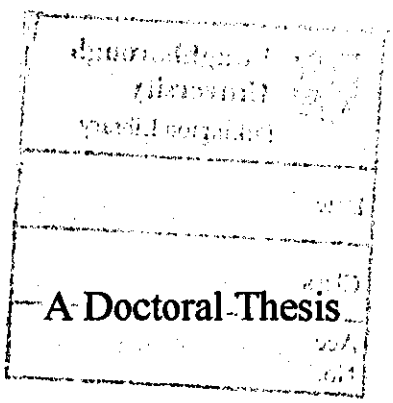
The Development and Application of the Anionic Amino-Cope Rearrangement

by

Catarina Horro Pita



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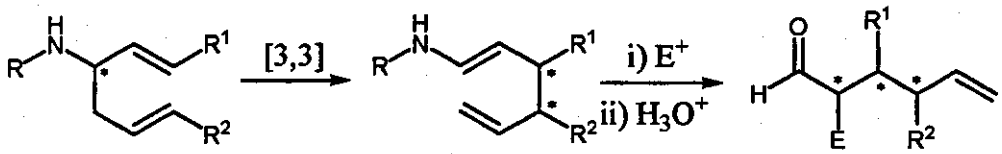
Abstract

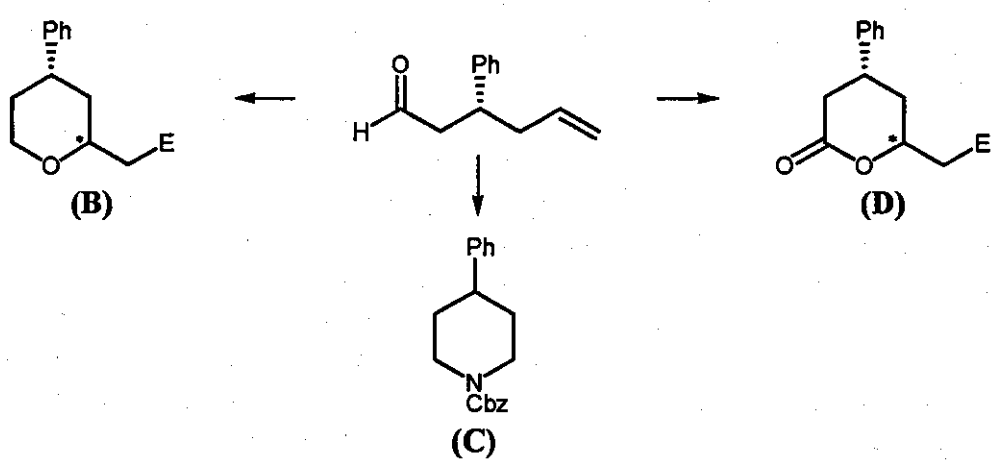
The anionic amino-Cope rearrangement is currently being developed by our group as a new synthetic protocol. Our ultimate goal is the one-pot asymmetric synthesis of compounds such as **(A)**, with up to 3 contiguous chiral centres, *via* an amino-Cope rearrangement and subsequent enamine derivatisation and hydrolysis.



(A)

The mechanism of the anionic amino-Cope rearrangement is still a matter of debate and we have investigated the effect of solvent and substituents on the enantioselectivity observed in the reaction. The aim of this study was to find the optimal conditions for the anionic amino-Cope rearrangement, eliminating - or at least minimising - competing reaction pathways that can reduce the enantioselectivity of the process.

In addition, the aldehyde product of the amino-Cope rearrangement has been used as a chiral building block for the synthesis of heterocycles such as tetrahydropyrans **(B)** and lactones **(D)**. The synthesis of piperidines **(C)** has now been achieved, enhancing the scope of this rearrangement.



(B) **(C)** **(D)**

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Abbreviations

*	-	denotes chiral centre
Å	-	amstrong
Ac	-	acetyl
BDE	-	bond dissociation energy
Bn	-	benzyl
Boc	-	*tert*-butoxycarbonyl
br	-	broad
Bu	-	butyl
°C	-	temperature in centigrades
c	-	cyclo-
Cbz	-	benzyloxycarbonyloxy
cm	-	centimetre(s)
CSA	-	camphor-10-sulphonic acid
δ	-	chemical shift
d	-	doublet
d.e.	-	diastereomeric excess
DET	-	diethyl tartrate
DIBAL-H	-	diisobutylaluminium hydride
dm	-	decimetre(s)
DMAP	-	4-dimethylaminopyridine
DME	-	1,2-dimethoxyethane
DMF	-	*N*,*N*-dimethylformamide
DMPU	-	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DOSP	-	*N*-[4-dodecylphenyl sulphonyl]-(*S*)-prolinato]
d.r.	-	diastereomeric ratio
E	-	electrophile
e.e.	-	enantiomeric excess

EI	-	electron impact
eq	-	equivalent(s)
Et	-	ethyl
exp	-	experimental value
FAB	-	fast atom bombardment
FT-IR	-	fourier transform infrared
h	-	hour(s)
Hex	-	hexyl
HMPA	-	hexamethylphosphoramide
HMPT	-	hexamethylphosphorous triamide
HPLC	-	high performance liquid chromatography
Hz	-	Hertz
i	-	*iso-*
J	-	coupling constant
k	-	rate constant
K	-	kelvin
Kcal	-	kilocalorie(s)
KHMDS	-	potassium hexamethyldisilazide
LA	-	Lewis acid
LDA	-	lithium diisopropylamide
LDEA	-	lithium diethylamide
LHMDS	-	lithium hexamethyldisilazide
lit	-	literature value
M	-	molar, metal, mega
m	-	multiplet
m-CPBA	-	*meta*-chloroperoxybenzoic acid
Me	-	methyl
min	-	minute(s)
mL	-	millilitre(s)
Mp	-	melting point
MS	-	molecular sieves

n	-	normal
N	-	normal (concentration)
NBS	-	*N*-bromosuccinimide
NHMDS	-	sodium hexamethyldisilazide
NIS	-	*N*-iodosuccinimide
nm	-	nanometre
NMM	-	4-methymorpholine
NMO	-	*N*-methylmorpholine-*N*-oxide
NMR	-	nuclear magnetic resonance
NPSP	-	*N*-(phenylseleno)phthalimide
o	-	*ortho-*
Pe	-	pentyl
Ph	-	phenyl
ppm	-	parts per million
PPTS	-	*p*-toluenesulphonate
Pr	-	propyl
psi	-	pound per square inch
rt	-	room temperature
s	-	second(s), singlet
SAMP	-	(*S*)-(-)-1-amino-2-(methoxymethyl)pyrrolidine
su	-	succinimide
t	-	triplet, time
t	-	*tert-*
T	-	temperature
TBDMS	-	*tert*-butyldimethylsilyl
TBHP	-	*tert*-butyl hydroperoxide
TFA	-	trifluoroacetic acid, trifluoroacetate
THF	-	tetrahydrofuran
TLC	-	thin layer chromatography
TMEDA	-	*N,N,N′,N′*-tetramethylethylenediamine
TMS	-	trimethylsilyl, trimethylsilane, tetramethylsilane
TPAP	-	tetra-*n*-propylammonium perruthenate

Ts	-	*para*-toluenesulfonyl
q	-	quartet
UV	-	ultraviolet

Chapter 1

Introduction

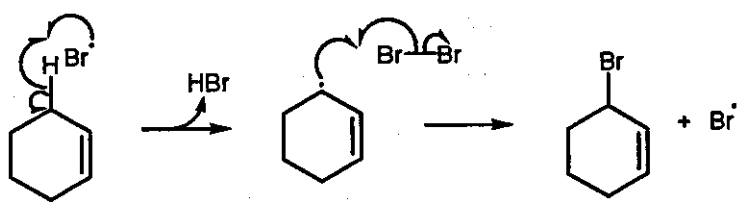
1.1 Ionic, Radical and Pericyclic Reactions

Despite the vast number and variety of organic reactions, three distinct groups can be classified: ionic, radical and pericyclic.[1]

Ionic reactions involve the movement of pairs of electrons from one component, called the nucleophile, to another, called the electrophile. An example of this category is an aldol condensation[2] **(Scheme 1)**.

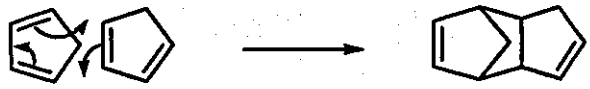
Scheme 1

In radical reactions, single electrons from two different components pair up to form a new bond **(Scheme 2)**.



Scheme 2

Pericyclic reactions were first studied by Woodward and Hoffmann[3] and are characterised by having a cyclic transition state in which all bond-forming and bond-breaking takes place simultaneously, without the existence of an intermediate. A Diels-Alder reaction[4] **(Scheme 3)** is a well-known pericyclic process.



Scheme 3

1.2 Pericyclic Reactions

Pericyclic reactions have been classified by Fleming[1] into four categories:

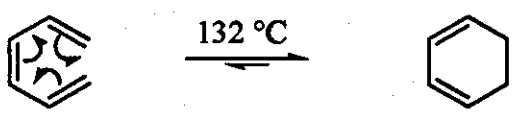
- Cycloadditions
- Electrocyclic reactions
- Sigmatropic rearrangements
- Group transfer reactions

1.2.1 Cycloadditions

In a cycloaddition,[1] two components react together to form a ring, by generation of two new σ-bonds and a reduction in length of the conjugated system in each substrate. A Diels-Alder[4] reaction **(Scheme 3)** is a cycloaddition mobilising 6 electrons.

1.2.2 Electrocyclic Reactions

Electrocyclic reactions are unimolecular processes defined[5] as the creation of a new σ-bond across the ends of a conjugated polyene with the concomitant formation of a ring **(Scheme 4)**.



Scheme 4

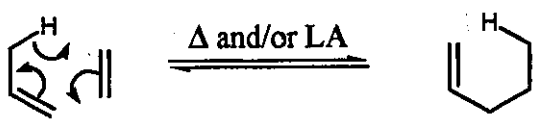
1.2.3 Sigmatropic Rearrangements

A sigmatropic rearrangement is defined[3,6] as a migration, in an uncatalysed intramolecular process, of a σ-bond to a new position in a molecule, with a π-system becoming reorganised during the process **(Scheme 5)**.

Scheme 5

1.2.4 Group Transfer Reactions

An ene-reaction is the most common example of a group transfer reaction and was defined by Hoffmann[7] as the addition of a compound with a double bond, called the enophile **(2)** **(Scheme 6)** to an olefin with an allylic hydrogen, called the "ene" **(1)**.



(1) **(2)**

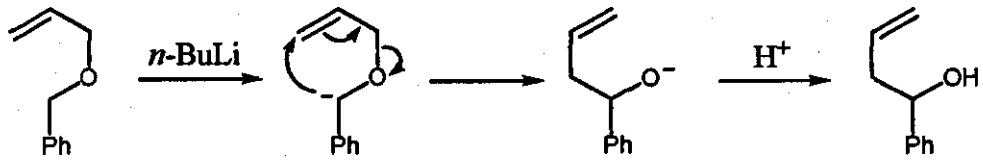
LA : $BF_3.OEt_2$, $SnCl_4$, $AlEtCl_2$, $AlMe_2Cl$

Scheme 6

1.3 Classification of Sigmatropic Rearrangements

Woodward and Hoffmann[6] developed a simple classification system for sigmatropic rearrangements that employs two numbers set in brackets, [*i*,*j*].

These numbers indicate the carbons where the new σ-bond is generated. Each of the original termini is given the number 1. Migration of one terminus of the σ-bond is therefore classified as [1,*j*] whilst, if both termini move, the classification uses two numbers other than 1. When these values are even, they are also equal to the number of electrons delocalised in the transition state of the pericyclic reaction.[8] Therefore, a [3,3]-sigmatropic rearrangement involves the movement of 6 electrons **(Scheme 5)**. However, when (*i*+*j*) is odd, the sigmatropic shift has cationic or anionic character and the participant electrons will be one less (cationic) or one greater (anionic) than these values. A well-known example is the [2,3]-Wittig rearrangement[9] **(Scheme 7)**, which involves the movement of 6 electrons and possesses anionic character.



Scheme 7

1.3.1 [1,*j*]-Sigmatropic Rearrangements

[1,*j*]-Sigmatropic rearrangements can be considered as shifts of atoms. According to Woodward and Hoffmann,[6] these shifts can be *suprafacial*, when the shifted atom is associated at all times with the same face of the π-system, or *antarafacial*, when the migrating atom is passed from the top face of one carbon to the bottom face of the other **(Figure 1)**.

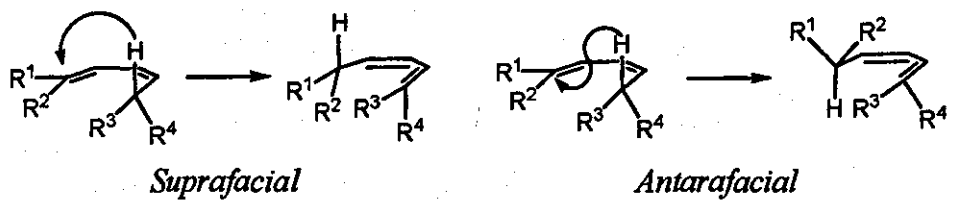
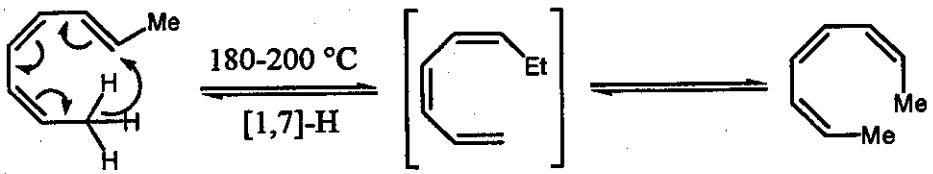


Figure 1

Considering only thermally allowed[6] [1,*j*]-sigmatropic rearrangements in neutral molecules, a large number of examples can be found in the literature.[10-14]

Shifts of hydrogen atoms are the most common [1,*j*]-sigmatropic rearrangements.[10,11] A simple literature example[11] is a [1,7]-H shift in the reversible isomerisation of **(3)** **(Scheme 8)**.



(3)

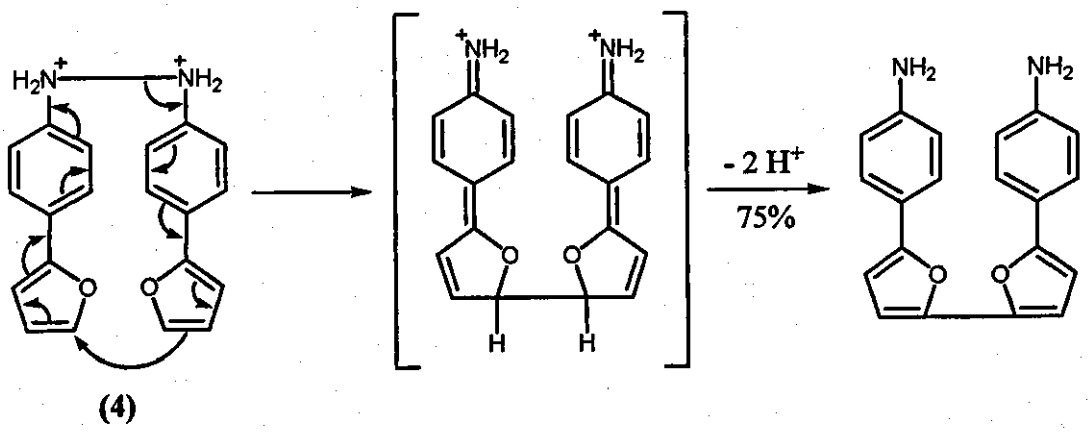
Scheme 8

[1,*j*]-Sigmatropic rearrangements have been observed with groups other than hydrogen. Thermal [1,3]-,[12] [1,5]-[13] and [1,7]-shifts[14] in neutral molecules can be found in the literature.

1.3.2 [*i*,*j*]-Sigmatropic Rearrangements

The previously described rearrangements **(Section 1.3.1)** take place at only one end of the σ-bond but it is also possible to have the σ-bond move *i* atoms along the conjugated system. Well-known examples in this category are the Wittig,[9] [5,5]-benzidine[15] or the Cope **(Section 1.4)** and Claisen **(Section 1.6)** rearrangements.

An interesting example of a benzidine-type rearrangement is the [9,9]-sigmatropic shift of **(4)** **(Scheme 9)** reported by Park and Kang.[16]



(4)

Scheme 9

1.3.3 [3,3]-Sigmatropic Rearrangements

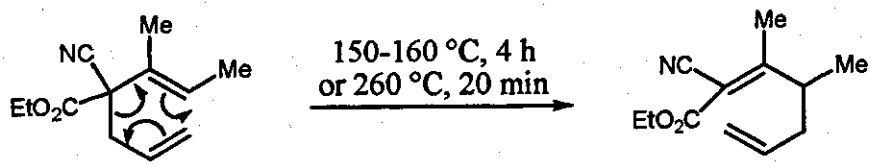
This type of rearrangement comprises the Cope[17] and Claisen,[18] as well as all their variants. A common feature of this category is that they proceed through highly-ordered transition state geometries, which allows the prediction and control of both relative and absolute stereochemistry in the desired product.[19] This is a powerful tool for the synthetic organic chemist and [3,3]-sigmatropic rearrangements have found many applications in organic synthesis, as shown in the subsequent sections.

1.4 The Cope Rearrangement

The Cope rearrangement[17] **(Figure 2)** is the archetype of all [3,3]-sigmatropic rearrangements.

Figure 2

The Cope rearrangement was discovered by Cope and Hardy in 1940.[17] During the synthesis of **(5)** **(Scheme 10)**, it was observed that this compound rearranged into **(6)**.



(5) **(6)**

Scheme 10

The driving force of this reaction was the higher stability of the product **(6)** due to the conjugation of a double bond with the cyano and ester groups.[20]

When a diene substrate is symmetrical about the C-3 and C-4 bond **(7)** **(Scheme 11)**, its rearrangement leads to a product that is identical to the starting material. In this reaction, called a degenerate Cope rearrangement,[21] the substrate and product are in equilibrium at rearrangement temperature.

(7)

Scheme 11

The equilibrium in the Cope rearrangement can be displaced towards the product in the following circumstances:

- The number of substituted double bonds (in the absence of any conjugating substituents) is increased[22]

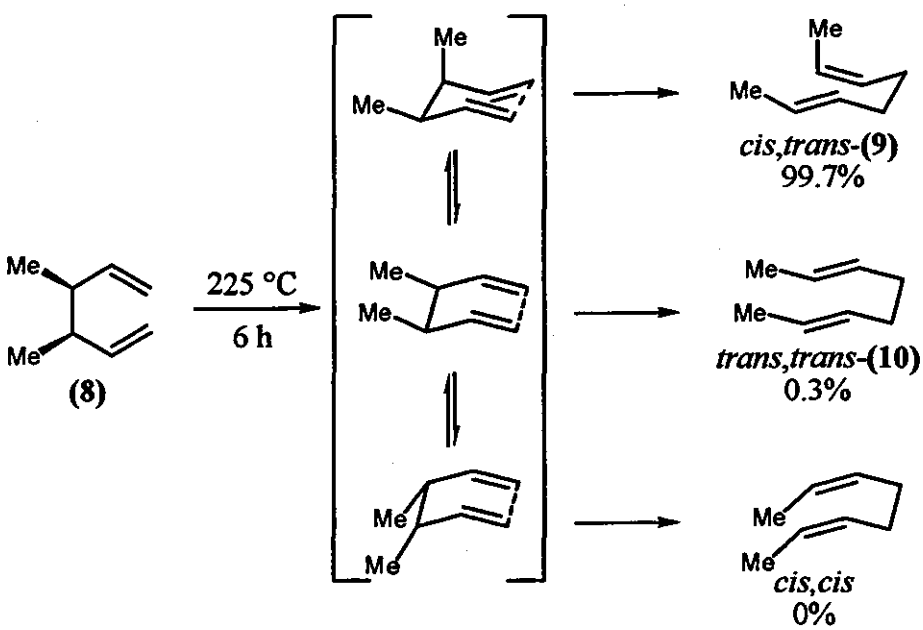
- The number of π-substituents, such as ketone, ester or cyano groups conjugated with a double bond **(Scheme 10)** is increased[8,20]

- A double bond is incorporated into an aromatic system[23]
- There is a decrease in ring strain by opening a three or four-membered ring[8,21]
- The rearrangement is included as a step in a cascade process leading to a stable product.[24]

1.4.1 Stereochemistry of the Cope Rearrangement

The Cope rearrangement and its analogues are extremely stereospecific reactions, due to highly-ordered transition state geometries. The mechanism of the uncatalysed Cope rearrangement is a 6-centred pericyclic process[21] with a 6-membered ring transition state, comparable to cyclohexane, which can therefore assume a chair or boat conformation.

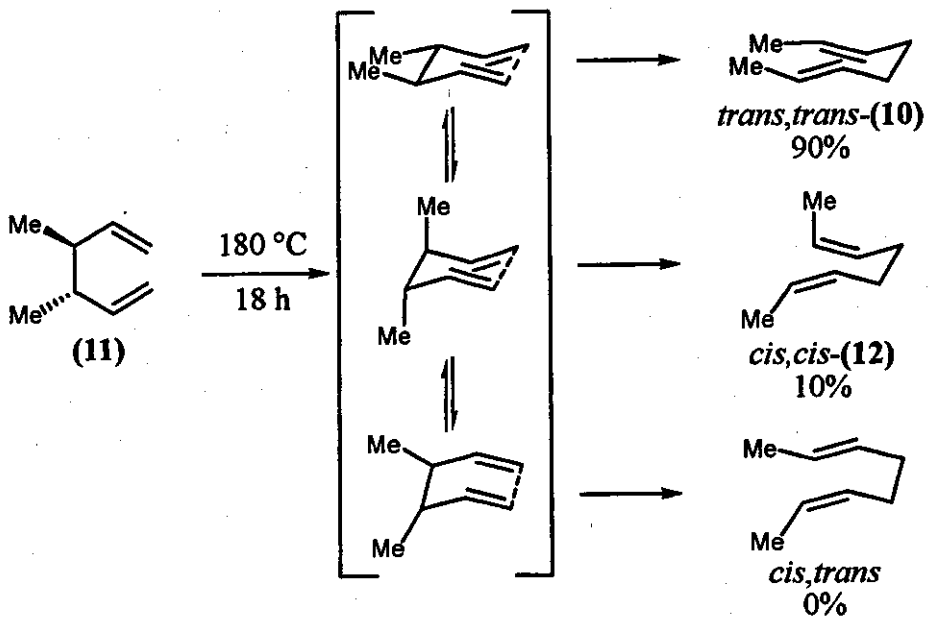
It has been possible to demonstrate the preference for a chair conformation in the transition state of simple substrates in the Cope rearrangement. Doering and Roth[25] studied the thermal rearrangement of **(8)** **(Scheme 12)** and **(11)** **(Scheme 13)**.



Scheme 12

The diene **(8)** rearranged at 225 °C to almost exclusively *cis,trans*-**(9)** (99.7%). This could only occur *via* a chair conformation transition state. Only 0.3% of *trans,trans*-**(10)** (*via* a boat conformation) was formed. The free energy in the boat conformation was at least 5.7 Kcal/mol higher than in the chair transition state.

The isomer **(11)** **(Scheme 13)** rearranged to a mixture of 90% *trans,trans*-**(10)** and 10% *cis,cis*-**(12)**, both of them formed through a chair conformation transition state.



Scheme 13

Doering and Roth[25] concluded that the preponderance of *trans,trans*-**(10)** was due to a difference in free energy by 2.0 Kcal/mol in the corresponding chair transition states. This energetic gap was due to a lower energy required for the formation of a *trans* double bond in **(10)** in comparison with a *cis* alkene **(12)** and a lower energy involved in a transition state with equatorially orientated methyl groups.

Perrin and Faulkner[26] observed a quantitative agreement between the observed *cis/trans* ratio in Cope rearrangement products and the observed axial/equatorial ratios in

cyclohexanes. It was concluded that the body of data on conformational preferences in cyclohexanes could be used to predict the *cis/trans* ratios in the Cope rearrangement.

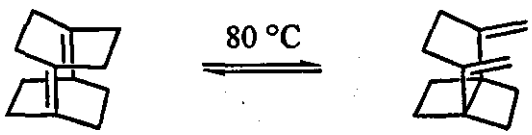
The preference for a chair conformation in the transition state of the Cope rearrangement has been attributed[27] to the entropy difference between a chair **(13)** and a boat conformation **(14)** in the transition state and secondary orbital interactions present in the boat **(14)** **(Figure 3)** but absent in the chair conformation **(13)**.

(13) **(14)**

Figure 3

The boat conformation is energetically accessible and may be required by special structural features. A boat transition state is usually the preferred pathway in cyclic systems.[28]

Wiberg[29] observed that compound **(15)** **(Scheme 14)** underwent a Cope rearrangement through a boat conformation transition state. The substrate was unable to adopt a chair conformation.

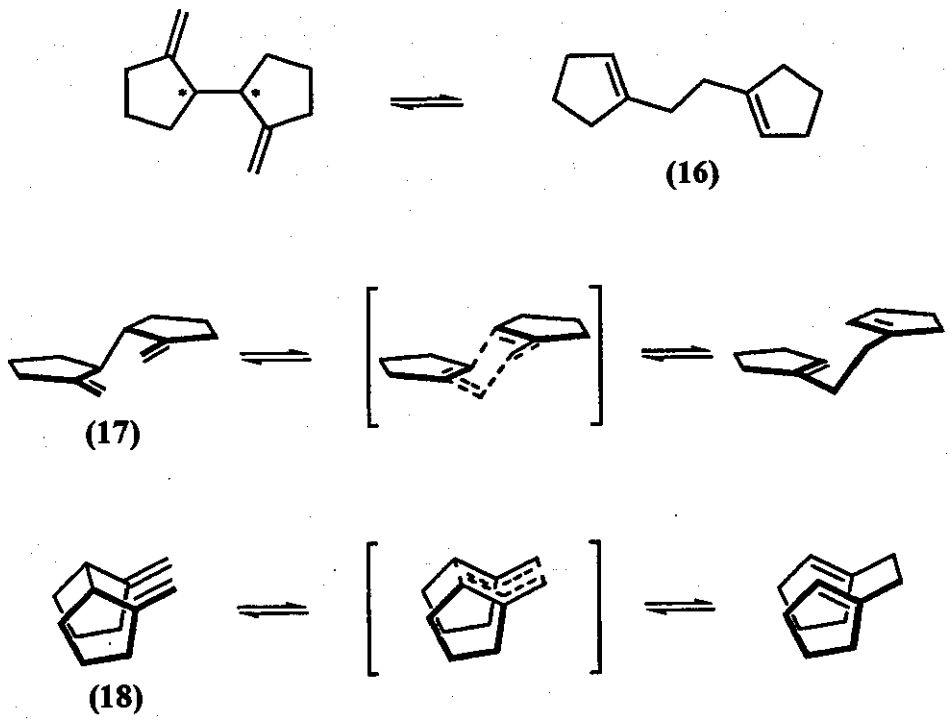


(15)

Scheme 14

Cope rearrangements that proceed through a boat transition state are slower and need higher temperatures to react. In simple aliphatic systems, the chair/boat energy difference is typically 5-10 Kcal/mol.[25,30]

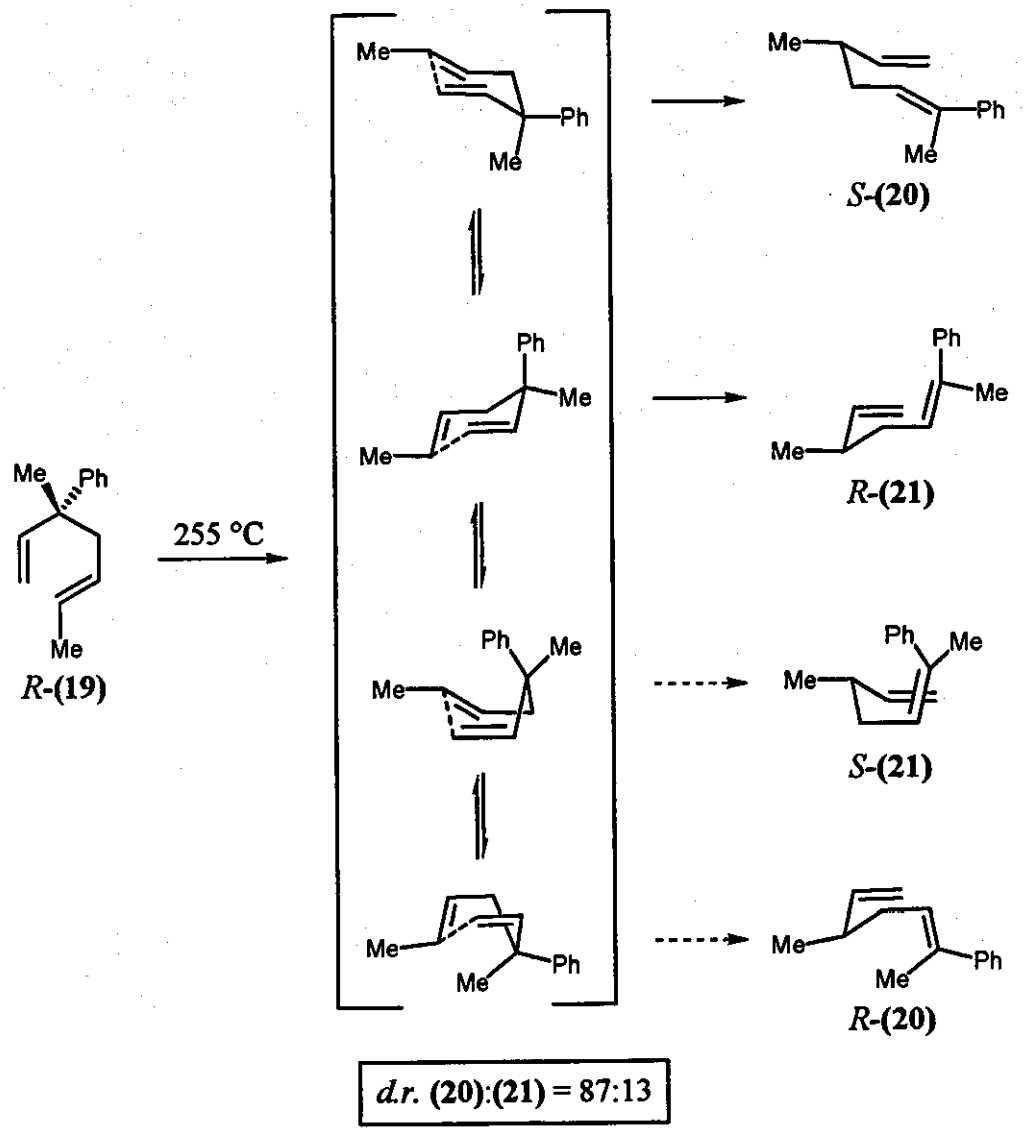
Shea[27] studied the Cope rearrangement of **(17)** and **(18)** **(Scheme 15)**. Both isomers rearranged into the same product **(16)**, but whereas **(17)** adopted a chair conformation in the transition state, a boat conformation was the only one accessible for the rearrangement of **(18)**.



Scheme 15

When isomer **(17)** was heated to 160 °C it was quantitatively converted to **(16)**, whereas **(18)** only began to react when heated to temperatures in excess of 250 °C. Rate constants of the individual diastereoisomers were measured after extrapolation to an intermediate temperature (200 °C) and it was observed that the rate ratio was k_{17}/k_{18} (200 °C) = 18000.

Hill[31] demonstrated the high degree of optical stereospecificity in the Cope rearrangement **(Scheme 16)**.

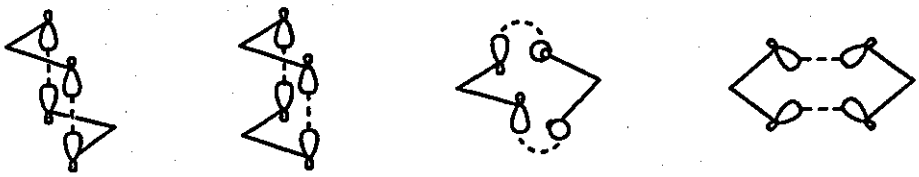


Scheme 16

Optically pure **(19)** rearranged quantitatively at 255 °C into an 87:13 mixture of isomers **(20)** and **(21)**, which proved to be optically active. Separate experiments demonstrated that the isomeric products were not interconverted at rearrangement temperature. The products were formed in optical purities of 91% *S*-**(20)** and 89% *R*-**(21)**, which confirmed the preference for a chair conformation in the transition state. The 87:13 preference for **(20)** corresponded to a free energy difference of about 2 Kcal/mol between the transition states with the phenyl substituent in equatorial **(20)** or axial position **(21)**.

This high degree of stereospecificity in the Cope and analogous [3,3]-sigmatropic rearrangements allows the prediction of the product stereochemistry and the design of appropriate precursors leading to products with the desired stereochemistry.[8]

Although a more thorough mechanistic analysis has revealed four possible transition-state geometries, chair **(22)**, boat **(23)**, twist **(24)** and plane **(25)**[32] **(Figure 4)**, this added complexity has not altered the impact of the classic investigation of Doering and Roth.[25]



(22) **(23)** **(24)** **(25)**

Figure 4

Gajewski[33] demonstrated that the latter two geometries **(24)** and **(25)**, which are *antarafacial* processes, are not involved at rearrangement temperatures.

1.4.2 Alternative Mechanism of the Cope Rearrangement

The Cope rearrangement[17] was initially represented in terms of a pericyclic reaction with an "aromatic" transition state **(27)** **(Figure 5)**, consisting of two partially bonded 3-carbon units. However, this representation was challenged by Doering,[34] who suggested an alternative mechanism involving a cyclohexan-1,4-dyil intermediate **(28)**. The alternative stepwise mechanism involving the cleavage to 2 allyl radicals **(26)** was calculated to be energetically inaccessible.

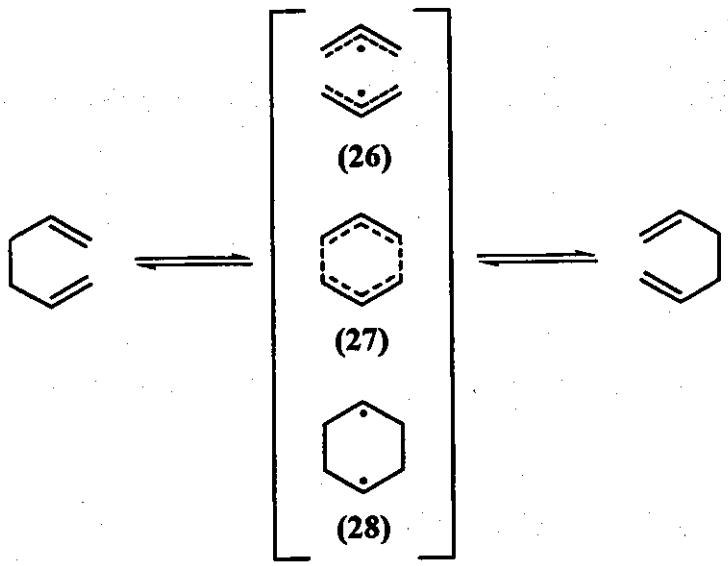
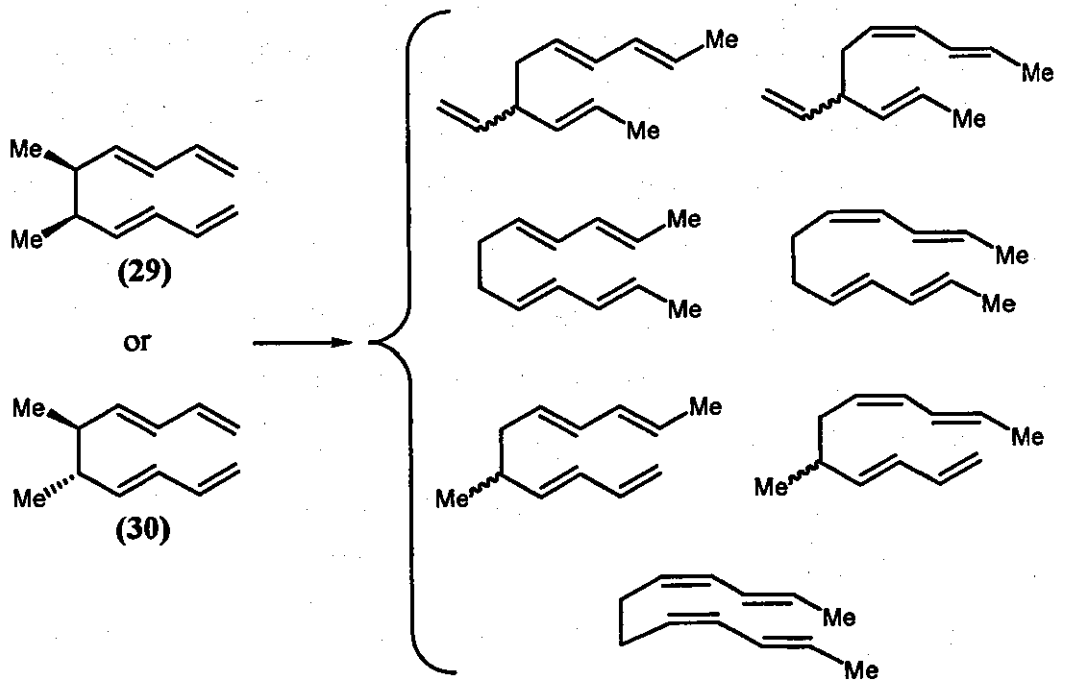


Figure 5

A number of subsequent theoretical studies[35] concluded that both transition states **(26)** and **(28)** were higher in energy than **(27)** and therefore a concerted mechanism was slightly favoured in the rearrangement of unsubstituted 1,5-hexadienes.

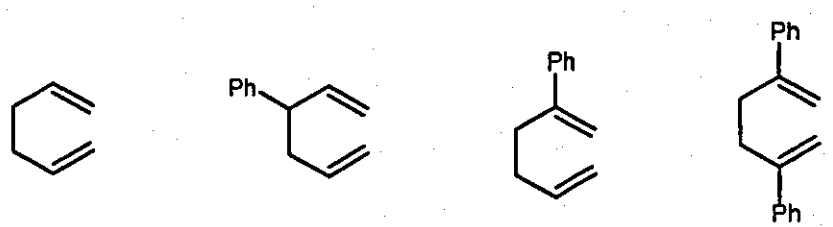
However, a significant change in mechanism has been observed due to structural features of the starting dienes. Gibson and Pettit[36] studied the rearrangement of **(29)** and **(30)** **(Scheme 17)**, vinylogous analogues to the compounds studied by Doering and Roth[25] **(Scheme 12** and **Scheme 13)**. Pyrolysis of **(29)** or **(30)** afforded the same product mixture, although with a slightly different distribution. The lack of stereospecificity was in complete contrast with that observed by Doering and Roth[25] and it was suggested that the reaction followed a radical mechanism. The starting materials would have dissociated into two pentadienyl radicals and subsequently recombined to generate the products.



Scheme 17

Two factors were considered responsible for this change in mechanism: the first was that pentadienyl radicals had greater stability than allyl radicals due to resonance. The second, that cyclic 6-membered transition states for the rearrangement of **(29)** or **(30)** would involve some loss in the conjugation energy of the diene units, whereas in 1,5-hexadienes no such destabilisation was encountered. It was reasoned that a change in mechanism would be feasible in those cases where strong stabilisation of free radicals was possible.

Dewar and Wade[37] studied the effects of phenyl substituents on the mechanism of the Cope rearrangement **(Figure 6)**.



(31) **(32)** **(33)** **(34)**

Figure 6

It was observed that the presence of phenyl groups at C-2 **(33)** and C-2 and C-5 **(34)** stabilised radical intermediates, promoting a biradical mechanism in the Cope rearrangement, whereas **(32)** reacted through a pericyclic process. It was concluded that **(31)** was poised between both mechanisms and that the balance could be displaced either way by appropriate substitution.

In a recent publication, Navarro-Vázquez[38] concluded, using computational studies, that a non-concerted reaction takes place when biradical intermediates are stabilised either by allyl or aromatic resonance, otherwise the reaction follows a concerted mechanism. This is in good agreement with previous studies by Gibson and Pettit[36] and Dewar and Wade.[37]

1.4.3 Asymmetric Cope Rearrangement

Asymmetric [3,3]-sigmatropic rearrangements have been conducted using chiral auxiliaries or chiral catalysts[19] and are discussed in the corresponding sections.

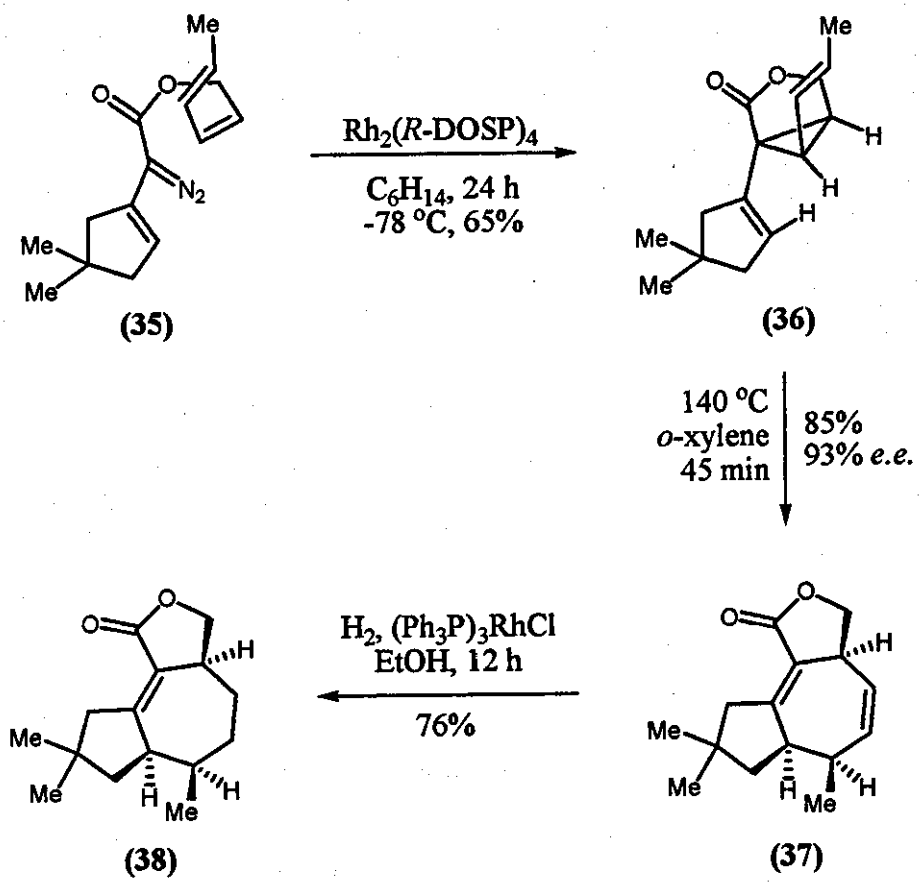
However, a truly asymmetric Cope rearrangement has not been discovered.[28] Generation of new stereogenic centres *via* a Cope rearrangement is often achieved by tandem processes[24] which incorporate an asymmetric inductive step and a Cope chirality transfer.[39,40]

1.4.4 Cope Rearrangement in Natural Product Synthesis

The Cope rearrangement has generally been utilised in cascade processes[24] and several examples[40,41] can be found in the literature.

Davies[41] developed an efficient method for the stereoselective synthesis of 7-membered rings by a tandem cyclopropanation/Cope rearrangement. This approach was used in the synthesis of tremulanes such as **(38) (Scheme 18)**.[41c]

Cyclopropanation of **(35)** using a chiral catalyst produced **(36)**, which underwent a Cope rearrangement to generate **(37)** *via* initial equilibration of **(36)** to a *cis*-divinylcyclopropane. Homolytic ring opening of the cyclopropane ring and subsequent free rotation of the alkyl group allowed the substrate **(36)** to adopt a suitable conformation for the rearrangement to occur.



Scheme 18

Although the Cope rearrangement of divinylcyclopropanes generally occurs at or below ambient temperature,[41b] compound **(36)** required forcing conditions (Kugelrohr distillation at 140 °C) to rearrange. This was due to the crowded boat transition state adopted by the substrate during rearrangement. Synthesis of **(38)** was achieved by hydrogenation of **(37)** with Wilkinson's catalyst.

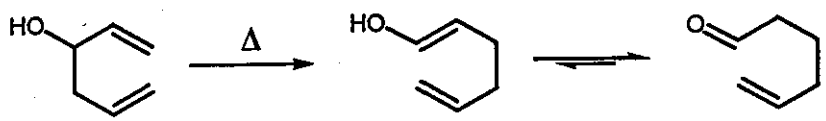
1.5 Variants of the Cope Rearrangement

There are several variants of the Cope rearrangement, which are listed below and subsequently discussed.

- Oxy-Cope rearrangement
- Amino-Cope rearrangement
- Aza-Cope rearrangement

1.5.1 The Oxy-Cope Rearrangement

The oxy-Cope rearrangement was discovered by Berson and Jones[42] in 1964 and is analogous to the Cope rearrangement, with the substitution of a hydroxy group at C-3 of a 1,5-diene **(39)** **(Scheme 19)**.



(39) **(40)** **(41)**

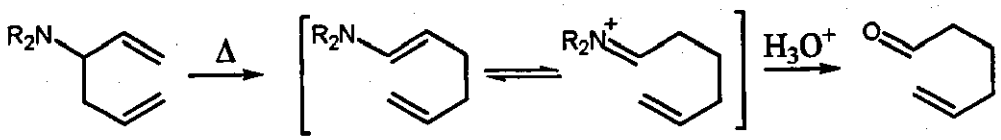
Scheme 19

Upon rearrangement of **(39)**, the resultant intermediate **(40)** tautomerises into a carbonyl compound **(41)**.

The oxy-Cope rearrangement is discussed in further detail in **Section 1.8**.

1.5.2 The Amino-Cope Rearrangement

The amino-Cope rearrangement[19] is analogous to the Cope rearrangement with the substitution of an amino group at C-3 of a 1,5-diene **(42)** **(Scheme 20)**.



(42) **(43)** **(44)** **(41)**

Scheme 20

Rearrangement of the 3-amino-1,5-diene **(42)** leads to an enamine **(43)** that tautomerises to an imine or iminium ion **(44)**, depending on the substitution of the starting amine. Hydrolysis of **(44)** produces a carbonyl compound **(41)**.

The amino-Cope rearrangement is discussed in further detail in **Section 1.9** and **Chapter 2**.

1.5.3 The Aza-Cope Rearrangement

The aza-Cope rearrangement occurs in hetero-Cope systems possessing a nitrogen atom in the 1, 2 or 3 position of a 1,5-diene[43] **(Figure 7)**.

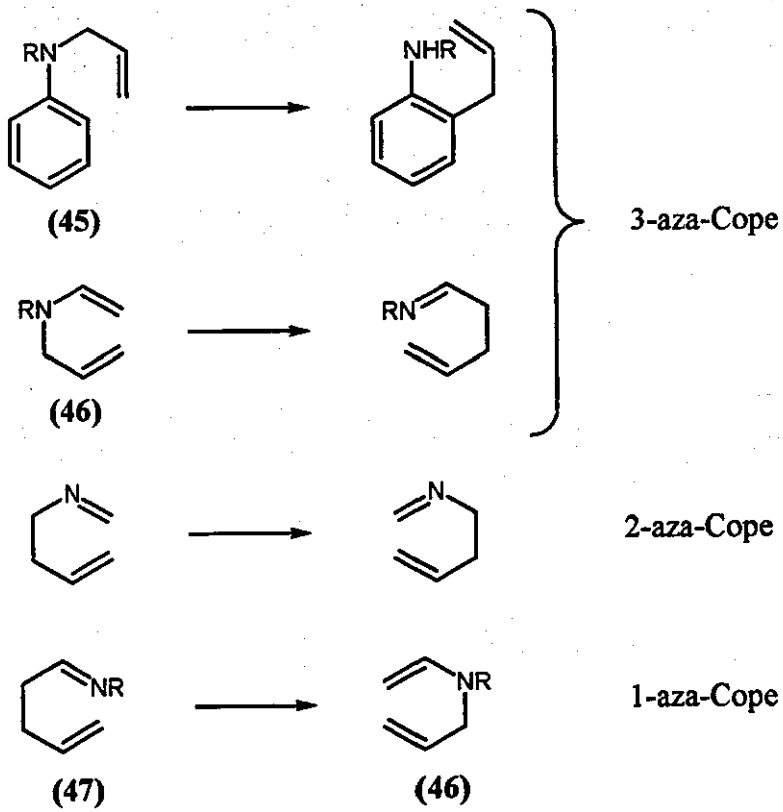


Figure 7

When the nitrogen is situated at position 3 (**(45)** and **(46)**), the reaction is called a 3-aza-Cope rearrangement, although it is sometimes referred to as an amino- or aza-Claisen.[43,44] The 3-aza-Cope rearrangement requires more drastic conditions than those reported for the analogous Claisen rearrangement.[44,45] In addition, undesirable side reactions are often present, especially [1,3]- instead of [3,3]-shifts.[29]

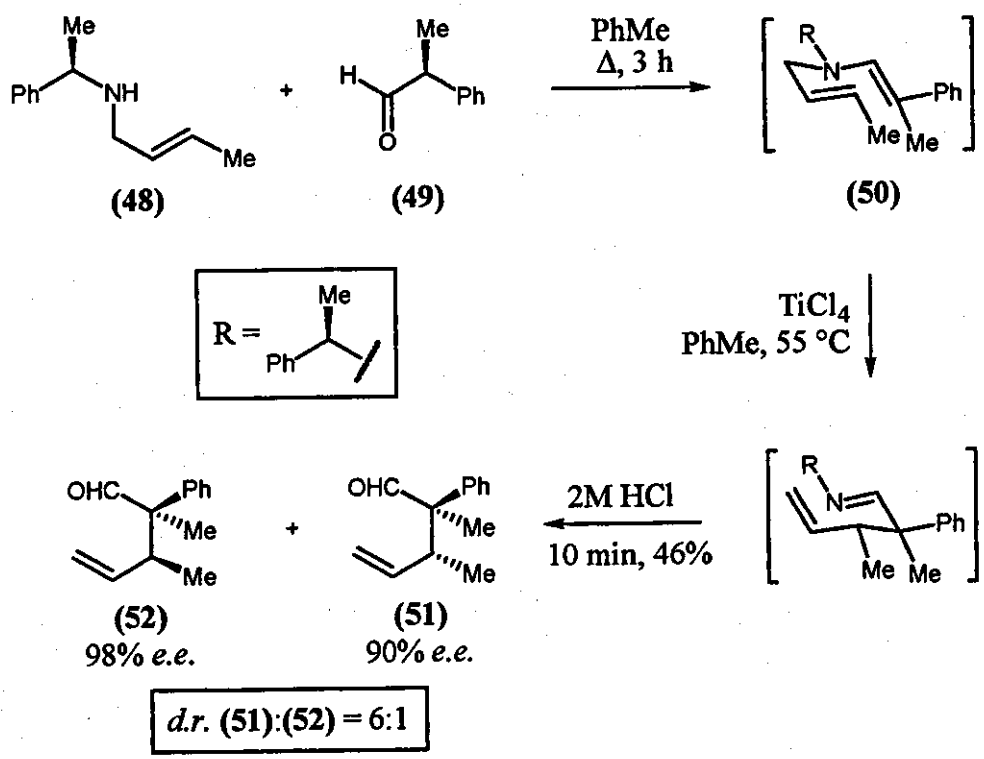
2-Aza-Cope rearrangements are reasonably common in organic synthesis[43] and have been used in the generation of alkaloids.[46]

1-Aza-Cope rearrangements have limited use in synthetic organic chemistry due to the greater stability of the starting material **(47)** in comparison with the product **(46)**, an amino-Claisen substrate.[43,47]

1.5.3.1 Asymmetric Aza-Cope Rearrangement

The presence of a nitrogen atom in an aza-Cope rearrangement substrate gives a potentially powerful opportunity for the introduction of stereocontrol *via* a chiral amine auxiliary. However, there are limited examples of asymmetric aza-Cope rearrangements with high asymmetric induction.[29]

Bayley[48] observed a simultaneous 1,4- and 1,5-asymmetric induction in a 3-aza-Cope rearrangement with a high degree of stereocontrol **(Scheme 21)**.

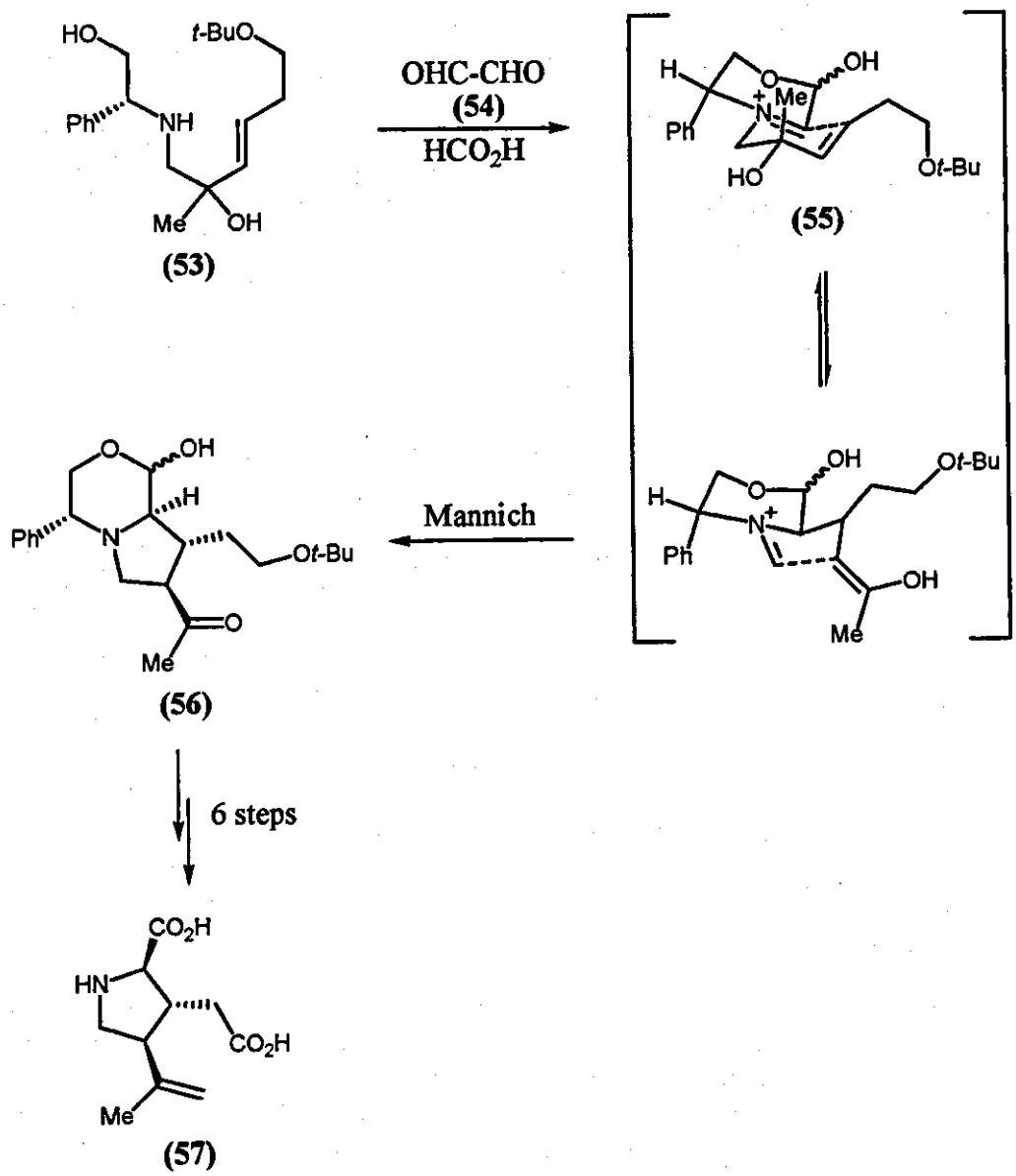


Scheme 21

The allylamine **(48)** was refluxed with **(49)** in toluene to produce the intermediate **(50)**. Titanium tetrachloride was added to the solution to catalyse the rearrangement of **(50)** and a diastereomeric mixture of **(51)** and **(52)** was isolated after acidic hydrolysis in a 6:1 *d.r.*

1.5.3.2 Aza-Cope Rearrangement in Natural Product Synthesis

Agami[49] utilised a tandem asymmetric aza-Cope rearrangement/Mannich reaction in the synthesis of (-)-allokainic acid **(57)** **(Scheme 22)**.



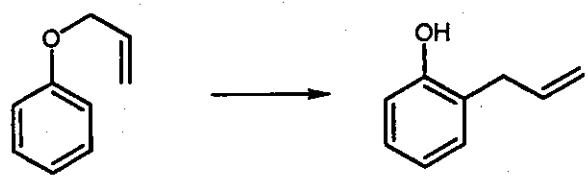
Scheme 22

The β-amino alcohol **(53)** was condensed with glyoxal **(54)** in formic acid to yield the intermediate **(55)**, which underwent an aza-Cope rearrangement. The final Mannich-type

cyclisation generated **(56)**, which had the correct stereogenic configuration as the target compound **(57)**.

1.6 The Claisen Rearrangement

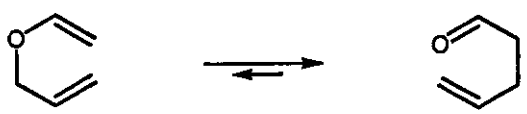
The term "Claisen rearrangement" was originally reported by Ludwig Claisen in 1912[18] and applied to rearrangements of allyl aryl ethers **(58)** to *ortho*-phenols **(59)** **(Scheme 23)** and occasionally *para*-phenols.



(58) **(59)**

Scheme 23

In subsequent years the term was extended to include the analogous rearrangements of allyl vinyl ethers **(60)** to unsaturated aldehydes **(61)** or ketones **(Scheme 24)**.[50]



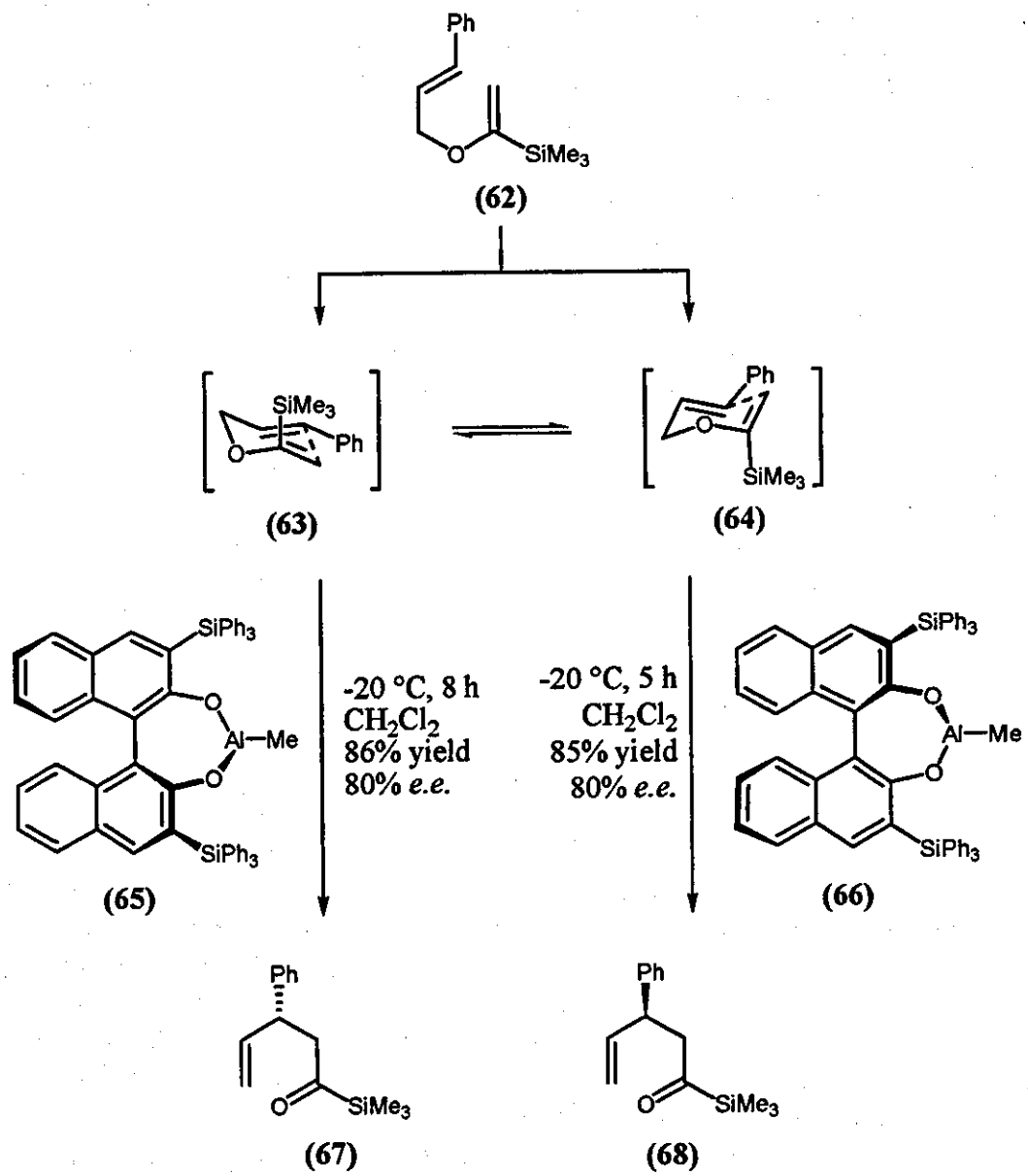
(60) **(61)**

Scheme 24

The Claisen, as with the Cope rearrangement, has been subjected to several studies to determine the possible biradical nature of its mechanism although no general agreement has been achieved.[51]

1.6.1 Asymmetric Claisen Rearrangement

Yamamoto[52] described the first example of an enantioselective Claisen rearrangement catalysed by the chiral Lewis acids **(65)** or **(66)** **(Scheme 25)**. The use of 1.1 to 2 equivalents of **(65)** discriminated the two enantiotopic chair transition states, **(63)** and **(64)**, to generate **(67)** with high optical purity.

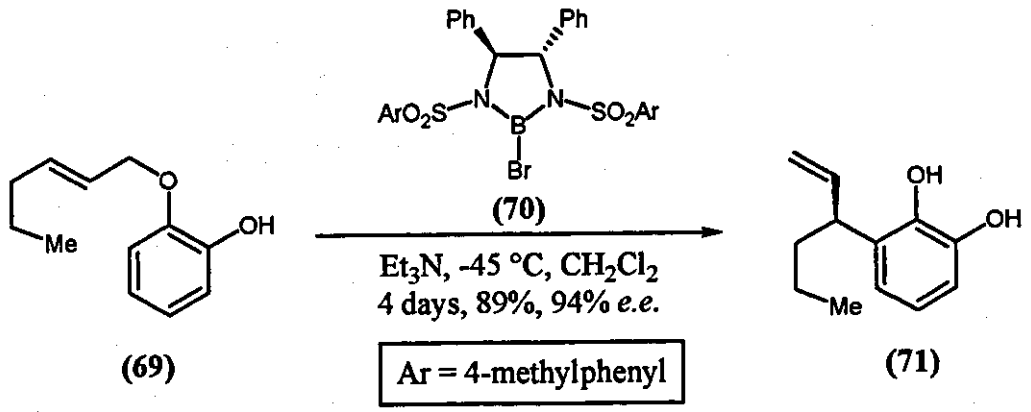


Scheme 25

The method was chirally flexible and allowed the synthesis of the antipodal products **(67)** or **(68)** by choosing the appropriate chiral aluminium reagent, **(65)** or **(66)**.

The enantiomeric outcome of the reaction was explained in terms of a more favourable fit for the cleft of the organoaluminium reagent **(65)** with conformation **(63)**. Alternatively, the conformation adopted in transition state **(64)** made a good match for the molecular cleft of the chiral organoaluminium reagent **(66)**.

Taguchi[53] reported the first highly enantio- and regio- (*ortho*) selective aromatic Claisen rearrangement of substrates such as **(69)** **(Scheme 26)**.



Scheme 26

A Claisen rearrangement of substrate **(69)**, catalysed by the chiral boron reagent **(70)**, proceeded smoothly in the presence of triethylamine to produce **(71)** in good yield and excellent enantioselectivity. The products formed by an abnormal Claisen rearrangement[54] could not be detected.

The high level of enantioselectivity was rationalised by invoking the transition state shown in **Figure 8**.

