degree of specificity are due to a number of characteristics:

- Thermal activation is possible thus accommodating acid/base sensitive groups.
- The location of the new single and double bonds is unambiguously and predictably fixed.
- The reaction is extremely stereospecific due to the highly ordered cyclic transition state.
- Development of new analogues has enabled the use of lower temperatures and allowed easier access to the diene substrates.

1.2.1. Stereocontrol in the Cope Rearrangement

The Cope rearrangement and its different analogues all exhibit high levels of stereocontrol and this is a consequence of the cyclic transition states involved. Considering only suprafacial-suprafacial geometries,[7] two limiting conformations are possible for the six-membered transition state, a 'chair' conformation resembling chair cyclohexane and a 'boat' conformation similar to boat cyclohexane (Fig 1).

Chair   Boat
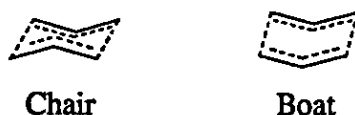
Figure 1. Transition States for the Cope Rearrangement

Doering and Roth[8] were first to show a preference for the chair conformation in the Cope rearrangements of acyclic 1,5-dienes (**Scheme 2**). *meso*-3,4-Dimethyl-1,5-hexadiene (1) rearranged to the (*E, Z*)-isomer of 2,5-octadiene with only 0.3% of the (*E, E*)-isomer whilst the racemic starting material (2) afforded 90% of the (*E, E*)-octadiene and 10% of the (*Z, Z*)-isomer. From these results they were able to calculate a difference of at least 5.7 kcal mol^{-1} in free energies of activation favouring the chair conformation.
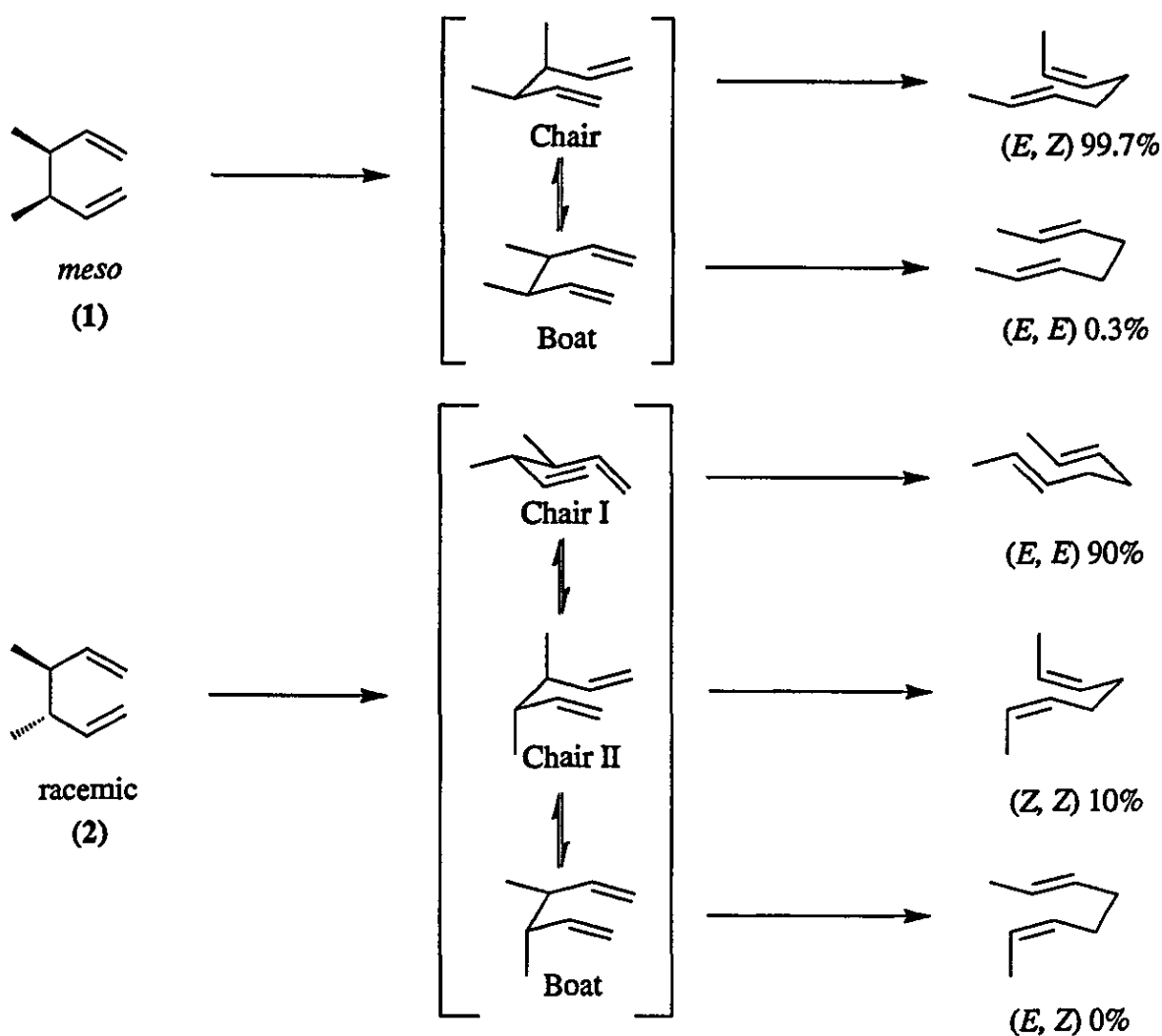
Scheme 2. Rearrangements performed by Doering and Roth[8]

Although most rearrangements proceed *via* the chair-like transition state, the boat conformation is still a viable alternative and in the example below (**Scheme 3**) the lactol ring forces the substrate (3) to rearrange in this manner.[9]

(3)
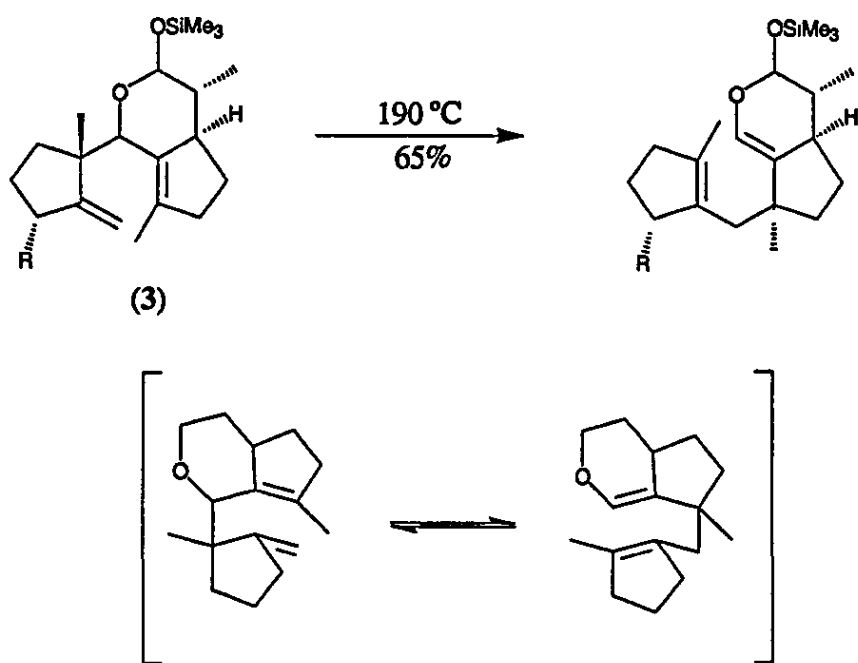
Scheme 3. Rearrangement Through a Boat-like Transition State[9]

The preference for a chair conformation during rearrangement is accompanied by a propensity for the substituents at sp^3 carbons to occupy equatorial, rather than axial, positions.[7] In **Scheme 2** the racemic diene rearrangement proceeds primarily through the *diequatorial* chair conformation leading to a product with (*E*)-double bonds and this is a common feature for most Cope rearrangements.[7]

Finally, and most importantly, the chair transition state enables the transfer of chirality from a stereogenic centre in the substrate to a new centre in the product. **Scheme 4** highlights the work done by Hill and Gilman[10] in determining that this was the case and they demonstrated that the degree of 'asymmetric transmission' was greater than 97%.
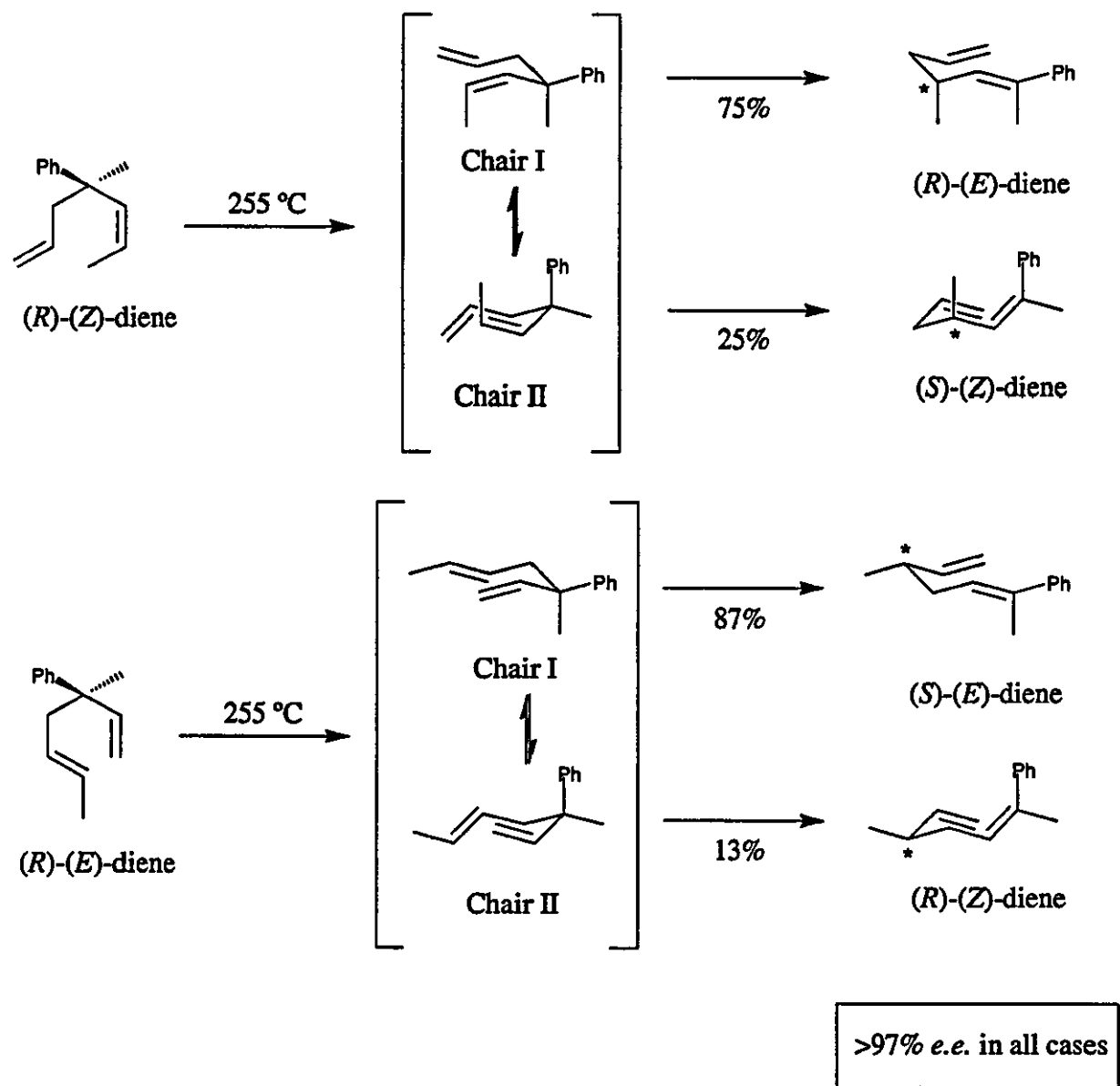
Scheme 4. Exclusive Transfer of Chirality During Cope Rearrangements[10]

1.2.2. Oxy-Cope Rearrangement

Despite the benefits of the Cope rearrangement few synthetic applications were seen following its discovery and this was probably because the methods available for the preparation of the 1,5-diene substrates could often be applied to the direct synthesis of the Cope product just as easily.

The discovery of the oxy-Cope rearrangement by Berson and Jones[11] in 1964 greatly altered the situation. Substitution of a hydroxy group at carbons C-3 or C-4 of a 1,5-diene resulted

in an enol (4) after rearrangement which tautomerizes to the δ,ϵ-unsaturated carbonyl compound (5) rendering it irreversible (**Scheme 5**).

(4)   (5)
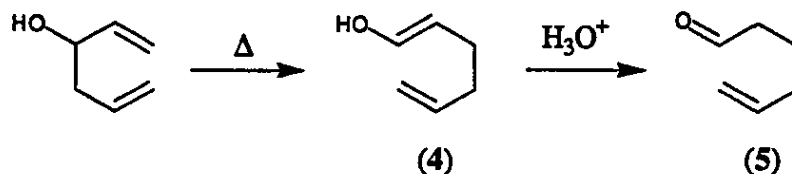
Scheme 5. Oxy-Cope Rearrangement

The carbonyl compound obtained after rearrangement is easily manipulated for further synthetic purposes. A further advantage of the oxy-Cope rearrangement is that the substrate is easily prepared using either vinyl organometallic reagents or allylic reagents to β,γ- and α,β-unsaturated carbonyl compounds respectively.

Rate enhancements of 10^{10} - 10^{17} in oxy-Cope rearrangements can be achieved by forming the sodium or potassium alkoxide of the 1,5-diene as a substrate[12] (**Scheme 6**). Theoretical calculations show that the rate acceleration is primarily due to a weakening of the 1, 1'-carbon-carbon single bond[13] by the alkoxide. Another explanation is that stabilisation of the negative charge in the enolate is also a contributing factor.[7]
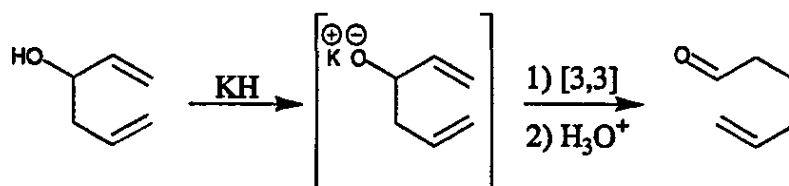
Scheme 6. Anionic Oxy-Cope Rearrangement

1.2.3. Amino-Cope Rearrangement

The amino-Cope rearrangement is analogous to the oxy-Cope rearrangement with an isoelectronic '*NH*' in place of the '*O*' of its oxygen bearing counterpart (**Scheme 7**). Rearrangement of 3-amino-1,5-dienes (6) thus leads to enamines (7) which tautomerise to imines or iminium ions (8), depending on the substitution of the starting amine, making the

product thermodynamically more favourable. Hydrolysis of the intermediate product then gives the familiar carbonyl compound (5) seen with the oxy-Cope rearrangement which can be used for further synthetic chemistry.
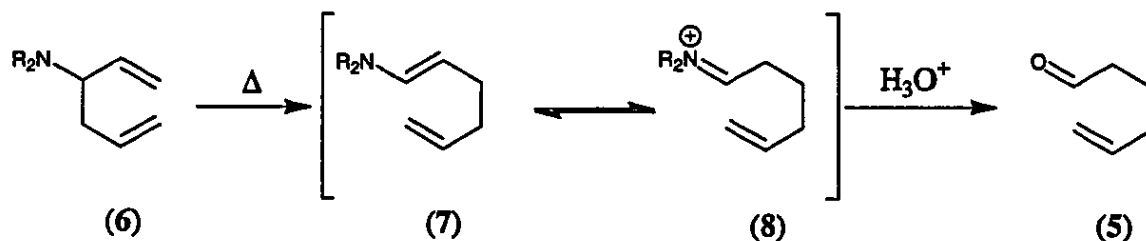
Scheme 7. Amino-Cope Rearrangement

Comparatively little information is available on the amino-Cope rearrangement since most of the work to date has concentrated on the effect of substituents on the reaction rate.[14] In 1979, Wender used the amino-Cope rearrangement in tandem with a Diels-Alder reaction to produce *cis*-hydroisoquinoline (9)[15] (Scheme 8).
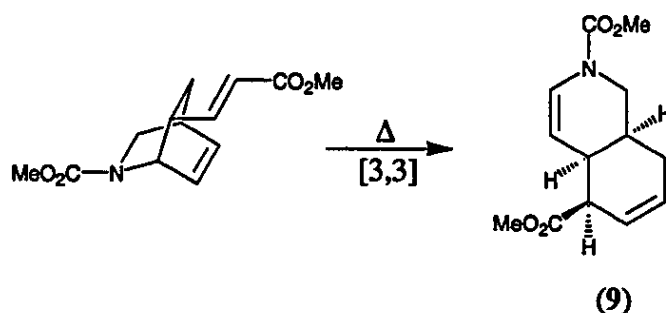
Scheme 8. Early Synthetic Use of the Amino-Cope Rearrangement

Interestingly ester (10), the isomer of the precursor to ester (9), does not undergo rearrangement because it cannot attain the required transition state and is recovered unchanged in high yield (Scheme 9)
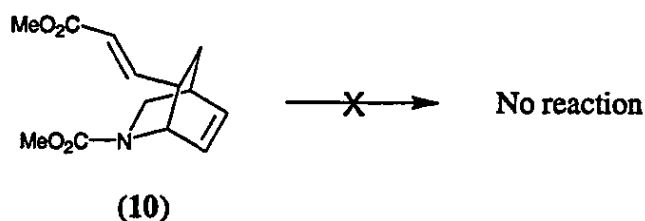
Scheme 9. Unsuccessful Rearrangement

Introduction

8

Macdonald and co-workers were first to report a charge accelerated amino-Cope rearrangement[16] displaying similar properties to the previously mentioned anionic oxy-Cope variant. Amines (**11** and **12**) were prepared from the corresponding alcohol *via* tosylation, and rearrangement was effected by deprotonation with *n*BuLi at –40 °C to give the aldehyde (**13**) after acidic workup (**Scheme 10**).

(**11**), R= *i*-Pr   (**13**)
(**12**), R= Bn
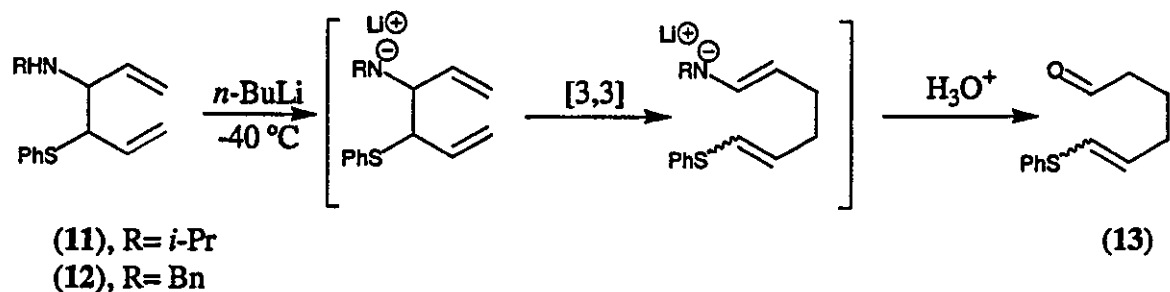
Scheme 10. Anionic Amino-Cope Rearrangement

Further examples of the various Cope rearrangements are given in **Section 1.5** but first it is important to discuss the Claisen rearrangement which has been widely studied over the past century.

1.3. Claisen Rearrangement

The Claisen rearrangement,[17] discovered in 1912, is closely related to the Cope rearrangement but contains a heteroatom within the hexadiene framework (**Fig 2**). Where X=O the reaction is a simple Claisen or 'oxa-Cope' rearrangement but other variants such as the *aza*-Claisen (3-aza-Cope, X=N) and *thia*- or *thio*-Claisen (X=S) are also known.[17-34]

X = O, N or S
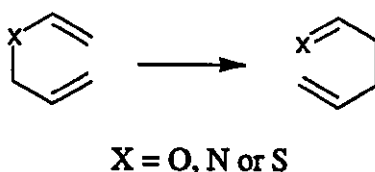
Fig 2. Claisen Rearrangements

The simple rearrangement of allyl vinyl ethers has become one of the most powerful tools for the stereoselective formation of carbon-carbon bonds[18] and can be formally considered as the intramolecular S_N2' addition of a carbonyl enol to an allylic ether, forming a new σ-bond.

The mechanism of the Claisen rearrangement is usually referred to as being concerted although there are a number of possible transition states and stabilisation of any of these by resonance interactions may influence the reaction[19] (Fig 3)

X = O, N or S
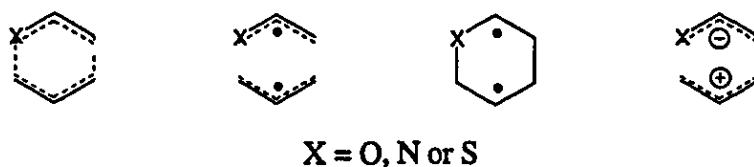
Figure 3. Possible Transition States of the Claisen Rearrangement

The template Claisen rearrangement, although useful, has been supplemented by a number of variants over the years and the main ones of interest synthetically are mentioned briefly below.

1.3.1. Variants of the Claisen Rearrangement

1.3.1.1. The Aromatic Claisen Rearrangement[20]

Allyl aryl ethers rearrange at temperatures between 150 and 225 °C to give either *ortho*-allylphenols (after enolization, **(14)** to **(15)** in **Scheme 11**), or *para*-allylphenols when the *ortho* position is substituted ((14) to (16) in **Scheme 11**).
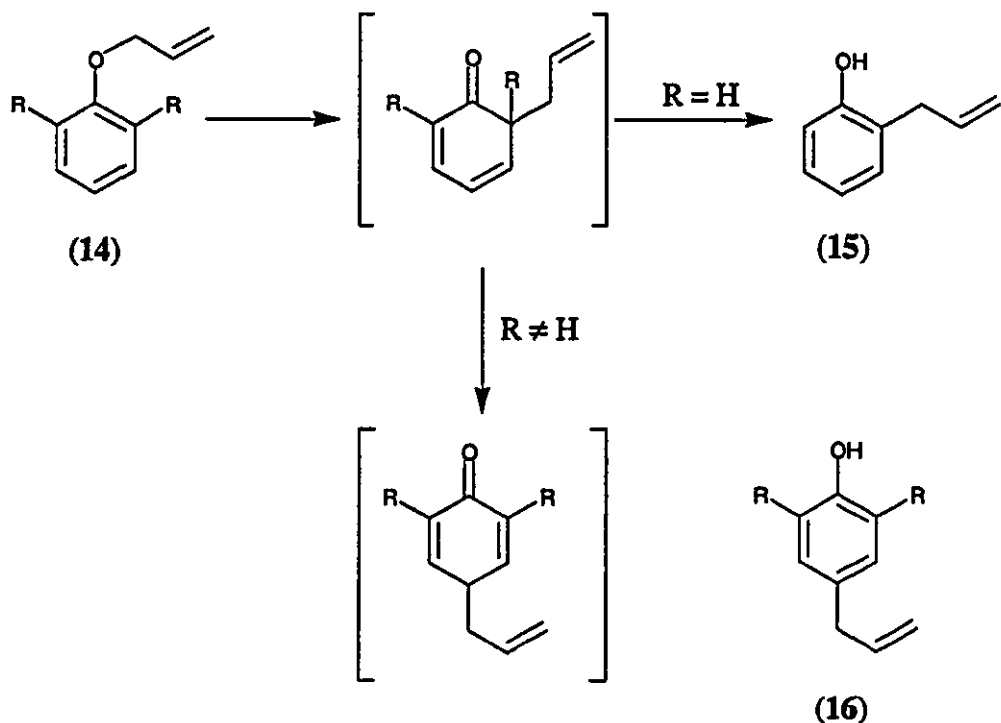
Scheme 11. Aromatic Claisen Rearrangement

1.3.1.2. The Carroll (Kimel-Cope) and Saucy-Marbet Rearrangements

Base-catalysed rearrangement of β-keto esters (**17**) and allylic alcohols to alkenic ketones (**18**) was performed by Carroll[21] as shown in **Scheme 12.**
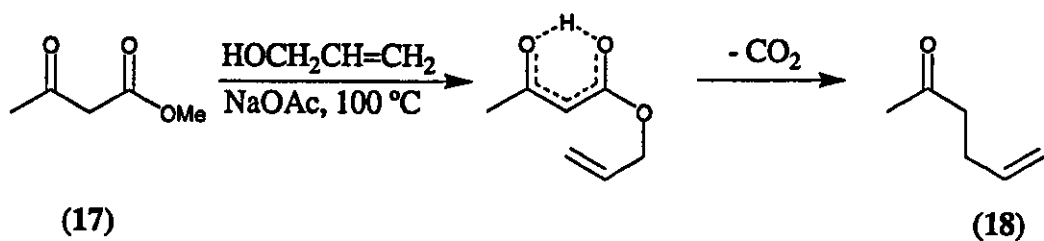
Scheme 12. Carroll Rearrangement

Saucy and Marbet[22] followed two decades later with the acid-catalysed reaction of tertiary propargylic alcohols (**19**) with isoprenyl methyl ether to give β-ketoallenes (**20**) in high yields (**Scheme 13**)

(19)   **(20)**
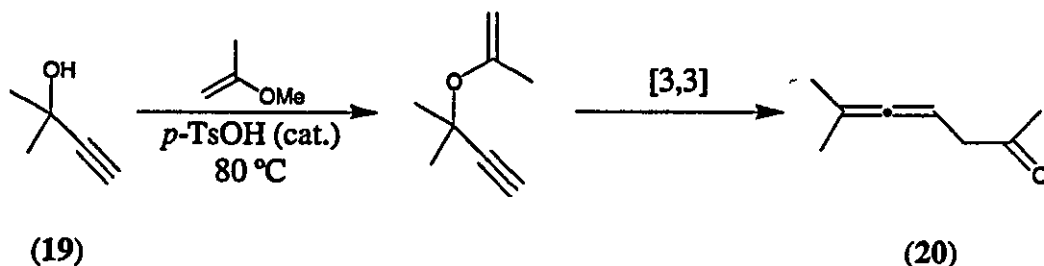
Scheme 13. Saucy-Marbet Rearrangement

1.3.1.3. The Eschenmoser and Johnson Orthoester Rearrangements

The preparation of carboxylic acids using the Claisen rearrangement was demonstrated as early as 1949[23] but Echenmoser and co-workers[24] developed a more robust method. Heating allylic alcohols (21) with amide acetals produced unsaturated ethers that underwent Claisen rearrangement *in situ* generating γ,δ-unsaturated amides (22) stereoselectively (Scheme 14).

(21)   **(22)**
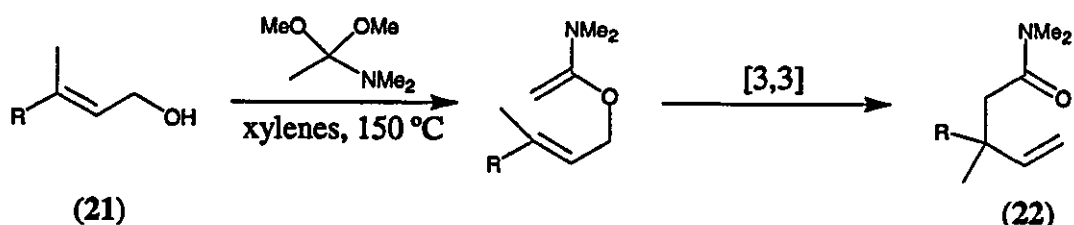
Scheme 14. Eschenmoser Rearrangement

The closely related acid-catalysed exchange of orthoacetals with allylic alcohols (21) was reported by Johnson and co-workers[25] shortly afterwards and further added to the utility of [3,3] sigmatropic rearrangements (Scheme 15).

(21)
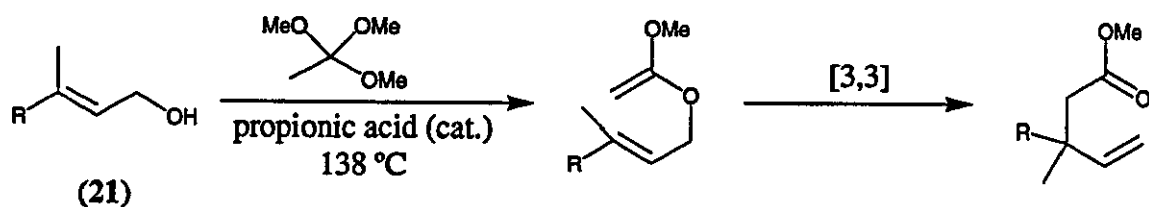
Scheme 15. Johnson Orthoester Rearrangement.

Although both of the above rearrangements are performed at elevated temperatures it is important to note that these conditions are required to promote alcohol exchange - the rearrangement can occur at significantly lower temperatures.[26]

1.3.1.4. The Ireland-Claisen Rearrangement

Perhaps the most important development of the Claisen rearrangement came when Ireland and co-workers[27] used lithium dialkylamide bases[28] followed by silylation with TMS-Cl to generate reactive silyl ketene acetals (23) at –78 °C (Scheme 16). These rearranged at ambient temperature to produce γ,δ-unsaturated silyl esters which readily hydrolysed thus providing a route to γ,δ-unsaturated carboxylic acids (24).
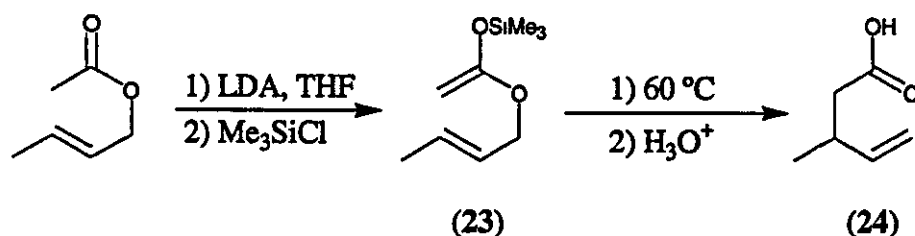
Scheme 16. Ireland Claisen Rearrangement

Simple control of enolate geometry could be achieved with careful solvent selection making the stereoselectivity of the reaction very well defined.

Some current synthetic examples of the stereoselective Claisen rearrangement can be found in **Section 1.5.**

1.4. Other [3,3]-Sigmatropic Rearrangements

Before exploring the applications of [3,3] sigmatropic rearrangements over the last few years it is necessary to touch briefly upon other rearrangements which have gained synthetic utility in the past.

1.4.1. The Aza-Cope Rearrangement
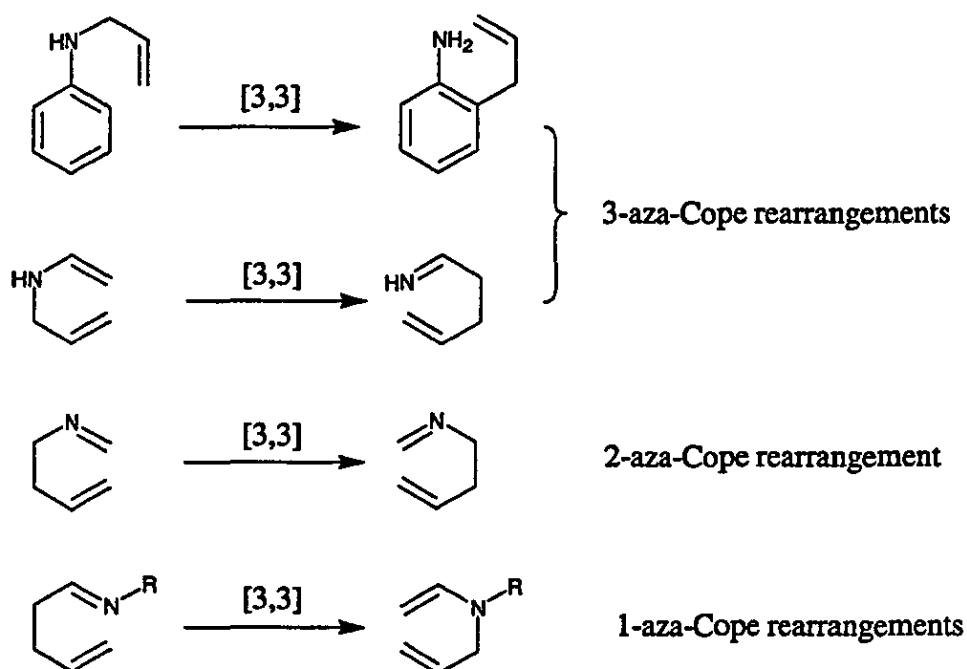
Scheme 17. Aza-Cope Rearrangements

Aza-Cope rearrangements are classified as such because the 1,5-hexadiene framework contains a nitrogen atom in the C-1, C-2 or C-3 position[29] (**Scheme 17**). As mentioned above the nitrogen counterpart of the Claisen rearrangement is also known as the 3-aza-Cope rearrangement and can occur in both N-allyl-N-aryl amine[30] and N-allyl-N-vinyl amine systems[31] (**Scheme 17**). 2-aza-Cope rearrangements are reasonably common in organic synthesis and the conditions necessary are relatively mild in most cases.[32] In contrast the 1-aza-Cope rearrangement[33] has received little use in synthetic chemistry and this is possibly due to the greater stability of the starting material when compared with that of the product, a 3-aza-Cope system (**Scheme 17**).

1.4.2. The Thia-Claisen Rearrangement

The *thio-* or *thia-* Claisen rearrangement[34] is a further extension of the hetero-Claisen family and involves a sulfur atom at C-3 of the hexadiene (**Scheme 18**). Allyl vinyl sulfides are converted to thioaldehydes, generally upon mild heating, which can be readily hydrolysed to the respective aldehydes. Further examples are noted in **Section 1.5**.
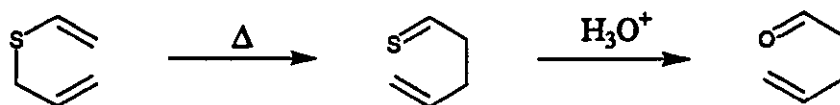
Scheme 18. Thio-Claisen Rearrangement

1.4.3. Further Examples

Other well established variations of the Cope and Claisen rearrangement which have not been discussed here include the ketene-Claisen rearrangement by Bellus and Malherbe[35] (1978) and the carbanion accelerated version by Denmark[36] (1982). Additionally the work of Bergman[37] (1935), Lauer[38] (1937), Hurd[39] (1938) and Arnold[40] (1949) is worth mentioning along with the less well known photo-[41], zwitterionic amino-[42], phospha-[43] and metallo-Claisen[44] rearrangements. Many more comprehensive reviews on the oxy-Cope[7,45], Claisen[18] and hetero-Cope[46] rearrangements are available along with articles on tandem [3,3]-sigmatropic rearrangements[18c] and general [3,3]-sigmatropic rearrangements[47].

1.5. [3,3]-Sigmatropic Rearrangements in Asymmetric Synthesis

There is continuing interest in asymmetric variants of sigmatropic rearrangements since these protocols can allow the highly stereoselective synthesis of products containing several contiguous chiral centres.

As we have seen, a common feature of the [3,3]-sigmatropic rearrangements covered in this section is that they proceed through highly ordered transition state geometries which allow the prediction, and control, of both relative and absolute stereochemistry in the desired product. This is a powerful tool for the synthetic chemist and asymmetric [3,3]-sigmatropic rearrangements have found many applications. This section serves as an update to the excellent report by Enders[47b] and co-workers that appeared in 1996 by covering selected examples of applications reported since this date, and also summarises work on the amino-Cope rearrangement done by our group.

1.5.1. Cope Rearrangements

1.5.1.1. Aza-Cope Rearrangement

Kunz[48] has used the cationic aza-Cope rearrangement in a useful synthesis of chain extended amino-sugars from *N*-galactosyl-*N*-homoallylamines (**Scheme 19**).
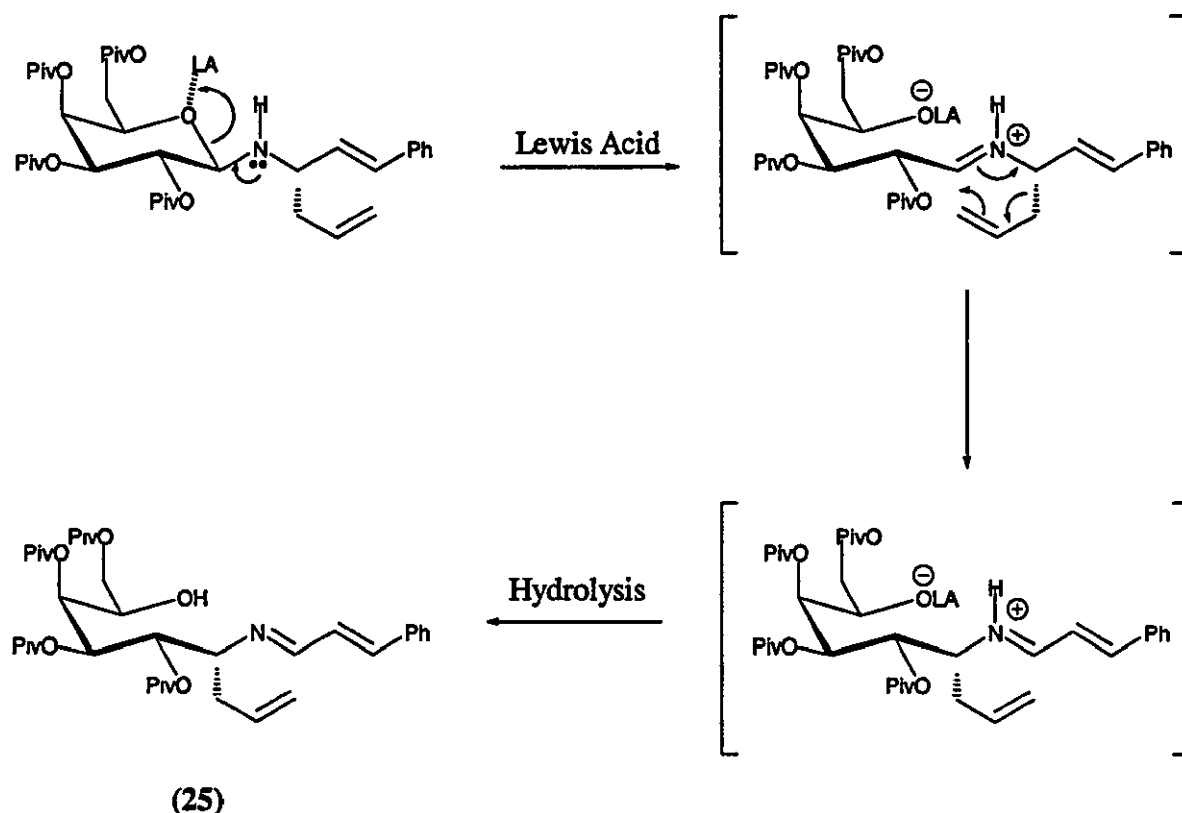
Scheme 19. Aza-Cope Rearrangement

Initially trying to obtain the isomeric 1,5-diene (*via* amino-Cope rearrangement - see **Section 1.5.1.3.**) to create a new stereogenic centre, the observed conversion yielded the chain extended imino derivative (**25**) in excellent yield and with high diastereoselectivity. The formation of (**25**) is explained by invoking a simple two step sequence, namely coordination of the Lewis acid to the ring oxygen atom inducing ring cleavage, followed by a [3,3] sigmatropic rearrangement of the intermediate iminium ion.

The aza-Cope rearrangement has been widely studied by Agami and has included the development of a practical synthesis of (-)-*allokainic acid*[49] (**Scheme 20**).

Scheme 20. Synthesis of Allokainic Acid using the Aza-Cope Rearrangement
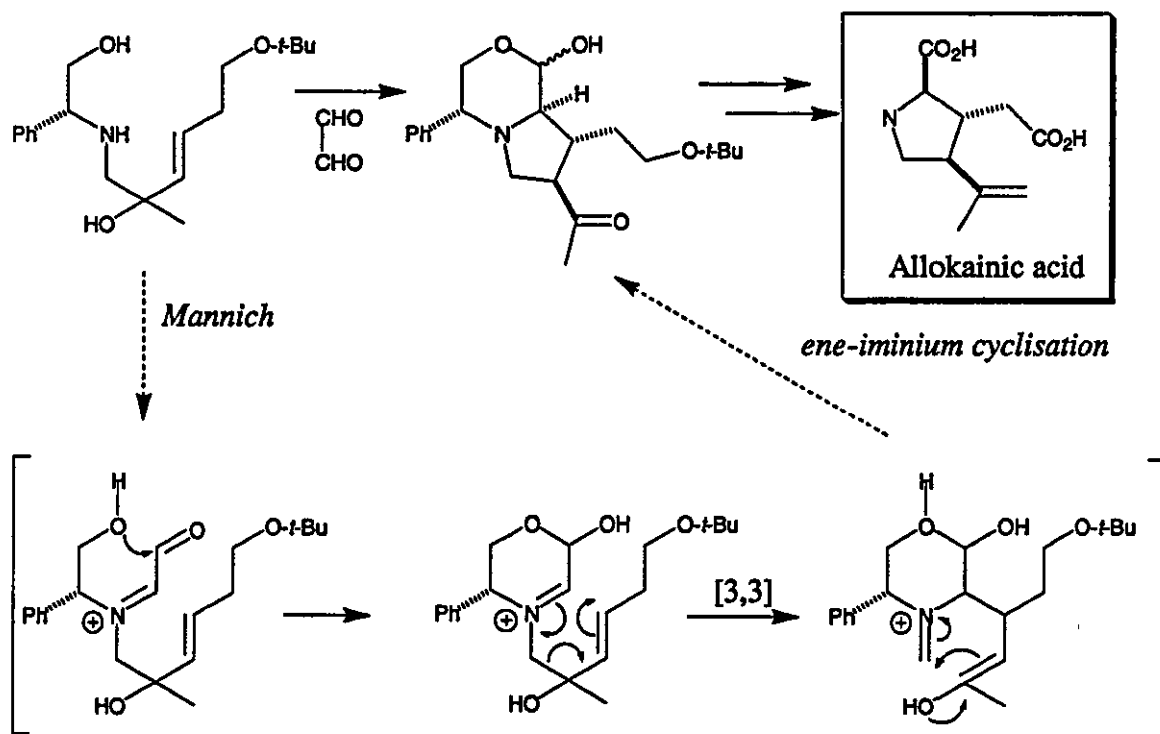
Prabhakar and Lobo[50] report using the BF_3·etherate induced rearrangement of L-tryptophan methyl ester (26) (Scheme 21). Formation of product (27) is presumed to occur *via* consecutive [3,3] and [3,5]- sigmatropic shifts.

(26)   (27)

Scheme 21. Tryptostatin B Synthesis
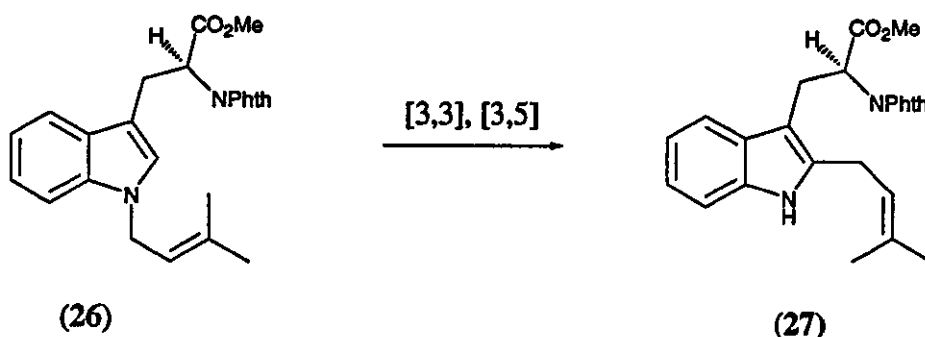
1.5.1.2. Oxy-Cope Rearrangement

The oxy-Cope rearrangement has emerged as a powerful tool in the synthesis of many complex targets. Paquette has recently reviewed this subject area in detail and readers are referred at this point to his report.[45a]

This section therefore concentrates on some recent synthetic applications of the stereoselective oxy-Cope rearrangement.

Schneider has developed a stereoselective oxy-Cope rearrangement in order to prepare the C1-C10 fragment of the macrolide antibiotic *nystatin A1.*[51] In this study the substrate (28), obtained *via* Evans asymmetric aldol chemistry underwent a thermal silyloxy-Cope rearrangement to give a 54% yield of the key intermediate (29) as a single diastereoisomer (**Scheme 22**). Transition state (30), having an axial hydroxy group and equatorial carboximide group was proposed to rationalise the stereochemical outcome.
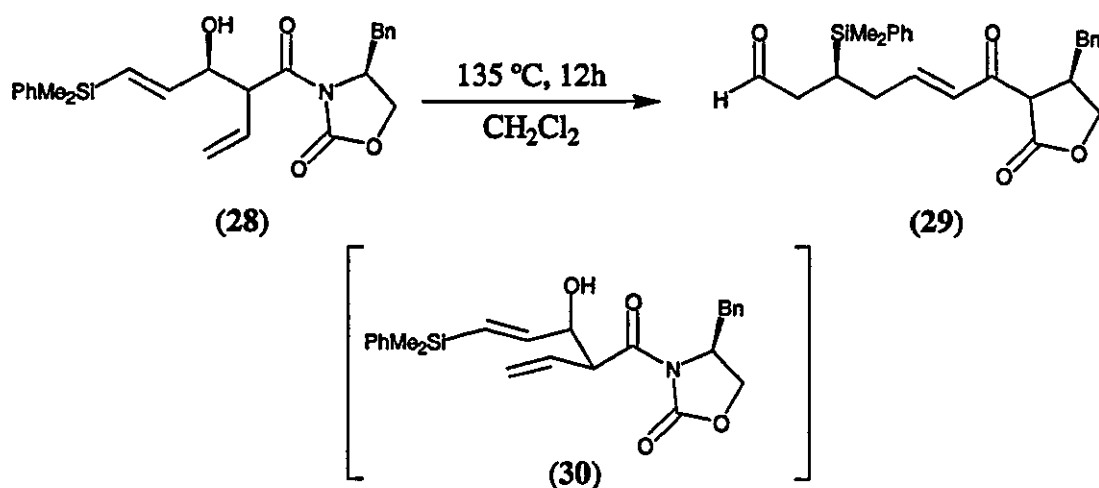
Scheme 22.

Interestingly it has been shown that, in the absence of steric effects, there is little selectivity between axial and equatorial oxy-anions in the transition states for anionic oxy-Cope rearrangement. This can lead to rather low levels of product stereoselectivity with non-racemic hydroxydiene substrates (**Scheme 23**).[52]
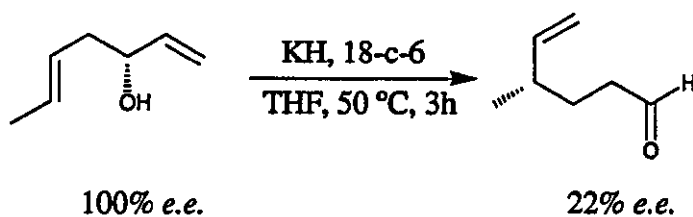
Scheme 23. Stereoselectivity of the Oxy-Cope Rearrangement

Based on the precedent[53,154] that efficient chirality transfer can be achieved when the C-3 oxyanion and a C-4 substituent are *syn* to each other since both would prefer to occupy a pseudo-equatorial orientation in the transition state, Hartley and Rutherford investigated the rearrangement of substrate (31), expecting to see exclusively the Z-enol ether (33) *via* transition state (32) leading to the cyclohexanone product (34), (Scheme 24).[54]

It was reasoned that electrostatic repulsion and steric factors would combine to disfavour the alternative transition state (35) leading to the E-enol ether and the subsequent cyclohexanone product (36).

Interestingly it was the unexpected product isomer (36) that was produced preferentially as a result of rearrangement through "disfavoured" transition state (35). The authors propose, for the first time, the involvement of a chelated transition state for anionic oxy-Cope rearrangement, with transition state (37) more properly representing the intermediate.
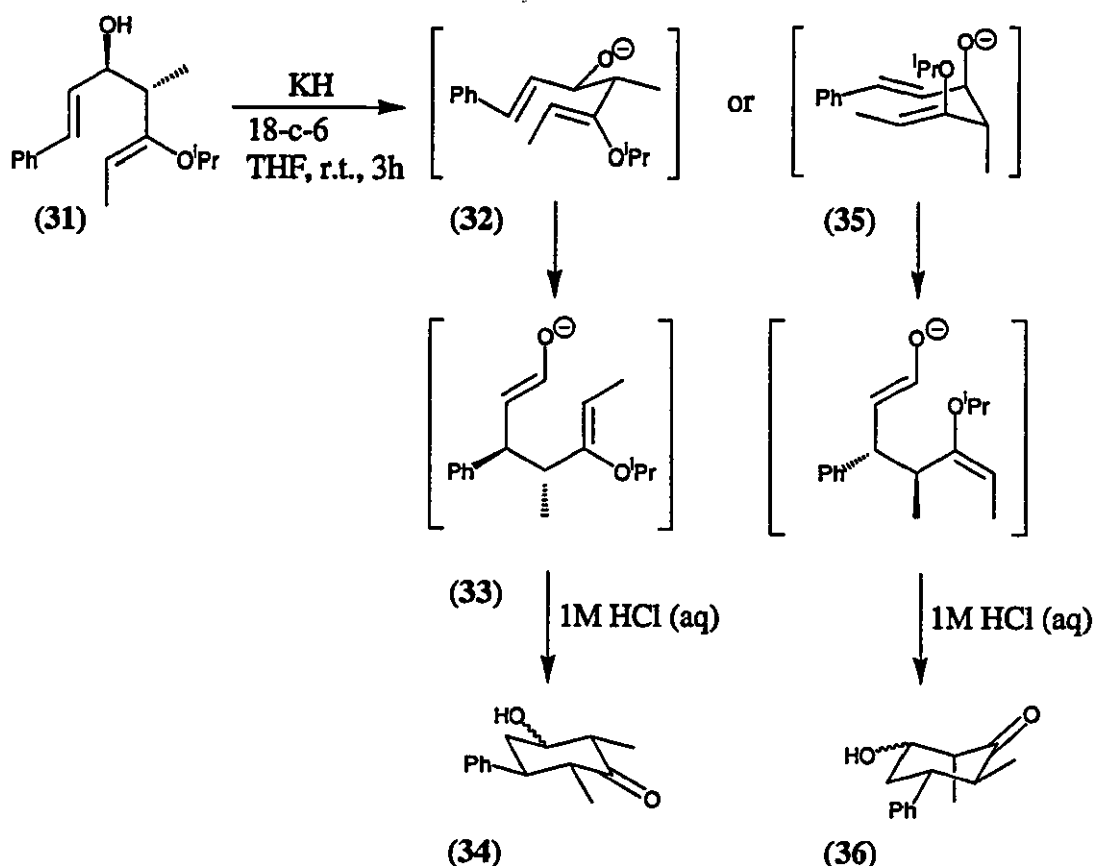
Scheme 24. Oxy-Cope Rearrangement by Hartley and Rutherford[54]
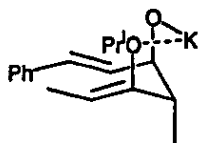
(37)

Other related recent work in the Hartley group has included the stereoselective synthesis of β-hydroxycyclohexanones[55] and the use of phosphazene bases[56] to induce anionic oxy-Cope rearrangement (metal-free conditions).

Paquette has applied the anionic oxy-Cope rearrangement of an enantiomerically pure substrate in a stereoselective synthesis of a decahydro-*as*-indacene ring system, a useful precursor in an approach to the insecticide *spinosyn A* (**Scheme 25**). The tricyclic target was obtained as a single diastereoisomer and is the product of a boat-like transition state.[57]
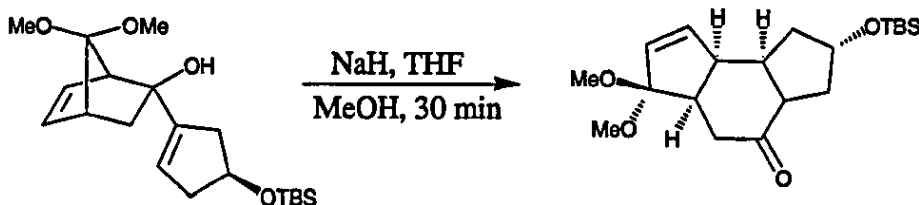
Scheme 25. Spinosyn A Precursor

An interesting approach to an enantiomerically enriched hydrazulenoid skeleton was reported by Rajagopalan. The target ring system was prepared by thermal oxy-Cope rearrangement of ethynyl alcohol substrate (**38**), a single diastereoisomer, followed by an *in situ* transannular ene-type reaction (**Scheme 26**).[58]
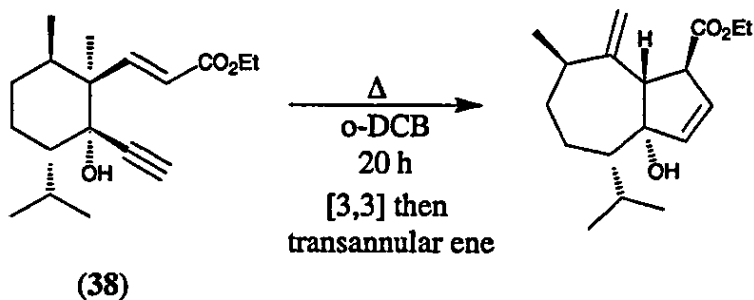
(38)

Scheme 26.

1.5.1.3. Amino-Cope Rearrangement

A short introduction to the amino-Cope and anionic amino-Cope rearrangements was given in Section 1.2.3. It is necessary here to give a more in-depth history of the amino-Cope rearrangement and its synthetic development over the past twenty years.

In 1980, Ollis published a series of papers looking at base catalysed rearrangements involving ylid intermediates.[59] Part of the detailed study involved looking at the [3,3] sigmatropic rearrangement of 3-dimethylaminohexa-1,5-dienes and in particular the effect of substituents – until now only documented in heteroatom systems for the related oxy-Cope rearrangement.

The required substrates (40 a-c) were synthesised by using the Stevens' rearrangement of quaternary ammonium salts (39 a-c) in good yield (Scheme 27).

$$a; R^1 = R^3 = Ph, R^2 = H$$
$$b; R^1 = R^2 = CH_3, R^3 = Ph$$
$$c; R^1 = R^2 = H, R^3 = Ph$$
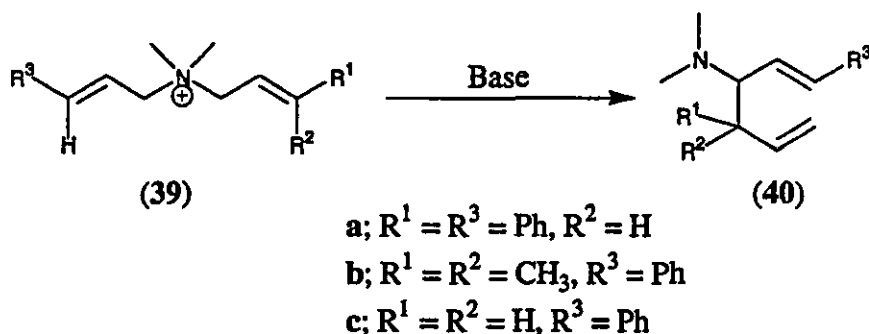
Scheme 27. Stevens' Rearrangement

Thermal amino-Cope rearrangements, monitored by NMR analysis were performed on all the substrates. Samples (25 mg) were heated in sealed ampoules under an inert nitrogen atmosphere at different temperatures and for varying durations. The rearrangement of (40a) took place at a relatively low temperature (80 °C) to give enamine (41a). This showed good first order kinetics at 100 °C and the enamine product formed had *trans*-stereochemistry (Scheme 28). They proposed that the stereochemical integrity was either as a consequence of the concerted rearrangement of diene (40a), which was present as a single diastereoisomer, or as a result of thermal equilibration between the diastereoisomeric enamines. Diene (40b) which is highly substituted rearranged at the slightly higher temperature of 100 °C to give the

trans-enamine (41b) and the less substituted diene (40c) required a much higher temperature of 170 °C for the rearrangement to proceed, again giving the *trans*-enamine (41c).
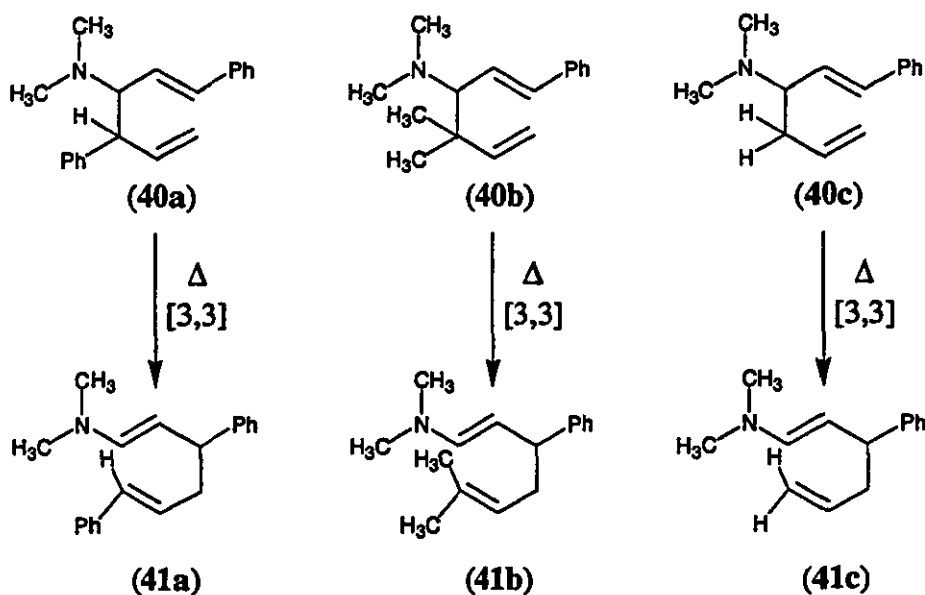
Scheme 28. Thermal Amino-Cope Rearrangements

Calculated energies for the rearrangements showed that the 4-dimethylamino-substituent had a notable effect ($\Delta G_{443}^{\#}$ 40c$\rightarrow$41c 35.1 kcal.mol^{-1}; $\Delta G_{443}^{\#}$ *hexa-1,5-diene rearrangement* 39.6 kcal.mol^{-1}). Similar rate accelerations were observed when both a phenyl substituent (40a$\rightarrow$41a) and 4,4-dimethyl substituent (40b$\rightarrow$41b) were present (**Table 1**).

Table 1 Substituent Effects on the Amino-Cope Rearrangement

Compound	Product	T / °C	k / s^{-1}	$\Delta G_{443}^{\#}$ / kcal.mol^{-1}
(40a)	(41a)	100	6.4×10^{-4}	27.4
(40b)	(41b)	100	3.0×10^{-5}	29.7
(40c)	(41c)	170	4.6×10^{-5}	35.1

The accelerating effects of 4-aryl substituents in Cope rearrangements has previously been noted by Doering *et al* (1971) and Dewar (1973, 1977).[60] The effects are thought to result from the electron donating properties of C-4 substituents although steric effects cannot be ruled out.

Ollis also examined the effects of 3-OR and 3-SR groups on the rearrangement of 3-hetero-substituted 1,5-dienes and concluded that the 3-NMe$_2$ substituent was more effective at lowering the energy of the Cope transition state than both of these. This influence was though to be a consequence of its more electron donating properties.

Kirmse investigated the effect of single heteroatom substituents on the activation parameters of [3,3]-sigmatropic rearrangements.[61] In order to study the donor substituent effect on the rate of rearrangement and gain insight into the reaction mechanism they prepared a series of heteroatom substituted 1,5-hexadienes. Amongst these was N,N-dimethyl-1,5-hexadien-3-amine (43) prepared via Stevens' rearrangement of diallyldimethylammonium bromide (42) (Scheme 29).
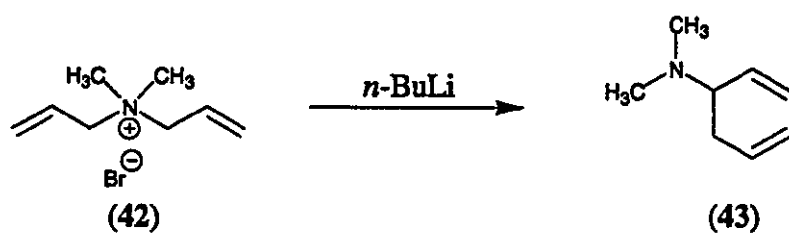
Scheme 29. Preparation of 1,5-Hexadiene Substrates

Thermolysis of substrate (43) at 224 °C for 12 hours generated the desired enamine (44) after amino-Cope rearrangement and the stereochemistry was shown to be exclusively *trans* from the NMR coupling. The rearrangement was found to be reversible and traces (5-10%) of aldehyde (45) were observed following enamine hydrolysis despite careful exclusion of water during the reaction (Scheme 30).
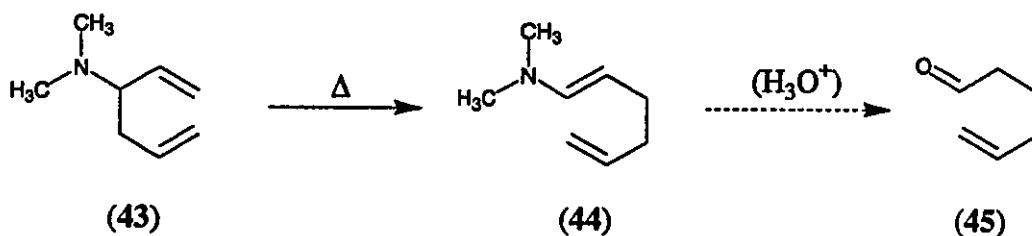
Scheme 30. Amino-Cope Rearrangement by Kirmse

The activation energy was found to be 1.4 kcal.mol^{-1} lower than that of the parent *unsubstituted* 1,5-hexadiene. The effect of substituent stabilisation on the product was

studied and it was observed that the considerable stabilisation effect of the product had only a moderate effect on the activation energy of the Cope rearrangement, the greatest effect being seen with the 3-dimethylamino substituent.

From these studies they concluded that the *alkoxy-*, *alkylthio-* and *dialkylamino-* groups in the C-3 position of 1,5-hexadiene and C-2 position of 3,3-dimethyl-1,5-hexadiene have only small effects of the rate of the Cope rearrangement (up to 60 times).

In 1995, Hagen used Hine's D values[62] to predict the position of equilibrium in the Cope rearrangement of multiply substituted 1,5-dienes.[63] They studied the Cope rearrangement of heterosubstituted 1,5-dienes including oxygen, amino, carbamoyl and thioalkyl (**46a-j**) variants (**Scheme 31**). Amine substrates (**46e**) and (**46f**) were prepared as in **Scheme 32**, *via* allylation of ethyl 2-dimethylaminoethanoate followed by [2,3]-sigmatropic rearrangement, reduction and Wittig olefination.

(46)   (47)
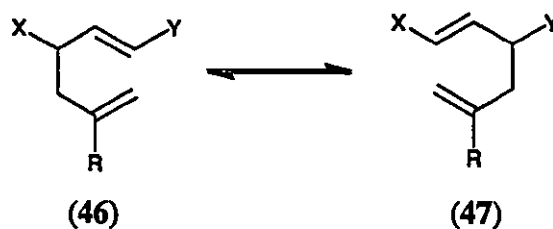
a) $X = OCH_3$, $Y = H$, $R = H$

b) $X = OCH_3$, $Y = CH_3$, $R = H$

c) $X = OCH_3$, $Y = CH_3$, $R = CH_3$

d) $X = N(CH_3)_2$, $Y = H$, $R = H$

e) $X = N(CH_3)_2$, $Y = CH_3$, $R = H$

f) $X = N(CH_3)_2$, $Y = OCH_3$, $R = H$

g) $X = N(CH_3)(CO_2Et)$, $Y = H$, $R = H$

h) $X = N(CH_3)(CO_2Et)$, $Y = CH_3$, $R = H$

i) $X = N(CH_3)(CO_2Et)$, $Y = OCH_3$, $R = H$

j) $X = SCH_3$, $Y = H$, $R = H$

Scheme 31. Cope Rearrangements

(46e) and (46f)
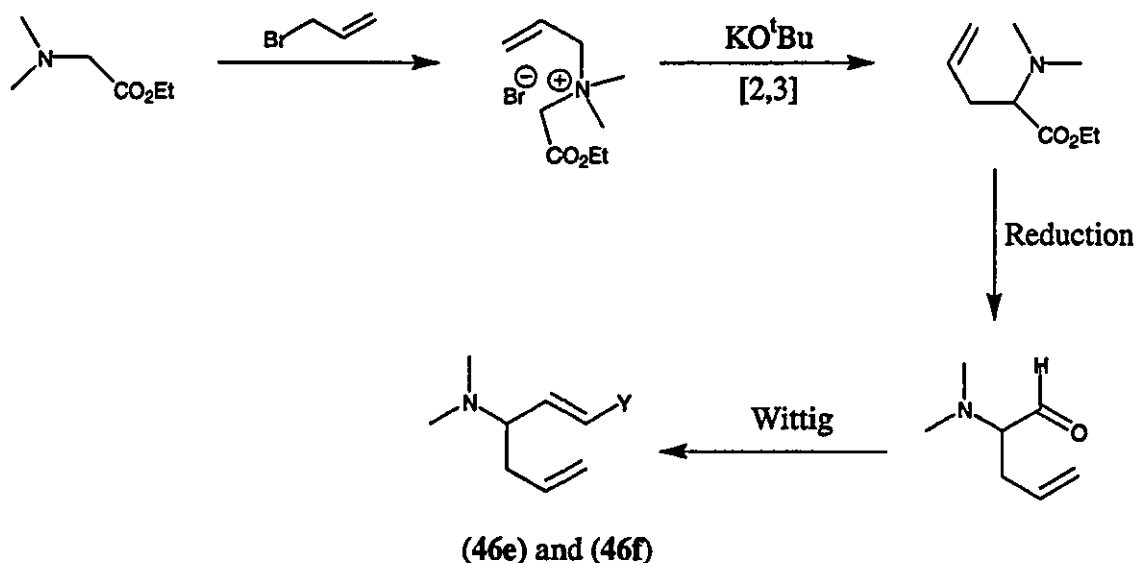
Scheme 32. Synthesis of Amine Substrates

Cope rearrangements were carried out on substrates **(46a-i)** in the gas phase and the extent of reaction was estimated from the ratio of **(46a-i)** to **(47a-i)** in the resulting NMR spectra. The calculated Hine D values were said to compare directly with the K_{eq} values. It was concluded that a reduction of the π-donating character of nitrogen (*dimethyamino vs. carbamoyl*) alters its directing ability giving an aggregate order for reaction rate of $N(CH_3)_2$ > OCH_3 > $EtO_2CN(CH_3)$ > CH_3 > H.