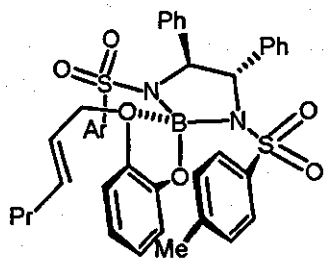


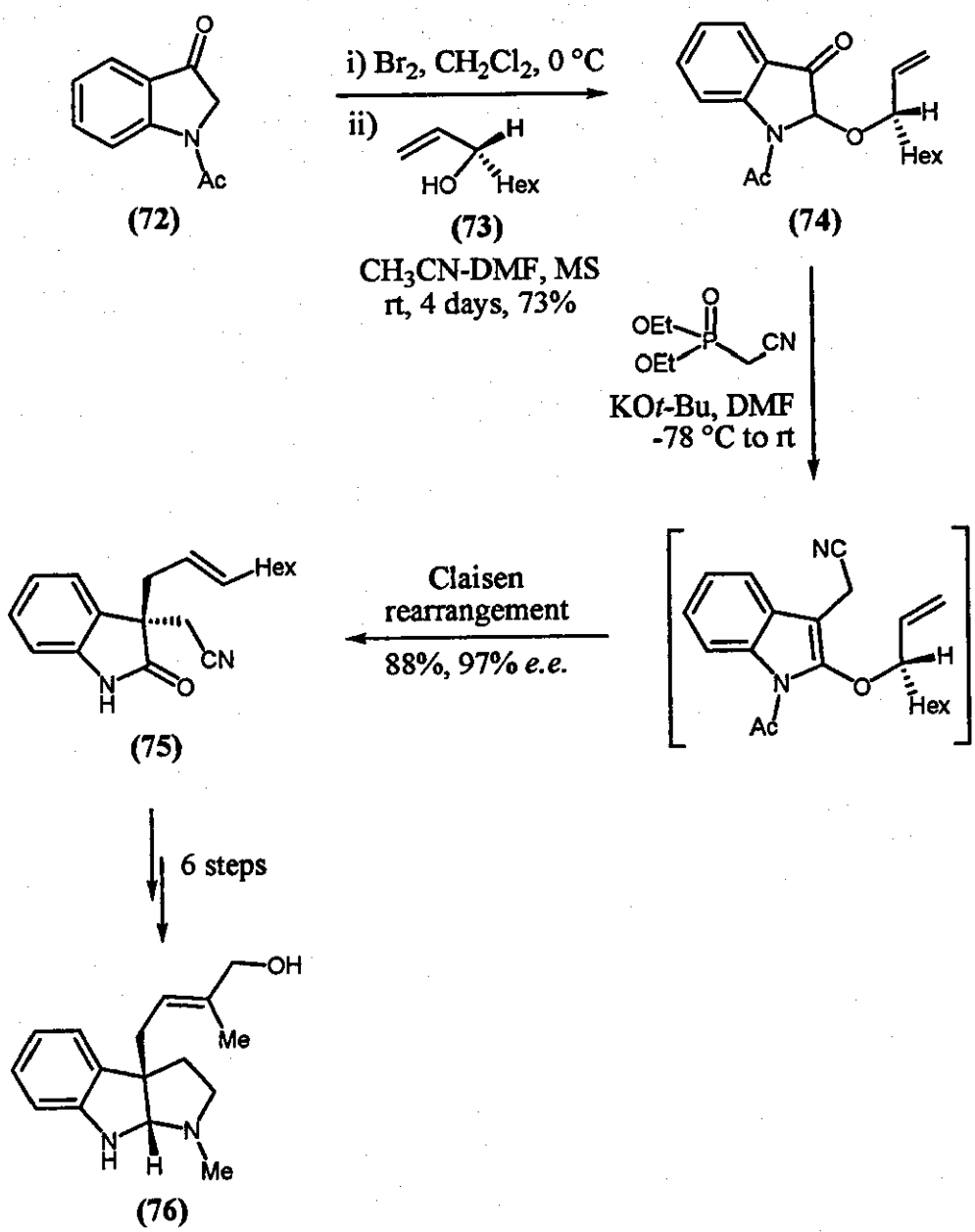
Figure 8

It was proposed that the substrate **(69)** formed a σ-bond between the phenolic alcohol and the boron reagent. In addition, the allylic oxygen coordinated to the boron atom to form a rigid five-membered cyclic complex. One tolyl group of the chiral ligand would shield the *re*-face of the benzene ring of **(69)** and therefore the approach of the allylic moiety could only occur on the *si*-face, leading to an enantioselective rearrangement.

1.6.2 Claisen Rearrangement in Natural Product Synthesis

The Claisen rearrangement has been developed into a widely applied tool in organic synthesis. This is due to a large versatility of the resulting products,[55] which bear two functional moieties (a carbonyl group and a double bond) as well as two potential chiral centres.

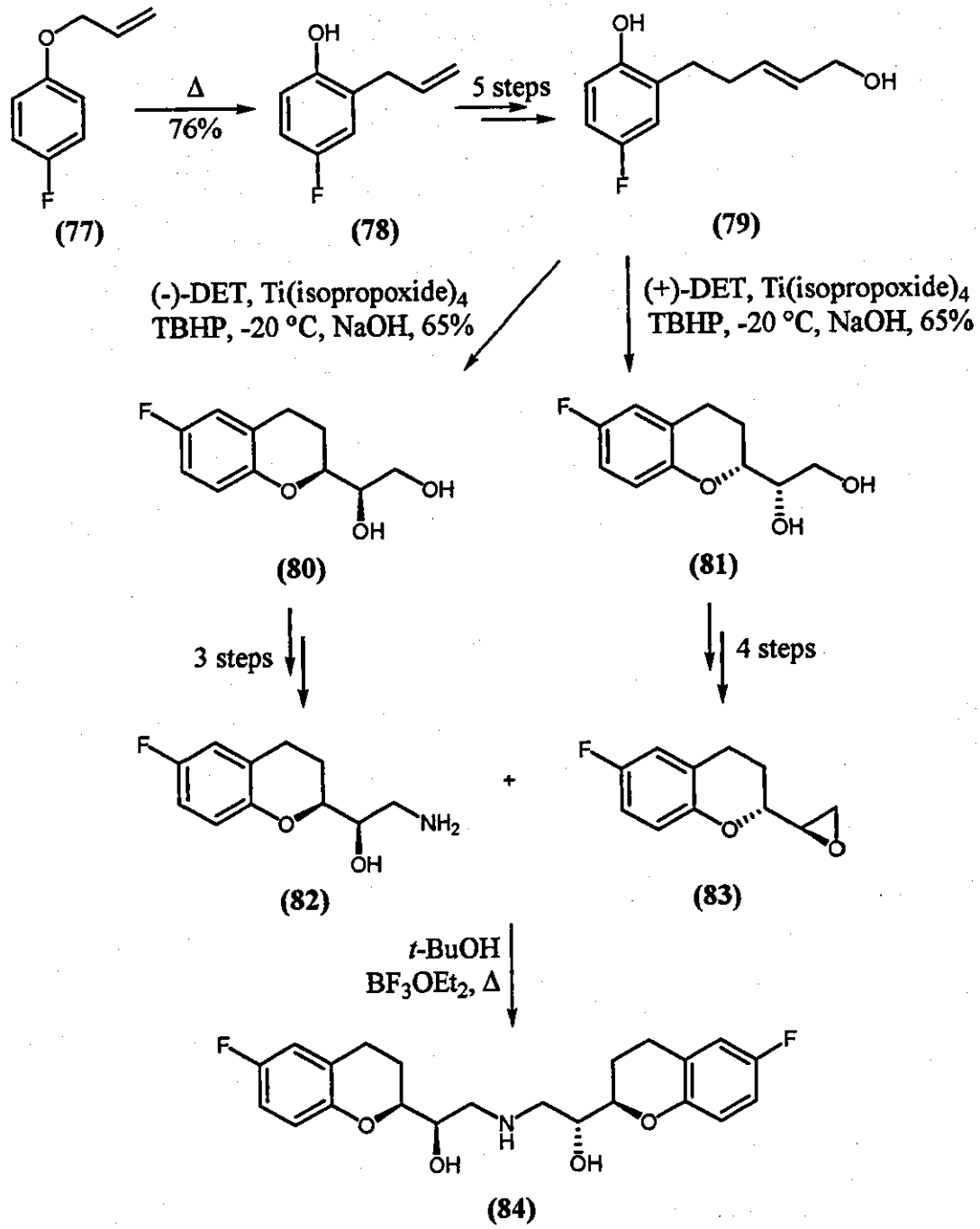
A tandem olefination, isomerisation and asymmetric Claisen rearrangement was used by Kawasaki[56] in the enantioselective synthesis of (-)-pseudophrynaminol **(76)** **(Scheme 27)**.



Scheme 27

Bromination of **(72)** and subsequent substitution with **(73)** afforded **(74)** in 73% yield. The cascade sequence from **(74)** proceeded smoothly to yield **(75)** in 88% yield and high enantiomeric excess (97% *e.e.*). The synthesis of **(76)** was achieved from **(75)** in 6 subsequent steps.

The antihypertensive reagent *S,R,R,R*-nebivolol **(84)** **(Scheme 28)**[57] was synthesised *via* an aromatic Claisen rearrangement and asymmetric Sharpless epoxidation.[58]



Scheme 28

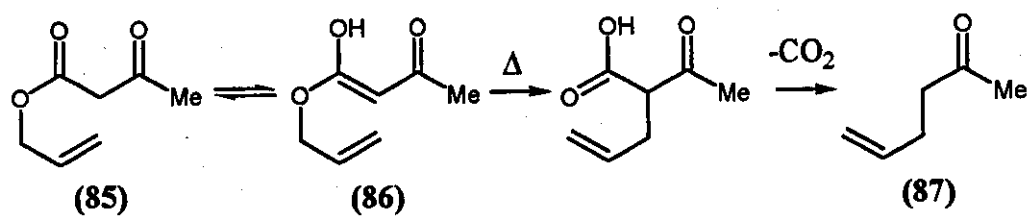
A thermal aromatic Claisen rearrangement of **(77)** generated **(78)**, which was converted into **(79)** in 5 steps. A Sharpless epoxidation[58] using (+)- and (-)-DET afforded **(80)** and **(81)** respectively. The total synthesis of **(84)** was completed by coupling the two fragments **(82)** and **(83)**.

1.7 Variants of the Claisen Rearrangement

The Claisen rearrangement has become one of the most powerful tools for stereoselective C-C bond formation[28] and its potential has been developed by the discovery of a number of variants, which are discussed in the following sections.

1.7.1 The Carroll (Kimel-Cope) Rearrangement

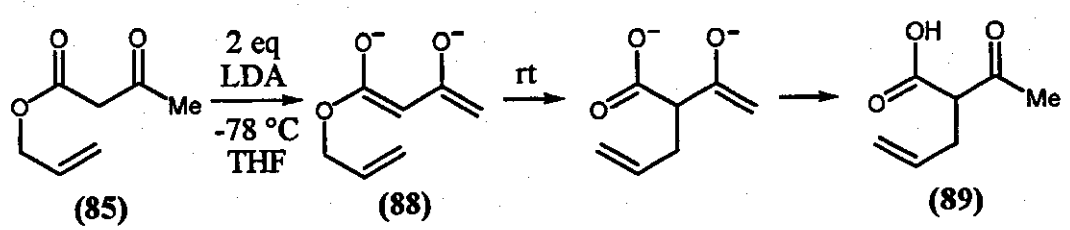
The Carroll rearrangement[59] denotes the synthesis of a γ,δ-unsaturated ketone **(87)** **(Scheme 29)** from an allylic β-ketoester **(85)**. Kimel and Cope[60] suggested a mechanism for this reaction based on the thermal rearrangement of **(86)** followed by a decarboxylation to yield **(87)**.



(85) **(86)** **(87)**

Scheme 29

The Carroll rearrangement was not widely employed due to the process requiring high temperatures (130-220 °C). However, its applicability has been extended by the utilisation of dianions such as **(88)** **(Scheme 30)**.[61]



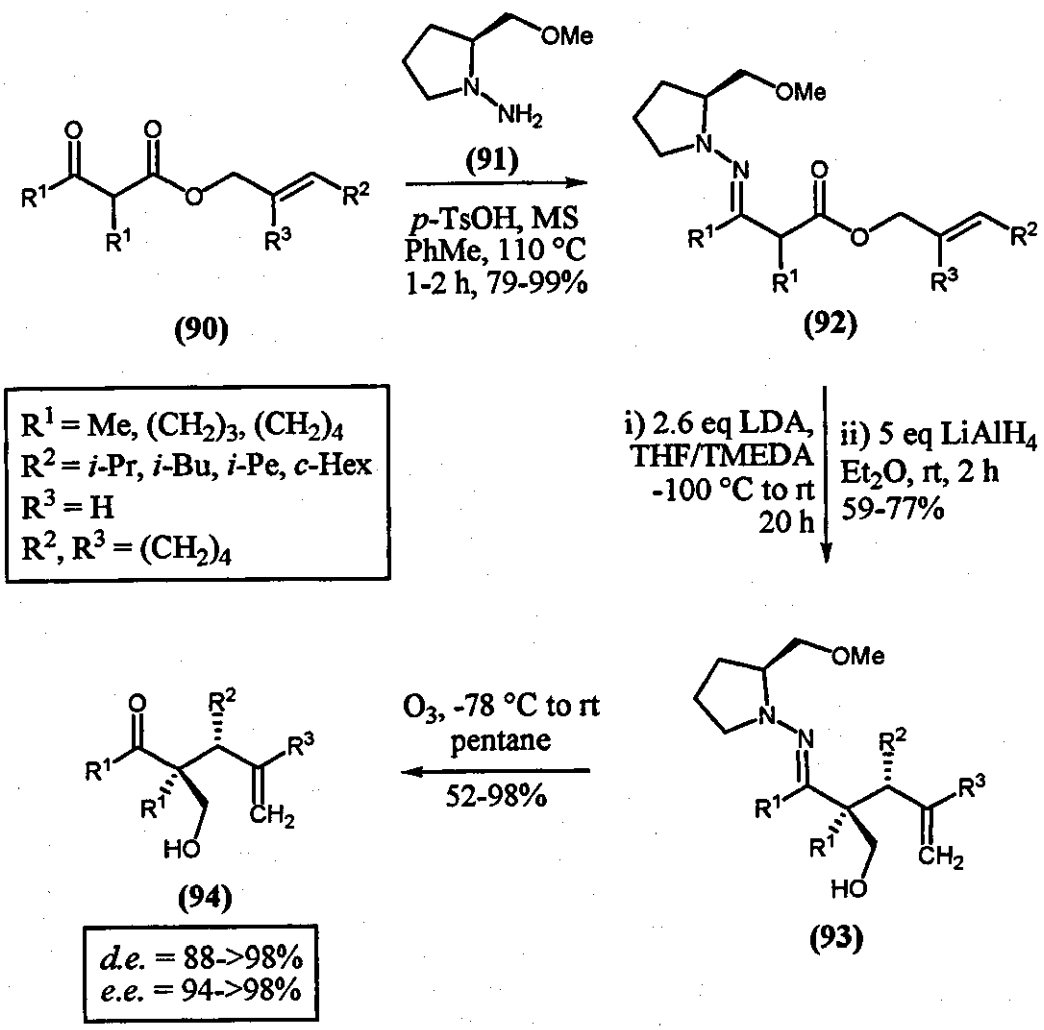
(85) **(88)** **(89)**

Scheme 30

Deprotonation of the β-ketoester **(85)** with 2 equivalents of LDA produced the dianion **(88)** that rearranged at room temperature leading to the β-ketoacid **(89)**.

1.7.1.1 Asymmetric Carroll Rearrangement

Enders[62] reported the first asymmetric Carroll rearrangement, using **(91)** (SAMP)[63] as a chiral auxiliary **(Scheme 31)**.



Scheme 31

Condensation of the β-ketoester **(90)** with **(91)** generated **(92)**. The latter compound underwent a double deprotonation at -100 °C, a Carroll rearrangement at room temperature and a subsequent reduction to produce **(93)**. The cleavage of the chiral auxiliary was achieved by ozonolysis (without epimerisation or oxidation of the terminal double bond) leading to **(94)** in good yield, diastereoselectivity and enantiomeric excess.

In order to explain the stereochemical outcome of the rearrangement, it was postulated that there was an initial double deprotonation to form the enolate with a high *E* selectivity **(Figure 9)**. In addition, a tricyclic rigid array would be formed by chelation of the Li cation by the enolate O, the aza-enolate N and the oxygen of the auxiliary methyl ether, forcing the allyl unit to attack the less shielded face, parallel to the α-hydrogen (*re-re* attack).

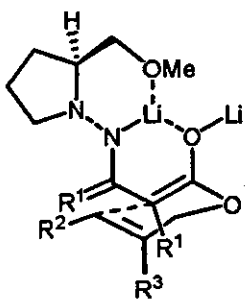
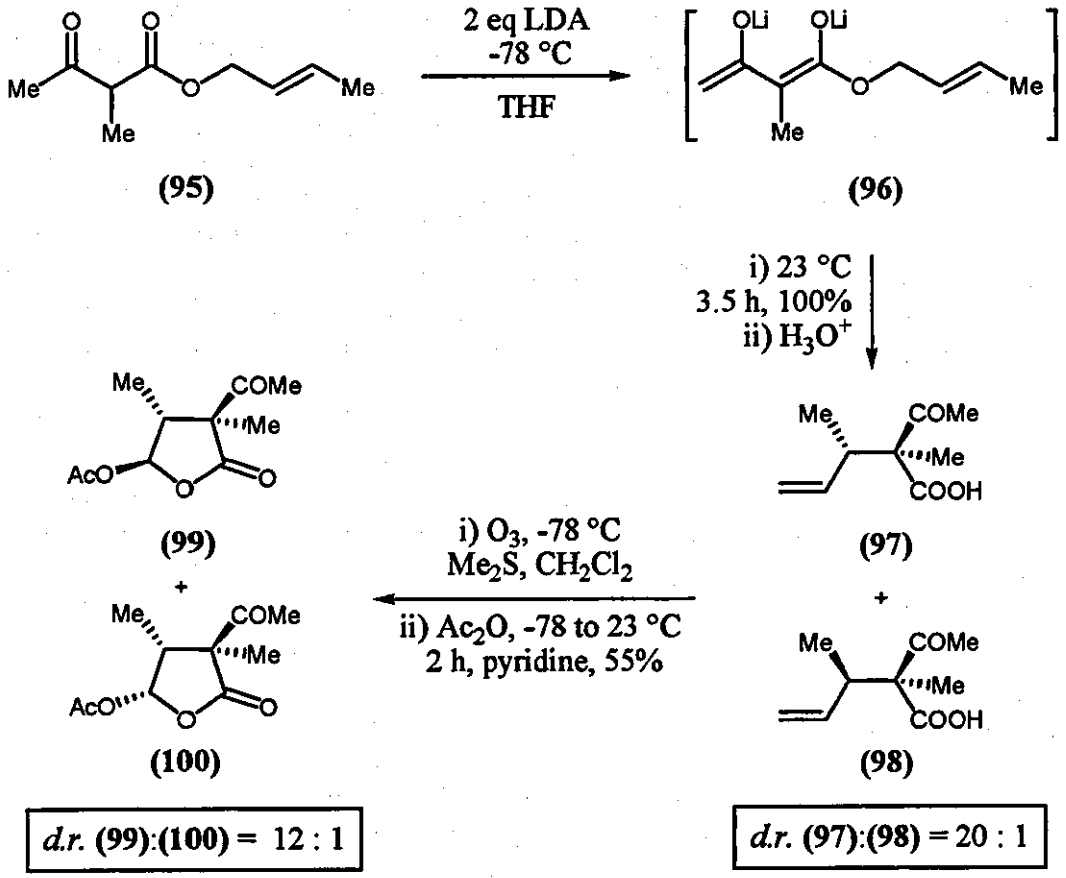


Figure 9

The enolate geometry would cause the *syn* configuration of R^1 and R^2 and the *anti* orientation of the newly formed centres with respect to the directing auxiliary subunit.

1.7.1.2 Carroll Rearrangement in Natural Product Synthesis

Echevarren[64] achieved the synthesis of (±)-4-epi-acetomycin **(99)** **(Scheme 32)** using a Carroll rearrangement as a key step. The antibiotic acetomycin is active against Gram-positive bacteria, fungi and protozoae and shows antitumour activity *in vitro*.

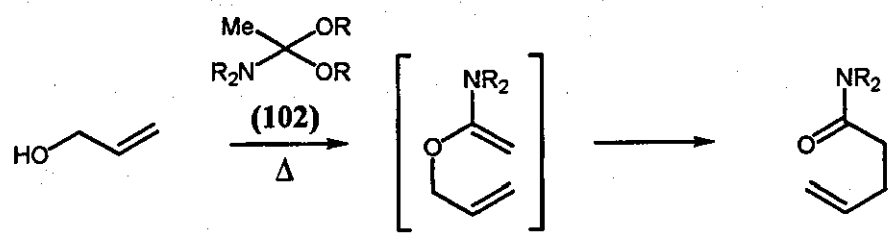


Scheme 32

Deprotonation of the β-ketoester **(95)** with LDA furnished **(96)**, which rearranged at 23 °C to yield a 20:1 mixture of **(97)** and **(98)** after acidic work up. The stereochemistry of the major isomer **(97)** was as expected from the rearrangement of the (*E*)-enolate through a chair conformation transition state. Ozonolysis of **(97)** and **(98)** and an *in situ* acetylation yielded a 12:1 mixture of the target compound **(99)** and its epimer **(100)** in 55% yield.

1.7.2 The Eschenmoser-Claisen Rearrangement

A [3,3]-sigmatropic rearrangement of a ketene *N,O*-acetal **(103)** **(Scheme 33)** was first reported by Eschenmoser.[65] Reaction of an allylic alcohol **(101)** with an acetal **(102)** and subsequent *in situ* rearrangement generated a γ,δ-unsaturated amide **(104)**.

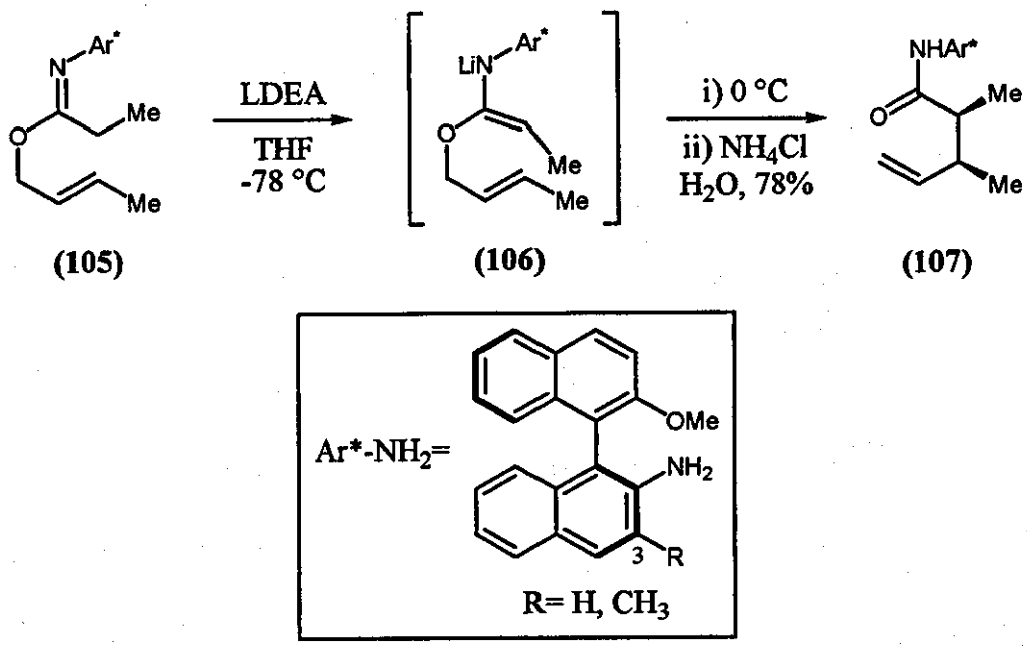


(101) (103) (104)

Scheme 33

1.7.2.1 Asymmetric Eschenmoser-Claisen Rearrangement

Metz[66] reported the chiral auxiliary induced asymmetric rearrangement of an imidate **(105) (Scheme 34)**.



(105) (106) (107)

Scheme 34

Deprotonation of **(105)** produced the lithiated species **(106)**, which rearranged at 0 °C to yield the desired γ,δ-unsaturated amide **(107)** with extremely high 2,3-*anti* selectivity

(>97:3 *anti*:*syn*) and an excellent auxiliary control over the absolute stereochemistry (94% *e.e.* for the *anti* isomer).

The stereochemical outcome could be rationalised as shown in **Figure 10**.

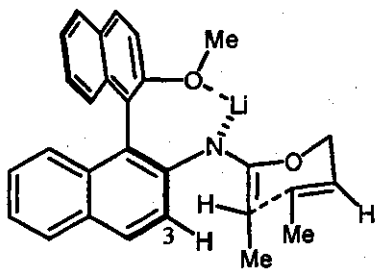
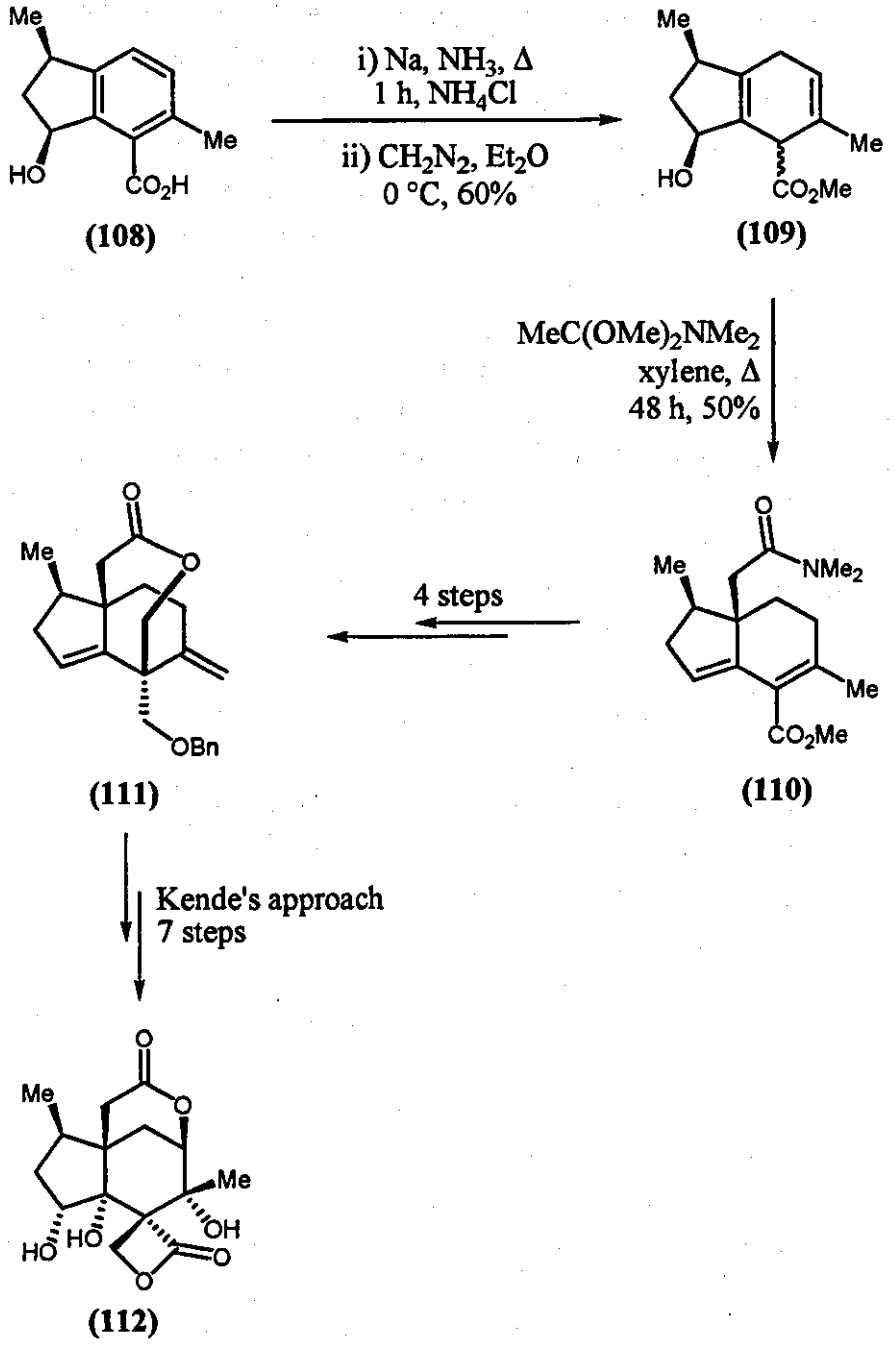


Figure 10

A E_{CN} configuration of the azaenolate was proposed for the transition state as well as a chelation of the lithium atom with the methoxy group. The naphthyl hydrogen *ortho* to the nitrogen atom (at C-3) would sterically hinder the bottom face of the azaenolate and the new C-C bond would be preferentially formed along the *re* face of the azaenolate. When the hydrogen at the auxiliary C-3 was substituted by a bulkier methyl group[66b] the diastereoselectivity was greater than 98%, which supported this hypothesis.

1.7.2.2 Eschenmoser-Claisen Rearrangement in Natural Product Synthesis

Loh[67] reported a total synthesis of (±)-8-deoxyanisatin **(112)** **(Scheme 35)** *via* an Eschenmoser-Claisen rearrangement.

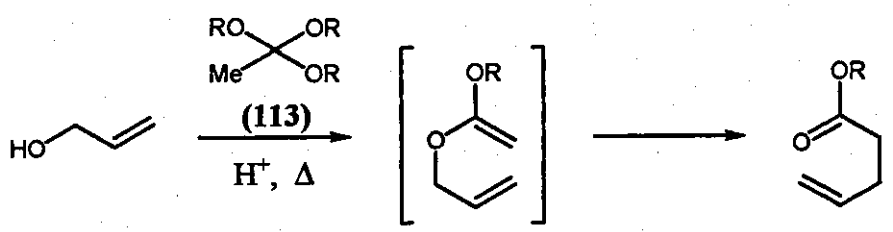


Scheme 35

Compound **(109)** was obtained *via* a Birch reduction[68] of **(108)**, followed by esterification with CH_2N_2 in 60% yield. An Eschenmoser-Claisen rearrangement of **(109)** generated **(110)** in 50% yield. The latter compound was converted into **(111)** over 4 steps and the total synthesis was completed using a literature procedure described by Kende.[69]

1.7.3 The Johnson-Claisen Rearrangement

The Johnson-Claisen rearrangement,[70] closely related to the Eschenmoser-Claisen, was first reported in 1970 **(Scheme 36)**.



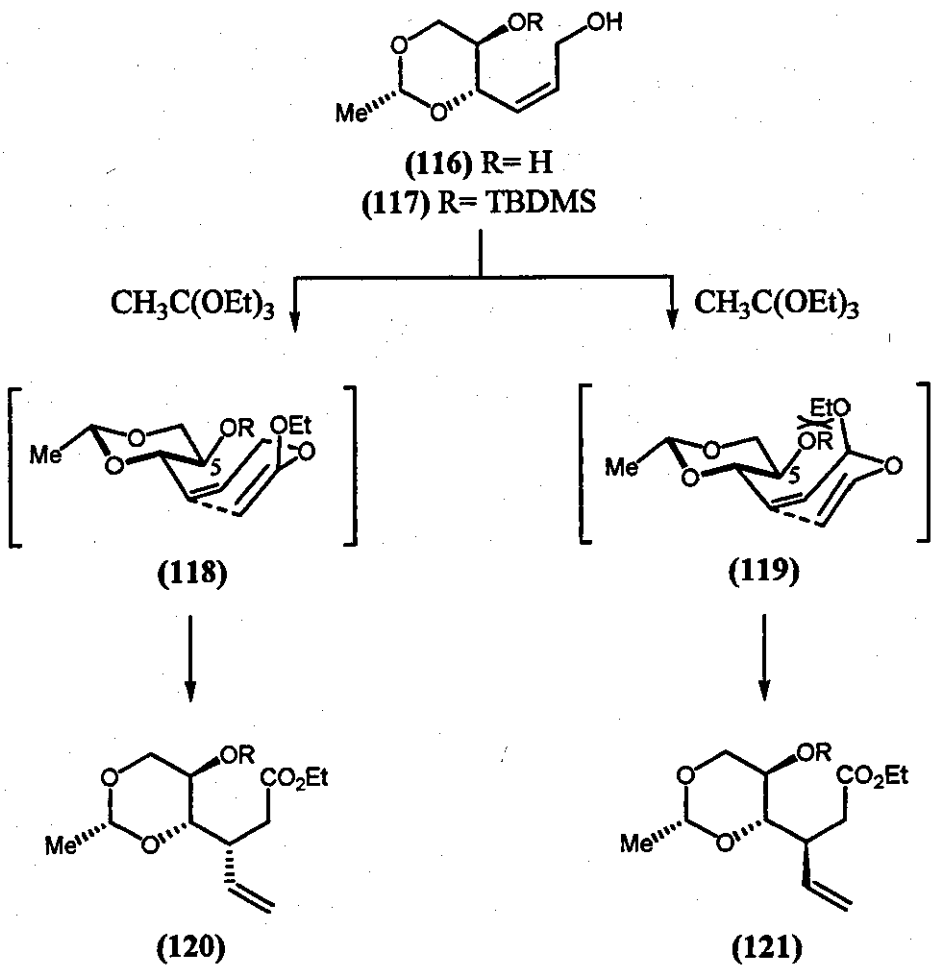
(101) **(114)** **(115)**

Scheme 36

An allylic alcohol **(101)** is heated with an excess of **(113)** in the presence of trace amounts of a weak acid (typically propionic acid) to form **(114)**, which undergoes rearrangement leading to a γ,δ-unsaturated ester **(115)**.

1.7.3.1 Asymmetric Johnson-Claisen Rearrangement

Tadano[71] observed high levels of diastereoselectivity in the rearrangement of **(116)** and **(117)** **(Scheme 37)**.

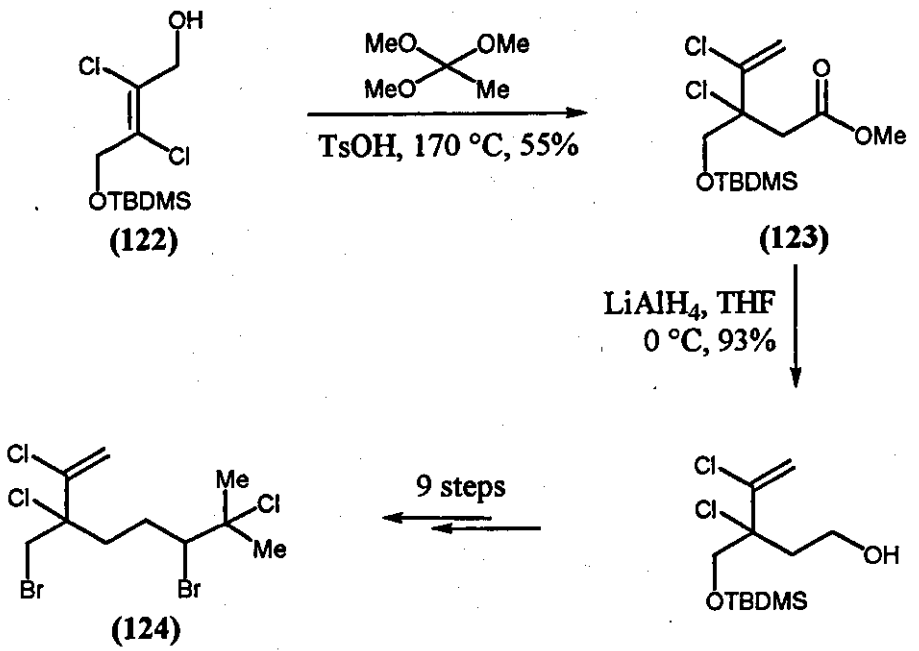


Scheme 37

Rearrangement of **(116)** produced a diastereomeric mixture of **(120)** and **(121)** in a ratio of 5:1. In order to explain the stereochemical outcome of the reaction, two chair transition states, **(118)** and **(119)** were considered. The transition state **(119)** has a non-bonded interaction between the ethoxy group and the substituent at C-5, which is not present in the transition state **(118)**, making the latter the preferred pathway for the rearrangement. This interaction was proportional to the bulkiness of the C-5 substituent. Consequently, when the hydroxy group at C-5 was substituted with a (*tert*-butyldimethylsilyl)oxy group **(117)**, a 12:1 *d.r.* was observed.

1.7.3.2 Johnson-Claisen Rearrangement in Natural Product Synthesis

Mioskowski[72] reported a total synthesis of the anticancer agent (±)-halomon **(124)** *via* a Johnson-Claisen rearrangement **(Scheme 38)**.



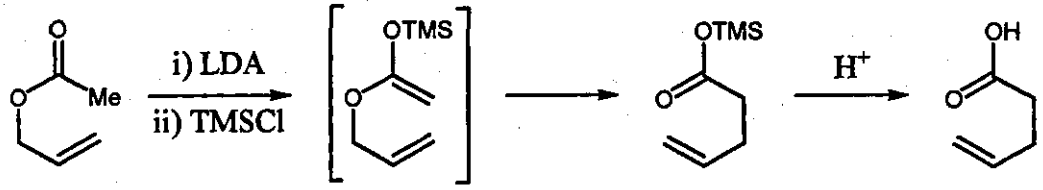
Scheme 38

The compound **(122)** was subjected to an extensive study to promote its rearrangement. Cope,[17] Claisen,[18] Stevens[73] or Ireland-Claisen[74] rearrangements were unsuccessful. However, the synthesis of **(123)** was accomplished in 55% yield *via* a Johnson-Claisen rearrangement with *p*-toluenesulfonic acid in the absence of solvent.

Reduction of **(123)** using lithium aluminium hydride and 9 subsequent steps achieved the total synthesis of **(124)** in an overall yield of 13%.

1.7.4 The Ireland-Claisen Rearrangement

The ester enolisation of **(125)** with a lithium dialkylamide base, followed by silylation, produces a reactive silyl ketene acetal **(126)** **(Scheme 39)**. The latter compound generates a γ,δ-unsaturated silyl ester **(127)** *via* an Ireland-Claisen rearrangement,[74] which can be further hydrolysed into a carboxylic acid **(128)**.



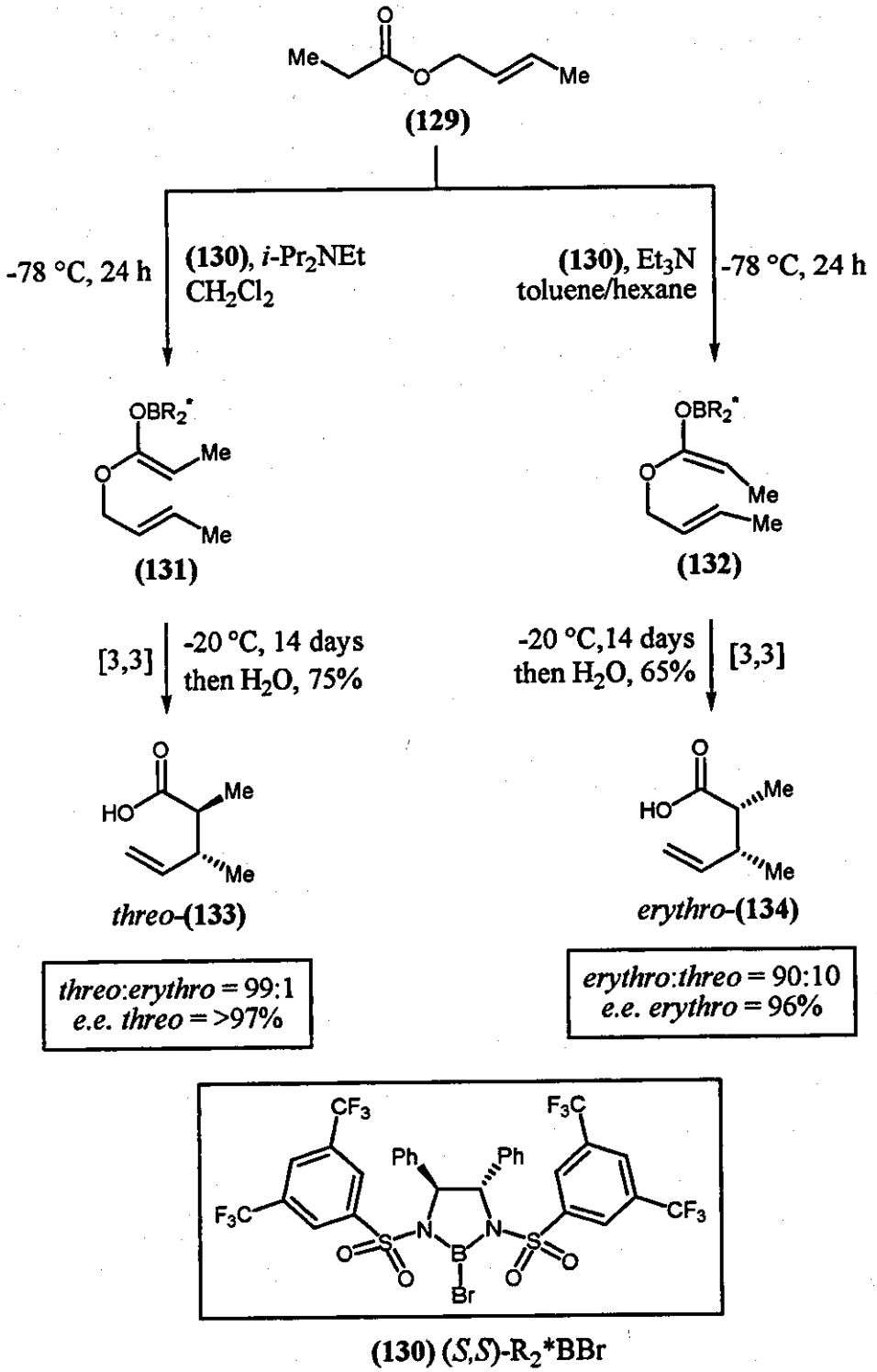
(125) **(126)** **(127)** **(128)**

Scheme 39

The Ireland-Claisen rearrangement has found broad application due to the ease of preparation of the reactants and the high degree of stereoselection as a result of highly-ordered transition states and efficient control of the ketene acetal geometry. By comparison to other Claisen rearrangements, the reaction is typically performed at or below room temperature and under basic conditions.[28,75]

1.7.4.1 Asymmetric Ireland-Claisen Rearrangement

Corey[76] reported the first enantioselective Ireland-Claisen rearrangement of an achiral ester **(129)** using a chiral boron reagent **(130)** **(Scheme 40)**.



Scheme 40

The achiral ester **(129)** was reacted with the chiral boron reagent **(130)** to produce either **(131)** or **(132)** depending on the reaction conditions. These enolates rearranged upon

storage at -20 °C for 14 days to afford the *threo*-**(133)** or the *erythro*-**(134)** after aqueous work-up. A precursor of the chiral reagent **(130)** was also isolated. The rearrangements proceeded in good yields and very good diastereomeric and enantiomeric excesses.

The absolute configuration of the rearranged product agreed with predictions based upon a more sterically favoured chair transition state, as shown in **Figure 11**.

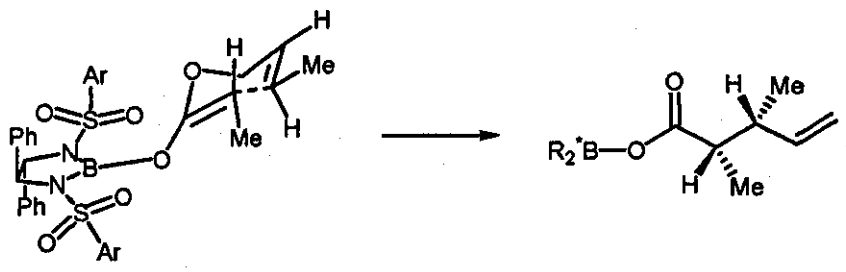


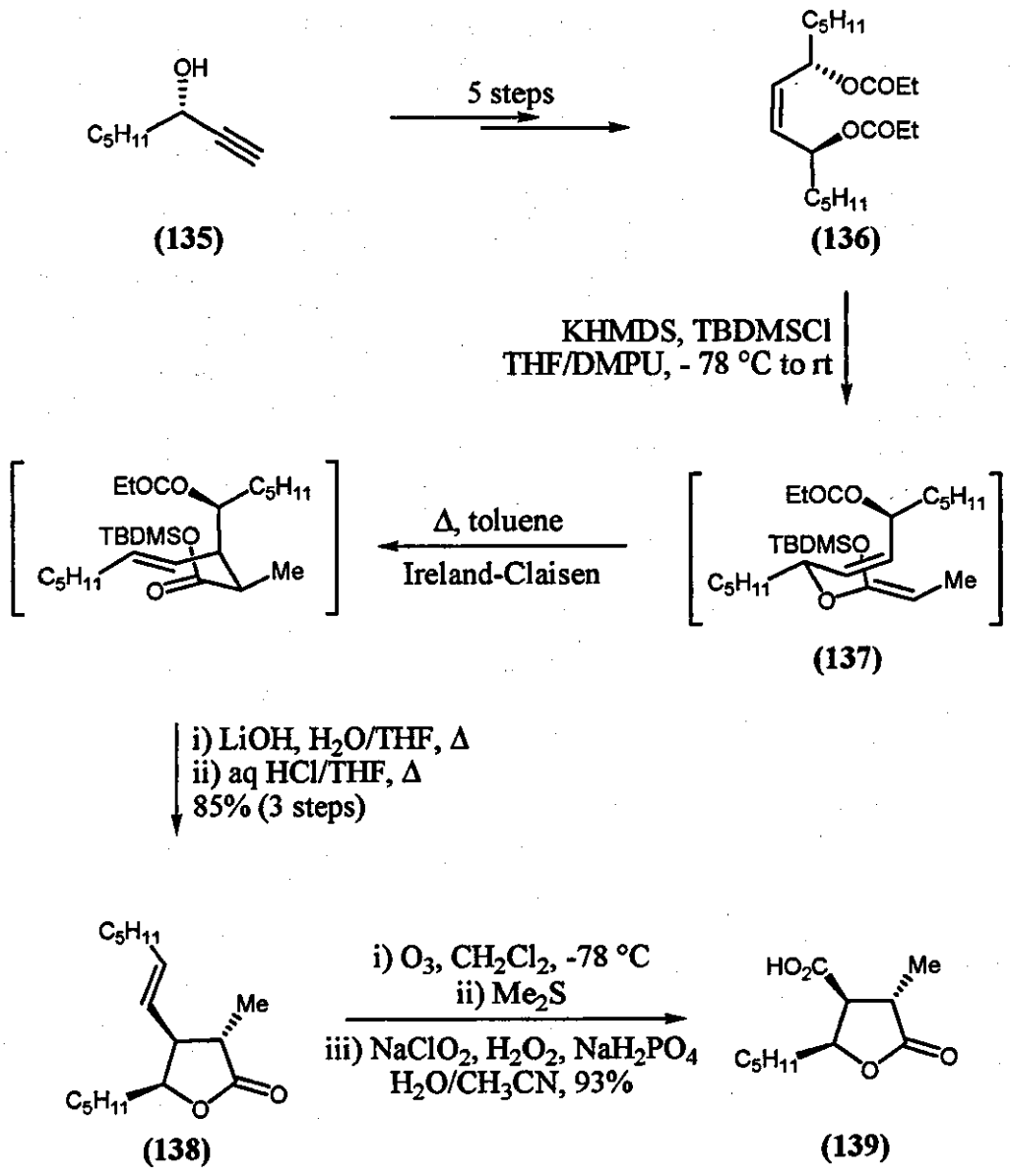
Figure 11

The usefulness of this rearrangement methodology is apparent due to the excellent stereoselectivity and the ability to recover the chiral boron reagent.[28]

1.7.4.2 Ireland-Claisen Rearrangement in Natural Product Synthesis

Ariza and García[77] disclosed a total synthesis of (-)-phaseolinic acid **(139)** **(Scheme 41)** from the commercially available **(135)** *via* an Ireland-Claisen rearrangement.

(-)-Phaseolinic acid **(139)**, isolated from the fungus *Macrophomina phaseolina*, exhibits antifungal, antitumour and antibacterial activity.

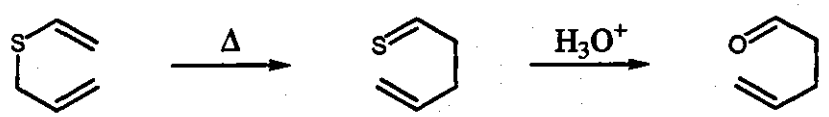


Scheme 41

Compound **(136)** was obtained in five steps from **(135)** in 56% overall yield. Enolisation and silylation of **(136)** produced **(137)**, which underwent an Ireland-Claisen rearrangement followed by hydrolysis and lactonisation to afford **(138)** in 85% yield. The synthesis was completed with an ozonolysis and subsequent oxidation of **(138)** to afford **(139)** in an overall yield of 40%.

1.7.5 The Thio-Claisen Rearrangement

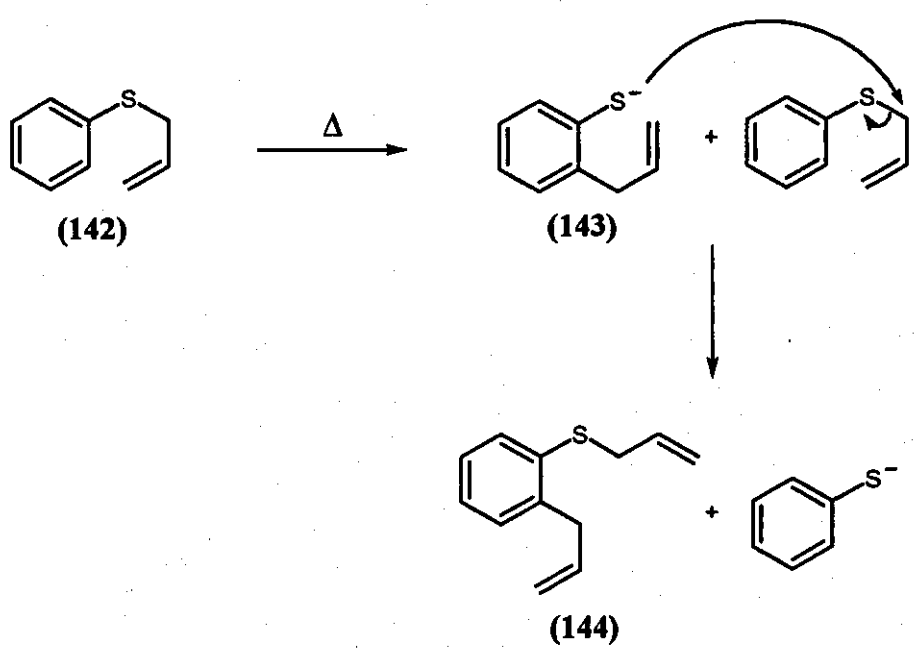
An allyl vinyl sulphide **(140)** can rearrange into a thioaldehyde **(141)** *via* a thio-Claisen rearrangement[78] **(Scheme 42)**. The latter compound can be hydrolysed into an aldehyde **(61)**, increasing the scope and applicability of the reaction.



(140) **(141)** **(61)**

Scheme 42

Aliphatic thio-Claisen rearrangements **(Scheme 42)** typically proceed under milder conditions than those reported for oxygenated substrates.[44] In contrast, in an aromatic thio-Claisen rearrangement, the substrate **(142)** **(Scheme 43)** does not rearrange under typical Claisen conditions but requires higher temperatures to produce the thiol product **(143)**. In addition, diallyl by-products **(144)** are readily obtained.[79]

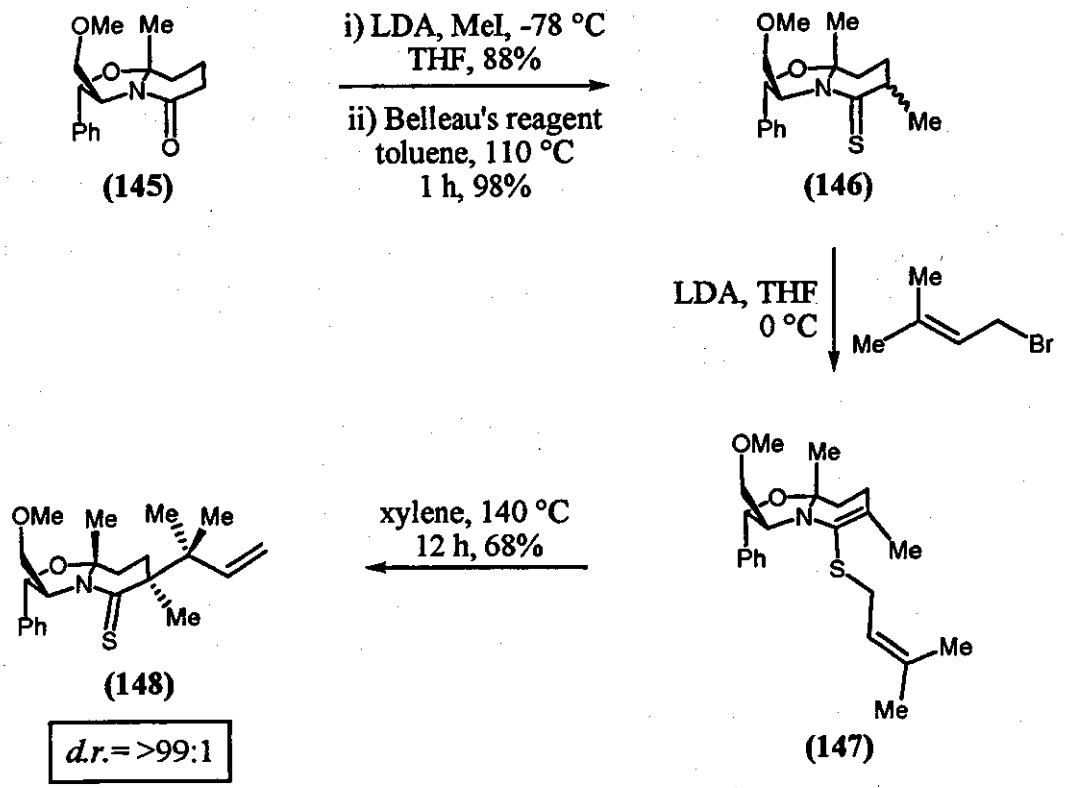


(142) **(143)** **(144)**

Scheme 43

1.7.5.1 Asymmetric Thio-Claisen Rearrangement

The bicyclic rigid array **(145)** **(Scheme 44)**, developed by Meyers,[80] allows an auxiliary controlled generation of chiral centres *via* a thio-Claisen rearrangement.



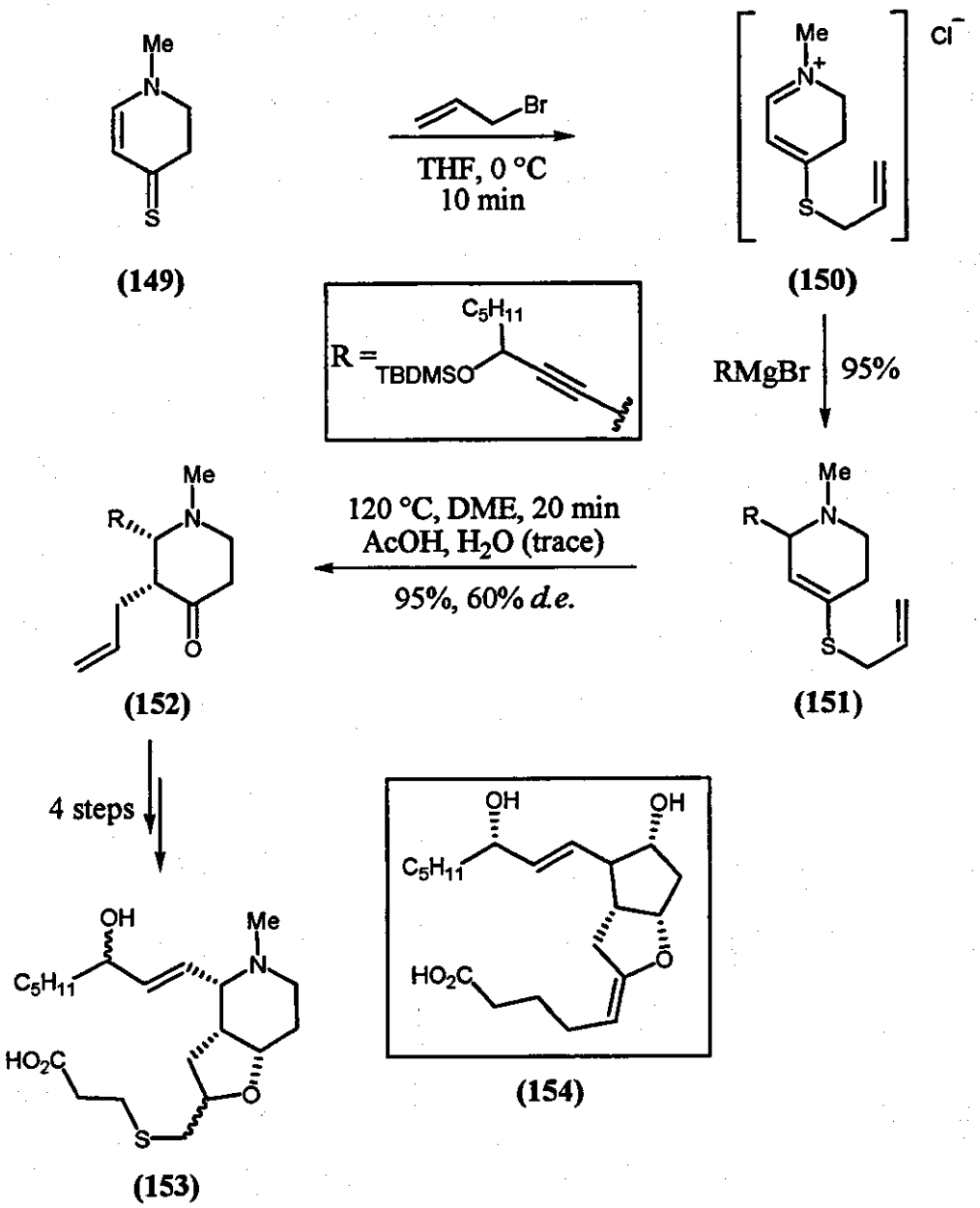
Scheme 44

The lactam **(145)** was converted into **(146)** by alkylation at the α-position and conversion of the carbonyl group into a thiocarbonyl group using Belleau's reagent.[81] Deprotonation of **(146)** and subsequent allylation produced **(147)**. Upon heating to 140 °C in xylene the system underwent a thio-Claisen rearrangement to yield **(148)** in good yield and excellent diastereoselectivity.

The stereochemical outcome of the reaction was due to a remote steric effect of the *endo* substituent on the oxazolidine ring (phenyl substituent), which hindered the *endo* face of the molecule. The absence of this substituent resulted in a lower diastereomeric ratio upon rearrangement.[80b]

1.7.5.2 Thio-Claisen Rearrangement in Natural Product Synthesis

Husson and Grierson[82] devised a novel procedure for the synthesis of the aza-prostacyclin analogue **(153)** *via* a thio-Claisen rearrangement **(Scheme 45)**. Prostacyclin PGI_2 **(154)** possesses potent pharmacological activity and has been extensively studied for the treatment of thrombosis and vascular diseases.

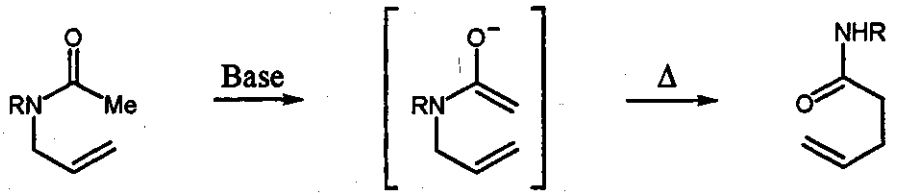


Scheme 45

The thiopiperidone **(149)** was reacted with allyl bromide in tetrahydrofuran to yield **(150)**. Reaction of **(150)** with a Grignard reagent generated **(151)** in 95% yield. The *thio*-Claisen rearrangement of the latter compound in refluxing 1,2-dimethoxyethane produced **(152)**. The stereochemical outcome of **(152)** could be due to a preferred axial orientation of the C-2 acetylenic substituent due to a stabilising anomeric effect. The substrate **(152)** was converted into the target compound **(153)** in four additional steps.

1.7.6 The Aza-Claisen Rearrangement

Deprotonation of a *N*-allylamide **(155)** and subsequent aza-Claisen rearrangement[83] of the intermediate **(156)** generates a γ,δ-unsaturated amide **(157)** **(Scheme 46)**.[84]



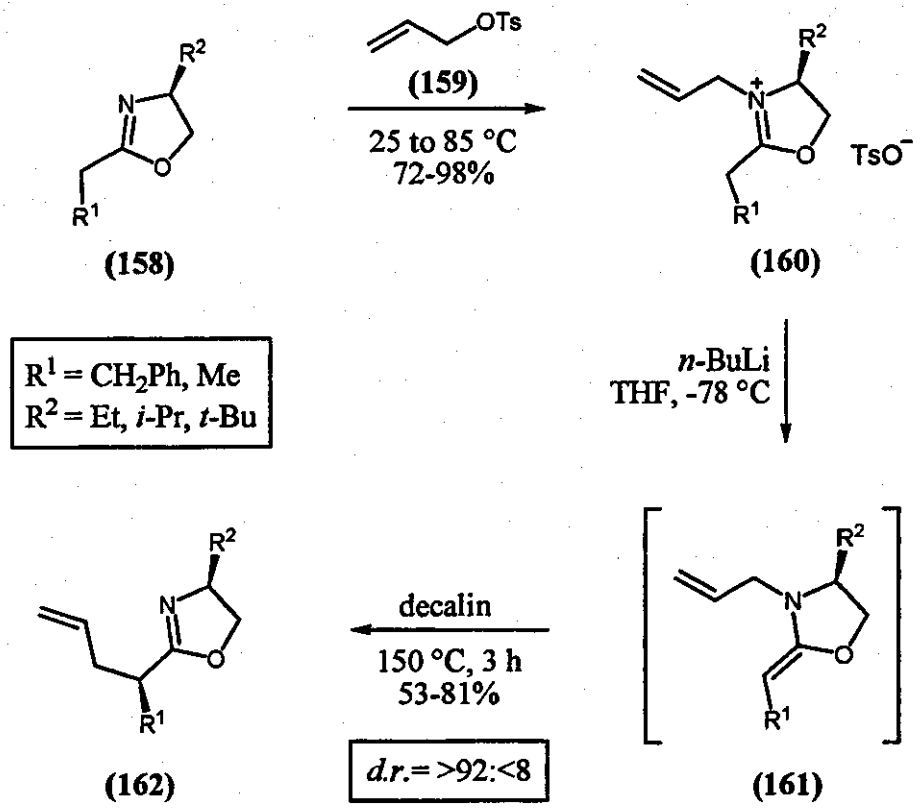
(155) **(156)** **(157)**

Scheme 46

1.7.6.1 Asymmetric Aza-Claisen Rearrangement

Kurth[85] investigated the asymmetric aza-Claisen rearrangement of substrates such as **(160)** **(Scheme 47)**.

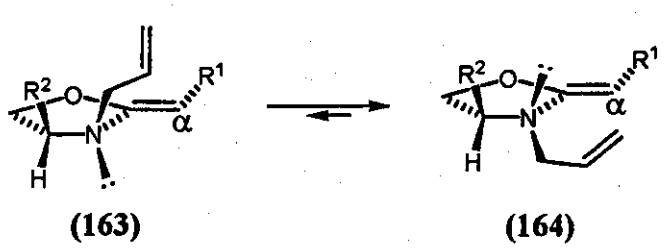
To maximise the asymmetric induction of the rearrangement, the chiral centre, the nitrogen atom and the C-1 at the vinyl moiety in **(160)** were confined in a 5-membered ring.



Scheme 47

The substrate **(158)** was treated with the allylic tosylate **(159)** to yield **(160)**. The compound **(160)** was deprotonated with *n*-BuLi to produce the ketene acetal **(161)**, which rearranged to **(162)** by heating in decalin.

The diastereoselectivity of the rearrangement could be explained as a result of the preference for a (*Z*)-*N*,*O*-acetal selectivity, non-epimerisation under the reaction conditions and a high face selectivity, which can be explained using the transition states shown in **Figure 12**.



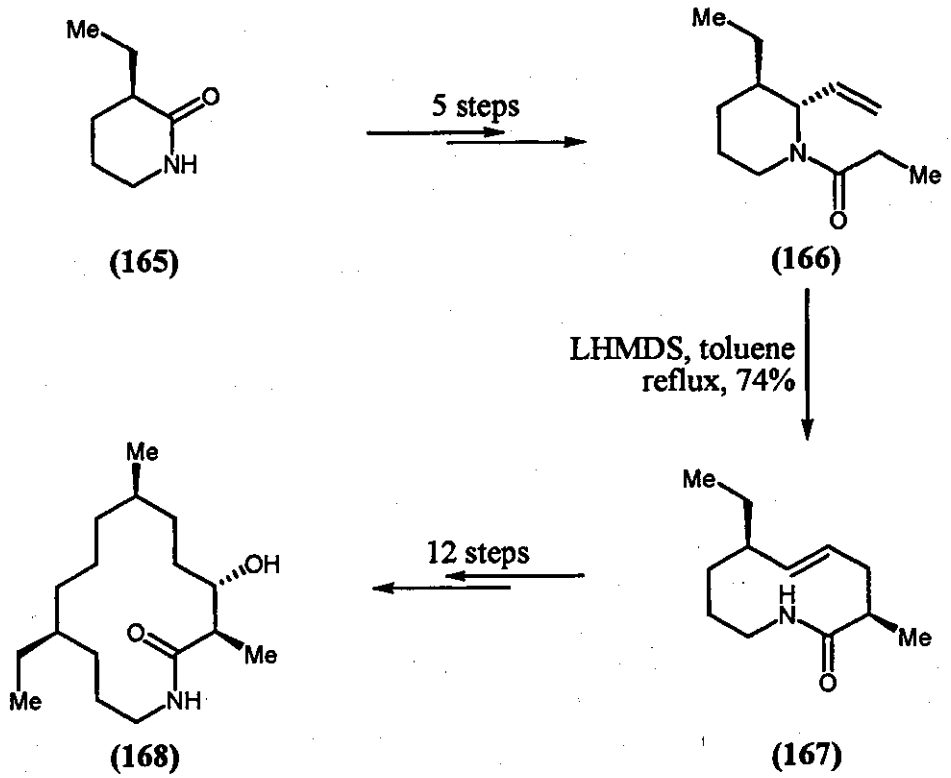
(163) **(164)**

Figure 12

Compound **(161)** **(Scheme 47)** could react *via* two possible transition states, **(163)** or **(164)** **(Figure 12)**, the former was less stable due to steric interactions. Rapid nitrogen inversion (**(163)** to **(164)**) prior to the rate determining rearrangement step resulted in a C_{α}-*si*-selectivity. Consequently, an increase in the bulkiness of the substituent at C-4 (R^2) resulted in enhanced rearrangement diastereoselectivity.[85b]

1.7.6.2 Aza-Claisen Rearrangement in Natural Product Synthesis

Suh[86] reported the synthesis of the antibiotic derivative fluvirucinine A_1 **(168)** **(Scheme 48)** using an aza-Claisen rearrangement as a key step.