From these early reports our group has recognized that the amino-Cope rearrangement of suitably functionalized 3-amino-1,5-diene substrates could potentially constitute a powerful tool for the stereoselective synthesis of highly functionalized product systems in a cascade-like sequence.
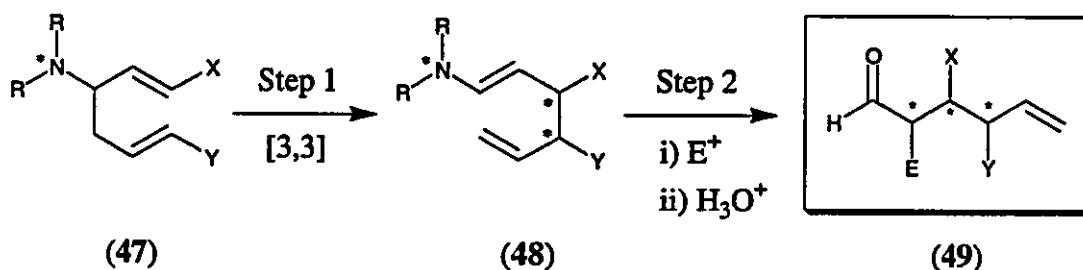
Scheme 33. Synthetic Potential of the Amino-Cope Rearrangement

As highlighted in **Scheme 33**, a successful sigmatropic rearrangement of 3-amino-1,5-diene substrates such as (47) would lead to formation of enamine product (48). Substitution at the 1- or 6-position of the diene moiety in (47) would allow, during Step 1, creation of new asymmetric centres in product (49). Indeed, high stereoselectivities are known to be induced at the chiral centres which are created in related [3,3]-sigmatropic rearrangements.[64,65] If this synthetic step could be further associated with typical enamine derivatization, as outlined in Step 2, up to 3 new asymmetric centres could be introduced in a one-pot reaction. An asymmetric centre within the amine component could essentially act as a chiral multiplier: producing (and controlling) the stereochemical induction at the three newly created asymmetric centres. We have recently reported one key step of the sequence outlined above: a successful tandem amino-Cope rearrangement/enamine derivatization reaction (**Scheme 34**).[128]
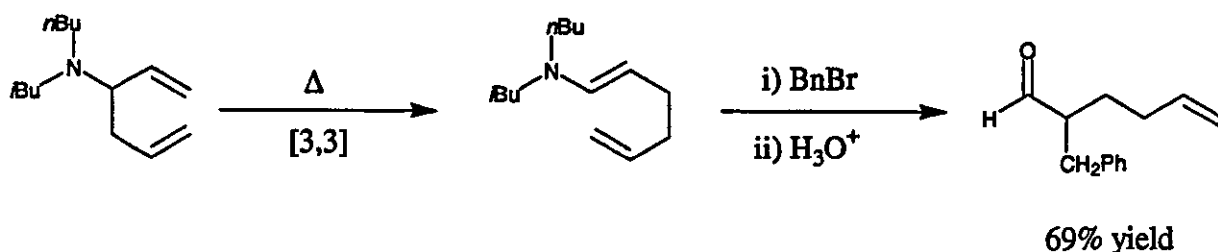
Scheme 34. Tandem Amino-Cope Rearrangement/Enamine Alkylation

In order to study the anionic amino-Cope rearrangement we were required to prepare suitably substituted secondary amine substrates. This was achieved as highlighted in **Scheme 35** by addition of allyl magnesium bromide to the corresponding imines derived from *trans*-cinnamaldehyde to yield the desired amines (51a-c) in good yield (**Table 2**).
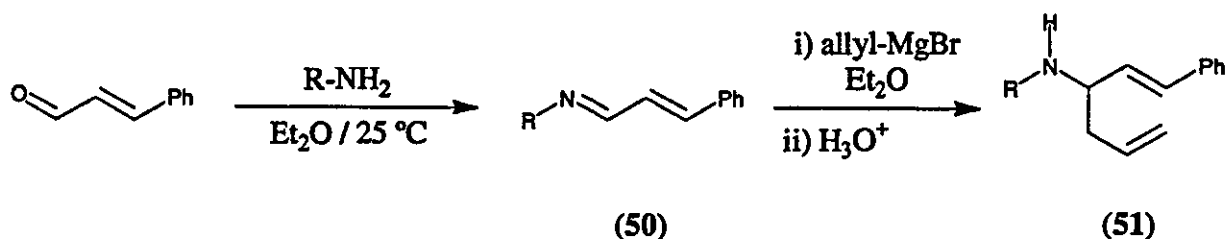
Scheme 35.

Table 2. Preparation of 3-amino-1,5-diene substrates

R	Yield 50a-c, %	Yield 51a-c, %
(a) PhCH$_2$-	94	95
(b) cyclohexyl-	87	72
(c) (±)-α-methylbenzyl-	89	82

We were pleased to find that the anionic amino-Cope rearrangement proceeded as expected with the racemic substrates (51a-c) on employing n-butyllithium as base. The reaction was complete in under three hours. The intermediate lithiated enamines were directly hydrolysed to yield the desired racemic aldehyde (52) in good yield in all cases (Scheme 36, Table 3). Interestingly no reaction was observed using potassium hydride as base, or with a range of non-nucleophilic bases (LDA, LHMDS, KHMDS, NHMDS) in THF.
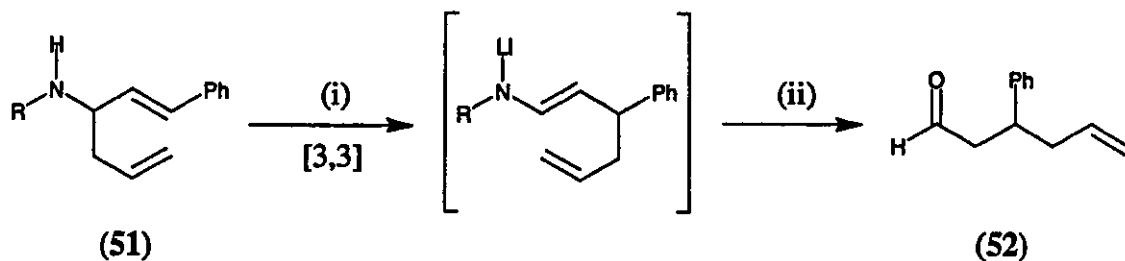
(i) n-BuLi (1.5 eq.), THF, 25 °C, 3 hr; (ii) NaOAc/HOAc/H$_2$O (1/1/2), Δ, 2 hr

Scheme 36.

Table 3. Anionic amino-Cope rearrangement of substrates 51a-c

Substrate	Yield 52, %
51a	81
51b	64
51c	78

These results were encouraging, prompting further investigation by our group, and development of the anionic amino-Cope rearrangement is reported in **Section 2.**

1.5.2. Claisen Rearrangements

1.5.2.1. Asymmetric Aromatic and Aliphatic Claisen Rearrangements

It was mentioned earlier that the Claisen rearrangement of allyl vinyl ethers (**Scheme 37**) has been developed into a useful and widely applied tool in organic synthesis. Substitution at C-3 (or C-3') of the substrate generates new chiral centres in the unsaturated aldehyde product and control over the relative and absolute stereochemistries at these centres is now known to be provided either through the use of chiral auxiliaries, chiral catalysts or reagents.[47b] Synthetic applications of the asymmetric Claisen rearrangement are contained in a recent review by Taguchi and Ito[65] and are not covered in great detail here but below are some more recent examples.
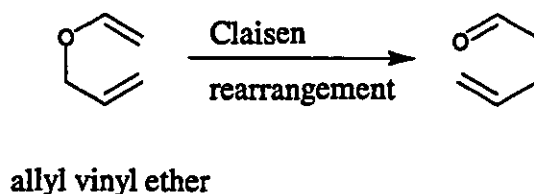
allyl vinyl ether

Scheme 37. The Claisen Rearrangement of Allyl Vinyl Ethers

Asymmetric aliphatic Claisen rearrangements have been known for some time,[66] but the related asymmetric *aromatic* rearrangement is a recent development. Taguchi and co-workers have reported highly enantioselective aromatic Claisen rearrangements of substrates such as (53) mediated by a stoichiometric chiral Lewis acid, (54), leading to products with *e.e.*'s as high as 95% (**Scheme 38**).[67]
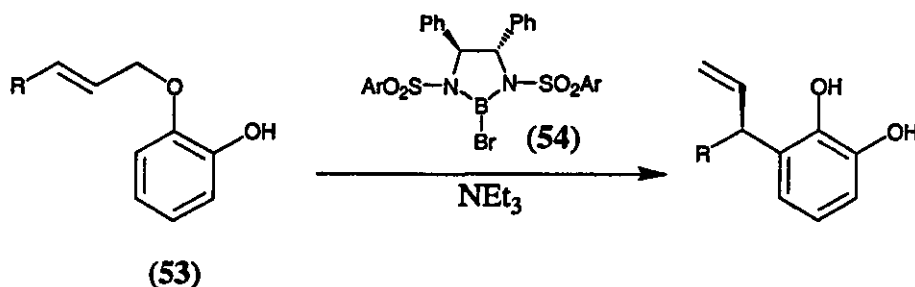
Scheme 38. Enantioselective Aromatic Claisen Rearrangement

The high level of enantioselectivity observed with a range of substrates was rationalised by invoking the transition state shown in **Figure 4**. In this proposed intermediate, the phenolic hydroxyl group forms a σ-bond with the chiral Lewis acid followed by co-ordination of the allylic oxygen to the boron atom to form a cyclic five-membered complex. Steric shielding provided by one of the sulfonamide ligands leads to selective *si*-face approach of the allyl system during rearrangement.
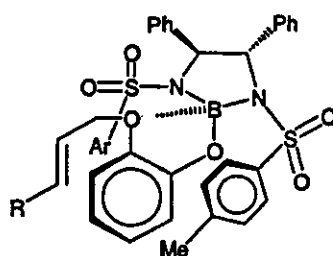
Figure 4

The utility of chiral Lewis acid (54) in asymmetric Claisen rearrangements has been extended by Taguchi to include the rearrangement of allyl difluorovinyl ethers (**Scheme 39**).[68] Enantiomeric excesses of up to 85% were noted, and a similar transition state model has been invoked.
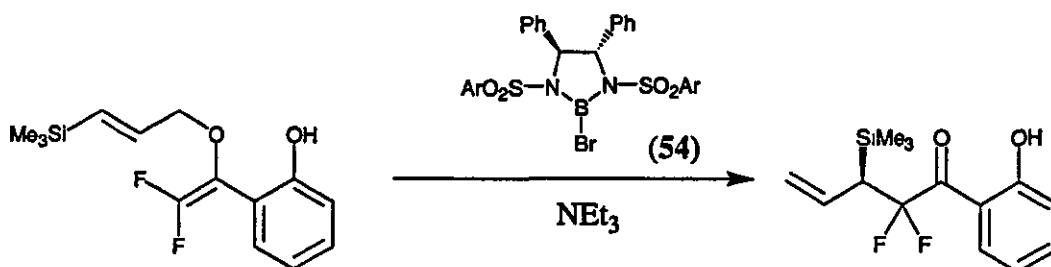
Scheme 39. Claisen Rearrangement of Allyl Difluorovinyl Ethers

Other so-called "designer" chiral Lewis acid catalysts such as (55) have been developed by Yamamoto to mediate the asymmetric Claisen rearrangement of simple substrates.[69] It was found that bulky substituents on the substrate, such as trialkylsilyl or trialkylgermyl groups, were necessary to achieve high levels of enantiomeric excess (**Scheme 40**).

(55)

-78 to - 40 °C
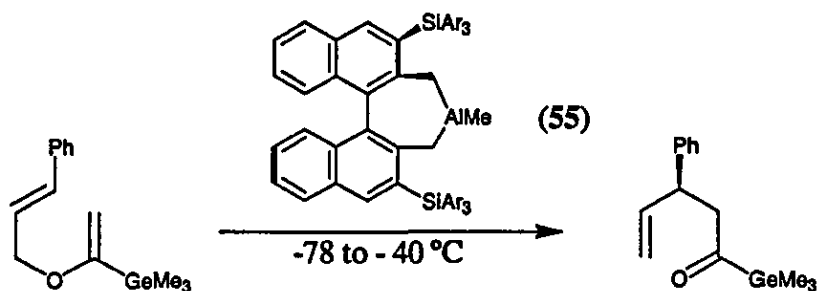
Scheme 40. Asymmetric Claisen Rearrangement Mediated by a Chiral Lewis Acid Complex

Drawbacks to the development of a general asymmetric *aromatic* Claisen rearrangement can include the high temperatures needed to initiate the rearrangement, racemization during rearrangement and synthesis of the non-racemic precursors.[70] Such factors were recently addressed by Trost in a report detailing the asymmetric *O*- and *C*-alkylation of phenols.[71] The preparation of enantiomerically enriched substrates required for the aromatic Claisen rearrangement study was achieved by enantioselective *O*-alkylation of phenols using an asymmetric Pd-catalyzed allylic alkylation protocol (**Scheme 41**).

1 % (dba)₃Pd₂, CHCl₃
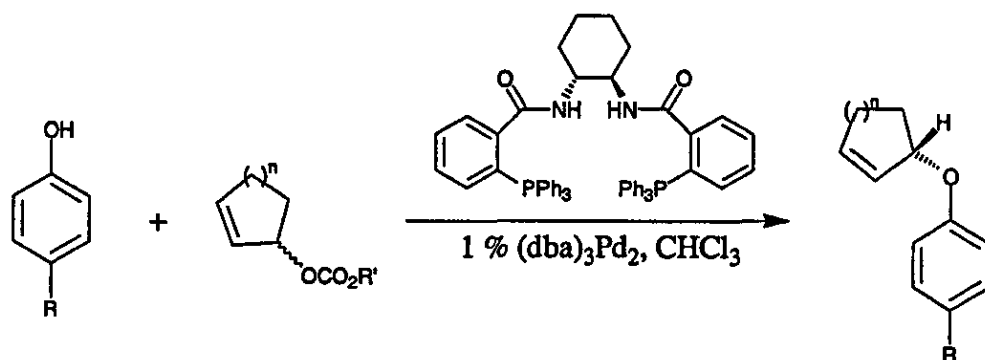
Scheme 41. Enantioselective *O*-Alkylation of Phenols

With the enantiomerically enriched allyl aryl ethers in hand, the Claisen rearrangement was attempted using typical Lewis acid catalysts such as BCl₃ and Et₂AlCl but was found to lead to significant racemization. Subsequent use of the lanthanide complex Eu(fod)₃ in chloroform at 50°C led to efficient chirality transfer affording *C*-alkylation products with up to 97% *e.e.* (**Scheme 42**).
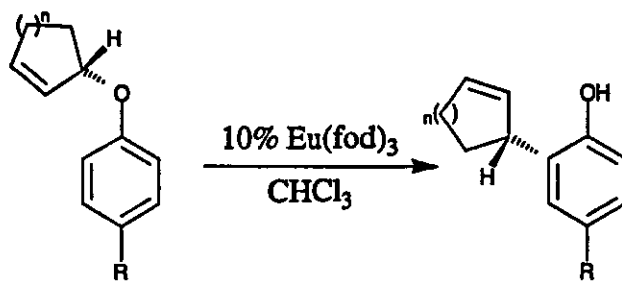
Scheme 42. Catalytic Asymmetric Claisen Rearrangement

A stereoselective Claisen rearrangement has been applied by Paquette as the key step in the synthesis of the natural product (+)-*acetoxycrenulide* (**56**), a marine toxin.[72] Diastereoisomerically pure substrate (**57**) was subjected to selenoxide elimination and Claisen rearrangement to yield the desired cyclooctenone core of the target (**Scheme 43**).
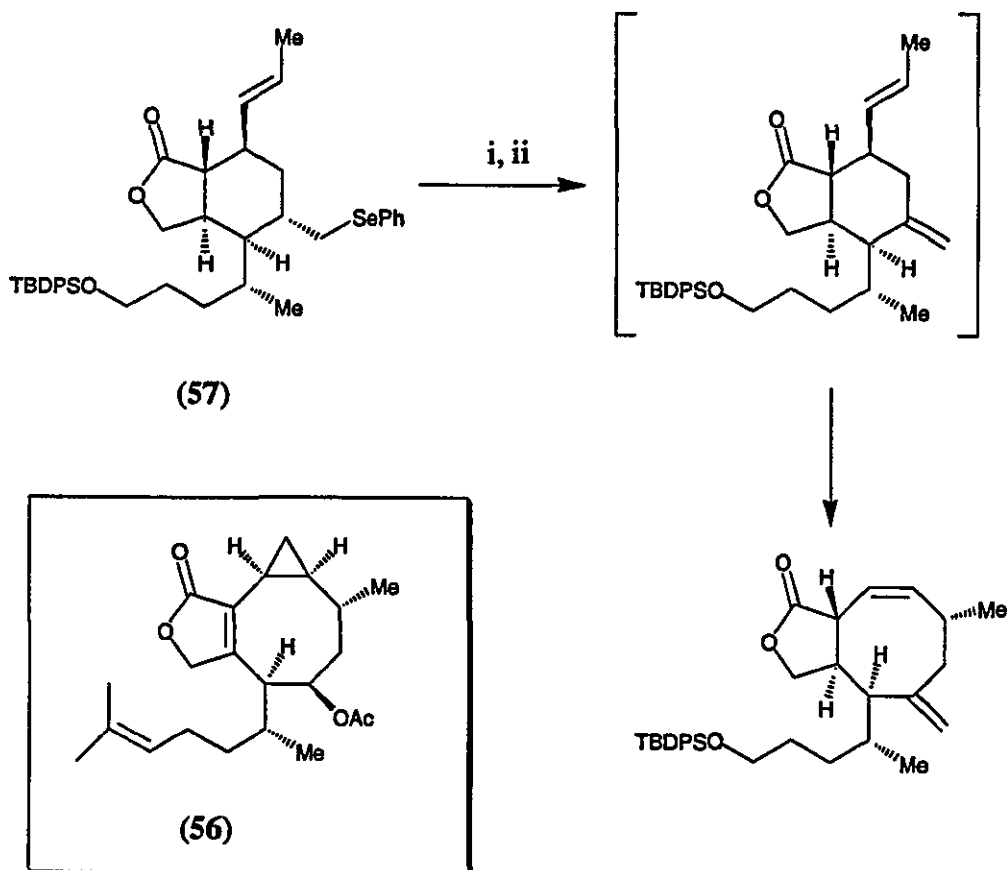
i) $NaIO_4$, $NaHCO_3$, MeOH, H_2O; ii) Et_3N, $CH_3CH_2OCH=CH_2$, $CH_3CON(CH_3)_2$, 220°C, sealed tube

Scheme 43.

The rearrangement was found to be most diastereoselective (7.8:1) when carried out by heating the substrate in *N,N*-dimethylacetamide in a sealed tube.

1.5.2.2 Asymmetric Ireland-Claisen Rearrangement

Section 1.3.1.4. describes the Ireland Claisen rearrangement as the [3,3]-sigmatropic rearrangement of allylic esters as their corresponding ester enolates to give 4,5-unsaturated acids (Schemes 16 and 44).[27] The more commonly used protocol is the trapping and subsequent rearrangement of the enolates as the silyl ketene acetals, a procedure also commonly termed an Ireland-Claisen rearrangement.[73]
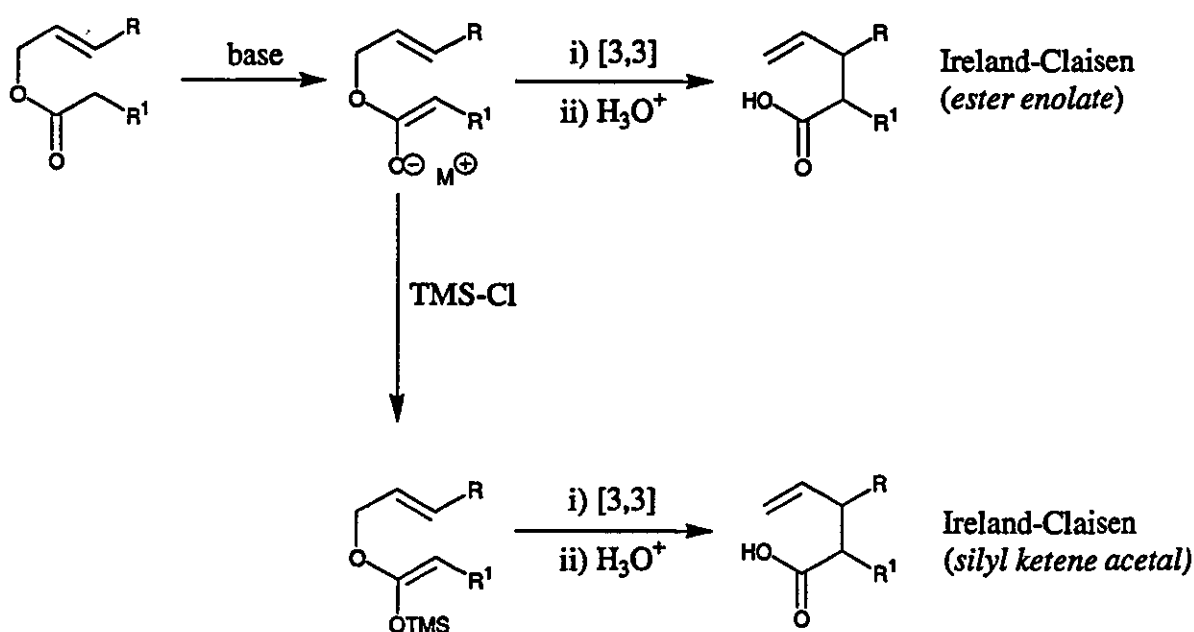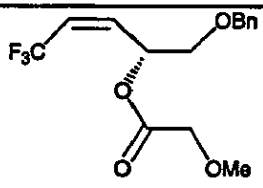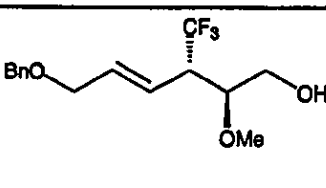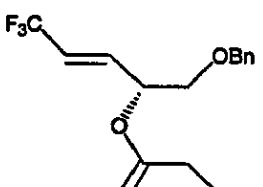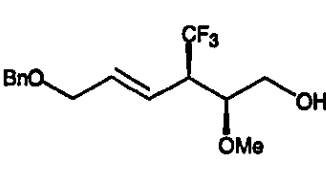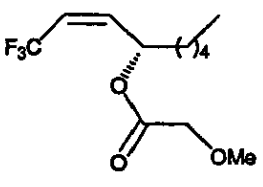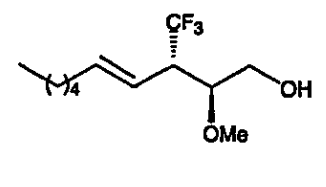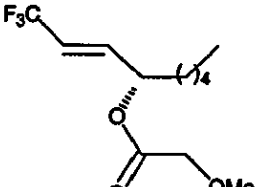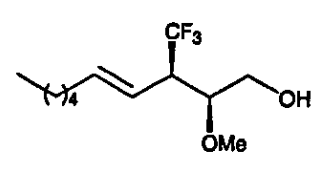
Scheme 44. Ireland-Claisen Rearrangement and Silyl Ketene Acetal Modification

There are many examples highlighting the synthetic application of the asymmetric Ireland-Claisen rearrangement. Its popularity in synthesis derives from its mild reaction conditions, a high degree of compatibility with substrate types and, not least, the high degree of stereoselectivity provided as a result of the control of ketene acetal geometry and the highly ordered transition state geometry achieved during rearrangement.[27] In general, the rearrangement usually proceeds *via* a chair-like transition state with the stereochemical issues determined by the stereochemistry of the silyl ketene acetal and allylic ether double bonds. In this section several recent applications are highlighted.

Kitazume and co-workers have applied the Ireland Claisen rearrangement in a stereoselective approach to trifluoromethylated compounds.[74] Such compounds are of general interest due to the fact that fluorination of biologically active molecules frequently confers significant changes in their chemical and biological activities.

Table 4 highlights the results obtained for several E and Z-substrates. The corresponding silyl ketene acetals needed for rearrangement were generated by adding the substrate to a mixture of LHMDS and TMSCl which was stirred at –78 °C for 0.5 hr, followed by warming to room temperature and acidic work-up.

Table 4. Synthesis of trifluoromethylated compounds *via* Ireland-Claisen rearrangement

Substrate	Product	*anti : syn*	Yield (%)
(Z)	anti	97 : 3	68
(E)	syn	1 : >99	59
(Z)	anti	96 : 4	75
(E)	anti	1 : >99	67

The *E*-substrates generated the *syn* product and the alternative *Z*-isomer delivered the *anti* product. The commonly used chair-like transition states were proposed to rationalise the stereochemical outcome. Rearrangement of the *Z*-isomers was slightly less diastereoselective than the corresponding *E*-isomer. It was suggested that the pseudo-axial trifluoromethyl group might destabilize transition state (58) causing this slight decrease in *anti* selectivity (Figure 5).
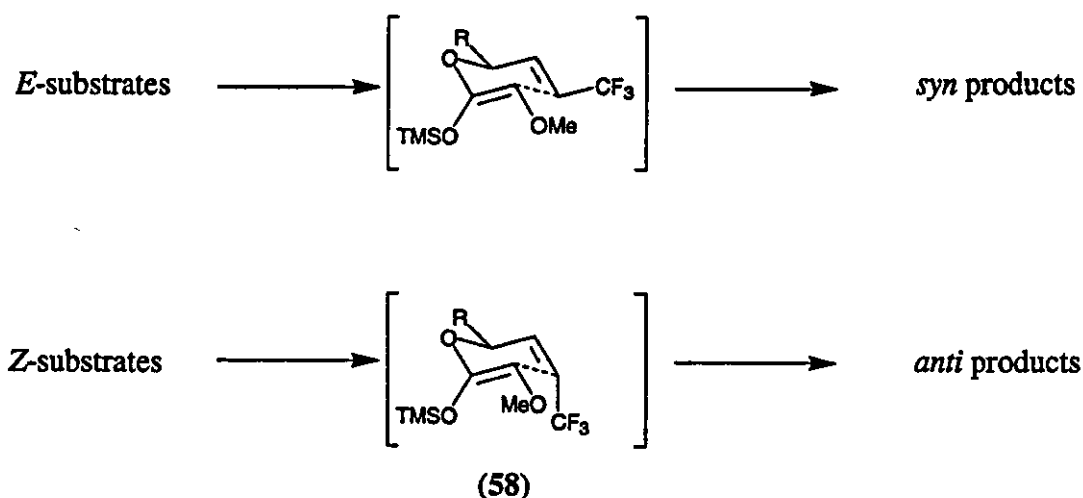
Figure 5.

This work was further extended by Kitazume and used to prepare trifluoromethylated iodolactones containing four consecutive asymmetric centres.[75] **Scheme 45** highlights the synthesis of one iodo-lactone as a single diastereoisomer, by consecutive Ireland-Claisen rearrangement and iodolactonization.
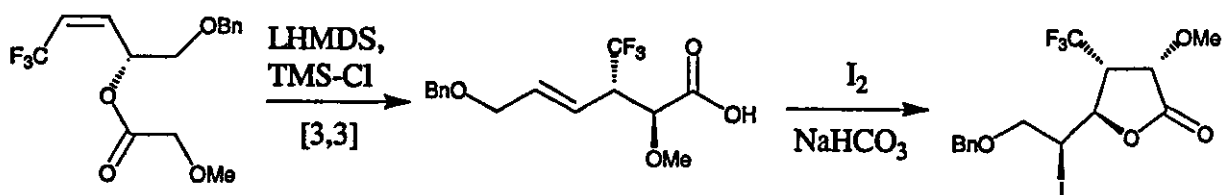
Scheme 45.

Careful control of enolate geometry and, accordingly, silyl ketene acetal geometry allowed Parsons to prepare a key intermediate in the synthesis of (+)-Prelog-Djerassi lactonic acid (59) from diastereoisomeric substrates (**Scheme 46**).[76]
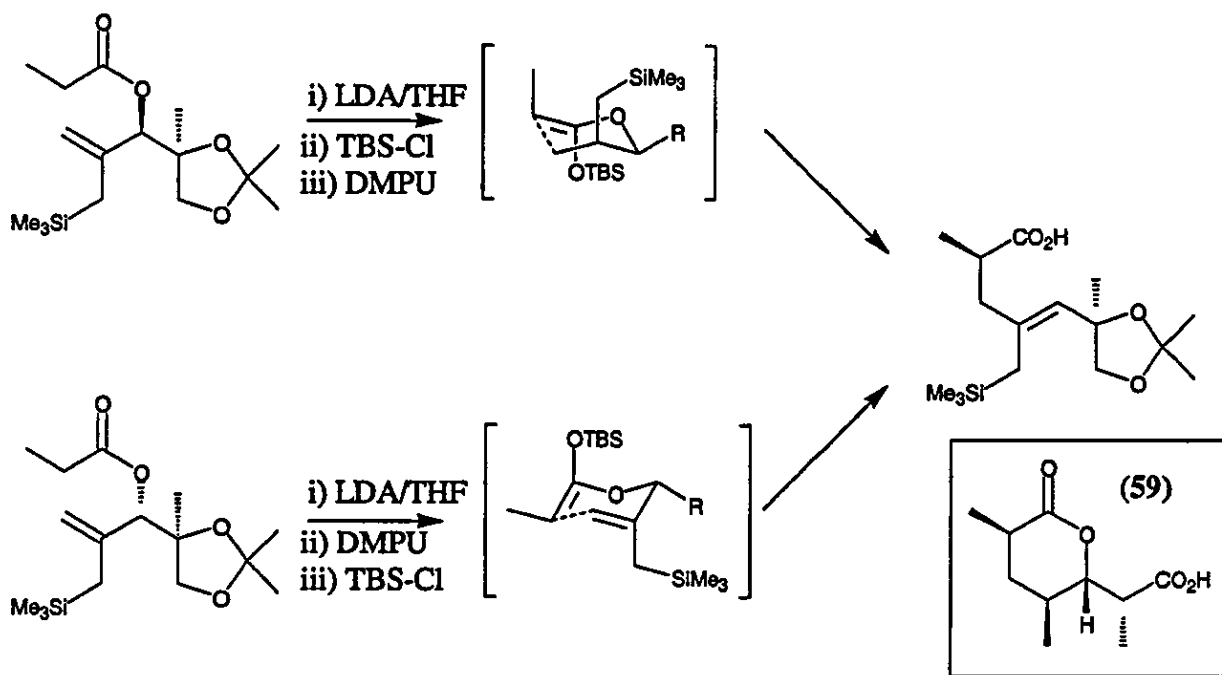
Scheme 46.

Rearrangement of the *syn* substrate was achieved *via* the *E*-silyl ketene acetal and rearrangement of the *anti* substrate *via* the *Z*-silyl ketene acetal. In both cases the rearrangement proceeded to give the **same** single product diastereoisomer.

Hodgson and co-workers have recently applied the Ireland-Claisen rearrangement in an asymmetric approach to a prostaglandin precursor (60) and to (+)-*iridomycin* (61).[77]

(60)   (61)
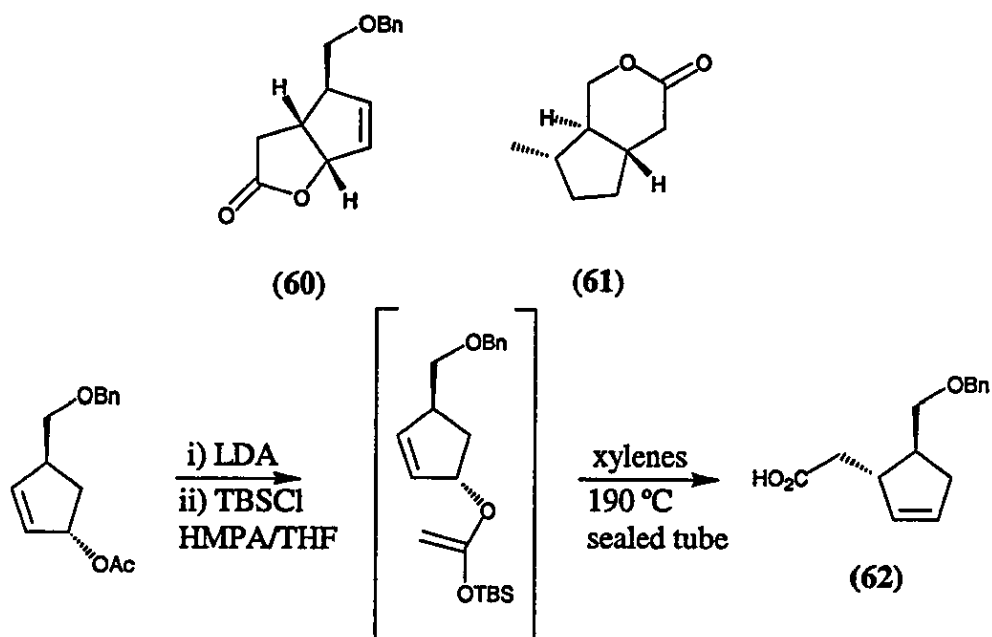
Scheme 47.

Lactone (60) is a known building block for prostaglandin A$_2$ and other primary prostaglandins. One key step in the synthesis of (60) is an Ireland Claisen rearrangement of a silyl ketene acetal (Scheme 47). The rearrangement takes place under thermal conditions (xylenes, 190 °C, sealed tube). Further elaboration of the acid product (62) delivers the desired lactone (60).

Acid (64), prepared *via* a similar enantioselective Ireland Claisen rearrangement of the diastereoisomeric substrate (63) was used as a key building block to access (+)-*iridomycin* (61) as shown in Scheme 48.
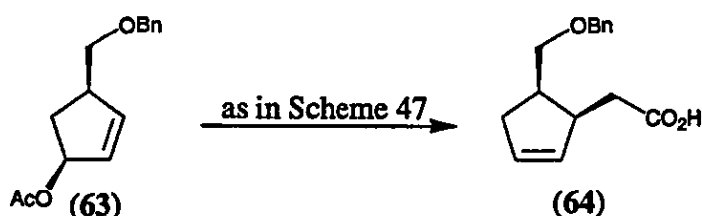
Scheme 48.

Kocienski has applied the stereoselective Ireland-Claisen rearrangement as a key step to set up the correct relative stereochemistry at C27 and C28 of the C21-C42 fragment of *rapamycin* (Scheme 49).[78]
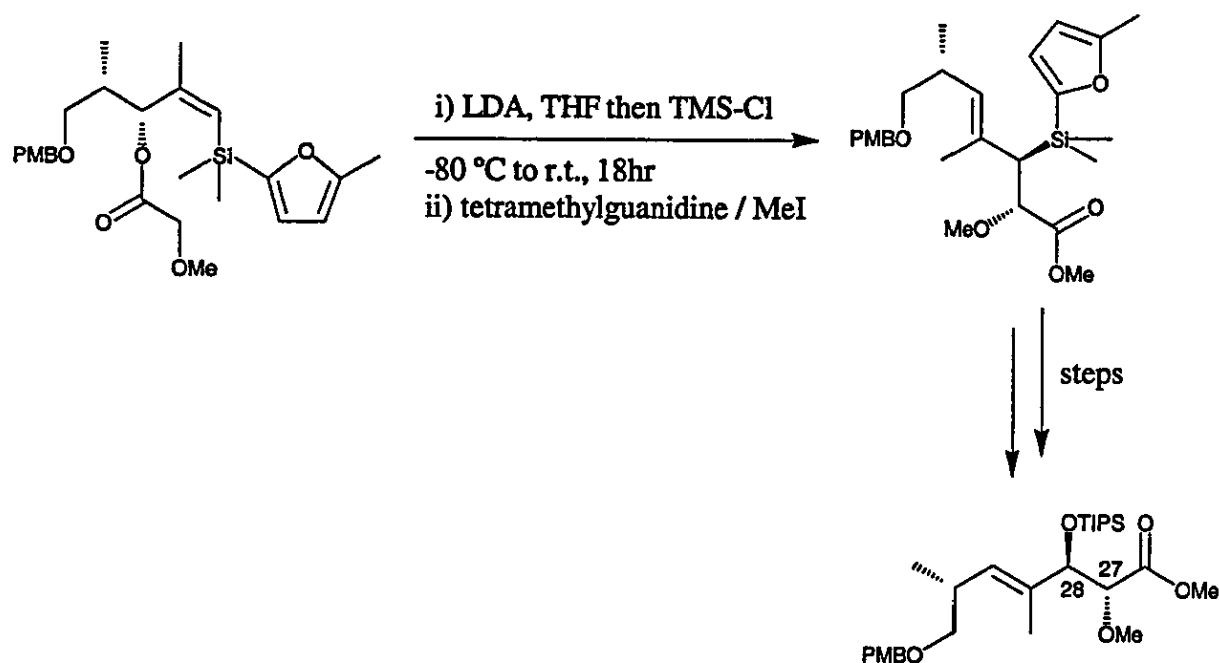
Scheme 49.

The Kocienski group has also recently applied the Ireland-Claisen rearrangement to the synthesis of the C11-C19 fragment of the natural herbicide *herboxidiene*.[79] Rearrangement of the *E*-silyl ketene acetal led to a diastereoisomeric mixture (86:14) of the target acid in good yield (**Scheme 50**).
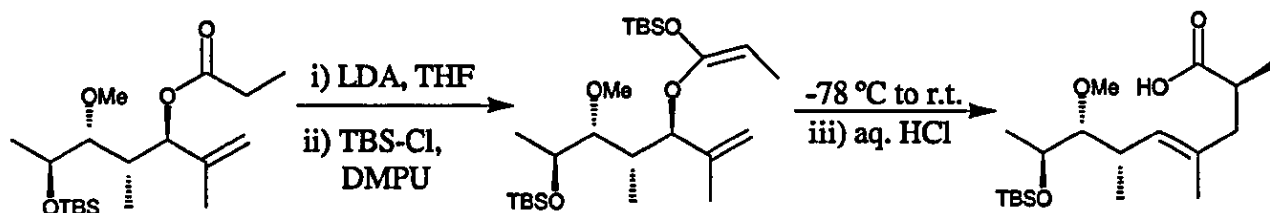
Scheme 50.

Magnus has applied the Ireland-Claisen rearrangement in an approach to the taxane skeleton.[80] **Scheme 51** highlights the key rearrangement step that delivers the target compound (**65**) as a single diastereoisomer. The newly formed C2-C3 bond was formed with the correct absolute stereochemistry as required in taxol.
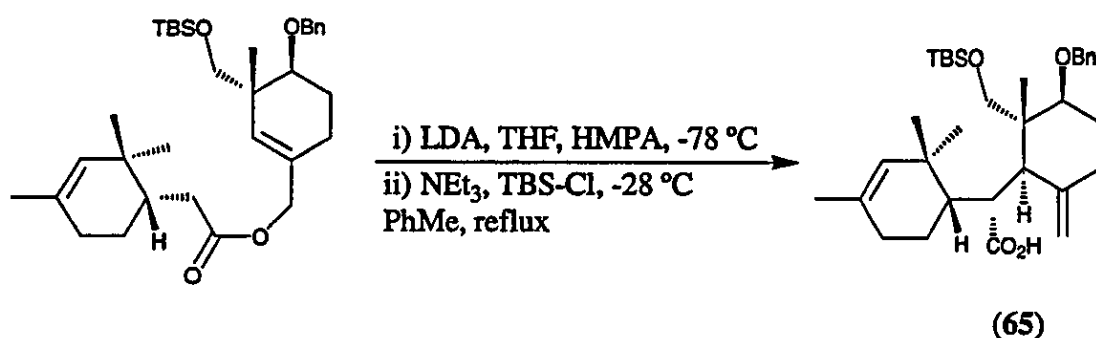
Scheme 51.

Angle has applied a conformationally restricted Ireland-Claisen rearrangement in his work towards the synthesis of piperidine alkaloids.[81] The pipecolic ester (**66**) was isolated in 96% yield from the rearrangement which was carried out at room temperature *via* generation of the silyl ketene acetal using TIPSOTf and triethylamine (**Scheme 52**).

(66)
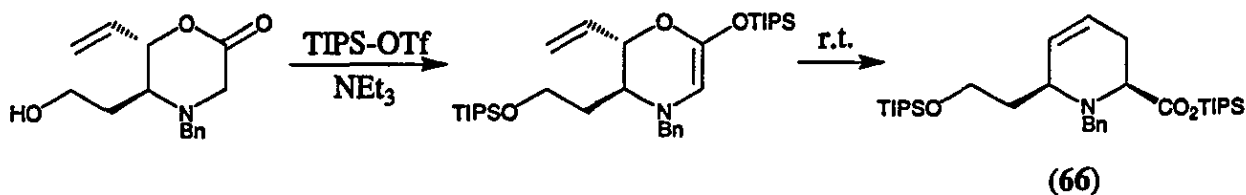
Scheme 52.

Knight used the Ireland-Claisen rearrangement of a nine-membered macrolide to lead, stereospecifically, to the tetrahydrofurancarboxylate (67), a key building block for the synthesis of several lignans (Scheme 53).[82]

(67)   (68)
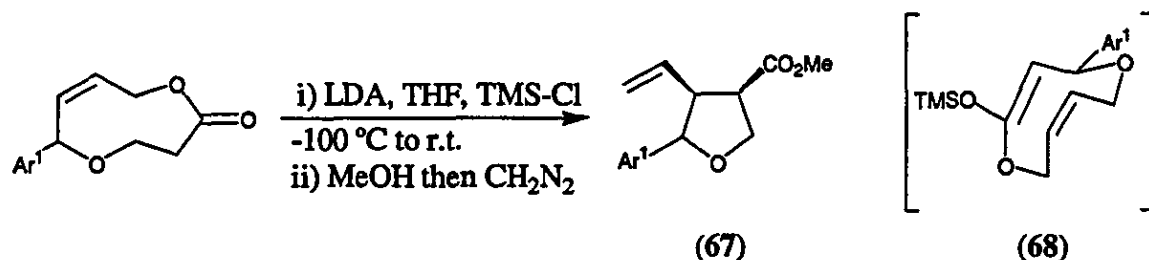
Scheme 53.

The rearrangement proceeded to give (67) as a single diastereoisomer, presumably *via* the boat-like transition state (68).

Kazmaier and co-workers have recently developed an "asymmetric ester enolate Claisen rearrangement" protocol (an Ireland-Claisen rearrangement) for the synthesis of γ,δ-unsaturated amino acids.[83] The reaction proceeds through a chelated allylic ester enolate intermediate, as shown in **Scheme 54**, and leads to products displaying high levels of diastereoselectivity. When carried out in the presence of a chiral ligand (quinine) the reaction proceeds with excellent levels of enantioselectivity (up to 93% *e.e.*).[84]
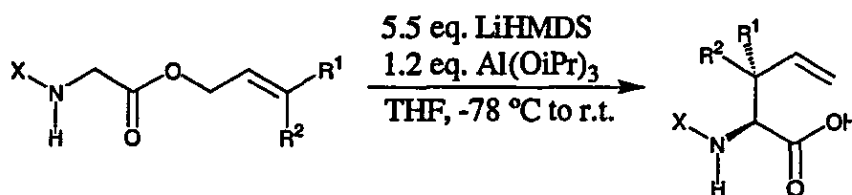
Scheme 54. Diastereoselective Ester Enolate Claisen Rearrangement

The reaction appears to be quite general and is applicable to a wide range of substrates, including peptides.[85] Other synthetic applications which apply this protocol as a key step include the synthesis of the potent β-glycosidase inhibitor 5-*epi*-isofagomine (69),[86] and the preparation of *N*-protected *isostatin* (70) which is an essential amino acid of the didemnine cyclic peptide group that show strong anti-tumour, anti-viral and immunosuppressive activity.[87]
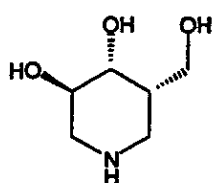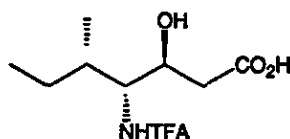
(69)   (70)

1.5.2.3. Aza-Claisen Rearrangement

Introduction of a nitrogen atom into the typical Claisen sub-structure gives rise to the aza-Claisen variant, and the stereochemistry of this sub-frame is transferred to the newly formed carbon-carbon bond with high degrees of stereocontrol. Aza-Claisen rearrangements are wide ranging in type and a few recent examples of these are presented here.

Somfai[88] has recently reported the use of vinylaziridines in the aza-Claisen rearrangement to produce seven-membered lactams in good yield and with excellent levels of diastereoselectivity. The results are rationalised by assuming that the reaction proceeds through a six-membered boat-like transition state as shown in **Scheme 55**. Attempts to rearrange the vinylaziridine (71), derived from the *cis*-vinylepoxide were unsuccessful and this provided additional support for the proposed model. Quenching of the corresponding enolate from (71) with D_2O gave only recovered starting material with complete incorporation of deuterium at the α position indicating the required transition state for rearrangement could not be attained.
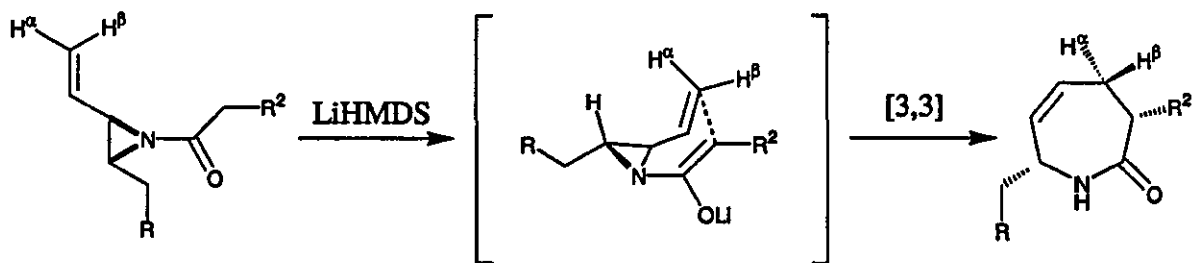
Scheme 55. Rearrangement of vinylaziridines
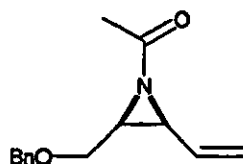
(71)

Investigation of the zwitterionic aza-Claisen rearrangement was performed by Nubbemeyer[89] during work towards the total synthesis of (+)-*dihydrocanadensolide*. Heterodienes were prepared by treating *N*-allylpyrrolidine (72) with several types of acid chloride (Table 5, Scheme 56) which then underwent [3,3] sigmatropic rearrangement to produce the amides (73-76).

Table 5. Zwitterionic Aza-Claisen Rearrangement of Allylpyrrolidines

Entry	R^1	Yield (%)	Ratio			
			73	74	75	76
a	H	82	60	40	-	-
b	Me	77	90	10	-	-
c	CH_2CH_2Cl	74	70	-	30	-
d	$CH(CH_3)_2$	45	>97	<1	<1	<1
e	$CH=CH_2$	62	>97	<1	<1	<1
f	$CH=CHCH=CH_2$	60	<1	<1	>97	<1
g	Ph	52	<1	<1	>97	<1
h	Cl	82	96	2	<1	<1
i	*O*-Bn	83	87	8.7	<1	4.3

In most cases the stereochemistry could be rationalised by invoking a chair-like transition state, although in the case of entries **f** and **g** more complex electronic considerations were necessary. Product (**73h**) was converted to *dihydrocanadensolide*, thus completing a short and highly stereoselective synthesis of this natural product.
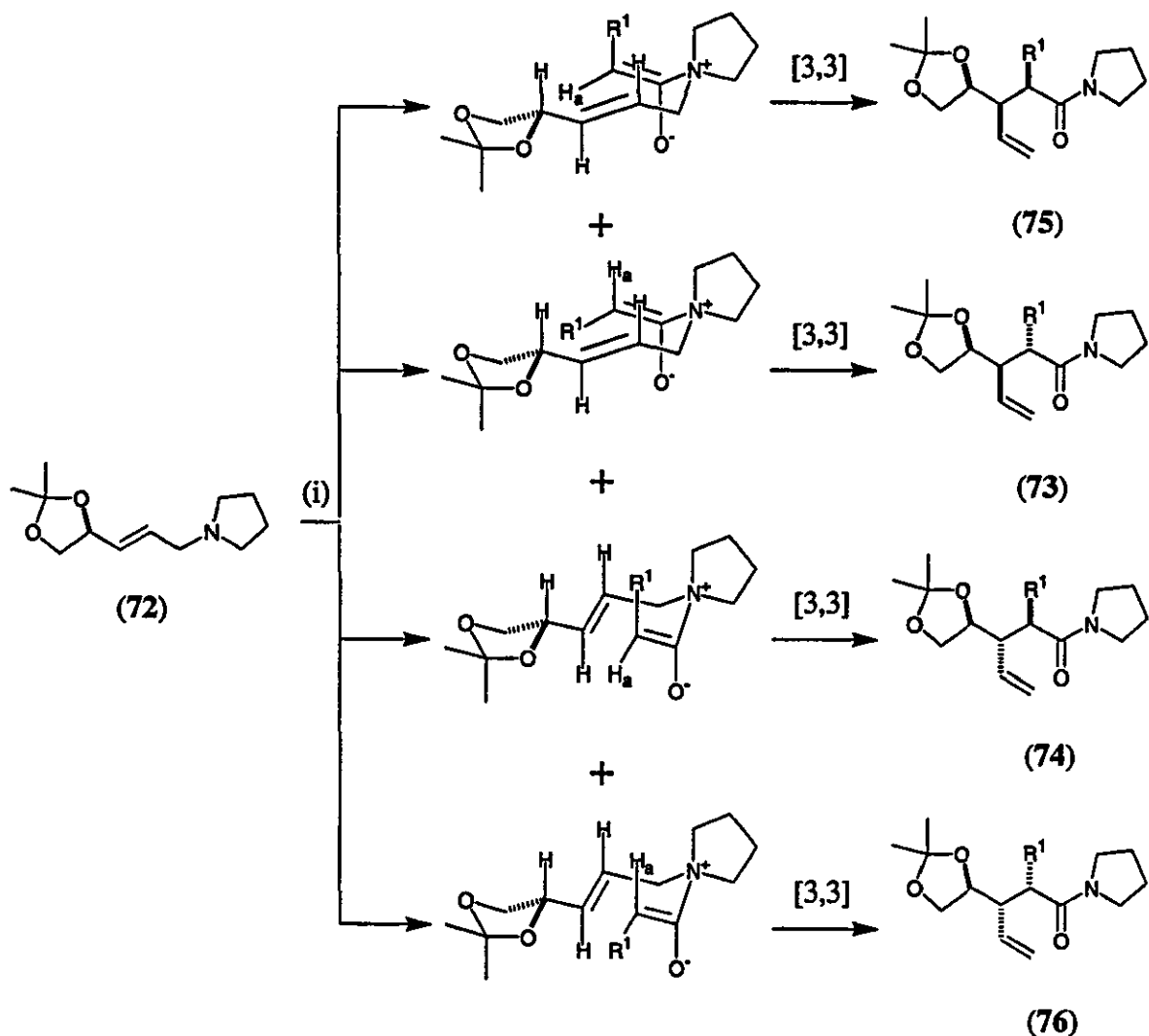
i) R_1CH_2COCl, K_2CO_3, Me_3Al, $CHCl_3$, $0°C$

Scheme 56. Aza-Claisen Rearrangement of Allylpyrrolidine Derivatives

Zhang[90] *et al* have investigated the catalytic enantioselective aza-Claisen rearrangement of allylic imidates using palladium (II) ambox ligands (**77-80**), with some initial success. They found that the reaction was very solvent and concentration dependent and the resulting enantioselectivity depended greatly on the catalyst system selected. However moderate yields and *e.e.*'s of up to 83% were observed in the preliminary study.

(77)   (78)   (79)   (80)

R¹	R²	R³
Ph	4-CF₃C₆H₄	Pr
Ph	4-CF₃C₆H₄	i-Pr
Ph	Ph	Pr
CCl₃	H	Pr
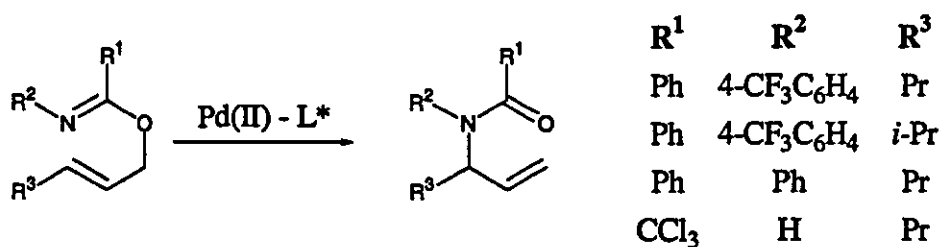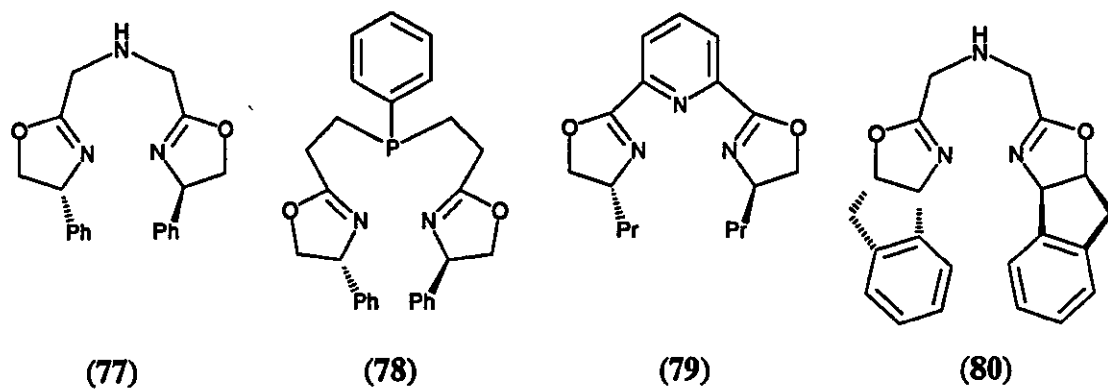
Scheme 57. Pd(II) Catalysis of the Asymmetric Aza-Claisen Rearrangement

Palladium catalysis of the imidate Claisen rearrangement has also been studied by Leung[91] giving an *e.e.* of 79% with Pd complex **(81)** (**Scheme 58**).
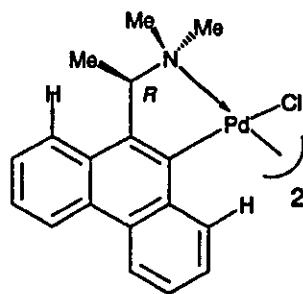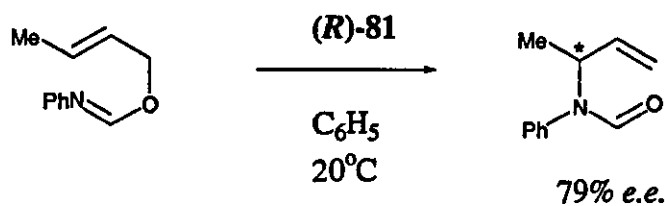
(R)-81

Scheme 58. Asymmetric Palladium-catalysed Imidate-Claisen Rearrangement

The [3,3]-sigmatropic rearrangement of allylic thiocyanates has recently been exploited by Gonda[92] during the course of work on the synthesis of branched-chain amino sugar nucleosides. Thermal rearrangement of thiocyanate (82) was carried out and gave a high yield of crystalline isothiocyanate (83) as the sole product in good yield. The importance of the 1,2-O-isopropylidene group as a key factor in the stereochemical outcome was investigated and was found to be more important than the C-4 side-chain in directing the rearrangement. A severe non-bonded interaction between the 1,2-isopropylidene group and the NCS substituent was thought to be the major factor controlling the stereoselectivity of the reaction.

70°C, 4h
xylene, N₂
89%

(82)   (83)
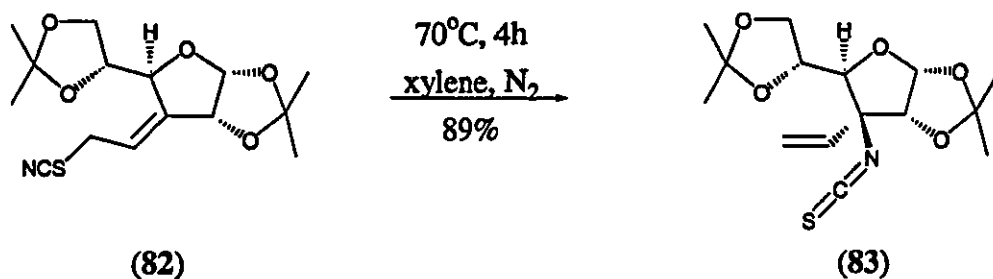
Scheme 59. Rearrangement of Allylic Thiocyanates

Use of a binaphthylamine auxiliary for asymmetric imidate-Claisen rearrangement was utilised by Metz[93] as part of ongoing work in this area. Introduction of a methyl group at C-3 of their existing auxiliary increased the stereochemical induction giving exclusively one product by NMR spectroscopy (**Scheme 60, Table 6**). Excellent auxiliary control as well as simple (*syn/anti*) diastereoselectivity was reported and it was found that using a larger excess of base in the reaction greatly increased the yield.
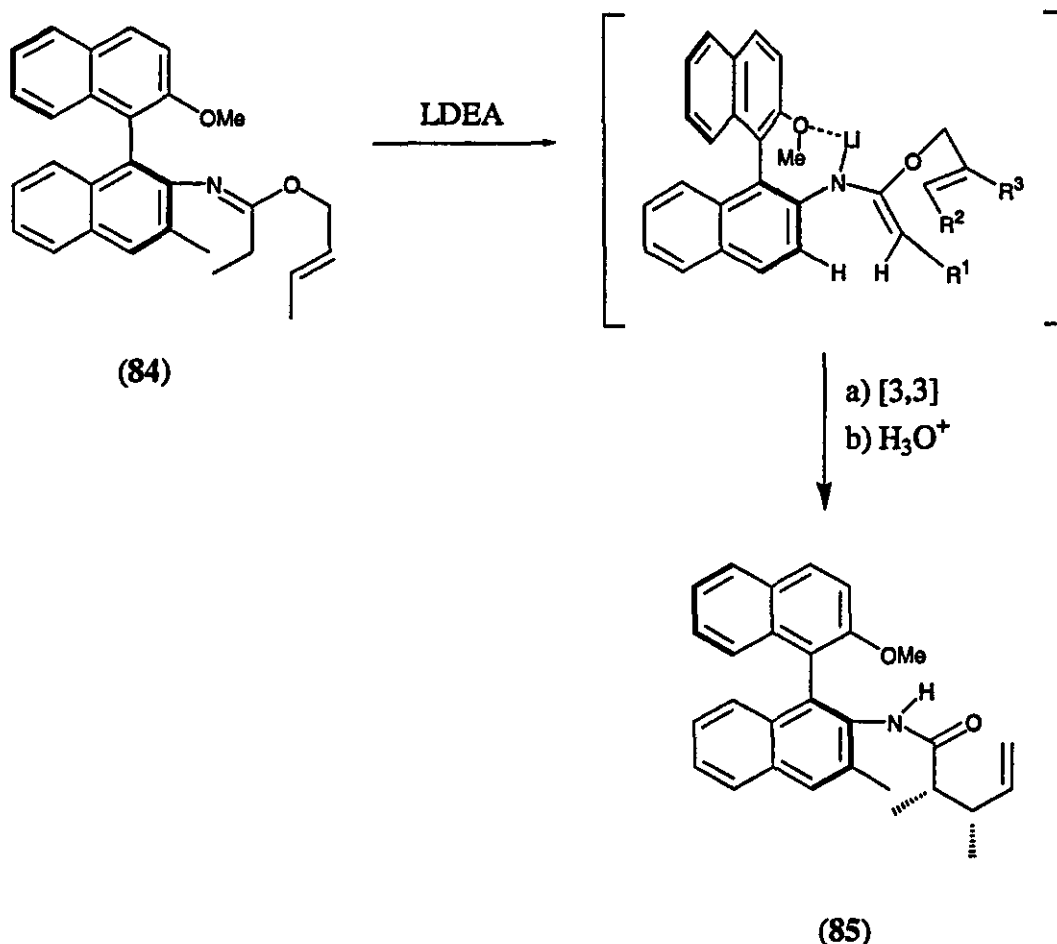
Scheme 60. Asymmetric Imidate Claisen Rearrangement

Table 6. Claisen Rearrangement of Imidate 84 to Amide 85

Rearrangement temp (°C)	LDEA (eq.)	Rearrangement time (h)	Yield (%)	d.s. (%)
0	2	6	23	98
0	4	6	54	98
-10	4	10	48	>98
-20	4	24	43	>98

Gonda[94] et al have used the aza-Claisen rearrangement in a novel synthesis of *lincosamine* and 7-*epi-lincosamine* precursors. This group described a simple approach to introducing a nitrogen atom at C-6 of galactose with high stereoselectivity *via* rearrangement of trifluoroacetimidates and thiocyanates (**Scheme 61, Table 7**).
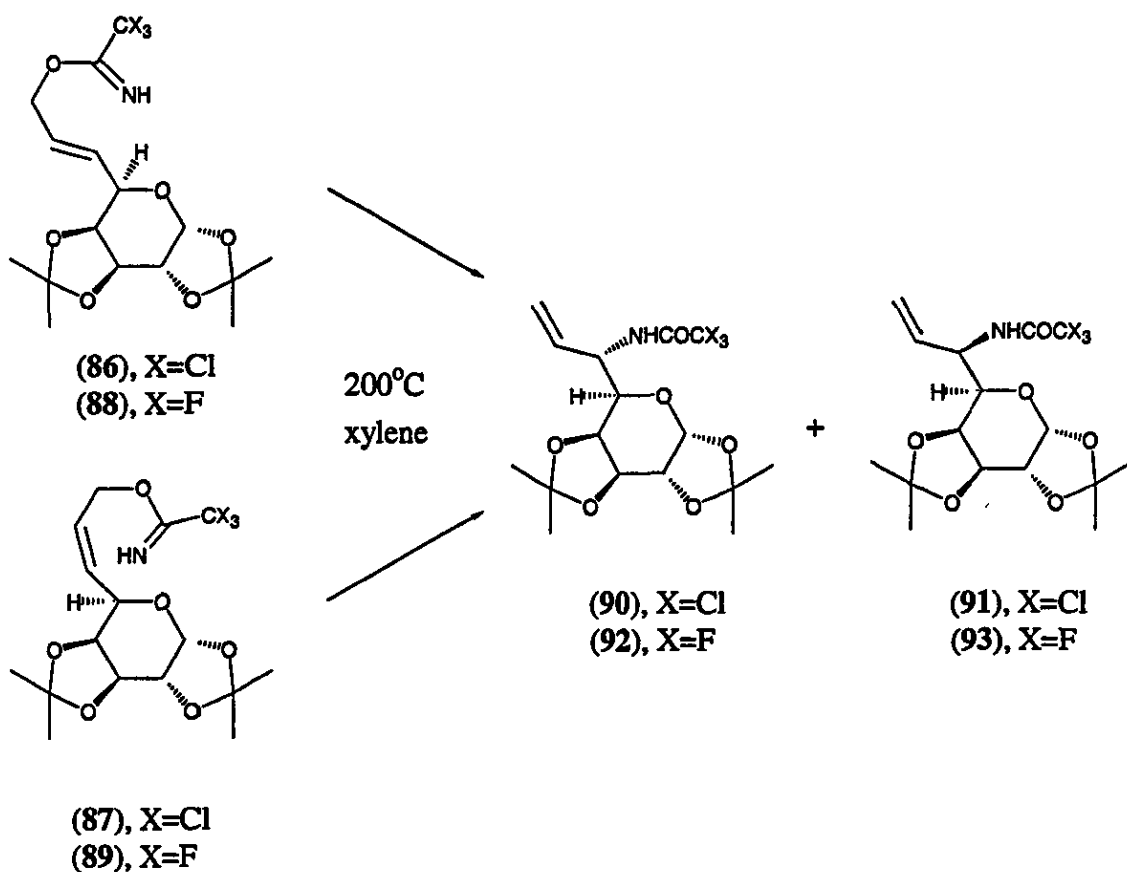
Scheme 61. Thermal Rearrangement of Acetimidates

Table 7. Comparison of trichloro- and trifluoroacetimidates

Compound	Ratio 90:91	Ratio 92:93	Yield (%)	Time (hr)
86	50:50	-	22	30
87	50:50	-	25	30
88	-	42:58	93	2
89	-	9:91	95	2

Thermal rearrangement of the trichloroacetimidates, however, proceeded with decomposition and gave poor yields with no stereoselectivity. Metal catalysis using Hg(II) and Pd(II) species was attempted on all the acetimidate substrates but gave no rearrangement products. Transformation of the rearrangement product (93) to a precursor of *lincosamine* was achieved in 4 subsequent steps. Rearrangement of the allylic thiocyanates (**Scheme 62**) was also achieved in good yield and showed moderate stereoselectivity (75:25).
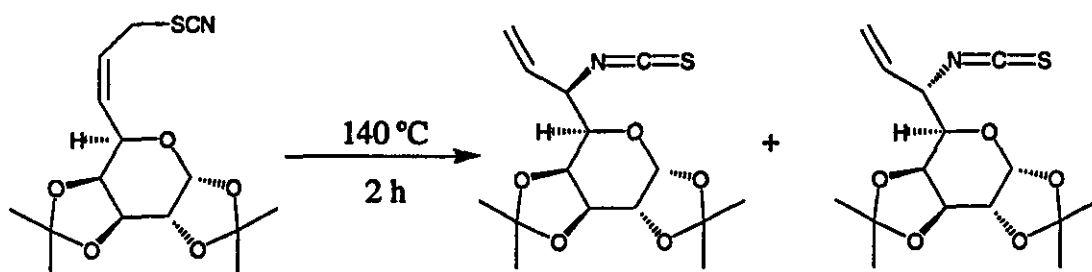
Scheme 62. Rearrangement of Allylic Thiocyanates

An unexpected aza-Claisen rearrangement was observed by Spilling[95] whilst attempting to halocyclise trichloroacetimidates (94a-e) with NBS or NIS. Good yields of amide were obtained with both alkyl and aryl allylic phosphonates.

(94a-e)
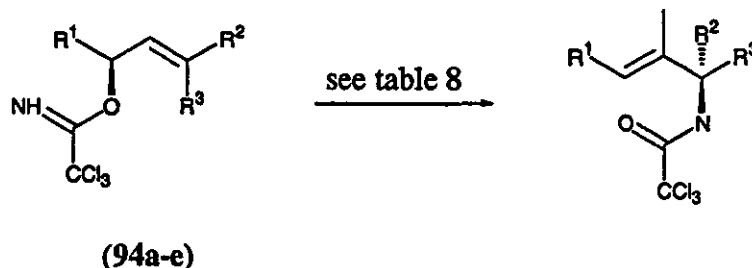
Scheme 63. Rearrangement of Allylic Trichloroacetimidates

Table 8. Reaction of Allylic Trichloroacetimidates with *N*-Halosuccinimides

	R^1	R^2	R^3	halide/solvent/time	Yield (%)
a	$(MeO)_2P(O)$-	Ph	H	NBS/CHCl$_3$/24hrs	91
b	$(MeO)_2P(O)$-	Me	H	NBS/CH$_2$Cl$_2$/CH$_3$CN/24hrs	82
b	$(MeO)_2P(O)$-	Me	H	NBS/CHCl$_3$/36hrs	53
c	$(MeO)_2P(O)$-	cyc-C$_6$H$_{11}$	H	NBS/CHCl$_3$/24hrs	89
d	$(MeO)_2P(O)$-	2-furanyl	H	NIS/CH$_2$Cl$_2$/24hrs	65
e	$(MeO)_2P(O)$-	*n*- C$_6$H$_{11}$	H	NBS/CHCl$_3$/24hrs	55

The mechanism in **Scheme 64** was postulated and fits well with the experimental observations.
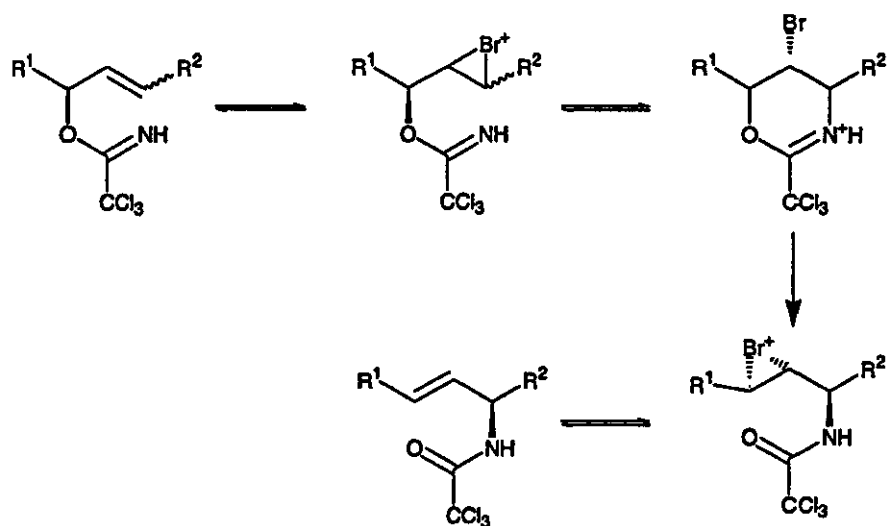
Scheme 64. Stepwise Mechanism for Rearrangement of Imidates
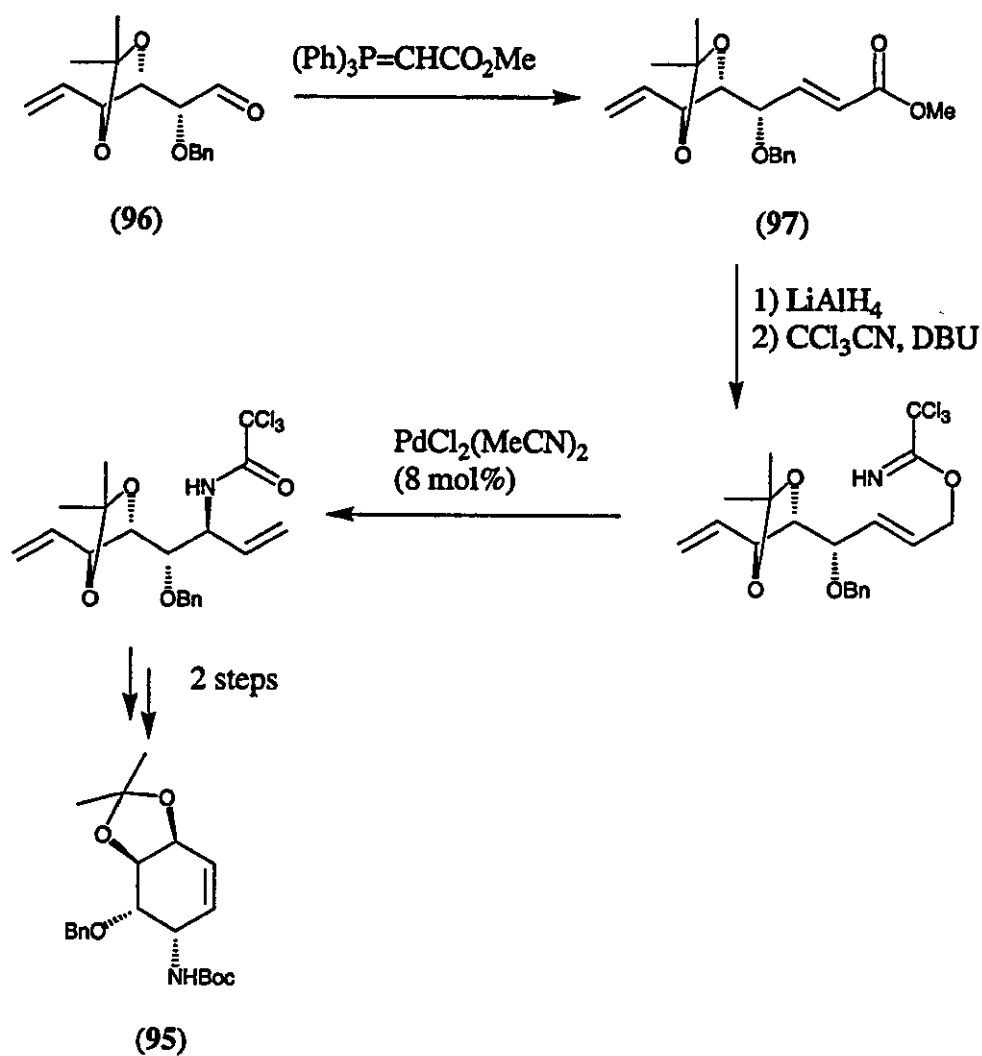
Scheme 65. Conduramine Synthesis

Synthesis of the conduramine derivative (95) was achieved by van Boom[96] *et al* using the aza-Claisen (Overman) rearrangement as a key step (**Scheme 65**). Acetonide (96) was further chain extended using Wittig chemistry and reduced with LiAlH$_4$. The acetimidate was formed by reaction of (97) with trichloroacetonitrile which upon treatment with catalytic PdCl$_2$(MeCN)$_2$ yielded the desired 1,7 diene. Conversion of the diene to its *N*-Boc derivative gave a suitable compound for ring closing metathesis which gave the conduramine derivative with the desired stereochemistry.

1.5.2.4. Thia-(Thio-) Claisen Rearrangement

The first example of asymmetric induction in the thio-Claisen rearrangement was recently documented by Metzner *et al.*[97] Preparation of a number of ketene dithioacetals was readily achieved in two steps and these compounds spontaneously rearranged at room temperature yielding products with excellent diastereoselectivity and in good yield (**Scheme 66**). The postulated mechanism (**Scheme 67**) involves attack of the allylic chain *anti* to the sulfinyl group lone pair, assuming a six-membered transition state, to give the predominant diastereoisomer. The range of substrates and results are shown in **Table 9**.
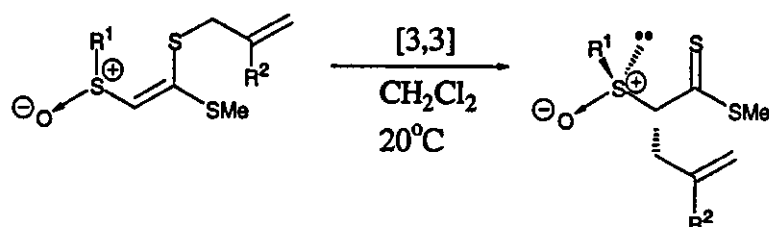
Scheme 66.

Table 9. Thio-Claisen Rearrangement

R^1	R^2	time[h]	Ratio	Yield (%)
Me	H	5	93:7	63
Me	Me	12	94:6	51
t-Bu	H	24	98:2	40
t-Bu	Me	45	>99:1	50
i-Pr	H	12	94:6	42
i-Pr	Me	12	>99:1	50
c-C$_6$H$_{11}$	H	20	95:5	47
c-C$_6$H$_{11}$	Me	24	>99:1	60
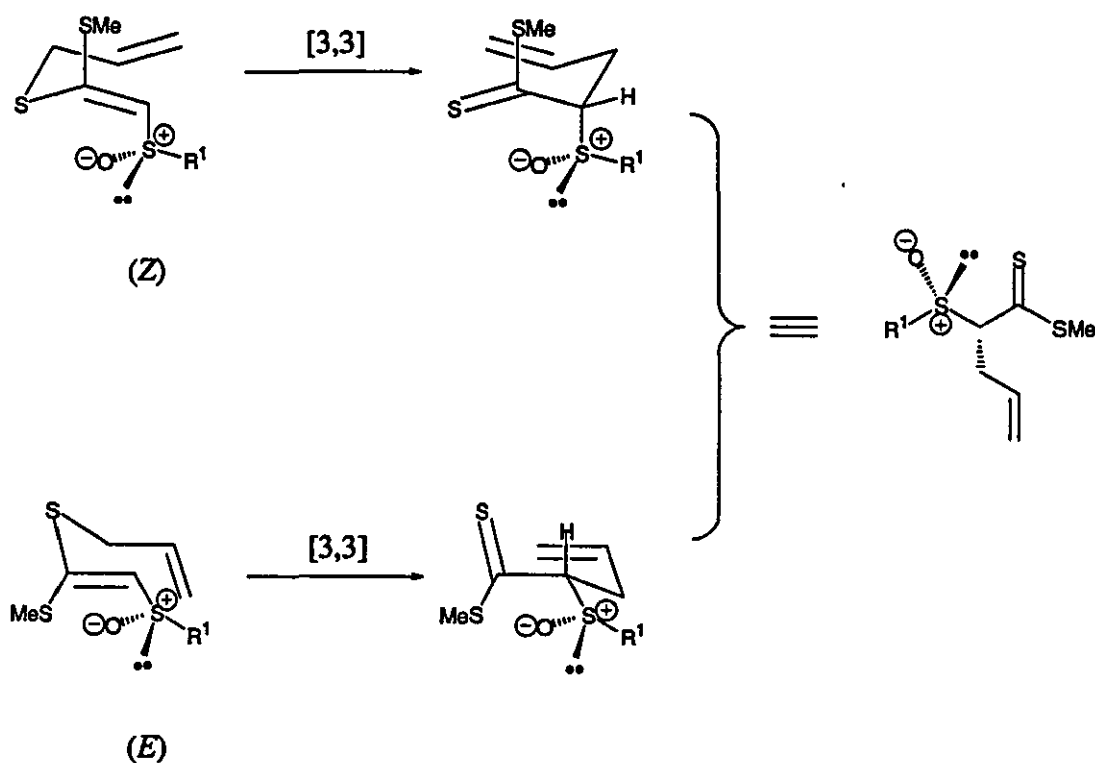
Scheme 67.

Sreekumar[98] employed zeolites to catalyse the asymmetric thio-Claisen rearrangement of simple γ-hydroxy ketene dithioacetals (**Scheme 68**). Simply stirring the substrates in dry hexanes under a nitrogen atmosphere with the zeolites generated single diastereoisomers of the desired products cleanly and in excellent yield. Interestingly the major isomer obtained in the uncatalysed reaction was of opposite stereochemistry to the single isomer obtained when

catalysis was used. Transition state model (98) was proposed to explain this observation: absorption of the dithioacetal inside the channels of the zeolites in such a way that the bulky groups are directed away from the catalytic surface.
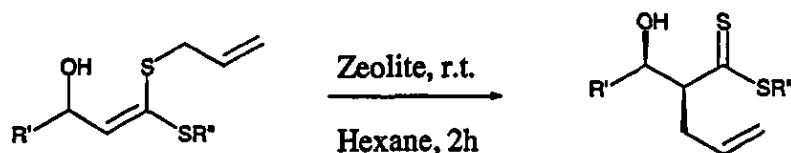
Scheme 68. Zeolite Catalysed Thio-Claisen Rearrangement

(98)
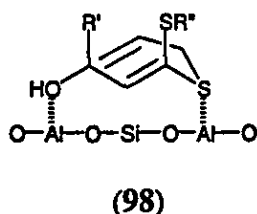
Stereocontrol induced by a hydroxy-substituted adjacent stereocentre was studied by Beslin.[99] Rearrangement of *S*-allylic ketene aminothioacetals was achieved with yields as high as 70% and *syn:anti* ratios of greater than 98:2 in some cases. It was thought that the control was governed by stereoelectronic effects with formation of the C-C bond occurring on the more electron rich face of the ketene acetal that is *syn* to the hydroxy group (Scheme 69).
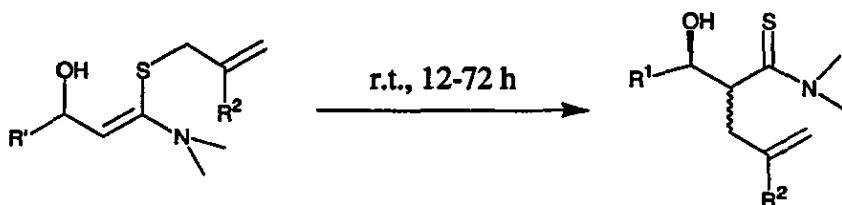
Scheme 69.

An asymmetric synthesis of the sesquiterpene (-)-*trichodiene* was realised by Meyers[100] using the thio-Claisen rearrangement to introduce the two vicinal stereocentres required (**Scheme 70**). An extensive study of solvent conditions was required in order to select the optimum conditions to boost the equilibrium in favour of the product. The rearrangement proceeds *via* an exo (β) face attack of the bicyclic system in a chair-like conformation.

(-)-trichodiene
10 steps, 14% overall yield
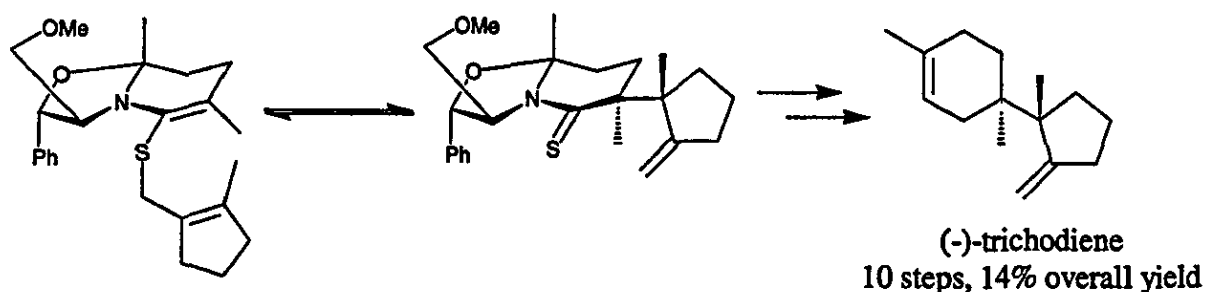
Scheme 70. Generation of Vicinal Stereocentres *via* the Thio-Claisen Rearrangement
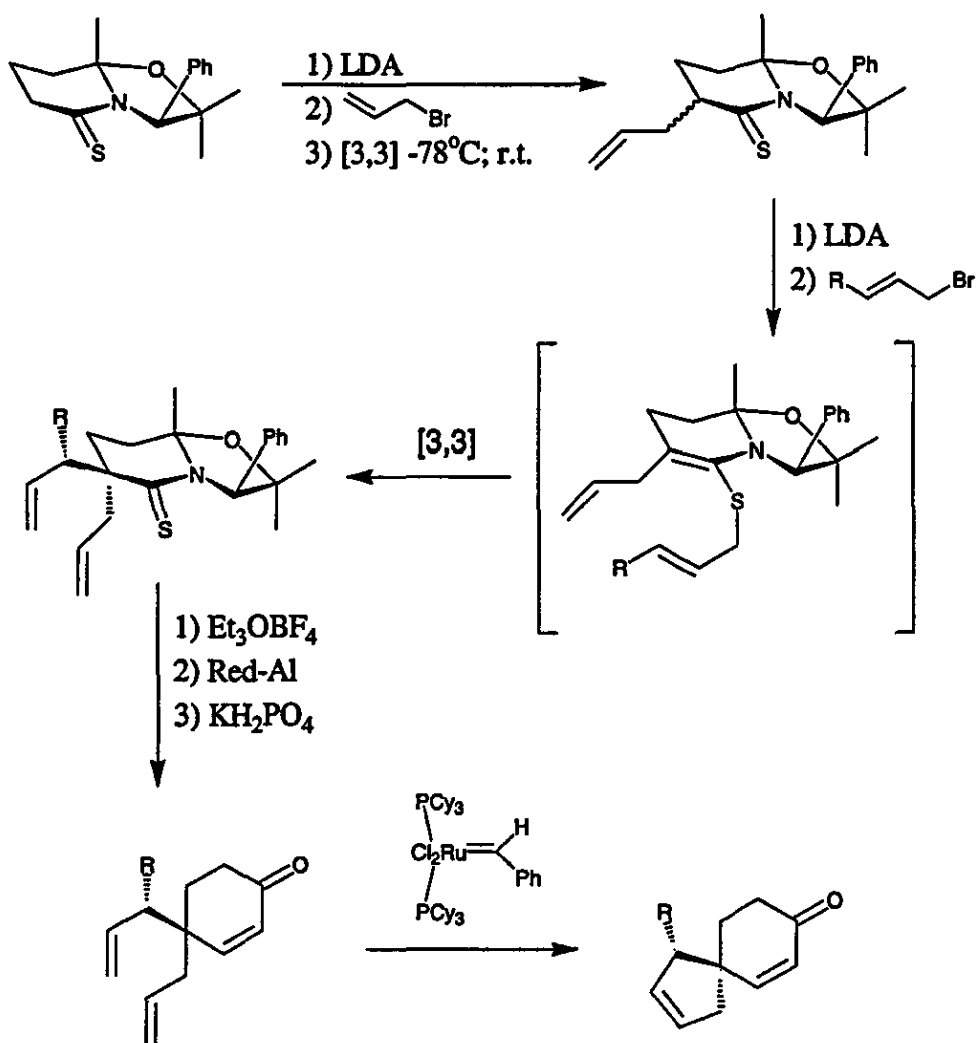
Scheme 71. Synthesis of Chiral Spiro[4.5]decane Systems

An asymmetric route to novel chiral cyclohexenones with spiro-connected cyclopentenes was developed by Meyers[101] following on from the previous work with *N,S*-ketene acetals (Scheme 71). Thio-Claisen rearrangement was utilised to introduce two different allylic

moieties in a diastereoselective fashion and treatment of the rearranged product with Meerwein's reagent generated an intermediate *S*-iminium ion that could be reacted with either a hydride or a carbon nucleophile to generate the corresponding ketoaldehyde or diketone. Aldol condensation and olefin metathesis using Grubbs' catalyst enabled the synthesis of chiral spiro[4.5]decane systems.

Chapter 2

Results and Discussion

Application of β-Aminoalcohol Auxiliaries in the Asymmetric Amino-Cope Rearrangement

2.1 Asymmetric Induction in the Anionic Amino-Cope Rearrangement Controlled by β-Aminoalcohol Auxiliaries

The introduction summarizes work on the amino-Cope rearrangement done by a former colleague, Dr Martin Button.

We believe that the asymmetric amino-Cope rearrangement may have significant advantages over the analogous oxy-Cope rearrangement in terms of asymmetric induction. The oxy-anion substituent in the anionic oxy-Cope rearrangement is reported to have little axial/equatorial preference in the proposed chair-like transition state and thus delivers products with only a moderate level of enantiomeric excess (*e.e.*).[103] Conversely we believe that an amine auxiliary is more likely to hold an equatorial position during rearrangement, due to its increased bulk, and should lead to much enhanced *e.e.*'s[104] (Scheme 72).

Amino-Cope Rearrangement developed by Button[104]

i) *n*-BuLi, THF, Δ

ii) H_3O^+

75% *e.e.*

Oxy-Cope Rearrangement reported by Lee[103]

i) KH, 18-crown-6, THF, Δ

ii) H_3O^+

30% *e.e.*

Scheme 72. Asymmetric Amino-Cope vs. Oxy-Cope Rearrangements
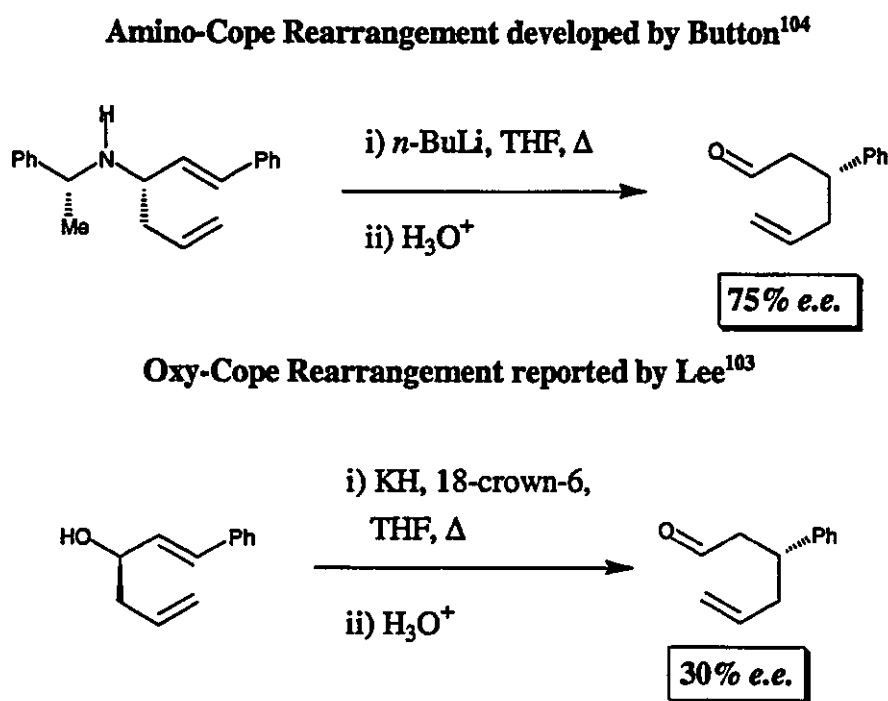
2.1.1 Synthesis of 3-Amino-1,5-Diene Substrates

The diastereoselectivity obtained during synthesis of the chiral amino-diene substrates is of considerable importance to us, as each diastereoisomer is known to lead to the opposite enantiomer of the rearranged product upon amino-Cope rearrangement[104] (Scheme 73).
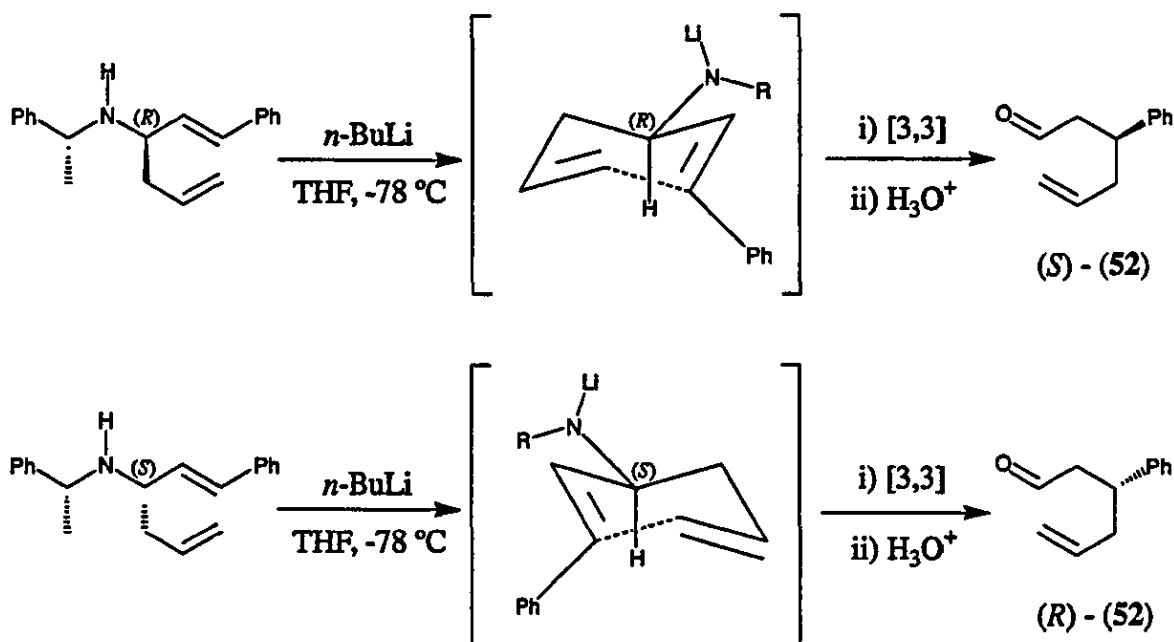
Scheme 73. Rearrangement of Diastereoisomers to Yield Opposite Enantiomers
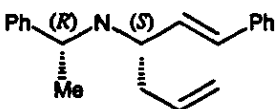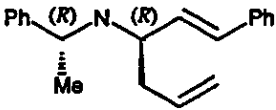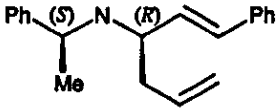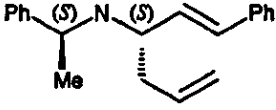
Button performed an extensive literature search of diastereoselective imine allylations[105] and the most suitable method was found to be Grignard addition. Early results using α-methylbenzylamine as the amine component gave poor *d.e.*'s during amino-diene synthesis, but more importantly the product diene diastereoisomers were separable using column chromatography on silica gel.

The results outlined in this section focus on the enhanced asymmetric induction obtained when using β-aminoalcohol-derived substrates and our investigations on expanding the scope of the amino-Cope rearrangement.

2.1.1.1. Preparation of 3-Amino-1,5-Diene Substrates using Cinnamaldehyde

Previous work by Button[105] has shown that by utilising α-methyl benzylamine the four diastereoisomers shown in **Table 10** could be obtained. After anionic amino-Cope rearrangement, and subsequent hydrolysis, aldehyde (52) was obtained with the *e.e.*'s ranging from 27-75%.

Table 10. Asymmetric Anionic Amino-Cope Rearrangement by Button

Substrate	Solvent	Yield / %	*e.e.* / %	Major enantiomer
Ph⌒(R)⌒N⌒(S)⌒⌒Ph, Me	THF	73	75	*R*
Ph⌒(R)⌒N⌒(R)⌒⌒Ph, Me	THF	66	33	*S*
Ph⌒(S)⌒N⌒(R)⌒⌒Ph, Me	THF	81	27	*S*
Ph⌒(S)⌒N⌒(S)⌒⌒Ph, Me	THF	64	41	*R*

It was postulated that an increase in the steric bulk of the amine component might lead to greater enantioselectivity during the amino-Cope rearrangement. This was based on the proposed six-membered transition state model, depicted in **Schemes 73** and **74**, that involves the favoured chair-like conformation, with the amine component occupying a pseudo-equatorial orientation. The absolute stereochemistry of the rearrangement product can be predicted using this model and we therefore believed that by increasing the steric bulk of the chiral auxiliary we would disfavour the competing chair-like transition state, in which the amine sits pseudo-axially shown in **Scheme 74**, and thus increase the enantioselectivity of the reaction.
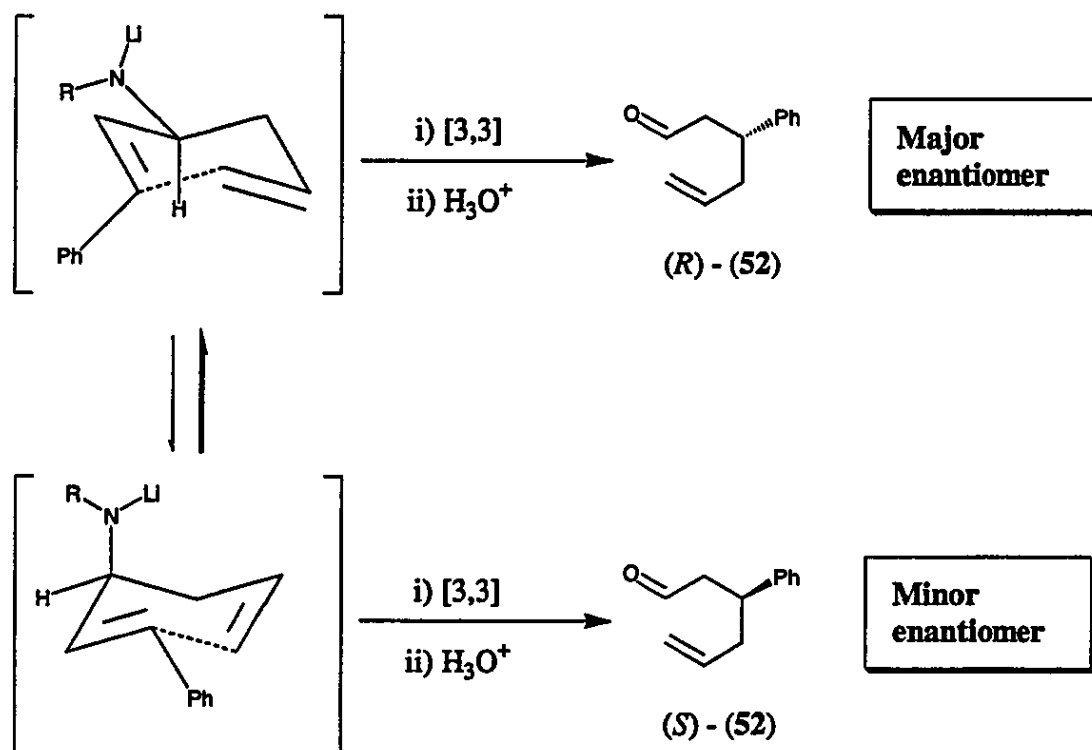
Scheme 74. Competing Transition State Conformations for the Amino-Cope Rearrangement

In order to study the effect of the relative size of the amine substituent on product *e.e.* we needed a reliable method of constructing the required 1,5-diene substrates. Our group has found that the most effective method involves the formation of a stabilised imine using cinnamaldehyde and then subsequent attack of this with a suitable nucleophilic allyl species. In this way we were able to synthesise a number of aminoalcohol substituted dienes for use in the study. The availability of both enantiomers of the aminoalcohols was of great importance to us, as we would be able to synthesise either enantiomer of our final product at will.
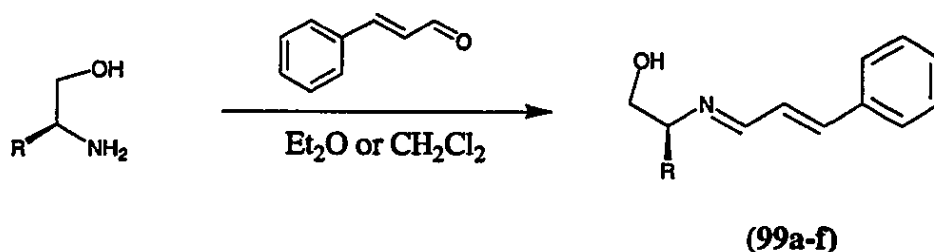
Scheme 75. Synthesis of Imines

Table 11. Imine Preparation

	R	Imine (%)
(a)[a]	(S) i-Pr	99
(b)	(R) i-Pr	99
(c)[a]	(S) t-Bu	99
(d)[a]	(S) i-Bu	86
(e)	(S) Ph	99
(f)	(S) PhCH$_2$	99

[a] Reaction performed by M. Button[105]

Imines (**99a-f**) were prepared by stirring equimolar amounts of the β-aminoalcohol and cinnamaldehyde in dry ether or DCM for up to 1h, monitoring by IR spectroscopy (C=N appears at 1634 cm^{-1}, whilst the C=O stretch of cinnamaldehyde decreases at 1676 cm^{-1}). Removal of the water formed during reaction was necessary and we found that the addition of anhydrous magnesium sulfate during the reaction worked well with the benefit that it acted as a mild Lewis acidic catalyst, thus driving the reaction to completion. The stabilisation afforded by the conjugated aryl unit was important in this work as it enabled us to handle the imines without them degrading during subsequent reactions. It is interesting that other workers[106] have observed that imines such as (**99e**) can exist as the ring closed oxazoline species (**Fig 6**) which may also offer increased stability. In the case of our imines however we observed solely the ring opened tautomer from our analysis of the ^{1}H NMR spectra in deuterated chloroform (C*H*=N ~ δ 8.1). A reason for this may be that our conditions for synthesis are very mild, in contrast Pridgen[106] reports refluxing over magnesium sulfate for 18 hours before work-up which may force further reaction and result in the formation of ring closed products.
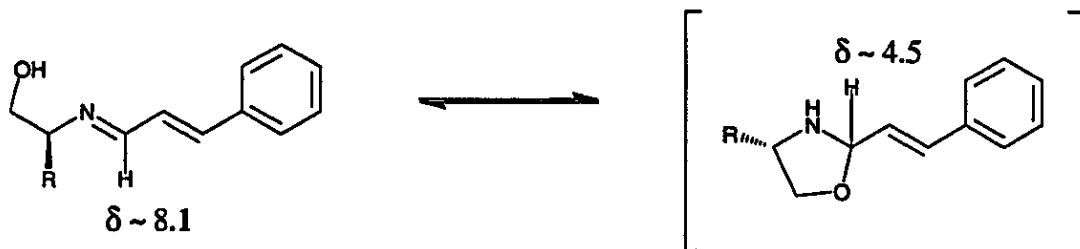
Fig 6. Tautomerisation of Imines Derived from β-Amino Alcohols

With the imines in hand we were able to generate the desired amines (**100a-f**) in good yield by reaction with freshly prepared allyl Grignard reagent in diethyl ether (**Scheme 76, Table 12**).
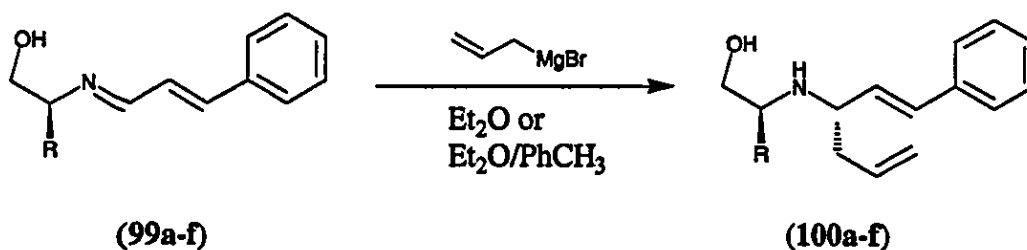
Scheme 76. Reaction of Imines with Allylmagnesium Bromide

Table 12. Results from Grignard Reaction

	R	Amine %	d.e. (%)[b]
(a)[a]	(S) i-Pr	78	97
(b)	(R) i-Pr	66	97
(c)[a]	(S) t-Bu	77	94
(d)[a]	(S) i-Bu	60	92
(e)	(S) Ph	83	96
(f)	(S) PhCH$_2$	71	82[c]

[a] Reaction performed by M. Button, see Ref 105 [b] Determined by 250 MHz ^{1}H NMR spectroscopy

[c] Stereochemistry of major isomer confirmed by single crystal X-ray analysis
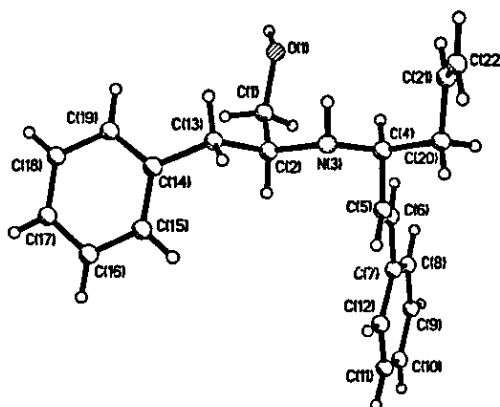
Fig 7. Single Crystal X-Ray of Amine 100f

We encountered some problems with the stability of the allyl Grignard reagent and it had to be used within an hour of preparation or the reaction yield was lowered. The imines were routinely dissolved in dry ether under an inert atmosphere before dropwise addition to the Grignard solution at room temperature. Some difficulty arose when a precipitate formed during the addition, which we believe to be the magnesium salt resulting from deprotonation of the alcohol moiety, and the substrate was rendered inactive. We could overcome this in most cases by using a large dilution or by gently heating the solution until addition was complete. The use of toluene was also beneficial in some instances and did not detract from the stereoselectivity, however we found that if THF was used a dramatic decrease in diastereoselectivity was seen. Faced with these difficulties and intrigued by the effect that solvent choice had on the final diastereoselectivity we decided to investigate the Grignard addition further.

The addition of organometallic species to imines derived from non-racemic β-aminoalcohols and their derivatives is known to be highly diastereoselective, and has been proposed by others to proceed through a chelated transition state (**Scheme 77**).[107] The absolute stereochemistry inherent to the chiral auxiliary then controls the "sense" of stereochemical induction during the imine addition, allowing accurate predictions to be made about the relative stereochemistry of the amine product.[107] The high degree of stereocontrol in this reaction may be attributed to a highly ordered transition state resulting from chelation of the alkoxide and imino nitrogen to the metal atom. A further equivalent of allylmagnesium bromide will attack from the least hindered face of the carbon-nitrogen double bond[108] (**Scheme 77**).

Grignard reagent attacks from below,
least hindered face
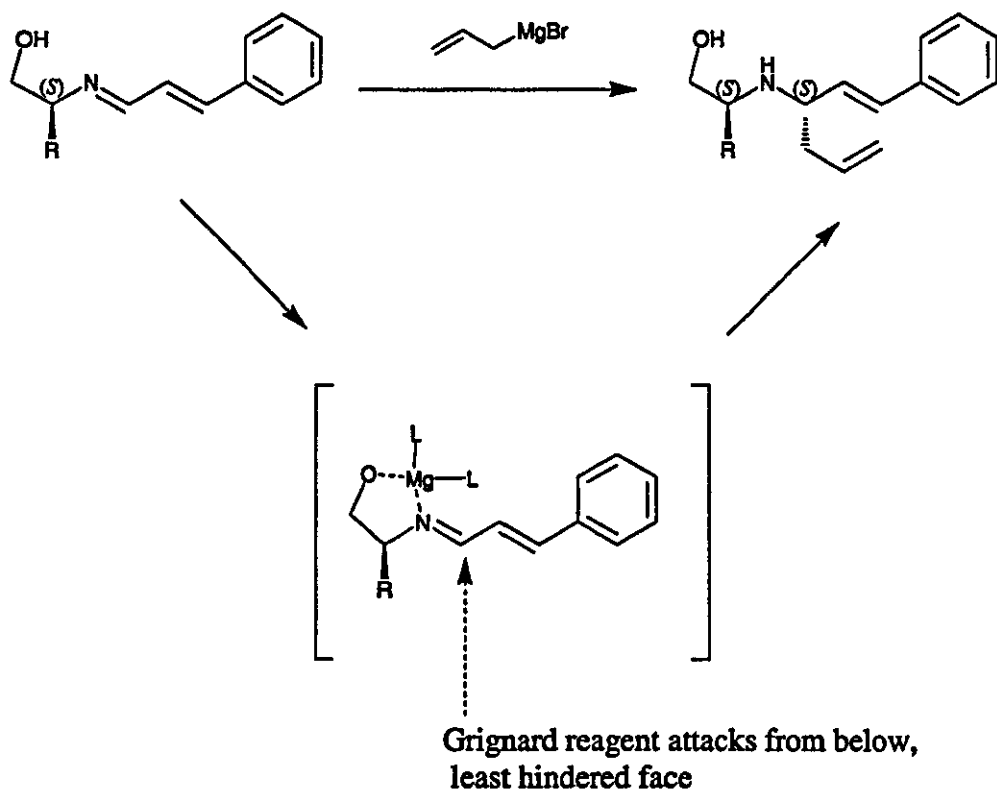
Scheme 77. Stereoselective Grignard Addition to Imines

Further competition also arises in the case of α,β-unsaturated imines: That of 1,2 (direct) *vs.* 1,4 (conjugate) addition. Other research groups have also addressed this[106,109] and the following generalisations have been made for α,β-unsaturated imine substrates containing β-aminoalcohol auxiliaries:

- organolithium, cerium and cuprate reagents undergo 1,2-addition
- Grignard reagents add exclusively in a 1,4-fashion

Our own results clearly contradict these findings as we observe no 1,4-addition products (**Scheme 76, Table 12**). During the allyl Grignard reaction it is reasonable to postulate a six-membered transition state for the addition to our conjugated imines, with magnesium co-ordinating to the imino nitrogen (**Scheme 78**).

6-membered transition state   1,2 addition

8-membered transition state   1,4 addition
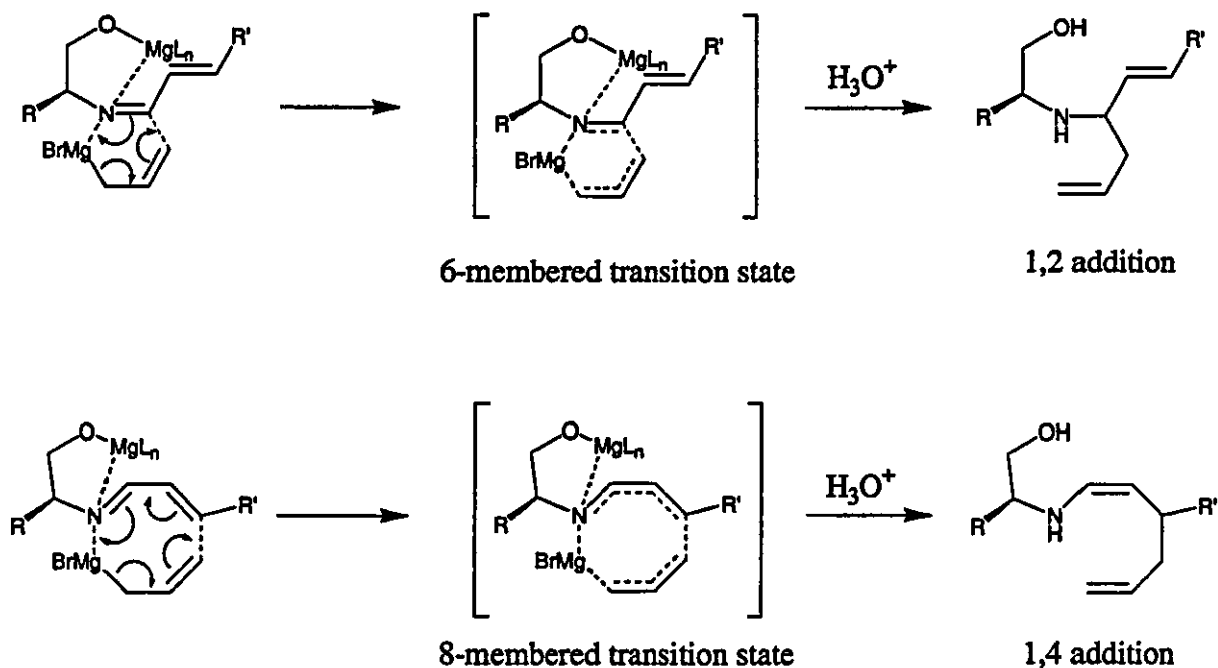
Scheme 78. Allyl Grignard Additions to Conjugated Imines

As shown in **Scheme 78,** for the allyl Grignard to react in a 1,4 fashion by this mechanism it would have to assume the less favoured eight-membered transition state. Our group has also prepared the analogous Grignard reagent from 1-bromo-2-butene shown in **Scheme 79** and we have observed that the reaction is much lower yielding, the major product however is still that arising from the concerted style of addition highlighted in **Scheme 78** above.

Major isomer
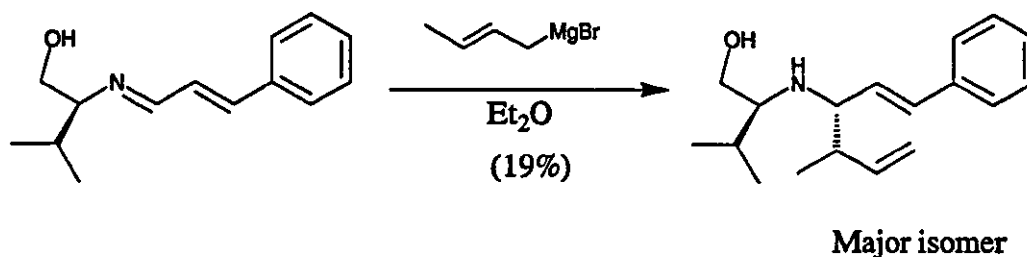
Scheme 79 Substituted Allyl Grignard Reaction[105]

Alkyl and aryl Grignard reagents are not able to react in this way and a six-membered transition state in these cases would lead to the conjugated addition product (**Scheme 80**).

6-membered transition state   1,4 addition
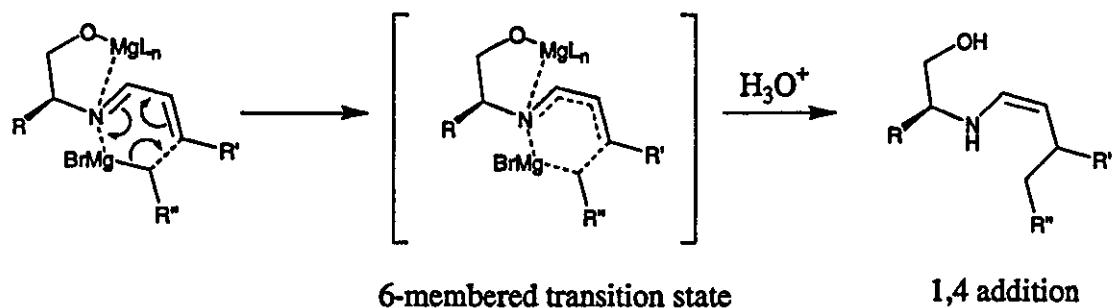
Scheme 80. Alkyl Grignard Addition to Conjugated Imines

Pridgen[106] has indeed observed this and to verify that the same was true with our own substrates we chose to prepare an alkyl Grignard reagent, ethylmagnesium bromide, and react this with one of our imines. We initially attempted the reaction at low temperatures, starting at –78 °C, but no reaction could be seen and the starting material was recovered in all cases (**Scheme 81, Table 13**). It was only when we performed the addition at room temperature followed by reflux of the resulting mixture for 1 hour that we observed any reaction.

(99e)   (101)
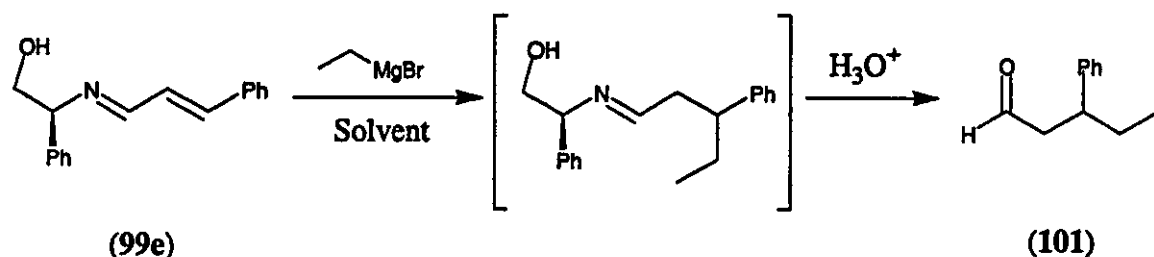
Scheme 81. Alkyl Grignard Addition

Table 13. Addition of Ethylmagnesium Bromide to Imine (99e)

Temp (°C)	Solvent	Result	Yield
-78	THF	no reaction	-
-50	THF	no reaction	-
-45	THF	no reaction	-
-30	Et$_2$O	no reaction	-
-45 to r.t.	THF	no reaction	-
0 to r.t.	Et$_2$O	no reaction	-
0 to Δ	Et$_2$O	*e.e.* 4%	19%[b]
0 to Δ	Et$_2$O	no reaction[a]	-

[a] Grignard preparation using ethyliodide [b] Yield of aldehyde isolated after column chromatography

The crude ^{1}H NMR spectrum indicated the product was that arising from conjugate addition to the imine and subsequent purification of the product using column chromatography on silica gel yielded the γ-substituted aldehyde. The *e.e.* of this aldehyde (measured by derivatisation with ephedrine[110]) was found to be only 4 % which suggests that the chiral centre in the imine is too remote to direct the addition in this case.

Until now we had routinely reacted the imines with a pre-formed Grignard reagent and the use of this had caused problems during the reaction because precipitation occurs if the Grignard addition is not carefully monitored. To overcome this we wondered if we might be able to perform the reaction in one pot thus eliminating the problem of adding the Grignard reagent too fast.

The formation of a Grignard reagent *in situ* is often referred to as the Barbier-type reaction[111] and its application to the allylation of imines was recently reported by Hou.[112] Aldimines could be efficiently allylated using magnesium foil or commercial zinc powder without any further activation (Scheme 82).

M= Mg, Zn (see **Table 14**)
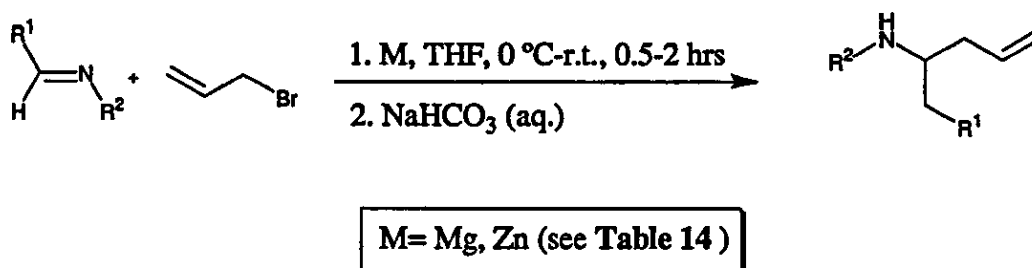
Scheme 82. Barbier-type Grignard Reaction Performed by Hou[112]

The high efficiency indicated that as soon as the Grignard reagents were generated they were instantaneously trapped by the electrophilic C=N bond[113] and the very low concentration of the allylic anion meant that the side reactions of imines (Stork[114] reports enolisation occurs rather than addition to the C=N bond in some cases, **Figure 8**) as well as the coupling and dimerization reactions involved in the preparation of allylmagnesium bromide reagents[115] were avoided.
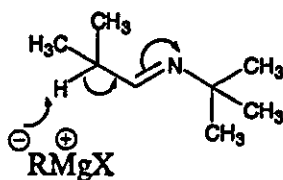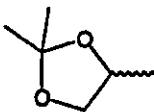
Figure 8. Enolisation of Imines Reported by Stork[114]

Excellent yields were obtained in all cases although the diastereoselectivity observed with the chiral imines was disappointingly low as shown in **Table 14.**

Table 14. Examples of the Barbier-type Grignard Reaction with Aldimines

Entry	R^1	R^2	Yield[a,b] Mg	Zn
1	Ph	Ph	99	97
2	Ph	Bn	92	95
3	p-ClC$_6$H$_4$	Bn	98	98
4	trans-PhCH=CH	Bn	82	91
5	2-Furyl	Bn	90	93
6		Ph	86	90
7	i-Butyl	Bn	85	92
8	Ph	(S)-PhCH(Me)	84 (1/1)	86 (1/1)
9	p-MeOC$_6$H$_4$	(S)-PhCH(Me)	93 (1/1.5)	88 (1/1)
10	o-MeOC$_6$H$_4$	(R)-PhCH(Me)	85 (2.5/1)	84 (2/1)

[a] Isolated yields. [b] Ratios in parentheses represent the diastereoisomeric ratios obtained by 300 MHz ^{1}H-NMR spectroscopy

It was interesting to note that when using a cinnamaldehyde derived imine (Entry 4) Hou *et al* observed, like ourselves, 1,2 addition although no reference to this was made in the paper. The high yields obtained prompted us to try this method with our β-aminoalcohol derived imines, in particular **(99f)** which was synthesised using phenylalaninol **(Scheme 83).**

(99f) → **(100f)**, Major isomer

Mg, ⟍⟍Br
Solvent, Temperature
(see **Table 15**)
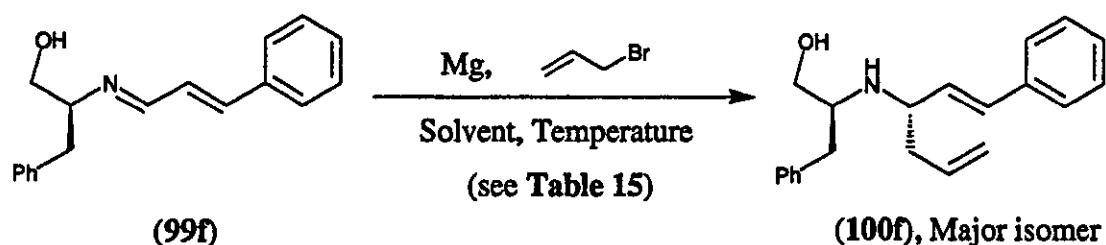
Scheme 83. Barbier-type Grignard Reaction on Phenylalaninol Substrate

The initial reaction was tried following conditions similar to those reported by Hou, stirring the dried imine in anhydrous THF with 1.2 equivalents of magnesium foil and 1.1 equivalents of allylbromide at 0 °C. There appeared to be no initial reaction however after the solution had warmed to room temperature. Over 90 minutes the colour of the reaction mixture darkened and the magnesium foil had been consumed. At this point the reaction was quenched and worked up in the usual manner to yield clean diene with excellent recovery but unfortunately the *d.e.* measured by ^{1}H NMR spectroscopy was only 57% (*c.f.* 82% when using the standard Grignard conditions). We then decided to examine other solvents and temperatures, the results of which are shown in **Table 15**.

Table 15. Effect of Solvent and Temperature on the Barbier-type Grignard Reaction

Solvent	Temperature (°C)	Time	*d.e.* (%)[a]	Yield[b]
THF	0 to r.t.	90 mins	57	70 %
Et$_2$O	0 to r.t.	18 h	81	50 % conversion[c]
THF	-78 to r.t.	90 mins	-	89 %[c]
Et$_2$O	-78 to r.t.	5 h	82	80 % conversion[c]
Et$_2$O/THF	0	90 mins	58	99 %[d]
THF	-40 to r.t.	18 h	75	<5 % conversion[c]
THF	0 to r.t.	18 h	-	87 %
1:1 PhCH$_3$/Et$_2$O	-78 to r.t.	3 h	78	99 %[d]
4:1 PhCH$_3$/Et$_2$O	r.t.	18 h	81	99 %[d]
DME	r.t.	18 h	10	70 % reaction

[a] Diastereoselectivity measured from crude 250 MHz ^{1}H NMR. [b] Purified yield unless otherwise stated.

[c] Estimated conversion from crude 250 MHz ^{1}H NMR. [d] Crude product mixture contained no starting material.

We found that the choice of solvent is crucial when trying to obtain the best diastereoselectivity from the Barbier-type reaction. Tetrahydrofuran proved to give a low *d.e.* even when the temperature was lowered during the initial reaction, although the worst solvent appeared to be dimethoxyethane giving just 10% diastereomeric excess. The use of diethyl ether seems to give consistently high diastereoselectivities but when used in conjunction with THF the *d.e.* is drastically reduced. Solubility of the imine was improved by adding toluene in varying amounts and this did not seem to detract from the selectivity of the reaction.

There is clearly a large effect on diastereoselectivity in this particular reaction when changing between the various solvents we have used. It is apparent from the work of others[116] that at low concentrations Grignard reagents exist in solution as monomers and there is evidence to suggest that the preferred structure is of the type RMgX·2OR'$_2$, with solvent stabilisation being of great importance. As shown in **Scheme 78** the diastereoselectivity induced during Grignard addition relies on the formation of a 5-membered chelate. Similar chelated structures have been proposed by Fallis[117] to be highly solvent dependent, with THF proving to be a poor solvent choice in such cases. It could be argued then that the poor diastereoselectivity we observed when using THF may arise from a disruption to the ordered transition state, although further study is required in this area.

Confirmation of the predicted stereochemistry was achieved when we prepared the diene using phenylalaninol as the chiral auxiliary. A crystalline solid was obtained from which we were able to grow crystals for single crystal X-ray analysis. Until now the relative stereochemistry of the diene had been postulated based on the work of Yamamoto[118] and our own previous findings.[105] Interpretation of the X-ray data (see **Appendix**) confirmed that the allyl nucleophile does indeed attack the imine from the less hindered face producing the expected '*anti*' stereochemistry as depicted in the preceding schemes.

2.1.1.2. Preparation of Amino-Diene Substrates using Furfural

So far we had only begun to examine the sigmatropic rearrangement of dienes which were not part of an aromatic framework. It is well known that during the Claisen rearrangement electrons from an aromatic system can participate[19] and during the Fischer-Indole synthesis

there is also an initial loss of aromaticity.[119a] It is worth noting however that in both these examples the aromaticity is regained at some stage after the initial rearrangement.

Furfural is a readily available aromatic aldehyde and we found it reacted well with valinol to produce a stable chiral imine in a similar manner to those made using cinnamaldehyde (Scheme 84).
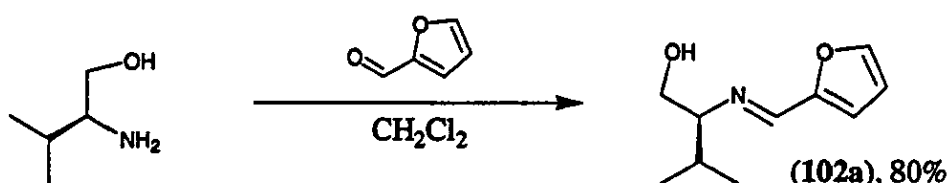
Scheme 84. Preparation of Furan Imine

The furan ring, like other heteroarenes, is able to take part in a wide range of electrophilic reactions[119b] and if incorporated into our final rearrangement product it could be used to further derivatise the substrate. For example furans are known to hydrolyse easily under mildly acidic conditions to produce a diketone which can be elaborated further if required (Scheme 85).[120]
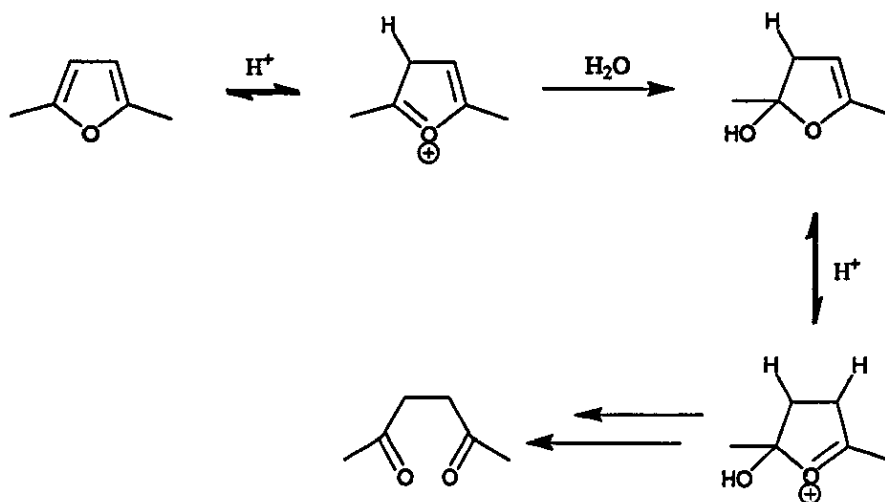
Scheme 85. Hydrolysis of Furan Ring[120]

Formation of the diene was done in a similar manner to before - using allylmagnesium bromide in diethyl ether to furnish the amine (103a) with exclusive *anti* stereochemistry (Scheme 86). In this series of experiments we encountered no problems with solubility and were able to work with a more concentrated imine solution which greatly simplified working under anhydrous conditions. During the course of other work (mentioned in **Section 2.2**) we were using allyl lithium and we found that this was equally effective for obtaining the diene, although on a much smaller scale because the reagent was more difficult to prepare in our hands.
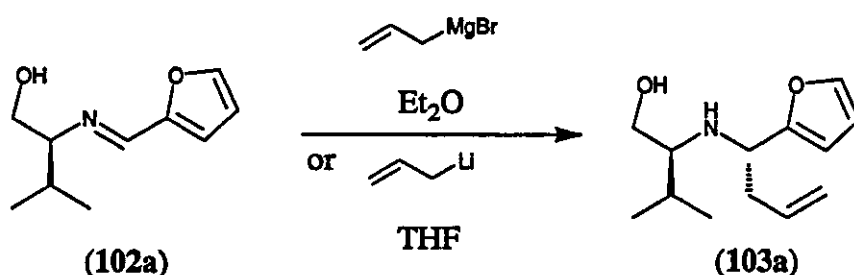
Scheme 86. Allyl Additions to Furan Imine

2.1.1.3 Preparation of Amino-Diene Substrates using 3-(2-Furyl)-acrolein

The construction of dienes containing different functional groups at the double bond termini has been one of the goals of this ongoing project. By using 3-(2-Furyl)-acrolein we were able to generate an imine analogous to those initially prepared using cinnamaldehyde, in that there was still some considerable stabilisation through conjugation to the aromatic ring. We chose to use valinol as the chiral aminoalcohol substituent because it was readily available and easy to handle following earlier work. The imine was easily prepared by stirring an equimolar amount of valinol and 3-(2-Furyl)-acrolein in dichloromethane at room temperature (102b, Scheme 87). At the same time we were able to use 5-nitro-2-furan acrolein to prepare a similar imine and we hoped to study the effects of the electron withdrawing group on the amino-Cope rearrangement (102c, Scheme 87)
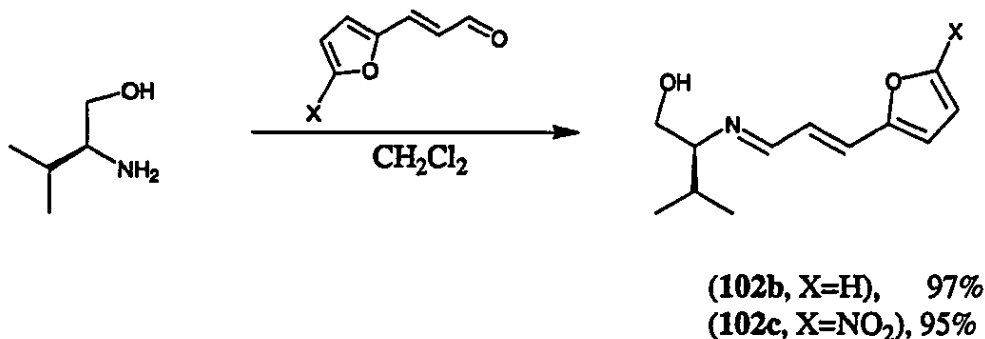
Scheme 87. Preparation of Imines from 3-(2-Furyl)-acrolein Derivatives

Imine (102b) reacted in the same manner as its phenyl substituted analogue and as shown in Scheme 88 we obtained the diene (103b) almost exclusively as a single diastereoisomer (*d.e.* > 95%). Problems were encountered when we tried to use the same conditions with the nitrofuran imine (102c) because it was only sparingly soluble in diethyl ether. In an attempt to overcome this hurdle we tried a number of other anhydrous solvents. Toluene initially showed some promise but still only dissolved about 10% of the reaction material. Tetrahydrofuran was no better than diethyl ether so we finally attempted to use dimethoxyethane. Although we were able to dissolve the imine in this solvent the Grignard reaction was unsuccessful yielding only starting material (Scheme 88). The failure of this reaction was disappointing as it would have been interesting to compare the reactivities of the two dienes. It is possible that the DME was not fully anhydrous at the time of use and this may have resulting in the Grignard reagent being quenched before it had chance to react with the imine.
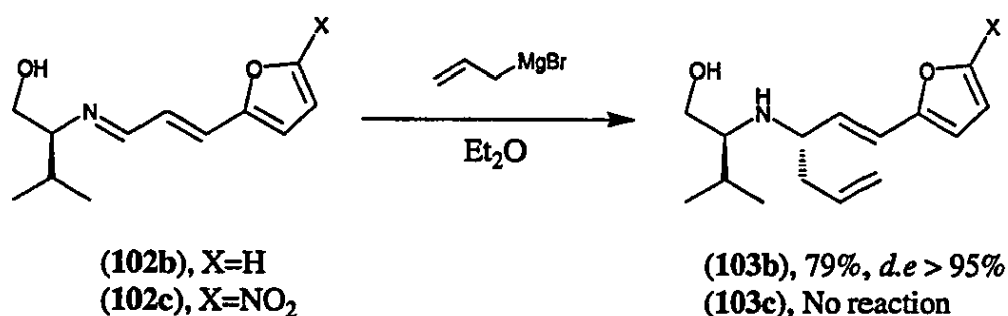
Scheme 88. Grignard Reactions on Furanacrolein Imines

2.1.1.4 Preparation of Amino-Diene Substrates Using Crotonaldehyde

To further expand the range of substrates used for the asymmetric amino-Cope rearrangement we sought to use a non-aromatic aldehyde and the most obvious choice was crotonaldehyde. The diene had been prepared by our group in the past[105] but had received little attention so it was important to investigate it further. From experience we knew that the imine was unstable and could not be isolated – a measure of the stability imparted by aromatic conjugation in the preceding examples. However, we could prepare the imine in diethyl ether and after a brief work-up this could be reacted with allylmagnesium bromide in the same manner as our other imines to form the desired amine (104) in reasonable yield (Scheme 89).