(165) **(166)** **(167)** **(168)**

Scheme 48

The piperidine **(166)** was prepared from 3-ethyl-valerolactam **(165)** in 5 steps. A facile aza-Claisen rearrangement of **(166)** afforded the lactam **(167)** as the sole product. The target compound **(168)** was generated from **(167)** in 12 additional steps.

The excellent diastereoselectivity of the aza-Claisen rearrangement could be explained by the combination of a favourable chair/chair-like transition state with an equatorial ethyl substituent and the formation of a preferred amide (*Z*)-enolate **(Figure 13)**.

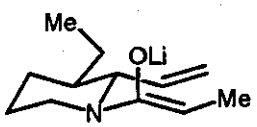


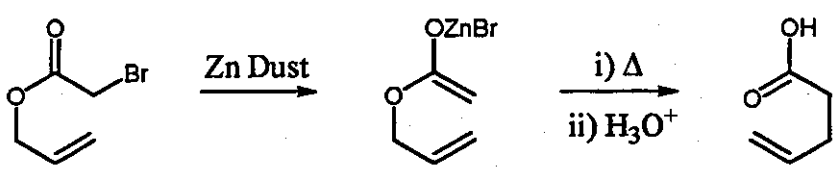
Figure 13

1.7.7 Miscellaneous Claisen Rearrangements

Other variants of the Claisen rearrangement are briefly highlighted in this section.

1.7.7.1 The Reformatsky-Claisen Rearrangement

The reaction of an α-bromo ester **(169)** **(Scheme 49)** with zinc dust,[87] followed by a [3,3]-sigmatropic rearrangement and subsequent hydrolysis of the intermediate zinc enolate **(170)** provides a useful synthesis of a γ,δ-unsaturated acid **(128)**.

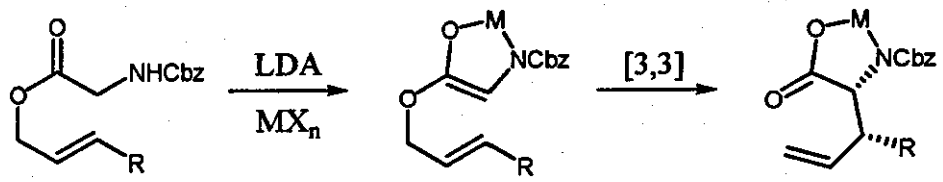


(169) **(170)** **(128)**

Scheme 49

1.7.7.2 The Chelate-Claisen Rearrangement

Deprotonation of a *N*-protected amino acid ester **(171)** **(Scheme 50)** at -78 °C and subsequent addition of a metal salt results in the formation of a chelate enolate **(172)**. The latter compound undergoes a chelate-Claisen rearrangement[88] to produce a chelate-bridged stabilised carboxylate **(173)** upon warming to room temperature.

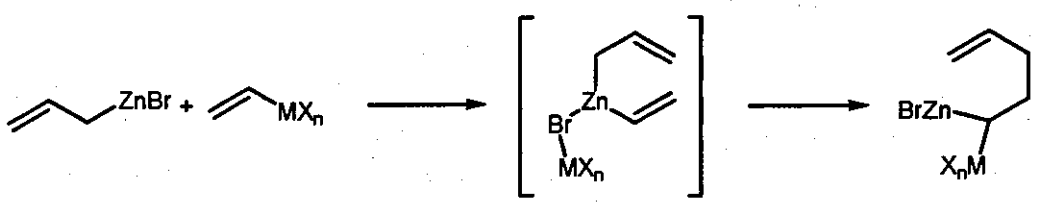


(171) **(172)** **(173)**

Scheme 50

1.7.7.3 The Metallo-Claisen Rearrangement

Reaction of an allyl zinc bromide **(174)** **(Scheme 51)** with an alkenyl organometallic derivative **(175)** generates **(176)**, which undergoes a metallo-Claisen rearrangement[89a] to afford a *gem*-dimetallic compound **(177)**.



(174) **(175)** **(176)** **(177)**

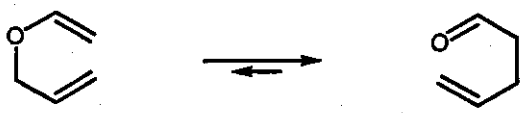
M= Mg, Li, Al

Scheme 51

The rearranged product **(177)** can react with a number of organic substrates leading to useful products such as aldehydes, dienes, iodides or stannanes.[89]

1.7.7.4 The Retro-Claisen Rearrangement

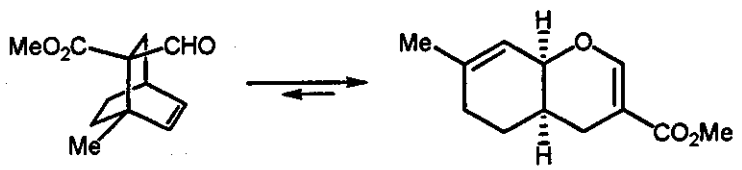
The Claisen rearrangement is apparently irreversible due to the typically greater stability of the product **(61)** **(Scheme 52)** relative to the substrate **(60)**. However, the equilibrium can be shifted towards the allyl vinyl ether **(60)** by conjugation of a double bond in **(60)** or presence of non-bonded repulsions or ring strain in **(61)**.[90]



(60) **(61)**

Scheme 52

The presence of vicinal quaternary carbons in **(178)** **(Scheme 53)** shifted the equilibrium towards the retro-Claisen isomer **(179)** as a result of ring strain relief.[90]



(178) **(179)**

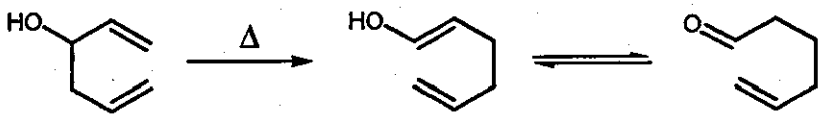
Scheme 53

1.7.7.5 Other Variants

In addition to the previously highlighted [3,3]-sigmatropic rearrangements, an extensive number of variants can be found in the literature,[28] as well as many comprehensive reviews on the Claisen,[55,75,91] oxy-Cope,[92] hetero-Cope[43] and [3,3]-sigmatropic rearrangements in general.[19,24,28,44]

1.8 Development of the Oxy-Cope Rearrangement

Berson and Jones[42] reported the first oxy-Cope rearrangement in 1964 **(Scheme 54)**.



(39)

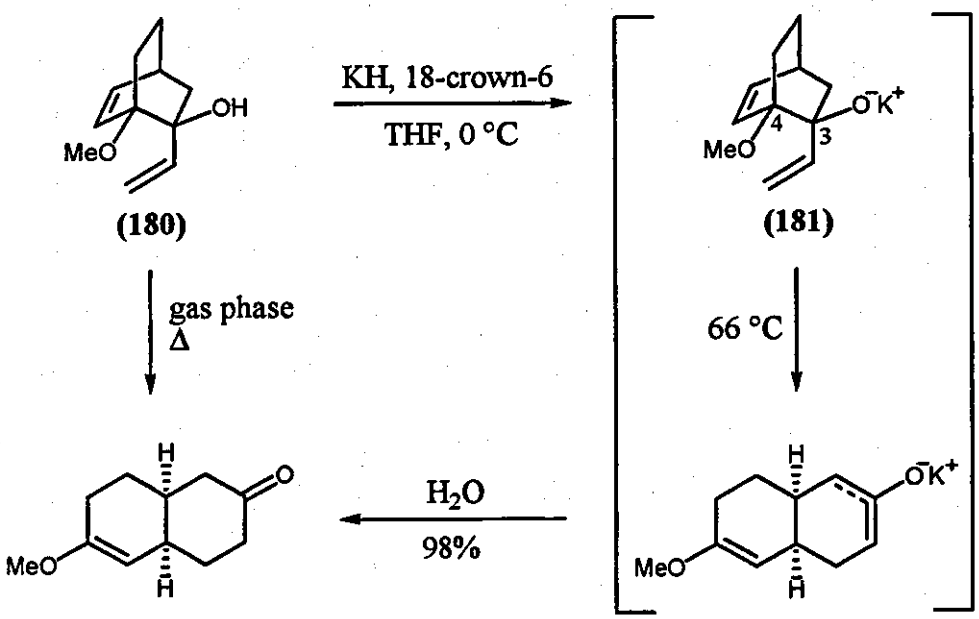
Scheme 54

The oxy-Cope rearrangement has been extensively used due to ease of preparation of the starting materials, such as **(39)**, the wide range of 3-hydroxy-1,5-dienes that undergo this reaction and its capacity for elaborating complex polycyclic structures in a small number of steps.[92]

The oxy-Cope rearrangement is known to proceed in many cases *via* a chair-like transition state[93] although there are some examples in which the rearrangement proceeds through a boat-like conformation.[94]

1.8.1 Anionic Oxy-Cope Rearrangement

Evans and Golob[95] reported a huge acceleration in the oxy-Cope rearrangement (10^{10}-10^{17}) when the hydroxy group in **(180)** **(Scheme 55)** was deprotonated into its corresponding alkoxide **(181)**.



Scheme 55

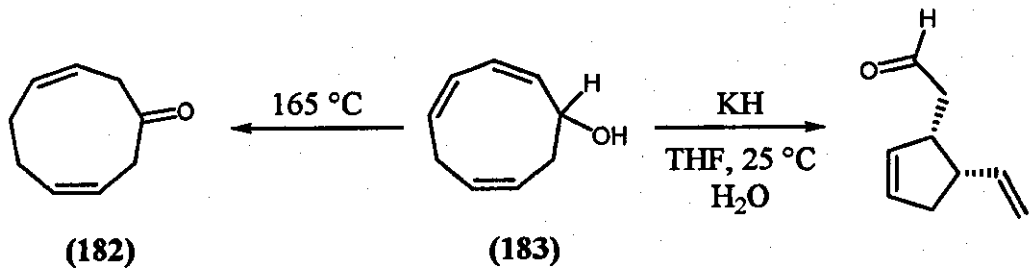
The study on the effect of different counter ions revealed that the use of potassium hydride in conjunction with 18-crown-6 or HMPT resulted in an excellent acceleration of the process. This rate increase was observed in gas phase and solution.[96]

Theoretical calculations have shown that the primary effect of the alkoxide is to weaken the C-3/C-4 bond in **(181)** **(Scheme 55)** due to an *n*-donation from the oxyanion rather than a transition state effect.[97] The *n*-donation is greatest (fastest rearrangement) when the oxyanion is completely naked;[97c] consequently, potassium salts rearrange faster than sodium salts, which rearrange faster than lithium salts.[98] Crown ethers and polar aprotic solvents are often used to reduce the association between the oxyanion and the cation.[98,99]

Hartley[99] reported the use of metal-free bases on the anionic oxy-Cope rearrangement. These bases are soluble in organic solvents and therefore easier to handle than the typical potassium hydride, which is supplied as a dispersion in mineral oil.

In addition to a reduction in the reaction temperature, anionic oxy-Cope rearrangements can favour otherwise unattainable rearrangements. Thermal activation of **(183)** **(Scheme 56)** resulted in an exclusive [1,5]-hydrogen migration to produce **(182)**.[100] By

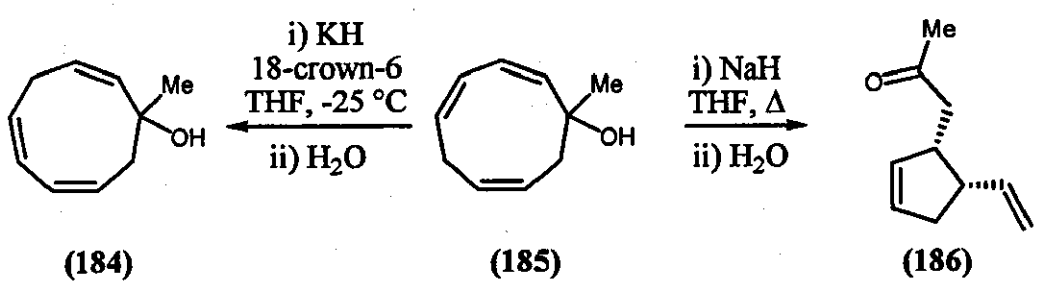
addition of potassium hydride, the [3,3]-sigmatropic pathway was highly accelerated (hydrogen shifting was not observed).



(182) **(183)**

Scheme 56

In the case of compound **(185)** **(Scheme 57)**, however, the use of potassium hydride and 18-crown-6 in tetrahydrofuran produced **(184)** by isomerisation. Alternatively, heating **(185)** with sodium hydride in the same solvent resulted in rearrangement into **(186)**.[101]

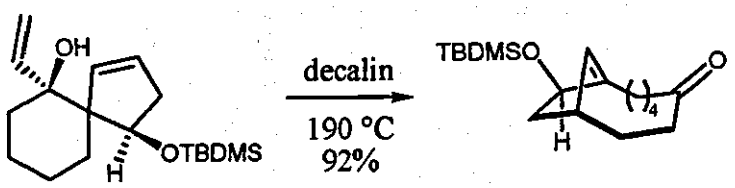


(184) **(185)** **(186)**

Scheme 57

The high basicity of the potassium alkoxide promoted intramolecular proton abstraction with double bond organisation. The sodium hydride is less basic, but sufficiently anionic to promote the sigmatropic process.[92]

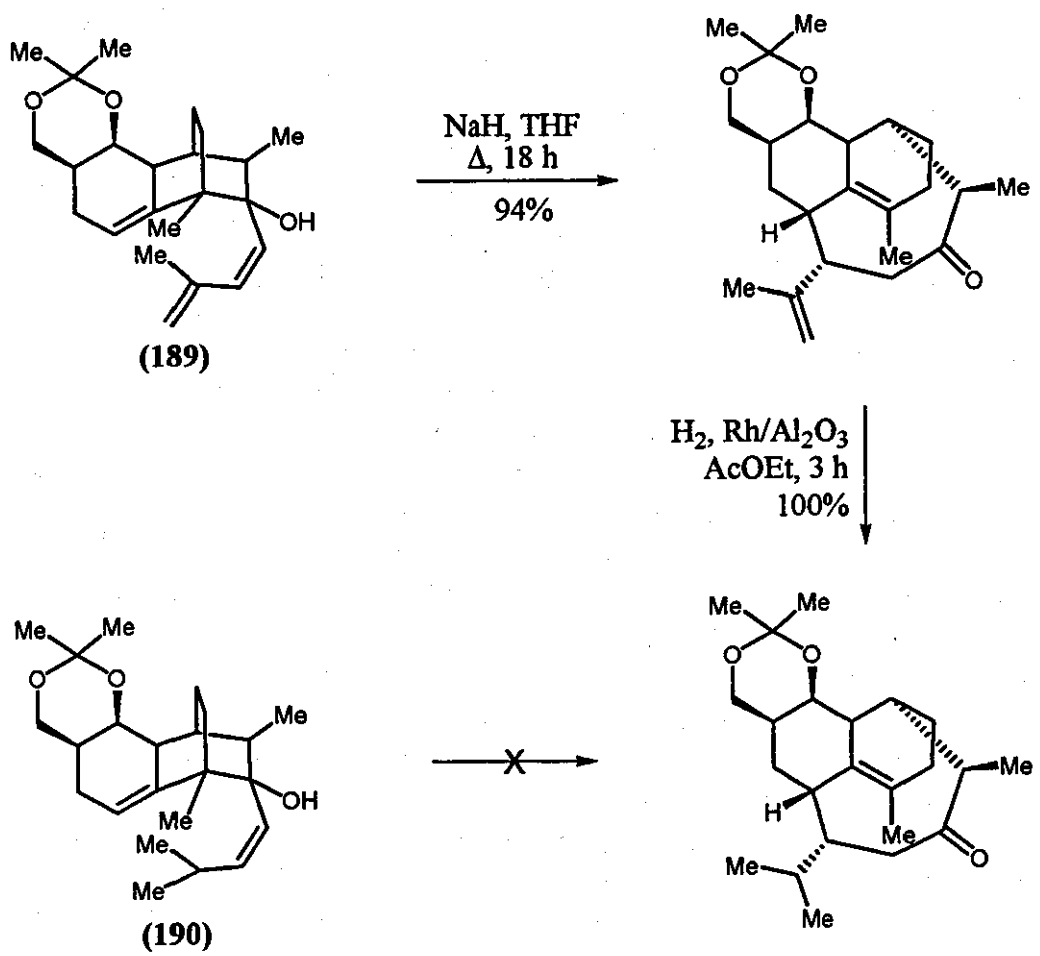
A thermal oxy-Cope rearrangement is used when the substrate is unstable under basic conditions. Compound **(187)** **(Scheme 58)** decomposed by addition of a base[102] but heating the substrate in decalin resulted in efficient conversion to **(188)**.



(187) **(188)**

Scheme 58

Hanna[103] reported a facile anionic oxy-Cope rearrangement of **(189)** **(Scheme 59)** using sodium hydride in refluxing tetrahydrofuran. In this reaction potassium hydride was not required.



(189) **(190)**

Scheme 59

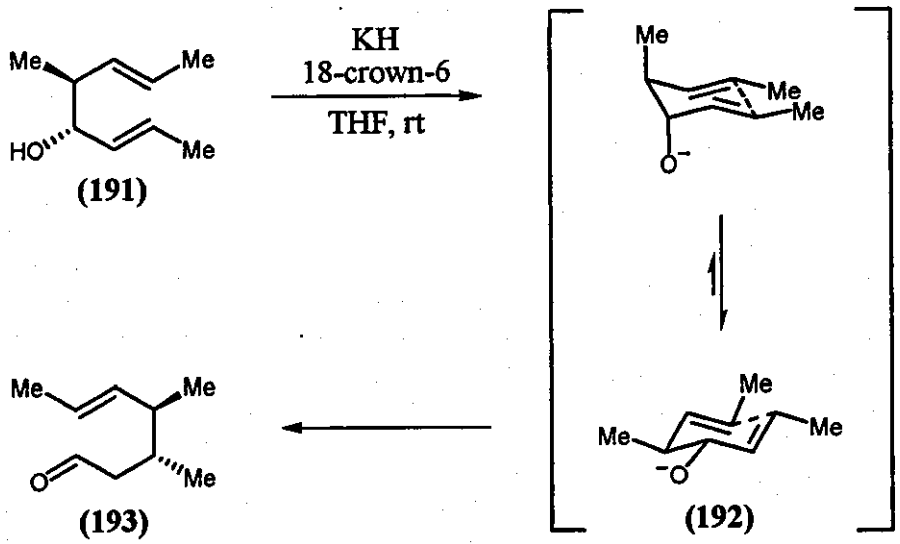
In contrast, rearrangement of compound **(190)** was unsuccessful. This effect was explained in terms of stabilisation of the transition state by the additional vinyl group in **(189)**.

1.8.2 Asymmetric Oxy-Cope Rearrangement

The anionic oxy-Cope rearrangement of cyclic substrates is commonly used in asymmetric synthesis due to its capability to access complex frameworks.[92]

The stereochemical outcome of the anionic oxy-Cope rearrangement of acyclic substrates depends on the orientation of the oxyanion in the chair-like transition state.[93,104] In the absence of steric effects, there is little difference in energy between the *pseudo*-axial and *pseudo*-equatorial orientations of the oxyanion,[93,104,105] resulting in poor chirality transfer.

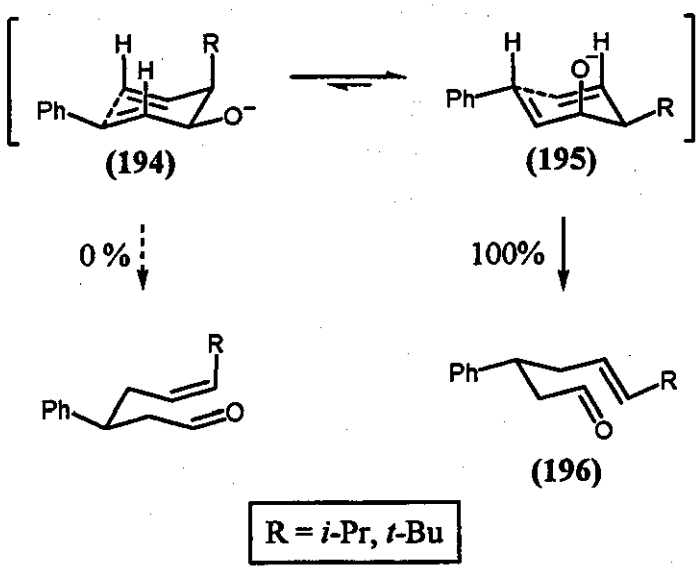
An increase in the stereoselectivity can be achieved by the introduction of a substituent at C-4 *syn* to the oxyanion **(191)** **(Scheme 60)**,[105] since both substituents would have a preference for occupying an equatorial position in the chair-like transition state.



Scheme 60

Nakai[105] observed that the oxy-Cope rearrangement of **(191)** (96% stereopurity) under standard conditions afforded the aldehyde **(193)** in 94% *d.e.* and 99% (*E*)-stereoselectivity. This result indicated that the rearrangement proceeded almost exclusively through the transition state **(192)**, with the oxyanion and the adjacent methyl group in *pseudo*-equatorial orientation.

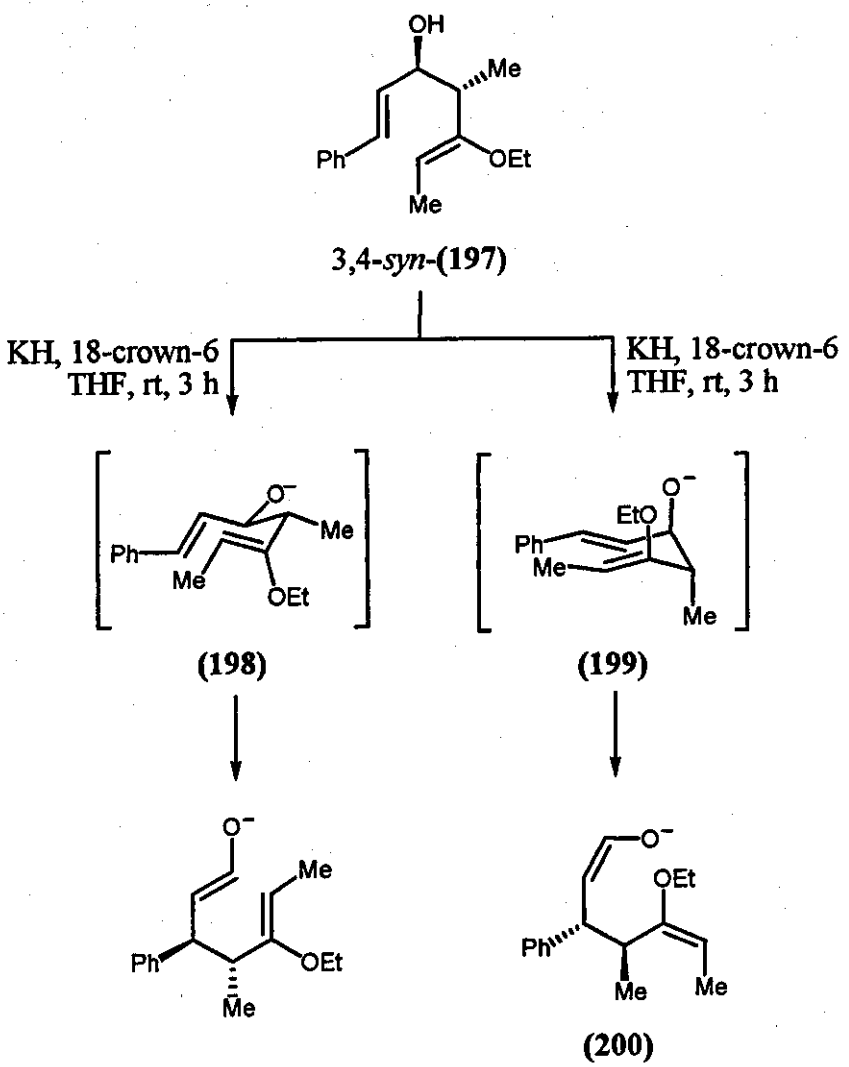
Greeves[106] demonstrated that efficient chirality transfer could be achieved when using bulky branched substituents at C-4 **(Scheme 61)**.



Scheme 61

The use of bulky R substituents exclusively formed the aldehyde **(196)**. This result suggested that only transition state **(195)** was formed during rearrangement. The transition state **(194)** was too unstable due to the *pseudo*-axial interaction between the R group and the protons shown in **Scheme 61**.

Hartley[107] reported the first example of chelation control in the anionic oxy-Cope rearrangement of compound **(197)** **(Scheme 62)**.



Scheme 62

In accordance with previous studies,[105] the substrate **(197)** was expected to rearrange *via* **(198)**. The alternative transition state **(199)** would be disfavoured due to electrostatic repulsions between the oxyanion and the enol ether oxygen in combination with steric factors.

Interestingly, the reaction produced isomer **(200)** as the major product. It was proposed that the potassium cation was chelated between the oxyanion and the oxygen atom of the enol ether during the rearrangement **(Figure 14)**.

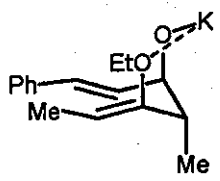
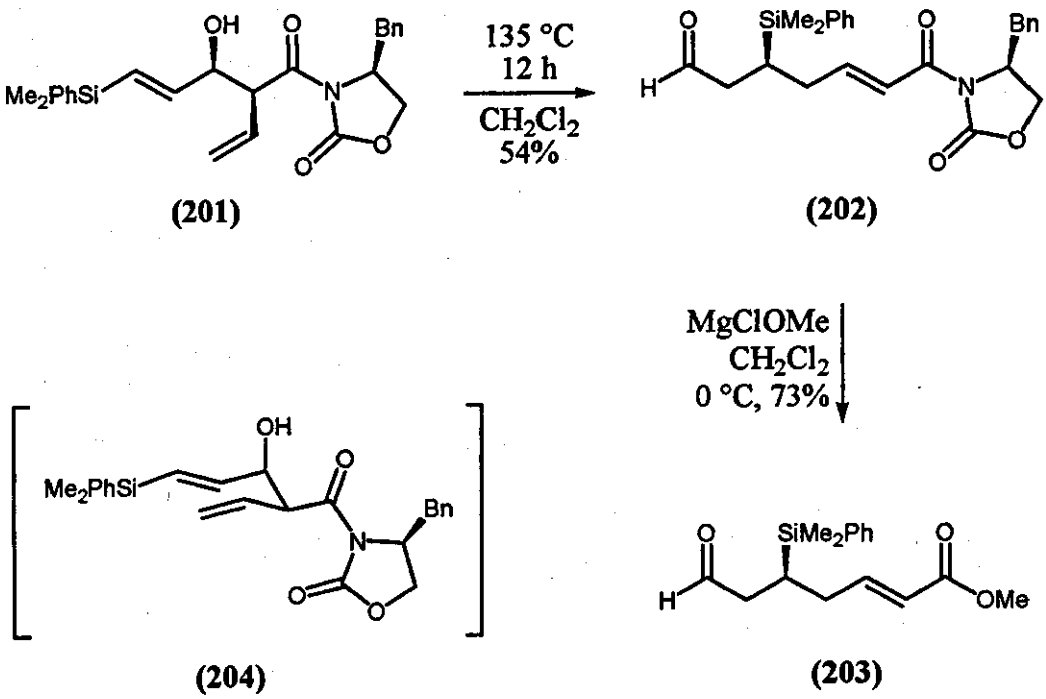


Figure 14

Schneider[108] described an asymmetric oxy-Cope rearrangement of the unprotected aldol **(201)** **(Scheme 63)**.



(201) **(202)** **(204)** **(203)**

Scheme 63

Thermal oxy-Cope rearrangement of **(201)** generated the compound **(202)** as a single isomer. It was proposed that the rearrangement proceeded through the transition state **(204)**, with an axial hydroxy and an equatorial carboximide group. Subsequent transesterification of **(202)** yielded the methyl ester **(203)** in 73% yield.

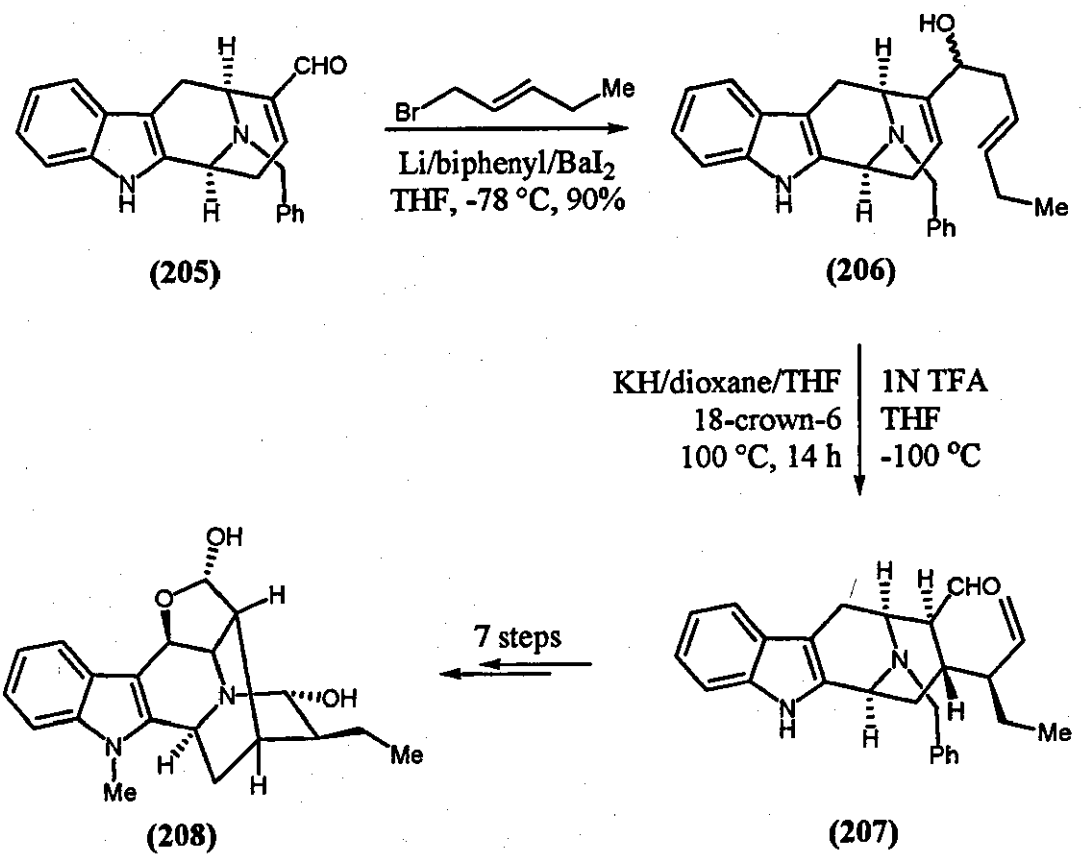
Unprotected aldols such as **(201)** generally undergo a retro-aldol reaction under oxy-Cope rearrangement conditions. However, the presence of a silyl group in **(201)**

reduced the activation energy of the rearrangement and hence decreased the quantity of retro-aldol by-products.

1.8.3 Oxy-Cope Rearrangement in Natural Product Synthesis

The oxy-Cope rearrangement can be profusely found in natural product synthesis[109] due to the ease of preparation of the substrates and the mild conditions utilised in the process.[92]

Cook[109a] achieved a stereocontrolled total synthesis of alkaloid G **(208)** **(Scheme 64)** *via* an anionic oxy-Cope rearrangement followed by protonation of the resulting enolate.



(205) **(206)** **(208)** **(207)**

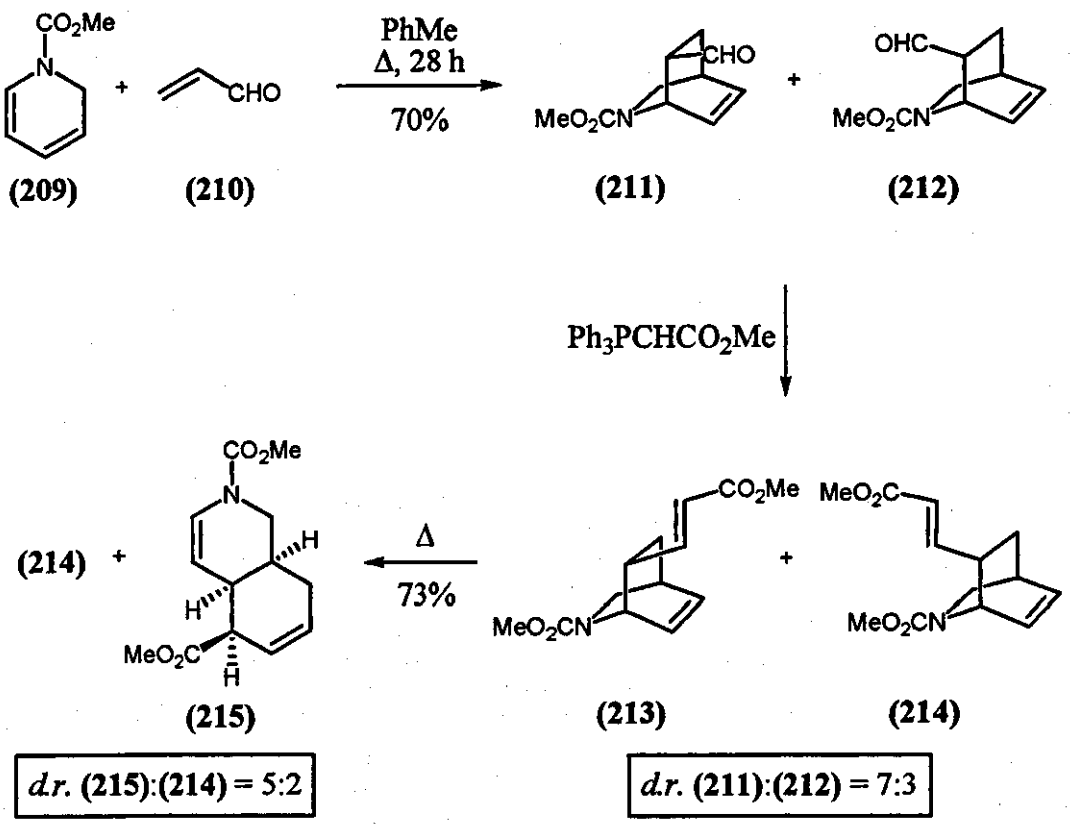
Scheme 64

The compound **(206)** was synthesised from **(205)** by a Barbier-like process. The substrate **(206)** rearranged at 100 °C and the resulting enolate was quenched by addition of a TFA/THF solution at -100 °C. The compound **(207)** was obtained in a 43:1 *d.r.* and the synthesis of **(208)** was completed in 7 additional steps in 13% overall yield.

1.9 Development of the Amino-Cope Rearrangement

In contrast to the numerous oxy-Cope rearrangement investigations, only a limited number of articles on the amino-Cope rearrangement can be found in the literature.

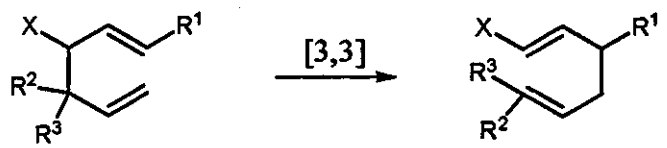
The first synthetic example of the amino-Cope rearrangement was described by Wender[110] in 1979 **(Scheme 65)**. The synthesis of *cis*-hydroisoquinoline **(215)** was achieved by a sequential Diels-Alder/Wittig/amino-Cope rearrangement.



Scheme 65

Cycloaddition of **(209)** and **(210)** produced the aldehydes **(211)** and **(212)**, which were converted into **(213)** and **(214)** *via* a Wittig reaction. Pyrolysis of the latter mixture produced hydroisoquinoline **(215)** (52%) and unreacted **(214)** (21%). The compound **(213)** underwent a [3,3]-sigmatropic rearrangement involving a boat transition state, whereas a similar low energy pathway for the rearrangement of **(214)** was geometrically impossible, producing only starting material.

Ollis[111] investigated the effect of different substituents on the Cope rearrangement of **(216)** **(Scheme 66)**.



(216) **(217)**

Scheme 66

	X	R^1	R^2	R^3	T/°C	$k/10^{-5}s^{-1}$	$\Delta G^{\ddagger}$ Kcal/mol
(216a)	Me_2N	Ph	Ph	H	100	64	27.4
(216b)	Me_2N	Ph	Me	Me	100	3.0	29.7
(216c)	Me_2N	Ph	H	H	170	4.6	35.1
(216d)	MeO	Ph	Me	Me	196	4.6	37.2
(216e)	EtS	Ph	Ph	H	170	51	33.0

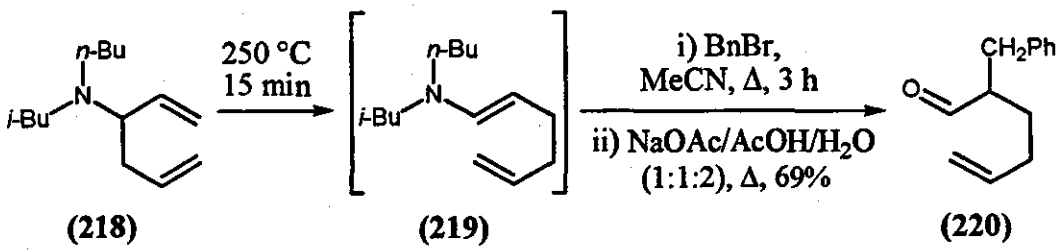
Table 1

The rearrangements were performed in sealed ampoules at different temperatures and periods of time and the products **(217)** were characterised by their spectroscopic properties.

Substrates **(216a)** and **(216b)** rearranged at 100 °C but **(216c)** required higher temperatures before a reasonably rapid amino-Cope rearrangement was observed. These results were due to the rate accelerating effect of electron donating groups (aryl or dimethyl) in the diene frame.

Compounds **(216d)** and **(216e)** had higher energies of activation than their analogous amino-Cope substrates **(216b)** and **(216a)**. It was concluded that a 3-amino substituent was more effective than either a 3-alkoxy or 3-alkylthio substituent in lowering the energy of the transition state for the Cope rearrangement. This influence appeared to be a consequence of the more effective electron-donating properties of the amino group.

Allin[112] established the first tandem amino-Cope rearrangement/enamine derivatisation of **(218)** **(Scheme 67)**.



(218) **(219)** **(220)**

Scheme 67

The amine **(218)** was heated in a sealed tube at 250 °C for 15 min to generate **(219)**. The latter compound was immediately cooled to room temperature and directly subjected to an alkylation in refluxing acetonitrile. Hydrolysis and extractive work-up furnished the desired alkylated product **(220)** in 69% yield.

The enamine **(219)** was isolated as a *trans* geometrical isomer. This result was in accordance with an expected chair-like transition state involving a *pseudo*-equatorial amino group **(Figure 15)**.

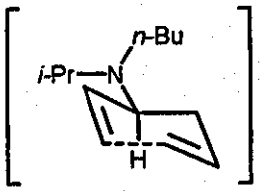
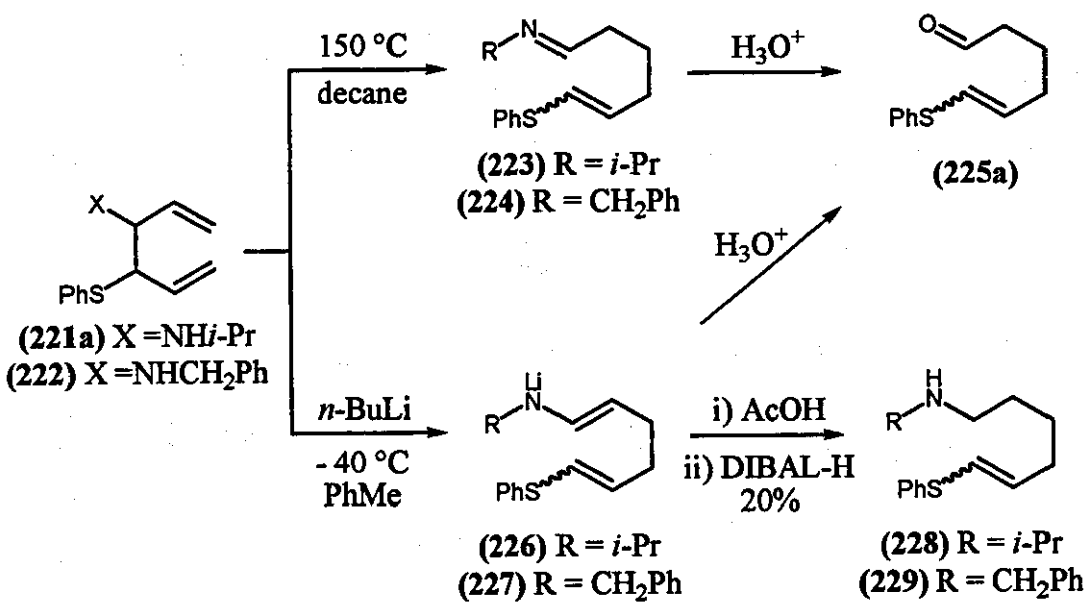


Figure 15

However, it was highlighted that the formation of the *trans*-enamine could also be due to an equilibration of any initially formed *cis*-enamine to the thermodynamically more stable *trans*-isomer.

1.9.1 Anionic Amino-Cope Rearrangement

Macdonald[113] reported the first charge-accelerated (anionic) amino-Cope rearrangement and compared this reaction to the better-known anionic oxy-Cope rearrangement[95,114] **(Scheme 68)**.



Scheme 68

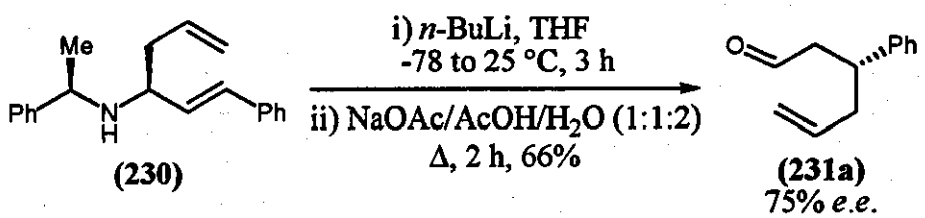
Pyrolysis of **(221a)** or **(222)** at 150 °C produced the corresponding rearranged products **(223)** and **(224)**, which were hydrolysed into **(225a)** in 48 and 45% overall yields. In contrast, compound **(221a)** was rearranged at -40 °C when deprotonated with *n*-BuLi, producing the aldehyde **(225a)** in 40% yield.

It was observed that the anionic amino-Cope rearrangement of **(221a)** took place at lower temperature (-40 °C) than the corresponding oxy-Cope rearrangement of its analogous alkoxide (X = OH) (KH, 25 °C, THF, 1 h).[114] In addition, the enamine intermediates **(226)** and **(227)** were isolated as their corresponding amines, **(228)** and **(229)**, by acid quench and subsequent reduction using DIBAL-H.

Macdonald concluded that [3,3]-sigmatropic rearrangements of 3-amino-1,5-dienes are considerably more facile than their corresponding 3-hydroxy-1,5-dienes. This was due to the increased basicity of the nitrogen anion in comparison with the alkoxide, which produced greater rate acceleration than that observed in the anionic oxy-Cope rearrangement.

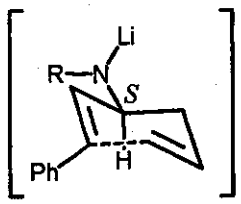
1.9.2 Asymmetric Amino-Cope Rearrangement

Allin[115] reported the first example of an asymmetric anionic amino-Cope rearrangement **(Scheme 69)**. The anionic rearrangement of the substrate **(230)** produced the aldehyde **(231a)** in high enantiomeric excess.



Scheme 69

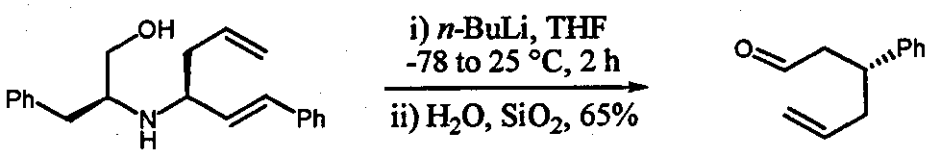
The stereochemistry at the β-position of the aldehyde **(231a)** resulted from a chair-like transition state with the chiral amine substituent in a *pseudo*-equatorial orientation **(232)** **(Figure 16)**.



(232) R = CHPhMe
(233) = $CH(CH_2OH)CH_2Ph$

Figure 16

The enantioselectivity of the process was improved[116] up to 94% *e.e.* by the use of a β-aminoalcohol auxiliary **(234a)** **(Scheme 70)**.



(234a)

94% *e.e.*

Scheme 70

An increase in the steric bulk of the chiral amine substituent (possibly provided by intramolecular chelation of the oxygen and nitrogen atoms with the lithium cation) would enhance the preference for a chair-like transition state with an equatorial amine substituent **(233)** **(Figure 16)**.

The amino-Cope rearrangement has been successfully utilised in the synthesis of simple heterocycles such as tetrahydropyrans[117,118] and lactones[118] as highlighted in **Chapter 2**.

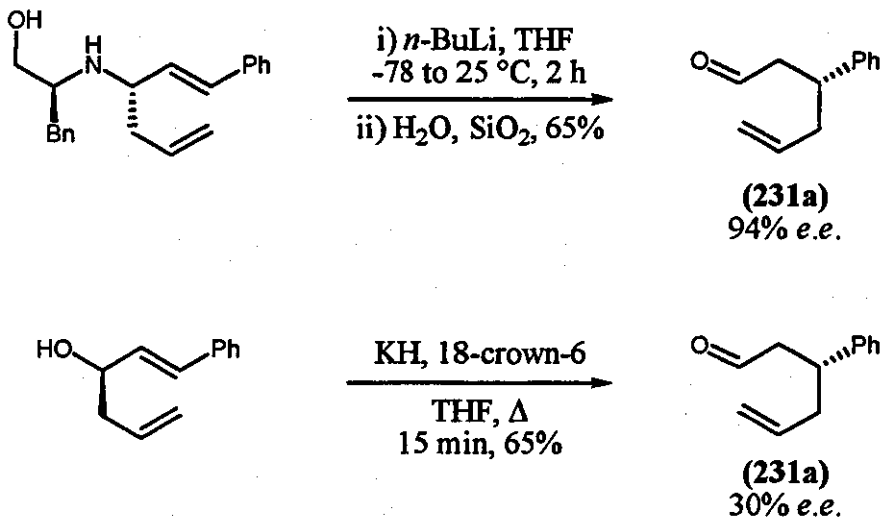
Chapter 2

Results and Discussion

2.1 Studies on the Anionic Amino-Cope Rearrangement

It is evident from the literature[113,115-122] that the anionic amino-Cope rearrangement has received limited attention to date, especially with respect to its synthetic applications, and has been performed on a limited number of substrates.

The anionic amino-Cope rearrangement has significant advantages over the analogous oxy-Cope rearrangement. As highlighted in **Section 1.8.2**, the stereoselectivity of the oxy-Cope rearrangement can be low in the absence of steric effects, as there is little energy difference between the *pseudo*-axial and *pseudo*-equatorial orientations of the oxyanion in the chair-like transition state.[93,104,105] The asymmetric amino-Cope rearrangement can generate an aldehyde product **(231a) (Scheme 71)** in 94% *e.e.*[116] whereas the oxy-Cope rearrangement yields the same product in 30% *e.e.*[93]



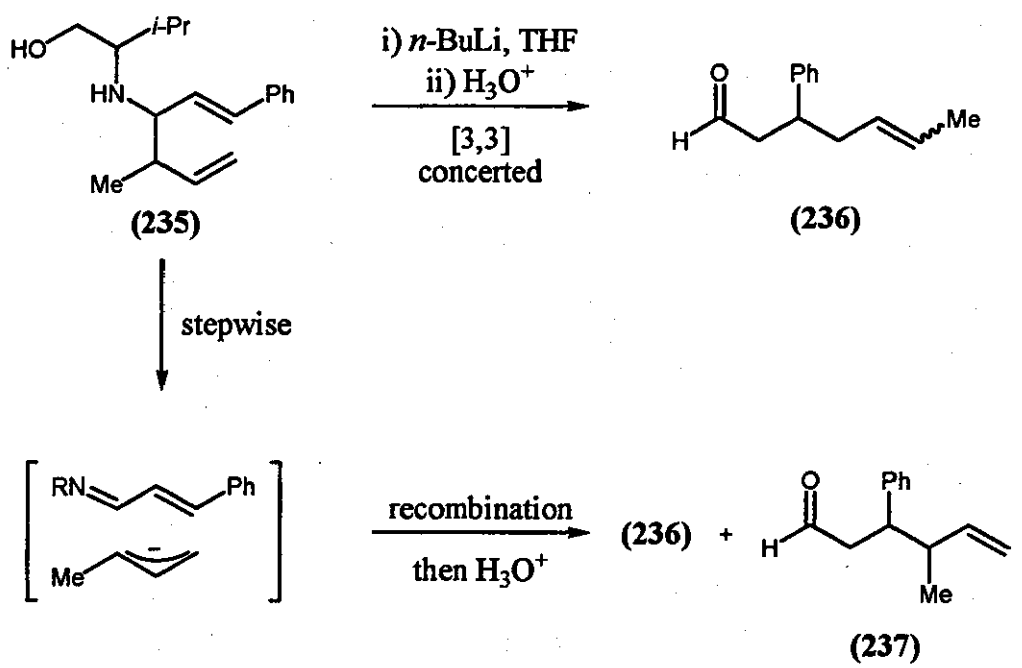
Scheme 71

It has also been reported that the anionic amino-Cope rearrangement typically requires lower reaction temperatures than the anionic oxy-Cope rearrangement on analogous substrates.[113]

2.1.1 Alternative Mechanism in the Anionic Amino-Cope Rearrangement

Previous theoretical and experimental studies from the Allin group[119] and others[113,120-122] have proposed that 3-amino-1,5-dienes can undergo a fragmentation/recombination process ([1,3]-shift) under anionic conditions, in addition to an amino-Cope rearrangement ([3,3]-shift).

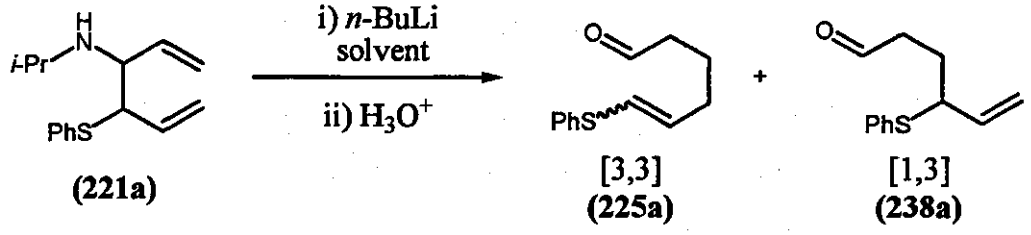
Allin[119] observed that the substrate **(235)** **(Scheme 72)** did not solely undergo a concerted [3,3]-sigmatropic rearrangement under anionic conditions but also a stepwise mechanism.



Scheme 72

A [3,3]-sigmatropic rearrangement of **(235)** would produce **(236)** as the sole product. However, when compound **(235)** was treated under anionic conditions, a 1:1 mixture of **(236)** and **(237)** was obtained. These results suggest that an alternative fragmentation/recombination pathway could be involved in the process.

Macdonald[120] indicated that with substrates such as **(221a)** **(Scheme 73)** the [3,3]- and [1,3]-shift product ratio could be controlled by solvent choice.



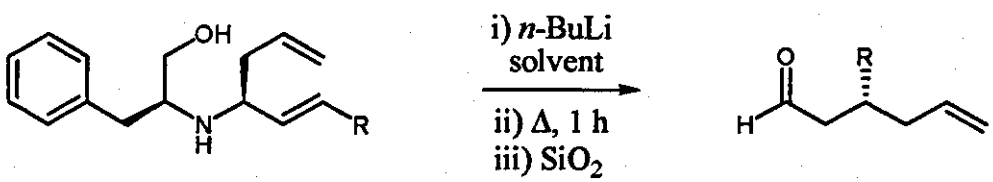
(221a) **[3,3] (225a)** **[1,3] (238a)**

Scheme 73

A 1:2 ratio of **(225a)** and **(238a)** was obtained when a polar solvent such as tetrahydrofuran was used. However, when the reaction was carried out in hexane, the substrate **(221a)** was converted into a 2:1 mixture of **(225a)** and **(238a)**. It was concluded that the use of a non-polar solvent favoured a [3,3]-sigmatropic rearrangement whereas a dissociative mechanism was preferred when the reaction was conducted in a polar solvent.

2.1.2 Anionic Amino-Cope Rearrangement of a Novel Range of Substrates

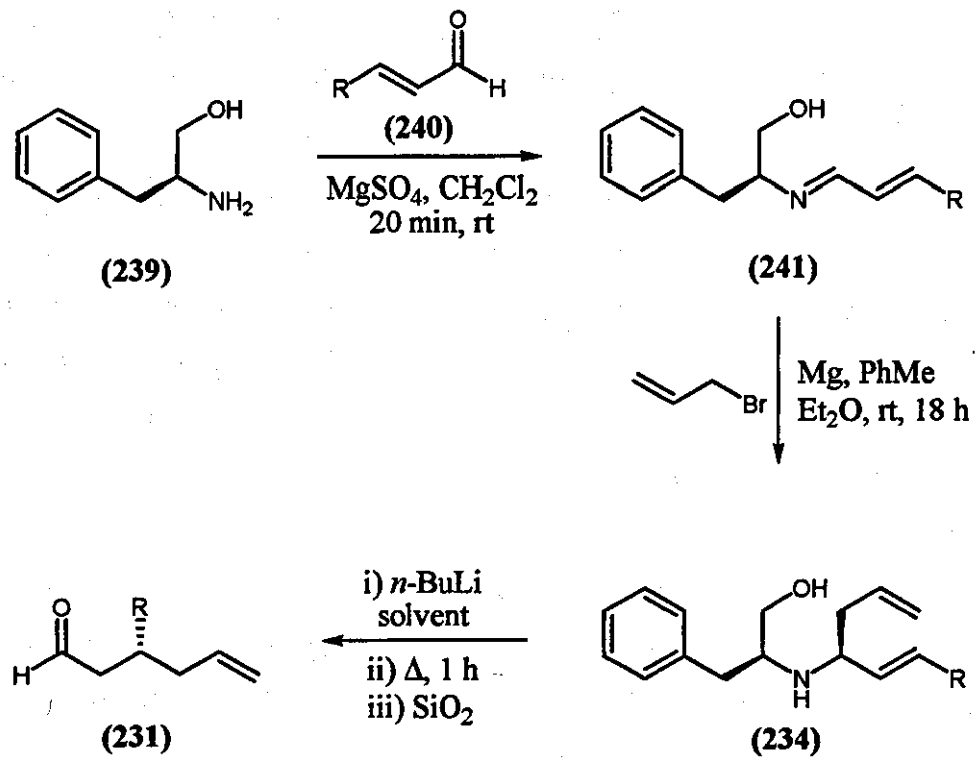
Prompted by these studies, we have conducted the anionic amino-Cope rearrangement on a novel range of substrates **(234)** **(Scheme 74)** and investigated the effect of different R substituents and solvents on the enantioselectivity of the sigmatropic process.



(234)

Scheme 74

In order to conduct this research, the synthetic strategy highlighted in **Scheme 75** was developed.

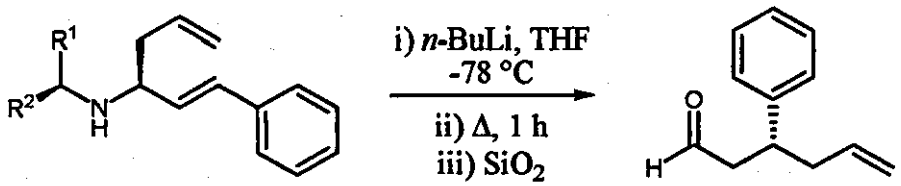


Scheme 75

An imine **(241)** was synthesised by condensation of (*S*)-phenylalaninol **(239)** with an α,β-unsaturated aldehyde **(240)**. Subsequent attack with an allyl species generated the substrate **(234)**. The latter compound was deprotonated and refluxed in the appropriate solvent in order to promote a sigmatropic rearrangement. The crude product was purified *via* flash column chromatography and an aldehyde **(231)** was obtained. This synthetic pathway is subsequently described in further detail.

2.1.2.1 Synthesis of (*S*)-Phenylalaninol

Previous work in our group[115,116] investigated the effect of different *N*-substituents on the enantioselectivity of the anionic amino-Cope rearrangement **(Scheme 76** and **Table 2)**.



(234a, 242a-e) **(231a)**

R^1, R^2 = See **Table 2**

Scheme 76

The 3-amino-1,5-dienes **(234a, 242a-e)** were rearranged under anionic conditions and it was demonstrated that **(234a)**, derived from (*S*)-2-amino-3-phenylpropan-1-ol ((*S*)-phenylalaninol) generated the aldehyde **(231a)** in the highest yield and *e.e.*

Substrate	R^1	R^2	Yield (%)	*e.e.* (%)
(234a)	CH_2OH	$PhCH_2$	65	94
(242a)	Me	Ph	66	75
(242b)	CH_2OH	*i*-Bu	57	71
(242c)	CH_2OH	Ph	61	83
(242d)	CH_2OH	*i*-Pr	60	84
(242e)	CH_2OH	*t*-Bu	53	88

Table 2

As shown in **Table 2**, a large steric bulk of the *N*-substituent resulted in a high enantiomeric excess, possibly due to the preference of the *N*-substituent for occupying a *pseudo*-equatorial orientation in the proposed transition state **(Figure 17)**.[115,116] The effective steric bulk of the β-amino alcohol auxiliaries **(234a, 242b-e)** is presumably enhanced due to the formation of a 5-membered chelate.[123]

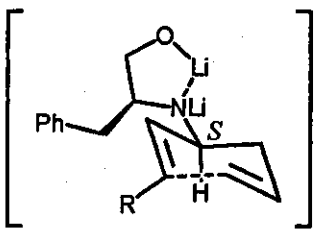
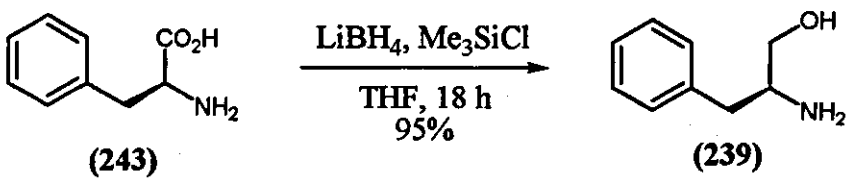


Figure 17

The synthesis of (*S*)-phenylalaninol **(239)** **(Scheme 77)** was accomplished *via* reduction of its parent amino acid **(243)**. There are a number of methods available for the reduction of amino acids to amino alcohols. Reagents used to effect this transformation include $LiAlH_4$,[124] a mixture of $NaBH_4$ and H_2SO_4[125] or $NaBH_4$ and I_2.[126]



(243) **(239)**

$$LiBH_4 + Me_3SiCl \longrightarrow LiCl + Me_3SiH + BH_3.THF$$

Scheme 77

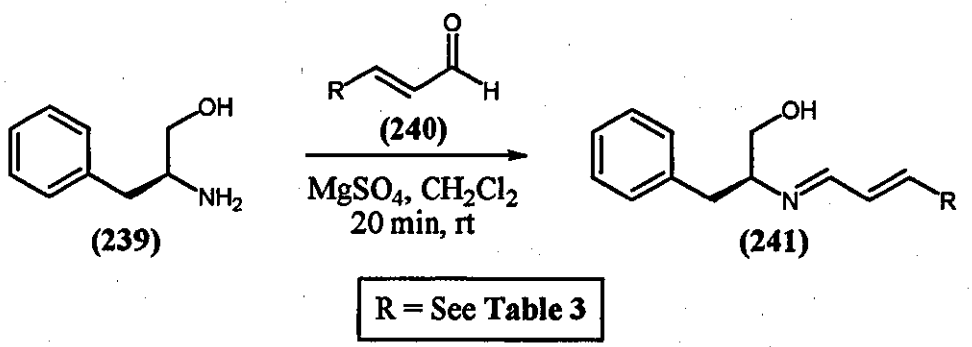
Giannis[127] developed an effective reductive procedure for a range of amino acids using lithium borohydride and chlorotrimethylsilane in dry tetrahydrofuran. Reduction of L-phenylalanine **(243)** using this methodology generated **(239)**. It was evident from the ^1H NMR spectrum of the crude reaction mixture that clean conversion of **(243)** to **(239)** had occurred.

The compound **(239)** was generated in near quantitative yield after purification by recrystallisation. Measurement of the optical rotation of the product and comparison with literature values[128] indicated that the reaction had proceeded without detectable racemisation.

Initial reactions were performed on 1 g of **(243)** and successfully scaled-up to 5 g without significant loss in yield. It was proposed[127] that a borane-tetrahydrofuran complex is produced *in situ,* which acts as the reducing agent **(Scheme 77)**. Care was necessary when conducting the reduction due to the rapid formation of the volatile silane, Me_3SiH.

2.1.2.2 Synthesis of Imines

A novel array of imines was generated from the condensation of (*S*)-phenylalaninol **(239)** **(Scheme 78)** and a range of commercially available aromatic and aliphatic α,β-unsaturated aldehydes **(240)** **(Table 3)**.

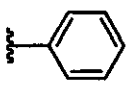
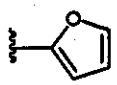
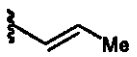
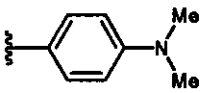
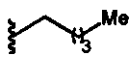
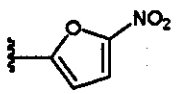
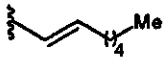
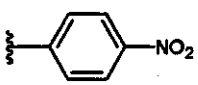


Scheme 78

The reactions were carried out by stirring equimolar quantities of **(239)** with the aldehydes **(240a-j)** in dichloromethane at room temperature. Anhydrous magnesium sulphate was added as a drying agent/mild catalyst.

Removal of the solvents under reduced pressure produced the imines **(241a-j)** in very good to quantitative yields **(Table 3)** and the products were utilised without additional

purification. No starting material was observed in the ^{1}H NMR spectra of the crude reaction mixtures.

Product	R	Yield (%)	Product	R	Yield (%)
241a		99	**241f**		96[a]
241b		98	**241g**		94
241c		97	**241h**		95
241d		92	**241i**		99
241e		94	**241j**		97

[a]Traces of solvent present in the ^{1}H NMR spectrum

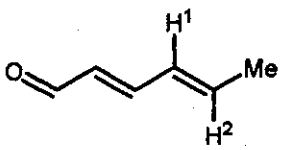
Table 3

The imino alcohol **(241a)** was stable and could be handled without degradation. This was presumably due to the presence of an aryl unit in conjugation with the C=N bond. The same high stability was observed in the imino alcohols **(241b-e)**, which also contained an aromatic conjugated unit. In contrast, imines **(241f-j)** were unstable and had to be utilised immediately after their synthesis.

The imino alcohol **(241f)** was extremely unstable and solvent could not be completely removed before degradation of the product. Only an estimated yield of the reaction could be provided (traces of dichloromethane were observed in the ^{1}H NMR spectrum).

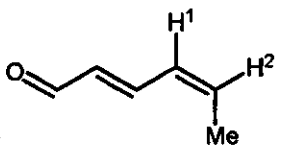
The ^{1}H NMR spectra of the imino alcohols **(241g)** and **(241i)** suggested traces of a minor isomer. On obtaining a ^{1}H NMR spectra of the aldehydes **(240g)** and **(240i)**, used as starting materials, there was an indication of a minor regioisomer.

The coupling constants and intensity of the signals in the ^{1}H NMR spectrum of the commercially available *trans,trans*-2,4-hexadienal **(240g)** **(Figure 18)** indicated the presence of 15% of *trans,cis*-2,4-hexadienal **(244)**. In an analogous manner, *trans,trans*-2,4-decadienal **(240i)** contained 6% of *trans,cis*-2,4-decadienal **(245)**.



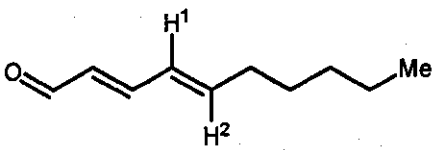
J_{H1H2} = 15.1 Hz

(240g)



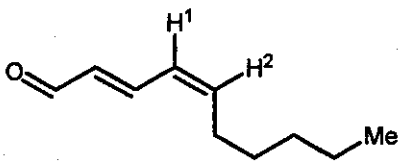
J_{H1H2} = 10.5 Hz

(244)



J_{H1H2} = 15.0 Hz

(240i)



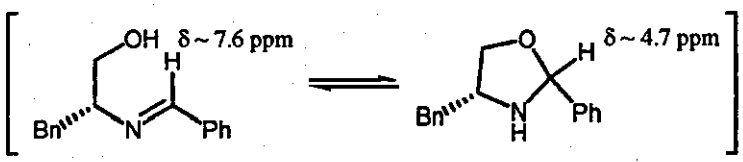
J_{H1H2} = 10.7 Hz

(245)

Figure 18

The imines **(241g)** and **(241i)** were highly unstable and were used in the next synthetic step **(Section 2.1.2.3)** without separation from the minor isomers.

Imines derived from β-amino alcohols are known[129,130] to exist in solution as a mixture of the imino alcohol **(246)** **(Figure 19)** and its oxazolidine **(247)** in a process known as ring-chain tautomerism.[131]



(246) **(247)**

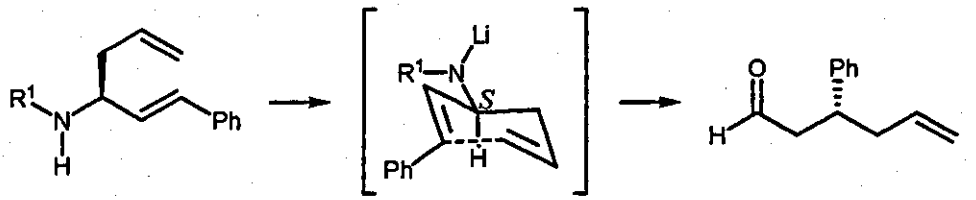
Figure 19

However, the imines **(241a-j)** were observed only as the open ring tautomer by 400 MHz ^{1}H NMR in deuterated chloroform (the imino proton signals were observed between 7.46 and 9.06 ppm).