(104)
79%, d.e. >95%
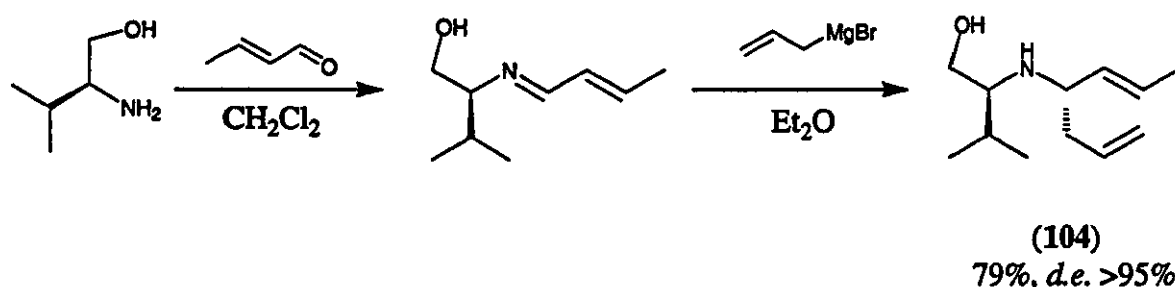
Scheme 89. Imine and Amine Preparation from Crotonaldehyde

Purification of amine (104) on silica gel was difficult and we often saw some decomposition to crotonaldehyde (seen in the IR spectra). For this reason rapid columning was required and as a result the isolated yield was lowered due to several contaminated fractions being discarded. The aliphatic nature of the crotonyl diene was hoped to afford increased solubility in the less polar solvents and we wished to study this aspect in light of some recent work by Macdonald,[121] described in **Section 2.2.4.**

2.2. Amino-Cope Rearrangements of Novel Amino-Diene Substrates

2.2.1. Anionic Amino-Cope Rearrangement of Cinnamaldehyde Substrates

The successful rearrangements of α-methylbenzylamine substrates performed by Button[104,105] were used as a basis for investigation of the aminoalcohol substrates. A study of the most efficient bases was also performed along with the use of different solvents and it was found that using tetrahydrofuran with 2.5 equivalents of base was most effective at this stage. Over one equivalent of base was required since the substrate contains a hydroxy group which is also deprotonated during the reaction. As shown in **Scheme 90** rearrangement was effected by dissolving the aminoalcohol-substituted diene in anhydrous THF and cooling to –78 °C before dropwise addition of the base and reflux of the resulting solution. Unexpectedly the rearrangement product appears to be formed as the oxazolidine (**105**) resulting from ring closure of the hydroxy group onto the intermediate enamine/imine. Purification of the crude product on silica gel hydrolysed the heterocycle yielding the aldehyde (**52**) in moderate to good yield as seen in **Table 15**.
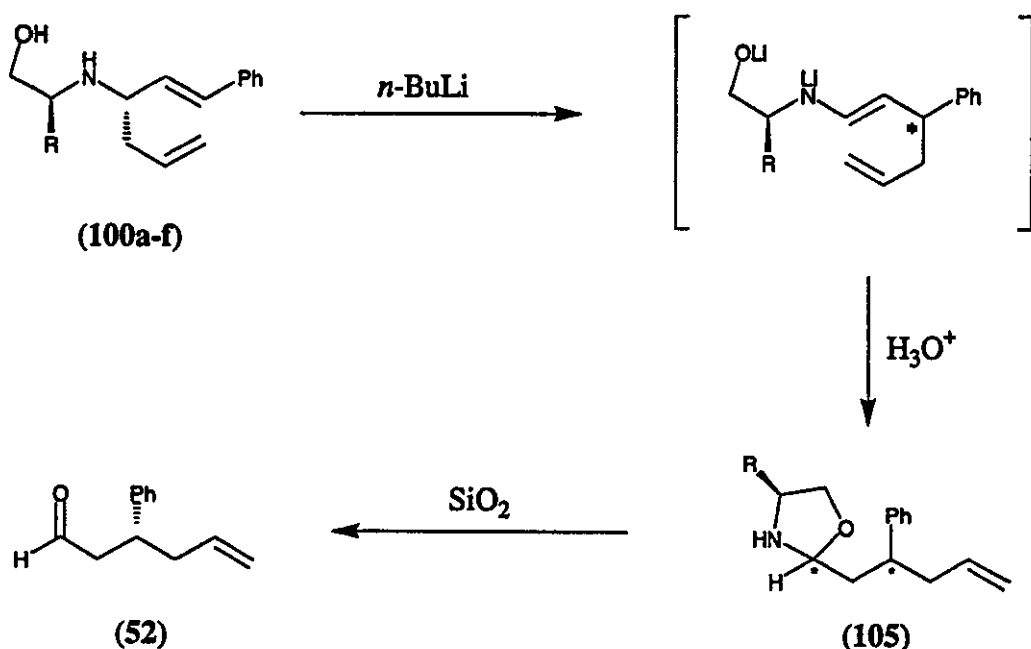
Scheme 90. Anionic Amino-Cope Rearrangement of β-Aminoalcohol Substituted Dienes

Measurement of the enantiomeric excess was achieved following the procedure described by Agami[110] which involves stirring the aldehyde in dichloromethane with (1R, 2S)-ephedrine and analysis of the diastereomeric oxazolidines formed by ^{1}H NMR spectroscopy. In general the enantiomeric excesses were good, ranging from 71-94%, the highest resulting from the use of phenylalaninol as an auxiliary (Table 16).

Table 16. Anionic Amino Cope Rearrangement of Dienes (100a-f)

	R	Aldehyde (%)	e.e. (%)
(a)[a]	(S) i-Pr	60	84
(b)	(R) i-Pr	54	84
(c)[a]	(S) t-Bu	53	88
(d)[a]	(S) i-Bu	57	71
(e)	(S) Ph	61	83
(f)	(S) PhCH$_2$	65	94

[a] Reaction performed by M. Button, see Ref 105

After further work by Button[105] using norephedrine it was revealed that β-substitution is most important in affecting the asymmetry of the rearrangement. Rearrangement of substrates derived from (R, S) and (S, R) ephedrine gave low e.e.'s of 38 and 39% respectively (Scheme 91) despite containing a bulky phenyl group in the α-position.
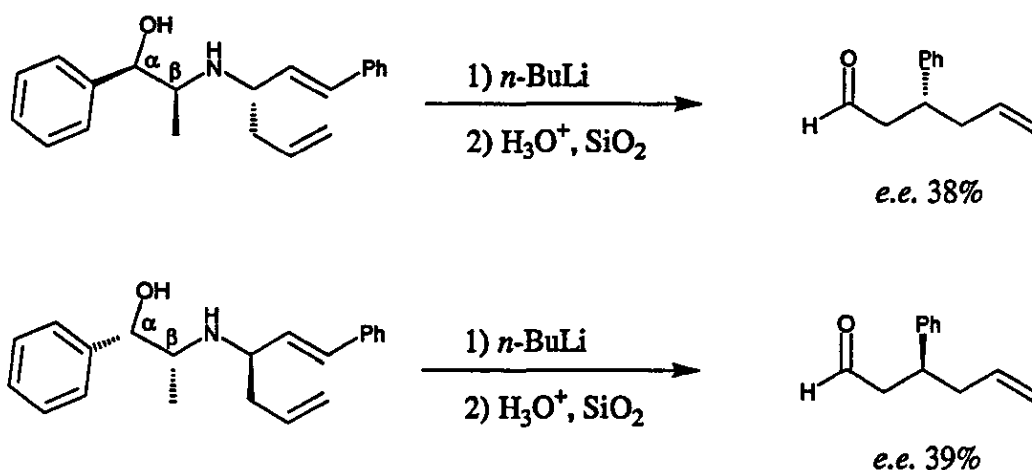
Scheme 91. Rearrangement of Norephedrine Derived Substrates[105]

These two results fit well with the observations of Normant[122] and Berlan[123] who found that during conjugate organometallic addition to ephedrine derived oxazolidines the diastereoselectivity obtained was only 40% (Scheme 92).
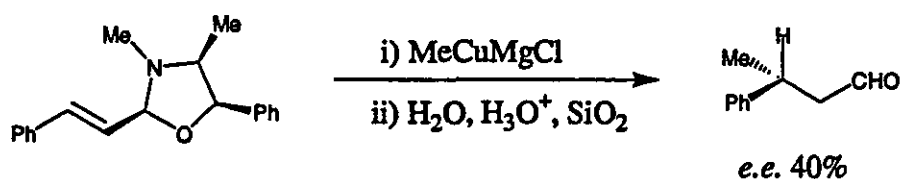
Scheme 92. Organometallic Addition to Ephedrine Derived Oxazolidines[123]

The stereoselectivity observed in both cases would suggest that the directing effect of α-substituents, whether it involves an external nucleophile or a 'concerted' attack by the allyl group during Cope rearrangement, is limited. It follows then that a substituent in the β-position with more steric bulk than a simple methyl group might induce greater stereoselectivity and indeed we have observed this in the case of the amino-Cope rearrangement of our substrates (Scheme 93).

where R =

| *e.e.* (%) = | 71 | 83 | 84 | 88 | 94 |

increase in enantioselectivity
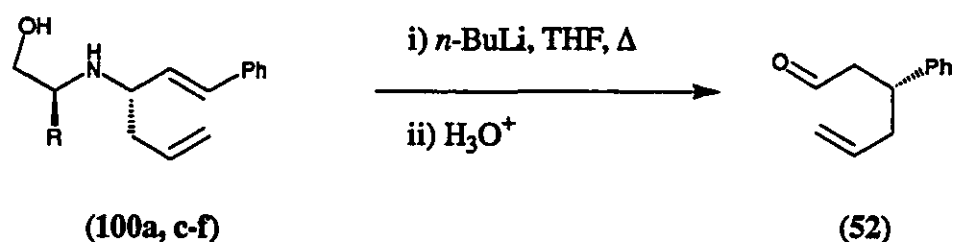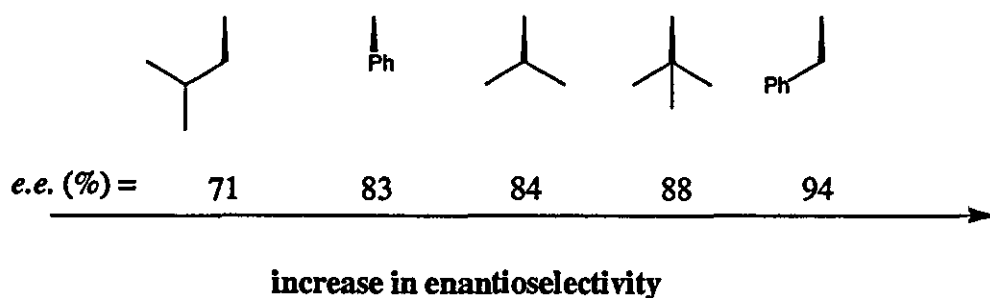
Scheme 93. Trend of Increasing Enantiomeric Excess with Increasing Steric Bulk

Assuming a six-membered transition state (**Scheme 73 and 74**) the phenylalaninol result fits into a trend that the increase in steric bulk leads to progressively higher *e.e.*'s as shown in **Scheme 93**. The presence of a 5-membered chelate is also thought to be responsible for the relative increase in stereoselectivity seen with this range of chiral auxiliaries[107a] – effectively increasing the bulk of the amine component and forcing the diene to react with the amine substituent occupying a pseudo-equatorial orientation (**Figure 9**).
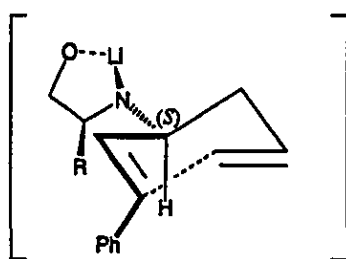
Figure 9. Proposed 5-Membered Chelate[107a,124]

Around the time we obtained these results, a report by Meyers and Houk[125] appeared in the literature aimed at examining the amino-Cope rearrangement and comparing it with the more developed oxy-Cope rearrangement. The mechanism of the oxy-Cope rearrangement is now widely considered to be concerted,[108] however the amino-Cope mechanism has yet to be fully investigated. Meyers' group prepared five diene systems (**106-110, Figure 10**) and subjected them to conditions similar to our own. They found that none of the compounds underwent rearrangement, instead giving (in one case) a dissociated / recombined addition product and in all other experiments only recovered starting materials. The full results are given in **Table 17.**

(106)   (107)

(108)   (109)   (110)
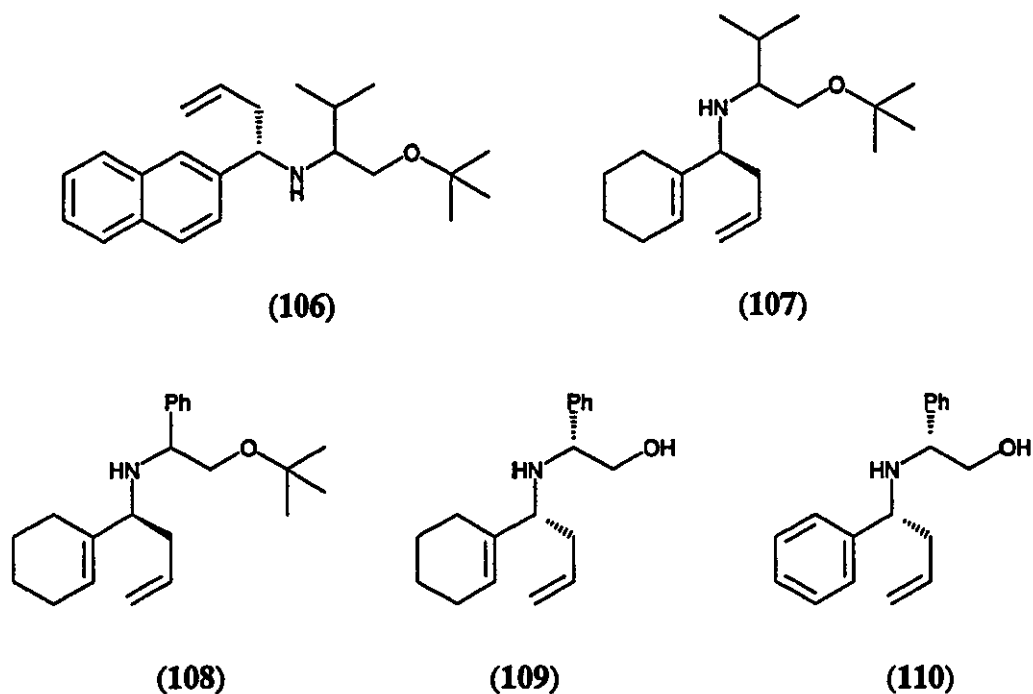
Figure 10. Diene Systems Synthesised by Meyers *et al*

Table 17 Results of the Amino-Cope Rearrangement Obtained by Meyers[125]

Amine	Conditions	Results
(106)	KH / toluene, Δ overnight,	no reaction
	MeI quench, KH/DMF, rt, H_3O^+	deallylated imine
(107)	KH / toluene, rt overnight,	no reaction
	n-BuLi / THF –78 °C to 0 °C	butyl addition product[a]
(108)	KH / toluene, rt to Δ	no reaction
	n-BuLi / THF –78 °C to rt	deallylated product
(109)	KH / toluene, rt to Δ,	no reaction
	n-BuLi / THF –78 °C to rt	decomposition
(110)	KH / toluene, rt to Δ,	no reaction
	n-BuLi / THF -78° C to rt	no reaction

[a] Addition of *n*-BuLi to the C=N bond of 'dissociated' (107) as determined by ^{1}H and ^{13}C NMR

Bond dissociation energies were calculated for the anionic amino-Cope rearrangement and compared with those of the oxy-Cope rearrangement. From these calculations they proposed

that the amino-Cope mechanism was in fact stepwise, proceeding *via* deallylation and subsequent conjugate addition at the double bond terminus (Figure 11). The relevant anionic oxy-Cope mechanism is included in **Figure 12** for comparison and shows the stationary points found. This reaction proceeds *via* a concerted pathway, with an activation energy of 9.9 kcal/mol and is exothermic overall generating 19.1 kcal/mol. An intrinsic reaction coordinate calculation indicates no intermediates and the dissociative transition structure occurs quite early. The anionic amino-Cope substrate has an unexpectedly different energy surface (Figure 11), and proceeds *via* a stepwise mechanism. The initial barrier to the reaction is 7.4 kcal/mol and leads to intermediate (111), a complex of allyl anion and acrolein imine. This ion complex then recombines to form the rearrangement product in an exothermic reaction, liberating 21.1 kcal/mol.
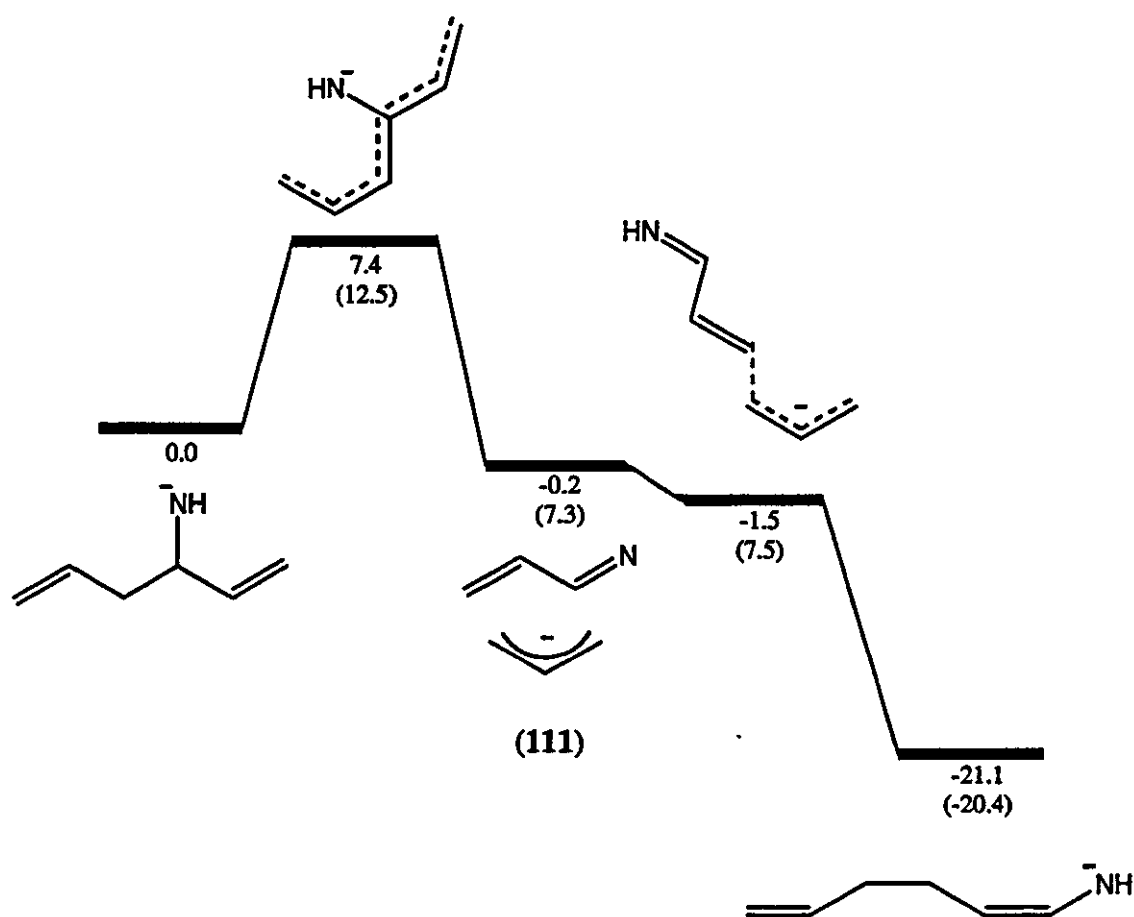
Figure 11. Proposed Dissociation During the Anionic Amino-Cope Rearrangement[125]

(106)

Too hindered for conjugate
attack of allyl fragment
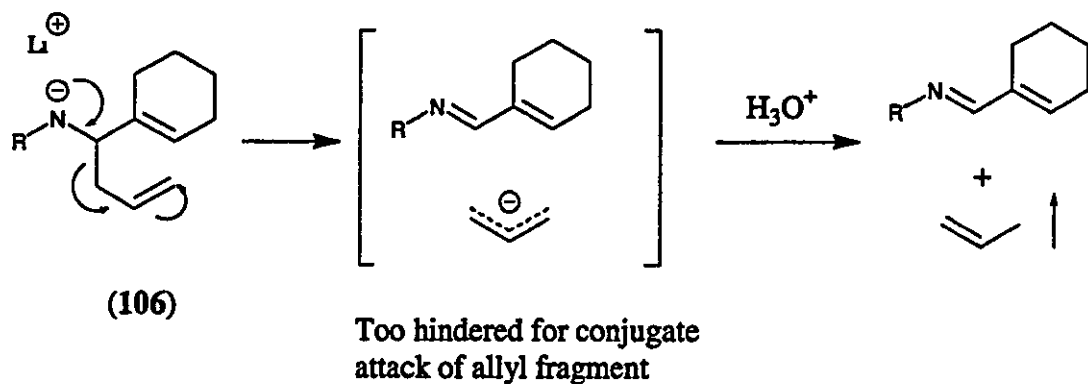
Scheme 94. Mechanism Resulting in Deallylation of Diene (106)
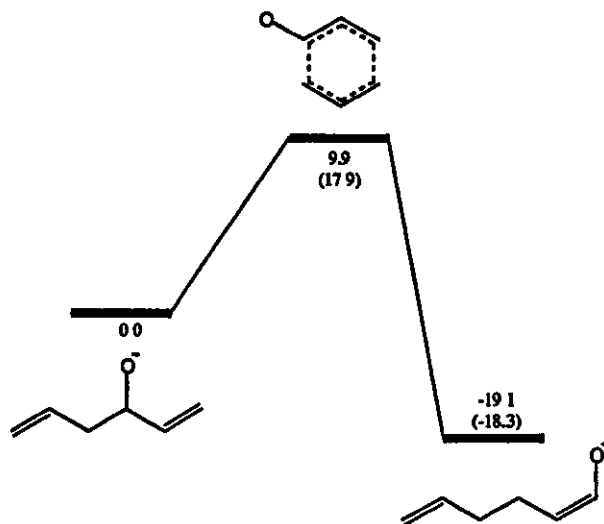
**Figure 12. Concerted Mechanism of the Oxy-Cope Rearrangement,[125] energies in kcal /
mol are given in parentheses**

Meyers and Houk suggested that in solution the intermediate (111) would be substantially
stabilised and dissociated, since it is an allyl anion weakly bonded to acrolein imine.
Therefore they concluded the anionic amino-Cope rearrangement proceeds *via* a stepwise
pathway involving dissociation. Their limited results seem to follow this proposition since
they saw no rearrangement, only fragmentation and trapping of the intermediate with *n*-butyl
anions. In contrast, our own results did not support this, since we observed only
rearrangement products with no evidence of *n*-butyl inclusion in any of the cases. It is still
possible however that the mechanism proceeds *via* homolytic or heterolytic cleavage of the
diene followed by recombination. During our own studies we would not be able to verify

this because the allyl fragment is symmetrical and would lead to the same product *via* either mechanism (**Scheme 95**).
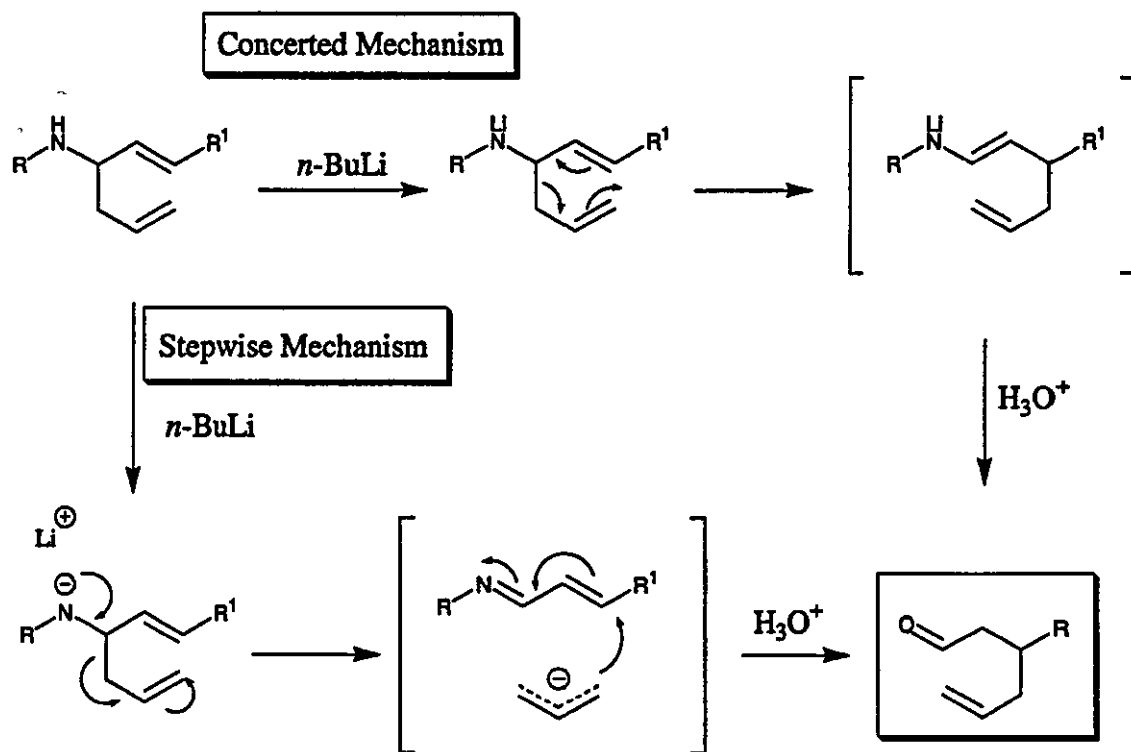
Scheme 95. Possible Mechanisms for the Anionic Amino-Cope Rearrangement

Recent results from the groups of MacDonald[121] and Allin[126] suggest that the findings of Meyers and Houk may be a truer representation of the mechanism with certain substrates under particular reaction conditions. MacDonald has reported seeing evidence of products resulting from a formal [1,3] sigmatropic shift in his studies (**Section 2.2.4.**) and we have also observed some cross-over when rearranging diene (**112**) under our usual conditions (**Scheme 96**).
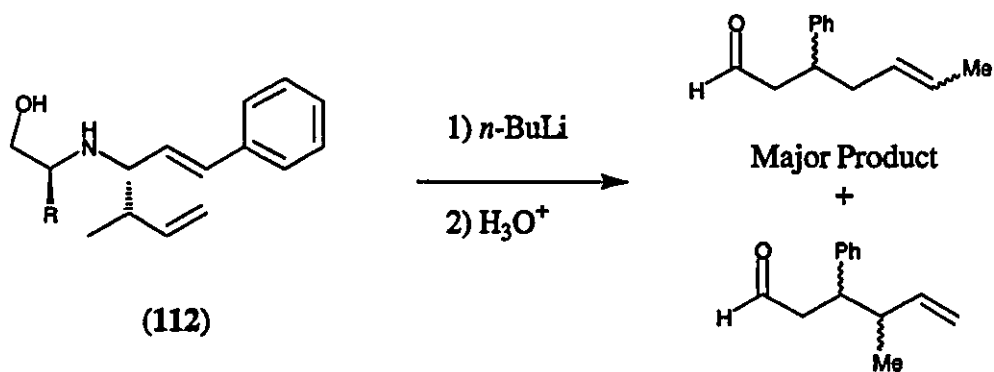
Scheme 96. Rearrangement of Diene (112) Showing Some Evidence of Dissociation

The suggestion that the anionic amino-Cope rearrangement may proceed *via* deallylation followed by conjugate attack of the liberated allyl fragment prompted us to investigate the addition of allyllithium to our imine precursors. Our first hurdle was the formation of allyllithium since there were few synthetic reports that relied on easily obtainable reagents [127] and it was not commercially available. We first attempted to use lithium metal and allylphenylether[127c] but the conversion was low and there seemed to be a large excess of phenol produced which could not easily be removed (**Scheme 97**).

Poor recovery Present in crude ^{1}H NMR
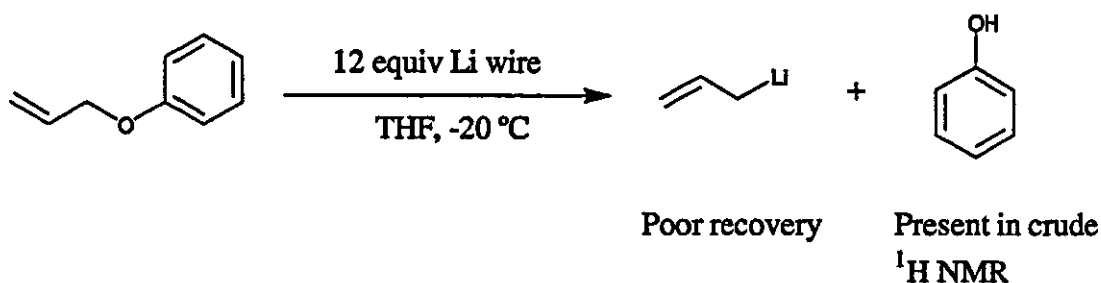
Scheme 97. Allylithium Preparation from Allylphenylether[127c]

A more viable method involved using phenyllithium and allyltriphenyl tin[127b] which produced the insoluble tetraphenyl tin as a by-product (**Scheme 98**).
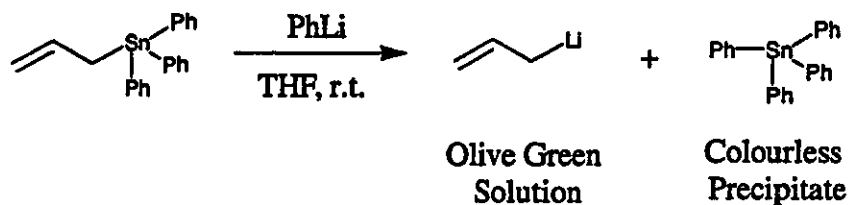
Scheme 98. Use of Allyltriphenyltin[127b]

Allyltriphenyltin was dissolved in anhydrous THF and stirred at room temperature whilst a solution of phenyllithium was added dropwise. The resulting characteristic olive green allyllithium solution was cooled to −78 °C before addition of a solution of imine (99e) in anhydrous THF. Stirring was continued at this temperature for 4 hours before warming to room temperature and refluxing for a further 2 hours. Work-up revealed that the major product was similar to the oxazolidine that we obtain from the amino-Cope rearrangement and after purification by column chromatography on silica gel aldehyde (52) was liberated (Scheme 99).

(99e)

(105e)

Major product

SiO₂

e.e. 27%

(52)
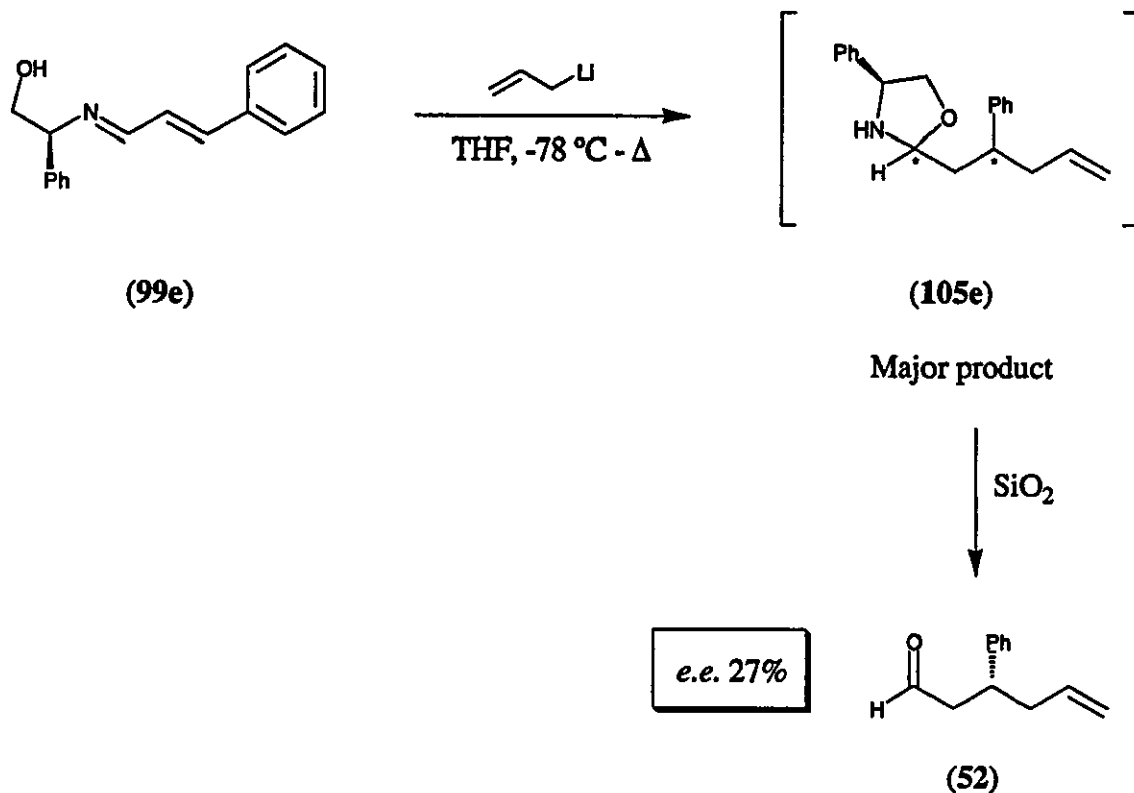
Scheme 99. Allyllithium Addition to Conjugated Imine (99e)

Derivatisation with ephedrine revealed that the *e.e.* was only 27 %, much lower than that obtained after amino-Cope rearrangement of the substrate containing the same chiral auxilliary.

We can view this result in one of two ways (**Scheme 100**) - either the initially formed product is an amino-diene with moderate diastereoselectivity (crude ^{1}H NMR spectroscopy indicates that some 1,2 addition occurs resulting in the diene) which then undergoes tandem amino-Cope rearrangement after deprotonation with either allyllithium or excess phenyllithium, *or* the major product is formed from 1,4-addition to the imine with some remote stereoselectivity induced by the aminoalcohol auxiliary.
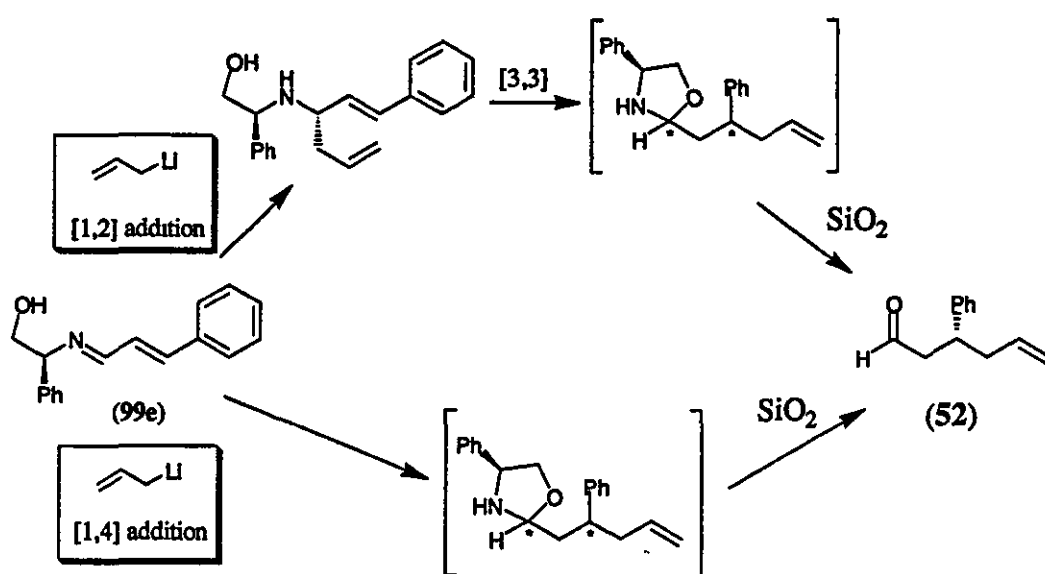
Scheme 100. Reactions Leading to the Formation of (52)

The latter process would suggest that if the amino-Cope rearrangement proceeds *via* a heterolytic pathway then the two species must form a close ion-pair that retains some of the stereochemistry of the parent substrate in order to achieve a high level of product *e.e.* The involvement of such an ion-pair has also been independently suggested by MacDonald.[121] Looking back at our initial Grignard reactions it is important to note here that the dienes formed do not spontaneously rearrange despite the presence of an dianion intermediate in solution (**Figure 13**).
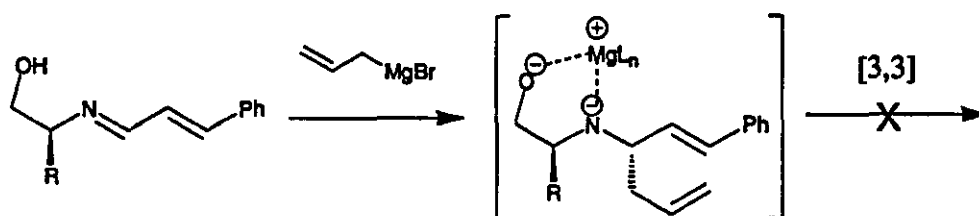
Fig 13. Grignard Reaction Leading to Dianion in Solution.

Although an in-depth study was not performed, a reasonable explanation for this is that the charge on both of the heteroatoms is sufficiently delocalised by the co-ordinating Grignard counterion that no further reaction can take place.

2.2.2. Anionic Amino-Cope Rearrangement of Furfural Substrates

The anionic amino-Cope rearrangement of substrates containing cyclic motifs, both aromatic and non-aromatic, within the diene framework was unsuccessful under the conditions employed by Meyers.[125] Failure of these substrates to rearrange may be due to their inability to attain the correct conformation for rearrangement and in addition the aromatic examples may simply be too stable to react.

We initially attempted rearrangement of furan-derived substrates using the anionic conditions previously developed for other substrates used by our group: deprotonation with 2.5 equivalents of n-BuLi at –78 °C in THF followed by warming to room temperature and then a period of reflux. The reaction was attempted in this manner a number of times but only starting material was recovered, even when reflux was continued overnight (Scheme 101).
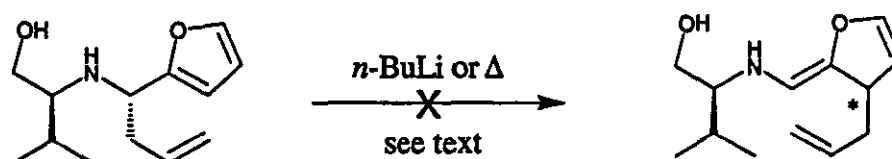
Scheme 101. Attempted Rearrangement of Furan Derivative

We reasoned that the temperature required to effect rearrangement of this substrate may need to be higher than reached in THF solvent, either to overcome the aromaticity of the furan ring or to force the diene into a more favourable reacting conformer. We changed to using

toluene as a solvent and the reaction was carried out as before but unfortunately there were only signs of decomposition after a 2 hour reflux period.

Undeterred by the lack of reactivity so far we decided to switch to thermal conditions as these had worked for some of our substrates in the past.[105,128] A small sample of the diene was heated in a sealed tube at 180 °C for 2 hours but extraction of the tarry residue showed only products of decomposition. The reaction was repeated at 210 °C and 230 °C but again we observed no sign of rearrangement.

The lack of reactivity of this substrate under our usual amino-Cope conditions – both anionic and thermal – was disappointing but in good agreement with the findings of Meyers *et al.*[125]

2.2.3. Anionic Amino-Cope Rearrangement of 3-(2-Furyl)-acrolein Substrates

The diene prepared from 3-(2-furyl)-acrolein was expected to behave in a similar manner to that derived from cinnamaldehyde. Unlike the preceding example, the furan ring is now adjacent to the double bond and should not affect the conformation of the substrate. Using the same anionic conditions as used previously the amine (103a) underwent rearrangement to afford the furan substituted aldehyde (113) in good yield after hydrolysis on silica (Scheme 102)

(103a)

1) *n*-BuLi, THF, -78 °C to Δ

2) SiO$_2$

(113)

73%, *e.e.* 36%
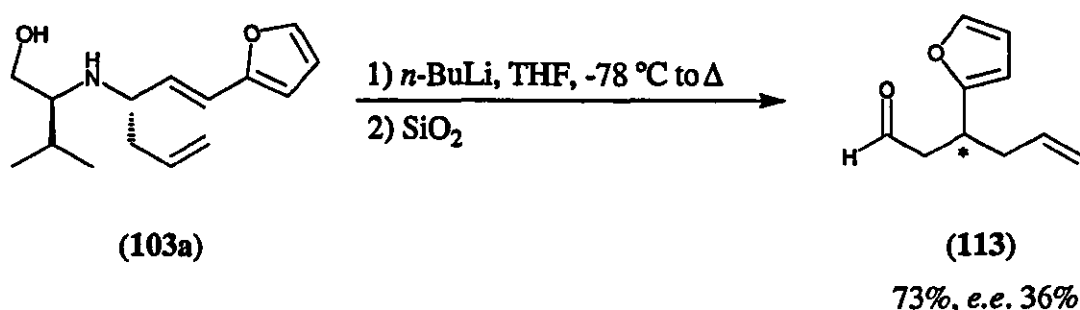
Scheme 102. Rearrangement of 3-(2-furyl)-acrolein Substrate

We were again able to measure the *e.e.* of this compound by derivatisation with (1*R*, 2*S*) ephedrine and to our surprise it was only 36%.

This important result indicates that the chiral auxiliary is not the only factor to consider when assessing the stereoselectivity of the amino-Cope rearrangement of such substrates. As mentioned earlier we can envisage that the rearrangement proceeds through a six membered chair-like transition state. To obtain high product *e.e.*'s one transition state must predominate with the amine auxiliary occupying either an equatorial or axial position (**Scheme 103**).

(103b)

n-BuLi

1) [3,3]
2) H₃O⁺

(113)
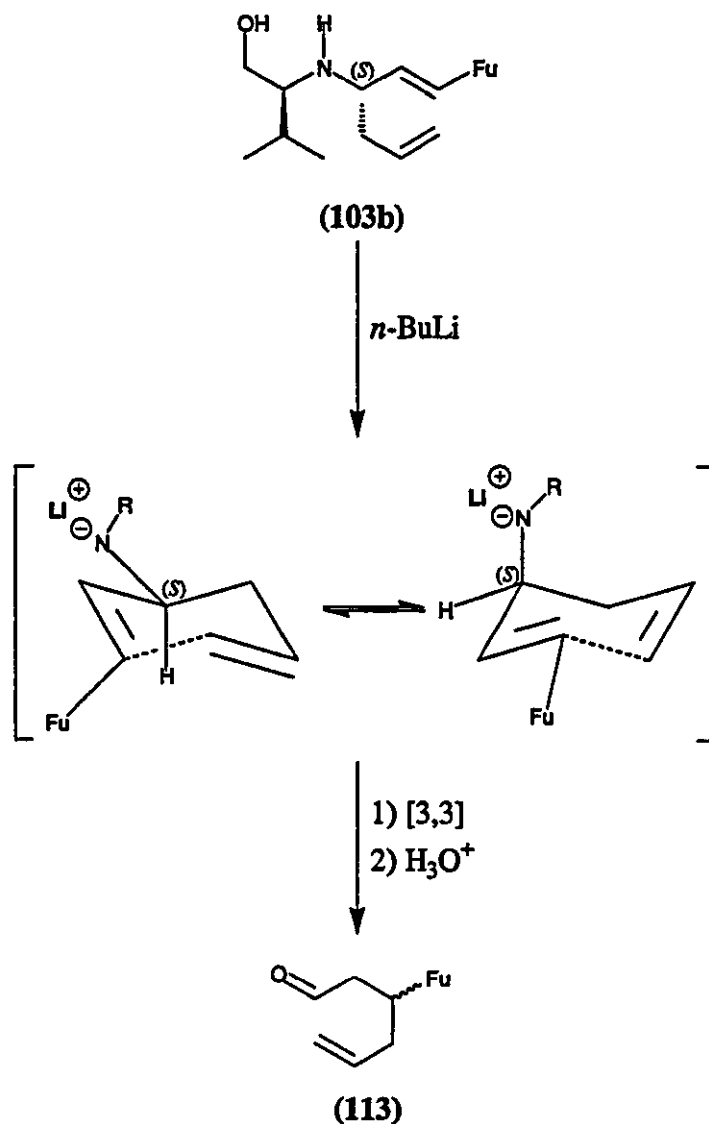
Scheme 103. Transition State Preferences for 3-(2-furyl)-acrolein Diene

Dienes derived from amino alcohols and cinnamaldehyde have so far been successful in delivering products in a highly enantioselective manner. As we have seen, however, in the case of the substrate prepared using 3-(2-furyl)-acrolein the rearrangement is not at all

enantioselective and this may be due to a lack of discrimination between the two competing transition states.

It has also been mentioned that there is evidence to suggest that the anionic amino-Cope rearrangement proceeds *via* a dissociative mechanism with some substrates. If this is indeed the case with our furyl substrate then the loss of enantioselectivity may be due to scrambling of the chiral centre (**Scheme 104**) or dispersion of the perceived close ion-pair formed by this mechanism.
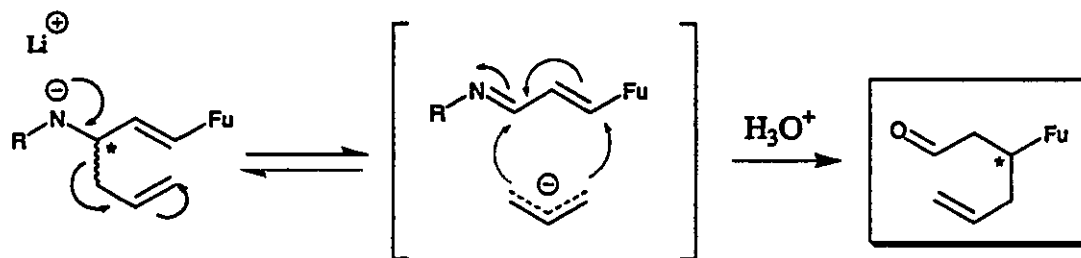
Scheme 104. Scrambling of Stereochemistry During Dissociation.

A more detailed study is required in this area before further comment can be made involving dienes with suitably diverse aromatic and aliphatic substitution at the 1- (and 6-) position.

2.2.4. Anionic Amino-Cope Rearrangement of Crotonaldehyde Substrates

MacDonald *et al*[121] have reported that under anionic conditions the 3-amino-1,5-hexadiene (**114**) rearranges to give a [1,3] (crossover) product in addition to the [3,3] (Cope) product. This is in sharp contrast to the thermal reaction of (**114**) which yields only the [3,3] product.
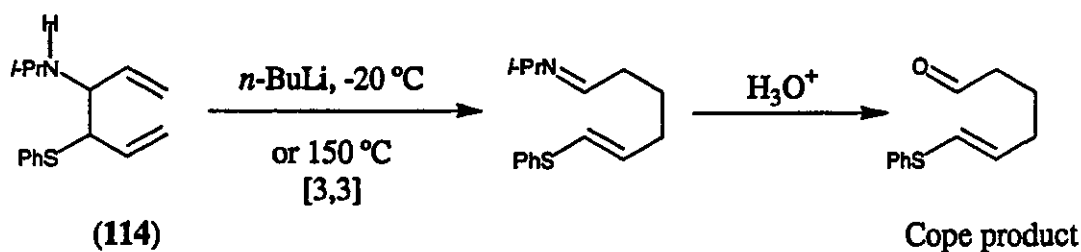
Scheme 105. Rearrangement of 3-SPh Substrates

They noted that with some substrates the regioselectivity of the reaction was strongly influenced by solvent polarity and that this may be due to a fragmentation pathway being favoured by the polar solvent while the non-polar solvents favour the concerted pathway. They also performed a cross-over experiment (**Scheme 106**) and found that little or no mixing of the starting material substituents occurred indicating that either a concerted pathway was operating to form the [1,3] product, or that a very rapid fragmentation-recombination pathway was taking place.

non-mixed: mixed > 5:1
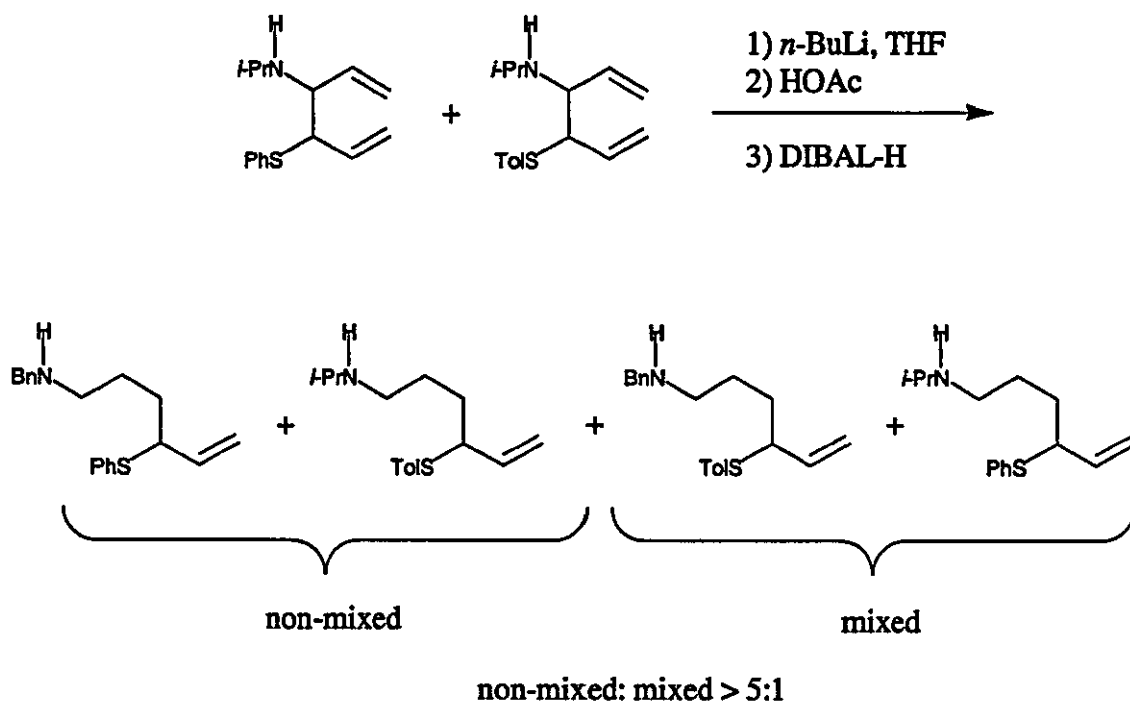
Scheme 106. Cross-over Experiment To Assess the Amino-Cope Mechanism

With some initial stability problems we were able to synthesise the 1-Me substituted diene (104) shown in **Scheme 107.** We wished to study the effect that using a non-polar solvent

would have on the rearrangement and whether the resulting product enantiomeric excess would be affected. An initial reaction using tetrahydrofuran under the usual conditions had yielded some of the expected rearrangement product but after column chromatography the ^{1}H NMR spectrum was too messy to interpret fully and there were peaks in the region that would interfere with *e.e.* measurement. Rearrangement in toluene gave similar results although the crude NMR spectrum was extremely messy indicating decomposition products were present. We were more optimistic about using hexanes as a solvent because the reflux temperature is lower than either of the previous solvents and the polarity may favour the concerted reaction thus yielding fewer side-products. The amine was dissolved in a small amount of anhydrous hexanes and cooled to –20 °C (below this temperature the solvent began to freeze) before addition of *n*-BuLi. The solution darkened suggesting that some deprotonation was occurring so the reaction mixture was warmed to room temperature and refluxed for 24 hours. Monitoring by TLC showed that some rearrangement product was forming after 2 hours but after this time there seemed to be no further reaction and subsequent work-up failed to yield enough of the product for NMR and *e.e.* measurement (Scheme 107).

(104)
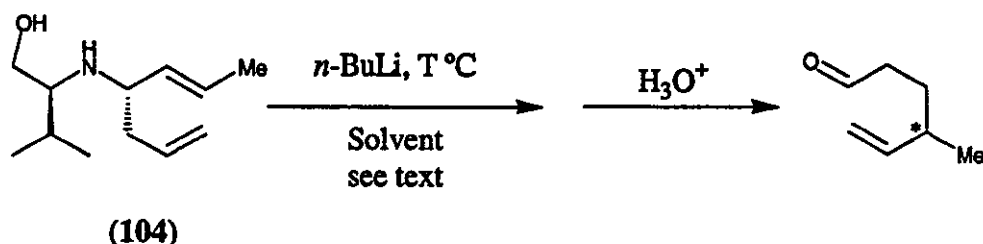
Scheme 107. Rearrangement of 6-Me Substituted Amine

2.3. Preparation of *O*-Me and *O*-Bn Protected Amine Auxiliaries

In the previous studies using aminoalcohols as chiral auxiliaries we obtained very high levels of enantioselectivity with *e.e.*'s up to 94% when the diene was prepared using phenylalaninol and cinnamaldehyde. We believed that the increase in asymmetric induction was due to the formation of a 5-membered chelate during the rearrangement which effectively increased the steric bulk of the amine component and we initially aimed to investigate this further by preparing amines in which the alcohol was protected as the *O*-methyl derivative.
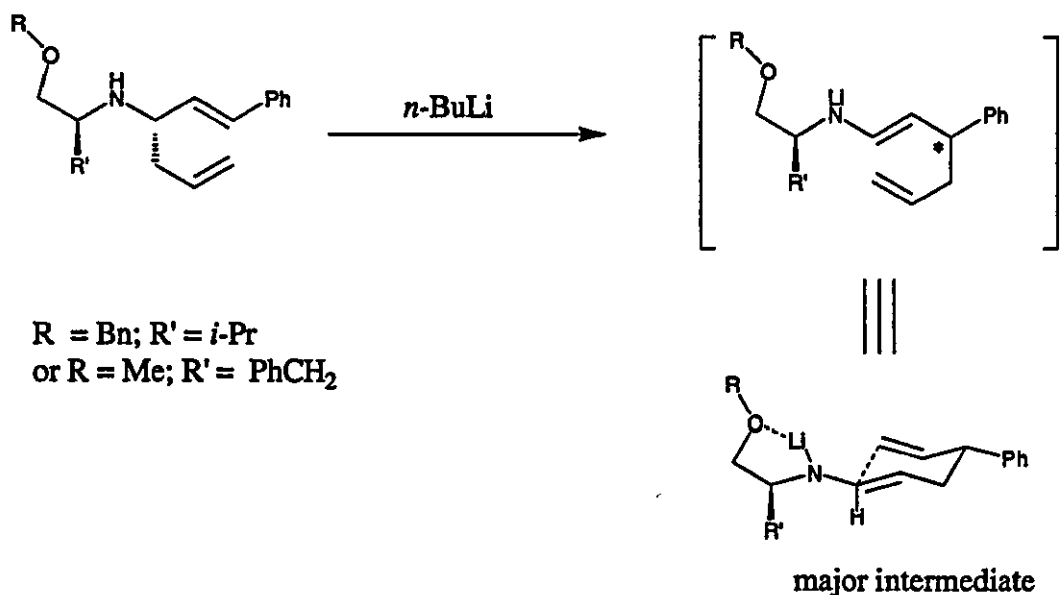
Scheme 108. Proposed Rearrangement Without Chelate Formation

A postdoctoral researcher, Dr Roger Lins, joined us at this point and proceeded to work on the synthesis of O-benzyl derivatives to give us further insight into the rearrangement. By protecting the alcohol moiety we would eliminate the need for an extra equivalent of base and, with this in mind, we also wondered if formation of the proposed 5-membered chelate would be inhibited or eradicated (**Scheme 108**). If this were the case we would expect to see a reduction in the enantioselectivity of the rearrangement.

2.3.1. Synthesis of O-Protected Amino Alcohols

In a related project we were interested in forming the O-Me amino alcohol as there were methods available in the literature to do this selectively.[129] We set about following a procedure by Meyers[129a] which used potassium hydride in THF with an overnight equilibration period before quenching with the appropriate electrophile, in this case iodomethane. Using phenylglycinol we tried a number of times to synthesise the methoxyamine (**115**) selectively but our best yield was only 40% and this still contained some impurity thought to be a dimethylated (O-Me/ N-Me) species from analysis of the crude ^{1}H NMR spectrum (**Scheme 109, Table 18**).

(R = Ph or *i*-Pr)   (115)   +   Major impurity
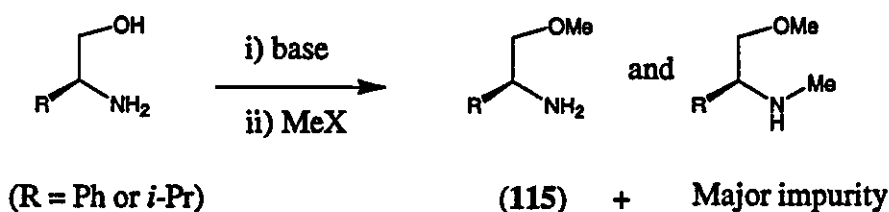
Scheme 109. Initial Attempts to Protect Phenylglycinol

As shown in **Table 18** we tried other conditions, including a change to using valinol as the β-aminoalcohol substrate, but without any improvements to the initial synthesis. Solvent choice was limited to those that would not react with a strong base but we found none that were as effective as tetrahydrofuran, although this could be related to the availability of anhydrous solvents as acetonitrile, DME and DMF were all difficult to dry effectively in our hands. We chose to use sodium hydride for some of the experiments to see if it would be more effective at removing the more acidic proton in the aminoalcohol but it seemed less effective at deprotonating *either* the alcohol or amine moieties. When we used methyltosylate in place of iodomethane we observed some reaction, possibly because of the better electrophile, although the excess reagent was difficult to remove and a number of side reactions seemed to be taking place which led to difficulties in purification.

Table 18. Protection of Aminoalcohols

R	Solvent	Base	MeX	Result
Ph	THF	KH	MeI	40% Yield
Ph	MeCN	KH	-	Effervesced
Ph	PhCH₃	KH	MeI	Impure
Ph	DME	KH	MeI	No reaction
Ph	DMF	KH	MeI	No reaction
Ph	THF	NaH	MeOTs	Impure
i-Pr	THF	NaH	MeI	No reaction
i-Pr	THF	NaH	MeOTs	Messy

This poor selectivity prompted us to try and protect the amine with a group that could be removed later in the sequence. Phenylalaninol reacted partly with phthalic anhydride to form the phthalimide derivative **(116)** shown in **Scheme 110**, but the yield was only 38% and

could not be consistently reproduced, with the majority of the product material appearing to be the uncyclised species (117) from the crude ^{1}H NMR spectrum. The reaction was also repeated in the presence of base, and toluene was used as solvent to try and force the intermediate to cyclise but none of these modifications led to any improvement in yield.
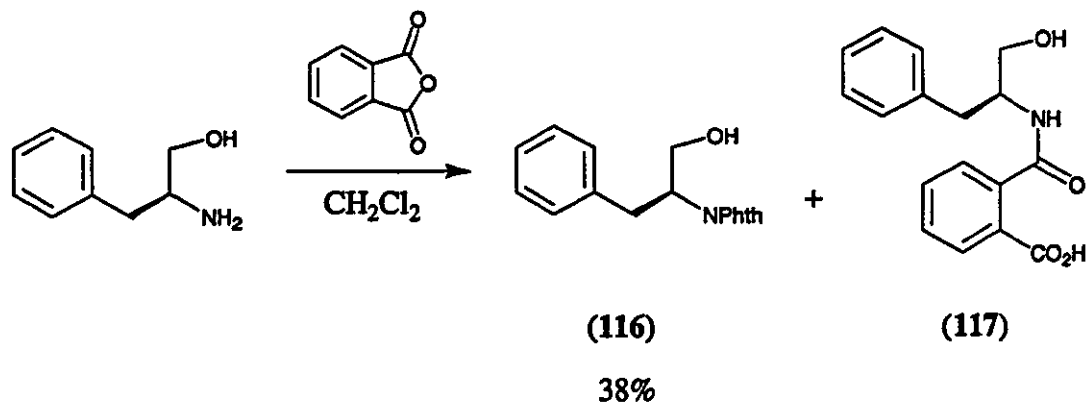
Scheme 110. Phthalimide Protection

In an alternative approach phenylglycinol was successfully protected as its Boc derivative (118) but again the yield was low. In this case however a poor recrystallisation step led to a further decrease in recovery. As **Scheme 111** shows our intended sequence involved deprotonation of the alcohol moiety with potassium hydride and we hoped the alkoxide would be stable enough to be reacted quickly with methyl tosylate.
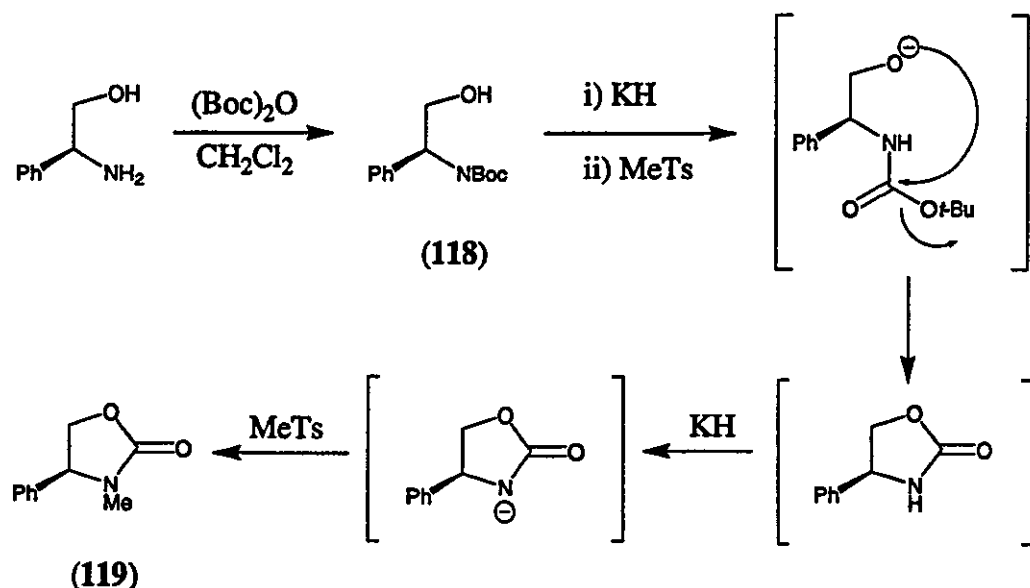
Scheme 111. Boc Protection and Elimination to form Oxazolidinone (119)

However, before the electrophile could be added, the Boc group was attacked by the alkoxide leading to an oxazolidinone species which was presumably deprotonated again and methylated when we added the methyl tosylate to form oxazolidinone (119). A similar cyclisation was found to have been performed by MacNeil[130] to produce bicyclic compounds.

Our failure to find a reliable method for protecting the β-aminoalcohols as their O-Me derivatives did not prevent us from synthesising a related hexadiene as we were able to use the commercially available O-Me phenylalaninol which is available as the hydrochloride salt.

After some modification of literature conditions,[131] Roger Lins was able to selectively prepare O-Bn valinol (120) in moderate yield with no sign of the troublesome N-alkylated species (Scheme 112). Refluxing for 1h after the addition of valinol to the sodium hydride seemed essential to effect deprotonation. The use of benzyl chloride was also important. When benzyl bromide was used the selectivity decreased and N-Bn aminoalcohols were formed as a by-product. In this case we believe that there may be some competing reaction from the free amine which is sufficiently nucleophilic in the presence of a good electrophile.

(120), 55%
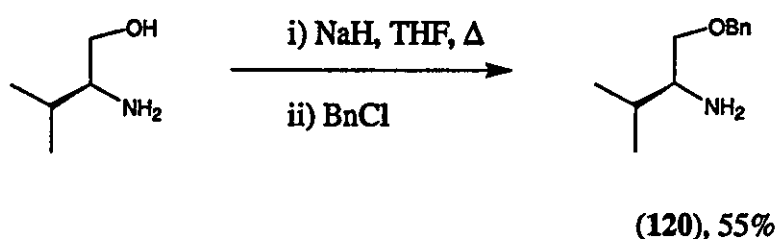
Scheme 112. *O*-Bn Protection of Valinol

2.3.2. Diene Synthesis from Protected Aminoalcohol Substrates

In the same manner as previously described, we were able to prepare imines (121a) and (121b) in excellent yield by stirring equimolar amounts of protected aminoalcohol and cinnamaldehyde in dichloromethane. At this stage we were developing better methods (as discussed earlier in **Section 2.1.1.1.**) for preparing our amino-Cope precursors and the Grignard reaction on imine (121b) was performed under Barbier conditions, yielding the desired diene in good yield and as a single diastereoisomer after column chromatography (Scheme 113).

(121a) 99%
(121b) 99%

(121a) : R = Bn, R' = *i*-Pr
(121b) : R = Me, R' = PhCH$_2$

Method A or B

Method A (R = Bn)
allylmagnesium bromide, THF, r.t. 30 mins

Method B (R = Me)
allyl bromide, Mg, THF, r.t. overnight

(122a) 65%, *d.e* >95%.
(122b) 60%, *d.e 81%*.
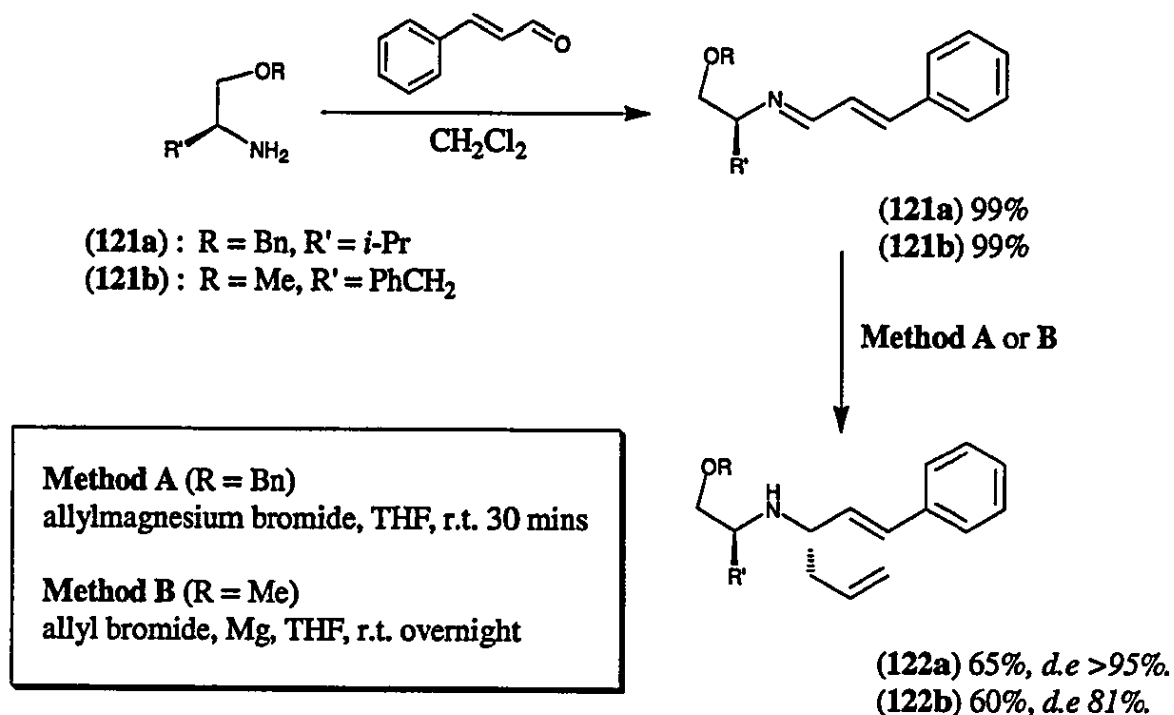
Scheme 113. Preparation of *O*-Protected Dienes

The use of Barbier conditions with the *O*-Bn imine led to a significant decrease in diastereoselectivity of the diene and it was therefore prepared using the standard Grignard conditions, also in good yield, with only one diastereoisomer visible in the crude ^{1}H NMR spectrum.