The imines **(241a-j)** were used as substrates in the synthesis of a range of 3-amino-1,5-dienes.

2.1.2.3 Synthesis of 3-Amino-1,5-Dienes

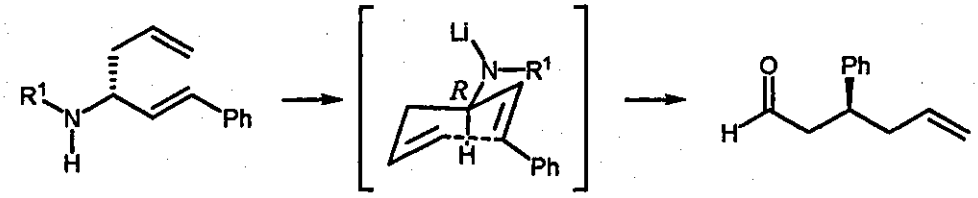
A highly diastereoselective synthesis of 3-amino-1,5-dienes (substrates for the anionic amino-Cope rearrangement) was required. Previous studies[115] demonstrated that each diastereoisomer, **(230)** and **(248)** **(Figure 20)**, generated the opposite enantiomer, **(231a)** and **(252a)** upon rearrangement.



(230) R^1 = CHPhMe
(234a) R^1 = $CH(CH_2OH)CH_2Ph$

(232)
(233)

(231a)



(248) R^1 = CHPhMe
(249) R^1 = $CH(CH_2OH)CH_2Ph$

(250)
(251)

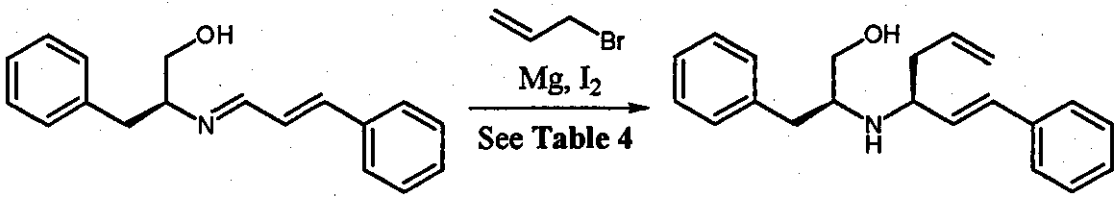
(252a)

Figure 20

It was proposed[115] that the 3-amino-1,5-dienes **(230)** and **(248)** **(Figure 20)** underwent a rearrangement through the chair-like transition states **(232)** and **(250)**, in an analogous manner to related rearrangements,[25] with the chiral auxiliary occupying a *pseudo*-equatorial orientation.

Although these models are considered to be an over simplification of the process,[116] they allow the prediction of the stereochemical outcome of the amino-Cope rearrangement: the diene **(234a)** would rearrange into the (*R*)-aldehyde **(231a)** *via* **(233)**, whereas the diastereoisomer **(249)** would generate the (*S*)-aldehyde **(252a)** *via* **(251)**.

The synthesis of the 3-amino-1,5-diene **(234a)** **(Scheme 79)** was conducted *via* allylation of the corresponding imine **(241a)** in a highly diastereoselective fashion. A Grignard addition using allylmagnesium bromide was initially utilised in the Allin group.[132] However, several problems were encountered using this methodology, such as poor solubility of the substrates in the solvent (diethyl ether), low stability of the allylic Grignard reagent and a decrease in yield when the reaction was scaled-up.[133] In order to overcome these difficulties, the Grignard reagent was generated *in situ* (Barbier-type[134] reaction).[133]



(241a) **(234a)**

Scheme 79

Different conditions for the synthesis of compound **(234a)** were investigated in the Allin group **(Table 4)**.[133]

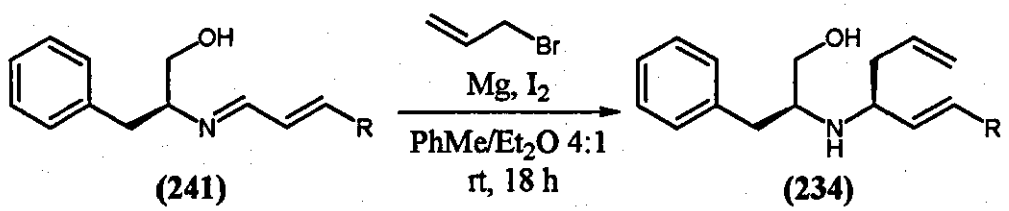
Solvent	T (°C)	t (h)	*d.e.* (%)[a]	Yield (%)[b]
DME	rt	18	10	70
THF	0 to rt	1.5	57	70
THF	-40 to rt	18	75	<5[c]
Et_2O	0 to rt	18	81	50[c]
Et_2O	-78 to rt	5	82	80[c]
Et_2O/THF	0	1.5	58	99[d]
1:1 PhMe:Et_2O	-78 to rt	3	78	99[d]
4:1 PhMe:Et_2O	rt	18	96	99[d]

[a]*d.e.* 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

Table 4

A low *d.e.* was observed when tetrahydrofuran or 1,2-dimethoxyethane were used as sole solvents. The use of diethyl ether generated **(234a)** in high *d.e.* but when tetrahydrofuran was added to increase the substrate solubility, a dramatic diastereoselectivity decrease was observed. A 4:1 mixture of toluene:diethyl ether at room temperature generated **(234a)** with the highest yield and *d.e.*

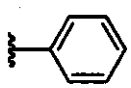
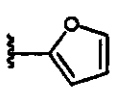
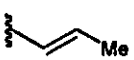
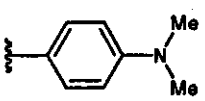
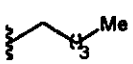
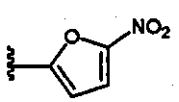
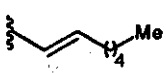
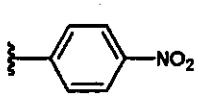
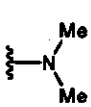
We attempted to synthesise a novel range of 3-amino-1,5-dienes **(234a-j)** **(Scheme 80** and **Table 5)** using the previously described optimal conditions.



(241) **(234)**

R = See Table 5

Scheme 80

Substrate	R	Yield (%)	Substrate	R	Yield (%)
241a		79	**241f**		59
241b		78	**241g**		65
241c		89	**241h**		62
241d		-	**241i**		67
241e		-	**241j**		64[a]

[a]Unexpected product observed (*vide infra*)

Table 5

The imines **(241a-j)** were dissolved with magnesium turnings (previously activated with an acidic wash) and a catalytic quantity of iodine in a 4:1 mixture of toluene:diethyl ether under an inert atmosphere. Allyl bromide was added dropwise to the reaction vessel and the initiation of the reaction was observed by a colouration change of the reaction mixture (from dark brown to light yellow) and a release of heat.

In order to avoid protection of the hydroxy group before the organometallic addition,[135] so reducing the number of steps, an excess of organometallic reagent (3.3 equivalents) was required.

The compounds **(234a-c)** **(Table 5)** were generated in good yields and purified by recrystallisation in diethyl ether/hexane.

The substrate **(241d)** was highly insoluble in the typical 4:1 mixture of toluene/diethyl ether. The volume of solvent was increased and the reaction was carried out on a partially dissolved imine **(241d)** but only starting material was obtained. The use of tetrahydrofuran resulted in a minor solubility increase and the Barbier reaction yielded only starting material.

Although compound **(241e)** had greater solubility than **(241d)** in the toluene:diethyl ether solvent mixture, the ^{1}H NMR spectrum of the crude reaction mixture suggested decomposition of starting material. The lack of success in the generation of **(234d)** and **(234e)** was disappointing, since the presence of electron withdrawing groups within their framework made these compounds interesting substrates for the study of the anionic amino-Cope rearrangement.

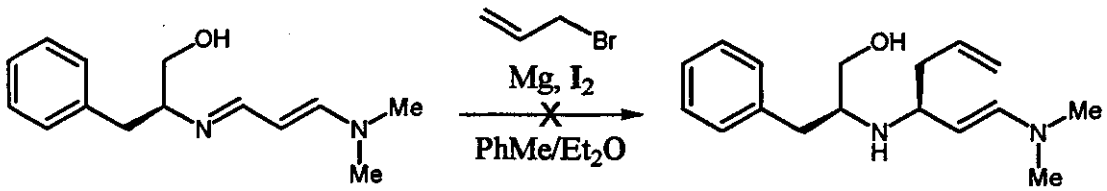
Other groups have observed that the addition of organometallic reagents is not possible on substrates bearing unsaturated polar functions such as nitro, carbonyl or ester groups.[136] Bartoli[137] reported that the reaction of allylmagnesium chloride with nitrobenzene resulted in the formation of an adduct that decomposed during attempts to trap or isolate it.

The synthesis of the 3-amino-1,5-diene **(234f)** was challenging due to the high instability of the starting material. The imine **(241f)** was freshly prepared and used in the nucleophilic addition after a brief work-up. Modest yields were obtained, presumably due to a rapid decomposition of the starting material during the Barbier reaction and partial decomposition of the product **(234f)** during purification. Thin layer chromatography of the crude product showed multiple spots and several contaminated fractions were obtained after flash column chromatography.

The unstable imine alcohols **(241g)** and **(241i)** had been synthesised as an isomeric mixture **(Section 2.1.2.2)** and were subjected to allylation without separation of the isomers. Their corresponding amines **(234g)** and **(234i)** were therefore synthesised as a mixture of regioisomers that could not be separated by column chromatography. Consecutive recrystallisations in hexane enabled the isolation of **(234i)**.

All the previously described 3-amino-1,5-dienes were generated in excellent diastereoselectivities (>96%). In most cases, only one diastereoisomer could be observed in the ^{1}H NMR spectra of the crude reaction mixtures.

Allylation of **(241j)** **(Scheme 81)** did not generate the expected product **(253)**.



(241j) **(253)**

Scheme 81

A single crystal X-ray analysis was obtained **(Figure 21)**, which suggested that the allyl group had added to the imine nitrogen with a concomitant loss of the dimethyl amine group **(Scheme 82)**.

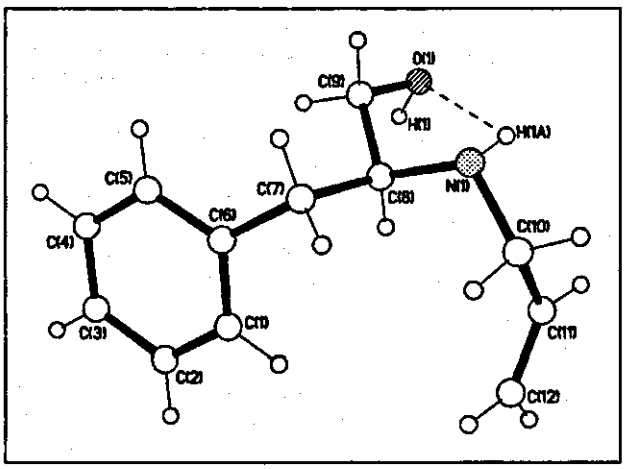
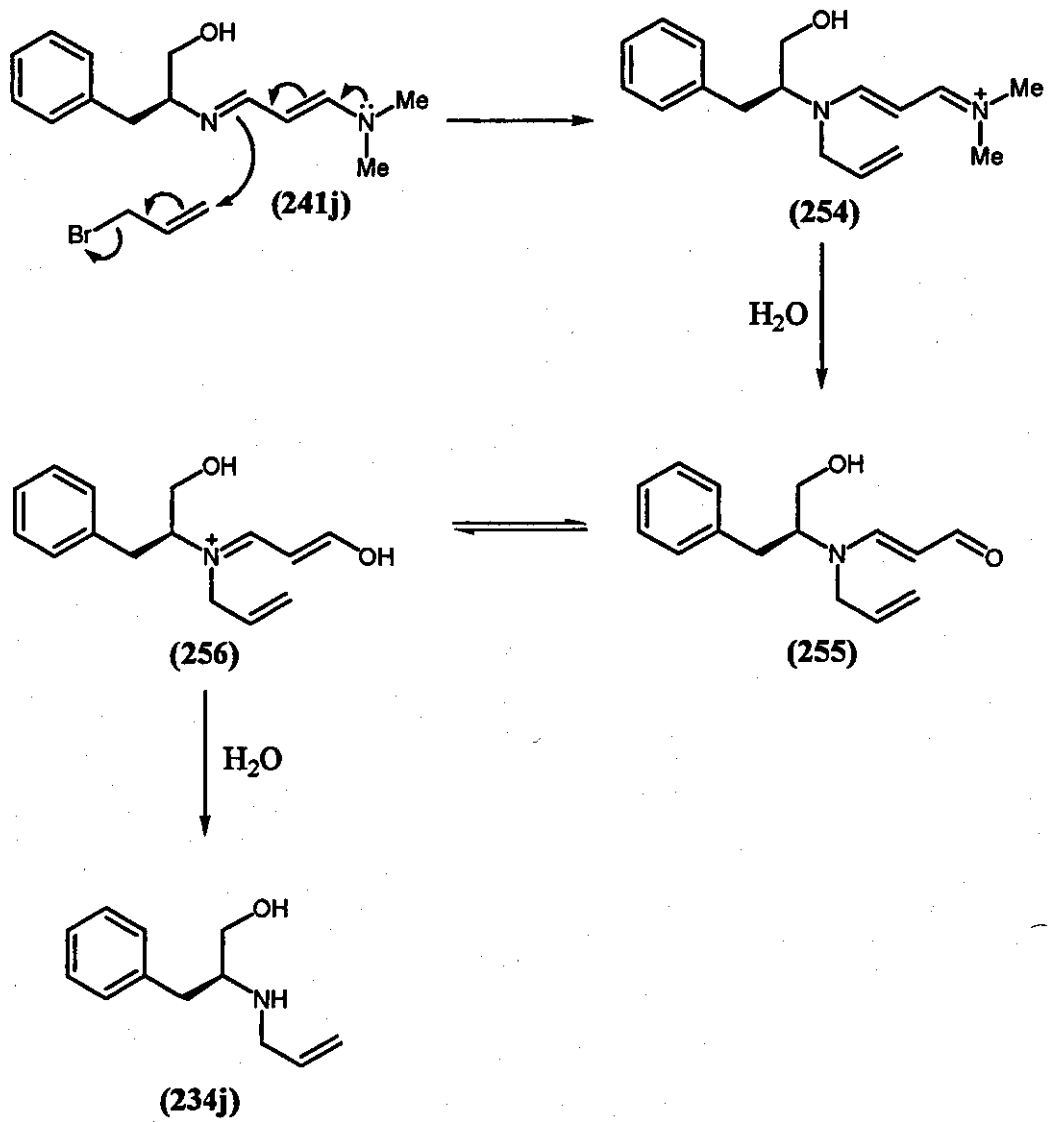


Figure 21



Scheme 82

Nucleophilic attack of the compound **(241j)** onto allyl bromide could generate **(254)**. The latter compound could be hydrolysed to form **(255)**, which then tautomerises into **(256)** and is subsequently hydrolysed to **(234j)**.

The addition of organometallic reagents to imines derived from β-amino alcohols is known to be highly diastereoselective and it has been proposed[138] to proceed through a chelated transition state **(Figure 22)**.

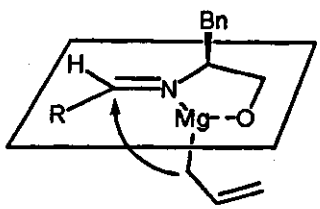


Figure 22

The remarkable stereocontrol observed in the reported allylations could be attributed to the formation of an internal chelate between the magnesium atom of the Grignard reagent with the oxygen and nitrogen atoms.[138] The strong Lewis basicity character of both the imino nitrogen and amino alcohol oxygen results in a very strong complexation to the Grignard reagent thus limiting the flexibility of the transition state.[130]

The *re* and *si* faces are differentiated toward the attack of the nucleophile due to the bulkiness of the benzyl group at the α-position of the imine. Consequently, the nucleophilic attack occurs from the less hindered face of the C=N bond, leading to a highly diastereoselective addition. Couty[139] reported a similar transition state for the addition of organolithium compounds onto imines derived from β-amino alcohols.

A single crystal X-ray analysis of **(234a)** was obtained **(Figure 23)** and it was confirmed that the diasteromeric outcome of the reaction was in accordance with the one predicted by the proposed transition state.

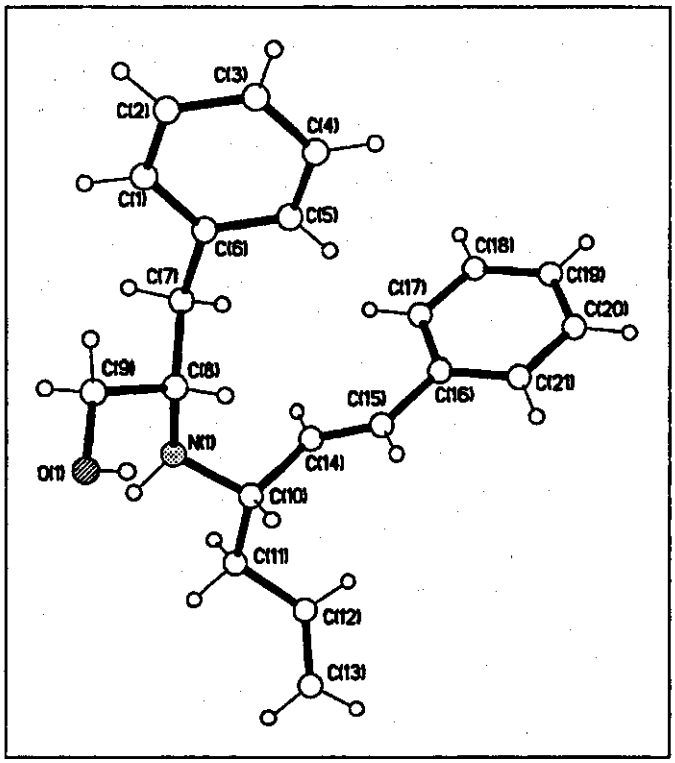
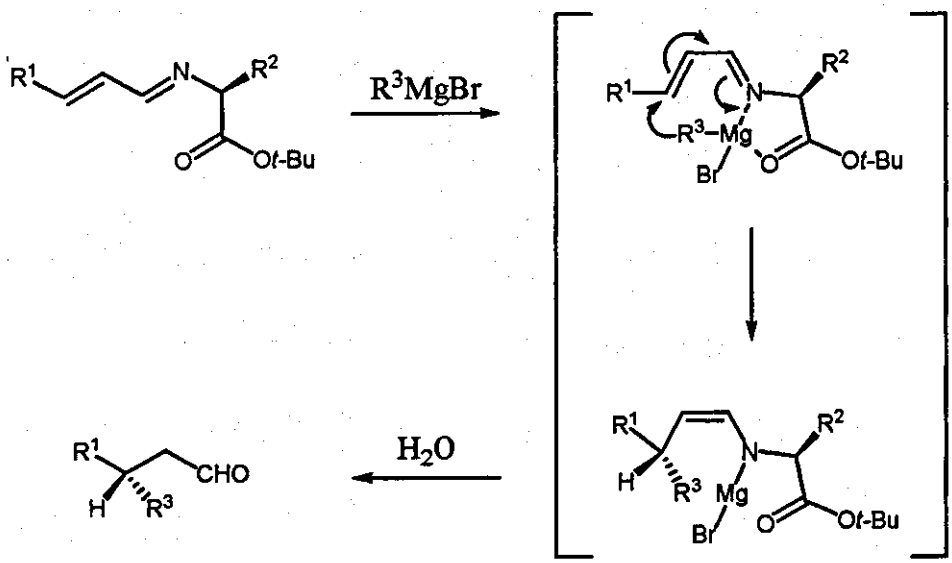


Figure 23

The allyl nucleophile attacks the imine from the least hindered face generating the amino alcohol **(234a)** with the expected stereochemistry.

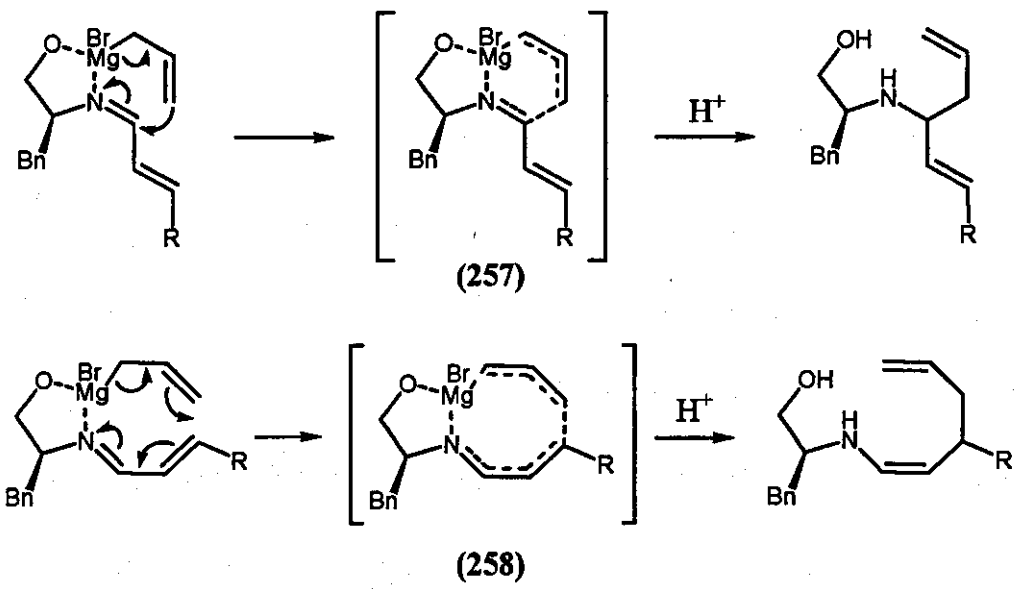
From this result we concluded that all of the 3-amino-1,5-dienes prepared **(234a-c,f-i)** should possess the same stereochemistry as shown in **Figure 23**. The sense of asymmetric induction in the addition of allylmetal species onto imines is not affected by the nature of the imine (the R group), the nature of the metal in the allylmetal species or the procedure followed (Grignard or Barbier).[140]

Pridgen[130] and Koga[141] observed that the addition of Grignard reagents onto α,β-unsaturated imines results in a 1,4-addition and proposed the transition state highlighted in **Scheme 83**. In contrast,[130] lithium, cerium and copper organometallic reagents undergo a 1,2-addition.



Scheme 83

There was no evidence of a 1,4-addition in any of our 3-amino-1,5-dienes **(234a-c,f-i)**. It was postulated[133] that the magnesium coordinated with the imine nitrogen and the addition occurred in a 1,2-fashion through a six-membered transition state **(257)** **(Scheme 84)**. A 1,4-addition of the Grignard reagent would imply a more unstable 8-membered transition sate **(258)**.

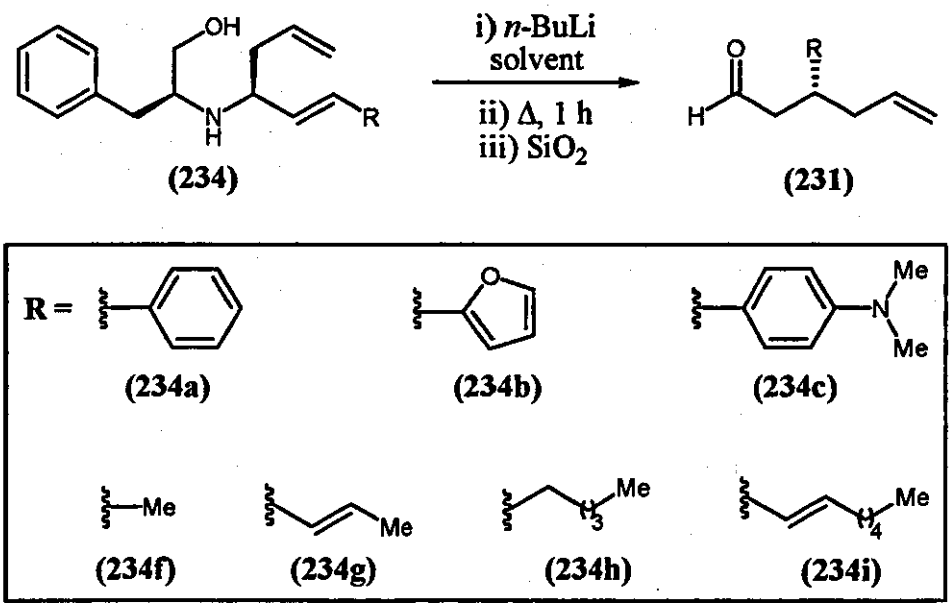


Scheme 84

The 3-amino-1,5-dienes **(234a-c,f-i)** were used as substrates to study the substituent and solvent effect on the anionic amino-Cope rearrangement.

2.1.2.4 Anionic Amino-Cope Rearrangements

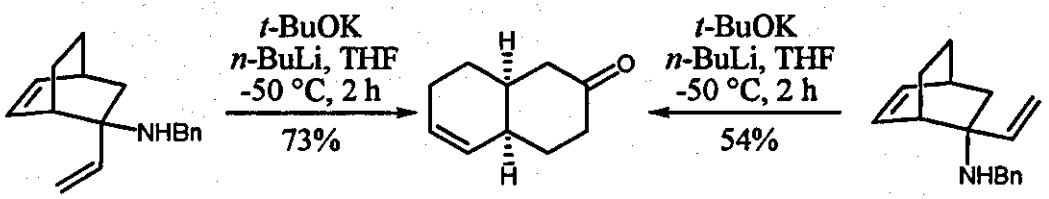
As highlighted in **Section 2.1**, the anionic amino-Cope rearrangement has been conducted on a limited number of substrates. We have now studied the rearrangement of a novel range of 3-amino-1,5-dienes **(234a-c,f-i) (Scheme 85)**. This was to investigate the effect of the substrate structure and the experimental conditions on the enantioselectivity of the reaction.



Scheme 85

Several publications[113,119-122] have highlighted the possible existence of an alternative mechanism to the anionic amino-Cope rearrangement. These observations are subsequently described.

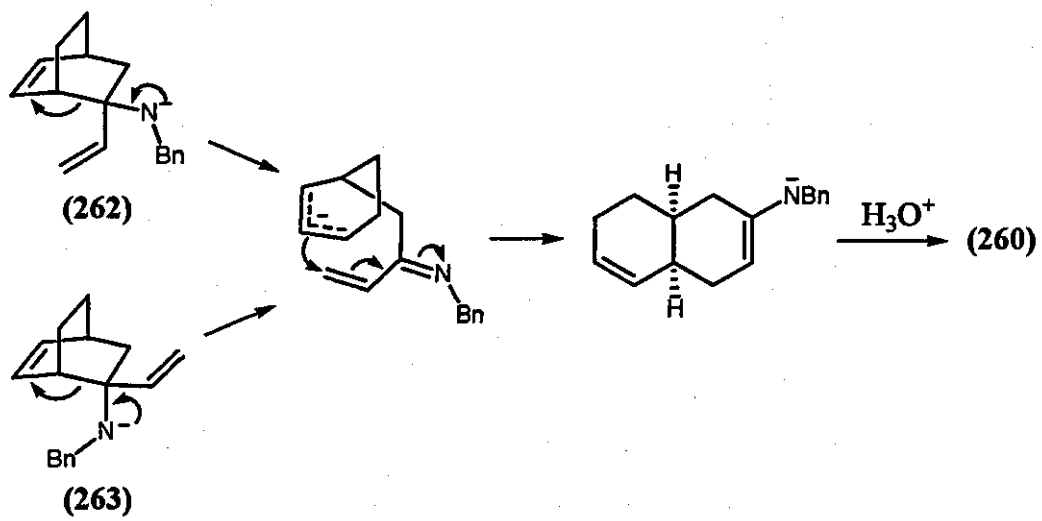
Macdonald[113] observed that the isomers **(259)** and **(261) (Scheme 86)** rearranged into the same product **(260)** under anionic conditions.



(259) **(260)** **(261)**

Scheme 86

This result suggested the possibility of an alternative fragmentation/recombination mechanism in the anionic amino-Cope rearrangement **(Scheme 87)**.

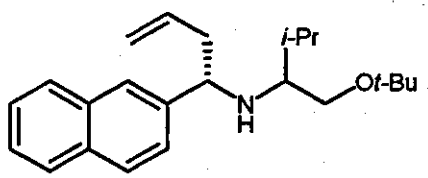


Scheme 87

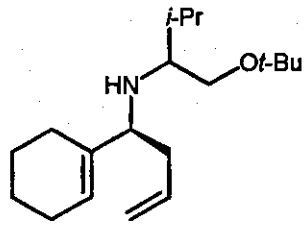
Both of the deprotonated compounds **(262)** and **(263)** could produce **(260)** *via* a fragmentation/Michael addition[142] and subsequent hydrolysis.

Houk and Meyers[121] concluded, using *ab initio* calculations, that anionic oxy-Cope substrates react *via* a concerted process, whereas anionic amino-Cope substrates react *via* a stepwise heterolytic cleavage pathway.

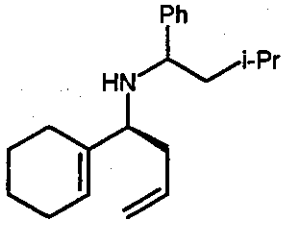
It was observed[121] that the *N*-allyl *N*-substituted amines **(264)** to **(268)** **(Figure 24)** did not rearrange under the conditions highlighted in **Table 6**.



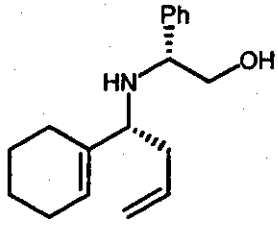
(264)



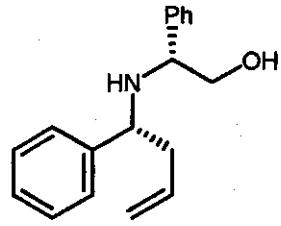
(265)



(266)



(267)



(268)

Figure 24

Substrate	Conditions	Results
(264)	KH/PhMe, reflux, overnight	No reaction
	MeI quench, KH/DMF, rt, H^+	Deallylated imine
(265)	KH/PhMe, rt, overnight	No reaction
	n-BuLi/THF, -78 to 0 °C	Butyl addition product[a]
(266)	KH/PhMe, rt to reflux	No reaction
	n-BuLi/THF, -78 °C to rt	Deallylated imine
(267)	KH/PhMe, rt to reflux	No reaction
	n-BuLi/THF, -78 °C to rt	Decomposition
(268)	KH/PhMe, rt to reflux	No reaction
	n-BuLi/THF, -78 °C to rt	No reaction

[a]Addition of *n*-BuLi to the C=N link of **(265)** as determined by ^1H and ^{13}C NMR

Table 6

Evans and Baillargeon[97a] proposed that the substantial acceleration of the anionic oxy-Cope rearrangement, in comparison with its thermal analogue, was due to a bond weakening effect of the alkoxy group in the adjacent C-3 - C-4 bond **(Section 1.8.1)**. Houk and Meyers[121] indicated that the bond weakening effect of the N^- was entirely comparable to that provided by the O^- and therefore the different nature of the anion was discarded as the reason for the lack of rearrangement in substrates **(264)** to **(268)**.

The stationary points for the oxy-Cope **(Figure 25)** and amino-Cope rearrangements **(Figure 26)** were calculated. It was concluded that the anionic oxy-Cope rearrangement proceeds *via* a concerted pathway with an activation energy of 9.9 Kcal/mol and the reaction is 19 Kcal/mol exothermic.

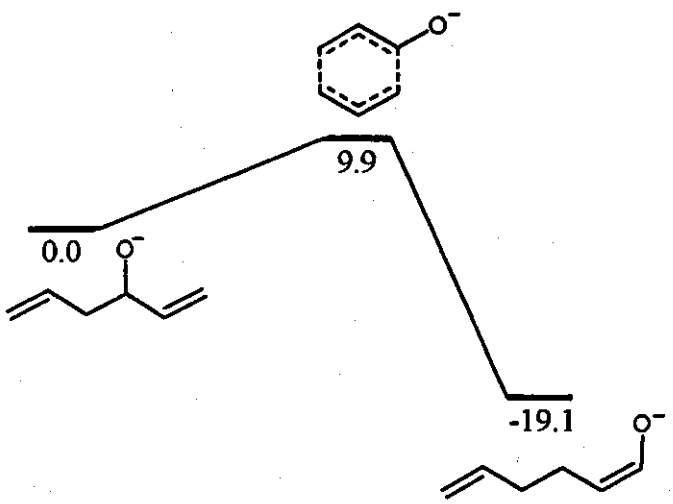


Figure 25

In contrast, the anionic amino-Cope rearrangement had a different energy surface and a stepwise mechanism was proposed for the reaction **(Figure 26)**.

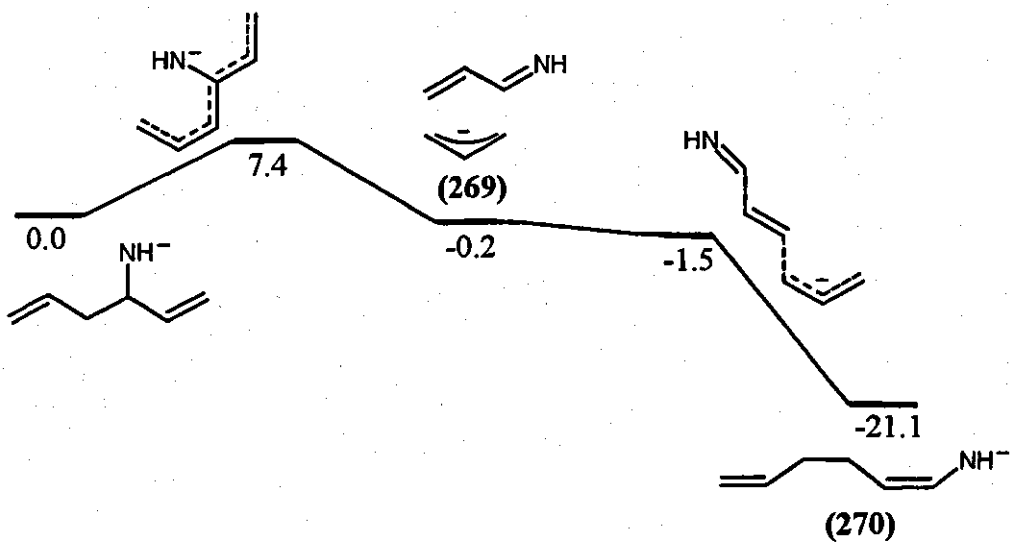


Figure 26

The initial reaction barrier was 7.4 Kcal/mol and would lead to the intermediate **(269)**, a complex of allyl anion and acrolein imine. The latter compound would then recombine to form the rearranged product **(270)** in an exothermic reaction (-21 Kcal/mol).

Houk and Meyers proposed that the intermediate **(269)** would proceed to the rearranged product **(270)** in gas phase, albeit through a stepwise mechanism. In contrast, **(269)** would be stabilised and dissociated in solution, due to the weak bonding between the allyl anion and the acrolein imine.

Houk, Haeffner and Lee[121,122] concluded that the preference for a rearrangement or a cleavage/recombination mechanism in the anionic amino- and oxy-Cope rearrangements could be predicted from comparison of the homolytic and heterolytic bond dissociation energies (BDE's) of their substrates **(Table 7)**.

Substrate	BDE's (Kcal/mol)		
	Homo	Hetero	Homo - Hetero
3-hydroxy-1,5-hexadiene	25.5	24.1	1.4
3-amino-1,5-hexadiene	20.0	9.5	10.5

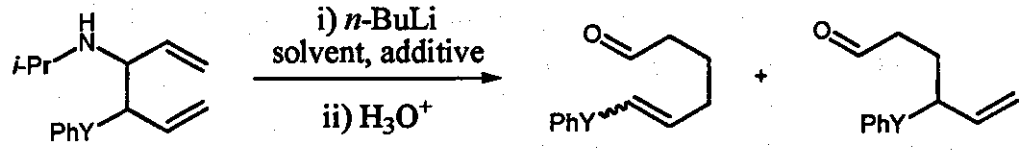
Table 7

The transition state of the anionic oxy-Cope rearrangement (concerted mechanism) can be considered as two weakly interacting allyl radicals. Consequently, the energy of the transition state could be estimated by homolytic dissociation of the reactant into two separate allyl radicals. The cleavage pathway of the anionic amino-Cope rearrangement can be described by the heterolytic dissociation of the reactant into acrolein and an allyl anion.

For the anionic oxy-Cope rearrangement the homolytic and heterolytic cleavage energies are comparable, differing by only 1.4 Kcal/mol **(Table 7)**. However, the anionic amino-Cope shows a clear preference for heterolytic cleavage and therefore the reaction follows a cleavage/recombination pathway.

These calculations conflict with empirical results obtained by Allin,[115,116] who conducted highly enantioselective anionic amino-Cope rearrangements, and Macdonald,[113] who observed sigmatropic rearrangements of deprotonated 3-amino-1,5-dienes in addition to a heterolytic cleavage. However, Houk, Haeffner and Lee[122] indicated that the presence of a lithium counter-ion on the deprotonated starting material could stabilise the anions and therefore favour concerted pathway.

Macdonald[120] studied the anionic amino-Cope rearrangement of substrates such as **(221a)** and **(221b) (Scheme 88)** and observed that the ratio of [1,3]- and [3,3]-product could be controlled by solvent choice **(Table 8)**.



(221a) Y = S
(221b) Y = O

(225a)
(225b)
[3,3]

(238a)
(238b)
[1,3]

Scheme 88

Y	Solvent	Additive	T (°C)	t (min)	(225)/(238)	*Cis/trans* (225)	Yield (%)[a]
S	THF	-	-78	10	1/2	1/5	54
		TMEDA	-70	30	1/2	1/9	57
		HMPA	-78	30	1/5	1/10	43[b]
	PhMe	-	-20	60	1/1	2/1	50
		TMEDA	-78	30	8/1	3/1	49[b]
		HMPA	-60	60	3/2	2/1	27
	C_6H_{14}	-	-20	60	2/1	2/1	31
		TMEDA	-78	30	10/1	4/1	37
		HMPA	-60	60	4/1	3/1	43
O	THF	TMEDA	25	45	3/1	1/2	20
		HMPA	25	45	2/1	1/1	36
	PhMe	TMEDA	25	45	4/1	1/3	13

[a]No starting material or other easily identifiable products were obtained except for small amounts of allyl phenyl sulphide; [b]6% of allyl phenyl sulphide was obtained in this example

Table 8

Macdonald[120] observed that the generation of the [3,3]-product **(225a)** (Y = S) was favoured when the reaction was carried out in a non-polar solvent such as hexane. However, the [1,3]-product predominated when a polar solvent (tetrahydrofuran) was used.

The effect of coordinative additives was also studied. Addition of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) or hexamethylphosphoramide (HMPA) resulted in more facile reactions and an enhanced solvent effect on the regioselectivity.

It was observed that compounds **(221a)** (Y = S) and **(221b)** (Y = O) **(Scheme 88)** had different behaviour under the same reaction conditions: the substrate **(221a)** reacted at -78 °C whereas **(221b)** required 25 °C under analogous reaction conditions. The enantioselective outcome of both substrates was also different. In the rearrangement of **(221b)**, the [3,3]-product predominated in all of the solvents. In contrast, the PhS substituent of **(221a)** had a significant effect on the course of the reaction, allowing the regioselectivity to be controlled toward either the [3,3]- or [1,3]-product depending on solvent choice.

The ratio of the *cis/trans* **(225a)** was also controlled by the reaction conditions. The use of hexane (non-polar) as a solvent favoured the *cis*-product whereas the use of tetrahydrofuran (polar) favoured the *trans*-product.

Macdonald concluded that the solvent effect on the reaction regioselectivity was due to a fragmentation pathway being favoured by the polar solvent while non-polar solvents favoured a concerted pathway. The solvent effect on the *cis/trans* [3,3]-product selectivity of **(225a)** was due to the *cis*-**(225a)** being preferentially formed by a concerted mechanism whereas the *trans*-**(225a)** was formed by a fragmentation pathway.

Following this report, we studied the solvent effect on the anionic amino-Cope rearrangements of the 3-amino-1,5-dienes **(234a-c,f-i)**. A [1,3]-shift **(271)** **(Figure 27)** or a [3,3]-sigmatropic rearrangement **(272)** of these substrates would lead to the same product **(273)**, which hydrolyses into the aldehyde **(231)**. However, higher *e.e.*'s are

expected in a concerted mechanism **(272)**, with a highly-ordered transition state, than in a dissociation/recombination pathway **(271)**, which would have the chiral auxiliary as sole contributor to the stereochemical induction of the process.

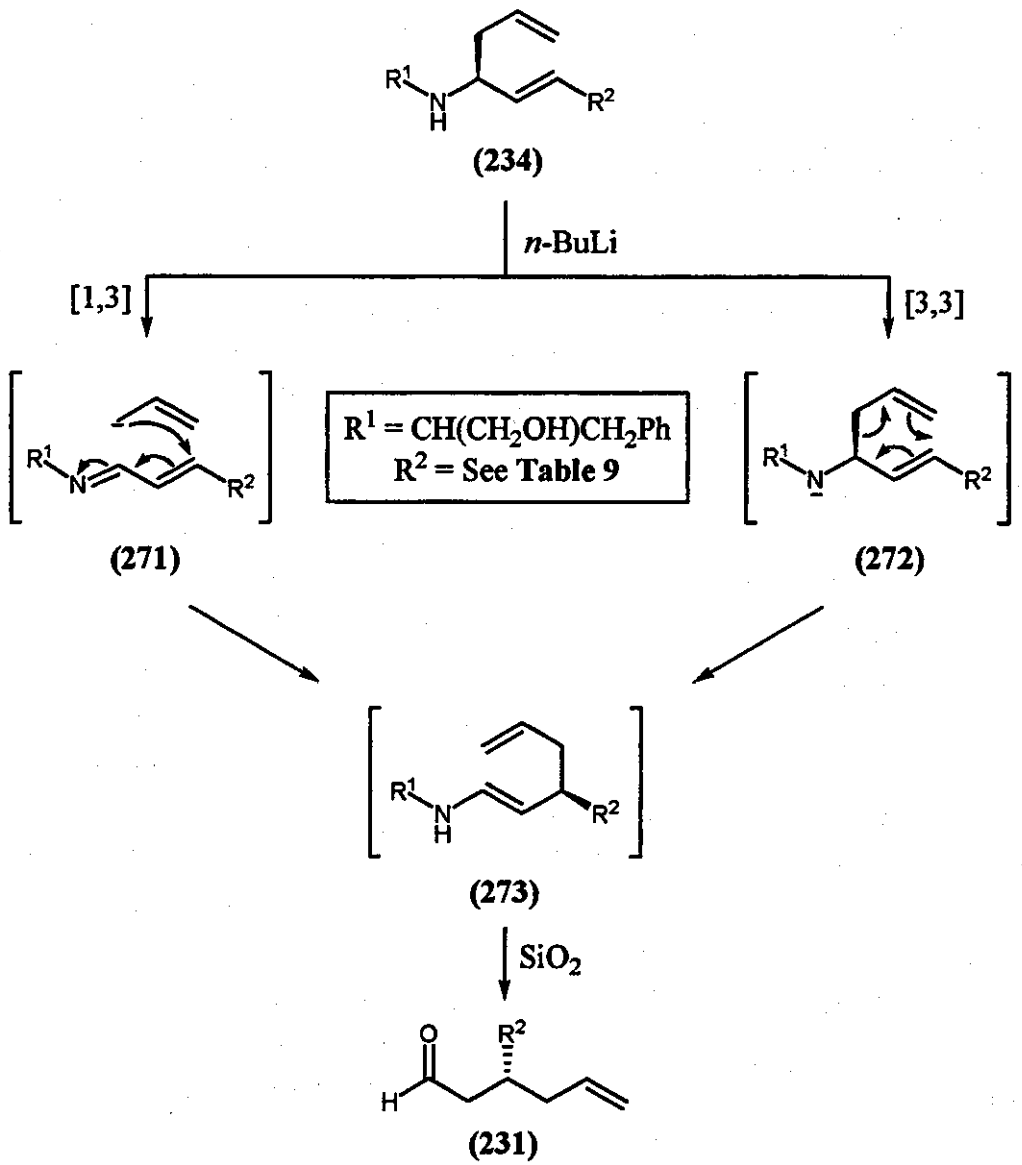


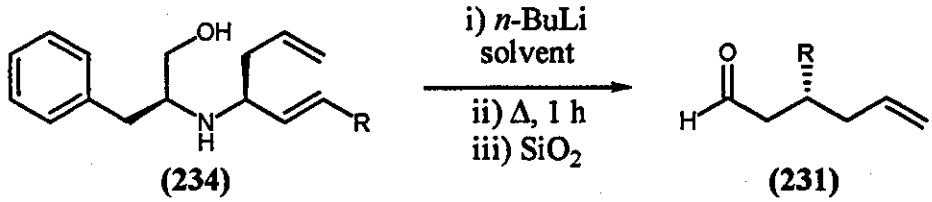
Figure 27

The effect of different substituents at C-1 (R^2) was also investigated, as previous studies by the Allin group[132,133] on the anionic amino-Cope rearrangement had only used cinnamyl derivatives **(234a)** (R^2 = Ph) as substrates. It is known[143] that substitution can

alter a reaction mechanism when there are two or more possible pathways separated by only a small energy gap, as in the case of the anionic amino-Cope rearrangement.

The aim of our study was to find the optimal conditions for a highly enantioselective anionic amino-Cope rearrangement, eliminating - or at least minimising - the competing fragmentation/recombination mechanism.

The 3-amino-1,5-dienes **(234a-c,f-i)** **(Scheme 89)** were dissolved in the appropriate solvent, 2.5 equivalents of *n*-BuLi were added and the reaction mixtures refluxed for 1 h. Over two equivalents of the base were required due to the presence of the hydroxy group.



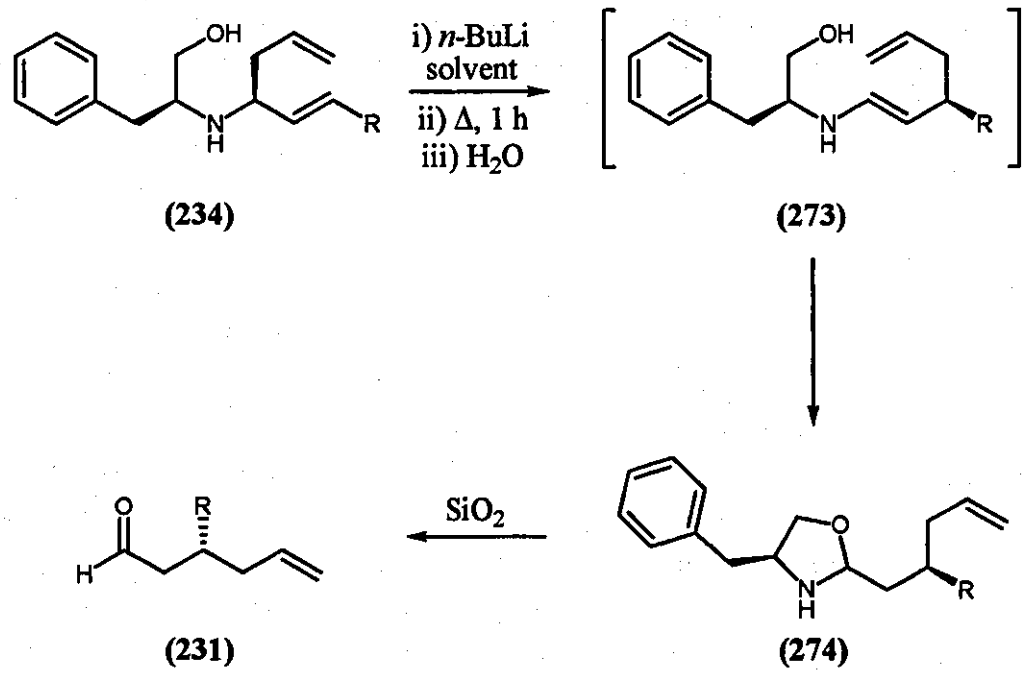
(234) **(231)**

R = see **Table 9**

Scheme 89

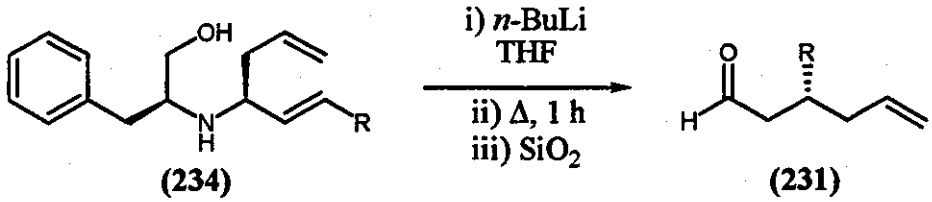
The anionic amino-Cope rearrangements were successfully conducted when *n*-BuLi was used as a base. In contrast, the use of potassium hydride, LDA, LHMDS, KHMDS, or NHMDS[115] and our own attempts using KHMDS and 18-crown-6 (typical base/additive for the oxy-Cope rearrangement[92]) or NaH resulted in isolation of starting material.

Upon rearrangement, the ^{1}H NMR spectrum of the crude reaction mixture suggested that the oxazolidine **(274)** **(Scheme 90)** had formed from ring closure of the hydroxy substituent of **(273)** onto the imine/enamine group. This imine-oxazolidine tautomerism has been previously observed by others[129,130] **(Section 2.1.2.2)**. Flash column chromatography hydrolysed the oxazolidine **(274)** to yield the aldehyde **(231)**.



Scheme 90

The rearrangements of substrates **(234a-c,f-i)** were initially conducted in tetrahydrofuran **(Scheme 91)**, as polar aprotic solvents are known to decrease the association between the cation and the anion in anionic oxy-Cope rearrangements and therefore increase the reaction rate.[99]



R = see **Table 9**

Scheme 91

The rearrangements were carried out with a varied range of success as highlighted in **Table 9.**

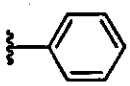
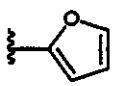
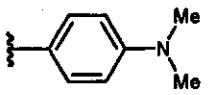
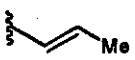
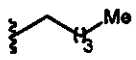
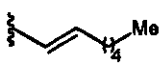
Rearrangements in THF			
Product	**R**	**Yield (%)**	***e.e.* (%)**
(231a)		69	*84*
(231b)		53	*67*
(231c)		65	*76*
(231f)		Unsuccessful	
(231g)		35	*44*
(231h)		20	*57*
(231i)		54	*70*

Table 9

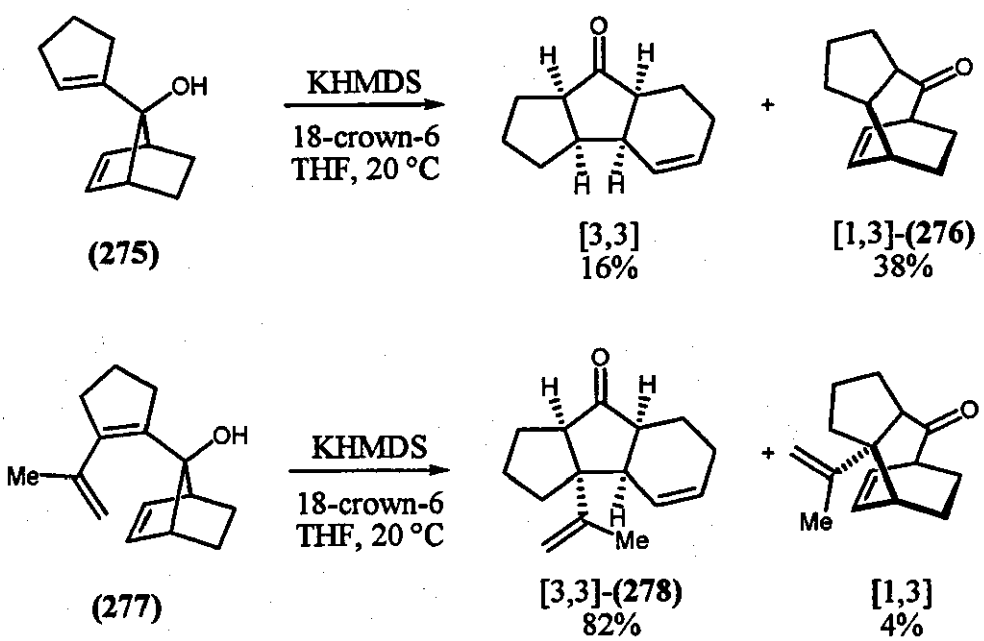
The aldehydes **(231a-c,g-i)** were generated with different enantiomeric excesses, ranging from 84% for **(231a)** to 44% for **(231g)**. These results suggest that a fragmentation/recombination mechanism (in addition to a concerted process) is taking place, since the enantioselectivity of the anionic amino-Cope rearrangement should not be influenced by the substituents at C-1 of the 3-amino-1,5-dienes.

Unstable aldehyde products were obtained upon rearrangement of the substrates **(231g-i)**. In particular, generation of the aldehyde **(231g)** was extremely problematic due to its

high instability and the enantiomeric excess had to be measured immediately after isolation.

Despite several attempts, the aldehyde **(231f)** could not be generated by rearrangement of **(234f)**. The 3-amino-1,5-diene **(234f)** was dissolved in dry tetrahydrofuran, *n*-BuLi was added and the reaction mixture was refluxed. A colour change (from orange to dark brown) implied that the rearrangement had occurred. The reaction was quenched and the ^{1}H NMR spectrum of the crude reaction mixture suggested that the oxazolidine product had formed. However, only decomposed material could be isolated by flash column chromatography. The aldehyde **(231f)** was observed in the ^{1}H NMR spectrum when the crude reaction mixture was filtered through a small pad of silica. Unfortunately, the *e.e.* could not be measured due to the low purity of the compound.

Hanna[103] reported that anionic oxy-Cope rearrangements are favoured by an additional unsaturation, conjugated to the double bond of a 3-hydroxy-1,5-diene **(Section 1.8.1)**. Paquette[144] observed such a substituent effect on the anionic oxy-Cope rearrangement of the substrates **(275)** and **(277)** **(Scheme 92)**.



Scheme 92

The compound **(275)** generated the [1,3]-product **(276)** as the major component *via* a fragmentation/recombination pathway whereas, under the same reaction conditions, the substrate **(277)** almost exclusively underwent a concerted anionic oxy-Cope rearrangement to generate **(278)**.

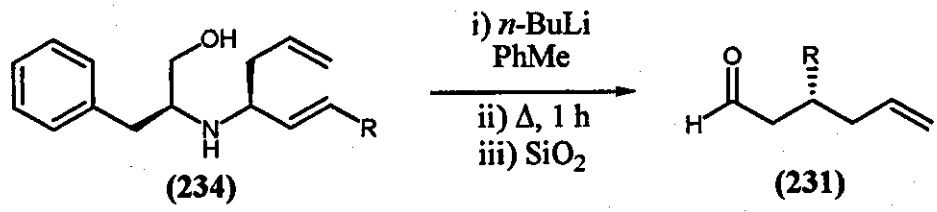
This effect was explained in terms of stabilisation of the concerted transition state by the additional unsaturation.[103]

The aldehyde **(231h)**, with a simple alkyl substituent was generated with the lowest yield. This substrate does not possess a conjugated diene and therefore its rearrangement would be less favoured than the rearrangements of **(234a-c,g,i)**, with aromatic and alkenyl substituents. This hypothesis could have been verified by rearrangement of **(231f)** (R = Me). Unfortunately, the aldehyde **(231f)** was extremely unstable and the yield and enantiomeric excess could not be measured.

In addition, compounds **(231a,c)**, with phenyl substituents, were generated with high and comparable yields and enantiomeric excesses. This could be due to an enhanced stabilising effect of the phenyl substituents on the concerted transition state, which would favour a [3,3]-sigmatropic pathway and hence increase the enantioselectivity of the reaction. The compound **(234b)** possesses a furan group as substituent which has less aromatic character than the phenyl groups of **(234a,c)**.[145] The furan group may not provide as great stabilisation of the concerted transition state and therefore generates **(231b)** in lower yield and *e.e.*

As highlighted in **Table 9**, the use of tetrahydrofuran does not always result in highly enantioselective rearrangements and a substituent effect appears to contribute to the outcome of the reaction. Macdonald,[120] observed that the use of non-polar solvents favoured a [3,3]-sigmatropic mechanism over the competitive fragmentation/recombination pathway. According to this observation, we expected higher enantiomeric excesses when reacting **(234a-c,g-i)** in toluene or hexane.

The rearrangements of **(234a-c,g-i)** **(Scheme 93)** were consequently carried out in refluxing toluene and the results are highlighted in **Table 10.**



(234) **(231)**

R = see **Table 10**

Scheme 93

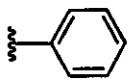
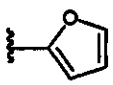
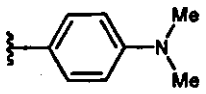
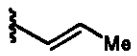
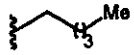
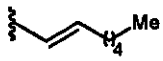
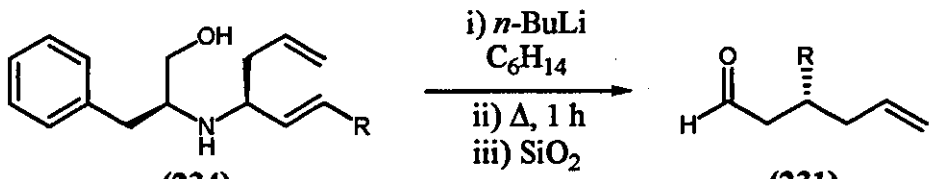
Rearrangements in Toluene			
Product	**R**	**Yield (%)**	***e.e.* (%)**
(231a)		69	*60*
(231b)		32	*56*
(231c)		59	*60*
(231g)		18	*36*
(231h)		14	*34*
(231i)		37	*67*

Table 10

Surprisingly, we observed that yields and enantiomeric excesses were decreased when substrates **(231a-c,g-i)** were rearranged in toluene. A [3,3]-sigmatropic rearrangement appears to be disfavoured and a higher participation of the stepwise mechanism would result in lower enantioselectivities. In addition, a [1,3]-shift could be taking place with a poor recombination of the molecule after fragmentation, which would contribute to a decrease in yield.[146]

The anionic amino-Cope rearrangements of the substrates **(234a-c,g-i)** were also conducted in hexane **(Scheme 94)**.



(234) **(231)**

R = see **Table 11**

Scheme 94

According to Macdonald,[120] the [3,3]-sigmatropic process should be clearly favoured in hexane and high enantioselectivities should therefore be expected upon rearrangement of our substrates. In contrast, a decrease in yield was observed with every substrate. In addition, the enantioselectivity was reduced in almost every case **(Table 11)**.

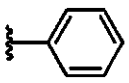
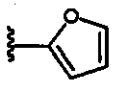
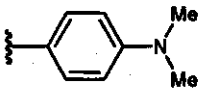
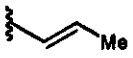
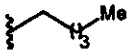
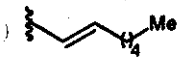
Rearrangements in Hexane			
Product	**R**	**Yield (%)**	***e.e.* (%)**
(231a)		44	*38*
(231b)		19	*52*
(231c)		53	*65*
(231g)		8	*55*
(231h)		8	*25*
(231i)		12	*62*

Table 11

Aldehyde **(231c)** was generated with the greatest yield and highest enantiomeric excess. This could be due to the presence of a dimethylamine substituent on the phenyl group. The aromatic substituent would be highly electron donating and this could favour a [3,3]-sigmatropic rearrangement over the stepwise mechanism.

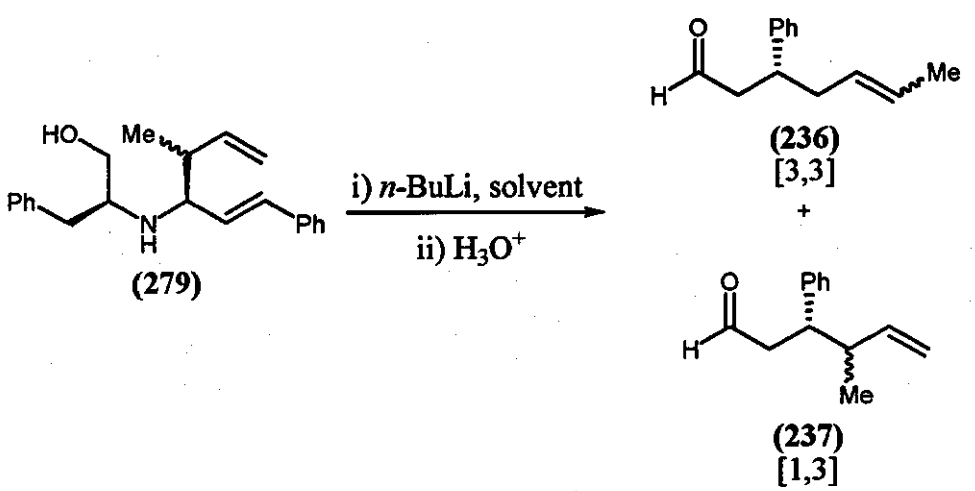
Low yields were obtained upon rearrangement of the aliphatic substrates **(231g-i)**. Starting materials, in addition to some decomposition product, were mainly recovered. Compound **(231i)** was, however, generated with a high *e.e.* The reason for this result is unknown and additional studies must be conducted.

The lowest yield and enantioselectivity were observed for aldehyde **(231h)**. As previously highlighted, the substrate **(234h)** does not possess a conjugated double bond within the 1,5-diene moiety that could favour a concerted process.

The aldehydes generated in low *e.e.* (presumably due to a cleavage/recombination mechanism being favoured) were also obtained in low yields. This fact could be explained by a poor recombination of the molecule after fragmentation, as highlighted by Houk and Paquette.[146]

In general, the enantioselectivity of the reaction was reduced when the polarity of the solvent was decreased. It is feasible that this is due to a favoured fragmentation/recombination pathway when a non-polar solvent is used.

A colleague[147] in the Allin group was concurrently investigating the rearrangement of substrate **(279)** **(Scheme 95)** in tetrahydrofuran, toluene and hexane **(Table 12)**. The presence of a methyl group in **(279)** enabled the differentiation between the [3,3]-**(236)** and [1,3]-product **(237)**.



Scheme 95

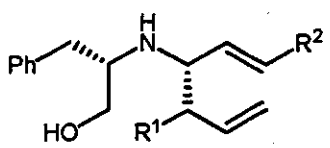
Solvent	(236)/(237)	*cis/trans*-(236)
THF	2/1	5/1
PhMe	1/2	1/1
C_6H_{14}	1/4	1/5

Table 12

In accordance with our own studies, the use of a polar solvent such as tetrahydrofuran increased the generation of the [3,3]-product **(236)**, whereas the use of a non-polar solvent (hexane) clearly favoured a dissociative process.

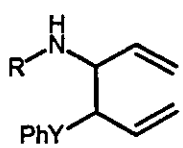
The results obtained in the Allin group for the rearrangement of **(234)** and **(279)** **(Figure 28)** are in conformity, although they are at odds with those reported by Macdonald for the rearrangement of **(221a)**.[120]

Allin's Substrates



(234) R^1 = H, R^2 = see **Table 11**
(279) R^1 = Me, R^2 = Ph

Macdonald's Substrates



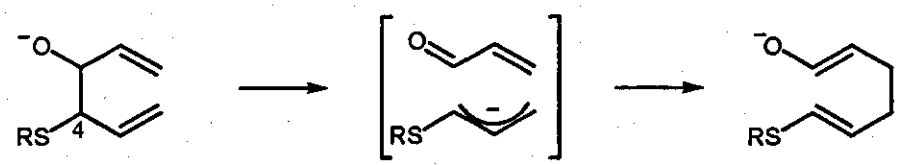
(221a) Y = S
(221b) Y = O

Figure 28

Macdonald observed a clear preference for a [3,3]-sigmatropic rearrangement of **(221a)** when a non-polar solvent (hexane) was used. In contrast, a [1,3]-process was favoured in tetrahydrofuran. We believe that the presence of a PhS group in **(221a)** has a great influence on the process, since compound **(221b)** underwent preferentially a sigmatropic process in tetrahydrofuran. In addition, the existence of a substituent at C-1 in our substrates **(234)** and **(279)** could also differentiate the behaviour of both types of molecules.

Several literature reports[146,148] refer to the effect of a sulphur substituent on the anionic oxy-Cope rearrangement.

Evans[148] observed that the anionic oxy-Cope rearrangements of 3-hydroxy-1,5-dienes with 4-thiophenoxy substituents **(280)** **(Scheme 96)** were subjected to large rate accelerations but fragmentation also occurred.



(280) R = Ph
(281) R = Me

(282)

(283)

Scheme 96

Houk and Paquette[146] concluded, using theoretical calculations, that the presence of a thiomethoxy substituent at C-4 on **(281)** accelerated the generation of **(283)** *via* a stepwise mechanism **(282)**. The presence of a thiomethoxy substituent on **(281)** decreases the activation energy of the reaction from 8.3 Kcal/mol for the parent anionic oxy-Cope rearrangement to 5-6 Kcal/mol. The length of the newly forming σ-bond was calculated to be 3.5 Å during the transition state, long enough that it is unlikely that any significant interaction between the termini occurred. The thiomethoxy substituent would stimulate cleavage and stabilise the allyl anion in **(282)**. In contrast, the presence of a methoxy group at C-4 was calculated to decelerate the process and promote a concerted mechanism.

Homolytic and heterolytic bond dissociations energies (BDE's) were calculated for thiomethoxy- and methoxy-substituted 3-hydroxy-1,5-hexadienes **(Table 13)**. As previously highlighted, the transition state of a concerted hetero-Cope rearrangement is considered to consist of two weakly interacting radicals and is favoured by a low homolytic bond dissociation. A low heterolytic bond dissociation energy would result in bond cleavage.

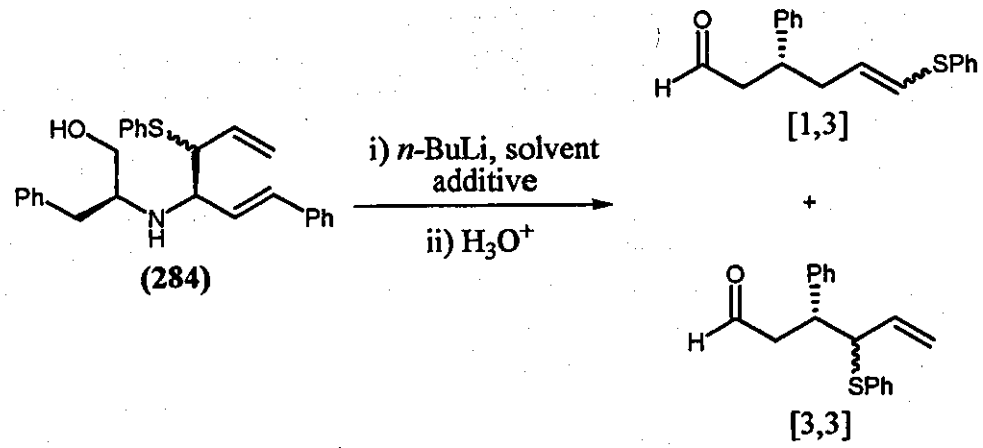
R	BDE's (Kcal/mol)		
	Homo	Hetero	Homo-Hetero
4-OMe SYN	19.4	23.4	- 4.0
4-OMe ANTI	19.6	23.7	- 4.1
4-SMe SYN	21.7	9.6	12.1
4-SMe ANTI	21.9	9.8	12.1

Table 13

The heterolytic BDE for the thiomethoxy-substituted substrate was 12.1 Kcal/mol lower than the homolytic BDE and therefore a stepwise mechanism would be favoured. It was concluded that the stabilising effect of the allyl anion by the RS substituent was caused by the polarisability of the R-S bond.[149] In contrast, a methoxy substituent would promote a concerted homolytic mechanism.

The sulphur anion on **(282) (Scheme 96)** would be more stabilised in a polar solvent and cleavage is therefore promoted. In a non-polar solvent, the weakly solvated metal cations will bind more strongly to the oxy-anion and rearrangement rather than cleavage would be favoured. These conclusions are in accordance with the experimental results obtained by Macdonald:[120] a thio-substituted substrate preferred a [1,3]-mechanism in a polar solvent such as tetrahydrofuran, whereas the oxy-substituted substrate preferentially underwent a concerted mechanism in every solvent.

Current work in our group targets the synthesis of compounds such as **(284) (Scheme 97)** in order to study the effect of a sulphur group on the anionic amino-Cope rearrangement.

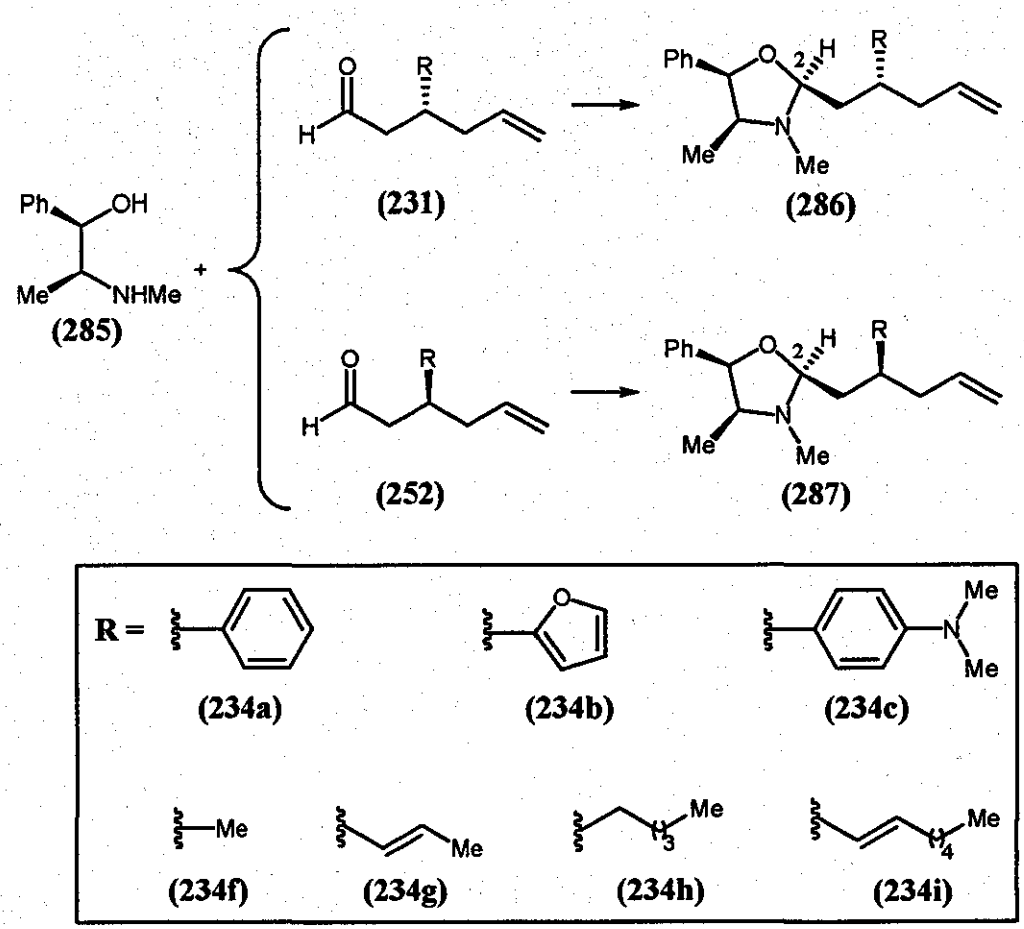


Scheme 97

2.1.2.5 Measurement of the Enantiomeric Excess

A literature procedure[150] was used to calculate the enantioselectivity of the anionic amino-Cope rearrangements and assign the absolute stereochemistry to the major enantiomer **(Scheme 98)**.

This method makes use of the stereoselective condensation of (1*R*,2*S*)-(-)-ephedrine **(285)** with the enantiomeric mixture of aldehydes **(231)** and **(252)** to generate a diastereomeric mixture of oxazolidines **(286)** and **(287)**. The *d.e.* of the oxazolidine mixture can be correlated to the enantiomeric excess of the aldehydes.



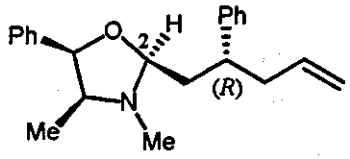
Scheme 98

The diastereomeric excess of the oxazolidines **(286)** and **(287)** (and therefore the enantiomeric excess of the aldehyde mixture) was calculated by integration of the proton signals at C-2 in the ^{1}H NMR spectrum of the crude reaction mixture.

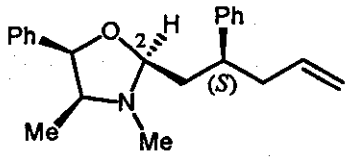
(-)-Ephedrine is a suitable derivatising agent for aldehydes, since very mild conditions (dichloromethane, molecular sieves and room temperature) are required for the synthesis of the oxazolidines.

Following this literature procedure, the aldehyde **(231a)** (with the minor enantiomer **(252a)**) was added to a solution of (-)-ephedrine in dry dichloromethane over molecular sieves. The accuracy of this method is highly dependant on the optical purity of the derivatising agent; (-)-ephedrine was purchased from Aldrich Chemical Co. Ltd., in 99% optical purity.

The reaction was stirred overnight and, upon filtration and solvent removal, a mixture of oxazolidines **(286a)** and **(287a)** **(Figure 29)** was obtained.



(286a)
$\delta_{lit} = 3.56$ ppm
$\delta_{exp} = 3.51$ppm

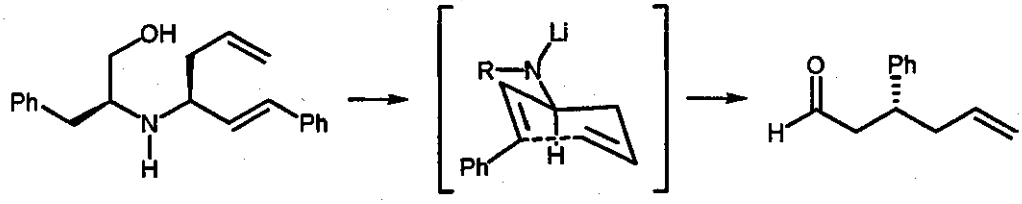


(287a)
$\delta_{lit} = 4.00$ ppm
$\delta_{exp} = 3.96$ ppm

Figure 29

The chemical shifts of the proton at C-2 for the oxazolidines **(286a)** and **(287a)** were in agreement with values reported by Agami[150] and the enantiomeric excess was calculated by measurement of the signal intensities. The larger peak (3.51 ppm) corresponded to the oxazolidine **(286a)** and therefore the (*R*)-configuration was assigned to the major enantiomer of the aldehyde mixture.

This result was in agreement with the transition state models proposed by Allin[116] for the anionic amino-Cope rearrangement **(Section 1.9.2)**, consisting of a chair-like conformation with the amine substituent in a *pseudo*-equatorial orientation **(233)** **(Figure 30)**.



(233)

Figure 30

In an analogous manner, the enantiomeric excess of the aldehydes **(231b,c,g-i)** was calculated by derivatisation with (-)-ephedrine and integration of the appropriate signals in the ^{1}H NMR spectra of the crude reaction mixtures.

Measurement of the enantiomeric excess of the aldehyde **(231g)** **(Figure 31)** was problematic, as an additional peak was observed in the ^{1}H NMR spectrum of the oxazolidine mixture. This peak corresponded to the oxazolidine obtained from aldehyde **(288)**. The latter compound had been generated from *trans,cis*-hexadienal **(244)**, a minor regioisomer present in the commercially available **(240g)**. This minor isomer could not be completely removed in any prior purification step **(Section 2.1.2.2** and **Section 2.1.2.3)**.

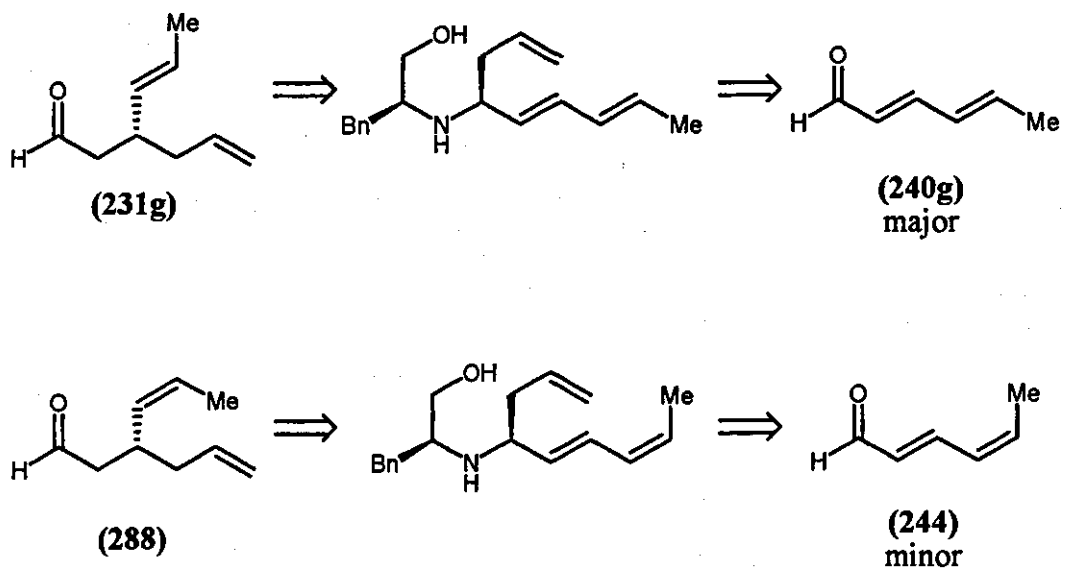
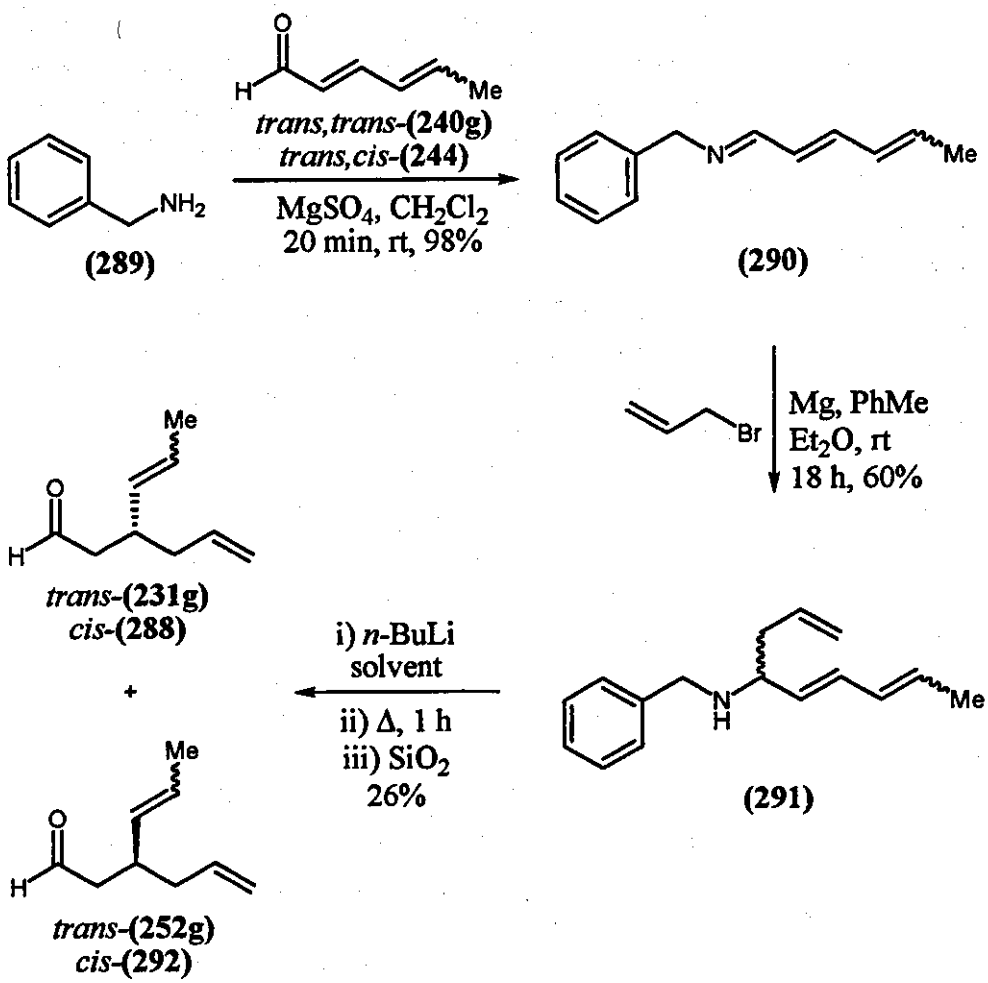


Figure 31

The synthesis of a racemic mixture of the aldehydes **(231g)** and **(252g)** **(Scheme 99)** enabled an accurate assignment of the ^{1}H NMR proton signals.



Scheme 99

Benzylamine **(289)** was reacted with *trans,trans*-hexadienal **(240g)** (containing the minor *trans,cis*-isomer **(244)**) and the imine **(290)** was generated in 98% yield. The latter compound was immediately reacted with allyl bromide and magnesium, and the 3-amino-1,5-diene **(291)** was obtained in 60% yield. The allyl addition was not diastereoselective due to the absence of a chiral auxiliary in **(290)**. A subsequent anionic amino-Cope rearrangement of **(291)** generated an isomeric mixture of aldehydes.

The aldehyde mixture was derivatised with (-)-ephedrine and the ^{1}H NMR spectrum of the crude reaction mixture indicated the presence of four oxazolidines (two major, derived from *trans*-**(231g)** and *trans*-**(252g)**, and two minor, derived form *cis*-**(288)** and *cis*-**(292)**. The ^{1}H NMR spectrum peaks with the lowest intensities corresponded to

aldehydes **(288)** and **(292)**, derived from **(244)** and were therefore discarded for the measurement of the enantiomeric excess.

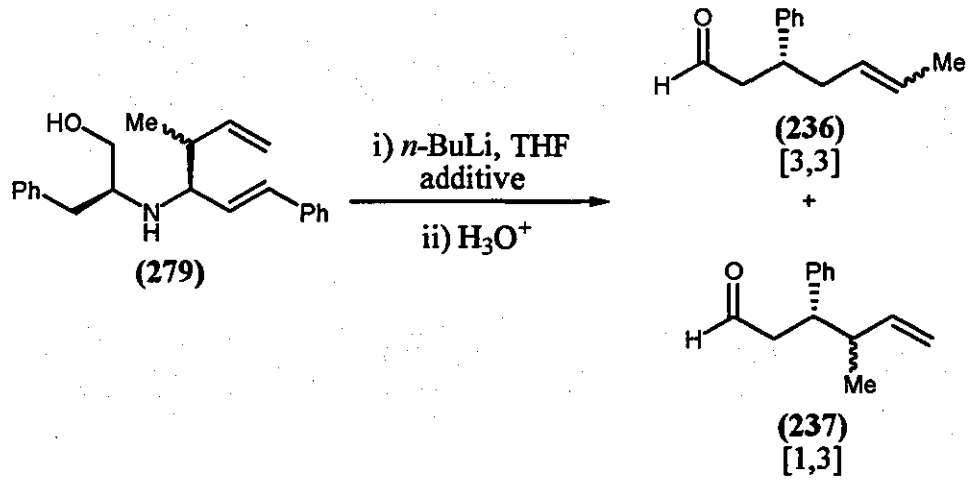
The signals of the protons at C-2 in the ^{1}H NMR spectrum of the oxazolidines **(286h)** and **(287h)** (R = C_5H_{11}) were seen to overlap and the enantiomeric excess of the corresponding aldehyde mixture could not be measured by integration of these peaks. Agami[150] indicated that the *e.e.* could also be calculated by integration of the corresponding peaks in a ^{13}C NMR spectrum. We observed a variation of 1-2% for the *e.e.*'s of aldehydes **(231a,c)** when they were measured by ^{1}H or ^{13}C NMR spectroscopy. The enantiomeric excess of **(231h)** was therefore calculated by integration of the peaks at 96.1 and 96.5 ppm on the ^{13}C NMR spectrum of the crude reaction mixture.

2.1.3 Use of Additives in the Anionic Amino-Cope Rearrangement

Previous studies on the anionic oxy-Cope rearrangement have demonstrated that the rearrangement is faster when the donor properties of the oxyanion are increased;[92] potassium salts are more reactive than sodium salts and the latter rearrange faster than lithium salts **(Section 1.8.1)**. The use of a complexing agent such as 18-crown-6 with potassium salts further enhances the rate of the reaction as the association between the oxyanion and the metal cation is decreased.[98]

The effect of lithium complexing agents on the anionic amino-Cope rearrangement has also been investigated. Macdonald[120] observed that the use of HMPA or TMEDA as co-solvent increased the solvent effect on the regioselectivity of the anionic amino-Cope rearrangement **(Section 2.1.2.4)**: the addition of TMEDA and HMPA increased the [1,3]/[3,3]-product ratio in tetrahydrofuran and the [3,3]/[1,3]-product ratio in hexane.

A colleague[147] in the Allin group studied the effect of several coordinative additives on the rearrangement of **(279)** **(Scheme 100** and **Table 14)**.



Scheme 100

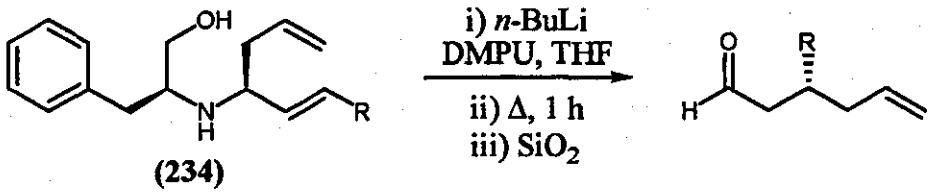
Solvent	Additive	(236)/(237)	*cis/trans*-(236)
THF	-	2/1	5/1
	TMEDA	2/1	5/1
	Sparteine	5/2	11/2
	DMPU	9/1	5/1

Table 14

Although the addition of TMEDA or (-)-sparteine did not have a major effect on the mechanism of the reaction (minor variation of the **(236)/(237)** ratio), the use of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) significantly increased the generation of the [3,3]-product **(236)**.

DMPU has been reported to alter the reactivity and stereoselectivity of organolithium reactions.[152,153] It has proven to be an effective substituent for the highly carcinogenic HMPA,[151,152] is compatible with highly nucleophilic and basic reagents and can be employed at dry ice temperature or below.[154]

We decided to investigate the effect of DMPU with three of our substrates (**Scheme 101** and **Table 15**): our previously favoured model **(234a)**, the furan derivative **(234b)** since this gave the lowest enantiomeric excess among the aromatic substituents and **(234g)**, the substrate that gave the lowest *e.e.* of all.



(234)

R = see **Table 15**

Scheme 101

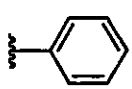
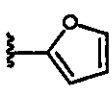
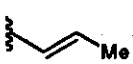
Product	R	DMPU							
		10 eq		5 eq		2.5 eq		0 eq	
		Yield (%)	*e.e.* (%)	Yield (%)	*e.e.* (%)	Yield (%)	*e.e.* (%)	Yield (%)	*e.e.* (%)
(231a)		6	*84*	29	*86*	50	*89*	69	*84*
(231b)		11	*74*	32	*82*	41	*82*	53	*67*
(231g)		8	*72*	10	*82*	18	*85*	35	*44*

Table 15

We expected an improvement in the enantioselectivity when DMPU was used, as a [3,3]-sigmatropic rearrangement should be favoured.

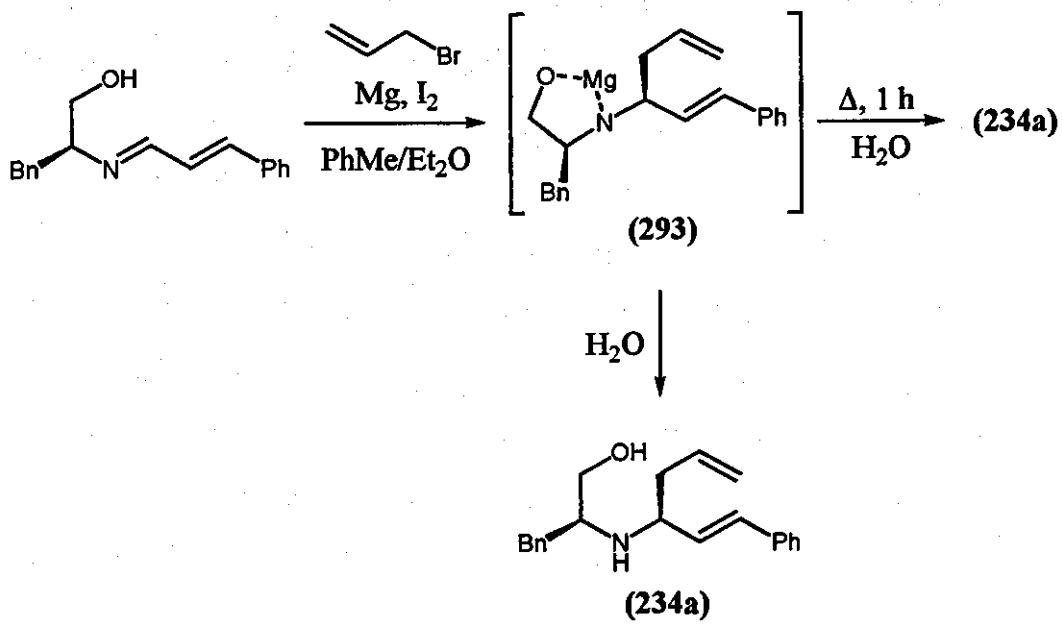
Ten equivalents of DMPU were initially utilised and, although a substantial increase in the *e.e.* was observed, the yields of the reactions were considerably reduced. The reason for the low yields is not clear, but it should be noted that, although DMPU is remarkably unreactive, it can react vigorously with a hexane solution of butyllithium at -78 °C if a more reactive species is not present.[153] The decrease in yield could be due to a competitive reaction of *n*-BuLi with DMPU.

When using an equimolar amount of DMPU and *n*-BuLi (2.5 equivalents), high and comparable enantiomeric excesses were observed for the three substrates. The yields were slightly lower that those obtained when the coordinative additive was absent from the reaction mixture.

The *e.e.* increase of the anionic amino-Cope rearrangement with DMPU could be due to a rate enhancement of the [3,3]-sigmatropic mechanism due to an increase of the donor properties of the nitrogen anion.[92] As **Table 15** indicates, high enantioselectivities were observed when DMPU was used with each substrate: the possible effect of the substituent at C-1 was diminished.

2.1.4 One-Pot Grignard Addition/Sigmatropic Rearrangement

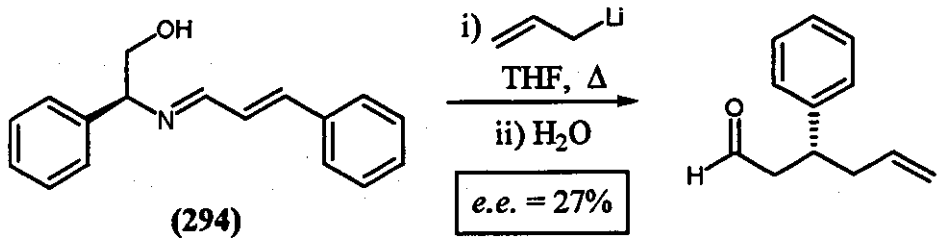
The anionic amino-Cope rearrangement of the substrate **(234a)** **(Scheme 102)** only occurs when the latter compound is deprotonated with *n*-BuLi and subsequently refluxed. However, no rearrangement has been observed during the synthesis of **(234a)** **(Section 2.1.2.3)** although, upon allylation and before water quench, a deprotonated 3-amino-1,5-diene **(293)** was generated. Even when **(293)** was refluxed, no rearrangement was observed.



Scheme 102

A feasible explanation for the lack of rearrangement is that the charge on both of the heteroatoms in **(293)** is highly delocalised by the coordinating Grignard counter-ion and an additional reaction cannot occur.

Previous workers[133] in the Allin group attempted a one-pot allylation/amino-Cope rearrangement by using an organolithium reagent during allylation of **(294)** **(Scheme 103)**.



Scheme 103

The enantioselectivity of the process was disappointingly low. Two possible reaction pathways were proposed: a poorly stereoselective 1,2-addition of the allyl group to form

(295) (**Figure 32**) and subsequent amino-Cope rearrangement or a 1,4-addition to generate (**296**) and subsequent hydrolysis into (**231a**).

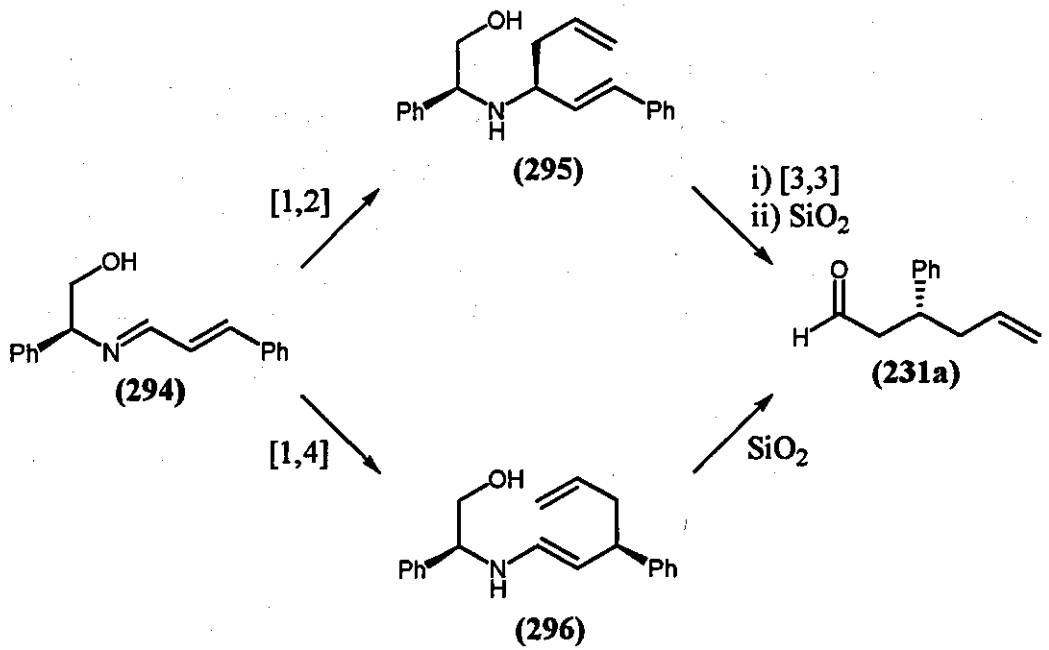
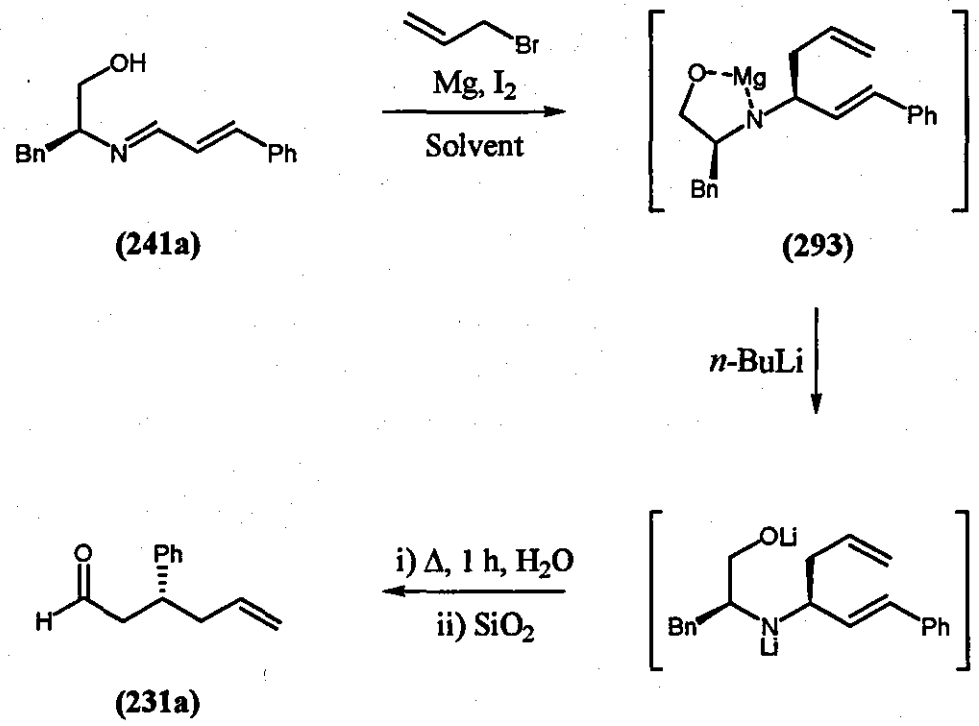


Figure 32

We decided to conduct the one-pot procedure following an alternative method: allylation of (**241a**) (**Scheme 104**) *via* the Grignard addition described in **Section 2.1.2.3** to generate (**293**), subsequent transmetallation (magnesium-lithium) and reflux in order to promote rearrangement. The reaction was conducted in two different solvent systems: tetrahydrofuran, which gives the best yield/enantiomeric excesses for the anionic amino-Cope rearrangement, and toluene/ether, which is the optimal solvent system for the Grignard addition (**Table 16**).



(241a) **(293)** **(231a)**

Scheme 104

Solvent	One-pot		Stepwise	
	Yield (%)	*e.e.* (%)	Yield (%)	*e.e.* (%)
THF	25	*56*	55	*82*
Toluene/Ether	10	*58*	55	*60*

Table 16

We were pleased to observe that the aldehyde **(231a)** was generated upon transmetallation of the magnesium cation with lithium. The enantiomeric excess obtained when the reaction was conducted in tetrahydrofuran was lower than when allylation and rearrangement were conducted as separate steps **(Table 16)**. We believe that the low *e.e.* was due to a poor diastereoselectivity of the Grignard addition in tetrahydrofuran, as previously observed by others[133] **(Section 2.1.2.3)**.

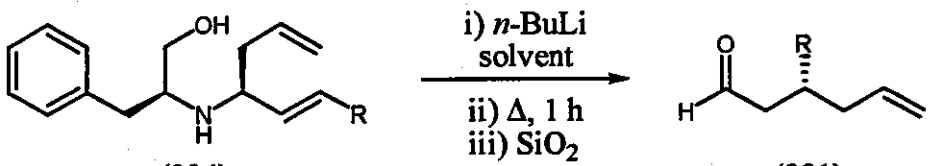
When a 4:1 mixture of toluene/ether was used as a solvent system the *e.e.* was comparable to that obtained when the 3-amino-1,5-diene was isolated and subsequently rearranged in toluene.

The yields of the reactions were disappointingly low and further studies must be conducted in order to find optimal conditions for the one-pot methodology

2.1.5 Conclusions and Final Remarks

Several literature reports[113,119-122] have highlighted the existence of a competitive, less stereoselective fragmentation/recombination mechanism in the anionic amino-Cope rearrangement.

We have rearranged a novel range of 3-amino-1,5-dienes **(234)** **(Scheme 105)** and investigated the solvent and substituent effect on the reaction enantioselectivity.



(234) **(231)**

Scheme 105

We have demonstrated that the anionic amino-Cope rearrangement is not always highly enantioselective and that the R substituent at C-1 in the 3-amino-1,5-diene **(234)** affects the reaction enantioselectivity. The nature of the R substituent presumably alters the ratio of the concerted /stepwise processes.

In addition, we have observed that the use of a polar aprotic solvent such as tetrahydrofuran favours an enantioselective rearrangement. In contrast, non-polar

solvents dramatically decrease both the yield and *e.e.* probably due to a fragmentation/recombination pathway being favoured.

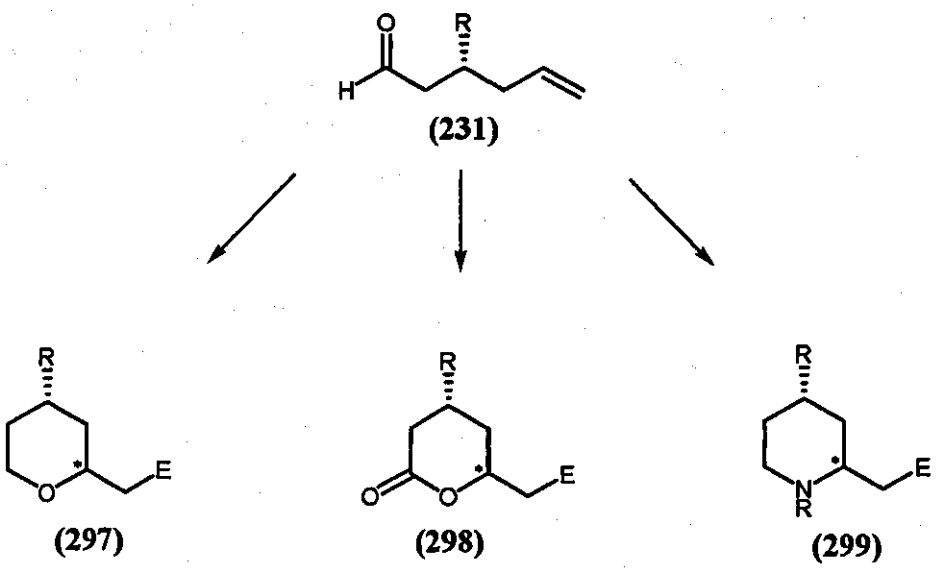
Interestingly, other groups[120] have observed that the presence of sulphur substituents at C-4 in a 3-amino-1,5-diene results in a increase of the stepwise mechanism when the reaction is conducted in a polar solvent. In this instance, hexane is the solvent of choice since the concerted process is clearly favoured.

We have also demonstrated that the unwanted substituent effect can be reduced by the use of DMPU as co-solvent. An optimal solvent system of THF/DMPU produces high and comparable levels of enantiomeric excess (82-89%) for substrates bearing an alkyl or aryl substituent at C-1, making the anionic amino-Cope rearrangement a general useful tool in asymmetric synthesis.

In addition, we have observed that a one-pot Grignard addition/sigmatropic rearrangement can be feasible and, although optimal conditions must be investigated, this could generate an asymmetric δ,ε-unsaturated aldehyde from inexpensive starting materials in a reduced number of steps.

2.2 Synthesis of Piperidines

Aldehydes such as **(231)** **(Figure 33)** are potentially excellent chiral building blocks for the synthesis of heterocycles such as tetrahydropyrans **(297)**, lactones **(298)** or piperidines **(299)**.

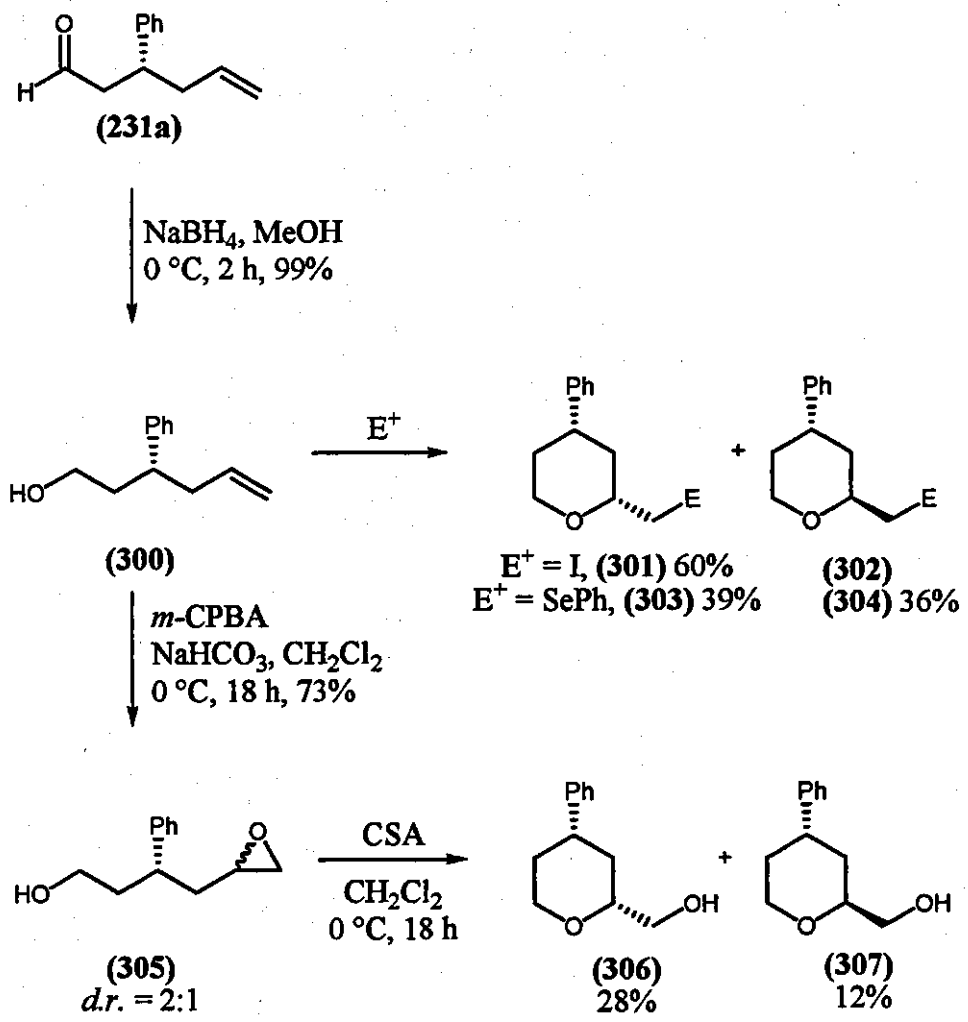


(231) **(297)** **(298)** **(299)**

Figure 33

An aldehyde such as **(231)**, product of the amino-Cope rearrangement, has been utilised by the Allin group to synthesise tetrahydropyrans[117] and lactones[117,118] following a procedure described by Greeves.[155,156]

The compound **(231a)** **(Scheme 106)** was reduced to the alcohol **(300)** using sodium borohydride. An iodine-induced cyclisation of **(300)** was conducted at room temperature and the iodo-tetrahydropyrans **(301)** and **(302)** were synthesised as a 4:1 mixture. The major isomer **(301)** was isolated in 60% yield after flash column chromatography.

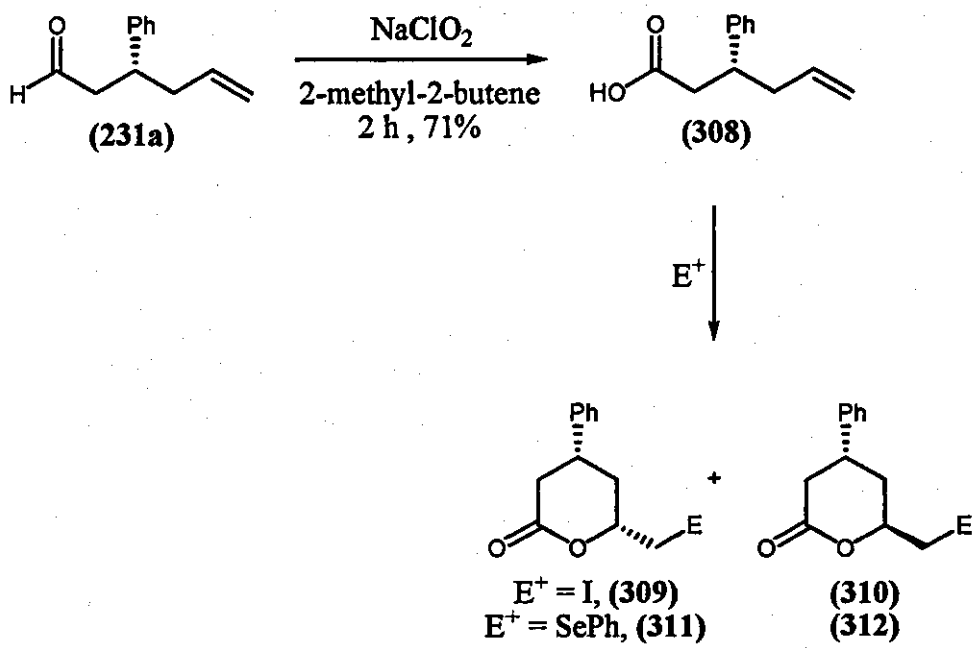


Scheme 106

Alternatively, *N*-(phenylseleno)phthalimide (NPSP) was used as an electrophile. The reaction was carried out in the presence of pyridinium *p*-toluenesulphonate (PPTS) in dichloromethane at -78 °C and a 1:1 diastereomeric mixture of **(303)** and **(304)** was obtained. The diastereoisomers were isolated in 39 and 36% yield respectively.

A third synthetic method involved the epoxidation of **(300)** by treatment with *meta*-chloroperoxybenzoic acid (*m*-CPBA). The resulting diastereomeric mixture of epoxides **(305)** was treated with a catalytic amount of camphor-10-sulphonic acid (CSA) in dichloromethane, which yielded the target tetrahydropyrans as a 2:1 mixture of **(306)** and **(307)**.

A similar approach has been utilised by the Allin group[118] to synthesise lactones **(Scheme 107)**.



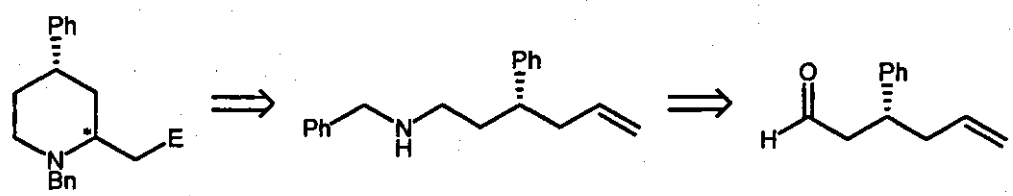
Scheme 107

The oxidation of **(231a)** yielded the carboxylic acid **(308)** in 71% yield. An iodine-induced cyclisation of **(308)** at -78 °C in tetrahydrofuran generated a 13:1 diastereomeric mixture of **(309)** and **(310)** in 70% overall yield. The major diastereoisomer **(309)** was shown to have 86% *e.e.* by chiral HPLC, confirming minimal loss of stereochemical integrity during the process.

The use of phenylselenyl chloride as an electrophile in the presence of pyridine generated a 3:1 mixture of **(311)** and **(312)** in 71% overall yield.

Following the successful synthesis of tetrahydropyrans and lactones, we attempted the generation of piperidines. Piperidine-derived heterocycles are ubiquitous structures in natural products. The synthesis of this type of compound is an attractive goal due to the wide range of biological activities associated with the piperidine moiety.[139,157]

Our initial approach for the synthesis of piperidines is highlighted in **Figure 34**.



(313) **(314)** **(231a)**

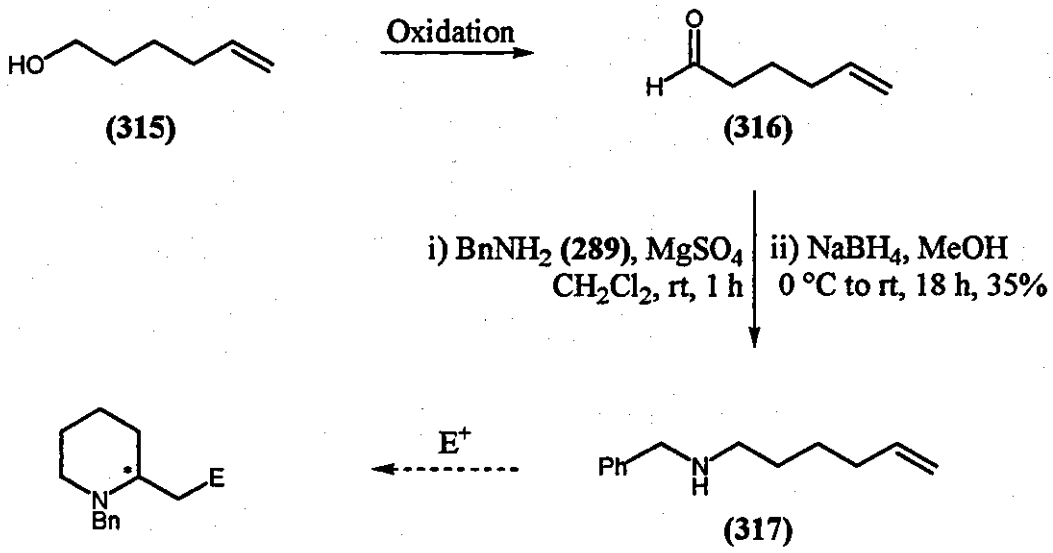
Figure 34

It was envisaged that the piperidine **(313)** could be synthesised *via* an electrophilic cyclisation of **(314)**. The latter compound could be generated by reductive amination of the aldehyde **(231a)** (product of the amino-Cope rearrangement).

We decided to conduct the initial cyclisations on a model system, which was primarily thought to be more accessible and cost-effective.

2.2.1 Synthesis of *N*-Benzylhex-5-en-1-amine

The initial approach towards the synthesis of the model system *N*-benzylhex-5-en-1-amine **(317)** is highlighted in **Scheme 108.**



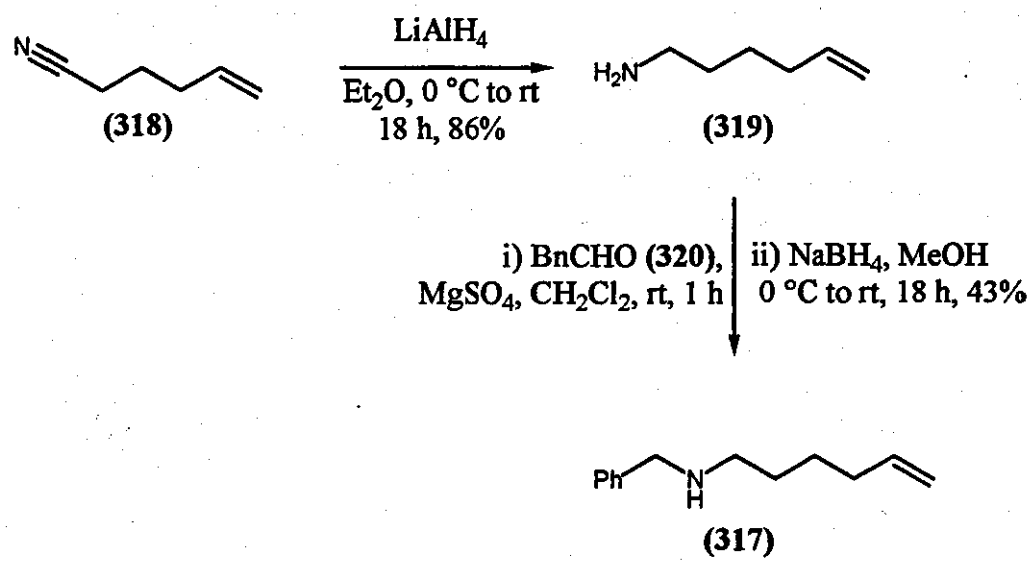
Scheme 108

Attempts to oxidise **(315)** to **(316)** were initially conducted using a Swern oxidation.[158] This procedure has been reported in the literature to yield **(316)** in 35[159] and 90%[160] yield. The substrate **(315)** was added to a solution of oxalyl chloride and dimethyl sulphoxide in dichloromethane at -78 °C. Addition of triethylamine and subsequent work-up generated the target aldehyde **(316)** as a yellow oil in 41% crude yield. Purification *via* flash column chromatography resulted in partial decomposition of the aldehyde. An alternative oxidative method was therefore investigated.

The use of tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) as an oxidative method for alcohols was first reported by Ley.[161] Solid TPAP was added to a solution of 5-hexenol **(315)**, NMO and powdered molecular sieves in dichloromethane. The reaction mixture was stirred for 3 hours, then filtered through a small pad of silica and the aldehyde **(316)** was obtained in 70% yield.

N-Benzylhex-5-en-1-amine **(317)** was generated by condensation of the aldehyde **(316)** with benzylamine **(289)** and subsequent reduction with sodium borohydride. The crude product was purified *via* flash column chromatography and the compound **(317)** was isolated in 35% yield. In order to obtain a more effective synthetic method, an alternative procedure was investigated.

N-Benzylhex-5-en-1-amine **(317)** was synthesised *via* a reductive alkylation of 5-hexenamine **(319)** **(Scheme 109)** with benzaldehyde **(320)**.

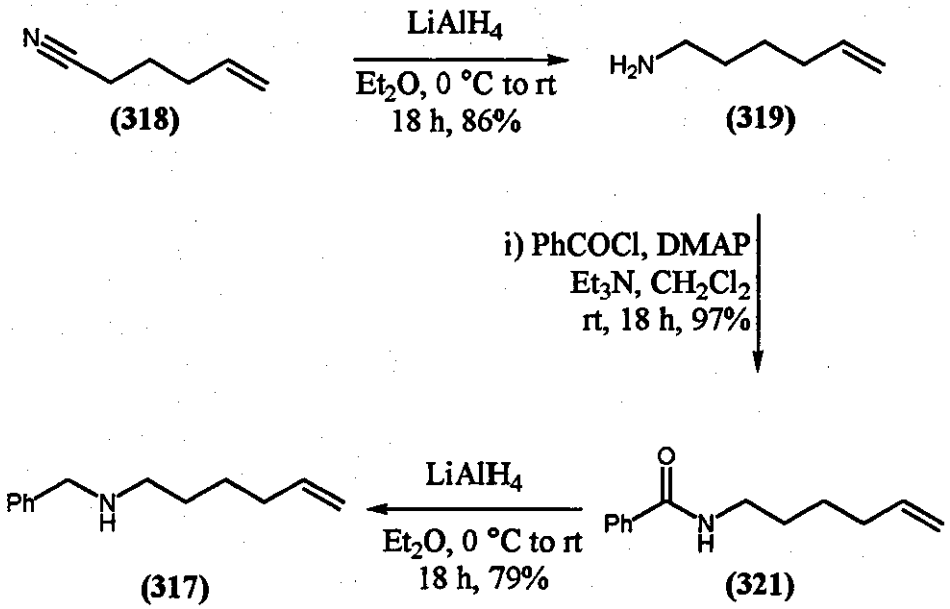


Scheme 109

The commercially available 5-hexenenitrile **(318)** was reduced to **(319)** with lithium aluminium hydride. One equivalent of the reducing agent was required in order to obtain a satisfactory yield, as previously observed by Nelson.[162] The reaction was carried out in dry diethyl ether for 18 h and a clean amine **(319)** was obtained in 86% yield. The latter compound was condensed with benzaldehyde **(320)** in dichloromethane and subsequently reduced with sodium borohydride to yield **(317)** in 43% yield.

Although the reason for the moderate yields for the generation of **(317)** is not clear, it must be highlighted that other groups[163] have reported analogous reactions in dry benzene, requiring more effective drying conditions during condensation (crushed 4Å molecular sieves) and longer periods of reaction time.

An alternative method was conducted following a procedure described by Carroll[164] **(Scheme 110)**.



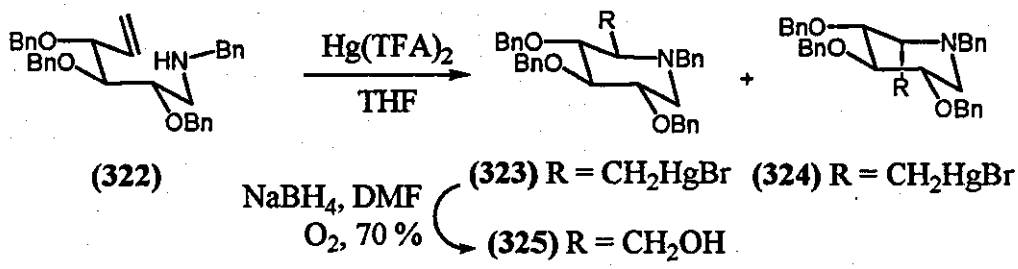
Scheme 110

Reduction of **(318)** using lithium aluminium hydride in diethyl ether, followed by benzoylation of **(319)** yielded **(321)**. The benzoylation was carried out in dichloromethane, using triethylamine and 4-dimethylaminopyridine (DMAP) as a catalytic agent. The reaction proceeded in excellent yield and a subsequent reduction of **(321)**, using lithium aluminium hydride, generated the target amine **(317)** in an overall yield of 66%.

2.2.2 Electrophilic Cyclisation of *N*-Benzylhex-5-en-1-amine

A variety of literature methods for the synthesis of piperidines *via* electrophilic cyclisation were investigated.

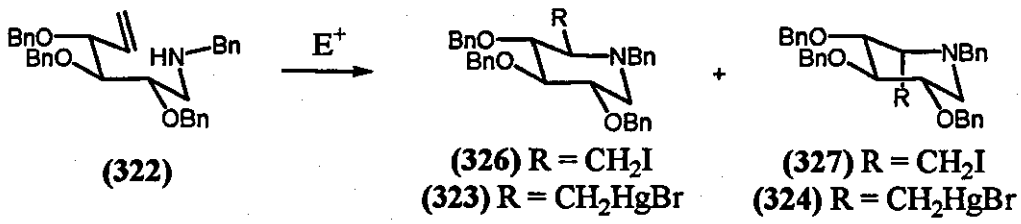
Ganem[165] reported an effective generation of piperidines *via* intramolecular aminomercuration of **(322)** **(Scheme 111)**.



Scheme 111

The cyclisation of **(322)** was conducted using mercuric trifluoroacetate in anhydrous tetrahydrofuran. The bromomercurials **(323)** and **(324)** were isolated in 61 and 39% yield after neutralisation, ligand exchange and flash column chromatography. The epimer **(323)** was converted into **(325)** by reductive oxygenation using sodium borohydride.

Hügel[166] performed alternative electrophilic cyclisations on **(322)** **(Scheme 112)**, the substrate previously utilised by Ganem.[165]



Scheme 112

Iodocyclisation of **(322)** in dry tetrahydrofuran resulted in the formation of the piperidines **(326)** and **(327)**, which were isolated in 59 and 35% yield **(Table 17)**.

Reaction Conditions	Yields (%) of products			
	(326)	(327)	(324)	(323) + (324)
I_2 (2.5 eq), $NaHCO_3$, THF	59	35	-	-
NIS (3.0 eq), THF	48[a]	29[a]	-	-
$Hg(OAc)_2$ (2.5 eq), THF	-	-	29	63[b]
$Hg(TFA)_2$ (1.1 eq), THF	-	-	-	74[b]
$Hg(TFA)_2$ (2.5 eq), THF	-	-	-	80[b]

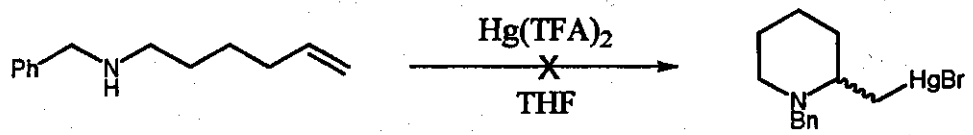
[a]Compound contaminated with succinimide; [b]Inseparable mixture of compounds

Table 17

The use of *N*-iodosuccinimide as an electrophile reduced the reaction yield and the products were contaminated with traces of succinimide. The use of 2.5 equivalents of mercuric acetate in tetrahydrofuran resulted in an optimal conversion and selectivity for **(324)** although the products were only partially separated. The use of Ganem conditions (1.1 eq of $Hg(TFA)_2$ in tetrahydrofuran) gave an inseparable mixture of isomers in 74% yield, where the diastereomeric ratio could not be measured. When an excess of trifluoroacetate was added, an enhanced overall yield (80%) was observed but the diastereomeric mixture of **(323)** and **(324)** (3:4) could not be separated.

An electrophilic cyclisation of **(322)** was also attempted using Br_2 and phenylselenyl chloride, but neither of these reagents generated any recognisable products.

Following the previously described methodologies, we initially reacted the secondary amine **(317)** **(Scheme 113)** with either 1.1 or 2.5 equivalents of mercury(II) trifluoroacetate in tetrahydrofuran.

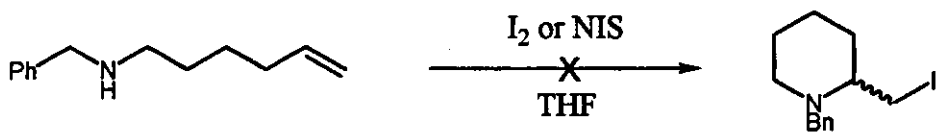


(317)

Scheme 113

Mercury(II) trifluoroacetate was dissolved in tetrahydrofuran and added to a stirred solution of **(317)** in tetrahydrofuran at room temperature. After 1 hour, thin layer chromatography of the reaction mixture indicated that a complex mixture of products had formed. A ^{1}H NMR spectrum of the crude reaction mixture suggested decomposition of the starting material. The reaction was conducted for shorter periods of time and monitored by TLC and ^{1}H NMR, but a complex mixture of compounds was persistently observed. Purification and isolation of the products proved to be impossible.

Due to the lack of success of the previously described procedure, alternative electrophiles (iodine and *N*-iodosuccinimide)[166] were investigated **(Scheme 114)**.



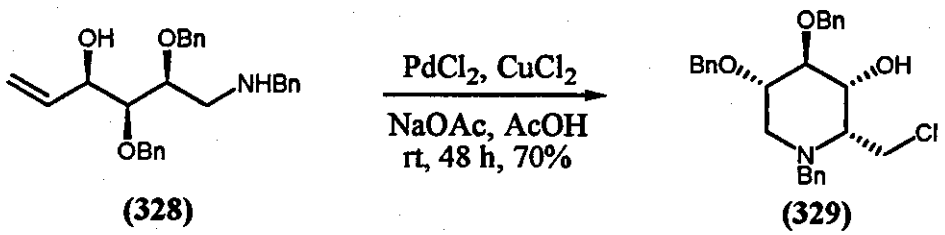
(317)

Scheme 114

An iodocyclisation of **(317)** was attempted at room temperature but, after 1 h, a ^{1}H NMR spectrum of the crude reaction mixture suggested decomposition of the starting material. The reaction was conducted in larger volumes of solvent and at 0 °C but only a mixture of unknown compounds was isolated. When the mixture was stirred at -78 °C, no reaction was observed and a complex mixture of compounds was formed when the temperature was increased.

The same procedure was conducted using *N*-iodosuccinimide as the electrophile but TLC and ^{1}H NMR spectrum of the crude reaction mixture indicated decomposition of the starting material.

An additional literature procedure was investigated; Gracza[167] reported a successful synthesis of **(329)** **(Scheme 115)** *via* a Pd(II)-catalysed cyclisation of **(328)**.

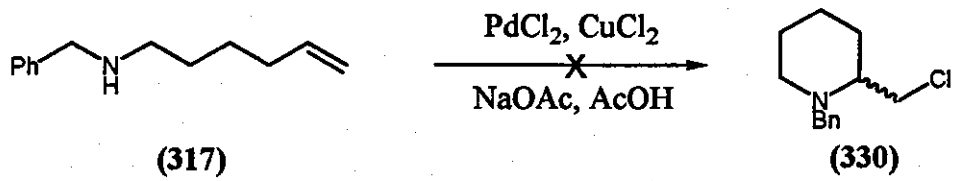


(328) **(329)**

Scheme 115

The compound **(328)** was reacted with a catalytic amount of palladium(II) chloride, copper chloride and sodium acetate in glacial acetic acid to yield the chlorinated piperidine **(329)** in 70% yield.

Following the reported experimental conditions, we attempted the cyclisation of substrate **(317)** **(Scheme 116)** to **(330)**.



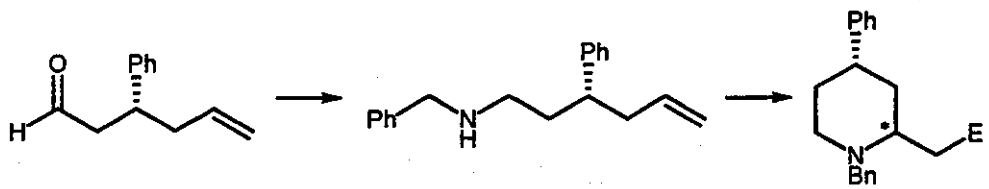
(317) **(330)**

Scheme 116

Despite several attempts at room temperature and 0 °C, only decomposition of the starting material was observed by ^{1}H NMR analysis of the crude reaction mixture.

2.2.3 Synthesis of (*R*)-*N*-Benzyl-3-phenylhex-5-en-1-amine

After the unsuccessful generation of a piperidine from *N*-benzylhex-5-en-1-amine **(317)** **(Scheme 116)**, we decided to attempt the previously described electrophilic cyclisations[165-167] on (*R*)-*N*-benzyl-3-phenylhex-5-en-1-amine **(314)** **(Figure 35)**. This substrate could be generated by reductive amination of **(231a)**, the product of the amino-Cope rearrangement.

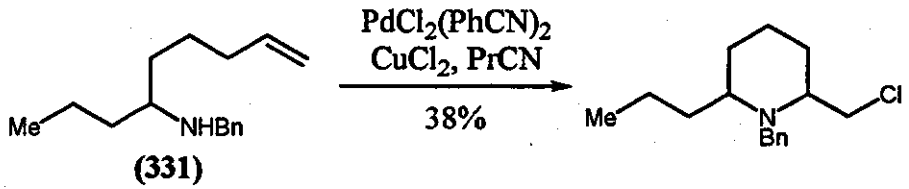


(231a) **(314)**

Figure 35

It was thought that the presence of a bulky substituent at C-3 in **(314)** would favour its cyclisation due to a change of conformation of the reacting substrate. The methods reported in the literature[165-167] used heavily substituted substrates. In addition, Toshimitsu[168] reported that the introduction of substituents into the carbon atoms between the double bond and the amide moiety on their substrates facilitated the cyclisation reaction.

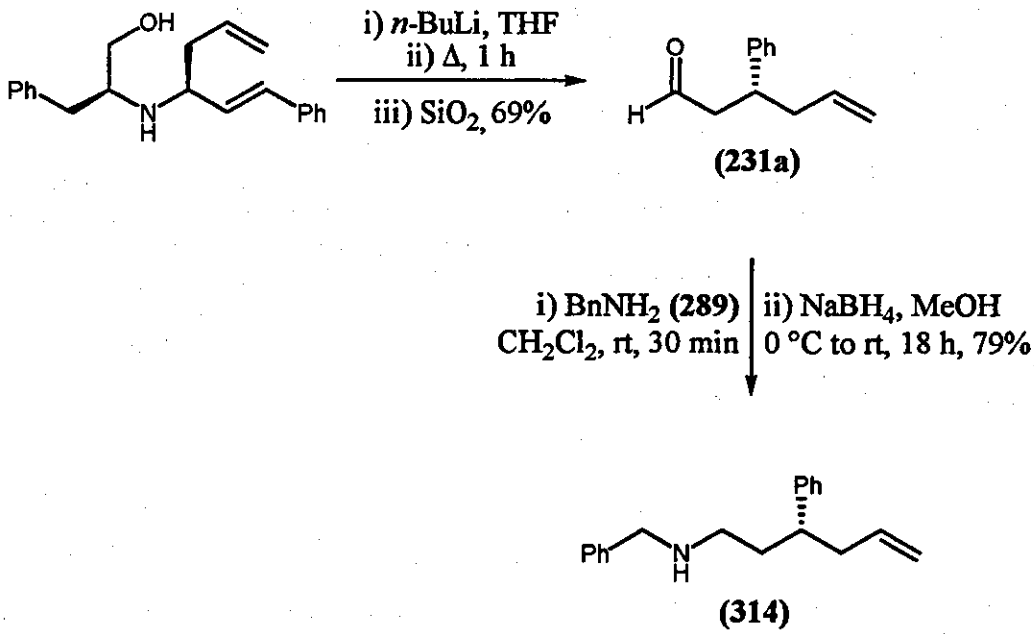
Only one example of an electrophilic cyclisation of a lightly substituted benzyl protected amine **(331)** **(Scheme 117)** has been encountered.[169] The reaction yield was low and no experimental conditions were reported.