2.3.3. Anionic Amino-Cope Rearrangement of *O*-Protected Amines

The rearrangement of *O*-Bn protected amines was studied by Roger Lins and the results will be reported in due course.[132] He found that the protected amine does not require conditions as harsh as our the previous studies and that amino-Cope rearrangement of such substrates can occur without the need for refluxing. Diene (122a) reacted cleanly below 0 °C to give enamine (123a) which was easily hydrolysed using column chromatography to yield aldehyde (52) (Scheme 114).

(122a), R = Bn, R' = *i*-Pr
(122b), R = Me, R' = Bn

(52)

(123a or b)
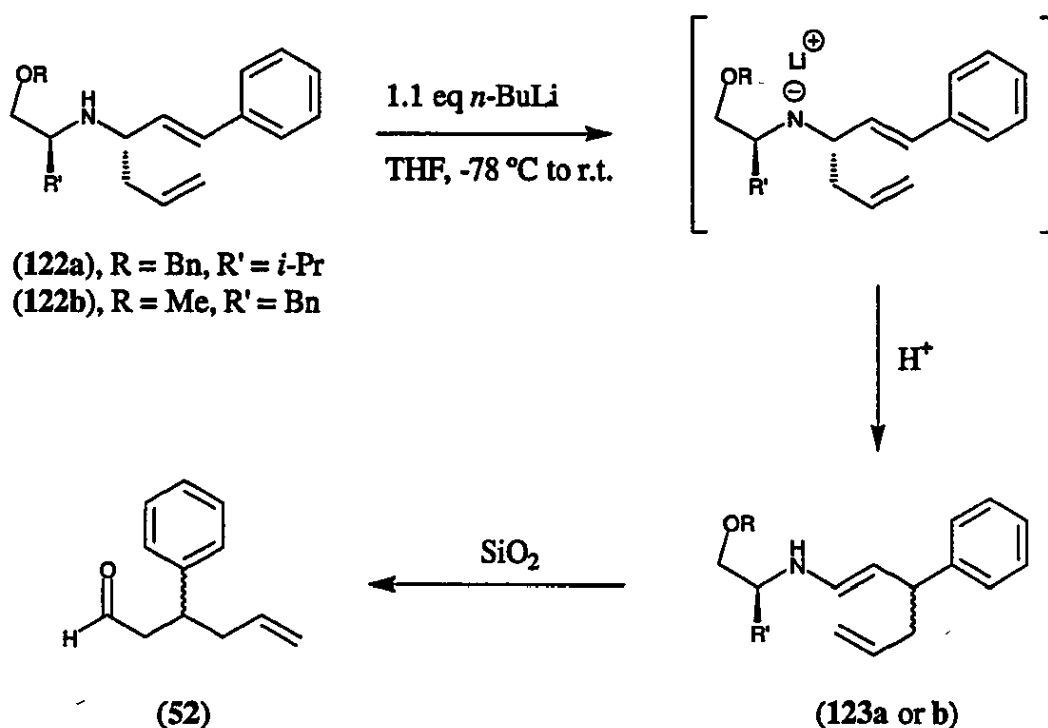
Scheme 114. Rearrangement of *O*-Bn Amine Performed by Lins[132]

We were interested to observe that the enantiomeric excess of the aldehyde this time was much lower, close to zero in some cases. It was found that the stereoselectivity could be increased to levels similar to those obtained from the unprotected species by carefully

controlling the temperature after addition of *n*-BuLi. Very slow warming in 10 °C intervals was required over a period of 2 hours until it reached –30 °C at which point the reaction could be warmed to room temperature and quenched. This finding suggests that if a 5-membered chelate is involved in the rearrangement it is much less effective at directing the stereochemistry than when the β-hydroxy substituent is unprotected, and additionally may be sensitive to very small increases in temperature.

A similar experiment on the *O*-Me Phenylalaninol diene, which shows excellent stereocontrol when unprotected (*e.e.* 94%), was performed. Amine (122b) was dissolved in THF, cooled to –78 °C and *n*-BuLi was added dropwise down the side of the flask to ensure any heating caused by the addition was minimised. The reaction was maintained at –78 °C for 30 minutes after which it was allowed to reach room temperature whilst still immersed in the dry ice / acetone cooling bath. After stirring at room temperature for 2 hours the reaction was quenched with water and work-up afforded enamine (123b) cleanly and in good yield. Hydrolysis and purification of the imine on silica gel yielded the aldehyde (52) with no enantiomeric excess which further suggests that chelation with the β-hydroxy group is an important aspect of this variant of the asymmetric anionic amino-Cope rearrangement.

2.4. Other Strategies

Difficulty encountered when attempting to selectively *O*-protect the aminoalcohol precursors of our substrates prompted us to try silyl protecting groups which are more selective for this procedure[133]. Instead of protecting the chiral auxiliary we hoped to use mild conditions to incorporate the silyl group in our hexadiene thus retaining any advantage that the free alcohol delivered during the Grignard reaction and previous steps (**Scheme 115**).
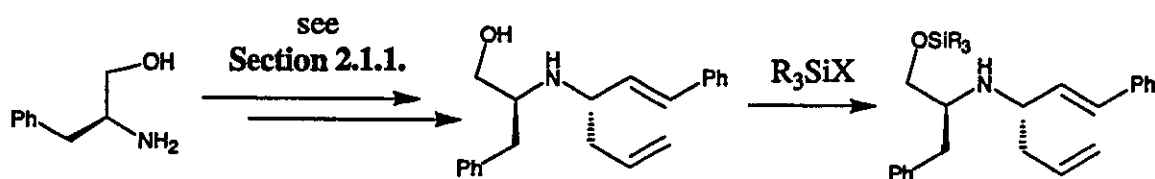
Scheme 115. Proposed Protection Scheme

2.4.1. Trimethylsilyl Protection and Attempted Rearrangement

Amino-diene (**100f**) was selectively silylated to form the protected compound (**124**) after deprotonation with *n*-BuLi at −78 °C and subsequent immediate quenching with chlorotrimethylsilane (**Scheme 116**). The yield from the reaction was only moderate however because the protected amine was not stable, reverting to the parent diene if left at room temperature for any period of time.
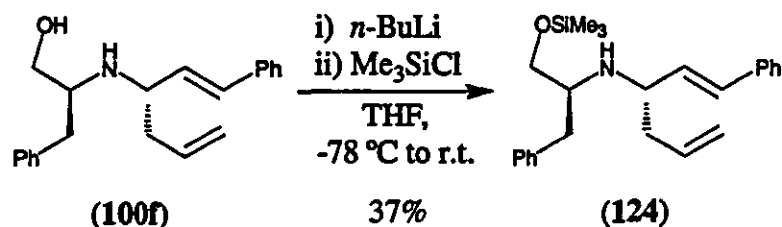
Scheme 116. Silyl Protection of Hexadiene

Purification was accomplished using flash chromatography on silica and the amine was used immediately for the anionic amino-Cope rearrangement. A solution of the *O*-TMS amine was cooled to −78 °C and deprotonated with one equivalent of *n*-BuLi, warmed to room temperature and stirred overnight before quenching. After the usual work-up ^{1}H NMR spectroscopy indicated that only starting material and desilylated starting material were present. As the protected amine was unstable we were reluctant to use harsher conditions such as reflux so we opted for using a different silyl protecting group that may be more robust.

2.4.2. *t*-Butyldimethylsilyl Protection

As the trimethylsilyl protecting group was unsuitable for our subtrate we hoped that the *t*-butyl variant would be more stable. In this case we planned to attempt protection of both *O* and *N* atoms of the aminodiene (**Scheme 117**) and expected to be able to remove this protection with TBAF[134] and generate a 'naked' dianion.
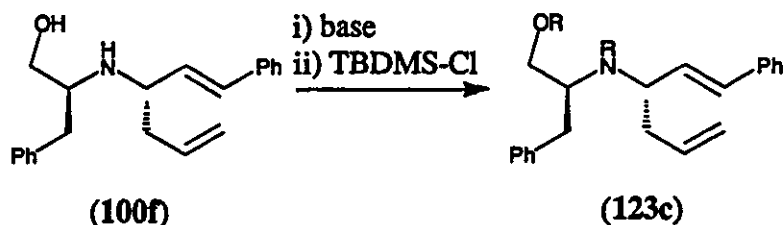
Scheme 117. Proposed Reaction of Amino-Diene with TBDMS-Cl

By utilising a large counterion we expected to observe no chelation control, thus altering the stereoselectivity of the anionic amino-Cope rearrangement (**Scheme 118**). We also wanted to see if the unshielded anion would have any effect on the strength of the C-3/C-4 bond, perhaps weakening it, as is widely perceived in the anionic oxy-Cope rearrangement,[6] and increasing the reaction rate.
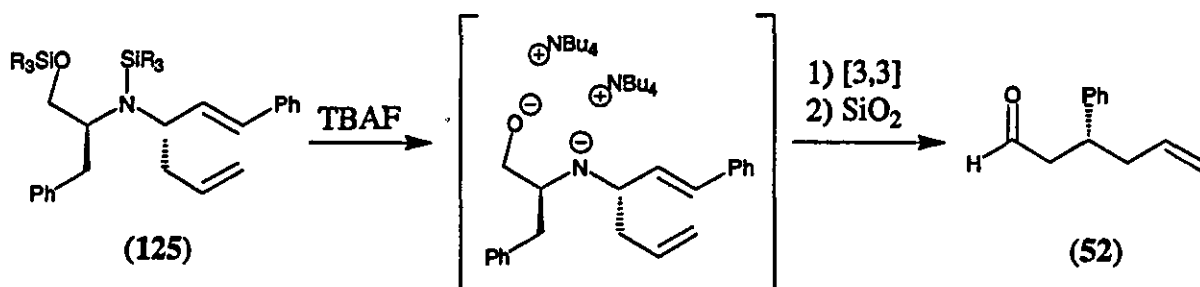
Scheme 118. Diprotected Amino-Diene

Repeated attempts to synthesise the desired substrate (**125**) however were fruitless and we recovered only the *O*-silyl protected diene (**123c**) using either *n*-BuLi, imidazole or triethylamine as base. This was not wholly unexpected as the literature indicates that *N*-silyl compounds are extremely difficult to purify - the protecting group is easily cleaved with mild acid[135]. Although we could have attempted to rearrange the *O*-protected diene using our normal conditions we chose instead to turn our attention towards the synthetic application of the amino-Cope rearrangement, discussed in the next chapter.

2.5. Conclusion

Formation of 3-amino-1,5-hexadienes *via* Grignard addition to imines is an excellent method that proceeds with almost exclusive diastereoselectivity and in moderate yield.

The anionic amino-Cope rearrangement has been performed on a number of substrates derived from β-amino alcohols with excellent enantioselectivity being demonstrated for the cinnamaldehyde series of dienes. Lower stereoselectivity was observed when cinnamaldehyde is substituted for 3-(2-furyl)-acrolein indicating that the choice of amino alcohol is not the only factor affecting the transition state of the rearrangement, and may suggest that an alternative fragmentation mechanism is operating. The selectivity of the amino-Cope rearrangement was also found to be altered when the alcohol moiety was protected as either the benzyloxy- or methoxy- compound. This reinforces the suggestion that the formation of a 5-membered chelate is important for the rearrangement to proceed with a high degree of stereocontrol.

Chapter 3

Results and Discussion

Synthetic Applications of the Anionic Amino-Cope Rearrangement
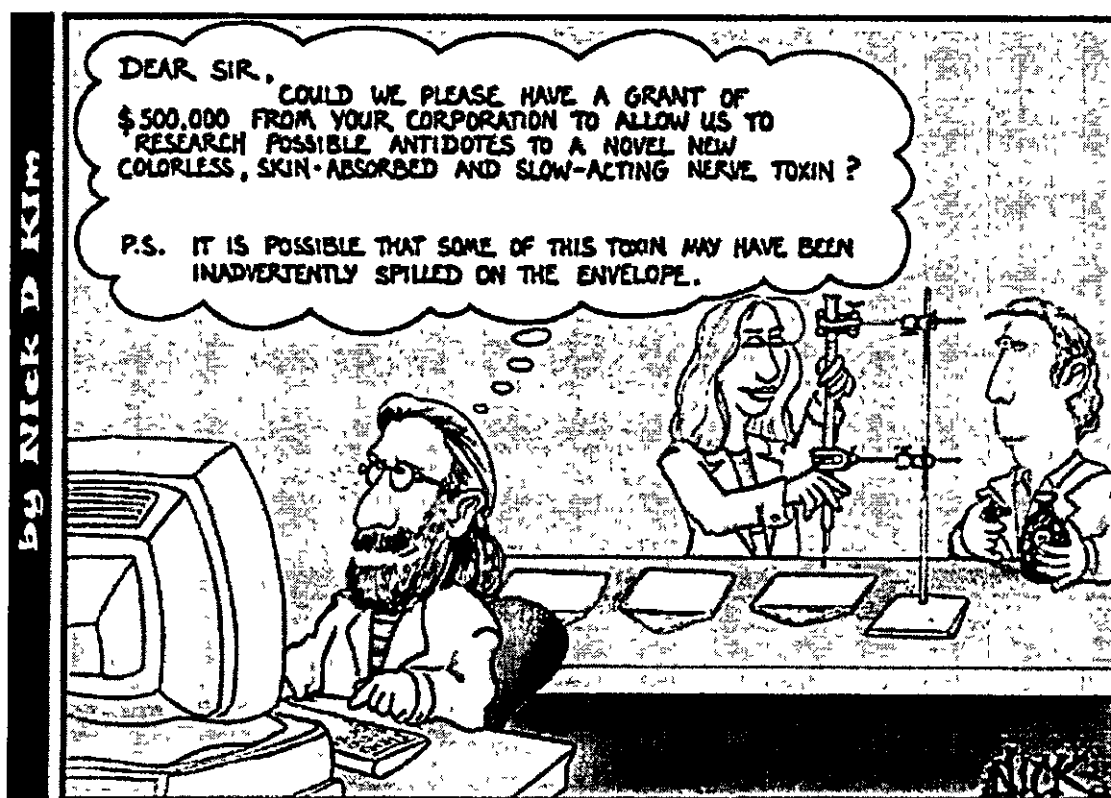
3.1. Synthetic Applications of the Asymmetric Amino-Cope Rearrangement

The work we had undertaken on developing the asymmetric amino-Cope rearrangement had so far only been used to synthesise the chiral aldehyde (52). We now wished to apply the amino-Cope rearrangement as a new approach to the synthesis of useful chiral building blocks, and demonstrate their subsequent application in the synthesis of heterocyclic targets.

(52)
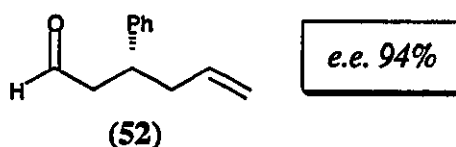
Our attention was drawn to the work of Greeves, as his group had published work on the tandem [2,3] Wittig / anionic oxy-Cope rearrangement[136] which led to the synthesis of racemic aldehyde (126) with excellent diastereoselectivity (Scheme 119).
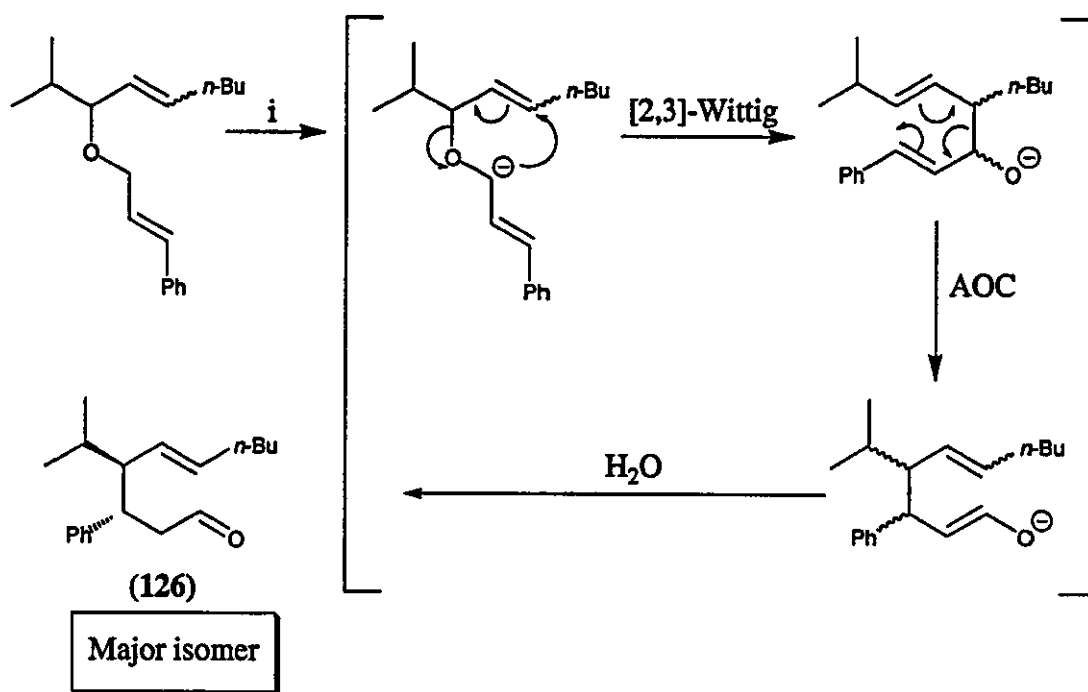
i) KH, 18-crown-6, DMSO, r.t., 1h.

Scheme 119. Tandem [2,3]-Wittig / Oxy-Cope Rearrangement by Greeves[136]

In order to measure the diastereoselectivity of the tandem reaction the aldehyde was reduced using sodium borohydride to form alcohol (127) which then underwent cyclisation with iodine in the presence of sodium hydrogen carbonate (Scheme 120).
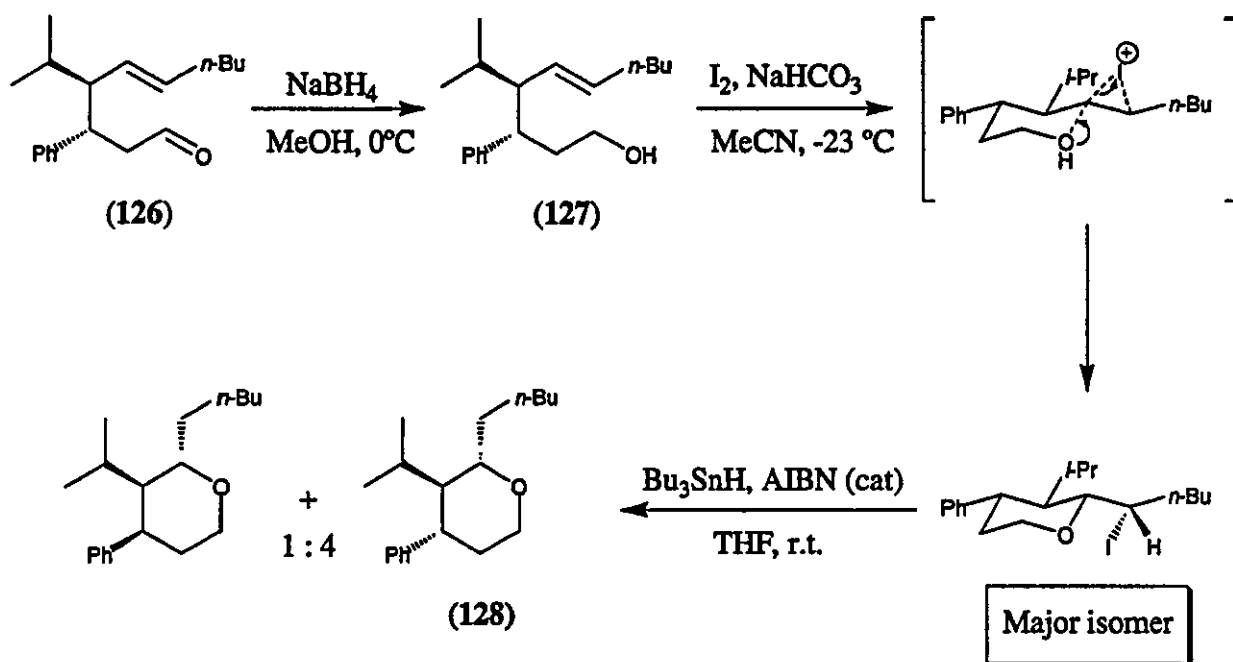
Scheme 120. Iodocyclisation of δ,ε-Unsaturated Alcohols

The resulting iodotetrahydropyran was reduced using tributyltin hydride to yield two products as a 4:1 ratio of diastereoisomers.

Greeves[136] reports that the cyclisation proceeds *via* a six-membered chair-like transition state with the iodonium cation, phenyl and isopropyl groups all attaining a *pseudo*-equatorial position to form the major isomer (128). The minor isomer resulting from cyclisation onto a *pseudo*-axial iodonium ion is also formed in around 20%. After analysis of the ^{1}H NMR spectrum, using COSY and decoupling experiments to aid assignment, the major isomer was shown to be the all-equatorial iodotetrahydropyran indicating that the *iso*-propyl and phenyl groups were *syn* in the acyclic molecule.

Similar cyclisation conditions were employed by Willis *et al*[137] although they report that the addition of base leads to the formation of kinetic products[138] with their substrates in excellent yield (Scheme 121). In the absence of base, thermodynamic control was achieved leading to a 4:1 ratio of tetrahydropyrans.

i) 98% yield 1:1
ii) 60% yield 4:1
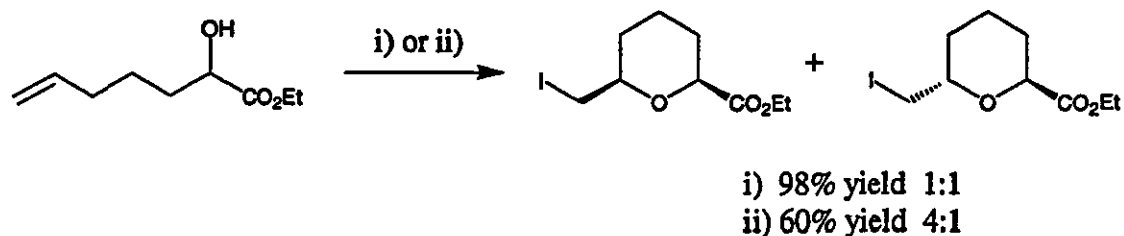
i) I_2 (3 eq), $NaHCO_3$, CH_3CN; ii) I_2, (3 eq), CH_3CN

Scheme 121. Tetrahydropyran Synthesis by Willis[137]

In a later publication Greeves[139] also reports that lactones can be formed if the aldehyde is oxidised to a carboxylic acid group and subjected to cyclisation with a suitable electrophile (Scheme 122).

R = *i*-Pr, cyclohexyl or *n*-Pr
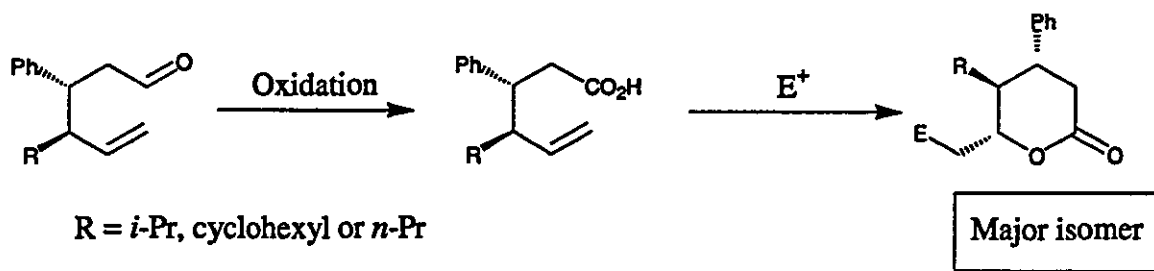
Scheme 122. Cyclisation of Carboxylic Acids by Greeves[139]

Interestingly the major isomer in most cases was seen to exist in a boat-like conformation, and there was a suggestion that a boat-like transition state might be involved in the cyclisation.

In 1985 Ganem[140] reported cyclisation of the highly substituted unsaturated amine (130), derived from bromoether (129) *via* reductive elimination, ring opening and reductive amination, to form piperidine (131) as shown in **Scheme 123**. The heterocycle was then be used to synthesise the aminoalditols *1-deoxynojirimycin* and *1-deoxymannojirimycin*, which are potent glycosidase inhibitors.

(129)   **(130)**   **(131)**

Major isomer, 61%
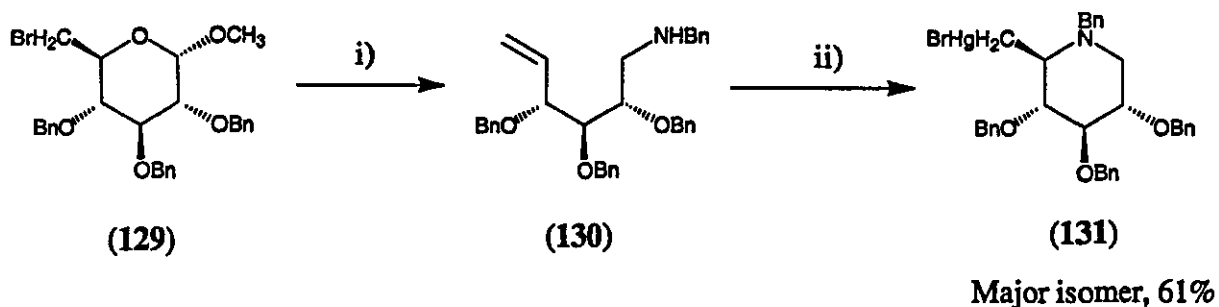
i) Zn dust, BnNH$_2$, NaBH$_3$CN, 19:1 n-PrOH/H$_2$O, Δ; ii) CF$_3$COOHgBr, THF

Scheme 123. Piperidine Synthesis by Ganem[140]

More recently Gracza *et al*[141] have reported the synthesis of *1-deoxy-L-idonojirimycin* (133) in a different manner, using Pd(II)-catalysed aminocarbonylation of the highly substituted benzylaminoalkene **(132)** followed by reductive ring opening and deprotection **(Scheme 124)**.

(132)   Major isomer   **(133)**
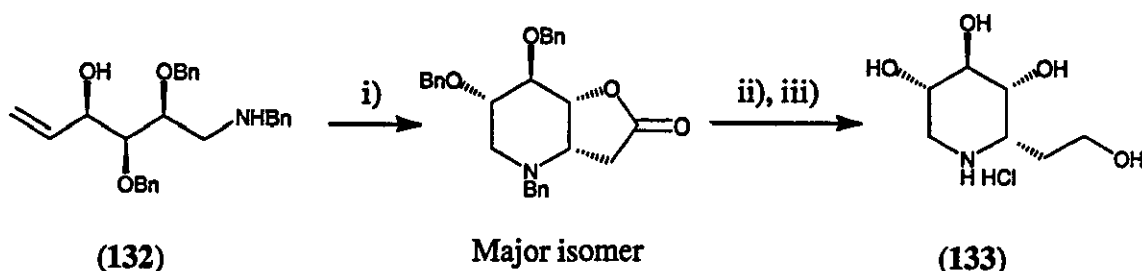
i) 0.1 equiv. PdCl$_2$, 3 equiv. CuCl$_2$, 3 equiv. NaOAc, AcOH, 7h, 50 °C; ii) LiBH$_4$, THF, 0 °C to r.t.; iii) H$_2$ (balloon), 10% Pd/C, HCl. MeOH, r.t. overnight

Scheme 124. Aminocarbonylation performed by Gracza[141]

Less substituted piperidines were synthesised by Ward[142] using PhSeCl or PhSeBr to induce cyclisation of carbamates, sulfonamides or amides with high yields and good stereocontrol in most cases **(Scheme 125, Table 19)**.

(134) (135) (136)
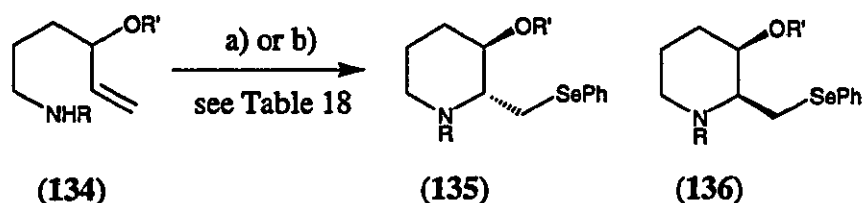
a: R=CO$_2$Et, R'=H
b: R=CO$_2$tBu, R'=H
c: R=SO$_2$C$_6$H$_4$CH$_3$, R'=H
d: R=COCH$_3$, R'=H
e: R=SO$_2$C$_6$H$_4$CH$_3$, R'=TBDPS

Scheme 125. Cyclisation of *N*-protected amines by Ward[142]

Table 19. Cyclisation Results

Substrate	Reaction Conditions[1]	Product Yield (ratio 135:136)[2]
134a	a, 48 h	57% (3:1)
	b, 18 h	61% (5:1)
134b	a or b, 5 days	No reaction
134c	a, 48 h	59% (3:1)
	b, 18 h	58% (5:1)
134d	a, 48 h	41% (3:1)
134e	a, 5 days	27% (3:1)

1. a = PhSeCl, CH$_2$Cl$_2$, -78 °C, 10 min. then to r.t.; b = PhSeBr, CHCl$_3$, 0 °C, 10 min. then to r.t.

2. isolated yield, product ratios determined by HPLC analysis

The selenides could be converted to dihydroxy-piperidines by treatment with *m*CPBA followed by aqueous sodium hydroxide (Scheme 126).
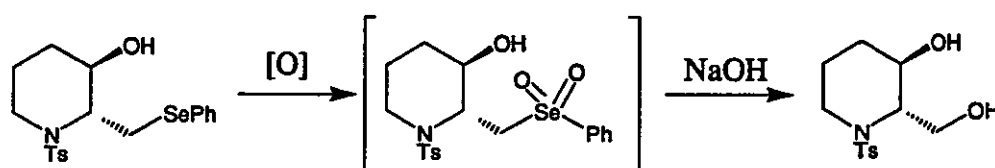
Scheme 126. Removal of Phenylselenyl Group

N-protected amines were also cyclised by Armstrong[143] during the stereoselective synthesis of a tricyclic guanidinium model of cylindrospermopsin (**Scheme 127**). Treatment of α,β-unsaturated methyl ketone (**137**) with a catalytic amount of *p*TsOH in refluxing benzene gave one diastereoisomer of the corresponding Z-protected piperidine (**138**).
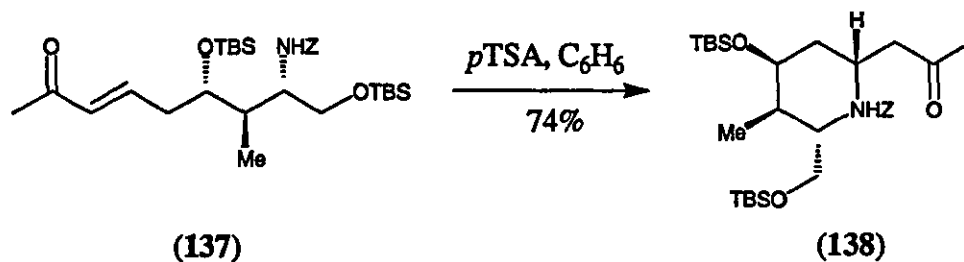
Scheme 127. Acid Catalysed Cyclisation of Z-Protected Amine (137)[143]

These methods clearly show that it is possible to form a range of heterocycles in a highly diastereoselective fashion using relatively simple chemistry. We therefore aimed to exploit the syntheses using our own aldehyde as a highly enantio-enriched precursor, with the hope that the enantiomeric excess would be carried through to the final heterocycles.

3.1.1. Large Scale Preparation of 3-Amino-1,5-Hexadienes

In order to work on the heterocycle synthesis we needed to find a repeatable large scale synthesis of the phenylalaninol derived diene to produce enough of the aldehyde (**52**) with high *e.e.* for subsequent reactions. To prove the enantioselectivity of the heterocycle syntheses we also required a comparable high yielding synthesis of racemic aldehyde to act as a reference throughout the synthetic development.

The most obvious way to prepare (**52**) racemically would be to react imine (**139**) with a 'Cu' Grignard reagent to effect 1,4 addition (**Scheme 128**).
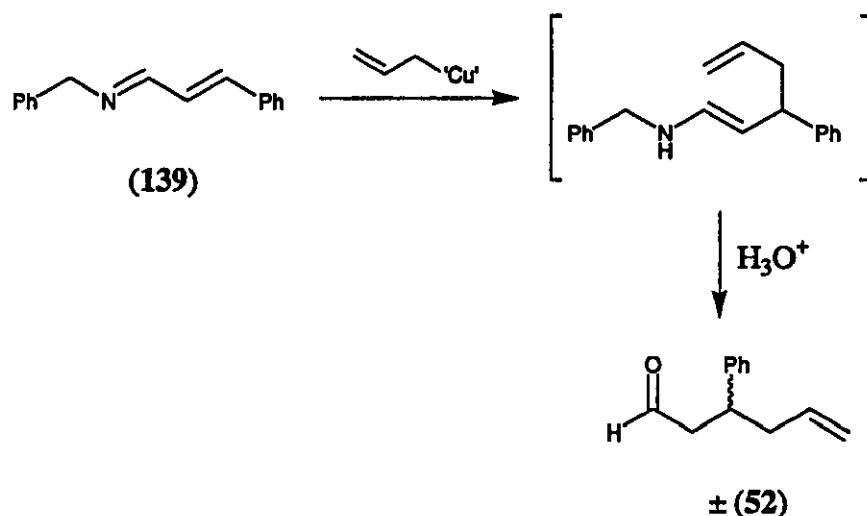
Scheme 128. Proposed Reaction of Benzylamine Imine with Cuprate Reagent

Despite a similar reaction being reported by Pridgen[106] (Scheme 129) we were unable to synthesise the required organometallic reagent from allylmagnesium bromide and copper (I) iodide and recovered only starting material from the reaction.
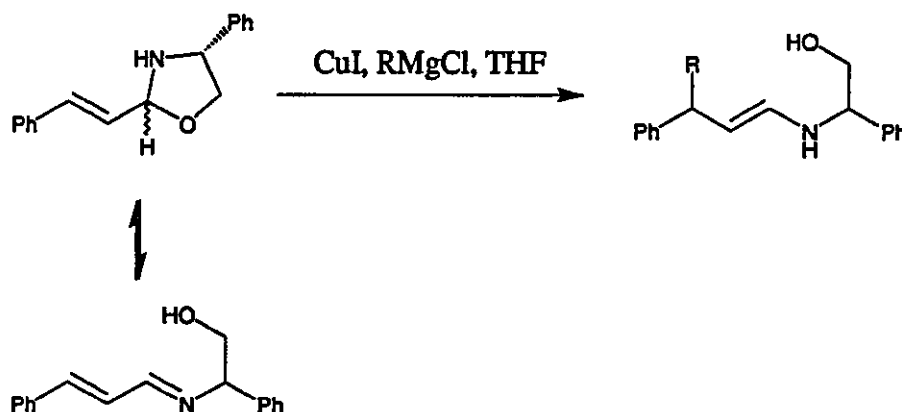
Scheme 129. 1,4 Addition Reported by Pridgen[106]

Using the same imine it was possible, however, to perform a standard Grignard reaction and obtain the racemic diene (**140**) in excellent crude yield.[105] We were then able to rearrange the diene using the conditions we developed for the anionic amino-Cope rearrangement but purification of the aldehyde using this method was difficult in large quantities (**Scheme 130**).
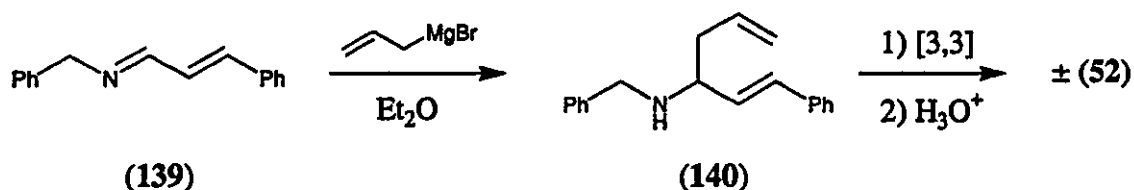
Scheme 130. Diene Preparation Using Benzylamine

Attempts to purify amine (140) before rearrangement using column chromatography were also ineffective as the amine has a strong affinity for silica and alumina, and could not be eluted in sufficient purity. Ethereal hydrochloric acid was used to form the salt but amine recovery using this method was extremely poor and we therefore decided to abandon this route to the aldehyde.

As purification was a problem we looked at other ways of forming a racemic diene and reasoned that by using a larger amine component we might form a crystalline intermediate that would be easier to purify. The obvious choice therefore was to use tritylamine and there was a literature method for preparing our desired imine.[144]

Following our earlier success at preparing imines we tried simply stirring tritylamine and cinnamaldehyde in dichloromethane at room temperature. In this case the method was not effective and we had to resort to the literature conditions which involved refluxing the reagents in toluene with azeotropic removal of water (Scheme 131). This led to a slightly lower yield than usual, but imine (141) could be easily recrystallised with recovery similar to that reported.[144]
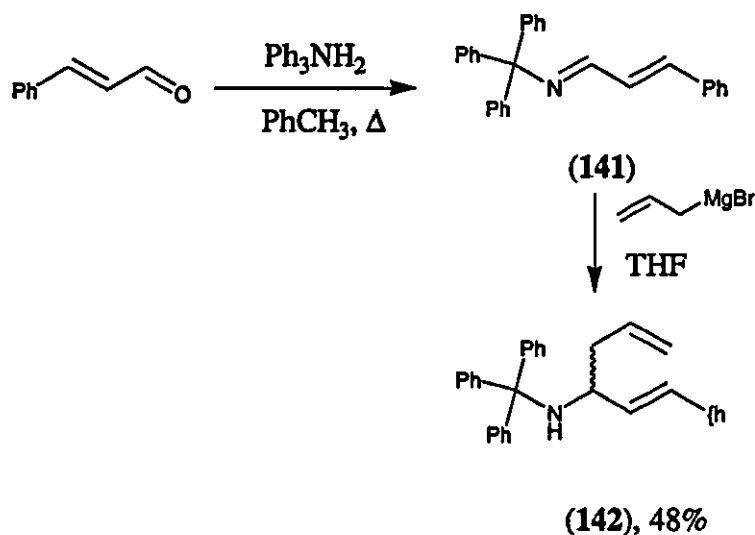
Scheme 131. Preparation of Amine from Tritylamine

Formation of the diene proved to be far from straightforward and we found that even when using refluxing tetrahydrofuran the conversion was low and we recovered only a fraction of the amine **(142)** by recrystallisation from the crude product. Interestingly in this case we noticed that we could perform column chromatography on silica without any hydrolysis of the remaining imine and we were able to recover further quantities of amine **(142)** along with recovered starting material. As this would not be practical on a large scale however we decided to explore other means of synthesising the racemic aldehyde.

We briefly looked at an alternative preparation shown in **Scheme 132** which was based on the work of Enders[145] using (*S*)- and (*R*)-2-methoxymethylpyrrolidine.
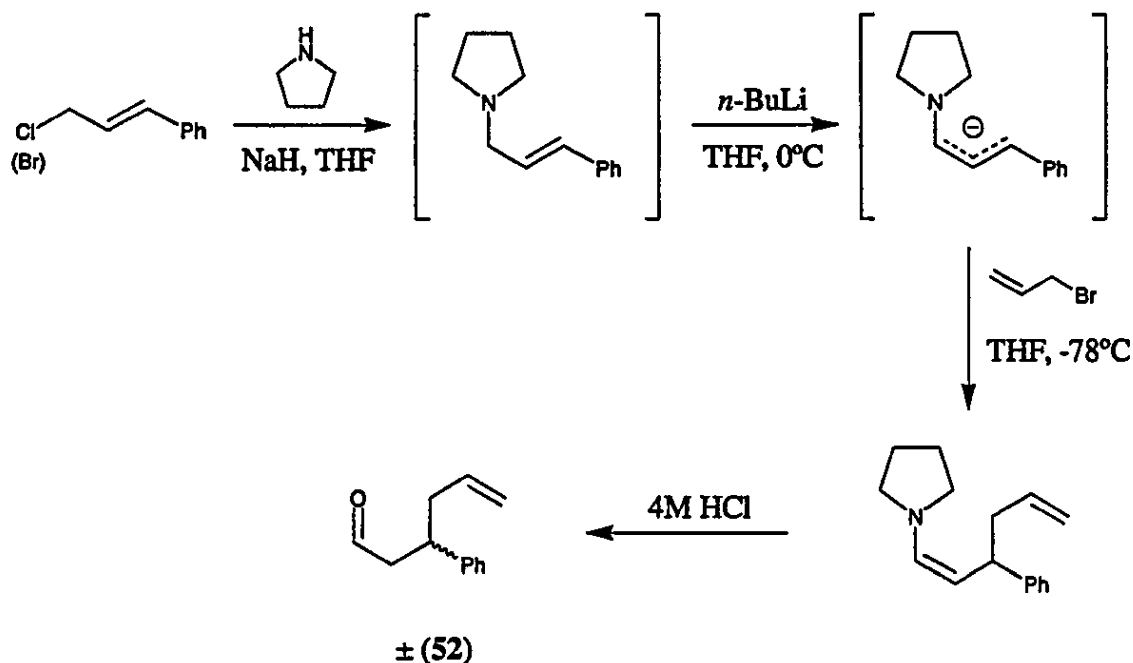
Scheme 132. Synthesis of Racemic 3-Phenylhex-1-enal

By substituting inexpensive pyrrolidine for the chiral auxiliaries (SMP and RMP) used by Enders we could feasibly obtain racemic aldehyde in *4 steps* (including hydrolysis). Formation of the enamine proceeded slowly when we used cinnamyl chloride and the purified yield was low. We managed to obtain enough material to use for the next step but this also proceeded in low yield and we were unable to recover significant amounts of the aldehyde (52) for study. Although the method could have been useful we were unwilling to devote too much time to its development and we opted for a more workable strategy.

With the failure of previous methods we decided to revert to our more developed synthesis using the anionic amino-Cope rearrangement.

Initially we examined the rearrangement using racemic alaninol as an auxilliary because it was available in our laboratory and had been used previously by Button[105]. Imine formation proceeded well to give a solid imine product (143) which was easily manipulated and using our standard Grignard reaction conditions we were able to form the hexadiene (144), although the yield was extremely poor after recrystallisation.
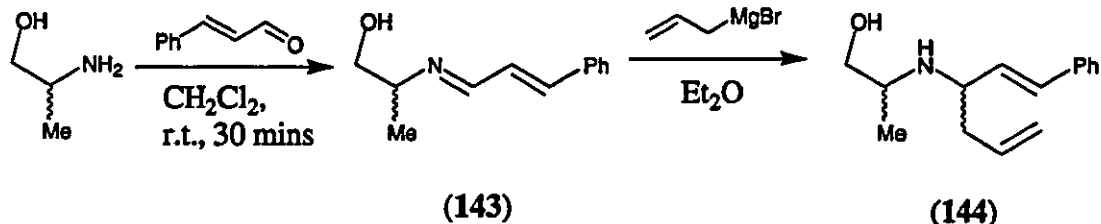
Scheme 133. Amine Preparation from Racemic Alaninol.

Rearrangement of this substrate however did not proceed well and we were unable to obtain any clean product from the reaction.

Following this failure we chose to use racemic phenylalaninol as we reasoned that we could obtain the aldehyde in good yield following our standard preparation techniques. In order to proceed with subsequent reactions of the aldehyde we needed to scale up our synthetic strategy and to do this we had to investigate the reduction of commercially available phenylalanine.

3.1.1.1. Preparation of Phenylalaninol

There are many methods available for the reduction of aminoacids[146] to aminoalcohols although most are reported to proceed with some degree of difficulty. The most obvious reagent choice would be lithium aluminium hydride but problems sometimes occur when the lithium salt precipitates from the reaction medium (**Scheme 134**).[147]
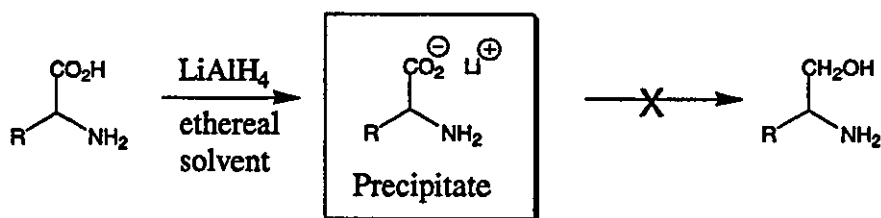
Scheme 134 Aminoacid Reduction

We found a convenient preparation for small quantities of material was that of Giannis[148] which used Me$_3$SiCl and LiBH$_4$ to generate borane *in situ* (**Scheme 135**).

$$\text{a) LiBH}_4/\text{Me}_3\text{SiCl}$$
$$\text{or}$$
$$\text{b) NaBH}_4/\text{H}_2\text{SO}_4$$
$$\text{THF}$$

(145), 87%
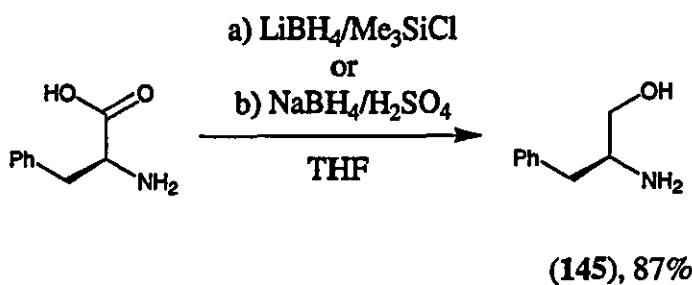
Scheme 135. Reduction of Phenylalanine with BH$_3$·THF

The reagents were too expensive to use on a large scale however and we searched for other similar methods that we could use to scale up the reduction. One such method was that of Meyers[149] which used iodine and sodium borohydride to generate the desired reductant but the method did not work in our hands. We then turned to a more recent report by Abiko[150] utilising a mixture of sodium borohydride and sulfuric acid in THF for the reduction of 100g of phenylglycinol with excellent reported yields. Again the reduction takes place by first forming borane *in situ* and in this case does not require the use of anhydrous solvents as an excess of reagents is enough to ensure the reaction is not affected by decomposition of the borane.

Following this method on a smaller scale we were able to prepare 20g of racemic phenylalaninol (145) which did not need any further purification. We were also able to successfully reduce *L*-phenylalanine to give *S*-phenylalaninol with an optical rotation identical to that reported in the literature.

With large amounts of racemic and chiral phenylalaninol we then set about optimising the conditions for synthesising the amine we required for our rearrangement.

3.1.1.2. Barbier Grignard Development

The Barbier Grignard mentioned in **Section 2.1.1.1.** was preferred over the normal Grignard reaction because it omitted the problems with preparing and adding the organometallic reagent on a large scale. The reaction was performed on up to 31 g of imine (99f) dissolved in *toluene:diethyl ether* (4:1) with consistently high yields, using three equivalents of allyl bromide and magnesium to generate the Grignard reagent *in situ*. Rigorous solvent or glassware drying was found not to be important although the reaction proceeded in slightly

higher yield when performed under an inert atmosphere. We were interested to find that along with the expected diene (100f) the reaction also produced a small amount of reduced imine (146) which we were able to isolate and characterise (Scheme 136).
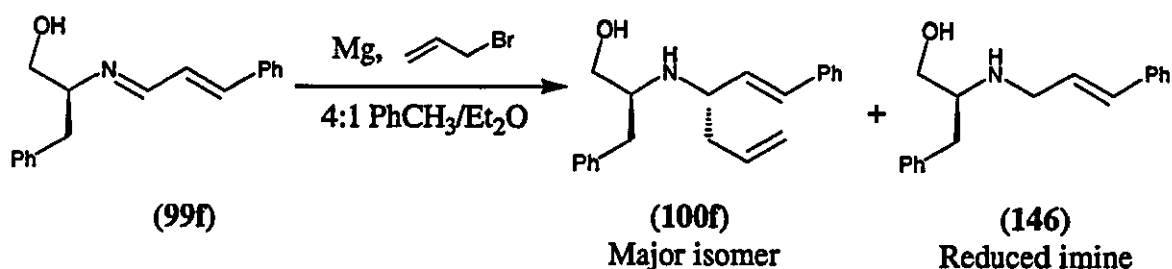
Scheme 136. Barbier Grignard with Anomalous Reduction

As yet we have no explanation for the formation of this compound other than to suggest that the mechanism proceeds *via* electron transfer from magnesium, suggested by Zhang[151] to explain side-reactions when performing Barbier reactions on aldehydes (Fig 14).
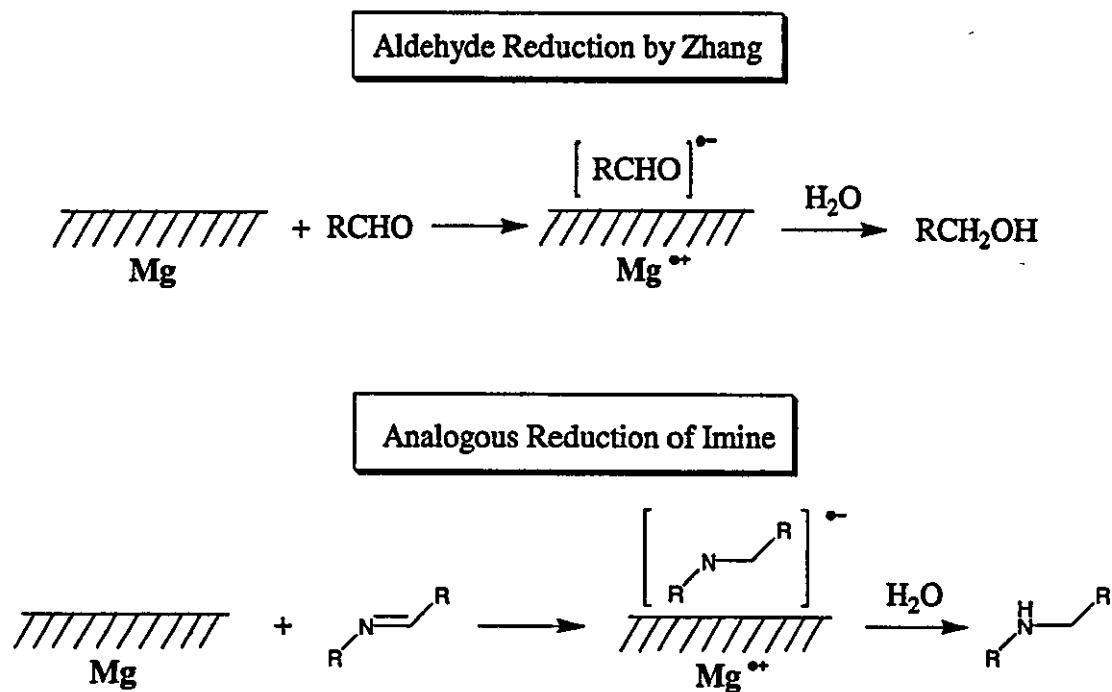
Figure 14. Pinacol Coupling and Proposed Reduction Mechanism

3.1.1.3. Improvements to the Anionic Amino-Cope Rearrangement

The anionic amino-Cope rearrangement had performed well in the small scale reactions we had previously tried, however we encountered some difficulty in isolating and purifying the

aldehyde product when the reaction was run on a larger scale. Whereas the crude ^{1}H NMR spectra seemed identical to our earlier examples, indicating complete conversion of diene (100f) into oxazolidine (105), it appeared that the aldehyde was not being liberated to a sufficient degree when we performed column chromatography on silica gel. To ensure complete hydrolysis of the oxazolidine we therefore used acidic Amberlite® resin before columning the crude product. The resin was first activated by stirring in 5M aqueous HCl then dried thoroughly by washing with acetonitrile several times. The crude oxazolidine dissolved in acetonitrile was then stirred with a large excess of resin and, although this made purification much simpler, the yield was still disappointingly low.

There are many procedures, including one by Zoretic,[152] which show the cleavage of oxazolidines using trifluoroacetic acid to form the parent aldehyde. The formation of acetals is a straightforward procedure when performed in methanol in the presence of acid. Since we had already determined that we could liberate the aldehyde using strongly acidic conditions on resin, without any apparent loss of yield, we therefore wished to attempt to isolate the dimethoxy acetal as a means of purification (Scheme 137).
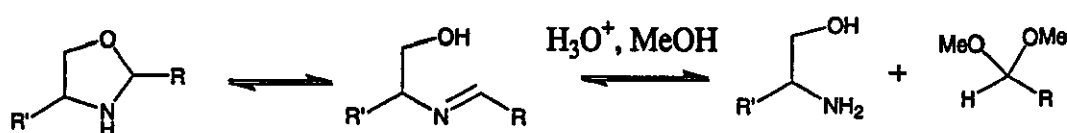
Scheme 137. Proposed Acetal Formation from Oxazolidine, *via* Aldehyde

To ensure complete hydrolysis we added an excess of trifluoroacetic acid to the crude oxazolidine in methanol and refluxed the solution overnight (Scheme 138).
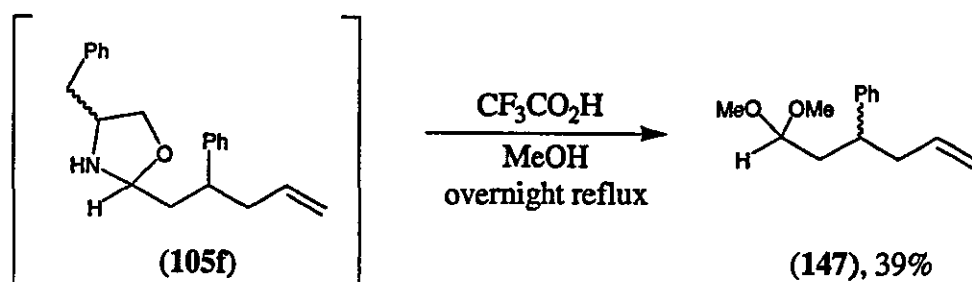
Scheme 138. One-Pot Acetal Formation from Crude Oxazolidine

The reaction appeared complete by tlc and simple purification using dry flash column chromatography on silica gel gave a moderate 39% yield of the *dimethoxy acetal* (147). This yield was still unacceptably low if we were to develop synthetic methods based on this protocol so it was necessary to investigate the amino-Cope conditions further.

Table 20. Variation of the Anionic Amino-Cope Rearrangement Conditions

Entry	Temperature (°C)	Solvent	Time	Yield
1	-78 → r.t.	THF	160 mins	no reaction
2	-78 → r.t.	THF	overnight	no reaction
3	-78 → r.t.	THF	60 mins then overnight [a]	25% reaction
4	-78 → r.t.	THF	overnight [b]	decomposed
5	-78 → r.t.	THF	220 mins	no reaction
6	-78 → r.t.	THF	overnight	47% [c]
7	-78 → r.t.	THF	overnight [d]	decomposed
8	-78 → 40	THF	overnight	no reaction
9	-10 → 40	THF	120 mins	50% reaction
10	0 → 40	THF	90 mins	40% reaction
11	-78 → r.t.	THF	overnight [e]	52%
12	-78 → r.t.	THF [f]	overnight	no reaction
13	-78 → reflux	Et₂O	overnight	63% (*e.e.* 54%)
14	-78 → reflux	Et₂O	overnight	78%
15	-78 → reflux	Et₂O:THF (3:1)	60 mins	67% (*e.e.* 63%)
16	-78 → r.t.	DME	overnight	no reaction
17	-78 → reflux	DME	120 mins	no reaction
18	-78 → reflux	Hexanes:Et₂O (4:1)	120 mins	no reaction
19	-78 → reflux	THF	60 mins	72%
20	-78 → reflux	THF	90 mins	80% (*e.e.* 90%)

a) Stirred with 1.1 eq KH for 60 minutes at r.t., cooled to –78 °C and added 1.1 eq *n*BuLi then warmed to r.t. b) Stirred with 2.2 eq KH and 18-crown-6. c) Only 50% reaction. d) 5 eq *n*BuLi used. e) Stirred with 2.2 eq *n*BuLi and 0.2 eq 12-crown-4. f) Increased dilution, 74mg amine dissolved in 40 cm³ THF.

Working with non-racemic substrates the amino-Cope rearrangement was carried out using different solvents, temperatures, additives and reaction times to try and find the optimum conditions giving us high *e.e.'s* and also high yields. *n*-Butyllithium was used in most cases as this had previously been determined as the most effective base for the rearrangement.[105] **Table 20** summarizes the results.

All attempts to carry out the rearrangement without a period of reflux (Entries 1-7 and 16) led to less than 50% reaction. This suggests that refluxing is required to force the equilibrium in favour of the oxazolidine which, when formed, makes the reaction irreversible. Simply heating the reaction above room temperature (Entries 8-10) did not aid the reaction in any way. Use of 12-crown-4 or 18-crown-6 with *n*BuLi and KH respectively also failed to drive the reaction past 50% conversion. Changing solvent to diethyl ether appeared to give a much cleaner reaction as evidenced by the crude ^{1}H NMR spectrum and column chromatography gave a much purer product than we had previously obtained on this scale. Unfortunately the *e.e.* of the aldehyde obtained was reduced to around 60%. Only starting material was recovered when we used either dimethoxyethane or a mixture of hexanes and diethyl ether (Entries 16 to 18). As none of these modifications appeared to be more successful than traditional methods we returned to the original conditions and ensured that all glassware and reagents were rigorously dried. After warming the deprotonated amine solution to room temperature it was placed in a pre-warmed oil bath and rapidly brought to reflux. This appeared to be an important practice as we were able to obtain high yields of clean aldehyde on a 500mg scale (after chromatography) with high *e.e.* (Entries 19 and 20).

With this method in hand we were ready to begin investigation of the synthesis of heterocycles.

3.2. Synthesis of Tetrahydropyrans.

3.2.1. Electrophilic Cyclisation.

The early work of Dr Nick Greeves[136] is outlined in **Section 3.1**, showing examples of the utility of aldehydes similar to that obtained after the amino-Cope rearrangement of our simple substrates. Later publications by Greeves[139,153] focus on optimisation of the cyclisation conditions, using a number of electrophiles, for the synthesis of both *di-* and *tri-*substituted tetrahydropyrans.

For disubstituted tetrahydropyrans, the racemic alcohols (**148a-e**) were synthesised by Greeves using a tandem [2,3]-Wittig-anionic oxy-Cope protocol[154] (**Scheme 139**).

a R = Me
b R = *n*-Bu
c R = *i*-Pr
d R = *t*-Bu
e R = *n*-Pr
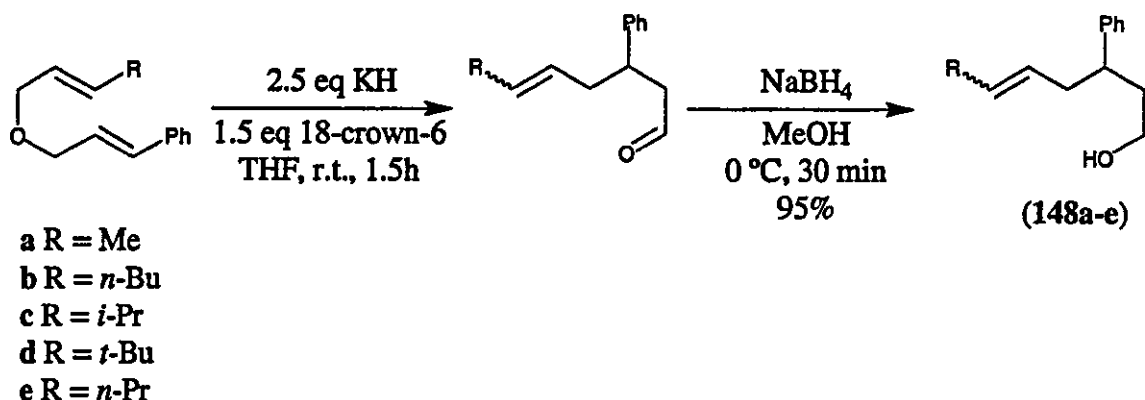
Scheme 139. Alcohol Synthesis

Cyclisation was performed using a number of electrophiles: Iodine, *N*-iodosuccinimide (NIS) and iodine monochloride (ICl) were examined as sources of I^+ and 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO) was chosen as a source of Br^+. Phenylsulfonium, PhS^+, and phenylselenium, $PhSe^+$, ions were also examined.

(148a-e)   (149)   (150)   (151)   (152)
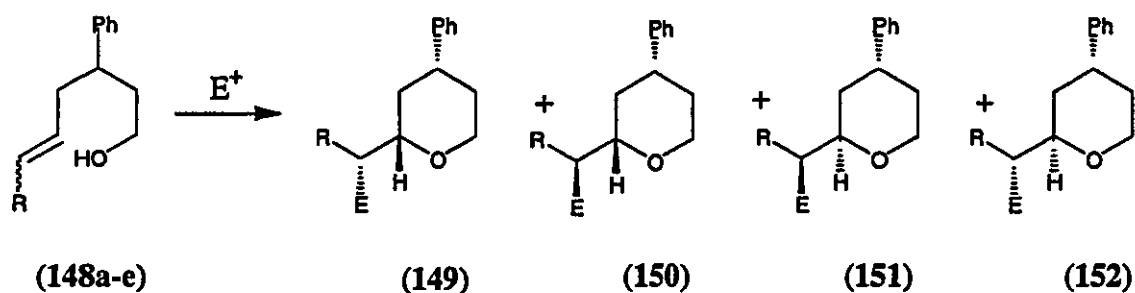
Method A: I₂ (3 eq), NaHCO₃ (3 eq), MeCN, -23 °C - r.t., 24h

Method B: NIS (1.2 eq), CH₂Cl₂, -78 °C - r.t.

Method C: ICl (2 eq), NEt₃ (2 eq), CH₂Cl₂, -78 °C - r.t.

Method D: TBCO (1.2 eq), CH₂Cl₂, dark, r.t., 1 week

Method E: Phenylthiomorpholine (1.1 eq), TfOH (1.1 eq), CH₂Cl₂, 0 °C, 2h

Method F: NPSP (1.7 eq), PPTS (0.3 eq), CH₂Cl₂, -78 °C - r.t., 9h

Scheme 140. Electrophilic Cyclisation of Alcohols.

Table 21

Entry	Substrate	R	Substrate geometry[a] E:Z	E⁺	Method	Yield / %	Product ratio[b] 149 : 150 : 151 : 152			
1	148a	Me	75:25	I⁺	A	65	77	23	-	-
2	148a	Me	75:25	I⁺	B	39	77	23	-	-
3	148a	Me	75:25	I⁺	C	26	77	23	-	-
4	148b	n-Bu	79:21	I⁺	A	78	87	13	-	-
5	148b	n-Bu	79:21	Br⁺	D	56	79	21	-	-
6	148c	i-Pr	100:0	I⁺	A	80	74[c]	-	26[c]	-
7	148d	t-Bu	100:0	I⁺	A	62	100	-	-	-
8	148e	n-Pr	84:16	PhS⁺	E	57	28[d]	6[d]	59[d]	7[d]
9	148e	n-Pr	84:16	PhSe⁺	F	86	28[d]	9[d]	57[d]	6[d]
10	148d	t-Bu	100:0	PhSe⁺	F	97	57[c]	-	43[c]	-

a) E:Z ratio measured by GC; b) Ratio measured by GC; c) Ratio measured by mass from flash column chromatography isolation; d) ratio measured by mass between diastereoisomer pair 149,150 and 151,152 and then GC analysis of each pair.

As shown in **Table 21** better yields were found when I₂ (Method A) was used as an electrophile, compared with NIS, ICl and TBCO. If the precursor alcohol was geometrically

pure (entries 6 and 7) a single diastereoisomer could be isolated, otherwise two diastereoisomers of halogenated tetrahydropyrans (149)/(150) were isolated in ratios relating to the starting geometry of the alkene. The cyclisation proceeded through a chair-like transition state with the halogen ion preferring to occupy an equatorial orientation (**Scheme 141**). When using phenylsulfonium or phenylselenium ions, generated by phenylthiomorpholine/ triflic acid and *N*-phenylselenophthalimide/ PPTS respectively, the cyclisation generally gave higher yields and the major product resulted from axial orientation of the electrophile.

R = *n*-Pr, E = PhS, PhSe
R = *i*-Pr, E = I
R = *t*-Bu, E = PhSe

almost exclusive

ca. 2:1 preference
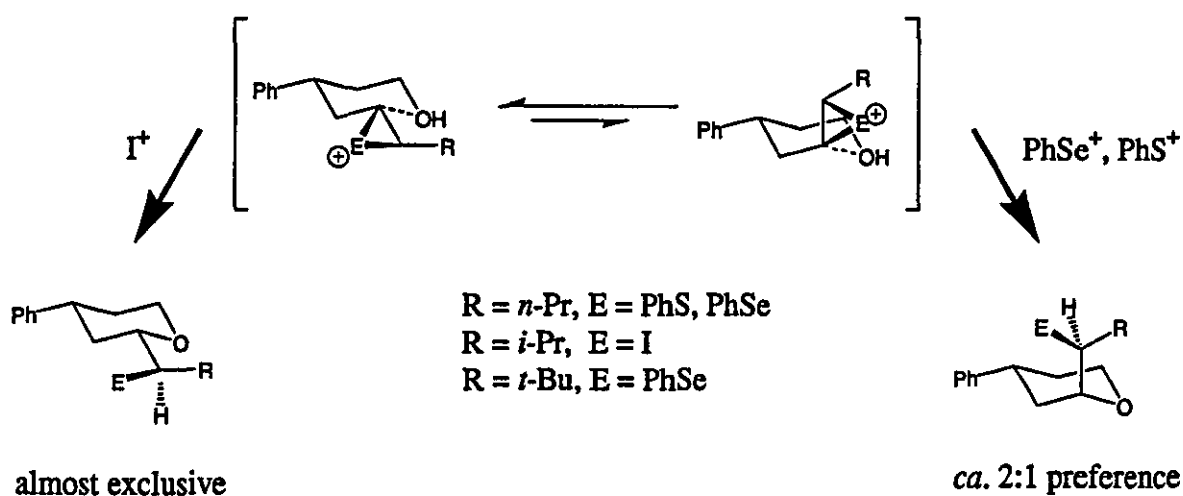
Scheme 141. Diastereoselectivity Induced by Different Electrophiles[153]

We chose to apply the same synthetic methods to our chiral aldehyde in the hope of demonstrating the potential of the amino-Cope rearrangement. In doing so we aimed to obtain tetrahydropyrans which were highly enantiomerically enriched and with defined stereochemistry.