(331)

Scheme 117

We generated the substrate **(314)** **(Scheme 118)** from the aldehyde **(231a)**, which was synthesised as reported in **Section 2.1.2**. The reactions were scaled-up and up to 2.5 g of **(231a)** were isolated without a substantial decrease in yield.

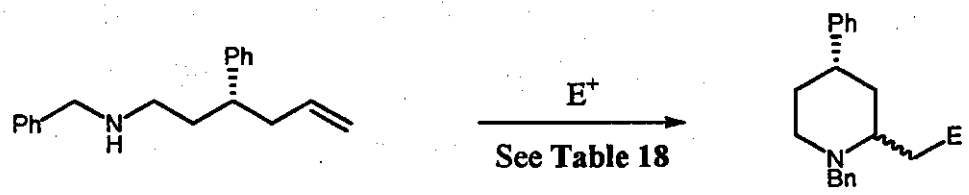


Scheme 118

The secondary amine **(314)** was synthesised by a reductive amination of the aldehyde **(231a)** with benzylamine **(289)** in 79% yield.

2.2.4 Electrophilic Cyclisations of (*R*)-*N*-Benzyl-3-phenylhex-5-en-1-amine

The amine **(314)** **(Scheme 119)** was reacted with mercury(II) trifluoroacetate, iodine and palladium(II) chloride following literature procedures[165-167] **(Table 18)**.



(314)

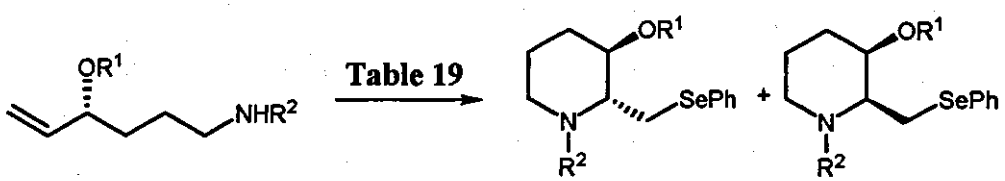
Scheme 119

Electrophile	Reaction Conditions	Product
$Hg(TFA)_2$	THF, rt or 0 °C	Decomposition of starting material
I_2	THF, rt or 0 °C	Decomposition of starting material
$PdCl_2$	AcOH, rt or 0 °C	Decomposition of starting material

Table 18

Disappointingly, both TLC and ^1H NMR spectra of the crude reaction mixtures indicated that a complex mixture of unknown compounds had formed. As a result of these findings an additional literature method was investigated.

Ward[170] successfully synthesised the hydroxypiperidines **(333)** and **(334)** **(Scheme 120)** in moderate yields and with good stereocontrol. These reactions were conducted using phenylselenyl halides in the presence of silica gel and anhydrous potassium carbonate as an acid trap[171] **(Table 19)**.



(332) (333) (334)

Scheme 120

Substrate	R^1	R^2	Reaction Conditions[a]	Yield (ratio (333):(334))
(332a)	H	CO_2Et	**a**, 48 h	57% (3:1)
(332a)	H	CO_2Et	**b**, 18 h	61% (5:1)
(332b)	H	CO_2t-Bu	**a** or **b**, 5 days	No reaction
(332c)	H	$SO_2C_6H_4Me$	**a**, 48 h	59% (3:1)
(332c)	H	$SO_2C_6H_4Me$	**b**, 18 h	58% (5:1)
(332d)	H	COMe	**a**, 48 h	41% (3:1)
(332e)	TBDPS	$SO_2C_6H_4Me$	**a**, 5 days	27% (3:1)

[a]Conditions **a**: PhSeCl, CH_2Cl_2, -78 °C, 10 min then rt; Conditions **b**: PhSeBr, $CHCl_3$, 0 °C, 10 min then rt

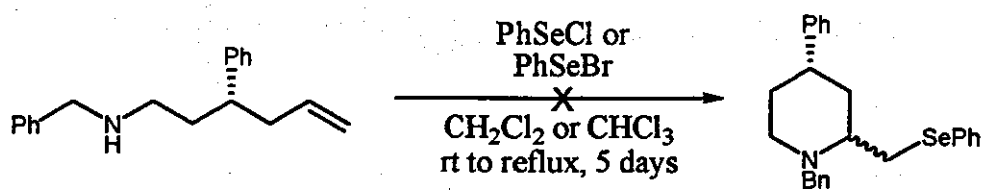
[b]Isolated yield. Product ratio determined by HPLC analysis

Table 19

The reactions highlighted in **Scheme 120** and **Table 19** were slow and under thermodynamic control. This was in direct contrast to the fast, kinetically controlled stereoselective electrophilic cyclisation of *N*-substituted pentenylamines to yield pyrrolidines.[172]

The Allin group has also reported the use of phenylseleno electrophiles for the synthesis of tetrahydropyrans[117,118] and lactones.[118] An advantage of this methodology is that the phenylseleno groups incorporated in the process allow a variety of modifications to be made to the product.[173]

We applied the previously described methodology to the electrophilic cyclisation of **(314) (Scheme 121)**.

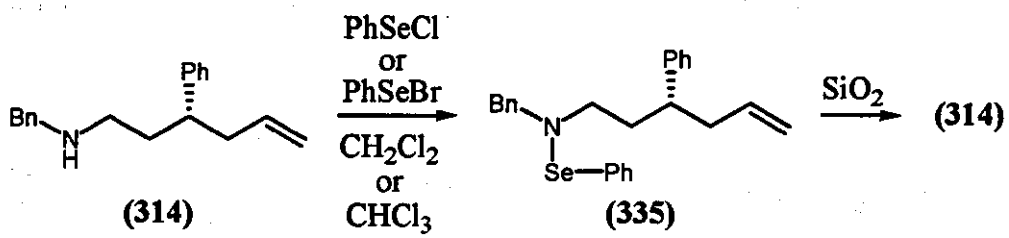


(314)

Scheme 121

The amine **(314)** was reacted with phenylselenyl chloride in dry dichloromethane or phenylselenyl bromide in chloroform at room temperature, following the experimental conditions described by Ward.[174] However, both TLC and ^{1}H NMR spectra of the crude reaction mixtures indicated that no reaction had occurred. The solutions were refluxed for up to 48 hours but only starting material was isolated.

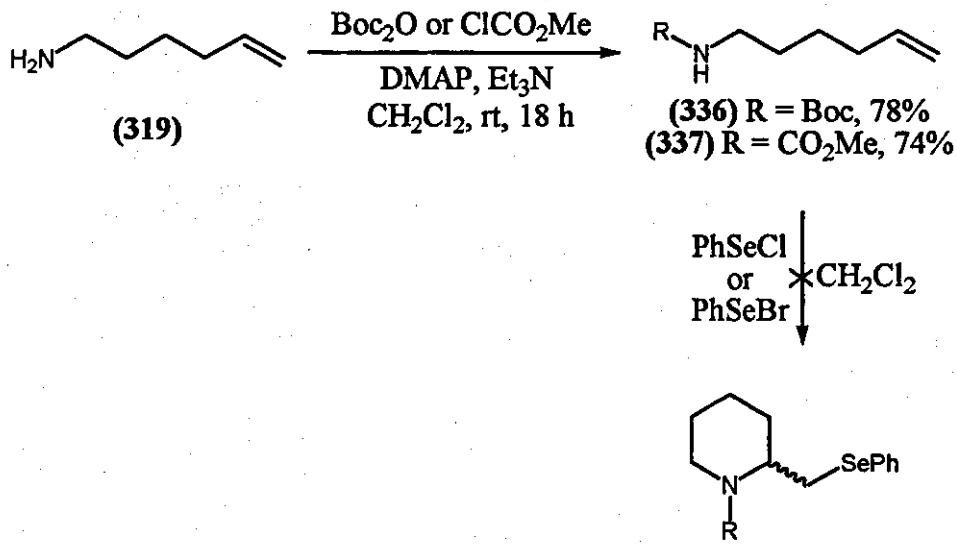
The desired transformation may not have proceeded due to a reaction of the phenylselenyl halides with the nitrogen atom, rather than with the alkene moiety.[169] Phenylselenyl chloride and phenylselenyl bromide can react with amines such as **(314)** to produce selenylamides **(335)** **(Scheme 122)**.[175] These compounds are easily hydrolysed and, in our case, only starting material was isolated.



(314) (335)

Scheme 122

Following this proposal, we conducted a model study on compounds **(336)** and **(337)** **(Scheme 123)**. These substrates posses an electron-withdrawing group attached to the nitrogen atom, reducing its nucleophilicity. In fact, many of the published electrophilic cyclisations[171,172,176,177] use electron withdrawing protecting groups for the amino moiety in order to favour the cyclisation process over the competing N-E^+ complexation.[178]

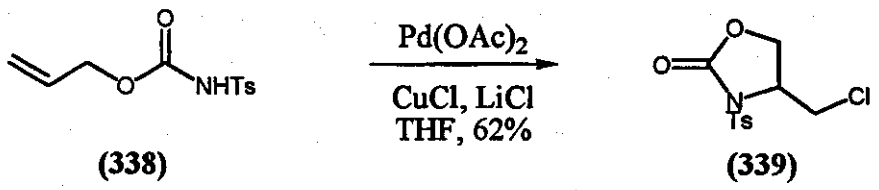


Scheme 123

The model substrates **(336)** and **(337)** were obtained by reaction of hexenamine **(319)** with di-*tert*-butyl dicarbonate or methyl chloroformate using triethylamine and 4-dimethylaminopyridine (DMAP) as a catalytic agent. The isolated products **(336)** and **(337)** were reacted with the phenylselenyl halides both at room temperature and at reflux. Unfortunately, only starting material was recovered.

These results are in accordance with work by Hügel[166] and Toshimitsu,[168] who reported unsuccessful cyclisations of *N*-protected hexenamines using selenium salts. Toshimitsu[168] reported the synthesis of a piperidine by electrophilic cyclisation using phenylselenyl iodide, but the yield was disappointingly low.

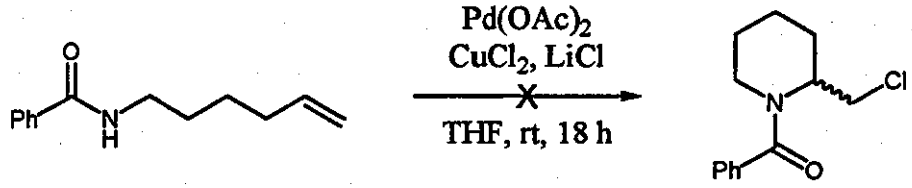
Lu[179] reported the generation of **(339)** **(Scheme 124)** *via* an electrophilic cyclisation of **(338)** with palladium acetate. This methodology was successfully applied to the synthesis of oxazolidinones by a co-worker in our laboratory.[180]



(338) (339)

Scheme 124

We attempted an electrophilic cyclisation of **(321)** **(Scheme 125)** following this procedure.



(321)

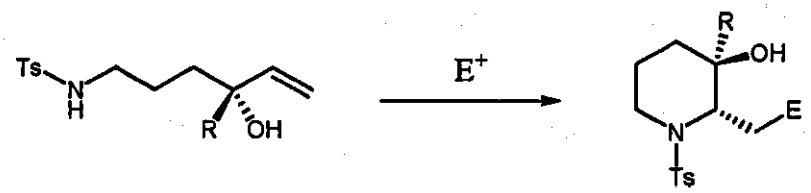
Scheme 125

The substrate **(321)**, generated as described in **Scheme 110 (Section 2.2.1)**, was dissolved in tetrahydrofuran at room temperature and palladium(II) acetate, copper(II) chloride and lithium chloride were added to the solution. The reaction was stirred overnight at room temperature but a ^{1}H NMR spectrum of the crude reaction mixture indicated that no reaction had occurred.

In general, *N*-substituted hexenylamines are much less reactive in comparison to pentenylamines[167,170] and only specific combinations of electrophiles/*N*-protecting groups tend to generate cyclised products.[181]

Tamaru[181,182] successfully synthesised pyrrolidines *via* electrophilic cyclisations of 3-hydroxy-4-pentenylamines. It was highlighted that the amino-cyclisations were strongly affected by the *N*-protecting group, the kind of electrophile and the steric environment in the transition state and in the product. When hexenylamine **(340)**

(Scheme 126) was reacted with electrophiles, all attempts of cyclisation into **(342)** were unsuccessful.



(340) R = H
(341) R = Me

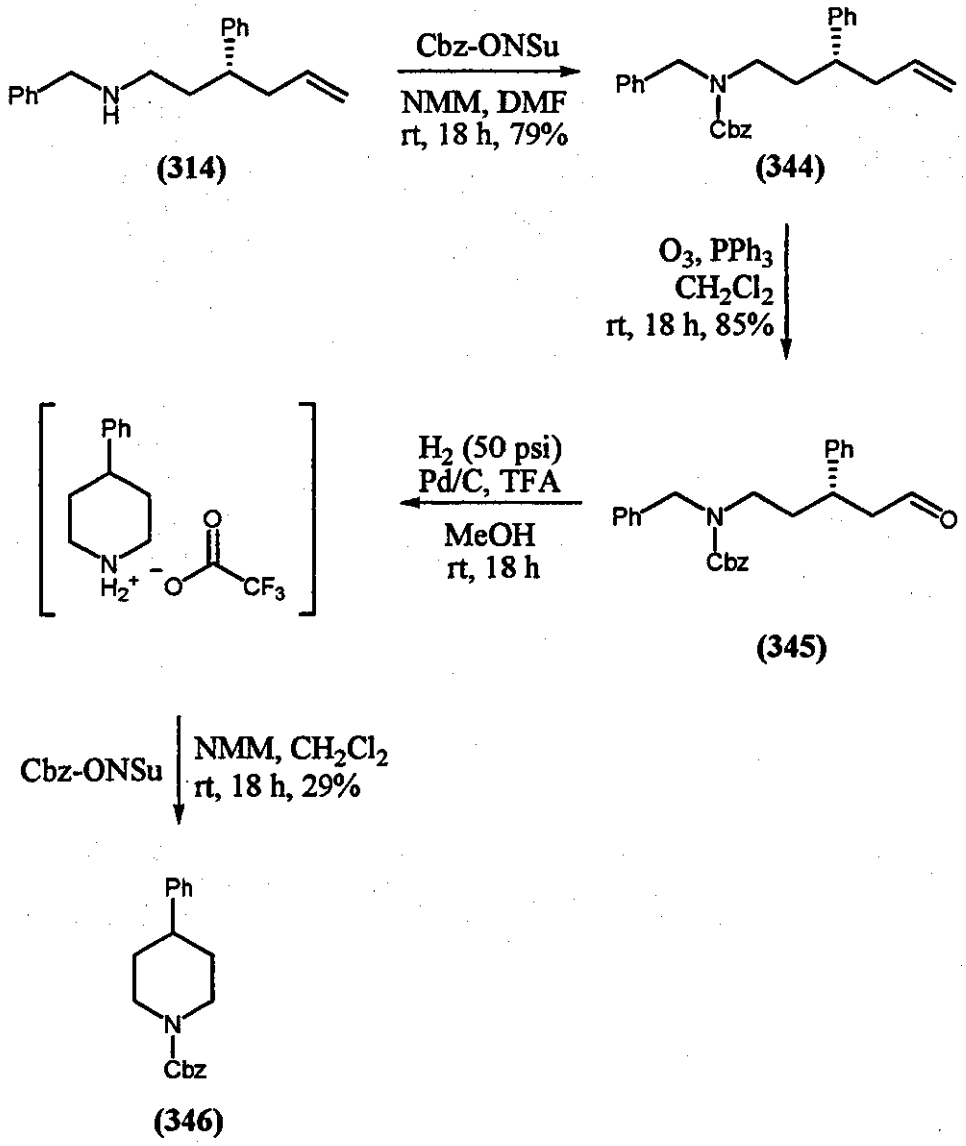
(342) R = H
(343) R = Me

Scheme 126

The use of *N*-bromosuccinimide (NBS) in dichloromethane or tetrahydrofuran generated at least seven or eight compounds that did not correspond to the cyclised product. All attempts to cyclise using iodine, *N*-iodosuccinimide (NIS), selenyl or mercury electrophiles resulted in the recovery of starting material. Only **(341)** (but not **(340)**) cleanly underwent cyclisation into **(343)** when using NBS in dry dichloromethane in the dark.

2.2.5 Successful Generation of a Piperidine

Due to the failure of the electrophilic cyclisation methodology, we investigated an alternative approach towards the synthesis of piperidines. An oxidative cleavage-cyclisation route was conducted, following the work described by Xue **(Scheme 127)**.[183]



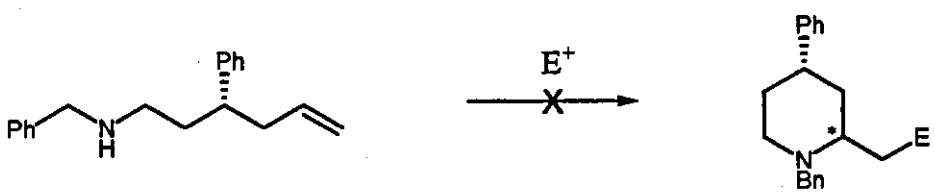
Scheme 127

The amine **(314)** was initially protected using *N*-(benzyloxycarbonyloxy)succinimide (Cbz-ONSu) with 4-methylmorpholine (NMM) in dimethylformamide. The product **(344)** was purified *via* flash column chromatography and reacted with ozone in dichloromethane. Triphenylphosphine was added and the reaction mixture was left to stir overnight. Following purification *via* flash column chromatography, the amino aldehyde **(345)** was obtained from **(344)** in 85% yield.

Hydrogenolysis of **(345)** at 50 psi and subsequent reaction with Cbz-ONSu and NMM in dimethylformamide produced the piperidine **(346)** in 29% overall yield.

2.2.6 Conclusions and Final Remarks

We have investigated the generation of a piperidine ring system from the aldehyde product of the anionic amino-Cope rearrangement. Our initial approach consisted of the generation of a secondary amine **(314)** **(Scheme 128)** and subsequent electrophilic cyclisation to generate **(313)**.



(314) **(313)**

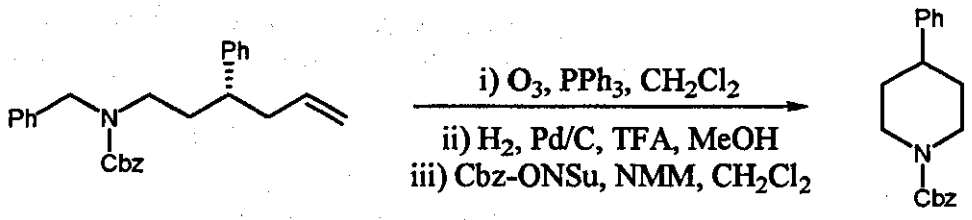
$E^+ = Hg(TFA)_2$, I_2, NIS, $PdCl_2$, PhSeCl, PhSeBr

Scheme 128

Several electrophiles were reacted with **(314)** but either a complex mixture of products or starting material were persistently isolated.

The difficulty in generating a piperidine ring *via* electrophilic cyclisation has been previously highlighted in the literature.[167,170,181,182] Only specific combinations of substrate/electrophile have succeeded in the synthesis of piperidines, in moderate to good yields.

An alternative procedure, by oxidative cleavage/cyclisation of **(344)** **(Scheme 129)** resulted in the successful generation of **(346)**.

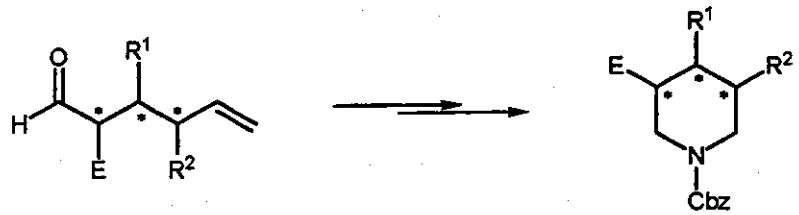


(344) **(346)**

Scheme 129

Although this method generated an achiral heterocycle (due to the plane of symmetry in **(346)**), we have demonstrated that piperidine rings can be obtained from simple products of the amino-Cope rearrangement.

An aldehyde such as **(347)** **(Scheme 130)** could be generated *via* an amino-Cope rearrangement/enamine derivatisation procedure (see **Future Work**). If the aldehyde **(347)** is used as a substrate in the route highlighted in **Scheme 129**, a piperidine **(348)** with up to three contiguous chiral centres could be generated.

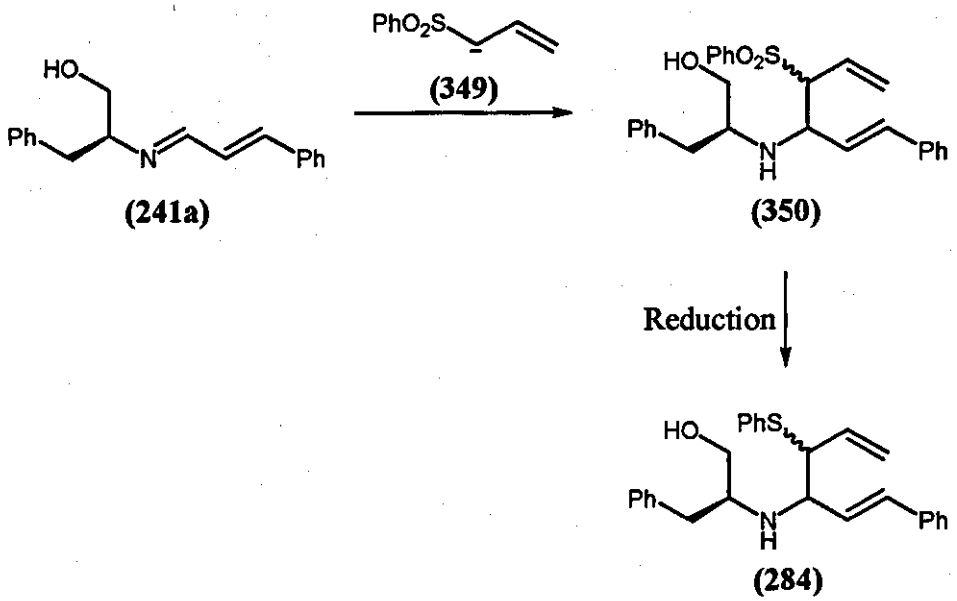


(347) **(348)**

Scheme 130

2.3 Future Work

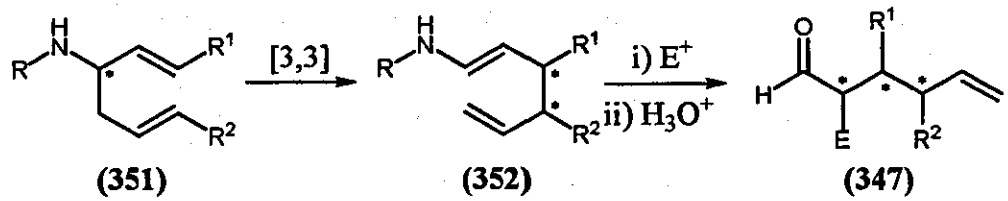
Future studies could focus on the generation of compounds such as **(284)** **(Scheme 131)** in order to investigate the effect of a sulphur substituent on the enantioselectivity of the anionic amino-Cope rearrangement.



Scheme 131

A feasible route toward the synthesis of **(284)** would be the reaction of **(241a)** with a deprotonated sulphone **(349)** followed by reduction of **(350)**.

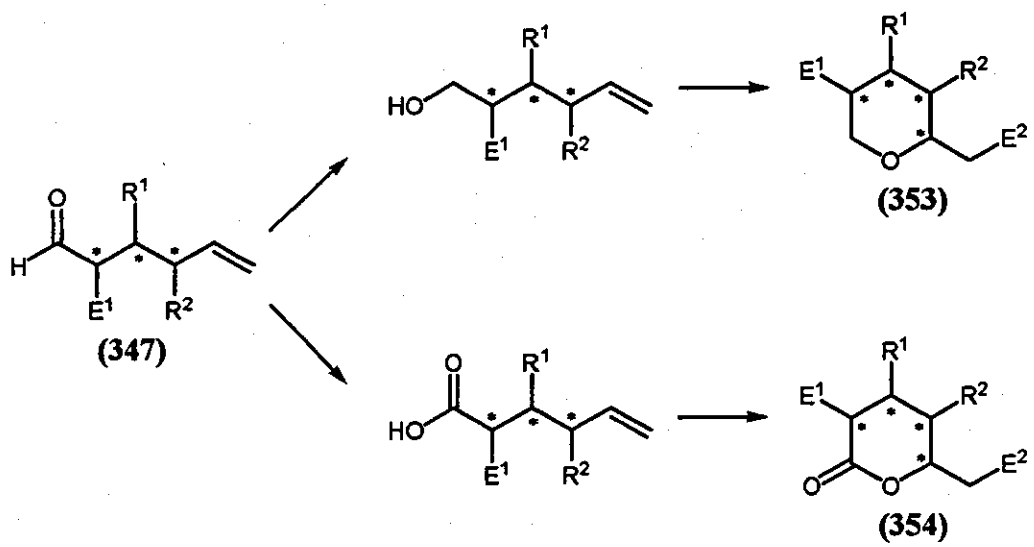
One goal of the research conducted in the Allin group is the generation of a target aldehyde such as **(347)** **(Scheme 132)**, possessing three contiguous chiral centres. Generation of **(347)** could be achieved *via* the amino-Cope rearrangement of a substrate such as **(351)** and subsequent enamine derivatisation and hydrolysis of **(352)**.



(351) (352) (347)

Scheme 132

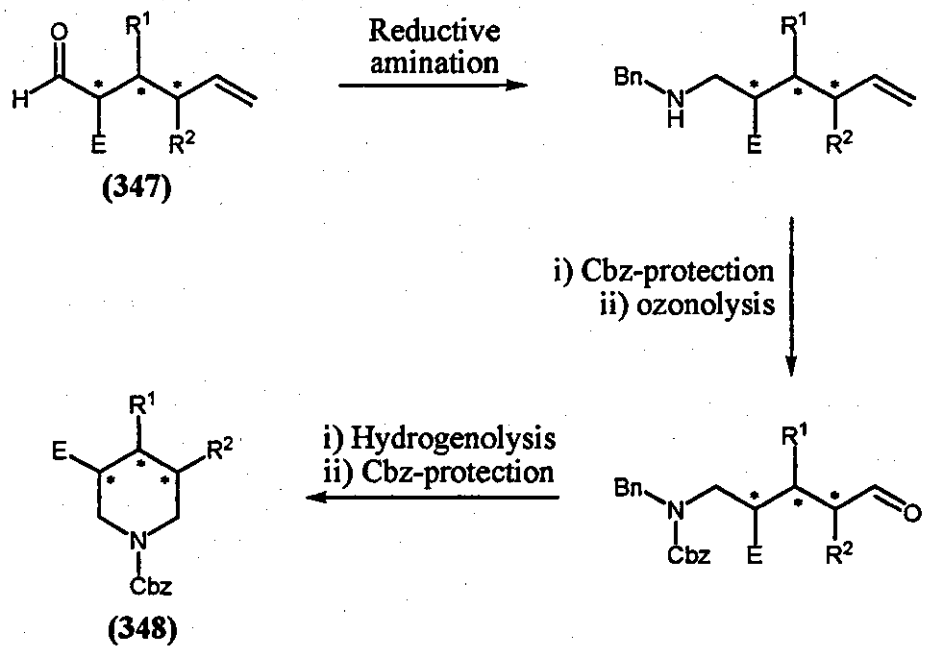
Highly-substituted tetrahydropyrans **(353)** and lactones **(354)** could be generated when **(347)** is used as a substrate in the synthetic routes previously established by Greeves[155,156] and Allin[117,118] **(Scheme 133)**.



(347) (353) (354)

Scheme 133

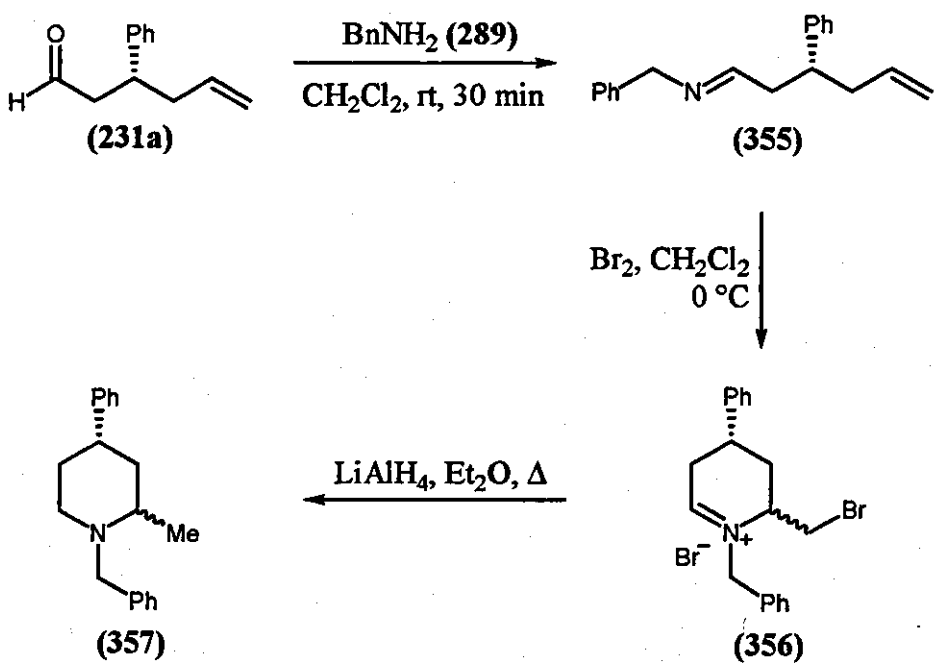
The aldehyde **(347)** could also be used in the synthesis of a piperidine such as **(348)** **(Scheme 134)** following the newly developed procedure described in **Section 2.2.5** of this thesis.



(347) (348)

Scheme 134

Synthesis of a piperidine **(357)** **(Scheme 135)** *via* electrophilic cyclisation of an imine **(355)** could also be attempted.



(231a) (355) (356) (357)

Scheme 135

Generation of a piperidine ring *via* an electrophilic cyclisation of a secondary amine has proven to be extremely difficult **(Section 2.2.2** and **Section 2.2.4)**. De Kimpe[177] successfully synthesised pyrrolidines *via* electrophilic cyclisation of γ,δ-unsaturated imines. The nitrogen atom would be reduced in nucleophilic power and less side reactions would be expected.[177]

The imine **(355)** could be generated by condensation of the aldehyde **(231a)**, product of the amino-Cope rearrangement, with benzylamine **(289)**. The electrophilic cyclisation of **(355)** would lead to an iminium ion **(356)**, which could be reduced with lithium aluminium hydride to generate **(357)**.

Chapter 3

Experimental

3.1 General Procedures

3.1.1 Solvents and Reagents

Where necessary solvents were dried, distilled and used immediately or stored over 4Å molecular sieves prior to use.

Acetic Acid (glacial)	Used as purchased from Fisher Scientific, UK.
Diethyl Ether (>99%)	Used as purchased from Fisher Scientific, UK or distilled from sodium and benzophenone.
Dichloromethane	Distilled from phosphorus pentoxide.
N,N-Dimethylformamide (>99.8%)	Used as purchased from Aldrich Chemical Co. Ltd.
Ethyl Acetate	Distilled from calcium chloride.
Hexane	Used as purchased from Fisher Scientific, UK.
Light Petroleum Ether (40-60 °C)	Distilled from calcium chloride.
Methanol	Distilled from magnesium and iodine.
Tetrahydrofuran	Distilled from sodium and benzophenone.
Toluene	Distilled from sodium.

Other chemicals used in this work were purchased from Acros (Fisher) Chemicals Ltd., Aldrich Chemical Co. Ltd., Lancaster Synthesis Ltd. and Merck Chemicals Ltd.

3.1.2 Chromatographic Procedures

Thin layer chromatography (TLC) was carried out using aluminium backed plates coated with silica gel (Merck Kiesegel 60 F_{254}). Plates were visualised under light (254 nm) or by staining with potassium permanganate or phosphomolybdic acid.

Flash column chromatography was conducted using silica gel (Merck Kiesegel 60 H). Pressure was applied to the column by hand bellows and samples were applied as

saturated solutions in an appropriate solvent or adsorbed onto the minimum quantity of silica.

3.1.3 Infrared and Nuclear Magnetic Resonance Spectroscopy

Infrared spectra were recorded on a Paragon 1000 Perkin Elmer FT-IR Spectrophotometer (with internal calibration) in the range 4000-600 cm^{-1}. Samples were dissolved in an appropriate solvent and run as a thin film.

^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were acquired using either a Bruker AC 250 or Bruker DPX 400 Spectrometer. All NMR samples were prepared in deuterated solvents with tetramethylsilane (TMS) as the internal standard. Multiplicities were recorded as broad peaks (br), singlets (s), doublets (d), triplets (t), quartets (q) and multiplets (m). Coupling constants (*J* values) are reported in Hertz (Hz). Diastereomeric ratios were calculated from the integration of suitable peaks in the ^{1}H NMR spectrum.

3.1.4 Mass Spectrometry

Mass spectra were recorded on a Jeol SX102 mass spectrometer using electron impact (EI) or fast atom bombardment (FAB) ionisation techniques.

3.1.5 Melting Points, Elemental Analysis and Optical Rotations

Melting points were determined on an Electrothermal 9100 melting point apparatus and are uncorrected.

Elemental analyses were determined on a Perkin Elmer 2400 CHN Elemental Analyser in conjunction with a Perkin Elmer AD-4 Autobalance.

Optical rotations were measured using an Optical Activity AA-2001 Automatic Polarimeter using a 0.25 dm cell.

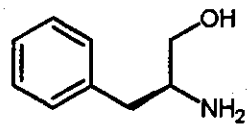
3.1.6 X-Ray Crystallography

Data sets were collected on a Bruker SMART 1000 CCD diffractometer with graphite monochromated Mo-Kα radiation operating at low temperature (150K). The software used for data collection was SMART (Bruker, 2001) and cell refinement/data reduction was achieved using the program SAINT (Bruker, 2001). The structures were solved by direct methods and refined by full-matrix least-squares on F^2 using the software SHELXTL (Sheldrick, G. M. (2001). Version 6.12, Bruker-AXS Inc., Madison, Wisconsin, USA).

3.2 Studies on the Amino-Cope Rearrangement

3.2.1 Synthesis of (*S*)-Phenylalaninol

(*S*)-2-Amino-3-phenylpropan-1-ol

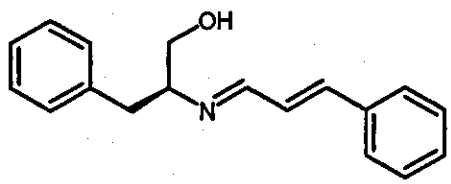


(239)

A solution of chlorotrimethylsilane (15.4 mL, 121.1 mmol) was added to $LiBH_4$ (1.32 g, 60.5 mmol) in dry THF (50 mL) under a nitrogen atmosphere. L-Phenylalanine **(243)** (5.0 g, 30.3 mmol) was added over a 5 min period and the reaction mixture stirred for 24 h at room temperature. MeOH (30 mL) was cautiously added to the reaction vessel and volatiles were removed under reduced pressure. A 20% KOH solution (25 mL) was added to the residue and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. The target compound **(239)** was isolated as a yellow solid which was recrystallised from CH_2Cl_2/hexane to yield colourless crystals (4.35 g, 95%). Mp 91-93 °C (lit.[128] 92-94 °C); $[\alpha]^{25}_D$ = -25.7 (*c* = 5.0, EtOH) (lit.[128] $[\alpha]^{20}_D$ = -23.0 (*c* = 5.0, EtOH)); ν_{max}/cm^{-1} (film) 3355, 3021, 2787, 1576, 1492, 1065, 753; δ_H ($CDCl_3$, 400 MHz) 2.52 (1H, dd, *J* 13.6, 8.7, PhC*H*(H)), 2.79 (1H, dd, *J* 13.6, 5.2, PhC*H*(H)), 3.08-3.15 (1H, m, C*H*NH_2), 3.39 (1H, dd, *J* 10.6, 7.3, C*H*(H)OH), 3.63 (1H, dd, *J* 10.6, 3.9, C*H*(H)OH), 7.18-7.32 (5H, m, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 40.8 (CH_2), 54.1 (CH), 66.3 (CH_2), 126.4 (CH), 128.5 (2 x CH), 129.2 (2 x CH), 138.6 (C); *m/z* (FAB) 152 ($(M+1)^+$, 100%), 152 (100%). Accurate mass: found 152.1081, $C_9H_{14}NO$ requires 152.1075.

3.2.2 Synthesis of Imines

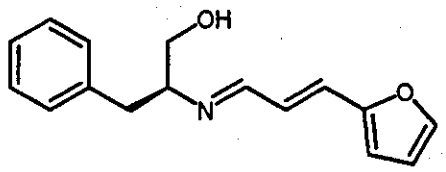
(*S*,2*E*)-2-((*E*)-3-Phenylallylideneamino)-3-phenylpropan-1-ol[133]



(241a)

trans-Cinnamaldehyde **(240a)** (1.66 mL, 13.2 mmol) was added dropwise to a stirred solution of (*S*)-2-amino-3-phenylpropan-1-ol **(239)** (2.0 g, 13.2 mmol) in CH_2Cl_2 (50 mL) at room temperature. The solution was stirred for 10 min, anhydrous $MgSO_4$ was added and the reaction mixture stirred for an additional 10 min. Filtration and removal of solvent under reduced pressure produced the target compound **(241a)** as a yellow solid (3.48 g, 99%), a portion of which was recrystallised from CH_2Cl_2/hexane to yield white crystals. Mp 115-116 °C; $[\alpha]^{25}_D$ = -220 (*c* = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (film) 3220, 3026, 2921, 2856, 1635, 1450, 749; δ_H ($CDCl_3$, 400 MHz) 2.78 (1H, dd, *J* 13.6, 8.8, PhC*H*(H)), 2.92 (1H, dd, *J* 13.6, 5.2, PhC*H*(H)), 3.40-3.44 (1H, m, C*H*CH_2OH), 3.78 (1H, dd, *J* 11.2, 3.6, C*H*(H)OH), 3.85 (1H, dd, *J* 11.2, 7.6, C*H*(H)OH), 6.64 (1H, d, *J* 16.0, C*H*Ph), 6.77 (1H, dd, *J* 16.0, 8.8, C*H*=CHPh), 7.12-7.37 (10H, m, Ar*H*), 7.63 (1H, d, *J* 8.8, N=C*H*); δ_C ($CDCl_3$, 100 MHz) 39.4 (CH_2), 66.2 (CH_2), 74.9 (CH), 126.6 (CH), 127.6 (2 x CH), 128.8 (2 x CH), 129.1 (2 x CH), 129.5 (CH), 129.9 (2 x CH), 135.9 (C), 138.9 (C), 142.8 (CH), 164.4 (CH); *m/z* (EI) 265 (M^+, 7%), 174 (100%). Accurate mass: found 265.1468, $C_{18}H_{19}NO$ requires 265.1467.

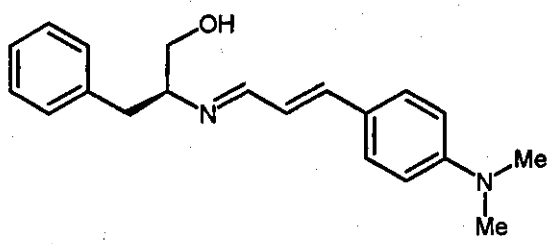
(*S*,2*E*)-2-((*E*)-3-(Furan-2-yl)allylideneamino)-3-phenylpropan-1-ol



(241b)

3-(2-Furyl)acrolein **(240b)** (1.62 g, 13.2 mmol) was added to a stirred solution of (*S*)-2-amino-3-phenylpropan-1-ol **(239)** (2.0 g, 13.2 mmol) in CH_2Cl_2 (50 mL) at room temperature. The solution was stirred for 10 min, anhydrous $MgSO_4$ was added and the reaction mixture stirred for an additional 10 min. Filtration and removal of solvent under reduced pressure produced the target compound **(241b)** as a yellow solid (3.31 g, 98%), a portion of which was recrystallised from Et_2O/hexane to yield yellow crystals. Mp 75-78 °C; $[\alpha]^{25}_D$ = -245.6 (*c* = 1.4, $CHCl_3$); ν_{max}/cm^{-1} (film) 3227, 2855, 1628, 1016, 745, 701; δ_H ($CDCl_3$, 400 MHz) 2.78 (1H, dd, *J* 13.4, 8.6, PhC*H*(H)), 2.92 (1H, dd, *J* 13.4, 8.4, PhC*H*(H)), 3.38-3.41 (1H, m, C*H*CH_2OH), 3.76 (1H, dd, *J* 11.3, 3.5, C*H*(H)OH), 3.83 (1H, dd, *J* 11.3, 7.5, C*H*(H)OH), 6.38-6.41 (2H, m, OCH=C*H* & OCH=CHC*H*), 6.50 (1H, d, *J* 15.9, N=CHCH=C*H*), 6.67 (1H, dd, *J* 15.9, 9.1, N=CHC*H*), 7.11-7.26 (5H, m, Ar*H*), 7.41 (1H, s, OC*H*), 7.58 (1H, d, *J* 9.1, N=C*H*); δ_C ($CDCl_3$, 100 MHz) 38.9 (CH_2), 65.8 (CH_2), 74.3 (CH), 111.9 (2 x CH), 125.4 (CH), 126.1 (CH), 128.2 (2 x CH), 129.0 (CH), 129.6 (2 x CH), 138.5 (C), 143.8 (CH), 151.7 (C), 163.6 (CH); *m/z* (EI) 255 (M^+, 18%), 164 (100%). Accurate mass: found 255.1258, $C_{16}H_{17}NO_2$ requires 255.1259.

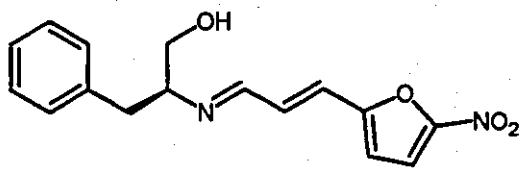
(*S*,2*E*)-2-((*E*)-3-(4-(Dimethylamino)phenyl)allylideneamino)-3-phenylpropan-1-ol



(241c)

4-Dimethylaminocinnamaldehyde **(240c)** (2.32 g, 13.2 mmol) was added to a stirred solution of (*S*)-2-amino-3-phenylpropan-1-ol **(239)** (2.0 g, 13.2 mmol) in CH_2Cl_2 (50 mL) at room temperature. The solution was stirred for 10 min, anhydrous $MgSO_4$ was added and the reaction mixture stirred for an additional 10 min. Filtration and removal of solvent under reduced pressure produced the target compound **(241c)** as a yellow solid (3.96 g, 97%), a portion of which was recrystallised from Et_2O/hexane to yield yellow crystals. Mp 161-164 °C; $[\alpha]^{25}_D$ = -217.0 (*c* = 1.1, $CHCl_3$); (Found: C, 77.61; H, 7.86; N, 9.07 $C_{20}H_{24}N_2O$ requires C, 77.89; H, 7.84; N, 9.08%); ν_{max}/cm^{-1} (film) 3156, 2922, 2843, 1631, 1603, 1367, 981, 814; δ_H ($CDCl_3$, 400 MHz) 2.79 (1H, dd, *J* 13.4, 8.0, PhC*H*(H)), 2.92 (1H, dd, *J* 13.4, 5.6, PhC*H*(H)), 3.00 (6H, s, N(CH_3)$_2$), 3.37-3.42 (1H, m, C*H*CH_2OH), 3.74-3.83 (2H, m, CH_2OH), 6.63-6.70 (4H, m, N=CHC*H*, N=CHCH=C*H* & 2 x (C*H*CN)), 7.15-7.34 (7H, m, Ar*H* & 2 x (NCCHC*H*)), 7.68 (1H, d, *J* 7.6, N=C*H*); δ_C ($CDCl_3$, 100 MHz) 39.6 (CH_2), 40.7 (2 x CH_3), 66.4 (CH_2), 74.8 (CH), 112.3 (2 x CH), 123.0 (CH), 124.0 (C), 126.5 (CH), 128.7 (2 x CH), 129.2 (2 x CH), 130.1 (2 x CH), 139.2 (C), 143.6 (CH), 151.4 (C), 165.2 (CH); *m/z* (EI) 308 (M^+, 42%), 217 (100%). Accurate mass: found 308.1893, $C_{20}H_{24}N_2O$ requires 308.1889.

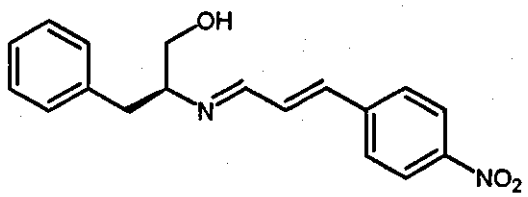
(*S*,2*E*)-2-((*E*)-3-(5-Nitrofuran-2-yl)allylideneamino)-3-phenylpropan-1-ol



(241d)

5-Nitro-2-furanacrolein **(240d)** (2.21 g, 13.2 mmol) was added to a stirred solution of (*S*)-2-amino-3-phenylpropan-1-ol **(239)** (2.0 g, 13.2 mmol) in CH_2Cl_2 (50 mL) at room temperature. The solution was stirred for 10 min, anhydrous $MgSO_4$ was added and the reaction mixture was stirred for an additional 10 min. Filtration and removal of solvent under reduced pressure produced the target compound **(241d)** as a brown solid (3.65 g, 92%), a portion of which was recrystallised from CH_2Cl_2/hexane to yield brown crystals. Mp 141-143 °C. $[\alpha]^{25}_D$ = -243.3 (*c* = 0.9, EtOH); ν_{max}/cm^{-1} (film) 3347, 3144, 2917, 2855, 1517, 1473, 1350, 737; δ_H ($CDCl_3$, 400 MHz) 2.80 (1H, dd, *J* 13.6, 8.8, PhC*H*(H)), 2.96 (1H, dd, *J* 13.6, 5.2, PhC*H*(H)), 3.44-3.48 (1H, m, C*H*CH_2OH), 3.78-3.85 (2H, m, C*H*$_2$OH), 6.57-6.62 (2H, m, O_2NC=CHC*H* & N=CHCH=C*H*), 7.00 (1H, dd, *J* 16.0, 8.8, N=CHC*H*), 7.11-7.30 (5H, m, Ar*H*), 7.32 (1H, d, *J* 3.6, O_2NC=C*H*), 7.65 (1H, d, *J* 8.8, N=C*H*); δ_C ($CDCl_3$, 100 MHz) 38.8 (CH_2), 65.8 (CH_2), 74.4 (CH), 112.8 (CH), 113.3 (CH), 126.0 (CH), 126.4 (CH), 128.4 (2 x CH), 129.6 (2 x CH), 132.2 (CH), 138.1 (C), 153.4 (2 x C), 161.9 (CH); *m/z* (EI) 300 (M^+, 4%), 209 (100%). Accurate mass found 300.1107, $C_{16}H_{16}N_2O_4$ requires 300.1110.

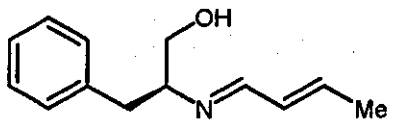
(*S*,2*E*)-2-((*E*)-3-(4-Nitrophenyl)allylideneamino)-3-phenylpropan-1-ol



(241e)

4-Nitrocinnamaldehyde **(240e)** (2.34 g, 13.2 mmol) was added to a stirred solution of (*S*)-2-amino-3-phenylpropan-1-ol **(239)** (2.0 g, 13.2 mmol) in CH_2Cl_2 (50 mL) at room temperature. The solution was stirred for 10 min, anhydrous $MgSO_4$ was added and the reaction mixture stirred for an additional 10 min. Filtration and removal of solvent under reduced pressure produced the target compound **(241e)** as an orange solid (3.86 g, 94%), a portion of which was recrystallised from CH_2Cl_2/hexane to yield yellow crystals. Mp 133-135 °C; $[\alpha]^{25}_D$ = -237.1 (*c* = 0.7, EtOH); ν_{max}/cm^{-1} (film) 3190, 2915, 2852, 1633, 1614, 1595, 1515, 1343, 746; δ_H ($CDCl_3$, 400 MHz) 2.80 (1H, dd, *J* 13.6, 8.4, PhC*H*(H)), 2.96 (1H, dd, *J* 13.6, 5.2, PhC*H*(H)), 3.44-3.50 (1H, m, C*H*CH_2OH), 3.79-3.88 (2H, m, C*H*$_2$OH), 6.76 (1H, d, *J* 16.0, N=CHCH=C*H*), 6.93 (1H, dd, *J* 16.0, 8.6, N=CHC*H*), 7.12-7.28 (5H, m, Ar*H*), 7.49 (2H, d, *J* 6.8, 2 x (O_2NCCHC*H*)), 7.70 (1H, d, *J* 8.6, N=C*H*), 8.18 (2H, d, *J* 6.8, 2 x (O_2NCC*H*)); δ_C ($CDCl_3$, 100 MHz) 38.8 (CH_2), 65.8 (CH_2), 74.3 (CH), 124.2 (2 x CH), 126.4 (CH), 127.7 (2 x CH), 128.4 (2 x CH), 129.6 (2 x CH), 131.7 (CH), 138.2 (C), 139.1 (CH), 141.8 (C), 147.8 (C), 162.9 (CH); *m/z* (EI) 310 (M^+, 6%), 219 (100%). Accurate mass: found 310.1322, $C_{18}H_{18}N_2O_3$ requires 310.1317.

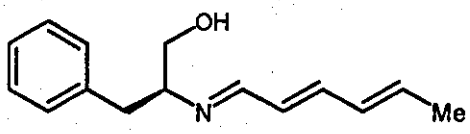
(*S*,2*E*)-2-((*E*)-But-2-enylideneamino)-3-phenylpropan-1-ol



(241f)

Crotonaldehyde **(240f)** (1.09 mL, 13.2 mmol) was added dropwise to a stirred solution of (*S*)-2-amino-3-phenylpropan-1-ol **(239)** (2.0 g, 13.2 mmol) in CH_2Cl_2 (50 mL) at room temperature. The solution was stirred for 10 min, anhydrous $MgSO_4$ was added and the reaction mixture stirred for an additional 10 min. Filtration and removal of solvent under reduced pressure produced the target compound **(241f)** as an orange oil (2.57 g, 96%), which was used without further purification. $[\alpha]^{25}_D$ = -178.1 (*c* = 1.4, $CDCl_3$); ν_{max}/cm^{-1} (film) 3277, 2926, 2862, 1653, 1452, 1030, 747, 710; δ_H ($CDCl_3$, 400 MHz) 1.80 (3H, d, *J* 6.6, C*H*$_3$), 2.73 (1H, dd, *J* 13.4, 8.4, PhC*H*(H)), 2.89 (1H, dd, *J* 13.4, 5.2, PhC*H*(H)), 3.30-3.33 (1H, m, C*H*CH$_2$OH), 3.45-3.50 (1H, br, O*H*), 3.71 (1H, dd, *J* 11.4, 3.6, C*H*(H)OH), 3.78 (1H, dd, *J* 11.4, 7.6, C*H*(H)OH), 6.00-6.17 (2H, m, N=CHC*H* & C*H*CH$_3$), 7.10-7.26 (5H, m, Ar*H*), 7.48 (1H, d, *J* 8.8, N=C*H*); δ_C ($CDCl_3$, 100 MHz) 18.7 (CH_3), 39.3 (CH_2), 66.1 (CH_2), 74.3 (CH), 126.6 (CH), 128.6 (2 x CH), 130.0 (2 x CH), 131.8 (CH), 139.0 (C), 141.9 (CH), 164.5 (CH).

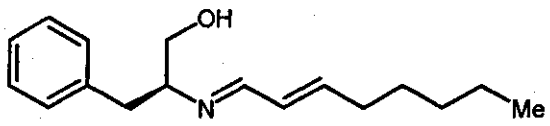
(*S*,2*E*)-2-((2*E*,4*E*)-Hexa-2,4-dienylideneamino)-3-phenylpropan-1-ol



(241g)

trans,trans-2,4-Hexadienal **(240g)** (1.46 mL, 13.2 mmol) was added dropwise to a stirred solution of (*S*)-2-amino-3-phenylpropan-1-ol **(239)** (2.0 g, 13.2 mmol) in CH_2Cl_2 (50 mL) at room temperature. The solution was stirred for 10 min, anhydrous $MgSO_4$ was added and the reaction mixture stirred for an additional 10 min. Filtration and removal of solvent under reduced pressure produced the target compound **(241g)** as a yellow oil (2.86 g, 94%), which was used without further purification. $[\alpha]^{25}_D$ = -146.8 (*c* = 0.9, $CHCl_3$); ν_{max}/cm^{-1} (film) 3244, 3025, 2914, 2856, 1628, 1453, 995, 737, 701; δ_H ($CDCl_3$, 400 MHz) 1.81 (3H, d, *J* 8.0, C*H*$_3$), 2.75 (1H, dd, *J* 13.5, 8.2, PhC*H*(H)), 2.89 (1H, dd, *J* 13.5, 5.4, PhC*H*(H)), 3.31-3.37 (1H, m, C*H*CH$_2$OH), 3.69-3.78 (2H, m, CHC*H*$_2$OH), 5.88-5.94 (1H, m, C*H*CH$_3$), 6.10-6.20 (2H, m, C*H*=CHCH$_3$ & N=CHC*H*), 6.43 (1H, dd, *J* 10.7, 5.3, N=CHCH=C*H*), 7.11-7.27 (5H, m, Ar*H*), 7.56 (1H, d, *J* 9.1, N=C*H*); δ_C ($CDCl_3$, 100 MHz) 18.5 (CH_3), 39.0 (CH_2), 65.9 (CH_2), 74.0 (CH), 126.1 (CH), 128.2 (2 x CH), 128.5 (CH), 129.6 (2 x CH), 130.8 (CH), 135.7 (CH), 138.5 (C), 142.9 (CH), 164.3 (CH); *m/z* (EI) 230 ($(M+1)^+$, 100%), 230 (100%). Accurate mass: found 230.1540, $C_{15}H_{20}NO$ requires 230.1545

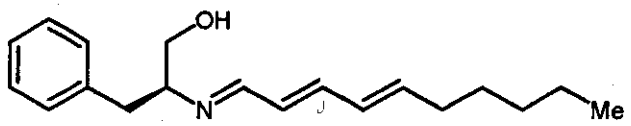
(*S*,2*E*)-2-((*E*)-Oct-2-enylideneamino)-3-phenylpropan-1-ol



(241h)

trans-2-Octenal **(240h)** (1.97 mL, 13.2 mmol) was added dropwise to a stirred solution of (*S*)-2-amino-3-phenylpropan-1-ol **(239)** (2.0 g, 13.2 mmol) in CH_2Cl_2 (50 mL) at room temperature. The solution was stirred for 10 min, anhydrous $MgSO_4$ was added and the reaction mixture stirred for an additional 10 min. Filtration and removal of solvent under reduced pressure produced the target compound **(241h)** as a yellow oil (3.25 g, 95%), which was used without further purification. $[\alpha]^{25}_D$ = -102.5 (*c* = 1.5, $CHCl_3$); ν_{max}/cm^{-1} (film) 3237, 2953, 2925, 2856, 1653, 1495, 1453, 1080, 1046, 747; δ_H ($CDCl_3$, 400 MHz) 0.88 (3H, t, *J* 7.2, C*H*$_3$), 1.23-1.50 (6H, m, (C*H*$_2$)$_3$CH$_3$), 2.03-2.14 (2H, m, CH=CHC*H*$_2$), 2.73 (1H, dd, *J* 13.5, 8.4, PhC*H*(H)), 2.89 (1H, dd, *J* 13.5, 5.3, PhC*H*(H)), 3.27-3.37 (1H, m, C*H*CH$_2$OH), 3.71 (1H, dd, *J* 11.4, 3.6, C*H*(H)OH), 3.79 (1H, dd, *J* 11.4, 7.6, C*H*(H)OH), 5.97-6.04 (1H, m, CH=C*H*CH$_2$), 6.11 (1H, dd, *J* 15.6, 8.5, N=CHC*H*), 7.10-7.28 (5H, m, Ar*H*), 7.44-7.48 (1H, m, N=C*H*); δ_C ($CDCl_3$, 100 MHz) 14.0 (CH_3), 22.4 (CH_2), 28.1 (CH_2), 31.3 (CH_2), 32.5 (CH_2), 39.0 (CH_2), 65.6 (CH_2), 74.1 (CH), 126.4 (CH), 128.2 (2 x CH), 129.7 (2 x CH), 129.8 (CH), 138.6 (C), 146.8 (CH), 164.3 (CH); *m/z* (EI) 259 (M^+, 3%), 168 (100%). Accurate mass: found 259.1932, $C_{17}H_{25}NO$ requires 259.1936.

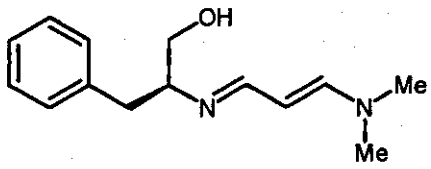
(*S*,2*E*)-2-((2*E*,4*E*)-Deca-2,4-dienylideneamino)-3-phenylpropan-1-ol



(241i)

trans,trans-2,4-Decadienal **(240i)** (2.30 mL, 13.2 mmol) was added dropwise to a stirred solution of (*S*)-2-amino-3-phenylpropan-1-ol **(239)** (2.0 g, 13.2 mmol) in CH_2Cl_2 (50 mL) at room temperature. The solution was stirred for 10 min, anhydrous $MgSO_4$ was added and the reaction mixture stirred for an additional 10 min. Filtration and removal of solvent under reduced pressure produced the target compound **(241i)** as a yellow oil (3.74 g, 99%), which was used without further purification. $[\alpha]^{25}_D$ = -101.6 (*c* = 1.2, $CHCl_3$); ν_{max}/cm^{-1} (film) 3276, 2924, 2855, 1629, 1453, 1046, 995, 700; δ_H ($CDCl_3$, 400 MHz) 0.88 (3H, t, *J* 7.2, CH_3), 1.25-1.41 (6H, m, $(CH_2)_3CH_3$), 2.08-2.13 (2H, m, $CH{=}CHCH_2$), 2.73 (1H, dd, *J* 13.4, 8.3, PhC*H*(H)), 2.88 (1H, dd, *J* 13.4, 5.1, PhC*H*(H)), 3.29-3.36 (1H, m, $CHCH_2OH$), 3.70-3.81 (2H, m, CH_2OH), 5.82-5.90 (1H, m, $CH{=}CHCH_2$), 6.04-6.23 (2H, m, N=CHC*H* & $CH{=}CHCH_2$), 6.37 (1H, dd, *J* 16.0, 8.0, N=CHCH=C*H*), 7.10-7.26 (5H, m, Ar*H*), 7.49 (1H, d, *J* 9.1, N=C*H*); δ_C ($CDCl_3$, 100 MHz) 14.0 (CH_3), 22.4 (CH_2), 28.5 (CH_2), 31.3 (CH_2), 32.8 (CH_2), 38.9 (CH_2), 65.7 (CH_2), 74.3 (CH), 126.1 (CH), 128.2 (2 x CH), 128.4 (CH), 129.3 (CH), 129.5 (2 x CH), 138.5 (C), 141.2 (CH), 143.1 (CH), 164.2 (CH); *m/z* (EI) 286 ($(M+1)^+$, 100%), 286 (100%). Accurate mass: found 286.2170, $C_{19}H_{28}NO$ requires 286.2171.

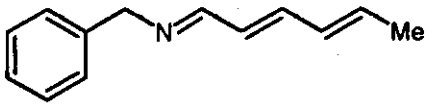
(*S*,2*E*)-2-((*E*)-3-(Dimethylamino)allylideneamino)-3-phenylpropan-1-ol



(241j)

Dimethylaminoacrolein **(240j)** (1.32 mL, 13.2 mmol) was added dropwise to a stirred solution of (*S*)-2-amino-3-phenylpropan-1-ol **(239)** (2.0 g, 13.2 mmol) in CH_2Cl_2 (50 mL) at room temperature. The solution was stirred for 10 min, anhydrous $MgSO_4$ was added and the reaction mixture stirred for an additional 10 min. Filtration and removal of solvent under reduced pressure produced the target compound **(241j)** as a yellow oil (3.01 g, 97%), which was used without further purification. $[\alpha]^{25}_D$ = -72.7 (*c* = 0.8, $CHCl_3$); ν_{max}/cm^{-1} (film) 3302, 2922, 1615, 1403, 1178, 1117; δ_H ($CDCl_3$, 400 MHz) 2.52 (1H, dd, *J* 13.4, 8.6, PhC*H*(H)), 2.80 (1H, dd, *J* 13.4, 5.0, PhC*H*(H)), 2.85 (3H, s, NC*H*$_3$(CH_3)), 3.09-3.13 (1H, m, C*H*CH_2OH), 3.13 (3H, s, NC*H*$_3$(CH_3)), 3.39 (1H, dd, *J* 10.6, 7.2, C*H*(H)OH), 3.63 (1H, dd, *J* 10.6, 3.8, C*H*(H)OH), 5.14 (1H, dd, *J* 12.5, 8.5, N=CHC*H*), 7.03 (1H, d, *J* 12.5, C*H*N(CH_3)$_2$), 7.17-7.32 (5H, m, Ar*H*), 9.06 (1H, d, *J* 8.5, N=C*H*); δ_C ($CDCl_3$, 100 MHz) 37.6 (CH_3), 41.2 (CH_2), 45.3 (CH_3), 54.6 (CH), 66.8 (CH_2), 102.0 (CH), 126.7 (CH), 128.9 (2 x CH), 129.6 (2 x CH), 139.2 (C), 160.8 (CH), 189.6 (CH); *m/z* (EI) 232 (M^+, 1%). 60 (100%). Accurate mass: found 232.1573, $C_{14}H_{20}N_2O$ requires 232.1576.

(7*E*)-*N*-((2*E*,4*E*)-Hexa-2,4-dienylidene)(phenyl)methanamine

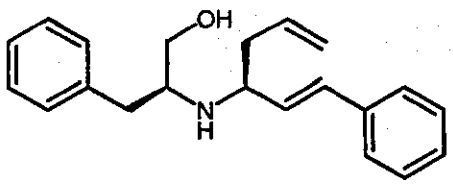


(290)

trans,trans-2,4-Hexadienal **(240g)** (2.05 mL, 18.7 mmol) was added dropwise to a stirred solution of benzylamine **(289)** (2.04 mL, 18.7 mmol) in CH_2Cl_2 (30 mL) at room temperature. The solution was stirred for 10 min, anhydrous $MgSO_4$ was added and the reaction mixture stirred for an additional 10 min. Filtration and removal of solvent under reduced pressure produced the target compound **(290)** as a yellow oil (3.39 g, 98%), which was used without further purification. ν_{max}/cm^{-1} (film) 3026, 2850, 1630, 1494, 1452, 1170, 1000, 734, 697; δ_H ($CDCl_3$, 400 MHz) 1.81-2.03 (3H, m, C*H*$_3$), 4.64 (2H, s, PhC*H*$_2$), 5.90-5.99 (1H, m, C*H*CH$_3$), 6.14-6.25 (1H, m, C*H*=CHCH$_3$), 6.28 (1H, dd, *J* 15.4, 9.0, N=CHC*H*), 6.59 (1H, dd, *J* 15.4, 10.7, N=CHCH=C*H*), 7.21-7.41 (5H, m, Ar*H*), 7.96 (1H, d, *J* 9.0, N=C*H*); δ_C ($CDCl_3$, 100 MHz) 18.5 (CH_3), 65.2 (CH_2), 127.0 (CH), 128.1 (2 x CH), 128.5 (2 x CH), 129.3 (CH), 130.9 (CH), 135.2 (CH), 139.4 (C), 142.4 (CH), 163.6 (CH); *m/z* (EI) 185 (M^+, 22%), 91 (100%). Accurate mass: found 185.1204, $C_{13}H_{15}N$ requires 185.1205.