The first step was to perform a simple reduction of the aldehyde (52) with sodium borohydride generating the alcohol (153) which we anticipated would retain the chirality from the previous reaction (**Scheme 142**).
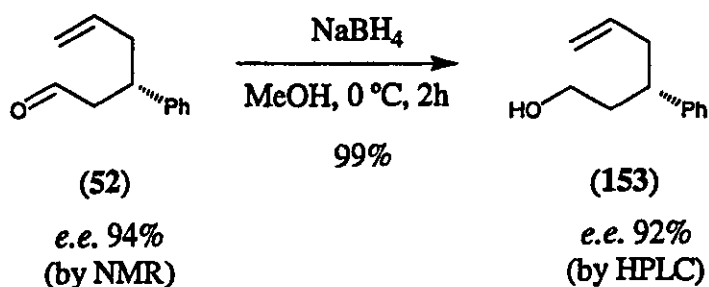
Scheme 142. Aldehyde Reduction.

The reduction proceeded in high yield as expected and measurement of the *e.e.* using chiral HPLC (ChiralCel OD, 95:5 Hexane/Propan-2-ol, 0.5mL min^{-1}) gave a value of 92% which was within experimental error of that previously determined by NMR methods for aldehyde (52). The racemic aldehyde was also reduced to provide a reference sample for HPLC method development during the tetrahydropyran syntheses.

3.2.1.1. Iodine as an Electrophile.

Cyclisation using iodine employed the simplest conditions so this reaction was investigated first. Following Greeves[153] conditions we were able to observe some reaction although the conversion was low and the major component isolated was unreacted starting material. We then performed the cyclisation at room temperature and in this way we observed almost full conversion to the tetrahydropyran (154a and b, Scheme 143).
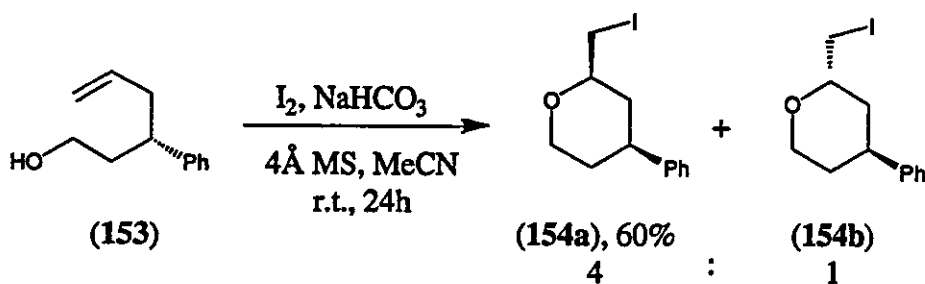
Scheme 143. Cyclisation using Iodine.

Analysis of the crude reaction mixture by ^{1}H NMR spectrum revealed a diastereomeric ratio of 4:1 which was in contrast to Greeves results that showed exclusive stereochemical control during cyclisation. A possible reason for this is that the alkene used in our case is

unsubstituted and the iodonium ion produced would be expected to have less steric bulk. The cyclisation temperature was also much higher in our case which may have decreased the selectivity of the reaction. However we were able to isolate the major diastereoisomer (154a) in 60% yield using column chromatography and examination of ^{1}H NMR and COSY spectra indicated to us that this product resulted from cyclisation onto the equatorial iodonium ion. A small amount of the minor isomer (154b) was isolated by preparative tlc and provided a useful ^{1}H NMR reference enabling us to calculate the diastereomeric ratio.

3.2.1.2. Enantiomeric Excess Measurement.

Determination of the enantiomeric excess proved to be very difficult as the isomers co-eluted when we used the ChiralCel OD column previously employed for measuring the enantiomeric excess of alcohol (153).

We were hopeful that by using NMR shift reagents[155] we could obtain an adequate analysis. Initial results using Yb(fod)₃ were encouraging as the peaks appeared to be shifted, however when we used a chiral shift reagent, Yb(tfc)₃, we saw no movement of the peaks despite using up to 40% of this reagent. Another lanthanide chiral shift reagent, Eu(hfc)₃, was also tried without success.

A widely used chiral derivatising reagent, Mosher's Acid[156], was available to us and we were able to react this with racemic tetrahydropyran (±154a) in the presence of potassium carbonate and silver nitrate (Scheme 144). Unfortunately we were unable to obtain full reaction of the tetrahydropyran so measurement of the e.e. from the crude ^{1}H NMR spectrum was impossible.
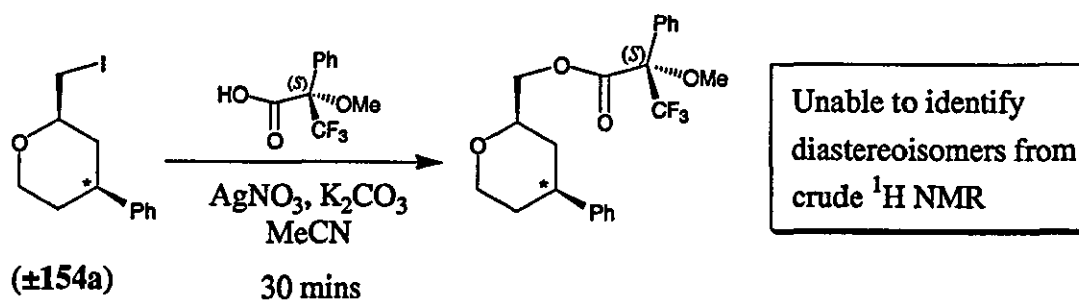
Scheme 144. Derivatisation with Mosher's Acid.

As a final attempt we decided to purchase a new chiral column recommended to us by the column manufacturers which they claimed had separated compounds similar to ours in the past. The ChiralCel OD-H should exhibit increased resolution due to the smaller particle size of the silica used. The racemic material containing both diastereoisomers (±154a and b) was used for method development and we found that by using a pre-mixed eluent of 99.5% hexane with 0.5% propan-2-ol we obtained baseline separation of the enantiomeric compounds, although the minor diastereoisomer in the mixture interfered with one of the peaks. It became necessary therefore to isolate the major diastereoisomer (154a) before measuring the *e.e.* in this way. We were pleased to finally obtain a reading of 92% using this method which demonstrates that we do not isomerise the chiral centre during cyclisation. Although we could not cleanly isolate sufficient amounts of the minor diastereoisomer (154b) for HPLC analysis we expect that the *e.e.* is the same as the major epimer.

3.2.1.3 Phenylselenium Ion as an Electrophile.

After our success at using iodine to initiate cyclisation we chose to investigate a further variant of this useful reaction. The phenylselenyl group is a useful 'handle' which allows further elaboration of the molecule, for example oxidative cleavage to form a hydroxy compound.[142] Following Greeves conditions we stirred alcohol (153) in dry dichloromethane with pyridinium *p*-toluenesulfonate (PPTS) at −78°C (Scheme 145).
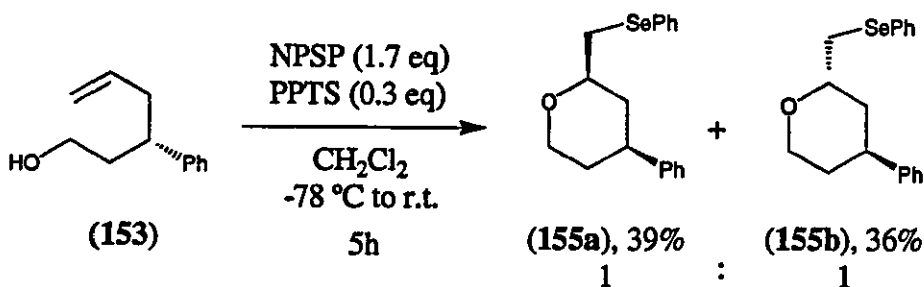
Scheme 145. Cyclisation using NPSP/PPTS.

After 10 minutes neat *N*-phenylselenylphthalimide (NPSP) was added generating the required cation *in situ* which initiated cyclisation. The reaction was stirred for 5 hours and after workup we were able to isolate each diastereoisomer using column chromatography. The major component (155a, 39%) was shown to be the *syn* isomer resulting from cyclisation

onto an equatorial phenylselenonium ion, whilst the minor tetrahydropyran (155b, 36%) arose from reaction with an axial intermediate. Analysis of the two separated compounds by chiral HPLC showed that tetrahydropyran (155b) had an *e.e.* of 92%, again in good agreement with the *e.e.* of the starting alcohol (153). Tetrahydropyran (155a) was not fully resolved although the HPLC trace clearly showed that the compound was highly enantiomerically enriched.

3.2.2. Cyclisation onto an Epoxide

A further example reported by Greeves[153] is the acid-catalysed epoxide opening of alcohol (157) in **Scheme 146** below.
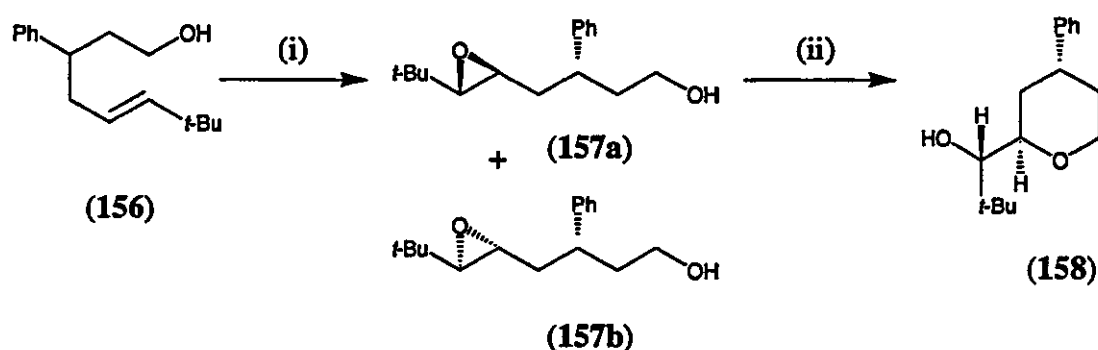
i) *m*CPBA (2.5 eq), NaHCO$_3$ (2.5 eq), DCM, 0 °C to r.t., 4.3:1, 70%; ii) CSA (0.1 eq), CH$_2$Cl$_2$, 0 °C, 79%

Scheme 146. Acid-catalysed Epoxide Opening

Epoxidation of unsaturated alcohol (156) led to the formation of two diastereoisomeric epoxides (157a and b) in the ratio 4.3:1 which was said to be consistent with the hydrogen-bonded interaction between oxygen and hydrogen atoms of peracid and the unsaturated alcohol.[157] The major *anti* diastereoisomer (157a) was isolated and exposed to a catalytic amount of camphorsulfonic acid (CSA) in dichloromethane inducing cyclisation which proceeded with complete diastereoselectivity to form the hydroxy-functionalised tetrahydropyran (158).

Following the same method we were able to synthesise epoxides (159a and b) in good yield by using purified *m*CPBA (**Scheme 147**). The crude ^{1}H NMR spectrum showed that the diastereomeric ratio was approximately 2:1 in favour of the *anti* epoxide but despite our best

efforts we were unable to separate the mixture using conventional chromatographic techniques. Although the compounds appeared as separate entities by tlc we found that chromatography on silica gel led to partial cyclisation and we were unable to recover either component with sufficient purity.
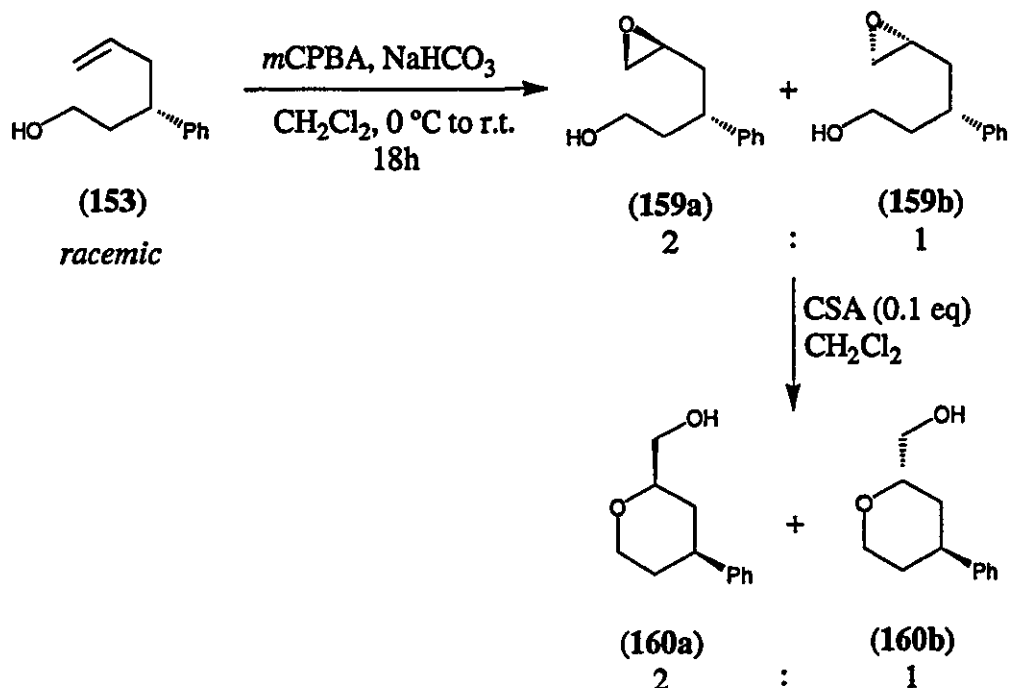
Scheme 147. Hydroxy-tetrahydropyran Synthesis.

Our inability to obtain a pure diastereoisomer of each epoxide was unimportant in this instance as the chiral centre is destroyed during cyclisation. The mixture of epoxides was therefore isolated using dry flash chromatography, in order to prevent significant cyclisation, then treated with a catalytic amount of CSA in dichloromethane at 0 °C (Scheme 147). We were pleased to observe conversion of the epoxide mixture, after overnight stirring, to the hydroxy-substituted tetrahydropyrans (160a and b).

The crude ^{1}H NMR spectrum showed that the diastereoisomers were present in approximately a 2:1 ratio indicating that with an unsubstituted epoxide, unlike Greeves, the cyclisation does not proceed stereoselectively. The tetrahydropyrans were isolated using column chromatography to give 28% of the major diastereoisomer (160a) and 12% of the minor diastereoisomer (160b) and by direct comparison with the ^{1}H NMR spectra of the iodotetrahydropyran we were able to determine to configuration of each epimer.

The key comparison in all the tetrahydropyran spectra arises from the proton attached at C-2, adjacent to the ring oxygen atom (Fig 15). Although the coupling is unclear in the hydroxy-tetrahydropyrans it is still possible to qualitatively detect differences in the coupling constants. In general the major diastereoisomer displays a large diaxial coupling (*ca.* 12 Hz) to the axial C-3 proton, whereas the minor isomer contains an equatorial proton on C-2 and a much weaker axial-equatorial coupling (*ca.* 4 Hz) is therefore seen.

X = I, SePh or OH

Major Diastereoisomer   Minor Diastereoisomer
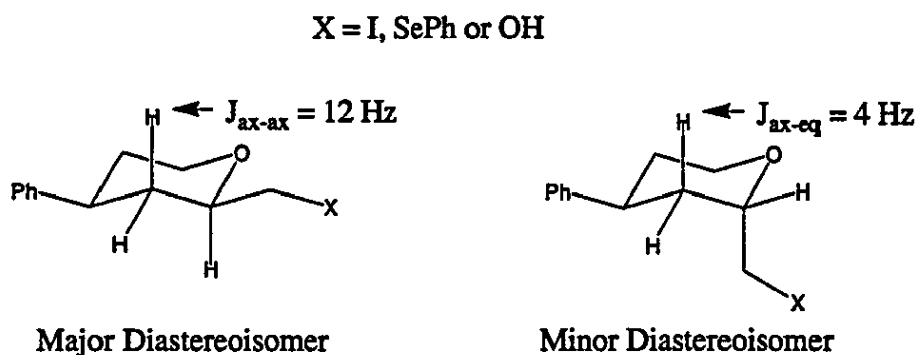
Fig 15. Coupling in the Tetrahydropyran Series.

3.3. Synthesis of Lactones.

The use of aldehydes such as (161a-c) by Greeves[139] to synthesise lactones was highlighted earlier in this section. Using sodium chlorite[158] in the presence of potassium orthophosphate buffer and 2-methyl-2-butene as chloride scavenger the aldehydes were converted cleanly to carboxylic acids (162a-c) in quantitative yield (Scheme 148).

Cyclisation Conditions

Method A : I_2 (3 eq), NaHCO$_3$ (3 eq), MeCN, 0 °C to r.t., 48h
Method B : PhSeCl (1.1 eq), pyridine (1.1 eq), CH$_2$Cl$_2$, -78 °C to r.t., 24h

(162a-c)   E$^+$ (163)   +   (164)   +   (165)

NaOCl$_2$
2-methyl-2-butene
THF

a R = i-Pr; b R = cyclohexyl; c R = n-Pr

(161a-c)
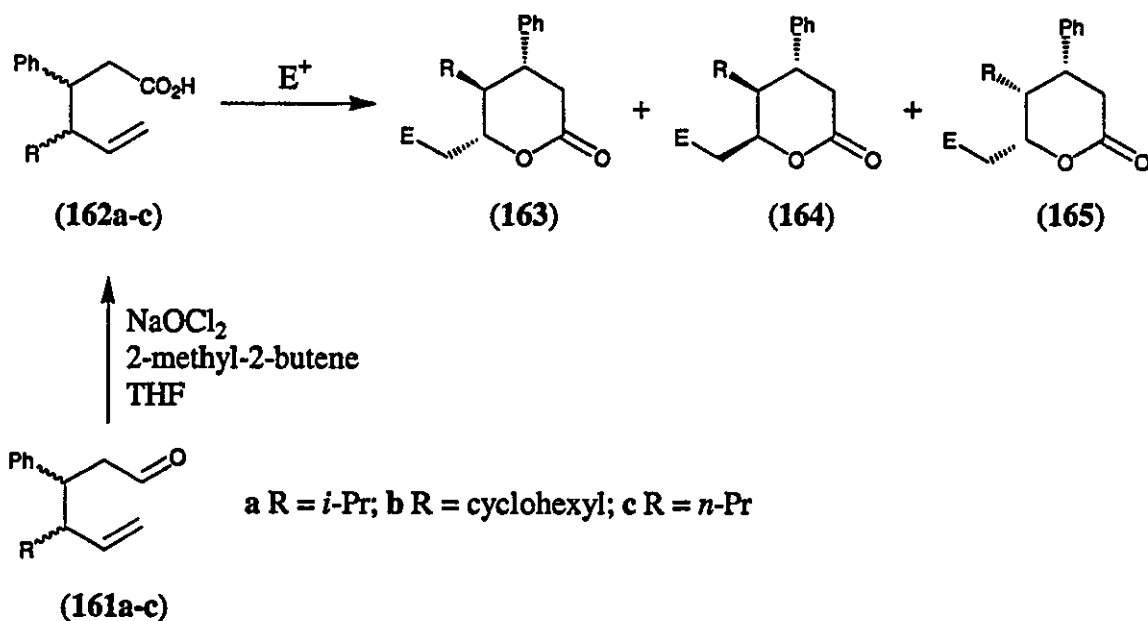
Scheme 148. Lactone Synthesis by Greeves[139]

The diastereomeric carboxylic acid mixtures underwent cyclisation, using iodine with sodium hydrogencarbonate in acetonitrile, to form δ-lactones (163 to 165a-c) in good yield as shown in **Table 21** and **Scheme 148**. Lactones were also readily obtained if phenylselenyl chloride and pyridine[159] were used to initiate cyclisation.

Table 21. δ-Lactone Synthesis

Entry	Substrate	R	E$^+$	Method	Yield/ %	Product ratio			Conformation of 163
						163	164	165	
1	162a	i-Pr	I$^+$	A	65	100	-	-	boat
2	162a	i-Pr	PhSe$^+$	B	71	96	-	4	boat
3	162b	cyclohexyl	I$^+$	A	59	94	-	6	boat
4	162b	cyclohexyl	PhSe$^+$	B	66	94	-	6	boat
5	162c	n-Pr	I$^+$	A	80	30	61	9	chair
6	162c	n-Pr	PhSe$^+$	B	79	71	29	trace	chair

The minor diastereoisomer of (162a) did not react and was recovered unchanged leading to the isolation of a single diastereoisomer of (163a). Whilst the preference for an equatorial iodonium ion during cyclisation was maintained both X-ray and ^{1}H NMR analysis of the methine proton next to the phenyl group showed this lactone to be in a boat conformation. Where R was changed to a less bulky group the selectivity of the reaction altered and the product was observed to be in the chair conformation. Formation of disubstituted lactones, where R=H, proceeded with much lower stereoselectivity (Scheme 149).

R'		Ratio
i-Pr, 71%	Method A	71 : 29
t-Bu, 78%	Method A	51 : 49
t-Bu, 75%	Method B	41 : 59
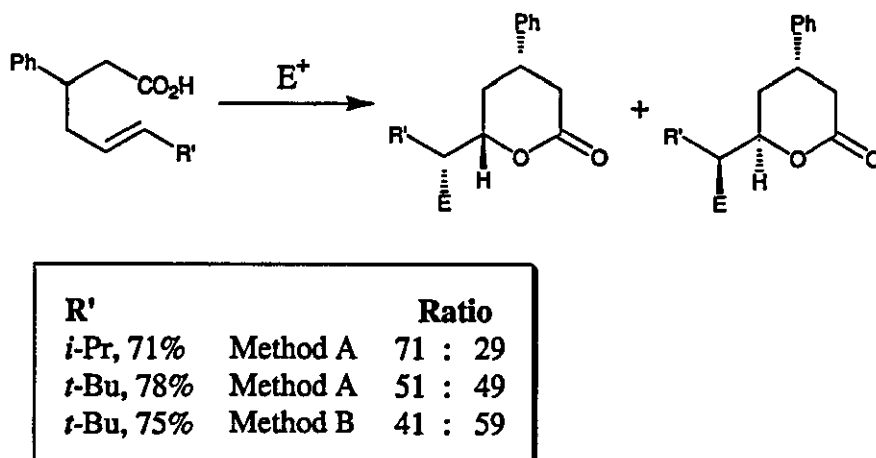
Scheme 149. Disubstituted Lactone Formation.

Greeves[139] suggests that the size of alkyl group R and the presence of the sp^2 carbonyl group govern the preference of boat-chair conformation and in turn the cyclisation stereoselectivity.

3.3.1. Electrophilic Cyclisation of Carboxylic Acids.

As with previous syntheses, we used the anionic amino-Cope rearrangement of amine (100f), using both chiral and racemic samples, to prepared aldehyde (52) in enough quantity for investigation of δ-lactone synthesis. Using Lingrens[158] conditions the aldehyde was converted cleanly to carboxylic acid (163) in good yield (Scheme 150).
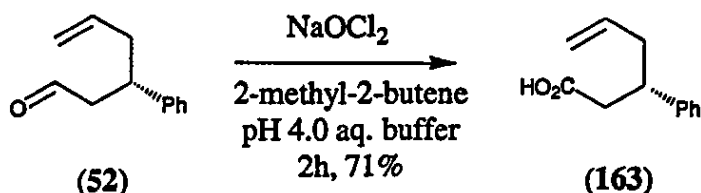
Scheme 150. Oxidation of Aldehyde.

Unfortunately we were unable to measure the *e.e.* of acid (163) using chiral HPLC, despite several attempts using different columns and solvent systems. The optical rotation suggested that the acid was non-racemic although it would be incorrect to suggest that the *e.e.* was unchanged from the aldehyde using such a measurement.

Because of problems with the *e.e.* determination of carboxylic acid (163) we decided to perform the initial δ-lactone syntheses using racemic compound. Once again we followed Greeves' examples using iodine and sodium hydrogencarbonate in acetonitrile to effect cyclisation (Scheme 151).
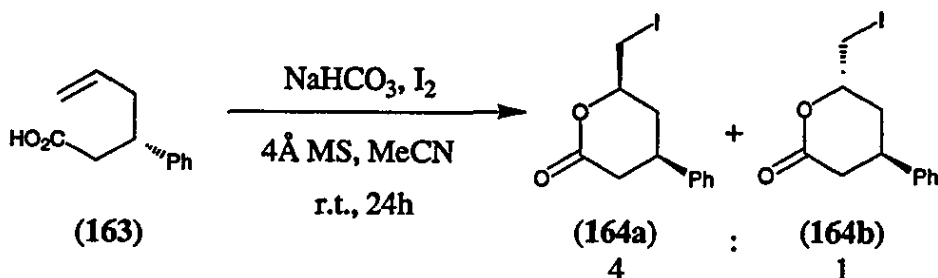
Scheme 151. Cyclisation of Racemic Acid.

The reaction was complete after overnight stirring and produced two diastereoisomeric lactones (**164a** and **b**) in an approximate ratio of 4:1 in favour of the *syn* isomer. The major isomer results from ring closure onto the equatorial iodonium ion as in the tetrahydropyran syntheses and the minor from cyclisation onto an axial intermediate. The stereochemistry of the two diastereoisomers was postulated on the basis of HETCOR and COSY data obtained (see **Appendix**) and also on the chemical shifts obtained from the ^{1}H NMR spectra.

As with the tetrahydropyrans one observes strong diaxial couplings throughout the ^{1}H NMR spectrum of the major isomer suggesting that the lactone exists in a chair-like configuration. The minor isomer however has a much less complex proton spectrum with no obvious diaxial or diequatorial couplings. Using coupling data alone it is difficult to be sure whether the δ-lactones exist wholly in the boat or chair conformation and we were unable to grow crystals for X-ray analysis of either isomer to clarify the situation.

Similar lactone syntheses have been performed on chiral amide (**165**) by Lutz[160] *et al* and the *e.e.* of the product was assigned on the basis of the optical purity of the starting material (**Scheme 152**). We therefore tentatively propose that our synthesis would proceed without loss of *e.e.* when using chiral acid as the starting material, thus constituting a 'formal' synthesis of enantiomerically enriched δ-lactones using the amino-Cope rearrangement.
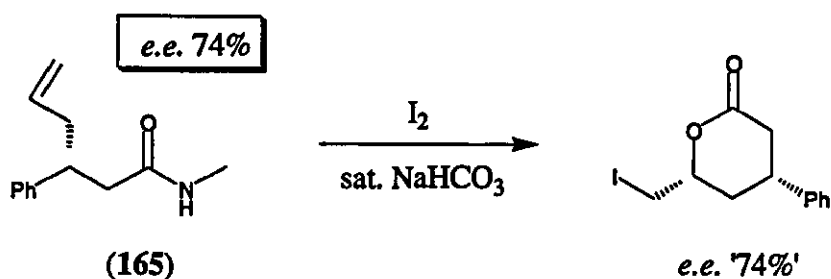
Scheme 152. Cyclisation of Chiral Amide.

3.3.2. Hydroxy-lactone Synthesis

Our previous success at epoxidising alcohol (**153**) to synthesise hydroxy-tetrahydropyrans led us to attempt the same transformation on the racemic carboxylic acid (±**163**). We treated the acid with purified *m*CPBA and sodium hydrogencarbonate in dichloromethane and obtained

a crude mixture of what appeared to be the desired diastereoisomeric epoxides (**166a** and **b**) and also some cyclised substrate (**167**) by ^{1}H NMR analysis (**Scheme 153**). Without attempting purification the crude mixture was treated with a catalytic amount of camphorsulfonic acid in dichloromethane to effect cyclisation. After column chromatography we obtained an excellent yield of the diastereoisomeric lactones (**167a** and **b**) which, after comparison with the iodolactone ^{1}H NMR spectra, appeared to show roughly a 2:1 ratio in favour of the diequatorial compound. The diastereisomeric ratio again appears to be determined by the axial / equatorial preference of the epoxide during cyclisation in a six membered chair-like conformation.
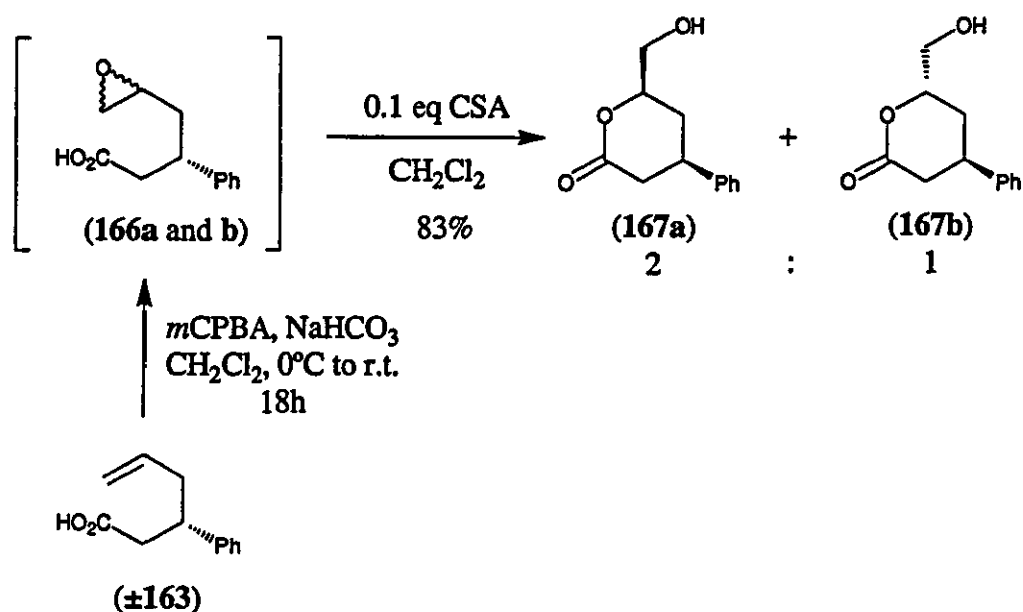
Scheme 153. Epoxidation and Cyclisation of Racemic Acid.

3.4. Attempted Synthesis of Piperidines

The introduction to this section highlighted several syntheses of chiral piperidines.[140-143] We were primarily interested in synthesising piperidines to demonstrate further applications of the amino-Cope rearrangement. Successful synthesis may in future lead to the preparation of azasugar analogues, which are known to be potent glycosidase inhibitors[161] whilst remaining metabolically inert.

Our initial strategy was similar to the syntheses of Ganem;[140] conversion of the aldehyde (52) to an *N*-protected amine (168) *via* reductive amination using benzylamine and sodium borohydride (Scheme 154). This strategy would also allow us to substitute the reducing agent with an organometallic nucleophile allowing for the synthesis of more heavily substituted amines if desired.

1) Ph-NH₂, CH₂Cl₂
r.t., 30 mins

2) NaBH₄, MeOH
0°C to r.t., 18h

(52)   79%   (168)
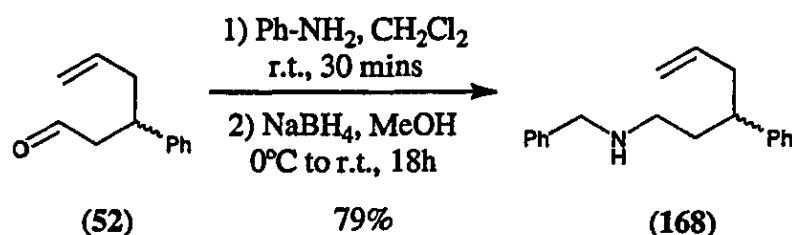
Scheme 154. Reductive Amination of Aldehyde.

The reaction proceeded well giving an overall yield of 79% over two steps. At this stage the reaction was performed solely on the racemic aldehyde whilst the synthetic methods were being developed.

The most obvious reaction with the protected amine was to attempt electrophilic cyclisation using iodine and sodium hydrogen carbonate as in the previous heterocycle syntheses. Despite a number of attempts we were unable to isolate any of the desired piperidine from the reaction mixture, both tlc and NMR evidence indicating that decomposition of the starting material had occurred (Scheme 155).

I₂, NaHCO₃
MeCN

(168)
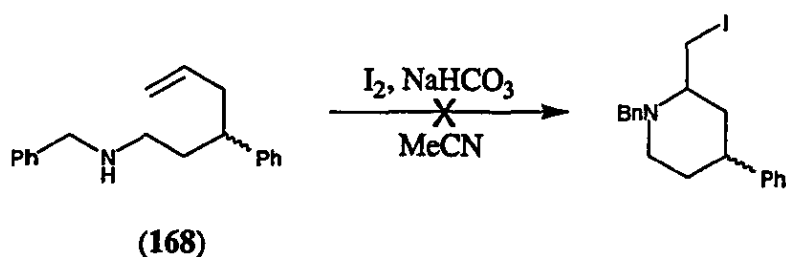
Scheme 155. Failed Electrophilic Cyclisation of Amine.

An alternative to electrophilic cyclisation is to form an epoxide and treat the compound with a catalytic amount of acid to induce ring closure as with the tetrahydropyrans and δ-lactones

synthesised previously. We first attempted react the amine (168) directly with mCPBA to generate either solely the epoxide or the N-oxidised epoxide, which we could later convert back to the amine with triphenylphosphine[162] (Scheme 156).
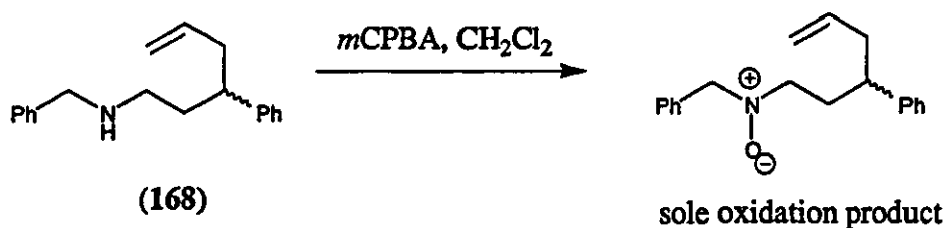
Scheme 156. Unsuccessful Epoxidation using mCPBA

Using a large excess of peracid however we were unable to obtain any epoxide and the crude ^{1}H NMR spectrum seemed to indicate that only the N-oxide was being formed. We therefore decided to protect the secondary amine as a carbamate adapting a simple method described by Greene.[163] By using the Cbz protecting group we reasoned that we could remove both N-protecting groups simultaneously using H_2/Pd or, if required, we could explore methods to selectively remove either group. The reaction did not appear to be proceeding at first using dichloromethane as a solvent so acetonitrile was added to try and increase the effectiveness of the base (Scheme 157). After 3h stirring at room temperature the sole product from the reaction was isolated in excellent yield using column chromatography and both IR and ^{1}H NMR data indicated that this was the Cbz-protected amine (169).
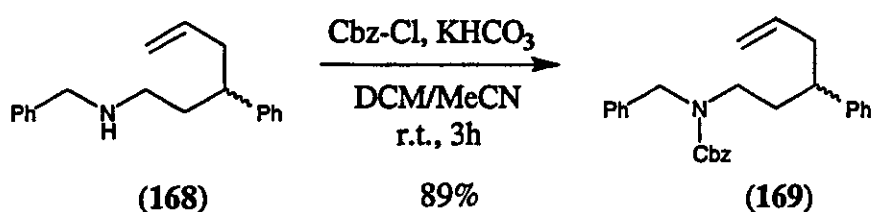
Scheme 157. Cbz Protection of Amine.

Using purified mCPBA as before we wished to epoxidise the di-protected amine but to our surprise the double bond remained intact despite performing the reaction at room temperature for 48 hours. As an alternative epoxidising reagent we chose to prepare dimethyldioxirane (DMDO) following a descriptive report by Adam.[164] A large excess of DMDO was made as

a solution in acetone and the protected amine was treated directly with this solution at −78 °C then allowed to warm slowly to room temperature. After overnight stirring at room temperature tlc indicated that the reaction had gone to completion. The crude ¹H NMR spectrum showed no traces of starting material and along with the IR spectrum it indicated that the sole product was the epoxide (170) as a mixture of diastereoisomers (Scheme 158).
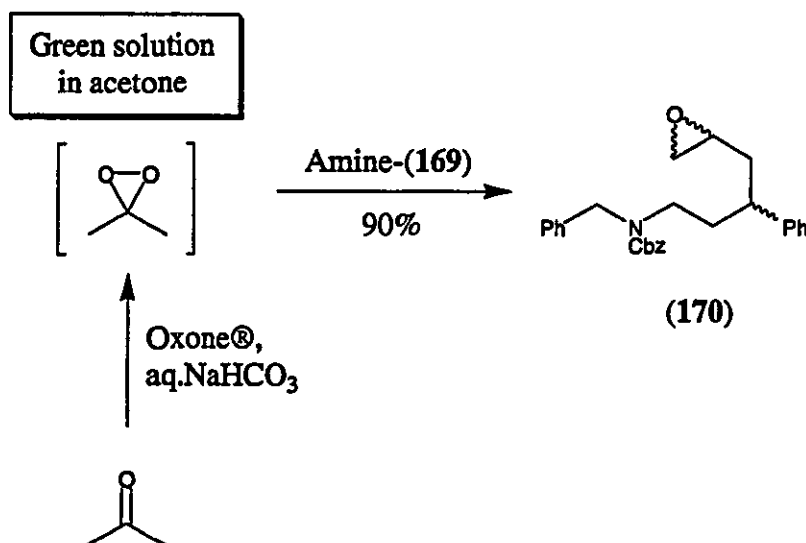
Scheme 158. Epoxidation using Dimethyldioxirane.

To complete the piperidine synthesis we simply needed to remove the amine protection and treat the free amine with an acid catalyst. Unfortunately we were unable to remove either protecting group using hydrogenation with Pd/C and the crude ¹H NMR spectrum appeared to show decomposition of the starting material. Although this was not a major set-back alternative protection/deprotection strategies would need to be explored in order to make this a viable synthetic route to hydroxy-piperidines.

3.5. Conclusions

The work undertaken in this section has demonstrated that it is possible to utilise the anionic amino-Cope rearrangement as a key step in the synthesis of a number of small heterocyclic targets that are themselves potentially useful chiral building blocks. A summary of the heterocycles synthesised during this work is shown in **Scheme 159** below.

1:1 ratio separable isomers

4:1 ratio separable isomers

2:1 ratio isomers

(155a) + **(155b)**

(154a) + **(154b)**

(160a) + **(160b)**

(164a) + **(164b)**

(167a) + **(167b)**

4:1 ratio separable isomers

2:1 ratio isomers
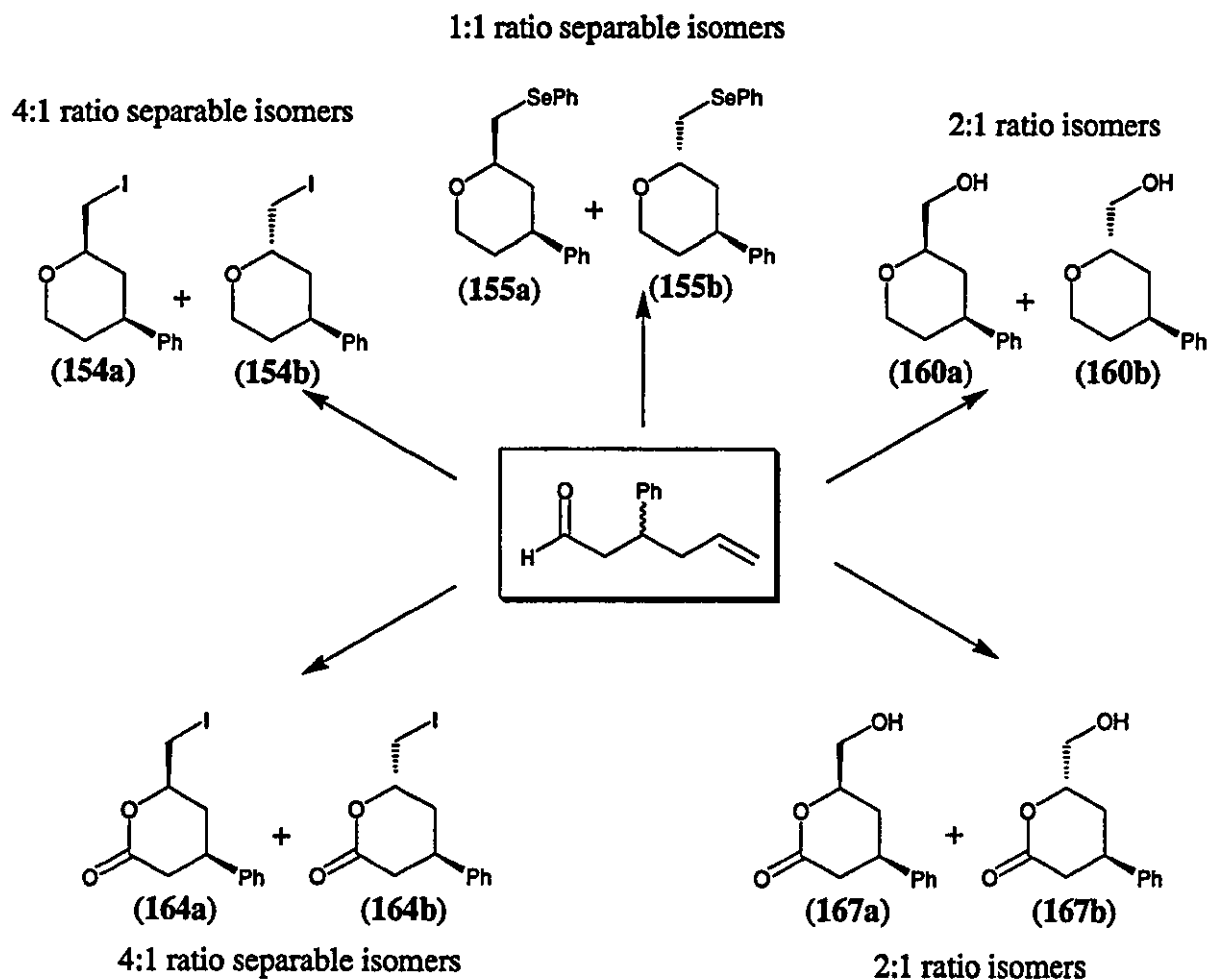
Scheme 159. Heterocyclic Targets Produced from Aldehyde (52).

With the ongoing development of the anionic amino-Cope rearrangement by other group members it is hoped that this preliminary set of compounds can be expanded on and provide an alternative, highly stereospecific, route to these important chiral building blocks.

Chapter 4

Experimental

by Nick D Kim
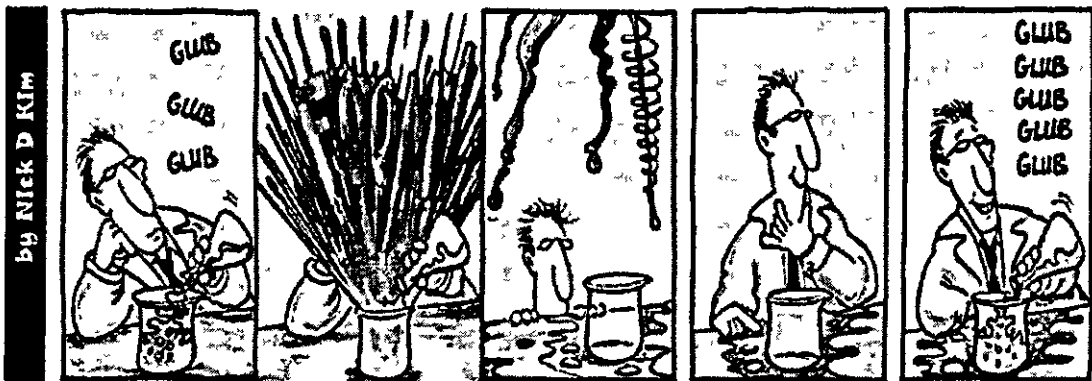
4.1 General Information

Solvents and Reagents

All solvents were dried, distilled and either used immediately or stored over 4Å molecular sieves.

acetonitrile:	distilled from calcium hydride
dichloromethane:	distilled from phosphorus pentoxide
diethyl ether:	distilled from lithium aluminium hydride or sodium/ benzophenone
ethyl acetate:	distilled from calcium chloride
40-60 petroleum ether:	distilled from calcium chloride
tetrahydrofuran:	distilled from sodium/ benzophenone

Unless otherwise stated light petroleum refers to 40-60 petroleum ether (fraction boiling between 40 and 60 °C). Anhydrous hexanes were purchased from Aldrich Chemical Co. Ltd. Other chemicals used in this work were obtained from Aldrich Chemical Co. Ltd, Lancaster Synthesis Ltd., or Acros (Fisher) Chemicals Ltd. and were distilled or recrystallised as required.

Chromatographic Procedures

Flash column chromatography was carried out using Merck Kieselgel 60 H silica. Samples were applied as saturated solutions in an appropriate solvent or pre-absorbed onto the minimum quantity of silica. Thin layer chromatography (tlc) was carried out using aluminum backed plates coated with Merck Kieselgel 60 GF$_{254}$. Plates were visualised under UV light (at 254 and/or 360 nm) or by staining with potassium permanganate or iodine.

Chiral HPLC was performed using a Thermoseparations modular machine (V100 UV Detector, P200 Pump and TSP Chromatographic Integrator) using ChiralCel OD and OD-H columns (250 x 4.6mm) purchased from Merck.

Spectra

Infra red spectra were recorded in the range 4000-600 cm^{-1} using a Perkin Elmer Paragon 1000 FT-IR Spectrometer, with internal calibration. Solid samples were run as Nujol® mulls or dissolved in an appropriate solvent and applied as a thin film to the IR plates. Liquid samples were applied neat to the plates and run as thin films.

^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded using a Bruker AC250 or DPX400 Spectrometer. Multiplicities were recorded as broad peaks (*br*), singlets (s), doublets (d), triplets (t), quartets (q) and multiplets (m). All NMR samples were prepared in deuterated solvents using tetramethylsilane (TMS) as an internal standard (0 ppm). Coupling constants (*J* values) are reported when possible in Hertz (Hz). Diastereoisomer ratios were calculated from the integration of suitable peaks in the ^{1}H NMR spectrum.

Electron Impact (E.I.) and Fast Atom Bombardment (F.A.B.) mass spectra were recorded on a Kratos MS80 Instrument.

Elemental Analysis

Elemental analyses were carried out on a Perkin Elmer 2400 CHN Elemental Analyser.

Other Data

Melting points were determined on a Leica Galen III instrument and are uncorrected. Optical rotations were performed where possible on a polAAR 2001 instrument using a 0.25dm cell. All yields are for isolated pure products except where diastereomeric mixtures are noted.

4.2 Experimental for Chapter 2

4.2.1. Preparation of Aminoalcohol Substituted Dienes

4.2.1.1. Preparation of Imines

1. (2R)-3-methyl-2-(3-phenylallylideneamino)-butan-1-ol
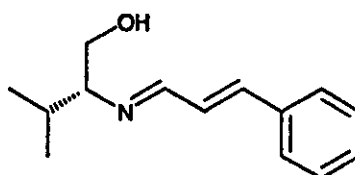
(99b)

trans-Cinnamaldehyde (1.36 g, 10.3 mmol) in dichloromethane (10 cm^3) was added dropwise to a stirred solution of R-valinol (1.06 g, 10.3 mmol) in dichloromethane (30 cm^3) at room temperature and the mixture was left to stir for 10 minutes. Anhydrous magnesium sulfate (1 g) was added and the reaction stirred for a further 10 minutes. Filtration and removal of the solvent under reduced pressure yielded imine **(99b)** (2.22 g, 99%) as a light yellow oil which was used without further purification, $[\alpha]_D^{25}$ -24.1 (c 1.43, CH$_2$Cl$_2$); ν_{max} (film)/cm^{-1} 3258 (O-H), 3060, 3027, 2959, 2872, 1636 (C=N), 1618 (C=C, Ar), 1449, 1387, 1164, 1075, 1028, 983, 750 and 691; δ_H (250MHz; CDCl$_3$) 0.86 (3H, d, J 6.8, CH(CH_3)(CH$_3$)), 0.94 (3H, d, J 6.8, CH(CH$_3$)(CH_3)), 1.89 (1H, m, CH(CH$_3$)$_2$), 2.75 (1H, br s, OH), 2.87 (1H, dt, J 6.8, CH), 3.81 (2H, m, CH_2OH), 6.88 (2H, m, CH=CHPh), 7.31-7.43 (5H, m, Ar-H) and 7.98 (1H, d, J 5.8, CH=N); δ_C (63MHz; CDCl$_3$) 19.3 (CH$_3$), 19.6 (CH$_3$), 30.1 (CH), 64.1 (CH$_2$), 79.1 (CH), 127.2 (2 x CH), 127.3 (CH), 128.6 (2 x CH), 129.1 (CH), 135.5 (q), 142.2 (CH) and 163.7 (CH); m/z (EI) 217 (M$^+$, 13%), 186 (100), 174 (31), 160 (29), 117 (21), 115 (40), 91 (16), 84 (19) and 49 (15). Found: 217.1467. C$_{14}$H$_{19}$NO requires M$^+$, 217.1480

2. (2S)-2-phenyl-2-(3-phenylallylideneamino)-ethanol
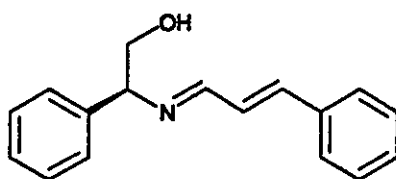
(99e)

trans-Cinnamaldehyde (1.89 g, 14.3 mmol) in dichloromethane (20 cm^3) was added dropwise to a stirred solution of S-phenylglycinol (2.04 g, 14.8 mmol) in dichloromethane (50 cm^3) at room temperature and the mixture was left to stir for 30 minutes. Anhydrous magnesium sulfate (1 g) was added and the reaction stirred for a further 10 minutes. Filtration and removal of the solvent under reduced pressure yielded imine (99e) (3.56 g, 99%) as a light yellow solid which was used without further purification, mp 103.0-103.7 °C (from ethyl acetate); $[\alpha]_D^{25}$ +136.2 (c 2.10, CHCl$_3$); v_{max} (film)/cm^{-1} 3222 (O-H), 3060, 3028, 2861, 1635 (C=N), 1493, 1450, 1386, 1164, 1066, 750 and 700; δ_H (250MHz; CDCl$_3$) 2.77 (1H, br s, OH), 3.87 (1H, dd, J 11.3 and 4.4, CHHOH), 4.00 (1H, dd, J 11.3 and 8.6, CHHOH), 4.39 (1H, dd, J 8.6 and 4.4, CHCH$_2$OH), 6.83 (1H, d, J 16.1, CH=CHPh), 6.96 (1H, dd, J 16.0 and 8.3, CH=CHPh), 7.23-7.41 (10H, m, Ar-H) and 8.10 (1H, d, J 8.3, CH=N); δ_C (63MHz; CDCl$_3$) 67.4 (CH$_2$), 77.0 (CH), 126.7 (CH), 127.1 (CH), 127.4 (CH), 127.9 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 129.4 (CH), 135.3 (q), 140.5 (q) and 164.8 (CH); m/z (EI) 251 (M$^+$, 3%), 220 (100), 115 (42), 91 (19) and 77 (7). Found: C, 81.0; H, 6.8; N, 5.5%; M$^+$, 251.13101. C$_{17}$H$_{17}$NO requires C, 81.2; H, 6.8; N, 5.6%; M$^+$, 251.13101

3. (2S)-3-phenyl-2-(3-phenylallylideneamino)-propan-1-ol
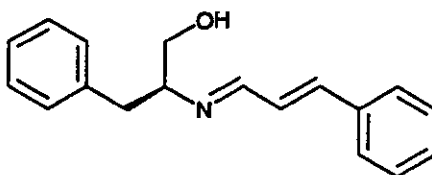
(99f)

trans-Cinnamaldehyde (1.01 g, 7.7 mmol) in dichloromethane (20 cm^3) was added dropwise to a stirred solution of S-phenylalaninol (1.16 g, 7.7 mmol) in dichloromethane (50 cm^3) at room temperature and the mixture was left to stir for 10 minutes. Anhydrous magnesium

sulfate (1 g) was added and the reaction stirred for a further 10 minutes. Filtration and removal of the solvent under reduced pressure yielded imine (99f) (2.00 g, 98%) as a colourless solid which was used without further purification, mp 115.7-116.7 °C (from ethyl acetate); $[\alpha]_D^{25}$ -9.8 (c 3.20, CH$_2$Cl$_2$); ν_{max} (film)/cm^{-1} 3224 (O-H), 3083, 3060, 3027, 2918, 2856, 1634 (C=N), 1618 (C=C, Ar), 1494, 1451, 1073, 1047, 979, 750, 700 and 691; δ_H (400MHz; CDCl$_3$) 2.78 (1H, dd, J 13.5 and 8.4, PhCH*H*), 2.93 (1H, dd, J 13.5 and 5.1, PhCH*H*), 3.42 (1H, m, C*H*CH$_2$OH), 3.78 (1H, dd, J 11.3 and 3.8, C*H*HOH), 3.87 (1H, dd, J 11.3 and 7.5, CH*H*OH), 4.23 (1H, br s, O*H*), 6.65 (1H, d, J 16.0, CH=C*H*Ph), 6.80 (1H, dd, J 16.0 and 8.5, C*H*=CHPh), 7.11-7.30 (10H, m, Ar-*H*) and 7.63 (1H, d, J 8.5, C*H*=N); δ_C (100MHz; CDCl$_3$) 39.4 (CH$_2$), 66.2 (CH$_2$), 75.0 (CH), 126.6 (CH), 127.5 (CH), 127.7 (2 x CH), 128.7 (2 x CH), 129.1 (2 x CH), 129.7 (CH), 130.0 (2 x CH), 135.8 (q), 138.9 (q), 142.9 (CH) and 164.5 (CH); m/z (EI) 265 (M$^+$, 12%), 234 (22), 174 (100), 115 (41) and 91 (34). Found: C, 81.3; H, 7.1; N, 5.3%; M$^+$, 265.14691. C$_{18}$H$_{19}$NO requires C, 81.5; H, 7.2; N, 5.3%; M$^+$, 265.14666.

4. (2S)-(1-methoxymethyl-2-phenylethyl)-(3-phenylallylidene)-amine
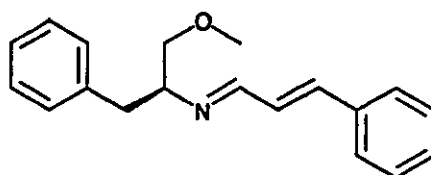
(121b)

The hydrochloride salt of S-(+)-2-amino-1-methoxy-3-phenylpropane (1.05 g, 0.52 mmol) was dissolved in saturated potassium carbonate solution (50 cm^3). The aqueous solution was extracted with dichloromethane (2 x 25 cm^3) and the organic extracts were dried over anhydrous potassium carbonate, filtered and the solvent removed under reduced pressure to yield S-(+)-2-amino-1-methoxy-3-phenylpropane as the free amine (0.84 g, 98% recovery).

trans-Cinnamaldehyde (0.69 g, 5.2 mmol) in dichloromethane (20 cm^3) was added dropwise to a stirred solution of S-(+)-2-amino-1-methoxy-3-phenylpropane (0.84 g, 5.1 mmol) in dichloromethane (20 cm^3) at room temperature and the mixture was left to stir for 30 minutes. Anhydrous magnesium sulfate (1 g) was added and the reaction stirred for a further 30 minutes. Filtration and removal of the solvent under reduced pressure yielded imine (121b) (1.43g, 98%) as a light yellow oil which was used without further purification,

$[\alpha]_D^{25}$ -18.9 (c 4.44 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3026, 2921, 2878, 2850, 1635 (C=N), 1619 (C=C, Ar), 1494, 1450, 1122, 1084, 980, 750, 700 and 692; δ_H (250MHz; CDCl$_3$) 2.80 (1H, dd, J 13.4 and 7.6, PhCHH), 2.98 (1H, dd, J 13.4 and 4.1, PhCHH), 3.33 (3H, s, OCH_3), 3.50 (3H, m, CH_2OMe and CHCH$_2$OMe), 6.77 (1H, d, J 16.0, CH=CHPh), 6.90 (1H, dd, J 16.0 and 8.7, CH=CHPh), 7.13-7.40 (10H, m, Ar-H) and 7.69 (1H, d, J 8.7, CH=N); δ_C (63MHz; CDCl$_3$) 39.3 (CH$_2$), 59.0 (CH$_3$), 72.1 (CH), 75.8 (CH$_2$), 126.1 (CH), 127.2 (2 x CH), 127.8 (CH$_2$), 128.2 (2 x CH$_2$), 128.7 (2 x CH), 129.1 (CH), 129.6 (2 x CH), 135.6 (q), 138.6 (q), 141.9 (CH) and 163.3 (CH); m/z (EI) 279 ((M + 1)$^+$, 100%). Found: 279.16240. C$_{19}$H$_{21}$NO requires (M + 1)$^+$, 279.16231

5. (2R)-2-[(Furan-2-ylmethylene)-amino]-3-methylbutan-1-ol[165]
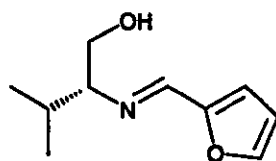
(102a)

2-Furaldehyde (0.76 cm^3, 9.2 mmol) in dichloromethane (20 cm^3) was added dropwise to a stirred solution of R-valinol (1.04 g, 10.1 mmol) in dichloromethane (20 cm^3) at room temperature and the mixture was left to stir for 1 hour. Anhydrous magnesium sulfate (1 g) was added and the reaction stirred for a further 10 minutes. Filtration and removal of the solvent under reduced pressure yielded imine (102a) (1.46 g, 80%) as a dark brown oil which was used without further purification,; ν_{max} (film)/cm^{-1} 3358 (O-H), 2959, 2877, 1645 (C=N), 1580, 1584, 1484, 1388, 1367, 1274, 1155, 1080, 1058, 1018, 932, 884 and 748; δ_H (250MHz; CDCl$_3$) 0.85 (3H, d, J 6.7, CH(CH_3)(CH$_3$)), 0.93 (3H, d, J 6.7, CH(CH$_3$)(CH_3)), 1.92 (1H, m, CH(CH$_3$)$_2$), 2.87 (1H, dt, J 7.5 and 3.8, CH), 3.65 (1H, br s, OH), 3.81 (2H, m, CH_2OH), 6.42 (1H, dd, J 3.5 and 1.7, Ar-H), 6.70 (1H, d, J 3.5, Ar-H) 7.47 (1H, d, J 1.6, Ar-H) and 7.93 (1H, s, N=CH); m/z (EI) 181 (M$^+$, 4%), 150 (100), 138 (40), 81 (45) and 55 (18). Found: 181.11065. C$_{10}$H$_{15}$NO$_2$ requires M$^+$, 181.11028.

6. (2S)-2-(3-furan-2-yl-allylideneamino)-3-methylbutan-1-ol
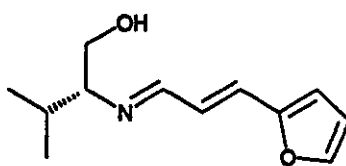
(102b)

3-(2-Furyl)-acrolein (1.00 g, 8.2 mmol) in dichloromethane (20 cm^3) was added dropwise to a stirred solution of S-valinol (0.86 g, 8.3 mmol) in dichloromethane (30 cm^3) at room temperature and the mixture was left to stir for 10 minutes. Anhydrous magnesium sulfate (1 g) was added and the reaction stirred for a further 10 minutes. Filtration and removal of the solvent under reduced pressure yielded imine (102b) (1.66 g, 97%) as an orange oil which was used without further purification [α]$_D^{25}$ +156.2 (c 3.40, CH$_2$Cl$_2$); ν_{max} (film)/cm^{-1} 3357 (O-H), 2959, 2871, 1629 (C=N), 1476, 1387, 1159, 1076, 1058, 1016 and 740; δ_H (400MHz; CDCl$_3$) 0.84 (3H, d, J 6.7, CH(CH$_3$)(CH$_3$)), 0.93 (3H, d, J 6.7, CH(CH$_3$)(CH$_3$)), 1.87 (1H, m, CH(CH$_3$)$_2$)), 2.85 (2H, dt, J 6.7 and 4.2, CH and OH), 3.79 (2H, m, CH$_2$OH), 6.41 (2H, d, J 1.4, Ar-H), 6.63 (1H, d, J 15.6, CH=CH-Fu), 6.75 (1H, dd, J 15.6 and 8.8, CH=CH-Fu), 7.43 (1H, s, Ar-H) and 7.89 (1H, J 8.8, CH=N); δ_C (100MHz; CDCl$_3$) 19.7 (CH$_3$), 20.0 (CH$_3$), 30.5 (CH), 64.7 (CH$_2$), 79.6 (CH), 112.1 (CH), 112.3 (CH), 126.0 (CH), 129.3 (CH), 144.2 (CH), 152.3 (q) and 163.7 (CH); m/z (EI) 207 (M$^+$, 40%), 176 (100), 164 (31), 134 (38), 117 (13), 107 (19), 91 (6) and 77 (11). Found: 207.12626. C$_{12}$H$_{17}$NO$_2$ requires M$^+$, 207.12593.

7. (2S)-3-Methyl-2-[3-(5-nitro-furan-2-yl)-allylideneamino]-butan-1-ol
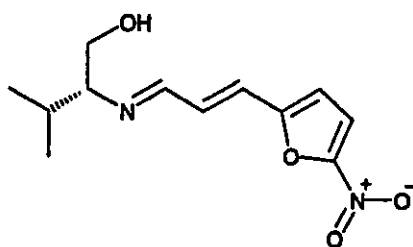
(102c)

5-Nitro-2-furylacrolein (1.00 g, 6.0 mmol) in dichloromethane (20 cm^3) was added dropwise to a stirred solution of S-valinol (0.66 g, 6.4 mmol) in dichloromethane (10 cm^3) at room

temperature and the mixture was left to stir for 20 minutes. Anhydrous magnesium sulfate (1 g) was added and the reaction stirred for a further 10 minutes. Filtration and removal of solvent under reduced pressure yielded imine (102c) (1.43 g, 95%) as an orange solid which was used without further purification, mp 124.3-124.9 °C (from ethyl acetate); $[\alpha]_D^{25}$ +38.5 (c 1.07, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3331 (O-H), 3150, 2960, 2871, 1624 (C=N), 1567, 1518, 1475, 1351, 1258, 1242, 1020, 971, 962, 810 and 737; δ_H (250MHz; CDCl$_3$) 0.86 (3H, d, J 6.8, CH(CH_3)(CH$_3$)), 0.95 (3H, d, J 6.8, CH(CH$_3$)(CH_3)), 1.89 (1H, m, CH(CH$_3$)$_2$)), 2.32 (1H, br s, OH), 2.92 (1H, q, CH), 3.80 (2H, d, J 5.6, CH_2OH), 6.66 (1H, d, J 3.8, Ar-H), 6.76 (1H, d, J 16.1, CH=CH-Fu), 7.09 (1H, dd, J 16.1 and 8.9, CH=CH-Fu), 7.33 (1H, d, J 3.8, Ar-H) and 8.01 (1H, J 8.9, CH=N); δ_C (63MHz; CDCl$_3$) 19.3 (CH$_3$), 19.5 (CH$_3$), 30.0 (CH), 64.3 (CH$_2$), 79.1 (CH), 111.7 (CH), 111.9 (CH), 125.6 (CH), 128.9 (CH), 143.7 (CH), 151.8 (q) and 163.2 (CH); m/z (EI) 253 ((M + 1)$^+$, 100%). Found: C, 56.9; H, 6.4; N, 10.8%; (M + 1)$^+$, 253.11853. C$_{12}$H$_{16}$N$_2$O$_4$ requires C, 57.13; H, 6.39; N, 11.10%; (M + 1)$^+$, 253.11883.

4.2.1.1. Preparation of Amines

8. (2R)-3-Methyl-2-((R)-1-styryl-but-3-enylamino)-butan-1-ol
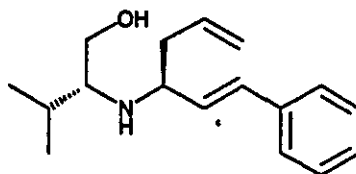
(100b)

Allyl bromide (2.09 cm^3, 24.2 mmol) was added dropwise *via* syringe to magnesium turnings (0.58 g, 24.2 mmol) in dry diethyl ether (30 cm^3) under an inert atmosphere. An ice bath was used to cool the reaction when it became too vigorous and after addition the reaction was stirred at room temperature for 30 minutes. Imine (99b) (2.10 g, 9.7 mmol) in dry diethyl ether (100 cm^3) under an inert atmosphere was added dropwise *via* cannulation to the stirred Grignard solution and the resulting mixture refluxed for 2 hours. The reaction was cooled to room temperature and quenched with water until a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue rinsed with diethyl ether (2 x 20 cm^3). The combined organic layers were washed twice with saturated aqueous sodium hydrogen carbonate solution, dried over sodium sulfate, filtered and the solvent removed under reduced

pressure to yield an orange oil. Flash column chromatography on silica gel, eluting with hexane-diethyl ether (6:1) gave amine (100b) (1.66 g, 66%) as a light orange oil, $[\alpha]_D^{25}$ +59.4 (c 2.04, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3407 (O-H), 3079, 3026, 2958, 1638 (C=C), 1599 (C=C, Ar), 1578, 1494, 1466, 1449, 1064, 968, 915, 749 and 694; δ_H (250MHz; $CDCl_3$) 0.90 (3H, d, J 6.8, CH(CH$_3$)(CH$_3$)) 0.94 (3H, d, J 6.8, CH(CH$_3$)(CH$_3$)) 1.77 (1H, m, CH(CH$_3$)$_2$) 2.32 (2H, m, CH$_2$CH=CH$_2$) 2.47 (1H, dt, J 6.7 and 4.5, CH) 3.31 (1H, dd, J 14.9 and 6.4, CH) 3.49 (1H, dd, J 10.7 and 4.9, CHHOH) 3.58 (1H, dd, J 10.7 and 4.3, CHHOH) 5.11 (2H, m, CH=CH$_2$) 5.84 (1H, m, CH=CH$_2$) 5.96 (1H, dd, J 15.8 and 8.6, CH=CHPh) 6.43 (1H, d, J 15.8, CH=CHPh) and 7.23-7.38 (5H, m, Ar-H); δ_C (63MHz; $CDCl_3$) 18.9 (CH), 19.7 (CH), 29.4 (CH), 40.6 (CH$_2$), 58.2 (CH), 60.1 (CH$_2$), 60.9 (CH), 117.5 (CH$_2$), 126.2 (2 x CH), 127.4 (CH), 128.5 (2 x CH), 131.0 (CH), 132.4 (CH), 134.9 (CH) and 137.0 (q); m/z (EI) 259 (M$^+$, 2%), 218 (100), 157 (13), 132 (18), 115 (30), 91 (22), 84 (24) and 49 (24). Found: 259.19329. $C_{17}H_{25}NO$ requires M$^+$, 259.19298.