3.2.3 Synthesis of 3-Amino-1,5-dienes

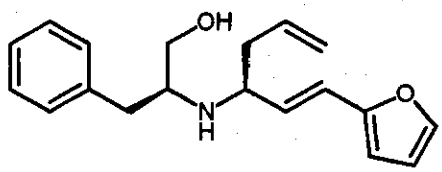
(*S*)-2-((*S*,*E*)-1-Phenylhexa-1,5-dien-3-ylamino)-3-phenylpropan-1-ol[133]



(234a)

(*S*,2*E*)-2-((*E*)-3-Phenylallylideneamino)-3-phenylpropan-1-ol **(241a)** (3.0 g, 11.3 mmol) was dissolved in a 4:1 mixture of dry toluene/Et_2O (75 mL) under a nitrogen atmosphere. Magnesium turnings (0.91 g, 37.3 mmol) and a catalytic amount of iodine were added to the solution. Allyl bromide (3.16 mL, 37.3 mmol) was cautiously added and the mixture stirred for 18 h. The reaction was quenched with water until a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue rinsed with Et_2O (2 x 50 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution (2 x 75 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and a yellow solid was obtained, which was recrystallised from Et_2O/hexane to yield the target compound **(234a)** as white crystals (2.74 g, 79%). Mp 73-74 °C; $[\alpha]^{25}_D$ = -43.3 (*c* = 1.6, $CHCl_3$); (Found: C, 81.67; H, 8.10; N, 4.42 $C_{21}H_{25}NO$ requires: C, 82.04; H, 8.20; N, 4.56%); ν_{max}/cm^{-1} (film) 3320, 3024, 2924, 1494, 1453, 1030, 967, 748, 700; δ_H ($CDCl_3$, 400 MHz) 2.22-2.25 (2H, m, CH_2CH=CH_2), 2.71-2.81 (2H, m, PhCH_2), 2.99-3.04 (1H, m, CHCH_2OH), 3.22-3.27 (1H, m, NCHCH), 3.34 (1H, dd, *J* 10.6, 3.2, CH(H)OH), 3.63 (1H, dd, *J* 10.6, 3.9, CH(H)OH), 5.04-5.10 (2H, m, CH=CH_2), 5.68 (1H, dd, *J* 15.9, 8.3, NCHCH), 5.73-5.81 (1H, m, CH=CH_2), 6.28 (1H, d, *J* 15.9, CHPh), 7.13-7.33 (10H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 38.9 (CH_2), 40.9 (CH_2), 56.4 (CH), 57.7 (CH), 62.0 (CH_2), 117.5 (CH_2), 126.3 (2 x CH), 126.4 (CH), 127.4 (CH), 128.49 (2 x CH), 128.52 (2 x CH), 129.2 (2 x CH), 130.7 (CH), 132.0 (CH), 134.8 (CH), 136.7 (C), 138.6 (C); *m/z* (EI) 308 ($(M+1)^+$, 100%), 308 (100%) Accurate mass: found 308.2012, $C_{21}H_{26}NO$ requires 308.2014

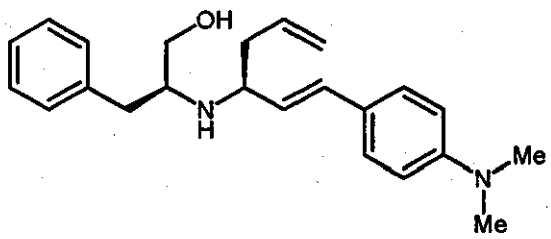
(*S*)-2-((*S*,*E*)-1-(Furan-2-yl)hexa-1,5-dien-3-ylamino)-3-phenylpropan-1-ol



(234b)

(*S*,2*E*)-2-((*E*)-3-(Furan-2-yl)allylideneamino)-3-phenylpropan-1-ol **(241b)** (3.0 g, 11.8 mmol) was dissolved in a 4:1 mixture of dry toluene/Et_2O (75 mL) under a nitrogen atmosphere. Magnesium turnings (0.94 g, 38.8 mmol) and a catalytic amount of iodine were added to the solution. Allyl bromide (3.28 mL, 38.8 mmol) was cautiously added and the mixture stirred for 18 h. The reaction was quenched with water until a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue was rinsed with Et_2O (2 x 50 mL). The combined organic layers were washed twice with a saturated $NaHCO_3$ solution (2 x 75 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and a brown solid was obtained, which was recrystallised from Et_2O/hexane to yield the target compound **(234b)** as yellow crystals (2.56 g, 78%). Mp 88-90 °C; $[\alpha]^{25}_D$ = -103.2 (*c* = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (film) 3386, 2923, 1453, 736; δ_H ($CDCl_3$, 400 MHz) 2.22 (2H, m, C*H*$_2$CH=CH$_2$), 2.70-2.81 (2H, m, PhC*H*$_2$), 2.97-3.03 (1H, m, C*H*CH$_2$OH), 3.20-3.25 (1H, m, NC*H*CH), 3.32 (1H, dd, *J* 10.7, 3.5, C*H*(H)OH), 3.60 (1H, dd, *J* 10.7, 3.8, C*H*(H)OH), 5.04-5.10 (2H, m, CH=C*H*$_2$), 5.69-5.81 (2H, m, C*H*=CH$_2$ & NCHC*H*), 6.03 (1H, d, *J* 16.1, NCHCH=C*H*), 6.13 (1H, d, *J* 3.2, OCH=CHC*H*), 6.36 (1H, d, *J* 3.2, OCH=C*H*), 7.15-7.28 (5H, m, Ar*H*), 7.33 (1H, s, OC*H*); δ_C ($CDCl_3$, 100 MHz) 38.8 (CH_2), 40.9 (CH_2), 56.5 (CH), 57.4 (CH), 61.9 (CH_2), 107.5 (CH), 111.2 (CH), 117.6 (CH_2), 119.1 (CH), 126.4 (CH), 128.5 (2 x CH), 129.2 (2 x CH), 130.7 (CH), 134.8 (CH), 138.5 (C), 141.7 (CH), 152.3 (C); *m/z* (EI) 298 ($(M+1)^+$, 83%), 147 (100%). Accurate mass: found 298.1818, $C_{19}H_{24}NO_2$ requires 298.1807.

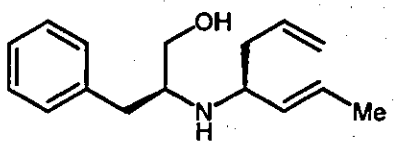
(*S*)-2-(*S*,*E*)-1-(4-(Dimethylamino)phenyl)hexa-1,5-dien-3-ylamino)-3-phenylpropan-1-ol



(234c)

(*S*,2*E*)-2-((*E*)-3-(4-(Dimethylamino)phenyl)allylideneamino)-3-phenylpropan-1-ol **(241c)** (3.0 g, 9.7 mmol) was dissolved in a 4:1 mixture of dry toluene/Et_2O (75 mL) under a nitrogen atmosphere. Magnesium turnings (0.78 g, 32.1 mmol) and a catalytic amount of iodine were added to the solution. Allyl bromide (2.72 mL, 32.1 mmol) was cautiously added and the mixture stirred for 18 h. The reaction was quenched with water and a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue rinsed with Et_2O (2 x 50 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution (2 x 75 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and a yellow solid was obtained, which was recrystallised from Et_2O/hexane to yield the target compound **(234c)** as orange crystals (3.04 g, 89%). Mp 116-118 °C; $[\alpha]^{25}_D$ = -65.7 (*c* = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (film) 2891, 1611, 1523, 1354, 965, 804, 700; δ_H ($CDCl_3$, 400 MHz) 2.24-2.29 (2H, m, C*H*$_2$CH=CH$_2$), 2.79-2.81 (2H, m, PhC*H*$_2$), 2.99 (6H, s, N(C*H*$_3$)$_2$), 3.02-3.08 (1H, m, C*H*CH$_2$OH), 3.24-3.26 (1H, m, NC*H*CH), 3.36 (1H, dd, *J* 10.4, 3.2, C*H*(H)OH), 3.66 (1H, dd, *J* 10.4, 4.0, C*H*(H)OH), 5.06-5.09 (2H, m, CH=C*H*$_2$), 5.53 (1H, dd, *J* 15.8, 8.4, NCHC*H*), 5.78-5.84 (1H, m, C*H*=CH$_2$), 6.23 (1H, d, *J* 15.8, C*H*Ph), 6.72 (2H, d, *J* 4.8, 2 x (C*H*CN)), 7.18-7.31 (7H, m, Ar*H* & 2 x (C*H*CHCN)); δ_C ($CDCl_3$, 100 MHz) 39.3 (CH_2), 41.0 (2 x CH_3), 41.6 (CH_2), 56.7 (CH), 58.5 (CH), 62.3 (CH_2), 112.9 (2 x CH), 117.7 (CH_2), 125.6 (C), 126.8 (CH), 127.7 (2 x CH), 128.1 (CH), 129.0 (2 x CH), 129.8 (2 x CH), 131.2 (CH), 135.7 (CH), 139.1 (C), 150.5 (C); *m/z* (EI) 350 (M^+, 1%), 309 (100%). Accurate mass: found 350.2365, $C_{23}H_{30}N_2O$ requires 350.2358.

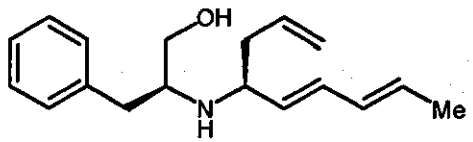
(*S*)-2-((*S*,*E*)-Hepta-1,5-dien-4-ylamino)-3-phenylpropan-1-ol



(234f)

(*S*,2*E*)-2-((*E*)-But-2-enylideneamino)-3-phenylpropan-1-ol **(241f)** (2.50 g, 12.3 mmol) was dissolved in a 4:1 mixture of dry toluene/Et_2O (75 mL) under a nitrogen atmosphere. Magnesium turnings (0.99 g, 40.6 mmol) and a catalytic amount of iodine were added to the solution. Allyl bromide (3.43 mL, 40.6 mmol) was cautiously added and the mixture stirred for 18 h. The reaction was quenched with water and a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue was rinsed with Et_2O (2 x 50 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution (2 x 75 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to yield a yellow solid, which was adsorbed onto silica and purified by flash column chromatography (100% CH_2Cl_2). The target compound **(234f)** was isolated as white crystals (1.78 g, 59%), a portion of which was recrystallised from Et_2O/hexane to yield colourless needles. Mp 58-59 °C; $[\alpha]^{25}_D$ = -38.9 (*c* = 1.4, $CHCl_3$); ν_{max}/cm^{-1} (film) 3384, 2918, 2854, 1454, 1031, 969, 914, 745, 700; δ_H ($CDCl_3$, 400 MHz) 1.63 (3H, dd, *J* 6.5, 1.6, C*H*$_3$), 2.10-2.15 (2H, m, C*H*$_2$CH=CH$_2$), 2.68-2.78 (2H, m, PhC*H*$_2$), 2.93-3.05 (2H, m, C*H*CH$_2$OH & NC*H*CH), 3.27 (1H, dd, *J* 10.7, 3.8, C*H*(H)OH), 3.55 (1H, dd, *J* 10.7, 3.8 C*H*(H)OH), 4.93-5.03 (3H, m, CH=C*H*$_2$ & NCHC*H*), 5.30-5.40 (1H, m, C*H*CH$_3$), 5.67-5.78 (1H, m, C*H*=CH$_2$), 7.11-7.31 (5H, m, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 17.6 (CH_3), 38.8 (CH_2), 40.8 (CH_2), 56.3 (CH), 57.6 (CH), 61.8 (CH_2), 117.0 (CH_2), 126.4 (CH), 126.6 (CH), 128.4 (2 x CH), 129.2 (2 x CH), 133.3 (CH), 135.3 (CH), 138.6 (C); *m/z* (FAB) 246 ($(M+1)^+$, 100%), 246 (100%). Accurate mass: found 246.1865, $C_{16}H_{24}NO$ requires 246.1858.

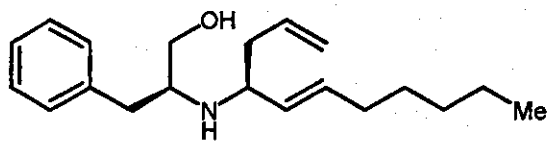
(*S*)-2-((*S*,5*E*,7*E*)-Nona-1,5,7-trien-4-ylamino)-3-phenylpropan-1-ol



(234g)

(*S*,2*E*)-2-((2*E*,4*E*)-Hexa-2,4-dienylideneamino)-3-phenylpropan-1-ol **(241g)** (2.50 g, 10.9 mmol) was dissolved in a 4:1 mixture of dry toluene/Et_2O (75 mL) under a nitrogen atmosphere. Magnesium turnings (0.87 g, 36.0 mmol) and a catalytic amount of iodine were added to the solution. Allyl bromide (3.04 mL, 36.0 mmol) was cautiously added and the mixture stirred for 18 h. The reaction was quenched with water until a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue was rinsed with Et_2O (2 x 50 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution (2 x 75 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and a yellow solid was obtained, which was adsorbed onto silica and purified by flash column chromatography (4:1 hexane:EtOAc) to produce a yellow solid. Traces of a minor isomer were partially removed by recrystallisation in hexane, yielding the target compound **(234g)** as white crystals (1.91 g, 65%). Mp 74-75 °C; $[\alpha]^{25}_D$ = -35.8 (*c* = 1.6, $CHCl_3$); (Found: C, 79.67; H, 9.29; N, 5.09. $C_{18}H_{25}NO$ requires: C, 79.66; H, 9.28; N, 5.16%); ν_{max}/cm^{-1} (film) 3403, 3023, 2927, 1639, 1495, 1453, 1265, 1030, 990, 739, 701; δ_H ($CDCl_3$, 400 MHz) 1.75 (3H, dd, *J* 6.7, 1.7, C*H*$_3$), 2.13-2.17 (2H, m, C*H*$_2$CH=CH$_2$), 2.68-2.78 (2H, m, PhC*H*$_2$), 2.93-2.98 (1H, m, C*H*CH$_2$OH), 3.07-3.12 (1H, m, NC*H*CH), 3.28 (1H, dd, *J* 10.7, 3.5, C*H*(H)OH), 3.51 (1H, dd, *J* 10.7, 3.8, C*H*(H)OH), 5.02-5.09 (3H, m, CH=C*H*$_2$ & NCHC*H*), 5.59-5.75 (2H, m, C*H*=CH$_2$ & C*H*CH$_3$), 5.84-5.98 (2H, m, C*H*CH=CHCH$_3$ & C*H*=CHCH$_3$), 7.15-7.31 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 18.1 (CH_3), 38.8 (CH_2), 40.9 (CH_2), 56.3 (CH), 57.3 (CH), 61.7 (CH_2), 117.3 (CH_2), 126.4 (CH), 128.5 (2 x CH), 129.1 (CH), 129.3 (2 x CH), 130.8 (CH), 131.2 (CH), 132.8 (CH), 135.0 (CH), 138.5 (C); *m/z* (FAB) 272 ($(M+1)^+$, 37%), 92 (100%) Accurate mass: found 272.2012, $C_{18}H_{26}NO$ requires 272.2014.

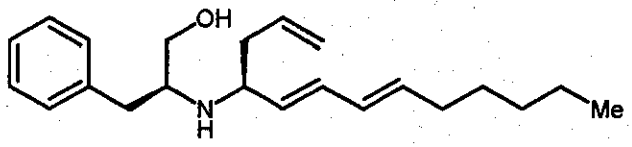
(*S*)-2-((*S*,*E*)-Undeca-1,5-dien-4-ylamino)-3-phenylpropan-1-ol



(234h)

(*S*,2*E*)-2-((*E*)-Oct-2-enylideneamino)-3-phenylpropan-1-ol **(241h)** (3.0 g, 11.6 mmol) was dissolved in a 4:1 mixture of dry toluene/Et_2O (75 mL) under a nitrogen atmosphere. Magnesium turnings (0.93 g, 38.2 mmol) and a catalytic amount of iodine were added to the solution. Allyl bromide (3.23 mL, 38.2 mmol) was cautiously added and the mixture was stirred for 18 h. The reaction was quenched with water until a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue was rinsed with Et_2O (2 x 50 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution (2 x 75 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and a yellow oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (9:1 hexane:EtOAc). The target compound **(234h)** was isolated as yellow crystals (2.15 g, 62%), a portion of which was recrystallised from Et_2O/hexane to yield pale yellow needles. Mp 54-57 °C; $[\alpha]^{25}_D$ = -44.7 (*c* = 1.6, $CHCl_3$); (Found: C, 79.58; H, 10.68; N, 4.67. $C_{20}H_{31}NO$ requires: C, 79.68; H, 10.36; N, 4.65%); ν_{max}/cm^{-1} (film) 3028, 2924, 1463, 1118, 967, 914, 701; δ_H ($CDCl_3$, 400 MHz) 0.90 (3H, t, *J* 6.8, C*H*$_3$), 1.24-1.34 (6H, m, (C*H*$_2$)$_3$CH$_3$), 1.93-1.98 (2H, m, CH=CHC*H*$_2$), 2.04-2.17 (2H, m, C*H*$_2$CH=CH$_2$), 2.69-2.79 (2H, m, PhC*H*$_2$), 2.94-2.98 (1H, m, C*H*CH$_2$OH), 3.00-3.05 (1H, m, NC*H*CH), 3.28 (1H, dd, *J* 10.6, 3.6, C*H*(H)OH), 3.55 (1H, dd, *J* 10.6, 3.9, C*H*(H)OH), 4.93 (1H, dd, *J* 15.3, 8.4, NCHC*H*), 5.00-5.06 (2H, m, CH=C*H*$_2$), 5.31-5.38 (1H, m, CH=C*H*CH$_2$), 5.67-5.78 (1H, m, C*H*=CH$_2$), 7.15-7.30 (5H, m, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 14.5 (CH_3), 22.9 (CH_2), 29.4 (CH_2), 31.8 (CH_2), 32.6 (CH_2), 39.7 (CH_2), 41.4 (CH_2), 56.6 (CH), 57.9 (CH), 62.1 (CH_2), 117.4 (CH_2), 126.8 (CH), 128.9 (2 x CH), 129.7 (2 x CH), 132.4 (CH), 132.7 (CH), 135.7 (CH), 139.0 (C); *m/z* (EI) 300 ((M-1)$^+$, 1%), 260 (100%). Accurate mass: found 300.2323, $C_{20}H_{30}NO$ requires 300.2327.

(*S*)-2-((*S*,5*E*,7*E*)-Trideca-1,5,7-trien-4-ylamino)-3-phenylpropan-1-ol

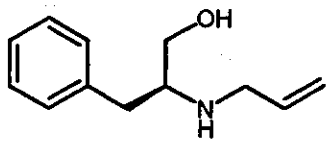


(234i)

(*S*,2*E*)-2-((2*E*,4*E*)-Deca-2,4-dienylideneamino)-3-phenylpropan-1-ol **(241i)** (3.5 g, 12.3 mmol) was dissolved in a 4:1 mixture of dry toluene/Et_2O (100 mL) under a nitrogen atmosphere. Magnesium turnings (0.98 g, 40.5 mmol) and a catalytic amount of iodine were added to the solution. Allyl bromide (3.42 mL, 40.5 mmol) was cautiously added and the mixture was stirred for 18 h. The reaction was quenched with water until a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue was rinsed with Et_2O (2 x 50 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution (2 x 75 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and a yellow solid was obtained, which was adsorbed onto silica and purified by flash column chromatography (4:1 hexane:EtOAc). Traces of a minor isomer were removed by recrystallisation in hexane, yielding the target compound **(234i)** as white crystals (2.69 g, 67%). Mp 62-63 °C; $[\alpha]^{25}_D$ = -32.1 (*c* = 1.1, $CHCl_3$); (Found: C, 80.83; H, 9.98; N, 4.15. $C_{22}H_{33}NO$ requires: C, 80.68; H, 10.16; N, 4.28%); ν_{max}/cm^{-1} (film) 3319, 2954, 2924, 1495, 1454, 989, 700; δ_H ($CDCl_3$, 400 MHz) 0.90 (3H, t, *J* 6.9, C*H*$_3$), 1.24-1.43 (6H, m, (C*H*$_2$)$_3$CH$_3$), 2.03-2.09 (1H, m, CH=CHC*H*$_2$), 2.12-2.17 (1H, m, C*H*$_2$CH=CH$_2$), 2.68-2.78 (2H, m, PhC*H*$_2$), 2.93-2.98 (1H, m, C*H*CH$_2$OH), 3.07-3.12 (1H, m, NC*H*CH), 3.28 (1H, dd, *J* 10.6, 3.5, C*H*(H)OH), 3.57 (1H, dd, *J* 10.6, 3.8, C*H*(H)OH), 5.02-5.11 (3H, m, CH=C*H*$_2$ & NCHC*H*), 5.56-5.64 (1H, m, CH=C*H*CH$_2$), 5.67-5.78 (1H, m, C*H*=CH$_2$), 5.84-5.96 (2H, m, C*H*CH=CHCH$_2$ & CHC*H*=CHCH$_2$), 7.15-7.31 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 14.1 (CH_3), 22.5 (CH_2), 28.9 (CH_2), 31.4 (CH_2), 32.6 (CH_2), 38.9 (CH_2), 40.9 (CH_2), 56.3 (CH), 57.3 (CH), 61.8 (CH_2), 117.2 (CH_2), 126.4 (CH), 128.5 (2 x CH), 129.28 (2 x CH), 129.33 (CH), 131.3 (CH), 133.0 (CH), 134.8 (CH), 135.0

(CH), 138.6 (C); *m/z* (EI) 328 ($(M+1)^+$, 100%), 328 (100%). Accurate mass: found 328.2649, $C_{22}H_{34}NO$ requires 328.2640.

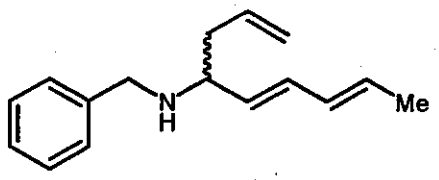
(*S*)-2-(Allylamino)-3-phenylpropan-1-ol



(234j)

(*S*,2*E*)-2-((*E*)-3-(Dimethylamino)allylideneamino)-3-phenylpropan-1-ol **(241j)** (2.80 g, 12.1 mmol) was dissolved in a 4:1 mixture of dry toluene/Et_2O (75 mL) under a nitrogen atmosphere. Magnesium turnings (0.97 g, 39.8 mmol) and a catalytic amount of iodine were added to the solution. Allyl bromide (3.36 mL, 39.8 mmol) was cautiously added and the mixture was stirred for 18 h. The reaction was quenched with water until a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue was rinsed with Et_2O (2 x 50 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution (2 x 75 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and a yellow solid was obtained, which was recrystallised from Et_2O/hexane to yield **(234j)** as orange crystals (1.48 g, 64%). Mp 55-57 °C; $[\alpha]^{25}_D$ = -36.2 (*c* = 1.2, $CHCl_3$); ν_{max}/cm^{-1} (film) 3125, 3066, 2918, 2857, 1494, 1451, 1109, 1054, 1036, 912, 748, 698; δ_H ($CDCl_3$, 400 MHz) 1.95 (1H, br, N*H*), 2.72 (1H, dd, *J* 13.6, 7.1, PhC*H*(H)), 2.80 (1H, dd, *J* 13.6, 6.7 PhC*H*(H)), 2.91-2.97 (1H, m, C*H*CH_2OH), 3.25 (2H, d, *J* 5.9, NCH_2), 3.32 (1H, dd, *J* 10.7, 5.6, C*H*(H)OH), 3.61 (1H, dd, *J* 10.7, 4.0, C*H*(H)OH), 5.05-5.15 (2H, m, CH=CH_2), 5.76-5.86 (1H, m, C*H*=CH_2), 7.17-7.32 (5H, m, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 38.1 (CH_2), 49.5 (CH_2), 59.3 (CH), 62.4 (CH_2), 116.0 (CH_2), 126.4 (CH), 128.5 (2 x CH), 129.2 (2 x CH), 136.6 (CH), 138.5 (C); *m/z* (EI) 191 (M^+, 1%), 100 (100%). Accurate mass: found 191.1306, $C_{12}H_{17}NO$ requires 191.1310.

(5*E*,7*E*)-*N*-Benzylnona-1,5,7-trien-4-amine

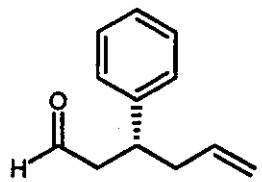


(291)

(7*E*)-*N*-((2*E*,4*E*)-Hexa-2,4-dienylidene)(phenyl)methanamine **(290)** (2.5 g, 13.5 mmol) was dissolved in a 4:1 mixture of dry toluene/Et_2O (75 mL) under a nitrogen atmosphere. Magnesium turnings (1.08 g, 44.5 mmol) and a catalytic amount of iodine were added to the solution. Allyl bromide (3.77 mL, 44.5 mmol) was cautiously added and the mixture was stirred for 18 h. The reaction was quenched with water until a gelatinous precipitate formed. The organic layer was decanted and the gelatinous residue was rinsed with Et_2O (2 x 50 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution (2 x 75 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and a brown oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (9:1 hexane:EtOAc). The target compound **(291)** was obtained as a yellow oil. (1.85 g, 60%). ν_{max}/cm^{-1} (film) 3017, 2911, 1639, 1453, 908, 914, 733, 700; δ_H ($CDCl_3$, 400 MHz) 1.52 (1H, br, N*H*), 1.25 (3H, d, *J* 7.0, C*H*$_3$), 2.22-2.34 (2H, m, C*H*$_2$CH=CH$_2$), 3.09-3.17 (1H, m, NC*H*), 3.61 (1H, d, *J* 13.3, PhC*H*(H)), 3.81 (1H, d, *J* 13.3, PhC*H*(H)), 5.03-5.12 (2H, m, CH=C*H*$_2$), 5.38-5.43 (1H, m, NCHC*H*), 5.63-5.76 (2H, m, C*H*=CH$_2$ & C*H*CH$_3$), 6.04-6.14 (2H, m, C*H*CH=CHCH$_3$, & C*H*=CHCH$_3$), 7.21-7.30 (5H, m, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 18.1 (CH_3), 40.71 (CH_2), 51.3 (CH_2), 59.2 (CH), 117.4 (CH_2), 126.8 (CH), 128.2 (2 x CH), 128.4 (2 x CH), 128.7 (CH), 131.2 (CH), 131.8 (CH), 133.5 (CH), 135.3 (CH), 140.7 (C); *m/z* (EI) 227 (M^+, 1%), 91 (100%). Accurate mass: found 227.1670, $C_{16}H_{21}N$ requires 227.1674.

3.2.4 Anionic Amino-Cope Rearrangements

(*R*)-3-Phenylhex-5-enal[133]



(231a)

Anionic Amino-Cope Rearrangement with *n*-BuLi

(*S*)-2-((*S*,*E*)-1-Phenylhexa-1,5-dien-3-ylamino)-3-phenylpropan-1-ol **(234a)** (2.50 g, 8.1 mmol) was dried *in vacuo* for 1 h, dissolved in dry THF (40 mL) under a nitrogen atmosphere and cooled to -78 °C. A 2.5M solution of *n*-BuLi in hexanes (8.13 mL, 20.3 mmol) was added dropwise and the mixture was stirred for 10 min before warming to room temperature. The resultant solution was heated at reflux for 1 h, quenched with water, dried over anhydrous Na_2SO_4 and filtered through a small pad of Celite, eluting with CH_2Cl_2. The solvent was removed under reduced pressure and an orange oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (9:1 light petroleum:Et_2O) to yield the target compound **(231a)** as a pale yellow oil (0.98 g, 69%). $[\alpha]^{25}_D$ = -21.3 (*c* = 1.7, $CHCl_3$); ν_{max}/cm^{-1} (film) 3028, 2923, 1724, 1494, 1453, 915, 700; δ_H ($CDCl_3$, 400 MHz) 2.34-2.46 (2H, m, C*H*$_2$CH=CH$_2$), 2.68-2.81 (2H, m, C*H*$_2$CHO), 3.26-3.33 (1H, m, C*H*Ph), 4.98-5.04 (2H, m, CH=C*H*$_2$), 5.60-5.70 (1H, m, C*H*=CH$_2$), 7.18-7.32 (5H, m, Ar*H*), 9.67 (1H, t, *J* 1.9 C*H*O); δ_C ($CDCl_3$, 100 MHz) 39.7 (CH), 41.0 (CH_2), 49.3 (CH_2), 117.2 (CH_2), 126.7 (CH), 127.5 (2 x CH), 128.5 (2 x CH), 135.8 (CH), 143.4 (C), 201.7 (CH); *m/z* (EI) 174 (M^+, 8%), 105 (100%). Accurate mass: found 174.1046, $C_{12}H_{14}O$ requires 174.1045. The enantiomeric excess was immediately measured, as reported in **Section 3.2.5**.

The same procedure was conducted in toluene and in hexane. Either solvent was removed under reduced pressure and the crude orange oil was adsorbed onto silica and purified by flash column chromatography (9:1 light petroleum:Et_2O) to yield the target compound **(231a)** as a pale yellow oil. Spectroscopic data were identical to those previously reported for **(231a)**.

The same procedure was conducted in tetrahydrofuran using either 2.5 equivalents of NaH or KH with 18-crown-6. Both reactions were refluxed for up to 24 h but only starting material was isolated in both cases.

Anionic Amino-Cope Rearrangement with *n*-BuLi and DMPU

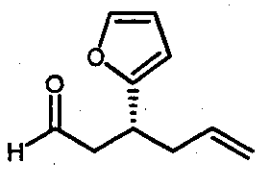
(*S*)-2-((*S*,*E*)-1-Phenylhexa-1,5-dien-3-ylamino)-3-phenylpropan-1-ol **(234a)** (0.8 g, 2.6 mmol) was dried *in vacuo* for 1 h and then dissolved in dry THF (40 mL) under a nitrogen atmosphere. 1,3-Dimethyl-3,4,5,6,-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (3.15 mL, 26.0 mmol) was added to the reaction vessel and the solution was cooled to -78 °C. A 2.5M solution of *n*-BuLi in hexanes (2.60 mL, 6.5 mmol) was added dropwise and the reaction mixture stirred for 10 min before warming to room temperature. The resultant solution was heated at reflux for 1 h, quenched with water, dried over anhydrous Na_2SO_4 and filtered through a small pad of Celite, eluting with CH_2Cl_2. The solvent was removed under reduced pressure and an orange oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (9:1 light petroleum:Et_2O), to yield the target compound **(231a)** as a pale yellow oil (0.027 g, 6%). Spectroscopic data were identical to those previously reported for **(231a)**.

One pot Grignard Addition/Anionic Amino-Cope Rearrangement

(*S*,2*E*)-2-((*E*)-3-Phenylallylideneamino)-3-phenylpropan-1-ol **(241a)** (0.7 g, 2.6 mmol) was dissolved in dry THF (50 mL) under a nitrogen atmosphere. Magnesium turnings (0.21 g, 8.7 mmol) and a catalytic amount of iodine were added to the solution. Allyl bromide (0.75 mL, 8.7 mmol) was cautiously added and the mixture stirred for 18 h. The reaction mixture was cooled to -78 °C, a 2.5M solution of *n*-BuLi in hexanes (10.5 mL, 26.3 mmol) was added dropwise and the mixture was stirred for 10 min before warming to room temperature. The resultant solution was heated at reflux for 1 h, cooled to 0 °C, quenched with water, dried over anhydrous Na_2SO_4 and filtered through a small pad of Celite, eluting with CH_2Cl_2. The solvent was removed under reduced pressure and an orange oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (9:1 light petroleum:Et_2O) to yield the target compound **(231a)** as a pale yellow oil (0.115 g, 25%). Spectroscopic data were identical to those previously reported for **(231a)**.

The same procedure was conducted in a 4:1 mixture of dry toluene/Et_2O. The solvents were removed under reduced pressure and the crude orange oil was adsorbed onto silica and purified by flash column chromatography (9:1 light petroleum:Et_2O) to yield the target compound **(231a)** as a pale yellow oil. Spectroscopic data were identical to those previously reported for **(231a)**.

(*R*)-3-(Furan-2-yl)hex-5-enal

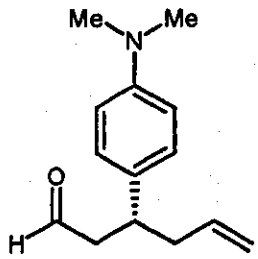


(231b)

(*S*)-2-((*S*,*E*)-1-(Furan-2-yl)hexa-1,5-dien-3-ylamino)-3-phenylpropan-1-ol **(234b)** (1.0 g, 3.4 mmol) was dried *in vacuo* for 1 h, dissolved in dry THF (30 mL) under a nitrogen atmosphere and cooled to -78 °C. A 2.5M solution of *n*-BuLi in hexanes (3.36 mL, 8.4 mmol) was added dropwise and the mixture stirred for 10 min before warming to room temperature. The resultant black solution was heated at reflux for 1 h, quenched with water, dried over anhydrous Na_2SO_4 and filtered through a small pad of Celite, eluting with CH_2Cl_2. The solvent was removed under reduced pressure and an orange oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (9:1 light petroleum:Et_2O) to yield the target compound **(231b)** as a pale yellow oil (0.29 g, 53%). $[\alpha]^{25}_D$ = -13.6 (*c* = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (film) 2923, 1724, 1506, 1011, 920, 734; δ_H ($CDCl_3$, 400 MHz) 2.33-2.41 (1H, m, C*H*(H)CH=CH_2), 2.46-2.54 (1H, m, C*H*(H)CH=CH_2), 2.66-2.78 (2H, m, CHOCH_2), 3.39-3.46 (1H, m, CH_2CHCH_2), 5.03-5.08 (2H, m, CH=CH_2), 5.64-5.75 (1H, m, C*H*=CH_2), 6.04 (1H, d, *J* 3.2, OC=C*H*), 6.28 (1H, dd, *J* 3.2, 1.8, OCH=C*H*), 7.32 (1H, dd, *J* 1.8, 0.7, OC*H*=CH), 9.73 (1H, t, *J* 1.9, C*H*O); δ_C ($CDCl_3$, 100 MHz) 32.9 (CH), 38.0 (CH_2), 46.6 (CH_2), 105.4 (CH), 110.0 (CH), 117.5 (CH_2), 135.1 (CH), 141.3 (CH), 156.3 (C), 201.3 (CH); *m/z* (EI) 164 (M^+, 11%), 95 (100%). Accurate mass: found 164.0835, $C_{10}H_{12}O_2$ requires 164.0837. The enantiomeric excess was immediately measured, as reported in **Section 3.2.5**.

The same procedure was conducted separately in toluene, hexane and tetrahydrofuran/DMPU. The solvents were removed under reduced pressure and the crude orange oil was adsorbed onto silica and purified by flash column chromatography (9:1 light petroleum:Et_2O) to yield the target compound **(231b)** as a pale yellow oil. Spectroscopic data were identical to those previously reported for **(231b)**.

(*R*)-3-(4-(Dimethylamino)phenyl)hex-5-enal



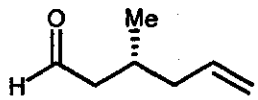
(231c)

(*S*)-2-(*S*,*E*)-1-(4-(Dimethylamino)phenyl)hexa-1,5-dien-3-ylamino)-3-phenylpropan-1-ol **(234c)** (1.0 g, 2.9 mmol) was dried *in vacuo* for 1 h, dissolved in dry THF (20 mL) under a nitrogen atmosphere and cooled to -78 °C. A 2.5M solution of *n*-BuLi in hexanes (2.85 mL, 7.1 mmol) was added dropwise and the mixture stirred for 10 min before warming to room temperature. The resultant solution was heated at reflux for 1 h, quenched with water, dried over anhydrous Na_2SO_4 and filtered through a small pad of Celite, eluting with CH_2Cl_2. The solvent was removed under reduced pressure and an orange oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (9:1 light petroleum:Et_2O) to yield the target compound **(231c)** as a pale yellow oil (0.41 g, 65%). $[\alpha]^{25}_D$ = -13.8 (*c* = 1.4, $CHCl_3$); ν_{max}/cm^{-1} (film) 2921, 1721, 1614, 1518, 1444, 1348, 1164, 947, 816; δ_H ($CDCl_3$, 400 MHz) 2.30-2.43 (2H, m, C*H*$_2$CH=CH$_2$), 2.62-2.75 (2H, m, C*H*$_2$CHO), 2.92 (6H, s, N(C*H*$_3$)$_2$), 3.16-3.24 (1H, m, CH$_2$C*H*CH$_2$), 4.98-5.04 (2H, m, CH=C*H*$_2$), 5.63-5.73 (1H, m, C*H*=CH$_2$), 6.69 (2H, d, *J* 8.6, 2 x (C*H*CN)), 7.06 (2H, d, *J* 8.6, 2 x (C*H*CHCN)), 9.65 (1H, t, *J* 2.2, C*H*O); δ_C ($CDCl_3$, 100 MHz) 38.9 (CH), 40.6 (2 x CH_3), 41.2 (CH_2), 49.5 (CH_2), 112.8 (2 x CH), 116.8 (CH_2), 128.0 (2 x CH), 131.1 (C), 136.2 (CH), 149.4 (C), 202.5 (CH); *m/z* (EI) 217 (M^+, 23%), 176 (100%). Accurate mass: found 217.1467, $C_{14}H_{19}NO$ requires 217.1467. The enantiomeric excess was immediately measured, as reported in **Section 3.2.5**.

The same procedure was conducted in toluene and in hexane. Either solvent was removed under reduced pressure and the crude orange oil was adsorbed onto silica and purified by flash column chromatography (9:1 light petroleum:Et_2O) to yield the target compound

(231c) as a pale yellow oil. Spectroscopic data were identical to those previously reported for **(231c)**.

(*R*)-3-Methylhex-5-enal

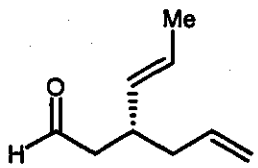


(231f)

(*S*)-2-((*S*,*E*)-Hepta-1,5-dien-4-ylamino)-3-phenylpropan-1-ol **(234f)** (1.50 g, 6.1 mmol) was dried *in vacuo* for 1 h, dissolved in dry THF (40 mL) under a nitrogen atmosphere and cooled to -78 °C. A 2.5M solution of *n*-BuLi in hexanes (6.11 mL, 15.3 mmol) was added dropwise and the mixture was stirred for 10 min before warming to room temperature. The resultant solution was heated at reflux for 1 h, quenched with water, dried over anhydrous Na_2SO_4 and filtered through a small pad of Celite, eluting with CH_2Cl_2. The solvent was removed under reduced pressure and an orange oil was obtained. Any attempt to isolate the aldehyde **(231f)** by flash column chromatography resulted in degradation of the product.

The target compound **(231f)** was observed by ^1H NMR when the crude was filtered through a small pad of silica. The enantiomeric excess could not be calculated due to the low purity of the product.

(*R*)-3-((*E*)-Prop-1-enyl)hex-5-enal

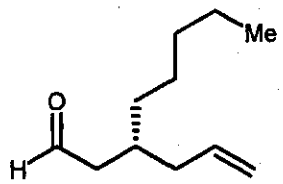


(231g)

(*S*)-2-((*S*,5*E*,7*E*)-Nona-1,5,7-trien-4-ylamino)-3-phenylpropan-1-ol **(234g)** (1.5 g, 5.5 mmol) was dried *in vacuo* for 1 h, dissolved in dry THF (40 mL) under a nitrogen atmosphere and cooled to -78 °C. A 2.5M solution of *n*-BuLi in hexanes (5.53 mL, 13.8 mmol) was added dropwise and the mixture stirred for 10 min before warming to room temperature. The resultant solution was heated at reflux for 1 h, quenched with water, dried over anhydrous Na_2SO_4 and filtered through a small pad of Celite, eluting with CH_2Cl_2. The solvent was removed under reduced pressure and an orange oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (9.5:1 light petroleum:Et_2O) to yield the target compound **(231g)** as a pale yellow oil (0.27 g, 35%). $[\alpha]^{25}_D$ = -15.7 (*c* = 1.1, $CHCl_3$); ν_{max}/cm^{-1} (film) 2916, 1724, 1686, 1439, 967; δ_H ($CDCl_3$, 400 MHz) 1.64-1.66 (3H, m, C*H*$_3$), 2.05-2.20 (2H, m, C*H*$_2$CH=CH$_2$), 2.28-2.38 (1H, m, C*H*(H)CHO), 2.43-2.52 (1H, m, C*H*(H)CHO), 2.64-2.73 (1H, m, CH$_2$C*H*CH$_2$), 4.99-5.07 (2H, m, CH=C*H*$_2$), 5.28-5.35 (1H, m, C*H*=CHCH$_3$), 5.44-5.57 (1H, m, CH=C*H*CH$_3$), 5.68-5.79 (1H, m, C*H*=CH$_2$), 9.70 (1H, s, C*H*O); δ_C ($CDCl_3$, 100 MHz) 17.9 (CH_3), 36.9 (CH), 39.6 (CH_2), 48.0 (CH_2), 116.9 (CH_2), 126.0 (CH), 133.1 (CH), 135.9 (CH), 202.8 (CH).[100b] The enantiomeric excess was immediately measured, as reported in **Section 3.2.5**.

The same procedure was conducted separately in toluene, hexane and tetrahydrofuran/DMPU. The solvents were removed under reduced pressure and the crude orange oil was adsorbed onto silica and purified by flash column chromatography (9.5:1 light petroleum:Et_2O) to yield the target compound **(231g)** as a pale yellow oil. Spectroscopic data were identical to those previously reported for **(231g)**.

(*R*)-3-Allyloctanal

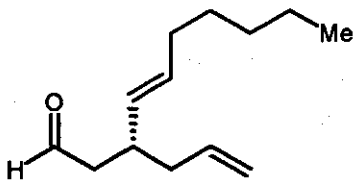


(231h)

(*S*)-2-((*S*,*E*)-Undeca-1,5-dien-4-ylamino)-3-phenylpropan-1-ol **(234h)** (1.5 g, 5.0 mmol) was dried *in vacuo* for 1 h, dissolved in dry THF (40 mL) under a nitrogen atmosphere and cooled to -78 °C. A 2.5M solution of *n*-BuLi in hexanes (5.0 mL, 12.4 mmol) was added dropwise and the mixture was stirred for 10 min before warming to room temperature. The resultant solution was heated at reflux for 1 h, quenched with water, dried over anhydrous Na_2SO_4 and filtered through a small pad of Celite, eluting with CH_2Cl_2. The solvent was removed under reduced pressure and a yellow oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (9.5:1 light petroleum:Et_2O) to yield the target compound **(231h)** as a pale yellow oil (0.165 g, 20%); $[\alpha]^{25}_D$ = -10.7 (*c* = 1.3, $CHCl_3$); ν_{max}/cm^{-1} (film) 2955, 2925, 2856, 1725, 913; δ_H ($CDCl_3$, 400 MHz) 0.88 (3H, t, *J* 7.0, CH_3), 1.27-1.32 (8H, m, $(CH_2)_4CH_3$), 1.99-2.10 (2H, m, $CHOCH_2CH$ & $CH(H)CH{=}CH_2$), 2.13-2.19 (1H, m, $CH(H)CH{=}CH_2$), 2.36 (2H, ddd, *J* 16.5, 6.4, 2.3, $CHOCH_2$), 5.01-5.06 (2H, m, $CH{=}CH_2$), 5.70-5.77 (1H, m, $CH{=}CH_2$), 9.76 (1H, t, *J* 2.3, *CHO*); δ_C ($CDCl_3$, 100 MHz) 14.1 (CH_3), 22.6 (CH_2), 26.4 (CH_2), 31.9 (CH_2), 32.8 (CH), 34.0 (CH_2), 38.5 (CH_2), 48.1 (CH_2), 117.1 (CH_2), 136.2 (CH), 203.1 (CH). The enantiomeric excess was immediately measured, as reported in **Section 3.2.5**.

The same procedure was conducted in toluene and in hexane. Either solvent was removed under reduced pressure and the crude yellow oil was adsorbed onto silica and purified by flash column chromatography (9.5:1 light petroleum:Et_2O) to yield the target compound **(231h)** as a pale yellow oil. Spectroscopic data were identical to those previously reported for **(231h)**.

(*R*,*E*)-3-Allyldec-4-enal



(231i)

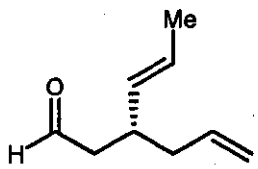
(*S*)-2-((*S*,5*E*,7*E*)-Trideca-1,5,7-trien-4-ylamino)-3-phenylpropan-1-ol **(234i)** (0.70 g, 2.1 mmol) was dried *in vacuo* for 1 h, dissolved in dry THF (30 mL) under a nitrogen atmosphere and cooled to -78 °C. A 2.5M solution of *n*-BuLi in hexanes (2.14 mL, 5.3 mmol) was added dropwise and the mixture stirred for 10 min before warming to room temperature. The resultant solution was heated at reflux for 1 h, quenched with water, dried over anhydrous Na_2SO_4 and filtered through a small pad of Celite, eluting with CH_2Cl_2. The solvent was removed under reduced pressure and a yellow oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (9.5:1 light petroleum:Et_2O) to yield the target compound **(231i)** as a pale yellow oil (0.225 g, 54%). $[\alpha]^{25}_D$ = -20.8 (*c* = 1.2, $CHCl_3$); ν_{max}/cm^{-1} (film) 2955, 2925, 2855, 1726, 1440, 971, 914; δ_H ($CDCl_3$, 400 MHz) 0.88 (3H, t, *J* 6.7, CH_3), 1.20-1.37 (6H, m, $(CH_2)_3CH_3$), 1.95-2.00 (2H, m, $CH{=}CHCH_2$), 2.10-2.18 (2H, m, $CH_2CH{=}CH_2$), 2.35 (1H, ddd, *J* 16.4, 8.6, 2.7, CHOC*H*(H)), 2.46 (1H, ddd, *J* 16.4, 5.6, 2.0, CHOC*H*(H)), 2.65-2.71 (1H, m, CH_2CHCH_2), 5.01-5.05 (2H, m, $CH{=}CH_2$), 5.25-5.31 (1H, m, $CH{=}CHCH_2$), 5.42-5.49 (1H, m, $CH{=}CHCH_2$), 5.68-5.79 (1H, m, $CH{=}CH_2$), 9.70 (1H, m, *CH*O); δ_C ($CDCl_3$, 100 MHz) 14.1 (CH_3), 22.5 (CH_2), 29.1 (CH_2), 31.3 (CH_2), 32.4 (CH_2), 37.0 (CH), 39.7 (CH_2), 48.1 (CH_2), 116.9 (CH_2), 131.7 (CH), 131.8 (CH), 135.9 (CH), 202.7 (CH); *m/z* (EI) 194 (M^+, 2%), 109 (100%). Accurate mass: found 194.1675, $C_{13}H_{22}O$ requires 194.1671. The enantiomeric excess was immediately measured, as reported in **Section 3.2.5**.

The same procedure was conducted in toluene and in hexane. Either solvent was removed under reduced pressure and the crude yellow oil was adsorbed onto silica and purified by flash column chromatography (9.5:1 light petroleum:Et_2O) to yield the target compound

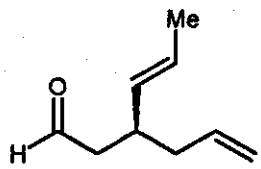
(231i) as a pale yellow oil. Spectroscopic data were identical to those previously reported for **(231i)**.

(*R*)-3-((*E*)-Prop-1-enyl)hex-5-enal (232g)

(*S*)-3-((*E*)-Prop-1-enyl)hex-5-enal (252g)



(231g)



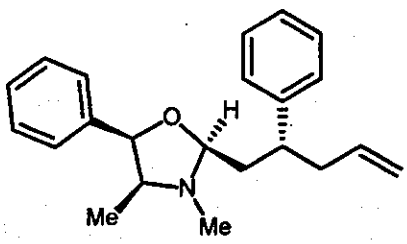
(252g)

(5*E*,7*E*)-*N*-Benzylnona-1,5,7-trien-4-amine **(291)** (1.5 g, 6.6 mmol) was dried *in vacuo* for 1 h, dissolved in dry THF (40 mL) under a nitrogen atmosphere and cooled to -78 °C. A 2.5M solution of *n*-BuLi in hexanes (6.60 mL, 16.4 mmol) was added dropwise and the mixture stirred for 10 min before warming to room temperature. The resultant solution was heated at reflux for 1 h, quenched with water, dried over anhydrous Na_2SO_4 and filtered through a small pad of Celite, eluting with CH_2Cl_2. The solvent was removed under reduced pressure and a yellow oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (9.5:1 light petroleum:Et_2O) to yield a racemic mixture of **(231g)** and **(252g)** as a pale yellow oil (0.209 g, 26%). Spectroscopic data were identical to those previously reported for **(231g)**.

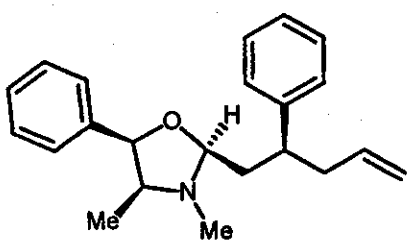
3.2.5 Measurement of the Enantiomeric Excess

(2*S*,4*S*,5*R*)-3,4-Dimethyl-5-phenyl-2-((*R*)-2-phenylpent-4-enyl)oxazolidine (286a)[133]

(2*S*,4*S*,5*R*)-3,4-Dimethyl-5-phenyl-2-((*S*)-2-phenylpent-4-enyl)oxazolidine (287a)



(286a)
R-isomer



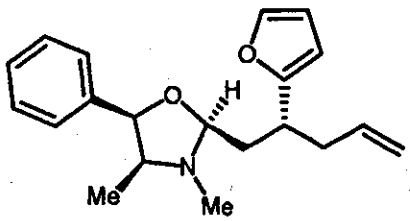
(287a)
S-isomer

(1*R*,2*S*)-(-)-Ephedrine **(285)** (0.047 g, 0.29 mmol) was added to (*R*)-3-phenylhex-5-enal **(231a)** (0.050 g, 0.29 mmol) and activated 4Å molecular sieves in dry CH_2Cl_2 (10 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred for 18 h and then filtered through a thin pad of Celite, eluting with CH_2Cl_2. The solvent was removed under reduced pressure and a mixture of oxazolidines **(286a)** and **(287a)** was obtained as a light yellow oil (0.086 g, 93%). Analysis of the ^1H NMR spectrum of the crude diastereoisomeric mixture enabled measurement of the *d.e.*, which could be directly related to the *e.e.* of the starting material. δ_H ($CDCl_3$, 400 MHz) 0.61 (3H, d, *J* 6.4, CHC*H*$_3$, *R*-isomer), 0.65 (3H, d, *J* 6.5, CHC*H*$_3$, *S*-isomer), 2.04-2.13 (2H, m, OCHC*H*$_2$, both isomers), 2.10 (3H, s, NC*H*$_3$, *R*-isomer), 2.24 (3H, s, NC*H*$_3$, *S*-isomer), 2.38-2.49 (C*H*$_2$CH=CH$_2$, both isomers), 2.58-2.65 (1H, m, C*H*CH$_3$, *R*-isomer), 2.74-2.77 (1H, m, C*H*CH$_3$, *S*-isomer), 3.04-3.09 (1H, m, CH$_2$C*H*Ph, both isomers), 3.50-3.52 (1H, m, OC*H*N, *R*-isomer), 4.00 (1H, dd, *J* 11.5, 5.1, OC*H*N, *S*-isomer), 4.91-5.00 (3H, m, CH=C*H*$_2$ & PhC*H*O, both isomers), 5.61-5.72 (1H, m, C*H*=CH$_2$, both isomers), 7.17-7.32 (10H, m, Ar*H*, both isomers); δ_C ($CDCl_3$, 100 MHz) 14.9 (C*H*$_3$, *R*-isomer), 15.1 (CH$_3$, *S*-isomer), 36.2 (CH$_3$, *R*-isomer), 36.9 (CH$_3$, *S*-isomer), 39.8 (CH$_2$, both isomers), 41.9 (CH, both isomers), 42.3 (CH$_2$, both isomers), 64.1 (CH, *R*-isomer), 64.3 (CH, *S*-isomer), 81.7 (CH, *S*-isomer), 81.9 (CH, *R*-isomer), 95.5 (CH, *R*-isomer), 95.8 (CH, *S*-isomer),

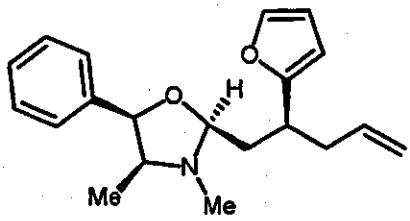
116.3 (CH_2, *R*-isomer), 116.4 (CH_2, *S*-isomer), 126.1 (CH, *S*-isomer), 126.2 (CH, *R*-isomer), 127.5 (CH, *S*-isomer), 127.6 (CH, *R*-isomer), 127.7 (2 x CH, both isomers), 127.8 (2 x CH, *S*-isomer), 127.88 (2 x CH, *R*-isomer), 127.93 (2 x CH, *S*-isomer), 128.0 (2 x CH, *R*-isomer), 128.3 (2 x CH, *S*-isomer), 128.4 (2 x CH, *R*-isomer), 136.5 (CH, *S*-isomer), 136.6 (CH, *R*-isomer), 140.0 (C, *S*-isomer), 140.2 (C, *R*-isomer), 144.7 (C, *R*-isomer), 145.4 (C, *S*-isomer).

(2*S*,4*S*,5*R*)-2-((*R*)-2-(Furan-2-yl)pent-4-enyl)-3,4-dimethyl-5-phenyloxazolidine (286b)

(2*S*,4*S*,5*R*)-2-((*S*)-2-(Furan-2-yl)pent-4-enyl)-3,4-dimethyl-5-phenyloxazolidine (287b)



(286b)
R-isomer



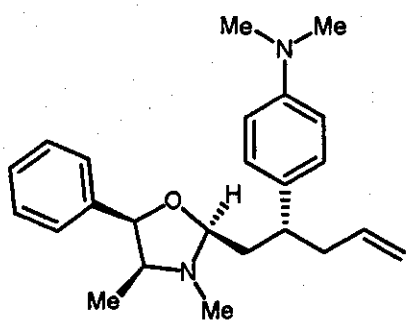
(287b)
S-isomer

(1*R*,2*S*)-(-)-Ephedrine **(285)** (0.050 g, 0.31 mmol) was added to (*R*)-3-(furan-2-yl)hex-5-enal **(231b)** (0.050 g, 0.31 mmol) and activated 4Å molecular sieves in dry CH_2Cl_2 (10 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred for 18 h and then filtered through a thin pad of Celite, eluting with CH_2Cl_2. The solvent was removed under reduced pressure and a mixture of oxazolidines **(286b)** and **(287b)** was obtained as a light yellow oil (0.091 g, 96%). Analysis of the ^{1}H NMR spectrum of the crude diastereoisomeric mixture enabled measurement of the *d.e.*, which could be directly related to the *e.e.* of the starting material. δ_H ($CDCl_3$, 400 MHz) 0.64 (3H, d, *J* 6.5, $CHCH_3$, *R*-isomer), 0.65-0.67 (3H, m, $CHCH_3$, *S*-isomer), 1.92-1.99 (2H, m, $OCHCH_2$, *R*-isomer), 2.15-2.19 (2H, m, $OCHCH_2$, *S*-isomer), 2.18 (3H, s, NCH_3, *R*-isomer), 2.24 (3H, s, NCH_3, *S*-isomer), 2.37-2.67 (2H, m, $CH_2CH{=}CH_2$, both isomers), 2.67-2.72 (1H, m, $CHCH_3$, *R*-isomer), 2.73-2.78 (1H, m, $CHCH_3$, *S*-isomer), 3.16-3.23 (1H, m, CH_2CH CH_2, both isomers), 3.63 (1H, dd, *J* 9.0, 1.6, $OCHN$, *R*-isomer), 3.92 (1H, dd, *J* 7.4, 3.0, $OCHN$, *S*-isomer), 4.97-5.07 (3H, m, $CH{=}CH_2$ & $PhCH$, both isomers), 5.66-5.76 (1H, m, $CH{=}CH_2$, both isomers), 6.05-6.07 (1H, m, $OC{=}CH$, both isomers), 6.27-6.29 (1H, m, $OC{=}CHCH$, both isomers), 7.25-7.34 (6H, m, ArH & $OC{=}CHCH{=}CH$, both isomers); δ_C ($CDCl_3$, 100 MHz) 14.9 (CH_3, *R*-isomer), 15.1 (CH_3, *S*-isomer), 35.5 (CH, both isomers), 36.3 (CH_3, *R*-isomer), 36.7 (CH_3, *S*-isomer), 37.5 (CH_2, both isomers), 39.7 (CH_2, both isomers), 64.1 (CH, *R*-isomer), 64.2 (CH, *S*-isomer), 81.8 (CH, *S*-isomer),

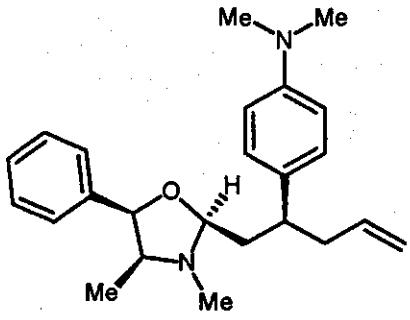
82.0 (CH, *R*-isomer), 95.4 (CH, *S*-isomer), 95.8 (CH, *R*-isomer), 105.0 (CH, *S*-isomer), 105.7 (CH, *R*-isomer), 110.0(CH, both isomers), 116.5 (CH_2, *R*-isomer), 116.6 (CH_2, *S*-isomer), 127.55 (CH, both isomers), 127.63 (2 x CH, both isomers), 127.9 (2 x CH, both isomers), 136.1 (CH, both isomers), 139.9 (C, *S*-isomer), 140.0 (C, *R*-isomer), 140.8 (CH, *S*-isomer), 140.9 (CH, *R*-isomer), 157.5 (C, both isomers).

***N*,*N*-Dimethyl-4-((*R*)-1-(2*S*,4*S*,5*R*)-3,4-dimethyl-5-phenyloxazolidin-2-yl)pent-4-en-2-yl)benzenamine (286c)**

***N*,*N*-Dimethyl-4-((*S*)-1-(2*S*,4*S*,5*R*)-3,4-dimethyl-5-phenyloxazolidin-2-yl)pent-4-en-2-yl)benzenamine (287c)**



(286c)
R-isomer



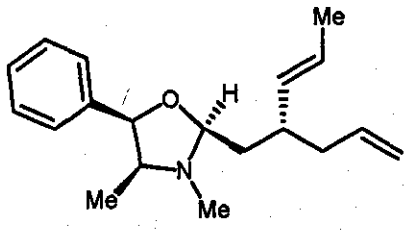
(287c)
S-isomer

(1*R*,2*S*)-(-)-Ephedrine **(285)** (0.038 g, 0.23 mmol) was added to (*R*)-3-(4-(dimethylamino) phenyl)hex-5-enal **(231c)** (0.05 g, 0.23 mmol) and activated 4Å molecular sieves in dry CH_2Cl_2 (10 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred for 18 h and then filtered through a thin pad of Celite, eluting with CH_2Cl_2. The solvent was removed under reduced pressure and a mixture of oxazolidines **(286c)** and **(287c)** was obtained as a light yellow oil (0.076 g, 89%). Analysis of the ^{1}H NMR spectrum of the crude diastereoisomeric mixture enabled measurement of the *d.e.*, which could be directly related to the *e.e.* of the starting material. δ_H ($CDCl_3$, 400 MHz) 0.54 (3H, d, *J* 6.5, C*H*CH_3, *R*-isomer), 0.58 (3H, d, *J* 6.7, C*H*CH_3, *S*-isomer), 1.95-1.99 (2H, m, OCHC*H*$_2$, both isomers), 2.05 (3H, s, NC*H*$_3$, *R*-isomer), 2.17 (3H, s, NC*H*$_3$, *S*-isomer), 2.27-2.35 (2H, m, C*H*$_2$CH=CH_2, both isomers), 2.52-2.59 (1H, m, C*H*CH_3, *R*-isomer), 2.65-2.72 (1H, m, C*H*CH_3, *S*-isomer), 2.86-2.94 (1H, m, CH_2C*H*CH_2, both isomers), 2.83-2.86 (6H, m, N(C*H*$_3$)$_2$, both isomers), 3.47-3.50 (1H, m, OC*H*N, *R*-isomer), 3.87 (1H, dd, *J* 6.9, 3.5, OC*H*N, *S*-isomer), 4.84-4.96 (3H, m, CH=C*H*$_2$ & PhC*H*O, both isomers), 5.55-5.68 (1H, m, C*H*=CH_2, both isomers), 6.60-6.65 (2H, m, 2 x (C*H*CN), both isomers), 6.97-7.09 (2H, m, 2 x (C*H*CHCN), both isomers), 7.14-7.28 (5H, m, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 14.8 (C*H*$_3$, *R*-isomer), 15.0 (CH_3, *S*-isomer), 36.2 (CH_3, *R*-isomer),

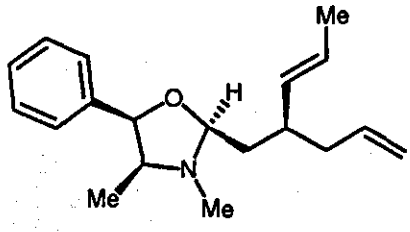
36.8 (CH_3, *S*-isomer), 39.7 (CH_2, *R*-isomer), 39.8 (CH_2, *S*-isomer), 40.71 (2 x CH_3, *R*-isomer), 40.74 (2 x CH_3, *S*-isomer), 40.8 (CH, both isomers), 42.4 (CH_2, both isomers), 64.0 (CH, *R*-isomer), 64.2 (CH, *S*-isomer), 81.6 (CH, *S*-isomer), 81.8 (CH, *R*-isomer), 95.6 (CH, *R*-isomer), 95.8 (CH, *S*-isomer), 112.7 (2 x CH, *R*-isomer), 112.8 (2 x CH, *S*-isomer), 115.85 (CH_2, *R*-isomer), 115.92 (CH_2, *S*-isomer), 127.3 (CH, *S*-isomer), 127.4 (CH, *R*-isomer), 127.5 (2 x CH, *S*-isomer), 127.6 (2 x CH, *R*-isomer), 127.77 (2 x CH, *S*-isomer), 127.82 (2 x CH, *R*-isomer), 128.2 (2 x CH, *S*-isomer), 128.3 (2 x CH, *R*-isomer), 132.6 (C, both isomers), 136.8 (CH, *S*-isomer), 137.0 (CH, *R*-isomer), 139.9 (C, *S*-isomer), 140.2 (C, *R*-isomer), 148.96 (C, *S*-isomer), 149.00 (C, *R*-isomer).

(2*S*,4*S*,5*R*)-3,4-Dimethyl-5-phenyl-2-((*R*)-2-((*E*)-prop-1-enyl)pent-4-enyl)oxazolidine (286g)

(2*S*,4*S*,5*R*)-3,4-Dimethyl-5-phenyl-2-((*S*)-2-((*E*)-prop-1-enyl)pent-4-enyl)oxazolidine (287g)



(286g)
R-isomer



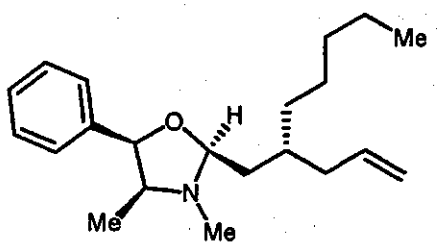
(287g)
S-isomer

(1*R*,2*S*)-(-)-Ephedrine **(285)** (0.050 g, 0.30 mmol,) was added to a solution of (*R*)-3-((*E*)-prop-1-enyl)hex-5-enal **(231g)** (0.042 g, 0.30 mmol) and activated 4Å molecular sieves in dry CH_2Cl_2 (10 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred for 18 h and then filtered through a thin pad of Celite, eluting with CH_2Cl_2. The solvent was removed under reduced pressure and a mixture of oxazolidines **(286g)** and **(287g)** was obtained as a light yellow oil (0.077 g, 89%). Analysis of the ^{1}H NMR spectrum of the crude diastereoisomeric mixture enabled measurement of the *d.e.*, which could be directly related to the *e.e.* of the starting material. δ_H ($CDCl_3$, 400 MHz) 0.66 (3H, t, *J* 6.5, NCHC*H*$_3$, both isomers), 1.63-1.78 (2H, m, OCHC*H*$_2$, both isomers), 1.68 (3H, dd, *J* 6.4, 1.6, CH=CHC*H*$_3$, both isomers), 2.10-2.20 (2H, m, C*H*$_2$CH=CH$_2$, both isomers), 2.22 (3H, m, NC*H*$_3$, *R*-isomer), 2.26 (3H, m, NC*H*$_3$, *S*-isomer), 2.41-2.49 (1H, m, CH$_2$C*H*CH$_2$, both isomers), 2.71-2.78 (1H, m, NC*H*CH$_3$, both isomers), 3.83 (1H, dd, *J* 9.0, 1.8, OC*H*N, *R*-isomer), 3.92 (1H, dd, *J* 7.4, 2.9, OC*H*N, *S*-isomer), 4.98-5.05 (3H, m, CH=C*H*$_2$ & PhC*H*, both isomers), 5.19-5.26 (1H, m, C*H*=CHCH$_3$, both isomers), 5.39-5.54 (1H, m, CH=C*H*CH$_3$, both isomers), 5.74-5.83 (1H, m, C*H*=CH$_2$, both isomers), 7.24-7.31 (5H, m, Ar*H*, both isomers); δ_C ($CDCl_3$, 100 MHz) 14.9 (CH_3, *R*-isomer), 15.0 (CH_3, *S*-isomer), 18.0 (CH_3, both isomers), 36.4 (CH_3, *R*-isomer), 36.8 (CH_3, *S*-isomer), 38,5 (CH_2, *S*-isomer), 38.6 (CH_2, *R*-isomer), 38.9 (CH, both isomers), 40.9 (CH_2, both isomers), 64.2 (CH, both isomers), 81.8 (CH, *S*-isomer), 81.9 (CH,

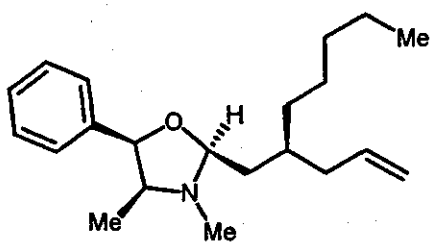
R-isomer), 95.9 (CH, *S*-isomer), 96.0 (CH, *R*-isomer), 115.9 (CH_2, *R*-isomer), 116.0 (CH_2, *S*-isomer), 124.8 (CH, both isomers), 127.4 (CH, *S*-isomer), 127.5 (CH, *R*-isomer), 127.6 (2 x CH, *S*-isomer), 127.7 (2 x CH, *R*-isomer), 127.9 (2 x CH, both isomers), 134.5 (CH, both isomers), 136.9 (CH, both isomers), 140.1 (C, *S*-isomer), 140.2 (C, *R*-isomer).

(2*S*,4*S*,5*R*)-2-((*R*)-2-Allylheptyl)-3,4-dimethyl-5-phenyloxazolidine (286h)

(2*S*,4*S*,5*R*)-2-((*S*)-2-Allylheptyl)-3,4-dimethyl-5-phenyloxazolidine (287h)



(286h)
R-isomer



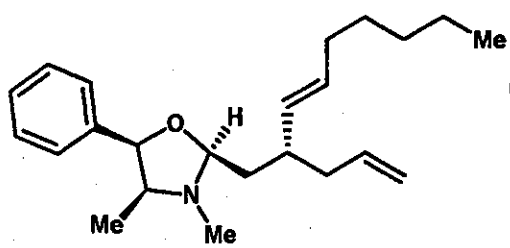
(287h)
S-isomer

(1*R*,2*S*)-(-)-Ephedrine **(285)** (0.052 g, 0.32 mmol) was added to (*R*)-3-allyloctanal **(231h)** (0.053 g, 0.32 mmol) and activated 4Å molecular sieves in dry CH_2Cl_2 (10 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred for 18 h and then filtered through a thin pad of Celite, eluting with CH_2Cl_2. The solvent was removed under reduced pressure and a mixture of oxazolidines **(286h)** and **(287h)** was obtained as a light yellow oil (0.089 g, 90%). Analysis of the ^{13}C NMR spectrum of the crude diastereoisomeric mixture enabled measurement of the *d.e.*, which could be directly related to the *e.e.* of the starting material. δ_H ($CDCl_3$, 400 MHz), 0.66 (3H, d, *J* 6.5, $CHCH_3$, both isomers), 0.83-0.90 (3H, m, CH_2CH_3, both isomers), 1.26-1.43 (8H, m, $(CH_2)_4CH_3$, both isomers), 1.68-1.75 (2H, m, $OCHCH_2$, both isomers), 1.78-1.82 (1H, m, CH_2CHCH_2, both isomers), 2.12-2.22 (2H, m, $CH_2CH{=}CH_2$, both isomers), 2.23 (3H, s, NCH_3, *S*-isomer), 2.24 (3H, s, NCH_3, *R*-isomer), 2.73-2.77 (1H, m, $CHCH_3$, both isomers), 3.88-3.93 (1H, m, OCHN, both isomers), 4.99-5.07 (3H, m, $CH{=}CH_2$ & PhCH, both isomers), 5.75-5.86 (1H, m, $CH{=}CH_2$, both isomers), 7.24-7.31 (5H, m, ArH, both isomers); δ_C ($CDCl_3$, 100 MHz) 14.1 (CH_3, both isomers), 14.9 (CH_3, both isomers), 22.7 (CH_2, both isomers), 26.1 (CH_2, *R*-isomer), 26.3 (CH_2, *S*-isomer), 32.1 (CH_2, *S*-isomer), 32.3 (CH_2, *R*-isomer), 33.3 (CH_2, both isomers), 33.9 (CH, *S*-isomer), 34.1 (CH, *R*-isomer), 36.5 (CH_3, both isomers), 37.3 (CH_2, *S*-isomer), 37.5 (CH_2, *R*-isomer), 37.8 (CH_2, *S*-isomer), 38.7 (CH_2, *R*-isomer), 64.1 (CH, both isomers), 81.9 (CH, both isomers), 96.1 (CH, *S*-isomer), 96.4 (CH, *R*-isomer), 116.1 (CH_2, *R*-isomer), 116.2 (CH_2, *S*-isomer),

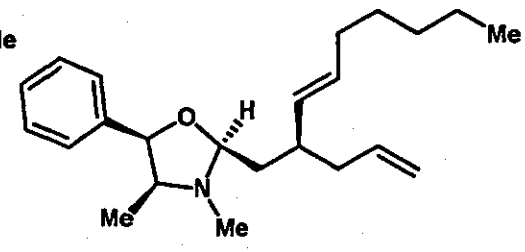
127.2 (CH, both isomers), 127.6 (2 x CH, both isomers), 127.8 (2 x CH, both isomers), 136.9 (CH, *S*-isomer), 137.2 (CH, *R*-isomer), 140.1 (C, both isomers).

(2*S*,4*S*,5*R*)-2-((*R*,*E*)-2-allylnon-3-enyl)-3,4-dimethyl-5-phenyloxazolidine (286i)

(2*S*,4*S*,5*R*)-2-((*S*,*E*)-2-allylnon-3-enyl)-3,4-dimethyl-5-phenyloxazolidine (287i)



(286i)
R-isomer



(287i)
S-isomer

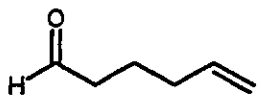
(1*R*,2*S*)-(-)-Ephedrine **(285)** (0.041 g, 0.25 mmol) was added to a solution of (*R*,*E*)-3-Allyldec-4-enal **(231i)** (0.048 g, 0.25 mmol) and activated 4Å molecular sieves in dry CH_2Cl_2 (10 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred for 18 h and then filtered through a thin pad of Celite, eluting with CH_2Cl_2. The solvent was removed under reduced pressure and a mixture of oxazolidines **(286i)** and **(287i)** was obtained as a light yellow oil (0.78 g, 92%). Analysis of the ^{1}H NMR spectrum of the crude diastereoisomeric mixture enabled measurement of the *d.e.*, which could be directly related to the *e.e.* of the starting material. δ_H ($CDCl_3$, 400 MHz) 0.57 (3H, d, *J* 6.4, CHC*H*$_3$, both isomers), 0.78-0.83 (3H, m, CH_2CH_3, both isomers), 1.17-1.30 (6H, m, $(CH_2)_3CH_3$, both isomers), 1.57-1.64 (1H, m, OCHC*H*(H), both isomers), 1.68-1.75 (1H, m, OCHC*H*(H), both isomers), 1.89-1.97 (2H, m, CH=CHCH_2, both isomers), 2.00-2.13 (2H, m, CH_2CH=CH_2, both isomers), 2.14 (3H, s, NCH_3, *R*-isomer), 2.17 (3H, s, NCH_3, *S*-isomer), 2.35-2.41 (1H, m, CH_2CHCH_2, both isomers), 2.61-2.69 (1H, m, C*H*CH_3, both isomers), 3.76 (1H, dd, *J* 9.0, 1.6, OC*H*N, *R*-isomer), 3.85 (1H, dd, *J* 7.3, 2.9, OC*H*N, *S*-isomer), 4.89-4.96 (3H, m, CH=CH_2 & C*H*Ph, both isomers), 5.08-5.18 (1H, m, C*H*=CHCH_2, both isomers), 5.34-5.43 (1H, m, CH=C*H*CH_2, both isomers), 5.66-5.73 (1H, m, C*H*=CH_2, both isomers), 7.14-7.24 (5H, m, Ar*H*, both isomers); δ_C ($CDCl_3$, 100 MHz) 14.2 (CH_3, both isomers), 14.9 (CH_3, *R*-isomer), 15.0 (CH_3, *S*-isomer), 22.6 (CH_2, both isomers), 29.3 (CH_2, both isomers), 31.6 (CH_2, both isomers), 32.5 (CH_2, both isomers), 36.4 (CH_3, *R*-isomer), 36.8 (CH_3, *S*-isomer), 38.6 (CH_2, *S*-isomer), 38.7 (CH_2, *R*-isomer), 39.0 (CH, both isomers), 41.0 (CH_2, both isomers), 64.3 (CH, both isomers),

81.7 (CH, *S*-isomer), 81.9 (CH, *R*-isomer), 95.9 (CH, both isomers), 115.9 (CH_2, *R*-isomer), 116.0 (CH_2, *S*-isomer), 127.4 (CH, *S*-isomer), 127.5 (CH, *R*-isomer), 127.6 (2 x CH, *S*-isomer), 127.7 (2 x CH, *R*-isomer), 127.9 (2 x CH, both isomers), 131.5 (CH, both isomers), 133.3 (CH, both isomers), 136.9 (CH, both isomers), 140.1 (C, *S*-isomer), 140.2 (C, *R*-isomer).

3.3 Synthesis of Piperidines

3.3.1 Synthesis of a Substrate for the Electrophilic Cyclisation

Hexen-5-enal



(316)

Swern Oxidation[160]

The Swern reagent was prepared from dimethyl sulphoxide (4.67 mL, 66 mmol) and oxalyl chloride (2.88 mL, 33 mmol) in CH_2Cl_2 (50 mL) at -78 °C. The mixture was stirred at -78 °C for 2 min and then a solution of 5-hexen-1-ol **(315)** (3.56 mL, 30 mmol) in CH_2Cl_2 (10 mL) was added *via cannula*. After 20 min triethylamine (21.0 mL, 150 mmol) was added and the reaction was stirred for 5 min at -78 °C and then at room temperature for 30 min. Distilled water (100 mL) was added to the mixture and the organic layer was removed. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with 5% HCl solution followed by a saturated NaCl solution and dried over anhydrous $MgSO_4$. The combined organic fractions were filtered and the solvent was removed under reduced pressure to yield the product **(316)** as a yellow oil, which was used without further purification (1.21 g, 41%). ν_{max}/cm^{-1} (film) 2934, 1735, 1640, 1171, 912; δ_H ($CDCl_3$, 250 MHz) 1.68-1.80 (2H, m, $CH_2CH_2CH_2$), 2.04-2.18 (2H, m, $CH_2CH{=}CH_2$), 2.46 (2H, td, *J* 11.5, 2.6, CH_2CHO), 4.95-5.08 (2H, m, $CH{=}CH_2$), 5.70-5.86 (1H, m, $CH{=}CH_2$), 9.79 (1H, s, CHO).[160]

TPAP Oxidation

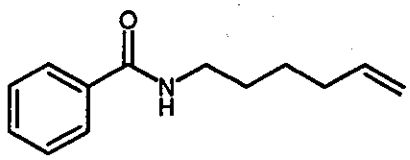
Tetra-*n*-propylammonium perruthenate (0.35 g, 1.0 mmol) was slowly added to 5-hexen-1-ol **(315)** (2.38 mL, 20 mmol), *N*-methylmorpholine-*N*-oxide (3.51 g, 30 mmol) and powdered molecular sieves (4Å, 0.50 g/mmol) in CH_2Cl_2 (50 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred for 3 h and then filtered through a small pad of silica, eluting with CH_2Cl_2. The filtrate was evaporated under reduced pressure and the product **(316)** was isolated as a yellow oil, which was used without further purification (1.38 g, 70%). Spectroscopic data were identical with those previously reported for **(316)**.

Hex-5-en-1-amine

(319)

5-Hexenitrile **(318)** (1.19 mL, 10.6 mmol) was cautiously added to a solution of lithium aluminium hydride (0.40 g, 10.6 mmol) in anhydrous Et_2O (30 mL) at 0 °C. The mixture was stirred for 18 h at room temperature, then cooled to 0 °C and distilled water (2 mL), 20% NaOH solution (3 mL) and water (5 mL) were added in succession until a white, granular precipitate formed. The supernatant Et_2O solution was decanted and the precipitate was washed with Et_2O (2 x 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the product **(319)** was obtained as a transparent oil, which was used without further purification (0.90 g, 86%). ν_{max}/cm^{-1} (film) 3290, 3074, 2928, 2857, 1640, 1457, 1437, 1000; δ_H ($CDCl_3$, 400 MHz) 1.38-1.50 (4H, m, $(CH_2)_2CH_2NH_2$), 1.56-1.59 (2H, br, NH_2), 2.04-2.09 (2H, m, $CH_2CH{=}CH_2$), 2.67-2.70 (2H, m, CH_2NH_2), 4.93-5.03 (2H, m, $CH{=}CH_2$), 5.77-5.84 (1H, m, $CH{=}CH_2$); δ_C ($CDCl_3$, 100 MHz) 26.5 (CH_2), 33.6 (CH_2), 34.0 (CH_2), 42.3 (CH_2), 114.9 (CH_2), 139.1 (CH).[184]

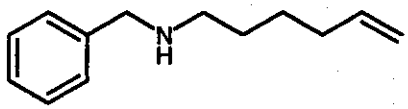
***N*-(Hex-5-enyl)benzamide**



(321)

Benzoyl chloride (1.69 mL, 14.5 mmol) was added to a stirred solution of 5-hexenamine **(319)** (1.20 g, 12.1 mmol), triethylamine (2.02 mL, 14.5 mmol) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in dry CH_2Cl_2 (20 mL). The mixture was stirred for 18 h, washed twice with $NaHCO_3$, dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and a yellow oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (4:1 hexane:EtOAc) to yield the target compound **(321)** as a transparent oil (2.38 g, 97%). ν_{max}/cm^{-1} (film) 3379, 3071, 2933, 1687, 1640, 1327, 1293, 708. δ_H ($CDCl_3$, 400 MHz) 1.41-1.47 (2H, m, $NCH_2CH_2CH_2$), 1.56-1.62 (2H, m, NCH_2CH_2), 2.03-2.09 (2H, m, $CH_2CH{=}CH_2$), 3.38-3.43 (2H, m, NCH_2), 4.93-5.02 (2H, m, $CH{=}CH_2$), 5.74-5.81 (1H, m, $CH{=}CH_2$), 6.78 (1H, br, NH), 7.37 (2H, t, *J* 6.5, ArH), 7.44 (1H, t, *J* 6.0, ArH), 7.78 (2H, d, *J* 7.9, ArH); δ_C ($CDCl_3$, 100 MHz) 26.2 (CH_2), 29.1 (CH_2), 33.4 (CH_2), 40.0 (CH_2), 114.8 (CH_2), 127.0 (2 x CH), 128.5 (2 x CH), 130.0 (CH), 134.8 (C), 138.4 (CH), 167.8 (C); *m/z* (EI) 203 (M^+, 7%), 105 (100%). Accurate mass: found 203.1309, $C_{13}H_{17}NO$ requires 203.1310.[185]

***N*-Benzylhex-5-en-1-amine**



(317)

Reductive Amination of 5-Hexen-1-al (316)

Benzylamine **(289)** (1.18 mL, 10.2 mmol) was slowly added to a solution of 5-hexen-1-al **(316)** (1.0 g, 10.2 mmol) in CH_2Cl_2 (50 mL) at room temperature. The mixture was stirred for 10 min, anhydrous $MgSO_4$ was added and the reaction stirred for an additional 50 min. Filtration and removal of the solvent under reduced pressure yielded a yellow oil, which was dissolved in dry MeOH (30 mL). The solution was cooled to 0 °C, $NaBH_4$ (0.77 g, 20.4 mmol) in MeOH (20 mL) was added *via cannula* and the mixture stirred for 18 h at room temperature. The solvent was removed under reduced pressure and a yellow oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (3:1 light petroleum:EtOAc), to yield the target compound **(317)** as a pale yellow oil (0.68 g, 35%). ν_{max}/cm^{-1} (film) 3303, 2929, 2856, 1640, 1495, 1454, 910, 734, 698; δ_H ($CDCl_3$, 400 MHz) 1.33-1.48 (4H, m, $NCH_2(CH_2)_2$), 1.96-2.01 (2H, m, $CH_2CH=CH_2$), 2.56 (2H, t, *J* 6.9, NCH_2), 3.71 (2H, s, $PhCH_2$), 4.85-4.94 (2H, m, $CH=CH_2$), 5.69-5.76 (1H, m, $CH=CH_2$), 7.16-7.26 (5H, m, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 25.6 (CH_2), 28.5 (CH_2), 32.6 (CH_2), 48.2 (CH_2), 53.0 (CH_2), 113.5 (CH_2), 125.9 (CH), 127.2 (2 x CH), 127.4 (2 x CH), 137.8 (CH), 139.4 (C); *m/z* (EI) 189 (M^+,6%), 91 (100%). Accurate mass: found 189.1514, $C_{13}H_{19}N$ requires 189.1518.[163]

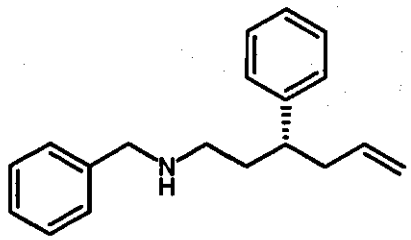
Reductive Alkylation of Hex-5-en-1-amine (319)

Benzaldehyde **(290)** (1.02 mL, 10.1 mmol) was slowly added to a solution of hex-5-en-1-amine **(319)** (1.02 g, 10.1 mmol) in CH_2Cl_2 (50 mL) at room temperature. The mixture was stirred for 10 min, anhydrous $MgSO_4$ was added and the reaction stirred for an additional 50 min. Filtration and removal of solvent under reduced pressure yielded a yellow oil, which was dissolved in dry MeOH (30 mL). The solution was cooled to 0 °C, $NaBH_4$ (0.76 g, 20.2 mmol) in MeOH (30 mL) was added *via cannula* and the mixture stirred for 18 h at room temperature. The solvent was removed under reduced pressure and a yellow oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (4:1 hexane:EtOAc), yielding the target compound **(317)** as a pale yellow oil (0.83 g, 43%). Spectroscopic data were identical with those previously reported for **(317)**.

Reduction of *N*-(Hex-5-enyl)benzamide (321) with Lithium Aluminium Hydride

N-(Hex-5-enyl)benzamide **(321)** (0.8 g, 3.9 mmol) was dissolved in dry Et_2O (5 mL) and cautiously added *via cannula* to a solution of lithium aluminium hydride (0.15 g, 3.9 mmol) in anhydrous Et_2O (30 mL) at 0 °C. The mixture was stirred for 18 h at room temperature, cooled to 0 °C and distilled water (2 mL), 20% NaOH solution (3 mL) and water (5 mL) were added in succession until a white, granular precipitate formed. The supernatant Et_2O solution was decanted and the precipitate was washed with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduce pressure and a transparent oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (3:1 hexane:EtOAc) (0.58 g, 79%). Spectroscopic data were identical with those previously reported for **(317)**.

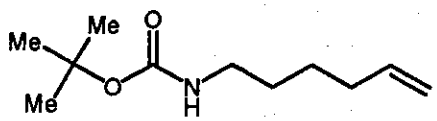
(*R*)-*N*-Benzyl-3-phenylhex-5-en-1-amine



(314)

Benzylamine **(289)** (1.25 mL, 11.5 mmol) was slowly added to a stirred solution of (*R*)-3-phenylhex-5-enal **(231a)** (2.0 g, 11.5 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred for 20 min, anhydrous $MgSO_4$ was added and the reaction stirred for an additional 40 min. Filtration and removal of the solvent under reduced pressure yielded a yellow oil, which was dissolved in dry MeOH (40 mL). The solution was cooled to 0 °C, $NaBH_4$ (0.87 g, 23.0 mmol) in MeOH (20 mL) was added *via cannula* and the mixture was stirred for 18 h at room temperature. Solvent was removed under reduced pressure and a yellow oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (3:2 hexane:EtOAc), to yield the target compound **(314)** as a pale yellow oil (2.42 g, 79%). $[\alpha]^{25}_D$ = -8.7 (*c* = 1.7, $CHCl_3$); ν_{max}/cm^{-1} (film) 3027, 2922, 1640, 1494, 1453, 912, 734, 700; δ_H ($CDCl_3$, 400 MHz) 1.40 (1H, br, s, N*H*), 1.73-1.81 (1H, m, $NHCH_2CH(H)$), 1.87-1.94 (1H, m, $NHCH_2CH(H)$), 2.36 (2H, m, $CH_2CH{=}CH_2$), 2.44-2.53 (2H, m, $NHCH_2CH_2$), 2.66-2.74 (1H, m, PhC*H*), 3.63-3.72 (2H, m, $PhCH_2$), 4.90-4.98 (2H, m, $CH{=}CH_2$), 5.60-5.68 (1H, m, $CH{=}CH_2$), 7.14-7.29 (10H, m, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 36.2 (CH_2), 41.5 (CH_2), 43.9 (CH), 47.5 (CH_2), 54.0 (CH_2), 116.1 (CH_2), 126.2 (CH), 126.9 (CH), 127.6 (2 x CH), 128.1 (2 x CH), 128.4 (4 x CH), 136.9 (CH), 140.4 (C), 144.8 (C); *m/z* (EI) 265 (M^+, 14%), 91 (100%). Accurate mass: found 265.1832, $C_{19}H_{23}N$ requires 265.1831.

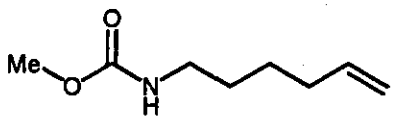
***tert*-Butyl hex-5-enylcarbamate**



(336)

Di-*tert*-butyl dicarbonate (1.58 g, 7.3 mmol) was added to a stirred solution of 5-hexenamine **(319)** (0.60 g, 6.1 mmol), triethylamine (1.0 mL, 7.3 mmol) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 (30 mL). The solution was stirred for 18 h, washed with a saturated $NaHCO_3$ solution (2 x 20 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the product **(336)** was obtained as a yellow oil, which was used without further purification (0.94 g, 78%). ν_{max}/cm^{-1} (film) 3357, 2977, 2932, 1700, 1523, 1366, 1251, 1174, 993, 910; δ_H ($CDCl_3$, 400 MHz) 1.39-1.51 (13H, m, $C(CH_3)_3$ & $CH_2(CH_2)_2CH_2$), 2.04-2.10 (2H, m, $CH_2CH{=}CH_2$), 3.09-3.17 (2H, m, CH_2N), 4.60 (1H, br, N*H*), 4.93-5.03 (2H, m, $CH{=}CH_2$), 5.75-5.82 (2H, m, $CH{=}CH_2$); δ_C ($CDCl_3$, 100 MHz) 26.1 (CH_2), 28.4 (3 x CH_3), 29.9 (CH_2), 33.4 (CH_2), 40.2 (CH_2), 114.7 (CH_2), 138.5 (CH), 156.1 (C), 158.7 (C); *m/z* (EI) 199 (M^+, 1%), 57 (100%). Accurate mass: found 199.1568, $C_{11}H_{21}NO_2$ requires 199.1572.

Methyl hex-5-enylcarbamate

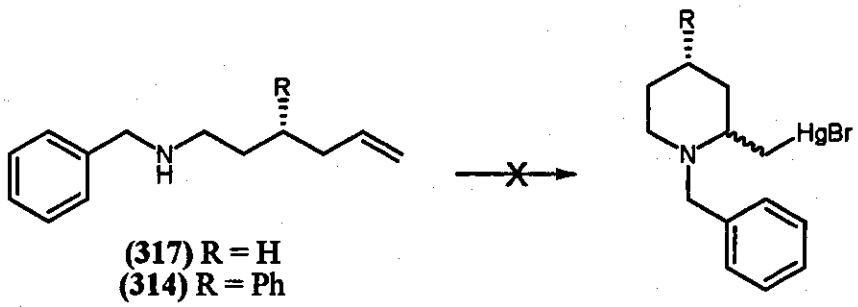


(337)

Methyl chloroformate (0.84 mL, 10.9 mmol) was added to a stirred solution of 5-hexenamine **(319)** (0.9 g, 9.1 mmol), triethylamine (1.52 mL, 10.9 mmol) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 (20 mL). The solution was stirred for 18 h, washed with a saturated $NaHCO_3$ solution (2 x 20 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the product **(337)** was obtained as a yellow oil, which was used without further purification (1.05 g, 74%). ν_{max}/cm^{-1} (film) 3333, 2931, 1699, 1538, 1256, 911; δ_H ($CDCl_3$, 400 MHz) 1.38-1.53 (4H, m, $CH_2(CH_2)_2CH_2$), 2.04-2.10 (2H, m, $CH_2CH{=}CH_2$), 3.15-3.20 (2H, m, NCH_2), 3.65 (3H, s, CH_3), 4.94-5.03 (2H, m, $CH{=}CH_2$), 5.74-5.82 (1H, m, $CH{=}CH_2$); δ_C ($CDCl_3$, 100 MHz) 25.5 (CH_2), 29.4 (CH_2), 33.4 (CH_2), 40.9 (CH_2), 52.0 (CH_3), 114.8 (CH_2), 138.5 (CH), 157.2 (C); *m/z* (EI) 128 (M^+, 9%), 88 (100%). Accurate mass: found 128.0836, $C_8H_{15}NO_2$ requires 128.0837.

3.3.2 Electrophilic Cyclisations

Mercury(II) Trifluoroacetate as an Electrophile



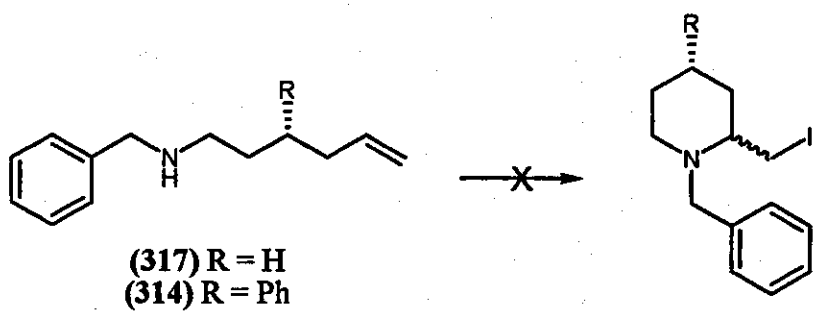
(317) R = H
(314) R = Ph

$Hg(TFA)_2$ (1.13 g, 2.6 mmol) in dry THF (15 mL) was added *via cannula* to a stirred solution of *N*-benzylhex-5-en-1-amine **(317)** (0.20 g, 1.1 mmol) in dry THF (40 mL) under a nitrogen atmosphere. The reaction mixture was stirred for 1 h at room temperature. A saturated $NaHCO_3$ solution (15 mL) was added and the reaction was stirred for 30 min. A saturated KBr solution (15 mL) was added and the mixture was stirred for an additional 18 h, then diluted with water (30 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to yield a brown oil. A ^1H NMR spectrum of the crude reaction mixture suggested decomposition of the starting material.

The reaction was conducted using shorter periods of time and at 0 °C but a complex mixture of compounds was persistently isolated. Purification and isolation of the products proved to be impossible.

The same procedure was conducted on (*R*)-*N*-Benzyl-3-phenylhex-5-en-1-amine **(314)** but ^1H NMR analysis of the crude reaction mixture suggested decomposition of the starting material.

Iodine as an Electrophile



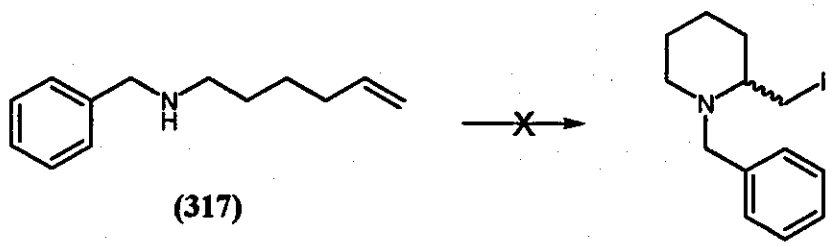
(317) R = H
(314) R = Ph

Iodine (0.67 g, 2.6 mmol) was added to a stirred solution of *N*-benzylhex-5-en-1-amine **(317)** (0.20 g, 1.1 mmol) in dry THF (30 mL) under a nitrogen atmosphere and the mixture was stirred for 1 h at room temperature. A saturated $NaHCO_3$ solution (20 mL) was added and the reaction was stirred for an additional 30 min, diluted with water (30 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. A ^1H NMR spectrum of the crude reaction mixture suggested decomposition of the starting material. Purification and isolation of the products proved to be impossible.

The reaction was conducted using shorter periods of time and at 0 °C but a complex mixture of compounds was persistently isolated. Only starting material was isolated when the reaction was conducted at -78 °C.

The same procedure was conducted on (*R*)-*N*-Benzyl-3-phenylhex-5-en-1-amine **(314)** but ^1H NMR analysis of the crude reaction mixture suggested decomposition of the starting material.

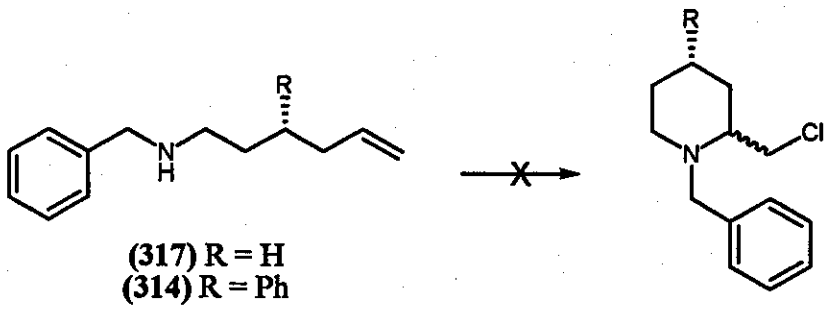
_N_-Iodosuccinimide as an Electrophile



(317)

_N_-Iodosuccinimide (0.74 g, 3.3 mmol) was added to a stirred solution of _N_-Benzylhex-5-en-1-amine **(317)** (0.20 g, 1.1 mmol) in dry THF (30 mL) under a nitrogen atmosphere and the mixture was stirred for 1 h at room temperature. A saturated $NaHCO_3$ solution (20 mL) was added and the reaction was stirred for an additional 30 min, diluted with water (30 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. A ^1H NMR spectrum of the crude reaction mixture suggested decomposition of the starting material. Purification and isolation of the products proved to be impossible.

Palladium(II) Chloride as an Electrophile



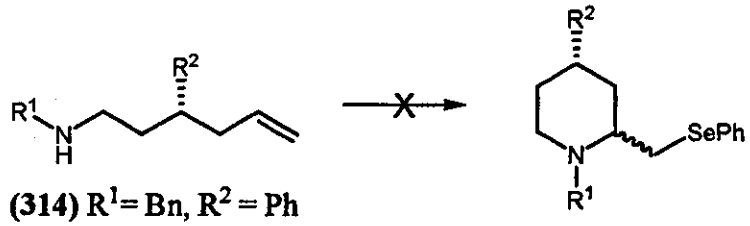
(317) R = H
(314) R = Ph

N-Benzylhex-5-en-1-amine **(317)** (0.20 g, 1.1 mmol) was dissolved in glacial AcOH (5 mL) and added *via cannula* to a stirred mixture of $PdCl_2$ (0.037g, 0.21 mmol), $CuCl_2$ (0.43 g, 3.2 mmol) and NaOAc (0.26 g, 3.3 mmol) in glacial AcOH (10 mL). The deep green mixture was stirred for 1 h at room temperature, filtered through a small pad of Celite, eluting with AcOH and the solvent was removed under reduced pressure. The last traces of residual solvent were removed by co-evaporation with toluene. A ^{1}H NMR spectrum of the crude reaction mixture suggested decomposition of the starting material. Purification and isolation of the products proved to be impossible.

The reaction was conducted using shorter periods of time and at 0 °C but a complex mixture of compounds was persistently isolated.

The same procedure was conducted on (*R*)-*N*-Benzyl-3-phenylhex-5-en-1-amine **(314)** but ^{1}H NMR analysis of the crude reaction mixture suggested decomposition of the starting material.

Phenylselenyl Chloride as an Electrophile

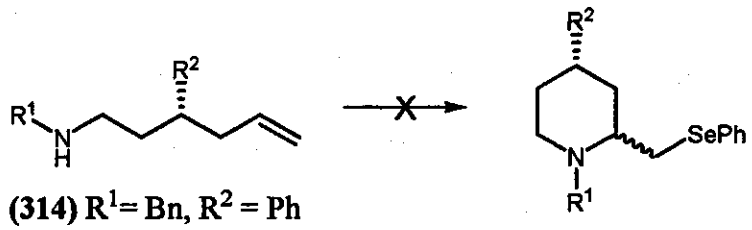


(314) R^1= Bn, R^2 = Ph
(336) $R^1 = CO_2C(Me_3)_3$, R^2 = H
(337) $R^1 = CO_2Me$, R^2 = H

(*R*)-*N*-Benzyl-3-phenylhex-5-en-1-amine **(314)** (0.25 g, 0.9 mmol) was added to a mixture of silica gel (0.25 g) and anhydrous K_2CO_3 (0.25 g) in dry CH_2Cl_2 (15 mL) at -78 °C under a nitrogen atmosphere. The solution was stirred for 10 min and phenylselenyl chloride (0.22 g, 1.1 mmol) in CH_2Cl_2 (5 mL) was added *via cannula*. The reaction was stirred at -78 °C for an additional 10 min and then at room temperature for up to 72 h. TLC and ^{1}H NMR analysis of the crude reaction mixture indicated that the cyclisation had not occurred. The reaction was then heated at reflux for an additional 48 h. The product was filtered through a pad of Celite and the solvent was removed under reduced pressure. A ^{1}H NMR spectrum of the crude reaction mixture suggested that no reaction had occurred.

The same procedure was conducted on *tert*-butyl hex-5-enylcarbamate **(336)** and methyl hex-5-enylcarbamate **(337)** at room temperature/reflux but only starting material was isolated.

Phenylselenyl Bromide as an Electrophile

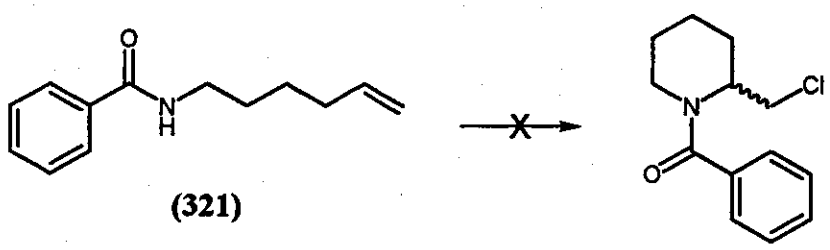


(314) R^1= Bn, R^2 = Ph
(336) $R^1 = CO_2C(Me_3)_3$, R^2 = H
(337) $R^1 = CO_2Me$, R^2 = H

(*R*)-*N*-Benzyl-3-phenylhex-5-en-1-amine **(314)** (0.25 g, 0.9 mmol) was added to a mixture of silica gel (0.25 g) and anhydrous K_2CO_3 (0.25 g) in dry $CHCl_3$ (15 mL) at 0 °C under a nitrogen atmosphere. The solution was stirred for 10 min and phenylselenyl bromide (0.27 g, 1.1 mmol) in CH_2Cl_2 (5 mL) was added *via cannula* and the reaction stirred at 0 °C for an additional 10 min and then at room temperature for up to 72 h. TLC and ^{1}H NMR analysis of the crude reaction mixture indicated that the cyclisation had not occurred. The reaction was then heated at reflux for an additional 48 h. The product was filtered through a pad of Celite and the solvent was removed under reduced pressure. A ^{1}H NMR spectrum of the crude reaction mixture suggested that no reaction had occurred.

The same procedure was conducted on *tert*-butyl hex-5-enylcarbamate **(336)** and methyl hex-5-enylcarbamate **(337)** at room temperature/reflux but only starting material was isolated.

Palladium Acetate as an Electrophile

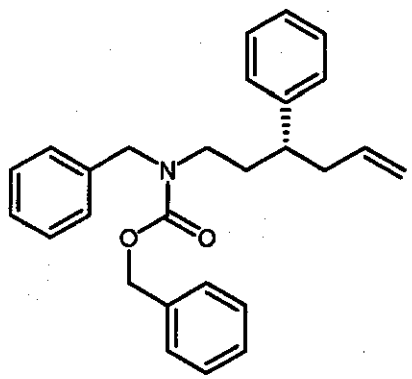


(321)

$Pd(OAc)_2$ (0.138 g, 0.06 mmol), $CuCl_2$ (0.835 g, 6.2 mmol) and LiCl (0.104 g, 2.5 mmol) were added to a solution of *N*-(Hex-5-enyl)benzamide **(321)** (0.25 g, 1.2 mmol) in dry THF (20 mL) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 18 h, filtered through a small pad of Celite and the solvent was removed under reduced pressure. Only starting material was observed in the ^1H NMR spectrum of the crude reaction mixture.

3.3.3 Ozonolysis/Oxidative Cleavage Methodology

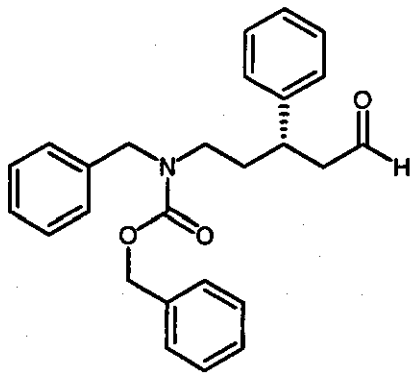
Benzyl benzyl(*R*)-3-phenylhex-5-enylcarbamate



(344)

To a solution of (*R*)-*N*-Benzyl-3-phenylhex-5-en-1-amine **(314)** (1.60 g, 6.0 mmol) in DMF (20 mL) was added *N*-(benzyloxycarbonyloxy)succinimide (1.65 g, 6.6 mmol) and 4-methylmorpholine (NMM) (2.65 mL, 24.1 mmol). The reaction was stirred for 18 h and EtOAc (20 mL) was added. The solution was acidified with aqueous 1N HCl, washed with a saturated NaCl solution (3 x 25 mL), dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure and a yellow oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (9:1 light petroleum:EtOAc) to yield the target compound **(344)** as a yellow oil (1.90 g, 79%). $[\alpha]^{25}_D$ = -1.4 (*c* = 1.5, $CHCl_3$); ν_{max}/cm^{-1} (film) 3027, 2924, 1700, 1452, 1421, 1228, 1214, 699; δ_H ($CDCl_3$, 400 MHz) 1.75-2.00 (2H, m, NCH_2CH_2), 2.25-2.32 (2H, m, $CH_2CH{=}CH_2$), 2.48-2.58 (1H, m, PhC*H*), 3.00-3.22 (2H, m, NCH_2CH_2) 4.29-4.49 (2H, m, $PhCH_2N$), 4.89-4.95 (2H, m, $CH{=}CH_2$), 5.11-5.18 (2H, m, OCH_2), 5.51-5.63 (1H, m, $CH{=}CH_2$), 6.97-7.35 (15H, m, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 33.4 (CH_2), 41.5 (CH_2), 43.4 (CH), 44.8 (CH_2), 50.6 (CH_2), 67.2 (CH_2), 116.2 (CH_2), 126.3 (2 x CH), 127.3 (CH), 127.5 (2 x CH), 127.9 (2 x CH), 128.4 (4 x CH), 128.5 (4 x CH), 136.5 (CH), 136.8 (C), 137.8 (2 x C), 144.1 (C); *m/z* (EI) 399 (M^+, 1%), 91 (100%). Accurate mass: found 399.2195, $C_{27}H_{29}NO_2$ requires 399.2198.

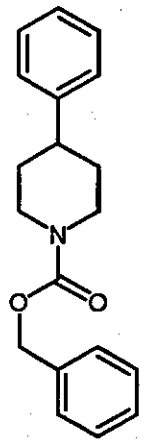
Benzyl benzyl(*S*)-4-formyl-3-phenylbutylcarbamate



(345)

To a solution of benzyl benzyl(*R*)-3-phenylhex-5-enylcarbamate **(344)** (1.55 g, 3.9 mmol) in CH_2Cl_2 (30 mL) at -78 °C was bubbled O_2 for 10 min, followed by O_3. The solution turned blue after 5 min and bubbling was continued for an additional 15 min. Triphenylphosphine (1.12 g, 4.3 mmol) was added and the solution stirred for 18 h at room temperature. The reaction was quenched by addition of aqueous 1N HCl and the organic layer was washed with a saturated NaCl solution (2 x 20 mL), dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure and a yellow oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (4:1 hexane:EtOAc) to yield the target compound **(345)** as a transparent oil (1.32 g, 85%). $[\alpha]^{25}_D$ = -5.0 (*c* = 1.3, $CHCl_3$); ν_{max}/cm^{-1} (film) 3028, 2932, 1721, 1698, 1452, 1422, 1231, 700; δ_H ($CDCl_3$, 400 MHz) 1.78-1.89 (2H, m, NCH_2CH_2), 2.53-2.70 (2H, m, CH_2CHO), 3.00-3.16 (3H, m, PhC*H* & NCH_2CH_2), 4.31-4.47 (2H, m, $PhCH_2N$), 5.10-5.18 (2H, m, OCH_2), 6.99-7.63 (15H, m, Ar*H*), 9.56 (1H, m, C*H*O); δ_C ($CDCl_3$, 100 MHz) 34.1 (CH_2), 37.6 (CH), 45.0 (CH_2), 50.6 (2 x CH_2), 67.3 (CH_2), 126.9 (2 x CH), 127.4 (2 x CH), 128.0 (2 x CH), 128.6 (5 x CH), 128.8 (4 x CH), 136.7 (C), 137.7 (C), 142.7 (C), 156.3 (C), 201.3 (CH). *m/z* (EI) 401 (M^+, 1%), 91 (100%). Accurate mass: found 401.1997 $C_{26}H_{27}NO_3$ requires 401.1991.

Benzyl 4-phenylpiperidine-1-carboxylate



(346)

TFA (0.11 mL, 1.4 mmol) and palladium 10% on carbon (0.15 g) were added to a solution of benzyl benzyl(*S*)-4-formyl-3-phenylbutylcarbamate **(345)** (0.50 g, 1.3 mmol) in MeOH (50 mL). The mixture was stirred for 18 h under H_2 at 50 psi. The reaction mixture was filtered through a thin pad of Celite, eluting with MeOH and the solvent was removed under reduced pressure. The crude product was dissolved in DMF (15 mL) and *N*-(benzyloxycarbonyloxy)succinimide (0.47 g, 1.4 mmol) and 4-methylmorpholine NMM (0.54 mL, 5.0 mmol) were added to the solution. The reaction was stirred for 18 h and EtOAc (20 mL) was added. The mixture was acidified with aqueous 1N HCl, washed with a saturated NaCl solution (3 x 25 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and a yellow oil was obtained, which was adsorbed onto silica and purified by flash column chromatography (4:1 hexane:EtOAc) to yield the target compound **(346)** as a light yellow oil (0.108 g, 29%). ν_{max}/cm^{-1} (film) 2936, 2850, 1700, 1696, 1452, 1429, 1221, 698; δ_H ($CDCl_3$, 400 MHz) 1.63-1.77 (2H, m, 2 x CHC*H*(H)), 1.83-1.90 (2H, m, 2 x CHC*H*(H)), 2.66 (1H, tt, *J* 12.1, 3.5, C*H*Ph), 2.88-2.94 (2H, m, 2 x NC*H*(H)), 4.25-4.40 (2H, m, 2 x NC*H*(H)), 5.16 (2H, s, OCH_2), 7.18-7.38 (10H, m, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 33.1 (2 x CH_2), 42.6 (CH), 44.7 (2 x CH_2), 67.1 (CH_2), 126.4 (CH), 126.8 (2 x CH), 127.9 (2 x CH), 128.0 (CH), 128.5 (2 x CH), 128.6 (2 x CH), 136.9 (C), 145.6 (C), 155.3 (C). *m/z* (EI) 296 ($(M+1)^+$, 13%), 91 (100%). Accurate mass: found 296.1655 $C_{19}H_{22}NO_2$ requires 296.1651.

Chapter 4

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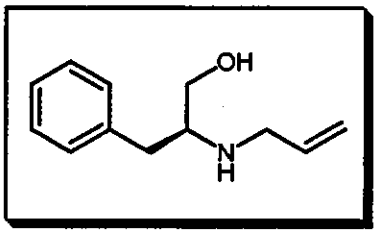
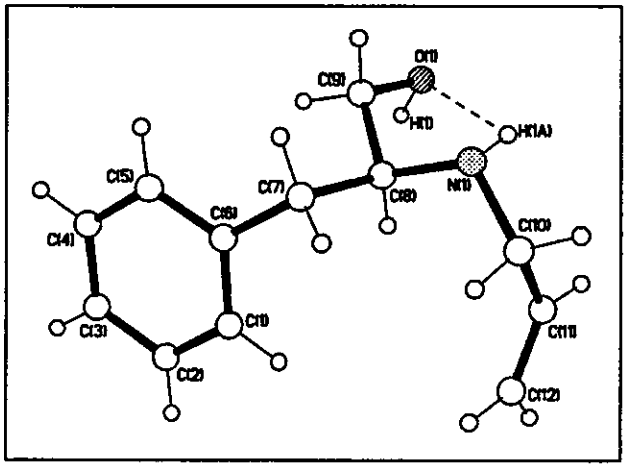
Appendix

Single Crystal X-Ray with Accompanying Data

(*S*)-2-(Allylamino)-3-phenylpropan-1-ol



(234j)



Crystal Data and Structure Refinement

Identification code	**(234j)**	
Chemical formula	$C_{12}H_{17}NO$	
Formula weight	191.27	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	Monoclinic, I2	
Unit cell parameters	a = 9.490(2) Å	α = 90°
	b = 4.8250(11) Å	β = 96.340(4)°
	c = 24.134(6) Å	γ = 90°
Cell volume	1098.3(4) $Å^3$	
Z	4	
Calculated density	1.157 g/cm^3	
Absorption coefficient μ	0.073 mm^{-1}	
F(000)	416	
Crystal colour and size	Colourless, 1.10 × 0.07 × 0.04 mm^3	
Reflections for cell refinement	1643 (θ range 2.40 to 27.13°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	1.70 to 26.00°	
Index ranges	h −11 to 11, k −5 to 5, l −29 to 29	
Completeness to θ = 26.00°	99.9%	
Intensity decay	0%	
Reflections collected	4121	
Independent reflections	2109 (R_{int} = 0.0254)	
Reflections with $F^2>2\sigma$	1648	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.924 and 0.997	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0659, 0.0026	
Data / restraints / parameters	2109 / 1 / 133	
Final R indices [$F^2>2\sigma$]	R1 = 0.0481, wR2 = 0.1111	
R indices (all data)	R1 = 0.0644, wR2 = 0.1198	
Goodness-of-fit on F^2	1.083	
Absolute structure parameter	2(2)	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.126 and −0.142 e $Å^{-3}$	

Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($Å^2$). U_{eq} is Defined as One Third of the Trace of the Orthogonalised U^{ij} Tensor

	x	y	z	U_{eq}
C(1)	0.3803(2)	0.2722(5)	0.42943(9)	0.0312(6)
C(2)	0.3104(3)	0.0727(6)	0.45724(9)	0.0358(6)
C(3)	0.1812(2)	–0.0299(6)	0.43415(10)	0.0343(6)
C(4)	0.1228(2)	0.0710(5)	0.38333(10)	0.0331(6)
C(5)	0.1915(2)	0.2732(6)	0.35584(9)	0.0290(6)
C(6)	0.3225(2)	0.3742(5)	0.37819(9)	0.0249(5)
C(7)	0.4040(2)	0.5827(5)	0.34760(9)	0.0269(5)
C(8)	0.5279(2)	0.4482(5)	0.32170(9)	0.0218(5)
C(9)	0.4732(2)	0.2905(5)	0.26931(9)	0.0261(5)
O(1)	0.58043(16)	0.1362(4)	0.24643(6)	0.0301(4)
N(1)	0.63141(19)	0.6559(4)	0.30772(8)	0.0251(4)
C(10)	0.7245(2)	0.7626(5)	0.35602(9)	0.0287(6)
C(11)	0.8241(2)	0.5532(5)	0.38447(9)	0.0304(6)
C(12)	0.8272(3)	0.4753(7)	0.43634(10)	0.0433(7)

Bond Lengths [Å] and Angles [°]

C(1)–C(2)	1.384(3)	C(1)–C(6)	1.387(3)
C(2)–C(3)	1.381(3)	C(3)–C(4)	1.378(3)
C(4)–C(5)	1.383(3)	C(5)–C(6)	1.387(3)
C(6)–C(7)	1.511(3)	C(7)–C(8)	1.535(3)
C(8)–N(1)	1.468(3)	C(8)–C(9)	1.476(3)
C(10)–C(11)	1.497(3)	C(11)–C(12)	1.304(3)
C(2)–C(1)–C(6)	121.0(2)	C(3)–C(2)–C(1)	120.4(2)
C(4)–C(3)–C(2)	119.0(2)	C(3)–C(4)–C(5)	120.8(2)
C(4)–C(5)–C(6)	120.7(2)	C(1)–C(6)–C(5)	118.1(2)
C(1)–C(6)–C(7)	119.9(2)	C(5)–C(6)–C(7)	121.9(2)
C(6)–C(7)–C(8)	111.97(19)	N(1)–C(8)–C(9)	109.07(17)
N(1)–C(8)–C(7)	111.52(18)	C(9)–C(8)–C(7)	110.12(17)
O(1)–C(9)–C(8)	113.12(17)	C(8)–N(1)–C(10)	114.45(17)
N(1)–C(10)–C(11)	114.8(2)	C(12)–C(11)–C(10)	125.5(2)

Anisotropic Displacement Parameters ($Å^2$). The Anisotropic Displacement Factor Exponent Takes the Form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	0.0303(12)	0.0369(15)	0.0266(12)	–0.0041(12)	0.0035(10)	–0.0060(13)
C(2)	0.0405(14)	0.0391(16)	0.0282(12)	0.0018(12)	0.0057(10)	–0.0025(13)
C(3)	0.0351(13)	0.0310(14)	0.0388(14)	0.0041(13)	0.0136(11)	–0.0029(12)
C(4)	0.0215(11)	0.0321(15)	0.0462(14)	–0.0025(12)	0.0055(10)	–0.0041(11)
C(5)	0.0229(11)	0.0301(13)	0.0340(13)	0.0024(12)	0.0033(10)	0.0029(11)
C(6)	0.0245(11)	0.0225(13)	0.0286(12)	–0.0047(10)	0.0070(10)	0.0016(10)
C(7)	0.0260(11)	0.0216(13)	0.0339(12)	–0.0012(10)	0.0073(9)	0.0023(10)
C(8)	0.0209(11)	0.0196(12)	0.0250(11)	0.0041(10)	0.0025(9)	0.0011(10)
C(9)	0.0243(11)	0.0235(13)	0.0307(12)	0.0000(11)	0.0041(10)	0.0028(10)

O(1)	0.0382(9)	0.0247(10)	0.0293(9)	–0.0012(8)	0.0127(7)	0.0024(8)
N(1)	0.0236(10)	0.0214(10)	0.0308(10)	–0.0004(9)	0.0055(8)	–0.0004(9)
C(10)	0.0232(11)	0.0237(12)	0.0392(13)	–0.0023(11)	0.0031(10)	–0.0034(11)
C(11)	0.0250(11)	0.0314(14)	0.0346(13)	–0.0036(12)	0.0028(10)	–0.0012(11)
C(12)	0.0399(15)	0.0498(18)	0.0387(15)	–0.0009(15)	–0.0025(12)	–0.0003(14)

Hydrogen Coordinates and Isotropic Displacement Parameters (Å^2)

	x	y	z	U
H(1B)	0.4693	0.3403	0.4457	0.037
H(2)	0.3515	0.0059	0.4924	0.043
H(3)	0.1333	–0.1679	0.4530	0.041
H(4)	0.0343	0.0008	0.3670	0.040
H(5)	0.1486	0.3437	0.3213	0.035
H(7A)	0.4411	0.7297	0.3739	0.032
H(7B)	0.3390	0.6707	0.3178	0.032
H(8)	0.5766	0.3147	0.3492	0.026
H(9A)	0.3973	0.1623	0.2781	0.031
H(9B)	0.4310	0.4237	0.2410	0.031
H(1)	0.585(3)	–0.040(7)	0.2665(10)	0.045
H(1A)	0.686(3)	0.573(6)	0.2845(9)	0.030
H(10A)	0.6645	0.8373	0.3836	0.034
H(10B)	0.7809	0.9184	0.3434	0.034
H(11)	0.8906	0.4701	0.3629	0.036
H(12A)	0.7626	0.5531	0.4594	0.052
H(12B)	0.8942	0.3406	0.4511	0.052

Torsion Angles [°]

C(6)–C(1)–C(2)–C(3)	0.3(4)	C(1)–C(2)–C(3)–C(4)	–0.5(4)
C(2)–C(3)–C(4)–C(5)	–0.4(4)	C(3)–C(4)–C(5)–C(6)	1.6(4)
C(2)–C(1)–C(6)–C(5)	0.8(3)	C(2)–C(1)–C(6)–C(7)	–177.3(2)
C(4)–C(5)–C(6)–C(1)	–1.7(3)	C(4)–C(5)–C(6)–C(7)	176.4(2)
C(1)–C(6)–C(7)–C(8)	74.2(3)	C(5)–C(6)–C(7)–C(8)	–103.9(2)
C(6)–C(7)–C(8)–N(1)	–162.18(18)	C(6)–C(7)–C(8)–C(9)	76.6(2)
N(1)–C(8)–C(9)–O(1)	63.7(2)	C(7)–C(8)–C(9)–O(1)	–173.66(19)
C(9)–C(8)–N(1)–C(10)	–161.96(18)	C(7)–C(8)–N(1)–C(10)	76.2(2)
C(8)–N(1)–C(10)–C(11)	66.0(2)	N(1)–C(10)–C(11)–C(12)	–119.3(3)

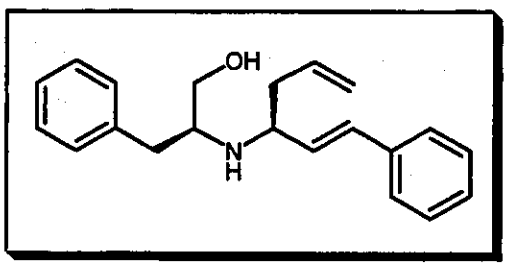
Hydrogen Bonds [Å and °]

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
O(1)–H(1)...N(1')	0.98(3)	1.80(3)	2.763(3)	168(2)
N(1)–H(1A)...O(1")	0.90(3)	2.43(2)	3.160(2)	138(2)
N(1)–H(1A)...O(1)	0.90(3)	2.47(3)	2.924(3)	111.9(18)

Symmetry operations for equivalent atoms
' x,y–1,z " –x+3/2,y+1/2,–z+1/2

Single Crystal X-Ray with Accompanying Data

(*S*)-2-((*S*,*E*)-1-Phenylhexa-1,5-dien-3-ylamino)-3-phenylpropan-1-ol



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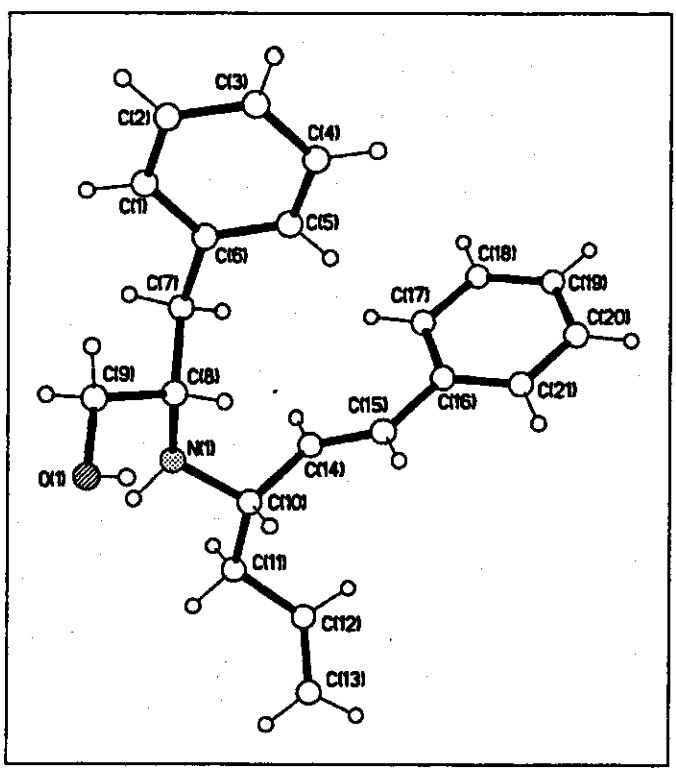

Crystal Data and Structure Refinement

Identification code	**(234a)**	
Empirical formula	$C_{21}H_{25}NO$	
Formula weight	307.42	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 4.9818(5) Å	α= 90°.
	b = 9.4157(10) Å	β= 90°.
	c = 37.792(4) Å	γ = 90°.
Volume	1772.7(3) $Å^3$	
Z	4	
Density (calculated)	1.152 Mg/m^3	
Absorption coefficient	0.070 mm^{-1}	
F(000)	664	
Crystal size	0.53 x 0.21 x 0.15 mm^3	
Crystal description	Colourless block	
Theta range for data collection	2.16 to 28.76°.	
Index ranges	-6<=h<=6, -12<=k<=12, -49<=l<=50	
Reflections collected	15019	
Independent reflections	4177 [R(int) = 0.0305]	
Completeness to theta = 25.00°	99.8%	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.931789	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4177 / 0 / 208	
Goodness-of-fit on F^2	1.032	
Final R indices [I>2sigma(I)]	R1 = 0.0432, wR2 = 0.0963	
R indices (all data)	R1 = 0.0618, wR2 = 0.1036	
Absolute structure parameter	-0.2(15)	
Largest diff. peak and hole	0.229 and -0.154 $e.Å^{-3}$	

Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$ x 10^3). U_{eq} is Defined as One Third of the Trace of the Orthogonalised U^{ij} Tensor.

	x	y	z	U_{eq}
C(1)	4246(4)	4372(2)	1224(1)	37(1)
C(2)	6155(4)	3820(2)	1451(1)	46(1)
C(3)	7025(4)	4601(2)	1740(1)	48(1)
C(4)	5955(4)	5921(2)	1798(1)	45(1)
C(5)	4053(4)	6482(2)	1570(1)	36(1)
C(6)	3189(3)	5721(2)	1276(1)	29(1)
C(7)	1276(3)	6401(2)	1016(1)	28(1)
C(8)	2760(3)	7344(2)	747(1)	25(1)
C(9)	4302(3)	6432(2)	484(1)	28(1)
O(1)	5978(2)	7223(1)	253(1)	32(1)
N(1)	899(3)	8277(1)	551(1)	25(1)
C(10)	802(3)	9762(2)	679(1)	28(1)
C(11)	-958(4)	10625(2)	426(1)	33(1)
C(12)	-1207(4)	12173(2)	518(1)	45(1)
C(13)	-764(4)	13227(2)	309(1)	52(1)
C(14)	-253(3)	9820(2)	1052(1)	29(1)
C(15)	1024(4)	10407(2)	1323(1)	29(1)
C(16)	84(3)	10509(2)	1692(1)	31(1)
C(17)	-2001(4)	9688(2)	1820(1)	47(1)
C(18)	-2855(5)	9818(3)	2170(1)	63(1)
C(19)	-1600(5)	10754(3)	2395(1)	61(1)
C(20)	441(6)	11574(3)	2271(1)	63(1)
C(21)	1305(5)	11450(2)	1922(1)	48(1)

Bond Lengths [Å] and Angles [°]

C(1)-C(2)	1.384(2)	C(10)-C(14)	1.506(2)
C(1)-C(6)	1.389(2)	C(10)-C(11)	1.533(2)
C(2)-C(3)	1.385(3)	C(11)-C(12)	1.503(2)
C(3)-C(4)	1.371(3)	C(12)-C(13)	1.287(3)
C(4)-C(5)	1.385(3)	C(14)-C(15)	1.324(2)
C(5)-C(6)	1.391(2)	C(15)-C(16)	1.476(2)
C(6)-C(7)	1.510(2)	C(16)-C(21)	1.382(2)
C(7)-C(8)	1.540(2)	C(16)-C(17)	1.382(2)
C(8)-N(1)	1.4762(19)	C(17)-C(18)	1.396(3)
C(8)-C(9)	1.522(2)	C(18)-C(19)	1.374(3)
C(9)-O(1)	1.4179(17)	C(19)-C(20)	1.359(3)
N(1)-C(10)	1.4812(19)	C(20)-C(21)	1.391(3)
C(2)-C(1)-C(6)	120.97(16)	N(1)-C(10)-C(11)	108.33(12)
C(1)-C(2)-C(3)	120.39(17)	C(14)-C(10)-C(11)	111.51(13)
C(4)-C(3)-C(2)	119.06(18)	C(12)-C(11)-C(10)	114.58(13)
C(3)-C(4)-C(5)	120.82(17)	C(13)-C(12)-C(11)	126.19(17)
C(4)-C(5)-C(6)	120.80(17)	C(15)-C(14)-C(10)	124.72(15)
C(1)-C(6)-C(5)	117.93(15)	C(14)-C(15)-C(16)	127.19(16)
C(1)-C(6)-C(7)	122.25(14)	C(21)-C(16)-C(17)	117.98(16)
C(5)-C(6)-C(7)	119.74(15)	C(21)-C(16)-C(15)	119.83(16)

C(6)-C(7)-C(8)	111.80(12)	C(17)-C(16)-C(15)	122.19(15)
N(1)-C(8)-C(9)	108.90(11)	C(16)-C(17)-C(18)	120.8(2)
N(1)-C(8)-C(7)	111.93(12)	C(19)-C(18)-C(17)	120.2(2)
C(9)-C(8)-C(7)	110.42(12)	C(20)-C(19)-C(18)	119.47(18)
O(1)-C(9)-C(8)	113.73(12)	C(19)-C(20)-C(21)	120.7(2)
C(8)-N(1)-C(10)	114.65(11)	C(16)-C(21)-C(20)	120.9(2)
N(1)-C(10)-C(14)	110.67(12)		

Anisotropic Displacement Parameters ($Å^2$ x 10^3). The Anisotropic Displacement Factor Exponent Takes the Form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	43(1)	37(1)	31(1)	5(1)	2(1)	-2(1)
C(2)	50(1)	43(1)	46(1)	13(1)	3(1)	7(1)
C(3)	44(1)	63(1)	36(1)	20(1)	-4(1)	1(1)
C(4)	46(1)	63(1)	26(1)	2(1)	-6(1)	-3(1)
C(5)	37(1)	44(1)	26(1)	1(1)	1(1)	0(1)
C(6)	26(1)	41(1)	21(1)	5(1)	5(1)	-3(1)
C(7)	24(1)	38(1)	22(1)	0(1)	3(1)	-2(1)
C(8)	20(1)	35(1)	20(1)	-1(1)	-1(1)	-3(1)
C(9)	25(1)	38(1)	22(1)	-1(1)	2(1)	-1(1)
O(1)	22(1)	54(1)	19(1)	1(1)	2(1)	-5(1)
N(1)	25(1)	35(1)	16(1)	-3(1)	0(1)	0(1)
C(10)	28(1)	35(1)	21(1)	-2(1)	1(1)	-4(1)
C(11)	37(1)	37(1)	25(1)	0(1)	-2(1)	0(1)
C(12)	60(1)	47(1)	30(1)	-6(1)	-4(1)	9(1)
C(13)	55(1)	40(1)	60(1)	-13(1)	2(1)	-1(1)
C(14)	28(1)	35(1)	25(1)	-1(1)	3(1)	2(1)
C(15)	35(1)	29(1)	24(1)	0(1)	-2(1)	2(1)
C(16)	41(1)	31(1)	22(1)	1(1)	-1(1)	11(1)
C(17)	54(1)	55(1)	32(1)	1(1)	6(1)	-1(1)
C(18)	64(1)	87(2)	37(1)	16(1)	16(1)	11(1)
C(19)	82(2)	80(2)	22(1)	1(1)	6(1)	36(1)
C(20)	97(2)	67(1)	26(1)	-10(1)	-11(1)	14(2)
C(21)	65(1)	52(1)	28(1)	-3(1)	-6(1)	-2(1)

Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters ($Å^2$ x 10^3)

	x	y	z	U_{eq}
H(1)	3649	3821	1028	45
H(2)	6872	2901	1409	55
H(3)	8346	4226	1895	57
H(4)	6524	6459	1997	54
H(5)	3330	7398	1615	43
H(7A)	-46	6984	1147	34
H(7B)	282	5649	888	34
H(8)	4071	7954	878	30
H(9A)	5421	5745	616	34
H(9B)	3003	5884	340	34
H(10)	2661	10162	676	34

H(11A)	-203	10546	184	40
H(11B)	-2776	10201	421	40
H(12)	-1742	12394	753	55
H(13A)	-225	13059	72	62
H(13B)	-976	14172	393	62
H(14)	-1958	9406	1097	35
H(15)	2734	10807	1273	35
H(17)	-2862	9027	1668	56
H(18)	-4309	9257	2254	75
H(19)	-2153	10828	2635	74
H(20)	1286	12237	2424	76
H(21)	2753	12020	1841	57
H(1N)	1328	8289	314	40
H(1O)	7373	7603	378	40

Torsion Angles [°]

C(6)-C(1)-C(2)-C(3)	0.8(3)	C(8)-N(1)-C(10)-C(11)	173.75(12)
C(1)-C(2)-C(3)-C(4)	0.5(3)	N(1)-C(10)-C(11)-C(12)	-178.87(15)
C(2)-C(3)-C(4)-C(5)	-0.8(3)	C(14)-C(10)-C(11)-C(12)	59.11(19)
C(3)-C(4)-C(5)-C(6)	-0.2(3)	C(10)-C(11)-C(12)-C(13)	127.7(2)
C(2)-C(1)-C(6)-C(5)	-1.8(2)	N(1)-C(10)-C(14)-C(15)	124.04(16)
C(2)-C(1)-C(6)-C(7)	174.87(16)	C(11)-C(10)-C(14)-C(15)	-115.30(17)
C(4)-C(5)-C(6)-C(1)	1.5(2)	C(10)-C(14)-C(15)-C(16)	179.36(15)
C(4)-C(5)-C(6)-C(7)	-175.26(16)	C(14)-C(15)-C(16)-C(21)	-163.76(17)
C(1)-C(6)-C(7)-C(8)	-93.84(18)	C(14)-C(15)-C(16)-C(17)	16.3(3)
C(5)-C(6)-C(7)-C(8)	82.74(17)	C(21)-C(16)-C(17)-C(18)	0.6(3)
C(6)-C(7)-C(8)-N(1)	-166.04(12)	C(15)-C(16)-C(17)-C(18)	-179.49(18)
C(6)-C(7)-C(8)-C(9)	72.46(16)	C(16)-C(17)-C(18)-C(19)	-1.0(3)
N(1)-C(8)-C(9)-O(1)	63.86(16)	C(17)-C(18)-C(19)-C(20)	1.4(3)
C(7)-C(8)-C(9)-O(1)	-172.86(12)	C(18)-C(19)-C(20)-C(21)	-1.4(3)
C(9)-C(8)-N(1)-C(10)	-136.94(12)	C(17)-C(16)-C(21)-C(20)	-0.6(3)
C(7)-C(8)-N(1)-C(10)	100.69(15)	C(15)-C(16)-C(21)-C(20)	179.48(18)
C(8)-N(1)-C(10)-C(14)	-63.72(16)	C(19)-C(20)-C(21)-C(16)	1.0(3)

Hydrogen Bonds [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1O)...N(1)#1	0.91	1.98	2.8741(16)	166.4
N(1)-H(1N)...O(1)#2	0.92	2.20	3.0750(15)	157.6

Symmetry transformations used to generate equivalent atoms:

#1 x+1,y,z #2 x-1/2,-y+3/2,-z