9. (2S)-2-Phenyl-2-((S)-1-styryl-but-3-enylamino)-ethanol

(100e)
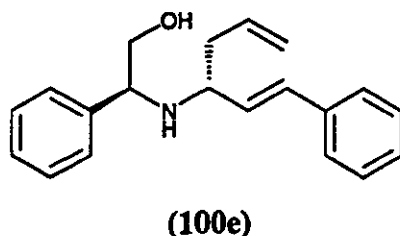
Allyl bromide (0.50 cm^3, 6.0 mmol) was added dropwise via syringe to magnesium turnings (0.14 g, 6.0 mmol) in dry diethyl ether (30 cm^3) under an inert atmosphere. An ice bath was used to cool the reaction when it became too vigorous and after addition the reaction was stirred at room temperature for 30 minutes. Imine (99e) (0.53 g, 2.1 mmol) in dry diethyl ether (40 cm^3) under an inert atmosphere was added dropwise via cannulation to the stirred Grignard solution and the resulting mixture refluxed for 2 hours. The reaction was cooled to room temperature and quenched with ice until a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue rinsed with diethyl ether (2 x 50 cm^3). The combined organic layers were washed twice with 2M aqueous sodium hydroxide solution, once with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and solvent removed under reduced pressure to yield a yellow oil. Flash column chromatography on silica gel, eluting with hexane-diethyl ether (3:1) gave amine (100e) (0.51 g, 83%) as a

light yellow oil, $[\alpha]_D^{25}$ -17.0 (c 3.50, CHCl₃); ν_{max} (film)/cm⁻¹ 3320 (O-H), 3060, 3025, 2975, 2925, 2867, 1638 (C=C), 1600 (C=C, Ar), 1493, 1451, 1061, 1027, 967, 916, 750 and 700; δ_H (400MHz; CDCl₃) 2.20 (1H, br s, O*H*), 2.36 (2H, m, C*H₂*CH=CH₂), 3.34 (1H, dd, *J* 14.2 and 6.4, CH), 3.54 (1, dd, *J* 10.6 and 7.4, C*H*HOH), 3.90 (1H, dd, *J* 10.6 and 4.6, CH*H*OH), 3.90 (1H, dd, *J* 7.4 and 4.6, C*H*CH₂OH), 5.11 (2H, m, CH=C*H₂*) 5.82 (1H, m, CH₂C*H*=CH₂), 5.95 (1H, dd, *J* 15.8 and 8.0, C*H*=CHPh), 6.38 (1H, d, *J* 15.8, CH=C*H*Ph) and 7.19-7.30 (10H, m, Ar-*H*); δ_C (100MHz; CDCl₃) 39.8 (CH₂), 58.2 (CH), 61.5 (CH), 66.0 (CH₂), 117.6 (CH₂), 126.3 (2 x CH), 127.3 (CH), 127.4 (3 x CH), 128.5 (2 x CH), 128.6 (2 x CH), 130.6 (CH), 132.7 (CH), 134.7 (CH), 136.9 (q) and 141.6 (q); *m/z* (EI) 293 (M+, <1%) and 115 (100). Found: 293.17738. C₂₀H₂₃NO requires M⁺, 293.17796.

10. (2*S*)-3-Phenyl-2-((*S*)-1-styryl-but-3-enylamino)-propan-1-ol
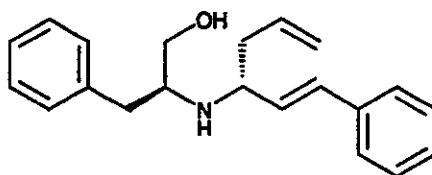
(100f)

Compound (**100f**) was prepared using two methods:

Method A

Allyl bromide (4.10 cm³, 47.4 mmol) was added dropwise *via* syringe to magnesium turnings (1.13 g, 47.2 mmol) in dry diethyl ether (50 cm³) under an inert atmosphere. An ice bath was used to cool the reaction when it became too vigorous and after addition the reaction was stirred at room temperature for 30 minutes. Imine (**99f**) (5.00 g, 18.9 mmol) in dry toluene/ dry diethyl ether (5:1, 100 cm³) under an inert atmosphere was added dropwise *via* cannulation to the stirred Grignard solution and the resulting mixture stirred at room temperature. After overnight stirring the reaction was quenched with water until a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue rinsed diethyl ether (2 x 100 cm³). The combined organic layers were washed twice with saturated aqueous sodium hydrogen carbonate solution, dried over sodium sulfate, filtered and the solvent removed under reduced pressure to yield a yellow solid. Recrystallisation from hexanes-diethyl ether gave amine (**100f**) (4.10 g, 71%) as a colourless powdery solid

Method B

Imine (99f) (4.61 g, 17.4 mmol) was dissolved in toluene/ diethyl ether (4:1, 100cm³) and stirred at room temperature with magnesium turnings (1.37 g, 57.1 mmol). Allyl bromide (4.93 cm³, 57.1 mmol) was added in two portions to the imine solution and the mixture was stirred under an inert atmosphere. After overnight stirring the reaction was quenched with water until a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue rinsed with diethyl ether (2 x 100 cm³). The combined organic layers were washed twice with saturated aqueous sodium hydrogen carbonate solution, dried over sodium sulfate, filtered and the solvent removed under reduced pressure to yield a yellow solid. Recrystallisation from hexane-diethyl ether gave amine (100f) (3.95 g, 74%) as a colourless powdery solid, mp 91.3-92.3 °C (from hexanes: diethyl ether); $[\alpha]_D^{25}$ -18.7 (c 1.11, CH₂Cl₂); ν_{max} (film)/cm⁻¹ 3406 (O-H), 3060, 3025, 2976, 2923, 1639 (C=C), 1600 (C=C, Ar), 1494, 1452, 1031, 968, 916, 749 and 699; δ_H (400MHz; CDCl₃) 2.23 (2H, t, CH_2CH=CH₂), 2.75 (2H, m, PhCH_2), 3.02 (1H, m, CH), 3.25 (1H, q, CHCH₂OH), 3.34 (1, dd, J 10.8 and 3.5, CHHOH), 3.63 (1H, dd, J 10.8 and 3.9, CHHOH), 5.07 (2H, m, CH=CH_2) 5.72 (2H, m, CH₂CH=CH₂ and CH=CHPh), 6.38 (1H, d, J 15.8, CH=CHPh) and 7.13-7.32 (10H, m, Ar-H); δ_C (100MHz; CDCl₃) 39.3 (CH₂), 41.3 (CH₂), 57.0 (CH), 58.3 (CH), 62.5 (CH₂), 118.0 (CH₂), 126.8 (2 x CH), 126.9 (CH), 127.9 (CH), 129.0 (4 x CH), 129.7 (2 x CH), 131.3 (CH), 132.5 (CH), 135.3 (CH), 137.2 (q) and 139.1 (q); m/z (FAB) 308 ((M + 1)⁺, 93%), 266 (82), 216 (20), 157 (91), 129 (50) and 115 (100). Found: C, 81.5; H, 8.1; N, 4.3%; (M + 1)⁺, 308.20144. C₂₁H₂₅NO requires C, 82.0; H, 8.1; N, 4.6%; (M + 1)⁺, 308.20119.

X-ray structure analysis of this compound confirmed that the relative stereochemistry is as drawn (Appendix).

11. ((2S)-1-Methoxymethyl-2-phenyl-ethyl)-((S)-1-styryl-but-3-enyl)-amine
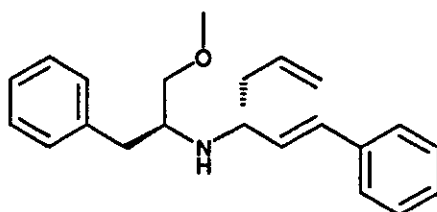
(122b)

Imine (121b) (0.53 g, 1.9 mmol) was dissolved in THF (20 cm³) and stirred with magnesium turnings (0.084g, 2.7 mmol) under an inert atmosphere. Allyl bromide (0.30 cm³, 3.5 mmol)

was added dropwise *via* syringe and the mixture stirred at room temperature. After overnight stirring the reaction was quenched with water until a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue rinsed with dichloromethane (3 x 20 cm^3). The combined organic layers were washed twice with saturated aqueous sodium hydrogen carbonate solution, dried over sodium sulfate, filtered and the solvent removed under reduced pressure to yield a yellow oil. Flash column chromatography on silica gel, eluting with hexane-diethyl ether (6:1) gave a 15: 1 inseparable mixture of (*S, S*)- and (*S, R*)-amines (**122b**) (0.30g, 49%) as a light yellow oil; v_{max} (film)/cm^{-1} 3322 (N-H), 3060, 3025, 2977, 2923, 1639 (C=C), 1600 (C=C, Ar), 1494, 1452, 1118, 1070, 967, 915, 748, 694; δ_H (400MHz; CDCl$_3$) (* = minor isomer) 1.52 (1H, br s, N*H*), 2.28 (2H, t, C*H$_2$*CH=CH$_2$), 2.77 (2H, m, PhC*H$_2$*), 3.02 (1H, m, C*H*CH$_2$OMe), 3.25 (1H, dd, *J* 9.4 and 4.4, C*H*HOMe), 3.35 (3H, s, CH$_2$OC*H$_3$*), 3.36 (2H, m, CH*H*OMe and C*H*), 5.09 (2H, m, CH=C*H$_2$*) 5.78 (2H, m, CH$_2$C*H*=CH$_2$ and C*H*=CHPh), 6.37 (1H, d, *J* 16.0, CH=C*H*Ph) 6.62* (1H, d, *J* 16.0, CH=C*H*Ph) and 7.07-7.22 (10H, m, Ar-*H*); δ_C (100MHz, CDCl$_3$) 39.7 (CH$_2$), 41.3 (CH$_2$), 56.4 (CH), 58.7 (CH), 59.4 (CH$_3$), 73.9 (CH$_2$), 117.8 (CH$_2$), 126.5 (CH), 126.7 (CH), 127.7 (2 x CH), 128.7 (2 x CH), 128.9 (2 x CH), 129.8 (2 x CH), 131.0 (CH), 132.0 (CH), 135.4 (CH), 137.4 (q) and 139.7 (q); *m/z* (FAB) 321 ((M + 1)$^+$, 60%). Found: 321.20960. C$_{22}$H$_{27}$NO requires (M + 1)$^+$, 321.20925

12. 2-Phenyl-1-trimethylsilanyloxymethyl-ethyl)-(1-styryl-but-3-enyl)-amine
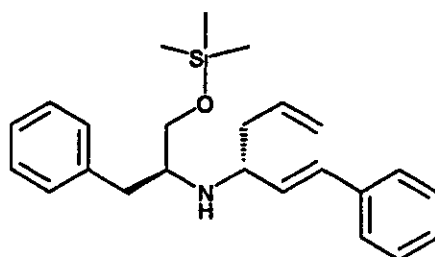
(±124)

Racemic amine (**100f**) (1.83 g, 6.0 mmol) was dissolved in THF (40 cm^3) and cooled to -78 °C in a dry ice/ acetone slush bath under an inert atmosphere. A 2.5M solution of *n*-BuLi in hexanes (2.86 mL, 7.2 mmol) was added dropwise and the mixture stirred for 5 minutes before addition of chlorotrimethylsilane (0.80 mL, 6.3 mmol) and the reaction was stirred at -78 °C for 15 minutes before warming to room temperature. After stirring for a further 12h the reaction was quenched with 5mL water, dried over sodium sulfate, filtered through a small

pad of Celite and the solvent removed *in vacuo* to yield a brown oil. Flash column chromatography on silica, eluting with light petroleum-ethyl acetate (4:1) gave *O*-protected amine (124) (0.84 g, 37%) as a light yellow oil, v_{max} (film)/cm^{-1} 3061, 3026, 2954, 2860, 1639 (C=C), 1601 (C=C, Ar), 1494, 1452, 1251, 1100, 1070, 967, 913, 875, 841, 747 and 699; δ_H (400MHz, CDCl$_3$) 0.10 (9H, s, Si(C*H*$_3$)$_3$), 1.64 (1H, br s, NH), 2.25 (2H, t, *J* 6.8, C*H*$_2$CH=CH$_2$), 2.68 (1H, dd, *J* 13.3 and 7.0, PhCH*H*), 2.79 (1H, dd, *J* 13.3 and 7.0, PhCH*H*), 2.92 (1H, m, C*H*CH$_2$OTMS), 3.32 (1H, dd, *J* 14.6 and 6.5, CH), 3.42 (1H, dd, *J* 10.2 and 4.3, C*H*HOTMS), 3.49 (1H, dd, *J* 10.2 and 5.0, CH*H*OTMS), 5.08 (2H, m, CH=C*H*$_2$) 5.76 (2H, m, CH$_2$C*H*=CH$_2$ and C*H*=CHPh), 6.35 (1H, d, *J* 15.8, CH=C*H*Ph) and 7.14-7.29 (10H, m, Ar-*H*); δ_C (100MHz; CDCl$_3$) 0.3 (3 x CH$_3$), 39.6 (CH$_2$), 41.5 (CH$_2$) 58.1 (CH), 58.8 (CH), 63.3 (CH$_2$), 117.9 (CH$_2$), 126.5 (CH), 126.8 (2 x CH), 127.7 (CH), 128.7 (2 x CH), 129.0 (2 x CH), 129.9 (2 x CH), 131.1 (CH), 133.7 (CH), 135.6 (CH), 137.6 (q) and 140.0 (q).

Further analysis of this compound was not possible as it decomposes during normal handling.

13. [1-(tert-Butyl-dimethyl-silanyloxymethyl)-2-phenyl-ethyl]-(1-styryl-but-3-enyl)-amine
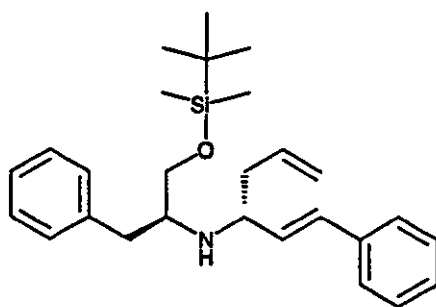
(±122c)

Racemic amine (100f) (108 mg, 0.35 mmol) was dissolved in THF (20 cm^3) and stirred at rt under an inert atmosphere. *tert*-Butyldimethylsilyl chloride was added neat in one portion and the reaction was stirred for 10 minutes before addition of triethylamine (0.11 cm^3, 0.72 mmol). After stirring for 72 h the reaction mixture was filtered through a small pad of Celite and the solvent removed under reduced pressure to yield a light yellow oil. Flash column chromatography on silica gel, eluting with hexanes-diethyl ether (4:1) gave *O*-protected amine (122c) (67 mg, 45%) as a colourless oil; v_{max} (film)/cm^{-1} 3304 (N-H), 3061, 3026, 2953, 2928, 2856, 1639 (C=C), 1601 (C=C, Ar), 1495, 1471, 1388, 1360, 1253, 1104, 966, 915, 836, 776, 747 and 698; δ_H (250MHz; CDCl$_3$) 0.10 (6H, s, Si(C*H*$_3$)$_2$), 0.94 (9H, s,

C(CH_3)$_3$), 1.76 (1H, br s, NH), 2.31 (2H, t, J 6.8, CH_2CH=CH$_2$), 2.70 (1H, dd, J 13.3 and 6.9, PhCHH), 2.82 (1H, dd, J 13.3 and 7.2, PhCHH), 2.92 (1H, m, CHCH$_2$OTBDMS), 3.38 (1H, dd, J 14.6 and 6.7, CH), 3.44 (1H, dd, J 10.1 and 3.8, CHHOTBDMS), 3.58 (1H, dd, J 10.1 and 4.5, CHHOTBDMS), 5.12 (2H, m, CH=CH_2), 5.77 (1H, m, CH$_2$CH=CH$_2$), 5.89 (1H, dd, J 16.0 and 8.1 CH=CHPh), 6.40 (1H, d, J 16.1, CH=CHPh) and 7.16-7.38 (10H, m, Ar-H); δ_C (63MHz; CDCl$_3$) –5.0 (2 x CH$_3$), 18.6 (q), 26.3 (3 x CH$_3$), 39.4 (CH$_2$), 41.6 (CH$_2$), 58.0 (CH), 58.5 (CH), 62.9 (CH$_2$), 117.9 (CH$_2$), 126.4 (CH), 126.7 (2 x CH), 127.6 (CH), 128.6 (2 x CH), 128.8 (2 x CH), 129.8 (2 x CH), 130.9 (CH), 133.6 (CH), 135.4 (CH), 137.4 (q) and 140.0 (q); m/z (FAB) 422 ((M + 1)$^+$, 82%), 380 (82), 330 (21), 157 (63), 129 (28) and 117 (100). Found: 422.28790. C$_{27}$H$_{39}$NOSi requires (M + 1)$^+$, 422.28792.

14. (2R)-2-((R)-1-Furan-2-yl-but-3-enylamino)-3-methyl-butan-1-ol[165]
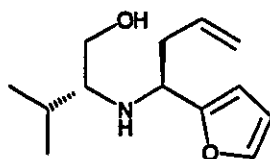
(103a)

Allyl bromide (2.80 cm^3, 31.1 mmol) was added dropwise *via* syringe to magnesium turnings (0.81 g, 33.7 mmol) in dry diethyl ether (25 cm^3) under an inert atmosphere. An ice bath was used to cool the reaction when it became too vigorous and after addition the reaction was stirred at room temperature for 30 minutes. Imine (102a) (1.95 g, 10.8 mmol) in dry diethyl ether (20 cm^3) under an inert atmosphere was added dropwise *via* cannulation over 20 minutes to the stirred Grignard solution and the resulting mixture refluxed for 3 hours. The reaction was cooled to room temperature and quenched with ice until a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue rinsed with diethyl ether (2 x 100 cm^3). The combined organic layers were washed twice with aqueous sodium hydroxide solution (2M), dried over sodium sulfate, filtered and the solvent removed under reduced pressure to yield a brown oil. Flash column chromatography on silica gel, eluting with light petroleum-ethyl acetate (4:1) gave amine (103a) (0.90 g, 38%) as a brown oil, v$_{max}$ (film)/cm^{-1} 3408 (O-H), 3078, 2959, 1642 (C=C), 1506, 1467, 1150, 1072, 1048, 1010, 919 and 734; δ_H (250MHz; CDCl$_3$) 0.82 (6H, d, J 6.8, CH(CH_3)$_2$), 1.65 (1H, m, CH(CH$_3$)$_2$), 2.27 (2H, dt, J 6.8 and 4.3, CHCH$_2$OH), 2.51 (1H, t, J 7.0, CH_2CH=CH$_2$), 3.40 (1H, dd, J 10.9 and 4.5, CHHOH), 3.57 (1H, dd, J 10.9 and 4.1, CHHOH), 3.74 (1H, t, J 7.0, CH), 5.06 (2H,

m, CH=CH$_2$), 5.74 (1H, m, CH=CH$_2$), 6.12 (1H, d, J 3.1, Ar-H) 6.28 (1H, dd, J 3.1 and 1.9, Ar-H) and 7.34 (1H, d, J 1.9, Ar-H).

## 15. (2R)-2-[(S)-1-(2-Furan-2-yl-vinyl)-but-3-enylamino]-3-methyl-butan-1-ol
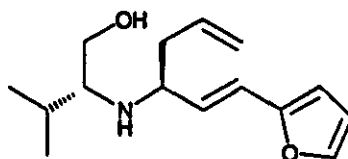
(103b)

Allyl bromide (1.90 cm^3, 22.0 mmol) was added dropwise *via* syringe to magnesium turnings (0.52 g, 21.6 mmol) in dry diethyl ether (70 cm^3) under an inert atmosphere. An ice bath was used to cool the reaction when it became too vigorous and after addition the reaction was stirred at room temperature for 30 minutes. Imine (102b) (1.50 g, 7.2 mmol) in dry toluene (25 cm^3) under an inert atmosphere was added dropwise *via* cannulation to the stirred Grignard solution and the resulting mixture warmed to 60 °C for 1.5 hours. The reaction was cooled to room temperature and quenched with water until a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue rinsed with diethyl ether (2 x 20 cm^3). The combined organic layers were washed twice with saturated aqueous sodium hydrogencarbonate solution, dried over sodium sulfate, filtered and the solvent removed under reduced pressure to yield an orange oil. Flash column chromatography on silica, eluting with hexane-diethyl ether (6:1) gave amine (103b) (1.42 g, 79%) as a light orange oil, [α]$_D^{25}$ -44.8 (c 5.30, CH$_2$Cl$_2$); ν$_{max}$ (film)/cm^{-1} 3407 (O-H), 3076, 2958, 2928, 2872, 1639 (C=C), 1561, 1490, 1466, 1151, 1060, 1013, 963, 926 and 733; δ$_H$ (400MHz; CDCl$_3$) 0.90 (3H, d, J 6.7, CH(CH$_3$)(CH$_3$)), 0.93 (3H, d, J 6.7, CH(CH$_3$)(CH$_3$)), 1.76 (1H, m, CH(CH$_3$)$_2$), 2.30 (2H, m, CH$_2$CH=CH$_2$), 2.45 (1H, dt, J 6.7 and 4.4, CH), 3.26 (1H, dt, J 8.6 and 6.5, CH), 3.41 (1H, dd, J 10.6 and 4.9, CHHOH), 3.56 (1H, dd, J 10.6 and 4.2, CHHOH), 5.11 (2H, m, CH=CH$_2$), 5.82 (1H, m, CH=CH$_2$), 5.94 (1H, dd, J 15.8 and 8.6, CH=CH-Fu), 6.21 (1H, d, J 3.4, Ar-H), 6.23 (1H, d, J 15.8, CH=CH-Fu), 6.37 (1H, dd, J 3.4 and 1.7, Ar-H) and 7.33 (1H, d, J 1.7, Ar-H); δ$_C$ (100MHz; CDCl$_3$) 19.3 (CH), 20.0 (CH), 30.0 (CH), 41.3 (CH$_2$), 58.4 (CH), 60.6 (CH$_2$), 61.3 (CH), 107.8 (CH), 111.5 (CH), 118.0 (CH$_2$), 119.8 (CH), 131.6 (CH), 135.3 (CH), 142.2 (CH) and 152.8 (q); m/z (FAB) 250 ((M + 1)$^+$, 35%). Found: 250.17280. C$_{15}$H$_{23}$NO$_2$ requires (M + 1)$^+$, 250.17288.

16. (2R)-2-((S)-1-Allyl-but-2-enylamino)-3-methyl-butan-1-ol[105]
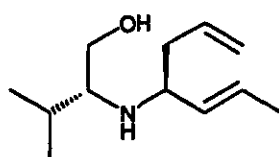
(104)

trans-Crotonaldehyde (1.34 g, 18.9 mmol) in dichloromethane (20 cm³) was added dropwise to a stirred solution of *R*-valinol (1.99 g, 19.2 mmol) in dichloromethane (30 cm³) at room temperature. The mixture was left to stir for 30 minutes before addition of magnesium sulfate (1 g) and stirred for a further 10 minutes. Filtration and removal of solvent under reduced pressure yielded the imine (2.89 g, 96%) (1657cm⁻¹, C=N) as a light yellow oil which was used without further purification for the next step.

Allyl bromide (5.00 cm³, 59.1 mmol) was added dropwise *via* syringe to magnesium turnings (1.43 g, 59.6 mmol) in dry diethyl ether (20 cm³) under an inert atmosphere. An ice bath was used to cool the reaction when it became too vigorous and after addition the reaction was stirred at room temperature for 30 minutes. The imine (2.89 g, 28.0 mmol) in dry diethyl ether (20 cm³) under an inert atmosphere was added dropwise *via* cannulation to the stirred Grignard solution and the resulting mixture refluxed for 1.5 hours. The reaction was cooled to room temperature and quenched with ice until a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue rinsed with diethyl ether (2 x 25 cm³). The combined organic layers were washed twice with saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield a light yellow oil. Flash column chromatography on silica gel, eluting with light petroleum-ethyl acetate (4:1) gave amine (104) (2.90 g, 79%) as a light yellow oil, v_{max} (film)/cm⁻¹ 3406 (O-H), 3076, 2959, 1640 (C=C), 1467, 1380, 1062, 995, 968, 913 and 821; δ_H (250MHz, CDCl₃) 0.89 (3H, d, *J* 6.7, CH(C*H₃*)(CH₃)), 0.92 (3H, d, *J* 6.7, CH(CH₃)(C*H₃*)), 1.69 (3H, dd, *J* 6.3 and 1.6, CH=C(H)C*H₃*), 1.75 (1H, m, C*H*(CH₃)₂), 1.87 (1H, br s, O*H*), 2.20 (2H, m, C*H₂*CH=CH₂), 2.41 (1H, dt, *J* 6.3 and 4.9, C*H*), 3.07 (1H, dt, *J* 8.4 and 6.6, C*H*CH₂OH), 3.36 (1H, dd, *J* 10.6 and 5.0, C*H*HOH), 3.52 (1H, dd, *J* 10.6 and 4.3, CH*H*OH), 5.07 (2H, m, CH=C*H₂*), 5.23 (1H, m, C*H*=C(H)CH₃), 5.50 (1H, dq, *J* 15.3 and 6.4, CH=C(*H*)CH₃), and 5.78 (1H, m, C*H*=CH₂); δ_C (63MHz, CDCl₃) 17.6 (CH), 18.8 (CH₃), 19.6 (CH₃), 29.4 (CH), 40.9 (CH₂), 57.8 (CH), 60.0 (CH₂),

60.7 (CH), 116.9 (CH$_2$), 126.6 (CH), 133.8 (CH), 135.4 (CH); m/z (EI, LRMS) 198 (M$^+$, 4%), 166 (36), 156 (86), 95 (74), 72 (91), 70 (100), 67 (67), 60 (57), 55 (69) and 41 (63).

4.2.2. Anionic Amino-Cope Rearrangements

17. **(S)-3-Phenylhex-5-enal** from (2R)-3-Methyl-2-((R)-1-styrylbut-3-enylamino)-butan-1-ol[105]

(52)
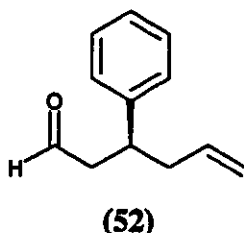
Amine **(100b)** (0.12 g, 0.46 mmol) was dried *in vacuo* for 1 h then dissolved in dry tetrahydrofuran (20 cm^3) under an inert atmosphere and cooled to -78 °C in a dry ice/ acetone slush bath. A 2.5M solution of nButyllithium in hexanes (0.5 cm^3, 1.25 mmol) was added dropwise *via* syringe over 5 minutes and the resulting mixture stirred for 30 minutes before warming to room temperature. The reaction was heated to reflux for 1.5 h then quenched with water (0.5 cm^3), dried over anhydrous sodium sulfate, filtered through a small pad of Celite and the solvent removed under reduced pressure to give an orange oil. Flash column chromatography on silica gel, eluting with light petroleum-diethyl ether (10:1) hydrolysed the crude oxazolidine giving aldehyde **(52)** (52 mg, 65%) as a light yellow oil, [α]$_D^{25}$ +4.5 (c 0.8, CHCl$_3$).

e.e. 84% measured by derivatisation with ephedrine (Experimental Entry **22**). Spectral analysis consistent with Entry **19** below.

18. **(R)-3-Phenylhex-5-enal** from (2S)-2-phenyl-2-(3-phenylallylideneamino)-ethanol[105]

(52)
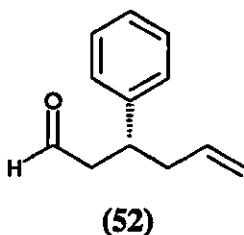
Amine (100e) (1.39 g, 4.8 mmol) was dried *in vacuo* for 1 h then dissolved in dry tetrahydrofuran (20 cm^3) under an inert atmosphere and cooled to -78 °C in a dry ice/ acetone slush bath. A 1.6M solution of *n*Butyllithium in hexanes (7.5 cm^3, 12.0 mmol) was added dropwise *via* syringe over 5 minutes and the resulting mixture stirred for 30 minutes before warming to room temperature. The reaction was heated to reflux for 2 h then quenched with water (0.5 cm^3), dried over anhydrous sodium sulfate, filtered through a small pad of Celite and the solvent removed under reduced pressure to give an orange oil. Flash column chromatography on silica gel, eluting with light petroleum-diethyl ether (10:1) hydrolysed the crude oxazolidine giving aldehyde (52) (0.50 g, 61%) as a light yellow oil.

e.e. 83% measured by derivatisation with ephedrine (Experimental Entry 22). Spectral data consistent with Entry 19 below.

19. (*R*)-3-Phenylhex-5-enal from (2*S*)-3-phenyl-2-(3-phenylallylideneamino)-propan-1-ol[105]

(52)
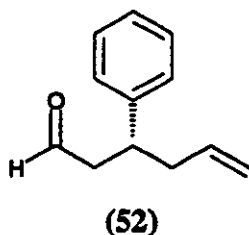
Amine (100f) (0.98 g, 3.2 mmol) was dried *in vacuo* for 1 h then dissolved in dry tetrahydrofuran (20 cm^3) under an inert atmosphere and cooled to -78 °C in a dry ice/ acetone slush bath. A 2.5M solution of *n*Butyllithium in hexanes (3.3 cm^3, 8.3mmol) was added dropwise *via* syringe over 5 minutes and the resulting mixture stirred for 30 minutes before warming to room temperature. The reaction was heated to reflux for 1 h then quenched with water (0.5 cm^3), dried over anhydrous sodium sulfate, filtered through a small pad of Celite and the solvent removed under reduced pressure to give an orange oil. Flash column chromatography on silica, eluting with light petroleum-diethyl ether (10:1) hydrolysed the crude oxazolidine giving aldehyde (52) (0.40 g, 72%) as a light yellow oil, $[\alpha]_D^{25}$ -8.3 (c 6.10, CHCl$_3$); ν_{max} (film)/cm^{-1} 3064, 3029, 3003, 2977, 2922, 2825, 2724, 1724 (C=O), 1640 (C=C), 1603, 1494, 1453, 1441, 1414, 996, 917, 762 and 701; δ_H (400 MHz; CDCl$_3$) 2.40 (2H, m, C(2)*H$_2$*), 2.71 (1H, ddd, *J* 16.6, 8.0 and 2.0, C*H$_2$*CH=CH$_2$), 2.79 (1H, ddd, *J* 16.6, 6.5 and 2.0, C*H*), 3.30 (1H, m, PhC*H*), 5.01 (2H, m, CH=C*H$_2$*) 5.66 (1H, m, C*H*=CH$_2$), 7.20 (3H, m, Ar-*H*), 7.31 (2H, m, Ar-*H*) and 9.67 (1H, t, *J* 2.0, C*H*=O); *m/z* (EI) 174 (M$^+$, 3%), 156

(26), 130 (31), 105 (100), 91 (7) and 77 (11). Found: 174.10464. $C_{12}H_{14}O$ requires M$^+$, 174.10446.

e.e. 94% measured by derivatisation with ephedrine (Experimental Entry 22).

20. (*R*)-3-Phenylhex-5-enal from ((2*S*)-1-Methoxymethyl-2-phenyl-ethyl)-((*S*)-1-styryl-but-3-enyl)-amine

(52)
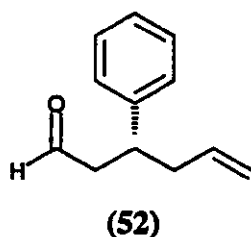
Amine **(122b)** (92 mg, 0.29 mmol) was dried *in vacuo* overnight then dissolved in dry tetrahydrofuran (10 cm^3) under an inert atmosphere and cooled to -78 °C in a dry ice/ acetone slush bath. A 2.5M solution of *n*Butyllithium in hexanes (0.20 cm^3, 0.5 mmol) was added dropwise *via* syringe over 5 minutes and the resulting mixture stirred for 30 minutes before warming to room temperature. The reaction was stirred for 1 h then quenched with water (0.5 cm^3), dried over anhydrous sodium sulfate, filtered through a small pad of Celite and the solvent removed under reduced pressure to give an orange oil. Flash column chromatography on silica gel, eluting with hexanes-diethyl ether (9:1) hydrolysed the crude oxazolidine giving aldehyde **(52)** (34mg, 68%) as a light yellow oil. The aldehyde was immediately derivatised with ephedrine (see Experimental Entry **22** for full method) and the *e.e.* measured from the resulting ^{1}H NMR spectrum was effectively 0%.

21. (3*R*)-3-Furan-2-ylhex-5-enal

(113)
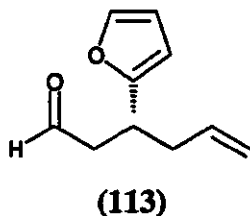
Amine **(103a)** (0.47 g, 1.9 mmol) was dried *in vacuo* for 1 h then dissolved in dry tetrahydrofuran (20 cm^3) under an inert atmosphere and cooled to -78 °C in a dry ice/ acetone

slush bath. A 1.6M solution of *n*Butyllithium in hexanes (3.2 cm³, 5.1 mmol) was added dropwise *via* syringe over 5 minutes and the resulting mixture stirred for 10 minutes before warming to room temperature. The reaction was heated to reflux for 1 h then quenched with water (0.5 cm³), dried over anhydrous magnesium sulfate, filtered through a small pad of Celite and the solvent removed under reduced pressure to give an orange oil. Flash column chromatography on silica gel, eluting with light petroleum-ethyl acetate (4:1) hydrolysed the crude oxazolidine giving *aldehyde* (113) (0.22 g, 73%) as a light yellow oil $[\alpha]_D^{25}$ -6.9 *(c 5.20, CHCl₃)*; ν_{max} (film)/cm⁻¹ 3117, 3078, 2926, 2828, 2725, 1725 (C=O), 1641 (C=C), 1506, 1148, 1012, 920, 735 and 598; δ_H (250 MHz; CDCl₃) 2.44 (2H, m, C(2)*H₂*), 2.72 (2H, m, C*H₂*CH=CH₂), 3.42 (1H, m, C*H*), 5.05 (2H, m, CH=C*H₂*) 5.69 (1H, m, CH₂C*H*=CH₂), 6.04 (1H, d, *J* 3.3, Ar-*H*), 6.28 (1H, dd, *J* 3.3 and 2.0, Ar-*H*) 7.32 (1H, d, *J* 2.0, Ar-*H*) and 9.73 (1H, t, *J* 2.0, C*H*=O); δ_C (63 MHz; CDCl₃) 32.9 (CH₂), 37.9 (CH₂), 46.5 (CH), 105.4 (CH₂), 110.0 (CH), 117.5 (CH), 135.1 (CH), 141.3 (CH), 163.2 (q) and 201.1 (CH); *m/z* (EI) 164 (M⁺, 17%), 147 (62), 121 (100), 95 (72), 81 (48), 67 (39), 55 (31) and 41 (36). Found: 164.08359. C₁₀H₁₂O₂ requires M⁺, 164.08373

e.e. 36% measured by derivatisation with ephedrine (see Experimental Entry **22** for example method).

4.2.3. Measurement of Enantiomeric Excess (and Determination of Absolute Configuration) by Derivatisation with (-)-Ephedrine[110]

22. (2*S*, 4*S*, 5*R*)-3,4-dimethyl-2-[(2*R*)-2-phenylpent-4-enyl]-1,3-oxazolidine and (2*S*, 4*S*, 5*R*)-3,4-dimethyl-2-[(2*S*)-2-phenylpent-4-enyl]-1,3-oxazolidine
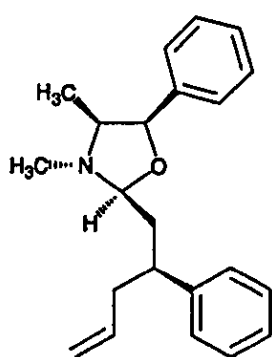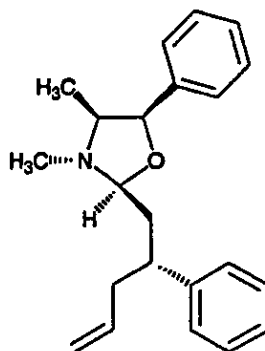
'(*S*)'-diastereoisomer   '(*R*)'-diastereoisomer

Derivatisation of (3*S*)-3-phenylhex-5-enal (*S*-52), (3*R*)-3-phenylhex-5-enal (*R*-52) and (3*R*)-3-Furan-2-ylhex-5-enal (*R*-113) with (-)-ephedrine to give the diastereoisomeric oxazolidines was undertaken as follows:

1 equivalent of aldehyde (52) was dissolved in dichloromethane(5 to 25 cm³) and stirred with activated 4Å molecular sieves. (-)-Ephedrine (1 equiv.) was added and the mixture was stirred at room temperature overnight then filtered through a thin pad of Celite. The solvent was removed under reduced pressure to give the mixture of oxazolidines as a light yellow oil. ^{1}H NMR analysis of the diastereoisomeric mixture enabled measurement of the *d.e.* which could be directly related to the *e.e.* of the starting aldehyde.

Oxazolidine data from derivatising (*R*)-3-phenylhex-5-enal (*e.e.* 94%); δ_H (400 MHz; CDCl₃) 0.53 (3H, d, *J* 6.8, C*H*₃CH, *S*-isomer), 0.57 (3H, d, *J* 6.8, C*H*₃CH, *R*-isomer), 2.00 (2H, m, C*H*₂CHPh, both isomers), 2.02 (3H, s, N-C*H*₃, *S*-isomer), 2.16 (3H, s, N-C*H*₃, *R*-isomer), 2.36 (2H, m, C*H*₂CH=CH₂, both isomers), 2.52-2.62 (1H, m, CH₃C*H*, both isomers), 3.00 (1H, m, C*H*Ph, both isomers), 3.43 (1H, m, C(4)-*H*, *S*-isomer), 3.95 (1H, m, C(4)-*H*, *R*-isomer), 4.88 (3H, m, PhC*H* and CH=C*H*₂, both isomers), 5.60 (1H, m, C*H*=CH₂, both isomers) and 7.12-7.25 (10H, m, Ar-*H*); δ_C (100 MHz; CDCl₃) 15.31 (CH, *S*-isomer), 15.52 (CH, *R*-isomer), 36.62 (CH₃, *S*-isomer), 37.29 (CH₃, *R*-isomer), 40.17 (CH₂, *S*-isomer), 40.69 (CH₂, *R*-isomer), 42.36 (CH, both isomers), 42.65 (CH₂, both isomers), 64.47 (CH, *S*-isomer), 64.67 (CH, *R*-isomer), 82.12 (CH, *R*-isomer), 82.31 (CH, *S*-isomer), 95.95 (CH, *S*-isomer), 96.18 (CH, *R*-isomer), 116.67 (CH₂, *S*-isomer), 116.75 (CH₂, *R*-isomer), 126.45 to 128.78 (10 x Ar-CH, both isomers), 136.92 (CH, *R*-isomer), 137.02 (CH, *S*-isomer), 140.56 (q, both isomers) and 145.07 (q, both isomers).

4.2.4. Ethyl Grignard Reaction and *e.e.* Determination

23. 3-Phenylpentanal[166]

(101)
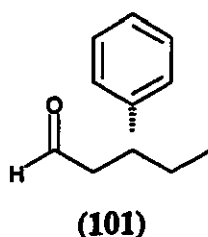
Ethyl bromide (0.45 cm^3, 2.0 mmol) was added dropwise *via* syringe to magnesium turnings (137mg, 5.7 mmol) in dry diethyl ether (5 cm^3) under an inert atmosphere. An ice bath was used to cool the reaction when it became too vigorous and after addition the reaction was stirred at room temperature for 15 minutes. Imine (99e) (0.47 g, 1.8 mmol) in dry diethyl ether (30 cm^3) was added dropwise *via* syringe to the stirred Grignard solution at 0 °C under an inert atmosphere and the resulting mixture refluxed for 3 hours. The reaction was cooled to room temperature and quenched with ice until a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue rinsed with diethyl ether (2 x 50 cm^3). The combined organic layers were washed twice with 2M aqueous sodium hydroxide solution, twice with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield an orange oil. Flash column chromatography on silica gel, eluting with light petroleum-acetone (24:1) gave aldehyde (101) (59 mg, 19%) as a light yellow oil, δ_H (250 MHz; CDCl$_3$) 0.80 (3H, t, J 7.3, CH$_2$CH_3), 1.66 (2H, m, CH_2CH$_3$), 2.71 (2H, dd, J 7.3 and 2.2, CH_2), 3.08 (1H, m, PhCH), 7.16-7.30 (5H, m, Ar-H) and 9.65 (1H, t, J 2.1, CH=O); δ_C (63 MHz; CDCl$_3$) 11.8 (CH), 27.5 (CH$_2$), 41.7 (CH), 50.2 (CH$_2$), 126.5 (CH), 127.5 (2 x CH), 128.1 (2 x CH), 143.6 (q) and 201.8 (CH).

e.e. 4% measured by derivatisation with ephedrine (Experimental Entry 22).

4.3 Experimental for Chapter 3

4.3.1. Tetrahydropyran Synthesis

24. (3R)-3-Phenylhex-5-enol[167]

(153)
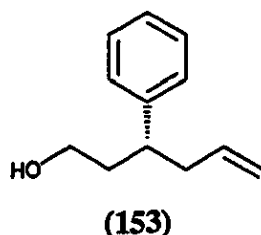
Aldehyde **(52)** (0.20 g, 1.2 mmol) was dissolved in methanol (20 cm^3) and cooled to 0 °C in an ice bath. Sodium borohydride (0.13 g, 3.5 mmol) was added neat in two portions and the mixture stirred for 2 h whilst warming slowly to rt. The solvent was removed under reduced pressure and the gelatinous residue was dissolved in dichloromethane (30 cm^3), to which flash silica (0.50 g) was added and the solvent removed again. Flash column chromatography on silica, eluting with hexane-diethyl ether (4:1) gave alcohol **(153)** (0.20 g, 99%) as a colourless oil, v_{max} (film)/cm^{-1} 3334 (OH), 3076, 3027, 2928, 1640, 1602, 1494, 1452, 1440, 1047, 1028, 994, 913, 761 and 701; δ_H (400 MHz; CDCl$_3$) 1.25 (1 H, br s, O*H*), 1.80 (1 H, m, C*H*HCH$_2$OH), 1.99 (1 H, m, CH*H*CH$_2$OH), 2.38 (2 H, t, *J* 7.0, C*H$_2$*CH=CH$_2$), 2.80 (1 H, m, C*H*Ph), 3.46 (1 H, m, C*H*HOH), 3.54 (1 H, m, CH*H*OH), 4.96 (2 H, m, CH=C*H$_2$*), 5.67 (1 H, m, C*H*=CH$_2$), 7.19 (3 H, m, Ar-*H*) and 7.30 (2 H, m, Ar-*H*); δ_C (100 MHz; CDCl$_3$) 39.0 (CH$_2$), 41.7 (CH$_2$), 42.7 (CH), 61.3 (CH$_2$), 116.6 (CH$_2$), 126.7 (CH), 128.0 (2 x CH), 128.8 (2 x CH), 137.1 (CH) and 144.9 (q); *m/z* (EI) 176 (M$^+$, 3%), 158 (9), 135 (43), 131 (8), 117 (9), 105 (100), 91 (52) and 77 (6). Found: 176.12008. C$_{12}$H$_{16}$O requires M$^+$, 176.12011.

HPLC analysis (ChiralCel OD, Hexanes/ Propan-2-ol 95: 5, 0.6 mL.min^{-1}, r.t. 18.9 (*R*) and 22.2 (*S*) mins) gave an *e.e.* of 92% which is in good agreement with the *e.e.* of the starting aldehyde measured by ^{1}H NMR.

25. (2R, 4S) and (2S, 4S)-2-Iodomethyl-4-phenyltetrahydropyran

major   *minor*

(154a) and (154b)
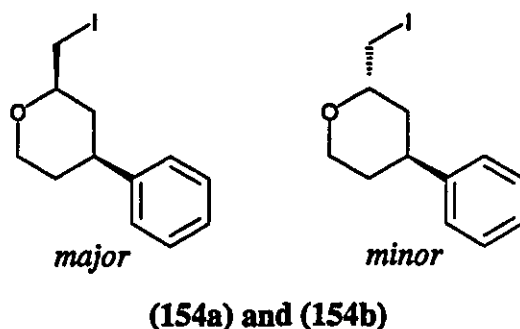
A solution of alcohol (**153**) (0.08 g, 0.57 mmol) in acetonitrile (15 cm^3) was stirred with 4Å MS and sodium hydrogencarbonate (0.15 g, 1.8 mmol) at room temperature. Iodine (0.44 g, 1.7 mmol) was added in one portion and the mixture stirred for 24 h before quenching with saturated aqueous sodium thiosulfate solution (2 cm^3). The acetonitrile was removed under reduced pressure and the residue was partitioned between ethyl acetate and water (40 cm^3, 1:1). The organic layer was removed and the aqueous portion extracted with a further 20 cm^3 of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to give a yellow oil which was shown to be a mixture of diastereoisomers (4:1) by ^{1}H NMR. Flash column chromatography on silica gel, eluting with light petroleum-ethyl acetate (10:1) gave the major diastereoisomer (**154a**) (0.08g, 60%) as a colourless oil (the minor diastereoisomer (**154b**) was isolated using preparative tlc to provide a ^{1}H NMR reference thus enabling *de* measurement).

(154a) analysis

v_{max} (film)/cm^{-1} 3060, 3026, 2934, 2828, 1602, 1494, 1452, 1378, 1254, 1193, 1125, 1084, 1029, 1012, 756 and 699; δ_H (400 MHz; CDCl$_3$) 1.39 (1 H, dt, *J* 12.3 and 11.1, C(3)H_{ax}H), 1.77 (2 H, m, C(5)H_2), 2.04 (1 H, m, C(3)HH_{eq}), 2.82 (1 H, tt, *J* 11.6 and 4.4, CH_{ax}Ph), 3.22 (1 H, dd, *J* 10.4 and 6.4, CHHI), 3.25 (1 H, dd, *J* 10.4 and 5.2, CHHI), 3.46 (1 H, m, C(2)H_{ax}), 3.63 (1 H, m, CH_{ax}HO), 4.19 (1 H, ddd, *J* 11.6, 4.4 and 1.8, CHH_{eq}O) and 7.21-7.34 (5 H, m, Ar-H); δ_C (100 MHz; CDCl$_3$) 9.9 (CH$_2$), 33.4 (CH$_2$), 39.6 (CH$_2$), 41.8 (CH), 68.9 (CH$_2$), 77.4 (CH), 126.9 (CH), 127.1 (2 x CH), 129.1 (2 x CH) and 145.4 (q); *m/z* (EI) 302 (M$^+$, 32%), 175 (33), 161 (100), 131 (28), 117 (23), 104 (25), 91 (43), 77 (12) and 43 (15). Found: 302.01672. C$_{12}$H$_{15}$IO requires M$^+$, 302.01676

HPLC analysis (ChiralCel OD-H, Hexanes/ Propan-2-ol 99.5: 0.5, 0.25 mL.min^{-1}) gave an *e.e.* of 92% which is in good agreement with the *e.e.* of the starting alcohol.

(154b) analysis

δ_H (400 MHz; CDCl$_3$) 1.91 (4 H, m, C(3)H_2 and C(5)H_2), 3.08 (1 H, m, CH_{ax}Ph), 3.41 (2 H, m, CH_2I), 3.80 (2 H, t, CH_2O), 3.95 (1 H, m, C(2)H_{eq}) and 7.22-7.37 (5 H, m, Ar-H).

26. (2R, 4S) and (2S, 4S)-4-Phenyl-2-phenylselenylmethyltetrahydropyran
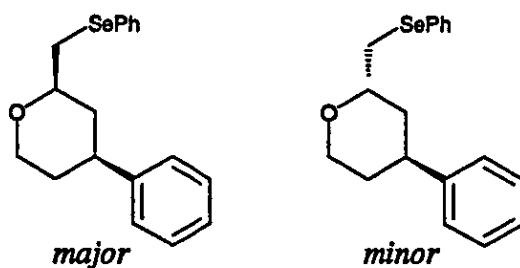
(155a) and (155b)

A solution of alcohol **(153)** (68 mg, 0.39 mmol) in dry dichloromethane (20 cm^3) was cooled to -78 °C. Pyridinium *p*-toluenesulfonate (32 mg, 0.12 mmol) was added and the mixture was stirred for 10 minutes before addition of *N*-phenylselenylphthalimide (208 mg, 0.68 mmol) neat in one portion. The reaction was stirred at -78 °C for 2 h then for a further 3h at 0 °C. When the reaction was complete by tlc the solution was filtered through Celite to remove excess diphenyldiselenide. Removal of solvent under reduced pressure furnished a yellow oil which was shown to be a mixture of diastereoisomers (1:1) by ^{1}H NMR. Flash column chromatography on silica gel, eluting with light petroleum-ethyl acetate (7:1) gave **(155a)** (48 mg, 39%) and **(155b)** (45mg, 36%) as a light yellow oils;

(155a) analysis

v_{max} (film)/cm^{-1} 3056, 3025, 2932, 2845, 1601, 1577, 1493, 1477, 1451, 1436, 1377, 1251, 1155, 1124, 1085, 1072, 1022, 1012, 756, 736, 691 and 669; δ_H (400 MHz; CDCl$_3$) 1.51 (1 H, m, C(3)H_{ax}H), 1.77 (2 H, m, C(5)H_2), 2.03 (1 H, m, C(3)HH_{eq}), 2.77 (1 H, m, CH_{ax}Ph), 2.98 (1 H, dd, J 12.0 and 5.6, CHHSePh), 3.13 (1 H, dd, J 12.0 and 6.8, CHHSePh), 3.60 (2 H, m, C(2)H_{ax} and CH_{ax}HO), 4.15 (1 H, m, CHH_{eq}O) and 7.19-7.30 (8H, m, Ar-H), 7.51-7.53 (2 H, m, Ar-H); δ_C (100 MHz; CDCl$_3$) 33.3 (CH$_2$), 33.5 (CH$_2$), 39.2 (CH$_2$), 41.6 (CH), 68.5 (CH$_2$), 77.3 (CH), 126.4 (CH), 126.7 (CH), 126.8 (2 x CH), 128.6 (2 x CH), 129.1 (2 x CH),

130.6 (q), 132.5 (2 x CH) and 145.4 (q); m/z (EI) 332 (M$^+$, 74%), 161 (99), 143 (23), 131 (31), 117 (38), 105 (46), 91 (100), 77 (32), 57 (19) and 43 (24). Found: 332.06827. $C_{18}H_{20}OSe$ requires M$^+$, 332.06793.

HPLC analysis (ChiralCel OD-H, Hexanes/ Propan-2-ol 99.5: 0.5, 0.25 mL.min^{-1}) clearly showed that the sample was greatly enantiomerically enriched when compared to an authentic racemic sample, although full baseline separation was not achieved.

(155b) analysis

$[\alpha]_D^{25}$ -20.0 (c 0.6, CHCl$_3$); ν_{max} (film)/cm^{-1} 3056, 3025, 2932, 2845, 1601, 1577, 1493, 1477, 1451, 1436, 1377, 1251, 1155, 1124, 1085, 1072, 1022, 1012, 756, 736, 691 and 669; δ_H (400 MHz; CDCl$_3$) 1.91 (3 H, m, C(3)H_2 and C(5)HH_{ax}), 2.09 (1 H, ddd, J 13.6, 9.2 and 4.4, C(5)H_{eq}H), 3.01 (1 H, m, CH_{ax}Ph), 3.10 (1 H, dd, J 12.0 and 7.2, CHHSePh), 3.35 (1 H, dd, J 12.0 and 7.2, CHHSePh), 3.79 (2 H, m, C(2)H_{eq} and CH_{ax}HO), 4.06 (1 H, tt, J 7.2 and 4.8, CHH_{eq}O), 7.18-7.32 (8H, m, Ar-H), 7.51-7.55 (2 H, m, Ar-H); δ_C (100 MHz; CDCl$_3$) 30.5 (CH$_2$), 32.1 (CH$_2$), 35.2 (CH), 35.3 (CH$_2$), 62.2 (CH$_2$), 72.4 (CH), 126.2 (CH), 127.0 (CH), 127.1 (2 x CH), 128.5 (2 x CH), 129.1 (2 x CH), 130.1 (q), 132.9 (2 x CH), 144.6 (q); m/z (EI) 332 (M$^+$, 40%), 161 (100), 143 (17), 131 (24), 117 (28), 105 (35), 91 (73), 77 (23), 57 (14) and 43 (18). Found: 332.06811. $C_{18}H_{20}OSe$ requires M$^+$, 332.06793.

The *e.e.* determined by HPLC analysis was in good agreement with that of the starting alcohol (92%, ChiralCel OD-H, Hexanes/ Propan-2-ol 99.5: 0.5, 0.25 mL.min^{-1}).

27. (3S, 5R) and (3S, 5S)-4-Oxiranyl-3-phenylbutan-1-ol

major   *minor*
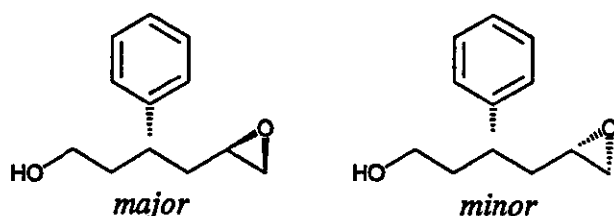
(159a) and (159b)

Alcohol (153) (0.20 g, 1.1 mmol) was dissolved in dichloromethane (20 cm^3) and cooled to 0 °C in an ice bath. Purified 3-chloroperbenzoic acid (0.49 g, 2.8 mmol) was added portion-wise over 5 minutes to the stirred alcohol solution followed by sodium hydrogen carbonate

(0.27 g, 3.2 mmol). After 18 h the crude reaction mixture was washed with saturated sodium sulfite solution (2 x 20 cm^3) to remove excess mCPBA and the organic layer was dried over anhydrous sodium sulfate. Filtration and evaporation of solvent under reduced pressure furnished the crude epoxide. To prevent spontaneous cyclisation, flash column chromatography on silica gel, eluting with diethyl ether-hexane (2:1), had to be performed quickly and gave a mixture of epoxides (159a) and (159b) (0.16 g, 73%) as a light yellow oil with a diastereomeric ratio of 2:1, v_{max} (film)/cm^{-1} 3405, 3027, 2930, 1602, 1494, 1453, 1261, 1047, 847, 764 and 702; δ_H (400 MHz, CDCl$_3$) (* = minor isomer) 1.66-2.07 (4 H, m, CH_2CH(Ph)CH_2), 2.22 (1 H, br s, OH), 2.29 (1 H, dd, J 4.9 and 2.8, CH(O)CHH), 2.44* (1 H, dd, J 4.9 and 2.8, CH(O)CHH), 2.58 (1 H, t, J 4.9, CH(O)CHH), 2.60* (1 H, t, J 4.9, CH(O)CHH), 2.73 (1 H, m, CH(O)CH$_2$), 2.80* (1 H, m, CH(O)CH$_2$), 2.99 (1 H, m, PhCH), 3.48 (2 H, m, CH_2OH) and 7.19-7.32 (5 H, m, Ar-H); δ_C (100 MHz, CDCl$_3$) (* = minor isomer) 39.1* (CH$_2$), 39.7 (CH$_2$), 39.9* (CH$_2$), 40.2* (CH), 40.4 (CH$_2$), 40.5 (CH), 47.7* (CH$_2$), 47.9 (CH$_2$), 51.2* (CH), 51.5 (CH), 60.9 (CH$_2$), 126.9 (CH), 127.9* (CH), 128.0 (2 x CH), 129.0 (2 x CH), 144.4* (q) and 144.5 (q); m/z (EI) 192 (M$^+$, 5%), 161 (45), 156 (16), 143 (36), 129 (48), 117 (52), 105 (100), 91 (92), 77 (22) and 71 (16). Found: 192.11486. C$_{12}$H$_{16}$O$_2$ requires M$^+$, 192.11503.

28. (2S, 4R) and (2R, 4R)-(4-Phenyltetrahydropyran-2-yl)-methanol

major   minor

(160a) and (160b)
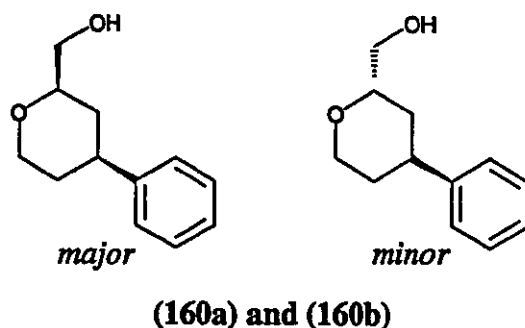
A solution of epoxides (159a and b) (153 mg, 0.80 mmol) in dichloromethane (20 cm^3) was stirred at room temperature with a catalytic amount of camphorsulfonic acid (19 mg, 0.08 mmol) for 20 h. The organic layer was washed once with saturated aqueous sodium hydrogen carbonate solution, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give a colourless oil which was shown to be a mixture of diastereoisomers (2:1) by ^{1}H NMR. Flash column chromatography on silica gel, eluting with

diethyl ether-hexanes (2:1) gave tetrahydropyrans **(160a)** (43 mg, 28%) and **(160b)** (18 mg, 12%) as colourless oils,

(160a) analysis

ν_{max} (film)/cm^{-1} 3421, 3027, 2934, 2849, 1602, 1495, 1452, 1381, 1259, 1131, 1086, 1069, 1040, 996, 758 and 700; δ_H (400 MHz; CDCl$_3$) 1.53 (1 H, m, C(3)H_{ax}H), 1.84 (3 H, m, C(3)HH$_{eq}$ and C(5)H_2), 2.43 (1 H, br s, OH), 2.81 (1 H, m, CH_{ax}Ph), 3.62 (4 H, m, CH_2OH, C(2)H_{ax} and CH_{ax}HO), 4.19 (1 H, ddd, J 11.6, 6.0 and 3.6, CHH_{eq}O) and 7.19-7.36 (5 H, m, Ar-H); δ_C (63 MHz, CDCl$_3$) 33.9 (CH$_2$), 35.3 (CH$_2$), 41.6 (CH), 66.6 (CH$_2$), 68.4 (CH$_2$), 78.5 (CH), 126.8 (CH), 127.1 (2 x CH), 128.9 (2 x CH) and 140.6 (q); m/z (EI) 192 (M$^+$, 10%), 161 (100), 143 (14), 131 (12), 117 (24), 105 (25), 91 (27) and 77 (8). Found: 192.11503. C$_{12}$H$_{16}$O$_2$ requires M$^+$, 192.11503

(160b) analysis

δ_H (400 MHz; CDCl$_3$) 1.82 (1 H, m, C(3)H_{ax}H), 2.00 (3 H, m, C(3)HH$_{eq}$ and C(5)H_2), 2.43 (1 H, br s, OH), 3.08 (1 H, m, CH_{ax}Ph), 3.57 (1 H, m, C(2)H_{eq}), 3.84 (4 H, CH_2OH and CH_{ax}CH$_{eq}$O) and 7.19-7.36 (5 H, m, Ar-H); δ_C (63 MHz, CDCl$_3$) 32.0 (CH$_2$), 32.7 (CH$_2$), 35.5 (CH), 62.7 (CH$_2$), 63.6 (CH$_2$), 73.7 (CH), 126.5 (CH), 127.6 (2 x CH), 128.9 (2 x CH) and 140.5 (q).

4.3.2. Lactone Synthesis

29. (3R)-3-Phenyl-hex-5-enoic acid[168]
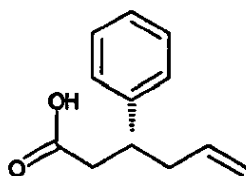
(163)

Aldehyde **(52)** (100 mg, 0.57 mmol) was dissolved in aqueous buffer (pH 4.0, 20 cm^3) and cooled to 0 °C in an ice bath. Sodium chlorite (80% w/w, 195 mg, 1.72 mmol) was added neat in two portions followed by 2-methyl-2-butene (2.0 M, 0.86 cm^3, 1.72 mmol) and the mixture stirred vigorously for 2 h. The aqueous solution was extracted with dichloromethane (3 x 30 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent removed

under reduced pressure to furnish a yellow oil. Flash column chromatography on silica gel, eluting with hexanes-diethyl ether (4:1) gave carboxylic acid (163) (77 mg, 71%) as a light yellow oil, $[\alpha]_D^{25}$ -22.9 (c 1.43, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3064, 3030, 2921, 1709 (C=O), 1640, 1604, 1495, 1454, 1418, 1241, 1157, 916, 865, 762 and 70; δ_H (250 MHz, CDCl$_3$) 2.44 (2 H, t, J 7.1, CH$_2$CH=CH$_2$), 2.64 (1 H, dd, J 15.7 and 8.2, CHHC(O)OH), 2.77 (1 H, dd, J 15.7 and 6.7, CHHC(O)OH), 3.24 (1 H, m, CHPh), 5.05 (2 H, m, CH=CH$_2$), 5.70 (1 H, m, CH=CH$_2$) and 7.22-7.34 (5 H, m, Ar-H); δ_C (63 MHz, CDCl$_3$) 40.6 (CH$_2$), 41.0 (CH$_2$), 41.7 (CH), 117.5 (CH$_2$), 127.0 (CH), 127.8 (2 x CH), 128.9 (2 x CH), 136.1 (CH), 143.6 (q), 179.2 (q); m/z (EI) 190 (M$^+$, 25%), 149 (100), 130 (94), 107 (99), 91 (39) and 79 (68). Found: 190.09937. C$_{12}$H$_{14}$O$_2$ requires M$^+$, 190.09938

30. (2R, 4R) and (2S, 4R)-6-Iodomethyl-4-phenyltetrahydropyran-2-one[160]

major   *minor*

(164a) and (164b)
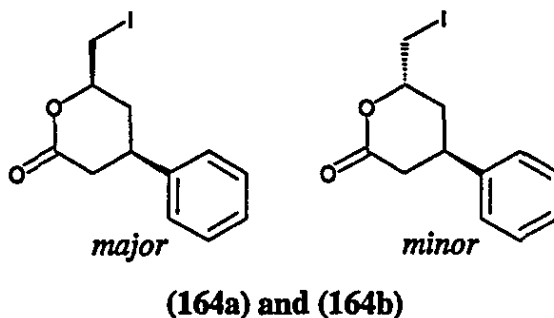
A solution of carboxylic acid (163) (45 mg, 0.24 mmol) in acetonitrile (15 cm^3) was stirred with 4Å MS and sodium hydrogen carbonate (197 mg, 0.79 mmol) at room temperature. Iodine (67 mg, 0.79 mmol) was added in one portion and the mixture stirred for 24 h before quenching with saturated aqueous sodium thiosulfate solution (2 cm^3). The acetonitrile was removed under reduced pressure and the residue was partitioned between dichloromethane and brine (40 cm^3, 1:1). The organic layer was removed and the aqueous portion extracted with a further 20 cm^3 of dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give a yellow oil which was shown to be a mixture of diastereoisomers (4:1) by ^{1}H NMR. Flash column chromatography on silica gel, eluting with hexanes-diethyl ether (1:1) gave the major diastereoisomer (164a) (40 mg, 54%) as a light yellow solid and the minor diastereoisomer (164b) (14 mg, 19%) as a colourless oil;

Experimental   163

(164a) analysis

mp 80.9-82.2 °C (from diethyl ether); ν_{max} (film)/cm^{-1} 3055, 2922, 1736 (C=O), 1496, 1454, 1381, 1265, 1229, 1181, 1073, 1050, 738 and 701; δ_H (400 MHz, CDCl$_3$) 1.86 (1 H, m, C(3)H_{ax}H), 2.43 (1 H, ddt, J 13.7, 3.4 and 2.1, C(3)HH_{eq}), 2.57 (1 H, dd, J 17.9 and 11.9, C(5)H_{ax}H), 2.92 (1 H, ddd, J 17.9, 5.6 and 2.1, C(5)HH_{eq}), 3.24 (1 H, ddt, J 12.2, 5.6 and 3.5, CH(Ph)), 3.39 (1 H, dd, J 10.6 and 6.2, CHHI), 3.44 (1 H, dd, J 10.6 and 4.4, CHHI), 4.40 (1 H, dddd, J 11.4, 6.2, 4.4 and 3.2, CH_{ax}CH$_2$I) and 7.20-7.39 (5 H, m, Ar-H); δ_C (100 MHz, CDCl$_3$) 8.2 (CH$_2$), 36.7 (CH$_2$), 37.4 (CH), 37.6 (CH$_2$), 78.9 (CH), 126.9 (2 x CH), 127.9 (CH), 129.5 (2 x CH), 142.5 (q) and 170.2 (q).

(164b) analysis

ν_{max} (film)/cm^{-1} 3055, 2922, 1736 (C=O), 1496, 1454, 1381, 1265, 1229, 1181, 1073, 1050, 738, 701; δ_H (400 MHz, CDCl$_3$) 2.25 (2 H, t, J 6.4, C(3)$H_{ax}H_{eq}$), 2.78 (1 H, dd, J 17.2 and 7.6, C(5)HH), 2.84 (1 H, ddd, J 17.2 and 6.0, C(5)HH), 3.34 (1 H, dd, J 10.6, and 6.8, CHHI), 3.39 (1 H, dd, J 10.6 and 4.8, CHHI), 3.40 (1 H, m, CH(Ph)), 4.36 (1 H, ddd, J 13.2, 6.8, and 4.8, CH_{eq}CH$_2$I) and 7.20-7.39 (5 H, m, Ar-H); δ_C (100 MHz, CDCl$_3$) 7.0 (CH$_2$), 34.8 (CH), 35.4 (CH$_2$), 35.9 (CH$_2$), 76.2 (CH), 126.9 (2 x CH), 127.8 (CH), 129.5 (2 x CH), 142.6 (q) and 170.7 (q).

The ^{1}H and ^{13}C assignment for the major isomer was done with the aid of HETCOR and for the minor isomer with COSY.

31. (2R, 4R)- and (2S, 4R)-6-Hydroxymethyl-4-phenyltetrahydropyran-2-one[169]
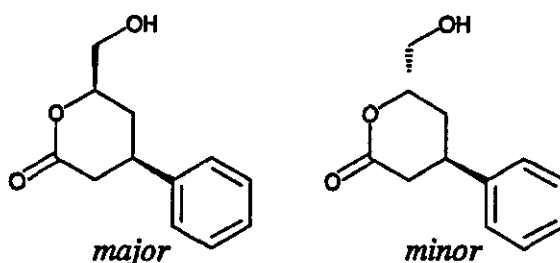
(167a) and (167b)

A solution of acid **(163)** (55 mg, 0.29 mmol) was dissolved in dichloromethane (20 cm^3) cooled to 0 °C in an ice bath. Purified 4-chloroperbenzoic acid (126 mg, 0.73 mmol) was added portionwise over 5 minutes to the stirred alcohol solution followed by sodium

hydrogen carbonate (59 mg, 70 mmol). After 18 h the crude reaction mixture was washed with saturated sodium sulfite solution (2 x 20 cm^3) to remove excess *m*CPBA and the organic layer was dried over magnesium sulfate. Filtration and evaporation of solvent under reduced pressure furnished a white semi-solid which appeared to a mixture of epoxide and cyclised material by crude ^{1}H NMR. No attempt was made to isolate the epoxide and the crude material was dissolved in dichloromethane (20 cm^3) and stirred at room temperature with a catalytic amount of camphorsulfonic acid (7 mg, 0.03 mmol) for 22 h. The organic layer was washed once with saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give a colourless oil. Flash column chromatography on silica gel, eluting with diethyl ether-hexanes (2:1) gave a mixture of lactones (167a) and (167b) (49 mg, 83%) as a light yellow oil with a diastereomeric ratio of 1:1, v_{max} (film)/cm^{-1} 3416 (br), 3029, 2921, 2850, 1725 (C=O), 1603, 1496, 1454, 1381, 1245, 1160, 1079, 973 and 760; δ_H (250 MHz, CDCl$_3$) (* = axial isomer) 1.91-2.34 (2 H, br m, C(3)H_2 + C(5)H_{ax}*), 2.56 (1 H, dd, *J* 17.8 and 11.8, C(5)H_{ax}H), 2.89 (1 H, m, C(5)HH_{eq}), 3.23 (1 H, m, CH_{ax}Ph) 3.43* (1 H, m, CH_{ax}Ph), 3.79 (2 H, m, CH_2OH), 4.46 (1 H, m, C(2)H_{ax}), 4.56* (1 H, m, C(2)H_{eq}) and 7.19-7.39 (5 H, m, Ar-*H*); δ_C (63 MHz, CDCl$_3$; Me$_4$Si) (* = axial isomer) 31.6 (CH$_2$), 32.0* (CH$_2$), 35.1 (CH), 36.1* (CH), 37.6 (CH$_2$), 38.0* (CH$_2$), 65.1 (CH$_2$), 65.2* (CH$_2$), 78.2 (CH), 81.3 (CH), 126.7* (2 x CH), 126.9 (2 x CH), 127.6 (2 x CH), 127.7* (2 x CH), 129.4 (CH [and *]), 142.4 (q [and *]), and 174.5 (q [and *]).

4.3.3. Piperidine Synthesis

32. Benzyl-(3-phenylhex-5-enyl)-amine
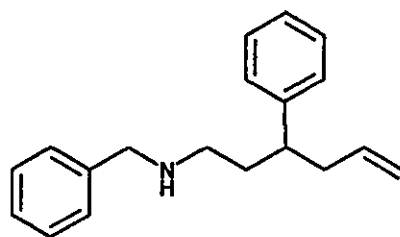
(168)

A solution of aldehyde (52) (294 mg, 1.69 mmol) in dichloromethane (15 cm^3) was stirred at room temperature while benzylamine (182 mg, 1.69 mmol) was added dropwise. Stirring

was continued for 30 minutes before addition of anhydrous magnesium sulfate. After a further 10 minutes the mixture was filtered and the solvent removed under reduced pressure. The resulting light yellow oil was re-dissolved in methanol (30 cm³) and the solution cooled to 0 °C in an ice bath. Sodium borohydride (204 mg, 5.39 mmol) in methanol (10 cm³) was added and the solution allowed to warm to room temperature overnight with stirring. The crude product was absorbed onto flash silica gel and subsequent flash column. chromatography, eluting with hexanes-ethyl acetate (9:1 to 1:1) gave amine (168) as a colourless oil (364 mg, 79%), v_{max} (film)/cm⁻¹ 3331 (N-H), 3061, 3026, 2974, 2923, 1639, 1602, 1493, 1452, 1358, 1118, 1028, 912, 760 and 734; δ_H (400 MHz; CDCl₃) 1.35 (1 H, br s, N*H*), 1.77 (1 H, m, C(2)*H*H), 1.91 (1 H, m, C(2)H*H*), 2.35 (2 H, t, C(4)*H₂*), 2.49 (2 H, m, C(1)*H₂*), 2.70 (1 H, m, C(3)*H*), 3.65 (1 H, d, *J* 8.3, PhC*H*H), 3.70 (1 H, d, *J* 8.3, PhCH*H*), 4.94 (2 H, m, CH=C*H₂*) 5.64 (1 H, m, C*H*=CH₂) and 7.13-7.28 (10 H, m, Ar-*H*); δ_C (100 MHz; CDCl₃) 36.6 (CH₂), 41.9 (CH₂), 44.2 (CH), 47.9 (CH₂), 54.4 (CH₂), 116.5 (CH₂), 126.6 (CH), 127.2 (CH), 128.0 (2 x CH), 128.6 (2 x CH), 128.8 (4 x CH), 137.3 (CH), 140.9 (q) and 145.3 (q); *m/z* (EI) 265 (M⁺, 9%), 236 (10), 176 (49), 117 (100), 91 (54), 77 (4) and 65 (7); Found: M⁺, 265.18380 C₁₉H₂₃N requires M⁺, 265.18305.

33. Benzyl-(3-phenylhex-5-enyl)-carbamic acid benzyl ester
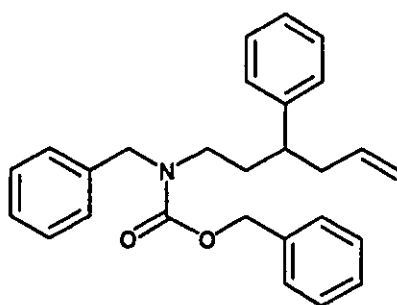
(169)

A solution of amine (168) (347 mg, 1.31 mmol) in dichloromethane (15 cm³) was stirred at room temperature with potassium hydrogen carbonate (205 mg, 2.05 mmol) while benzylchloroformate (0.32 cm³, 2.24 mmol) was added dropwise *via* syringe. After 2 h stirring no reaction was seen so acetonitrile (20 cm³) was added to increase the effectiveness of the base. The reaction immediately began to change colour (light yellow to peach) and was stirred for a further hour before quenching with dilute aqueous hydrochloric acid (5 cm³). The organic layer was washed with saturated aqueous sodium chloride solution, dried

over anhydrous magnesium sulfate and the solvent removed under reduced pressure to furnish a pink oil. Flash column chromatography on silica gel, eluting with light petroleum-ethyl acetate (12:1) gave Cbz-amine (169) as a colourless oil (467 mg, 89%), v_{max} (film)/cm^{-1} 3064, 3029, 2926, 1698 (C=O), 1640 (C=C), 1604, 1495, 1471, 1454, 1422, 1366, 1229, 1165, 1112, 1076, 1029, 993, 914, 765 and 735; δ_H (400 MHz; CDCl$_3$) 1.67 (1 H, br s, C(2)HH), 1.76 (1 H, br s, C(2)HH), 2.28 (2 H, br d, C(4)H_2), 2.49 (1 H, br d, C(3)H_2), 3.08 (2 H, m, C(1)H_2), 4.39 (2 H, m, PhCH_2), 4.91 (2 H, m, CH=CH_2), 5.14 (2 H, m, OCH_2Ph), 5.58 (1 H, br s, CH=CH$_2$) and 7.02-7.64 (15 H, m, Ar-H).

34. Benzyl-(4-oxiranyl-3-phenylbutyl)-carbamic acid benzyl ester
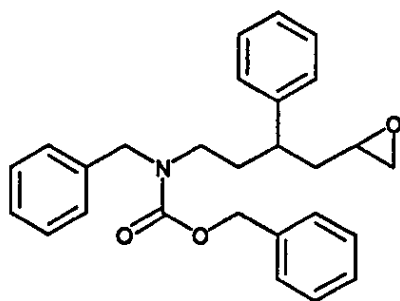
(170)

Dimethyldioxirane was prepared by stirring sodium hydrogen carbonate (29 g) and Oxone® (60 g) in a mixture of HPLC grade acetone and deionised water (1.5:1). The reaction was cooled with ice when it became too vigorous and after 15 minutes a moderate vacuum (20 mmHg) was applied to remove the dimethyldioxirane (DMDO), formed as a solution in acetone (50 cm^3, ca 0.04 M). This solution was used without any further purification or characterisation.

Protected amine (169) (185 mg, 0.46 mmol) was dissolved in a solution of acetone containing DMDO (50 cm^3, ca 0.04 M) at -78 °C and allowed to warm to room temperature with stirring. The reaction was monitored by TLC and after 18 h the reaction was dried over sodium sulfate, filtered and the acetone removed under reduced pressure to yield epoxide (170) as a colourless oil (173 mg, 90%) which needed no further purification, v_{max} (film)/cm^{-1} 3061, 3029, 2928, 1702 (C=O), 1603, 1495, 1474, 1452, 1421, 1365, 1231, 1166, 1122, 1075, 1028, 913, 833 and 737; δ_H (250 MHz; CDCl$_3$) (* = syn isomer) 1.50-2.08 (4 H, m, CH_2CH(Ph)CH_2 H), 2.25 (1 H, m, CH(O)CHH), 2.36* (1 H, m, CH(O)CHH), 2.56 (1 H, t, J 4.6, CH(O)CHH), 2.63* (1 H, m, CH(O)CHH), 2.74 (1 H, m, CH(O)CH$_2$), 2.75 (1 H, m,

PhC*H*), 3.04 (2 H, m, NC*H₂*), 4.40 (2 H, m, PhC*H₂*), 5.14 (1 H, br s, OC*H₂*Ph) and 7.06-7.32 (15H, m, Ar-*H*).

4.3.4. Miscellaneous Compounds from Chapter 3.

35. (±)-2-(3-Phenylallylideneamino)-propan-1-ol[105]
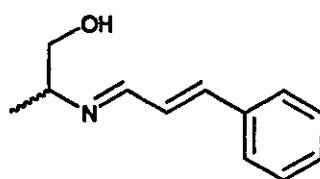
(±143)

rac-Alaninol (1.16 g, 15.4 mmol) in dichloromethane (20 cm³) was added dropwise to a stirred solution of *trans*-Cinnamaldehyde (2.04 g, 15.4 mmol) in dichloromethane (30 cm³) at room temperature and the mixture was left to stir for 10 minutes. Anhydrous magnesium sulfate (1 g) was added and the reaction stirred for a further 10 minutes. Filtration and removal of the solvent under reduced pressure yielded a light yellow solid. Trituration with light petroleum-diethyl ether (4:1) furnished imine **(143)** (2.30 g, 79%) as a light yellow powder, v_{max} (film)/cm⁻¹ 3328 (O-H), 3059, 2967, 2928, 2865, 1635 (C=N), 1618 (C=C, Ar), 1493, 1450, 1167, 1051, 983, 750 and 691; δ_H (400MHz; CDCl₃) 1.16 (3H, d, *J* 6.4, C*H₃*), 3.40 (1H, m, CH₃C*H*), 3.66 (2H, m, C*H₂*OH), 4.01 (1H, br s, O*H*), 6.84 (2H, m, C*H*=C*H*Ph), 7.29-7.40 (5H, m, Ar-*H*) and 8.01 (1H, dd, *J* 7.6 and 0.8, C*H*=N); δ_C (100MHz; CDCl₃) 18.3 (CH₃), 67.0 (CH₂), 67.6 (CH), 127.3 (2 x CH), 127.5 (CH), 128.8 (2 x CH), 129.2 (CH), 135.5 (q), 142.3 (CH) and 163.0 (CH); *m/z* (EI) 189 (M⁺, 11%), 158 (100), 130 (6), 115 (59), 103 (4), 91 (10) and 77 (4). Found: 189.11515. C₁₂H₁₅NO requires M⁺, 189.11536.

36. 2-(1-Styryl-but-3-enylamino)-propan-1-ol[105]
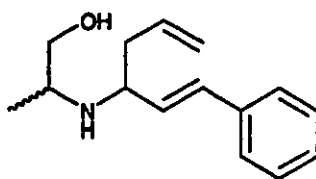
(±144)

Allyl bromide (2.70 cm³, 31.9 mmol) was added dropwise *via* syringe to magnesium turnings (0.76 g, 31.7 mmol) in dry diethyl ether (50 cm³) under an inert atmosphere. An ice bath was used to cool the reaction when it became too vigorous and after addition the reaction was stirred at room temperature for 30 minutes. Imine (143) (2.00 g, 10.6 mmol) in dry diethyl ether (150 cm³) under an inert atmosphere was added dropwise *via* cannulation to the stirred Grignard solution and the resulting mixture refluxed for 2.5 hours. The reaction was cooled to room temperature and quenched with water until a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue rinsed with diethyl ether (2 x 20 cm³). The combined organic layers were washed three times with sodium hydroxide solution (2M), once with brine and dried over sodium sulfate. Filtration and removal of solvent under reduced pressure gave an orange solid. The crude product was recrystallised from light petroleum-diethyl ether yielding amine (144) (0.57 g, 23%) as a light yellow solid, δ_H (400MHz, CDCl₃) 1.07 (3H, d, *J* 6.5 C*H*₃), 2.05 (1H, br s, O*H*), 2.31, (2H, t, *J* 7.0, C*H*₂CH=CH₂), 2.88 (1H, m, C*H*CH₃), 3.25 (1H, dd, *J* 10.5 and 5.6, C*H*HOH), 3.33 (1H, dd, *J* 14.9 and 6.4, C*H*), 3.59 (1H, dd, *J* 10.5 and 4.2, CH*H*OH), 5.11 (2H, m, CH=C*H*₂), 5.82 (1H, m, C*H*=CH₂) 6.04 (1H, dd, *J* 15.8 and 8.3, C*H*=CHPh) 6.44 (1H, d, *J* 15.8, CH=C*H*Ph) and 7.22-7.39 (5H, m, Ar-*H*); δ_C (100MHz, CDCl₃) 19.1 (CH₃), 41.2 (CH₂), 51.8 (CH), 58.7 (CH), 65.1 (CH₂), 118.0 (CH₂), 126.7 (2 x CH), 127.9 (CH), 129.0 (2 x CH), 131.1 (CH), 133.2 (CH), 135.3 (CH) and 137.3 (q).

37. 3-Phenyl-2-(3-phenyl-allylamino)-propan-1-ol
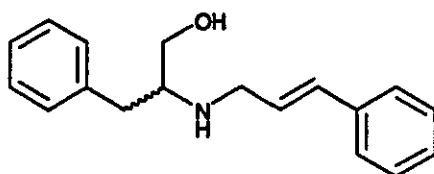
(±146)

Following the usual Barbier Grignard reaction conditions (*cf* Grignard **Method B**, Entry **11**) on a large scale enabled the isolation of an impurity. Racemic imine (**99f**) (31.40 g, 118.5 mmol) was dissolved in toluene (1500 cm^3) and tetrahydrofuran (200 cm^3) and stirred at room temperature with magnesium turnings (7.74 g, 322.5 mmol). Allyl bromide (27.0 cm^3, 312.4 mmol) was added in four portions over 2 h to the imine solution and the mixture was stirred under an inert atmosphere. After overnight stirring the reaction was quenched with water until a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue rinsed with diethyl ether (2 x 200 cm^3). The combined organic layers were washed twice with saturated aqueous sodium hydrogencarbonate solution, dried over sodium sulfate, filtered and the volume reduced under vacuum to yield a light brown oil. Recrystallisation from hexane-diethyl ether gave amine (**146**) (3.88g, 12%) as a colourless powdery solid, mp 115.8-116.8 °C (from hexanes: diethyl ether); v_{max} (Nujol®)/cm^{-1} 3272 (N-H), 3025, 1344, 1306, 1120, 1040, 984, 971, 922, 871, 804, 738. 703 and 693; δ_H (400MHz, CDCl$_3$) 1.94 (1H, br s, O*H*), 2.75 (1H, dd, *J* 13.6 and 7.2, PhC*H*H), 2.81 (1H, dd, *J* 13.6 and 6.8, PhCH*H*), 2.99 (1H, m, C*H*), 3.35 (1H, dd, *J* 10.8 and 5.2, C*H*HOH), 3.40 (2H, dd, *J* 6.4 and 1.6, NHC*H₂*), 3.64 (1H, dd, *J* 10.8 and 4.0, CH*H*OH), 6.15 (1H, dt, *J* 16.0 and 6.0, C*H*=CHPh), 6.44 (1H, d, *J* 16.0, CH=C*H*Ph) and 7.18-7.32 (10H, m, Ar-*H*); δ_C (100MHz, CDCl$_3$) 38.6 (CH$_2$), 49.4 (CH$_2$), 59.7 (CH), 63.0 (CH$_2$), 126.7 (2 x CH), 126.9 (CH), 127.8 (CH), 128.6 (CH), 128.9 (2 x CH), 129.0 (2 x CH), 129.6 (2 x CH), 131.7 (CH), 137.3 (q) and 138.9 (q); *m/z* (EI) 267 (M$^+$, <1%), 236 (10), 176 (53), 117 (100), 91 (22), 77 (2) and 65 (4). Found: C, 80.7; H, 7.9; N, 5.15%; M$^+$, 267.16236. C$_{18}$H$_{21}$NO requires C, 80.9; H, 7.9; N, 5.2%; M$^+$, 267.16231.

38. [1-(2,2-Dimethoxyethyl)-but-3-enyl]-benzene
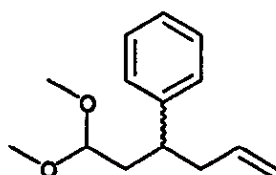
(147)

Trifluoroacetic acid (0.53 cm^3, 6.8 mmol) was added to a stirred solution of *oxazolidine* **(105f)** (0.51 g, 1.76 mmol) in methanol (25 cm^3) and the resulting dark orange solution refluxed overnight. The solvent was removed under reduced pressure to yield an orange oil that was purified by dry flash chromatography, eluting with 3 x 30 cm^3 portions of light petroleum-ethyl acetate (4:1), to furnish acetal **(147)** (0.15 g, 39%) as a yellow oil, ν_{max} (film)/cm^{-1} 3062, 3027, 2927, 2830, 1640, 1602, 1494, 1453, 1385, 1369, 1189, 1127, 1055, 1030, 994, 914, 761 and 701; δ_H (400 MHz, CDCl$_3$) 1.82 (1H, ddd, *J* 13.9, 10.4 and 3.7, C(2)*H*H), 2.07 (1H, ddd, *J* 13.9, 8.1 and 4.9, C(2)H*H*), 2.39 (2H, t, *J* 7.0, C*H$_2$*CH=CH$_2$), 2.81 (1H, m, PhC*H*), 3.24 (3H, s, OC*H$_3$*), 3.30 (3H, s, OC*H$_3$*), 4.13 (1H, dd, *J* 8.3 and 3.9, C*H*(OMe)$_2$), 5.00 (2H, m, CH=C*H$_2$*), 5.65 (1H, m, C*H*=CH$_2$) and 7.16-7.30 (5H, m, Ar-*H*); δ_C (100 MHz, CDCl$_3$) 38.9 (CH$_2$), 41.8 (CH$_2$), 41.9 (CH), 53.0 (CH$_3$), 53.1 (CH$_3$), 103.2 (CH), 116.7 (CH$_2$), 126.7 (CH), 128.1 (2 x CH), 129.0 (2 x CH), 136.9 (CH), 144.9 (q).

Chapter 5

References

Hmmm...wrong bottle...
I guess this one must have been the elixir of death...

by Nick D Kim
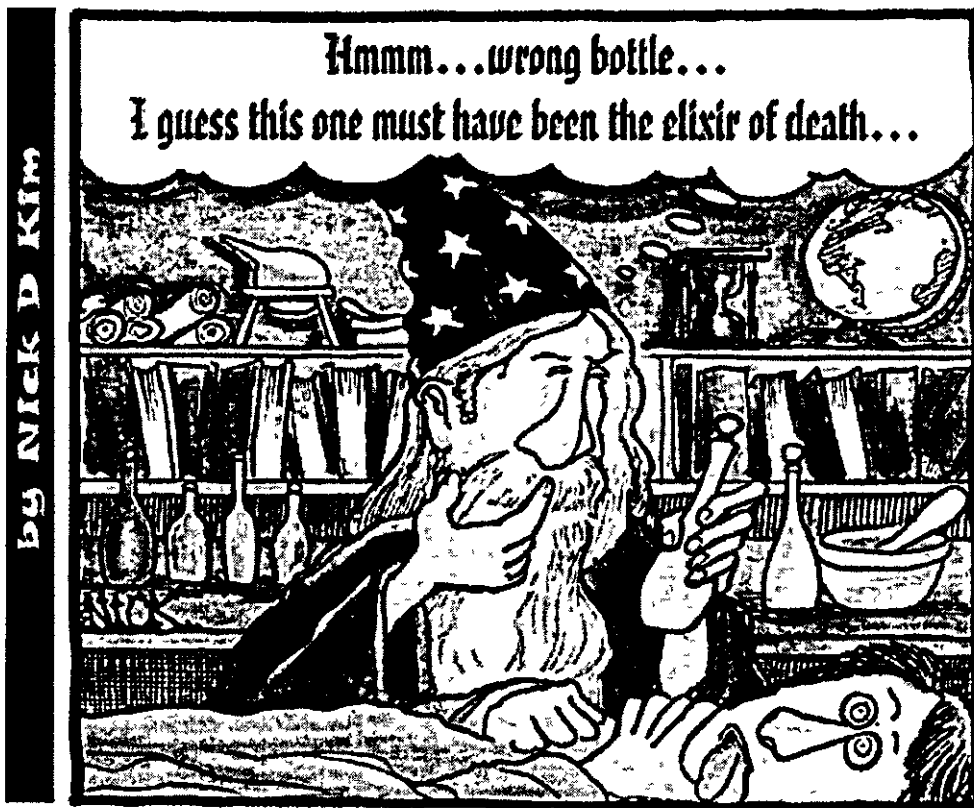
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Appendix
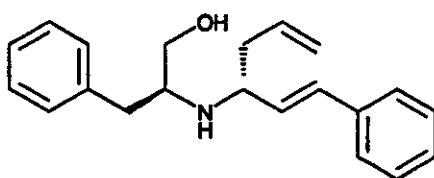
(2*S*)-3-Phenyl-2-((*S*)-1-styryl-but-3-enylamino)-propan-1-ol (**100f**)

- ^{1}H NMR
- ^{13}C NMR
- Single crystal X-ray and accompanying data

rdb 20?-2?/02 recrystallised from 95:5 LP/Et2O

Integral

40 909

3 671

7 485

7.602

40.333

ppm

7.318
7.302
7.300
7.297
7.282
7 264
7.260
7 255
7 241
7 233
7 228
7.223
7 220
7.150
7 146
7 130
6 274
6 234
5 707
5 686
5 667
5.646
5 093
5.061
5 058
5 055
5 050
5 035
3.642
3.632
3 615
3 605
3.358
3.350
3.332
3 323
3.258
3.238
2 776
2 760
2 756
2.735
2.244
2.236
2 227
2.219

0 000

rdb208

ppm
139.05
137.15
135.29
132.46
131.26
130.06
129.72
129.27
129.00
128.96
128.76
127.91
127.74
126.89
126.83
126.76
117.95

77.84
77.52
77.21
74.60

62.54
58.25
56.96

41.33
39.47
39.30

=CH2

PhCH2SH

Current Data Parameters
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PROCNO   1

F2 - Acquisition Parameters
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INSTRUM   dpx400
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DS   2
SWH   31847 133 Hz
FIDRES   0 485949 Hz
AQ   1 0289652 sec
RG   13004
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DE   7 50 usec
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d12   0 00002000 sec
PL13   120 00 dB
D1   1 00000000 sec
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PCPD2   100 00 usec
SFO2   400 1316005 MHz
NUC2   1H
PL2   -6 00 dB
PL12   12 00 dB
P1   5 50 usec
SFO1   100 6254358 MHz
NUC1   13C
PL1   -6 00 dB

F2 - Processing parameters
SI   32768
SF   100 6127290 MHz
WDW   EM
SSB   0
LB   1 00 Hz
GB   0
PC   1 40

1D NMR plot parameters
CX   20 00 cm
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F1   15946 04 Hz
F2P   -5 538 ppm
F2   -557 18 Hz
PPMCM   8 20136 ppm/cm
HZCM   825 16119 Hz/cm
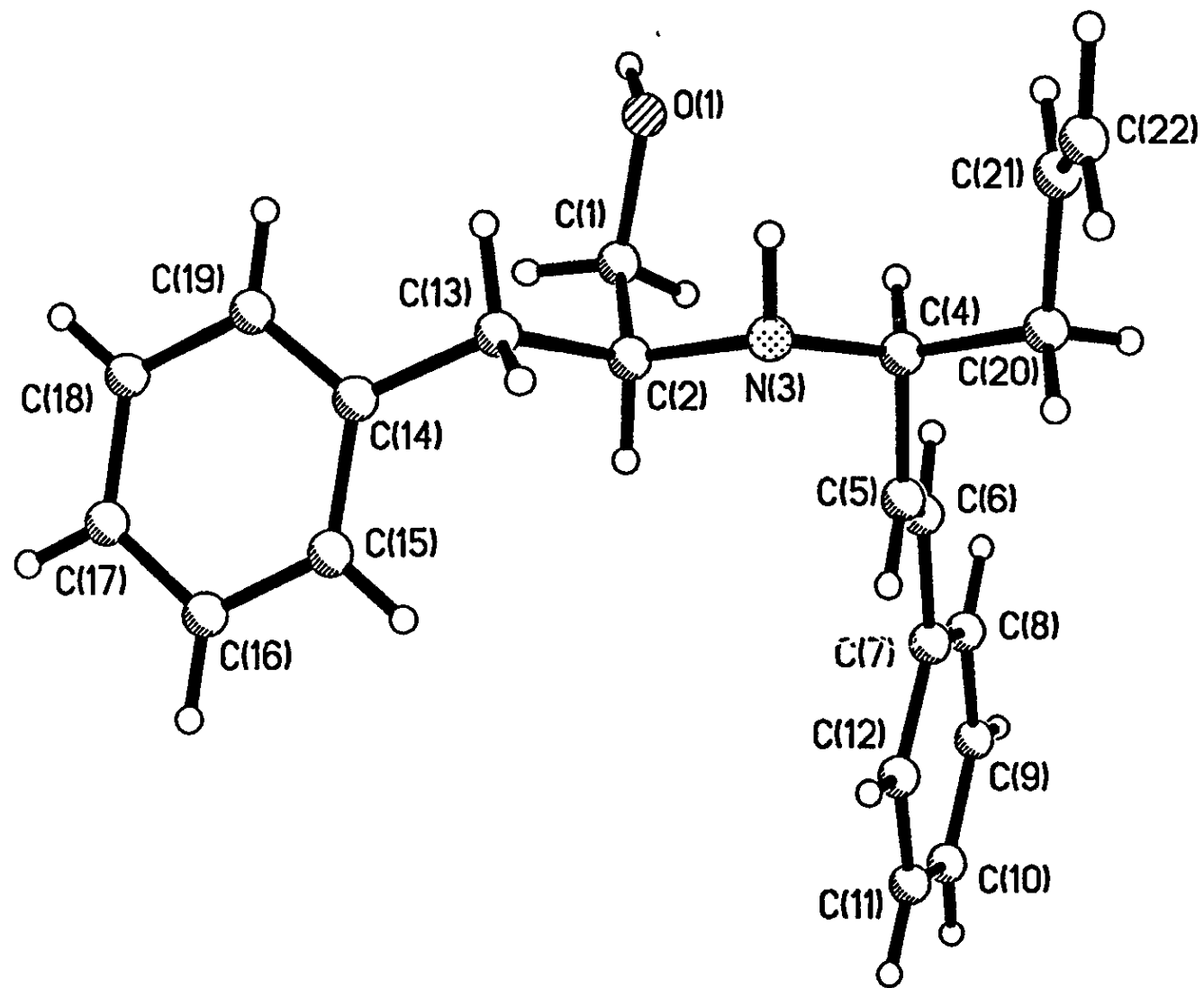
Table 1. Crystal data and structure refinement for 1.

Identification code	rbsal
Empirical formula	$C_{21}H_{25}NO$
Formula weight	307.42
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2
Unit cell dimensions	$a = 23.918(3)$ Å alpha = 90°
	$b = 5.5314(6)$ Å beta = $106.248(2)^\circ$
	$c = 14.665(2)$ Å gamma = 90°
Volume, Z	1862.8(3) $Å^3$, 4
Density (calculated)	1.096 Mg/m^3
Absorption coefficient	0.066 mm^{-1}
F(000)	664
Crystal size	.17 x .08 x .01 mm
θ range for data collection	1.77 to 23.29°
Limiting indices	$-26 \leq h \leq 26, -6 \leq k \leq 6, -16 \leq l \leq 16$
Reflections collected	5373
Independent reflections	2545 ($R_{int} = 0.0566$)
Absorption correction	SADABS
Max. and min. transmission	1.00000 and 0.570392
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2495 / 3 / 217
Goodness-of-fit on F^2	0.960
Final R indices [I>2σ(I)]	R1 = 0.0663, wR2 = 0.1397
R indices (all data)	R1 = 0.1264, wR2 = 0.1873
Absolute structure parameter	1(4)
Extinction coefficient	0.0043(14)
Largest diff. peak and hole	0.120 and -0.153 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	9112(2)	6260(6)	9206(2)	73(1)
C(1)	8950(2)	7239(9)	8270(3)	61(1)
C(2)	9074(2)	9928(8)	8332(3)	49(1)
N(3)	8815(2)	11214(7)	8997(2)	49(1)
C(4)	8182(2)	10812(9)	8832(3)	60(1)
C(5)	7847(2)	11563(10)	7850(3)	61(1)
C(6)	7440(2)	10257(9)	7267(4)	64(1)
C(7)	7073(2)	10876(10)	6310(4)	61(1)
C(8)	6623(3)	9369(12)	5867(4)	86(2)
C(9)	6254(3)	9843(16)	4971(5)	102(2)
C(10)	6355(3)	11881(15)	4503(4)	101(2)
C(11)	6798(3)	13344(15)	4917(5)	95(2)
C(12)	7164(3)	12893(12)	5805(4)	83(2)
C(13)	9728(2)	10459(9)	8618(3)	56(1)
C(14)	10014(2)	9966(9)	7843(3)	50(1)
C(15)	9937(2)	11540(11)	7087(3)	73(2)
C(16)	10200(3)	11189(14)	6378(4)	89(2)
C(17)	10526(3)	9190(14)	6385(5)	97(2)
C(18)	10606(3)	7578(12)	7106(6)	112(3)
C(19)	10346(3)	7976(11)	7848(4)	90(2)
C(20)	7981(2)	12251(10)	9574(4)	73(2)
C(21)	8283(3)	11559(14)	10563(4)	88(2)
C(22)	8546(3)	12880(17)	11186(5)	132(3)

Table 3. Bond lengths [Å] and angles [°] for 1.

O(1)-C(1)	1.425(5)	C(1)-C(2)	1.514(6)
C(2)-N(3)	1.476(5)	.C(2)-C(13)	1.531(6)
N(3)-C(4)	1.484(5)	C(4)-C(5)	1.498(6)
C(4)-C(20)	1.530(6)	C(5)-C(6)	1.317(6)
C(6)-C(7)	1.472(7)	C(7)-C(8)	1.374(7)
C(7)-C(12)	1.390(7)	C(8)-C(9)	1.388(8)
C(9)-C(10)	1.376(9)	C(10)-C(11)	1.336(9)
C(11)-C(12)	1.373(7)	C(13)-C(14)	1.506(6)
C(14)-C(19)	1.356(7)	C(14)-C(15)	1.381(6)
C(15)-C(16)	1.371(7)	C(16)-C(17)	1.351(8)
C(17)-C(18)	1.355(8)	C(18)-C(19)	1.414(8)
C(20)-C(21)	1.478(7)	C(21)-C(22)	1.201(8)
O(1)-C(1)-C(2)	108.7(4)	N(3)-C(2)-C(1)	113.7(4)
N(3)-C(2)-C(13)	108.2(3)	C(1)-C(2)-C(13)	111.9(4)
C(2)-N(3)-C(4)	114.7(4)	N(3)-C(4)-C(5)	111.2(4)
N(3)-C(4)-C(20)	108.4(4)	C(5)-C(4)-C(20)	110.5(4)
C(6)-C(5)-C(4)	124.8(5)	C(5)-C(6)-C(7)	128.8(5)
C(8)-C(7)-C(12)	117.0(5)	C(8)-C(7)-C(6)	119.3(5)
C(12)-C(7)-C(6)	123.7(5)	C(7)-C(8)-C(9)	122.7(6)
C(10)-C(9)-C(8)	118.2(6)	C(11)-C(10)-C(9)	119.8(6)
C(10)-C(11)-C(12)	122.3(7)	C(11)-C(12)-C(7)	119.9(6)
C(14)-C(13)-C(2)	113.8(4)	C(19)-C(14)-C(15)	117.6(4)
C(19)-C(14)-C(13)	122.1(4)	C(15)-C(14)-C(13)	120.3(4)
C(16)-C(15)-C(14)	122.2(5)	C(17)-C(16)-C(15)	119.7(6)
C(16)-C(17)-C(18)	120.0(6)	C(17)-C(18)-C(19)	120.0(6)
C(14)-C(19)-C(18)	120.4(5)	C(21)-C(20)-C(4)	113.5(4)
C(22)-C(21)-C(20)	126.6(8)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$\text{Å}^2 \times 10^3$] for 1.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2 [(ha^*)^2 U_{11} + \ldots + 2hka^*b^*U_{12}]$

	U11	U22	U33	U23	U13	U12
O(1)	105(3)	44(2)	69(2)	0(2)	23(2)	2(2)
C(1)	73(4)	56(4)	56(3)	-11(3)	20(3)	4(3)
C(2)	57(3)	43(3)	47(3)	-4(2)	17(2)	-2(2)
N(3)	46(2)	46(2)	54(2)	-2(2)	12(2)	2(2)
C(4)	50(3)	52(3)	78(3)	1(3)	16(3)	-2(3)
C(5)	44(3)	61(3)	78(3)	6(3)	16(3)	-3(3)
C(6)	54(3)	55(3)	83(4)	8(3)	22(3)	3(3)
C(7)	48(3)	65(4)	73(3)	-4(3)	20(3)	3(3)
C(8)	82(5)	96(5)	80(4)	-10(4)	23(4)	-10(4)
C(9)	79(5)	137(7)	79(5)	-25(5)	6(4)	-18(5)
C(10)	104(6)	135(7)	61(4)	-3(5)	17(4)	6(5)
C(11)	88(6)	107(6)	89(5)	10(4)	24(4)	8(4)
C(12)	69(5)	85(5)	91(5)	5(4)	13(4)	-7(4)
C(13)	53(3)	63(4)	50(3)	1(2)	10(2)	0(3)
C(14)	49(3)	53(3)	48(3)	3(3)	16(2)	5(2)
C(15)	74(4)	89(4)	60(3)	7(3)	25(3)	14(3)
C(16)	92(4)	124(6)	63(3)	12(4)	39(3)	16(5)
C(17)	106(6)	109(6)	99(5)	-22(4)	67(4)	-6(5)
C(18)	140(7)	67(4)	170(7)	9(5)	108(6)	27(4)
C(19)	107(5)	75(4)	112(5)	25(4)	68(4)	29(4)
C(20)	58(4)	85(4)	82(4)	-8(3)	30(3)	8(3)
C(21)	79(4)	111(5)	81(4)	-17(4)	34(4)	0(4)
C(22)	105(6)	150(8)	117(6)	-39(6)	-7(5)	43(6)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(1O)	9044(30)	4520(26)	9109(44)	147(29)
H(1A)	8539(2)	6958(9)	7972(3)	73
H(1B)	9170(2)	6460(9)	7889(3)	73
H(2A)	8906(2)	10615(8)	7698(3)	58
H(3N)	9021(15)	10665(68)	9636(12)	48(12)
H(4A)	8113(2)	9089(9)	8913(3)	73
H(5A)	7933(2)	13063(10)	7636(3)	73
H(6A)	7375(2)	8738(9)	7490(4)	76
H(8A)	6562(3)	7975(12)	6181(4)	103
H(9A)	5947(3)	8809(16)	4693(5)	122
H(10A)	6116(3)	12239(15)	3900(4)	121
H(11A)	6860(3)	14717(15)	4593(5)	114
H(12A)	7472(3)	13935(12)	6067(4)	100
H(13A)	9789(2)	12142(9)	8804(3)	68
H(13B)	9917(2)	9481(9)	9167(3)	68
H(15A)	9699(2)	12883(11)	7057(3)	88
H(16A)	10155(3)	12322(14)	5894(4)	107
H(17A)	10695(3)	8920(14)	5895(5)	116
H(18A)	10833(3)	6208(12)	7113(6)	135
H(19A)	10402(3)	6867(11)	8342(4)	108
H(20A)	8047(2)	13957(10)	9492(4)	87
H(20B)	7566(2)	12014(10)	9466(4)	87
H(21A)	8268(3)	9934(14)	10718(4)	106
H(22A)	8574(3)	14521(17)	11066(5)	158
H(22B)	8722(3)	12263(17)	11788(5)	158
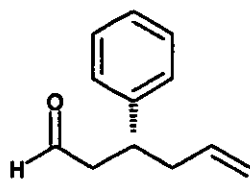
(S)-3-Phenylhex-5-enal (52)
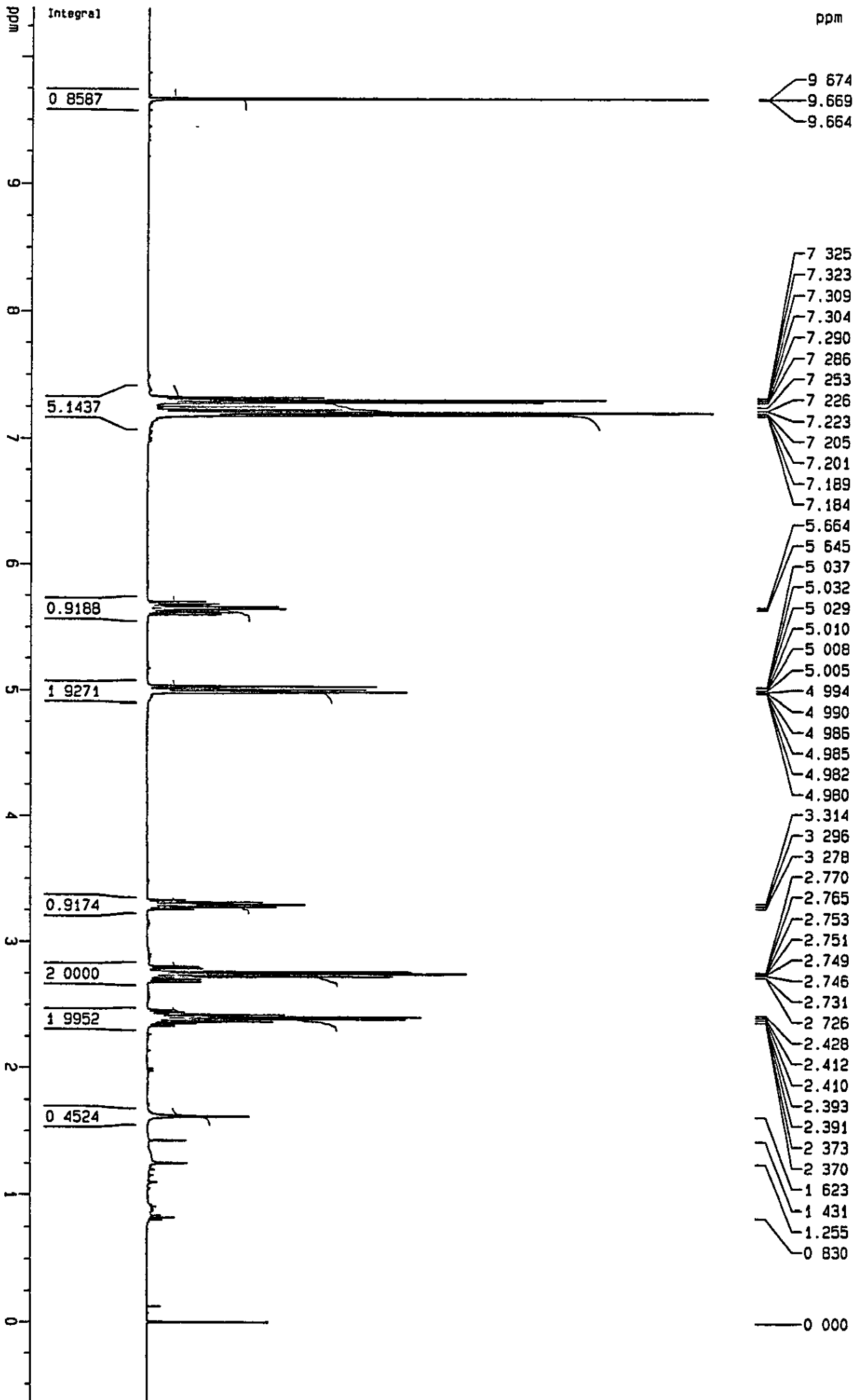
- ¹H NMR

rdb 209-24/02 dried aldehyde
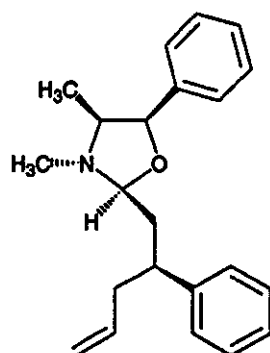
Integral

ppm
9.674
9.669
9.664

0.8587

ppm
7.325
7.323
7.309
7.304
7.290
7.286
7.253
7.226
7.223
7.205
7.201
7.189
7.184

5.1437

ppm
5.664
5.645
5.037
5.032
5.029
5.010
5.008
5.005
4.994
4.990
4.985
4.985
4.982
4.980

0.9188

1.9271

ppm
3.314
3.296
3.278
2.770
2.765
2.753
2.751
2.749
2.746
2.731
2.726

0.9174

2.0000

1.9952

ppm
2.428
2.412
2.410
2.393
2.391
2.373
2.370
1.623
1.431
1.255
0.830

0.4524

0.000

(2*S*, 4*S*, 5*R*)-3,4-Dimethyl-2-[(2*R*)-2-phenylpent-4-enyl]-1,3-oxazolidine

- ^{1}H NMR of aldehyde derivative demonstrating an *e.e.* of 84%

(*e.e.* = (peak area δ 3.51- δ 3.95 / peak area δ 3.51 + δ 3.95) x 100)

rdb 209-24/02 ephedrine deriv.

Integral

ppm
7.252
7.240
7.238
7.236
7.229
7.222
7.207
7.186
7.166
7.162
7.148
7.144
7.141
7.123

35.755

5.606
5.588
5.171

3.085

4.921
4.920
4.916
4.879
4.877
4.873
4.868
4.863
4.843
4.838

10.072

3.446
3.439
3.437
3.429
3.426
3.419

3.088

2.560
2.544
2.540
2.524
2.398
2.379
2.361
2.347
2.344
2.341
2.324
2.162
2.029
2.018
2.003
1.997
1.994
1.985

47.261

0.761
0.745
0.579
0.563
0.545
0.528

0.739

0.000

rdb 209-24/02 ephedrine deriv.

ppm		
	3.962	
	3.955	
	3.944	
	3.936	
	3.732	
	3.524	
	3.517	
	3.515	
	3.506	
	3.503	
	3.497	
	3.488	
	3.475	
	3.474	
	3.471	
	3.458	
	3.440	

Integral

0.0890

1.0000

ppm 4.00 3.95 3.90 3.85 3.80 3.75 3.70 3.65 3.60 3.55 3.50 3.45 3.40

rdb 209-24/02 aldehyde deriv.

(210)

ppm

145.07
140.56
137.02
128.78
128.69
128.55
128.44
128.34
128.26
128.18
128.06
127.96
127.93
127.86
127.52
126.58
126.51
126.45
116.75
116.67
96.18
95.95
82.31
82.12
77.82
77.70
77.50
77.18
73.23
64.67
64.47
60.94
42.65
42.36
41.76
40.69
40.17
37.29
36.62
34.25
31.34
15.52
15.31
14.29

1.47

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PROCNO   1
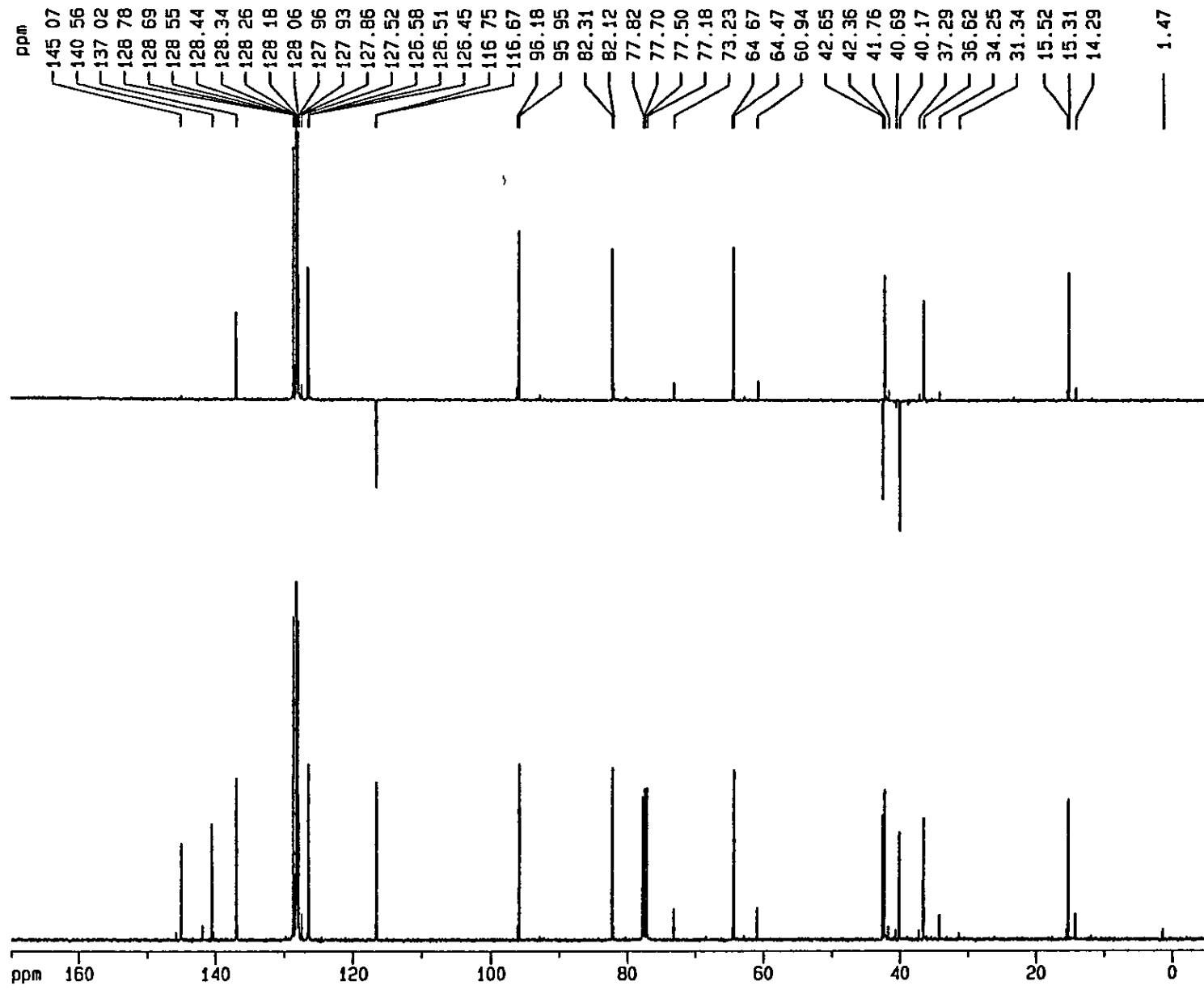
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PULPROG   zgpg30
TD   65536
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NS   2048
DS   2
SWH   31847.133 Hz
FIDRES   0 485949 Hz
AQ   1 0289652 sec
RG   8192
DW   15.700 usec
DE   7 50 usec
TE   300 0 K
d11   0 03000000 sec
d12   0 00002000 sec
PL13   120 00 dB
D1   1 00000000 sec
CPDPRG2   waltz16
PCPD2   100 00 usec
SFO2   400 1316005 MHz
NUC2   1H
PL2   -6 00 dB
PL12   12 00 dB
P1   5 50 usec
SFO1   100 6254358 MHz
NUC1   13C
PL1   -6 00 dB

F2 - Processing parameters
SI   32768
SF   100 6127290 MHz
WDW   EM
SSB   0
LB   1 00 Hz
GB   0
PC   1 40

1D NMR plot parameters
CX   20.00 cm
F1P   170 000 ppm
F1   17104 17 Hz
F2P   -5 000 ppm
F2   -503 06 Hz
PPMCM   8 75000 ppm/cm
HZCM   880 36151 Hz/cm
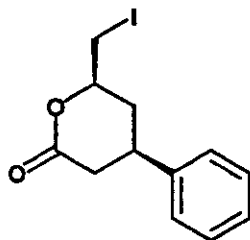
ppm 160   140   120   100   80   60   40   20   0

(2*R*, 4*R*)-2-Iodomethyl-4-phenyltetrahydropyran-2-one (**164a**)

- ^{1}H NMR showing detailed coupling constants
- ^{13}C NMR
- HETCOR

rdb432-1007-ma

ppm
7 390
7.372
7 353
7 308
7 305
7.294
7 289
7.271
7 263
7.225
7.222
7 204

| 4.419 |
| 4 416 |
| 4.411 |
| 4 408 |
| 4 400 |
| 4.396 |
| 4 391 |
| 4 383 |
| 3.444 |
| 3 428 |
| 3 417 |
| 3.410 |
| 3.394 |
| 3.384 |
| 3 368 |
| 2 953 |
| 2.948 |
| 2 939 |
| 2 909 |
| 2.903 |
| 2 895 |
| 2.889 |
| 2.609 |
| 2.580 |
| 2 565 |
| 2 535 |
| 2.445 |
| 2 440 |
| 2.411 |
| 2.406 |
| 1.894 |
| 1.863 |
| 1.860 |
| 1 834 |
| 1.831 |
| 1.432 |
| 1.290 |
| 1.284 |
| 1.253 |
| 1 222 |
| 0.896 |
| 0 880 |
| 0 072 |
| 0 000 |

Integral

1.989
1 108
2.217
0 970
2 000
0 993
0.924
0.961
0 946
1.183

rdb432-1007-ma

ppm 170.24 142.47 129.49 127.89 127.00 126.85 125.98 78.87 77.80 77.48 77.16 37.64 37.41 36.71 30.12 8.20

F2 - Acquisition Parameters
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PULPROG   invbtp
TD   1024
SOLVENT   DMSO
NS   8
DS   16
SWH   3396 739 Hz
FIDRES   3 317128 Hz
AQ   0 1507828 sec
RG   1824 6
DW   147 200 usec
DE   7 50 usec
TE   300 0 K
D1   1 50000000 sec
P1   15 00 usec
SFO1   400 1315086 MHz
NUC1   1H
PL1   -6 00 dB
D2   0 00344828 sec
PL2   -6 00 dB
P2   30 00 usec
P4   15 60 usec
SFO2   100 8197719 MHz
NUC2   13C
D7   0 60000002 sec
P3   7 80 usec
D0   0 00000300 sec
PL12   12 00 dB
CPDPRG2   garp
PCPD2   85 00 usec
IN0   0 00001775 sec

F1 - Acquisition parameters
ND0   4
TD   256
SFO1   100 6198 MHz
FIDRES   55 017605 Hz
SW   139 978 ppm

F2 - Processing parameters
SI   2048
SF   400 1300000 MHz
WDW   QSINE
SSB   2
LB   0 00 Hz
GB   0
PC   1 00

F1 - Processing parameters
SI   2048
MC2   TPPI
SF   100 6127290 MHz
WDW   SINE
SSB   2
LB   0 00 Hz
GB   0

2D NMR plot parameters
CX2   15 00 cm
CX1   15 00 cm
F2PLO   8 015 ppm
F2LO   3206 99 Hz
F2PHI   -0 474 ppm
F2HI   -189 75 Hz
F1PLO   139 994 ppm
F1LO   14085 15 Hz
F1PHI   0 006 ppm
F1HI   0 64 Hz
F2PPMCM   0 56594 ppm/cm
F2HZCM   226 44928 Hz/cm
F1PPMCM   9 33249 ppm/cm
F1HZCM   938 96710 Hz/cm

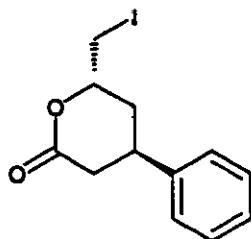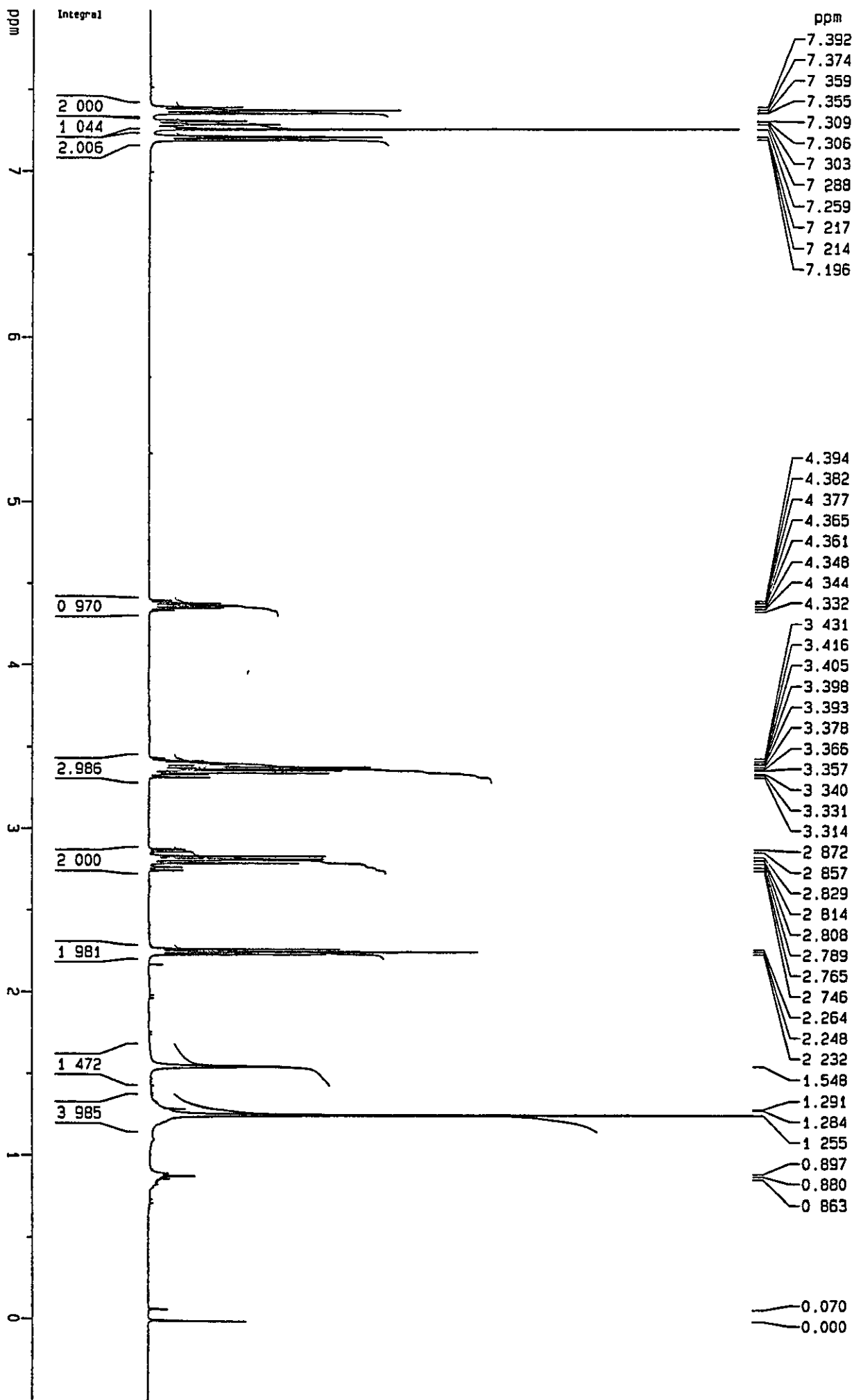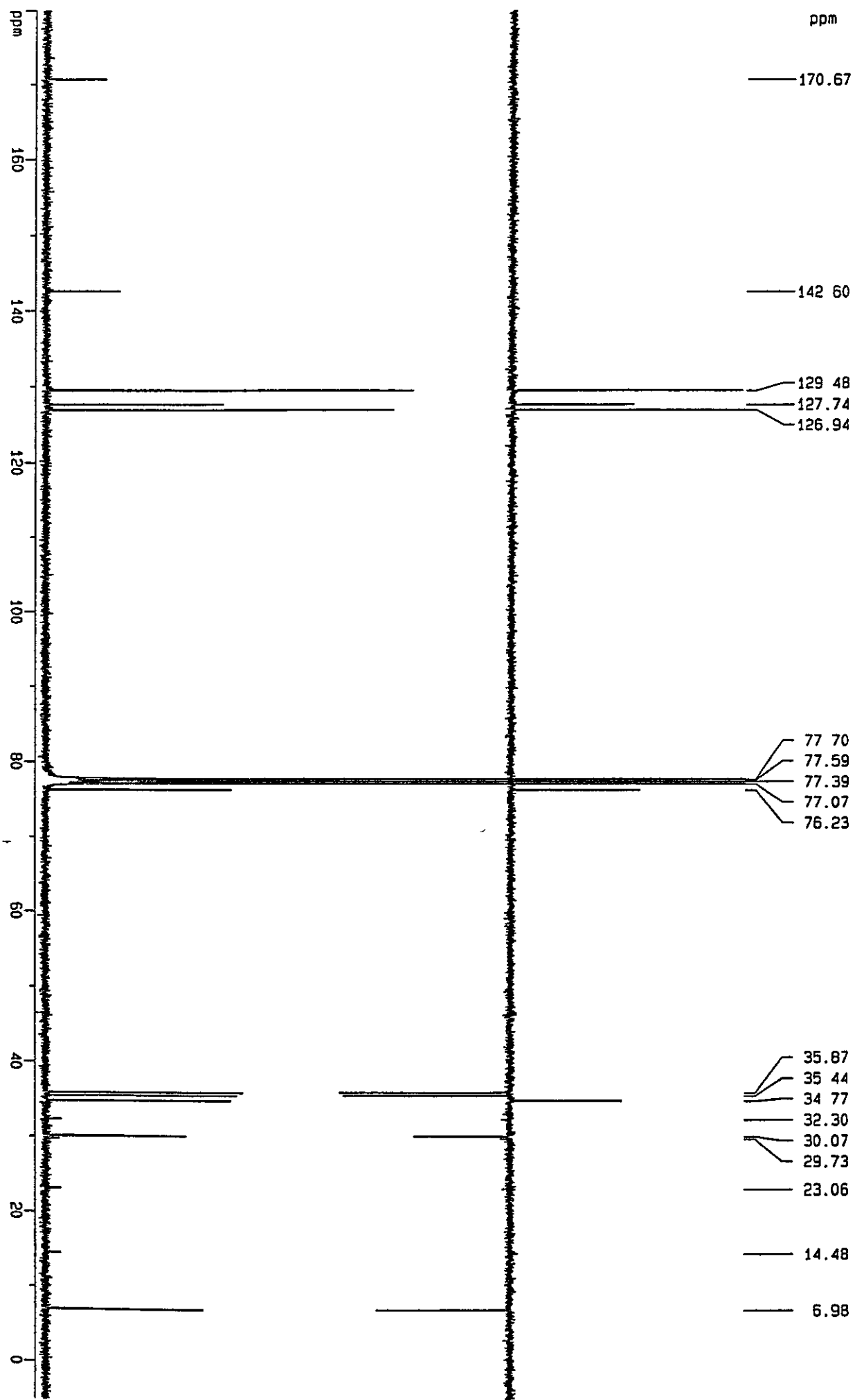(2*S*, 4*R*)-2-Iodomethyl-4-phenyltetrahydropyran-2-one (**164b**)
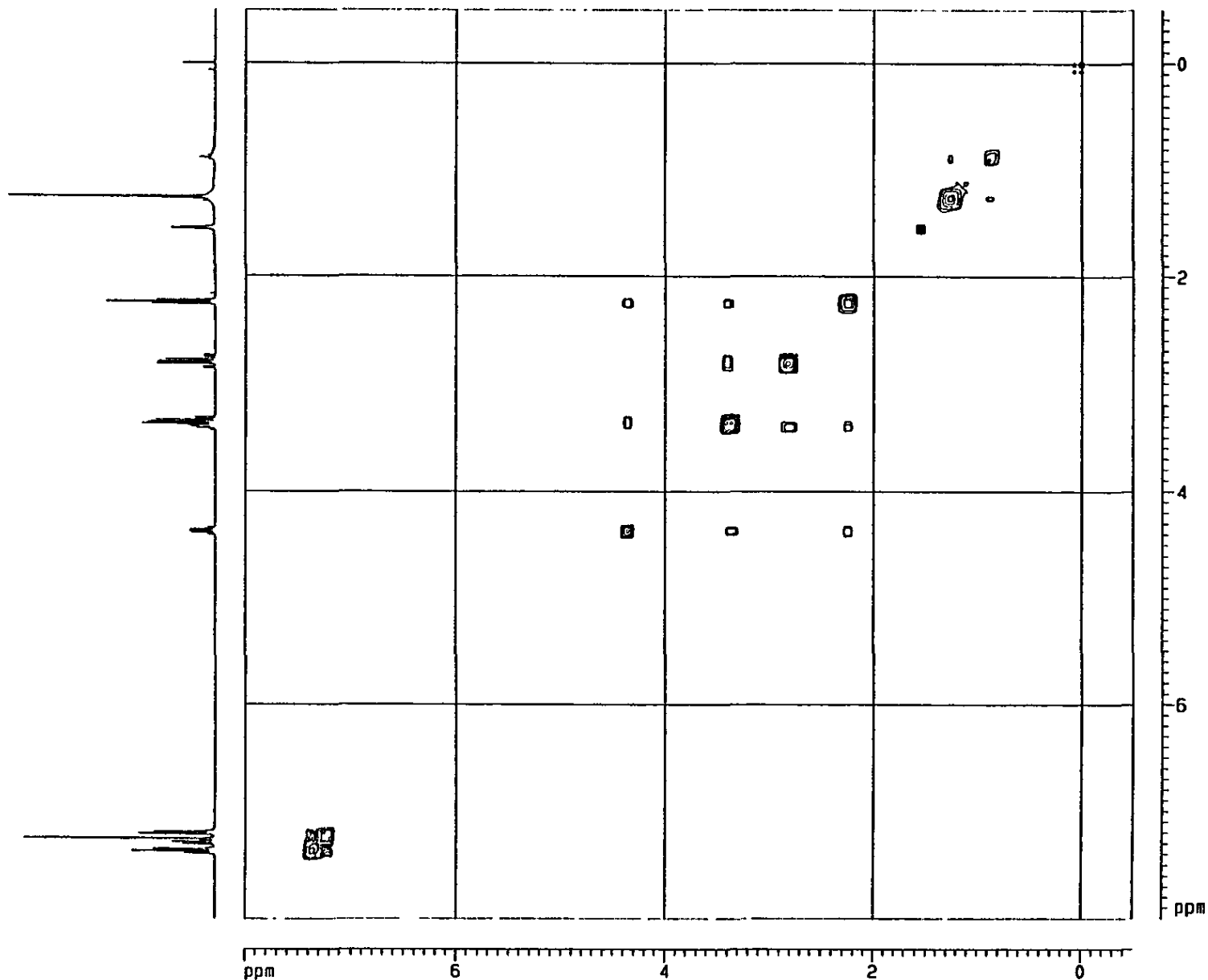
- ^{1}H NMR with expansions showing coupling
- ^{13}C NMR
- COSY

E

rdb-432-1007

ppm

170.67

142.60

129.48
127.74
126.94

77.70
77.59
77.39
77.07
76.23

35.87
35.44
34.77
32.30
30.07
29.73

23.06

14.48

6.98

rdb-432-1007

F2 - Acquisition Parameters
Date_   20000719
Time   9 35
INSTRUM   dpx400
PROBHD   5 mm Multinu
PULPROG   cosy45
TD   1024
SOLVENT   D2O
NS   8
DS   16
SWH   3396 739 Hz
FIDRES   3 317128 Hz
AQ   0 1507828 sec
RG   912 3
DW   147 200 usec
DE   7 50 usec
TE   300 0 K
D1   3 00000000 sec
P1   15 00 usec
SF01   400 1315100 MHz
NUC1   1H
PL1   -6 00 dB
D0   0 00000300 sec
IN0   0 00029440 sec

F1 - Acquisition parameters
ND0   1
TD   66
SF01   400 1315 MHz
FIDRES   51 465744 Hz
SW   8 489 ppm

F2 - Processing parameters
SI   512
SF   400.1300073 MHz
WDW   SINE
SSB   0
LB   0 00 Hz
GB   0
PC   1 00

F1 - Processing parameters
SI   512
MC2   QF
SF   400 1300075 MHz
WDW   SINE
SSB   0
LB   0 00 Hz
GB   0

2D NMR plot parameters
CX2   15 00 cm
CX1   15 00 cm
F2PLO   8 000 ppm
F2LO   3201 04 Hz
F2PHI   -0 489 ppm
F2HI   -195 69 Hz
F1PLO   8 000 ppm
F1LO   3200 89 Hz
F1PHI   -0 489 ppm
F1HI   -195 85 Hz
F2PPMCM   0 56594 ppm/cm
F2HZCM   226 44928 Hz/cm
F1PPMCM   0 56594 ppm/cm
F1HZCM   226 44928 Hz/cm